

**New methods for the arylation of trivalent phosphorus
species
and
Studies towards the synthesis of sesqui-lignan natural
products**

By Adam Fearnley

**Thesis submitted to the University of Nottingham for the
degree for Doctor of Philosophy**

I declare that the work embodied in this thesis is the result of my own investigations.

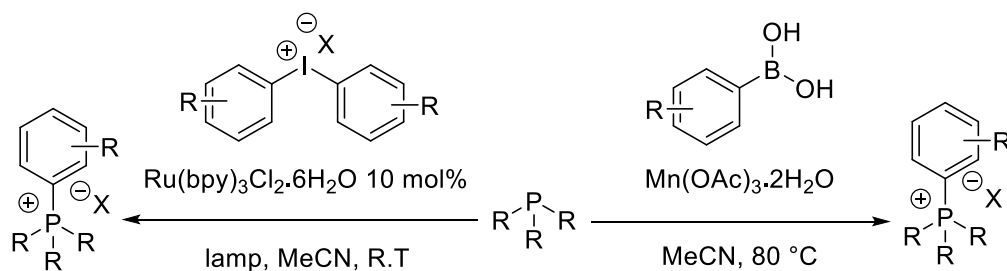
Where the work of other investigators has been used, this has been fully
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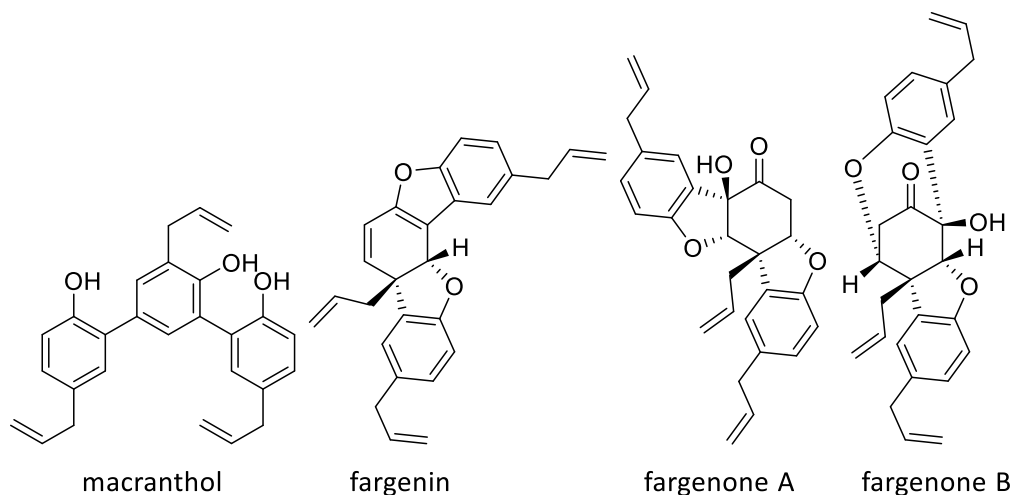
Acknowledgements

I would like to thank Dr Ross Denton for all the help and support he has provided over my PhD. I would also like to thank The Denton Group members past and present, especially Andy Shannon-Little, Keith Andrews and Jan Saska. Without them the 4 years would have been a far more daunting and challenging experience. In addition to The Denton Group, the University of Nottingham technical staff have always been on hand to provide assistance and support.

Abstract



Chapter one describes two efficient synthesis methods for the preparation of functionalised phosphonium salts. The first method utilises aryl radicals generated by a photo-induced decomposition of diaryliodonium salts, with the second method generating aryl radicals from arylboronic acids and manganese acetate. In both cases a broad substrate scope is demonstrated with respect to both the phosphorus and arylating species.



Chapter two describes approaches to the total synthesis of plant sesqui-neolignans. The synthesis of macranthol was achieved in 5 steps from commercially available 4-allylanisole in 7% yield. As well as the first synthesis of the core [4.3.0] ring structure of the fargenin/fargenone family of natural products.

Abbreviations

AIBN - azobisisobutyronitrile

bpy - 2,2'-bipyridine

COD - 1,5-cyclooctadiene

dba - dibenzylideneacetone

DCE - dichloroethane

DCM - dichloromethane

DMF - dimethylformamide

DMS - dimethylsulfide

dppf - 1,1'-bis(diphenylphosphanyl)ferrocene

dtbpy - 4,4'-di-*tert*-butyl-2,2'-bipyridyl

ee - enantiomeric excess

HMBC - heteronuclear multiple bond correlation spectroscopy

KHMDS - potassium bis(trimethylsilyl)amide

ppm - parts per million

NBS - N-bromosuccinimide

NOESY – nuclear overhauser effect spectroscopy

*m*CPBA - 3-chloroperbenzoic acid

MLCT - metal to ligand charge transfer

MIDA - methyliminodiacetic acid

TBSCl - *tert*-butyldimethylsilyl ether

TEMPO - (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl

THF - tetrahydrofuran

TLC - thin layer chromatography

TMEDA - *N,N,N',N'*-tetramethylethane-1,2-diamine

TFE - trifluoroethanol

S-Phos - 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl

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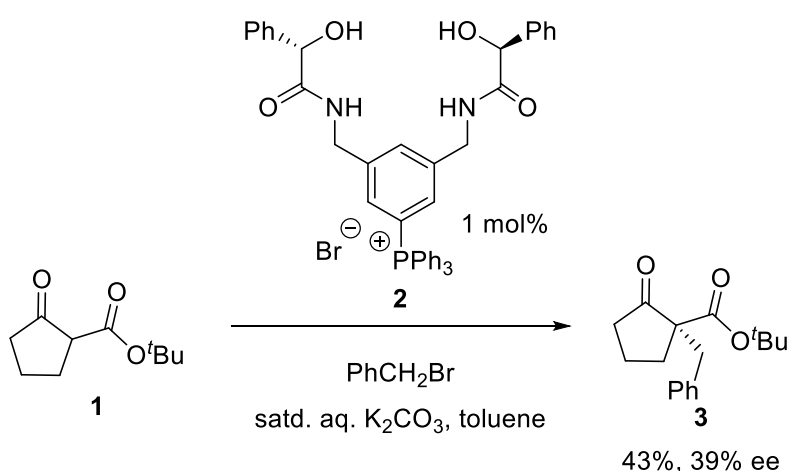
Chapter 1

1. Introduction

1.1 The uses of phosphonium salts

Quaternary phosphonium salts are an important class of organophosphorus compounds, which have been applied in a wide range chemical contexts including use as synthesis reagents,¹ ionic liquids² and phase transfer catalysts.³ In addition, phosphonium salts have been investigated in the areas of biochemistry and medicinal chemistry, where aryl-substituted lipophilic phosphonium salts have applications in cellular biology,⁴ anti-cancer agents⁵ and drug delivery.⁶

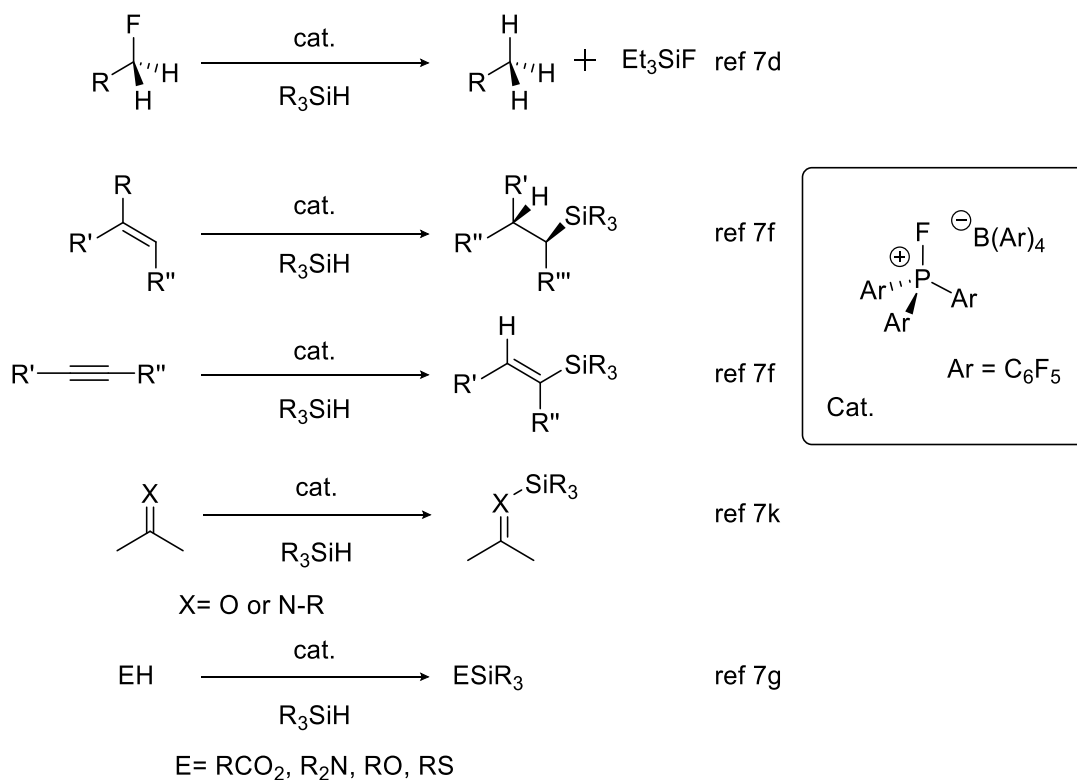
The use of phosphonium salts as phase transfer catalysts is outlined in Scheme 1. This example illustrates how chiral tetraarylphosphonium salt **2** can be used to perform the catalytic asymmetric benzylation reaction of dicarbonyl **1**.^{3b}



Scheme 1. Catalytic asymmetric phase-transfer alkylation reactions mediated by a chiral non-racemic phosphonium salt.

More recently, phosphonium salts have been investigated as Lewis acids,⁷ providing evidence that [(C₆F₅)₃PF]⁺ is more Lewis acidic than B(C₆F₅)₃, which is attributed to the formal positive charge on the phosphorus and the salt's low lying σ* orbitals. This Lewis acidity has been demonstrated through a number of Lewis acid-catalysed

reactions such as, the hydrodefluorinations of fluoroalkanes,^{7d} isomerisations and polymerisations of alkenes, hydrosilylation of alkenes, alkynes,^{7f} ketones, imines and nitriles^{7k} and the dehydrocoupling of silanes with anilines, phenols, thiophenols and acids.^{7g} Therefore opening up a new and exciting area of organocatalysis.

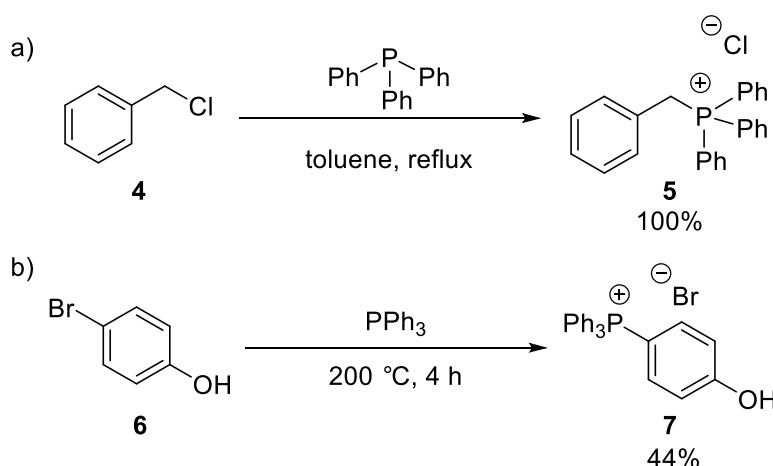


Scheme 2. Reactions catalysed by phosphonium salt Lewis acids. Cat. $[(\text{C}_6\text{F}_5)_3\text{PF}]^+ [\text{B}(\text{C}_6\text{F}_5)_3]^-$.

1.2 Phosphonium salt synthesis

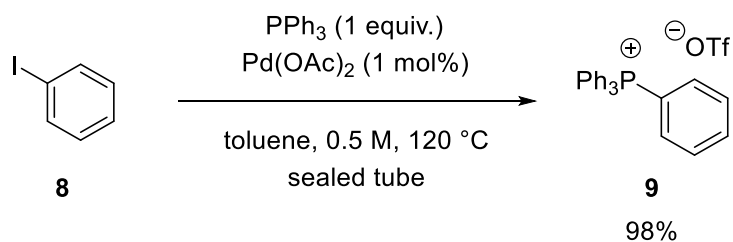
Even though there are a diverse range of applications for phosphonium salts, there are relatively few methods for their synthesis, especially tetraarylphosphonium salts. Classically, phosphonium salts are synthesised *via* alkylation of phosphines using alkyl halides,⁸ however, arylation reactions are rather more difficult and very few examples have been reported (Scheme 3).⁹ The increased difficulties associated with the formation of tetraarylphosphonium salts *via* this method are due to the inability

of the aryl halides to undergo S_N2 reactions. Therefore, the formation of phosphonium salt **7** occurs *via* a different mechanistic pathway and harsh reaction conditions are required, which limit the substrate scope. More recently the synthesis of tetraarylphosphonium salts have been investigated, revealing transition metal-catalysed couplings of aryl halides^{10,11} and the *in situ* trapping of arynes¹² (generated from 2-(trimethylsilyl)aryltriflates)¹³ by phosphines.



Scheme 3. a) Classical approach to the synthesis of alkyltriarylphosphonium salts, b) early example of tetraarylphosphonium salt formation.

Charette and co-workers developed the transition metal catalysed coupling of phosphines with aryl halides, using palladium and nickel catalysts. Their palladium catalysed reaction was established through investigation of previous examples of the quaternisation of phosphines *via* palladium(0) complexes. The first reported synthesis of tetraarylphosphonium salts was reported by Heck and co-workers in 1976, when it was observed as a by-product in their palladium catalysed reactions.¹⁴ Subsequently, in 1983, Migita and co-workers published the palladium catalysed synthesis of tetraarylphosphonium salts from aryl iodides (Scheme 4).¹⁵



Scheme 4. Migita's conditions for the palladium catalysed formation of tetraarylphosphonium salts from aryl iodides.

Charette and co-workers found that when Pd_2dba_3 is used as the precatalyst, aryl iodides, bromides and triflates can be coupled with triphenylphosphine in good to excellent yields over relatively fast reaction times (0.5 -5 h) (Table 1).¹⁰ The reaction requires low catalyst loading (1 mol%) and a number of functional groups can be tolerated, such as aldehydes, halides, alcohols and ethers. However, aryl halides containing *ortho* substituents, esters, phenols and carboxylic acids do not undergo efficient coupling reactions.

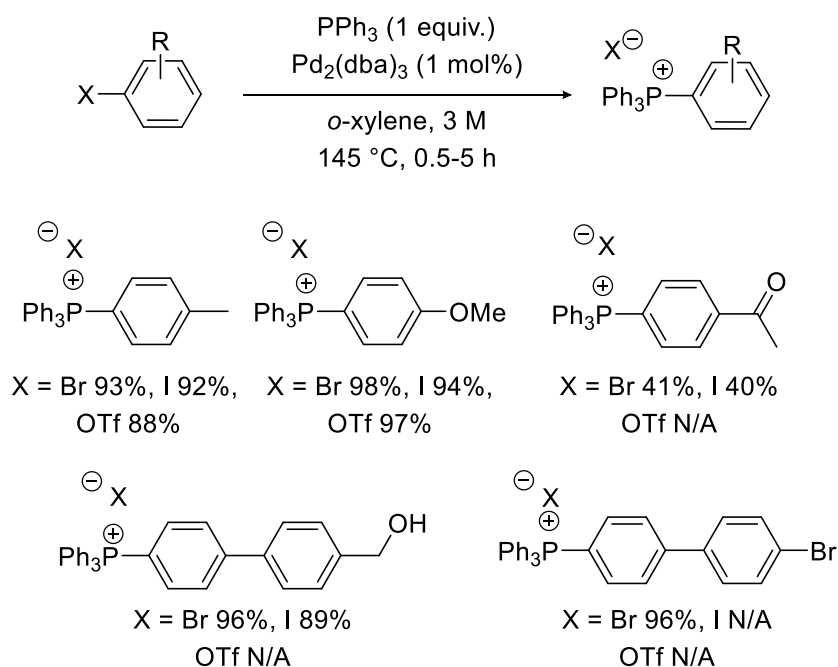
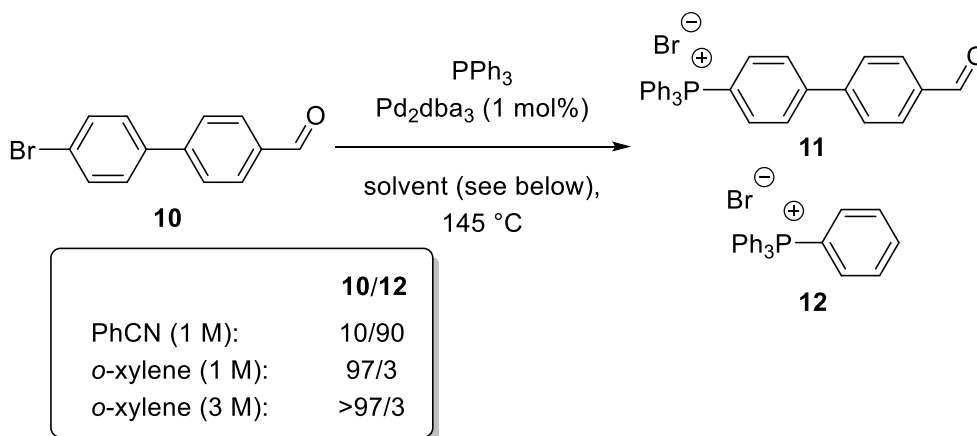


Table 1. Palladium-catalysed arylation of phosphines using aryl halides and triflates.

A major advantage of this reaction is that it allows for simple purification of the phosphonium salt product, due to the salt's insolubility in the reaction solvent (*o*-xylene). Therefore, purification can be achieved through simple filtration. It has also been shown that benzonitrile can be used for this reaction, providing a comparable yield of 91% (95% in *o*-xylene) for tetraphenylphosphonium bromide **12**. However, when functionalised aryl bromides are used, benzonitrile generates a mixture of products (Scheme 5). This does not occur as freely in *o*-xylene due to the heterogeneous nature of the reaction mixture in this case.



Scheme 5. Example of the aryl group scrambling with functionalised aryl bromides under palladium catalysed arylation conditions.

This type of aryl group scrambling has been previously described in the literature, relating to its effect in standard palladium cross coupling reactions,¹⁶ as well as the formation of tetraarylphosphonium salts.¹⁷ It was rationalised that the mixture resulted from palladium insertion into the reactive P-C bond of the product.^{1b} After this oxidative addition to the palladium centre, it is believed that reductive elimination occurs, resulting in the formation of a new phosphonium salt (Scheme 6).¹⁸

The nickel-mediated synthesis of tetraphenylphosphonium salts has also been investigated by Charette and co-workers. However, the first studies into such a reaction were undertaken by Horner,¹⁹ who demonstrated that nickel(II) salts could facilitate this transformation. The original coupling required harsh reaction conditions, such as high reaction temperatures and a high nickel loading of 50 mol%.²⁰ In addition to the use of Ni(II) salts, Ni(0) complexes have also been shown to effectively catalyse the formation of phosphonium salts.^{3b}

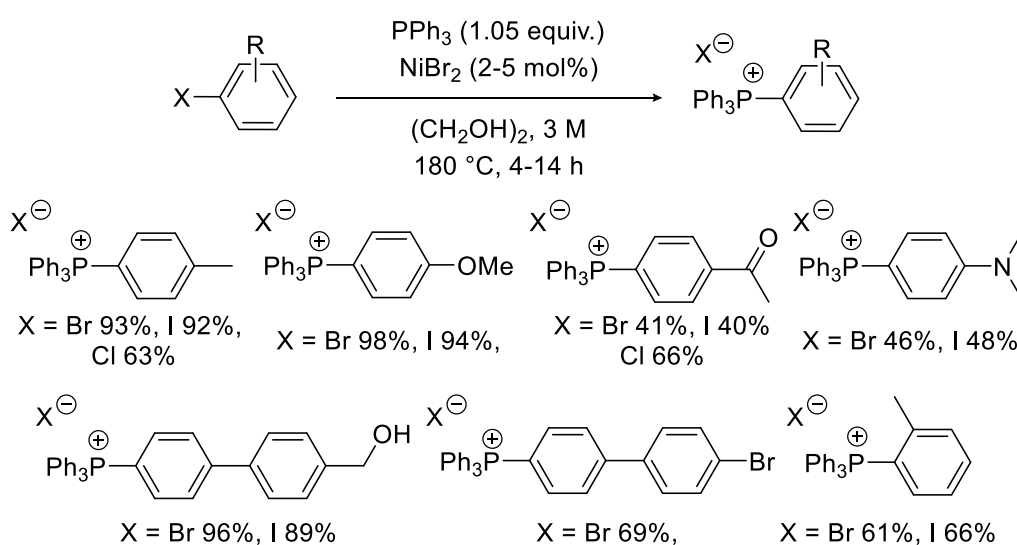


Table 2. Nickel catalysed synthesis of tetraarylphosphonium salts.

The conditions developed by Charette and co-workers, use NiBr₂ as the pre-catalyst at a low catalyst loading of 2-5 mol% to afford tetraarylphosphonium salts in good to excellent yields (Table 2).¹¹ Charette and co-workers found that the nickel conditions tolerated functional groups that were incompatible with the palladium conditions, such as phenols, amides, phosphines and tertiary amines. Unfortunately esters and primary amines were not tolerated; however, protected amines were formed in good yields. Again the reaction conditions were compatible with aryl iodides, bromides, triflates as well as chlorides, which were previously unreactive when

subjected to the palladium coupling reaction. However, chlorides provided lower yields and reduced functional group tolerance.

Charette and co-workers have designed two transition metal catalysed couplings of triphenylphosphine and aryl halides/triflates; however, there are major limitations with both reactions, such as the requirement for high reaction temperatures. The substrate scope is also limited due to the fact there is no evidence that phosphines other than triphenylphosphine can be used. This means that the functionalisation of the tetraarylphosphonium salts can only be associated with one of the aryl substituents.

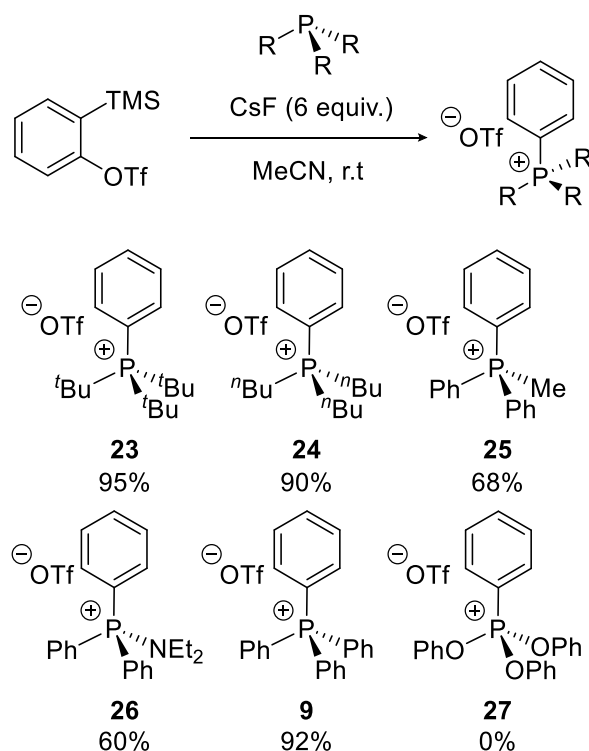
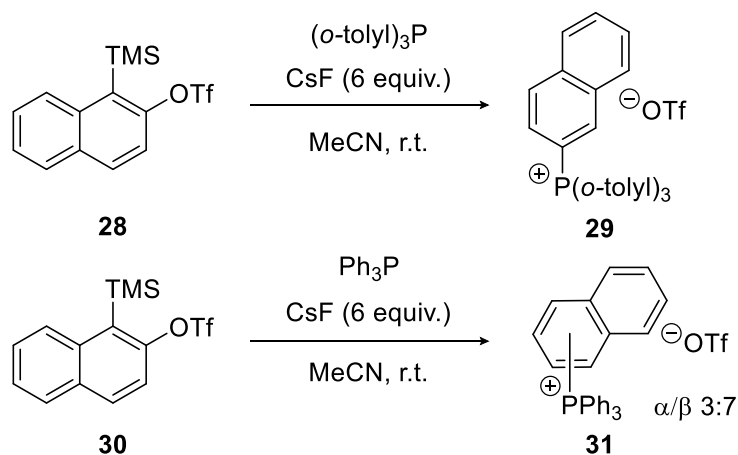


Table 3. Synthesis of phosphonium and arsinium salts via capture of benzyne.

Further investigation of the synthesis of tetraarylphosphonium salts has led to the development of a room temperature procedure by Juge and co-workers. This involves the *in situ* capture of arynes by phosphines at room temperature, where the (o-trimethylsilyl)phenyltriflate can be synthesised in 3 steps from phenol in 66%.¹²

Under the optimised conditions, CsF (6 equiv.), (*o*-trimethylsilyl)phenyltriflate (2.5 equiv.) in acetonitrile, the quaternisation of various P(III)-phosphorus compounds has been investigated (Table 3).

This investigation illustrated that phosphines containing alkyl and/or aryl groups can be tolerated with differing degrees of substitution, allowing increased steric bulk around the phosphorus centre (*n*-Bu, *t*-Bu). *N*, *N*-Diethylaminodiphenylphosphine was also shown to undergo quaternisation under these conditions, but triphenylphosphite cannot, most likely due to the reduced nucleophilicity of the latter phosphorus centre.



Scheme 8. Regioselective nature of the synthesis of tetraarylphosphonium salts via unsymmetrical arynes.

After investigation of the scope of the reaction with respect to the phosphine, illustrating improvements on the existing transition metal catalysed synthesis methods, it was demonstrated that the aryne precursor can also be modified. In addition to results indicating more challenging aromatic species could be introduced, it was revealed that unsymmetrical arynes produced a mixture of regioisomers. However, an interesting result was discovered when tris(*o*-tolyl)phosphine was

reacted with aryl triflate **28** as shown in Scheme 8, providing a single regioisomer. Whereas, the reaction with triphenylphosphine yielded a mixture of regioisomers, thus providing evidence indicating that regioselectivity is dependent upon the steric bulk surrounding the phosphine.

Juge and co-workers examined the arylation of P-stereogenic triarylphosphines, due to their interest in the asymmetric synthesis of P-stereogenic phosphorus compounds. However, previous synthesis methods for the formation of chiral phosphonium salts have been limited to alkylation reactions.²¹ Owing to the mild reaction conditions of this new synthesis method, Juge and co-workers have reported the arylation of chiral tetraarylphosphines, Figure 1.

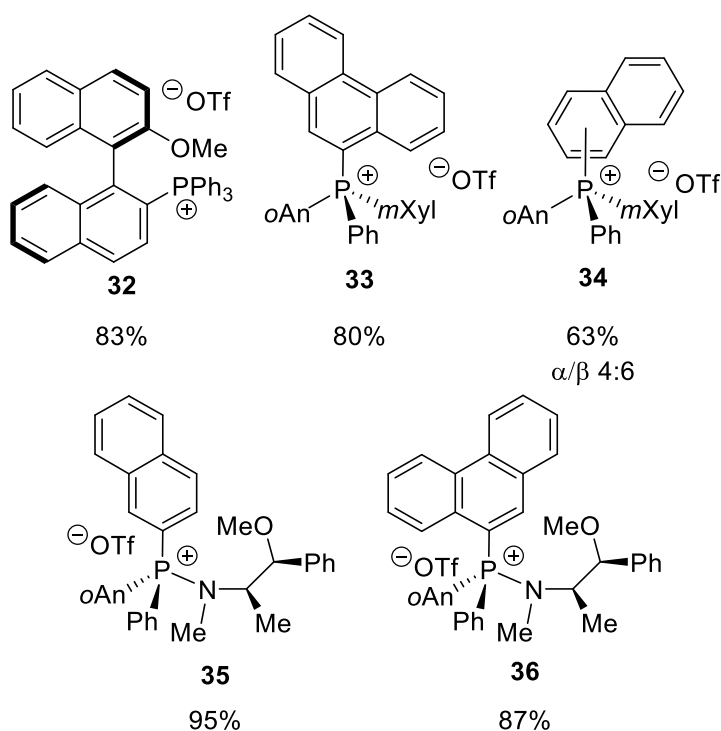


Figure 1. The arylation of chiral phosphines.

Inspection of the above methods reveals several limitations with respect to the arylation of trivalent phosphorus species:

- Low substrate scope with respect to the phosphine, especially for transition metal catalysed quaternisation;
- Poor regioselective transfer of the aryl group for non-symmetrical aryl species as is the case for arylation *via* arynes;
- Availability of starting materials limits the versatility as for ((*o*-trimethylsilyl)aryl)triflates-arylation *via* arynes).

After investigation of the current literature methods and their limitations we wished to develop a more versatile synthesis method, which could: (a) be conducted under mild conditions; (b) was regiospecific with respect to the formation of the new carbon-phosphorus bond; and (c) uses readily available reagents.

1.3 Arylation Methods – Diaryliodonium Salts

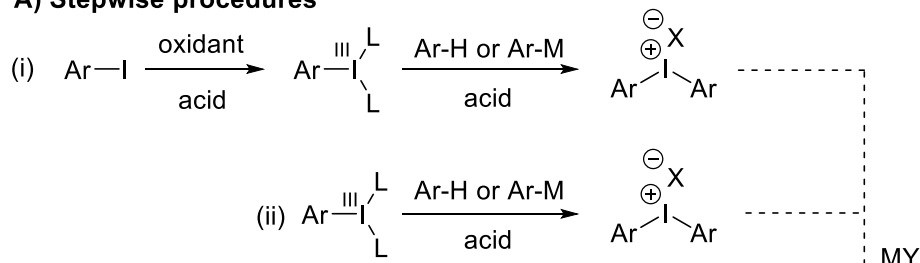
After investigations into the current methods of tetraarylphosphonium salt synthesis, we considered the use of diaryliodonium salts as aryl transfer reagents. Diaryliodonium salts are already well known in the area of aryl transfer,²² with various examples utilising the reactivity of diaryliodonium salts in conjunction with various metals, such as copper²³ and palladium.²⁴ We therefore believed it was a reasonable assumption that diaryliodonium salts could be applied to the arylation of phosphines. This was supported by literature evidence illustrating the decomposition of diaryliodonium salts into aryl radicals and aryl iodides following photo irradiation,²⁵ chemistry that has been utilised in the synthesis of tetraarylphosphonium salts.²⁶

1.4 Synthesis of Diaryliodonium Salts

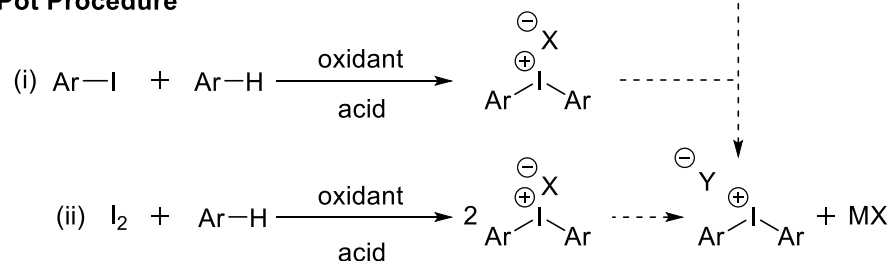
The synthesis of diaryliodonium salts requires the use of iodine(III) species, these can either be preformed or generated *in situ*, often *via* the oxidation of the

corresponding aryl iodide. Therefore, the synthesis can require up to three steps depending on the oxidation state of the starting iodide species. A general overview of the synthesis procedures is shown in Scheme 9.

A) Stepwise procedures



B) One Pot Procedure



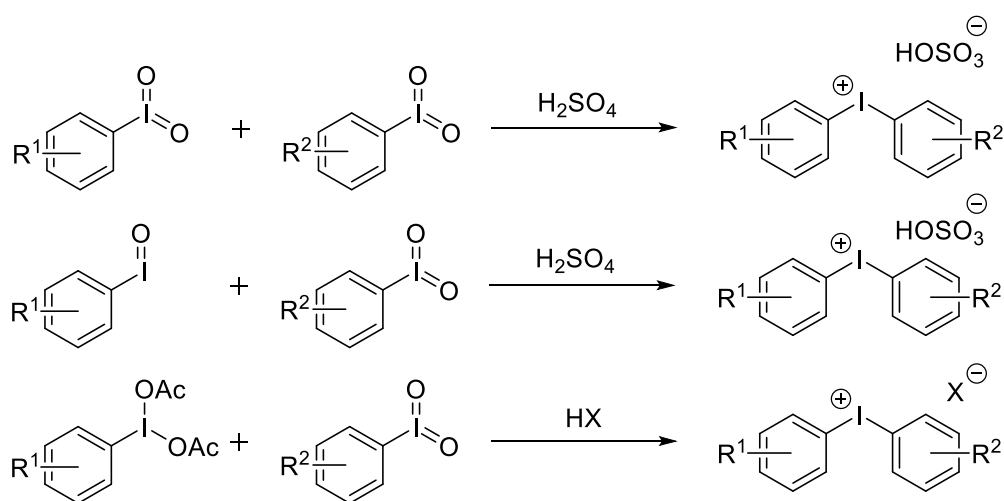
Scheme 9. General synthesis methods for the generation of diaryliodonium salts.

Scheme 9 A, illustrates that depending on the complexity of the aryl iodide required, it is possible to oxidise to the iodine(III) reagent or start from a commercially available material ((diacetoxyiodo)benzene is one such example). With the iodine(III) reagent in hand, it is then possible to perform ligand exchange with arenes or organometallic reagents, thus obtaining the diaryliodonium salt. The vast majority of these reactions are carried out under acidic conditions, with the acid providing the counter anion; however, counter anion exchange is often carried out to tune the solubility of the resultant diaryliodonium salt.

Scheme 9 B, demonstrates that it is also possible to carry out the oxidation and ligand exchange in a one pot procedure, where no isolation or purification of the

iodine(III) species is required. Therefore diaryliodonium salts can be carried out directly from aryl iodides (Scheme 9 B(i)) and molecular iodine (Scheme 9 B(ii)).^{20c}

The first synthesis of diaryliodonium salts was reported by Hartmann and Meyer in 1894.²⁷ Even though this method was carried out in acidic media, other early synthesis strategies also involved the reaction of iodosoarenes and iodoxyarenes in basic conditions.^{24, 28} Investigations into the synthesis of diaryliodonium salts has been carried out by Beringer and co-workers, who demonstrated that it was possible to condense iodoso, iodoso diacetate or iodoxy compounds with arenes in the presence of an acid (Scheme 10).^{29, 30}



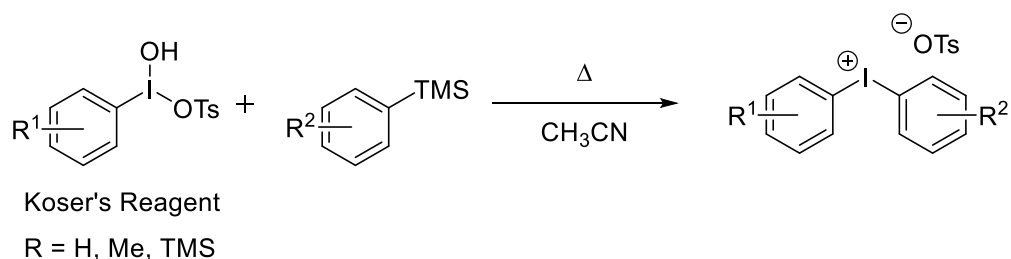
X = sulfuric acid, trifluoroacetic acid
 $\text{R}^1/\text{R}^2 = \text{NO}_2, \text{OMe}, \text{Br}, \text{F}, \text{Cl}, \text{Me}, \text{H}$

Scheme 10. Iodonium salt synthesis from iodine(III) reagents, carried out by Beringer and co-workers.

They also showed that the *in situ* oxidation of an iodo compound could be performed, followed by condensation with an arene in the presence of acid, to generate diaryliodonium salts.²⁷ Beringer and co-workers investigated sulfuric acid, acetic acid and trifluoroacetic acid conditions; discovering that electron releasing

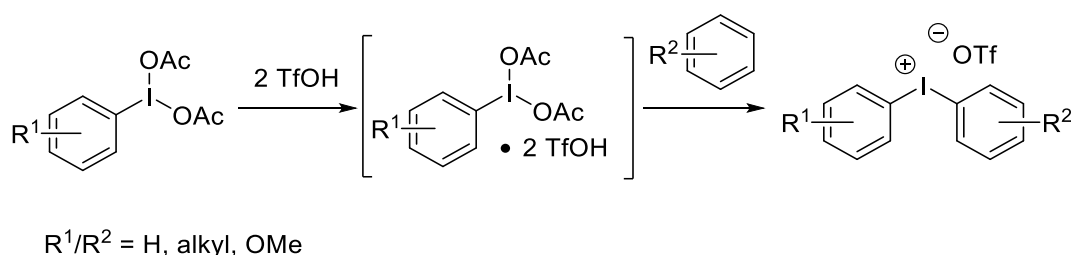
substituents worked best in an acetic acid-acetic anhydride-sulfuric acid mixture, whereas electron withdrawing aryl groups proceeded in sulfuric acid.²⁷ It was also illustrated that reactions involving anisole and thiophene moieties could be catalysed by trifluoroacetic acid.³¹

In 1980 the first regiospecific synthesis method for diaryliodonium salts was reported by Koser and co-workers; utilising the reaction between Koser's reagent and arylsilanes under neutral conditions. The reaction allowed regiospecific carbon-iodine bond formation, due to the selective cleavage of the silicon-carbon bond. It should also be noted that when bis(trimethylsilyl)arenes were used, only mono addition was observed.³²



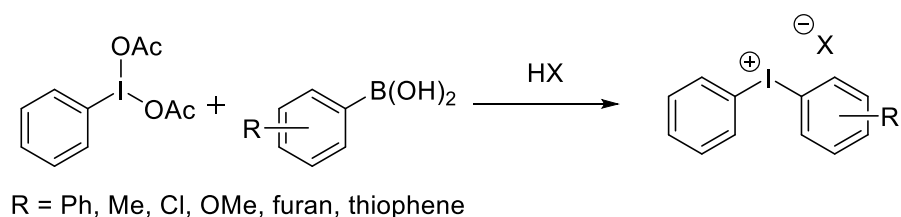
Scheme 11. Synthesis of diaryliodonium tosylates via Koser's reagent under neutral conditions.

(Diacetoxy)iodobenzene has also been found to be an effective reagent for the synthesis of diaryliodonium salts, when mixed with 2 equivalents of triflic acid (Scheme 12). The subsequent reagent, which is formed *in situ*, can react with electron-rich and weakly deactivating halo arenes.³³ Further studies have developed a wider substrate scope through the utilisation of more complex (diacetoxy)iidoarenes.³⁴



Scheme 12. Synthesis of diaryliodonium triflates.

In addition to the use of iodine(III) reagents in conjunction with arenes, it has also been shown that organometallic reagents can be used to prepare diaryliodonium salts. An important example of this is the regiospecific reaction between (diacetoxy)iodobenzene and arylboronic acids in the presence of triflic acid, producing diaryliodonium triflates. It has been shown that a wide range of boronic acids can be tolerated in this process, allowing the addition of both electron rich and electron poor aryl groups. It has also been demonstrated that heteroaryl(aryl)iodonium salts can be formed in this manner, however, the less reactive Koser's reagent was used to generate the tosylates, due to a reduction in by-products leading to more efficient purification.³⁵



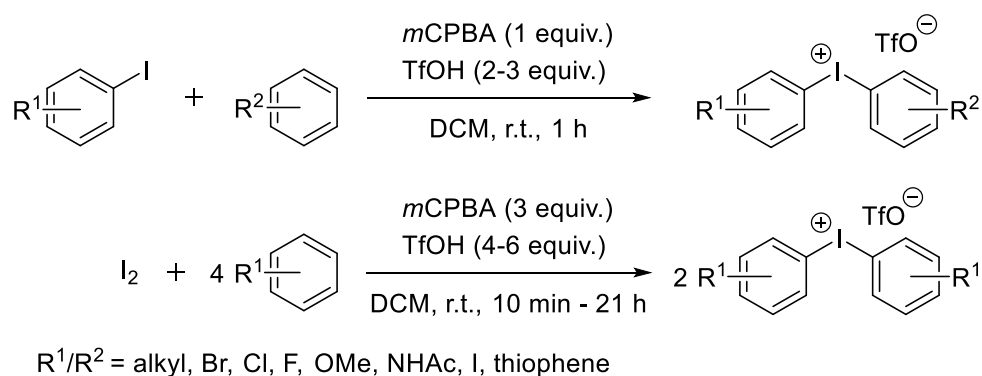
Scheme 13. Synthesis of diaryliodonium salts via boronic acids and (diacetoxy)arenes.

Alternative synthesis routes for the formation of diaryliodonium salts have been based around a one pot approach, this requires the *in situ* formation of the iodine(III) species *via* oxidation. In recent years this type of approach has been widely

investigated, with a variety of examples being developed by the groups of Kitamura³⁶ and Olofsson.³⁷

The synthesis methods developed by Kitamura, demonstrate the use of inorganic oxidant $K_2S_2O_8$, whereas Olofsson and co-workers applied *m*CPBA as the oxidant. The methods discussed below are those developed by Olofsson, due to the fact we utilised these methods for the synthesis of our diaryliodonium salt starting materials.

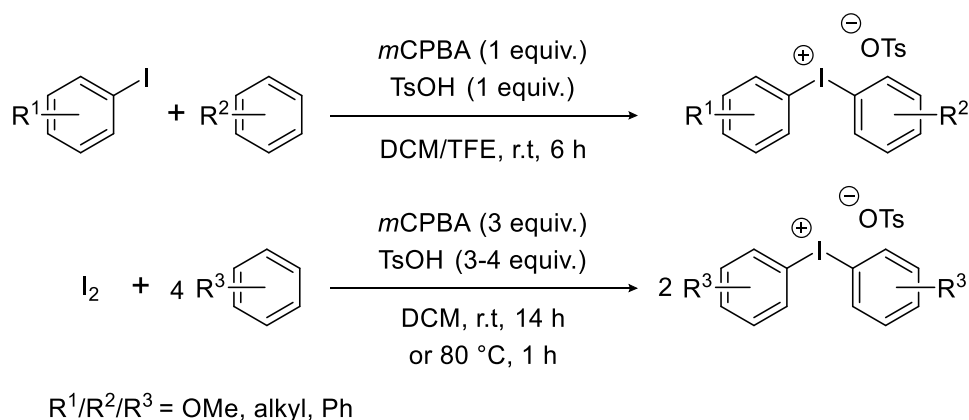
Olofsson and co-workers first approach, uses *m*CPBA as the oxidant to generate (diacyloxy)iodoarenes, which are then activated by triflic acid. This method has been shown to generate a wide range of symmetrical and unsymmetrical iodonium salts with varying electronic properties, whilst allowing straightforward purification. It has also been illustrated that this approach is effective with aryl iodides and molecular iodine as the starting material, however the substrate scope is larger and more atom efficient when aryl iodides are used.^{38a}



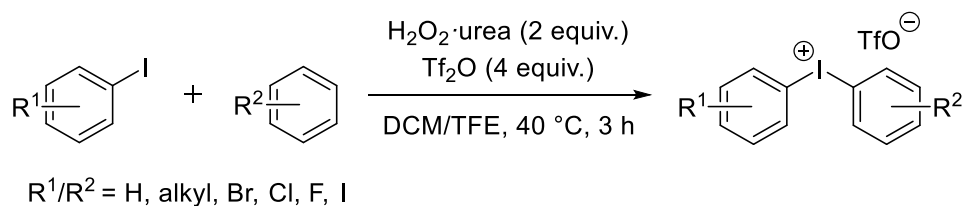
Scheme 14. One pot synthesis methods for the generation of diaryliodonium triflates.

Olofsson and co-workers have also shown that symmetric, electron rich iodonium salts can be synthesised by replacing the triflic acid with the less reactive tosic acid, generating diaryliodonium tosylates (Scheme 15).^{38b} In addition to varying the acid

used, it has also been illustrated that *m*CPBA can be replaced as the oxidant with H₂O₂-urea in conjunction with triflic anhydride.^{38c}

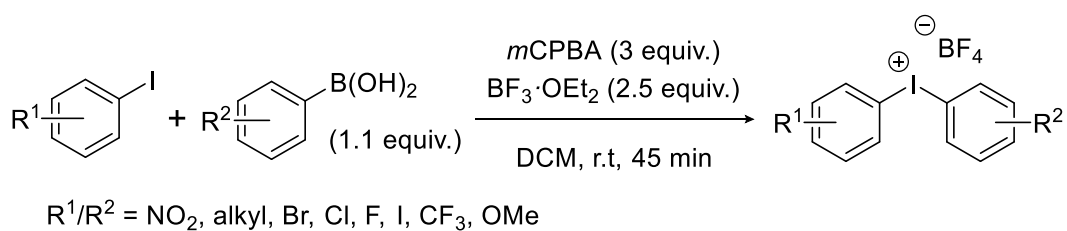


Scheme 15. Olofsson and co-workers one pot synthesis of diaryliodonium triflates.



Scheme 16. Synthesis of diaryliodonium salts using hydrogen peroxide-urea as environmentally friendly oxidising agent.

As previously shown boronic acids have been demonstrated as efficient reagents for the formation of diaryliodonium salts in a regiospecific manner. This was utilised by Olofsson and co-workers to generate another one pot procedure, using *m*CPBA and boron trifluoride etherate. It was shown that this method could produce a wide range of symmetrical and unsymmetrical tetrafluoroborate salts, without the need for an extra anion exchange step. It has also been reported that this method is applicable with both electron deficient and electron rich aryl moieties.^{33d}

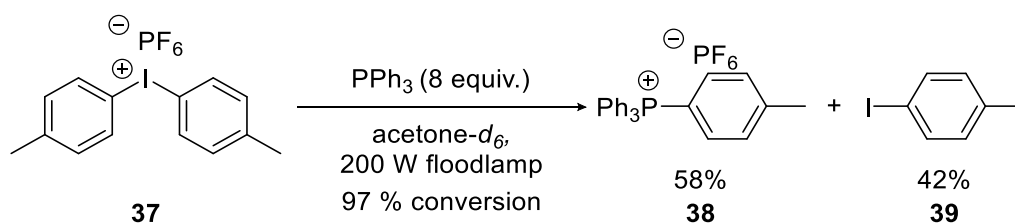


Scheme 17. One pot synthesis method for the preparation of diaryliodonium tetrafluoroborates from boronic acids

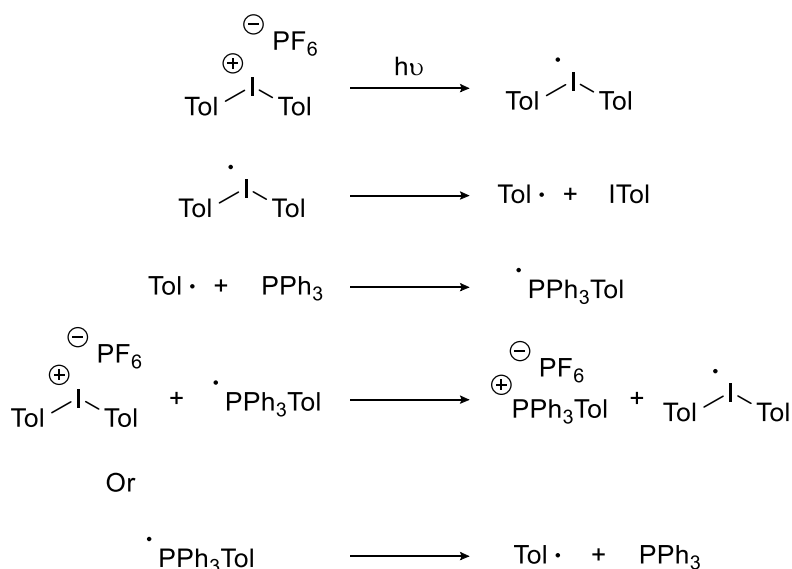
Even though this section does not provide a complete list of the synthesis methods for diaryliodonium salts, it provides sufficient evidence to conclude that diaryliodonium salts can be a readily available source of starting material for the arylation of trivalent phosphorus reagents. This is due to the fact diaryliodonium salts can be synthesised in one pot from easily available reagents (aryl iodides) in good to excellent yield, with a wide range of electronic and steric properties.

1.5 Precedent for the arylation of trivalent phosphorus species

The proposed arylation reaction between diaryliodonium salts and trivalent organophosphorus compounds has literature precedent, having been first reported in 1965 by Reutov and co-workers.^{27a} This work was returned to by Krapmeier and co-workers in 1993;^{27b} however, this non-preparative mechanistic investigation did not report a synthetically useful reaction. The mechanistic study demonstrated that triphenyl(*p*-tolyl)phosponium hexafluorophosphate **38** could be synthesised from di(*p*-tolyl)iodonium hexafluorophosphate **37** and triphenylphosphine (scheme 18), providing evidence that the reaction proceeds *via* a redox radical chain process.



Scheme 18. Reaction investigated by Krapmeier and co-workers.

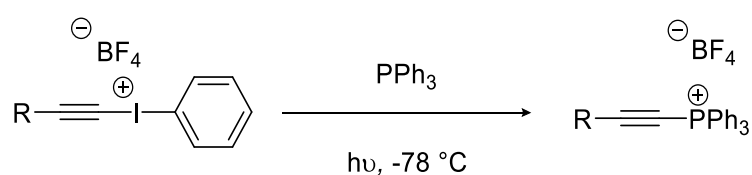


Scheme 19. Radical chain propagation mechanism proposed by Krapmeier and co-workers.

It is reported that the redox radical chain process involves an aryl radical generated from decomposition of the diaryliodonium salt, as previously reported. This goes on to generate a phosphoranyl radical after addition to a phosphine, which can subsequently propagate the radical chain through reduction of an additional iodonium salt molecule (Scheme 19). Alternatively the phosphoranyl radical can eliminate an aryl radical, regenerating a phosphine. Therefore the generation of a phosphonium salt is dependent on the relative rates of the decomposition and reduction.

Another example of the utilisation of the photoinitiation of iodonium salts, is the formation of (alkylethynyl)triphenylphosphonium from the corresponding phenyl(alkynyl)iodonium salts, which occurs through the selective cleavage of the sp-carbon-iodine bond by irradiation with light at $-78\text{ }^{\circ}\text{C}$.³⁸

With this information in hand we believed that a more synthetically useful arylation reaction could be developed between diaryliodonium salts and trivalent organophosphorus compounds.



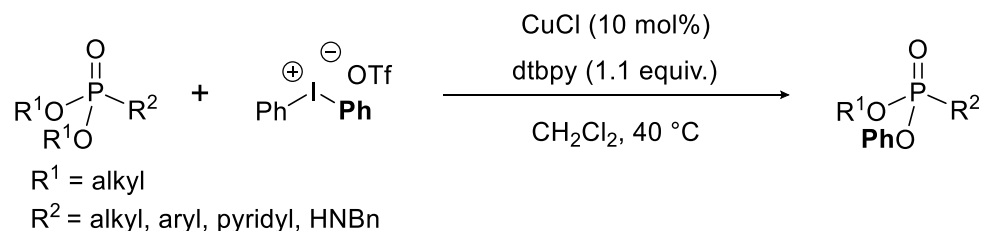
Scheme 20. The synthesis of (alkylethynyl)triphenylphosphonium salts via irradiation of the corresponding phenyl(alkynyl)iodonium salts.

1.6 Arylation of phosphorus species with iodonium salts

In addition to the mechanistic studies investigating the formation of tetraarylphosphonium salts, there have been numerous examples of the utilisation of the reactive nature of iodonium salts with phosphorus species. These examples demonstrate the reactivity of the P-H and P-OH bonds to arylation *via* iodonium salts, under a range of conditions.

It has been shown that diaryliodonium salts can be reduced in the presence of a copper(I) source to generate a highly electrophilic aryl-Cu(III) species,³⁹ which can therefore react with a nucleophilic phosphorus species. An example of such a reaction is shown in scheme 21; direct oxygen arylation of dialkyl phosphonates by

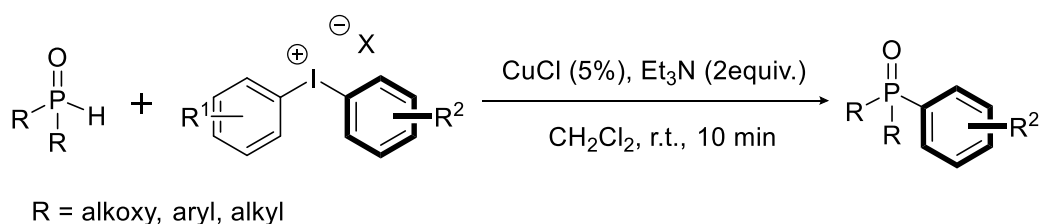
diaryliodonium salts is demonstrated, proceeding with a wide range of dialkyl phosphonates.



Scheme 21. Copper-catalysed synthesis of mixed alkyl aryl phosphonate esters via symmetrical/unsymmetrical diaryliodonium triflates.

Investigation of the scope of the reaction with respect to the diaryliodonium salt, demonstrated that both electron withdrawing and donating functionalities can be tolerated. It also demonstrated that mesityl(aryl)iodonium triflates can be employed as the aryl source, utilising the selective nature of aryl transfer, when considering sterically different aryl moieties.^{13c, 40} This supports data previously published illustrating that metal catalysed reaction conditions lead to the selective transfer of the most electron-rich and least hindered aryl groups. In this case the ratio of products isolated was >99:1.

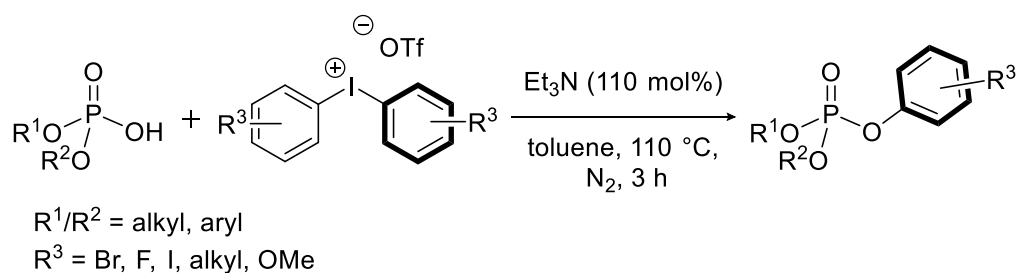
In addition to the copper catalysed arylation of P-OH bonds, investigations have examined the arylation of P-H bonds, here CuCl (5 mol%), triethylamine (2 equiv.) and diaryliodonium salts are used to generate tertiary phosphine oxides and aryl phosphonates, Scheme 22.⁴¹



Scheme 22. Copper catalysed P-arylation of phosphorus nucleophiles with diaryliodonium salts.

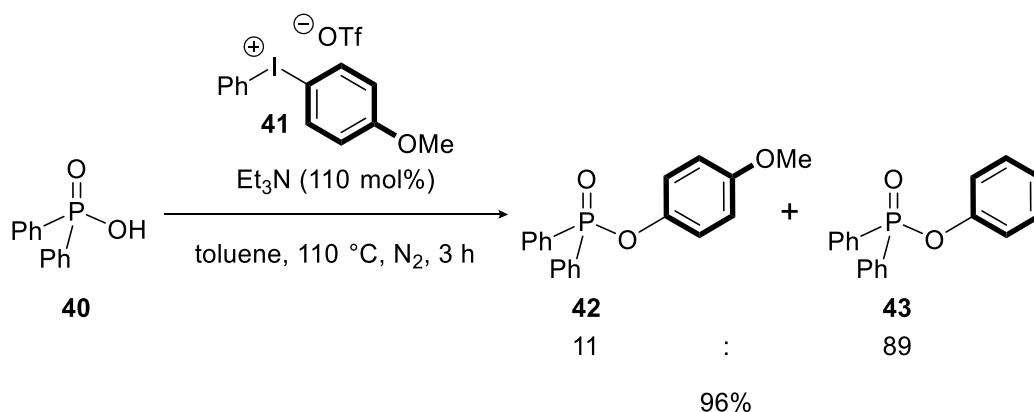
The scope with respect to both the phosphorus species and the diaryliodonium salts were examined. Interestingly, the selectivity of the aryl transfer, when using unsymmetrical iodonium salts produced contrasting results to those previously seen in the literature and discussed above. In this case, it was demonstrated that the reverse was true and the most hindered and electron rich aryl groups were transferred. This result was attributed to a difference within the mechanism of the reaction. As stated above Cu(I) salts are believed to reduce iodonium salts generating a highly electrophilic species, however, in this case the authors suggest the reaction proceeds via a radical mechanism. In addition to the reversed selectivity this mechanism is further corroborated through the addition of TEMPO (1 equiv.), which leads to the termination of the reaction.

The metal-free arylation of the P-OH bond *via* diaryliodonium salts has also been described and can be employed to synthesise a broad range of functionalised phosphonates, phosphinates and phosphates in good to excellent yields. The optimised reaction conditions, devised after investigation of a wide range of inorganic bases found that Et₃N (110 mol%) was optimal. The reaction is carried out in toluene at 110 °C under an atmosphere of nitrogen, Scheme 23.



Scheme 23. Metal free arylation of P-OH bond via diaryliodonium triflates.

As with previously discussed arylation reactions, unsymmetrical iodonium salts were examined. In this case, where no metal is being used the selectivity was different, resulting in the selective transfer of the most electron-deficient aryl moiety, Scheme 24. These results are consistent with those previously observed, for metal free conditions.⁴²



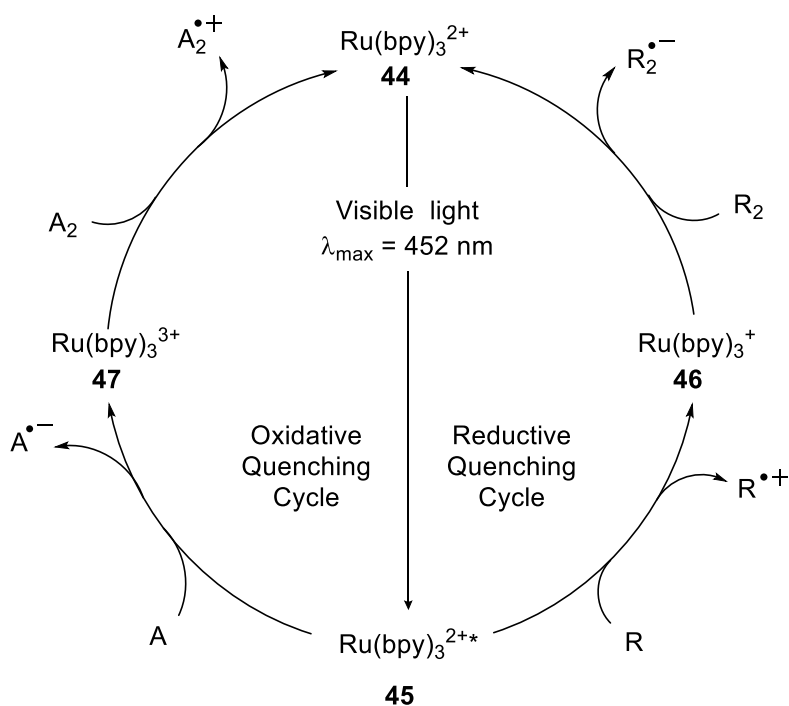
Scheme 24. Chemoselectivity of the metal-free arylation of the P-OH bond.
(Methoxy:phenyl 11:89 (96%))

1.7 Photochemical initiation

In order to establish a more convenient reaction procedure at ambient temperature we began to investigate new methods for the initiation of the radical chain reaction. This led to the examination of photoredox reaction conditions and the use of $\text{Ru}(\text{bpy})_3\text{Cl}_2$ and visible light as an initiation source for our desired reaction.⁴³

Therefore utilising visible light, a clean, inexpensive and readily available source of energy, and $\text{Ru}(\text{bpy})_3\text{Cl}_2$ an extensively investigated photoredox complex.

The mechanism by which $\text{Ru}(\text{bpy})_3\text{Cl}_2$ operates, begins with absorption of visible light (400-700 nm) leading to the formation of a $\text{Ru}(\text{II})^*$ excited state species **45**. The excited state species is generated through electron transfer from a d orbital on the Ru to a low-lying π^* orbital on the bipyridyl ligands, this MLCT species can then behave as an electron-donor or electron-acceptor. This means that once excitation has occurred the Ru complex can be reduced to $\text{Ru}(\text{III})$ **47** or oxidised to $\text{Ru}(\text{I})$ **46** (Scheme 25).



Scheme 25. The oxidative and reductive cycles of photoredox catalysis with visible light.

Examples utilising visible light mediated photoredox catalysis have increased in recent years, since work carried out by MacMillan, Yoon and Stephenson demonstrated the potential of photoredox catalysis in organic chemistry. One

benefit of the use of photoredox catalysis in organic synthesis is that typical colourless organic compounds cannot absorb visible light, thus reducing the number of possible side reactions by providing a highly chemoselective reaction.

Numerous examples of photoredox mediated arylations can be found in the literature using a variety of starting materials such as aryl sulfonyl chlorides,⁴⁴ aryl diazonium salts⁴⁵ and iodonium salts⁴⁶. Investigation of iodonium salts in photoredox catalysis demonstrates the wide ranging utility of this type of chemistry, due to the fact iodonium salts have been used in polymerisations, oxy/aminoarylations^{44e} and C-H arylations (in combination with Pd catalysis).^{44a}

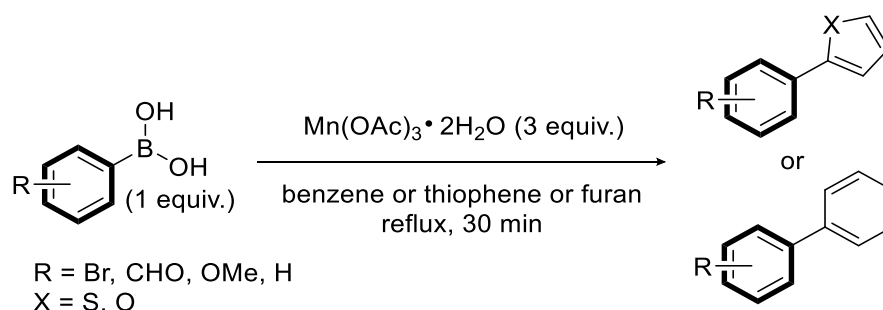
1.8 Arylation methods – arylboronic acids and Mn(III) acetate

In addition to investigating the use of diaryliodonium salts in conjunction with photoredox catalysis, to bring about the arylation of trivalent phosphorus compounds, we believe that arylboronic acids provide another interesting route to aryl radicals. It has previously been reported that this transformation is possible through an oxidative process, often utilising the single electron oxidant, manganese(III) acetate.⁴⁷ However other oxidative processes have been used,⁴⁸ including iron catalysis and di-*tert*-butyl peroxide as the oxidant.⁴⁹

Manganese(III) acetate is a d^4 octahedral high spin complex that behaves as a one electron oxidant, owing to the fact Manganese(II) acetate is a d^5 complex generating increased stability. In addition to its reactivity with arylboronic acids, $Mn(OAc)_3$ is also reactive with a number of substrates⁵⁰ including arylhydrazines, also producing aryl radicals.⁵¹

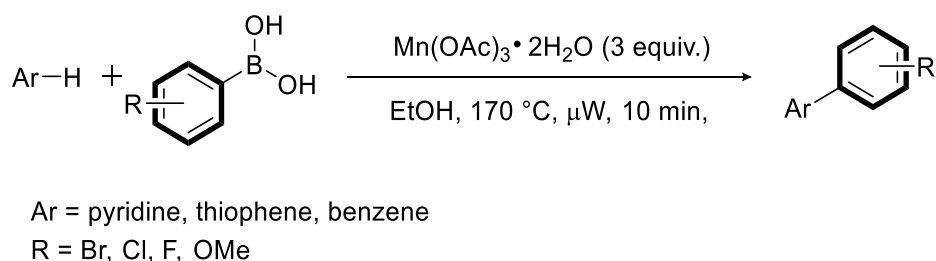
The first reported example of the Mn(III) mediated arylation *via* arylboronic acids, investigated the formation of biaryl compounds. This work carried out by Demir and

co-workers, demonstrated that when $\text{Mn}(\text{OAc})_3$ and arylboronic acids are combined in a 3:1 ratio in an aromatic solvent, biaryls are formed in good to excellent yields (Scheme 26).^{47a}



Scheme 26. Synthesis of biaryls via aryl radicals generated from boronic acids.

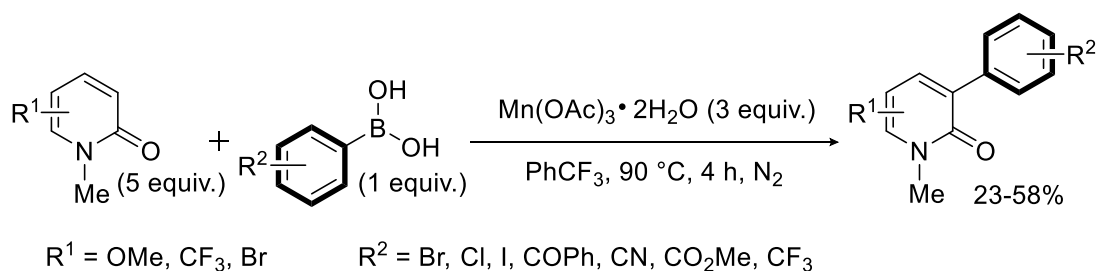
Improvements to this biaryl formation strategy have been developed through the use of microwave irradiation.^{47e} This change in heating source allowed for a reduction of the arene reagent, which was previously used as the reaction solvent. When microwave irradiation was used the arene excess was reduced to 10 equivalents, with the reaction performed in EtOH. It was found that the optimal conditions, when considering the arylboronic acid as the limiting reagent, were arene (10 equiv.) and $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ (3 equiv.) in EtOH under microwave irradiation at 170 °C for 10 mins (Scheme 27).



Scheme 27. Microwave assisted direct C-H bond arylation of arenes with boronic acids.

The combination of $\text{Mn}(\text{OAc})_3$ and arylboronic acids has also been utilised in the C-3 selective arylation of 2-pyridones, as it was found that this combination resulted in aryl radical generation and product formation. It is reported that other aryl radical generation methods were investigated, resulting in the formation of biaryls as opposed to the desired product.

In this case the reaction was run in trifluorotoluene, with a 3:1 ratio of $\text{Mn}(\text{OAc})_3$ to arylboronic acid and is shown in Table 4. It is important to note that during this investigation a number of organoboron compounds (including MIDA boronate, sodium borate and potassium trifluoroborate) were tested but it was found that boronic acids provided the best results.



1-methyl-3-phenylpyridin-2(1H)-one product formation with various organoboron reagents

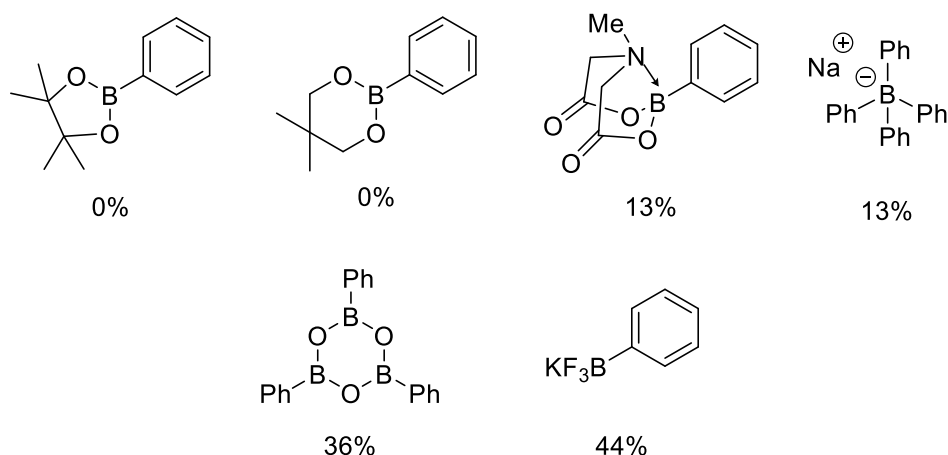
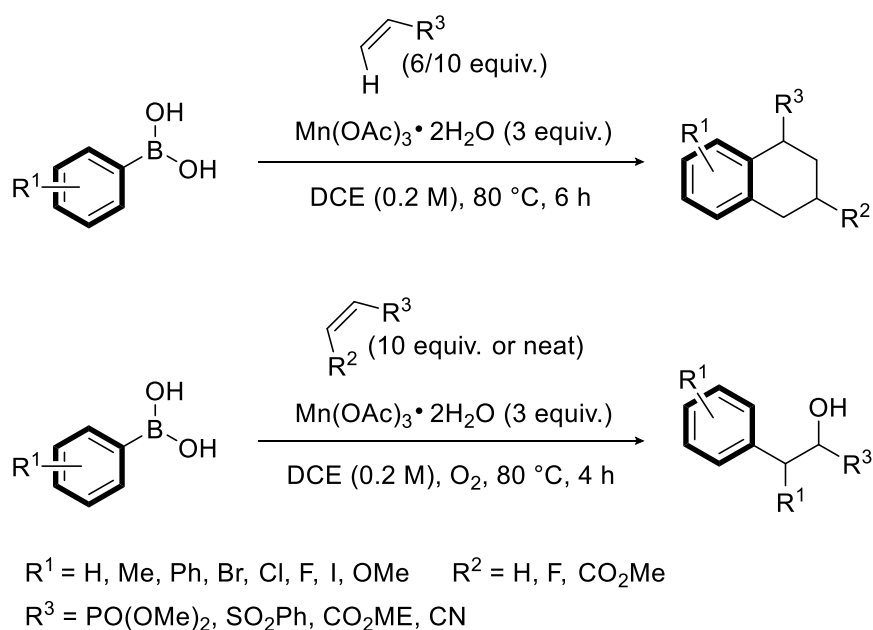


Table 4. *Mn(III) acetate mediated C-3 selective arylation of 2-pyridones with arylboronic acids.*

This established procedure for aryl radical generation has also been used to facilitate the arylation of a number of activated alkenes. It was found that in the absence of oxygen, aryl radical addition to an electron poor alkene, such as phenylvinylsulfone and vinyl dimethylphosphonate, could result in the formation of tetrahydronaphthalene derivatives in good yield. However, when methyl acrylate and acrylonitrile were used the yields were significantly reduced.

It was found that if the reaction was performed under an atmosphere of oxygen, radical hydroxyalkylations resulting in the formation of arylhydroxylation products could be achieved. This change in product results from the reaction of dioxygen with the intermediate radical formed from the initial addition of the aryl moiety, which in the absence of oxygen underwent a second addition to the vinyl reagent.



Scheme 28. Aryl radical addition to activated alkenes.

These examples from literature demonstrate that the aryl radical generation from a mixture of manganese(III) acetate and arylboronic acids is a well-established procedure, used for the oxidative radical arylation of various substrates. Therefore,

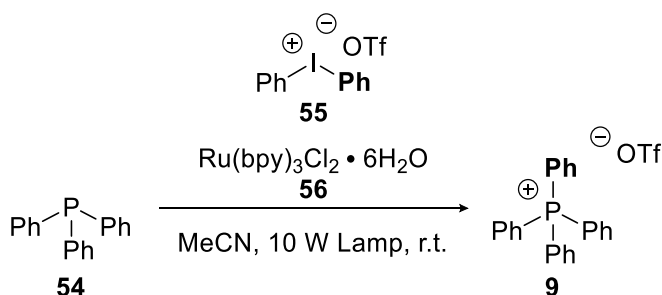
providing evidence that this protocol is a viable route to the quaternisation of trivalent phosphorus compounds.

2. Results and discussion

Two new methods for the arylation of trivalent phosphorus compounds, generating functionalised phosphonium salts have been investigated. In each case the arylation is achieved through the formation of an aryl radical, generated by the photo-induced decomposition of diaryliodonium salts and the reaction between manganese acetate and arylboronic acids.

2.1 Phosphonium salts *via* diaryliodonium salts

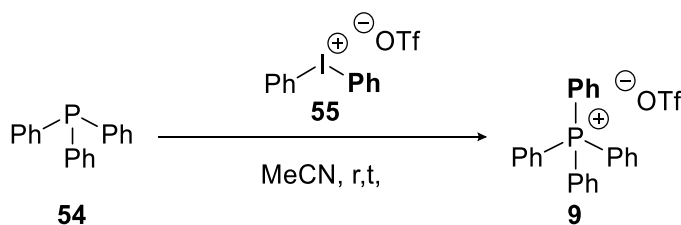
In order to create a more synthetically useful reaction between diaryliodonium salts and trivalent organophosphorus compounds; we developed a new method for the generation of aryl radicals, under photo redox conditions and ambient temperatures. We found that $\text{Ru}(\text{bpy})_3\text{Cl}_2 \cdot 6\text{H}_2\text{O}$ **56** combined with visible light (10 W lamp) produced phosphonium salts in good conversions (^{31}P NMR), Scheme 29.⁵²



Scheme 29. Newly developed strategy for the preparation of tetraarylphosphonium salts, using visible light and photoredox complex **56**.

With the initiation method in hand, we investigated the possible background reactions that could potentially be involved in product formation (Table 5). Initially we removed the $\text{Ru}(\text{bpy})_3\text{Cl}_2 \cdot 6\text{H}_2\text{O}$ **56** from the reaction mixture, which reduced the conversion from 73% (entry 1) to 12% (entry 2). Next, we reintroduced complex **56** but removed the 10 W lamp giving 23% conversion (entry 3), proving the

combination of complex **56** and the 10 W lamp was essential for rapid generation of the phosphonium salt product. We also demonstrated that the reaction does not proceed in the absence of visible light and complex **56** (entry 4). Entry 5 proves that the temperature resulting from the close proximity of the 10 W lamp to the reaction vessel does not lead to product formation. Finally, we compared the photo redox initiation method with the more conventional radical initiator AIBN; this provided 50% conversion whilst generating increased quantities of the phosphine oxide side-product (entry 6).



Entry	Initiator	Time (min)	Conversion ^a		
			PPh ₃	O=PPh ₃	⁺ PPh ₄
1	10 W lamp Ru(bpy) ₃ Cl ₂ ·6H ₂ O 56 2 mol%	20	19	10	73
2	10 W lamp	20	84	6	12
3	Ru(bpy) ₃ Cl ₂ ·6H ₂ O 56 2 mol%	20	71	6	23
4	None	120	100	0	0
5	32 °C (NO LAMP or Ru(bpy) ₃ Cl ₂ ·6H ₂ O 56)	60	92	6	3
6	AIBN (80 °C) 10 mol %	240	0	50	50

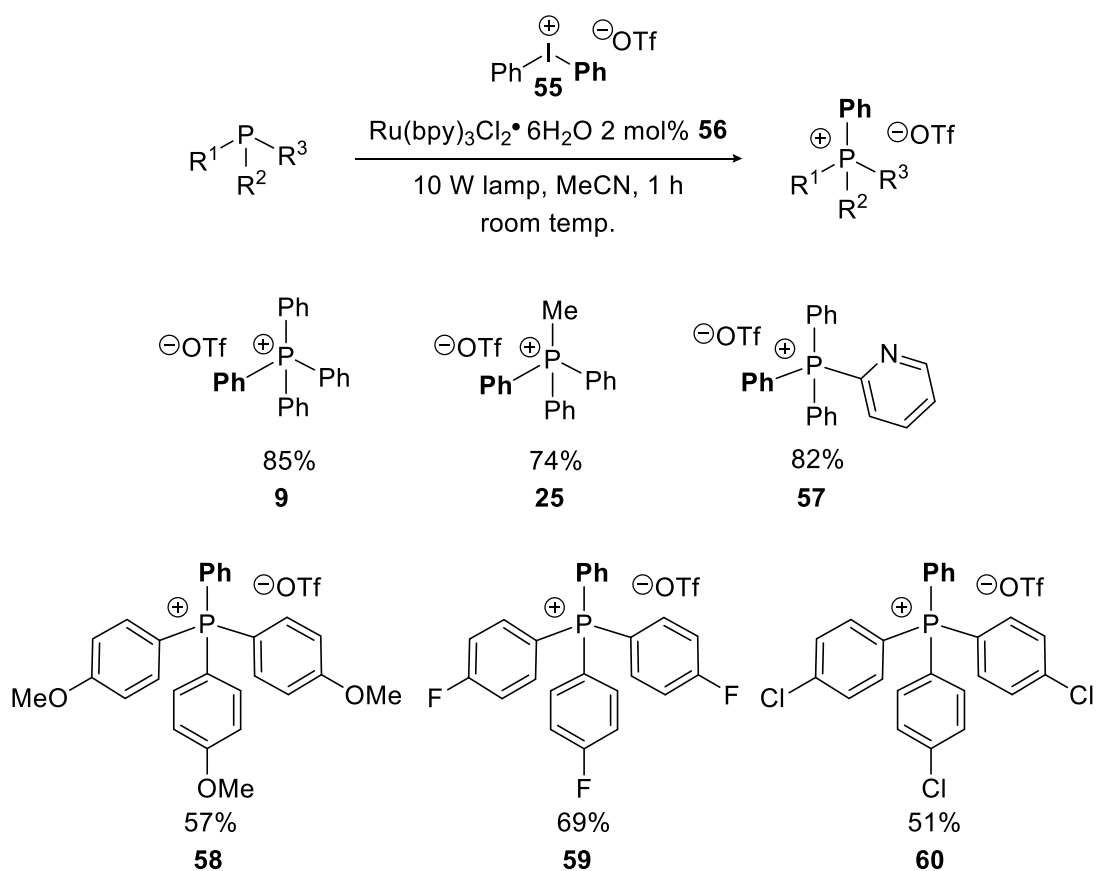
^a Conversions determined via ³¹P NMR analysis of crude reaction mixtures⁵³

Table 5. Investigation of initiation methods

2.1.1 Optimisation and reaction scope

With the initiation method in hand, optimised reaction conditions were developed. Through a preliminary investigation, it was highlighted that acetonitrile would be the

optimal solvent for the reaction but we subsequently exposed serious purification issues. These arose due to the problems encountered when attempting to purify a mixture containing both the phosphonium salt and iodonium salt species, due to very similar R_f values and solubility. With this in mind, we chose to perform the reaction with excess phosphine, providing the best opportunity for complete conversion of the iodonium salt.



All yields shown refer to material isolated.

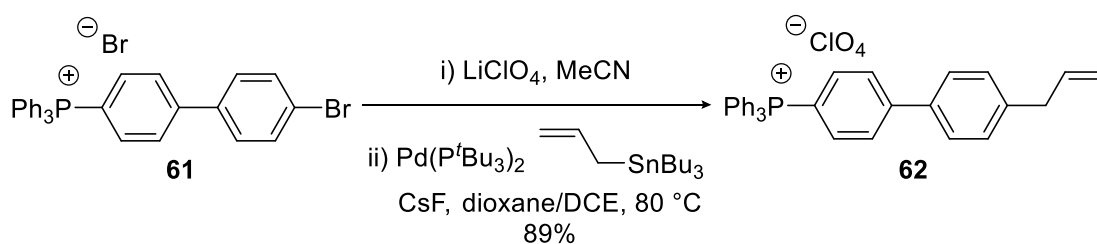
Table 6. Reaction scope with respect to the phosphine.

The final optimised conditions used 1.5 equivalents of phosphine, 1 equivalent of diaryliodonium triflate and 2 mol% Ru(bpy)₃Cl₂·6H₂O **56** in the presence of a 10 W lamp over 1 h. Using these optimised conditions, we investigated the scope of the reaction with respect to the phosphine. A range of phosphines were selected containing alkyl and aryl substituents, the results demonstrate that

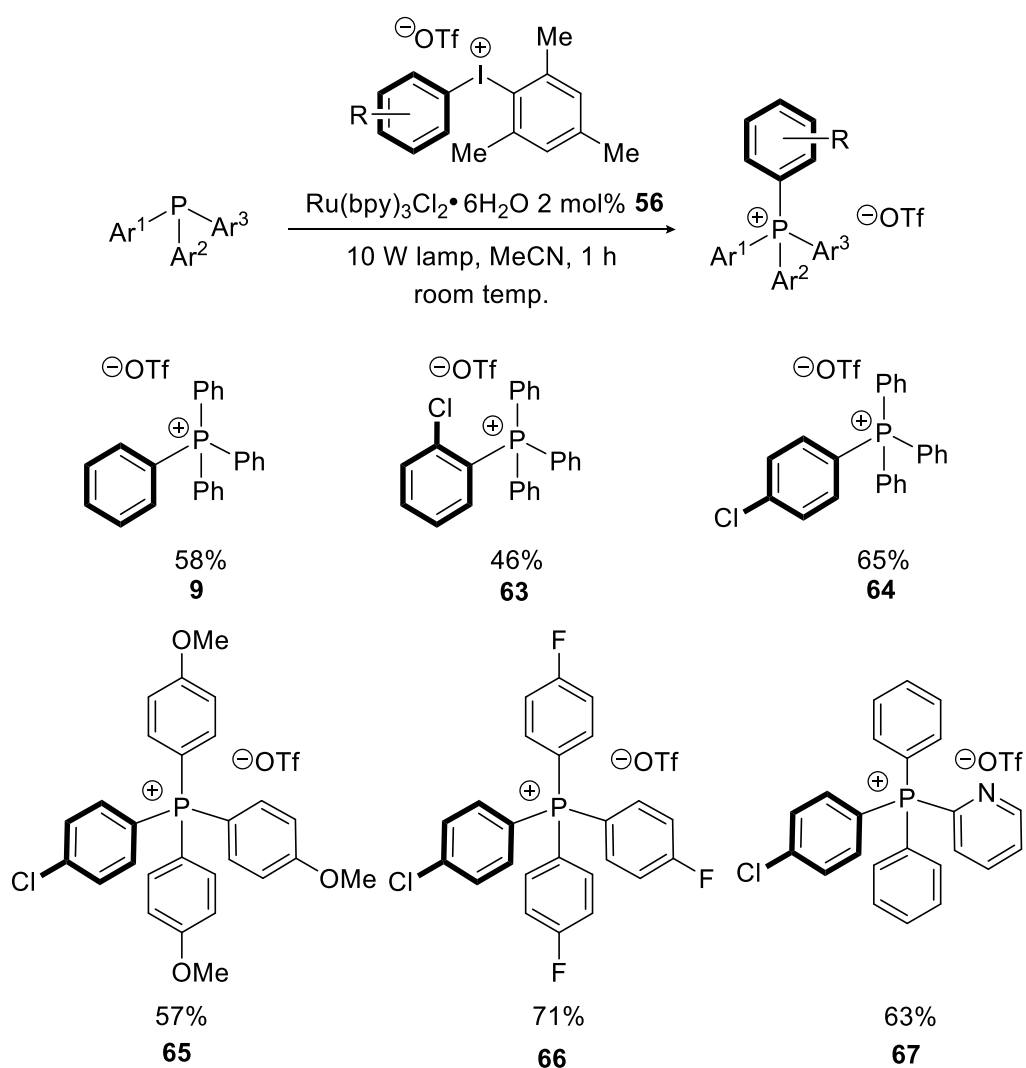
triarylphosphines, alkyl diarylphosphines and alkoxydiarylphosphinites can be effectively arylated under these conditions (Table 6).

Table 6 illustrates that a wide variety of phosphines can be arylated under these conditions in good to excellent yields. Both triarylphosphines and alkyl diarylphosphines are tolerated and electron deficient/rich substituents on the aryl moiety do not affect product formation. Even though we believe that the substituents on the aryl ring do not affect the yield of the phosphonium salt, we have seen yield variation. We attribute this to the difficulties in purification, which required column chromatography and recrystallisation, and due to the nature of the products yields were not always consistent.⁵⁴ This was most evident in the purification of the phosphonium salt **58**, due to the fact the product was an oil and therefore trituration was required over recrystallisation, resulting in loss of phosphonium salt product in the trituration solvent.

After investigation of the scope with respect to the phosphine we turned our attention to the transfer of more complex aryl groups, with the intention of preparing functionalised phosphonium salts with handles for further derivatisation. We believed that further functionalisation could be achieved through the introduction of aryl halides and a subsequent palladium cross-coupling reaction. Owing to the reactivity of phosphonium salts towards oxidative addition to catalytic palladium species, it could be considered a problematic route to further functionalisation. However, previous reports of such reactions have been described, for example the synthesis of (4'-Allyl-1,1'-biphenyl-4-yl)(triphenyl)phosphonium perchlorate **61** from (4'-bromobiphenyl-4-yl)triphenylphosphonium bromide **62** (Scheme 30). Here the Stille cross-coupling reaction was achieved by employing the mild conditions described by Fu and co-workers in 2002.⁵⁵



Scheme 30. Functionalisation of tetraarylphosphonium salts under Fu's mild conditions.



All yields shown, refer to material isolated.

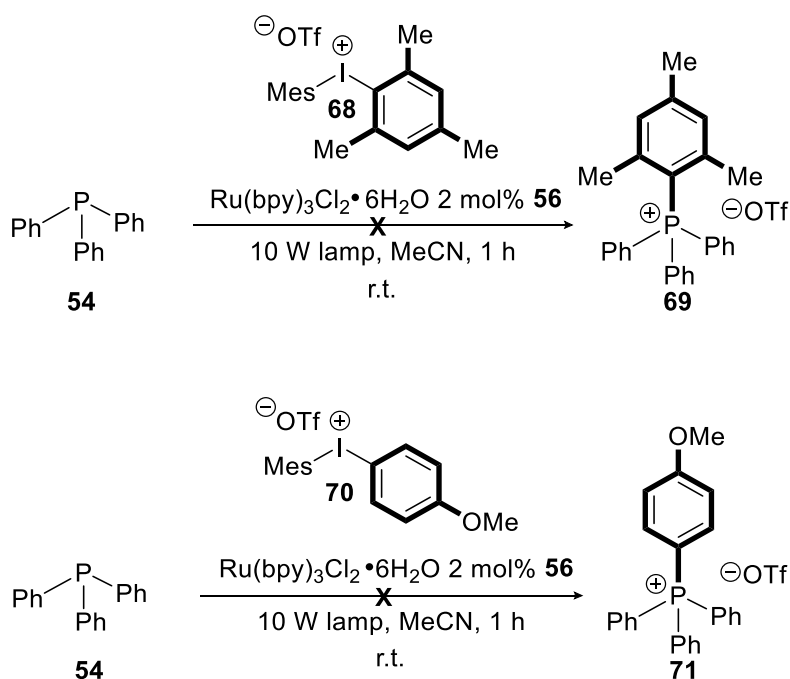
Table 7. Reaction scope with respect to the diaryliodonium triflate.

For the transfer of functionalised aryl groups we decided to synthesise mesityl(aryl)iodonium triflates, which have previously been used to facilitate selective aryl transfer, with the mesityl group acting as a spectator and generating 2,4,6-trimethyliodide as a by-product. This type of transformation has been described for both metal catalysed^{23,24} and metal free reactions,⁵⁶ demonstrating the selective aryl transfer of the most electron deficient aryl ring. Our results are shown in Table 7.

We first carried out the formation of tetraphenylphosphonium triflate **9** in 58% *via* mesitylphenyliodonium triflate, demonstrating the selective transfer for the phenyl group, supporting the previously published data. We then moved to the transfer of phenyl chloride moieties and due to the increased electron deficiency, it was believed the selective transfer would be more facile. This prediction proved accurate when using mesityl(4-chlorophenyl)iodonium triflate, generating phosphonium salt **64** in 65%. However, when transferring 2-chlorophenyl, the yield was reduced to 49% (phosphonium salt **63**), suggesting that the increased steric bulk hindered addition to the reactive phosphorus species. Further investigation using mesityl(4-chlorophenyl)iodonium triflates illustrated the functional group tolerance of the reaction, demonstrating that both electron rich/poor substituents were tolerated.

In order to better understand the selectivity of the aryl transfer, we investigated the use of bis(mesityl)iodonium triflate **68** and mesityl(4-methoxyphenyl)iodonium triflate **70**. First of all the introduction of the bis(mesityl) salt to the reaction conditions resulted in only trace formation of mesityltriphenylphosphonium triflate **69**. It should also be noted that full conversion of the iodonium salt did not occur in this case, suggesting that the electron rich nature of the iodonium salt reduces reactivity. This observation is also supported by the results obtained when iodonium

salt **69** was used, as no reaction was observed for the tetrafluoroborate or triflate salts.

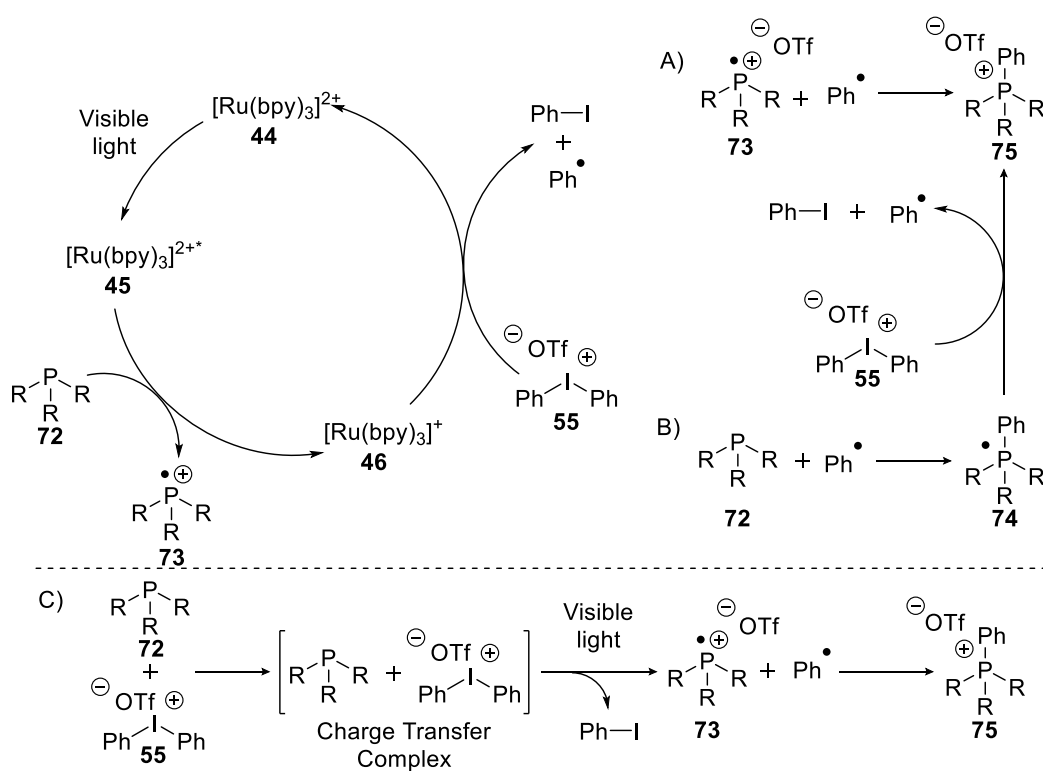


Scheme 31. Unsuccessful arylation reactions with sterically hindered and electron-rich diaryliodonium salts.

Taking into account the near absence of reactivity when considering the symmetrical mesityliodonium triflates, we can gain insights into the nature of the selective aryl transfer. This is because complete conversion of the iodonium salt was evident in all of the reactions using mesityl(aryl)iodonium triflates in Table 7. However, yields are lower than their direct comparisons in Table 6, most evidently for tetraphenylphosphonium triflate **9**. This suggests that radical formation is not 100% selective and that both the mesityl and aryl radicals were generated, with the mesityl radical being too sterically hindered for successful addition to the phosphorus centre.

In summary the photo-redox mediated arylation of organophosphorus(III) compounds, *via* diaryliodonium triflates, can generate functionalised tetraarylphosphonium triflates containing both electron-withdrawing and electron-donating substituents. However, the electron-donating functionality has to be associated to the phosphorus species, owing to the reactivity of electron-rich iodonium salts.⁵⁷

2.1.2 Mechanistic Study



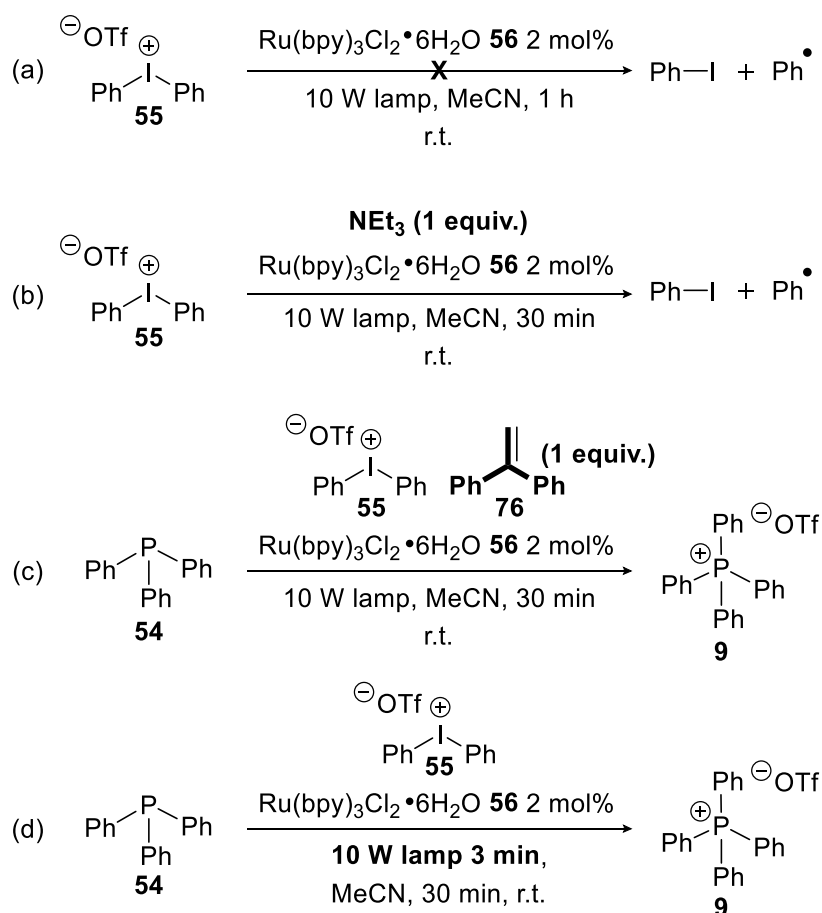
Scheme 32. Proposed reaction mechanisms for the synthesis of phosphonium salts via arylation with diaryliodonium salts under photoredox conditions.

As previously discussed in the introduction, the excitation of complex **44** by visible light (400-700 nm) leads to MLCT and the formation of Ru(II)* excited state species **45**. This species can then undergo either oxidation or reduction to generate Ru(I) or Ru(III), leading to the belief that this excited state species could facilitate the

reduction of the diaryliodonium salt, producing aryl radicals and ultimately arylation. However, after a series of experiments (Scheme 33) this was proved inaccurate, leading to the belief the reaction mechanism involved the reduction of Ru(II)* complex **45** *via* oxidation of the phosphine. With this in mind, we have proposed the reaction mechanism depicted in Scheme 32.

We propose that after excitation, the ruthenium species **45** is reductively quenched to Ru(I), oxidising the phosphine and generating a phosphoniumyl radical species **73**. The Ru(I) species **46** can then reduce the diaryliodonium salt liberating aryl radicals and phenyl iodide, returning the ruthenium to its original oxidation state. This cycle outlines the role of the ruthenium complex, illustrating its role as a catalyst. We then propose that once the aryl radicals have been generated there can be two reaction pathways resulting in product formation. Pathway (A) results from the combination of the aryl radical with phosphoniumyl radical **73** and pathway (B) begins with radical attack of phosphine **72**, generating phosphoranyl radical **74**. Phosphoranyl radical **74** is then believed to have the reductive power to reduce additional diaryliodonium salts, leading to the propagation of a radical chain reaction pathway.

It should also be noted that we propose a third reaction pathway (C), due to the experimental observation that the reaction can proceed in the absence of Ru(bpy)₃Cl₂·6H₂O (Table 5, entry 2). We propose that this reaction occurs through the combination of a phosphine and an iodonium salt resulting in a charge transfer complex, which can subsequently absorb visible light resulting in the generation of aryl and phosphoniumyl radicals.⁵⁸ The radicals then combine in a similar way to reaction pathway (A).



Scheme 33. Experimental evidence supporting the proposed reaction mechanism (Scheme 32).

In order to provide experimental evidence for the above proposal, we carried out a number of reactions, which are outlined in Scheme 33. The first experiment carried out (a), demonstrates that in the absence of the phosphine, the diaryliodonium triflate is not decomposed to benzene and phenyl iodide, under identical reaction conditions, thus ruling out a Ru(III) intermediate. Further evidence to support the proposed reductive quenching of the Ru(II)* excited state **45** is illustrated by reaction (b). Here, the phosphine was switched with triethylamine, resulting in the formation of benzene and phenyl iodide.

Experiment C demonstrates the changes in product conversion upon the addition of 1,1-diphenylethylene **76**. This gave rise to a significant reduction in phosphonium salt generation (16% compared with 73% (Table 5), which is consistent with the covalent trapping of phenyl radicals. It was also observed that this reaction produced increased quantities of triphenylphosphine oxide, occurring through the trapping of the phosphoniumyl radical with water.⁵⁹

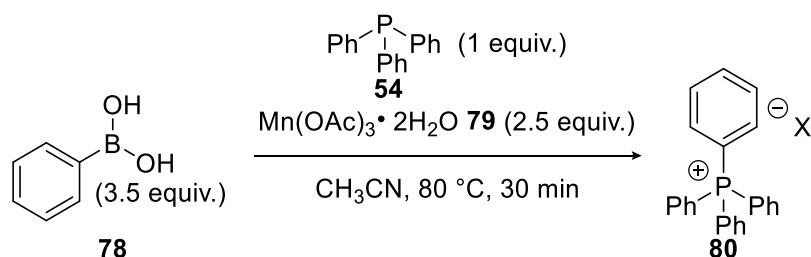
Finally, we investigated how the conversion was effected through a brief 3 minute initiation period followed by the removal of light.⁶⁰ This converted 26% of the triphenylphosphine into tetraphenylphosphonium triflate **9**, demonstrating that the conversion was significantly reduced. This illustrates that product formation results from a combination of pathway (A) and (B), with the arylation more heavily weighted towards pathway (A) than the radical chain process.

2.1.3 Conclusion

An efficient method for the formation of functionalised phosphonium salts has been developed. The photo-induced arylation reaction of diaryliodonium salts, using $\text{Ru}(\text{bpy})_3\text{Cl}_2$ and visible light has provided phosphonium salts in good to excellent yields. It has been demonstrated that the varied functionality can be derived from either the trivalent phosphorus species or the diaryliodonium salt. It has also been shown that under the reaction conditions, selectivity can be achieved, so that functionalised aryl groups can be selectively transferred when using unsymmetrical diaryliodonium salts, such as mesityl(aryl)iodonium triflates.

2.2 Mn(III) mediated radical arylation of organophosphorus compounds *via* arylboronic acids

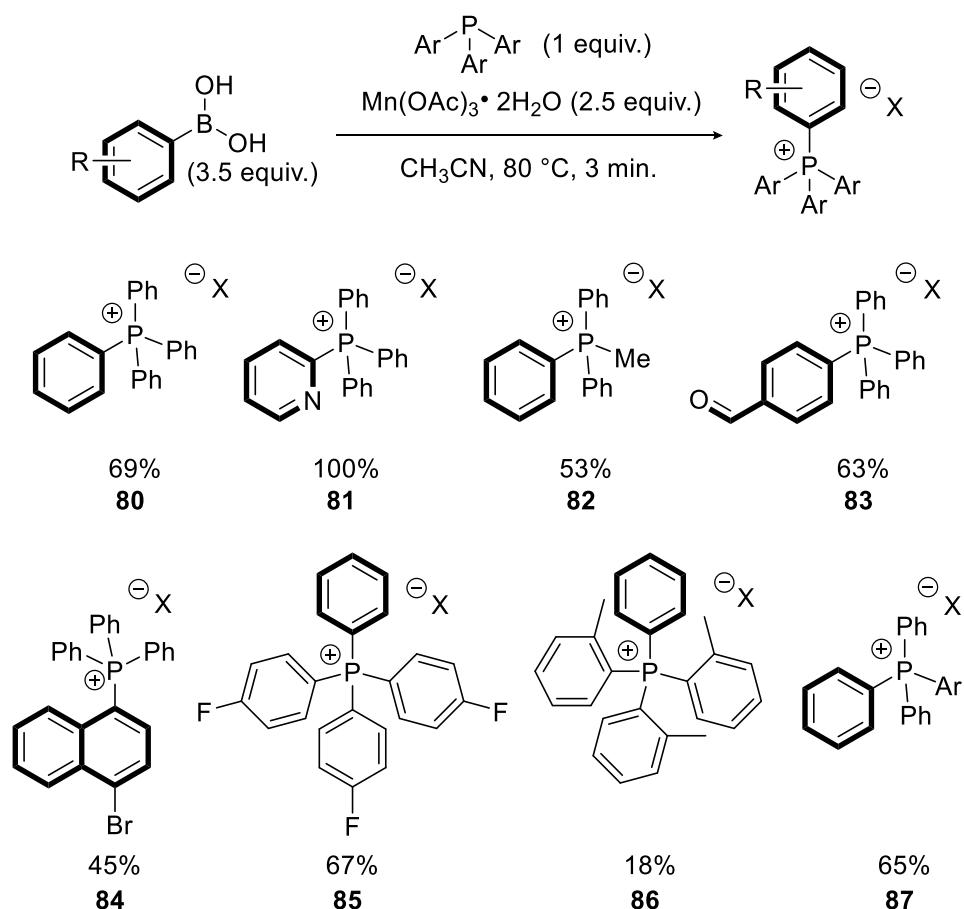
The second synthesis method created for the formation of tetraarylphosphonium salts, utilised the oxidative radical generation conditions previously described, using manganese(III) acetate and arylboronic acids. Work on this area had previously been conducted by our group, providing evidence that this was a viable synthetic route to tetraarylphosphonium salts and supplying a set of optimised conditions.⁶¹ The inherited conditions required 2.5 equivalents of $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ **79**, 3.5 equivalents of an arylboronic acid and set the phosphine as the limiting reagent. The reagents were heated in MeCN at 80 °C for 30 minutes, in an inert atmosphere (Ar/N_2), resulting in the formation of tetraphenylphosphonium salt's (Scheme 34).



Scheme 34. Optimised conditions for the formation of tetraarylphosphonium salts *via* arylboronic acids.

With these optimised conditions in hand, the substrate scope of the reaction was investigated and the results are outlined in Table 8. The results illustrate that the reaction conditions can tolerate a large range of functionality, originating from either the phosphine or boronic acid reagents. Compounds **80**, **81**, **83**, **85**, **87** show excellent conversions, however, this is not universally true for all of the examined phosphines. The lower conversions associated with methyldiphenylphosphine and tri(*o*-tolyl)phosphine, can be explained by the former's increased reactivity towards

oxidation and the latter's increased steric bulk. The reduced reactivity of tri(*o*-tolyl)phosphine was also observed during the diaryliodonium salt investigation.



All conversions calculated from ^{31}P NMR of the crude reaction mixtures⁵⁴

Table 8. Investigation into the scope of the Mn(III) mediated arylation of phosphines.

During the investigation into the scope of the reaction it had become apparent that purification of the phosphonium salts generated *via* this procedure would prove extremely difficult. Due to this difficulty in purification, establishing the identity of the counter ion and therefore the overall product from this Mn(III) mediated radical arylation reaction proved very challenging.

2.2.1 Purification

Throughout the course of the investigation into the Mn(III) mediated radical arylation of organophosphorus compounds, there have been various attempts to isolate the phosphonium salt product. The investigation began with column chromatography; however, this resulted in the hydrolysis of the phosphonium salt product, leading to the isolation of the corresponding phosphine oxide with high mass recovery. Crystallisation was then examined, which resulted in the removal of the unwanted phosphorus impurities. In spite of this improvement, crystallisation did not provide a completely pure sample, due to contamination by manganese impurities.

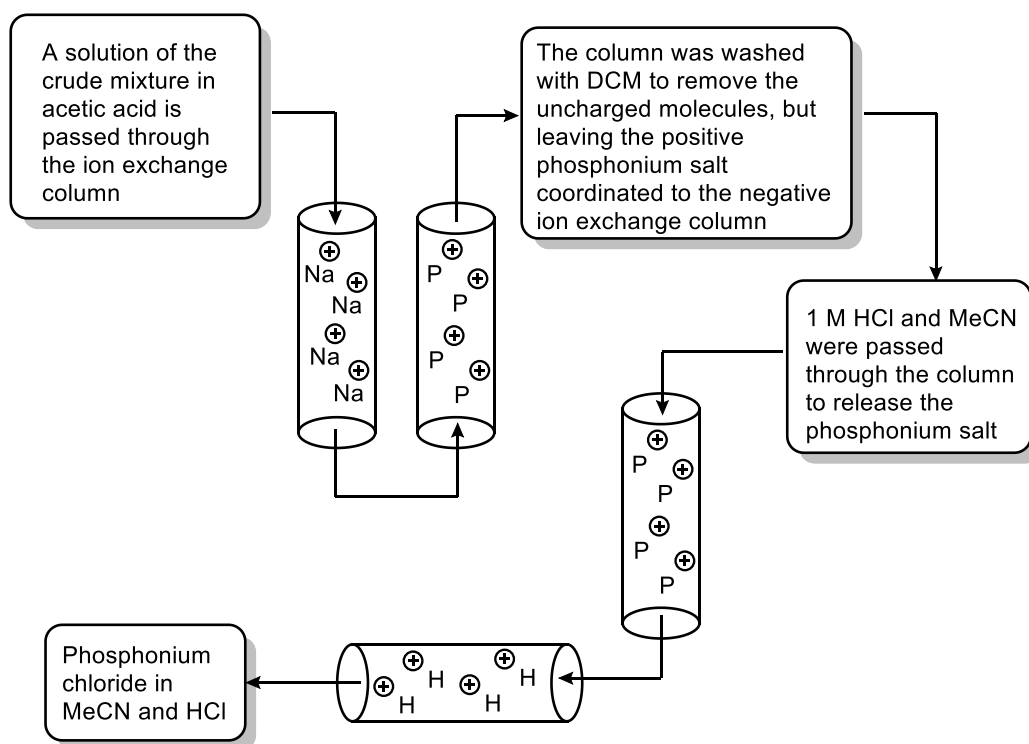


Figure 2. Outline of the ion exchange chromatography procedure.

Following the failure of common purification methods, it was decided that ion exchange chromatography would be tested. The procedure followed for ion

exchange chromatography is outlined in Figure 2, however, this proved to be ineffective. In this case, the failure resulted from contamination with manganese impurities, as was the case with crystallisation.

This initial investigation into the purification highlighted that the main issue was the removal of manganese impurities, which led to the investigation of manganese scavengers.

Quadrapure IDA (shown in Table 9) is a polymer-based metal scavenger resin that can be used to remove manganese impurities from crude reaction mixtures. We employed the scavenger through addition to a solution of the crude reaction mixture in acetonitrile, which was heated at 80 °C for 18 h. In addition to the metal scavenger, NaCl (10 equiv.) was also added to the crude mixture in an attempt to switch the original counter ion, for ease of identification and NMR assignment. This procedure resulted in the removal of manganese impurities from the crude material and following a subsequent crystallisation, samples of pure phosphonium chlorides were obtained. It was established that counter ion exchange had occurred, through the determination of the compound's crystal structure, as shown in Figure 3.

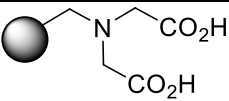
	Structure	Functional Group	Scavenged Metals
Quadrapure IDA		Iminodiacetic acid	Cu, Al, Ga, In, V, Pb, Ni, Zn, Cd, Be, Mn, Sr, Ba, Co, Fe

Table 9. Quadrapure IDA Scavenger

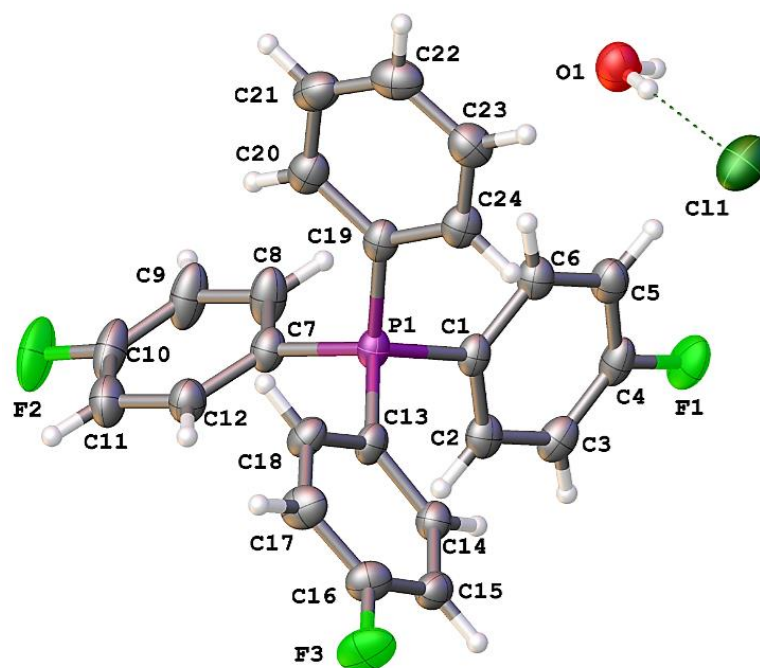


Figure 3. Crystal structure of tris(4-fluorophenyl)phenylphosphonium chloride.

Even though this result was a vast improvement on previous purification efforts; it failed to lead to the reproducible purification of a wide range of phosphonium salts. The problems associated with this method include diminished yields, relative to the calculated conversion from ^{31}P NMR. This was attributed to the hydrolysis of the phosphonium salt product and the fact manganese removal was not consistently successful, often resulting in multiple purifications. This resulted in large variations in the yield of isolated phosphonium chlorides. Figure 4 demonstrates the extent to which this purification method was inconsistent, as phosphonium salt **90** was isolated in 70%, but when the same procedure was used for phosphonium salt's **88** and **89**, an additional purification step was required and the yield was significantly reduced.

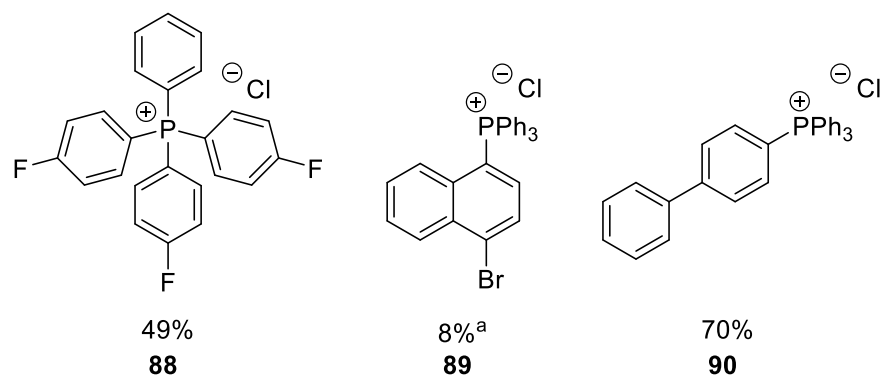


Figure 4. Purified phosphonium chlorides via Quadrapure IDA and NaCl.

In addition to the isolation of some tetraarylphosphonium chlorides, this purification method also permitted the identification of the counter ion produced during the reaction. This was achieved through a similar procedure to the one described above, however, NaCl was excluded from the method. Following the recrystallisation of the scavenged material, a single crystal was isolated and the crystal structure is shown in Figure 5. This shows the counter ion arises from the oligomerisation of five aryl boronic acid units.

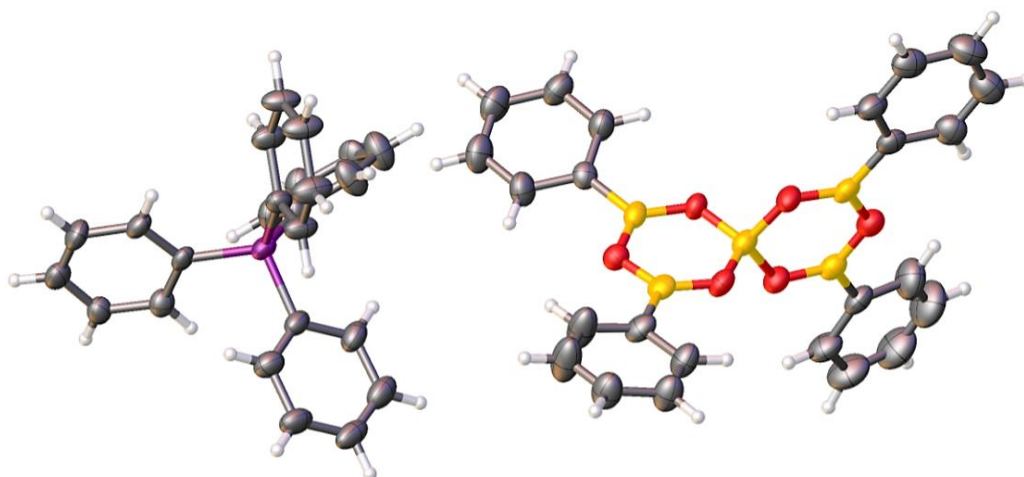


Figure 5. Crystal structure revealing the phosphonium salt counter ion produced via the Mn(III) mediated arylation of phosphines.

2.2.2 Modification of the reaction conditions

The identification of the counter ion revealed that for every molecule of phosphonium salt synthesised, 5 equivalents of arylboronic acid were required; thus outlining a problem with the current reaction conditions. In order to correct the reaction conditions and provide the chance for complete conversion of phosphine to phosphonium salt, the amount of arylboronic acid was increased. However, this created problems with solubility, ultimately leading to a more thorough investigation of the reaction conditions.

Solvent	Solvent Ratio	Time	Ph ₃ P=O	Ph ₄ P ⁺	Ph ₃ P
MeCN	n/a	0.5	26	69	5
Toluene	n/a	1	-	45	55
Toluene	n/a	18	-	56	44
DMF	n/a	21	19	54	27
MeCN/DMF	1:1	2	-	86	14
MeCN/DMF	3:1	1	-	85	15
MeCN/DMF	9:1	1	-	89	11

Table 10. Investigation into the optimal reaction solvent.

Due to the low solubility of arylboronic acids in MeCN, toluene was investigated as the reaction solvent. However, this reduced reactivity and after 1 h only 45% conversion had been achieved, increasing the reaction time to 18 h, resulted in only a slight increase in conversion. DMF was then explored, but again this reduced the reactivity and after 21 h only 54% conversion occurred.

The initial results suggested that MeCN was the most efficient solvent for the reaction, so in order to improve the solubility a combination of MeCN and DMF was investigated. A 1:1 ratio resulted in a homogeneous mixture of phosphine and arylboronic acid, providing a high conversion of 86% in 2 h. Further modification of the solvent ratio led to the selection of 3:1 MeCN/DMF as the desired reaction

solvent, this was due to the fact 9:1 MeCN/DMF did not lead to a homogeneous mixture of phosphine and arylboronic acid.

2.2.3 Purification 2

With the modified conditions in hand, the purification of the phosphonium salt product was again investigated. Due to the complex nature of the identified counter ion, it was believed that counter ion exchange would provide the simplest route to identification and characterisation of a range of phosphonium salts. In order to facilitate counter ion exchange, the crude reaction mixture was stirred overnight in a biphasic solution of DCM and saturated $\text{NaBF}_4(\text{aq})$. This resulted in complete ion exchange, confirmed through NMR examination.

In addition to ion exchange occurring upon treatment with the biphasic solution, it was also observed that the manganese impurities were removed. Therefore, after extraction of the aqueous solution with DCM, a mixture of phosphorus compounds was obtained; thus removing the major problem associated with the previous purification investigation.

Once counter ion exchange was complete, purification of the resultant phosphine/phosphonium salt/phosphine oxide mixture was carried out through recrystallisation. Flash column chromatography was also investigated but this proved inadequate, resulting in complex mixtures containing the tetraarylphosphonium salt as its major component and only phosphorus species. It is therefore believed that the impurities generated result from decomposition of boronic acid derivatives.

Table 11 shows the tetraarylphosphonium tetrafluoroborates isolated, following counter ion exchange and recrystallisation. The results show that the Mn(III)

mediated radical arylation reaction can tolerate phosphines containing both electron withdrawing and electron donating functionality.

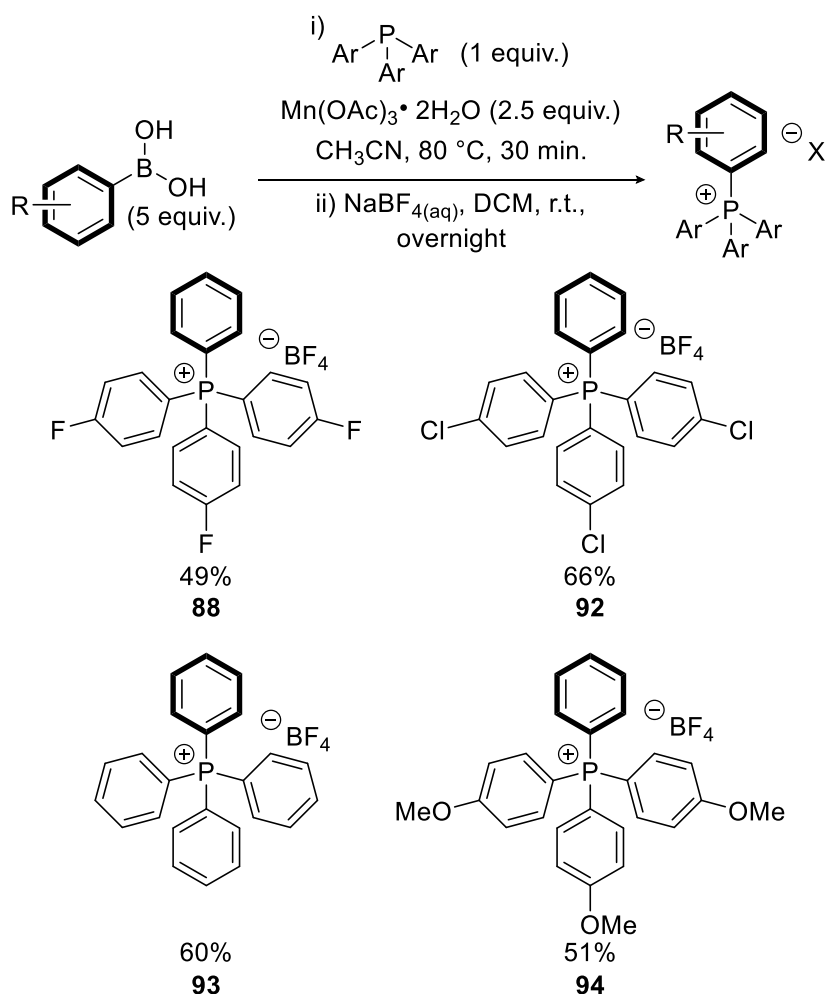


Table 11. Synthesis of tetraarylphosphonium tetrafluoroborates

2.2.4 Conclusions

We have described the synthesis of tetraarylphosphonium salts *via* a Mn(III) mediated radical arylation reaction, demonstrating the formation of an intriguing and complex counter ion. However, it has also been illustrated that the counter ion can be changed to afford a more conventional phosphonium salt product. In addition a wide variety of functional groups have been shown to be compatible with the reaction conditions.

Chapter 2

3. Introduction

Lignans are widely distributed throughout the plant kingdom, where they are found in roots, rhizomes, stems, bark, leaves, seeds and the fruit of plants of more than seventy families. Lignans are a class of secondary metabolites, derived from the oxidative coupling of two phenylpropanoid units. Even though the molecular backbone of lignans consist of only two phenylpropane (C_6-C_3) units, there is still huge structural diversity within this class of compound.⁶²

Traditionally lignans are classified into two types, classical lignans and neolignans. The classification is due to the differing position in the linkage of the two C_6-C_3 units. Classical lignans, such as compound **95**⁶³ are linked at the 8-8' positions, whereas neolignans (e.g. compound **96**)⁶⁴ are linked through any position other than the 8-8' positions (Figure 6). Further organisation of the structural diversity leads to formation of sub-groups, classical lignans are split into six sub-groups and neolignans due to greater structural diversity are split into 15 sub-groups. Additional nomenclature is required for the naming of compounds containing more than two rings, for example neolignans containing three C_6-C_3 units are referred to as sesqui-neolignans.⁶⁵

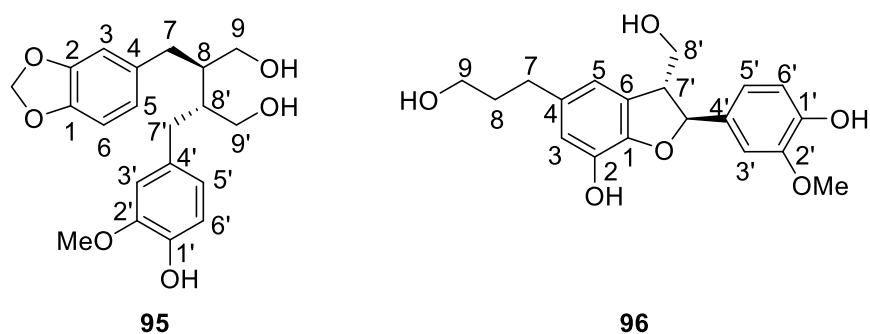


Figure 6. An example of a classical lignan **95** joined at the 8-8' positions and a neolignan **96** joined at the 6-7' positions.

The biological functions of plant lignans are still unclear but the antimicrobial, antifungal, antifeedant and insecticidal properties of lignans gives some evidence to suggest they are involved in the plants defence system. In addition to this activity in nature, lignans also possess interesting pharmacological properties such as, anti-tumor, anti-inflammatory, cardiovascular, antioxidant and antiviral activity.⁶⁶

3.1 Macranthol

Macranthol **97** (Figure 7), a sesqui-neolignan was first isolated in 1989 from the pericarps (fruit walls) of *Illicium macrantum*, which is mainly distributed in southern China and is regarded as toxic.⁶⁷ Macranthol has been shown to possess anti-depressant activity in mice,⁶⁸ however, there are no known syntheses of macranthol to date.

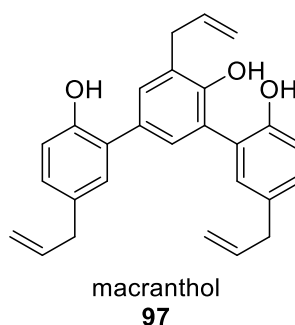


Figure 7. Structure of macranthol **97**

3.2 Fargenin and Fargenones A and B

In 2007 fargenin **98** and fargenones A **99** and B **100** were first isolated from the methanol extract of the pericarps (fruit walls) of *illicium fargesii*.⁶⁹ These structures including the unnamed natural product **101** (isolated from *illicium dunnianum*)⁷⁰ can be traced back to chavicol **102**, a naturally occurring phenol that has been isolated from various plant species.⁷¹ The study by Fukuyama investigated the neurotropic activity of compounds **98-100**, due to previous biphenyl-type neolignans, such as

honokiol and magnolol demonstrating this type of activity. However it was found compounds **98-100** (Figure 8), showed no activity at similar concentrations *in vitro*.⁶⁷

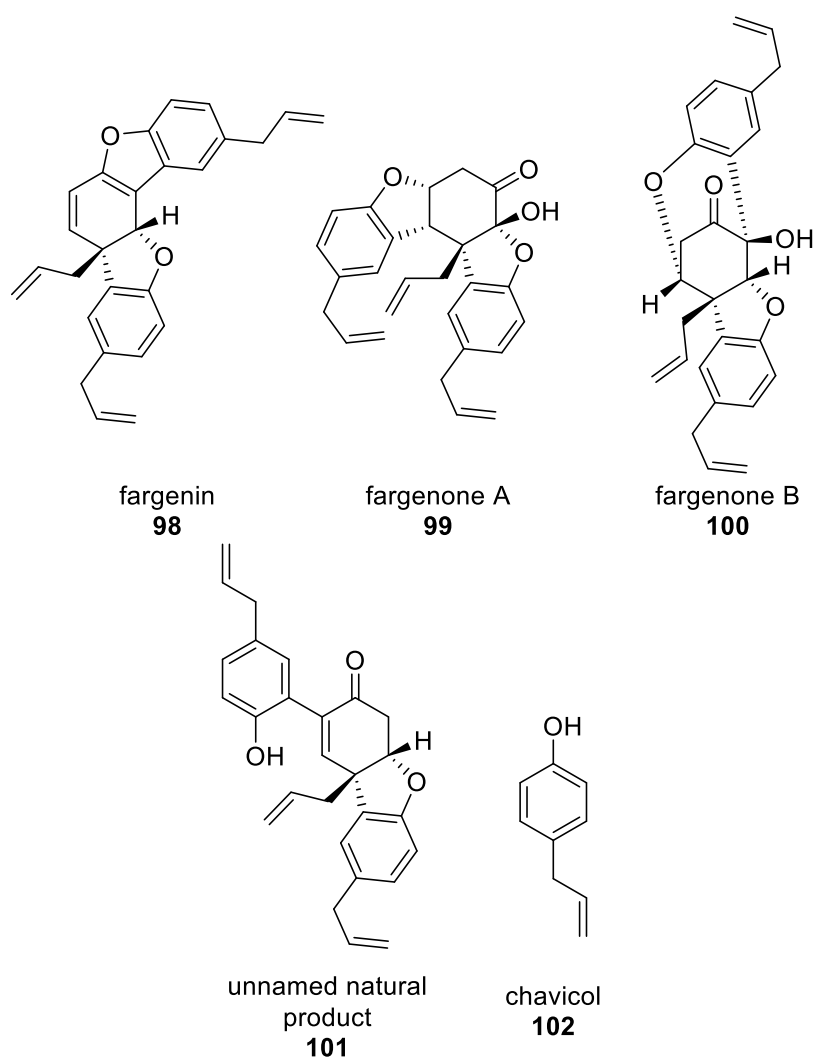
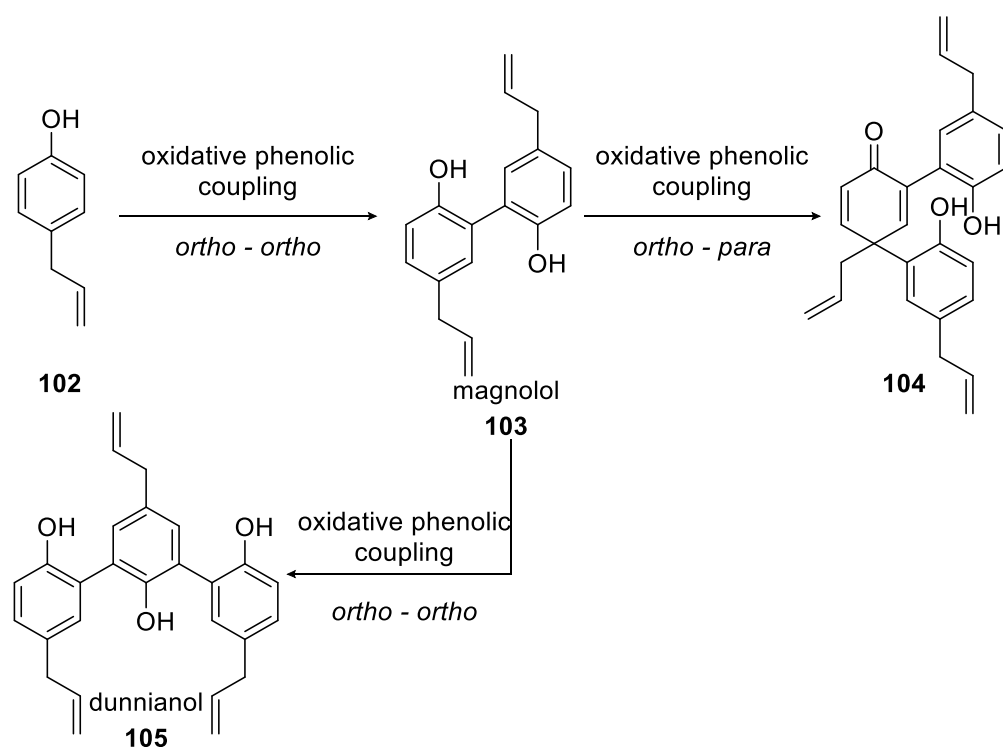


Figure 8. Natural products of the fargenin/fargenone family and their likely biosynthetic precursor chavicol.

3.3 Biosynthetic speculation on the origins of fargenin and fargenones A and B

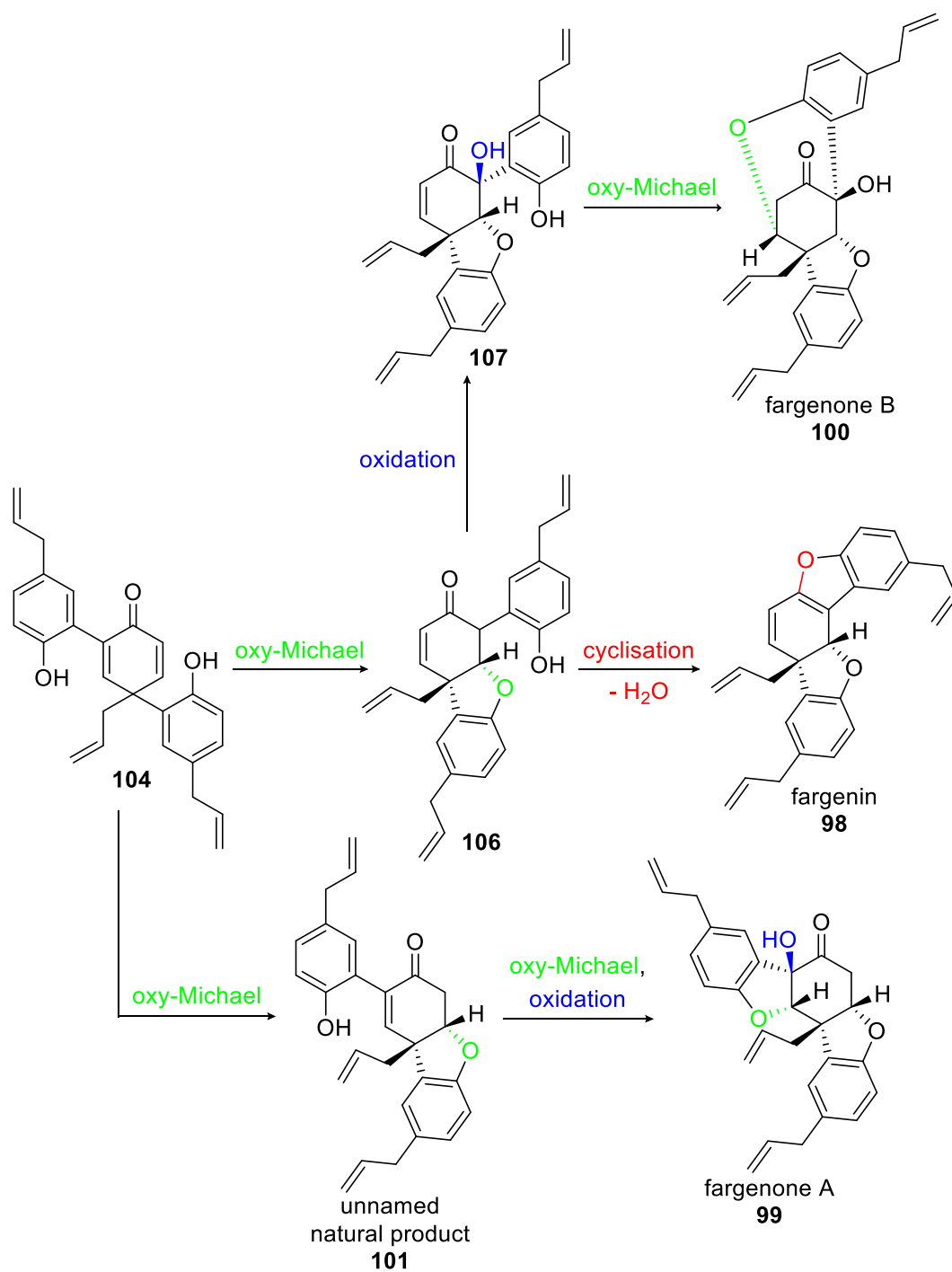
The relationship between chavicol **102** and compounds **98-100**, previously identified by Fukuyama, reveals that compounds **104-105** can be derived by the oxidative phenolic coupling of three chavicol **102** units. This biosynthesis begins with an *ortho-ortho* coupling producing magnolol **103**,⁷² magnolol can then either undergo a second *ortho-ortho* coupling to produce dunnianol **105**,⁷³ or an *ortho-para* reaction

to generate dienone **104**, an intermediate in the biosynthesis of the fargenin family (Scheme 35).



Scheme 35. Biosynthetic speculation of dienone **104**.

Dienone **104** can undergo two different oxy-Michael reactions, both of which establish the characteristic [4.3.0] ring system found in the fargenin/fargenone family. The first of these oxy-Michael reactions occurs at the C3 position on the central dienone ring, generating compound **106**, which can proceed down two reaction pathways leading to fargenin **98** or fargenone B **100**. Fargenin **98** is formed *via* a cyclisation of the phenol moiety into the carbonyl, which is followed by elimination of H₂O. Alternatively, oxidation of the benzylic position α to the enone, followed by a second oxy-Michael reaction can generate fargenone B **100**.



Scheme 36. Proposed biosynthesis of target neolignan natural products via dieone **104**.

The second possible oxy-Michael reaction of dienone **104** occurs at the C5 position of the dienone ring, forming compound **101**. Compound **101** is an unnamed natural

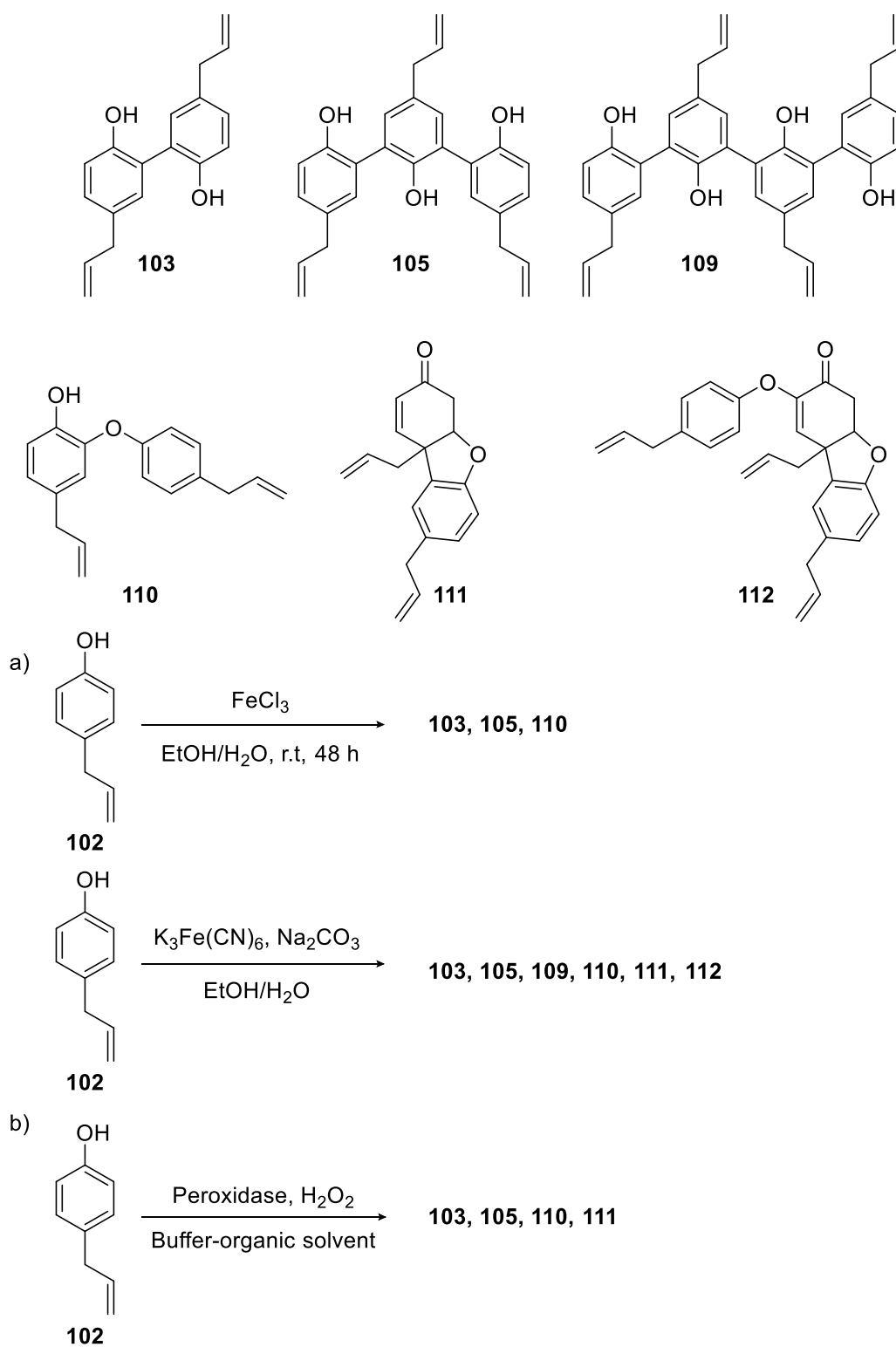
product of the same family and an intermediate of fargenone A **99**, which is generated *via* an oxidative oxy-Michael reaction.

Investigations into the probable biosynthesis of this family of natural products have been carried out by Brown and co-workers.⁷⁴ They examined the oxidative coupling of compound **102** using Fe(III) oxidants *in vitro*, resulting in the formation of a number of structurally similar products, including magnolol **103**, a proposed intermediate in the biosynthesis of the more complex members of this family.

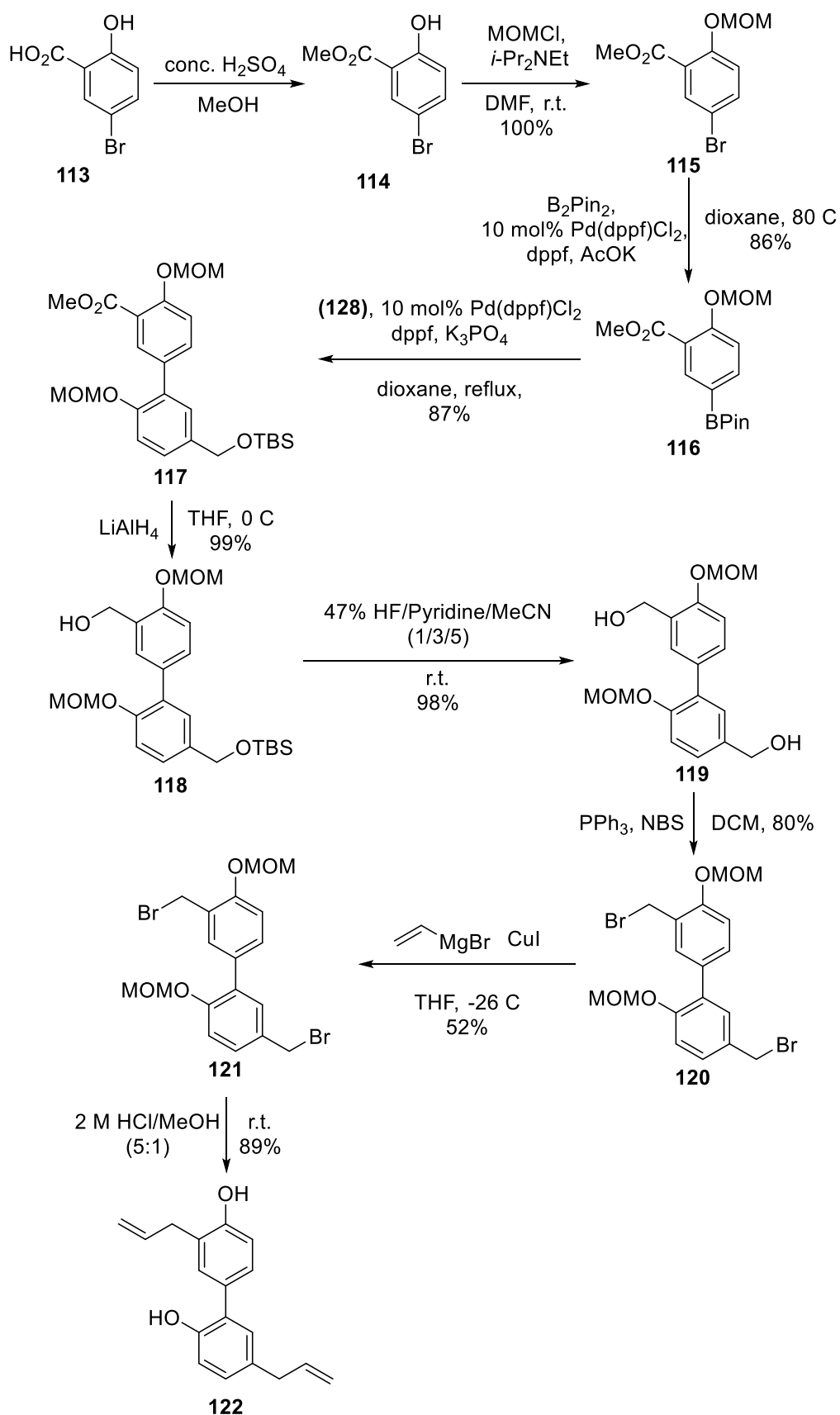
3.4 Previous syntheses of lignan natural products

In order to synthesise lignan natural products there are major obstacles to overcome, such as the formation of the biaryl C-C bonds, found within this class of natural product. In the proposed biosynthesis these bonds are formed through oxidative phenolic couplings, however, attempts to apply this synthesis strategy have proved difficult. This is a result of the unselective nature of such reactions, resulting in a large product distribution, as demonstrated by Brown and co-workers.⁷⁴

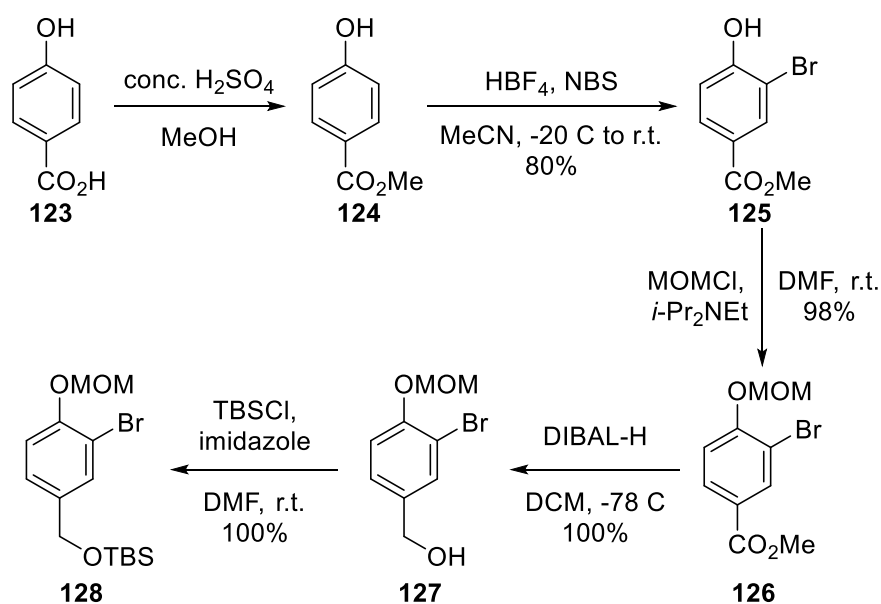
As described above, Brown and co-workers investigated the oxidative phenolic coupling of chavicol **102** using Fe(III) reagents, generating a complex mixture of compounds, due to the uncontrolled nature of the reaction. Further work examining the oxidative phenolic coupling of chavicol **102** was undertaken by Lui and co-workers, who found that peroxidase enzymes could afford increased selectivity towards the *ortho-ortho* coupling and the formation of magnolol **103**; however multiple products were still generated.⁷⁵



Scheme 37. Investigations into compound distributions generated through the oxidative coupling of chavicol **102**. a) Brown and co-workers; b) Lui and co-workers.



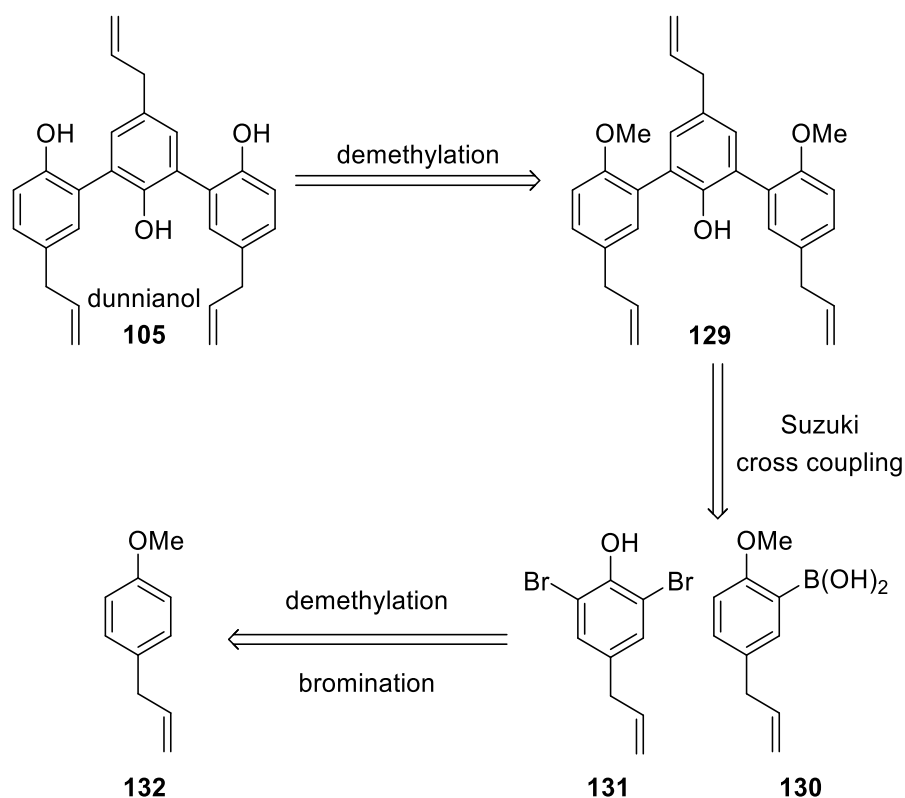
Scheme 38. Synthesis of honokiol **122** by Fukuyama in 2004.



Scheme 39. Synthesis of compound **125**, used in Fukuyama's synthesis of honokiol.

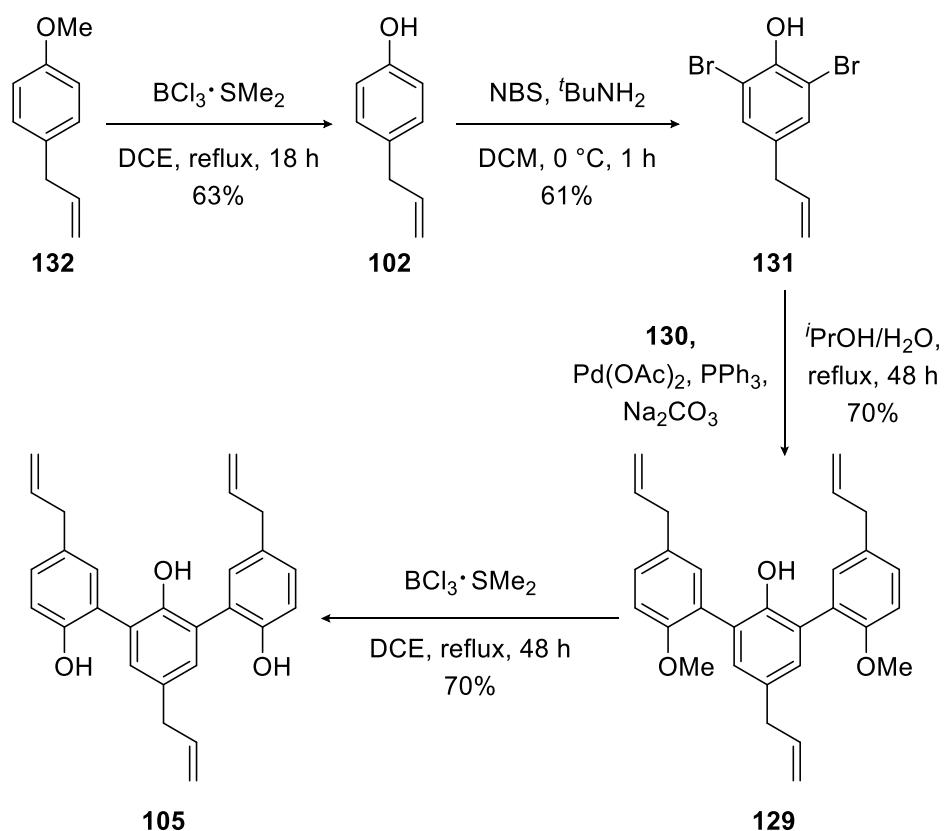
Another major concern is the nature of the allylic groups, which are sensitive to isomerisation, due to the formation of a more conjugated and therefore stable double bond. Previous syntheses of lignan natural products, such as the route designed by Fukuyama for the formation of honokiol **122** in 2004 (Schemes 38 and 39), which demonstrated that late addition of the trouble-some allyl groups leads to an increased step count (honokiol **122** was prepared in 14 steps from 5-bromo-2-hydroxybenzoic acid **113**).⁷⁶ Therefore, starting with materials containing the allylic groups will provide improved synthetic efficiency. Solutions to such problems can be found in the literature, due to the research carried out by multiple groups, including the Denton group. Previous work in the Denton group has led to the synthesis of dunnianol **105**, honokiol **122** and 4'-O-methyl honokiol and can therefore provide information on the sensitivity of the allylic groups and conditions successfully employed to generate the biaryl bonds.

3.5 Synthesis of dunnianol



Scheme 40. Retrosynthetic analysis for the formation of dunnianol **105**.

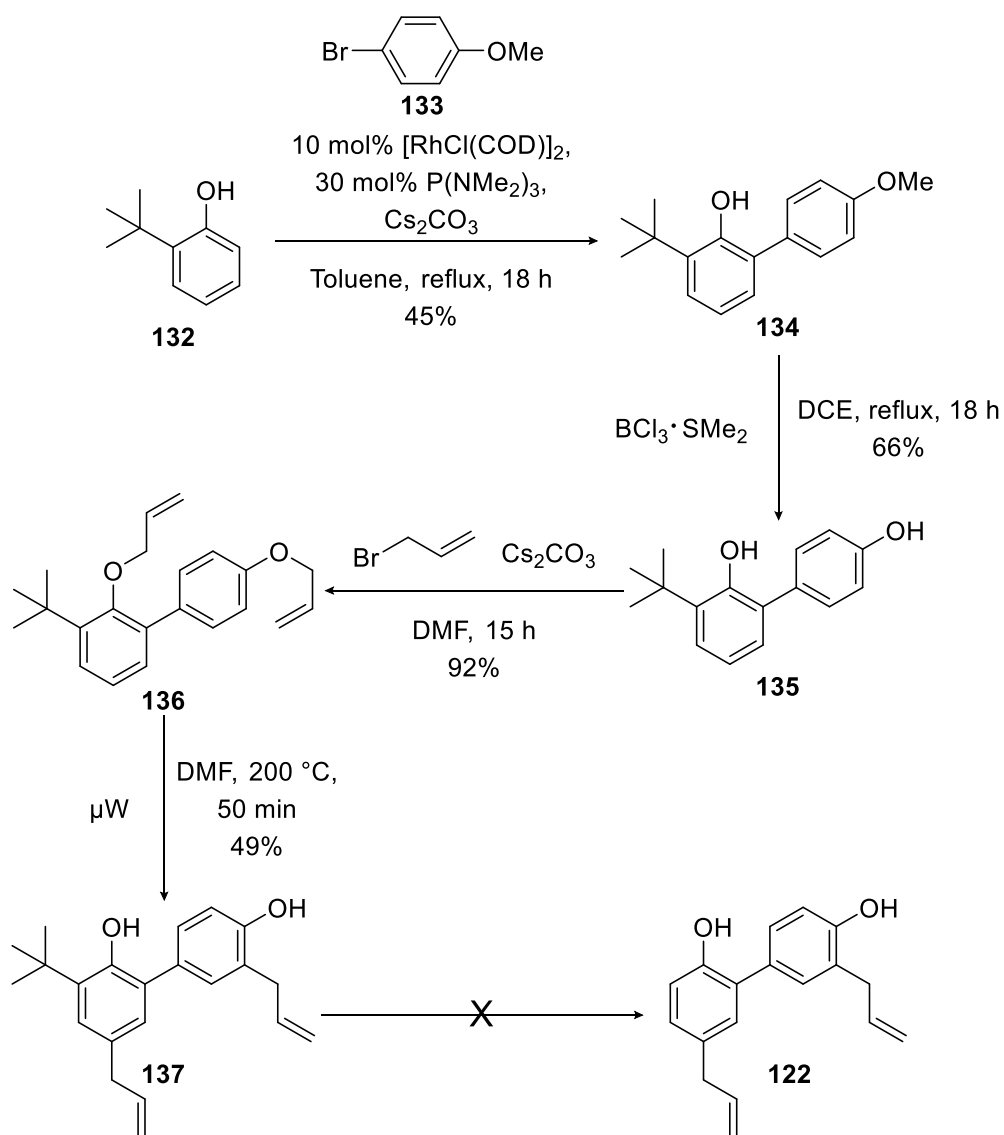
The synthesis plan developed by Denton and co-workers aimed at the synthesis of dunnianol **105** involved the formation of the key biaryl bonds *via* a double Suzuki-Miyaura cross coupling reaction. This palladium catalysed cross coupling strategy has also been used by various groups as a successful alternative method to oxidative phenolic coupling. The full retrosynthetic analysis and forward synthesis are outlined in Scheme 40 and 41 respectively, demonstrating that dunnianol **105** can be generated in 4 steps and 17% overall yield.



Scheme 41. Synthesis route to dunnianol **105** in 4 steps and 17% overall yield.

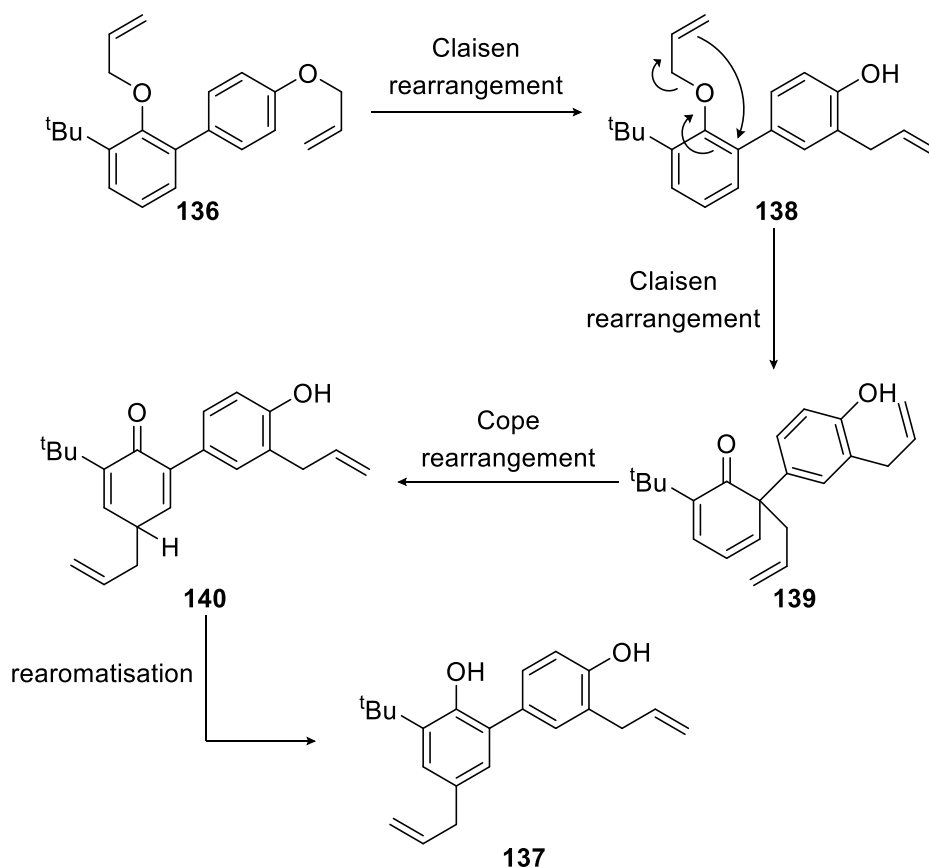
3.6 Synthesis of honokiol

Following the successful synthesis of dunnianol **105**, Denton and co-workers explored the synthesis of honokiol **122**. The originally proposed synthesis method moved away from the utilisation of the Suzuki-Miyaura cross coupling strategy to investigate a rhodium catalysed direct arylation approach, developed by Bedford and co-workers.⁷⁷



Scheme 42. Forward synthesis of honokiol **122** via direct arylation and Claisen rearrangement.

Ultimately the proposed synthesis method depicted in Scheme 42, was unsuccessful due to the failure to remove the *tert*-butyl group, which was essential for the formation of compound **137**. As it results in the Claisen rearrangement transferring the allylic functionality onto the unsubstituted *para* position, as depicted in Scheme 43.

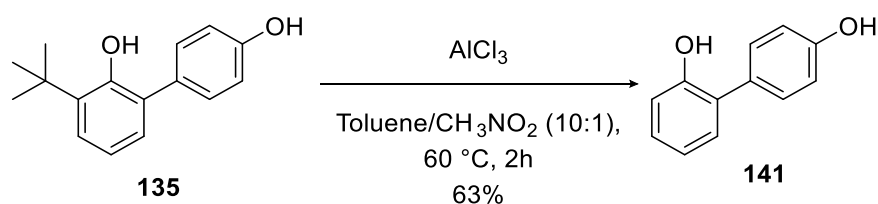


Scheme 43. The reaction pathway leading to the transfer of an allylic group to the para position of an aromatic ring.

Initial investigation of the retro Friedel Crafts alkylation conditions, required for removal of the *tert*-butyl group, which proved successful on a model system (Scheme 44, proved problematic. The introduction of the allylic functionality caused major difficulties, due to decomposition of compound **137** through isomerisation. This isomerisation was also observed when commercial honokiol **122** was subjected to the reaction conditions below.

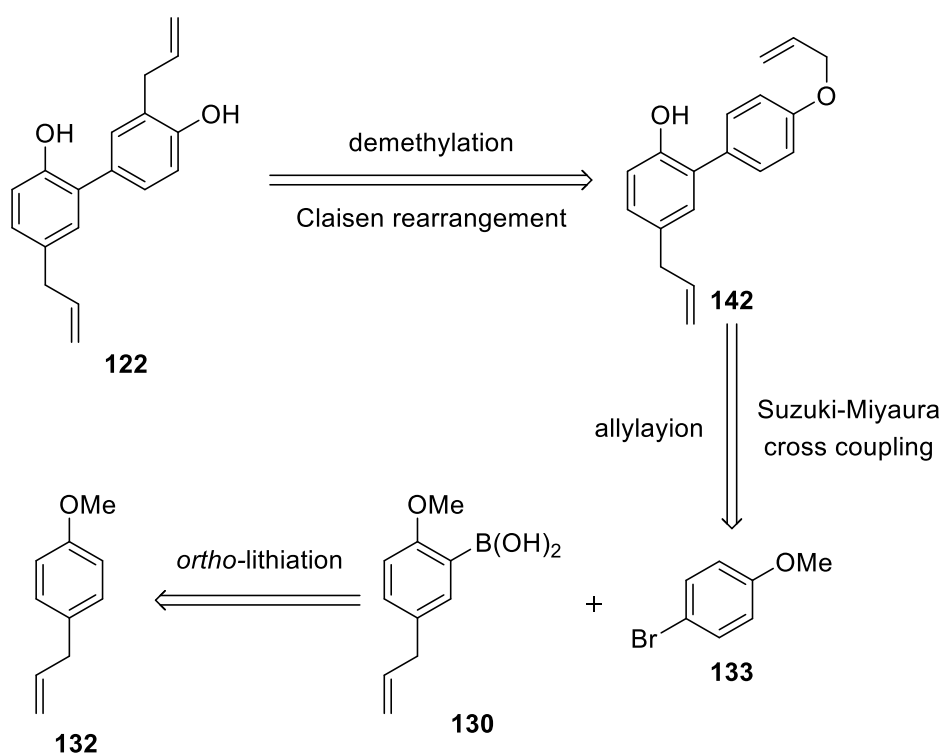
Following this observation, milder reaction conditions were investigated, utilising the milder AlCl_3 nitromethane complex, due to the stability of honokiol **122** under room temperature conditions.⁷⁸ However, it was found that when AlCl_3 nitromethane

complex was used with compound **137**, no reaction occurred at r.t. and increasing the temperature to 60 °C caused decomposition.

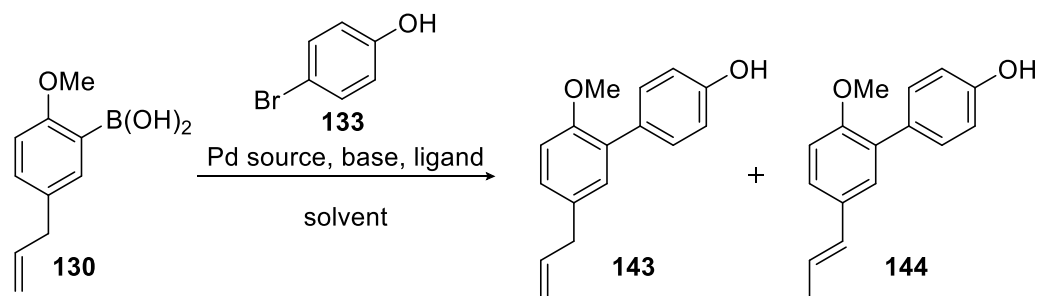


Scheme 44. Conditions required for the removal of the tert-butyl blocking group.

Due to the unsuccessful synthesis described above, an approach employing a Suzuki-Miyaura cross coupling strategy was developed (Scheme 45). The initial conditions first employed for the formation of **143**, were identical to those used in the synthesis of dunnianol **105**. However, large amounts of isomerisation were observed, leading to a thorough investigation of the cross coupling reaction conditions, Table 11.



Scheme 24. Retrosynthesis plan for the formation of honokiol **122** via Suzuki-Miyaura cross coupling.



Pd source (10 mol%)	Ligand (30 mol%)	Base (5 equiv.)	Solvent (10:1)	Ratio 143:144 ^a
Pd(OAc)₂	PPh ₃	Na ₂ CO ₃	<i>i</i> PrOH/H ₂ O	3:2
Pd(OAc)₂	PPh ₃	Na ₂ CO ₃	DMF/H ₂ O	3:10
Pd(OAc)₂	PPh ₃	Na ₂ CO ₃	CH ₃ CN/H ₂ O	3:8
Pd(OAc)₂	PPh ₃	K ₂ CO ₃	<i>i</i> PrOH/H ₂ O	3:4
-	PPh ₃	Na ₂ CO ₃	<i>i</i> PrOH/H ₂ O	Trace ^b
-	PPh ₃	K ₂ CO ₃	<i>i</i> PrOH/H ₂ O	Trace ^b
Pd(PPh₃)₄	-	Na ₂ CO ₃	<i>i</i> PrOH/H ₂ O	1:6
Pd(PPh₃)₄	-	K ₂ CO ₃	<i>i</i> PrOH/H ₂ O	9:2
Pd₂dba₃	PPh ₃	Na ₂ CO ₃	<i>i</i> PrOH/H ₂ O	3:2
Pd₂dba₃	PPh ₃	K ₂ CO ₃	<i>i</i> PrOH/H ₂ O	3:2
Pd₂dba₃	S-Phos	KF	1,4-dioxane/H ₂ O	1:0 ^c
Pd₂dba₃	S-Phos	KF	THF/H ₂ O	1:0
Pd₂dba₃	PPh ₃	KF	THF/H ₂ O	9:4
Pd₂dba₃	S-Phos	Na ₂ CO ₃	THF/H ₂ O	3:2

^a Compound ratios determined *via* integration of the C7 and C9 regions of the crude ¹H NMR spectra.

^b Due to the absence of palladium, no cross coupling was observed, however, trace amounts of isomerisation were identified.

^c Protocol of Liu and Chen

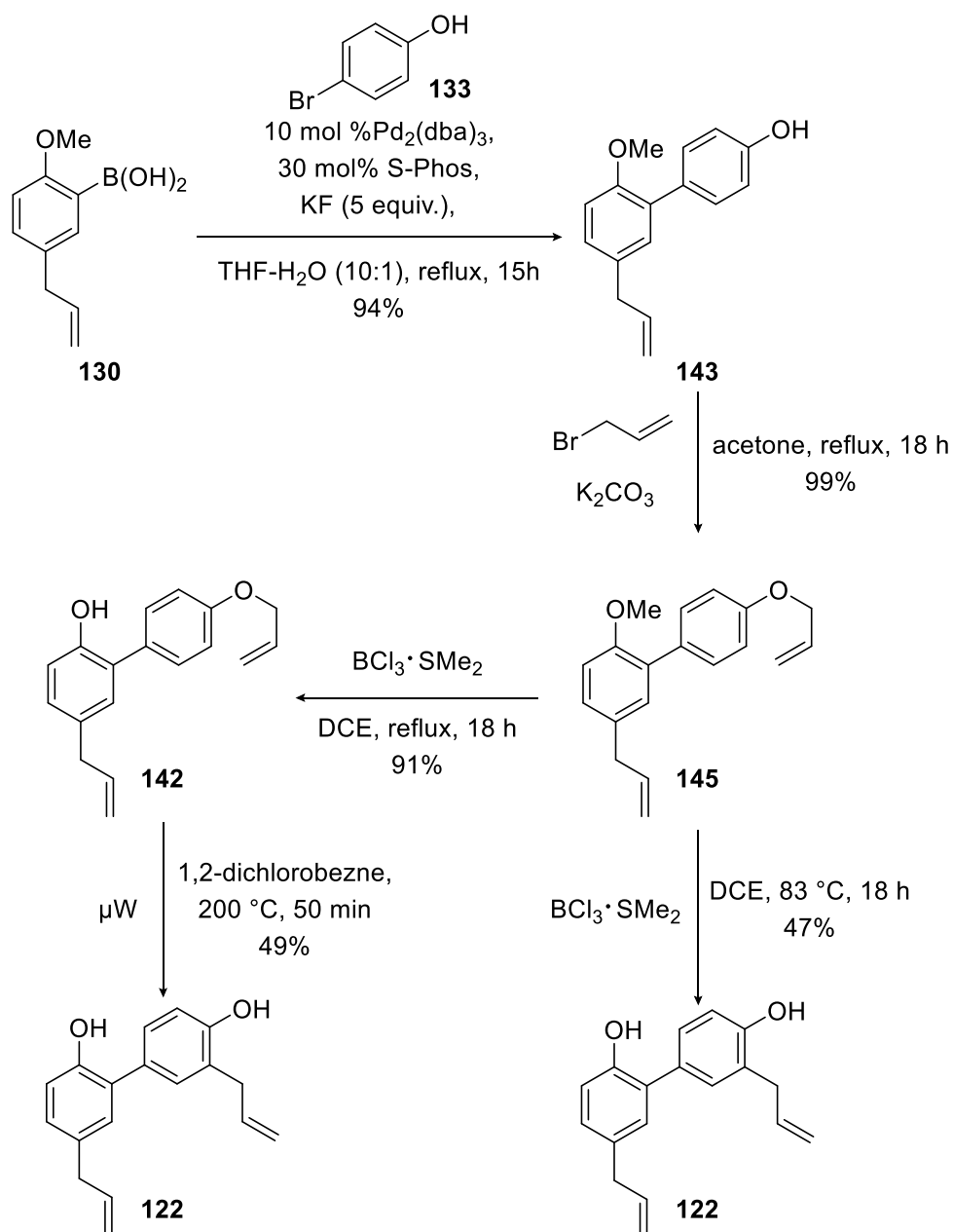
Table 11.

In order to reduce isomerisation, examination of the reaction solvent was examined by Denton and co-workers; however, it was found that both DMF and acetonitrile resulted in increased formation of side product **144**. This was also the case, when K₂CO₃ was used as a replacement for Na₂CO₃. Removal of the Pd(OAc)₂ from the

reaction mixture resulted in significantly reduced isomerisation, therefore a change of palladium source was investigated. When $\text{Pd}(\text{PPh}_3)_4$ was used, isomerisation was still observed, it is interesting to note that lower quantities of isomerisation were observed with K_2CO_3 over Na_2CO_3 . This was not the case when Pd_2dba_3 was used, as alterations of base resulted in no change in reaction outcome.

At this stage Denton and co-workers utilised the conditions developed by Lui and Chen during their synthesis of honokiol **122**, which was achieved in 4 steps and 32% overall yield.⁷⁹ The conditions employed Pd_2dba_3 , S-Phos and KF in 1,4-dioxane/ H_2O , successfully eliminating any isomerisation from occurring. Adaptation of the successful conditions demonstrated that 1,4-dioxane could be replaced by THF, but any alterations of ligand and base resulted in isomerisation. Under these conditions Denton and co-workers were able to generate biaryl **143** in 94% isolated yield.

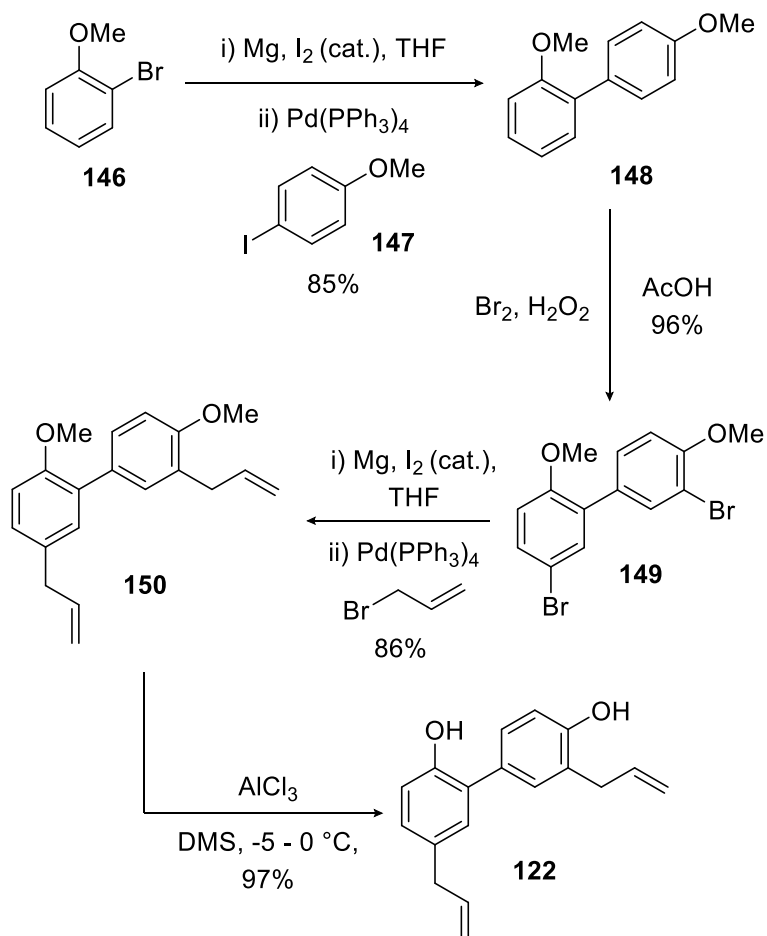
Following the successful cross coupling of 4-bromophenol **133** with boronic acid **130**, the synthesis of honokiol **122** was completed as depicted in Scheme 46, with a Claisen rearrangement as the final key step. Denton and co-workers showed that the Claisen rearrangement and demethylation can be achieved in one pot (34%); however, this resulted in a lower yield than the classical thermal conditions (55%).



Scheme 46. Synthesis of honokiol **122** in 4 and 5 steps.

In addition to the syntheses discussed above, further studies have been carried out on the synthesis of honokiol **122**. In both cases the synthesis strategy involves palladium catalysed cross coupling to form both the aryl-aryl bonds and the addition of the allylic groups, whilst providing a step efficient synthesis. The first of these syntheses was developed by Kumar and co-workers, the key carbon-carbon bonds

were constructed *via* a tetrakis(triphenylphosphine)palladium [Pd(PPh₃)₄] catalysed Kumada coupling. This led to the synthesis of honokiol **122** in 68% overall yield.⁸⁰

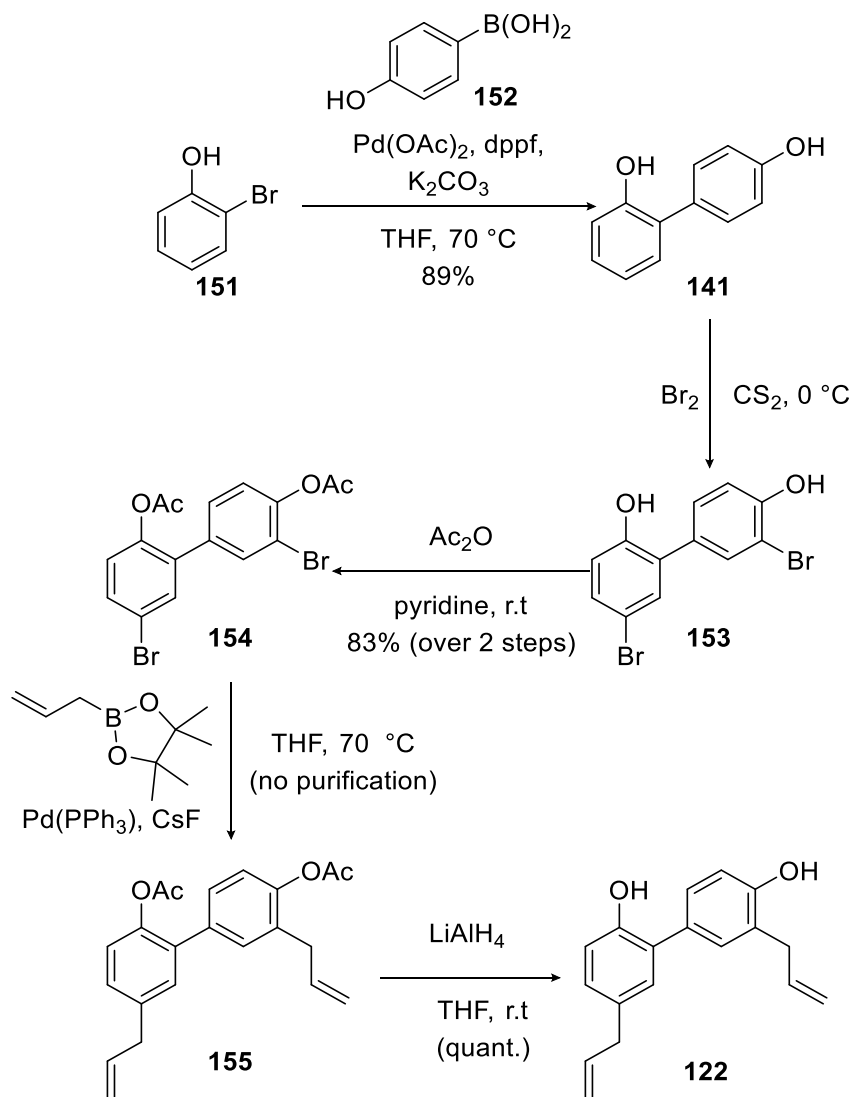


Scheme 47. Synthesis of honokiol **122** via palladium catalysed Kumada coupling.

The second synthesis was developed by Fukuyama, leading to major improvements on his previous 14 step synthesis. In this synthesis, Suzuki-Miyaura cross coupling reactions were employed in the formation of the key carbon-carbon bonds, leading to a successful five step synthesis of honokiol **122** in 83% overall yield (Scheme 48).⁸¹

After investigating the synthesis of small neolignans, such as honokiol **122** and dunnianol **105**, it is evident that there are multiple strategies that can be employed to generate the triaryl core of the target natural products. It has also been observed that the problematic allylic functionality can be carried through the synthesis route

or added at a later stage in a step efficient process, thus providing encouragement in our efforts to synthesise the members of the fargenin/fargenone family of sesqui-neolignans.



Scheme 48. Synthesis of honokiol **122** via two Suzuki-Miyaura reactions.

3.7 Synthesis of the tricyclic core of the fargenin/fargenone family

Following the groups investigation of small neolignan natural products, it was our aim to synthesise more complex neolignan structures, such as those of the fargenin/fargenone family, detailed above. To date there have been no total synthesis completed of this family of natural products, however, our group has

begun studies in this area, by targeting the tricyclic core of this family of compounds, Figure 8 (page 62).⁸² The synthesis plan is based on the biosynthesis described above (Schemes 35 and 36, pages 63-64), therefore requiring the synthesis of dienone **104** or a structurally similar compound.

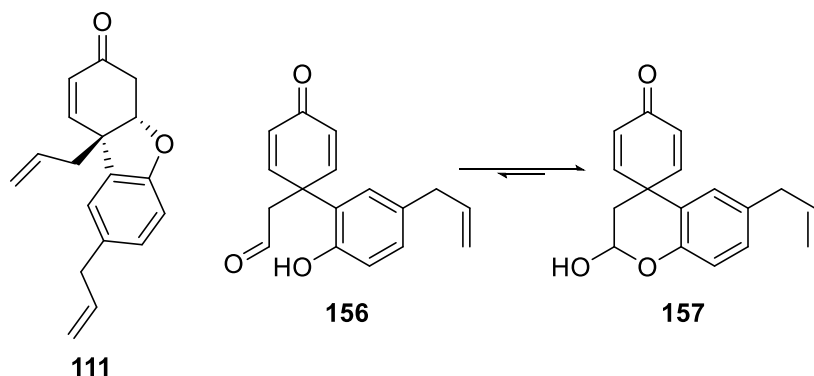
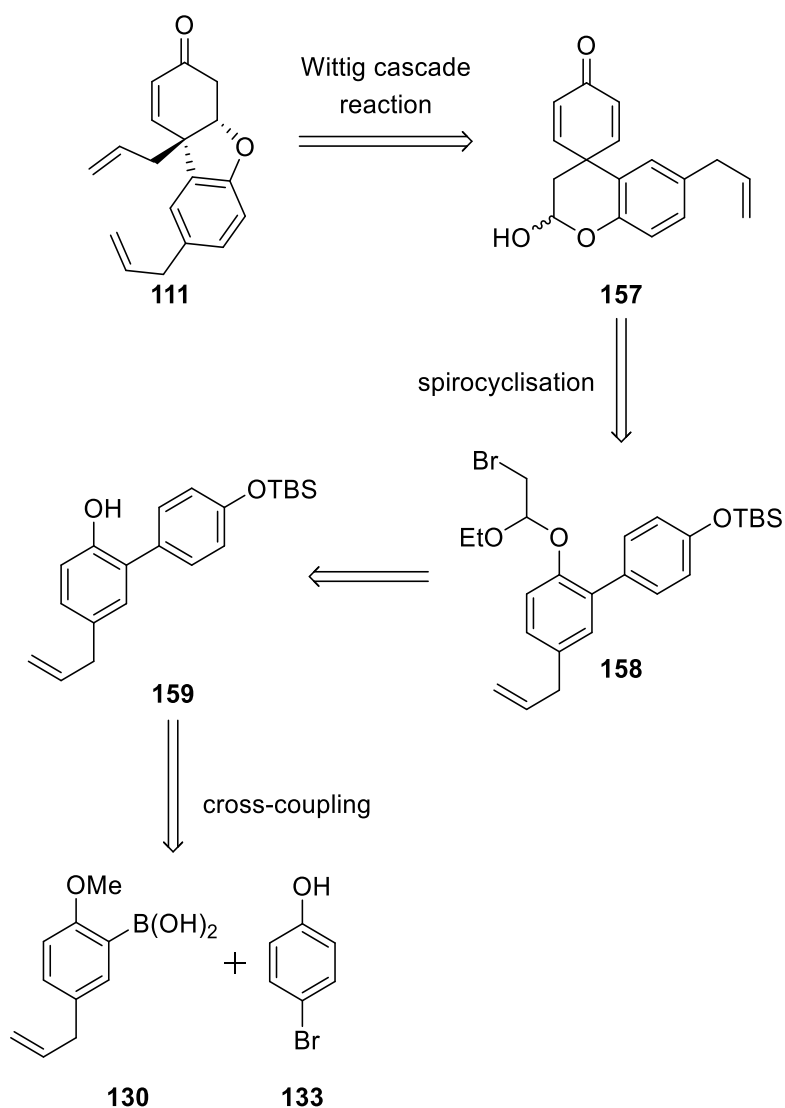


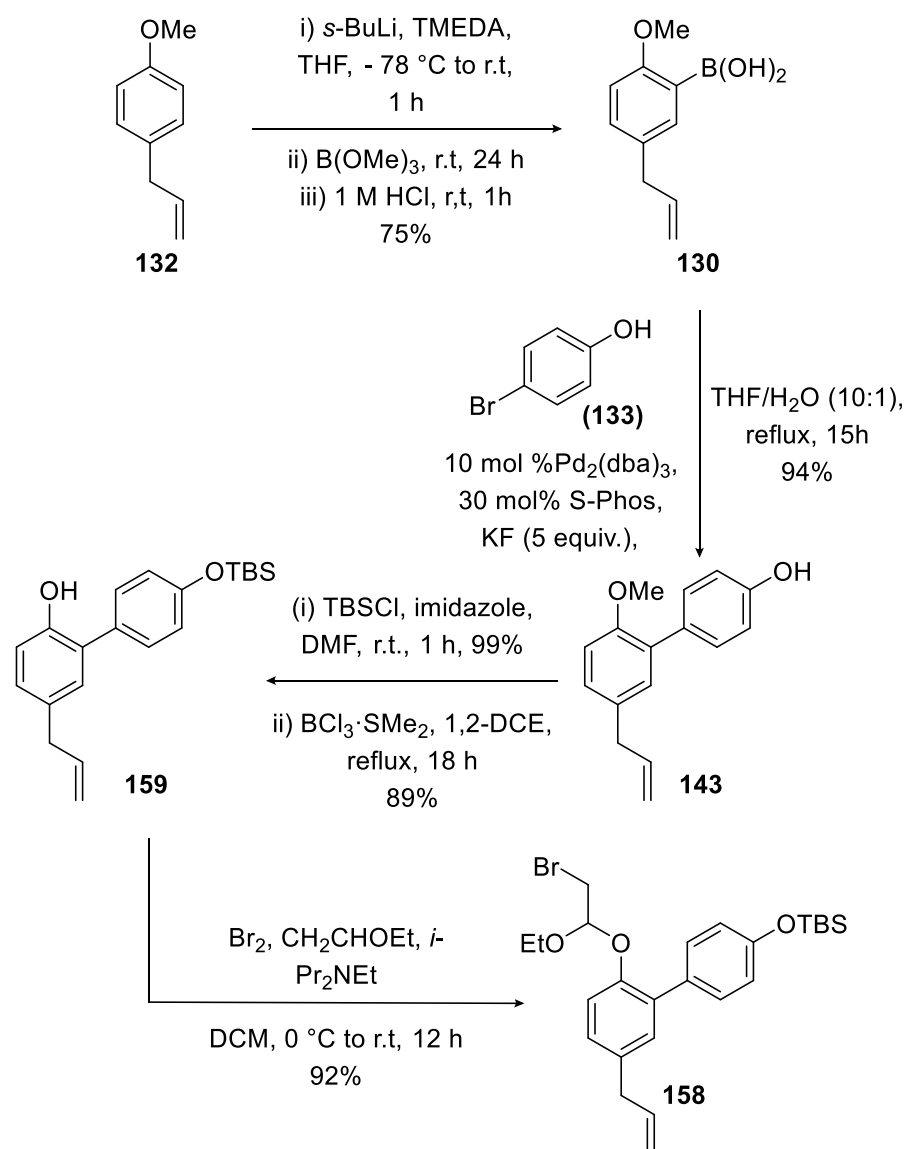
Figure 9. The Core ring structure of the fargenin/fargenone family of natural products.

This led to the selection of spirocyclic dienone **157** as a suitable synthetic target in the synthesis of the tricyclic core (Figure 9). This strategy is based upon the hemi-acetal functionality within compound **157**, existing as a protected aldehyde. It was proposed that hemi-acetal **157** could be transformed into the tricyclic core through a cascade reaction, involving an oxy-Michael cyclisation and subsequent trapping of the aldehyde *via* Wittig olefination.



Scheme 49. Full retrosynthetic analysis of tricyclic core **111**.

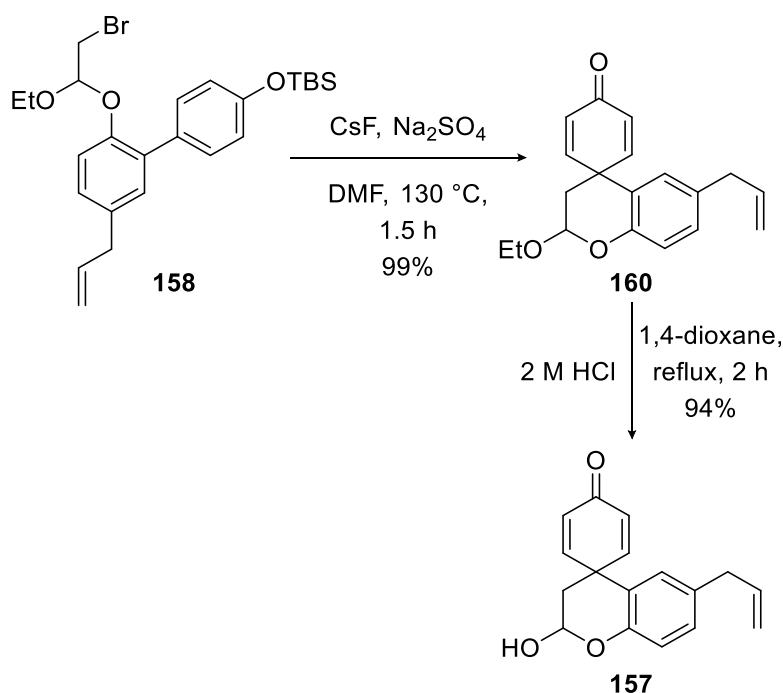
The full retrosynthetic analysis is depicted in Scheme 49, illustrating that the planned synthetic route involved a Suzuki-Miyaura cross coupling reaction, followed by protecting group manipulation to generate compound **159**. Mixed acetal **158** would then be obtained through a bromo-acetalisation, and after spirocyclisation key intermediate **157**, would be generated *via* hydrolysis. Hemi-acetal **157** would then be subjected to a Wittig cascade reaction to generate the tricyclic core of the fargenin/fargenone family of natural products.



Scheme 50. Synthesis route to intermediate **158**.

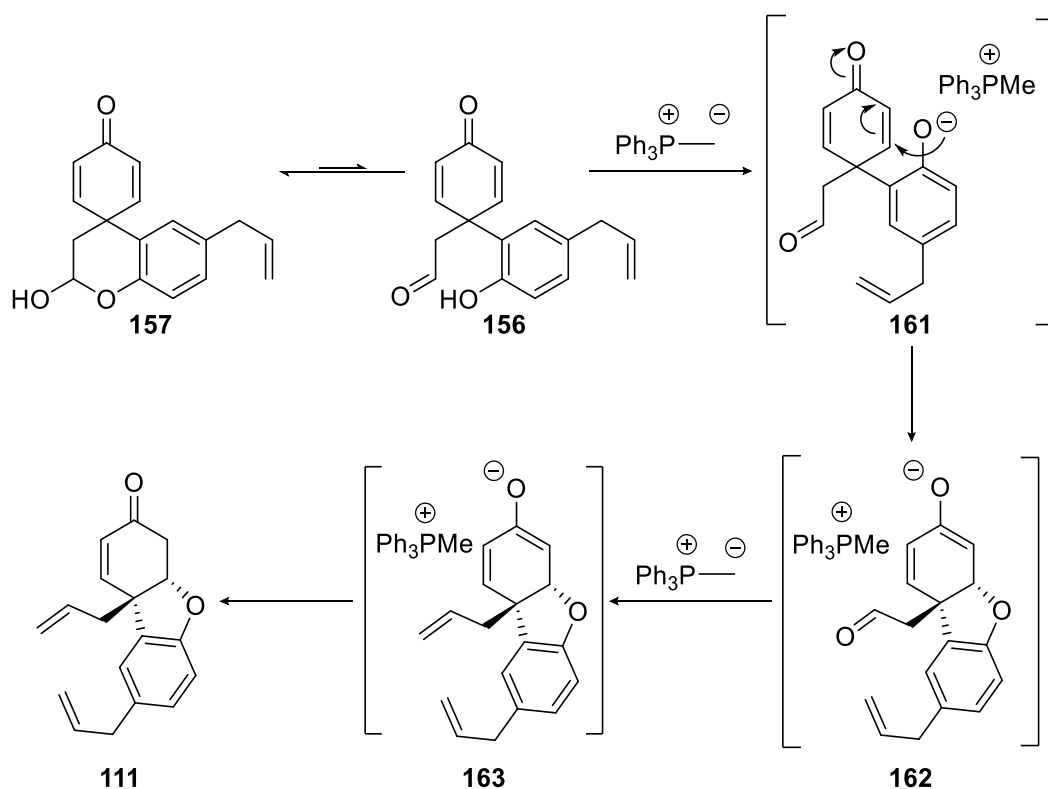
The synthesis of the tricyclic core started from 4-allylanisole **132**, formed from the methylation of chavicol **104**, the proposed biosynthetic starting material. The boronic acid **130**, formed in 75% (previously used for the synthesis of honokiol **122** and dunnnianol **105**) underwent a Suzuki-Miyaura cross coupling reaction in 94% to give compound **143** (conditions used in the synthesis of honokiol **122**, which were found to prevent isomerisation of the sensitive allylic functionality, following a thorough investigation of the reaction conditions (Table 11, page 74)). After

protecting group manipulation compound **159** was converted into mixed acetal **158** using bromine and ethyl vinyl ether in 92% yield.



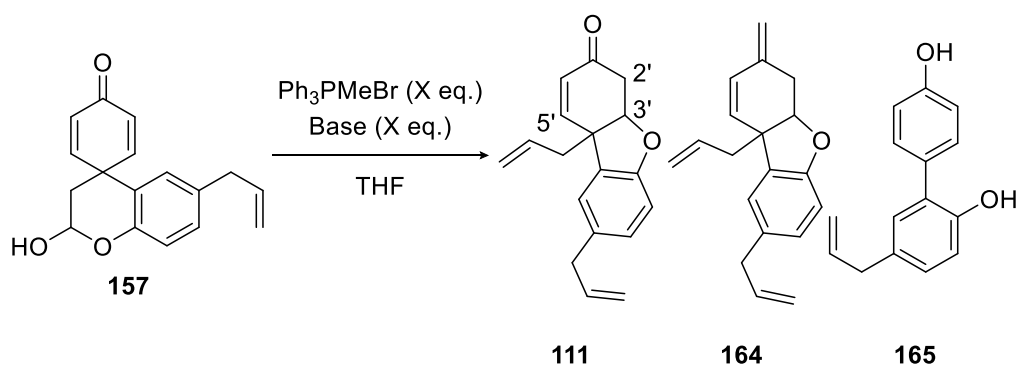
Scheme 51. Synthesis of spirocyclic dienone **157**, a key intermediate in the synthesis of the tricyclic core **111**.

Compound **158** was then subjected to conditions developed by Magnus and co-workers,⁸³ resulting in the formation of spirocyclic dienone **160** in excellent yield, as a result of deprotection and dearomatising spirocyclisation. Hydrolysis of spirocyclic dienone **160** was achieved through reflux in dioxane and provided the most important intermediate in the synthesis, which would be subjected to the Wittig cascade reaction conditions, in order to generate the tricyclic core of the fargenin/fargenone family (Scheme 52).



Scheme 52. Synthetic strategy for the generation of tricyclic core **111**, via a Wittig cascade reaction.

Investigations into the conditions required for the successful transformation of spirocyclic dienone **157** into tricyclic core **111**, via the planned cascade approach proved ineffective, the results are summarised in Table 12. Initially spirocyclic dienone **157** was subjected to 3 equivalents of ylide, in THF at room temperature; however, this generated a complex mixture of compounds. Through examination of the ^1H and ^{13}C NMR spectra, and comparisons made against the data obtained by Brown and co-workers; it was reported that peaks could be identified at δ 6.51, 4.70, 3.00 and 2.75 ppm in the ^1H spectra, which related to protons at the 2'a, 2'b, 3' and 5' positions of the enone ring. Thus suggesting tricyclic core **111** could be formed via this approach, through manipulation of the reaction conditions.



Ylide source	Base	Solvent	Temperature	Time (h)	Product (Yield)
Ph ₃ PMeBr (3.0 eq.)	KHMDS (2.5 eq.)	THF	r.t.	1.5 h	111 (trace)
Ph ₃ PMeBr (3.5 eq.)	KHMDS (3.0 eq.)	THF	50 °C	1.5 h	164 (55%)
Ph ₃ PMeBr (1.1 eq.)	KHMDS (2.7 eq.)	THF	50 °C	1.5 h	165 (48%)
-	^t BuOK (2.5 eq.)	THF	50 °C	1.0 h	165 (37%)

Table 12. Conditions explored for formation of **111**, via the Wittig cascade reaction.

In order to improve the formation of the tricyclic core **111**, Denton and co-workers increased the reaction temperature to 50 °C. This resulted in a cleaner reaction, however, no desired product was observed due to formation of compound **164**, resulting from an unwanted Wittig olefination on the enone carbonyl. Product **164** contains the desired [4.3.0] ring structure, therefore it was envisioned that reduction of the quantity of ylide used, could prevent this unwanted second olefination. This proved inaccurate with the formation of biaryl **165** occurring in 48% yield. Biaryl **165** was also reported, when hemi-acetal **157** was exposed to other bases including ^tBuOK at 50 °C.

Examination of product **164** was undertaken to determine that the correct diastereoisomer of the [4.3.0] ring system was obtained. This was achieved through NOESY experiments, which demonstrated that the correct proton interactions were

present between the proton at the 3' position and the protons at the 7' position, Figure 10.

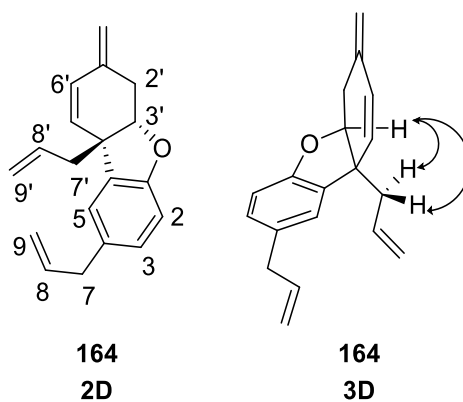


Figure 10. NOSEY interactions, corroborating the proposed stereochemistry of product **164**.

Even though this investigation into the formation of the tricyclic core of the fargenin/fargenone family of natural products did not yield the required structure, it has demonstrated that the construction of the desired [4.3.0] ring system is possible *via* this method. Therefore, if a strategy can be developed that can prevent the unwanted second Wittig olefination from occurring, there will be a viable route to the target natural products.

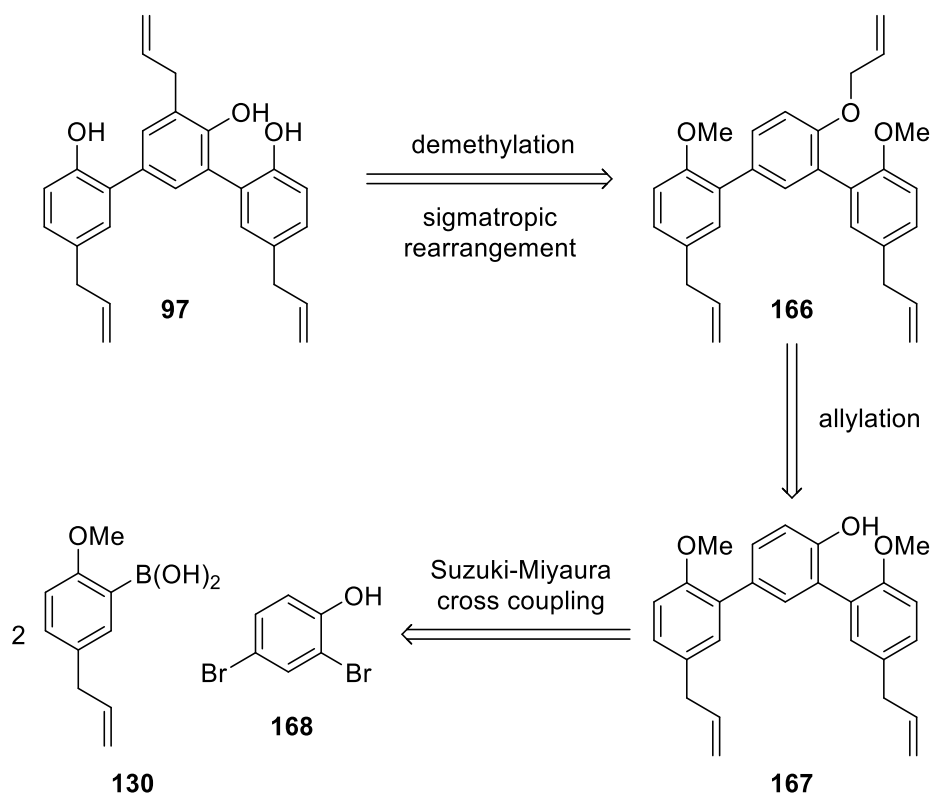
4. Results and discussion

In order to successfully undertake the synthesis of neolignan natural products in the fargenin/fargenone family (Figure 8, page 62); it was important to apply the information generated through the group's previous synthesis efforts in this area. As previously discussed in the introduction, the group has conducted the synthesis of small lignan natural products (magnonol **103**, honokiol **122** and dunnianol **105**), in addition to the synthesis of the tricyclic core of the fargenin/fargenone family. These synthesis efforts provided crucial information on the potential difficulties associated with the total synthesis of the target neolignans, thus aiding their eventual synthesis.

One potential problem associated with the synthesis of these neolignan natural products is the presence of the allyl functionality within their structures and whether these sensitive alkenes can be carried through the synthesis without isomerisation. The previous syntheses completed, demonstrated that conditions can and have been developed to allow for unprotected allyl groups to be present through multiple synthetic steps, therefore allowing flexibility within the synthesis strategy. For example, Suzuki-Miyaura cross coupling reactions were identified as a possible method for the formation of the biaryl bonds. After extensive investigations during the honokiol **122** synthesis it was determined that successful cross-coupling could be achieved in the presence of allyl groups, without isomerisation.

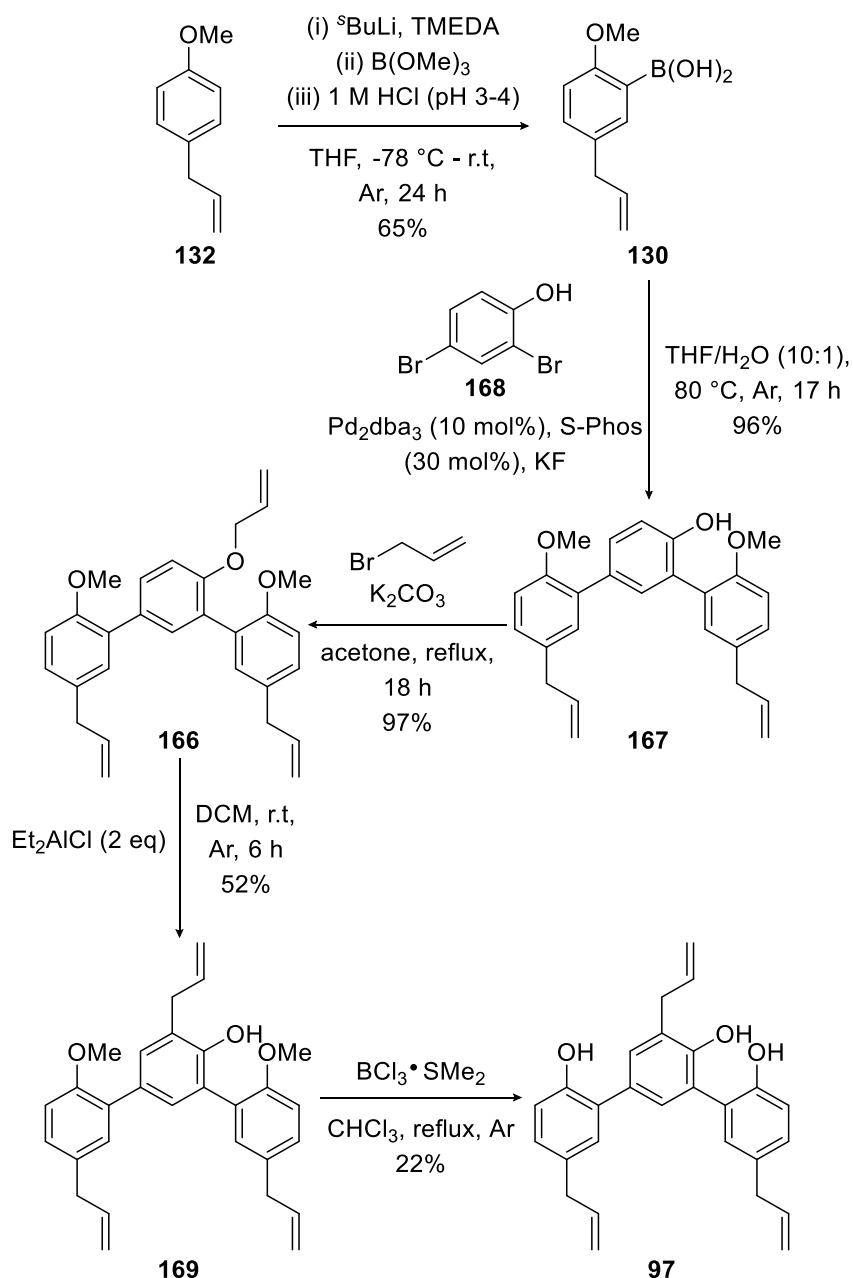
Other notable findings include the use of Brønsted and Lewis acidic conditions in the presence of allyl groups, for example the cleavage of methyl ether protecting groups using boron trichloride dimethylsulfide complex. With this information in hand, the synthesis of macranthol **97** and the fargenin/ fargenone family was investigated.

4.1 Concise total synthesis of macranthol



Scheme 53. Retrosynthetic analysis of macranthol **97**.

The retrosynthetic analysis is shown in scheme 53, illustrating that the synthesis of macranthol **97** can be traced back to boronic acid **130**, a boronic acid derivative of 4-allylanisole **132** (methylated chavicol) and 2,4-dibromophenol **168**. Therefore, the synthesis plan involves the adaptation of the previous Suzuki-Miyaura cross coupling reaction, generating triaryl **167**, thus requiring a more demanding cross coupling reaction *ortho* to the phenol. Allylation of triaryl **167** generates compound **166**, which can be converted to macranthol **97** via Claisen rearrangement and deprotection.



Scheme 54. The final synthesis route to macranthol **97**.

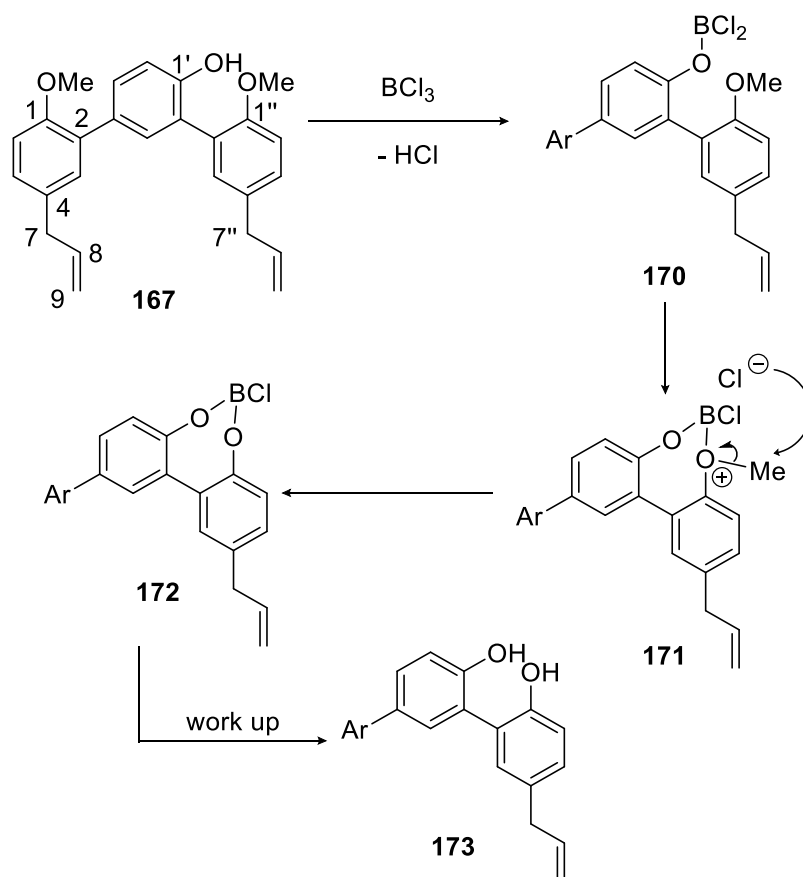
The synthesis began with the formation of arylboronic acid **130**, generated from commercially available 4-allylanisole **132** in 65% yield. This was then subjected to Suzuki-Miyaura cross coupling reaction conditions, previously used in the synthesis of honokiol **122**, resulting in a 96% yield. Even though these conditions successfully eradicated isomerisation during the synthesis of honokiol **122**, the extra demand of the additional cross coupling *ortho* to the phenol did result in minor quantities of

isomerised material. However, the result was deemed acceptable, as the unwanted material could be removed and therefore was not present during the subsequent steps of the synthesis.

Triaryl **167** was then allylated in 97% yield using allyl bromide and potassium carbonate. The Claisen rearrangement was then performed using diethylaluminium chloride, resulting in a 52% yield of methyl protected macranthol **169**, which was deprotected in 22% yield using $\text{BCl}_3 \cdot \text{SMe}_2$ (Scheme 54). Analysis of the remaining material revealed the major component resulted from mono-deprotection of compound **169**.

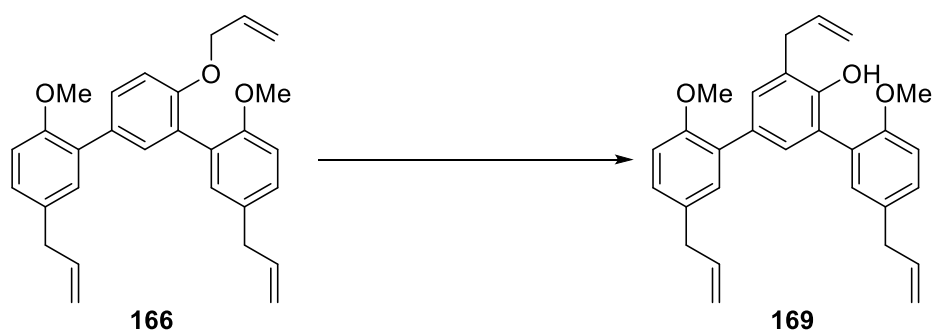
Methyl deprotection with $\text{BCl}_3 \cdot \text{SMe}_2$, resulted in a mixture of mono-methyl protected and fully deprotected macranthol **97**. This mixture proved difficult to separate *via* flash column chromatography with 42% of the recovered material remaining a mixture of macranthol **97** and mono-protected product. An interesting observation revealed that the first deprotection was rapid and selective for a single methyl group, however, the second deprotection was very slow requiring a large excess of the $\text{BCl}_3 \cdot \text{SMe}_2$. The selective deprotection occurred on the *ortho* aryl moiety and provides a viable route to the selective functionalisation of the *para* aryl ring, which will be important during the adaptation of the previous synthesis of the tricyclic core of the fargenin/fargenone family.

It is believed that the BCl_3 Lewis acid initially coordinates to the phenol moiety, therefore positioning itself in close proximity to the methyl ether attached to C-1''. A proposed mechanistic pathway is depicted in Scheme 55.



Scheme 55. Proposed mechanism for the selective deprotection of the C-1'' methyl ether.

The key step in the macranthol **97** synthesis was the Claisen rearrangement, previous syntheses within the group, used microwave irradiation to produce the rearrangement or $\text{BCl}_3 \cdot \text{SMe}_2$ to achieve the Claisen reaction and deprotection in one pot. However, attempts to implement these conditions did not result in the desired transformations, generating large amounts of isomerisation. In addition to $\text{BCl}_3 \cdot \text{SMe}_2$ many other Lewis acids have been shown to catalyse the Claisen rearrangement.⁸⁴



Lewis acid	Equiv.	Temperature	Ratio (167/169)	Yield
AlMe ₃	2	r.t.	0:1	n/a
Et ₂ AlCl	2	r.t.	1:0.34	42%
Et ₂ AlCl	1	r.t.	1:0.91	n/a
Et ₂ AlCl	3	r.t.	1:0.44	n/a
Et ₂ AlCl ^a	2	r.t.	1:0.75	n/a
Et ₂ AlCl	2	-78 °C	No reaction	n/a
Et ₂ AlCl	2	-40 °C	No reaction	n/a
Et ₂ AlCl	2	-20 °C	No reaction	n/a

^a Concentration for the reaction was doubled

Table 13. Optimisation of the Claisen rearrangement of compound **166**.

Investigation into the Lewis acid catalysed Claisen rearrangement of compound **166** was undertaken to obtain optimised reaction conditions for this transformation (see Table 13). The first Lewis acid examined was AlMe₃. However, no product resulted with ¹H NMR data identifying that deallylated compound **167** was the sole product. Et₂AlCl provided greater success with a mixture of compound **167** and the desired compound **169**, being formed in a 0.34:1 ratio. The amount of Lewis acid required for the transformation was then investigated, 1 equivalent resulted in a greater formation of compound **167** as did 3 equivalents of Et₂AlCl. It was also found that increasing the concentration of the reaction resulted in a greater amount of deallylated compound **167**.

Literature examples were identified demonstrating that the Claisen rearrangement could be run at sub-zero temperatures.^{84b} In this case it was found that the reaction product could be obtained at – 20 °C, however, attempts with our substrate at lower

temperatures resulted in recovery of the starting material. During this investigation it was found that compound **166** was unstable at r.t. and therefore low temperature storage (– 20 °C freezer) was required to prevent decomposition.

In summary macranthol **97** has been synthesised for the first time in 5 steps from commercially available 4-allylanisole **132** in 7% overall yield. Comparison of the ^1H NMR and ^{13}C NMR data was found to be identical to that reported for the isolation of the natural product (See Table 14). The synthesis of macranthol **97** has also led to the discovery of a viable route to the selective methyl deprotection of triaryl **166**.

Natural material ⁶⁷	Synthetic material 97	Natural material ⁶⁷	Synthetic material 97
151.2	151.2 (C _q)	127.5	127.4 (C _q)
150.9	150.8 (C _q)	124.7	124.7 (C _q)
150.8	150.7 (C _q)	123.3	123.3 (C _q)
137.7	137.7 (CH)	116.8	116.7 (CH)
137.4	137.3 (CH)	116.7	116.7 (CH ₂)
136.2	136.1 (CH)	116.0	115.9 (CH ₂)
133.4	133.4 (C _q)	115.8	115.8 (CH)
132.4	132.4 (C _q)	115.6	115.7 (CH ₂)
131.3	131.3 (CH)	39.4	39.4 (CH ₂)
130.9	130.9 (CH)	39.3	39.3 (CH ₂)
130.3	130.3 (CH)	35.0	35.1 (CH ₂)
130.3	130.3 (CH)		
130.2	130.1 (C _q)		
130.0	130.0 (CH)		
129.0	128.9 (CH)		
128.3	128.3 (C _q)		

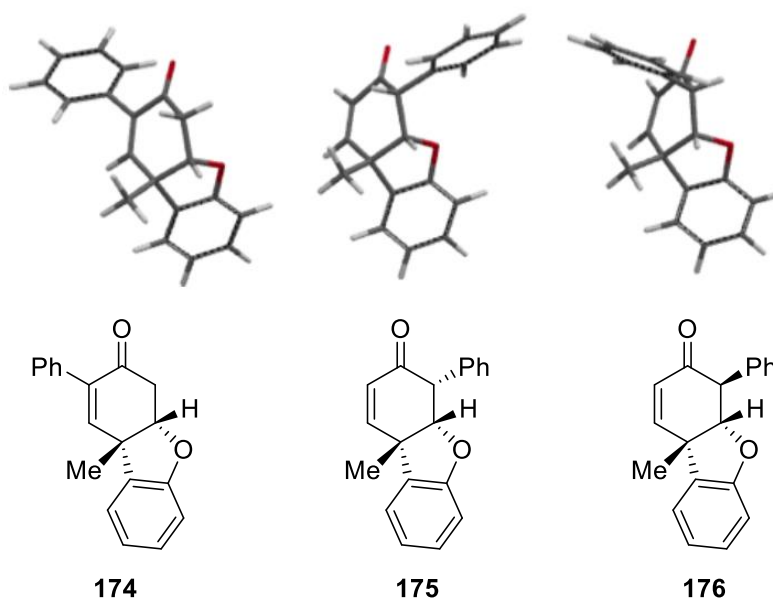
Table 14. Comparison of the published and synthesised ^{13}C NMR data for macranthol **97**.

4.2 Studies towards the synthesis of the fargenin/fargenone family of natural products

As previously reported, the group has developed a synthesis strategy for the [4.3.0] ring system, present in the fargenin/fargenone family of natural products *via* a cascade reaction, involving oxy-Michael addition and Wittig olefination. However, despite the fact the resultant product contained the required ring system; the dienone was destroyed through an undesired Wittig methylenation (compound **164**). Therefore it is our aim to develop a modified strategy, preventing the unwanted methylenation, thus generating the tricyclic core with the correct functionality.

In order to prevent the undesirable Wittig reaction occurring on the dienone moiety, it is believed the installation of a third aryl group could hinder the trajectory for nucleophilic attack by the phosphonium ylide, ultimately rendering the dienone carbonyl unreactive. The introduction of this third aryl group creates the possibility of multiple products due to the desymmetrisation of the dienone ring.

To understand the oxy-Michael reaction further, quantum chemical calculations were undertaken (Table 15).⁸⁵ This presented compound **174** as the thermodynamic product of the oxy-Michael reaction, resulting from attack of the dienone ring at the least hindered position. Therefore, the unnamed natural product within the fargenin/fargenone family was selected as the simplest target compound.



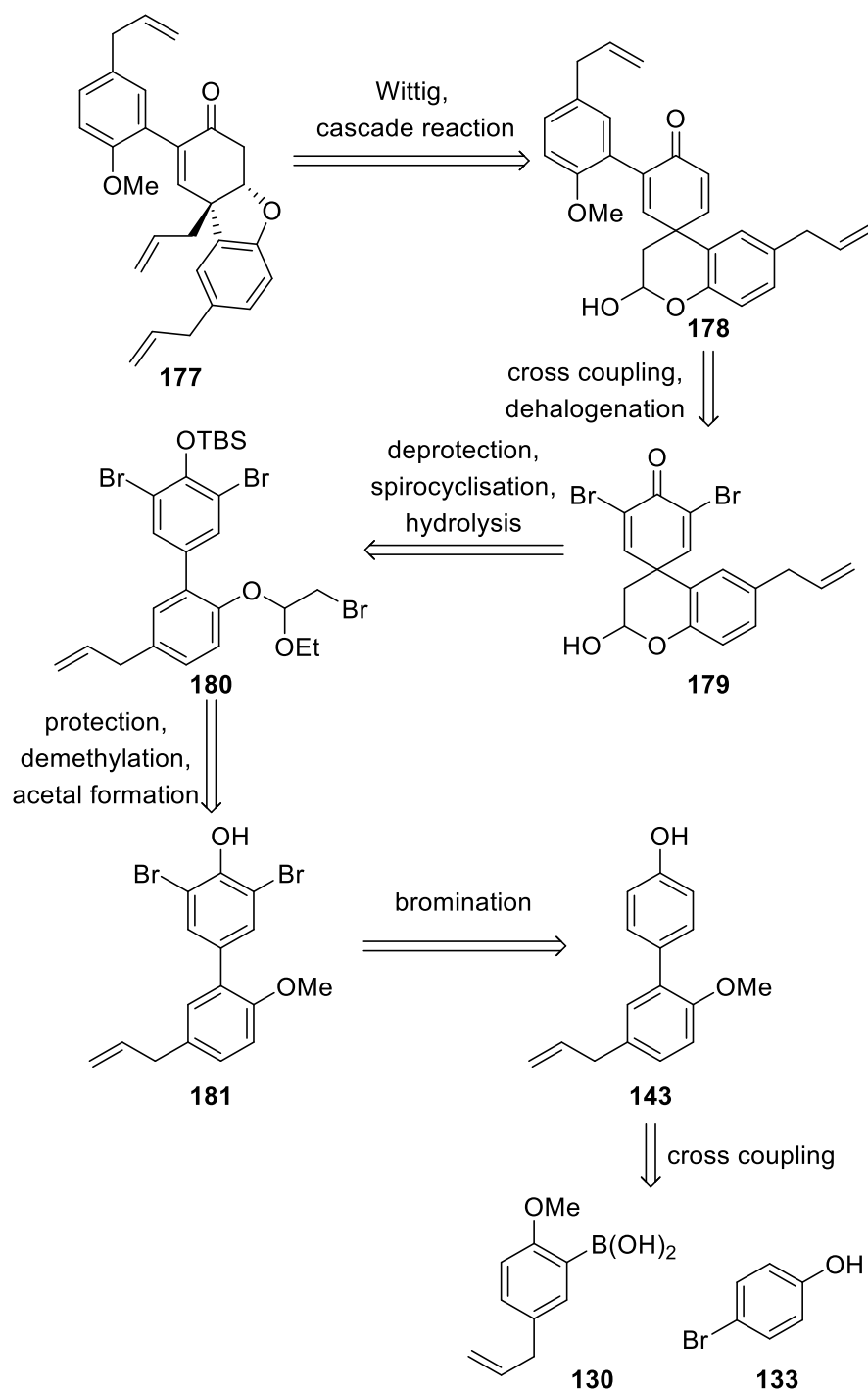
Model system	E_{rel} (Kcal mol ⁻¹)
174	0
175	5.29
169	6.05

Table 15. Relative energy at the B3LYP/B-31G* level of theory for the products resulting from the cascade reaction (model system).

However, if the kinetic product differed from the thermodynamic product it was hoped that manipulation of the reaction conditions could provide access to both products. Therefore, potentially providing a synthesis route to each of the natural products in the fargenin/fargenone family, *via* this cascade reaction approach.

4.2.1 The first synthesis strategy

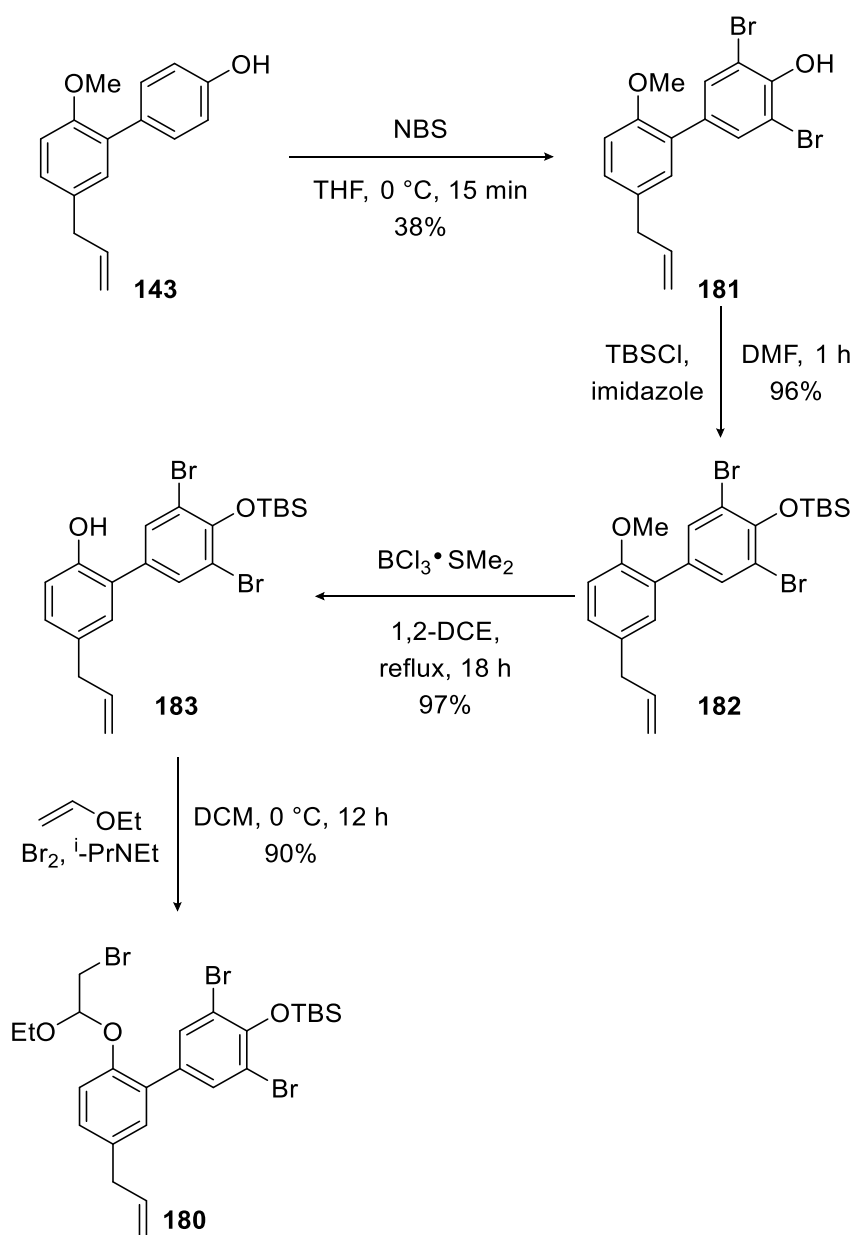
In order to design the first adapted route for the synthesis of the tricyclic core of the fargenin/fargenone family, a retrosynthetic analysis of the unnamed natural product **101** was undertaken (Scheme 56).



Scheme 56. Retrosynthetic analysis of the unnamed natural product **101**.

Scheme 56 illustrates that the addition of the third aryl moiety will be introduced *via* a second Suzuki-Miyaura cross coupling reaction. As was the case with the original synthesis, boronic acid **130** was selected as a suitable starting material, which can undergo cross coupling to generate biaryl **143**. At this stage the first alteration of the

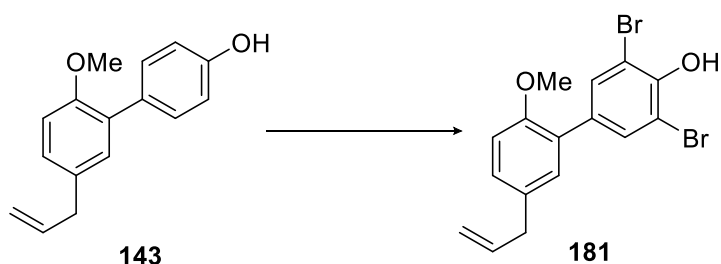
original synthesis leads to the introduction of a bromination reaction, generating a handle for later stage cross coupling. The synthesis then follows an identical path of protecting group manipulation, acetal formation and dearomatic spirocyclisation. Hemi-acetal **172** can then undergo the second Suzuki-Miyaura cross coupling reaction, followed by dehalogenation generating the key intermediate required for the crucial Wittig cascade reaction.



Scheme 57. Preliminary synthesis of unnamed natural product **101**.

Preliminary investigations previously carried out within the group⁸⁶ are shown in Scheme 57. The bromination of compound **143** using NBS in THF at 0 °C provided phenol **181** in 38% yield, with the subsequent silyl protection generating compound **182** in 96% yield. Once the TBS protecting group was in place, demethylation was carried out in 97% yield using BCl₃·SMe₂ and acetal formation provided compound **180** in 90% yield.

Examination of these preliminary results identified the bromination step as problematic, due to the low yield and reproducibility of the reaction. Introduction of a sodium thiosulfate quench led to improved reproducibility, through the prevention of unwanted side reactions, which had previously been occurring during solvent evaporation. The reaction conditions were more thoroughly investigated in the hope a set of optimised conditions could be identified; results are outlined in Table 16.



Reagents	Equiv.	Solvent	Temperature	Time	Yield
NBS	2	THF	0 °C	15 min	40%
NBS ^a , <i>i</i> -Pr ₂ NEt	2	MeCN	0 °C	1 h	-
NBS	2	THF	0 °C to r.t.	4 h	No product isolated ^b
NBS	2	THF	0 °C to r.t.	18 h	48%
NBS	2.5	THF	0 °C to r.t.	18 h	-
NBS	2	THF	0 °C to 30 °C	18 h	11%

^a NBS added *via* syringe pump over 1 h, ^b ¹H NMR shows **181** to be major component

Table 16. Optimisation study of the bromination reaction of compound **143**.

A second set of conditions, using NBS (addition *via* syringe pump), *i*-Pr₂NEt in MeCN were investigated. However, it was found the acetonitrile solution was highly

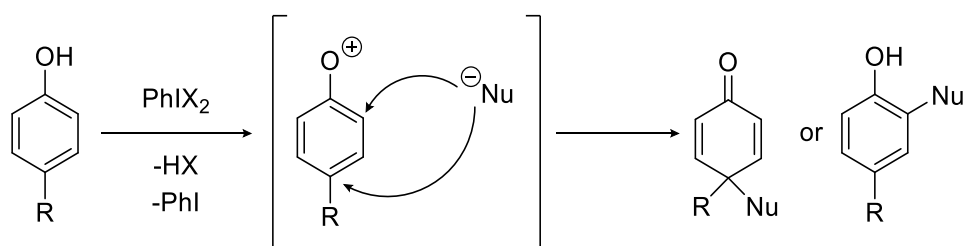
sensitive and decomposed in the syringe, ultimately generating a complex mixture of compounds. Due to the sensitive nature of the NBS solution, the THF conditions were revisited and increased reaction times were examined. It was found that increasing the reaction time to 18 h and allowing the reaction to warm to r.t., resulted in only a slight increase in yield. The temperature was then increased to 30 °C but this resulted in a reduced yield of 11%, as did an increase in the amount of NBS reagent, due increased by-product formation.

Examination of the reaction by ^1H NMR spectroscopy provided an insight into how the reaction mixture developed over time. A sample was taken from the reaction mixture after 1 h, quenched with $\text{Na}_2\text{S}_2\text{O}_3$ and extracted with DCM. Examination of the ^1H NMR spectrum showed a clean mixture of starting material and product. The reaction was then monitored after 4, 7.5 and 18 h, which demonstrated that the reaction mixture decomposed over time, leading to decomposition of both the starting material and product.

Due to the bromination of compound **143** appearing early within the proposed synthesis strategy and the problems associated with this step, it was decided that a new synthesis route was required, eliminating the need for early stage bromination.

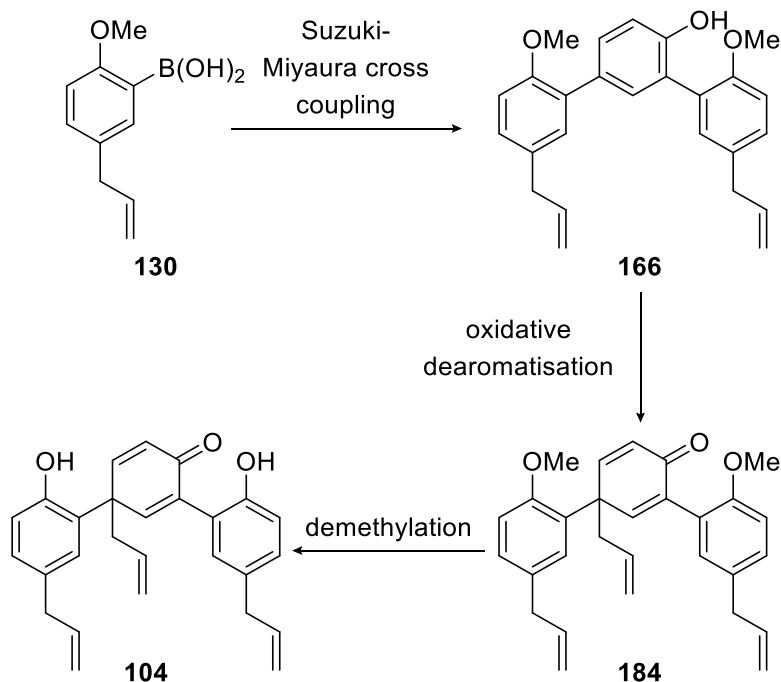
4.2.2 Synthesis route utilising an oxidative allylation strategy

In order to develop a new synthesis strategy we reviewed the literature and identified a possible route to the synthesis of dienone **104**, an intermediate in the proposed biosynthesis of the fargenin/fargenone family (Scheme 36, page 64). It was proposed that dienone **104** could be generated by an oxidative allylation reaction mediated by a hypervalent iodine oxidant (Scheme 58).⁸⁷



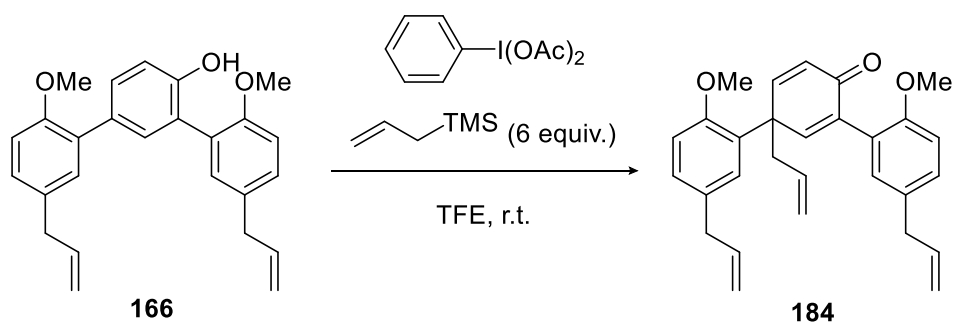
Scheme 58. Oxidative dearomatisation of phenols using hypervalent iodine oxidants.

The new synthesis route is outlined in Scheme 59. Utilising previously established conditions, devised during the macranthol synthesis, the formation of compound **166** can be achieved *via* a double Suzuki-Miyaura cross coupling reaction. It is then proposed that compound **166** can undergo an oxidative dearomatisation to give dienone **184** and following demethylation the key intermediate in the biosynthesis can be formed in 3 steps.



Scheme 59. Proposed synthesis of dienone **104**, the key intermediate of the biosynthesis.

The biosynthetic speculation suggests that upon demethylation of compound **184** there would be spontaneous oxy-Michael reactions leading to a mixture of compounds containing the core structures of the target natural products. Therefore, this synthesis route could lead to the intermediates required to access all of the natural products in the fargenin/fargenone family.



Scheme 60.

A range of conditions were surveyed in order to effect the key oxidative allylation reaction. Initial reactions were conducted using literature conditions, however, a mixture of products was observed and attempts to purify were unproductive. An optimisation study of the reaction was undertaken, modifying the reaction conditions through changes in hypervalent iodine oxidant ([Bis(trifluoroacetoxy)iodo]benzene), addition time of the reagents, solvent (MeCN, trifluoroethanol and hexafluoroisopropanol) and equivalents of the silane nucleophile. However, improvements on the initial results were not achieved.

After attempts to purify the crude reaction mixtures, obtained from reactions carried out during the optimisation study, proved unsuccessful, analysis of the ^1H NMR spectrum of the partially purified mixtures was carried out. This identified two distinct products within the mixtures, corresponding to peaks at 3.54 ppm and 2.74 ppm/2.38 ppm. The peaks observed, suggest that allylation occurred at the

unsubstituted *ortho* position, giving rise to compound **169**, in addition to either the substituted *ortho* or *para* position of compound **166**, generating compound **184/185** (Figure 11a).

The doublet at 3.54 ppm is characteristic of an allylic CH₂ connected to an aryl ring and correlates with data obtained from the macranthol synthesis for phenol **169**. Presence of the desired dienone structure would give rise to characteristic peaks, such as the ones identified at 2.74 ppm and 2.38 ppm. Each of these signals is split into a double doublet due to the diastereotopic nature of the CH₂ group next to the allylic double bond (Figure 11b).

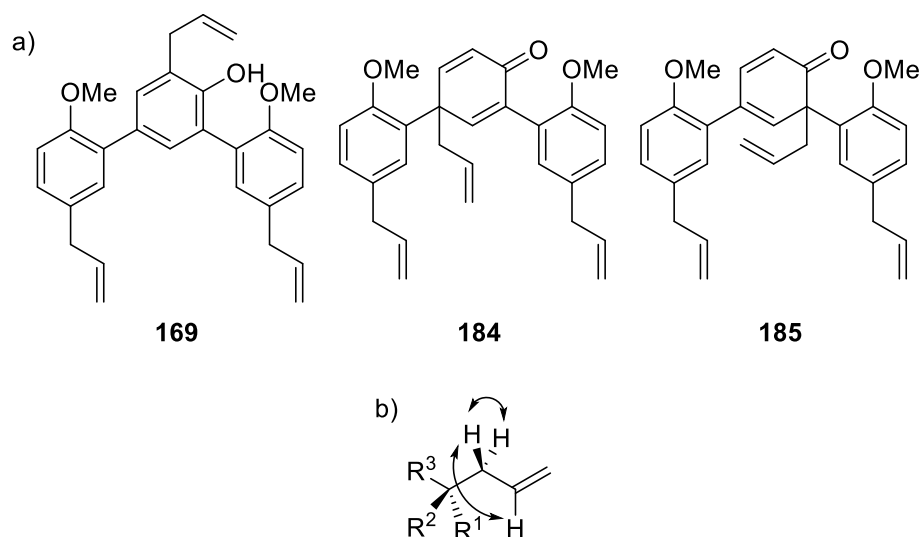


Figure 11. a) Potential compounds resulting from the oxidative dearomatisation reaction. b) Proton-proton interactions of the diastereotopic protons, resulting in a *dd* NMR signal.

A more extensive NMR study was completed to investigate the position of the allyl group within the molecule. This is because after oxidation of phenol **169**, there are two possible routes of attack that would produce structurally similar products with diastereotopic protons. This is through attack at either the substituted *ortho* or *para*

positions on the phenol ring as shown in Figure 12. Correlation NMR experiments suggested that the dienone component within the mixture, resulted from attack of the substituted *ortho* position. This conclusion was reached due to peaks observed in the HMBC spectrum, due to the coupling of the diastereotopic CH₂ and the dienone carbonyl.

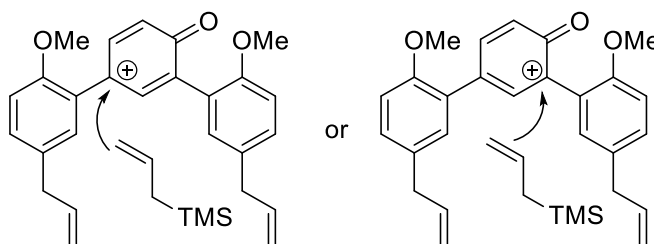


Figure 12. Possible routes of nucleophilic attack leading to a dienone structure.

After extensive attempts to optimise the reaction it was decided that this devised synthesis plan was not a feasible route to dienone **104**. Therefore a new method was required for the formation of dienone **104** from compound **169**.

4.2.3 Synthesis route utilising an organoaluminium promoted Claisen rearrangement

Following the failure of the oxidative dearomatisation strategy a new synthesis route was required for the formation of dienone **104**. Examination of the literature during the macranthol synthesis revealed examples of organoaluminium promoted Claisen rearrangements with unusual product formation, not observable in the standard thermal and Lewis acid induced rearrangements.⁸⁸ It has been demonstrated that extremely bulky oxophilic aluminium reagents, such as compound **186**, can successfully promote the rearrangement of an allylic group to the *para* position of a phenol ring.

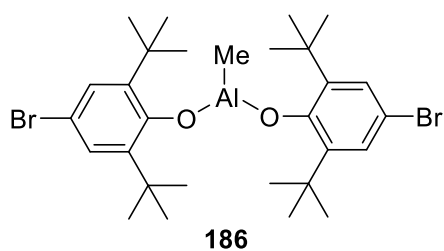
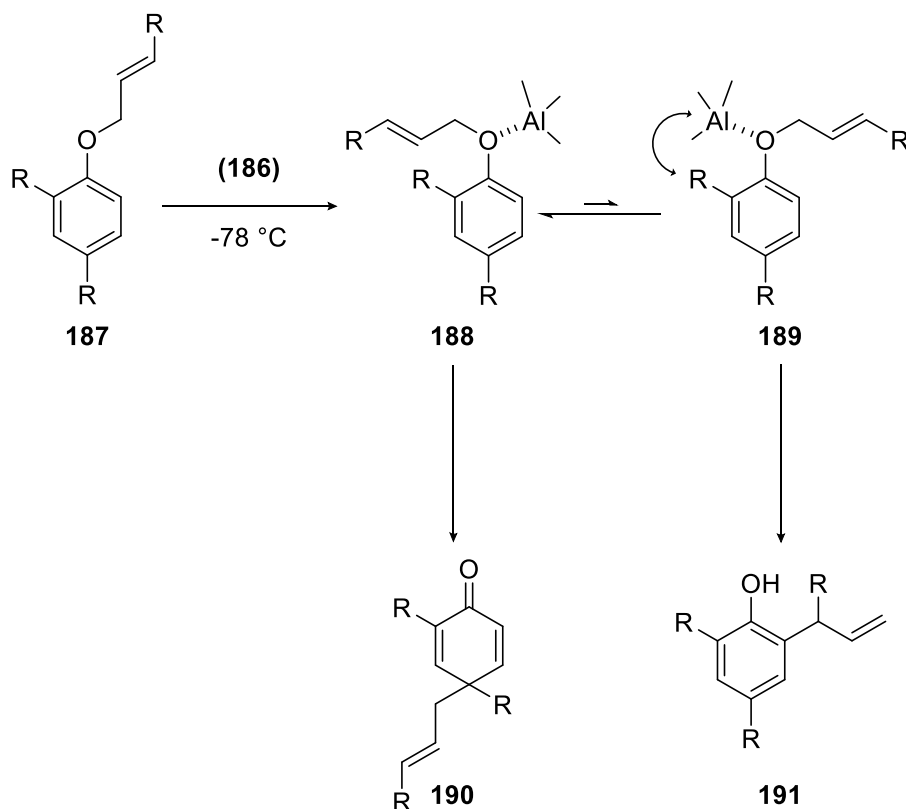


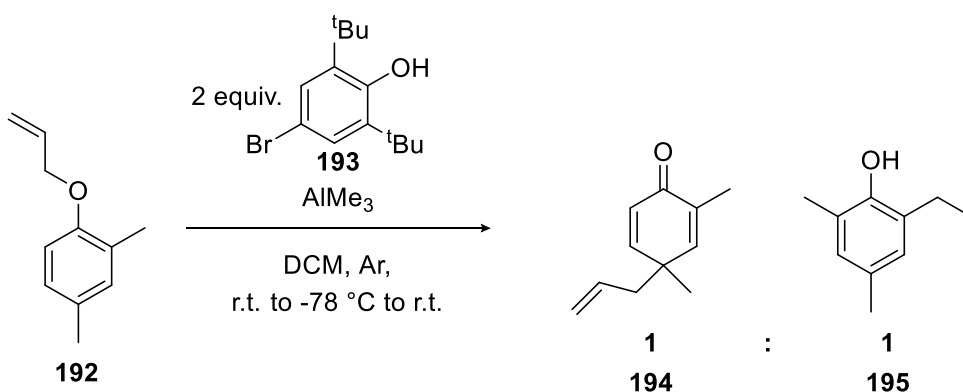
Figure 13. Methylaluminium bis(4-bromo-2,6-di-tert-butylphenoxide) **186**.

It is proposed that coordination of these bulky aluminium reagents to *ortho* substituted phenols leads to the formation of two sterically distinct species (Scheme 61). At $-78\text{ }^{\circ}\text{C}$, the equilibrium is shifted resulting in the formation of the least sterically demanding complex, which results in the allyl group being forced over the substituted *ortho* position (complex **188**). This provides access to the formation of compound **190**, as shown in Scheme 61.



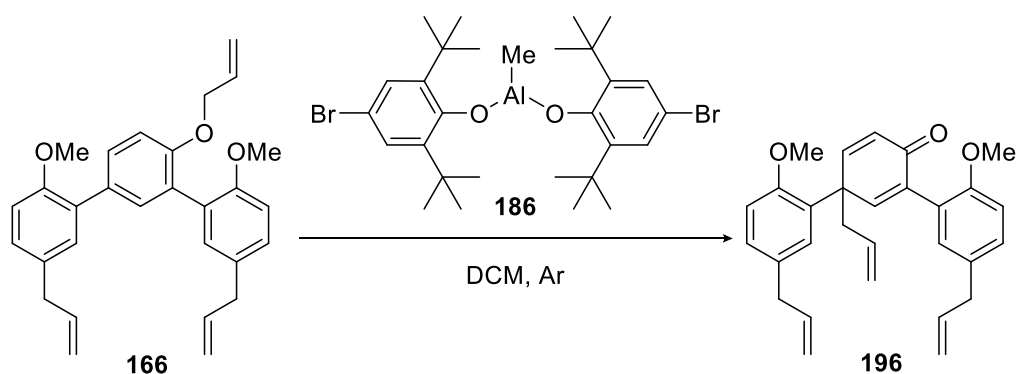
Scheme 61. Proposed reaction sequence leading to a regioselective Claisen rearrangement.

In order to investigate this transformation, a model system was studied using 2,6-dimethylphenol **192**, previously synthesised in the original paper⁸⁸ (Scheme 62). We examined the reaction using phenol **192** in order to better understand the reaction conditions and test the reaction in our hands through repetition of a previously studied example. A number of reactions were conducted but reproduction of the published results proved difficult, with only starting material identified in the crude ¹H NMR spectra. This suggested the reaction would not proceed at -78 °C and a higher temperature was required. Therefore the reaction was conducted at -78 °C and slowly warmed over a period of 5 h, resulting in the formation of a 1:1 mixture of the desired product and standard Claisen product (Scheme 62). This result was very similar to the result previously reported, where they obtained a 4:3 ratio.



Scheme 62. Preliminary results using a model system.

With this success, it was decided that the optimisation of the reaction conditions would be investigated on the actual system. This was because of a concern that conditions were substrate dependent and that by increasing the steric bulk in the *ortho* position, we would increase the selectivity. Our results are outlined in Table 17.



Catalyst formation time	Time	Temperature	Equiv. of 186	NMR Peaks ^a
15 min	8 h	-78 °C	2	Starting material 166
15 min	8 h	-20 °C	2	d at 3.55 ppm standard Claisen product 169
20 min	22 h	-20 °C	2.5	d at 3.55 ppm standard Claisen product 169

^a ¹H NMR referenced to d-chloroform

Table 17. Optimisation of the Claisen rearrangement promoted by organoaluminium reagent **186**.

At first the reaction was carried out at -78 °C, which did not result in product formation with ¹H NMR analysis of the crude reaction mixture only exhibiting starting material. The reaction temperature was raised to -20 °C, resulting in the formation of the undesired Claisen rearrangement product **169**. However, only trace amounts were identified, leading to investigation of the reaction time. Increasing the reaction time from 8 h to 22 h did not increase conversion of compound **166** and no desired dienone **196** was observed.

A major concern during the investigation was the actual identity of the Lewis acidic species, catalysing the Claisen rearrangement. As ineffective formation of the desired bulky aluminium reagent **186** would greatly influence the reaction outcome. With this in mind, compound **166** was submitted to reaction conditions using AlMe₃ as the Lewis acid. When 2 equivalents of AlMe₃ were used in DCM at -78 °C, no reaction

was observed, however, at r.t. complete deallylation of compound **159** occurred. This deallylation was concerning as numerous reactions carried out during the investigation of Lewis acid **186** resulted in deallylation.

Due to the concerns regarding the Lewis acidic species, examination of the formation of aluminium reagent **186** was investigated. The formation of Lewis acid **186** required the addition of AlMe_3 to 2 equivalents of phenol **193** in DCM at r.t.; this resulted in an observable colour change (yellow to colourless). This colour change suggests complete conversion of phenol **193**, and therefore formation of the desired Lewis acid **186**. However, for increased confidence, NMR analysis of the resultant solution was carried out. This illustrated that the peaks associated with the phenol had shifted and complete removal of the OH peak from the ^1H NMR spectrum had occurred, thus suggesting formation of the desired aluminium reagent was successful. Multiple reactions were carried out to test the reproducibility of the Lewis acid formation, which provided evidence to suggest this was problematic.

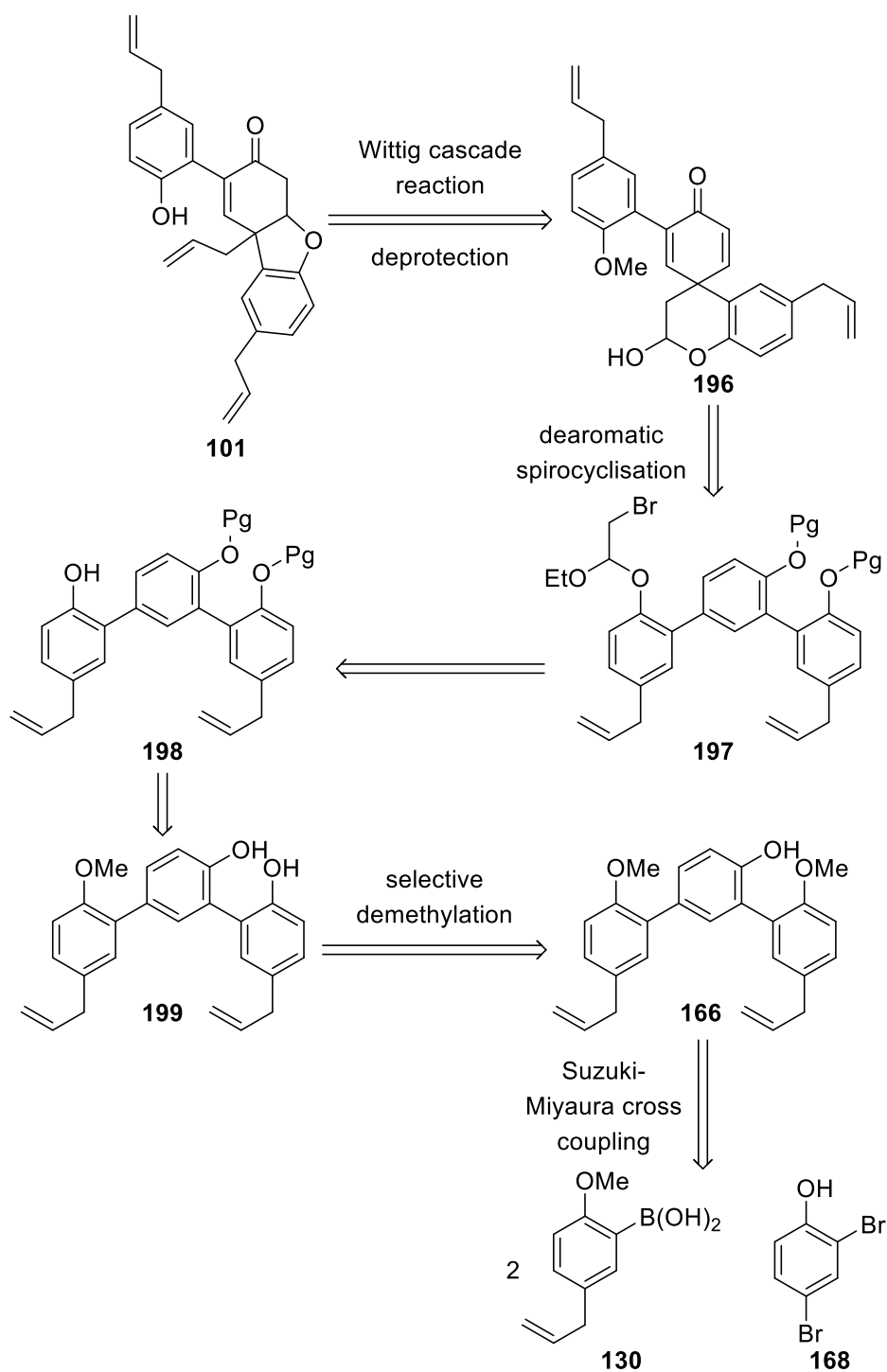
However, information obtained from the Lewis acid formation study and the early investigation of the reaction conditions proved difficult to interpret, due to the sensitive nature of Lewis acid **186**. As it was difficult to ascertain whether or not Lewis acid **186** was formed and for how long it survived under the reaction conditions. The major problem during the formation study occurred during the preparation of the NMR samples. As it was unclear whether the sample was destroyed due to contamination of the inert reaction atmosphere with air, when samples were taken for analysis, or that formation of Lewis acid **186** had been unsuccessful.

Therefore initial indications suggested that numerous problems were associated with the bulky Lewis acid mediated Claisen rearrangement and that optimisation and

product formation would require major investigation and could still prove unsuccessful. With this in mind, it was decided that this would not be a feasible synthesis route to the fargenin/fargenone family of natural products.

4.2.4 Double Suzuki-Miyaura cross-coupling strategy

Following the failure of the oxidative allylation and aluminium promoted Claisen rearrangement strategies, which targeted the synthesis of dienone **104** *via* a direct and short synthesis. It was decided that modification of the initial synthesis strategy (Scheme 56, page 95) should be investigated. This would require the removal of the problematic bromination step, which would be achieved through the introduction of a double Suzuki-Miyaura cross coupling reaction identical to that carried out during the total synthesis of macranthol **97**. The modified retrosynthetic analysis is outlined in Scheme 63, showing that after formation of compound **198**, the newly proposed synthesis would follow a near identical route to that shown in Scheme 57, page 96; however, no dehalogenation step would be required. Therefore the modified synthesis strategy would reduce the overall step count by two reactions.



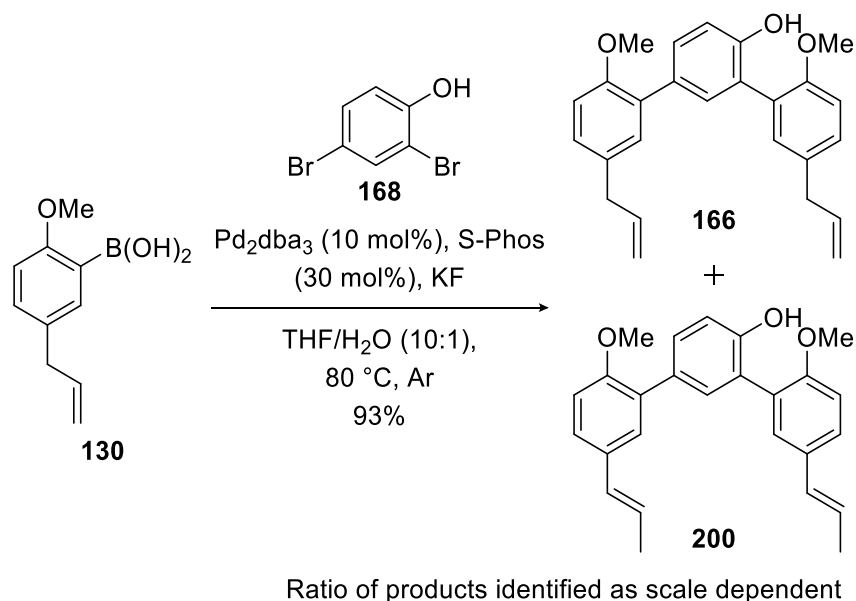
Scheme 63. Modified retrosynthetic analysis of the unnamed natural product **101**.

Originally, bromination was favoured over the double Suzuki-Miyaura cross coupling strategy; due to the fact compound **166** required the selective demethylation of very similar methylated phenol moieties. However, due to the observations made during the macranthol **97** synthesis, it became apparent that this could be successfully

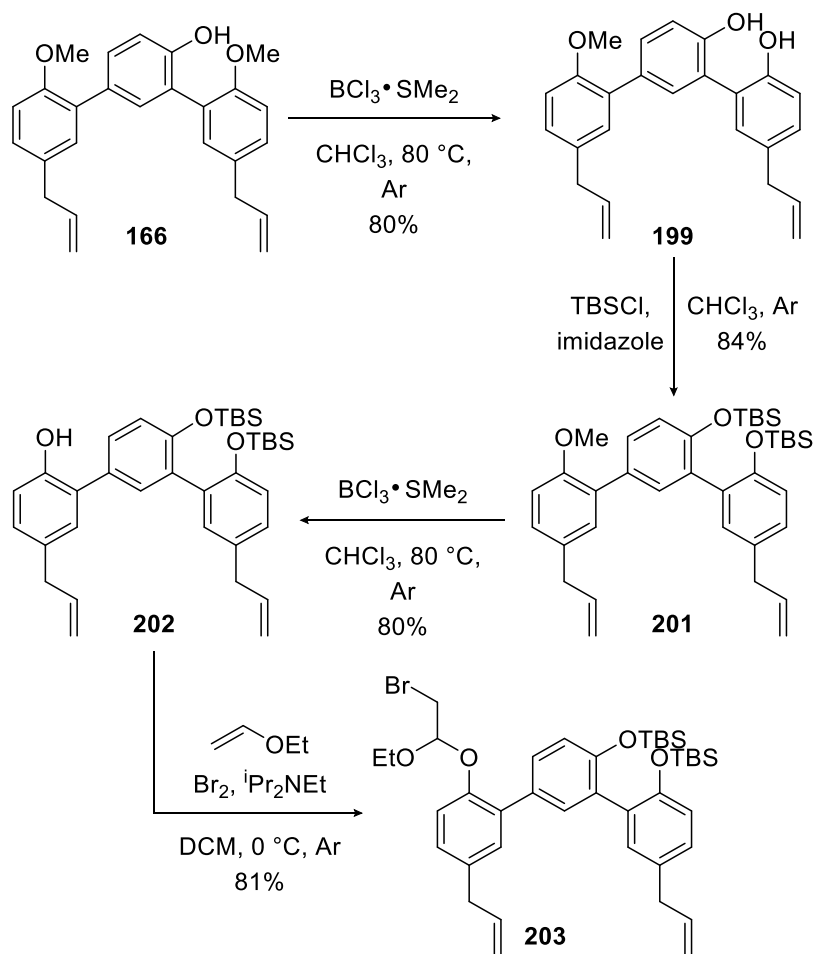
achieved in high yield. A proposed mechanistic pathway is depicted in Scheme 55, page 90.

The synthesis route began *via* a double Suzuki-Miyaura cross coupling reaction identical to that carried out in the macranthol **97** synthesis, providing a 93% yield of compound **166**. In spite of this high yield, the cross coupling reaction was identified as a problematic step. This was due to isomerisation of the sensitive allylic functionality and the generation of compound **200**. As previously discussed in the synthesis of macranthol **97** the additional *ortho* cross coupling led to trace amounts of isomerisation, however, it was now found that the isomerisation was scale dependent. Therefore, reactions conducted above a 0.8 mmol scale, resulted in a dramatic increase in the extent of isomerisation, which has not been fully explained.

The fact isomerisation was found to be scale dependent, reduced the overall efficiency of the synthesis route. In order to synthesise quantities large enough to carry through the synthesis route, the Suzuki-Miyaura cross coupling reaction was performed as a batch procedure, leading to many small scale reactions.



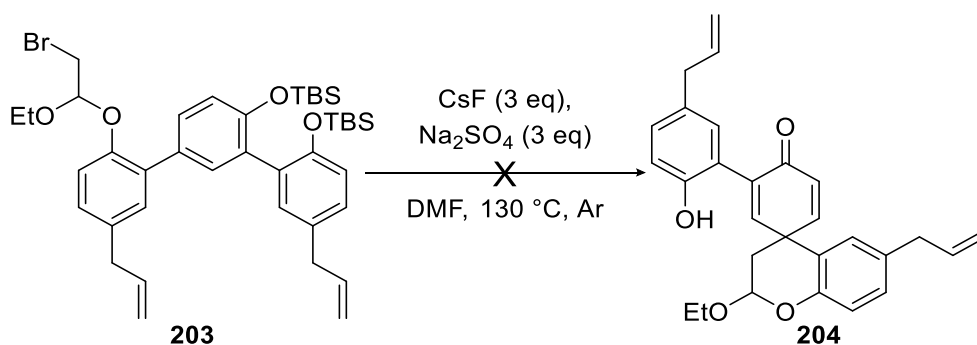
Scheme 64. Suzuki-Miyaura cross coupling reaction



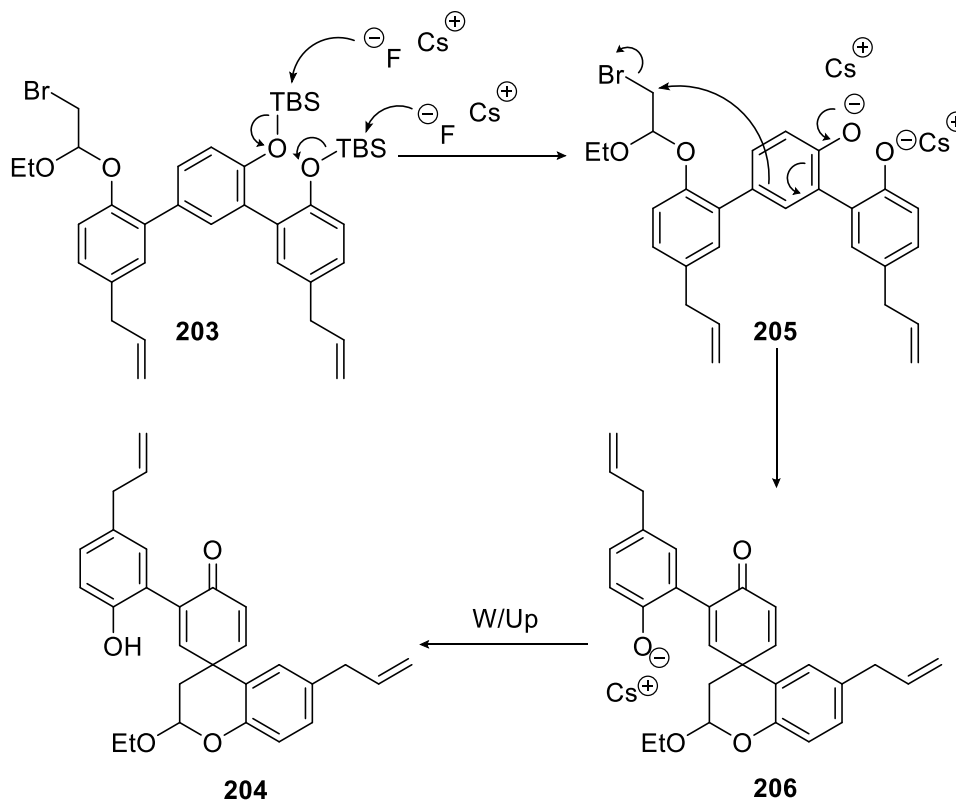
Scheme 41. Synthesis of acetal **203**, the intermediate required for the dearomatic spirocyclisation.

Compound **166** was then submitted to the selective demethylation conditions, which were 80 °C in chloroform; increased temperatures reduced the selectivity of the reaction. Protecting group manipulation, resulted in the TBS protection of diphenol **199** in 84% yield, followed by a second demethylation giving compound **202** in 80% yield. Bromo-acetalisation was then achieved using bromine and ethyl vinyl ether, generating the intermediate required for the dearomatic spirocyclisation. The first key step in the synthesis, introducing the protected allylic functionality, which will ultimately be unmasked by means of the Wittig cascade reaction.

With compound **203** in hand, dearomatic spirocyclisation was attempted using Magnus's reaction conditions,⁸³ previously applied in the original synthesis strategy for the tricyclic core.⁸² This required 3 equivalents of both sodium sulphate and cesium fluoride in DMF at 130 °C, however, in this case the reaction was not as straight forward as it was for the previous substrate, generating a complex mixture of compounds.



Scheme 66. Unsuccessful dearomatic spirocyclisation of compound **203**.



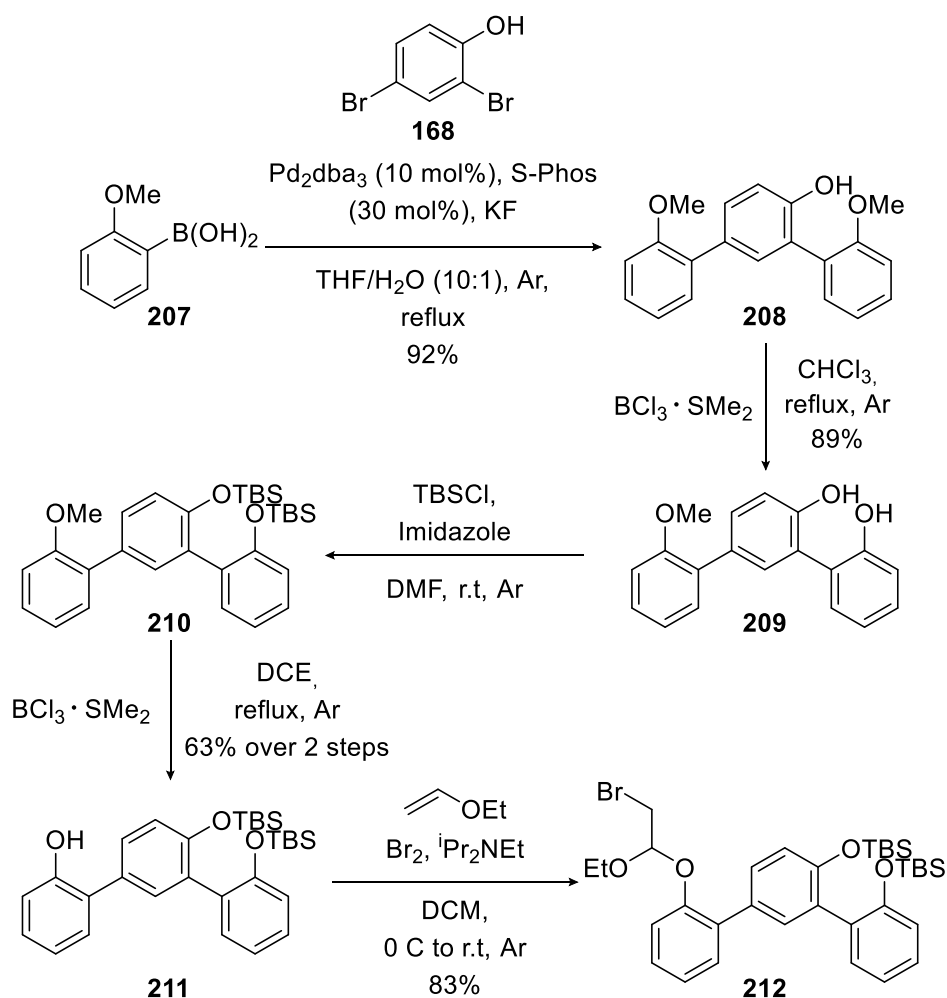
Scheme 67. Mechanism of the dearomatic spirocyclisation.

Under the reaction conditions, it was predicted that deprotection of the silylated phenols would occur, followed by spirocyclisation, as depicted in Scheme 67. However due to the presence of an additional silylated phenol, as opposed to compound **158** (substrate used during the original synthesis strategy for the tricyclic core), a number of unwanted side reactions resulted. These unwanted side reactions led to complex crude reaction mixtures, resulting in difficult to interpret ^1H NMR spectra. The ^1H NMR spectra were complicated further due to the introduction of the third aryl group (compared to compound **160**), as the desired product was now formed as a mixture of diastereoisomers, due to the desymmetrisation of the dienone ring.

This double deprotection was not unexpected, as both the silylated phenols are in very similar environments, however, it was anticipated that following the spirocyclisation, addition of the remaining phenolate to the newly formed dienone would arise. If this did in fact occur it was predicted that the addition would be reversible under certain conditions and therefore would not affect the overall synthesis route. However, this was not the case and after extensive chromatography and NMR analysis of the isolated compounds, only trace quantities of the desired compound were identified. The overall NMR analysis of the reaction proved difficult, due to the complex nature of the compounds in question; therefore an adequate understanding of the reaction and its products was not achieved. In order to better understand the results obtained, the synthesis was repeated without the allyl groups, in the hope of a clearer NMR picture of this key step. Removal of the allylic functionality also allowed large scale Suzuki-Miyaura cross coupling reactions, therefore, providing a quicker and more efficient synthesis of the required key intermediate.

4.2.5 Removal of the allyl groups

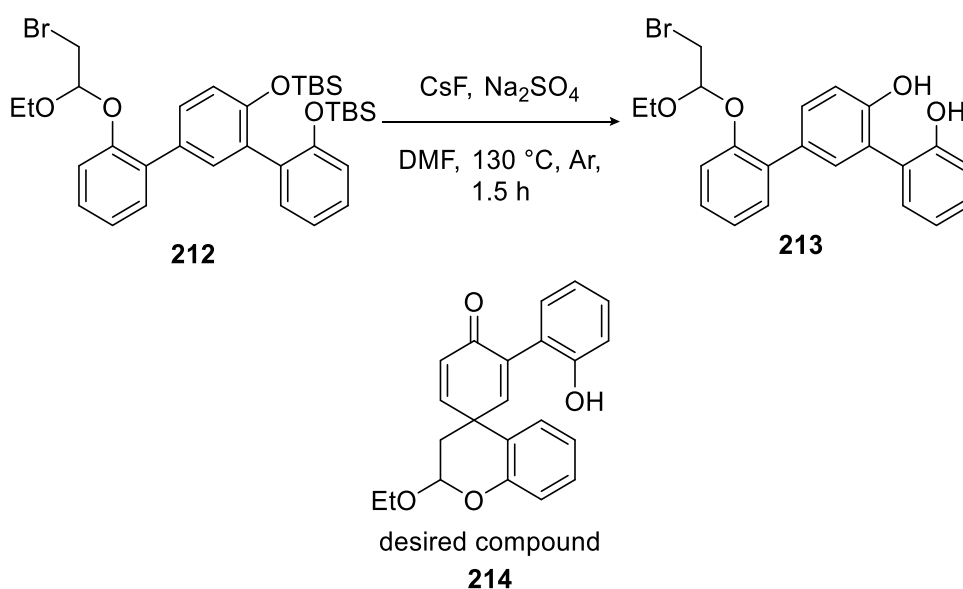
The synthetic route was identical to that designed for the synthesis of compound **196**, with all steps providing good yields (Scheme 68). This allowed the production of gram quantities of compound **212**, which was used in the investigation of the dearomatic spirocyclisation.



Scheme 68. Synthesis of compound **212**, intermediate required for the spirocyclisation investigation after removal of the allyl groups.

With compound **212** in hand, the investigation of the dearomatic spirocyclisation was investigated. In order to directly compare the behaviour of compounds **203** and

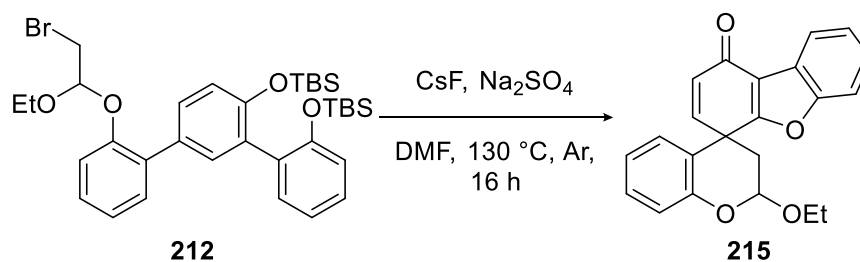
212, the newly formed compound was subjected to the conditions successfully employed during the first attempted synthesis of the tricyclic core. This required 3 equivalents of CsF and 1 equivalent of Na₂SO₄, reacted in anhydrous DMF at 130 °C for 1.5 h. As anticipated due to the results obtained when using compound **203**, the reaction was unsuccessful. However, ¹H NMR analysis of the crude reaction mixture revealed the main component of the complex mixture was diol **213**, generated *via* deprotection of the silylated phenols (Scheme 69).



Scheme 69. Initial conditions used for the dearomatic spirocyclisation only resulted deprotection and not desired compound **214**.

In order to convert compound **212** into desired product **214**, the reaction time was increased. This resulted in complete conversion of acetal **212**, however, a more complicated crude ¹H NMR spectra was obtained, which was attributed to the interference of the additional phenol moiety. It was proposed that dimerisation was one of the potential side reactions that could be occurring; therefore, the reaction was carried out at a lower concentration. However, this did not simplify the reaction mixture by ¹H NMR.

However, attempts to isolate the different components of the crude reaction mixture *via* column chromatography were carried out. This provided a number of fractions and from the analysis of the NMR spectra for each of these fractions, one component of the mixture was assigned as compound **215**.

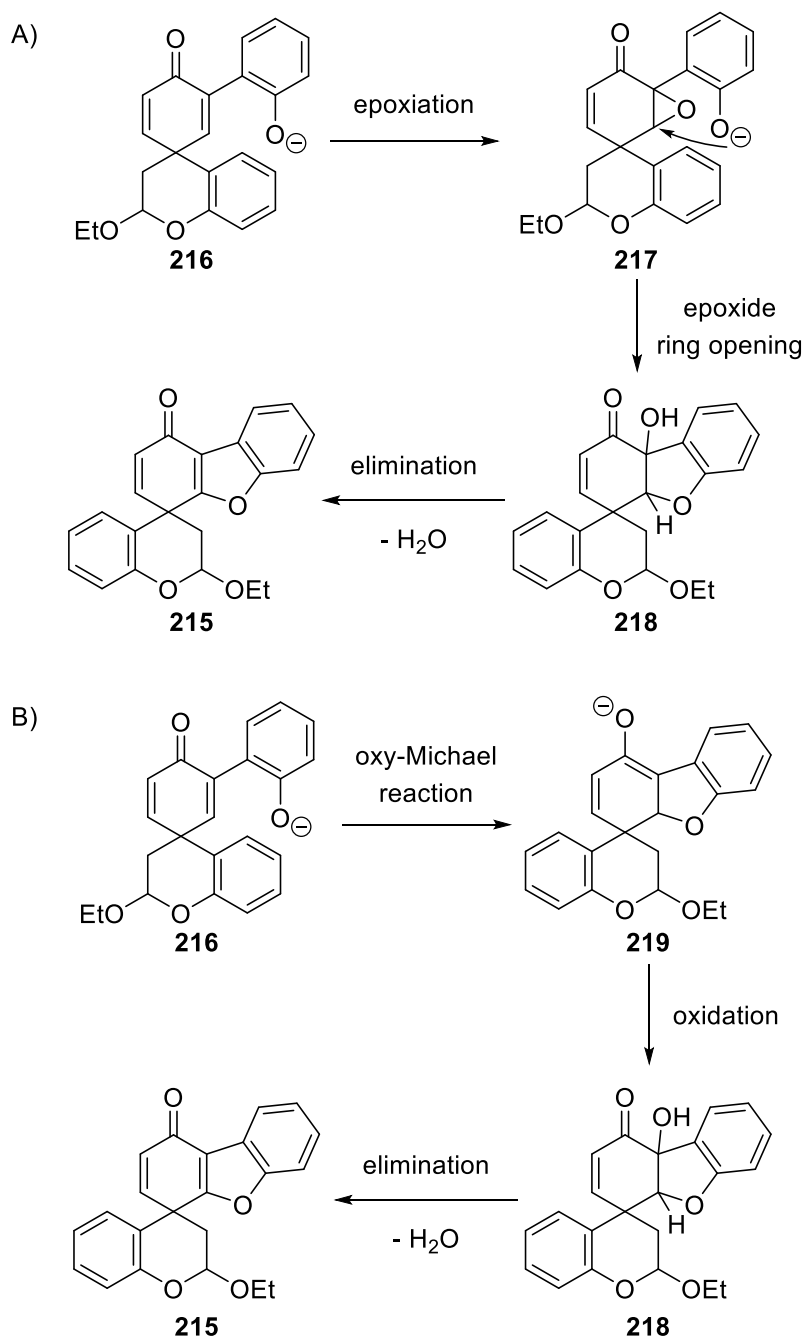


Scheme 70. Compound **215** was identified as a product of the dearomatic cyclisation reaction of compound **212**.

Compound **215** reveals that the desired reaction was carried out, generating a spirocyclic structure. However, the desired product underwent additional transformations ultimately resulting in the formation of a 5-membered ring. It was anticipated that the additional phenol moiety could undergo addition onto the dienone ring, forming a 5-membered ring similar to those contained in the fargenin/fargenone family of natural products. However, the 5-membered ring in product **215** has undergone additional transformations leading to regeneration of the dienone double bond. Two proposed synthesis pathways to product **215** are outlined in scheme 71.

In Scheme 71 A, it is proposed that following dearomatic spirocyclisation, compound **216** can undergo oxidation of the double bond closest to the phenol moiety, resulting in epoxidation. Epoxide ring opening would then give rise to a benzylic alcohol, which could eliminate H₂O to reform the dienone double bond. Alternatively, it is feasible that the additional phenol moiety undergoes an oxy-

Michael reaction onto the dienone ring generating enolate **219**. Oxidation of enolate **219**, would generate compound **218**, which could undergo elimination of H₂O to generate compound **215** (Scheme 71 B).



Scheme 71. Proposed synthesis pathways for the formation of compound **215**.

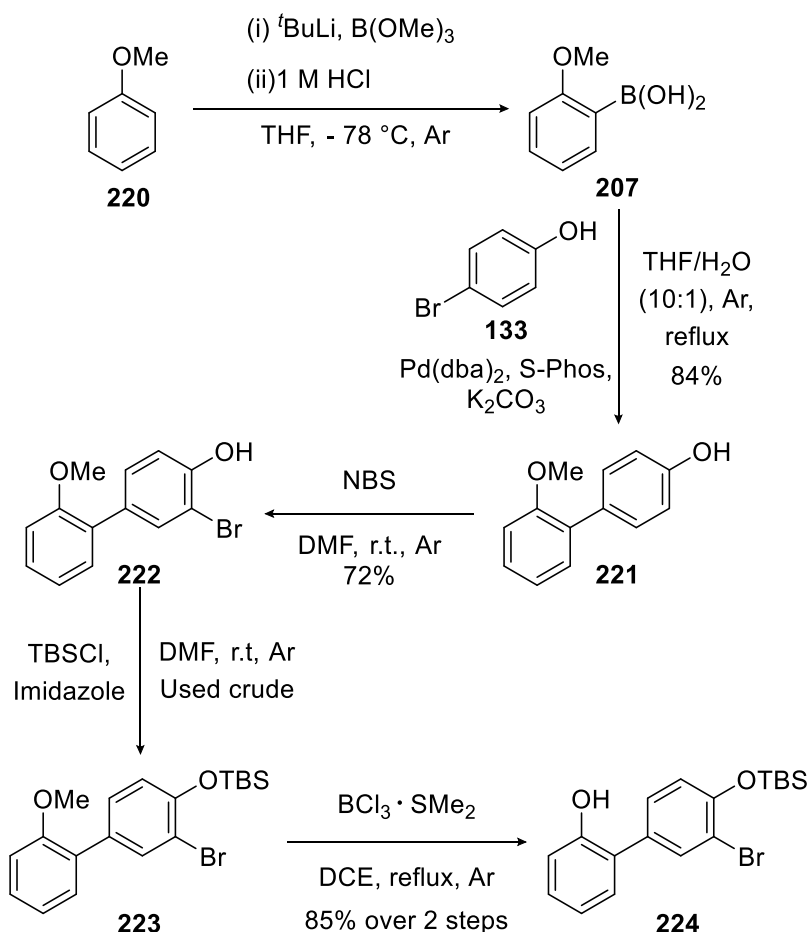
After conducting the investigation into the dearomatic spirocyclisation reaction and assigning the major product to be compound **215**, it was believed elimination of the unwanted side reactions, through removal of the interfering phenol moiety, would provide a more efficient synthesis route. Therefore, alterations to the synthesis route were required.

The major change to the synthesis route was the removal of the double Suzuki-Miyaura cross coupling reaction, opting for a stepwise addition of the aryl groups. A stepwise approach was favoured due to the problems encountered with protecting group manipulation.

In order to prevent the unwanted oxy-Michael reaction each of the phenol moieties required a different protecting group. In the above synthesis method the selective demethylation was brought about through utilisation of the free OH, but this resulted in the generation of diol **209**, which cannot be selectively reprotected. However, protection of phenol **208** would destroy the chemoselective nature of the demethylation step and ultimately prevent the above synthesis methods success. Therefore, stepwise aryl group incorporation provides a route to the selective functionalisation of each aryl group, either by addition of unique aryl groups or late stage addition of the third aryl moiety.

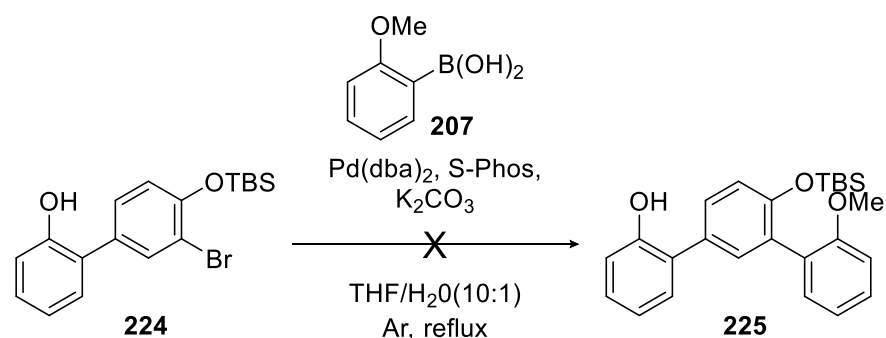
Our newly altered synthesis route is outlined in Scheme 72, demonstrating our desire to explore the possibility of the later stage addition of the third aryl moiety. The synthesis starts from commercially available anisole **220**, which is transformed into corresponding boronic acid **207** via *ortho* lithiation, before being subjected to Suzuki-Miyaura cross coupling conditions to generate biaryl **221**. Biaryl **221** is then selectively brominated *ortho* to the phenol in 72% yield in DMF, providing a handle for the second Suzuki-Miyaura cross coupling reaction. It is important to note that

this reaction was also attempted in THF, but was found to provide a mixture of compounds. Following bromination, protecting group manipulation gave phenol **224** in 85% yield over two steps.



Scheme 72. Synthesis of phenol **224**.

Following protecting group manipulation, the Suzuki-Miyaura cross coupling was attempted using boronic acid **207**, as this would give rise to a triaryl species with three unique phenol moieties. However, initial examination of the reaction suggested an extensive optimisation study would be required, in order to provide suitable conditions, due to the stability of the TBS silyl ether.

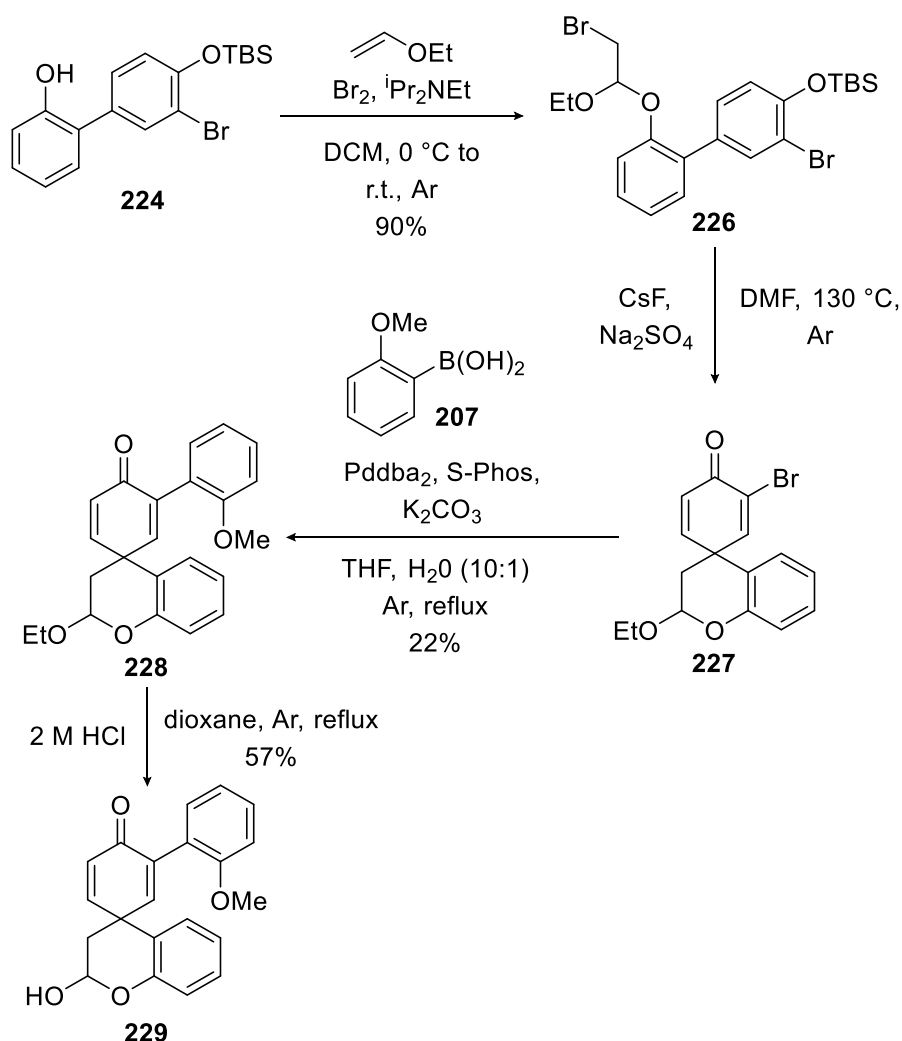


Scheme 73. Unsuccessful Suzuki-Miyaura cross coupling of boronic acid **207** and phenol **224**.

Due to the complications of the Suzuki-Miyaura cross coupling reaction it was decided that generation of the spirocyclic dienone would be carried out before incorporation of the third aryl group, therefore removing any possibility of interference from an additional phenol moiety. Following the spirocyclisation, the third aryl group would be introduced in order to provide the highest level of steric hindrance around the dienone carbonyl. It was proposed that the introduction of this steric hindrance before the Wittig cascade reaction would obstruct the unwanted attack of the carbonyl, previously generating compound **164** (Table 12, page 84).

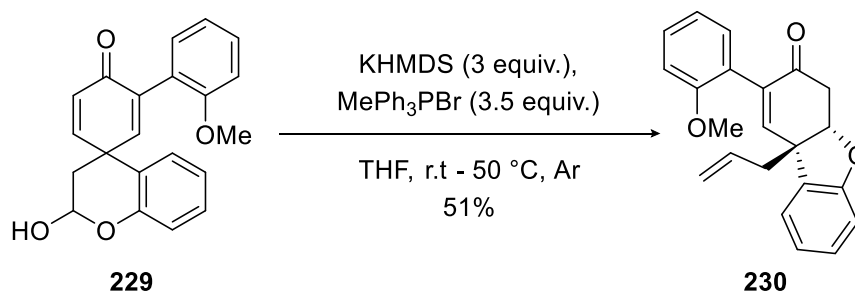
The bromo-acetalisation of phenol **224** was carried out under the previously established reaction conditions, generating acetal **226** in 90% yield. The spirocyclisation was then carried out. Analysis of the crude reaction mixture revealed that the desired spirocyclic dienone was formed with good conversion. However, it was detected that compound **227** readily decomposed; therefore, compound **227** was subjected to the Suzuki-Miyaura conditions without additional purification. Following the cross coupling step, compound **228** was isolated as a mixture of distereoisomers. Obtaining compound **228** as a mixture of distereoisomers was not problematic, as destruction of the acetal stereogenic centre occurs during the Wittig

cascade reaction. Hydrolysis was then performed on compound **228**, using 2 M HCl in dioxane generating hemi-acetal **229**.



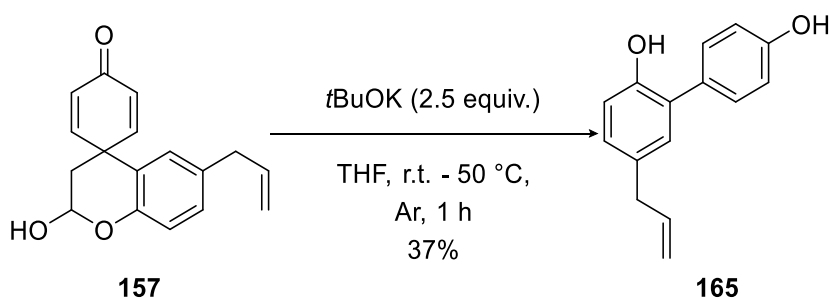
Scheme 74. Synthesis of Spirocyclic hemi-acetal **229**.

With hemi-acetal **229** in hand, the key step within the synthesis route could be investigated. As depicted in scheme 75, the hemi-acetal functionality can undergo a Wittig reaction due to the concealed aldehyde functionality of compound **229**. This is possible due to the ability of the hemi-acetal to open into an aldehyde, which can be observed in the ^1H NMR spectrum of hemi-acetal **229**, due to the existence of triplet signals between 9.50 – 10.00 ppm.



Scheme 75. Wittig cascade reaction.

Hemi-acetal **229** was subjected to the reaction conditions designed during the previous synthesis of the tricyclic core (Table 12, page 84). Therefore, hemi-acetal **229** was added to a THF solution of the phosphonium ylide, generated through the addition of 3 equivalents of KHMDs to 3.5 equivalents of methyltriphenylphosphonium bromide. In the previous investigation, it was found that an excess of the phosphonium salt was required due to an unwanted side reaction occurring when base remained in the reaction mixture upon substrate addition. This was illustrated by heating a solution of hemi-acetal **157** and potassium *tert*-butoxide in THF to 50 °C, which gave biaryl **165** in 37% yield (Scheme 76).⁸⁶



Scheme 76. Biaryl **165** formation resulting from basic reaction conditions.

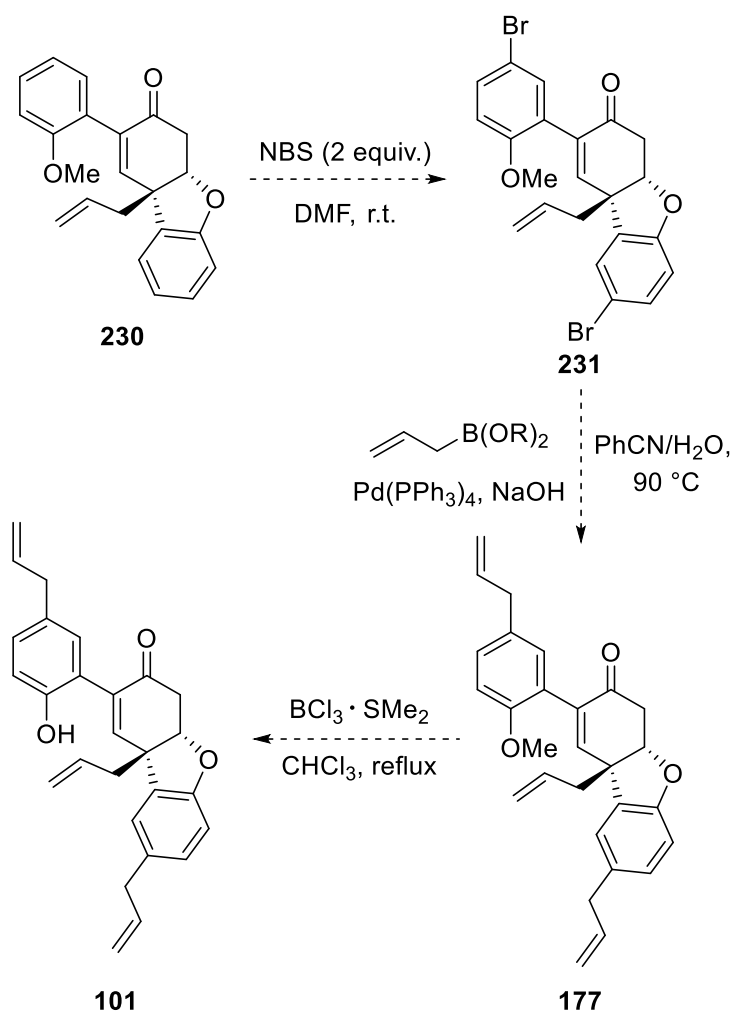
Under these reaction conditions our new substrate successfully underwent the Wittig cascade reaction, converting the hemi-acetal functionality into the desired allylic group and generating the desired ring system. After NMR analysis of the crude

reaction mixture, which showed the presence of a carbonyl moiety within the ^{13}C NMR spectrum, column purification generated compound **230** in a 51% yield.

Following examination of the NMR spectra it was observed that the cyclisation of the phenolate moiety, through oxy-Michael addition to the dienone, occurred on the opposite side to the third aryl group, as predicted by quantum chemical calculations (Table 15, page 94). Therefore, the addition of the third aryl ring to compound **157** prevented the unwanted Wittig reaction occurring on the dienone carbonyl, thus providing the first synthesis route to the core ring system of the fargenin/fargenone family of natural products.

4.3 Future work towards the synthesis of the fargenin/fargenone family of natural products

Following the successful synthesis of the core [4.3.0] ring structure of the fargenin/fargenone family (Scheme 75), the next step will be to complete the synthesis of the unnamed natural product within this family. This will be achieved through bromination of the *para* aryl positions, in order to provide a handle for the introduction of the required allylic functionality, followed by a final demethylation, as depicted in Scheme 77.



Scheme 77. Proposed synthesis route to the unnamed natural product **101** of the fargenin/fargenone family.

The required bromination will be achieved using the previously employed reaction conditions (NBS in DMF at r.t.). It is believed diallylation of compound **230** can be achieved through Suzuki-Miyaura cross coupling conditions, using Pd(PPh₃)₄ and allylboronic acid esters,⁸⁹ which have previously been applied in the synthesis of caryolanemagnolol and clovanemagnolol⁹⁰. Finally, the demethylation will be achieved using BCl₃·SMe₂ in chloroform, thus generating the unnamed natural product **101** in 13 steps.

5. Experimental

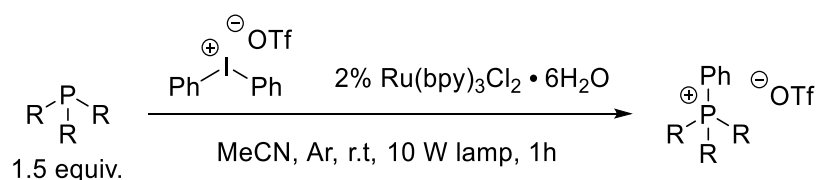
5.1 Chapter 1

5.1.1 General Experimental

All glassware was oven-dried (iodonium salt method) or flame dried (boronic acid method) and allowed to cool under a stream of nitrogen/argon before use. Cooling to $-40\text{ }^{\circ}\text{C}$ was effected using dry ice/acetonitrile mixtures. Degassing was achieved by purging nitrogen through the appropriate solution for 10 minutes. Commercial solvents and reagents were used as supplied with the following exceptions. Acetonitrile was dried over calcium hydride powder, distilled and stored over $4\text{ }\text{\AA}$ molecular sieves. Dichloromethane was dried over calcium hydride powder, distilled and stored over $4\text{ }\text{\AA}$ molecular sieves. Activation of $4\text{ }\text{\AA}$ molecular sieves was achieved by heating to $200\text{ }^{\circ}\text{C}$ under high vacuum. Reactions were monitored using TLC on Polygram[®] SIL G/UV254 0.25 mm silica gel pre-coated glass sheets with fluorescent indicator. Sheets were visualised using ultra-violet light (254 nm) and/or anisaldehyde or KMnO_4 solutions as appropriate. Flash chromatography was performed using Fluorochem silica gel 60, $35\text{--}70\text{ }\mu\text{m}$. Melting points were acquired on a Stuart[®] SMP3 melting point instrument. Infrared spectra were recorded on a Pelkin-Elmer 1600 FTIR instrument as a dilute solution in the indicated solvent. ^1H , ^{13}C , ^{31}P NMR spectra were recorded on either Bruker DPX 400, Bruker AV400, Bruker AV(III) 400 or Bruker DPX 300 instruments as dilute solutions in the indicated deuterated solvent. All chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent peaks. Coupling constants (J) are reported in Hertz (Hz). The multiplicity of a ^1H NMR signal is designated by one of the following abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad

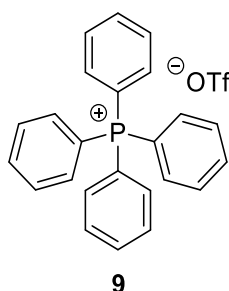
signal. Mass spectra were acquired on either VG Micromass 70E, VG Autospec or Micromass LCTOF instruments.

5.1.2 General method for the formation of phosphonium salts from diphenyliodonium triflates



To a solution of phosphine (0.239 mmol, 1.5 equiv.) in acetonitrile (1.60 mL) was added diphenyliodonium trifluoromethanesulfonate (68 mg, 0.159 mmol) and tris(bipyridine)ruthenium(II) dichloride hexahydrate (2-3 mg, 0.003-0.004 mmol (2 mol%)). The reaction mixture was irradiated using a 10 W lamp for 1 h. The solvent removed *in vacuo* and the crude mixture was purified by flash column chromatography (10% methanol in dichloromethane) followed by recrystallisation from dichloromethane and diethyl ether to give a phosphonium trifluoromethanesulfonate.

Tetraphenylphosphonium trifluoromethanesulfonate¹² **9**



Triphenylphosphine (63 mg, 0.239 mmol) was used to generate tetraphenylphosphonium trifluoromethanesulfonate as a white solid (65 mg, 85%).

Mp: 315 -317;

³¹P NMR (162 MHz, CDCl₃) δ: 23.2 (m, 1 P);

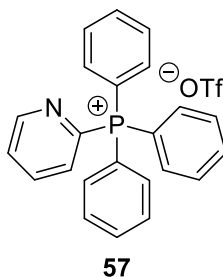
¹H NMR (400 MHz, CDCl₃) δ: 7.93 – 7.85 (4H, m, H_{Ar}), 7.80 – 7.72 (8H, m, H_{Ar}), 7.68 – 7.56 (8H, m, H_{Ar});

¹³C NMR (100 MHz, CDCl₃) δ: 135.9 (d, *J* = 3.0 Hz, C_{Ar}), 134.5 (d, *J* = 10.3 Hz, C_{Ar}), 130.9 (d, *J* = 13.0 Hz, C_{Ar}), 117.6 (d, *J* = 89.9 Hz, C_q);

HRMS (ESI⁺): *m/z* calculated for [C₂₄H₂₀P (M⁺)] calcd. 339.1297, found 339.1291;

IR ν_{max} (CHCl₃)/cm⁻¹: 3008, 1485, 1438, 1274, 1162, 1109, 1031, 998, 637.

Triphenyl(pyridin-2-yl)phosphonium trifluoromethanesulfonate⁵⁷ 57



Diphenyl(pyridin-2-yl)phosphine (63 mg, 0.239 mmol) was used to generate triphenyl(pyridin-2-yl)phosphonium trifluoromethanesulfonate as a solid (64 mg, 82%).

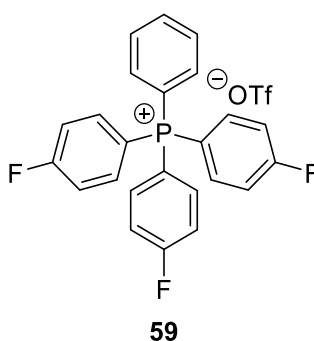
³¹P NMR (162 MHz, CD₃CN) δ: 23.2 (m, 1 P);

¹H NMR (400 MHz, CD₃CN) δ: 9.04 – 8.96 (1H, m, H_{Ar}), 8.07 (1H, tdd, *J* = 7.9, 5.3, 1.8 Hz, H_{Ar}), 7.95 – 7.88 (3H, m, H_{Ar}), 7.83 – 7.70 (14H, m, H_{Ar});

^{13}C NMR (100 MHz, CD_3CN) δ : 153.4 (d, $J = 19.9$ Hz, C_{Ar}), 145.8 (d, $J = 120.5$ Hz, C_{q}), 139.2 (d, $J = 10.7$ Hz, C_{Ar}), 136.5 (d, $J = 2.7$ Hz, C_{Ar}), 135.9 (d, $J = 10.3$ Hz, C_{Ar}), 133.2 (d, $J = 24.6$ Hz, C_{Ar}), 131.3 (d, $J = 13.0$ Hz, C_{Ar}), 129.4 (d, $J = 3.3$ Hz, C_{Ar}), 118.4 (d, $J = 89.1$ Hz, C_{q});

HRMS (ESI^+): m/z calculated for $[\text{C}_{23}\text{H}_{19}\text{NP}^+ (\text{M}^+)]$ calcd. 427.0625, found 427.0623.

Tris(4-fluorophenyl)(phenyl)phosphonium trifluoromethanesulfonate⁵⁷ 59



Tris(4-fluorophenyl)phosphine (76 mg, 0.239 mmol) was used to generate tris(4-fluorophenyl)(phenyl)phosphonium trifluoromethanesulfonate as a white solid (59 mg, 69%).

mp: 230-232 °C;

^{31}P NMR (162 MHz, CD_3CN) δ : 22.0 (m, 1 P);

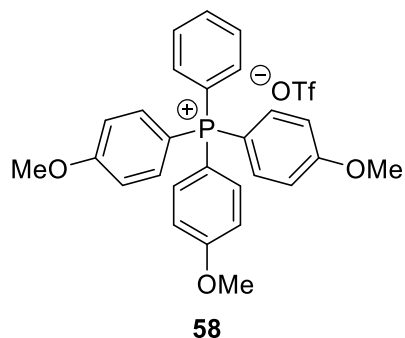
^1H NMR (400 MHz, CD_3CN) δ : 7.99 – 7.88 (1H, m, H_{Ar}), 7.83 – 7.62 (10H, m, H_{Ar}), 7.59 – 7.44 (6H, m, H_{Ar});

^{13}C NMR (100 MHz, CDCl_3) δ : 167.2 (dd, $J = 261.6, 3.3$ Hz, C_{q}), 137.5 (dd, $J = 12.3, 10.0$ Hz, C_{Ar}), 136.0 (d, $J = 3.0$ Hz, C_{Ar}), 134.4 (d, $J = 10.6$ Hz, C_{Ar}), 131.0 (d, $J = 13.1$ Hz, C_{Ar}), 118.8 (dd, $J = 22.5, 14.5$ Hz, C_{Ar}), 117.4 (d, $J = 90.9$ Hz, C_{q}), 113.2 (dd, $J = 94.6, 3.5$ Hz, C_{q});

HRMS (ESI⁺): *m/z* calculated for [C₂₄H₁₇F₃P (M⁺)] calcd. 393.1014, found 393.1013;

IR ν_{max} (CHCl₃)/cm⁻¹: 3011, 1593, 1501, 1272, 1252, 1165, 1110, 1031, 834, 637.

Tris(4-methoxyphenyl)(phenyl)phosphonium trifluoromethanesulfonate⁵⁷ **58**



Tris(4-methoxyphenyl)phosphine (84 mg, 0.239 mmol) was used to generate tris(4-methoxyphenyl)(phenyl)phosphonium trifluoromethanesulfonate as a brown oil (52 mg, 57%).

³¹P NMR (162 MHz, CDCl₃) δ : 21.2 (m, 1P);

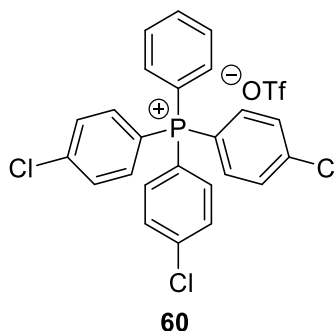
¹H NMR (400 MHz, CDCl₃) δ : 7.86 – 7.79 (1H, m, H_{Ar}), 7.74 – 7.66 (2H, m, H_{Ar}), 7.61 – 7.53 (2H, m, H_{Ar}), 7.52 – 7.44 (6H, m, H_{Ar}), 7.24 – 7.15 (6H, m, H_{Ar}), 3.93 (9H, s, CH₃);

¹³C NMR (100 MHz, CDCl₃) δ : 165.1 (d, *J* = 2.6 Hz, C_q), 136.2 (d, *J* = 11.9 Hz, C_{Ar}), 135.1 (d, *J* = 3.0 Hz, C_{Ar}), 134.0 (d, *J* = 10.3 Hz, C_{Ar}), 130.4 (d, *J* = 13.1 Hz, C_{Ar}), 119.9 (d, *J* = 91.0 Hz, C_q), 116.4 (d, *J* = 14.0 Hz, C_{Ar}), 108.3 (d, *J* = 98.1 Hz, C_q), 56.1 (s, CH₃);

HRMS (ESI⁺): *m/z* calculated for [C₂₇H₂₆O₃P⁺ (M⁺)] calcd. 429.1614, found 429.1614;

IR ν_{max} (CHCl₃)/cm⁻¹: 3011, 1595, 1568, 1504, 1440, 1299, 1186, 1113, 1030, 834, 637.

Tris(4-chlorophenyl)(phenyl)phosphonium trifluoromethanesulfonate⁵⁷ 60



Tris(4-chlorophenyl)phosphine (87 mg, 0.239 mmol) was used to generate tris(4-chlorophenyl)(phenyl)phosphonium trifluoromethanesulfonate as an off-white solid (48 mg, 51%).

mp: 244 – 246 °C;

³¹P NMR (162 MHz, CDCl₃) δ: 22.8 (m, 1 P);

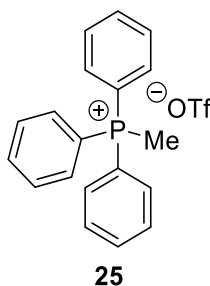
¹H NMR (400 MHz, CDCl₃) δ: 7.99 – 7.90 (1H, m, H_{Ar}), 7.84 – 7.58 (16H, m, H_{Ar});

¹³C NMR (100 MHz, CDCl₃) δ: 143.5 (d, *J* = 3.7 Hz, C_q), 136.3 (d, *J* = 3.1 Hz, C_{Ar}), 135.9 (d, *J* = 11.3 Hz, C_{Ar}), 134.5 (d, *J* = 10.4 Hz, C_{Ar}), 131.5 (d, *J* = 13.8 Hz, C_{Ar}), 131.2 (d, *J* = 13.2 Hz, C_{Ar}), 116.7 (d, *J* = 90.7 Hz, C_q), 115.5 (d, *J* = 92.9 Hz, C_q);

HRMS (ESI⁺): *m/z* calculated for [C₂₄H₁₇Cl₃P (M⁺)] calcd. 441.0128, found 441.0133;

IR ν_{max} (CHCl₃)/cm⁻¹: 3069, 3048, 3009, 1579, 1483, 1439, 1394, 1271, 1163, 1088, 1030, 1013, 823, 637.

Tris(phenyl)methylphosphonium triflate¹² 25



Diphenylmethylphosphine (44 μ L, 0.239 mmol) was used to generate tri(phenyl)methylphosphonium triflate as an amorphous solid (50 mg, 74%).

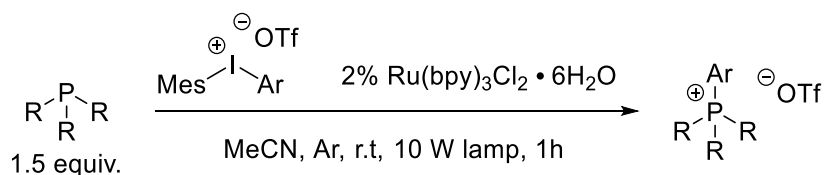
³¹P NMR (162 MHz, CDCl₃) δ : 22.5 (m, 1 P);

¹H NMR (400 MHz, CDCl₃) δ : 7.84 – 7.75 (3H, m, H_{Ar}), 7.73 – 7.59 (12H, m, H_{Ar}), 2.92 (3H, d, $J = 13.4$ Hz, H_{Ar});

¹³C NMR (100 MHz, CD₃CN) δ : 135.1 (d, $J = 3.0$ Hz, C_{Ar}), 133.3 (d, $J = 10.3$ Hz, C_{Ar}), 130.2 (d, $J = 12.7$ Hz, C_{Ar}), 119.4 (d, $J = 88.9$ Hz, C_q), 8.3 (d, $J = 58.4$ Hz, CH₃);

HRMS (ESI⁺): m/z calculated for [C₁₉H₁₈P⁺ (M⁺)] calcd. 277.1141, found 277.1125.

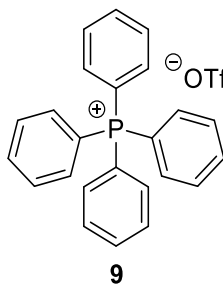
5.1.3 General method for the formation of phosphonium salts *via* (mesityl)aryliodonium triflates



To a solution of phosphine (0.239 mmol, 1.5 equiv.) in acetonitrile (1.60 mL) was added (mesityl)aryliodonium trifluoromethanesulfonate (0.159 mmol, 1 equiv.) and tris(bipyridine)ruthenium(II) dichloride hexahydrate (2-3 mg, 0.003-0.004 mmol, 2 mol%). The reaction mixture was irradiated using a 10 W lamp for 1 h. The solvent

removed *in vacuo* and the crude mixture was purified by flash column chromatography (10% methanol in dichloromethane) followed by recrystallisation from dichloromethane and diethyl ether to give a phosphonium trifluoromethanesulfonate.

Tetraphenylphosphonium trifluoromethanesulfonate⁵⁷ 9



Triphenylphosphine (63 mg, 0.239 mmol) and phenyl(mesityl)iodonium trifluoromethanesulfonate (75 mg, 0.159 mmol) were used to generate tetraphenylphosphonium trifluoromethanesulfonate as a white solid (45 mg, 58%).

³¹P NMR (162 MHz, CDCl₃) δ: 23.2 (m, 1 P);

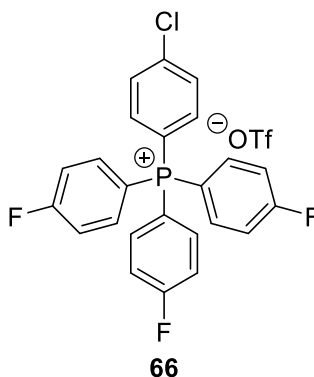
¹H NMR (400 MHz, CDCl₃) δ: 7.95 – 7.88 (4H, m, H_{Ar}), 7.83 – 7.75 (8H, m, H_{Ar}), 7.68 – 7.59 (8H, m, H_{Ar});

¹³C NMR (100 MHz, CDCl₃) δ: 135.9 (d, *J* = 3.1 Hz, C_{Ar}), 134.5 (d, *J* = 10.3 Hz, C_{Ar}), 130.9 (d, *J* = 12.7 Hz, C_{Ar}), 117.6 (d, *J* = 89.8 Hz, C_q);

HRMS (ESI⁺): *m/z* calculated for [C₂₄H₂₀P (M⁺)] calcd. 339.1297, found 339.1293;

IR ν_{max} (CHCl₃)/cm⁻¹: 3011, 1588, 1485, 1439, 1274, 1161, 1109, 1031, 998.

(4-chlorophenyl)tris(4-fluorophenyl)phosphonium trifluoromethanesulfonate⁵⁷ 66



Tris(4-fluorophenyl) phosphine (76 mg, 0.239 mmol) and (4-chlorophenyl)(mesityl)iodonium trifluoromethanesulfonate (81 mg, 0.159 mmol) were used to generate (4-chlorophenyl)tris(4-fluorophenyl)phosphonium trifluoromethanesulfonate as an off-white solid (65 mg, 71%).

mp: 229 – 230 °C,

³¹P NMR (162 MHz, CD₃CN) δ: 22.0 (m, 1 P);

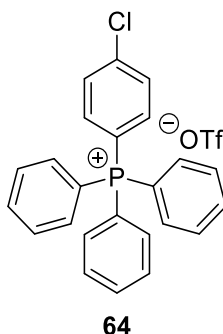
¹H NMR (400 MHz, CD₃CN) δ: 7.76 – 7.65 (8H, m, H_{Ar}), 7.64 – 7.56 (2H, m, H_{Ar}), 7.50 – 7.41 (6H, m, H_{Ar});

¹³C NMR (100 MHz, CDCl₃) δ: 167.3 (dd, *J* = 262.2, 3.4 Hz, C_q), 143.4 (d, *J* = 3.6 Hz, C_q), 137.6 (dd, *J* = 12.4, 9.9 Hz, C_{Ar}), 135.8 (d, *J* = 11.6 Hz, C_{Ar}), 131.5 (d, *J* = 13.8 Hz, C_{Ar}), 119.0 (dd, *J* = 22.4, 14.6 Hz, C_{Ar}), 116.0 (d, *J* = 93.4 Hz, C_q), 112.9 (dd, *J* = 95.2, 3.4 Hz, C_q);

HMRS (ESI⁺): *m/z* calculated for C₂₄H₁₆ClF₃P [M⁺] calcd. 427.0625, found 427.0647.

IR ν_{max} (CHCl₃)/cm⁻¹: 3011, 1593, 1500, 1402, 1253, 1165, 1110, 1031, 834, 638.

(4-chlorophenyl)triphenylphosphonium trifluoromethanesulfonate⁵⁷ 64



Triphenylphosphine (63 mg, 0.239 mmol) and (4-chlorophenyl)(mesityl)iodonium trifluoromethanesulfonate (81 mg, 0.159 mmol) were used to generate (4-chlorophenyl)triphenylphosphonium trifluoromethanesulfonate as an off-white solid (54 mg, 65%).

³¹P NMR (162 MHz, CDCl₃) δ: 23.0 (m, 1P);

¹H NMR (400 MHz, CDCl₃) δ: 7.91 - 7.88 (3H, m, H_{Ar}), 7.80 – 7.72 (8H, m, H_{Ar}), 7.65 - 7.59 (8H, m, H_{Ar});

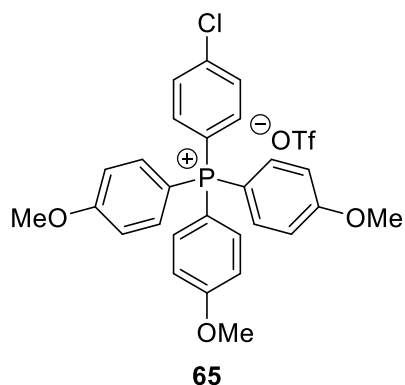
¹³C NMR (100 MHz, CDCl₃) δ: 143.1 (d, *J* = 3.7 Hz, C_q), 136.0 (d, *J* = 3.0 Hz, C_{Ar}), 135.9 (d, *J* = 11.2 Hz, C_{Ar}), 134.5 (d, *J* = 10.5 Hz, C_{Ar}), 131.3 (d, *J* = 13.4 Hz, C_{Ar}), 131.0 (d, *J* = 13.1 Hz, C_{Ar}), 117.2 (d, *J* = 89.8 Hz, C_q), 116.2 (d, *J* = 92.1 Hz, C_q);

HRMS (ESI⁺): *m/z* calculated for [C₂₄H₁₉ClP (M⁺)] calcd. 339.1297, found 339.1293;

IR ν_{max} (CHCl₃)/cm⁻¹: 3053, 3008, 1581, 1484, 1440, 1393, 1273, 1162, 1110, 1090, 1030, 824, 637.

(4-chlorophenyl)tris(4-methoxyphenyl)phosphonium trifluoromethanesulfonate⁵⁷

65



Tris(4-methoxyphenyl)phosphine (84 mg, 0.239 mmol) and (4-chlorophenyl)(mesityl)iodonium trifluoromethanesulfonate (81 mg, 0.159 mmol) were used to generate (4-chlorophenyl)tris(4-methoxyphenyl)phosphonium trifluoromethanesulfonate as a brown oil (53 mg, 55%).

³¹P NMR (162 MHz, CDCl₃) δ: 21.0 (m, 1P);

¹H NMR (400 MHz, CDCl₃) δ: 7.67 (dd, *J* = 8.5, 2.7 Hz, 2H, H_{Ar}), 7.58 – 7.44 (6H, m, H_{Ar}), 7.21 (6H, dd, *J* = 8.8, 2.8 Hz, H_{Ar}), 3.94 (9H, s, CH₃);

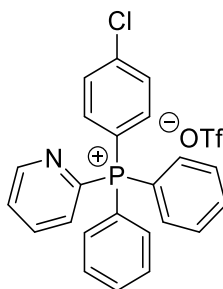
¹³C NMR (100 MHz, CDCl₃) δ: 165.2 (d, *J* = 3.1 Hz, C_q), 142.3 (d, *J* = 3.6 Hz, C_q), 136.2 (d, *J* = 12.1 Hz, C_{Ar}), 135.4 (d, *J* = 11.3 Hz, C_{Ar}), 130.8 (d, *J* = 13.6 Hz, C_{Ar}), 118.5 (d, *J* = 93.1 Hz, C_q), 116.5 (d, *J* = 14.1 Hz, C_{Ar}), 107.8 (d, *J* = 98.6 Hz, C_q), 56.1 (s, CH₃);

HMRS (ESI⁺): *m/z* calculated for [C₂₇H₂₅ClO₃P⁺ (M⁺)] calcd. 463.1224, found 463.1253;

IR ν_{max} (CHCl₃)/cm⁻¹: 3011, 1595, 1568, 1270, 1185, 1113, 1030, 9909, 834, 637.

(4-chlorophenyl)diphenyl(pyridin-2-yl)phosphonium trifluoromethanesulfonate⁵⁷

67



67

Diphenyl(pyridine-2-yl)phosphine (63 mg, 0.239 mmol) and (4-chlorophenyl)(mesityl)iodonium trifluoromethanesulfonate (81 mg, 0.159 mmol) were used to generate (4-chlorophenyl)diphenyl(pyridin-2-yl)phosphonium trifluoromethanesulfonate as a brown oil (52 mg, 63%).

³¹P NMR (162 MHz, CDCl₃) δ: 14.8 (m, 1P);

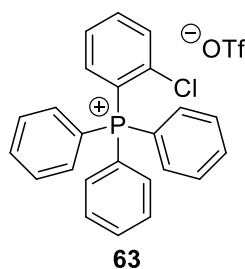
¹H NMR (400 MHz, CDCl₃) δ: 9.01 – 8.95 (1H, m, H_{Ar}), 8.25 – 8.12 (1H, m, H_{Ar}), 7.95 – 7.85 (3H, m, H_{Ar}), 7.81 – 7.61 (13H, m, H_{Ar});

¹³C NMR (100 MHz, CDCl₃) δ: 152.5 (d, *J* = 19.8 Hz, C_{Ar}), 144.3 (d, *J* = 120.8 Hz, C_q), 143.1 (d, *J* = 3.7 Hz, C_q), 139.2 (d, *J* = 10.8 Hz, C_{Ar}), 136.2 (d, *J* = 11.0 Hz, C_{Ar}), 136.0 (d, *J* = 3.1 Hz, C_{Ar}), 134.8 (d, *J* = 10.2 Hz, C_{Ar}), 132.7 (d, *J* = 24.9 Hz, C_{Ar}), 131.1 (d, *J* = 13.9 Hz, C_{Ar}), 130.8 (d, *J* = 13.0 Hz, C_{Ar}), 128.7 (d, *J* = 3.6 Hz, C_{Ar}), 116.9 (d, *J* = 89.2 Hz, C_q), 115.9 (d, *J* = 91.8 Hz, C_q);

HRMS (ESI⁺): *m/z* calculated for [C₂₃H₁₈ClNP⁺ (M⁺)] calcd. 374.0860, found 374.0856;

IR ν_{max} (CHCl₃)/cm⁻¹: 3011, 1580, 1483, 1440, 1394, 1273, 1161, 1112, 1031, 909.

(2-chlorophenyl)triphenylphosphonium trifluoromethanesulfonate 63



Triphenylphosphine (63 mg, 0.239 mmol) and (2-chlorophenyl)(mesityl)iodonium trifluoromethanesulfonate (81 mg, 0.159 mmol) were used to generate (2-chlorophenyl)triphenylphosphonium trifluoromethanesulfonate as an off-white solid (38 mg, 46%).

³¹P NMR (162 MHz, CDCl₃) δ: 23.0 (m, 1P);

¹H NMR (400 MHz, CDCl₃) δ: 7.94 – 7.84 (4H, m, H_{Ar}), 7.80 – 7.71 (7H, m, H_{Ar}), 7.71 – 7.62 (8H, m, H_{Ar}), 7.31 (1H, ddd, *J* = 14.6, 7.9, 1.6 Hz, H_{Ar});

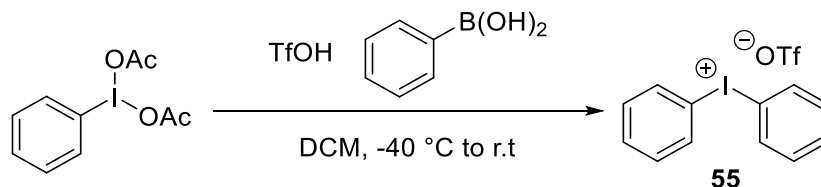
¹³C NMR (100 MHz, CDCl₃) δ: 139.0 (d, *J* = 4.1 Hz, C_q), 138.4 (d, *J* = 10.3 Hz, C_{Ar}), 137.8 (d, *J* = 2.8 Hz, C_{Ar}), 135.7 (d, *J* = 3.0 Hz, C_{Ar}), 134.3 (d, *J* = 10.5 Hz, C_{Ar}), 133.1 (d, *J* = 6.7 Hz, C_{Ar}), 130.9 (d, *J* = 13.5 Hz, C_{Ar}), 129.5 (d, *J* = 12.4 Hz, C_{Ar}), 117.3 (d, *J* = 90.8 Hz, C_q);

HMRS (ESI⁺): *m/z* calculated for [C₂₄H₁₉ClP⁺ (M⁺)] calcd. 373.0907, found 373.0908;

IR ν_{max} (CHCl₃)/cm⁻¹: 3070, 3008, 1578, 1485, 1456, 1439, 1273, 1162, 1124, 1108, 1044, 1030, 999, 909, 637.

5.1.4 Formation of diaryliodonium triflates

Diphenyliodonium trifluoromethanesulfonate⁹¹ **55**



Triflic acid (1.33 mL, 15.0 mmol) was added slowly dropwise to a solution of diacetoxyiodobenzene (2.42 g, 7.50 mmol) in dichloromethane (75 mL) at $-40\text{ }^\circ\text{C}$ (acetonitrile/ $\text{CO}_{2(\text{s})}$ bath) and stirred for 30 minutes. The reaction mixture was then warmed to room temperature and stirred for a further 30 minutes. The reaction mixture was cooled to $-40\text{ }^\circ\text{C}$ and phenyl boronic acid (914 mg, 7.50 mmol) was added and the reaction mixture was stirred overnight. The solvent was removed *in vacuo* and diethyl ether was added. The resulting solid was filtered and washed with diethyl ether to give diphenyliodonium trifluoromethanesulfonate as a white solid (2.86 g, 89%).

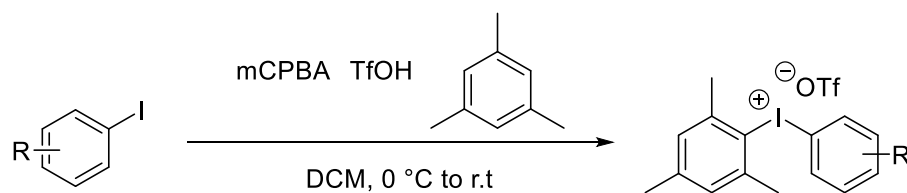
^1H NMR (400 MHz, CD_3CN) δ : 8.11 – 8.06 (1H, m, H_{Ar}), 7.75 – 7.69 (1H, m, H_{Ar}), 7.58 – 7.51 (1H, m, H_{Ar});

^{13}C NMR (100 MHz, CD_3CN) δ : 136.3 (C_{Ar}), 133.9 (C_{Ar}), 133.4 (C_{Ar}), 114.4 (C_{q});

HRMS (ESI^+): m/z calculated for $[\text{C}_{12}\text{H}_{10}\text{I}]^+ (\text{M}^+)$ calcd. 280.9822, found 280.9814;

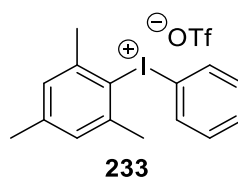
IR ν_{max} (CHCl_3)/ cm^{-1} : 3011, 1472, 1444, 1289, 1243, 1170, 1026, 986, 637.

5.1.5 Formation of mesityl(aryl)iodonium triflates



To a solution of iodoarene and *m*CPBA (dried under vacuum at room temperature for 1 hour, assume 65%) in dichloromethane, cooled in an ice bath was added trifluoromethanesulfonic acid slowly dropwise. The reaction was warmed to room temperature and stirred for 2 h. The reaction mixture was then cooled in an ice bath and mesitylene was added slowly dropwise. The reaction mixture was then stirred overnight at room temperature. The solvent was removed *in vacuo* and diethyl ether was added. The resulting solid was filtered and washed with diethyl ether to give mesityl(phenyl)iodonium trifluoromethanesulfonate (dried under vacuum at 100 °C for 1 h) as a white solid.

Mesityl(phenyl)iodonium trifluoromethanesulfonate⁹² (233)



Prepared according to the procedure above where iodobenzene (0.55 mL, 4.90 mmol), *m*CPBA (1.42 g, 8.23 mmol), triflic acid (0.72 mL, 8.04 mmol) and mesitylene (0.75 mL, 5.39 mmol) were used to generate mesityl(phenyl)iodonium trifluoromethanesulfonate (2.07 g, 90%).

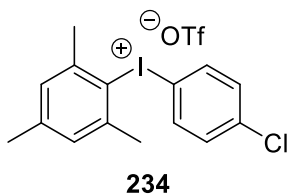
¹H NMR (400 MHz, CDCl₃) δ: 7.71 – 7.66 (2H, m, H_{Ar}), 7.58 – 7.51 (1H, m, H_{Ar}), 7.45 – 7.38 (2H, m, H_{Ar}), 7.11 (2H, s, H_{Ar}), 2.63 (6H, s, CH₃), 2.36 (3H, s, CH₃);

^{13}C NMR (100 MHz, CDCl_3) δ : 144.6 (C_q), 142.6 (C_q), 133.1 (C_{Ar}), 132.3 (C_{Ar}), 131.9 (C_{Ar}), 130.5 (C_{Ar}), 120.5 (C_q), 111.9 (C_q), 27.2 (CH_3), 21.3 (CH_3);

HRMS (ESI^+): m/z calculated for $[\text{C}_{15}\text{H}_{16}\text{I}] (\text{M}^+)$ calcd. 323.0291, found 323.0290;

IR ν_{max} (CHCl_3)/ cm^{-1} : 3011, 1472, 1444, 1284, 1242, 1172, 1027, 637.

(4-chlorophenyl)(mesityl)iodonium trifluoromethanesulfonate²³ 234



Prepared according to the procedure above where 4-chloro-1-iodobenzene (1.05 g, 4.42 mmol), *m*CPBA (1.28 g, 7.42 mmol), triflic acid (0.64 mL, 7.25 mmol) and mesitylene (0.63 mL, 4.86 mmol) were used to generate mesityl(4-chlorophenyl)iodonium trifluoromethanesulfonate (1.89 g, 84%).

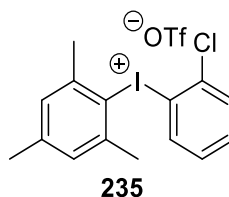
^1H NMR (400 MHz, CDCl_3) δ : 7.7 – 7.6 (2H, m, H_{Ar}), 7.4 – 7.3 (2H, m, H_{Ar}), 7.1 (2H, s, H_{Ar}), 2.6 (6H, s, 6H, CH_3), 2.3 (3H, s, CH_3);

^{13}C NMR (100 MHz, CDCl_3) δ : 144.5 (C_q), 142.5 (C_q), 138.6 (C_q), 134.5 (C_{Ar}), 132.2 (C_{Ar}), 130.4 (C_{Ar}), 121.0 (C_q), 109.0 (C_q), 27.0 (CH_3), 21.2 (CH_3);

HRMS (ESI^+): m/z calculated for $[\text{C}_{15}\text{H}_{15}\text{ClI}] (\text{M}^+)$ calcd. 356.9901, found 356.9898;

IR ν_{max} (CHCl_3)/ cm^{-1} : 3011, 2927, 1471, 1388, 1286, 1243, 1170, 1093, 1026, 1000, 637.

(2-chlorophenyl)(mesityl)iodonium trifluoromethanesulfonate 235



Prepared according to the procedure above where 2-chloro-1-iodobenzene (0.42 mL, 3.45 mmol), *m*CPBA (1.00 g, 5.79 mmol), triflic acid (0.31 mL, 3.53 mmol) and mesitylene (0.53 mL, 3.80 mmol) were used to generate mesityl(4-chlorophenyl)iodonium trifluoromethanesulfonate (1.14 g, 65%).

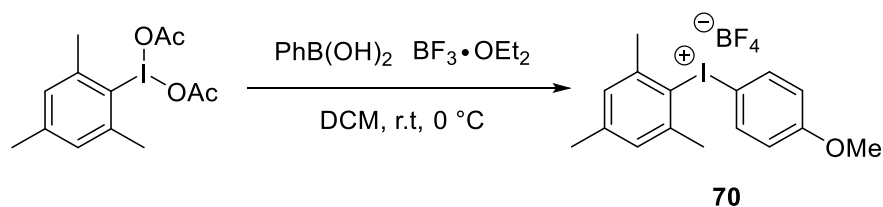
¹H NMR (400 MHz, CDCl₃) δ: 7.61 (1H, dd, *J* = 8.0, 1.5 Hz, H_{Ar}), 7.53 (1H, td, *J* = 7.7, 1.4 Hz, H_{Ar}), 7.29 (1H, ddd, *J* = 8.6, 7.4, 1.5 Hz, H_{Ar}), 7.17 (2H, s, H_{Ar}), 7.10 (1H, dd, *J* = 8.2, 1.4 Hz, H_{Ar}), 2.62 (6H, s, CH₃), 2.39 (3H, s, CH₃);

¹³C NMR (100 MHz, CDCl₃) δ: 145.4 (C_q), 143.0 (C_q), 135.5 (C_q), 133.5 (C_{Ar}), 132.6 (C_{Ar}), 131.4 (C_{Ar}), 130.9 (C_{Ar}), 130.6 (C_{Ar}), 120.8 (C_q), 112.5 (C_q), 27.2 (CH₃), 21.3 (CH₃);

HRMS (ESI⁺): *m/z* calculated for [C₁₅H₁₅ClI (M⁺)] calcd. 356.9901, found 356.9899;

IR ν_{max} (CHCl₃)/cm⁻¹: 3011, 1448, 1292, 1242, 1170, 1025, 637

Mesityl(4-methoxyphenyl)iodonium tetrafluoroborate^{37d} 70



To a solution of 4-methoxyphenyl boronic acid (340 mg, 2.24 mmol) in DCM (22.4 mL) at 0 °C was added BF₃·OEt₂ (0.30 mL, 2.46 mmol), followed by addition of 2-(diacetoxyiodo)mesitylene (897 mg, 2.46 mmol) in DCM (8.2 mL). After 2 h a

saturated aqueous solution of sodium tetrafluoroborate (40 mL) was added to the reaction mixture and stirred for 30 minutes. The aqueous layer was then extracted with DCM and washed with brine, dried over MgSO_4 and the solvent removed *in vacuo*. The product was then crystallised with a mixture of DCM/ Et_2O and the solid filtered to give mesityl(4-methoxyphenyl)iodonium tetrafluoroborate as an off white solid (754 mg, 76%).

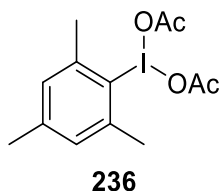
^1H NMR (400 MHz, CDCl_3) δ : 7.66 (2H, d, $J = 9.0$ Hz, H_{Ar}), 7.02 (2H, s, H_{Ar}), 6.86 (1H, d, $J = 9.1$ Hz, H_{Ar}), 3.77 (3H, s, CH_3), 2.64 (6H, s, CH_3), 2.29 (3H, s, CH_3);

^{13}C NMR (100 MHz, CDCl_3) δ : 161.8 (C_q), 143.3 (C_q), 141.8 (C_q), 134.8 (C_{Ar}), 130.0 (C_{Ar}), 124.1 (C_q), 117.5 (C_{Ar}), 104.5 (C_q), 55.6 (CH_3), 27.0 (CH_3), 21.0 (CH_3);

HRMS (ESI^+): m/z calculated for $[\text{C}_{16}\text{H}_{18}\text{IO} (\text{M}^+)]$ calcd. 353.0397, found 353.0410;

IR ν_{max} (CHCl_3)/ cm^{-1} : 3043, 2968, 1584, 1574, 1460, 1442, 1057, 1030, 851.

2-(Diacetoxyiodo)mesitylene⁹³ 236



A solution of 2,4,6-trimethyliodobenzene (1.60 g, 6.50 mmol) in acetic acid (65 mL) was heated to 45 °C. Sodium perborate monohydrate (4.22 g, 42.3 mmol) was added in small portions over 1 h. The reaction mixture was then stirred for 3.5 h at 45 °C, before being cooled to r.t. and diluted with (120 mL) of water. The aqueous layer was extracted with DCM (3 x 60 mL), dried over MgSO_4 , filtered and the solvent removed *in vacuo*. The product was crystallised by addition of Et_2O , the solid filtered

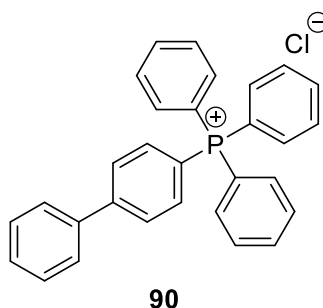
and washed with Et₂O to give 2-(diacetoxyiodo)mesitylene as a white solid (897 mg, 38%).

¹H NMR (400 MHz, CDCl₃) δ: 7.09 (2H, s, H_{Ar}), 2.70 (6H, s, CH₃), 2.35 (3H, s, CH₃), 1.96 (6H, s, CH₃);

¹³C NMR (100 MHz, CDCl₃) δ: 176.5 (C_q), 143.2 (C_q), 141.3 (C_q), 129.6 (C_q), 129.0 (C_{Ar}), 26.7 (CH₃), 21.2 (CH₃), 20.3 (CH₃)

5.1.6 Formation of phosphonium salts from arylboronic acids

[1, 1'-biphenyl]-4-yltriphenylphosphonium chloride **90**



To a solution of triphenylphosphine (50 mg, 0.191 mmol) in MeCN (1 mL) was added 4-biphenyl boronic acid (132 mg, 0.669 mmol). The reaction mixture was heated to 80 °C and manganese acetate dehydrate (128 mg, 0.478 mmol) was added, after 30 min the reaction mixture was cooled to r.t. and filtered through a sinter funnel. The residue was washed with DCM (3 mL) and the solvent was removed *in vacuo*. To a solution of the crude material in MeCN (4 mL) was added Quarapure IDA ((0.16 mmol/g) 748 mg) and NaCl (142 mg, 2.43 mmol). The solution was heated at 75 °C for 48 h, filtered and the solvent removed *in vacuo*. The solid was recrystallised from diethyl ether/DCM to give [1,1'-biphenyl]-4-yltriphenylphosphonium chloride as a yellow solid (57 mg, 70%).

³¹P NMR (162 MHz, CDCl₃) δ: 23.0 (s, 1P);

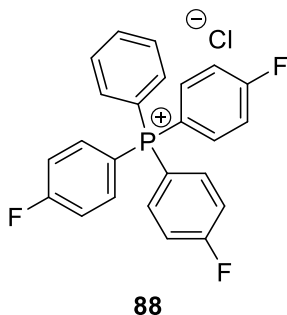
¹H NMR (400 MHz, CDCl₃) δ: 7.93-7.28 (24H, m, H_{Ar});

¹³C NMR (100 MHz, CDCl₃) δ: 148.4 (d, *J* = 3.1 Hz, C_q), 141.8 (d, *J* = 78.2 Hz, C_q), 135.7 (d, *J* = 3.1 Hz, CH), 134.8 (d, *J* = 7.7 Hz, CH), 134.8 (d, *J* = 3.1 Hz, CH), 134.2 (d, *J* = 10.0 Hz, CH), 130.7 (d, *J* = 12.3 Hz, CH), 129.3 (d, *J* = 4.6 Hz, CH), 129.0 (d, *J* = 13.8 Hz, CH), 127.0 (d, *J* = 12.3 Hz, CH), 117.4 (d, *J* = 89.7 Hz, C_q), 115.3 (d, *J* = 92.0 Hz, C_q);

HMRS (ESI⁺): *m/z* calculated for C₃₀H₂₄P [M⁺] calcd. 415.1610, found 415.1612;

IR ν_{max} (CHCl₃)/cm⁻¹: 3010, 2958, 1598, 1519, 1485, 1379, 1242, 1111, 1007.

Tris(4-fluorophenyl)(phenyl)phosphonium chloride 88



To a solution of triphenylphosphine (100 mg, 0.316 mmol) in MeCN (1.7 mL) was added phenyl boronic acid (135 mg, 1.11 mmol). The reaction mixture was heated to 80 °C and manganese acetate dihydrate (212 mg, 0.790 mmol) was added, after 30 min the reaction mixture was cooled to r.t. and filtered through a sinter funnel. The residue was washed with DCM (3 mL) and the solvent was removed *in vacuo*. To a solution of the crude material in MeCN (5 mL) was added Quadrapure IDA ((0.16 mmol/g) 1.37 g) and NaCl (185 mg, 3.16 mmol). The solution was heated at 75 °C for 48 h, filtered and the solvent removed *in vacuo*. The solid was recrystallised from diethyl ether/DCM to give tris(4-fluorophenyl)(phenyl)phosphonium chloride as a white solid (61 mg, 49%).

³¹P NMR (162 MHz, CDCl₃) δ: 21.9 (s, 1P);

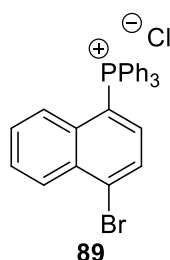
¹H NMR (400 MHz, CDCl₃) δ: 7.85 - 7.93 (1H, m, H_{Ar}), 7.66 - 7.82 (8H, m, H_{Ar}), 7.64 - 7.59 (2H, m, H_{Ar}), 7.46 (6H, app. td, *J* = 8.3, 2.5 Hz, H_{Ar});

^{13}C NMR (100 MHz, CDCl_3) δ : 167.1 (dd, $J = 263, 3.8$ Hz, C_q), 137.6 (dd, $J = 12.7, 9.6$ Hz, CH), 136.0 (d, $J = 3.1$ Hz, CH), 134.3 (d, $J = 10.7$ Hz, CH), 131.0 (d, $J = 13.0$ Hz, CH), 118.8 (dd, $J = 23.0, 14.6$ Hz, CH) 117.4 (d, $J = 92.0$ Hz, CH), 113.0 (dd, $J = 94.3, 3.8$ Hz, CH);

HMRS (ESI^+): m/z calculated for $\text{C}_{24}\text{H}_{17}\text{F}_3\text{P}$ [M^+] calcd. 393.1014, found 39.1010;

IR ν_{max} (CHCl_3)/ cm^{-1} : 2930, 159, 1500, 143, 1402, 1252, 1165, 1110, 1013.

(4-bromonaphthalen-1-yl)triphenylphosphonium chloride 89



To a solution of triphenylphosphine (50 mg, 0.191 mmol) in MeCN (1.50 mL) was added 4-bromonaphthalene boronic acid (168 mg, 0.669 mmol). The reaction mixture was heated to 80 °C and manganese acetate dehydrate (128 mg, 0.478 mmol) was added, after 30 min the reaction mixture was cooled to r.t. and filtered through a sinter funnel. The residue was washed with DCM (3 mL) and the solvent was removed *in vacuo*. To a solution of the crude material in MeCN (4 mL) was added Quarapure IDA ((0.16 mmol/g) 1.09 mg) and NaCl (142 mg, 2.43 mmol). The solution was heated at 75 °C for 48 h, filtered and the solvent removed *in vacuo*. The solid was recrystallised from diethyl ether/DCM followed by flash column chromatography (5% methanol/DCM) to give (4-bromonaphthalen-1-yl)triphenylphosphonium chloride (8 mg, 8%) as a yellow oil.

^{31}P NMR (162 MHz, CDCl_3) δ : 22.5 (m, 1P);

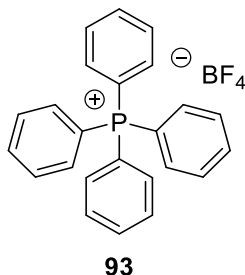
^1H NMR (400 Hz, CDCl_3) δ : 8.58-8.49 (1 H, m, H_{Ar}), 8.05 (1H, dd, $J = 7.9, 2.3$ Hz, H_{Ar}), 7.92-7.84 (3H, m, H_{Ar}), 7.76 (7H, app. td, $J = 7.9, 3.7$ Hz, H_{Ar}), 7.72-7.62 (6H, m, H_{Ar}), 7.47-7.34 (3H, m, H_{Ar});

^{13}C NMR (100 Hz, CDCl_3) δ : 138.7 (d, $J = 11.7$ Hz), 135.8 (d, $J = 2.9$ Hz), 134.4 (d, $J = 10.2$ Hz), 133.4 (d, $J = 8.8$ Hz), 133.0 (d, $J = 10.2$ Hz), 131.0 (d, $J = 12.4$ Hz), 130.4 (d, $J = 14.6$ Hz), 129.7 (d, $J = 2.2$ Hz), 129.3 (s), 126.7 (d, $J = 6.6$ Hz), 117.7 (d, $J = 89.3$ Hz), 113.5 (d, $J = 89.3$ Hz);

HMRS (ESI^+): m/z calculated for $\text{C}_{30}\text{H}_{24}\text{P}$ [M^+] calcd. 467.0559, found 467.0573;

IR ν_{max} (CHCl_3)/ cm^{-1} : 2995, 2928, 1602, 1504, 1440, 1373, 1242, 1107, 909, 885.

Tetraphenylphosphonium tetrafluoroborate **93**



To a solution of triphenylphosphine (50 mg, 0.191 mmol) in MeCN (0.75 mL) and DMF (0.25 mL) was added phenyl boronic acid (116 mg, 0.995 mmol). The reaction mixture was heated to 80 °C and manganese acetate dehydrate (154 mg, 0.573 mmol), after 1 h the reaction mixture was cooled to r.t. and filtered through a sinter funnel. The residue was washed with DCM (2 mL) and the solvent was removed *in vacuo*. To a solution of the crude material in DCM (6 mL) was added $\text{NaBF}_4(\text{aq})$ (10 mL) and stirred at r.t. overnight. The organic layer was washed with H_2O (x 3), brine (x 2), dried over MgSO_4 , filtered and the solvent removed *in vacuo*. The crude

material was then purified by recrystallisation (MeCN/Et₂O) to give tetraphenylphosphonium tetrafluoroborate as a white solid (49 mg, 60%).

³¹P NMR (162 MHz, CD₃CN) δ: 22.9 (m, 1P);

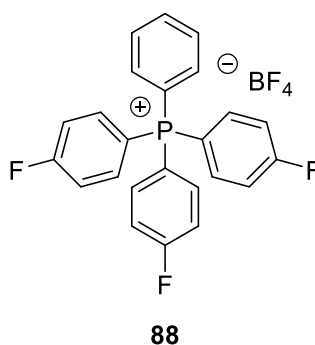
¹H NMR (400 Hz, CD₃CN) δ: 8.03 – 7.85 (4H, m, H_{Ar}), 7.82 – 7.59 (16H, m, H_{Ar});

¹³C NMR (100 Hz, CDCl₃) δ: 136.0 (d, *J* = 3.1 Hz, C_{Ar}), 134.5 (d, *J* = 10.4 Hz, C_{Ar}), 131.0 (d, *J* = 13.0 Hz, C_{Ar}), 117.5 (d, *J* = 89.5 Hz, C_q).

HMRS (ESI⁺): *m/z* calculated for C₂₄H₂₀P [M⁺] calcd. 339.1297, found 339.1300;

IR ν_{max} (CHCl₃)/cm⁻¹: 3045, 2988, 1435, 1106, 1052, 752, 721, 688, 524.

Tris(4-fluorophenyl)(phenyl)phosphonium tetrafluoroborate 88



To a solution of tris(4-fluorophenyl)phosphine (60 mg, 0.191 mmol) in MeCN (0.75 mL) and DMF (0.25 mL) was added phenyl boronic acid (116 mg, 0.995 mmol). The reaction mixture was heated to 80 °C and manganese acetate dehydrate (154 mg, 0.573 mmol) was added, after 1 h the reaction mixture was cooled to r.t. and filtered through a sinter funnel. The residue was washed with DCM (2 mL) and the solvent was removed *in vacuo*. To a solution of the crude material in DCM (6 mL) was added NaBF₄(aq) (10 mL) and stirred at r.t. overnight. The organic layer was washed with H₂O (x 3), brine (x 2), dried over MgSO₄, filtered and the solvent removed *in vacuo*.

The crude material was then purified by recrystallisation (MeCN/Et₂O) to give tris(4-fluorophenyl)(phenyl)phosphonium tetrafluoroborate as a white solid (60 mg, 65%).

³¹P NMR (162 MHz, CD₃CN) δ: 22.9 (m, 1P);

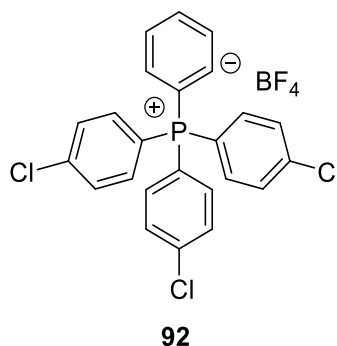
¹H NMR (400 Hz, CD₃CN) δ: 8.02 – 7.90 (1H, m, H_{Ar}), 7.86 – 7.62 (10H, m, H_{Ar}), 7.60 – 7.42 (6H, m, H_{Ar});

¹³C NMR (100 Hz, CDCl₃) δ: 167.2 (d, *J* = 261.3 Hz C_q), 138.9-137.4 (m, C_{Ar}), 136.2 (s, C_{Ar}), 135.1-134.2 (m, C_{Ar}), 131.2 (d, *J* = 11.5 Hz, C_{Ar}), 120.0-118.8 (m, C_{Ar}), 117.5 (d, *J* = 90.3 Hz, C_q), 113.2 (d, *J* = 94.3 Hz, C_q)

HMRS (ESI⁺): *m/z* calculated for C₂₄H₁₇F₃P [M⁺] calcd. 394.1093, found 394.1050;

IR ν_{max} (CHCl₃)/cm⁻¹: 3026, 2970, 1589, 1496, 1401, 1235, 1166, 1107, 1053, 830, 525, 502, 466.

Tris(4-chlorophenyl)(phenyl)phosphonium tetrafluoroborate 92



To a solution of tris(4-chlorophenyl)phosphine (70 mg, 0.191 mmol) in MeCN (0.75 mL) and DMF (0.25 mL) was added phenyl boronic acid (116 mg, 0.995 mmol). The reaction mixture was heated to 80 °C and manganese acetate dehydrate (154 mg, 0.573 mmol) was added, after 1 h the reaction mixture was cooled to r.t. and filtered through a sinter funnel. The residue was washed with DCM (2 mL) and the solvent was removed *in vacuo*. To a solution of the crude material in DCM (6 mL) was added

NaBF₄(aq) (10 mL) and stirred at r.t. overnight. The organic layer was washed with H₂O (x 3), brine (x 2), dried over MgSO₄, filtered and the solvent removed *in vacuo*. The crude material was then purified by recrystallisation (MeCN/Et₂O) to give tris(4-chlorophenyl)(phenyl)phosphonium tetrafluoroborate (66 mg, 65%) as a white solid.

³¹P NMR (162 MHz, CD₃CN) δ: 22.8 (m, 1P);

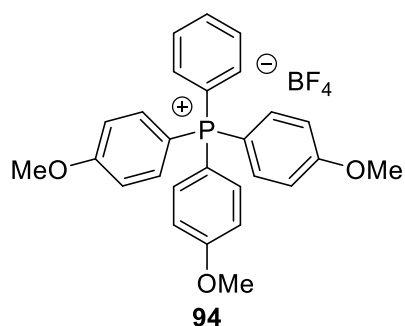
¹H NMR (400 Hz, CD₃CN) δ: 7.92 – 7.84 (1H, m, H_{Ar}), 7.81 – 7.68 (8H, m, H_{Ar}), 7.67 – 7.54 (8H, m, H_{Ar});

¹³C NMR (100 Hz, CDCl₃) δ: 143.4 (d, *J* = 3.7 Hz, C_q), 136.3 (d, *J* = 2.9 Hz, C_{Ar}), 135.9 (d, *J* = 11.7 Hz, C_{Ar}), 134.5 (d, *J* = 10.4 Hz, C_{Ar}), 131.5 (d, *J* = 13.9 Hz, C_{Ar}), 131.1 (d, *J* = 13.1 Hz, C_{Ar}), 116.6 (d, *J* = 90.7 Hz, C_q), 115.4 (d, *J* = 92.9 Hz, C_q);

HMRS (ESI⁺): *m/z* calculated for C₂₄H₁₇Cl₃P [M⁺] calcd. 441.0128, found 441.0139;

IR ν_{max} (CHCl₃)/cm⁻¹: 3089, 2988, 1576, 1481, 1438, 1391, 1083, 1055, 1008, 690, 587, 547, 498.

Tris(4-methoxyphenyl)(phenyl)phosphonium tetrafluoroborate **94**



To a solution of tris(4-methoxyphenyl)phosphine (67 mg, 0.191 mmol) in MeCN (0.75 mL) and DMF (0.25 mL) was added phenyl boronic acid (116 mg, 0.995 mmol). The reaction mixture was heated to 80 °C and manganese acetate dehydrate (154 mg, 0.573 mmol) was added, after 1 h the reaction mixture was cooled to r.t. and filtered

through a sinter funnel. The residue was washed with DCM (2 mL) and the solvent was removed *in vacuo*. To a solution of the crude material in DCM (6 mL) was added NaBF₄(aq) (10 mL) and stirred at r.t. overnight. The organic layer was washed with H₂O (x 3), brine (x 2), dried over MgSO₄, filtered and the solvent removed *in vacuo*. The crude material was then purified by recrystallisation (MeCN/Et₂O) to give tris(4-methoxyphenyl)(phenyl)phosphonium tetrafluoroborate as an oil (9:1 phosphonium salt: phosphine oxide (50 mg, 51%)).

³¹P NMR (162 MHz, CD₃CN) δ: 20.9 (m, 1P);

¹H NMR (400 Hz, CD₃CN) δ: 7.91 – 7.83 (1H, m, H_{Ar}), 7.71 (2H, td, *J* = 7.9, 3.6 Hz, H_{Ar}), 7.67 – 7.60 (2H, m, H_{Ar}), 7.59 – 7.50 (6H, m, H_{Ar}), 7.26 – 7.18 (6H, m, H_{Ar}), 3.91 (9H, s, CH₃);

¹³C NMR (100 Hz, CDCl₃) δ: 165.2 (d, *J* = 2.7 Hz, C_q), 136.3 (d, *J* = 11.8 Hz, C_{Ar}), 135.2 (d, *J* = 2.9 Hz, C_{Ar}), 134.1 (d, *J* = 10.3 Hz, C_{Ar}), 130.5 (d, *J* = 12.9 Hz, C_{Ar}), 120.0 (d, *J* = 90.7 Hz, C_q), 116.5 (d, *J* = 13.9 Hz, C_{Ar}), 108.4 (d, *J* = 98.1 Hz, C_q);

HMRS (ESI⁺): *m/z* calculated for C₂₇H₂₆O₃P [M⁺] calcd. 429.1614, found 429.1646;

IR ν_{max} (CHCl₃)/cm⁻¹: 2947, 2843, 1593, 1503, 1265, 1184, 1110, 1020, 536.

5.2 Chapter 2

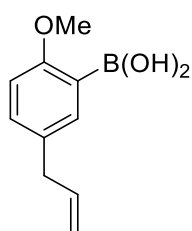
5.2.1 General experimental

All glassware was oven-dried and allowed to cool under a stream of nitrogen/argon before use unless otherwise stated. Cooling to $-78\text{ }^{\circ}\text{C}$ was effected using dry ice/acetone mixtures. Degassing was achieved by purging nitrogen through the appropriate solution for 10 minutes. The petroleum ether used refers to the fraction with bp $40\text{--}60\text{ }^{\circ}\text{C}$. Commercial solvents and reagents were used as supplied with the following exceptions. THF was pre-dried over sodium wire and obtained from a solvent tower, where degassed THF was passed through two columns of activated alumina and a 7 micron filter under a 4 bar pressure. Acetonitrile was dried over calcium hydride powder, distilled and stored over $4\text{ \AA}$ molecular sieves. CH_2Cl_2 was dried over calcium hydride powder, filtered, distilled and stored over $4\text{ \AA}$ molecular sieves. NBS was recrystallised from hot water and stored in the dark. Activation of $4\text{ \AA}$ molecular sieves was achieved by heating under high vacuum with a Bunsen burner. Microwave reactions were carried out on a CEM Explorer microwave. Reactions were monitored using TLC on Polygram® SIL G/UV254 0.25 mm silica gel pre-coated glass sheets with fluorescent indicator. Sheets were visualised using ultra-violet light (254 nm) and/or anisaldehyde or KMnO_4 solutions as appropriate. Flash chromatography was performed using Fluorochem silica gel 60, $35\text{--}70$ micron. Melting points were acquired on a Stuart® SMP3 melting point instrument. Infrared spectra were recorded on a Pelkin-Elmer 1600 FTIR instrument as a dilute solution in the indicated solvent. ^1H , ^{13}C , ^{31}P NMR spectra were recorded on either Bruker DPX 400, Bruker AV400, Bruker AV(III) 400 or Bruker DPX 300 instruments as dilute solutions in the indicated deuterated solvent. All chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent peaks. Coupling constants (J) are reported in Hertz

(Hz) and are recorded after averaging. The multiplicity of a ^1H NMR signal is designated by one of the following abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad signal. Mass spectra were acquired on either VG Micromass 70E, VG Autospec or Micromass LCTOF instruments.

5.2.2 Experimental procedures

(5-allyl-2-methoxyphenyl)boronic acid⁷⁹ **130**



130

To a solution of 4-allylanisole (2.08 mL, 13.5 mmol) in THF (50 mL) at $-78\text{ }^{\circ}\text{C}$ was added TMEDA (2.02 mL, 13.5 mmol) and $^t\text{BuLi}$ (9.64 mL, 20.2 mmol) *via* a syringe pump over 15 minutes and the solution was stirred for 1 h. The solution was warmed to r.t. for 1 h before trimethylborate (1.39 mL, 13.5 mmol) was added and the solution stirred for 24 h. The solution was acidified (1 M HCl to pH 3-4) and stirred for an additional 1 h. The solution was diluted with EtOAc (50 mL), washed with brine (3 x 50 mL), dried over MgSO_4 and the solvent was removed *in vacuo*. The crude material was purified by flash column chromatography (petroleum ether 40-60 $^{\circ}\text{C}$ /EtOAc, 3:1) to give (5-allyl-2-methoxyphenyl)boronic acid as a white solid (892mg, 65%).

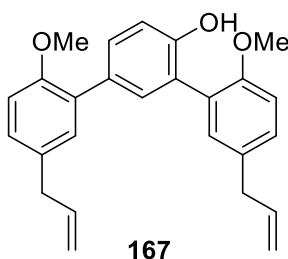
^1H NMR (400 MHz, CDCl_3) δ : 7.70 (1H, d, $J = 2.4\text{ Hz}$, H_{Ar}), 7.26 (1H, dd, $J = 8.4, 2.4\text{ Hz}$, H_{Ar}), 6.86 (1H, d, $J = 8.4\text{ Hz}$, H_{Ar}), 6.64 (2H, s, B(OH)_2), 5.97 (1H, ddt, $J = 16.9, 10.1, 6.7\text{ Hz}$, CH), 5.13-5.07 (2H, m, CH_2), 3.90 (3H, s, CH_3), 3.36 (2H, d, $J = 6.6\text{ Hz}$, CH_2);

^{13}C NMR (100 MHz, CDCl_3) δ : 163.0 (C_q), 137.6 (CH), 136.9 (CH), 132.8 (C_q), 132.5 (C_q), 115.5 (CH_2), 110.0 (CH), 55.5 (CH_3), 39.2 (CH_2);

HRMS (ESI^+): m/z calculated for $\text{C}_{10}\text{H}_{13}\text{BO}_3$ [$\text{M}+\text{H}$] calcd. 193.1031, found 193.1045;

IR ν_{max} (CHCl_3)/ cm^{-1} : 3622, 3517, 3011, 1639, 1606, 1492, 1344, 1179, 1049, 919.

5,5''-diallyl-2,2''-dimethoxy-[1,1':3',1''-terphenyl]-4'-ol 167



To 2,4-dibromophenol (78 mg, 0.308 mmol), Pd_2dba_3 (28 mg, 0.031 mmol), potassium fluoride (89 mg, 1.54 mmol) and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (S-Phos) (38 mg, 0.093 mmol) was added a solution of (5-allyl-2-methoxyphenyl)boronic acid (148 mg, 0.771 mmol) in THF (8 mL) and H_2O (0.80 mL). The solution was heated to reflux and stirred for 16 h. The solution was cooled to r.t. and diluted with EtOAc (25 mL), washed with 1 M HCl (25 mL x 2) and brine (25 mL x 2), dried over MgSO_4 , filtered and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (petroleum ether/EtOAc, 9:1) to give 5,5''-diallyl-2,2''-dimethoxy-[1,1':3',1''-terphenyl]-4'-ol as a yellow oil (111 mg, 93%).

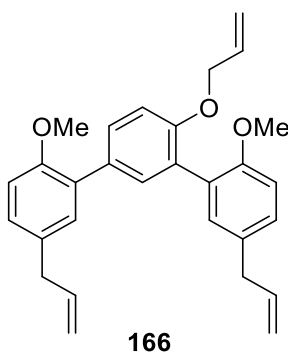
^1H NMR (400 MHz, CDCl_3) δ : 7.50 (1H, dd, $J = 8.4, 2.0$ Hz, H_{Ar}), 7.45 (1H, d, $J = 2.0$ Hz, H_{Ar}), 7.24-7.21 (1H, m, H_{Ar}), 7.18 (1H, d, $J = 2.4$ Hz, H_{Ar}), 7.12 (1H, dd, $J = 8.4, 2.0$ Hz, H_{Ar}), 7.08 (1H, d, $J = 8.0$ Hz, H_{Ar}), 7.01 (1H, d, $J = 8.0$ Hz, H_{Ar}), 6.93 (2H, d, $J = 8.4$ Hz, H_{Ar}), 6.49 (1H, s, OH), 5.98 (2H, app. ddq, $J = 16.8, 10.2, 6.5$ Hz, CH), 5.12-5.05 (4H, m, CH_2), 3.93 (3H, s, CH_3), 3.82 (3H, s, CH_3), 3.39 (4H, app. t, $J = 6.8$ Hz, CH_2);

¹³C NMR (100 MHz, CDCl₃) δ: 154.9 (C_q), 153.8 (C_q), 152.9 (C_q), 137.7 (CH), 137.3 (CH), 133.8 (C_q), 132.9 (CH), 132.4 (CH), 132.3 (C_q), 131.2 (C_q), 131.0 (CH), 130.4 (CH), 130.2 (C_q), 129.1 (CH), 128.0 (CH), 127.3 (C_q), 125.9 (C_q), 117.2 (CH), 115.9 (CH₂), 115.6 (CH₂), 111.6 (CH), 111.2 (CH), 56.4 (CH₃), 55.7 (CH₃), 39.4 (CH₂), 39.3 (CH₂);

HRMS (ESI⁺): *m/z* calculated for C₂₆H₂₆O₃ [M+H] calcd. 387.1955, found 387.1944;

IR ν_{max} (CHCl₃)/cm⁻¹: 3389, 3011, 1639, 1605, 1490, 1242, 1043, 919.

5,5''-diallyl-4'-(allyloxy)-2,2''-dimethoxy-1,1':3',1''-terphenyl 166



To a solution of 5,5''-diallyl-2,2''-dimethoxy-[1,1':3',1''-terphenyl]-4'-ol (177 mg, 0.458 mmol) in acetone (11 mL) was added allyl bromide (80 μL, 0.916 mmol) and potassium carbonate (95 mg, 0.687 mmol). The solution was heated to reflux and stirred for 17 h. The solution was cooled to r.t., quenched with MeOH and stirred for 20 min. The solution was diluted with EtOAc (25 mL), washed with brine (3 x 25 mL), filtered and the solvent removed *in vacuo* to give 5,5''-diallyl-4'-(allyloxy)-2,2''-dimethoxy-1,1':3',1''-terphenyl as a yellow oil (182 mg, 93%).

¹H NMR (400 MHz, CDCl₃) δ: 7.50 (1H, dd, *J* = 8.4, 2.4 Hz, H_{Ar}), 7.46 (1H, d, *J* = 2.4 Hz, H_{Ar}), 7.20-7.09 (4H, m, H_{Ar}), 6.99 (1H, d, *J* = 8.4 Hz, H_{Ar}), 6.91 (2H, d, *J* = 8.4 Hz, H_{Ar}), 6.05-5.92 (3H, m, CH), 5.29 (1H, ddt, *J* = 17.2, 1.8, 1.8 Hz, CH), 5.17 (1H, ddt, *J* = 10.7,

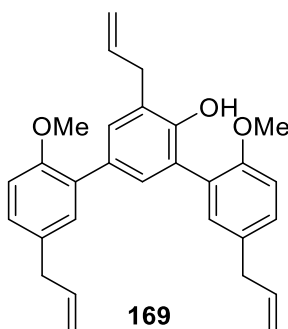
1.6, 1.6 Hz, CH), 5.13-5.03 (4H, m, CH₂), 4.57 (2H, dt, *J* = 4.7, 1.7 Hz, CH₂), 3.80 (3H, s, CH₃), 3.77 (3H, s, CH₃), 3.38-3.37 (4H, m, CH₂);

¹³C NMR (100 MHz, CDCl₃) δ: 155.6 (C_q), 155.2 (C_q), 154.9 (C_q), 137.8 (CH), 137.8 (CH), 133.7 (CH), 132.7 (CH), 132.2 (C_q), 131.9 (CH), 131.5 (C_q), 131.1 (CH), 130.7 (C_q), 130.2 (C_q), 129.5 (CH), 128.3 (CH), 127.8 (CH), 127.8 (C_q), 116.3 (CH₂), 115.5 (CH₂), 115.4 (CH₂), 112.1 (CH), 111.2 (CH), 110.7 (CH), 69.1 (CH₂), 55.6 (CH₃), 55.6 (CH₃), 39.4 (CH₂);

HRMS (ESI⁺): *m/z* calculated for C₂₉H₃₀O₃ [M+Na] calcd. 449.2108, found 449.2087;

IR ν_{max} (CHCl₃)/cm⁻¹: 3081, 2979, 2837, 1605, 1503, 1964, 1243, 1136, 1030, 997, 917.

5,5',5''-triallyl-2,2''-dimethoxy-[1,1':3',1''-terphenyl]-4'-ol 169



To a solution of 5,5''-diallyl-4'-(allyloxy)-2,2''-dimethoxy-1,1':3',1''-terphenyl (58 mg, 0.136 mmol) in DCM (2.4 mL) at – 78 °C was added diethylaluminium chloride (0.30 mL, 0.272 mmol). The reaction mixture was stirred for 4 h, warmed to r.t. and quenched with 2 M HCl. Extracted with DCM (10 mL x 3), dried over MgSO₄, filtered and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (petroleum ether/ethyl acetate 9:1) to give 5,5',5''-triallyl-2,2''-dimethoxy-[1,1':3',1''-terphenyl]-4'-ol as a yellow oil (30 mg, 52%).

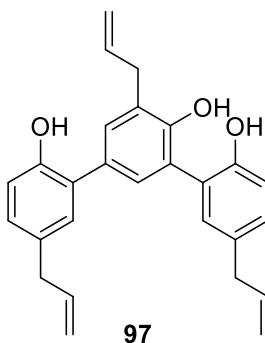
¹H NMR (400 MHz, CDCl₃) δ: 7.36 (1H, d, *J* = 1.9 Hz, H_{Ar}), 7.32 (1H, d, *J* = 2.3 Hz, H_{Ar}), 7.21-7.19 (2H, m, H_{Ar}), 7.16 (1H, d, *J* = 2.3 Hz, H_{Ar}), 7.10 (1H, dd, *J* = 8.3, 2.3 Hz, H_{Ar}), 7.00-6.98 (1H, m, H_{Ar}), 6.91 (1H, d, *J* = 8.3 Hz, H_{Ar}), 6.42 (1H, s, OH), 6.11 (1H, ddt, *J* = 17, 10.2, 6.7 Hz, CH), 5.97 (2H, app. dddt, *J* = 16.9, 10.1, 8.3, 6.7 Hz, CH₂), 5.16-5.03 (6H, m, CH₂), 3.91 (3H, s, CH₃), 3.80 (3H, s, CH₃), 3.54 (2H, d, *J* = 6.6 Hz, CH₂), 3.39-3.36 (4H, m, CH₂);

¹³C NMR (100 MHz, CDCl₃) δ: 154.9 (C_q), 153.9 (C_q), 150.7 (C_q), 137.8 (CH), 137.4 (CH), 137.2 (CH), 133.7 (C_q), 133.0 (CH), 132.2 (C_q), 131.1 (CH), 130.8 (C_q), 130.8 (CH), 130.6 (CH), 130.4 (C_q), 129.0 (CH), 127.9 (CH), 127.7 (C_q), 127.4 (C_q), 125.9 (C_q), 115.9 (CH₂), 115.5 (CH₂), 115.4 (CH₂), 111.5 (CH), 111.3 (CH), 56.3 (CH₃), 55.7 (CH₃), 39.4 (CH₂), 39.4 (CH₂), 34.9 (CH₂);

HRMS (ESI⁺): *m/z* calculated for C₂₉H₃₀O₃ [M+Na] calcd. 449.2097, found 449.2087;

IR ν_{max} (CHCl₃)/cm⁻¹: 3389, 2907, 2834, 1499, 1466, 1231, 1141, 1026, 994, 808, 729.

5,5',5''-triallyl-[1,1':3',1''-terphenyl]-2,2'',4'-triol **97**



To a solution of 5,5',5''-triallyl-2,2''-dimethoxy-[1,1':3',1''-terphenyl]-4'-ol (69.0 mg, 0.162 mmol) in chloroform (2 ml) was added BCl₃·SMe₂ (2 M solution in DCM) (0.24 mL, 0.774 mmol). The reaction mixture was heated to reflux for 23 h and monitored by TLC. A second addition of BCl₃·SMe₂ (2 M solution in DCM) (0.20 mL, 0.400 mmol)

was added and the reaction mixture was stirred at reflux for a further 24 h. The reaction mixture was cooled to r.t., quenched with water and extracted with DCM (10 mL x 3). The DCM solution was dried over MgSO_4 , filtered and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (petroleum ether/ethyl acetate 2:1) to give 5,5',5''-triallyl-[1,1':3',1''-terphenyl]-2,2'',4'-triol as a white solid (13 mg, 22%).

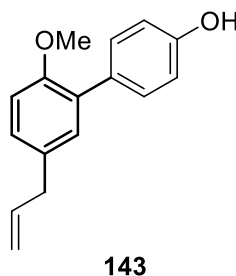
^1H NMR (400 MHz, CDCl_3) δ : 7.30 (1H, d, $J = 2.1$ Hz, H_{Ar}), 7.27-7.26 (1H, m, H_{Ar}), 7.15 (1H, dd, $J = 8.3, 2.3$ Hz, H_{Ar}), 7.11 (1H, d, $J = 2.1$ Hz, H_{Ar}), 7.06-7.04 (2H, m, H_{Ar}), 6.97 (1H, $J = 8.3$ Hz, H_{Ar}), 6.89 (1H, d, $J = 8.9$ Hz, H_{Ar}), 6.07 (1H, ddt, $J = 17.1, 10.2, 6.6$ Hz, CH), 5.96 (2H, m, CH), 5.74 (1H, br s, OH), 5.46 (1H, br s, OH), 5.24-5.04 (7H, m, CH_2/OH), 3.53 (2H, d, $J = 6.7$ Hz, CH_2), 3.36 (4H, dd, $J = 5.9$ Hz, CH_2);

^{13}C NMR (100 MHz, CDCl_3) δ : 151.2 (C_q), 150.8 (C_q), 150.7 (C_q), 137.7 (CH), 137.3 (CH), 136.1 (CH), 133.4 (C_q), 132.4 (C_q), 131.3 (CH), 130.9 (CH), 130.3 (CH), 130.3 (CH), 130.1 (C_q), 130.0 (CH), 128.9 (CH), 128.3 (C_q), 127.4 (C_q), 124.7 (C_q), 123.3 (C_q), 116.7 (CH), 116.7 (CH_2), 115.9 (CH_2), 115.8 (CH), 115.7 (CH_2), 39.4 (CH_2), 39.3 (CH_2), 35.1 (CH_2);

HRMS (ESI^+): m/z calculated for $\text{C}_{27}\text{H}_{26}\text{O}_3$ [$\text{M}+\text{H}$] calcd. 399.1955, found 399.1943;

IR ν_{max} (CHCl_3)/ cm^{-1} : 3548, 3011, 1639, 1603, 1498, 1468, 1179, 996, 918.

5'-allyl-2'-methoxy-[1,1'-biphenyl]-4-ol⁸⁶ 143



To 4-bromophenol (138 mg, 0.800 mmol), Pd₂dba₃ (37 mg, 0.040 mmol), potassium fluoride (232 mg, 4.00 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (S-Phos) (49 mg, 0.120 mmol) was added a solution of (5-allyl-2-methoxyphenyl)boronic acid (230 mg, 1.20 mmol) in THF (10 mL) and H₂O (1 mL). The solution was heated to reflux and stirred for 17.5 h. The solution was cooled to r.t. and diluted with EtOAc (25 mL), washed with 1 M HCl (25 mL x 2) and brine (25 mL x 2), dried over MgSO₄, filtered and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (petroleum ether/EtOAc, 9:1) to give 5'-allyl-2'-methoxy-[1,1'-biphenyl]-4-ol as an orange oil (189 mg, 98%).

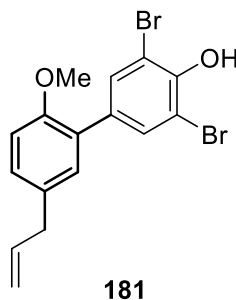
¹H NMR (400 MHz, CDCl₃) δ: 7.42 (2H, d, *J* = 8.8 Hz, H_{Ar}), 7.13-7.08 (2H, m, H_{Ar}), 6.90 (1H, d, *J* = 8.5 Hz, H_{Ar}), 6.87 (2H, d, *J* = 8.8 Hz, H_{Ar}), 5.98 (1H, ddt, *J* = 16.9, 10.1, 6.7 Hz, CH) 5.15-5.00 (2H, m, CH₂), 4.79 (1H, br. s, OH), 3.79 (3H, s, CH₃), 3.37 (2H, d, *J* = 6.7 Hz, CH₂);

¹³C NMR (100 MHz, CDCl₃) δ: 154.9 (C_q), 154.6 (C_q), 137.8 (CH), 132.3 (C_q), 131.1 (C_q), 130.9 (CH), 130.8 (CH), 130.2 (C_q), 128.0 (CH), 115.6 (CH₂), 114.9 (CH), 111.4 (CH), 55.7 (CH₃), 39.4 (CH₂);

HRMS (ESI⁺): C₁₆H₁₆O₂ [M+H]⁺ calcd. 241.1223, found 241.1229;

IR ν_{max} (CHCl_3)/ cm^{-1} : 3598, 3011, 1672, 1621, 1517, 1422, 1175, 1113, 1071, 1043, 918.

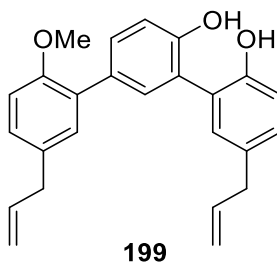
5'-allyl-3, 5-dibromo-2'-methoxy-[1,1'-biphenyl]-4-ol⁸⁶ 181



To a solution of 5'-allyl-2'-methoxy-[1,1'-biphenyl]-4-ol (38 mg, 0.158 mmol) in THF (3.3 mL) at 0 °C was added NBS (56 mg, 0.316 mmol) in one portion. The solution was stirred and allowed to warm to r.t. over 18 h. The reaction mixture was quenched with $\text{Na}_2\text{S}_2\text{O}_3$, stirred for 15 min and diluted with water. The mixture was extracted with EtOAc (5 mL x 3), dried over MgSO_4 , filtered and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (petroleum ether/EtOAc 3:1) to give 5'-allyl-3,5-dibromo-2'-methoxy-[1,1'-biphenyl]-4-ol as a yellow oil (30 mg, 48%).

^1H NMR (400 MHz, CDCl_3) δ : 7.62 (2H, s, H_{Ar}), 7.14 (1H, dd, $J = 8.3, 2.3$ Hz, H_{Ar}), 7.06 (1H, d, $J = 2.1$ Hz, H_{Ar}), 6.90 (1H, d, $J = 8.4$ Hz, H_{Ar}), 5.97 (1H, ddt, $J = 16.9, 10.2, 6.7$ Hz, CH), 5.87 (1H, s, OH), 5.09 (2H, m, CH_2), 3.80 (3H, s, CH_3), 3.36 (2H, d, $J = 6.7$ Hz, CH_2)

5,5''-diallyl-2''-methoxy-[1,1':3',1''-terphenyl]-2,6'-diol 199



To a solution of 5,5''-diallyl-2,2''-dimethoxy-[1,1':3',1''-terphenyl]-4'-ol (637 mg, 1.65 mmol) in chloroform (14 mL) was added $\text{BCl}_3 \cdot \text{SMe}_2$ (296 mg, 1.65 mmol) and the resultant mixture was heated to 70 °C overnight. The reaction mixture was cooled to r.t and quenched with 1 M HCl and extracted with DCM. The organics were dried over MgSO_4 , filtered and the solvent removed *in vacuo*. The crude mixture was purified by flash column chromatography (petroleum ether 40-60 °C/ethyl acetate (3:1)) to give 5,5''-diallyl-2''-methoxy-[1,1':3',1''-terphenyl]-2,6'-diol as a brown oil (491 mg, 80%).

^1H NMR (400 MHz, CDCl_3) δ : 7.52-7.44 (2H, m, H_{Ar}), 7.19-7.10 (4H, m, H_{Ar}), 7.08-7.03 (1H, m, H_{Ar}), 7.00-6.96 (1H, m, H_{Ar}), 6.92 (1H, d, $J = 8.3$ Hz, H_{Ar}), 6.18 (1H, s, OH), 6.13 (1H, s, OH), 6.04-5.90 (2H, m, CH), 5.24-4.90 (4H, m, CH_2), 3.81 (3H, s, CH_3), 3.44-3.31 (4H, m, CH_2);

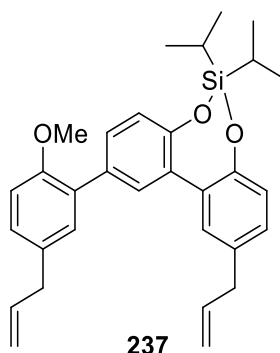
^{13}C NMR (100 MHz, CDCl_3) δ : 154.9 (C_q), 152.2 (C_q), 151.5 (C_q), 137.8 (CH), 137.6 (CH), 133.2 (C_q), 132.5 (C_q), 132.4 (CH), 131.9 (C_q), 131.5 (CH), 131.1 (CH), 131.0 (CH), 129.9 (CH), 129.9 (C_q), 128.4 (CH), 124.3 (C_q), 123.9 (C_q), 116.9 (CH), 116.5 (CH), 115.9 (CH_2), 115.8 (CH_2), 111.4 (CH), 55.8 (CH_3), 39.5 ($\text{CH}_2 \times 2$);

HRMS (ESI⁺): m/z calculated for $\text{C}_{25}\text{H}_{24}\text{O}_3$ [$\text{M}+\text{H}$] calcd. 373.1798, found 373.1785;

IR ν_{max} (CHCl_3)/ cm^{-1} : 3547, 3028, 3006, 2929, 1490, 1259, 1228, 1179, 920, 797, 780.

2-allyl-10-(5-allyl-2-methoxyphenyl)-6,6-diisopropyldibenzo[d,f][1,3,2]dioxasilepine

237



To a solution of 5, 5''-diallyl-2''-methoxy-[1,1':3',1''-terphenyl]-2,6'-diol (47 mg, 0.126 mmol) in DCM (1.30 mL) was added imidazole (13 mg, 0.189 mmol) and dichlorodiisopropylsilane (13 μ L, 0.069 mmol). The reaction was stirred overnight, diluted with DCM, washed with H₂O, NaHCO₃ and brine, dried over MgSO₄ and the solvent removed *in vacuo*. The crude mixture was purified by flash column chromatography (9:1 petroleum ether 40-60 °C/ethyl acetate) to give 2-allyl-10-(5-allyl-2-methoxyphenyl)-6,6-diisopropyldibenzo[d,f][1,3,2]dioxasilepine (38 mg, 62%).

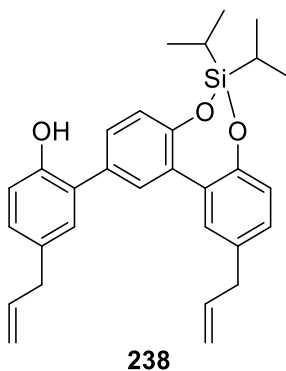
¹H NMR (400 MHz, Chloroform-*d*) δ : 7.53 (1H, d, J = 2.2 Hz, H_{Ar}), 7.45 (1H, dd, J = 8.3, 2.3 Hz, H_{Ar}), 7.21 (2H, dd, J = 8.7, 2.3 Hz, H_{Ar}), 7.16 – 7.04 (3H, m, H_{Ar}), 7.01 (1H, d, J = 8.2 Hz, H_{Ar}), 6.93 (1H, d, J = 8.3 Hz, H_{Ar}), 5.99 (2H, ddt, J = 16.8, 10.1, 6.7 Hz, CH), 5.16 – 5.01 (4H, m, CH₂), 3.81 (3H, s, CH₃), 3.44 – 3.34 (4H, m, CH₂), 1.29 – 1.19 (2H, m, CH), 1.15 – 1.07 (12H, m, CH₃);

¹³C NMR (100 MHz, CDCl₃) δ : 154.9 (C_q), 151.8 (C_q), 151.1 (C_q), 137.8 (CH), 137.6 (CH), 134.3 (C_q), 133.0 (C_q), 132.4 (CH), 131.5 (CH), 131.1 (CH), 130.2 (C_q), 130.1 (CH), 129.6 (C_q), 129.2 (C_q), 129.0 (CH), 128.2 (CH), 121.0 (CH), 120.6 (CH), 115.7 (CH₂), 115.6 (CH₂), 111.5 (CH), 55.8 (CH₃), 39.6 (CH₂), 39.4 (CH₂), 17.0 (CH₃), 12.5 (CH);

HRMS (ESI⁺): m/z calculated for C₃₁H₃₆O₃Si [M+Na] calcd. 507.2326, found 507.2306;

IR ν_{max} (CHCl₃)/cm⁻¹: 2947, 2867, 1487, 1267, 1117, 994, 906, 731.

4-allyl-2-(10-allyl-6,6-diisopropyldibenzo[d,f][1,3,2]dioxasilepin-2-yl)phenol 238



To a solution of 2-allyl-10-(5-allyl-2-methoxyphenyl)-6,6-diisopropyldibenzo[d,f][1,3,2]dioxasilepine (60 mg, 0.124 mmol) in 1,2-dichloroethane (1 mL) was added BCl₃·SMe₂ (67 mg, 0.372 mmol) and heated to reflux (95 °C) overnight. The reaction mixture was cooled to r.t., quenched with 1 M HCl, extracted with DCM, dried over MgSO₄ and the solvent removed *in vacuo*. The crude mixture was purified by flash column chromatography (petroleum ether 40-60 °C/ethyl acetate (3:1)) to give 4-allyl-2-(10-allyl-6,6-diisopropyldibenzo[d,f][1,3,2]dioxasilepin-2-yl)phenol (41 mg, 71%).

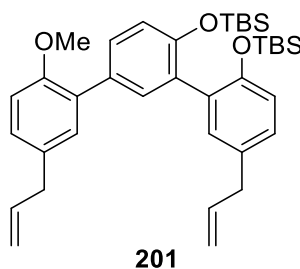
¹H NMR (400 MHz, CDCl₃) δ : 7.47 (1H, d, J = 2.3 Hz, H_{Ar}), 7.37 (1H, dd, J = 8.2, 2.3 Hz, H_{Ar}), 7.20 – 7.06 (5H, m, H_{Ar}), 7.01 (1H, d, J = 8.2 Hz, H_{Ar}), 6.97 – 6.90 (1H, m, H_{Ar}), 6.08 – 5.89 (2H, m, CH), 5.16 – 4.99 (4H, m, CH₂), 3.41 – 3.34 (4H, m, CH₂), 1.30 – 1.19 (2H, m, CH), 1.15 – 1.07 (12H, m, CH₃);

¹³C NMR (126 MHz, CDCl₃) δ : 152.7 (C_q), 151.1 (C_q), 150.9 (C_q), 137.9 (CH), 137.6 (CH), 134.7 (C_q), 132.4 (C_q), 132.0 (CH), 131.6 (C_q), 131.4 (CH), 130.7 (C_q), 130.4 (CH), 129.7 (CH), 129.6 (CH), 129.2 (CH), 129.0 (C_q), 127.7 (C_q), 122.1 (CH), 121.3 (CH), 116.0 (CH₂), 115.9 (CH), 115.8 (CH₂), 39.6 (CH₂), 39.6 (CH₂), 17.1 (CH₃), 12.5 (CH);

HRMS (ESI⁺): *m/z* calculated for C₃₀H₃₄O₃Si [M+Na] calcd. 493.2169, found 493.2165;

IR ν_{max} (CHCl₃)/cm⁻¹: 3433, 2867, 1490, 1267, 1116, 907, 828, 695, 598.

((5,5''-diallyl-2''-methoxy-[1,1':3',1''-terphenyl]-2,6'-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) 201



To a solution of 5,5''-diallyl-2''-methoxy-[1,1':3',1''-terphenyl]-2,6'-diol (96 mg, 0.258 mmol) in chloroform (2mL) was added imidazole (92 mg, 1.35 mmol) and *tert*-butyldimethylsilyl chloride (175 mg, 1.16 mmol). The reaction was stirred overnight, diluted with EtOAc, washed with H₂O, 1 M HCl, NaHCO₃ and brine, dried over MgSO₄ and the solvent removed *in vacuo*. The crude mixture was purified by flash column chromatography (petroleum ether 40-60 °C to 10% ethyl acetate in petroleum ether 40-60 °C) to give ((5,5''-diallyl-2''-methoxy-[1,1':3',1''-terphenyl]-2,6'-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) (129 mg, 84%).

¹H NMR (400 MHz, CDCl₃) δ : 7.40-7.31 (2H, m, H_{Ar}), 7.15-7.05 (3H, m, H_{Ar}), 6.99 (1H, dd, *J* = 8.2, 2.4 Hz, H_{Ar}), 6.88 (1H, d, *J* = 8.3 Hz, H_{Ar}), 6.84 (1H, d, *J* = 8.3 Hz, H_{Ar}), 6.77 (1H, d, *J* = 8.2 Hz, H_{Ar}), 6.03-5.88 (2H, m, CH), 5.12-4.98 (4H, m, CH₂), 3.76 (3H, s, CH₃), 3.38-3.29 (4H, m, CH₂), 0.77 (9H, s, CH₃), 0.74 (9H, s, CH₃), 0.04 (6H, s, CH₃), -0.04 (6H, s, CH₃);

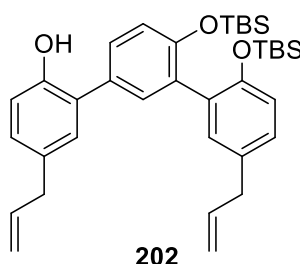
¹³C NMR (100 MHz, CDCl₃) δ : 155.1 (C_q), 152.4 (C_q), 151.7 (C_q), 138.1 (CH), 138.0 (CH), 133.1 (CH), 132.3 (CH), 131.9 (C_q), 131.2 (CH), 131.1 (C_q), 130.8 (C_q), 130.8 (C_q), 130.4

(C_q), 129.4 (CH), 128.1 (CH), 127.9 (CH), 119.4 (CH), 118.5 (CH), 115.6 (CH₂), 115.4 (CH₂), 111.5 (CH), 55.8 (CH₃), 39.7 (CH₂), 39.6 (CH₂), 25.6 (CH₃), 25.5 (CH₃), 18.1 (C_q), -4.3 (CH₃), -4.5 (CH₃);

HRMS (ESI⁺): *m/z* calculated for C₃₇H₅₂O₃Si₂ [M+H] calcd. 623.3347, found 623.3336;

IR ν_{max} (CHCl₃)/cm⁻¹: 2928, 2856, 1485, 1250, 910, 838, 805, 777.

5,5''-diallyl-2'',4'-bis((*tert*-butyldimethylsilyl)oxy)-[1,1':3',1''-terphenyl]-2-ol 202



To a solution of ((5,5''-diallyl-2''-methoxy-[1,1':3',1''-terphenyl]-2,6'-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) (372 mg, 0.619 mmol) in 1,2-dichloroethane (6 mL) was added BCl₃·SMe₂ (333 mg, 1.86 mmol) and heated to reflux (95 °C) overnight. The reaction mixture was cooled to r.t., quenched with 1 M HCl, extracted with dichloromethane, dried over MgSO₄ and the solvent removed *in vacuo*. The crude mixture was purified by flash column chromatography (petroleum ether 40-60 °C/ethyl acetate (9:1)) to give 5,5''-diallyl-2'',4'-bis((*tert*-butyldimethylsilyl)oxy)-[1,1':3',1''-terphenyl]-2-ol as brown oil (287 mg, 79%).

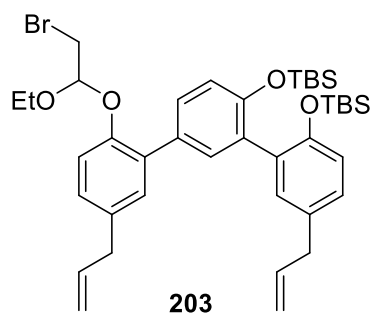
¹H NMR (400 MHz, CDCl₃) δ : 7.34 (1H, d, *J* = 2.3 Hz, H_{Ar}), 7.31-7.24 (1H, m, H_{Ar}), 7.10 (1H, d, *J* = 2.3 Hz, H_{Ar}), 7.09-6.99 (3H, m, H_{Ar}), 6.96 (1H, d, *J* = 8.8 Hz, H_{Ar}), 6.92 (1H, d, *J* = 8.8 Hz, H_{Ar}), 6.79 (1H, d, *J* = 8.2 Hz, H_{Ar}), 6.05-5.91 (2H, m, CH), 5.17 (1H, s, OH), 5.13-5.02 (4H, m, CH₂), 3.35-3.31 (4H, m, CH₂), 0.80 (9H, s, CH₃), 0.74 (9H, s, CH₃), 0.07 (6H, s, CH₃), 0.02 (6H, s, CH₃);

^{13}C NMR (100 MHz, CDCl_3) δ : 153.3 (C_q), 151.5 (C_q), 151.0 (C_q), 138.0 (CH), 138.0 (CH), 132.9 (CH), 132.2 (C_q), 132.1 (C_q), 132.0 (CH), 130.3 (CH), 130.1 (C_q), 129.1 (C_q), 128.9 (CH), 128.7 (CH), 128.5 (CH), 127.9 (C_q), 120.0 (CH), 119.3 (CH), 115.6 (CH_2), 115.6 (CH), 115.5 (CH_2), 39.6 (CH_2), 39.6 (CH_2), 25.5 (CH_3), 25.5 (CH_3), 18.1 (C_q), 18.1 (C_q), -4.35 (CH_3), -4.39 (CH_3);

HRMS (ESI $^+$): m/z calculated for $\text{C}_{36}\text{H}_{50}\text{O}_3\text{Si}_2$ [$\text{M}+\text{Na}$] calcd. 609.3191, found 609.3191;

IR ν_{max} (CHCl_3)/ cm^{-1} : 2929, 2857, 1484, 1251, 910, 837, 777.

((5,5''-diallyl-2''-(2-bromo-1-ethoxyethoxy)-[1,1':3',1''-terphenyl]-2,6'-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) 203



To a solution of bromine (34 μL , 0.678 mmol) in DCM (1 mL) at 0 $^{\circ}\text{C}$ (ice bath) was added ethyl vinyl ether (81 μL , 0.848 mmol). The reaction mixture was stirred for 20 minutes before addition of a solution of 2'',4'-bis((*tert*-butyldimethylsilyl)oxy)-[1,1':3',1''-terphenyl]-2-ol (199 mg, 0.339 mmol) and diisopropylethylamine (237 μL , 1.36 mmol) in DCM (1 mL). The reaction mixture was left to warm up overnight in an ice bath. The reaction mixture was diluted with DCM and the organics were washed with NaHCO_3 , brine, dried over MgSO_4 and the solvent removed *in vacuo*. The crude mixture was purified by flash column chromatography (10% ethyl acetate in petroleum ether 40-60 $^{\circ}\text{C}$) to give ((5,5''-diallyl-2''-(2-bromo-1-ethoxyethoxy)-[1,1':

3',1''-terphenyl]-2,6'-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) as brown oil (202 mg, 81%).

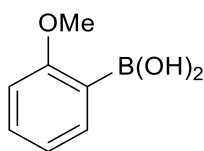
¹H NMR (400 MHz, CDCl₃) δ: 7.43 – 7.34 (2H, m, H_{Ar}), 7.16 (1H, d, *J* = 2.0 Hz, H_{Ar}), 7.11 – 7.03 (3H, m, H_{Ar}), 7.00 (1H, dd, *J* = 8.2, 2.4 Hz, H_{Ar}), 6.85 (1H, d, *J* = 8.2 Hz, H_{Ar}), 6.77 (1H, d, *J* = 8.2 Hz, H_{Ar}), 6.03 – 5.89 (2H, m, CH), 5.17 (1H, dd, *J* = 6.1, 4.5 Hz, CH), 5.12 – 4.99 (4H, m, CH₂), 3.65 (1H, dq, *J* = 9.3, 7.0 Hz, CH), 3.49 (1H, dq, *J* = 9.3, 7.0 Hz, CH), 3.40 – 3.30 (6H, m, CH₂), 1.13 (3H, t, *J* = 7.0 Hz, CH₃), 0.78 (9H, s, CH₃), 0.75 (9H, s, CH₃), 0.02 (6H, app d, *J* = 2.0 Hz, CH₃), -0.02 (6H, s, CH₃);

¹³C NMR (101 MHz, CDCl₃) δ: 152.6 (C_q), 151.8 (C_q), 151.6 (C_q), 138.1 (CH), 137.6 (CH), 134.9 (C_q), 133.0 (CH), 132.2 (CH), 132.0 (C_q), 131.4 (CH), 130.8 (C_q), 130.5 (C_q), 129.5 (CH), 128.2 (CH), 128.1 (CH), 119.3 (CH), 118.8 (CH), 118.4 (CH), 115.9 (CH₂), 115.4 (CH₂), 102.1 (CH), 62.9 (CH₂), 39.7 (CH₂), 31.7 (CH₂), 29.9 (CH₂), 25.6 (CH₃), 25.5 (CH₃), 18.1 (C_q), 18.1 (C_q), 15.2 (CH₃), -4.4 (CH₃), -4.4 (CH₃);

HRMS (ESI⁺): *m/z* calculated for C₄₀H₅₇BrO₄Si₂ [M+H]⁺ calcd. 759.2871, found 759.2859;

IR ν_{max} (CHCl₃)/cm⁻¹: 2927, 2855, 1482, 1417, 1251, 1122, 910, 838, 778.

(2-methoxyphenyl)boronic acid⁹⁴ 207



207

To a solution of 2-bromoanisole (1.00 mL, 8.01 mmol) in THF (30 mL) at -78 °C (acetone/CO₂(s)) was added ^tBuLi (5.20 mL, 8.82 mmol) over 15 minutes *via* a syringe pump. After 1 h trimethylborate (0.90 mL, 8.01 mmol) was added and the resultant

mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 minutes before warming to r.t. for 1.5 h. The reaction mixture was acidified with 1 M HCl (pH 3-4) and stirred for 45 minutes, before dilution with EtOAc. The organics were washed with brine, dried over MgSO_4 and the solvent removed *in vacuo* to give (2-methoxyphenyl)boronic acid as a white solid (1.18 g, 97%).

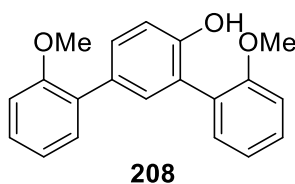
^1H NMR (400 MHz, CDCl_3) δ : 7.86 (1H, dd, $J = 7.3, 1.9\text{ Hz}$, H_{Ar}), 7.46 (1H, ddd, $J = 8.3, 7.3, 1.9\text{ Hz}$, H_{Ar}), 7.04 (1H, app. td, $J = 7.4, 1.0\text{ Hz}$, H_{Ar}), 6.92 (1H, dd, $J = 8.3, 0.9\text{ Hz}$, H_{Ar}), 6.27 (2H, s, OH), 3.92 (3H, s, CH_3);

^{13}C NMR (100 MHz, CDCl_3) δ : 164.7 (C_q), 137.0 (C_{Ar}), 133.0 (C_{Ar}), 121.4 (C_{Ar}), 110.1 (C_{Ar}), 55.6 (CH_3);

HRMS (ESI^+): m/z calculated for $\text{C}_7\text{H}_9\text{BO}_3$ [$\text{M}-\text{H}$] calcd. , found ; Did not ionise.

IR ν_{max} (CHCl_3)/ cm^{-1} : 3457, 3349, 3207, 1599, 1434, 1194, 1163, 1052, 1023, 742, 640, 526.

2,2''-dimethoxy-[1,1': 3',1''-terphenyl]-4'-ol **208**



A solution of (2-methoxyphenyl)boronic acid (150 mg, 0.957 mmol), 2,4-dibromophenol (100 mg, 0.395 mmol), $\text{Pd}(\text{dba})_2$ (23 mg, 0.040 mmol), potassium fluoride (115 mg, 1.98 mmol) and s-Phos (49 mg, 0.120 mmol) in THF (10 mL) and H_2O (1 mL) was heated at $95\text{ }^{\circ}\text{C}$ overnight. The reaction mixture was cooled to r.t., diluted with ethyl acetate, washed with 1 M HCl and brine, dried over MgSO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column

chromatography (petroleum ether 40-60 °C/ethyl acetate(3:1)) to give 2,2''-dimethoxy-[1,1':3',1''-terphenyl]-4'-ol as a yellow oil (111 mg, 92%).

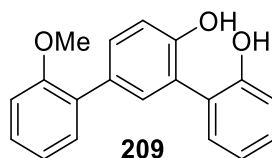
¹H NMR (400 MHz, CDCl₃) δ: 7.56-7.51 (1H, m, H_{Ar}), 7.48 (1H, d, *J* = 2.2 Hz, H_{Ar}), 7.45-7.35 (3H, m H_{Ar}), 7.31 (1H, ddd, *J* = 8.2, 7.4, 1.8 Hz, H_{Ar}), 7.17-7.06 (3H, m, H_{Ar}), 6.41 (1H, s, OH), 3.95 (3H, s, CH₃), 3.84 (3H, s, CH₃);

¹³C NMR (100 MHz, CDCl₃) δ: 156.6 (C_q), 155.6 (C_q), 153.0 (C_q), 132.7 (CH), 132.6 (CH), 131.3 (C_q), 130.9 (CH), 130.6 (CH), 130.4 (C_q), 129.3 (CH), 128.3 (CH), 127.4 (C_q), 126.0 (C_q), 122.3 (CH), 120.9 (CH), 117.2 (CH), 111.6 (CH), 111.3 (CH), 56.3 (CH₃), 55.6 (CH₃);

HRMS (ESI⁺): *m/z* calculated for C₂₀H₁₈O₃ [M+H] calcd. 307.1329, found 307.1322;

IR ν_{max} (CHCl₃)/cm⁻¹: 3548, 3045, 2941, 2839, 1598, 1578, 1482, 1436, 1249, 1026.

2''-methoxy-[1,1':3',1''-terphenyl]-2,6'-diol **209**



To a solution of 2,2''-dimethoxy-[1,1':3',1''-terphenyl]-4'-ol (2.66 mg, 8.68 mmol) in 1,2-dichloroethane (44 mL) was added BCl₃·SMe₂ (1.56 g, 8.68 mmol) and heated at 70 °C overnight. The reaction mixture was cooled to r.t. and quenched with 1 M HCl. The organics were extracted with DCM, dried over MgSO₄ and the solvent removed *in vacuo*. The crude mixture was purified by flash column chromatography (petroleum ether 40-60 °C/ethyl acetate (3:1)) to give 2''-methoxy-[1,1':3',1''-terphenyl]-2,6'-diol as a yellow oil (2.26 g, 89%).

¹H NMR (400 MHz, CDCl₃) δ: 7.51 (1H, dd, *J* = 8.3, 2.3 Hz, H_{Ar}), 7.47 (1H, d, *J* = 2.2 Hz, H_{Ar}), 7.36-7.28 (4H, m, H_{Ar}), 7.11-6.95 (5H, m, H_{Ar}), 5.77 (1H, s, OH), 5.64 (1H, s, OH), 3.83 (3H, s, CH₃);

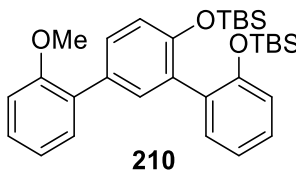
¹³C NMR (100 MHz, CDCl₃) δ: 156.5 (C_q), 153.3 (C_q), 152.2 (C_q), 132.3 (CH), 132.0 (C_q), 131.3 (CH), 130.8 (CH), 130.2 (CH), 129.8 (C_q), 128.6 (CH), 123.5 (C_q), 122.9 (C_q), 121.7 (CH), 121.1 (CH), 116.9 (CH), 116.5 (CH), 111.3 (CH), 55.70 (CH₃);

HRMS (ESI⁺): *m/z* calculated for C₁₉H₁₆O₃ [M-H] calcd. 291.1027, found 291.1025;

IR ν_{max} (CHCl₃)/cm⁻¹: 3547, 3008, 2838, 1578, 1480, 1375, 1251, 1182, 1046, 1029.

((2''-methoxy-[1,1':3',1''-terphenyl]-2,6'-diyl)bis(oxy))bis(*tert*-butyldimethylsilane)

210



To a solution of give 2''-methoxy-[1,1':3',1''-terphenyl]-2,6'-diol (2.26 mg, 7.73 mmol) in dimethylformamide (39 mL) was added imidazole (2.63 g, 38.7 mmol) and *tert*-butyldimethylsilyl chloride (2.80 mg, 18.6 mmol). The reaction was stirred for 17.5 h, diluted with diethyl ether, washed with H₂O, 1 M HCl, NaHCO₃ and brine, dried over MgSO₄ and the solvent removed *in vacuo* to give ((2''-methoxy-[1,1':3',1''-terphenyl]-2,6'-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) as an oil (3.83 g, 95%). Used without additional purification.

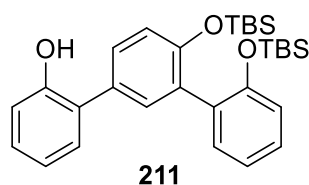
¹H NMR (400 MHz, CDCl₃) δ: 7.42 (1H, d, *J* = 2.4 Hz, H_{Ar}), 7.38 (1H, dd, *J* = 8.3, 2.4 Hz, H_{Ar}), 7.34-7.24 (3H, m, H_{Ar}), 7.23-7.15 (1H, m, H_{Ar}), 7.04-6.92 (3H, m, H_{Ar}), 6.89-6.81

(2H, m, H_{Ar}), 3.80 (3H, s, CH_3), 0.78 (9H, s, CH_3), 0.76 (9H, s, CH_3), 0.05 (6H, s, CH_3), -0.02 (6H, m, CH_3);

^{13}C NMR (100 MHz, $CDCl_3$) δ : 156.7 (C_q), 153.5 (C_q), 152.5 (C_q), 133.1 (CH), 132.0 (CH), 131.4 (C_q), 130.9 (CH), 130.8 ($2C_q$), 130.5 (C_q), 129.4 (CH), 128.1 (CH), 128.1 (CH), 120.8 (CH), 120.7 (CH), 119.6 (CH), 118.6 (CH), 111.4 (CH), 55.6 (CH_3), 25.5 (CH_3), 25.5 (CH_3), 18.1 ($2C_q$), -4.4 (CH_3), -4.5 (CH_3);

HRMS (ESI⁺): m/z calculated for $C_{31}H_{44}O_3Si_2$ [M+H] calcd. 521.2902, found 529.2899;

2'',4'-bis((*tert*-butyldimethylsilyl)oxy)-[1,1':3',1''-terphenyl]-2-ol 211



To a solution of ((2''-methoxy-[1,1':3',1''-terphenyl]-2,6'-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) (4.03 g, 7.73 mmol) in 1,2-dichloroethane (25 mL) was added $BCl_3 \cdot SMe_2$ (4.16 g, 23.2 mmol) and the resultant mixture was heated to 95 °C for 22 h. The reaction mixture was quenched with 1 M HCl, extracted with DCM, dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude mixture was purified by flash column chromatography (petroleum ether 40-60 °C/ethyl acetate (9:1)) to give 2'',4'-bis((*tert*-butyldimethylsilyl)oxy)-[1,1':3',1''-terphenyl]-2-ol as an oil (2.47 g, 63%).

^1H NMR (400 MHz, $CDCl_3$) δ : 7.33 (1H, d, J = 2.4 Hz, H_{Ar}), 7.29-7.14 (5H, m, H_{Ar}), 7.01-6.92 (4H, m, H_{Ar}), 6.83 (1H, dd, J = 8.1, 1.2 Hz, H_{Ar}), 5.28 (1H, s, OH), 0.77 (9H, s, CH_3), 0.73 (9H, s, CH_3), 0.04 (6H, s, CH_3), 0.00 (6H, s, CH_3);

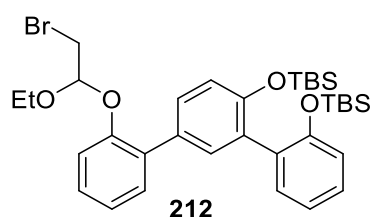
^{13}C NMR (100 MHz, $CDCl_3$) δ : 153.2 (C_q), 153.2 (C_q), 152.5 (C_q), 132.6 (CH), 132.1 (C_q), 131.6 (CH), 130.3 (C_q), 130.1 (CH), 128.9 (C_q), 128.7 (CH), 128.6 (CH), 128.4 (CH),

127.9 (C_q), 120.6 (CH), 120.6 (CH), 119.9 (CH), 119.2 (CH), 115.5 (CH), 25.3 (CH₃), 25.3 (CH₃), 17.9 (C_q), -4.55 (2 x CH₃);

HRMS (ESI⁺): *m/z* calculated for C₃₁H₄₄O₃Si₂ [M+H] calcd. 507.2747, found 507.2745;

IR ν_{max} (CHCl₃)/cm⁻¹: 3553, 2929, 1475, 1250, 910, 837, 778, 751.

((2''-(2-bromo-1-ethoxyethoxy)-[1,1':3',1''-terphenyl]-2,6'-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) 212



To a solution of bromine (0.48 mL, 9.44 mmol) in DCM (14 mL) at 0 °C (ice bath) was added ethyl vinyl ether (1.13 mL, 11.8 mmol). The reaction mixture was stirred for 15 minutes before addition of a solution of 2'',4'-bis((*tert*-butyldimethylsilyl)oxy)-[1,1':3',1''-terphenyl]-2-ol (2.39 g, 4.72 mmol) in DCM (12 mL). The reaction mixture was left to warm up overnight in an ice bath. The organics were washed with NaHCO₃ and brine, dried over MgSO₄ and the solvent removed *in vacuo*. The crude mixture was purified by flash column chromatography (5% ethyl acetate in petroleum ether 40-60 °C) to give ((2''-(2-bromo-1-ethoxyethoxy)-[1,1':3',1''-terphenyl]-2,6'-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) as brown oil (2.59 g, 83%).

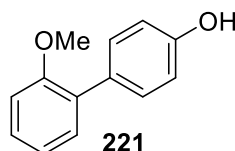
¹H NMR (400 MHz, CDCl₃) δ : 7.47-7.40 (2H, m, H_{Ar}), 7.37 (1H, dd, *J* = 7.6, 1.8 Hz, H_{Ar}), 7.31-7.25 (2H, m, H_{Ar}), 7.24-7.16 (2H, m, H_{Ar}), 7.16-7.07 (1H, m, H_{Ar}), 7.02-6.95 (1H, m, H_{Ar}), 6.91-6.83 (2H, m, H_{Ar}), 5.25 (1H, dd, *J* = 6.1, 4.6 Hz, H_{Ar}), 3.72-.93 (1H, m, CH), 3.69-3.62 (1H, m, CH), 3.54-3.46 (2H, m, CH₂), 1.14 (3H, *J* = 7.0 Hz, CH₃), 0.80 (9H, s, CH₃), 0.78 (9H, s, CH₃), 0.02 (12H, app. dd, *J* = 12.1, 2.3 Hz, CH₃).

¹³C NMR (100 MHz, CDCl₃) δ: 153.5 (C_q), 153.5 (C_q), 152.7 (C_q), 133.1 (C_q), 132.9 (CH), 131.9 (CH), 131.2 (C_q), 131.2 (CH), 130.9 (C_q), 130.5 (C_q), 129.6 (CH), 128.3 (CH), 128.1 (CH), 123.3 (CH), 120.7 (CH), 119.4 (CH), 118.9 (CH), 118.2 (CH), 102.1 (CH), 62.9 (CH₂), 31.7 (CH₂), 25.5 (CH₃), 25.5 (CH₃), 18.1 (C_q), 15.2 (CH₃), -4.4 (CH₃);

HRMS (ESI⁺): *m/z* calculated for C₃₄H₄₉BrO₄Si₂ [M+H] calcd. 679.2245, found 679.2237;

IR ν_{max} (CHCl₃)/cm⁻¹: 2929, 2857, 1478, 1250, 911, 835, 778, 752.

2'-methoxy-[1,1'-biphenyl]-4-ol⁹⁵ 221



A solution of (2-methoxyphenyl)boronic acid (2.00 g, 13.2 mmol), 2,4-dibromophenol (1.52 g, 8.80 mmol), Pd(dba)₂ (506 mg, 0.880 mmol), potassium fluoride (2.56 g, 44.0 mmol) and s-Phos (1.08 g, 2.64 mmol) in THF (44 mL) and H₂O (4mL) was heated at 95 °C overnight. The reaction mixture was cooled to r.t., diluted with ethyl acetate, washed with 1 M HCl and brine, dried over MgSO₄ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (petroleum ether 40-60 °C/ethyl acetate (9:1 to 3:1)) to give 2'-methoxy-[1,1'-biphenyl]-4-ol as a yellow oil (1.97 g, >100%).

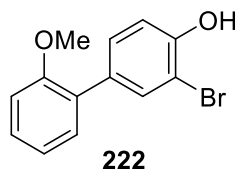
¹H NMR (400 MHz, CDCl₃) δ: 7.45-7.40 (2H, m, H_{Ar}), 7.33-7.27 (2H, m, H_{Ar}), 7.02 (2H, app. td, *J* = 7.5, 1.1 Hz, H_{Ar}), 6.98 (2H, dd, *J* = 8.6, 1.1 Hz, H_{Ar}), 4.88 (1H, s, OH), 3.82 (3H, s, CH₃);

¹³C NMR (100 MHz, CDCl₃) δ: 156.6 (C_q), 154.8 (C_q), 131.2 (C_q), 130.9 (CH), 130.8 (CH), 130.4 (C_q), 128.3 (CH), 121.0 (CH), 115.1 (CH), 111.4 (CH), 55.7 (CH₃)

HRMS (ESI⁺): m/z calculated for C₁₃H₁₂O [M-H] calcd. 199.0765, found 199.0759;

IR $\nu_{\max}$ (CHCl₃)/cm⁻¹: 3596, 3009, 2960, 2911, 2837, 1613, 1596, 1518, 1487, 1464, 1421, 1331, 1259, 1174, 1123, 1056, 1029, 834.

3-bromo-2'-methoxy-[1,1'-biphenyl]-4-ol 222



To a solution of 2'-methoxy-[1,1'-biphenyl]-4-ol (1.48 g, 7.39 mmol) in dimethylformamide (37 mL) was added a solution of N-bromosuccinimide (1.45 g, 8.13 mmol) in dimethylformamide (12 mL) over 30 minutes. After 6 h the reaction was quenched with Na₂S₂O₃ saturated solution, the organics were washed with H₂O and brine, dried over MgSO₄ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (petroleum ether 40-60 °C to petroleum ether/ethyl acetate (9:1)) to give 3-bromo-2'-methoxy-[1,1'-biphenyl]-4-ol as a brown oil (1.49 g, 72%).

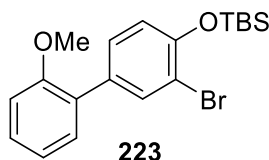
¹H NMR (400 MHz, CDCl₃) δ : 7.66 (1H, d, J = 2.1 Hz, H_{Ar}), 7.40 (1H, dd, J = 8.4, 2.1 Hz, H_{Ar}), 7.32 (1H, ddd, J = 8.2, 7.4, 1.8 Hz, H_{Ar}), 7.27 (1H, dd, J = 7.6, 1.8 Hz, H_{Ar}), 7.06 (1H, J = 8.4 Hz, H_{Ar}), 7.02 (1H, app. td, J = 7.5, 1.1 Hz, H_{Ar}), 6.97 (1H, dd, J = 8.3, 1.0 Hz, H_{Ar}), 5.25 (1H, s, OH), 3.82 (3H, s, CH₃);

¹³C NMR (100 MHz, CDCl₃) δ : 156.3 (C_q), 151.2 (C_q), 132.8 (CH), 132.4 (C_q), 130.6 (CH), 130.4 (CH), 128.8 (C_q), 128.8 (CH), 120.9 (CH), 115.5 (CH), 111.2 (CH), 109.9 (C_q), 55.6 (CH₃);

HRMS (EI⁺): m/z calculated for C₁₃H₁₁BrO₂ [M-H] calcd. 277.9926, found ; 277.9936

IR $\nu_{\max}$ (CHCl₃)/cm⁻¹: 3397, 3011, 2839, 1731, 1598, 1578, 1482, 1249, 1045, 909.

((3-bromo-2'-methoxy-[1,1'-biphenyl]-4-yl)oxy)(tert-butyl)dimethylsilane 223



To a solution of 3-bromo-2'-methoxy-[1,1'-biphenyl]-4-ol (1.34 g, 4.80 mmol) in dimethylformamide (5 mL) was added imidazole (817 mg, 12.0 mmol) and *tert*-butyldimethylsilyl chloride (1.09 g, 7.20 mmol). The reaction was stirred overnight, diluted with diethyl ether, washed with H₂O, 1 M HCl, NaHCO₃ and brine, dried over MgSO₄, filtered and the solvent removed *in vacuo* to give ((3-bromo-2'-methoxy-[1,1'-biphenyl]-4-yl)oxy)(*tert*-butyl)dimethylsilane (carried into the next stage, > 100%).

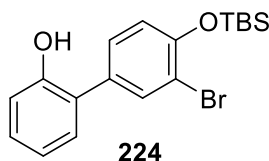
¹H NMR (400 MHz, CDCl₃) δ : 7.74 (1H, d, *J* = 2.2 Hz, H_{Ar}), 7.37 (1H, dd, *J* = 8.4, 2.2 Hz, H_{Ar}), 7.34-7.28 (2H, m, H_{Ar}), 7.02 (1H, app. td, *J* = 7.5, 1.1 Hz, H_{Ar}), 6.98 (1H, dd, *J* = 8.2, 1.1 Hz, H_{Ar}), 6.92 (1H, d, *J* = 8.4 Hz, H_{Ar}), 3.83 (3H, s, CH₃), 1.09 (9H, s, CH₃), 0.31 (6H, s, CH₃);

¹³C NMR (100 MHz, CDCl₃) δ : 156.5 (C_q), 151.6 (C_q), 134.3 (CH), 132.8 (C_q), 130.7 (CH), 129.5 (CH), 129.1 (C_q), 128.8 (CH), 121.0 (CH), 119.5 (CH), 114.9 (C_q), 111.3 (CH), 55.7 (CH₃), 25.9 (CH₃), 18.5 (C_q), -4.0 (CH₃);

HRMS (ESI⁺): *m/z* calculated for C₁₉H₂₅BrO₂Si [M+H] calcd. 393.0880, found 393.0884;

IR $\nu_{\max}$ (CHCl₃)/cm⁻¹: 3011, 2932, 2860, 1597, 1481, 1384, 1253, 1182, 1122, 1029, 921, 830, 776, 712.

3'-bromo-4'-((*tert*-butyldimethylsilyl)oxy)-[1,1'-biphenyl]-2-ol 224



To a solution of ((3-bromo-2'-methoxy-[1,1'-biphenyl]-4-yl)oxy)(*tert*-butyl)dimethylsilane (1.82 g, 4.80 mmol) in 1,2-dichloroethane (24 mL) was added $\text{BCl}_3 \cdot \text{SMe}_2$ (2.58 g, 14.4 mmol) and heated to 95 °C for 17 h. The reaction mixture was cooled to r.t. and quenched with 1 M HCl. The HCl was extracted with DCM, washed with brine, dried over MgSO_4 , filtered and the solvent removed *in vacuo*. The crude mixture was purified by flash column chromatography (petroleum ether 40-60 °C to petroleum ether/ethyl acetate) to give 3'-bromo-4'-((*tert*-butyldimethylsilyl)oxy)-[1,1'-biphenyl]-2-ol as an oil (1.58 g, 87%).

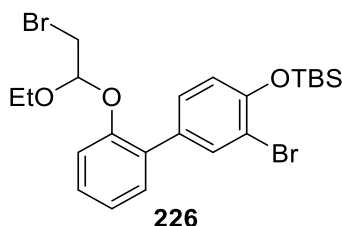
^1H NMR (400 MHz, CDCl_3) δ : 7.66 (1H, d, $J = 2.2$ Hz, H_{Ar}), 7.29 (1H, dd, $J = 8.3, 2.2$ Hz, H_{Ar}), 7.27-7.18 (2H, m, H_{Ar}), 7.01-6.94 (3H, m, H_{Ar}), 5.13 (1H, s, OH), 1.08 (9H, s, CH_3), 0.30 (6H, s, CH_3);

^{13}C NMR (100 MHz, CDCl_3) δ : 152.5 (C_q), 152.5 (C_q), 134.2 (CH), 131.4 (C_q), 130.4 (CH), 129.3 (CH), 129.1 (CH), 126.8 (C_q), 121.1 (CH), 120.6 (CH), 116.2 (C_q), 116.0 (CH), 25.6 (CH_3), 18.5 (C_q), -4.0 (CH_3);

HRMS (ESI⁺): m/z calculated for $\text{C}_{18}\text{H}_{23}\text{BrO}_2\text{Si}$ [$\text{M}+\text{H}$] calcd. 379.0723, found 379.0716;

IR ν_{max} (CHCl_3)/ cm^{-1} : 3558, 2959, 2932, 2860, 1598, 1464, 1300, 1182, 1046, 921, 842.

((3-bromo-2'-(2-bromo-1-ethoxyethoxy)-[1,1'-biphenyl]-4-yl)oxy)(tert-butyl)dimethylsilane 226



To a solution of bromine (0.21 mL, 4.06 mmol) in DCM (6 mL) at 0 °C (ice bath) was added ethyl vinyl ether (0.47 mL, 4.87 mmol). The reaction mixture was stirred for 15 minutes before addition of a solution of 3'-bromo-4'-((*tert*-butyldimethylsilyl)oxy)-[1,1'-biphenyl]-2-ol (770 mg, 2.03 mmol) in DCM (5 mL). The reaction mixture was left to warm up overnight in an ice bath. The organics were washed with NaHCO₃, brine, dried over MgSO₄, filtered and the solvent removed *in vacuo* to give ((3-bromo-2'-(2-bromo-1-ethoxyethoxy)-[1,1'-biphenyl]-4-yl)oxy)(*tert*-butyl)dimethylsilane as a brown oil (970 mg, 90%).

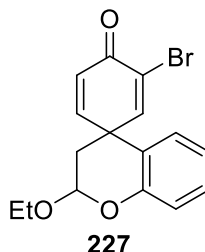
¹H NMR (400 MHz, CDCl₃) δ: 7.73 (1H, d, *J* = 2.2 Hz, H_{Ar}), 7.36 (1H, dd, *J* = 8.4, 2.2, H_{Ar}), 7.33-7.25 (2H, m H_{Ar}), 7.16 (1H, dd, *J* = 8.2, 1.2 Hz, H_{Ar}), 7.11 (1H, app. td, *J* = 7.4, 1.2 Hz, H_{Ar}), 6.90 (1H, d, *J* = 8.4 Hz, H_{Ar}), 5.22 (1H, t, *J* = 5.3 Hz, CH), 3.63 (1H, dq, *J* = 9.2, 7.1 Hz, CH), 3.49 (1H, dq, *J* = 9.2, 7.0 Hz, CH), 3.41 (2H, d, *J* = 5.3 Hz, CH₂), 1.14 (3H, t, *J* = 7.1 Hz, CH₃), 1.07 (9H, s, CH₃), 0.28 (6H, s, CH₃);

¹³C NMR (100 MHz, CDCl₃) δ: 153.5 (C_q), 151.9 (C_q), 134.5 (CH), 132.5 (C_q), 131.4 (C_q), 131.0 (CH), 129.7 (CH), 128.8 (CH), 123.4 (CH), 119.7 (CH), 177.9 (CH), 115.0 (C_q), 102.1 (CH), 62.9 (CH₂), 31.5 (CH₂), 25.9 (CH₃), 18.5 (C_q), 15.2 (CH₃), -4.0 (CH₃);

HRMS (ESI⁺): *m/z* calculated for C₂₂H₃₀Br₂O₃Si [M-H] calcd. 551.0236, found 551.0223;

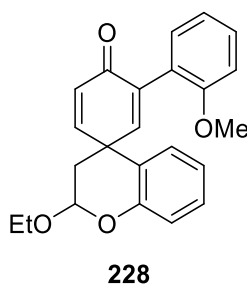
IR ν_{max} (CHCl_3)/ cm^{-1} : 2927, 1478, 1248, 911, 835, 777, 750.

3'-bromo-2-ethoxyspiro[chromane-4,1'-cyclohexane]-2',5'-dien-4'-one 227



To a solution of ((3-bromo-2'-(2-bromo-1-ethoxyethoxy)-[1,1'-biphenyl]-4-yl)oxy)(*tert*-butyl)dimethylsilane (370 mg, 0.698 mmol) in dimethylformamide (233 mL) was added cesium fluoride (317 mg, 2.09 mmol) and sodium sulfate (297 mg, 2.09 mmol). The reaction mixture was heated to 130 °C for 17 h and 40 minutes before being cooled to r.t., diluted with ethyl acetate and washed with H_2O (x 3) and brine (x 2). The organics were dried over MgSO_4 , filtered and the solvent removed *in vacuo* to give 3'-bromo-2-ethoxyspiro[chromane-4,1'-cyclohexane]-2',5'-dien-4'-one. The crude material was used in the next cross coupling step.

Spirocyclicketone No. 228



To a flask containing $\text{Pd}(\text{dba})_2$ (45 mg, 0.079 mmol), potassium carbonate (547 mg, 3.96 mmol), S-Phos (97 mg, 0.237 mmol) and (2-methoxyphenyl)boronic acid (181 mg, 1.19 mmol) was added a solution of 3'-bromo-2-ethoxyspiro[chromane-4,1'-cyclohexane]-2',5'-dien-4'-one (265 mg, 0.791 mmol) in THF (7.9 mL). H_2O (0.79 mL)

was added and the reaction mixture was heated to reflux overnight and then cooled to r.t. The reaction mixture was diluted with ethyl acetate, washed with 1 M HCl (x 2) and brine (x 2), dried over MgSO₄ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (petroleum ether 40-60 °C/ethyl acetate (4:1)) to give spirocyclic ketone No. **228** as a brown oil (156 mg, 54%) over 2 steps.

Mixture of diastereoisomers

¹H NMR (400 MHz, CDCl₃) δ: 7.47 (1H, dd, *J* = 10.1, 3.0 Hz, CH), 7.35-7.27 (3H, m, H_{Ar}), 7.24-7.17 (2H, m, H_{Ar}), 7.16-7.05 (4H, m, H_{Ar}), 6.99-6.88 (8H, m, H_{Ar}), 6.85 (1H, dd, *J* = 9.9, 2.9 Hz, CH), 6.76 (1H, d, *J* = 2.9 Hz, CH), 6.42 (1H, d, *J* = 9.9 Hz, CH), 6.31 (1H, d, *J* = 10.0 Hz, CH), 5.45-5.35 (2H, m, CH), 3.94 (2H, m, CH), 3.77 (3H, s, CH₃), 3.72-3.58 (2H, m, CH), 2.38-2.22 (4H, m, CH₂), 1.25 (6H, app. dt, *J* = 8.2, 7.2 Hz, CH₃).

¹³C NMR (100 MHz, CDCl₃) δ: 184.4 (C_q), 184.4 (C_q), 157.5 (C_q), 157.4 (C_q), 153.5 (CH), 152.6 (CH x2), 152.23 (CH), 151.5 (C_q), 151.3 (C_q), 137.1 (C_q), 135.5 (C_q), 130.8 (CH), 130.7 (CH), 129.6 (CH), 129.5 (CH), 129.4 (CH), 129.3 (CH), 129.1 (CH), 128.5 (CH), 126.6 (CH), 125.9 (C_q), 125.5 (C_q), 121.8 (CH), 121.8 (CH), 120.6 (CH), 120.5 (CH), 120.4 (C_q), 120.2 (C_q), 118.5 (CH), 111.2 (CH), 111.2 (CH), 64.5 (CH₂), 64.5 (CH₂), 55.8 (CH₃), 55.8 (CH₃), 41.2 (C_q), 40.9 (C_q), 36.9 (CH₂), 36.4 (CH₂), 15.3 (CH₃), 15.2 (CH₃);

HRMS (ESI⁺): *m/z* calculated for C₂₃H₂₂O₄ [M+Na] calcd. 385.1410, found 385.1414;

IR ν_{max} (CHCl₃)/cm⁻¹: 2930, 1665, 1485, 1240, 1449, 1110, 1031, 752

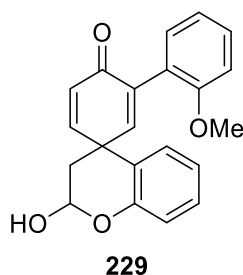
Isolated one of the two diastereoisomers

¹H NMR (400 MHz, CDCl₃) δ: 7.32-7.27 (2H, m, H_{Ar}), 7.19 (1H, ddd, *J* = 8.2, 7.2, 1.7 Hz, H_{Ar}), 7.12 (1H, dd, *J* = 7.4, 1.7 Hz, H_{Ar}), 7.08-7.04 (1H, m, H_{Ar}), 6.97-6.87 (4H, m, H_{Ar}),

6.85 (1H, dd, $J = 9.9, 3.0$ Hz, CH), 6.42 (1H, d, $J = 9.9$ Hz, CH), 5.40 (1H, dd, $J = 4.1, 2.9$ Hz, CH), 3.93 (1H, dq, $J = 9.7, 7.1$ Hz, CH), 3.77 (3H, s, CH₃), 3.65 (1H, dq, $J = 9.6, 7.1$ Hz, CH), 2.34 (1H, dd, $J = 14.0, 2.9$ Hz, CH), 2.26 (1H, dd, $J = 14.0, 4.1$, CH), 1.18 (3H, t, $J = 7.1$ Hz, CH₃);

¹³C NMR (100 MHz, CDCl₃) δ : 184.2 (C_q), 157.5 (C_q), 152.6 (CH), 152.6 (CH), 151.5 (C_q), 135.5 (C_q), 130.8 (CH), 129.5 (CH), 129.4 (CH), 129.1 (CH), 128.5 (CH), 125.9 (C_q), 121.8 (CH), 120.6 (CH), 120.4 (C_q), 118.5 (CH), 111.2 (CH), 96.0 (CH), 64.5 (CH₂), 55.9 (CH₃), 41.2 (C_q), 36.9 (CH₂), 15.2 (CH₃);

Spirocyclicketone No. 229



To a solution of spirocyclicketone No. **228** (156 mg, 0.430 mmol) in dioxane (5 mL) was added 2 M HCl (5 mL) and the resultant mixture was heated to 110 °C for 3 h. The reaction mixture was cooled to r.t., diluted with ethyl acetate, washed with H₂O (x 4) and brine, dried over MgSO₄ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (petroleum ether 40-60 °C/ethyl acetate (1:1)) to give spirocyclicketone No. **229** as a brown oil (82 mg, 57%).

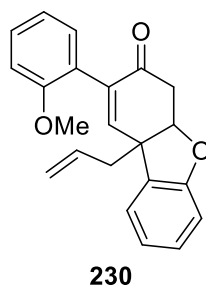
¹H NMR (400 MHz, CDCl₃) δ : 7.44-7.39 (1H, m, CH), 7.36-7.29 (2H, m, H_{Ar}), 7.27-7.20 (4H, m, H_{Ar}), 7.18-7.09 (4H, m, H_{Ar}), 6.99-6.90 (8H, m, H_{Ar}), 6.83 (1H, d, $J = 3.0$ Hz, CH), 6.44 (1H, d, $J = 9.9$ Hz, CH), 6.39 (1H, d, $J = 10.0$ Hz, CH), 5.78 (2H, app. br s, CH), 3.79 (6H, s, CH₃), 3.64 (2H, s, OH), 2.36 (2H, app. dt, $J = 13.8, 2.6$ Hz, CH), 2.32-2.26 (2H, m, CH)

^{13}C NMR (100 MHz, CDCl_3) δ : 184.3 (C_q), 184.2 (C_q), 157.3 (C_q), 157.2 (C_q), 153.2 (CH), 152.3 (CH), 152.1 (CH), 151.7 (CH), 151.5 (C_q), 136.7 (C_q), 136.0 (C_q), 130.7 (CH), 130.6 (CH), 129.5 (CH), 129.5 (CH), 129.4 (CH), 129.4 (CH), 129.0 (CH), 128.9 (CH), 128.1 (CH), 127.1 (CH), 125.5 (C_q), 125.3 (C_q), 121.7 (CH), 120.4 (CH), 119.8 (C_q), 119.7 (C_q), 118.4 (CH), 111.1 (CH), 111.1 (CH);

HRMS (ESI $^+$): m/z calculated for $\text{C}_{21}\text{H}_{18}\text{O}_4$ [M+H] calcd. 335.1278, found 335.1292;

IR ν_{max} (CHCl_3)/ cm^{-1} : 3389, 2928, 1662, 1486, 1241, 1113, 1030, 754.

9b-allyl-2-(2-methoxyphenyl)-4a,9b-dihydrodibenzo[b,d]furan-3(4H)-one **230**



To a suspension of methyltriphenylphosphonium bromide (154 mg, 0.431 mmol) in THF (3.7 mL) was added KHMDS (0.5 M in toluene) (0.74 mL, 0.369 mmol) over 15 minutes at r.t. The reaction mixture was stirred at r.t. for an additional 30 minutes before addition of a solution of siprocyclisketone No. **229** (41.0 mg, 0.123 mmol) in THF (3.7 mL) over 15 minutes. The resultant solution was stirred for another 30 minutes before being heated to 50 °C for 18.5 h. The reaction mixture was then cooled to r.t. and diluted with ethyl acetate, washed with H_2O and brine, dried over MgSO_4 , filtered and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (petroleum ether 40-60 °C/ethyl acetate (5:1)) to give 9b-allyl-2-(2-methoxyphenyl)-4a,9b-dihydrodibenzo[b,d]furan-3(4H)-one as a brown oil (21 mg, 51%).

¹H NMR (400 MHz, CDCl₃) δ: 7.30 – 7.24 (1H, m, H_{Ar}), 7.23 – 7.15 (2H, m, H_{Ar}), 6.99 – 6.93 (2H, m, H_{Ar}), 6.90 – 6.82 (3H, m, H_{Ar}), 6.49 (1H, d, *J* = 1.7 Hz, CH), 5.89 (1H, app. dddd, *J* = 16.9, 10.2, 8.1, 6.6 Hz, CH), 5.28 – 5.19 (2H, m, CH₂), 4.92 (1H, ddd, *J* = 4.3, 3.7, 1.7 Hz, CH), 3.70 (3H, s, CH₃), 3.11 (1H, dd, *J* = 16.4, 3.7 Hz, CH), 2.98 (1H, dd, *J* = 16.4, 4.3 Hz, CH), 2.84 (1H, ddt, *J* = 14.1, 6.6, 1.4 Hz, CH), 2.73 – 2.64 (1H, m, CH);

¹³C NMR (100 MHz, CDCl₃) δ: 194.1 (C_q), 158.8 (C_q), 157.0 (C_q), 146.0 (CH), 136.7 (C_q), 132.6 (CH), 131.4 (C_q), 130.8(CH), 129.7(CH), 129.2(CH), 125.7 (C_q), 123.1 (CH), 121.5 (CH), 120.6 (CH), 119.7 (CH₂), 111.1 (CH), 110.7 (CH), 84.9 (C_q), 55.8 (CH₃), 49.1 (C_q), 41.8 (CH₂), 40.1 (CH₂);

HRMS (ESI⁺): *m/z* calculated for C₂₂H₂₀O₃ [M+H] calcd. 333.1485, found 333.1487;

IR ν_{max} (CHCl₃)/cm⁻¹: 2918, 1683, 1596, 1474, 1435, 1234, 1026, 998, 908, 751, 729.

6. Refereneces

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- 2** (a) H. Coa, L. McNamee, H. Apler, *J. Org. Chem.* 2008, **73**, 3530. (b) J. McNulty, A. Capretta, J. Wilson, J. Dyck, G. Adjabeng, A.J.J. Robertson, *Chem. Soc., Chem. Commun.* 2002, 1986; (c) D.A. Gerritsma, A.J. Robertson, J. McNulty, A. Capretta, *Tetrahedron Lett.* 2004, **45**, 7629; (d) J. McNulty, A. Capretta, S. Cheekoori, J.A.C. Clyburne, A. Robertson, *J. Chemica Oggi*, 2004, **22**, 13; (e) J. McNulty, S. Cheekoori, J.J. Nair, V. Larichev, A. Capretta, A.J. Robertson, *Tetrahedron Lett.* 2005, **46**, 3641; (f) J. McNulty, J.J. Nair, S. Cheekoori, V. Larichev, A. Capretta, A.J. Robertson, *Chem. Eur. J.*, 2006, **12**, 9314; (g) J. McNulty, S. Cheekoori, T.P. Bender, J.A. Coggan, *Eur. J. Org. Chem.* 2007, **9**, 1423; (h) J. McNulty, J.J. Nair, A.J. Robertson, *Org. Lett.* 2007, **9**, 4575.
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- 6** R. A. J. Smith, C. M. Porteous, A. M. Gane, M. P. Murphy, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 5407.
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