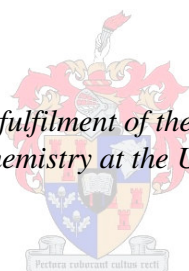# Studies in the Selective Synthesis of Bidentate Resorcinarene Ligands

by
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Thesis presented in partial fulfilment of the requirements for the degree
Master of Science in Chemistry at the University of Stellenbosch

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Department of Chemistry and Polymer Science

March 2010

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 qualification.

March 2010

Summary

Resorcinarenes are macrocyclic products formed from the condensation of aldehydes (aliphatic or aromatic) and resorcinol and have been used in a wide range of applications since their first synthesis. Applications include: HPLC stationary phases for the separation of pyrimidine bases, racemic drugs and isomers, the selective extractions of lanthanides and actinides, as molecular receptors, catalysis, NMR chiral shift agents, GC separations and as starting materials for the synthesis of macrocyclic compounds (e.g. cavitands and carcerands) to name but a few. The use of resorcinarenes in catalysis is still quite new and unexplored, while catalysis using calix[4]arenes, a related macrocycle, has been widely studied. In this thesis it was attempted to synthesise a C_{2v} symmetric resorcinarene precursor that could be further functionalised to form distal bidentate ligands for coordination to transition metals. These compounds would then ultimately be used in catalytic testing, especially for Pd catalysed C-C bond formation.

A dibromo resorcinarene precursor was synthesised starting from resorcinarene, using methodology developed by Shivanyuk. This molecule was functionalised with a small range of different electrophiles using lithium halogen exchange methodology, although low yields were returned for the expected distal resorcinarene compounds. Other methods of functionalisation of the resorcinarene, using an anionic *ortho*-Fries rearrangement and the reduction of a dinitrile resorcinarene to amine and aldehyde functionalities proved unsuccessful.

Using a dithioether resorcinarene a di-nuclear coordination compound was formed with Pd(II). This compound was tested for catalytic activity with a Heck reaction, showing low yields for the coupling of styrene with bromobenzene.

Opsomming

Resorsinarene is makrosikliese produkte wat gevorm word deur die kondensasie van aldehiede (alifaties of aromaties) met resorsinol en word in 'n verskeidenheid van toepassings gebruik sedert hulle eerste sintese. Tipiese voorbeelde sluit in: stationêre fases vir die HPLC-skeiding van pirimidien-basisse, rasemiese farmaseutiese middels en isomere, die selektiwe ekstraksie van lantaniede en aktiniede, molekulêre reseptore, katalise, chirale verskuiwingsreagense vir KMR spektrometrie, GC-skeidings en as uitgangverbindings vir die sintese van ander makrosikliese verbindings (bv. kavitande en karserande). Die gebruik van resorsinarene in katalise is 'n splinternuwe onontginde veld. In teenstelling hiermee is calix[4]areen, 'n verwante makrosikliese verbinding, baie meer bestudeer en vir katalise gebruik. Die doel van hierdie tesis was om 'n C_{2v} simmetriese uitgangstof te sintetiseer wat verder gefunksionaliseer kan word om distale, bidentate ligande vir koordinasie met oorgangsmetale te lewer. Daar is beplan om die katalitiese eienskappe van die komplekse te toets, veral vir Pd-gekataliseerde C–C-koppelings reaksies.

Deur gebruik te maak van 'n protokol wat deur Shivanyuk ontwikkel is, is 'n dibromo-resorsinareen gesintetiseer uit resorsinareen. Verskillende elektrofiele is in 'n litium-halogeen uitruilreaksie gebruik om 'n beperkte verskeidenheid nuwe ligande te sintetiseer wat verskillende funksionele groepe besit. Ongelukkig was die opbrengste aan distale ligande baie laag en ander metodes is dus ook ondersoek om die funksionalisering te bewerkstellig. 'n Anioniese *orto*-Fries herrangskikkingsreaksie en die reduksie van 'n dinitriel-resorsinareen om amien- en aldehiedfunksies te lewer, was ook onsuksesvol.

Die reaksie tussen 'n Pd(II) sout en 'n ditioeter-gederivatiseerde resorsinareen het 'n koordinasie verbinding met twee metaalkerne gelewer. Hierdie kompleks is deur middel van 'n Heck-koppelingsreaksie vir katalitiese aktiwiteit getoets, maar het lae opbrengste gelewer in die koppeling van stireen en bromobenseen.

Acknowledgements

A research project like this cannot be undertaken if you don't have the support and tutelage of a truly passionate teacher and mentor. That is why I first and foremost want to thank Dr. Gareth Arnott for the countless hours spent on teaching me not only the finer details of chemistry, but also of life. Thank you for your constant motivation, support, honesty and the needed stern word if the situation required it.

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To all my friends (outside chemistry) I truly want to say thank you. Your constant inquiries into the welfare of me and my studies are truly appreciated, even if I know you don't have a clue what I am talking about.

Then lastly to my family and especially the three most important women in my life: my girlfriend Hestie, my sister Ilse and my mother Isabel. Thank you for all the support, love, encouragement, wisdom and the odd food parcel from home. Without all of you I would be a mere shadow of the person I am and could not have done this.

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>   Dr. J Brand, Elsa Malherbe en Trevor Wright for NMR help

Table of Contents

List of Technical Abbreviations

ATR-IR	Attenuated Total Reflection Infrared Spectroscopy
COSY	Correlation Spectroscopy
DoM	Directed Ortho Metallation
ESI	Electrospray Ionization
HMBC	Heteronuclear Multiple Bond Coherence
HSQC	Heteronuclear Single Quantum Coherence
IR	Infrared Spectroscopy
m-CPBA	*meta*-Chloroperoxybenzoic acid
NMR	Nuclear Magnetic Resonance
Tlc	Thin Layer Chromatography

Introduction

1.1 Review of Resorcinarene Chemistry

Resorcinarenes (Figure 1.1) are macrocyclic products formed from the condensation of aldehydes (aliphatic or aromatic) and 1,3-dihydroxybenzene (resorcinol). The first recorded synthesis of resorcinarenes was in 1872 by Adolf von Baeyer, in his studies on the condensation of phenol-type dyes with aldehydes in acidic media.[1] The correct structure of these compounds was proposed in 1940 by Niederl and Vogel,[2] and confirmed in 1968 by Ertdman *et al.* using single crystal X-ray diffraction.[3, 4] These compounds are known by a host of trivial names which includes calix[4]resorcinarenes,[5] Högberg compounds,[6] octols[7, 8] and recently resorcinarenes became the staple term used in the literature.[9]

Resorcinarenes have been used in a wide range of applications since their first synthesis. Applications include: HPLC stationary phases[10-15] for the separation of pyrimidine bases,[13] racemic drugs[10] and isomers,[11, 14] the selective extractions of lanthanides and actinides,[16-24] as molecular receptors,[25-36] NMR chiral shift agents,[37, 38] GC separations[39, 40] and as starting materials for the synthesis of macrocyclic compounds (e.g. cavitands and carcerands) to name but a few.[41-43] A few reviews on different aspects of these molecules have been published, [44-50] with the early review of Timmerman being a good general introduction to these molecules.[50]
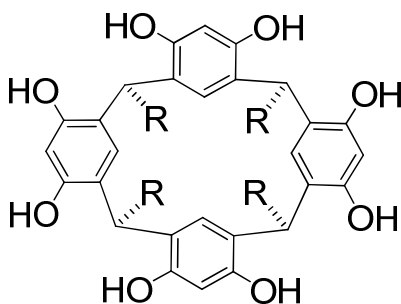
Figure 1.1.   General Structure of Resorcinarenes (R=aliphatic/aromatic)

1.1.1 Synthesis of Resorcinarenes

The synthesis of resorcinarenes can be achieved in high yields using a simple one-pot reaction. The general method entails the condensation of an aldehyde (aromatic or aliphatic) with resorcinol in an acidic alcoholic medium after which the cyclic product crystallises out of solution; depending on the aldehyde used, different reaction conditions are needed for optimum product formation.[8] In some cases it is also necessary to add water to the mixture to facilitate the crystallisation process.[51] The simplicity of this is that the product can be collected by filtration and purified using recrystallisation. In the late 1980's Cram

et al. reported a methodical study on the influences of functional groups on the aldehyde and resorcinol in the synthesis of resorcinarenes.[8] It was shown that using deactivating groups (e.g. NO_2, Br) on the 2 position in resorcinol lead to no cyclic products being formed. This was also the case when using very bulky aldehydes or aliphatic aldehydes with functionalities too close to the reaction centre e.g. glucose or $ClCH_2CHO$.[8, 52]

Alternative methods of synthesising these compounds were also developed over the past few years, since using the standard method hindered the formation of certain products, for example those of partially alkylated resorcinol units.[52] Most of these alternative methods use Lewis acids to perform the condensation. Examples of this include the condensation of benzaldehyde with resorcinol,[53] the treatment of 2,4-dimethoxybenzyl alcohol with trifluoroacetic acid,[54] a tetrameric condensation of 2,4-dimethoxycinnamates,[55-57] and an condensation using 2 equivalents of $BF_3 \cdot OEt_2$ in anhydrous dichloromethane.[58, 59]

More recent methods include a condensation of aldehydes with electron withdrawing groups on the 2 position of resorcinol in alkaline conditions,[60] microwave assisted synthesis using either mineral acids or a Keggin type 12-tungstophosphoric acid[61] and a solvent free synthesis by grinding the aldehyde and resorcinol together with a catalytic amount of *p*-toluenesulfonic acid.[62] This variety of methods indicates the flexibility and wide range of products that can be formed by a simple reaction under various conditions.
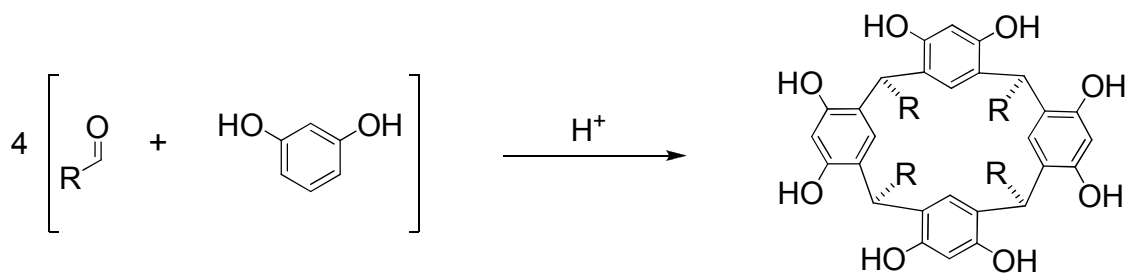
Scheme 1.1. General synthesis of resorcinarenes: R = aliphatic or aromatic

1.1.2 Mechanism of Resorcinarene Condensation
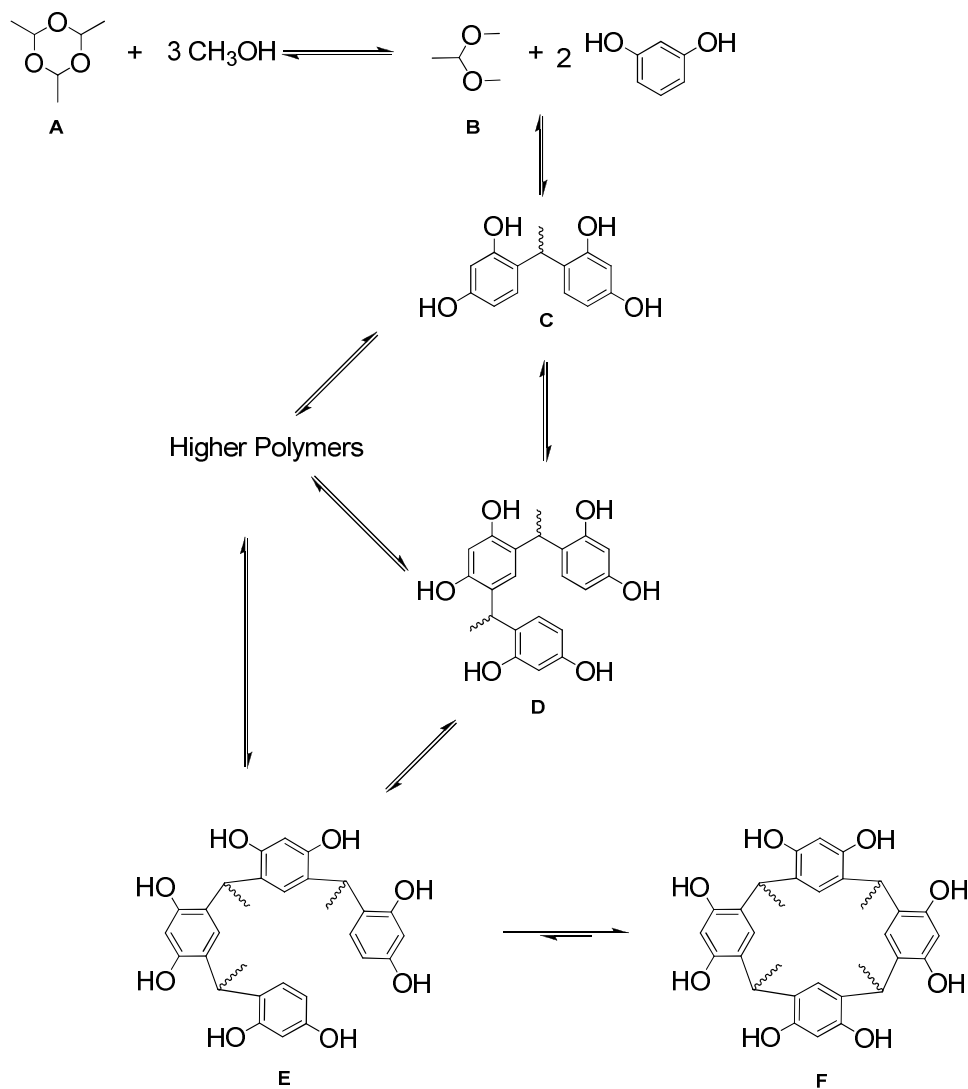
Scheme 1.2. Proposed mechanism for resorcinarene condensation according to the work of Weinelt and Schneider.

In 1991 Weinelt and Schneider proposed a mechanism for the acid-catalysed formation of resorcinarenes under homogeneous conditions (Scheme 1.2).[52] For this they chose to study the condensation of resorcinol and ethanal in a methanol/HCl solution. Using high-field ^{1}H NMR spectroscopy they could follow the build-up of intermediate oligomers and rings and could quantitatively assign these.

Under the reaction conditions the electrophile stems not from the aldehyde, but from the rapidly formed dimethyl acetal **B**. It was ascertained that the formation of the tetrameric **F** occurred via sequential additions of **B** with resorcinol units to form intermediate oligomers **C-E** or higher polymerisation compounds with more than four resorcinol units. These higher polymers are present in concentrations of

up to 45% at intermediate reaction times, but largely disappeared towards the end due to the condensation reaction being reversible. The dimers **C** and trimers **D** can be followed and assigned in the reaction, but no tetramers **F** were found on the NMR time scale in sufficiently high yields, due to the fast cyclisation of the tetramer. The fast cyclisations could be explained by the conformation that the tetramer adopts. The tetramer folds itself in such a way as to maximise the amount of hydrogen bonds that the different phenolic groups can form. This ensures that the two ends of the tetramer are close to one another and it is cyclised rapidly by **B**. It was also found that all intermediate compounds were found as resorcinol and not as hydroxyethyl units at the terminal positions, which was attributed to the fast reaction of such benzhydrols under the acidic conditions used.[63]

Kinetic studies showed that the chain growth and depolymerisation occurs quite fast and that cyclisation occurs faster than ring opening. This and the fact that under homogeneous conditions the resorcinarene tetramer is insoluble in the reaction media, forces the equilibrium to the far right and results in high yields of product.

1.1.3 Conformational Aspects of Resorcinarenes

Due to the non-planarity of resorcinarenes they can exist in many different isomeric forms. The stereochemistry of these molecules is generally defined as a combination of three stereochemical elements:
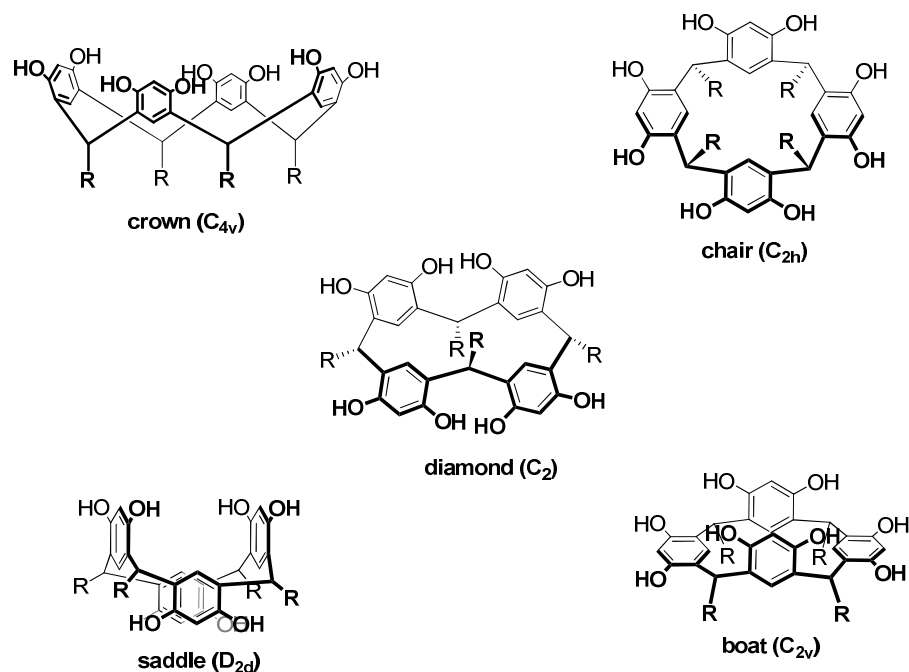
Figure 1.2. The five principle symmetrical arrangements that resorcinarens can adopt.

1) The conformation of the macrocyclic ring which can adopt five principle symmetrical arrangements. These include a crown (C_{4v}), boat (C_{2v}), chair (C_{2h}), saddle (D_{2d}) and diamond (C_s) conformations (Figure 1.2).

2) The relative configuration of the substituents at the methylene bridges giving all *cis* (ccc), *cis-trans-cis* (ctc), *cis-cis-trans* (cct) and *cis-trans-trans* (ctt) arrangements (Figure 1.3).

3) The individual configuration of the substituents at the methylene bridges which, in conformations of the macrocycle with C symmetry, may be either axial or equatorial.

Although a great many combinations can be formed from these three elements only four stereoisomers have been found experimentally.[50] These were investigated in detail by various groups using dynamic NMR and X-ray diffraction studies of resorcinarenes and their octaester derivatives.[8, 51, 64-66]
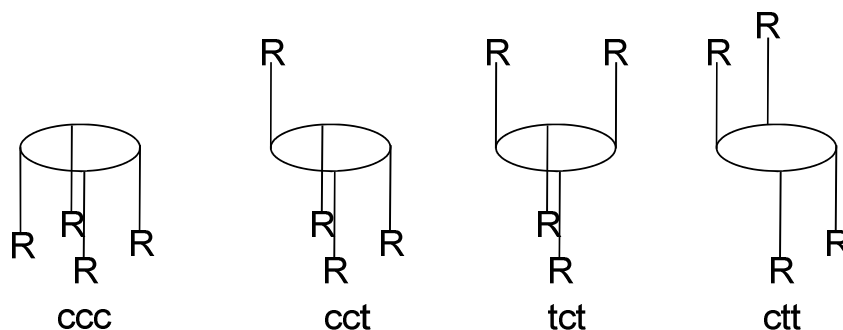
Figure 1.3.   The relative configurations that the substituents on the methylene bridges can adopt.

1.2 Functionalisation of Resorcinarenes

Resorcinarene molecules have two zones that could be accessed for functionalisation, namely the upper and lower rim of the molecule (Figure 1.4). Functionalisation of the lower rim usually begins from an already functionalised aldehyde;[67-70] These reactions will not be covered in this review. The upper rim of the molecule also exhibits two possible sites for chemical modifications: the phenolic groups and the ortho positions of the resorcinol moiety. For this review we will focus on the functionalisation of the ortho positions on the resorcinarene with special reference to selective methods of forming distal functionalised products.
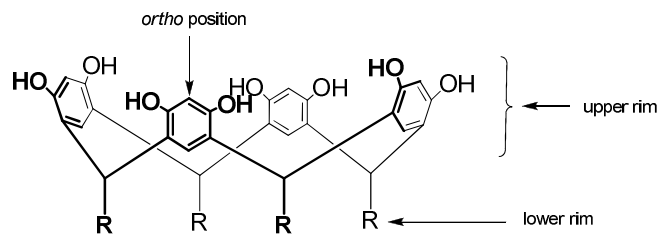
Figure 1.4.   Representation of the different areas of functionalisation on a resorcinarene

1.2.1 *Electrophilic Aromatic Substitution*

Owing to the presence of two electron donating phenolic groups the ortho position of the resorcinarene is highly activated for electrophilic aromatic substitution reactions. One of the easiest methods of functionalising this is by bromination with *N*-bromosuccinimide (NBS) returning the tetrabrominated product in up to 80% yield (Scheme 1.3).[7]
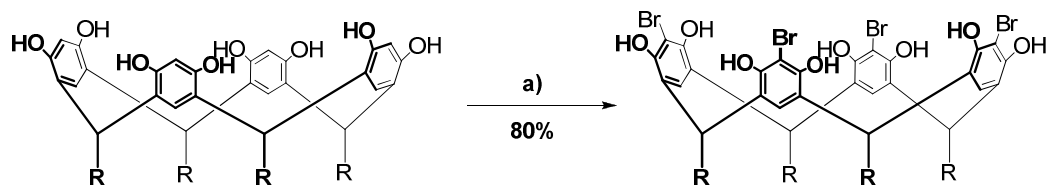
Scheme 1.3 Bromination of resorcinarenes. Reagents and reaction conditions: a) NBS, 2-butanone

The Mannich reaction, also known as α-aminoalkylation, is one of the main reactions employed in functionalisation of resorcinarenes and is a very flexible and essential method of forming carbon-carbon bonds.[71] This method relies on the reaction of amines (ammonia, primary, secondary) with aldehydes (mostly formaldehyde) on CH-acidic compounds. These reactions can be base- or acid-catalysed and yields depend greatly on the reagents used.
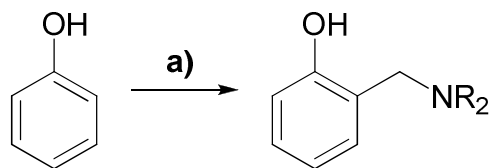
Scheme 1.4. Typical example of an aromatic Mannich reaction. Reagents and reaction conditions: a) HNR$_2$, formaldehyde, H$^+$/OH$^-$

The first example of this reaction on resorcinarenes was performed by Matsushita in 1993 (Scheme 1.5).[72] Mannich reactions with primary and secondary amines were performed in the presence of formaldehyde to form tetra-substituted resorcinarenes in good yields. It was also found that the primary amines reacted in a second Mannich-type reaction to form 1,3-dioxazine rings (product **b** in Scheme 1.5) with one of the phenolic hydroxyl groups. This was followed by an increasing number of publications using this methodology and especially in the synthesis of chiral resorcinarenes of which only a few are referenced here.[9, 73-77]
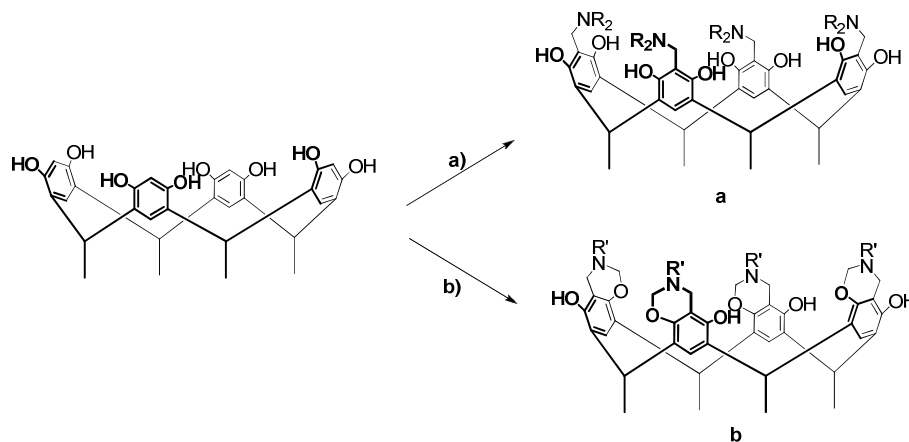
Scheme 1.5. Matsushita's functionalisation of resorcinarenes with the Mannich reaction using various secondary (a) and primary (b) amines.

1.2.2 Synthesis of distal-functionalised resorcinarenes

In 1997 Konishi reported a selective distal bromination of resorcinarenes using two equivalents of NBS in methyl ethyl ketone (product in Figure 1.5).[78] However, other authors reported that this method was not entirely effective in producing distal products in high yields as originally published.[78-80]
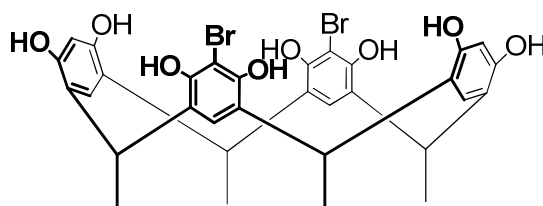
Figure 1.5.   Product from Konishi's selective bromination

An earlier method of selective synthesis was attempted by the group of Reinhoudt in 1996 (Scheme 1.6).[81] A tetramethyl resorcinarene cavitand was brominated using a free radical process with AIBN and NBS. This tetrakis(bromomethyl) product was allowed to react with less than four equivalents of potassium phthalimide to form a general statistical mixture of products that could be separated by column

chromatography. This was the first example of the formation of a distally substituted cavitand, without loss of functionality on the other two positions.

Various groups also reported that by using triply bridged resorcinarene skeletons, the different rates of reactivity of the bromines on these rings could be used to functionalise the molecule. These reactions are generally low yielding and need a lot of tailoring to obtain the final product.[82-84]

The poor selectivities obtained in this approach would not suffice for our use and two other, more effective, methods will be introduced. Due to the importance of each method in this work a short overview of the chemistry will be given followed by the uses of it on resorcinarenes.
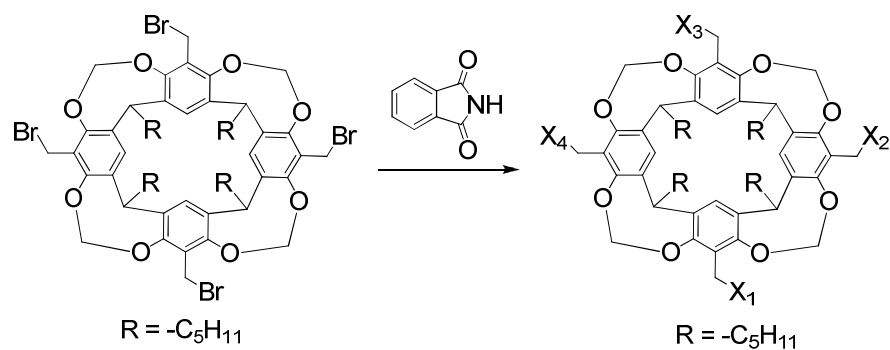
X$_1$	X$_2$	X$_3$	X$_4$	Yield (%)
phth	phth	phth	phth	2
phth	Br	Br	Br	8
phth	Br	phth	Br	25
phth	phth	Br	Br	12
phth	phth	phth	Br	28

Scheme 1.6. Reinhoudt's synthesis of distal resorcinarenes in refluxing toluene using two equivalents of potassium phthalimide.

1.2.2.1   Selective lithium-halogen exchange-an overview[85]

In the late 1930's Wittig and Gilman described the use of lithium reagents to synthesise aryllithium intermediates via a lithium-halogen exchange reaction.[86-89] This discovery prompted Gilman to use this reaction as a method of introducing electrophiles onto aryls in a regiospecific manner (Scheme 1.7).[89]
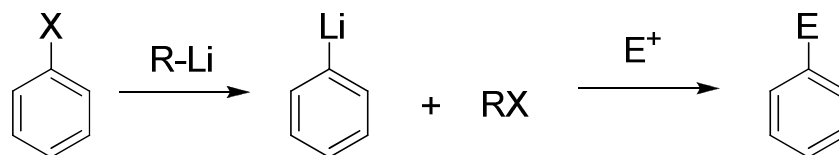
Scheme 1.7. Simplified synthesis of a new product through lithium-halogen exchange (step 1) and quenching with an electrophile (step 2). (X=halogen, R=alkyl/aryl, E$^+$=electrophile)

Subsequent studies on aryl compounds brought three important features of these reactions to the fore:[90, 91]

1) The litium-halogen exchange reaction is an equilibrium process favouring the formation of a less basic, stable organolithium. This meant that *n*BuLi could be used to form organolithiums from aryl halides at low temperature, due to the reaction of the formed aryllithium being slow with the BuX.[92]

2) The rate of the reaction is significantly influenced by the aryl halide used for the exchange reaction. Aryl iodides and bromides are the most useful, with the iodide exchange occurring faster than the bromine-lithium exchange. Aryl chlorides and fluorides tend to rather deprotonate (ortholithiate),[85] leaving benzyne intermediates, than undergoing exchange and thus making them not suitable for use in a system where an exchange reaction is needed.[93, 94] Some instances of chlorine-lithium exchange on vinyl carbons have been shown to occur if there are other halogens to stabilise the resultant vinyllithium.[95] Therefore the order of the rate of exchange is as follows; ArI > ArBr > ArCl >> ArF.

3) Performing these reactions in ethereal solvents accelerates the exchange, even at temperatures close to the freezing point of diethyl ether and tetrahydrofuran. This fast reaction allows the exchange to be favoured over deprotonation and the formation of by-products.

intermediate ate complex
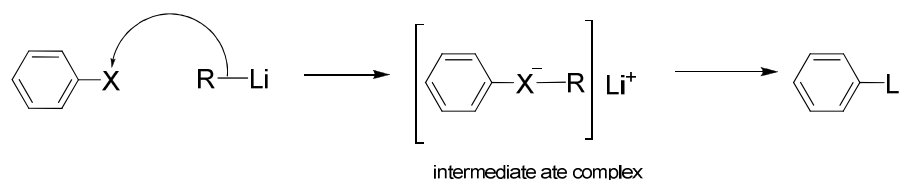
Scheme 1.8. Polar mechanism of aryllithium formation via the ate complex

The mechanism by which exchange reactions proceed can be through either one of two possiblilities; a radical mechanism,[96, 97] or one involving a nucleophilic substitution at the halogen with an ate complex as an intermediate (Scheme 1.8).[98-100] Studies have shown that aryl halides tend to react via an ate complex,

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primary alkyl iodides via a polar mechanism, secondary alkyl iodides reacts via both mechanisms and alkyl bromides via a radical mechanism.[101]

i) nBuLi (2.1 equiv)

ii) Electrophile (E)

(E=COOH/H)
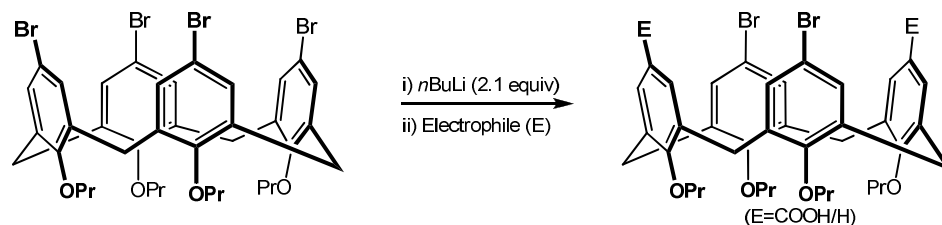
Scheme 1.9. Larsen's selective functionalisation on calix[4]arene

In 1996 Larsen *et al.*[102] reported a selective lithium-halogen exchange reaction on tetrabrominated calix[4]arenes (Scheme 1.9). They demonstrated that by using two equivalents (and in some cases an excess) of nBuLi as lithiating agent, followed by electrophilic quench, they could selectively synthesise the distal functionalised calix[4]arene product in high yields and purity (61-93% depending on electrophile and starting material).

This same concept was also applied on resorcinarene molecules by Sherburn.[79, 103, 104] A tetrabromo resorcinarene cavitand was treated with 2.1 equivalents of nBuLi at −78 °C in tetrahydrofuran and quenched after 15-20 minutes with a variety of electrophiles (DMF, methyl iodide, iodine, methanol, etc.), to produce the distal functionalised product in good yields (60-71% depending on the electrophile used). They also found that the proximal product was formed in low yields with a ratio of distal to proximal being 8:1. This was interesting, since the calix[4]arene example gave exclusively the distal product. With this method mono-functionalised products were also furnished selectively to produce some interesting supramolecular products.[105]

i) nBuLi (2.1 equiv), THF

ii) Electrophile (E)

R = -C$_5$H$_{11}$/-C$_{11}$H$_{23}$

R = -C$_5$H$_{11}$/-C$_{11}$H$_{23}$
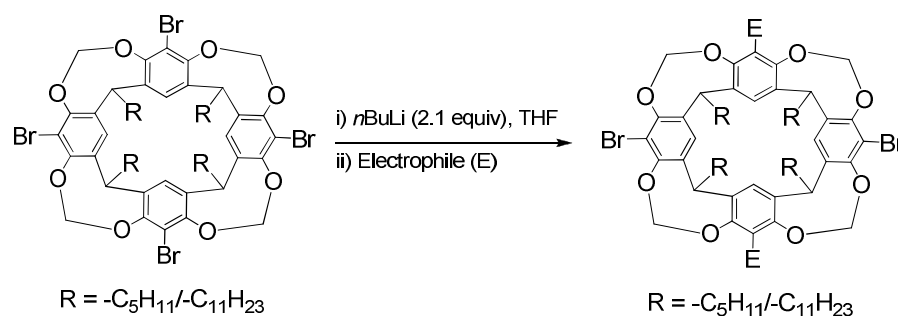
Scheme 1.10. Sherburn's selective lithium-halogen exchange reaction

In 2007 Kleinhans *et al.*,[106] systematically investigated the Sherburn methodology applied to a flexible resorcinarene system (Scheme 1.11). During the study only one instance was found where the selective distal functionalisation of flexible resorcinarenes was achieved by Mattay in 2004.[107] This reaction was performed using nBuLi and methyl chloroformate as one of the functionalisation steps. The reaction

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returned a yield of 48%, but no mention was made about by-products or any difficulty in the course of the synthesis, which was in contrast to what was found in the course of the Kleinhans study. This synthesis was also used in another paper by Mattay, attaching Kemp's triacid to the resorcinarene skeleton. [108]

In the Kleinhans study, using an octamethoxy tetrabromo resorcinarene, optimization was performed with nBuLi at different temperatures and in different reaction solvents, using methanol as an electrophile. The optimised reaction conditions were found to mimic those that Sherburn found for his system, namely using 2.2 equivalents of lithiating agent at −78 °C in tetrahydrofuran. The lithiating reactions revealed a remarkable solvent and temperature effect, with reactions in diethyl ether and toluene proceeding slower than in tetrahydrofuran. It was found that lower yields for the distal functionalised products (c in Scheme 1.11) and a greater spread of the other functionalised products, with the best ratio of proximal to distal (b:c in Scheme 1.11) being about 1:5. This demonstrated that a flexible resorcinarene system could be used as a basis for selective functionalisation with an exchange reaction. The lower yields and selectivity were attributed to greater steric interference of the flexible methoxy goups.
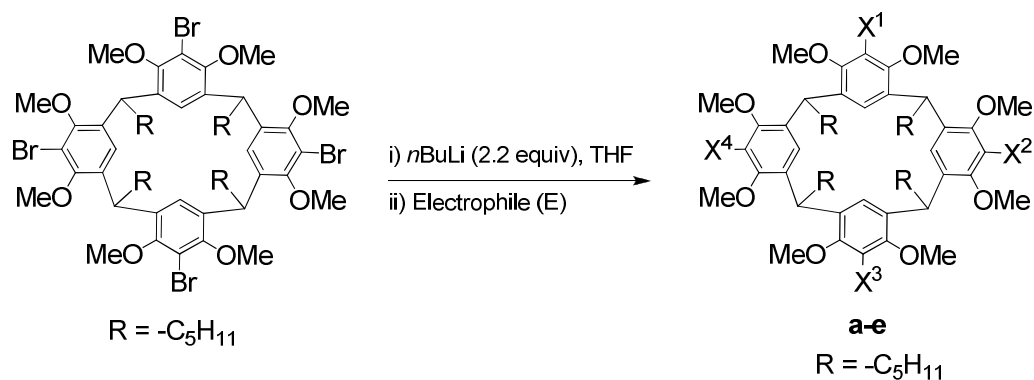
Product	X^1	X^2	X^3	X^4
a	Br	Br	Br	H
b	Br	Br	H	H
c	Br	H	Br	H
d	Br	H	H	H
e	H	H	H	H

Scheme 1.11. Selective synthesis of distal products on a flexible resorcinarene system

If these methods on the resorcinarenes were compared to the reaction with the calix[4]arene it is clear that they are at a disadvantage. In the case of the resorcinarenes a spread of products is seen if more than 2.2 equivalents of lithium base is used, whereas with the calix[4]arene exclusively distal products are formed even at great excesses of base used. The lithium halogen exchange reaction however is a vital cog in the functionalisation of resorcinarenes due to the ease at which a wide range of electrophiles, with different functionalities, can in theory be easily introduced.

1.2.2.2 *Selective Acylation*

In 1994 Shivanyuk *et al*.[109] published a paper on the selective functionalisation of resorcinarenes (Scheme 1.12). They found that by treating resorcinarenes with four equivalents of a variety of phosphoryl groups that they could regioselectively protect the four phenols of the two resorcinol moieties opposite each other.[109] In 1995 this method was extended to the use of sulfonyl groups and in both cases the formed products were of C_{2v}-symmetry.[110]
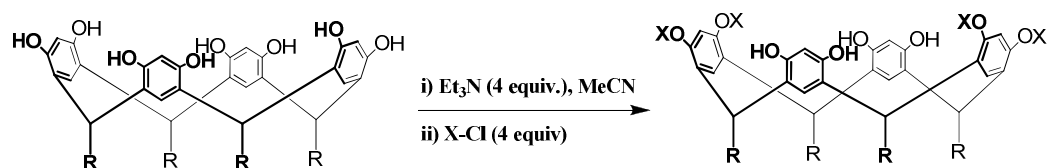
Scheme 1.12. Shivanyuk's regioselective functionalisation of resorcinarenes. (R = alkyl, X= various acylating agents)

Two factors made this reaction very attractive:

1) the partially protected product precipitated out of the solution if the correct combination of solvent and base was used. It was found that if triethylamine and acetonitrile were used in most cases that the product precipitated out as the hydrochloric triethylammonium salt complexed with the resorcinarene product.[111] This was however not the case for all products, since resorcinarenes with pendant chains longer that seven carbons did not precipitate out. In resorcinarenes with short alkyl pendant groups changing the solvent to tetrahydrofuran caused the formation of a mixture of partial protected resorcinarenes. Arnott has shown that by using tetrahydrofuran as solvent resorcinarenes with undecyl chains could also be selectively protected and separated with column chromatography.[77]

2) the partially acylated resorcinarenes could be selectively functionalised by electrophilc substitutions, bromination or α-aminoalkylation, on the unfunctionalised aromatic rings of the molecule, since these aryl rings have a higher reactivity than the di-protected rings (Scheme 1.13).

The drawback to all this was that the yields were generally very low (20-55%) and that as the unprotected aromatic rings were functionalised the protecting groups, in the case of the sulfonyl and phosphoryl groups, could not be removed which meant that the products could not be further developed.[109-112] This

problem was solved by the use of acid chlorides.[112] It was demonstrated that various aroyl and heteroaroyl chlorides, as well as benzyl chloroformate, formed C_{2v}-symmetrical products under the same reaction conditions. This gave a method of forming an interesting array of C_{2v} resorcinarene products by using the reactivities of the newly formed products. Options include electrophilic substitution followed by deprotection of the resorcinarene or using a different protection group on the free phenol groups and then removing the original group. Extensive use of these methods, or variation on these have been used by Arnott[76, 77, 113, 114] Reinhoudt[115] and Puddephatt[116] to synthesise C_{2v} resorcinarenes for their individual needs.
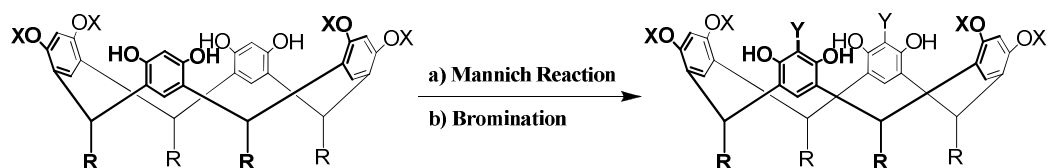
Scheme 1.13. Selective functionalisation of the resorcinarene skeleton using electrophilic substitution reactions a) Mannich conditions or b) Bromination. (R= alkyl, X= various acylating agents, Y= Mannich product/ -Br).

1.3 Coordination Chemistry and Catalytic Capabilities of Resorcinarenes

The coordination chemistry and subsequent catalytic application of resorcinarenes, although extensive, are not as well developed as that of calix[4]arenes. Reviews on this subject demonstrate the fact that resorcinarenes are not used to their full potential, whereas calix[4]arenes have a wide range of application.[49, 116, 117] For this part of the review we will focus on just the resorcinarene coordination chemistry and especially the coordination of transition metals in forming bridged compounds between the donating ligands in forming distal products. Catalysis using resorcinarenes will also be discussed.

1.3.1 Coordination chemistry of resorcinarenes

Resorcinarenes have been utilised as ligands for coordination chemistry through all three of their constituent parts; the lower rim, functionalisation of the phenolic groups and the *ortho* position on the aromatic rings. All three of these areas will be dealt with briefly with relevant examples so as to show the different modes of bonding for these molecules and especially in the formation of distal coordinated compounds.

1.3.1.1   Lower rim

The use of the lower rim of resorcinarenes in coordination chemistry is very limited in the literature. Resorcinarenes with long pendant thioalkyl groups (**G-J** in Figure 1.6) have been shown to form stable

monolayers on gold surfaces and show good potential as sensors.[118, 119] In the case of **G** the gold monolayer showed a marked increase in the absorption of polar compounds (e.g. vitamin C) from dilute solutions.[119]
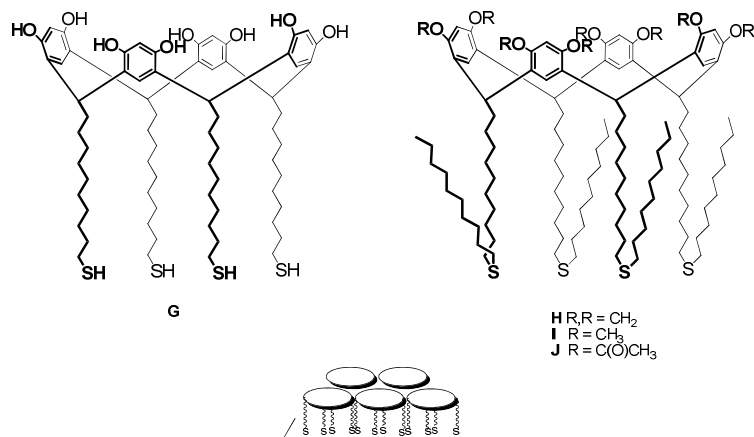
Figure 1.6.   Resorcinarenes with long pendant thioalkyl groups and their formation of monolayers on gold surfaces

In 2001 Dalcanale *et al.*, utilised resorcinarenes, with different nitrogen donors on the lower rim, in an attempt to study the self-assembly of these with different transition metal precursors in a study towards the selective formation of dimeric complexes.[69] These functionalities included cyano (**K**) and pyridyl groups (**L-N**) with different lengths of tether carbon chains (Figure 1.7).
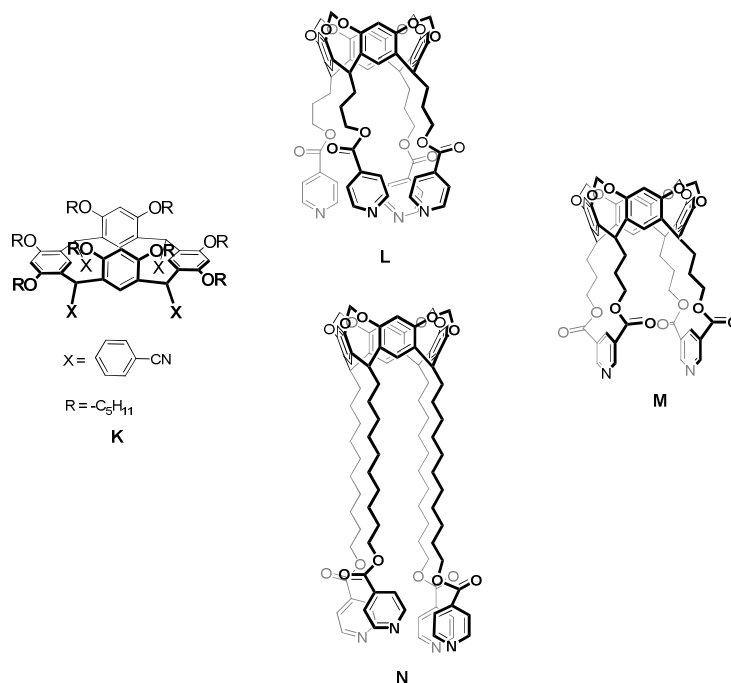
Figure 1.7.   The lower rim functionalised resorcinarene ligands used by Dalcanale.

To study the formation of linear Ag(I) complexes **K** was synthesised in an attempt to gauge if dimers or oligomers would form on complexation with these metals. ^{1}H NMR spectroscopy and ESI-MS confirmed the formation of a polymeric product with the Ag(I) salts and this was attributed to the lower rim aromatic groups being slightly tilted and not linear as expected. In an effort to force the formation of dimers (two ligand molecules with one metal centre) the aromatic nitrile groups were exchanged with pyridine groups attached to different lengths of carbon tethers to form ω-isonicotinoyl tails **L** and **N**. **L** was reacted with Ni(II), Pd(II) and Ag(I) metal precursors form octahedral, square planar and a linear dinuclear coordination motif with each metal respectfully. Interestingly the Pd(II) exhibited a *trans* coordination with two ω-isonicotinoylpropyl groups and in the process catalysed the hydrolysis of the ester bonds of the other two opposite pyridine rings in the presence of a trace amount of water (see **N1** in Figure 1.8).[69]
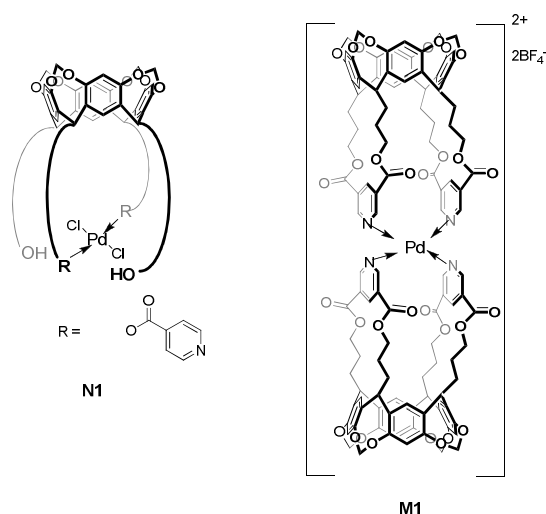
Figure 1.8. Examples of the different modes of coordination using Dalcanale's ligands **M** and **N**. In **N1** the alkyl chains are drawn as looping single bonds to simplify the structure.

Using a shorter and more rigid ligand **L** with metal precursors that have fixed *cis* coordination also did not produce the target dimers. These only afforded dinuclear intramolecular products with Pt(II) and Pd(II) metals. Dimerisation was achieved by using bidentate pyridyl ligand **M** with a Pd(II) precursor (see **M1** in Figure 1.8).

These are not the sole examples of complexation through the lower rim of resorcinarenes, but do give the best example of the type of coordination that can be formed. A few more examples are given for the interested reader.[120-122]

1.3.1.2   Phenolic groups

As with the coordination to the lower rim of resorcinarenes a wide variety of methods of coordination to the phenol groups occur. The two most used are through direct coordination to the oxygen of the phenol

group or by adding another functionality to it that could coordinate on its own. One of the most intriguing methods of coordination occurs through the metalation of the phenol groups themself. In 1998 Jones demonstrated the successful isolation of mono-, di-, tri- and tetranuclear metallocycles from the reaction of tetrahexylresorcinarene with a molybdenum precursor $[Mo(NO)(Tp)I_2]$ $[Tp^- =$ hydrotris(pyrazol-1-yl)borate] that could be successfully separated using column chromatography (**O** as example of the tetra-nuclear metallocycle in Figure 1.9).[123] The formed metallocycles contain the redox-active $[Mo(NO)]^{3+}$ centre and showed in electrochemical studies that the reduction behaviour depended on the number and geometric arrangement of the centres present. Inclusion studies with cations showed no definite complexation, but these complexes demonstrted some hydrogen-bonding with different deuterated solvents in a ^1H NMR spectroscopy study.[123]

In their study of macrocyclic polyhapto organic ligands, Munakata,[124] used resorcinarenes, calix[4]arenes and calix[6]arenes to synthesise new Ag(I) complexes based on cation π interactions. The reaction of tetramethylresorcinarene with $AgClO_4$ resulted in the formation of a product that showed coordination through the hydroxyl groups of the phenol as adjudged by IR spectroscopy. X-ray diffraction of a single crystal revealed two symmetry related metal centres, each coordinated through the two phenol groups on opposite aromatic rings and one η^1-aromatic ring of the resorcinarene (**P** in Figure 1.9). A fourth coordination is supplied by a benzene molecule to form a distorted tetrahedral geometry around the Ag(I) metal centre. This distal formed coordination is one of the only ones found in resorcinarene chemistry. The formed molecular cavity showed no inclusion of solvents or counter ions (e.g. ClO_4^-) and it was postulated that these counter ions block off the complexes so that no guest molecules can enter the host.
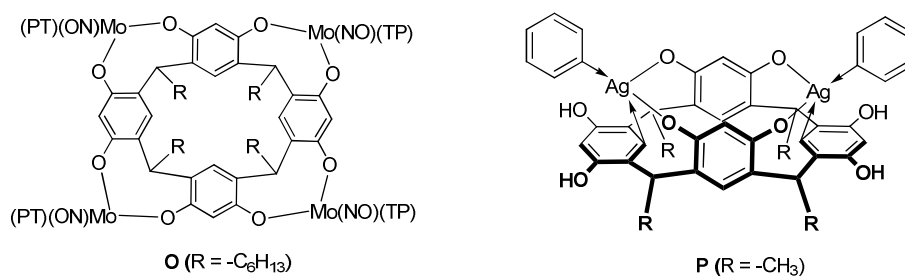
Figure 1.9. Examples of the coordination of the phenol groups of resorcinarene direct to metal centres. **O** is the tetra-nuclear example of Jones's work and **P** that of Munataka.

Another method of enhancing the coordination of metals through the phenol groups is by attaching sufficient functional groups, usually phosphorous and nitrogen containing groups, to it. Phosphocavitands are an interesting application of this, but will not be reviewed.[116, 125] Attention will however be given to the seminal work of Puddephatt *et al*. in the creation of a vast range of different coordination motifs using phenylphosphonite and thiophosphinate based moieties, which was discussed in a recent review.[116] Due to

the depth and breath of the work three examples will be discussed to show the wide range of coordination possibilities.

The reaction of an octopus-like resorcinarene ligand, with eight phosphinite groups, with a platinum(II) precursor formed a tetrabidentate ligand with four metal centres. Due to different *cis* or *trans* coordination to the phosphorus atom, four possible structures could be formed. Molecular modelling and the high degree of symmetry in ^{31}P NMR spectroscopy indicated that complex **Q**, the *cis* coordination on the same aryl ring, was the most likely product (Figure 1.10). Using a gold(I) precursor with the same ligand produced an octa-nuclear product.[126] Using Shivanyuk's selective protection methodology ligands were synthesised that contained phosphinite groups on opposite resorcinol moieties (Figure 1.10). These interacted with a wide range of transition metals to form different coordination motifs which almost always included either a form of bridging between the opposite aryl rings or a linear bonding on the same ring between the phosphorous donors.[127-129] Due to the large bite angle between the two donors on the same ring no chelation of a single metal ion occurred. They are however well suited to bind two metals that are connected with a bridging ligand with complexes formed with Ag(I) and Hg(II) metals showing tetrahedral geometry, and that of the rhodium(I) having planar geometry (**R** in Figure 1.10) The atypical *syn* arrangement of the phosphinite groups is imposed by the geometry of the parent ligand, thus leading to the unusual stereochemistry of the complexes.[127, 129] Interestingly bridging between opposite aryl rings also lead to cluster compounds of Ag(I) or Cu(I) halide salts (**S** in Figure 1.10).[128]
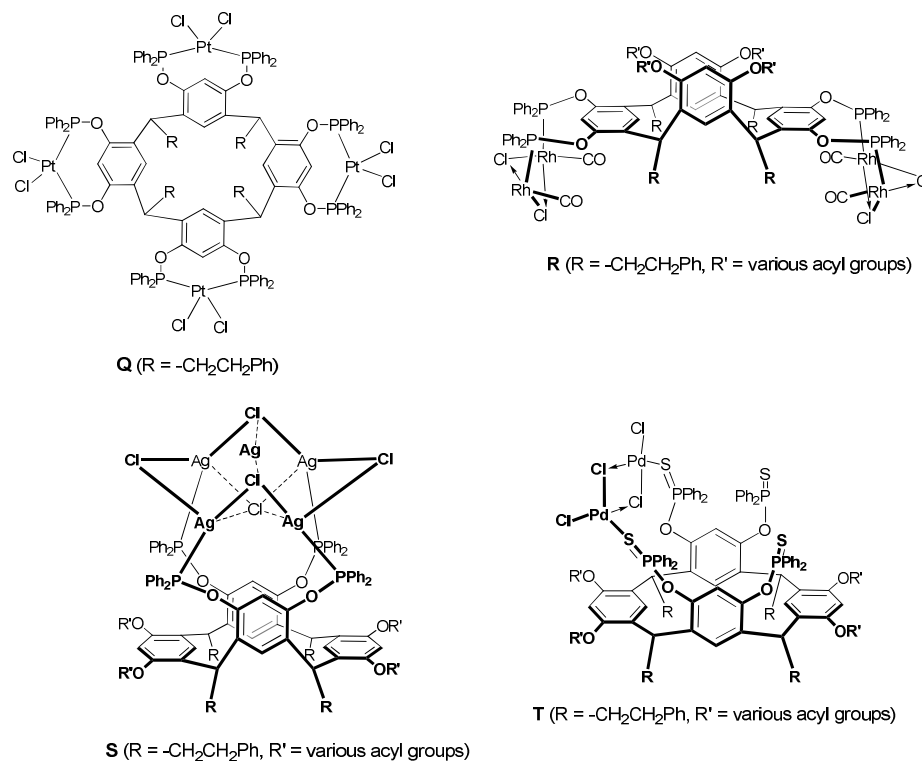
Figure 1.10. Examples of coordination compounds formed from functionalisation of the phenol groups.

Similar results were recorded when thiophosphonate groups were used as chelating agents. **T** was formed from the reaction of a tetrakis(thiophosphonate) resorcinarene with $PdCl_2$. The rigid, square planar dinuclear Pd(II) compound is formed through a chloride bridge between opposite aromatic groups and no easy exchange between the coordinated and uncoordinated donor groups could be observed.[130] As with the functionalisation to the lower rim these examples are not the only ones found in literature, but they do pertain to what we envisaged for our target compounds. Other examples are given for the interested reader.[131-135]

1.3.1.3 Ortho position

In supramolecular chemistry the synthesis of molecular cages and container molecules from resorcinarenes and calix[4]arenes is widely studied due to their unique encapsulation properties.[136-141] The molecules are generally formed by the self assembly of two or more molecules of resorcinarene with transition metals, in the process encapsulating solvents, counter ions or in some cases even fullerenes. [136-141] An example of these cage molecules synthesised by Dalcanale *et al.,*[136] can be seen in Figure 1.11. These robust cage molecules where synthesised using square-planar *cis* metal bis(triflate), M(dppp)X$_2$ [X = BF$_4$$^-$, PF$_6$$^-$] or M(dppp)(CH$_3$COO)$_2$ metal precursors of Pd(II) and Pt(II) and a tetracyano cavitand. The example **U** is of a Pt(dppp) bis(triflate) precursor. The crystal structure revealed that the Pt(II) centres showed a slightly distorted square planar geometry and that the coordinating nitrile groups are not axial as predicted, but slightly bent towards the Pt(II) centre. The data also revealed the inclusion of the triflate ion, seen as the dark ellipsoid in **U**.[136]

U (R= -C$_{11}$H$_{23}$, M= Pt, L$_2$= dppp, X= CF$_3$SO$_3$$^-$)

V (M= Ag$^+$)
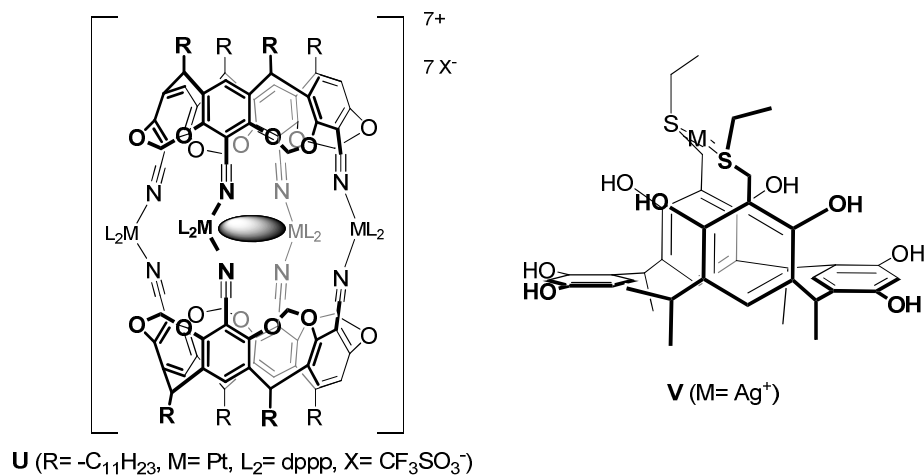
Figure 1.11. Examples of coordination compounds formed through the ortho position of resorcinarenes. In **U** the ellipsoid shows the enclosed triflate ion. **V** is a drawing from the proposed molecular calculation data for the compound synthesised by Danil de Namor.

Central to our investigation was the synthesis of transition metal complexes of resorcinarenes where the donating ligand functionality was attached to the aromatic ring, thus forming a bidentate ligand complex

with the metal atom in the centre of the bowl of the molecule. Examples of this could not be found in the literature, but there were some examples where coordination of this kind occurred if the functionality was removed one carbon from the aromatic ring.[142, 143] Danil de Namor used ^{1}H NMR spectroscopy, conductometric and calorimetric measurements of the reaction of a range of cations on a distal and fully functionalised ethylthiomethyl resorcinarene.[142, 143] They revealed that in the case of the partially functionalised resorcinarene a 1:1 (ligand:metal) complex of could be formed with Hg(II) in propylene carbonate and with Ag(I) in methanol. In the case of the Hg(II) a 1:2 complex was formed when the reactions were performed in other solvents. Molecular calculation studies predicted the conformation of the Ag(I) complex as **V** in Figure 1.11, with the Ag(I) atom being ligated by both of the thioether groups to form a bidentate complex.[142] Similarly Korovin established using spectroscopic and elemental analysis that his tetra(diethyl)aminomethyl functionalised resorcinarene formed a 1:1 complex with ytterbium.[144] In both cases no physical evidence is given about the possible coordination of the metal centre and we can only speculate to the form of the bonding.

By using the *ortho* position on the bowl, multi-nuclear complexes can be formed using various functionalities. These complexes are benefitted by the structural rigidity of the resorcinarene, which if correctly used, provide a basis where the metal centres can be quite close to one another. This, along with a bowl that is known for its molecular recognition abilities, can produce the possibility of a good catalysis base. Two different examples will be dealt with to illustrate the practical use of these compounds. In 1999 Beer used bypyridal derived groups to form Ru(II) complexes (**W** in Figure 1.12). These complexes showed an affinity as anion receptors, with a preference of carboxylate ions.[145] No detail is however given about the coordination of the metal centres to these ligands. In 2000 Harrison formed four bis(pyridylmethylamine) groups on the resorcinarene.[146] Coordination with Cu(II) salts formed a tetra-nuclear complex (**X** in Figure 1.12) with each of the Cu(II) centres structurally different due to the different forms of hydrogen and acetate coordination to the metals as well as the individual conformations of the bis(pyridylmethylamine) groups around the ring.[146] This compound and others formed from Zn(II) and Fe(III) were used with success as anion transports in polymer imbedded membranes.[147]
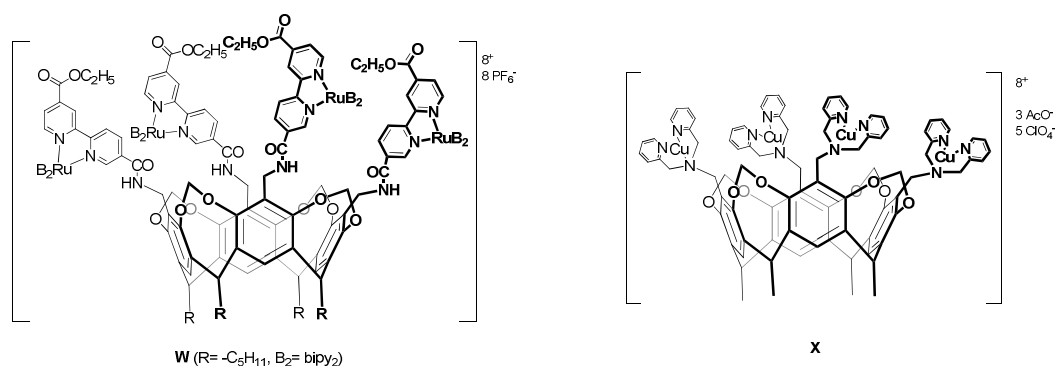
Figure 1.12. Examples of multi-nuclear complexes formed from resorcinarenes

From these few examples it is clear that although a lot of interesting work in coordination chemistry has been performed with resorcinarenes, there is still a lot to investigate. In the next section we will be looking at the use of resorcinarenes in catalysis and especially in C-C bond forming reactions.

1.3.2 Catalysis using Resorcinarenes

The use of resorcinarenes in catalytic reactions is a subject that is not that well studied thus far. This is in stark contrast to the amount of research performed using calix[4]arenes. One only has to look at the work of Matt *et al*. on calix[4]arenes to see that the use of these molecules, especially in C-C forming reactions, holds much promise as future catalyst (included are selected references from the vast amount of work performed by them).[148-152]

The use of resorcinarenes as catalysts can be roughly divided into two separate ideas and therefore of functionalisation of these molecules. The first idea uses the resorcinarene as a basis onto which functional groups are placed in a logical manner to facilitate catalysis. The second idea draws some inspiration from nature and more specifically enzymes. The concave bowl structure of resorcinarenes allows for molecular recognition and this is used as a docking station for small molecules, along with carefully placed functional groups within the bowl to facilitate bonding and catalysis. A recent review of Rebek explains the use of resorcinarenes in this manner.[46] A few examples of both ideas will be explained in briefly, especially looking at the formation of C-C bonds.

In 2002 Rebek tested the use of a structurally rigid cavitand in a palladium catalysed allylic alkylation of dimethyl malonate with various substrates (Figure 1.13).[134] This system showed good yields in forming the necessary products (38-96% yields), but suffered from long reaction times of 2-6 days till completion. In contrast to this the same products were formed in two hours in 78-91% yield by a model ligand. Using competition experiments it was observed that the resorcinarene based ligand showed a remarkable degree of substrate specifity, which would justify further studies on this system.

R= -C(O)C$_7$H$_{16}$

Graphical representation
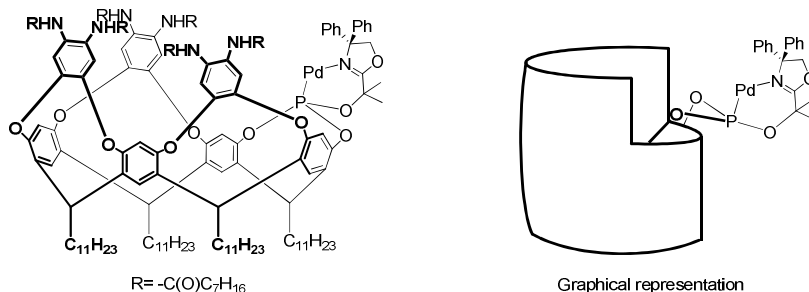
Figure 1.13. The structurally rigid cavitand used by Rebek for palladium catalysed allylic alkylations

Various authors have also exploited the reaction of chiral resorcinarenes, predominantly formed by the Mannich type reactions, with dialkylzinc on benzaldehyde to induce chirality in the product (Figure 1.14).[76, 77, 113, 114, 153]

Using a variety of chiral bridged resorcinarenes (**Y** as example in Figure 1.14) as ligands in the catalysis of this reaction, Arnott could produce satisfying yields for the alkylation reactions but the introduction of chirality in the benzaldehyde was quite low, with *ee*'s of 12-51%.[76, 77, 113, 114] Mechanistic studies of this reaction however indicated that the catalysis could possibly be performed in the cavity formed by the functionalisation.[114] In a later study by Heaney, using a simpler resorcinarene system (**Z** as example in Figure 1.14), *ee*'s of 25-73% could be achieved.[153] These systems show positive results, but still don't compare well with other systems where *ee*'s > 95% are often achieved.[154]
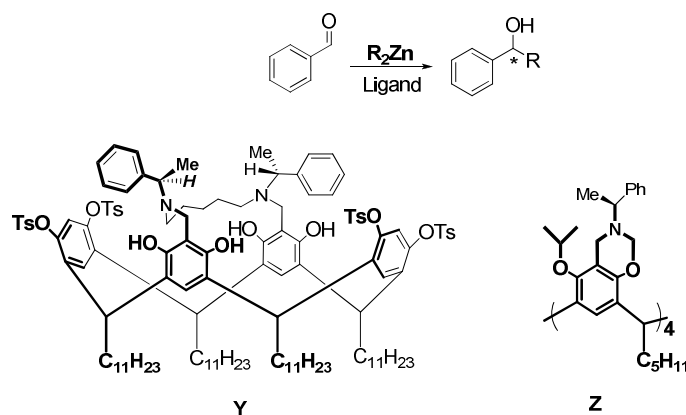
Figure 1.14. Chiral introduction on benzaldehyde with dialkylzinc using chiral resorcinarene ligands **Y** and **Z** as examples.

In a recent report Matt formed two coordination complexes of a tetraphosphine resorcinarene ligand with Ru(II) and Pd(II) precursors (Figure 1.15).[155] The ligand was tested for catalytic capability in a Heck reaction of various aryl bromides with styrene in DMF with different bases and palladium sources. The optimum Pd/ligand ratio was found to be 1:1, when Cs_2CO_3 was used as base and $Pd(OAc)_2$ as metal precurser, with a conversion of 100%. The use of a higher or lower metal/ligand ratio resulted in trace or low percentages of product being formed.

R= -C_5H_{11}
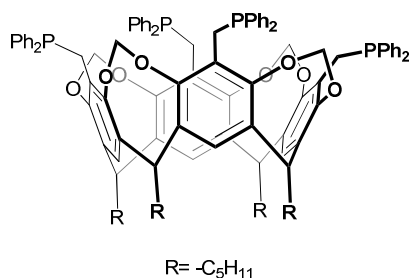
Figure 1.15. Matt's tetraphosphine ligand

These few examples show the direction in which the research in using resorcinarenes as ligands for catalytic reactions is moving. Other examples include the use of resorcinarenes as phase transfer catalysts in various reactions,[156, 157] in the Wacker oxidation,[28] as organocatalyst[158] and in the hydrolysis of phosphorus acid esters[159] to name but a few.

1.4 Conclusion

The aim of this review was to introduce the reader to some of the general aspects of resorcinarene chemistry, especially in the light of the selective synthesis of resorcinarene compounds for use as potential ligands. Although a lot of work has been performed on this subject it is still in its infancy as a research area and offers some interesting and challenging work still to be performed.

1.5 Objectives of this study

The synthesis of resorcinarene coordination compounds is well documented in the literature, especially from a cavitand starting point. There is however not a lot of focus put on the use of these compounds as catalytic agents in reactions. To add to this there is no indication of complexes where the ligand atom is attached to the *ortho* position of the aromatic rings of the resorcinarene. Most complexes are formed by functional groups further away from the aromatic ring.

For this study it was decided to investigative the formation of coordination compounds of resorcinarenes starting from a flexible system on the *ortho* position. It was believed that this system would allow enough freedom in the resorcinarene ring to form a distal, bidentate ligand as seen in Figure 1.16 with the metal atom in the centre of the ring, as been shown in calix[4]arenes.[152] This system would then be used to observe if catalysis is possible through the use of the Heck reaction and, if possible, to determine the centre of the catalytic reaction.
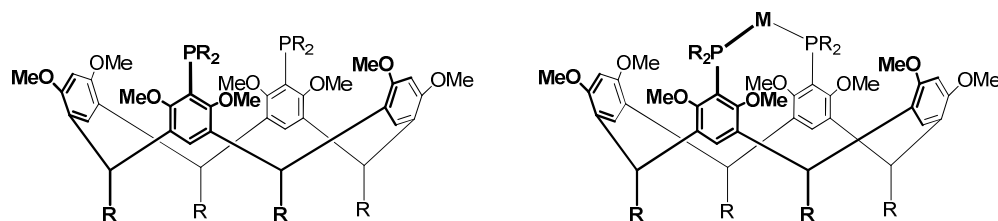
Figure 1.16. The target distal resorcinarene ligand and metal compounds.

To synthesise these distal compounds, a C_{2v} symmetric precursor was needed. Earlier work in the selective synthesis of flexible resorcinarenes applying the methodology of Sherburn revealed that this method does form the distal product, along with a range of other functionalised products, but not in very good yields. It was envisaged to synthesise a C_{2v} symmetrical starting compound using the methology of Shivanyuk, that could then be further functionalised using lithium halogen exchange. This method of

functionalisation allows for the formation of a wide range of functionalities (P, S, N, O) functionalities on the resorcinarene rings, with a diphosphine ligand as the main aim (Figure 1.16). These could then be used for coordination compounds and study of the catalytic behaviour of these compounds.

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Chapter 2

# Synthesis of a Distal Functionalised Resorcinarene

2.1 Introduction

As described in chapter 1, the efficient synthesis of distally functionalised resorcinarenes has been achieved in a number of ways in the literature of which we investigated two in detail. The first method, the distally-selective lithium-halogen exchange reaction as described by Sherburn *et al.,*[1-3] was extensively covered in chapter 1. Work using this methodology on non-rigid resorcinarene systems was fully investigated in our group and the findings are also covered sufficiently in the same chapter.

The second method consists of a selective tetra-acylation reaction to form a resorcinarene with C_{2v}-symmetry, a concept first described in 1995 by Shivanyuk *et al.*[4-7] Another methodology that could also be mentioned is the regioselective distal di-bromination of resorcinarenes with two equivalents of *N*-bromosuccinimide in methyl ethyl ketone as performed by Konishi *et al.*[8] However, other authors showed that this method was not entirely effective in producing distal products in high yield.[3, 9, 10] In this chapter Shivanyuk's methodology to synthesise distally functionalised resorcinarenes is described.

2.2 Synthesis of a Distal Di-bromoresorcinarene

Synthesis of the resorcinarene **1** (Scheme 2.1) was achieved using a different approach to the original aqueous alcohol, acid-catalysed reaction as reported by Cram.[11] Using a variant of a synthesis by Botta *et al.*,[12, 13] a suspension of resorcinol and butanal in dichloromethane at 0 °C, was slowly treated with a Lewis acid, boron trifluoride etherate (BF$_3$·Et$_2$O). The mixture was stirred for 26 hours at room temperature and an orange-red precipitate formed. The precipitate was filtered off, washed with dichloromethane and dried under vacuum to furnish the propyl-footed resorcinarene **1** in 73% yield.
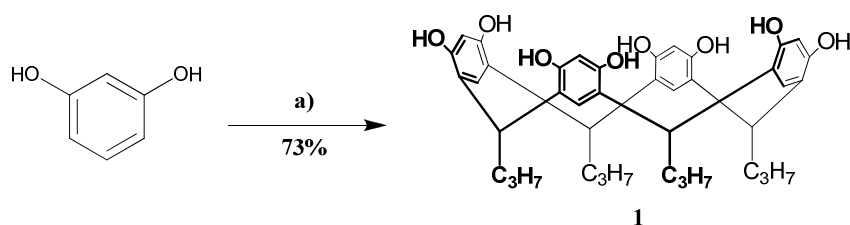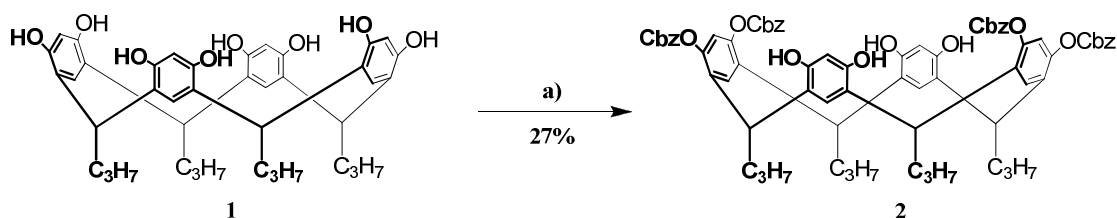

Scheme 2.1: Synthesis of resorcinarene **1**. Reagents and reaction conditions: a) Butanal, DCM, BF$_3$·Et$_2$O, 0 °C→rt

^{1}H NMR spectroscopy and melting point determination confirmed the successful synthesis of resorcinarene **1**.[11] Inspection of the ^{1}H NMR spectrum reveals that resorcinarene **1** is in a bowl conformation and is of C_{4v}-symmetry.[11, 14, 15]

The following step was the regioselective protection of resorcinarene **1** with benzyl chloroformate (Cbz-Cl) according to the protocol reported by Shivanyuk (Scheme 2.2).[6] Benzyl chloroformate was chosen since the benzylcarbonate could be easily removed by catalytic hydrogenation over palladium supported on carbon (Pd/C); this has been successfully used previously by Shivanyuk[6] and Arnott *et al*.,[10, 16] in their regioselective protections of resorcinarenes.

Resorcinarene **1** was stirred in acetonitrile at room temperature with 4 equivalents of triethylamine and benzyl chloroformate (Cbz-Cl) for 48 hours. The white precipitate (**2**·2Et$_3$NHCl) that formed was collected by filtration and washed with cold acetonitrile after which it was taken up in 1M HCl and extracted into dichloromethane. Final purification of tetraCbz-resorcinarene **2** was achieved by recrystallization from a dichloromethane-ethanol mixture to form fine powdery white crystals. As reported by Shivanyuk,[6] this reaction is very low yielding, with the highest yield obtained at 27% and average yields being around 17-21%. This step was a very atom costly step; however the regioselective control and ease of purification that it brings to the synthesis is crucial for the selective formation of distal functionalised resorcinarenes. Analysis of the reaction mixture filtrate by tlc showed a complex mixture of partially acylated intermediates that could not be separated by column chromatography.
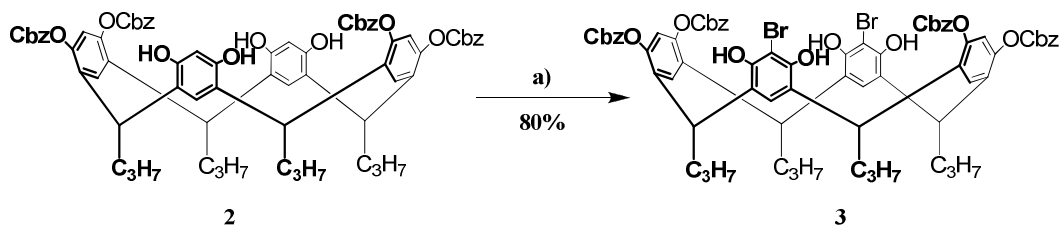

Scheme 2.2. Regioselective protection of resorcinarene **1**. Reagents and reaction conditions: a) Cbz-Cl, Et$_3$N, CH$_3$CN, rt

The tetraCbz-resorcinarene **2** was fully characterised by NMR, IR, melting point and mass spectroscopy. Investigation of the ^{1}H and ^{13}C NMR spectra of the tetraCbz-resorcinarene **2** confirms the C_{2v}-symmetry of the molecule. This can be seen by four singlets in the aromatic region (see Figure 2.1), all integrating for two protons (5.94, 6.67, 6.92 and 7.12 ppm); a singlet signal (6.71 ppm) accounting for the four phenolic protons; a broad triplet (4.33 ppm) for the four benzylic methine protons and finally a single set of signals integrating for 20 protons, forming a multiplet (7.30-7.36 ppm) for the Cbz group. The ^{1}H NMR spectrum of resorcinarene **2** run at 50 °C showed increased resolution of the spectra, but no further information could be gained from this. IR spectroscopy of the molecule revealed very broad bands and confirms the introduction of the carbonate group (1759 cm^{-1}) and the free hydroxyls (3426 cm^{-1}). Due to

the broadness in the thin film IR of **2** no conclusions could be drawn to the degree of intramolecular hydrogen bonding in the molecule as noted by others.[6] High resolution mass spectroscopy also indicated a peak at 1193.4918 accounting for $(M+H)^+$.

N-Bromosuccinimide (NBS) is conventionally used to selectively brominate the tetraprotected resorcinarene.[4, 6] It was however decided to perform the bromination reaction using molecular bromine. Three equivalents of a 1 M solution of bromine in glacial acetic acid were added slowly to a solution of tetraCbz-resorcinarene **2** dissolved in dry dichloromethane at −78 °C, and the reaction carefully monitored by tlc. It was found that adding another equivalent of the bromine reagent after 30 minutes and then leaving it to stir to completion (~ 30 minutes) afforded the best yields. After an aqueous work-up, purification was performed using flash column chromatography and recrystallization from a dichloromethane-ethanol mixture to yield the dibromo-tetraCbz resorcinarene **3** in yields of up to 80% (Scheme 2.3).


Scheme 2.3. Bromination of resorcinarene **2**. Reagents and reaction conditions: a) Br$_2$, AcOH, DCM, −78 °C.

The dibromo-tetraCbz resorcinarene **3** could be fully characterised by NMR, IR, melting point and mass spectroscopy. The ^{1}H NMR spectra (Figure 2.1) of the product revealed some interesting differences to that of the tetraCbz precursor. In the aromatic region only three singlets (each integrating for two protons, at 6.53, 7.08 and 7.11 ppm) can be observed, thus indicating that distal bromination had occurred. The singlet that accounted for the four phenolic protons had shifted upfield to 5.22 ppm. This could be explained that although the negative inductive effect of the bromine should make the phenolics more acidic (and therefore move downfield), the positive resonance effect (π-electron donation through overlapping orbitals) of the bromine makes the phenolic hydrogens more basic and they thus move upfield.

ATR-IR spectroscopy of resorcinarene **3** revealed two bands at 3508 and 3454 cm^{-1}, indicating that there are two different H-bonding modes occurring in the solid state of the molecule. A band at 1744 cm^{-1}, with a slight shoulder at 1765 cm^{-1} indicated the presence of a carbonate C=O.
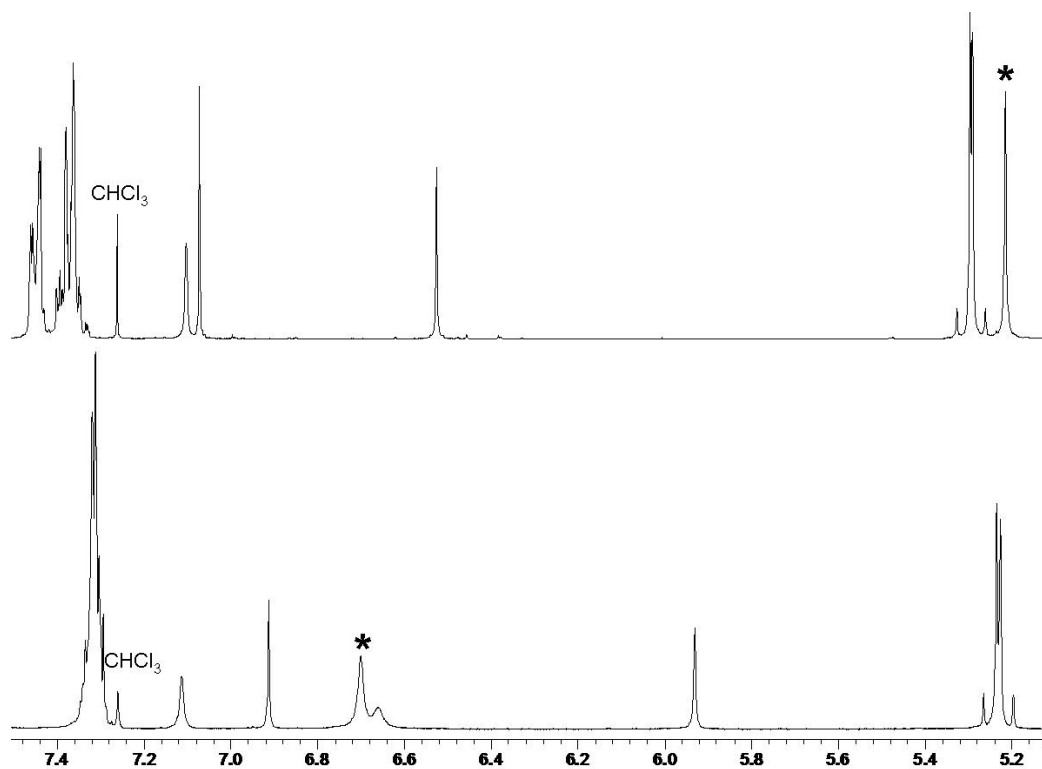
Figure 2.1. ^{1}H NMR spectrum of resorcinarene **2** (bottom) and resorcinarene **3** (top) over the area of 7.5-4.2 ppm. (*) indicates the phenolic hydrogens**.**

The synthesis of resorcinarene **4** was achieved over two steps with no purification in between, since the purification of the octamethoxy protected resorcinarene was much easier than that of the deprotected resorcinarene **3**. The first reaction involved a catalytic hydrogenation over palladium supported on carbon to remove the Cbz groups on resorcinarene **3** after which the phenols were protected as methyl ethers (Scheme 2.4).
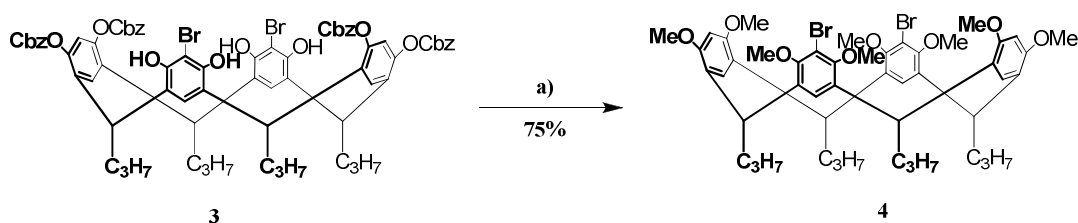

Scheme 2.4. Reagents and reaction conditions: a) (i) H$_2$, Pd/C, EtOH/THF, rt (ii) Me$_2$SO$_4$, K$_2$CO$_3$, CH$_3$CN, reflux

Due to the limited solubility of dibromo-tetraCbz resorcinarene **3** in alcoholic solvents it was dissolved in a mixture of dry ethanol and tetrahydrofuran (1:1) and 10 mol% of 10% Pd/C was added to the mixture. The addition of tetrahydrofuran helped with the solubility of the intermediates as well as decreasing the amount of undesired reduction of the aryl-bromine bond; the only disadvantage to this being the longer reaction time. The reaction was capped with a hydrogen balloon and stirred at room temperature until

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completion of the reaction as judged by tlc (~24 hours). In some cases it was necessary to add one or more equivalents of Pd/C to drive the reaction to completion.

One critical observation of this was that the reaction was extremely temperature dependant. A reaction performed at 37 °C was judged to be complete within four hours whereas one at 17 °C took three days until completion. It was however found that if the reaction was gently heated or pure ethanol was used as solvent that the aryl-bromine bonds were also rapidly reduced. This could only be ascertained after the protection of the free OH groups as methyl ethers.

The residue was suspended in acetonitrile and dimethyl sulfate (16 equivalents; two equivalents per phenol) and potassium carbonate added and the mixture heated under reflux for up to 42 hours. Shorter reaction times and less than a two-fold excess of reagents resulted in the formation of a mixture of hepta- and octamethoxy resorcinarenes. The polarities of the two products were similar on tlc and only ^{1}H NMR spectroscopy could confirm the successful synthesis of resorcinarene **4**. After work-up and purification using flash column chromatography, recrystilization from a dichloromethane-ethanol mixture yielded resorcinarene **4**, in up to 75% over the two steps (Scheme 2.4). Even after careful chromatography and recrystallization (twice), of resorcinarene **4** there was still a small amount of mono-bromo resorcinarene present in the final product (indicated by * in Figure 2.2). This however did not influence the subsequent reactions performed on **4**. It was later found that recrystallization from toluene and drying the collected crystals at 90 °C under vacuum (1 mmHg) resulted in purer product and better yields in subsequent reactions.
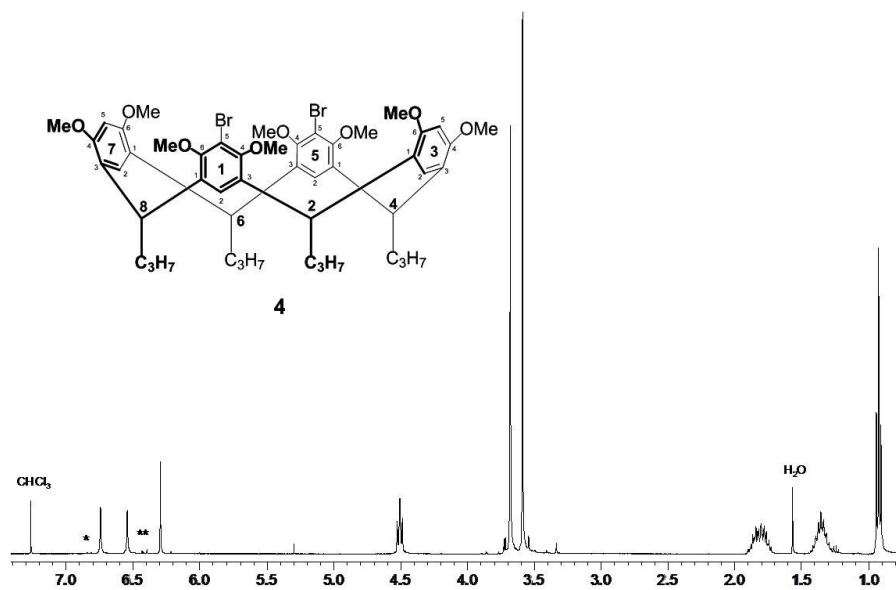
Figure 2.2. ^{1}H NMR spectrum of resorcinarene **4**. (*) marks the positions where the mono-bromo resorcinarene by-product can be seen.

Resorcinarene **4** was fully characterised using melting point, 1D and 2D NMR (^{1}H, ^{13}C, HMBC and HSQC), IR and mass spectroscopy. Detailed ^{1}H and ^{13}C NMR spectral assignments of this compound were needed to understand the conformation that the molecule was adopting, and this in turn would help with the determination of the conformations that the future products would adopt. This would give an indication of the probability of complex formation with metals. To clarify the NMR assignments a method employed by Arnott[10] would be used whereby only a part of the molecule was numbered (Figure 2.3) and described. Thus instead of mentioning the signal for H-2,4,6,8 (see Figure 2.2 for the full numbering of dibromo **4**) it would be assigned as [2]. The reader is asked to carry out the necessary extrapolation.[10]
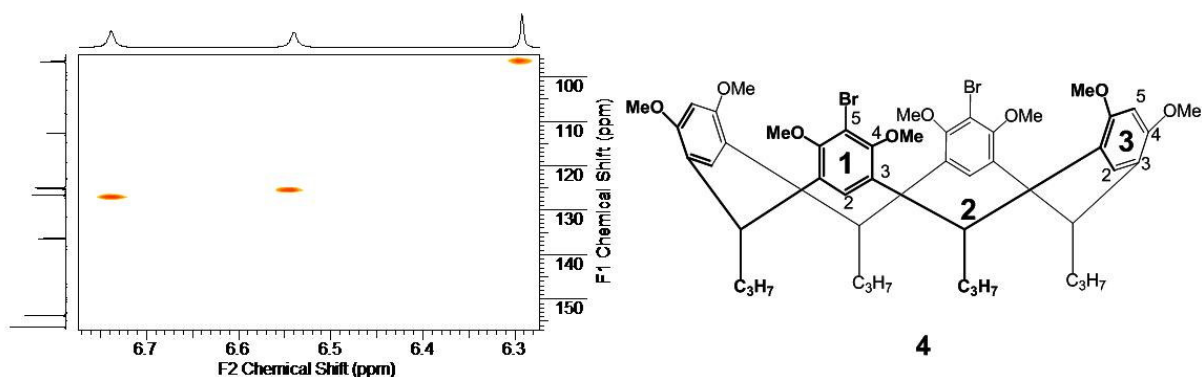

Figure 2.3.   HSQC NMR of the aromatic region of resorcinarene **4**

The ^{1}H NMR spectrum (Figure 2.2) of dibromo **4** in CDCl$_3$ reveals a symmetrical product with the three most important areas those being that of the aromatic region (6.00-7.00 ppm), the methoxy region (3.50-4.00 ppm) and the signals that account for the methine potons (4.20-4.70 ppm). Using HSQC (for one bond H-C couplings) and 1D NMR (^{1}H, ^{13}C) most of the upfield signals could be assigned intuitively according to chemical environments and multiplicities. The challenge lay in the correct assignment of the three singlets in the aromatic region. It could be seen in the HSQC spectrum that the signals at 6.30, 6.55 and 6.75 ppm in the ^{1}H NMR correlated with those of 96.3, 125.0 and 126.4 ppm respectively in the ^{13}C NMR.

Investigation of the long range H-C couplings in the HMBC spectrum (Figure 2.4) revealed some interesting insights. The protons at 6.30 and 6.75 ppm both showed cross peaks at 156.1 ppm and the proton at 6.55 ppm showed a cross peak at 153.6 ppm in the ^{13}C NMR spectrum. The signals at 153.6 and 156.1 ppm were assigned to either [1⁴] or [3⁴] and the occurrence of two cross peaks to one signal indicated that these protons were on the same aromatic ring and could thus be assigned to either [3²] or [3⁵]. The carbon of the benzylic methines [2] of the resorcinarene ring showed strong cross coupling with the proton at 6.75 ppm and weak interactions with the proton at 6.30 ppm. This proton in turn showed stronger interaction with the carbon signal of [3⁴], indicating a much shorter coupling. Therefore proton

[3^5] could be assigned to 6.30 ppm and [3^2] to the signal at 6.75 ppm. This then left the singlet at 6.55 ppm to be attributed to the proton of [1^2] due to its coupling with the carbon of [1^4] and the strong cross peaks seen with the carbon signal of [2]. Very weak cross peaks of [1^2] with an aromatic carbon signal at 112.5 ppm could also be seen, and thus this signal can be assigned to [1^5].
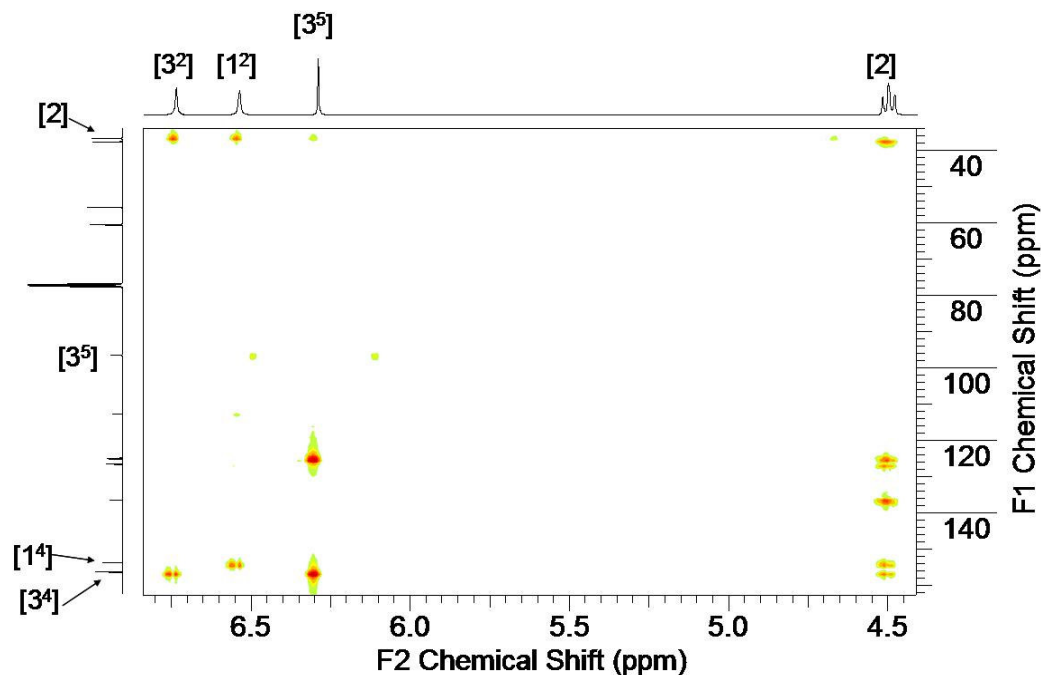
Figure 2.4.   Selected HMBC spectrum of resorcinarene **4**

The aromatic quaternary carbons attached to [2] can either be assigned to the signals at 136.1 or 124.7 ppm due to the cross peaks seen in the HMBC spectrum. These assignments were also verified as the aromatic attachment carbons due to their long range coupling to the –CH$_2$- hydrogens of the propyl feet. The signal at 124.7 ppm showed long range coupling to [3^5] and could thus be assigned as [3^3]. This left [1^3] to be assigned to 136.1 ppm in the carbon spectra. With the full NMR spectral assignment performed for **4,** attention could be given to the conformation that the molecule adopted.

The conformation of resorcinarenes has been studied in great detail in the literature and was also discussed in chapter 1.[5, 11, 14, 15, 17, 18] It is clear from these sources that the two signals for the protons on the lower rim of the resorcinarene play a very important role in determining the symmetry and therefore the conformation of the molecule. This is due to the minimal effect that the nature of substituents on the upper rim plays on the chemical shift of these protons.[5] Careful examination of the ^{1}H NMR spectrum of resorcinarene **2** and **4** reveals that the difference in chemical shifts (Δδ) between the lower rim protons stay constant (Δδ 0.2 ppm between [1^2] and [3^2]). This points to a molecule that has C$_{2v}$ symmetry and in the boat conformation. This claim can be strengthened due to the similarities in the shapes of the signals, especially the triplet that forms for the benzylic methine protons [2]. This implies that the opposite

aromatic rings could either be situated axial or equatorial. Due to the deshielding seen in $[1^2]$ it can be assumed that the [1] aromatics (i.e. bromines) are sitting axially and that the [3] aromatics are in an equatorial position and the signals more shielded due to the protons lying in the anisotropic region of the aromatic rings next to them.

With the distal dibromo-resorcinarene **4** in hand, functionalisation of the resorcinarene backbone to form ligands that could be used in transition metal catalysed reactions could now be pursued. In the following chapters the methodology to synthesise these molecules will be explained in greater detail.

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Chapter 3

Functionalisation of Distal Resorcinarenes via Lithium-Halogen Exchange

3.1 Introduction

Initial lithium halogen exchange reactions using resorcinarene **4** returned poor yields, with the main product being octamethoxy resorcinarene **5**. A model study, using 2-bromo-1,3-dimethoxybenzene **6** (Figure 3.1), was used to investigate reaction conditions for the lithiation reaction, owing to the lengthy synthesis time of resorcinarene **4**.


6
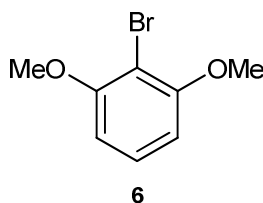
Figure 3.1. The model compound 1-bromo-2,6-dimethoxybenzene **6**

3.2 Testing the reactions using model compounds

3.2.1 Synthesis of model compounds

The synthesis of 1-bromo-2,6-dimethoxybenzene (Scheme 3.1) was attempted in two steps using variations of known literature procedures.[1, 2] The first reaction consisted of a protection of the phenols as methyl ethers. Thus resorcinol, dimethyl sulphate and potassium carbonate were heated under reflux in acetonitrile for two hours and after work-up a yellow oil, the crude product **7**, was recovered. The product was purified using vacuum distillation (88-92 °C/20 mm Hg). The ^{1}H NMR spectrum revealed that the product still contained some dimethyl sulphate and the residue was heated under reflux in methanol and potassium carbonate to trap out the last of the impurity. It was later found that passing the oil through a small plug of silica gel removed most of the impurities. The final product, 1,3-dimethoxybenzene **7**, was purified again by distillation and successfully characterized according to ^{1}H NMR spectroscopy.
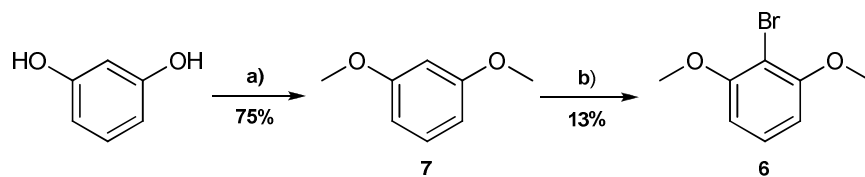
Scheme 3.1. Synthesis of 2-bromo-1,3-dimethoxybenzene **6**. Reagents and reaction conditions: a) Me$_2$SO$_4$, K$_2$CO$_3$, CH$_3$CN, reflux; b) i) TMEDA, nBuLi, Et$_2$O, 0 °C ii) C$_2$H$_4$Br$_2$, 0 °C→ rt.

Using a literature procedure from MacLachlan *et al.*,[2] **6** was subjected to a directed ortho metalation (DoM) reaction, using 1,2-dibromoethane as the bromine donor. The dimethoxybenzene was slowly added to a mixture of n-buthyllithium in diethyl ether and tetramethylethylenediamine (TMEDA) as the metal-chelating co-solvent at 0 °C. After 90 minutes of stirring the 1,2-dibromoethane was added and the reaction stirred overnight. After work-up and purification by flash column chromatography and recrystalization from ethanol at −20 °C, 2-bromo-1,3-dimethoxybenzene **6** was found in only 13% yield. This differed drastically from the 65% that was achieved by the literature procedure.[2] Melting point and ^{1}H NMR spectroscopy confirmed the synthesis. It was however decided to synthesize the product via an alternative route.
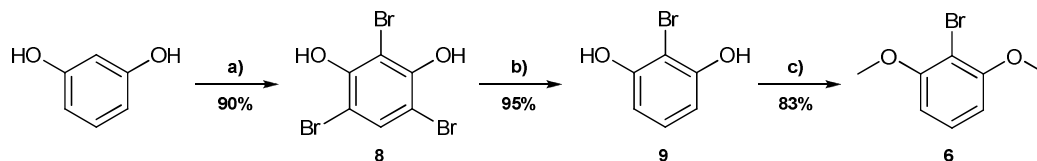
Scheme 3.2. Alternative synthesis of **7**. Reagents and reaction conditions: a) Br$_2$ (3 equiv), chloroform, 0 °C→ reflux; b) NaOH (2 equiv), Na$_2$S$_2$O$_3$ (2 equiv), MeOH:H$_2$O (1:5); c) Me$_2$SO$_4$, K$_2$CO$_3$, CH$_3$CN, reflux

The three step synthesis (Scheme 3.2) was adapted from known literature methods.[3-6] The first step was a tribromination of resorcinol as reported by Davis.[3] Three equivalents of bromine were added to resorcinol in chloroform at 0 °C and the reaction was heated under reflux to remove the HBr. The solution was then treated with activated charcoal to remove any impurities. It was found that shaking the crude product up in a 10% sodium thiosulfate solution helped with removal of excess bromine and other impurities and thus increased the purity of the product. After recrystillisation in chloroform the successful synthesis of tribromoresorcinol **8** was confirmed using melting point and ^{1}H NMR analysis.[5] Yields of 90% could be achieved, whereas the literature reported that yields of up to theoretical amounts could be achieved.

Secondly, using another procedure by Davis *et al.*[4] two of the bromine atoms on the tribromoresorcinol were selectively reduced via pseudo-quinone intermediates to leave 1-bromoresorcinol **9**. Thus tribromoresorcinol was suspended in a 17% aqueous methanol solution and treated with two equivalents of sodium hydroxide and sodium sulfite at room temperature. After an hour's stirring the reaction mixture

was acidified with 1M HCl and extracted into diethyl ether. The product was in most cases pure enough to proceed to the next step, although it could be separated with flash column chromatography and recrystallized from dichloromethane/petroleum ether. Yields of up to 95% were achieved with this reaction. Melting point and ^{1}H NMR analysis confirmed the successful synthesis.[6] The last step of the synthesis involved protection of the phenols as with methyl ethers to form **6**. The bromoresorcinol was dissolved in acetonitrile and potassium carbonate and dimethyl sulphate was added to the solution. The reaction was heated under reflux for 2.5 hours after which all the starting material was consumed as judged by tlc. The reaction was worked-up in H_2O and extracted into dichloromethane. After flash column chromatography and recrystalization from ethanol at −20 °C, **6** was collected as fine white needles in a good yield of 83%. Melting point and ^{1}H NMR analysis confirmed the correct synthesis.[2]

3.2.2 *Testing lithiation reaction*

In the literature there are a number of instances where functional groups were introduced into the ortho position of 1,3-dimethoxybenzene and related systems via DoM chemistry (Scheme 3.3).[7-14] The introduction of P(III) functionalities onto the *ortho* position of 2,6-dimethoxybenzene and similar systems held relevance to our need to introduce these functionalities onto the resorcinarene scaffold. Therefore the work of Wada *et al.*[12, 13] and Shaw *et al.*[7] were given special attention. They demonstrated that this could be achieved in fairly high yields (63% and 76% respectively in the case of 1,3-dimethoxybenzene).

Literature however shows only a few instances where **6** and related systems are used in lithium halogen reactions[2, 15-17] (see Scheme 3.3) owing to the fact that it is easier to functionalise via DoM chemistry.[18] Most of the lithiation reactions were performed at 0 °C[2, 16, 17] or at room temperature[15] and the electrophilic quench usually at the lithiation temperature. One exception is where the electrophilic quench was performed at −78 °C.[17] This was seen as problematic, since previous studies in our group have shown that higher reaction temperatures produce more unwanted side products in the resorcinarenes.[19] This phenomenon of by-product formation at elevated reaction temperatures was also noted by Parham,[20] in his well-known article on lithium-halogen exchange.
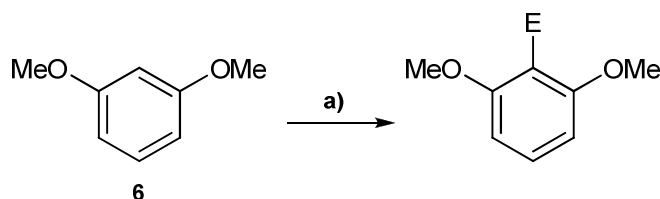

Scheme 3.3. The introduction of various functionalities via DoM chemistry. Reagents and conditions: a) i) R-Li, TMEDA(optional), solvent (ethers or alkanes), varying temperatures ii) Electrophile (E, example SiMe$_3$Cl).

It was therefore decided to start with conditions similar to what was found to work best for our resorcinarenes.[19] Chlorotrimethylsilane (SiMe$_3$-Cl, see Table 3.1) was selected as the first electrophile, since this is a large and bulky group and will give an idea of the reaction conditions needed to introduce such groups.

Table 3.1. Conversion of **6** via lithium-halogen exchange reactions
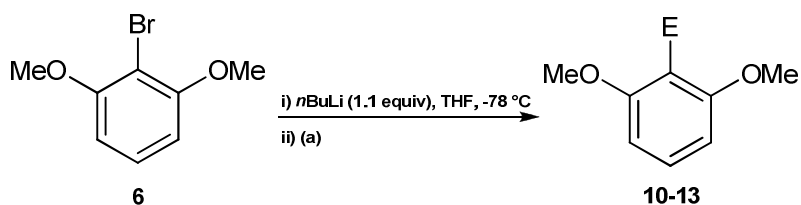
| Entry	Electrophile(a) [a]	E	Product [b]	Yield [c]
1	SiMe$_3$Cl	- SiMe$_3$	**10**	19%
2	MeI	- Me	**11**	42%[d]
3	S$_2$Me$_2$	- SMe	**12**	47%
4	PPh$_2$Cl	- POPh$_2$	**13**	45%

[a] Reaction times, quantities of electrophiles employed and work-up vary [b] In all reactions **7** was isolated as by-product [c] Yield after column chromatography [d] Crude ^{1}H NMR was used to determine yield

A standard procedure for this reaction was performed as follows: The model compound **6** was dissolved in dry THF and cooled to −78 °C. After about 10 minutes 1.1 equivalents of *n*BuLi were added and the reaction stirred for 10 minutes. The solution usually turned a light yellow colour which only lasted a few seconds with the addition of the lithium reagent. The electrophile was added and the reaction mixture stirred for 10 minutes at −78 °C, after which it was warmed to room temperature and stirred for another 10 minutes. The first few reactions were performed on a small scale and only monitored with tlc. After work up and separation using preparative tlc or column chromatography the product(s) were investigated with the help of NMR spectroscopy (^{1}H and ^{31}P for entry 4) and melting point determination and then compared to literature values. It was found that the yield of the product, 1-trimethylsilyl-2,6-

dimethoxybenzene **10**, was about 10%, with most of the material being the protonated compound **7**. A small amount of other products were formed, but could not be identified due to the small quantities recovered. Changing the reaction temperature to 0 °C only resulted in lower yields.

To test if the electrophile was the problem a simultaneous reaction was performed: for one of them the electrophile was passed through basic alumina to neutralize any acid/water byproducts that could have formed due to handling of the reagents. The reactions were performed at −78 °C and the lithiation time was lengthened to 15 minutes. After the quench with TMS-Cl the reactions were stirred at room temperature for 20 hours. The yield of the silated product **10** did not differ between the reactions, but both were almost double that of the previous reaction (19% vs 10%), thus showing that longer lithiation and exchange times were necessary for a decent yield, although a great deal of protonated product was still detected in the reaction mixture. This meant that the reaction was somehow quenched in situ; either by the reaction solvent being still wet or by some external air/moisture coming into the reaction set-up. The optimization of the reaction was left for a later stage. Using methyl iodide (**11**) and dimethyl disulfide (**12**) as electrophiles (Table 3.1, entries 2 and 3) also showed unsatisfactory yields, with **12** giving the best result at 46% yield after column chromatography. Both these reactions were left for relatively short periods (1-4 hours) at room temperature after electrophile quench and longer reaction times did not significantly increase the yields. With methyl **11** (entry 2) the yield was determined using ^{1}H NMR spectroscopy of the crude reaction mixture owing to the problems encountered in the purification thereof.

The final electrophile that was tested was diphenylphosphine chloride (entry 4). The reaction mixture was left to stir for 18 hours at room temperature after electrophile quench. Tlc after aqueous work-up revealed a range of distinctive spots, with three being on the baseline or slightly above it, expectations were that the phosphorylated product would be quite non-polar. NMR (^{1}H) analysis of the non-polar products showed no sign of electrophile introduction. NMR (^{31}P and ^{1}H) analysis of the polar products showed that the more stable phosphine oxide **13** was formed and not the phosphine as was expected. This was verified by using ^{31}P NMR, due to the differences in the shifts of the phosphorous atom (−24.86 ppm for the phosphine[8] and 22.72 ppm for the phosphine oxide[21]) and the slight differences in the ^{1}H NMR spectrum. This confirmed that the phosphorous was introduced into the *ortho* position of the model compound via lithium-halogen exchange and oxidised during the aqueous work up to the phosphine oxide.
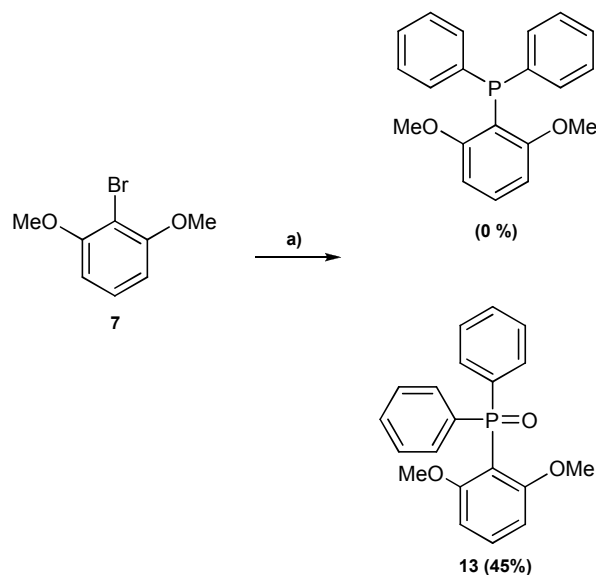
Scheme 3.4. Attempted synthesis of (2,6-dimethoxyphenyl)diphenylphosphine (top). Reagents and reaction conditions: a) i) *n*Buli (1.1 equiv), THF, −78 °C ii) PPh$_2$Cl (excess), −78 °C → rt

A review of the literature brought to our attention a possible answer to why our metal exchange reactions showed such dismal yields. Resorcinarenes are mostly known for their potent ability to form host-guest relationships with a wide array of solvents and molecules.[22-32] Initially our thoughts were that heating the molecules for an extended time under vacuum would be sufficient to remove all possible solvent, but careful review of proton NMR spectra revealed that there were always a small quantity of H$_2$O and recrystalization solvents (usually dichloromethane and/or ethanol) present in some of the samples. These solvents could react with the aryl-lithiated intermediate compound and quench the reaction before the electrophile could be introduced. Two possible methods of solving the problem came to the fore: The first method constitutes a process of solvation and de-solvation of the molecules in an azeotropic removal of the crystallization solvents with dry reaction solvents that will not interfere with the lithiation reaction.[27, 33-36] The reasoning behind this is that by solvating and de-solvating the molecule the solvents trapped in the crystal structure can be removed and replaced with another guest, the reaction solvent. In the second method, solutions of the reagent are stirred with a drying agent (NaH in most cases) to remove excess water and other solvents.[37, 38] One problem with this method is that some electrophiles (e.g. *N,N*-dimethylformamide) are prone to disintegration under highly basic conditions and should be treated rather with the first method.[39] Both methods were tested on bromo **6** with MeI as electrophile (entry 2 Table 3.1), returning **11** at 80% as the highest yield with the solvation/de-solvation method.

3.2.3 *Testing the model with Grignard methodology*

One of the best known metal-halogen exchange reactions is the Grignard reaction[40, 41] which has been updated by Knochel *et al.*,[42-44] with their use of so-called "Turbo-Grignards". Their work concentrates on

using simple Grignard reagents complexed with lithium salts (e.g. LiCl) to accomplish the metal-halogen exchange reaction, e.g. *i*PrMgCl·LiCl (Scheme 3.5). The addition of the lithium salts helps to increase the reactivity of the Grignard reagent and in some cases Cu(I) complexes are also used to help with the introduction of the electrophiles via transmetalation with the magnesiate complex.[42] The advantage of using this methodology is that the chemistry can be executed at more moderate temperatures, ranging from −15 °C to room temperature, and the methodology can be applied to a wide range of functional groups.
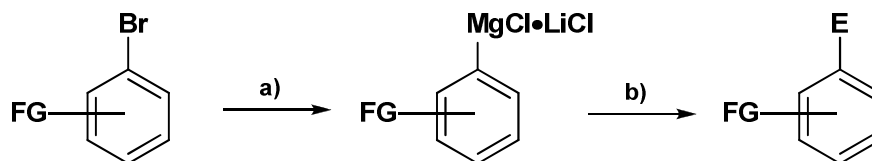
Scheme 3.5. Preparation of compounds via Knochel's "Super-Grignards": Reagents and conditions: a) THF, *i*PrMgCl·LiCl b) Electrophile (FG=functional group = OMe, Br, Cl, F, CN, COOR$_2$).

Unfortunately attempts to introduce electrophiles onto model **6** via this method or by using standard Grignard methodology were not sucessful.[45, 46] High percentages of starting material and protonated **7** were returned after each reaction. It is postulated that the recovery of high amounts of **6** is due to the high degree of electron donation from the two methoxy groups ortho to the reaction center, thus making this position electron rich and slowing down the exchange reaction drastically. Knochel also remarks that introduction of electrophiles on aryl carbon centres are facilitated by an electron withdrawing group ortho to the reaction centre; Br/Mg exchanges are also known to be slower that I/Mg, further explaining the poor yield.[42] The use of electron withdrawing groups in the synthesis of resorcinarenes will be explored in chapter 4.

3.3 Lithiations on the resorcinarene backbone

To demonstrate that lithium-halogen exchange as a viable method of introducing functionality on resorcinarenes a small array of electrophiles was used (Table 3.2). A general representation of the reaction was performed as follows: An oven-dried (120 °C) Schlenk flask was cooled under vacuum to room temperature. The flask was backfilled with inert gas (argon or nitrogen) and charged with resorcinarene **4** and dry, freshly distilled tetrahydrofuran, enough to solvate the precursor. The solvent was removed under vacuum and the residue was gently heated for 5-10 minutes while still under vacuum and left to cool to ambient temperature. The flask was then refilled with inert gas and the solvation/de-solvation process was repeated two more times. The dried residue was dissolved in dry tetrahydrofuran (0.02 M) and cooled to −78 °C with vigorous stirring. 2.2 equivalents of freshly titrated alkyllithium (in most cases *n*BuLi) were added to the mixture and left to stir for 15 minutes after which an excess of electrophile was added to ensure the reaction was driven to completion and that the excess of alkyllithium

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(if any) was quenched. The reaction solution was warmed to room temperature and further reaction times and work-up procedures varied according to the electrophile used.

Table 3.2.   Synthesis of di-functionalised resorcinarenes **14-18** via lithium-halogen exchange from resorcinarene **4**.
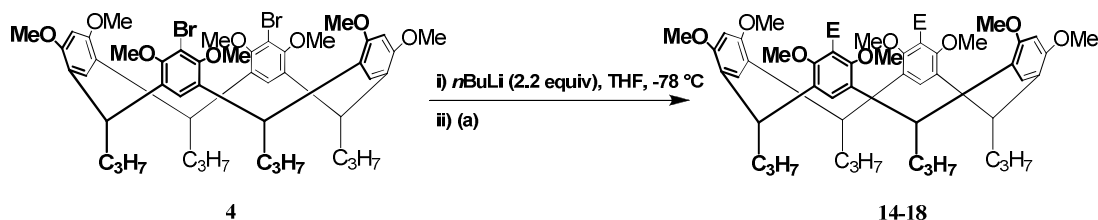
Entry	Electrophile (a) [a]	E	Product [b]	Yield [c]
1	SiMe₃Cl	- SiMe₃	**14**	15%
2	MeI	- Me	**15**	37%
3	S₂Me₂	- SMe	**16**	70%
4	PPh₂Cl	- POPh₂	**17**	<10%
5	ClCO₂Me	- CO₂Me	**18**	68%

[a] Reaction times, quantities of electrophiles employed and work-up may vary [b] In all reactions octamethoxy **5** was isolated as well as the mono-substituted products [c] Highest yield obtained after purification

All new products were characterised using NMR (^{1}H, ^{13}C and ^{31}P for entry 4), mass and IR spectroscopy as well as melting point determination. In the case of the mono-functionalised by-products some could only be partially characterised due to separation problems.

Initially, reactions were warmed to room temperature after electrophile quench, stirred for an hour and finally quenched with water or 1M HCl. Low yields of the target resorcinarenes were achieved, with octamethoxy **5** and mono substituted products **14a-18a** being the most abundant. The reactions were then left for longer after the electrophile quench, usually overnight (~20 hours), and gradually better yields were achieved for most of the products. With secondary alkyl lithium reagents (sBuLi, iPrLi) longer lithiation times were needed to form the intermediate lithiated product, but no significant increases in

yields were seen and therefore all the reactions were performed with *n*BuLi. An attempted exchange reaction in diethyl ether met with failure due to the limited solubility of resorcinarene **4** in the solvent.

The yields for the reactions were relatively low, except in the cases of **16** and **18**. When using big, bulky eletrophiles such as TMS-Cl and PPh₂Cl a large amount of the mono-functionalised product formed, even when all precautions were followed to avoid this. This could possibly point to a scenario where as soon as the first electrophile is introduced onto the resorcinarene, it inhibits or slows down the reaction of the second electrophile reacting with the lithiated intermediate. This would then allow a smaller electrophile (e.g. H_2O) to react with the available reactive centre. In an effort to purify the disilyl **14** by recrystallisation the molecule broke up and formed mainly the protonated resorcinarene **5**. This is quite unusual, since resorcinarene compounds are normally considered to be quite stable.

The synthesis and purification of the diphosphine oxide **17** proved to be a very taxing undertaking. It was known from the synthesis of the model **13** that the product of the resorcinarene would probably also be oxidised to the phosphine oxide. This would not be such a problem, since there are methods to reduce the phosphine oxide to the corresponding phosphine using silane reagents.[47] In an effort to halt the process degassed solvents and reagents were used throughout the synthesis, to no avail. The reaction suffered the formation of mainly protonated, monophosphine oxide **17a** and the by-products of the reaction of the excess diphenylphosphine chloride with the alkyllithium, making purification by column chromatography very difficult. This led to the product only being partially characterised and yields calculated from crude ¹H NMR spectroscopy. An effort to extract the product using crystallisation and solubility techniques were also not successful. Owing to the low yields and time consuming purification it was decided not to further investigate the reaction.[a] In stark contrast to this, other studies in our group using DoM chemistry to selectively introduce functionality on the resorcinarene, revealed the synthesis of the diphosphine resorcinarene in low yields after purification by column chromatography. Reasons for this are unknown and are currently being investigated.

The introduction of a carbonyl moiety on the resorcinarene also proved to be troublesome. Solid carbon dioxide (forms a carboxylic acid) and dimethylformamide (forms an aldehyde on work-up) were used but not with any great success, owing to formation of mainly protonated and mono-functionalised products and the difficulty in purification of the polar compounds. This problem was overcome by using methyl chloroformate which can be transformed to the carboxylic acid, alcohol or aldehyde if needed.

Analysis of the $\Delta\delta$ of the aromatic protons on the lower rim of the resorcinarenes with ¹H NMR spectroscopy revealed them to be of C_{2v} symmetry, with **17** forming a slightly distorted boat shape. The analysis of the ¹H NMR spectra of **16** revealed some differences to those of the other products and it was postulated that this compound could sit in another conformation. To verify the structure of this, a crystal

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[a] In the last week of writing this thesis an effort to characterise a by-product of the reaction was attempted, which resulted in **17** being synthesised in 50% yield.

structure of the dithioether **16** was obtained from a crystal grown by the slow evaporation of methanol and dichloromethane (Figure 3.2).

The crystal structure of **16** was solved as two molecules in the asymmetric unit. These molecules were not related by symmetry operators and are unique. Only one of the structures is shown in Figure 3.2 for clarity. From the structure it can be observed that the two thioether functionalised aromatic rings are lying in the plane of the cavity, with the ring containing S7A in a more upright position and thus forming a slightly distorted boat shape. The two unfunctionalised aromatic rings also lie at a slightly distorted angle from the vertical plane. This was not what was expected, especially since the conformation of the dibromo has the functionalised rings in the axial position.
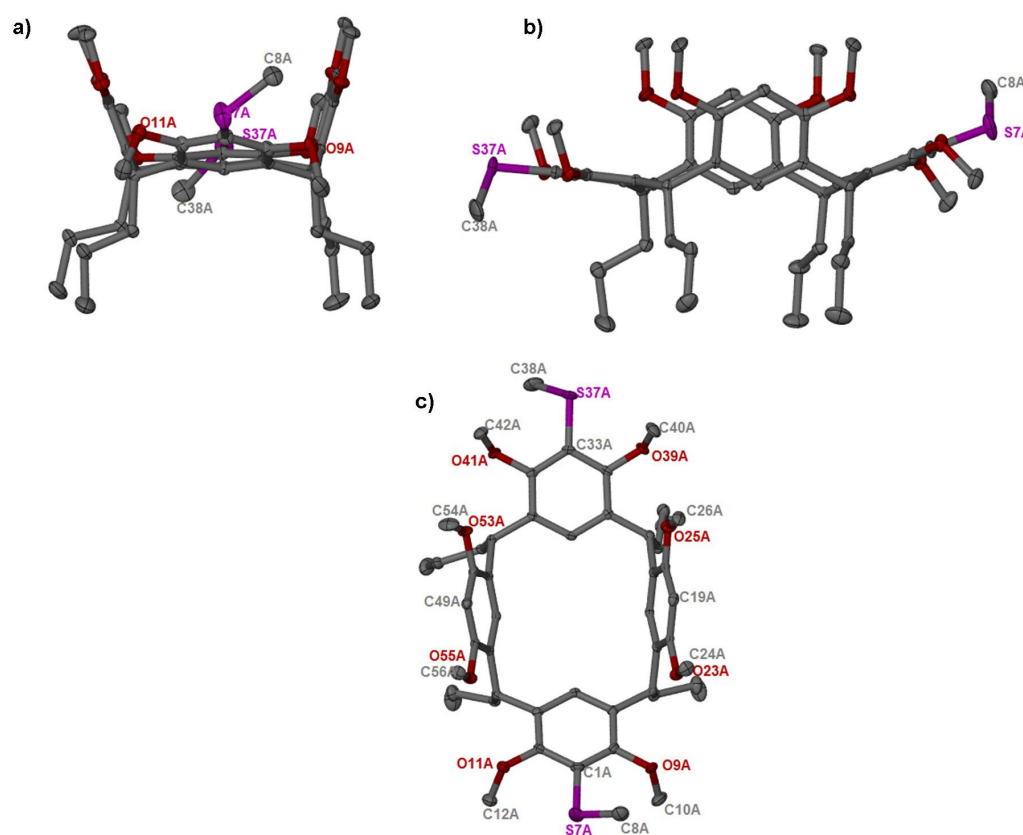
Figure 3.2 Views of the single x-ray crystal structure of resorcinarene **16**. All hydrogens were removed for clarity. Colours: grey = carbon, purple = sulfur and red = oxygen. Only selected numbering is shown for the molecule. a) and b) are side views, and c) is a view from above, down the cavity.

The functionalisation of the resorcinarene backbone using lithium halogen exchange was not as successful as was expected, although we were able to introduce different functionalities on our backbone. The low yields and problems incurred with the separation of the products suggested that another better

method should be found in which the number of by-products would be decreased and a simple purification of the products obtained. Failure to synthesise the diphosphine target compound dampened the further studies of the resorcinarene compounds. It was however decided to investigate other means of functionalisation of the distal resorcinarene and these exploits will be described in chapter 4.

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Further Functionalisation of Resorcinarenes

4.1 Introduction

It was clear that the selective functionalisation of the upper rim of resorcinarenes using lithium-halogen exchange proved to be a difficult methodology. This prompted an investigation into other methodologies to introduce functional groups onto the upper rim of resorcinarenes, keeping in mind that the functionalities should be useful as coordination sites for metals. The two methods discussed here are the anionic *ortho*-Fries rearrangement[1] and the Rosenmund-von Braun cyanation.[2-5]

4.2 Anionic *ortho*-Fries Rearrangement

As a result of the low yields being attributed to the electron donating methoxy groups on the resorcinarene it was questioned what the effect would be if electron withdrawing groups were used instead. Snieckus remarked in a review that these groups should exhibit schizophrenic properties, meaning that they should be a good coordination site for the alkyllithium, but not electrophilic enough to react with the base.[6]

tert-Butoxycarbonyl (Boc) was selected to be the protecting group for the phenols, since the chemistry[7-9] of this compound is well understood and it has been used as a protecting group on resorcinarenes previously.[10-13] What needed to be kept in mind is that the Boc and other acyl groups can rearrange under certain lithiation reaction conditions via the well known anionic *ortho*-Fries rearrangement. Indeed a great deal of work in this area has been reported by Snieckus *et al*.[6] This rearrangement would also be beneficial, since this would allow a method to functionalise the resorcinarene skeleton using orthogonal protection and deprotection chemistry, allowing for further structural modifications. It was first decided to use model compounds to test the scope the reaction and smooth out any possible problems before the reaction was attempted on a resorcinarene.

4.2.1 Synthesis of a Boc-protected model compound

To synthesise the Boc-protected model compound **19** (Scheme 4.1) a modified procedure of Nishibuko *et al.* was followed.[10] Bromoresorcinol **9** was dissolved in pyridine and triethylamine added as base. The pyridine had two functions in the reaction: that of solvent as well as an acyl-transfer agent. After about 15 minutes of stirring at room temperature, di-*tert*-butyl dicarbonate was added and the yellow coloured reaction mixture stirred for 18 hours. The reaction mixture was added to water and extracted with chloroform. The organic phases were washed with 1M HCl to wash out the pyridine and triethylamine.

After the solvent was removed under vacuum the resulting brown oil was purified by flash column chromatography to yield an off white viscous oil. It was observed that if the product was retained too long on the SiO$_2$ column it started to deprotect the molecule, attributed to the slight acidity of the SiO$_2$ gel. After 5 days on a high vacuum pump (0.1 mmHg) the oil solidified, yielding diBoc **19** in 85% yield. Attempts to further purify the compound by recrystallisation were met with failure.
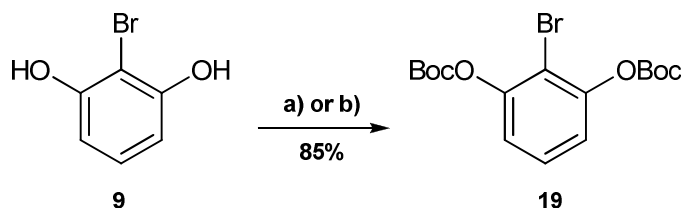

Scheme 4.1. Synthesis of the di-Boc protected model **19**: Reagents and reaction conditions: a) Et$_3$N, pyridine, rt ii) Boc$_2$O, rt. b) i) Et$_3$N, DMAP (0.05 equiv), DCM, rt ii) Boc$_2$O, rt

Due to pyridine's toxicity another procedure was found to protect **9** (Scheme 4.1, reaction conditions b). By exchanging the pyridine for 4-dimethyl aminopyridine (DMAP), a better acyl-transfer agent which could be used in catalytic amounts, and dichloromethane used as solvent. Bromoresorcinol **9**, triethylamine and DMAP (0.05 equiv) were dissolved in dichloromethane at room temperature and di-*tert*-butyl dicarbonate was added after 15 minutes. The yellow coloured reaction was stirred at room temperature for about 18 hours after which it was worked up using successive acid and base washes. The product was purified by flash column chromatography to yield an off white oil. This oil also solidified after a few days on a high vacuum pump returning a yield of 85%.

DiBoc **19** was fully characterised by NMR (^{1}H, ^{13}C), mass and IR spectroscopy. ^{1}H NMR analysis of the aromatic region revealed a triplet at 7.31 ppm accounting for one proton. This was assigned to the proton *para* to the bromine. A doublet at 7.10 ppm, accounting for two protons was assigned to the two hydrogen atoms *meta* to the bromine groups. One other signal, a singlet at 1.54 ppm, accounting for 18 protons was assigned to the two *tert*-butyl groups. ^{13}C NMR (150.3 ppm) and IR (1766 cm^{-1}) signals confirmed the introduction of the carbonate carbons as well as the symmetry in the molecule.

4.2.2 Testing of the Boc Model

To test the Boc model a lithium-halogen exchange reaction was performed, using *n*BuLi and methyl iodide as electrophile (Scheme 4.2).
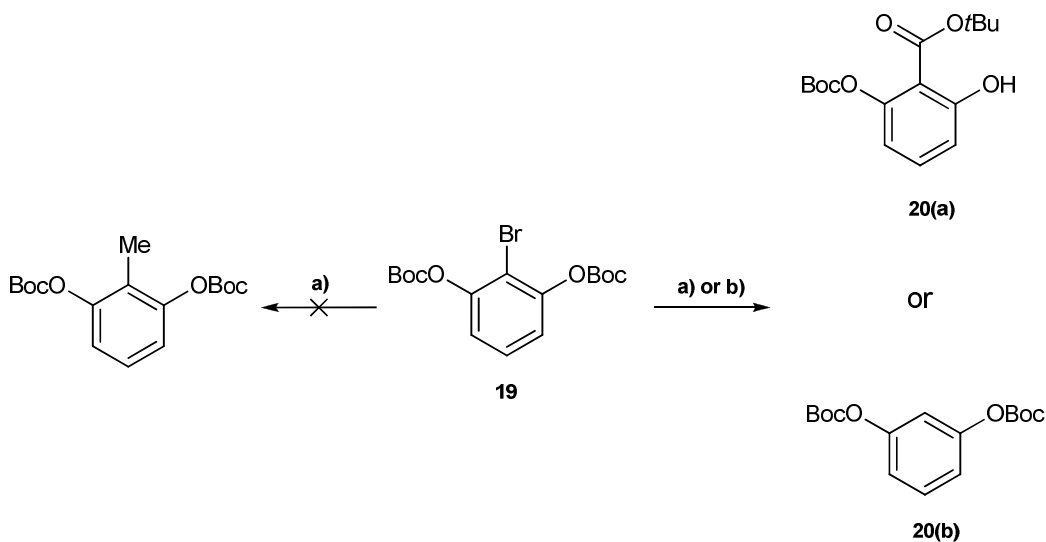
Scheme 4.2. Testing of diBoc **19** with lithium-halogen exchange: Reagents and reaction conditions: a) i) *n*BuLi, THF, −78 °C, ii) MeI, −78 °C→ rt. b) i) *n*BuLi, THF, −78 °C, ii) Sat. NH$_4$Cl, −78 °C→ rt.

DiBoc **19** was dissolved in tetrahydrofuran and cooled to −78 °C. 1.1 equivalents of the alkyllithium were added to the solution and this was stirred for 15 minutes, after which methyl iodide was added. The reaction solution was warmed to room temperature and stirred for 30 minutes. After work-up in acidified water and dichloromethane the tlc revealed two new spots. One slightly less polar than **19** and one very faint more polar spot. The mixture was purified by column chromatography to give the main product as a yellow oil.

The ^{1}H NMR (Figure 4.1) spectrum of the main product revealed that the desired methylated product did not form and that some sort of protonated compound was obtained. The *t*-butyl groups of the new compound were split into two singlets, and there was a very acidic proton at 11.39 ppm and a less symmetrical aromatic region. The aromatic region contained a triplet at 7.37 ppm and two doublet of doublets at 6.23 and 6.88 ppm. This product appeared to be consistent with a metal promoted anionic *ortho*-Fries rearrangement. Mass spectra of the compound could not clearly identify the product due to the other possibilities being constitutional isomers.
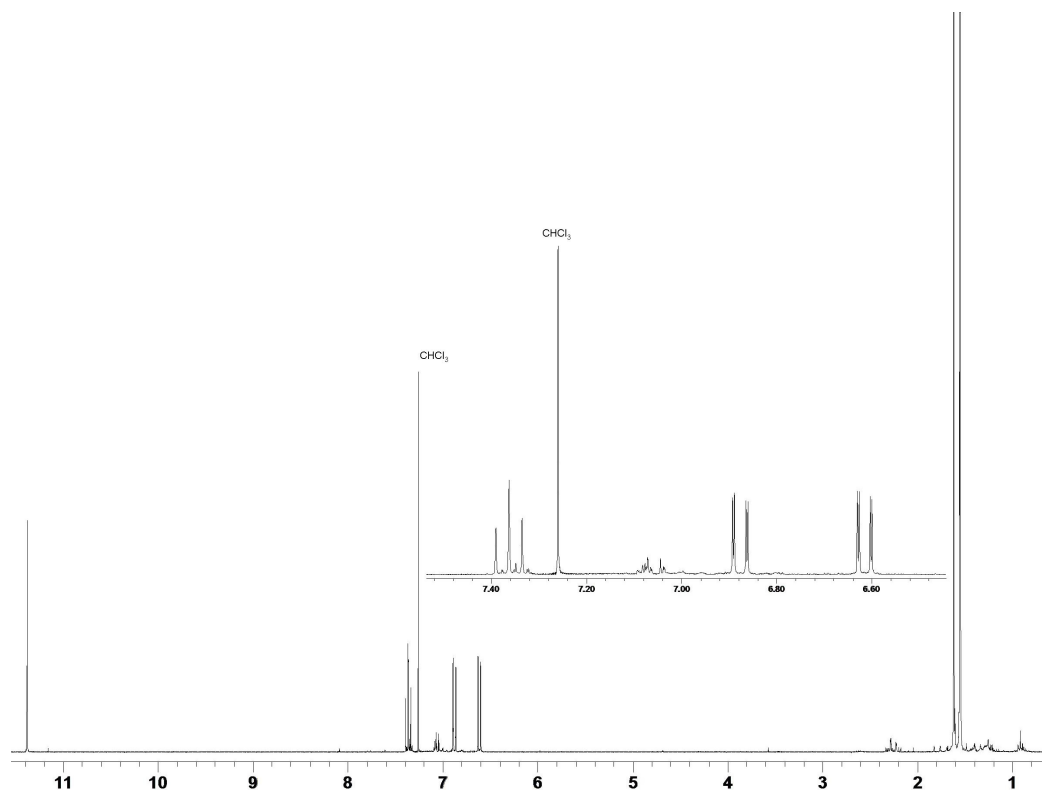
Figure 4.1. ^{1}H NMR spectrum of the unknown product after the lithiation reaction on **19**. An expanded view of the aromatic region is given to show the fine coupling in the molecule.

To establish if the product was the protonated compound the reaction was repeated, only this time it was quenched with a saturated solution of ammonium chloride (Scheme 4.2). The result of this reaction was identical, thus confirming that the electrophile was not introduced and that the product was the rearranged product.
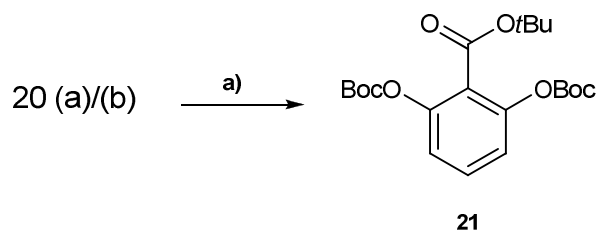
Scheme 4.3. Reaction of the unknown products with the acylation protection methodology: Reagents and reaction conditions: a) i) Et$_3$N, DMAP (0.05 equiv), DCM, rt ii) Boc$_2$O, rt

A literature search revealed that these metal promoted Fries rearrangements occur quite easily under the conditions that were used for lithiation;[14-16] in 2001 Reinhoudt *et al.* demonstrated that by using DoM chemistry they could simultaneously perform four anionic-Fries rearrangements to introduce carbamate functionalities on the upper rim of a resorcinarene.[17] As final verification that this had happened the

unknown compound was subjected to the protection methodology as was used on **9** (Scheme 4.3). Following work-up and flash column chromatography a yellow oil was separated that solidified on standing. ^{1}H NMR analysis revealed very symmetrical, tri-substituted aromatic signals with two signals in the aromatic region. The two signals, a triplet at 7.41 ppm and doublet at 7.11 ppm closely resembled the signals of the brominated compound. Investigation of the *t*-butyl region revealed two singlets at 1.58 ppm and at 1.55 ppm integrating for 27 protons. This suggested that the solidified oil was the di-Boc protected rearrangement product which was confirmed by mass spectronomy. It is thus now known that the rearranged product **20(a)** (Scheme 4.2) formed in an excellent yield of 91%, and not the protonation of **19**. The triBoc **21** was obtained in an 89% yield. This reaction gave a method to introduce carboxylic groups in high yields onto the resorcinarene. Thinking ahead, the reactivity of these remaining Boc-groups would be a problem for further functionalisation of the resorcinarenes. It was decided therefore to test methodology to replace them with more inert groups; e.g. methoxy groups on the phenol ring.

Deprotection (Scheme 4.4) of the molecule was first attempted using a procedure by Hansen.[9] Stirring **21** in THF with 3M HCl showed no desired product, even if the reaction was heated under reflux overnight. An alternative method where trifluoroacetic acid (TFA) is used to remove the Boc groups was persued.[7, 9] **21** was dissolved in dichloromethane and treated with excess of TFA at room temperature and the reaction progress monitored by tlc. After two hours tlc revealed that all the starting material was consumed and a new spot on the baseline emerged. The solution was taken up in ethyl acetate and neutralized with a 10% solution of sodium bicarbonate, care being taken to keep the pH at about 7.
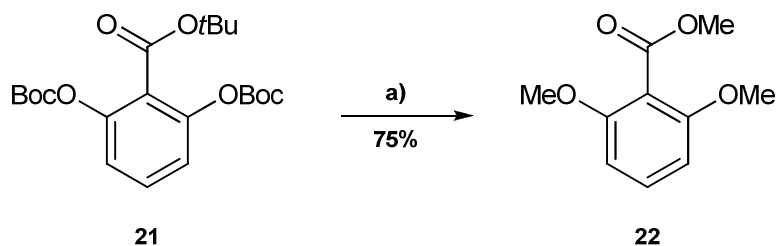
Scheme 4.4. Synthesis of methyl 2,6-dimethoxybenzoate **22** via deprotection of **21**. Reagents and reaction conditions: a) i) TFA (excess), DCM, rt ii) Me_2SO_4, K_2CO_3, CH_3CN, reflux

Due to the high polarity of the compound it was decided to forego purification and protect the phenols and carboxylic acid as methyl ethers and ester (Scheme 4.4). Thus, the crude mix of the deprotection step was suspended in acetonitrile and an excess of potassium carbonate and dimethyl sulfate was added. The reaction was heated under reflux for 18 hours after which a standard work-up was performed resulting in a yellow-brown oil. Tlc after the reaction revealed a lot of by-products and a ^{1}H NMR spectrum was obtained to see if any product was in the crude mixture. The ^{1}H NMR spectrum revealed the main product to be **22**, with small amounts of impurities on the baseline and revealed the now characteristic triplet and doublet of the tri-substituted aromatic ring as well as two singlets more upfield. The triplet at 7.30 ppm

and the doublet at 6.57 ppm showed a significant shift upfield, due to the electron donating methoxy groups. The singlets at 3.92 and 3.83 ppm, the methyl ester and methoxy protons, corresponded to three and six protons respectively and the spectrum corresponded well with the literature values for methyl 1.3-dimethoxybenzoate **22**.[18] With the chemistry worked out for the necessary transformations on the model compounds it was decided to attempt this on a resorcinarene.

4.2.3 Testing the anionic ortho-Fries rearrangement on resorcinarenes

To test the rearrangement on the resorcinarenes, dibromo tetraCbz resorcinarene **3** was chosen as the starting material, since it would impart the necessary C_{2v}-symmetry that was needed to introduce the distal functionalisation on our molecules.
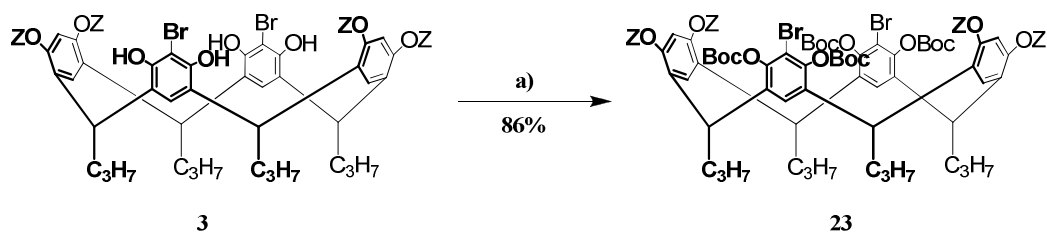
Scheme 4.5. Synthesis of resorcinarene **23** (Z = -Cbz): Reagents and reaction conditions: a) i) Et$_3$N, DMAP (0.05 equiv), DCM, rt ii) Boc$_2$O, rt

Resorcinarene **3** was subjected to both the acylation methodologies used for the model compounds, but it was found again that following the DMAP procedure resulted in the work-up and purification being simpler. **3** was dissolved in dichloromethane and treated with four equivalents of triethylamine and 0.05 equivalents of DMAP at room temperature (Scheme 4.5). After 15 minutes Boc$_2$O (five equivalents) was added and the reaction mixture left to stir for 24 hours after which tlc analysis showed the complete consumption of starting material. After work-up and purification through column chromatography the resultant yellow foam was recrystallised from an ethanol/dichloromethane mixture to yield fine yellowish crystals of dibromo diBoc tetraCbz resorcinarene **23** in 86% yield. Characterisation using ^{1}H NMR spectroscopy was hampered due to the extremely broad signals especially in the aromatic region. This was attributed to the slow free rotation of the eight carbonate groups on the resorcinarene upper rim. It was however possible to verify the introduction of the *t*-butyl groups at 1.48 ppm. IR spectroscopy indicated the disappearance of the hydroxyl peaks found in **3**'s spectrum as well as the appearance of a new carbonyl stretch at 1759 cm^{-1}. Mass spectroscopy returned a peak at 1768.5 which correlated to M+H$_2$O, thus giving proof for the formation of the product **23**.

In an attempt to cause the *ortho*-Fries rearrangement, **23** was dissolved in THF and treated for 20 min with *n*BuLi at −78 °C, after which the reaction was quenched with a saturated ammonium chloride solution (Scheme 4.6). After warming the reaction mixture to room temperature it was worked-up and tlc revealed two new spots. This was expected since two diastereomers could result depending on which one

of the Boc groups reacted with the aryllithium intermediate (Figure 4.2). Flash column chromatography was not suitable to separate the products and thus preparative tlc was used. Although the products were separated successfully no clear evidence could be gained of what products were formed using ^{1}H NMR spectroscopy. The spectra of both of these molecules revealed the same broad and featureless aspects as that of the starting material, the only indication that something happened were the now broad signals in the region of 1.20-1.60 ppm where the *t*-butyl groups were expected.

As with the model study, it was decided to transform these groups to other simpler functionalities so that the spectroscopic identification of these products might be easier. The mixture of A and B should form one product if the *t*-butyl and Cbz groups are removed and replaced by methyl ethers. Throughout the transformations the reactions were followed by ^{1}H NMR spectroscopy and tlc to determine if the reactions were successful.
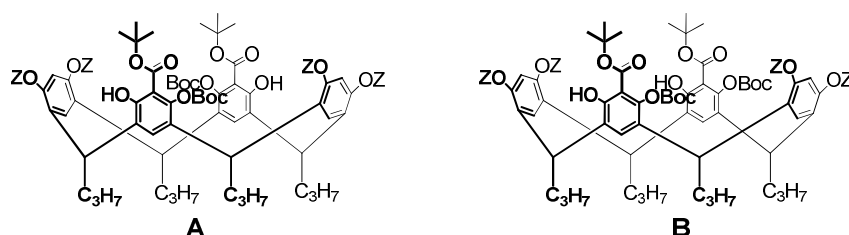
Figure 4.2. The two possible diastereomers that can be formed after the anionic-Fries rearrangement on resorcinarene **23** (Z = -Cbz).

The synthetic steps taken can be followed in Scheme 4.6. To make the transformations easier to follow the resorcinarene ring was simplified to the two core rings that are attached and drawn out as a flat 2D drawing (the rearrangement reaction is shown as only one Boc group rearranging).
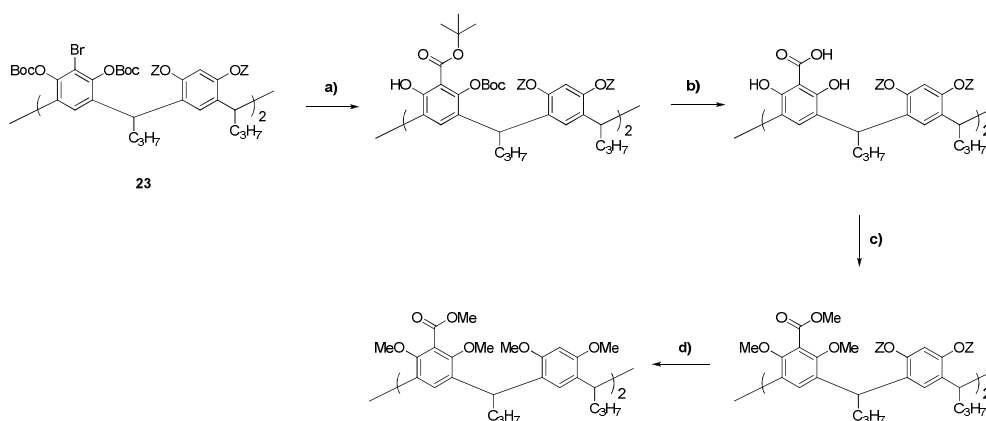
Scheme 4.6. Synthesis and transformations of the products of the anionic ortho-Fries rearrangement on resorcinarene **23**. Reagents and reaction conditions: a) i) *n*BuLi, THF, −78 °C ii) Sat. NH$_4$Cl, −78 °C→ rt b) TFA (excess) DCM, rt c) Me$_2$SO$_4$, K$_2$CO$_3$, CH$_3$CN, reflux d) i) H$_2$, Pd/C, THF:EtOH (1:1), rt ii) Me$_2$SO$_4$, K$_2$CO$_3$, CH$_3$CN, reflux

The *t*-butyl groups were first removed using excess TFA in dichloromethane at room temperature. After a standard work-up an orange solid was obtained. The ^{1}H NMR spectrum of the crude product showed that the *t*-butyl groups were successfully removed, but it was not possible to separate the products owing to their very polar nature.

To see if purification could be performed the products were heated under reflux in acetonitrile with an excess of dimethyl sulfate and potassium carbonate to protect the phenols and carboxylic acid. After 24 hours all the starting material was consumed according to tlc, but a plethora of new spots (products) formed. These were also not separated with chromatography and a crude ^{1}H NMR spectrum of the product showed the introduction of the methoxy groups (3.37-3.88 ppm), but no clear identification could be made. Arnott *et al*. commented that in an effort to protect their C_{2v}-symmetrical acylated resorcinarenes (tetraCbz and tetratoluenate) with methoxy groups resulted in a range of products that could be explained by a rearrangement of the –Cbz groups on the phenols of the resorcinarenes and that this could explain the range of products that were formed.[20]

For the last transformation the –Cbz groups were removed using catalytic hydrogenation over palladium on carbon and the resulting products again protected as methyl ethers. The four products of the last step were separated by column chromatography and ^{1}H NMR spectra were taken. These revealed that distal substituted compounds were formed, but due to the relative low amounts that was recovered it was decided not to pursue this method any further since it had become too cumbersome a method for functionalisation.

4.3 Rosenmund-von Braun Cyanation

One of the biggest challenges for this project was to functionalise the resorcinarene backbone with a wide range of functional groups. Amines[21-23] and Schiff bases[24] are very important ligand functionalities in transition metal chemistry and it was decided to investigate if resorcinarenes could be selectively functionalised with these (Figure 4.2). One method to introduce amines on resorcinarenes is through the well known Mannich reaction as used for example by Shivanyuk[11, 25-27] and Arnott.[20, 28, 29] It was considered that nitrile groups might be an appropriate targets.[19] The nitrile has been previously introduced onto resorcinarenes: in work by Chen *et al.*[30-32] and by various groups in their research into forming transition metal cavitand cages.[33-35] However no subsequent transformations of the nitrile groups have been reported.
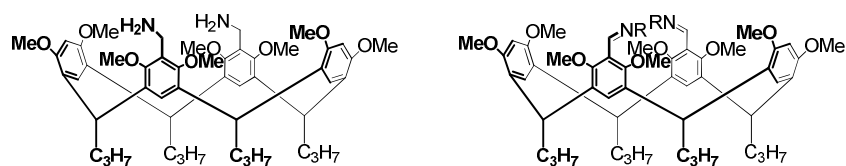

Figure 4.3.   Target amine and Schiff base resorcinarenes

4.3.1 Synthesis of dicyano resorcinarene precursor

Dicyano resorcinarene **24** was synthesised using a procedure by Chen *et al.*[31] Dibromo resorcinarene **4** was dissolved in dry *N,N*-dimethylformamide and eight equivalents of copper(I) cyanide were added. This mixture was heated under reflux for 23 hours after which it was cooled to room temperature and treated with iron(III) chloride in concentrated HCl for 1 hour to help with the isolation of the nitrile compounds. It is known that the resulting nitriles form complexes with the cuprous halide byproducts that are formed in the reaction. These complexes are soluble in *N,N*-dimethylformamide and to decompose them various methods have been employed.[4] The iron(III) in concentrated HCl oxidized the Cu(I) in the reaction mixture to Cu(II) which is more soluble in water and facilitates the work up.[4] The Fe(III) in turn is reduced to Fe(II) and this could also be removed in the water layer during work up. At this point extreme care had to be taken since HCN gas is given off in the process. The green solution was extracted into chloroform and after work up **24** was recovered by column chromatography in 50% yield. The product was recrystallised in boiling ethanol and this formed fine white crystals.
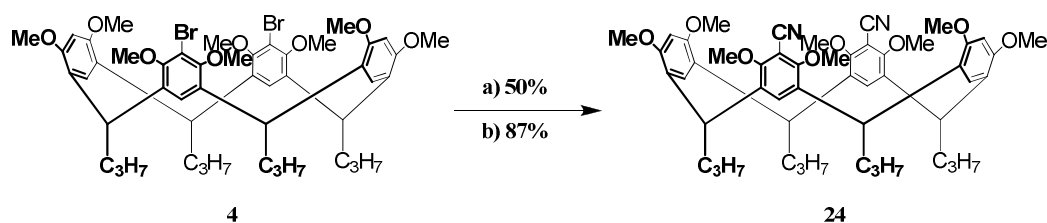
Scheme 4.7. Synthesis of dicyano resorcinarene **24** via Rosenmund-von Braun cyanation: Reagents and reaction conditions: a) i) CuCN, DMF, reflux ii) FeCl$_3$, conc. HCl b) i) CuCN, DMF, microwave ii) FeCl$_3$, conc. HCl

The literature also reports the use of microwave technology in the synthesis of cyano aromatic compounds.[36, 37] One advantage of using microwave assisted reactions is that solvents can be heated to a temperature higher than their boiling point since the reactions are performed in sealed vessels. It is also important to use solvents with a high dielectric constant. *N,N*-dimethylformamide and *N*-methylpyrrolidinone are seen as excellent solvents for use in these reactions owing to them being exemplary in all of the above conditions.[37] These circumstances cause reactions to be finished in relatively shorter times than what would normally be the case. Availability of a microwave reactor caused us to explore the optimisation of the reaction using this technology (Table 4.1).

Table 4.1.   Optimisation of the Rosenmund-von Braun cyanation on resorcinarene **4** using microwave technology. Other reaction conditions can be seen in Scheme 4.7.

Run	CuCN equiv	Time (min)	Temp (°C)	Yield[a]
1	8	25	200	10 %
2	8	30	210	42 %
3	8	35	210	52 %
4	4	60	210	60 %
5	8	45	210	87 %

[a] Yield after column chromatography

It is clear from the above table that a longer reaction time and four equivalents of Cu(I) salt per bromine were needed to ensure a successful reaction. Shorter reaction times and using less Cu(I) were not as successful, even in the case of run 4 where the reaction time was lengthened to one hour. As seen from the above table the best reaction conditions were at 210 °C for 45 minutes and using 8 equivalents of copper(I) cyanide. What was found in later reactions with these conditions is that the dryer the *N,N*-dimethylformamide, the better the yields were.

Dicyano **24** was characterised using 1D and 2D NMR (^{1}H, ^{13}C, HSQC and HMBC), IR and mass spectroscopy, as well as melting point determination. IR spectroscopy revealed an absorption at 2229 cm^{-1} giving a clear indication of the introduction of the cyano group as well as a signal at 115.1 ppm in the ^{13}C NMR spectrum typical of an aryl-CN. 2D NMR spectroscopy was used to fully characterise the molecule and to determine the conformation of the molecule. C_{2v} symmetry was assigned to **24**, but due to the formation of a slight doublet of doublets at 4.47 ppm it would be assumed that it is in a slightly distorted boat shape.

4.3.2 *Attempted synthesises of amine and Schiff base resorcinarenes*

4.3.2.1   *Amine Synthesis*

With **24** in hand it was decided to first synthesise a di-amine resorcinarene. There is a fair amount of literature reporting the reduction of nitrile groups and it was decided to find a method that did not need

high pressure catalytic hydrogenations or expensive coordination compounds to perform the transformations.[19]

The first method that was chosen was the reduction of nitriles to amines using sodium borohydride and transition metal salts, with the most important ones being those of Co(II), Ni(II) and Al(III).[38-40] These metals form a fine black precipitate of metal borides (Co_2B in the case of Co(II)) due to the breakdown of the borohydride which in turn produces hydrogen *in situ*. These reactions are mostly performed in alcoholic solvents with stoichiometric amounts of metal salts and an excess of sodium borohydride (2-10 equiv). It has been shown that ethereal and coordinating solvents cause the reaction to slow down and form secondary products.[39, 40]

Dicyano **24** and two equivalents of anhydrous nickel(II) bromide were added to dry ethanol and the solution cooled to 0 °C. To the mixture were added six equivalents of sodium borohydride in two portions. The reaction turned black almost instantaneously after addition and hydrogen gas was evolved. After warming to room temperature the reaction solution was examined after 30 minutes and tlc analysis revealed only starting material, with a small spot on the baseline. The reaction mixture was left to stir and tested again after a further 60 minutes passed. Tlc of the reaction again revealed no product formation and the reaction was stopped and worked up. This result was also found if the reaction was left to stir for 20 hours at room temperature. Considering that this could be due to **24** being sparely soluble in ethanol, the reaction solvent was changed to a 1:1 mixture of ethanol and tetrahydrofuran. This also resulted in no product formation after 20 hours and the reaction was stopped. Changing the metal to cobalt(II) chloride hexahydrate also returned similar results, even after using more equivalents (four→eight) of metal salt and of sodium borohydride (20→40) and heating under reflux for 24 hours. Catalytic hydrogenation at atmospheric pressure using palladium over carbon and hydrogen also did not result in any new products.

Reduction of the dicyano **24** was then attempted using lithium aluminium hydride. Dicyano **24** was dissolved in tetrahydrofuran and the solution was added to six equivalents of lithium aluminium hydride in tetrahydrofuran at room temperature. The reaction was heated under reflux for three hours after which it accidently went dry due to a leak in the reaction setup. The solid was worked up and tlc of the reaction revealed mostly starting material and a small spot on the baseline. The reaction was repeated, this time using 10 equivalents of reducing agent. The reaction was heated under reflux for 10 hours after which it was left to stir at room temperature overnight (for a further 18 hours) to ensure that it did not go dry again. Returning to the reaction it was revealed that the solution had taken on a gel-like consistency and would not change even on heating. The reaction was quenched and worked up. Tlc revealed no starting material and a spot on the baseline. This was moved up in more polar elution solvents to indicate three new spots. Due to their polarity it was decided to acetylate the products to see if it would not be easier to recover and separate via chromatographic methods. The products were dissolved in dichloromethane and

cooled to 0 °C. DMAP (0.1 equiv), pyridine (10 equiv) and acetic anhydride (10 equiv) were added to it and the reaction was stirred at room temperature for 20 hours.

After work up the products were analysed using ^{1}H and ^{13}C NMR spectroscopy to investigate if the acetyl groups were introduced onto the resorcinarene. Both of these methods indicated that the acetylation did occur, with signals in the region of 169-171 ppm and at 1.90-2.10 ppm in the ^{13}C and ^{1}H NMR spectra respectively. The ^{1}H NMR spectrum reveals the formation of a major product that is distally substituted and also contains a doublet at 4.34 ppm that is indicative of the prochiral sp^3 carbon that is attached to the amine. Separation of the products proved difficult with column chromatography and it was decided to leave this reaction, owing to the practical difficulties encountered.

4.3.2.2 *Schiff base synthesis*

For the synthesis of the Schiff bases the reduction of the nitrile to an aldehyde was necessary. Dicyano **24** was stirred in dichloromethane with four equivalents of diisobutyl aluminium hydride at −78 °C for six hours after which it was worked up. Tlc indicated only starting materials and a small amount of another product. The reaction was repeated in tetrahydrofuran, unfortunately with the same result even after warming and stirring at room temperature for 24 hours. At this point the attempts to transform the nitrile groups on the resorcinarene were not further pursued.

It is evident from these results that relatively harsh conditions are needed to transform these groups on the resorcinarenes. This stands in contrast with simpler systems where reactions are completed in relative short times and at ambient temperatures.[38-40] Although a clear answer to why this is the case is not evident, the size of the macrocycle should be taken into reckoning, as well as possible interactions of the ring(s) with the reducing agents and therefore influencing the transition states and mechanisms. One argument that could also be included is the possible deactivation of the nitrile group through resonance in the aromatic ring. It is reasoned that the both of the methoxy groups can donate, through resonance, electrons onto the carbon of the nitrile group, thus making it less electrophilic and thus less reactive to reduction.
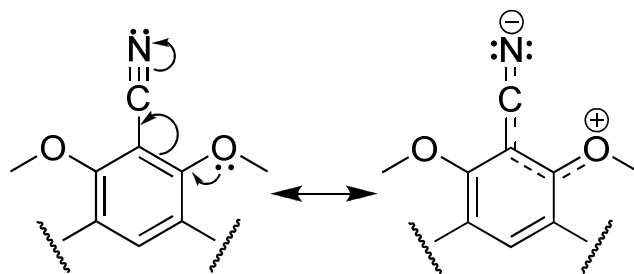
Scheme 4.8. Possible delocalisation of electrons in the resorcinarene ring that could reduce the reactivity of the nitrile resorcinarene **24**.

With the synthesis of the possible resorcinarene ligands completed attention was given to the formation of coordination compounds with transition metals. The study of the coordination and testing of the compounds' catalytic capabilities will be the focus of the next chapter.

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Resorcinarene Metal Complexes and their Catalytic Activity

5.1 Introduction

The formation of metal complexes of resorcinarenes was dealt with in detail in chapter 1. Owing to our inability to introduce phosphine, amine or Schiff bases onto our resorcinarenes in high yields we were left with very little choice for a model to study the possible distal coordination of metals in resorcinarenes. Because of the thioether moieties attachment to the resorcinarene skeleton, dithioether **16** was the only ligand that fitted our initial criteria and this was then used as a model for our complexation study. The crystal structure that we had for this compound would also give us something to compare the coordination structures between the different complexes. Dicyano **24** was not regarded for these studies due to their axial complexation and cavitand cage formation as demonstrated by the work of Dalcanale *et al.*[1]

5.2 Synthesis of a Resorcinarene Metal Complex

5.2.1 Thioether Coordination Chemistry

Transition metal complexes of thioether ligands have been studied intensively since the beginning of coordination chemistry.[2-7] Neutral thioether moieties are generally considered as being sp^3-hybridized and thus having two lone pairs of electrons through which coordination can take place. The most common coordination is through one pair of electrons (terminal), although some cases of both donating (i.e. bridging) are known.[3] The sulfur atom of thioethers is considered soft and therefore bonds strongly to soft metals (e.g. palladium). They are seen as weak σ-donors as well as weak π-acceptor ligands via the σ^* orbitals of the S-X bond, this last attribute contributes greatly to the strength of the sulfur-metal bond. The *trans*-effect of sulfur ligands is considered higher than that of nitrogen and oxygen-based ligands but is found to be lower than phosphine ligands.[2]

Coordination of metals to dissymmetric sulfur ligands (e.g. RSR') form a new stereogenic centre at the sulfur, but because of their low inversion barrier (10-15 kcal mol^{-1}), owing to pyramidal inversion, there is little control of the formed configuration. Sulfur ligands however are easier to store, handle and synthesise than most phosphine ligands and are therefore an attractive option for use in catalysis.

5.2.2 Complex Synthesis

For the formation of resorcinarene complexes it was decided to use simple metal salts of Pd(II), Ni(II), Pt(II) and Ag(I) in different metal to ligand ratios and reaction conditions (Scheme 5.1). Owing to the

2006 and 2008 reports of Danil de Namor *et al.*[8, 9] the coordination of Ag(I) to resorcinarene **16** was first investigated.
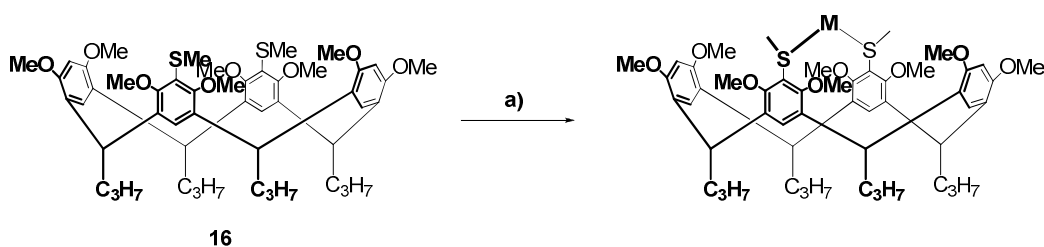
Scheme 5.1. Proposed formation of bidentate distal coordination compounds with resorcinarene **16**: Reagents and reaction conditions: a) Metal salt (M), various reaction conditions

To a solution of **16** in dichloromethane was added one equivalent of silver perchlorate and the mixture stirred in a darkened flask for 30 minutes at room temperature. The mixture was filtered over Celite and the filtrate solvent removed in vacuo. The ^{1}H NMR spectrum revealed only starting material. Due to concerns over solubility, the reaction was reattempted in tetrahydrofuran as solvent. The silver salt was dissolved in acetonitrile and added to the darkened flask and the reaction mixture stirred for three hours. The mixture was then worked up as previously to form a whitish solid. A small sample of the crude product was investigated with the use of ^{1}H NMR spectroscopy (Figure 5.1, bottom spectra). Investigation of the spectra revealed some very interesting features.
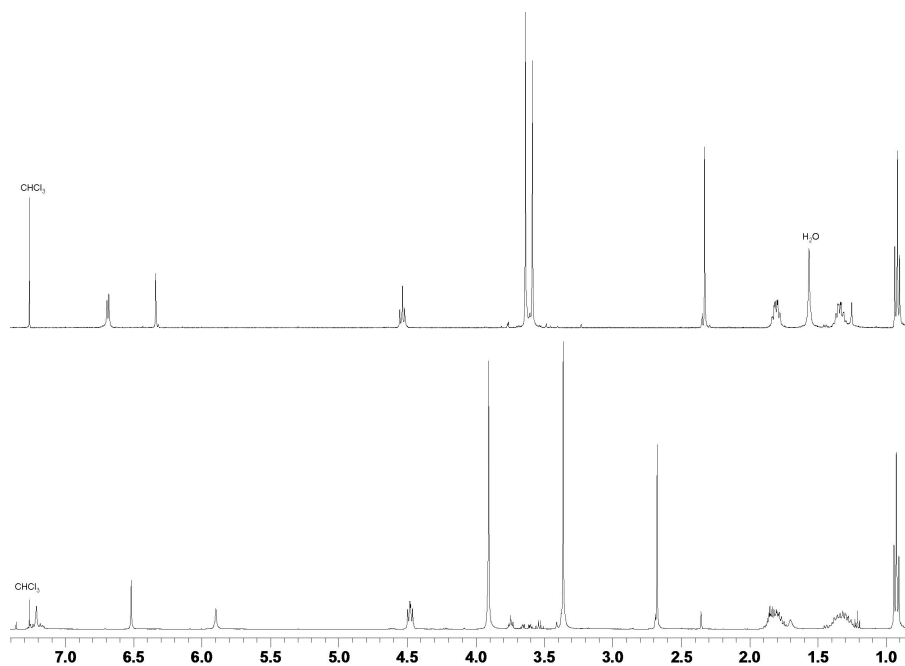
Figure 5.1. ^{1}H NMR spectra of the crude resorcinarene silver complex (bottom) and the dithioether **16** (top).

The downfield shift of the signal for the thioether-methyl (from 2.32 to 2.68 ppm) indicated that coordination with the Ag(I) salt occured through the S moiety. It is also interesting to note that there was only one signal, which suggests that both of the thioethers bonded in the same manner, justifying a distal bidentate coordination. This is also supported by the fact that only one equivalent of metal salt to the resorcinarene ligand was used. Shifts in the methoxy, methine and aromatic regions revealed a configuration change in the resorcinarene, with the thioether functionalised resorcinol units moving into an axial orientation and the other two rings lying in an equatorial orientation giving it a slightly distorted boat configuration. This also supports the formation of a bidentate bonded resorcinarene ligand. Unfortunately repeated attempts to grow diffraction quality crystals for X-ray diffraction proved unsuccessful and further attempts at characterisation of the complex ended in failure, possibly due to the instability of the silver complex.

Anhydrous nickel(II) bromide was investigated next. One equivalent of salt dissolved in methanol was added to **16** in tetrahydrofuran at room temperature. After 40 minutes the greenish solution turned to an orange-brown suspension and this was stirred at room temperature for 20 hours. The mixture turned a light yellow colour overnight and the reaction was worked up by filtration and the solvent of the filtrate was removed *in vacuo*. The yellow residue did not dissolve in dichloromethane, but did with the addition of methanol to the solution. When a NMR sample of the product was prepared in deuterated acetone an insoluble substance precipitated out of solution deterring the characterisation of the compound. As with the Ag salt repeated attempts to grow crystals for X-ray diffraction failed due to decomposition of the product, returning **16** and the metal salt.

The synthesis of platinum complexes also proved to be unsuccessful. For the initial studies potassium tetrachloroplatinate(II) was used as the platinum precursor. Resorcinarene **16** and one equivalent of the platinum salt were refluxed in toluene for 24 hours returning a pink precipitate. The precipitate was filtered off and the solvent of the colourless filtrate was removed *in vacuo*. Analysis revealed this as quantitative recovery of the starting ligand. The reaction was performed again, only this time in tetrahydrofuran with the metal salt dissolved in water with the addition of a few drops of concentrated HCl. Precipitation of a black solid occurred immediately and the reaction was discontinued. The reaction was also attempted using a two phase system, with the metal salt dissolved in water and the ligand in dichloromethane, with no result. A more organic, solvent soluble and labile precursor, bis(dimethylsulfide)platinum(II)chloride $(SMe_2)_2PtCl_2$ **25**, was synthesised in 75% yield according to the procedure published by Roodt.[10] Stirring the Pt precursor with ligand **16** in dichloromethane for 24 hours and longer at room temperature also did not produce any complexed compounds. This was confirmed by ^{1}H NMR spectroscopy of the crude product and the fact that the two compounds crystallised out separately after work-up.

Finally the synthesis of a palladium(II) resorcinarene complex was attempted. Based on the synthesis of coordination complexes of various metals by Puddephatt *et al.*,[11] one equivalent of palladium chloride was stirred with resorcinarene **16** in dichloromethane at room temperature for 24 hours. After filtering through Celite and careful washing with dichloromethane the filtrate was evaporated to leave a yellow-brown residue. This residue was dissolved in dichloromethane and layered with pentane and left to crystallise in a fridge at −15 °C. After three days small brown crystals formed and these were collected by filtration. The amount of material recovered was very little in each case and this was used to characterise the complex.
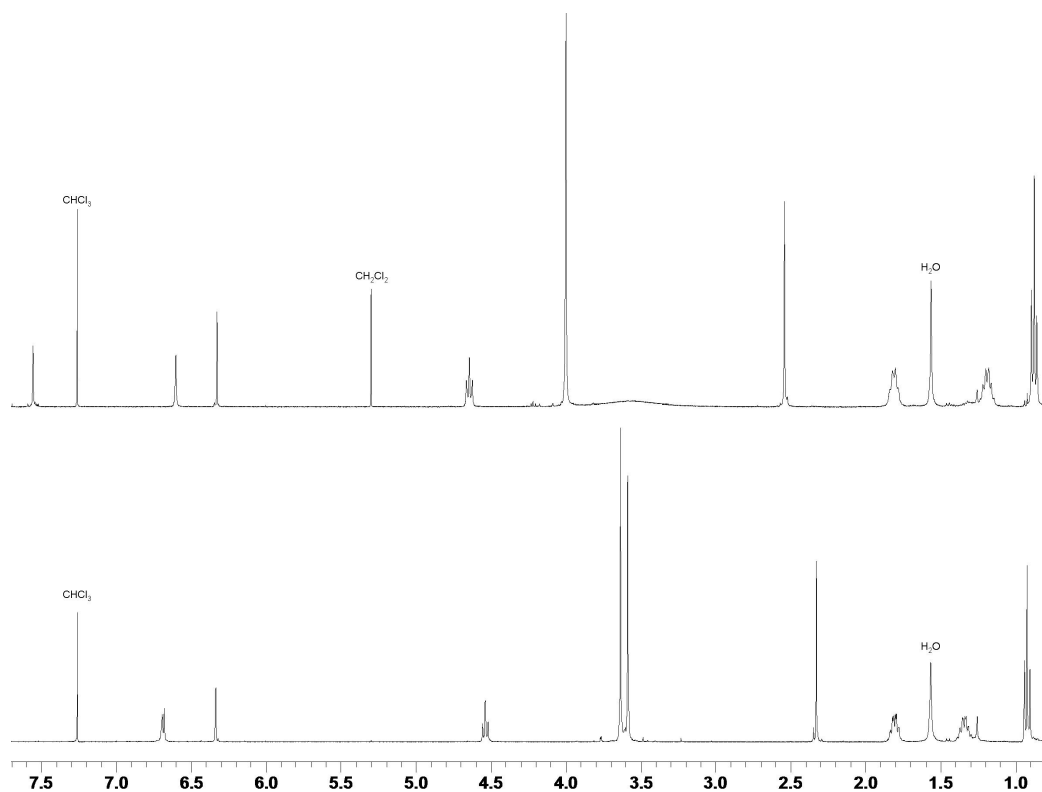
Figure 5.2. ^{1}H NMR spectra of the palladium chloride complex of resorcinarene **16** (top) and the dithioether **16** (bottom) in CDCl$_3$. Dichloromethane is present as a possible adduct in all the spectra.

The ^{1}H NMR spectrum (Figure 5.2) of the crystals in CDCl$_3$ revealed similar features to that of the crude NMR spectrum of the silver complex. From the more downfield signal for the thiomethyl ether at 2.55 ppm it was concluded that coordination of the complex was through the S atoms. The aromatic region also indicated significant shifts for the three aromatic signals, suggesting a change in the conformation of the parent ligand to a distorted boat, with the thiomethyl functionalised rings being in an axial position. Of surprise and concern was the disappearance of a signal for four of the methoxy groups (12 protons). The one signal at 4.01 ppm integrated for 12 protons only and therefore half of the total amount expected.

A very broad signal at 3.58 ppm was observed and it was suspected that this could be the missing methoxy groups due to some form of restricted rotation causing it to appear as a broad hump. 2D NMR (HSQC, HMBC, COSY) did not help in finding the lost signals.

To investigate our hypothesis a sample of the complex was subjected to variable temperature ^{1}H NMR spectroscopy (Figure 5.3). The sample in CDCl$_3$ was warmed in steps of 10 °C from 20 °C to 50 °C (the safe maximum temperature for CDCl$_3$ in the spectrometer) and spectra were recorded after each step. As the NMR sample was warmed a gradual change could be seen in the region of the broad signal. At 50 °C a obvious signal could be observed, (see blocked part in Figure 5.3) which integrated for the expected 12 protons. As for the rest of the spectrum there were no changes, only the resolution of some of the signals increased.
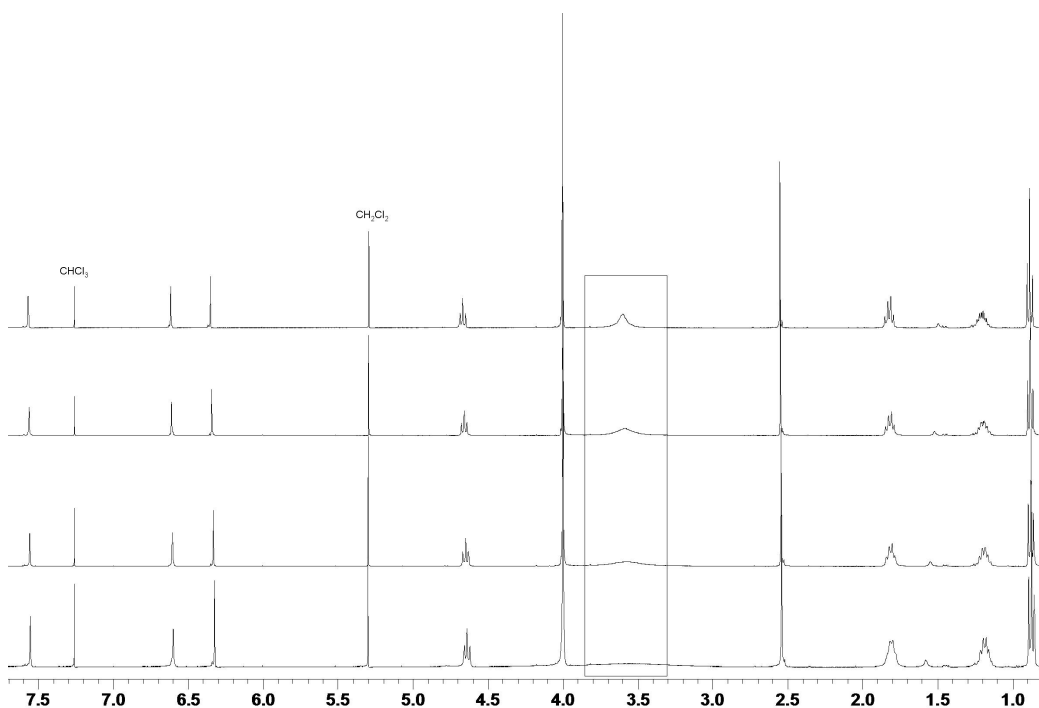
Figure 5.3. Variable temperature ^{1}H NMR spectra of the palladium complex of **16**. The block shows the formation of the lost signal owing to the increase in resolution of the spectra as the temperature is increased stepwise (Δ10 °C) from 20 °C (bottom) to 50 °C (top).

It was expected that the compound would exist in two conformations (Figure 5.4) at low temperatures due to the relative position that the thioethers' methyl groups could be found in: a more symmetrical C_2-conformation, with both methyl groups on the same side, and a more unsymmetrical C_s-conformation, with the methyl groups on different sides.
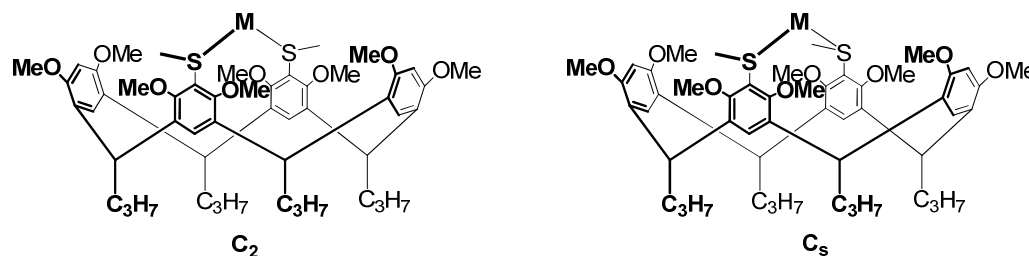
Figure 5.4.   The possible two different conformations that the resorcinarene complex could adopt.

The ^{1}H NMR sample was cooled in steps of 10 °C from 20 °C to −50 °C to investigate if the coordination compound's different conformations could be isolated (Figure 5.5).
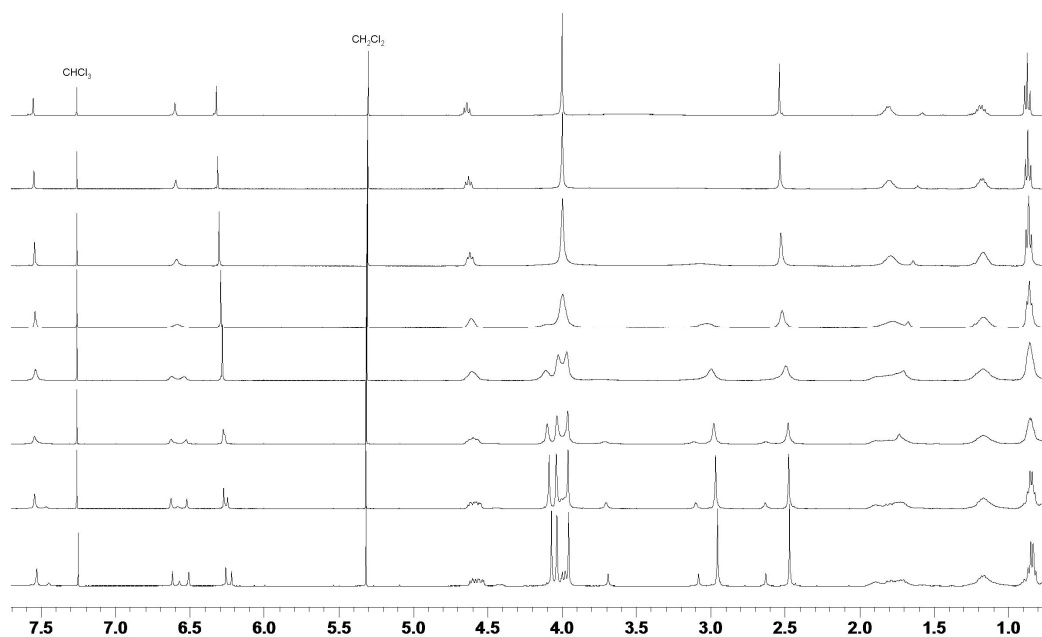
Figure 5.5.   Variable temperature ^{1}H NMR spectra of the palladium complex of **16.** Temperature was decreased in 10 °C steps from 20 °C (top) to −50 °C (bottom).

Analysis of the ^{1}H NMR spectra indicated the appearance of new signals as the sample was cooled. The broad signal of the methoxy groups disappeared and at about 0 °C reappeared as two signals: one near the thioether signal at 2.97 ppm and the other with the other methoxy signals at 3.96-4.11 ppm. As the sample is cooled down further the methoxy signals are resolved into three major signals and some smaller ones. In the aromatic region this also becomes apparent with the formation of five major signals for the

aromatic protons as well as three (two clear and one hidden under the signal at 6.27 ppm) minor signals. The benzylic methine protons, whose signals could generally be used as an aid in pointing out a certain symmetry elements, was revealed as two multiplets, one major and the other one as a minor product.

The ratio of the different conformations could be calculated as 6:1 from the relative integration between the major and minor signals (seen as * in Figure 5.6) for the comparative chemical signals. The minor signals showed a more symmetrical orientation and could thus be assigned to a possible C_2-conformation, while the major signals were assigned to the more unsymmetrical C_s-configuration (Figure 5.4).
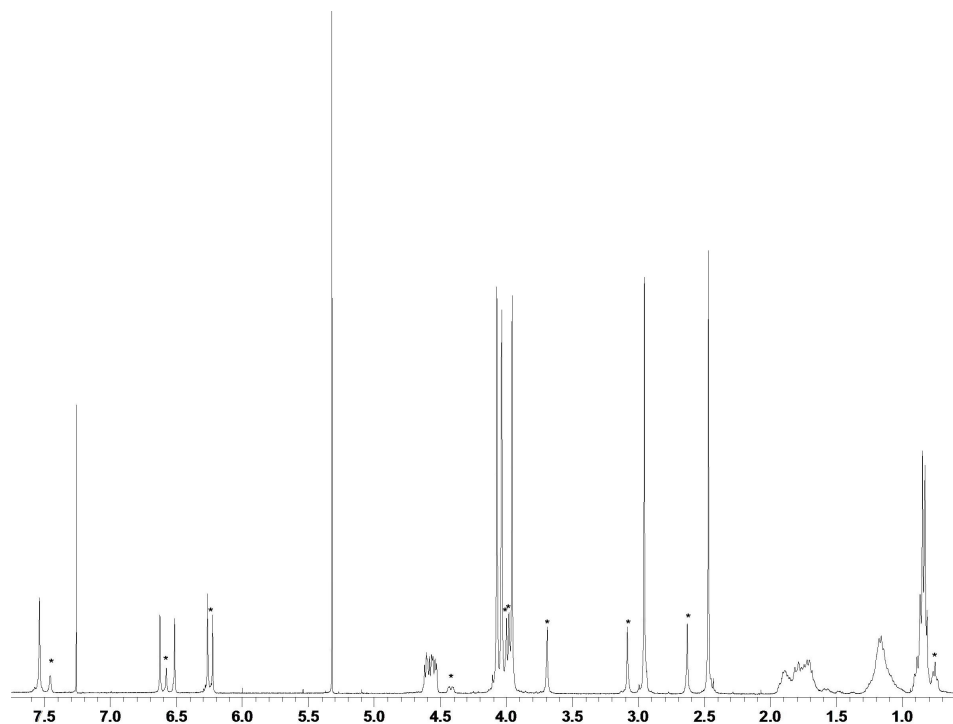
Figure 5.6. ^{1}H NMR spectrum of the coordination compound at -50 °C. (*) indicates the minor product.

Mass spectroscopy of the compound only returned the molecular ion peak for the parent ligand **16** and IR could not shine any further light on the composition of the complex. The original crystals were however large enough to perform X-ray diffraction studies.

5.2.3 Crystal Structure of Complex

The crystal structure (see Figure 5.7) of the complex did not show the distal coordination of one metal centre, but the thioether moieties bonded distally with two Pd centres via a chloride bridge (μ-Cl)$_2$, to form a 16e$^-$ Pd$_2$Cl$_2$(μ-Cl)$_2$ unit. This was in accordance with what Puddephatt found with the coordination of Pd salts in his work on thiophosphinato-based resorcinarenes.[11] This also explained the low yields of

the reaction and subsequent reactions with two equivalents of the palladium salt returned an increase in the yield of the reaction to 70%.
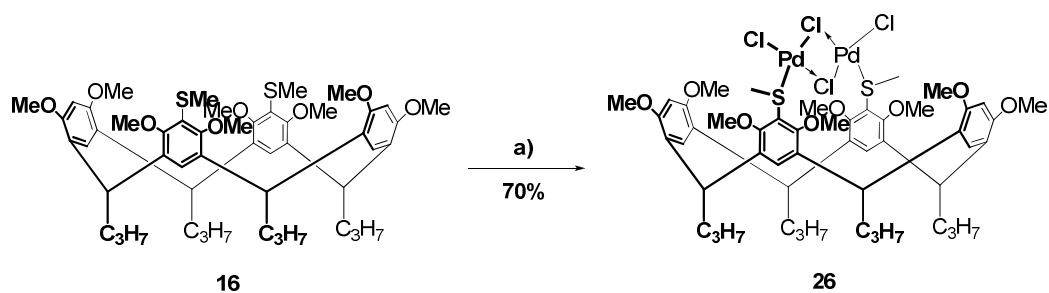
Scheme 5.2. Synthesis of resorcinarene **26**: Reagents and reaction conditions: a) PdCl$_2$ (2 equiv.), DCM, rt
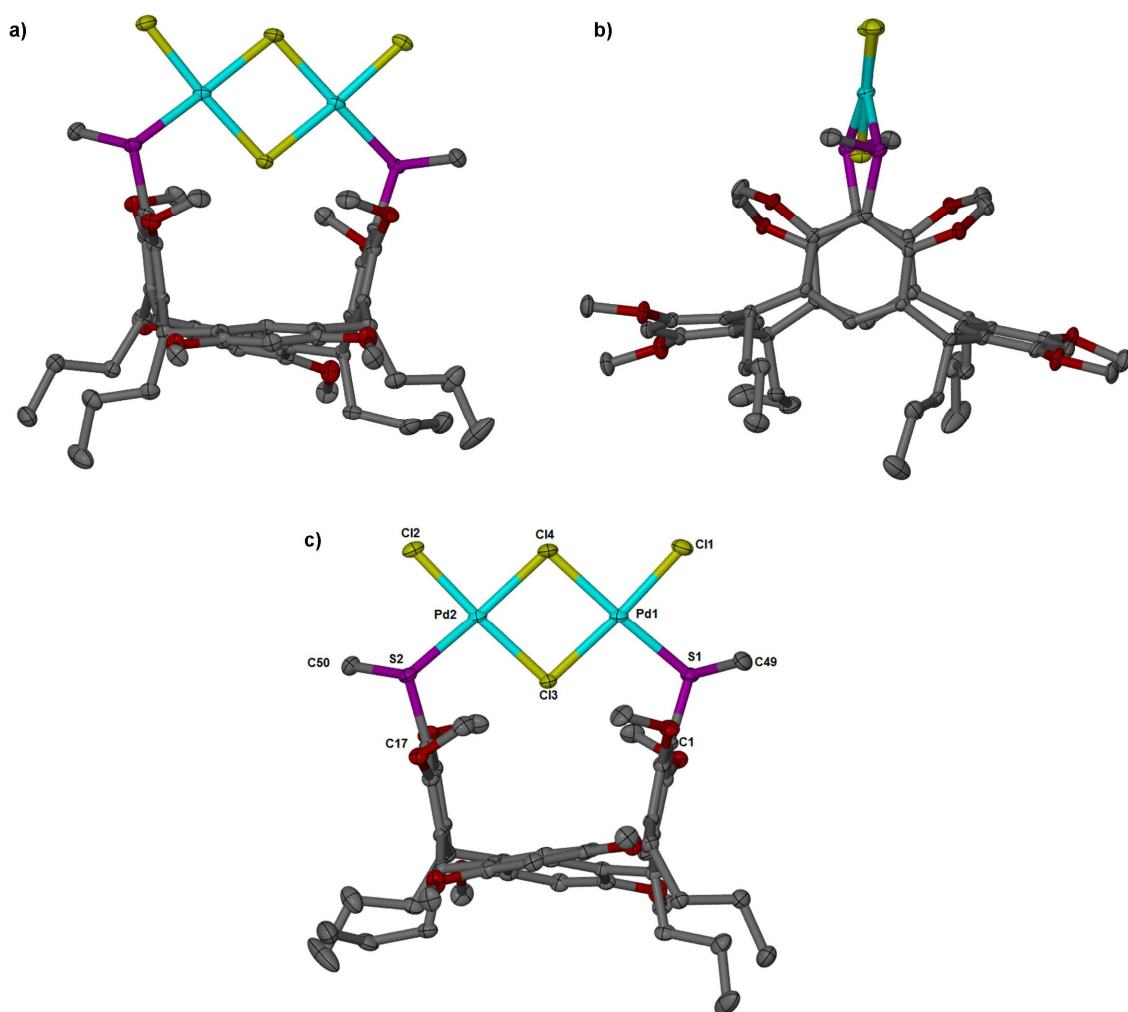
Figure 5.7. Views of the single X-ray crystal structure of resorcinarene **26**. All hydrogens and solvents of crystallisation (dichloromethane) were removed for clarity. Colours: grey = carbon, purple = sulfur, red = oxygen, yellow = chlorine and light blue = palladium. In c) only

selected numbering is shown for the molecule. All atoms are shown as thermal ellipsoids (50% probability).

Table 5.1.   Selected bond lengths (Å) and angles (°) for resorcinarene **26**. Numbering can be seen in Figure 5.7 (c).

Pd1-S1	2.2711(8)	Pd2-S2	2.2653(8)
Pd1-Cl1	2.2718(8)	Pd2-Cl2	2.2725(7)
Pd1-Cl3	2.3494(7)	Pd2-Cl3	2.3446(7)
Pd1-Cl4	2.3418(8)	Pd2-Cl4	2.3363(8)
S1-Pd1-Cl1	86.68(3)	S2-Pd2-Cl2	87.97(3)
S1-Pd1-Cl4	169.33(3)	S2-Pd2-Cl4	171.30(3)
Cl1-Pd1-Cl4	90.38(3)	Cl2-Pd2-Cl4	90.74(3)
S1-Pd1-Cl3	97.38(3)	S2-Pd2-Cl3	96.00(3)
Cl1-Pd1-Cl3	175.89(3)	Cl2-Pd2-Cl3	175.22(3)
Cl4-Pd1-Cl3	85.51(3)	Cl4-Pd2-Cl3	85.74(3)

Interestingly the crystal structure revealed that the molecule crystallised in the more symmetrical conformation, which was shown as the minor product in the low temperature ^{1}H NMR experiments (see Figure 5.4). This could possibly be due to the symmetrical product being more crystalline, thus as it starts to crystallise out it forces the molecules around it into a similar conformation. The crystal structure also indicated the inclusion of 1.5 parts of dichloromethane in the structure and according to existing knowledge this is the first reported case of a distally coordinated metal complex of resorcinarenes with functionality on the *ortho* position of the resorcinarene ring.

The molecular structure of **26** adopted a slightly distorted boat conformation with the two non-bonding rings lying equatorial and the two bonding rings sitting in an axial orientation, validating the information

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gained from the ^{1}H NMR spectrum. Both of the palladium centres display a somewhat distorted square planar geometry, with the angles around Pd1 [85.51(3) - 97.38(3)°] and Pd2 [85.74(3) - 96.00(3)°] differing very slightly, as seen from the bond angles in Table 5.1. The bond angles for S1-Pd1-Cl4 and S2-Pd2-Cl4 [169.33(3) and 171.30(3)°] as well as those of Cl1-Pd1-Cl3 and Cl2-Pd2-Cl3 [175.89(3) and 175.22(3)°] are also below 180°, further indicating the distortion. This distortion is not only around the metal centres but can also be seen in the whole of the molecular structure as seen in Figure 5.7 (b). This distortion of $Pd_2Cl_2(\mu\text{-}Cl)_2L_2$ complexes is also mentioned by other authors.[11, 12] It is also clear that the lengths of the Pd-Cl bonds of the terminal chlorines (Pd1-Cl1 [2.2718(8) Å] and Pd2-Cl2 [2.2725(7) Å]) are shorter than those for the bridging chlorines (Pd1-Cl3 [2.3494(7) Å] and Pd2-Cl3 [2.3446(7) Å]). Pd1-S1 [2.2711(8) Å] and Pd2-S2 [2.2653(8) Å] have nearly identical bond lengths which are shorter than those of Pd1-Cl4 [2.3418(8) Å] and Pd2-Cl4 [2.3363(8) Å], thus clearly indicating the greater *trans* influence of the thioether than the chlrorine ligands.

5.3 Catalysis

With resorcinarene palladium complex **26** in hand it was decided to test if this compound would exhibit some form of catalytic activity using the Mizoroki-Heck reaction (also known as the Heck reaction).[13, 14] Sulfur and thioether ligands have previously been used with good success in these reactions and especially when used in asymmetric C-C coupling reactions.[4-7, 15-17] To study the catalysis reaction it was decided to use bromobenzene and styrene as the arylhalide and vinylic reagents (Table 5.2). The products, *geminal-* and *trans*-stilbene, can be identified and quantified using ^{1}H NMR spectroscopy, since there is a difference in the chemical shifts of the alkene protons (7.14 ppm *trans* and 5.49 ppm *geminal*).

To dry degassed *N,N*-dimethylformamide (5 ml) was added bromobenzene (2.5 mmol), styrene (2 mmol), base (4 mmol) and the catalyst precursor **26**. The reaction mixture was warmed to a 120 °C and the reaction followed by tlc, withdrawing 20 μl aliquots with a syringe, and using a standard for the *trans*-stilbene as guide to product formation. The reaction was stopped after a set time, filtered through Celite. The filtrate was extracted into dichloromethane from an aqueous solution. After the solvent was removed the crude product was loaded on a column and separated using flash column chromatography. The products could be carefully dried under vacuum and were analysed using ^{1}H NMR spectroscopy in CDCl$_3$.

Table 5.2.   Results from the testing of resorcinarene **26** in Heck catalysis. Reagents and Conditions: a) bromobenzene (2 mmol), styrene (2.5 mmol), base (4 mmol), **26**[a], DMF, 120 °C.
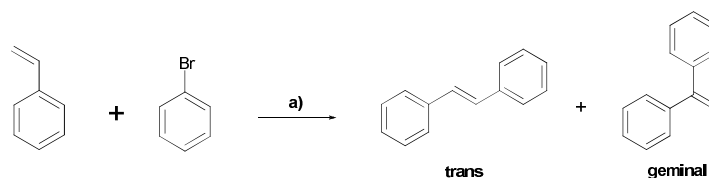
Run	Base	Pd (mmol)	Time (h)	Yield (%)[b]
1	Et$_3$N	0.02	4	0
2	Et$_3$N	0.02	72	5
3	Et$_3$N	0.05	6	7
4	NaOAc	0.05	6	8
5	Et$_3$N	0.05	30	6

[a] Ligand half of Pd (mmol) [b] Total yield of products after column chromatography

When **26** was added to the mixture it turned a light brown colour and as the reaction progressed the colour darkened to a deep mahogany. As the reaction was followed on tlc the significant formation of Pd black could be observed, thus indicating that there was considerable metal leaching in the reaction. This could possibly be due to the effective monodentate thioether ligands not being able to stabilise the Pd(0) that was formed during the reaction mechanism. In reports by other authors it was mentioned that they have encountered the problem with metal leaching in their use of thioether ligands, but not to the effect that was experienced in this study.[18, 19]

From the data in Table 5.2 it was clear that resorcinarene **26** was not an effective catalyst, with the best result being that of run 4 where sodium acetate was used as base. What was interesting was the relatively constant yield that was achieved for runs 3-5. This constitutes a turn over number of about three mol product.mol cat[-1] which is rather dismal. From the limited amount of product recovered it was also observed by ^{1}H NMR spectroscopy that the major product was *trans*-stilbene and only a trace amount of *gem*-stilbene could be seen in the ^{1}H NMR spectra of run 4.

Although our reaction was very selective in the formation of *trans*-stilbene at low catalyst loading it was decided to leave the reaction as such and not to continue with testing of the compound's catalytic

capabilities. Higher catalyst loadings would mean higher yields, but it was felt that this model would tend towards becoming a stoichiometric reaction and not catalytic as was desired.

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<div align="center">C h a p t e r   6</div>

<div align="center"># Conclusions and Future Work</div>

6.1 Conclusions

In conclusion, the successful synthesis of a small range of distally functionalised resorcinarenes was achieved using a variety of methods, starting from a selectively synthesised di-bromo precursor using the methodology of Shivanyuk. The preferred synthetic route, using a lithium halogen exchange, proved to be troublesome. This was attributed to the formation of protonated by-products and the difficulty in purifying the products.

In an effort to investigate the effect of other protecting groups on the exchange reaction on the resorcinarene, an anionic *ortho*-Fries rearrangement occurred with the Boc protecting group. Elaboration of the resorcinarene skeleton was attempted using this rearrangement, but with little success. Using a di-nitrile resorcinarene (via the Rosenmund-von Braun cyanation of the di-bromo resorcinarene) to synthesise di-amine and aldehyde resorcinarenes also met with no success.

For the study of the coordination of the distal resorcinarenes with transition metals di-thioether resorcinarene was used as a model. Attempts to coordinate Ni(II) and Pt(II) metal failed, but a tentative product was formed with Ag(I). Using a Pd(II) precursor we were able to synthesise the first reported case of a distally coordinated metal complex of resorcinarenes with functionality on the ortho position of the resorcinarene ring. This di-nuclear, chlorine bridged resorcinarene was tested for catalytic activity using a Heck reaction. Low yields were returned for the coupling of styrene with bromobenzene, but the product of the reaction was almost exclusively that of the *trans*-stilbene. Thus we could show that these types of resorcinarene coordination compounds show some catalytic capabilities and should be further studied in an effort to build on the current knowledge.

6.2 Future work

Therefore, this project has opened up a wide area of different possible research areas into the synthesis of selectively functionalised resorcinarenes and their uses, of which a few of these will be mentioned in closing.

6.2.1 Pincer ligands[1]

Preliminary studies were also performed on the synthesis of pincer-type ligands using resorcinarenes (Figure 6.1). Using resorcinarene **3** it was envisaged to form two metal centre reactive sites distal to each other. This should allow these molecules to act as stable platforms for catalytic reactions. It was found

that the molecule could be phosphorylated on the phenol groups, but the introduction of the Pd(0) precursor could not be achieved. This was possibly due to the steric crowding in the molecule. When the reaction was performed the other way around no products were formed as well. Further studies need to be performed, starting from a simple resorcinarene and then moving to more complicated systems, since this could lead to the formation of a reaction platform with four possible reactive sites for catalysis (Figure 6.1).
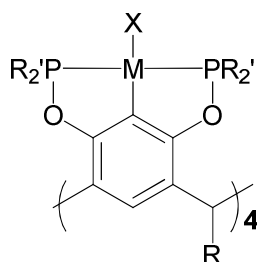
Figure 6.1. A pincer type resorcinarene ligand with four reactive sites (M=transition metal, R= R'=alkyl/aryl, X= Halide/other leaving group).

6.2.2 Ortholithiation

As mentioned in chapter 3 the use of DoM chemistry in selective synthesis of C_{2v}-symmetrical resorcinarenes is also an active research area in our group (Scheme 6.1). The main advantage of this method is the relative ease of synthesising the precursor, the octamethoxy resorcinarene, thereby improving the total atom cost of the reaction as a whole. Initial studies have shown that the selectivity of the distal to the proximal product can be adjusted using different alkyllithiums and reaction temperatures, with a maximum of 5:1 for distal to proximal. The drawback of this reaction is the formation of a wide range of products that needs to be separated with chromatographic methods.
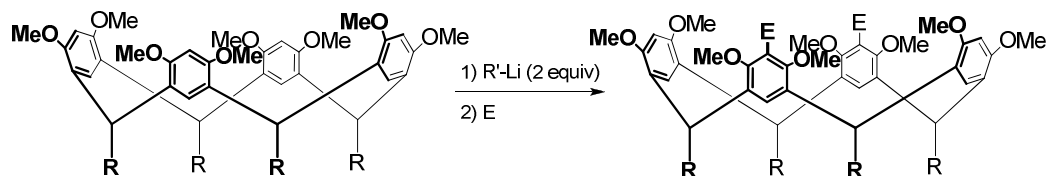
Scheme 6.1. The use of DoM chemistry to selectively introduce functionality on the resorcinarene

6.2.3 Sulfoxide ligands

The use of sulfoxide ligands in transition metal chemistry is well documented.[2] In an attempt to synthesise sulfoxide ligands on resorcinarenes, the thioether resorcinarene were reacted with two equivalents of *m*-CPBA. The reaction returned two products, a di-sulfoxide and a mono-sulfoxide resorcinarene as a minor product. Initial studies point to a form of chirality transfer through the molecule in the oxidation process, due to the fact that the di-sulfoxide was obtained as only one diastereomer.

Studies into the mechanism behind the formation of this, and the possible use of the molecule as a ligand for asymmetric catalysis will be attempted in the future.

6.3 References

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Experimental

7.1 General Procedures

All chemicals used were bought from Merck or Aldrich. Tetrahydrofuran, pentane, diethylether and toluene were dried over sodium wire/sand and distilled under nitrogen with benzophenone as an indicator. Dichloromethane and acetonitrile were distilled over calcium hydride under nitrogen. Other reagents were purified according to standard procedures.[1, 2] The molarity of *n*BuLi was determined using a method as described in the literature.[3]

All reactions were performed under anhydrous conditions and nitrogen or argon atmosphere, unless stated otherwise. Low temperature reactions were performed in a Dewar using dry ice in acetone (−78 °C), ice in water (0 °C) or a slurry of ethanol, sodium chloride and ice (−20 °C). Microwave reactions performed in a Biotage Initiator microwave reactor.

All ^{1}H, ^{13}C and ^{31}P nuclear magnetic resonance spectra were obtained using a 300 MHz Varian VNMRS (75 MHz for ^{13}C), a 400 MHz Varian Unity Inova (100 MHz for ^{13}C) or a 600 MHz Varian Unity Inova (150 MHz for ^{13}C). Chloroform-*d* and was used as standard solvent, unless otherwise stated. Chemical shifts (δ) were recorded using the residual chloroform peaks (δ 7.26 in ^{1}H NMR and δ 77.0 in ^{13}C NMR) or the residual DMSO peaks (δ 2.50 in ^{1}H NMR and δ 39.5 in ^{13}C NMR) in DMSO-d_6, as reference. ^{31}P NMR was referenced to neat H_3PO_4 (δ 0 ppm). All chemical shifts are reported in ppm and all resorcinarene spectra were obtained at 25 °C, unless otherwise stated.

All chromatography was performed using either (or a combination of) petrol ether, ethyl acetate, methanol and dichloromethane. Thin layer chromatography (tlc) was carried out on aluminium backed Merck silica gel 60 F_{254} plates. Visualization was achieved with UV lamp, iodine vapour or by spraying with a Cerium Ammonium Molybdate solution (CAM) and then heating. Preparative layer chromatography (PLC) was performed on Precoated PLC Merck silica gel F_{254} plates. All column chromatography was carried out with Merck silica gel 60 (particle size 0.040-0.063 mm).

Melting points were obtained using a Gallenkamp Melting Point Apparatus and are uncorrected. Infrared spectra were obtained using a Nexus Thermo-Nicolet FT-IR instrument using thin film solutions of chloroform or dichloromethane on NaCl plates, or using the ATR. High resolution mass spectrometry was performed by the CAF (Central Analytical Facility) Institute at Stellenbosch University using a Waters API Q-TOF Ultima spectrometer. Routine mass spectronomy was performed using a Waters API Quattro Micro spectrometer. In both cases ESI+ was used as ionisation method.

7.2 Compounds

$1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6$-Octahydroxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane (1)[4]
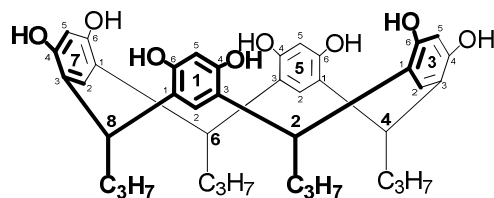
Resorcinol (8.26 g, 75 mmol) was dissolved in dry dichloromethane (250 ml). The solution was cooled to 0 °C and butanal (6.76 ml, 75 mmol) was added. Boron trifluoride diethyl ether complex (19.4 ml, 153 mmol) was added slowly over a period of 30 minutes, via a syringe pump, to the solution and the reaction was allowed to warm to room temperature, and left stirring for 26 hours. The solution formed a red colour, with a light pink precipitate. The resulting precipitate was filtered off and washed with dichloromethane to yield a light pink product. The precipitate was dried on high vacuum for 12 hours to leave the tetrapropyl resorcinarene **1** (8.97 g, 73%).

Mp >350 °C(dec) (Water/Ethanol), (Lit.[4] m.p. >360 °C); ^{1}H NMR (DMSO–D$_6$, 400 MHz, 25 °C): δ = 0.89 (t, J = 7.3 Hz, 12H, –(CH$_2$)$_2$CH_3), 1.19 (sxt, J = 7.3 Hz, 8H, –CH$_2$CH_2CH$_3$), 2.08 (m, 8H, –CH_2CH$_2$CH$_3$), 4.22 (t, J = 7.9 Hz, 4H, H–2,4,6,8), 6.14 (s, 4H, H–$1^2,3^2,5^2,7^2$), 7.24 (s, 4H, H–$1^5,3^5,5^5,7^5$), 8.92 (s, 8H, Ar–OH).

$3^4,3^6,7^4,7^6$-Tetra(benzyloxycarbonyloxy)-$1^4,1^6,5^4,5^6$-tetrahydroxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane (2)
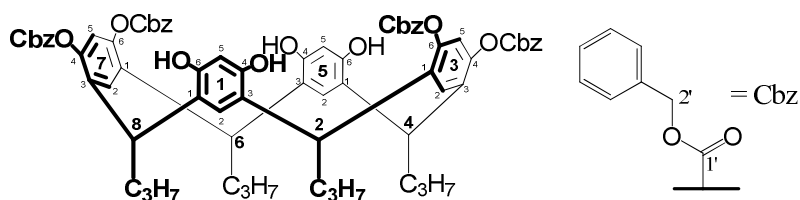
Resorcinarene **1** (1.98 g, 3 mmol) was dissolved in dry acetonitrile (30 ml) at room temperature and to this mixture was added triethylamine (1.68 ml, 12 mmol) and the resulting pink suspension was stirred for 20 minutes after which benzyl chloroformate (1.70 ml, 12 mmol) was added. The solution turned light red/orange within 5 minutes and the reaction was left stirring for 48 hours at room temperature. The resulting light pink precipitate was collected via filtration and washed with cold portions of acetonitrile. The precipitate was taken up in 1M HCl (25 ml) and extracted with dichloromethane (4×30 ml), the organic phases combined and dried over anhydrous magnesium sulfate. The drying agent was filtered off

and the solvent removed under reduced pressure to leave a fine white solid, the tetraCBz resorcinarene **2** (0.94 g, 27%).

Mp 170 °C (dichloromethane/petroleum ether); R_f = 0.13 (ethyl acetate/petroleum ether, 2:3); IR (film): 3426, 2956, 2871, 1759, 1620, 1493, 1267, 1224, 911, 736 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz, 25 °C): δ = 0.89 (t, J = 7.3 Hz, 12H, –(CH$_2$)$_2$CH_3), 1.13–1.22 (m, 4H, –CH$_2$CH_2CH$_3$), 1.29–1.40 (m, 4H, –CH$_2$CH_2CH$_3$), 1.74–1.83 (m, 4H, –CH_2CH$_2$CH$_3$), 1.92–2.00 (m, 4H, –CH_2CH$_2$CH$_3$), 4.33 (br t, J = 7.3 Hz, 4H, H–2,4,6,8), 5.21–5.27 (m, 8H, H–2'), 5.94 (s, 2H, H–1^5,5^5), 6.67 (br s, 2H, H–3^5,7^5), 6.71 (s, 4H, Ar–OH), 6.92 (s, 2H, H–1^2,5^2), 7.12 (s, 2H, H–3^2,5^2), 7.3–7.36 (m, 20H, Ph); ^{13}C NMR (CDCl$_3$, 100 MHz, 25 °C): δ = 14.1 (–(CH$_2$)$_2$CH$_3$), 20.9 (–CH$_2$CH$_2$CH$_3$), 35.0 (C–2,4,6,8), 37.4 (–CH$_2$CH$_2$CH$_3$), 70.9 (C–2'), 102.9 (C–1^5,5^5), 115.1 (C–1^2,5^2), 118.6 (C–3^2,7^2), 124.1 (C–3^1,3^3,7^1,7^3), 127.9 (C-3^5,7^5), 128.6 (Ph), 134.5 (Ph), 136.2 (C–1^1,1^3,5^1,5^3), 146.0 (C–3^4,3^6,7^4,7^6), 153.6 (C–1'), 153.9 (C–1^4,1^6,5^4,5^6); MS (ESI+): m/z (%) = 1211 (100) [M+H$_2$O]$^+$, 1193 (22) [M]$^+$; HRMS–ESI+: m/z [M+H]$^+$ calcd for C$_{72}$H$_{73}$O$_{16}$: 1193.4899; found: 1193.4918.

3^4,3^6,7^4,7^6-Tetra(benzyloxycarbonyloxy)-1^5,5^5-dibromo-1^4,1^6,5^4,5^6-tetrahydroxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane (3)
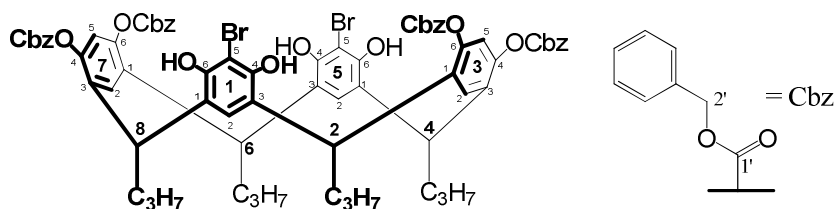
Resorcinarene **2** (2.04 g, 1.7 mmol) was dissolved in dry dichloromethane (85.5 ml) and cooled to −78 °C. To this solution was added, via a dropping funnel, a solution of 1M bromine in acetic acid (6 ml, 6 mmol). The reaction was stirred for 30 minutes after which another equivalent of the 1M bromine in acetic acid (1.7 ml, 1.7 mmol) was added and the reaction was stirred for another 30 minutes until completion (monitored with tlc). The reaction mixture was quenched with a 10% sodium thiosulfate (w/v, 60 ml) solution and warmed to room temperature. The reaction mixture was neutralized with a 10% sodium carbonate (w/v, 100 ml) solution, carried over to a separatory funnel and the organic phase separated. The water layer was extracted with dichloromethane (3×60 ml), the organic phases combined and dried over anhydrous magnesium sulfate. The drying agent was filtered off and the solvent removed under reduced pressure to leave yellow-orange foam (2.31 g, >100%). The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: petroleum ether 3:17 followed by ethyl acetate: petroleum ether 1:4). The resulting product was recrystallized in petroleum ether/dichloromethane to yield fine pale white crystals of dibromo-tetraCBz-resorcinarene **3** (1.85 g, 80%).

Mp 220 °C (dichloromethane/petroleum ether); R_f = 0.56 (ethyl acetate/petroleum ether, 2:3); IR (ATR): 3508, 3454, 2956, 2871, 1765, 1744, 1610, 1214, 971, 696 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz, 25 °C): δ = 0.88 (t, J = 7.3 Hz, 12H, –(CH$_2$)$_2$CH_3), 1.14–1.24 (m, 4H, –CH$_2$CH_2CH$_3$), 1.28–1.37 (m, 4H, –CH$_2$CH_2CH$_3$), 1.71–1.80 (m, 4H, –CH_2CH$_2$CH$_3$), 1.88–1.97 (m, 4H, –CH_2CH$_2$CH$_3$), 4.33 (t, J = 7.6 Hz, 4H, H–2,4,6,8), 5.22 (s, 4H, Ar–OH), 5.30 (m, 8H, H–2'), 6.53 (s, 2H, H–3^5,7^5), 7.08 (s, 2H, H–1^2,5^2), 7.11 (s, 2H, H–3^2,7^2), 7.34–7.47 (m, 20H, Ph); ^{13}C NMR (CDCl$_3$, 100 MHz, 25 °C): δ = 13.9 (–(CH$_2$)$_2$CH_3), 20.7 (–CH$_2$CH_2CH$_3$), 35.8 (C–2,4,6,8), 37.4 (–CH_2CH$_2$CH$_3$), 70.5 (C–2'), 100.6 (C–1^5,5^5), 115.4 (C–3^5,7^5), 120.2 (C–3^1,3^3,7^1,7^3), 123.6 (C–1^2,5^2), 126.8 (C–3^2,7^2), 128.6 (Ph), 128.7 (Ph), 128.8 (Ph), 134.8 (Ph), 135.5 (C–1^1,1^3,5^1,5^3), 146.4 (C–3^4,3^6,7^4,7^6), 149.2 (C–1^4,1^6,5^4,5^6), 153.8 (C–1'); MS (ESI+): m/z (%) = 1368.33 (100) [M+NH$_4$]$^+$; HRMS–ESI+: m/z [M+NH$_4$]$^+$ calcd for C$_{72}$H$_{74}$O$_{16}$NBr$_2$: 1366.3374; found: 1366.3375.

1^5,5^5-Dibromo-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 (4)
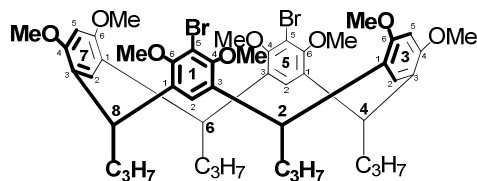
To a mixture of Resorcinarene **3** (1.80 g, 1.3 mmol) in ethanol/THF (1:1 v/v, 75 ml) was added Pd/C (10%, 0.138 g, 0.13 mmnol) and a hydrogen-filled balloon connected. The mixture was stirred at room temperature in a waterbath for 24 hours after which another equivalent of Pd/C (10%, 0.138 g, 0.13 mmnol) was added and stirred until completion as monitored by tlc (24 hours). The mixture was filtered over a Celite plug and washed with ethanol and THF. The solvent was removed under reduced pressure to leave a solid (1.22 g, >100%).

The solid and potassium carbonate (3.31 g, 24 mmol) were suspended in dry acetonitrile (40 ml) and dimethyl sulfate (2.29 ml, 24 mmol) was added. The solution was heated to reflux for 42 hours. The reaction was stopped and cooled to room temperature. The solvent was removed under reduced pressure and the resulting solid added to H$_2$O (50 ml) and extracted with dichloromethane (3×50 ml). The organic layers were combined and dried over anhydrous magnesium sulfate. The drying agent was filtered off and the solvent removed under reduced pressure to leave an orange solid. The product was purified using flash column chromatography (silica gel eluting with dichloromethane followed by dichloromethane: methanol 99:1). The resulting product was recrystallized in boiling ethanol to yield white crystals (0.94 g, 75% over 2 steps).

Mp 209–210 °C (ethanol/dichloromethane); R_f = 0.62 (ethyl acetate/petroleum ether, 2:3); IR (ATR): 2933, 2871, 1613, 1582, 1237, 1081, 1037 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz, 25 °C): δ = 0.93 (t, J = 7.3 Hz, 12H, –(CH$_2$)$_2$CH_3), 1.34 (m, 8H, –CH$_2$CH_2CH$_3$), 1.82 (m, 8H, –CH_2CH$_2$CH$_3$), 3.60 (s, 12H, Ar–OCH_3), 3.68 (s, 12H, Ar–OCH_3), 4.51 (t, J = 7.4 Hz, 4H, H–2,4,6,8), 6.30 (s, 2H, H–3^5,7^5), 6.55 (s, 2H, H–1^2,5^2), 6.75 (s, 2H, H–3^2,7^2); ^{13}C NMR (CDCl$_3$, 100 MHz, 25 °C): δ = 14.2 (–(CH$_2$)$_2$CH$_3$), 21.2 (–CH$_2$CH$_2$CH$_3$), 36.5 (C–2,4,6,8), 37.5 (–CH$_2$CH$_2$CH$_3$), 55.6 (Ar–OCH$_3$), 60.3 (Ar–OCH$_3$), 96.3 (C–3^5,7^5), 112.5 (C–1^5,5^5), 124.7 (C–3^1,3^3,7^1,7^3), 125.0 (C–1^2,5^2), 126.4 (C–3^2,7^2), 136.1 (C–1^1,1^3,5^1,5^3), 153.6 (C–1^4,1^6,5^4,5^6), 156.1 (C–3^4,3^6,7^4,7^6); MS (ESI+): m/z (%) = 944.3 (100) [M+NH$_4$]$^+$; HRMS–ESI+: m/z [M+NH$_4$]$^+$ calcd for C$_{48}$H$_{66}$O$_{16}$NBr$_2$: 942.3155; found: 942.3160.

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 (5)
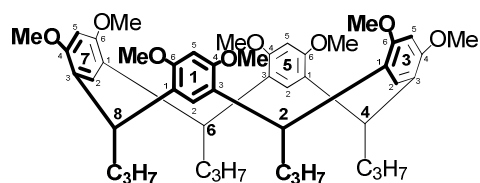
By-product formed during resorcinarene reactions.

Mp 272–274 °C (dichloromethane); R_f = 0.55 (ethyl acetate/petroleum ether, 1:1); IR (ATR): 2950, 2867, 1608, 1508, 1292, 1038, 814 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz, 25 °C): δ = 0.92 (t, J = 7.3 Hz, 12H, –(CH$_2$)$_2$CH_3), 1.26–1.38 (m, 8H, –CH$_2$CH_2CH$_3$), 1.77–1.84 (m, 8H, –CH_2CH$_2$CH$_3$), 3.60 (s, 24H, Ar–OCH_3), 4.48 (t, J = 7.5 Hz, 4H, H–2,4,6,8), 6.32 (s, 4H, H–1^5,3^5,5^5,7^5), 6.63 (s, 4H, H–1^2,3^2,5^2,7^2); ^{13}C NMR (CDCl$_3$, 75.5 MHz, 25 °C): δ = 14.3 (–(CH$_2$)$_2$CH$_3$), 21.2 (–CH$_2$CH$_2$CH$_3$), 35.1 (C–2,4,6,8), 37.1 (–CH$_2$CH$_2$CH$_3$), 56.2 (Ar–OCH$_3$), 97.1 (C–1^5,3^5,5^5,7^5), 126.1 (C–1^1,1^3,3^1,3^3,5^1,5^3,7^1,7^3), 126.3 (C–1^2,3^2,5^2,7^2), 155.8 (C-1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6); MS (ESI+): m/z (%) = 786.49 (100) [M+NH$_4$]$^+$, 769.47 (20) [M]$^+$; HRMS–ESI+: m/z [M+H]$^+$ calcd for C$_{48}$H$_{65}$O$_8$: 769.4679; found: 769.4681.

2-Bromo-1,3-Dimethoxybenzene (6)
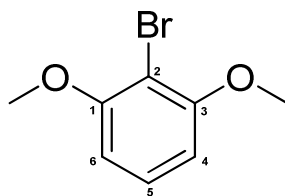
6 was synthesised from two different starting materials. Method 1 was performed according to a literature procedure.[6]

Method 1: To dry diethylether (40 ml) was added TMEDA (0.05 ml, 0.30 mmol) and the mixture was cooled to 0 °C. *n*BuLi (20.5 ml of a 1.47M solution in hexane, 30 mmol) was added dropwise to the solution over a 10 minute period. The solution was stirred for an additional 10 minutes, after which 1,3-dimethoxybenzene **7** (4.0 ml, 30 mmol) was added slowly and stirred for 1,5 hours at 0 °C. 1.2-Dibromoethane (10.4 ml, 120 mmol) was added dropwise over a period of three hours and the reaction was warmed to room temperature and stirred overnight (20 hours). To the reaction mixture was added H_2O (40 ml) and conc. H_2SO_4 (0.1 ml) and the organic phase separated. The organic layer was washed with H_2O (2×20 ml), dried over anhydrous magnesium sulfate. The drying agent was filtered off and the solvent removed under reduced pressure to leave an orange solid. The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: petroleum ether 1:19). The resulting product was dissolved in boiling ethanol and placed in a refrigerator at −20 °C. White crystals of **7** precipitated out of solution. The crystals was collected by filtration, washed with cold ethanol and dried to yield **6** (847 mg, 13%).

Method 2: 2-Bromo-1,3-dihydroxybenzene **9** (2.66 g, 14 mmol) and potassium carbonate (7.74g, 56 mmol) were suspended in dry acetonitrile (100 ml) and dimethyl sulfate (5.35 ml, 56 mmol) added. The solution was heated to reflux for 2.5 hours. The reaction was stopped and cooled to room temperature. The solvent was removed under reduced pressure and the resulting light green solid added to H_2O (120 ml) and extracted with dichloromethane (4×75 ml). The organic layers were combined and dried over anhydrous magnesium sulfate. The drying agent was filtered off and the solvent removed under reduced pressure to leave a light yellow solid. The product was purified using flash column chromatography (silica gel eluting with petroleum ether followed by petroleum ether:ethyl acetate 9:1) leaving a white solid (2.82 g, 92%). The resulting product was recrystallized in boiling ethanol and placed in a refrigerator at −20 °C. White crystals of **6** precipitated out of solution. The crystals were collected by filtration, washed with cold ethanol and dried to yield **7** (2.54 g, 83%). Characterisation in both methods corresponded to literature values.[6]

Mp 92 °C (Ethanol), (Lit.[6] m.p. 91 °C); ^{1}H NMR (CDCl$_3$, 300 MHz, 25 °C): δ = 3.91 (s, 6H, –OCH_3), 6.59 (d, J = 8.4 Hz, 2H, H–4,6), 7.24 (t, J = 8.4 Hz, 1H, H–5).

1,3-Dimethoxybenzene (7)[5]
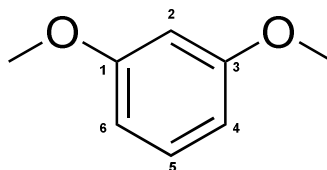
To a dark-brown suspension of resorcinol (5.50 g, 50 mmol) and potassium carbonate (27.6 g, 200 mmol) in dry acetonotrile (200 ml) was added dimethyl sulfate (19 ml, 200 mmol). The solution was warmed to

reflux and monitored with tlc till completion (2 hours). The solvent was removed under reduced pressure and the resulting orange oil was added to H_2O (100 ml), 1M HCl (40 ml) and extracted with dichloromethane (5×50 ml). The organic layers were combined and dried over anhydrous magnesium sulfate. The drying agent was filtered off and the solvent removed under reduced pressure to leave an orange oil. Vacuum distillation (88-92 °C/20 mmHg) afforded a colourless oil. ^{1}H NMR spectroscopy revealed dimethyl sulfate still present in the product. Final purification was achieved by flash column chromatography (silica gel eluting with ethyl acetate: petroleum ether 1:9) followed by vacuum distillation to afford **6** as a colourless oil (5.18 g, 75%). ^{1}H NMR spectroscopy conformed to literature values.

^{1}H NMR (CDCl$_3$, 400 MHz, 25 °C): δ = 3.80 (s, 6H, –OCH_3), 6.47 (t, J = 2.4 Hz, 1H, H–2), 6.51 (dd, J = 8.2, 2.3 Hz, 2H, H–4,6), 7.20 (t, J = 8.2 Hz, 1H, H–5).

1,3,5-Tribromo-2,4-dihydroxybenzene (8)[6, 7]
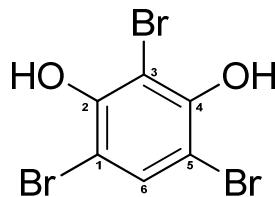
8 was synthesised from an adapted literature procedure.[6] Resorcinol (3.30 g, 30 mmol) was suspended in chloroform (50 ml) and cooled to 0 °C. A solution of bromine (4.6 ml, 90 mmol) in chloroform (8 ml) was added via dropping funnel to the solution over 25 minutes, after which it was left stirring at 0 °C for 15 minutes. The dark orange reaction was warmed to reflux until no hydrogen bromide developed. The reaction mixture was cooled to room temperature. Activated charcoal (1.00 g) was added and the reaction stirred for 30 minutes after which it was filtered off over a plug of Celite. The solution was added to 10% sodium thiosulfate (w/v, 50 ml) solution in a separatory funnel and the organic phase extracted. The aqueous phase was further extracted with chloroform (2×50 ml), the organic phases combined and dried over anhydrous magnesium sulfate. The drying agent was filtered off and the solvent removed under reduced pressure to leave a white crystalline solid. The solid was recrystallized in chloroform to yield tribromoresorcinol **8** (9.37 g, 90%).

Mp 109 °C (chloroform), (Lit.[6] m.p. 111 °C); ^{1}H NMR (CDCl$_3$, 300 MHz, 25 °C): δ = 5.93 (s, 2H, Ar–OH), 7.61 (s, 1H, Ar–H).

2-Bromo-1,3-dihydroxybenzene (9)[8, 9]
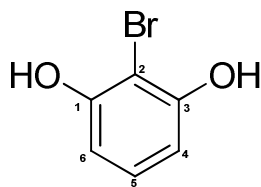
9 was synthesised from an adapted literature procedure.[8, 9] Aqueous methanol (54 ml, 16.7% v/v) was added to tribromoresorcinol (3.77 g, 10.9 mmol) and stirred at room temperature. To the solution a mixture of sodium sulphite (2.74 g, 21.7 mmol) and sodium hydroxide (0.868 g, 21.7 mmol) in distilled H_2O (54 ml) was added dropwise over 20 minutes. The resulting light yellow solution was stirred for 1 hour at room temperature. The solution was acidified with 1M HCl and extracted with diethyl ether (4×50 ml). The organic phases were combined and dried over anhydrous magnesium sulfate. The drying agent was filtered off and the solvent removed under reduced pressure to leave 2-bromo-1,3-dihydroxybenzene **9** as a whitish solid (1.97 g, 95%). The purity of the solid was suitable enough to proceed with the next step without further purification, as judged by ^{1}H NMR.[9]

^{1}H NMR (CDCl$_3$, 300 MHz, 25 °C): δ = 5.36 (s, 2H, Ar–O*H*), 6.61 (d, *J* = 8.2 Hz, 2H, H–4,6), 7.12 (t, *J* = 8.2 Hz, 1H, H–5).

Standard lithiation protocol for model compounds

Dry, freshly distilled tetrahydrofuran (0.1 M) was added to model **7** in a reaction vessel, fitted with a stirrer bar, purged under an anhydrous nitrogen atmosphere. The resulting solution was cooled to −78 °C and stirred for 10 minutes. To this solution *n*BuLi (1.1 equivalents, molarity 0.97-1.5 M solution in hexanes) was added and left stirring for 15 minutes at −78 °C. The solution was quenched with an electrophile at −78 °C and left stirring for 5 minutes after which it was allowed to warm to room temperature. Length of stirring at room temperature, work-up and purification varies for each electrophile.

1,3-Dimethoxy-2-trimethylsilylbenzene (10)
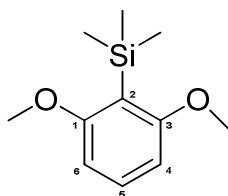
To **7** (184.4 mg, 0.848 mmol) was added tetrahydrofuran (8 ml). After cooling to −78 °C, *n*BuLi (0.61 ml, 0.85 mmol, 1.39 M solution in hexane) was added. After 15 minutes trimethylsilyl chloride (0.16 ml, 1.27

mmol) was added and the reaction warmed to room temperature and stirred overnight (18 hours). The reaction was quenched with a sat. NH_4Cl solution (5 ml), added to H_2O (15 ml) and extracted with dichloromethane (3×15 ml). The organic phases were combined and dried over anhydrous magnesium sulfate. The drying agent was filtered off and the solvent removed under reduced pressure to leave a yellow oil. Purification was achieved using preparative tlc (ethyl acetate: petroleum ether 1:9) to leave the silated **10** as an oil that hardens on standing (23 mg, 19%). ^{1}H NMR spectroscopy data corresponded with literature values.[10]

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 0.28 (s, 9H, –Si(CH_3)$_3$), 3.75 (s, 6H, –OCH_3), 6.50 (d, *J* = 8.2 Hz, 2H, H–4,6), 7.27 (t, *J* = 8.2 Hz, 1H, H–5).

1,3-Dimethoxy-2-methylbenzene (11)
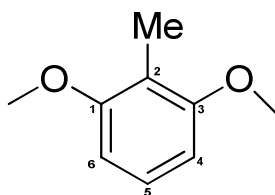
To **7** (133.8 mg, 0.61 mmol) was added tetrahydrofuran (6 ml). After cooling to −78 °C, *n*BuLi (0.68 ml, 0.67 mmol, 0.99 M solution in hexane) was added. After 15 minutes methyliodide (0.13 ml, 2.0 mmol) was added and the reaction warmed to room temperature and stirred for four hours. The reaction was quenched with H_2O (15 ml) and extracted with ethyl acetate (3×15 ml). The organic phases were combined and dried over anhydrous magnesium sulfate. The drying agent was filtered off and the solvent removed under reduced pressure to leave a colourless oil. The yield of the methylated **11** was determined using crude ^{1}H NMR spectroscopy owing to the trouble in purification of the reaction product (40 mg, 42%). Characterisation data corresponded with literature values.[11]

^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 2.16 (s, 3H, Ar–CH_3), 3.86 (s, 6H, –OCH_3), 6.58 (d, *J* = 8.2 Hz, 2H, H–4,6), 7.16 (t, *J* = 8.2 Hz, 1H, H–5).

1,3-Dimethoxy-2-methylthiylbenzene (12)
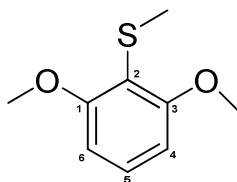
To **7** (170.0 mg, 0.78 mmol) was added tetrahydrofuran (8 ml). After cooling to −78 °C, *n*BuLi (0.87 ml, 0.86 mmol, 0.99 M solution in hexane) was added. After 15 minutes dimethyl disulfide (0.30 ml, 3.4 mmol) was added and the reaction warmed to room temperature and stirred for four hours. The reaction was quenched with H_2O (15 ml) and extracted with ethyl acetate (3×20 ml). The organic phases were combined and dried over anhydrous magnesium sulfate. The drying agent was filtered off and the solvent removed under reduced pressure to leave a white solid. Final purification was achieved by flash column chromatography (silica gel eluting with ethyl acetate: petroleum ether 1:9) to leave a white solid, the thioether **12** (67 mg, 47%). Characterisation data corresponded with literature values.[12]

Mp 78–79 °C (ethanol), (Lit.[12] m.p. 81-82 °C) ; ^{1}H NMR (CDCl$_3$, 400 MHz, 25 °C): δ = 2.37 (s, 3H, −SC*H*$_3$), 3.90 (s, 6H, −OC*H*$_3$), 6.58 (d, *J* = 8.4 Hz, 2H, H−4,6), 7.24 (t, *J* = 8.4 Hz, 1H, H−5).

(1,3-Dimethoxyphenyl)diphenylphosphine oxide (13)
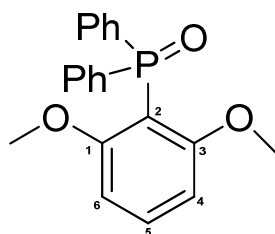
To **7** (99.5 mg, 0.46 mmol) was added tetrahydrofuran (5 ml). After cooling to −78 °C, *n*BuLi (0.51 ml, 0.50 mmol, 0.99 M solution in hexane) was added. After 15 minutes diphenylphosphine chloride (0.28 ml, 1.5 mmol) was added and the reaction warmed to room temperature and stirred overnight (17 hours). The reaction was quenched with 1M HCl (5 ml), H_2O (15 ml) added and extracted with ethyl acetate (3×15 ml). The organic phases were combined and dried over anhydrous magnesium sulfate. The drying agent was filtered off and the solvent removed under reduced pressure to leave a grey oil. Final purification was achieved by flash column chromatography (silica gel eluting with ethyl acetate: petroleum ether 3:7 followed by ethyl acetate: petroleum ether 1:1 followed by ethyl acetate) to leave a white solid, the phosphine oxide **13** (70 mg, 45%). Characterisation data corresponded with literature values.[13]

^{1}H NMR (CDCl$_3$, 400 MHz, 25 °C): δ = 3.31 (s, 6H, −OC*H*$_3$), 6.48 (dd, *J* = 8.4, 4.3 Hz, 2H, H−4,6), 7.33–7.43 (m, 7H, H−5,Ph), 7.66–7.71 (m, 4H, Ph); ^{31}P NMR (CDCl$_3$, 161.5 MHz, 25 °C): δ = 22.7.

Standard lithiation protocol for resorcinarenes

An oven-dried (120 °C) Schlenk flask was cooled under vacuum to room temperature. The flask was backfilled with inert gas (argon or nitrogen) and charged with resorcinarene **4** and dry, freshly distilled

tetrahydrofuran, enough to solvate the precursor. The solvent was removed under vacuum and the residue was heated with an industrial heat-gun for 5-10 minutes while still under vacuum and left to cool to ambient temperature. The flask was then refilled with inert gas and the solvation/de-solvation process was repeated two more times. The dried residue was dissolved in dry tetrahydrofuran (0.02 M) and cooled to −78 °C with vigorous stirring. 2.2 equivalents of freshly titrated nBuLi (molarity 0.97-1.5 M solution in hexanes) were added to the mixture and left to stir for 15 minutes after which an excess of electrophile was added. The reaction was warmed to room temperature and further reaction times and work-up procedures vary according to the electrophile used.

$1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6$-Octamethoxy-$1^5,5^5$-bis(trimethylsiliyl)-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzencyclooctaphane (14)

$1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6$-Octamethoxy-$1^5$-trimethylsiliyl-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane (14a)

14 **14a**
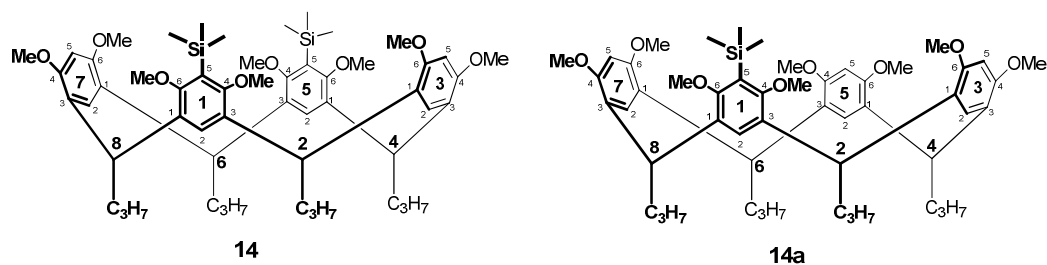
Resorcinarene **4** (119 mg, 0.13 mmol) was dissolved in tetrahydrofuran (6.5 ml). After cooling, nBuLi (0.29 ml, 0.28 mmol, 0.99 M solution in hexane) was added. The reaction was quenched with trimethylchlorosilane (0.18 ml, 1.41 mmol), warmed to room temperature and stirred for four hours. A sat. NH_4Cl solution (5 ml) and H_2O (15 ml) was added and the product extracted into ethyl acetate (3×20 ml). The organic phases were combined and dried over anhydrous magnesium sulfate. The drying agent was filtered off and the solvent removed under reduced pressure to leave a white solid. Final purification was achieved by flash column chromatography (silica gel eluting with ethyl acetate: petroleum ether 1:9) to leave a white solid, the disilyl **14** (18 mg, 15%) Attempts to purify through recrystallization failed due to the molecule disintegrating.

R_f = 0.84 (ethyl acetate/petroleum ether, 2:3); ^{1}H NMR (CDCl$_3$, 400 MHz, 25 °C): δ = 0.26 (s, 18H, –Si(CH_3)$_3$), 0.88 (t, J = 7.3 Hz, 12H, –(CH$_2$)$_2$CH_3), 1.22–1.33 (m, 8H, –CH$_2$CH_2CH$_3$), 1.75–1.87 (m, 8H, –CH_2CH$_2$CH$_3$), 3.34 (s, 12H, Ar–OCH_3), 3.68 (s, 12H, Ar–OCH_3), 4.51 (t, J = 7.4 Hz, 4H, H–2,4,6,8), 6.38 (s, 2H, Ar–H), 6.78 (s, 2H, Ar–H), 6.19 (s, 2H, Ar–H).

14a was separated as a by-product (32 mg, 30 %).

R_f = 0.76 (ethyl acetate/petroleum ether, 2:3); ^{1}H NMR (CDCl$_3$, 400 MHz, 25 °C): δ = 0.29 (s, 9H, –Si(CH_3)), 0.89 (t, J = 7.3 Hz, 6H, –(CH$_2$)$_2$CH_3), 0.92 (t, J = 7.3 Hz, 6H, –(CH$_2$)$_2$CH_3), 1.26–1.37 (m, 8H, –CH$_2$CH_2CH$_3$), 1.80–1.84 (m, 8H, –CH_2CH$_2$CH$_3$), 3.19 (s, 6H, Ar–OCH_3), 3.54 (s, 6H, Ar–OCH_3), 3.71 (s, 6H, Ar–OCH_3), 3.72 (s, 6H, Ar–OCH_3), 4.44–4.50 (m, 4H, H–2,4,6,8), 6.21 (s, 1H, Ar–H), 6.40 (s, 2H, Ar–H), 6.49 (s, 2H, Ar–H), 6.85 (s, 1H, Ar–H), 6.93 (s, 1H, Ar–H).

$1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6$-Octamethoxy-$1^5,5^5$-dimethyl-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane (15)

$1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6$-Octamethoxy-$1^5$-methyl-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane (15a)
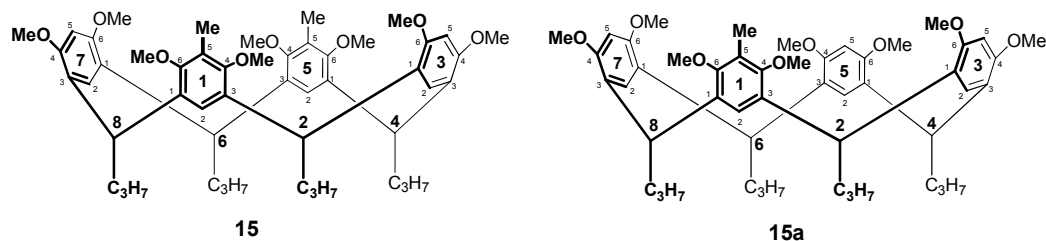
Resorcinarene **4** (106 mg, 0.12 mmol) was dissolved in tetrahydrofuran (6 ml). After cooling, nBuLi (0.26 ml, 0.25 mmol, 0.99 M solution in hexane) was added. The reaction was quenched with methyl iodide (0.1 ml, 0.75 mmol), warmed to room temperature and stirred overnight. H$_2$O (15 ml) was added and the product extracted into ethyl acetate (3×20 ml). The organic phases were combined and dried over anhydrous magnesium sulfate. The drying agent was filtered off and the solvent removed under reduced pressure to leave a white solid. Final purification was achieved by flash column chromatography (silica gel eluting with ethyl acetate: petroleum ether 1:9 followed by ethyl acetate: petroleum ether 3:17 followed by ethyl acetate: petroleum ether 1:3) to leave a white solid, the dimethyl **15** (34 mg, 37%).

R_f = 0.38 (ethyl acetate/petroleum ether, 1:3); IR (film): 2954, 2869, 1612, 1583, 1298, 1203, 1037, 910 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz, 25 °C): δ = 0.92 (t, J = 7.3 Hz, 12H, –(CH$_2$)$_2$CH_3), 1.31–1.37 (m, 8H, –CH$_2$CH_2CH$_3$), 1.78–1.84 (m, 8H, –CH_2CH$_2$CH$_3$), 2.06 (s, 6H, Ar–CH_3), 3.37 (s, 12H, Ar–OCH_3), 3.70 (s, 12H, Ar–OCH_3), 4.53 (t, J = 7.5 Hz, 4H, H–2,4,6,8), 6.39 (s, 2H, H–$3^5,7^5$), 6.58 (s, 2H, H–$1^2,5^2$), 6.72 (s, 2H, H–$3^2,7^2$); ^{13}C NMR (CDCl$_3$, 100 MHz, 25 °C): δ = 9.8 (Ar–CH$_3$), 14.2 (–(CH$_2$)$_2$$CH_3$), 21.2 (–CH$_2$$CH_2CH_3$), 35.6 (C–2,4,6,8), 37.7 (–CH$_2$CH$_2$CH$_3$), 55.8 (Ar–OCH$_3$), 59.8 (Ar–OCH$_3$), 96.1 (C–$3^5,7^5$), 123.1 (C–$1^5,5^5$), 123.5 (C–$3^1,3^3,7^1,7^3$), 126.5 (H–$3^2,7^2$), 126.7 (H–$1^2,5^2$), 133.0 (C–$1^1,1^3,5^1,5^3$), 155.4 (C–$1^4,1^6,5^4,5^6$), 155.6 (C–$3^4,3^6,7^4,7^6$); MS (ESI+): m/z (%) = 815 (50) [M+H$_2$O]$^+$, 797 (100) [M]$^+$.

15a was separated as a by-product (27 mg, 30%).

R_f = 0.29 (ethyl acetate/petroleum ether, 1:3); IR (film): 2953, 2869, 1610, 1583, 1466, 1299, 1039, 911 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz, 25 °C): δ = 0.89–0.94 (m, 12H, –(CH$_2$)$_2$CH_3), 1.26–1.40 (m, 8H, –CH$_2$CH_2CH$_3$), 1.73–1.88 (m, 8H, –CH_2CH$_2$CH$_3$), 2.04 (s, 3H, Ar–CH_3), 3.12 (s, 6H, Ar–OCH_3), 3.49 (s, 6H, Ar–OCH_3), 3.76 (s, 2×6H, Ar–OCH_3), 4.47 (t, J = 7.6 Hz, 2H), 4.54 (t, J = 7.5 Hz, 2H), 6.15 (s, 1H, Ar–H), 6.40 (s, 2H, Ar–H), 6.43 (s, 2H, Ar–H), 6.81 (s, 1H, Ar–H), 6.92 (s, 1H, Ar–H); ^{13}C NMR (CDCl$_3$, 100 MHz, 25 °C): δ = 10.1, 14.3, 21.2, 35.0, 35.6, 35.8, 37.2, 37.4, 37.7, 55.3, 55.8, 56.3, 59.4, 59.8, 95.0, 96.3, 123.0, 123.4, 124.2, 126.1, 126.6, 127.1, 127.3, 132.4, 133.0, 155.3, 155.6, 155.7, 155.8; MS (ESI+): m/z (%) = 801 (35) [M+H$_2$O]$^+$, 783 (100) [M]$^+$.

$1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6$-Octamethoxy-$1^5,5^5$-dimethylthiyl-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane (16)

$1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6$-Octamethoxy-$1^5$-methylthiyl-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane (16a)
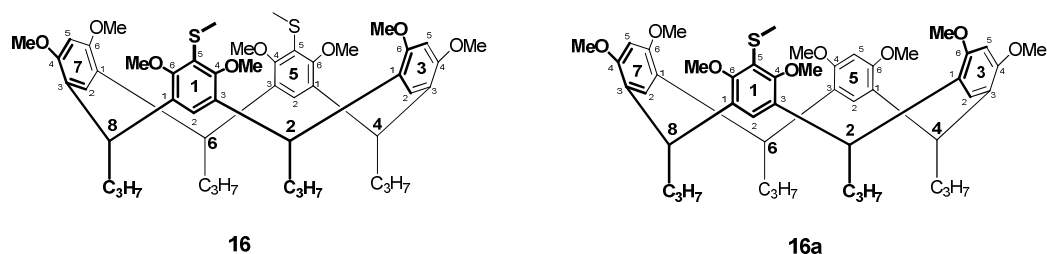
Resorcinarene **4** (350 mg, 0.38 mmol) was dissolved in tetrahydrofuran (19 ml). After cooling, *n*BuLi (0.84 ml, 0.83 mmol, 0.99 M solution in hexane) was added. The reaction was quenched with dimethyl disulfide (0.15 ml, 1.66 mmol), warmed to room temperature and stirred overnight. H$_2$O (15 ml) was added and the product extracted into ethyl acetate (3×30 ml). The organic phases were combined and dried over anhydrous magnesium sulfate. The drying agent was filtered off and the solvent removed under reduced pressure to leave a white solid. Final purification was achieved by flash column chromatography (silica gel eluting with ethyl acetate: petroleum ether 3:22 followed by ethyl acetate: petroleum ether 3:17 followed by ethyl acetate: petroleum ether 1:3) to leave a white solid. Final purification was achived by recrystallisation in ethanol/dichloromethane to yield the dithioether **16** (228 mg, 70%).

Mp 208–209 °C (ethanol/dichloromethane); R_f = 0.64 (ethyl acetate/petroleum ether, 2:3); IR (ATR): 2952, 2930, 2869, 1611, 1582, 1409, 1296, 1010, 915, 812 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz, 25 °C): δ = 0.93 (t, J = 7.4 Hz, 12H, –(CH$_2$)$_2$CH_3), 1.29–1.37 (m, 8H, –CH$_2$CH_2CH$_3$), 1.78–1.84 (m, 8H, –CH_2CH$_2$CH$_3$), 2.33 (s, 6H, –SCH_3), 3.59 (s, 12H, Ar–OCH_3), 3.64 (s, 12H, Ar–OCH_3), 4.54 (t, J = 7.6 Hz, 4H, H–2,4,6,8), 6.35 (s, 2H, H–$3^5,7^5$), 6.69 (s, 2H, H–$1^2,5^2$), 6.71 (s, 2H, H–$3^2,7^2$); ^{13}C NMR (CDCl$_3$,

75.5 MHz, 25 °C): δ = 14.2 (–(CH$_2$)$_2$CH$_3$), 18.1 (–CH$_2$CH$_2$CH$_3$), 21.2 (Ar–SCH$_3$), 35.9 (C–2,4,6,8), 37.7 (–CH$_2$CH$_2$CH$_3$), 55.7 (Ar–OCH$_3$), 60.4 (Ar–OCH$_3$), 96.3 (C–3^5,7^5), 122.9 (C–1^5,5^5), 125.6 (C–3^1,3^3,7^1,7^3), 128.9 (C–1^2,5^2), 126.3 (C–3^2,7^2), 134.6 (C–1^1,1^3,5^1,5^3), 155.8 (C–1^4,1^6,5^4,5^6), 157.2 (C–3^4,3^6,7^4,7^6); MS (ESI+): m/z (%) = 878.47 (100) [M+NH$_4$]$^+$; HRMS–ESI+: m/z [M+NH$_4$]$^+$ calcd for C$_{50}$H$_{72}$O$_8$NS$_2$: 878.4699; found: 878.4676.

16a was separated as a by-product (58 mg, 19%)

R$_f$ = 0.61 (ethyl actate/petroleum ether, 2:3); ^{1}H NMR (CDCl$_3$, 400 MHz, 25 °C): δ = 0.90 (m, 12H, –(CH$_2$)$_2$CH$_3$), 1.28–1.45 (m, 8H, –CH$_2$CH$_2$CH$_3$), 1.73–189 (m, 8H, –CH$_2$CH$_2$CH$_3$), 2.30 (s, 3H, Ar–SCH$_3$), 3.24 (s, 6H, Ar–OCH$_3$), 3.49 (s, 6H, Ar–OCH$_3$), 3.77 (s, 2×6H, 2×Ar–OCH$_3$), 4.44–4.56 (m, 4H, H–2,4,6,8), 6.15 (s, 1H, Ar–H), 6.34 (s, 2H, Ar–H), 6.44 (s, 2H, Ar–H), 6.92 (s, 1H, Ar–H), 6.93 (s, 1H, Ar–H).

1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-Octamethoxy-1^5,5^5-bis(diphenylphosphine oxide-2,4,6,8 tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane (17)

1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-Octamethoxy-1^5-diphenylphosphine oxide-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane (17a)
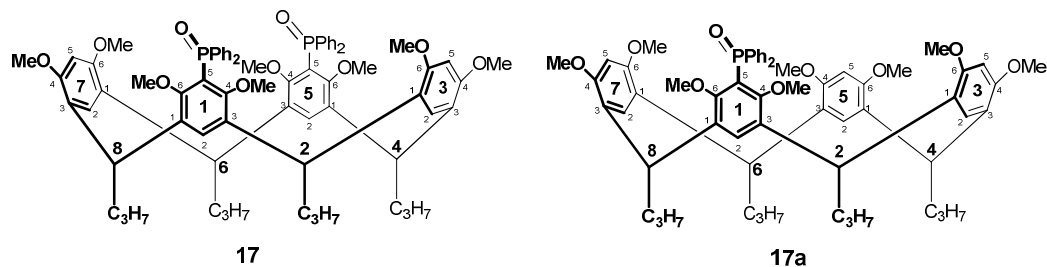
Resorcinarene **4** (141 mg, 0.15 mmol) was dissolved in tetrahydrofuran (8 ml). After cooling, nBuLi (0.34 ml, 0.33 mmol, 0.99 M solution in hexane) was added. The reaction was quenched with diphenylphosphine chloride (0.13 ml, 0.70 mmol), warmed to room temperature and stirred overnight. H$_2$O (15 ml) was added and the product extracted into ethyl acetate (3×30 ml). The organic phases were combined and dried over anhydrous magnesium sulfate. The drying agent was filtered off and the solvent removed under reduced pressure to leave a white solid. Final purification was achieved by flash column chromatography (silica gel eluting with ethyl acetate: petroleum ether 3:7 followed by ethyl acetate: petroleum ether 2:3 followed by ethyl acetate: petroleum ether 3:2 followed by ethyl acetate: petroleum ether 3:1 followed by ethyl acetate) to leave a white solid (14 mg, 8%).

IR (film): 3057, 2955, 2870, 1612, 1300, 1200 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz, 25 °C): δ = 0.86 (t, J = 7.2 Hz, 12H, –(CH$_2$)$_2$CH$_3$), 1.18–1.38 (m, 8H, –CH$_2$CH$_2$CH$_3$), 1.61–1.69 (m, 4H, –CH$_2$CH$_2$CH$_3$), 1.81–

1.91 (m, 4H, –CH_2CH$_2$CH$_3$), 3.34 (s, 12H, Ar–OCH_3), 3.69 (s, 12H, Ar–OCH_3), 4.26 (dd, J = 8.4, 6.2 Hz, 4H, H–2,4,6,8), 6.08 (s, 2H, Ar–H), 6.40 (s, 2H, Ar–H), 7.18 (s, 2H, Ar–H), 7.34–7.84 (m, 20H, Ph); ^{13}C NMR (CDCl$_3$, 75.5 MHz, 25 °C): δ = 14.2, 20.9, 36.0, 37.6, 55.1, 62.7, 96.4, 118.0, 119.3, 122.6, 126.1, 127.5, 127.7, 128.5–128.7, 130.2, 130.3, 131.5–131.8, 132.3, 136.3, 137.6, 137.7, 137.8, 156.4, 159.4; ^{31}P NMR (CDCl$_3$, 121.5 MHz, 25 °C): δ = 20.97; MS (ESI+): m/z (%) = 1170 (100) [M+H]$^+$

17a was separated as a mixture of products and could not be characterised.

$1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6$-Octamethoxy-$1^5,5^5$-dimethoxycarbonyl-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane (18)

$1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6$-Octamethoxy-$1^5$-methoxycarbonyl-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane (18a)

18   **18a**
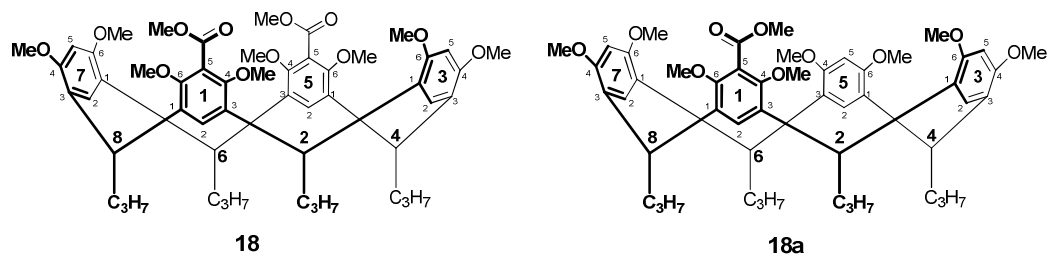
Resorcinarene **4** (154 mg, 0.17 mmol) was dissolved in tetrahydrofuran (8.5 ml). After cooling, *n*BuLi (0.37 ml, 0.36 mmol, 0.99 M solution in hexane) was added. The reaction was quenched with methyl chloroformate (0.10 ml, 1.10 mmol), warmed to room temperature and stirred overnight. H$_2$O (15 ml) was added and the product extracted into ethyl acetate (3×25 ml). The organic phases were combined and dried over anhydrous magnesium sulfate. The drying agent was filtered off and the solvent removed under reduced pressure to leave a white solid. Final purification was achieved by flash column chromatography (silica gel eluting with ethyl acetate: petroleum ether 3:17 followed by ethyl acetate: petroleum ether 1:4 followed by ethyl acetate: petroleum ether 1:3) to leave a fine white solid, the dimethoxy carbonyl (100 mg, 68%).

Mp 272–273 °C (ethyl acetate/petroleum ether); R$_f$ = 0.45 (ethyl acetate/petroleum ether, 1:1); IR (ATR): 2951, 2868, 1726, 1612, 1467, 1202, 918 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz, 25 °C): δ = 0.91 (t, J = 7.3 Hz, 12H, –(CH$_2$)$_2$CH_3), 1.28–1.40 (m, 8H, –CH$_2$CH_2CH$_3$), 1.71–1.89 (m, 8H, –CH_2CH$_2$CH$_3$), 3.52 (s, 12H, Ar–OCH_3), 3.73 (s, 12H, Ar–OCH_3), 3.93 (s, 6H, –COOCH_3), 4.45 (dd, J = 8.5,6.3 Hz, 4H, H–2,4,6,8), 6.24 (s, 2H, H–3^5,7^5), 6.53 (s, 2H, H–1^2,5^2), 6.93 (s, 2H, H–3^2,7^2); ^{13}C NMR (CDCl$_3$, 75.5 MHz, 25 °C): δ = 14.1 (–(CH$_2$)$_2$CH_3), 21.2 (–CH$_2$CH_2CH$_3$), 35.8 (C–2,4,6,8), 37.6 (–CH_2CH$_2$CH$_3$), 52.4 (–COOCH_3), 55.5 (Ar–OCH_3), 62.0 (Ar–OCH_3), 96.4 (C–35,75), 122.5 (Ar–C), 123.8 (Ar–C), 126.2 (Ar–

C), 127.6 (Ar–C), 135.5 (C–$1^1,1^3,5^1,5^3$), 152.9 (C–$1^4,1^6,5^4,5^6$), 156.2 (C–$3^4,3^6,7^4,7^6$), 168.0 (–COOCH$_3$); MS (ESI+): m/z (%) = 903 (100) [M+NH$_4$]$^+$, 886 (30) [M]$^+$

The mono methoxy carbonyl **18a** was partially characterised from crude ^{1}H NMR spectroscopy, due to problems separating this from octamethoxy **5**. The yield was adjudged to be about 20% for this compound from the crude NMR.

R_f = 0.60 (ethyl acetate/petroleum ether, 1:1); IR (film): 1730 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz, 25 °C): δ = 0.88–0.95 (m, 12H, –(CH$_2$)$_2$CH_3), 1.26–1.38 (m, 8H, –CH$_2$CH_2CH$_3$), 1.77–1.85 (m, 8H, –CH_2CH$_2$CH$_3$), 3.29 (s, 6H, Ar–OCH_3), 3.55 (s, 6H, Ar–OCH_3), 3.72 (s, 2×6H, 2×Ar–OCH_3), 3.85 (s, 3H, –COOCH_3), 4.47–4.51 (m, 4H, H–2,4,6,8), 6.26 (s, 1H, Ar–H), 6.32 (s, 2H, Ar–H), 6.44 (s, 2H, Ar–H), 6.83 (s, 1H, Ar–H), 6.96 (s, 1H, Ar–H)

2-Bromo-1,3-di(*tert*-butyl carbonate) benzene (19)
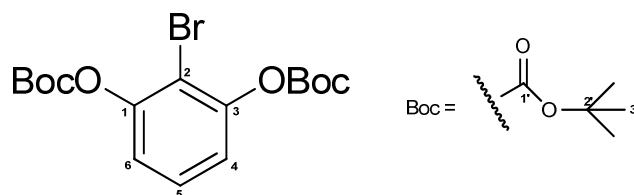
1-Bromo-2,6-dihydroxybenzene (1.96 g, 10.3 mmol) was dissolved in dry dichloromethane (35 ml). To this solution was added triethylamine (3.16 ml, 22.7 mmol) and 4-dimethyl aminopyridine (0.064 g, 0.516 mmol) and the resulting solution was stirred for 15 minutes at room temperature. Di-*tert*-butyl dicarbonate (6.76g, 31 mmol) was added in two portions to the reaction and the solution was left to stir at room temperature for 18 hours. The solution was then washed with 1M HCl (2×45ml), saturated sodium bicarbonate, H$_2$O and brine (60 ml). The organic phase was dried over anhydrous magnesium sulfate, the drying agent was filtered off and the solvent removed under reduced pressure to leave a yellow brown oil (5.24 g, >100%). The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: petroleum ether 1:9) to leave an off-white oil, which solidified after 5 days on a high vacuum pump to yield the diBoc **19** (3.40 g, 85%).

R_f = 0.48 (ethyl acetate/petroleum ether, 1:4); IR (film): 2983, 2936, 1766, 1588, 1371, 1144, 948, 858 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz, 25 °C): δ = 1.54 (s, 18H, –C(CH_3)$_3$), 7.10 (d, J = 8.2 Hz, 2H, H–4,6), 7.31 (t, J = 8.2 Hz, 1H, H–5); ^{13}C NMR (CDCl$_3$, 100 MHz, 25 °C): δ = 27.4 (–C(CH_3)$_3$), 84.1 (C–2'), 111.5 (C–1), 120.7 (C–4,6), 128.0 (C–5), 149.4 (C–1,3), 150.3 (C–1'); MS (ESI+): m/z (%) = 406.09 (68) [M+NH$_4$]$^+$; HRMS–ESI+: m/z [M+NH$_4$]$^+$ calcd for C$_{16}$H$_{25}$NO$_6$Br: 406.0865; found: 406.0872.

tert-Butyl-1-(tert-butoxycarbonyloxy)-3-hydroxybenzoate (20)
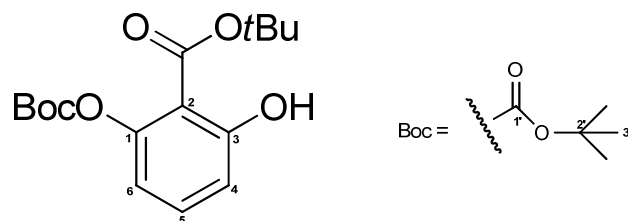
DiBoc **19** (715 mg, 1.84 mmol) was dissolved in dry tetrahydrofuran (10 ml) and cooled to −78 °C. To the solution was added nBuLi (1.85 ml, 2.76 mmol, 1.49 M in hexane) and the reaction stirred for 15 minutes. Sat. NH_4Cl (5 ml) was added to the reaction and the solution was warmed to room temperature and left to stir for an hour. To the reaction was added H_2O (20 ml) and extracted with dichloromethane (3×25 ml). The organic phases were combined and dried over anhydrous magnesium sulfate. The drying agent was filtered off and the solvent removed under reduced pressure to leave a brown oil. Final purification was achieved by flash column chromatography (silica gel eluting with ethyl acetate: petroleum ether 1:19 followed by ethyl acetate: petroleum ether 1:9) to leave a yellow oil, the rearranged-diBoc **20** (520 mg, 91%).

R_f = 0.57 (ethyl acetate/petroleum ether, 1:4); IR (film): 2982, 2935, 1759, 1665, 1276, 1154, 977 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz, 25 °C): δ = 1.55 (s, 9H, –C(CH_3)$_3$), 1.62 (s, 9H, –C(CH_3)$_3$), 6.62 (dd, J = 8.1,1.2 Hz, 1H, Ar–H), 6.88 (dd, J = 8.5,1.2 Hz, 1H, Ar–H), 7.32–7.39 (m, 1H, A–H), 11.38 (s, 1H, Ar–OH); MS (ESI+): m/z (%) = 328 (100) [M+NH$_4$]$^+$, 311 (5) [M+H]$^+$, 102 (58) [CO$_2$C$_4$H$_{10}$]$^+$; HRMS–ESI+: m/z [M+Na]$^+$ calcd for C$_{16}$H$_{22}$O$_6$Na: 333.1314; found: 333.132.

tert-Butyl-2,6-bis(tert-butoxycarbonyloxy)benzoate (21)
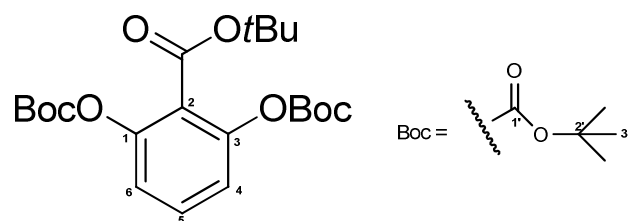
The rearranged diBoc (567 mg, 1.81 mmol) was subjected to the protection methodology used to synthesise **19**; with 4-dimethyl aminopyridine (11 mg, 0.09 mmol), triethylamine (0.28 ml, 2.00 mmol) and di-_tert_-butyl dicarbonate (480.15 mg, 2.20 mmol) in dichloromethane (7 ml). The product was purified using column chromatography (silica gel eluting with ethyl acetate: petroleum ether 1:19 followed by ethyl acetate: petroleum ether 1:9) to yield a yellow oil that hardens slowly on standing (659 mg, 89%).

R_f = 0.52 (ethyl acetate/petroleum ether, 1:4); IR (film): 2982, 2936, 1766, 1725, 1613, 1227, 1081, 864 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz, 25 °C): δ = 1.54 (s, 18H, –OC(CH_3)$_3$), 1.57 (s, 9H, –COOC(CH_3)$_3$), 7.10 (d, J = 8.3 Hz, 2H, H–4,6), 7.40 (t, J = 8.3 Hz, 1H, H–5); MS (ESI+): m/z (%) = 4.28 (100) [M+NH$_4$]$^+$; HRMS–ESI+: m/z [M+NH$_4$]$^+$ calcd for C$_{21}$H$_{34}$O$_8$N: 428.2284; found: 428.2304.

Methyl 1,3-dimethoxybenzoate (22)
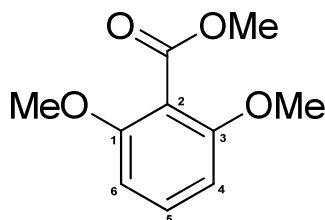
To a solution of the reprotected **20** (659 mg, 1.60 mmol) in dichloromethane (7 ml) was added trifluoroacetic acid (6.2 ml, 80 mmol) and stirred for two hours at room temperature. The mixture was added to H$_2$O (10 ml), ethyl acetate (20 ml) and the pH adjusted to ~7 using a sat. sodium bicarbonate solution. The organic layer was separated. The aqueous layer was further extracted using ethyl acetate (2×25 ml), the organic layers combined and washed with H$_2$O (25 ml) and brine (25 ml). The organic phase was dried over anhydrous magnesium sulfate, the drying agent was filtered off and the solvent removed under reduced pressure to leave an orange solid (250 mg, >100%). This was used as is in the next reaction.

The crude product and potassium carbonate (1.38 g, 10 mmol) were suspended in dry acetonitrile (30 ml) and dimethyl sulfate (0.91 ml, 10 mmol) was added. The solution was heated to reflux for 18 hours. The reaction was stopped and cooled to room temperature. The solvent was removed under reduced pressure and the resulting solid added to H$_2$O (25 ml) and extracted with ethyl acetate (3×30 ml). The organic layers were combined and dried over anhydrous magnesium sulfate. The drying agent was filtered off and the solvent removed under reduced pressure to leave an orange oil. The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: petroleum ether 1:9 followed by ethyl aceate: petroleum ether 1:1) to leave a white solid (238 mg, 75%). ^{1}H NMR spectroscopy corresponded to literature values.[14]

^{1}H NMR (CDCl$_3$, 300 MHz, 25 °C): δ = 3.82 (s, 6H, –OCH_3), 3.91 (s, 3H, –CO$_2$CH_3), 6.56 (d, J = 8.5 Hz, 2H, H–4,6), 7.29 (t, J = 8.4 Hz, 1H, H–5).

3⁴,3⁶,7⁴,7⁶-Tetra(benzyloxycarbonyloxy)-1⁵,5⁵-dibromo-1⁴,1⁶,5⁴,5⁶-tetra(*tert*-butoxycarbonyloxy)-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane (23)
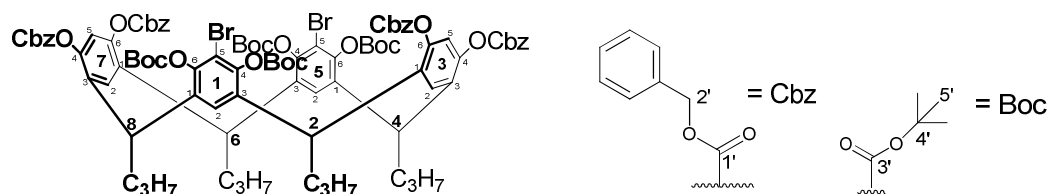
To a mixture of resorcinarene **3** (2.35 g, 1.74 mmol) in dichloromethane (12 ml) was added triethylamine (0.97 ml, 6.96 mmol) and 4-dimethyl aminopyridine (31.9 mg, 0.261 mmol) the dark green solution was stirred for 15 minutes at room temperature. Di-*tert*-butylcarbonate (1.90 g, 8.70 mmol) was added and the solution stirred at room temperature for 24 hours. To the reaction mixture was added H_2O (70 ml), 1M HCl (10 ml) and dichloromethane (70 ml) and the organic phase extracted. The aqueous phase was further extracted with dichloromethane (3×30 ml) and the organic phases collected. The organic phase was washed with 1M HCl, saturated sodium bicarbonate, H_2O and brine (30 ml) and dried over anhydrous magnesium sulfate. The drying agent was filtered off and the solvent removed under reduced pressure to leave a dark orange foam. The product was purified using flash column chromatography (silica gel eluting starting with ethyl acetate: petroleum ether 1:9 followed by ethyl acetate: petroleum ether 1:4). The resulting product was recrystallized in ethanol/dichloromethane to yield fine light yellow crystals (2.62 g, 86%).

Mp 176–178 °C (ethanol/dichloromethane); R_f = 0.55 (etyl acetate/petroleum ether, 3:7); IR (ATR): 2954, 2871, 1759, 1497, 1219, 1141, 1056, 886, 773 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz, 50 °C): δ = 0.86–0.91 (m, 12H, –(CH$_2$)$_2$C*H*$_3$), 1.25–1.35 (m, 8H, –CH$_2$C*H*$_2$CH$_3$), 1.44–1.48 (m, 36H, –C(C*H*$_3$)$_3$), 1.85–1.92 (m, 8H, –C*H*$_2$CH$_2$CH$_3$), 4.41 (t, *J* = 7.3 Hz, 4H, H–2,4,6,8), 5.02–5.22 (m, 8H, H–2'), 6.64, 6.80, 6.95–6.98 (br s, 6H, Ar–*H*), 7.27–7.49 (m, 20H, Ph); ^{13}C NMR (CDCl$_3$, 75.5 MHz, 50 °C): δ = 13.8, 20.8, 20.9, 27.6, 36.7, 36.7, 37.0, 70.2, 83.5, 113.6, 116.5, 125.2, 126.0, 128.3, 128.3, 128.4, 128.6, 131.9, 135.1, 135.2, 145.8, 146.1, 147.5, 147.8, 149.8, 152.7; MS (ESI+): *m/z* (%) = 1768 (100) [M+H$_2$O]$^+$, 893 (22) [M+H$_2$O]$^+$; HRMS–ESI+: *m/z* [M+H$_2$O]$^+$ calcd for C$_{92}$H$_{104}$O$_{25}$Br$_2$: 1766.5233; found: 1768.5247.

1⁵,5⁵-Dicyano-1⁴,1⁶,3⁴,3⁶,5⁴,5⁶,7⁴,7⁶-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane (24)
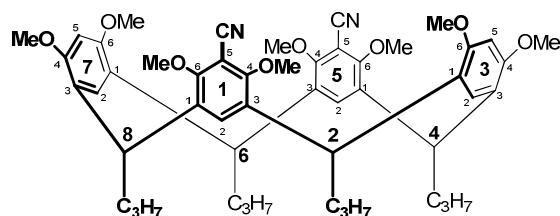
Resorcinarene **4** (500 mg, 0.54 mmol) and copper(I) cyanide (387 mg, 4.32 mmol) were added to dry N,N-dimethylformamide (11 ml) and placed in a microwave reactor at 210 °C for 45 minutes. The reaction was allowed to cool to room temperature and added to a mixture of iron(III) chloride (1.40 g, 8.64 mmol), H_2O (25 ml) and conc. HCl (15 ml) and the green solution was stirred for an hour. The mixture was extracted with chloroform (6×30 ml), the organic phases combined and washed with H_2O (30 ml) and brine (30 ml). The organic phase was dried over anhydrous magnesium sulfate. The drying agent was filtered off and the solvent removed under reduced pressure to leave a yellow solid. The product was purified using flash column chromatography (silica gel eluting starting with ethyl acetate: petroleum ether 3:7 followed by ethyl acetate: petroleum ether 2:3) to leave a white solid. The resulting product was recrystallized in ethanol/dichloromethane to yield fine white crystals (387 mg, 87%).

Mp 230–231 °C (ethanol); R_f = 0.18 (ethyl acetate/petroleum ether, 2:3); IR (ATR): 2952, 2867, 2229, 1614, 1578, 1203, 1035 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz, 25 °C): δ = 0.94 (t, J = 7.3 Hz, 12H, –(CH$_2$)$_2$CH_3), 1.27–1.45 (m, 8H, –CH$_2$CH_2CH$_3$), 1.66–1.75 (m, 4H, –CH_2CH$_2$CH$_3$), 1.83–1.93 (m, 4H, –CH_2CH$_2$CH$_3$), 3.52 (s, 12H, Ar–OCH_3), 3.96 (s, 12H, Ar–OCH_3), 4.47 (dd, J = 8.4, 6.6 Hz, 4H, H–2,4,6,8), 6.21 (s, 2H, H–3^5,7^5), 6.62 (s, 2H, H–1^2,5^2), 6.90 (s, 2H, H–3^2,7^2); ^{13}C NMR (CDCl$_3$, 100 MHz, 25 °C): δ = 14.2 (–(CH$_2$)$_2$CH$_3$), 21.0 (–CH$_2$CH$_2$CH$_3$), 35.5 (C–2,4,6,8), 37.3 (–CH$_2$CH$_2$CH$_3$), 55.4 (Ar–OCH$_3$), 61.6 (Ar–OCH$_3$), 96.2 (C–3^5,7^5), 99.8 (C–1^5,5^5), 115.1 (–CN), 123.3 (C–3^1,3^3,7^1,7^3), 125.9 (H–3^2,7^2), 131.0 (H–1^2,5^2), 135.8 (C–1^1,1^3,5^1,5^3), 156.3 (C–1^4,1^6,5^4,5^6), 158.6 (C–3^4,3^6,7^4,7^6); MS (ESI+): m/z (%) = 836 (100) [M+H$_2$O]$^+$, 819 (30) [M+H]$^+$; HRMS–ESI+: m/z [M+H]$^+$ calcd for C$_{50}$H$_{63}$N$_2$O$_8$: 819.4584; found: 819.4589.

(*cis/trans*)-Bis(dimethylsulfide) platinum(II) chloride (25)[15]
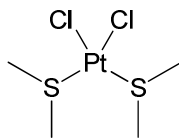
The compound was synthesised using a literature procedure.[15] Potassium tetrachloroplatinate(II) (150 mg, 0.36 mmol) was dissolved in H_2O (6 ml) and stirred at room temperature. To the mixture was added dimethyl sulfide (0.16 ml, 2.16 mmol) and warmed to 80 °C for one hour. The yellow solution was cooled to room temperature, added to H_2O (10 ml) and extracted into dichloromethane (4×15 ml) until the aqueous layer was colourless. The organic phases were combined and dried over anhydrous magnesium sulfate. The drying agent was filtered off and the solvent removed under reduced pressure to leave a yellow solid (105 mg, 75%). This solid was judged to be pure enough to continue as is from ^{1}H NMR spectroscopy.[15]

^{1}H NMR (CDCl$_3$, 300 MHz, 25 °C): δ = 2.47 (t, J_{Pt-H} = 41.4 Hz, 12H, *cis*–[PtCl$_2$(SMe$_2$)$_2$]), 2.58 (t, J_{Pt-H} = 49.2 Hz, 12H, *trans*–[PtCl$_2$(SMe$_2$)$_2$]).

S,S'-{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}-bis[palladium chloride(μ$_2$-chlorine)$_2$] (26)
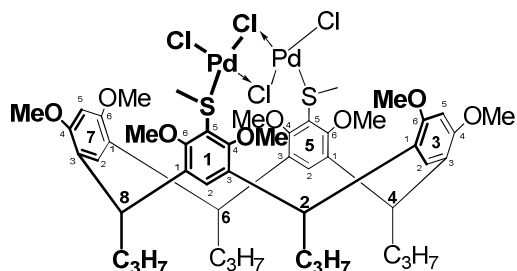
To resorcinarene **16** (75 mg, 0.087 mmol) dissolved in dry dichloromethane (3 ml) was added palladium(II) chloride (30.5 mg, 0.174 mmol) and the resulting brown reaction mixture stirred for 24 hours at room temperature. The solution was filtered through Celite and carefully washed with dichloromethane. The solvent was evaporated and the brown solid was re-dissolved in dichloromethane, layered with pentane and placed in a refrigerator at −15 °C. After a few days small brown crystals formed and were collected by filtration and dried to give the dipalladium complex **26** (74 mg, 70%).

Mp 239–243 °C(dec) (dichloromethane/pentane); IR (ATR): 2949, 2869, 1610, 1581, 1288, 1160, 966, 816 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz, 50 °C): δ = 0.88 (t, J = 7.3 Hz, 12H, –CH$_2$CH$_2$C*H*$_3$), 1.16–1.27 (m, 8H, –CH$_2$C*H*$_2$CH$_3$), 1.82 (q, J = 7.5 Hz, 8H, –C*H*$_2$CH$_2$CH$_3$), 2.55 (s, 6H, –SC*H*$_3$), 3.60 (br s, 12H, Ar–OC*H*$_3$), 4.00 (s, 12H, Ar–OC*H*$_3$), 4.67 (t, J = 7.5 Hz, 4H, H–2,4,6,8), 6.35 (s, 2H, H–3^2,7^2), 6.61 (s, 2H, H–3^5,7^5), 7.57 (s, 2H, H–1^2,5^2); ^{13}C NMR (CDCl$_3$, 100 MHz, 50 °C): δ = 13.9 (–CH$_2$CH$_2$C*H*$_3$), 21.0 (–CH$_2$C*H*$_2$CH$_3$), 23.6 (–SC*H*$_3$), 35.7 (C–2,4,6,8), 38.2 (–C*H*$_2$CH$_2$CH$_3$), 55.7–55.9 (Ar–OC*H*$_3$), 62.1, 95.3 (C–3^5,7^5), 115.9 (C–1^1,1^3,5^1,5^3), 125.8–125.9 (C–3^2,7^2), 126.8 (C–3^1,3^3,7^1,7^3), 132.6 (C–1^2,5^2), 155.6 (C–3^4,3^6,7^4,7^6), 157.8 (C–1^4,1^6,5^4,5^6).

7.3 Crystal Structures

A single crystal was covered in a small amount of paratone oil and mounted on a glass fibre. X-ray intensity data were collected at 100 K on a Bruker SMART APEX CCD with 1.75 kW graphite monochromated Mo radiation. The detector to crystal distance was 60 mm. Data were collected by omega scans. The data were scaled and reduced using the *APEXII* software suite. Unit cell dimensions were refined on all data and the space group was assigned on the basis of systematic absences and intensity statistics. The structure was solved and refined using *SHELX97*.[16] Hydrogen atoms are placed in

calculated positions and included in the model during later stages of the refinement. The program *X-SEED*,[17] an interface to *SHELX*, was used during the structure solution and refinements.

$1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6$-Octamethoxy-$1^5,5^5$-dimethylthiyl-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane (16)

Empirical formula	$C_{50}H_{68}O_8S_2$
Formula weight	861.16
Temperature (K)	100(2)
Wavelength (Å)	0.71073
Crystal system	triclinic
Space group	*P*-1
Unit cell dimensions (Å, °)	$a = 15.6205(10)$ $\alpha = 68.2220(10)$
	$b = 16.9158(11)$ $\beta = 76.8050(10)$
	$c = 20.1948(13)$ $\gamma = 72.5700(10)$
Volume ($Å^3$)	4686.3(5)
Z	4
Calculated density (g cm^{-3})	1.221
Absorption coefficient (mm^{-1})	0.166
F_{000}	1856
Crystal size (mm^3)	$0.53 \times 0.44 \times 0.22$
θ range for data collection (°)	1.10 to 27.92
Miller index ranges	$-20 \leq h \leq 20, -22 \leq k \leq 22, -26 \leq l \leq 25$
Reflections collected	52712
Independent reflections	20234 [$R_{int} = 0.0285$]
Completeness to θ$_{max}$ (%)	90.0
Max. and min. transmission	0.9637 and 0.9173
Refinement method	Full-matrix least-squares on F^2

Data / restraints / parameters	20234 / 0 / 1101
Goodness-of-fit on F^2	1.050
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0629$, $wR2 = 0.1670$
R indices (all data)	$R1 = 0.0819$, $wR2 = 0.1866$
Largest diff. peak and hole (e $\mathring{A}^{-3}$)	2.506 and -0.440

S,S'-{$1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6$-octamethoxy-$1^5,5^5$-dimethylthiyl-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane}-bis[palladium chloride(μ_2-chlorine)$_2$] (26)

Empirical formula	$C_{51.50}H_{71}Cl_7O_8Pd_2S_2$		
Formula weight	1343.15		
Temperature (K)	173(2)		
Wavelength ($\mathring{A}$)	0.71073		
Crystal system	triclinic		
Space group	P-1		
Unit cell dimensions ($\mathring{A}$, °)	$a = 13.4931(11)$	$\alpha =$	81.372(1)
	$b = 14.4968(12)$	$\beta =$	84.347(1)
	$c = 15.5364(12)$	$\gamma =$	70.855(1)
Volume ($\mathring{A}^3$)	2834.5(4)		
Z	2		
Calculated density (g cm^{-3})	1.574		
Absorption coefficient (mm^{-1})	1.088		
F_{000}	1374		
Crystal size (mm^3)	$0.23 \times 0.21 \times 0.15$		
θ range for data collection (°)	1.50 to 28.15		
Miller index ranges	$-17 \le h \le 16$, $-19 \le k \le 19$, $-19 \le l \le 19$		
Reflections collected	32160		

Independent reflections	12633 [R_{int} = 0.0321]
Completeness to θ_{max} (%)	91.0
Max. and min. transmission	0.8538 and 0.7879
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	12633 / 0 / 686
Goodness-of-fit on F^2	1.026
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0359, wR2 = 0.0783
R indices (all data)	R1 = 0.0549, wR2 = 0.0867
Largest diff. peak and hole (e Å^{-3})	0.797 and -1.035

7.4 References

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