Synthesis of 2-bromo-8-methyltetracene and investigation into C-Br functionalisation in tetracene precursors

Jonathan Shine

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Abstract

The research project reported in this thesis describes the synthesis of novel compound 2-bromo-8-methyltetracene. The synthetic method developed in the Woodward laboratory for the straightforward and efficient synthesis of 2 and 2,8-substituted tetracenes is adapted for the difficult Bradsher cyclisation of an electron poor phenylene ring. Treatment with 4 equivalents of neat $TiCl_4$ left to stir at room temperature for 48 hours yielded the compound at 4% yield after purification. This protocol was extended to attempt to synthesise 2,8-dibromotetracene, however this treatment only gave monocyclised product 6-bromo-3-(4-bromobenzyl)-2-naphthaldehyde.

The next stage of the project was the attempted C-Br functionalisation of tetracene precursors, to enable the quick application of structural complexity. The Suzuki, Stille and Buchwald-Hartwig cross coupling reactions were investigated, as well as methylation with a trimethylaluminum adduct. These all led to undesirable results halting any further investigation. Lithium-halogen exchange and electrophilic substitution with dimethyl disulfide did provide the functionalised product in unseparable mixtures with the hydrodebromination product. More promising was the Negishi coupling utilising a highly active palladium *N*-heterocyclic-carbene catalyst. On some occasions the coupling provided the coupling product at high purity and yield. Unfortunately in other cases the reaction would not initiate, leading to the conclusion that this reaction is capricious. An attempt to optimise the procedure was carried out by coupling to the iodinated analogue, however, this failed to yield the product cleanly.

Further work resulted in the successful scale up of the synthesis of parent tetracene and tetracene derivative tetrathiotetracene. Upon alteration of the quenching procedure the synthesis of tetracene was successfully carried out on a 2 g scale. Tetrathiotetracene synthesis was scaled up to 1 g without purity or yield deterioration.

The potentially novel reaction of tetrathiotetracene with nitric acid was then investigated. Initial suggestions of the production of nitrated tetrathiotetracene could not be replicated, only a trace amount of this compound was detected with the major product having different analytical data. Attempts to identify the major product failed to resolve the issue.

Acknowledgements

Firstly I would like to thank my supervisor Professor Simon Woodward for giving me the opportunity to study at the University of Nottingham as well as his encouragement and guidance throughout the project.

Extended thanks to everyone I shared the laboratory with this year, not only for the practical support but for creating a highly friendly and engaging work environment: Alex Kingsbury, Antonio Pedrina, Björk Tyril, Ellen Nichols, Evie Newby, John Ritchie, Dr Liam Ball, Lorenzo Maggi, Maria Jesus Duran-Pena, Mark Jurrat, Dr Mary Robert Garrett, Miriam Ackermann, Mohammed Abid, Mustafa Aljumaili, Ryan Nouch, Teresina Ambrosio and Thomas Barber.

I am grateful to all the technical staff in the Department of Chemistry for enabling my research to continue smoothly.

Not least, I would like to give my extended thanks to my parents and brother for the encouragement and support which enabled me to carry out this masters degree in the first place.

Abbreviations

This thesis uses the standard abbreviations documented by the American Chemical Society[1] together with the following abbreviations:

DABAL-Me_3	Bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane adduct
dba	Dibenzylideneacetone
DMAD	Dimethyl acetylenedicarboxylate
DMDS	Dimethyl disulfide
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
IPr	Di*iso*propyl-phenylimidazolium
NMI	*N*-methylimidazole
OFET	Organic field effect transistor
OLED	Organic light emitting diode
PAH	Polyaromatic hydrocarbon
PEPPSI	Pyridine-enhanced precatalyst preparation, stabilisation and initiation
SPhos	2-dicyclohexylphosphino-2,6-dimethoxybiphenyl
TE	Thermoelectric
TEA	Triethylamine
TTT	Tetrathiotetracene
XPhos	2-Dicyclohexylphosphino-2',4',6'-tri*iso*propylbiphenyl

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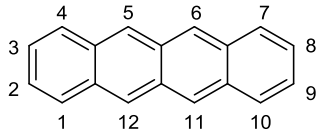
Introduction

This thesis discusses the development of a new method for the synthesis of 2-bromo-8-methyltetracene, the attempted C-Br functionalisation in the precursor stage of this molecule's synthesis and the scale up of tetracene and tetrathiotetracene synthesis. For this reason a review of the application, substituent effect and synthesis of tetracene derivatives over the period of 1934 to September 2017 is given in the following sections. After this an overview of the use of cross coupling reactions in the synthesis of tetracenes will be given, followed by an overview of the application and synthesis of tetrathiotetracene.

1.1 Organic electronics and tetracene

Tetracene (**1**) is a polyaromatic hydrocarbon (PAH) and a member of the acene series containing four laterally fused benzene rings (Figure 1). Its electronic structure (planar with an extended π system) gives rise to a variety of physical properties useful in a range of organic electronics applications. Most commonly, acenes are used in organic field effect transistors (OFETs), organic light emitting diodes (OLEDs) and solar cell devices.[2]



1

Figure 1 Structure of parent tetracene **1**

The field of organic electronics started in 1977 with the discovery that polyacetylene is a highly conducting polymer.[3] Since then there has been much attention to π-conjugated systems for use in a wide variety of electronic devices. Organic materials offer the distinct advantages of being lighter, more flexible and easier to process, as well as not using rare, highly priced metals that are commonly used in inorganic electronic materials. They also offer a wide range of properties that can be finely tuned by introducing variations into their molecular structure.[4] Some key challenges still remain in the utilisation of acenes in organic electronics, namely their low solubility and stability, as well as the lack of knowledge of how structural features affect the resulting electronic properties.[5]

Electronic properties of organic electronic materials depend primarily on the energy of the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO). Molecules with low HOMO/LUMO gaps can act as both electron donors and acceptors, called electrochemically amphoteric compounds; this is the basic principle of organic electronic devices. PAHs achieve low HOMO/LUMO gap through extended π-conjugation, making them one of the most highly desired and widely researched organic molecules for organic electronic purposes.[6]

Another important property of acenes that makes them useful in organic electronics is their highly crystalline structure. The packing motif is important because the interactions between molecules is crucial to carrying of electrical charge.[2] Reorganisation energy is another important factor in organic electronics' design. This is the energy loss when a charge carrier passes through the molecule and is dependent on the amount of conjugation and packing of the molecules. The smaller this value, the higher the mobility.[5]

A disadvantage of utilising acenes in organic electronic devices is that their preparation requires somewhat difficult techniques: sublimation is required to produce highly ordered thin films of extreme purity. It is important to control defects in the material as well as the overall structural quality during this process.[7] Another issue is that the strong intermolecular forces in acenes leads to poor solubility. This can be counteracted by the introduction of bulky substituents to partially disrupt the intermolecular interactions.[2] Solids made from these low molecular weight organic molecules are also rather soft and fragile which is overcome by deposition of the thin organic films onto solid substrates such as silicon dioxide or organic polymers.[7]

Lower members of the acene family, from benzene to anthracene, can be extracted from coal, however higher members must be obtained through multistep synthesis.[6] Only unsubstituted acenes up to heptacene have been isolated in bulk, with decacene being the largest detected in trace amounts.[8] The difficulties of synthesis of higher acenes partially arise from their instability to light (due to narrow energy gaps) and oxygen (due to high HOMO energy level), as well as their low solubility.[5] Tetracene is a good illustration of the trade-off between stability and device performance, being more active than anthracene due to higher intermolecular overlap of the π-orbitals[5], but decomposing at a significantly slower rate than pentacene.[2]

1.2 Substitution of acenes

There are two common packing motifs that acenes adopt in solid state: the herringbone structure, which can have two variations depending on the strength of face-to-face π–π interactions (a + b), and the lamellar motif (c) (Figure 2). All un-functionalised acenes adopt an edge-to-face herringbone arrangement where molecules have predominantly edge-to-face interactions with other molecules. This arises from a balance between π–π interactions and electrostatic repulsion, which results in the herringbone angle. The lamellar motif, where molecules are stacked with some degree of displacement to each other, is adopted when face-to-face π–π interactions are strong. Interactions with adjacent stacks yields two dimensional electronic coupling. In the lamellar motif, the strong intermolecular π–π overlap and the shorter distance of travel leads to the most efficient electronic transportation. Hence much research is focused on molecular design to obtain lamellar packing.[2,5]

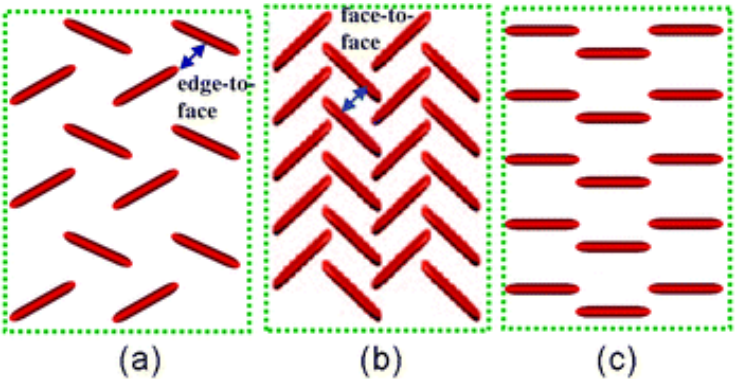


Figure 2 Three packing motifs of acenes: (a) herringbone packing motif without face-to-face π–π overlap to adjacent molecules, (b) herringbone packing motif with face-to-face π–π overlap to adjacent molecules and (c) lamellar stacking motif[9]

This exemplifies the reasons that much research is carried out on the effect of adding different substitutions to acenes. Substitution on smaller acenes are usually conjugated units used to extend the π system and on larger acenes substitution aims to improve their solubility, stability and molecular packing motif.

Lamellar packing can be induced by substitution at the *peri*-positions of acenes (Figure 3), these are thought to prevent edge-to-face interactions and improve face-to-face interactions. *Peri*-positions are also active centers of acenes, so are more easily functionalised. Substitutions include introduction of polarity, increase C/H ratio or addition of heteroatoms which can create hydrogen, halogen-halogen or chalcogen-chalcogen bonds.[5] For example, with the introduction of polar groups, such as in the dione **2** (Figure 4), a lamellar stacking is adopted due to the electronic interactions.[10] However, *peri*-substituted tetracene derivatives have not been studied extensively, substituted pentacenes are more widely used.[5]

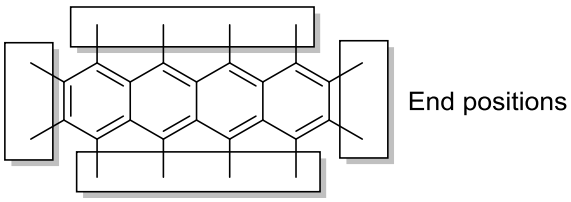
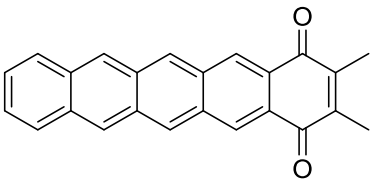


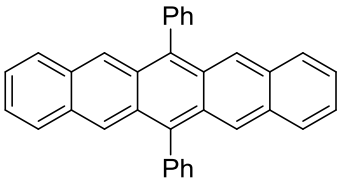
Figure 3 Diagram indicating end and *peri*-/side-positions of acenes[5]



2

Figure 4 Structure of tetracene derivative **2**

It has been found that introduction of phenyl groups to pentacene (**3**) (Figure 5) block herringbone packing and create a cage like superstructure with acene cores arranged parallel but with the long axis of neighbouring acenes at a right angle to each other (Figure 6). The packing is dictated through interaction of the C-H's of pendant phenyl rings and carbons on the acene backbone [(phenyl)edge-to-(acene)face interactions]. Alkyl or aryl substitutions in *peri*-positions can be used to not only change packing motifs but improve the stability and solubility of molecules. Stability is increased due to the removal of active *peri*-positions.[11]



3

Figure 5 Structure of aryl substituted pentacene **3**[11]

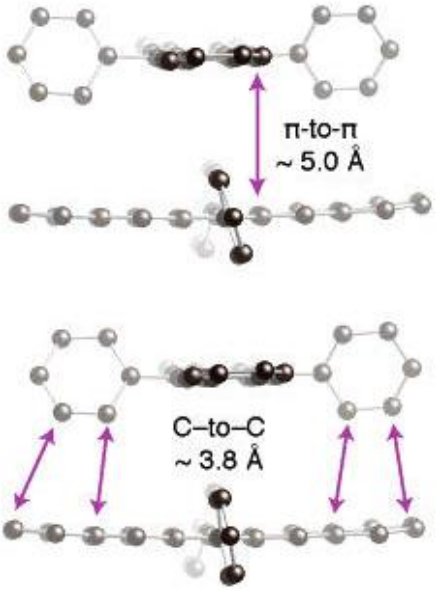
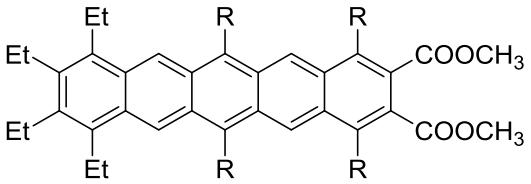


Figure 6 Crystal structure of **3** showing a cage superstructure of co-facial acene faces with the long axis of neighbouring acenes at a right angle to each other. Magenta arrows show the close contacts between acene faces and pendent aromatic groups[11]

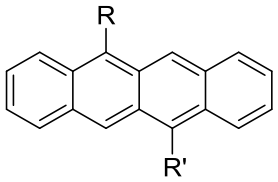
An example of the effect of alkyl substituents on the packing motif was shown by Takahashi *et al.*[12] when examining the crystal structure of molecules **4a** and **4b** (Figure 7). Upon changing of the R substituents from ethyl to propyl the packing motif changed from herringbone to lamellar. Anthony *et al.* hypothesised that if the length of the substituents was half the length of the acene core then the packing motif would become lamellar, otherwise a herringbone or slipped π-stacking motif is adopted.[5,13]



4a R = Ethyl
4b R = Propyl

Figure 7 Structure of *peri*-alkylated pentacenes **4a** and **4b**[12]

Introduction of halogen groups to aromatic hydrocarbons has been shown to induce changes to the packing motif through halogen-halogen interactions.[14] The packing motifs of a range of 5- and 5,11-substituted halogenated tetracenes were investigated by Moon *et al.*[15] (Figure 8). Monosubstituted tetracenes, **5a** and **5b**, had a herringbone motif whereas disubstituted tetracenes, **5c** and **5d**, were arranged in a π stacking motif. 5,11-substituted tetracenes showed up to 3 orders of magnitude higher electron mobility than 5-substituted tetracenes as a result of this adopted structure.[15]



R = Cl, R' = H, **5a**
R = Br, R' = H, **5b**
R = Cl, R' = Cl, **5c**
R = Br, R' = Br, **5d**

Figure 8 Range of *peri*-halogenated tetracenes synthesised by Moon *et al.*[15]

Substitution at the end-position (Figure 3) of acenes are used to extend the π system, increase solubility and/or increase planarity which in turn increases crystallinity. Aryl and alkyl substitution at end positions doesn't have a clear effect on alteration of π-π interactions and the packing motif, or the stability of the acenes.[5] It has been shown that the electron mobility decreased with an increase in alkyl length of end-substituted pentacenes.[16]

Substitution of electron-withdrawing groups (such as halogen, cyano or trifluromethyl groups) at end-positions of pentacenes (Figure 9) has been used to improve their stability, through the lowering of the HOMO energy level and the reactivity of the acene core.[5] The highest performance of these molecules was displayed by **6c** which was proven to be stable to air and light for 80 days.[17]

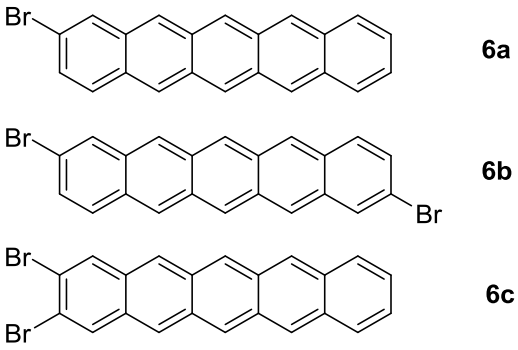


Figure 9 Example of 3 synthesised end-brominated pentacenes, **6a-c**[17]

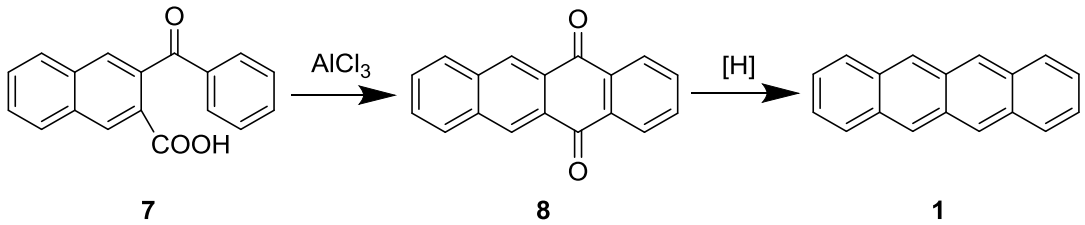
Like their *peri*-substituted counterparts, end-substituted tetracenes have rarely been reported compared to their pentacene analogues, this is likely due to the inactivity of these positions and their unknown effect on packing motif.[5]

1.3 Synthesise of acenes

Due to the lack of terrestrial sources of acenes higher than anthracene and the high utility of the acene family, a variety of synthetic methods have been developed for the preparation of these molecules.[18]

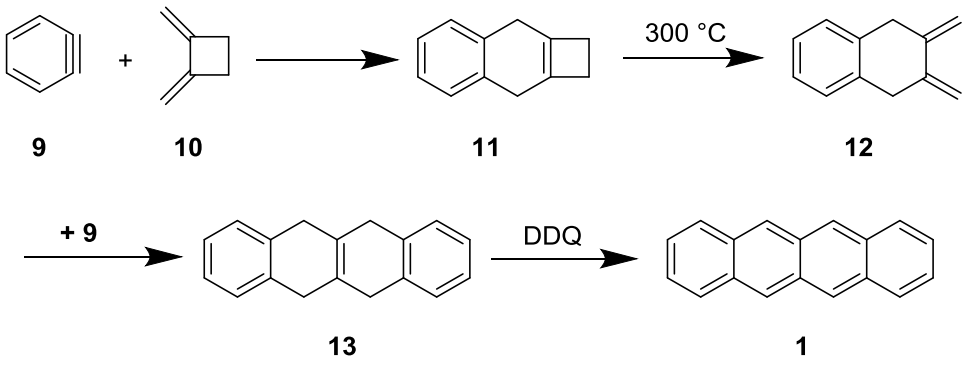
1.3.1 Synthesis of parent tetracene (1)

Given below are some key examples of the synthesis of parent tetracene **1**. For example **1** can be synthesised by the intramolecular Friedel-Crafts reaction of 3-benzoyl-2-naphthoic acid **7**, followed by the reduction of quinone **8** (Scheme 1).[19–21]



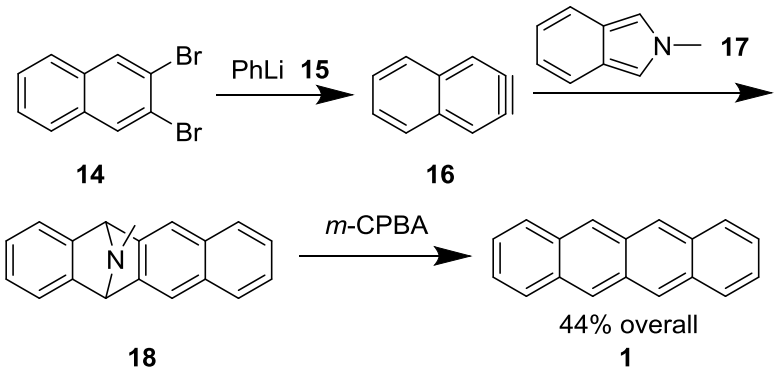
Scheme 1 [19–21]

A very commonly employed reaction in tetracene synthesis is the Diels-Alder reaction. A synthesis reported in 1978 by Thummel *et al.* utilises this reaction to achifeve the synthesis of **1** and alkyl derivatives of acenes (Scheme 2). The Diels-Alder reaction of 1,2-dimethylenecyclobutane **10** with benzyne **9** produces 1,2,3,8-tetrahydrocyclobuta[b]naphthalene **11** at a low (25%) yield. Pyrolysis of **11** at 300 °C produces diene **12**. A second Diels-Alder reaction with another molecule of **9** yields 5,6,11,12-tetrahydrotetracene **13**, which under oxidation by DDQ, is transformed into **1**.[22]



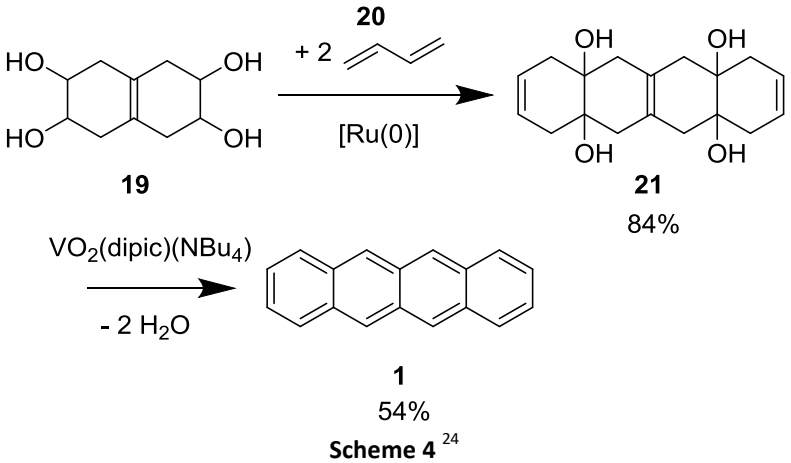
Scheme 2 [22]

Another employment of the Diels-Alder reaction of an aryne was developed by LeHoullier and Gribble (Scheme 3).[23] Treatment of 2,3-dibromonaphthalene **14** with phenyllithium **15** provides aryne **16**. Reaction of 2-methyl-2H-isoindole **17** with **16** produces naphthacenimine **18**. Oxidation with *m*-CPBA affords **1** in an overall yield of 44%.



Scheme 3 [23]

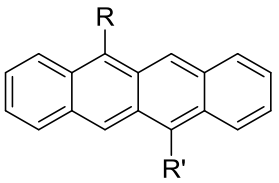
In 2014 a bidirectional ruthenium catalysed diol–diene [4+2] cycloaddition and subsequent aromatisation was used to synthesise **1** (Scheme 4).[24] Two equivalents of diene **20** added to tetraol **19** in the presence of the ruthenium catalyst provides triene **21** in 84% yield. Double diol dehydration and aerobic dehydrogenation aromatises **21** to parent tetracene **1**, which occurs in the presence of a dioxovanadium catalyst, in 51% yield.



Scheme 4 [24]

1.3.2 Synthesis of halogenated tetracenes

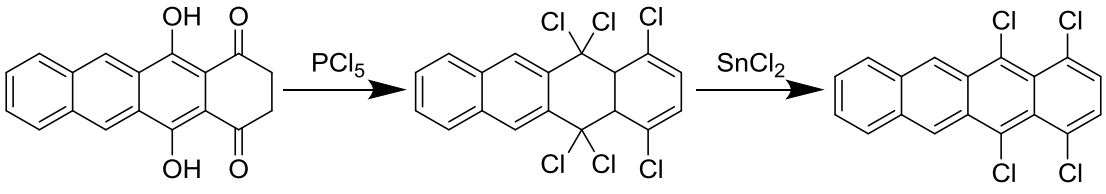
The study of Moon *et al.*[15] into the packing motif of a range of halogenated tetracenes has already been discussed (Figure 8). These tetracenes were synthesised by the direct reaction of **1** with $CuCl_2$ in chlorobenzene for **5a** and **5c**, *N*-bromosuccinimide (NBS) in DMF for **5b** and $CuBr_2$ in bromobenzene to synthesise **5d**.[15]



R = Cl, R' = H, **5a**
R = Br, R' = H, **5b**
R = Cl, R' = Cl, **5c**
R = Br, R' = Br, **5d**

Figure 8 Range of *peri*-halogenated tetracenes synthesised by Moon *et al.*[15]

Some halogenated tetracenes cannot be created from **1** and are the result of multistep synthesis, for example, the halogenated tetracene derivative 1,4,5,12-tetrachlorotetracene **24** (Scheme 5). Treatment of **22** with PCl_5 provides hexachloro-tetrahydro-tetracene **23** at 49% yield. Dechlorination with $SnCl_2$ aromatises the **23** to **24** at 39% yield.[25]

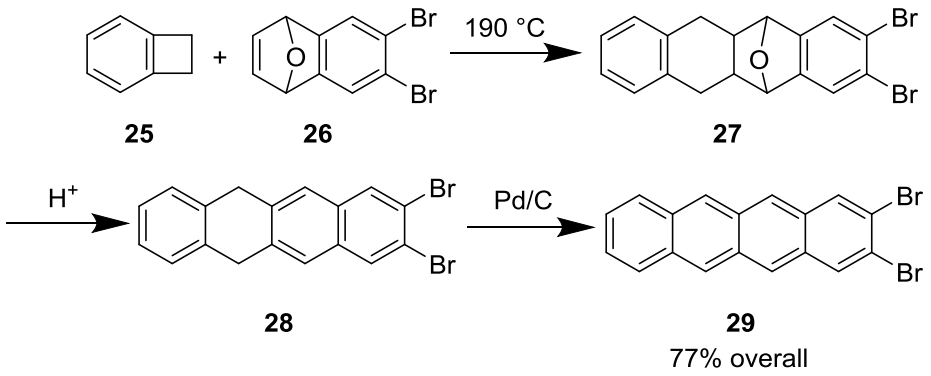


22 **23** 49% **24** 39%

Scheme 5 [25]

The Diels-Alder reaction has also been used to synthesise halogenated tetracenes, Luo and Hart synthesised 2,3-dibromotetracene **29** with this reaction (Scheme 6). Pyrolysis of **25** and subsequent reaction with dienophile **26** produces **27**.

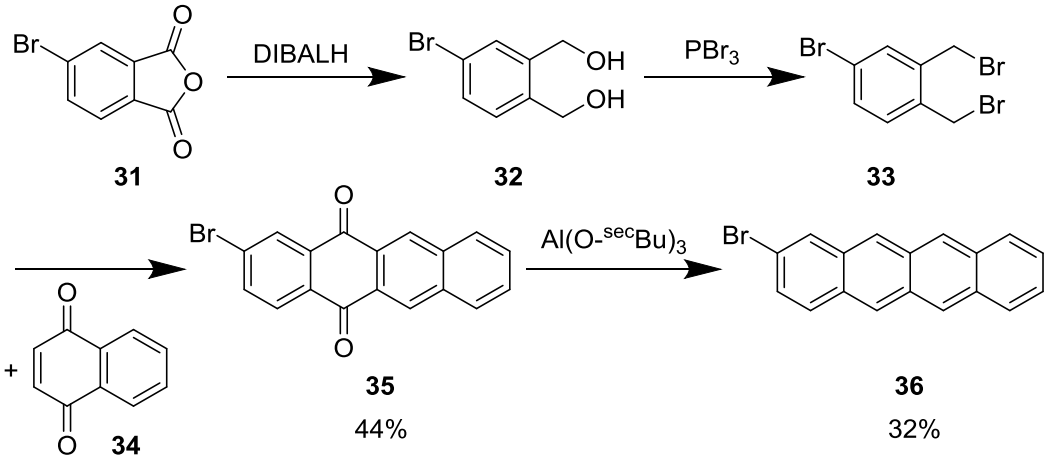
Dehydration with acid removes the bicyclic ring and dehydrogenation over Pd/C synthesises 2,3-dibromotetracene **29**. The total yield of this reaction was 77%.[26]



Scheme 6 [26]

Using the same methodology as above (Scheme 6), 2,8-dibromotetracene **30** was synthesised.[27]

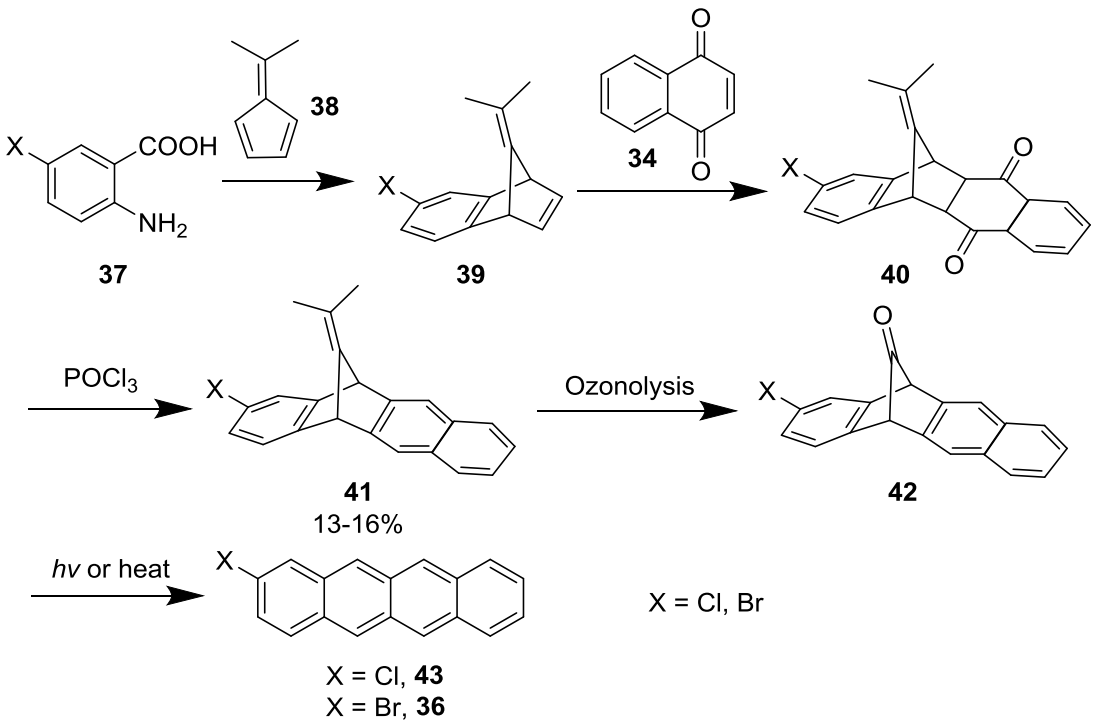
2-Halogenated tetracenes have been prepared from tetracene quinone derivatives. Halogenated tetracene quinones can be prepared using a variety of synthetic techniques such as an analogous reaction to Scheme 1[28] or a Diels-Alder reaction (Scheme 7).[29] Reduction of **31** with DIBALH provides **32**, which is brominated by PBr_3 to 4-bromo-1,2-bis(bromomethyl)benzene **33**. Quinone derivative **35** is formed from the reaction of **33** with naphthalene-1,4-dione **34** in 44% yield. Treatment of **35** with aluminium alkoxide $Al(O\text{-}^{sec}Bu)_3$ affords 2-bromotetracene **36** in 32% yield.



Scheme 7 [29]

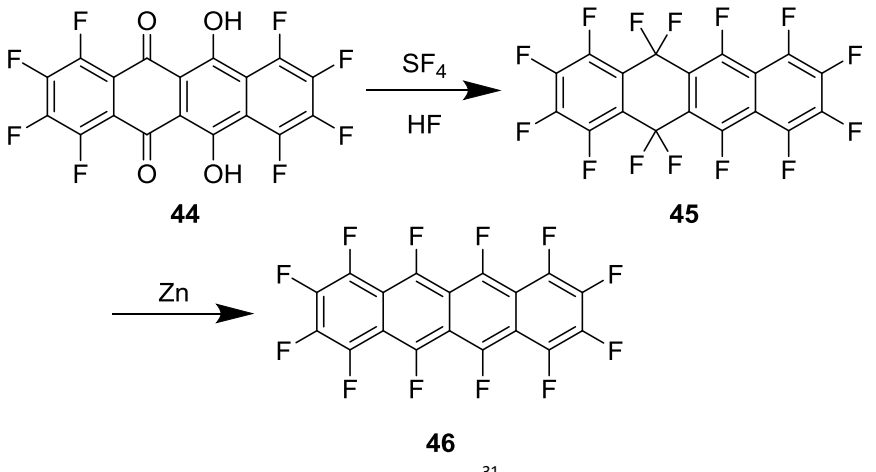
Another method for the synthesis of 2-halogenated tetracenes was developed by Watanabe *et al.* (Scheme 8).[30] This is a multistep synthesis which utilises the *in situ* generation of an aryne from **37** and the Diels–Alder reaction with 6,6-dimethylfulvene **38**. Retro Diels-Alder with naphthalene-1,4-dione **34** affords diketone **40**, which is aromatised to **41** using $POCl_3$. Monoketone **42** is generated by ozonolysis of **41**. Conversion to **36**/**43** occurs thermally or photochemically. Like

many of the syntheses described, at least one of these steps occurs at low yields, for example, the 3 step conversion of **40** to **41** occurs in 13–16% yield.[30]



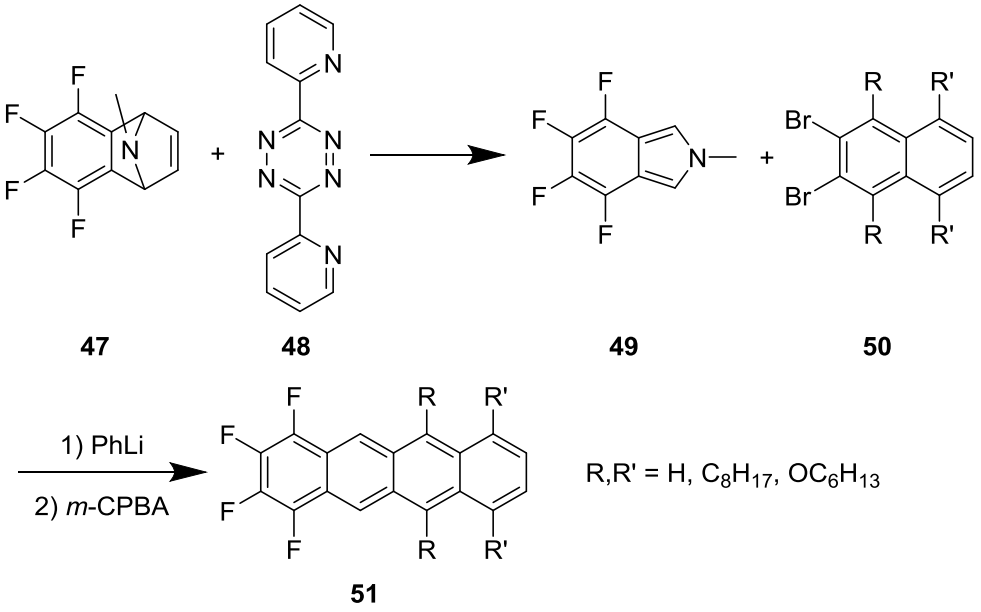
Scheme 8 [30]

Fluorinated tetracenes are of interest to the study of organic electronics because of the highly electron withdrawing nature of fluorine atoms. Perfluorotetracene **46** has been synthesised from octo-fluorinated quinone derivative **44** (Scheme 9).[31] Fluorination of **44** by SF_4 in the presence of HF affords perfluorotetrahydrotetracene **45**. Defluorination by Zn gives **46**, which shows very close cofacial packing because of electrostatic interaction between the electropositive acene core and electronegative fluorine atoms.[19]



Scheme 9 [31]

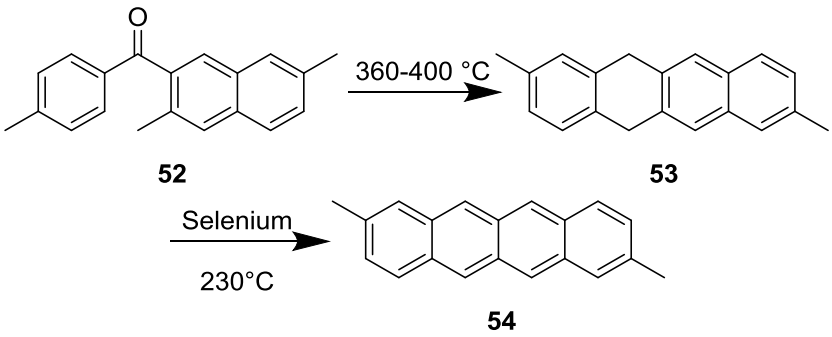
A series of partially fluorinated alkyl/alkoxy-functionalised tetracene derivatives **51** were synthesised by Chen *et al.* in 2005 (Scheme 10).[32] The Diels-Alder reaction of **47** with 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine **48** and subsequent thermally allowed electrocyclic fragmentation affords n-methyl-4,5,6,7-tetrafluoroisoindole **49.** The procedure then follows the reaction developed by LeHoullier and Gribble (Scheme 3)[23] by formation of aryne from **50** and a Diels-Alder reaction with **49**. Deamination by treatment with *m*-CPBA synthesises tetracene derivatives **51**. These derivatives stack in a slipped cofacial motif, substitution of long alkyl/alkoxy groups are used to increase the solubility in organic solvents.



Scheme 10 [32]

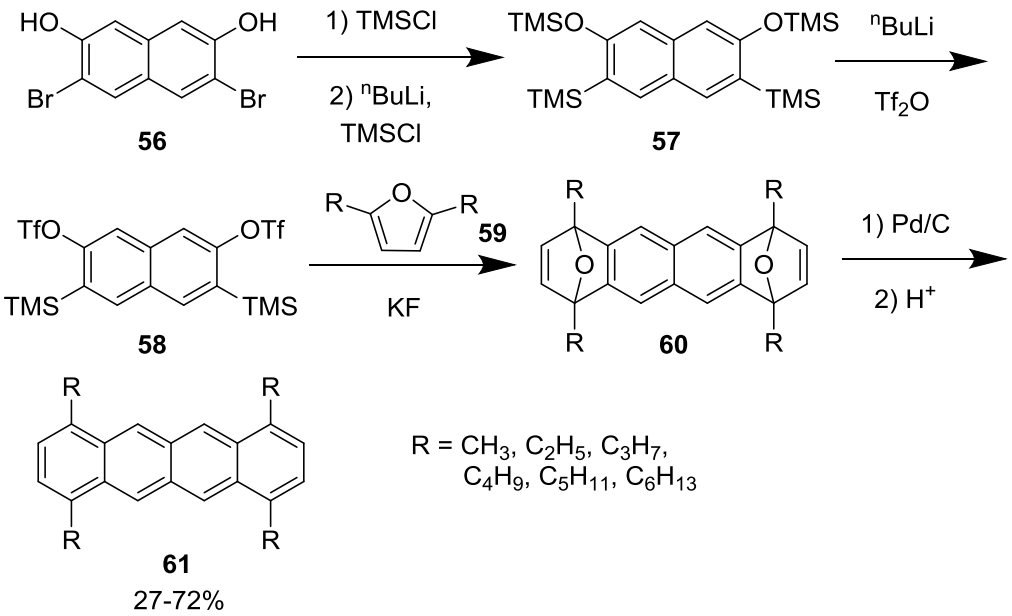
1.3.3 Synthesis of alkylated tetracenes

The only synthesis of 2,8-dimethyltetracene **54**[33] and 2-methyltetracene **55**[34], were reported by Coulson in 1934 and 1935 and make use of the Elbs reaction. Both syntheses suffered from low yields and chemoselectivity, showing the need for the new synthetic method reported. Synthesis of **54** is described as a representative example (Scheme 11): on pyrolysis of ketone derivative **52**, both dihydrotetracene **53** and **54** can be isolated. Dehydrogenation of **53** in the presence of selenium causes a conversion to **54**. Original preparation of **52** occurs from the condensation reaction of 3,7-dimethyl-2-naphthoyl chloride and toluene, in the presence of aluminium chloride.



Scheme 11 [33]

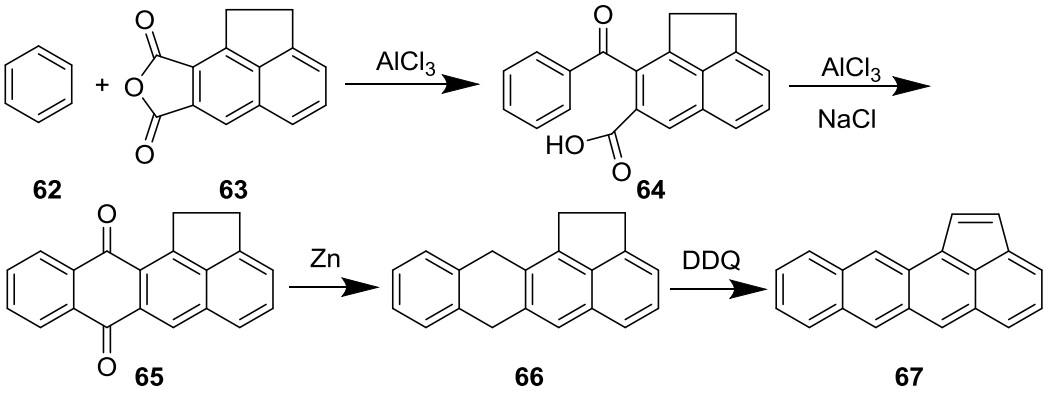
Synthesis of 1,4,7,10-tetraalkyltetracenes **61** was described by Gribble *et al.*[35] utilising bidirectional synthesis and was later expanded to produce a higher yield with longer alkyl group derivatives by Kitamura *et al.* (Scheme 12).[36] Like previous reactions described, this process utilises the generation of an aryne and subsequent Diels-Alder reaction. Bis(aryne) precursor **58** is produced from 3,6-dibromo-2,7-dihydroxynaphthalene **56**. Reaction of **56** with trimethylsilyl chloride (TMSCl) and subsequent reaction with ^{n}BuLi and TMSCl again, yields trimethylsilyl ether **57**. Further treatment with ^{n}BuLi, then trifluoromethanesulfonic anhydride (Tf_2O) affords said bis(aryne) precursor **58**. The bis(aryne) is produced via addition of KF, which then undergoes two Diels-Alder reactions with 2 equivalents of corresponding furan **59** to give **60**. Hydrogenation with Pd/C and then addition of acid gives 1,4,7,10-tetraalkyltetracenes **61** in 27–72% yields.[19]



Scheme 12 [35,36]

The synthesis of alkyl tetracene derivatives such as **67** are of interest due to their predicted high level of biological activity.[19] The synthesis of **67** and similar derivatives was derived by Sangaiah and Gold in 1986 (Scheme 13).[37] Anhydride **63** was synthesised in 6 steps from 1-bromoindane. A Friedel-Crafts reaction of **63** with

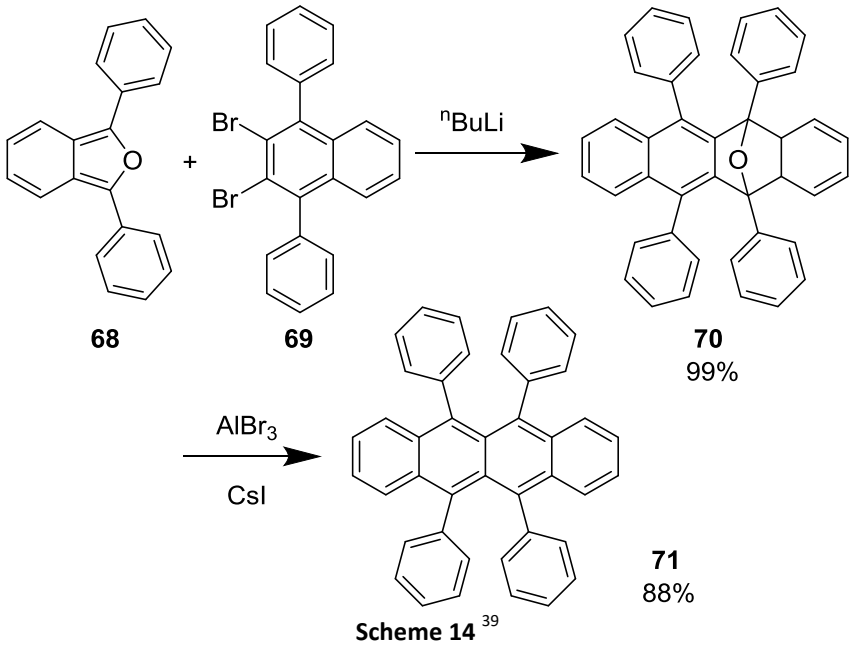
benzene **62** and further intramolecular Friedel-Crafts reaction yields quinone **65**. Reduction of the ketone groups by Zn provides **66**, which under oxidative dehydrogenation produces **67**.



Scheme 13 [37]

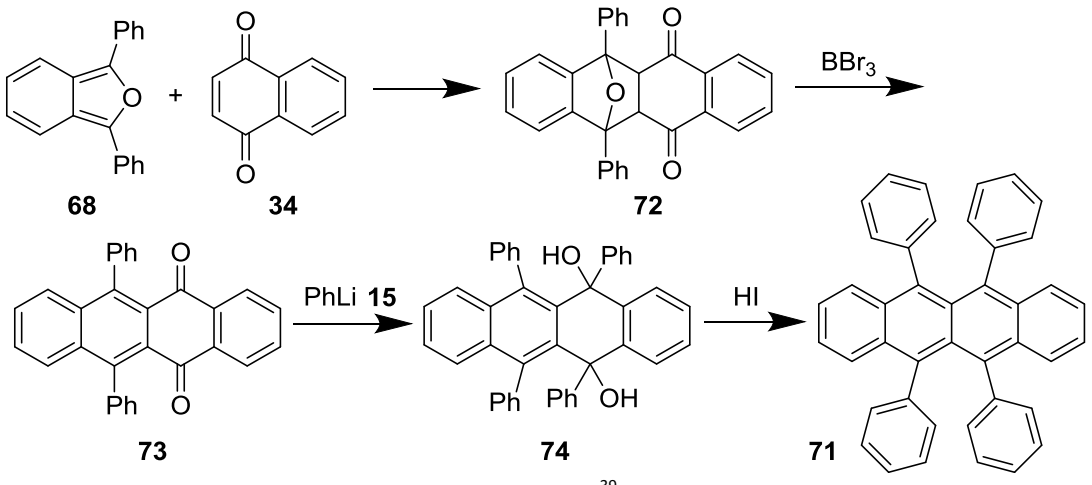
1.3.4 Synthesis of arylated tetracenes

Arylated tetracene 5,6,11,12-tetraphenyltetracene **71**, commonly known as rubrene, is of particular interest because thin platelets of **71** single crystals have been shown to have the highest carrier mobility of any organic semiconductor (20–40 $cm^2 Vs^{-1}$).[38] Dodge *et al.* offered two general synthetic routes to 5,6,11,12-tetraaryltetracene derivatives (Scheme 14 and Scheme 15).[39] The first (Scheme 14) involves the treatment of **69** with ^{n}BuLi to give an aryne, this performs a Diels-Alder reaction with aryl-functionalized furan **68** to gives the oxo-bridged adduct **70** in 99% yield. Aromatisation of **70** is carried out by addition of $AlBr_3$ and CsI to provide **71** in 88% yield.[39]



Scheme 14 [39]

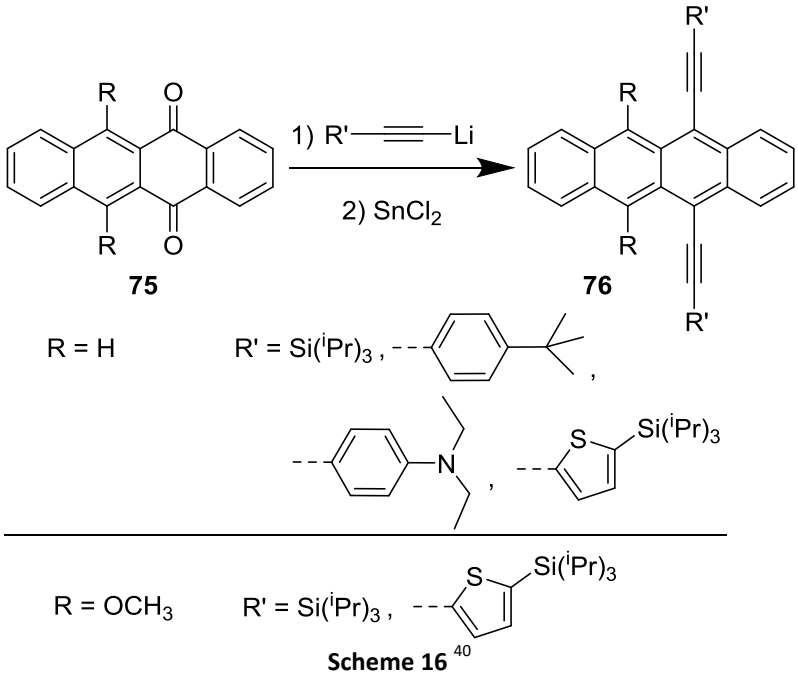
The second synthetic route (Scheme 15) to **71** involves the initial Diels-Alder reaction of furan **68** with dienophile naphthalene-1,4-dione **34** to give **72**. Treatment with BBr_3 causes dehydration to give **73.** The next step is the nucleophilic addition of two equivalents of phenyllithium **15** to give diol **74**. HI-promoted aromatisation gives **71**. Other 5,6,11,12-tetraaryltetracene derivatives were synthesised using these two methods, the latter approach (Scheme 15) being useful for the synthesis of asymmetrically substituted rubrenes.[39]



Scheme 15 [39]

1.3.5 Synthesis of alkynyl tetracenes

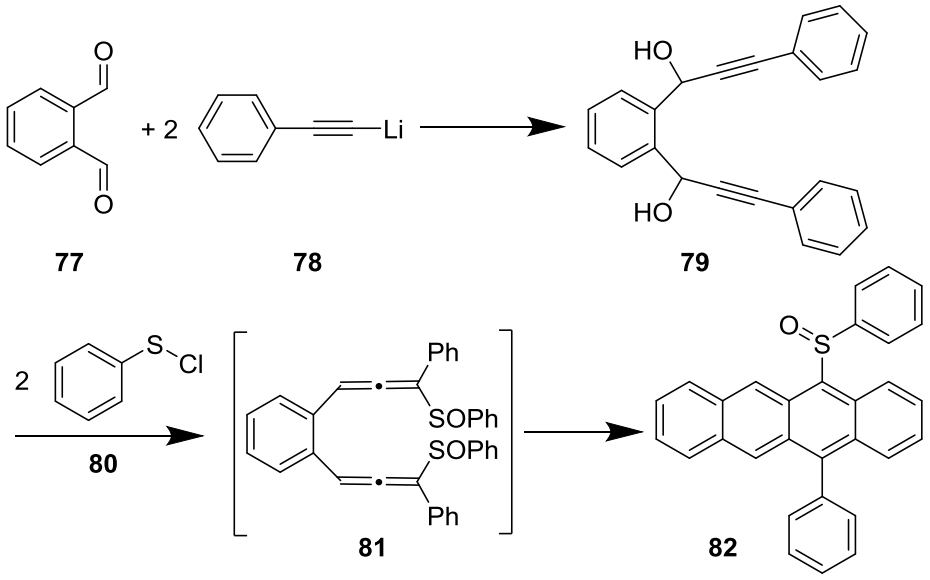
Anthony's group worked out a way to synthesise alkynyl functionalised tetracene derivatives **76** from the corresponding quinones **75** (Scheme 16).[40] Two steps effected this transformation, nucleophilic substitution with an alkynyl lithium reagent and acid assisted $SnCl_2$ reduction.



Scheme 16 [40]

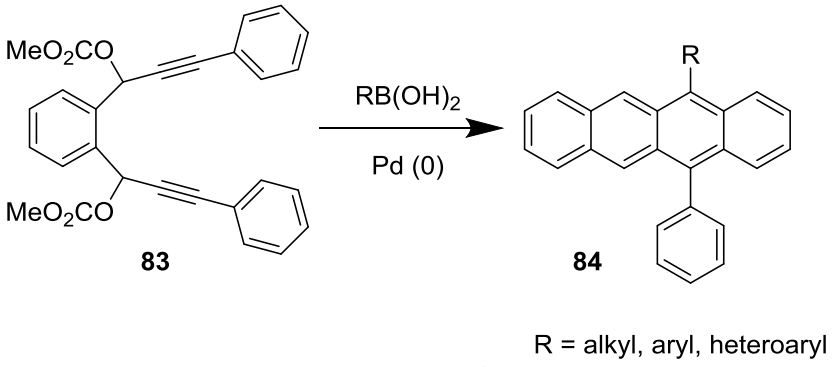
1.3.6 Synthesis of tetracenes via benzene-bridged diallene cascades

In 2007 Lin and Lin introduced the synthesis of tetracenes via the electrocyclic cascade of 1,2-bis-allenes such as **81** (Scheme 17).[41] Reaction of dialdehyde **77** with 2 equivalents of (phenylethynyl)lithium **78** provides **79**. Following addition of phenylsulfenylchloride **80**, 2,3-sigmatropic rearrangement causes formation of **81**. Its transformation to tetracene sulfoxide **82** occurs by an electrocyclic cascade, with elimination of PhSOH. This approach has since been expanded to other tetracene derivates such as 12-aryl-5-(methylthiocarbonylthio)tetracenes.[42]



Scheme 17 [41]

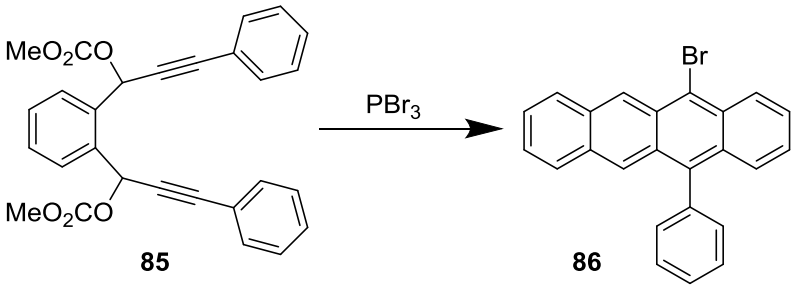
This methodology was expanded on by Chen *et al.* in 2012 to enable the synthesis of alkyl or aryl substituted tetracenes and pentacenes **84** (Scheme 18).[43] The method uses a palladium catalysed cascade reaction of **83** mediated by organoboronic acids.



Scheme 18 [43]

The same group have very recently used this method for the synthesis of 5-bromo-12-phenyltetracene **86** (Scheme 19).[44] Treatment of **85** with a suitable brominating reagent initiated the cascade to produce **86**. The reaction has the advantages of

easily accessible starting materials, high efficiency and wide functional group compatibility. Cross coupling was then demonstrated on **86** (Section 1.5.2).

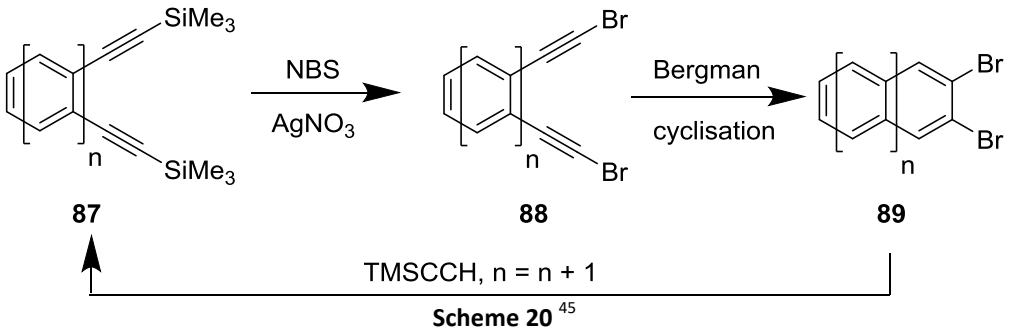


Scheme 19 [44]

1.3.7 Iterative synthesis of acenes

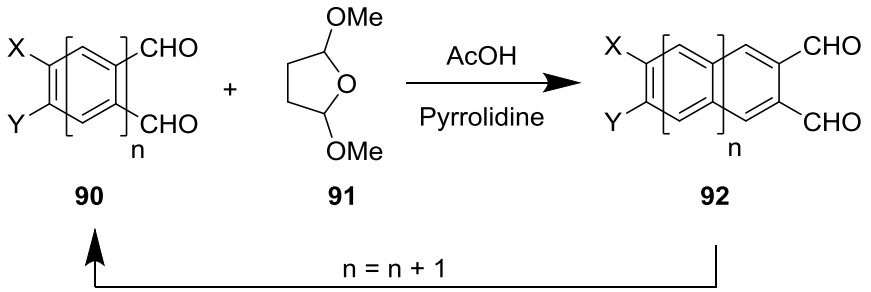
Due to the repeating unit nature of acenes, iterative synthesis is a promising route for the construction of these molecules. Iterative synthesis is the stepwise creation of a molecule by repeated successions of reactions which add a repeating unit.

An example of this methodology was developed by Bowles and Anthony in 2000 (Scheme 20).[45] Silver catalysed desilylative halogenation of easily prepared diyne **87** produces the corresponding brominated derivative **88**. Cycloaromatisation of **88** leads to 2,3-dibromoarenes **89** in good yield. Alkynylation with trimethylsilylacetylene by Sonogashira coupling regenerates **87**, homoelongated by one aromatic ring. The iterative synthesis can be terminated by a variety of ways, such as desilylation of **87** with sodium methoxide and cycloaromatisation of unsubstituted diyne to an acene hydrocarbon. This synthetic method encountered problems in the synthesis of acenes higher than tetracene due to the increasing insolubility of the intermediates.[19,45]



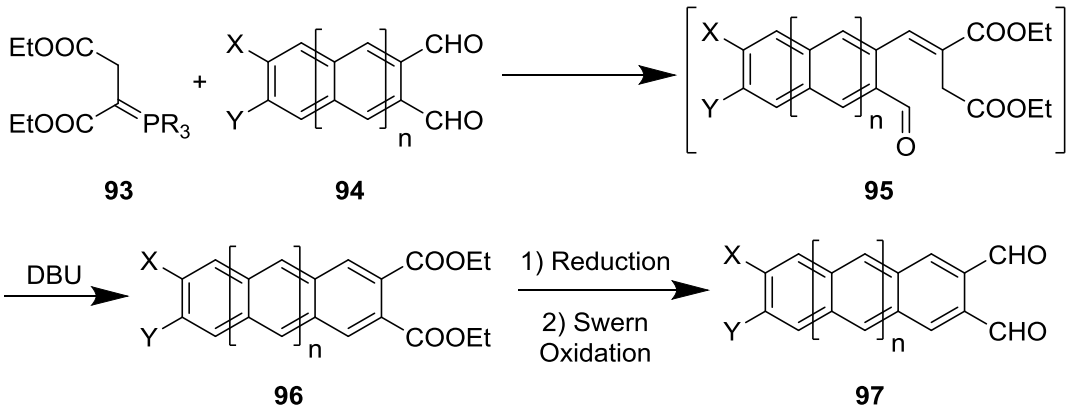
Scheme 20 [45]

An iterative bis-aldol approach to acenes was reported by Mallouli and Lepage in 1980 (Scheme 21).[46] In this methodology dialdehyde **90** was reacted with 2,5-dimethoxytetrahydrofuran **91** to give a dialdehyde with one more aromatic ring **92**. It can then react further without the need for an activation step. The issue with this methodology was the poor chemoselectivity. Since the starting materials, intermediate and products are all dialdehydes, the aldol reaction can occur at any of these stages in an uncontrollable manner. Another issue is the polar solvent system which is incompatible with the synthesis of poorly soluble acenes.[4]



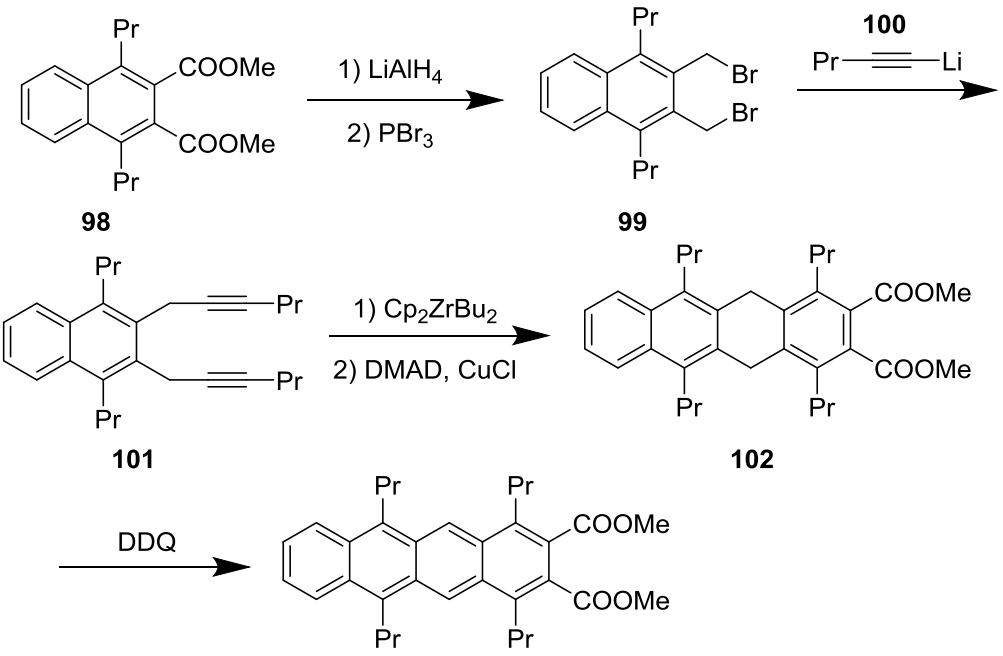
Scheme 21 [46]

An upgraded version of this procedure was developed by Lin *et al.*, which enables control of the synthesis of acenes using protected dialdehydes (Scheme 22).[4] Starting material, 2-(trialkyl-5-phosphanylidene)-succinic acid diester **93** was generated from the reaction of dialkyl maleate and trialkyl phosphine. Wittig reaction of **93** with dialdehyde **94** formed the intermediate diester **95**. Intermediate **95** then undergoes a base catalysed Knoevenagel condensation to masked dialdehyde **96**. Conversion back to a dialdehyde **97** occurs via reduction with diisobutylaluminum hydride (DIBALH) and the Swern oxidation, enabling further rounds of elongation. Acenes up to heptacene have been made using an altered version of the methodology.[4]



Scheme 22 [4]

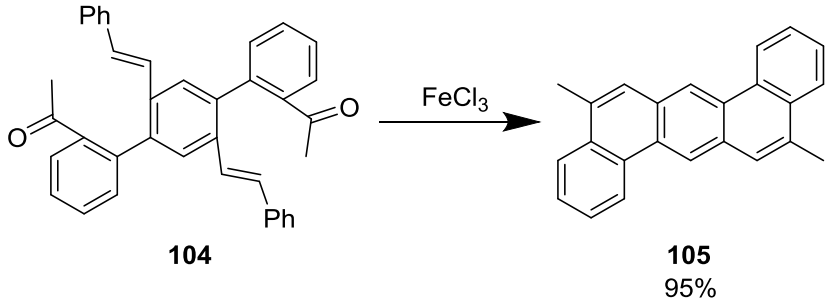
An additional method for the iterative synthesis of tetracenes and pentacenes came about from the studies of Takahashi *et al.* on zirconium-mediated benzene formation (Scheme 23). Starting from diester naphthalene derivative **98**, reduction of the ester groups to alcohols with $LiAlH_4$ and bromination with PBr_3, afforded dibromonaphthalene derivative **99**. Alkynylation of **99** and zirconium-mediated cyclisation of the resulting diyne **101** with dimethyl acetylenedicarboxylate (DMAD) afforded dihydrotetracene **102.** Subsequent aromatisation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), then gave tetracene derivative **103**.[47]



Scheme 23 [47]

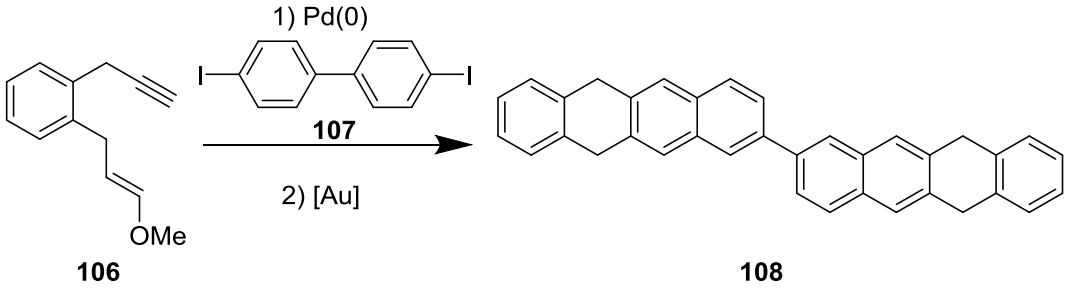
1.3.8 Alternative recent (2016 - 2017) synthetic approaches

Very recently the synthesis of PAHs has been obtained *via* an iron(III)-catalyzed carbonyl−olefin metathesis reaction.[48] 5,12-Dimethylbenzo[k]tetraphene **105** could be prepared via biscarbonyl−olefin metathesis of **104** to excellent (95%) yield (Scheme 24). The approach is operationally simple, has high functional group tolerance, is regioselective and uses an environmentally benign and available metal catalyst.



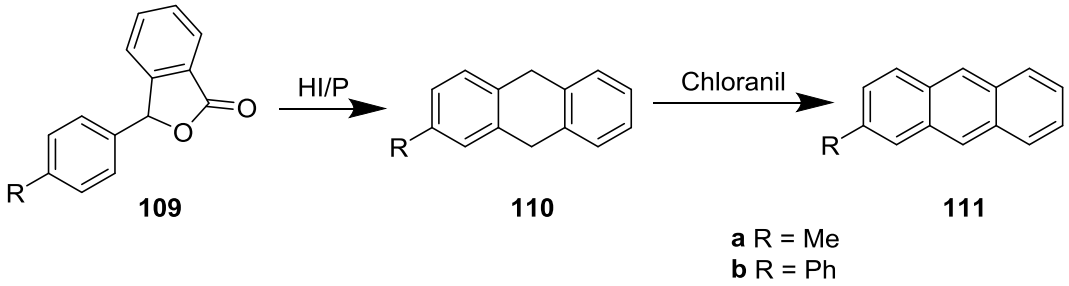
Scheme 24 [48]

Another recently developed methodology is the preparation of partially saturated acene derivatives using a palladium catalysed Sonogashira cross coupling reaction followed by a gold(I) catalysed cyclisation reaction of 1,7-enynes. By combining these methodologies a wide range of hydroacenes, up to nonacene, were obtained. For example a double cyclisation can be used to synthesise two joined dihydrotetracenes **108** (Scheme 25).[49]

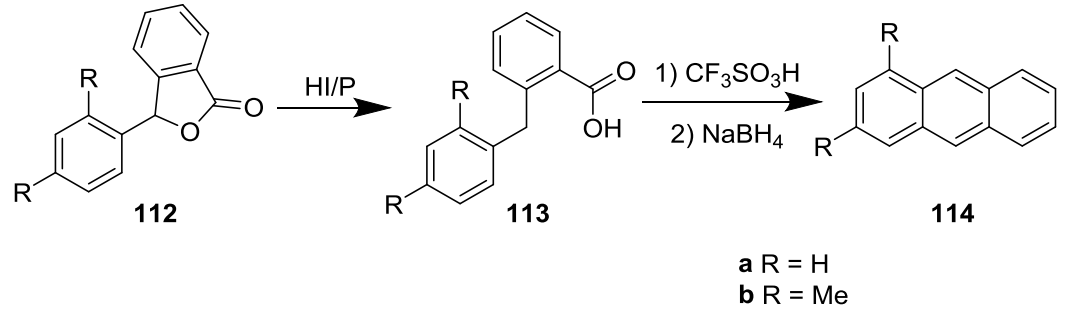


Scheme 25 [49]

Anthracene derivatives can be synthesised from phthalides **109** and **112** in good yields by hydriodic acid/red phosphorus mediated reductive cyclisation (Scheme 26 and Scheme 27).[50] In the case of phthalides **109**, treatment with hydriodic acid/red phosphorus provides dihydroanthracenes **110**, which upon dehydrogenation with chloranil furnish the corresponding anthracenes **111** (Scheme 26). However, for the substitution patterns found in **112**, intramolecular cyclisation does not occur under the same conditions, instead carboxylic acids **113** are obtained. The less nucleophilic nature of **112a** and the sterically demanding *ortho* methyl substituent of **112b** are the explanations for these observations. Cyclisation to anthracenes **114** could still be achieved in the presence of triflic acid, followed by reductive dehydration with $NaBH_4$ (Scheme 27).



Scheme 26 [50]

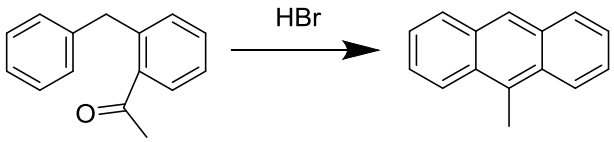


Scheme 27 [50]

1.3.9 The Bradsher cyclisation

A highly useful reaction in the synthesis of acenes is the Bradsher (hydroxyalkylation) cyclisation which is used for the formation of a new aromatic ring(s). Despite this, there are relatively few examples of its use in the synthesis of PAHs.[18] The Bradsher cyclisation is the reaction of an aldehyde or ketone group on an arene or alkene, with

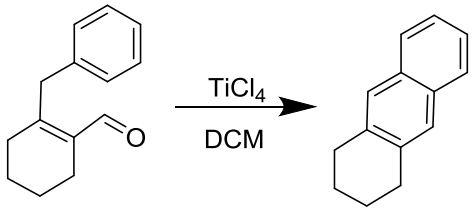
a sp^2 hybridised carbon atom that is in a suitable relationship to it.[51] For example, 1-(2-benzylphenyl)ethan-1-one **115** undergoes Bradsher cyclisation to 9-methylanthracene **116**, via an acid catalysed process (Scheme 28).[52]



115 **116**

Scheme 28 [52]

The Bradsher cyclisation can be catalysed by either H^+ or Lewis acids. Tius and Gomez-Galeno[53] established the closure of various *cis*-1,2-substituted alkene(CHO)(CH_2Ph) fragments, such as **117,** using the Lewis acid $TiCl_4$ in DCM (Scheme 29). The result was 1,2,3,4-tetrahydroanthracene **118**. This report inspired the conditions for the bidirectional Bradsher closure in the final step of our synthesis.



117 **118**

Scheme 29 [53]

Important examples of the H^+/Lewis acid catalysed synthesis of PAHs using the Bradsher cyclisation of CHO and CH_2Ph fragments have been carried out by Reddy and Rao[54], Yu and Lu[55], Kuninobu *et al.*[56], Rafiq *et al.*[57] and Fujita *et al.*[58].

1.3.10 Summary of acene synthesis

As has been demonstrated, there are various methods that can be used to synthesise tetracene and its derivatives. Particularly utilised are the Diels-Alder reaction (most commonly with an aryne) and the formation of bridged heterobicycles, dihydro- or quinone tetracene derivatives. These derivatives are transformed into the corresponding tetracene following dehydration with reagents such as Pd/C, DDQ and *m*-CPBA, or in the case of quinones reducing agents. Other methods have proven useful such as electrocyclic cascades going through benzene-bridged diallene intermediates (1.3.6), iterative synthesis (1.3.7) and utilisation of the Bradsher cyclisation (1.3.9).

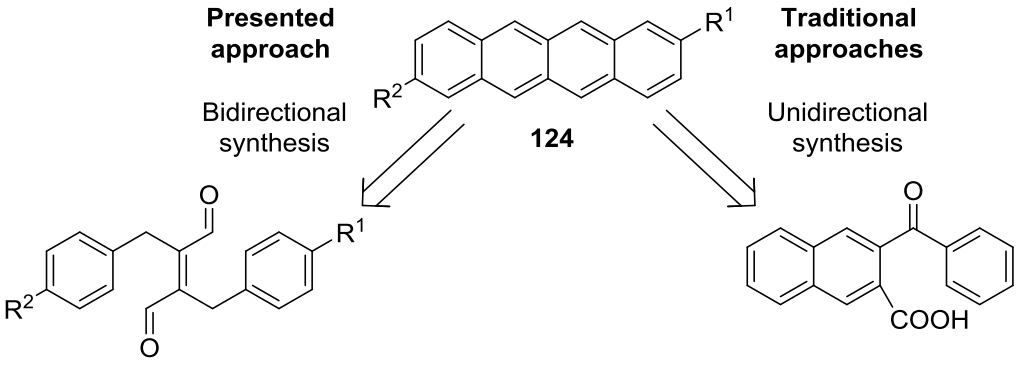
Particular substitution patterns can also be achieved through the functionalisation of already synthesised tetracene or tetracene quinone compounds. Contemporary alternatives have highlighted gold and ruthenium catalysed bidirectional cyclisations as well as hydriodic acid/red phosphorus mediated reductive cyclisation (1.3.8).

1.4 Developed synthesis of 2- and 2,8-substituted tetracenes

1.4.1 Bidirectional Bradsher cyclisations to tetracenes

While many synthetic strategies have been devised to tetracenes and other acene derivatives, these often suffer from one or more significant flaws, such as being step intensive and occurring in low yields due to the issues of isolation and scale-up of poorly soluble and stable acenes.[59] The lack of generality, use of high cost and/or unsustainable starting materials, relatively complex work-up procedures and need for further reduction or oxidation steps are other key flaws of reported synthetic methods. The result is that a more straightforward and efficient synthesis of substituted tetracenes is required.[18,44]

Our group sought to develop a new bidirectional synthesis, a method commonly used in natural product synthesis, which can create symmetrical molecules in a highly efficient manner.[60] This approach has been rarely used in the synthesis of acenes (Scheme 5, Scheme 12, Scheme 24, Scheme 25).[18] We proposed to use two synchronous Bradsher cyclisation reactions (1.3.9) to bring dialdehyde **123** to tetracene **124** in a single step (Scheme 30).



Scheme 30 [18]

Traditionally approaches utilise the reaction of **120** to **1** in a unidirectional manner (Scheme 30). For example, the intramolecular Friedel–Crafts reaction of a benzyl group and carboxylic acid is used to create acene quinone derivatives (Scheme 1 and Scheme 13). The result of a bidirectional approach is that precursor **123** has better solubility, crystallinity, does not require chromatographic purification and can have a wider range of derivatives compared to **119**.[18]

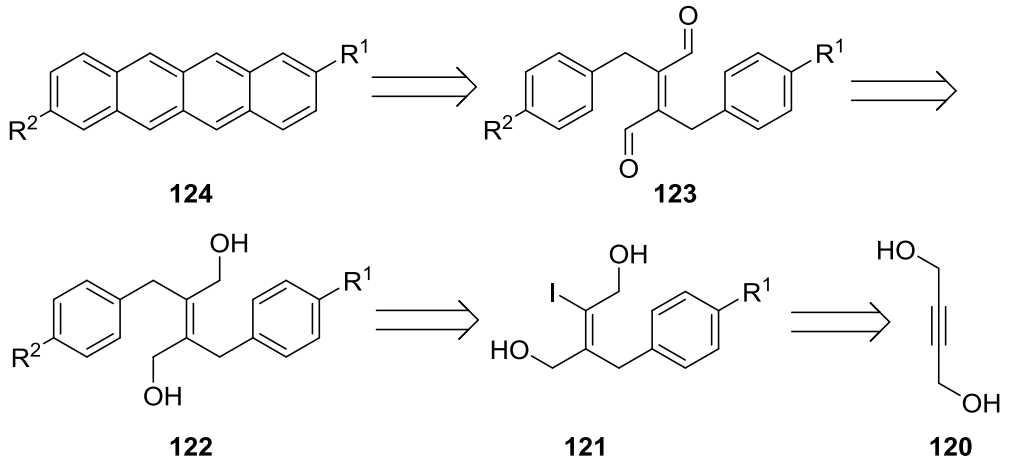
Contemporary approaches (1.3.8) are step and chromatographically intensive and/or require post cyclisation carbon oxidation state manipulation to produce the acene. Post cyclisation aromatisation is not favourable due to the potential for degradation of the desired tetracene and issues of solubility. In the developed synthetic method the tetracene is formed directly with water being formally the only by-product.[18]

The Bradsher cyclisation can be promoted by either H^+ or a Lewis acid. Promotion by H^+ is unfavourable because such conditions are known to oxidise tetracenes to

unstable radical cations.[61] A Lewis acid promoter is the preferred choice, however in some cases these can be overly oxidising towards tetracenes.[18,62] If this is overcome, the route is very attractive for the synthesis of tetracenes.

1.4.2 Synthesis of the dialdehyde precursor

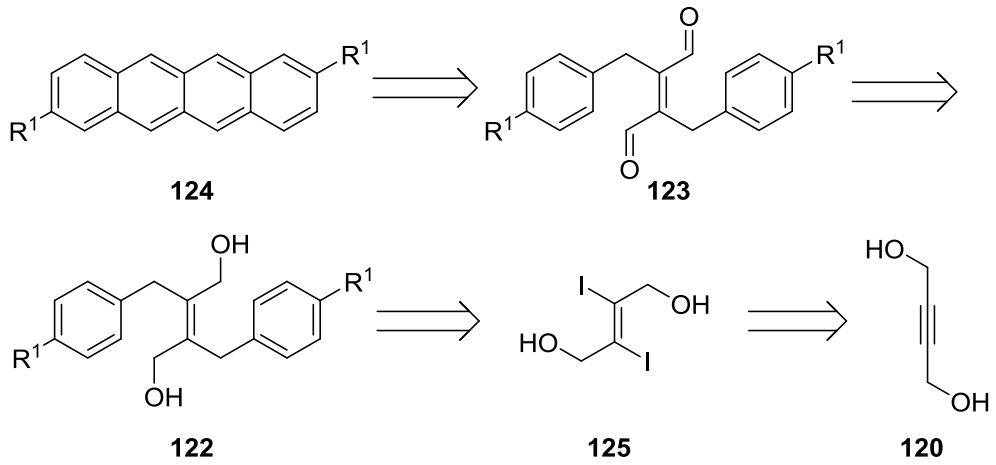
Our synthesis of precursor **123**, occurs from diol **122** *via* copper catalysed aerobic oxidation (Scheme 31). In the case of asymmetric tetracenes, diol **122** is created through simple Negishi coupling of diversity core **121** (method I), which was first synthesised from low cost alkenyl diol **120**. This reaction scheme was designed so that all carbon atoms in the tetracene products are sourced from low cost alkenyl diol **120** and benzyl chlorides. Detailed descriptions of these steps are given in the results and discussion section (Chapter 2.1).



124 **123** **122** **121** **120**

Scheme 31

The synthesis of symmetrical tetracenes can be carried out using a slightly simpler protocol up to the synthesis of **122** (Scheme 32). Following a literature procedure[63], reaction of **120** with iodine results in diversity core **125**. Symmetrical diols are then synthesised through a double Negishi coupling of **125** using 2.4 equiv. of organozinc reagent (method II). This method allows quick and simple access to certain symmetrical diols. Tetracenes **124** can then be synthesised using the same oxidation and cyclisation reactions as asymmetric tetracenes. Detailed descriptions of these steps are given in the results and discussion (Chapter 2.2).

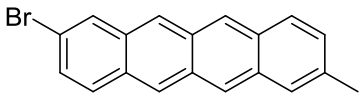


Scheme 32

1.5 Project goals

1.5.1 Synthesis of 2-bromo-8-methyltetracene

The goal of this project is to develop the method to synthesise a novel tetracene derivative, 2-bromo-8-methyltetracene **126** (Figure 10). Halogenated acenes have attracted much attention not only due to their potentially increased electrical performance, but also the ability to quickly build structural complexity through metal catalysed cross coupling reactions.[44]



126

Figure 10 Structure of target compound

The derivative is methylated at the 8-position to increase its solubility, enabling the cross coupling reactions to proceed. The synthesis of **126** is novel, however synthetic methods to 2-bromotetracene **36** are outlined in Scheme 7 and Scheme 8. Literature methods for the synthesis of differently substituted halogenated tetracenes are described in chapter 1.3.2, as well as in Scheme 19.

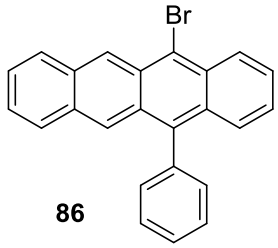
Bradsher cyclisations are subject to the normal restrictions of Friedel-Crafts chemistry meaning the electron poor 4-bromophenyl ring is deactivated in the cyclisation, resulting in a less favoured reaction profile. It was not known whether it would be possible to carry out the final closure to **126**. If a synthetic method is devised, it will be applied to the synthesis of 2,8-dibromotetracene **30**.

1.5.2 Cross coupling of 2-bromo-8-methyltetracene

Once brominated tetracenes have been synthesised, the next goal is to carry out C-Br functionalisation to quickly introduce structural complexity. Although cross-coupling of halogenated acenes looks very attractive as a general synthetic route to

substituted tetracenes, this methodology is somewhat rare. Difficulties arise from the lack of availability of bromo and iodo-acenes, as well as their low stability.[64]

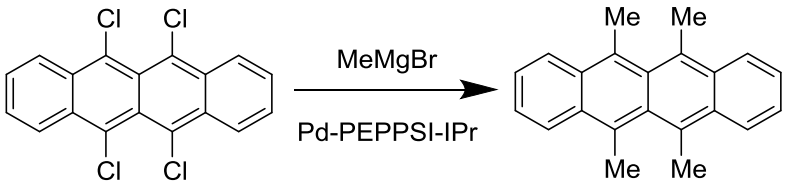
Despite these issues, there is literature precedence for this methodology: recently, brominated tetracene **86** (Figure 11) has been used in four separate palladium catalysed cross coupling reactions, Sonogashira, Suzuki, Heck and Buchwald−Hartwig amination, with all proceeding in high yields (68-99%).[44]



86

Figure 11 Structure of brominated tetracene **86**

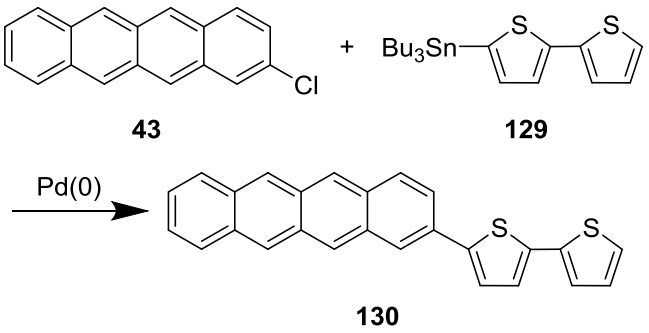
Chloroacenes are more readily available but suffer more from complications associated with coupling sterically hindered aryl chlorides. Cross coupling of aryl chlorides with two *ortho* substituents is notoriously difficult.[65] In 2010 Yagodkin and Douglas reported the first cross coupling reaction of linear acenes substituted at the *peri*-positions **128** (Scheme 33). They used the Kumada coupling of **127** with MeMgBr at room temperature, utilising the *N*-heterocyclic-carbene (NHC)-based catalyst Pd-PEPPSI-IPr (PEPPSI is an acronym for pyridine-enhanced precatalyst preparation, stabilisation and initiation; IPr = diisopropyl-phenylimidazolium derivative). Issues arose with the cross coupling of more hindered Grignard reagents such as PhMgBr to the tetracene derivatives.[65]



127 **128**

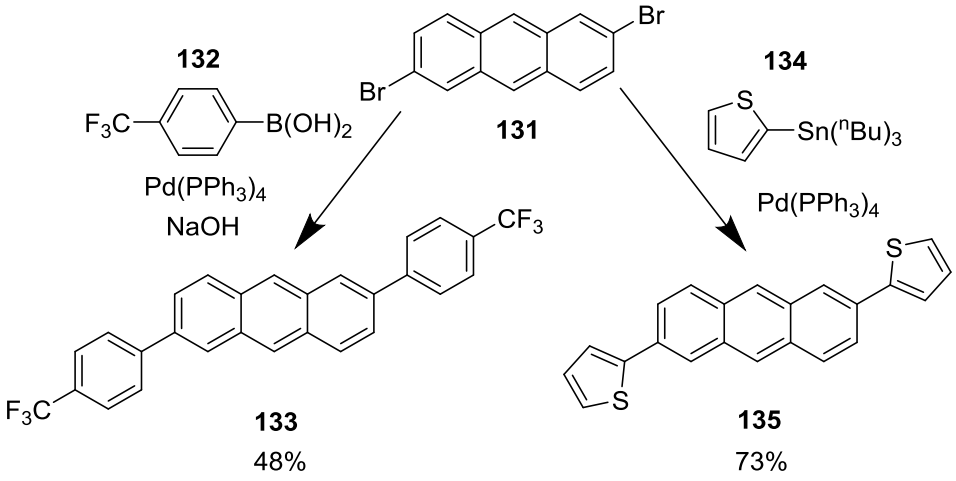
Scheme 33 [65]

Cross coupling has also been carried out on end-substituted chlorotetracenes, with the goal to make acene-thiopene derivatives such as **130** (Scheme 34). The Stille coupling has been employed to couple 2-chlorotetracene **43** with [2,2'-bithiophen]-5-yltributylstannane **129**.[28]



Scheme 34 [28]

Cross coupling to higher acenes can be challenging due to the low solubility in conditions normally employed in cross coupling reactions, as well as their poor stability. For this reason anthracene is more easily derivatised.[66] 2,6-dibromoanthracene **131** has been coupled in both Suzuki (**133**) and Stille (**135**) cross coupling reactions (Scheme 35) in 48% and 73% yields respectively. These yields are obtained after refluxing in toluene for 24 hours. This represents another answer to issues of low solubility, use of harsher reaction conditions.[67]



Scheme 35 [67]

Substitutions of the acene core which increase the stability and solubility is another solution to potentially alleviate these problems. The increased solubility was the reason for the methylation of **126** at the 8-position.

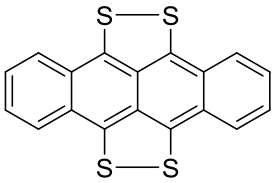
As will be seen, it was not possible to carry out C-Br functionalisation on **126** because too low yields were obtained as a result of the difficulties in applying the Bradsher closure to electron poor phenylene fragments. The solution to this was derivatisation at the precursor stage on either dial or diol. The result would then be brought to the tetracene derivative individually. This method was the secondary choice because of the higher throughput required.

1.5.3 Scale up of tetracene synthesis

A minor goal of the project was to create a successful scale-up procedure for parent tetracene (**1**), to multiple gram scales, without purity or yield deterioration. It will be of use to know how to carry out a large scale synthesis so that large amounts of tetracenes can be synthesised quickly and to establish the viability of selling the synthesised tetracenes commercially.

1.5.4 Synthesis of tetrathiotetracene

Tetrathiotetracene (TTT) **136** is a derivative of tetracene, useful for its application in thermoelectric (TE) devices. It is estimated that at least 20% of the 15 terawatts required for annual global power consumption is wasted as low level heat (< 200 °C).[68] TE devices can be used to convert this waste heat to electrical energy.



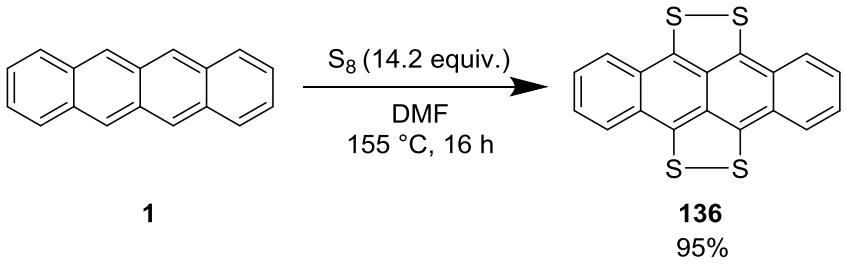
136

Figure 12 Structure of parent tetrathiotetracene

Current materials used for efficient TE devices are expensive, not widely available and contain toxic and unsustainable elements such as Te, Pb and Se. Organic materials could be the solution to these issues. Organic materials are also attractive due to their low thermal conductivity and the possibility to fine tune their properties via chemical synthesis.[68]

TTT is an electron rich tetracene derivative, making it a good electron donor and enabling it to form very conductive complexes with electron acceptors.[19] It has been shown that radical cation salts obtained by oxidation of TTT, such as ditetrathiotetracene triiodide (TTT_2I_3), can be used as materials for TE active organic thin films. TTT_2I_3 can be generated by the doping of TTT with iodine during or post vacuum deposition of its thin films.[68]

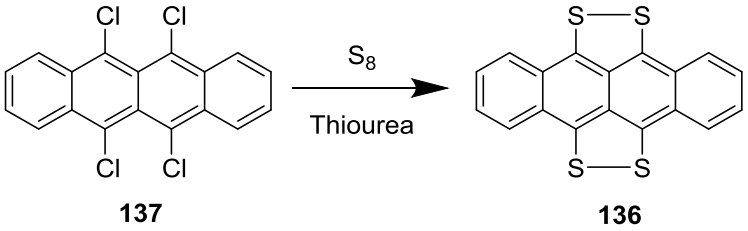
TTT **136** can be synthesised from **1** directly by treatment with 14.2 equivalents of sulfur and heating overnight in refluxing DMF (Scheme 36).[69] By filtering when still hot, **136** is obtained as a dark green solid in 95% yield. This is our preferred method due to the availability of 2- and 2,8-substituted tetracene from our newly reported synthesis.



1 **136** 95%

Scheme 36 [69]

TTT can also be synthesised from halogenated tetracene derivatives. Treatment of 5,6,11,12-tetrachlorotetracene **137** with sulfur and thiourea affords **136** in high yield and purity (Scheme 37).[70] The study of TTT has been extended to other chalcogens such as Se and Te, as well as non-symmetrical TTT analogs.[25]



137 **136**

Scheme 37 [70]

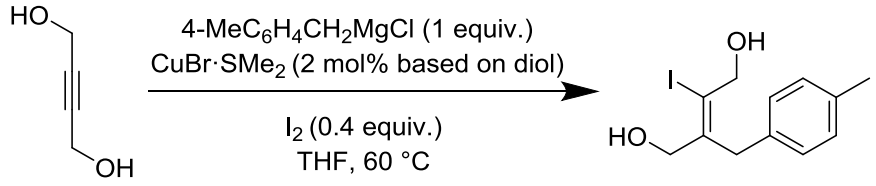
Using a literature procedure[69] we set out to synthesise and characterise a range of substituted TTTs using our library of efficiently synthesised 2- and 2,8-substituted tetracenes. The goal of this report's study into TTT is to adjust the methodology to successfully synthesise **136** on a gram scale, without yield or purity deterioration.

2 Results and discussion

2.1 Synthesis of 2-bromo-8-methyltetracene

2.1.1 Synthesis to 2-(4-Bromobenzyl)-3-(4-methylbenzyl)fumaraldehyde

The first transformation in the four-step synthesis of **126** is the modification of a literature procedure[71] which involves the copper catalysed nucleophilic reaction of the Grignard reagent 4-methylbenzylmagnesium chloride with 2-butyne-1,4-diol **120**. The carbomagnesiation reaction is carried out at 60 °C in order to attain high conversion with lower reactivity benzylmagnesium chlorides. The (*E*)-carbomagnesiation intermediates are then trapped with iodine to produce the desired iodide diversity core (**138**). A good yield (72%) was obtained after large (>10 g) scale synthesis of **138**, by crystallisation from Et_2O (Scheme 38). If necessary the iodide can be obtained analytically pure by recrystallisation from toluene, forming colourless glinting needles.

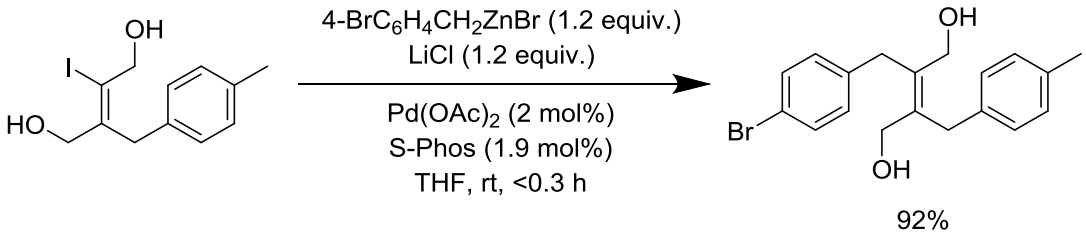


0.3 equiv. — **120**

72% — **138**

Scheme 38

Subsequently **138** is subjected to Negishi cross coupling, utilising $Pd(OAc)_2$ as a catalyst and either SPhos or PCy_3 as associated ligand, transforming **138** into the diol **139** (Scheme 39). It is known in the literature that unprotected alcohol functional groups can cause issues in the Negishi reaction because they competitively protonate organozinc reagents, however this was not the case for **138** which undergoes cross coupling faster than deprotonation in the presence of 1.2 equivalents of organozinc. Similar conditions have been used by Manolikakes *et al.* to the same effect.[72] Strong ligand inhibition was found to occur at L/Pd ratios of >1 but a L/Pd ratio of 1.9:2.0 prevented this from becoming an issue. Subsequent trituration of the crude material with Et_2O provided an off-white solid of **139** in up to 92% yield that is pure enough to be reacted in the next step. Alternatively analytically pure colourless needles can be obtained via recrystallisation from 1:1 MeOH/EtOAc with cooling to 4 °C.

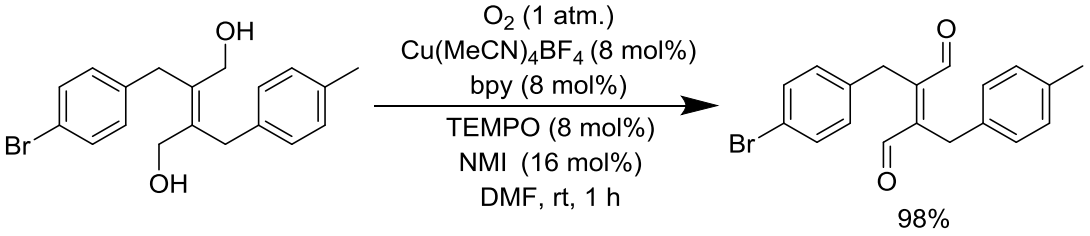


138

92% — **139**

Scheme 39

The alcohol functional groups on **139** must first be oxidised to aldehyde groups, to obtain the precursor **140**, for Bradsher cyclisation to a tetracene. After investigation of various oxidation procedures the best was determined to be an aerobic oxidation developed by Stahl utilising a Cu^{I}/ 2,2′-bipyridine (bpy)/ 2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO) / *N*-methylimidazole (NMI) catalyst system.[73] Thankfully the method showed good functional group tolerance to the C-Br bond in the molecule. The oxidation is complete when the dark orange-brown colour turns emerald green, usually within 0.3-1 h. After acidic washings, extraction with EtOAc and drying under vacuum, the crude product is obtained as a bright yellow solid in near quantitative yield (Scheme 40). The product was of high enough purity (>98%) to be closed immediately to the tetracene. Alternatively it can be recrystallised from 1:1 EtOAc/MeOH to give glinting yellow flakes upon cooling to 4 °C.



139 **140**

Scheme 40

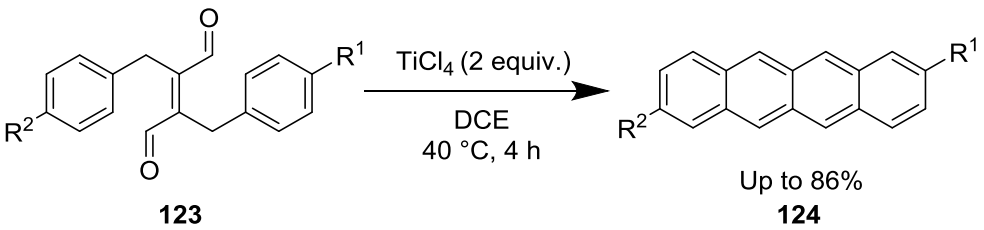
2.1.2 Initial attempts to synthesise 2-bromo-8-methyltetracene

A small screen of the effect of 14 Lewis acids on the dial revealed three that caused tetracene formation: $In(OTf)_3$, $BF_3{\cdot}OEt_2$ and $TiCl_4$. Use of $In(OTf)_3$ proved impractical because of the need for prolonged heating at high temperature (83–115 °C) and high catalyst loading (0.6 equiv.), as well as its poor sustainability.[18,56]

In accordance with literature precedence[57], on small scales (<1 mmol) $BF_3{\cdot}OEt_2$ provided tetracenes at good yields (>80%). However at larger scales (>3 mmol) the reaction became capricious, less clean and provided little or no yield of **1**. This can be explained by the effect of the water formed as a by-product of the Bradsher cyclisation. Use of 4 Å molecular sieves in the reaction headspace allowed production of **1** at gram scales, but the reaction remained slow and capricious.[18]

Following investigation of the methodology of Tius[53], treatment of **123** with $TiCl_4$ (2 equiv.) at 40 °C for up to 4 h, allowed the successful cyclisation of the dial to tetracene **124**. Quench with 1:1 acetone/MeOH realised an orange precipitate containing tetracene **124**. Prompt filtration using Whatman glass microfiber filter paper (grade GF/A[74] which is designed for particle sizes down to 1.6 µm) isolated the product. Generally the dial derivatives investigated could be successfully cyclised by this method, with yields up to 86% and purities above 95% (Scheme 41).[18] These samples could be purified by the use of sublimation (200-230 °C, 0.1-0.2 mbar, 1 h) to provide pure tetracene as brilliant orange microcrystals. However it was decided

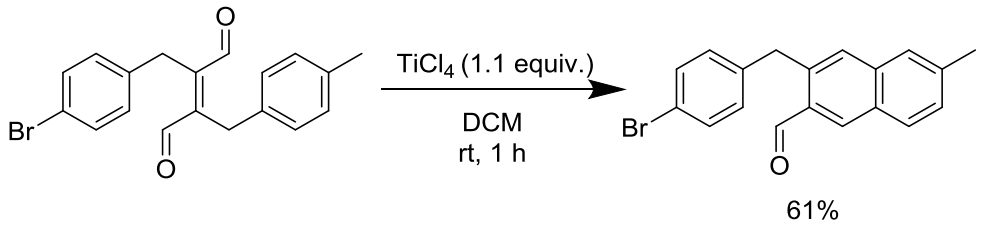
that reactivity issues may be raised in attempts to cyclise electron withdrawn dialdehydes such as **140**.



123 **124**

Scheme 41

Effort was made to bring about the closure of dial **140** under the same reaction conditions as non-electron withdrawn aromatic systems (e.g. $R^1 = R^2 = H$). This resulted in isolation of monocyclised product **141** and no detection of tetracene **126**. Naphthalene **141** can be synthesised in 61% yield by addition of 1.1 equivalents of $TiCl_4$, at room temperature for 1 h (Scheme 42). Isolation by column chromatography (14:1, pentane/EtOAc), followed by recrystallisation from 1:1 EtOAc/hexane, gives colourless rhomboidal crystals.



140 **141**

Scheme 42

2.1.3 Revised attempts to synthesise 2-bromo-8-methyltetracene

In an attempt to facilitate the synthesis of electron withdrawn tetracenes the temperature and time of reaction were both increased. Following alteration of the reaction conditions up to 110 °C for 18 hours, the monocyclised aldehyde **141** was still the major product. After heating to above 130 °C decomposition of the starting materials was observed and no monocyclised product was obtained. This suggested that high temperature and length of reaction were not parameters that could be altered to synthesise **126**.

Another option for conditions to bring about the synthesis of **126** was to use more equivalents and/or higher concentrations of $TiCl_4$. To test this idea, 4 equivalents of neat $TiCl_4$ were added to **140** and the mixture allowed to stir at room temperature for 48 hours. To our delight upon quenching, manual break up of the reaction mass and filtration, an orange solid was isolated. On a 100 mg scale, 23 mg of crude orange product was obtained; in the filtrate **141** was present. The crude solid was found to contain a large amount of polymeric by-product, however, characteristic signals in the UV-Vis spectrum revealed the presence of at least trace amounts of **126**.

Experiments were then made to find optimal reaction conditions to effect the tetracene formation. To do this, the concentration of $TiCl_4$ was gradually decreased, bringing it to the value used during our initial screenings (0.4 mol dm^{-3}) and the time of reaction was varied from 96 h down to 4 h. All reactions were carried out at room temperature using 100 mg of **140**. Monitoring the success of the reaction was carried out by optimising the amount of material obtained and the ratio of **126** to polymeric material. Ratios of tetracene: polymer are estimated from the ^{1}H NMR spectrum in CS_2 with an external DMSO-d_6 lock.[75] The results are summarised in Table 1.

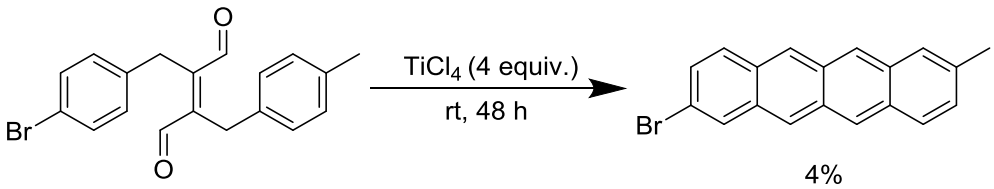
Table 1 Summary of conditions used in attempt to affect synthesis of **126** from **140** and the resulting product obtained.

$TiCl_4$ equiv.	**Dial conc. (mol dm^{-3})**	**$TiCl_4$ conc. (mol dm^{-3})**	**Time (hours)**	**Mass obtained; Composition of solid product**	**Computer integration** [a] **(tetracene: polymer)**	**Hand / triangular integration** [b] **(tetracene: polymer)**
4.0	-	Neat	48	23 mg; Tetracene and polymer	1:1.6	1:2.8
4.0	1.27	5.09	96	23 mg; Tetracene and polymer [c]	1:2.6	1:4.0
4.0	1.27	5.09	24	52 mg; Tetracene and polymer	1:1.8	1:7.1
4.0	0.50	2.00	24	4 mg; Tetracene and polymer	1:4.2	1:22.0
3.0	0.13	0.40	48	9 mg; Tetracene, monoclosure and polymer	1:3.2	1:11.3
2.7	0.20	0.80	5	10 mg; Tetracene and polymer	1:3.0	1:9.4
2.5	0.16	0.40	4	Trace; Tetracene and polymer	1:1.0	1:1.2

[a] Computer integration refers to integration methodology using the functionality of MestReNova.[76]
[b] Hand / triangular integration involves printing out the NMR spectrum and calculating the area of triangles drawn to represent the area under the signal. Hand integration would be expected to be more reliable considering the insolubility of the solid formed resulting in high signal-to-noise and a variable baseline. Both of which can create errors in the computer integration program.
[c] Also contains unknown aromatic peaks by ^{1}H NMR.

The very poor solubility of **126** means that error bars in the studies of Table 1 are large. Despite this it was determined that the best conditions were those of the initial test reaction: 4 equivalents of neat $TiCl_4$ left to stir at room temperature for 48 hours (Scheme 43). These conditions best balances the ratio of tetracene/polymer and the overall amount of material obtained. Purification of **126** from the 23 mg of material was attempted using vacuum sublimation, the same methodology utilised in the purification of non-electron withdrawn tetracenes.

Vacuum sublimation (230-240 °C, 0.2 mbar) was successful in removing the polymeric material and other impurities, resulting in a brilliant orange powder of pure 2-bromo-8-methyltetracene (Scheme 43). The powder was pure by CHN analysis, however, its very low solubility (<0.05 mg/mL in CS_2) ensures that trace impurities from the Bradsher cyclisation with higher solubility appear strongly in the compound's ^{1}H NMR spectrum.

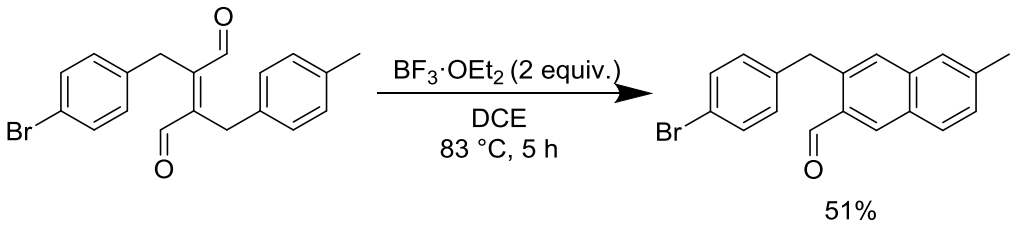


140 **126**

Scheme 43

Overall, 4% yield was obtained, which is poor compared to our original hopes for the project. However, considering the extreme difficulty in synthesising electron withdrawn tetracenes using this methodology it is significant, being the first reported synthesis of **126**.

Following the initial screening of a suitable Lewis acid for the Bradsher cyclisation, $BF_3{\cdot}OEt_2$ was added to **140** to determine whether this would be successful on small scales (Scheme 44).[18] Unfortunately, the result was the same as with low concentrations of $TiCl_4$, producing **141**.



140 **141**

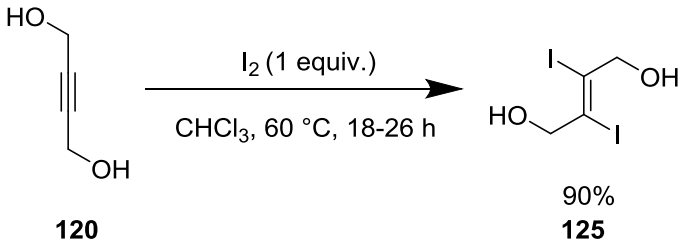
Scheme 44

The original aim of the project was to conduct substitution on the brominated tetracene. This was deemed unfeasible due to the poor yield of **126** attained. It may be that even if the yield was more substantial, the very low solubility would prevent organic reactions being carried out at this stage.

2.2 Attempted synthesis of 2,8-dibromotetracene

Following the development of a protocol for the synthesis of electron poor tetracenes, an investigation was carried out to determine whether this could furthered to various other electron withdrawn tetracenes such as 2,8-dibromotetracene **30**. The yield is likely to be low, but this molecule and its precursors are also of interest for cross coupling reactions.

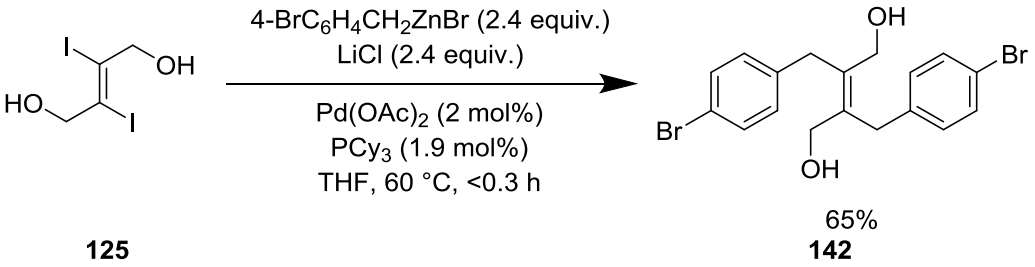
The molecule was synthesised using our convenient synthesis of symmetrical tetracenes (Scheme 32). One equivalent of iodine is dissolved in a solution of $CHCl_3$ and 2-butyne-1,4-diol **120** added. Upon stirring for 18-26 h at reflux, **125** can be isolated by filtration and dried to a colourless powder in 90% yield (Scheme 45).[63]



120 **125**

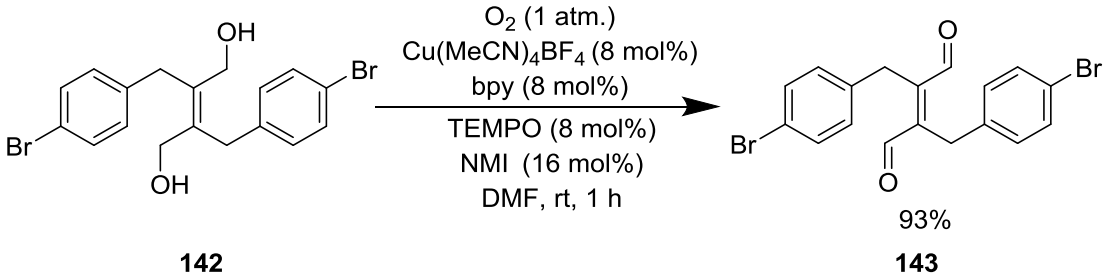
Scheme 45

Employing method II (Scheme 46) for diol synthesis, reaction of **125** with 2.4 equivalents of 4-bromobenzylzinc bromide at 60 °C, in the presence of $Pd(OAc)_2$ and PCy_3, provides **142** after <0.3 h. Product **142** could be crystallised from MeCN on cooling to -20 °C. It was found that SPhos could not be used for this coupling. The scope of method II is lower to that of method I, for example (*E*)-2,3-bis(4-methoxybenzyl)but-2-ene-1,4-diol could not be synthesised using method II.[18] However, the method is useful for providing certain symmetrical diols, like **142**, quickly and efficiently.



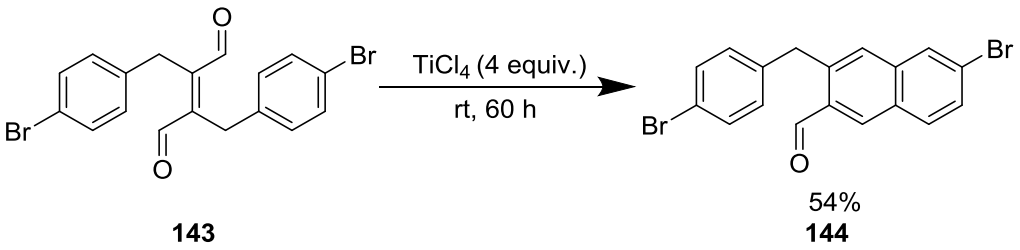
Scheme 46

Under the same oxidation conditions used to synthesise **140**, **143** was given in 93% yield (Scheme 47).



Scheme 47

Attempts were made to synthesise **30** using the conditions developed for electron poor tetracenes**.** Disappointingly, although an orange suspension was produced upon addition of 1:1 MeOH/acetone, **30** was not produced in a quantifiable amount. The main product of the reaction, the monocyclised aldehyde **144**, could be isolated in a yield of 54% (Scheme 48). The conditions have been tested on further halogenated dialdehydes (R^1 = H, R^2 = F; R^1 & R^2 = F; R^1 = OMe, R^2 = F) by others, successfully producing pure tetracenes in yields up to 9%.[18]



Scheme 48

As anticipated, **30** like **126**, could not be synthesised for use in a cross coupling reaction. Luckily there is an alternative to this approach, the substitution reactions can be carried out at either the dialdehyde or dialcohol stage of the synthesis and then each be brought to the respective tetracenes. The result would be an approach that requires more steps after the diversification stage, but would still be able to produce a vast array of substituted tetracenes. Investigation into the cross coupling of the precursors was carried out using **139** and **140**, any successful coupling reaction will then be implemented onto the dibrominated molecules, **142** and **143**. It would

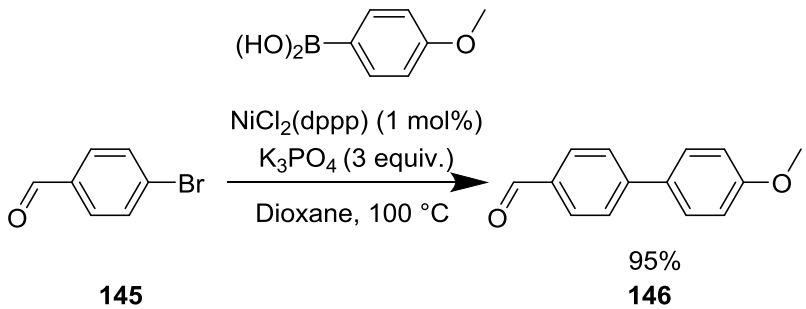
be optimal for the substitution to be carried out on the **140** rather than **139**, as fewer steps are then required to obtain each tetracene.

2.3 Substitution of tetracene precursors

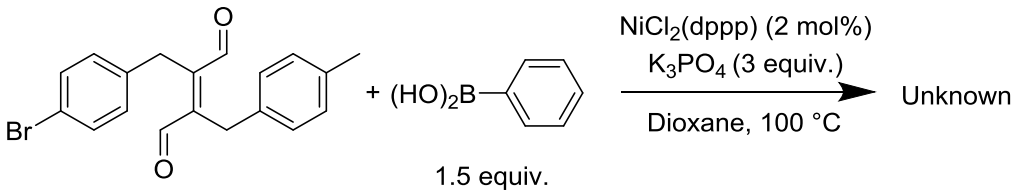
2.3.1 Suzuki cross coupling reaction

It was decided to first investigate the feasibility of the Suzuki cross coupling reaction on **140**. The Suzuki reaction is the transition metal catalysed cross coupling of organoboron reagents with aryl and alkenyl halides. Since its demonstration by Suzuki and Miyaura[77] in 1979 the reaction has become one of the most popular cross coupling reactions in organic chemistry.[78] Its popularity can be understood by the simplicity of operation, non-toxic components and by-products, mild reaction conditions and the catalytic stability to water. Of particular importance to our application is the functional group tolerance compared to Negishi and Kumada reactions;[79,80] due to the fact that the aldehyde functional groups would likely not be tolerated using either organozinc or organomagnesium reagents. For these reasons the Suzuki reaction is an attractive solution for coupling to **140**.

A literature search was made to find conditions for a Suzuki reaction that has both functional group tolerance to aldehyde groups as well as substitution at an aromatic bromide. Of the publications that have been used to effect this transformation, Zhao *et al.* utilised an attractive alternative set of conditions (Scheme 49).[81] Their method uses a highly active, cheap and stable nickel catalyst, $NiCl_2$(dppp), without the need for additional ligands. The reaction could be carried out on a broad range of substrates and requires a low catalyst loading of less than 1 mol%. Of particular interest to our application is the proof of stability to aldehyde functional groups at 95% yield, shown in Scheme 49. The reaction and conditions replicated in our laboratory can be seen in Scheme 50. The catalyst loading was increased to determine if the reaction was viable. The resulting crude product could not be identified by NMR spectroscopy, being a complex mixture of products including polymeric material. As a result the conditions for the Suzuki were altered.



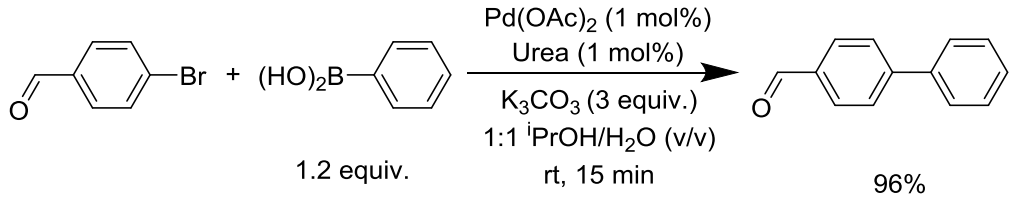
Scheme 49 [81]



140 **147**

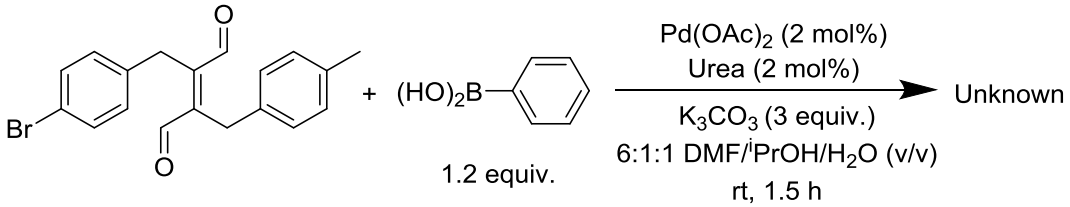
Scheme 50

The investigated conditions were somewhat atypical of Suzuki reactions which are usually carried out in the presence of Pd(0)[82], therefore the next experiments utilised this metal. Saikia *et al.* developed a set of reaction conditions shown to be stable to aldehyde functional groups (Scheme 51).[83] The $Pd(OAc)_2$ and urea have catalysed the coupling of a variety of aryl halides and aryl boronic acids in high yields. The reaction was simple to effect, phosphine-free and only required a low (1 mol%) catalyst loading.[83] The reaction conditions were replicated with reaction of **140** with phenylboronic acid (**147**) (Scheme 52). The catalyst loading was doubled to enable success and the solvent system was changed to 6:1:1 DMF/^{i}PrOH/H_2O to dissolve all of the starting material. The result of the reaction path was not what was hoped, as the starting material (**140**) could be detected as well as an unusual product that could not be identified after extensive analysis. As a result these conditions were not repeated.



145 **147** **148**

Scheme 51 [83]

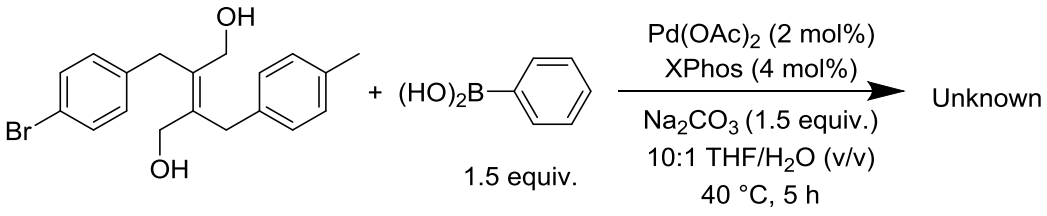


140 **147**

Scheme 52

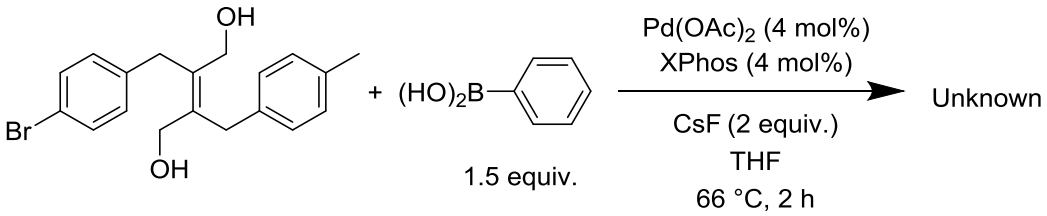
The issues resulting in the failure of the previous Suzuki reactions may have been a result of the relatively reactive aldehyde functional groups. It was decided that the next stage of experimentation would be carried out on **139**, as alcohol functional groups are of lower reactivity than aldehyde group and would utilise a more typical catalyst system.

Reaction of **139** was attempted with a combination of $Pd(OAc)_2$ and XPhos. This catalyst system has proven itself to be a wide ranging and highly active system for Suzuki reactions.[84] A test reaction was carried out in an attempt to couple the **139** with **147**, in the presence of Na_2CO_3 (Scheme 53). However, the resulting product was another complex mix of starting material and unidentified product. The reaction was then repeated using higher catalyst loading (2 mol% to 4 mol%), a different base, higher temperature and an inert atmosphere (Scheme 54). None of these changes made a difference to the resulting product which, by ^1H NMR spectroscopy, was remarkably similar to the reaction in Scheme 53. As a result of failure when changing both the starting material and catalyst system, other cross coupling reactions were then investigated.



139 **147**

Scheme 53



139 **147**

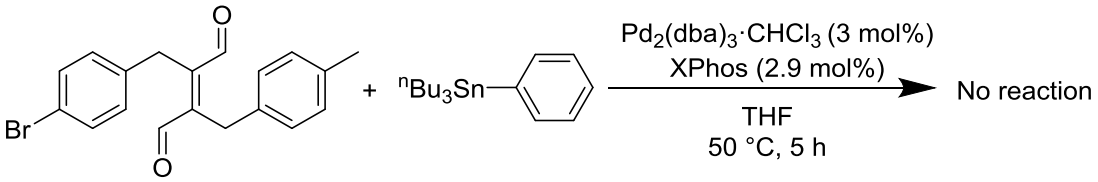
Scheme 54

2.3.2 Stille cross coupling reaction

Another option for coupling to **139** is the Stille reaction. Although it uses toxic tin reagents, the Stille reaction is well known to tolerate a wide range of functional groups, as a result it is frequently used in the synthesis of complex molecules.[85] Organotin reagents are also air and moisture stable allowing harsher reaction conditions and simplified storage.[86] The problem of toxicity is also mitigated by considering the relatively low toxicity of commonly used tri-^{n}butyltin derivatives (LD_{50} = 100–300 mg kg^{-1}) compared to triethyl- and trimethyltin derivatives (LD_{50} < 15 mg kg^{-1}).[85]

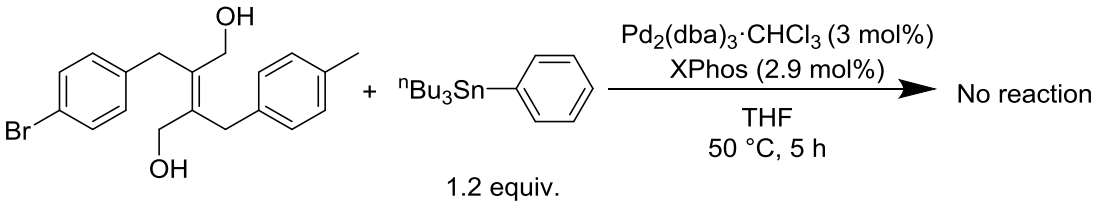
Organotin reagents have been shown to couple with aryl halides in the presence of non-participating alcohol[87,88] and aldehyde[89–91] functional groups. Commercial $Pd_2(dba)_3$ was used as the palladium source in our cross coupling reaction due to its use in similar Stille reactions[87,92]. Tri-^{n}butylphenylstannane (**149**) was used as the coupling partner and was first prepared from tributyltin chloride following a literature procedure.[93]

Disappointingly the organotin reagent failed to couple either **140** or **139** with **149**, in both cases the starting materials were recovered (Scheme 55 and Scheme 56). From this it can be seen that the transmetallation step did not initiate as the carbon-bromine bond is still present. As $Pd_2(dba)_3{\cdot}CHCl_3$ and XPhos has been successful in similar Stille reactions, this result is unexplained and it was decided that the Stille reaction was another unpromising line of investigation.



140 **149**

Scheme 55



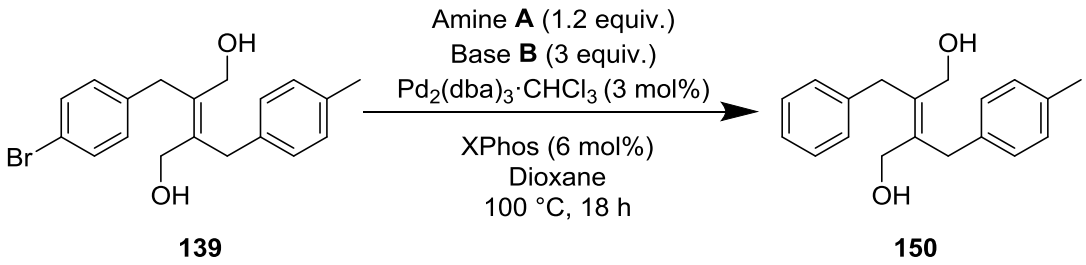
139 **149**

Scheme 56

2.3.3 Buchwald-Hartwig cross coupling reaction

Following this result another cross coupling reaction, the Buchwald-Hartwig reaction, was investigated to determine whether it would successfully substitute **139**. The Buchwald-Hartwig reaction is a palladium catalysed cross coupling reaction used to form C-N and C-O bonds[94], named after the separate contributions of Buchwald[95] and Hartwig[96]. The method was chosen because of its ability to connect highly functionalised reagents and compatibility with a wide range of functional groups.[97] Consequently there are multiple examples of the Buchwald-Hartwig reaction being used to couple amines with aryl halides containing alcohol functional groups.[98–100]

The catalytic system of the Buchwald-Hartwig reaction has 4 components, a palladium precatalyst, ligand, base and solvent.[94] Previous work in our group identified XPhos/$Pd_2(dba)_3$/1,4-dioxane as an optimal catalyst system for the coupling of sterically hindered aryl triflates and nonaflates with the primary amines.[101] Several tester reactions were carried out with this catalyst system to determine whether alterations to the substituents on the amine (**A**) or strength of base (**B**) would facilitate the desired reaction (Scheme 57, Table 2).



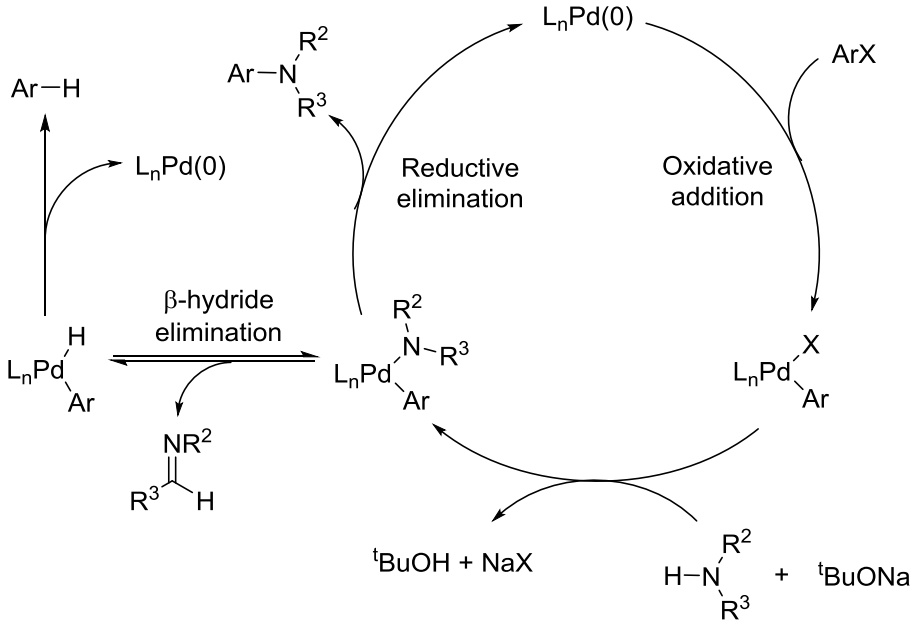
139 **150**

Scheme 57

Table 2 Result of different amines and bases used in Buchwald-Hartwig reaction (Scheme 57)

Amine (A)	Base (B)	Result
Morpholine	Cs_2CO_3	**150**
Diphenylamine	Cs_2CO_3	**150**
Diphenylamine	^tBuONa	**150**

As can be seen in the tabulated data (Table 2), the desired product was not afforded under any of the conditions used, with the hydrodebromination product (**150**) obtained instead of the aryl amine. Hydrodebromination is obtained from β-hydride elimination after the coordination of the amine to the aryl-palladium complex (Scheme 58). Undesired β-hydride elimination is a known issue in Buchwald-Hartwig reactions as well as other cross coupling reactions and can explain the result for morpholine. There are multiple ways to prevent the β-hydride elimination pathway, such as accelerating the reductive elimination pathway. The most feasible methods in this reaction is the use of electron donating groups on the amine[102] and the use of bidentate phosphine ligands, such as BINAP[103], $(DPPF)PdCl_2$[104] or Xantphos[105], which have been shown to significantly inhibit β-hydride elimination.



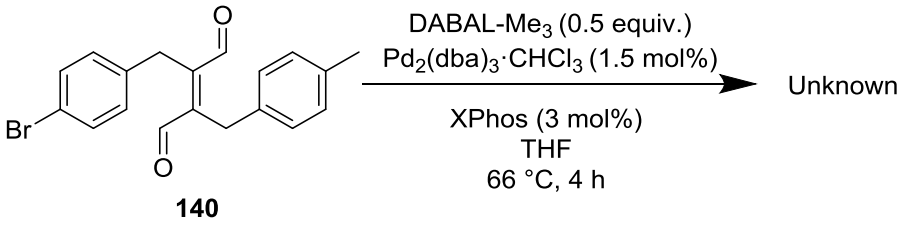
Scheme 58 Mechanism of Buchwald-Hartwig elimination. Adapted from Li[106]

However in the case of diphenylamine there are no β hydrogen atoms to carry out elimination meaning the production of **150** remained unexplained. This suggests there is a separate issue in the reaction causing hydrodebromination. Given that the Buchwald-Hartwig reaction is known to have issues, for example inhibition due to steric factors[101], and no evidence of the correct coupling product could be detected, the Buchwald-Hartwig reaction was not investigated further in the scope of this study.

2.3.4 Methylation using DABAL-Me_3

Another potential methodology for substituting the brominated compounds is methylation using the air stable trimethylaluminium source, bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane adduct (DABAL-Me_3). Previous work in our group identified $Pd_2(dba)_3$/XPhos/DABAL-Me_3 as a highly robust procedure for the methylation of aryl halides ArX (X = Cl, Br, I).[107] The reaction has been shown to tolerate a wide range of functional groups including aldehydes. If the methodology is successful the reaction could be expanded to ethylation by using DABAL-Et_3, which does not usually show any issues of β-hydride elimination.[107]

In the event, work-up of the reaction of **140** with DABAL-Me_3 gave a black oil which could not be identified though analytical techniques (Scheme 59). It is likely clear that **140** decomposed during the process, to intractable materials. As a result these conditions were not promising enough to continue investigations.



140

Scheme 59

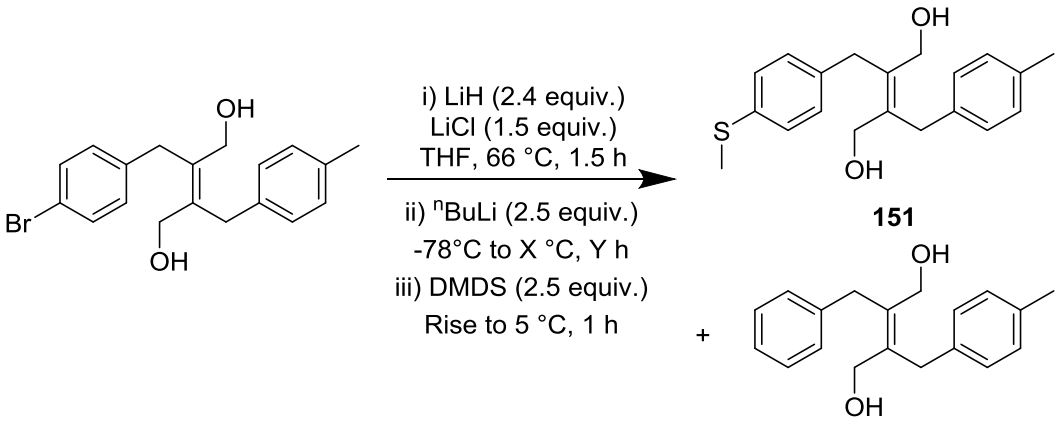
2.3.5 Lithium-halogen exchange and electrophilic substitution

An idea to cleanly effect substitution at the aryl halide was to carry out lithium-halogen exchange on the aryl bromide and to this add an electrophile, resulting in a range of substituted diols. In testing the feasibility of this method, dimethyl disulfide (DMDS) was used to make a thioether. Similar reactions have been carried out in the literature.[108,109] In the cases where an alcohol is present on the aryl halide, a base is added to prevent reaction with the organolithium reagent[108], LiH was employed as the base in this transformation.

The reaction was started by the addition of LiH and LiCl, which is used to break up aggregates in the reaction mixture, in refluxing THF. It was found that without heating in refluxing THF, the starting materials (**139**) were obtained, as well as a small amount of the hydrodebromination product **150**. This is likely due to the alcohol groups still being protonated in solution during ^{n}BuLi addition, which are incompatible with the organolithium. The hydrodebromination side product is

formed when lithium-halogen exchange does take place but is quenched by a proton before the electrophilic substitution. This side reaction is a major issue as separation from the desired product (**151**) is highly challenging due to its similar chromatographic properties.

After 1.5 h of heating the reaction mixture was cooled to -78 °C and ^{n}BuLi added dropwise. After a certain amount of time, the lithium-halogen exchange was complete and DMDS added. During initial tests of this method, both **150** and **151** were detected. An experiment was set up to compare the ratio of each product. When adjusting the temperature, the reaction mixture was left to rise to X °C, for a certain amount of time (Y), after the addition of ^{n}BuLi (Scheme 60, Table 3).



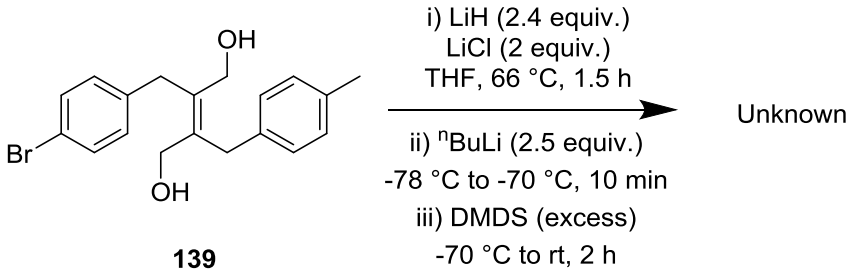
139 **151** **150**

Scheme 60

Table 3 Ratio of **151**:**150** when leaving the organolithiation reaction (Scheme 60) to rise to temperature X for amount of time Y, before DMDS addition. Ratio calculated using integration in ^{1}H NMR spectrum

Temperature for addition of DMDS, X (°C)	Amount of time after addition of ^{n}BuLi before DMDS is added, Y (h)	Ratio of desired product to hydrodebromination product (151:150)
5	1.50	1:2.2
-5	1.25	1:1.4
-15	1.00	1:0.6
-30	0.50	1:0.5

The presence of **151** and **150** were both confirmed by mass spectroscopy. In all cases **150** was present at levels that prevented purification of **151** by recrystallisation. The experimental data (Table 3) indicates that the amount of hydrodebromination product decreases as the temperature and time until DMDS addition occurs is lowered. Following this, the next step in the optimisation was reducing the temperature of DMDS addition whilst still giving the ^{n}BuLi enough time to exchange with the aryl bromide. In the next stage, DMDS was added at -70 °C after 10 minutes had passed (Scheme 61).

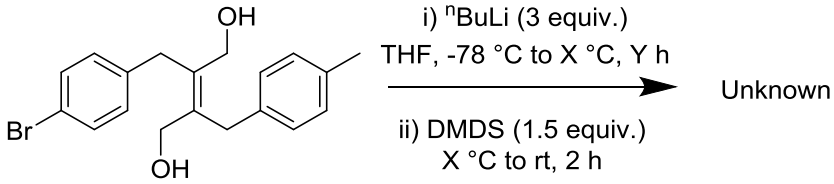


139

Scheme 61

The result was a much more complex mixture than had been obtained previously. The aromatic region was somewhat comparable, however, in the region where the two methyl peaks of **151** occur, there are six distinct peaks. It was confirmed that one of these three products was **151** but the source the extra methyl peaks is unknown.

It seems this result is common when the DMDS is added quickly to the reaction mixture, as even when the methodology was changed, a very similar result was obtained. The change in methodology was made to simplify the reaction by not adding LiH as a base, instead adding three equivalents of ^{n}BuLi, to ensure there is enough organolithium to react with both diol groups as well as the aryl bromide. Two reactions in these conditions were carried out, varying the amount of time before DMDS was added (Y), both are summarised in (Scheme 62, Table 4).



139

Scheme 62

Table 4 Result of two variations of the reaction carried out in Scheme 62

Temperature for addition of DMDS, X (°C)	**Amount of time after addition of ^{n}BuLi before DMDS is added, Y (h)**
-60	0.50
-70	0.25

Both results of Scheme 62 were remarkably similar to that of Scheme 61, however, the ratio of the 3 products differs (Figure 13), this confirmed that there were 3 different products.

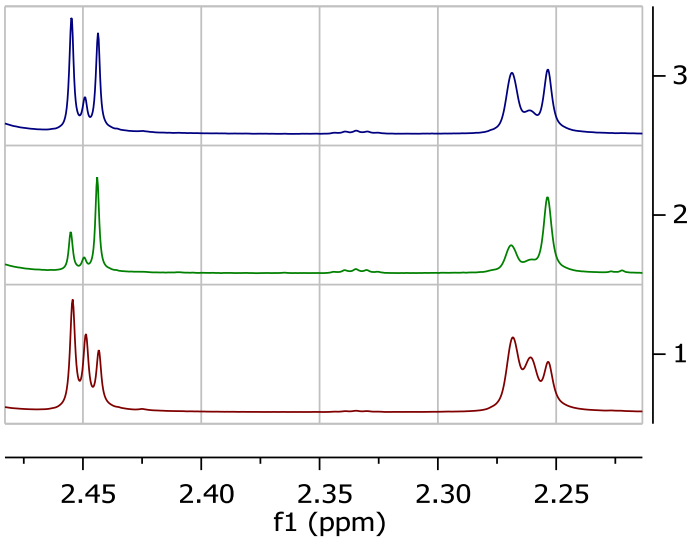


Figure 13 Methyl region of the ^{1}H NMR spectrum indicating that 3 separate products are formed in the reaction of **139** with DMDS. 1 represents the reaction in Scheme 61, 2 represents the reaction in Scheme 62 at -60 °C and 3 represents the reaction in Scheme 62 at -70 °C. Peaks from 2.25 to 2.28 ppm represent aryl methyl groups and peaks from 2.44 to 2.46 ppm represent thiomethyl groups. ^{1}H NMR spectra were carried out at 400.1 Hz in DMSO-d_6.

Column chromatography (1:1 EtOAc:pentane, then 6:1 EtOAc:pentane) was utilised to separate the 3 products that appeared in the crude product mixture. Some **151** was separated using this method, however **150** was still present in this sample. Sadly after recrystallisation, **151** could not be isolated in high enough purity for characterisation, **150** was still too prevalent (**151**/**150** = 1:0.07). The other products in the crude reaction could not be isolated from each other by column chromatography nor be identified from the spectroscopic data, they are still unknown. One suggestion for the cause of these issues is the methyl group in **139**, which may be suffering deprotonation and functionalisation but this could not be confirmed.

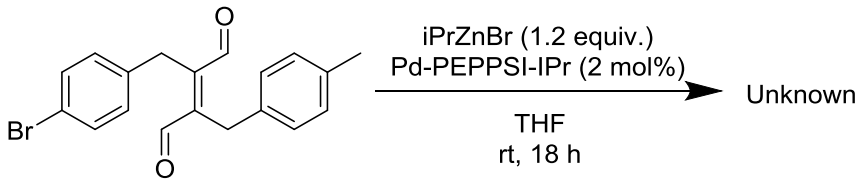
Given that the reaction never provided **151** cleanly, amounts of **151** provided were at a low yield and all attempts to improve the selectivity resulted in an increase in the number of unknown products. This method for substitution was not investigated further in favour of one more type of cross coupling reaction.

2.3.6 Negishi coupling using palladium *N*-heterocyclic-carbene (NHC) catalyst system: Pd-PEPPSI-IPr

One common cross coupling reaction not investigated so far is the Negishi coupling, which couples organic halides and with organozinc compounds.[110] The Negishi coupling has received considerably less attention than its peer the Suzuki reaction primarily because of the relative functional group intolerance of the organozinc reagents.[111] However recent developments of milder and more efficient preparation routes to organozinc reagents has revealed compatibility with a wide range of functional groups once thought to be intolerable; unprotected alcohol and aldehyde functional groups have both be utilised in Negishi reactions.[72,111] Research by

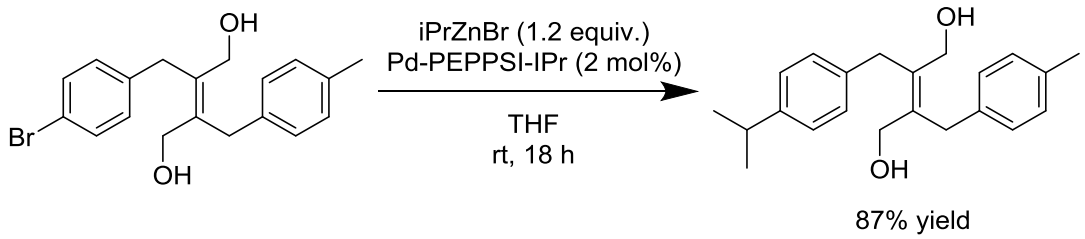
Professor Mike Organ into the Negishi reaction led to the development of Pd-PEPPSI-IPr, the first highly active NHC-based catalyst for the Negishi reaction.[112]

Pd-PEPPSI-IPr is a commercially available air- and water-stable catalyst useful for its high efficiency, functional group tolerance and lack of need for additional ligands.[111] The reported tolerance of alcohol and aldehyde functional groups[113] makes this an attractive proposition for the successful cross coupling both **140** (Scheme 63) and **139** (Scheme 64).



140

Scheme 63



139 **152**

Scheme 64

The preparation of the organozinc and cross coupling reaction were carried out in accordance with the method of Çalimsiz and Organ.[114] Unfortunately, dialdehyde **140** did not react cleanly and none of the expected product **152** was detected in a very broad and complex ^{1}H NMR spectrum of the crude product. On the other hand the dialcohol **139** reacted cleanly to product **152** at 87% crude yield. The product did not need to be purified further before oxidation to the corresponding dialdehyde. This was an ideal result and with high optimism about the possibilities, further tests were carried out to determine other cross coupling substrates. Two organozinc reagents were investigated based on their availability and likelihood to successfully react (Table 5).

Table 5 Result of the Negishi reaction of two organozinc reagents with **139**, following the methodology of Scheme 64

Organozinc reagent	Product formed
Cyclohexylzinc(II) bromide	Starting material, **139**
4-fluorobenzylzinc(II) chloride	Starting material, **139**

Unfortunately neither organozinc reagent coupled to **139**. It was at this point that the original successful Negishi coupling was repeated. Four alternative reaction

conditions were utilised to try and effect consistent conversion of **139** to **152** (Table 6).

Table 6 Summary of reaction conditions and resulting product of repeat of the Negishi cross coupling reaction of dialcohol **139** and iPrZnBr

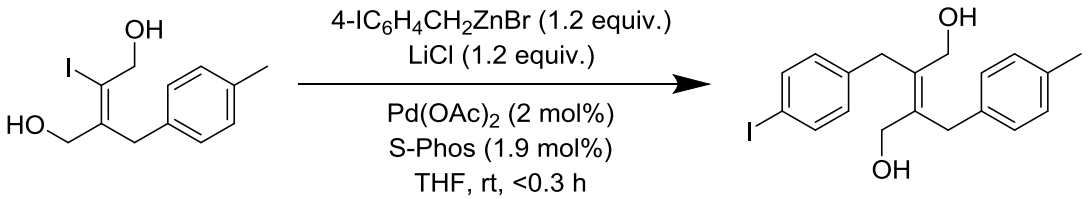
Reaction number	Alternative conditions	Product formed
1	1.5 equiv. of ^{i}PrZnBr	Starting material, **139**
2	Heating to 50 °C	Cross coupling product, **152**
3	Heating to 50 °C	Starting material, **139**
4	1.5 equiv. of ^{i}PrZnBr, 5 mol% of Pd-PEPPSI-IPr, refluxing THF	Starting material, **139**

The conclusion from this study was that the reaction is capricious. Even when the reactions were carried out in tandem with seemingly no difference between them, some produced **152** but most would not react, remaining as **139.** Given that successful runs occurred at high conversion, high regioselectivity and could potentially be expanded to a vast array of substrates, this methodology is still a very promising line of investigation. There are still various options that could achieve a consistent set of conditions, however the time limitation on the completion of this project resulted in the investigation of only one.

2.3.7 Coupling to the iodinated dialcohol

An idea to achieve clean cross coupling at the dialcohol stage was to weaken the carbon-halogen bond by changing the bromine to iodine (phenyl-Br: 84 kcal/mol; phenyl-I: 67 kcal/mol).[115] It was suggested that this weakening may be what is required to make the Pd-PEPPSI-IPr Negishi cross coupling consistent. The first challenge of this methodology is to synthesise the iodinated diol **153** cleanly and efficiently. It is entirely possible that problems would be caused by the high reactivity of the C-I bond in the organozinc, which could potentially react with another organozinc reagent, creating polymeric material.

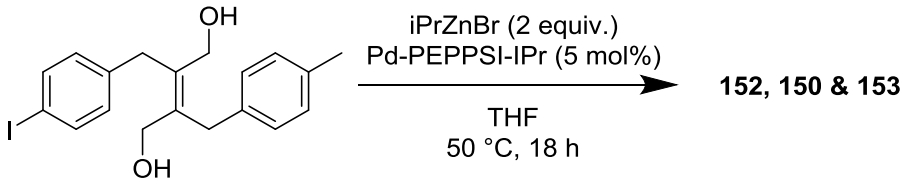
A sample of 4-iodobenzylzinc bromide was synthesised from commercially available 4-iodobenzyl bromide using the same methodology that was used to synthesise 4-bromobenzylzinc bromide (Scheme 65). Complete conversion was not attained with a mixture of the desired product **153** and the starting material **138**. By ^{1}H NMR spectroscopy **153** accounted for 40% of the crude material. By use of a silica plug, **153** could be isolated at high enough purity to carry out recrystallisation from EtOAc/MeOH (1:1), which on cooling to 4 °C, gave **153** as colourless cuboidal microcrystals (0.14 g, 0.35 mmol, 15%). The yield and selectivity was low so further work is required to optimise this synthesis. Nevertheless, the Negishi coupling using Pd-PEPPSI-IPr was carried out to determine whether this line of investigation is worth pursuing.



138 **153**

Scheme 65

The method that led to the successful coupling of **139** (Scheme 64) was repeated using slightly more aggressive reaction conditions (Scheme 66). The resulting solid was a mixture of desired product **152**, hydrodebromination product **150** and the starting material **153** (**152**:**150**:**153** = 1:0.88:0.47). This methodology has also proven unsuccessful for the cross coupling to the dialcohol in our tetracene synthesis. Similar to the Negishi coupling to **139**, coupling to **153** requires a fair amount of optimisation.



153

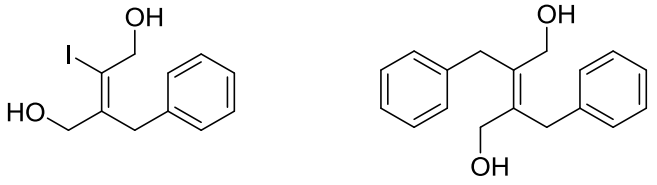
Scheme 66

For various reasons, each of the cross coupling methods tested in this project could not be utilised for the synthesis of a large library of substituted tetracenes. Each seemingly simple methodology resulted in a complex product mixture that was difficult to understand, indicating that both **139** and **140** are arduous compounds to cross couple. Due to this the cross coupling to dibrominated alcohol **30** was not investigated as it was deemed very likely to produce the same result. There are various potential improvements for the problems encountered thus far as well as new methods that could be investigated to achieve the result. Due to the time limitations on this project none of these were investigated but are discussed in the conclusion. It is expected that study will continue on this problem.

2.4 Scale-up of parent tetracene

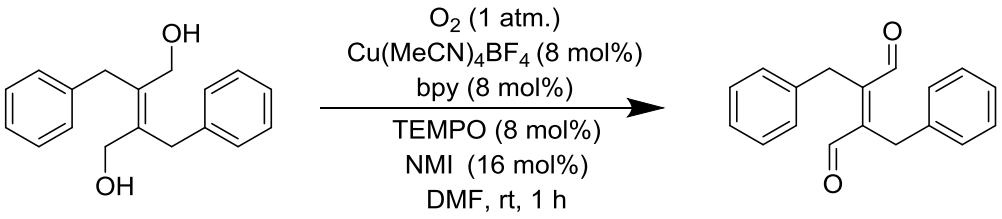
One of the initial objectives of designing the synthesis route to tetracenes was that it would be scalable above a gram without yield or purity degradation issues. Moving on from the cross coupling reaction, the next objective of my project was to create a successful scale-up procedure for the parent tetracene, **1**, on one gram and then multigram scales.

The first requirement was the successful scale-up of **154**, **155** and **156** production. Previously the synthesis of **154** and **155** had already been successfully carried out on multigram scales by others, **154** on > 10 g and **155** on > 5 g scales without reduction in purity and yield (Scheme 67). Investigation on both 2 g and 3 g scales revealed that dialdehyde (**156**) could be successfully synthesised in high purity with > 98% yield (Scheme 68).



154 **155**

Scheme 67

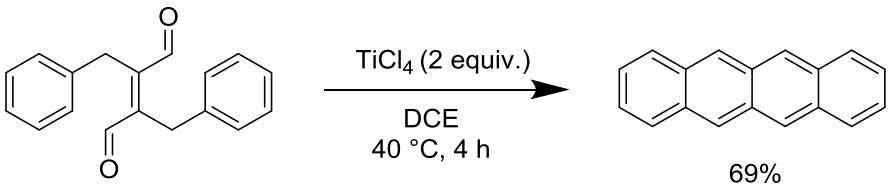


155 **156**

2g and 3g scales >98%

Scheme 68

The next step was to carry out the final closure on **156**. In the first 1 g scale synthesis to make **1**, the yield was significantly lower (56%) compared to the 72% yield obtained in small scale reactions, typically 0.40 g (1.51 mmol) of **156**.[18] This was attributed to decomposition of the tetracene product during the quench and filtering process. A number of improvements to the protocol were made during the next 1 g scale up, namely the quench mixture was dried with molecular sieves, stirred throughout, cooled to -10 °C and the reaction mixture added to the quench mixture via cannula. The main cause of degradation was thought to be due to protons generated during the quenching procedure. In order to neutralise these, 3 equivalents of cyclohexene epoxide were added to the quench mixture. Using this methodology the yield of **1** obtained from the 1 g reaction increased to 68% (Scheme 69). This is a negligible reduction from the 72% obtained on small scale preparations. After this success the reaction was scaled up further to 2 g of **156** utilising these improved conditions. A yield of 69% was obtained; this is excluding minor impurities found in the product which could be removed using sublimation.



156 **1**

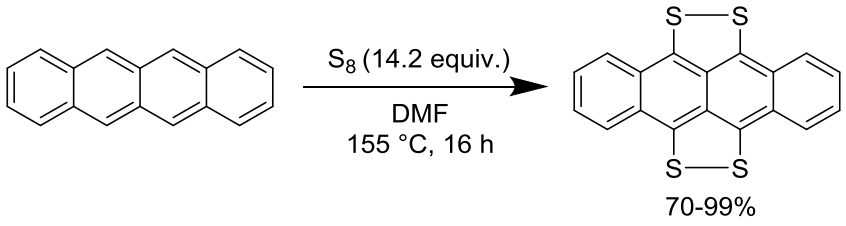
Scheme 69

Through the modification of the reported procedure, the synthesis of tetracenes can now be carried out at multigram scales to produce material at a yield and purity close to the small scale synthesis.

2.5 Synthesis and reaction of tetrathiotetracenes (TTT)

2.5.1 Synthesis of tetrathiotetracene (TTT)

A derivative of tetracenes, tetrathiotetracene (TTT) can be synthesised by the treatment of tetracene, for example **1**, with 14.2 equivalents of sulfur and heating overnight in refluxing DMF (Scheme 36). Throughout, the reaction is left under a flow of nitrogen to remove H_2S formed in the reaction. Upon completion, the reaction mixture is filtered hot (>110 °C) and sucked dry, providing TTT as a dark green powder, with typical yields of 70-99% and >90% purity. The crude TTT is then treated under vacuum, to remove traces of DMF and sulfur, providing 95-98% pure material. Typically these reactions were carried out using 0.22 mmol of tetracene derivative**.**



1 **136**

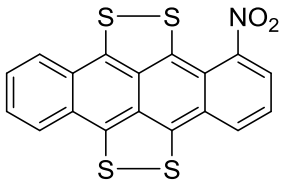
Scheme 36 [69]

2.5.2 Scale-up of parent tetrathiotetracene

It was desired to know if the successful synthesis of TTT could be repeated on a gram scale. To scale-up the reaction a number of adjustments were made. It was made sure that the Schlenk tube the reaction was carried out had enough height (*ca* diameter 40 mm, height 240 mm) to cause the DMF to condense on its sides. The Hartley funnel used for filtering was a larger size (75 mm compared to 25 mm) and the sublimation of the crude TTT was carried out in a Kugelrohr apparatus rather than a relatively small sublimation tube. After sublimation, **136** was obtained at 69% yield and 93% purity, lower than on a small scale which was obtained at 83% yield and 95% purity. There has been slight degradation of yield and purity when scaling up this reaction but not to a highly detrimental level.

2.5.3 Reaction of tetrathiotetracene with concentrated nitric acid

A final line of investigation was initiated when, during the routine quenching of TTT with concentrated nitric acid, an unknown solid was observed in the resulting solution. Dilution with water caused a dark semi-crystalline compound to precipitate out of the solution. It was hoped that the nitric acid had reacted with TTT producing a novel compound, the result would may be a novel and exciting line of TTT derivatisation. Preliminary investigations suggested that the nitric acid had nitrated TTT to **157** (Figure 14). The goal of this section of my project was to recreate the synthesis of this compound by treating the parent TTT **136** with the conditions previously used and to determine the identity of the compound formed.



157

Figure 14 Proposed structure of product formed from the treatment of **136** with concentrated nitric acid

The reaction was replicated by addition, to small amounts of **136**, of excess concentrated nitric acid (68 w/w%, approximate molar ratio of 108:1). After release of gas, the result was a dark brown solution. The mixture was diluted with water resulting in a dark semi-crystalline precipitate, the same observation that had occurred previously. The acidic solution was then neutralised with aqueous NaOH, resulting in a dark brown solid at the bottom of the flask. After filtration onto Whatman glass microfiber GF/A[74] paper, a dark brown/red compound was obtained. However analysis by ^{1}H NMR revealed that the compounds formed in several reactions conducted with these conditions were not a replication of the previously reported result **157** but led instead to different product(s). It can be seen in Figure 15, that the obtained spectrum does not match those previously obtained. Instead of a series of complex doublets and double doublets, a new splitting pattern, is obtained at δ 6.9 and 6.8.

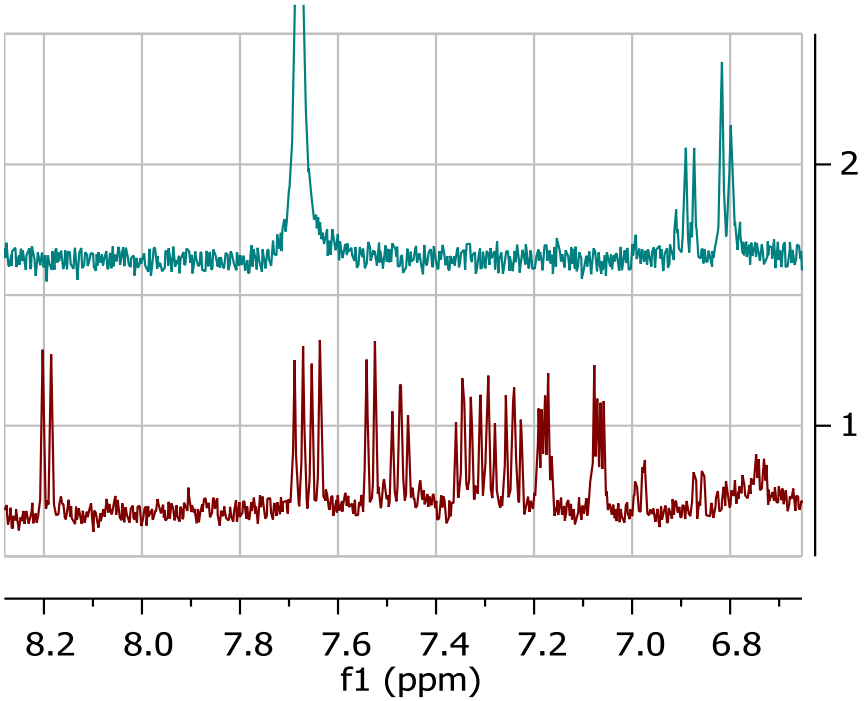


Figure 15 ^{1}H NMR spectrum of aromatic region of product of reaction of TTT with nitric acid, carried out at 400.1 Hz in CS_2 with a DMSO-d_6 insert. 1 is the previously obtained spectrum seemingly indicating a nitrated TTT (which should appear as 4 doublets and 3 double doublets) as well as parent TTT (multiplets at δ 7.25-7.20 and δ 7.14-7.09) and other unknown products. 2 is spectrum obtained after attempts to replicate the procedure, the peak at δ 7.7 is thought to be residue DMF from the TTT synthesis.

It is thought that the treatment may have been too strong, as a result of addition of concentrate nitric acid as well as quenching to basic conditions with NaOH, may have resulted in decomposition of the **136** rather than the desired reaction. Another suggestion is that a new product such as a nitrated TTT polymer was formed. Following dissection of the result further improvements were made to the procedure.

To reduce the aggressiveness of the treatment, lower concentrations of nitric acid were used (down to 6.8 w/w%). The result was higher levels of the starting material, **136**, but the same splitting pattern occurred around δ 6.9 and 6.8.

In continuation of this, further adjustments were experimented with, such as cooling the solution to 0 °C during the acid addition, reducing the time before neutralisation and use of a neutral buffer solution instead of NaOH solution. It was found that under these conditions a trace amount of the splitting pattern indicating **157** was produced. However, the major product still produced the splitting pattern at δ 6.9 and 6.8. As a result this line of study has been halted. The optimal reaction conditions which replicated the previously observed splitting pattern are given in the experimental section (section 2.5.3).

3 Conclusions and future work

3.1 Conclusions

In conclusion a new synthetic method has been developed for the synthesis of 2-bromo-8-methyltetracene (**126**). Precursor iodide (**138**), dialcohol (**139**) and dialdehyde (**140**) were successfully synthesised in equivalent yields to alternatively substituted precursors. Initial attempts to cyclise (**140**) resulted in the monocyclised product (**141**). Investigations determined that treatment with 4 equivalents of neat $TiCl_4$ left to stir at room temperature for 48 hours was the most effective treatment for conversion to **126**. Due to the difficulties of Bradsher cyclisation of the electron withdrawn dialdehyde precursor **140**, the yield of pure **126** was low (4%). Considering the extreme difficulty in synthesising electron poor tetracenes using this methodology and that this is the first reported synthesis of **126**, the result was deemed acceptable.

Following this development, the protocol was extended to other electron withdrawn tetracenes, namely 2,8-dibromotetracene **30**. Unfortunately **30** could not be synthesised utilising this methodology, the main product of the reaction being the monocyclised aldehyde **144** which was formed in yield of 54%.

The next stage of the project was the attempted C-Br functionalisation of tetracene precursors **139** and **140**. A wide variety of methods were investigated with very limited success. A variety of catalyst systems were used for the Suzuki reaction of both **140** and **139**, such as $NiCl_2$(dppp), Pd(0)/urea and Pd(0)/XPhos. The result in each case was a complex mix of unidentifiable products. The Stille cross coupling reaction did not proceed, leaving only the starting materials. Only hydrodebromination product **150** was obtained in Buchwald-Hartwig cross coupling reactions with several amine and base combinations. Trimethylaluminum adduct DABAL-Me_3 added to **140** but caused degradation of the starting material. Due to there being no evidence of the correct coupling product in any of these reactions, they were considered not worthy of further investigations.

Lithium-halogen exchange and electrophilic substitution with DMDS on diol **139** did show evidence of the desired product **151**. However yields were low and **151** could never be purified from hydrodebromination product **150**. Attempts to raise the selectivity resulted in the synthesis of at least two alternative products that could not be identified. As a result this methodology still requires plenty of optimisation to become the clean and efficient route that we are searching for. More promising was the Negishi coupling to **139**.

In two cases the Negishi coupling using the palladium NHC catalyst system Pd-PEPPSI-IPr provided the coupling product **152** in high yield and purity. However, the reaction was found to be capricious, failing to convert the starting material **139** on multiple occasions with the same treatment. This reaction is still very promising however requires more optimisation to reach a practical procedure. In an effort to

achieve this, the synthesis of iodinated diol **153** was attempted. The result was a mixture of the desired product **153** and the starting material **138.** Isolation by a silica plug and recrystallisation yielded **153** in 15% yield. Negishi coupling with Pd-PEPPSI-IPr was continued despite this to determine the feasibility of this optimisation method. The resulting solid was a mixture of desired product **153**, hydrodebromination product **150** and the starting material **153.** As a result, use of iodinated diol **153** reveals itself as an unpromising route to optimisation of this Negishi coupling.

On the other hand the scale-up of the synthesis of parent tetracene **1** was successful. First the synthesis of aldehyde **156** was carried out on up to 3 g scales without yield or purity deterioration. The scale-up of the synthesis of **1** required modification of the quenching procedure. The quench mixture was dried with molecular sieves, stirred throughout, cooled to -10 °C and the reaction mixture added to the quench mixture via cannula. In order to neutralise H^+ created during the quenching procedure, 3 equivalents of cyclohexene epoxide were also added to the quench mixture. After these adjustments **1** was successfully synthesised on 2 g scales.

The last goal of this project was to scale-up the synthesis of parent TTT **136** to gram scales and investigate the potential reaction of **136** with nitric acid. Use of larger reaction equipment and sublimation in a Kugelrohr apparatus allowed the synthesis of 1 g of **136** with only slight deterioration of yield and purity. With regards to the novel reaction of **136** and nitric acid, the results remain unexplained. The resulting product was consistent but not a replication of previous observations of nitrated TTT **157**. A minimal amount of **157** was observed however in an inconsistent manner and to levels too low to allow identification. The identification of the major product could also not be determined but is expected to be a degradation product and/or a TTT polymer.

3.2 Future work

Due to the time limitation on this project, there is still much optimisation that needs to be carried out. Several routes could result in the synthesis of **126** in higher yields, as well as a consistent protocol for the functionalisation of halogenated tetracene precursors and a full understanding of the reaction of **136** with nitric acid.

One suggestion to bring about the synthesis of **126** is to transform the aldehyde group(s) on **140** to a more reactive electrophile such as a 1,1-dibromoalkyl group. Aliphatic and aromatic aldehydes can be converted into 1,1-dibromoalkyl derivatives using a 1:1 (v/v) mixture of $P(OPh)_3$ and Br_2, which is in fact a 70:30 mixture of $[(PhO)_4PBr]$ and PBr_3.[116] Aromatic aldehydes such as the monocyclised product **141** have also been shown to undergo this transformation using BBr_3.[117] The increased electrophilic nature of this functional group compared to aldehydes may be what is required to bring about higher conversion to **126**.

Alternatively, the use of a *meta*-brominated phenyl ring could enable the second Bradsher cyclisation through utilisation of the *ortho* and *para* directing nature of halogen substituents. However, use of 3-bromobenzyl bromide for diol formation could potentially lead to the formation of 2 tetracene isomers (bromide in the 1- or 3- position of the tetracene) and the use of 3,5-dibromobenzyl bromide would require the nucleophilic attack of an aromatic ring with two electron withdrawing substituents. As a result this potential improvement appears less appealing than the creation of a 1,1-dibromoalkyl group for the final closure.

If neither of these potential improvements successfully provide **126** at a higher yield it should be remembered that alternative methods have been utilised for the synthesis of 2-bromotetracene **36** (8-bromo-5,12-tetracenequinone **35** can be synthesised at 44% yield and closed to **36** at 32% yield [Scheme 7]).[29] This methodology is very likely to be safely expanded to synthesise **126**. It is likely that the best methodology to synthesise 2- and 2,8-halogenated tetracenes will not utilise a Bradsher cyclisation.

Future work on the cross coupling of tetracene precursors should focus on the Negishi cross coupling of **139**. Coupling to iodinated diol **153** does not seem a promising route for this optimisation. The reason of reaction failing on some occasions remains unclear, further repeats in the similar conditions and careful observation should lead to greater clarification. Another modification that may lead to a reliable cross coupling reaction is to switch the catalyst to Pd-PEPPSI-iPent. This is a more sterically demanding, second generation catalyst that outperforms Pd-PEPPSI-IPr in a variety of sp^2–sp^2 Negishi cross coupling reactions. The iPent derivative is particularly suited for the cross coupling of sterically hindered substrates which may be the reason for the raised issues.[111]

Instead of optimisation of the Negishi coupling, the approach could instead be to introduce protecting groups onto the alcohols of **136**. These functional groups are a likely cause of many of the issues in the attempted functionalisation reactions carried out in this report. Initially we were reluctant to investigate this due to the increased total step count which the synthesis was designed to avoid and due to the literature precendence for functional group tolerance to alcohol and aldehyde groups in many cross coupling reactions. Nevertheless, if high yield as well as clean protection and deprotection can be achieved, this is a very promising approach to the synthesis of a large library of substituted tetracenes. Moreover, previously disregarded reactions may be used for this transformation. Once a protocol has been established for C-Br functionalisation it will be expanded to the dibrominated diol precursor **142**.

The reaction of **136** with nitric acid requires further investigation. Additional analytical data may reveal the identity of the resulting products. Further repetitions of the treatment previously used may result in understanding of why the reaction is behaving differently and how to nitrate TTT.

It is expected that the improvements suggested in this report will be implemented in the future and with hope, will achieve the original goals of this project.

4 Experimental

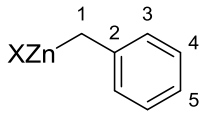
4.1 General Information

Reactions involving air-sensitive reagents were carried out under an argon atmosphere using flame dried Schlenk apparatus. Those involving oxygen were under >99% O_2 (BOC) at 1 atm. Reaction temperatures refer to those of external baths. Ambient temperature was typically 19-28 °C during these studies. Dichloromethane and 1,2-dichloroethane were used distilled from calcium hydride; tetrahydrofuran from sodium/benzophenone ketyl respectively. Dry dimethylformamide (DMF) was bubbled with nitrogen for 10 minutes before use. All other solvents were used as received from commercial suppliers. The compounds 2-butyne-1,4-diol, iodine, PCy_3 (Cy = cyclohexyl), SPhos (2-dicyclohexylphosphino-2,6-dimethoxybiphenyl), $Pd(OAc)_2$, 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), CuCN, $CuBr{\cdot}SMe_2$, XPhos (2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl), Pd-PEPPSI-IPr (PEPPSI = Pyridine-enhanced precatalyst preparation, stabilisation and initiation; IPr = diisopropyl-phenylimidazolium derivative), $NiCl_2$(dppp), $Pd_2(dba)_3{\cdot}CHCl_3$, $Pd_2(dba)_3$, 1,2-dibromoethane, $^nBu_3SnCl$, phenylboronic acid, urea, imidazole, morpholine, diphenylamine, dimethyl disulfide, 2-bromopropane, bromobenzene, sulfur, nitric acid (68 w/w %), KH_2PO_4, NaOH, K_3PO_4, K_2CO_3, Na_2CO_3, Cs_2CO_3 and celite were purchased from Alfa-Aesar, Fisher, Merck and Sigma-Aldrich, and used without further purification. The compound $[Cu(MeCN)_4]BF_4$ was prepared by a literature route.[118] Lithium chloride (Aldrich, anhydrous, >99%), $TiCl_4$ (Fluka, >98%), $BF_3{\cdot}OEt_2$ (distilled at 20 mbar), *N*-methylimidazole (NMI), ^{n}BuLi (1.6 M in hexanes), ^{t}BuONa, DABAL-Me_3, LiH and CsF were stored and handled under argon. Benzyl halides were commercial (Sigma-Aldrich). Liquid benzylic halides were purified by distillation under reduced pressure (typically 20 mbar), solid halides were pre-dried (10 min 4Å Sieves) as ethereal solutions prior to use. Zinc dust (<10 µm, Sigma-Aldrich: 209988-1KG), used for benzylzinc halides, was activated *in situ* by trimethylsilyl chloride (purchased from Alfa-Aesar) used as supplied. The grade of zinc selected promotes both rapid benzylic C-X (X = Cl, Br) insertion and fast settling of the excess zinc, post organometallic formation, while minimising deactivation through excessive surface oxide formation. Magnesium turnings were of Grignard quality. Benzylzinc halide reagents were titrated against I_2;[119] Grignard reagents were Gilman double titrated before use.[120] Slow addition of benzylic reagents were carried out using standard syringe pumps or a DOSCA HPLH20[121] microprocessor controlled pump for larger quantities (>50 mL). Chromatographic silica gel 60 (220–240 mesh) was supplied by Fluorochem. Thin layer chromatography was performed on foil-backed plates coated with Merck Silica gel 60 F_{254}. Plates were developed using ultraviolet light and basic aqueous potassium permanganate. Infrared spectra were recorded on a Bruker Alpha FT-IR spectrometer by attenuated total reflection (diamond-ATR) on solid films. Nuclear magnetic resonance spectra were recorded on Bruker DPX-400 (400.1 MHz), AV400 (400.1 MHz), AV(III)400 (400.1 MHz) or a Bruker Ascend 500 (500.1 MHz) spectrometers at ambient temperature. Chemical shifts are quoted in parts per million (ppm) and referenced to residual solvent peaks using values provided by the MestReNova processing software.[76] Coupling constants (*J*) are quoted in Hertz and

coupling correlations were based on standard COSY, DEPT, HMQC, HMBC experiments. Proton and ^{13}C NMR studies of tetracenes **124** and tetrathiotetracenes **136** were carried out in CS_2 (Sigma-Aldrich, ≥99%) deoxygenated before use. This commercial sample gave residual signals in its ^{1}H NMR (500.1 MHz, DMSO-d_6) spectrum at 5.03, 1.11-0.98, 0.83, 0.70-0.53, and -0.22 ppm as supplied. In the ^{13}C NMR spectrum (124.7 MHz, DMSO-d_6) CS_2 appeared at δ_C 192.1 ppm. UV-Vis spectra were recorded on an Agilent Cary spectrophotometer as ca. 10^{-5} M dichloromethane solutions. Semi-quantitative log(ε) values are given as a guide to relative peak height, accurate quantification is complicated by slow kinetic dissolution and sample air/light sensitivity. Mass spectrometry was performed using a Bruker MicroTOF or VG Micromass AutoSpec spectrometers using electrospray (ESI), electron impact (EI) or field desorption (FD) ionization modes; theoretical HRMS molecular weights were determined using ChemDraw software;[122] for HRMS analyses deviations from expected values (σ) are given in ppm. Melting points were determined with a Gallenkamp MFB-600-010F melting point apparatus. Elemental CH analyses were conducted on a CE-440 Elemental Analyzer; observed %carbon vs. calculated ideal values were used to estimate tetrathiotetracene purities.

4.2 Starting materials

4.2.1 Benzylzinc halide reagent preparation for synthesis of 122, representative examples: $PhCH_2ZnX$ (X = Cl, Br)



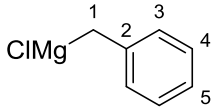
X = Cl, Br

Chloride reagents: Zinc dust (5-9 µm, 52.4 g, 0.801 mol, 2 equiv.) was dried under vacuum at >200 °C (2-5 min), then cooled to room temperature under an atmosphere of argon. Tetrahydrofuran (400 mL) was then added, forming a grey suspension. The reaction mixture was cooled to 0 °C and trimethylsilyl chloride (2.05 mL, 16.1 mmol, 4 mol%) was added in one portion and the mixture stirred (0.5 h). Freshly distilled benzyl chloride (46.1 mL, 0.401 mol) was subsequently added over a period of 10 minutes. After addition of the $PhCH_2Cl$ was complete the reaction mixture was warmed to 40 °C (4 h). Cooling to room temperature provided a turbid white suspension (which typically titrated[119] at >0.7 M, >80% yield) over the remaining residual zinc powder. The supernatant solution could be stored for at least one week at 4 °C (resulting in clear or pale yellow supernatants), but typically the organometallic was used within 48 h. Bromide reagents: were prepared from $ArCH_2Br$ and elemental zinc in THF at 0 °C using the method of Shannon[123] and titrated as above.

4.2.2 Preparation of secondary alkylzinc bromide reagents, representative example: isopropylzinc bromide

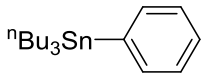
Zinc dust (5-9 µm, 1.31 g, 20.0 mmol, 2 equiv.) and LiCl (0.85 g, 20.0 mmol, 2 equiv.) were added to a dry Schenk tube equipped with a magnetic stir bar and dried under high vacuum at >200 °C (10 min), then cooled to room temperature under an atmosphere of nitrogen. Dry THF (10 mL) and 1,2-dibromoethane (43.1 µL, 0.50 mmol, 5 mol%) were added via syringe and the reaction mixture was heated at 60 °C for 20 min. After cooling to rt, trimethylsilyl chloride (12.7 µL, 0.1 mmol, 1 mol%) and a solution of iodine (12.7 mg, 0.05 mmol, 0.5 mol%) in THF (50.0 µL) were added via syringe. The reaction mixture was heated at 60 °C for 20 min and then cooled to rt. Dry 2-bromopropane (0.94 mL, 10.0 mol) was subsequently added over a period of 10 minutes. After addition was complete the reaction mixture was warmed to 50 °C and stirred (16 h). Cooling to room temperature provided a turbid white suspension (which typically titrated[119] at >0.7 M, >80% yield) over the remaining residual zinc powder. The supernatant solution could be stored for at least one week at 4 °C (resulting in clear or pale yellow supernatants), but typically the organometallic was used within 48 h. Method adapted from Çalimsiz and Organ.[114]

4.2.3 Grignard reagent preparation, representative example: $PhCH_2MgCl$



Grignard quality magnesium turnings (55.0 g, 2.26 mol, 1.1 equiv.) were activated by mechanical stirring[124] under argon (20 °C, 14 h) until black in colour. Tetrahydrofuran (1.00 L) was then added, forming a suspension of activated magnesium. Distilled benzyl chloride (250 mL, 2.17 mol) was then added dropwise to the reaction mixture at a rate of *ca* 0.2 mL min^{-1} (a micrometering pump[121] was found to be useful for this task). After completion of the addition the reaction mixture was filtered through a sinter under argon and titrated (1.6 M) to provide the desired Grignard reagent as a dark grey solution (on small scales the reagent could be simply syringed off). The solutions should be used within 48 h. **CAUTION!** Use of *undistilled* benzyl chloride can result in delayed vigorous exotherms that are *potentially explosive at large scale*. This is attributed to the propylene oxide commonly present in commercial $PhCH_2Cl$ (as supplied) as a radical inhibitor. This appears to delay initiation of Grignard formation resulting in a build-up of unreacted benzyl chloride. When the reaction does initiate uncontrolled exotherms result. Thus, all commercial benzyl chlorides were distilled before use, especially at larger scales.

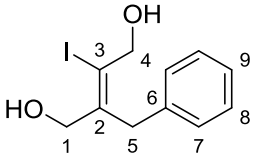
4.2.4 Organotin reagent preparation: tributylphenyltin (149)[93]



A dry Schlenk tube containing bromobenzene (0.42 mL, 4 mmol) was cooled to -78°C and ^{n}BuLi (3.03 mL, 1.45 M, 4.40 mmol, 1.1 equiv.) was added dropwise over 10 min with vigorous stirring. The reaction was maintained for 40 min at −78°C under continuous stirring during which it changed from yellow to colourless. Then $^nBu_3SnCl$ (1.19 mL, 4.40 mmol, 1.1 equiv.) was added dropwise over 10 min and the reaction

mixture left to slowly rise to room temperature overnight. The organotin was purified by filtering through celite, washing with DCM (4 x 5 mL) and the mother liquors evaporated under vacuum. The presence of **149** was confirmed through ^{1}H NMR analysis.

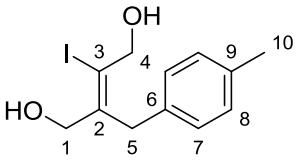
4.3 Diversity cores (121) for dissymmetric tetracenes, representative example: (*Z*)-2-benzyl-3-iodobut-2-ene-1,4-diol (154)



Benzylmagnesium chloride (143 mL, 1.05 M tetrahydrofuran solution, 150 mmol) was added to a stirred solution of 2-butyne-1,4-diol **120** (3.87 g, 45.0 mmol, 0.3 equiv.) in tetrahydrofuran (25 mL) at 0 °C to form a colourless precipitate in a grey solution. After 5 min at 20 °C solid cuprous bromide dimethyl sulfide (185 mg, 0.90 mmol, 2 mol% based on diol) was added, against an argon counter flow, and the reaction mixture promptly warmed to 60-65 °C (using a pre-heated oil bath). Over 1 h the solid dissolved and a dark solution formed. Completion of the carbocupration was monitored by TLC (in EtOAc the initial diol $\mathbf{R}_f$ 0.52 is replaced by $\mathbf{R}_f$ 0.46). The reaction mixture was cooled first to ambient temperature and then to -60 °C in a lightly lagged bath. Solid I_2 (15.24 g, 60.0 mmol, 0.4 equiv.) was added, against an argon counterflow, and the mixture stirred as it came to 0 °C over ca. 1 h. Analysis (TLC, EtOAc, $\mathbf{R}_f$ 0.69) revealed the presence of **154**. The reaction mixture was extracted with EtOAc (3 × 160 mL) and washed with sodium metabisulfite (2 × 200 mL of 5% w/w aqueous solution) and water (1 × 150 mL). The resulting pale solution was dried ($MgSO_4$) and filtered. The residual drying agent was re-extracted with EtOAc (3 × 70 mL) and the combined dry organic phases were evaporated to a pale oil that could be solidified from Et_2O containing traces of EtOAc (9.92 g, 32.6 mmol, 72%) over three crops. TLC: $\mathbf{R}_f$ (ethyl acetate) 0.68; colourless microneedles from EtOAc/CH_2Cl_2 (1:1) on cooling from 20 to 4 °C with **mp** 94-95 °C; **IR** (diamond-ATR): ν_{max}/cm^{-1} 3219, 3058, 3025, 2923, 2861, 1492, 1450, 1361, 1314, 1241, 1067, 1019, 993, 734, 694, 574, 491, 469, 430; **^{1}H NMR** (400.1 MHz, $CDCl_3$): δ 7.36-7.28 (m, 2H, H-7), 7.25-7.16 (m, 3H, H-8 and H-9), 4.50 (d, *J* = 6.5 Hz, 2H, H-4), 4.24 (d, *J* = 6.5 Hz, 2H, H-1), 3.81 (s, 2H, H-5), 1.96 (t, *J* = 6.5 Hz, 1H, OH), 1.59 (t, *J* = 6.5 Hz, 1H, OH); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 145.6 (C), 139.9 (C), 129.5 (CH), 129.4 (CH), 127.3 (CH), 106.6 (C), 71.2 (CH_2), 68.1 (CH_2), 35.6 (CH_2); **MS** (+ESI) *m/z* 304 (M); **HRMS** (+ESI) calcd. For $C_{11}H_{13}IO_2$ *m/z* 303.9960 (M), found *m/z* 303.9941 (M) (σ = 6 ppm); **Anal:** Calcd. For $C_{11}H_{13}IO_2$ C, 43.44; H, 4.31; found C, 43.49; H, 4.24%. Very rarely, Grignard reagents containing appreciable amounts of Wurtz-coupling impurities or high boiling lipophilic Grignard hydrolysis products inhibited crystallisation. In problematic cases, easy purification could be effected by dissolution of crude **154** in CH_2Cl_2 (10 mL g^{-1}) and gravity filtration chromatography. After loading of the dichloromethane suspension containing **154** onto a CH_2Cl_2 solvated silica plug initial elution with

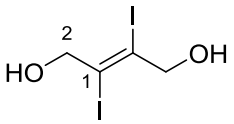
CH_2Cl_2 afforded low polarity by-products while **154** was strongly retained; elution with CH_2Cl_2/EtOAc (1:4 to 1:1) provided **154**. Between 4-8 g of crude materials could be purified on a 70 mm high x 50 mm diameter plug this way, but this was not normally necessary.

4.3.1 (*Z*)-2-iodo-3-(4-tolyl)but-2-ene-1,4-diol (138)



Prepared analogously to **154** using: 4-methylbenzylmagnesium chloride (145 mL, 0.80 M tetrahydrofuran solution, 156 mmol), 2-butyne-1,4-diol (4.03 g, 46.8 mmol) in tetrahydrofuran (25 mL), $CuBr{\cdot}SMe_2$ (193 mg, 0.94 mmol) and I_2 (15.84 g, 62.4 mmol) to yield **138** as a colourless powder 9.46 g, 29.7 mmol (66%) on trituration with Et2O. TLC: $\mathbf{R_f}$ (EtOAc:pentane, 1:1) 0.56; colourless microneedles from hot EtOAc on cooling to 4 °C with **mp** 115- 116 °C; **IR** (diamond-ATR): ν_{max}/cm^{-1} 3242, 3046, 3018, 2920, 2874, 1510, 1476, 1493, 1440, 1414, 1316, 1237, 1169, 1072, 1036, 1017, 990, 961, 921, 831, 800, 751, 658, 552, 480, 435; **^{1}H NMR** (400.1 MHz, $CDCl_3$): δ 7.09 (AB system, *JAB* = 8.0 Hz, 4H, H-7 and H-8), 4.50 (d, *J* = 6.5 Hz, 2H, H-4), 4.24 (d, *J* = 6.5 Hz, 2H, H-1), 3.76 (s, 2H, H-5), 2.32 (s, 3H, H-10), 1.94 (t, *J* = 6.5 Hz, 1H, OH), 1.58 (t, *J* = 6.5 Hz, 1H, OH); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 144.4 (C), 135.5 (C), 135.4 (C), 128.7 (CH), 128.0 (CH), 105.1 (C), 69.8 (CH_2), 66.7 (CH_2), 33.9 (CH_2), 19.7 (CH_3); **MS** (+ESI) *m/z* 318 (M); **HRMS** (+ESI) calcd. for $C_{12}H_{15}IO_2$ *m/z* 318.0117 (M), found *m/z* 318.0118 (M) (σ <1 ppm); **Anal:** Calcd. for $C_{12}H_{15}IO_2$ C, 45.30; H, 4.75; found C, 45.30; H, 4.80%.

4.3.2 Core for symmetrical tetracenes: (*E*)-2,3-diiodobut-2-ene-1,4-diol (125)

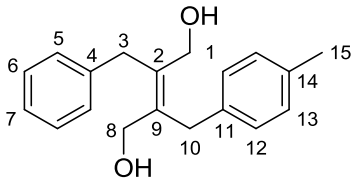


Granular solid iodine (9.00 g, 35.5 mmol, 1 equiv.) was suspended in $CHCl_3$ (120 mL) and a large (50 mm long x 15 mm wide) egg-shaped stir bar added. The stirred mixture was brought to reflux briefly, effecting I_2 dissolution, and then re-cooled to ambient temperature. Finely ground 2-butyne-1,4-diol **120** (3.11 g, 36.1 mmol) was added. The mixture was refluxed and stirred (18-26 h) during which time it became almost colourless. Heating was stopped and the mixture allowed to come to room temperature. Any large masses of **125** or residual solid iodine were gently broken up with a glass rod and the suspension gently warmed to ca. 40 °C. Diiodide (**125**) was isolated by filtration and washed with chloroform (2 × 30 mL) and Et_2O (2 × 30 mL). Drying afforded **125** as a colourless powder 10.94 g (90%). This procedure gives much improved yields over those described in the literature in our hands,[63] but with identical spectroscopic data and improved melting point. TLC: $\mathbf{R_f}$ (EtOAc:hexane, 1:1) 0.55; **mp** 176-178 °C (lit.[63] mp 155-157 °C); **^{1}H NMR** (400.1 MHz, DMSO-d_6): δ 5.52 (t,

J = 6.0 Hz, 2H, OH), 4.21 (d, *J* = 6.0 Hz, 4H, H-2); **^{13}C NMR** (100.6 MHz, DMSO-d_6): δ 105.1 (C), 73.9 (CH_2).

4.4 Preparation of diols (122)

4.4.1 Method I by heterocoupling to (122) for dissymmetric diols, representative example: (*E*)-2-benzyl-3-(4-methylbenzyl)but-2-ene-1,4-diol (150)



Lithium chloride (0.33 g, 7.86 mmol, 1.0 equiv.) was dried under vacuum (ca. 1 millibar) at >200 °C until free flowing (ca. 5 min), then cooled under an atmosphere of argon. Tetrahydrofuran (25 mL) was then added followed by (*Z*)-2-benzyl-3-iodobut-2-ene-1,4-diol (2.40 g, 7.86 mmol), forming a colourless pale reaction mix. Solid S-Phos (61.6 mg, 150 µmol, 1.9 mol%) was added and the reaction initiated by subsequent addition of solid $Pd(OAc)_2$ (35.3 mg, 157 µmol, 2 mol%) forming a chocolate brown coloured reaction mixture (see Figure 16a). If catalyst formation did not initiate immediately this was induced by addition of small (ca. 0.15 mmol, 2 mol%) amounts of arylzinc chloride solution and by localised short 'spot' heating (ca. 60 °C) of the reaction flask. Promptly, 4-methylbenzylzinc chloride (10.4 mL of 0.9 M THF solution, 9.4 mmol, 1.2 equiv.) was added. Upon addition of the benzylzinc reagent the colour of the reaction mixture became bright orange (Figure 16b); which darkened indicating the commencement of the cross-coupling reaction. Typically, the total addition-coupling process took 15-20 min. TLC analysis (EtOAc) showed replacement of iodide (R_f 0.81) by **150** (R_f 0.70). The reaction mixture was quenched with saturated aqueous ammonium chloride solution (10 mL) and extracted with ethyl acetate (4 × 20 mL). The organic layer was separated, and the aqueous layer re-extracted with ethyl acetate (2 × 10 mL). In the case of lower solubility diols small quantities (ca. 5% v/v) of THF were used as a cosolvent in the EtOAc extractions. The combined organic extracts were dried with $MgSO_4$. The residual drying agent was re-extracted with EtOAc [3 × 10 ml; warm EtOAc/THF (1:1) was used for lower solubility diols, e.g. 5af, if any lustrous product had prematurely crystallised on it]. The crude orange-brown product attained on evaporation of the combined organics was triturated with Et_2O and filtered to provide a colourless solid (1.87 g, 6.62 mmol, 84%) after three cycles. TLC: R_f (EtOAc) 0.70; glinting colourless needles from EtOAc/MeOH (1:1) on cooling to ambient, then 4 °C with **mp** 150-151 °C; **IR** (diamond-ATR): ν_{max}/cm^{-1} 3373, 3021, 2952, 2916, 2894, 1600, 1510, 1492, 1451, 1434, 1331, 1294, 1265, 1129, 1059, 991, 928, 806, 754, 699, 609, 472; **^{1}H NMR** (400.1 MHz, DMSO-d_6): δ 7.28-7.22 (m, 2H, H-6), 7.21-7.11 (m, 3H, H-5 and H-7), 7.08- 7.04 (m, near app. s, 4H, H-15), 4.72 (t, *J* = 5.2 Hz, 1H, OH) overlapped by 4.71 (t, *J* = 5.2 Hz, 1H, OH), 3.94 (d, *J* = 5.2 Hz, 2H, H-1 or H-8) overlapped by 3.93 (d, *J* = 5.2 Hz, 2H, H-1 or H-8), 3.60 (s, 2H, H-3 or H-10), 3.55 (s, 2H, H-3 or H-10), 2.25 (s, 3H, H-12 and H-13); **^{13}C NMR** (100.6 MHz, DMSO-d_6): δ 140.6 (C), 137.4 (C), 135.5 (C), 135.1 (C), 134.5 (C), 128.8 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 125.6 (CH), 59.3

(2 × CH_2), 34.1 (CH_2), 33.7 (CH_2), 20.6 (CH_3); **MS** (+ESI) 305 (M+Na); **HRMS** calcd. for $C_{19}H_{22}NaO_2$ *m/z* 305.1517 (M+Na), found *m/z* 305.1524 (M) (σ = 2 ppm); **Anal:** Calcd. for $C_{19}H_{22}O_2$, 80.82; H, 7.85; found C, 80.69; H, 7.73%.

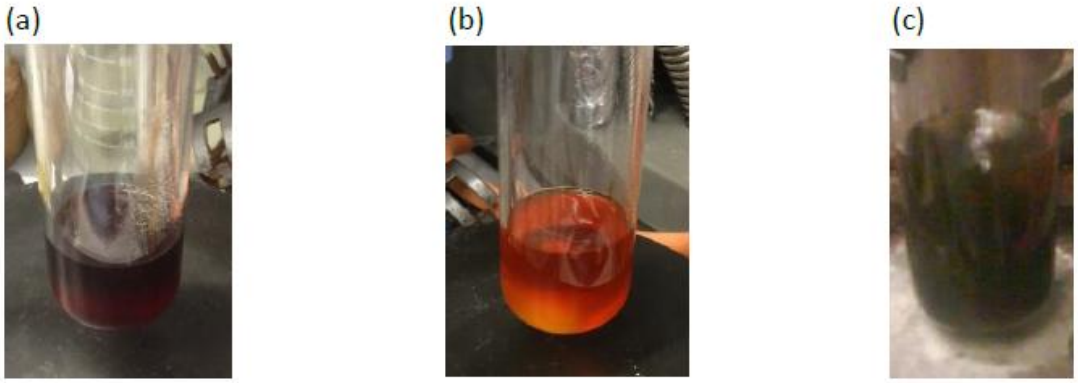
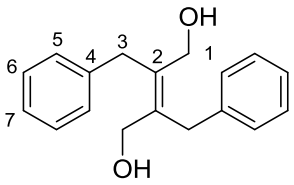


Figure 16 (a) colour of active catalyst; (b) colour of the benzylated catalyst; (c) typical colour of reaction mixture at completion of the coupling.

4.4.2 Method II by homocoupling to (121) for symmetrical diols, representative example: (*E*)-2,3-dibenzylbut-2-ene-1,4-diol (155)



In appropriate Schlenkware LiCl (1.62 g, 38.4 mmol, 2.4 equiv.) was dried under vacuum at >200 °C until free flowing (ca. 5 min), then cooled under an atmosphere of argon. Solid (*E*)-2,3-diiodobut-2-ene-1,4-diol **125** (5.44 g, 16.0 mmol) was added followed by THF (40 mL) forming a colourless suspension that was heated to 60±5 °C. Tricyclohexylphosphine (85.2 mg, 304 µmol, 1.9 mol%) was added to the reaction mixture followed by $Pd(OAc)_2$ (72.0 mg, 320 µmol, 2 mol%) forming a dark chocolate brown coloured reaction mixture [see Figure 17a]. Benzylzinc chloride (0.8 M in tetrahydrofuran, 47.6 mL, 38.4 mmol, 2.4 equiv.) was then added promptly. Upon immediate initial addition of the benzylzinc reagent the colour of the reaction mixture becomes bright orange (Figure 17b), darkening during the last part of the addition indicating the cross-coupling reaction proceeding. After addition of the entirety of the zinc reagent the reaction was dark/black (Figure 17c). Typically, the total addition-coupling process took about 2-3 min. [On larger scales the addition took slightly longer and the reaction vessel was equipped with a reflux condenser as significant heat is generated on addition of the benzylzinc halide reagent and reflux of the THF solvent can occur.] TLC analysis (EtOAc) shows replacement of diiodide **125** ($\mathbf{R}_f$ 0.66) by **155** ($\mathbf{R}_f$ 0.52). The reaction was cooled to room temperature and quenched with saturated ammonium chloride solution (80 mL). The resultant mixture was extracted with ethyl acetate (4 × 30 mL). The organic layer was separated, and the aqueous layer re-extracted with ethyl acetate (2 × 50 mL). For less soluble diols EtOAc containing small amounts of THF (ca. 5% v/v) was used. The

combined organic extracts were then dried with $MgSO_4$ and filtered. The residual drying agent was re-extracted with warm EtOAc/THF (1:1) (50 mL) if any product had prematurely crystallised on it. The crude product attained on evaporation of the combined organics. It was found that keeping the rotary evaporator water bath cool (ca. 30 °C) minimised the formation of dark non-crystalline by-products that inhibited subsequent crystallisation. Trituration with Et_2O containing and filtered to provide a colourless solid (typically 2.64-3.07 g, 9.84-11.43 mmol, 62-72%) after 3 cycles. TLC: $\mathbf{R_f}$ (EtOAc) 0.52; glinting colourless needles from EtOAc/MeOH (1:1) on cooling to ambient, then 4 °C with **mp** 157-158 °C; **IR** (diamond-ATR) ν_{max}/cm^{-1} 3398, 3080, 3063, 3051, 3021, 2985, 2951, 2928, 2918, 2889, 1600, 1492, 1281, 1452, 1429, 1321, 1292, 1191, 1155, 1127, 1082, 1054, 1027, 1012, 993, 930, 914, 818, 807; **^{1}H NMR** (400.1 MHz, DMSO-d_6): δ 7.28-7.23 (m, 4H, H-6), 7.22-7.12 (m, 6H, H-4, H-5), 4.75 (t, *J* = 5.2 Hz, 2H, OH), 3.95 (d, *J* = 5.2 Hz, 4H, H-1), 3.61 (s, 4H, H-3); **^{13}C NMR** (100.6 MHz, DMSO-d_6): δ 140.5 (C), 135.3 (C), 128.5 (CH), 128.2 (CH), 125.6 (CH), 59.3 (CH_2), 34.1 (CH_2); **MS** (+ESI) 291 (M+Na); **HRMS** calcd. for $C_{18}H_{20}NaO_2$ *m/z* 291.1361 (M+Na), found *m/z* 291.1345 (M+Na) (σ = 5 ppm); **Anal:** Calcd. for $C_{18}H_{20}O_2$ C, 80.56; H, 7.51; found C, 80.54; H, 7.53%. Details of crystallisation procedure: **155** (1.0 g) dissolved in refluxing 1:1 MeOH/EtOAc (28 mL) and hot filtered gave ca. 65% mass recovery on slow cooling to 4 °C. Evaporation of the mother liquors allowed the process to be repeated (85- 90+% mass recovery over two cycles). Compound **155** could also be prepared from **154** using Method I with PCy_3. The use of hot MeCN in conjunction with decolourising charcoal was also effective in solidifying alternative functionalised diols.

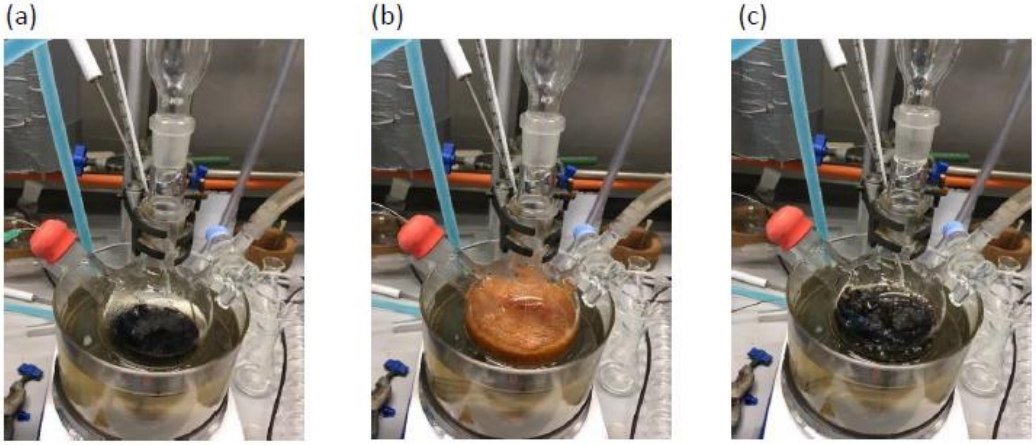
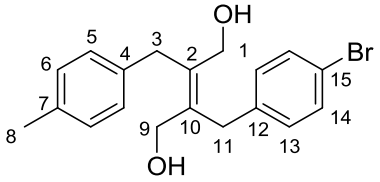


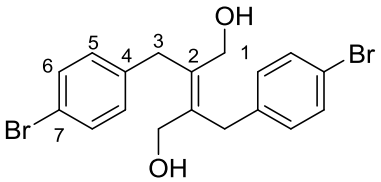
Figure 17 (a) colour of active catalyst; (b) mid-addition of $PhCH_2ZnCl$ showing solvent at reflux; (c) colour of reaction mixture at the end of the addition showing completion of the coupling.

4.4.3 (*E*)-2-(4-bromobenzyl)-3-(4-methylbenzyl)but-2-ene-1,4-diol (139)



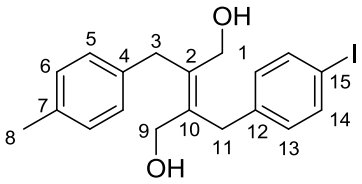
Prepared by a method analogous to **150** from (*Z*)-2-iodo-3-(4-methylbenzyl)but-2-ene-1,4-diol **138** (2.50 g, 7.48 mmol), 4-bromobenzylzinc chloride (10.8 mL, 0.84 M THF solution, 9.07 mmol) to yield **139** as a beige solid (2.48 g, 6.86 mmol, 92%) on trituration with Et_2O (3 cycles). TLC: $\mathbf{R_f}$ (ethyl acetate) 0.74; lustrous thin colourless flakes from EtOAc/MeOH (1:1) on cooling to 4 °C with **mp** 153-154 °C; **IR** (diamond-ATR): ν_{max}/cm^{-1} 3371, 3301, 3016, 2952, 2914, 2894, 1510, 1484, 1433, 1333, 1289, 1129, 1067, 1012, 994, 842, 794, 623, 616, 481; **^{1}H NMR** (400.1 MHz, DMSO-d_6): δ 7.43 (app d, *J* = 8.4 Hz, 2H, H-14), 7.43 (app d, *J* = 8.4 Hz, 2H, H-13), 7.06 (app s, 4H, H-5 and H-6), 4.74 (t, *J* = 5.1 Hz, 1H, OH) overlapped by 4.73 (t, *J* = 5.1 Hz, 1H, OH), 3.93 (d, *J* = 5.1 Hz, 2H, H-1 or H-9), 3.90 (d, *J* = 5.1 Hz, 2H, H-1 or H-9), 3.56 (s, 2H, H-3 or H-11), 3.53 (s, 2H, H-3 or H-11), 2.24 (s, 3H, H-8); **^{13}C NMR** (100.6 MHz, DMSO-d_6): δ 140.1 (C), 137.3 (C), 135.8 (C), 134.8 (C), 134.5 (C), 130.9 (CH), 130.8 (CH), 128.8 (CH), 128.3 (CH), 118.6 (C), 59.3 (2 × CH_2) C-1 and C-9 coincident, 33.8 (CH_2), 33.5 (CH_2), 20.6 (CH_3); **MS** (+ESI) 383 (M+Na, ^{79}Br); **HRMS** calcd. For $C_{19}H_{21}BrNaO_2$ *m/z* 383.0623 (M+Na, ^{79}Br), found *m/z* 383.0635 (M+Na, ^{79}Br) (σ = 3 ppm); **Anal:** Calcd. for $C_{19}H_{21}BrO_2$ C, 63.17; H, 5.86; found C, 62.78.; H, 5.77%. Compound **139** was also attained in 92% yield using PCy_3 as a ligand in place of S-Phos.

4.4.4 (*E*)-2,3-*bis*(4-bromobenzyl)but-2-ene-1,4-diol (142)



Prepared by a method analogous to **155** using: (*E*)-2,3-diiodobut-2-ene-1,4-diol **125** (3.06 g, 9.00 mmol), 4-bromobenzylzinc chloride (26 mL, 0.83 M tetrahydrofuran solution, 21.6 mmol) to yield **142** as colourless solid (2.48 g, 5.82 mmol, 65%). TLC: $\mathbf{R_f}$ (EtOAc:hexane, 2:1) 0.33; recrystallised from MeCN on cooling to -10 °C with **mp** 139-140 °C; **IR** (diamond-ATR): ν_{max}/cm^{-1} 3373, 3305, 2991, 2957, 2911, 2894, 2850, 1483, 1433, 1400, 1339, 1294, 1267, 1232, 1187, 1129, 1104, 1067, 1010, 992, 924, 884, 834, 811, 788, 713, 636, 511, 553; **^{1}H NMR** (400.1 MHz, DMSO-d_6): δ 7.44 (app d, *J* = 8.4 Hz, 4H, H-6), 7.15 (app d, *J* = 8.4 Hz, 4H, H-5), 4.78 (t, *J* = 5.0 Hz, 2H, OH), 3.91 (d, *J* = 5.0 Hz, 4H, H-1), 3.55 (s, 4H, H-3); **^{13}C NMR** (100.6 MHz, DMSO-d_6): δ 140.0 (C), 135.3 (C), 131.0 (CH), 130.8 (CH), 118.7 (C), 59.4 (CH_2), 33.6 (CH_2); **MS** (+ESI) 442 (M+NH_4, ^{79}Br); **HRMS** calcd. for $C_{18}H_{22}Br_2NO_2$ *m/z* 442.0012 (M+NH_4, ^{79}Br), found *m/z* 442.0015 (M+NH_4, ^{79}Br) (σ = <1 ppm).

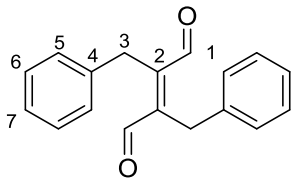
4.4.5 (*E*)-*2*-(4-iodobenzyl)-3-(4-methylbenzyl)but-2-ene-1,4-diol (153)



Prepared by a method analogous to **150** from (*Z*)-2-iodo-3-(4-methylbenzyl)but-2-ene-1,4-diol **138** (0.750 g, 2.36 mmol), 4-iodobenzylzinc bromide (3.25 mL, 0.87 M THF solution, 2.83 mmol) to yield a crude mixture of **153** and **138**, **153**/**138** = 1:0.4. Purification by silica plug (1:1 hexane/EtOAc then EtOAc) provided a sample of **153** in high enough purity for recrystallisation from EtOAc/MeOH (1:1) on cooling to 4 °C, obtaining **153** as colourless cuboidal microcrystals (0.14 g, 0.35 mmol, 15%). TLC: $\mathbf{R_f}$ (EtOAc:Hexane, 2:1) 0.51; **mp** 151-152 °C; **IR** (diamond-ATR): ν_{max}/cm^{-1} 3374, 2915, 1739, 1510, 1481, 1434, 1333, 1190, 1129, 1065, 1007, 994, 928, 833, 792, 759, 715, 625, 535, 478, 455; **^{1}H NMR** (400.1 MHz, DMSO-d_6): δ 7.60 (d, *J* = 8.3 Hz, 2H, H-14), 7.06 (app s, 4H, H-5 and H-6), 7.01 (d, *J* = 8.1 Hz, 2H, H-13), 4.74 (t, *J* = 3.1 Hz, 1H, OH) overlapped by 4.73 (t, *J* = 3.1 Hz, 1H, OH), 3.93 (d, *J* = 3.1 Hz, 2H, H-1 or H-9), 3.89 (d, *J* = 3.1 Hz, 2H, H-1 or H-9), 3.54 (s, 2H, H-3 or H-11), 3.52 (s, 2H, H-3 or H-11), 2.25 (s, 3H, H-8); **^{13}C NMR** (100.6 MHz, DMSO-d_6) δ 141.0 (C), 137.7 (C), 137.3 (CH), 136.3 (C), 135.2 (C), 135.0 (C), 131.5 (CH), 129.3 (CH), 128.8 (CH), 91.7 (C), 59.8 (2 × CH_2) C-1 and C-9 coincident, 34.2 (CH_2), 34.1 (CH_2), 21.1 (CH_3); **MS** (+ESI) 431 (M+Na); **HRMS** calcd. For $C_{19}H_{21}INaO_2$ *m/z* 431.0478 (M+Na), found *m/z* 431.0478 (M+Na) (σ = <1 ppm); **Anal:** Calcd. for $C_{19}H_{21}IO_2$ C, 55.9; H, 5.18; found C 56.1; H, 5.39%.

4.5 Preparation of dials (123)

4.5.1 Preparation of dialdehydes by copper-catalysed oxidation of 123, representative example: 2,3-dibenzylfumaraldehyde (156)



Aerobic oxidation was carried out by modifying the procedure of Stahl.[73] Reactions were carried out in the 100-mL apparatus shown in Figure 18a were the O_2 inlet pipe had an internal diameter of *ca*. 5 mm. The flask was charged with a suitable stirrer, (*E*)-2,3-dibenzylbut-2-ene-1,4-diol **155** (1.00 g, 3.73 mmol) and DMF (18 mL). Without any O_2 flowing the following solids and liquids were promptly added to the reaction mixture: $Cu(MeCN)_4BF_4$ (93.1 mg, 0.30 mmol, 8 mol%) [causing formation of a yellow or very pale green solution], 2,2-bipyridyl (46.6 mg, 0.30 mmol, 8 mol%) [causing the solution to become very dark], TEMPO (46.3 mg, 0.30 mmol, 8 mol%) [leading to a dark orange/brown solution] and finally *N*-methylimidazole (NMI, 46.6 µL, 48.0 mg, 16 mol%) [causing no further colour change, Figure 18b]. The oxygen flow was promptly started (flow rate ~5 bubbles/sec) as the reaction stirred. [NOTE: Rarely the reaction mixture turned a pale, absinthe green colour within the first 5 min, this typically indicated premature catalyst deactivation which could be overcome by a second charge of all oxidation catalyst components.] After 20-50 minutes the reaction mixture became a deep, emerald green colour (Figure 18c) and TLC analysis (1:2 EtOAc/hexanes) showed consumption of diol **155** ($\mathbf{R_f}$ 0.60) and complete formation of **156** ($\mathbf{R_f}$ 0.90, yellow, visible to naked eye). The O_2 flow was stopped and the oxidation flask extracted with EtOAc (4 × 30 mL). The EtOAc extracts were

washed with 2 M HCl (4 × 25 mL) and water (2 ×25 mL). The blue aqueous washings were re-extracted with EtOAc (30 mL) which was itself washed with water (2 × 10 mL). The combined canary yellow EtOAc extracts were dried ($MgSO_4$) and evaporated to a lustrous, yellow solid in near quantitative yield after drying at 0.1 mbar (0.985 g, 3.73 mmol, >99%). TLC: $\mathbf{R_f}$ (EtOAc:hexane, 1:2) 0.90; glinting, yellow flakes from ^{i}PrOH on cooling to 4 °C with **mp** 91-92 °C; **IR** (diamond-ATR): ν_{max}/cm^{-1} 3061, 3027, 2937, 2910, 2766, 1751, 1667 (C=O), 1494, 1453, 1396, 1192, 1129, 1078, 1031, 974, 914, 871, 809, 739, 694, 598, 478; **^{1}H NMR** (400.1 MHz, $CDCl_3$): δ 10.48 (s, 2H, H-1), 7.32-7.26 (m, 4H, H-6), 7.23-7.18 (m, 2H, H-7), 7.15-7.11 (m, 4H, H-5), 4.14 (s, 4H, H-3); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 193.5 (CH), 147.5 (C), 138.3 (C), 129.0 (CH), 128.4 (CH), 126.8 (CH), 29.3 (CH_2); **MS** (+ESI) 287 (M+Na); **HRMS** calcd. for $C_{18}H_{16}NaO_2$ *m/z* 287.1048 (M+Na), found *m/z* 287.1042 (M+Na) (σ = 2 ppm); **Anal:** Calcd. for $C_{18}H_{16}O_2$ C, 81.79; H, 6.10; found C, 81.48; H, 6.07%. Use of DMF is dictated by diol **123** solubility. The oxidation catalyst has somewhat lower stability in DMF (vs. the normal Stahl solvent choice of MeCN[73]). On larger scales the initial DMF was deoxygenated by argon bubbling (5 min) prior to catalyst component addition which aided in catalyst initiation/stability.

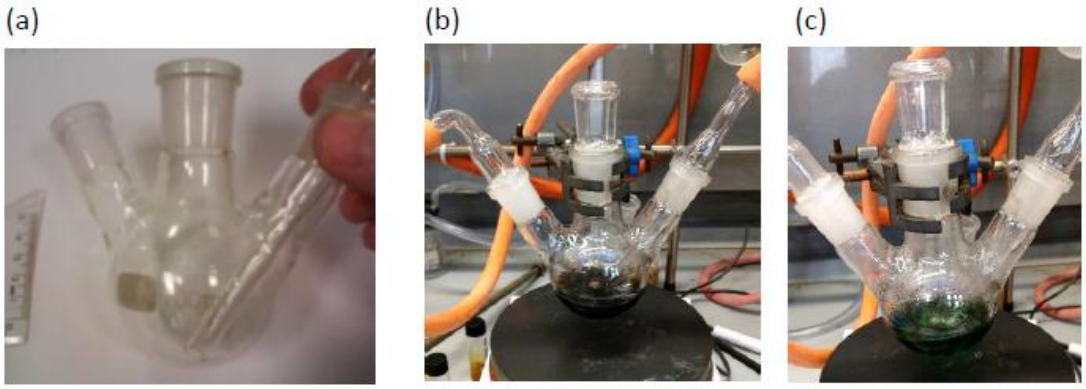
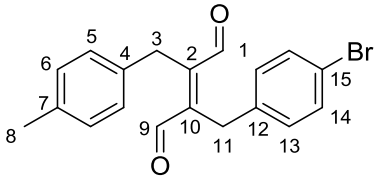


Figure 18 (a) experimental apparatus; (b) colour of active catalyst; (c) colour of reaction mixture at completion of the aerobic oxidation.

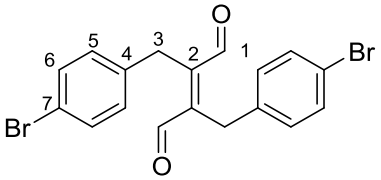
4.5.2 2-(4-Bromobenzyl)-3-(4-methylbenzyl)fumaraldehyde (140)



Prepared by a method analogous to **156** from (*E*)-2-(4-bromobenzyl)-3-(4-methylbenzyl)but-2-ene-1,4-diol **139** (0.31 g, 0.86 mmol), to yield **140** as a pale yellow powder (0.30 g, 0.84 mmol, 98%) on drying at 0.1 mbar. TLC: $\mathbf{R_f}$ (EtOAc:hexane, 1:2) 0.92; yellow microcrystals from EtOAc/^{i}PrOH (1:1) with **mp** 126-127 °C; **IR** (diamond-ATR): ν_{max}/cm^{-1} 2912, 1668 (C=O), 1513, 1487, 1447, 1397, 1189, 1129, 1073, 1012, 880, 799, 789, 528, 477; **^{1}H NMR** (400.1 MHz, $CDCl_3$): δ 10.47 (s, 1H, H-1 or H-9), 10.42 (s, 1H, H-1 or H-9), 7.39 (app d, *J* = 8.3 Hz, 2H, H-14), 7.08 (app d, *J* = 7.8 Hz, 2H, H-5 or H-6), 7.04-6.97 (m, 4H, H-13 and H-5 or H-6), 4.09 (s, 2H, H-11), 4.05 (s, 2H, H-3), 2.30 (s, 3H, H-8); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 193.6 (CH)

overlapped by 193.5 (CH), 148.3 (C), 146.7 (C), 137.5 (C), 136.9 (C), 135.1 (C), 132.3 (CH), 130.3 (CH), 130.0 (CH), 128.5 (CH), 121.0 (C), 29.3 (CH_2), 29.0 (CH_2), 21.3 (CH_3); **MS** (+ESI) 379 (M+Na, ^{79}Br); **HRMS** calcd. for $C_{19}H_{17}BrNaO_2$ *m/z* 379.0310 (M+Na, ^{79}Br), found *m/z* 379.0303 (M+Na, ^{79}Br) (σ = 2 ppm); **Anal:** Calcd. for $C_{19}H_{17}BrO_2$ C,63.88; H, 4.80; found C, 63.60; H, 4.61%.

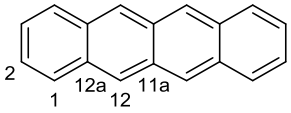
4.5.3 2,3-*Bis*(4-bromobenzyl)fumaraldehyde (143)



Prepared by a method analogous to **156** from (*E*)-2,3-*bis*(4-bromobenzyl)but-2-ene-1,4-diol **142** (1.28 g, 3.00 mmol), to yield **143** as a yellow solid (1.18 g, 2.80 mmol, 93%) on drying at 0.1 mbar. TLC: $\mathbf{R_f}$ (EtOAc:hexane, 1:2) 0.68; solid from ^{i}PrOH with **mp** 151-152 °C; **IR** (diamond-ATR): ν_{max}/cm^{-1} 2941, 2913, 1667 (C=O), 1486, 1449, 1405, 1397, 1129, 1103, 1011, 880, 702, 636, 499; **^{1}H NMR** (400.1 MHz, $CDCl_3$): δ 10.43 (s, 2H, H-1), 7.40 (app d, *J* = 8.4 Hz, 4H, H-5), 6.99 (app d, *J* = 8.4 Hz, 4H, H-6), 4.07 (s, 4H, H-3); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 193.0 (CH), 147.1 (C), 137.0 (C), 132.2 (CH), 130.1 (CH), 121.0 (C), 28.9 (CH_2); **MS** (+ESI) 419 (M-H, ^{79}Br); **HRMS** calcd. for $C_{18}H_{13}Br_2O_2$ *m/z* 418.9288 (M-H, ^{79}Br), found *m/z* 418.9290 (M-H, ^{79}Br) (σ = 0 ppm); **Anal:** Calcd. for $C_{18}H_{14}Br_2O_2$ C, 51.22; H, 3.34; found C, 51.13; H, 3.25%.

4.6 Cyclisation to tetracenes

4.6.1 Preparation of tetracenes, representative example: tetracene (1)



Dialdehyde **156** (0.40 g, 1.51 mmol) was dissolved with stirring in dry 1,2-dichloroethane (10 mL) under argon. The bright yellow solution was cooled to 0 °C and $TiCl_4$ (**CAUTION!** Corrosive, toxic) (0.35 mL, 3.2 mmol, 2.1 equiv.) added over ca. 1 min. producing a deep orange suspension of the $TiCl_4$-aldehyde adduct. The reaction was stirred and warmed to 40 °C (4 h) during which time it became dark brown-green and viscous. TLC (10:1:1 hexane:EtOAc:CH_2Cl_2) indicated complete consumption of **156** ($\mathbf{R_f}$ 0.51) and half-closure product ($\mathbf{R_f}$ 0.61) and orange staining indicative of poorly eluting **1**. The reaction was cooled to ambient temperature and then to 0 °C and 1:1 acetone:MeOH (10 mL) was slowly added causing immediate precipitation of a fine precipitate of tetracene **1**. The tetracene was filtered off onto Whatman glass microfiber GF/A[74] on a 47-mm 3-piece (Hartley) filter and washed with 1:1 acetone:MeOH (2 × 3 mL), Et_2O (2 × 3 mL) and dried under a cushion of argon in dim light to provide an orange powder (0.25 g, 1.09 mmol, 72%). This material was of sufficient purity for use in further chemistry directly but could be purified further by vacuum sublimation (190-200 °C, 0.1 mbar, Figure 19) to afford

brilliant orange powders. Tetracene **1** showed expected spectroscopic and physical properties: **mp** >250 °C; **IR** (diamond-ATR): ν_{max}/cm^{-1} 3043, (pseudo emission 2165, 2027)[18], 1805, 1734, 1696, 1627, 1537, 1493, 1462, 1386, 1294, 1196, 1164, 1121, 995, 957, 901, 738, 469; **^{1}H NMR** (500.1 MHz, CS_2, external DMSO-d_6 lock[75]): δ 8.30 (s, 4H, H-12), 7.60-7.62 (m, 4H, H-1), 7.13-7.03 (m, 4H, H-2); **^{13}C NMR** (124.7 MHz, CS_2, external DMSO-d_6 lock): δ 131.37 (C), 130.11 (C), 128.28 (CH), 126.43 (CH), 125.14 (CH); **UV/Vis** (CH_2Cl_2, 10^{-5} M): λ_{max}/nm 474 (log ε 4.2), 444 (log ε 4.2), 419 (log ε 3.9), 396 (log ε 3.6), 375 (log ε 3.2); **MS** (+EI) 228 (M); **HRMS** calcd. for $C_{18}H_{12}$ *m/z* 228.0939 (M), found *m/z* 228.0928 (M) (σ = 5 ppm); **Anal:** Calcd. for $C_{18}H_{12}$ C, 94.70; H, 5.30; found C, 94.51; H, 5.02%. This data was concordant with recent published data.[24,125]

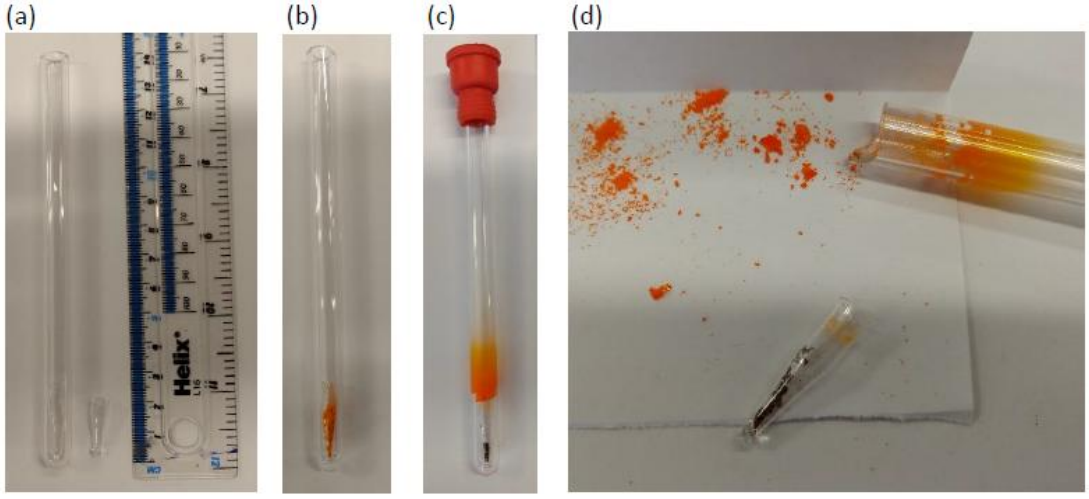
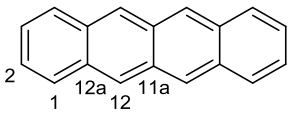


Figure 19 (a) Sublimation set-up: tube and boat. (b) Loaded assembly. (c) Post sublimation; the heated sand bath top was ca. 2-3 mm below the bottom end of the sublimed band. (d) Extraction of the tetracene, post tube-cut (CARE! – tube wrapped in electrical tape to minimise 'sharp' injury potential during cutting). The dark, non sublimed, residue typically accounted for 2-8% w/w of the original mass (typically ~4% w/w). Pressures quoted are those at the sublimation tube, those at the pump-head were typically 10^{-2} mbar.

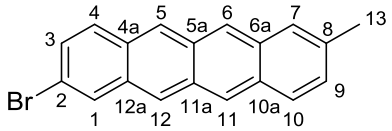
4.6.2 Preparation of tetracenes at a large scale, representative example: tetracene (1)



Dialdehyde **156** (2.00 g, 7.57 mmol) was dissolved with stirring in dry 1,2-dichloroethane (50 mL) under argon. The bright yellow solution was cooled to 0 °C and $TiCl_4$ (**CAUTION!** Corrosive, toxic) (1.74 mL, 15.9 mmol, 2.1 equiv.) added over ca. 1 min. producing a deep orange suspension of the $TiCl_4$-aldehyde adduct. The reaction was stirred and warmed to 40 °C (4 h) during which time it became dark brown-green and viscous. TLC (10:1:1 hexane:EtOAc:CH_2Cl_2) indicated complete consumption of **156** ($\mathbf{R}_f$ 0.51) and half-closure product ($\mathbf{R}_f$ 0.61) and orange staining indicative of poorly eluting **121**. The reaction was cooled to -10 °C and added slowly to a stirring mixture dried 1:1 acetone:MeOH (50 mL) and cyclohexene epoxide (2.30

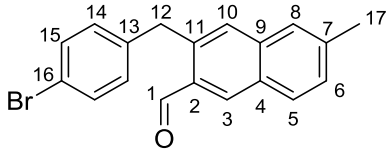
mL, 22.6 mmol, 3 equiv.) at -10 °C. Addition was carried out via cannula, causing immediate precipitation of a fine precipitate of tetracene **1**. The tetracene was filtered off onto Whatman glass microfiber GF/A[74] using a 75-mm 3-piece (Hartley) filter, washed with 1:1 acetone:MeOH (2 × 15 mL), Et_2O (2 × 15 mL) and dried under a cushion of argon in dim light to provide an orange powder (1.19 g, 5.21 mmol, 69%). Tetracene **1** prepared in this way provided equivalent analytical data to **1** prepared on a small scale.

4.6.3 2-Bromo-8-methyltetracene (126)



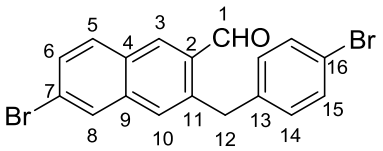
Dialdehyde **140** (0.30 g, 1.51 mmol) was cooled to 0 °C and treated under argon with neat $TiCl_4$ (0.37 mL, 3.36 mmol, 4 equiv.) over ca. 10 min. (**CARE!** $TiCl_4$ is a corrosive aggressive Lewis acid; faster additions or warming too quickly to ambient temperature could result in uncontrolled exotherms). Allowing the orange suspension to come to room temperature produced a dark brown-green thick suspension that was allowed to stand at 22 °C (48 h). The reaction was cooled to 0 °C and 1:1 acetone:MeOH (10 mL) was carefully added (**CARE!** vigorous reaction). The reaction mass was broken up manually leading to a fine, orange precipitate of tetracene **126** which was filtered off onto Whatman glass microfiber GF/A[74] on a 47-mm 3-piece (Hartley) filter and washed with 1:1 acetone:MeOH (2 × 3 mL), Et_2O (2 × 3 mL) under a cushion of argon in dim light to provide crude **126** as an orange powder (69.5 mg, 0.22 mmol, 26%). This material contained significant quantities of polymerization products which could be removed by vacuum sublimation (230-240 °C, 0.2 mbar) to afford **126** as a brilliant orange powder in 4% yield (based on initial **140** used). **mp** >250 °C; **IR** (diamond-ATR): ν_{max}/cm^{-1} 3026, 2973, 2928, 2904, 1632, 1556, 1440, 1291, 1045, 905, 796, 644, 580, 468; **UV/Vis** (CH_2Cl_2, ca. 10^{-6}): λ_{max}/nm 479 (log ε 5.4), 449 (log ε 5.4), 423 (log ε 5.2), 401 (log ε 5.1),379 (log ε 4.9); **Partial ^{1}H NMR** (500.1 MHz, CS_2 external DMSO-d_6 lock[75]): δ 8.26 (app s, 2H, H-5 or H-6 or H-11 or H-12), 8.20 (s, 1H, H-5 or H-6 or H- 11 or H-12), 8.17 (s, 1H, H-5 or H-6 or H-11 or H-12), 7.81 (s, with unresolved long range couplings, 1H, H-1), 7.59 (d, *J* = 8.7 Hz, 1H, H-4), 7.56 (d, *J* = 9.0 Hz, 1H, H-10), 7.40 (s, with unresolved long range couplings, 1H, H-7), 2.30 (s, 3H, Me). The very low solubility for **126** (<0.05 mg/mL in CS_2) causes H-3 and H-9 to overlap with trace, but more soluble, impurities from the Bradsher cyclisation limiting assignment: 6.94 (d, *J* = 9.0 Hz, 1H, H-9), 6.72 (app d, *J* = 8.7 Hz, 1H, H-3) were estimated by comparison with other synthesised tetracenes[18]; **MS** (+EI) 320 (M, ^{79}Br); **HRMS** calcd. for $C_{19}H_{13}Br$ *m/z* 320.0201 (M, ^{79}Br), found *m/z* 320.0199 (M, ^{79}Br) (σ = 1 ppm); **Anal:** Calcd. for $C_{19}H_{13}Br$ C, 71.05; H, 4.08; found C, 71.29; H, 4.04%. Some related 2-bromotetracenes have been noted previously, prepared by a complimentary procedure.[29]

4.6.4 3-(4-Bromobenzyl)-6-methyl-2-naphthaldehyde (141)



Reaction of (*E*)-2-(4-bromobenzyl)-3-(4-methylbenzyl)fumaraldehyde **140** (200.0 mg, 0.56 mmol), $TiCl_4$ (0.07 mL, 0.66 mmol. 1.1 equiv.) in dichloromethane (3.7 mL) at room temperature for 1 h. The reaction was quenched with MeOH/acetone (1:1) and extracted into EtOAc (30 mL). The organic layer was washed with water (2 × 20 mL), dried ($MgSO_4$) and evaporated. Column chromatography (14:1, pentane/EtOAc) followed by crystallization from 1:1 EtOAc/hexane yielded **141** as colourless rhomboidal crystals (112 mg, 0.33 mmol, 61%). TLC: $\mathbf{R_f}$ (hexane:EtOAc, 8:1) 0.56; **mp** 123-124 °C; **IR** (diamond-ATR): ν_{max}/cm^{-1} 3350, 3028, 2959, 2906, 2851, 2751, 1691 (C=O), 1631, 1573, 1482, 1463, 1427, 1403, 1317, 1262, 1234, 1180, 1153, 1110, 1067, 1007, 904, 826, 785, 734, 703, 686, 617, 563, 520, 472, 444; **^{1}H NMR** (400.1 MHz, $CDCl_3$): δ 10.18 (s, 1H, H-1), 8.29 (s, 1H, H-3), 7.87 (d, *J* = 8.4 Hz, 1H, H-5), 7.59 (s, 1H, H-10), 7.51 (s, 1H, H-8), 7.43 -7.32 (m, 3H, H-6 and H-15), 7.07 (d, *J* = 8.5 Hz, 2H, H-14), 4.51 (s, 2H, H-12), 2.54 (s, 3H, H-17); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 192.7 (CHO), 140.0 (C), 140.0 (C), 137.6 (CH), 137.0 (C), 135.9 (C), 131.8 (C), 131.5 (CH), 130.8 (CH), 129.8 (CH), 129.7 (C), 129.1 (CH), 129.0 (CH), 126.6 (CH), 120.0 (C), 38.3 (CH_2), 22.1 (CH_3); **MS** (+ESI): 361 (M+Na, ^{79}Br); **HRMS** calcd. for $C_{19}H_{15}BrNaO$ *m/z* 361.0204 (M+Na, ^{79}Br), found *m/z* 361.0187 (M+Na, ^{79}Br) (σ = 3 ppm). **Anal:** Calcd. for $C_{19}H_{15}BrO$ C, 67.27; H, 4.46; found C, 67.18; H, 4.45%.

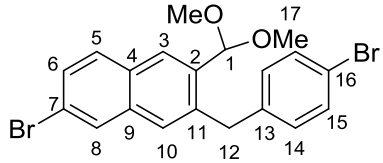
4.6.5 6-Bromo-3-(4-bromobenzyl)-2-naphthaldehyde (144)



144

-MeOH
cat. H^+

+MeOH
cat. H^+



144'

Solid **143** (0.20 g, 0.47 mmol) was cooled to 0 °C and treated under argon with neat $TiCl_4$ (0.21 mL, 1.90 mmol, 4 equiv.) over ca. 10 min (**CARE!** $TiCl_4$ is a corrosive aggressive Lewis acid; faster additions or warming too quickly to ambient temperature risks uncontrolled exotherms). Allowing the orange suspension to come to room temperature produced a dark brown-green thick suspension that was allowed to stand at 22 °C (48 h). The reaction was recooled to 0 °C and 1:1 acetone:MeOH (10 mL) was carefully added under an argon atmosphere (**CARE!** vigorous reaction). The reaction mass was broken up manually leading to an orange

solution which was separated using ethyl acetate (20 mL) and washed with water (3 x 20 mL). Upon drying (Na_2SO_4), the combined organic phases were evaporated to an orange oil (0.206 g), which ^{1}H NMR spectroscopy revealed to be **144** and its acetal derivative **144'**; the latter forms from the quenching MeOH, due to acidic by-products of the Bradsher cyclisation. Column chromatography (1:20 ethyl acetate:pentane) was used to isolate the half-closure products: **144** as a light orange solid (31 mg, 0.08 mmol, 16%) and dimethoxyacetal **144'** as a light orange solid (80 mg, 0.18 mmol, 38%), combined yield 54%. For **144:** $\mathbf{R_f}$ (hexane:EtOAc, 10:1) 0.53; **mp** 132-133 °C; **IR** (ATR): ν_{max}/cm^{-1} 2367, 2338, 2168, 1693 (C=O), 1626, 1567, 1483, 1453, 1430, 1402, 1356, 1256, 1172, 1105, 1062, 1008, 907, 828, 803, 790, 758, 684, 561, 520, 475, 460, 444, 421; **^{1}H NMR** (400.1 MHz, $CDCl_3$): δ 10.23 (s, 1H, H-1), 8.33 (s, 1H, H-8), 8.01 (s plus unresolved long range couplings, 1H, H-3), 7.86 (d, *J* = 8.7 Hz, 1H, H-6), 7.65 (dd, *J* = 8.7, 1.9 Hz, 1H, H-5), 7.53 (s, 1H, H-10), 7.45 – 7.39 (m, 2H, H-15), 7.08 (d, *J* = 8.4 Hz, 2H, H-14), 4.54 (s, 2H, H-12); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 192.3 (CHO), 139.0 (C), 138.3 (C), 137.1 (CH), 136.5 (C), 132.7 (C), 131.6 (CH), 130.7 (CH), 130.6 (CH), 130.4 (CH), 129.9 (C), 129.7 (CH), 129.4 (CH), 124.1 (C), 120.2 (C), 38.21 (CH_2); **MS** (+ESI): 403 (M+H, ^{79}Br); **HRMS** Calculated for $C_{18}H_{13}Br_2O_1$ *m/z* 402.9328 (M+H, ^{79}Br), found *m/z* 402.9312 (M+Na, ^{79}Br) (σ = 4 ppm). For **144'**: $\mathbf{R_f}$ (10:1 hexane:EtOAc) 0.69; **IR** (ATR): ν_{max}/cm^{-1} 3098, 3064, 2988, 2929, 2898, 2823, 1737, 1630, 1485, 1444, 1402, 1355, 1321, 1275, 1188, 1169, 1115, 1048, 1008, 986, 869, 839, 789, 756, 677, 538, 510, 474, 457; **^{1}H NMR** (400.1 MHz, C_6D_6): δ 8.10 (s, 1H, H-8), 7.63 (s, 1H, H-3), 7.29 (AB system, J_{AB} = 1.3 Hz, 2H, H-5/6), 7.29-7.25 (m, 2H, H-15), 7.05 (s, 1H, H-10), 6.76-6.72 (m, 2H, H-14), 5.36 (s, 1H, H-1), 4.01 (s, 2H, H-12), 3.03 (s, 6H, H-17); **^{13}C NMR** (100.6 MHz, C_6D_6): δ 139.3 (C), 137.2 (C), 134.6 (C), 134.5 (C), 131.5 (CH), 130.7 (CH), 130.1 (C), 129.7 (CH), 129.4 (CH), 129.2 (CH), 128.4 (CH), 127.1 (CH), 120.5 (C), 120.1 (C), 100.9 [$CH(OMe)_2$], 51.9 (OMe), 37.6 (CH_2); **MS** (+ESI): 471 (M+Na, ^{79}Br); **HRMS** Calculated for $C_{20}H_{18}Br_2NaO_2$ *m/z* 470.9566 (M+Na, ^{79}Br), found *m/z* 470.9557 (M+Na, ^{79}Br) (σ = 2 ppm).

4.7 Attempted Suzuki cross coupling reactions

4.7.1 Nickel catalysed Suzuki reaction on 2-(4-Bromobenzyl)-3-(4-methylbenzyl)-fumaraldehyde (140)[81]

To a Schlenk tube equipped with a magnetic stir bar were added 2-(4-bromobenzyl)-3-(4-methylbenzyl)fumaraldehyde **140** (150 mg, 0.42 mmol), phenylboronic acid (**110**) (76.8 mg, 0.63 mmol, 1.5 equiv.), $NiCl_2$(dppp) (4.55 mg, 8.40 µmol, 2 mol%) and anhydrous K_3PO_4 (0.27 g, 1.26 µmol, 3 equiv.). The tube was then evacuated (10 min) under vacuum and backfilled with N_2. Dried 1,4-dioxane (1.8 mL) was injected via a syringe and the reaction mixture was stirred at 100 °C for 4 h. The reaction mixture was poured into water (30 mL) and then extracted with DCM (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Analysis by ^{1}H NMR produced a complex spectrum with broad peaks seemingly indicating polymeric material, no product could be identified.

4.7.2 $Pd(OAc)_2$ catalyzed, urea accelerated Suzuki reaction on 2-(4-Bromobenzyl)-3-(4-methylbenzyl)-fumaraldehyde (140)[83]

In an open 50 mL round bottomed flask, a mixture of **140** (150 mg, 0.42 mmol), **147** (60.8 mg, 0.50 mmol, 1.2 equiv.), $Pd(OAc)_2$ (1.86 mg, 8.30 µmol, 2 mol %), urea (0.50 mg, 8.30 µmol, 2 mol%) and K_2CO_3 (174 mg, 1.26 mmol, 3 equiv.) were dissolved in DMF/^{i}PrOH/H_2O (6:1:1, v/v, 16 mL) and the mixture was stirred at room temperature for 1.5 h. The reaction was then diluted with EtOAc (50 mL) and washed with 2M HCl (2 x 50 mL) and water (2 x 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$. The filtrate was concentrated under reduced pressure. Attempted purification by column chromatography using EtOAc:hexane, 2:1. Leading to separation of the starting material **140** and another solid that could not be identified.

4.7.3 $Pd(OAc)_2$/XPhos catalysed Suzuki reaction of (*E*)-2-(4-bromobenzyl)-3-(4-methylbenzyl)but-2-ene-1,4-diol (139) with 2 mol% catalyst loading

In an open 50 mL round bottomed flask, a mixture of **139** (100 mg, 0.28 mmol), **147** (50.6 mg, 0.42 mmol, 1.5 equiv.), $Pd(OAc)_2$ (1.24 mg, 5.54 µmol, 2 mol %), XPhos (5.28 mg, 11.1 µmol, 4 mol%) and Na_2CO_3 (44.0 mg, 0.42 mmol, 1.5 equiv.) were dissolved in THF/H_2O (10:1, v/v, 5 mL) and the mixture was stirred at 40°C for 5 h. After this time, the reaction was diluted with EtOAc (20 mL) and washed water (3 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. The crude material was a complex mix of starting material **139** and unidentified products.

4.7.4 $Pd(OAc)_2$/XPhos catalysed Suzuki reaction of (*E*)-2-(4-bromobenzyl)-3-(4-methylbenzyl)but-2-ene-1,4-diol (139) with 4 mol% catalyst loading

To a dry Schlenk tube equipped with a magnetic stir bar were added **139** (100 mg, 0.28 mmol), **147** (50.6 mg, 0.42 mmol, 1.5 equiv.), $Pd(OAc)_2$ (2.49 mg, 11.1 µmol, 4 mol %), XPhos (5.28 mg, 11.1 µmol, 4 mol%) and CsF (84.1 mg, 0.55 mmol, 2 equiv.). The tube was then evacuated (10 min) under vacuum and backfilled with N_2. Dry THF (3 mL) was added and the mixture was stirred at 66°C for 2 h. After this time, the reaction was diluted with EtOAc (20 mL) and washed water (3 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. The crude material was a complex mix of starting material **139** and unidentified products.

4.8 Attempted Stille cross coupling reaction

To a dry Schlenk tube was added (*E*)-2-(4-bromobenzyl)-3-(4-methylbenzyl)but-2-ene-1,4-diol **139** (0.10 g, 0.28 mmol) or 2-(4-bromobenzyl)-3-(4-methylbenzyl)-fumaraldehyde **140** (0.12 g, 0.28 mmol). To **139** or **140** was added $Pd_2(dba)_3{\cdot}CHCl_3$ (8.60 mg, 8.30 µmol, 3 mol%) and XPhos (3.83 mg, 8.03 µmol, 2.9 mol%). Following dissolving of this mixture in dry THF (3 mL), the synthesised tributylphenyltin **149** (0.11 mL, 0.33 mmol, 1.2 equiv.) was added dropwise over 5 min. The mixture was

heated at 50°C for 5 h. After this time, H_2O (10 mL) was added and the solution extracted with EtOAc (3 x 10 mL). After drying with Na_2SO_4 and filtering, the crude mixture was concentrated in vacuo and washed through a silica plug with pentane (200 mL) then EtOAc (200 mL). Pentane washings were found to contain **149** (0.11 mL, 0.33 mmol) and the EtOAc washings the starting material **139** (0.10 g, 0.28 mmol) or **140** (0.12 g, 0.28 mmol)**.**

4.9 Attempted Buchwald-Hartwig cross coupling reaction

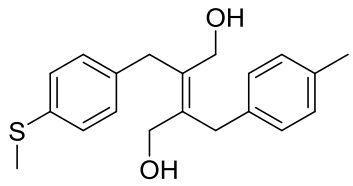
In a flame-dried Schlenk tube, (*E*)-2-(4-bromobenzyl)-3-(4-methylbenzyl)but-2-ene-1,4-diol **139** (50.0 mg, 0.14 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (4.30 mg, 4.15 µmol, 3 mol%), XPhos (3.96 mg, 8.30 µmol, 6 mol%), amine **A** (0.17 mmol, 1.2 equiv.) and base **B** (0.42 mmol, 3 equiv.) were added. After drying under high vacuum, dry 1,4-dioxane (1 mL) was added. The reaction mixture was then heated to 100 °C and left stirring overnight. After 18 h the reaction mixture was cooled to room temperature, water added (5 mL) and the product extracted with EtOAc (3 x 5 mL). Following drying over $MgSO_4$, the solvent was removed in vacuo. The result of these reactions were either the hydrodebromination product **150** or the starting material **139**.

4.10 Attempted methylation with DABAL-Me_3

To a dried Schlenk tube equipped with a magnetic stir bar and rubber septum were added 2-(4-bromobenzyl)-3-(4-methylbenzyl)fumaraldehyde **140** (150 mg, 0.42 mmol), $Pd_2(dba)_3$ (5.80 mg, 6.30 µmol, 1.5 mol%) and X-Phos (6.00 mg, 12.6 µmol, 3 mol%) which were then evacuated for 5 min. Dry THF (2 mL) and DABAL-Me_3 (53.8 mg, 0.21 mmol, 0.5 equiv.) were then added and the joint sealed with a glass stopper. The dark purple reaction mixture was heated at reflux for 4 h in an oil bath (66 °C). After this time the reaction mixture was allowed to cool to room temperature and then further cooled in an ice bath for 15 min. The reaction was quenched by cautious, portion-wise, addition of 2 M aqueous HCl (10 mL) and the resulting biphasic mixture separated with EtOAc (3 x 10 mL). The organic phases are combined, dried over $MgSO_4$ and concentrated in vacuo. The result was a black oil that could not be identified. Methodology adapted from Vinogradov and Woodward.[107]

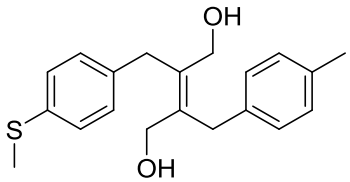
4.11 Attempted lithium-halogen exchange and electrophilic substitution with DMDS

4.11.1 Lithium-halogen exchange with a base, synthesis of (*E*)-2-(4-methylbenzyl)-3-(4-(methylthio)benzyl)but-2-ene-1,4-diol (151)



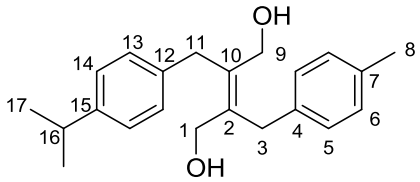
LiCl (8.90 mg, 0.21 mmol, 1.5 equiv.) was added to a dry Schenk tube equipped with a magnetic stir bar then dried under high vacuum at >200 °C (10 min) and cooled to room temperature under an atmosphere of nitrogen. It was then charged with LiH (2.67 mg, 0.34 mmol, 2.4 equiv) and (*E*)-2-(4-bromobenzyl)-3-(4-methylbenzyl)but-2-ene-1,4-diol **139** (50.0 mg, 0.14 mmol). The vial was sealed with a rubber septum and purged with argon (3x). Dry THF (2.5 mL) was added and the reaction mixture stirred at 66°C for 1.5 h, forming a white suspension. After cooling to -78°C, ^{n}BuLi (0.24 mL, 1.45 M, 0.35 mmol, 2.5 equiv.) was added dropwise over 5 min. After stirring for a certain amount of time (Y h) and allowing the temperature to rise to X °C (See Table 3), dimethyl disulfide (30.7 µL, 0.35 mmol, 2.5 equiv.) was added dropwise over 5 min. The reaction mixture was allowed to warm slowly to room temperature over 1 h. After quenching with H_2O (4 mL), the resulting solution was extracted with EtOAc (3 x 5 mL), then the combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude product was found to contain **151** and **150**; **151** could not be purified to a degree suitable for characterisation. The presence of **151** was indicated by **HRMS** calculated for $C_{20}H_{24}NaO_2S$ m/z 351.1389 (M+Na), found m/z 351.1387 (M+Na) (σ = 0.7 ppm). The presence of **150** was indicated by **HRMS** calculated for $C_{19}H_{22}NaO_2$ m/z 305.1512 (M+Na), found m/z 305.1513 (M+Na) (σ = 0.4 ppm) respectively.

4.11.2 Lithium-halogen exchange without a base, synthesis of (*E*)-2-(4-methylbenzyl)-3-(4-(methylthio)benzyl)but-2-ene-1,4-diol (151)



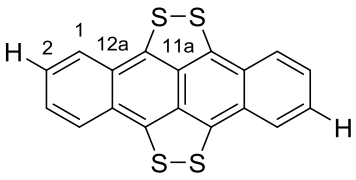
A Schenk tube equipped with a magnetic stir bar was dried under high vacuum at >200 °C (10 min), then cooled to room temperature under an atmosphere of nitrogen. (*E*)-2-(4-bromobenzyl)-3-(4-methylbenzyl)but-2-ene-1,4-diol **139** (250 mg, 0.69 mmol) was added, the tube sealed with a rubber septum and purged with argon (3x). Dry THF (10 mL) was added and the reaction mixture cooled to -78°C. ^{n}BuLi (1.43 mL, 1.45 M, 2.08 mmol, 3 equiv.) was added dropwise over 5 min. After a certain amount of time (Y h) and allowing the temperature to rise to X °C (See Table 4), dimethyl disulfide (92.0 mL, 1.03 mmol, 1.5 equiv.) was added dropwise over 5 minutes. The reaction mixture was allowed to warm slowly to room temperature over 2 h. After quenching with H_2O (20 mL), the resulting solution was extracted with EtOAc (3 x 20 mL), the combined organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude product was found to contain 3 distinct components by TLC, one of with contained both **151** and **150**. Column chromatography (1:1 EtOAc:pentane, then 6:1 EtOAc:pentane) followed by recrystallisation from hot 1:1 EtOAc:methanol on cooling to 4°C, yielded **151** and **150** in a ratio of **151**/**150** = 1:0.07. For **151**, TLC: $\mathbf{R_f}$ (EtOAc:pentane, 2:1) 0.43; **MS** (+ESI) 346 ($M+NH_4$); **HRMS** calcd. for $C_{20}H_{28}NO_2S$ m/z 346.1835 ($M+NH_4$), found m/z 346.1828 ($M+NH_4$) (σ = 2 ppm).

4.12 General procedure for Pd-PEPPSI-IPr catalysed Negishi coupling of 139 with secondary alkylzinc bromides, representative example: (*E*)-2-(4-isopropylbenzyl)-3-(4-methylbenzyl)but-2-ene-1,4-diol (152)



An oven-dried Schlenk tube equipped with a stir bar was charged with Pd-PEPPSI-IPr (1.90 mg, 2.80 µmol, 2 mol%) and (*E*)-2-(4-bromobenzyl)-3-(4-methylbenzyl)but-2-ene-1,4-diol **139** (50.0 mg, 0.14 mmol). The vial was sealed with a rubber septum and purged with argon (3x). The solution was cooled to 0 °C for 5 min and isopropylzinc bromide (0.20 mL of 0.83 M THF solution, 0.17 mmol, 1.2 equiv.) was added slowly via syringe over 2 min. The ice bath was removed after the addition and the reaction was stirred at rt for 18 h. The reaction mixture was then quenched by addition of 1 M hydrochloric acid (5 mL), extracted with ethyl acetate (3 × 5 mL), and the organic phase washed with brine (1 x 5 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. **152** was obtained as a colourless solid (39.1 mg, 0.12 mmol, 87% crude yield). TLC: $\mathbf{R_f}$ (EtOAc) 0.73; glinting colourless plates from EtOAc/MeOH (1:1) with **mp** 155-156 °C; **IR** (diamond-ATR): vmax/cm^{-1} 3378, 3313, 2954, 2918, 2890, 2863, 1509, 1433, 1334, 1294, 1129, 1066, 1011, 991, 928, 839, 802, 602, 547, 491; **^{1}H NMR** (400.1 MHz, DMSO-d_6): δ 7.14-7.01 (m, 8H, H-5, H-6 and H-13, H-14), 4.695 (t, J = 5.2 Hz, 1H, OH) overlapped by 4.69 (t, J = 5.2 Hz, 1H, OH), 3.93 (d, J = 5.2 Hz, 2H, H-1 or H-8) overlapped by 3.92 (d, J = 5.2 Hz, 2H, H-1 or H-9), 3.55 (s, 2H, H-3 or H- 11), 3.54 (s, 2H, H-3 or H-11), 2.83 (sept, J = 6.8 Hz, 1H, H-16), 2.25 (s, 3H, H-8), 1.17 (d, 6H, J = 6.9 Hz, H-17); **^{13}C NMR** (100.6 MHz, DMSO-d_6): δ 145.6 (C), 137.8 (C), 137.4 (C), 135.5 (C), 135.2 (C), 134.5 (C), 128.8 (CH), 128.4 (CH), 128.3 (CH), 126.0 (CH), 59.3 (CH_2), 59.2 (CH_2), 33.65 (CH_2), 33.6 (CH_2), 33.0 (CH), 24.0 (CH_3), 20.6 (CH_3); **MS** (+ESI) 347 (M+Na); **HRMS** calcd. for $C_{22}H_{28}NaO_2$ m/z 347.1987 (M+Na), found *m/z* 347.1991 (M+Na) (σ = 1 ppm); **Anal:** Calcd. for $C_{22}H_{28}O_2$ C, 81.44; H, 8.70; found C, 81.43; H, 8.83%. Method adapted from Çalimsiz and Organ.[114]

4.13 Preparation of tetrathiotetracenes on a large scale, representative example: tetrathiotetracene, 136



Tetracene **1** (1.00 g, 4.38 mmol) and sulfur (1.99 g, 62.2 mmol, 14.2 equiv.) were added to a long, flame-dried Schlenk tube (ca. diameter 40 mm, height 240 mm) fitted with a stir bar and equipped with a rubber septum. Deoxygenated dimethyl formamide (28 mL) (to give a concentration of 0.15 M in **1**) was added and the septum was replaced with a mineral oil bubbler and a slow flow of nitrogen established to remove H_2S that is emitted over the transformation (**CARE!** Toxic malodorous gas emitted). The reaction was then heated to reflux (>155 °C) under nitrogen for 16 h during which time the reaction mixture changed from orange, to dark brown, to a deep, emerald-green colour. The reaction mixture was filtered hot (>110 °C) onto Whatman glass microfiber GF/A[74] paper using a 75 mm 3-piece Hartley filter, washed with toluene (4 x 5 mL) and Et_2O (4 x 5 mL) and dried in dim light to provide **136** as a dark green powder (1.82 g). The crude tetrathiotetracene was heated, using a Kugelrohr apparatus, under vacuum (10 mbar) at 50 °C to remove traces of DMF and under higher vacuum (0.2 mbar) at 130 °C to remove traces of DMF and sulfur (that were trapped out at -78 ^{o}C). Tetrathiotetracene **136** was recovered from the non-sublimed portion in the Kugelrohr bulb as a dark green powder (1.06 g, 3.01 mmol, 69%, typical range 69-99%). Based on the carbon CHN analysis and weights recovered, sulfur derivatives purified this way were 93%±3% pure. **mp** >250 ^{o}C; **IR** (diamond-ATR): ν_{max}/cm^{-1} (pseudo emission 2165, 2032)[18], 1611, 1516, 1384, 1362, 1316, 1302, 1247, 1236, 1146, 1010, 966, 942, 895, 833, 743, 714, 683, 449, 437; **^{1}H NMR** (500.1 MHz, CS_2, external DMSO-d_6 lock[75]): δ 7.19-7.16 (m, 4H, H-1 or H-2), 7.14-7.09 (m, 4H, H-1 or H-2); **^{13}C NMR** (124.7 MHz, CS_2, external DMSO-d_6 lock[S5]): δ 134.7 (C), 132.3 (C), 125.3 (CH), 124.8 (CH), 124.4 (C); **UV/Vis** (CH_2Cl_2, 10^{-5} M): λ_{max}/nm 695 (log ε 5.0), 639 (log ε 4.9), 588sh (log ε 4.7), 470 (log ε 4.9); **MS** (+EI) 351 (M^+); **HRMS** calcd. for $C_{18}H_8S_4$ *m/z* 351.9509 (M), found *m/z* 351.9516 (M) (σ = 1.9 ppm); **Anal:** Calcd. for $C_{18}H_8S_4$ C, 61.33; H, 2.29; found C, 56.85; H, 1.63% corresponding to 93% purity. Our IR[126] and UV-vis[127] data are within experimental error of literature reports.

4.14 Attempted nitration of tetrathiotetracene

The optimal reaction conditions which replicated the previously observed splitting pattern is given: Concentrated nitric acid (~0.2 mL, 68 w/w %) was added to **136** (7.0 mg, 19.9 µmol) after cooling to 0 °C. This created an orange colour and caused the release of a gas. After making sure all of **136** was exposed to the nitric acid, the mixture was diluted with deionised H_2O (5 mL), creating a dark precipitate. All this was carried out within 30 sec. Promptly a pH 7.4 phosphate buffer solution ($NaOH/KH_2PO_4$) was added until the mixture became pH 7.4. The resulting solid was collected by filtration through Whatman glass microfiber GF/A[74] paper using a 25-mm 3-piece (Hartley) filter. The dark green/black solid was dried under high vacuum and analysed by ^{1}H NMR using CS_2 as a solvent and an external DMSO-d_6 lock.[75]

References

(1) The Journal of Organic Chemistry Guidelines for Authors http://pubs.acs.org/paragonplus/submission/joceah/joceah_authguide.pdf (accessed Sep 25, 2017).

(2) Anthony, J. E. Functionalized Acenes and Heteroacenes for Organic Electronics. *Chem. Rev.* **2006**, *106*, 5028–5048.

(3) Chiang, C. K.; Fincher, C. R.; Park, Y. W.; Heeger, A. J.; Shirakawa, H.; Louis, E. J.; Gau, S. C.; MacDiarmid, A. G. Electrical Conductivity in Doped Polyacetylene. *Phys. Rev. Lett.* **1977**, *39*, 1098–1101.

(4) Lin, C.-H.; Lin, K.-H.; Pal, B.; Tsou, L.-D. Iterative Synthesis of Acenes via Homo-Elongation. *Chem. Commun.* **2009**, *7*, 803–805.

(5) Wang, C.; Dong, H.; Hu, W.; Liu, Y.; Zhu, D. Semiconducting π-Conjugated Systems in Field-Effect Transistors: A Material Odyssey of Organic Electronics. *Chem. Rev.* **2012**, *112*, 2208–2267.

(6) Bendikov, M.; Wudl, F.; Perepichka, D. F. Tetrathiafulvalenes, Oligoacenenes, and Their Buckminsterfullerene Derivatives: The Brick and Mortar of Organic Electronics. *Chem. Rev.* **2004**, *104*, 4891–4946.

(7) Witte, G.; Wöll, C. Growth of Aromatic Molecules on Solid Substrates for Applications in Organic Electronics. *J. Mater. Res.* **2004**, *19*, 1889–1916.

(8) Krüger, J.; García, F.; Eisenhut, F.; Skidin, D.; Alonso, J. M.; Guitián, E.; Pérez, D.; Cuniberti, G.; Moresco, F.; Peña, D. Decacene: On-Surface Generation. *Angew. Chem. Int. Ed.* **2017**, *56*, 11945–11948.

(9) Dong, H.; Wang, C.; Hu, W. High Performance Organic Semiconductors for Field-Effect Transistors. *Chem. Commun.* **2010**, *46*, 5211–5222.

(10) Miao, Q.; Lefenfeld, M.; Nguyen, T. Q.; Siegrist, T.; Kloc, C.; Nuckolls, C. Self-Assembly and Electronics of Dipolar Linear Acenes. *Adv. Mater.* **2005**, *17*, 407–412.

(11) Miao, Q.; Chi, X.; Xiao, S.; Zeis, R.; Lefenfeld, M.; Siegrist, T.; Steigerwald, M. L.; Nuckolls, C. Organization of Acenes with a Cruciform Assembly Motif. *J. Am. Chem. Soc.* **2006**, *128*, 1340–1345.

(12) Takahashi, T.; Li, S.; Huang, W.; Kong, F.; Nakajima, K.; Shen, B.; Ohe, T.; Kanno, K. I. Homologation Method for Preparation of Substituted Pentacenes and Naphthacenes. *J. Org. Chem.* **2006**, *71*, 7967–7977.

(13) Anthony, J. E.; Eaton, D. L.; Parkin, S. R. A Road Map to Stable, Soluble, Easily Crystallized Pentacene Derivatives. *Org. Lett.* **2002**, *4*, 15–18.

(14) Sarma, J. A. R. P.; Desiraju, G. R. The Role of Cl---Cl and C-H---O Interactions in the Crystal Engineering of 4Å Short Axis Structures. *Acc. Chem. Res.* **1986**, *19*, 222–228.

(15) Moon, H.; Zeis, R.; Borkent, E.-J.; Besnard, C.; Lovinger, A. J.; Siegrist, T.; Kloc, C.; Bao, Z. Synthesis, Crystal Structure, and Transistor Performance of Tetracene Derivatives. *J. Am. Chem. Soc.* **2004**, *126*, 15322–15323.

(16) Kunugi, Y.; Ikari, M.; Okamoto, K.; Ogino, K. Organic Field-Effect Transistors Based on Vapor Deposited 2,9-Dialkylpentacene Films. *J. Photopolym. Sci. Technol.* **2008**, *21*, 197-201.

(17) Okamoto, T.; Senatore, M. L.; Ling, M. M.; Mallik, A. B.; Tang, M. L.; Bao, Z.

Synthesis, Characterization, and Field-Effect Transistor Performance of Pentacene Derivatives. *Adv. Mater.* **2007**, *19*, 3381–3384.
(18) Woodward, S.; Ackermann, M.; Ahirwar, S. K.; Burroughs, L.; Garrett, M. R.; Ritchie, J.; Shine, J.; Tyril, B.; Simpson, K.; Woodward, P. Straightforward Synthesis of 2- and 2,8-Substituted Tetracenes. *Chem. Eur. J.* **2017**, *23*, 7819–7824.
(19) Qu, H.; Chi, C. Synthetic Chemistry of Acenes and Heteroacenes. *Curr. Org. Chem.* **2010**, *14*, 2070–2108.
(20) Gerlach, C.; McCormick, F. Electroluminescent Devices Containing Trans-1,2-Bis(acenyl)ethylene Compounds. US Patent Application 20060105199, May 18, 2006.
(21) Mondal, R.; Shah, B. K.; Neckers, D. C. Synthesis and Photophysical Properties of Dihydroheptacenes: New Blue-Emitting Materials. *J. Org. Chem.* **2006**, *71*, 4085–4091.
(22) Thummel, R. P.; Cravey, W. E.; Nutakul, W. Diels-Alder Approach to Naphthocyclobutenes and Anthrocyclobutenes. *J. Org. Chem.* **1978**, *43*, 2473–2477.
(23) LeHoullier, C. S.; Gribble, G. W. A Convenient Generation of 2,3-Naphthalyne. Linear Annulation of Naphthalene and a New Naphthacene Synthesis. *J. Org. Chem.* **1983**, *48*, 2364–2366.
(24) Geary, L. M.; Chen, T.-Y.; Montgomery, T. P.; Krische, M. J. Benzannulation via Ruthenium-Catalyzed Diol–Diene [4+ 2] Cycloaddition: One- and Two-Directional Syntheses of Fluoranthenes and Acenes. *J. Am. Chem. Soc.* **2014**, *136*, 5920–5922.
(25) Miyamoto, H.; Aso, Y.; Otsubo, T.; Ogura, F. Naphthaceno [1-12-cd:4,5-c'd'] Bis [1,2]Diselenole as a New Electron Donor. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2441–2443.
(26) Luo, J.; Hart, H. Linear Acene Derivatives: New Routes to Pentacene and Naphthacene and the First Synthesis of a Triptycene with Two Anthracene Moieties. *J. Org. Chem.* **1987**, *52*, 4833–4836.
(27) Zhang, J.; Chen, Z.; Yang, L.; Pan, F.-F.; Yu, G.-A.; Yin, J.; Liu, S. H. Elaborately Tuning Intramolecular Electron Transfer Through Varying Oligoacene Linkers in the Bis(diarylamino) Systems. *Sci. Rep.* **2016**, *6*, 36310.
(28) Gerlach, C. P. Acene-Thiophene Semiconductors. US Patent 6,998,068, February 14, 2006.
(29) Kitamura, C.; Taka, N.; Kawase, T. Synthesis of 8-Bromo-5,12-Tetracenequinone and 2-Bromotetracene Derivatives. *Res. Chem. Intermed.* **2013**, *39*, 139–146.
(30) Watanabe, M.; Chao, T. H.; Chien, C. T.; Liu, S. W.; Chang, Y. J.; Chen, K. Y.; Chow, T. J. 2-Halo-Subsituted Tetracenes: Their Generation and Single Crystal OFET Characteristics. *Tetrahedron Lett.* **2012**, *53*, 2284–2287.
(31) Sakamoto, Y.; Suzuki, T.; Kobayashi, M.; Gao, Y.; Inoue, Y.; Tokito, S. Perfluoropentacene and Perfluorotetracene: Syntheses, Crystal Structures, and FET Characteristics. *Mol. Cryst. Liq. Cryst.* **2006**, *444*, 225–232.
(32) Chen, Z.; Muller, P.; Swager, T. M. Syntheses of Soluble, π-Stacking Tetracene

Derivatives. *Org. Lett.* **2006**, *8*, 273–276.
(33) Coulson, E. A. 305. Homologues of Naphthacene. Part I. 2 : 6-Dimethylnaphthacene. *J. Chem. Soc.* **1934**, *0*, 1406–1412.
(34) Coulson, E. A. 16. Homologues of Naphthacene. Part II. 2-Methyl- and 2 : 7-Dimethyl-Naphthacene: Synthetic Applications of 2 : 6- and -2 : 7-Dimethyl-1 : 2 : 3 : 4-Tetrahydronaphthalene. *J. Chem. Soc.* **1935**, *0*, 77–83.
(35) Gribble, G. W.; Perni, R. B.; Onan, K. D. Twin Benzoannulation of Naphthalene via 1, 3-, 1, 6-, and 2, 6-Naphthodiyne Synthetic Equivalents. New Syntheses of Triphenylene, Benz[a]anthracene, and Naphthacene. *J. Org. Chem.* **1985**, *50*, 2934–2939.
(36) Kitamura, C.; Abe, Y.; Ohara, T.; Yoneda, A.; Kawase, T.; Kobayashi, T.; Naito, H.; Komatsu, T. Synthesis and Crystallochromy of 1, 4, 7, 10-Tetraalkyltetracenes: Tuning of Solid-State Optical Properties of Tetracenes by Alkyl Side-Chain Length. *Chem. Eur. J.* **2010**, *16*, 890–898.
(37) Sangaiah, R.; Gold, A. Synthesis of New Cyclopenta-Fused PAH Isomers of Cata-Annelated Benzenoid Systems. *J. Org. Chem.* **1987**, *52*, 3205–3211.
(38) Hasegawa, T.; Takeya, J. Organic Field-Effect Transistors Using Single Crystals. *Sci. Technol. Adv. Mater.* **2009**, *10*, 24314.
(39) Dodge, J. A.; Bain, J. D.; Chamberlin, A. R. Regioselective Synthesis of Substituted Rubrenes. *J. Org. Chem.* **1990**, *55*, 4190–4198.
(40) Odom, S. A.; Parkin, S. R.; Anthony, J. E. Tetracene Derivatives as Potential Red Emitters for Organic LEDs. *Org. Lett.* **2003**, *5,* 4245–4248.
(41) Lin, Y. C.; Lin, C. H. Synthesis of Tetracene Sulfoxide and Tetracene Sulfone via a Cascade Cyclization Reaction. *Org. Lett.* **2007**, *9*, 2075–2078.
(42) Burroughs, L.; Ritchie, J.; Ngwenya, M.; Khan, D.; Lewis, W.; Woodward, S. Anionic Sigmatropic-Electrocyclic-Chugaev Cascades: Accessing 12-Aryl-5-(Methylthiocarbonylthio)tetracenes and a Related anthra[2,3-B]thiophene. *Beilstein J. Org. Chem.* **2015**, *11*, 273–279.
(43) Chen, M.; Chen, Y.; Liu, Y. Palladium-Catalyzed Highly Efficient Synthesis of Tetracenes and Pentacenes. *Chem. Commun.* **2012**, *48*, 12189.
(44) Sun, N.; Chen, H.; Li, X.; Xu, M.; Gan, Y.; Zhang, L.; Liu, Y. PBr_3-Mediated Cyclization of 1,7-Diyn-3,6-bis(propargyl carbonate)s: Synthesis of 5-Bromotetracenes. *J. Org. Chem*. **2017**, *82*, 10051-10061.
(45) Bowles, D. M.; Anthony, J. E. A Reiterative Approach to 2,3-Disubstituted Naphthalenes and Anthracenes. *Org. Lett.* **2000**, *2*, 85–87.
(46) Mallouli, A.; Lepage, Y. Convenient Syntheses of Naphthalene-, Anthracene-, and Naphthacene-2, 3-Dicarboxaldehydes. *Synthesis* **1980**, *1980*, 689.
(47) Takahashi, T.; Kitamura, M.; Shen, B.; Nakajima, K. Straightforward Method for Synthesis of Highly Alkyl-Substituted Naphthacene and Pentacene Derivatives by Homologation. *J. Am. Chem. Soc.* **2000**, *122*, 12876–12877.
(48) McAtee, C. C.; Riehl, P. S.; Schindler, C. S. Polycyclic Aromatic Hydrocarbons via Iron(III)-Catalyzed Carbonyl-Olefin Metathesis. *J. Am. Chem. Soc.* **2017**, *139*, 2960–2963.
(49) Dorel, R.; McGonigal, P. R.; Echavarren, A. M. Hydroacenes Made Easy by Gold(I) Catalysis. *Angew. Chem. Int. Ed.* **2016**, *55*, 11120–11123.

(50) Rafiq, S. M.; Mohanakrishnan, A. K. Synthesis of Annulated Arenes and Heteroarenes by Hydriodic Acid and Red Phosphorus Mediated Reductive Cyclization of 2-(Hetero)aroylbenzoic Acids or 3-(Hetero)arylphthalides. *Synlett.* **2017**, *28*, 362–370.
(51) Bradsher, C. K. Formation of Six-Membered Aromatic Rings by Cyclialkylation of Some Aldehydes and Ketones. *Chem. Rev.* **1987**, *87*, 1277–1297.
(52) Bradsher, C. K. A New Route to 9-Alkyl- and 9-Arylanthracenes. *J. Am. Chem. Soc.* **1940**, *62*, 486–488.
(53) Tius, M. A.; Gomez-galeno, J. Aromatic Annelation - Synthesis of Naphthalenes. *Tetrahedron Lett.* **1986**, *27*, 2571–2574.
(54) Reddy, M. P.; Krishna Rao, G. S. Applications of the Vilsmeier Reaction. 13. Vilsmeier Approach to Polycyclic Aromatic Hydrocarbons. *J. Org. Chem.* **1981**, *46*, 5371–5373.
(55) Yu, X.; Lu, X. Efficient Synthesis of 9-Tosylaminofluorene Derivatives by Boron Trifluoride Etherate-Catalyzed Aza-Friedel-Crafts Reaction of in Situ Generated N-Tosylbenzaldimines. *Adv. Synth. Catal.* **2011**, *353*, 569–574.
(56) Kuninobu, Y.; Tatsuzaki, T.; Matsuki, T.; Takai, K. Indium-Catalyzed Construction of Polycyclic Aromatic Hydrocarbon Skeletons via Dehydration. *J. Org. Chem.* **2011**, *76*, 7005–7009.
(57) Rafiq, S. M.; Sivasakthikumaran, R.; Karunakaran, J.; Mohanakrishnan, A. K. Synthesis of Annulated Anthracenes, Carbazoles, and Thiophenes Involving Bradsher-Type Cyclodehydration or Cyclization-Reductive-Dehydration Reactions. *Eur. J. Org. Chem.* **2015**, *2015*, 5099–5114.
(58) Fujita, T.; Takahashi, I.; Hayashi, M.; Wang, J.; Fuchibe, K.; Ichikawa, J. Facile Synthesis of Polycyclic Aromatic Hydrocarbons: Brønsted Acid Catalyzed Dehydrative Cycloaromatization of Carbonyl Compounds in 1,1,1,3,3,3-Hexafluoropropan-2-Ol. *Eur. J. Org. Chem.* **2017**, *2017*, 262–265.
(59) Burroughs, L.; Ritchie, J.; Woodward, S. Understanding Anionic Chugaev Elimination in Pericyclic Tetracene Formation. *Tetrahedron* **2016**, *72*, 1686–1689.
(60) Magnuson, S. R. Two-Directional Synthesis and Its Use in Natural Product Synthesis. *Tetrahedron* **1995**, *51,* 2167–2213.
(61) Malachesky, P. A.; Marcoux, L. S.; Adams, R. N. Improved Methods for Preparing Hydrocarbon Cation Radicals. *J. Phys. Chem.* **1966**, *70*, 2064–2065.
(62) Dworkin, A. S.; Brown, L. L.; Buchanan III, A. C.; Smith, G. P. Oxidation of Arenes by Molten Gallium(III) Chloride. *Tetrahedron Lett.* **1985**, *26*, 2727–2730.
(63) Luo, L.; Resch, D.; Wilhelm, C.; Young, C. N.; Halada, G. P.; Gambino, R. J.; Grey, C. P.; Goroff, N. S. Room-Temperature Carbonization of Poly (Diiododiacetylene) by Reaction with Lewis Bases. *J. Am. Chem. Soc.* **2011**, *133*, 19274–19277.
(64) Papagni, A.; Trombini, C.; Lombardo, M.; Bergantin, S.; Chams, A.; Chiarucci, M.; Miozzo, L.; Parravicini, M. Cross-Coupling of 5,11-Dibromotetracene Catalyzed by a Triethylammonium Ion Tagged Diphenylphosphine Palladium Complex in Ionic Liquids. *Organometallics* **2011**, *30*, 4325–4329.

(65) Yagodkin, E.; Douglas, C. J. Low Temperature Kumada-Corriu Cross-Coupling of Polychlorinated Acene Derivatives and a Synthesis of Sterically Demanding Acenes. *Tetrahedron Lett.* **2010**, *51*, 3037–3040.
(66) Tang, M. L.; Bao, Z. Halogenated Materials as Organic Semiconductors. *Chem. Mater.* **2011**, *23*, 446–455.
(67) Ando, S.; Nishida, J. I.; Fujiwara, E.; Tada, H.; Inoue, Y.; Tokito, S.; Yamashita, Y. Novel P- and N-Type Organic Semiconductors with an Anthracene Unit. *Chem. Mater.* **2005**, *17*, 1261–1264.
(68) Pudzs, K.; Vembris, A.; Rutkis, M.; Woodward, S. Thin Film Organic Thermoelectric Generator Based on Tetrathiotetracene. *Adv. Electron. Mater.* **2017**, *3*, 1600429.
(69) Perez-Alberne, E. Synthesis of Chalcogenated Polyacenes. US Patent 3,723,417, March 27, 1973.
(70) Alder, A. Process for the Preparation of 5,6,11,12-Tetrathiotetracene. US Patent 5,206,388, April 27, 1993.
(71) Ishino, Y.; Wakamoto, K.; Hirashima, T. A New Synthesis of Trans-2-Substituted-2-Butene-1,4-Diols from 2-Butyne-1,4-Diol Via Nucleophilic-Addition of Grignard-Reagents. *Chem. Lett.* **1984**, *5*, 765–768.
(72) Manolikakes, G.; Schade, M. A.; Hernandez, C. M.; Mayr, H.; Knochel, P. Negishi Cross-Couplings of Unsaturated Halides Bearing Relatively Acidic Hydrogen Atoms with Organozinc Reagents. *Org. Lett.* **2008**, *10*, 2765–2768.
(73) McCann, S. D.; Stahl, S. S. Copper-Catalyzed Aerobic Oxidations of Organic Molecules: Pathways for Two-Electron Oxidation with a Four-Electron Oxidant and a One-Electron Redox-Active Catalyst. *Acc. Chem. Res.* **2015**, *48*, 1756–1766.
(74) Whatman Glass Microfibre GF/A Filter Paper Is Designed for the Fast Filtration of Fine Particles (down to 1.6 Mm). At Larger Scales This Was Most Readily Attained on 47-75 Mm Hartley Filter Funnels with PTFE Backing Plates.
(75) Most of the tetracenes isolated in this paper show poor solubility in common NMR solvents. Both C_6F_6 and CS_2 allowed sufficient solubility (*ca* 1 mg/0.6 mL) to allow prompt collection of ^{1}H NMR data. Although CS_2 showed minor, batch dependant, impurities [δH 7.01 (s), 1.12-0.98 (m), 0.83 (s), 0.70-0.51 (m), -0.21 (s), none of these species give prominent ^{13}C NMR signals] in our experience its use was preferred for combined ^{1}H-^{13}C NMR studies. Typically adequate signal-to-noise ^{13}C NMR spectra of tetracenes were acquired at 124.7 MHz after 8-16k transients; CS_2 gave an intense resonance at 192.3 ppm.
(76) Available from: Mestrelab Research.
(77) Miyaura, N.; Suzuki, A. Stereoselective Synthesis of Arylated (E)-Alkenes by the Reaction of Alk-1-Enylboranes with Aryl Halides in the Presence of Palladium Catalyst. *J. Chem. Soc., Chem. Commun.***1979**, *19*, 866–867.
(78) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. The B-Alkyl Suzuki-Miyaura Cross-Coupling Reaction: Development, Mechanistic Study, and Applications in Natural Product Synthesis. *Angew. Chem. Int. Ed.* **2001**, *40*, 4544–4568.
(79) Suzuki, A. Recent Advances in the Cross-Coupling Reactions of Organoboron Derivatives with Organic Electrophiles, 1995-1998. *J. Organomet. Chem.* **1999**,

576, 147–168.

(80) Jana, R.; Pathak, T. P.; Sigman, M. S. Advances in Transition Metal (Pd,Ni,Fe)-Catalyzed Cross-Coupling Reactions Using Alkyl-Organometallics as Reaction Partners. *Chem. Rev.* **2011**, *111*, 1417–1492.

(81) Zhao, Y. L.; Li, Y.; Li, S. M.; Zhou, Y. G.; Sun, F. Y.; Gao, L. X.; Han, F. S. A Highly Practical and Reliable Nickel Catalyst for Suzuki-Miyaura Coupling of Aryl Halides. *Adv. Synth. Catal.* **2011**, *353*, 1543–1550.

(82) Miyaura, N.; Ishiyama, T.; Ishikawa, M.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of B-Alkyl-9-Bbn or Trialkylboranes with Aryl and 1-Alkenyl Halides. *Tetrahedron Lett.* **1986**, *27*, 6369–6372.

(83) Saikia, B.; Boruah, P. R.; Ali, A. A.; Sarma, D. Simple and Efficient Phosphine-Free $Pd(OAc)_2$ Catalyzed Urea Accelerated Suzuki–Miyaura Cross-Coupling Reactions in iPrOH–H_2O at Room Temperature. *Tetrahedron Lett.* **2015**, *56*, 633–635.

(84) Martin, R.; Buchwald, S. L. Palladium-Catalyzed Suzuki-Miyaura Cross-Coupling Reactions Employing Dialkylbiaryl Phosphine Ligands. *Acc. Chem. Res.* **2008**, *41*, 1461–1473.

(85) Cordovilla, C.; Bartolome, C.; Martinez-Ilarduya, J. M.; Espinet, P. The Stille Reaction, 38 Years Later. *ACS Catal.* **2015**, *5*, 3040–3053.

(86) Farina, V.; Krishnamurthy, V.; Scott, W. J. The Stille Reaction. In *Organic Reactions*; John Wiley & Sons, Inc., **2004**.

(87) Matralis, A. N.; Tsantrizos, Y. S. Synthesis of Benzothiophene-Containing 10- and 11-Membered Cyclic Phostones. *Eur. J. Org. Chem.* **2016**, *22*, 3728–3736.

(88) Steadman, V. A.; Pettit, S. B.; Poullennec, K. G.; Lazarides, L.; Keats, A. J.; Dean, D. K.; Stanway, S. J.; Austin, C. A.; Sanvoisin, J. A.; Watt, G. M.; *et al.* Discovery of Potent Cyclophilin Inhibitors Based on the Structural Simplification of Sanglifehrin A. *J. Med. Chem.* **2017**, *60*, 1000–1017.

(89) DiMauro, E. F.; Kozlowski, M. C. Development of Bifunctional Salen Catalysts: Rapid, Chemoselective Alkylations of Alpha-Ketoesters. *J. Am. Chem. Soc.* **2002**, *124*, 12668–12669.

(90) Kelly, T. R.; Sestelo, J. P.; Tellitu, I. New Molecular Devices: In Search of a Molecular Ratchet. *J. Org. Chem.* **1998**, *63*, 3655–3665.

(91) Zhuravel, M. A.; Nguyen, S. T. Preparation of 3-Aryl-Substituted Salicylaldehydes via Suzuki Coupling. *Tetrahedron Lett.* **2001**, *42*, 7925–7928.

(92) Pal, A.; Ghosh, R.; Adarsh, N. N.; Sarkar, A. Pyrazole-Tethered Phosphine Ligands for Pd(0): Useful Catalysts for Stille, Kumada and Hiyama Cross-Coupling Reactions. *Tetrahedron* **2010**, *66*, 5451–5458.

(93) Justicia, J.; Oltra, J. E.; Cuerva, J. M. General Approach to Polycyclic Meroterpenoids Based on Stille Couplings and Titanocene Catalysis. *J. Org. Chem.* **2004**, *69*, 5803–5806.

(94) Schlummer, B.; Scholz, U. Palladium-Catalyzed C-N and C-O Coupling - A Practical Guide from an Industrial Vantage Point. *Adv. Synth. Catal.* **2004**, *346*, 1599–1626.

(95) Guram, A. S.; Rennels, R. A.; Buchwald, S. l. A Simple Catalytic Method for the Conversion of Aryl Bromides to Arylamines. *Angew. Chem. Int. Ed.* **1995**, *34*,

1348–1350.
(96) Louie, J.; Hartwig, J. F. Palladium-Catalyzed Synthesis of Arylamines from Aryl Halides. Mechanistic Studies Lead to Coupling in the Absence of Tin Reagents. *Tetrahedron Lett.* **1995**, *36*, 3609–3612.
(97) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. Industrial-Scale Palladium-Catalyzed Coupling of Aryl Halides and Amines - A Personal Account. *Adv. Synth. Catal.* **2006**, *348*, 23–39.
(98) Chen, H. M.; Wang, D. P.; Wang, X. Y.; Huang, W. L.; Cai, Q.; Ding, K. Mild Conditions for Copper-Catalyzed N-Arylation of Imidazoles. *Synthesis* **2010**, *9*, 1505–1511.
(99) Dong, J. Y.; Li, T. B.; Dai, C.; Weng, W.; Xue, X. H.; Zhang, Y. Y.; Zeng, Q. L. Protecting-Group-Free Palladium-Catalyzed Hydroxylation, C-O and C-N Coupling of Chiral 6-Bromo- and 6,6'-Dibromo- 1,1'-binaphthols. *Appl. Organomet. Chem.* **2013**, *27*, 337–340.
(100) Neustadt, B. R.; Hao, J.; Liu, H.; Boyle, C. D.; Chackalamannil, S.; Shah, U. G.; Stamford, A.; Harris, J. M. Pyrazolo-[4,3-E]-1,2,4-Triazolo-[1,5-c]-Pyrimidine Adenosine A_{2a} Receptor Antagonists. *J. Med. Chem.* **1996**, *39*, 1164–1171.
(101) Meadows, R. E.; Woodward, S. Steric Effects in Palladium-Catalysed Amination of Aryl Triflates and Nonaflates with the Primary Amines $PhCH(R)NH_2$ (R=H, Me). *Tetrahedron* **2008**, *64*, 1218–1224.
(102) Driver, M. S.; Hartwig, J. F. Carbon-Nitrogen-Bond-Forming Reductive Elimination of Arylamines from Palladium(II) Phosphine Complexes. *J. Am. Chem. Soc.* **1997**, *119*, 8232–8245.
(103) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. An Improved Catalyst System for Aromatic Carbon-Nitrogen Bond Formation: The Possible Involvement of Bis(phosphine) Palladium Complexes as Key Intermediates. *J. Am. Chem. Soc.* **1996**, *118*, 7215–7216.
(104) Driver, M. S.; Hartwig, J. F. A Second-Generation Catalyst for Aryl Halide Amination: Mixed Secondary Amines from Aryl Halides and Primary Amines Catalyzed by $(DPPF)PdCl_2$. *J. Am. Chem. Soc.* **1996**, *118*, 7217–7218.
(105) Yin, J. J.; Buchwald, S. L. Pd-Catalyzed Intermolecular Amidation of Aryl Halides: The Discovery That Xantphos Can Be Trans-Chelating in a Palladium Complex. *J. Am. Chem. Soc.* **2002**, *124*, 6043–6048.
(106) Li, J. J. Buchwald–Hartwig Amination. In *Name Reactions: A Collection of Detailed Mechanisms and Synthetic Applications*; Springer Berlin Heidelberg: Berlin, Heidelberg, 2009; pp 80–83.
(107) Vinogradov, A.; Woodward, S. Palladium-Catalyzed Cross-Coupling Using an Air-Stable Trimethylaluminum Source. Preparation of Ethyl 4-Methylbenzoate. In Organic *Syntheses*; John Wiley & Sons, Inc., 2003.
(108) Kees, K. L.; Fitzgerald, J. J.; Steiner, K. E.; Mattes, J. F.; Mihan, B.; Tosi, T.; Mondoro, D.; McCaleb, M. L. New Potent Antihyperglycemic Agents in Db/db Mice: Synthesis and Structure-Activity Relationship Studies of (4-Substituted benzyl)(trifluoromethyl)pyrazoles and -Pyrazolones. *J. Med. Chem.* **1996**, *39*, 3920–3928.
(109) Li, H. L.; Kuninobu, Y.; Kanai, M. Lewis Acid-Base Interaction-Controlled Ortho-

Selective C-H Borylation of Aryl Sulfides. *Angew. Chem. Int. Ed.* **2017**, *56*, 1495–1499.
(110) Negishi, E.; King, A. O.; Okukado, N. Selective Carbon-Carbon Bond Formation via Transition-Metal Catalysis. 3. Highly Selective Synthesis of Unsymmetrical Biaryls and Diarylmethanes by Nickel-Catalyzed or Palladium-Catalyzed Reaction of Aryl Derivatives and Benzylzinc Derivatives with Aryl H. *J. Org. Chem.* **1977**, *42*, 1821–1823.
(111) Valente, C.; Belowich, M. E.; Hadei, N.; Organ, M. G. Pd-PEPPSI Complexes and the Negishi Reaction. *Eur. J. Org. Chem.* **2010**, *2010*, 4343–4354.
(112) Organ, M. G.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Valente, C. A User-Friendly, All-Purpose Pd-NHC (NHC=*N*-Heterocyclic Carbene) Precatalyst for the Negishi Reaction: A Step towards a Universal Cross-Coupling Catalyst. *Chem. Eur. J.* **2006**, *12*, 4749–4755.
(113) Fushimi, N.; Teranishi, H.; Shimizu, K.; Yonekubo, S.; Ohno, K.; Miyagi, T.; Itoh, F.; Shibazaki, T.; Tomae, M.; Ishikawa-Takemura, Y.; *et al.* Design, Synthesis, and Structure-Activity Relationships of a Series of 4-Benzyl-5-Isopropyl-1H-Pyrazol-3-Yl Beta-D-Glycopyranosides Substituted with Novel Hydrophilic Groups as Highly Potent Inhibitors of Sodium Glucose Co-Transporter 1 (SGLT1). *Bioorg. Med. Chem.* **2013**, *21*, 748–765.
(114) Calimsiz, S.; Organ, M. G. Negishi Cross-Coupling of Secondary Alkylzinc Halides with Aryl/heteroaryl Halides Using Pd-PEPPSI-IPent. *Chem. Commun.* **2011**, *47*, 5181–5183.
(115) Blanksby, S. J.; Ellison, G. B. Bond Dissociation Energies of Organic Molecules. *Acc. Chem. Res.* **2003**, *36*, 255–263.
(116) Hoffmann, R. W.; Bovicelli, P. Conversion of Aldehydes into 1,1-Dibromoalkanes. *Synthesis* **1990**, *1990*, 657–659.
(117) Lansinger, J. M.; Ronald, R. C. Reactions of Aromatic Aldehydes with Boron Halides. *Synth. Commun.* **1979**, *9*, 341–349.
(118) Osterlof, J. Copper Compounds of Acetylene. 1. Acetylene Compounds with Cuprous Chloride. *Acta Chem. Scand.* **1950**, *4*, 374–385.
(119) Krasovskiy, A.; Knochel, P. Convenient Titration Method for Organometallic Zinc, Magnesium, and Lanthanide Reagents. *Synthesis* **2006**, *2006*, 890–891.
(120) Gilman, H.; Cartledge, F. K. The Analysis of Organolithium Compounds. *J. Organomet. Chem.* **1964**, *2*, 447–454.
(121) Available from: Ingenieurbüro CAT, M. Zipperer GmbH. Etzenbach 16, 79219 Staufen, Germany.
(122) Available from: Perkin-Elmer/Cambridgesoft.
(123) Blake, A. J.; Shannon, J.; Stephens, J. C.; Woodward, S. Demonstration of Promoted Zinc Schlenk Equilibria, Their Equilibrium Values and Derived Reactivity. *Chem. Eur. J.* **2007**, *13*, 2462–2472.
(124) Baker, K. V; Brown, J. M.; Hughes, N.; Skarnulis, A. J.; Sexton, A. Mechanical Activation of Magnesium Turnings for the Preparation of Reactive Grignard Reagents. *J. Org. Chem.* **1991**, *56*, 698–703.
(125) Nakagawa, T.; Suzuki, T.; König, M.; Guldi, D. M.; Matsuo, Y. Synthesis, Photophysical Properties, and Excited State Dynamics of a Platinum Complex

of Tetracene Imide Disulfide. *Chem. Commun.* **2013**, *49*, 10394–10396.
(126) Perez-Albuerne, E. A.; Johnson Jr, H.; Trevoy, D. Highly Conducting Ion-Radical Salts of Tetrathiotetracene. *J. Chem. Phys.* **1971**, *55*, 1547–1554.
(127) Nogami, T.; Tanaka, H.; Ohnishi, S.; Tasaka, Y.; Mikawa, H. Electrical Conductivities of the Complexes of Naphthaceno[5,6-cd:11,12-c'd']bis[1,2]dithiole and its Analogs Obtained by Electrochemical Crystallization and Diffusion Method. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 22–25.