Dearomative Phenol Diversification

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This thesis is dedicated to my Mum and Dad

Thank you for granting me the ambition to start a doctoral degree,

and thank you for teaching me the resilience to complete one.

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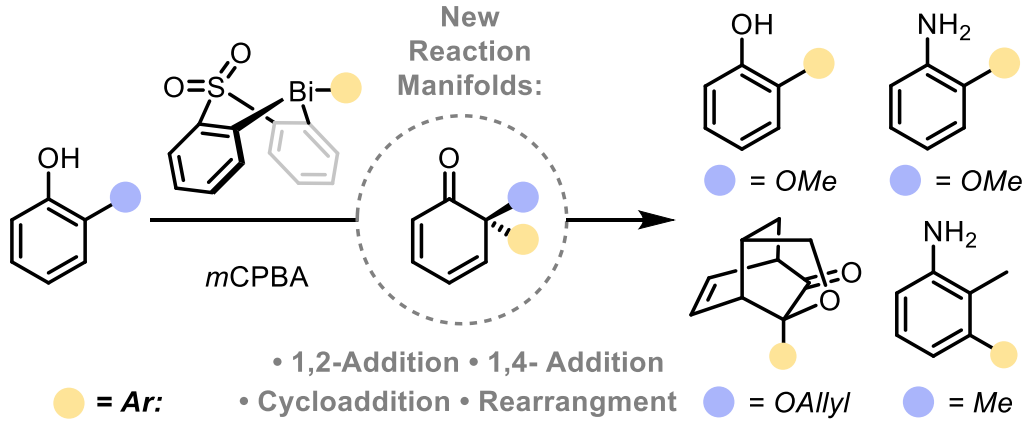
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Abstract

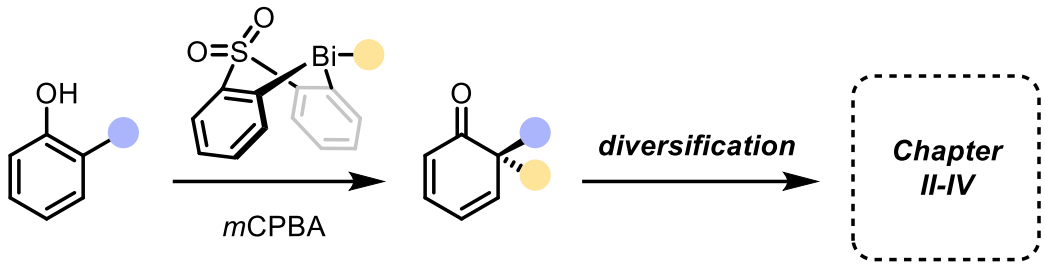
Phenol dearomatisation is a useful synthetic strategy that permits access to reactive cyclohexadienone intermediates which display reaction manifolds unavailable to the starting phenol. Traditional procedures to access cyclohexadienones are limited to oxygenation of the phenolic nucleus, inherently limiting the accessible chemical space to oxygenated cyclohexadienones. This thesis describes developments to phenol diversification *via* Bi(V)-mediated arylative dearomatisation, allowing access to arylated phenols and arylated cyclohexadienone derivatives.

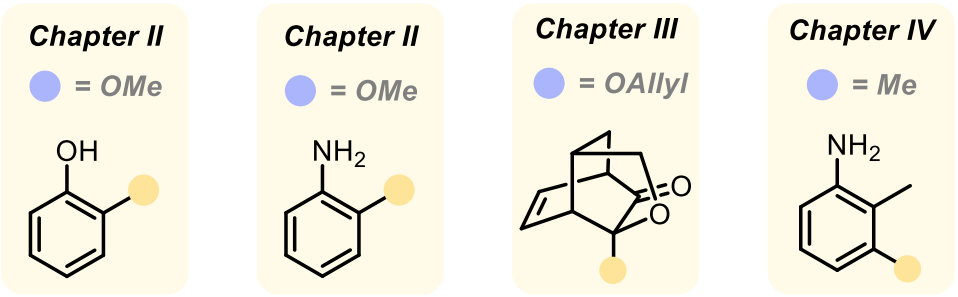


The work in Chapter II reports a novel demethoxylative arylation of guaiacol, en route to *ortho*-arylated phenols. This proceeds *via* initial formation of an aryl cyclohexadienone, and subsequent 1,2-reduction before an elimination-rearomatisation step. Despite the variable stability of the resultant cyclohexadienone, deoxygenation of the core affords rapid access to 2-aryl phenols with a good tolerance for electronically and sterically diverse partners.

Chapter III describes the transformation of simple allyloxy phenols to a novel class of aryl- bicyclo[2.2.2]octenones. In this instance, dearomatisation of 2-allyloxy phenol produces a transient cyclohexadienone that undergoes a rapid intramolecular Diels-Alder reaction. This protocol presents a modular route to the bicyclo[2.2.2]octenone core, allowing for variation of the phenol, olefin and the aryl bismacycle.

Chapter IV documents investigations towards a novel phenol deoxyamination protocol en route to *meta*-arylated anilines. This proceeds *via* the formation of an aryl cyclohexadienimine which rearranges to the *meta*-arylated aniline, analogous to the dienone-phenol rearrangement. Preliminary investigations toward a substrate scope proves this methodology to exhibit moderate functional group tolerance, permitting access to a notoriously difficult-to-access substitution pattern.





Acknowledgements

As I write these acknowledgements, I anticipate a cheesy few pages (maybe more, depending on who makes the cut), acknowledging those who have tolerated me throughout this journey. I think it's fair to say that completing a doctoral degree in the early-to-mid-twenties lends itself to being a part of quite momentous life events, while being a hectic endeavour in itself. It is therefore important to me to express my thankfulness to my friends and family, be it for academic encouragement or personal. I am not sure how I can express my thankfulness in Constantia, size: 11, but I can only do my best.

I will begin this by thanking Liam. I must admit that I started my PhD pretty clueless, as many post graduate students do, however for a long time I wasn't sure I would academically excel past a rookie 1st year PhD student. I think I have proven myself wrong under your supervision, and while I acknowledge I have worked hard to do that, your persistent encouragement, (usually realistic) project ideas and undeniable wit are partially responsible. Despite the uprooting of my final year, I am truly excited for your group to flourish in Bristol, and I look forward to hearing about the inevitable successes that the group behold in the future. Finally, I must thank you for the friendships I have made along the way, and that can only be attributed to your type in hiree, which is apparently freakishly neurodivergent post-graduates (and post doctorates). These are people which have shaped me into whatever I am today, and for that, I would like to thank you.

Before I move onto the Ball group, I want to thank other SoC staff members: Prof Fran Paradisi for her always lending and empathetic ear over the course of my undergrad, and to Dr. James Dowden for looking out for me over my years at the University.

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inspiring work ethic, so Katie, thank you for setting the bar so high and motivating me to get my shit together. Aaron, I can only wish that we had a greater crossover; something tells me we would have gotten on outside of what would have been a shared distress of handling cyclohexadienones. To Gemma, Martyna and Sam, I owe you three sincere thank yous for contributing to a healthy amount of chaos to the lab. I think many could agree now that this is very much lacking. Despite my grievances towards the Bermuda Triangle, I must admit the importance of this treasured space to ~~propagate SoC gossip~~. Ben Joynson, thank you for sharing my love of music that sounds like its coming out of a microwave, it's what the people need while working up reactions, but they just don't know it yet. Charlie, you've looked out for me an awful lot over the years. I certainly struggled to find my footing early on, but you helped me recalibrate and become a functional chemist. Most importantly, thank you for talking me down from my former nitro***** nightmares, I probably would have started huffing it if we hadn't got past that phase.

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To my little lugg. They say there is no such thing as love at first sight, but that all changed for me when I saw you in your little red snapback! I count myself very lucky to have had you these years; this degree would have been so much more painstaking if not for our companionship. I will forever miss the sound of your leathers making their way down the lab, knowing I was soon to be faced with a ridiculous slur thrown my way.

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To my Klaudia. You have certainly seen the worst of me over the last 4 years, whether it be a rough day in the lab or a rough time in life. Nonetheless, you have always made sure to find a way to make things simpler for me, no matter how much it demanded of you. I will forever cherish the memories of you bringing me coffee at silly O'clock while I finish off my chemistry, or having to go to the lab because *someone* needed to take off their acrylics. I couldn't be luckier that our lives aligned in the way they did, and I will forever be indebted to you for the unrest I caused you at the beginning of this degree (and throughout, but I blame chemistry for that). I promise I will return the favour when you inevitably begin your PhD.

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And lastly, to my Mum and my Dad. Ever since I was little, you have both advocated for me to pursue science in a way that was never assertive or insistent. In your respective ways, you inspired me to do whatever I wanted to do and made sure to support whatever that decision was. Mum, your perseverance to do, apparently anything, has been undeniably inspiring in my adult and academic life. I have been lucky enough to count on your help, be it though helping me rhyme off 'conditions to form an alkene from an alkane!', or where I demand a chit-chat while I wash up in the lab. Dad, I have invaluable memories of you projecting my life prospects as a child, flippantly yet dreamily suggesting that I could have letters in front of my name if I were to obtain a doctorate. Well, that will (hopefully) happen soon. I would never have glorified and worked towards this aspiration if you hadn't planted that seed in my head, while always teaching me to believe in myself. I adore you both so much, and I will never ever be able to find the words to describe how much I have always recognised your support. From the bottom of my heart, thank you for everything.

List of Abbreviations

The main abbreviations used in this thesis are listed below, SI units are omitted. Other abbreviations can be found in the Journal of Organic Chemistry abbreviations guideline for authors.[*]

aq.	aqueous
Ar	generic aryl group
BCO	bicyclo[2.2.2]octenone
[Bi], Bismacycle	10*H*-dibenzo[*b,e*][1,4]thiabismine 5,5-dioxide
cat.	catalyst, catalytic
CHD	cyclohexadienone
DA	Diels-Alder
DA_{INV}	Diels-Alder; inverse electronic demand
δ	chemical shift
EDG	electron-donating group
EWG	electron-withdrawing group
FMO	frontier molecular orbital
HMDS	hexamethyldisilazane
HOMO	highest occupied molecular orbital
IMDA	intramolecular Diels-Alder
J	coupling constant
k	rate constant
LA	Lewis acid
LED	light emitting diode

[*]pubs.acs.org/userimages/ContentEditor/1218717864819/joceah_abbreviations.pdf

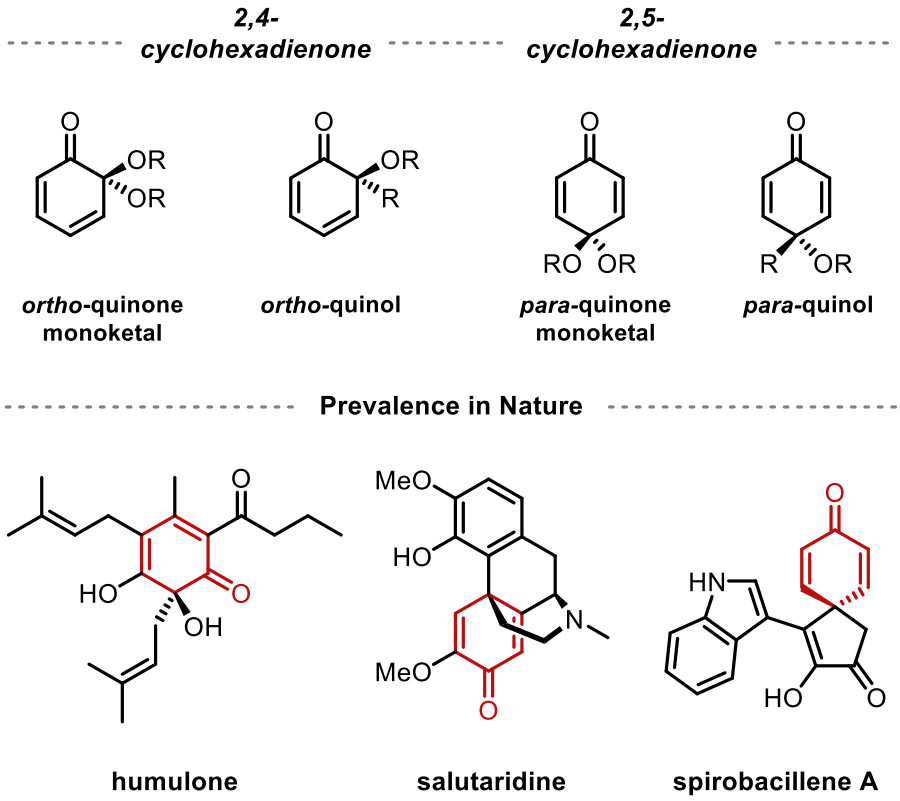
LTA	lead tetraacetate
LUMO	lowest unoccupied molecular orbital
***m*CPBA**	*meta*-chloroperoxybenzoic acid
NMR	nuclear magnetic resonance
O*m*CB	*meta*-chlorobenzoate
PIDA	phenyliodine(III) diacetate
R	generic side group
rt	room temperature
sat.	saturated
S_EAr	electrophilic aromatic substitution
σ	Hammett substituent constant
S_NAr	nucleophilic aromatic substitution
SPE / SCX	solid phase extraction / strong cation exchange

Chapter I

An Introduction to Cyclohexadienones

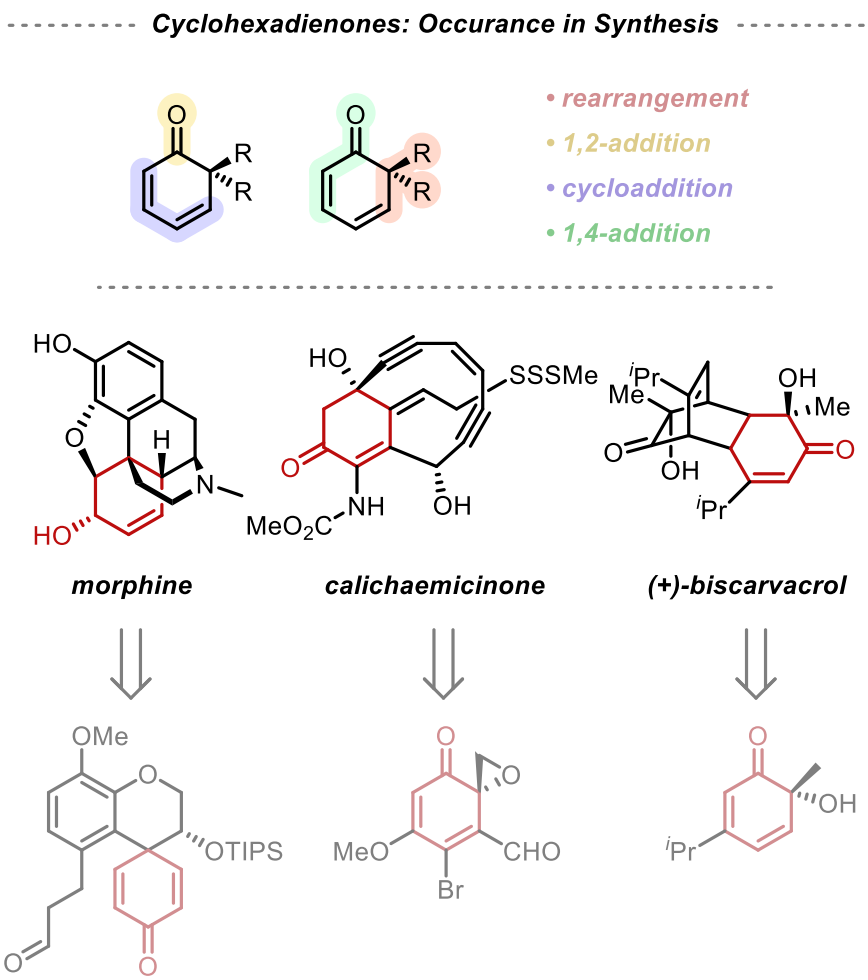
1.1. Introduction

The cyclohexadienone motif is of great interest to organic and medicinal chemists. Their core structure can be found among natural products and bioactive molecules,[1–4] while serving as versatile building blocks to synthesise complex organic architectures.[5] Cyclohexadienones can be identified as one of four archetypes; the *ortho*-quinol monoketal and *ortho*-quinol types of the 2,4-cyclohexadienone, as well as the *para*-quinone monoketal and *para*-quinol types of the 2,5-cyclohexadienone (Scheme 1).



Scheme 1: Types of cyclohexadienone; cyclohexadieneone skeleton highlighted in natural product salutaridine, and bioactive spirobacillene.

Crucially, cyclohexadienones deserve merit for the number of reactive sites they constitute, which enable their rapid diversification to complex organic architectures. This multifaceted reactivity is reflected in their abundance as an intermediate in many syntheses of natural products (Scheme 2).[6–8]



Scheme 2: Occurrence of the cyclohexadienone scaffold in natural product synthesis.

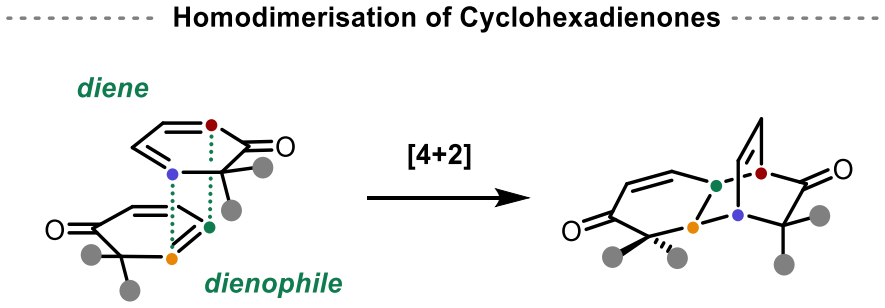
This introduction will begin by informing the reader on the chemistries that cyclohexadienones can undergo, thus emphasising their utility in synthesis. An overview of methods by which they can be prepared will follow, including the application of bismuth chemistry in the synthesis of this class of compound.

1.2. Cyclohexadienone Chemistry

With multiple carbons of the cyclic skeleton exhibiting electrophilic character, cyclohexadienones are able to undergo a plethora of reaction types. These encompass 1,2-ketone additions,[9–14] 1,4-conjugate additions,[13,15–25] [4+2] cycloadditions,[7,26–32] [2+2] electrocyclisations,[32] sigmatropic shifts,[33–36] and photochemically induced ring openings.[37,38] This section will highlight some of the key transformations of cyclohexadienones, and discuss the methodologies developed from these transformations.

Diels Alder Reactions

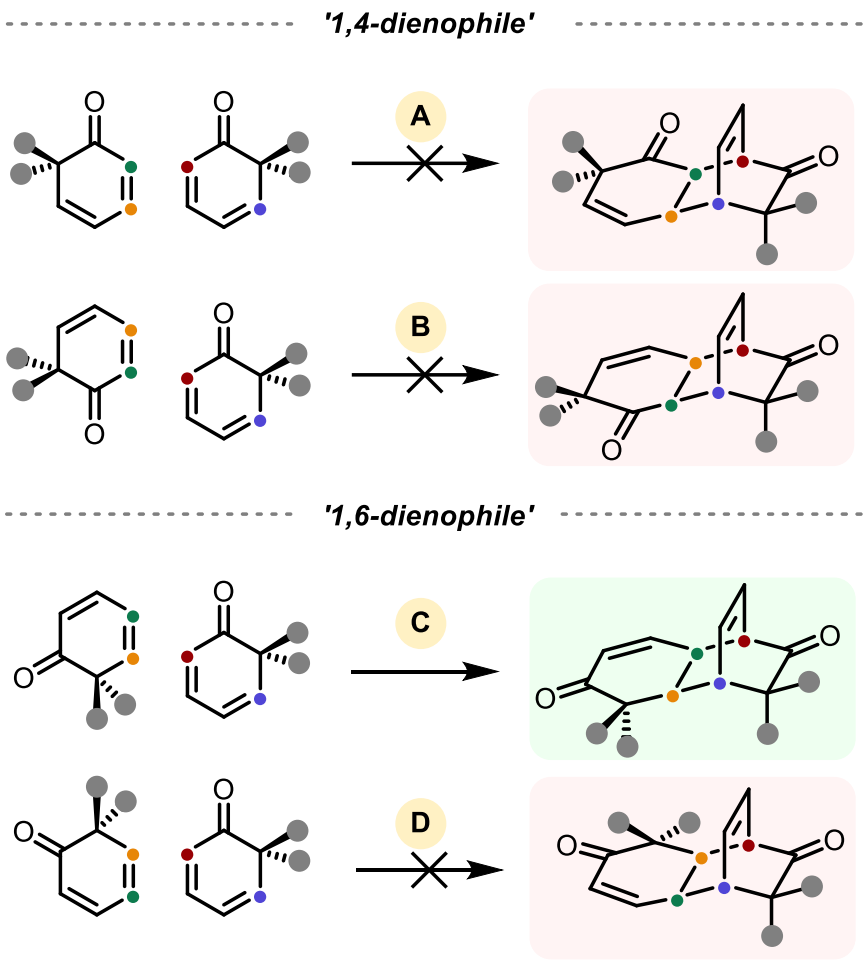
The most characteristic aspect of the reactivity of 2,4-cyclohexadienones is undoubtably their ability to dimerize through [4+2] cycloadditions. This propensity toward Diels–Alder processes is evidently due to the reactivity of their dienone unit, which can behave either as a diene or as a dienophile (Scheme 3). The Diels-Alder reactions of cyclohexadienones will be reviewed in more detail in Chapter III; this section serves to introduce the reader to the control and exploitation of cyclohexadienone cycloaddition in synthesis.



Scheme 3: Dimerization of cyclohexadienones.

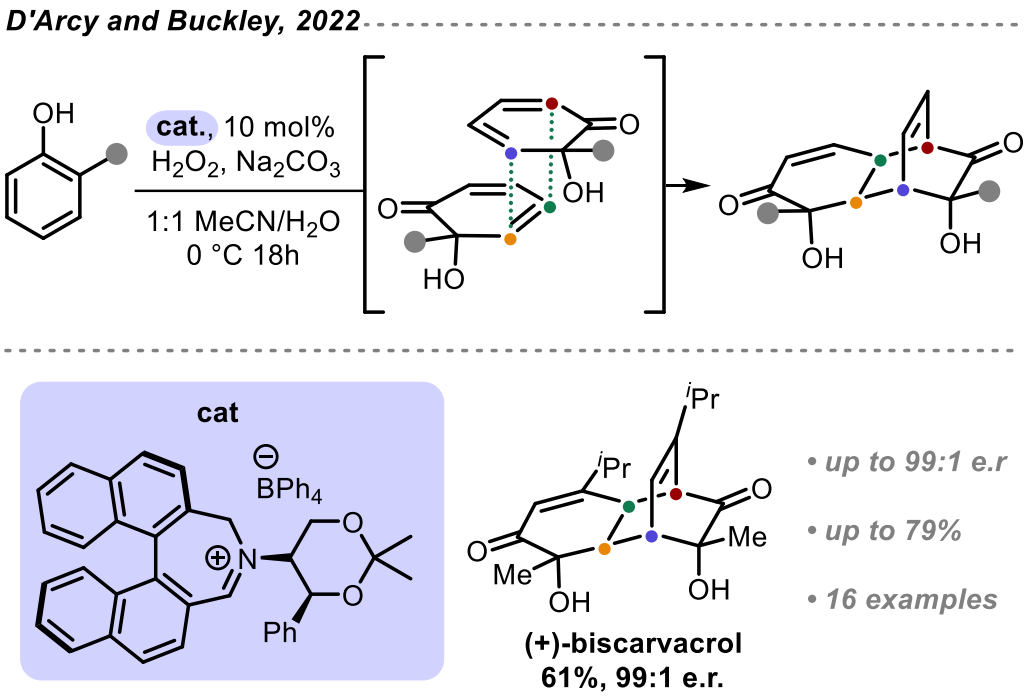
If we consider the homodimerization of a cyclohexadienone, it becomes clear that there are several possible regio-isomeric outcomes of this process. If one cyclohexadienone behaves as the diene unit, the second cyclohexadienone can be dienophilic at the 1,4-site (path A and B) or the 1,6-site (path C and D, Scheme 4). Each of these options have two further regio-isomeric outcomes depending on the approach of each unit, leading to four potential regio-isomeric cycloadducts.

In practice, only cycloadducts resulting from route C is observed; this preference for a dienophilic 1,6-site can be rationalised by the electron-poor profile of the enone, which would be required to react with an electron-poor diene in path A or B. Of the '1,6-dienophiles', it is not known why route D does not occur; Quideau *et al.* [32] performed calculations of atomic coefficients of the cyclohexadienone HOMOs and LUMOs in order to understand this, however, no clear-cut rationale was observed.



Scheme 4: Possible regioisomers of cyclohexadienone cycloaddition.

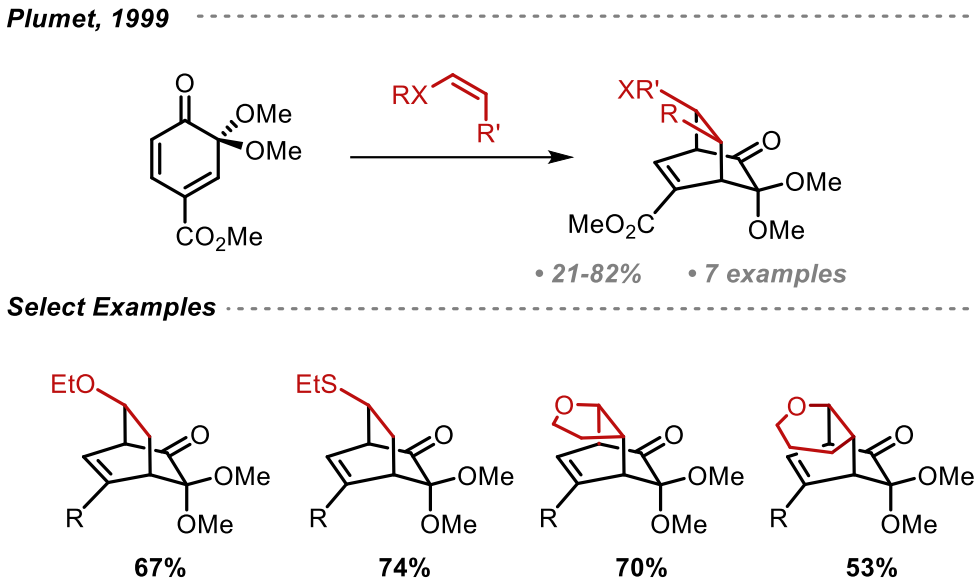
This proclivity to dimerize with such high regioselectivity has been exploited heavily among natural product synthesis. The dimerization product is a bicyclo[2.2.2]octenone; an architecture which constitutes the core of several natural products and bioactive molecules. Buckley *et al.* has recently reported a highly diastereoselective [4+2] dimerization of the cyclohexadienones furnished from an asymmetric dearomatisation of *ortho*-alkyl phenols. (Scheme 5).[7]



Scheme 5: Buckley's diastereoselective [4+2] dimerization of *ortho*-quinols.[7]

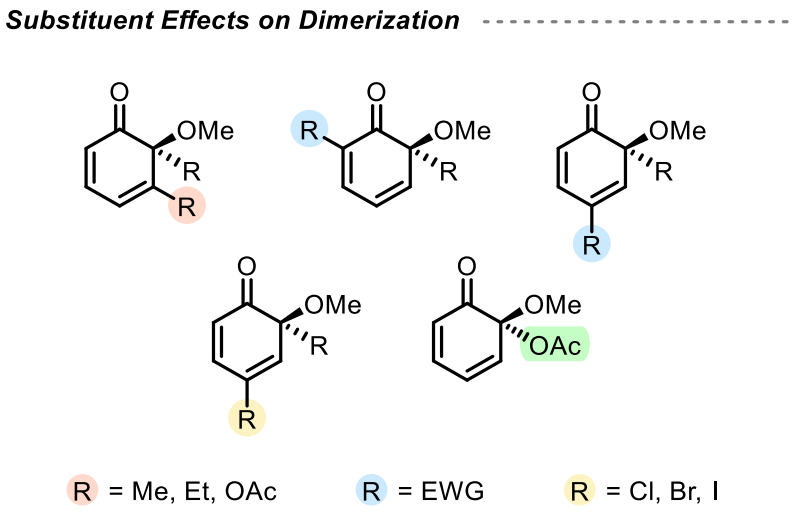
The dearomative method employed utilises an enantioselective oxaziridinium catalyst, which oxidises the phenol at the *ortho*-position. Their methodology possesses good compatibility with all phenols of various substitution patterns, but suffers with sterically hindered, 2,4-substituted and electron-deficient phenols.

Diels-Alder reactions have also been employed on cyclohexadienones with external dienes and dienophiles. This has been showcased by Plumet, who investigated the reactions of *ortho*-quinol and *ortho*-quinone monoketal type cyclohexadienones in inverse demand Diels-Alder reactions with enol and thioenol ethers. (Scheme 6)



Scheme 6: Inverse demand Diels Alder reactions of *ortho*quinols and *ortho*quinone monoketals.

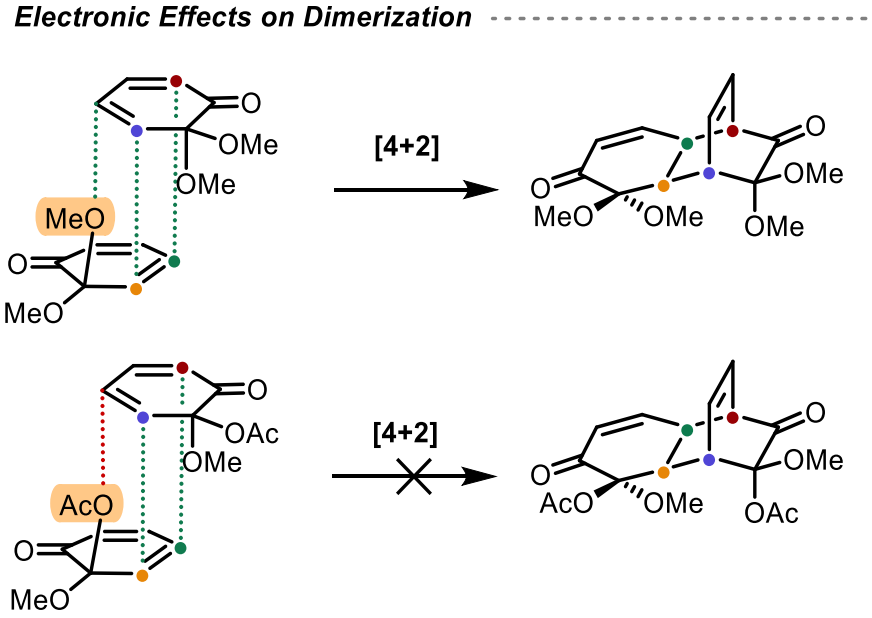
This proclivity for cyclohexadienones to undergo Diels-Alder reactions can be undesirable if their reactivity towards other compounds is the topic of investigation. Empirical observations from the Liao group reveals that dimerization can be blocked, or at least retarded, if the cyclohexadienone core bears substituents at some specific positions shown in Scheme 7.[26–30]



Scheme 7: Substitution patterns *on ortho-quinols* and *ortho*-quinone monoketals which limit dimerization.

Experiments have been undertaken by the Liao group to understand how installation of the acetoxy group on the 6-position in particular inhibits dimerisation.[30] It was claimed that in the case of a 6-methoxy-cyclohexadienone, which does readily dimerize, the *endo*-transition state possesses secondary

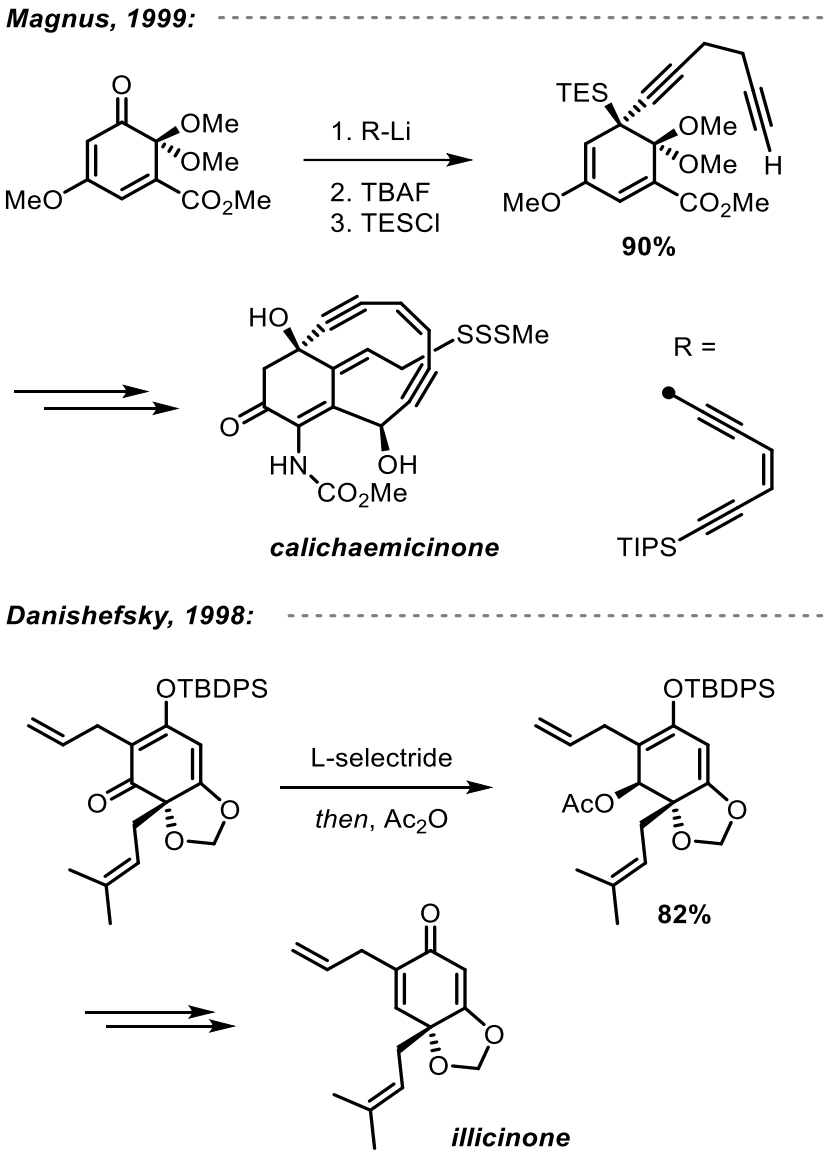
orbital interactions from lone pair, shown in Scheme 8. In this publication, they claim that these interactions are not present if this is swapped for an electron-withdrawing acetoxy group. Weather this rationale is true or not, acetoxylative dearomatisation is often employed in order to exploit other facets of cyclohexadienone reactivity, owing to their inertness towards dimerization.



Scheme 8: *Endo* transition states of cyclohexadienones partaking in Diels-Alder dimerizations, according to Liao. [30]

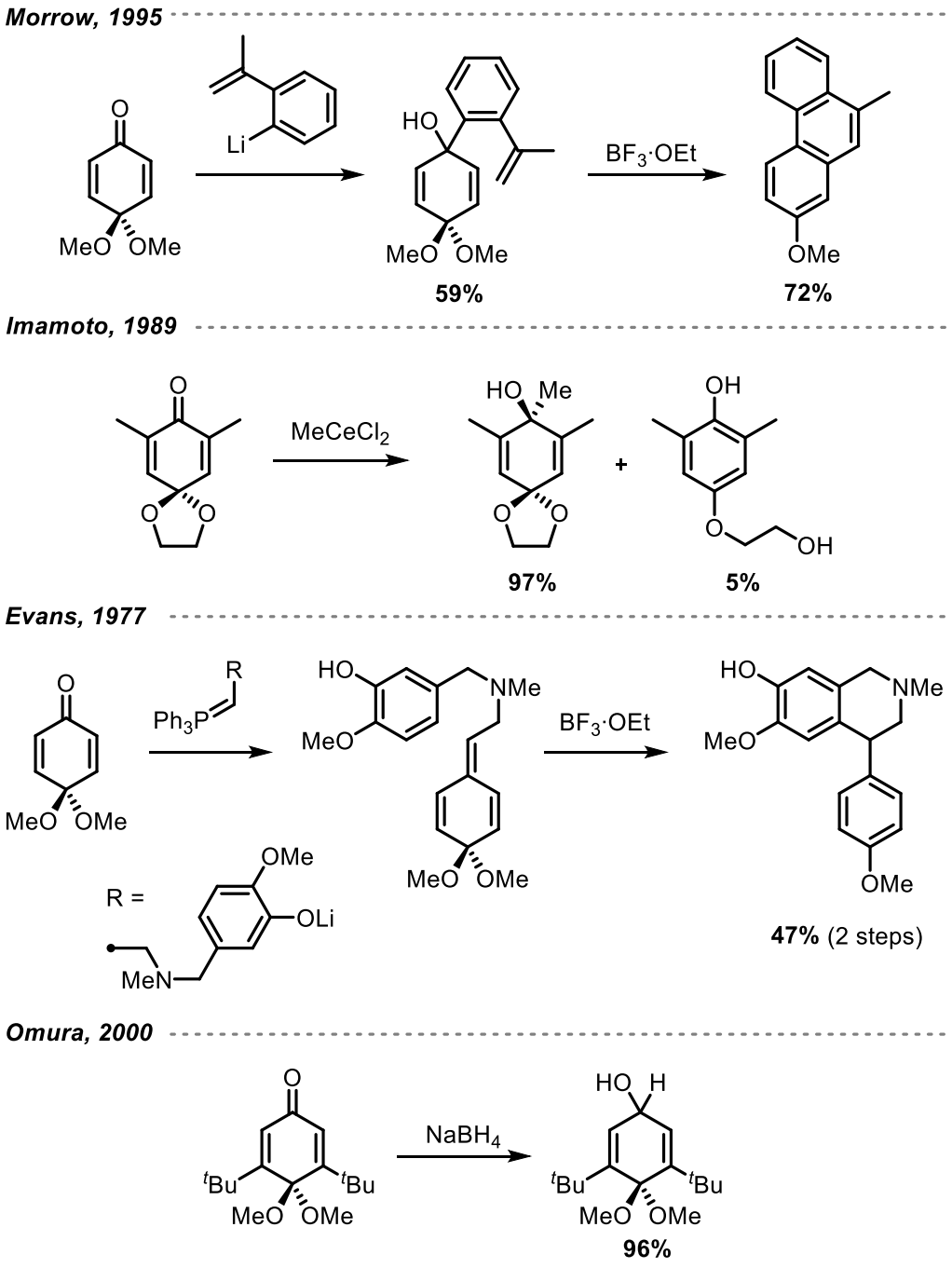
1,2- Addition Reactions

Cyclohexadienones can undergo 1,2-addition reactions with hard nucleophiles at the carbonyl. The reactivity of 2,4-cyclohexadienones with respect to 1,2-additions is somewhat limited due to their propensity to dimerize, however there are a few of examples utilising organolithium and organoborane reagents. Such reactions have been employed in the total syntheses of calicheamicinone and illicinone, as depicted in Scheme 9.[11,12]



Scheme 9: 1,2-addition reactions onto 2,4-cyclohexadienones; showcased in Magnus' total synthesis of calichaemicinone [12] , and Danishefsky's total synthesis of illicinone.[11]

The product of these functionalisation reactions can typically undergo some rearomatizing event to furnish an elaborated arene. This has been demonstrated among the 1,2-addition reactions of 2,5-cyclohexadienones, which displays a broader scope with respect to the nucleophiles with which it can react. These include organolithium and organocerium reagents, phosphonium ylides, borohydrides and amines (Scheme 10.)[9,10,13,14,39–41]

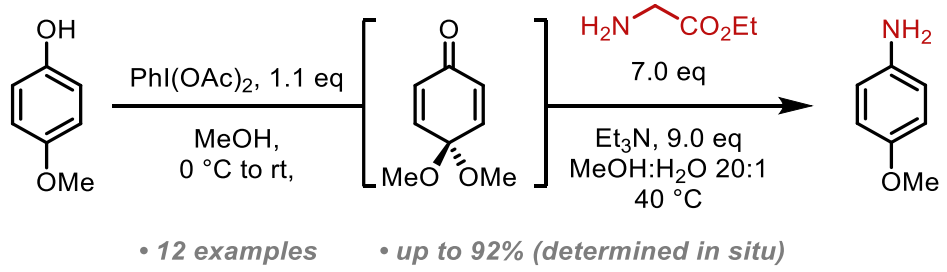


Scheme 10: 1,2-addition reactions onto 2,5-cyclohexadienones.

A general 1,2-addition of amines with 2,5-cyclohexadienones has been reported by Alaniz, enabling a direct synthesis of anilines from phenols (Scheme 11).[41] The intermediate dienone, furnished *via* a PIDA oxidation of 4-methoxyphenol, is treated with excess ethyl glycinate in the presence of base. This is proposed to form a cyclohexadiene-imine intermediate, which can then rearomatize following the loss of methanol, furnishing the arene core. In an aqueous reaction medium, the second iminium intermediate would then hydrolyse to afford the aniline. Alaniz successfully applied this one-pot tandem dearomatisation-

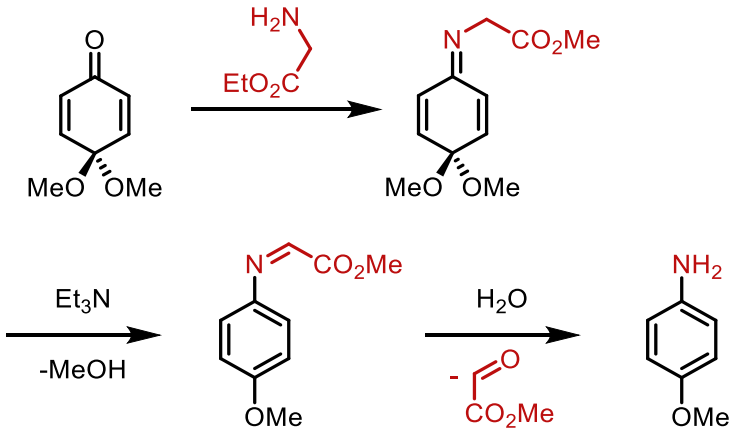
condensation-rearomatisation strategy to a series of phenols, reporting up to 92% NMR yields of the corresponding anilines.

Alaniz, 2016



• 12 examples ***• up to 92% (determined in situ)***

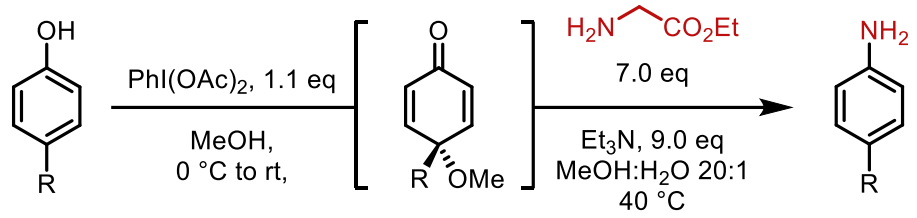
Reaction Sequence



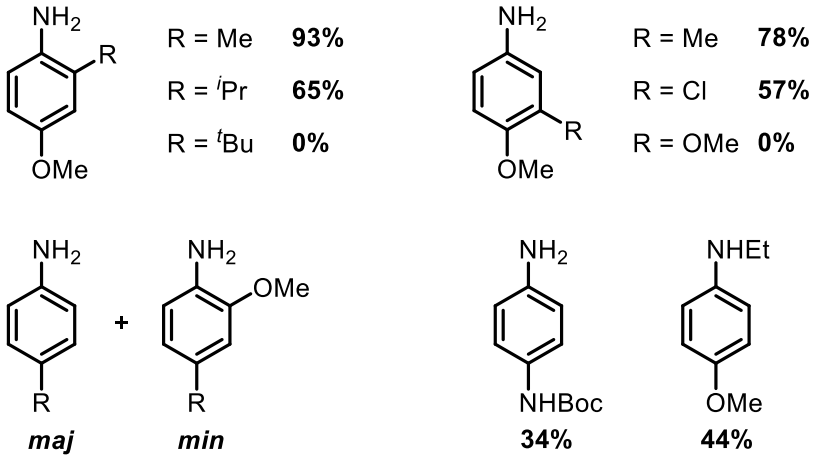
Scheme 11: Alaniz' synthesis of anilines from phenols *via* glycine condensation onto 2,5-cyclohexadienones.

The reaction tolerates *ortho*-substituents, however yields begin to suffer as the substituent becomes larger. This is apparent with the size of the alkyl chain: the *ortho*-methyl substrate affords 93% aniline, isopropyl affords 65% while the tertbutyl does not react.

Alaniz, 2016



Substrate Scope

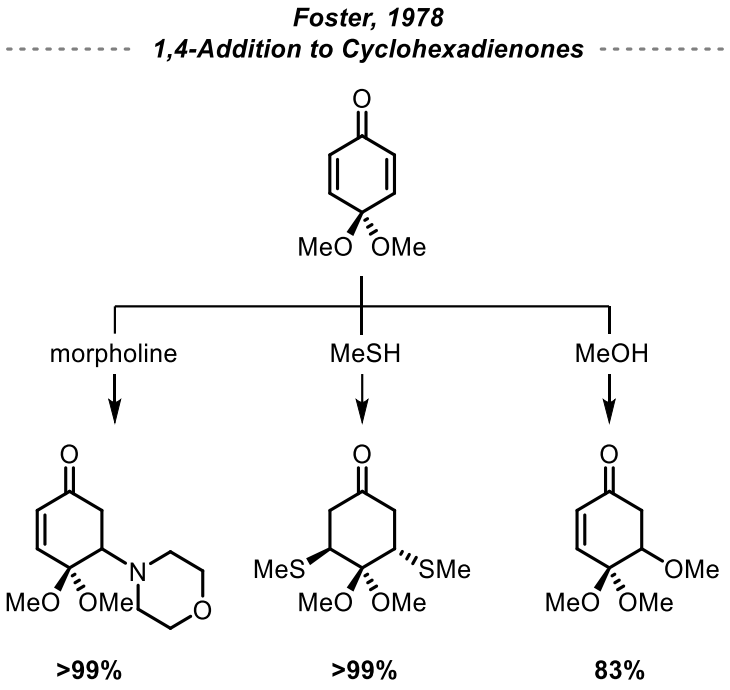


Scheme 12: Phenol compatibility with respect to the 1,2-addition of ethyl glycine onto its 2,5-cyclohexadienone.

Similarly, the di-*ortho*-substituted phenol does not react, suggesting there must be one vacant *ortho*-position for the iminium to form. The reaction has some tolerance towards *meta*-substitution on the phenol, however as electron-donating groups are introduced at these positions, reactivity halts. The methodology could also be extended to the *para*-amino phenol in a moderate yield, although, varying the *para*-substituent from methoxy to methyl gives rise to regioisomers, a consequence of the PIDA oxidation. Also reported is the condensation of ethyl sarcosine, albeit in a poorer yield with respect to the glycine.

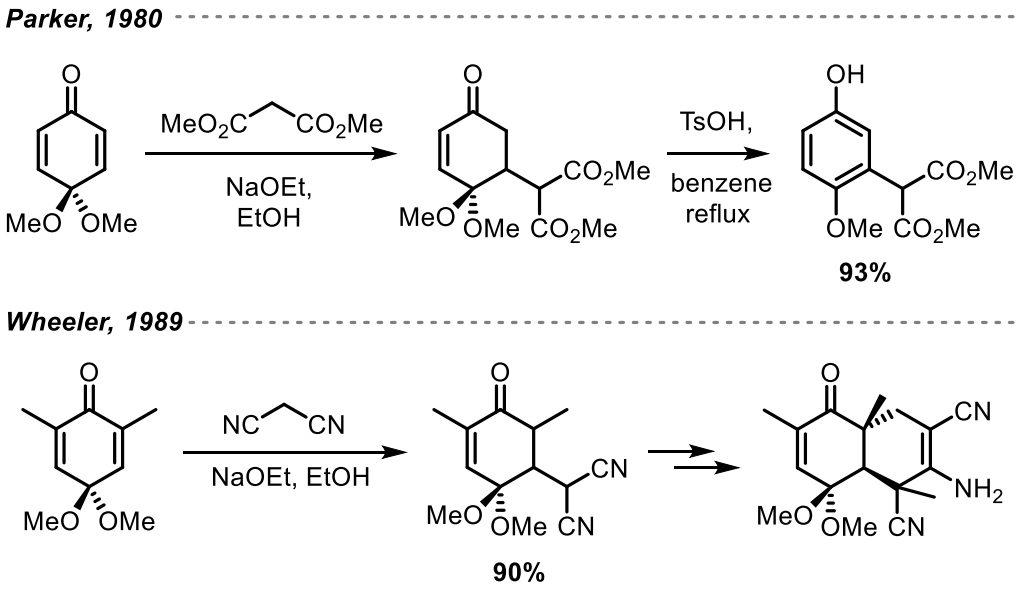
1,4-Additon Reactions

Just as the carbonyl of the cyclohexadienones can take part in 1,2-additions with hard nucleophiles, the enone can participate in 1,4-additions with soft nucleophiles. One might consider traditional conjugate additions with organocuprates; however, they usually transfer electrons to the cyclohexadienone forming a radical anion, that subsequently undergoes reductive elimination to the phenol. Softer heteroatom nucleophiles do, on the other hand, partake in standard 1,4-addition reactions with both 2,5- and stabilised 2,4-cyclohexadienones. This has been showcased by Foster, in the conjugate addition of oxygen, sulfur and nitrogen nucleophiles onto 2,5-cyclohexadienones (Scheme 13). [42]



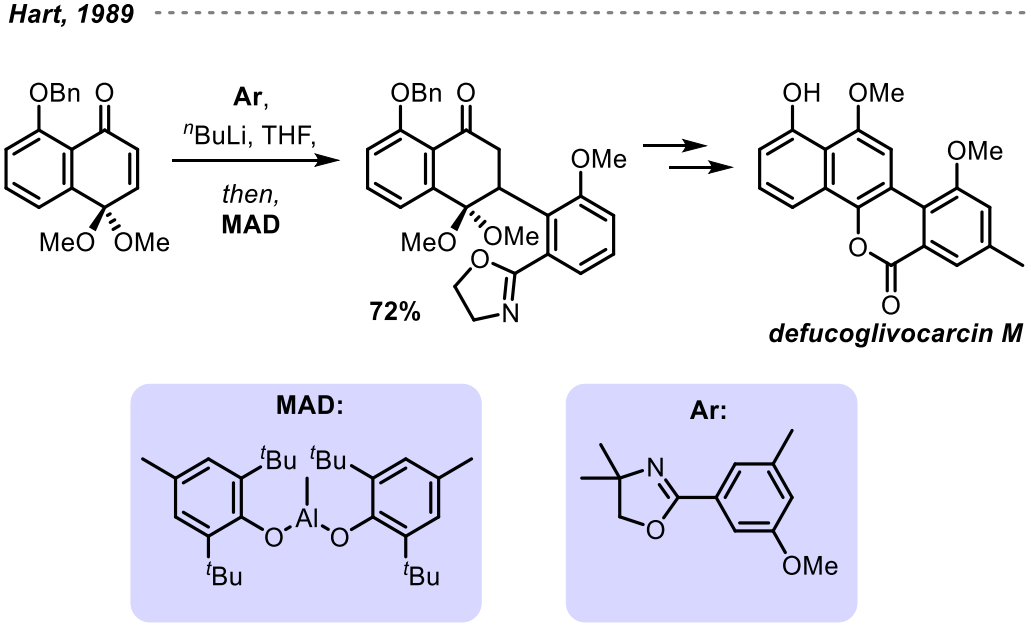
Scheme 13: Foster's 1,4-additions of oxygen, sulfur and nitrogen nucleophiles onto *para-quinone* monoketals.[42]

Wheeler [16] and Parker [17] have independently demonstrated Michael additions onto 2,5-cyclohexadienones with stabilised enolates; in the former case, Parker was able to effect acid mediated aromatisation of the Michael adduct, furnishing the *meta*-functionalised phenol.



Scheme 14: Parker and Wheeler's Michael additions *onto para-qui*none monoketals.[16,17]

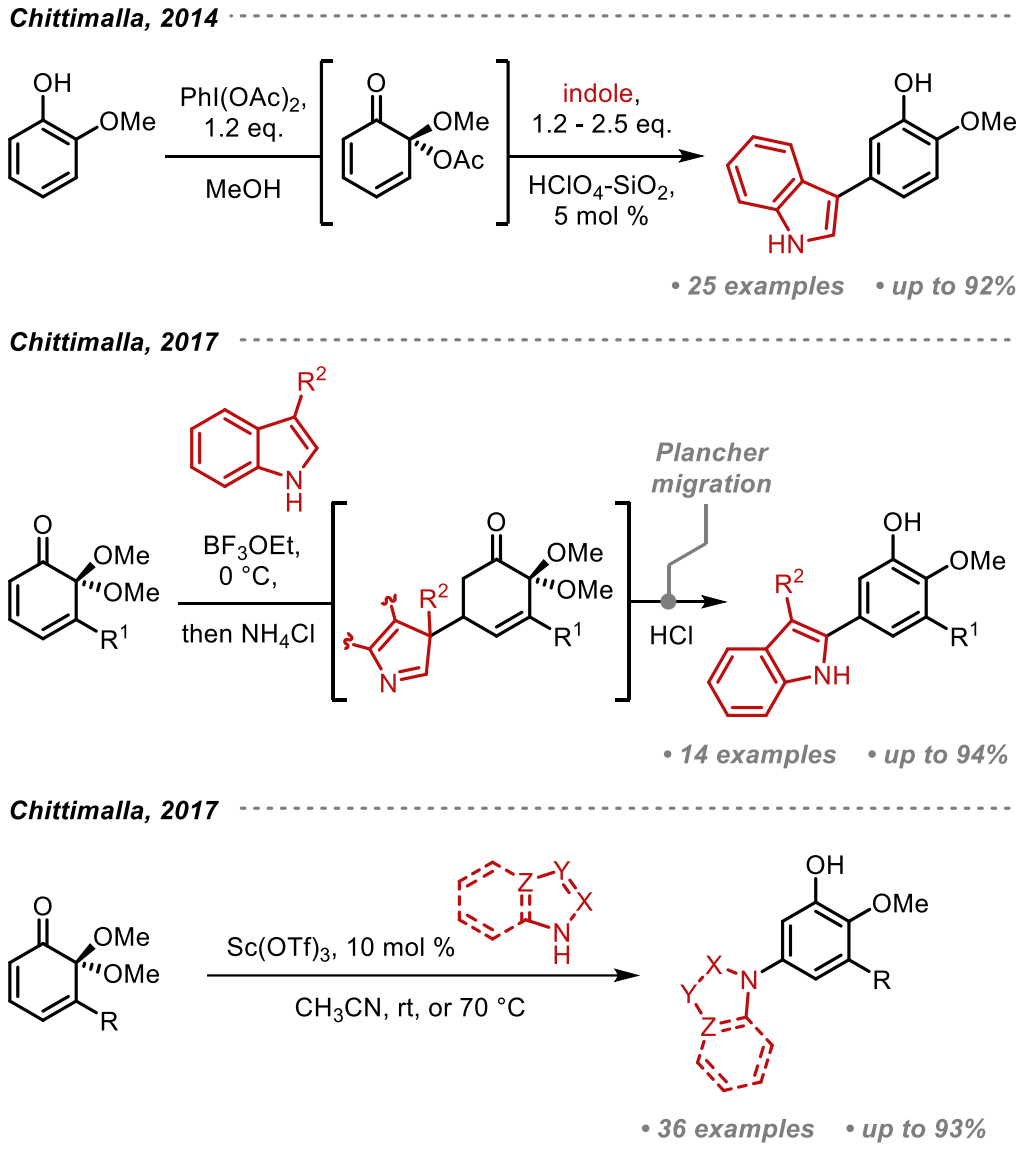
Complexation of the carbonyl of the cyclohexadienone with a Lewis acid, such as MAD, can override the innate preference for hard nucleophiles to undergo 1,2-addion. Hart uses MAD in combination with a substituted phenyllithium reagent and a 2,5-cyclohexadienone in the synthesis of defucogilvocarcin M (Scheme 15).



Scheme 15: Hart's 1,4-addition using an organolithium in the synthesis of defucoglivocarcin M.[15]

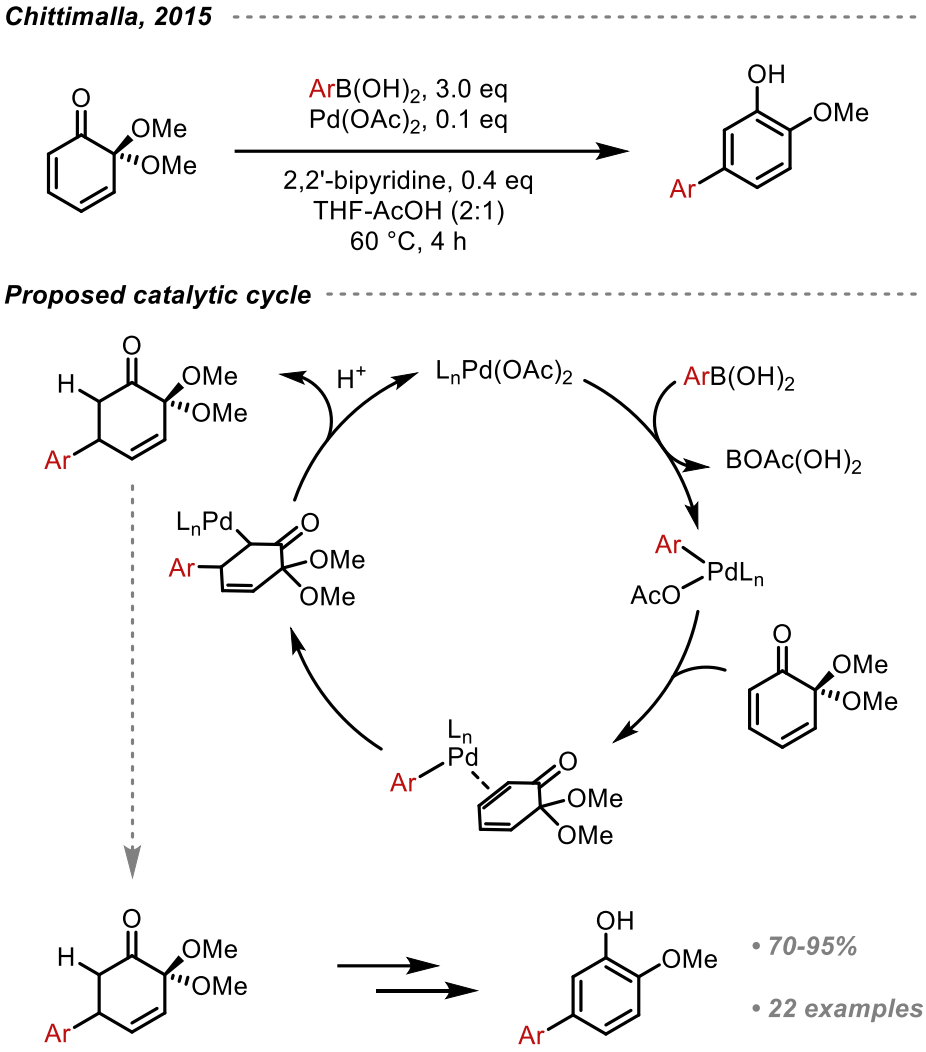
The 1,4-adduct can be viewed as a masked *meta*-functionalised arene, a highly sought-after substitution pattern. Aromatisation to furnish this substitution is achieved in Parker's chemistry as previously shown. Chittimalla has exploited this

tandem Michael addition rearomatisation strategy to 2,4-cyclohexadienones with electron-poor heterocycles, thus reporting general and robust methods to procure 2- and 3-aryl indoles, in addition to N-heterocyclic phenols (Scheme 16).[19,22,25]



Scheme 16: 1,4-addition of heterocycles onto *ortho*-quinone monoketals.[19,22,25]

Perhaps one of the most useful methodologies developed by Chittimalla is the palladium catalysed addition of boronic acids onto the cyclohexadienone core (Scheme 17).[23] This enables access to *meta*-arylated phenols, a notoriously difficult position to arylate, and a topic of interest within this thesis.

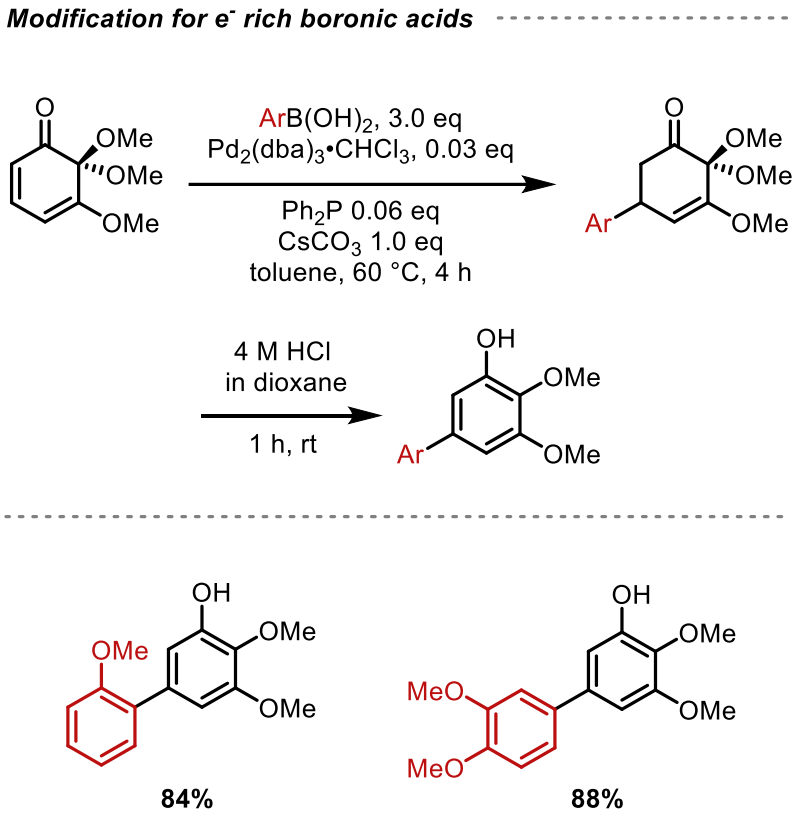


Scheme 17: Proposed mechanism of palladium catalysed 1,4-addition of boronic acids onto 2,4-cyclohexadienones.

The reaction is proposed to proceed *via* an initial aryl-palladium species, whereby the dienone can insert into the Pd-C bond. Subsequent protonolysis in acidic conditions can afford the Michael adduct, liberating the active palladium species back into the catalytic cycle. The adduct can then undergo facile rearomatisation, *via* elimination of methanol, producing the now *meta*-functionalised phenol.

Their methodology tolerates phenols of various substitution patterns in good to excellent yields. Boronic acid modifications are also well tolerated, however it is known that electron-rich boronic acids are prone to protodeboronation in acidic reaction media.[43] As such, Chittimalla demonstrates a successful modification to the developed methodology, which allows for the use of electron-rich substrates, in a non-acidic system. It was proposed that swapping the palladium species to $Pd_2(dba)_3 \cdot CHCl_3$, and the solvent to toluene, would enable Michael adduct

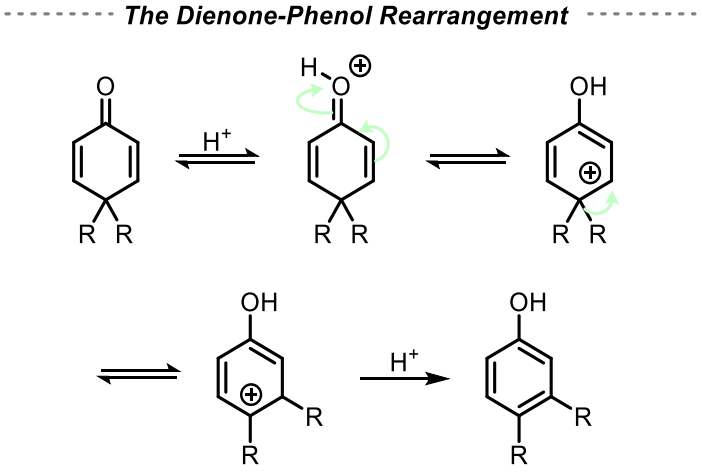
formation. Subsequent treatment with acid would affect the rearomatisation to provide the phenol. These conditions, shown in Scheme 18, are compatible with the methoxyphenyl boronic acids, affording the biphenyls in excellent yields.



Scheme 18: Chittimalla's modification for electron-rich aryl boronic acids.

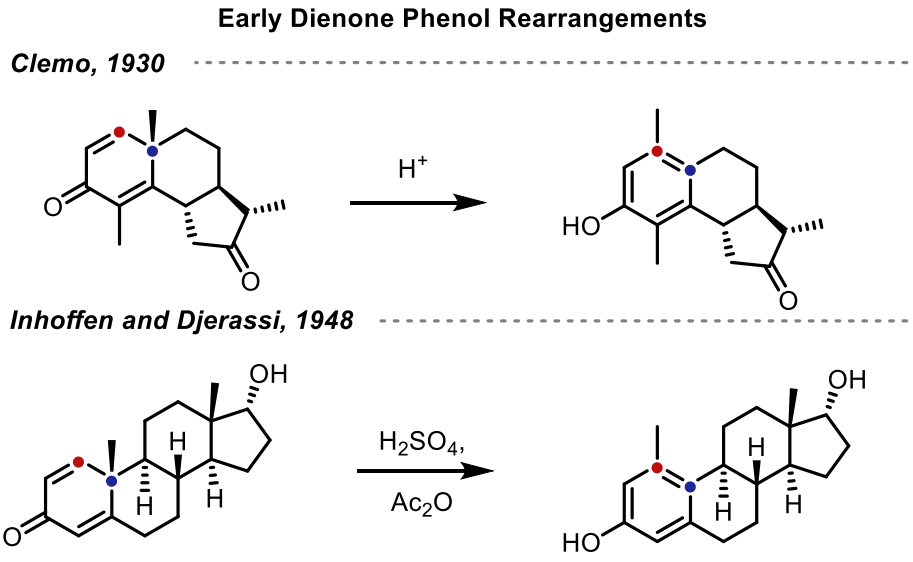
Dienone-Phenol Rearrangements

The dienone-phenol rearrangement is one of the many observed acid catalysed sigmatropic shifts that cyclohexadienones can undergo. It entails the migration of one substituent on the cyclohexadienone to an intermediate capable of rearomatizing to its corresponding phenol, Scheme 19. It is best known for its ability to migrate alkyl groups, however allylic and benzylic migrations have also been reported. [35]



Scheme 19: General dienone-phenol rearrangement.

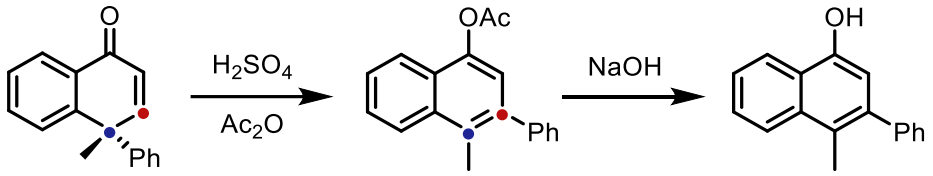
The dienone-phenol rearrangement was first described by Clemo in 1930, in the conversion of santonin to desmotroposantonin (Scheme 20).[44,45] This was followed by Inhoffen, who reported aromatisation of cholestadienones and androstadienones. [46,47]



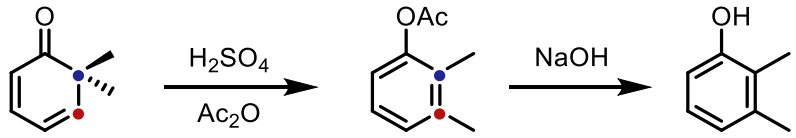
Scheme 20: First reports of the dienone-phenol rearrangement.

The rearrangement was exploited in the synthesis of 1-naphthols by Arnold in 1947, who, two years later, probed the mechanism through a competition reaction between the migration of a phenyl and methyl group. (Scheme 21, top).[48] The product was found to follow the migration of the phenyl, consistent with other 1,2-migration reactions which proceed through a carbocationic intermediate. The migration was also showcased for 2,4-cyclohexadieenones by Marvell and Magoon,[49] highlighting that the reaction is not limited to *para*-cyclohexadienones. (Scheme 21, bottom).

Arnold, 1949



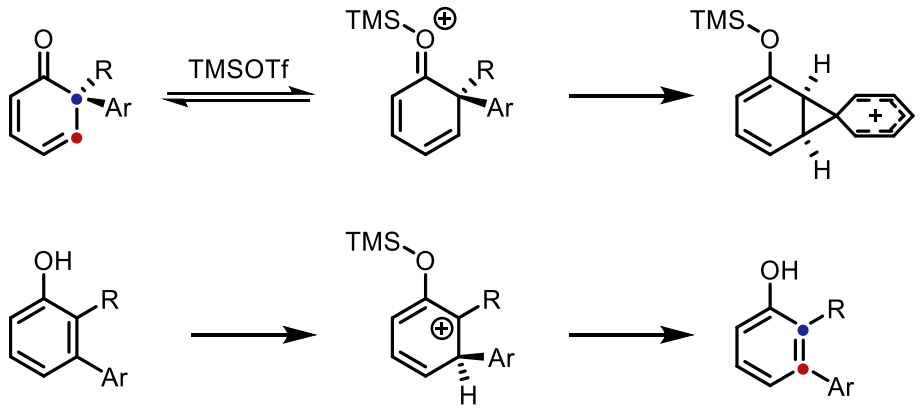
Marvell and Magoon, 1955



Scheme 21: Competition between migration of the phenyl and methyl group (top), 1,2-migration on 2,4-cyclohexadienones (bottom).

A recent and general protocol applying similar chemistry has been conducted by the Ball group in 2022. In their publication reporting the synthesis of aryl cyclohexadienones, it was hypothesised the arene could migrate to the *meta*-position. This proposal was met with success; a series of cyclohexadienones were subject to trimethylsilyl triflate to afford an intermediate phenonium cation, producing the corresponding biphenyl. [33]

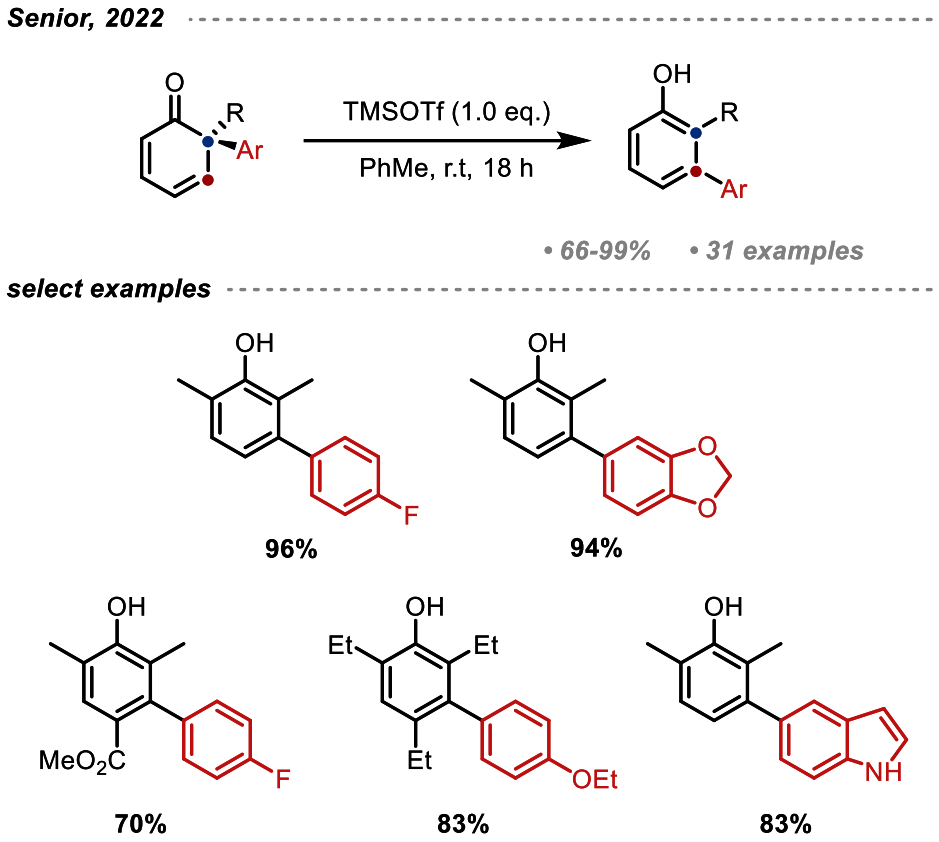
Senior, 2022



Scheme 22: Mechanism of the 1,2-aryl migration of 6-aryl 2,4-cyclohexadienones.

The reaction tolerates a large scope of electron-withdrawing and electron-donating aryl groups (Scheme 23). Indoles are also able to undergo migration, as well as naphthalenes (83% and 72% respectively). With respect to the

cyclohexadienone, substituents at the *ortho*-and *para*-positions are compatible in all cases, and the rearrangement proceeds in good to excellent yields.

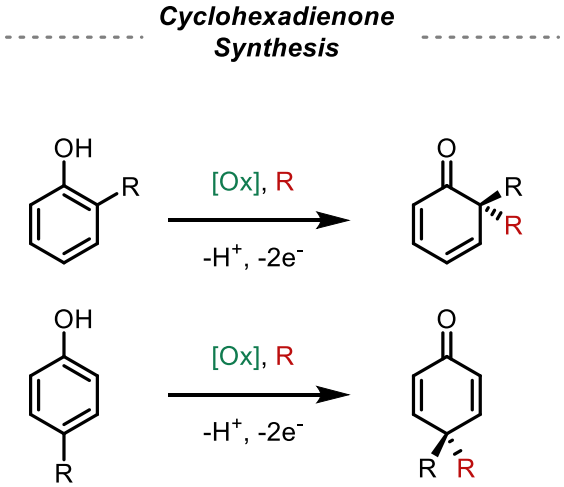


Scheme 23: 1,2- aryl migration of aryl 2,4-cyclohexadienones.

From the preceding discussion, it is evident that the cyclohexadienone core is rich in diversifiable handles. Its ability to participate in a multitude of reaction conditions undoubtedly awards the scaffold with a vast synthetic potential. Having explored these chemistries, the remainder of this introduction will survey the possible routes to the synthesis of this compound class.

1.3. Cyclohexadienone Synthesis

The dearomatisation of phenol is the most widely used strategy to prepare a cyclohexadienone. This strategy requires an *ortho*-or *para*-substituted phenol and installs a group *ipso* to this position, thus preventing reductive rearomatisation of the cyclohexadienone.

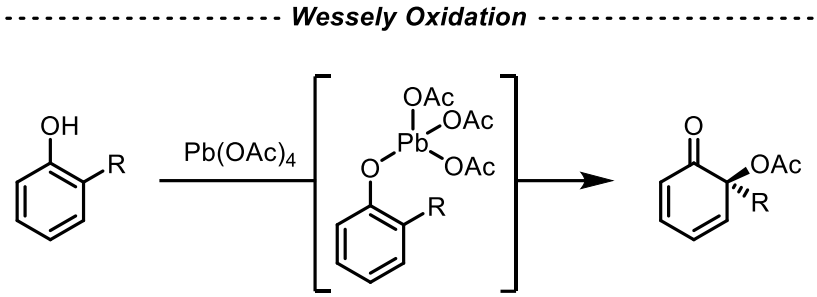


Scheme 24: Phenol dearomatisation to 2,4-/2,5-cyclohexadienones.

Oxidants able to permit this transformation include, but are not limited to, Pb(IV), I(III) and Bi(V) reagents. These methods enable alkoxylative, acetoxylative, and more recently, arylative dearomatisation. This section will discuss each of these chemistries' utility in cyclohexadienone synthesis, leading onto the more recent advances that bismuth chemistry has presented in the preparation of aryl-cyclohexadienones.

Pb(IV) Chemistry

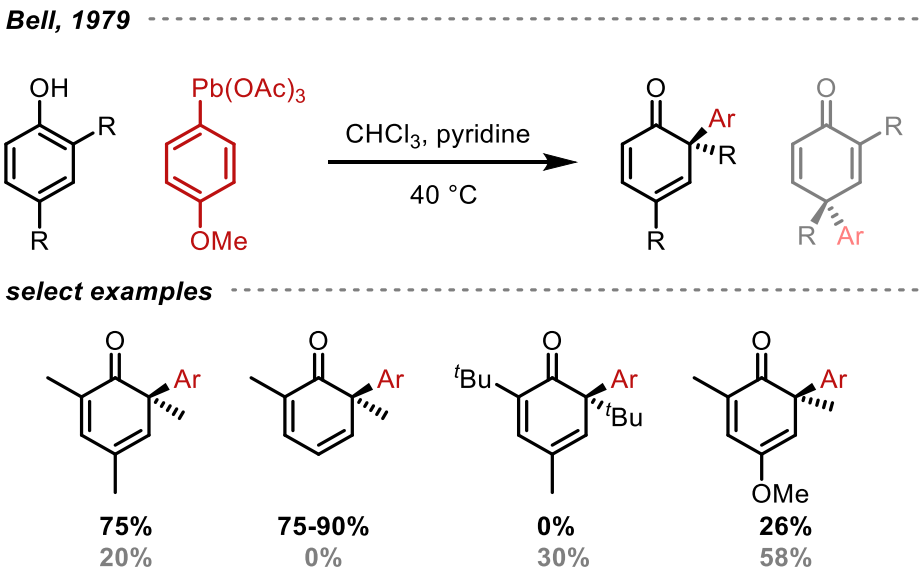
Pb(IV) mediated acetoxylative dearomatisation of phenol was first realised in the 1950's by Wessely's studies on the dearomatizing capability of lead tetraacetate (LTA).[50] This work led to the discovery of the eponymously named Wessely acetoxylation, one of the few general methods of phenol dearomatisation available today (Scheme 25).



Scheme 25: General scheme for the Wessely acetoxylation of phenol.

The Wessely acetoxylation is believed to proceed through an aryloxy-lead intermediate, followed by delivery of the acetate in a reductive ligand coupling event; LTA displays a strong proclivity for oxidation at the *ortho*-position bearing the more electron-rich substituent.[50,51] This is a general observation for organometallic or hypervalent iodane mediated phenol dearomatisation, which will be discussed throughout this chapter. While the Wessely oxidation sees utility in organic synthesis, it is generally less favourable to employ than hypervalent iodine methods. This is largely due to the fact that lead is notoriously neurotoxic, whereas I(III) reagents are relatively benign.

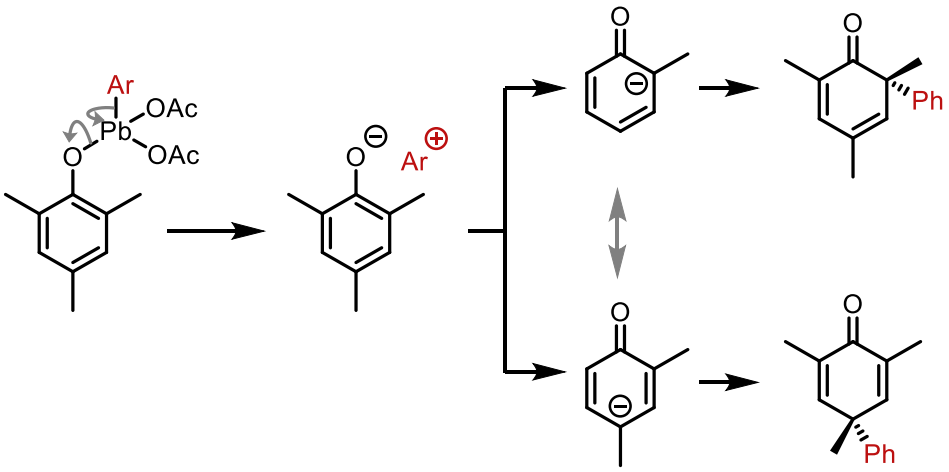
Pb(IV) mediated dearomatizing phenylation of phenols has been showcased by Bell *et al.*,[52] although this methodology is only compatible with specific substrates. This was realised by their studies of the reaction between phenols and *para*-methoxyphenyllead triacetate in 1979 (Scheme 26).



Scheme 26: The methodology of Bell et al. for Pb(IV)-mediated dearomatizing phenylation of substituted phenols. Yields in grey = amount of 2,5- cyclohexadienone regio-isomer.

The highest yields using this methodology are obtained for the dearomatisation of di-ortho-substituted phenols, for example, mesitol and 2,6-dimethyl phenol. Crucially, if an electron-donating group is present in the para-position, the para-arylated 2,5-cyclohexadienone is formed as a minor product. Formation of the 2,5-cyclohexadienone can be biased electronically, placing a more electron-rich substituent on the para-position, and sterically, by hindering the ortho-position (see 2,6-dimethyl-4-methoxy phenol and 2,6-di-tert-butyl-4-methyl phenol). These results are consistent with those in the Wessely acetoxylation, whereby the arene is preferentially delivered ipso to an electron-donating ortho-(or para-) substituent on the phenol.

Proposed Mechanism



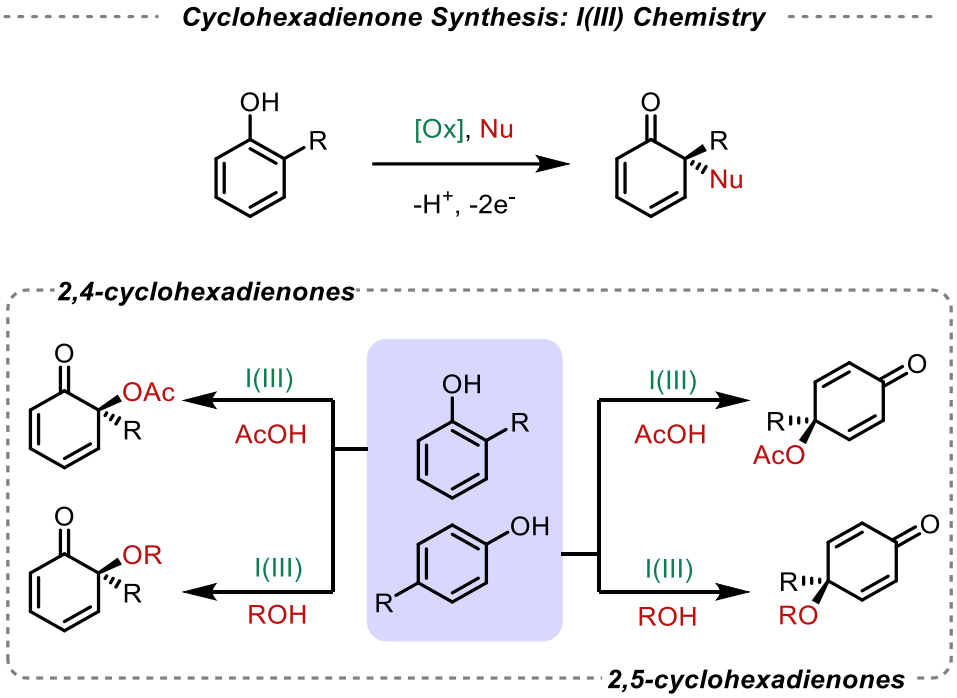
Scheme 27: Proposed mechanism of Pb(IV)-mediated dearomatizing phenylation of substituted phenols.

Bell postulated a varied mechanism to Scheme 25 for this transformation, whereby dearomatisation proceeds through complexation of the phenol and the aryl-lead compound. This complex could break down to form a transient phenoxide ion and aryl cation, allowing for competing reaction pathways for the formation of both 2,4-cyclohexadienones and 2,5-cyclohexadienones (Scheme 27).

While this methodology describes a rare example of arylative dearomatisation, is only synthetically useful for the dearomatisation of 2,6-dimethyl phenol. Furthermore, it is not compatible with electron-poor phenols, and the reaction requires an excess of phenol to go to completion. In addition, dermatoxic Hg(II) catalysts are typically employed to access the aryllead species.[53]

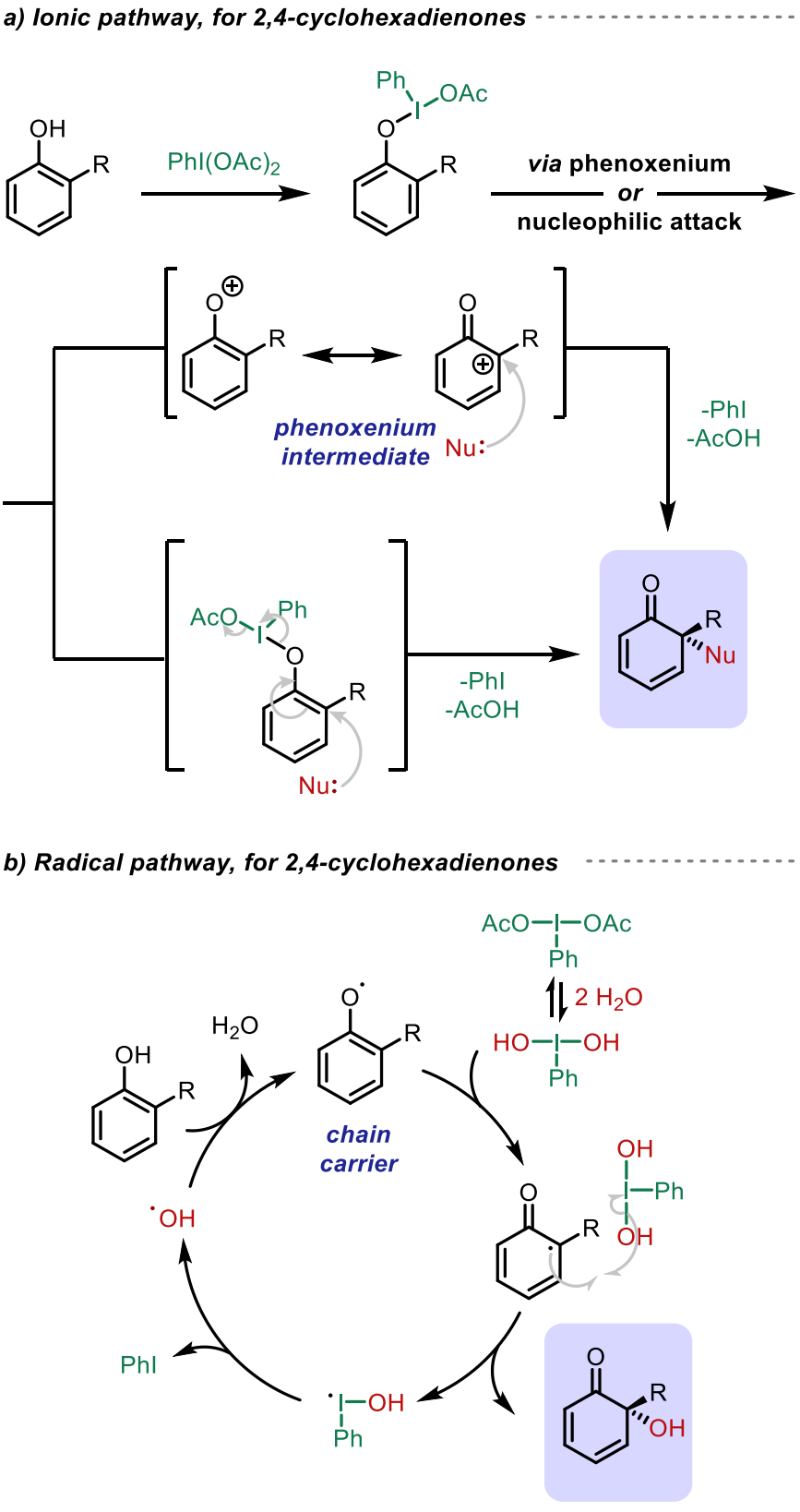
I(III) Chemistry

The use of hypervalent iodine chemistry is well established in phenol dearomatisation, for it has become the most widely used method in the synthesis of 2,4- or 2,5- cyclohexadienones.[54–56] The general protocol for hypervalent iodine mediated dearomatisation requires the oxidant, which usually takes the form of PIFA or PIDA, the phenol, and an intercepting nucleophile (Scheme 28). Typical nucleophiles include alcohols or acetates, which form cyclohexadienones of the *ortho*/*para*-quinone mono ketal type.[57]



Scheme 28: Protocol for hypervalent iodine mediated phenol oxidative dearomatisation.

The mechanism by which hypervalent iodine enables dearomatisation is a matter of debate in the literature, and it may depend on the method of dearomatisation which takes place. For example, there is president for radical pathways in the case of hydroxylative dearomatisation, whereas alkoxylative strategies are thought to proceed *via* ionic ones. Both of these routes are depicted in Scheme 29, showcased for the dearomatisation of *ortho*-substituted phenols.[58,59]



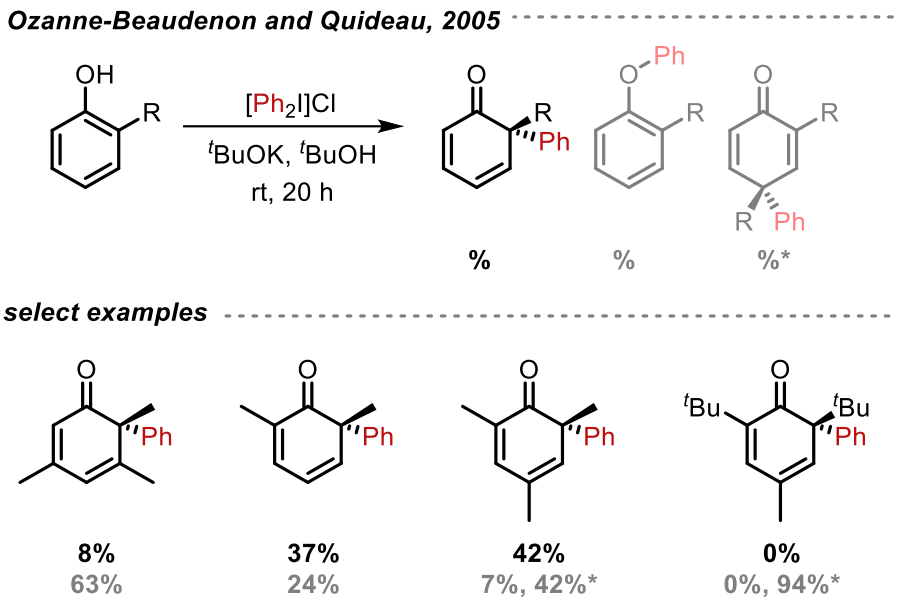
Scheme 29: Possible mechanisms for hypervalent iodine mediated phenol dearomatisation.

In an ionic mechanism, the reaction may proceed *via* ligand exchange with the phenol nucleophile at the electrophilic I(III) centre, where the resultant aryloxy-

diphenyl-λ_3-iodane can eliminate iodobenzene to afford a phenoxenium intermediate. (Scheme 29, a). This phenoxenium can exist as its resonance form, bearing the positive charge *ipso* to a stabilising electron-donating group; subsequent nucleophilic attack at this position furnishes the 2,4-cyclohexadienone. Alternatively, the aryloxy-diphenyl-λ_3-iodane can undergo nucleophilic attack *ipso* to an electron-donating group on the ring, which would then affect elimination of iodobenzene in a concerted fashion.

In the instance of hydroxylative dearomatisation (*i.e.* Nu = H_2O), this reaction could proceed *via* a radical mechanism. A recent study by Kraszewski *et al.* provided confirmation of phenoxy radicals among the PIDA mediated dearomatizing hydroxylation of 2,4-*tert*-butylphenol. [59] The authors of this investigation claim to only present their understanding of the propagation steps of the radical chain, not the specific course of initiation or termination. Nonetheless, their current understanding of the propagation steps are depicted in in Scheme 29, b. The aryloxy radical is described as the key chain-carrying intermediate which can undergo radical coupling with an I(III)-H_2O adduct (or other related I^{III}-O oxidising species) to the cyclohexadienone. In turn, this liberates an iodanyl (II) radical, or related species. Fragmentation of this generates iodobenzene and an OH radical, which is quenched by the phenolic starting material and regenerates the key aryloxy radical propagator.

As well as alkoxylative and acetoxylative dearomatisations, Quideau and co-workers developed a methodology whereby the cyclohexadienone can be trapped by an arene using $[Ph_2I]Cl$.[60] It was found that treating phenols with this iodane in the presence of a protic base in DMF would afford arylated cyclohexadienones and diary ethers, depending on the steric and electronic profile of the starting phenol.

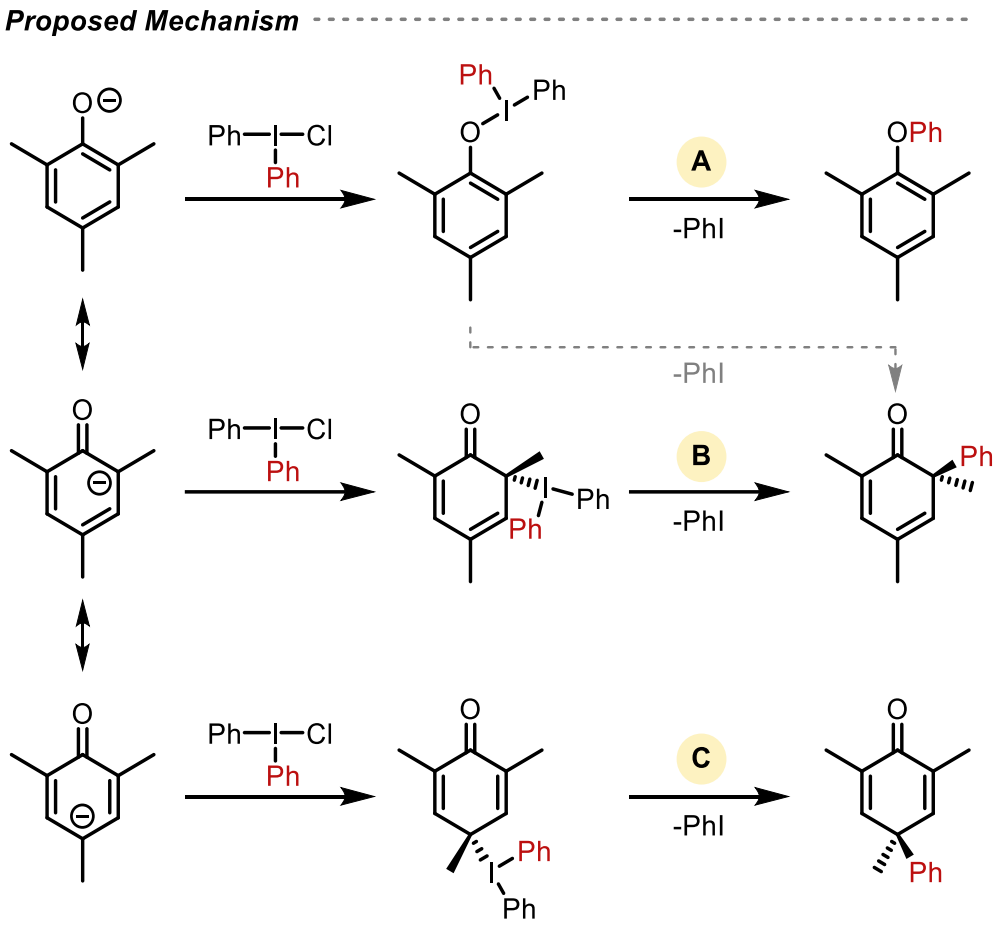


Scheme 30: Hypervalent iodine mediated dearomatizing phenylation of phenol

Initial observations using 2,3,5-methyl phenol gave the 2,4-cyclohexadienone as a major product, as well as the O-arylated ether. This dearomatisation is consistent with the previously discussed mechanisms, in which nucleophilic attack occurs *ipso* to an *ortho*-or *para*-electron-donating substituent. In accordance with this, the use of 2,6-dimethyl phenol affords the respective cyclohexadienone as the major product, whereas mesitol affords both the 2,4- and 2,5-cyclohexadienone. Biasing the system with sterically demanding groups on the *ortho*-position allows for selectivity to the 2,5-cyclohexadienone, in the case of 2,6-di-*tert*-butyl-3-methyl-phenol. In addition, 2,6-di-*tert*-butyl-phenol gives no product, alluding to the fact that a small electron-donating group must be present for arylative dearomatisation to occur.

While the mechanisms of hypervalent iodine mediated dearomatisations have been discussed, Quideau explored potential pathways which would explain the formation of the phenyl ethers. This is analogous to Bell's postulation and is also observed in Bi(V) mediated dearomatisations (*vide infra*). Given that reactivity ceased in the presence of weak bases, Quideau hypothesised the formation of a delocalised phenolate nucleophile. This could attack the iodine(III) centre in competing reaction pathways (Scheme 31), effecting the loss of chloride in a ligand-exchange step. This would then furnish aryloxy-diphenyl-iodanes following path A and/or their C-iodanylated cyclohexadienone variants following path B or C, depending on the steric and electronic demands of the starting

phenol. This would follow with the formation of the O-arylated phenol, the 2,4-cyclohexadienone or the 2,5-cyclohexadienone.



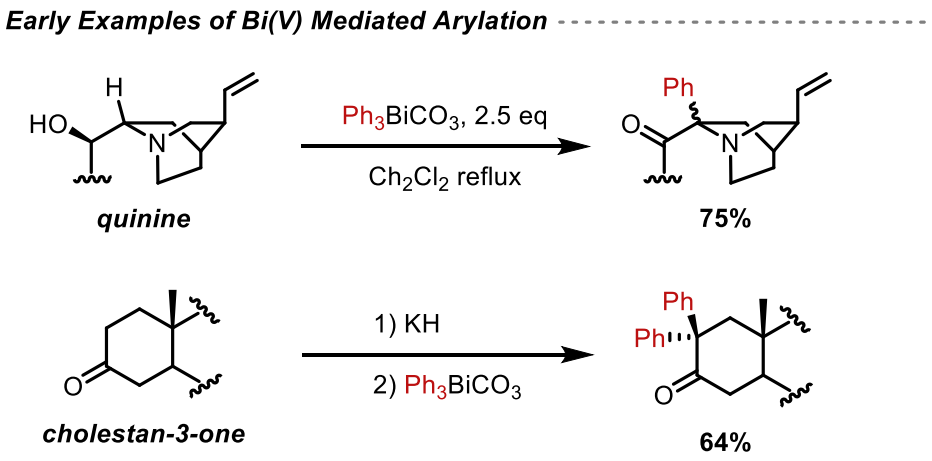
Scheme 31: Proposed mechanism for hypervalent iodine mediated dearomatizing phenylation of phenols.

Similar to Bell's work in phenylation using Pb(IV) reagents, Quideau's attempt fails to accomplish a regioselective and general methodology. Moreover, the yield with respect to the aryl substituents on the I(III) reagent is capped at 50%. It does, however, move towards more benign regents and excess phenol is not required for reactivity.

Bi(V) Chemistry – Barton

Like those previously discussed, the method by which bismuth is utilised in cyclohexadienone synthesis is *via* an oxidative arylation reaction of phenol. This is one of the many arylation reactions discovered by Prof. Sir Derek Barton, who pioneered organobismuth(V) chemistry between the 1980s and 90s.[61–68] This section will discuss Barton's key findings and mechanistic proposals. These detail the foundations for which more recent bismuth chemistry advances have built upon.

Barton serendipitously realised the first arylation reaction using an organobismuth reagent in 1980.[62] During his studies on the oxidation of alcohols using Bi(V) regents, he found that treating quinine with triphenylbismuth carbonate would lead not only to oxidation of the alcohol, but a modest 75% of the diastereomeric α-arylated ketone (Scheme 32, top). Barton postulated that the reaction proceeds *via* an enolate intermediate, which was supported by his subsequent observation of the α-arylation of cholestane-3-one (Scheme 32, bottom).

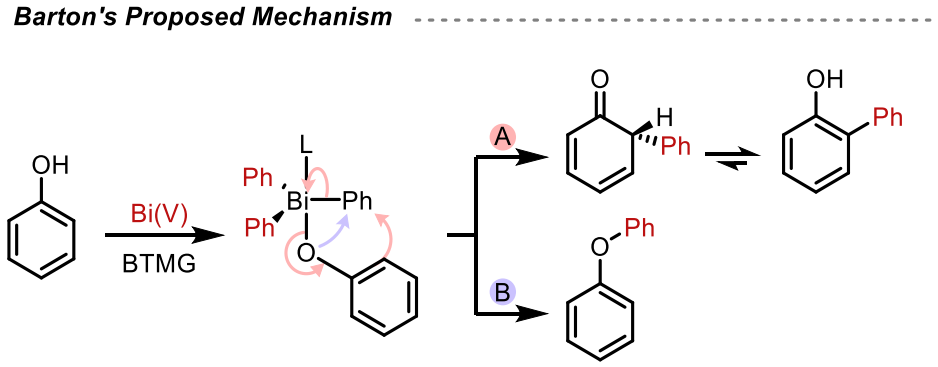


Scheme 32: First examples of Bi(V)-mediated arylation.

In the years following these discoveries Barton was able to arylate a multitude of materials, including carbonyls, diones and indoles to name a few. These findings built his 14-part series of publications, titled 'The Chemistry of Pentavalent Organobismuth Reagents'. [37,61–64,66–70]

Among these, phenol arylation was of particular interest, as the transformation effects formal *ortho*-C-H activation. Barton explored numerous phenol and

naphthol substrates with differing electronic and steric profiles. A general scheme for the *ortho*-arylation is depicted in Scheme 33, path A.[63,66–68]

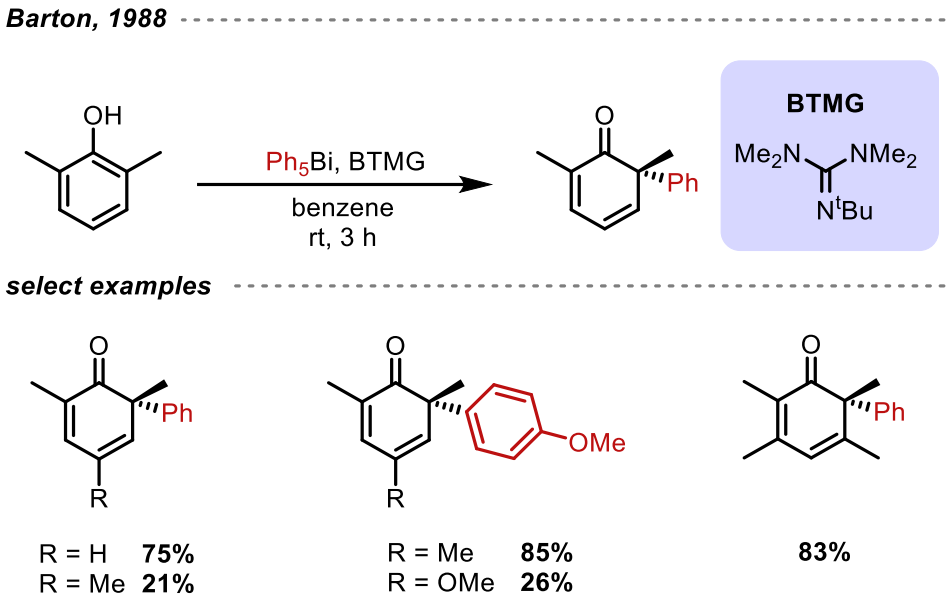


Scheme 33: Competing C_{ortho}- and O-arylation covalent mechanisms.

The mechanism was hypothesised to progress *via* complexation of the Bi(V) species to the deprotonated phenol, placing the phenyl group in close proximity to the *ortho*-position of the phenol. Subsequent attack from this *ortho*-position of the arene to the phenyl would cause cleavage of the Bi-O bond, forming a 2,4-cyclohexadienone intermediate. This would then tautomerize to the more thermodynamically stable *ortho*-arylated phenol.

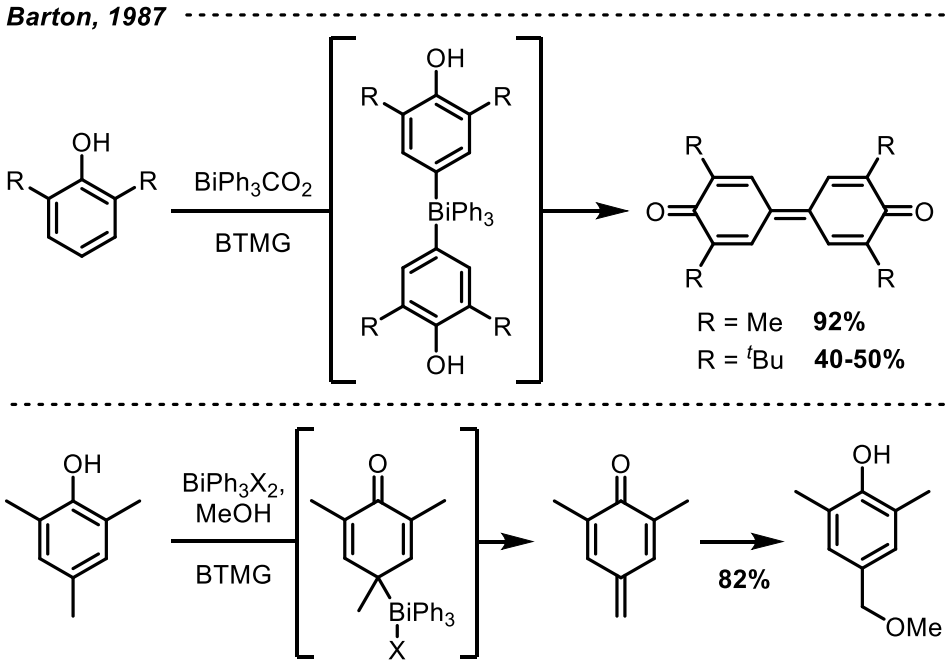
Competing with this pathway, is the ligand coupling of the oxygen atom and the phenyl to form a diaryl ether (Scheme 33, path B). Which path the reaction proceeds *via* was found to be dependent on the substrate, reaction conditions, and Bi(V) species. Crucially, If the phenol possesses electron-withdrawing groups, it becomes too electron-poor to attack the phenyl attached to bismuth *via* the *ortho*-position. In this case, pathway B dominates to give the diaryl ether.

Barton also investigated the reaction when the 2 and 6 positions of the phenol are substituted, such that rearomatisation cannot occur. In his publications dedicated to the arylation of sterically encumbered phenols, Barton reported the formation of 2,4-cyclohexadienone products, Scheme 34.[69] Notably, the reaction of 2,6-dimethyl phenol forms the corresponding arylated cyclohexadienone in a pleasing 75% yield.



Scheme 34: Barton's phenol dearomatisation.

In addition to cyclohexadienones, other products of phenol oxidation were also observed.[66] Interestingly, it was found that reacting 2,6-dimethyl phenol or 2,6-di-tertbutyl phenol with triphenylbismuth carbonate afforded the corresponding quinone dimer, Scheme 35 top. Furthermore, by treating mesitol with triphenylbismuth dichloride, Barton reported the formation of a *para*-methoxymethyl-substituted phenol. This was presumed to proceed *via* a *para*-methylene quinone intermediate (Scheme 35, bottom).



Scheme 35: Barton's oxidation of phenols using Bi(V) reagents.

To support these mechanisms, Barton sought to rule out the possibility of a radical pathway. To do this, a series of phenol arylations were conducted in the presence of a spin trap- among these, trace ESR signals were found. The yields of arylation products in the presence and absence of excess spin trap were compared, and no significant difference was observed. Thus, it was concluded that while trace radicals are formed in the reaction, they are not competent intermediates in the arylation, and reaction likely proceeds *via* a covalent mechanism, previously depicted in Scheme 33.

By analogy to this reactivity, Barton proposed that the mechanisms of formation for the cyclohexadienones follows a similar argument, proceeding *via* a common Bi-O-Ar intermediate. With respect to the more sterically congested 2,6-*tert*-butyl cyclohexadienones, Barton remained in favour of the mechanisms in Scheme 33, but claimed further investigation would be necessary.[69]

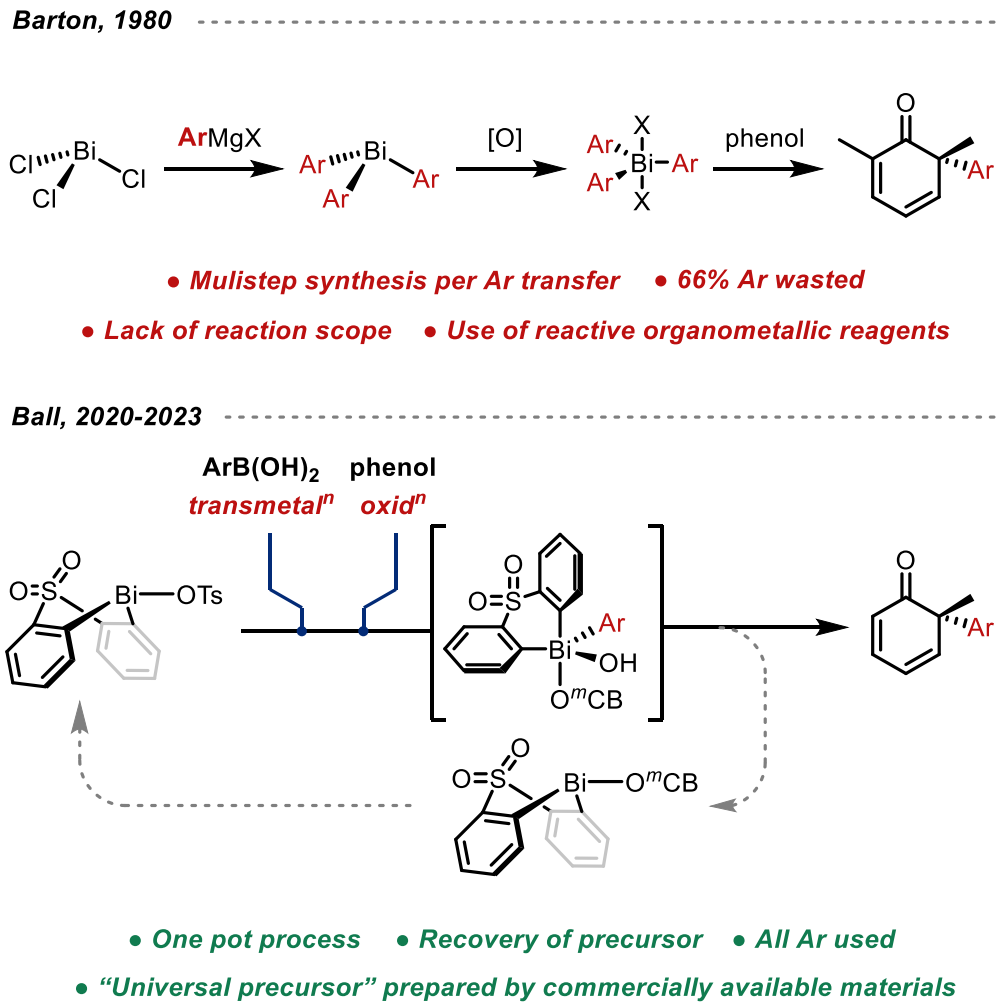
With respect to phenol dearomatisation, the early work in Bi(V) methodologies appear to suffer from some of the limitations I(III) and Pb(IV) methods do. These include:

- the yields with respect to the aryl substituents on the arylating agent is capped at 20% (for pentaphenyl bismuth),
- each Bi(V) arylating oxidant requires its own multistep synthesis,
- pentaphenyl bismuth is explosive on heating.

However, given that this method exhibits almost complete selectivity for *ortho*-arylation (except in the extreme case of 2,6-di-tert-butyl-4-methylphenol), and performs in excellent yields for the few substrates shown (Scheme 34), Bi(V) displays much potential in the field of C-H arylation and phenol dearomatisation chemistry. This potential has recently been exploited in the Ball group, 40 years after Barton's pioneering work.

Bi(V) Chemistry – Ball

In 2022, Ball presented convenient and general protocols for the Bi(V)-mediated oxidative arylation of 2,6-dimethylphenols to prepare 2,4-cyclohexadienones. This methodology addresses each of the challenges previously outlined in Barton's chemistry (Scheme 36).[71]

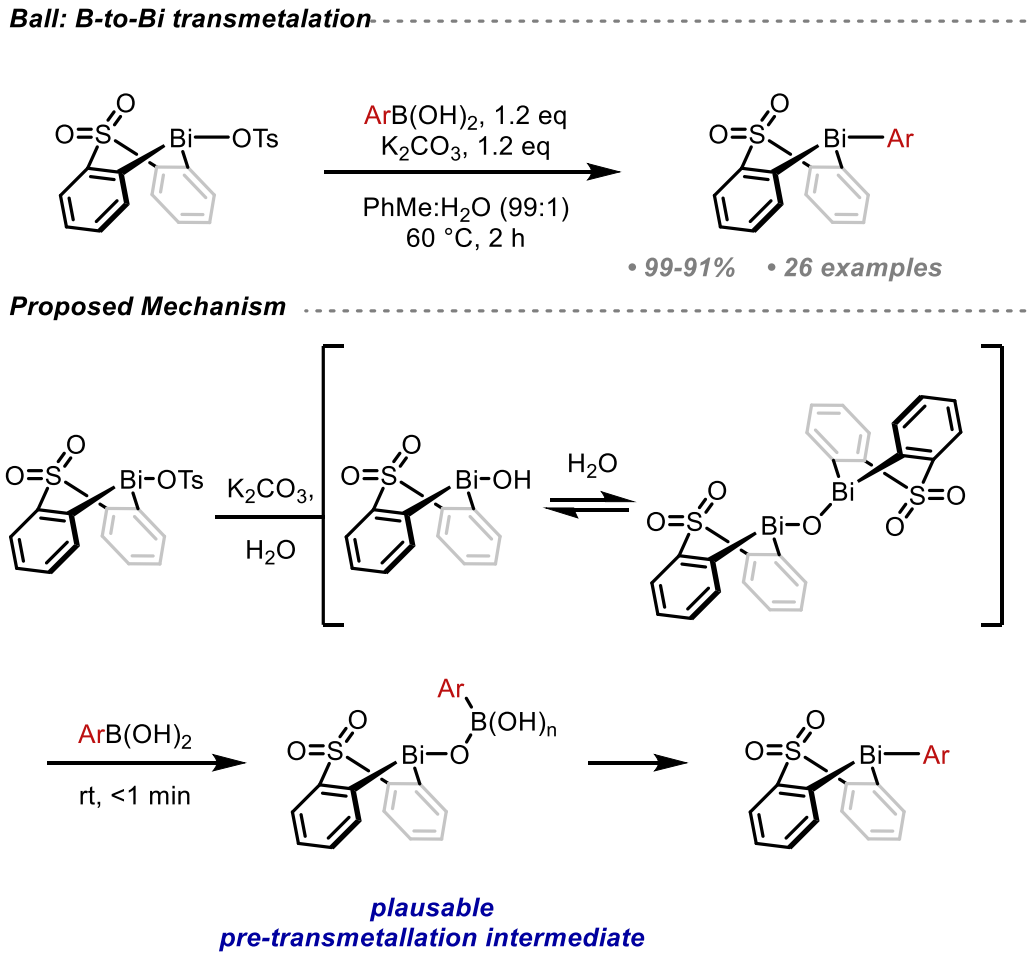


Scheme 36: Recent advances in Bi(V)-mediated phenol dearomatisation.

In overcoming poor yields with respect to the arene, the group designed a Bi(III) species bearing a bidentate sulfone backbone, referred to hereafter as the 'bismacycle'. Transmetallation of an aryl boronic acid onto the bismacycle affords a precursor to the Bi(V) arylating agent. The bidentate backbone acts to expose only one valuable aryl group, maximising the theoretical yield based on transferrable aryl groups to 100%. By subjecting this to an oxidant such as *m*CPBA, the Bi(V) species is generated *in situ* and effects oxidative arylation of a

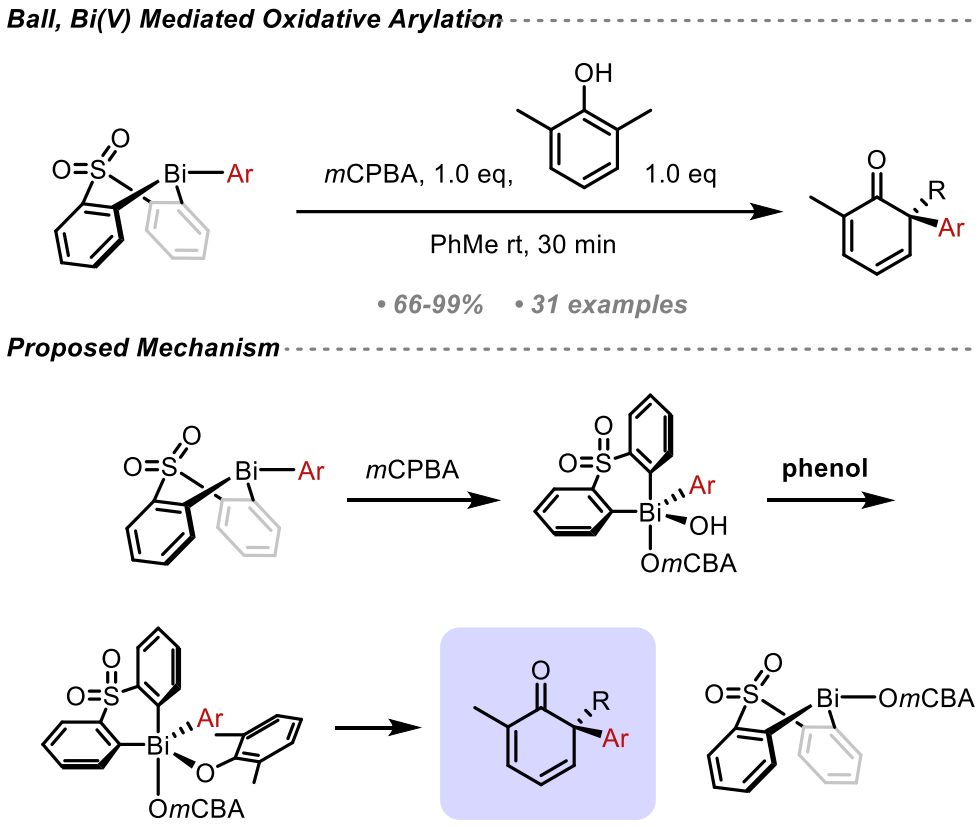
di-*ortho*-substituted phenol. Following arylation, the bismacycle *meta*-chlorobenzoate co-product is observed, which can be isolated and recycled to the bismacycle tosylate in near-quantitative yields.

By probing the mechanism for the transmetallation, the Ball group found the bismacycle tosylate hydrolyses to a bismacycle hydroxide, which exists in equilibrium with a dimeric Bi-O-Bi species (Scheme 37). Treatment of the isolated dimer with the aryl boronic acid in the absence of base affords the aryl bismacycle at a higher rate than when the bismacycle undergoes the reaction normally. This highlights the need for water and base to permit the transmetallation step. The potential involvement of a Bi-O-B pre transmetallation intermediate was also postulated and described as analogous to the Pd-oxo transmetallation pathway in the Suzuki cross coupling reaction. [72]



Scheme 37: Proposed mechanism for the transmetallation of an arylboronic acid onto the bismuth tosylate.

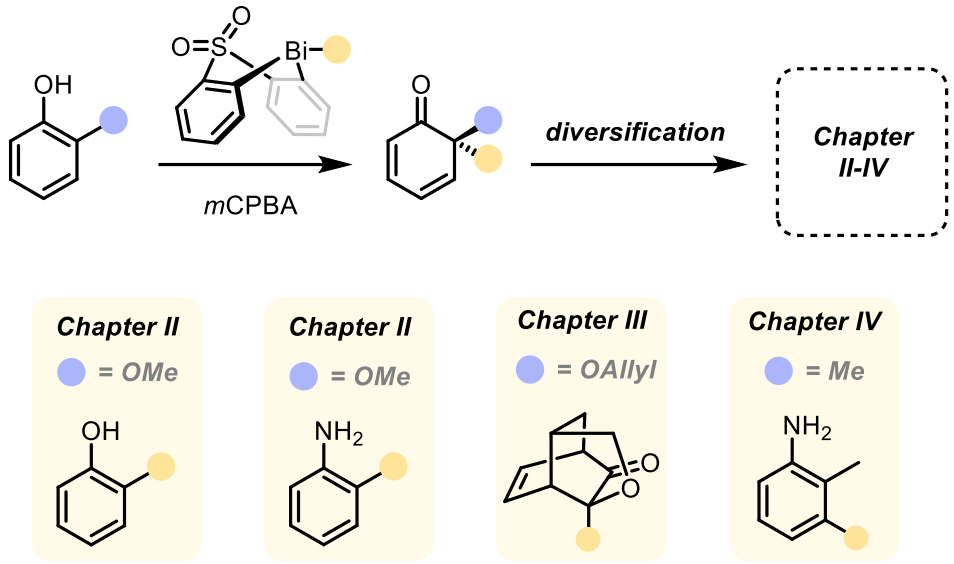
The proposed mechanism for the electrophilic arylation step is shown in Scheme 38. Oxidation of the aryl bismacycle with *m*CPBA affords the Bi(V) intermediate, in which the phenol can displace the OH. It is hypothesised that the intermediate following this rearranges positions the phenol apical, and perpendicular to the (equatorial) aryl moiety. A subsequent ligand coupling reaction between the *ortho*-position of the phenol and the aryl moiety affords the 2,4-cyclohexadienone.[71] These two transmetallation-oxidative arylation events were telescoped into a 2-step one pot process.



Scheme 38: Proposed mechanism for oxidative arylation of di-*ortho*-substituted phenols.

These advances have provided a regioselective method for the synthesis of 2,4-cyclohexadienones in good to excellent yields using benign and bench stable reagents (Scheme 38). This recent strategy additionally presents a synthetically useful route towards a novel class of cyclohexadienone by arylation of the phenolic nucleus rather than oxygenation. The success of this work poses the question of whether other *ortho* substituted phenols are compatible with the Bi(V) mediated arylation, and how the reactivity of these novel intermediates can be exploited.

This thesis presents 4 unique diversifications of the aryl cyclohexadienone core to synthetically desirable products, as inspired from Senior's seminal work. These interconversions and their respective Chapters are shown in Scheme 39:



Scheme 39: Interconversions of the aryl cyclohexadienone reported in this thesis.

Chapter II explores the application of this chemistry to guaiacols, thus forming cyclohexadienones that serve as masked biphenyls. A reduction-rearomatisation sequence of these cyclohexadienones provides a route to *ortho*-arylated phenols. Application of this methodology to the synthesis of *ortho*-arylated anilines is investigated, following the condensation of an N-donor onto the cyclohexadienone intermediate. Chapter III constitutes the arylative dearomatisation of 2-allyloxy-cyclohexadienones, which undergo a Diels-Alder reaction to form a novel class of bicyclo[2.2.2]octenone. We have seen in this introduction that the cyclohexadienones undergo 1,2-aryl migrations to afford *meta*-arylated phenols; Chapter IV will explore the developments of an analogous transformation in the synthesis of *meta*-arylated anilines.

Chapter II

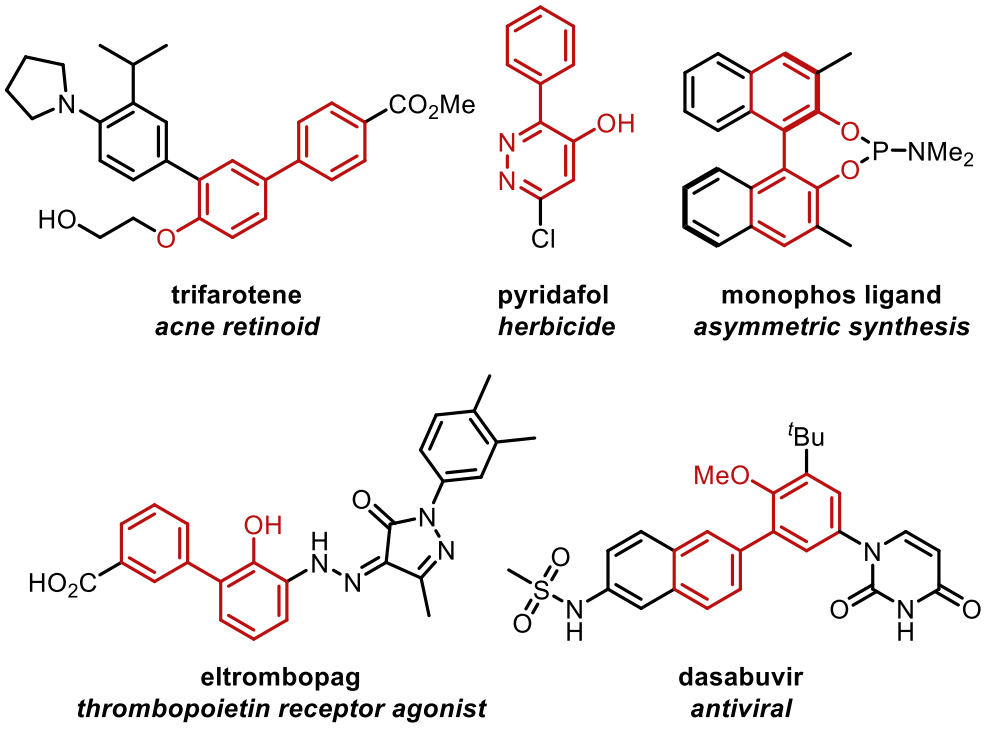
Dealkoxylative Arylation of Guaiacol

The results presented in this Chapter have been published in the following manuscript:

N. F. M. Ansarian and L. T. Ball*, *Org. Lett*. 2025, **27**, 2769–2774

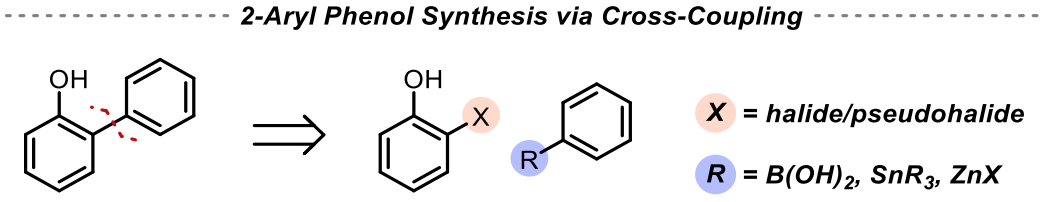
2.1. Introduction

The *ortho*-arylated phenol motif is present in numerous biologically and synthetically important molecules.[73,74] The prevalence of this scaffold among bioactive compounds is by virtue of its defined rigidity coupled with its ability to hydrogen bond at the phenol, features which are often ancillary to the design of lead like compounds. [75,76]



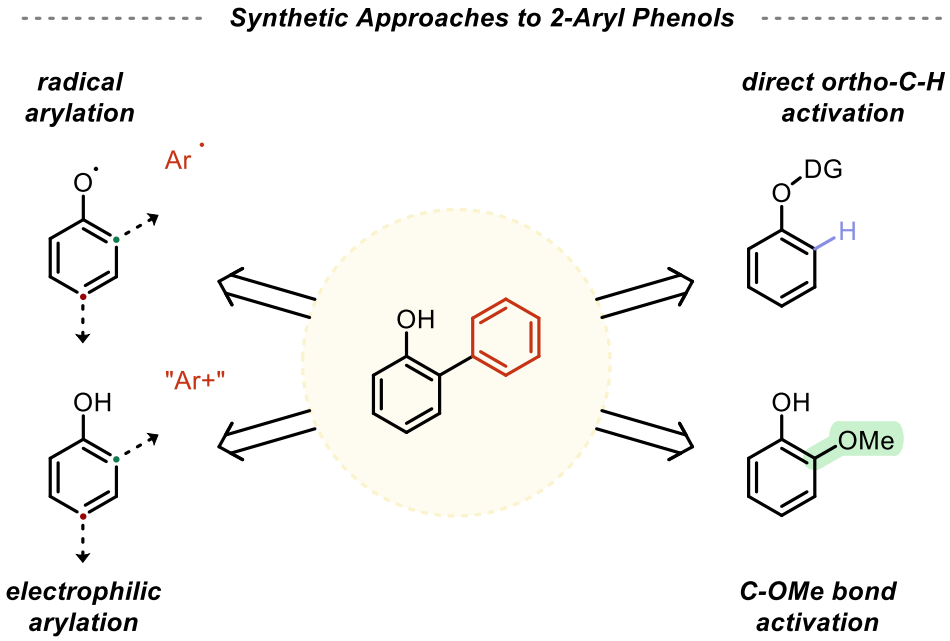
Scheme 40: *ortho*-arylated phenol motif presented in biologically and chemically relevant systems.

Preparation of this motif is typically reliant on metal catalysed cross coupling. While the coupling partners of this disconnection are accessible for simple biphenyls, complex molecules with this core require the regioselective synthesis of their corresponding partners. (Scheme 41)



Scheme 41: Common cross coupling disconnection for the synthesis of *ortho*-arylated phenols.

This chapter will begin by exploring alternative strategies to furnish the ortho-arylated phenol, including directed ortho-C-H arylation and non-metal catalysed routes (Scheme 42). A preface to C(sp2)-OR arylation and Bi(V) mediated phenol arylation will follow. These two concepts have inspired our research discussed herein: the synthesis of ortho-arylated phenols from widely abundant guaiacols.



Scheme 42: Alternative manifolds for the synthesis of *ortho*-arylated phenols.

Synthesis of *Ortho*-Arylated Phenols

Via Direct *ortho*-C-H arylation

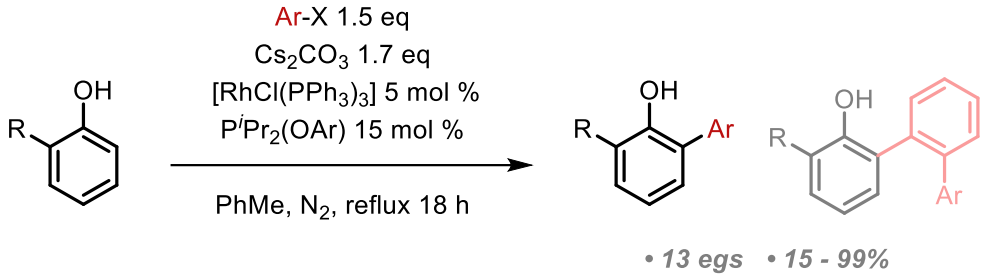
With the advance of metal-catalysed C–H bond activation,[77–79] direct *ortho*- C–H functionalization of phenols has recently been explored as an alternative to cross coupling.[80] The use of directing groups to promote *ortho*-arylation partially addresses the major drawback of cross-coupling strategies: only one of the coupling partners require prefunctionalisation. However, the direct C-H activation using an unprotected electron-rich arene is problematic for two main reasons:

- the nucleophilicity of the exocyclic heteroatom may give rise to chemo selectivity issues, [80]
- direct *ortho*-metalation using the exocyclic heteroatom is disfavoured due to the instability of the resulting high-energy 4-membered metallacycle.[81,82]

In the context of phenol arylation, various directing groups fused to the oxygen atom have been developed to ensure the formation of a stable 5- or 6-membered metallacycle, as well as to protect the hydroxyl group. This section will explore the different directing groups researchers have employed in their methodologies to access *ortho*-arylated phenols *via* direct C-H functionalisation.

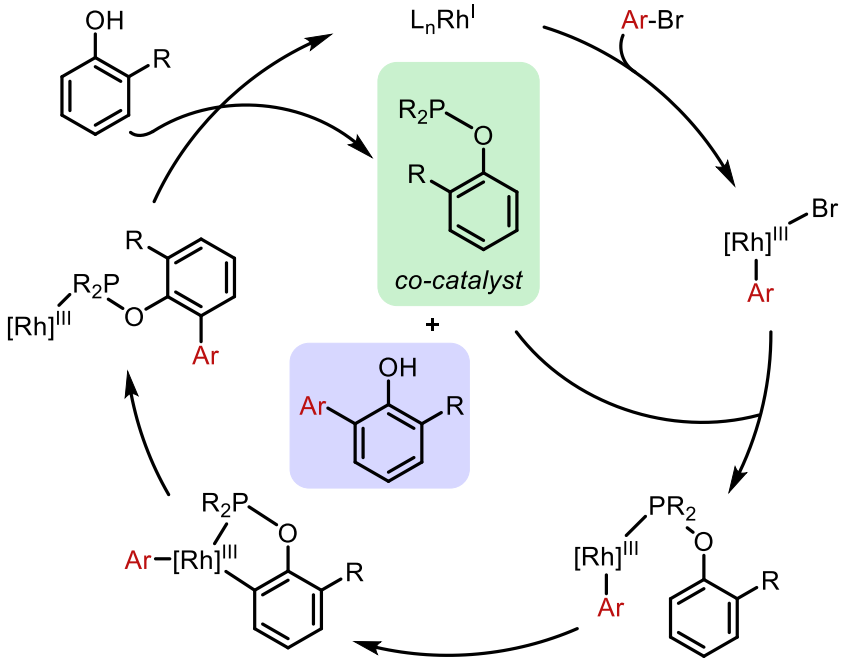
In 2003, Bedford reported the rhodium catalysed *ortho*-arylation of phenols using a transient phosphinite directing group capable of forming a stable 5 membered rhodacycle (Scheme 43).[83] This work was inspired by Lewis' disclosure in 1986, in which the *ortho*-alkylation of phenols was realised using a ruthenium/ phosphinite catalyst/cocatalyst system.[84]

Bedford; 2003



• 13 egs • 15 - 99%

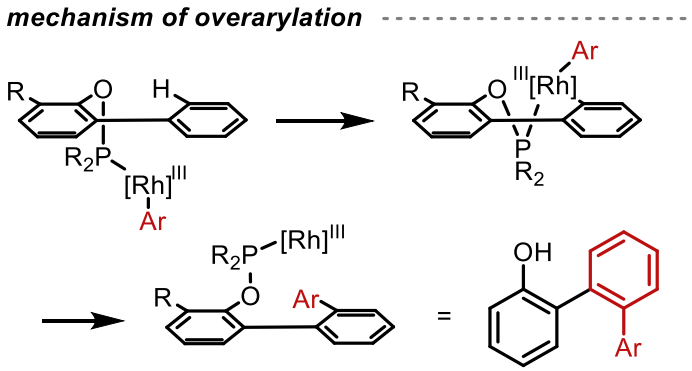
Proposed Mechanism



Scheme 43: Bedford's Rh-catalysed *ortho*-C-H arylation of phenols.

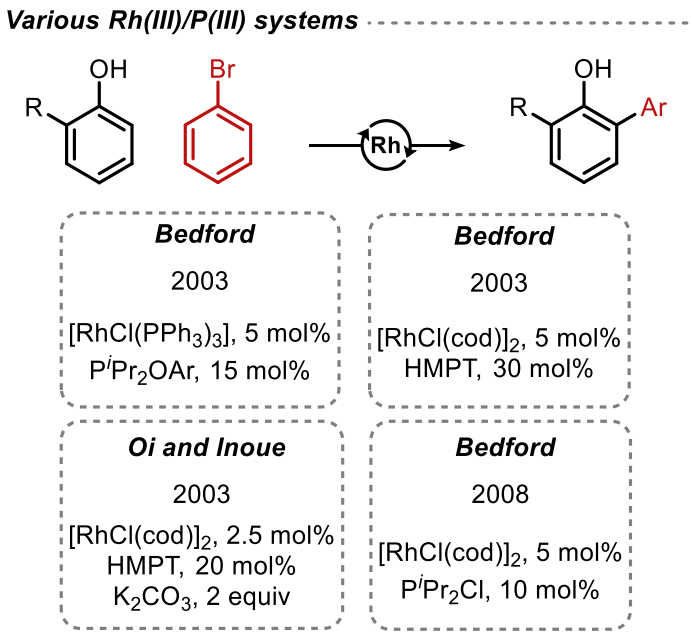
Bedford proposes that the catalytic cycle begins with reversible transesterification of the phenol with the phosphinite. This ligand can bind to the rhodium centre following oxidative addition of an aryl halide. The resulting Rh(III) phosphinite species can then undergo the key *ortho*-rhodation step, before reductive elimination affords the *ortho*-arylated aryl dialkyl phosphinite ligand. The alternative possibility, where *ortho*-metalation occurs at the Rh(I) centre prior to oxidative addition, is also proposed. Catalytic transesterification with the starting phenol regenerates the co catalyst while liberating the *ortho*-arylated phenol. This procedure is compatible with electron-rich and electron-poor aryl halides, however, a small amount of secondary arylation is observed with bromobenzene. This occurs where the OH of the product can direct *ortho*-

functionalisation of the newly installed arene, providing the terphenyl product shown in Scheme 44.



Scheme 44: Secondary arylation pathway for the Rh-catalysed *ortho*-C-H arylation of phenols.

While this methodology represents the first catalytic *ortho*-C-H functionalisation of phenols, it suffers from issues associated with the ligand and overarylation. The aryl dialkyl phosphinite co-catalysts must incorporate the same phenolic component as the starting phenol substrate; this is for ease of product identification and purification. This means each synthesis of a desired *ortho*-arylated phenol *via* this methodology requires synthesis of each aryl phosphinite ligand. In addition, this methodology requires one of the *ortho*-positions to be functionalised, limiting the generality of this route.



Scheme 45: Rh-Catalyzed intermolecular *ortho*-arylation of phenols with aryl halides.

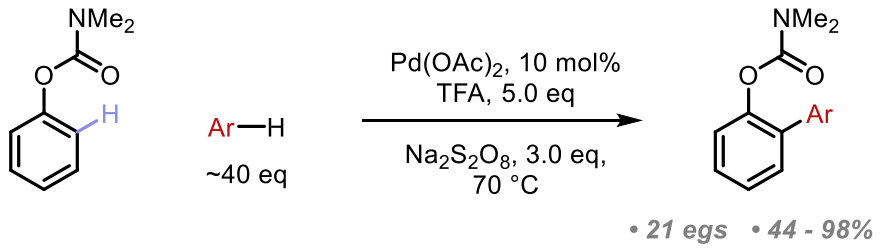
In efforts to develop the 2008 route, Bedford and Oi independently developed a more practical methodology using HMPT (Scheme 45)[83,85] HMPT is commercially available and enables the *in situ* generation of the corresponding aryloxy phosphorus ligand. Similarly, Bedford sought an alternative protocol in which a commercially available chlorophosphine cocatlalyst is employed rather than HMPT; this also enables the *in-situ* generation of the corresponding aryloxy phosphorus ligand.

Alternatively, the direct *ortho*-arylation of O-phenyl carbamates was reported by Dong in 2010.[86] Rather than an *ortho*-metalation – oxidative reduction – reductive elimination pathway, such as those disclosed previously, Dong envisioned an alternative series of steps: an *ortho*-metalation, a second C-H functionalisation *via* electrophilic metalation, and subsequent reductive elimination (Scheme 46).

Fundamentally, this methodology is able to achieve *ortho*-arylation by treatment of the O-phenyl carbamate with TFA and sodium persulfate; in this instance aryl source is the benzene/dichlorobenzene solvent, and the system operates under Pd(0)/Pd(II) catalysis.

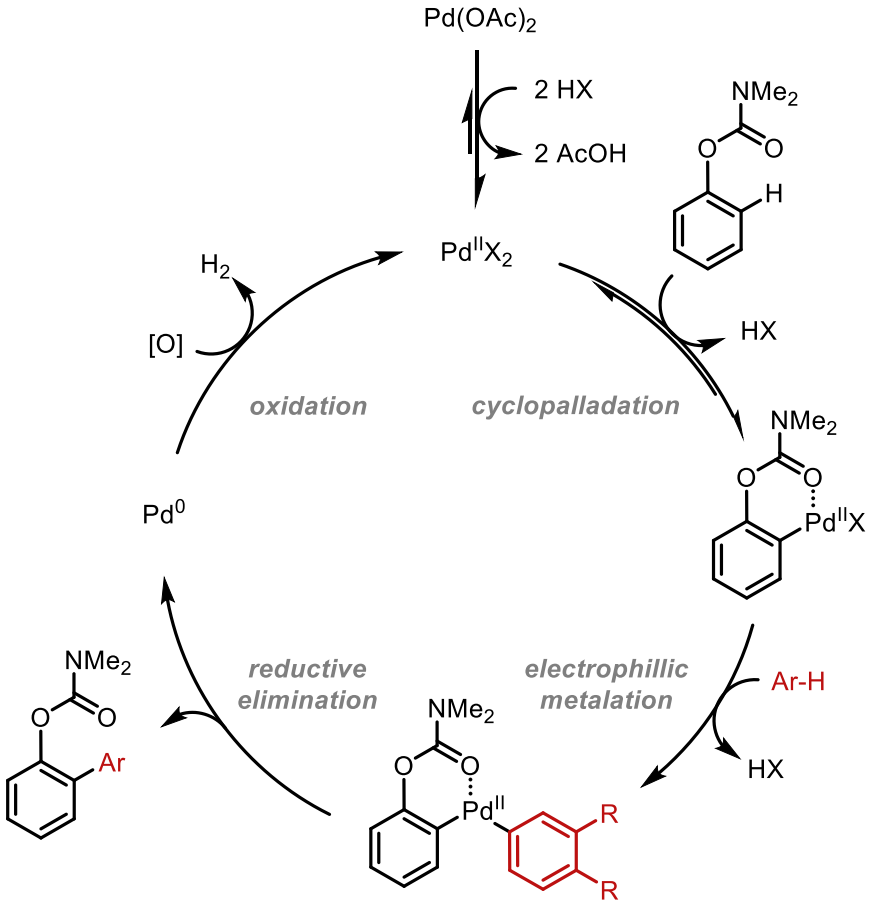
Mechanistically, the author proposes this transformation occurs as follows: (i) O-carbamate directed *ortho*-C-H palladation; (ii) aryl-C-H palladation *via* electrophilic metalation; (iii) reductive elimination, and; (iv) reoxidation of Pd(0) to the active Pd(II) with sodium persulfate. It was found that TFA was critical in achieving high reaction efficiency; this is thought to be because the TFA facilitates electrophilic metalation by increasing the electrophilicity of the Pd(II) centre.

Dong; 2010



• 21 egs • 44 - 98%

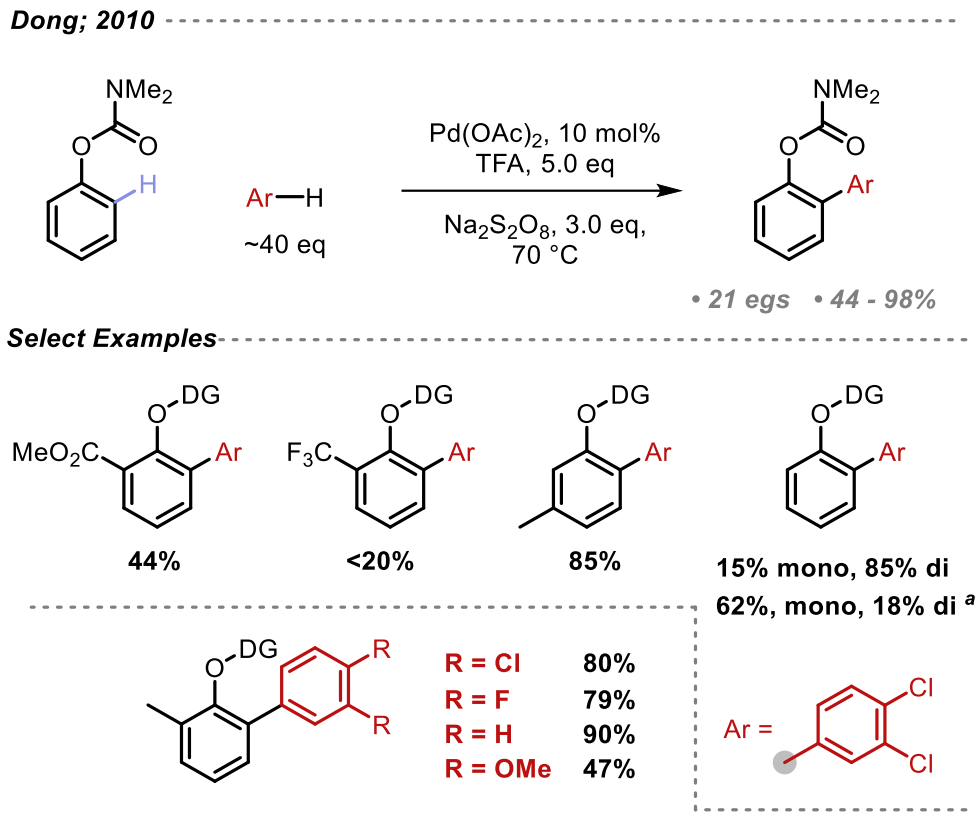
Proposed Mechansim



Scheme 46: The direct *ortho*-arylation of O-phenyl carbamates by V. M. Dong.

This protocol tolerates protected *ortho*- and/or *meta*-substituted phenols of various electronic profiles, affording good to excellent yields (Scheme 47). With respect to the arene counterpart; arylation is high yielding when this is electron-poor. For example, *o*-dichlorobenzene and *o*-difluorobenzene outperform benzene, which outperforms *o*-dimethoxybenzene. This is consistent with the second C-H activation step occurring *via* an electrophilic metalation. Among these *o*-disubstituted arenes, exclusive functionalisation is observed at the 4-position. Furthermore, over arylation is tuneable with by varying the equivalents

of the terminal oxidant; for the simple carbamate protected phenol, halving the equivalents of sodium persulfate affords a 1:0.29 ratio of mono arylation to di-arylation. (*c.f.* 1:5.67).

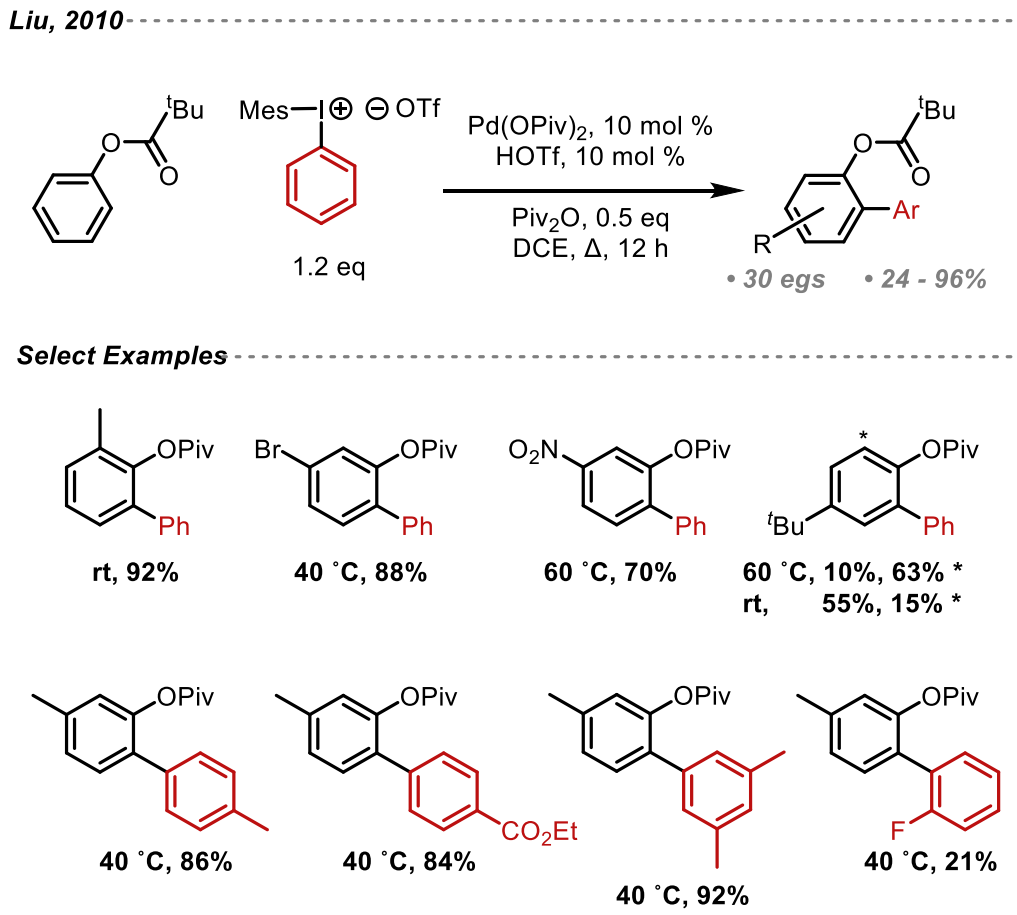


Scheme 47: Substrate scope for the direct *ortho*-arylation of O-phenyl carbamates (a) 1.5 eq. $Na_2S_2O_8$

This methodology advances on Bedford's work on several counts. Crucially, it can avoid over arylation and expands the scope to non-*ortho*-substituted starting phenols. It also employs C-H activation of a simple arene, removing the consumption of valuable aryl halides or boronic acids. Conversely, the lack of arenes beyond the *o*-dihalobenzenes is a clear limitation of this protocol, preventing it from becoming a general procedure for the synthesis of *ortho*-arylated phenols.

Phenolic ester directing groups are also able to direct *ortho*-metalation under a Pd(II)/Pd(IV) catalysis system, as disclosed by Liu.[87] In this protocol, a phenyl pivalate is subject to Pd(OPiv)2, catalytic triflic acid, acetic anhydride, and an excess of diaryl iodonium salt as the aryl source (Scheme 48). This transformation is proposed to proceed *via* initial *ortho*-C-H activation to form the palladacycle, oxidation with the aryl iodonium salt, followed by reduction elimination to the

ortho-arylated phenol. The author reports that the presence of triflic acid is essential for the formation of a stable palladacycle; it is proposed that the triflic acid is able to tune the electrophilicity of the Pd(II) centre.



Scheme 48: Liu's direct *ortho*-arylation of phenolic pivalates.

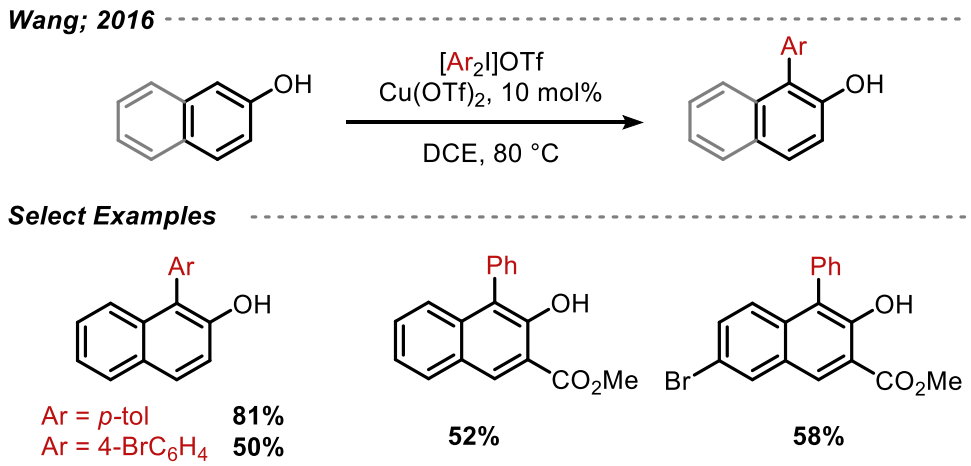
The reaction conditions tolerate phenyl pivalates carrying various substituents. *Ortho*-and *meta*-substituted phenyl pivalates arylate in good to excellent yields; in the case of the single *para*-substituted example (*para-tert*-butyl), over arylation becomes competitive. This is controlled by lowering the reaction temperature – the ratio of mono to di arylation is increased from 1:6.3 to 1:0.25 by reducing the temperature from 60 ˚C to rt. The scope of the reaction with respect to the arylating agent shows tolerance to both electron-poor and electron-rich-substituents. However, *ortho*-substituents suffer from reduced coupling yields, possibly due to increased steric hinderance about the Pd(II)-Pd(IV) oxidation step.

This protocol includes the same key advances that Dong reports, compared to Bedford's earlier work; mono *vs* di arylation is tuneable and the scope is not limited to *ortho*-substituted substrates. In addition, there is a wider scope of arylating agents available, and there is no need for a large excess of arylating agent (*c.f.* Dong).

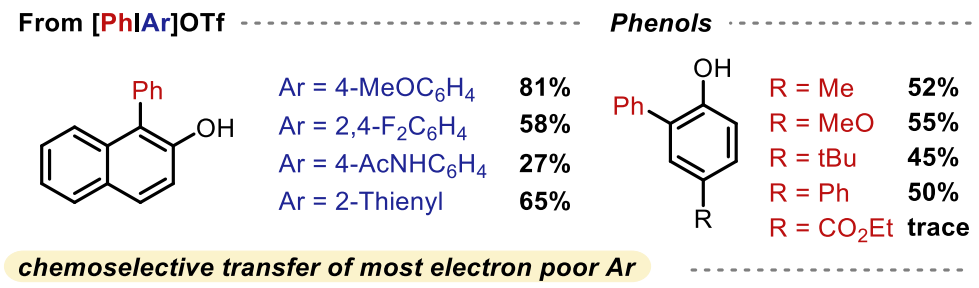
Toward a general synthesis of *ortho*-arylated phenols, the methodologies described in this section are typically marred by either the waste associated with using large directing groups, which later need to be cleaved to provide the free phenol, or risk of over-arylation in substrates that are not *ortho*-substituted. The subsequent section of this chapter will explore alternative methods that research groups have explored in order to circumvent these flaws.

via Non-Directed Methods

In 2016, L. Wang presented a copper-catalysed *ortho*-arylation of 2-naphthols and phenols with diaryliodonium salts (Scheme 50).[88] Given that diaryliodonium salts are electrophilic arylating agents, selectivity is governed by the electronics of the starting naphthol or phenol. Gaunt had previously exploited these electronics in realising a regioselective *para*-C-H functionalisation of phenols with diaryliodonium triflates.[89] Based on the same strategy, Wang demonstrated that *ortho*-arylation takes place exclusively if the *para*- position is blocked. Similar use of diaryliodonium salts under copper catalysis is described later in this thesis (see Chapter IV, Section 4.1) in the *meta*-selective arylation of anilides.[90]



Scheme 49: Wang's copper-catalysed *ortho*-arylation of 2-naphthols and phenols with diaryliodonium salts.



Scheme 50: Wang's substrate scope

Halides and alkyl groups on the arylating agent are tolerated in this methodology, however strongly electron-rich or electron-poor groups are not. It is also clear that, as with the other methods previously described, steric bulk hampers reactivity (*e.g.* mesityl). Unsymmetrical [PhIAr]OTf coupling partners selectively transfer the phenyl group over mesityl, 2,4-difluorophenyl, 4-acetaminophenyl, and 2-thienyl groups. The observed chemoselectivity of aryl transfer to the naphthol is consistent with the electronically controlled transfer of the more electron-deficient aryl group.[91] Treatment of the diphenyl iodonium tosylate with various 2-naphthols and phenols of various electronics gives very moderate yields.

This methodology showcases the regiocontrol which accompanies electrophilic arylations. By virtue of this, the starting phenol must be *para*-substituted to prevent the formation of regioisomeric mixtures. In addition, the diaryliodonium salt needs to be prepared over a number of steps for each aryl group we want to transfer.

A recent communication by Li reports the blue light mediated *ortho*-C-H arylation of non-protected phenols with aryl bromides, as shown in Scheme 51.[92] Inspired by a previous report on photoinduced C-X / C-S cross coupling *via* EDA complexation,[93,94] Li considered whether aryl halides could do the same with phenolates. By treating 4-bromoacetophenone and phenol with Cs_2CO_3 and blue LEDs, Li reported that the reaction did not form C–O cross coupling products; instead, they produced 2-arylated phenols.

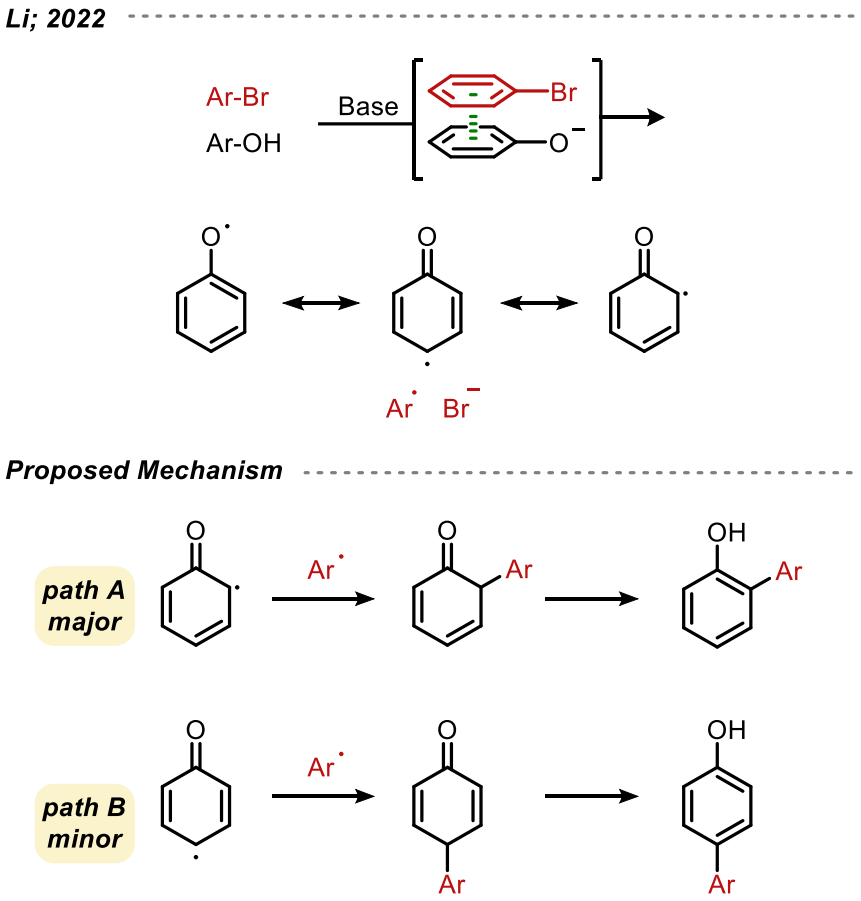
Li; 2022



Scheme 51: Li's blue light mediated *ortho*-C-H arylation of non-protected phenols with aryl bromides.

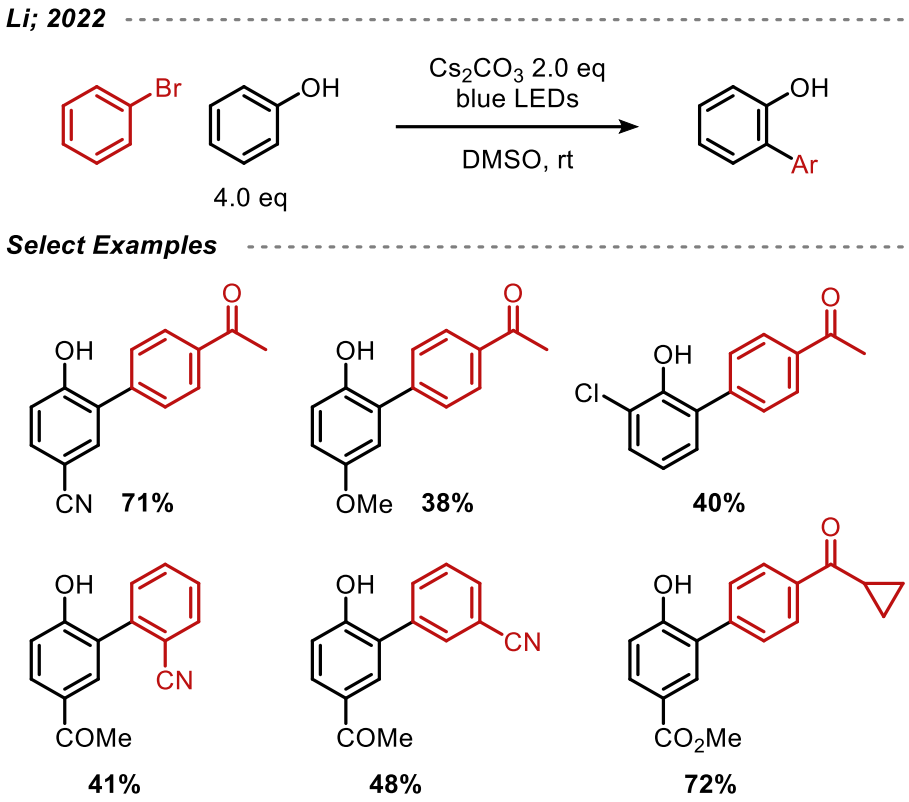
To test the possibility of EDA complexation, the reaction was probed such that a titration of the 4-bromoacetophenone against the phenolate was carried out using ^{1}H NMR spectroscopy. The ^{1}H NMR signals of the 4-bromoacetophenone gradually shifted, giving upfield peaks that were proportional to the amount of phenolate. Additionally, a solution of 4-bromobenzaldehyde had almost no absorption in the visible light region, however, addition into a solution of phenolate caused a dramatic colour change from colourless to yellow. The author concludes that these findings validate the hypothesis of EDA complexation between the aryl bromide and phenolate. Given that the coupling was also found to be sensitive to O_2 and no reactivity was observed when 2 equivalents of TEMPO was added; the author proposes a radical pathway of arylation shown in Scheme 52.

It is proposed that once the EDA complex forms, single electron transfer from the phenolate to the aryl bromide occurs, forming a phenoxyl radical and an aryl radical. The phenoxy radical can resonate between two species, where the radical is localised on the *ortho*- or *para*-position. These can couple with the aryl radicals, resulting in *ortho*-arylation (path A) or *para*-arylation respectively (path B).



Scheme 52: Li's proposed radical pathways of phenol arylation.

With respect to the substrate scope, this method generally shows good functional group compatibility. Among a series of *para*-substituted phenols, electron-withdrawing groups are better tolerated than electron-donating groups. (Scheme 53). The *ortho*-arylation of *ortho*-substituted phenols gives moderate yields, possibly because *para*-arylation is viable. Aryl bromides show good functional group tolerance, with good yields accessible from various steric profiles.

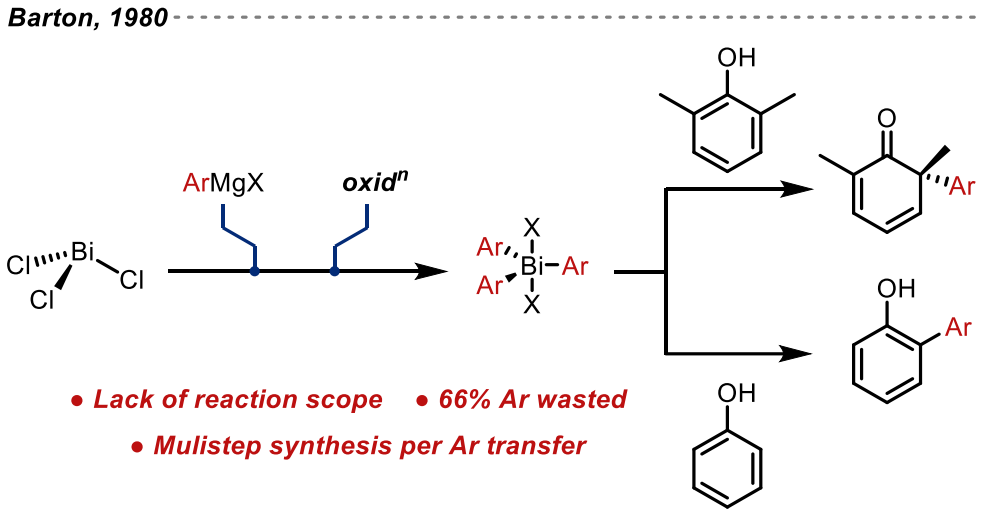


Scheme 53: Scope of Li's methodology.

Li's work showcases a rare example of *ortho*-selective phenol arylation without the use of metal catalysts. Unfortunately, as this route likely proceeds *via* a phenoxy radical, *para*-arylation is competent with *ortho*-arylation. Consequently, this methodology suffers with limitations on the scope. There are also no examples with exposed *ortho*- and *para*-positions; possibly as over arylation would become problematic. Provided the requirement of EDA complexation, the aryl bromide must have the capacity to accept electron density from the phenolate. This draws further limitations on the scope such that the aryl bromide must be electron-poor.

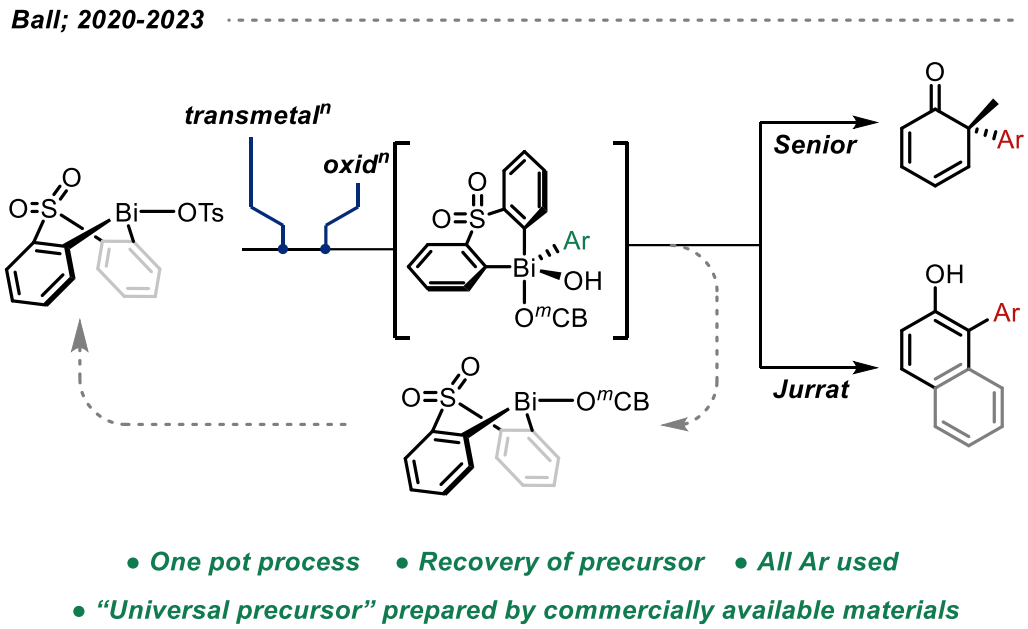
Bi(V) Mediated Phenol Arylation

Chapter I introduced the developments Ball made on the Bi(V)-mediated oxidative dearomatisation of phenols since Barton's seminal work in the 1980s. Barton's discovery of cyclohexadienone synthesis came about following his study of the Bi(V)-mediated *ortho*-arylation of phenols. Indeed, both these methodologies display the same drawbacks discussed previously, and is recapped for clarity in Scheme 54.



Scheme 54: Barton's Bi(V) mediated oxidation of phenol.

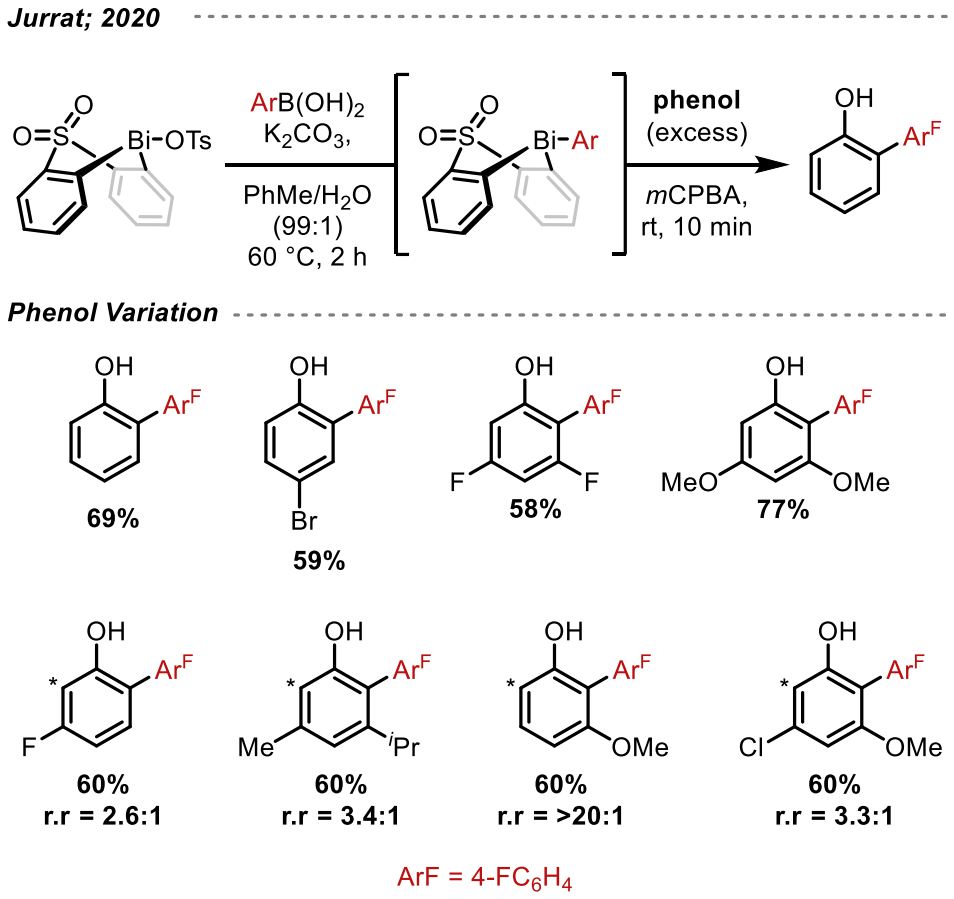
Much like the improved and general protocol Ball and Senior realised for the Bi(V) mediated synthesis of cyclohexadienones, Ball and Jurrat developed a refined protocol for the synthesis of *ortho*-arylated naphthols and phenols (Scheme 55). In this procedure, the arylating agent takes the form of an aryl-Bi(V) intermediate, generated *in situ* upon the oxidation of an aryl Bi(III) species. This aryl-Bi(III) species is prepared from what is known as the bismacycle tosylate, a 'universal precursor', by transmetalation with a boronic acid. This is the exact same protocol used in the phenol dearomatisation by Senior, and is displayed for clarity in Scheme 55 Jurrat's protocol was able to produce a wide scope of *ortho*-arylated naphthols.



Scheme 55: Ball's developments on Bi(V) mediated phenol oxidation.

For phenols, diarylation is still problematic. This can be supressed using a large excess of substrate; this excess remains unreacted and can often be recovered in excellent yields. The scope of phenols extends from electron-rich to moderately electron-poor, as shown in Scheme 56. Unsymmetrical phenols react to give regioisomeric mixtures; Ball and Jurrat explored the factors that govern this regioselectivity by biasing the stereoelectronic profile of the starting phenol.

For the arylation of 3-fluorophenol—where the 2- and 6- positions are electronically different but sterically similar, a moderate selectivity (2.6:1) is observed for the more electron-rich 6-position. This regioselectivity was not appreciably improved by varying the reaction temperature or the electronic profile of the aryl moiety being transferred. Where the 2- and 6-positions are sterically different but electronically similar, moderate regioselectivity is observed again. This is exemplified for the arylation of 3-isopropyl-5-methylphenol (3.4:1). This preference for arylation at the most electron-rich site and least sterically encumbered is consistent throughout the scope of unsymmetrical phenols.



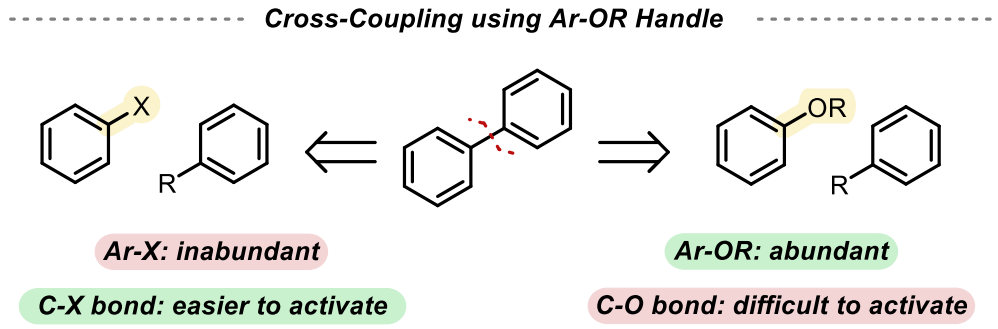
Scheme 56: Ball and Jurrat's Bi(V) mediated *ortho*-arylation of phenols.

Relative to Barton's work, the developments of Ball and Senior's methodology are also seen in Ball and Jurrat's developments of the Bi(V)-mediated arylation of phenol. 'Ar transfer' is maximised to 100%, the 'universal precursor' can be recycled, the reagents are bench stable and accessible from commercially available materials. While the generality of unsymmetrical phenols is limited, this protocol demonstrates an atom economic method for the preparation of *ortho*-arylated phenols and naphthols in the wider context of *ortho*-C-H functionalisation.

Literature coverage thus far showcases the limitations associated with the inherent reactivity of the starting phenol. Almost all the discussed methods suffer from either regioselectivity problems or over arylation. This next section is not a route towards *ortho*-arylated phenols, however it aims to expose the reader to one of the only available methods of using aryl methyl ethers as coupling partners. This is introductory to the next section, which discusses Bi(V) mediated dearomatisation of 2-methoxyphenols for the synthesis of 2-arylphenols.

C-OR Bond Activation

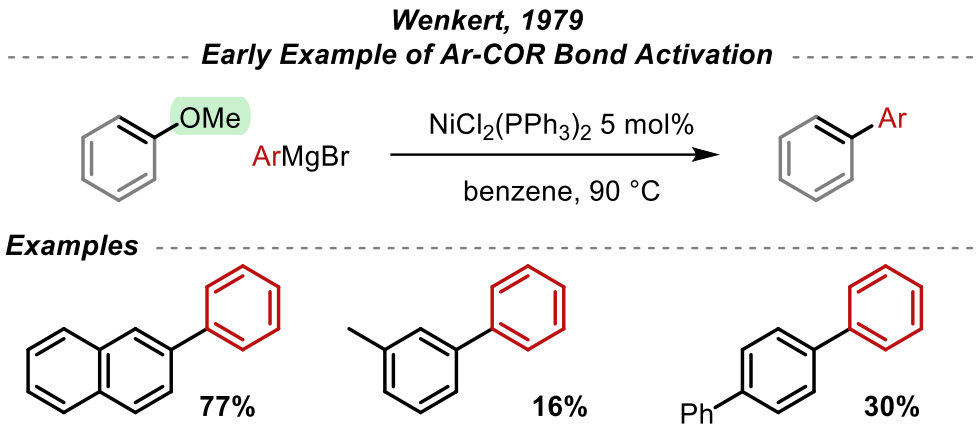
Biaryl synthesis has been revolutionised by metal catalysed cross coupling strategies. These methods have become so integral among reaction design that chemists anticipate catalytic C(sp^2)-C(sp^2) bond-forming reactions to include an aryl halide as one of the partners. There are still certain drawbacks associated with their use in synthesis, including the inherent formation of halogenated waste, and crucially, the modest accessibility of densely functionalised aryl halides.



Scheme 57: Comparison of aryl ethers and aryl halides as cross coupling partners.

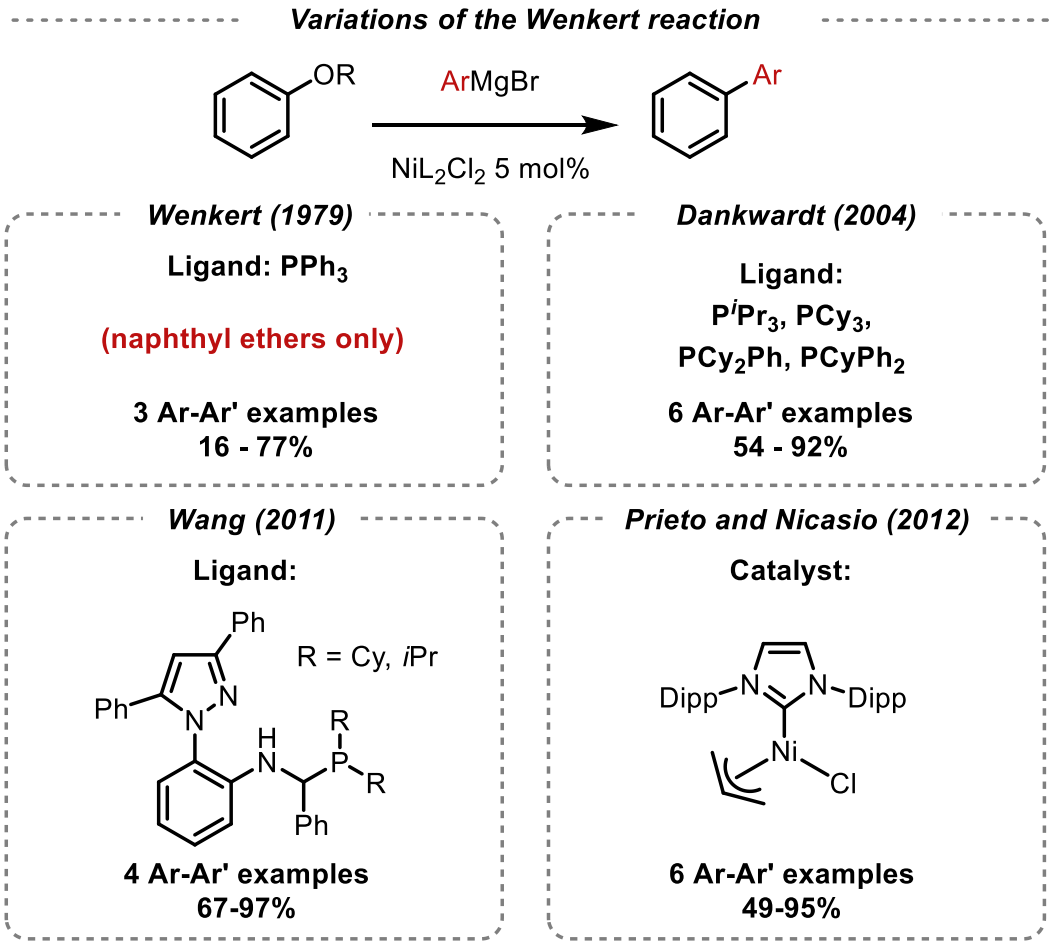
The use of aryl ethers in place of aryl halides (Scheme 57) would hypothetically address these two limitations of cross coupling; there would be an absence of halogenated waste, and phenol derivatives have far greater availability.[95] In addition, there would be the possibility for orthogonal approaches in the presence of aryl halides. In reality, the activation energy for effecting this C-OR bond cleavage is higher than that of the C-halide. This is likely due to the greater bond strength,[96] therefore displaying a reluctance to engage in oxidative addition. [96–98]

Method development based on the unique reactivity of low-valent nickel in the otherwise unreactive C-OR bond has emerged in the last decade. [99–101] These methodologies build upon a pioneering study by Wenkert, who demonstrated that aryl or vinyl methyl ethers could be coupled with aryl Grignard reagents in Ni-catalysed Kumada-Tamao-Corriu reactions (Scheme 58).[102]



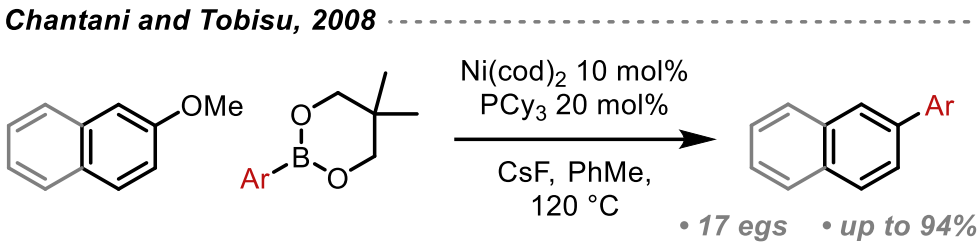
Scheme 58: Wenkert's Ni-catalysed coupling of aryl methyl ethers with aryl Grignard reagents. [102]

The scope of these reactions included the coupling of methyl or phenyl magnesium bromide using commercially available $NiCl_2(PPh_3)_2$. This study found that aryl ethers afforded lower yields compared to naphthyl ethers or enol ethers. This limitation was addressed by Dankwardt in 2004, who employed an electron-rich phosphine ligand with a high cone angle and conducted the reactions in ethereal solvents (Scheme 59).[103]



Scheme 59: Variants of the Wenkert reaction: variation of ligands and nickel catalysts. [102–105]

The use of highly reactive Grignard reagents in this strategy inherently leads to poor chemoselectivity in the presence of sensitive functional groups. This limits the application and generality of these methodologies. To this end, Chatani and Tobisu designed a Nickel catalysed Suzuki coupling of aryl methyl ethers with neopentyl boronates (Scheme 6o). [106]



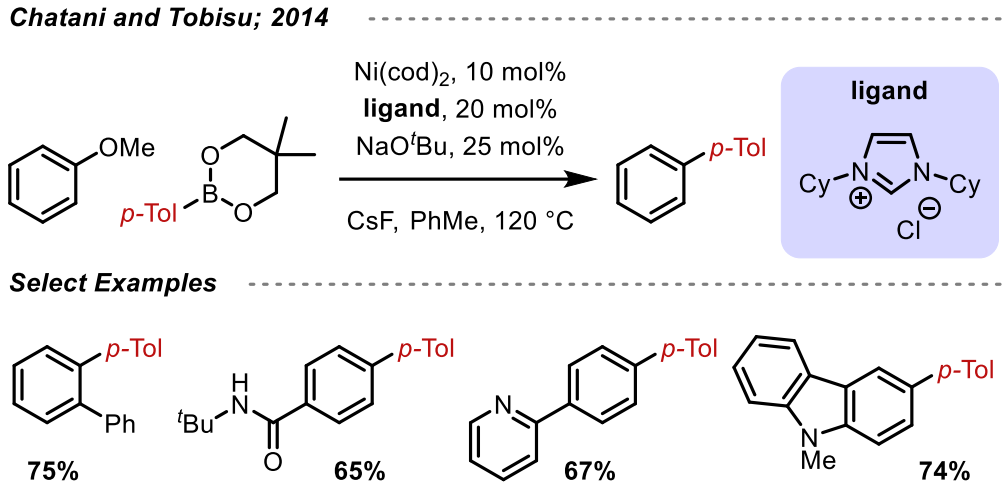
Scheme 6o: Chatani and Tobisu's nickel catalysed Suzuki-type coupling of aryl methyl ethers with neopentyl boronates.[106]

Their system exhibits higher functional group compatibility, however only two examples of phenyl methyl ether couplings are reported, and these give poor yields. The remainder of the scope was conducted on naphthyl methyl ethers.

We can see that a recurrent problem in this area of research is the considerably lower reactivity of anisoles compared to naphthalenes or π-extended substrates. This has been coined the naphthalene problem,[100,107] and it is not unique to the Wenkert reaction. In fact, it is apparent under all Nickel catalysed cross coupling reactions of less-reactive aromatic electrophiles.[108–112] While this chapter is focused on the utility of the Wenkert reaction for $C(sp^2)$- $C(sp^2)$ bond formation, methods which couple nucleophiles including hydrosiloxanes [113] and amines [114] have been developed; it has become apparent that the naphthalene problem is highly dependent on the nature of the nucleophile. We have seen that ligand modifications have overcome this limitation when the nucleophile is an aryl Grignard; however, synthetically useful reagents for aromatic coupling partners are limited.

Toward this limitation, Chatani and Tobisu proposed that a possible solution may be the generation of a more electron-rich nickel species through tuning the nature of the ligands. This was postulated to facilitate the oxidative addition of the C-O bond. NHC ligands are successful in their ability to facilitate aryl ether coupling reactions with amines[114] and, the reductive cleavage of aryl ethers with

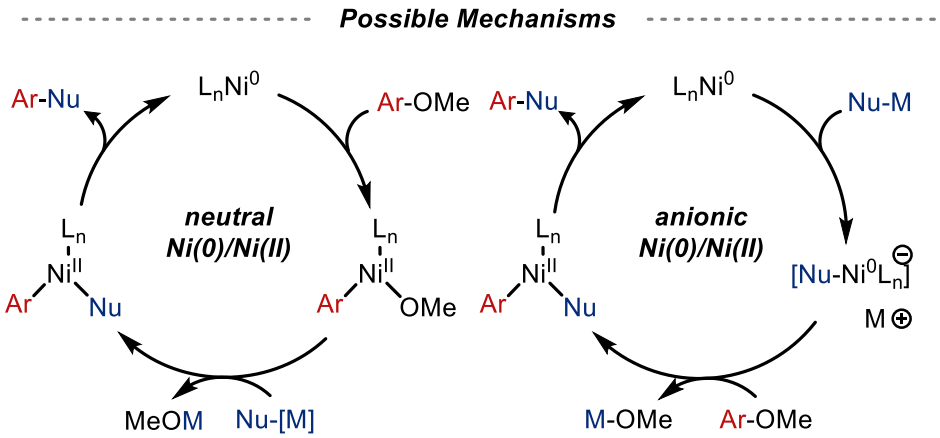
H_2.[115] As such, Chatani and Tobisu explored their utility with organoboron reagents (Scheme 61). [116]



Scheme 61: Chatani and Tobisu's Ni(0)/cyclohexyl-substituted NHC (ICy) ligand system for the coupling of aryl methyl ethers with organoboron reagents.

By employing a cyclohexyl-substituted NHC ligand (ICy), an expanded array of aryl ether substrates was accessible compared to that described previously (Scheme 60). Unfortunately, however, electron-rich anisoles do not react with the Ni-NHC system, posing a remaining challenge for further development of a universally active catalyst.

These reactions are thought to proceed *via* a pathway similar to the Kumada coupling, however, there is no experimental or theoretical evidence to support these mechanisms. A safe assumption may be that oxidative addition is turnover-limiting, given the strength of the C-O bond. What the Kumada type model shown in Scheme 62 does not account for is the poor scope of less reactive nucleophiles with aryl ethers. On this basis, a turnover-determining oxidative addition step is unlikely to be affected by the identity of the nucleophile.



Scheme 62: Possible operating catalytic cycles in Wenkert-type reactions.

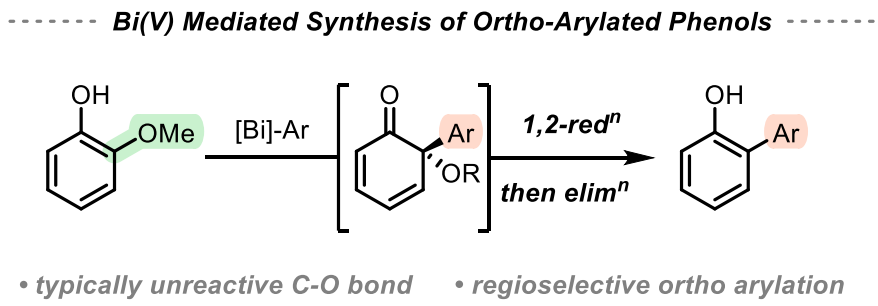
A possible scenario that can account for the wider substrate scope when using Grignard reagents is that the Lewis acidic magnesium centre can activate the C-O bond, facilitating its oxidative addition to the electron-rich nickel centre.[117,118] A contradictory report by Hartwig shows that addition of Lewis acids such as MgX_2, ZnX_2 *etc* in $Ni(cod)_2/PCy_3$ systems is unsuccessful.[115]

An alternative scenario may be the generation of an anionic nickelate species by the reaction of Ni(0) with ArMgX. This nickelate centre, now with increased electron density, may be competent in anisole activation. Nickelate generation has been experimentally proven in the case of Grignard nucleophiles, [119] however it is likely that this is not a competent pathway for organoboron reagents. This dependency of the substrate scope on the nature of nucleophile might be caused by the switch between neutral and anionic mechanisms.

2.2. Project Proposal

Thus far, the literature coverage in this thesis encompasses Bi(V)-mediated phenol arylation and Ni-catalysed C(sp^2)-C(sp^2) bond formation using Ar-OMe handles as coupling partners. These two areas of research have inspired the work which constitutes this chapter: the Bi(V) mediated alkoxylative arylation of guaiacol.

The synthesis of 2-aryl phenols *via* Bi(V)-mediated arylation is simple in its design. We propose that subjecting the aryl-cyclohexadienone, derived from *ortho*-arylation of guaiacol (*ipso* to OMe), to a 1,2-reduction, and subsequent elimination-rearomatisation step may enable a formal demethoxylative aromatisation (Scheme 63). Such transformations are scarce in the literature and are limited to those inspired by Wenkert's work as discussed.[100,102,106,114,116]



Scheme 63: Proposed oxidative arylation-Luche reduction of guaiacol to access *ortho*-arylated phenols.

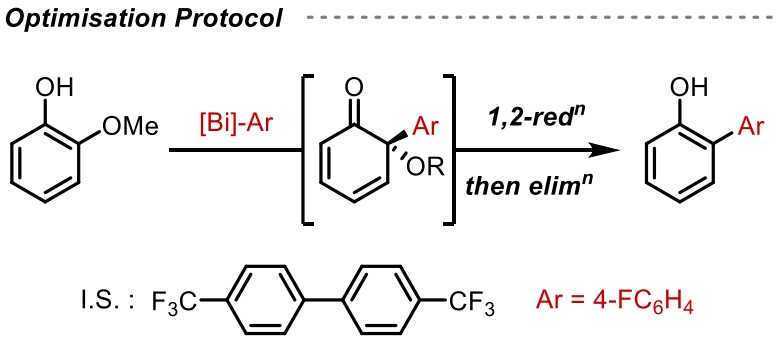
This strategy fulfils the criteria of using bioderived and accessible phenol starting materials to access a highly desirable scaffold, while functionalising a typically unreactive C-OR bond. It also provides an alternative to the shortcomings of those methodologies discussed:

- Over-arylation is reduced, as the cyclohexadienones products are inert to further oxidative arylation;
- arylation predominantly occurs *ipso* to *ortho*-substituents in mono *ortho*-substituted phenols because electronic factors dominate selectivity, and
- the use of directing groups and large ligands is avoided, maximising atom economy.

This section will begin by reporting the compatibility of 2-methoxy phenol (guaiacol) with the oxidative arylation conditions realised by Senior and Ball. This will be followed by the development of a telescoped procedure in *ortho*-arylated phenol synthesis, and subsequent assessment of substrate compatibility.

2.3. Optimisation

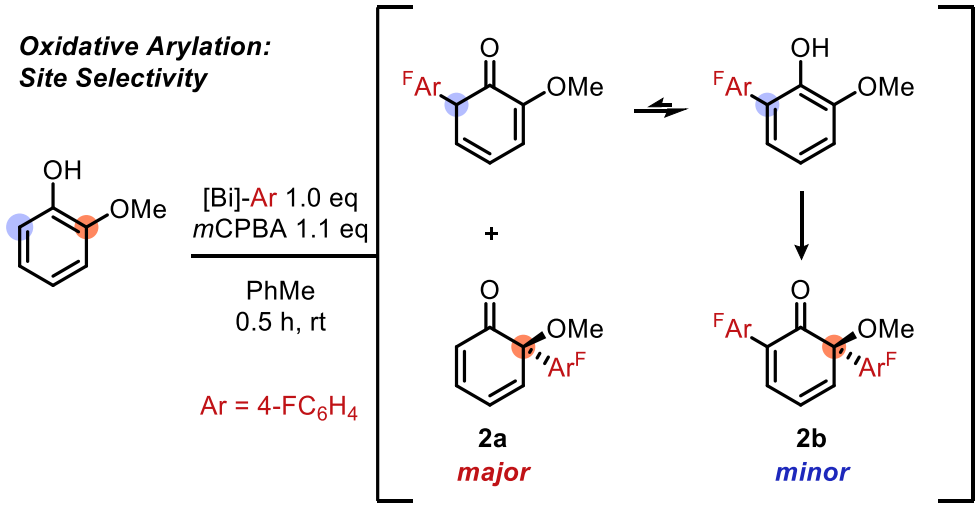
Optimisation was performed on the oxidative arylation to access cyclohexadienone intermediates, and the 1,2-reduction to access the ortho-arylated phenols. These reactions were performed using an aryl bismacycle bearing a fluorine atom on the para-position. This allows for accurate *in situ* calculation of yields by quantitative ^{19}F NMR spectroscopy, without significantly changing the electronic profile of the substrate. Yields are calculated against an internal standard, 4,4'-bis(trifluoromethyl)-1,1'-biphenyl. To ensure the accuracy of this process, the relaxation delay (D_1) was set to 30 seconds to allow for complete spin relaxation.



Scheme 64: Optimisation outline using 4,4'-bis(trifluoromethyl)-1,1'-biphenyl as an internal standard

Oxidative Arylation

Symmetrically di-*ortho*-substituted phenols present only one site for arylation using Bi(V) reagents and – following the first arylation - are inert to further arylation. This is not the case for mono *ortho*-substituted phenols, which can undergo C2 arylation to form the phenol, or C6 arylation to the cyclohexadienone. By reacting guaiacol with 1 equivalent of aryl bismacycle (**1**) and excess oxidant, 50% of the desired cyclohexadienone (**2a**), and 8% of the diarylated cyclohexadienone (**2b**) is observed (Table 1). The initial product of C-2 arylation can rearomatize to the corresponding phenol, which is a candidate for a second arylation. The second arylation event occurs *ipso* to the OMe group, affording the undesirable 2,6-diaryl cyclohexadienone.

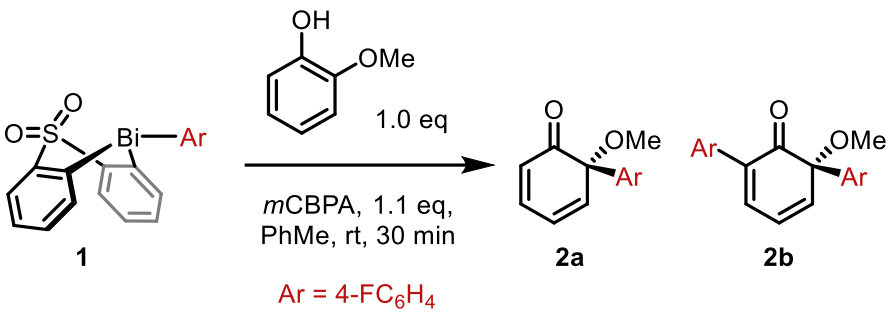


Scheme 65: Pathway of mono *vs* diarylation.

In attempts to access higher yields of cyclohexadienone, it was thought the reaction may be sensitive to the operating concentration. In the dearomatisation methodology developed by Senior,[33] the transmetalation-oxidative arylation steps were telescoped into a one pot process. Practically, this meant the volume of solvent may vary from reaction to reaction, and the concentration was not thought to be crucial to reactivity. Initially, the dearomatisation of guaiacols were maintained at 0.2 M. An experimental observation during these oxidations is that the *m*CPBA must be added slowly to obtain higher yields of cyclohexadienone. It was noted that in cases where *m*CPBA was added too quickly, less cyclohexadienone is formed. To investigate this, it was thought larger volumes of solvent, and hence lower concentrations of guaiacol and *m*CPBA, would mimic slow addition. Pleasingly, the concentration screen highlighted that the reaction works optimally when the reaction mixture is more dilute (Table 1).

The reaction at 0.4 M affords only 50% **2a** and 5% unreacted guaiacol (entry 1). Oxidation at high concentrations is associated with mass intensity loss, as observed in the ^{19}F NMR spectrum; no definitive conclusion for this has been drawn. Conversely, halving the concentration to 0.2 M affects a 15% increase in cyclohexadienone (entry 2). Given that there is a 5% increase in yield upon a 10-fold increase in dilution, 0.04 M was selected as the optimal reaction concentration among those investigated.

Oxidative Arylation: Variation of Concentration

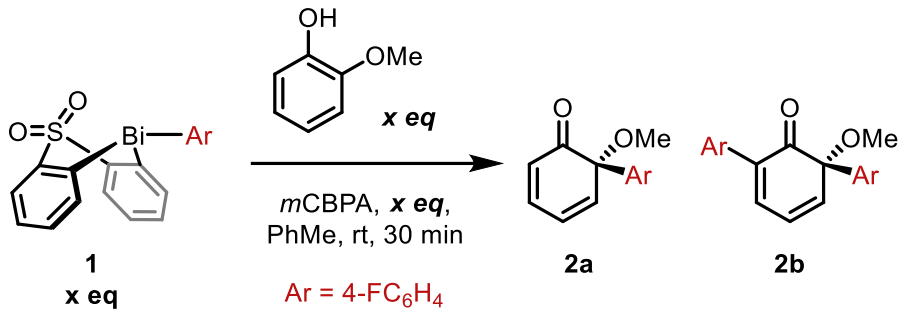


entry	$[1]_0$ /M	% 2a	% 2b	2a : 2b
1	0.4	50	8	6.3
2	0.2	65	14	4.6
3	0.04	68	10	6.8
4	**0.02**	**77**	**13**	**5.9**

Table 1: Effect of varying concentration of arylative dearomatisation. Yields determined *via* quantitative ^{19}F NMR spectroscopy.

It was thought that the relative stoichiometry of the aryl bismacycle with respect to guaiacol may also mimic the effect of slow addition of oxidant. However, using 1.5 equivalents of aryl bismacycle relative to guaiacol and *vice versa* affords comparable results to that of equimolar conditions (Table 2).

Oxidative Arylation: Variation of Stoichiometry



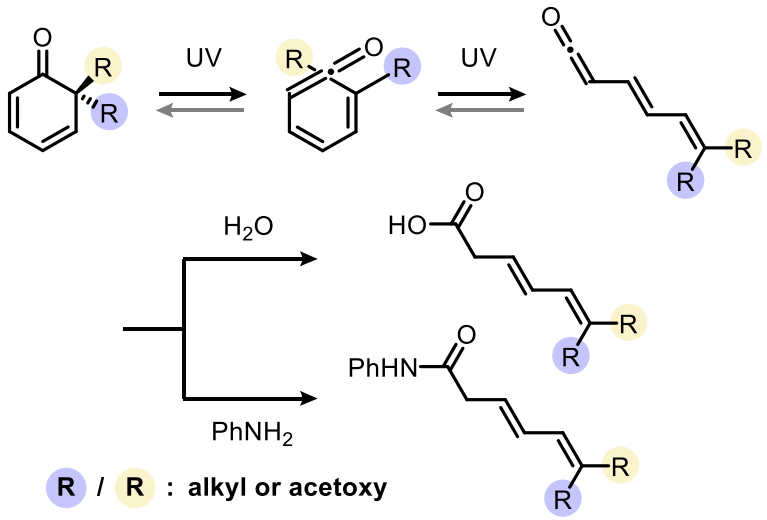
entry	equiv. 1	equiv. guaiacol	equiv. *m*CPBA	% 2a	% 2b	2a : 2b
1	1	1	1.1	77	13	5.9
2	1.5	1	1.65	75	10	7.5
3	1	1.5	1.1	75	10	7.5

Table 2: Effect of varying equivalents of **1** and guaiacol on the arylative dearomatisation. Yields determined via quantitative ^{19}F NMR spectroscopy.

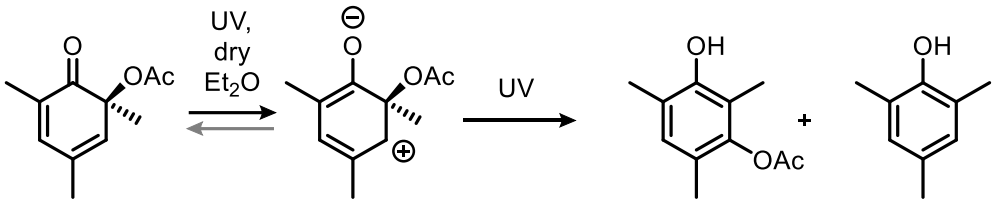
As reviewed in Chapter 1, it is apparent that cyclohexadienones dimerise spontaneously. Thus far, no evidence of dimerization was found by ^{1}H NMR spectroscopy or HRMS. Alternatively, the possibility of photoisomerization was considered. During his work on Bi(V) chemistry and phenol dearomatisation, Barton reported the conversion of cyclohexadienones to acyclic acids and amides.[37] This rapid interconversion was achieved *via* photoisomerization to a reactive ketene intermediate, followed by trapping with an oxygen or nitrogen nucleophile.

In dry ethereal solvents, *i.e.* where no nucleophile is present, Barton reported the rearomatized phenol accompanied by migration of the acetoxy group. This likely occurs *via* charge localisation on the oxygen and C-3 in the S_1 state followed by migration of the acetoxy group. An alternative photoisomerization is the formation of bicyclo[3.1.0]hexenones. Throughout the literature on the decomposition of cyclohexadienones, it appears as though the formation of products (particularly between open chain acids *versus* bicycloketones) is highly dependent on the substituents on the starting substrate. [37,38,120–124]

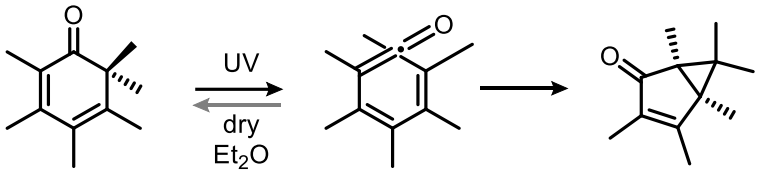
Barton, 1959: photoisomerisation to ketene:



Barton, 1959: photo-induced rearomatisation



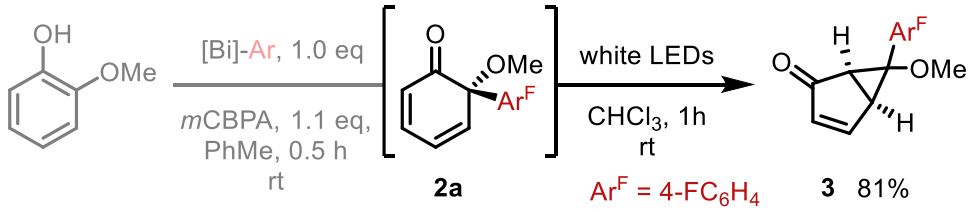
Hart, 1965: photoisomerisation to bicycloketone:



Scheme 66: Photodecomposition of cyclohexadienones.

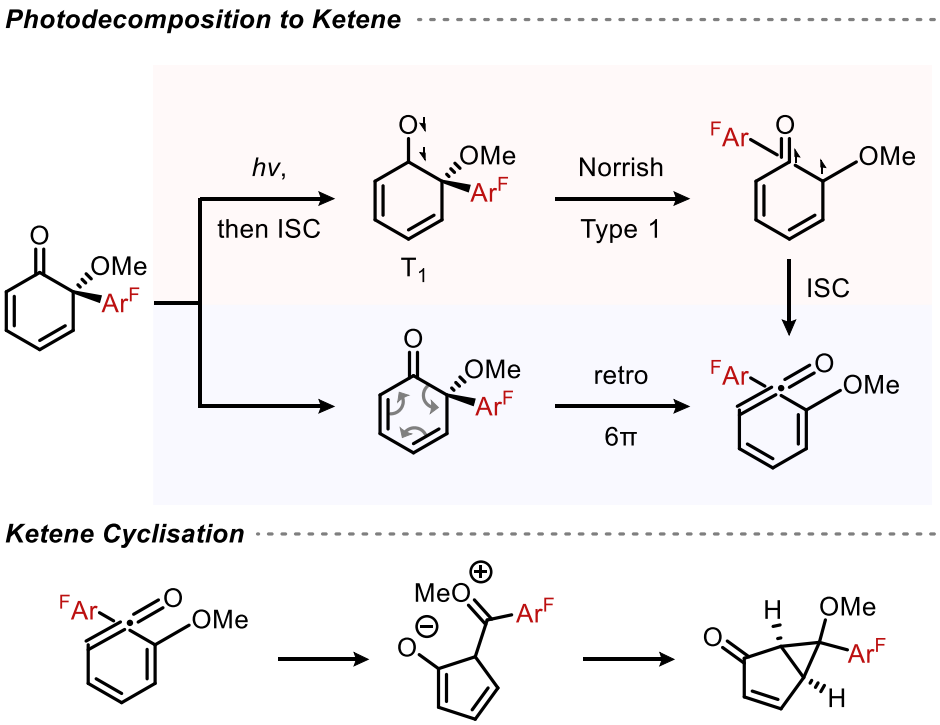
By irradiating a crude sample of cyclohexadienone **2a** with white LEDs for 1 h, we observe complete consumption of starting material and 81% of photorearrangement product **3** (Scheme 67).

Cyclohexadienone Photoisomerisation



Scheme 67: Photodecomposition of **2a**. Yield determined by ^{19}F NMR spectroscopy.

The bicyclo[3.1.0]hexenone **3** was confirmed by 2D NMR spectroscopy, however, the relative stereochemistry could not be determined unambiguously. It is possible that the LEDs facilitate this *via* a two-electron mechanism (*i.e.* retro 6π) or a radical mechanism (*i.e. via* Norrish Type 1 pathway; Scheme 68). Once it was realised that this was a possible decomposition pathway of the cyclohexadienone, amberised flasks were employed in their synthesis and manipulation. Pleasingly, the yields for the arylation were reproducible with the reaction carried out under these conditions.

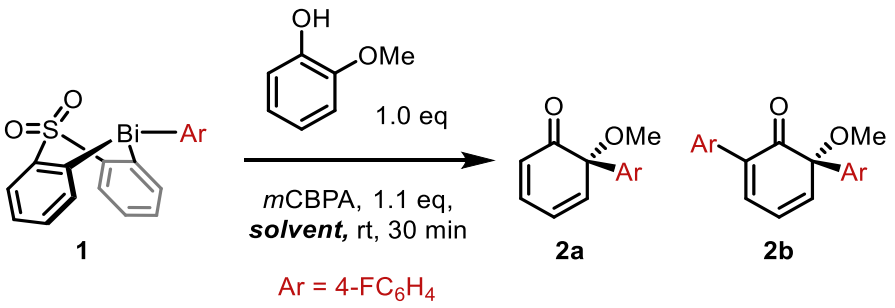


Scheme 68: Possible mechanisms of cyclohexadienone photodecomposition *via* a reactive ketene.

It is possible that the use of non amberised flasks has a marginal impact on the results reported for optimisation thus far. However, provided that the reaction arylation is fast, high yielding and highly selective, it was decided that the conditions in hand would remain, and no repeats of previous optimisation would be taken.

The final factor investigated was the effect of solvent on the reaction and selectivity. The selected solvents were chosen to represent various classes (*i.e.*, polar aprotic, ethereal, apolar, aromatic); alcohol solvents were omitted from this screen as they may react under the oxidising conditions.

Oxidative Arylation: Variation of Solvent



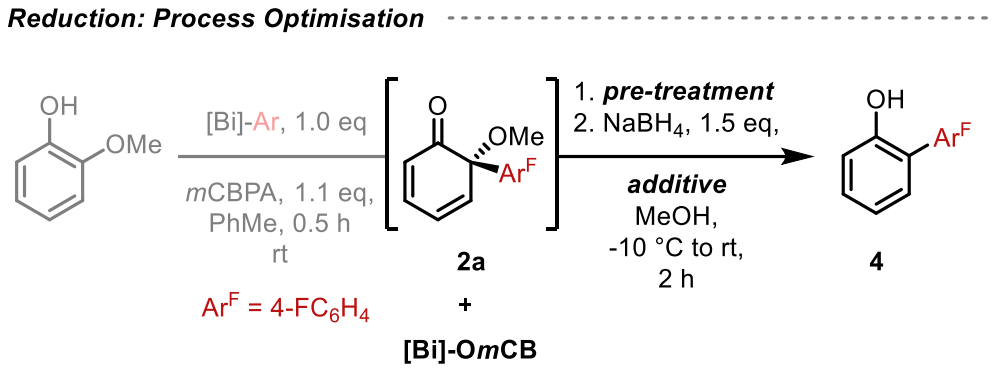
entry	solvent	% 2a	% 2b	2a : 2b
1	**PhMe**	**77**	**13**	**5.9**
2	THF	68	10	6.8
3	EtOAc	63	10	6.3
4	$PhCF_3$	59	10	5.9
5	DMF	50	8	6.3

Table 3: Effect of varying solvent on the arylative dearomatisation. Yields determined by ^{19}F NMR spectroscopy.

Polar aprotic solvents such as EtOAc and DMF appear to be deleterious to the oxidation, affording 63% and 50% respectively. The reaction works, albeit less efficiently, in ethereal solvents such as THF (entry 2). Trifluorotoluene was chosen (entry 4) because, although aromatic, it has a very contrasting electronic profile. However, a low yield of 59% in trifluorotoluene. In all cases, the ratio of mono:diarylation appears to be insensitive to reaction solvent. With toluene as the best performing solvent, optimisation of the subsequent reduction step was initiated.

Optimisation: Reduction

Investigation of the reduction step was initiated by first concentrating the oxidative arylation reaction mixture, then subjecting it to reducing conditions. In the first instance, treatment of the intermediate cyclohexadienone to Luche conditions provided the desired phenol (**4**) in a 50% yield (Table 4; entry 1).



entry	pre-treatment	additive (eq.)	$NaBH_4$ (eq.)	% 4
1	solvent swap	$CeCl_3 \cdot H_2O$ (1.0)	1.0	20-50
2	basic alumina, then solvent swap	None	1.0	<5
3	**basic alumina, then solvent swap**	**$CeCl_3 \cdot H_2O$ (1.5)**	**1.5**	**>99**
4	basic alumina, then solvent swap	$CeCl_3 \cdot H_2O$ (1.5) **Bi-O*m*CB** (1.0)	1.5	<5

Table 4: Conditions for 1,2-reducton of **2a**. Yields determined by ^{19}F NMR spectroscopy.

Under these conditions, complete consumption of cyclohexadienone is observed and a second peak at δ_F -115.2 ppm appears in a 20% yield. It is possible that this species is the cyclohexadienol (*i.e.* reduced cyclohexadienone, but not

rearomatized), however repeat experiments to confirm this were met with inconsistent results.

The possibility that co-products of the oxidative arylation were competent substrates for reduction was considered. Theoretically, the main co-product of the oxidative arylation is the bismacycle *meta*-chlorobenzoate. The reduction was carried out with a semi-pure sample of cyclohexadienone. This was obtained by purification *via* column chromatography; however, photodecomposition is fast and consequently leads to difficult isolation of pure material. Crucially, this sample contained no bismacycle benzoate – the hypothesised poison. Pleasingly, subjecting this sample to Luche conditions furnished the desired phenol in a quantitative yield.

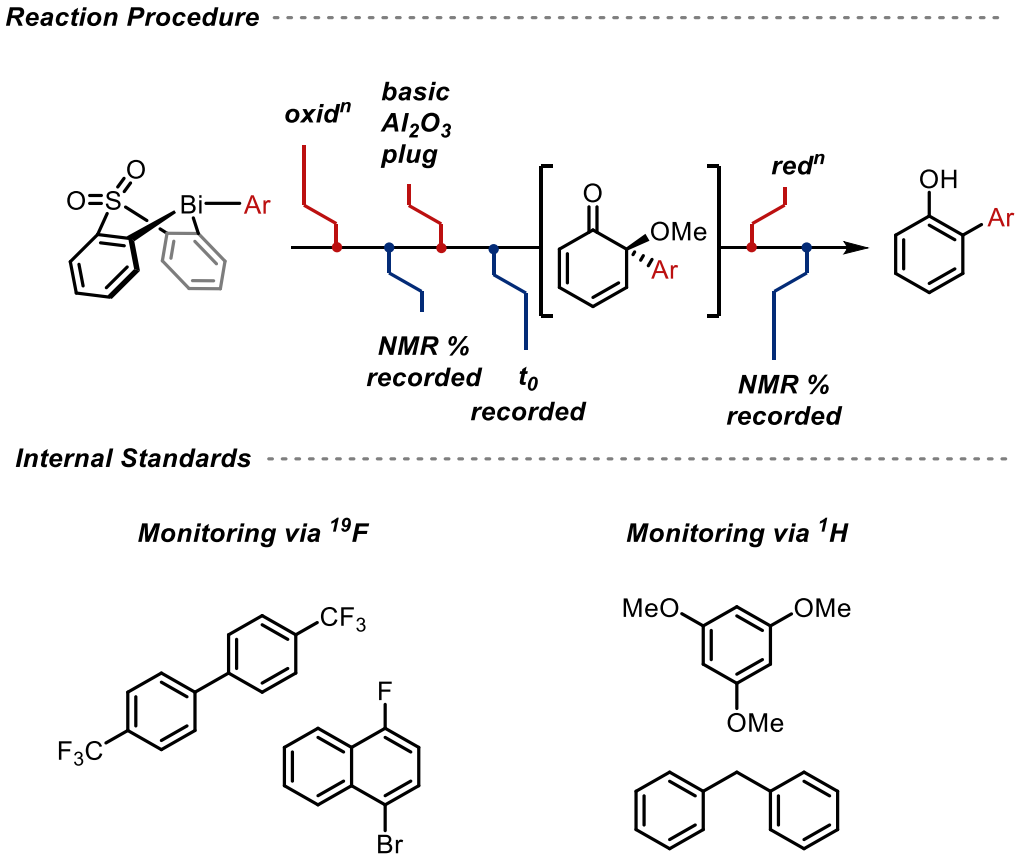
To streamline the cyclohexadienone reduction, the removal of bismacycle benzoate could be achieved by passing the crude material (after oxidative arylation) though a plug of basified alumina. This provides a simple substitute to column chromatography. By employing this short purification step prior to the reduction, quantitative conversion is observed (Table 4; entry 3).

To confirm the hypothesis that the bismacycle benzoate poisons reactivity in the 1,2-reduction step, 1 equivalent of authentic sample was subject to the reaction conditions prior to the addition of reductant. In this instance, 5% of the desired phenol is observed, confirming the theory that the presence of the bismacycle benzoate is deleterious to reactivity (Table 4; entry 4).

Before assessment of the substrate scope, the requirement of cerium chloride in the reduction step was tested. Hypothetically, the sodium borohydride has two sites for reduction (*i.e.* 1,2- or 1,4-). It is possible for the product of 1,4-reduction to rearomatize to the phenol, in which case, the requirement for Luche conditions would not be necessary. Repetition of the optimal conditions (Table 4; entry 2) without cerium chloride shows this is not the case, as a complex mixture of products is observed. As such, the remainder of this project explores the compatibility of these reaction conditions to various starting phenols and aryl bismacycles.

2.4. Substrate Scope

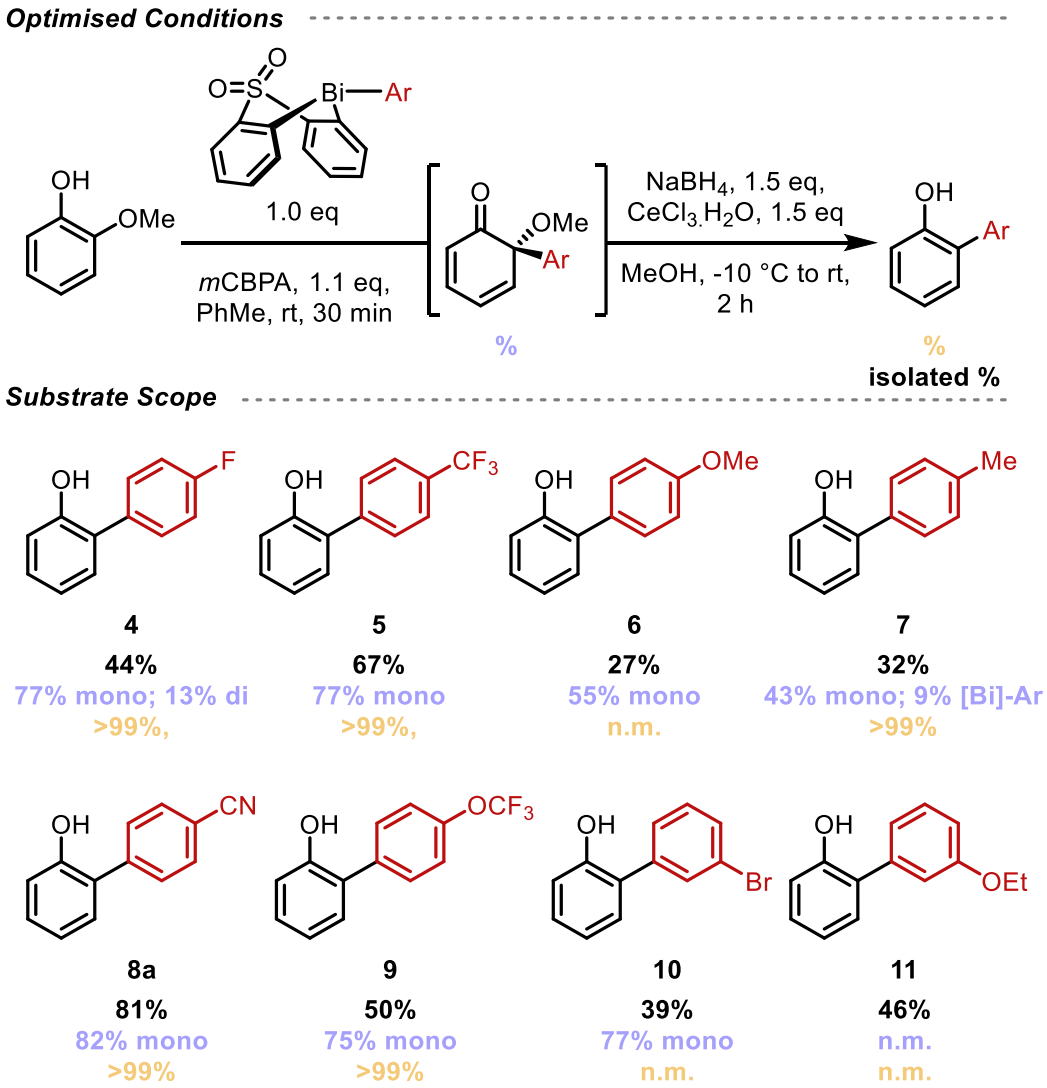
A comprehensive investigation of substrate scope was designed to explore the compatibility of this transformation with sterically and electronically diverse functional groups. This was achieved by altering the arene, originating from the aryl bismacycle, and altering the guaiacol core. The oxidation and reduction were monitored using ^{1}H or ^{19}F NMR spectroscopy in the presence of an internal standard to assess substrate compatibility with respect to each step. An aliquot was taken after the arylation to record the yield for the oxidative arylation, and an aliquot was taken after the basified alumina plug to record the initial concentration of cyclohexadienone being employed in the subsequent reduction. At t = 2 h, the reaction was sampled to record the NMR yield of the reduction.



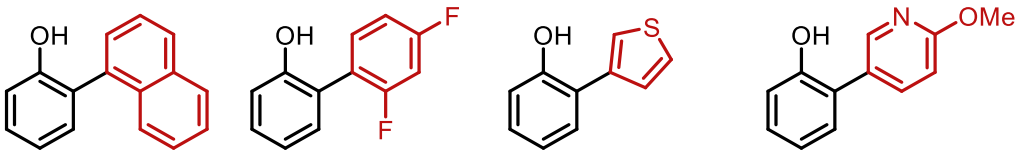
Scheme 69: Outline of reaction procedure to obtain NMR yields.

Variation of Aryl Bismacycle

Generally, the developed oxidation conditions exhibit good compatibility with both electron-rich and electron-poor aryl bismacycles, providing rapid access to a diverse array of aryl cyclohexadienones. It can be seen by comparing aryl bismacycle of contrasting electronic profiles that electron-poor (*i.e.*, *para*-cyano; **8a**) are much higher yielding than electron-rich (*i.e.*, *para*-methoxy; **6**). This can be rationalised by the reduced electrophilicity that electron-donating groups impart on the transient Bi(V) arylating agent.



Scheme 70: Scope of aryl bismacycles towards oxidative arylation-Luche reduction. NMR yield of arylation (blue); NMR yield of reduction (yellow); isolated yield over 2 steps (black). Yields determined by NMR spectroscopy vs internal standard.



12	**13**	**14**	**15**
11%	**n.d.**	**n.d.**	**24%**
38%	45%; 46% [Bi]-Ar	35%; 40% dimer	76%; 16% [Bi]-Ar
n.m.	n.m.	n.m.	n.m.

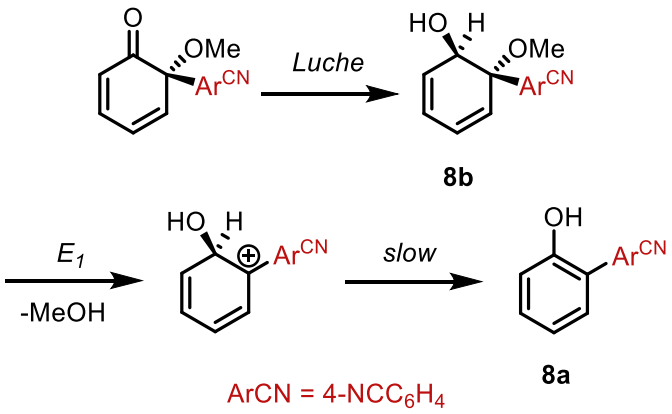
Scheme 71: Continued substrate scope

Pleasingly, halo-substituted aryl bismacycles are well tolerated (**10**), presenting compatibility with further diversification (*e.g.*, Pd-catalysed cross-coupling). Compounds **12** and **13** both expose the limitation towards *ortho*-substituents; this is likely due to the steric strain which accompanies the Bi(V) intermediate prior to reductive elimination. An experimental observation is that where yields of cyclohexadienone are <50%, particularly with an appreciable amount of unreacted aryl bismacycle, their isolation following the Luche reduction becomes increasingly difficult. It was observed that isolated yields often fall by 20% from that after the oxidative arylation. Consequently, **13**, was omitted from the reaction scope and was not subject to Luche reduction.

Attempts to expand this methodology to pyridyl bismacycles (**15**) is hindered due to the instability of the corresponding cyclohexadienone to basified alumina. This is a caveat that has been addressed in other projects demanding partial purification of oxidative arylation products bearing heterocycles (see Chapter III, Section 3.4). Thienyl bismacycles (**14**) are also not tolerated; the corresponding thienyl cyclohexadienone undergoes rapid dimerization *via* a Diels-Alder reaction. This is identified by ^{1}H NMR analysis of the post basified alumina plug reaction mixture. Cyclohexadienones without stabilising groups (*i.e.* acetoxy) are prone to [4+2] dimerization. (see Chapter 1). Why this cyclohexadienone in particular presents a propensity to dimerise is not fully understood.

All the intermediate aryl cyclohexadienones undergo a rapid and efficient reduction under Luche conditions. There is one incidence of the intermediate cyclohexadienol not rapidly rearomatisating to the desired phenol: upon quenching the reduction of the *para*-cyanophenyl cyclohexadienone at 2 h with 1 M HCl, **8b** is observed in a 44% NMR yield (Scheme 72) as a single diastereomer.

Dienol Rearomatisation

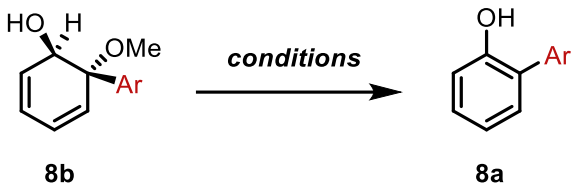


Scheme 72: Reduction to intermediate cyclohexadienol **8b**.

^{1}H-^{1}H nOe experiments reveal that the proton *ipso* to the OH is *syn*-to the methoxy group, suggesting that $NaBH_4$ delivers the hydride at the less hindered face of the carbonyl. This also reveals that the elimination of the methoxy, and subsequent rearomatisation, likely proceeds in an E_1 fashion. It is possible that the incipient positive charge *ipso* to the aryl group is destabilised by the *para*-cyano group, decelerating rearomatisation.

Treatment of the dienol **8b** with various acids and bases reveals that Lewis (Table 5; entry 2) and Brønsted acids (entry 3 and 4) facilitate rapid rearomatisation to the phenol **8a**. As such, the remainder of the scope was carried out employing a 4 M HCl quench upon completion of the Luche reduction.

Rearomatisation



entry	conditions	8a (%)
1	1 M HCl	44
2	$Bi(OTf)_3$	>99
3	Conc H_2SO_4	>99

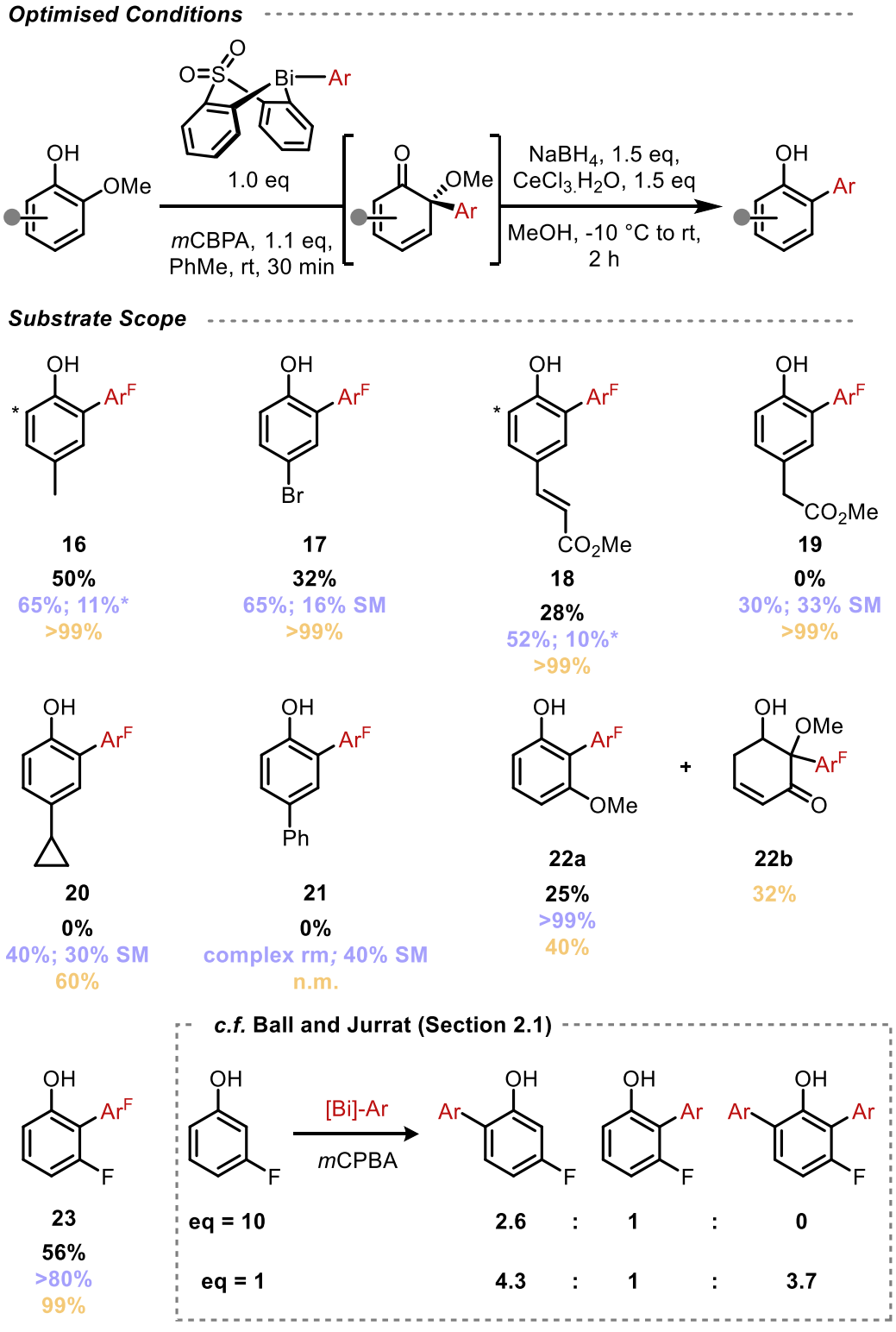
4	4 M HCl	>99
5	Et_3N	0

Table 5: Conditions to effect rearomatisation of cyclohexadienol **8b**. Yields determined *via* quantitative ^{1}H NMR spectroscopy.

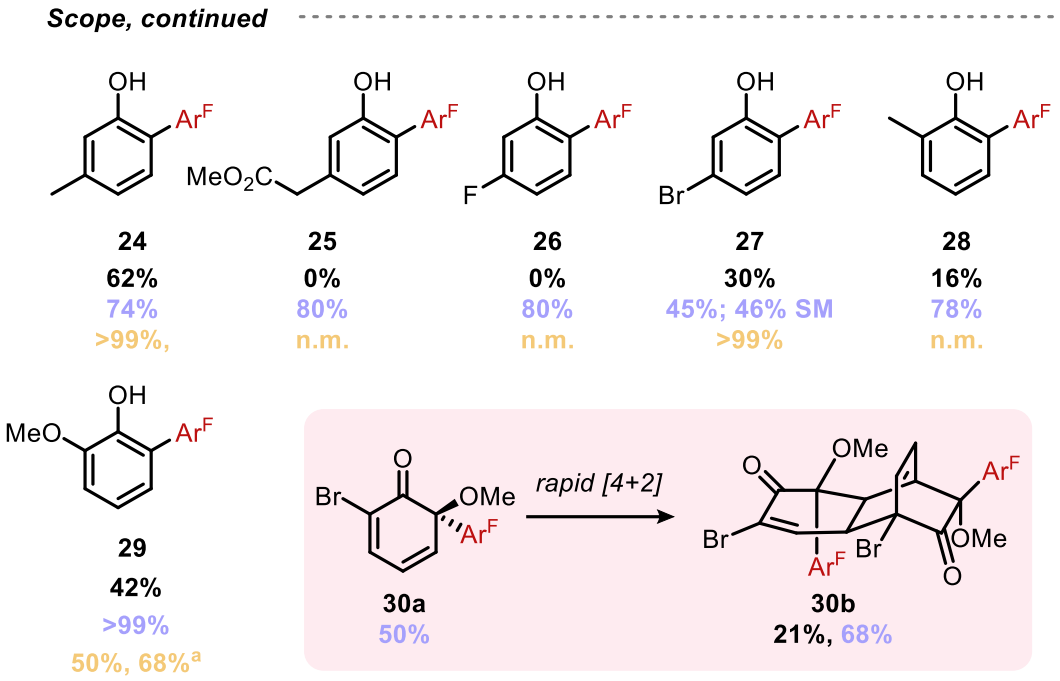
Variation of Guaiacol

The compatibility of substituted guaiacols with the developed demethoxylative arylation is more varied, presumably due to the unpredictable stability of the intermediate cyclohexadienone. Tolerance of 4-substituted guaiacols show a great dependence on the substituent. Small substituents, *i.e.* -Me (**16**), -Br (**17**) show comparable reactivity to the non-substituted guaiacol, although unreacted starting material is observed. Increasing π-character at this site leads to decreased yields; this trend is observed with 4-cyclopropyl guaiacol (**20**), 4-phenyl guaiacol (**21**) and methyl ferulate (**18**). In the instance of 4-phenyl guaiacol, arylation affords a complex mixture of products including unreacted aryl bismacycle. Examination with ^{19}F spectroscopy reveals peaks of equal intensity at 20% each. Two equally intense peaks can be diagnostic of (i) dimerization, or (ii) diarylation affording the 2,6-diaryl cyclohexadienone. Examination of the ^{1}H spectrum is used to confirm these possibilities. For example, two sets of 1:1 -OMe peaks can help validate dimerization (along with HRMS/ presence of sp^3 protons) whereas the integration of olefinic protons can evidence over arylation. In this instance, the ^{1}H spectrum displays 2 sets of 1:1 3H methoxy-like peaks, however there is no evidence of dimerization. Over-arylation is possible, however this does not explain the presence of multiple 3H protons.

Arylation of the 4-cyclopropyl guaiacol provides 40% of the desired cyclohexadienone, however the reduction is moderately yielding with unidentifiable side products. The remaining aryl bismacycle is consumed in the reduction step, which may be limiting the reductant available to the cyclohexadienone. Conversely, this is not observed in other reductions where aryl bismacycle is present.



Scheme 73: Scope of guaiacols towards oxidative arylation-Luche reduction. NMR yield of arylation (blue); NMR yield of reduction (yellow); isolated yield (black). Yields determined by NMR spectroscopy vs internal standard.



Scheme 74: Continuation of scope. NMR yield of arylation (blue); NMR yield of reduction (yellow); isolated yield (black). Yields determined by NMR spectroscopy vs internal standard. (a) 3.0 eq $NaBH_4$

Exploration of 3-substituted guaiacols affords exceptional yields of cyclohexadienone with selectivity. In the case of the 3-methoxy guaiacol, decreased yields are observed at the reduction step which can be attributed to the decreased electrophilicity at the carbonyl centre. Product **22b** is observed after the hydrolysis-reduction of the respective cyclohexadienone the structure of which was elucidated by 2D NMR spectroscopy.

Arylation of 3-fluoro guaiacol provides the cyclohexadienone in an excellent yield with good regioselectivity; a useful complement to the Bi(V) mediated C-H arylation of unsymmetrical phenols (see Section 2.1 of this Chapter). With equimolar amounts of phenol and aryl bismacycle, arylation of 3-fluoro phenol under the Juratt protocol affords the 2-aryl phenol, the 6-aryl phenol and the 2,6-diarylated phenol (4.3:1:3.7); Scheme 56. To outcompete diarylation, 10 equivalents of phenol are required. In contrast, the arylation of guaiacol gives preferential C-2 selectivity with no observable C-6 arylation or consequent diarylation.

5-Substituted guaiacols present good yields for both arylation and reduction. While **25** and **26** undergo high yielding arylations, the corresponding

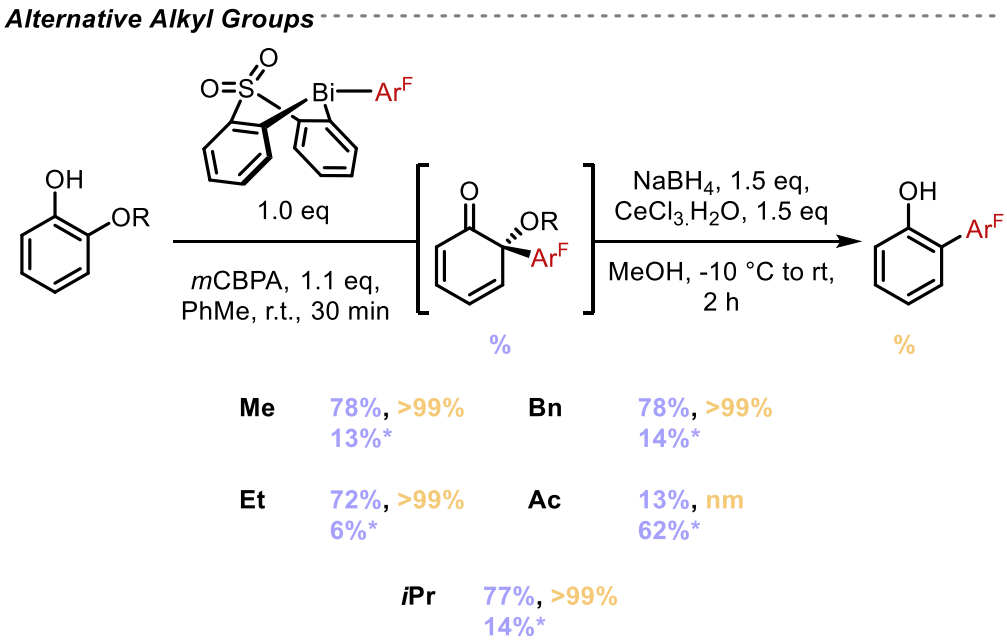
cyclohexadienones are not stable to the basified alumina plug. It is possible that the former is subject to addition-elimination during elution from the basified alumina, whereas the latter decomposes by virtue of its acidic proton.

Investigation of 6-substituted guaiacols presents a complication observed by many synthetic methodologies involving 2,4-cyclohexadienone intermediates – dimerization *via* a Diels Alder cycloaddition. By subjecting the 6-bromo guaiacol to the oxidative arylation, 50% of the corresponding cyclohexadienone **30a** is observed at 30 min. Within 1 h, there is complete consumption of **30a** and formation of dimeric **30b** (Scheme 74). The same is observed following the dearomatisation of 6-methyl guaiacol, however dimerization appears to be slower than that of the 6-bromide. These relative rates are consistent with the Houk-Halide effect, where halo-dienes are found to undergo rapid Diels-Alder reactions compared to their non-halogenated congeners.[125–127] As such, the yield for the resultant phenol (**28**) was recorded, albeit in a low yield.

In contrast, arylation of syringol affords quantitative conversion to the cyclohexadienone and no dimerization is observed. Unfortunately, yield of the reduction to **29** is marred by the decreased electrophilicity of the cyclohexadienone. A larger excess of reductant (3.0 eq) enables a more efficient reduction (68%); however, an isolated yield was not obtained from this variation.

Alternative 2-Alkoxy Groups and Lignans

Next, the compatibility of alkoxy groups alternative to -OMe was assessed (Scheme 75). In the case where the introduced arene is the *para*-fluorophenyl group, other electron-donating alkoxy substituents are well tolerated, affording comparable dearomatisation (and C-6 arylation/over-arylation) yields to that of guaiacol.

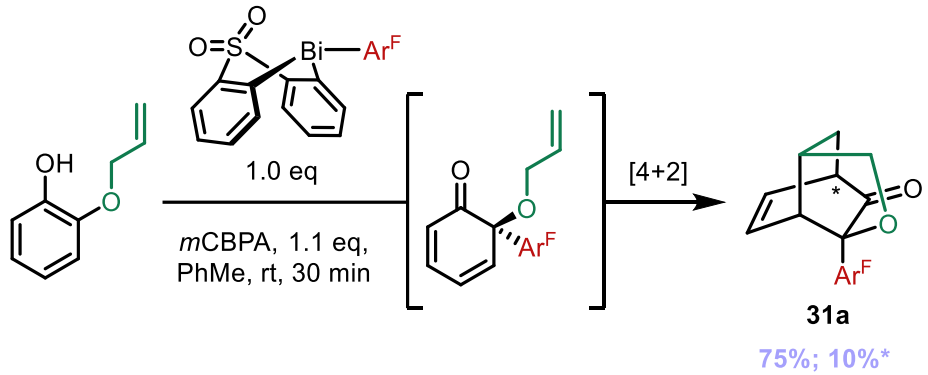


Scheme 75: Application of methodology to alternative 2-alkoxyl phenols. Yields determined *via* quantitative ^{19}F NMR spectroscopy against internal standard.

Treatment of 2-acetoxy phenol to the oxidative dearomatisation affords the diarylated cyclohexadienone as the major product. Initial C-6 arylation is predictable considering the electron-withdrawing nature of the acetoxy substituent. The second arylation event can occur *ipso* to the *para*-fluorophenyl group, or the acetoxy group. Interestingly, the latter is observed as evidenced by the ^{19}F two integrals of equal intensity. This suggests that inductive effects of the *ipso*-oxygen atom predominate over the electron-donating resonance effects of the arene. In all cases except the 2-acetoxy phenol, excellent yields are presented for the Luche reduction and subsequent elimination of alkoxy group.

Also investigated was the ability for the allyloxy group to eliminate. This reaction presents complete consumption of phenol, although no intermediate cyclohexadienone is observed. Instead, the product of an intramolecular Diels-Alder reaction is detected (**31a**). This serendipitous discovery is exploited in the synthesis diversified bicyclo[2.2.2]octenones which entitles Chapter III.

Serendipitous Discovery of Novel Bicyclo[2.2.2]octenone



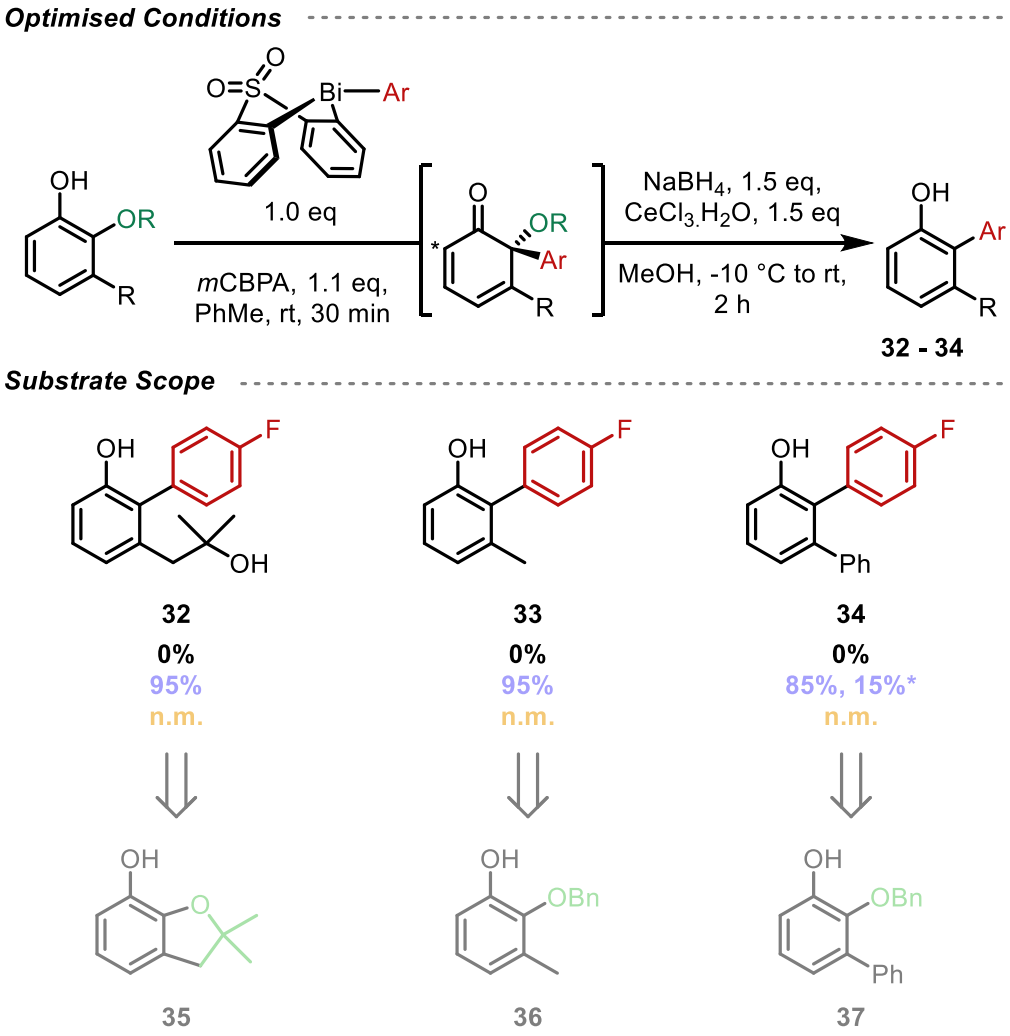
Scheme 76: Formation of bicyclo[2.2.2]octenone **31a** *via* intramolecular Diels-Alder reaction. NMR yield determined *via* quantitative ^{19}F NMR spectroscopy against internal standard 4,4' bis(trifluoromethyl)-1,1'-biphenyl.

Now understanding the compatibility of alternative 2-alkoxy phenols, expansion to a general dealkoxylative arylation protocol was attempted. The arylation-reduction sequence was conducted on compounds **35** to **36**, Scheme 77. This was to predict the broader compatibility of this protocol to complex lignin derivatives.

3-Substituted 2-benzyloxy phenols (**35-37**) were chosen to apply to the protocol. The substitution pattern was chosen as 3-substituted guaiacols performed well in assessment of guaiacol scope. The benzyloxy leaving group was chosen as this easily and appropriately models the functionality bound to the guaiacyl core in complex lignans. For **35-37,** excellent yields are presented for the arylation step, however the reduction does not yield an appreciable amount of phenol.

Dihydrobenzofuran example **35** presents a high-yielding arylation and was found to undergo rearomatisation in the presence of $Bi(OTf)_3$; 1 M HCl alone was not able to facilitate rearomatisation of the cyclohexadienol. Unfortunately, the use of a Lewis acid also appears to facilitate the formation of multiple side products, thus complicating the isolation of **32**. It is possible that the desired product of rearomatisation undergoes facile elimination, owing to the relatively high stability of the incipient tertiary carbocation. Further attempts at isolating this

compound were made, although it appears that decomposition is rapid thereby complicating isolation.

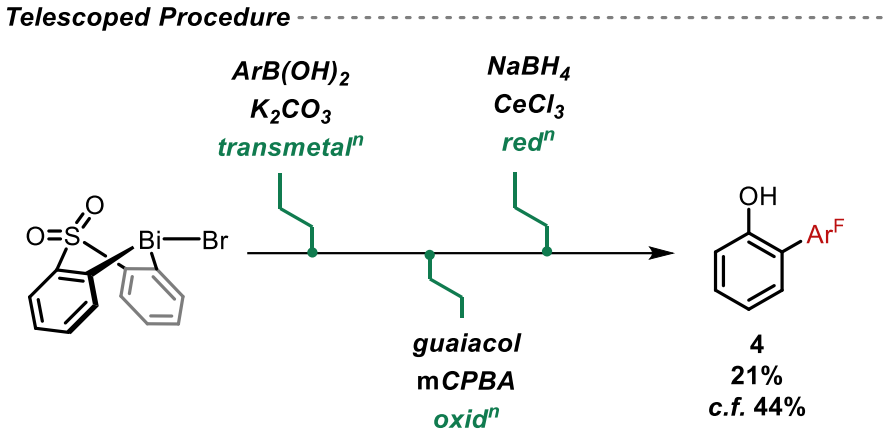


Scheme 77: Elimination of alternative alkoxyl groups. NMR yield of arylation (blue); NMR yield of reduction (yellow); isolated yield (black). Yields determined by NMR spectroscopy vs internal standard.

In the case of the 3-methyl phenol **36**, the corresponding cyclohexadienone is unreactive to $NaBH_4$. Treatment with 3.0 equivalents of reductant did not lead to any reactivity, nor did increase reaction temperatures or extended reaction times. Unfortunately, substitution of the borohydride for K-selectride presented an ill-defined reaction mixture. Similarly, treatment with DIBAL led to a poor yielding reduction-elimination with unidentifiable side products. The 3-phenyl phenol **37** presents a similar outcome. Despite a high yielding arylation, treatment of the intermediate cyclohexadienone affords a complex mixture of products. Alternative treatment with DIBAL does not improve this result.

Telescoped Arylation and Bismacycle Recovery

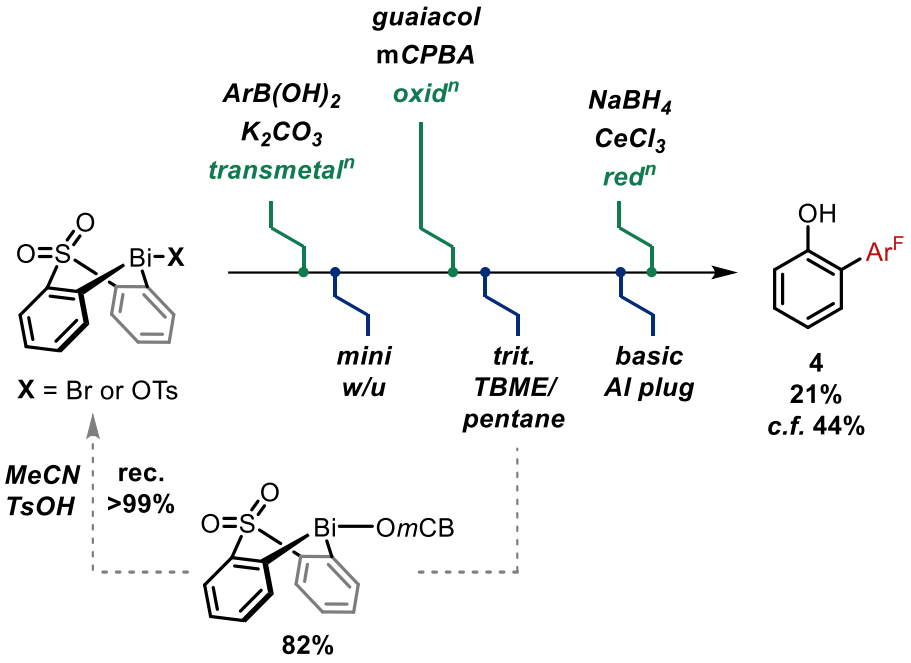
Efforts to include the transmetalation step (*i.e.* formation of the aryl bismacycle) in this telescoped arylative dealkoxylation procedure were made. Pleasingly, extraction of the organic liquor and treatment with guaiacol and oxidant affords NMR yield of cyclohexadienone comparable to that of the standard procedure. The isolated yield of the resultant phenol suffers a decreased yield of 21% (*c.f.* 44%; standard procedure); this is likely due to the several manipulations which the intermediate undergoes.



Scheme 78: Telescoped procedure.

The bismacycle benzoate (side product of arylation) is recoverable in other Bi(V)-mediated arylations which employ *m*CPBA as an oxidant. In Senior's work, the post-arylation reaction mixture is concentrated and suspended in a volume of TBME, cooled, then triturated with 10 times the volume of pentane. The resultant solids are pure bismacycle *meta*-chlorobenzoate. Application of this procedure to the oxidation of guaiacol recovers 82% of **Bi-O*m*CB**, however the poisoning experiment (see Table 4) reveals that the bismacycle benzoate must be removed for the subsequent Luche reduction to take place. As such, a modified procedure including bismacycle recovery is conducted as follows: oxidative arylation, concentration of reaction mixture, trituration in TBME/pentane, recovery of **Bi-O*m*CB**, basified alumina plug (to move remnants), concentration of reaction mixture and finally, Luche reduction.

Telescoped Procedure and Recovery

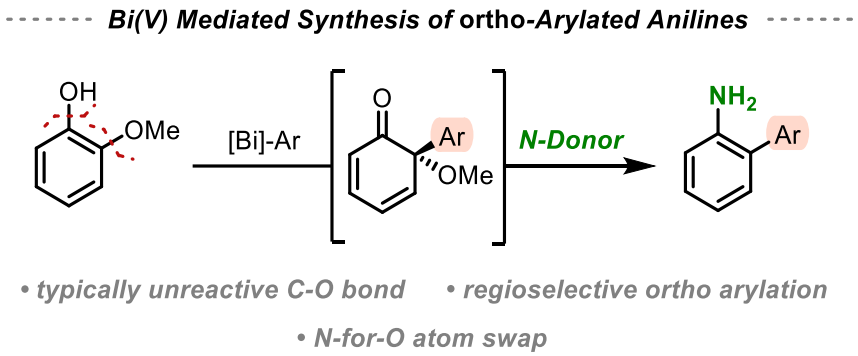


Scheme 79: Procedure for Bismacycle recovery.

Indeed, the recovered **Bi-OmCB** after the oxidative dearomatisation can be treated with tosic acid in near quantitative yields to prepare **Bi-OTs**.

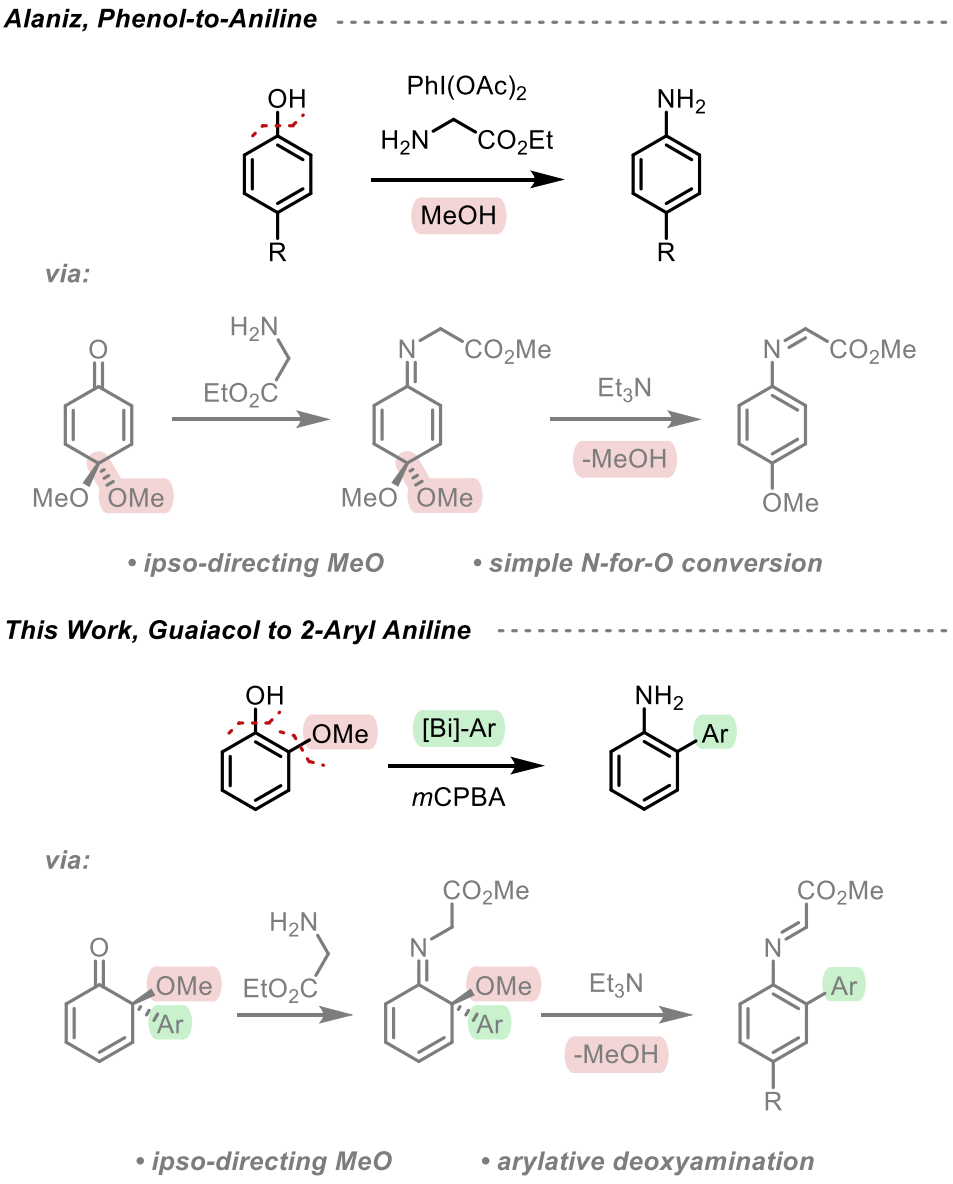
2.5. Towards a Deoxyaminative Arylation

We have recently been able to extend our deoxygenative arylation strategy to the synthesis of *ortho*-arylated anilines. The application of *ortho*-anisidine in this context was considered, however previous studies from the group have shown that the direct Bi(V) mediated arylation of aniline leads to uncontrolled oxidation. Therefore, we proposed that a cyclohexadienone derived from the dearomatisation of guaiacol may be intercepted with an amine prior to rearomatisation, thereby providing a direct route towards a 2-aryl aniline. This section presents preliminary studies directed towards realising this objective and outlines future studies that could be performed.



Scheme 80: Hypothesised Bi(V)-mediated arylative deoxyamination of guaiacol.

The direct synthesis of anilines from phenols *via* 2,5-cyclohexadienone intermediates has been reported by Alaniz in 2016. This was discussed in Chapter I and is displayed in Scheme 81 for clarity. This methodology constitutes the PIDA mediated alkoxylative dearomatisation of 4-methoxy phenol, where the intermediate cyclohexadienone is intercepted by a glycine ester, thereby enabling the direct synthesis of an aniline from a *para*-substituted phenol.



Scheme 81: Alaniz' direct synthesis of anilines *via* 2,5-cyclohexadienones, (top). Our hypothesised phenol to *ortho*-arylated aniline synthesis via 6-aryl-2,4-cyclohexadienones, (bottom).

It was considered that this strategy could be applied to the successful arylative dearomatisation of guaiacol, therefore allowing the rapid synthesis of 2-aryl anilines from widely abundant, bioderived guaiacols. Our proposed strategy resembles that of Alaniz', where the methoxy group behaves as an *ipso*-director, as well as the leaving group that facilitates rearomatisation. By utilising Bi(V) chemistry, we have the additional generation of complexity (*i.e.* arylation) prior to deoxyamination.

In order to realise this transformation, several points were considered based on our preceding understanding of the cyclohexadienone reactivity. Some of these points are understood from the chemistry discussed in this chapter:

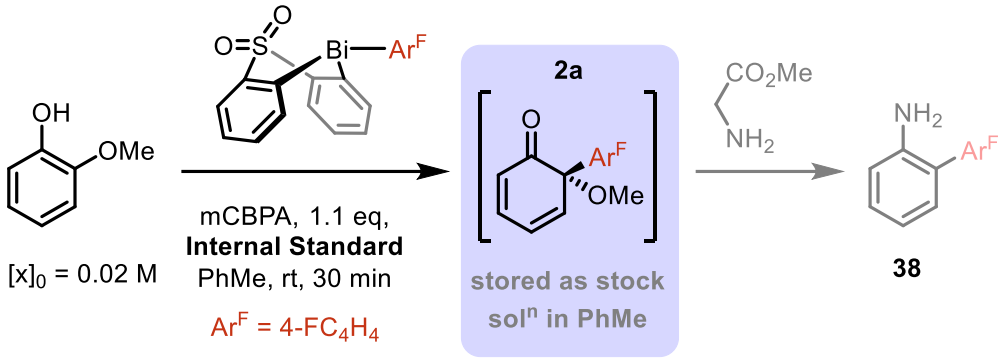
- cyclohexadienones have been found to degrade over time at ambient temperatures, indicating their temperature sensitivity;
- cyclohexadienones, particularly those exhibiting 2-EDG groups are known to undergo homo-dimerization;
- the cyclohexadienone framework is prone to photoisomerization, thus manipulation should be conducted under the exclusion of light, and,
- there are other electrophilic sites available for nucleophilic attack on the cyclohexadienone, potentially resulting in competitive side-reactions.

We have also developed an understanding of an analogous deoxyamination protocol in the synthesis of *meta*-arylated anilines. This is disclosed in Chapter IV, however the key findings to be mindful of are as follows:

- Lewis acids have been shown to facilitate the condensation of amines onto cyclohexadienones, as well as dienone-phenol rearrangements. The use of such may therefore promote aniline formation, or facilitate the rearrangement to a *meta*-arylated phenol;
- successful condensation of an N-donor may require high reaction conditions, as appreciable deoxyamination of the cyclohexadienone was only realised at temperatures over 100 °C (Chapter IV).

Therefore, it was understood that conditions would have to be selected with these factors in mind. Working towards our aim of developing a telescoped phenol to aniline procedure, optimisation of the condensation was initially conducted on the crude cyclohexadienone following dearomatisation. To do this, a stock solution of crude cyclohexadienone was prepared, and aliquots would be taken for each test reaction. Being mindful of the cyclohexadienone stability, these were kept covered in foil, or amberised glassware during manipulation in the laboratory, and were stored at -80 °C. Stock solutions were prepared in chloroform and calculated using the theoretical yield of cyclohexadienone. By preparing these, the amount of crude cyclohexadienone is controlled for each experiment during optimisation. The oxidative arylation was conducted under the same conditions as those for the *ortho*-arylation of guaiacol.

Optimisation Sequence

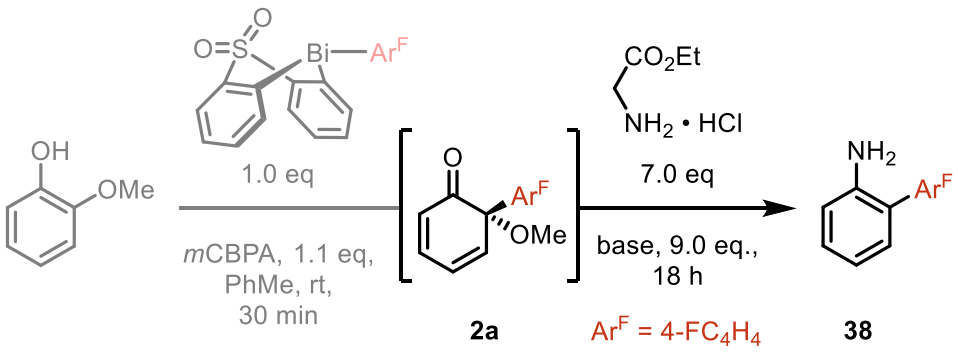


***in situ* yields ~ 70 - 75%**

Scheme 82: Protocol for optimising the deoxyaminative arylation of guaiacol. Internal standard: against internal standard 4,4'-bis(trifluoromethyl)-1,1'-biphenyl or 1-bromo-4-fluoronaphthalene.

At the outset, the reaction conditions reported by Alaniz were applied to the crude aliquot of cyclohexadienone **2a.** Unfortunately, this led to no desired aniline formation: while the cyclohexadienone intensity decreases, the abundance of the two peaks present after dearomatisation grow. This may suggest that **2a** undergoes decomposition rather than condensation with glycine under these conditions.

Optimisation: Addition of Glycine



entry	solvent	T (°C)	base	LA	% 2a	% 38
1	MeOH:H_2O	40	Et_3N	-	64	0
2	PhMe	reflux	Et_3N	-	6	0
3	**MeOH:H_2O**	**40**	**Et_3N**	**$Sc(OTf)_3$**	**<5%**	**13**

4	**MeOH:H_2O**	**40**	**Et_3N**	**$Bi(OTf)_3$**	**<5%**	**13**
5	$CDCl_3$	50	Pyr	-	64	0
6	MeOD	50	Pyr	-	64	0
7	HFIP	40	Et_3N	-	53	5

Table 6: Addition of glycine onto **2a**. Yields determined *via* quantitative ^{19}F NMR spectroscopy. (a) 10 mol% Lewis acid. (b) 14 equivalents of glycine ethyl ester hydrochloride used. MeOH:H_2O = 99:1.

Since high temperatures were required for ammonia to condense onto the cyclohexadienone (See Chapter IV), it was anticipated this transformation may demand similar conditions. Given that the reaction led to decomposition at 40 °C, it was hoped that the rate of aniline formation would be faster than cyclohexadienone decomposition. This was not the case (entry 2). Heating the reaction mixture to 80 °C in toluene led to a heterogenous mixture, possibly to due oligomerisation of the cyclohexadienone.

It is also known Lewis acids promote the deoxyamination of cyclohexadienones; this is largely to permit the migration towards a *meta*-arylated aniline (Chapter IV); however it may also aid the condensation of ammonia. Scandium triflate and bismuth triflate showed promise in the deoxyamination optimisation, thus these two Lewis acids were subject to the otherwise initial reaction conditions. This led to 12% formation of **38** in both cases, however the reaction mixture formed a complex mixture of unknown products.

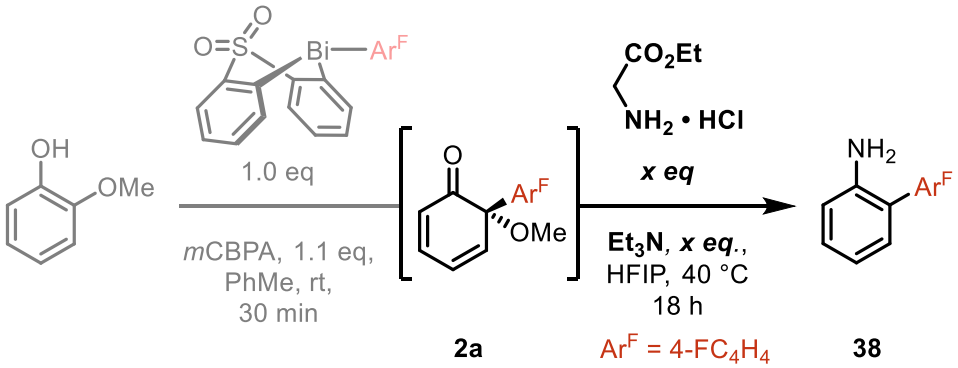
In an analogous transformation involving the condensation of hydrazines onto 2,5-cyclohexadienones, Zhang reports that pyridine performs better than triethylamine.[14] Their reaction was conducted at 50 °C in chloroform, however these conditions did not lead to any desired reactivity for this system (entry 5). Similarly, swapping the solvent for methanol, which aids homogeneity of this reaction mixture, did not lead to aniline formation (entry 6).

In their investigation of α-C-H functionalisation of pyrrolidinols *via* 2,5-cyclohexadienones, Yu and co-workers reports that fluorinated alcohol solvents are advantageous over nonfluorinated solvents, as their solvating power can

stabilise iminium intermediates.[128] Conversely for this system, hexafluoroisopropanol (HFIP) led to just 5% aniline formation. (entry 7).

Thus far, only HFIP and methanol were able to fully solubilise the reaction mixture. While HFIP affords less aniline, methanol results in a complex reaction mixture. Subsequent investigation exploring the ratio of glycinate to cyclohexadienone **2b** therefore employed HFIP as the solvent. (See Table 7). In this investigation, the ratio of triethylamine to glycinate was maintained at 7:9, as per Alaniz' procedure.

Optimisation: Addition of Glycine



entry	glycinate : base	% 2a	% 38
1	7:9	53	5
2	9:11.6	47	11
3	11:14	47	16
4	**13:17**	**31**	**25**

Table 7: Glycinate: base equivalent screen for the 1,2-Addition of glycine onto **2a**. Yields determined *via* quantitative ^{19}F NMR spectroscopy against internal standard 4,4'-bis(trifle-oromethyl)-1,1'-biphenyl.

Gratifyingly, these results show that increasing the equivalents of glycine ethyl ester hydrochloride from 7 to 13 effect a 5-fold increase in aniline yield. Increasing the equivalents of glycine from 9 to 11 did not lead to any increase in cyclohexadienone consumption, however it did afford a higher yield of aniline. This suggests that perhaps the increased equivalents of base with respect to **2a**

accelerates the aniline formation step, however no peak corresponding to the intermediate imine could be observed by ^{19}F NMR spectroscopy. Generally, the increased concentration of glycinate may accelerate condensation before the cyclohexadienone **2a** decomposes.

At present, we are able to achieve 25% of aniline formation *in situ*, as determined *via* ^{19}F reaction monitoring. There is lots of optimisation yet to be conducted on this transformation, as well as an understanding of substrate compatibility. An important point of discussion is that removal of the bismacycle benzoate by-product in the previous chemistry was necessary to obtain appreciable reactivity in the Luche reduction step, as this species poisons the reductant. It is not fully understood how the presence of the bismacycle benzoate leads to complete loss of reactivity, however, its removal should be considered in further optimisation of this transformation. It is also worth noting that the bismacycle benzoate is extremely insoluble in many solvents, therefore leading to a highly heterogeneous reaction in its presence. Its removal may allow for a homogenous reaction which, in turn, could facilitate aniline formation.

Conclusion

A rapid transformation of simple guaiacols to valuable *ortho*-arylated phenols is reported. This methodology provides a highly modular route towards aryl cyclohexadienones, a class of compound which is relatively scarce in the literature owing to their instability and reliance on I(III) chemistry to synthesise. The alkoxy group of the guaiacol core behaves as an *ipso*-director, thus minimizing C-6 arylation and consequently, over-arylation. This highly desirable regio-diversion overcomes the innate selectivity expected for a phenolic core using methods based on electrophilic aromatic substitution such as Bi(V)-mediated C-H arylation. Despite the variable stability of the resultant cyclohexadienone, deoxygenation of the core affords rapid access to 2-aryl phenols with good compatibility of electronically and sterically diverse partners.

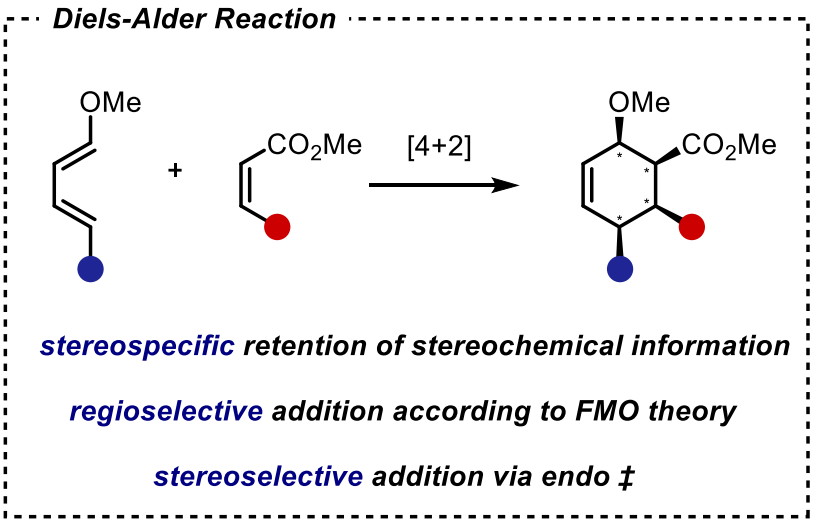
Extension of this successful protocol has been initiated towards the synthesis of *ortho*-arylated anilines. Treatment of an intermediate cyclohexadienone with a large excess of glycine ester and base leads to appreciable formation of 2-aryl aniline *in situ*. It is hoped that the foundational investigation into this project will eventually lead to the successful conversion of abundant bioderived phenols to a diverse array of *ortho*-arylated anilines.

Chapter III

Planar Phenols to sp^3 Rich Architectures

3.1. Introduction

The development of simple strategies for the rapid construction of complex, stereo-defined molecules presents an enduring challenge in organic synthesis. The development of such methodologies is not only beneficial to the field of natural product synthesis but greatly facilitates the discovery of novel sp^3-bioisosteres for planar aromatic moieties.[129,130] The Diels-Alder reaction is one of the most widely used protocols to synthesise densely functionalised ring systems, owing to its ability to generate four contiguous stereocenters with high and predictable stereoselectivity.[131] This is illustrated in Scheme 83.

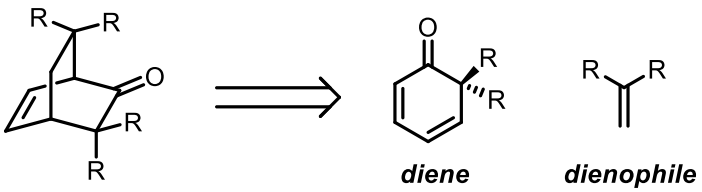


Scheme 83: The Diels-Alder reaction, exemplified for the normal electron demand archetype.

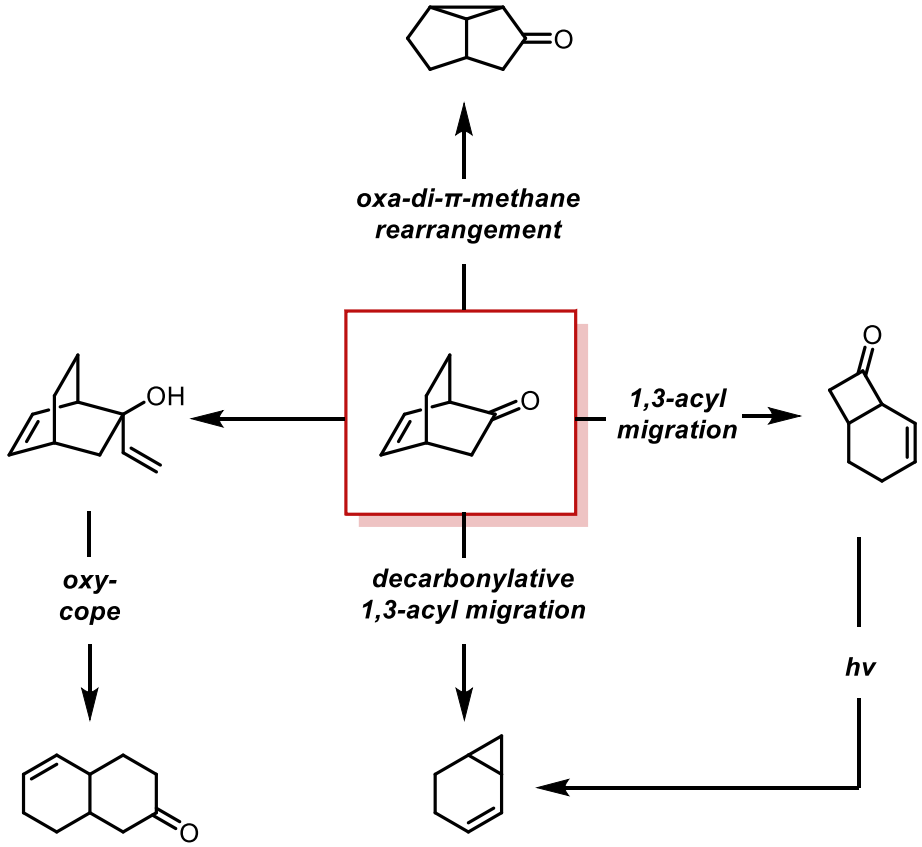
A particular class of Diels-Alder adduct that has gained attention in target-oriented synthesis is the bicyclo[2.2.2]oct-5-en-2-one* scaffold, for it has been shown to undergo many useful complexity generating reactions.[132–134] These include 1,3-acyl migration, decarbonylation,[135] oxa-di-π-methane rearrangement,[136,137] and the anionic oxy-Cope rearrangement.[138–140] The resulting products consist of a variety of structures which resemble key intermediates in natural product synthesis.

* Referred to hereafter more simply, the bicyclo[2.2.2]octenone

Bicyclo[2.2.2]octenones via Diels Alder



Bicyclo[2.2.2]octenone Chemistry

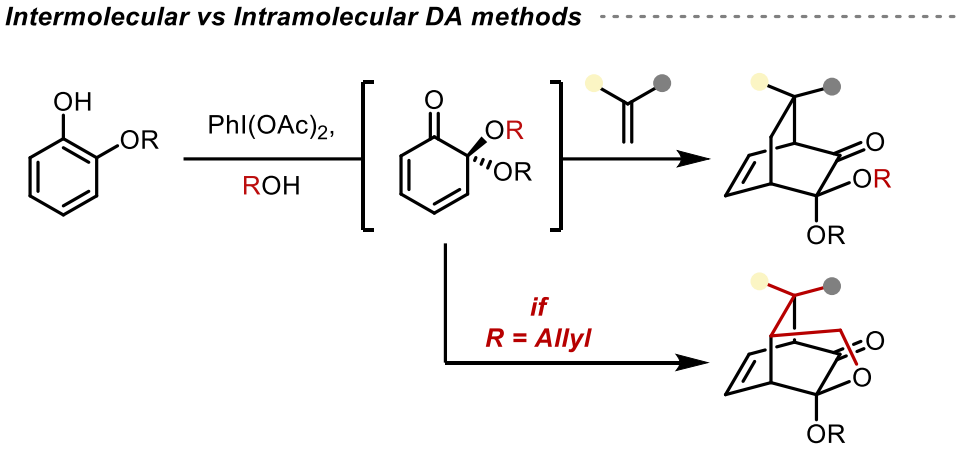


Scheme 84: Rearrangements of bicyclo[2.2.2]octenones.

The synthesis of these compounds typically entails the [4+2] cycloaddition between a 2,4-cyclohexadienone that behaves as the diene counterpart, and a dienophile. The former is frequently prepared *via* an alkoxylative I(III)-mediated phenol dearomatisation which has been covered at length in Chapter I. This chapter will begin by exploring the syntheses of bicyclo[2.2.2]octenones in more depth, both *via* intra- and intermolecular Diels Alder reactions. Their utility in natural product synthesis will follow, and finally, how Bi(V)-mediated phenol oxidation can provide a complementary approach for the synthesis of this class of compound will be proposed.

Bicyclo[2.2.2]octenone Synthesis

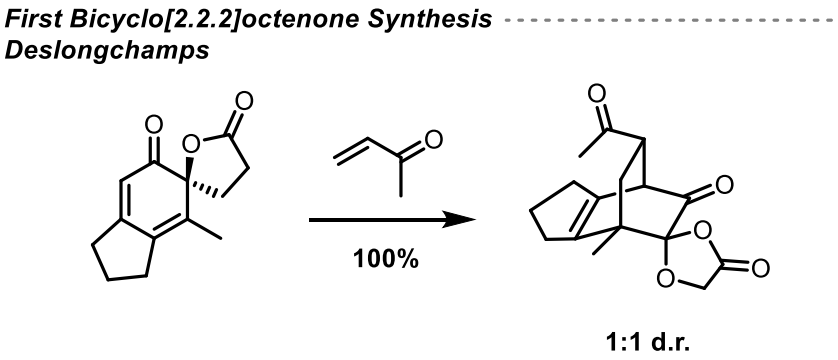
Bicyclo[2.2.2]octenones can be synthesised by intercepting a cyclohexadienone with an external dienophile. Intramolecular Diels-Alder (IMDA) reactions have also been developed by tethering the diene and dienophile. This can be achieved *via* an allyloxylative dearomatisation, *i.e.* using allyl alcohol as the nucleophile in an I(III) mediated phenol dearomatisation rather than methanol (Scheme 85).



Scheme 85: Intermolecular vs intramolecular Diels-Alder reactions with cyclohexadienones.

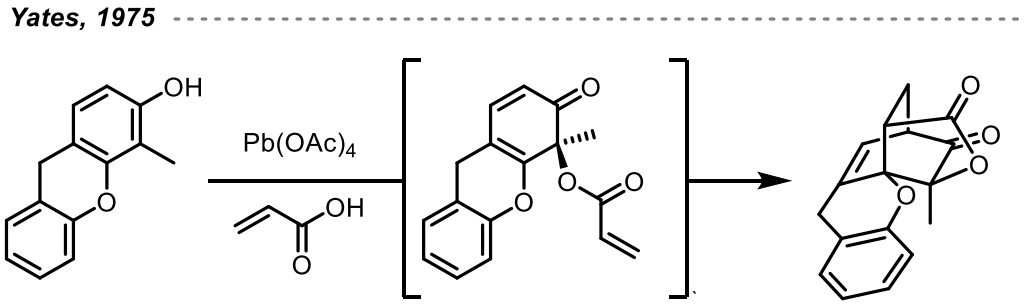
Methods to prepare bicyclo[2.2.2]octenones other than from a cyclohexadienone exist, albeit there are very few examples in the literature. As such, literature coverage will encompass their preparation proceeding *via* phenol dearomatisation, which was discovered between the 1960's and 1970's.

The first reported example of the bicyclo[2.2.2]octenone scaffold appeared in 1969 by Deslongchamps.[141] In this work, the bicyclo[2.2.2]octenone is prepared *via* a Diels-Alder reaction between an *ortho*-spirodienone lactone and methyl vinyl ketone. This work later led to the development of the first total synthesis of (+)-ryanodol.[142] Here, the parent cyclohexadienone is prepared *via* an NBS mediated spirolactonisation.



Scheme 86: First example of bicyclo[2.2.2]octenone synthesis by Deslongchamps and co-workers.[141]

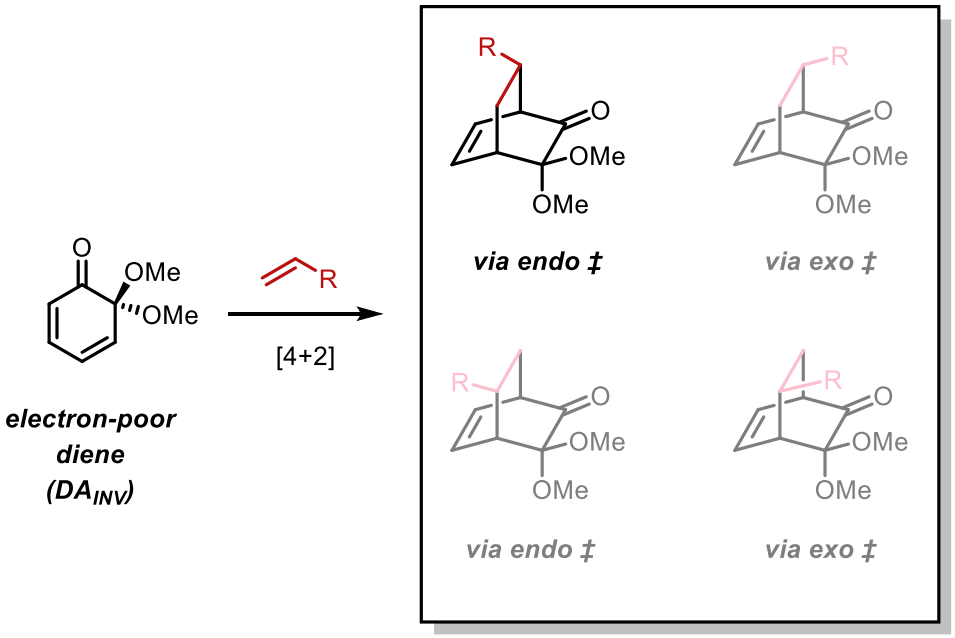
Less than 10 years later, the Yates group was challenged by the synthesis of bridged xanthines, and in 1975 sought a route towards them *via* an intramolecular Diels-Alder reaction of a dienophile-tethered-cyclohexadienone.[143,144] The cyclohexadienone was synthesized *via* a modified Wessely oxidation (see Chapter I). Traditional Wessely oxidations entail the $Pb(OAc)_4$-mediated acetoxylative dearomatisation of an *ortho*-(or *para*-) substituted phenol; in this instance, the oxidation takes place in the presence of lead tetraacrylate to affect an acryloxative dearomatisation to the bicyclo[2.2.2]octenone precursor (Scheme 87).



Scheme 87: Yates' use of Pb(IV) chemistry to access an acrylate-tethered cyclohexadienone IMDA substrate.

In the years following these two seminal publications, the Liao Group sought to investigate the scope of dienophiles that bicyclo[2.2.2]octenones can react with. To preface the discussion of the following accounts, it is pertinent to mention that there are 4 possible outcomes of the [4+2] reaction; there are two regioisomers, of which there are 2 stereoisomers (Scheme 88). Generally, the Diels-Alder reaction between the cyclohexadienone and dienophile is highly regio- and stereoselective, thus furnishing *ortho*-products formed *via endo*

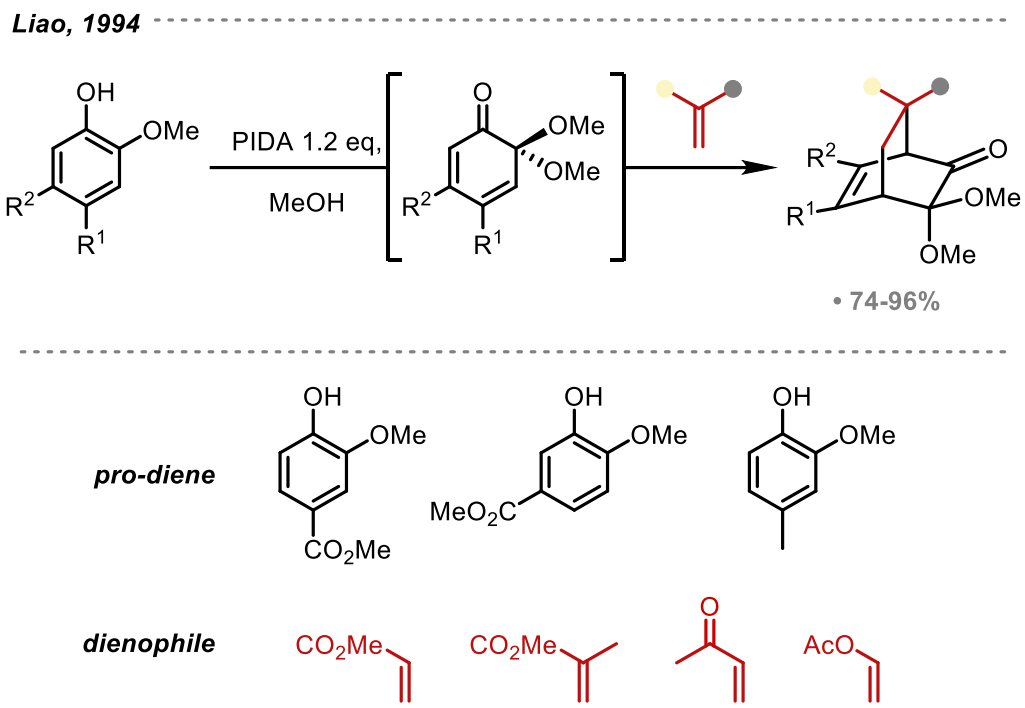
transition states. In almost all cases, there is exclusive formation of this bicylclo[2.2.2]octenone unless otherwise stated.



Scheme 88: Possible regio- and stereoisomers resulting from the inverse electronic demand Diels-Alder reaction between cyclohexadienone and dienophile.

Liao's first publication in the field reports a series of normal electronic demand Diels-Alder reaction of cyclohexadienones with electron-withdrawing dienophiles.[145] The parent cyclohexadienones are synthesised *via* phenol dearomatisation using hypervalent iodine chemistry, the first example of such in the synthesis of bicyclo[2.2.2]octenones. A general reaction sequence for the Diels-Alder reaction between a matrix of phenols and dienophiles is shown in Scheme 89.

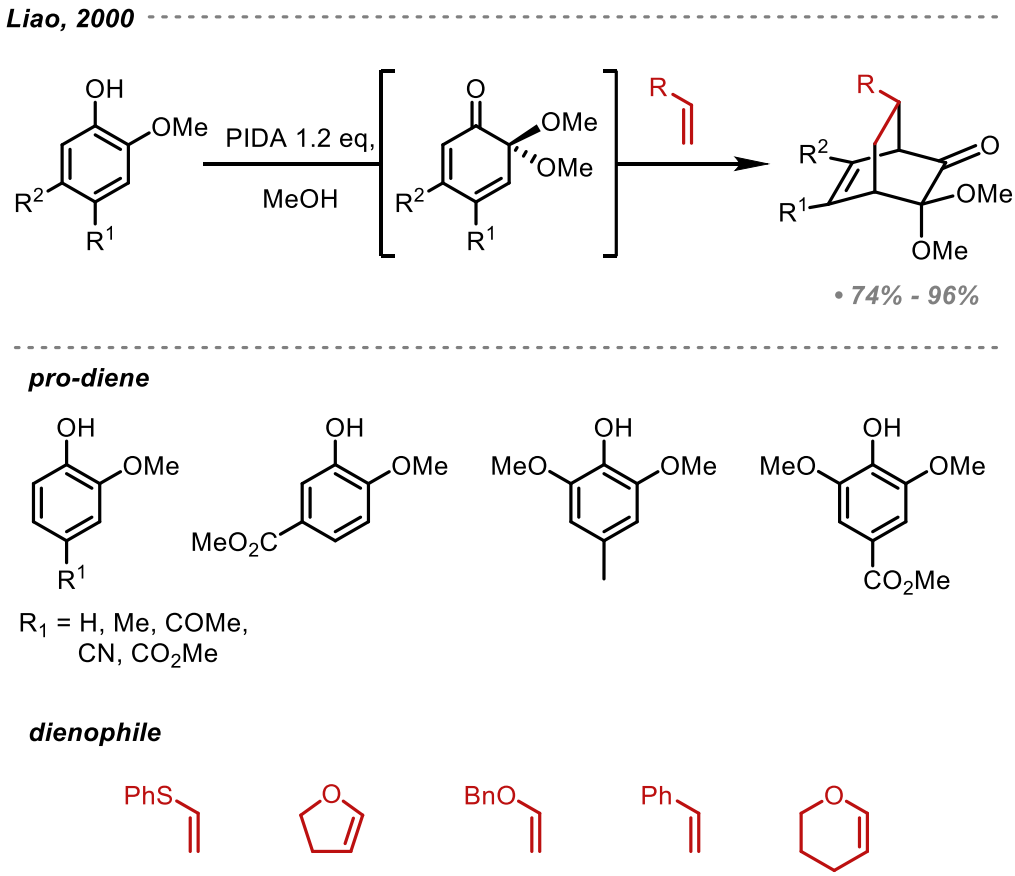
Dienophiles including methyl acrylate, methyl methacrylate and methyl vinyl ketone perform well in the cycloaddition with various guaiacols, however vinyl acetate was found to be inefficient and non-stereoselective.



Scheme 89: Liao's Diels-Alder reaction between cyclohexadienones derived from guaiacols and electron-poor dienophiles.[145]

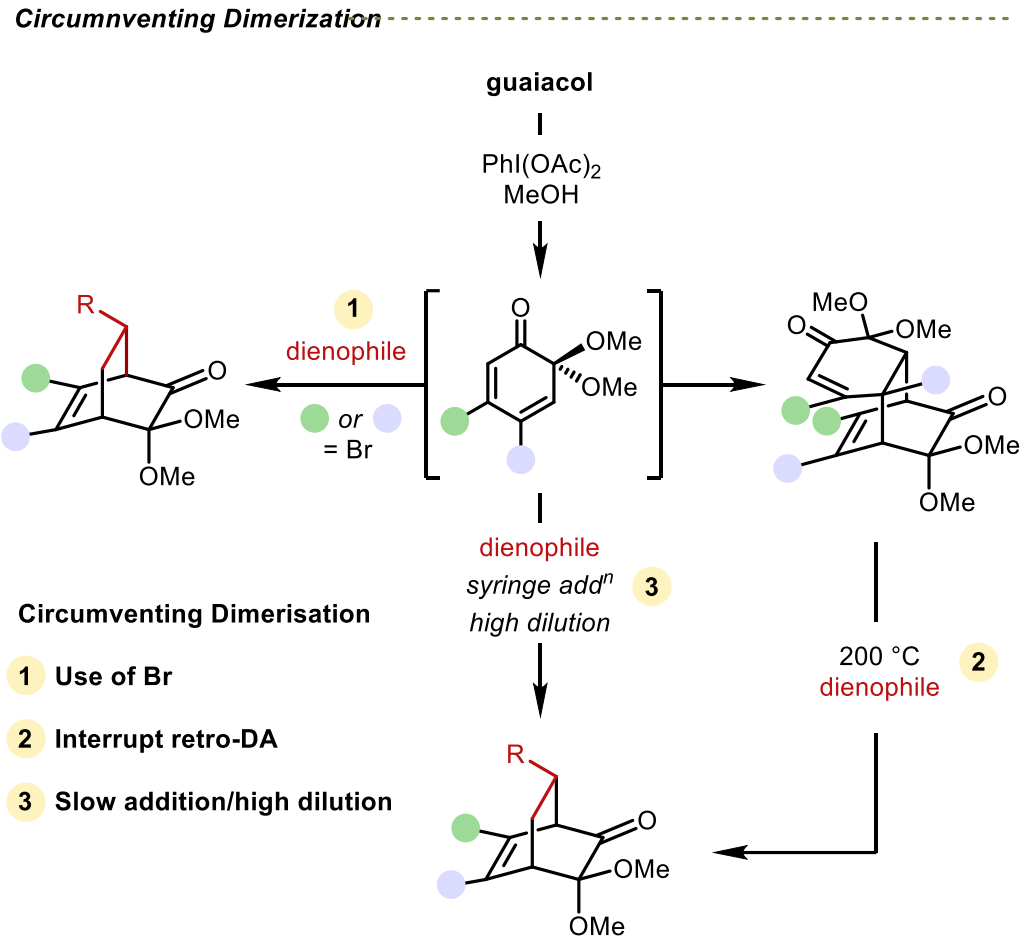
In the early investigation of this chemistry, Liao reports that the formation of the desired bicyclo[2.2.2]octenone is complicated due to the propensity of the cyclohexadienones to dimerise. This is well-documented in the literature, and apparently depends on the electronics of the parent cyclohexadienone (see Chapter I, Section 1.2).[30] Liao employs high-dilution conditions to disfavour this competitive side reaction, a strategy which has exploited by others in this area of research.

Building on this publication, Liao subsequently reported the inverse electronic demand Diels-Alder reaction of cyclohexadienones with electron-rich dienophiles such as benzyl vinyl ether, dihydrofuran, styrene, and phenyl vinyl sulfide.[146,147] In these reactions, parent cyclohexadienones with electron-withdrawing groups at the 4-position (*e.g.*, methyl vanillate, acetovanillone) display much better reactivity compared to those without (*i.e.* guaiacol).



Scheme 90: Liao's Diels-Alder reaction between cyclohexadienones derived from guaiacols and electron-rich dienophiles.[146,147]

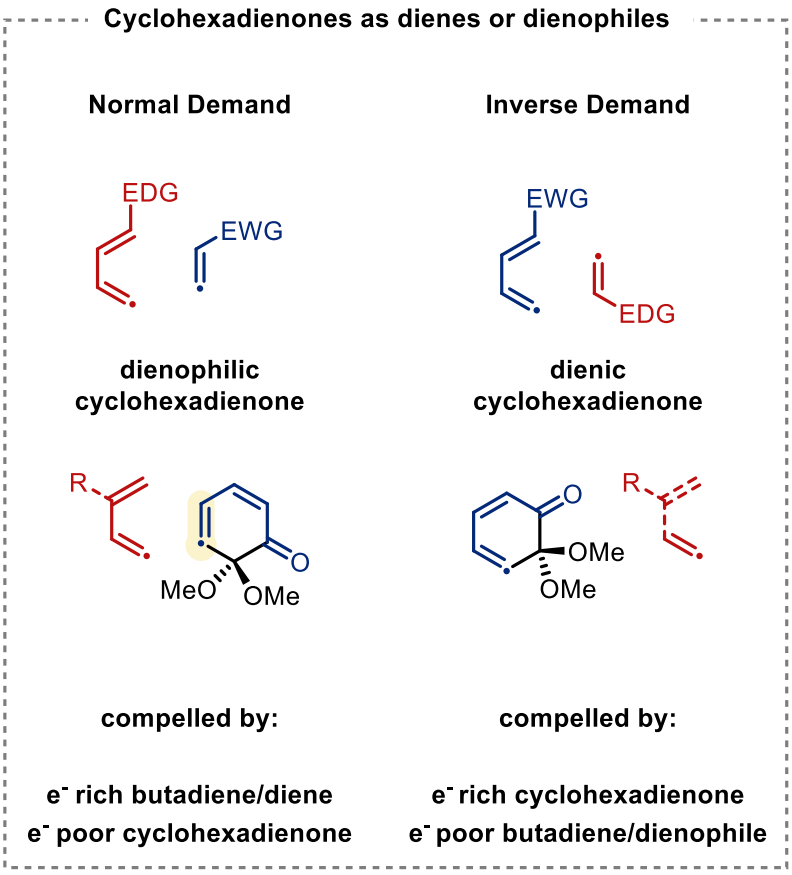
An alternative route to overcoming the competing dimerization is by introducing a 'transient bromine handle'. An empirical observation made by Liao (Chapter I, Section 1.2) is that the presence of the bromine atom on the ring retards dimerization. As such, the halo-cyclohexadienone undergoes the [4+2] reaction, and the bromine is later removed to provide a higher net yield of the bicyclo[2.2.2]octenone. Another option is to isolate the undesired dimer, subject this to a retro-Diels-Alder reaction, and intercept the monomeric dienone using excess dienophile.



Scheme 91: Liao's reported strategies for inhibiting or reversing dimerization of the cyclohexadienone.

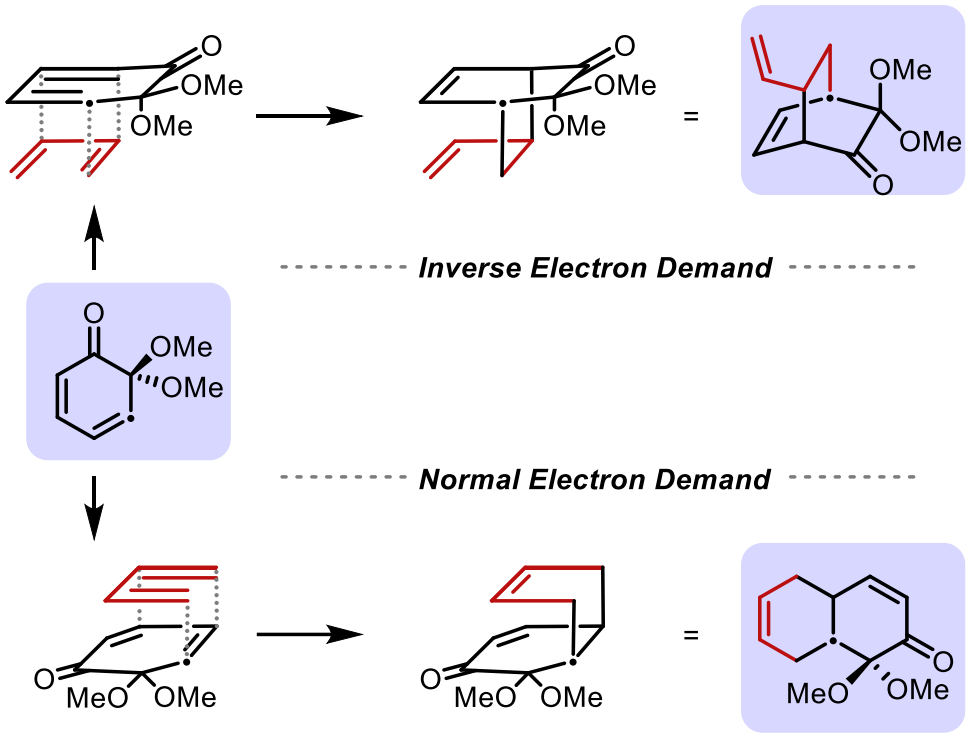
Liao also published their findings on the propensity of cyclohexadienones to behave as dienophiles rather that dienes.[140] In this study, cyclohexadienones derived from cresol, methyl vanillate, methyl isovanillate, and methyl syringate are treated with electronically and sterically varied butadienes. The reactions provide two Diels-Alder adducts: bicyclo[2.2.2]octenones and *cis*-decalins. The ratio of these two adducts is apparently dependent on the substituents on the phenolic nucleus.

To preface the discussion of these findings, two competent reactions which take place are highlighted in Scheme 92; these are the inverse electron demand Diels-Alder (DA_{INV}) and the normal demand Diels-Alder reaction.



Scheme 92: Required electronic profile of dienic and dienophilic partners to engage in Diels-Alder chemistry

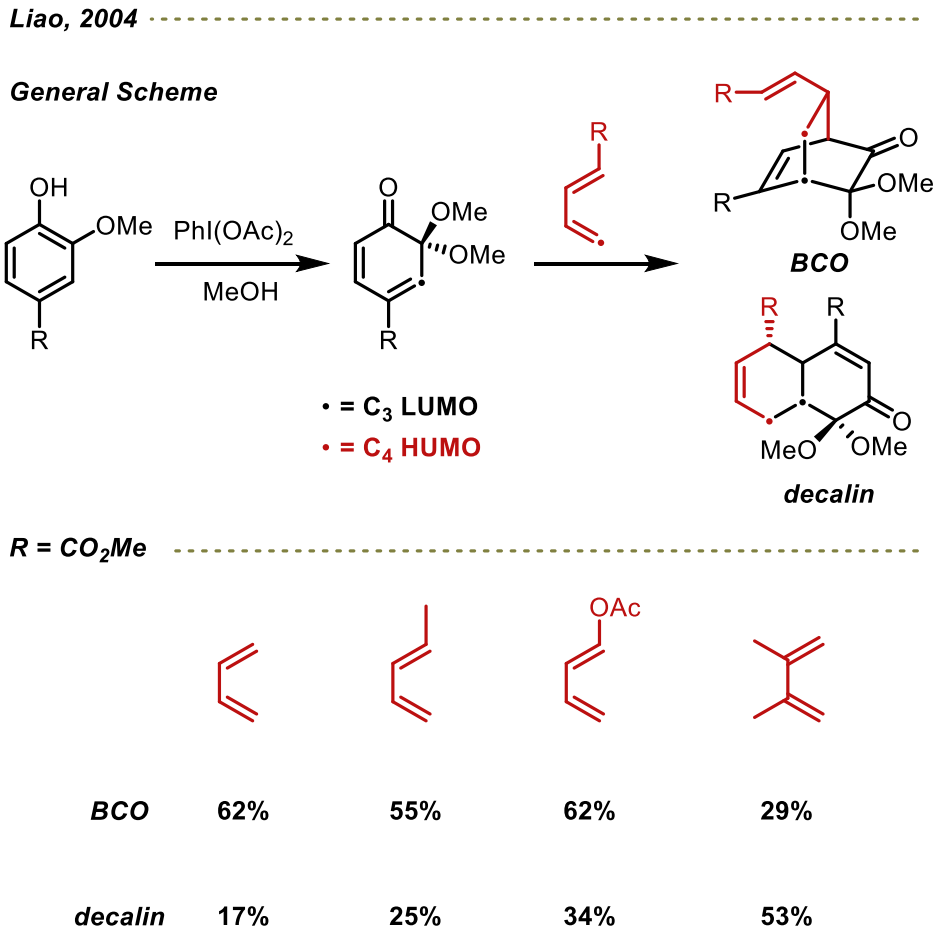
In theory, good electronic complementarity should facilitate one Diels-Alder reaction over the other. For example, matching an electron-rich dienophile (butadiene) with an electron-poor diene (cyclohexadienone) should facilitate an inverse electron demand Diels-Alder reaction, thus favouring the formation of a bicyclo[2.2.2]octenone. On the contrary, an electron-poor dienophile (cyclohexadienone) and electron-rich diene (butadiene) should facilitate a standard demand Diels-Alder to the decalin. As the cyclohexadienone nucleus is inherently electron-poor, bicyclo[2.2.2]octenone formation *via* the inverse electron demand reaction is typically dominant. Liao's work demonstrates that cyclohexadienone *dienophilicity* can be engaged by tuning the electronics of each reactant.



Scheme 93: Competent DA_{INV}/DA reactions en route to decalins/bicyclo[2.2.2]octenones. DA reaction pathways exemplified for prefferable *endo* transition states.[140]

In their study, Liao treats the aforementioned guaiacols with the panel of butadienes shown in Scheme 94. In the first instance, the cyclohexadienone derived from methyl vanillate is tested among the butadienes. This study reveals that this cyclohexadienone can behave as a 2π counterpart towards butadienes, albeit in varied yields.

The reaction with butadiene affords only 17% of the decalin. However, when electron-donating groups are substituted onto the butadiene, formation of the decalin increases. For example, 53% of the decalin can be accessed using 2,3-methyl butadiene. This increase can be attributed to the hyperconjugative effects of the two methyl groups, thus increasing diene character of the butadiene.

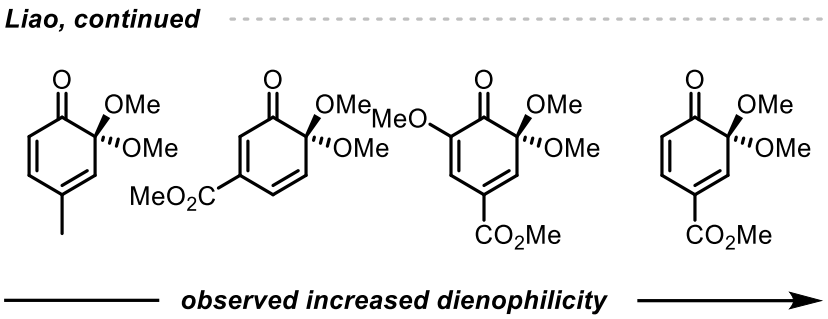


Scheme 94: General scheme for Liao's dienophilic cyclohexadienones.

BCO = bicyclo[2.2.2]octenone.

It is worth noting that the addition of unsymmetrical butadienes in the DA_{INV} reaction is accompanied with high stereo- and regioselectivity. According to FMO theory, regioselectivity is likely governed by the largest LUMO and HOMO coefficients on the cyclohexadienone and butadiene respectively. In the former, this resides on C_3, and the latter on C_4 (as highlighted). The formation of the decalins is also regio and stereoselective; the same logic can be applied to rationalise this.

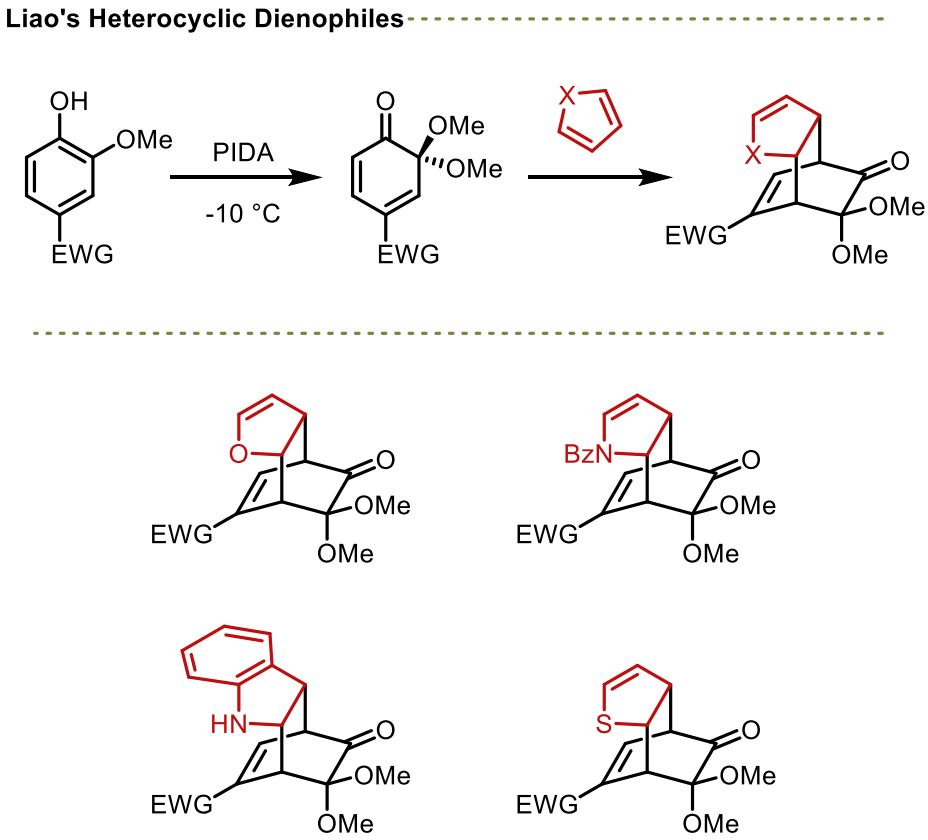
Across the series of selected guaiacols, a general trend can be observed: where there are electron-donating groups conjugated to the ring, the cyclohexadienone is more likely compelled towards diene behaviour. In the cases of the cyclohexadienones derived from cresol and iso-methylvanillate, almost exclusive formation of the bicyclo[2.2.2]octenone is observed. This is likely due to the electron-donating effects the methyl group has on the ring in cresol, and the effects of cross-conjugation in the latter.



Scheme 95: Observed increase in dienophilic character in cyclohexadienones, which appears to be compelled by electron-withdrawring groups on the dienophilic moiety.

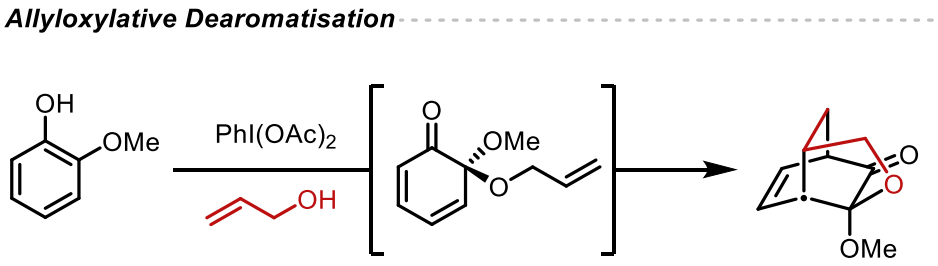
Despite their aromaticity, furans are known to participate in Diels-Alder reactions, typically as 4π counterparts. Their reactions with cyclohexadienones, however compel them to participate as 2π counterparts, *i.e.* as dienophiles.[139] It is interesting to note that the regioselectivity is reversed with respect to that of the dihydrofuran dienophiles in Liao's previous work (Scheme 90).

Cycloadditions with pyrroles and indoles are generally less efficient than their furan counterparts; this can be attributed to their higher resonance energies and capability to undergo Michael additions. Despite this, these heterocycles have been employed as dienophiles towards 4-EWG cyclohexadienones, as shown in Scheme 96.[148,149] The successful reports of these heterocyclic dienophiles prompted the Liao group to investigate the dienophilic capability of thiophenes.[150] In this study, substituted thiophenes provides an array of bicyclo[2.2.2]octenones, whereas unsubstituted thiophene furnishes a small amount of the bis-adduct (*i.e.* result of a second DA reaction between cyclohexadienone and resultant dihydrothiophene.)



Scheme 96: Use of various heterocycles as dienophiles with dienic cyclohexadienones.[139,149–151]

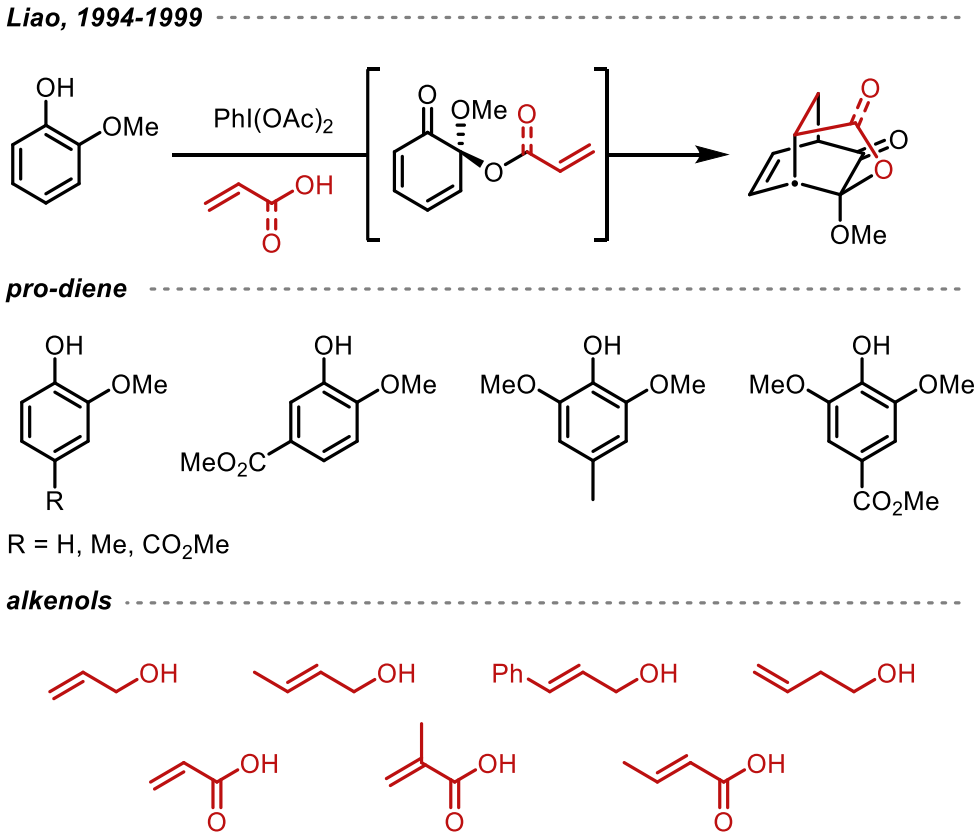
As mentioned, if methanol is substituted for an allyl alcohol in the I(III)-mediated dearomatisation, a cyclohexadienone with dienophile tether can be constructed (Scheme 97). This intermediate can undergo a rapid *intramolecular* Diels-Alder reaction to furnish a tricyclic ring system.



Scheme 97: General scheme for the allyloxylative dearomatisation of guaiacol. The resultant cyclohexadienone can undergo an intramolecular Diels-Alder reaction.

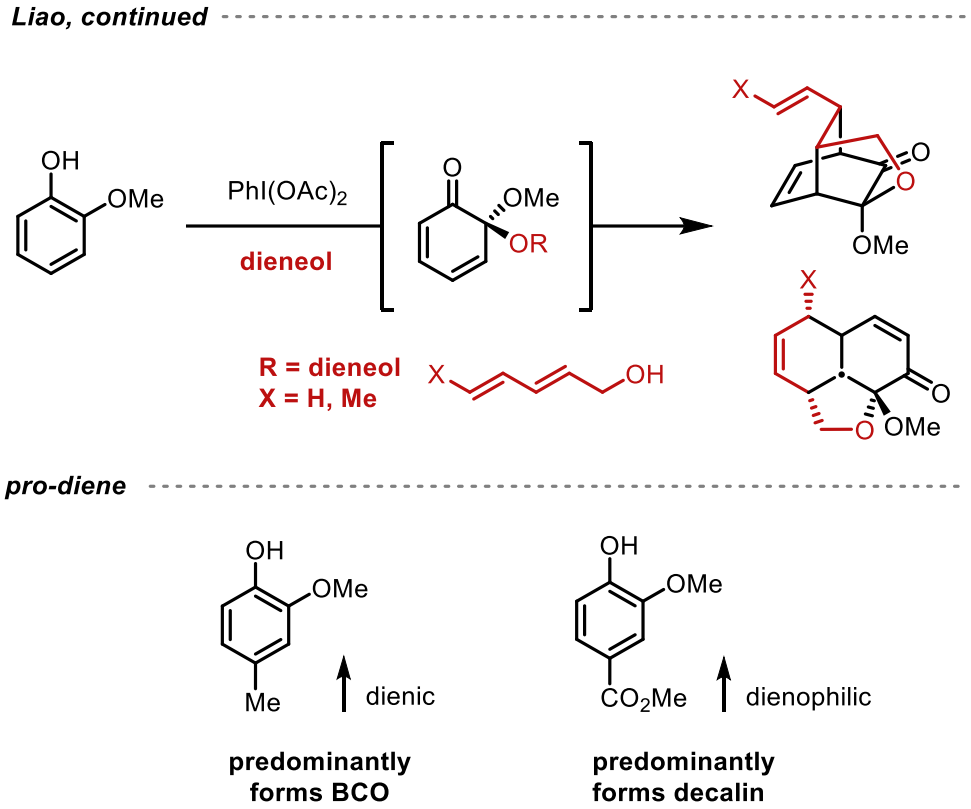
The synthesis of bicyclo[2.2.2]octenones using this strategy was first demonstrated by Peter Yates, as discussed in Scheme 87, however this was limited to one example and required the use neurotoxic organolead reagents. [143,144,152] The methods to be discussed have been demonstrated on a wider range of substrates

and use I(III) chemistry to access the parent cyclohexadienone. Liao first demonstrated this using allyl alcohols and extended this to alkenoic acids (Scheme 98).[145]



Scheme 98: Intramolecular Diels-Alder reactions of dienophile-tethered cyclohexadienones.[145]

When allyl alcohols were replaced with 2,4-dienols, the cyclohexadienone can, once again, display dual behaviour *i.e.* both dienic and dienophilic.[153] The products are a mixture of bicyclo[2.2.2]octenones and *cis*-decalins following the *endo* rule. By the same rationale previously discussed, 4-EDG groups on the cyclohexadienone increase dienic behaviour, whereas 4-EWG groups increase dienophilic behaviour.

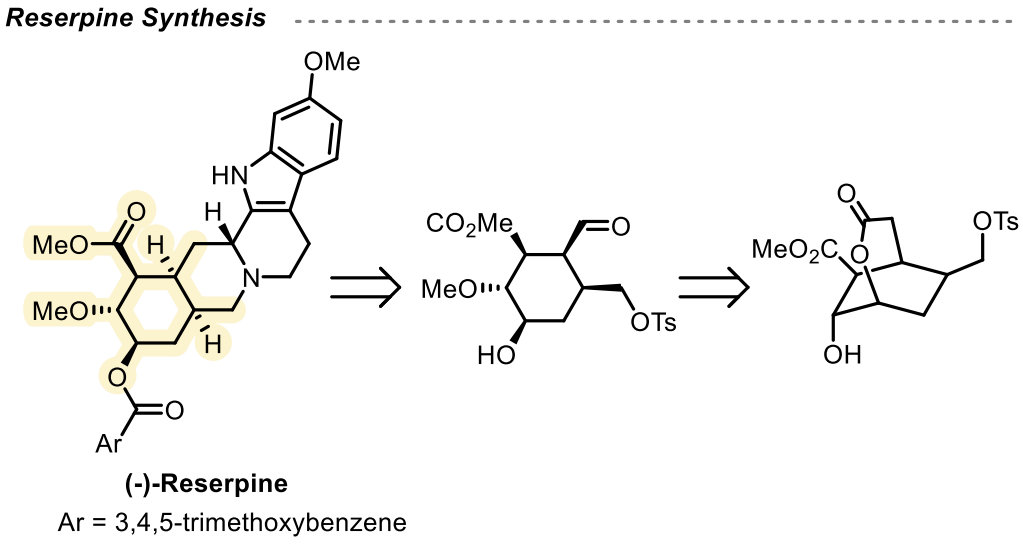


Scheme 99: Intramolecular Diels-Alder of cyclohexadienones with dienes: rare case of dienophilic behaviour of cyclohexadienones in intramolecular variant.[153]

Bicyclo[2.2.2]octenones in Natural Product Synthesis

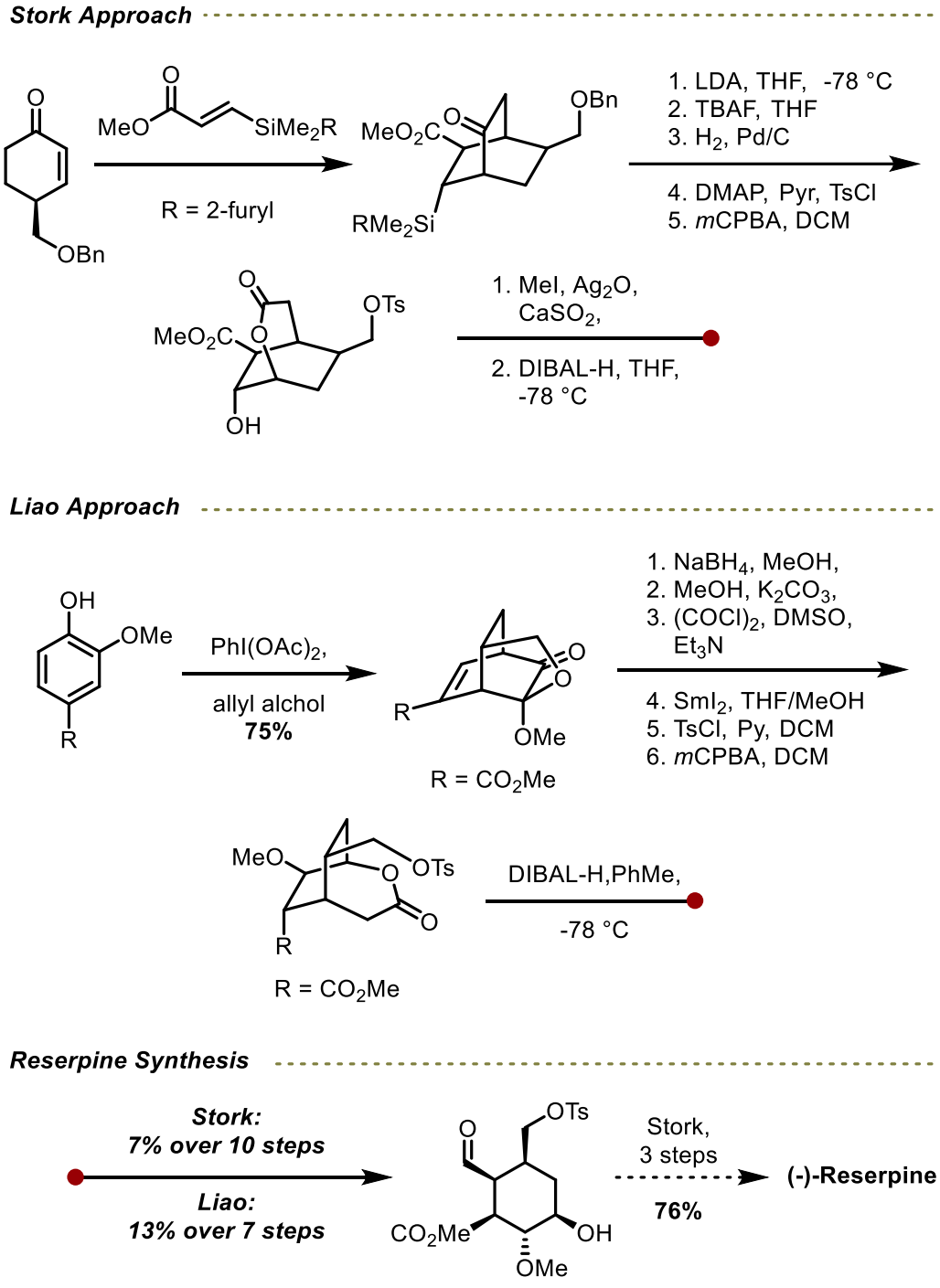
There are few examples of complex natural products which exhibit the bicyclo[2.2.2]octenone nucleus, indeed it is their ability to transform into stereo defined architectures which is of more value. This section will introduce the reader to the various ways bicyclo[2.2.2]octenones present themselves as invaluable synthetic intermediates in total synthesis.

The anti-hypertensive drug reserpine can be synthesized from a highly functionalised formyl cyclohexane (Scheme 100), which can in turn be prepared by ring opening of a corresponding bicyclo[2.2.2]octane. This analysis has been utilized by Stork and Liao.



Scheme 100: Retrosynthetic analysis of Reserpine.

The Stork bicyclo[2.2.2]octane is prepared *via* a double Michael addition of a silyl acrylate and cyclohexene enolate (Scheme 101), each of which require multi-step syntheses.[154] Liao reports that an analogue of this can be constructed in fewer steps *via* the cyclohexadienone derived from methyl vanillate.[155] Following manipulation of the bicyclic core, the bicyclo[2.2.2]octenone is opened to provide the aldehyde partner required for the penultimate Pictet-Spengler reaction en-route to reserpine.

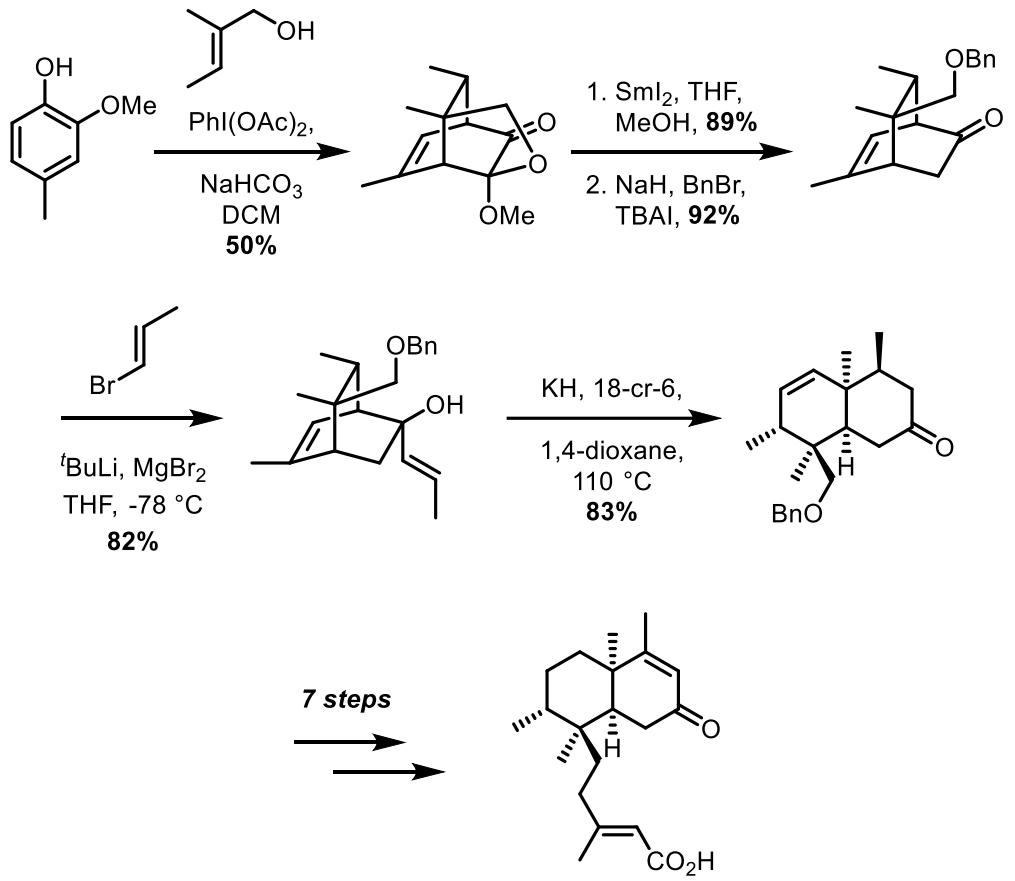


Scheme 101: Stork vs Liao group strategies towards the synthesis of Reserpine. [154,155]

In the exploration of their inherent reactivity, we have seen that dienophilic cyclohexadienones can be used to construct a *cis*-decalin. If this is the desired scaffold, it is possible to perform an oxy-cope reaction from the bicyclo[2.2.2]octenone. This interconversion has been employed in a racemic synthesis of *cis*-clerodane diterpenic acid (Scheme 102).[138] In this synthesis, the parent bicyclo[2.2.2]octenone, following the IMDA reaction, exhibits all four required stereocenters of the target compound. Following the samarium iodide

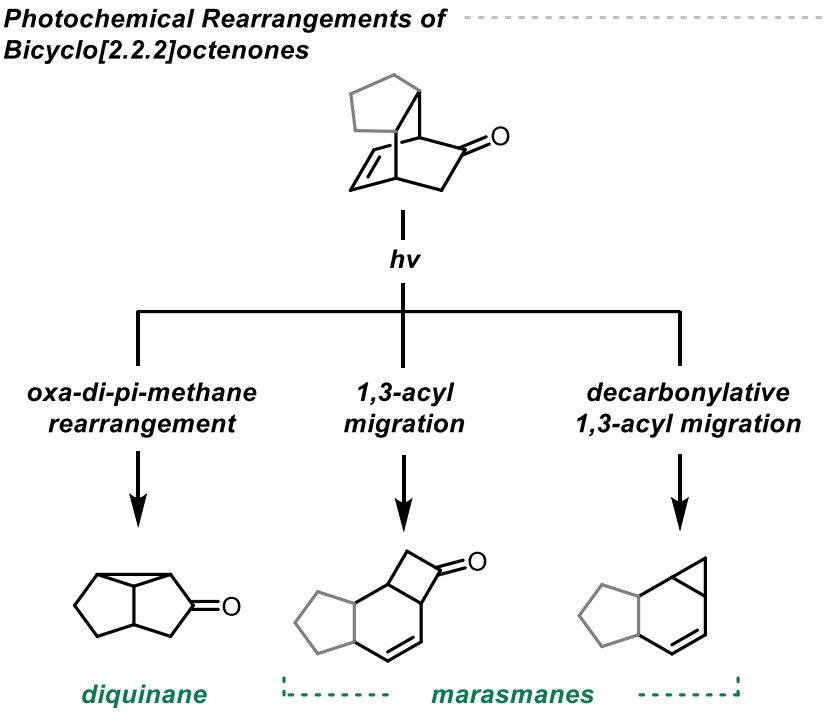
mediated furan cleavage, Grignard addition into the carbonyl furnishes the dienol substrate which undergoes the anionic oxy-cope rearrangement. Final manipulation of the key decalin ring provides the target compound.

Liao, 1996



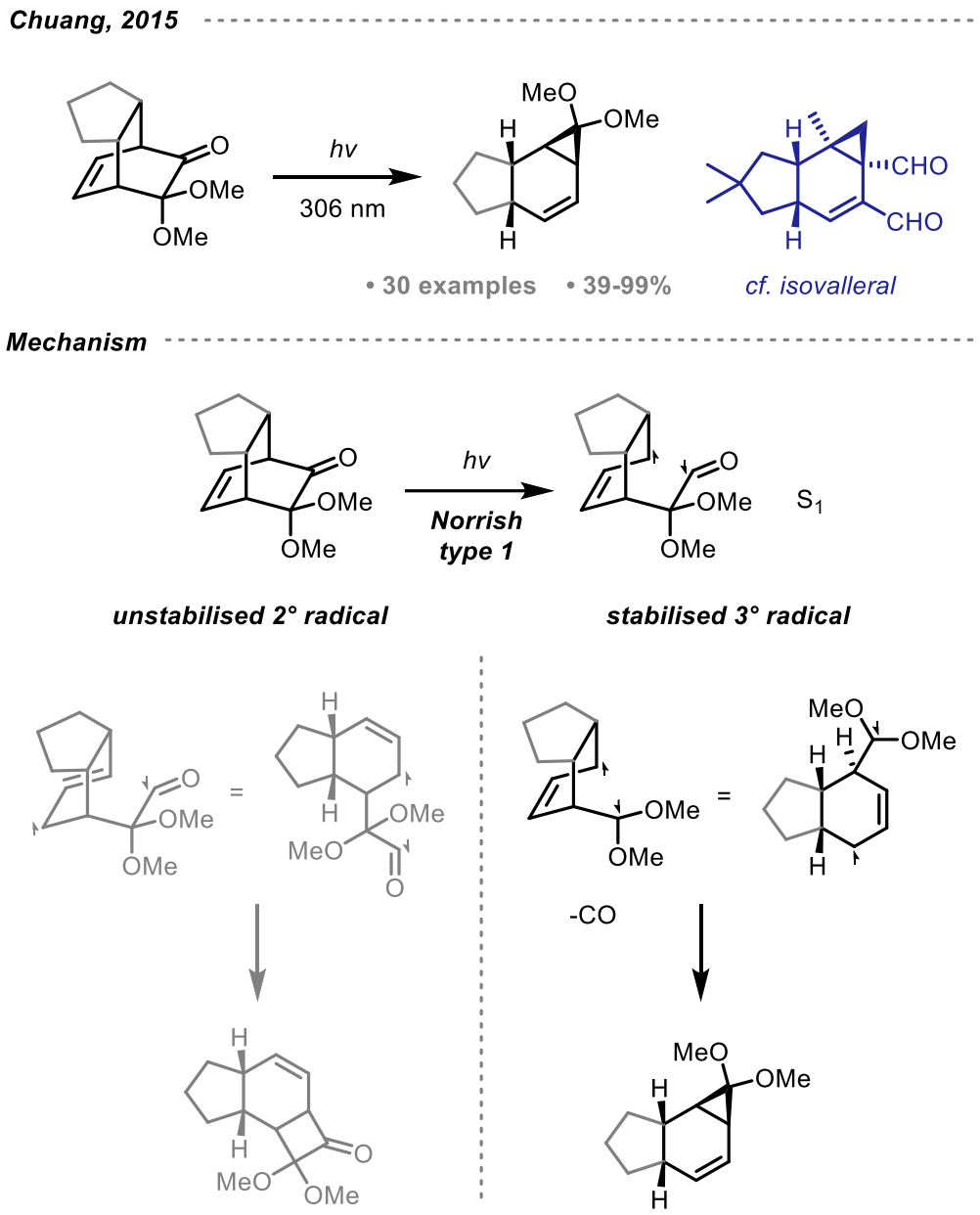
Scheme 102: Anionic oxy-cope rearrangement in the synthsis of cis-decalins.[138]

In addition to its thermally enabled interconversions, the bicyclo[2.2.2]octenone is rich in photochemistry by virtue of its β,γ-unsaturated ketone. In the absence of photosensitisation, their singlet photochemistry consists of 1,3-acyl migrations and decarbonylations en route to the marasmane scaffold, whereas triplet sensitisation enables an oxa-di-π-methane rearrangement to produce a diquinane. Each of these motifs diversified from the parent bicyclo[2.2.2]octenone present desirable skeletons in natural product synthesis.



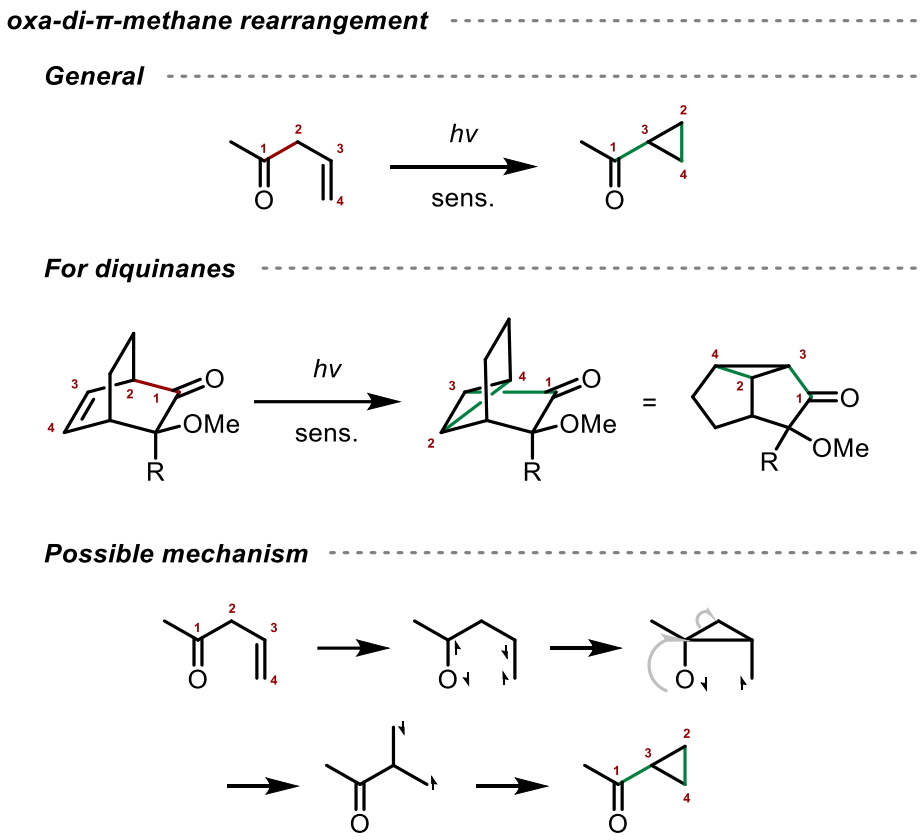
Scheme 103: Photochemical rearrangements of bicyclo[2.2.2]octenones.

In 2015, the Chuang group sought to investigate the singlet state photochemistry of 1,3-acyl shifts to produce a range of marasmanes. This was found to be possible *via* irradiation of the parent bicyclo[2.2.2]octenone in acetonitrile. This singlet state chemistry exhibits two possible pathways, one forming the 6,4-ring conjuncture or another forming the 6,3-ring conjuncture following decarbonylation. In their report, only the decarbonylated product was found, likely due to the highly stabilised tertiary radical. When this reaction was performed in acetone, formation of the desired product is low. This can be attributed to acetone being a triplet sensitizer.



Scheme 104: Chuang's methodology on the photochemical transformation to the marasmane framework.

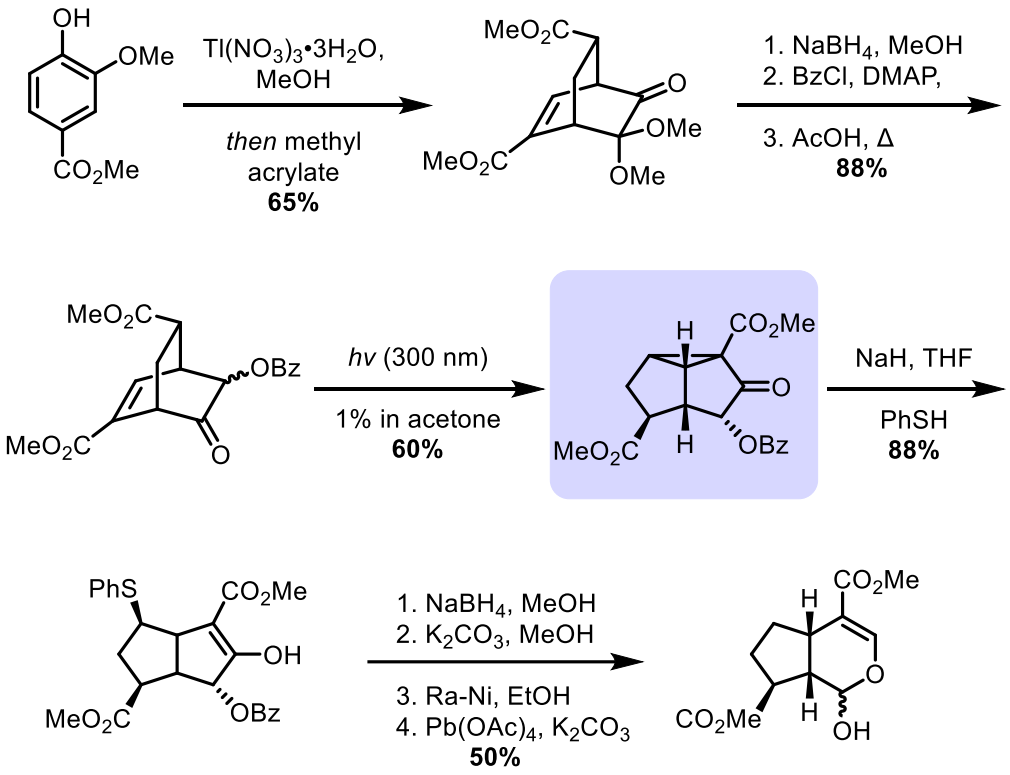
The triplet state chemistry of bicyclo[2.2.2]octenones is perhaps more widely explored, and has been employed in the synthesis of multiple diquinane containing natural products.[137,156,157] Triplet sensitized reactions of bicyclo[2.2.2]octenones consist of oxa-di-π-methane rearrangements. This is a variant of the di-π-methane rearrangement, whereby photoexcitation of the β,γ-unsaturated ketone facilitates α-scission of the C-O bond and subsequent radical recombination to an α-cyclopropane (Scheme 105).[158]



Scheme 105: The oxa-di-π-methane rearrangement in the context of bicyclo[2.2.2]octenones.

An example of this triplet chemistry in natural product synthesis is the racemic preparation of forsythide aglucone dimethyl ester. In this synthesis, Liao shows that irradiation of the parent bicyclo[2.2.2]octenone in the presence of acetone (as a photosensitiser) provides the diquinane in a 60% yield. The target natural product is then furnished by initial ring opening of the cyclopropane using sodium hydride and phenyl silane to afford an intermediate enol. Reduction of the enol and removal of the aryl sulfide with Raney nickel provides a diasteromeric diol, and final treatment with $Pb(OAc)_4$ furnishes (±)-forsythide.

Liao, 1988



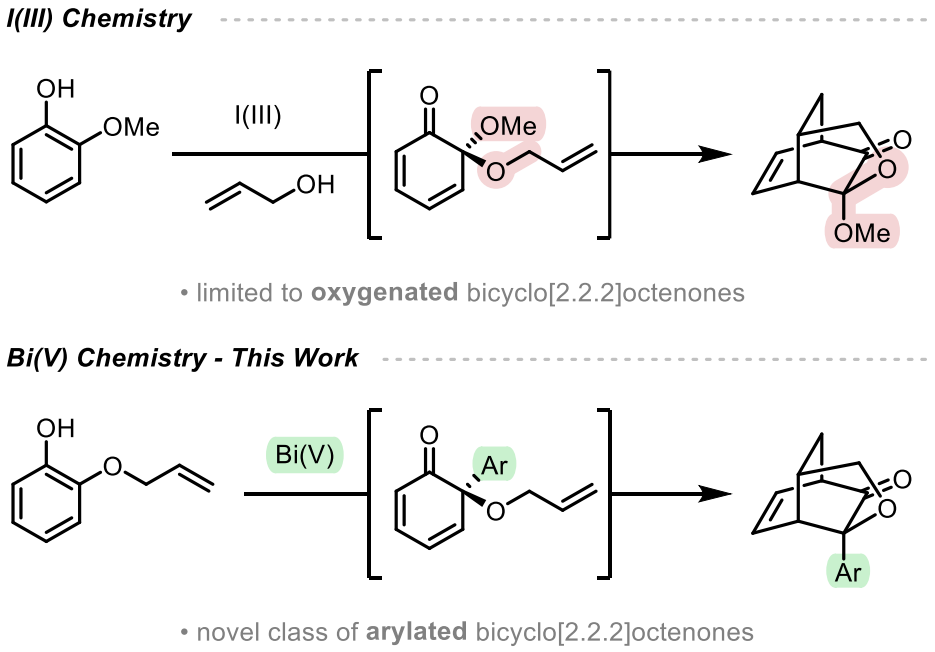
Scheme 106: oxa-di-π-methane rearrangements of bicyclo[2.2.2]octenones in total synthesis: preparation of a diquinane as a target iridoid precursor.[136]

It is clear that the bicyclo[2.2.2]octenone core offers a whole host of stereochemically defined transformations, however, all the above methods prepare the cyclohexadienone *via* an alkoxylative dearomatisation. As discussed throughout this thesis, there is a reliance on I(III) chemistry in the synthesis of cyclohexadienones, and very few non-oxygenative transformations are available. In turn, this severely limits the variety of bicyclo[2.2.2]octenone derivatives that can be designed. The following section of this chapter will explore an alternative disconnection in this context *via* the Bi(V) mediated arylative dearomatisation of phenols, en route to a novel class of arylated bicyclo[2.2.2]octenone scaffold.

3.2. Project Proposal

In this thesis, the synthetic community's reliance on I(III) chemistry for the preparation of cyclohexadienones and its derivatives has been discussed. In Chapter I, a more contemporary and alternative Bi(V) oxidant for this chemistry was introduced, and in Chapter II, a successful Bi(V) mediated oxidative dearomatisation of 2-alkoxy phenols was reported.

With the preceding understanding of this work, this 3rd chapter reports on an alternative route to the bicyclo[2.2.2]octenone scaffold. We propose a Bi(V) mediated oxidative arylation of 2-allyloxy phenols towards novel allyloxyl cyclohexadienone intermediates. The intramolecular Diels-Alder reactions of these cyclohexadienones to novel aryl-bicyclo[2.2.2]octenones is presented herein.



Scheme 107: I(III) chemistry in 6-allyloxy-cyclohexadienone synthesis. Proposed Bi(V) route - This work.

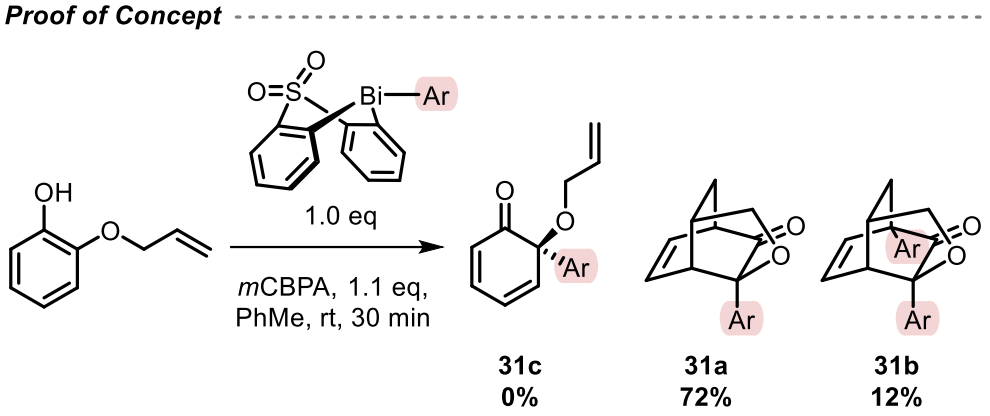
On the preparation of a 6-allyl-cyclohexadienone using I(III) chemistry, the allyloxy group is introduced as the nucleophile in the dearomatisation. We propose an alternative disconnection where the allyl tether is incorporated into the phenolic starting material (i.e 2-allyloxy phenol); this directs the electrophilic arylation to the *ipso*-position. As with the chemistry discussed in Chapter II, the

proposed Bi(V) route offers an alternative C-C disconnection, rather than the typical oxygenative methods using I(III)-based manifolds.

This section will begin by reporting the serendipitous discovery of bicyclo[2.2.2]octenone formation using Bi(V) chemistry. Following this, a substrate scope with respect to variation of the (i) introduced arene, (ii) allyl group, and (iii) phenol will be conducted. To showcase the utility of these bicyclo[2.2.2]octenones in synthesis, we report on multiple routes of diversification *via* simple functional group interconversions.

3.3. Reaction Discovery

In Chapter II, the compatibility of various 2-alkyloxy phenols in the dealkoxylative arylation protocol was investigated. In this study, the 2-allyloxy group was tested. Rather than providing the anticipated 6-allyl-cyclohexadienone, the bicyclo[2.2.2]octenone **31a** was characterised instead.

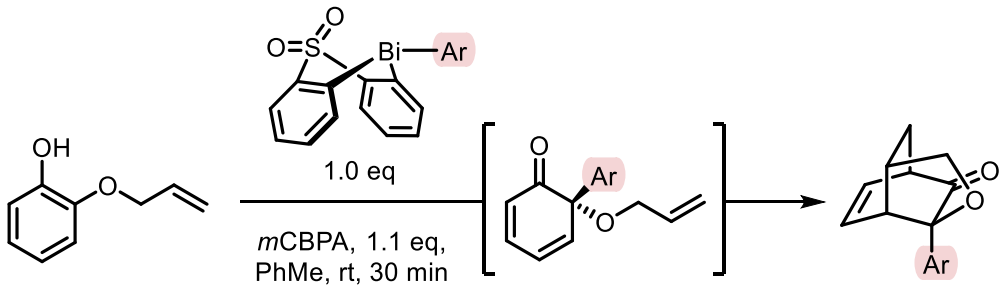


Scheme 108: Bi(V) mediated dearomatisation of 2-allyloxyphenol: serendipitous discovery of a novel bicyclo[2.2.2]octenone.

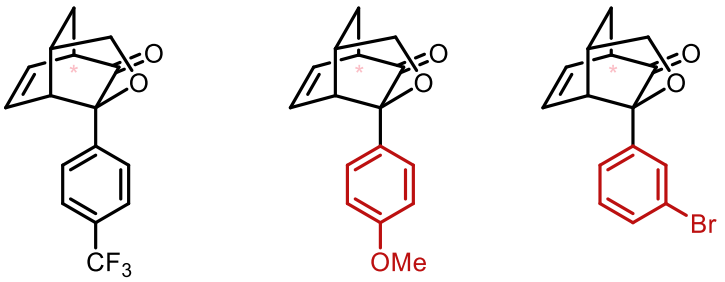
In this reaction, 72% of the bicyclo[2.2.2]octenone is present at 30 minutes, with no detectable amount of cyclohexadienone. This yield is comparable to that of the dearomatisation of guaiacol using the same aryl bismacycle (*c.f.* 74%), indicating that the cycloaddition is fast and quantitative and that the arylation proceeds equally efficiently *ipso* to an allyloxy or a methoxy substituent. This analysis is mirrored upon observation of the diaryl-bicyclo[2.2.2]octenone (**31b**) derived from the cycloaddition of the diaryl-cyclohexadienone. This compares to the guaiacol dearomatisation, where the yield of diaryl-cyclohexadienone is 12%.

This led us to question if the preparation of these cyclohexadienones and the resultant cycloaddition exhibits generality. As such, a short, NMR-scale screen was conducted, in which three electronically varied aryl bismacycles were applied to the oxidative arylation of 2-allyloxy phenol. In addition, two variants of the allyoxy group were tested: 1,3-dimethyl allyloxy and homoallyloxy analogues (Scheme 109). These were tested to assess if there is any diastereoinduction at the electrophilic arylation, and limitations of chain length on the cycloaddition, respectively.

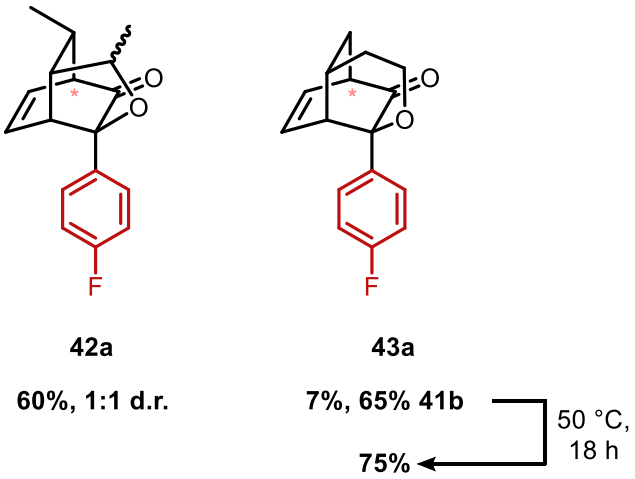
Proof of Concept: contd



Assessment of generality (NMR Scale)



	39a	**40a**	**41a**
	85%	**73%, 10% di**	**82%, 10% di**
c.f. guaiacol chemistry	77%	55%	77%



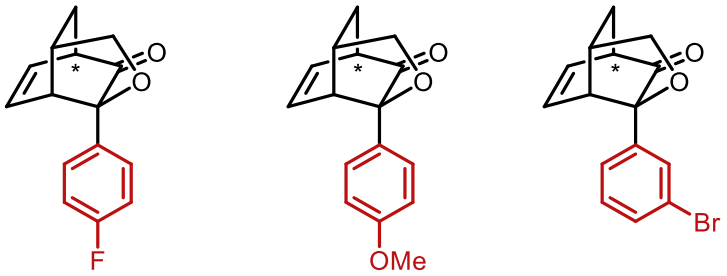
42a	**43a**
60%, 1:1 d.r.	**7%, 65% 41b**
	75%

Scheme 109: Short assessment of generality for the synthesis of aryl-bicyclo[2.2.2]octenones.

Pleasingly, it was observed that this dearomatisation-cycloaddition protocol does exhibit generality with respect to the arene and allyoxy group. It is interesting to note that on variation of the aryl bismacycle, formation of the cycloadducts **39a-41a** were higher than that of the comparable guaiacol dearomatisation. This apparent higher yielding dearomatisation is not fully understood.

Dearomatisation of the homoallyloxy phenol affords 65% of the cyclohexadienone **43b** and 7% of the bicyclo[2.2.2]octenone **43a**. The fact that some bicyclo[2.2.2]octenone was present at 30 minutes led to the conclusion that the cycloaddition is slow by virtue of the longer chain length. By heating the crude reaction mixture to 50 °C overnight, the **43b** completely converges to 72% of the bicyclo[2.2.2]octenone. In the case of the 1,3-dimethyl allyloxy phenol, the reaction provides 60% yield of a 1:1 mixture of the two diastereoisomers of **42a**, indicating that there is no facial selectivity in the electrophilic arylation of the chiral phenol.

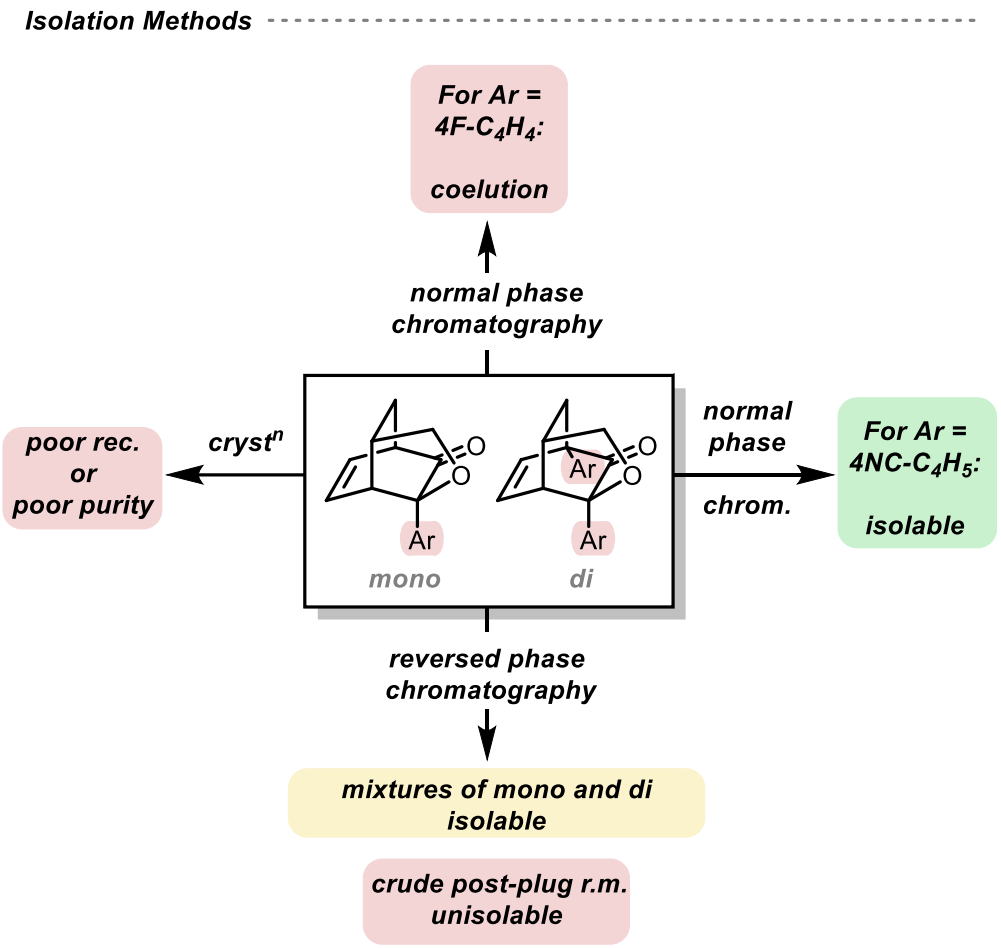
Scope and Isolation



31a, 31b*	**40a, 40b***	**41a, 41b***
72% (31a)	60% (40a)	90% (41a)
58% 31a:31b (1:10)	**44% 40a:40b (1:10)**	**72% 41a:41b (1:10)**

Scheme 110: Attempts at isolation of varied bicyclo[2.2.2]octenone complexes. Yields in grey represent NMR yields; yields in black are isolated. NMR Yields determined *via* quantitative ^{19}F or ^{1}H NMR spectroscopy.

At this point, we sought a general isolation method. In the first instance, the technique used to remove the bismacycle benzoate co-product in the previous methodology (see Chapter II) was applied to model compound **31a**. Subsequent purification using column chromatography frustratingly revealed significant coelution with the diaryl-bicyclo[2.2.2]octenone **31b**. Only very minimal separation could be observed with alternative column conditions. It was hoped that this problematic coelution would not occur for different entries in the investigation of substrate scope. However, all of the aryl bismacycles repeated from the initial screen afforded consistent results.

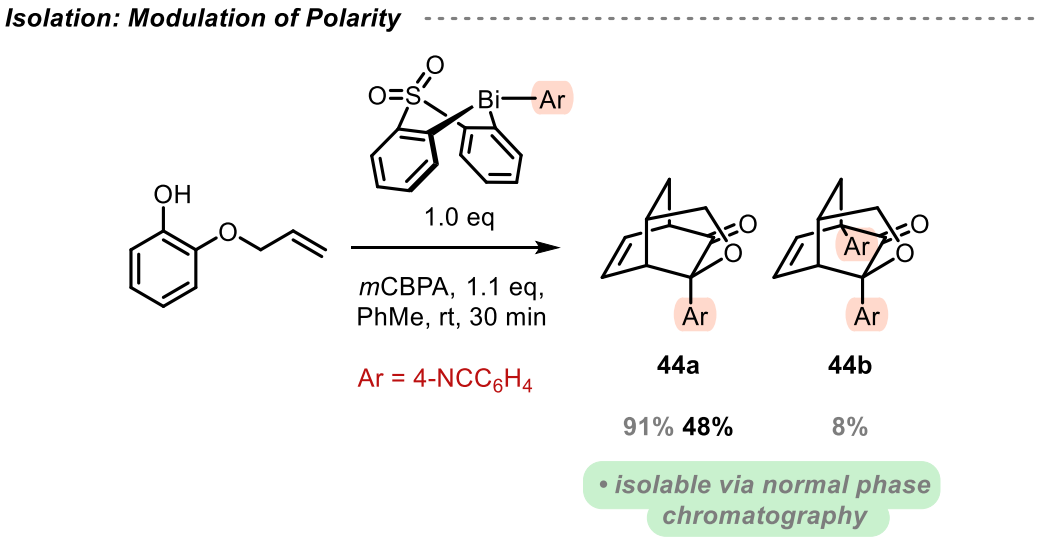


Scheme 111: Tested methods of isolation of the bicyclo[2.2.2]octenone. Reversed phase chromatography refers to C-18 functionalised silica gel.

Alternatives to standard chromatography were sought in efforts to isolate the single mono aryl-bicyclo[2.2.2]octenone. Initially, it was considered that the mono-product may crystallize from a suitable solvent mixture, given that it typically constitutes 90% of the crude mixture. Combinations of minimal DCM with cyclohexane or pentane were attempted; these were promising in their purity, but lacked mass recovery. Crystallization from hot ethanol provided a co-crystalline mixture of the same two species.

The two bicyclo[2.2.2]octenones are minimally different with respect to their polarity, or lack thereof. Therefore, it was considered whether they could be separated using reversed phase column chromatography. Pleasingly, a clean sample of mono and diaryl-bicyclo[2.2.2]octenone was found to be separable in mixtures of MeCN and water. To our discontent, however, direct treatment of the post-plug reaction mixture to reversed phase chromatography did not lead to facile isolation of the desired bicyclo[2.2.2]octenone.

Further consideration of relative polarity led to the idea that polar substituents on the introduced *via* arylation (for example, a cyano group) may enable facile separation. More explicitly, if a polar substituent is present on the arene, then crudely, the diaryl-bicyclo[2.2.2]octenone would exhibit a significantly higher polarity, and should be separable using standard phase chromatography. To our delight, the oxidative arylation-cycloaddition reaction using a *para*-cyanophenyl bismacycle furnishes the two mono (**44a**) and diaryl (**44b**) bicyclo[2.2.2]octenones which are isolable using simple cyclohexane/ EtOAc solvent systems (Scheme 112). It was then decided that the phenolic moietiy could be varied in a full substrate scope while using the *para*-cyanophenyl aryl bismacycle.

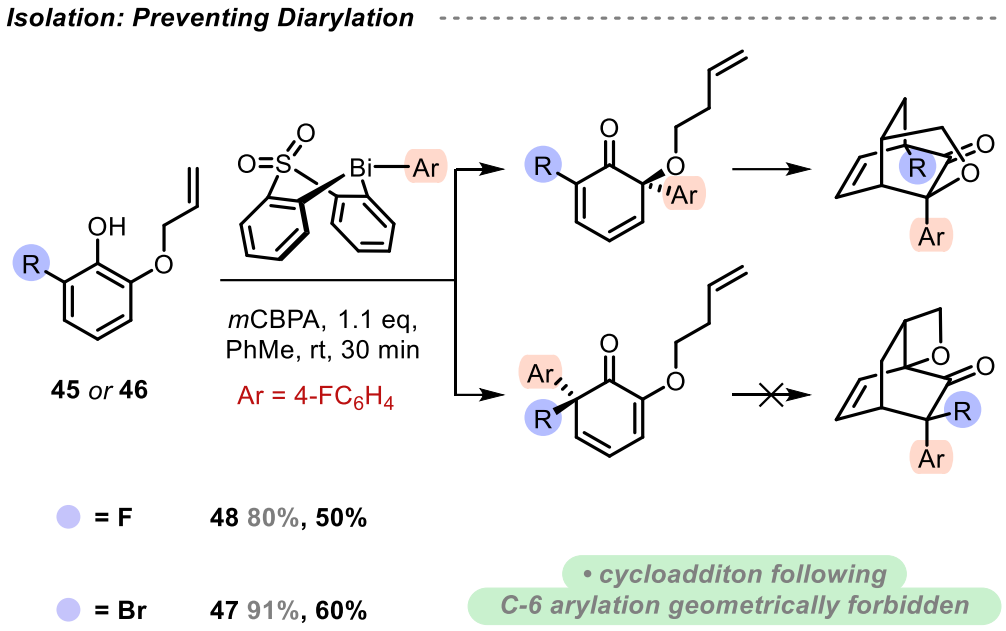


Scheme 112: Successful isolation of mono and diaryl-bicyclo[2.2.2]octenone using Ar = 4-CNC_6H_4. Yields in grey represent NMR yields, yields in black represent isolated yields.

For variation of the phenolic component, our attention moved away from solving the separation problem, and towards halting the formation of the diaryl bicyclo[2.2.2]octenone altogether. It was considered that a 6-EWG substituted allyloxy phenol may be an ideal candidate for this. In theory, oxidative arylation should occur *ipso* to the more electron-donating allyloxy group, thus undergoing the cycloaddition to the bicyclo[2.2.2]octenone.

If addition occurs *ipso* to the electron-withdrawing group, the subsequent cycloaddition will be disfavoured due to formation of the strained 4- membered ring (Scheme 113). As such, the 6-bromo (**45**) and 6-fluoro 2-allyloxyphenols (**46**)

were tested as possible phenolic partners in the dearomatisation-cycloaddition protocol.



Scheme 113: Hindering diarylation by using 6-EWG allyloxyphenols. NMR Yields (grey) determined *via* quantitative ^{19}F spectroscopy against internal standard.

Pleasingly, selectivity for arylation *ipso* to the allyloxy is high in both cases, and the isolation of the bicyclo[2.2.2]octenone is feasible using standard chromatography. Interestingly, the reaction with the 6-fluoro substrate affords a small amount of homo-dimer. It is possible that the fluorine substituent marginally accelerates the Diels-Alder reactions allowing the dimerization to become competent, however this has not been further investigated.

Owing to the higher yield associated with the 6-bromo analogue and absence of dimerization, variation of the arene was tested using this phenolic partner. As such, the next section of this chapter will report on the wider substrate compatibility using these second-generation phenol and arene partners.

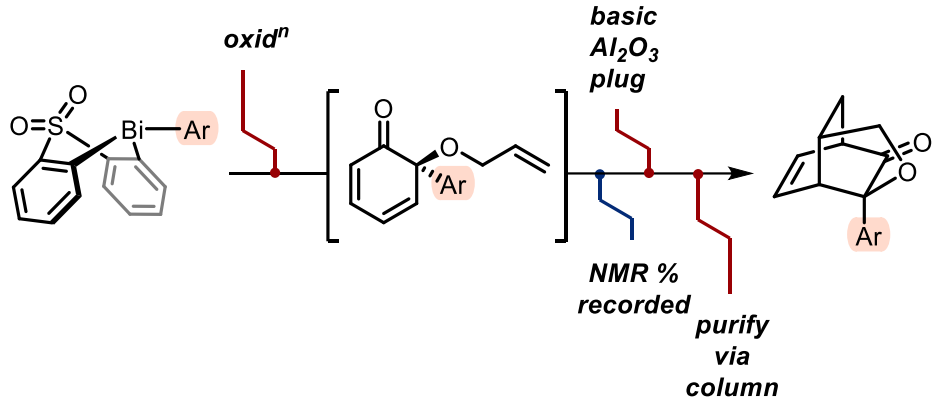
3.4. Substrate Scope

An investigation of substrate scope was designed to explore the compatibility of this transformation with sterically and electronically diverse functional groups. This was achieved by altering the arene originating from the aryl bismacycle, the phenolic core, and the allyloxy group. In this assessment, it was decided that aliquots of the post-dearomatisation reaction mixture would be analysed by NMR spectroscopy to record an *in situ* yield. This was decided for two reasons:

(i) to monitor if any cyclohexadienone is present at t = 0.5 h indicating a slow Diels-Alder reaction, and if this converts to bicyclo[2.2.2]octenone over longer time periods.

(ii) to infer any electronic or steric dependency on the dearomatisation or cycloaddition, as *in situ* yields generally do not translate directly to isolated yields.

Reaction Procedure

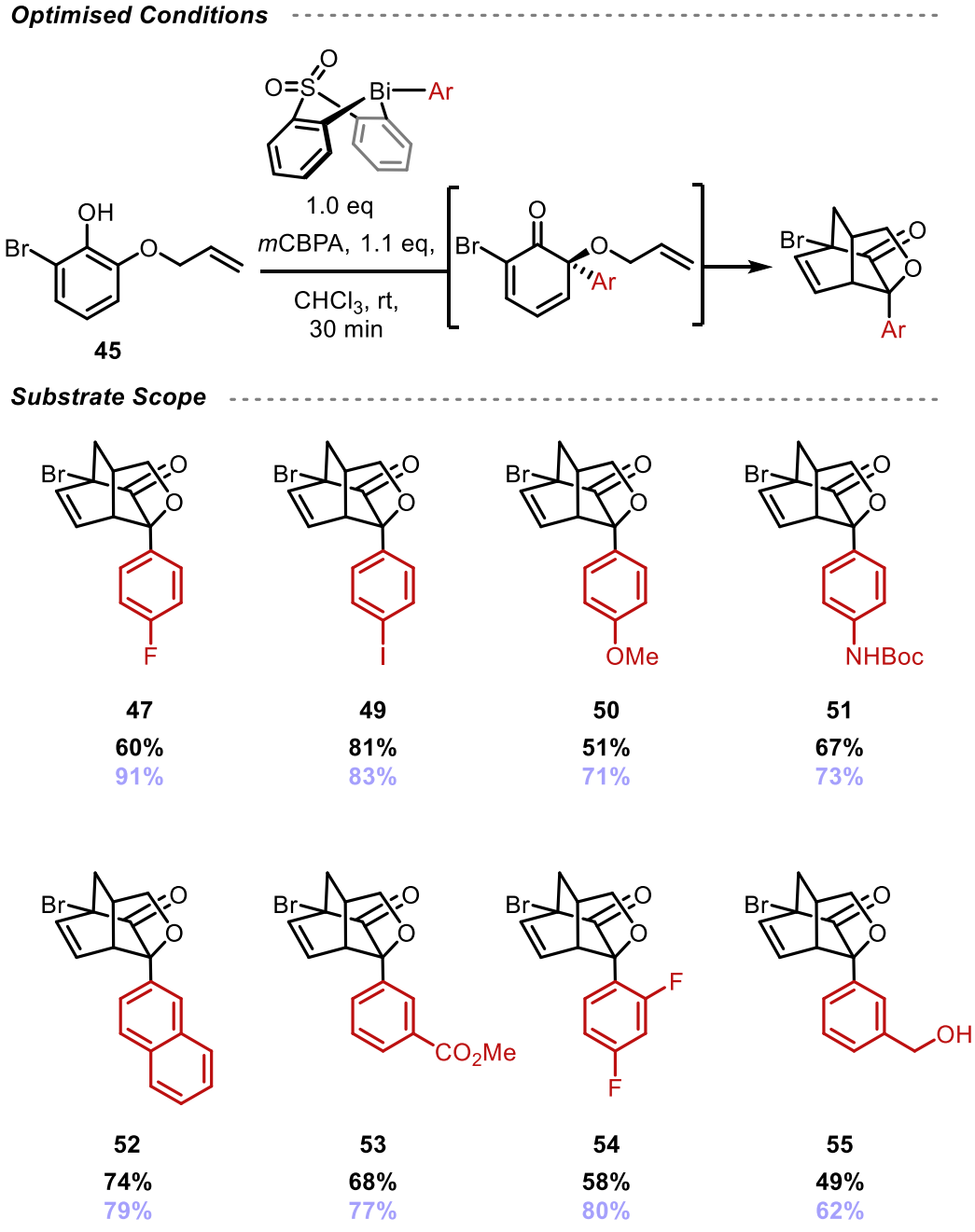


Scheme 114: Oxidative arylation-Diels Alder reaction sequence.

To clarify the design of the forthcoming scope, 6-bromo-2-allyloxy phenol serves as the phenolic partner for variation with respect to the introduced arene. The *para*-cyanophenyl bismacycle serves as the arene partner with respect to variation of the allyloxy group and the phenolic core to which it is bound.

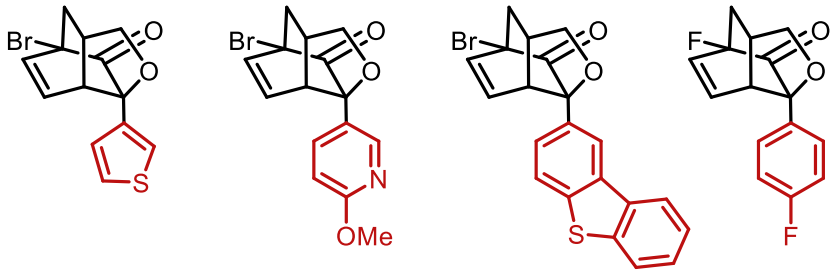
Variation of Aryl Bismacycle

The developed oxidative arylation-cycloaddition protocol exhibits good compatibility using the 6-bromo-2-allyloxy phenol **45** with electronically and sterically varied aryl bismacycles. Pleasingly, the array of bicyclo[2.2.2]octenones are simple to isolate using standard chromatographic techniques.



Scheme 115: Variation aryl bismacycle towards oxidative arylation-IMDA reaction. NMR yield (blue); isolated yield (black). Yields determined by NMR spectroscopy vs internal standard.

Substrate Scope: Continued



56	**57**	**58**	**48**
57%	**68%**	**36%**	**50%**
64%	82%	75%	80%

Scheme 116: Continuation of scope: variation of aryl bismacycle. Yields determined by NMR spectroscopy vs internal standard.

If we assume that the conversion of cyclohexadienones to bicyclo[2.2.2]octenones is quantitative, then we can determine the success of the oxidative arylation using phenol **45** with Bi(V) reagents. Using this assumption, it is clear that the **45** guaiacol using the same aryl bismacycles in the synthesis of intermediate cyclohexadienone.

Considering the two possible sites for arylation, it is likely that the addition of the electron-withdrawing halide disfavours C-6 arylation more than that of an unsubstituted C-H. By disfavouring this competing pathway, C-2 arylation (*ipso* to allyloxy) becomes the predominant process. This improved selectivity is particularly pronounced when we compare the arylation of the two phenols with the *para*-methoxy phenyl bismacycle (**50,** 71%, *c.f.* 55% with guaiacol.)

In addition to the higher yielding formation of transient cyclohexadienone, this methodology appears to exhibit higher functional group compatibility compared to the Bi(V) mediated dearomatisation of guaiacol. For example, introduced arenes bearing esters (**53**), protected anilines (**51**) and aliphatic alcohols (**55**) are all well tolerated.

An altered work up procedure has made the isolation of the 4-methyoxypyridyl bicyclo[2.2.2]octenone, **57** feasible. Previously, this group was a problem due to the heterocycle instability with respect to basified alumina, which was a necessary step in removing the bismacycle benzoate co-product. In this chemistry, base washes (*i.e.* sat. aq, $NaHCO_3$) were sufficient in removing the bismacycle benzoate, thus enabling facile purification of the product *via*

subsequent column chromatography. As well as this pyridyl example, other heterocycles are compatible with this protocol, including thiophenes (**56**) and dibenzothiophenes (**58**).

It is also interesting to note that the dearomatisation using 2,4-difluorophenyl bismacycle is high yielding in this procedure (**54**), whereas the reaction with guaiacol yields only 45% of the cyclohexadienone. *Ortho*-substituted arenes usually display poor reactivity due to the steric strain which accompanies the Bi(V) intermediate prior to reductive elimination. Indeed, this is perhaps the first successful example using an *ortho*-substituted phenol in the Bi(V)-mediated arylation of phenols.

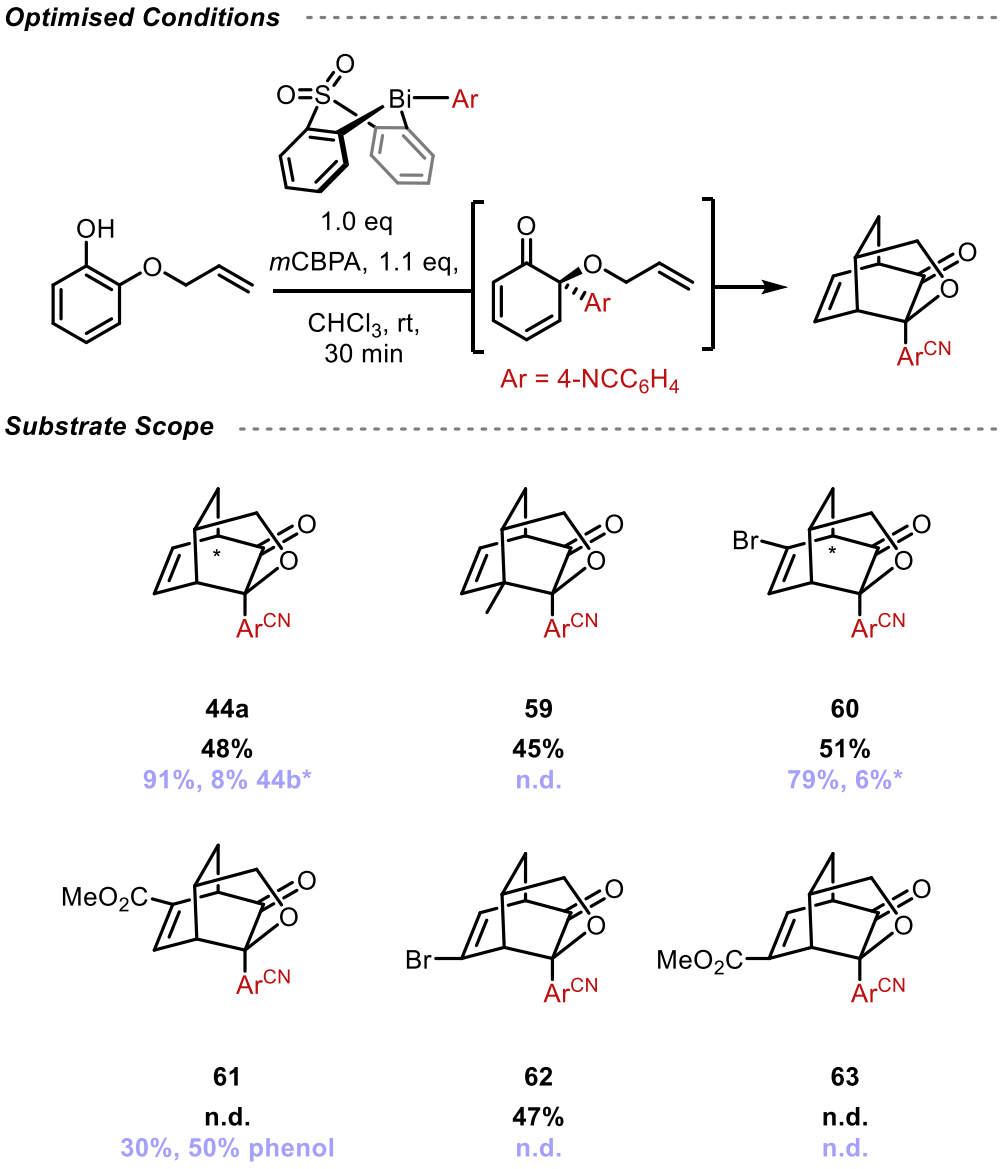
Variation of Allylic Chain and Phenol

In this investigation of substrate scope, the *para*-cyano phenyl bismacycle is tested with various allyloxy phenols diversified at the ring and olefin. In this system where we have an electron-withdrawing arene partner and phenol that is not di-*ortho*-substituted, similar conclusions can be drawn from those in Chapter II:

- electron-withdrawing aryl bismacycles give higher yields of cyclohexadienone than their electron-donating counterparts;
- the yields of the cyclohexadienone / bicyclo[2.2.2]octenone when the phenolic ring is substituted are more nuanced. This can be attributed to the variation in cyclohexadienone stability depending on what substituents are bound to its core.

While the second point is observed with 2-allyloxy phenols, it is not so pronounced as in the case of guaiacol dearomatisation. For example, 6-substituted guaiacols were found to undergo rapid homo-dimerization reactions, whereas this half of this scope hinges on 6-substituted phenols for the sake of practical isolation. Some substituted guaiacols were also found to undergo photodecomposition and hydrolysis. While some of these pathways may be competitive in this chemistry, there is an entropically more favourable intramolecular cycloaddition which will very likely outcompete.

Substituents on the 4- and 5- positions furnish the bicyclo[2.2.2]octenone in good yields, with the exception of the methyl benzoates. These are accompanied with low (**61**) or no (**63**) yield of bicyclo[2.2.2]octenone, where analysis of the post-arylation reaction mixture of the former reveals unreacted phenol. 4- and 5-bromo substituted phenols provide the respective bicyclo[2.2.2]octenones **62** and **60** bearing vinyl bromide moieties: useful handles for further diversification.

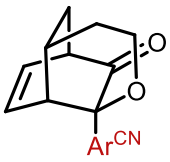


Scheme 117: Variation of phenol and dienophile towards oxidative arylation-IMDA reaction. NMR yield (blue); isolated yield (black).

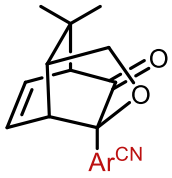
Substrate Scope, continued



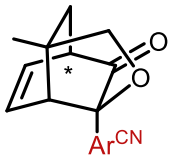
64
49%
0%, 50% CHD
50%[a], 0%[a] CHD



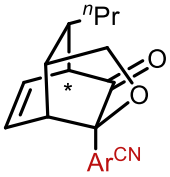
65
43%
0%, 60% CHD
60%[b], 0%[b] CHD



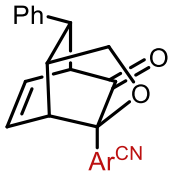
66
45%
66%



67a
45%
53%, 14% 67b*



68a
59%
62%, 10% 68b*



69
53%
n.d.

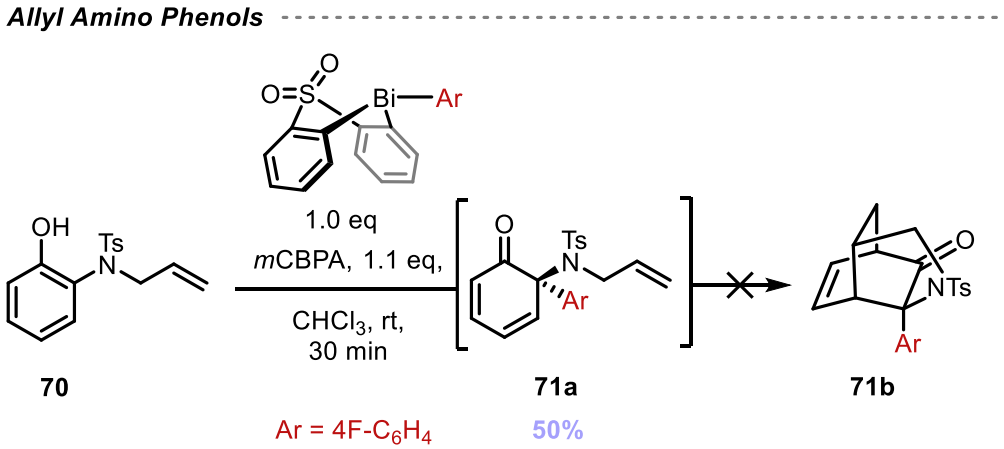
Scheme 118: Continued. [a]Reaction mixture stirred at rt for 18 h; [b]Reaction mixture heated to 50 °C for 18 h. CHD = intermediate cyclohexadienone.

It is interesting to note that dearomatisation of the 4-methoxy phenol affords a mixture of cyclohexadienone and bicyclo[2.2.2]octenone **64**. By leaving the reaction mixture for 18 h at rt, the cyclohexadienone converges to the **64**. This slower cycloaddition can be attributed to the increased electron density the methoxy group imparts on the dienic cyclohexadienone. This reduced reactivity is consistent with Liao's observations, where electron-donating groups on the 4-position behave less dienophilic, and more dienic, towards external dienes.[140]

Substituents on the dienophile present good compatibility with this protocol. Mono and disubstituted alkenes **67a** and **66** perform well, in addition to both *E*- and *Z*-olefins **68a** and **69**. In both cases, stereochemistry is retained as expected in Diels-Alder reactions. The homoallyloxy phenol undergoes a facile Diels-Alder reaction when heated to 50 °C for 18 h, thus furnishing the THP fused bicyclo[2.2.2]octenone **65**.

We were interested in extending this methodology to *ortho*-allylamino phenols in addition to allyloxy phenols. As such, our protocol was applied to amino phenol **70**. Dearomatisation of **70** afforded 50% cyclohexadienone **71a**, however

no cycloadduct was observed. (Scheme 119). This was monitored using ^{19}F NMR spectroscopy in the presence of internal standard.

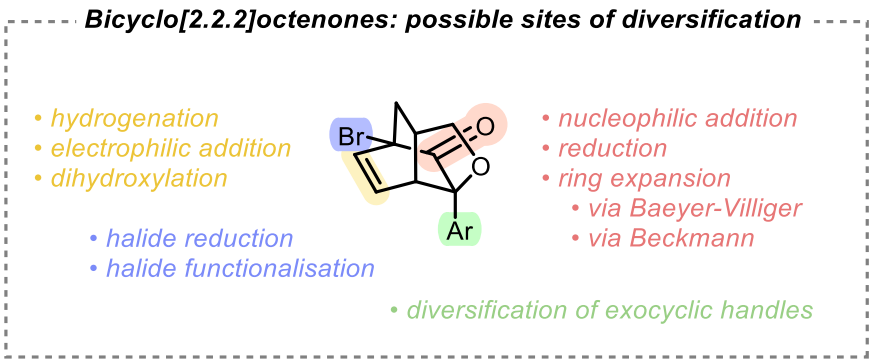


Scheme 119: Dearomatisation and cycloaddition attempts using allyl amino phenol

In order to facilitate cycloaddition, the cyclohexadienone was left to stir overnight at 80 °C which unfortunately led to no bicyclo[2.2.2]octenone **71b**; stirring the cyclohexadienone at 120 °C led to decomposition. This reluctance toward cycloaddition may be due to the steric hindrance imposed by the tosyl group that is bound to nitrogen. Alternative allyl amino phenols may be more fruitful in this endeavour, however they are yet to be tested.

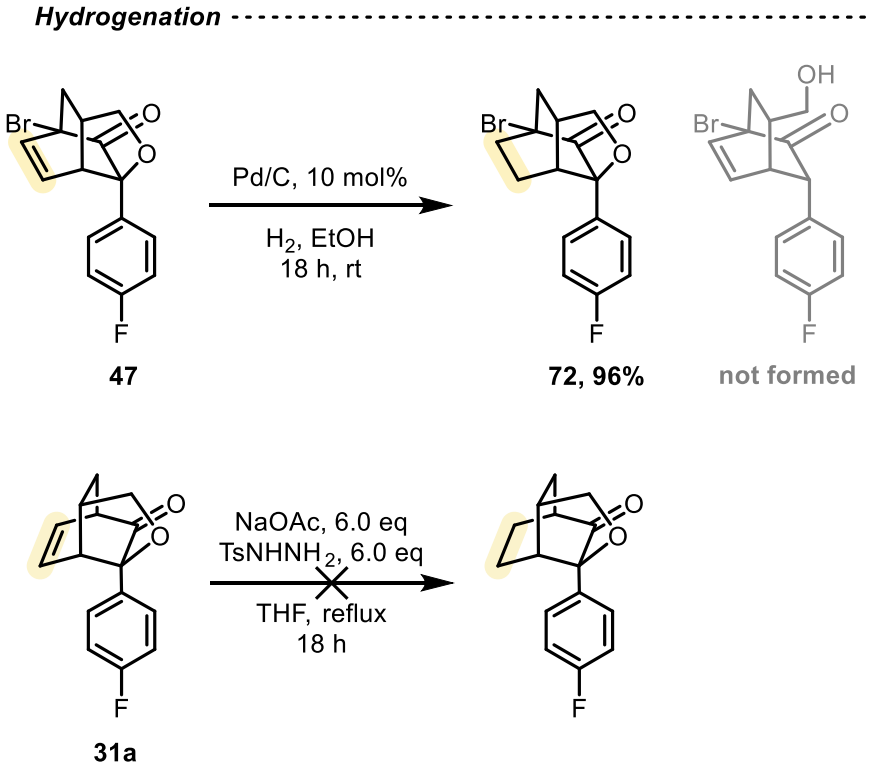
3.5. Diversification

As introduced to this chapter, the bicyclo[2.2.2]octenone framework is rich in handles for further diversification (Scheme 120). Various analogues of this scaffold may be accessed *via* the functionalisation of the olefin, carbonyl, bromide or introduced arene. Achieving these bicyclo[2.2.2]octenone analogues serves the purpose of showcasing its reactivity, and therefore its possible utility in natural product synthesis. This investigation is currently an ongoing area of research in this project, and so an up-to-date account of tested reactions will be reported. To preface this discussion, the model compound shown in Scheme 120 and the *des*-bromo analogue are used to explore the scope of bicyclo[2.2.2]octenone reactivity.



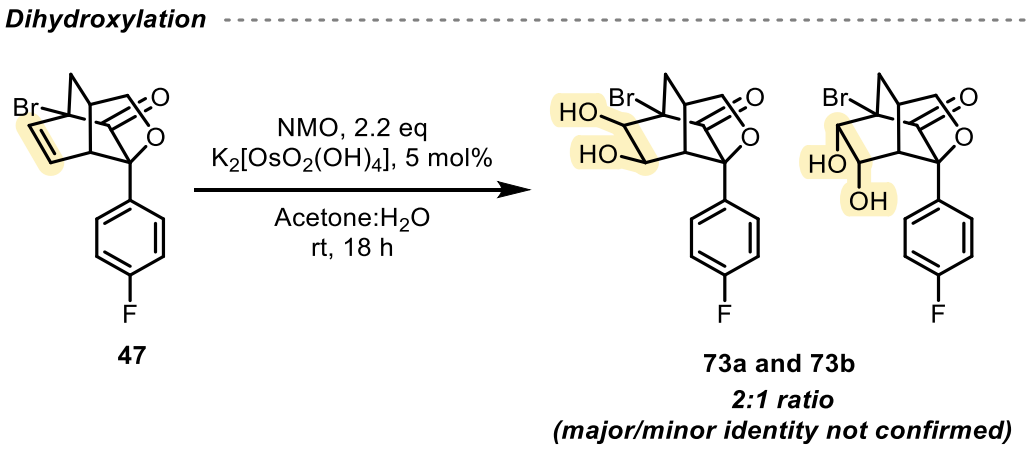
Scheme 120: Possible sites of diversificaiton to the bicyclo[2.2.2]octenone.

In the first instance, reduction of the olefin was investigated to access the bicyclo[2.2.2]octanone. It was acknowledged that hydrogenation of the bicyclo[2.2.2]octenone using palladium on carbon may result in competitive reduction at the benzylic position, thus opening the 5 membered ring (Scheme 121). Pleasingly, the reaction of **47** affords near quantitative conversion to the saturated bicyclo[2.2.2]octanone **72**, with no observed reduction at the benzylic position. Application of these conditions to the *des*-bromo analogue also reveals bicyclo[2.2.2]octanone formation, however this has not been quantified. An alternative route to reduction of the olefin **31a** was attempted *via* a diimide reduction, however only unreacted starting material could be identified from the reaction mixture.



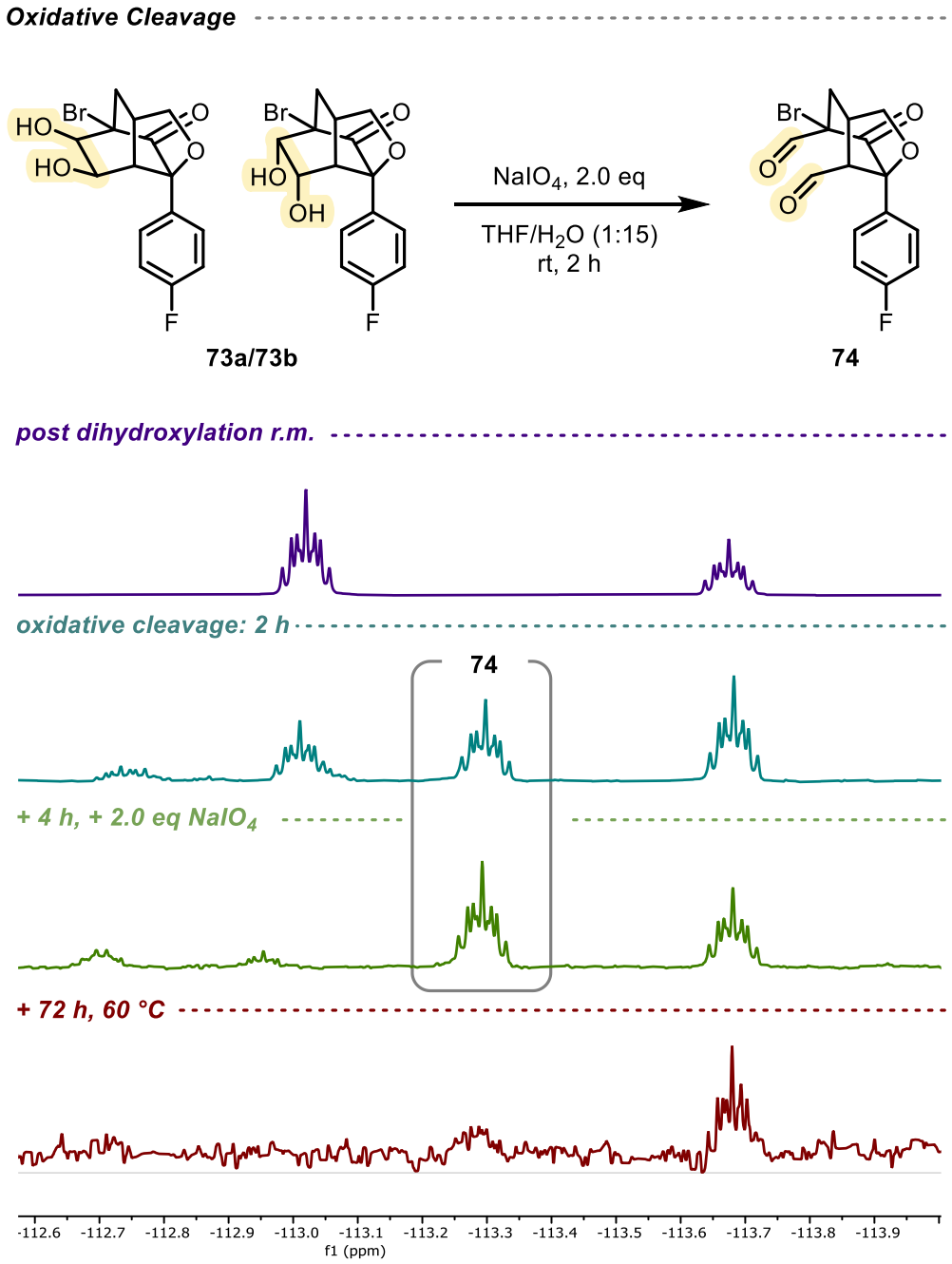
Scheme 121:Bicyclo[2.2.2]octanone formation *via* hydrogenation.

Next, functionalization of the olefin was sought. A dihydroxylation-oxidative cleavage sequence was investigated to ultimately furnish the dialdehyde: a possible tropone precursor following a double reductive amination reaction. Dihydroxylation using NMO and potassium osmate lead to complete consumption of starting material **47**, revealing a 2:1 ratio of diastereoisomeric **73a**/**73b**(identity of major/minor isomer not confirmed).



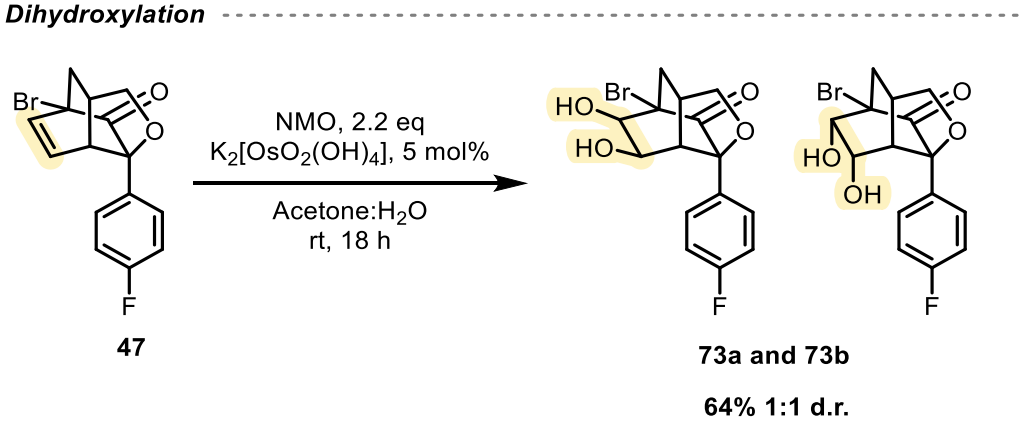
Scheme 122: Dihydroxylation of the bicyclo[2.2.2]octenone.

Treatment of the post dihydroxylation reaction mixture with sodium periodate leads to cleavage of the major diastereoisomer, as characterised by analysis of ^{19}F spectrum (Scheme 123), and presence of aldehydic peaks in the ^{1}H NMR spectrum. Unfortunately, cleavage of the other diastereoisomer is not achieved by extended reaction times, increased equivalents of oxidant, nor increasing the reaction temperature.



Scheme 123: Reaction monitoring of the oxidative cleavage of **73a** and **73b**, indicating the inertness of the minor diastereoisomer to oxidation.

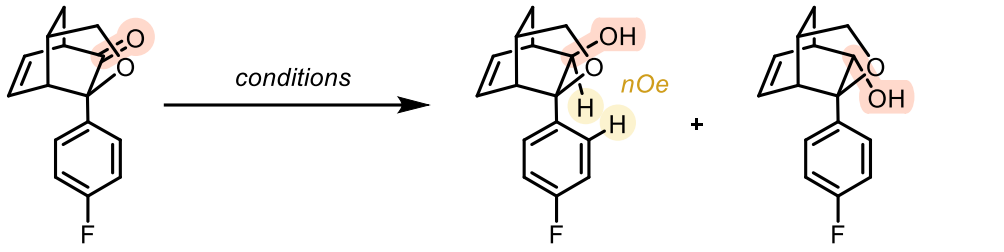
Consequently, the dihydroxylation alone was conducted on **47**, to furnish the diols as an inseparable mixture of diastereoisomers (Scheme 124). It may be possible that dihydroxylation of the *des*-bromo analogue may yield one diastereoisomer capable of undergoing complete oxidative cleavage to the dialdehyde, however this is yet to be tested.



Scheme 124: Isolation of the diastereoisomeric diols.

Next, the reactivity of the carbonyl was explored. This was initiated by investigating the reduction using a hydride source, thus forming the bicyclo[2.2.2]octenol (Scheme 125). Interestingly, the diastereomeric ratio does not vary significantly depending on the presence of the bromide. The predominant diastereoisomer in the instance of the bromo bicyclo[2.2.2]octenone **47** and *des*-bromo analogue **31a** is the product of hydride delivery below the carbonyl, *i.e.* the same face as the arene. This implies that the concave of the bridgehead carbons and the fused 5 membered ring hinders hydride delivery more that of the arene (and in the case of **47**, the bromide), giving rise to **75a** as the major diasteroisomer.

Carbonyl Reduction

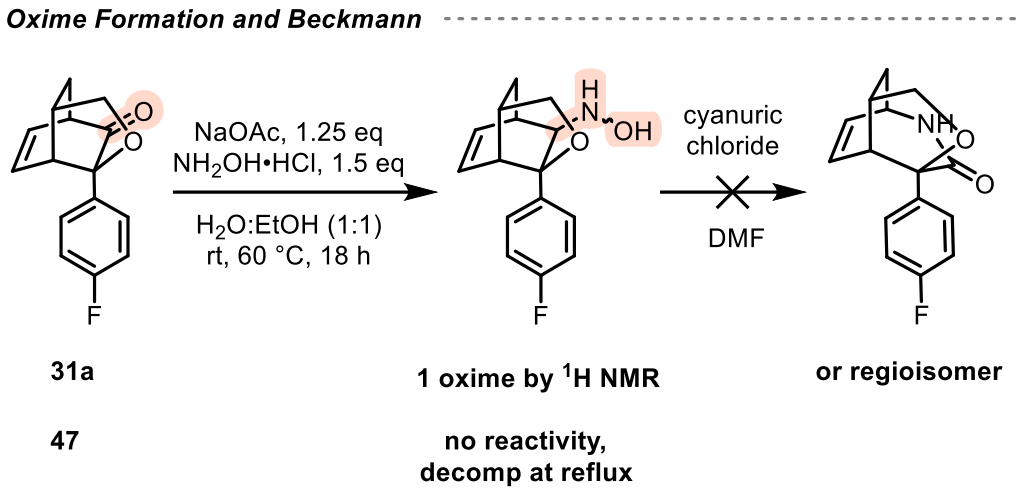


using		75 a *major*		75b *minor*	
31a	$NaBH_4$	2.2	:	1	
31a	K-Selectride	1	:	1	
47	$NaBH_4$	2.0	:	1	97%

Scheme 125: Reduction of the bicyclo[2.2.2]octenone to bicyclo[2.2.2]octenol. Conditions: 1.5 eq $NaBH_4$, MeOH, 0 °C to rt, 3 h OR: K-Selectride, 3.0 eq, THF, -78 °C to rt, 18 h.

K-selectride was considered as an alternative reductant that may improve diastereoselectivity by virtue of its increased steric bulk. It was thought this may bias site selectivity towards what might be the less hindered site, possibly in favour of diastereoisomer **75a**. Unfortunately, its use is associated with lower diastereoselectivity compared to that of $NaBH_4$. No other reductants have been tested as yet, however there it is hoped a screen of alternatives will identify a more selective one.

The addition of hydroxylamines into the carbonyl was briefly investigated, as the resultant oximes may be able to undergo Beckmann rearrangements. (Scheme 126) Condensation of the hydroxylamine onto the *des*-bromo analogue **31a** reveals one product, as indicated by analysis of the ^{1}H NMR spectrum, suggesting that formation of one oxime is favoured over the other. Attempts as the subsequent Beckmann reaction was conducted in cyanuric chloride to generate the Vilsmeir reagent *in situ*, however, the reaction mixture revealed only unreacted starting material.

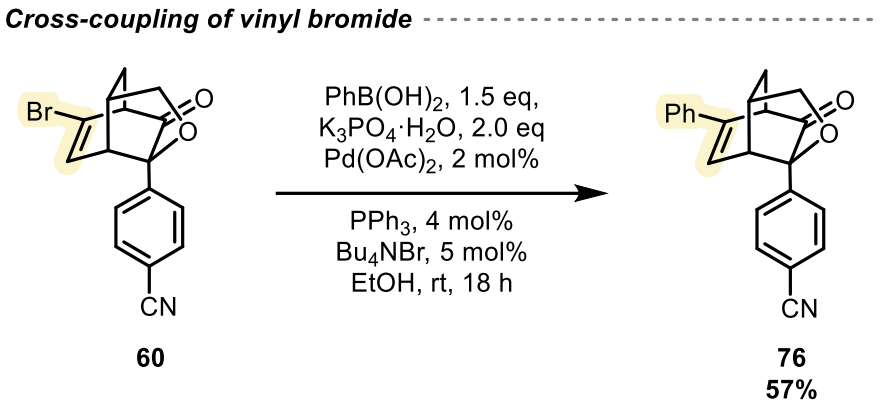


Scheme 126: Condensation of hydroxylamine onto bicyclo[2.2.2]octenone.

Thus far, no attempt to identify the oxime, or alternative routes to Beckmann reaction have been conducted. Use of Lewis acid activated methods, *i.e.* tosyl chloride and NaOH protocols may be more fruitful. Application of the previously used conditions to **47** reveal that condensation of the hydroxylamine requires heating to higher temperatures for longer reaction times in order for the bicyclo[2.2.2]octenone to be consumed. This is likely due to the steric hinderance the bromide imparts on the carbonyl centre. Unfortunately, the requirements of these harsher conditions lead to decomposition of the bicyclo[2.2.2]octenone or product, as characterised by the multiple peaks found in the ^{19}F NMR spectrum.

From these results, it is clear that the more synthetically accessible bromo-bicyclo[2.2.2]octenone **47** is more inert to nucleophilic attack at the carbonyl, which is likely due to the steric hindrance at the α-carbon. A solution to this might be nucleophilic addition at the carbonyl following removal of the bromide using AIBN and $SnBu_3H$, for example. Given that the hydroxylamine can condense onto the *des*-bromo **31a**, it is possible to that larger nucleophiles may be able to add into the carbonyl.

An additional point of diversification is at the vinyl bromide of **60**. This was subject to a Suzuki reaction with phenyl boronic acid, thus furnishing the aryl-bicyclo[2.2.2]octenone **76** in a 57% yield. (Scheme 127).



60 **76** **57%**

Scheme 127: Suzuki reaction of bromo-bicyclo[2.2.2]octenone **60** to aryl bicyclo[2.2.2]octenone **76.**

At present, a small series of reactions have been employed exploiting each functional handle the bicyclo[2.2.2]octenone possesses. Overall, it is clear that the bromo-bicyclo[2.2.2]octenone **47** exhibits a relative inertness towards nucleophilic attack at the carbonyl center, which severely limits the scope of analogues that are accessible using our developed protocol. A route to circumvent this may be removal of the bromide followed by addition of the nucleophile, as discussed. Aside from the poor reactivity at the carbonyl, there are several other challenges to address, including:

- diastereoselective reduction at the carbonyl;
- diastereoselective dihydroxylation, and therefore facile oxidative cleave to furnish the dialdehyde; and,
- further diversifications at the dialdehyde, *i.e.* reductive amination.

In theory, there are endless possible bicyclo[2.2.2]octenone analogues that could be accessed following the sequential diversification at each reactive centre. It is therefore desirable to obtain a general understanding of how to functionalise these products of our protocol, thus showcasing their possible utility in natural product synthesis.

Conclusion

A rapid transformation of simple allyloxy phenols to a novel class of aryl-bicyclo[2.2.2]octenone is reported. This methodology hinges on the successful oxidative dearomatisation of alkyloxy phenols, as reported in Chapter II. In this instance, the arylative dearomatisation of 2-*allyloxyphenol* forms a transient cyclohexadienone, which undergoes a fast Diels-Alder reaction forming an aryl-bicyclo[2.2.2]octenone. The contra-electronic profile of the 2-allyloxy-6-bromo phenol leads to a highly regioselective arylation, in favour of the more electron-donating allyloxy site.

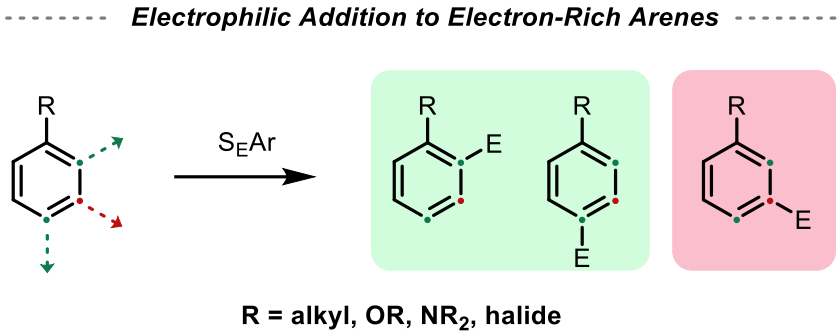
Utility of this Bi(V) mediated arylative dearomatisation enables access a new class of bicyclo[2.2.2]octenone. Crucially, this is constructed *via* arylation of the phenolic core rather than oxygenation using I(III) chemistry. This protocol presents a highly modular route to the bicyclo[2.2.2]octenone, allowing for diversification at the phenolic core, the olefin and the aryl bismacycle. Assessment of substrate compatibility produces a diverse array of aryl bicyclo[2.2.2]octenones, with moderate to excellent yields. Functionalization of the bicyclo[2.2.2]octenone framework has been initiated, and it is evidently possible to access a range of analogous *bicyclo[2.2.2]octane* scaffolds from simple functional group interconversions.

Chapter IV

Phenol Deoxyamination

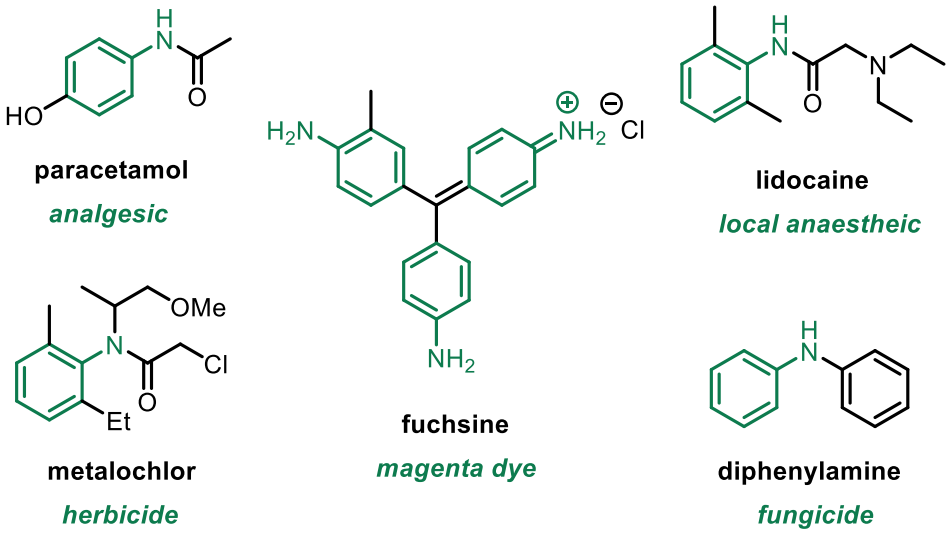
4.1. Introduction

Electrophilic aromatic substitution (S_EAr) is among the most widely employed synthetic tools for the diversification of benzenoid rings. Ever since the pioneering work of Friedel and Crafts, it has been widely established that electron-donating substituents direct incoming electrophiles to the *ortho*- and *para*-positions, while electron-withdrawing groups steer to the *meta*-position.[159] This highly predictable reactivity assists the preparation pharmaceuticals, agrochemicals, and industrial products; however, it inherently limits the diversity of *meta*-substituted, electron-rich arenes.



Scheme 128: Inaccessibility of *meta*-substituted electron-rich arenes *via* S_EAr.

Anilines constitute an important major class of electron-rich arene whose distribution of substituted analogues is highly limited by their electronic profile. Nonetheless, they are vital and well-exploited building blocks towards a wide range of pharmaceuticals, agrochemicals, plastics, electronic materials, dyes, and resins (Scheme 129).



Scheme 129: Diverse application of aniline scaffolds.

Synthetic approaches to *meta*-functionalised anilines are lacking in comparison, however it is clear that these scaffolds possess high potential in their synthetic utility, owing to that of their *ortho*- and *para*- functionalised congeners. Therefore, strategies designed to furnish this substitution pattern are highly desirable in order to fulfil this void in benzenoid chemical space.

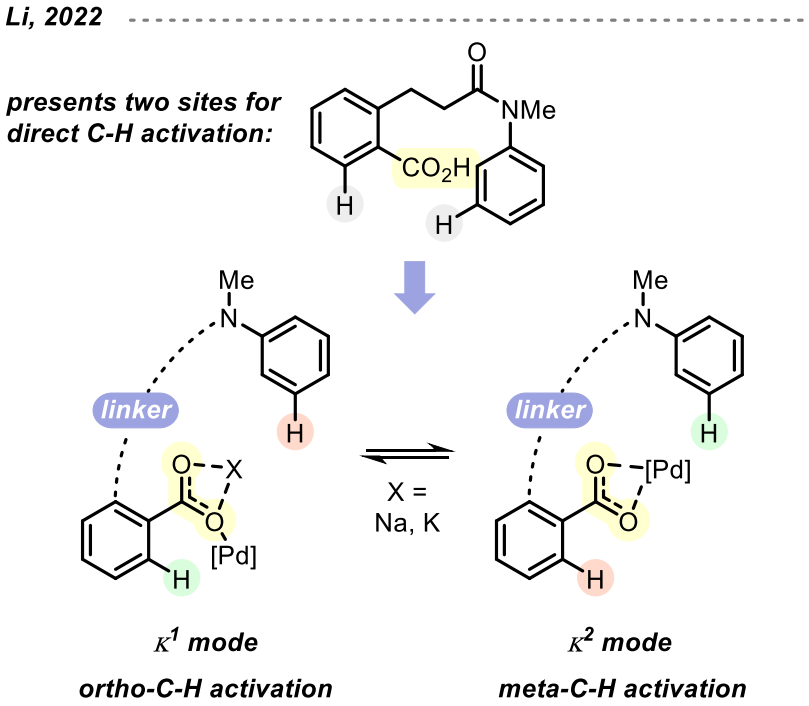
This introduction aims to inform the reader of methodologies available to achieve the *meta*-substitution pattern, particularly in the context of *meta*-arylated anilines. Literature coverage will begin with direct *meta*-C-H activation, before discussing the possible conversions of relatively abundant phenols to anilines. Finally, the dienamine-aniline rearrangement will be introduced; this reaction resembles that of the dienone-phenol rearrangement we have seen previously in (Chapter I). The dienamine-aniline rearrangement in conjunction with phenol deoxyamination are two concepts which have inspired our proposed route towards *meta*-arylated anilines from cyclohexadienone intermediates.

Synthesis of *Meta*-Arylated Anilines

Direct *meta*-C-H-Arylation of Anilines

The *meta*-arylation of aniline is a formal C-H activation. This transformation has been showcased by directing halogenation or arylation to the *meta*-position using specifically designed directing auxiliaries extending from the amine.

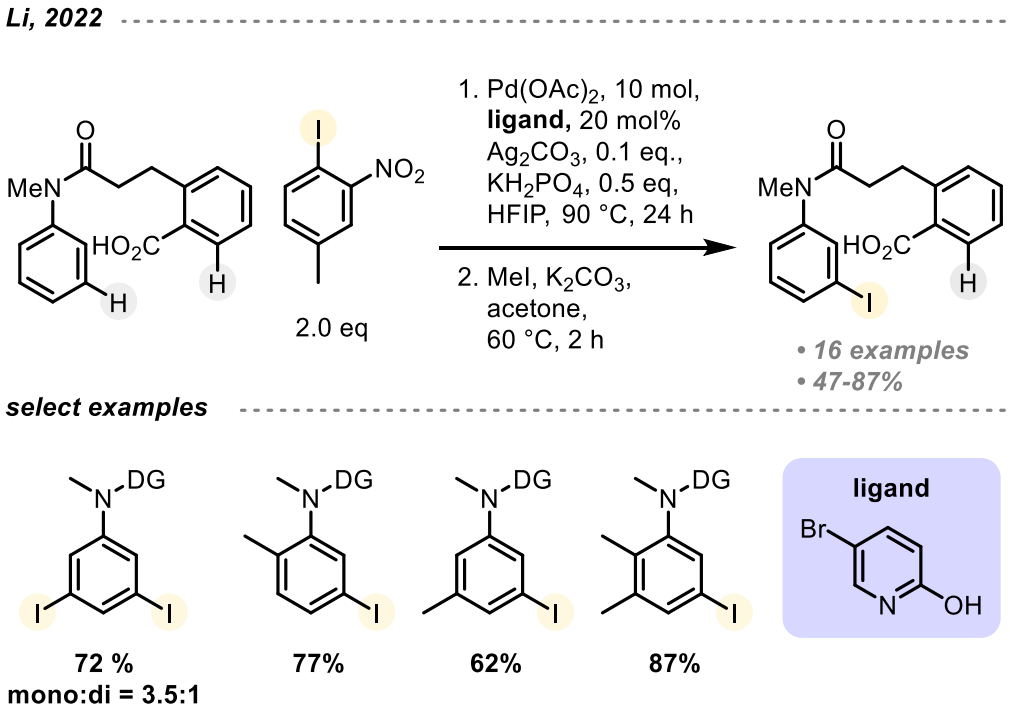
Li recently published a palladium catalysed *meta*-C-H/C-I metathesis between aryl iodides and anilines bearing a distal aryl-carboxyl directing group. The design of this template was explored following its successful application in Li's direct *meta*-C-H olefination of anilides.[160] The aryl-carboxyl functionality can direct iodination to two sites of the molecule: the proton *ortho* to the carboxyl group, and the proton *meta* to the anilide. This can proceed *via* the two coordination modes which may take place between the carboxyl and palladium.



Scheme 130: Carboxy group assisted remote-selective C-H activation through κ² coordination.[161,162]

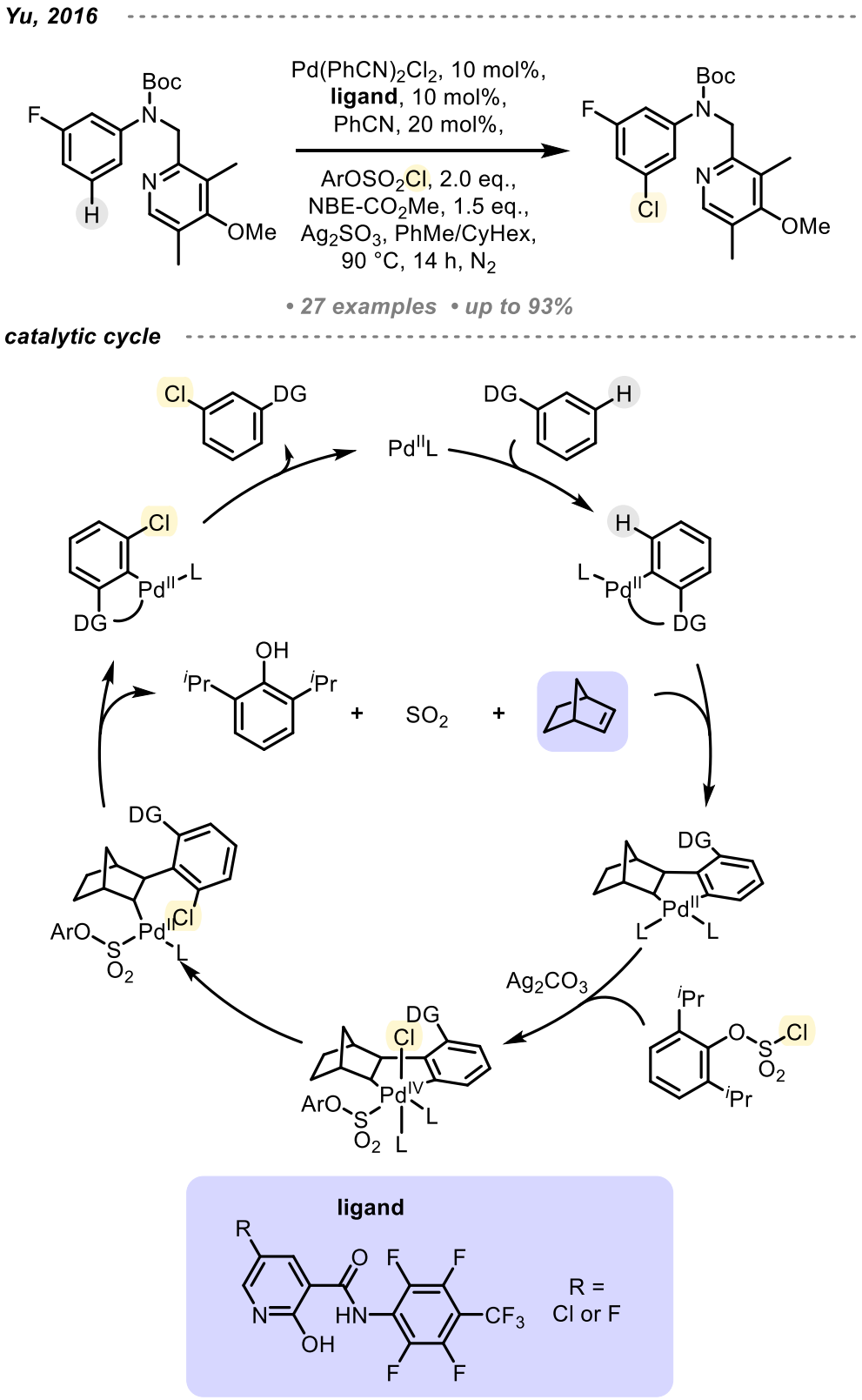
In the κ_1 mode, the palladium resides proximal to the *ortho*-position of the benzoic acid ring. This proximity is facilitated by the presence of a counteranion such as sodium or potassium and is often employed in *ortho*-C-H activation using aryl carboxylates.[163] In the absence of these counteranions, the palladium becomes proximal to the *meta*-position of the distal anilide, thus enabling *meta*-C-H palladation in the κ_2 mode.

By subjecting the benzoic acid tethered anilides to aryl iodides under their optimised reaction conditions, Li demonstrated 16 examples of *meta*-iodinated anilides (Scheme 131). The reaction conditions are compatible with *ortho*-and *meta*-substituted substrates bearing electron-withdrawing and electron-donating groups, but not *para*-substituents.



Scheme 131: Li's *meta*-C-H/C-I metathesis. [162]

In 2016, Yu reported *meta*-C-H direct chlorination of anilines using norbornene as a transient mediator.[164] This strategy has been employed widely among directed *meta*-C-H activation, whereby initial direct *ortho*-carbo-palladation is relayed to the *meta*-position by norbornene. This relay process is the key step in the well documented Catellani reaction. [165]

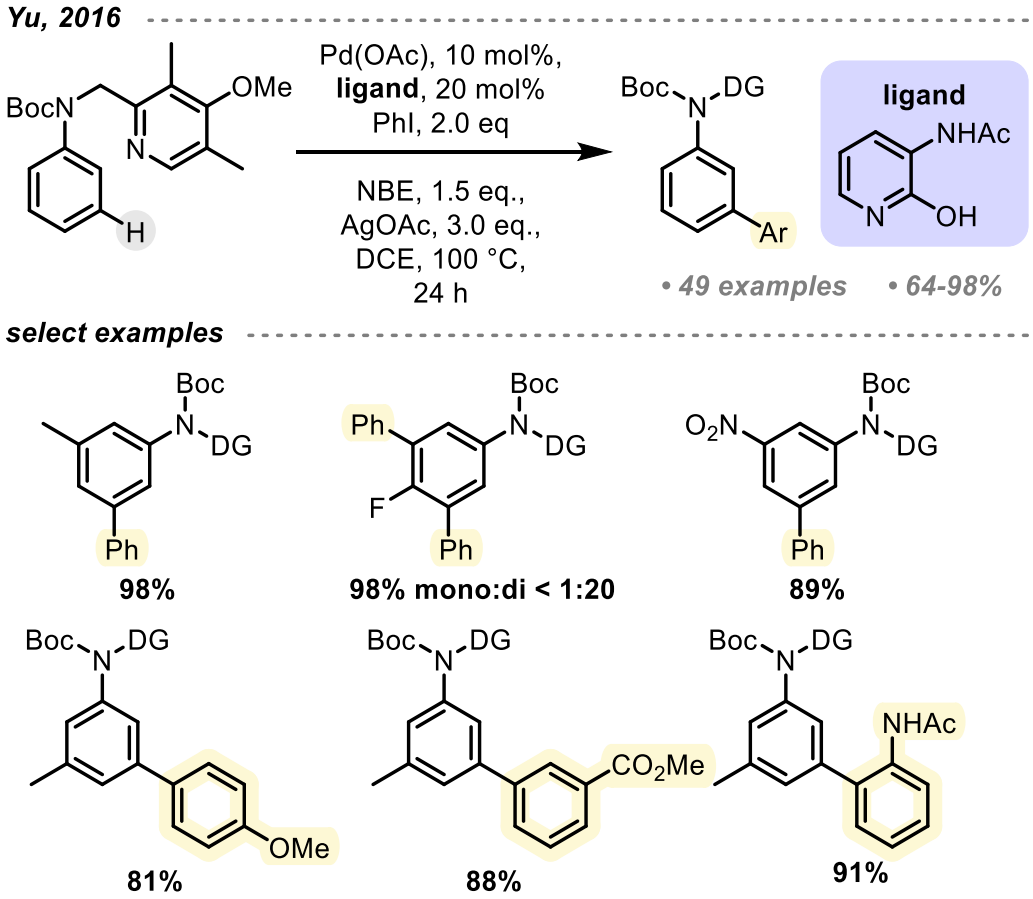


Scheme 132: Modified Catellani reaction to furnish *meta*-chlorinated anilines.

Following carbo-palladation and norbornene insertion, the mechanism is hypothesised to proceed *via* oxidative addition of chlorosulfate onto the palladacycle, affording the Pd(IV) intermediate. Here, the chlorine and arene can

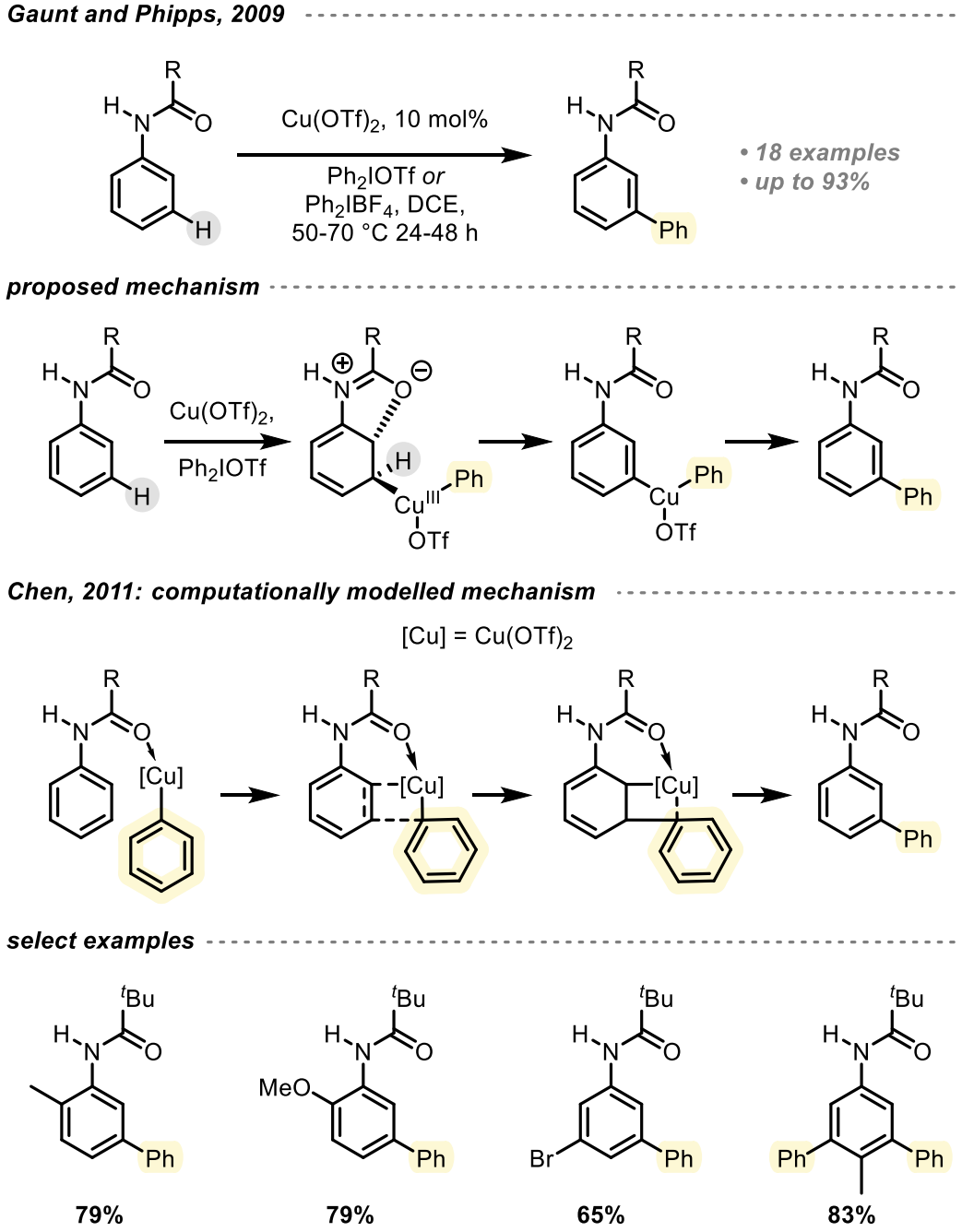
reductively eliminate to the *meta*-substituted arene. The sulfonate on palladium may degrade into sulfur dioxide and phenol, while norbornene can extrude *via* beta carbon elimination. Protodepalladation of the subsequent intermediate affords the *meta*-chlorinated product, regenerating the palladium catalyst (Scheme 132). The generality of this reaction is limited by its need for the other *meta*-position to be substituted to prevent di-chlorination. Nonetheless, these conditions are compatible with electron-rich and electron-poor arenes. It is tolerant of alkynyl and vinyl groups, which demonstrates the reaction's mildness and selectivity given that these groups are known to react with electrophilic sources of chlorine. Further, aryl borates remain intact in the presence of silver salts during the *meta*-chlorination.

Yu presented another publication employing directed *ortho*-palladation to a protected aniline, whereby norbornene mediates the addition of an aryl group to the *meta*-position (Scheme 133). As for the *meta*-chlorination illustrated in Scheme 132, this reaction is limited to mono-*meta*-substituted anilines to prevent diarylation. [166]



Scheme 133: Yu's norbornene relayed *meta*-arylation of anilines. [166]

Other than palladium catalysed methodologies, a seminal publication by Gaunt and Phipps shows the copper catalysed selective *meta*-C-H arylation of anilides, using diphenyliodonium triflate as the arylating agent.[90] In attempts to rationalise this observed site-selectivity, the authors propose a Cu(I)-Cu(III) system involving a key *meta*-C-H bond cupration step (Scheme 134.)



Scheme 134: Gaunt and Phipps' copper catalysed *meta*-arylation of pivanilides.[90]

Highly electrophilic Cu(III) is anticipated to 'activate' the arene. In a *meta*-cupration step, the amide oxygen attacks the *ortho*-position of the ring, thus breaking aromaticity. Subsequent rearomatisation followed by reductive

elimination of the phenyl and anilide furnishes the *meta*-arylated phenol, while the Cu(I) species is returned to the cycle.

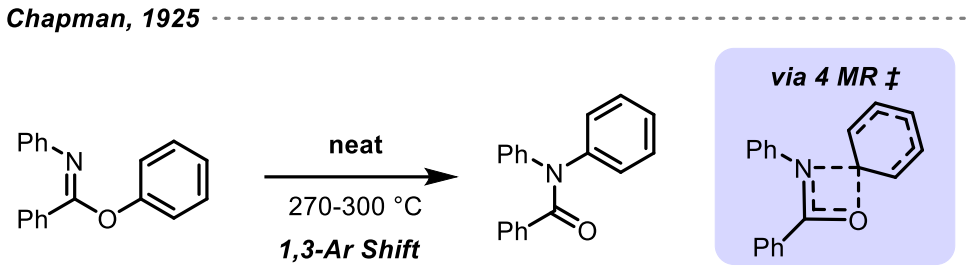
DFT calculations performed later by Chen in 2011 disputed this mechanistic hypothesis.[167] Their work suggests the amide oxygen initially coordinated to the intermediate Cu(III) species, enabling the phenyl to reside in close proximity to the *meta*-position. This could then form a 4-memebered 'Heck-like' transition state, according to their calculations, aromaticity it not completely destroyed in this step. Finally, the Cu(III)-C bond can break to regenerate the Cu(I) catalyst, while the triflate ion abstracts the *meta*-hydrogen to recover the aromaticity, furnishing the *meta*-arylated anilide.

This methodology exhibits broad substrate scope and is tolerant of a range of substitutions on both arenes, on all positions of the ring. Notably, exclusive *meta*-arylation is observed in the presence of the competing *meta*-directing sulfone substituent, in line with the hypothesised mechanism. Cases of diarylation of the unsubstituted and *para*-substituted anilides are observed, however the authors claim that the mono arylated substrate is accessible by controlling the stoichiometry of the reaction.

Phenols to Anilines

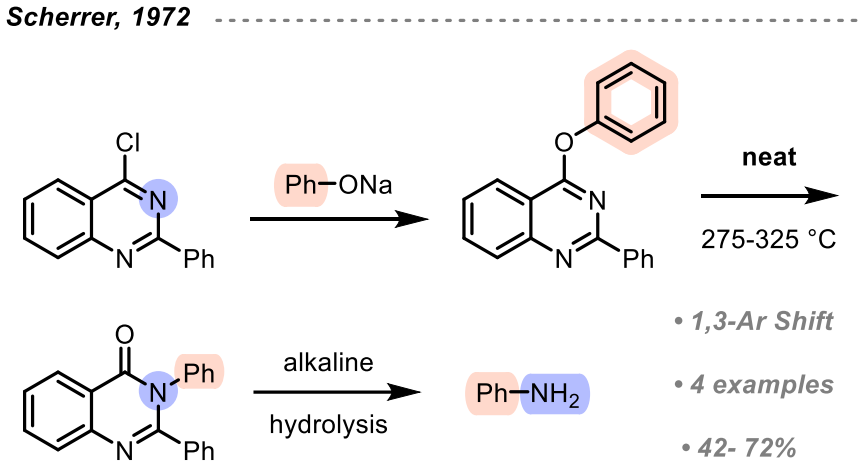
Phenols are abundant in nature and can be obtained from renewable feedstocks.[95] Because of their sustainable nature, it is highly desirable to develop a method to convert phenols directly into anilines. This section will begin by introducing early accounts of phenol deoxyamination and follow with more contemporary and practical methods of such.

A particular strategy to effect an aryl-O to aryl-N conversion is *via* the intramolecular heteroatomic rearrangements from phenols. An early account of such was realised by Chapman in 1925, who reported the intramolecular migration of an aryl group from an oxygen atom of an imidate to the nitrogen atom. This was eponymously named the Chapman rearrangement (Scheme 135).[168]



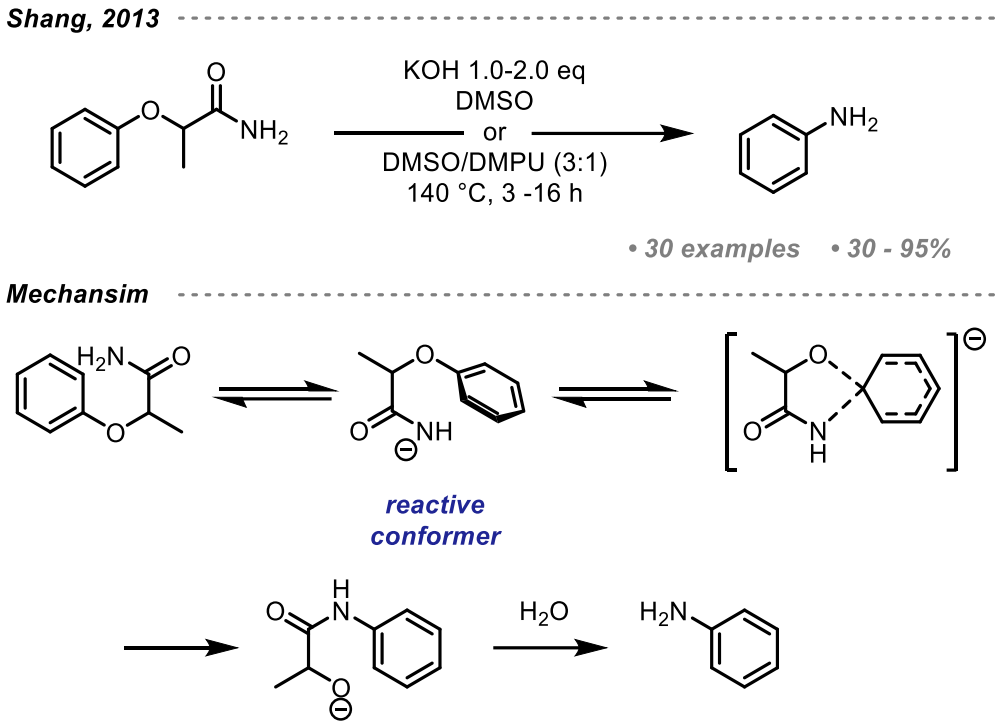
Scheme 135: Chapman rearrangement

Just under 50 years later, Scherrer reported an analogous transformation constituting the 1,3-aryl shift in 4-phenoxy-2-phenylquinazolines (Scheme 136).[169] Subsequent hydrolysis of the resultant N-aryl amide and imine moieties provides the free aniline. This was extended to 4 examples producing varied yields.



Scheme 136: Quinazoline mediated phenol-to-aniline conversion (bottom).[168,169]

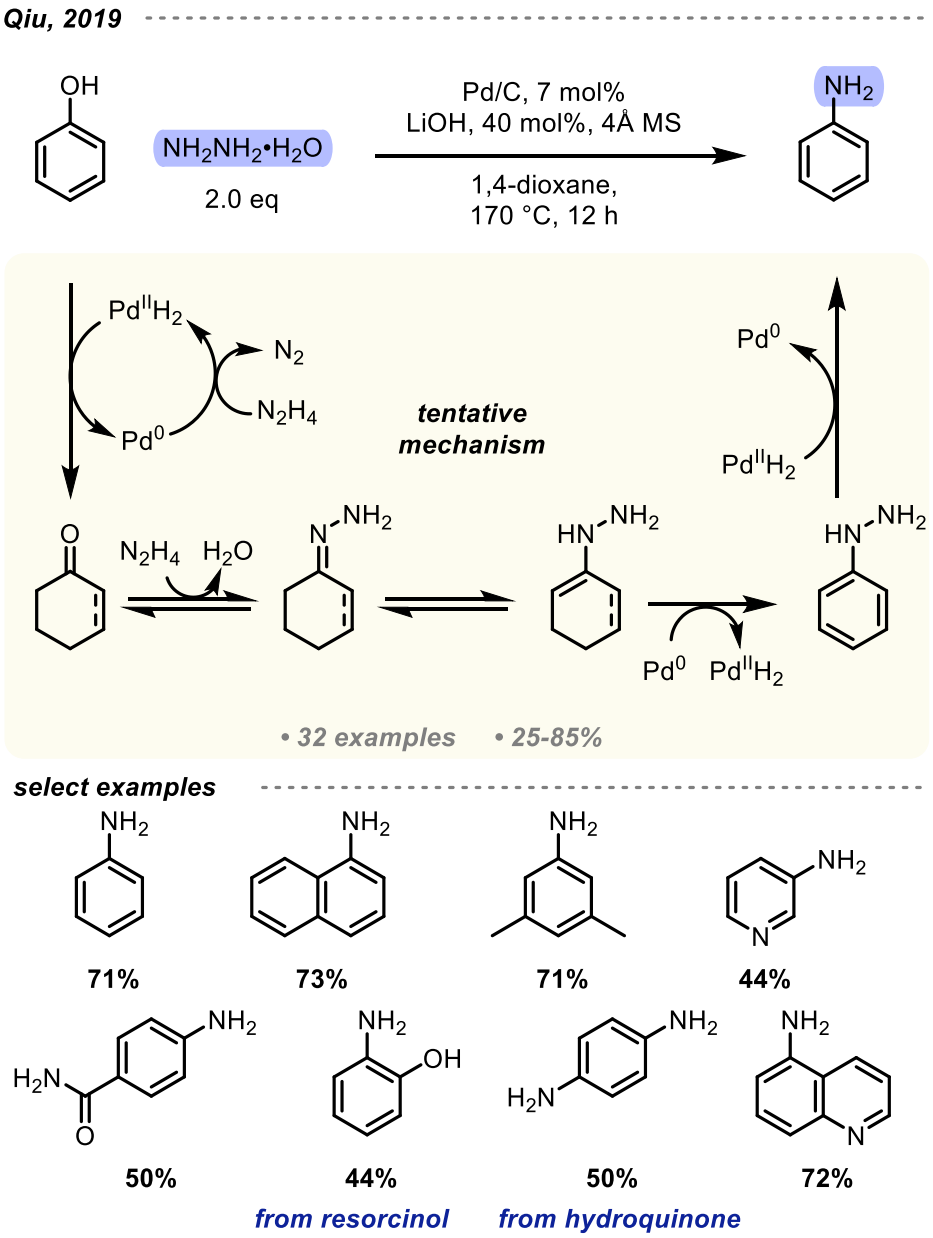
A more recent and general protocol has been reported by Shang, whereby the conceptually similar Smiles rearrangement of aryloxyamide leads to formation of the corresponding aniline (Scheme 137).[170] This methodology presents a broad substrate scope, tolerating halogens and base sensitive functional groups.



Scheme 137: Aniline synthesis *via* Smiles rearrangement.[170]

Deoxyamination reactions of phenols, as opposed to aryl ethers, are also feasible. Until recently, this transformation proved to be cumbersome; the direct amination of phenol was developed by Halcon International in 1966, however this reaction demands high temperatures (>200 °C) and a large excess of ammonia and hydrogen gas.[171] Research in recent years has employed catalytic methods to circumvent this high barrier to reactivity.

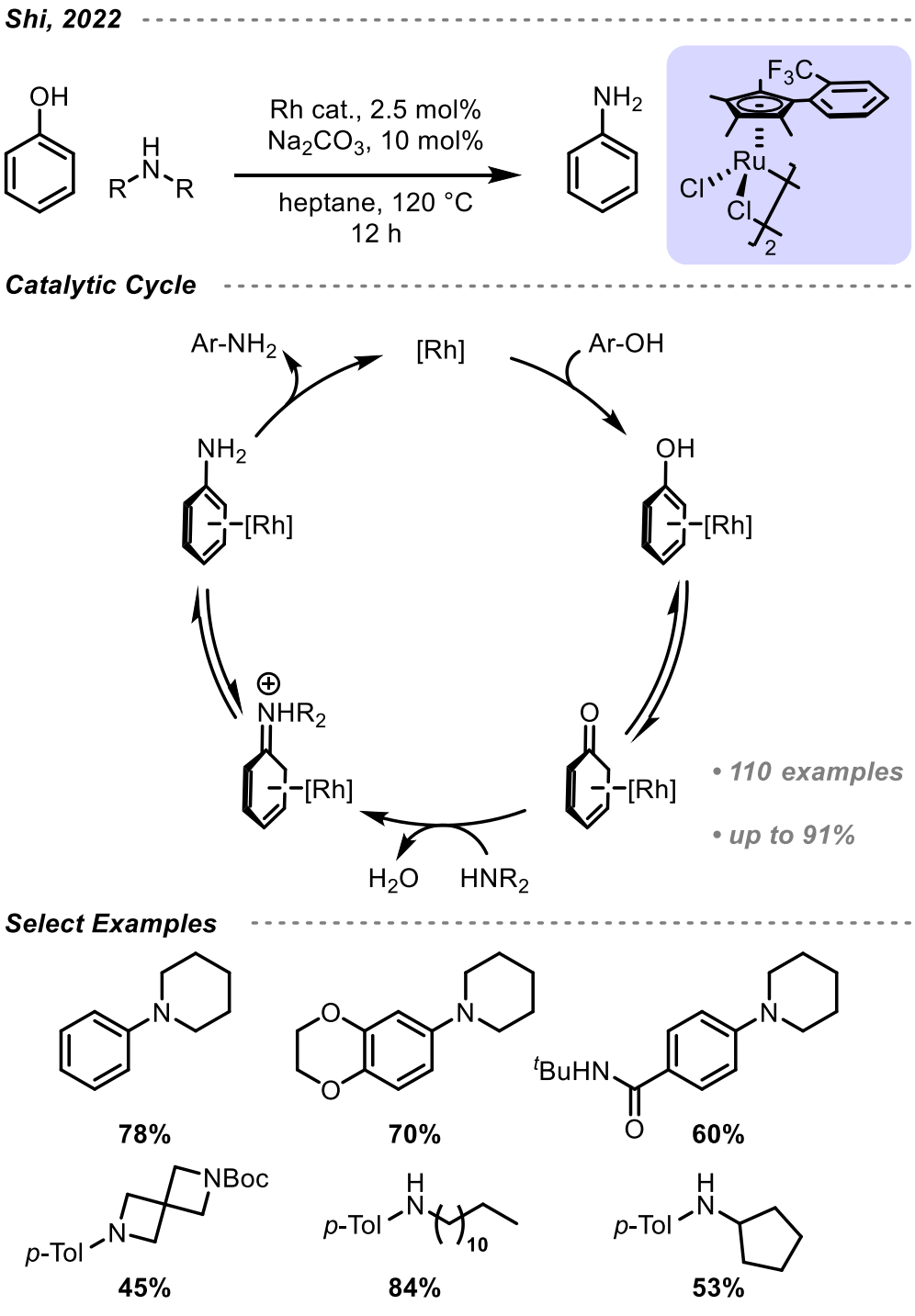
A recent study published by Qiu describes a hydrazine mediated Pd/C catalysed direct phenol-aniline transformation *via* a dearomatized cyclohexadienone intermediate (Scheme 138).[172] The reaction is hypothesised to proceed *via* initial generation of palladium hydride by decomposition of hydrazine under the action of the Pd/C catalyst. The palladium hydride then reduces the phenol to a cyclohexanone, which undergoes attack by hydrazine to form the cyclic azine. This tautomerizes to the enehydrazine, which readily undergoes dehydrogenation by Pd^0, regenerating the palladium hydride. Finally, reductive N-N bond cleavage produces the desired aniline and regenerates Pd(0) back into the cycle.



Scheme 138: Deoxyamination strategy developed by Qiu.[172]

This methodology presents a broad substrate scope, with good compatibility to phenols with alkyl and aryl substituents and moderate tolerability to methoxy phenols, amino phenols and hydroxyphenols.

Shi *et al.* recently described a rhodium catalysed amination of phenol.[173] It was postulated that, if tautomerisation exists between an activated arene and cyclohexadienone, subsequent dehydrative condensation with an amine could provide means of accessing the corresponding aniline. The described strategy is redox neutral and does not require exogenous activating agents. (Scheme 139).



Scheme 139: Rh catalysed deoxyamination of phenol.

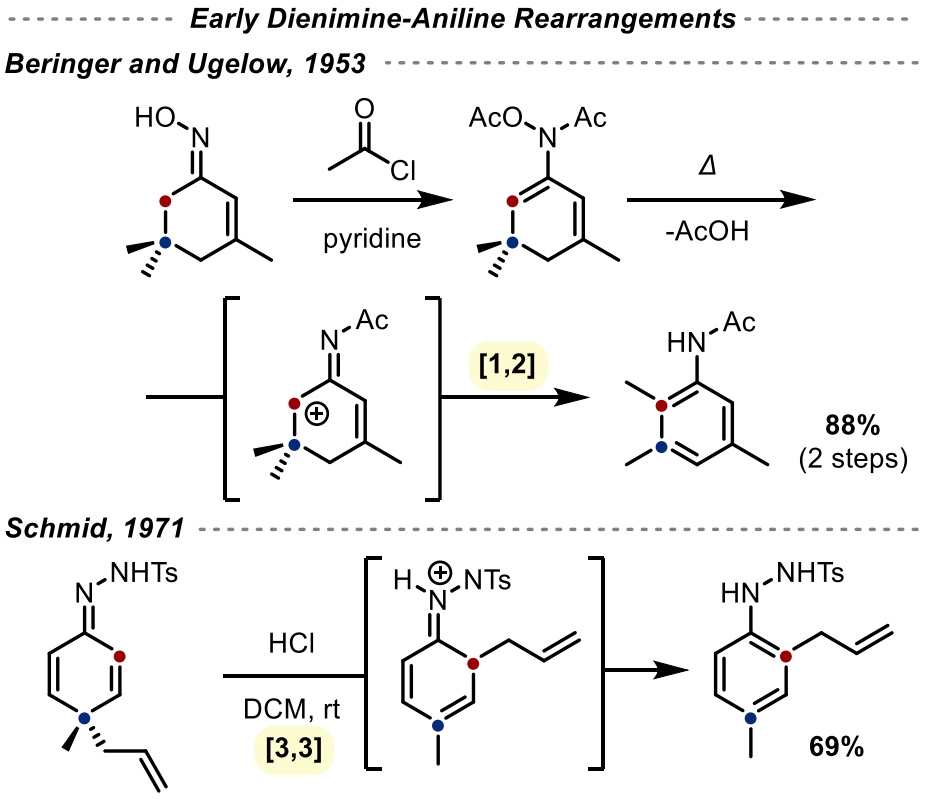
The reaction progresses *via* initial ligation of arenophilic Rh[III] catalyst with the phenol through π-coordination, providing the transient η^6-phenoxo complex after deprotonation. Condensation of an amine onto the carbonyl affords the iminium intermediate, which tautomerizes and dissociates from the arene, providing the free aniline and catalyst.

This procedure features a broad substrate scope with respect to both amines and phenols. It is tolerant of a range of *meta*-and *para*-substituted phenols with both electron-donating and withdrawing groups. Further, amination of multi substituted phenols or fused rings smoothly affords anilines in moderate to good yields. Various linear and branched primary amines are compatible with the reaction conditions, corresponding to moderate to excellent yields. Crucially, the reaction also tolerates a range of reactive functional groups, such as nitriles, carboxylates, amines, amides, carbamates and pyridyl groups.

These two protocols described by Qiu and Shi highlight phenol to aniline transformations which can be performed at far more accessible temperatures and pressures.

Dienimine-Aniline Rearrangement

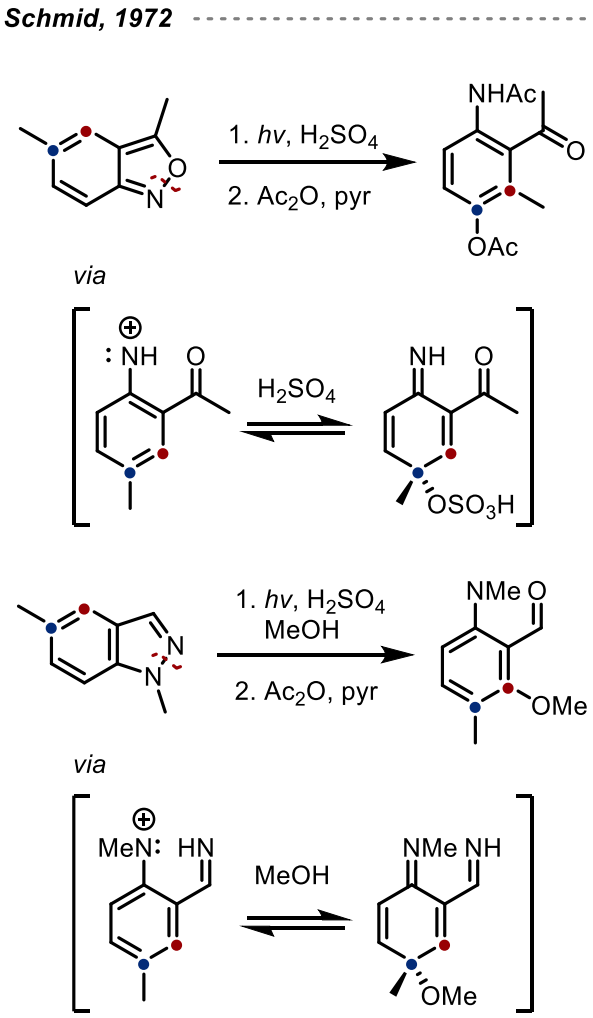
The dienamine-aniline rearrangement is much less explored than the analogous dienone-phenol rearrangement, however it features the same acid or thermally promoted sigmatropic shift which enables rearomatisation to an arene.



Scheme 140: Earliest accounts of the dienamine-aniline rearrangement.

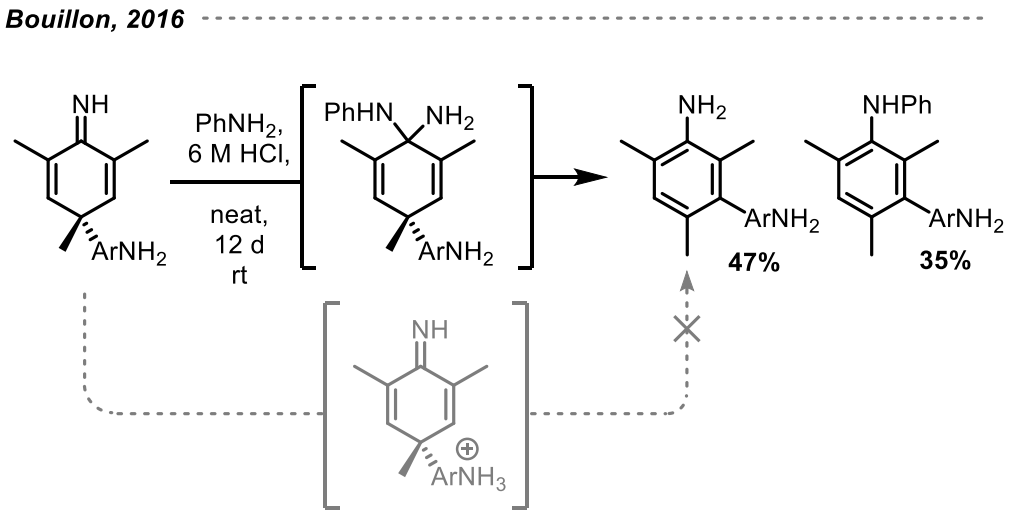
The earliest account of the dienamine-aniline rearrangement was reported by Beringer and Ugelow. (Scheme 140, top).[174] It was found that subjecting an oxime to acyl chloride in the presence of pyridine affords a di-acetylated species, which subsequently forms a cationic intermediate on heating. This carbocation undergoes a 1,2-migration, providing the aniline following tautomerisation.

Decades later, Schmid reported that tosyl hydrazones of 2,5-cyclohexadienones appeared to undergo a [3,3]-sigmatropic rearrangement, forming anilines in the presence of acid (Scheme 140, bottom).[175] Further to this, the dienimine-aniline rearrangements were observed following Schmid's investigation of photolytic ring opening of anthranils and indazoles, (Scheme 141).[176,177] The resultant aryl nitreniums appear to dearomatize in the presence of acid and/or methanol, affording dienimines which undergo 1,2-rearrangemntes to the corresponding aniline.



Scheme 141: Dienimine-aniline rearrangements.[174–177]

A more recent example has been showcased by Bouillon in 2016. (Scheme 142).[178] Upon their investigations on the benzidine rearrangement of 4-alkyl substituted hydrazobenzenes, Bouillon reported the formation of a 2,5-cyclohexadienimine. In attempts to probe the dienimine rearrangement of these species, the authors found that protonation of the more basic amine group would deactivate the ring, preventing a 1,2- aryl migration. To bypass the basicity of the amine, the imine was intercepted with aniline to form the aminal. This was then able to undergo the desired 1,2-aryl migration.



Scheme 142: Aniline promoted dienimine-aniline rearrangement.[178]

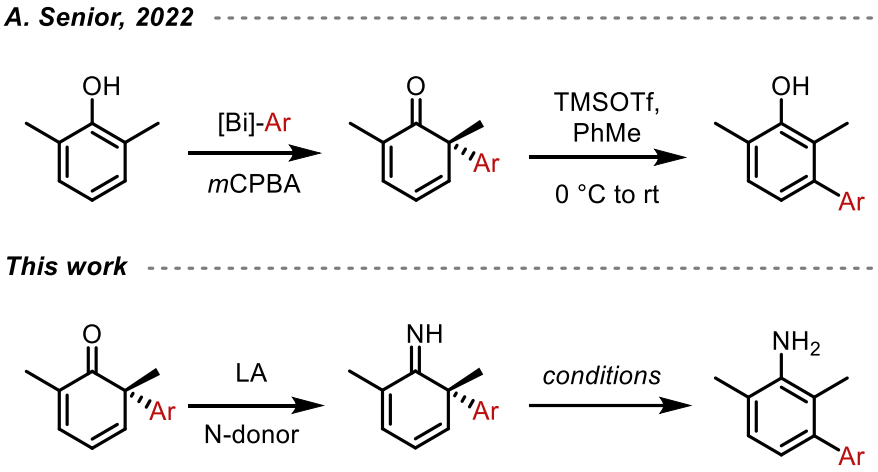
Toward a general synthesis of *meta*-arylated anilines, the methodologies described in this chapter are typically marred by one of three flaws:

- the waste associated with using large ligands in stoichiometric amounts;
- the waste associated with using large directing groups, which later need to be cleaved to provide the free aniline, and,
- risk of over-arylation in substrates that are not *meta*-substituted

The remainder of this chapter will explore the development of a *meta*-arylated aniline synthesis which hinges on the previously described dienimine-aniline rearrangement. This strategy aims to evade these flaws from the methodologies currently available.

4.2. Project Proposal

This section will explore a novel transformation of aryl 2,4-cyclohexadienones, which are accessible using chemistry developed within the Ball group (Chapter I), to form *meta*-arylated anilines. This methodology builds upon preceding understanding of the *meta*-arylation of phenol strategy, recently presented by Senior *et al.* (Scheme 143).



Scheme 143: Dienone-phenol rearrangement strategy to prepare *meta*-arylated phenols (top), project strategy to prepare *meta*-arylated anilines (bottom).

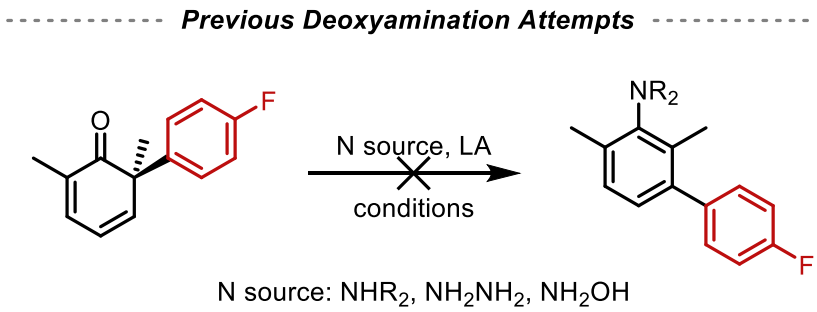
By analogy to the dienone phenol rearrangement, diversion of the cyclohexadienone to a cyclohexadienimine can undergo a dienamine-aniline rearrangement, furnishing *meta*-arylated anilines. (Scheme 143). This strategy fulfils the criterion of using renewable and accessible phenol starting materials, while exploring an underdeveloped field of reaction class. It also circumvents the observed shortcomings of the methodologies available:

- Over-arylation is reduced, as the cyclohexadienone products are inert to further oxidative arylation;
- arylation occurs on the same side of the *ortho*-substituent in mono *ortho*-substituted phenols as electronic factors dominate selectivity, and
- the use of directing groups and large ligands is evaded, maximising atom economy.

The following section will discuss the preliminary studies which have facilitated the realisation of this transformation. The developed chemistry described in this section has been performed by Dr Aaron Senior, unless otherwise stated. Following this discussion, the remaining studies required to develop this protocol into a general reaction procedure will be identified.

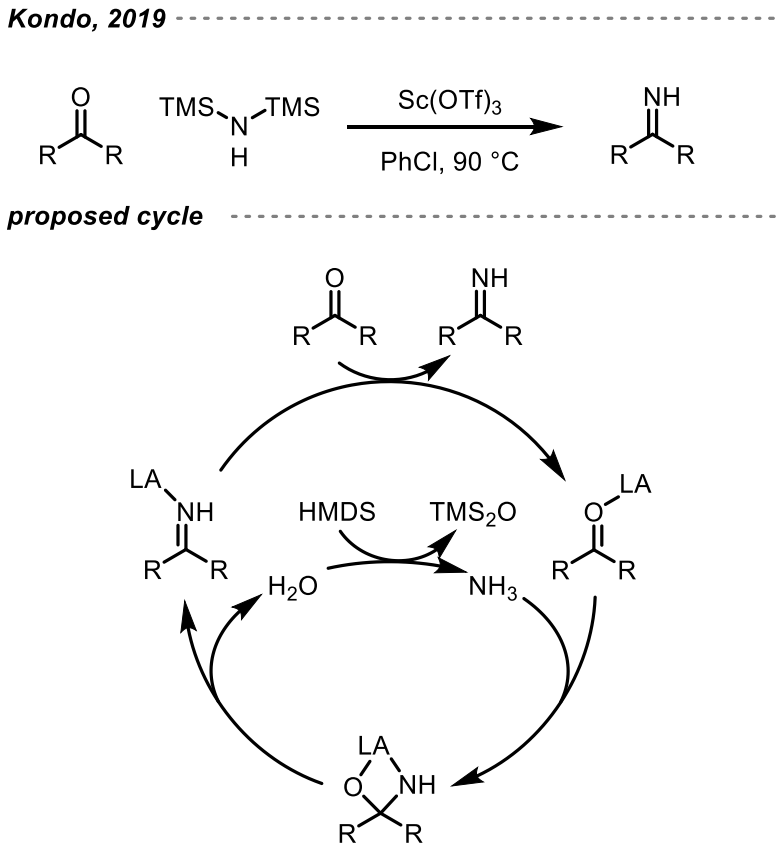
Preliminary Work and Considerations

Direct treatment of the 2,4- cyclohexadienone to an amine in the presence of a Lewis acid was attempted in the first instance to permit the formation of the *meta*-arylated aniline. Unfortunately, these initial studies saw no success. Employing hydroxylamine and hydrazine as nitrogen sources did not provide the aniline either. (Scheme 144).



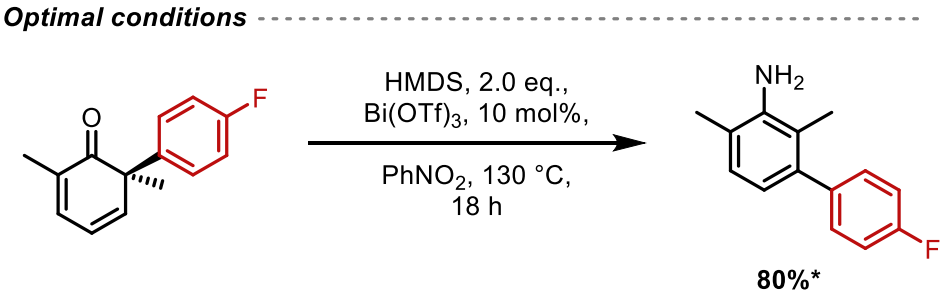
Scheme 144: Amine, hydroxylamine, and hydrazine as nitrogen sources for deoxyamination reactions performed by Dr Aaron Senior. LA = Lewis Acid.

To explain the lack of reactivity among these test reactions, it was postulated that stoichiometric amounts of amine relative to sub-stoichiometric amounts of Lewis acid may poison reactivity. Methodology developed by Kondo *et al.* was used to mitigate this possible catalyst poisoning.[179] Kondo employs hexamethyldisilazane (HMDS) as an ammonia source: it was observed that the deoxyamination reaction can proceed with super-stoichiometric equivalents of HMDS relative to Lewis acid, conditions which had not previously been possible. It was assumed that HMDS releases ammonia slowly into the reaction mixture, potentially preventing any poisoning of Lewis acid. (Scheme 145).



Scheme 145: Proposed cycle for scandium(III) triflate catalysed deoxyamination reaction with HMDS.[179]

Following extensive screens including the use of HMDS as source of ammonia, optimal conditions were found to permit the deoxygenation of a *para*-fluorophenyl cyclohexadienone to the corresponding *meta*-arylated aniline. (Scheme 146).

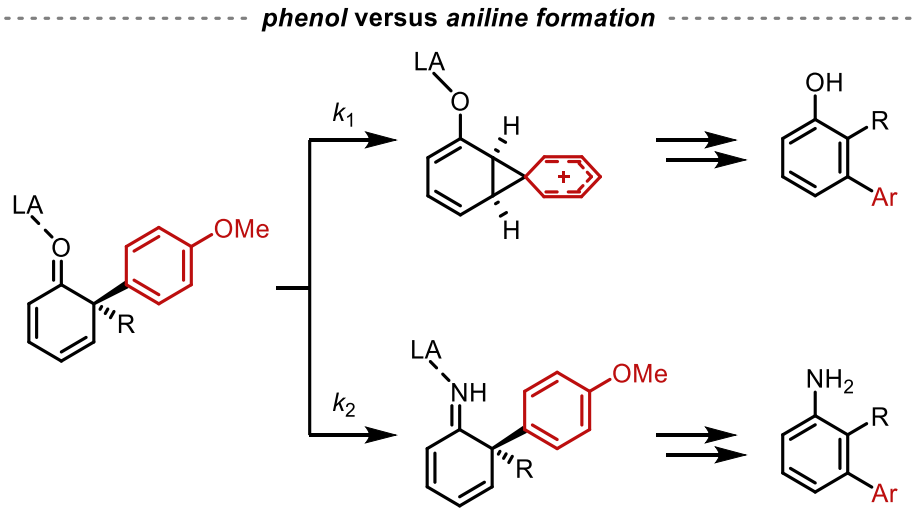


Scheme 146: Deoxyamination of *para*-fluorophenyl cyclohexadienone performed by Dr Aaron Senior. *Yield reported using quantitative ^{19}F NMR spectroscopy against internal standard 4,4'-bis(trifluoromethyl)-1,1'-biphenyl.

The conditions shown Scheme 146 present a high-yielding deoxyamination protocol. However, there are a number of points to consider in the realisation of

a general procedure. Most importantly, it was anticipated that the deoxyamination-migration conditions found for the *para*-fluorophenyl cyclohexadienone may not be compatible with cyclohexadienones bearing electron-rich or electron-poor groups. From mechanistic studies of Senior's 1,2-aryl migration of cyclohexadienones,[33] the relative migratory aptitude of electronically different arenes appears to vary by up to 4 orders of magnitude from very electron-rich (*p*-OMe) to very electron-poor (*p*-CF_3).* As the proposed mechanisms for the phenol and imine both proceed from the cyclohexadienone, the dienone-phenol rearrangement (k_1) and imine condensation (k_2) are competent reaction pathways. It was hypothesised that, for cyclohexadienones bearing electron-rich introduced arenes which are very prone to migration, the dieneone-phenol rearrangement may outcompete imine condensation (which is required for the desired dienimine-aniline rearrangement). Conversely, arenes bearing electron-withdrawing substituents may fail to migrate, resulting in poor overall yields.

To test this hypothesis, the compatibility of the working reaction conditions – identified by Senior – will be investigated on two other cyclohexadienones: *para*-trifluoromethylphenyl-cyclohexadienone as the -CF_3 group is deactivates the arene (σ_p = 0.54) [180], and *para*-methoxyphenyl-cyclohexadienone, as the -OMe strongly activates the arene, (σ_p = 0.27). [180]



Scheme 147: Competing reactions of phenol formation, k_1, versus imine formation, k_2.

* Relative rate of aryl migration: $\frac{k_{p\mathrm{OMe}}}{k_{p\mathrm{H}}} = 53.1$ $\frac{k_{p\mathrm{CF_3}}}{k_{p\mathrm{H}}} = 3.72 \times 10^{-3}$

In addition to reoptimization for electron-poor and electron-rich substrates, the development of a general protocol requires isolation of the aniline from the post deoxyamination reaction mixture. While being the most promising solvent for this reaction, nitrobenzene has a boiling point of 210 °C, making it practically difficult to isolate products upon reaction completion. Further, it is classed as a 1B reproductive toxin, it is toxic to the blood on repeated exposure, and has a TWA of 1 mg m^{-3}.* As such, minimizing exposure to nitrobenzene and product isolation, or, identification of a more benign reaction solvent present additional challenges by the current reaction conditions.

The remainder of this chapter will report the studies conducted to meet these aims thus far. These aims will be discussed in the following order:

(i) assessment of reproducibility and attempts to further improve the current conditions;

(ii) identification of alternative reaction solvent;

(iii) reoptimization for the deoxyamination-migration of cyclohexadienones bearing electron-rich and electron-poor introduced arenes, and,

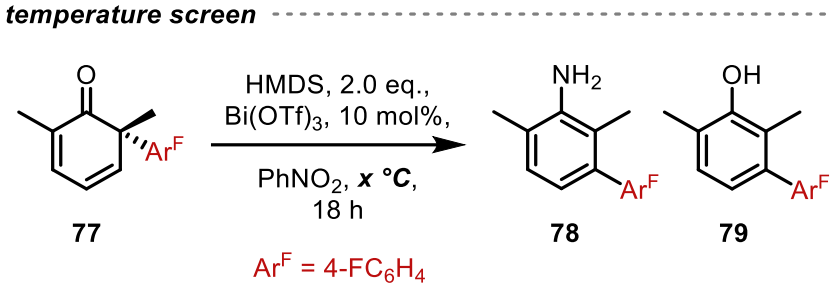
(iv) aniline isolation and assessment of substrate scope.

* According to nitrobenzene SDS provided by Merck https://www.sigmaaldrich.com/GB/en/product/sigald/n10950 accessed on May 2023.

TWA = Time-Weighted Average concentration of a hazardous substance in the air averaged over an 8-hour workday and a 40-hour workweek to which it is believed that workers may be repeatedly exposed, day after day, for a working lifetime without adverse effects.

4.3. Optimization

The optimal reaction conditions shown in Scheme 146 were repeated to assess the reproducibility of Senior's preliminary observations. In addition, a small screen of temperature was conducted to understand the dependence on high reacting temperatures (Table 8). Pleasingly, an initial test reaction saw deoxyamination of **77** providing 77% aniline and <5% phenol (entry 2). The presence of both species was confirmed by quantitative ^{19}F NMR spectroscopy against internal standard 4,4'-bis(trifluoromethyl)-1,1'-biphenyl.



entry	T (°C)	% **77**	% **78**	% **79**	N:O
1	120	17	61	4	14:1
2	**130**	**0**	**77**	**2**	**33:1**
3	140	0	75	10	7.7:1

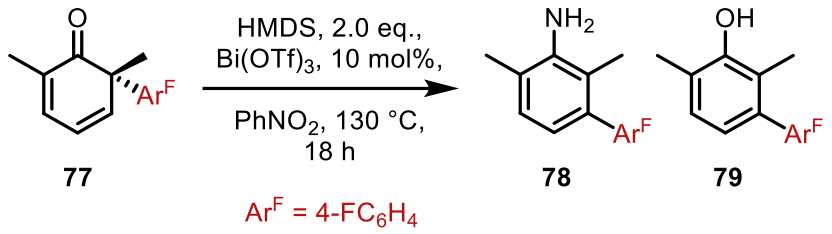
Table 8: Temperature screen for the deoxyamination of **77** to **78**. Yields determined *via* quantitative ^{19}F NMR spectroscopy

It was confirmed that heating to 130 °C was optimal among the range selected. Heating to 130 °C (entry 2) yields the most aniline well as delivering higher selectivity over the phenol. The reaction at 140 °C (entry 3) affords a similar yield within error, however it is accompanied with poorer selectivity. This may be due to loss of ammonia or HMDS in solution at higher temperatures, thus limiting aniline formation. With the reproducibility confirmed, optimisation and isolation were attempted.

A brief concentration screen at 0.2 M, 0.5 M and 1 M was carried out. This was to aid the isolation of aniline **78** from nitrobenzene and limit exposure to the

solvent, for reasons previously discussed. Results for this screen are shown in Table 9, which indicate moderate changes in concentration have minimal effect on both yield and selectivity of the reaction.

concentration screen



77 **78** **79**

Ar^F = 4-FC_6H_4

entry	concentration (M)	% **77**	% **78**	% **79**	N:O
1	0.2	0	79	7	11:1
2	0.5	0	80	4	20:1
3	1	39	82	0	>100:1
4	1*	3	54	3	18:1

Table 9: Concentration screen for the deoxyamination of **77** to **78**. Yields determined *via* quantitative ^{19}F NMR spectroscopy.*Reaction conducted in Wheaton V-Vial™ .

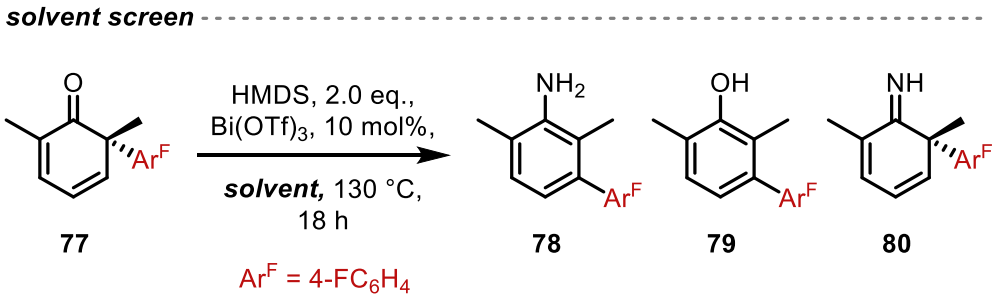
Considering improving selectivity further, it was proposed that raising the concentration of ammonia in the reaction vessel would favour aniline formation. This could be done by increasing the amount of HMDS, which has previously appeared to have little effect on the reaction, or by reducing the headspace in the vessel. Wheaton- "V-vials" were selected as vessels to limit the headspace however, upon subjecting **77** to the otherwise optimal conditions, only 54% **78** was observed with no increased selectivity (entry 4). Interestingly, another peak was observed using ^{19}F NMR spectroscopy at -117.4 ppm, which has been preliminarily identified as the cyclohexadienimine (*vide infra*). This was present in 14%.

The lack of reactivity could be explained by having too much ammonia in solution. As discussed in Section 4.2 of this Chapter, it was previously shown that super-stoichiometric amounts of amine with respect to Lewis acid was to

reactivity. It is assumed that the Lewis basic amine poisons the catalyst when in excess. The use of HMDS in this reaction is proposed to release ammonia *slowly* into the reaction mixture to mitigate this effect (Scheme 145). With the observed decrease in aniline formation, headspace effects were not investigated further with this substrate.

Having confirmed the reproducibility and found suitable conditions for this methodology, a reassessment of solvents was made. It is understood that high temperatures permit this transformation, particularly for cyclohexadienones bearing electron-poor arenes. To avoid using the highly toxic nitrobenzene, a series of alternative solvents were investigated (Table 10).

High boiling solvents which showed some promise in the optimisation process were retested using the optimal conditions; these include anisole and *p*-cymene. In addition, Senior's initial solvent screen indicated that non-aromatic solvents were deleterious to reactivity whereas aromatic ones facilitate it. Despite its known toxicity, dichlorobenzene was tested to probe this possible trend. Given that nitrobenzene performs well, propylene carbonate and DMSO were chosen as more benign and similarly dipolar aprotic solvents. Their safety compared to nitrobenzene can be quantified by their lower LD_{50} values, and lack of reported TWA.



entry	solvent	% **77**	% **78**	% **79**	% **80**
1	**$PhNO_2$** [a]	**0**	**80**	**0**	**4**
2	PhOMe [b]	45	0	13	37
3	o-dichlorobenzene[a]	42	4	17	0

4	*p*-cymene [a]	70	<5	<5	<5
5	propylene carbonate [b]	80	0	0	0
6	DMSO [b]	69	0	0	0

Table 10: Solvent screen for the deoxyamination of **77** to **78**. Yields determined *via* quantitative ^{19}F NMR spectroscopy. (a) Dried over calcium hydride, (b), dried over 4 Å molecular sieves.

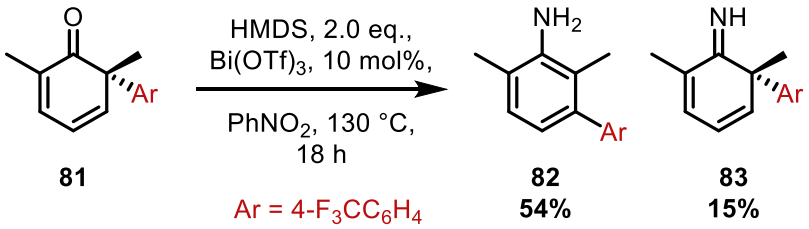
From the results shown in Table 10, it appears nitrobenzene remains superior with respect to cyclohexadienone consumption and aniline formation. Anisole and DCB (entries 2 and 3) enable some conversion to the intermediate imine **80**, alluding to the idea that aromatic solvents may facilitate reactivity. *p*-Cymene performed poorly, with almost only cyclohexadienone remaining. Propylene carbonate and DMSO (entries 4 and 5) also performed poorly with no reactivity observed, suggesting aromatic compounds are preferable. Given that there are few solvents that meet the criteria of polar aprotic, aromatic, and high boiling, nitrobenzene was retained as the solvent of choice for this reaction.

With satisfactory conditions for the deoxyamination reaction of electron-neutral substrates in hand, assessment of these conditions with electron-poor and rich cyclohexadienone congeners was undertaken.

Reoptimization for Electron-Poor Systems

As discussed, electron-deficient arenes that are introduced in the dearomatisation step would likely decelerate migration, which may in turn necessitate high temperatures. This may lead to side reactions such as dimerization by a Diels-Alder reaction, which cyclohexadienones are known to undergo (see Chapter 1; Section 1.2 and Chapter 3). In addition to the -CF_3 moiety withdrawing electron density from the arene, *para*-trifluoromethylphenyl-cyclohexadienone was chosen as a model substate, as the fluorine-containing substituent enables monitoring by quantitative ^{19}F NMR spectroscopy.

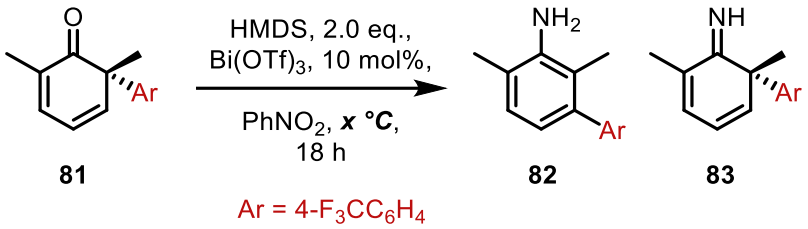
By subjecting **81** to the pseudo-optimised reaction conditions, aniline **82** was found in a 54% yield in addition to a second species in 15%. Spectroscopic evidence suggests this is the intermediate imine **83.**



Scheme 148: Deoxyamination of **81** to **82** using pseudo-optimal conditions applied to 77. Yields determined *via* quantitative ^{19}F NMR spectroscopy.

It was proposed that a stronger Lewis acid could replace the $Bi(OTf)_3$, activating the intermediate imine further, thus accelerating the formation of aniline. The reaction was repeated with 1 equivalent TMSOTf added after the imine was observed by ^1H NMR, however this did not appear to yield any more aniline. Alternatively, it was thought that the reaction could be accelerated by raising the temperature. A fruitful temperature screen, shown in (Table 11) proved this to be true. The reaction was carried out initially from 100 °C to 160 °C to highlight any observable trends.

temperature screen



81 **82** **83**

Ar = 4-$F_3CC_6H_4$

entry	T (°C)	% **81**	% **83**	% **82**
1	100	13	46	11
2	120	4	54	21
3	140	3	63	29
4	160	2	10	78
5	180	3	7	66
6	**180**[a]	**3**	**3**	**84**

Table 11: Temperature scheme for the deoxyamination of **81** to **82**. Yields determined *via* quantitative ^{19}F NMR spectroscopy. (a) yield obtained *in situ* after 1 h.

The screen revealed that the conversion of **81** to **83** increases from 100 to 140 °C, while heating to 160 °C appears to consume imine, affording 78% aniline (entry 4). The formation of aniline is associated with a characteristic dark brown colour change, which was observed within a couple of hours for reactions at 140 °C and 160 °C. To see if the yield could be raised further, a repeat was performed at 180 °C, with yields measured at 1 h and 18 h. Pleasingly, increasing the temperature to 180 °C affords 84% **82** after just 1 h, while leaving the reaction over 18 hours causes decomposition. No temperatures beyond this were investigated, given that the nitrobenzene boils at 210 °C.

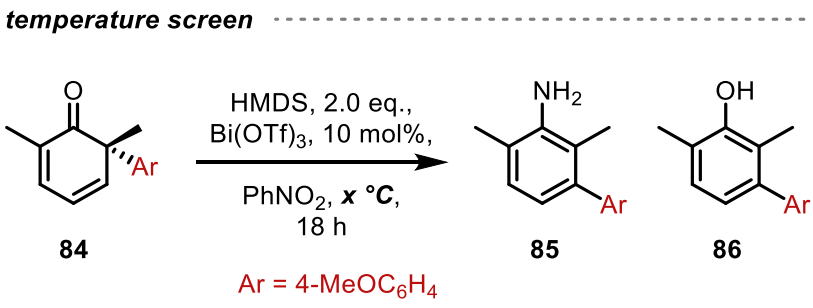
With excellent analytical yields achieved for the deoxyamination of **81**, the focus moved to optimisation of cyclohexadienones bearing electron-rich arenes.

However, there are still several points to consider for cyclohexadienones bearing electron-poor arenes, which will be investigated in future studies:

- The aniline appears to decompose over 18 hours at 180 °C. Higher yields might be accessible if the reaction is stopped before its decomposition at lower temperatures.
- The use of biguanidines has been used to inhibit aniline decomposition, thus their inclusion in this reaction will be investigated.[181]

Reoptimization for Electron-Rich Systems

As mentioned, the deoxyamination of cyclohexadienone exhibits two kinetically competitive pathways; the desired imine condensation and the undesired 1,2-aryl migration to the phenol. It was hypothesised that this undesired reactivity may become more pronounced for cyclohexadienones with electron-rich arenes, as they may accelerate phenol formation over imine formation. To test this, and to assess the substrate compatibility with the pseudo-optimal conditions, the deoxyamination of **84** was conducted. (Table 12) The temperature was adjusted slightly from 130 to 120 °C, as electron-rich cyclohexadienones are prone to decomposition (entry 1). As expected, the formation of a phenolic species (**86**) is favoured under these conditions, thus reoptimization was sought. In attempts to decelerate the rate of phenol formation, a screen of temperatures below 120 °C was carried out.

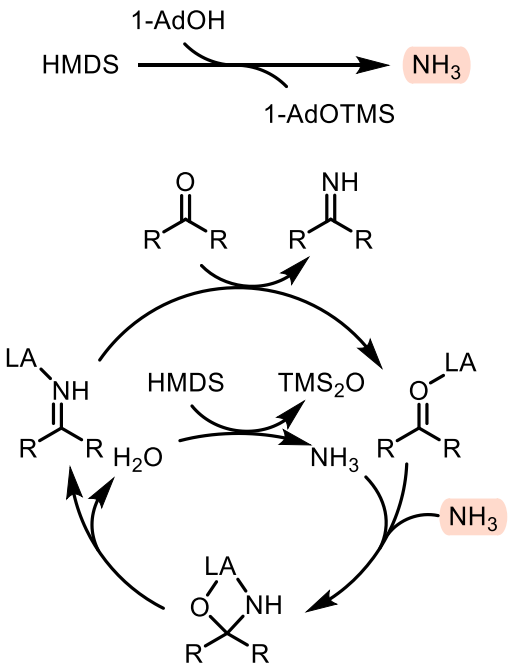


entry	T (°C)	% **84**	% **85**	% **86**	N:O
1	120	0	3	70	1:1.2
2	**100**	**0**	**50**	**50**	**1:1**
3	90	3	42	56	1:0.8
4	80	15	43	32	1:0.7
5	60	73	9	11	1:1.2

Table 12: Temperature screen for the deoxyamination of **84** to **85.** Yields determined *via* quantitative ^{1}H NMR spectroscopy.

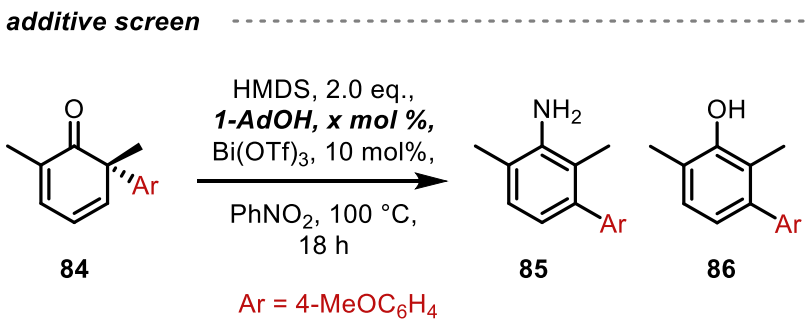
The results revealed that the reaction requires heating between 90 and 100 °C to completely consume the cyclohexadienone, and to 100 °C to afford equal amounts of phenol **86** and aniline **85**. Thus 100 °C appears to be optimal, as it fully consumes the cyclohexadienone while forming the least amount of phenol among the temperatures investigated.

adamantanol as a water equivalent



Scheme 149: Proposed catalytic cycle for imine condensation; 1-adamantanol as a water equivalent.

If it were possible to increase slightly the concentration of ammonia in the reaction, the system may favour aniline formation. By consideration of the proposed catalytic cycle by which the cyclohexadienone forms the cyclohexadienimine, trace amounts of water react with stoichiometric amounts of HMDS to evolve ammonia *in situ*. Thus, raising the concentration of ammonia may be possible by introducing catalytic amounts of 1-adamantanol as a water equivalent. Loadings of 1-AdOH are reported in Table 13.



entry	1-AdOH (mol%)	% **84**	% **85**	% **86**	N:O
1	0	0	50	50	1:1
2	10	0	56	46	1:1.2
3	20	0	60	40	1:1.5
4	30	4	66	26	1:2.5
5	40	3	67	28	1:2.39
6	**50**	**7**	**68**	**25**	**1:2.72**

Table 13: 1-Admantanol loading screen for the deoxyamination of **84** to **85**. Yields determined *via* quantitative ^{1}H NMR spectroscopy against internal standard diphenylmethane.

Fortunately, these data support the stated hypothesis; adding 1-adamantanol appears to raise aniline selectivity. Initial investigations using 10 mol% (Table 13, entry 2) indicated some increase in selectivity, whereas 20 mol% afforded a +10% aniline/-10% phenol with respect to no additive. Raising 1-adamantol from 20 to 50 mol% was associated with small amounts of unconsumed **84**. This could represent a threshold loading of 1-adamantanol in the system which affords a

concentration of ammonia that leads to poisoning of the Lewis acid. Given that 50% loading (entry 6) affords 68% aniline, a very small increase with respect to 30 and 40% loadings (entries 4 and 5), this was selected as the optimal amount of 1-adamantanol for this reaction. With the reoptimized conditions in hand, the focus of the project moved toward aniline isolation before a substrate scope was carried out.

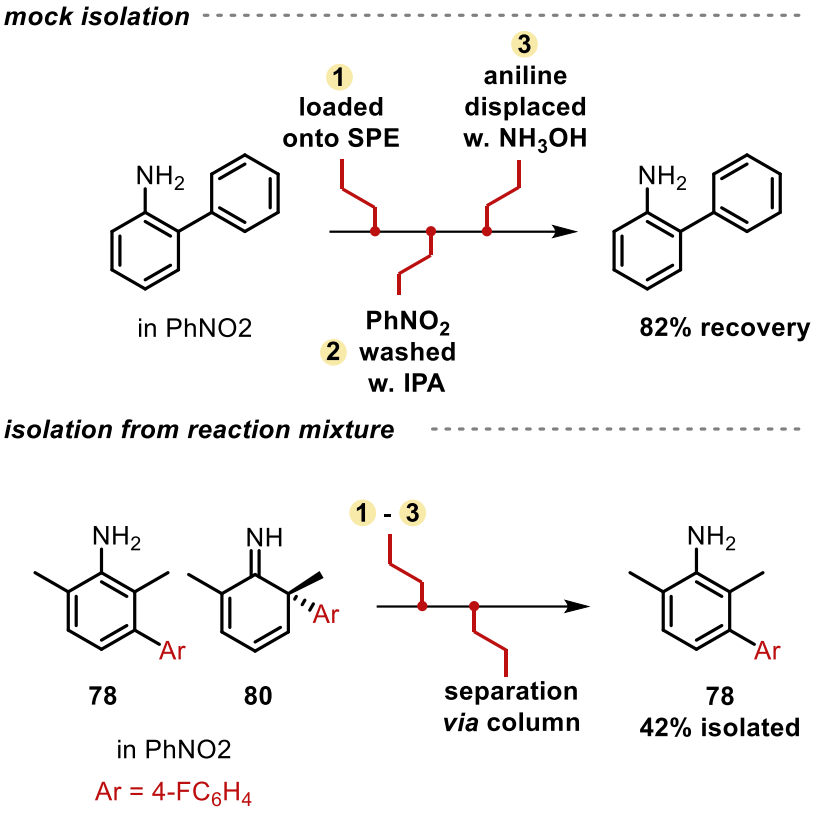
Isolation from Nitrobenzene

The isolation of aniline from nitrobenzene is a difficult procedure to develop. This is due to several reasons:

- Nitrobenzene has a boiling point of 210 °C,
- nitrobenzene co-distils with the aniline product when subjecting to a distillation;
- nitrobenzene exhibits solubility in organic solvents and partial solubility in water,
- its quantity as a solvent causes it to streak on silica upon removal *via* column chromatography;
- the reaction yields multiple unknown products, which appear insoluble in various solvents, and,
- it is toxic to the blood upon repeated exposure, and is a category 1B reproductive toxin, thus exposure should be kept to a minimal.

This section will explore the various methods of isolation that have been tested on deoxyamination reaction mixtures and model biphenyls in nitrobenzene.

At the outset, solid phase extraction (SPE) was considered a possible route to isolation. To assess this possibility, commercially available 2-aminobiphenyl was dissolved in nitrobenzene and passed through an SPE tube. Washings with isopropyl alcohol followed by aniline elution with ammonium hydroxide in methanol (18.1 M), afforded 82% recovery. This procedure was tested against the post deoxyamination reaction mixture, however following separation of the **78** and **80**, the isolated yield of pure **78** was just 43% (Scheme 150).

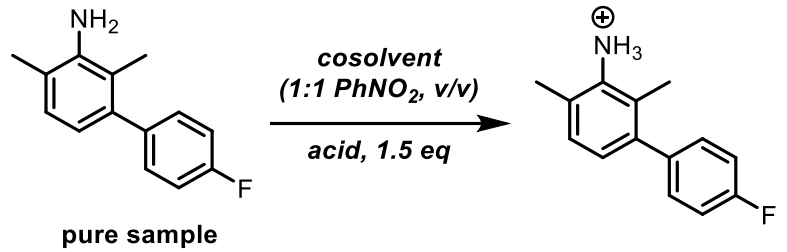


Scheme 150: Mock isolation using SPE and application to reaction mixture.

An alternative strategy to access the anilinium salt was attempted. In this case, an authentic sample of aniline was prepared, and aliquots were subject to 1.5 equivalents of acid to induce crystallisation. These were in a 1:1 solution of nitrobenzene and cosolvent, in the presence of internal standard such that the amount of aniline remaining in solution could be quantified.

A series of co-solvents of varying polarity were employed against a series of acids. The prepared samples were left in the fridge overnight to help induce crystallisation, after which time they were qualitatively observed. The liquor of combinations which appeared to crystalise were identified (yellow), and those with significant crystallisation (green) were subject to NMR spectroscopy; the quantities of remaining aniline and therefore crystalised anilinium are reported in Table 14 .

mock isolation via crystallisation

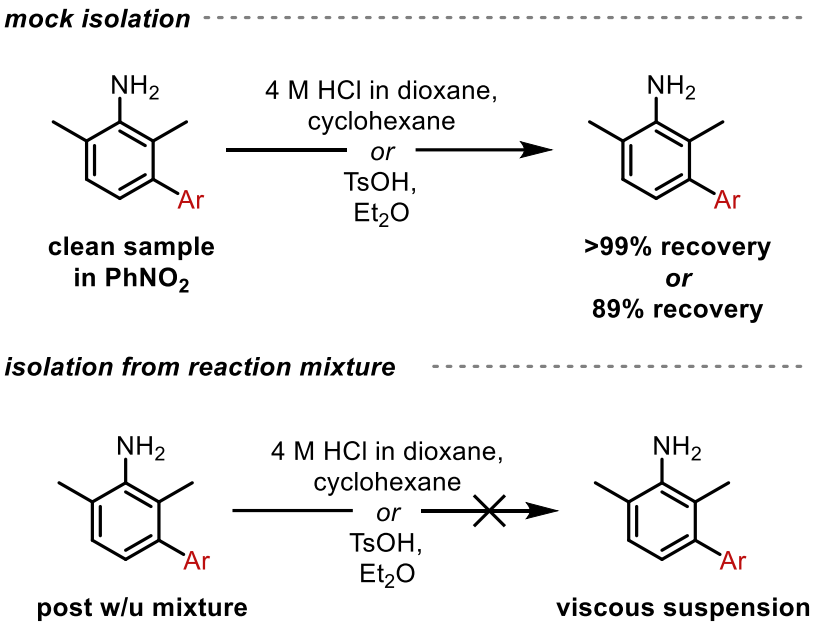


pure sample

	CyHex	PhMe	Et_2O	IPA	None
4 M HCl in dioxane	**89**		63		46
BF_3		4	1		0
TsOH			**90**		
3,5-dinitrobenzoic acid					
Dibenzoyl tartaric acid					

Table 14 Qualitative indication of amount of anilinuim salt formation (%). Actual yields of anilinium reported in bold. Yields determined *via* quantitative ^{19}F NMR spectroscopy.

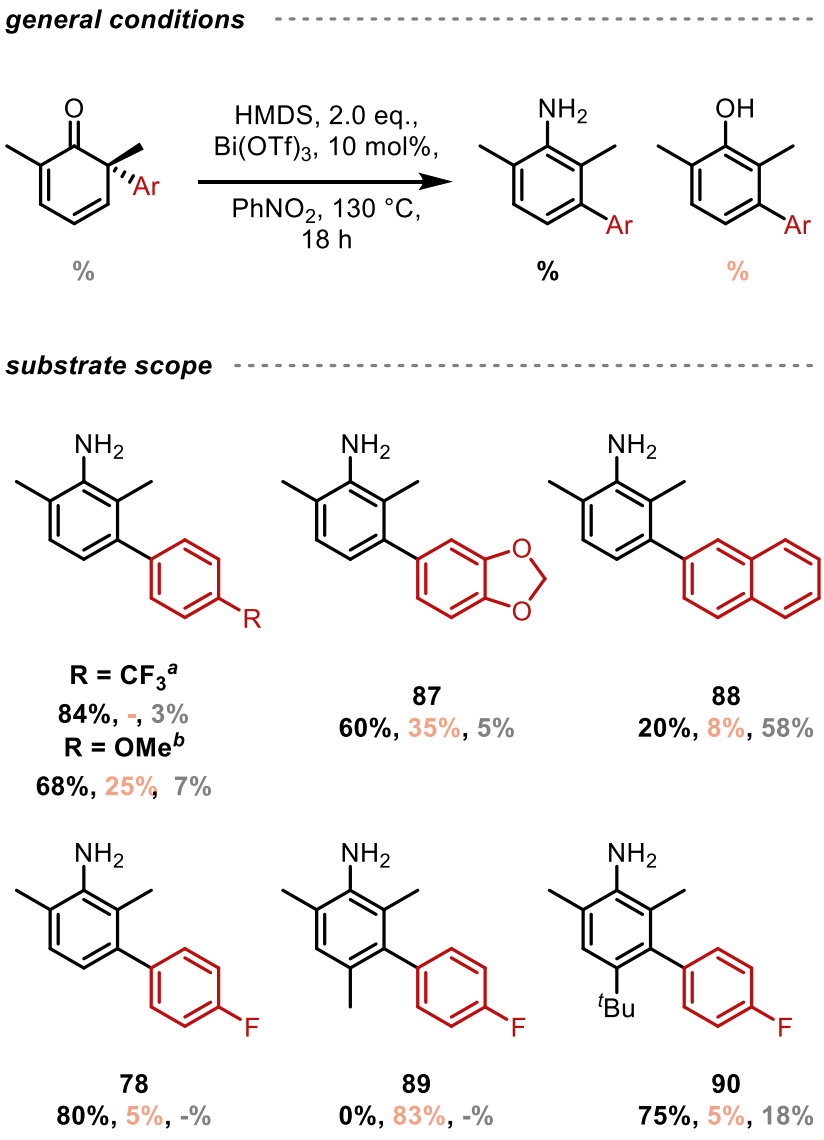
The combinations which led to the most crystallisation was HCl in cyclohexane, and tosic acid in ether. 0.5 mmol scales of these samples in a 0.5 M solution in nitrobenzene were prepared, and subject to these crystallisation conditions (Scheme 151, top). Pleasingly, >99% of the anilinium was recovered from the HCl in cyclohexane sample, however only 89% of from the tosic acid in ether. These conditions were then attempted on reaction mixtures (Scheme 151, bottom). Unfortunately, these samples proved much more difficult to crystallise, as the reaction mixture itself is not homogenous and the suspension is viscous. This method was therefore not employed in an isolation procedure and efforts to realise an alternative procedure are to be explored.



Scheme 151: Application of the optimal crystallisation conditions to clean aniline (top) and crude aniline following deoxyamination.

Substrate Scope and Monitoring

Despite not yet having an isolation procedure, substrate compatibility with these reaction conditions were assessed using their *in situ* yields. These were recorded *via* quantitative NMR spectroscopy. (Scheme 152). Conditions developed for the *para*-fluorophenyl cyclohexadienone were employed except for the substrates discussed.



Scheme 152: Substrate scope for the deoxyamination of cyclohexadienones. Yields determined *via* quantitative ^{19}F NMR spectroscopy. (a) reaction conducted at 180 °C and yield taken at 1 h. (b) reaction conducted in the presence of 50 mol% 1-adamantanol at 100 °C.

Fortunately, these conditions have a mild tolerance to various substrates. Exchanging the phenyl for a benzodioxole group affords a modest 64% (**87**), whereas the naphthyl example provides **88** in a 20% yield. It was considered that substituents in the 4-position of the phenol may hinder the migration step; pleasingly, this was not the case as demonstrated by the 4-tertbutyl cyclohexadienone (**90**). Conversely, placing a methyl (**89**) on this position was associated with a low yield of aniline.

The consumption of cyclohexadienone and evolution of products and intermediates of the deoxyamination was also investigated. As the consumption of the *para*-trifluoromethyl phenyl cyclohexadienone **81** was found to be slow at 130°C, it was thought this would be an ideal system for monitoring. Thus, **81** was subject to the initial pseudo-optimal conditions. Aliquots of the reaction mixture were taken at 1, 2, 3, and 20 hour time points.

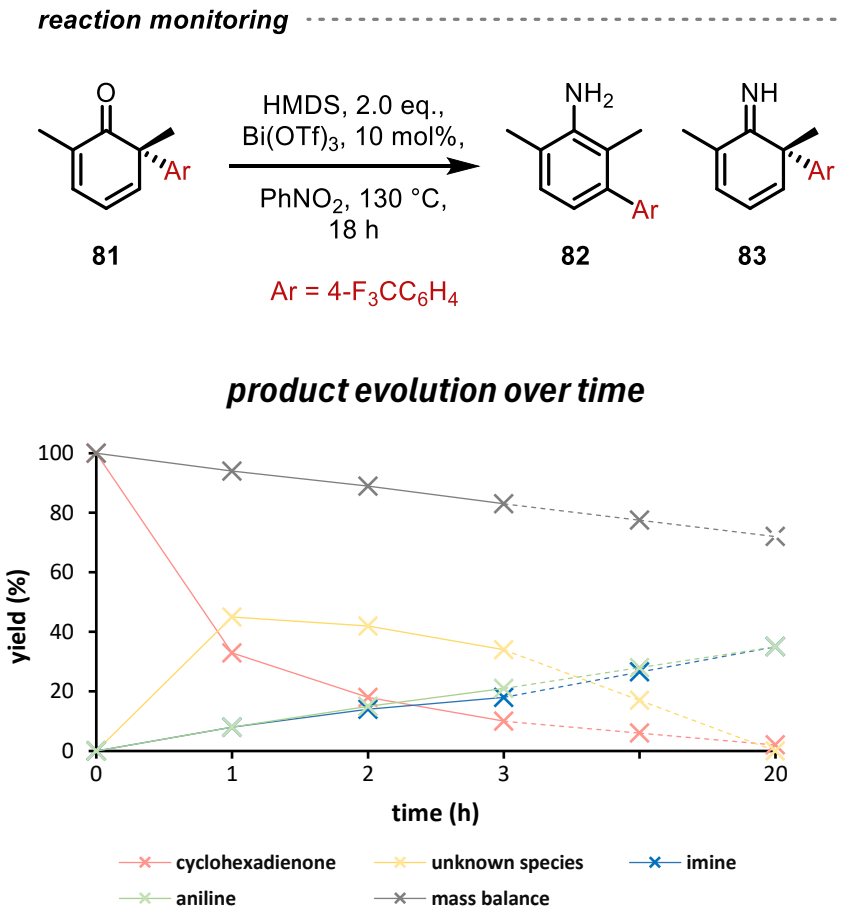


Figure 1: Abundance of species in reaction mixture over 20 hours. Yields determined *via* quantitative ^{19}F NMR spectroscopy.

Throughout the reaction, there appear to be 4 major species present by ^{19}F NMR spectroscopy with only 2 remaining once the starting material is consumed. Almost 70% of the **81** (pink) was consumed in the first hour of the reaction and was completely consumed over the reaction course. There is an unidentified species (yellow) which appears to form at a similar rate as the cyclohexadienone is consumed, though its abundance dropped to 0% between 1 and 20 h. This identity of this apparent reaction intermediate has not yet been elucidated. Interestingly, aniline **82** (green) appears to grow in abundance at a similar rate as imine **83** (blue). Further, the sum of the yields of each species (grey) decreases over the 20 hours. It is not yet known why this is, although dimerization *via* Diels-Alder cycloaddition or polymerisation processes are suspected.[182,183]

Conclusion and Future Work

Investigations towards a novel phenol deoxyamination protocol constituting the conversion of aryl cyclohexadienones to *meta*-arylated aniline is reported. This methodology hinges on the successful dienone-phenol rearrangement reported by Senior in the synthesis of *meta*-arylated phenols. In this work, an analogous dienamine-aniline rearrangement enables the synthesis of *meta*-arylated anilines.

As anticipated, cyclohexadienones bearing electronically different arenes require alternative reaction conditions to permit the deoxyamination. Electron-poor arenes require higher temperature to facilitate the deoxyamination to the aniline, whereas electron-rich systems demand 1-adamantanol as a water equivalent. This is hypothesised to raise the concentration of ammonia in the reaction mixture, thus favouring aniline selectivity over phenol.

Product isolation from nitrobenzene remains a key deterrent to the progress of this methodology. Our attempts including recovery of the anilinium salt, use of solid cationic exchange, acid base extraction, distillation *via* kugelrohr, vacuum distillation of nitrobenzene and elution of nitrobenzene upon adsorption to silica have not been fruitful. Therefore, future work on this methodology predominantly lies in a robust isolation procedure, or identification of a high yielding, lower boiling solvent.

It is hoped that the foundational investigation into this methodology will eventually lead to the realisation of a successful deoxyamination protocol, following assessment of substrate compatibility and practical aniline isolation.

Chapter V

Experimental

General Information

Procedures employing oxygen- and/or moisture-sensitive materials were performed with anhydrous solvents using standard inert-atmosphere techniques (atmosphere of anhydrous dinitrogen). Analytical thin-layer chromatography was performed on precoated aluminium-backed plates (Silica Gel 60 F254; Merck), and visualized using a combination of UV light (254 nm) and staining (acidic ethanolic vanillin, aqueous basic potassium permanganate, or aqueous methanolic iron(III) chloride). Manual flash column chromatography was performed using Scharlab 60 silica gel (35-70 mesh); automated flash column chromatography was performed on disposable columns pre-packed with 50 μm spherical silica gel using a Büchi C-850 or C-815 equipped with a UV-vis DAD (200-800 nm) and an ELSD.

NMR spectra were recorded at 25 °C on Bruker Avance 500 or 400 spectrometers (^{1}H, 500 / 400 MHz; ^{13}C{^{1}H}, 125 / 100 MHz; ^{19}F NMR, 471 / 376 MHz). Chemical shifts are reported in ppm; coupling constants, *J*, are reported in Hz and are uncorrected for digitization. The following abbreviations (and their combinations) are used to label the multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), m (multiplet) and br (broad), and app (apparent). Structural assignments were made with the assistance of COSY, HSQC, HMBC and NOESY.

^{1}H and ^{13}C{^{1}H} chemical shifts are reported relative to tetramethylsilane, and are referenced to the appropriate residual solvent peaks:

- $CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm
- DMSO-d_6: δ_H = 2.50 ppm, δ_C = 39.52 ppm
- C_6D_6: δ_H = 7.16 ppm, δ_C = 128.06 ppm

^{19}F chemical shifts are reported relative to $CFCl_3$.

Infrared spectra of neat compounds were recorded over the range 4000-600 cm^{-1} using either a PerkinElmerSpectrum 1000 Series FTIR spectrometer with an ATR diamond cell, or a Bruker Alpha FTIR spectrometer fitted with a Bruker Platinum ATR QuicksnapTM diamond cell. Melting points were measured using Stuart

SMP10 or Gallenkamp melting point apparatus in open capillaries. High resolution electrospray ionization mass spectra (HRMS) were recorded using a Bruker ESI-TOF MicroTOF II spectrometer.

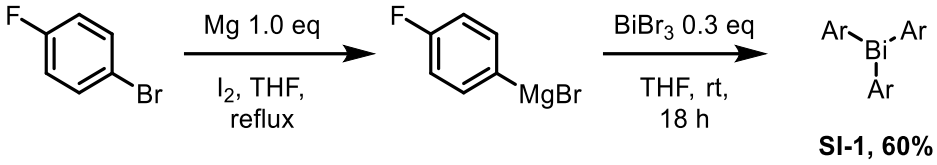
Reagent grade solvents (Fisher Technical) were employed. CH_2Cl_2 was dried over activated 3Å molecular sieves. THF was dried using an Inert PureSolv Grubbs-type system (activated alumina columns, argon atmosphere). All reagents were obtained from commercial sources and, with the following exceptions, were used as received:

- $BiBr_3$ (99.9%; Acros) was dried by stirring under vacuum (*ca* 10^{-2} mbar) at 40 °C for 1 h before use.
- *n*-Butyllithium (*ca* 2.5 M in hexanes; Sigma-Aldrich) was titrated against *N*-benzyl benzamide before use.
- *m*CPBA (*ca* 70%; Sigma-Aldrich) was titrated against triphenylphosphine before use.
- Bismacycle bromide (10-Bromo-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide) was prepared by Andy Fox, according to literature procedure.[184]

Procedures and Data for Organo-bismuth Compounds

Synthesis of Bismacycle Precursors

Tri(4-fluorophenyl)bismuth (SI-1)



SI-1, 60%

A flame dried flask was evacuated and back-filled three times with anhydrous dinitrogen before magnesium turnings (8.05 g, 330 mmol) and 2-3 crystals of iodine were added under a flow of nitrogen. Anhydrous THF (150 mL) was added *via* cannula on stirring and the suspension was cooled to 0 °C, before the dropwise addition of 4-bromofluorobenzene (36.3 mL, 330 mmol) *via* syringe over 20 min to generate the Grignard reagent. The reaction mixture was heated at reflux over 1 h.

A second flame dried flask containing bismuth tribromide (44.8 g, 100 mmol) was evacuated and back-filled three times with anhydrous dinitrogen and dissolved in a minimum volume of anhydrous THF. The solution of Grignard reagent was added dropwise *via* cannula and the reaction mixture was left to stir for 18 h at rt. The reaction was quenched with methanol (30 mL), filtered through a pad of silica gel (5 mL) which was eluted with Et_2O (2 × 50 mL). The resulting solution was stirred with water (50 mL) for 5 min and the aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The collected organic portions were dried over $MgSO_4$, filtered through a pad of silica gel (5 mL) once more, eluted with Et_2O (2 × 50 mL) and the solvents removed in *vacuo* to obtain the crude triaryl bismuth. The solids were recrystallised from the minimum volume of hot ethanol to afford the title compound as an off white powder (29.4 g, 59.5 mmol, 60%). Characterisation data were consistent with literature values: ^1H, $^{13}C\{^1H\}$, ^{19}F NMR and MP.[185]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.64 (6H, dd, J = 8.5, 6.2 Hz), 7.08 (6H, app. t, J = 9.4).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ_C 163.0 (d, J = 247.3 Hz), 149.7, 139.3 (d, J = 7.0 Hz), 118.1 (d, J = 19.8 Hz).

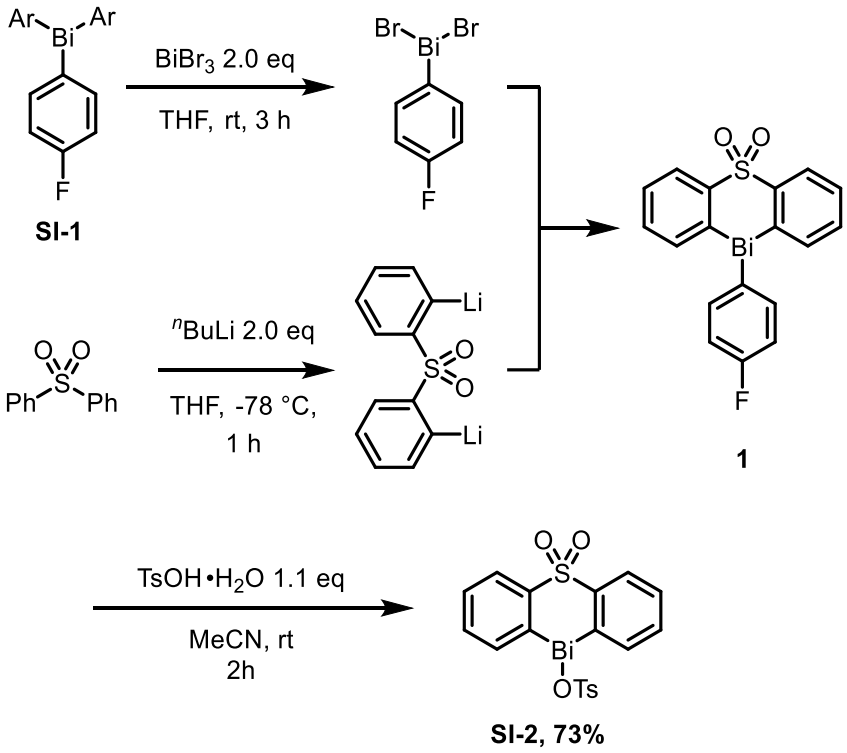
^{19}F NMR (376 MHz, $CDCl_3$): δ_F -112.8 (tt, J = 9.4, 6.0 Hz).

IR (ATR-IR, neat) υ_{max}: 2980, 1895, 1710, 1638, 1572, 1482, 1442, 1406, 1382, 1310, 1268, 1209, 1156, 1084, 1043, 1013, 981.

HRMS (ESI$^-$): m/z calcd. for $[C_{12}H_8BiF_2]^-$ [M-Ar^F]$^-$: 399.0398. Found: 399.0396.

MP: 95-96 °C.

5,5-Dioxido-10*H*-dibenzo[*b*,*e*][1,4]thiabismin-10-yl 4-methylbenzenesulfonate (SI-2)



A flame dried flask containing diphenylsulfone (6.55 g, 30.0 mmol) was evacuated and back-filled three times with anhydrous dinitrogen before anhydrous THF was added (60 mL). The solution was cooled to -78 °C before *n*BuLi (2.5 M in hexanes; 24 mL, 60.0 mmol) was added dropwise *via* syringe over 20 min and left to stir for 1 h at -78 °C, forming a cream suspension.

A flame dried flask containing tri(4-fluorophenyl)bismuthane (4.94 g, 10.0 mmol) and $BiBr_3$ (9.02 g, 20.0 mmol) was evacuated and backfilled three times with anhydrous dinitrogen before anhydrous THF (60 mL) was added at -78 °C. The resulting yellow suspension was stirred for 3 h at rt. This was then added dropwise into the previously prepared suspension of dilithiodiphenylsulfone *via* cannula,

and the resulting orange suspension was left to stir at rt over 18 h. MeOH (30 mL) was added to the suspension and stirred for 5 min before it was concentrated *in vacuo*. The remaining solids were dissolved in DCM (100 mL), filtered through a pad of silica gel (5 mL) and eluted with DCM (2 × 100 mL) to afford a yellow solution which was then stirred vigorously with aqueous saturated $NaHCO_3$ (100 mL) for 30 min. The aqueous portions were separated and extracted with DCM (3 × 20 mL), and the combined organic portions were dried over $MgSO_4$, filtered through a pad of silica gel (5 mL) once again, eluted with DCM (2 × 100 mL) then concentrated *in vacuo* to afford the intermediate aryl bismacycle **1** as an off-white foam.

The crude aryl bismacycle **1** was dissolved in MeCN (60 mL) at rt, *p*-toluenesulfonic acid monohydrate (6.27 g, 33.0 mmol) was added and left to stir. After 2 h, the white suspension was filtered under reduced pressure through glass fibre filter paper and the resulting solid was washed with cold MeCN (3 × 20 mL), then Et_2O (20 mL) to afford **SI-2** as a colourless solid (11.4 g, 21.9 mmol, 73% over 2 steps from tri(4-fluorophenyl)bismuth. Characterisation data were consistent with literature values: ^1H, ^{13}C, IR, and MP.[71]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.93 (2H, dd, *J* = 7.4, 0.6 Hz), 8.40 (2H, dd, *J* = 7.7, 0.7 Hz), 7.87-7.77 (4H, m; including app. td at 7.79 ppm, *J* = 7.5, 1.3 Hz), 7.50 (2H, app. td, *J* = 7.6, 1.1 Hz), 7.29 (2H, d, *J* = 8.2 Hz), 2.42 (3H, s).

^{1}H NMR (400 MHz, DMSO-d_6): δ_H 8.82 (2H, dd, *J* = 7.3, 1.2 Hz), 8.46 (2H, dd, *J* = 7.7, 1.2 Hz), 7.88 (2H, app. td, *J* = 7.4, 1.2 Hz), 7.55 (2H, app. td, *J* = 7.7, 1.2 Hz), 7.48 (2H, d, *J* = 8.1 Hz), 7.11 (2H, d, *J* = 7.9), 2.29 (3H, s)

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ_C 201.7, 145.8, 141.9, 137.6, 136.2, 135.3, 128.8, 128.0, 127.2, 125.5, 20.8.

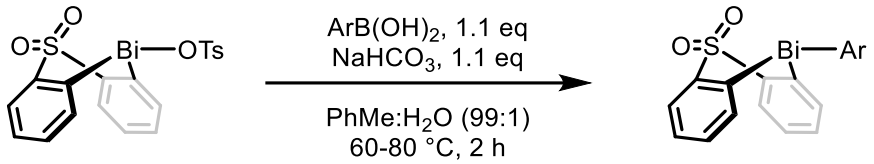
IR (ATR-IR, neat) υ_{max}: 3293, 3071, 2914, 1598, 1467, 1440, 1377, 1294,1242, 1199, 1158, 1100, 1039, 1011, 980, 907.

HRMS (ESI$^+$): *m*/*z* calcd. for $[C_{19}H_{15}BiO_5S_2Na]^+$ $[M+Na]^+$: 619.0057. Found: 619.0056.

MP: 189-190 °C.

Synthesis of Aryl Bismacycles

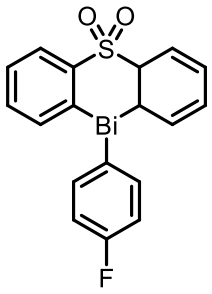
General Procedure for Transmetallation (GP1)



SI-2

SI-2 (1.00 mmol), $NaHCO_3$ (84.0 mg, 1.10 mmol) and arylboronic acid (1.10 mmol) were suspended in a mixture of toluene (10 mL) and water (0.5 mL) and stirred at 60 °C until no starting material was observed by ^1H NMR spectroscopy. Aqueous NaOH (2.0 M; 10 mL) was added once the reaction mixture was cooled to rt and stirred vigorously for 15 min. The organic phase was removed and remaining aqueous portion was extracted with EtOAc (3 × 10 mL). The combined organic portions were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to obtain the title compound.

10-(4-Fluorophenyl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide (1)



Synthesised according to **GP-1** on a 1 mmol scale using (4-fluorophenyl)boronic acid to yield the title compound as a colourless solid (437 mg, 0.84 mmol, 84%). Characterisation data were consistent with literature values: ^{1}H, ^{13}C{^{1}H}, ^{19}F NMR and MP. [71]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.38 (2H, dd, *J* = 7.6, 1.3 Hz), 7.85 (2H, dd, *J* = 7.1, 1.2 Hz), 7.71 (2H, dd *J* = 8.5, 6.2 Hz), 7.41 (2H, app. td, J = 7.5, 1.3 Hz), 7.36 (2H, app. td, *J* = 7.4, 1.4 Hz), 7.07 (2H, dd, *J* = 9.3, 8.5 Hz).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ_C 163.1 (d, *J* = 248.4 Hz), 160.7 (br), 158.8 (br), 141.8, 141.0 (d, *J* = 7.2 Hz), 137.6, 133.7, 128.4, 127.3, 118.4 (d, *J* 19.9 Hz).

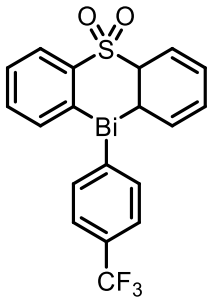
^{19}F NMR (376 MHz, $CDCl_3$): δ_F -111.15 (1F, tt, *J* = 9.3, 6.2 Hz).

IR (ATR-IR, neat) υ_{max}: 3051, 1572, 1484, 1438, 1383, 1300, 1285, 1252, 1219, 1149, 1122, 1087, 1073, 1044, 1012, 907.

HRMS (ESI^{+}): *m*/*z* calcd. for $[C_{18}H_{12}BiFO_2SNa]^{+}$ $[M+Na]^{+}$: 543.0238. Found: 543.0235.

MP: 178-180 °C.

10-(4-(Trifluoromethyl)phenyl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide (SI-3)



Synthesised according to **GP-1** on a 1 mmol scale using (4-(trifluoromethyl)phenyl)boronic acid to yield the title compound as a colourless solid (475 mg, 0.83 mmol, 83%). Characterisation data were consistent with literature values: ^{1}H, ^{13}C{^{1}H} and ^{19}F NMR.[71]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.40 (2H, dd, *J* = 7.6, 1.2 Hz), 7.90 (2H, d, *J* = 7.6 Hz), 7.83 (2H, dd, *J* = 7.2, 1.2 Hz), 7.62 (2H, d, *J* = 7.6 Hz), 7.43 (2H, app. td, *J* = 7.6, 1.4 Hz), 7.37 (2H, app. td, *J* = 7.2, 1.4).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ_C 170.0, 158.9, 141.7, 139.2, 137.5, 133.7, 130.6 (q, *J* = 32.4 Hz), 128.5, 127.4, 127.3 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 272.2 Hz).

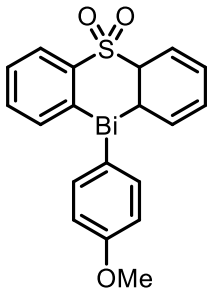
^{19}F NMR (376 MHz, $CDCl_3$): δ_F -62.84.

IR (ATR-IR, neat) υ_{max}: 3052, 1565, 1653, 1440, 1388, 1322, 1286, 1252, 1150, 1122, 1089, 1074, 1041, 1009, 908.

HRMS (ESI^{+}): *m*/*z* calcd. for $[C_{19}H_{13}BiF_3O_2S]^+$ $[M+H]^+$: 571.0387. Found: 571.0393

MP: 188-190 °C.

10-(4-Methoxyphenyl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide (SI-4)



Synthesised according to **GP-1** on a 3 mmol scale using (4-methoxyphenyl)boronic acid to yield the title compound as a colourless solid with no further purification (1.43 g, 2.70 mmol, 89%). Characterisation data were consistent with literature values: ^{1}H, ^{13}C{^{1}H} NMR and MP.[71]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.37 (2H, dd, *J* = 7.6, 1.0 Hz), 7.87 (2H, dd, *J* = 7.1, 1.0 Hz), 7.65 (2H, d, *J* = 8.5 Hz), 7.39 (2H, app. td, *J* = 7.6, 1.0 Hz) 7.33 (2H, app td. *J* = 7.2, 1.0 Hz), 6.93 (2H, d, *J* = 8.5 Hz), 3.80 (3H, s).

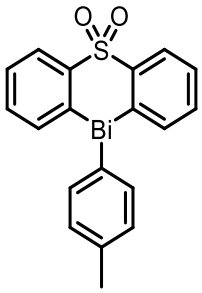
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 160.0, 158.5 (br), 156.9 (br), 141.8, 140.4, 137.7, 133.5, 128.2, 127.1, 116.9, 55.1.

IR (ATR-IR, neat) υ_{max}: 3044, 2939, 2834, 1579, 1569, 1488, 1438, 1393, 1298, 1282, 1242, 1178, 1149, 1122, 1087, 1073, 1057, 1024, 907.

HRMS (ESI^{+}): *m*/*z* calcd. for $[C_{19}H_{16}BiO_3S]^+$ $[M+H]^+$: 533.0619. Found: 533.0615

MP: 217-219 °C.

10-(*p*-Tolyl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide (SI-5)



Synthesised according to **GP-1** on a 0.8 mmol scale using *p*-tolylboronic acid to yield the title compound as a colourless solid with no further purification (401 mg, 0.78 mmol, 97%). Characterisation data were consistent with literature values: ^{1}H, ^{13}C{^{1}H} NMR and MP.[71]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.38 (2H, dd, *J* = 7.6, 1.4 Hz), 7.87 (2H, dd, *J* = 7.3, 1.4 Hz), 7.65 (2H, d, *J* = 7.8 Hz), 7.39 (2H, app. td, *J* = 7.6, 1.4 Hz), 7.33 (2H, app. td, *J* = 7.3, 1.4 Hz), 7.24 (2H, d, *J* = 7.8 Hz), 2.34 (3H, s).

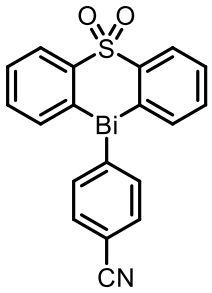
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 162.4, 158.5, 141.8, 138.9, 138.7, 137.7, 133.5, 131.8, 128.2, 127.1, 21.8.

IR (ATR-IR, neat) υ_{max}: 3048, 2922, 2855, 1562, 1487, 1439, 1386, 1303, 1286, 1252, 1209, 1185, 1151, 1122, 1109, 1088, 1074, 1054.

HRMS (ESI^{+}): *m*/*z* calcd. for $[C_{19}H_{15}BiNaO_2S]^{+}$ $[M+Na]^{+}$: 539.0489. Found: 539.0497.

MP: 213-215 °C.

4-(5,5-Dioxido-10*H*-dibenzo[*b*,*e*][1,4]thiabismin-10-yl)benzonitrile (SI-6)



Synthesised according to **GP-1** on a 0.7 mmol scale using *p*-cyanophenylboronic acid to yield the title compound as a colourless solid with no further purification (282 mg, 0.54 mmol, 77%). Characterisation data were consistent with literature values: ^{1}H, ^{13}C{^{1}H} NMR and HRMS.[71]

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 8.41 (2H, dd, *J* = 7.6, 1.4 Hz), 7.90 (2H, d, *J* = 8.0 Hz), 7.81 (2H, dd, *J* = 7.2, 1.4 Hz), 7.64 (2H, d, *J* = 8.0 Hz), 7.44 (2H, dd, *J* = 7.6, 1.4 Hz), 7.39 (2H, dd, *J* = 7.2, 1.4 Hz).

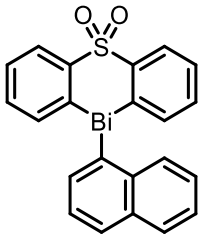
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ_C 171.9, 159.3, 141.8, 139.6, 137.5, 134.0, 133.9, 128.8, 127.6, 118.9, 112.4.

IR (ATR-IR, neat) υ_{max}: 3019, 1513, 1473, 1214, 1111, 1028, 928.

HRMS (ESI^{+}): *m*/*z* calcd. for $[C_{19}H_{12}BiNNaO_2S]^{+}$ [M+Na]$^{+}$: 550.0290. Found: 550.0275.

MP: decomp. 210 ˚C.

10-(Naphthalen-1-yl)-4a,10a-dihydro-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide (SI-7)



Synthesised according to **GP-1** on a 0.7 mmol scale using naphthalen-1-ylboronic acid to yield the title compound as a colourless solid with no further purification (290 mg, 0.53 mmol, 76%). Characterisation data were consistent with literature values: ^{1}H, ^{13}C{^{1}H} NMR and MP.[71]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.43 (2H, d, *J* = 7.7 Hz), 8.11 – 7.88 (4H, m), 7.81 (2H, d, *J* = 7.3 Hz), 7.56 – 7.47 (1H, m), 7.49 – 7.35 (4H, m), 7.26 (2H, appt. t, *J* = 7.3 Hz).

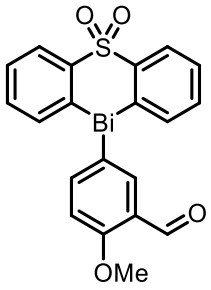
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 167.7, 157.9, 141.8, 140.3, 139.1, 138.1, 134.9, 133.5, 130.8, 129.7, 129.3, 128.9, 128.4, 127.2, 126.5, 126.1.

IR (ATR-IR, neat) υ_{max}: 2922, 2854, 2325, 2248, 2208, 2163, 2050, 2023, 1998, 1980, 1918, 1563, 1303, 1286, 1252, 1151, 1109, 1087, 1073, 1013.

HRMS (ESI^{+}): *m*/*z* calcd. for $[C_{22}H_{15}BiO_2NaS]^{+}$ $[M+Na]^{+}$: 575.0489. Found: 575.0503.

MP: 223-225 °C.

5-(5,5-Dioxido-10*H*-dibenzo[*b*,*e*][1,4]thiabismin-10-yl)-2-methoxybenzaldehyde (SI-8)



Synthesised according to **GP1** on a 0.6 mmol scale using (3-formyl-4-methoxyphenyl)boronic acid. This synthesis was conducted in a 2% biphasic solution of water in toluene and was heated to 80 °C. Further purification *via* automated column chromatography (20% EtOAc in cyclohexane) provided the title compound as a colourless solid (160 mg, 0.29 mmol, 48%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.55 (1H, s), 8.38 (2H, dd, *J* = 7.6, 1.4 Hz), 8.31 (1H, d, *J* = 1.7 Hz), 7.84 (2H, dd, *J* = 7.2, 1.4 Hz), 7.78 (1H, dd, *J* = 8.4, 1.7 Hz), 7.41 (2H, app. td, *J* = 7.6, 1.4 Hz), 7.35 (2H, app. td, *J* = 7.2, 1.4 Hz), 6.94 (1H, d, *J* = 8.4 Hz), 3.91 (3H, s).

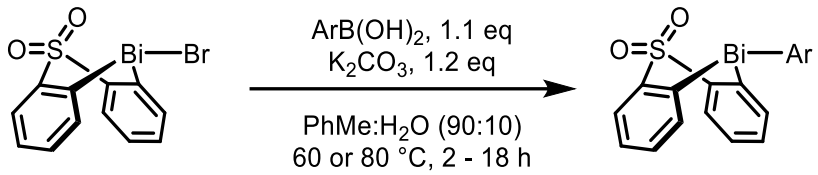
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 189.8, 162.0, 158.5, 156.5, 147.3, 141.7, 138.3, 137.4, 133.5, 128.3, 127.2, 126.2, 114.9, 55.6.

IR (ATR-IR, neat) υ_{max}: 3019, 2979, 1712, 1681, 1581, 1565, 1505, 1469, 1440, 1387, 1368, 1304, 1286, 1252, 1215, 1151, 1121, 1088, 1074, 1047, 1022, 1014, 997.

HRMS (ESI^{+}): *m*/*z* calcd. for $[C_{20}H_{15}BiNaO_4S]^{+}$ $[M+Na]^{+}$: 583.0387. Found: 583.0393.

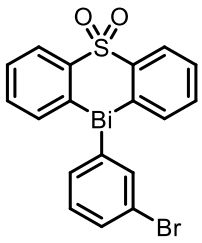
MP: 194-196 °C.

General Procedure for Transmetallation (GP2)



10-Bromo-10*H*-dibenzo[*b,e*][1,4]thiabismine 5,5-dioxide (505 mg, 1.00 mmol), arylboronic acid (1.10 mmol) and K_2CO_3 (165 mg, 1.2 mmol) were suspended in a 10 mL biphasic solution of 10% H_2O in PhMe and stirred at 60 °C for 18 h. The reaction was cooled to rt and diluted with EtOAc (10 mL); aqueous NaOH (2.0 M; 10 mL) was added and the suspension was stirred for 5 min. The aqueous phase was removed, and the remaining organic potion was subsequently washed with H_2O (2 × 10 mL) and brine (2 × 10 mL). The organic portion was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to obtain the title compound.

10-(3-Bromophenyl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide (SI-9)



Synthesised according to **GP-2** on a 1.5 mmol scale using (3-bromophenyl)boronic acid to yield the title compound as a colourless solid with no further purification (714 mg, 1.23 mmol, 81%). Characterisation data were consistent with literature values: ^{1}H, ^{13}C{^{1}H} NMR and HRMS.[71]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.39 (2H, dd, *J* = 7.5, 1.5 Hz), 7.93 (1H, dd, *J* = 2.0, 1.0 Hz), 7.87 (2H, dd, *J* = 7.1, 1.4 Hz), 7.65 (1H, app. td, *J* = 7.3, 1.0 Hz), 7.48 (1H, ddd, *J* = 7.7, 2.0, 1.0 Hz), 7.41 (2H, dd, *J* = 7.5, 1.4 Hz), 7.37 (2H, app. td, *J* = 7.0, 1.5 Hz), 7.34 – 7.27 (1H, m)

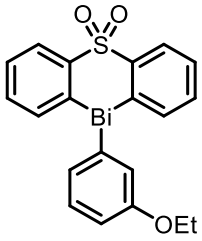
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 167.5, 159.2, 141.8, 141.0, 137.5, 137.1, 133.8, 132.8, 131.8, 128.5, 127.4, 126.4.

IR (ATR-IR, neat) υ_{max}: 3018, 2972, 1576, 1381, 1305, 1286, 1253, 1214, 1152, 1124, 1088, 1013, 946.

HRMS (ESI^{+}): *m*/*z* calcd. for $[C_{18}H_{12}Bi^{79}BrNaO_2S]^{+}$ $[M+Na]^{+}$: 602.9443. Found: 602.9427.

MP: 215-217 °C.

10-(3-Ethoxyphenyl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide (SI-10)



Synthesised according to **GP-2** on a 1.5 mmol scale using (3-ethoxyphenyl)boronic acid to yield the title compound as a colourless solid with no further purification (744 mg, 1.36 mmol, 90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.38 (2H, dd, *J* = 7.5, 1.5 Hz), 7.90 (2H, dd, *J* = 7.0, 1.4 Hz), 7.44 – 7.29 (7H, m), 6.87 (1H, ddd, *J* = 8.1, 5.0, 2.6, 1.1 Hz), 3.91 (2H, q, *J* = 7.0 Hz), 1.34 (3H, d, *J* = 7.0 Hz)

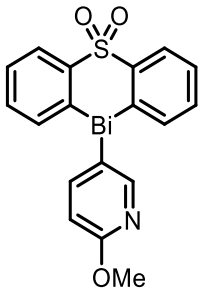
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 166.4, 161.4, 158.6, 141.7, 137.6, 133.4, 131.8, 130.5, 128.2, 127.1, 124.8, 114.7, 63.4, 14.8.

IR (ATR-IR, neat) υ_{max}: 3018, 2978, 1574, 1499, 1467, 1425, 1351, 1302, 1284, 1252, 1215, 1150, 1121, 1087, 1073, 1045, 1013, 989, 948, 927.

HRMS (ESI$^+$): *m*/*z* calcd. for $[C_{20}H_{17}BiNaO_3S]^+$ $[M+Na]^+$: 569.0600. Found: 569.0595.

MP: 158-161 °C.

10-(6-Methoxypyridin-3-yl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide (SI-11)



Synthesised according to **GP-2** on a 1.5 mmol scale using (6-methoxypyridin-3-yl)boronic acid to yield the title compound as a colourless solid with no further purification (658 mg, 1.19 mmol, 79%). Characterisation data were consistent with literature values: ^{1}H, ^{13}C{^{1}H} NMR and MP.[71]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.40 – 8.35 (3H, m), 7.87 (2H, dd, *J* = 7.3, 1.4 Hz), 7.74 (1H, dd, *J* = 8.3, 1.9 Hz), 7.41 (2H, app. td, *J* = 7.5, 1.4 Hz), 7.36 (2H, app. td, *J* = 7.4, 1.5 Hz), 6.70 (1H, dd, *J* = 8.3, 0.8 Hz), 3.94 (3H, s).

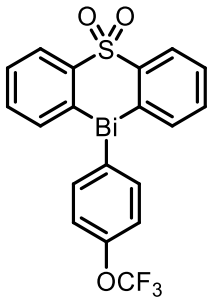
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 164.3, 157.6, 156.0, 151.8, 149.1, 141.8, 137.6, 133.7, 128.5, 127.3, 114.7, 53.5.

IR (ATR-IR, neat) υ_{max}: 3018, 1571, 1551, 1499, 1477, 1427, 1350, 1302, 1283, 1252, 1214, 1178, 1150, 1124, 1087, 1073, 1013, 948.

HRMS (ESI^{+}): *m*/*z* calcd. for $[C_{18}H_{15}BiNO_3S]^{+}$ $[M+H]^{+}$: 534.0577. Found: 534.0569.

MP: 233-235 ˚C.

10-(4-(Trifluoromethoxy)phenyl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide (SI-12)



Synthesised according to **GP-2** on a 1.5 mmol scale using (4-(trifluoromethoxy)phenyl)boronic acid to yield the title compound as a colourless solid (820 mg, 1.40 mmol, 93%). Characterisation data were consistent with literature values: ^{1}H, ^{13}C{^{1}H} NMR and MP.[71]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.40 (2H, d, *J* = 7.5 Hz), 7.85 (2H, d, *J* = 7.2 Hz), 7.78 (2H, d, *J* = 8.0 Hz), 7.42 (2H, app. t, *J* = 7.5 Hz), 7.37 (2H, app. t, *J* = 7.2 Hz), 7.22 (2H, d, *J* = 8.0 Hz).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 163.6, 158.8, 149.5 (q, *J* = 1.9 Hz), 141.7, 140.5, 137.5, 133.7, 128.4, 127.3, 123.2, 120.4 (q, *J* = 257.6 Hz).

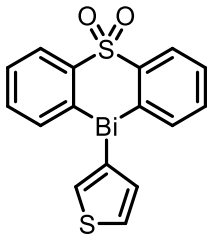
^{19}F NMR (376 MHz, $CDCl_3$): δ_F -57.68.

IR (ATR-IR, neat) υ_{max}: 3052, 2258, 1902, 1563, 1486, 1438, 1388, 1302, 1250, 1217, 1202, 1149, 1123, 1108, 1087, 1073, 1050, 1029, 1010, 953, 907.

HRMS (ESI^{+}): *m*/*z* calcd. for $[C_{19}H_{12}BiF_3NaO_3S]^{+}$ $[M+H]^{+}$: 609.0161. Found: 609.0147.

MP: 173-176 ˚C.

10-(Thiophen-3-yl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide (SI-13)



Synthesised according to **GP-2** on a 1.5 mmol scale using thiophen-3-ylboronic acid to yield the title compound as a colourless solid with no further purification (711 mg, 1.40 mmol, 93%). Characterisation data were consistent with literature values: ^{1}H, ^{13}C{^{1}H} NMR and MP.[71]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.37 (2H, dd, *J* = 7.5, 1.5 Hz), 7.90 (2H, dd, *J* = 7.5, 1.5 Hz), 7.66 (1H, dd, *J* = 2.5, 1.0 Hz), 7.44 – 7.32 (5H, m), 6.97 (1H, dd, *J* = 4.8, 1.0 Hz).

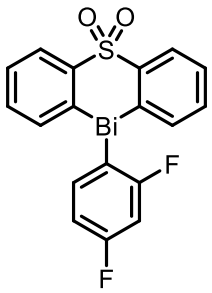
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 158.8, 157.2, 141.8, 137.7, 136.8, 136.0, 133.4, 129.0, 128.4, 127.3.

IR (ATR-IR, neat) υ_{max}: 3048, 1562, 1438, 1426, 1368, 1301, 1286, 1252, 1215, 1197, 1178, 1149, 1121, 1107, 1087, 1072, 1013, 954.

HRMS (ESI^{+}): *m*/*z* calcd. for $[C_{16}H_{11}BiNaO_2S_2]^{+}$ $[M+Na]^{+}$: 530.9902. Found: 530.9882.

MP: 188-190 ˚C.

10-(2,4-Difluorophenyl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide (SI-14)



Synthesised according to **GP-2** on a 0.79 mmol scale using (2,4-difluorophenyl)boronic acid. This reaction was conducted in a 2% biphasic solution of water in toluene and was heated to 80 °C to yield the title compound as a colourless solid with no further purification (380 mg, 0.70 mmol, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.37 (2H, dd, *J* = 7.5, 1.5 Hz), 7.91 (2H, dd, *J* = 7.0, 1.5 Hz), 7.45 – 7.35 (5H, m), 6.99 (1H, ddd, *J* = 9.3, 7.0, 2.4 Hz), 6.75 (1H, app. td, *J* = 8.4, 2.4 Hz).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 166.6 (dd, *J* = 236.8, 11.7 Hz), 163.9 (dd, *J* = 250.3, 12.0 Hz), 158.3, 144.2 (d, *J* = 41.1 Hz), 141.9, 141.7 (dd, *J* = 14.7, 9.1 Hz), 137.73, 133.73, 128.5, 127.4, 115.8 (dd, *J* = 20.0, 3.3 Hz), 103.6 (dd, *J* = 31.9, 24.3 Hz).

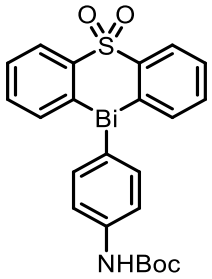
^{19}F NMR (376 MHz, $CDCl_3$): δ_F -91.2 – -91.3 (1F, m), -108.1 (1F, ddd, *J* = 15.7, 8.4, 7.0 Hz).

IR (ATR-IR, neat) υ_{max}: 2923, 2852, 1594, 1579, 1564, 1472, 1462, 1437, 1396, 1304, 1281, 1262, 1253, 1223, 1150, 1128, 1108, 1089, 1074, 1026, 1012, 956.

HRMS (ESI^{+}): *m/z* calcd. for $[C_{18}H_{11}BiF_2NaO_2S]^{+}$ $[M+Na]^{+}$: 561.0144. Found: 561.0146.

MP: 240-242 °C.

***tert*-Butyl (4-(5,5-dioxido-10*H*-dibenzo[*b*,*e*][1,4]thiabismin-10-yl)phenyl)carbamate (SI-15)**



Synthesised according to **GP-2** on a 0.8 mmol scale using (4-((tert-butoxycarbonyl)amino)phenyl)boronic acid to yield the title compound as a colourless solid with no further purification (289 mg, 0.47 mmol, 58%). Characterisation data were consistent with literature values: ^{1}H, ^{13}C{^{1}H} and IR. [71]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.36 (2H, d, *J* = 7.6 Hz), 7.86 (2H, d, *J* = 7.2 Hz), 7.66 (2H, d, *J* = 7.8 Hz), 7.40 – 7.36 (4H, m), 7.32 (2H, app. t, *J* = 7.2 Hz), 6.53 (1H, s), 1.50 (9H, s).

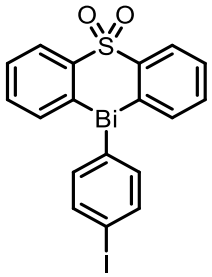
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 159.5, 158.5, 152.7, 141.0, 139.8, 138.8, 137.7, 133.5, 128.2, 127.1, 120.9, 80.9, 28.4.

IR (ATR-IR, neat) υ_{max}: 3349, 3013, 2977, 2927, 1712, 1582, 1505, 1440, 1387, 1367, 1302, 1284, 1251, 1227, 1149, 1121, 1088, 1073, 1046, 1022, 953, 900.

HRMS (ESI^{+}): *m*/*z* calcd. for $[C_{23}H_{22}BiNNaO_4S]^{+}$ $[M+Na]^{+}$: 640.0966. Found: 640.0991.

MP: decomp at 230 °C.

10-(4-Iodophenyl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide (SI-16)



Synthesised according to **GP-2** on a 0.8 mmol scale using (4-iodophenyl)boronic acid to yield the title compound as a colourless solid with no further purification (466 mg, 0.74 mmol, 92%). Characterisation data were consistent with literature values: ^{1}H, ^{13}C{^{1}H} and MP. [71]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.38 (2H, dd, *J* = 7.6, 1.5 Hz), 7.85 (2H, dd, *J* = 7.2, 1.4 Hz), 7.73 (2H, d, *J* = 8.0 Hz), 7.49 (2H, d, *J* = 8.0 Hz), 7.41 (2H, app. td, *J* = 7.6, 1.4 Hz), 7.36 (2H, app. td, *J* = 7.2, 1.5 Hz).

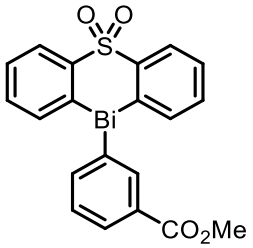
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 164.9, 158.3, 141.8, 140.6, 139.9, 137.6, 133.7, 128.4, 127.3, 95.6.

IR (ATR-IR, neat) υ_{max}: 2978, 1706, 1583, 1563, 1546, 1511, 1468, 1437, 1426, 1387, 1365, 1302, 1285, 1252, 1221, 1150, 1122, 1108, 1087, 1073, 1046, 1034, 1022, 1013, 996, 953.

HRMS (ESI^{+}): *m*/*z* calcd. for $[C_{18}H_{12}BiINaO_2S]^{+}$ $[M+Na]^{+}$: 650.9299. Found: 650.9322.

MP: 176-178 °C.

Methyl 3-(5,5-dioxido-10*H*-dibenzo[*b*,*e*][1,4]thiabismin-10-yl)benzoate (SI-17)



Synthesised according to **GP-2** on a 0.6 mmol scale using (3-(methoxycarbonyl)phenyl)boronic acid to yield the title compound as a colourless solid with no further purification (236 mg, 0.42 mmol, 70%). Characterisation data were consistent with literature values: ^{1}H, ^{13}C{^{1}H} and MP.[186]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.56 (1H, s), 8.39 (2H, d, *J* = 7.7, Hz), 8.03 (1H, d, *J* = 7.9 Hz), 7.88 – 7.80 (3H, m), 7.47 – 7.38 (3H, m), 7.34 (2H, app. td, *J* = 7.3, 1.4 Hz), 3.89 (3H, s).

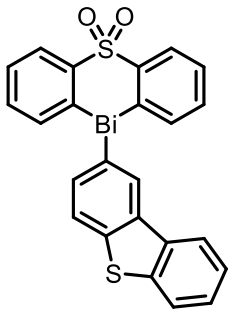
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 167.3, 165.7, 158.8, 143.7, 141.7, 139.1, 137.5, 133.7, 131.9, 131.2, 129.8, 128.4, 127.3, 52.3.

IR (ATR-IR, neat) υ_{max}: 3019, 2400, 1214, 929.

HRMS (ESI^{+}): *m*/*z* calcd. for $[C_{20}H_{15}BiNaO_4S]^{+}$ [M+Na]$^{+}$: 583.0387. Found: 583.0409.

MP: 162-163 °C.

10-(Dibenzo[*b*,*d*]thiophen-2-yl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide (SI-18)



Synthesised according to **GP-2** on a 0.8 mmol scale using dibenzo[*b*,*d*]thiophen-2-ylboronic acid to yield the title compound as a colourless solid with no further purification (117 mg, 0.19 mmol, 24%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.69 (1H, s), 8.45 (2H, dd, *J* = 7.8, 1.4 Hz), 8.08 (1H, d, *J* = 7.2 Hz), 7.92 (2H, dd, *J* = 7.2, 1.1 Hz), 7.90 – 7.86 (2H, m), 7.75 (1H, dd, *J* = 8.0, 1.1 Hz), 7.53 – 7.41 (4H, m), 7.36 (2H, app. td, *J* = 7.4, 1.4 Hz).

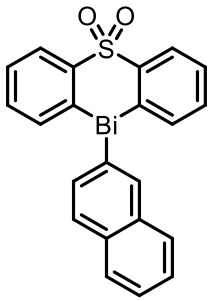
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ_C 161.1, 158.8, 141.0, 140.1, 139.4, 137.7, 137.7, 137.2, 135.3, 133.6, 131.7, 128.4, 127.3, 127.1, 125.8, 124.7, 123.0, 121.7.

IR (ATR-IR, neat) υ_{max}: 3364, 3049, 2924, 2852, 1718, 1580, 1562, 1508, 1438, 1426, 1387, 1366, 1302, 1285, 1251, 1226, 1150, 1121, 1108, 1087, 1074, 1046, 1023, 1013, 956.

HRMS (ESI$^+$): *m*/*z* calcd. for $[C_{24}H_{15}BiNaO_2S_2]^+$ $[M+Na]^+$: 631.0215. Found: 631.0238.

MP: 244-246 °C.

10-(Naphthalen-2-yl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide (SI-19)



Synthesised according to **GP-2** on a 0.1 mmol scale using naphthalen-2-ylboronic acid to yield the title compound as a colourless solid with no further purification (348 mg, 0.63 mmol, 79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.44 (1H, s), 8.42 (2H, dd, *J* = 7.8, 1.2 Hz), 7.87 (2H, dd, *J* = 7.3, 1.2 Hz), 7.83 – 7.76 (3H, m), 7.63 (1H, dd, *J* = 8.2, 1.1 Hz), 7.59 – 7.46 (2H, m), 7.41 (2H, app. td, *J* = 7.8, 1.2 Hz), 7.31 (2H, app. td, *J* = 7.3, 1.2 Hz).

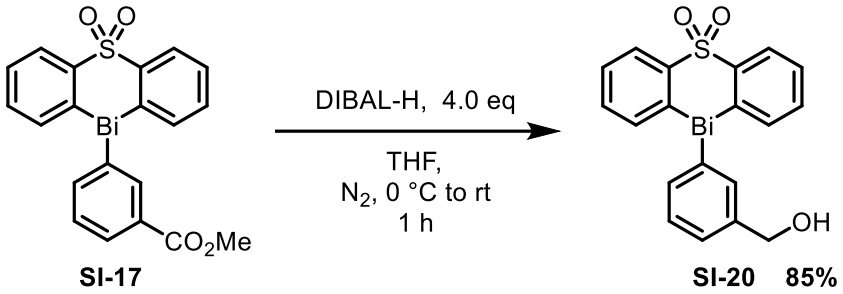
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 163.1, 158.6, 141.8, 138.6, 137.7, 135.8, 135.1, 133.5, 133.2, 130.7, 128.3, 128.1, 127.9, 127.3, 126.7, 126.5.

IR (ATR-IR, neat) υ_{max}: 3019, 1306, 1214, 1152.

HRMS (ESI$^+$): *m*/*z* calcd. for $[C_{22}H_{15}BiNaO_2S]^+$ $[M+Na]^+$: 575.0494. Found: 575.0468.

MP: 231-232 °C.

10-(3-(Hydroxymethyl)phenyl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide (SI-20)



SI-17 **SI-20 85%**

Ester **SI-17** (294 mg, 0.53 mmol) dissolved in anhydrous THF (10 mL), and the solution was cooled to 0 °C. DIBAL-H (1.0 M in hexanes; 2.10 mL, 2.10 mmol) was added dropwise, and the resulting mixture was stirred and allowed to warm to room temperature over 1 h. The reaction was then diluted with Et_2O (20 mL) and cooled to 0 °C. Water (0.5 mL) was added dropwise followed by NaOH (1.0 M; 0.5 mL). The mixture was stirred at room temperature for 20 min then water (10 mL) was added, and the organic layer was separated, dried over $MgSO_4$, filtered and concentrated in vacuo to afford **SI-20** as a white solid (238 mg, 0.45 mmol, 85%). Characterisation data were consistent with literature values: ^1H, $^{13}C\{^1H\}$ and IR.[186]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.39 (2H, d, J = 7.6 Hz), 7.87 (2H, d, J = 7.3 Hz), 7.84 (1H, s), 7.64 (1H, d, J = 6.8 Hz), 7.40 (4H, m), 7.34 (2H, app. t, J = 7.3 Hz), 4.66 (2H, d, J = 5.8 Hz), 1.66 (1H, t, J = 5.8 Hz).

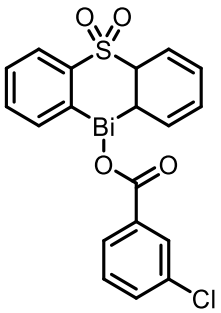
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 165.8, 158.6, 142.8, 141.6, 138.2, 137.6, 136.8, 133.4, 131.2, 128.2, 127.3, 127.1, 65.2.

IR (ATR-IR, neat) υ_{max}: 3512, 3045, 2871, 1562, 1439, 1414, 1388, 1300, 1286, 1252, 1198, 1150, 1121, 1108, 1088, 1073, 1013, 998, 916.

HRMS (ESI$^+$): *m*/*z* calcd. for $[C_{19}H_{15}BiNaO_3S]^+$ $[M+Na]^+$: 555.0444. Found: 555.0464.

MP: 158-160 °C.

5,5-Dioxido-10*H*-dibenzo[*b*,*e*][1,4] thiabismin-10-yl 3-chlorobenzoate (SI-21)



SI-21 can be recovered from the post arylation recation mixture, and can be converted into the bismacycle tosylate (*vide infra).* The recovery of this compound is exemplified for the synthesis of **4'-fluoro-[1,1'-biphenyl]-2-ol (4)** in *Procedures and Data for Chapter II*. Characterisation data are consistent with literature values: ^{1}H, $^{13}C\{^{1}H\}$, ^{19}F, HRMS and MP.[71]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.79 (2H, d, *J* = 7.4 Hz), 8.39 (2H, d, *J* = 7.7 Hz), 8.07 (1H, app. t, *J* = 1.1 Hz), 7.99 (1H, app. dt, J 7.7, 1.1 Hz), 7.72 (2H, app. td, *J* = 7.4, 1.0), 7.54 - 7.50 (1H, m), 7.47 (2H, app. td, *J* = 7.7, 1.0 Hz), 7.39 (1H, app. t, *J* = 7.9 Hz).

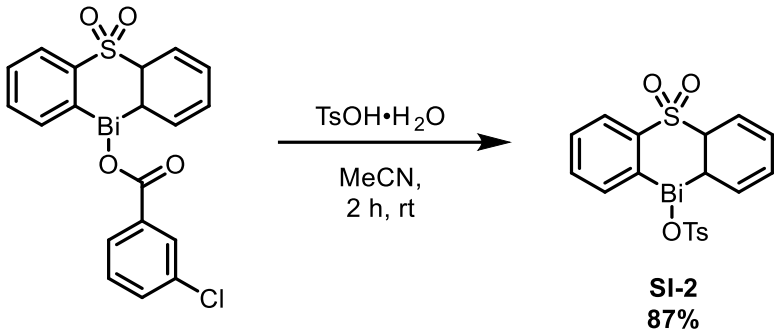
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ_C 141.1, 136.1, 135.5, 132.7, 130.5, 129.7, 129.0, 128.8, 128.5.

IR (ATR-IR, neat) υ_{max}: 2978, 1709, 1638, 1607, 1569, 1490, 1433, 1406, 1366 ,1339, 1307, 1270, 1253, 1221, 1202, 1161, 1141, 1110, 1086, 1068, 1035, 1012, 979.

HRMS (ESI^{+}): *m*/*z* calcd. for $[C_{12}H_8BiO_2S]^+$ $[M\text{-}C_7H_4ClO_2]^+$: 425.0049. Found: 425.0040.

MP: 197-200 °C.

Procedure for Bismacycle Recovery



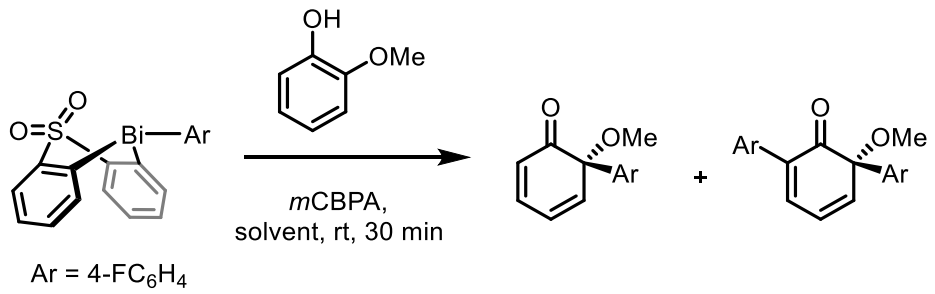
SI-2
87%

SI-21 (7.20 g, 12.4 mmol) was suspended in MeCN (60 mL) at rt; *p*-tolunesulfonic acid monohydrate (2.34 g, 13.6 mmol) was added and left to stir. After 2 h, the white suspension was filtered under reduced pressure through glass fibre filter paper and the resulting solid was washed with cold MeCN (3 × 20 mL), then Et_2O (20 mL) to afford **SI-2** as a colourless solid (6.44 g, 10.8 mmol, 87%).

Procedures and Data for Compounds in Chapter II

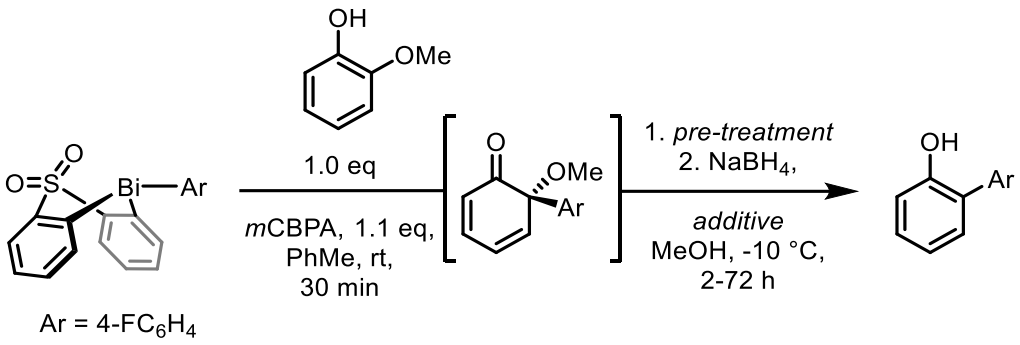
General Screening Procedures

General Procedure for the Optimization of Arylative Dearomatisation:



Aryl bismacycle (**1**) and guaiacol were suspended in the appropriate solvent in the presence of internal standard (4,4'-bis(trifluoromethyl)-1,1'-biphenyl at rt. *m*CPBA was added in 10 equal portions at 30 second intervals while stirring, and the reaction mixture was left for 30 min. The resulting orange solution was quenched with sat. aq. $Na_2S_2O_5$, left to stir for 5 min. An aliquot was taken and concentrated *in vacuo*. The residue was dissolved in $CDCl_3$ and analysed by ^{1}H NMR spectroscopy and quantitative ^{19}F NMR spectroscopy.

General Procedure for the Optimization of Luche Reduction and Rearomatisation:

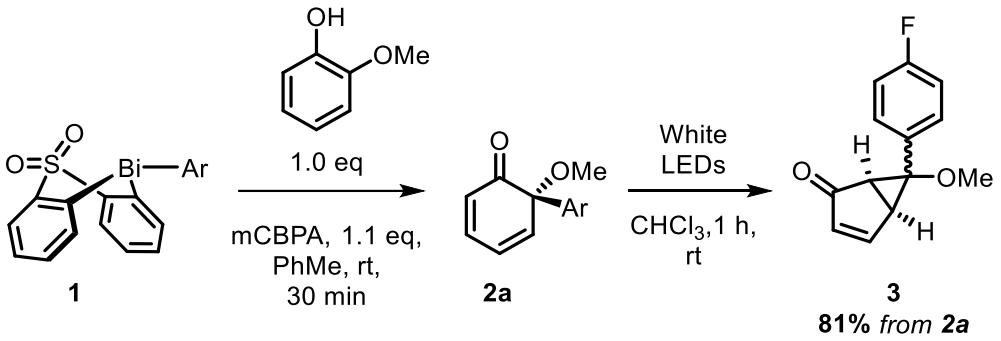


Aryl bismacycle **(1)** (103 mg, 0.2 mmol) and guaiacol (24.8 mg, 0.2 mmol) were suspended in PhMe (2 mL) in the presence of internal standard (4,4'-bis(trifluoromethyl)-1,1'-biphenyl; 0.117 mmol) at rt. *m*CPBA (54 mg, 0.22 mmol, 69% purity) was added in 10 equal portions at 30 second intervals while stirring, and the reaction mixture was left for 30 min. The resulting orange solution was quenched with sat. aq. $Na_2S_2O_5$ (0.01 mL), and the reaction mixture was then either concentrated into a microwave vial, or passed through a plug of basic alumina (*ca* 6 mL), eluted with EtOAc (10 mL) and then concentrated into a microwave vial.

The residue was then diluted with methanol (1.0 mL) in the presence or absence of cerium chloride hydrate (75.5 mg, 0.2 mmol).* The solution was cooled to -10 °C, after which time sodium borohydride (7.56 mg, 0.2 mmol) was added in 10 equal portions at 40 second intervals while stirring. The reaction was left to warm to rt over 2 h and quenched with aq. HCl (1 M, 1.0 mL), left to stir for 5 min, then concentrated *in vacuo*. The residue was dissolved in $CDCl_3$ and analysed by ^1H NMR spectroscopy and quantitative ^{19}F NMR spectroscopy.

*In order to confirm that the bismacycle benzoate poisons reactivity at this step, point, **SI-21** (116 mg, 0.2 mmol) is added before the reductant.

Identification of Photodecomposition Product: (1*R*,5*S*)-6-(4-fluorophenyl)-6-methoxybicyclo[3.1.0]hex-3-en-2-one (3)



Aryl bismacycle **1** (364 mg, 0.7 mmol) and guaiacol (86.8 mg, 0.7 mmol) were suspended in PhMe in the presence of internal standard (4,4'-bis(trifluoromethyl)-1,1'-biphenyl; 0.02 mmol) at rt. *m*CPBA (192 mg, 0.77 mmol, 70% purity) was added in 10 equal portions at 30 second intervals while stirring, and the reaction mixture was left for 30 min. The resulting orange solution was quenched with sat. aq. $Na_2S_2O_5$ (0.01 mL), left to stir for 5 min, then passed through a plug of basic alumina (*ca* 21 mL). The intermediate cyclohexadienone was eluted with EtOAc (70 mL) and concentrated *in vacuo* to afford crude cyclohexadienone **2a**. The residue was dissolved in $CHCl_3$ (*ca* 5 mL) and irradiated with white LEDs for 1 h at rt under an aerobic atmosphere. The reaction mixture was then concentrated *in vacuo* and analysed by ^{1}H NMR spectroscopy and quantitative ^{19}F NMR spectroscopy to reveal **3** (81%; single diastereoisomer). The structure of **3** was confirmed by 2D NMR spectroscopy; the relative stereochemistry could not be determined unambiguously.

^{1}H NMR (500 MHz, C_6D_6): δ_H 7.04 (2H, dd, *J* = 8.6, 5.4 Hz), 6.64 (2H, app. t, *J* = 8.6 Hz), 6.40 (1H, ddd, *J* = 5.6, 2.8, 0.9 Hz), 5.31 (1H, dd, *J* = 5.6, 1.0 Hz), 2.69 (3H, s), 2.58 (1H, dd, *J* = 5.4, 2.7 Hz), 2.42 (1H, app. dt, *J* = 5.4, 1.0 Hz).

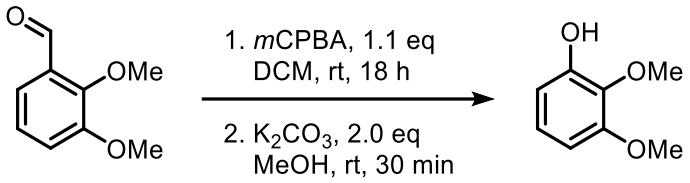
^{13}C{^{1}H} NMR (126 MHz, C_6D_6) δ_C 201.7, 163.1 (d, *J* = 247.6 Hz), 156.7, 133.7 (2 × C, determined by HSQC, including: d, *J* = 8.9 Hz), 127.7 (quaternary carbon obscured by C_6D_6 peak, determined by HMBC), 115.3 (d, *J* = 21.7 Hz), 86.9, 54.3, 36.6, 35.9.

^{19}F NMR (377 MHz, $CDCl_3$) δ_F -113.5 (tt, *J* = 8.6, 5.4 Hz).

HRMS (ESI$^+$): *m*/*z* calcd. for $[C_{13}H_{11}FO_2]^+$ [M+H]$^+$: 219.0821. Found: 219.0815.

Synthesis and Characterization of Guaiacol Substrates

2,3-Dimethoxyphenol (SI-22)



SI-22, 72%

2,3-Dimethoxybenzaldehyde (359 mg, 2.17 mmol) was dissolved in DCM (6 mL) at rt, then *m*CPBA (593 mg, 2.38 mmol, 70% purity) was added in 5 equal portions at one-minute intervals while stirring. The reaction mixture was left to stir at rt for 18 h. The reaction was then quenched with sat. aq. $Na_2S_2O_3$ (3 mL), diluted with DCM (10 mL) and washed subsequently with sat. aq. Na_2SO_3 (1 × 20 mL) and brine (1 × 20 mL). The organic portion was then dried with Na_2SO_4 and concentrated *in vacuo*.

The resultant residue was diluted with MeOH (10 mL), to which K_2CO_3 (598 mg, 4.34 mmol) was added on stirring at rt. After 30 min, the reaction mixture was concentrated *in vacuo*, and suspended in EtOAc (15 mL). The organic portion was washed with H_2O (2 × 10 mL), dried with Na_2SO_4 and concentrated *in vacuo* to afford the crude phenol. This was purified *via* automated silica gel column chromatography (0 to 40% EtOAc in cyclohexane) to yield **SI-22** as a yellow oil (241 mg, 1.56 mmol, 72%). Characterisation data were consistent with literature values: ^{1}H, ^{13}C{^{1}H} NMR. [187]

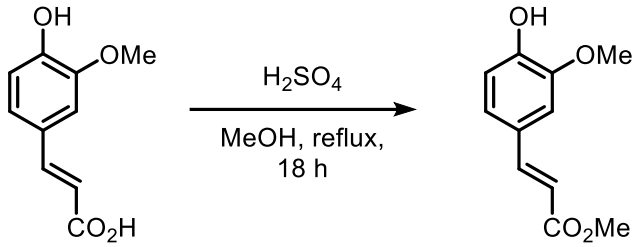
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.93 (1H, app. t, *J* = 8.3 Hz), 6.62 (1H, dd, *J* = 8.3, 1.4 Hz), 6.48 (1H, dd, *J* = 8.3, 1.4 Hz), 6.04 (1H, s), 3.89 (3H, s), 3.85 (3H, s).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 152.6, 149.6, 135.7, 124.1, 108.3, 104.2, 60.9, 55.8.

IR (ATR-IR, neat) υ_{max}: 3413, 2941, 2838, 1595, 1497, 1479, 1437, 1344, 1310, 1267, 1232, 1203, 1156, 1086, 996, 946.

HRMS (ESI$^+$): *m/z* calcd. for $[C_8H_{10}NaO_3]^+$ $[M+Na]^+$: 177.0528. Found: 177.0534.

Methyl (*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylate (SI-23)



SI-23
95%

To a solution of (*E*)-ferulic acid (292 mg, 1.50 mmol) in MeOH (1.9 mL) was added conc. H_2SO_4 (0.1 mL), and the reaction was heated to reflux for 18 h. The reaction mixture was then cooled to rt, diluted with DCM (2 mL), washed with sat. aq. $NaHCO_3$ (2 × 2 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude phenol; this was purified *via* automated silica gel column chromatography (10 to 30% EtOAc in cyclohexane) to yield (**SI-23**) as colourless crystals (296 mg, 1.42 mmol, 95%). Characterisation data were consistent with literature values: ^{1}H, ^{13}C{^{1}H} NMR.[188]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.61 (1H, d, *J* = 15.9 Hz), 7.05 (1H, dd, *J* = 8.1, 2.0 Hz), 7.00 (1H, d, *J* = 2.0 Hz), 6.90 (1H, d, *J* = 8.1 Hz), 6.28 (1H, d, *J* = 15.9 Hz), 6.11 (1H, s), 3.89 (3H, s), 3.78 (3H, s).

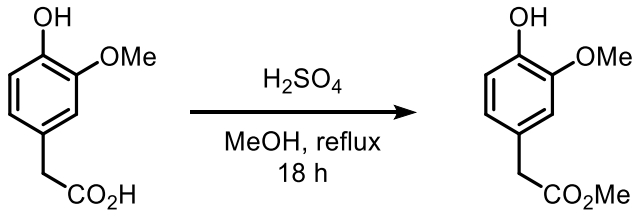
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 167.9, 148.1, 146.9, 145.1, 127.0, 123.1, 115.1, 114.9, 109.5, 56.0, 51.7.

IR(ATR-IR, neat) υ_{max}: 3391, 3011, 2950, 2843, 1695, 1633, 1590, 1511, 1433, 1376, 1324, 1264, 1156, 1122, 1031, 979, 919.

HRMS (ESI$^-$): *m/z* calcd. for $[C_{11}H_{11}O_4]^-$ [M-H]$^-$: 207.0657. Found: 207.0670.

MP: 61-63 °C.

Methyl 2-(4-hydroxy-3-methoxyphenyl)acetate (SI-24)



SI-24
77%

To a solution of homovanillic acid (364 mg, 2 mmol) in MeOH (2.6 mL) was added conc. H_2SO_4 (0.1 mL), and the reaction was heated to reflux for 18 h. The reaction mixture was then cooled to rt, diluted with DCM (5 mL), washed with sat. aq. $NaHCO_3$ (2 × 2 mL), and the organic portion was dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound as an off-white solid (300 mg, 1.53 mmol, 77%). Characterisation data were consistent with literature values: ^{1}H, ^{13}C{^{1}H} NMR.[189]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.86 (1H, d, *J* = 8.0 Hz), 6.80 (1H, d, *J* = 2.0 Hz), 6.76 (1H, dd, *J* = 8.0, 2.0 Hz), 5.59 (1H, s), 3.88 (3H, s), 3.69 (3H, s), 3.55 (2H, s).

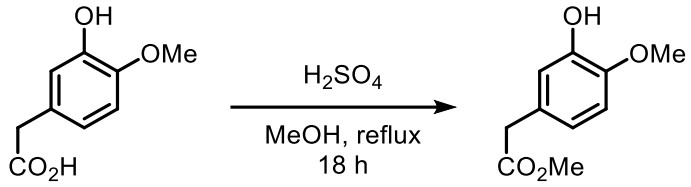
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 172.5, 146.6, 144.9, 125.9, 122.3, 114.5, 111.8, 56.0, 52.2, 40.9.

IR(ATR-IR, neat) υ_{max}: 3019, 1699, 1595, 1515, 1409, 1268, 1214, 1173, 1123, 1033.

HRMS (ESI$^+$): *m/z* calcd. for $[C_{10}H_{12}NaO_4]^+$ $[M+Na]^+$: 219.0633. Found: 219.0618.

MP: 108-110 °C.

Methyl 2-(3-hydroxy-4-methoxyphenyl)acetate (SI-25)



SI-25
82%

To a solution of 2-(3-hydroxy-4-methoxyphenyl)acetic acid (364 mg, 2 mmol) in MeOH (2.6 mL) was added conc. H_2SO_4 (0.1 mL), and the reaction was heated to reflux for 18 h. The reaction mixture was then cooled to rt, diluted with DCM (5 mL), and washed with sat. aq. $NaHCO_3$ (2 × 2 mL), then the organic potion was dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound as an off-white solid (320 mg, 1.76 mmol, 82%). Characterisation data were consistent with literature values: ^1H, $^{13}C\{^1H\}$ NMR.[190]

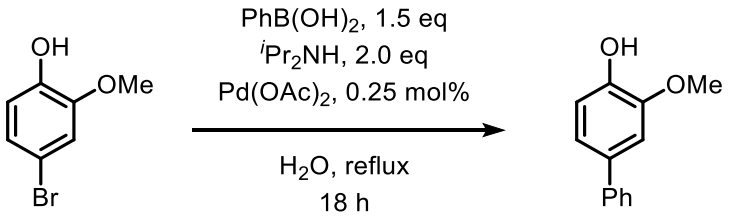
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.86 (1H, d, J = 2.1 Hz), 6.80 (1H, d, J = 8.2 Hz), 6.75 (1H, dd, J = 8.2, 2.1 Hz), 5.62 (1H, s), 3.87 (3H, s), 3.68 (3H, s), 3.53 (2H, s).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 172.4, 145.9, 145.7, 127.3, 120.9, 115.7, 110.8, 56.1, 52.2, 40.7.

IR(ATR-IR, neat) υ_{max}: 3246, 2930, 2854, 2116, 1739, 1597, 1576, 1504, 1465, 1442, 1422, 1360, 1346, 1287, 1242, 1191, 1100, 1082, 1063, 1032, 1009, 949.

HRMS (ESI$^+$): *m*/*z* calcd. for $[C_{10}H_{13}O_4]^+$ $[M+H]^+$: 197.0814. Found: 197.0810.

3-Methoxy-[1,1'-biphenyl]-4-ol (SI-26)



SI-26
77%

Prepared according to literature procedure:[191] 4-Bromoguaiacol (820 mg, 4.08 mmol), phenyl boronic acid (747 mg, 6.13 mmol) and $Pd(OAc)_2$ (2.34 mg, 0.25 mol%) were suspended in H_2O (8 mL). $^{i}Pr_2NH$ (1.14 mL, 8.16 mmol) was added, and the reaction mixture was left to stir at reflux for 18 h. The reaction was cooled to rt, diluted with brine (2 mL), and extracted with EtOAc (3 × 5 mL). The collected organic portions were dried with Na_2SO_4 and concentrated *in vacuo*. The crude material was purified *via* automated silica gel column chromatography (0 to 20% Et_2O in pentane) to yield the title compound as a colourless solid (632 mg, 3.16 mmol, 77%). Characterisation data were consistent with literature values: ^{1}H, $^{13}C\{^{1}H\}$ NMR.[192]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.77 (2H, dd, *J* = 8.4, 1.4 Hz), 7.66 – 7.57 (2H, m), 7.51 (1H, d, *J* = 7.3 Hz), 7.34 (1H, dd, *J* = 8.1, 2.0 Hz), 7.29 (1H, d, *J* = 2.0 Hz), 7.27 (1H, d, *J* = 8.1 Hz), 6.27 (1H, s), 4.01 (3H, s).

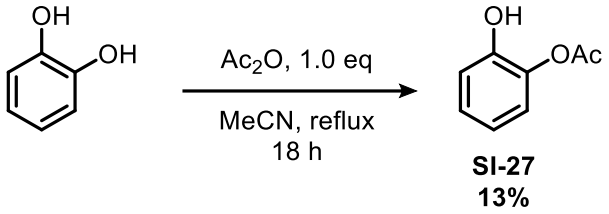
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 147.2, 145.6, 141.4, 134.0, 129.0, 127.1, 127.0, 120.4, 115.3, 110.1, 56.1.

IR (ATR-IR, neat) υ_{max}: 3019, 2359, 1598, 1521, 1499, 1415, 1305, 1260, 1214, 1153, 1123, 1090, 1035, 933.

HRMS (ESI$^-$): *m/z* calcd. for $[C_{13}H_{11}O_2]^-$ [M-H]$^-$: 199.0759. Found: 199.0741.

MP: 66-69 °C.

2-Hydroxyphenyl acetate (SI-27)



To a stirring solution of catechol (603 mg, 5.48 mmol) in MeCN (4.7 mL) was added Ac_2O (520 µL, 5.48 mmol). The reaction was heated to reflux for 18 h. The reaction was then cooled to rt, quenched with sat. aq. $NaHCO_3$ (5.0 mL), and the organics were extracted with EtOAc (3 × 5 mL). The collected organic portions were dried over sodium sulfate and concentrated *in vacuo*. The crude material was purified *via* automated silica gel column chromatography (0 to 20% Et_2O in cyclohexane) to yield the title compound as a grey crystalline solid (608 mg, 0.71 mmol, 13%). Characterisation data were consistent with literature values: ^1H, $^{13}C\{^1H\}$ NMR.[193]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.14 – 7.05 (2H, m), 6.96 (1H, dd, *J* = 8.1, 1.5 Hz), 6.91 (1H, ddd, *J* = 8.1, 7.3, 1.5 Hz), 5.75 (1H, s), 2.33 (3H, s).

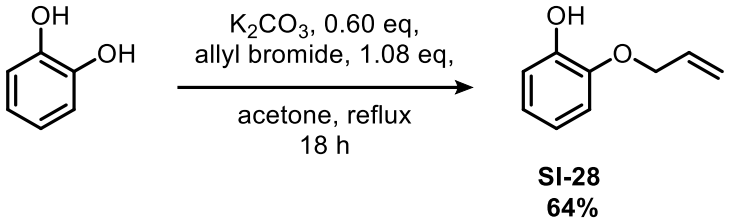
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 169.8, 147.2, 138.7, 127.2, 122.6, 121.1, 117.8, 21.0.

IR(ATR-IR, neat) υ_{max}: 3388, 3020, 2927, 1743, 1596, 1496, 1461, 1370, 1285, 1264, 1214, 1174, 1151, 1097, 1032, 1012, 936, 911.

HRMS (ESI$^+$): *m*/*z* calcd. for $[C_8H_8NaO_3]^+$ $[M+Na]^+$: 175.0371. Found: 175.0361.

MP: 62-64 °C.

2-(Allyloxy)phenol (SI-28)



SI-28
64%

Prepared according to literature procedure:[194] Catechol (1.06 g, 9.63 mmol) and K_2CO_3 (796 mg, 5.78 mmol) were suspended in acetone (150 mL) before allyl bromide (900 µL, 10.4 mmol) was added. The reaction was heated at reflux for 18 h and subsequently cooled to rt, then quenched with sat. aq. NH_4Cl (15 mL). The mixture was extracted with EtOAc (3 × 50 mL), the collected organic portions were washed once with brine (40 mL), dried over sodium sulfate, and concentrated *in vacuo*. The crude material was purified *via* automated silica gel column chromatography (0 to 100% Et_2O in pentane) to yield the title compound as a colourless oil (921 mg, 6.14 mmol, 64%). Characterisation data were consistent with literature values: ^1H, $^{13}C\{^1H\}$ NMR. [195]

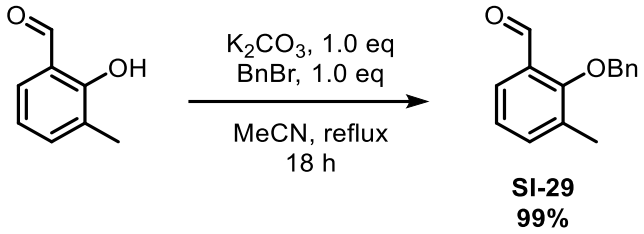
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.98 – 6.79 (4H, m), 6.07 (1H, ddt, *J* = 17.2, 10.7, 5.5 Hz), 5.71 (1H, s), 5.42 (1H, d, *J* = 17.2), 5.33 (1H, d, *J* = 10.5), 4.61 (2H, dt, *J* = 5.5, 1.5 Hz).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 146.0, 145.7, 133.0, 121.9, 120.2, 118.4, 114.9, 112.4, 70.0.

IR (ATR-IR, neat) υ_{max}: 3523, 3053, 2927, 2871, 2358, 1750, 1648, 1595, 1497, 1464, 1424, 1370, 1302, 1257, 1216, 1195, 1153, 1106, 1035, 1013, 993.

HRMS (ESI$^-$): *m*/*z* calcd. for $[C_9H_9O_2]^-$ [M-H]$^-$: 149.0603. Found: 149.0598.

2-(Benzyloxy)-3-methylbenzaldehyde (SI-29)



SI-29
99%

To a suspension of 2-hydroxy-3-methylbenzaldehyde (449 mg, 3.30 mmol) and K_2CO_3 (455 mg, 3.30 mmol) in MeCN (7 mL) was added benzyl bromide (356 µL, 3.00 mmol). The reaction was heated at reflux for 18 h, then cooled to rt, quenched with aq. NaOH (2.0 M; 10 mL), and stirred for 5 min. MeCN was then removed *in vacuo* and the resultant aqueous mixture was extracted with EtOAc (3 × 10 mL). The collected organic portions were dried over Na_2SO_4 and concentrated to dryness to afford the title compound as a brown oil (671 mg, 2.97 mmol, 99%). Characterisation data were consistent with literature values: ^{1}H NMR.[196]

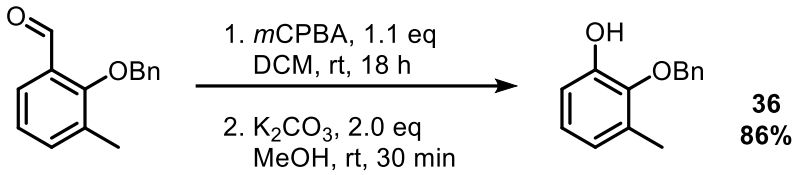
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.27 (1H, s), 7.70 (1H, dd, *J* = 7.7, 1.8 Hz), 7.48 (1H, app. dt, *J* = 7.7, 1.8 Hz), 7.45 – 7.33 (5H, m), 7.18 (1H, t, *J* = 7.7 Hz), 4.98 (2H, s), 2.37 (3H, s).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 190.4, 160.3, 137.7, 136.2, 132.7, 129.8, 128.9, 128.8, 128.4, 126.6, 124.7, 77.9, 16.1.

IR (ATR-IR, neat) υ_{max}: 3065, 3032, 2928, 2861, 2741, 2361, 2342, 1693, 1677, 1588, 1518, 1498, 1468, 1455, 1391, 1303, 1247, 1199, 1084, 971, 918.

HRMS (ESI$^+$): *m*/*z* calcd. for $[C_{13}H_{11}O_2]^+$ [M+Na]$^+$: 249.0891. Found: 249.0882.

2-(Benzyloxy)-3-methylphenol (36)



2-(Benzyloxy)-3-methylbenzaldehyde (520 mg, 2.3 mmol) was dissolved in DCM (6 mL) at rt, then *m*CPBA (630 mg, 2.53 mmol, 70% purity) was added in 5 equal portions at one-minute intervals while stirring. The reaction mixture was left to stir at rt for 18 h. The reaction was then quenched with sat. aq. $Na_2S_2O_3$ (3 mL), diluted with DCM (10 mL) and washed sequentially with sat. aq. Na_2SO_3 (1 × 20 mL) and brine (1 × 20 mL). The organic portion was then dried with Na_2SO_4 and concentrated *in vacuo*.

The resultant residue was diluted with MeOH (10 mL), and K_2CO_3 (634 mg, 4.60 mmol) was added on stirring at rt After 30 min, the reaction mixture was concentrated *in vacuo*, and the residue suspended in EtOAc (15 mL). The mixture was washed with H_2O (2 × 10 mL), and the organic potion was dried with Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a brown oil (422 mg, 1.97 mmol, 86%). Characterisation data were consistent with literature values: ^{1}H NMR.[197]

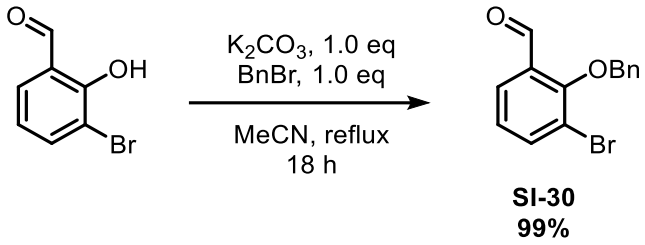
^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.48 – 7.36 (5H, m), 6.93 (1H, t, *J* = 7.8 Hz), 6.79 (1H, dd, *J* = 8.2, 1.6 Hz), 6.73 (1H, app. dt, *J* = 7.8, 1.6 Hz), 5.47 (1H, s), 4.91 (2H, s), 2.35 (3H, s).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz)**:** δ 149.1, 144.5, 137.0, 131.1, 128.9, 128.7, 128.2, 124.8, 122.5, 113.2, 75.4, 16.2.

IR(ATR-IR, neat) υ_{max}: 3523, 3030, 2927, 1681, 1610, 1593, 1497, 1473, 1454, 1378, 1341, 1282, 1268, 1214, 1173, 1157, 1078, 1023, 969, 949, 915.

HRMS (ESI$^-$): *m*/*z* calcd. for $[C_{14}H_{13}O_2]^-$ [M-H]$^-$: 213.0916. Found: 213.0918.

2-(Benzyloxy)-3-bromobenzaldehyde (SI-30)



SI-30
99%

To a solution of 3-bromo-2-hydroxybenzaldehyde (1105 mg, 5.50 mmol) and K_2CO_3 (765 mg, 5.50 mmol) in MeCN (10 mL) was added benzyl bromide (594 µL, 5.00 mmol). The reaction was heated at reflux for 18 h, then cooled to rt, quenched with aq. NaOH (2.0 mL; 10 mL) and stirred for 5 min. MeCN was then removed *in vacuo* and the resultant aqueous mixture was extracted with EtOAc (3 × 10 mL). The collected organic potions were dried over Na_2SO_4 and concentrated to dryness to afford the title compound as a grey-green solid (1.44 g, 4.97 mmol, 99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.12 (1H, s), 7.86 (1H, dd, *J* = 7.8, 1.6 Hz), 7.76 (1H, dd, *J* = 7.8, 1.6 Hz), 7.50 – 7.37 (5H, m), 7.15 (1H, td, *J* = 7.8, 0.9 Hz), 5.14 (2H, s).

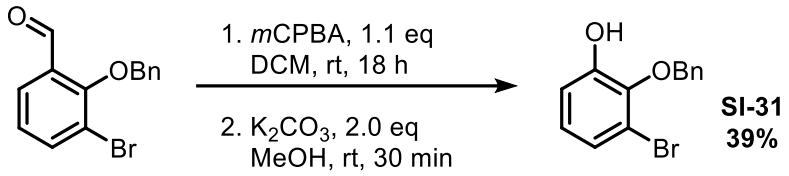
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 189.1, 158.5, 139.7, 135.5, 131.7, 129.1, 129.0, 128.9, 127.8, 126.0, 118.6, 78.0.

IR(ATR-IR, neat) υ_{max}: 3019, 2361, 1683, 1587, 1519, 1498, 1438, 1369, 1308, 1244, 1214, 1152, 1120, 1071, 962, 916.

HRMS (ESI$^+$): *m*/*z* calcd. for $[C_{14}H_{11}{}^{79}BrNaO_2]^+$ $[M+Na]^+$: 312.9840. Found: 312.9817.

MP: 60-63 ˚C.

2-(Benzyloxy)-3-bromophenol (SI-31)



2-(Benzyloxy)-3-bromobenzaldehyde (1.30 g, 4.5 mmol) was dissolved in DCM (12 mL) at rt, then *m*CPBA (1.23 g, 4.95 mmol, 70% purity) was added in 5 equal portions at one-minute intervals while stirring. The reaction mixture was left to stir at rt for 18 h. The reaction was then quenched with sat. aq. $Na_2S_2O_3$ (3 mL), diluted with DCM (20 mL) and washed sequentially with sat. aq. Na_2SO_3 (1 × 20 mL), brine (1 × 20 mL) and $NaHSO_3$ (3 × 50 mL). The organic portion was then dried with Na_2SO_4 and concentrated *in vacuo*.

The resultant residue was diluted with MeOH (12 mL), and K_2CO_3 (1.24 g, 9.00 mmol) was added on stirring at rt. After 30 min, the reaction mixture was concentrated *in vacuo*, and suspended in EtOAc (15 mL). The mixture was washed with H_2O (2 × 10 mL), and the organic phase was separated, dried with Na_2SO_4 and concentrated *in vacuo* to afford the crude phenol; this was purified *via* automated silica gel column chromatography (0 to 4% EtOAc in cyclohexane) to yield the title compound as a brown oil (485 mg, 1.74 mmol, 39%).

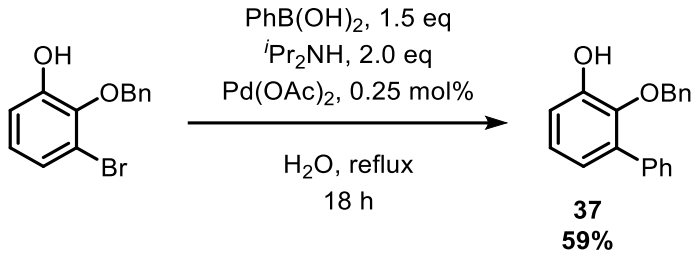
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.53 – 7.32 (5H, m), 7.11 (1H, dd, *J* = 7.6, 2.1 Hz), 6.98 – 6.72 (2H, m), 5.48 (1H, s), 5.07 (2H, s).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ_C 150.4, 143.4, 136.4, 129.0, 128.9, 128.6, 126.1, 124.7, 116.3, 115.0, 75.9.

IR(ATR-IR, neat) υ_{max}: 3507, 3064, 3031, 1577, 1496, 1466, 1451, 1379, 1334, 1278, 1213, 1158, 1128, 1061, 956, 914.

HRMS (ESI$^-$): *m*/*z* calcd. for $[C_{13}H_{10}{}^{79}BrO_2]^-$ [M-H]$^-$: 276.9864. Found: 276.9870.

2-(Benzyloxy)-[1,1'-biphenyl]-3-ol (37)



Prepared according to literature procedure:[191] 2-(Benzyloxy)-3-bromophenol (405 mg, 1.45 mmol), phenyl boronic acid (273 mg, 2.25 mmol) and $Pd(OAc)_2$ (1.00 mg, 0.25 mol%) were suspended in H_2O (3 mL). $^iPr_2NH$ (420 µL, 3.00 mmol) was added, and the reaction mixture was left to stir at reflux for 2 days. The reaction was then cooled, diluted with brine (2 mL), and extracted with EtOAc (3 × 5 mL). The collected organic portions were dried with Na_2SO_4 and concentrated *in vacuo*. The crude material was purified *via* automated silica gel column chromatography (0 to 10% EtOAc in cyclohexane) to yield the title compound as a brown oil (243 mg, 0.88 mmol, 59%). Characterisation data were consistent with literature values: ^{1}H NMR.[198]

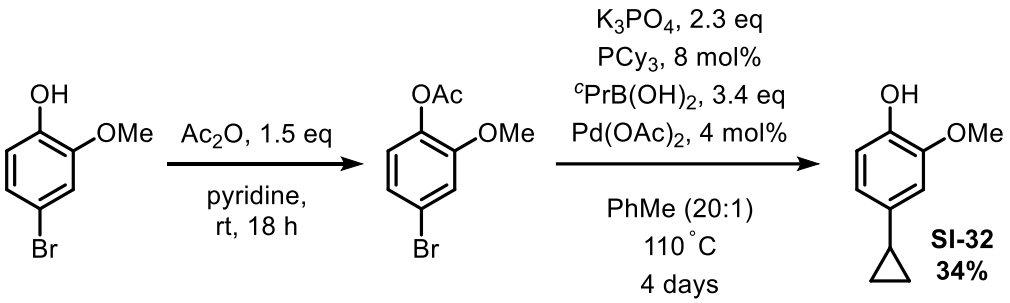
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.70 – 7.62 (2H, m), 7.48 (2H, t, *J* = 7.6 Hz), 7.40 (1H, app. dt, *J* = 7.1, 1.9 Hz), 7.34 – 7.30 (3H, m), 7.19 – 7.13 (2H, m), 7.10 (1H, t), 6.99 – 6.89 (2H, m), 5.80 (1H, s), 4.46 (2H, s).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 149.5, 143.2, 138.1, 136.6, 134.8, 129.1, 128.8, 128.72, 128.66, 128.63, 127.7, 125.1, 122.2, 114.6, 75.5.

IR(ATR-IR, neat) υ_{max}: 3518, 3020, 1588, 1574, 1499, 1467, 1435 ,1380, 1344, 1313, 1297, 1276, 1214, 1195, 1160, 1066, 1028, 968, 916.

HRMS (ESI$^-$): *m/z* calcd. for $[C_{19}H_{15}O_2]^-$ $[M-H]^-$: 275.1072. Found: 275.1078.

4-Cyclopropyl-2-methoxyphenol (SI-32)



Acetic anhydride (354 µL, 3.75 mmol) was added to a stirring solution of 4-bromo-2-methoxyphenol (502 mg, 2.5 mmol) in pyridine (8.3 mL). The reaction mixture was left to stir at rt for 18 h. This was quenched with sat. aq. $NaHCO_3$ (10 mL) and stirred vigorously for 5 min. The organics were extracted with Et_2O (3 × 15 mL) and the collected portions were washed with sat. aq. $CuSO_4$ (3 × 10 mL), and once with brine (10 mL). The organic portions were then dried with Na_2SO_4 and concentrated *in vacuo*.

The resultant residue was suspended in a biphasic mixture of toluene (20 mL) and water (1.0 mL). To this, was added cyclopropylboronic acid (728 mg, 8.56 mmol), $Pd(OAc)_2$ (20.2 mg, 0.09 mmol), K_3PO_4 (1.24 g, 5.85 mmol) and PCy_3 (55.8 mg, 0.20 mmol). This suspension was sparged with anhydrous dinitrogen for 5 min, then heated to 110 °C for 4 days. The reaction mixture was cooled to rt, diluted with EtOAc (20 ml) and washed with water (2 × 10 mL). The organics were then dried with Na_2SO_4 and concentrated *in vacuo*. The crude phenol was purified *via* automated silica gel column chromatography (0 to 5% TBME in pentane) to yield the title compound as a colourless oil (140 mg, 0.85 mmol, 34%).

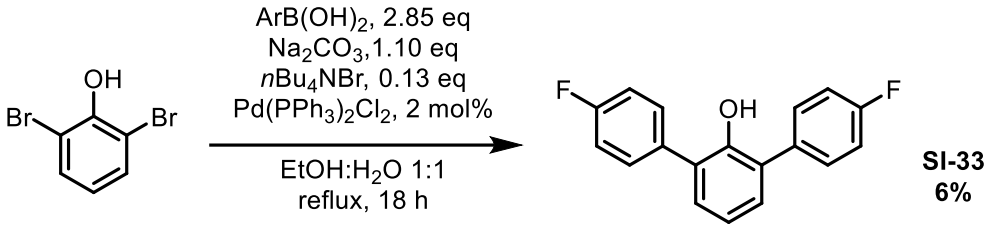
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.84 (1H, d, *J* = 8.1 Hz), 6.65 (1H, d, *J* = 2.0 Hz), 6.61 (1H, dd, *J* = 8.1, 2.0 Hz), 5.52 (1H, s), 3.88 (3H, s), 1.87 (1H, tt, *J* = 8.4, 5.1 Hz), 0.96 – 0.80 (2H, m), 0.72 – 0.49 (2H, m).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 146.5, 143.6, 135.8, 118.5, 114.3, 109.1, 56.0, 15.3, 8.6.

IR(ATR-IR, neat) υ_{max}: 3432, 3081, 3004, 2938, 2849, 2363, 1604, 1516, 1467, 1451, 1427, 1376, 1355, 1264, 1233, 1204, 1150, 1122, 1090, 1032, 942.

***HRMS** was not obtained for this compound.*

Synthesis of Authentic Sample: **4,4''-Difluoro-[1,1':3',1''-terphenyl]-2'-ol (SI-33)**



2,6-Dibromophenol (202 mg, 0.80 mmol), (4-fluorophenyl)boronic acid (318 mg, 2.28 mmol), Na_2CO_3 (93.0 mg, 0.88 mmol), tetrabutylammonium bromide (33.0 mg, 0.10 mmol) and bis(triphenylphosphine)palladium(II) dichloride (12.0 mg, 17.0 μmol) were suspended in a 1:1 mixture of EtOH:H_2O (86 mL) and heated to reflux for 4 days. The reaction mixture was cooled to rt, and the EtOH was removed *in vacuo*. The reaction was extracted with DCM (3 × 15 mL), and the combined organic potions were dried over sodium sulfate and concentrated *in vacuo*. The crude material was purified *via* automated silica gel column chromatography (1% Et_2O in pentane) to **SI-33** as off-white crystals (14.0 mg, 0.05 mmol, 6%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.54 (4H, dd, *J* = 8.7, 5.4 Hz), 7.27 (2H, d, *J* = 7.6 Hz), 7.19 (4H, app. t, *J* = 8.7 Hz), 7.08 (1H, t, *J* = 7.6 Hz), 5.26 (1H, s).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 162.5 (d, *J* = 247.2 Hz), 149.4, 133.5 (d, *J* = 3.3 Hz), 131.2 (d, *J* = 8.1 Hz), 130.2, 128.0, 121.0, 115.9 (d, *J* = 21.6 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ_F -114.26 (tt, *J* = 8.7, 5.4 Hz).

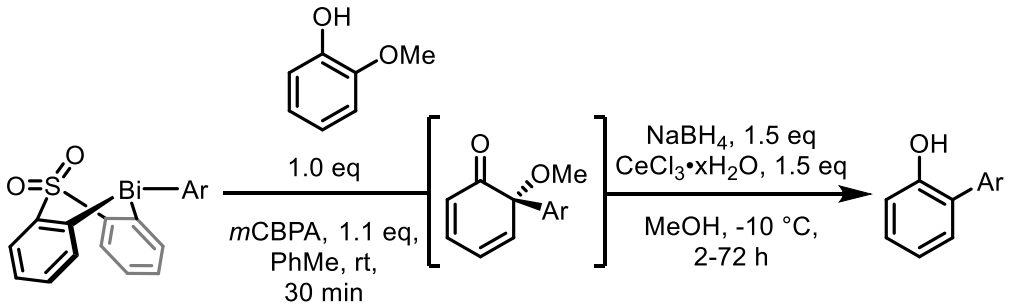
IR (ATR-IR, neat) υ_{max}: 3542, 2923, 2855, 2252, 1892, 1666, 1506, 1468, 1445, 1327, 1271, 1228, 1165, 1091, 1018, 666.

HRMS (ESI$^-$): *m/z* calcd. for $[C_{18}H_{11}F_2O]^-$ $[M-H]^-$: 281.0778. Found: 281.0784.

MP: 76-78 °C.

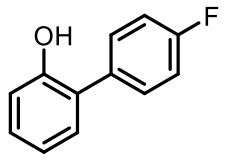
Characterisation Data for *ortho*-Arylated Phenols

General Procedure for Dealkoxylative Arylation (GP3)



In an amberised RBF, the aryl bismacycle (0.7 mmol) and phenol substrate (0.7 mmol) were suspended in PhMe (35 mL) in the presence of internal standard (diphenyl methane (1.05 mmol) *or* 4,4'-bis(trifluoromethyl)-1,1'-biphenyl (0.117 mmol)) at rt. *m*CPBA (192 mg, 0.77 mmol, 69% purity) was added in 10 equal portions at 30 second intervals while stirring, and the reaction mixture was left for 30 min. The resultant orange solution was quenched with sat. aq. $Na_2S_2O_5$ (0.01 mL), left to stir for 5 min, then passed through a plug of basic alumina (*ca* 21 mL). The intermediate cyclohexadienone was eluted with EtOAc (70 mL) and concentrated into a flask containing cerium chloride hydrate (392 mg, 1.05 mmol). This was diluted with MeOH (7.0 mL) and cooled to -10 °C, after which time sodium borohydride (40 mg, 1.05 mmol) was added in 10 equal portions at 40 second intervals while stirring. The reaction was left to warm to rt until no intermediate cyclohexadienone could be observed by TLC. The reaction mixture was then quenched with HCl in dioxane (4 M, 2 mL), left to stir for 5 min, and concentrated *in vacuo* to afford the crude arylated phenol, which was purified by automated silica gel column chromatography using the eluent system described for each compound entry.

4'-Fluoro-[1,1'-biphenyl]-2-ol (4)



Synthesised according to **GP-3** on a 0.7 mmol scale using guaiacol and 10-(4-fluorophenyl)-10*H*-dibenzo[*b,e*][1,4]thiabismine 5,5-dioxide. The crude compound was purified by automated silica gel column chromatography (5-10% Et_2O in pentane) to yield the title compound as a colourless oil (57.3 mg, 0.3 mmol, 44%). Characterisation data were consistent with literature values: ^{1}H, $^{13}C\{^{1}H\}$,^{19}F NMR and MP.[191]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.50 – 7.40 (2H, m), 7.30 – 7.24 (1H, m), 7.22 (1H, dd, *J* = 7.6, 1.6 Hz), 7.18 (2H, app. tt, *J* = 8.7, 3.1 Hz), 7.00 (1H, dd, *J* = 7.5, 1.1 Hz), 6.97 (1H, dd, *J* = 8.0, 1.1 Hz), 5.01 (1H, s).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ_C 162.5 (d, *J* = 247.4 Hz), 152.4, 133.1 (d, *J* = 3.5 Hz), 130.9 (d, *J* = 8.0 Hz), 130.4, 129.3, 127.2, 121.0, 116.1 (d, *J* = 21.4 Hz), 115.9.

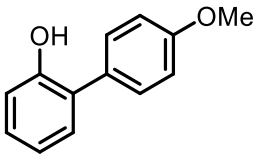
^{19}F NMR (377 MHz, $CDCl_3$): δ_F -114.2 (dd, J = 8.7, 5.4 Hz).

IR (ATR-IR, neat) υ_{max}: 3541, 3416, 3041, 1901, 1603, 1580, 1514, 1493, 1482, 1452, 1402, 1332, 1286, 1267, 1224, 1181, 1158, 1106, 1094, 1044, 1009, 937.

HRMS (ESI$^-$): *m/z* calcd. for $[C_{12}H_8FO]^-$ $[M-H]^-$: 187.0559. Found: 187.0575.

MP: 47-49 ˚C (lit. 44-45 ˚C).[191]

4'-Methoxy-[1,1'-biphenyl]-2-ol (6)



Synthesised according to **GP-3** on a 0.56 mmol scale using guaiacol and 10-(4-methoxyphenyl)-10*H*-dibenzo[*b,e*][1,4]thiabismine 5,5-dioxide. The crude compound was purified by automated silica gel column chromatography (5-10% Et_2O in pentane) to yield the title compound as a colourless oil (29.5 mg, 0.15 mmol, 27%). Characterisation data were consistent with literature values: ^{1}H, $^{13}C\{^{1}H\}$.[199]

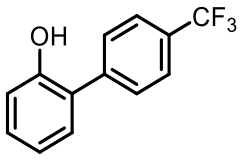
^{1}H NMR (400 MHz, $CDCl_3$): 7.46 – 7.41 (2H, m), 7.30 – 7.23 (2H, m), 7.08 – 6.98 (4H, m), 5.28 (1H, s), 3.89 (3H, s).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 159.3, 152.5, 130.40, 130.38, 129.2, 128.8, 127.9, 120.8, 115.7, 114.7, 55.4.

IR (ATR-IR, neat) υ_{max}: 3369, 2924, 2852, 1652, 1607, 1516, 1495, 1483, 1452, 1410, 1336, 1297, 1274, 1246, 1178, 1104, 1034, 1017, 1002.

HRMS (ESI$^-$): *m/z* calcd. for $[C_{13}H_{11}O_2]^-$ [M-H]$^-$: 199.0759. Found: 199.0762.

4'-(Trifluoromethyl)-[1,1'-biphenyl]-2-ol (5)



Synthesised according to **GP-3** on a 0.70 mmol scale using guaiacol and 10-(4-(trifluoromethyl)phenyl)-10*H*-dibenzo[*b,e*][1,4]thiabismine 5,5-dioxide. The crude compound was purified by automated silica gel column chromatography (5-10% Et_2O in pentane) to yield the title compound as a colourless solid (100 mg, 0.42 mmol, 60%). Characterisation data were consistent with literature values: ^1H, $^{13}C\{^1H\}$,^{19}F NMR, HRMS and MP.[191]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.77 – 7.70 (2H, m), 7.67 – 7.61 (2H, m), 7.34 – 7.26 (2H, m), 7.04 (1H, app. td, *J* = 7.5, 1.2 Hz), 6.97 (1H, ddd, *J* = 8.0, 1.2, 0.3 Hz), 5.07 (1H, s)

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ_C 152.4, 141.2, 130.4, 129.8, 129.7 (q, *J* = 32.0 Hz), 129.6, 126.9, 125.9 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 272.0 Hz), 121.3, 116.2.

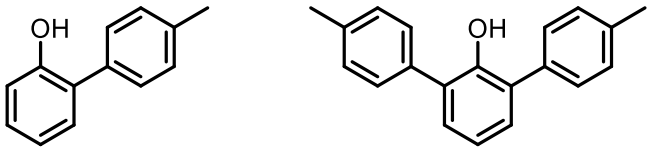
^{19}F NMR (376 MHz, $CDCl_3$): δ_F -62.5.

IR (ATR-IR, neat) υ_{max}: 3522, 3033, 2923, 2852, 1615, 1605, 1588, 1523, 1495, 1450, 1404, 1326, 1296, 1273, 1163, 1129, 1112, 1100, 1069, 1044, 1021, 1008, 955, 945.

HRMS (ESI$^-$): *m/z* calcd. for $[C_{13}H_8F_3O]^-$ $[M-H]^-$: 237.0533. Found: 237.0534.

MP: 110-112 °C.

4'-Methyl-[1,1'-biphenyl]-2-ol (7) and 4,4''-dimethyl-[1,1':3',1''-terphenyl]-2'-ol (7')



Synthesised according to **GP-3** on a 0.78 mmol scale using guaiacol and 10-(*p*-tolyl)-10*H*-dibenzo[*b,e*][1,4]thiabismine 5,5-dioxide. The crude compound was purified by automated silica gel column chromatography (0-10% Et_2O in pentane) to yield 2-(*para*-tolyl)phenol **7** as a yellow oil (46.4 mg, 0.25 mmol, 32%), and 2,6-di(*para*-tolyl)phenol as a colourless solid (6.4 mg, 23.4 μmol, 3%).

4'-Methyl-[1,1'-biphenyl]-2-ol (7)

Characterisation data were consistent with literature values: ^1H, $^{13}C\{^1H\}$ and HRMS.[191]

^1H NMR (400 MHz, $CDCl_3$): 7.38 (2H, d, *J* = 8.0 Hz), 7.32 (2H, d, *J* = 8.0 Hz), 7.29 – 7.22 (2H, m), 7.04 – 6.96 (2H, m), 5.29 (1H, s), 2.44 (3H, s).

$^{13}C\{^1H\}$ NMR (MHz, $CDCl_3$): δ_C 152.6, 137.8, 134.2, 130.3, 130.1, 129.1 (2 × C, determined by HSQC), 128.2, 120.9, 115.8, 21.3.

IR (ATR-IR, neat) υ_{max}: 3529, 3433, 3024, 2920, 2858, 1703, 1608, 1580, 1517, 1481, 1448, 1404, 1333, 1284, 1267, 1222, 1180, 1152, 1104, 1043, 1024, 1007, 937.

HRMS (ESI$^-$): *m/z* calcd. for $[C_{13}H_{11}O]^-$ $[M-H]^-$: 183.0815. Found: 183.0824.

4,4''-Dimethyl-[1,1':3',1''-terphenyl]-2'-ol (7')

Characterisation data were consistent with literature values: ^{1}H, $^{13}C\{^{1}H\}$.[200]

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.44 (4H, app. dt, *J* = 8.1, 1.8 Hz), 7.28 (4H, d, *J* = 8.1 Hz), 7.25 (2H, d, *J* = 7.6 Hz), 7.03 (1H, t, *J* = 7.6 Hz), 5.41 (1H, s), 2.41 (6H, s).

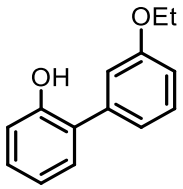
$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ_C 149.6, 137.5, 134.8, 129.9, 129.7, 129.3, 128.8, 120.7, 21.4.

IR (ATR-IR, neat) υ_{max}: 3543, 3024, 2953, 2922, 2852, 1739, 1588, 1515, 1445, 1397, 1377, 1326, 1246, 1224, 1184, 1166, 1097, 1077, 1021.

HRMS (ESI$^-$): *m*/*z* calcd. for $[C_{20}H_{17}O]^-$ [M-H]$^-$: 273.1284. Found: 273.1295.

MP: 78-81 °C.

3'-Ethoxy-[1,1'-biphenyl]-2-ol (11)



Synthesised according to **GP-3** on a 0.7 mmol scale using guaiacol and 10-(3-ethoxyphenyl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide. The crude compound was purified by automated silica gel column chromatography (0 to 4% TBME in pentane) to yield the title compound an orange oil (77.7 mg, 0.32 mmol, 46%).

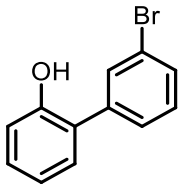
^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 7.40 (1H, app. t, *J* = 7.9 Hz), 7.31 – 7.23 (2H, m), 7.0 (1H, dd, *J* = 7.6), 7.01 – 6.97 (3H, m), 6.94 (1H, ddd, *J* = 8.3, 2.6, 1.0 Hz), 5.38 (1H, s), 4.08 (2H, q, *J* = 7.0 Hz), 1.45 (3H, t, *J* = 7.0 Hz)

$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ_C 159.7, 152.5, 138.4, 130.4, 130.1, 129.2, 128.0, 121.1, 120.8, 115.8, 115.1, 114.2, 63.6, 14.9.

IR (ATR-IR, neat) υ_{max}: 3018, 1599, 1474, 1412, 1214, 1025, 933.

HRMS (ESI$^-$): *m*/*z* calcd. for $[C_{14}H_{13}O_2]^-$ [M-H]$^-$: 213.0916. Found: 213.0923.

3'-Bromo-[1,1'-biphenyl]-2-ol (10)



Synthesised according to **GP-3** on a 0.7 mmol scale using guaiacol and 10-(3-bromophenyl)-10*H*-dibenzo[*b,e*][1,4]thiabismine 5,5-dioxide. The crude compound was purified by automated silica gel column chromatography (0 to 5% Et_2O in pentane) to yield the title compound as colourless solid (68.4 mg, 0.27 mmol, 39%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.67 (1H, app. t, *J* = 1.8 Hz), 7.53 (1H, ddd, *J* = 7.9, 1.8, 1.5 Hz), 7.43 (1H, app. dt, *J* = 7.9, 1.3 Hz), 7.34 (1H, app. t, *J* = 7.9 Hz), 7.28 (1H, app. td, *J* = 8.2, 1.8 Hz), 7.24 (1H, dd, *J* = 7.6, 1.8 Hz), 7.01 (1H, app. td, *J* = 7.6, 1.2 Hz), 6.96 (1H, dd, *J* = 8.2, 1.2 Hz), 5.15 (1H, s).

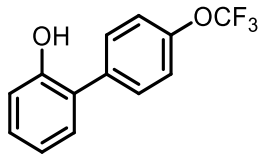
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 152.4, 139.5, 132.3, 130.9, 130.6, 130.4, 129.7, 127.8, 126.9, 123.2, 121.2, 116.2.

IR (ATR-IR, neat) υ_{max}: 3018, 1724, 1593, 1515, 1409, 1214, 1091.

HRMS (ESI$^-$): *m/z* calcd. for $[C_{12}H_8{}^{79}BrO]^-$ $[M-H]^-$: 246.9759. Found: 246.9766.

MP: 75-78 °C.

4'-(Trifluoromethoxy)-[1,1'-biphenyl]-2-ol (9)



Synthesised according to **GP-3** on a 0.7 mmol scale using guaiacol and 10-(4-(trifluoromethoxy)phenyl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide. The crude compound was purified by automated silica gel column chromatography (0 to 3% TBME in pentane) to yield the title compound as a colourless solid (88.0 mg, 0.35 mmol, 50%). Characterisation data were consistent with literature values: ^{1}H, ^{13}C{^{1}H} and HRMS.[191]

^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 7.52 (2H, d, *J* = 8.3 Hz), 7.33 (2H, d, *J* = 8.3 Hz), 7.28 (1H, dd, *J* = 7.8, 1.7 Hz), 7.24 (1H, dd, *J* = 7.8, 1.7 Hz), 7.01 (1H, app. td, *J* = 7.8, 1.2 Hz), 6.97 (1H, dd, *J* = 7.8, 1.2 Hz), 5.00 (1H, s)

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ_C 152.5, 148.9 (q, *J* = 1.70 Hz), 136.1, 130.8, 130.5, 129.6, 127.0, 121.6, 121.3, 120.7 (q, *J* = 257.4 Hz), 116.2

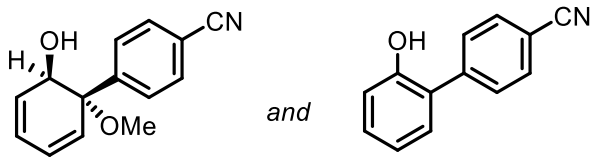
^{19}F NMR (377 MHz, $CDCl_3$): δ_F -57.76 (s)

IR (ATR-IR, neat) υ_{max}: 3525, 3432, 2925, 2855, 1703, 1603, 1592, 1512, 1493, 1452, 1405, 1254, 1207, 1159, 1101, 1044, 1021, 1007, 939, 920.

HRMS (ESI$^-$): *m*/*z* calcd. for $[C_{13}H_8F_3O_2]^-$ [M-H]$^-$: 253.0476. Found: 253.0488.

MP: 64-67 ˚C.

2'-Hydroxy-[1,1'-biphenyl]-4-carbonitrile (8a) and dienol (8b)



(±)-8b **8a**

Synthesised according to a modified version of **GP-3** on a 0.716 mmol scale using guaiacol and 4-(5,5-dioxido-10*H*-dibenzo[*b,e*][1,4]thiabismin-10-yl)benzonitrile. The modification follows from the Luche reduction, as detailed below. Dienol **(±)-8b** was formed in *ca* 44% yield, as determined by ^{1}H NMR spectroscopic analysis (vs 1,3,5-trimethoxybenzene).

The reaction mixture was quenched with aq. HCl (2 M, 7.0 mL), left to stir for 5 min, then extracted with Et_2O (3 × 10 mL). The combined organic portions were washed once with brine (10 mL), dried with anhydrous sodium sulfate, and concentrated *in vacuo* to afford the crude arylated phenol, which was purified by automated silica gel column chromatography (5-10% Et_2O in pentane) to yield the title compound **8a** as off-white crystals (36.6 mg, 0.19 mmol, 26%). Characterisation data were consistent with literature values: ^{1}H, ^{13}C{^{1}H}.[201]

The column was flushed with IPA and the eluent was concentrated under reduced pressure. Crude dienol **8b** was obtained from the resulting residue *via* preparative thin layer chromatography (10 % Et_2O in a 1% solution of Et_3N in pentane).

Characterisation data for **8b**

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.67 (2H, d, *J* = 8.2 Hz), 7.61 (2H, d, *J* = 8.2 Hz), 6.38 (1H, dd, *J* = 9.9, 5.1 Hz), 6.07 (1H, dd, *J* = 9.7, 5.1 Hz), 6.01 (1H, d, *J* = 9.9 Hz), 5.96 (1H, dd, *J* = 9.7, 3.8 Hz), 4.59-4.42 (1H, m), 3.25 (3H, s), 1.39 (1H, d, *J* = 6.7 Hz).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 144.0, 132.0, 130.4, 128.6, 128.1 (2 × C, determined by HSQC), 123.8, 119.0, 111.9, 81.8, 72.1, 52.4.

Aryl phenol **8a** was also synthesised according to **GP-3** on a 0.55 mmol scale using guaiacol and 4-(5,5-dioxido-10*H*-dibenzo[*b,e*][1,4]thiabismin-10-yl)benzonitrile (**SI-6**). The crude compound was purified by automated silica gel column

chromatography (0-20% Et_2O in pentane) to yield the title compound (87 mg, 0.44 mmol, 81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.73 (2H d, *J* = 8.3 Hz), 7.66 (2H, d, *J* = 8.3 Hz), 7.34 – 7.32 (2H, m), 7.04 (1H dd, *J* = 7.6 Hz, 1.1 Hz), 6.94 (1H, d, *J* = 8.0 Hz), 5.24 (1H, s).

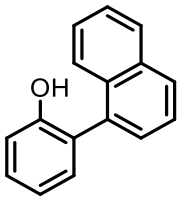
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 152.6, 142.8, 132.6, 130.6, 130.2, 130.1, 126.7, 121.5, 119.0, 116.5, 111.1.

IR (ATR-IR, neat) υ_{max}: 3355, 2231, 1604, 1492, 1450, 1401, 1356, 1294, 1274, 1205, 1180, 1106, 909.

HRMS (ESI$^-$): *m/z* calcd. for $[C_{13}H_9NO]^-$ $[M-H]^-$: 194.0611. Found: 194.0612.

MP: 116-119 ˚C.

2-(Naphthalen-1-yl)phenol (12)



Synthesised according to **GP-3** on a 0.53 mmol scale using guaiacol and 10-(naphthalen-1-yl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide. The crude compound was purified by automated silica gel column chromatography (0-10% Et_2O in pentane) to yield the title compound as a colourless oil (13 mg, 0.06 mmol, 11%). Characterisation data were consistent with literature values: ^1H, $^{13}C\{^1H\}$.[202]

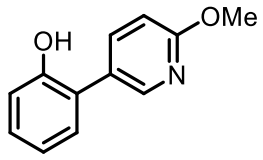
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.00-7.93 (2H, m), 7.67 (1H, d, *J* = 8.6 Hz), 7.58 (1H, dd, *J* = 8.3 Hz), 7.56 – 7.44 (3H, m), 7.41 – 7.35 (1H, m), 7.31 – 7.25 (1H, m), 7.11 – 7.01 (2H, m), 4.80 (1H, s).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 153.3, (134.1 2 × C, determined by HSQC), 132.0, 131.4, 129.7, 129.0, 128.6, 128.4, 126.9, 126.5, 126.4, 125.9, 125.8, 120.7, 115.7.

IR (ATR-IR, neat) υ_{max}: 3019, 2324, 2036, 1944, 1562, 1524, 1499, 1438, 1303, 1286, 1252, 1214, 1150, 1123, 1087, 1073, 1012, 915.

HRMS (ESI$^-$): *m*/*z* calcd. for $[C_{16}H_{11}O]^-$ $[M-H]^-$: 219.0815. Found: 219.0817.

2-(6-Methoxypyridin-3-yl)phenol (15)



Synthesised according to a **GP-3** on a 0.7 mmol scale using guaiacol and 10-(6-methoxypyridin-3-yl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide. Synthesis features an alternative work-up following the Luche reduction: The reaction mixture was quenched with HCl (4.0 M; 7 mL) and stirred for 10 min. Following neutralisation with K_2CO_3, the phenol was extracted with Et_2O (3 × 10 mL) and the collected organic portions were dried over sodium sulfate before the solvent was removed *in vacuo*. The resultant crude compound was purified by automated silica gel column chromatography (3 % Et_2O in pentane) to yield the title compound as a white solid (32.8 mg, 0.16 mmol, 24%).

^{1}H NMR (DMSO, 400 MHz): δ_H 9.64 (1H, s), 8.33 (1H, d, *J* = 2.4 Hz), 7.90 (1H, ddd, *J* = 8.5, 2.4, 1.1 Hz), 7.27 (1H, d, *J* = 7.5 Hz), 7.22 – 7.11 (1H, m), 7.96 (1H, d, *J* = 8.2 Hz), 6.87 (1H, d, *J* = 7.5 Hz), 6.85 (1H, d, *J* = 8.5 Hz), 3.88 (3H, d, *J* = 1.1 Hz).

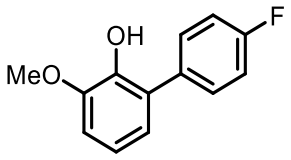
^{13}C{^{1}H} NMR (DMSO, 101 MHz)**:** δ_C 162.3, 154.4, 146.4, 139.8, 130.0, 128.7, 127.7, 124.3, 119.6, 116.0, 109.6, 53.1.

IR (ATR-IR, neat) υ_{max}: 3018, 1603, 1514, 1487, 1409, 1289, 1214, 1023.

HRMS (ESI$^-$): *m*/*z* calcd. for $[C_{12}H_{10}NO_2]^-$ [M-H]$^-$: 200.0712. Found: 200.0721.

MP: decomp. at 240 °C.

4'-Fluoro-3-methoxy-[1,1'-biphenyl]-2-ol (29)



Synthesised according to **GP-3** on a 0.7 mmol scale using 2,6-dimethoxyphenol and 10-(4-fluorophenyl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide. The crude compound was purified by automated silica gel column chromatography (5-10% Et_2O in pentane) to yield the title compound as a yellow powder (64 mg, 0.29 mmol, 42%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.61 (2H, dd, *J* = 8.8, 5.5 Hz), 7.13 (2H, appt. tt, *J* = 8.8, 2.9 Hz), 7.00 – 6.84 (3H, m), 5.92 (1H, s), 3.95 (3H, s).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 162.1 (d, *J* = 245.9 Hz), 146.9, 142.8, 133.7 (d, *J* = 3.3 Hz), 130.8 (d, *J* = 7.9 Hz), 126.7, 122.6, 119.8, 115.1 (d, *J* = 21.4 Hz), 109.7, 56.2.

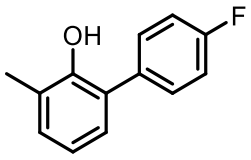
^{19}F NMR (377 MHz, $CDCl_3$): δ_F -115.6 (tt, *J* = 8.8, 5.5 Hz).

IR (ATR-IR, neat) υ_{max}: 3520, 3015, 2937, 2847, 1601, 1584, 1512, 1472, 1441, 1401, 1361, 1296, 1267, 1216, 1186, 1158, 1109, 1077, 1026, 1014, 946.

HRMS (ESI$^-$): *m*/*z* calcd. for $[C_{13}H_{10}FO_2]^-$ $[M-H]^-$: 217.0665. Found: 217.0674.

MP: 88-90 °C.

4'-Fluoro-3-methyl-[1,1'-biphenyl]-2-ol (28)



Synthesised according to **GP-3** on a 0.7 mmol scale using 2-methoxy-6-methylphenol and 10-(4-fluorophenyl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide. The crude compound was purified by automated silica gel column chromatography (0 to 20% Et_2O in pentane) to yield the title compound as a colourless oil (23 mg, 0.11 mmol, 16%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.44 (2H, dd, *J* = 8.8, 5.4 Hz), 7.11 – 7.01 (3H, m), 7.06 (1H, ddd, *J* = 7.6, 1.8, 0.6 Hz), 6.91 (1H, d, *J* = 7.6 Hz), 5.09 (1H, s), 2.32 (3H, s).

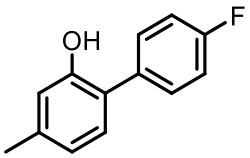
^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ_C 162.6 (d, *J* = 247.3 Hz), 150.7, 133.4 (d, *J* = 3.5 Hz), 131.1 (d, *J* = 8.0 Hz), 130.7, 128.0, 126.9, 124.8, 120.5, 116.3 (d, *J* = 21.4 Hz), 16.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ_F -114.2 (tt, *J* = 8.6, 5.4 Hz).

IR (ATR-IR, neat) υ_{max}: 3502, 3488, 3385, 3336, 3301, 2981, 2925, 1597, 1510, 1473, 1420, 1401, 1215, 1159, 1086, 1024, 935.

HRMS (ESI$^-$): *m*/*z* calcd. for $[C_{13}H_{10}FO]^-$ [M-H]$^-$: 201.0716. Found: 201.0724.

4'-Fluoro-4-methyl-[1,1'-biphenyl]-2-ol (24)



Synthesised according to **GP-3** on a 0.7 mmol scale using 2-methoxy-5-methylphenol and 10-(4-fluorophenyl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide. The crude compound was purified by automated silica gel column chromatography (5-10% Et_2O in pentane) to yield the title compound as colourless solid (87.6 mg, 0.43 mmol, 62%). Characterisation data were consistent with literature values: ^1H, $^{13}C\{^1H\}$.[203]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.44 (2H, dd, *J* = 8.6, 5.6 Hz), 7.16 (2H, app. t, *J* = 8.6 Hz), 7.12 (1H, d, *J* = 7.8 Hz), 6.82 (1H, d, *J* = 7.8 Hz), 6.80 (1H, s), 5.00 (1H, s), 2.36 (3H, s).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ_C 162.5 (d, *J* = 247.1 Hz), 152.3, 139.6, 133.3 (d, *J* = 3.2 Hz), 131.0 (d, *J* = 7.8 Hz), 130.2, 124.5, 121.9, 116.6, 116.2 (d, *J* = 21.4 Hz), 21.3.

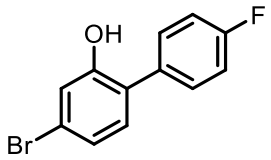
^{19}F NMR (377 MHz, $CDCl_3$): δ_F -114.6 (tt, *J* = 8.6, 5.6 Hz).

IR (ATR-IR, neat) υ_{max}: 3534, 3426, 3036, 2921, 2858, 1703, 1620, 1602, 1569, 1517, 1496, 1452, 1423, 1397, 1287, 1222, 1189, 1157, 1121, 1095, 1038, 1009, 943, 908.

HRMS (ESI$^-$): *m*/*z* calcd. for $[C_{13}H_{10}FO]^-$ $[M-H]^-$: 201.0721. Found: 201.0722.

MP: 54-60 °C.

4-Bromo-4'-fluoro-[1,1'-biphenyl]-2-ol (27)



Synthesised according to **GP-3** on a 0.7 mmol scale using methyl 5-bromo guaiacol and 10-(4-fluorophenyl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide. The crude compound was purified by automated silica gel column chromatography (5 to 10 % Et_2O in cyclohexane) to yield the title compound as colourless oil (55.0 mg, 0.21 mmol, 30%). ^{1}H, $^{13}C\{^{1}H\}$,^{19}F NMR and HRMS.[71]

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.41 (2H, dd, *J* = 8.5, 5.2 Hz), 7.18 (2H, app. t, *J* = 8.5 Hz), 7.15 – 7.12 (2H, m), 7.08 (1H, d, *J* = 8.0 Hz), 5.14 (1H, s).

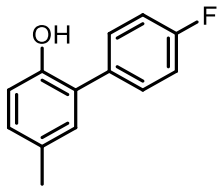
$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 126 MHz) δ_C 162.7 (d, *J* = 248.1 Hz), 153.2, 132.1 (d, *J* = 3.3 Hz), 131.5, 130.9 (d, *J* = 8.1 Hz), 126.4, 124.3, 122.3, 119.3, 116.5 (d, *J* = 21.5 Hz).

^{19}F NMR (377 MHz, $CDCl_3$): δ_F -113.36 (tt, *J* = 8.5, 5.2 Hz).

IR (ATR-IR, neat) υ_{max}: 3064, 2196, 1842, 1596, 1514, 1490, 1417, 1322, 1221, 1145.

HRMS (ESI$^-$): *m*/*z* calcd. for $[C_{12}H_8{}^{79}BrFO]^-$ $[M-H]^-$: 264.9670. Found: 264.9674.

4'-Fluoro-5-methyl-[1,1'-biphenyl]-2-ol (16)



Synthesised according to **GP-3** on a 0.7 mmol scale using 2-methoxy-4-methylphenol and 10-(4-fluorophenyl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide. The crude compound was purified by automated silica gel column chromatography (5-10% Et_2O in pentane) to yield the title compound as a brown oil (70 mg, 0.35 mmol, 50%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.51 – 7.34 (2H, m), 7.17 (2H, app. t, *J* = 8.7 Hz), 7.07 (1H, dd, *J* = 8.1, 2.1 Hz), 7.04 (1H, d, *J* = 2.1 Hz), 6.87 (1H, d, *J* = 8.1 Hz), 4.96 (1H, s), 2.33 (3H, s)

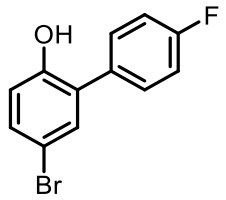
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 162.5 (d, *J* = 247.1 Hz), 150.2, 133.4 (d, *J* = 3.3 Hz), 131.0, 130.9, 130.3, 129.8, 127.1, 116.1 (d, *J* = 21.4 Hz), 115.9, 20.6.

^{19}F NMR (377 MHz, $CDCl_3$): δ_F -114.4 (tt, *J* = 8.7, 5.4 Hz).

IR (ATR-IR, neat) υ_{max}: 3539, 3416, 3019, 2921, 2861, 1603, 1494, 1463, 1394, 1329, 1299, 1267, 1222, 1158, 1127, 1094, 1038, 1015, 942, 909.

HRMS (ESI$^-$): *m*/*z* calcd. for $[C_{13}H_{10}FO]^-$ [M-H]$^-$: 201.0721. Found: 201.0727.

5-Bromo-4'-fluoro-[1,1'-biphenyl]-2-ol (17)



Synthesised according to **GP-3** on a 0.7 mmol scale using 4-bromo-2-methoxyphenol and 10-(4-fluorophenyl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide. The crude compound was purified by automated silica gel column chromatography (0 to 5% Et_2O in pentane) to yield the title compound as colourless oil (60 mg, 0.23 mmol, 32%). ^1H, $^{13}C\{^1H\}$,^{19}F NMR and HRMS.[71]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.42 (2H, dd, *J* = 8.7, 5.3 Hz), 7.36 – 7.31 (2H, m), 7.18 (2H, app t, *J* = 8.7 Hz), 6.88 – 6.81 (1H, m), 5.12 (1H, s).

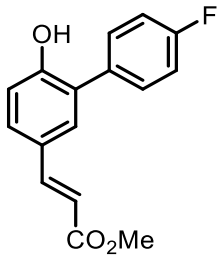
^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ_C 162.8 (d, *J* = 248.5 Hz), 151.7, 132.9, 132.0, 131.9 (d, *J* = 3.4 Hz), 131.0 (d, *J* = 8.1 Hz), 129.3, 117.9, 116.4 (d, *J* = 21.6 Hz), 113.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ_F -113.10 (tt, *J* = 8.7, 5.3 Hz).

IR (ATR-IR, neat) υ_{max}: 3536, 3406, 2925, 1599, 1511, 1487, 1477, 1419, 1388, 1324, 1301, 1259, 1224, 1158, 1123, 1095, 1023, 1014.

HRMS (ESI$^-$): *m*/*z* calcd. for $[C_{12}H_7{}^{79}BrFO]^-$ $[M-H]^-$: 264.9664. Found: 264.9674.

Methyl (*E*)-3-(4'-fluoro-6-hydroxy-[1,1'-biphenyl]-3-yl)acrylate (18)



Synthesised according to **GP-3** on a 0.6 mmol scale using methyl (*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylate and 10-(4-fluorophenyl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide. The crude compound was purified by automated silica gel column chromatography (0 to 20 % Et_2O in pentane) to yield the title compound as colourless solid (45.0 mg, 0.17 mmol, 28%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.66 (1H, d, *J* = 16.0 Hz), 7.49 – 7.37 (4H, m), 7.23 – 7.14 (2H, m), 6.99 (1H, d, *J* = 8.5 Hz), 6.33 (1H, d, *J* = 16.0 Hz), 5.91 (1H, s), 3.80 (3H, s).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ_C 168.1, 162.7 (d, *J* = 247.9 Hz), 154.9, 144.7, 132.5 (d, *J* = 3.4 Hz), 131.0 (d, *J* = 8.1 Hz), 130.7, 129.3, 128.0, 127.5, 116.7, 116.2 (d, *J* = 21.4 Hz), 115.6, 51.9.

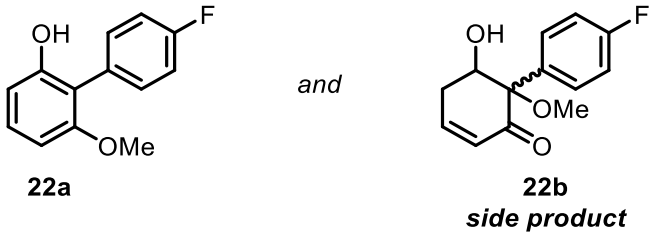
^{19}F NMR (376 MHz, $CDCl_3$): δ_F -113.58 (tt, *J* = 8.5, 5.3 Hz).

IR (ATR-IR, neat) υ_{max}: 3018, 2925, 1599, 1475, 1420, 1214, 1025, 934.

HRMS (ESI$^-$): *m*/*z* calcd. for $[C_{16}H_{12}FO_3]^-$ [M-H]$^-$: 271.0770. Found: 271.0776.

MP: 98-90 °C.

4'-Fluoro-6-methoxy-[1,1'-biphenyl]-2-ol (22a) and 4'-fluoro-6-hydroxy-1-methoxy-5,6-dihydro-[1,1'-biphenyl]-2(1H)-one (22b)



Synthesised according to **GP-3** on a 0.7 mmol scale using 2,3-dimethoxyphenol and 10-(4-fluorophenyl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide. The crude compound was purified by automated silica gel column chromatography (5 % Et_2O in pentane) to yield aryl phenol **22a** as an off white solid (38 mg, 0.17 mmol, 25%) and the side product **22b** as a yellow oil (32% yield, determined by ^{19}F NMR spectroscopic analysis prior to purification).

4'-Fluoro-6-methoxy-[1,1'-biphenyl]-2-ol (22a):

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.35 (2H, dd, *J* = 8.6, 5.4 Hz), 7.28 – 7.14 (3H, m), 6.66 (1H, dd, *J* = 8.3, 1.0 Hz), 6.58 (1H, dd, *J* = 8.3, 0.9 Hz), 4.93 (1H, s), 3.74 (3H, s).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ_C 162.6 (d, *J* = 247.2 Hz), 157.6, 153.8, 132.7 (d, *J* = 8.0 Hz), 129.4, 128.3 (d, *J* = 3.3 Hz), 116.3 (d, *J* = 21.4 Hz), 116.3, 108.6, 103.3, 55.9.

^{19}F NMR (377 MHz, $CDCl_3$): δ_F -113.79 (tt, *J* = 8.6, 5.4 Hz).

IR (ATR-IR, neat) υ_{max}: 3550, 3432, 3049, 3010, 2937, 2838, 1597, 1584, 1513, 1466, 1438, 1401, 1323, 1306, 1253, 1221, 1197, 1170, 1156, 1077, 1008, 94.

HRMS (ESI$^-$): *m*/*z* calcd. for $[C_{13}H_{10}FO_2]^-$ $[M-H]^-$: 217.0665. Found: 217.0673.

MP: 106-109 °C.

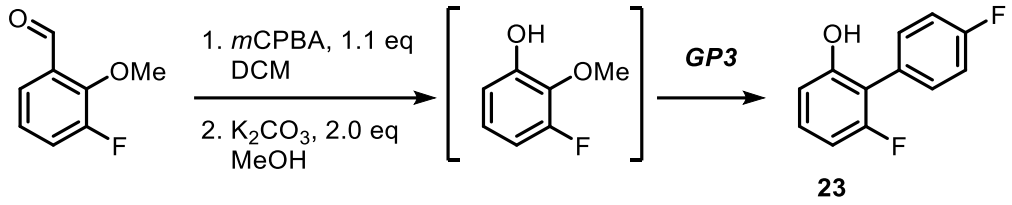
4'-Fluoro-6-hydroxy-1-methoxy-5,6-dihydro-[1,1'-biphenyl]-2(1H)-one (22b)

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.46 (2H, dd, *J* = 8.6, 5.4 Hz), 7.10 (2H, d, *J* = 8.6 Hz), 6.87 (1H, dt, *J* = 10.2, 4.2 Hz), 6.20 (1H, dt, *J* = 10.2, 2.0 Hz), 4.23 (1H, dd, *J* = 6.5, 4.2 Hz), 3.30 (3H, s), 2.86 (1H, dtd, *J* = 18.8, 4.2, 2.0 Hz), 2.29 (1H, ddd, *J* = 18.8, 6.5, 2.0 Hz).

$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 101 MHz) δ_C 198.1, 162.9 (d, *J* = 248.1 Hz), 146.5, 131.0 (d, *J* = 8.1 Hz), 130.3 (d, *J* = 3.4 Hz), 129.6, 115.3 (d, *J* = 21.3 Hz), 85.2, 73.8, 53.9, 31.9

^{19}F NMR (376 MHz, $CDCl_3$): δ_F -113.18 (tt, *J* = 8.6, 5.4 Hz).

4',6-Difluoro-[1,1'-biphenyl]-2-ol (23)



The synthesis of aryl phenol **23** was performed in a telescoped fashion from 3-fluoro-2-methoxybenzaldehyde, with **GP3** resuming after the Baeyer-Villiger oxidation / methanolysis to form 3-fluoroguaiacol**.**

3-Fluoro-2-methoxybenzaldehyde (539 mg, 3.5 mmol) was dissolved in DCM (9 mL) at rt, and *m*CPBA (959 mg, 3.85 mmol, 70% purity) was added in 5 equal portions at one-minute intervals while stirring. The reaction mixture was left to stir at rt for 18 h. The reaction was then quenched with sat. aq. $Na_2S_2O_3$ (3 mL), diluted with DCM (20 mL) and washed sequentially with sat. aq. Na_2SO_3 (1 × 20 mL), brine (1 × 20 mL) and $NaHSO_3$ (3 × 50 mL). The organic portion was then dried with Na_2SO_4 and concentrated in vacuo.

The resultant residue was diluted with MeOH (9 mL), to which K_2CO_3 (966 mg, 7.00 mmol) was added on stirring at rt. After 30 min, the reaction mixture was concentrated in vacuo, and suspended in Et_2O (15 mL). The mixture was washed with H_2O (2 × 10 mL), dried with Na_2SO_4 and concentrated in vacuo to afford the crude phenol; this was purified *via* automated silica gel column chromatography (0 to 5% Et_2O in pentane) to yield 3-fluoroguaiacol as a colourless oil (160 mg, 1.13 mmol, 38%). This compound is volatile; as such its yield was calculated by dissolving the product in PhMe and adding a known amount of internal standard.

Aryl phenol **23** was synthesised according to **GP3** on a 0.13 mmol scale using 3-fluoroguaiacol and 10-(4-fluorophenyl)-10*H*-dibenzo[*b,e*][1,4]thiabismine 5,5-dioxide. The crude compound was purified by automated silica gel column chromatography (0 to 10 % Et_2O in pentane) to yield the title compound as an off white solid (135 mg, 0.66 mmol, 56%). Characterisation data were consistent with literature values: ^1H, $^{13}C\{^1H\}$, ^{19}F, HRMS and MP.[71]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.40 (2H, dd, J = 8.9, 5.3, Hz), 7.27 – 7.16 (3H, m), 6.80 (1H, app. dt, J = 8.3, 1.1 Hz), 6.75 (1H, ddd, J = 9.3, 8.3, 1.1 Hz), 5.03 (1H, s).

$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 101 MHz) δ_C 162.8 (d, J = 248.5 Hz), 160.2 (d, J = 245.6 Hz), 153.9 (d, J = 5.6 Hz), 132.3 (d, J = 7.8 Hz), 129.4 (d, J = 10.5 Hz), 125.9 (d, J = 3.4 Hz), 116.4 (d, J = 21.6 Hz), 115.7 (d, J = 18.9 Hz), 111.4 (d, J = 3.1 Hz), 107.8 (d, J = 22.8 Hz).

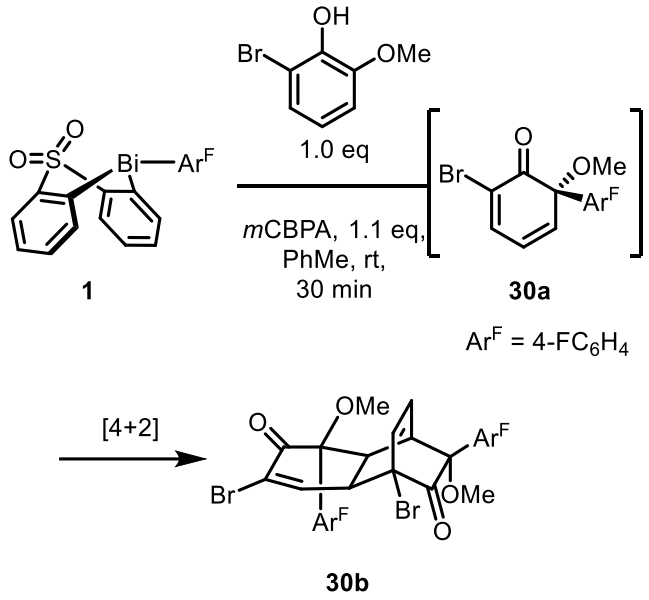
^{19}F NMR (377 MHz, $CDCl_3$): δ_F -112.69 (1F, tt, J = 8.5, 5.3 Hz), -115.32 (1F, dd, J = 9.3, 6.7 Hz).

IR (ATR-IR, neat) υ_{max}: 3547, 3019, 2926, 1622, 1601, 1517, 1464, 1404, 1330, 1294, 1214, 1176, 1159, 1094, 1001.

HRMS (ESI^-): m/z calcd. for $[C_{12}H_7F_2O]^-$ $[M-H]^-$: 205.0465. Found: 205.0474.

MP: 73-76 ˚C.

1,7-Dibromo-5,9-bis(4-fluorophenyl)-5,9-dimethoxy-1,4a,5,8a-tetrahydro-1,4-ethanonaphthalene-6,10(4H)-dione (30b)



30b

In an amberised RBF, **1** (83.0 mg, 0.16 mmol) and 6-bromo guaiacol (33.1 mg, 0.16 mmol) were suspended in PhMe (8 mL) in the presence of internal standard 4,4'-bis(trifluoromethyl)-1,1'-biphenyl (5.00 mg, 0.02 mmol) at rt. *m*CPBA (44 mg, 0.18 mmol, 69% purity) was added in 10 equal portions at 30 second intervals while stirring, and the reaction mixture was left for 30 min. The resultant orange solution was quenched with sat. aq. $Na_2S_2O_5$ (0.01 mL), left to stir for 5 min, then passed through a plug of basic alumina (*ca* 21 mL). The solution was eluted with EtOAc (70 mL) and concentrated in vacuo. Analysis of the crude material by ^{19}F NMR spectroscopy indicated that none of the expected cyclohexadienone remained **30a**, and that the corresponding dimer **30b** was formed in 68% yield. The crude material was purified by automated silica gel column chromatography (0 to 5% EtOAc in cyclohexane) to yield the title compound as a yellow solid (10 mg, 16.8 μmol, 21%).

Observed as single diastereoisomer; relative stereochemistry could not be determined unambiguously.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.31 – 7.26 (2H, m), 7.20 (2H, dd, *J* = 8.5, 5.1 Hz), 7.11 (2H, app. t, *J* = 8.3 Hz), 7.03 (2H, app. t, *J* = 8.4 Hz), 6.90 (1H, d, *J* = 4.3 Hz),

5.98 (1H, s), 5.96 (1H, d, *J* = 1.8 Hz), 4.33 (1H, d, *J* = 8.3 Hz), 3.82 – 3.76 (1H, m), 3.54 (1H, dd, *J* = 8.3, 4.3 Hz), 3.24 (3H, s), 3.08 (3H, s).

$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 101 MHz) δ_C 199.6, 191.5, 164.2 (d, *J* = 24.0 Hz), 161.7 (d, *J* = 23.0 Hz), 141.9, 135.3, 134.3, 133.3 (d, *J* = 3.4 Hz), 133.3 (d, *J* = 3.5 Hz), 130.0 (d, *J* = 8.2 Hz), 129.4 (d, *J* = 8.3 Hz), 124.0, 116.4 (d, *J* = 21.7 Hz), 115.7 (d, *J* = 21.6 Hz), 83.1, 79.8, 71.7, 53.4, 52.1, 49.6, 43.9, 39.7.

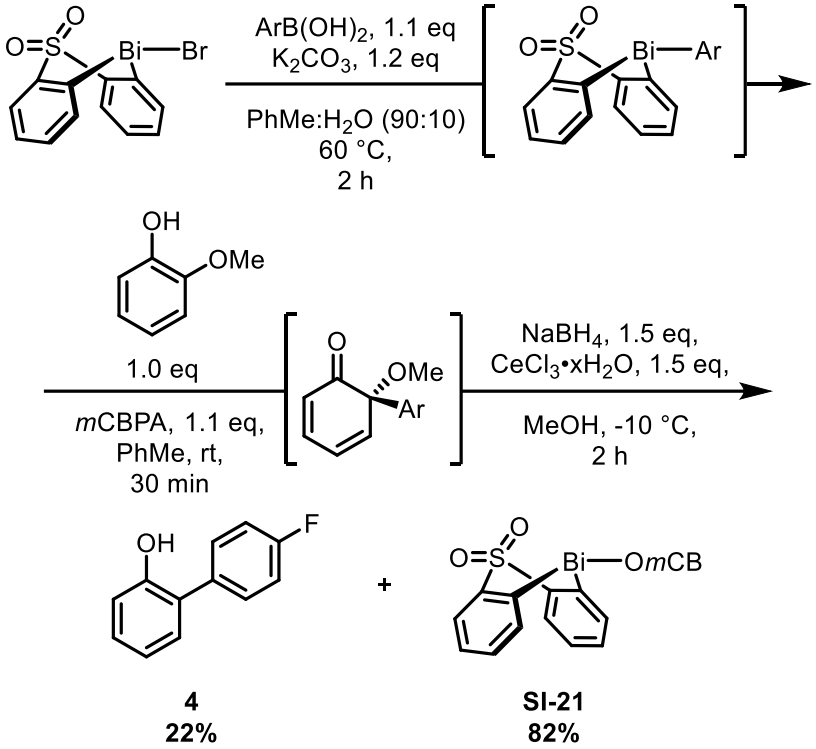
^{19}F NMR (376 MHz, $CDCl_3$): δ_F -111.4 (tt, *J* = 8.4, 5.1 Hz), -112.3 (tt, *J* = 8.4, 5.1 Hz).

IR (ATR-IR, neat) υ_{max}: 3068, 2935, 2835, 1717, 1508, 1236, 1163, 1106, 1090.

HRMS (ESI$^+$): *m/z* calcd. for $[C_{26}H_{20}{}^{79}Br_2F_2NaO_4]^+$ $[M+Na]^+$: 616.9574. Found: 616.9582.

MP: 189-193 ˚C.

Telescoped Arylation and Bismacycle Recovery



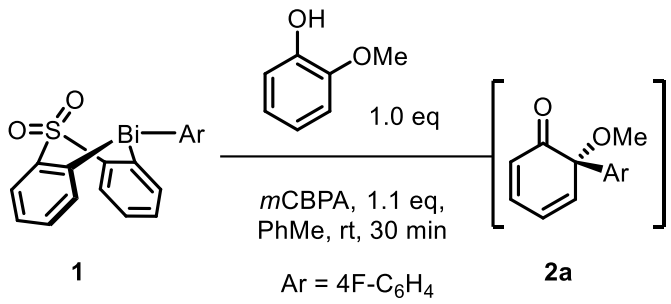
10-Bromo-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide (759 mmol, 1.5 mmol), K_2CO_3 (182 mg, 1.32 mmol), (4-fluorophenyl)boronic acid (231 mg, 1.65 mmol) and 4,4'-bis(trifluoromethyl)-1,1'-biphenyl (internal standard; 13.6 mg, 0.04 mmol) were suspended in a mixture of toluene (15 mL) and water (1.5 mL) and stirred at 60 °C until no starting material was observed by ^{1}H NMR spectroscopy. Once cooled, aqueous NaOH (2.0 M; 50 mL) was added to the reaction mixture, which was then diluted with 50 mL EtOAc. The aqueous phase was separated and the organic portion was washed with water (3 × 50 mL) and brine (3 × 50 mL). The combined organic portions were dried over $MgSO_4$, filtered and concentrated *in vacuo*. To the residue was added guaiacol (185 mg, 1.5 mmol) and toluene (75 mL). *m*CPBA (410 mg, 1.65 mmol, 70% purity) was added in 10 equal portions at 30-second intervals while stirring. The reaction mixture was left for 30 min.

The resultant orange solution was then quenched with sat. aq. $Na_2S_2O_5$ (0.01 mL), left to stir for 5 min, then concentrated *in vacuo*. The residue was suspended in TBME (10 mL) and stirred for 5 min, then pentane (90 mL) was added. The suspension was left stirring at 0 °C for 5 min, and the resultant solids were filtered

under reduced pressure and collected as 5,5-dioxido-10*H*-dibenzo[*b,e*][1,4] thiabismin-10-yl 3-chlorobenzoate **SI-21** (716 mg, 1.23 mmol, 82%) as a colourless solid. The filtrate was then passed through a plug of basified alumina (25 mL) and the intermediate cyclohexadienone was eluted with EtOAc (70 mL) and concentrated into a flask containing cerium chloride hydrate (392 mg, 1.05 mmol) and 1-bromo-4-fluoronaphthalene (internal standard; 59.67 mg, 0.26 mmol). This was diluted with MeOH (7.0 mL) and cooled to -10 °C, after which time sodium borohydride (40 mg, 1.05 mmol) was added in 10 equal portions at 40 second intervals while stirring. The reaction was left to warm to rt until no intermediate cyclohexadienone could be observed by TLC. The reaction mixture was then quenched with HCl (4 M, 7.0 mL), left to stir for 5 min, and the organics extracted with Et_2O (3 × 10 mL). The combined organics were washed once with brine (10 mL), dried with anhydrous sodium sulfate, and concentrated *in vacuo* to afford the crude arylated phenol **4**, which was purified by automated silica gel column chromatography (5-10 % Et_2O in pentane) to yield 4'-fluoro-[1,1'-biphenyl]-2-ol (60 mg, 0.32 mmol, 22%).

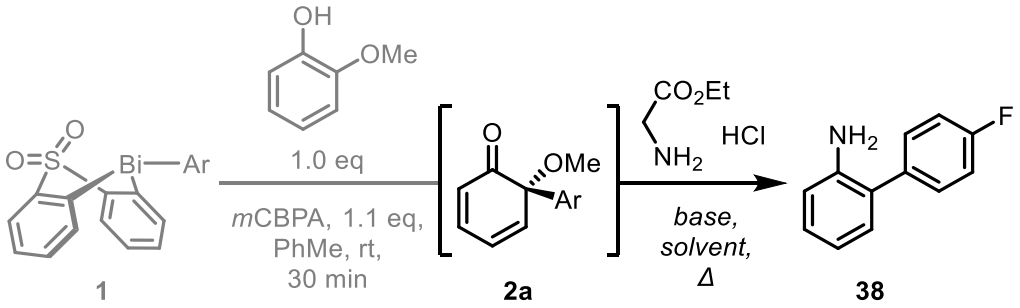
General Procedures for Deoxyaminative Arylation

Preparation of Stock Solution of 2a for Aniline Synthesis



10-(4-Fluorophenyl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide dioxide (1.0 eq) and guaiacol (1.0 eq) were suspended in toluene, ($[phenol]_0$ = 0.2 M). *m*CPBA (1.1 eq) was added portion wise over 5 minutes and the reaction was left to stir for 30 minutes. The resultant orange solution was then quenched with sat. aq. $Na_2S_2O_5$ (0.01 mL), left to stir for 5 min, then concentrated *in vacuo*. The residue was suspended in TBME (10 mL) and stirred for 5 min, then pentane (30 mL) was added. The resultant solids were filtered under reduced pressure and collected as 5,5-dioxido-10*H*-dibenzo[*b*,*e*][1,4] thiabismin-10-yl 3-chlorobenzoate as a colourless solid (**SI-21**). To the filtrate was added a known mass of 4,4'-bis(trifluoromethyl)-1,1'-biphenyl. An aliquot (0.05 mL) was removed and diluted with $CDCl_3$ for analysis by ^1H NMR spectroscopy, quantitative ^{19}F NMR spectroscopy, and HRMS. The filtrate was concentrated under reduced pressure and the crude 4'-fluoro-1-methoxy-[1,1'-biphenyl]-2(1H)-one (**2a**) was diluted with DCM ($[(theoretical\ \mathbf{2a})]_0$ = 0.2 M).

General Optimisation Procedure for Aniline Synthesis *via* Demethoxylative Aromatisation



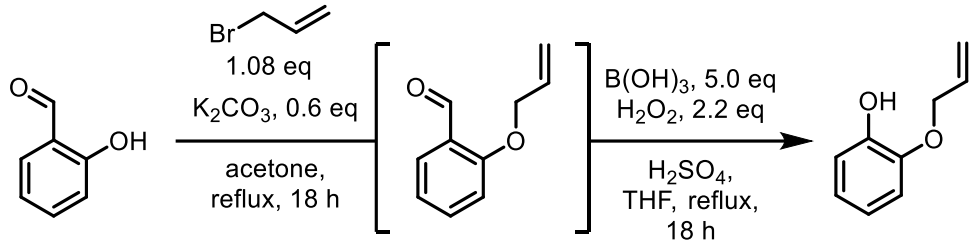
Crude **2a** (1.0 eq)* containing 4,4'-bis(trifluoromethyl)-1,1'-biphenyl was suspended in solvent to a desired concentration. To this was added the desired amount of glycine ethyl ester hydrochloride and base. The reaction was then heated to the required temperature and stirred for 18 h. An aliquot (0.05 mL) was removed and diluted with $CDCl_3$, CD_3OD or DMSO-d_6 for analysis by ^1H NMR spectroscopy, quantitative ^{19}F NMR spectroscopy, and HRMS.

* 1.0 eq based on theoretical amount of cyclohexadienone. Sample obtained by concentrating a known volume from stock solution.

Procedures and Data for Compounds in Chapter III

Synthesis and Characterisation of 2-Allyloxy Phenols

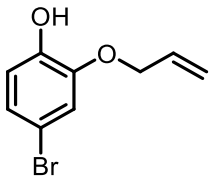
General Procedure and for synthesis of 2-allyloxy substrates *via* telescoped allylation-Baeyer-Villiger reaction (GP4)



To a suspension of the phenol substrate (2.0 mmol) and K_2CO_3 (165 mg, 1.2 mmol) in acetone (50 mL) was added allyl bromide (187 µL, 2.16 mmol). The reaction was heated at reflux for 18 h, then cooled to rt, quenched with sat. aq. NH_4Cl (5 mL), and stirred for 5 min. The mixture was extracted with EtOAc (3 × 20 mL), the collected organic portions were washed once with brine (40 mL), dried over sodium sulfate, and concentrated *in vacuo*. Formation of the allyl ether was confirmed by ^{1}H NMR spectroscopic analysis of the crude material, before it was used directly in the next step without purification.

In a separate round bottomed flask, boric acid (618 mg, 10 mmol) and H_2O_2 (30% aqueous; 435 µL, 4.4 mmol) were dissolved in THF (6 mL). Conc. H_2SO_4 (200 µL) was added, and the solution was left to stir for 30 min at rt. The crude allyloxy benzaldehyde (2.0 mmol) was dissolved in THF (2.0 mL), and the resultant solution was added dropwise to the stirring solution of boric acid. Upon complete addition of the allyloxy benzaldehyde, the reaction mixture was heated at reflux for 18 h. The reaction mixture was allowed to cool to rt and filtered under reduced pressure. The residue was washed with THF (5.0 mL), and the filtrate was neutralised with sat. aq. $NaHCO_3$ and extracted with $CHCl_3$ (3 × 20 mL). The organic portions were collected, washed with water (1 × 10 mL), dried over sodium sulfate, and concentrated *in vacuo*. The phenol product was purified *via* automated or manual silica gel column chromatography using the solvent system described for each compound entry.

2-(Allyloxy)-4-bromophenol (SI-34)



Synthesised according to **GP4** using 2-(allyloxy)-4-bromobenzaldehyde (1.99 g, 9.94 mmol). The intermediate allyl benzaldehyde was separated from unreacted starting material *via* manual column chromatography (0-5% EtOAc in cyclohexane). The subsequent Baeyer-Villiger reaction was heated to reflux for 5 days, and the crude product was purified *via* automated silica gel chromatography (3% EtOAc in cyclohexane) to yield **SI-34** as a brown oil (427 mg, 1.86 mmol, 19%).

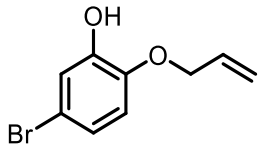
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.03 – 6.89 (2H, m), 6.82 (1H, d, *J* = 8.3 Hz), 6.04 (1H, ddt, *J* = 17.2, 10.7, 5.5 Hz), 5.58 (1H, s), 5.41 (1H, dd, *J* = 17.2, 1.4 Hz), 5.35 (1H, dd, *J* = 10.7, 1.4 Hz), 4.59 (2H, app. dt, *J* = 5.5, 1.4 Hz).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 146.3, 145.2, 132.2, 124.6, 119.0, 116.0, 115.6, 111.5, 70.2.

IR (ATR-IR, neat) υ_{max}: 3514, 3078, 2922, 2870, 1649, 1605, 1585, 1491, 1460, 1418, 1369, 1353, 1257, 1216, 1191, 1114, 1074, 994, 929.

HRMS (ESI$^-$): *m/z* calcd. for $[C_9H_8{}^{79}BrO_2]^-$ $[M-H]^-$: 226.9713. Found: 226.9714.

2-(Allyloxy)-5-bromophenol (SI-35)



Synthesised according to **GP4** using 5-bromo-2-hydroxybenzaldehyde on a 10 mmol scale. The crude product was purified *via* automated silica gel chromatography (3% EtOAc in cyclohexane) to yield **SI-35** as a brown oil (712 mg, 3.10 mmol, 31%).

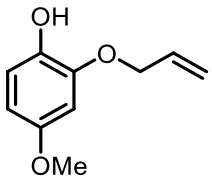
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.08 (1H, d, *J* = 2.1 Hz), 6.94 (1H, dd, *J* = 8.6, 2.1 Hz), 6.72 (1H, d, *J* = 8.6 Hz), 6.03 (1H, ddt, *J* = 17.4, 10.8, 5.5 Hz), 5.69 (1H, s), 5.40 (1H, d, *J* = 17.4 Hz), 5.33 (1H, d, *J* = 10.8 Hz), 4.58 (2H, d, *J* = 5.5 Hz).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 146.9, 144.9, 132.5, 122.9, 118.8, 118.1, 113.7, 113.5, 70.1.

IR (ATR-IR, neat) υ_{max}: 3508, 3078, 2921, 2872, 1649, 1590, 1492, 1461, 1424, 1363, 1328, 1284, 1258, 1209, 1125, 1011, 993, 932.

HRMS (ESI$^-$): *m/z* calcd. for $[C_9H_8{}^{79}BrO_2]^-$ [M-H]$^-$: 226.9711. Found: 226.9713.

2-(Allyloxy)-4-methoxyphenol (SI-36)



Synthesised according to **GP4** 2-hydroxy-4-methoxybenzaldehyde on a 5 mmol scale. The intermediate allyl benzaldehyde was separated from unreacted starting material *via* automated column chromatography (0-5% EtOAc in cyclohexane). The crude title compound was purified *via* automated silica gel chromatography (15-20% EtOAc in cyclohexane) to yield 2-(allyloxy)-4-bromophenol as an off white solid (88 mg, 0.48 mmol, 8%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.84 (1H, d, *J* = 8.7 Hz),6.49 (1H, d, *J* = 2.6 Hz), 6.40 (1H, dd, *J* = 8.7, 2.6 Hz), 6.06 (1H, ddt, *J* = 17.0 10.6, 5.6 Hz), 5.40 (1H, d, *J* = 17.0 Hz), 5.32 (1H, d, *J* = 10.6 Hz), 5.24 (1H, s), 4.58 (2H, d, *J* = 5.6 Hz), 3.75 (3H, s).

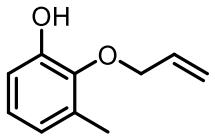
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 153.5, 146.0, 140.1, 132.8, 118.5, 114.3, 104.8, 100.8, 69.9, 55.9.

IR (ATR-IR, neat) υ_{max}: 3440, 2938, 2837, 1620, 1508, 1463, 1425, 1382, 1302, 1263, 1227, 1193, 1158, 1117, 1041, 1018, 998, 930, 880.

HRMS (ESI^{+}): *m/z* calcd. for $[C_{10}H_{12}NaO_3]^+$ $[M+Na]^+$: 203.0684. Found: 203.0663.

MP: 74-76 °C.

2-(Allyloxy)-3-methylphenol (SI-37)



Synthesised according to **GP4** using 2-hydroxy-3-methylbenzaldehyde on a 4 mmol scale. The crude product was purified *via* automated silica gel chromatography (0-5% EtOAc in cyclohexane) to yield 2-(allyloxy)-3-methylphenol as a pale orange oil (199 mg, 1.21 mmol, 30%).

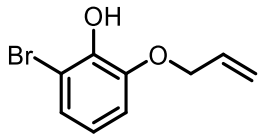
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.92 (1H, app. t, *J* = 7.8 Hz), 6.80 (1H, dd, *J* = 7.8, 1.6 Hz), 6.70 (1H, ddd, *J* = 7.8, 1.6, 0.8 Hz), 6.11 (1H, ddt, *J* = 17.1, 10.6, 5.8 Hz), 5.60 (1H, s), 5.45 (1H, app. dq, *J* = 17.1, 1.3 Hz), 5.32 (1H, app. dq, *J* = 10.6, 1.3 Hz), 4.40 (2H, app. dt, *J* = 5.8, 1.3 Hz), 2.30 (3H, s).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 149.1, 144.4, 133.5, 131.1, 124.8, 122.6, 118.7, 113.2, 74.2, 16.2.

IR (ATR-IR, neat) υ_{max}: 3511, 3423, 2980, 2925, 2867,1646, 1610, 1594, 1473, 1422, 1378, 1363, 1339, 1268, 1213, 1174, 1156, 1078, 1022, 979.

HRMS (ESI$^-$): *m/z* calcd. for $[C_{10}H_{11}O_2]^-$ [M-H]$^-$: 163.0765. Found: 163.0763.

2-(Allyloxy)-6-bromophenol (45)



Synthesised according to **GP4** using 2-bromo-6-hydroxybenzaldehyde on an 8 mmol scale. The intermediate allyl benzaldehyde was separated from unreacted starting material *via* automated column chromatography (2-5% Et_2O in cyclohexane). The crude title compound was purified *via* automated column chromatography (5-10% EtOAc in cyclohexane) to yield 2-(allyloxy)-6-bromophenol as a brown oil (283 mg, 1.24 mmol, 15%).

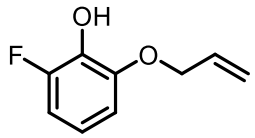
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.10 (1H, dd, *J* = 8.2, 1.4 Hz), 6.82 (1H, dd, *J* = 8.2, 1.4 Hz), 6.72 (1H, app. t, *J* = 8.2 Hz), 6.05 (1H, ddt, *J* = 17.1, 10.7, 5.5 Hz), 5.96 (1H, s), 5.40 (1H, dd, *J* = 17.1, 1.5 Hz), 5.33 (1H, dd, *J* = 10.7, 1.5 Hz), 4.62 (2H, d, *J* = 5.5 Hz).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 146.3, 143.5, 132.5, 125.2, 120.6, 118.8, 111.5, 108.5, 70.4.

IR (ATR-IR, neat) υ_{max}: 3497, 2927, 2872, 1648, 1598, 1483, 1459, 1422, 1365, 1345, 1278, 1257, 1216, 1169, 1136, 1072, 1016, 996.

HRMS (ESI$^-$): *m/z* calcd. for $[C_9H_8{}^{79}BrO_2]^-$ $[M-H]^-$: 226.9713. Found: 226.9709.

2-(Allyloxy)-6-fluorophenol (46)



Synthesised according to **GP4** using 2-fluoro-6-hydroxybenzaldehyde on a 16 mmol scale. The crude title compound was purified *via* automated silica gel chromatography (5-10% EtOAc in cyclohexane) to yield 2-(allyloxy)-6-fluorophenol as an orange oil (1.85 g, 11.1 mmol, 69%). Characterisation data were consistent with literature values: ^{1}H and $^{13}C\{^{1}H\}$. [204]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.81 – 6.63 (3H, m), 6.06 (1H, ddt, *J* = 17.3, 10.6, 5.6 Hz), 5.46, (1H, s), 5.41 (1H, dd, *J* = 17.3, 1.4 Hz), 5.33 (1H, dd, *J* = 10.6, 1.4 Hz), 4.62 (2H, d, *J* = 5.6 Hz).

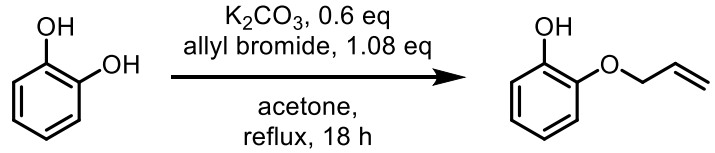
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ_C 151.0 (d, *J* = 242.2 Hz), 147.3 (d, *J* = 5.4 Hz), 134.3 (d, *J* = 13.4 Hz), 132.6, 119.0 (d, *J* = 8.7 Hz), 118.7, 109.4 (d, *J* = 18.2 Hz), 108.1 (d, *J* = 2.9 Hz), 70.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ_F -137.10 (1F, m)

IR (ATR-IR, neat) υ_{max}: 3517, 2981, 1623, 1601, 1507, 1479, 1424, 1366, 1349, 1285, 1253, 1210, 1158, 1110, 1057, 995, 936.

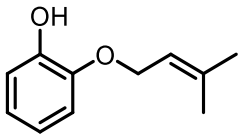
HRMS (ESI^-): *m/z* calcd. for $[C_9H_8FO_2]^-$ $[M-H]^-$: 167.0514. Found: 167.0514.

General Procedure for synthesis of 2-allyloxy phenol substrates *via* allylation of catechol (GP5)



To a suspension of the phenol substrate (1.0 eq,) and K_2CO_3 (0.6 eq.) in acetone (0.04 M) was added the allyl halide (1.08 eq.). The reaction was heated at reflux for 18 h, then cooled to rt, quenched with sat. aq. NH_4Cl (5 mL), and stirred for 5 min. The mixture was extracted with EtOAc (3 × 20 mL), the collected organic portions were washed once with brine (40 mL), dried over sodium sulfate, and concentrated *in vacuo*. The phenol product was purified *via* automated or manual silica gel column chromatography using the solvent system described for each compound entry.

2-((3-Methylbut-2-en-1-yl)oxy)phenol (SI-38)



Synthesised according to **GP5** on a 5.5 mmol scale using 1-bromo-3-methylbut-2-ene, where the reactants where heated at 50 °C rather than at reflux. The crude compound was purified *via* automated silica gel chromatography (5-15% EtOAc in cyclohexane) to yield 2-((3-methylbut-2-en-1-yl)oxy)phenol as a brown oil (726 mg, 4.06 mmol, 74%). Characterisation data were consistent with literature values: ^{1}H, ^{13}C{^{1}H} and IR. [205]

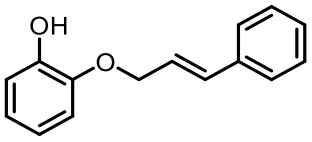
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.96 – 6.78 (4H, m), 5.68 (1H, s), 5.51 – 5.47 (1H, m), 4.57 (2H, d, *J* = 6.8 Hz), 1.80 (3H, s), 1.74 (3H, s).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 146.0, 145.9, 138.8, 121.5, 120.0, 119.4, 114.5, 112.1, 65.8, 25.8, 18.2.

IR (ATR-IR, neat) υ_{max}: 3524, 3052, 2972, 2914, 1673, 1611, 1595, 1498, 1466, 1383, 1358, 1255, 1217, 1196, 1105, 1034, 993, 914.

HRMS (ESI$^-$): *m/z* calcd. for $[C_{11}H_{13}O_2]^-$ [M-H]$^-$: 177.0921. Found: 177.0921.

2-(Cinnamyloxy)phenol (SI-39)



Synthesised according to **GP5** on a 5.0 mmol scale using catechol and cinnamyl bromide. The crude material was purified *via* automated silica gel column chromatography (0 to 5% EtOAc in cyclohexane) to yield the title compound as a colourless solid (144 mg, 0.63 mmol, 12%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.42 (2H, d, *J* = 7.8 Hz), 7.35 (2H, app. t, *J* = 7.4 Hz), 7.29 (1H, d, *J* = 7.1 Hz), 6.99 – 6.80 (4H, m), 6.73 (1H, d, *J* = 15.9 Hz), 6.43 (1H, dt, *J* = 15.9, 6.0 Hz), 5.69 (1H, s), 4.77 (2H, d, *J* = 6.0 Hz).

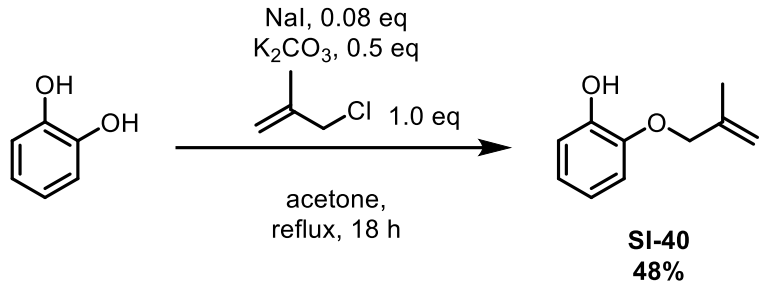
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 146.1, 145.8, 136.2, 134.0, 128.8, 128.3, 126.8, 123.9, 121.9, 120.3, 114.9, 112.4, 69.9.

IR (ATR-IR, neat) υ_{max}: 3525, 3055, 3027, 1596, 1497, 1464, 1449, 1384, 1356, 1301, 1257, 1216, 1156, 1107, 1066, 1035, 1001, 966, 915.

HRMS (ESI$^-$): *m/z* calcd. for $[C_{15}H_{13}O_2]^-$ [M-H]$^-$: 225.0921. Found: 225.0916.

MP: 53-54 °C.

2-((2-Methylallyl)oxy)phenol (SI-40)



To a suspension of catechol (225 mg, 1.50 mmol), K_2CO_3 (103 mg, 0.75 mmol) and sodium iodide (18 mg, 0.12 mmol) in acetone (22 mL) was added 3-chloro-2-methylprop-1-ene (147 µL, 1.5 mmol). The reaction was heated at reflux for 18 h, then cooled to rt, quenched with sat. aq. NH_4Cl (5 mL), and stirred for 5 min. The mixture was extracted with EtOAc (3 × 10 mL), the collected organic portions were washed once with brine (10 mL), dried over sodium sulfate, and concentrated *in vacuo*. The allylated product was purified *via* automated silica gel column chromatography (0-5% EtOAc in cyclohexane) to provide 2-((2-methylallyl)oxy)phenol as a colourless oil (118 mg, 0.72 mmol, 48%). Characterisation data were consistent with literature values: ^{1}H, ^{13}C{^{1}H} and IR. [206]

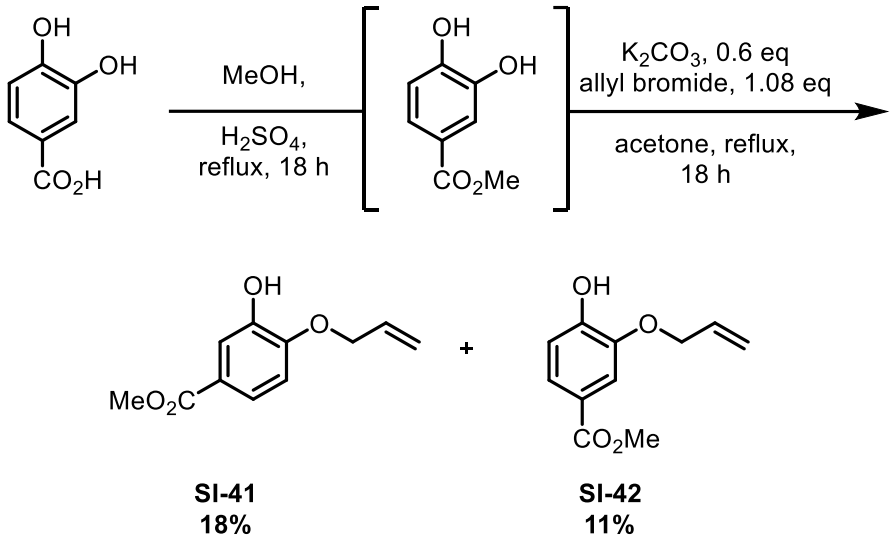
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.98 – 6.77 (4H, m), 5.65 (1H, s), 5.09 (1H, s), 5.02 (1H, s), 4.51 (2H, s), 1.84 (3H, s)

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 145.8, 145.6, 140.4, 121.7, 120.7, 114.6, 113.3, 112.1, 72.6, 19.4.

IR (ATR-IR, neat) υ_{max}: 3529, 2980, 2916, 1655, 1596, 1498, 1452, 1372, 1303, 1255, 1215, 1192, 1106, 1034, 1008, 966.

HRMS (ESI$^-$): *m/z* calcd. for $[C_{10}H_{11}O_2]^-$ [M-H]$^-$: 163.0765. Found: 163.0759.

Methyl 4-(allyloxy)-3-hydroxybenzoate (SI-41) and methyl 3-(allyloxy)-4-hydroxybenzoate (SI-42)



A solution of 3,4-dihydroxybenzoic acid (1.82 g, 11.8 mmol) and conc. H_2SO_4 (200 µL) in methanol (12 mL) was heated at reflux for 18 h. The reaction mixture was cooled to rt and concentrated under reduced pressure. The crude residue was diluted with EtOAc (15 mL) and washed with NaOH (2 × 10 mL) and brine (1 × 10 mL). The organic portion was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure.

The crude ester was dissolved in acetone (100 mL), then K_2CO_3 (967 mg, 7.00 mmol) and allyl bromide (1.09 mL, 12.6 mmol) were added. The reaction was heated at reflux for 18 h, then cooled to rt, quenched with sat. aq. NH_4Cl (50 mL), and stirred for 5 min. The mixture was extracted with EtOAc (3 × 30 mL), the collected organic portions were washed once with brine (40 mL), dried over sodium sulfate, and concentrated *in vacuo*. The phenol product was purified *via* automated silica gel column chromatography (0-5% EtOAc in cyclohexane) to provide methyl 4-(allyloxy)-3-hydroxybenzoate (**SI-41**) as a colourless solid (486 mg, 2.10 mmol, 18%), and methyl 3-(allyloxy)-4-hydroxybenzoate (**SI-42**) as a colourless solid (270 mg, 1.30 mmol, 11%). Characterisation data were consistent with literature values: ^1H, $^{13}C\{^1H\}$ and MP.[207]

Methyl 4-(allyloxy)-3-hydroxybenzoate (SI-41)

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.63 – 7.48 (2H, m),6.87 (1H, d, *J* = 8.2 Hz), 6.06 (1H, ddt, *J* = 17.3, 10.7, 5.4 Hz), 5.68 (1H, s), 5.42 (1H, d, *J* = 17.3 Hz), 5.35 (1H, d, *J* = 10.7 Hz), 4.67 (2H, d, *J* = 5.4 Hz), 3.88 (3H, s).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 166.9, 149.4, 145.5, 132.2, 123.7, 122.7, 119.1, 115.9, 111.2, 69.9, 52.1.

IR (ATR-IR, neat) υ_{max}: 3400, 3079, 2953, 1693, 1651m 1611, 1588, 1507, 1455, 1437, 1258, 1097, 988, 934.

HRMS (ESI$^+$): *m*/*z* calcd. for $[C_{11}H_{12}NaO_4]^+$ $[M+Na]^+$:231.0628. Found: 231.0641.

MP 58-60 °C.

Methyl 3-(allyloxy)-4-hydroxybenzoate (SI-42)

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.64 (1H, d, *J* = 8.3 Hz), 7.55 (1H, s), 6.95 (1H, d, *J* = 8.3 Hz), 6.13 – 6.01 (2H, m), 5.43 (1H, d, *J* = 17.2 Hz), 5.35 (1H, d, *J* = 10.3 Hz), 4.67 (2H, d, *J* = 5.6 Hz), 3.88 (3H, s).

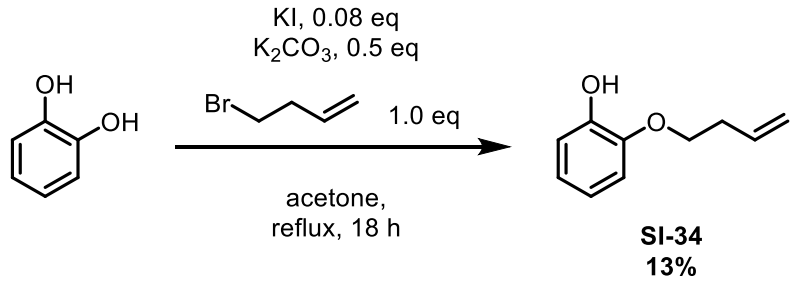
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 166.9, 150.3, 145.2, 132.4, 124.2, 122.4, 119.0, 114.4, 113.2, 70.1, 52.1.

IR (ATR-IR, neat) υ_{max}: 3527, 3019, 2981, 1706, 1599, 1510, 1480, 1440, 1385, 1282, 1214, 1102, 1063, 1018, 995, 935.

HRMS (ESI$^-$): *m*/*z* calcd. for $[C_{11}H_{11}O_4]^-$ $[M-H]^-$: 207.0663. Found: 207.0662.

MP: 38-40 °C.

2-(But-3-en-1-yloxy)phenol (SI-43)



To a suspension of catechol (1.12 g, 10.1 mmol), K_2CO_3 (688 mg, 4.98 mmol) and potassium iodide (119 mg, 0.8 mmol) in acetone (250 mL) was added 4-bromo-1-butene (1.02 mL, 10 mmol). The reaction was heated at reflux for 18 h, then cooled to rt, quenched with sat. aq. NH_4Cl (50 mL), and stirred for 5 min. The mixture was extracted with EtOAc (3 × 20 mL), the collected organic portions were washed once with brine (40 mL), dried over sodium sulfate, and concentrated *in vacuo* at 30 °C. The phenol product was purified *via* automated silica gel column chromatography (2-5% Et_2O in pentane) to provide the title compound (221 mg, 1.35 mmol, 13%; isolated as a 90% pure sample in Et_2O). Characterisation data were consistent with literature values: ^1H, $^{13}C\{^1H\}$ and IR.[208]

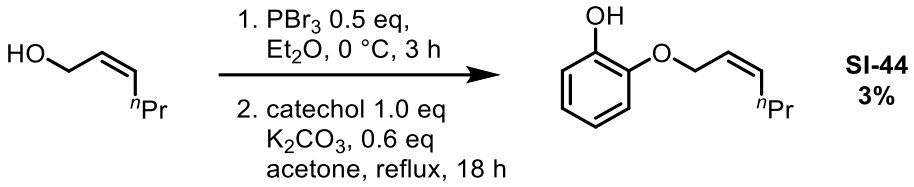
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.95 – 6.80 (4H, m), 5.89 (1H, ddt, *J* = 17.0, 10.2, 6.5 Hz), 5.65 (1H, s), 5.19 (1H, app. dq, *J* = 17.0, 1.6 Hz), 5.15 (1H, app. dq, *J* = 10.2, 1.6 Hz), 4.11 (2H, t, *J* = 6.5 Hz), 2.57 (2H, app. qt, *J* = 6.5, 1.6 Hz).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 146.1, 145.9, 134.3, 121.8, 120.2, 117.7, 114.7, 112.2, 68.2, 33.8

IR (ATR-IR, neat) υ_{max}: 3525, 3075, 2979, 2927, 1641, 1611, 1596, 1499, 1469, 1431, 1389, 1358, 1301, 1257, 1219, 1197, 1154, 1107, 1034, 990, 916.

HRMS (ESI$^-$): *m/z* calcd. for $[C_{10}H_{11}O_2]^-$ $[M-H]^-$: 163.0759. Found: 163.0757.

(*Z*)-2-Hex-2-en-1-yloxy)phenolphenol (SI-44)



A flame dried microwave vial equipped with a stir bar was evacuated and back-filled three times with anhydrous dinitrogen before (*Z*)-hex-2-en-1-ol (1.42 mL, 12.0 mmol) was added. This was dissolved in anhydrous Et_2O (8.8 mL) and cooled to 0 °C. Then, PBr_3 (560 µL, 5.97 mmol) was added portion-wise over 6 minutes at 0.1 mL intervals, and the resulting reaction mixture was left to stir at 0 °C for 3 h under an atmosphere of nitrogen. The reaction mixture was quenched with water (5 mL), and the organic portion was washed subsequently with sat. aq. Na_2CO_3 and brine. The organics were then dried over $MgSO_4$ and concentrated *in vacuo*.

The resulting residue was dissolved in acetone (300 mL), to which catechol (1.33 g, 12.1 mmol), and K_2CO_3 (1.00 g, 7.25 mmol) were added. The suspension was heated to reflux for 18 h, after which time the reaction mixture was cooled to rt and quenched with sat. aq. NH_4Cl (20 mL). The mixture was extracted with EtOAc (3 × 20 mL), the collected organic portions were washed once with brine (40 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Crude **SI-44** was purified *via* automated silica gel column chromatography (0 to 5% EtOAc in cyclohexane) to yield **SI-44** as a colourless oil (74 mg, 0.38 mmol, 3%).

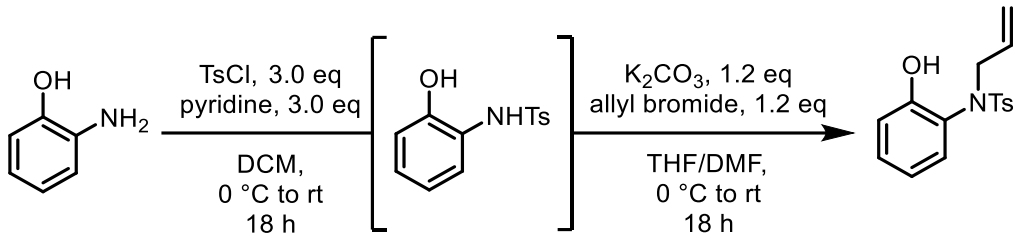
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.94 (1H, dd, *J* = 8.1, 1.9 Hz), 6.91 – 6.75 (3H, m), 5.71 – 5.68 (2H, m), 5.66 (1H, s), 4.64 (2H, d, *J* = 4.6 Hz), 2.11 (2H, app. q, *J* = 7.2 Hz), 1.44 (2H, app. sext, *J* = 7.2 Hz), 0.93 (3H, t, *J* = 7.2 Hz).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 146.1, 145.8, 135.1, 124.4, 121.7, 120.1, 114.7, 112.2, 65.0, 29.9, 22.7, 13.8.

IR (ATR-IR, neat) υ_{max}: 3534, 2959, 2930, 2871, 1611, 1597, 1499, 1465, 1374, 1302, 1258, 1219, 1196, 1107, 1035, 1005.

HRMS (ESI$^-$): *m*/*z* calcd. for $[C_{12}H_{15}O_2]^-$ [M-H]$^-$: 191.1072. Found: 191.1076.

N-Allyl-N-(2-hydroxyphenyl)-4-methylbenzenesulfonamide (70)



A solution of 2-aminophenol (1.58 g, 14.5 mmol) in DCM (70 mL) was cooled to 0 °C. TsCl (872 mg, 43.0 mmol) and pyridine (3.5 mL, 43.3 mmol) were added, and the reaction mixture was allowed to warm to rt on stirring over 18 h. The reaction was quenched with HCl (1 M, 20 mL), and the organics were subsequently washed with brine (1 × 20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The intermediate N-tosylated aminophenol was then purified by recrystallisation (hot cyclohexane/EtOAc) to provide a black crystalline solid (460 mg, 1.75 mmol, 12%); the product was confirmed using ^{1}H NMR spectroscopy and was used in the subsequent step without further characterization.

The crystals were dissolved in a 5:1 mixture of THF: DMF (10.3 mL), to which K_2CO_3 (342 mg, 2.48 mmol) was added. The suspension was cooled to 0 °C, and allyl bromide (214 µL, 2.48 mmol) was added in 10 equal portions at 2-minute intervals while stirring. The reaction mixture was allowed to warm to rt over 18 h. After this time, the reaction mixture was filtered, and the residue was washed with EtOAc (10 mL). The filtrate was concentrated to dryness and redissolved in EtOAc (10 mL). The organics were washed with brine (3 × 20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was initially purified *via* automated column chromatography (2.5% EtOAc in cyclohexane), and then *via* recrystallisation (hot cyclohexane) to provide the title compound as colourless crystals (244 mg, 0.81 mmol, 6%). Characterisation data were consistent with literature values: ^{1}H, ^{13}C{^{1}H} and MP. [209]

***N*-(2-Hydroxyphenyl)-4-methylbenzenesulfonamide**

^{1}H NMR (400 MHz, DMSO): δ_H 9.53 (1H, s), 9.11 (1H, s), 7.63 (2H, d, *J* = 8.3 Hz), 7.30 (2H, d, *J* = 8.3 Hz), 7.13 (1H, dd, *J* = 7.9, 1.6 Hz), 6.92 (1H, app. td, *J* = 8.1, 1.6 Hz), 6.72 (1H, dd, *J* = 8.1, 1.4 Hz), 6.69 (1H, app. td, *J* = 7.9, 1.4 Hz), 2.34 (3H, s).

***N*-Allyl-*N*-(2-hydroxyphenyl)-4-methylbenzenesulfonamide (70)**

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.54 (2H, d, *J* = 8.2 Hz), 7.28 (2H, d, *J* = 8.2 Hz), 7.18 (1H, app. td, *J* = 8.2, 1.6 Hz), 7.04 (1H, dd, *J* = 8.2, 1.5 Hz), 6.69 (1H, td, *J* = 7.9, 1.5 Hz), 6.56 (1H, s), 6.36 (1H, dd, *J* = 7.9, 1.6 Hz), 5.72 (1H, ddt, *J* = 16.7, 9.9, 6.5 Hz), 5.09 – 5.05 (2H, m), 4.16 (2H, br), 2.45 (3H, s).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 154.8, 144.2, 133.7, 131.8, 129.9, 129.5, 128.1, 127.5, 125.6, 120.3, 119.8, 117.4, 54.6, 21.6.

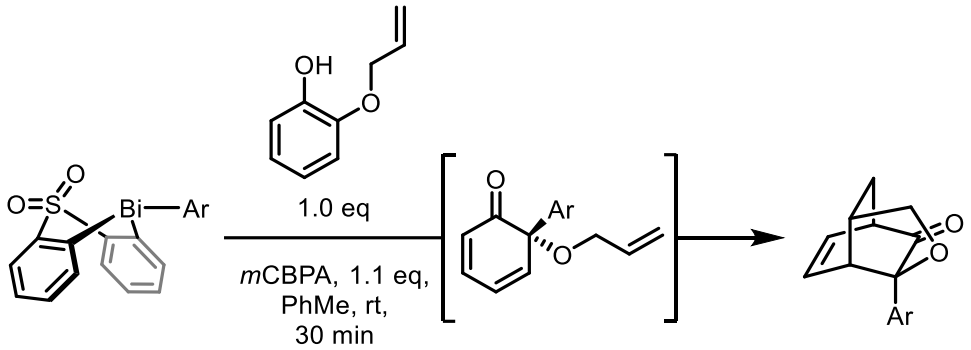
IR (ATR-IR, neat) υ_{max}: 3435, 2926, 2856, 1645, 1594, 1492, 1454, 1419, 1337, 1289, 1253, 1218, 1183, 1158, 1109, 1089, 1054, 1036, 1018, 995, 924.

HRMS (ESI$^-$): *m/z* calcd. for $[C_{16}H_{16}NO_3S]^-$ $[M-H]^-$: 302.0851. Found: 302.0858.

MP: 115-117 °C.

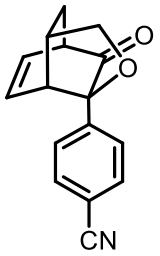
Synthesis and Characterisation of Bicyclo[2.2.2]octenones

General Procedure for Tandem Arylative Dearomatisation-IMDA Reaction (GP6)



The aryl bismacycle (0.3 mmol) and phenol substrate (0.3 mmol) were suspended in PhMe or $CHCl_3$ (15mL) in the presence of internal standard (diphenyl methane (0.05 mmol) *or* 4,4'-bis(trifluoromethyl)-1,1'-biphenyl (0.05 mmol)) at rt. *m*CPBA (81 mg, 0.33 mmol, 70% purity) was added in 10 equal portions at 30 second intervals while stirring, and the reaction mixture was left for 30 min. The resultant orange solution was quenched with sat. aq. $Na_2S_2O_5$ (0.01 mL), left to stir for 5 min, then passed through a plug of basic alumina (*ca* 12 mL). The crude bicyclo[2.2.2]octenone was eluted with EtOAc (30 mL) and further purified by automated or manual silica gel column chromatography using the eluent system described for each compound entry.

4-(7-Oxo-3,3a,6,7-tetrahydro-3,6-methanobenzofuran-7a(2*H*)-yl)benzonitrile (44a)



Synthesised according to **GP6** on a 0.45 mmol scale using 4-(5,5-dioxido-10*H*-dibenzo[*b*,*e*][1,4]thiabismin-10-yl)benzonitrile and 2-(allyloxy)phenol. The crude compound was purified by manual silica gel column chromatography (25% EtOAc in cyclohexane) to yield the title compound as an off white solid (55 mg, 0.22 mmol, 48%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.60 (2H, d, *J* = 8.5 Hz), 7.48 (2H, d, *J* = 8.5 Hz), 6.47 (1H, ddd, *J* = 8.0, 6.7, 1.8 Hz), 6.35 (1H, ddd, *J* = 8.0, 6.4, 1.4 Hz), 4.18 (1H, dd, *J* = 8.0, 3.4 Hz), 4.01 (1H, d, *J* = 8.0 Hz), 3.42 – 3.29 (1H, m), 3.21 (1H, ddd, *J* = 6.4, 4.2, 2.0 Hz), 2.66 – 2.52 (1H, m), 1.98 (1H, ddd, *J* = 13.2, 3.4, 2.0 Hz), 1.91 (1H, ddd, *J* = 13.2, 9.7, 2.0 Hz).

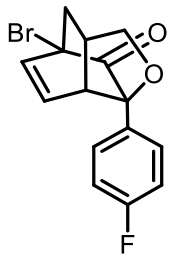
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 203.7, 144.3, 132.0, 131.5, 130.1, 127.0, 118.9, 111.8, 82.1, 76.2, 50.4, 45.8, 36.0, 32.0.

IR (ATR-IR, neat) υ_{max}: 3091, 2927, 1735, 1503, 1109, 1074, 1043, 1008, 940.

HRMS (ESI$^+$): *m*/*z* calcd. for $[C_{16}H_{13}NNaO_2]^+$ $[M+Na]^+$: 274.0838. Found: 274.0843.

MP: 170-172 °C.

6-Bromo-7a-(4-fluorophenyl)-2,3,3a,7a-tetrahydro-3,6-methanobenzofuran-7(6*H*)-one (47)



Synthesised according to **GP6** on a 0.4 scale using 10-(4-fluorophenyl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide and 2-(allyloxy)-6-bromophenol. The crude compound was purified by manual silica gel column chromatography (5-10% EtOAc in cyclohexane) to yield the title compound as an off white solid (78 mg, 0.24 mmol, 60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.33 (2H, dd, *J* = 8.7, 5.3 Hz), 7.00 (2H, app. t, *J* = 8.7 Hz), 6.48 (1H, dd, *J* = 8.5, 1.7 Hz), 6.28 (1H, dd, *J* = 8.5, 6.4 Hz), 4.17 (1H, dd, *J* = 8.2, 3.5 Hz), 4.04 (1H, d, *J* = 8.2 Hz), 3.27 (1H, ddd, *J* = 6.4, 4.2, 1.7 Hz), 2.76 – 2.65 (1H, m), 2.48 (1H, dd, *J* = 12.8, 10.0 Hz), 2.38 (1H, d, *J* = 12.8 Hz).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 195.9, 162.7 (d, *J* = 246.8 Hz), 136.2, 133.7 (d, *J* = 3.2 Hz), 129.8, 128.0 (d, *J* = 8.2 Hz), 115.1 (d, *J* = 21.7 Hz), 81.5, 76.2, 63.7, 49.6, 43.9, 38.7.

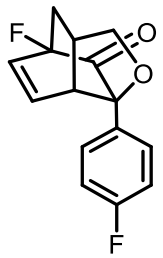
^{19}F NMR (377 MHz, $CDCl_3$): δ_F -113.96 (1F, tt, *J* = 8.7, 5.3 Hz).

IR (ATR-IR, neat) υ_{max}: 2959, 2882, 1744, 1600, 1508, 1445, 1407, 1354, 1295, 1260, 1226, 1186, 1159, 1103, 1076, 1002, 982, 950.

HRMS (ESI$^+$): *m*/*z* calcd. for $[C_{15}H_{12}{}^{79}BrFNaO_2]$ $[M+Na]^+$: 344.9897. Found: 344.9904.

MP: 92-94 °C.

6-Fluoro-7a-(4-fluorophenyl)-2,3,3a,7a-tetrahydro-3,6-methanobenzofuran-7(6*H*)-one (48)



Synthesised according to **GP6** on a 0.4 scale using 10-(4-fluorophenyl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide and 2-(allyloxy)-6-fluorophenol. The crude compound was purified by manual silica gel column chromatography (5-10% EtOAc in cyclohexane) to yield the title compound as a colourless oil (42 mg, 0.16 mmol, 40%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.32 (2H, dd, *J* = 8.8, 5.3 Hz), 7.01 (2H, app. t, *J* = 8.8 Hz), 6.46 (1H, dddd, *J* = 11.6, 8.8, 1.8, 1.2 Hz), 6.30 (1H, ddd, *J* = 11.6, 6.3, 4.6 Hz), 4.23 (1H, dd, *J* = 8.2, 3.6, Hz), 4.12 (1H, d, *J* = 8.2 Hz), 3.25 (1H, ddd, *J* = 6.3, 4.3, 1.8 Hz), 2.71 – 2.67 (1H, m), 2.23 (1H, ddd, *J* = 12.3, 10.1, 2.2 Hz), 2.15 (1H, app. ddt, *J* = 12.3, 6.9, 1.2 Hz).

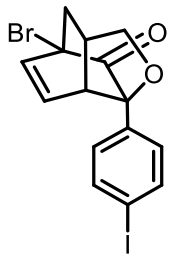
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 199.0 (d, *J* = 14.0 Hz), 162.7 (d, *J* = 246.9 Hz), 133.1 (dd, *J* = 3.0, 2.1 Hz), 131.7 (d, *J* = 26.5 Hz), 128.4 (d, *J* = 8.9 Hz), 128.0 (d, *J* = 8.3 Hz), 115.2 (d, *J* = 21.6 Hz), 95.7 (d, *J* = 206.8 Hz), 81.4 (d, *J* = 2.9 Hz), 76.5, 49.7 (d, *J* = 2.6 Hz), 36.7 (d, *J* = 26.7 Hz), 36.6 (d, *J* = 2.1 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ_F -113.94 (1F, tt, *J* = 8.8, 5.3 Hz), -184.28 – 184.34 (1F, m)

IR (ATR-IR, neat) υ_{max}: 3517, 2981, 1623, 1601, 1507, 1479, 1424, 1366, 1349, 1285, 1253, 1210, 1158, 1110, 1057, 995, 936

HRMS (ESI^{+}): *m*/*z* calcd. for $[C_{15}H_{12}F_2NaO_2]^+$ $[M+Na]^+$: 285.0698. Found: 285.0713.

6-Bromo-7a-(4-iodophenyl)-2,3,3a,7a-tetrahydro-3,6-methanobenzofuran-7(6*H*)-one (49)



Synthesised according to **GP6** on a 0.23 scale using 10-(4-iodophenyl)-10*H*-dibenzo[*b,e*][1,4]thiabismine 5,5-dioxide and 2-(allyloxy)-6-bromophenol. The crude compound was purified by automated silica gel column chromatography (5-10% EtOAc in cyclohexane) to yield the title compound as an off white solid (80 mg, 0.18 mmol, 81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.67 (2H, d, *J* = 8.1 Hz), 7.11 (2H, d, *J* = 8.1 Hz), 6.51 (1H, d, *J* = 8.4 Hz), 6.29 (1H, dd, *J* = 8.4, 6.3 Hz), 4.18 (1H, dd, *J* = 8.2, 3.3 Hz), 4.07 (1H, d, *J* = 8.2 Hz), 3.26 (1H, ddd, *J* = 6.3, 3.3, 1.8 Hz), 2.72 (1H, app. dt, *J* = 10.0, 3.3 Hz), 2.51 (1H, dd, *J* = 12.9, 10.0 Hz), 2.41 (1H, d, *J* = 12.9 Hz).

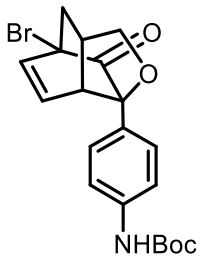
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 195.6, 137.8, 137.3, 136.3, 129.7, 128.1, 94.2, 81.7, 76.3, 63.6, 49.6, 43.9, 38.8.

IR (ATR-IR, neat) υ_{max}: 2942, 2878, 1747, 1600, 1586, 1509, 1484, 1444, 1390, 1353, 1324, 1291, 1259, 1217, 1185, 1153, 1105, 1075, 1063, 1025, 998, 950, 826, 805, 777.

HRMS (ESI$^+$): *m/z* calcd. for $[C_{15}H_{12}{}^{79}BrINaO_2]^+$ $[M+Na]^+$: 452.8963. Found: 452.8966.

MP: 164-166 °C.

tert-Butyl (4-(6-bromo-7-oxo-3,3a,6,7-tetrahydro-3,6-methanobenzofuran-7a(2*H*)-yl)phenyl)carbamate (51)



tert-Butyl (4-(5,5-dioxido-10*H*-dibenzo[*b,e*][1,4]thiabismin-10-yl)phenyl)carbamate (185 mg, 0.30 mmol) and 2-(allyloxy)-6-bromophenol (68.7 mg, 0.30 mmol) were suspended in $CHCl_3$ (15mL) in the presence of internal standard 4,4'-bis(trifluoromethyl)-1,1'-biphenyl (5.80 mg, 0.02 mmol)) at rt. *m*CPBA (81 mg, 0.33 mmol, 70% purity) was added in 10 equal portions at 30 second intervals while stirring, and the reaction mixture was left for 30 min. The resultant orange solution was quenched with sat. aq. $Na_2S_2O_5$ (0.01 mL), left to stir for 5 min, then concentrated under reduced pressure. The crude product was purified by automated silica gel column chromatography (20% EtOAc in cyclohexane). The fractions containing product were collected and diluted in EtOAc (10 mL), washed with sat. aq. $NaHCO_3$ (3 × 10 mL), and the organic portion was dried over Na_2SO_4. Concentration of the dried organics yielded the title compound as a brown solid (85 mg, 0.202 mmol, 67%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.32-7.24 (4H, m), 6.49 (1H, s), 6.47 (1H, d, *J* = 8.0 Hz), 6.25 (1H, app. t, *J* = 8.0 Hz), 4.16 (1H, dd, *J* = 8.2, 3.3 Hz), 4.03 (1H, d, *J* = 8.2 Hz), 3.25 (1H, app. t, *J* = 5.4 Hz), 2.73 – 2.60 (1H, m), 2.47 (1H, dd, *J* = 12.8, 9.8 Hz), 2.37 (1H, d, *J* = 12.8 Hz), 1.51 (9H, s).

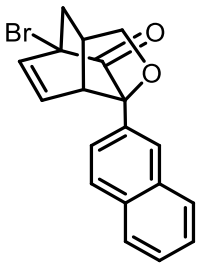
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 196.1, 152.8, 138.4, 136.0, 132.4, 129.9, 126.9, 118.3, 81.7, 80.7, 76.2, 64.0, 49.7, 44.0, 38.6, 28.4.

IR (ATR-IR, neat) υ_{max}: 3382, 3067, 2926, 2878, 1748, 1711, 1588, 1523, 1485, 1444, 1406, 1391, 1355, 1317, 1291, 1260, 1227, 1184, 1156, 1106, 1075, 1063, 1026, 999, 951

HRMS (ESI$^+$): *m/z* calcd. for $[C_{20}H_{22}{}^{79}BrNNaO_4]^+$ $[M+Na]^+$: 442.0630. Found: 442.0630.

MP: decomp at 210°C.

6-Bromo-7a-(naphthalen-2-yl)-2,3,3a,7a-tetrahydro-3,6-methanobenzofuran-7(6*H*)-one (52)



Synthesised according to **GP6** on a 0.3 mmol scale using 10-(naphthalen-2-yl)-10*H*-dibenzo[*b,e*][1,4]thiabismine 5,5-dioxide and 2-(allyloxy)-6-bromophenol. The crude compound was purified by automated silica gel column chromatography (5-10% EtOAc in cyclohexane) to yield the title compound as an off white solid (78 mg, 0.21 mmol, 74%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.86 – 7.77 (4H, m), 7.51 – 7.41 (3H, m), 6.55 (1H, d, *J* = 8.4 Hz), 6.31 (1H, dd, *J* = 8.4, 6.5 Hz), 4.26 (1H, dd, *J* = 8.1, 3.4 Hz), 4.12 (1H, d, *J* = 8.1 Hz), 3.38 - 3.35 (1H, m), 2.84 – 2.65 (1H, m), 2.53 (1H, dd, *J* = 13.0, 9.8 Hz), 2.44 (1H, d, *J* = 13.0 Hz).

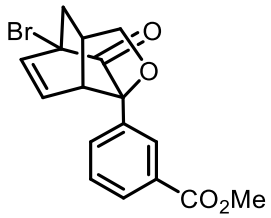
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 195.9, 136.0, 135.3, 133.1, 132.8, 129.9, 128.2, 127.9, 127.5, 126.2, 126.2, 125.3, 123.6, 82.0, 76.2, 63.9, 49.9, 43.9, 38.7.

IR (ATR-IR, neat) υ_{max}: 3056, 2938, 2881, 1744, 1600, 1507, 1484, 1444, 1354, 1288, 1272, 1238, 1216, 1196, 1181, 1152, 1129, 1104, 1076, 1025, 999, 981, 957, 940.

HRMS (ESI^{+}): *m/z* calcd. for $[C_{19}H_{15}{}^{79}BrNaO_2]^+$ $[M+Na]^+$: 377.0148. Found: 377.0145.

MP: 147-149 °C.

Methyl 3-(6-bromo-7-oxo-3,3a,6,7-tetrahydro-3,6-methanobenzofuran-7a(2*H*)-yl)benzoate (53)



Synthesised according to **GP6** on a 0.3 mmol scale using methyl 3-(5,5-dioxido-10*H*-dibenzo[*b,e*][1,4]thiabismin-10-yl)benzoate and 2-(allyloxy)-6-bromophenol. The crude compound was purified by automated silica gel column chromatography (5-10% EtOAc in cyclohexane) to yield the title compound as an off white solid (73 mg, 0.20 mmol, 68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.03 (1H, s), 7.99 (1H, d, *J* = 7.8 Hz), 7.55 (1H, d, *J* = 7.8 Hz), 7.40 (1H, app. t, *J* = 7.8 Hz), 6.52 (1H, d, *J* = 8.3 Hz), 6.31 (1H, dd, *J* = 8.3, 6.7 Hz), 4.20 (1H, dd, *J* = 8.2, 3.4 Hz), 4.07 (1H, d, *J* = 8.2 Hz), 3.91 (3H, s), 3.30 – 3.27 (1H, m), 2.73 – 2.68 (1H, m), 2.50 (1H, dd, *J* = 13.0, 9.9 Hz), 2.40 (1H, d, *J* = 13.0 Hz).

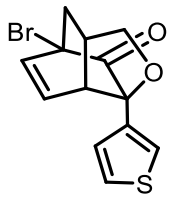
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C δ 195.5, 166.9, 138.4, 136.3, 130.9, 130.2, 129.7, 129.5, 128.4, 127.1, 81.7, 76.3, 63.6, 52.3, 49.5, 43.9, 38.7.

IR (ATR-IR, neat) υ_{max}: 2950, 2927, 2881, 1747, 1717, 1441, 1302, 1278, 1246, 1222, 1188, 1113.

HRMS (ESI$^+$): *m/z* calcd. for $[C_{17}H_{15}{}^{79}BrNaO_4]^+$ $[M+Na]^+$: 385.0046. Found: 385.0040.

MP: 147-148 °C.

6-Bromo-7a-(thiophen-3-yl)-2,3,3a,7a-tetrahydro-3,6-methanobenzofuran-7(6*H*)-one (56)



Synthesised according to **GP6** on a 0.43 mmol scale using 10-(thiophen-3-yl)-10*H*-dibenzo[*b,e*][1,4]thiabismine 5,5-dioxide and 2-(allyloxy)-6-bromophenol. The crude compound was purified by automated silica gel column chromatography (5-10% EtOAc in cyclohexane) to yield the title compound as an off white solid (77 mg, 0.25 mmol, 57%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.31 (1H, dd, *J* = 3.0, 1.4 Hz), 7.28 (1H, dd, *J* = 5.0, 3.0 Hz), 7.05 (1H, dd, *J* = 5.0, 1.4 Hz), 6.47 (1H, dd, *J* = 8.5, 1.7, Hz), 6.27 (1H, dd, *J* = 8.5, 6.3 Hz), 4.18 (1H, dd, *J* = 8.2, 3.7 Hz), 4.01 (1H, d, *J* = 8.2 Hz), 3.37 (1H, ddd, *J* = 6.3, 4.3, 1.7 Hz), 2.72 – 2.67 (1H, m), 2.47 (1H, dd, *J* = 12.9, 10.0 Hz), 2.35 (1H, d, *J* = 12.9 Hz).

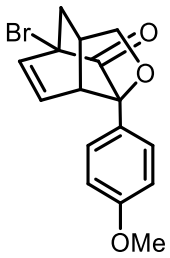
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 195.8, 138.1, 136.3, 129.5, 125.8, 125.8, 123.0, 80.0, 76.1, 63.5, 48.8, 43.8, 38.3.

IR (ATR-IR, neat) υ_{max}: 2980, 2884, 1746, 1719, 1249, 1076.

HRMS (ESI$^+$): *m/z* calcd. for $[C_{13}H_{11}{}^{79}BrNaO_2S]$ $[M+Na]^+$: 332.9561. Found: 332.9552.

MP: 128-130 °C.

6-Bromo-7a-(4-methoxyphenyl)-2,3,3a,7a-tetrahydro-3,6-methanobenzofuran-7(6*H*)-one (50)



Synthesised according to **GP6** on a 0.3 mmol scale using 10-(4-methoxyphenyl)-10*H*-dibenzo[*b,e*][1,4]thiabismine 5,5-dioxide and 2-(allyloxy)-6-bromophenol. The crude compound was purified by automated silica gel column chromatography (0-20% EtOAc in cyclohexane) to yield the title compound as a brown solid (54 mg, 0.15 mmol, 51%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.31 (2H, d, *J* = 8.8 Hz), 6.88 (2H, d, *J* = 8.8 Hz), 6.49 (1H, ddd, *J* = 8.4, 1.7, 0.9 Hz), 6.30 (1H, dd, *J* = 8.4, 6.4 Hz), 4.19 (1H, dd, *J* = 8.1, 3.5 Hz), 4.06 (1H, d, *J* = 8.1 Hz), 3.82 (3H, s), 3.31 (1H, ddd, *J* = 6.4, 4.2, 1.7 Hz), 2.74 – 2.66 (1H, m), 2.50 (1H, dd, *J* = 13.0, 9.9 Hz), 2.40 (1H, d, *J* = 13.0 Hz).

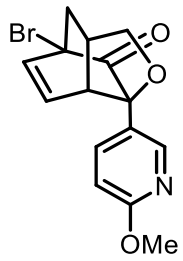
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 196.3, 159.6, 136.0, 130.0, 129.9, 127.5, 113.6, 81.5, 76.1, 64.0, 55.4, 49.6, 44.1, 38.7.

IR (ATR-IR, neat) υ_{max}: 2956, 2935, 2881, 2837, 1745, 1610, 1581, 1512, 1462, 1443, 1415, 1354, 1301, 1248, 1178, 1153, 1114, 1076, 1025, 1000, 951.

HRMS (ESI$^+$): *m/z* calcd. for $[C_{16}H_{16}{}^{79}BrO_3]^+$ [M+H]$^+$: 335.0277. Found: 335.0295.

MP: 112-114 °C.

6-Bromo-7a-(6-methoxypyridin-3-yl)-2,3,3a,7a-tetrahydro-3,6-methanobenzofuran-7(6*H*)-one (57)



10-(6-Methoxypyridin-3-yl)-10*H*-dibenzo[*b,e*][1,4]thiabismine 5,5-dioxide (119 mg, 0.223 mmol) and 2-(allyloxy)-6-bromophenol (51.4 mg, 0.30 mmol) were suspended in $CHCl_3$ (12mL) in the presence of internal standard 4,4'-bis(trifluoromethyl)-1,1'-biphenyl (5.00 mg, 0.017 mmol)) at rt. *m*CPBA (60 mg, 0.25 mmol, 70% purity) was added in 10 equal portions at 30 second intervals while stirring, and the reaction mixture was left for 30 min. The resulting orange solution was quenched with sat. aq. $Na_2S_2O_5$ (0.01 mL), left to stir for 5 min, then concentrated under reduced pressure. The residue was dissolved in DCM (15 mL) and washed with sat. aq. $NaHCO_3$ (3 × 10 mL), and the organic portion was dried over Na_2SO_4. The dried organic portion was concentrated under reduced pressure and purified by automated silica gel column chromatography (10-20% EtOAc in cyclohexane) to provide **57** as a brown oil (50 mg, 0.148 mmol, 68%).

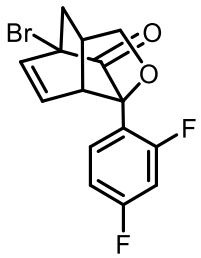
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.12 (1H, d, *J* = 2.5 Hz), 7.61 (1H, dd, *J* = 8.7, 2.5 Hz), 6.71 (1H, d, *J* = 8.7 Hz), 6.46 (1H, d, *J* = 8.5 Hz), 6.29 (1H, dd, *J* = 8.5, 6.5 Hz), 4.14 (1H, dd, *J* = 8.2, 3.5 Hz), 4.03 (1H, d, *J* = 8.2 Hz), 3.91 (3H, s), 3.32 (1H, dd, *J* = 6.5, 4.1, Hz), 2.75 – 2.64 (1H, m), 2.48 (1H, dd, *J* = 13.0, 10.1 Hz), 2.37 (1H, d, *J* = 13.0 Hz).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 195.7, 164.1, 144.6, 137.3, 136.3, 129.5, 126.2, 110.4, 80.3, 76.2, 63.4, 53.6, 49.0, 43.9, 38.5.

IR (ATR-IR, neat) υ_{max}: 3050, 2920, 2850, 1580, 1495, 1430, 1375, 1250, 1170, 1100, 1020, 950.

HRMS (ESI$^+$): *m/z* calcd. for $[C_{15}H_{14}{}^{79}BrNNaO_3]^+$ [M+Na]$^+$: 358.0049. Found: 358.0044.

6-Bromo-7a-(2,5-difluorophenyl)-2,3,3a,7a-tetrahydro-3,6-methanobenzofuran-7(6*H*)-one (54)



Synthesised according to **GP6** on a 0.3 mmol scale using 10-(2,4-difluorophenyl)-10*H*-dibenzo[*b,e*][1,4]thiabismine 5,5-dioxide and 2-(allyloxy)-6-bromophenol. The crude compound was purified by automated silica gel column chromatography (0-5% EtOAc in cyclohexane) to yield the title compound as a viscous oil (60 mg, 0.18 mmol, 59%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.52 (1H, app. td, *J* = 8.7, 6.4 Hz), 6.86 (1H, app. td, *J* = 8.4, 2.6 Hz), 6.75 (1H, ddd *J* = 11.1, 8.7, 2.6), 6.46 (1H, d, *J* = 8.3 Hz), 6.14 (1H, ddd, *J* = 8.3, 6.5, 1.5 Hz), 4.18 (1H, dd, *J* = 8.1, 3.3 Hz), 4.03 (1H, d, *J* = 8.1 Hz), 3.38 (1H, ddd, *J* = 6.5, 4.1, 1.6 Hz), 2.79 – 2.64 (1H, m), 2.46 (1H, dd, *J* = 12.9, 10.0 Hz), 2.34 (1H, d, *J* = 12.9 Hz).

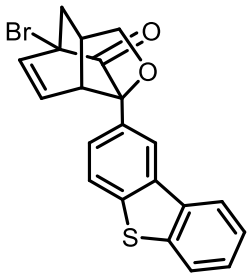
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 194.8, 162.9 (dd, *J* = 250.0, 12.0 Hz), 160.1 (dd, *J* = 252.3, 11.9 Hz), 136.3 (d, *J* = 2.5 Hz), 130.5 (dd, *J* = 9.7, 5.3 Hz), 129.0 (d, *J* = 2.9 Hz), 121.0 (dd, *J* = 12.5, 3.9 Hz), 111.2 (dd, *J* = 21.0, 3.5 Hz), 105.4 – 104.1 (m), 79.6 (d, *J* = 3.8 Hz), 76.0, 63.5, 49.0, 43.6, 39.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ_F -104.31 (1F, dd, *J* = 11.1, 8.4 Hz), -109.97 (1F, ddd, *J* = 8.4, 8.4, 6.4 Hz).

IR (ATR-IR, neat) υ_{max}: 2926, 2883, 1749, 1614, 1600, 1503, 1470, 1445, 1424, 1292, 1269, 1219, 1183, 1142, 1109, 1078, 1025, 1010, 998, 971, 944.

HRMS (ESI^{+}): *m/z* calcd. for $[C_{15}H_{11}{}^{79}BrF_2NaO_2]^+$ $[M+Na]^+$: 362.9803. Found: 362.9784.

6-Bromo-7a-(dibenzo[*b,d*]thiophen-2-yl)-2,3,3a,7a-tetrahydro-3,6-methanobenzofuran-7(6*H*)-one (58)



Synthesised according to **GP6** on a 0.15 mmol scale using 10-(dibenzo[*b,d*]thiophen-2-yl)-10*H*-dibenzo[*b,e*][1,4]thiabismine 5,5-dioxide and 2-(allyloxy)-6-bromophenol. The crude compound was purified by automated silica gel column chromatography (0-10% EtOAc in cyclohexane) to yield the title compound as an off white solid (22 mg, 0.05 mmol, 36%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.22 (1H, d, *J* = 1.8, Hz), 8.20 – 8.17 (1H, m), 7.88 – 7.85 (1H, m), 7.82 (1H, dd, *J* = 8.4, 0.6 Hz), 7.50 – 7.46 (2H, m), 7.42 (1H, dd, *J* = 8.4, 1.8 Hz), 6.59 (1H, dd, *J* = 8.4, 1.8, Hz), 6.37 (1H, dd, *J* = 8.4, 6.6 Hz), 4.30 (1H, dd, *J* = 8.1, 3.4 Hz), 4.16 (1H, d, *J* = 8.1 Hz), 3.40 (1H, ddd, *J* = 6.6, 4.2, 1.8 Hz), 2.81 – 2.73 (1H, m), 2.57 (1H, dd, *J* = 13.0, 9.9 Hz), 2.47 (1H, d, *J* = 13.0 Hz).

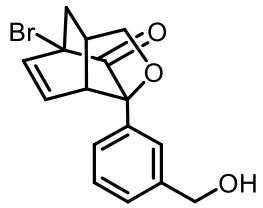
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 196.0, 139.7, 139.3, 136.1, 135.4, 135.3, 134.4, 129.9, 126.8, 124.4, 124.3, 122.8, 122.4, 121.8, 119.3, 82.0, 76.2, 63.8, 50.0, 43.9, 38.7.

IR (ATR-IR, neat) υ_{max}: 2956, 2923, 2853, 1745, 1469, 1431, 1068, 1023, 1004, 953.

HRMS (ESI$^+$): *m/z* calcd. for $[C_{21}H_{15}{}^{79}BrNaO_2S]^+$ $[M+Na]^+$: 432.9874. Found: 432.9880.

MP: 161-162 °C.

6-Bromo-7a-(3-(hydroxymethyl)phenyl)-2,3,3a,7a-tetrahydro-3,6-methanobenzofuran-7(6*H*)-one (55)



10-(3-(Hydroxymethyl)phenyl)-10*H*-dibenzo[*b,e*][1,4]thiabismine 5,5-dioxide (160 mg, 0.3 mmol) and 2-(allyloxy)-6-bromophenol (68.4 mg, 0.30 mmol) were suspended in $CHCl_3$ (15 mL) in the presence of internal standard diphenyl methane (5.00 mg, 0.029 mmol) at rt. *m*CPBA (81 mg, 0.33 mmol, 70% purity) was added in 10 equal portions at 30 second intervals while stirring, and the reaction mixture was left for 30 min. The resultant orange solution was quenched with sat. aq. $Na_2S_2O_5$ (0.01 mL), left to stir for 5 min, then concentrated under reduced pressure. The residue was dissolved in EtOAc (15 mL) and washed with sat. aq. $NaHCO_3$ (3 × 10 mL), and the organic portion was dried over Na_2SO_4. The dried organic portion was concentrated under reduced pressure and purified by automated silica gel column chromatography (30% EtOAc in cyclohexane) to provide the title compound as an of white solid (49 mg, 0.147 mmol, 49%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.41 (1H, s), 7.36 – 7.32 (2H, m), 7.28 (1H, m), 6.52 (1H, dd, J = 8.5, 1.7 Hz), 6.31 (1H, dd, J = 8.5, 6.6 Hz), 4.71 (2H, s), 4.21 (1H, dd, *J* = 8.1, 3.4 Hz), 4.09 (1H, d, *J* = 8.1 Hz), 3.31 (1H, ddd, *J* = 6.6, 4.2, 1.7 Hz), 2.80 – 2.69 (1H, m), 2.52 (1H, dd, *J* = 13.0, 9.9 Hz), 2.42 (1H, d, *J* = 13.0, Hz), 1.69 (1H, s)

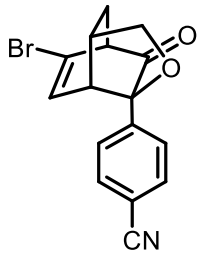
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 196.0, 140.9, 138.4, 136.1, 129.9, 128.5, 127.0, 125.4, 124.6, 81.9, 76.2, 65.4, 63.9, 49.7, 44.0, 38.7.

IR (ATR-IR, neat) υ_{max}: 3391, 3014, 2928, 2880, 1746, 1667, 1651, 1607, 1556, 1538, 1514, 1504, 1486, 1443, 1354, 1294, 1215, 1173, 1153, 1063, 1044, 1019, 1000, 982, 954.

HRMS (ESI$^+$): *m/z* calcd. for $[C_{16}H_{15}{}^{79}BrNaO_3]^+$ $[M+Na]^+$: 357.0097. Found: 357.0094.

MP: 124-126 °C.

4-(5-Bromo-7-oxo-3,3a,6,7-tetrahydro-3,6-methanobenzofuran-7a(2*H*)-yl)benzonitrile (6o)



Synthesised according to **GP6** on a 0.3 mmol scale using 4-(5,5-dioxido-10*H*-dibenzo[*b,e*][1,4]thiabismin-10-yl)benzonitrile and 2-(allyloxy)-5-bromophenol. The crude compound was purified by automated silica gel column chromatography (10-20% EtOAc in cyclohexane) to yield the title compound as a yellow soild (51 mg, 0.16 mmol, 51%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.62 (2H, d, *J* = 8.1 Hz), 7.45 (2H, d, *J* = 8.1 Hz), 6.48 (1H, d, *J* = 7.2 Hz), 4.17 (1H, dd, *J* = 8.2, 3.8 Hz), 4.00 (1H, d, *J* = 8.2 Hz), 3.51 - 3.48 (1H m), 3.26 (1H, dd, *J* = 7.2, 3.8 Hz), 2.68 (1H, app. dt, *J* = 9.5, 3.8 Hz), 2.16 (1H, ddd, *J* = 12.7, 9.5, 2.1 Hz), 2.01 (1H, dd, *J* = 12.7, 3.1 Hz).

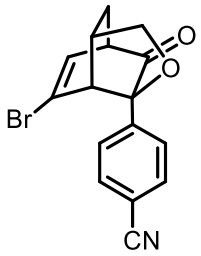
^{13}C{^{1}H} NMR (101MHz, $CDCl_3$): δ_C 200.6, 143.4, 132.1, 128.7, 126.8, 120.3, 118.7, 112.0, 81.6, 75.8, 55.2, 52.0, 36.2, 32.3.

IR (ATR-IR, neat) υ_{max}: 3019, 2230, 1742, 1607, 1504, 1407, 1332, 1309, 1274, 1215, 1106, 1091, 1055, 1008, 958, 922.

HRMS (ESI$^+$): *m/z* calcd. for $[C_{16}H_{12}{}^{79}BrNNaO_2]^+$ $[M+Na]^+$: 351.9949. Found: 351.9927.

MP: 124-126 °C.

4-(4-Bromo-7-oxo-3,3a,6,7-tetrahydro-3,6-methanobenzofuran-7a(2*H*)-yl)benzonitrile (62)



Synthesised according to **GP6** on a 0.3 mmol scale using 4-(5,5-dioxido-10*H*-dibenzo[*b,e*][1,4]thiabismin-10-yl)benzonitrile and 2-(allyloxy)-4-bromophenol. The crude compound was purified by automated silica gel column chromatography (10-20% EtOAc in cyclohexane) to yield the title compound as off white crystals (47 mg, 0.14 mmol, 51%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.65 (2H, d, *J* = 8.1 Hz), 7.53 (2H, d, *J* = 8.1 Hz), 6.64 (1H, dd, *J* = 7.4, 2.5 Hz), 4.17 (1H, dd, *J* = 8.2, 3.5 Hz), 4.01 (1H, d, *J* = 8.2 Hz), 3.41 – 3.36 (2H, m), 2.86 – 2.82 (1H, m), 2.06 – 1.94 (2H, m).

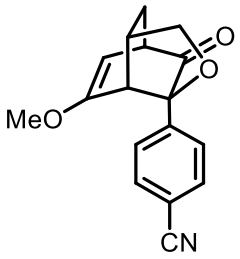
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 201.5, 142.7, 132.0, 130.0, 126.8, 120.3, 118.6, 112.1, 81.7, 75.3, 59.4, 47.5, 36.2, 31.6.

IR (ATR-IR, neat) υ_{max}: 2956, 2923, 2853, 2228, 1733, 1607, 1505, 1406, 1288, 1197, 1109, 1091, 1076, 1038, 1010, 943.

HRMS (ESI$^+$): *m/z* calcd. for $[C_{16}H_{12}{}^{79}BrNNaO_2]^+$ $[M+Na]^+$: 351.9949. Found: 351.9944.

MP: 175-177 °C.

4-(4-Methoxy-7-oxo-3,3a,6,7-tetrahydro-3,6-methanobenzofuran-7a(2*H*)-yl)benzonitrile (64)



Synthesised according to **GP6** on a 0.19 mmol scale using 4-(5,5-dioxido-10*H*-dibenzo[*b,e*][1,4]thiabismin-10-yl)benzonitrile and 2-(allyloxy)-4-methoxyphenol. The eluent after the basified alumina plug was stirred at rt for 18 h. The crude compound was purified by automated silica gel column chromatography (0-25 % EtOAc in cyclohexane) to yield the title compound as a colourless solid (26 mg, 0.09 mmol, 49%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.61 (2H, d, *J* = 8.5 Hz), 7.48 (2H, d, *J* = 8.5 Hz), 5.08 (1H, dd, *J* = 7.6, 2.9 Hz), 4.14 (1H, dd, *J* = 8.0, 3.5 Hz), 3.98 (1H, d, *J* = 8.0 Hz), 3.63 (3H, s), 3.23 (1H, d, *J* = 7.6 Hz), 3.09 (1H, dd, *J* = 4.3, 2.9 Hz), 2.74 – 2.69 (1H, m), 1.97 – 1.94 (2H, m).

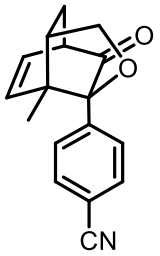
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 202.1, 158.2, 143.5, 132.0, 126.9, 118.9, 111.8, 92.6, 82.2, 76.1, 55.6, 53.2, 42.9, 35.8, 33.2.

IR (ATR-IR, neat) υ_{max}: 2959, 2884, 2203, 1732, 1635, 1371, 1221, 1046, 1025, 1010.

HRMS (ESI$^+$): *m/z* calcd. for $[C_{17}H_{15}NNaO_3]^+$ $[M+Na]^+$: 304.0944. Found: 304.0942.

MP: 103-104 °C.

4-(3a-Methyl-7-oxo-3,3a,6,7-tetrahydro-3,6-methanobenzofuran-7a(2*H*)-yl)benzonitrile (59)



Synthesised according to **GP6** on a 0.3 mmol scale using 4-(5,5-dioxido-10*H*-dibenzo[*b,e*][1,4]thiabismin-10-yl)benzonitrile and 2-(allyloxy)-3-methylphenol. The crude compound was purified by automated silica gel column chromatography (10-20% EtOAc in cyclohexane) to yield the title compound as a colourless solid (54 mg, 0.20 mmol, 68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.59 (2H, d, *J* = 8.7 Hz), 7.45 (2H, d, *J* = 8.7 Hz), 6.51 (1H, dd, *J* = 8.1, 6.8 Hz), 6.02 (1H, dd, *J* = 8.1, 1.4 Hz), 4.33 (1H, dd, *J* = 8.3, 4.0 Hz), 3.94 (1H, d, *J* = 8.3 Hz), 3.33 – 2.29 (1H, m), 2.26 (1H, app. dt, *J* = 7.8, 4.0 Hz), 2.01 – 1.96 (2H, m), 0.94 (3H, s).

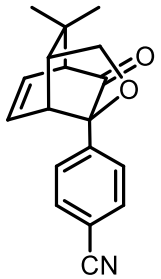
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 205.3, 142.8, 136.4, 131.7, 130.9, 127.3, 118.9, 111.7, 85.4, 75.0, 50.9, 45.5, 41.7, 34.5, 18.8.

IR (ATR-IR, neat) υ_{max}: 2966, 2933, 2891, 2227, 1730, 1609, 1050, 1016.

HRMS (ESI$^+$): *m/z* calcd. for $[C_{17}H_{16}NO_2]^+$ $[M+H]^+$: 266.1181. Found: 266.1169.

MP: 103-105 °C.

4-(8,8-Dimethyl-7-oxo-3,3a,6,7-tetrahydro-3,6-methanobenzofuran-7a(2*H*)-yl)benzonitrile (66)



Synthesised according to **GP6** on a 0.3 mmol scale using 4-(5,5-dioxido-10*H*-dibenzo[*b,e*][1,4]thiabismin-10-yl)benzonitrile and 2-((3-methylbut-2-en-1-yl)oxy)phenol. The crude compound was purified by automated silica gel column chromatography (5-20% EtOAc in cyclohexane) to yield the title compound as a yellow oil (37 mg, 0.14 mmol, 45%).

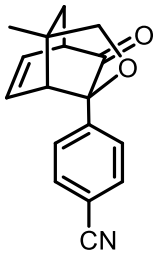
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.57 (2H, *J* = 8.2 Hz), 7.47 (2H, *J* = 8.2 Hz), 6.44 – 6.25 (2H, m), 4.17 (1H, d, *J* = 8.8 Hz), 3.97 (1H, dd, *J* = 8.8, 3.3 Hz), 3.20 – 3.17 (1H, m), 2.90 (1H, dd, *J* = 6.3, 1.8 Hz), 2.05 – 2.03 (1H, m), 1.22 (3H, s), 1.00 (3H, s).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 203.6, 144.7, 131.8, 130.8, 129.4, 127.1, 118.9, 111.6, 80.8, 70.9, 59.7, 51.3, 47.2, 35.8, 27.9, 25.3.

IR (ATR-IR, neat) υ_{max}: 2958, 2873, 2227, 1730, 1608, 1503, 1468, 1447, 1405, 1390, 1366, 1329, 1309, 1277, 1249, 1215, 1201, 1162, 1118, 1092, 1064, 1040, 1029, 1006, 953, 922.

HRMS (ESI$^+$): *m/z* calcd. for $[C_{18}H_{17}NNaO_2]^+$ $[M+Na]^+$: 302.1151. Found: 302.1155.

4-(3-Methyl-7-oxo-3,3a,6,7-tetrahydro-3,6-methanobenzofuran-7a(2*H*)-yl)benzonitrile (67)



Synthesised according to **GP6** on a 0.3 mmol scale using 4-(5,5-dioxido-10*H*-dibenzo[*b,e*][1,4]thiabismin-10-yl)benzonitrile and 2-((2-methylallyl)oxy)phenol. The crude compound was purified by automated silica gel column chromatography (5-10% EtOAc in cyclohexane) to yield the title compound as an off white solid (36 mg, 0.14 mmol, 45%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.60 (2H, d, *J* = 7.8 Hz), 7.46 (2H, d, *J* = 7.8 Hz), 6.50 (1H, app. t, *J* = 7.5 Hz), 6.33 (1H, app. t, *J* = 7.5 Hz), 3.98 (1H, d, *J* = 7.7 Hz), 3.88 (1H, d, *J* = 7.7 Hz), 3.31 (1H, d, *J* = 6.7 Hz), 2.86 (1H, d, *J* = 6.4 Hz), 2.17 (1H, d, *J* = 13.1 Hz), 1.53 (1H, d, *J* = 13.1 Hz), 1.15 (3H, s)

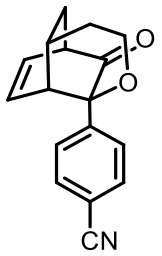
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 203.4, 144.5, 131.9, 131.5, 129.5, 126.8, 118.9, 111.7, 82.7, 81.2, 56.4, 46.6, 42.7, 38.2, 21.9.

IR (ATR-IR, neat) υ_{max}: 2954, 2870, 2227, 1731, 1609, 1503, 1454, 1405, 1363, 1329, 1308, 1293, 1279, 1255, 1233, 1208, 1178, 1161, 1142, 1122, 1088, 1063, 1041, 1005, 992, 975, 953, 933.

HRMS (ESI$^+$): *m/z* calcd. for $[C_{17}H_{15}NNaO_2]^+$ $[M+Na]^+$: 288.0995. Found: 288.0986.

MP: 152-154 °C.

4-(8-Oxo-2,3,4,4a,7,8-hexahydro-8a*H*-4,7-methanochromen-8a-yl)benzonitrile (65)



Synthesised according to **GP6** on a 0.3 mmol scale using 4-(5,5-dioxido-10*H*-dibenzo[*b,e*][1,4]thiabismin-10-yl)benzonitrile and 2-(but-3-en-1-yloxy)phenol. The eluent after the basified alumina plug was heated to 50 °C for 18 h while stirring. The crude compound was purified by automated silica gel column chromatography (5-10% EtOAc in cyclohexane) to yield the title compound as an off white solid (34 mg, 0.13 mmol, 43%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.54 (2H, d, *J* = 8.2 Hz), 7.48 (2H, d, *J* = 8.2 Hz), 6.29 (1H, app. t, *J* = 6.6 Hz), 6.22 (1H, app. t, *J* = 6.6 Hz), 3.89 (1H, dd, *J* = 12.9, 5.7 Hz), 3.78 (1H, app. td, *J* = 12.9, 2.6 Hz), 3.42 – 3.26 (1H, m), 2.96 (1H, ddd, *J* = 5.0, 3.4, 1.8 Hz), 2.33 (1H, app. dt, *J* = 11.2, 3.3 Hz), 2.16 – 1.98 (2H, m), 1.86 (1H, app. dt, *J* = 13.8, 3.3 Hz), 1.68 (1H, d, *J* = 13.8, Hz).

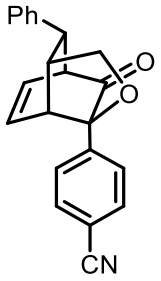
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 211.2, 146.7, 135.7, 131.5, 129.2, 128.6, 118.6, 111.5, 78.0, 59.8, 48.8, 45.9, 30.3, 30.1, 26.7.

IR (ATR-IR, neat) υ_{max}: 2947, 2870, 2227, 1732, 1723, 1504, 1478, 1455, 1379, 1250, 1209, 1184, 1120, 1089, 1055, 994, 976.

HRMS (ESI$^+$): *m/z* calcd. for $[C_{17}H_{15}NNaO_2]^+$ $[M+Na]^+$: 288.1000. Found: 288.0998.

MP: 154-156 °C.

4-(7-Oxo-8-phenyl-3,3a,6,7-tetrahydro-3,6-methanobenzofuran-7a(2*H*)-yl)benzonitrile (69)



Synthesised according to **GP6** on a 0.3 mmol scale using 4-(5,5-dioxido-10*H*-dibenzo[*b,e*][1,4]thiabismin-10-yl)benzonitrile and 2-(cinnamyloxy)phenol. The crude compound was purified by automated silica gel column chromatography (5-10% EtOAc in cyclohexane) to yield the title compound as a colourless solid (52 mg, 0.16 mmol, 53%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.62 (2H, d, *J* = 8.6 Hz), 7.52 (2H, d, *J* = 8.6 Hz), 7.36 – 7.24 (3H, m), 7.16 (2H, dd, *J* = 8.1, 1.8 Hz), 6.54 (1H, ddd, *J* = 8.0, 6.5, 1.3 Hz), 6.17 (1H, ddd, *J* = 8.0, 5.9, 1.1), 4.28 (1H, dd, *J* = 8.1, 3.3 Hz), 4.17 (1H, d, *J* = 8.1 Hz), 3.52 – 3.47 (2H, m), 3.40 (1H, ddd, *J* = 6.5, 4.1, 1.7 Hz), 2.94 – 2.92 (1H, m).

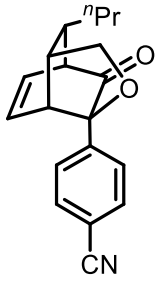
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 202.8, 144.1, 141.7, 132.0, 130.5, 128.6, 128.5, 128.4, 127.2, 127.0, 118.9, 111.9, 81.4, 76.5, 53.8, 51.0, 47.6, 45.0.

IR (ATR-IR, neat) υ_{max}: 3023, 2958, 2882, 2227, 1731, 1608, 1501, 1101, 1069, 1007.

HRMS (ESI$^+$): *m/z* calcd. for $[C_{22}H_{17}NNaO_2]^+$ $[M+Na]^+$: 350.1151. Found: 350.1148.

MP: 163-164 °C.

4-(7-Oxo-8-propyl-3,3a,6,7-tetrahydro-3,6-methanobenzofuran-7a(2*H*)-yl)benzonitrile (68)



Synthesised according to **GP6** on a 0.29 mmol scale using 4-(5,5-dioxido-10*H*-dibenzo[*b,e*][1,4]thiabismin-10-yl)benzonitrile and (*Z*)-2-(hex-2-en-1-yloxy)phenol. The crude compound was purified by automated silica gel column chromatography (5-10 % EtOAc in cyclohexane) to yield the title compound as a colourless solid (51 mg, 0.17 mmol, 59%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.59 (2H, d, *J* = 8.5 Hz), 7.49 (2H, d, *J* = 8.5 Hz), 6.52 (1H, ddd, *J* = 8.0, 6.8, 1.9 Hz), 6.28 (1H, ddd, *J* = 8.0, 6.2, 1.4 Hz), 4.15 (1H, d, *J* = 8.8 Hz), 4.01 (1H, dd, *J* = 8.8, 3.9 Hz), 3.23 (1H, ddd, *J* = 6.2, 3.9, 1.9 Hz), 3.14 (1H, app. dt, *J* = 6.8 Hz, 1.4), 2.52 (1H, app. dt, *J* = 9.2, 3.9 Hz), 1.82 – 1.75 (1H, m), 1.57 – 1.33 (4H, m), 0.97 (3H, t, *J* = 6.9 Hz).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 203.4, 144.5, 132.7, 131.9, 129.2, 127.1, 118.9, 111.7, 82.4, 69.3, 51.3, 50.8, 39.4, 38.4, 32.6, 21.4, 14.2.

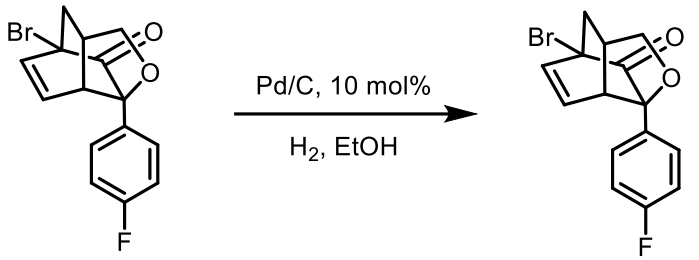
IR (ATR-IR, neat) υ_{max}: 3059, 2956, 2928, 2872, 2227, 1730, 1635, 1503, 1098, 1073, 1014.

HRMS (ESI$^+$): *m/z* calcd. for $[C_{19}H_{19}NNaO_2]^+$ $[M+Na]^+$: 316.1308. Found: 316.1298.

MP: 84-86 °C.

Diversification of Bicyclo[2.2.2]octenones

6-Bromo-7a-(4-fluorophenyl)hexahydro-3,6-methanobenzofuran-7(4*H*)-one (72)



47 **72, 96%**

6-Bromo-7a-(4-fluorophenyl)-2,3,3a,7a-tetrahydro-3,6 methanobenzofuran-7(6*H*)-one, **47** (258 mg, 0.8 mmol) and palladium on carbon (84 mg, 0.08 mmol, 10 mol%) were suspended in EtOH (8 mL). The reaction flask was evacuated and backfilled three times with H_2 from a balloon, and left to stir under an atmosphere of H_2 (balloon) for 18 h at rt. The palladium on carbon was then removed by filtration through a pad of celite (*ca* 2 mL), which was eluted with EtOH (5 mL). The filtrate was concentrated to dryness to afford the title compound as an off white solid (249 mg, 0.77 mmol, 96%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.35 (2H, dd, *J* = 8.8, 5.3 Hz), 7.08 (2H, app. t, *J* = 8.8 Hz), 4.25 (1H, dd, *J* = 8.1, 4.7 Hz), 3.90 (1H, d, *J* = 8.1 Hz), 2.86 – 2.74 (2H, m), 2.56 – 2.34 (4H, m), 2.13 (1H, dddd, *J* = 14.9, 11.7, 5.8, 2.7 Hz), 1.94 (1H, app. ddt, *J* = 14.9, 11.3, 4.0 Hz).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ_C 201.8, 162.6 (d, *J* = 247.0 Hz), 132.7 (d, *J* = 3.2 Hz), 127.9 (d, *J* = 8.2 Hz), 115.3 (d, *J* = 21.7 Hz), 87.6, 76.4, 64.3, 46.4, 41.8, 39.0, 36.0, 17.7.

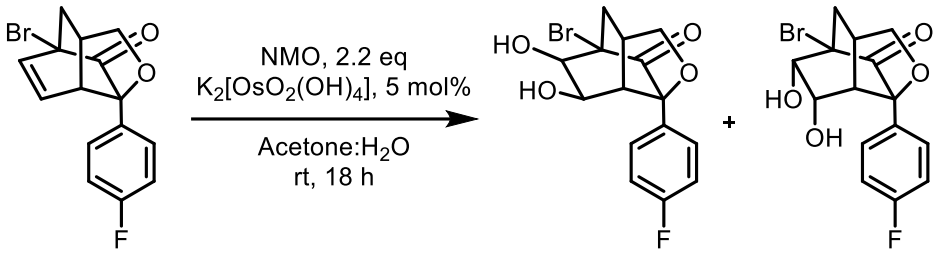
^{19}F NMR (377 MHz, $CDCl_3$): δ_F -113.81 (tt, *J* = 8.8, 5.3 Hz)

IR (ATR-IR, neat) υ_{max}: 2928, 2877, 2253, 1744, 1602, 1510, 1468, 1301, 1263, 1233, 1160, 1103, 1080, 1055, 1009, 954, 905.

HRMS (ESI$^+$): *m*/*z* calcd. for $[C_{15}H_{14}{}^{79}BrFNaO_2]^+$ $[M+Na]^+$: 347.0053. Found: 347.0055.

MP: 128-130 °C.

6-Bromo-7a-(4-fluorophenyl)-4,5-dihydroxyhexahydro-3,6-methanobenzofuran-7(4*H*)-one (73a and 73b)



47 **73a and 73b**
64% 1:1 dr

To a solution of 6-bromo-7a-(4-fluorophenyl)-2,3,3a,7a-tetrahydro-3,6-methanobenzofuran-7(6*H*)-one, **47** (260 mg, 0.80 mmol) in acetone (6.0 mL) and water (4.0 mL) was added potassium osmate (15.3 mg, 0.04 mol) and NMO (307 mg, 1.73 mmol). The suspension was stirred at rt for 18 h, and the reaction mixture was quenched in sat. aq. sodium thiosulfate (0.5 mL) and diluted with EtOAc (5.0 mL). The biphasic mixture was stirred for 1 h at rt, after which time the aqueous portion was removed, and the organics were dried over $MgSO_4$ and concentrated under reduced pressure. The crude products were purified *via* manual column chromatography (2% MeOH in DCM) to provide both diastereoisomers of 6-bromo-7a-(4-fluorophenyl)-4,5-dihydroxyhexahydro-3,6-methanobenzofuran-7(4*H*)-one (**73a**) and (**73b**) in a 1:1 ratio (182 mg, 0.51 mmol, 64%)

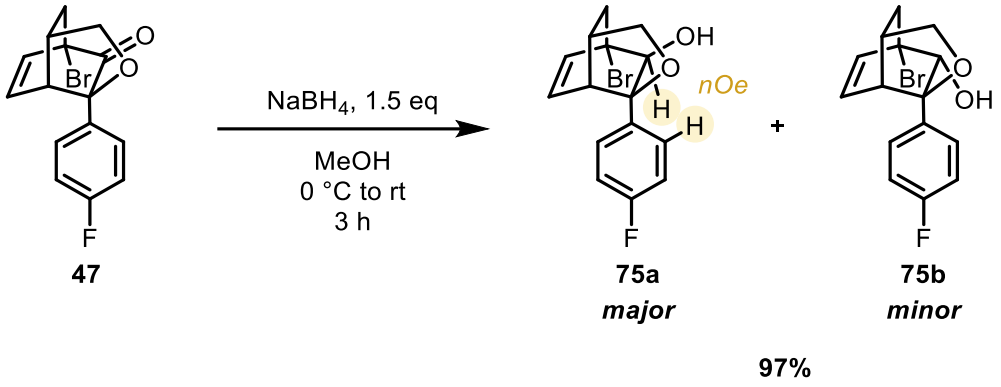
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.42 (2H, dd, *J* = 9.0, 5.3 Hz), 7.29 (2H, dd, *J* = 9.0, 5.2 Hz), 7.08 – 7.01 (4H, m), 4.38 (1H, app. dt, *J* = 8.5, 2.8 Hz), 4.32 (1H, app. t, *J* = 4.0 Hz), 4.27 (1H, dd, *J* = 8.2, 3.8 Hz), 4.22 (1H, dd, *J* = 8.3, 3.6 Hz), 4.13 – 4.12 (1H, m), 4.03 (1H, ddd, *J* = 8.5, 3.4, 2.1 Hz), 3.98 (1H, d, *J* = 8.2 Hz), 3.91 (1H, d, *J* = 8.3 Hz), 3.23 (1H, d, *J* = 2.8 Hz), 3.13 (1H, dd, *J* = 13.4, 9.7 Hz), 3.08 – 3.00 (2H, m), 2.95 (1H, d, *J* = 3.4 Hz), 2.86 (1H, dd, *J* = 14.0, 9.5 Hz), 2.77 – 2.73 (2H, m), 2.60 (1H, app. t, *J* = 4.0 Hz), 2.33 (1H, d, *J* = 14.0 Hz), 2.21 (1H, d, *J* = 4.0 Hz), 1.98 (1H, dd, *J* = 13.4, 2.1 Hz).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 200.5, 200.0, 162.9 (d, *J* = 248.0 Hz), 162.8 (d *J* = 247.2 Hz), 132.5 (d, *J* = 3.2 Hz), 132.1 (d, *J* = 3.2 Hz), 128.5 (d, *J* = 8.2 Hz), 128.2 (d, *J* = 8.2 Hz), 115.6 (d, *J* = 21.7 Hz), 115.2, 85.4, 84.8, 84.5, 76.7, 76.5, 73.2, 73.2, 70.4, 69.0, 63.8, 53.6, 51.8, 37.7, 35.3, 35.0, 32.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ_F -112.96 (1F, tt, *J* = 8.5, 5.2 Hz), -113.66 (1F, tt, *J* = 8.5, 5.3 Hz).

HRMS (ESI$^-$): *m*/*z* calcd. for $[C_{15}H_{13}{}^{79}BrFO_4]^-$ $[M-H]^-$: 354.9981. Found: 354.9975.

6-Bromo-7a-(4-fluorophenyl)-2,3,3a,6,7,7a-hexahydro-3,6-methanobenzofuran-7-ol (75a and 75b)



A solution of 6-bromo-7a-(4-fluorophenyl)-2,3,3a,7a-tetrahydro-3,6-methanobenzofuran-7(6*H*)-one, **47** (64.7 mg, 0.2 mmol) in MeOH (2.0 mL) was cooled to 0 °C, and $NaBH_4$ (11.1 mg, 0.29 mmol) was added in 5 equal portions over 3 minutes. The reaction mixture was left to warm to rt over 3 h, and was subsequently quenched with water (0.5 mL) and left to stir for 5 min. The mixture was diluted with HCl (1M, 1.0 mL) and extracted with DCM (3 × 2 mL). The organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to afford the title compounds as a 2:1 ratio of inseparable diastereoisomers (63 mg, 0.19 mmol, 97%). The ^{1}H NMR spectroscopic data for the two diastereoisomers can be resolved and are reported separately below; the $^{13}C\{^1H\}$ NMR data cannot be reliably resolved and so are reported for both diastereoisomers together.

Major diastereoisomer (75a)

^{1}H NMR (400 MHz, C_6D_6): δ_H 7.13 (2H, dd, *J* = 8.8, 5.4 Hz), 6.78 (2H, app. t, *J* = 8.8 Hz), 6.41 (1H, d, *J* = 8.6 Hz), 5.40 (1H, dd, *J* = 8.6, 6.5 Hz), 3.66 (1H, dd, *J* = 8.4, 2.0 Hz), 3.63 (1H, d, *J* = 8.4 Hz), 3.21 (1H, dd, *J* = 7.9, 3.4 Hz), 3.10 (1H, d, *J* = 7.9 Hz), 2.17 – 2.12 (1H, m), 1.93 (1H, dd, *J* = 13.0, 1.5 Hz), 1.41 – 1.36 (1H, m).

Minor diastereoisomer (75b)

^{1}H NMR (400 MHz, C_6D_6): δ_H 7.27 (2H, dd, *J* = 8.7, 5.5 Hz), 6.85 (2H, app. t, *J* = 8.7 Hz), 6.32 (1H, d, *J* = 8.5 Hz), 5.68 (1H, dd, *J* = 8.5, 6.7 Hz), 3.84 (1H, d, *J* = 4.5 Hz), 3.29 – 3.27 (2H, m), 2.31 (1H, dd, *J* = 6.7, 3.5 Hz), 1.94 (1H, dd, *J* = 13.0, 10.5 Hz), 1.82 (1H, d, *J* = 13.0 Hz), 1.45 (1H,dd, *J* = 10.5, 3.5 Hz), 1.25 (1H, d, *J* = 4.5 Hz).

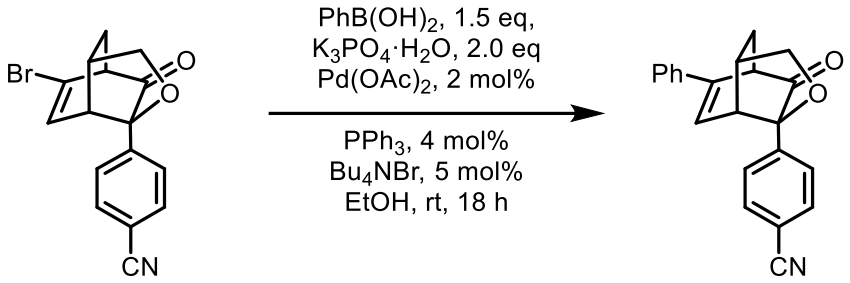
2:1 mixture of diastereoisomers 75a and 75b

^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ_C 162.6 (d, *J* = 245.6 Hz), 162.4 (d, *J* = 244.9 Hz), 140.7, 139.4 (d, *J* = 3.2 Hz), 138.2, 136.6 (d, *J* = 3.2 Hz), 128.9 (d, *J* = 7.8 Hz), 127.1 (d, *J* = 7.9 Hz), 126.6, 126.2, 115.0 (d, *J* = 21.2 Hz), 114.6 (d, *J* = 21.2 Hz), 88.6, 86.9, 81.6, 80.6, 74.8, 73.3, 64.1, 63.4, 47.1, 46.1, 43.7, 40.0, 39.7, 39.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ_F -114.82 (1F, tt, *J* = 8.7, 5.4 Hz), -115.09 (2F, tt, *J* = 8.8, 5.5 Hz).

HRMS (ESI$^+$): *m*/*z* calcd. for $[C_{15}H_{14}{}^{79}BrFNaO_2]^+$ $[M+Na]^+$: 347.0059. Found: 347.0052.

4-(7-Oxo-5-phenyl-3,3a,6,7-tetrahydro-3,6-methanobenzofuran-7a(2*H*)-yl)benzonitrile (76)



60 **76** **57%**

A suspension of 4-(5-bromo-7-oxo-3,3a,6,7-tetrahydro-3,6-methanobenzofuran-7a(2*H*)-yl)benzonitrile, **60** (33 mg, 0.10 mmol), phenyl boronic acid (17 mg, 0.14 mmol), tripotassium phosphate (43 mg, 0.20 mmol), tetrabutylammonium bromide (1.78 mg, 5.5 μmol), palladium acetate (0.44 mg, 1.9 μmol) and triphenyl phosphine (1.16 mg, 4.4 μmol) in ethanol (1.2 mL) was stirred at rt for 18 h. The reaction mixture was diluted with brine (2 mL) and the organics were extracted with DCM (3 × 2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was isolated *via* automated column chromatography (5-10%) to provide the title compound as an inseparable 4:1 mixture of **76** and **60** (23 mg combined **60** and **76**, corresponding to 0.05 mmol, 57% of **76**).

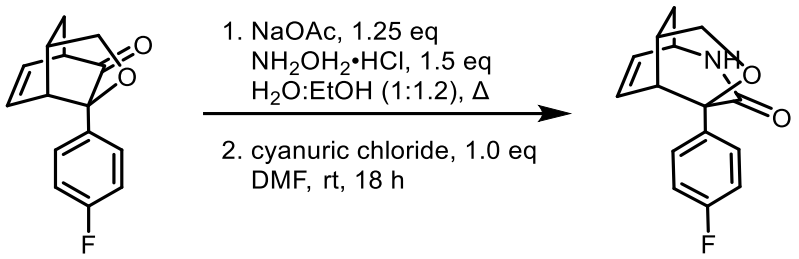
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.61 (2H, d, *J* = 8.6 Hz), 7.52 – 7.37 (7H, m), 6.53 (1H, dd, *J* = 6.8, 2.0 Hz), 4.28 (1H, dd, *J* = 8.0, 3.5 Hz), 4.11 (1H, d, *J* = 8.0 Hz), 3.90 (1H, app. dt, *J* = 3.5, 2.0 Hz),3.38 (1H, dd, *J* = 6.8, 4.3 Hz), 2.78 – 2.69 (1H, m), 2.15 (1H, ddd, *J* = 13.3, 3.5, 1.7 Hz), 2.10 – 2.06 (1H, m).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 203.3, 144.2, 142.8, 136.1, 132.0, 129.0, 128.7, 126.9, 125.3, 122.6, 118.9, 111.8, 82.5, 76.3, 50.7, 48.4, 36.6, 32.0.

HRMS (ESI$^+$): *m/z* calcd. for $[C_{22}H_{17}NNaO_2]^+$ $[M+Na]^+$:350.1157. Found: 350.1165.

Procedures for Test Diversification Reactions

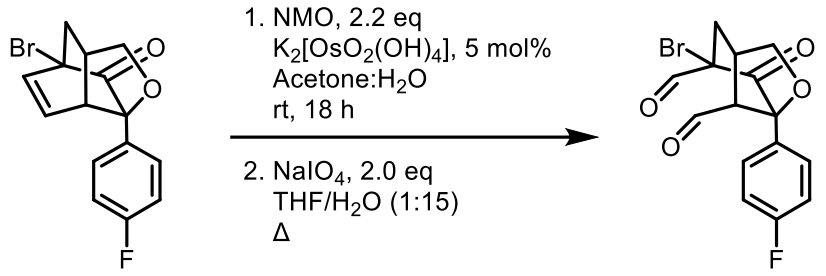
Procedure for Oxime Formation and Beckmann Rearrangement



Hydroxylamine hydrochloride (1.5 eq) and sodium acetate (1.25 eq) were dissolved in a solution of ethanol and water (1.2:1, 0.025 M with respect to hydroxylamine) before a solution of bicyclo[2.2.2]octenone (1.0 eq) in ethanol (0.5 M) was added on stirring. The mixture was heated to the desired temperature for 18 h. The reaction mixture was concentrated, diluted with EtOAc (*ca* 1 volume) and washed once with water (*ca* 1 volume). The organics were dried over $MgSO_4$, concentrated and subject to analysis *via* ^{1}H and ^{19}F NMR spectroscopy to confirm the presence of oxime.

In a separate vessel, cyanuric chloride (1.0 eq) was dissolved in DMF (0.5 M) and stirred at rt. After the formation of a white solid, the reaction was monitored by TLC until complete disappearance of cyanuric chloride. A solution of the formed oxime in DMF (0.5 M) was added, and the reaction was stirred at rt for 18 h. Water (*ca* 5 volumes) was added, then the organic phase washed once with sat. aq. Na_2CO_3 and once with brine. The organics were dried over $MgSO_4$, concentrated and subject to analysis *via* ^{1}H and ^{19}F NMR spectroscopy.

Procedure for the Telescoped Dihydroxylation-Oxidative Cleavage of Dialdehyde

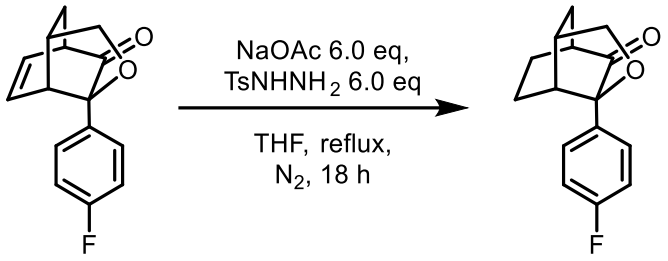


47 **74**

To a solution of 6-bromo-7a-(4-fluorophenyl)-2,3,3a,7a-tetrahydro-3,6-methanobenzofuran-7(6*H*)-one, **47** (15.8 mg, 0.05 mmol) in acetone (0.65 mL) and water (0.25 mL) was added potassium osmate (1.56 mg, 4.23 μmol) and NMO (23 mg, 0.2 mmol). The suspension was stirred at rt for 18 h, and the reaction mixture was quenched in sat. aq. $Na_2S_2O_5$ (0.1 mL) and diluted with EtOAc (1.0 mL). The biphasic mixture was stirred for 1 h at rt, after which time the aqueous portion was removed, and the organics were dried over $MgSO_4$ and concentrated under reduced pressure.

The residue was diluted with a solution of THF (5.7 mL) and water (380 μL). $NaIO_4$ (21 mg, 0.1 mmol) was added, and the reaction was stirred at the desired temperature for the desired amount of time, until no more starting material was observed by ^1H and ^{19}F NMR spectroscopy.

Procedure for the Diimide Reduction



31a

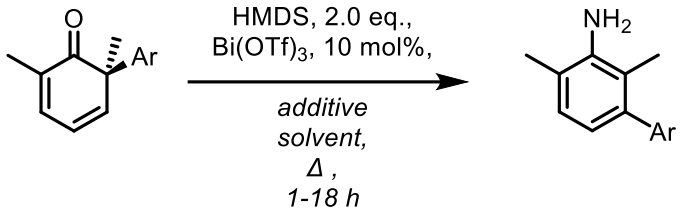
7a-(4-fluorophenyl)-2,3,3a,7a-tetrahydro-3,6-methanobenzofuran-7(6*H*)-one, **31a** (12.1 mg, 0.05 mmol), sodium acetate (24.9 mg, 0.3 mmol)* and tosyl hydrazine (55.6 mg, 0.3 mmol) were dissolved in THF (3.3 mL) and heated to reflux under an atmosphere of anhydrous dinitrogen for 18 h. The reaction mixture was cooled to rt, diluted with EtOAc (5 mL) and washed once with water (5 mL). The organic portion was dried over $MgSO_4$, concentrated under reduced pressure and subject to analysis *via* ^{1}H and ^{19}F NMR spectroscopy.

*__31a__ was used as a 9:1 mixture of mono: diarylated bicyclo[2.2.2]octenone, **31b** as confirmed *via* ^{1}H and ^{19}F NMR spectroscopy. This was synthesised according to **GP6**, and purified *via* automated silica column chromatography (5-10% EtOAc). This was not subject to full characterisation or further purification and was use directly in the diimide reduction step.

Procedures and Data for Compounds in Chapter IV

General Screening Procedures

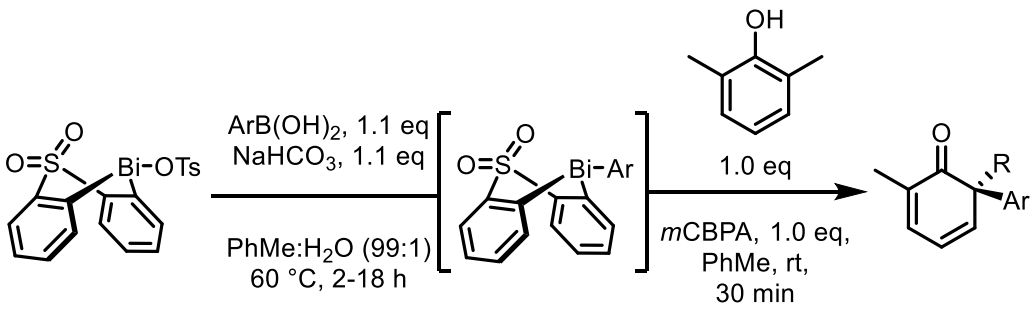
General Procedure for the Optimization of Deoxyamination



To an oven dried flask was added cyclohexadienone (1.00 eq) and 4,4'-bis(trifluoromethyl)-1,1'- biphenyl (0.167 eq; internal standard for ^{19}F NMR spectroscopy). For the reactions including 1-adamantanol, the required amount was added to the flask before being evacuated and backfilled with anhydrous dinitrogen three times. HMDS (2.0 eq) was freshly distilled over 4 Å molecular sieves and added to the flask. The solvent was then added to achieve the desired concentration. An aliquot (0.05 mL) was removed and diluted with $CDCl_3$ and analysed by ^{1}H and quantitative ^{19}F NMR spectroscopy to determine the t_0 of the reaction mixture. $Bi(OTf)_3$ (0.01 eq) was then added under a flow of anhydrous dinitrogen before the cap was replaced and the mixture heated to the desired temperature. Aliquots of 0.05 mL were removed and diluted with $CDCl_3$ for analysis by ^{1}H NMR spectroscopy, quantitative ^{19}FNMR spectroscopy, and HRMS.

Synthesis of Cyclohexadienones

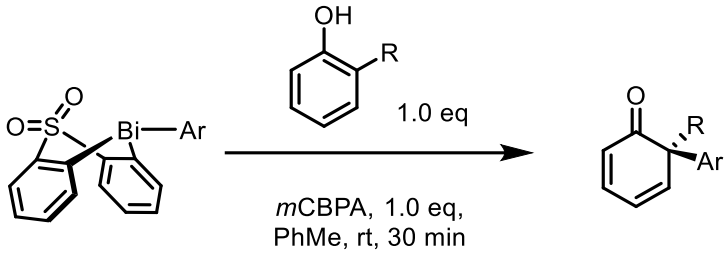
General Procedure for Telescoped Cyclohexadienone Synthesis (GP7)



5,5-Dioxido-10*H*-dibenzo[*b,e*][1,4]thiabismin-10-yl 4-methylbenzenesulfonate (596 mg, 1.00 mmol), $NaHCO_3$, (92.4 mg, 1.10 mmol) and arylboronic acid (1.10 mmol) was suspended in a mixture of toluene (10 mL) and water (0.5 mL) and stirred at 60 °C until no starting material was observed by ^{1}H NMR spectroscopy. Aqueous NaOH (2.0 M; 10 mL) was added once the reaction mixture was cooled to rt and stirred vigorously for 15 min. The organic phase was removed and remaining aqueous portion was extracted with toluene (3 × 10 mL). The combined organic portions were dried over $MgSO_4$ and filtered into a round bottomed flask containing the phenol substrate (1.00 mmol). *m*CPBA (193 mg, 1.00 mmol, 89% purity) was added in 5 equal portions at one-minute intervals while stirring. The reaction mixture was left for 30 min.

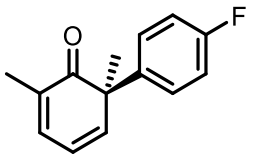
The resultant orange solution was quenched with sat. aq. $Na_2S_2O_5$ (0.01 mL), left to stir for 5 min, then concentrated *in vacuo*. The residue was suspended in TBME (10 mL) and stirred for 5 min, then pentane (30 mL) was added. The resultant solids were filtered under reduced pressure and collected as 5,5-dioxido-10*H*-dibenzo[*b,e*][1,4] thiabismin-10-yl 3-chlorobenzoate (**SI-21**). The filtrate was concentrated *in vacuo* and the crude cyclohexadienone purified by automated silica gel column chromatography using the eluent system described for each compound entry.

General procedure for non-telescoped cyclohexadienone synthesis (GP8)



The aryl bismacycle (1.00 mmol) and the phenol substrate (1.00 mmol) were suspended in toluene ([aryl bismacycle]$_0$ = 0.2 M). *m*CPBA (193 mg, 1 mmol, 89% purity) was added in 5 equal portions at one-minute intervals while stirring. The reaction mixture was left for 30 min. The resultant orange solution was quenched with sat. aq. $Na_2S_2O_5$ (0.01 mL), left to stir for 5 min, then concentrated *in vacuo*. The residue was suspended in TBME (10 mL) and stirred for 5 min, then pentane (30 mL) was added. The resultant solids were filtered under reduced pressure and collected as 5,5-dioxido-10*H*-dibenzo[*b,e*][1,4] thiabismin-10-yl 3-chlorobenzoate (**SI-21**). The filtrate was concentrated *in vacuo* and the crude cyclohexadienone purified by automated silica gel column chromatography using the eluent system described for each compound entry.

4'-Fluoro-1,3-dimethyl-[1,1'-biphenyl]-2(1*H*)-one (77)



Synthesised according to **GP7** on a 3 mmol scale using 4-fluorophenyl boronic acid, and purified by automated silica gel column chromatography (0 to 3% EtOAc in cyclohexane) to provide **77** as a yellow oil (419 mg, 1.94 mmol, 65%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.26 (2H, m), 6.98 (2H, app. t, *J* = 8.6 Hz), 6.0 (1H app. dp, *J* = 5.9, 1.5 Hz), 6.35 (1H, dq, *J* = 9.5, 1.1 Hz), 6.27 (1H, dd, *J* = 9.5, 5.9 Hz), 1.87 (3H, s, br), 1.59 (3H, s).

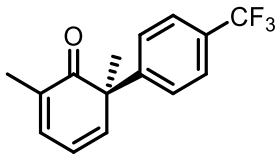
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 203.3, 162.0 (d, *J* = 245.4 Hz), 144.9, 138.0, 136.6 (d, *J* = 3.8 Hz), 132.5, 128.4 (d, *J* = 8.1 Hz), 120.0, 115.4 (d, *J* = 21.3 Hz), 53.6 , 24.2, 15.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ_F -115.66 (1F, tt, *J* = 8.6, 5.3 Hz).

IR (ATR-IR, neat) υ_{max}: 3040, 2923, 1658, 1643, 1602, 1580, 1506, 1488, 1450, 1366, 1297, 1283, 1233, 1177, 1162, 1149, 1085, 1057, 1014.

HRMS (ESI^{+}): *m/z* calcd. for $[C_{14}H_{13}FONa]^{+}$ $[M+Na]^{+}$: 239.0843. Found: 239.0841.

1,3-Dimethyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-2(1*H*)-one (81)



Synthesised according to **GP7** on a 3 mmol scale using (4-(trifluoromethyl)phenyl)boronic acid, and purified by automated silica gel column chromatography (0-2% EtOAc in cyclohexane) to yield the title compound as a yellow oil (510 mg, 1.92 mmol, 64%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.56 (2H, d, *J* = 8.2*)*, 7.42 (2H, d, *J* = 8.2 Hz), 6.97-6.89 (1H, m), 6.35 (1H, dd, *J* = 9.5 Hz, 2.0), 6.31 (1H, dd, *J* = 9.5, 5.5 Hz), 1.88 (3H, d, *J* = 1.5 Hz), 1.64 (3H, s).

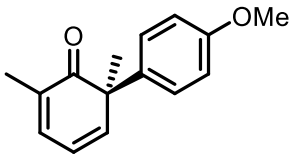
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 202.8, 145.1, 144.4, 138.3, 132.8, 129.6 (q, *J* = 32.3 Hz), 127.4, 125.7 (q, *J* = 3.7 Hz), 122.9 (q, *J* = 271.6 Hz), 120.6, 54.3, 24.1, 15.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ_F -62.61.

IR (ATR-IR, neat) υ_{max}: 2978, 1718, 1659, 1644 1617, 1584 1451, 1411, 1367, 1326,1165, 1122, 1073, 1016, 923.

HRMS (ESI^{+}): *m/z* calcd. for $[C_{15}H_{14}F_3O]^+$ $[M+H]^+$: 267.0991. Found: 267.0979.

4'-Methoxy-1,3-dimethyl-[1,1'-biphenyl]-2(1*H*)-one (84)



Synthesised according to **GP7** on a 3 mmol scale using (4-methoxyphenyl)boronic acid, and purified by automated silica gel column chromatography (0-3% EtOAc in cyclohexane) to yield the title compound as a yellow oil (425 mg, 1.86 mmol, 62%).

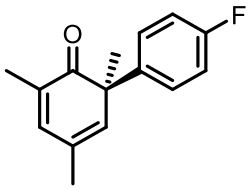
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.22 (2H, d, *J* = 8.9 Hz), 6.88 (1H, app. dp, *J* = 5.9, 1.6 Hz), 6.84 (2H, d, *J* = 8.9 Hz), 6.36 (1H, dq, *J* = 9.5, 0.8 Hz), 6.24 (1H, dd, *J* = 9.5, 5.9 Hz), 3.77 (3H, s), 1.86 (3H, s, br), 1.58 (3H, s).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 203.9, 158.9, 145.6, 138.1, 133.0, 132.6, 127.9, 119.8, 114.2, 55.4, 53.7, 24.2, 15.8.

IR (ATR-IR, neat) υ_{max}: 2933, 2835, 2037, 1982, 1656, 1608, 1580, 1509, 1444, 1365, 1298, 1283, 1249, 1180, 1150, 1123, 1058, 1031, 910.

HRMS (ESI$^+$): *m/z* calcd. for $[C_{15}H_{17}O_2]^+$ $[M+H]^+$: 229.1223. Found: 229.1217.

4'-Fluoro-1,3,5-trimethyl-[1,1'-biphenyl]-2(1*H*)-one (SI-45)



Synthesised according to **GP8** on a 1 mmol scale using 10-(4-fluorophenyl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide and (4-fluoro phenyl)boronic acid, then purified by automated silica gel column chromatography (0-5% EtOAc in cyclohexane). **SI-45** was found to coelute with unreacted mesitol, thus the crude dissolved in DCM (10 mL), washed with aqueous NaOH (2 M, 3 × 5 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield the title compound as a yellow oil (94.6 mg, 0.41 mmol, 41%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.31 – 7.24 (m, 2H), 7.03 – 6.95 (app. tt, *J* = 8.6, 3.2, 2H), 6.79 - 6.78 (m, 1H), 6.04 - 6.03 (m, 1H), 2.02 (d, *J* = 1.5 Hz, 3H), 1.88 (s, 3H), 1.58 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ_C 203.4, 161.9 (d, *J* = 245.7 Hz), 142.4, 139.3, 137.3 (d, *J* = 3.0 Hz), 131.9, 128.4 (d, *J* = 7.9 Hz), 127.3, 115.4 (d, *J* = 21.3 Hz), 52.8, 24.5, 21.1, 15.6.

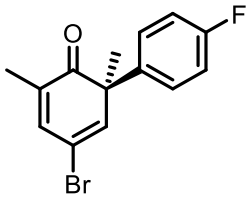
^{19}F NMR (377 MHz, $CDCl_3$): -116.04 (tt, *J* = 8.6, 5.3 Hz).

IR (ATR-IR, neat) υ_{max}: 2921, 2854, 1737, 1651, 1601, 1505, 1451, 1405, 1377, 1336, 1307, 1231, 1163, 1112, 1038, 1014, 979, 938, 925.

HRMS (ESI$^+$): *m*/*z* calcd. for $[C_{15}H_{16}FO]^+$ $[M+H]^+$: 231.1185. Found: 231.1179

The following cyclohexadienones (SI-46 and SI-47) have been synthesized, but not tested in the deoxyamination protocol

5-Bromo-4'-fluoro-1,3-dimethyl-[1,1'-biphenyl]-2(1*H*)-one (SI-46)



Synthesised according to **GP8** on a 1.89 mmol scale using 10-(4-fluorophenyl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide and (4-fluoro phenyl)boronic acid. **SI-46** was found to coelute with unreacted phenol, thus the crude dissolved in 10 mL EtOAc, washed with aqueous NaOH (2 M, 3 × 5 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Crude purified by automated silica gel column chromatography (0-4% Et_2O in cyclohexane) to yield the title compound as a yellow oil (285 mg, 0.97 mmol, 51%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H δ 7.31 – 7.26 (m, 2H), 7.02 (app. tt, *J* = 8.5, 3.3 Hz, 2H), 6.96 – 6.93 (m, 1H), 6.58 (app. dd, *J* = 2.5, 0.7 Hz, 1H), 1.91 (dd, *J* = 1.5, 0.7 Hz, 3H), 1.64 (s br., 3H).

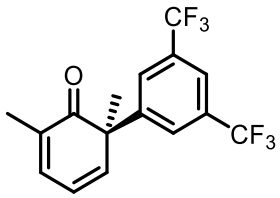
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ_C 200.7, 162.2 (d, *J* = 246.9 Hz), 143.0, 141.5, 135.7 (d, *J* = 3.3 Hz), 134.5, 128.3 (d, *J* = 8.1 Hz), 115.6 (d, *J* = 21.4 Hz), 113.3, 56.0, 24.2, 15.4.

^{19}F NMR (377 MHz, $CDCl_3$): -114.86 (dd, *J* = 8.5, 5.2 Hz).

IR (ATR-IR, neat) υ_{max}: 3044, 2972, 2921, 2871, 2322, 1885, 1663, 1628, 1600, 1582, 1505, 1446, 1405, 1357, 1303, 1231, 1163, 1126, 1014, 946.

HRMS (ESI$^+$): *m*/*z* calcd. for $[C_{14}H_{13}{}^{79}BrFO]^+$ $[M+H]^+$: 295.0134. Found: 295.0113.

1,3-Dimethyl-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2(1*H*)-one (SI-47)



Synthesised according to **GP8** on a 1.54 mmol scale using 10-(4-fluorophenyl)-10*H*-dibenzo[*b*,*e*][1,4]thiabismine 5,5-dioxide and (3,5-bis(trifluoromethyl)phenyl)boronic acid. Purification carried out by automated silica gel column chromatography (0-5% EtOAc in cyclohexane) to yield the title compound as a yellow oil (309 mg, 0.92 mmol, 62%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.78 – 7.71 (m, 3H), 6.97 (dq, *J* = 5.6, 1.8 Hz, 1H), 6.44 – 6.33 (m, 2H), 1.89 (s, br, 3H), 1.67 (s, 3H).

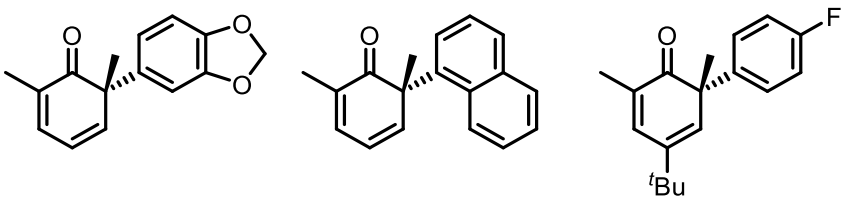
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 201.7, 143.6, 142.9, 138.4, 132.82, 131.7 (q, *J* = 33.3 Hz), 127.3 (q, *J* = 3.4 Hz), 123.3 (q, *J* = 272.6 Hz), 121.4, 121.3 (sept, *J* = 3.8 Hz), 53.9, 24.5, 15.6.

^{19}F NMR (377 MHz, $CDCl_3$): δ_F -62.74.

IR (ATR-IR, neat) υ_{max}: 2927, 1726, 1660, 1645, 1621, 1583, 1451, 1366, 1276, 1172, 1129, 1104, 1059, 1017, 942.

HRMS (ESI^{+}): *m*/*z* calcd. for $[C_{16}H_{13}F_6O]^+$ $[M+H]^+$: 335.0871. Found: 335.0871.

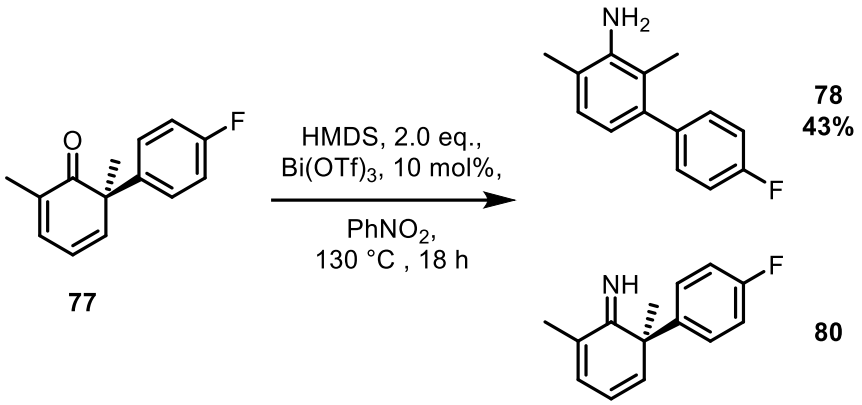
The following compounds were prepared by Dr. Aaron Senior according to GP7:



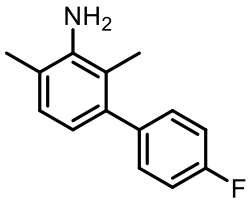
SI-48 **SI-49** **SI-50**

meta-Arylated Aniline Synthesis using SPE

Isolation of 4'-fluoro-2,4-dimethyl-[1,1'-biphenyl]-3-amine (78) and 4'-Fluoro-1,3-dimethyl-[1,1'-biphenyl]-2(1*H*)-imine (80) using Solid Cationic Exchange



An oven dried flask containing **77**, (97.2 mg, 0.45 mmol) and 4,4'-bis(trifluoromethyl)-1,1'-biphenyl (21.70 mg, 0.07 mmol; internal standard) was evacuated and back-filled three times with anhydrous dinitrogen. The solids were dissolved in anhydrous nitrobenzene ($[\mathbf{77}]_0$ = 0.5 M) before HMDS (190 µL, 0.90 mmol; freshly distilled over 4 Å molecular sieves) was added. Bismuth(III) trifluoromethanesulfonate (29.53 mg, 0.05 mmol) was added under a flow of nitrogen before replacing the septum. The reaction was heated to 130 °C and left to stir for 18 h. The resultant solution was diluted with methanol (*ca* 2 mL) before being passed through SCX cartridge, which was then washed with IPA (2 × 10 mL). The products were eluted with ammonia in methanol (2M; 10 mL) and IPA (2 × 10 mL). The eluent was concentrated under reduced pressure to afford a crude mixture of **78** and **80**. These were isolated and purified by automated silica gel column chromatography (0-10% EtOAc in cyclohexane) to afford **80** as a yellow oil (1.60 mg, 7.41 µmol) and **78** as a colourless solid (41.7 mg, 0.19 mmol, 43%).



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.24 (2H, m), 7.07 (2H, app. t, *J* = 8.8 Hz), 6.99 (1H, d, *J* = 7.6 Hz), 6.62 (1H, d, *J* = 7.6 Hz), 3.69 (2H, s), 2.23 (3H, s), 2.06 (3H, s).

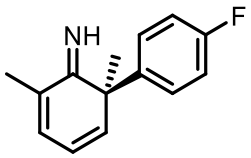
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 161.9 (d, *J* = 245.1 Hz), 143.2, 140.0, 138.7 (d, *J* = 3.3 Hz), 131.1 (d, *J* = 7.8 Hz), 127.6, 121.0, 120.0, 119.3, 114.9 (d, *J* = 21.2 Hz), 17.9, 14.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ_F -116.7 (1F, tt, *J* = 8.8, 5.5 Hz).

IR (ATR-IR, neat) υ_{max}: 3447, 3349, 2935, 2858, 1632, 1596, 1570, 1511, 1484, 1457, 1423, 1398, 1299, 1276, 1212, 1154, 1113, 1090, 1014, 995.

HRMS (ESI$^+$): *m*/*z* calcd. for $[C_{14}H_{15}FN]^+$ $[M+H]^+$: 216.1183. Found: 216.1177.

MP: 100-102 °C.



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.48 (1H, dd, *J* = 4.8, 1.3 Hz), 7.37 (1H, dd, *J* = 7.6, 1.0 Hz), 7.19 (2H, dd, *J* = 8.7, 5.5 Hz), 7.06 (1H, dd, *J* = 7.6, 4.8 Hz), 6.93 (2H, app t, *J* = 8.8 Hz), 4.36 (1H, q, *J* = 7.0 Hz), 2.21 (3H, s), 1.66 (3H, d, *J* = 7.0 Hz).

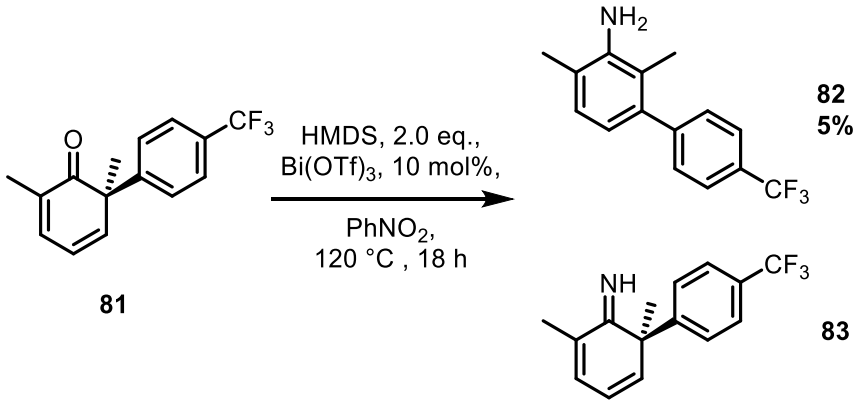
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 161.9, 161.4 (d, *J* = 243.9 Hz), 146.8, 141.0 (d, *J* = 3.1 Hz), 138.1, 131.2, 129.3 (d, *J* = 7.7 Hz), 121.6, 115.2 (d, *J* = 21.2 Hz), 42.8, 21.8, 19.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ_F -117.42 (1F, tt, *J* = 8.7, 5.5 Hz).

HRMS (ESI$^+$): *m*/*z* calcd. for $[C_{14}H_{15}FN]^+$ $[M+H]^+$: 216.1183. Found: 216.1185.

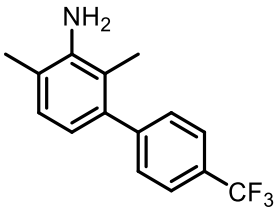
IR (ATR-IR, neat) υ_{max}: 2971, 2928, 1710, 1638, 1603, 1571, 1507, 1491, 1448, 1423, 1367, 1309, 1269, 1219, 1202, 1158, 1092, 1059, 1036, 1013, 982.

Isolation of dimethyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-amine (82) and 1,3-dimethyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-2(1*H*)-imine (83) using Solid Cationic Exchange



An oven dried flask containing **81,** (120 mg, 0.45 mmol) and 1-bromo-4-fluoronaphthalene (304 mg, 1.35 mmol; internal standard) was evacuated and back-filled three times with anhydrous dinitrogen. The solids were dissolved in anhydrous nitrobenzene (2.25 mL) before HMDS (190 µL, 0.90 mmol; freshly distilled over 4 Å molecular sieves) was added on stirring. Bismuth(III) trifluoromethanesulfonate (29.53 mg, 0.05 mmol) was added against a flow of nitrogen before replacing the septum. The reaction was heated to 120 °C and left to stir for 18 h.

The resultant solution was diluted in methanol (*ca* 2 mL) before being passed through SCX cartridge, which was then washed with IPA (2 × 10 mL). The products were eluted with a 1:1 mixture of ammonium hydroxide solution (18.1 M, 10 mL) in methanol (3 × 10 mL), and IPA (2 × 10 mL). The eluent was concentrated under reduced pressure to afford a crude mixture of **82** and **83**. These were isolated and purified by automated silica gel column chromatography (0-10% EtOAc in cyclohexane) to afford **83** as colourless oil (3.81 mg, 14.4 µmol) and **82** as a colourless solid (5.72 mg, 20.0 µmol, 5%).



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.65 (2H, d, *J* = 7.9 Hz, *H-11*), 7.41 (2H, d, *J* = 7.9 Hz, *H-10*), 7.02 (1H, d, *J* = 7.6 Hz, *H-3*), 6.62 (1H, d, *J* = 7.6 Hz, *H-4*), 3.72 (2H, s, *N-H*), 2.25 (3H, s, *H-7*), 2.07 (3H, s, *H-8*).

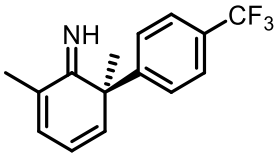
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 146.5, 143.3, 139.6, 129.9, 128.9 (q, *J* = 32.4 Hz), 127.8, 125.1 (q, *J* = 3.8 Hz), 124.53 (q, *J* = 272.2 Hz), 121.6, 119.6, 119.0, 17.9, 14.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ_F -62.32.

IR (ATR-IR, neat) υ_{max}: 3436, 3335, 2931, 2857, 1631, 1614, 1570, 1487, 1458, 1422, 1403, 1322, 1186, 1156, 1101, 1065, 1017, 995.

HRMS (ESI$^+$): *m/z* calcd. for $[C_{15}H_{15}F_3N]^+$ $[M+H]^+$: 266.1151. Found: 266.1148.

MP: 116-118 °C.



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.50 (1H, dd, *J* = 4.8, 1.3 Hz), 7.51 (2H, d, *J* = 8.1 Hz), 7.39 (1H, dq, *J* = 7.6, 0.8 Hz), 7.35 (2H, d, *J* = 8.1 Hz), 7.07 (1H, dd, *J* = 7.6, 4.8 Hz), 4.44 (1H, q, *J* = 7.0 Hz), 2.22 (3H, s), 1.70 (3H, d, *J* = 7.0 Hz).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ_C 161.2, 149.4, 146.9, 138.2, 131.3, 128.5 (q, *J* = 32.3 Hz), 128.2, 125.5 (q, *J* = 3.7 Hz), 124.4 (q, *J* = 271.9 Hz), 121.8, 43.4, 21.5, 19.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ_F -62.36

IR (ATR-IR, neat) υ_{max}: 2930, 1617, 1572, 1447, 1417, 1322, 1161, 1118, 1066, 1017.

HRMS (ESI$^+$): *m/z* calcd. for $[C_{15}H_{15}F_3N]^+$ $[M+H]^+$: 266.1151. Found: 266.1158.

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