

Synthesis of Distally Substituted Thioether Resorcinarene Ligands

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Declaration

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the owner of the copyright thereof (unless to the extent explicitly otherwise stated) and that I have not previously in its entirety or in part submitted it for obtaining any qualifications.

December 2017

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Acknowledgements

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Abstract

In this thesis it is reported the attempts to synthesise a series of distal thioether functionalised resorcinarene ligands. Chapter 1 provides an overview in order to familiarize the reader about the history and synthesis of resorcinarenes as well as methods pertaining to the functionalization of resorcinarenes. In particular the synthesis of resorcinarenes for use as ligands in metal complexes as well as some examples of such resorcinarene-metal complexes are provided within this chapter. It is reported that resorcinarenes are mostly exploited within the application of host-guest complexes, but that only a few examples of resorcinarenes that are used as ligands for catalysis exist and are reported within the literature. Chapter 2 discusses the synthesis of parent resorcinarenes and the attempted synthesis of distal thioether resorcinarene ligands via the ortholithiation approach, using disulphides and sulphenyl chlorides as electrophiles. The ortholithiation procedure was compatible when using dimethyl disulphide as the electrophile; however the use of di-*tert*-butyl disulphide and benzenesulphenyl chloride as electrophiles returned negative results. Benzenesulphenyl chloride was successful when used as an electrophile within the ortholithiation procedure of the model system, 1,3-dimethoxybenzene, whereas di-*tert*-butyl disulphide was unsuccessful in this regard. Chapter 3 discusses the investigation into the attempted synthesis of a series of distal thioether resorcinarene ligands. This was attempted via transition metal catalysis as resorcinarenes can easily be functionalized with bromine which can be compared to aryl bromides which are commonly used as precursors in such coupling reactions. The literature suggested that copper and palladium would be good candidates to perform thioetherification, the coupling of thiols to aryl bromides, on the resorcinarene. Copper mediated thioetherification reactions were tested on the pre-functionalized model system, 2-bromo-1,3-dimethoxybenzene, and showed low conversion of starting materials. Palladium mediated thioetherification reactions were also tested on the same model system, performed with the reportedly highly active $[\text{Pd}(\text{IPr}^{\text{OMe}})(\text{cin.})(\text{Cl})]$ catalytic species, and returned near quantitative yields of the coupled product. When the same catalytic species was tested on a distal dibromo resorcinarene precursor, however only starting material was isolated from the reaction. Chapter 4, Conclusions and Future Work, and Addendum A discusses work that was only preliminary and not thoroughly investigated due to time constraints. Future work towards the attempted synthesis of distal thioether resorcinarene ligands via catalysis, the use of sulphur nucleophiles or using different types of sulphur-derived electrophiles within the ortholithiation approach are also discussed within these two chapters.

Opsomming

In hierdie tesis word die pogings van die sintese van 'n reeks van distaal tio-eter gefunksioneerde resorsinareenligande gerapporteer. Hoofstuk 1 bied 'n oorsig om die leser bekend te stel aan die geskiedenis en sintese van resorsinarene. In besonder word die sintese van resorsinarene vir die gebruik as ligande in metaalkomplekse bespreek sowel voorbeelde van resorsinareen-metaalkomplekse word verskaf in die hoofstuk. Dit word gerapporteer in die literatuur dat resorsinarene word meestal gebruik in die toepassing van gas-gasheer komplekse. Daar ontstaan net 'n klein hoeveelheid resorsinarene wat word gebruik as ligande vir katalise. Hoofstuk 2 bespreek die sintese van resorsinarene en die poging tot die sintese van distaal tio-eter resorsinareenligande deur die *orto*-litiëringbenadering wanneer di-sulfiede en sulfenielchloriede word gebruik as elektrofiel. Die *orto*-litiëring prosedure was versoenbaar wanneer dimetiel disulfied gebruik word as die elektrofiel; alhoewel die gebruik van di-*tert*-butiel disulfied en benseensulfenielchloried as elektrofiel negatiewe resultate opgelewer het. Benseensulfenielchloried was suksesvol wanneer dit gebruik was in die *orto*-litiëring prosedure van 'n model sisteem, 1,3-dimethoksybenseen, terwyl di-*tert*-butiel disulfied was onsuksesvol in die verband. Hoofstuk 3 bespreek die ondersoek in 'n poging tot die sintese van distaal tio-eter resorsinareenligande deur oorgangsmetaal katalise as gevolg van die feit dat resorsinarene kan maklik gefunksionaliseer word met broom wat kan vergelyk word met ariëlbromied wat in die algemeen gebruik as voorlopers in sulke koppelingsreaksies. Die literatuur het aangedui dat koper en palladium goeie kandidate sou wees om tio-eterfikasie uit te voer, die koppeling van tiolêre aan ariëlbromiede, op die resorsinarene. Die bemiddeling van koper tio-eterfikasie was getoets op 'n ariëlbromied model sisteem, 2-broom-1,3-dimethoksybenseen, en het laag omskakeling van uitgangsmateriaal getoon. Die bemiddeling van palladium tio-eterfikasie reaksies was ook getoets op dieselfde model sisteem, uitgevoer deur die gerapporteerde hoogs aktiewe $[Pd(IPr^{OMe})(cin.)(Cl)]$ katalitiese spesie, en het 'n baie na aan kwantitatiewe opbrengs van die gekoppelde produk opgelewer. Wanneer dieselfde katalitiese spesie getoets was op die distaal dibroom resorsinareen voorloper, het die reaksie net uitgangsmateriaal opgelewer. Hoofstuk 4 (Gevolgtrekkings en Toekomstige Werk) en Aanhangsel A bespreek voorlopige werk wat nie deeglik ondersoek en nagevors was nie as gevolg van beperkings in terme van tyd. Toekomstige werk teenoor die pogings tot die sintese van distaal tio-eter resorsinareenligande deur katalise, die gebruik van swaelnukleofiele of die gebruik van verskillende tipe swael-afgeleide elektrofiel in die *orto*-litiëringbenadering word ok bespreek in die twee hoofstukke.

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List of Abbreviations

AIBN	Azoisobutyronitrile
API	Atmospheric Pressure Ionization
bs	broad singlet
CAF	Central Analytical Facility
CAM	Cerium Ammonium Molybdate
cin.	cinnamyl
d	doublet
dd	doublet of doublets
DCM	Dichloromethane
DG	Directing Group
DMG	Directing Metalation Group
DMSO	Dimethylsulphoxide
DoM	Directed ortho-Metalation
GC	Gas Chromatography
HPLC	High Pressure Liquid Chromatography
HRMS	High Resolution Mass Spectroscopy
IPr ^{*OMe}	N,N'-Bis(2,6-bis(diphenylmethyl)-4-methoxyphenyl)imidazol-2-ylidene
NBS	N-Bromosuccinimide
NCS	N-Chlorosuccinimide
NHC	N-Heterocyclic Carbene
NMR	Nuclear Magnetic Resonance
m	multiplet
q	quartet
Q-TOF	Quadrupole Time of Flight
s	singlet
sxt	sextet
t	triplet
tt	triplet of triplets
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
UV	Ultra Violet
vbs	very broad singlet

Chapter 1

Introduction

1.1 Resorcinarenes

Cyclophanes are hydrocarbons that consist of either a single aromatic ring that is linked to itself, or a number of aromatic rings that are linked to one another, by aliphatic chains which forms the bridge(s) between the substituted positions on the aromatic ring(s) (Figure 1). Cyclophanes are cyclic molecules, “in which more than two atoms of an aromatic ring are incorporated into a larger ring system”.^{1,2} Cyclophanes that consist of a single aromatic ring are mostly strained. Resorcinarenes³ (Figure 2) are flexible macrocyclic molecules that contain at least four aromatic rings and belong to the family of [1]₄-metacyclophanes.

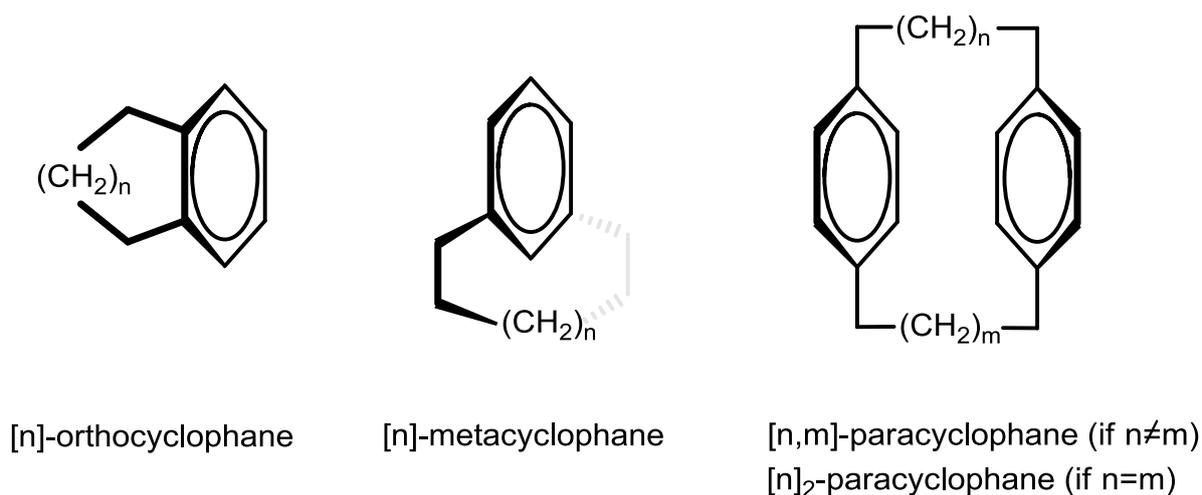


Figure 1 - Cyclophanes.

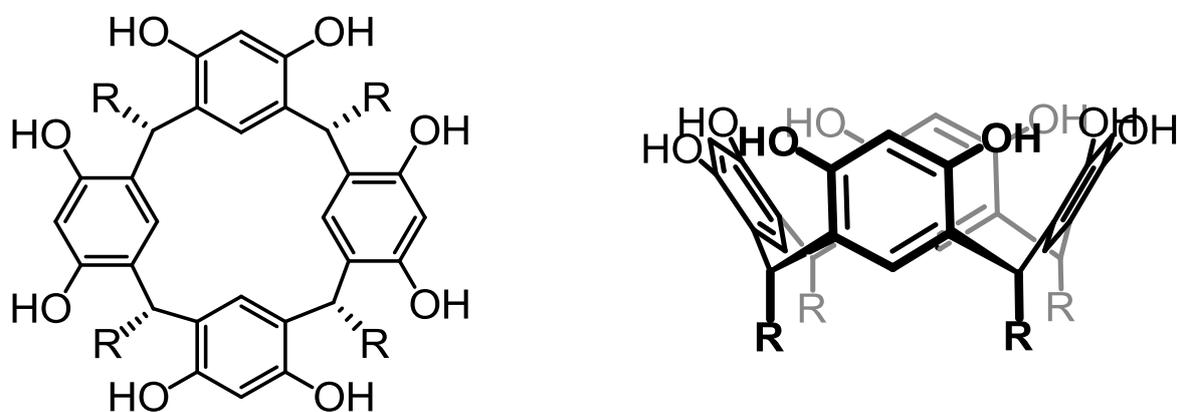


Figure 2 - A flat representation (left) and three-dimensional representation (right) of resorcinarenes.

The prefix 'meta' corresponds to the substitution pattern as to how the aromatic unit(s) is/are bridged and the number in brackets refers to the number of linker atoms that are found in the aliphatic bridges that connect the aromatic unit(s) to one another. The subscript number is there for convenience and indicates how many aliphatic bridges are present within the entire macrocycle, instead of repeating them all within the brackets. This nomenclature is only applicable to cyclophanes that contain more than one aromatic subunit and contain the same sized bridges within the macrocycle (i.e. when $n=m$ in Figure 1). This number is also the same number $[n]$ that is found in brackets within the nomenclature of resorcin $[n]$ arenes and calix $[n]$ arenes and is also indicative of how many subunits are present within the calix $[n]$ arene or resorcin $[n]$ arene (Figure 3). Within literature calix $[n]$ arenes have only reported to have methylene (methanediyl) bridges whereas resorcin $[n]$ arenes mostly have methine (methanetriyl) bridges, but may also have methylene bridges.^{4,5} The current literature also indicates that resorcin $[n]$ arenes⁶ can have up to six subunits (i.e. $n=4-6$) where calix $[n]$ arenes⁷ can have up to as much as ten (i.e. $n=4-10$) (Figure 3). The aliphatic bridges provide resorcinarenes and calixarenes with a well-defined shape that render these macrocycles with a characteristic feature of having a three-dimensional cavity within the centre of the molecule. This cavity found within resorcinarenes are mostly exploited as host-guest complexes; hence they are categorically referred to as cavitands and carcerands ever since the term was first coined by Donald Cram in 1982 when he described resorcinarene molecules that had a well-defined three-dimensional cavity.⁸ It was Cram's work on host-guest complexes that motivated his claim to be bestowed with a Nobel Prize in Chemistry in 1987,⁹ along with Charles Pederson¹⁰ and Jean-Marie Lehn.¹¹ These chemists were jointly awarded the Nobel Prize for their pioneering work into macrocyclic chemistry and since then they became known as the founders of supramolecular chemistry. Before the trivial name of resorcinarenes became universally accepted for these compounds in 1994,¹² they were referred to as calix $[n]$ resorcinarenes,^{13,14} calix $[n]$ resorcinolarenes,^{15,16} octols¹⁷⁻²⁰ and even Högberg compounds,²¹ named after one of the chemists who confirmed the structure of resorcinarenes in the 1968.²²

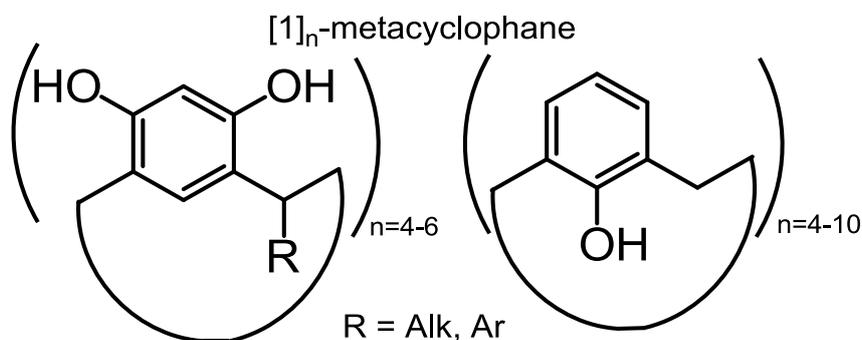


Figure 3 - Resorcin $[n]$ arenes (left) and calix $[n]$ arenes (right).

1.2 History of Resorcinarenes

Resorcinarenes were first synthesised in 1872 by one of the greatest organic chemists of the 19th century, Johann Friedrich Wilhelm Adolph von Baeyer, within his studies into condensation-type reactions between phenol-type dyes and aldehydes within acidified alcoholic media.²³ Von Baeyer was awarded the Nobel Prize in Chemistry in 1905 “in recognition of his services in the advancement of organic chemistry and the chemical industry, through his work on organic dyes and hydroaromatic compounds”.²⁴ The elucidation of the structures of the products of the reactions he conducted between phenols and aldehydes was not possible as the analytical techniques that were available at the time were still in their infancy and were not advanced enough to provide any insight into the structures of these molecules. Among the phenols that he used was resorcinol, which forms the aromatic repeating subunit of resorcinarenes; however he decided not to pursue the investigation towards the characterization of the compounds, as these molecules lacked the dye-stuff properties he was seeking such as those that were exhibited by calixarenes. He did, however, conclude that these products are formed in a 1:1 ratio of starting reagents.

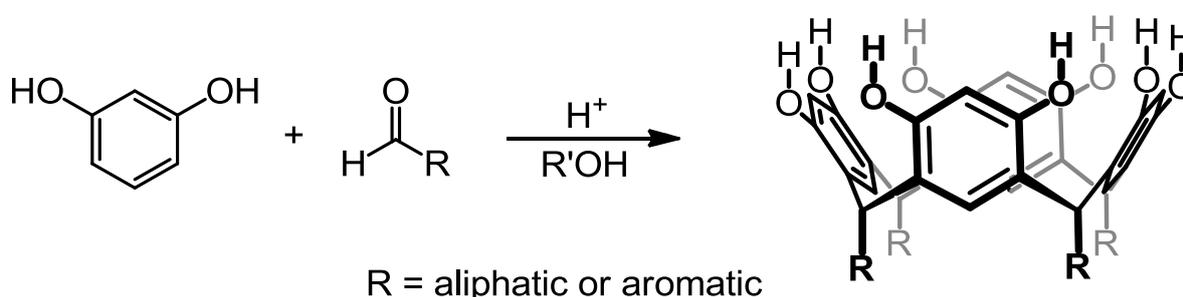
After these compounds were discovered by von Baeyer, they were re-investigated by the likes of Michael in 1883,²⁵ Möhlau and Koch in 1894,²⁶ followed by Liebermann and Lindebaum (1904),²⁷ all of whom were not able to obtain any insight into their structures. Michael was not able to determine the molecular weight of the compound but was able to deduce the elemental composition of the products isolated by von Baeyer and concluded that the product was formed from a combination of equal number of starting reagents as von Baeyer suggested, resulting in the loss an equal number of water molecules. Resorcinarenes remained untouched for nearly 40 years when they were investigated by Niederl and Vogel²⁸ in 1940, who postulated based on their findings of molecular weight determinations that the product is best described as a cyclic tetramer and that the exact ratio of aldehyde to resorcinol should be 4:4.

It was only until 1968; almost a century after von Baeyer first discovered them, that the structure of these compounds was finally proven by Erdtman, Högberg and co-workers²² by single crystal X-ray analysis to be the structure that was postulated by Niederl and Vogel. Since the confirmation of their structures, these compounds have received much interest in the 1980's and 1990's by researchers such as Högberg^{22,29,30} and Cram,^{8,9,17-20,31-51} who studied them and their applications in great detail. After the studies done by Högberg, Cram and other pioneers; resorcinarenes have been extensively studied by various research groups for their potential use in a variety of applications.

These applications are vast and include the following, among others:

1. starting materials for host-guest complexes (cavitands and carcerands),^{6,7,17-21,30-52}
2. molecular receptors (sensors),⁵³⁻⁶²
3. GC (Gas Chromatography) stationary phases,⁶³⁻⁶⁸
4. HPLC (High Pressure Liquid Chromatography) stationary phases^{64,68-72}, some which are effective in the separation of isomers⁷³ and pyrimidine bases,⁷⁴
5. ligands for organometallic catalysts.⁷⁵⁻⁷⁹

1.3 Synthesis of Resorcinarenes



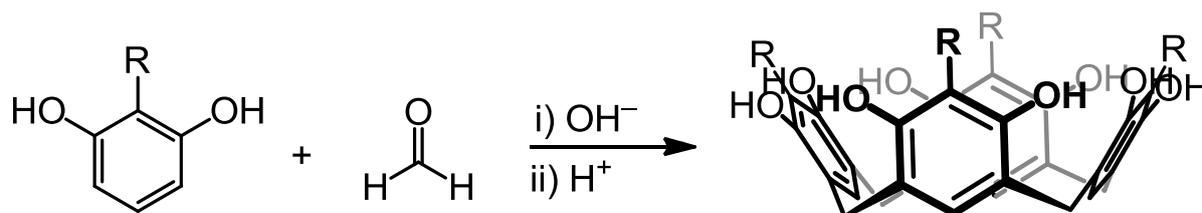
Scheme 1 - General traditional synthesis of resorcinarenes. Reagents and conditions: resorcinol (1 equiv.), aldehyde (1 equiv.), H⁺ (1 equiv.), alcoholic solvent (R'OH), T = 0 °C to reflux, overnight.

Resorcinarenes are traditionally synthesised in one step and in mostly reasonable to excellent yields³ overnight using a Brønsted acid (usually hydrochloric acid) within a suitable alcoholic solvent (usually ethanol) at mild temperatures ranging from 0 °C to reflux (Scheme 1). The simplicity of this procedure is that the product can be collected by filtration and purified using recrystallization. Sometimes it is necessary to add some water to allow the recrystallization process to occur.³⁰ The fact that the macrocycles are insoluble in the reaction solvent forces the reaction equilibrium towards the right. The reaction has been shown to tolerate a wide variety of aldehydes (aromatic and aliphatic). In order to obtain appreciable yields; different reaction conditions are required depending on the aldehyde that is used.^{17,20,21} Alternative and more modern procedures exist for synthesising resorcinarenes in even better yields which are achieved by using Lewis acids instead of Brønsted acids.^{13,80-82} Some Lewis acids even provide selectivity into which stereoisomer is formed within the reaction, making them even more beneficial towards the synthesis of resorcinarenes.⁸² One of these modern procedures reports obtaining resorcinarenes up to excellent yields (90%) in as short as five minutes by using a Keggin-type 12-tungstophosphoric acid in a microwave-assisted synthesis.⁸³

Another green procedure has been reported in obtaining resorcinarenes in a solvent-free synthesis which involves grinding resorcinol with the aldehyde together with a catalytic amount of p-toluenesulfonic acid.⁸⁴ Resorcinol derivatives that contain an electron-donating substituent at the 2-position (referred to henceforth as the *ortho*-position) are known to prefer the usual acidic conditions in order to cyclize into macrocycles.^{85,86} While resorcinol derivatives that contain an electron-withdrawing substituent at the *ortho*-position require basic conditions to be synthesised in appreciable yields (Scheme 2).⁴

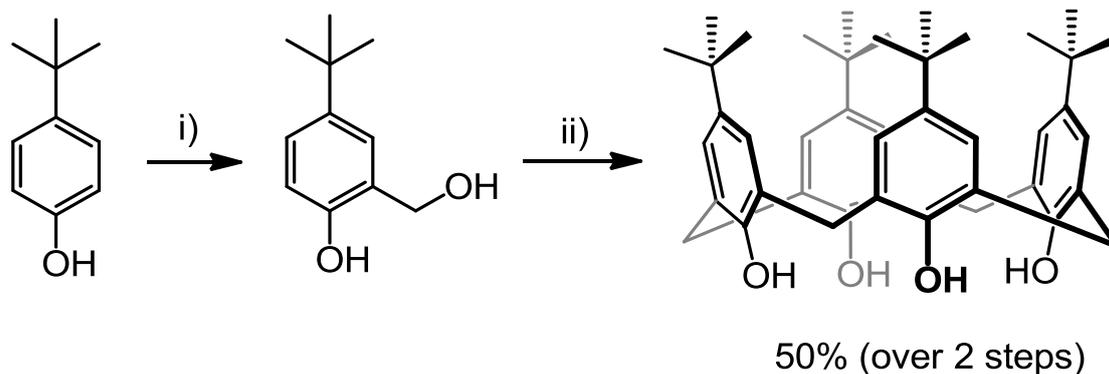
Table 1 - A table showing the specifications and results of the reaction depicted in Scheme 2.⁴

R =	Yield (%)
H	16
Ac	37
CO ₂ H	50
NO ₂	60



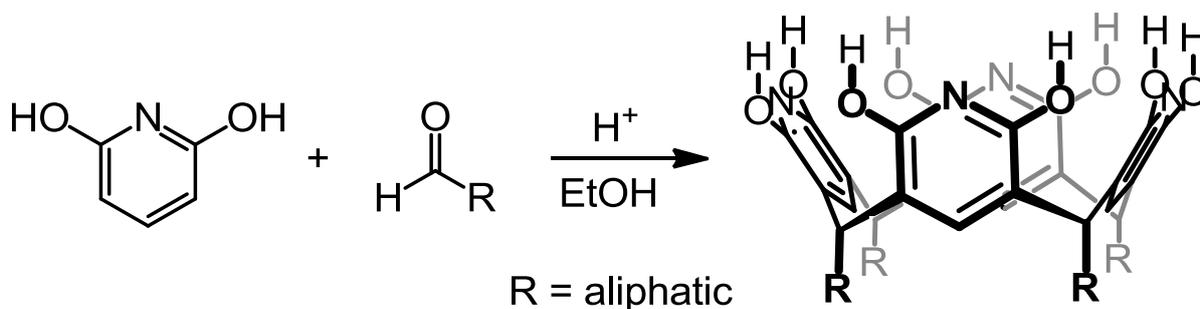
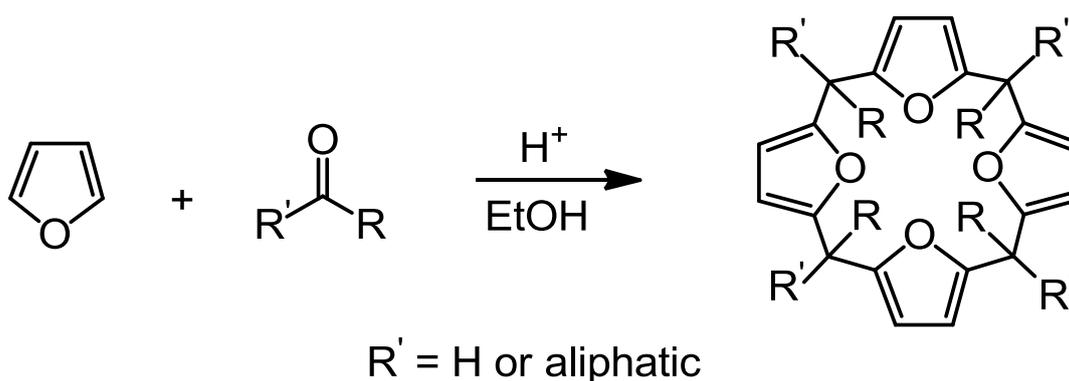
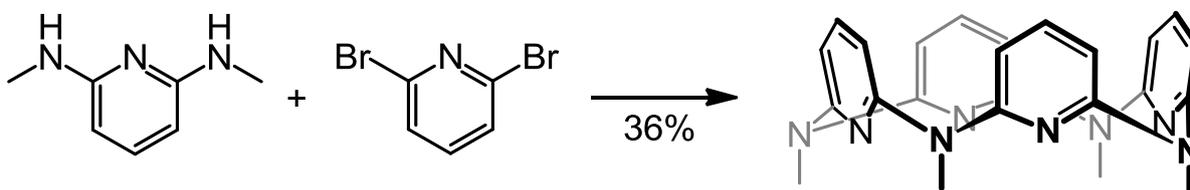
Scheme 2 - Synthesis of resorcinarenes from resorcinol derivatives that contain electron-withdrawing substituents at the 2-position (*ortho*-position).⁴

Calixarenes are considered as the rather more popular cousins to resorcinarenes as they too belong to the family of [1]₄-metacyclophanes. These calixarenes, however, are synthesised quite laboriously in a fair overall yield of 50%. The synthesis of calixarenes utilized within our group was adapted from a modified version of the Zinke-Cornforth procedure reported by Gutsche.⁸⁷ Calixarenes require reaction temperatures up to 250 °C to be synthesised, which requires expensive high boiling point solvents such as diphenyl ether (Scheme 3).



Scheme 3 - Synthesis of calix[4]arenes reported by Gutsche.⁸⁷ Reagents and conditions:
 i) 37% formalin (1.25 equiv.), NaOH (0.03 equiv.) in H₂O, 120 °C, 2 hours; ii) diphenyl ether, reflux, 2 hours.

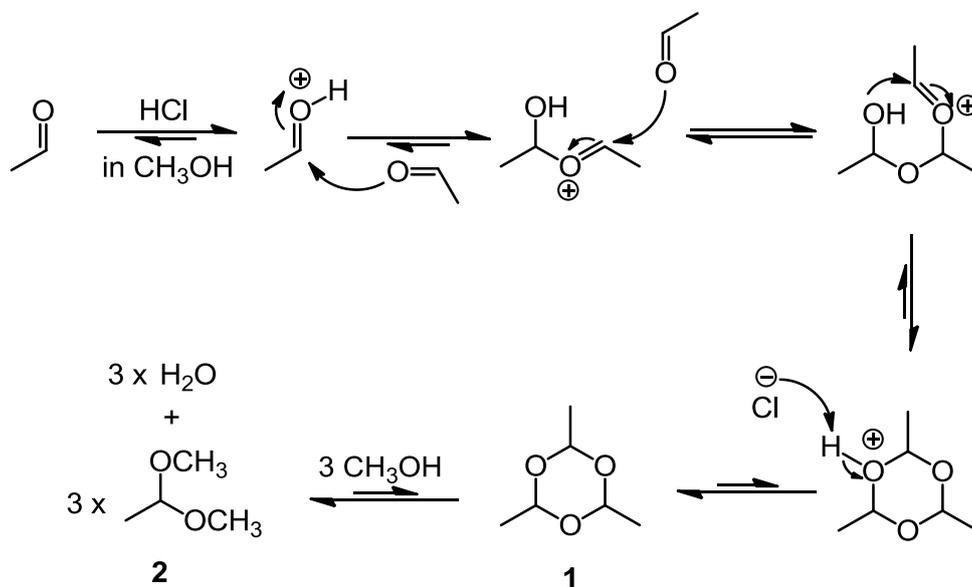
Resorcinarene methyl ethers can be synthesised by methylating parent octahydroxy resorcinarenes or can also be synthesised directly from the lesser nucleophilic and protected version of resorcinol, namely 1,3-dimethoxybenzene and meta-alkylated derivatives thereof in most cases.^{5,80–82,88,89} Pyridine, pyrogallol and furan analogues of resorcinarenes, which are called pyridine[4]arenes,⁹⁰ pyrogallol[4]arenes⁸⁶ and [1]₄(2,5)furanophanes^{91,92} respectively, have also been synthesised from their corresponding starting materials using similar reaction conditions when preparing resorcin[4]arenes (Scheme 4 and 5). The [1]₄(2,5)furanophanes have even been successfully condensed with the lesser electrophilic ketones under strongly acidic conditions. The synthesis of heterocalixaromatics, which are resorcinarene-type molecules that contain heteroatomic aliphatic bridges such as nitrogen and oxygen functionalities, have also been reported and provides a very interesting modification to [1]₄-metacyclophanes (Scheme 6).⁹³ Nitrogen can adopt either a sp³ or sp² hybridization giving rise to resorcinarene systems that may have different conjugation between the bridging unit and adjacent aromatic rings resulting in various C-N bond lengths and C_(Ar)-N-C_(Ar) bond angles. However it should be mentioned that these molecules resemble calixarenes more than resorcinarenes, since they contain heteroatom functionalities (however underivatizable) at the lower rim of each aromatic ring as well as three derivatizable aromatic positions at the upper rim.

Scheme 4 - Synthesis of pyridin[4]arenes.⁹⁰Scheme 5 - Synthesis of [1]₄(2,5)furanophanes.^{91,92}Scheme 6 - Synthesis of heterocalixaromatics.⁹³ Reagents and conditions:
Pd(dba)₃, dppp, NaOtBu, PhMe, reflux.

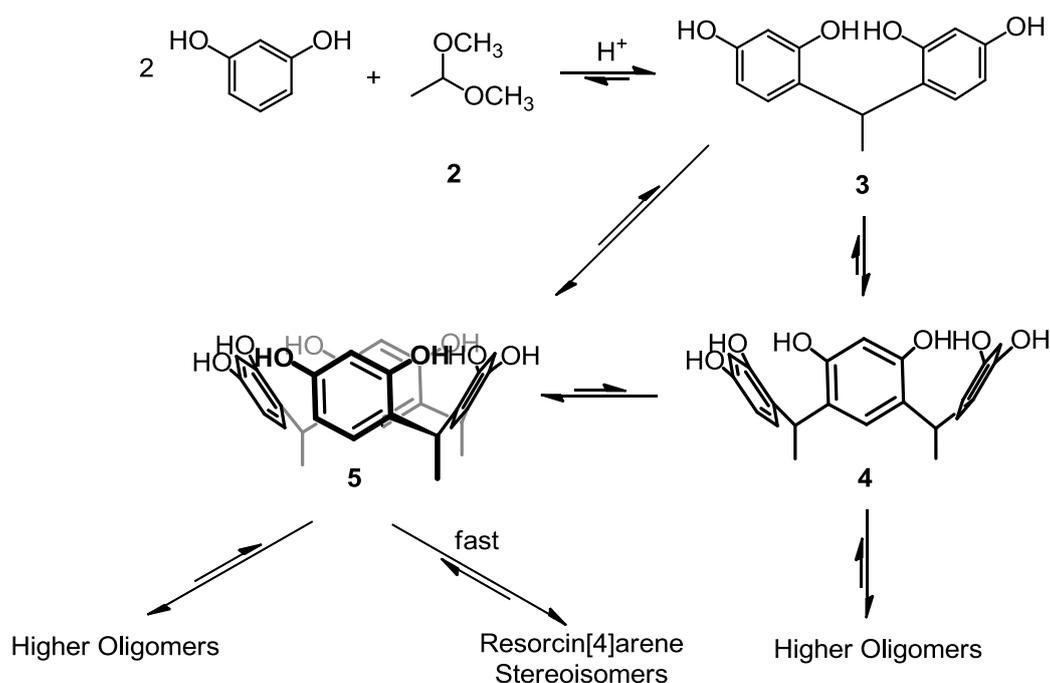
1.4 Mechanism of Macrocyclic Condensation

Investigation into the mechanistic aspects of the acid-catalyzed macrocyclic condensation of resorcinol with aldehydes was done in 1990 by Weinhelt and Schneider⁹⁴ as it was of importance to them to understand how the macrocycle can be synthesised in such good yields without the use of templates or high dilution techniques such as those used when synthesizing strained cyclophanes.² They investigated mechanistic aspects (both kinetic and thermodynamic) on resorcinarenes by studying the reaction involving resorcinol and acetaldehyde within a hydrogen chloride in methanol solution using NMR (Nuclear Magnetic Resonance) techniques.

According to their studies, the electrophilic species does not stem from the aldehyde itself but rather from its corresponding acetal (**2**) which is rapidly formed in solution when methanol reacts with paraldehyde (**1**), the cyclic trimer of acetaldehyde which forms under acidic conditions (Scheme 7). Thereafter resorcinol can attack the active electrophilic species, acetal (**2**), under acidic conditions in order to form linear intermediates **3** – **5** as well as higher linear oligomers (Scheme 8).



Scheme 7 - Mechanistic formation of the active electrophilic species, acetal (**2**), from the resorcinol-acetaldehyde (in HCl in MeOH) reaction.⁹⁴



Scheme 8 - Formation of resorcin[4]arenes via linear oligomers from the reaction of resorcinol with acetaldehyde in a HCl in MeOH solution.⁹⁴

The build-up of oligomers **3** – **4** as well as three stereoisomeric macrocyclic products was quantitatively observed throughout the reaction with the use of high field ^1H NMR spectroscopy. Weinhelt and Schneider⁹⁴ stipulated that the tetramers (**5**) cyclize too fast to be observed within the reaction by ^1H NMR spectroscopy, which is why they are never observed within the spectrum throughout the reaction. All isolated intermediates had terminal resorcinol moieties and not methoxy groups which is in accordance with other known examples of acid-catalyzed condensations.⁹⁵ The fast cyclization has been speculated due to their lack of conformational strain (high degree of freedom) as well as the high affinity to form favourable intramolecular hydrogen bonding interactions induces the tetramers to fold onto itself which results in the terminal chains of the tetramer to be in close proximity of one another. The flexibility of the tetramer as well as the formation of hydrogen bonds provides the driving force for cyclization. Furthermore higher oligomers (pentamers and hexamers) were present within the concentrations up to 45% together with the tetramers at intermediate reaction times. It is impossible to distinguish which signals belong to which oligomer within the ^1H NMR spectrum when dealing with oligomers that have more than five repeating subunits, due to severe overlap of signals. The signals attributed to the higher oligomers rapidly disappear towards the end of the reaction within the spectrum as they deoligomerize into tetramers, since the condensation reaction is reversible under the conditions used, resulting in further cyclization into macrocycles.

1.5 Stereochemical Aspects of Resorcinarenes

As subtly mentioned in Section 1.4; resorcinarenes are produced as conformational isomers and therefore the isolation of more than one resorcinarene is most likely when condensing resorcinol with aldehydes. Three aspects govern their stereochemistry:

- 1) The positions of the aromatic rings relative to one another (Figure 4). In principle many possible stereoisomers can exist due to the orientation of the aromatic rings relative to one another, however only five have been speculated to exist. The most symmetrical stereoisomer, the crown conformation (C_{4v}) (as shown on the right of Figure 2), has all the aromatic rings in the same orientation facing upwards forming a bowl-like shape. Starting from the crown conformation the boat conformation (C_{2v}) can be formed by flipping two opposite aromatic rings downwards so that they lie perpendicular to the other two aromatic rings. Further rotation of one of upward-facing rings by 180° so that it faces in the opposite direction to the unchanged ring produces the chair conformation (C_{2h}). Rotating both the flat perpendicular rings another 90° downwards starting from the boat isomer, produces the saddle conformation (D_{2d}).

The least symmetrical conformation, diamond conformation (C_s), has two adjacent rings facing upwards and the two other adjacent rings facing downwards.

- 2) The relative configuration of the R-groups to one another at the aliphatic bridges (Figure 5) which results in four possible stereoisomers. The relative configuration of these groups is specified arbitrarily to a reference R-group (indicated by **R** in Figure 5). Each R-group's relative configuration to the reference R-group (**R**) is listed in order moving in a clockwise direction starting from the reference R-group. These R-groups can be in an all *cis*-configuration (*rccc*) relative to the **R**. One R-group could be *trans* to **R** while the others have a *cis*-relationship with **R** (*rcct*). When the R-group directly opposite to **R** is in a *cis*-relationship with **R** while the other two diametrical R-groups are in a *trans*-relationship to each other, the *rtct* stereoisomer is formed. Having the R-group directly opposite to **R** in a *trans*-relationship with **R** while the other two diametrical R-groups also have a *trans*-relationship to each other, the *rctt* stereoisomer is formed. Three of remaining four permutations of the relative configurations (*rctc*, *rtcc*, *rttt*) are identical to the *rcct* relationship while the remaining permutation (*rttc*) is identical to the *rctt* relationship since the choice of **R** is arbitrary.
- 3) The last aspect concerns the individual stereochemistry of the R-groups at the aliphatic bridges, which can either be equatorial or axial. Axial orientations for the R-groups are strongly favoured over equatorial orientations due to steric hindrance, which is contrary to what is seen for cyclic chains such as cyclohexane. These R-groups usually suppress the flexibility of the resorcinarene and inhibit ring inversion.⁸⁵

Combination of these three stereochemical aspects would result in a large number of stereoisomers. Aspects one and two are largely dependent on one another as rotation of the aromatic rings also results in rotation of the aliphatic bridges (the actual orientation of the R-groups in Figure 4 after rotating the aromatic ring(s) are omitted for clarity). The crown and boat conformation have a *rccc* relationship, the chair has a *rcct* relationship, while the *rctt* conformation belongs to the diamond conformation and lastly the saddle conformation has a *rtct* relationship between the pendant R-groups. All five stereoisomers have been isolated experimentally and the ratios in which these stereoisomers are formed are largely dependent on the reaction conditions that are used. For a long time the saddle conformation could not be isolated as it converts into the more thermodynamic boat isomer too rapidly. The saddle conformation has since been isolated when self-condensing certain 2,4-dimethoxycinnamates that are able to conformationally lock the macrocyclic product in this stereoisomeric form.

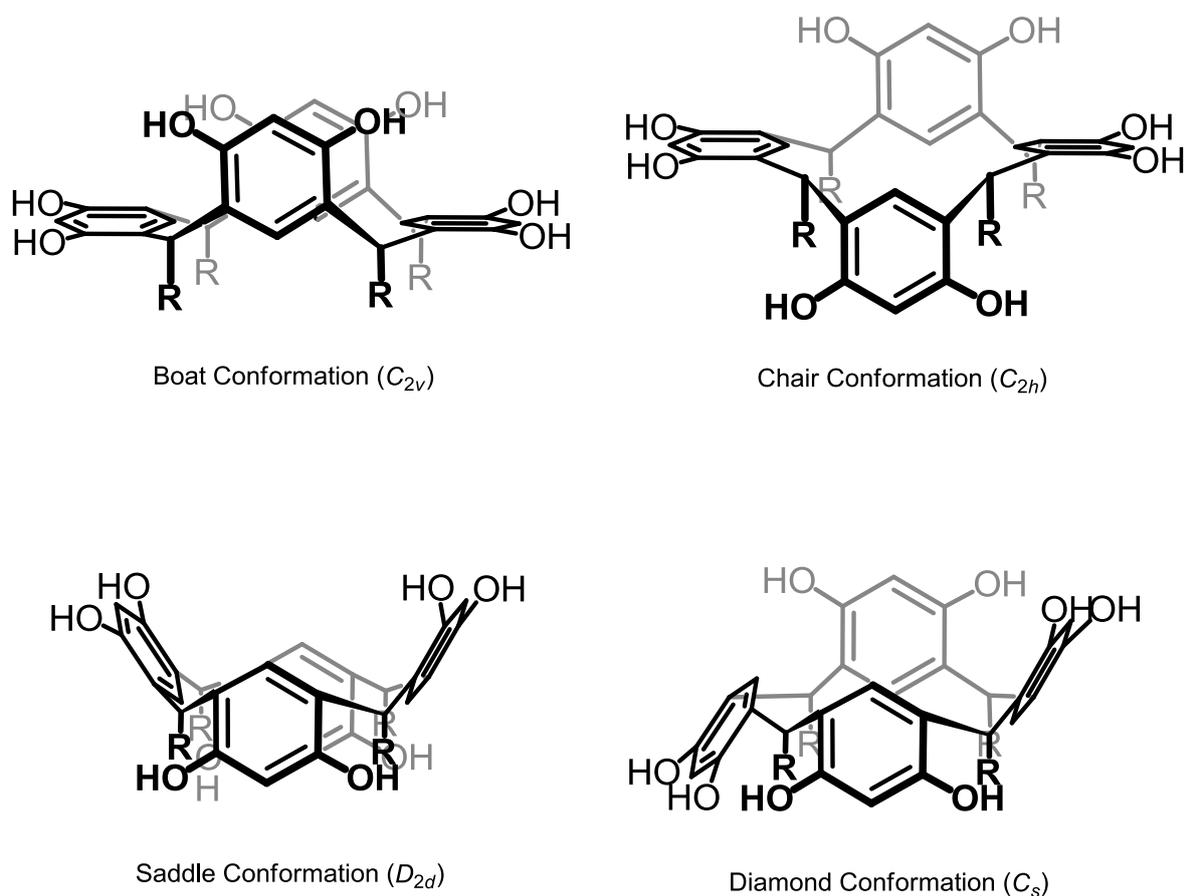


Figure 4 - Stereoisomers of the crown conformation (refer to the three-dimensional representation of resorcinarenes in Figure 2) which are brought about by the different relative orientations of the aromatic rings.

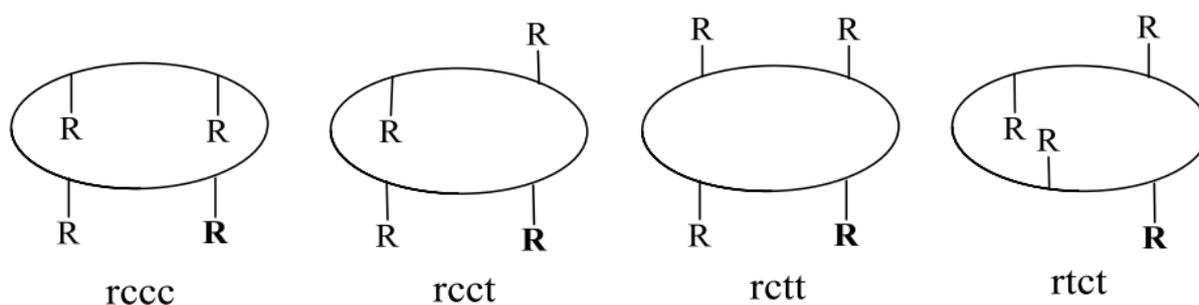


Figure 5 - Relative configuration of the pendant chains of the aliphatic bridges to one another (reproduced from reference 96).⁹⁶

When the reaction is carried out under homogenous acidic conditions, the product ratio equilibrium ratio is mainly governed by the thermodynamic stability of the different isomers, since the condensation reaction is reversible under these conditions. Under heterogeneous conditions, this ratio is mainly determined by the relative solubilities of the different isomers in the reaction solvent.³ Weinhelt and Schneider⁹⁴ found that isomerization of stereoisomers is possible when they performed equilibration studies with the rccc (boat) isomer in a 5% HCl

in a MeOH solution at 50 °C. They found isomerization to proceed via the *rcct* isomer (chair) and to occur quite slowly. Rate constants for the isomerization from the other isomers towards the *rcct* isomer is always favoured, except for the isomerization of the *rccc* isomers (crown and boat) which has a rate constant of isomerization almost equal to the rate constant of isomerization towards the chair isomer (from the *rccc* isomers). Furthermore, no isomerization towards the *rtct* isomer (saddle) was seen; however a rate constant for isomerization of the saddle towards the chair isomer was reported.

1.6 Functionalization of Resorcinarenes

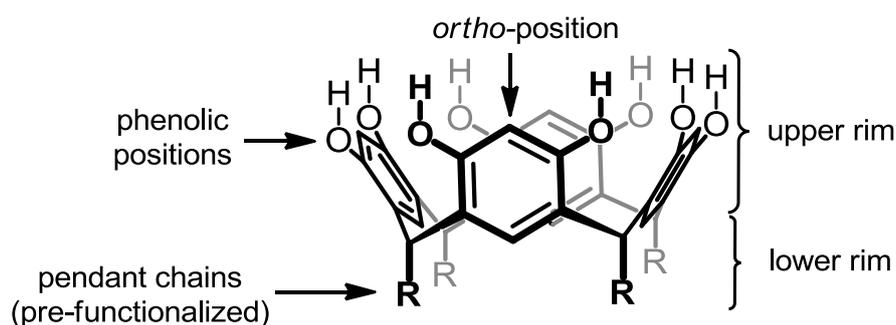


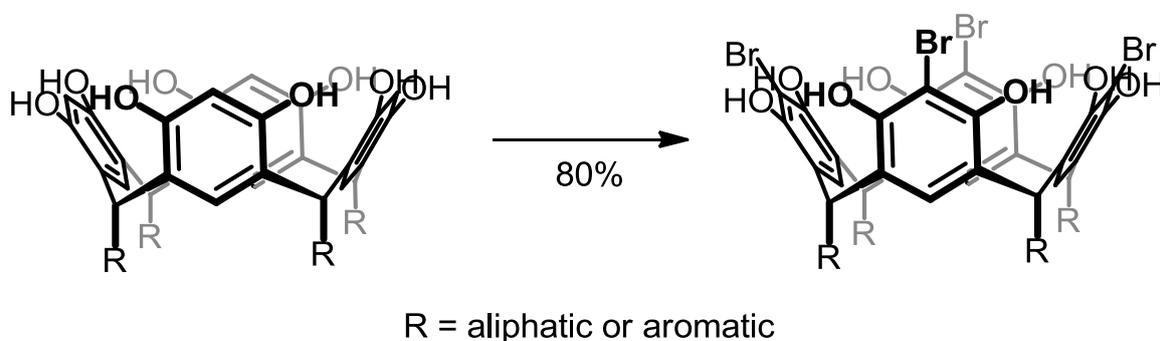
Figure 6 - Regions and derivatizable positions of the resorcinarene.

Many procedures have been envisioned and implemented in obtaining functionalized resorcinarenes. Resorcinarenes have two regions that are able of being functionalized (Figure 6). The border where these two regions meet are the aliphatic bridges connecting the aromatic rings together. Therefore the aromatic positions that are above the *meta*-positions constitute the upper rim of the resorcinarene while any positions (aromatic or aliphatic) below these *meta*-positions are a part of the lower rim. The single position on each aromatic ring found on the lower rim is usually unfunctionalizable. Therefore functionalization of the lower rim usually only involves functionalization of the pendant chains, which can be derivatized when condensing resorcinol with an already pre-functionalized aldehyde (that contains functional groups within the chain of the aldehyde itself). The synthesis of 'mixed-feet' resorcinarenes has also been investigated and reported in literature.⁹⁷⁻¹⁰⁰ The synthesis involves the condensation of resorcinol with a mixture of aldehydes in different ratios to obtain 'mixed-feet' resorcinarenes (usually 3:1 to obtain a resorcinarene that contains one derivatizable pendant chain). The upper rim contains two different derivatizable positions: the phenolic positions and the *ortho*-positions. The phenolic positions can be functionalized just the same as any phenol or alcohol, i.e. etherification, esterification, phosphorylation etc. The phenolic positions within the resorcinarene have the same *meta*-relationship as the aliphatic

bridges have with each other and provide the resorcinarenes with the capability of being made rigid by bridging neighbouring phenolic positions with each other which forms cavitands or bridging phenolic substituents with another resorcinarene molecule to form carcerands.

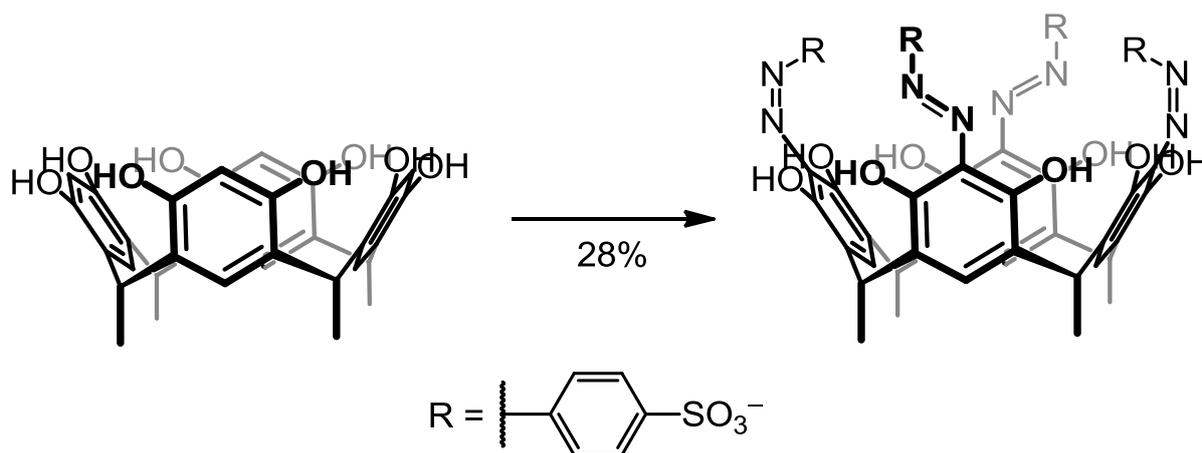
1.6.1 Electrophilic Aromatic Substitution

The *ortho*-positions of the resorcinarene can be pre-functionalized by using resorcinol-derivatives that contain substituents at the *ortho*-position or can be functionalized after the plain resorcinol-derived macrocycles are formed. The presence of two neighbouring hydroxyl groups strongly activates the *ortho*-position and allows electrophilic aromatic substitution to be performed on the resorcinarene (Scheme 9).²⁰



Scheme 9 - Synthesis of tetrabromoresorcin[4]arene.²⁰ Reagents and conditions: NBS (excess), methyl ethyl ketone.

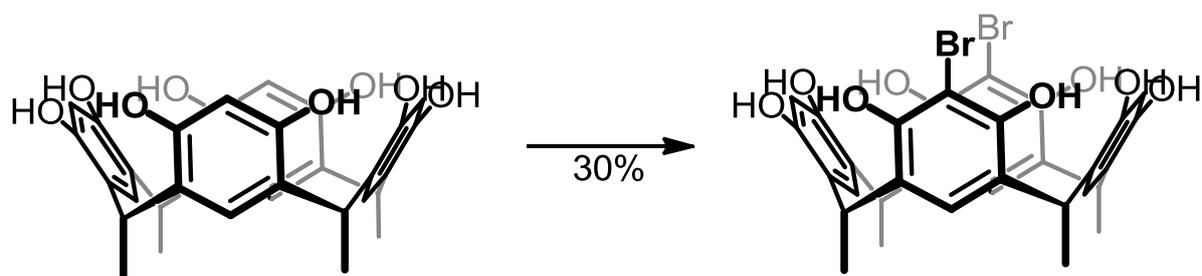
Manabe and co-workers¹⁰¹ in their attempts of synthesizing water-soluble resorcinarenes have managed to couple diazo functionalities onto the *ortho*-position of resorcinarenes, albeit in low yields (Scheme 10). In 2008 Jain and co-workers¹⁰² improved this method of diazo coupling and managed to synthesise tetra-azo resorcinarenes in good yields (70%). They managed to isolate tetramino resorcinarenes for the first time thereafter via reduction of the azo functionalities, but could not determine the yield for the reduction as the product was to unstable and was used directly in the next step to form Schiff-base resorcinarenes, which they have mentioned has not been explored as ligands for metal catalysts as of yet at that point in time. Previous unsuccessful methods of incorporating amine functionalities onto the *ortho*-position(s) of resorcinarenes included conventional nitration ($\text{HNO}_3/\text{H}_2\text{SO}_4$) followed by subsequent conventional reduction as well as the conventional acid-catalyzed condensation of 2-nitroresorcinol with acetaldehyde (as mentioned before electron-poor resorcinarenes require basic conditions in order to cyclize).



Scheme 10 - Diazo-coupling of 'methyl-footed' resorcinarene. Reagents and conditions: p-sulfonatobenzenediazonium (4.8 equiv.), pyridine (excess), 0-5 °C, 40 hours.¹⁰¹

1.6.1.1 Selective Electrophilic Aromatic Substitution

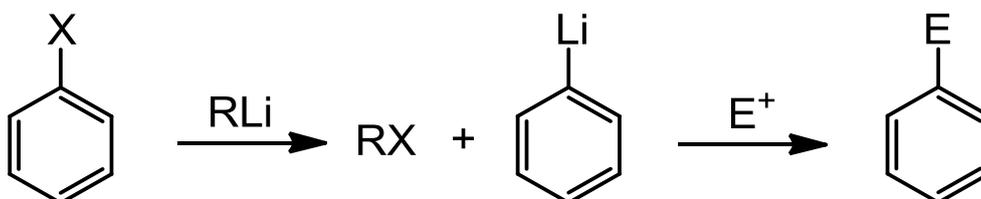
Konishi and co-workers¹⁰³ have reported the selective electrophilic aromatic substitution of resorcinarenes. By limiting the amount of N-Bromosuccinimide (NBS) to two equivalents and performing the reaction at room temperature they managed to obtain the distal product in an overall yield of 30% and selectivity favoured the distal product in a 10:1 over the proximal product (Scheme 11). They speculated that the reason why selectivity favours the formation of the distal dibromo-resorcinarene over the proximal dibromo-resorcinarene is due to the fact that a second bromination which occurs at a neighbouring resorcinol ring is much slower than brominating the diametrical (opposite) resorcinol ring. This is due to the fact that the first bromination decreases the nucleophilicity of the *ortho*-positions of the adjacent resorcinol rings as the electronic effect of the presence of the first bromine atom is transferred to, and felt by, the neighbouring resorcinol rings through the hydrogen bonds that exist between the resorcinol rings. The electronic effect of the first bromine atom does not affect the resorcinol ring opposite to it in the same way as the hydrogen bonds within resorcinarenes only exist between adjacent resorcinol rings, so the effect of the first bromine does not affect the nucleophilicity of the resorcinol ring opposite to it. However other authors reported this method to have poor selectivity in obtaining the distal product.^{104,105}



Scheme 11 - Synthesis of distal dibromo-octahydroxyresorcinarene. Reagents and conditions: NBS (2 equiv.), 2-butanone, r.t., 24 hours.

1.7 Lithium-Halogen Exchange

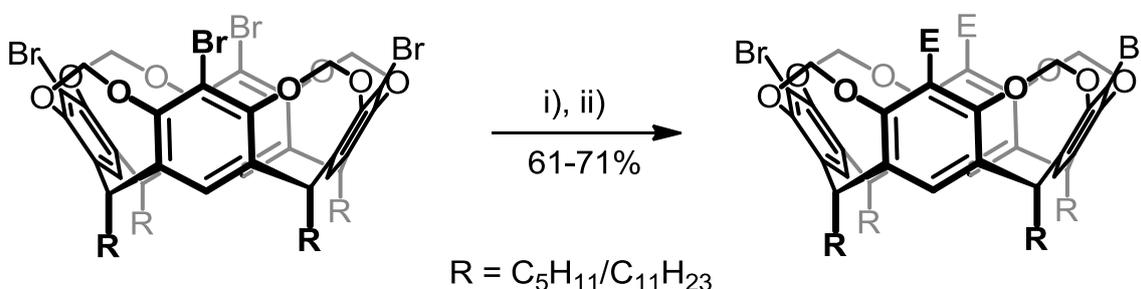
Lithium-halogen exchange is a metathesis reaction in which a lithium atom such as those supplied by alkyllithiums substitutes itself for a halogen atom of an organohalide. This reaction was discovered independently by Gilman¹⁰⁶ and Wittig¹⁰⁷ in the late 1930's. Lithium-halogen exchange is an equilibrium process which favours the formation of the less basic, more stable organolithium and has been shown to occur faster than the protonation of the organolithiums by acidic reagents.¹⁰⁸ The generated alkyllithium intermediate is highly nucleophilic in nature and when quenched with an electrophile leads to formation of functionalized organic compounds (Scheme 12). Many factors influence the rate of lithium-halogen exchange such as the type of halogen and alkyllithium used.¹⁰⁹



Scheme 12 - Functionalization via lithium-halogen exchange followed by quenching with an electrophile.

In most cases the halogen atom that is utilized for this method is bromine, as bromine can easily be installed in most organic frameworks. Iodine undergoes lithium-halogen exchange faster than bromine, and the halogens chlorine and fluorine are not used for lithium-halogen exchange reactions as they tend to deprotonate rather than undergoing an exchange, resulting in benzyne intermediates.^{109,110} Therefore the reactivity of halogens to undergo lithium-halogen is in the following order; $I > Br > Cl \gg F$.¹¹¹ Lithium-halogen exchange also occurs faster in ethereal solvents as ethereal solvents are known to de-oligomerize alkyllithium clusters, increasing their availability within solution. The mechanism of this

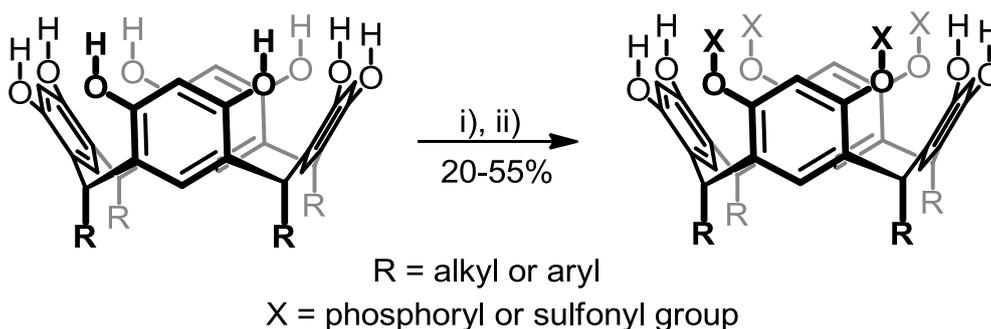
metathesis has been debated for many years as investigations into the mechanistic aspects of lithium-halogen exchange has produced two different, plausible theories as to how lithium-halogen exchange occurs.¹¹²⁻¹¹⁶ Studies have shown that different organohalides react by either of the mechanisms or both.¹¹⁷ In the years 2000 and 2001 Sherburn, Irwin and co-workers have reported optimal procedures for the synthesis of monobromo-, proximal dibromo-, distal dibromo- and tribromo-resorcinarene cavitands starting from a tetrabromo resorcinarene cavitands via lithium-halogen exchange.^{104,118-120} By adding slightly more than 2 equivalents of alkyllithium, the tetrabromo resorcinarene is transformed into a distal dilithio dibromo resorcinarene intermediate, which is then functionalized with an electrophile of choice resulting in a resorcinarene ligand that contains the desired functional groups, as well as two original bromine atoms, in a distal fashion in a very short time (Scheme 13). Thereafter the remaining two bromine atoms can be functionalized with the same procedure using a different electrophile, or removed and reverted back to the original *ortho*-protons by quenching with a proton source, such as methanol. They have even demonstrated the possibility of obtaining bis-distal resorcinarene cavitands in one-pot.^{118,119} This procedure was first reported by Larsen and Jørgensen¹²¹ in their synthesis of distally functionalized calixarenes from tetrabromo calixarenes. These cavitands need to be decorated with long pendant chains (R-groups) as resorcinarenes that contain smaller pendant chains suffer from solubility issues.



Scheme 13 - Selective functionalization of resorcinarene cavitands reported by Sherburn and co-workers.¹¹⁹
Reagents and conditions: i) *n*BuLi (2.1 equiv.), THF, 20 min. ii) electrophile (E⁺).

However Sherburn discovered that this method of obtaining distally functionalized resorcinarenes also returned the proximal product in small yields (approximately 8:1 distal to proximal) whereas functionalization of calixarenes via this method gave exclusively the distally functionalized product, even when using excess base.¹²¹ Kleinhans¹²², a former student of Arnott, attempted the method reported by Sherburn on the flexible tetrabromo octamethoxyresorcinarene scaffold (Scheme 14) in his MSc thesis, however the results indicated decreased yields and a loss of selectivity (i.e. greater spread of regioisomers) than

1.8 Selective Acylation



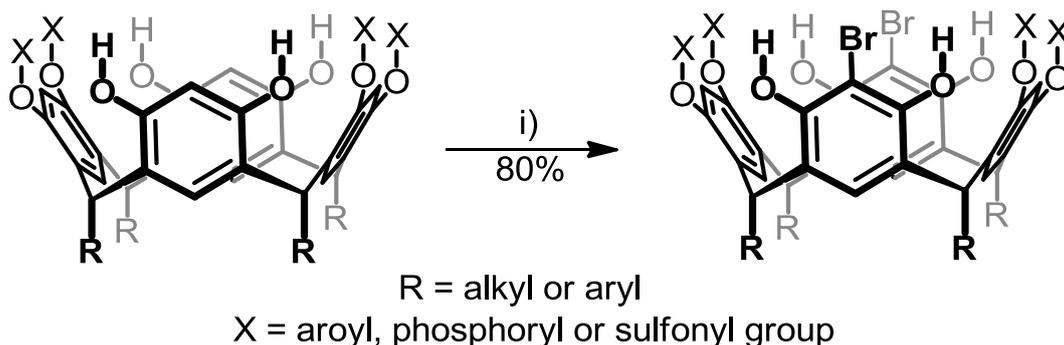
Scheme 15 - Regioselective protection of resorcinarenes reported by Shivanyuk and co-workers.¹²³
Reagents and conditions: i) Et₃N (4 equiv.), MeCN; ii) X-Cl (4 equiv.).

Since lithium-halogen exchange was found to be unsatisfactory in selectively functionalizing flexible tetrabromo resorcinarenes an additional method was needed to work in tandem with lithium-halogen exchange in order to obtain flexible distally substituted resorcinarene ligands, such as the selective protection of the phenolic groups by more rigid protecting groups that could be subsequently removed thereafter and re-protected as methoxy groups. Shivanyuk and co-workers¹²³ reported the regioselective protection of resorcinarenes in which four phenolic groups can be protected in a distal fashion using phosphoryl or sulfonyl groups (Scheme 15).

This procedure has two positive points;

- 1) The product can be precipitated out of solution as the hydrochloric triethylammonium salt, when using the correct ratio of base to solvent.
- 2) Selective distal functionalization is made possible through the unprotected aromatic rings which are activated (by the adjacent phenolic groups) to undergo aromatic electrophilic substitution, leaving the *ortho*-positions of the protected aromatic rings unfunctionalized (Scheme 16).

This type of reaction is also deemed unattractive as it suffers from drawbacks such as low yields and the fact that the products cannot be further developed as the protecting groups cannot be removed; however this problem can be eliminated by using aroyl chlorides as protecting agents. The same type of regioselective protection is possible using aroyl chlorides under the same conditions and these aroyl groups can then be easily removed after distal functionalization; however these reactions are even lower yielding than compared to the sulfonyl groups. This method is also time-consuming as it involves a multi-step process (see Section 1.11) in order to form the desired distally functionalized resorcinarene.



Scheme 16 - Distal bromination of the unprotected rings of a regioselective protected resorcinarene. Reagents and conditions: i) NBS (2.1 equiv.), 2-butanone.

1.9 Coordination Chemistry of Resorcinarenes

As stated in Section 1.2, the applications of resorcinarenes are vast and they are mostly exploited as cavitands and carcerands in host-guest complexes and for analytical applications. Very few examples are stated within the literature of functionalized resorcinarenes being used as ligands for organometallic catalysts. Calixarenes are more popular than resorcinarenes in the amount of applications that have been published for [1]₄-metacyclophanes and the amount of reported calixarenes used as ligands for catalysts is no exception to this fact. However calixarenes are analogous to resorcinarenes in the fact that the use of calixarenes as ligands for metal catalysts is largely unexploited when compared to its other applications. It is for this reason that our research group is interested in synthesizing more examples of calixarene- and resorcinarene-transition metal complexes (especially calixarenes and resorcinarenes that are functionalized at the *ortho*-position(s)) and subsequently comparing their catalytic activities to the traditionally and more well-known ligand-transition metal complexes which the calixarene- and resorcinarene-catalytic systems are based on and are modelled after. This section provides the reader with some examples of resorcinarene-metal complexes that are found in literature. Reviews that was published in 1997¹²⁴ and 2013¹²⁵ also provides more examples of resorcinarene- as well as calixarenes-metal ligand complexes. Resorcinarenes have shown to produce ligand-metal complexes through all three of the derivatizable positions (i.e. pendant chains (R-groups) that contain functional groups, phenolic positions and *ortho*-positions). Of these three positions, coordination to metals through functional groups attached to the *ortho*-position(s) and the lower rim pendant chains is utilized the least in forming resorcinarene-metal complexes. Moreover, most reported resorcinarene-metal complexes that have complexation occurring through the *ortho*-position(s) contain a methylene bridge in between the aromatic ring and the functional group through which coordination occurs.

1.9.1 Coordination via the Lower Rim Pendant Chains

Resorcinarenes that have been decorated with long thioalkyl or thioether pendant chains have shown to be good sensors for gold as they have shown to form stable monolayers on a gold surface (Figure 7).^{126–129} The monolayer of long thioalkyl pendant chain resorcinarenes coordinated to a gold surface has also shown to have a marked increase in the absorbance of polar compounds such as vitamin C in dilute solutions.¹²⁶

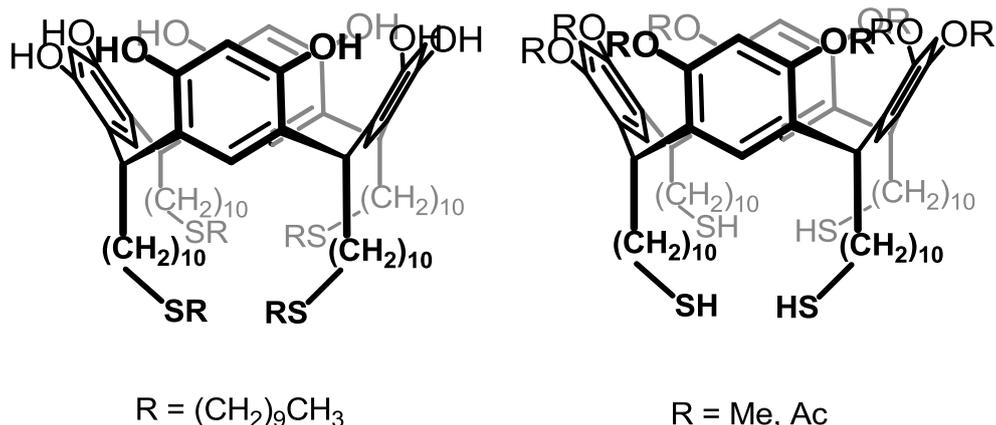


Figure 7 – Thiolalkyl and thioether pendant chain resorcinarenes.

Dalcanale and co-workers¹³⁰ have formed carcerand-metal complexes with rigid resorcinarenes that have long isonicotinoyl pendant chains (Figure 8). They managed to complex these ligands with metals such as Ni(II), Pd(II) and Ag(I) to form octahedral, square planar and a linear dinuclear coordination motif with each metal respectively. Interestingly the Pd(II) which exhibited a *trans*-coordination with two isonicotinoyl groups and two chlorine atoms catalysed the hydrolysis of the ester bonds of the other two opposite isonicotinoyl groups in the presence of trace amount of water.

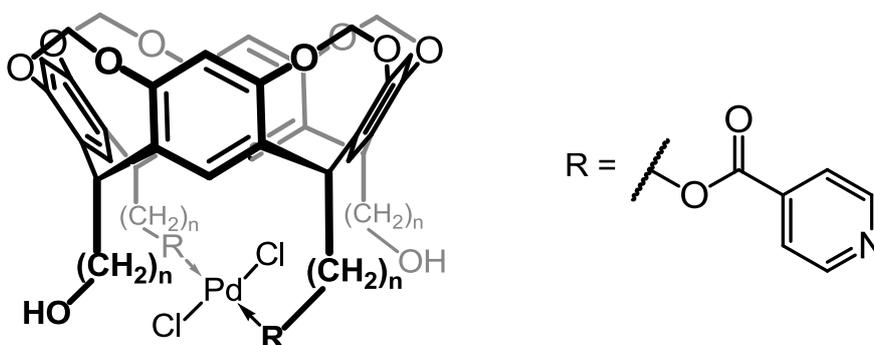


Figure 8 – *Trans*-coordination of isonicotinoyl pendant chain groups of a resorcinarene to a palladium(II) chloride motif.

1.9.2 Coordination via the Upper Rim Phenolic Positions

A wide variety of resorcinarene-transition metal complexes are produced when coordination is achieved through the phenolic positions. The coordination can occur directly through the oxygen atoms themselves, or through another heteroatom that is attached to oxygen such as phosphorous functionalities, and one example of each has been supplied (Figure 9). The second example is particularly interesting as it shows coordination through not only the diametrical phenol groups but also individual η^1 -coordination of two of the remaining aromatic rings of the resorcinarene through the vacant position on the lower rim along with an additional η^1 -coordination by benzene solvent molecules.

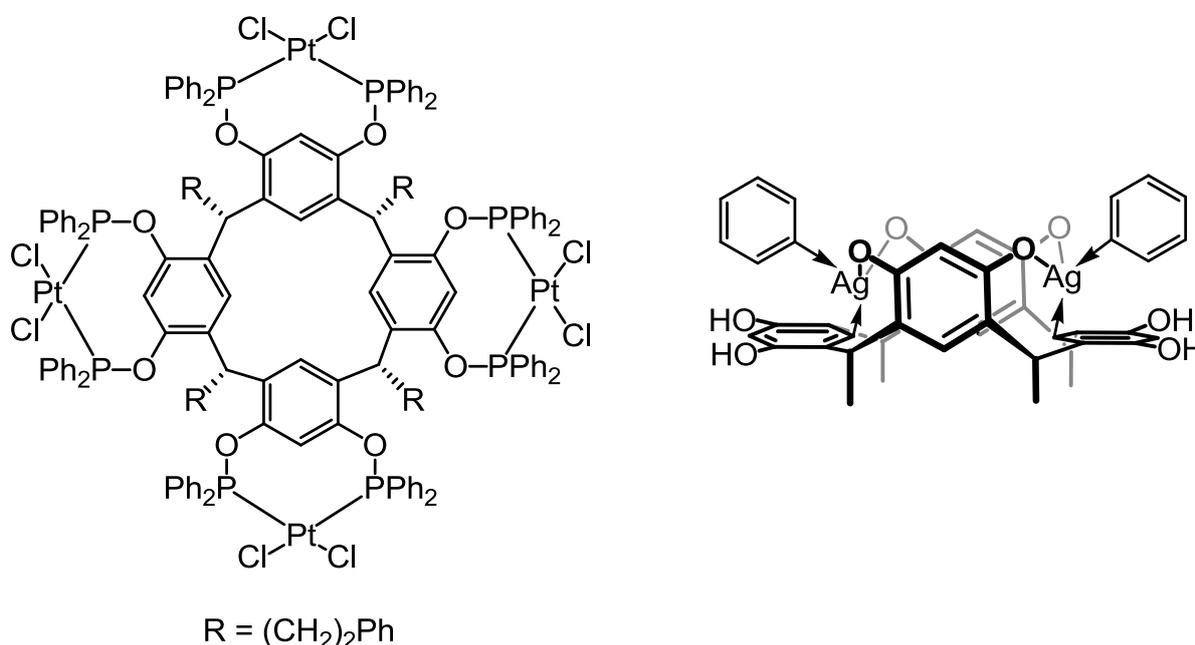


Figure 9 – Examples of coordination of resorcinarenes to metals through the phenolic positions of the resorcinarene reported by Puddephatt¹³¹ (left) and Munataka¹³² (right).

1.9.3 Coordination via the Upper Rim *Ortho*-Positions

A unique case of a carcerand in which the resorcinarene molecules are connected to one another by coordination bonds through metal atoms that acts as linkers has been reported by Dalcanale and co-workers.¹³³ This carcerand has been tetrafunctionalized with cyano functionalities on the *ortho*-position and has shown to encapsulate a single triflate anion (Figure 10).

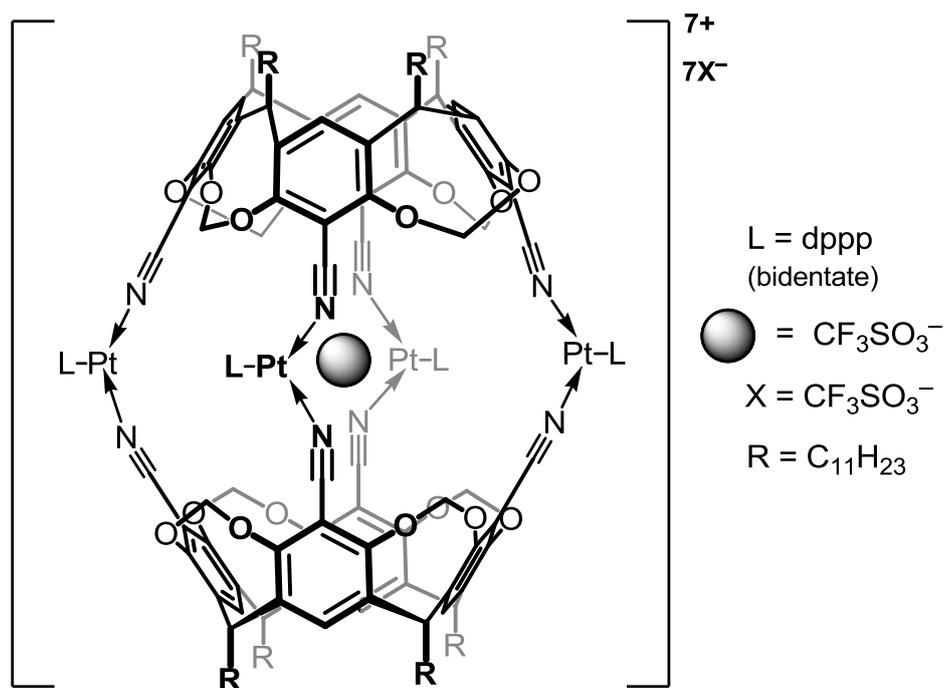
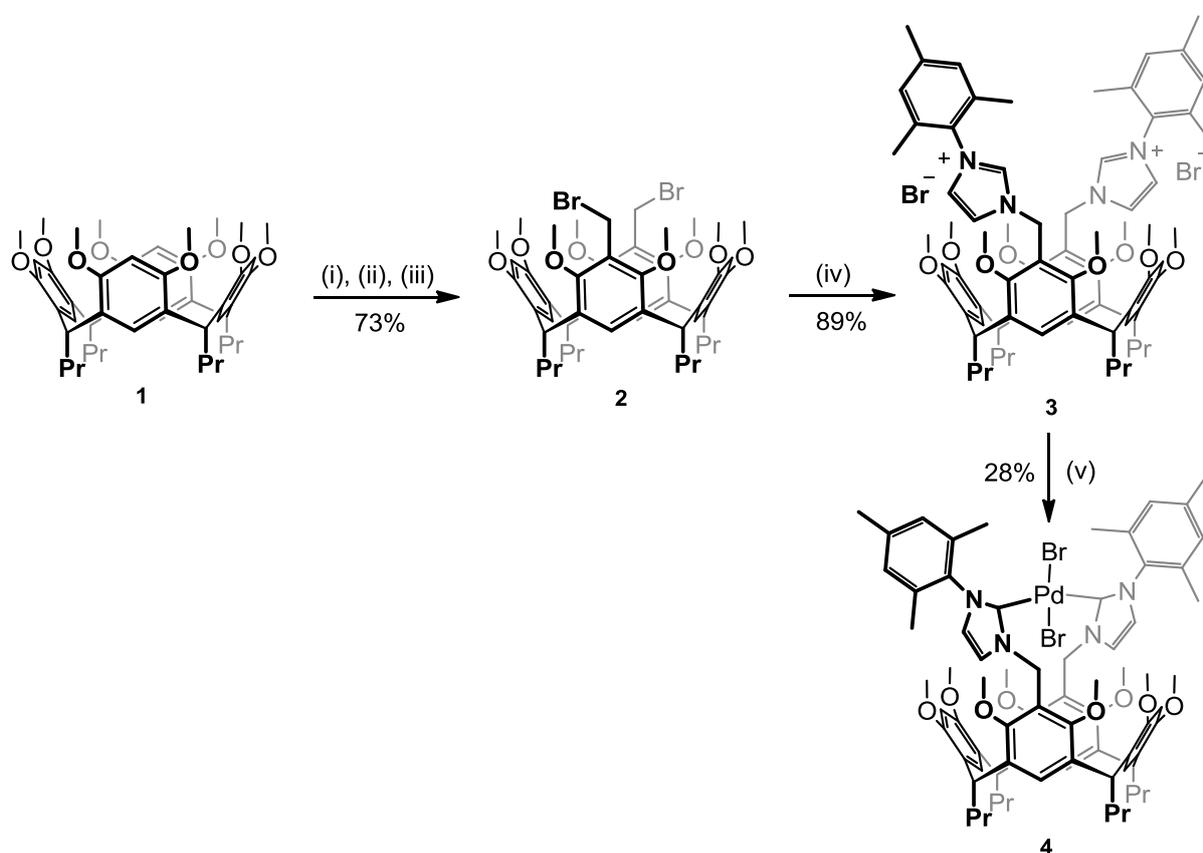


Figure 10 – Encapsulation of an anion by a tetracyano carcerand dimer linked together by metal atoms.

Arnott and co-workers⁷⁹ have also, very recently, published the synthesis of a distal bidentate NHC (N-Heterocyclic Carbene) resorcinarene-based ligand (Scheme 17). Unfortunately these NHC moieties were linked onto the *ortho*-position of the resorcinarene scaffold by means of a methylene bridge and therefore, however, the electronic effects of the electron-rich aromatic rings of the resorcinarene do not play a role on the electronic effect of NHC moieties themselves. The reason for installing an NHC moiety onto a resorcinarene was to produce more examples of macrocyclic ligand-metal complexes derived from calixarenes or resorcinarenes platforms, as only few examples of such systems are mentioned within literature. The synthesis towards such ligands made use of the ortholithiation procedure (see Section 2.2.2) in order to synthesis the ligand in a decent overall yield. This resorcinarene-NHC-Pd complex returned quantitative yields when used as a catalyst in the Suzuki-Miyaura and the Tsuji-Trost reaction. One example of a resorcinarene-metal complex in which the metal ion is coordinated to by heteroatom functionalities that are directly coupled onto the *ortho*-position of the resorcinarene have been synthesised by Arnott and co-workers.⁷⁸ A distal bidentate methyl thioether resorcinarene-metal complex (Figure 11) that coordinated to a palladium dichloride source through the sulphur moieties which were employed on the *ortho*-positions of the resorcinarene represented the first structure of such a motif that were stabilised by thioether ligands (see Section 1.11 for synthetic strategy). This complex also represented the first bidentate resorcinarene ligand that coordinated to a metal centre via the functionalized *ortho*-positions of the resorcinarene. Moreover, it was found that two palladium centres were

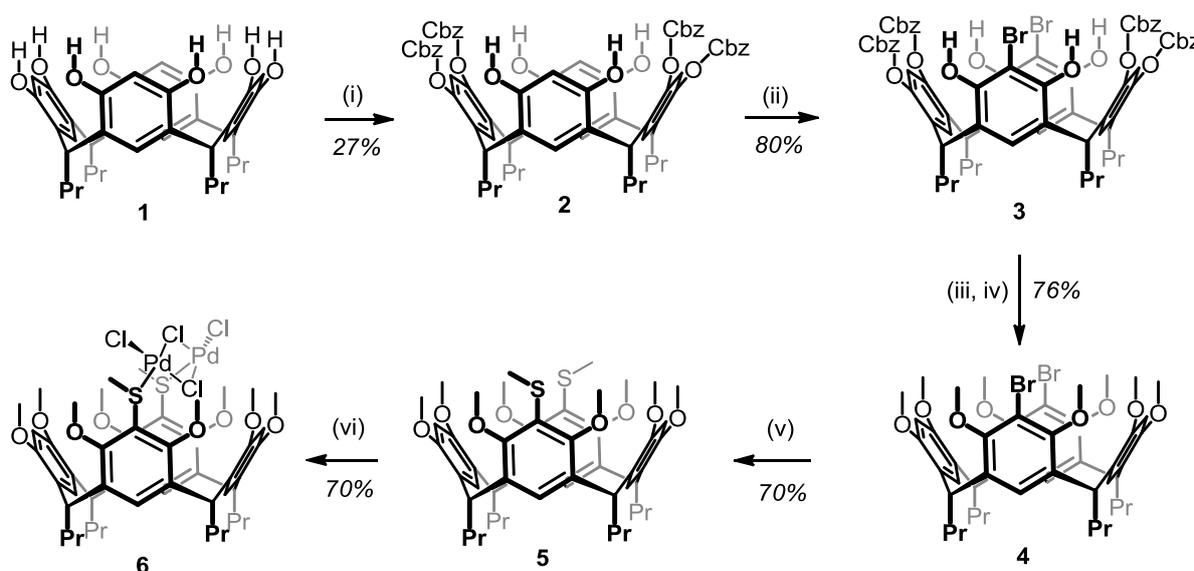
involved in the motif that coordinated to the ligand and these two palladium atoms were connected to one another by a dichloride bridge $[(\mu\text{-Cl})_2]$ to form a $16e^- \text{Pd}_2\text{Cl}_2(\mu\text{-Cl})_2$ motif in the centre of the resorcinarene cavity (see Figure 12 for crystal structures). Only two other examples of such structures containing the same geometric motif (slightly distorted square planar) are reported within literature, however these dipalladium dichloride motifs are stabilised by other types of sulphur moieties such as sulfoxides¹³⁴ and thiophosphonates,¹³⁵ in which coordination occurs through the phenolic positions of the resorcinarene in the latter. Unsurprisingly this complex returned very poor yields when it was tested in the Heck reaction, as it is known that sulphur functionalities are not good when used as ligands for metal catalysts; however coordination of resorcinarene ligands to metals, especially direct coordination through the *ortho*-positions, to form resorcinarene-metal complexes were, and continues to be a topic of interest to our research group.



Scheme 17 - Synthesis of a distal bis-carbene resorcinarene complex (reproduced from reference 79).
 Reagents and conditions: (i) *n*BuLi, THF, 40 °C b) MeOCOCl, r.t.; (ii) LiAlH₄, THF, r.t.; (iii) PBr₃, CHCl₃, r.t.; (iv) 1-mesityl-1H-imidazole, PhCH₃, reflux; (v) PdCl₂, KBr, CsCO₃, 1,4-dioxane, 80 °C.

1.11 Objectives of this study

The synthetic strategy in synthesizing the distal methyl thioether resorcinarene ligand **5** (Scheme 18) previously used by Arnott and co-workers⁷⁸ was inspired by the work reported by Shivanyuk.¹²³ This strategy had its limitations in the sense that it involved a protracted multi-step process in order to synthesise such ligands and contained a low yielding first step (27%). Therefore it was evident that another synthetic strategy needed to be implemented towards the synthesis of such ligands.



Scheme 18 - The synthesis of the $(\mu\text{-Cl})_2\text{Pd}_2\text{Cl}_2$ -resorcinarene complex as described by Kleinhans (reproduced from reference 78). Reagents and conditions: (i) Cbz-Cl, Et₃N, CH₃CN, r.t.; (ii) Br₂, AcOH, DCM, -78°C; (iii) H₂, Pd/C, EtOH, THF, r.t.; (iv) K₂CO₃, Me₂SO₄, CH₃CN, reflux; (v) (a) *n*BuLi, THF, -78°C; (b) Me₂S₂, -78°C to r.t.; (vi) PdCl₂, DCM, r.t.

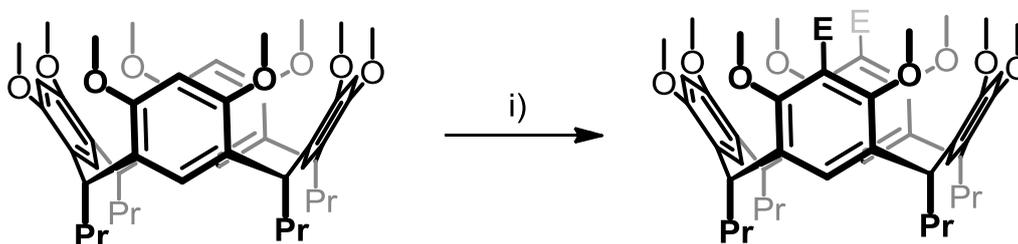
In 2013 Arnott and co-workers¹³⁶ published a paper concerning the selective functionalization towards distal resorcinarenes via an ortholithiation method, something that had previously captured their attention in the calix[4]arene field.¹²¹ This method uses an excess of alkyl lithium as base along with a set of optimal conditions in order to selectively functionalize the *ortho*-positions of the calixarene or resorcinarene in a distal fashion in one step by exploiting the fact that the *ortho*-protons are made acidic enough by the adjacent methoxy substituents. This method was then applied with a variety of different functional groups and was found to be satisfactorily successful in this regard (Scheme 19). The advantage of this method was that it greatly simplified the strategy towards synthesizing distal bidentate resorcinarene ligands by shortening the process that was first used by us and also greatly increased the overall yield of the process. We were therefore interested to see whether it was possible to synthesise other thioether resorcinarene-metal complexes via this approach.

Table 2 - A table showing the specifications and results of the reaction depicted in Scheme 19.¹³⁶

Electrophile (E ⁺)	E =	Yield (%)
CICO ₂ Me	CO ₂ Me	75
S ₂ Me ₂	SMe	74
CO ₂	CO ₂ H	71
MeI	Me	70
SiMe ₃ Cl	SiMe ₃	65
(CH ₂ Br) ₂	Br	50
B(OMe) ₃	OH ^a	48
PPh ₂ Cl	POPh ₂ ^b	<10

^aIsolation of the boronic acid intermediate gave low yields and a subsequent *in situ* oxidation with H₂O₂ after quenching yielded the dihydroxyl functionality

^bUnavoidable oxidation returns diphenylphosphine oxide instead of the desired diphenylphosphine functionality

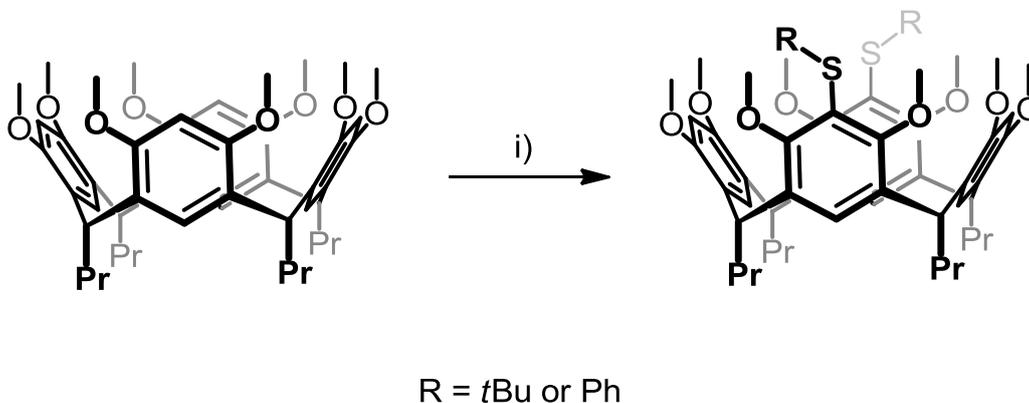


Scheme 19 - Synthesis of distal bidentate resorcinarene ligands via an ortholithiation approach as reported by Ngodwana (reproduced from reference 134).

Reagents and conditions: (i) (a) *n*BuLi, 40°C, THF, 2 hours; (b) E⁺ (electrophile), -78°C to r.t., overnight.

Thus, the main objective of this study was to further evaluate the use of the ortholithiation approach in synthesizing distal bidentate resorcinarene ligands by attempting the synthesis of a small range of distal thioether resorcinarene ligands (Scheme 20). The formation of this small homologous series of thioether resorcinarene ligands was planned to compliment the already previously synthesised distal methyl thioether resorcinarene ligand **5** (Scheme 18). Therefore the synthesis of a distal *tert*-butyl and phenyl thioether resorcinarene ligand was attempted. These functionalities were chosen as the R-groups found on the sulphur atom are relatively larger and thus more sterically demanding. The phenyl thioether moiety was of a particular interest to us in order to establish whether it is possible to have aryl functionalities coupled to the sulphur atom on the *ortho*-position of the resorcinarene. Kleinhans also attempted to complex the ligand **5** with different metal sources such as silver, nickel and platinum.¹²² Of the metals that were investigated platinum was unsuccessful and only starting material was isolated from the reaction, however silver and nickel seemed to be successful in complexing with the resorcinarene ligand. The silver complex was analysed by ¹H NMR spectroscopy and the signals that were obtained suggested coordination through the sulphur moieties, however the exact structure and composition of the complex could not

be determined by X-ray diffraction, as crystals of the complex could not be successfully grown. Analysis of the nickel complex was completely obscured as not even a ^1H NMR spectrum of the complex could be obtained as the complex seemed to degrade into starting material when attempting to dissolve the compound in suitable deuterated solvents.



Scheme 20 - Synthetic strategy for attempting the synthesis of larger thioether resorcinarenes ligands (via the ortholithiation method). Reagent and conditions: (i) (a) $n\text{BuLi}$, 40°C , THF, 2 hours; (b) E^+ (sulphur electrophile), -78°C to r.t., overnight.

Therefore a secondary objective of this study was to potentially expand on the initial groundwork done by Mr. Kleinhans on these complexes he managed to obtain and this was done by re-synthesizing the complexes and re-attempting their elucidation through any type of spectroscopic analysis.

1.12 References

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Chapter 2

Synthesis towards Distally Substituted Thioether Resorcinarene Ligands via the Ortholithiation Approach

2.1 Synthesis of Parent Resorcinarenes

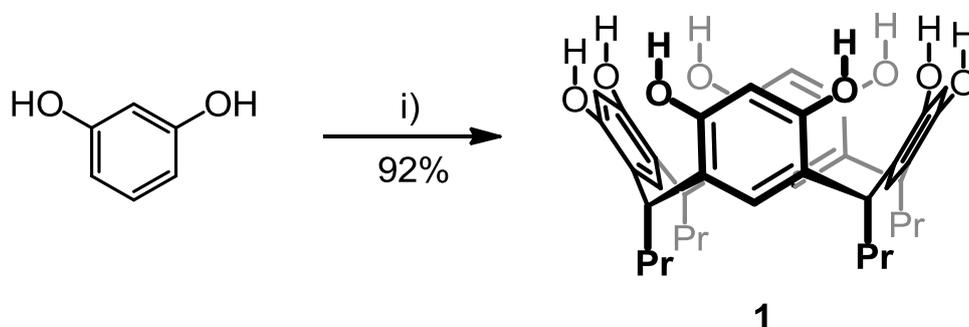
2.1.1 Introduction

As mentioned in Chapter 1, resorcinarenes were first synthesised in a quick and easy one-step condensation reaction between aldehydes (aromatic or aliphatic) and resorcinol (1,3-dihydroxybenzene) within an acidified alcoholic media.^{1,2}

A variety of alternative methods have since been used to synthesise resorcinarenes, which have advantages over the acidified aqueous media procedure originally discovered by von Baeyer. The approaches within these alternative methods are largely governed by the type of aldehyde that is used within the reaction.²

2.1.2 'Propyl-Footed' Resorcinarenes

A popular method for synthesizing the 'propyl-footed' resorcinarenes is achieved by using a variant synthesis of the procedure reported by Botta and co-workers³ which makes use of chlorinated (anhydrous) solvents such as chloroform and dichloromethane (Scheme 1).



Scheme 1 - Synthesis of the 'propyl-footed' resorcinarene. Reagents and conditions: i) resorcinol (1 equiv.), DCM; butanal (1 equiv.), $\text{BF}_3 \cdot \text{OEt}_2$ (1 equiv.), -20°C to r.t., overnight.

The procedure of synthesizing resorcinarene **1** was originally used by Botta and co-workers^{3,4} in directly synthesizing resorcinarene methyl ethers starting from an already methylated derivative of resorcinol, (*E*)-2,4-dimethoxycinnamic acid methyl ester. Thus the aldehyde (butanal) was added to a white coloured suspension of resorcinol that was partially dissolved in anhydrous dichloromethane (DCM), which was then followed by the slow addition of boron trifluoride etherate ($\text{BF}_3 \cdot \text{OEt}_2$), at $-20\text{ }^\circ\text{C}$ producing a dark red-coloured solution that changed into a transient pink colour as it slowly warmed back to room temperature. Thereafter the solution subsequently changed into a permanent orange-colour. This procedure is preferred for synthesizing alkyl-footed resorcinarenes that have chains that are not longer than pentyl groups as it greatly eases the isolation process as no subsequent purification is needed. Resorcinarenes that have alkyl chains longer than pentyl groups are soluble in chlorinated solvents such as DCM, due to the fact that the hydrophobic nature of the molecule becomes greater as the length of the alkyl chain becomes longer. Furthermore the use of chlorinated solvents is quite beneficial as it provides a simple and efficient route of synthesizing resorcinarenes without the use of protic solvents, which can be difficult to remove as they become trapped within the resorcinarene cavity due to hydrogen bonding interactions between the solvent and the phenolic groups. Alcoholic solvents such as ethanol can form such favourable interactions with resorcinarenes that the entrapped solvent molecules can only be removed at temperatures higher than its natural boiling point and by uninterrupted heating for at least 48 hours under high vacuum. DCM also becomes entrapped within the cavity of the resorcinarene, as shown by the ^1H NMR spectrum of the product (Figure 1), but can be removed from the cavity with more ease than ethanol.

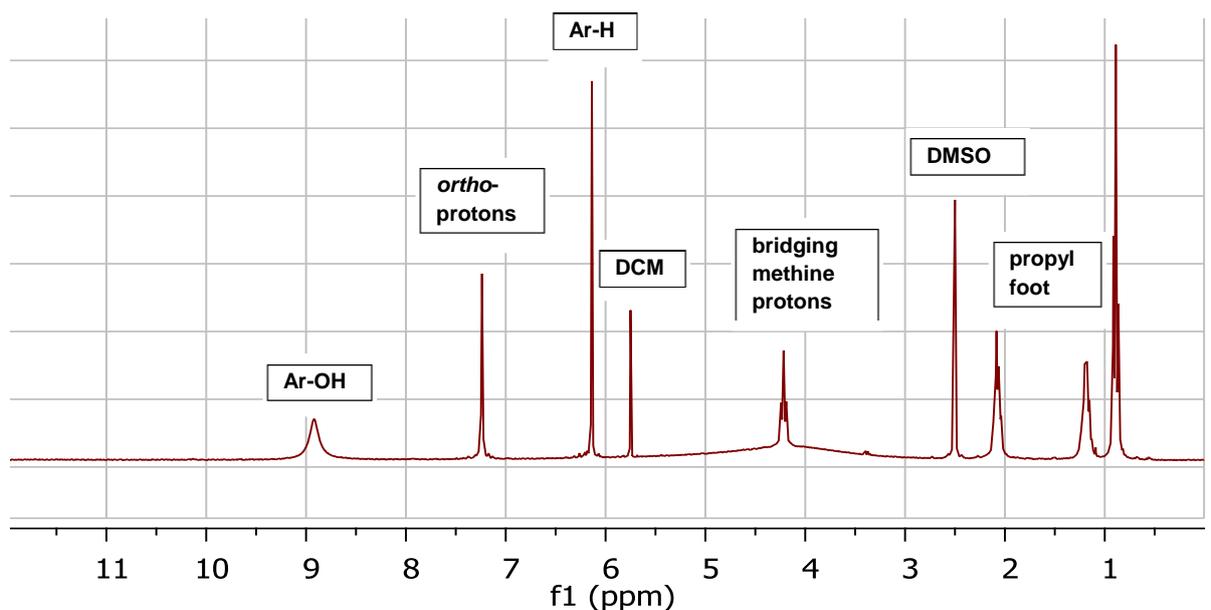
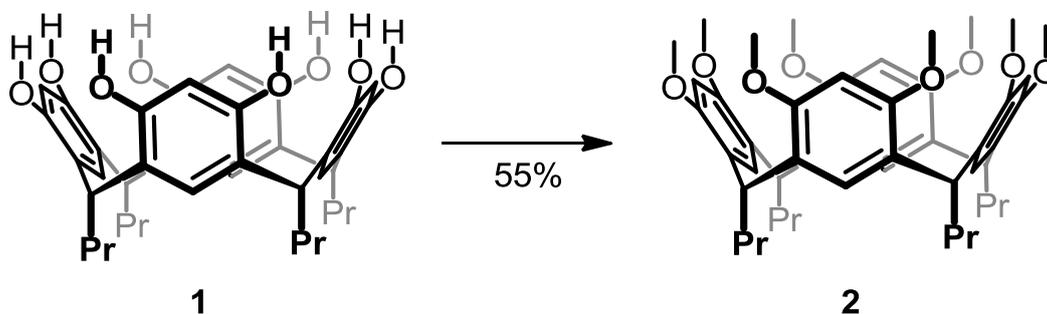


Figure 1 - ^1H NMR spectrum of the 'propyl-footed' resorcinarene using the variant procedure of Botta and co-workers³ (Scheme 1).

After stirring the reaction mixture overnight, the orange coloured 'propyl-footed' parent resorcinarene can easily be recovered from the reaction mixture by filtration and dried under reduced pressure, obtaining the product **1** without the need for further purification and in excellent yields. Botta's milder procedure also doesn't require reflux temperatures as does the acidified aqueous media procedure reported by Cram.² This is due to the Lewis acid, boron trifluoride etherate, which is used within the procedure which makes the electrophilic centre of the aldehyde more electron-deficient in nature than the acidified aldehyde. The ¹H NMR spectrum of the product resorcinarene (Figure 1) did not reveal any (lesser) signals or additional splitting of signals that could be attributed to minor conformations, which indicated that the product that was obtained was in the highly symmetrical crown conformation (C_{4v} -symmetry).^{2,5} This was expected as the reaction was given sufficient time for all the conformers that were formed in solution to equilibrate to the conformer that is lowest in energy, which happens to be the most symmetrical one.⁶ The apparent broad signal around 4.2 ppm was unusual, but could be caused by water in the dimethylsulphoxide (DMSO) that slowly exchanges with the phenolic protons, which itself is a broad signal at around 9 ppm.

2.1.3 Resorcinarene Methyl Ethers



Scheme 2 - Synthesis of the 'propyl-footed' resorcinarene methyl ether. Reagents and conditions: K_2CO_3 (24 equiv.), MeI (18 equiv.), MeCN, reflux, overnight.

Resorcinarene methyl ethers are synthesised for two purposes; 1) to protect the phenolic protons from the alkyllithium reagents that are used to deprotonate the *ortho*-position of the resorcinarene in the ortholithiation procedure and 2) it permits the use of ethereal solvents in order to dissolve the resorcinarene. This is mutually beneficial as ethereal solvents, such as tetrahydrofuran (THF), are known to help facilitate the stabilization and therefore the availability of alkyllithiums within solution, similar to how ligands like tetramethylethylenediamine (TMEDA) work in breaking up tetramers and hexamers of alkyllithiums (refer to Figure 4 in Section 2.2.2).^{7,8}

Thus having the choice of using THF as the reaction solvent in order to functionalize the resorcinarene further increases the efficiency of the ortholithiation procedure for its intended purpose. The hydroxyl groups are protected as methoxy substituents to provide the resorcinarene with much flexibility as possible as methyl groups will provide the least amount of steric hindrance between the functional group on the *ortho*-position and the adjacent protecting groups. Resorcinarene **1** can therefore be converted to the methyl ether resorcinarene **2** overnight with the use of a mild base such as potassium bicarbonate followed by a methylating agent in suitable polar solvent such as acetonitrile (MeCN) under reflux (Scheme 2). After standard work-up the 'propyl-footed' octamethoxy resorcinarene was purified and isolated as white crystals in a fair 55% yield using hot acetone. The use of a volatile methylating agent, such as methyl iodide which has a boiling point of 43 °C, is not ideal because the addition of methyl iodide to a refluxing mixture of MeCN would result in the vaporization of the methylating agent before it has time to react with the substrate. Therefore the methylating agent was added after allowing the reaction mixture sufficient time to cool down to a suitable temperature (no higher than 45 °C) and in addition the methylating agent was added in aliquots over one hour periods to ensure a maximum yield. Previously we used a more suitable methylating agent, dimethyl sulphate, to protect the phenolic protons as methyl ethers. The use of Me₂SO₄ returned yields of about up to 80% for this reaction, due to the fact the methylating agent could be introduced directly as its boiling point is more than 100 °C higher than MeCN. However, Me₂SO₄ was not available as it was, at the time, no longer attainable as suppliers such as Merck or Aldrich discontinued the product due to the toxicity issues.

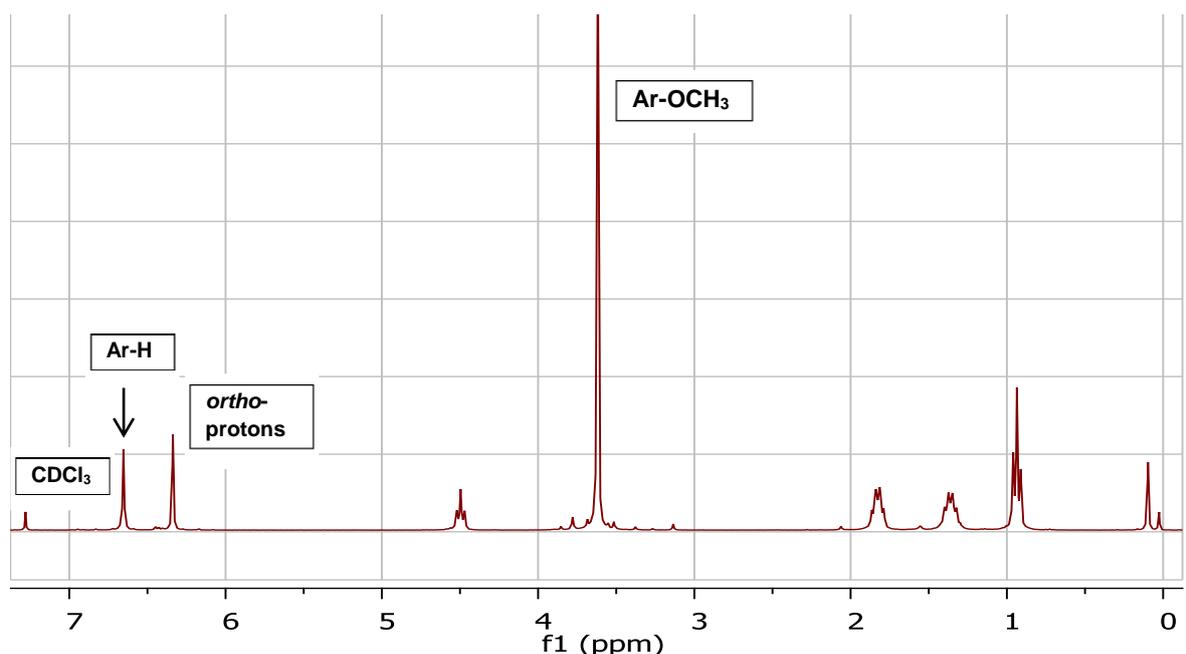


Figure 2 - ¹H NMR spectrum of the 'propyl-footed' resorcinarene methyl ether.

Therefore the methylated resorcinarene ether had to be produced using the lesser suitable methyl iodide as the methylating agent. The phenolic protons that appear at about 9 ppm in ^1H NMR spectrum of the octahydroxy resorcinarene disappeared and a new signal at about 3.7 ppm, which is characteristic of aromatic methoxy groups, was seen in the ^1H NMR spectrum obtained from the product. This signal integrated to 24 protons which confirmed that all the phenolic protons were methylated. Also, the fact that the ^1H NMR spectrum of the recrystallized product did not contain any phenolic signals confirmed that the product was pure and devoid from side-products which would result from partially methylated products. It was noticed that the *ortho*-protons experienced a significant downfield shift of about 0.9 ppm. This was expected as the inductive effect experienced by the protons which is caused by the neighbouring oxygen atoms is less than before now that phenolic protons have been removed and replaced by methyl groups. Furthermore the lower rim aromatic protons (annotated as Ar-H in Figure 2) experienced a downfield shift of about 0.5 ppm, as the aromatic rings are become less electron-rich after functionalization of the phenolic groups, making it seem as if these two signals had swapped positions upon first glance.

2.2 Synthesis of Distally Functionalized Resorcinarene Ligands

2.2.1 Introduction

In this section the ortholithiation strategy developed within our group was employed in synthesizing distal resorcinarene ligands. This procedure greatly simplifies the synthetic strategy towards synthesizing distally functionalized ligands, as mentioned in Chapter 1.

2.2.2 Ortholithiation

Directed *ortho*-Metalation (DoM) has proved to be one of the most efficient methods of functionalizing aromatic compounds that are already substituted with one or more heteroatom functionalities.⁹ These heteroatom functionalities are referred to as directing metalation groups (DMG) or just directing groups (DG) and acts Lewis basic points which acidifies the adjacent position through intramolecular interactions and also subsequently enables stabilization of the organolithium intermediate through coordination to the metal atom by the lone pairs found on the DG resulting in highly regioselective metalation (Figure 3).¹⁰

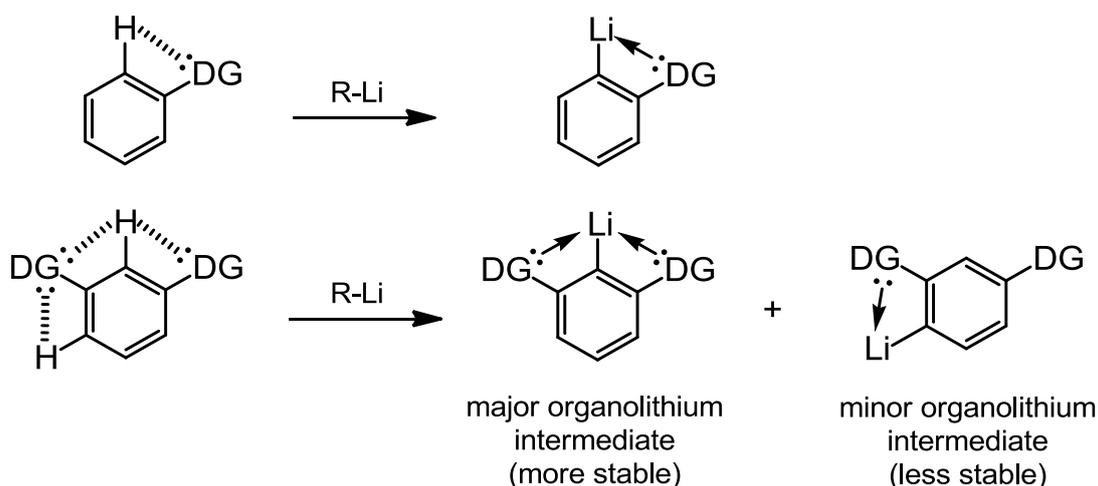


Figure 3 – Functional groups (DGs) that acidify *ortho*-protons and subsequently stabilize organolithium intermediates.

Aromatic substitution reactions occurs at a position that is adjacent to an electron-withdrawing heteroatom functionality is thus made possible through DoM. Ethers, in general, are rather poor DGs however small ether groups (such as methyl ethers) make good DGs.¹¹ Some DGs suffer from drawbacks as these DGs also contain electrophilic moieties, such as carbonyl carbons, which themselves can react with the alkyllithiums. Ether directing groups also help to facilitate de-oligomerization of alkyllithiums, similar to how solvents such as THF and additives such as TMEDA de-oligomerize alkyllithium clusters and aggregates (Figure 4).¹²

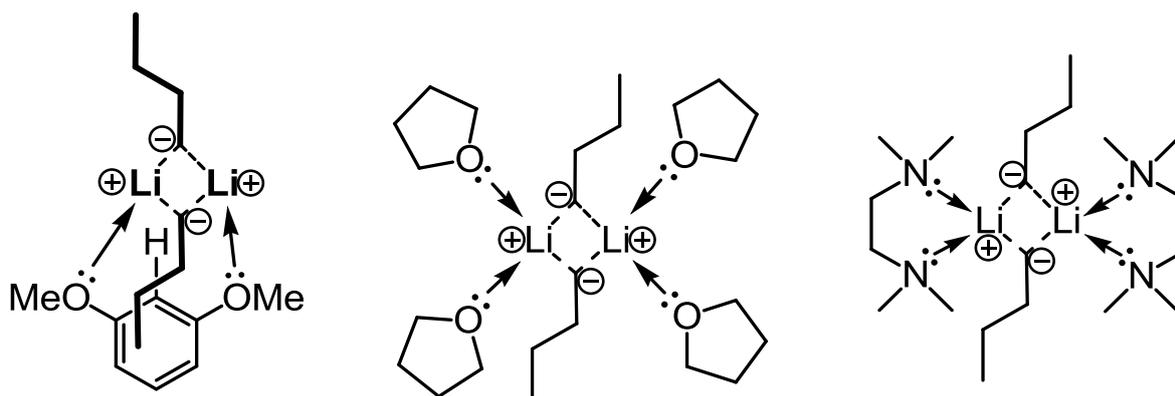
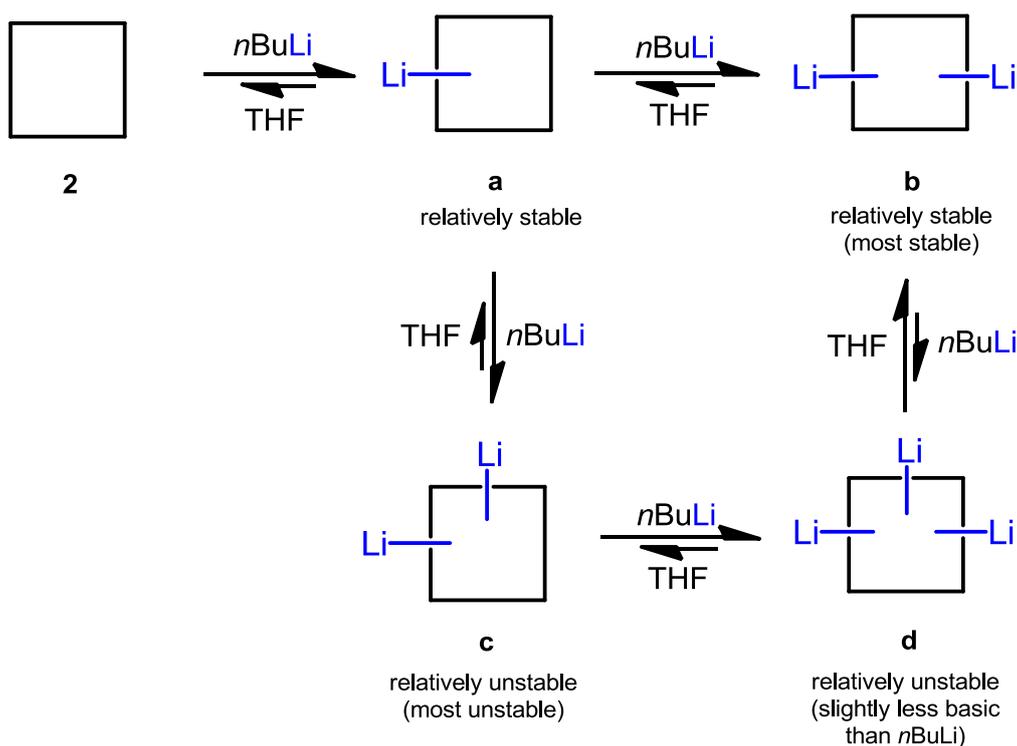


Figure 4 – De-oligomerization and stabilization of alkyllithiums by methyl ether directing groups (left), THF solvent molecules (middle), and additives (TMEDA) (right).

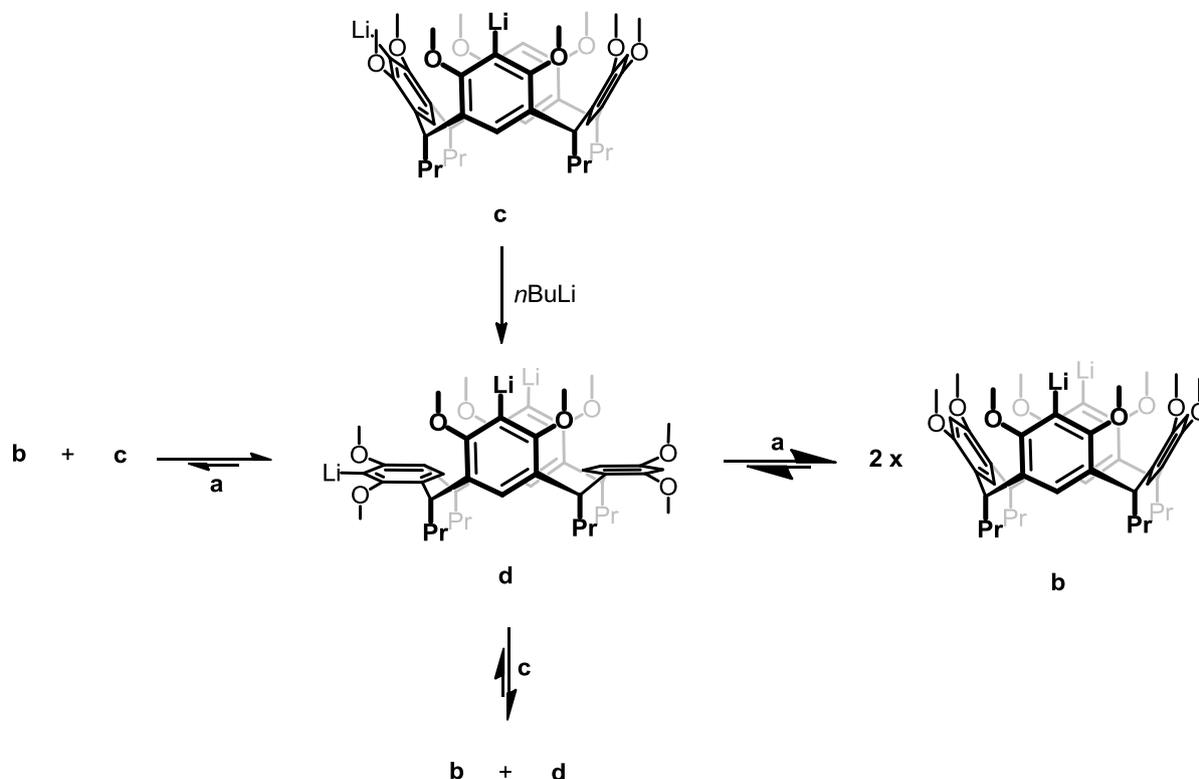
In 2013 Arnott and co-workers reported an optimized procedure for the selective functionalization towards distally substituted resorcinarenes via a (directed) ortholithiation approach, which can be achieved in one step in good yields.^{13,16} We have speculated that incubating the resorcinarene methyl ether for 2 hours at 40 °C with slightly more than a two-fold excess of alkyllithium (optimal conditions) allows sufficient time for all the lithiated species within solution to thermodynamically equilibrate to the distal lithio intermediate (Scheme 3), which has been speculated to be the most stable intermediate under these conditions.



Scheme 3 - Possible pathway towards the equilibration of the distal dilithio resorcinarene intermediate (resorcinarene rings are depicted as squares for simplicity).

However, the above simplified scheme does not account for the fact as to why any proximal or tri-functionalized products are not obtained upon quench. The following scheme (Scheme 4) depicts the postulated mechanism to a more accurate extent and accounts for the fact as to how the proximal and tri-lithiated intermediates can equilibrate towards the distal-lithiated intermediate. The scheme suggests that the distal product is obtained via the tri-lithiated intermediate (which is slightly less basic than $n\text{BuLi}$) which acts the active base when it encounters and deprotonates lesser lithiated intermediates. The middle lithiated aromatic ring within the tri-lithiated intermediate is forced into a boat orientation due to repulsion from the two neighbouring lithiated aromatic rings. This makes the middle ring a lot more exposed and it thus a lot more basic than the other lithiated aromatic rings. Thus the middle lithiated

ring can interact and deprotonate lesser lithiated intermediate such as the mono-lithiated (crown conformation) or the proximal intermediate (crown conformation). Therefore, the tri-lithiated is always protonated by lesser lithiated intermediates in such a way as to form into the distal intermediate (crown conformation). The mono intermediate can be lithiated by the tri intermediate to form the distal or the proximal intermediate. The proximal intermediate has been speculated to be most unstable intermediate under these conditions due to the fact that it has been observed, according to results obtained from optimization studies, that the proximal disappears faster in solution than the tri intermediate.¹⁶ The proximal intermediate is converted into the more stable intermediates, distal and tri, by either being lithiated by excess *n*BuLi into the lesser basic and more stable tri-lithiated intermediate or by being lithiated by the lesser basic tri intermediate itself to form another molecule of the tri intermediate as well as one molecule of the distal intermediate. Through these routes the proximal intermediate can equilibrate into more stable intermediates (Scheme 4). Any remaining tri-lithiated intermediates disappear thereafter as they lithiate the remaining unlithiated resorcinarene molecules (**2**) in solution into the mono-lithiated intermediate. Thus after quench we obtain the distal functionalized product is obtained in adequate to very good yields (depending on the electrophile that is used) as well as the mono functionalized product in negligible yields (usually lower than 10%).

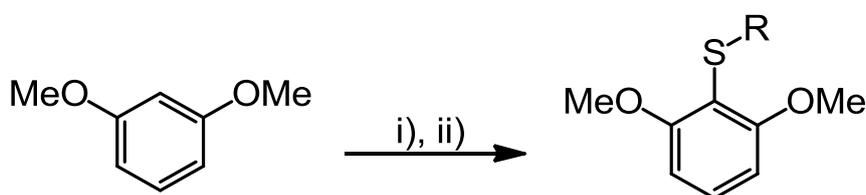


Scheme 4 – A more accurate postulated pathway towards the equilibration of the distal dilithio resorcinarene intermediate

It was decided to first perform ortholithiation reaction on a model compound, 1,3-dimethoxybenzene, as it was of interest to establish whether the functionalities to be introduced onto the resorcinarene scaffold could be introduced on a simpler model system. Theoretically the same type of transformations that can be performed on the model system should be possible on the resorcinarene as well. If the model compound is able to be functionalized via the ortholithiation procedure, while the resorcinarene is unable to then the most likely reason therefore could be steric hindrance, as the resorcinarene methoxy groups are known to be less flexible than the methoxy groups of the model compound.

2.2.2.1 Ortholithiation procedure performed on the model compound

1,3-dimethoxybenzene was dissolved and stirred in anhydrous THF and treated with 2.5 equivalents of *n*-butyllithium at 40 °C for two hours under inert conditions, before the solution is quenched with excess electrophile at 0 °C and then slowly warmed to room temperature. The reaction mixture was left to stir overnight to return the product (Scheme 5).



Scheme 5 - The ortholithiation procedure performed on a model compound. Reagents and conditions: i) *n*BuLi (2.5 equiv.), THF, 40 °C for 2 h. ii) E⁺ (sulphur-derived electrophile) (5 equiv.), 0 °C to r.t., overnight.

2.2.2.2 Testing the ortholithiation approach on the model compound:

a) Using disulphides

Table 1 - A table showing the results obtained when performing the ortholithiation procedure on the model compound using disulphides as electrophiles.

E ⁺ (Electrophile)	R	Yield (%)
Dimethyl disulphide	Me	85
Di- <i>tert</i> -butyl disulphide	<i>t</i> Bu	-

As shown in Table 1; good yields were achieved in the ortholithiation procedure in obtaining 1,3-dimethoxy-2-methylthiylbenzene when using dimethyl disulphide as the electrophile on the model system providing a relatively clean ^1H NMR spectrum (Figure 5) without the need of further purification as the product self-crystallized overnight.

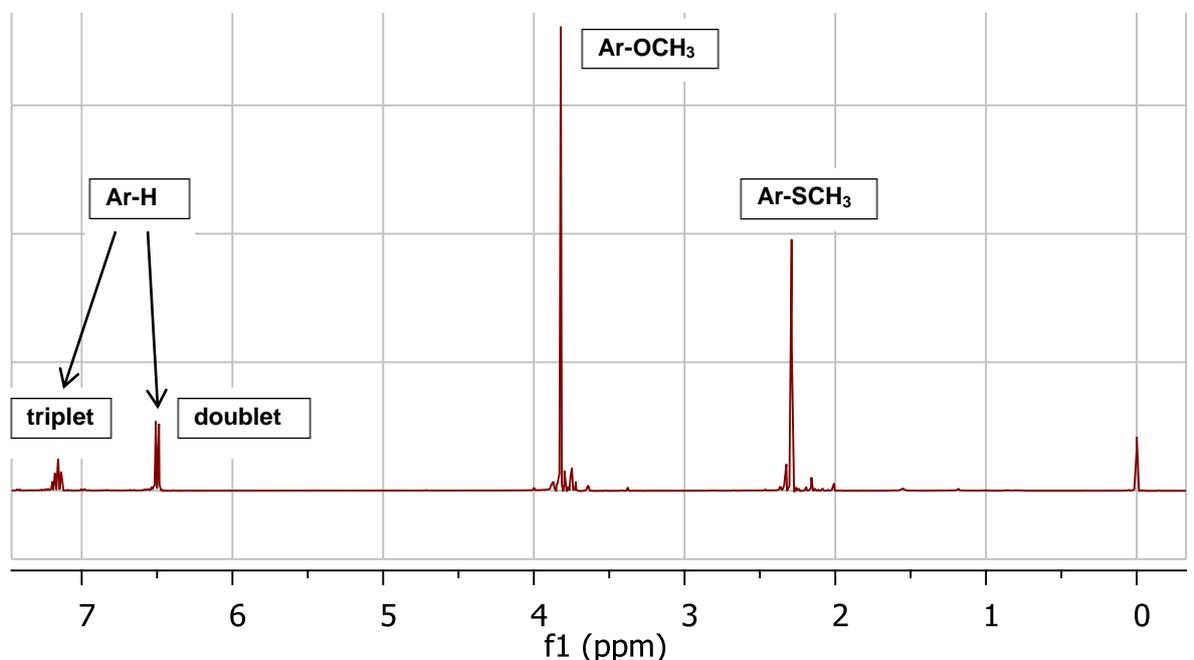
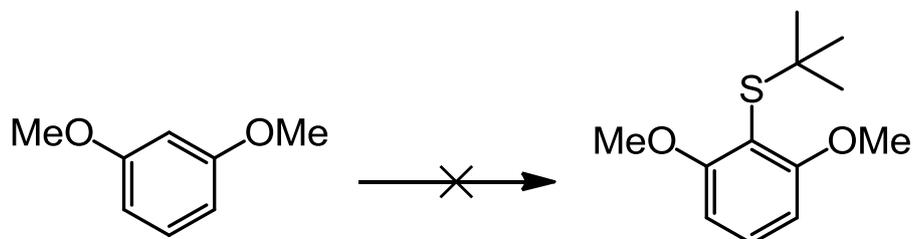


Figure 5 - ^1H NMR spectrum of 1,3-dimethoxy-2-methylthiylbenzene.

Unfortunately, negative results were obtained when testing di-*tert*-butyl disulphide as an electrophile (Scheme 6). After addition of the electrophile an off-white precipitate was seen forming within the reaction mixture, an observation which was not seen when using the electrophile, dimethyl disulphide, in the ortholithiation procedure. A recovery of less than 20% was achieved and TLC (Thin Layer Chromatography) analysis of the crude reaction mixture revealed that a new compound had formed within reaction that was more polar than 1,3-dimethoxybenzene. However, the compound appeared very faint in comparison to the starting materials which appeared quite prominent on TLC. Unfortunately this new compound was insufficient to characterize as the compound was not successfully separated by column chromatography from the starting material, 1,3-dimethoxybenzene. The only ^1H NMR spectrum that was obtained was therefore a mixture of the 1,3-dimethoxybenzene, residual di-*tert*-butyl disulphide and the new compound and returned a very messy spectrum (Figure 6) that was swamped with aliphatic signals (Figure 7). This prevented the analysis of the mixture and no additional information could be gathered from the spectrum. It should be mentioned that the reaction was only attempted twice, however the purity of the electrophile

was deemed fit in both attempts. Therefore it was concluded that di-*tert*-butyl disulphide was incompatible with the ortholithiation procedure of the model compound as it is known the procedure itself does work on a variety of electrophiles. And since the procedure is already optimized, no adjustments could be implemented within the reaction to afford the desired transformation, except for alteration of the leaving group of the sulphur-derived electrophile.



Scheme 6 - Attempted functionalization of the model compound with di-*tert*-butyl disulphide using ortholithiation conditions.

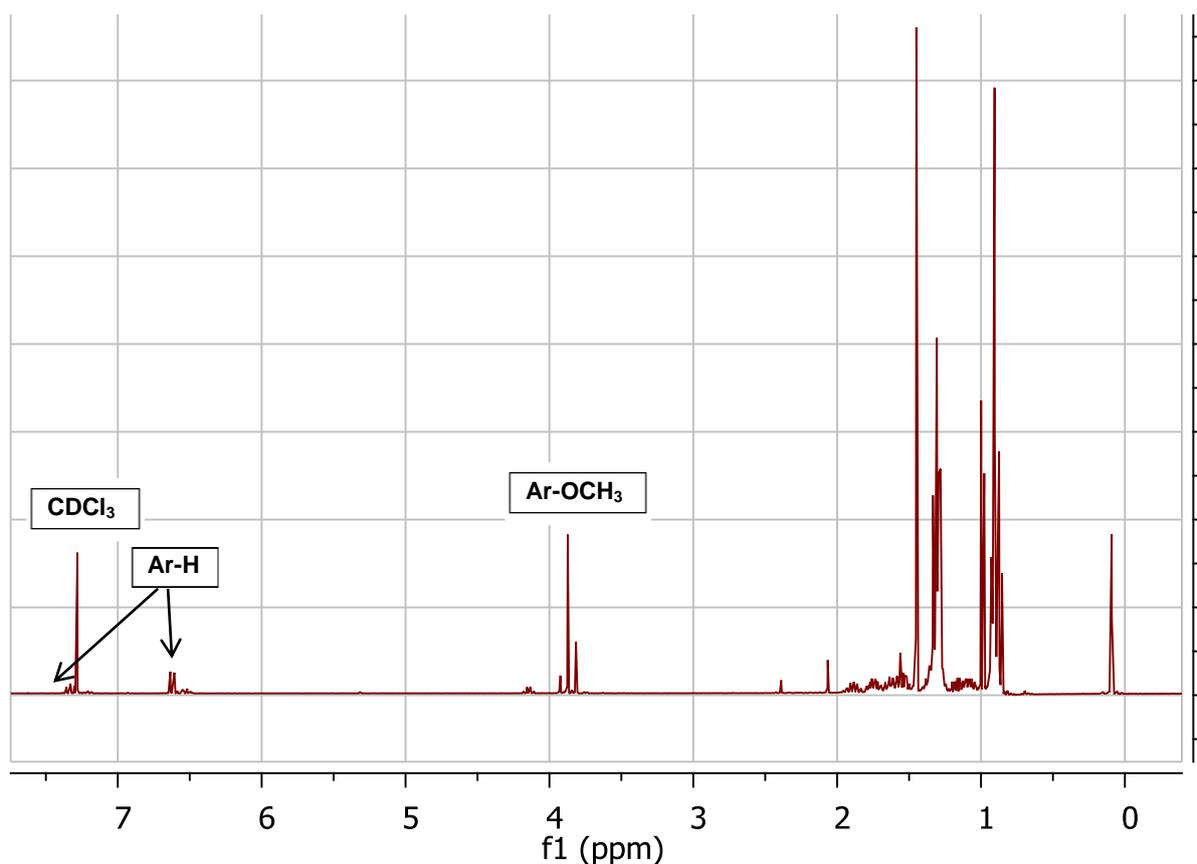


Figure 6 – ¹H NMR spectrum of the compound isolated from the reaction between the model compound and di-*tert*-butyl disulphide using ortholithiation conditions.

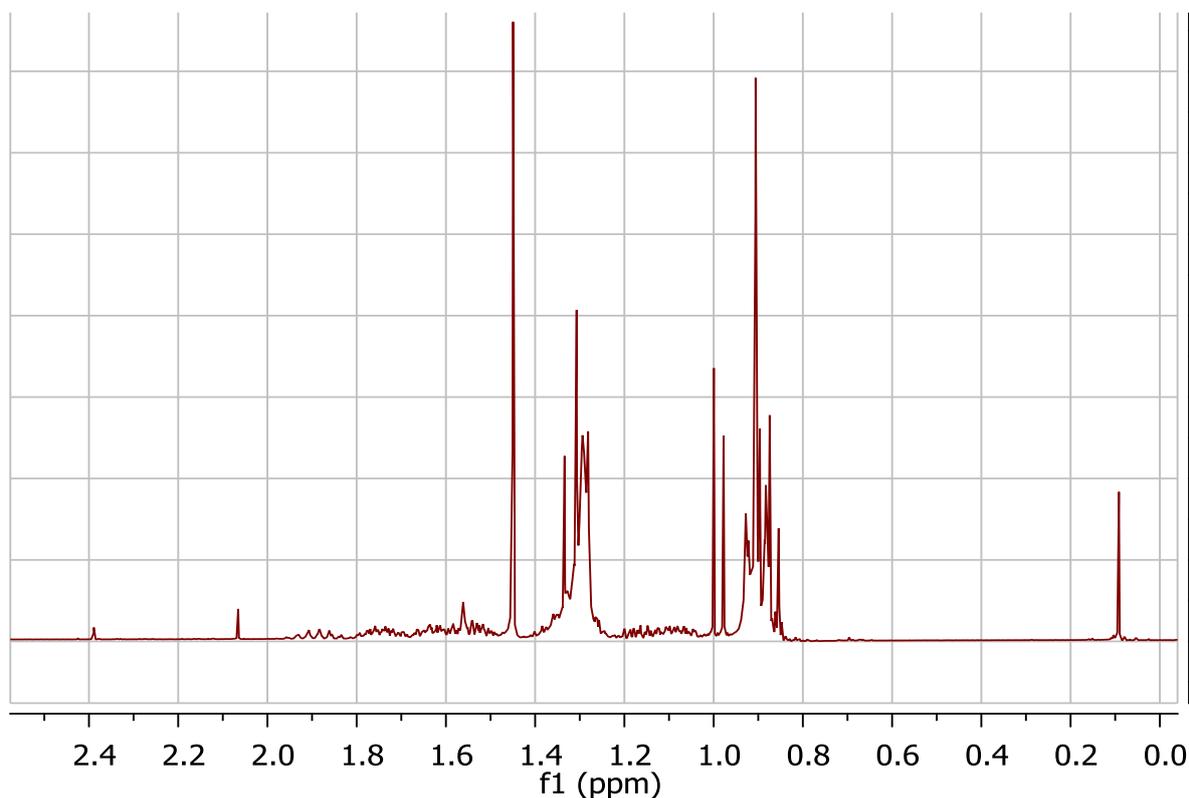
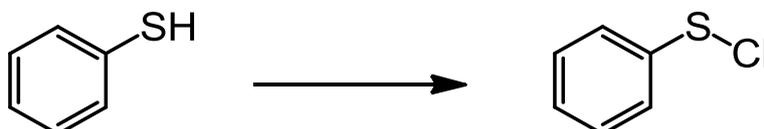


Figure 7 – Magnified aliphatic region of the ^1H NMR spectrum illustrated in Figure 6.

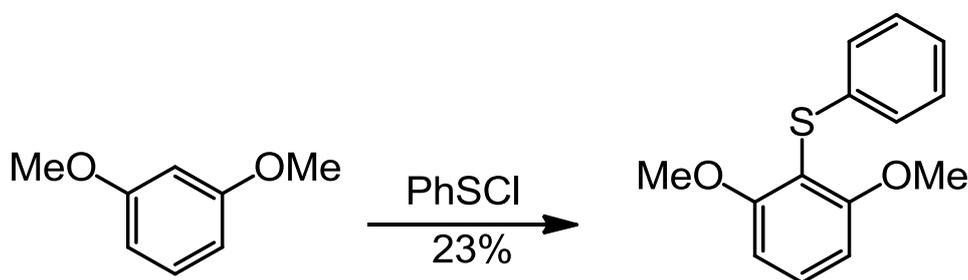
b) Using sulfenyl chlorides:



Scheme 7 - Synthesis of benzenesulfenyl chloride. Reagents and conditions: NCS (2.0 equiv.), DCM, 0 °C to r.t., 30 min.

Diphenyl disulphide was, however, not tested in the ortholithiation approach. The chemical was not available within our chemical stores and we were deterred from ordering the chemical as we wanted to investigate the installation of the desired functionalities onto the resorcinarene using other types of sulphur-derived electrophiles, that contain better leaving groups, within the ortholithiation procedure. Therefore the installation of a phenyl thioether moiety onto the *ortho*-position of both the model compound and the resorcinarene was attempted using benzenesulfenyl chloride as the electrophile. Benzenesulfenyl chloride was synthesised from a procedure that involved reacting thiophenol with N-chlorosuccinimide at 0 °C using DCM as the solvent in a reaction that takes less than 30 minutes to run to completion (Scheme 7).¹⁴

The drawback of using such electrophiles is due to the fact that the use of halogens as leaving groups on electrophiles when using an alkyllithium as a base presents a potential for lithium-halogen exchange. However this was expected not to be a problem since chlorine, on its own, does not undergo lithium-halogen exchange readily.¹⁵ After work-up the electrophile was purified by distillation as a dark orange liquid in a 98% yield which was in exact accordance with the literature.¹⁴ The electrophile was then directly used in the ortholithiation approach thereafter as to minimize exposure to water as the compound has been reported to be very hygroscopic and therefore the electrophile was not characterized using NMR spectroscopy. The synthesis of benzenesulfonyl chloride was confirmed when the electrophile was successfully used in the ortholithiation approach of the model system, but was only partially successful as an electrophile returning a low yield of the product (Scheme 8). The product was purified by column chromatography and provided a neat and clean ¹H NMR spectrum that was devoid of any impurities (Figure 8). When the synthesis of benzenesulfonyl chloride was performed again, it was monitored in five minute intervals. TLC analysis showed the presence of two new compounds within the first five minutes of the reaction. After time another new compound could also be visualized that was slightly less polar than thiophenol. This explains why the yield for the use of this electrophile in the ortholithiation reaction was so poor. This highlights the importance of evaluating the identity of compounds within crude reaction mixtures after completion of the reaction and that one should not ascertain the success of a reaction solely based on observations. Even though low yields were achieved, the isolation of the product proved that the electrophile is compatible with the ortholithiation procedure and that this same transformation should also be theoretically possible on the resorcinarene using the same conditions, albeit low yields would be expected due to the impurities (side-products).



Scheme 8 - Synthesis of 1,3-Dimethoxy-2-phenylthiylbenzene via the ortholithiation approach.

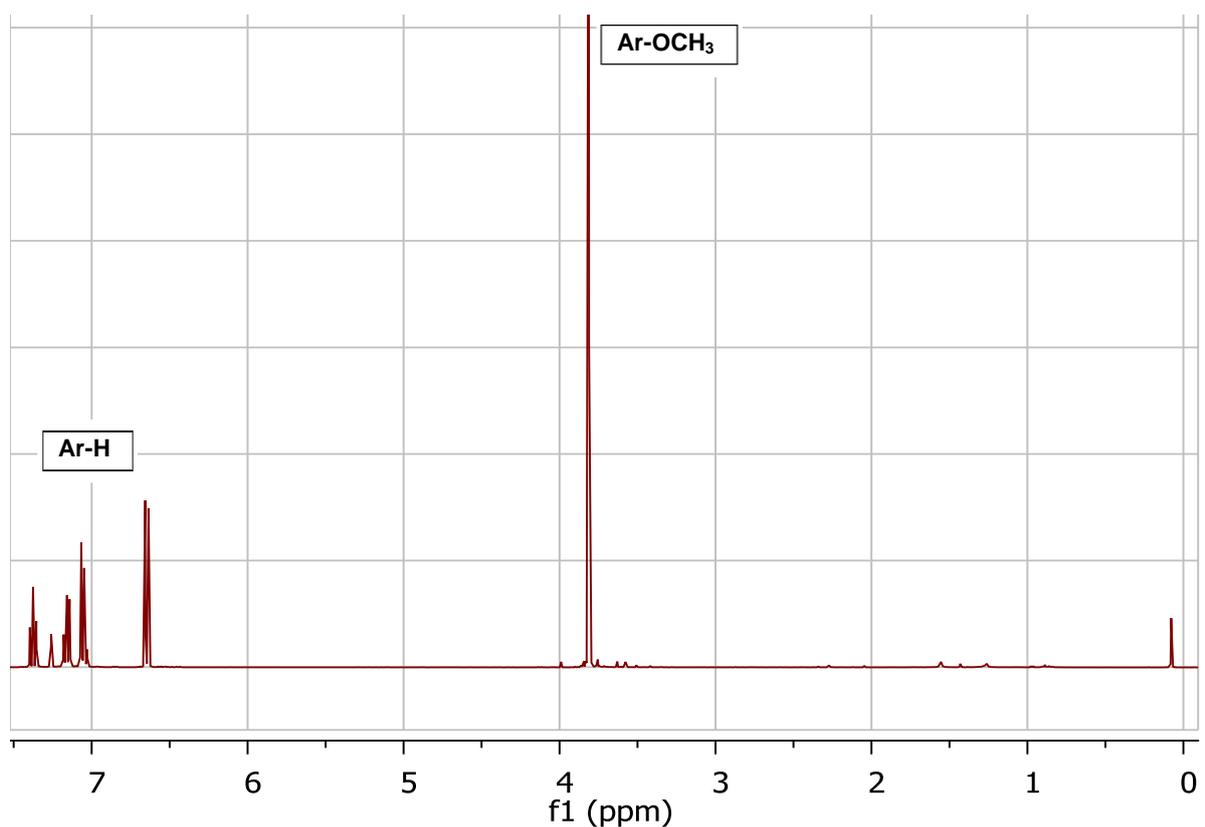
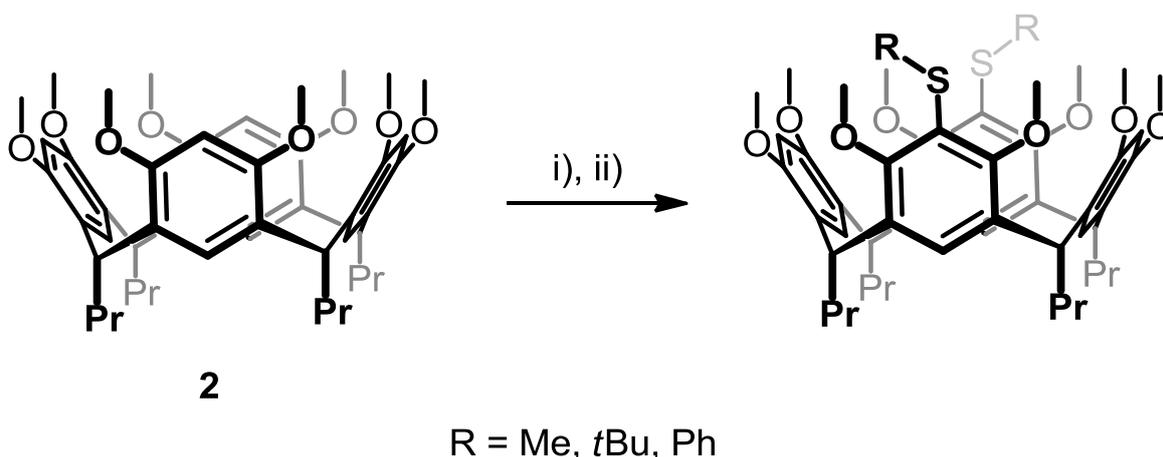


Figure 8 - ^1H NMR spectrum of 1,3-dimethoxy-2-phenylthiylbenzene (Scheme 6).

2.2.2.3 Ortholithiation procedure performed on resorcinarenes

Ortholithiation reactions conducted on the protected resorcinarene methyl ether were performed using the same conditions as for the model compound, 1,3-dimethoxybenzene, except the reaction was quenched at $-78\text{ }^\circ\text{C}$ and the equivalents of the reagents were doubled, since two of the four *ortho*-positions are intended to be functionalized on the resorcinarene scaffold (Scheme 9). Thus the 'propyl-footed' resorcinarene methyl ether **2** was dissolved and stirred in anhydrous THF and treated with five equivalents of *n*-butyllithium at $40\text{ }^\circ\text{C}$ for two hours under inert conditions, before the solution was quenched with excess electrophile (10 equivalents) at $-78\text{ }^\circ\text{C}$ and then slowly warmed to room temperature. The reaction mixture was left to stir overnight to return the distally substituted product in reasonably good yields, and also the monosubstituted resorcinarene as a side product in negligible yields.

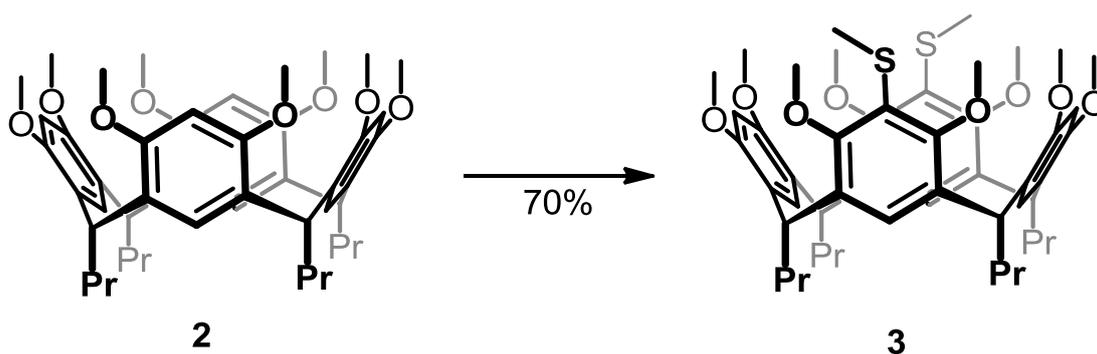


Scheme 9 - Selective functionalization towards distally substituted thioether resorcinarenes. Reagents and conditions: i) *n*BuLi (5 equiv.), THF, 40 °C for 2h. ii) E⁺ (sulphur-derived electrophile) (10 equiv.), -78 °C to r.t., overnight.

2.2.2.4 Testing the ortholithiation approach on the resorcinarene

a) Using disulphides

The use of dimethyl disulphide as an electrophile for the selective functionalization via the ortholithiation approach returned reproducible yields in synthesizing the distal dimethyl thioether resorcinarene ligand (Scheme 10).



Scheme 10 - Synthesis of distal dimethyl thioether resorcinarene ligand (3) via the ortholithiation procedure. Reagents and conditions: i) *n*BuLi (5 equiv.), THF, 40 °C for 2h. ii) S₂Me₂ (10 equiv.), -78 °C to r.t., overnight.

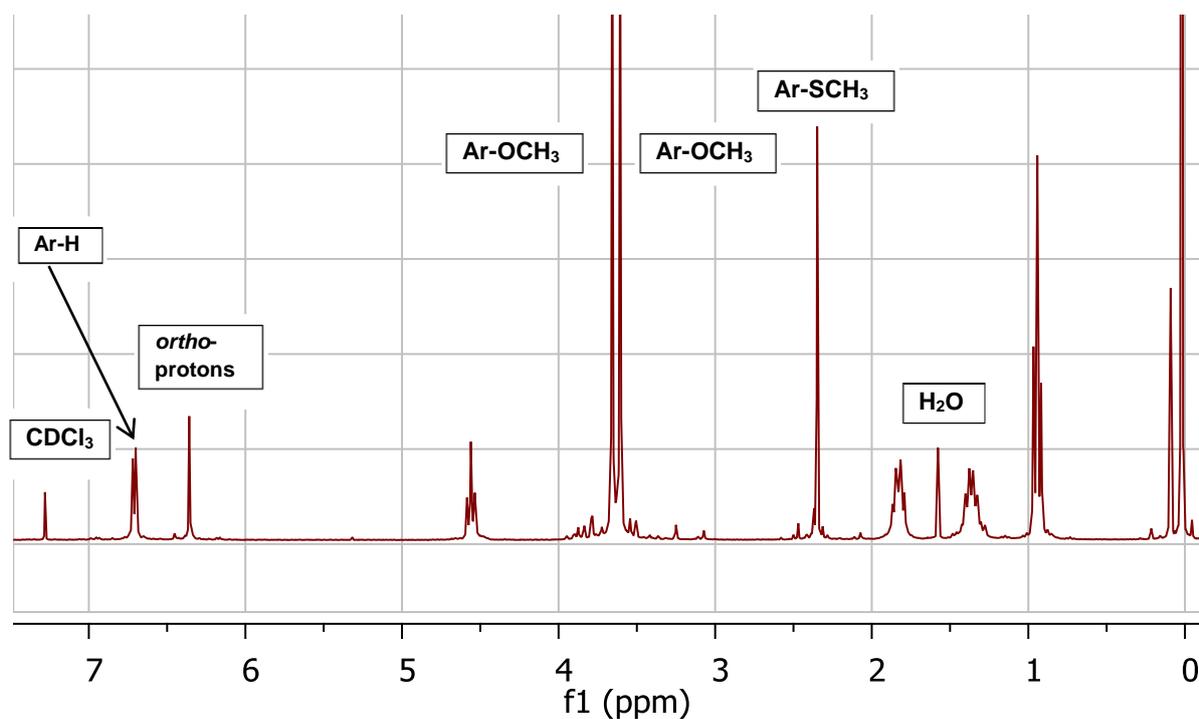
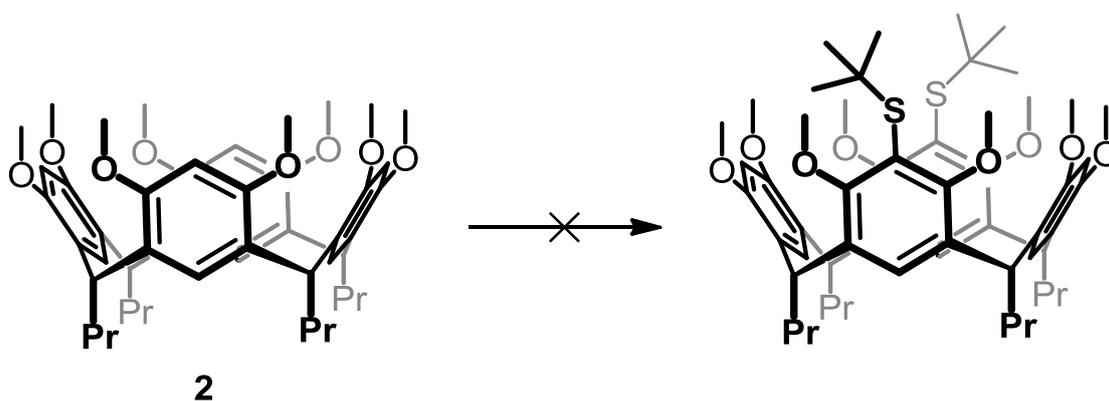


Figure 9 - ^1H NMR spectrum of the distal methyl thioether resorcinarene.

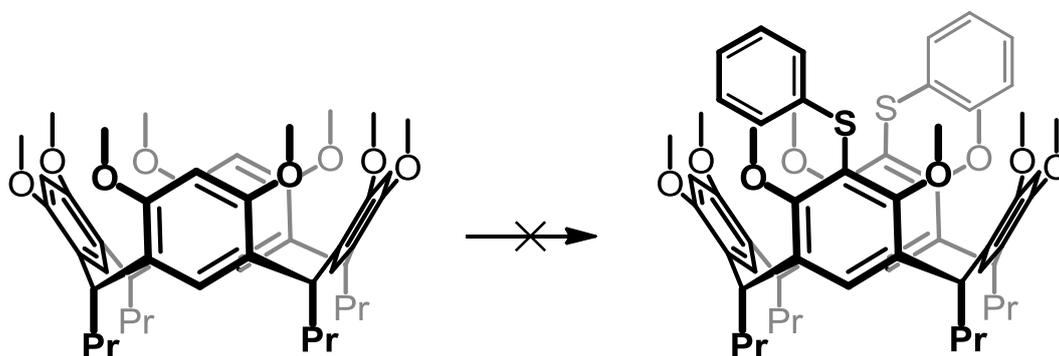
The entire ^1H NMR spectrum completely matched the spectrum previously obtained and reported by Ngodwana^{13,16} (Figure 9). The splitting of the methoxy signals and the presence of an aromatic methylthiyl peak at about 2.4 ppm confirmed the success of the reaction. At first glance the signal produced by Ar-H in Figure 9 looks like a doublet but is actually two overlapping singlets, one singlet belongs to the functionalized lower rim aromatic protons and the other singlet belongs to the unfunctionalized lower rim aromatic protons. The use of the ortholithiation method in functionalizing the resorcinarene methyl ether **2** using the sulphur-derived electrophiles that was used in functionalizing the model compound was then investigated. The attempt of functionalizing the model compound using di-*tert*-butyl disulphide using the ortholithiation procedure provided negative results and indicated that the same result would be obtained when testing this procedure on the methyl ether resorcinarene. The reaction was attempted nonetheless and found these suspicions to be valid as similar results were obtained proving the reaction of being unsuccessful (Scheme 11) as mostly starting material was isolated from the reaction. TLC analysis indicated the formation of two new compounds which were faint and difficult to separate with column chromatography. Any pure material that was isolated from the reaction was insufficient to characterise by ^1H NMR spectroscopy. Di-*tert*-butyl disulphide was tested in the ortholithiation procedure with the resorcinarene twice and both experiments provided the same result.



Scheme 11 - Attempted synthesis of the distal di-*tert*-butyl thioether resorcinarene ligand via the ortholithiation approach. Reagents and conditions: i) *n*BuLi (5 equiv.), THF, 40 °C for 2h. ii) S₂(*t*Bu)₂ (10 equiv.), -78 °C to r.t., overnight.

b) Using sulfenyl chlorides:

The synthesis of benzenesulfenyl chloride was confirmed when it tested successful in the functionalization of the model compound via ortholithiation approach (Section 2.2.2.2b). Unfortunately, the use of benzenesulfenyl chloride as an electrophile in the functionalization of resorcinarenes returned similar results as those when using di-*tert*-butyl disulphide as the electrophile; namely the return of mostly starting material. Again any compounds that were managed to be separated and isolated by column chromatography were insufficient to submit for NMR analysis (Scheme 12). Benzenesulfenyl chloride was tested in the ortholithiation procedure with the resorcinarene three times and all three experiments gave the same result. However these results are inconclusive since the electrophile, benzenesulfenyl chloride, was shown to be quite impure by TLC analysis. However it should be noted that the impure electrophile was compatible with the ortholithiation procedure of the model compound, albeit in low yields.



Scheme 12 - Attempted synthesis of the distal dithiophenyl ether resorcinarene ligand via the ortholithiation approach. Reagents and conditions: i) *n*BuLi (5 equiv.), THF, 40 °C for 2h. ii) PhSCI (10 equiv.), -78 °C to r.t., overnight.

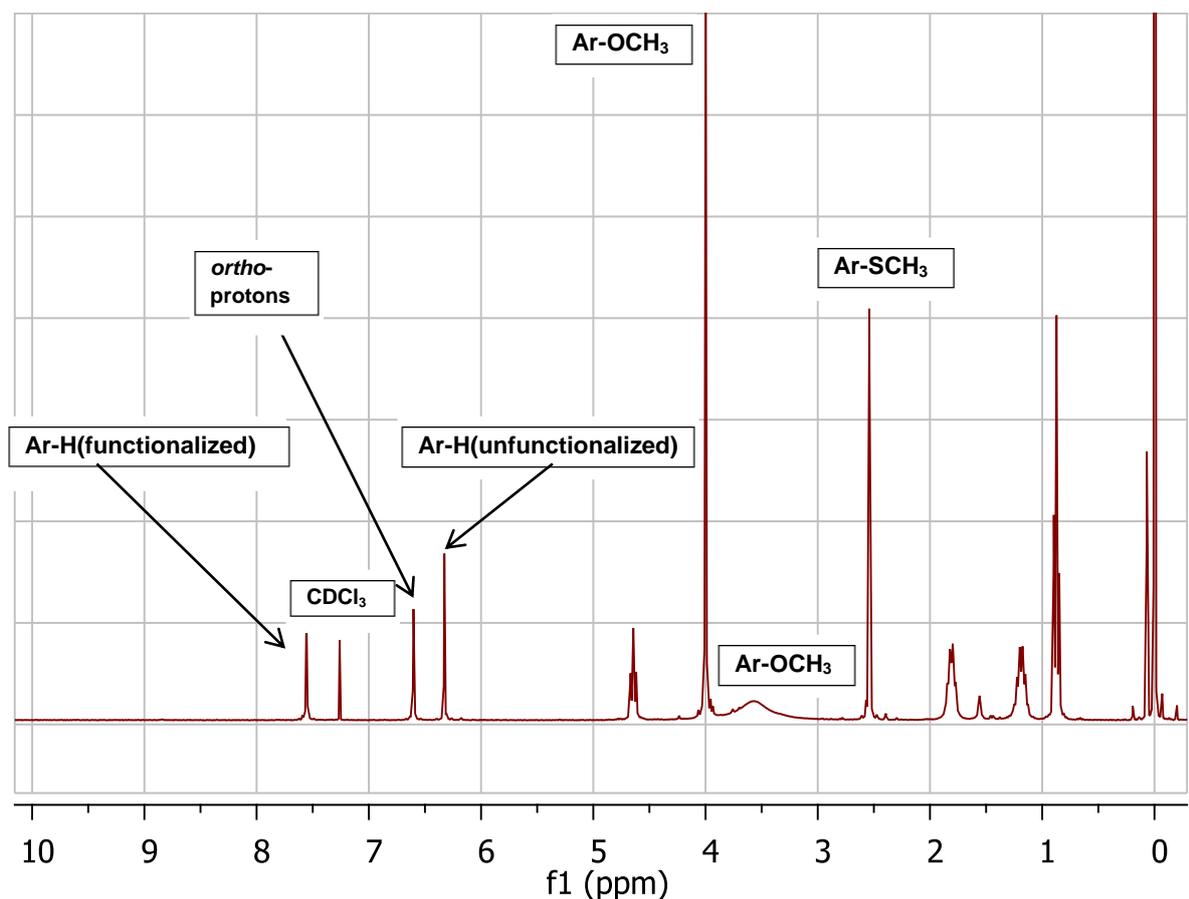


Figure 10 - ^1H NMR spectrum of the crystals grown of the $(\mu\text{-Cl})_2\text{Pd}_2\text{Cl}_2$ -resorcinarene complex (4).

The large splitting between the methoxy signals (about 0.4 ppm) and the slightly more downfield shift (0.1 ppm) of the methylthiyl protons is a strong indication of complexation through the distal thioether moieties as previously reported by Kleinhans. This was later confirmed when Kleinhans obtained a crystal structure of the complex. A significant shift of about 1.2 ppm was seen between the functionalized and unfunctionalized lower rim aromatic protons. Kleinhans suggested that this large difference in chemical shifts is attributed to a change in conformation of the parent ligand to a distorted boat conformation, with the functionalized rings being in an axial position. Moreover Kleinhans also suggested that one of the aromatic methoxy signals appeared as a broad signal due to a form of restricted rotation. This signal is most likely the methoxy groups attached to the functionalized rings of the resorcinarene. Kleinhans was able to deduce from low temperature ^1H NMR experiments that the ratio of major to minor conformation is 6:1. Interestingly the data obtained from X-ray diffraction analysis showed that the molecule crystallizes out in the minor conformation which happens to be the more symmetrical conformation. He speculated that because the more symmetrical conformation is more crystalline that this allows the other molecules (the major conformers) within solution to crystallize out in the same conformation as the minor (Figure 11).

This suggests that the small concentration of minor conformers acts as seed crystals which provide the means for the major conformers to crystallize out in the more crystalline minor conformation.

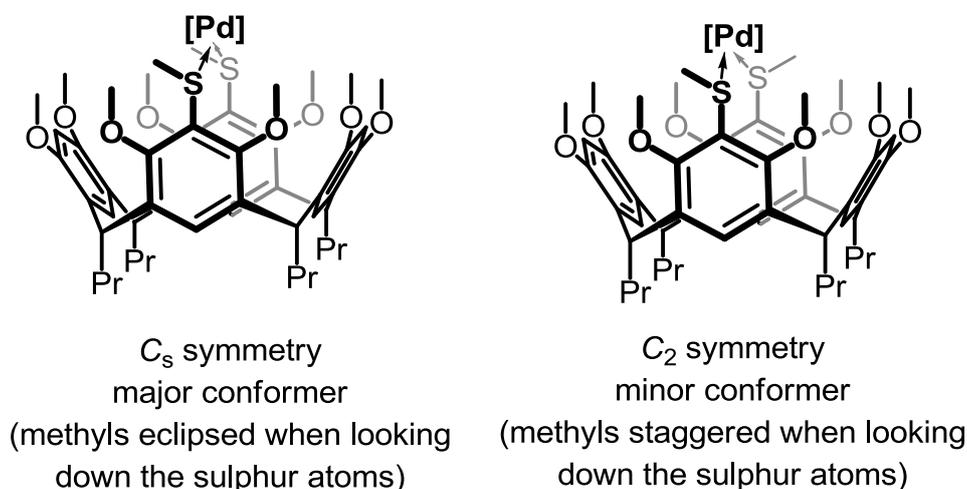
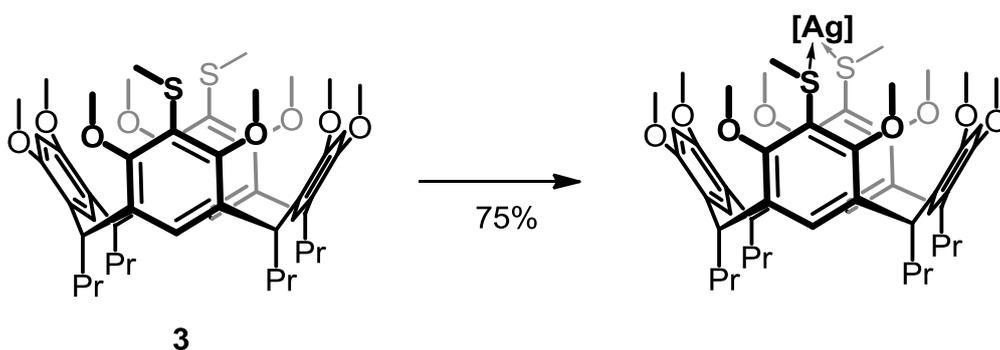


Figure 11 - The major and minor conformers of the $(\mu\text{-Cl})_2\text{Pd}_2\text{Cl}_2$ -resorcinarene complex (4).



Scheme 14 - Complexation of silver perchlorate to the distal methyl thioether resorcinarene ligand.¹⁷
Reagents and conditions: AgClO_4 (1 equiv.) dissolved in minimal MeCN, THF, r.t., 24 hours.

Secondly, identical results were obtained when complexing the ligand with silver and nickel. An unidentified silver-resorcinarene complex was obtained when performing a similar procedure using silver(I) perchlorate (Scheme 14). Thus to a solution of **3** in anhydrous THF was added one equivalent of silver perchlorate that was dissolved in a minimum amount of methanol. The flask was covered with aluminium foil as silver salts are known to be light sensitive. The reaction mixture was stirred overnight and worked-up in the same way as for complexation of the resorcinarene using PdCl_2 . Crystals of the complex could not be successfully grown out of a solution of DCM and hexane as trituration occurred, preventing structure elucidation of the silver complexed resorcinarene. Other solvent and solvent systems were used in attempts to grow crystals of the complex, all of which failed.

The ^1H NMR spectrum from the compound was identical to one obtained by Kleinhans (Figure 11). Similar interesting features were found in the ^1H NMR spectrum of the product, such as an ever larger split between the methoxy signals (0.6 ppm) and even larger downfield shift of the methylthiyl protons (0.4 ppm) as compared to the $(\mu\text{-Cl})_2\text{Pd}_2\text{Cl}_2$ -resorcinarene complex which suggests complexation of the resorcinarene ligand through the thioether moieties to silver. In this case the more upfield methoxy signal is not broad as was seen in the case of the $(\mu\text{-Cl})_2\text{Pd}_2\text{Cl}_2$ -resorcinarene complex, which suggests that the different methoxy groups have the same degree of freedom within the macrocycle. As for the complexation of the resorcinarene ligand to nickel(II) bromide similar inconclusive results were obtained as reported by Kleinhans. To a solution of **3** in anhydrous THF was added one equivalent of NiBr_2 that was dissolved in a minimum amount of methanol and the reaction mixture was stirred overnight. The reaction mixture was worked-up in the same manner as the previous two complexation reactions with PdCl_2 and AgClO_4 . The complex that was obtained degraded into starting material when attempting to dissolve the complex in solvents such as methanol, preventing characterization of the compound.

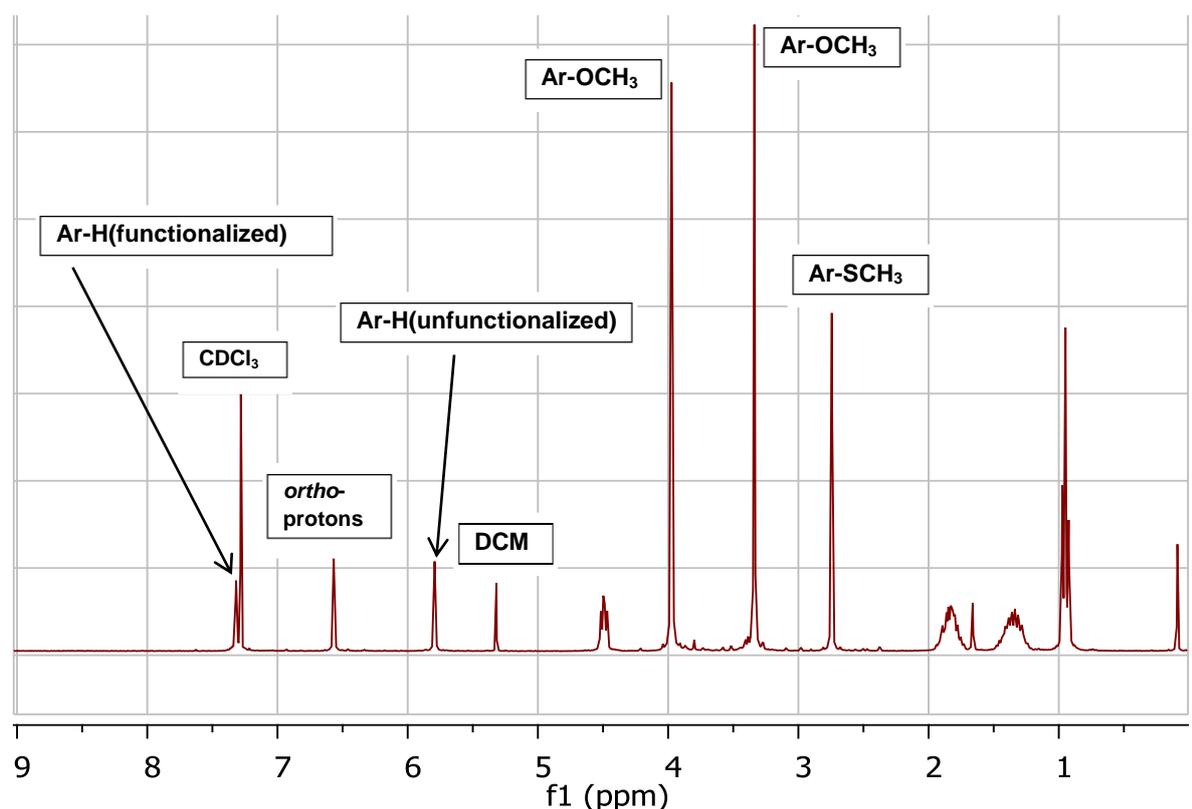
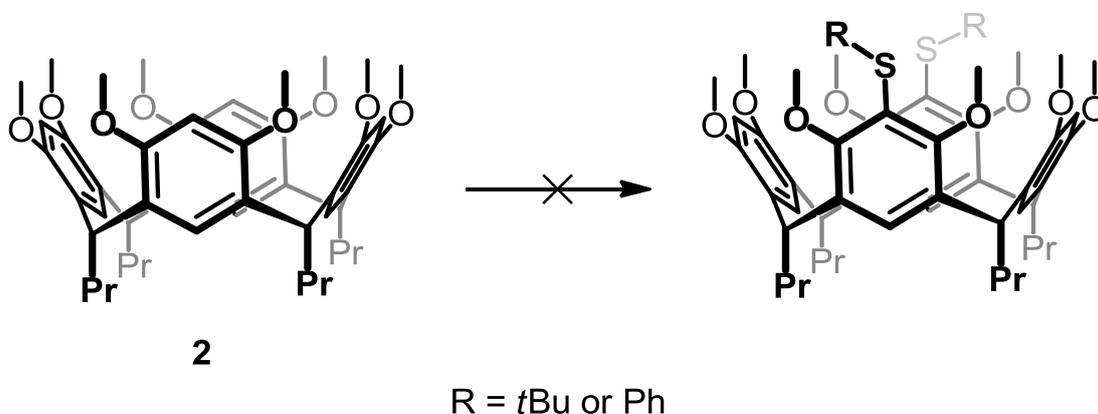


Figure 12 - ^1H NMR spectrum obtained of the product from complexing resorcinarene ligand (**3**) with silver perchlorate.

2.4 Conclusions

The ortholithiation procedure was recreated and was found to be reproducible in synthesizing the distal dimethyl thioether resorcinarene ligand **3** as the results that were obtained matched those previously obtained by Kleinhans^{17,18} and Ngodwana^{13,16} (Scheme 10). The resorcinarene-Pd complex **4** was easily obtained thereafter (Figure 9). Exactly the same results were obtained when complexing the distal methyl thioether resorcinarene ligand with AgClO₄ and NiBr₂, as previously reported by Kleinhans.¹⁷ Furthermore the ortholithiation method failed when the installation of other thioether functionalities onto the resorcinarene was attempted when using di-*tert*-butyl disulphide and benzenesulfonyl chloride as the electrophiles. Di-*tert*-butyl disulphide was unsuccessful in being coupled to the *ortho*-position of both the model system and the resorcinarene scaffold while benzenesulfonyl chloride was successful in the functionalization of the model system, but was inconclusive on the resorcinarene, using the ortholithiation approach. Therefore from these findings it can be concluded that functionalization of the resorcinarene scaffold using sterically hindered disulphides such as *tert*-butyl is just not possible via the ortholithiation approach while the use of sulfonyl chlorides such as benzenesulfonyl chloride remains inconclusive (Scheme 15).



Scheme 15 – Attempted functionalization of the resorcinarene scaffold via the ortholithiation procedure using sulphur-derived electrophiles (di-*tert*-butyl disulphide and benzenesulfonyl chloride).

2.5 References

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Chapter 3

Investigation towards the Synthesis of Thioether Resorcinarene Ligands via Catalysis

3.1 Introduction

As reported and discussed in Chapter 2; the use of dimethyl disulphide as an electrophile in the ortholithiation approach was successful in producing the distal methyl thioether resorcinarene ligand in good yields. Shortly thereafter it was established that the ortholithiation method was unsuccessful in obtaining distal thioether resorcinarene ligands in which the R-group attached to the sulphur atom is a *tert*-butyl or phenyl group when using the appropriate disulphide and sulfenyl chloride as electrophiles. Therefore it was decided to take the project a step further through exploring possible alternative strategies in order to attach the *tert*-butyl and phenyl thioether moieties onto the resorcinarene such as the use of transition metals in catalysis, which will be discussed in this chapter.

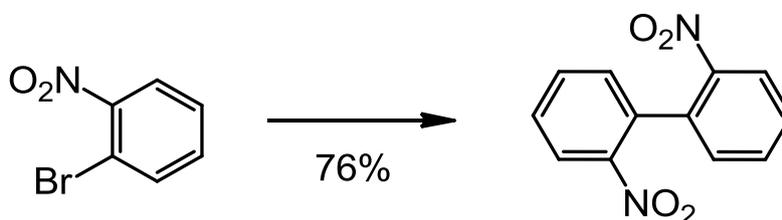
3.2 Catalysis

The term catalysis, which was first coined by Jöns Jakob Berzelius in 1835, comes from the Greek words *katas* meaning down and *lyein* meaning loosen. He described “catalytic power” as “the ability of substances to awaken affinities, which are asleep at a particular temperature, by their mere presence and not by their own affinity”.¹ Catalysts are defined as chemical species which increases the rate of a reaction by introducing a new and more attractive reaction pathway, to help facilitate the formation of new bonds between organic substrates. This new reaction pathway, that may involve many steps and intermediates, requires less activation energy than the uncatalyzed pathway. The catalyst brings reagents in very close proximity of each other in a reactive state.² A catalyst, usually a transition metal, achieves this by forming short-lived metal-carbon/heteroatom bonds which activates the substrates in order to allow them to couple to each other. This in turn increases the rate of the reaction, as less energy is needed in order to form new bonds between the substrates. Catalysts take part in chemical reactions but are regenerated at the end of the catalytic cycle and thus can be recovered from the reaction. Moreover, the catalyst can be used in trace amounts, i.e. the number of equivalents of catalyst used is a small percentage relative to the starting material and doesn't need to be present in stoichiometric quantities. These two facts makes catalysis widely attractive to chemists as they make it possible to obtain products with high turnover efficiency, i.e. in quantitative yields, that would be otherwise impossible to achieve without their presence.

Since then different transition metals have been investigated and have become prominent in the literature primarily to their unique ability of catalyzing chemical transformations, especially within cross coupling reactions. Cross coupling³ is a very powerful tool of any synthetic chemist to create intricate organic scaffolds. These are important reactions as they facilitate the formation of a wide variety of bonds (C-C and C-heteroatom) which is core to the world of organic synthesis. Since the ortholithiation method failed in obtaining the desired transformations, the use of transition metals was then investigated in order to attempt to couple the desired sulphur functionalities onto the resorcinarene scaffold. Within the literature a few metals have been reported to catalyse sulphur coupling reactions, such as copper(I)⁴⁻⁶ and palladium(0)^{7,8}.

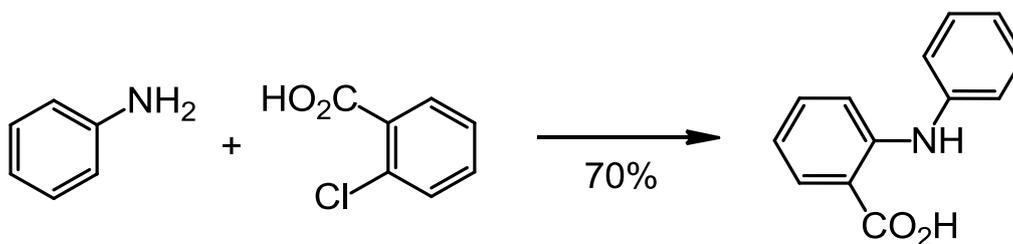
3.2.1 Copper Catalysed Cross-Coupling Reactions

It was at the start of the 20th century when Fritz Ullmann stumbled upon the formation of C-C bonds via cross coupling reactions when he reported the synthesis of biaryl compounds using aryl bromides in 1901. Ullmann managed to couple *o*-nitrobromobenzene with itself in the presence of stoichiometric amounts of metallic copper to produce 2,2-dinitrobiphenyl, in a reaction which ultimately became known as the Ullmann reaction or Ullmann coupling (Scheme 1).⁹



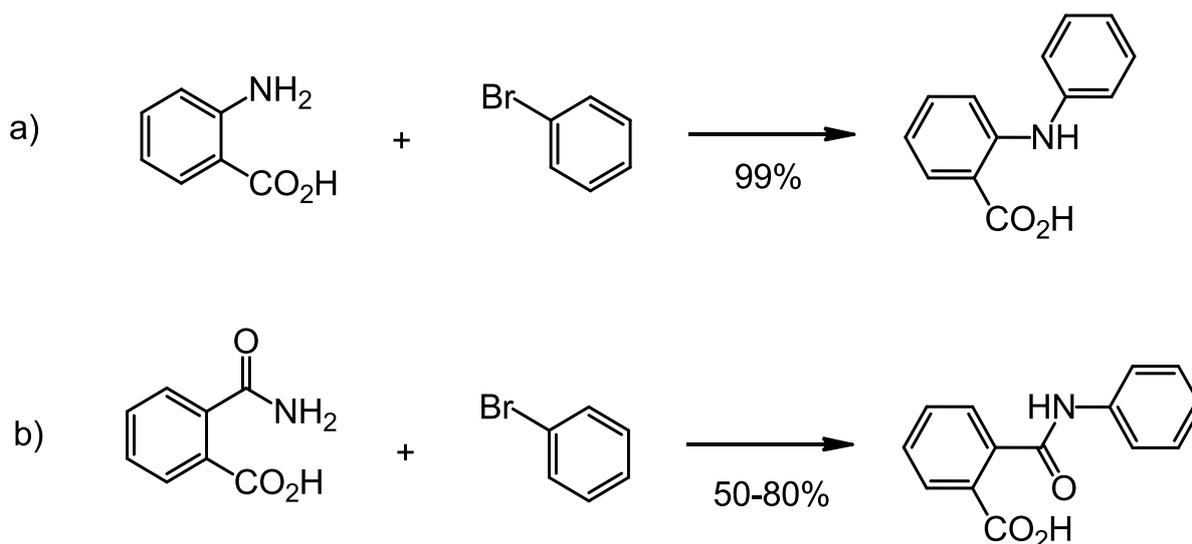
Scheme 1 - Synthesis of 2,2-dinitrobiphenyl via the Ullmann reaction.⁹
Reagents and Conditions: Cu (stoichiometric), 220 °C.

Two years later Ullmann continued to establish the foundations of copper-mediated cross coupling reactions by publishing the arylation of anilines with the lesser reactive aryl chlorides with high efficiency, also in the presence of stoichiometric amounts of metallic copper, which became known as the Ullmann condensation reaction (Scheme 2).¹⁰ In 1905 Ullmann reported and stated that “if you try to react potassium phenoxide with bromobenzene, the yield of biphenyl ether is 0.9%. If you however add small quantities of copper to the reaction, the yield goes to 90%”,¹¹ indicating an increase in yield of a hundred fold when trace amounts of copper is present in the reaction mixture.



Scheme 2 - The Ullmann Condensation.¹⁰
Reagents and conditions: Cu (stoichiometric), reflux.

It was one year thereafter when Irma Goldberg, Ullmann's assistant, confirmed these findings when she reported similar results to the ones Ullmann reported in the cross coupling reaction of phenols with aryl bromides; namely that only trace amounts of metallic copper are needed for the reaction to show high efficiency. Goldberg reinvestigated the Ullmann condensation by condensing anthranilic acid with bromobenzene using potassium carbonate as a base in refluxing nitrobenzene, returning the biarylamine in quantitative yields (Scheme 3a). More interestingly, the lesser reactive amides can also be arylated, known nowadays as the Goldberg condensation, using these conditions (Scheme 3b).¹² It was the remarkable discoveries made by these two chemists, who would later become married to one another in 1910, that marked the beginning of cross coupling reactions and paved the way forward towards all recent developments in the field thereof.¹³

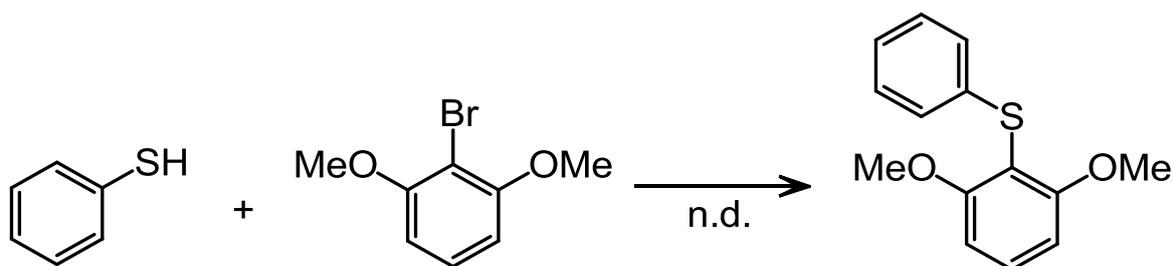


Scheme 3 - a) Arylation of an aniline and b) arylation of an amide (the Goldberg Condensation).¹²
Reagents and conditions: Cu (catalytic), K₂CO₃ or NaOAc, nitrobenzene, reflux.

The Ullmann condensation reaction was extensively reinvestigated by Paine¹⁴ who identified the active catalytic species to be cuprous ions. The introduction of chelating ligands was a remarkable breakthrough for copper-mediated cross coupling reactions and was reported by Bryant,¹⁵ Capdevielle,¹⁶ and Goodbrand¹⁷ to increase their catalytic efficiency. Chemists have since then optimized the copper catalysed cross coupling reactions discovered by Ullmann, Goldberg, Rosenmund-von Braun¹⁸⁻²⁰ and Hurtley²¹ and such cross-couplings can now be conducted under milder conditions due to these breakthroughs. As remarkable as these reactions were, copper catalysts have only found a limited number of applications despite their impressive potential. Even though copper is known to be relatively less expensive and less toxic than metals such as palladium and nickel, these metals have replaced copper due to the fact that the copper-mediated cross coupling reactions usually suffer from the drawbacks of harsh reaction conditions, such as the need of: 1) strong bases, 2) stoichiometric quantities of copper in some cases and 3) high reaction temperatures. Metals such as palladium, and the ligands usually complexed to them in catalytic species, are however rather expensive which prompted chemists to revisit copper-mediated cross coupling reactions.

3.2.2 Investigation into Sulphur-Coupling via Copper Catalysis

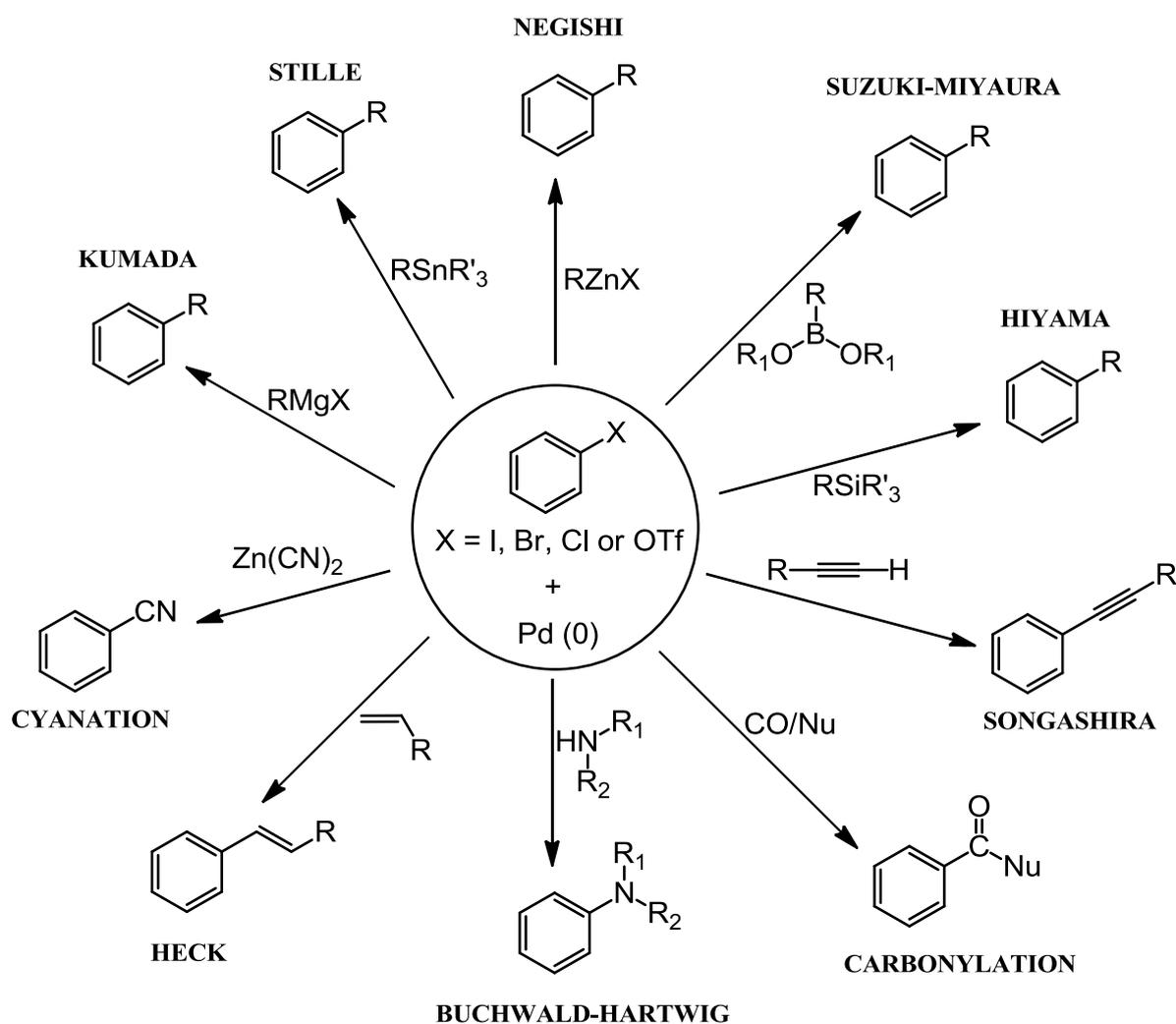
The use of copper in the coupling of thiols to aryl halides was then investigated. Thus the synthesis of 1,3-dimethoxy-2-phenylthiylbenzene was attempted in a simple one-pot coupling reaction between 2-bromo-1,3-dimethoxybenzene and thiophenol using a literature procedure that achieved the same type of couplings on electron-rich aryl halides.⁵ The coupling was performed in the presence of copper(I) iodide as catalyst together with benzotriazole as a ligand and using potassium *tert*-butoxide as a base (Scheme 4). TLC analysis indicated the formation of the desired coupled product albeit in very low yields as a low conversion of starting material was seen. Since TLC analysis indicated a low conversion of starting materials, it was decided to investigate the route of sulphur-coupling through the more superior palladium catalysts.^{22,23}



Scheme 4 - Sulphur coupling with a copper catalyst.⁵ Reagents and conditions: CuI (1 mol%), BtH (2 mol%), KO^tBu (5 equiv.), thiophenol (2 equiv.), DMSO, reflux, overnight.

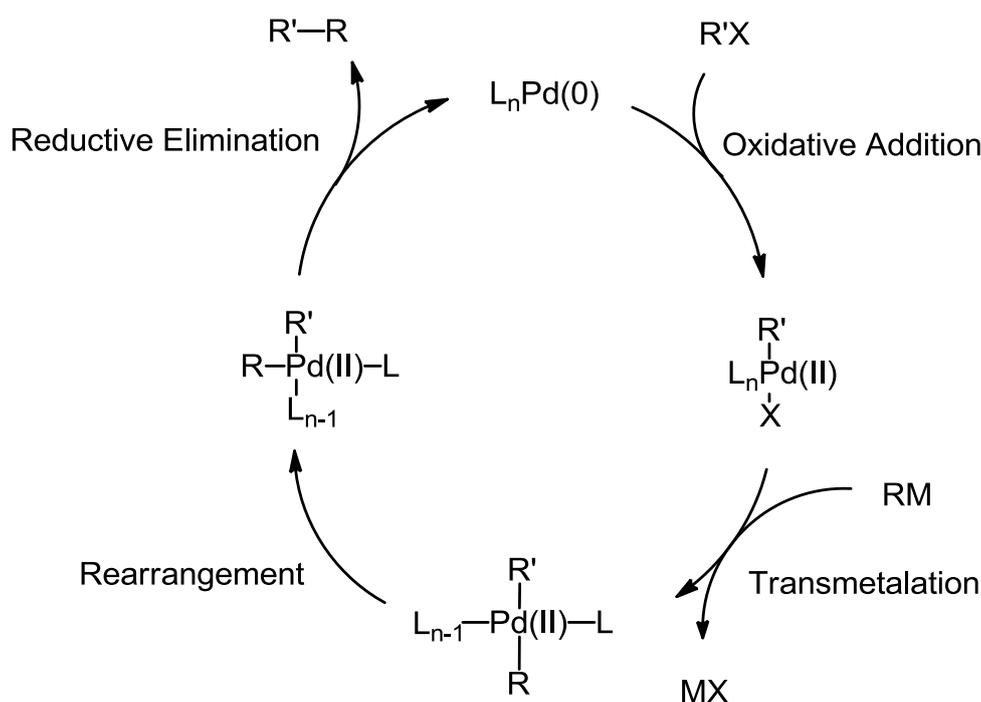
3.2.3 Palladium Catalysed Cross-Coupling Reactions

In 2010 the Nobel Prize in chemistry was jointly awarded to chemists Richard F. Heck, Ei-ichi Negishi and Akira Suzuki for the formation of carbon-carbon single bonds through palladium-catalysed cross-coupling reactions. Palladium, however more expensive, seems to have superiority over copper when it comes to cross coupling reactions. In its zero-valent state, palladium can facilitate a wide variety of organic transformations within cross coupling reactions illustrating how versatile the metal can be as a catalyst (Scheme 5).²³ Palladium is also able to facilitate carbon-heteroatom bond formation such as the amination (Buchwald-Hartwig coupling)²⁴⁻²⁷ and etherification^{28,29} of organic compounds, just as copper has been reported to do. More recently thioetherification^{7,8} has been added to the list of carbon-heteroatom bond formation made possible via cross coupling reactions catalysed by palladium and also by copper which suits the intended purposes of this project of installing carbon_(aryl)-sulphur bonds on the *ortho*-position of the resorcinarene, as the resorcinarene can be easily pre-functionalized as macrocyclic aryl halides.



Scheme 5 - C-C and C-heteroatom bond formations made possible via cross coupling reactions facilitated by palladium.

The choice of ligand to be complexed with palladium is important, as the ligand can help facilitate two key steps in the catalytic cycle of such coupling reactions.³⁰ Ligands that push electron density onto palladium help facilitate the oxidative addition step when palladium(0) inserts into the organohalide (R-X), which is the electrophilic coupling partner, oxidizing itself into palladium(II). Electron-donating ligands help facilitate oxidative addition, which is believed to be the rate determining step, by stabilizing the electron-deficient palladium intermediate (R-Pd-X) after it is oxidized (Scheme 6). The ligand that is chosen also determines the mechanism at which oxidative addition occurs. Palladium catalysts that have bulky ligands attached to it are even more sterically hindered and favour reductive elimination within the catalytic cycle by destabilizing the rearranged complex through imparting steric encumbrance onto the palladium by the bulky ligands complexed to it (Scheme 6). Therefore ligands that are strong σ -donors that are also bulky are superior ligands for palladium for these reasons.^{24,25,27}



Scheme 6 - Catalytic cycle of palladium catalysed cross-coupling reactions.

3.2.3.1 Phosphine Ligands for Palladium

Phosphine compounds (Figure 1) have long been traditionally used as ancillary ligands for palladium. Phosphine atoms are strong σ -donors and are weakly π -acidic, which strongly favours the oxidative addition step, making them excellent ligands for palladium for cross-coupling reactions.³¹ A wide variety of organic substituents can be attached to phosphine

and these ligands can be made as either chiral or achiral. Bulky groups can be employed onto phosphine atoms, making them very sterically hindered, which helps facilitate the reductive elimination step. These bulky ligands exhibit a cone angle, known as the Tolman angle, the larger this angle is the more accelerated the reductive elimination step will be.^{32,33}

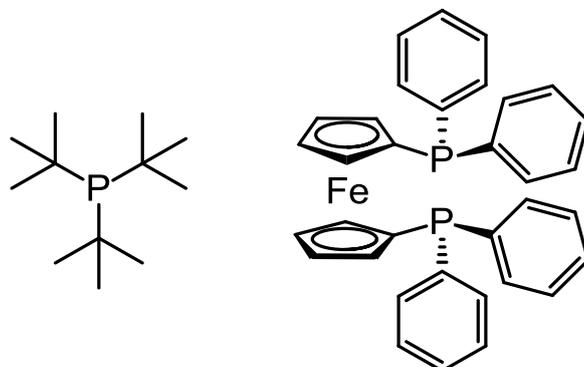


Figure 1 - The monodentate tri(*tert*-butyl)phosphine (left) and bidentate dppf (bis(diphenylphosphino)ferrocene) (right).

3.2.3.2 N-Heterocyclic Carbene (NHC) Ligands for Palladium

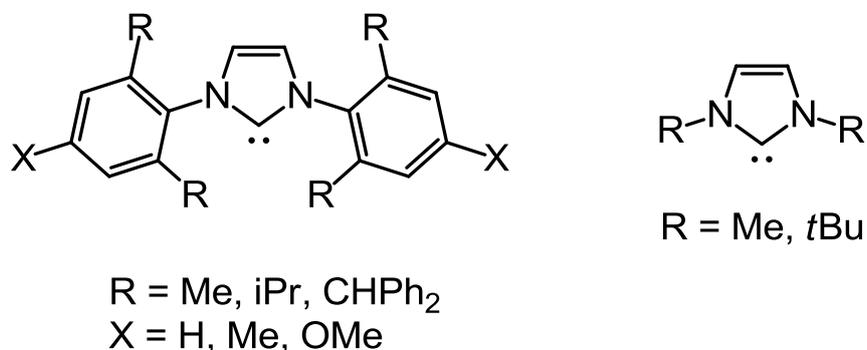


Figure 2 - N-Heterocyclic Carbene Ligands.

Phosphine ligands, especially tertiary substituted and chiral phosphine ligands, are cost ineffective to produce and are very air-sensitive as these ligands can easily degrade by oxidizing into phosphine oxides. Even more worrisome, is the fact that they are subjective to ligand dissociation and P-C bond degradation at elevated temperatures, which deactivates the catalyst and requires higher phosphine ligand concentrations, making them unfit as catalysts for cross-coupling reactions to a certain extent.³⁴ Triaryl phosphines also suffer from the drawback in the difficulty of removing these ligands and their catalysts from reaction mixtures. For these reasons phosphine ligands have recently started to be replaced by the

rather recent discovery of the very popular, thermally stable N-heterocyclic carbene (NHC) ligands (Figure 2).^{35–38} Carbenes are neutral ligands, just like phosphine ligands, and consist of a divalent carbon atom that has 6 valence electrons and only 2 single covalent bonds coordinated to the carbon atom.^{39,40} Their synthesis has been attempted since as early as 1835⁴¹ but their isolation and characterization remained hindered until the late 20th century. Until the 1990's chemists could only generate carbenes *in situ*, which thwarted efforts into their investigation as their isolation was made impossible due to the unstable nature of carbenes. Carbenes are unstable due to their incomplete electron octet and coordinative unsaturation, making them very reactive as they have the propensity to complete their valence and become naturally fully saturated with a total of 4 covalent bonds. Thus they could traditionally only be studied indirectly by means of trapping reactions (*in situ*), as they were investigated in 1950 by Hine when he investigated the alkaline hydrolysis of chloroform.⁴² NHCs were first reported by Wanzlick^{43–56} in the 1960's and early 1970's. Wanzlick investigated the reactivity of nucleophilic carbenes extensively, but was never able to isolate and study carbenes directly. It wasn't until 1991 when Arduengo and co-workers⁵⁷ reported the first successful isolation the of a stable carbene ligand (where R₁ = Ad in Figure 2) in which the carbene was employed within a nitrogen heterocycle. This carbene was stable at room temperature and melted without decomposition (in the absence of oxygen or moisture) and could be stored under nitrogen indefinitely. The molecules brought about an explosion of interest from the scientific community as their successful isolation presented the possibility of studying carbenes directly. Six years later Arduengo reported the isolation of an air- and moisture-insensitive carbene.⁵⁸

These 'stable' carbenes were able to be isolated and stored in normal atmosphere and are also known as persistent carbenes or Arduengo carbenes. Their stabilisation is achieved by a number of factors such as conjugation or Hückel-type aromaticity, which in this case is brought about by the double bond within the imidazole backbone that the carbene resides on (Figure 3).⁵⁹ Substituents that are found on the backbone of the NHC affect the electronics of the carbene carbon itself.^{60–62} It should be noted that acyclic version N-Heterocyclic carbenes also exist and that the stabilization brought about by a cyclic structure isn't a requirement for a carbene to exist. There have even been mentions of carbenes that are stabilized by electron-deficient organoboron substituents, rather than the more conventional electron-donating substituents such as nitrogen, sulphur and oxygen.⁶³ Furthermore, the neighbouring heteroatoms achieve further stabilization of the NHC by both an inductive effect by being σ -electron-withdrawing and a mesomeric effect by being π -electron-donating through the lone pairs on the heteroatoms. Lastly the substituents found on the heteroatoms also stabilize the NHC via electronic stabilization (i.e. aromatic substituents) and kinetic stabilization provided by the steric bulk of these substituents.⁵⁹ Carbenes can exist in two states; a singlet state

(spin paired), which is generally the less stable state, where both electrons reside within the same sp^2 -hybridized orbital resulting in a trigonal planar structure (Figure 3), and a triplet state (spin unpaired) where the electrons reside within two degenerate p-orbitals resulting a slightly bent structure. The ground-state multiplicity of carbenes dictates their reactivity: singlet carbenes are ambiphilic but are regarded more as nucleophilic than electrophilic whereas triplet carbenes are essentially diradicals, which behave more electrophilically.^{64,65} Singlet carbenes can be stabilized and become the more stable state by being attached to electron-donating substituents, such as the nitrogen substituents found in NHC systems.

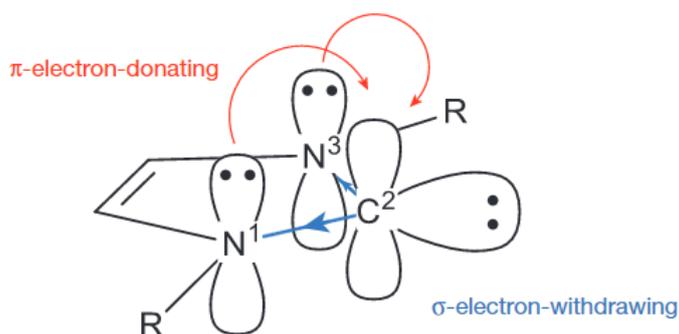
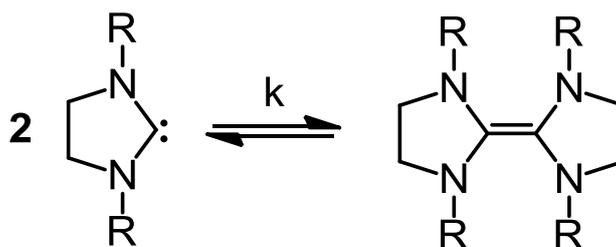


Figure 3 - Stabilization within NHCs resulting in a singlet ground-state (both electrons contained within the sp^2 orbital) (reproduced from reference 59).

Therefore N-heterocyclic carbenes exist mostly in the singlet ground state, which is in contrast to classical carbenes which are in a triplet state. Few examples of triplet carbenes exist as they can only be stabilized by the aryl substituents which are neither electron-donating nor electron-accepting. Furthermore the cyclic nature of NHCs favours the singlet state by sterically forcing the carbene carbon into a bent, trigonal planar, sp^2 -like arrangement. In contrast to transient carbenes (usually triplet carbenes) which exhibit an electrophilic nature, NHCs are nucleophilic in nature. These ligands contribute to the formation of a strong metal-carbenic bond on the palladium centre, which favours tight binding kinetics and thus lessens ligand dissociation. NHC ligands, just like the phosphine ligands, report quantitative yields for cross coupling reactions when complexed with palladium at very low catalyst loadings.²⁴ Moreover these ligands are even better ligands for palladium than phosphines, namely due to two properties; their strong σ -donor character, which is stronger than the σ -donor character provided by the phosphines, and their great steric bulk. The σ -donor character is brought about by the electrons of the singlet ground-state carbene itself. Carbenes that are found in the triplet state are a lot more reactive, and thus unstable, than singlet carbenes due to the fact that these carbenes are essentially diradicals since they contain two unpaired electrons within different orbitals.

The steric bulk of the ligands are provided by varying the size of the substituents on the nitrogen atoms on both sides of the imidazole ring. The steric bulk imparted by these nitrogen substituents prevents the dimerization of carbenes to the corresponding olefin by physically preventing them from coming in close proximity of each other.⁶⁶ Persistent carbenes exist in equilibrium, known as the Wanzlick equilibrium, with their respective dimers (Figure 4).^{44,67–69}



k is small for large R-groups

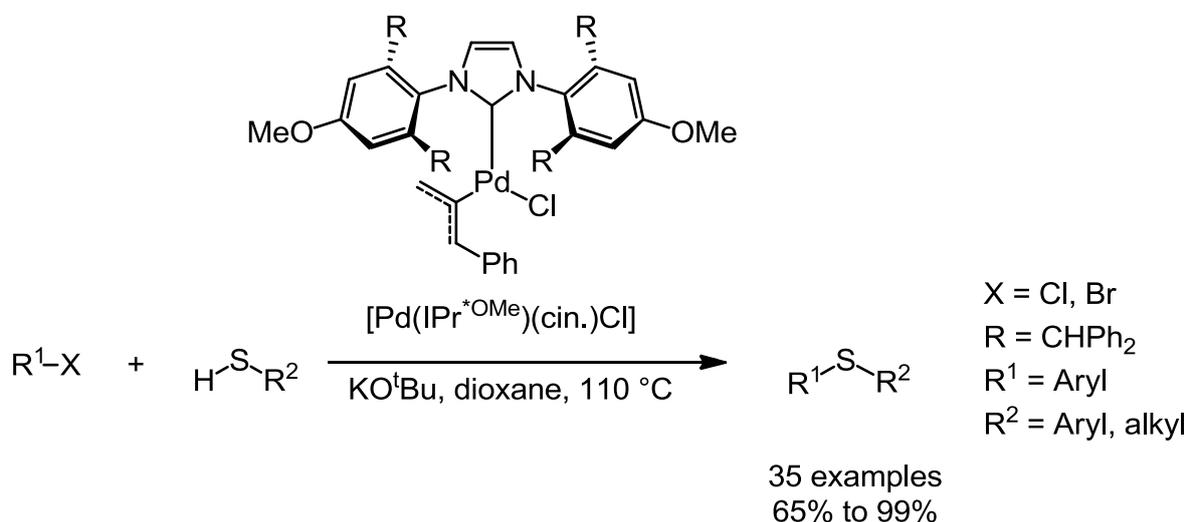
Figure 4 - Dimerization of persistent carbenes (the Wanzlick Equilibrium).

NHC ligands that have alkyl substituents (as shown on the right of Figure 2), except for the stable carbene ligand firstly isolated by Arduengo,⁵⁷ are generally still slightly unstable and cannot be isolated and stored as the free carbene, due to dimerization. This problem can be eliminated by forming the free carbene *in situ* before it is complexed to a palladium source. The free carbene can be formed *in situ* starting from the very stable imidazolium salt precursor by deprotonation using a suitable base as first achieved by Arduengo in 1991.⁵⁷ NHC ligands that contain aryl substituents (as shown on the left of Figure 2) are even more stabilised by the further conjugation of these aromatic groups. These ligands can be isolated and stored since the free carbene is even more stabilized by further conjugation provided by these substituents. These aryl substituted NHC ligands can be made as bulky as the alkyl substituted NHC ligands, such as the adamantyl substituted NHC ligands, by increasing the size of the R groups *ortho* to the nitrogen. Since the successful isolation of nucleophilic carbenes, they have investigated extensively in the beginning of the 21st century by various research groups, such as Nolan and co-workers,^{8,24–27,35,36,38} to their roles pertaining to ancillary ligands for metal catalysts. The most potent NHC ligand reported by Nolan and co-workers,²⁴ IPr^{*OMe} (as shown in Scheme 7), is an even more nucleophilic than all other NHC ligands due to the resonance of electrons of the para-substituted methoxy groups, which pushes electrons onto the imidazole ring, making the carbene itself more electron-rich.

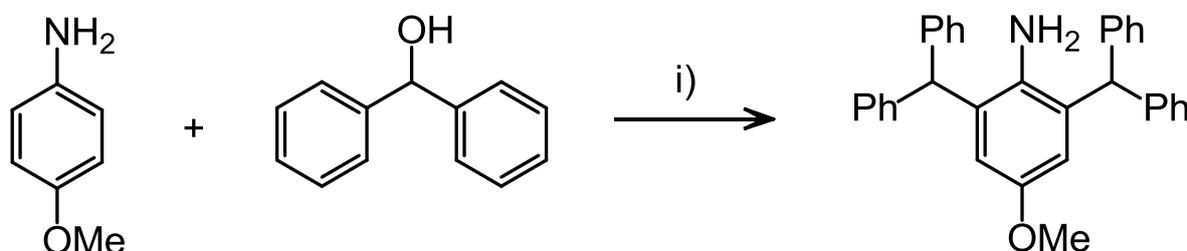
3.2.3.3 Investigation into Sulphur-Coupling via Palladium-NHC Catalytic Complexes

Synthesis of IPr*OMe

The synthesis of the IPr*OMe NHC ligand, to be used in the coupling of large sulphur functionalities onto the upper rim of the resorcinarene, was attempted as reported by Nolan and co-workers.²⁴ This ligand, when complexed to palladium, is able to facilitate carbon-sulphur bond formation on a wide variety of organic substrates, as reported by Bastug and Nolan⁸ (Scheme 7), however the synthesis of this ligand was not as simple as it was reported as many problems were encountered.



Scheme 7 - Thiol coupling as reported by Bastug and Nolan.⁸



Scheme 8 - Dialkylation of p-anisidine with diphenylmethanol.²⁴ Reagents and conditions: i) diphenylmethanol (2 equiv.), ZnCl₂ (0.5 equiv.) in conc. HCl(aq) (1 equiv.), 160 °C, 30 min.

The first step of the synthesis (Scheme 8) proved to be very problematic, difficult to control and time consuming, which thwarted attempts in synthesizing the desired compound in good yields and decent purity. Nolan and co-workers reported yields up to 90% for the first step of the synthesis of the IPr^{OMe} NHC ligand, a mere maximum yield of 18% was obtained for this reaction after numerous purifications via recrystallization, however it should be noted that the obtained yield was more of a minimum yield as there was still product remaining in the crude mixture as indicated by TLC analysis. The ^1H NMR spectrum obtained from the recrystallized product (Figure 5) contained all the signals that was expected and was devoid from impurities (as compared to the spectrum provided by the crude mixture which made characterization impossible). TLC analysis showed the formation of at least three new compounds along with residual starting material that appeared very faint. TLC analysis also indicated that separation of the products by column chromatography would be problematic as co-elution would most likely occur due to the similar polarities of the products. Column chromatography was attempted nonetheless and as suspected co-elution occurred. It was suspected that the unwanted side-products were forming due to the high reaction temperature, taking into to consideration the short reaction time. Therefore the reaction was attempted at lower temperatures and for longer times; however the reaction seem to be considerably inhibited when the reaction temperature was dropped below $100\text{ }^\circ\text{C}$. Reactions performed at lower temperatures suggested that better control over the products was possible, however the reaction seemed to be very slow which suggest that perhaps the intermediate or transition state is highly energetic and requires high temperatures to be attained.

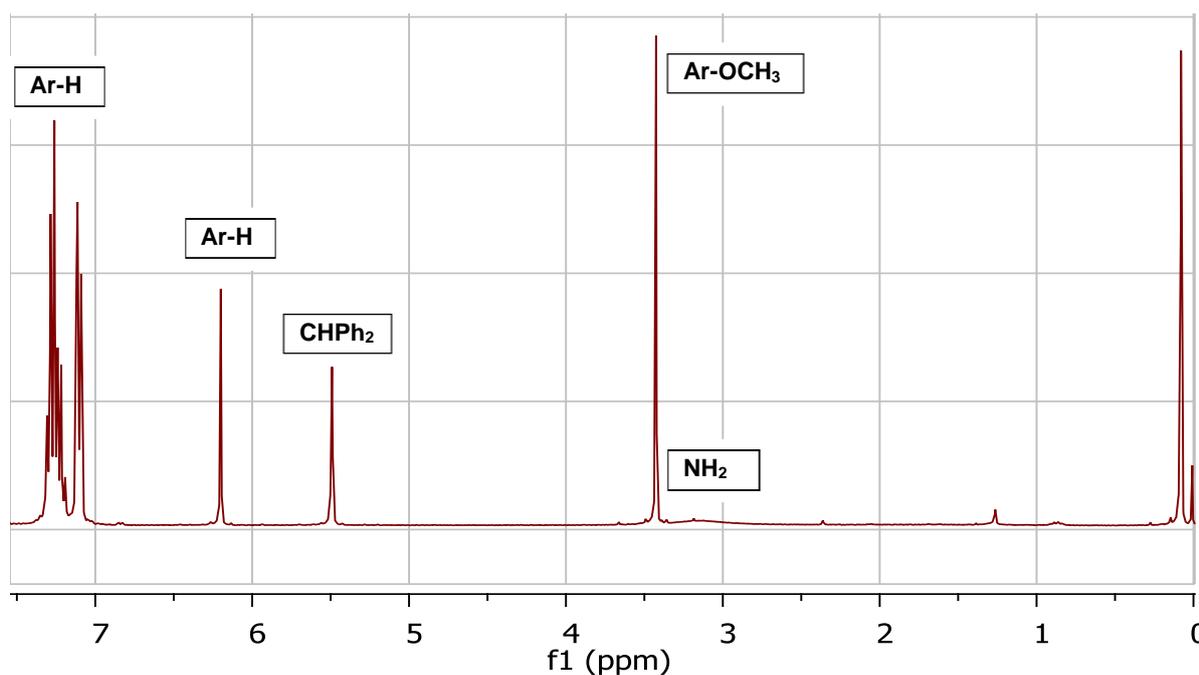


Figure 5 - ^1H NMR spectrum of the pure desired product isolated from the reaction depicted in Scheme 8.

A reaction was conducted at 160 °C and was monitored over the duration of one hour, sampling in 30 minute intervals. After the first half hour TLC analysis showed three new compounds that appeared very dark all of which were very similar in polarity. It is evident that control is a problem in this reaction at such high temperatures. A similar experiment was conducted at 60 °C for two hours, sampling in one hour intervals. After two hours TLC analysis indicated two of the three compounds previously produced by the reaction. The compounds appeared very small and faint on TLC and no clear indication could be seen for diphenylmethanol, however p-anisidine appeared very dark and prominent on TLC. After 24 hours at 60 °C, TLC analysis of the reaction mixture showed p-anisidine to be still quite prominent and the new compounds appeared to be a bit darker but still seemed very faint. Also the missing third compound seemed to become more prominent but still much more faint than the other two compounds. Better recoveries were obtained for reactions done at lower temperatures, reactions done at 160 °C usually returned a recovery of usually 50-60% of the crude whereas reactions done at 60 °C returned a recovery of about >80%.

Table 1 - Summary of the results obtained for the reaction outlined in Scheme 8.

Acid	Molarity of acid (M)	Equiv. of Acid	Equiv. of ZnCl ₂	Reaction Temperature (°C)	Time (hours)	Result
HCl(aq)	12	2.0	1.0	0	48	Starting material
HCl(aq)	12	2.0	1.0	30	24	Mixture of products + mostly starting material
HCl(aq)	12	2.0	1.0	40	24	Mixture of products + mostly starting material
H ₂ SO ₄	conc.	1.0	0.5	40	15	Mixture of products + mostly starting material
HCl(aq)	12	1.0	0.5	60	24	Mixture of products + mostly starting material
H ₂ SO ₄	conc.	1.0	0.5	60	1	Mixture of products + mostly starting material
H ₂ SO ₄	conc.	2.0	1.0	80	1	Mixture of products + mostly starting material
H ₂ SO ₄	conc.	1.0	0.5	110	1	Mixture of products + starting material
HCl(aq)	12	1.0	0.5	140	6	Mixture of products
HCl(aq)	10	1.0	0.5	160	0.33	Mixture of products
HCl(aq)	12	1.0	0.5	160	0.33	Mixture of products
HCl(aq)	10	1.0	0.5	160	0.5	Mixture of products
HCl(aq)	12	1.0	0.5	160	0.5	Mixture of products
HCl(aq)	10	1.0	0.5	160	1	Mixture of products
HCl(aq)	12	1.0	0.5	160	1	Mixture of products
HCl(aq)	12	1.0	0.5	160	2	Mixture of products
HCl(aq)	12	2.0	1.0	160	15	Mixture of products

Zinc(II)chloride, along with HCl(aq), is used to interact with the secondary alcohol substituent of diphenylmethanol in order to convert it into a better leaving group. However the Lewis acid can also co-ordinate to the methoxy substituents as well and in effect could render the positions adjacent to this group less nucleophilic rendering the *ortho*-positions next to amine functionality activated for nucleophilic substitution. Even though ZnCl₂ is known to be more oxaphilic than azaphilic, it might be possible for ZnCl₂ to co-ordinate to the amine group and even the methoxy group as well. This could result in the possible alkylation of any of the unsubstituted positions on the aromatic ring resulting in a mixture of regioisomers of both mono- and disubstituted products (Figure 6), especially in the cases where one equivalent of ZnCl₂ was used (Table 1).

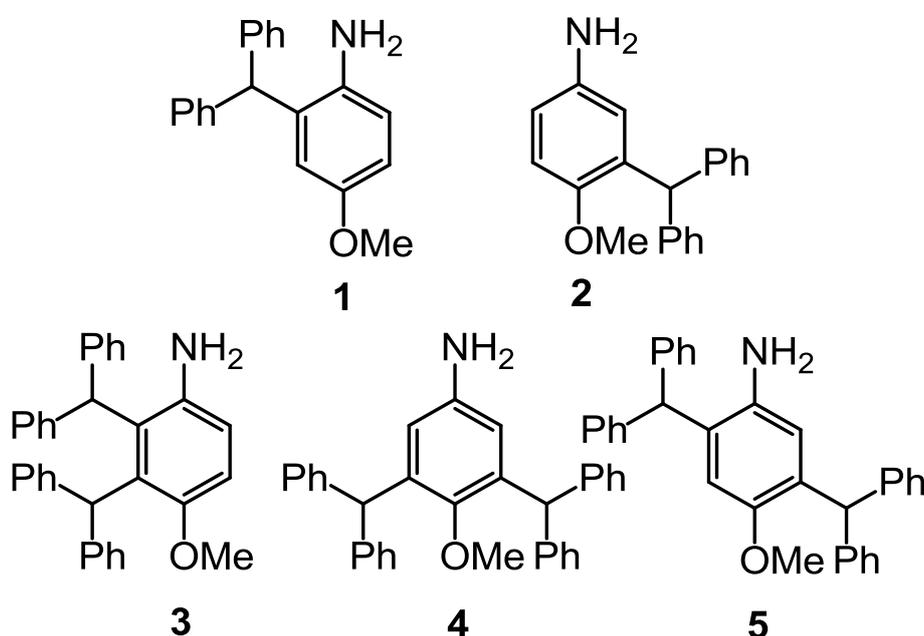
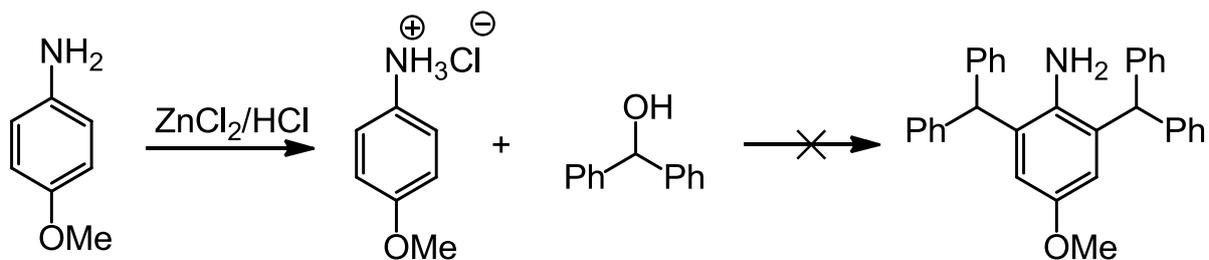


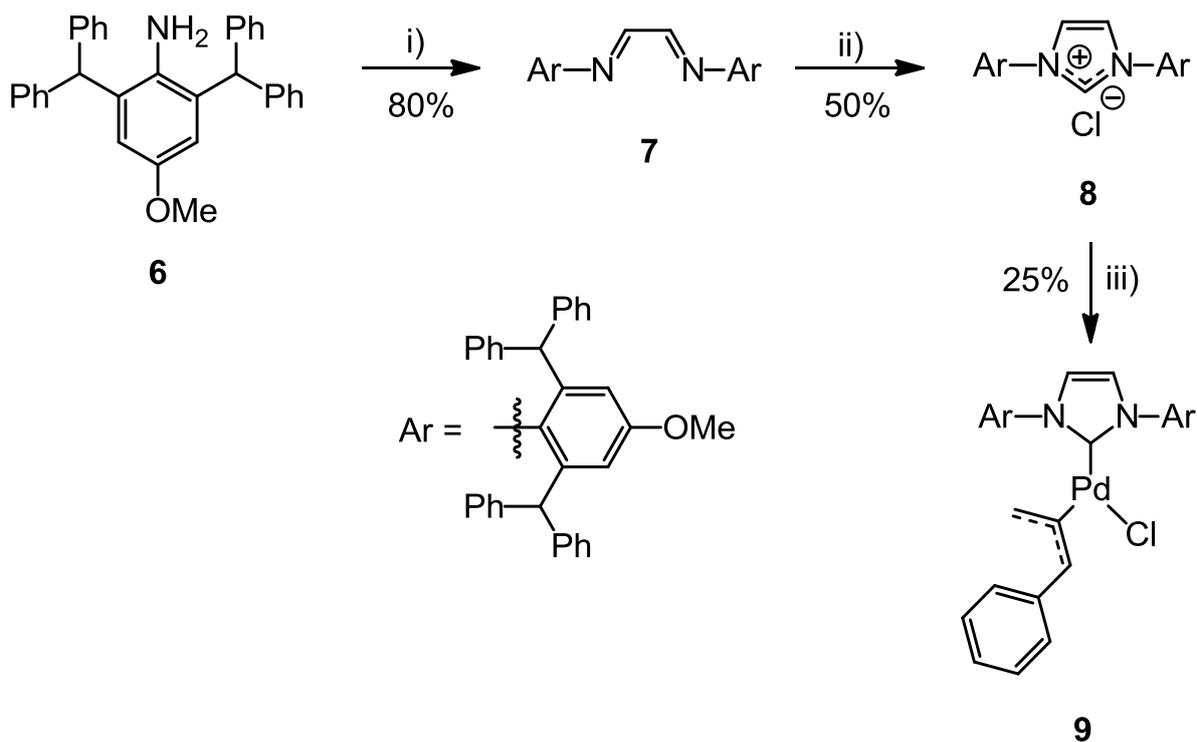
Figure 6 - Possible products produced by the reaction in Scheme 9.

Molecules **4** and **5** (Figure 6) are speculated to be the most probable regioisomers produced by the reaction as seen on TLC as **3** is an unlikely product due to the steric hindrance brought about by neighbouring bisphenyl substituents. In one case, the hydrochloric acid would instead react with p-anisidine to form the hydrochloric salt of the aniline instead of protonation of the alcohol. This completely inhibits the reaction from occurring as there is no longer a lone pair of electrons available on the nitrogen, which is needed to resonate into the aromatic ring to activate the positions *ortho* to the amine (Scheme 9). An attempt was made to control the reaction by heating the p-anisidine in the presence of ZnCl₂ and mixing the alcohol along with hydrochloric acid separately prior to adding it to the p-anisidine/ZnCl₂ liquid; this also seemed to have no difference on the results obtained.



Scheme 9 - Formation of the hydrochloric salt of p-anisidine, inhibiting the desired reaction from occurring.

The use of a stronger proton source (sulphuric acid) had an adverse effect as in some rare cases it seemed the sulphuric acid stripped off the methoxy substituent as the signal completely disappeared in the proton NMR spectrum. The synthesis also involves a step where the reaction mixture is placed under high vacuum at the mentioned reaction temperature, which was assumed to remove the water by-product from the reaction. This step could possibly promote the formation of unwanted side and degradation products as the very low pressure in combination with the high temperature are extreme reaction conditions and it is also unclear whether the reaction is completed within the stipulated time. However, when skipping this step no difference was observed on TLC. In order to synthesize enough of the product to carry on with the next step of the synthesis, the reaction was done on large scale. The rest of the synthesis in producing the IPr^{*OMe} NHC ligand was not as troublesome as the first step and was found to be satisfactorily reproducible (Scheme 10). The products that were synthesized were all purified by recrystallization and were not as tedious as the recrystallization process for the product synthesized from the first step of the reaction. The products that were isolated (as depicted in Scheme 10) provided the correct ¹H NMR spectra that were devoid of impurities with the exception of residual solvent signals. The ¹H NMR spectrum of the diimine (Figure 7) showed the disappearance of the amine signal at about 3.3 ppm that was present in the starting material (Figure 5) and it was therefore evident that the reaction was a success. The ¹H NMR spectrum of the salt (Figure 8) showed the presence of the acidic imidazolium proton attached to the carbon atom that is bonded to the two nitrogen atoms at about 13 ppm, which was an indication that the reaction was successful. Furthermore the ¹H NMR spectrum of the final compound (Figure 9), Pd(IPr^{*OMe})(cin.)(Cl), exactly matched the literature.²⁴ Also note that the imidazole backbone protons (annotated as N-CH=CH-N) experienced a significant downfield shift from being a part of the aromatic region (Ar-H signals) to a chemical shift of about 5.3 ppm, which is an indication of successful complexation of the imidazole carbene to the palladium centre.



Scheme 10 - Synthesis of Pd(IPr^{*OMe})(cin.)(Cl) (9). Reagents and conditions:
 i) aniline (**6**) (2.0 equiv.), MgSO₄ (4.2 equiv.), glyoxal (40% in H₂O, 1.0 equiv.), formic acid (0.3 equiv.), r.t., DCM, 4 days.
 ii) diimine (**7**) (1.0 equiv.), ZnCl₂ (1.0 equiv.), p-formaldehyde (1.0 equiv.), HCl in dioxane (4.5M, 1.5 equiv.), THF, 75 °C, 2 hours.
 iii) IPr^{*OMe}-HCl (**8**) (1.0 equiv.), KOtBu (1.5 equiv.), THF, r.t., 4 hours; [Pd(cin.)(μ-Cl)]₂ (0.5 equiv.), r.t., overnight.

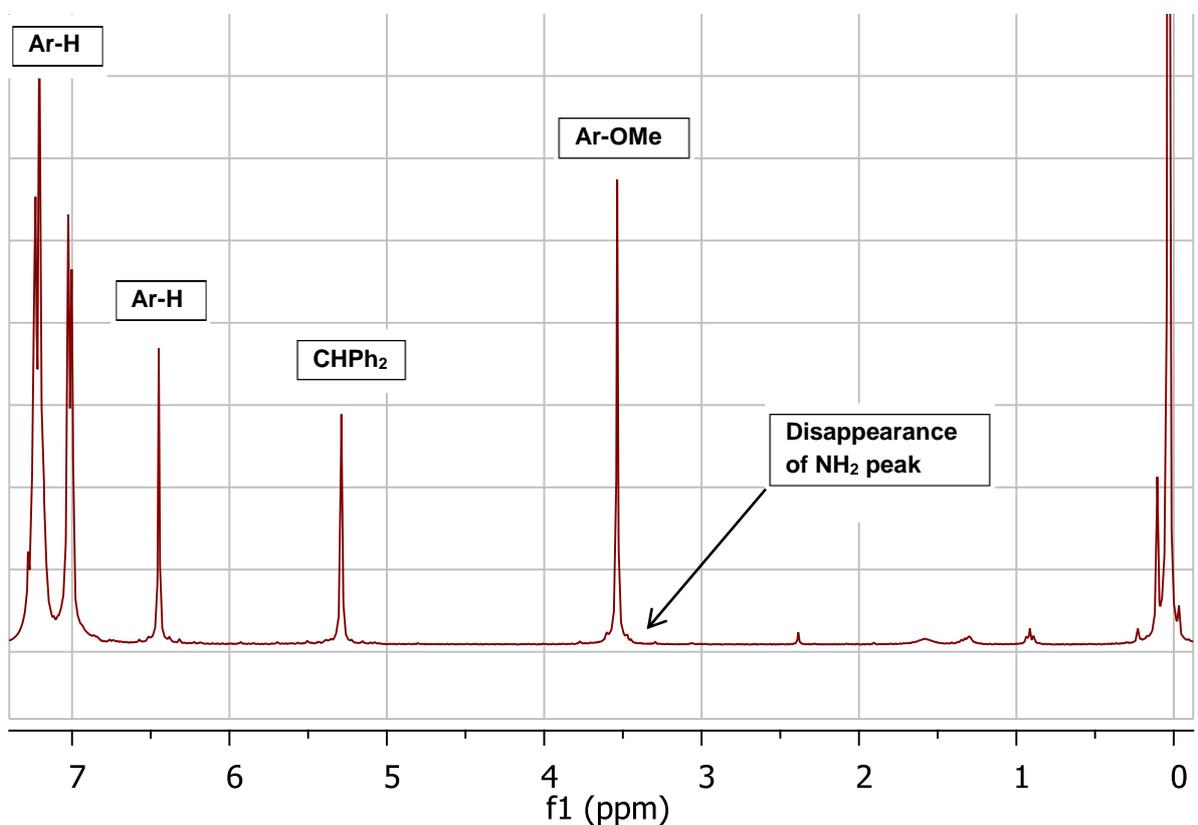
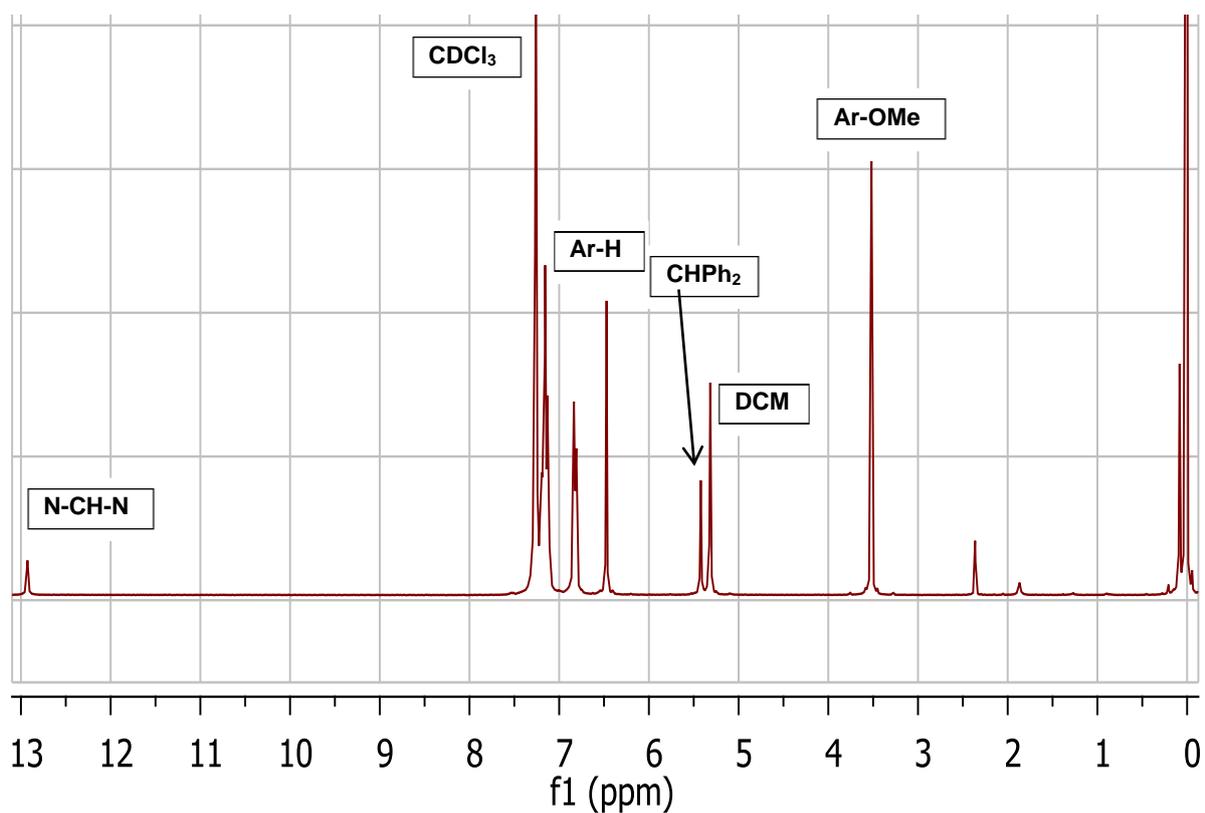
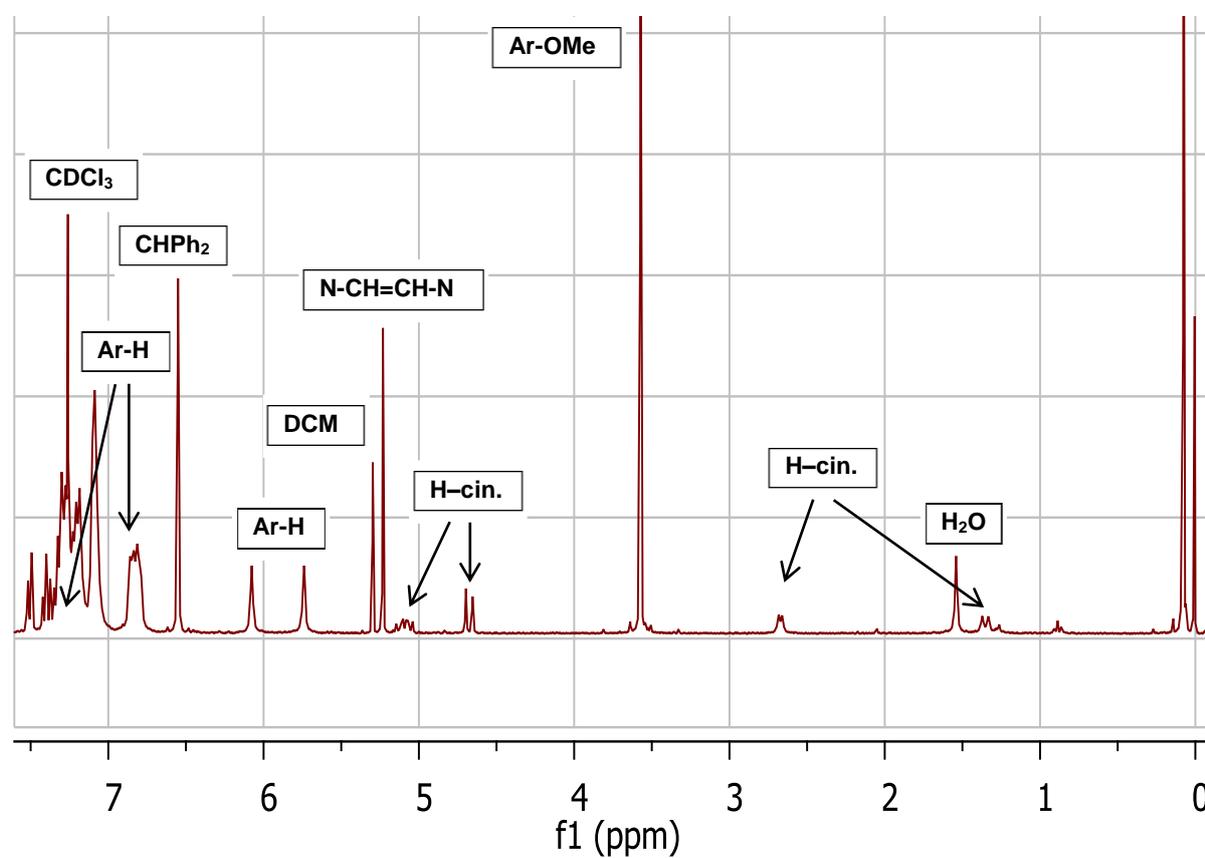
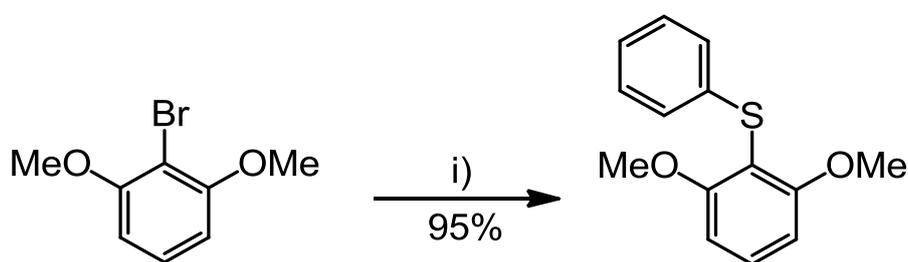


Figure 7- ¹H NMR spectrum of diimine (**7**).

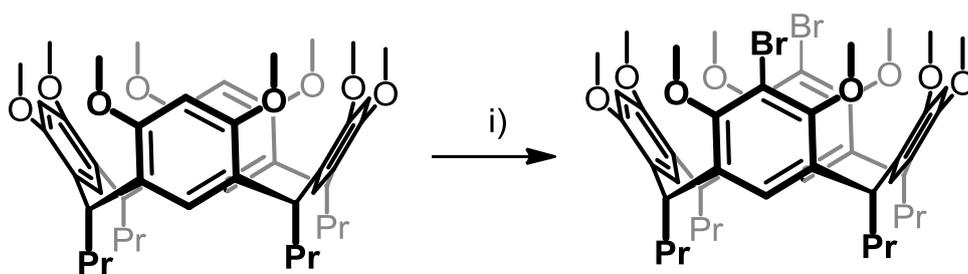
Figure 8 - ^1H NMR spectrum of imidazolium salt (8).Figure 9 - ^1H NMR spectrum of $\text{Pd}(\text{IPr}^{\text{OMe}})(\text{cin.})(\text{Cl})$ (9).

After the ligand was synthesised and complexed with a palladium source, i.e. $[\text{Pd}(\text{cin.})(\text{Cl})]_2$ dimer, the air- and moisture-insensitive catalytically active species $\text{Pd}(\text{IPr}^{\text{*OMe}})(\text{cin.})(\text{Cl})$ was finally synthesised. The low yield that was established in the formation of the catalytic palladium species can be attributed to fact that unsublimed and slightly wet potassium *tert*butoxide (KOtBu) was used. The coupling of thiophenol with the arylhalide model compound, 2-bromo-1,3-dimethoxybenzene using KOtBu as base, that was purified by sublimation prior to use, was tested in order to determine if the catalyst is as efficient as the literature suggests (Scheme 11). The coupling was successful and yielded a near quantitative yield of the product at a catalyst loading of 0.2 mol%.



Scheme 11 - Coupling of 2-bromo-1,3-dimethoxybenzene with thiophenol in the presence of $\text{Pd}(\text{IPr}^{\text{*OMe}})(\text{cin.})(\text{Cl})$.
 Reagents and conditions: thiophenol (1.2 equiv.), KOtBu (2 equiv.), $\text{Pd}(\text{IPr}^{\text{*OMe}})(\text{cin.})(\text{Cl})$ (0.2 mol%), 1,4-dioxane, reflux.

After it was established that the catalyst was active and efficient, the coupling of thiophenol onto a distal dibromo resorcinarene scaffold was attempted using twice as much catalyst loading as used for the model system. The distal dibromo resorcinarene was synthesised via the ortholithiation approach by quenching with 1,2-dibromoethane (Scheme 12). The ^1H NMR spectrum that was obtained of the product (Figure 10) after purification by column chromatography revealed slight differences when compared to reference spectrum that was previously synthesised by Ngodwana⁷⁰ (Figure 11). The ^1H NMR spectrum that was obtained of the dibromo resorcinarene showed splitting of the individual methoxy signals into two overlapping signals, which indicated that the compound was not pure and that we possibly had a mixture between monobromo and distal dibromo resorcinarene with a small amount of residual starting material. This was confirmed by mass spectrometry (Figure 12). However, the fact that a mixture of mono-, dibromo resorcinarene and starting material was obtained would not affect the results of the coupling reaction as the resorcinarene sample was (mostly) derivatised as an aryl bromide, regardless if a mixture of brominated products were obtained and used within the coupling reaction. Furthermore, the two sets of lower rim aromatic protons (annotated as Ar-H in Figure 10) appeared to be overlapping as well, whereas in the reference spectrum (Figure 11) they appear to have a separation of about 0.2 ppm.



Scheme 12 – Synthesis of the distal dibromo resorcinarene by means of i) ortholithiation conditions.

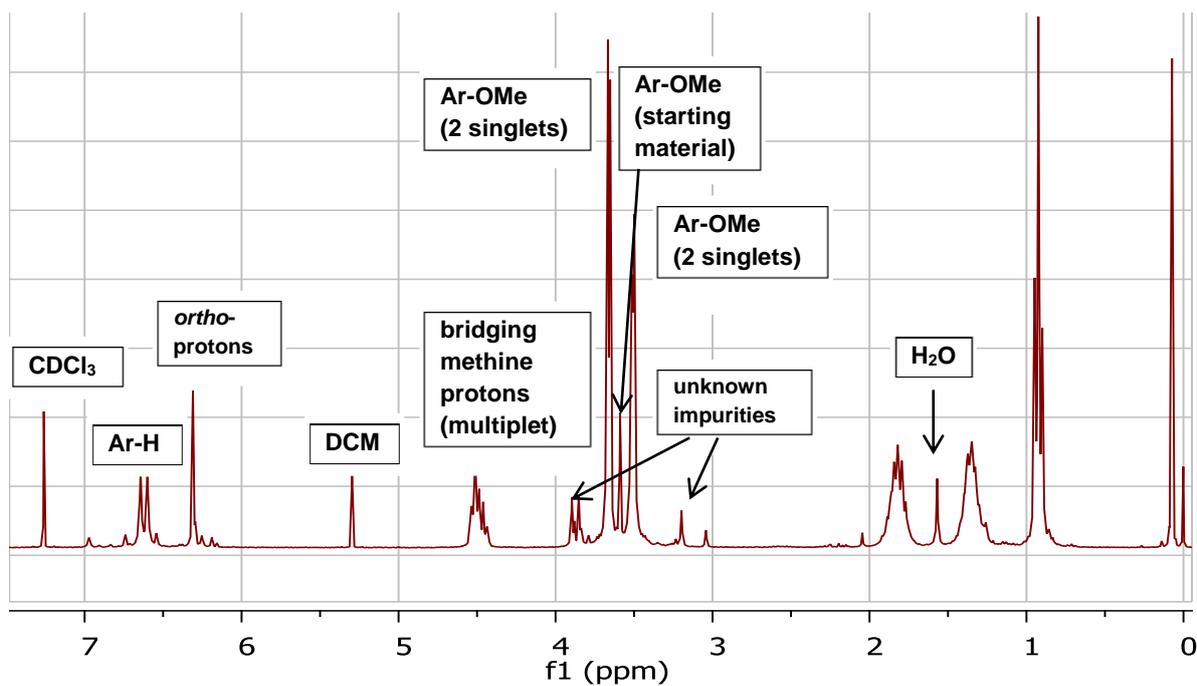


Figure 10 – ^1H NMR spectrum of the product that was obtained as depicted in Scheme 14 (after purification).

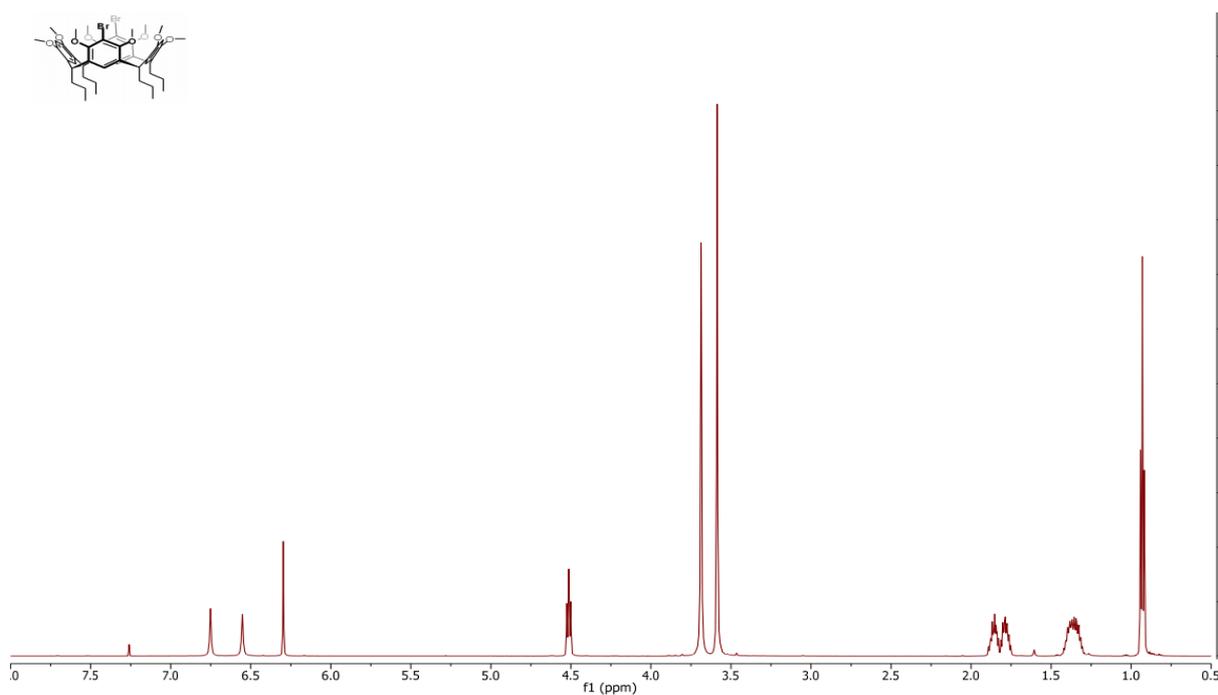


Figure 11 – ^1H NMR spectrum of distal dibromo resorcinarene obtained by Ngodwana (reproduced from reference 70).

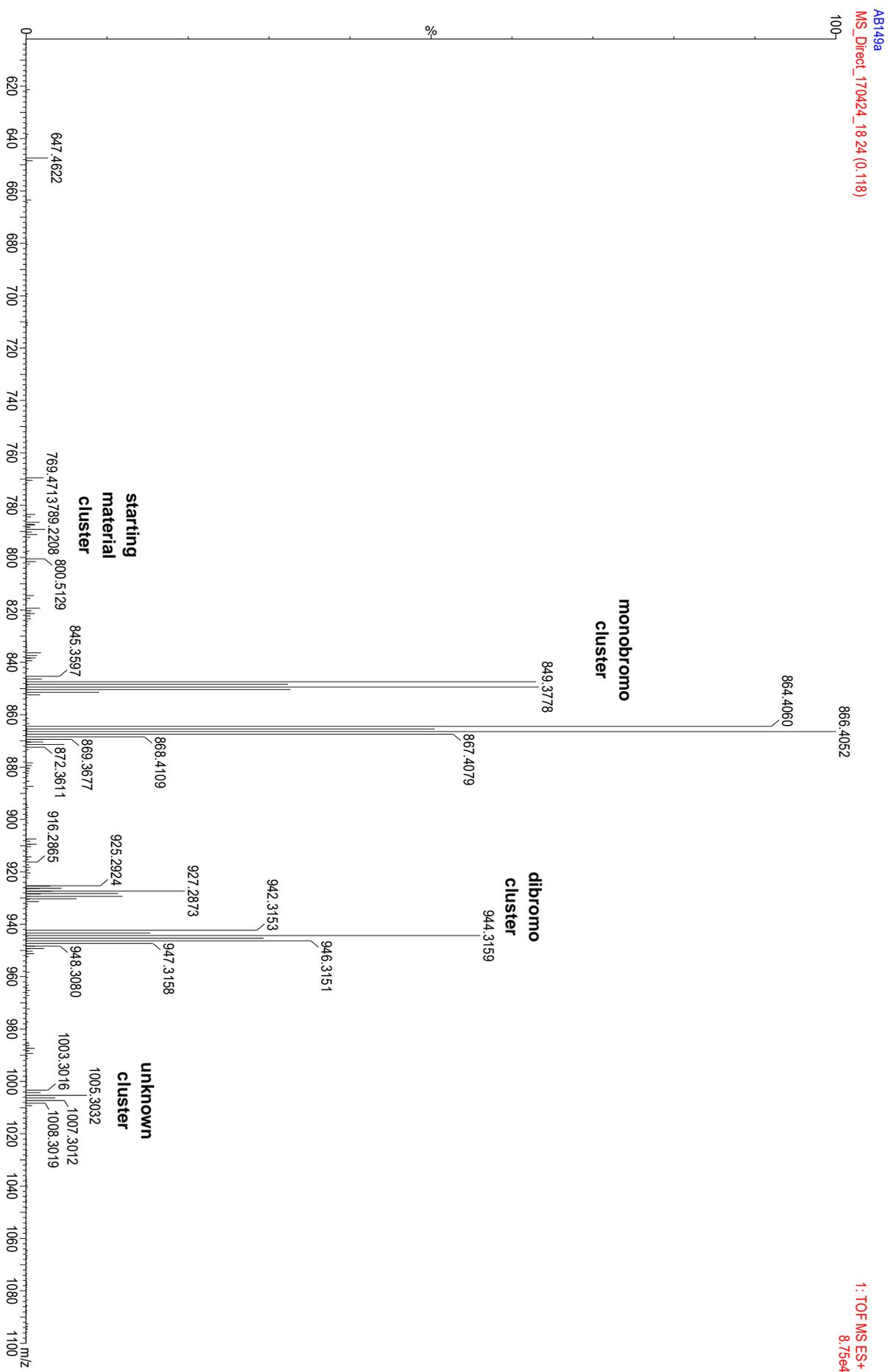
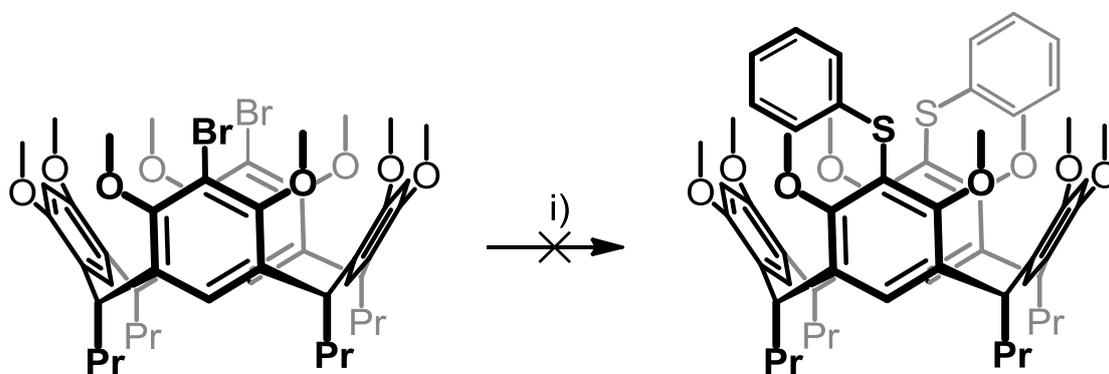
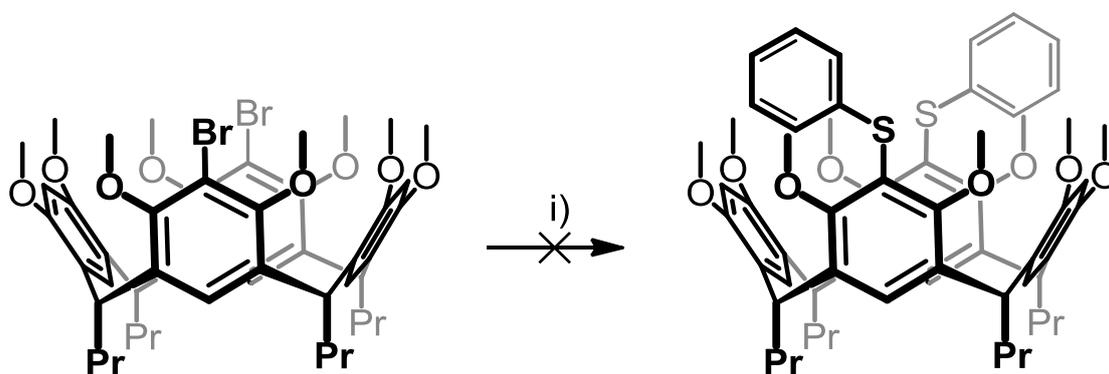


Figure 12 – Mass spectrum of the product of the reaction depicted in Scheme 14 (mono- and dibromo).

The molecular ion signal of 769 amu belongs to starting material (low abundance), whereas the cluster of signals centred around 849 to 872 amu belongs to the monobromo product and the cluster of signals centred around 927 to 948 amu belongs to the dibromo product. Furthermore an unknown cluster of peaks can be seen at 1005 amu. The coupling was then attempted on the mixture of brominated resorcinarenes (mono and distal) using twice as much catalyst loading. Unfortunately, after 24 hours, only starting material was recovered from the reaction (Scheme 12). The reaction was then re-attempted and the reaction was left for three days and with a catalyst loading of 5 mol%, however the result did not differ and unfortunately the catalyst seemed to be unable to perform the coupling on the resorcinarene scaffold (Scheme 13).



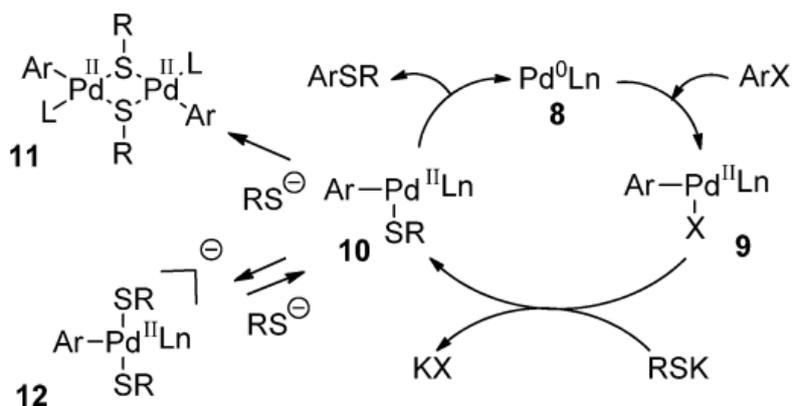
Scheme 12 – Attempted synthesis of distal diphenyl thioether resorcinarene via palladium catalysis.
Reagents and conditions: i) KOtBu (2.5 equiv.), Pd(IPr^{*OMe})(cin.)(Cl) (0.2 mol %), thiophenol (2 equiv.), reflux, 1,4-dioxane, 24 hours.



Scheme 13 – Attempted synthesis of distal diphenyl thioether resorcinarene via palladium catalysis.
Reagents and conditions: i) KOtBu (2.5 equiv.), Pd(IPr^{*OMe})(cin.)(Cl) (5 mol %), thiophenol (2 equiv.), reflux, 1,4-dioxane, 3 days.

3.3 Conclusions

The investigated routes of the attempted synthesis of a distal phenyl thioether resorcinarene ligand via copper and palladium catalysis proved unsuccessful. In the case of copper little conversion is seen for the starting materials for the model compound. Palladium proved very successful in the coupling of the model compound, but proved unsuccessful in coupling the pre-functionalised distal dibromo resorcinarene. It was speculated that the combination of resorcinarene and the NHC ligand results in too much steric hindrance around the palladium centre, hindering the palladium from inserting itself into the carbon-halogen bond. With the oxidative addition step being hindered in this way, the catalyst cannot continue the catalytic cycle (Scheme 14). It is also possible that too much steric hindrance exists between the phenyl thioether functionality and the adjacent methoxy groups (Scheme 14). The result from the attempted synthesis of this resorcinarene ligand by means of the ortholithiation method also supports this reasoning and could be the reason why this transformation is not possible on the resorcinarene.



Scheme 14 - Simplified catalytic cycle (reproduced from reference 8).

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Chapter 4

Conclusions and Future Work

4.1 Conclusions

Firstly, the use of the ortholithiation method in the synthesis of thioether resorcinarene using disulphides as electrophiles is only possible when using the less sterically hindered dimethyl disulphide. It should be mentioned that disulphide homologues smaller than *tert*-butyl disulphide but larger than dimethyl disulphide, such as diethyl disulphide or diisopropyl disulphide, were not investigated. Furthermore the use of benzenesulfonyl chloride remains inconclusive in the attempted synthesis of the phenyl thioether resorcinarene ligand via the ortholithiation approach as it was discovered afterwards that the electrophile was not pure. Diphenyl disulphide was not tested within the ortholithiation procedure as the chemical was not available within our chemical stores and furthermore we wanted to investigate the compatibility of the ortholithiation procedure with other types of sulphur-derived electrophiles. However, diphenyl disulphide should be tempted within the future work of this project as the electrophile is not as bulky as di-*tert*-butyl disulphide and furthermore the phenylthiolate anion is a good leaving group due to the fact that the negative charge imparted on the sulphur atom can resonate within the aromatic ring. If the results from the use of pure benzenesulfonyl chloride as well as diphenyl disulphide within the ortholithiation procedure with the resorcinarene turn out negative then alternative strategies have to be considered and investigated in the attempt of installing phenyl and *tert*-butyl thioether functionalities onto the *ortho*-position of the resorcinarene (in a distal fashion).

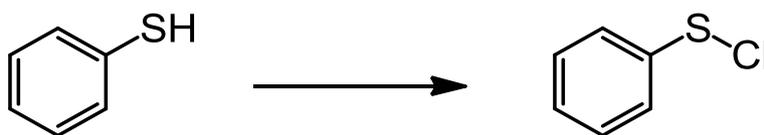
Secondly, the use of catalysts seemed promising when considering the sulphur-coupling of a model system, but deemed unfit when considering macrocycles such as resorcinarenes. It has been speculated that the catalytic centre becomes too sterically hindered, hindering complexation of the already very sterically hindered catalytic species to a large macrocycle or that too much steric hindrance exists between phenyl- and *tert*-butyl thioether on the *ortho*-position and the neighbouring methoxy substituents.

4.2 Future Work

Future work for this study mostly includes work that either remains unfinished or as potential ideas that could not be completed within the duration of this project due to time constraints. They include re-investigation of other sulphur-derived electrophiles to be used within the ortholithiation procedure, cavitands starting materials, and the use of sulphur reagents as

nucleophiles (**please refer to Addendum A**). Also the re-investigation into the use of less sterically demanding palladium catalysts should be explored as a wide variety of different palladium mediated coupling reaction exist within literature.

4.2.1 Benzenesulphenyl Chloride



Scheme 1 - Synthesis of benzenesulphenyl chloride.¹ Reagents and conditions: NCS (2.0 equiv.), DCM, 0 °C to r.t., 30 min.

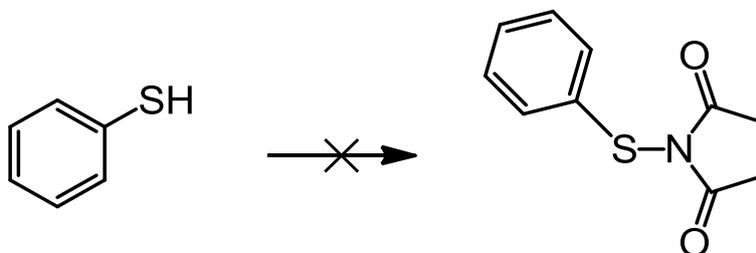
As mentioned in Chapter 2, the synthesis of benzenesulphenyl chloride by thiophenol and N-Chlorosuccinimide (NCS) provided poor selectivity in producing the desired compound (Scheme 1).¹ Other compounds were seen on TLC when performing the reaction again when trying to obtain a ¹H NMR spectrum of the electrophile. However, 1,3-dimethoxybenzene successfully reacted with benzenesulphenyl chloride, albeit in poor yields, even though electrophile was not pure and theoretically similar results should have been obtained when reacting the impure electrophile with the resorcinarene scaffold in the ortholithiation approach, which was not the case. Therefore, the reaction should be attempted again with pure benzenesulphenyl chloride in order to ascertain if this electrophile is compatible with the resorcinarene scaffold in the ortholithiation procedure. This can be done by performing the synthesis of benzenesulphenyl chloride on a larger scale (for example two grams of starting material) and purifying the crude reaction mixture thereafter by column chromatography, which has shown to be quite feasible but due to time constraints the use of the pure electrophile within the ortholithiation was not investigated thereafter.

4.2.2 Other-Sulphur Electrophiles

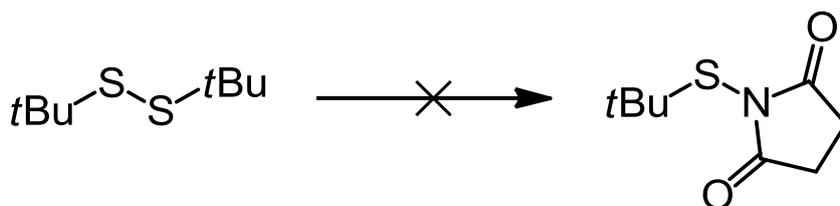
The investigation into other sulphur-derived electrophiles were investigated with the idea of replacing the poorer leaving group, the thiolate anion, with a better leaving group, such as a succinimide- or sulfonate-group, would bring about better results when using these electrophiles in the ortholithiation procedure. A chlorine atom serves as the best leaving group, which can be used within the ortholithiation procedure, as the chlorine atom is both a good leaving group as well as provides the least amount of steric hindrance about the sulphur atom. (**please refer to Addendum A**).

4.2.2.1 Thiosuccinimides

The synthesis of thiosuccinimides remained unsuccessful as only starting material was isolated from these reactions (Scheme 2 and 3). However they should be reinvestigated as these reactions were only performed in duplicate within the course of this study.



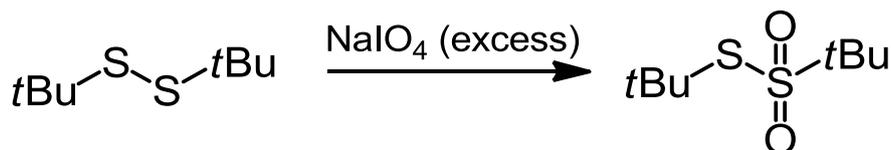
Scheme 2 – Attempted synthesis of phenylthiosuccinimide reported by Abe and co-workers.²
Reagents and conditions: i) NCS (1.1 equiv.), benzene, r.t.; ii) Et₃N (1.2 equiv.), 0°C to r.t.



Scheme 3 - Attempted synthesis of *tert*-butylthiosuccinimide reported by Büchel and co-workers.³
Reagents and conditions: NBS (1 equiv.), benzene, reflux, 2 hours.

4.2.2.2 Thiosulfonates

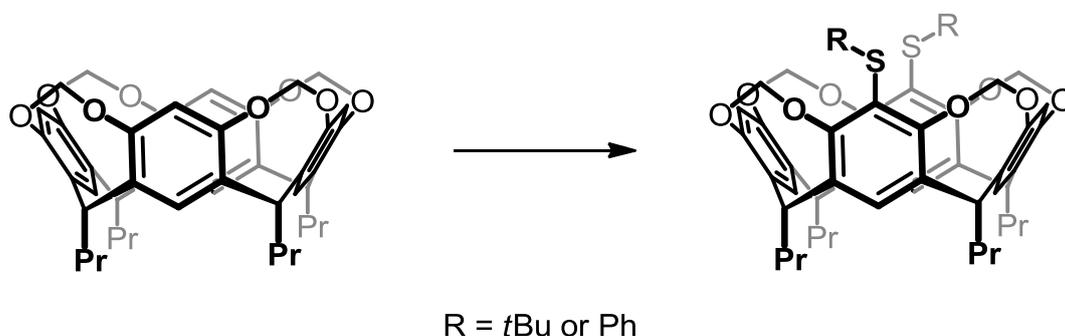
The attempts of synthesizing *tert*-butylthiosulfonate returned the thiosulphoxide as the major product and the desired thiosulfonate as a minor product amongst others. Oxidation with a stronger oxidizing agent such as NaIO₄ in excess could possibly render the desired thiosulfonate (Scheme 4).⁴



Scheme 4 - Possible route towards the synthesis of *tert*-butylthiosulfonates.

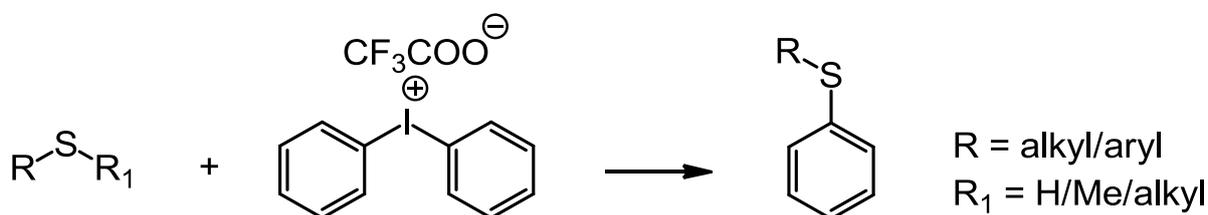
4.2.3 'Propyl-footed' CavitanDs

CavitanDs (rigid resorcinarenes that have bridges between neighbouring phenolic positions) should have less steric hindrance between the bridged phenolic functionalities and the *ortho*-position. The protected ether groups, which are methylene groups in this case, are locked into position and are kept from rotating within the vicinity *ortho*-position. Therefore the coupling of the phenyl- and *tert*-butyl thioether functionalities onto the *ortho*-positions of the resorcinarene should be tested on the 'propyl-footed' cavitanDs as this may ascertain whether steric hindrance between the methoxy groups and the thioether functionality to be the culprit as why these functionalities cannot be installed on the flexible resorcinarene methyl ether scaffold (Scheme 5). If the syntheses of the target ligands are successful on the cavitanD scaffold then the cavitanDs can be transformed back into the flexible octamethoxy resorcinarene thereafter if desired.



Scheme 5 – Possible synthesis of phenyl- and *tert*-butyl cavitanDs ligands by i) ortholithiation or ii) catalysis.

4.2.4 Sulphur Nucleophiles



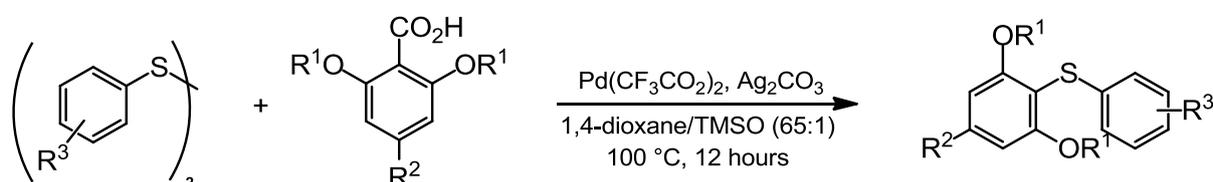
Scheme 6 - Synthesis of arylthioethers as reported by Wagner and Sanford.⁵ Reagents and conditions: TFA (8 equiv.), 1,4-dioxane, reflux, 15 hours.

Coupling of thioethers to diaryliodonium salts to form new thioethers (Scheme 6) were erroneously attempted with 2 equivalents of trifluoroacetic acid (TFA). These reactions should be investigated again since the literature mentions using the diphenyl trifluoroacetate

iodonium salt as the precursor and they reported optimal conditions of using 8 equivalents of TFA. Another suggestion would be to use the thiol version instead of the thioether as the thiol is more nucleophilic.

4.2.5 Catalysis

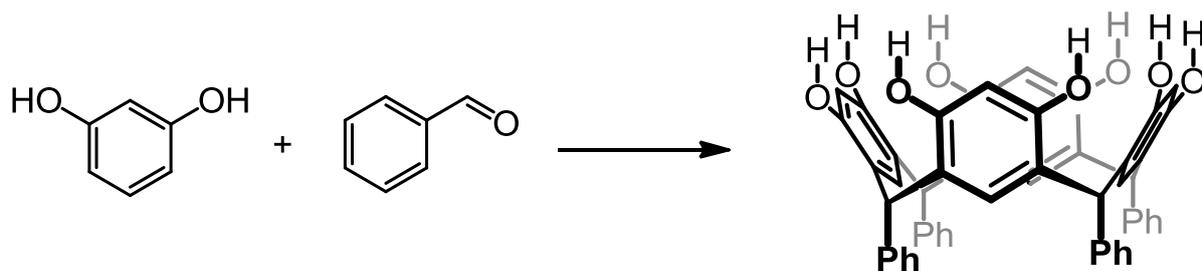
In 2011 Becht and Le Drian⁶ reported the coupling of diaryl sulphides with dialkoxybenzoic acids in the presence of palladium-silver catalytic system and the synthesis provides another means to couple thioether functionalities onto the *ortho*-position of the resorcinarene (Scheme 7). The synthesis has also reported the first example of successful coupling of carbon-selenium bonds.



Scheme 7 - Synthesis of arylthioethers as reported by Becht and Le Drian.⁶

4.2.6 'Phenyl-footed' Resorcinarenes

Our attempts at recrystallizing the 'phenyl-footed' resorcinarenes as reported by Högberg⁷ (Scheme 8) remain inconclusive, however it should be mentioned that ¹H, ¹³C NMR data and mass spectrometry data provides evidence that these macrocycles were successfully synthesized (**please refer to Addendum A**). Investigation into longer chained 'phenyl-footed' resorcinarenes should be investigated in producing more crystalline thioether resorcinarene ligand-metal complexes in the hopes of ascertaining the identity of the structures of the complexes of silver and nickel that were synthesised on the 'propyl-footed' methyl thioether resorcinarene ligands previously by Kleinhans.



Scheme 8 - Synthesis of 'phenyl-footed' resorcinarenes as reported by Högberg.⁷ Reagents and conditions: resorcinol (1 equiv.), benzaldehyde (1 equiv.), 32% HCl(aq) (2 equiv.), EtOH, reflux, overnight.

4.3 Discussion

Other types of sulphur-derived electrophiles (thiosuccinimides and thiosulfonates) were investigated, as well as the use of sulphur-nucleophiles in combination with electrophilic diaryliodonium salts to form thioethers. Unfortunately all of these routes were not thoroughly investigated due to time constraints (**please refer to Addendum A**). The route towards synthesizing more crystalline versions of thioether resorcinarene ligand-metal complexes via phenyl-tethered resorcinarene scaffolds was also halted due to time constraints and should be reinvestigated (**please refer to Addendum A**). Cavitands in combination with di-*tert*-butyl disulphide and benzenesulfonyl chloride within the ortholithiation procedure should be attempted as well as other types of catalysis routes.

4.4 References

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Chapter 5

Experimental

5.1 General Procedures

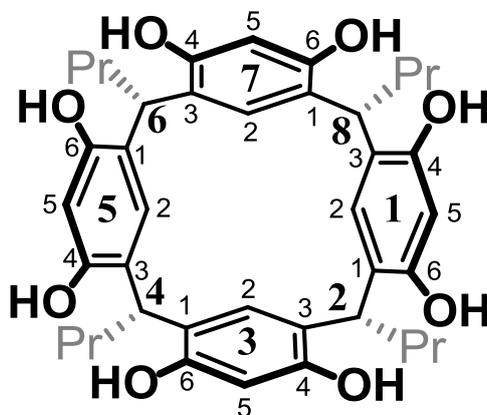
All chemicals used were acquired from Merck, Aldrich or Fluka. THF was dried over sodium wire and distilled under nitrogen with benzophenone as an indicator. 1,4-Dioxane was dried over sodium and distilled under nitrogen. Dichloromethane and acetonitrile were distilled over anhydrous calcium hydride under nitrogen. The molarity of *n*-butyllithium (*n*BuLi) was determined by titration with *N*-benzylbenzamide, or with menthol and bipyridine as indicator, in anhydrous THF. Other reagents were purified according to standard procedures within the literature. All reactions were performed under an atmosphere of argon, unless stated otherwise. Low temperature reactions were performed in a Dewar using a slurry of dry ice in acetone ($-78\text{ }^{\circ}\text{C}$) or using a cryostat, ice in acetone or ethanol ($-20\text{ }^{\circ}\text{C}$), or ice in water ($0\text{ }^{\circ}\text{C}$). All ^1H and ^{13}C nuclear magnetic resonance data were obtained using a 300 MHz Varian VNMRS (75 MHz for ^{13}C) at $25\text{ }^{\circ}\text{C}$ and a spin of 20Hz. Chloroform-*d* or dimethylsulphoxide-*d*6 were used as standard solvents, unless stated otherwise. Chemical shifts (δ) were reported in ppm and determined using the residual chloroform peak (δ 7.26 in ^1H NMR and δ 77.0 in ^{13}C NMR) or the residual DMSO peaks (δ 2.50 in ^1H NMR and δ 39.5 in ^{13}C NMR). Flash chromatography was performed using an ethyl acetate-hexane mixture (EtOAc/hexane) as a mobile phase, and Fluka silica gel (230-400 mesh) as stationary phase. TLC was carried out on aluminium backed Merck silica gel 60 F₂₅₄ plates. Visualization was achieved using either (or a combination of) a UV lamp or dipping in CAM (Cerium Ammonium Molybdate) solution followed by heating. HRMS was conducted by CAF (Central Analytical Facility) at the University of Stellenbosch using a Waters API Q-TOF Ultima spectrometer.

5.1.1 Standard protocol for ortholithiation reactions:

Octamethoxy resorcinarene (**2**) was placed in a Schlenck vessel that has been cooled down under argon after being dried in a $100\text{ }^{\circ}\text{C}$ oven, before being dissolved in dry, freshly distilled tetrahydrofuran. The vessel was then fitted with a dry stirrer bar and heated to $40\text{ }^{\circ}\text{C}$ and *n*BuLi was added quickly and carefully and left to stir at $40\text{ }^{\circ}\text{C}$ for two to three hours. Thereafter the solution is cooled down to $-78\text{ }^{\circ}\text{C}$ and quenched with an electrophile and left to warm to room temperature and stirred overnight. Work-up involves quenching the solution with 1M of a hydrochloric acid solution and extraction into an organic phase with DCM. For all purposes, the protocol for ortholithiation reactions on the model compound (1,3-dimethoxybenzene) is almost identical to the standard protocol for ortholithiation on resorcinarenes, with the exception that the solution was cooled to $0\text{ }^{\circ}\text{C}$ before being quenched with an electrophile and the number of equivalents of alkyllithium used was halved.

5.2 Compounds

1⁴,1⁶,3⁴,3⁶,5⁴,5⁶,7⁴,7⁶-Octahydroxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane (1)¹



Resorcinol (5.51 g, 50.0 mmol, 1 equiv.) was suspended and stirred in anhydrous dichloromethane (250 mL). The solution was then cooled to $-20\text{ }^{\circ}\text{C}$ followed by the addition of butanal (4.40 mL, 50.0 mmol, 1 equiv.). Boron trifluoride etherate (6.30 mL, 50.0 mmol, 1 equiv.) was then added over a period of ten minutes during which the solution was seen to change colour from white to a transient yellow and subsequently became orange shortly thereafter. The solution was then warmed up to room temperature and left to stir overnight and after about one hour the solution was seen to change colour from orange to dark red and about two hours thereafter the solution reverted back to a permanent bright orange colour. The product precipitated out of solution and was isolated by filtration and does not require any purification. The orange solid was then dried under high vacuum overnight to obtain the product (**1**) (7.60 g, 92%). The ^1H NMR data was in full agreement with the literature.²

^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 8.92 (bs, 8H, Ar-OH), 7.24 (s, 4H, H – 1⁵, 3⁵, 5⁵, 7⁵), 6.14 (s, 4H, H – 1², 3², 5², 7²), 4.22 (t, $J = 7.9\text{ Hz}$, 4H, H – 2, 4, 6, 8), 2.07 (q, $J = 6.1\text{ Hz}$, 8H, $\text{CH}_2\text{CH}_2\text{CH}_3$) 1.19 (sxt, $J = 7.1\text{ Hz}$, 8H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.89 (t, $J = 7.1\text{ Hz}$, 12H, $\text{CH}_2\text{CH}_2\text{CH}_3$).

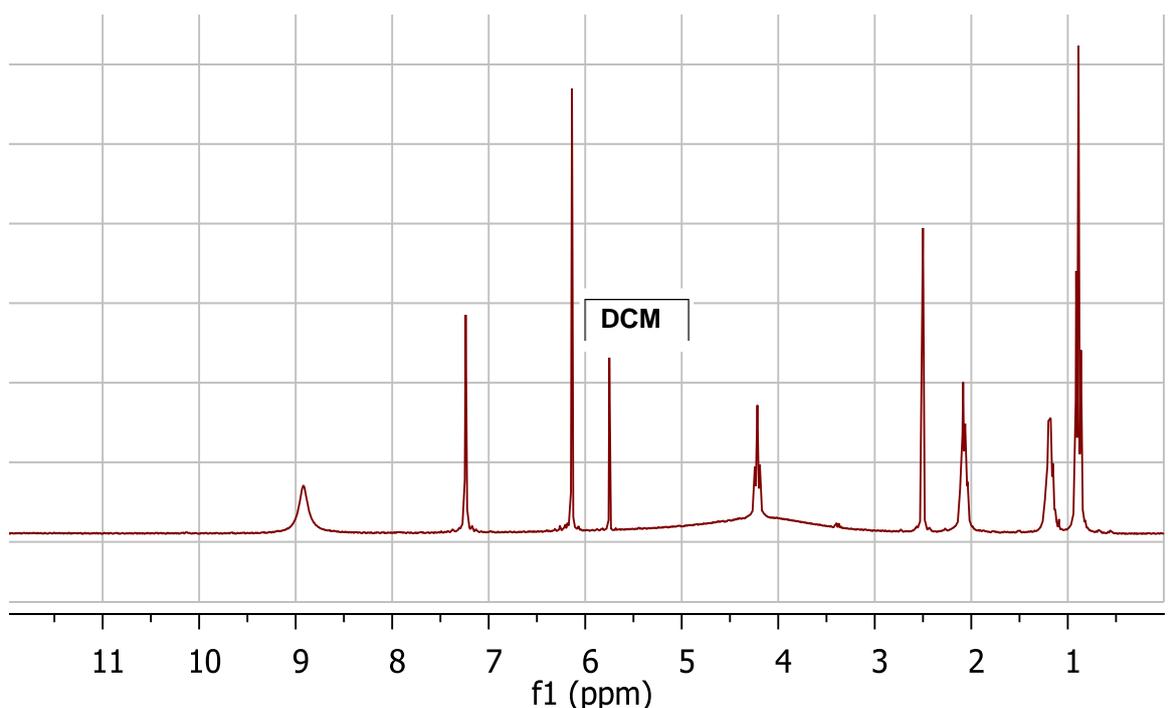
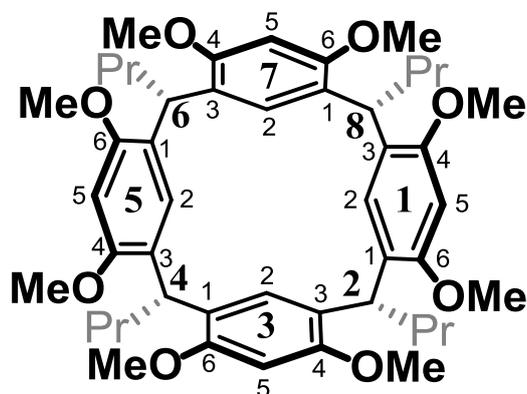


Figure 1 - ^1H NMR spectrum of the 'propyl-footed' octahydroxyresorcinarene (1).

$1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6$ -Octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane (2)³



Resorcinarene (1) (4.70 g, 7.16 mmol, 1 equiv.) was dissolved and stirred in anhydrous acetonitrile (80 mL). Potassium carbonate (21.7 g, 157 mmol, 22 equiv.) was added and the solution was left to reflux for one to two hours. Iodomethane (10.6 mL, 171 mmol, 24 equiv.) was added and the solution was left to reflux overnight. It was found that cooling down the solution (usually to about 40 °C) before the addition of iodomethane lead to increased yields. The yield was further optimized by adding the iodomethane in aliquots. The reaction was then quenched with approximately distilled water (100 mL), and the crude product was extracted into an organic phase by 3 x 40 mL washes of DCM. The organic phases were combined and dried over anhydrous MgSO_4 which was subsequently removed from the solution by filtration. The solvent was then evaporated under reduced vacuum to leave

behind an orange solid. The solid was then purified and isolated by recrystallization using hot acetone, and dried under the high vacuum overnight to obtain the product (**2**) (3.05 g, 55%) as a white crystalline solid. The ^1H NMR data was in full agreement with the literature.³

^1H NMR (300 MHz, CDCl_3) δ 6.63 (s, 4H, H – 1², 3², 5², 7²), 6.32 (s, 4H, H – 1⁵, 3⁵, 5⁵, 7⁵), 4.47 (t, J = 7.5 Hz, 4H, H – 2, 4, 6, 8), 3.60 (s, 24H, Ar-OCH₃), 1.79 (q, J = 7.5 Hz, 8H, CH₂CH₂CH₃) 1.33 (sxt, J = 7.5 Hz, 8H, CH₂CH₂CH₃), 0.91 (t, J = 7.4 Hz, 12H, CH₂CH₂CH₃).

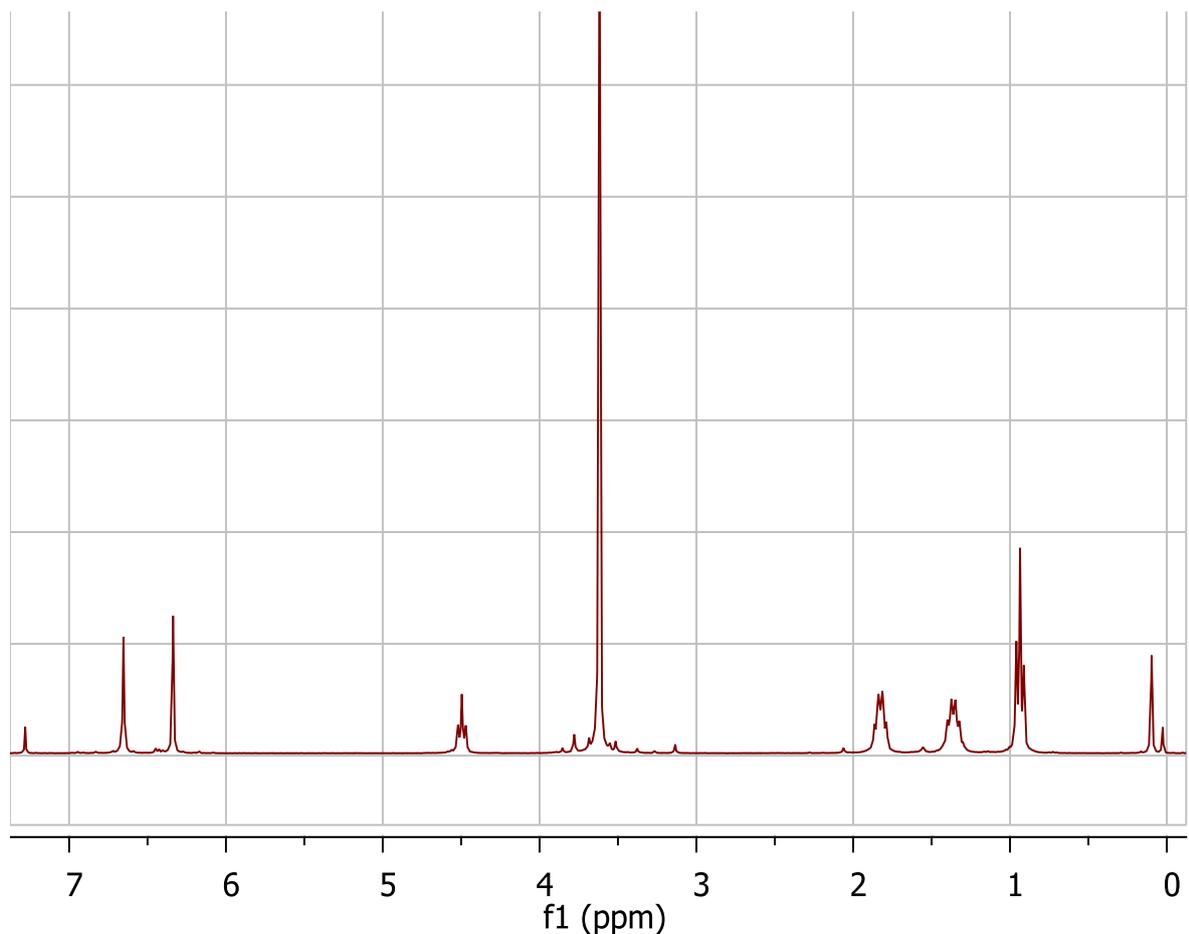
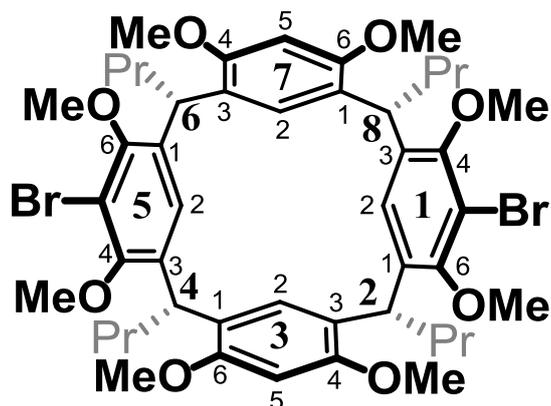


Figure 2 - ^1H NMR spectrum of the 'propyl-footed' octamethoxyresorcinarene (**2**).

1⁴,1⁶,3⁴,3⁶,5⁴,5⁶,7⁴,7⁶-Octamethoxy-1⁵,5⁵-dibromo-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane (3)³



Resorcinarene (**2**) (0.400 g, 0.520 mmol, 1 equiv.) was dissolved in anhydrous tetrahydrofuran (5 mL) and the solution warmed to 40 °C. *n*BuLi (1.34 mL, 2.60 mmol, 5 equiv.) was added rapidly and carefully and the solution was left to stir for two hours, which resulted in a yellow solution. Thereafter the mixture was cooled down to near -78 °C and freshly distilled 1,2-dibromoethane (0.50 mL, 5.20 mmol, 10 equiv.) was added rapidly, which resulted in a transparent solution, and left to stir overnight. After the addition of the electrophile, the reaction was warmed back to 40 °C and returned a yellow solution initially which darkened further as time progressed and was found to be dark red in colour the following day. The reaction is then quenched with 1M hydrochloric acid (20 mL), and the crude product was extracted into an organic phase by 3 x 15 mL washes of DCM. The organic phases were then combined and dried over anhydrous MgSO₄ which was subsequently removed from the solution by filtration. The solvent was then evaporated under reduced pressure to leave behind a dark orange solid. The crude solid was then unsuccessfully purified by column chromatography (EtOAc/hexane), the fractions combined and the solvent evaporated under reduced pressure, and dried under high vacuum overnight thereafter to obtain the product (**3**) (0.310 g, 65%) as a white crystalline solid (a mixture of mono-brominated and distal dibrominated resorcinarene as well as residual starting material). The spectroscopic data was in partial agreement with the literature.³

¹H NMR (300 MHz, CDCl₃) δ 6.64 (s, 2H, H - 3², 7²), 6.60 (s, 2H, H - 1², 5²), 6.31 (s, 2H, H - 3⁵, 7⁵), 4.54 – 4.44 (m, 4H, H - 2, 4, 6, 8), 3.67 (s, 12H, Ar-OCH₃), 3.59 (s, 12H, Ar-OCH₃), 1.85 – 1.77 (m, 8H, CH₂CH₂CH₃), 1.40 – 1.28 (m, 8H, CH₂CH₂CH₃), 0.92 (t, *J* = 7.3 Hz, 12H, CH₂CH₂CH₃).

m/z (%): 849.37 [M+H]⁺ (60), 866.41 [M+ NH₄]⁺ (100) (Monobromo), 927.28 [M+H]⁺ (20), 944.31 [M+ NH₄]⁺ (55). (Dibromo)

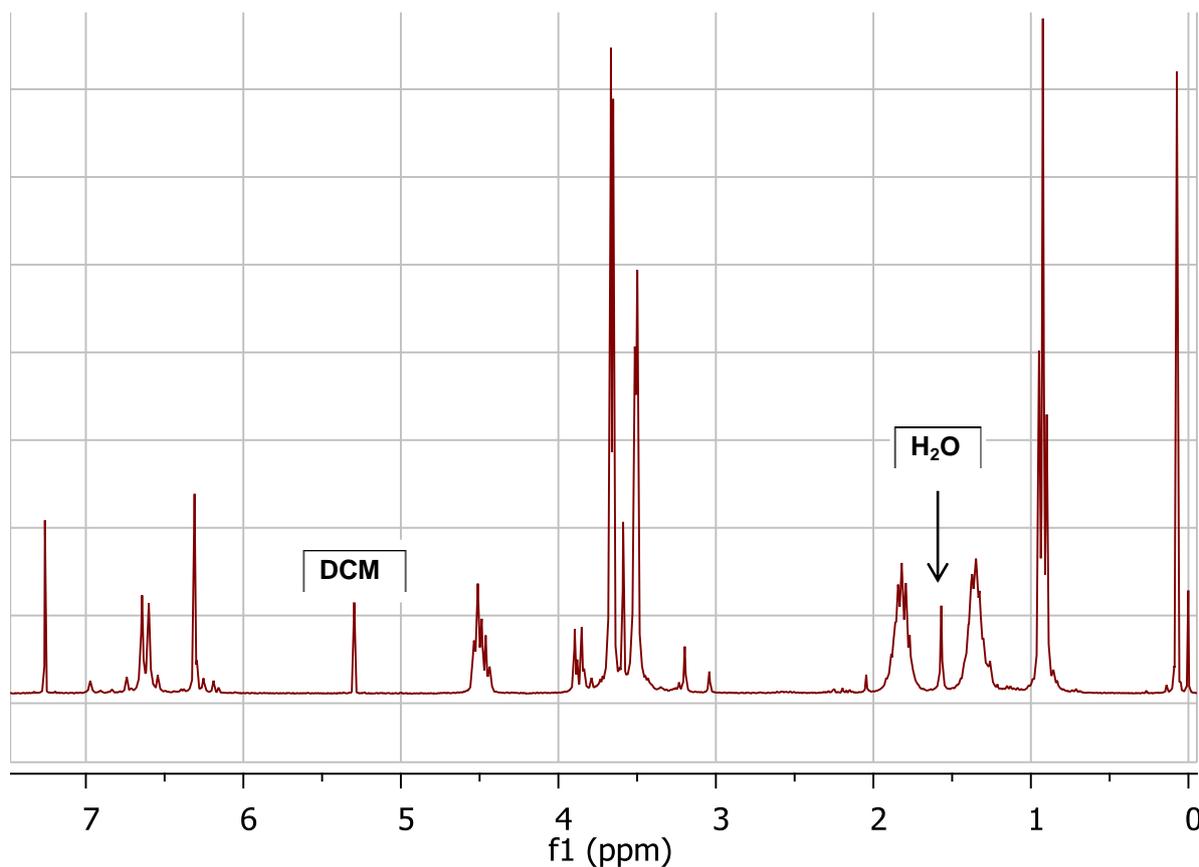
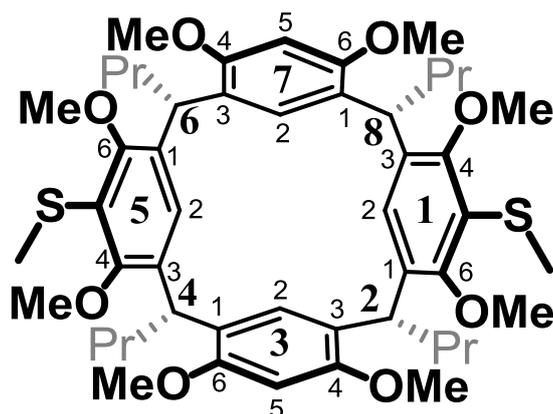


Figure 3 - ^1H NMR spectrum of the product (3) (a mixture of 2, mono-brominated and distal dibrominated resorcinarene).

$1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6$ -Octamethoxy- $1^5,5^5$ -dimethylthiyl-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane (4)³



Resorcinarene (2) (1.20 g, 1.56 mmol, 1 equiv.) was dissolved in anhydrous THF (60 mL) and the solution warmed to 40 °C. Freshly distilled TMEDA (1.40 mL, 9.36 mmol, 6 equiv.) was added to solution followed by the rapid and careful addition of *n*BuLi (3.65 mL, 7.80 mmol, 5 equiv.) and the solution was left to stir for two hours which resulted in a yellow

solution. Thereafter the mixture was cooled down to near $-78\text{ }^{\circ}\text{C}$ and dimethyl disulphide (1.40 mL, 15.6 mmol, 10 equiv.) was added gradually which resulted in a cloudy-white solution. After the addition of the electrophile the reaction was left to warm to room temperature overnight and the solution was found to be light brown in colour the following day. The reaction was then quenched with 1M hydrochloric acid (50 mL), and the crude product was extracted into an organic phase by 3 x 50 mL washes of DCM. The organic phases were then combined and dried over anhydrous MgSO_4 which was subsequently removed from the solution by filtration. The solvent was then evaporated under reduced pressure to leave behind a light brown solid. The solid was then purified by column chromatography (EtOAc/hexane), the fractions combined and the solvent evaporated under reduced pressure, and dried under high vacuum thereafter to obtain the product (**3**) (0.941 g, 70%) as light beige solid. The spectroscopic data was in full agreement with the literature.³

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 6.70 (s, 2H, H - 3², 7²), 6.68 (s, 2H, H - 1², 5²), 6.34 (s, 2H, H - 3⁵, 7⁵), 4.54 (t, $J = 7.5$ Hz, 4H, H - 2, 4, 6, 8), 3.64 (s, 12H, Ar-OCH₃), 3.59 (s, 12H, Ar-OCH₃), 2.33 (s, 6H, Ar-SCH₃), 1.85 – 1.77 (m, 8H, CH₂CH₂CH₃), 1.40 – 1.28 (m, 8H, CH₂CH₂CH₃), 0.92 (t, $J = 7.3$ Hz, 12H, CH₂CH₂CH₃).

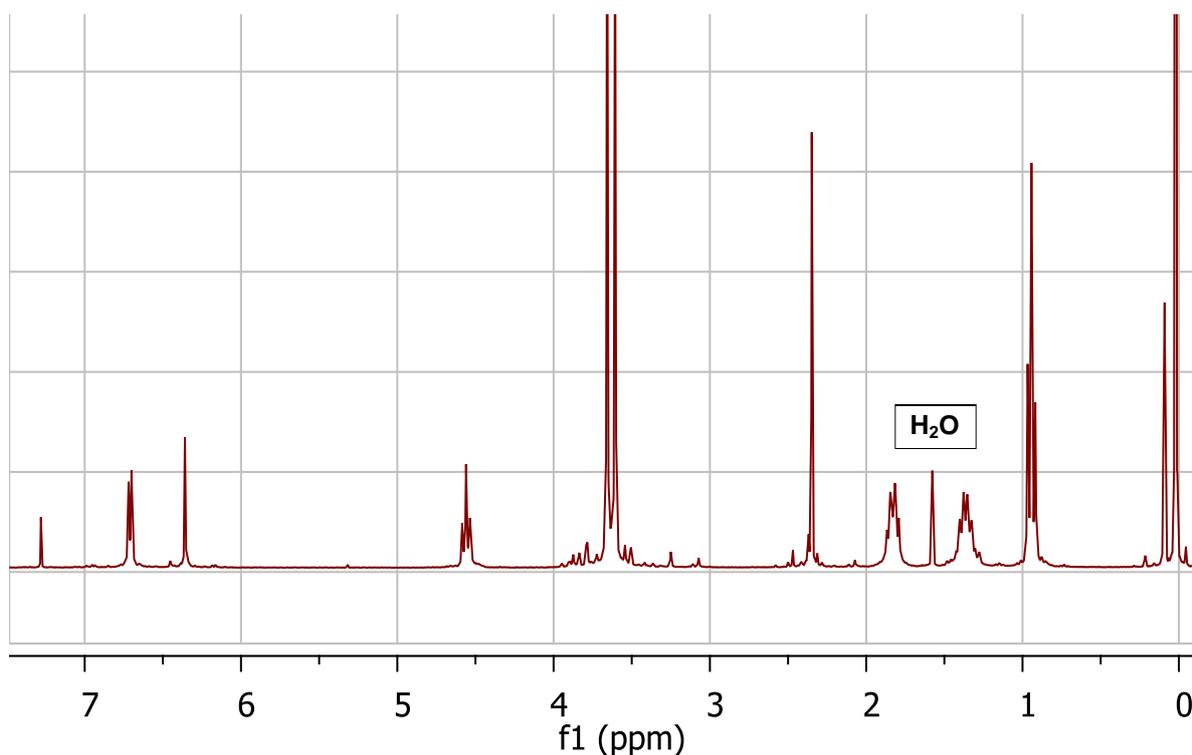
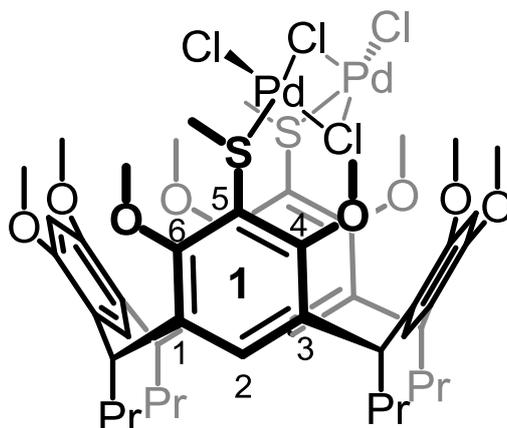


Figure 4 - $^1\text{H NMR}$ spectrum of the 'propyl-footed' distal di(methylthiyl) octamethoxyresorcinarene (**4**).

S,S'-{1⁴, 1⁶, 3⁴, 3⁶, 5⁴, 5⁶, 7⁴, 7⁶-octamethoxy-1⁵, 5⁵-dimethylthiyl-2, 4, 6, 8-tetrapropyl-1, 3, 5, 7(1, 3)-tetrabenzenacyclooctaphane}-bis[palladium chloride(μ₂-chlorine)₂] (5)²



Distal dimethyl thioether resorcinarene ligand (**4**) (0.200 mg, 0.232 mmol, 1 equiv.) was dissolved in 7 mL of anhydrous DCM and the solution was stirred at room temperature. To this solution, palladium (II) chloride (90 mg, 0.51 mmol, 2.2 equiv.) was added turning the solution into a dark brown colour. The solution was further stirred overnight at room temperature. Thereafter, the reaction mixture was filtered through Celite and eluted with DCM. The crude was then re-dissolved with a minimum amount of regular DCM and layered with pentane and placed into a $-15\text{ }^{\circ}\text{C}$ fridge in a sealed round bottom flask to return the dipalladium complex (**5**) as red-brownish crystals (0.198 g, 70%) overnight. The spectroscopic data was in full agreement with the literature.²

¹H NMR (300 MHz, CDCl₃) δ 7.56 (s, 2H, H – 1², 5²), 6.60 (s, 2H, H – 3⁵, 7⁵), 6.33 (s, 2H, H – 3², 7²), 4.64 (t, *J* = 7.5 Hz, 4H, H – 2, 4, 6, 8), 4.00 (s, 12H, Ar–OCH₃), 3.60 (bs, 12H, Ar–OCH₃), 2.54 (s, 6H, Ar–SCH₃), 1.81 (q, *J* = 7.5 Hz, 8H, CH₂CH₂CH₃), 1.25 – 1.13 (sxt, *J* = 7.5 Hz, 8H, CH₂CH₂CH₃), 0.87 (t, *J* = 7.2 Hz, 12H, CH₂CH₂CH₃).

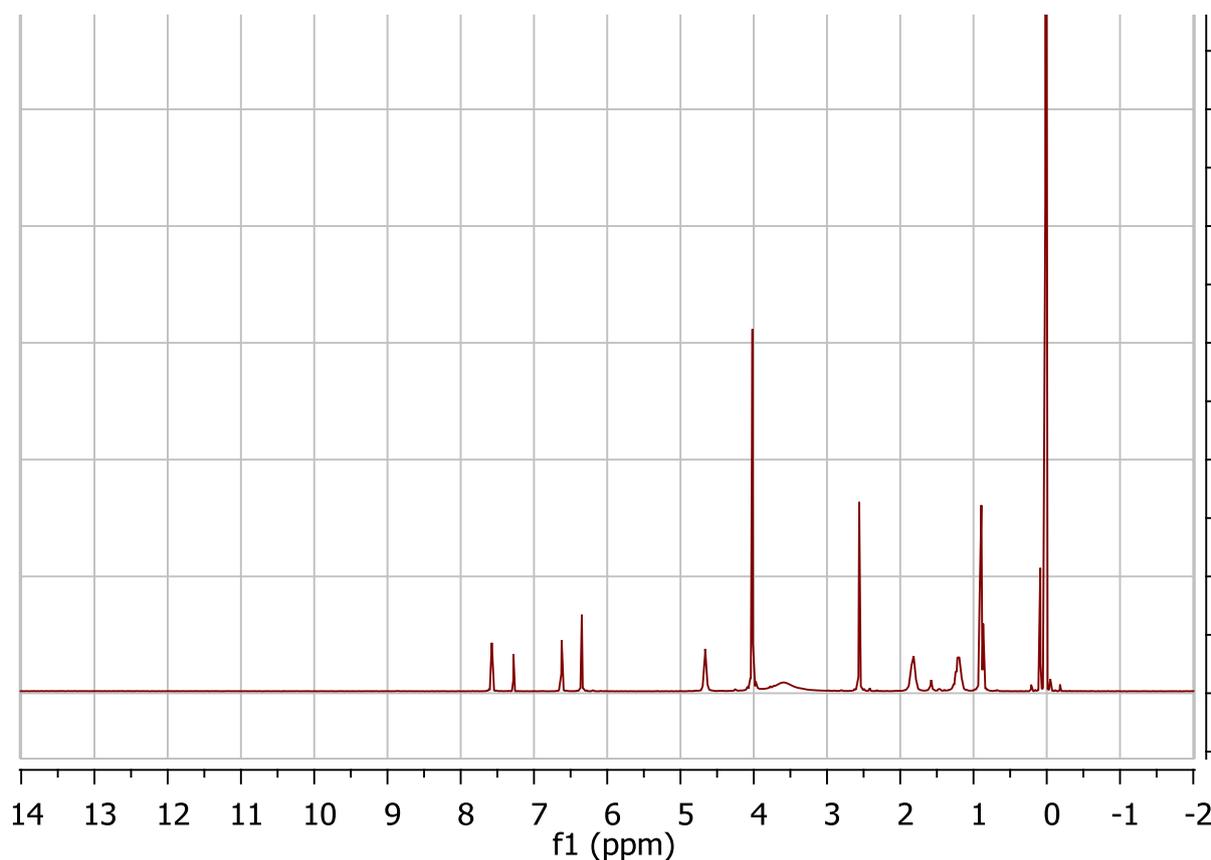
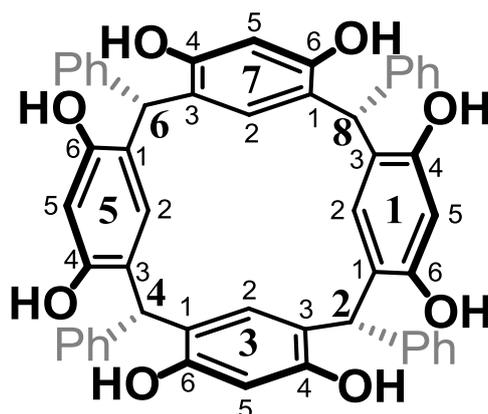


Figure 5 - ^1H NMR spectrum of the 'propyl-footed' distal di(methylthiyl) octamethoxyresorcinarene- $\text{Pd}_2\text{Cl}_2(\mu\text{-Cl})_2$ complex (5).

$1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6$ -Octahydroxy-2,4,6,8-tetraphenyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane (6)⁴



Resorcinol (5.5 g, 50 mmol, 1 equiv.) and distilled benzaldehyde (5.1 mL, 50 mmol, 1 equiv.), which was stored under argon prior to use, was dissolved in 75 mL of undistilled 98% reagent grade ethanol. 32% hydrochloric acid (9.80 mL, 100 mmol, 2 equiv.) was added to the solution and fitted with a reflux condenser, heated to 75 °C and stirred under argon

overnight resulting in transient colour changes from an initial transparent colour to yellow and then rapidly to orange and ultimately became a beige-yellow colour shortly thereafter.

The following day, the solution was found to be brownish-orange in colour and was cooled in an ice bath, resulting in a murky-green precipitate being formed. The precipitate was collected by filtration and washed with methanol turning the precipitate from a green colour to a brown colour and leaving behind a red filtrate that contained more precipitate. The filtrate was re-filtered and a second precipitate was collected and washed with water thereafter which instantaneously turned the precipitate, as well as the filtrate, into a lighter shade of colour. As the water is added to filtrate, more precipitate could be seen forming in the solution. The third precipitate seemed lighter in colour than the other precipitates, resulting ultimately in a light orange colour. The third precipitate and was collected by filtration and washed with more water. The precipitates were dried under high vacuum for 48 hours at a temperature of 70 °C. The first two precipitates resulted in the same conclusive ^1H NMR spectrum.

m/z (%): 793.28 $[\text{M}+\text{H}]^+$ (40), 805.25 (100), 810.31 $[\text{M}+\text{NH}_4]^+$ (75).

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.55 (s, 8H, Ar-OH), 6.96 (m, 12H, Ph-H), 6.74 (m, 8H, Ph-H), 6.31 (s, 4H, H – 1⁵, 3⁵, 5⁵, 7⁵) 6.14 (s, 4H, H – 1², 3², 5², 7²), 5.64 (s, 4H, H – 2, 4, 6, 8).^a

^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 152.5 (C-1^{4,6}, 3^{4,6}, 5^{4,6}, 7^{4,6}), 145.7 (C-Ph), 128.6 (C-Ph), 127.1 (C-Ph), 124.5 (C – 1^{1,3}, 3^{1,3}, 5^{1,3}, 7^{1,3}), 120.4 (C – 1⁵, 3⁵, 5⁵, 7⁵), 102.1 (C – 1², 3², 5², 7²), 41.4 (C – 2, 4, 6, 8).^b

^a Assignments are not absolute and have been tentatively made based on similar structures (compound 1).

^b Assignments are not absolute and have been tentatively made based on NMR prediction software.

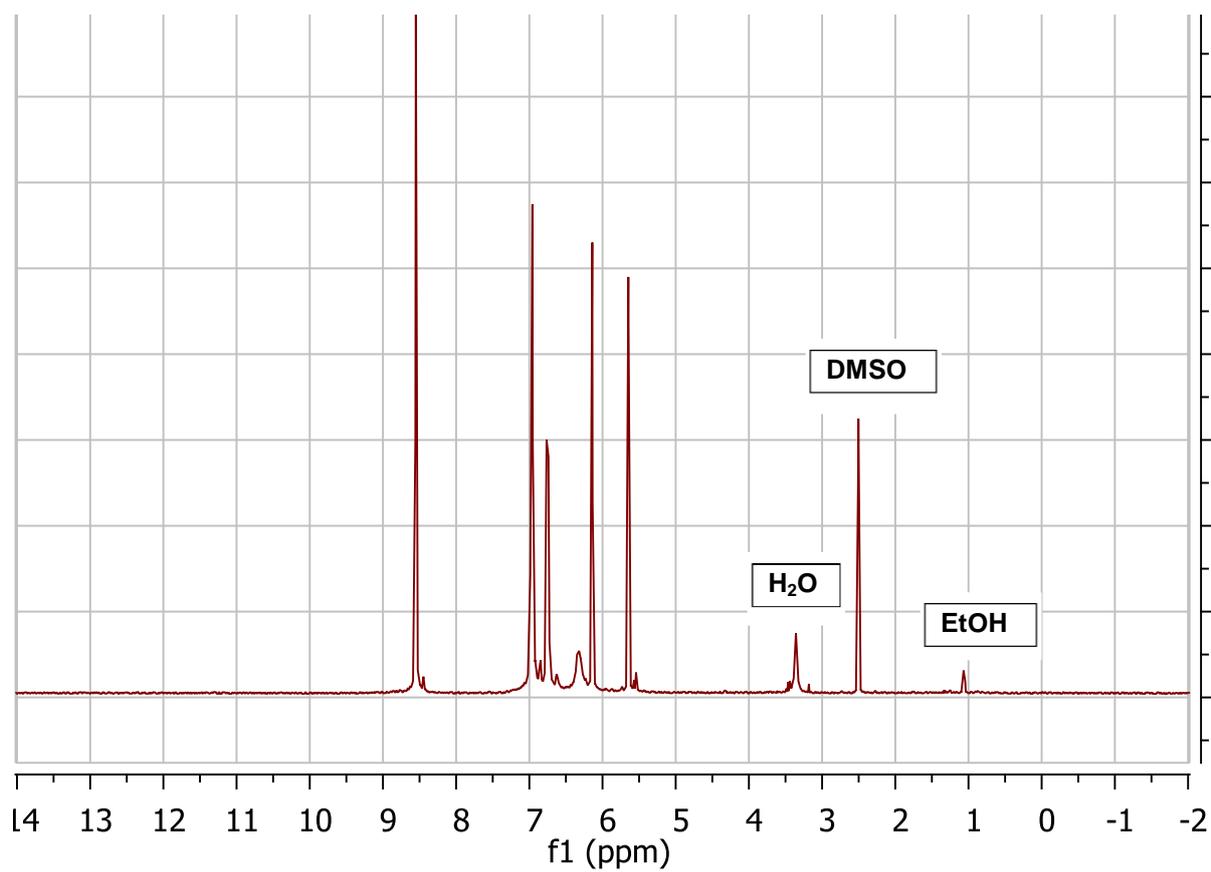


Figure 6 - ^1H NMR spectrum of the 'phenyl-footed' octahydroxyresorcinarene (6).

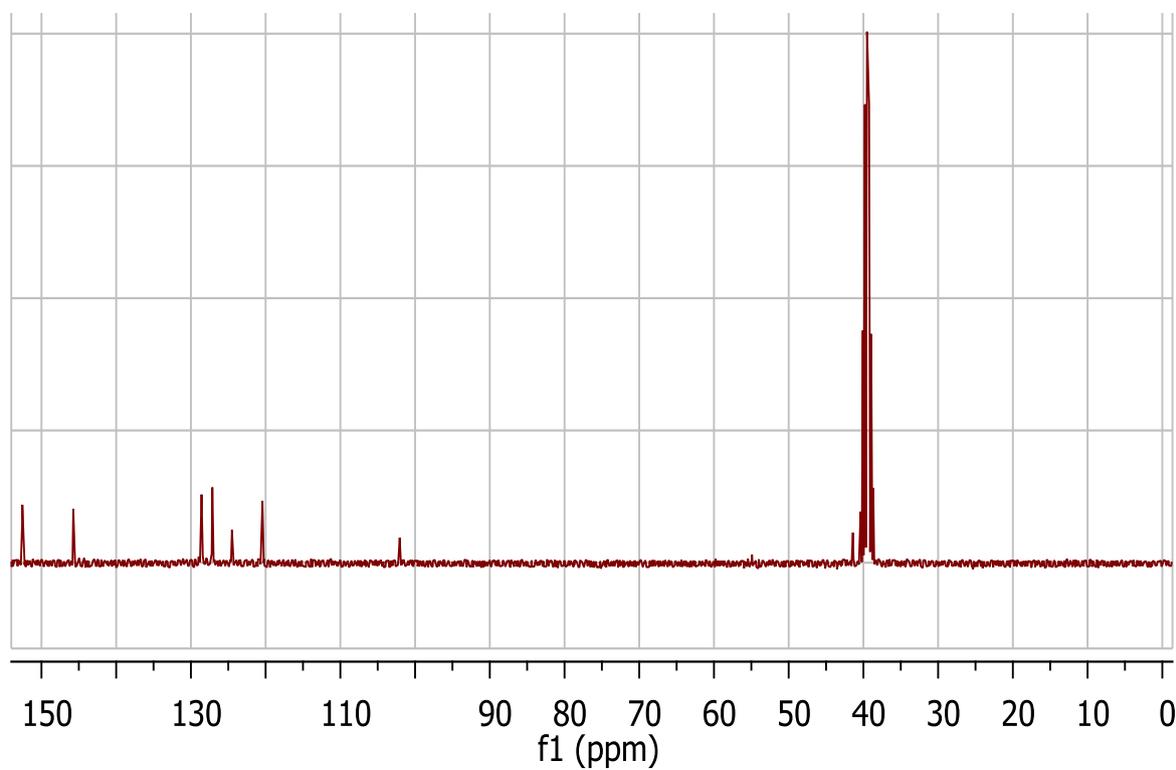
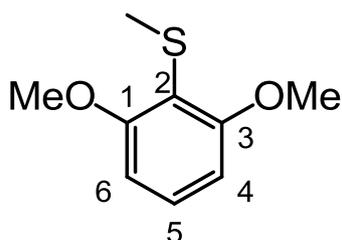


Figure 7 - ^{13}C NMR spectrum of the 'phenyl-footed' octahydroxyresorcinarene (6).

1,3-Dimethoxy-2-methylthiylbenzene (7)

1,3-Dimethoxybenzene (0.300 g, 2.17 mmol, 1 equiv.) was dissolved in anhydrous THF (5 mL) and the solution warmed to 40 °C. *n*BuLi (1.74 mL, 4.34 mmol, 2 equiv.) was added rapidly and carefully and left to stir for two hours which resulted in a yellow solution. Thereafter the mixture was cooled down to 0 °C and dimethyl disulphide (0.50 mL, 5.42 mmol, 2.5 equiv.) was added gradually which resulted in a cloudy-white solution. After the addition of the electrophile the reaction was left to warm to room temperature and left to stir overnight returned a brown solution the following day. The reaction is then quenched with 1M hydrochloric acid (20 mL), and the crude product was extracted into an organic phase by 3 x 15 mL washes of DCM. The organic phases were then combined and dried over anhydrous MgSO₄ which was subsequently removed from the solution by filtration. The solution was concentrated under reduced pressure to a minimum volume and left to cool to room temperature which provided the product (7) (0.340 g, 85%) as off-white crystals. The spectroscopic data was in full agreement with the literature.⁵

¹H NMR (300 MHz, CDCl₃) δ 7.22 (t, *J* = 8.4 Hz, 1H, H – 5), 6.56 (d, *J* = 8.4 Hz, 2H, H – 4, 6), 3.89 (s, 6H, Ar-OCH₃), 2.36 (s, 3H, Ar-SCH₃).

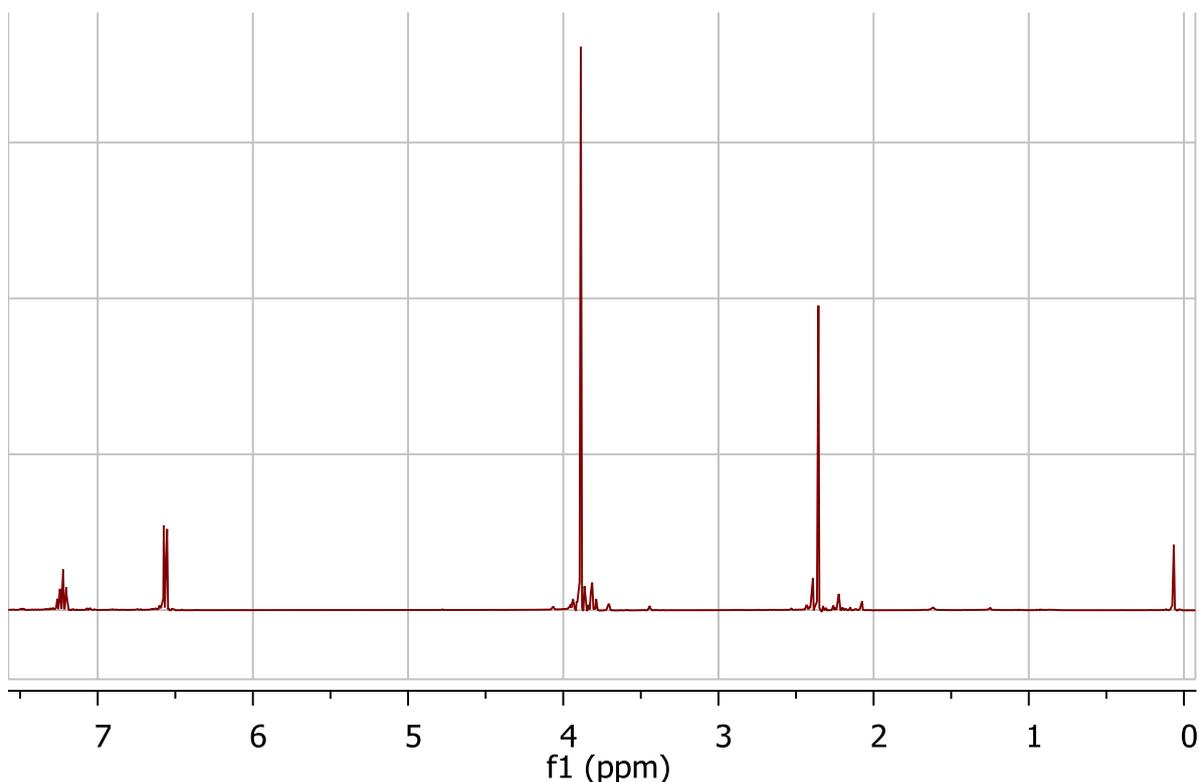
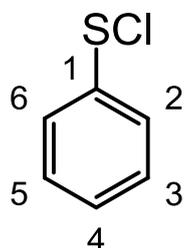
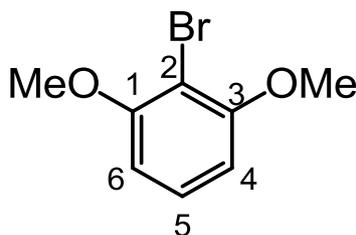


Figure 8 - ^1H NMR spectrum of 1,3-Dimethoxy-2-methylthiylbenzene (7).

Benzenesulfonyl chloride (**8**)⁶

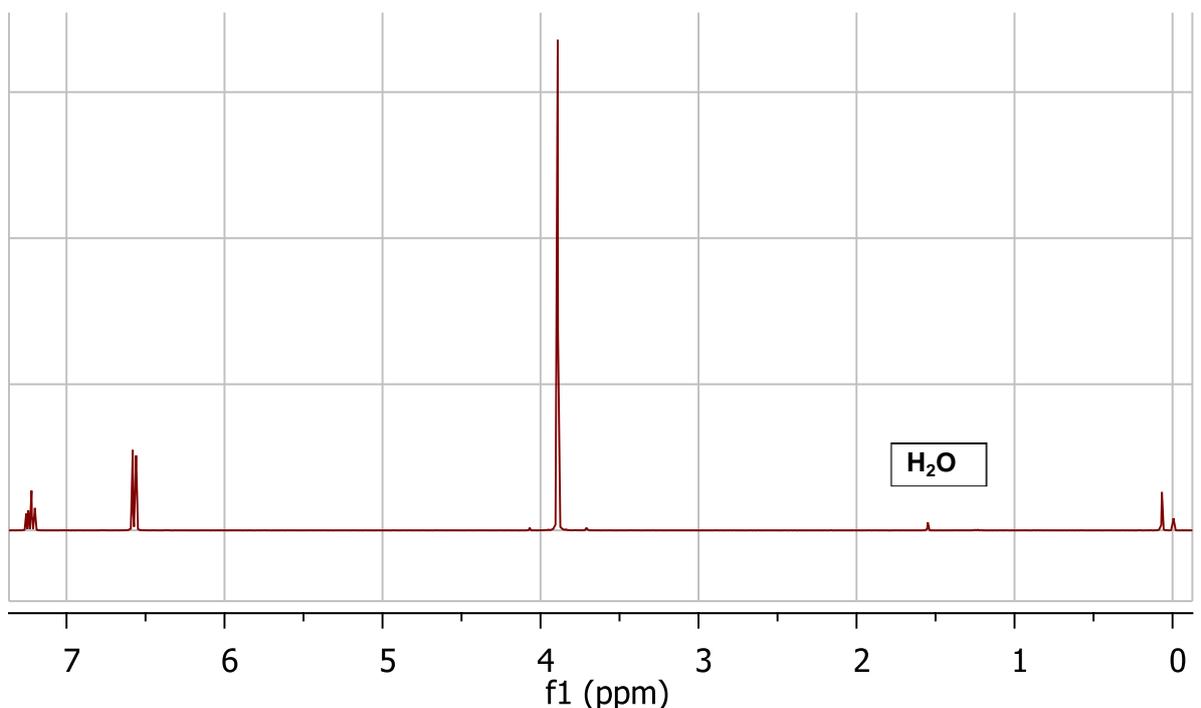


N-chlorosuccinimide (5.13 g, 38.4 mmol, 1 equiv.) was dissolved in anhydrous DCM (80 mL) and the solution was stirred at room temperature. Thiophenol (3.92 mL, 38.4 mmol, 1 equiv.) was then slowly added to the solution at 0 °C and stirred at this temperature for 15 min, followed by the addition of more N-chlorosuccinimide (5.13 g, 38.4 mmol, 1 equiv.) and stirred for a further 15 min. The solvent was then removed under reduced pressure, and hexane (30 mL) was added to the residue which precipitated residual succinimide which was removed by filtration. The solvent was evaporated under reduced pressure and the resulting solution was distilled under high vacuum to obtain the product (**8**) (5.45 g, 98%) as a dark orange liquid. The resulting product was not pure (as indicated by TLC analysis) and used as mixture in the ortholithiation procedure thereafter.

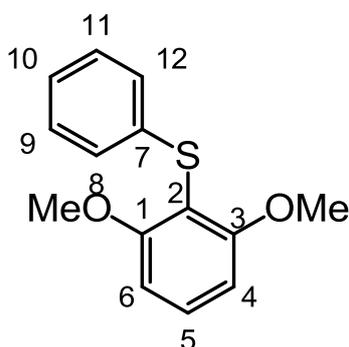
2-Bromo-1,3-dimethoxybenzene (9)

1,3-Dimethoxybenzene (0.95 mL, 7.24 mmol, 1 equiv.) was dissolved in anhydrous THF (15 mL) and the solution warmed to 40 °C. *n*BuLi (3.14 mL, 14.5 mmol, 2 equiv.) was added rapidly and carefully and left to stir for two hours which resulted in a yellow solution. Thereafter the mixture was cooled down to 0 °C and freshly distilled 1,2-dibromoethane (3.14 mL, 36.2 mmol, 5 equiv.) was added rapidly which resulted in a transparent solution. After the addition of the electrophile the reaction was warmed back up to 40 °C and left to stir overnight and initially the mixture was seen to become murky-white, thereafter yellow and subsequently orange over time. The reaction darkened further and was found to be dark-red the following day. The reaction is then quenched with 1M hydrochloric acid (50 mL), and the crude product was extracted into an organic phase by 3 x 25 mL washes of DCM. Brine (50 mL) was added to the mixture in order to help separate the layers. The organic phases were then combined and dried over anhydrous MgSO₄ which was subsequently removed from the solution by filtration. The solvent was then evaporated under reduced pressure and residual 1,2-dibromoethane was removed by placing the wet solid under the high vacuum at 100 °C overnight. The resulting orange solid was purified and isolated by recrystallization using hot ethanol and dried under the high vacuum to obtain the product (**9**) (1.11 g, 71 %) as white crystals. The spectroscopic data was in full agreement with the literature.⁷

¹H NMR (300 MHz, CDCl₃) δ 7.23 (t, J = 8.4 Hz, 1H, H – 5), 6.58 (d, J = 8.4 Hz, 2H, H – 4, 6), 3.90 (s, 6H, Ar-OCH₃).

Figure 9 - ^1H NMR spectrum of 2-Bromo-1,3-dimethoxybenzene (9).

1,3-Dimethoxy-2-phenylthiylbenzene (10)



Procedure 1:

1,3-Dimethoxybenzene (0.300 g, 2.17 mmol, 1 equiv.) was dissolved in anhydrous THF (5 mL) and the solution warmed to 40 °C. *n*BuLi (1.74 mL, 4.34 mmol, 2 equiv.) was added quickly and carefully and left to stir for two hours which resulted in a tan (yellowish-brown) solution. Thereafter the mixture was cooled down to 0 °C and benzenesulfonyl chloride (**8**) (0.784 g, 5.42 mmol, 2.5 equiv.) was added gradually which resulted in a reddish-brown solution. After the addition of the electrophile the reaction was left to warm to room temperature and returned a brown solution overnight. The reaction is then quenched with 1M hydrochloric acid (20 mL), and the crude product was extracted into an organic phase by 3 x 15 mL washes of DCM. The organic phases were then combined and dried over anhydrous MgSO_4 which was subsequently removed from the solution by filtration. The solvent was evaporated under reduced pressure. The brownish-beige solid was dried further under high

vacuum overnight to leave behind the product (**10**) (0.210 g, 23%). The spectroscopic data was in full agreement with the literature.⁸

¹H NMR (300 MHz, CDCl₃) δ 7.38 (t, *J* = 8.4 Hz, 1H, H – 10), 7.18 – 7.14 (m, 2H, H – 9, 11), 7.07 – 7.03 (m, 3H, H – 8, 12, 5), 6.66 (d, *J* = 8.4 Hz, 2H, H – 4, 6), 3.81 (s, 6H, Ar-OCH₃).

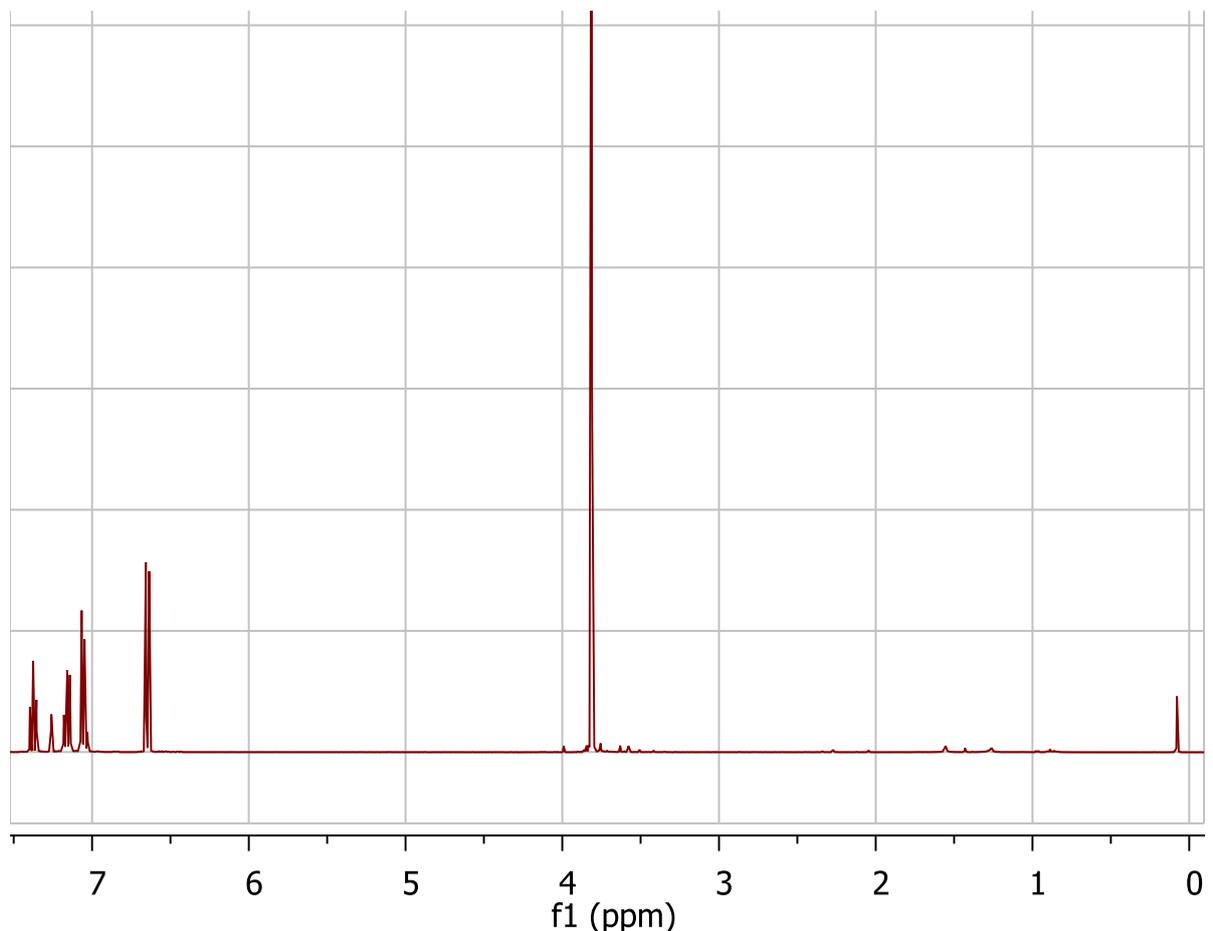


Figure 10 - ¹H NMR spectrum of 1,3-Dimethoxy-2-phenylthiylbenzene (**10**) synthesized via procedure 1.

Procedure 2:⁸

One-pot synthesis of 2-Bromo-1,3-dimethoxybenzene (**9**) (0.100 g, 0.461 mmol, 1 equiv.), dry potassium tert-butoxide (0.105 g, 0.922 mmol, 2 equiv.), thiophenol (0.057 mL, 0.553 mmol, 1.2 equiv.) and Pd(IPr^{*OMe})(cin.)(Cl) (**14**) (0.001 g, 0.001 mmol, 0.2 mol%) dissolved in anhydrous and degassed 1,4-dioxane (2.5 mL) was left to reflux overnight in a sealed tube, which resulted in a yellowish-white colour almost immediately. Thereafter the solution was diluted with DCM (20 mL) and filtered through Celite, which resulted in the removal of an off-white precipitate and the isolation of a yellow filtrate. The solvent was then evaporated under reduced pressure and the residual thiophenol was removed by flash column chromatography

(EtOAc/hexane), the fractions combined and the solvent removed, to obtain the product (**10**) (0.107 g, 95%) as a yellow solid. The spectroscopic data was in full agreement with the literature.⁸

¹H NMR (300 MHz, CDCl₃) δ 7.38 (t, *J* = 8.4 Hz, 1H, H – 10), 7.19 – 7.14 (m, 2H, H – 9, 11), 7.07 – 7.02 (m, 3H, H – 8, 12, 5), 6.66 (d, 2H, H – 4, 6), 3.81 (s, 6H, Ar-OCH₃).

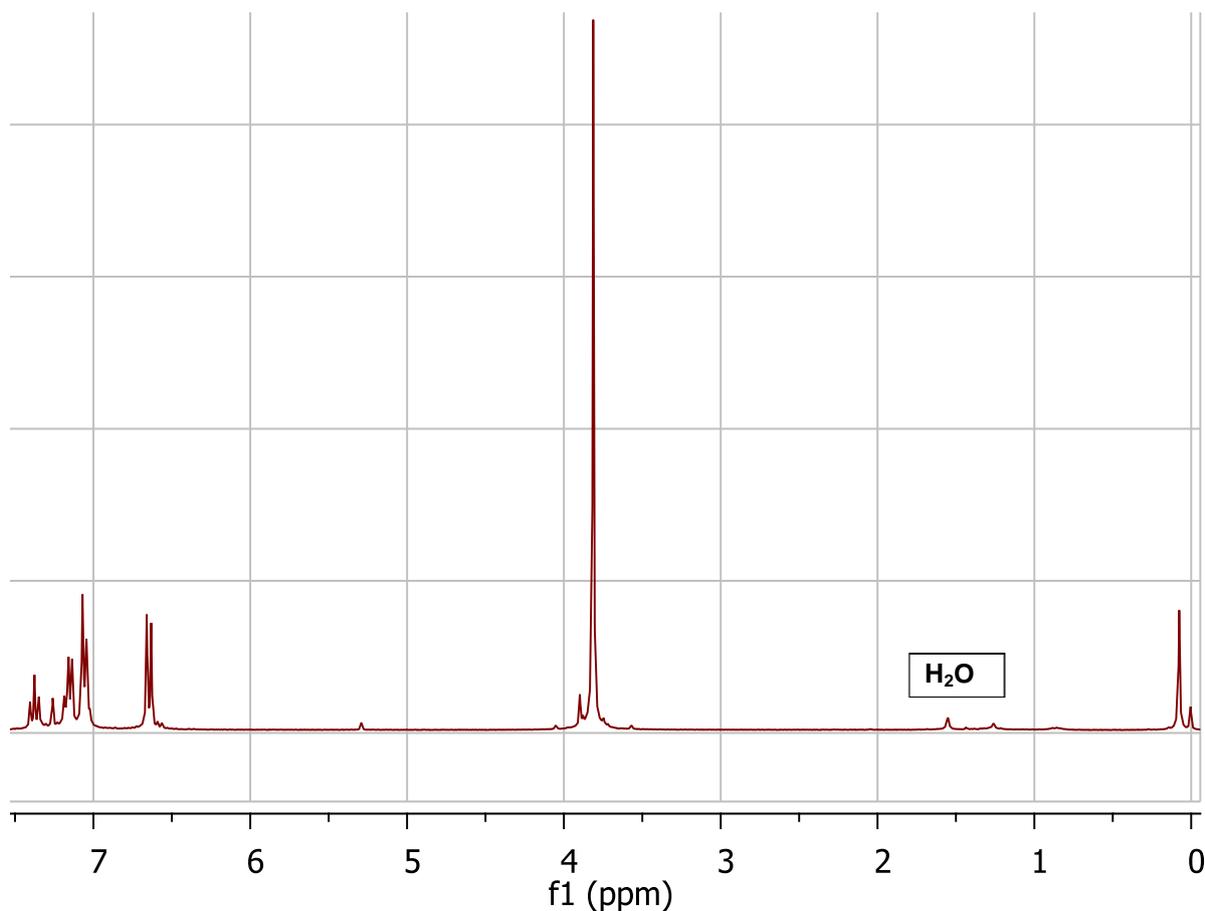
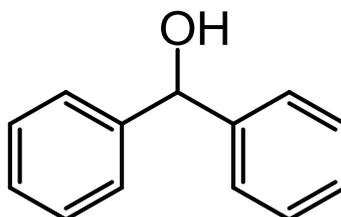


Figure 11 - ¹H NMR spectrum of 1,3-Dimethoxy-2-phenylthiylbenzene (**10**) synthesized via procedure 2.

Diphenylmethanol (Benzhydrol) (**11**)



Under an atmosphere of argon, to a round bottom flask (500 mL) was added benzophenone (30.50 g, 0.167 mol, 1 equiv.) followed by a slurry of NaBH₄ (3.17 g, 0.084 mol, 0.5 equiv.) dissolved in 2-propanol (200 mL). A reflux condenser was added to the setup and the mixture was allowed to reflux for about three hours. Thereafter, the boric ester complex that precipitates out of solution was decomposed by adding 10% aqueous NaOH assisted by vigorous stirring until the precipitate dissolved completely. Thereafter 150 mL of water was added to the solution and the organic phase was extracted using 2 x 200 mL washes of DCM using a separating funnel. The organic phases were combined and dried over anhydrous MgSO₄ which was subsequently removed by filtration. Thereafter the solvent was evaporated under reduced pressure and the crude was recrystallized numerous times in a mixture of water and methanol (3:2) to obtain the product (**11**) (28.98 g, 94%) as white crystals.

¹H NMR (300 MHz, CDCl₃) δ 7.33 – 7.16 (m, 10H, Ph-H), 5.77 (d, *J* = 3.2 Hz, 1H, C(sp³)-H).

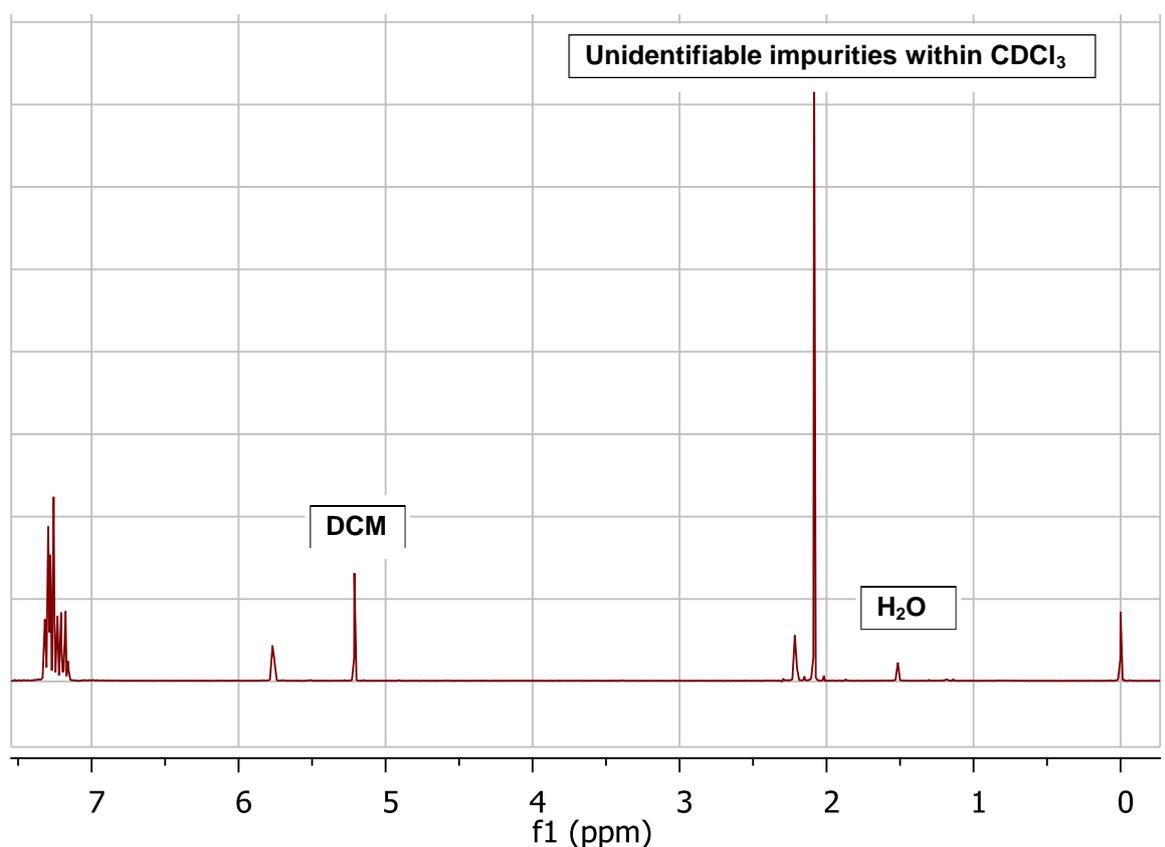
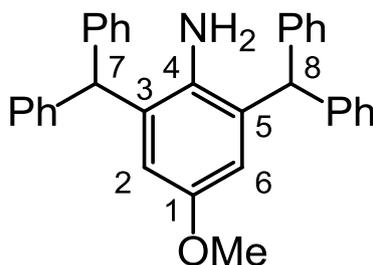


Figure 12 - ¹H NMR spectrum of diphenylmethanol (**11**).

2,6-Bis(diphenylmethyl)-4-methoxyaniline (12)⁹

Diphenylmethanol (**11**) (28.2 g, 153 mmol, 2 equiv.) and p-anisidine (9.40 g, 76.3 mmol, 1 equiv.) were heated together at 160 °C to form a eutectic homogenous liquid. Thereafter a premade solution of anhydrous zinc chloride (5.20 g, 38.2 mmol, 0.5 equiv.) in conc. hydrochloric acid (32%, 7.50 mL, 76.3 mmol, 1 equiv.) was added to the liquid at a constant rate over 30 min using a syringe pump which caused the liquid to darken and became more viscous until it became almost solid-like. The reaction was then placed under high vacuum at 160 °C for 15 min, causing the liquid to become completely solid. Thereafter the crude solid was dissolved in hot DCM (200 mL). The reaction mixture was then quenched with 3 x 150 mL washes of H₂O and the layers separated. The organic phase was then dried over anhydrous MgSO₄ which was subsequently removed from the solution by filtration. The solvent was then evaporated under reduced pressure to leave behind a sticky dark brown solid which was dissolved in a minimum amount of hot toluene. The product was then triturated by the addition of the entire solution to a large volume of room temperature pentane (200 mL) which resulted in the isolation of a dark purple solid by filtration. The solid was then re-dissolved in hot toluene and was purified through numerous recrystallizations which were initiated by the addition of pentane to obtain the product (**12**) (6.20 g, 18%) as a white crystalline solid. The spectroscopic data was in full agreement with the literature.⁹

¹H NMR (300 MHz, CDCl₃) δ 7.31 – 7.09 (m, 20H, Ph-H), 6.20 (s, 2H, H – 2, 6), 5.49 (s, 2H, H – 7, 8), 3.43 (s, 3H, Ar-OCH₃), 3.16 (vbs, 2H, NH₂).

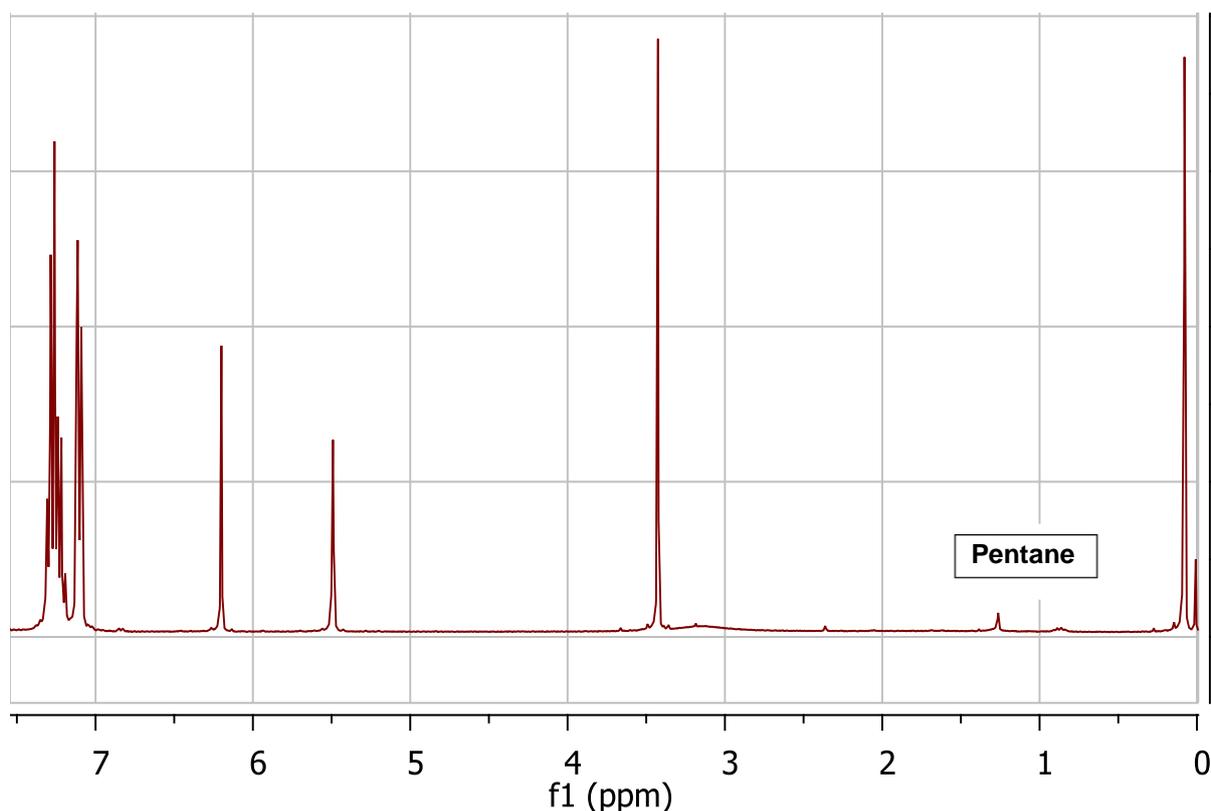
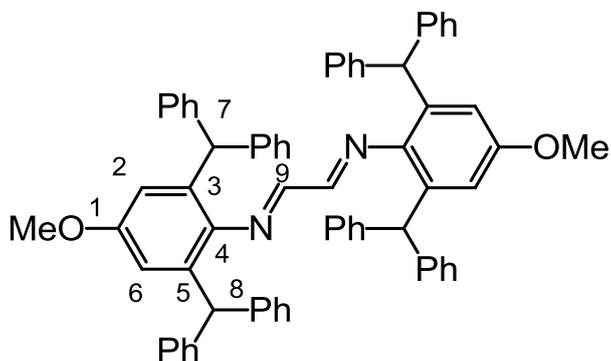


Figure 13 - ^1H NMR spectrum of aniline (**12**).

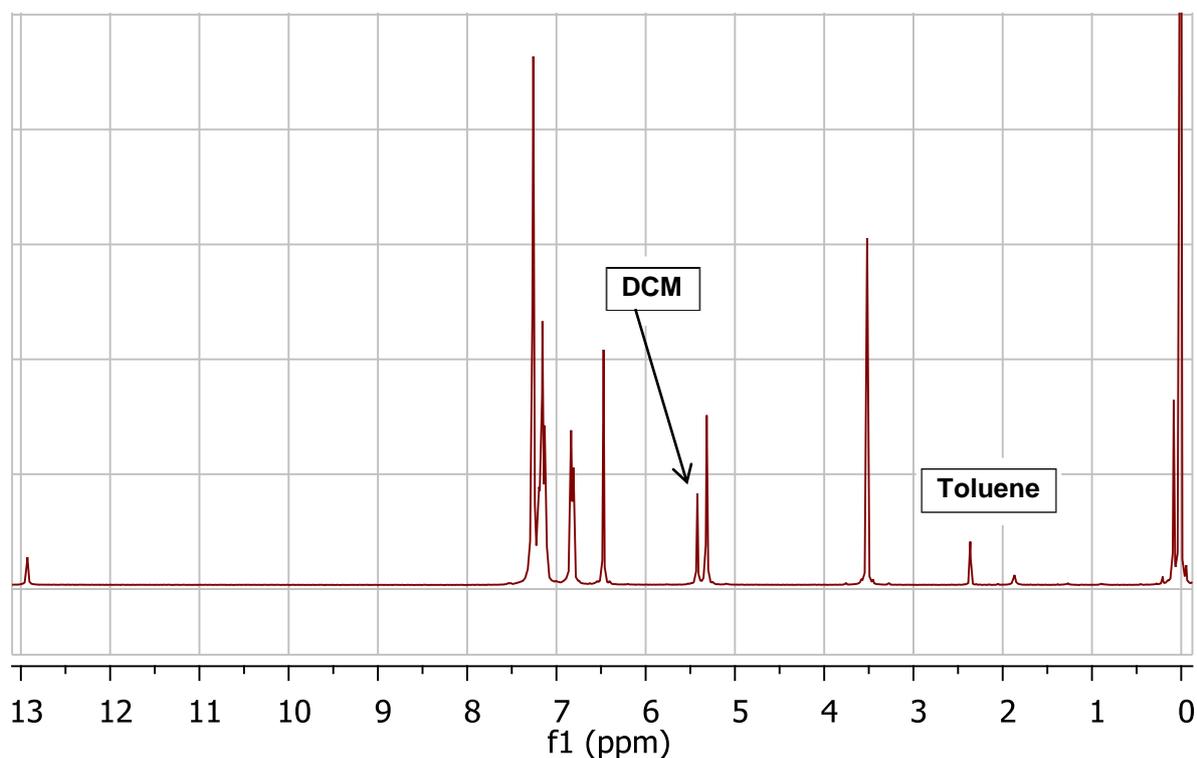
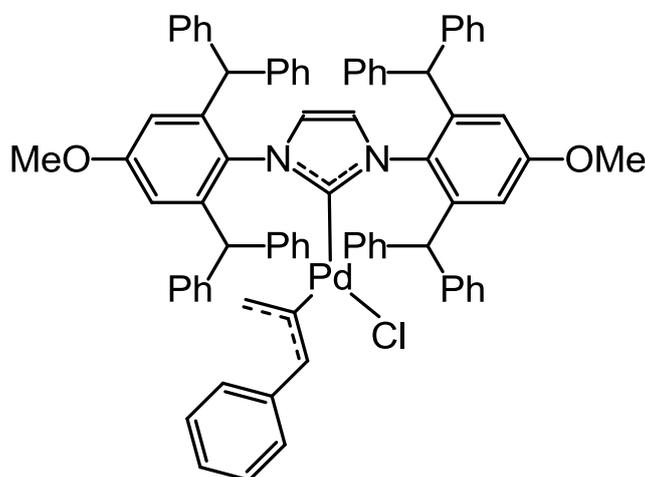
N,N'-Bis(2,6-bis(diphenylmethyl)-p-anisidyl)diazabutadiene (13**)⁹**



Aniline (**12**) (5.65 g, 12.4 mmol, 2 equiv.) was dissolved in regular DCM (120 mL). MgSO_4 (3.15 g, 26.0 mmol, 4.2 equiv.) was added to the solution, followed by glyoxal (40% in H_2O , 0.90 mL, 6.2 mmol, 1 equiv.) and formic acid (0.070 mL, 1.86 mmol, 0.3 equiv.) and the solution was stirred at room temperature for a minimum of four days. MgSO_4 was then removed from the solution by filtration and the filtrate was evaporated under reduced pressure to form a shiny yellowish-brown amorphous film that collapses when returned to atmospheric pressure. The crude solid was then purified by recrystallization by dissolution in

Diimine (**13**) (3.85 g, 4.13 mmol, 1 equiv.) was dissolved and stirred in anhydrous THF (150 mL) at 75 °C (slow reflux). The solution was then treated with anhydrous ZnCl₂ (0.565 g, 4.13 mmol, 1 equiv.) causing the yellow solution to turn red. The solution was then treated with p-formaldehyde (0.125 g, 4.13 mmol, 1 equiv.), followed by the slow addition of hydrogen chloride in dioxane (1.40 mL, 6.20 mmol, 1.5 equiv.) which caused the solution to darken (black). Stirring was continued for two hours, which caused the solution to lighten up (brown). The solvent was evaporated under reduced pressure and replaced by EtOAc (150 mL). The solution was then washed with H₂O (3 x 50 mL) and then brine (100 mL). The organic phase was dried over anhydrous MgSO₄ which was subsequently removed from the solution by filtration. The solvent was concentrated under reduced pressure until the formation of a brownish solid was seen. The remaining solution was then diluted with pentane (80 mL) and the solid isolated by filtration. The filtrate was diluted with more pentane until precipitation of the solid ceased. The solids were combined and purified by recrystallization in DCM, which was initiated by the addition of pentane, which returned a solid that was lighter in colour than before. The solid was then further purified by a second recrystallization, by using hot toluene as the solvent and pentane as the anti-solvent, to obtain the product (**14**) (2.03 g, 50%) as an off-white solid. The spectroscopic data was in full agreement with the literature.⁹

¹H NMR (300 MHz, CDCl₃) δ 12.93 (s, 1H, H – 10), 7.30 – 7.21 (m, 18H, Ar-H), 7.21 – 7.10 (m, 16H, Ar-H), 6.83 (m, 8H, Ar-H), 6.47 (s, 4H, H – 2, 6), 5.42 (s, 4H, H – 7, 8), 3.52 (s, 6H, Ar-OCH₃).

Figure 15 - ^1H NMR spectrum of imidazolium salt (**14**).**Pd(IPr^{*OMe})(cin.)(Cl) (**15**)⁸**

IPr^{*OMe}·HCl (**14**) (0.250 g, 0.256 mmol, 1 equiv.) was dissolved in anhydrous THF (15 mL) and stirred at room temperature, resulting in a creamy-white solution. KO^tBu (unsublimed prior to use) (0.043 g, 0.385 mmol, 1.5 equiv.) was then added, which resulted in an off-white transparent solution, and stirred for four hours. [Pd(cin.)(μ-Cl)]₂ (0.067 g, 0.111 mmol, 1 equiv.) was then added, which caused the solution to darken (beige-brown), and left to stir for 24 hours. The solvent was then evaporated under reduced pressure and the

resulting crude solid was dissolved in DCM and filtered through a pad of silica covered with Celite and eluted with DCM. The solvent was the evaporated under reduced pressure and the resulting material was purified by recrystallization in hot toluene which was assisted by the addition of pentane to obtain the product (**15**) (0.077 mg, 25%) as a beige solid. The spectroscopic data was in full agreement with the literature.⁸

¹H NMR (300 MHz, CDCl₃) δ 7.52 – 7.18 (m, 26H, Ar-H), 7.13 – 7.02 (m, 12H, Ar-H), 6.86 – 6.81 (m, 8H, Ar-H), 6.55 (s, 4H, CHPh₂), 6.08 (s, 2H, Ar-H), 5.74 (s, 2H, Ar-H), 5.23 (s, 2H, N-CH=CH-N), 5.17 – 5.04 (m, 1H, H – cin.), 4.70 (d, *J* = 13.1 Hz, 1H, H – cin.), 3.57 (s, 6H, Ar-OCH₃), 2.67 (d, *J* = 6.6 Hz, 1H, H – cin.) 1.35 (d, *J* = 11.7 Hz, 1H, H – cin.).

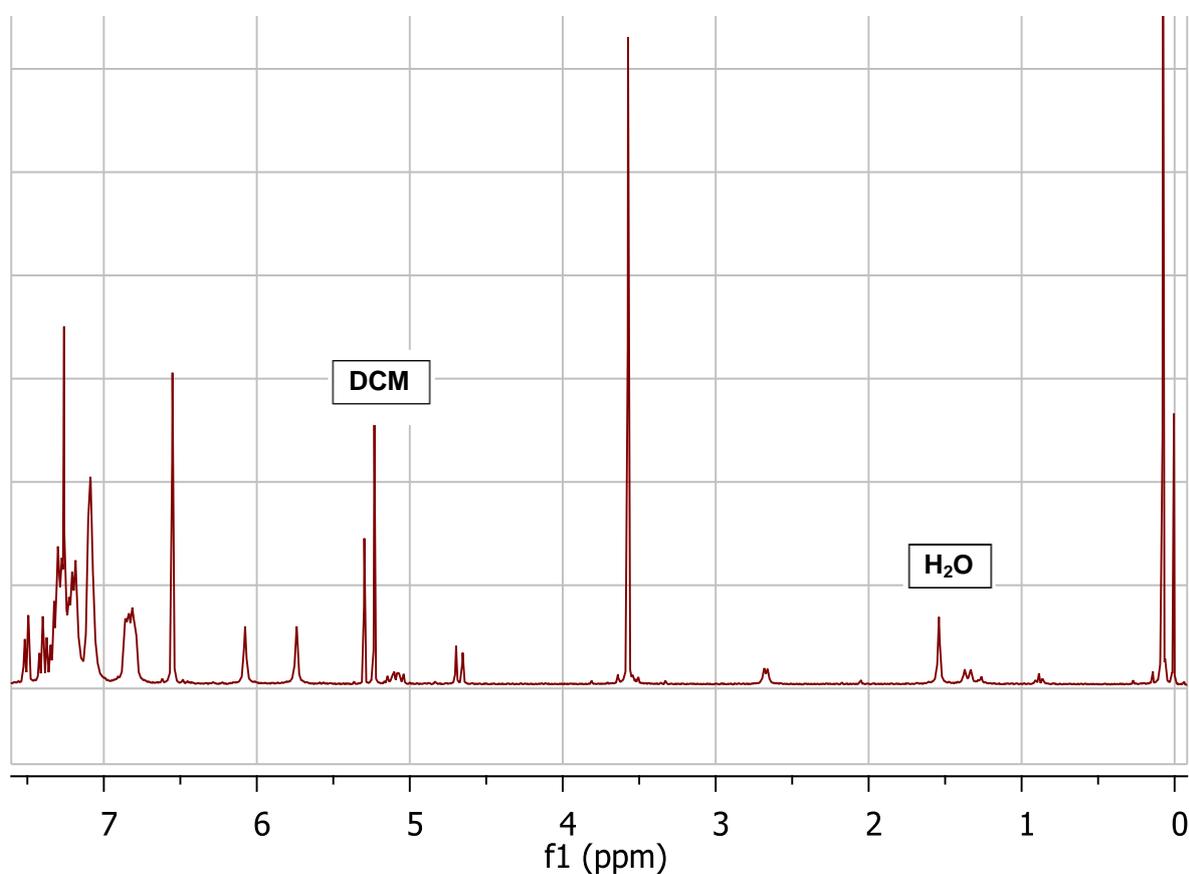
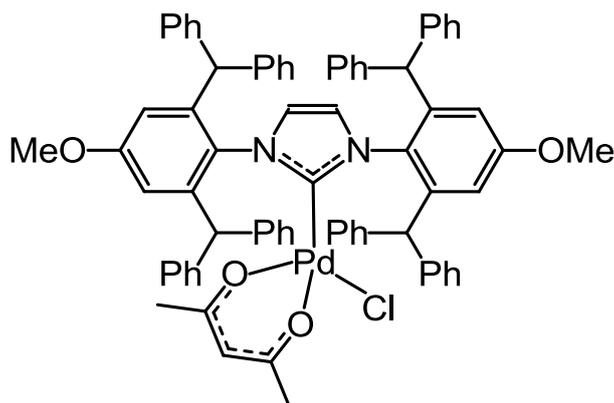
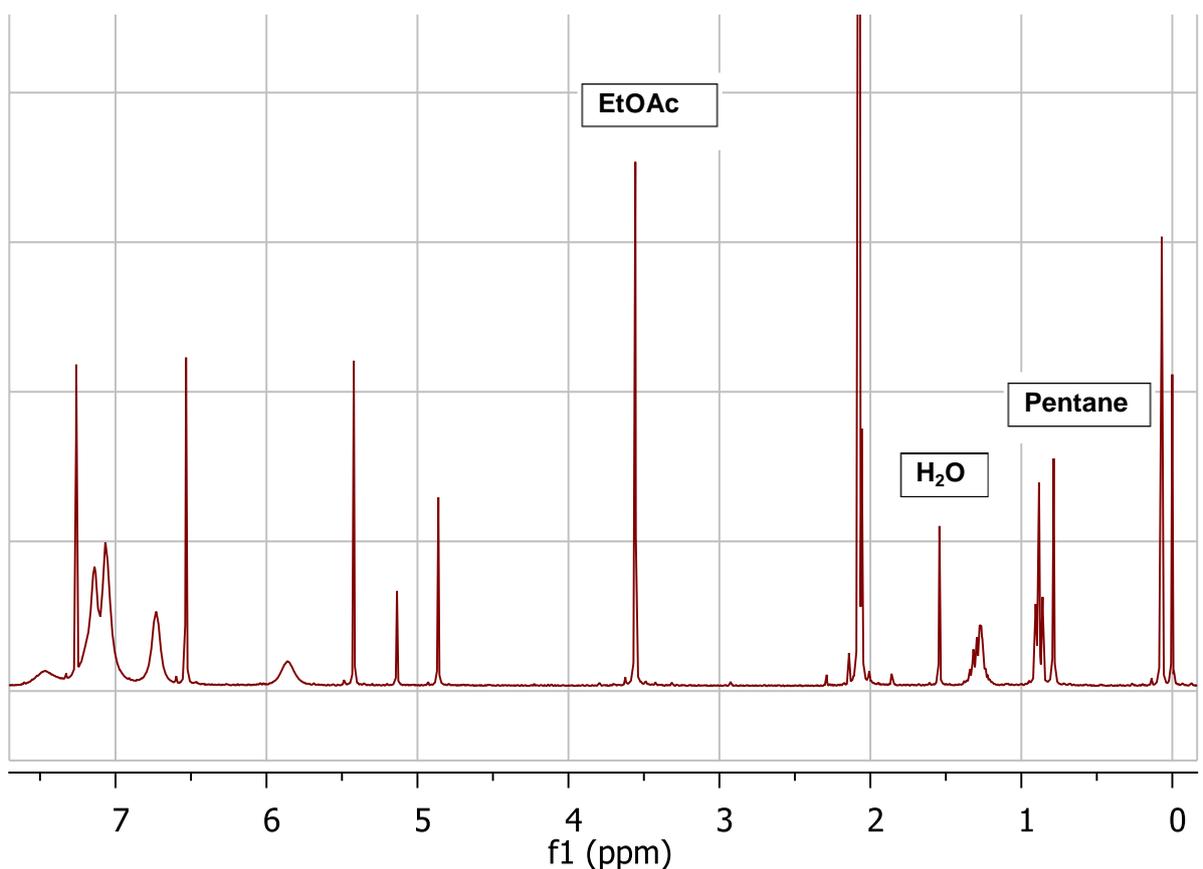


Figure 16 - ¹H NMR spectrum of Pd(IPr*^{OMe})(cin.)(Cl) (**15**).

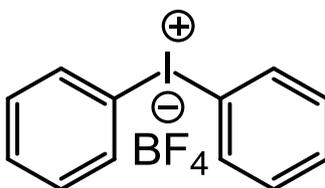
Pd(IPr^{*OMe})(acac)(Cl) (16)⁹

IPr^{*OMe}·HCl (**14**) (0.120 g, 0.122 mmol, 1.1 equiv.) was dissolved and stirred in anhydrous and degassed 1,4-dioxane (5 mL) and heated to 100 °C, resulting in a creamy-white solution. Pd(acac)₂ (0.034 g, 0.111 mmol, 1 equiv.) was then added, which caused the solution to darken to a creamy-yellow colour, and the solution was stirred for 24 hours. The solvent was then evaporated under reduced pressure and the resulting crude solid was dissolved in DCM and eluted with DCM by filtering through a pad of silica covered with Celite. The solvent was then evaporated under reduced pressure and the resulting material was purified by recrystallization in hot toluene which was assisted by the addition of pentane to obtain the product (**16**) (0.085 g, 65%) as a bright yellow solid. The spectroscopic data was in full agreement with the literature.⁹

¹H NMR (300 MHz, CDCl₃) δ 7.47 (vbs, 4H, Ar-H), 7.26 – 7.07 (vbs, 32H, Ar-H), 6.73 (vbs, 8H, Ar-H), 6.53 (s, 4H, Ar-H), 5.86 (vbs, 4H, CHPh₂), 5.14 (s, 1H, CH^{acac}), 4.86 (s, 2H, N-CH=CH-N), 3.56 (s, 6H, Ar-OCH₃), 2.06 (s, 3H, CH^{acac}), 0.79 (s, 3H, CH^{acac}).

Figure 17 - ^1H NMR spectrum of $\text{Pd}(\text{IPr}^*\text{OMe})(\text{acac})(\text{Cl})$ (16).

Diphenyliodonium tetrafluoroborate (17)¹⁰



Dry and recrystallized mCPBA (81% active oxidant, 0.640 g, 3.00 mmol, 1.1 equiv.) was dissolved and stirred in anhydrous DCM (12 mL). To this solution, distilled iodobenzene (0.31 mL, 2.7 mmol, 1 equiv.) was added followed by the slow addition of $\text{BF}_3 \cdot \text{OEt}_2$ (0.85 mL, 6.8 mmol, 2.5 equiv.), changing the solution from colourless to yellow instantaneously. As more Lewis acid was added, the solution was seen changing colour from a bright yellow to a bright orange colour. The solution was continued to stir at room temperature for 30 min. The solution was then cooled to 0 °C thereafter and phenylboronic acid (0.370 g, 3.00 mmol, 1.1 equiv.) was added which caused the solution to turn light brown. After 15 min of stirring at room temperature, the reaction mixture was filtered through a silica plug (6 g) and eluted with DCM, to remove any unreacted aryl halide, boronic acid and oxidant, followed by DCM/MeOH (120 mL, 20:1) to elute the product. The filtrate was concentrated under

reduced pressure and to this solution was added diethyl ether (10 mL) to induce precipitation and to partition any iodine (III) intermediates and BF_3 derivatives into an ether phase, turning the solution milky-white. The solution was allowed to stir for 15 min and the ether phase containing impurities (white solution) was decanted from the DCM phase which contained the product (brown solution). The precipitate that formed was then washed twice more with diethyl ether (2 x 10 mL) and the dried under high vacuum to obtain the salt (**17**) (0.763 g, 74%). The spectroscopic data was in full agreement with the literature.¹⁰

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.25 (dd, $J = 8.2$ Hz, 4H), 7.67 (tt, $J = 7.5$ Hz, 2H), 7.53 (tt, $J = 7.7$ Hz, 4H).

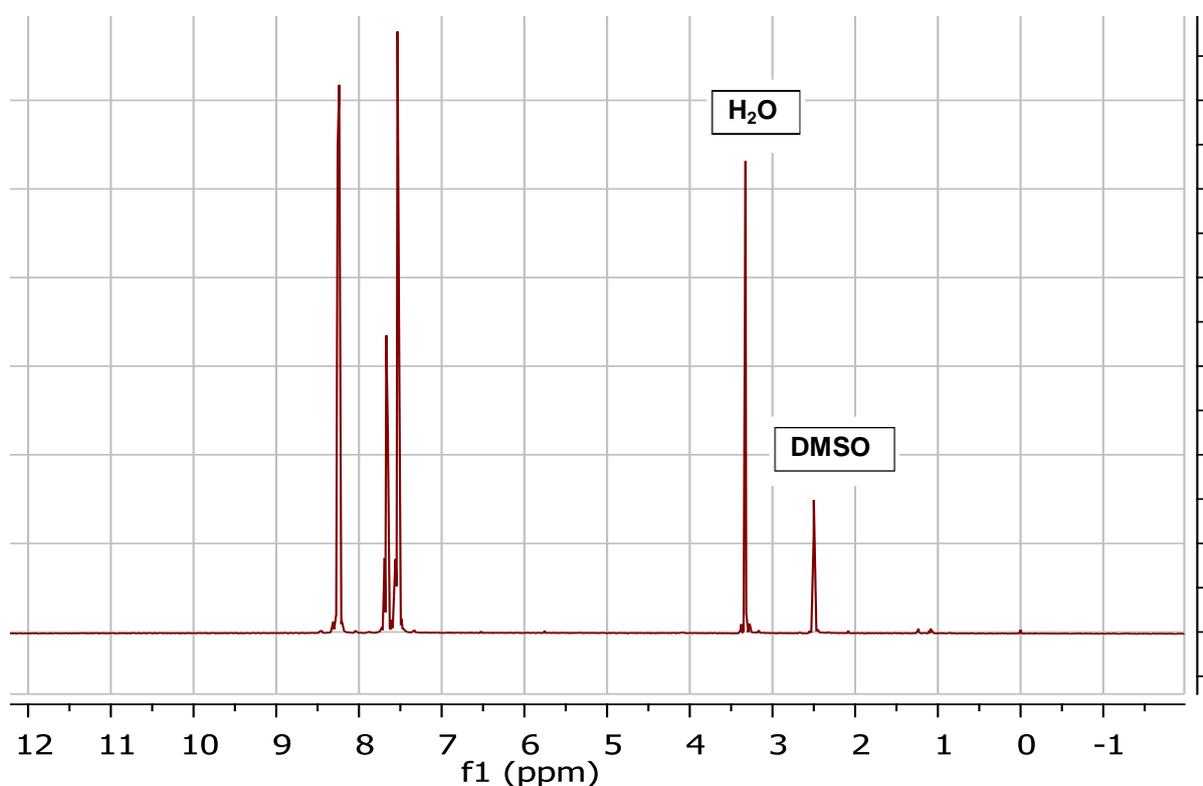


Figure 18 - $^1\text{H NMR}$ spectrum of diphenyliodonium tetrafluoroborate (**17**).

5.3 References

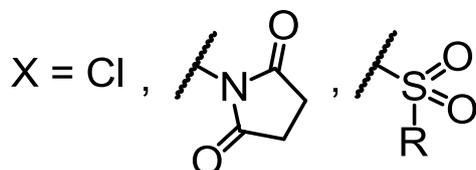
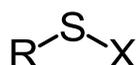
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Addendum A

Introduction

The ortholithiation method, when using benzenesulphenylchloride and *tert*-butyl disulphide as electrophiles, proved unsuccessful in the attempts of synthesizing the phenyl and *tert*-butyl thioether resorcinarene respectively. The route of catalysis via Pd(IPr^{*OMe})(cin.)(Cl) was also investigated in the attempt of coupling the phenyl thioether functionality onto the resorcinarene, but also proved unsuccessful. It was of interest to evaluate the compatibility of other sulphur-derived electrophiles with the ortholithiation procedure in the synthesis of said ligands. A procedure of synthesizing diaryl thioethers from other alkyl thioether and thiols was also found in the literature and investigated. Lastly, it was of interest to shed some light on the ambiguity around the identity of the structures of silver and nickel resorcinarenes complexes that was synthesised on the 'propyl-footed' resorcinarene scaffold. Therefore the synthesis of more crystalline resorcinarene platforms were attempted in the hopes of synthesizing more crystalline versions of these complexes, which may allow the use of X-ray diffraction analysis to elucidate the identity of their structures. However, due to time constraints these investigations could not be completed and therefore should be considered as future work for this project (refer to **Conclusions and Future Work – Chapter 4**).

Other Sulphur-derived Electrophiles



It was decided to investigate other sulphur-derived electrophiles to be used in the ortholithiation approach in the hopes that altering the leaving group would bring about the installation of the phenyl and *tert*-butyl thioether functionalities (in a distal fashion) onto the *ortho*-position of the resorcinarene. Sulphenyl chlorides are the best sulphur-derived electrophiles to use within the ortholithiation procedure.

Thiosuccinimides

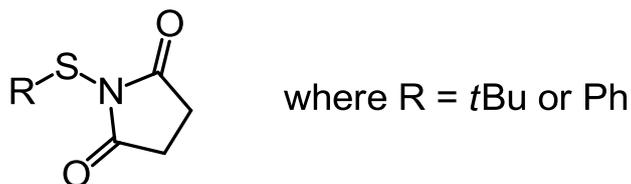
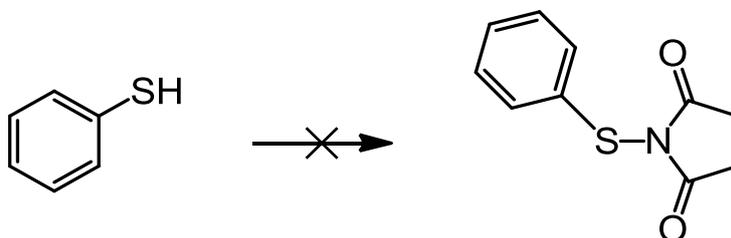


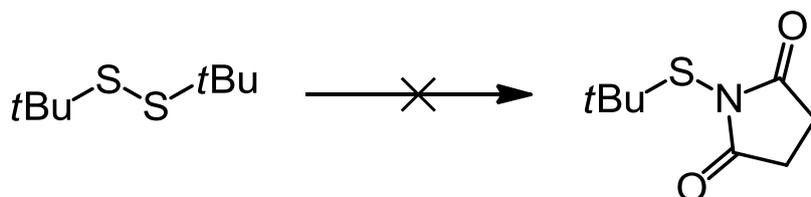
Figure 1 - Thiosuccinimides.

Thiosuccinimides (Figure 1) are regarded as good sulphur-derived electrophiles as the conjugate base, the succinimide group, are good leaving groups, as compared to the thiolate leaving group that is generated when using disulphides as electrophiles. This is due to the fact that their conjugation can stabilize the negative charge imparted on them when the electrophilic centre (sulphur) is attacked by a nucleophile. The synthesis of phenylthiosuccinimide¹ (Scheme 1) involves a typical S_N2 mechanism; however no reaction occurred as only unreacted starting material was recovered from the reaction.



Scheme 1 - Attempted synthesis of phenylthiosuccinimide.¹ Reagents and conditions:
i) NCS (1.1 equiv.), benzene, r.t.; ii) Et₃N (1.2 equiv.), 0°C to r.t.

Synthesis of the *tert*-butylthiosuccinimide² from the corresponding disulphide (Scheme 2) involves a radical mechanism that homolytically cleaves the disulphide bridge; again no reaction occurred as only unreacted NBS and disulphide was isolated after the reaction was complete. The reaction was also attempted with a catalytic amount of azoisobutyronitrile (AIBN) in order to help facilitate radical formation, but had no effect as the same end result was obtained.



Scheme 2 - Attempted synthesis of *tert*-butylthiosuccinimide.² Reagents and conditions: NBS (1 equiv.), benzene, reflux, 2 hours.

Thiosulfonates

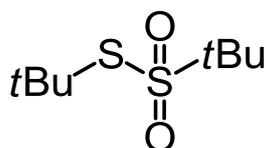
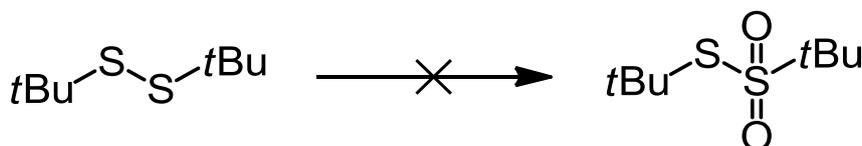


Figure 2 - Di-*tert*-butylthiosulfonate.

Thiosulfonates (Figure 2) are better sulphur-derived electrophiles than disulphides for the same reason why succinimides are better electrophiles than disulphides; a better leaving group is employed within the molecule. Synthesis of thiosulfonates from disulphides³ (Scheme 3), using excess oxidizing agent (peracetic acid formed *in situ*), suffers heavily from side reactions returning the sulphoxide as the major product and polysulphides, thioanhydrides and the desired thiosulfonate as minor products in negligible yields.

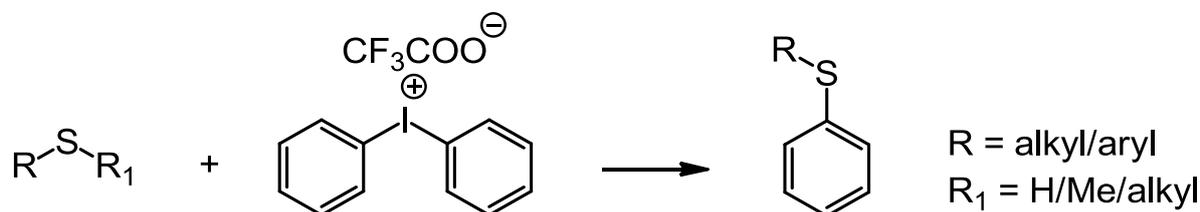


Scheme 3 - Attempted synthesis of *tert*-butylthiosulfonate.³ Reagents and conditions: AcOH (25 equiv.), H₂O₂ (25 equiv.), EtOAc, r.t., overnight.

Sulphur Nucleophiles

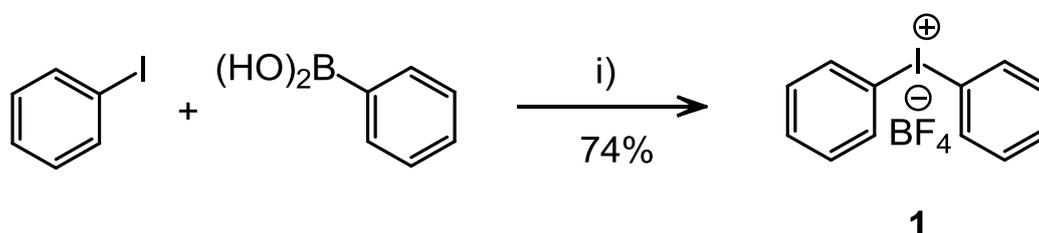
Other procedures using sulphur-derived reagents as nucleophiles to acquire the desired transformation on the resorcinarene scaffold were investigated. It was thought that the use of sulphur-derived reagents as nucleophiles instead of electrophiles might deliver more positive results in attempts to derivatise the resorcinarene with thioether moieties. Wagner and co-

workers⁴ has reported a transition-metal-free, acid-mediated synthesis of arylthioethers from alkylthioethers and thiols (Scheme 4).



Scheme 4 - Synthesis of arylthioethers as reported by Wagner.⁴
Reagents and conditions: TFA (2 equiv.), 1,4-dioxane, reflux, 15 hours.

The synthesis involves an aryl transfer using diaryliodonium salts as a source of electrophilic aryl reagents (Scheme 5). Diaryliodonium salts have received much interest for their high reactivity, non-toxicity, being easily synthesised and their efficiency in employing aryl groups onto molecular frameworks.⁵ Diphenyliodonium tetrafluoroborate salt (**1**) was easily synthesised as depicted in Scheme 5.⁶ Since the methyl thioether moiety can be employed onto both the model system and the resorcinarene within reasonably good yields, these compounds can be used starting materials from which the arylthioether can theoretically be synthesised. The synthesis of 1,3-dimethoxy-2-phenylthiylbenzene via the method reported by Wagner was then attempted starting from the model compound of the methyl thioether resorcinarene ligand, namely 1,3-dimethoxy-2-methylthiylbenzene (**2**) (Scheme 6). However, no reaction occurred between the functionalized model system and the diphenyliodonium tetrafluoroborate salt which suggested that reaction is not possible on the resorcinarene.



Scheme 5 - Synthesis of diphenyliodonium tetrafluoroborate.⁶ Reagents and conditions:
i) m-CPBA (1.1 equiv.), BF₃·OEt₂ (2.5 equiv.), DCM, r.t., 1 hour.

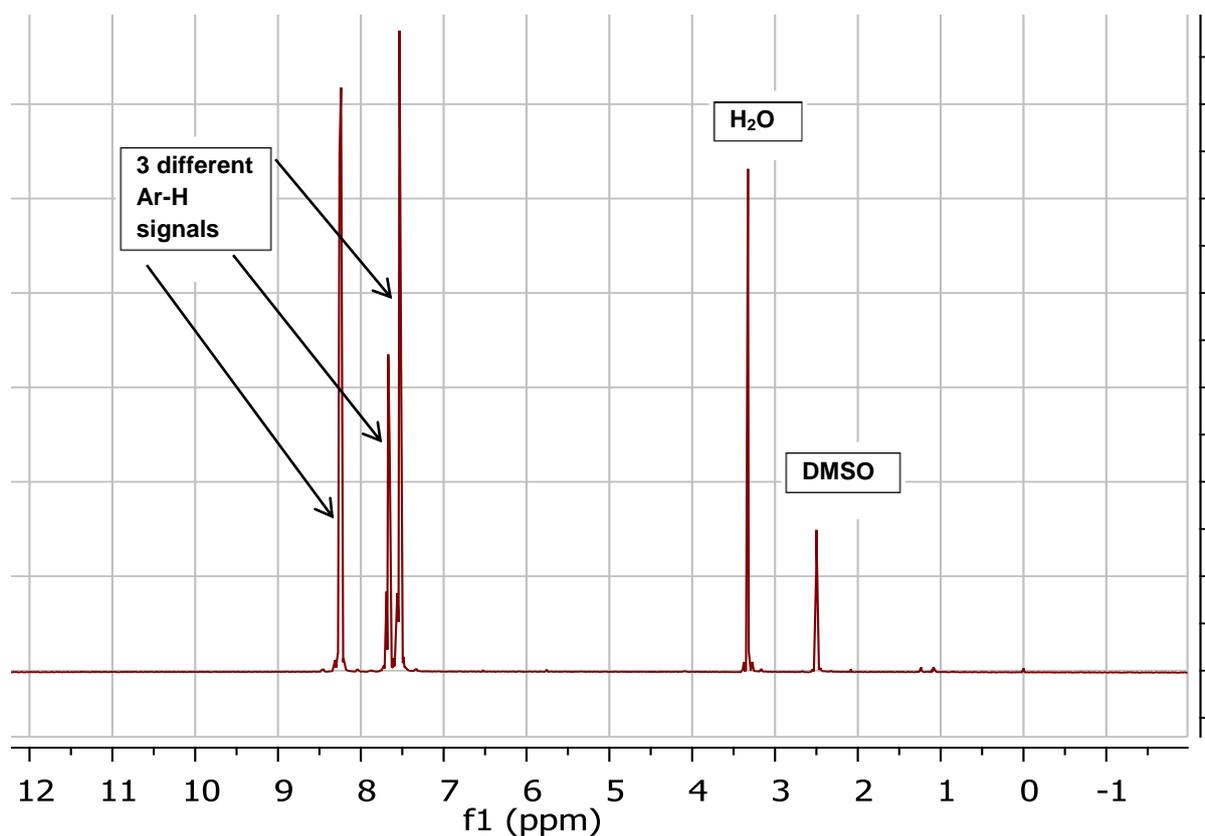
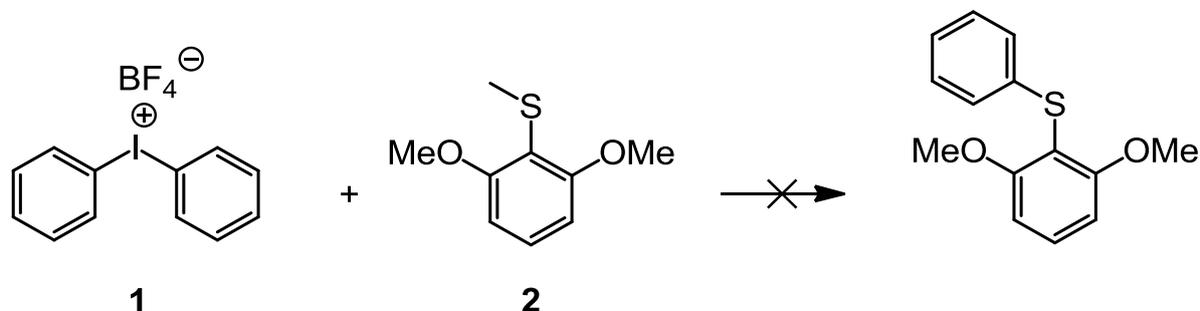


Figure 3 - ^1H NMR spectrum of diphenyliodonium tetrafluoroborate.

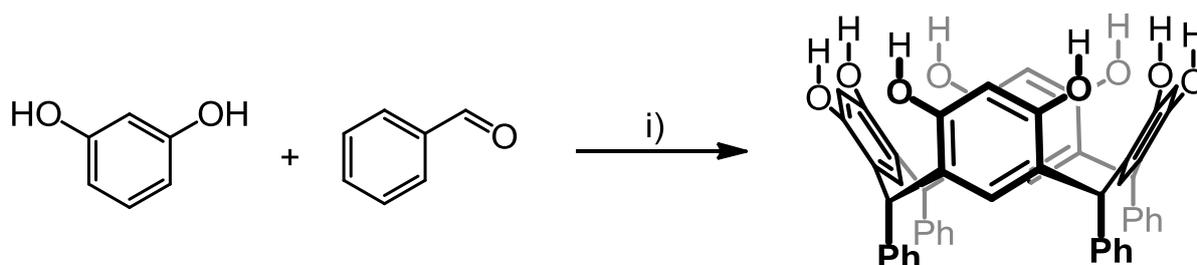


Scheme 6 - Attempted synthesis of 1,3-Dimethoxy-2-phenylthiylbenzene via the procedure reported by Wagner.⁴
Reagents and conditions: TFA (2 equiv.), 1,4-dioxane, reflux, 15 hours.

The synthesis reports diphenyliodonium trifluoroacetate as the used precursor salt, however it was speculated that the role of the counter-ion that is involved in the reaction to be insignificant. Two equivalents of trifluoroacetic acid (TFA) was mistakenly used within the procedure instead of eight equivalents. The procedure emphasizes on using eight equivalents of TFA, as optimization showed to return the best yields when using eight equivalents.

'Phenyl-Footed' Resorcinarenes

'Phenyl-footed' resorcinarenes can be synthesised by reacting benzaldehyde with resorcinol under acidic conditions. These types of resorcinarenes are well-known within in the literature and have been synthesised and studied by the likes of Adolf von Baeyer and Hans-Erik Högberg. It was speculated that these phenyl tethered resorcinarenes, or the longer phenyl tether chained resorcinarenes, to be more crystalline than the alkyl-footed resorcinarenes due to possible π - π (π - π) stacking of these phenyl tether chains. These resorcinarenes could then be theoretically be derivatised in the same distal fashion as their alkyl-footed brothers, and could subsequently be complexed with the same metal sources as the alkyl-footed resorcinarene ligands have shown to do. It was decided to synthesise the 'phenyl-footed' resorcinarenes as this may have presented a way to provide insight around the identity of the structure of the metal centre motifs that were produced when the 'propyl-footed' methyl thioether resorcinarene ligands were complexed with nickel and silver, as these propyl-footed complexes were too unstable and therefore crystals of the complexes couldn't be grown successfully. The synthesis described by Högberg and others⁷ (Scheme 2) that used the conventional way of producing resorcinarenes i.e. in ethanol and using hydrochloric acid was recreated, but at first there was some slight uncertainty whether the synthesis of the 'phenyl-footed' resorcinarene was successful or not as the only reference proton spectrum that was provided by Högberg and others were for the acylated protected 'phenyl-footed' resorcinarene ethers.



Scheme 7 - Synthesis of 'phenyl-footed resorcinarenes as reported by Högberg.⁷ Reagents and conditions: resorcinol (1 equiv.), benzaldehyde (1 equiv.), 32% HCl(aq) (2 equiv.), EtOH, reflux, overnight.

The ¹H NMR spectrum (Figure 4) was collected in deuterated DMSO and showed signals containing the relative correct integration one would expect to obtain for the intended product. The ¹³C spectrum (Figure 5) further re-affirmed that the synthesis of the 'phenyl-footed' resorcinarene was successful as eight distinct signals were found in the spectrum which corresponds to the eight chemically inequivalent carbons of the intended product. The compound that was obtained via this procedure matched the colour reported by Högberg, but

also slightly different colours of solids were isolated in the reaction as reported by Högberg, most of these different coloured solids produced almost identical ^1H NMR spectra, with the addition of a few minor signals. It was suspected that these different colours could be brought about by the different conformational isomers that the resorcinarenes can adopt, as reported by Högberg. Crystals were attempted of being grown by using a variety of different solvents and solvent systems; however no crystals could be grown. The return of a brighter orange coloured solid was found in most recrystallization attempts. A ^1H spectrum of the solid material that was returned from the attempted recrystallizations showed the disappearance of the minor signals that were previously seen within the ^1H spectrum of the crude material. All of solids that were synthesised by this reaction were sent for analysis by mass spectroscopy in an attempt to confirm if the products that were isolated contained the molecular ion peak one would expect for a 'phenyl-footed' resorcinarene. The HRMS (High Resolution Mass Spectroscopy) spectrum for the same compound shown in the ^1H NMR spectrum is presented (Figure 6). The HRMS spectrum contained the molecular ion cluster of signals ($[\text{M}+\text{H}]^+$) for the intended product centred at 793 amu, however in relatively low abundance. The HRMS spectrum also contained the signal for the $[\text{M}+\text{NH}_4]^+$ at 823 amu in a slightly higher abundance than compared to $[\text{M}+\text{H}]^+$. Surprisingly an unknown signal at 805 amu was detected that was 100% abundant. Unfortunately due to time constraints the 'phenyl-footed' resorcinarenes was not further investigated.

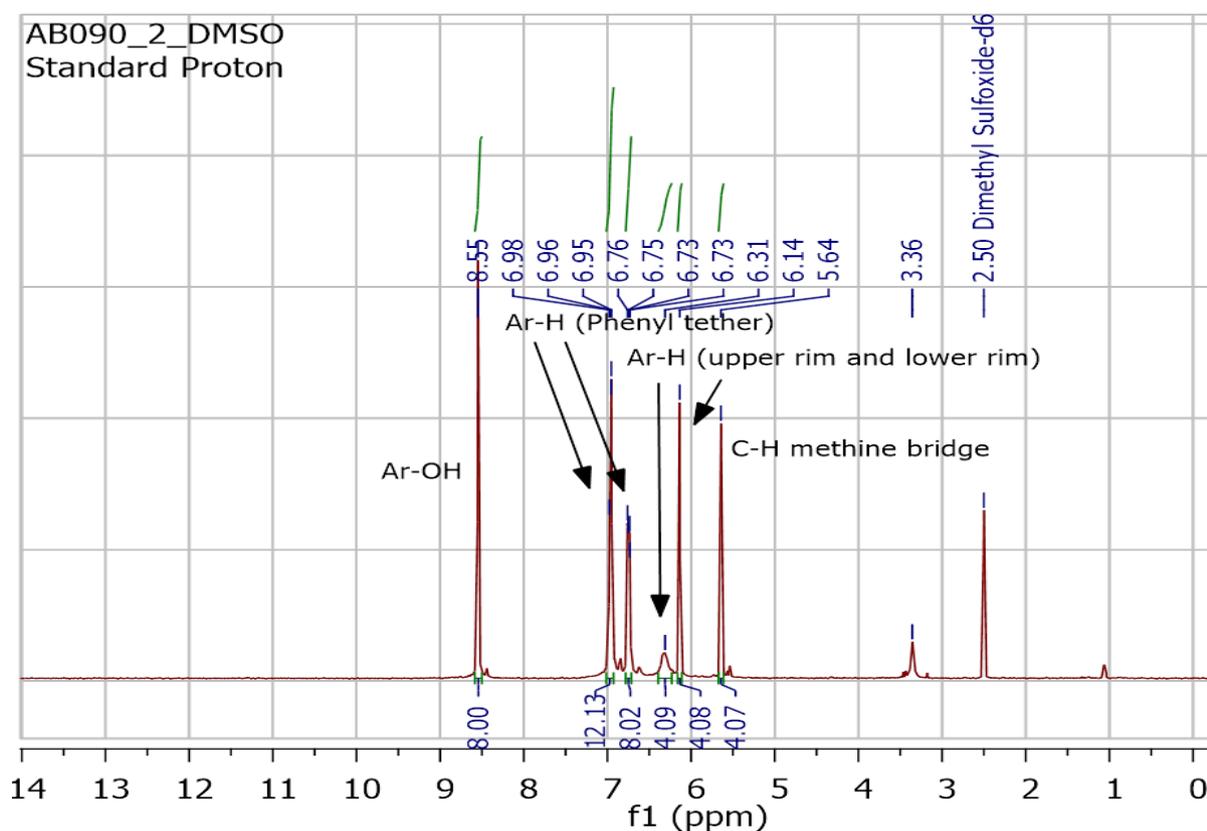


Figure 4 - ^1H NMR spectrum of one of the compounds that was synthesised as reported by Höberg (Scheme 2). Assignments are not absolute and have been tentatively made based on similar structures (refer to Experimental).

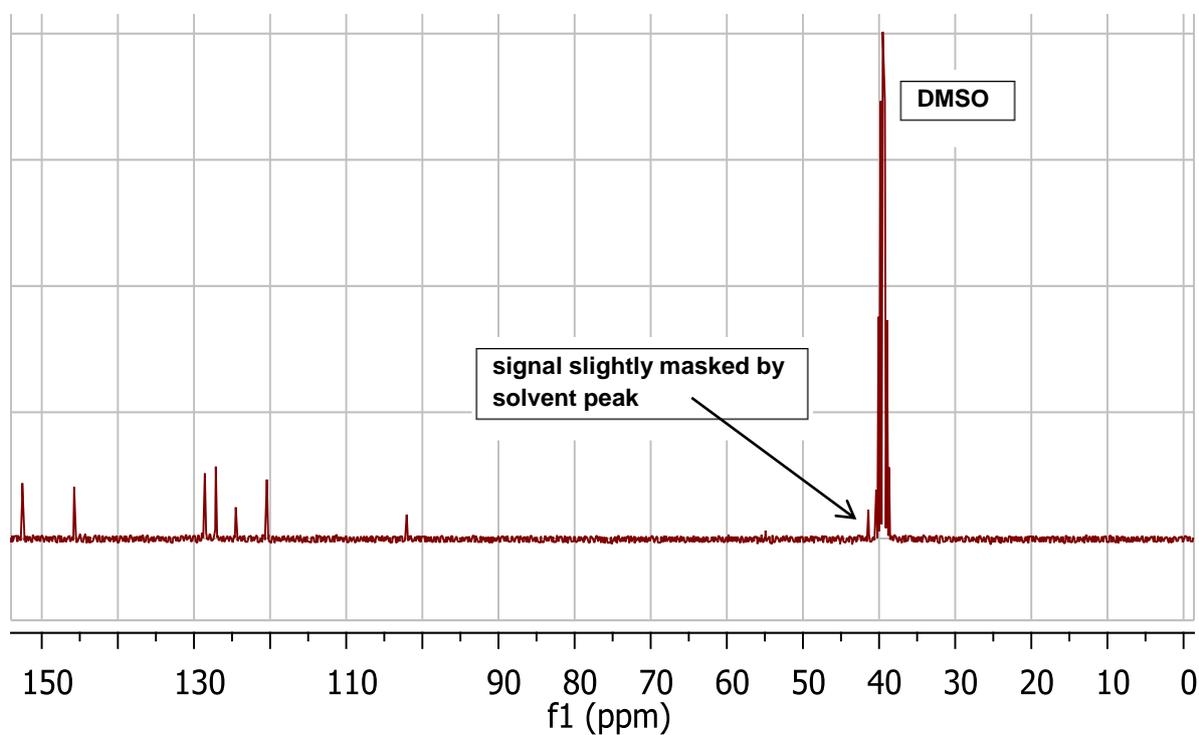


Figure 5 - ^{13}C NMR spectrum of the 'phenyl-footed' resorcinarenes as reported by Höberg (Scheme 2). Assignments are not absolute and have been tentatively made based on NMR prediction software (refer to Experimental).

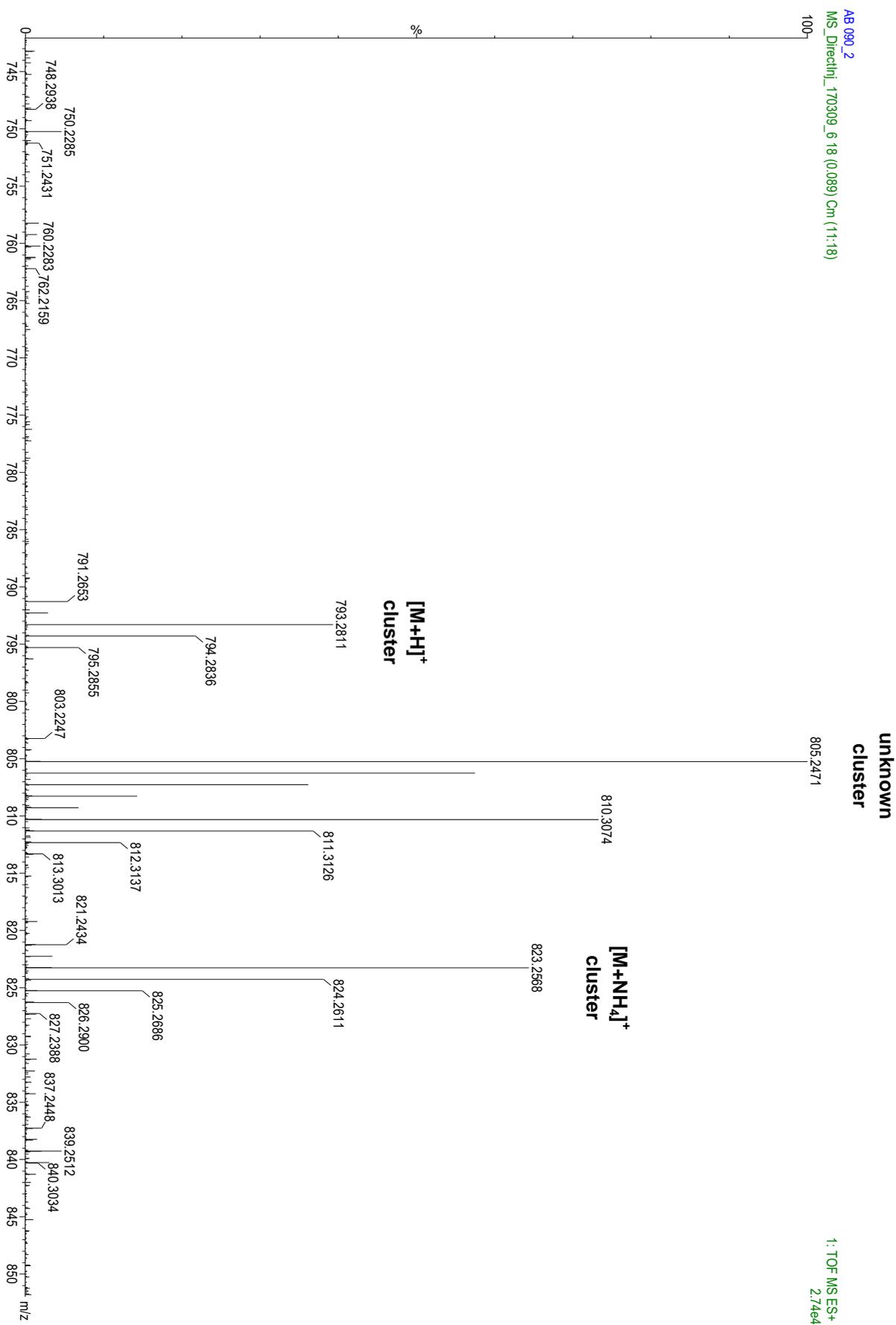


Figure 6 - HRMS spectrum of the product produced from the reaction depicted in Scheme 2.

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