Investigation of Resorcin[4]arenes

Upper Rim Functionalization

by

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Pentru familia mea extraordinara. Va iubesc din tot sufletul.

[For my extraordinary family. I love you with all my soul.]

Preface

The research in this thesis is, to the best of my knowledge, original and my own work except where due reference has been made. Neither the thesis nor the original work contained therein has been submitted to this or any other institution for a degree.

Cristina-Adriana Macarov

May 2018

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Abstract

The research in this thesis depicts aspects in the area of resorcin[4]arenes upper rim functionalization and presents the importance of this type of structures.

The first chapter covers past and present literature regarding general background and synthetic approaches towards building these cage-like cyclic oligomers, and discusses the possible applications as synthetic enzymes.

Chapter two is separated into two main research areas; (i) preparation of a series of monofunctionalized substrates, attaching on each ring desired groups, such as: amines, esters, ethers, carboxylic acids, alcohols, boronic acids, and (ii) design and synthesis of multifunctionalized resorcin[4]arenes, where we aimed to couple two or more of the mentioned functional groups on each aromatic unit.

In the first part of chapter two, two main strategies for upper rim functionalization are reported; (i) at the phenolic OH, reactions that take place almost quantitative, excepting the Buchwald-Hartwig amination (yield 43-94 %, depending on the primary amine used), and (ii) at the ortho position, where, although the unsatisfying yields, some new compounds were successfully synthesized and characterised.

The second part of chapter two details the attempts to multifunctionalize each aromatic unit, using the same methodologies applied to the preparation of the monofunctionalized precursors. The step was found to be challenging due to steric hindrance and low reactivity of the monosubstituted derivatives, and, despite applying longer time, higher temperature and/or pressure, the targeted structures were unsuccessful.

Chapter three includes the experimental data for all the compounds mentioned in chapter two, with chapter four containing some NMR spectra and crystal structure additional information.

List of Abbreviations

°C	degrees Celsius
Ac	acetyl
aq.	aqueous
Ar	aryl
B_2pin_2	bis(pinacolato)diboron
b.p.	boiling point
Bu	butyl
cat.	catalysed
$CDCl_3$	deuterated chloroform
cm^{-1}	wavenumber
conc.	concentrated
d	doublet
DBU	1,8-diazabicycloundec-7-ene
DCM	dichloromethane
dd	doublet of doublet
DIPA	diisopropyl amine
DMAP	4-*N,N*-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethylsulfoxide
EDG	electron donating group
equiv.	equivalent(s)
Et	ethyl
Et_3N	trimethylamine

EtOAc	ethyl acetate
EtOH	ethanol
EWD	electron withdrawing group
g	gram(s)
HBcat	catecholborane
HBpin	pinacolborane
hr	hour(s)
HRMS	high resolution mass spectrometry
IR	infrared
J	coupling constant
LAB	lithium aluminium borohydride
M	molar
m	multiplet
m.p.	melting point
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MHz	Megahertz
min	minute
MJOD	Multi-Jet Oscillating Disk Reactor
ml	millilitre
mmol	milimole(s)
MS	mass spectrometry
n-BuLi	*n*-butyllithium
NMR	nuclear magnetic resonance
Oxone©	potassium monoperoxysulfate ($2KHSO_5.KHSO_4.K_2SO_4$)

Ph	phenyl
PhCl	chlorobenzene
PhCN	benzonitrile
PhMe	toluene
PIM	Polymer Inclusion Membrane
ppm	parts per million
rbf	round bottomed flask
r.t.	room temperature
s	second(s)
sat.	saturated
SLM	Supported Liquid Membrane
SM	starting material
t	triplet
t-BuLi	*t*-butyllithium
TEA	triethylamine
Tf	trifluoromethanesulfonate (triflate)
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TPP	triphenylphosphine
TPPP	tetraphenylphosphonium monoperoxysulfate
UV	ultraviolet
δ	chemical shift
Δ	heat
µW	microwave

CHAPTER I: Introduction.

Summary

This work focuses on calix[4]resorcinarenes, otherwise known as resorcinarenes, resorcarenes or octols. They are cage-like cyclic oligomers that possess two hydroxyl groups on benzene units.

Resorcinarene complexes may serve as *enzyme metalosite models, redox sensors, selective extractants for radioactive ions and molecular magnetic materials and catalysis.*[1] Significant industrial applications for resorcinarenes have been reported.[2] Current interests in the possible applications include binding and incorporation of guest compounds.[3,4] Other applications of resorcinarenes include: ion chromatography columns,[5] dyes,[6] membranes/films,[7] supported liquid membrane (SLM),[8] polymer inclusion membranes (PIM),[9] biomimetic membranes,[10] ligands in metal chemistry,[11] chiral NMR solvating agent,[12] detecting electrodes,[13] biomimetic and biomedical applications,[14] biopharmaceutical applications,[15] chromatographic separation and analysis,[16] chemosensors,[17] electrical and optical applications,[18] electrochemical sensors,[19] chemical imaging,[20] amperometric detectors.[21]

Thus the interest in working with these compounds that have a wide range of applications and that established their importance in synthetic chemistry.

1.1 Resorcinarenes – General information.

Supramolecular chemistry, where the focus is the overall chemical system as opposed to individual molecules, has been explored in detail in the last century. First established by *Pedersen*, *Lehn* and *Cram* through their extensive work with crown ethers, spherands and cryptands, supramolecular chemistry has exhibited potential for the construction of elaborate molecular architectures and advanced materials.

Research has broadened, and the overall sophistication and specificity of the macrocyclic molecules have become more advanced, opening up more potential applications as nanoscale reaction containers, catalysts and drug encapsulation.[22, 23]

An example of such macrocyclic molecules are calix[n]arenes (usually *n* = 4, 5, 6, 8). The root "*calyx*" has been used to name other cup-shaped molecules, such as the proteins termed "*calins*". The word calixarene is derived from "*calix"* or "*chalice"* because this type of molecule resembles a vase and from the word "*arene"*, that refers to the aromatic building block (**Fig. 1.1.**).

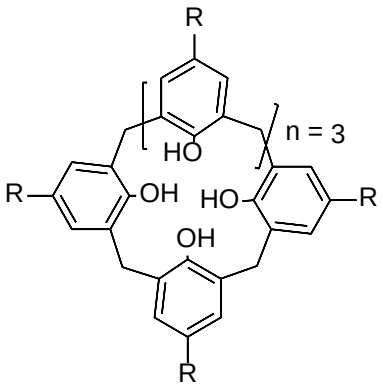


Figure 1.1. Calixarene general structure.[24]

Calixarenes are metacyclophanes having a hydrophobic cavity formed between the lower (narrow) and upper (wide) rims, formed by phenol units bridged with methylene links; they are easily synthesized using a base-catalysed, single-step condensation of phenol with formaldehyde.

Calixarenes possess a soft π–donor cavity consisting of benzene rings and a hard oxygen cavity formed by hydroxyl groups. The hydrophilic narrow rim and hydrophobic wide rim encompassing a cavity may be functionalized. The cavity dimensions depend on the conformation of the calixarene and the functional groups.[25, 26]

This work focuses on calix[4]resorcinarenes, otherwise known as resorcinarenes, resorcarenes or octols. They are cage-like oligomers that possess two hydroxyl groups on each benzene unit (**Fig. 1.2.**). The synthesis of resorcinarenes involves the condensation of resorcinol, instead of phenol as in the case of calixarenes, with aldehydes.

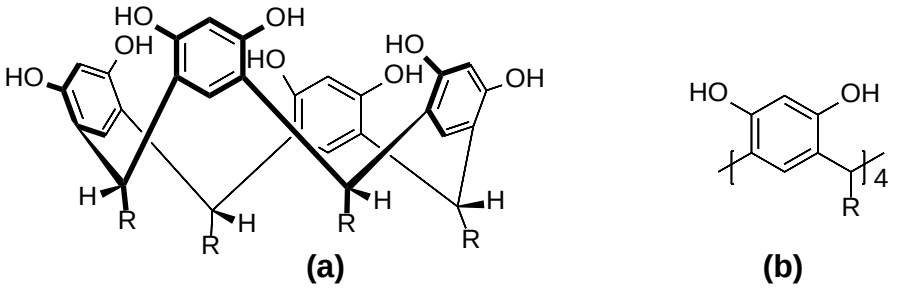


Figure 1.2. Resorcinarene core: (a) in space representation, (b) planar view.

Resorcinarenes, were first discovered in 1872 by *Adolf von Baeyer*, during a general study of phenol-based dyes. During this study, *Baeyer* observed that, upon addition of concentrated sulphuric acid to a mixture of benzaldehyde and resorcinol, a reddish resinous product was formed. This product changed colour to violet under basic conditions, and gave an isometric crystalline product of a similar colour when heated further.[27] At the time, the product formed could not be classified and it was not until several years later when *Michael* would attempt to assess it further. He reported that the product was formed by combination of resorcinol and benzaldehyde in 1:1 ratio, structure **1** (**Fig. 1.3.**), with an equal number of water molecules, and even speculated upon a phenolic structure.[22]

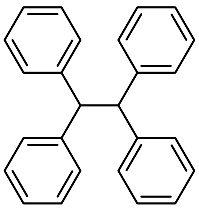
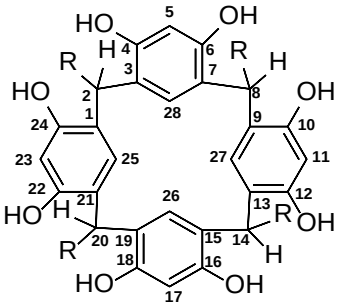


Figure 1.3. Proposed structure *by Michael*.[27]

Investigation of the compound continued until more powerful analytical techniques were developed, and in 1940, *Niederl* and *Vogel* showed that the ratio between aldehyde and resorcinol is 4:4 according to molecular weight determinations. Structure **2** (**Fig. 1.4.**) was then proposed: a cyclic tetramer not unlike porphyrins. Using X-ray

crystallography, the structure of resorcinarenes was finally determined in 1968 by *Erdtman* and associates.[22, 27]



2

R = Alkyl

Figure 1.4. Resorcinarenes structure proposed by *Nierdel and Vogel* and confirmed by *Erdtman*.[22, 26] The official IUPAC name for resorcinarene **2** is 2,8,14,20-tetraalkylpentacyclo [19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octa-cosa-1-(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodeca-ene-4,6,10,12,16,18,22,24-octol.

Gutsche[2] and *Vicens*[28] classified these molecules as calixarenes by calling them calix[4]resorcinarenes, or resorcinol-derived calix[4]arenes. Some other names, including Högberg compounds[29] and octols[30, 31] also appear in the literature. In the absence of any suitable trivial name in the literature, *Schneider* and *Schneider*[32] suggested the name resorcinarene in 1994.[33]

1.2 Resorcinarenes – Synthesis and Conformation.

1.2.1 Conformation.[22]

Calix[4]resorcinarenes are non-planar molecules, and they exist in different isomeric forms. The stereochemistry is generally defined by a combination of the following three stereochemical criteria (these criteria are not independent):

1. The *conformation of the macrocyclic ring*, which can adopt five symmetrical arrangements: the crown (C_{4v}), boat (C_{2v}), chair (C_{2h}), diamond (C_s), and saddle (D_{2d}) conformation (**Fig. 1.5.**).

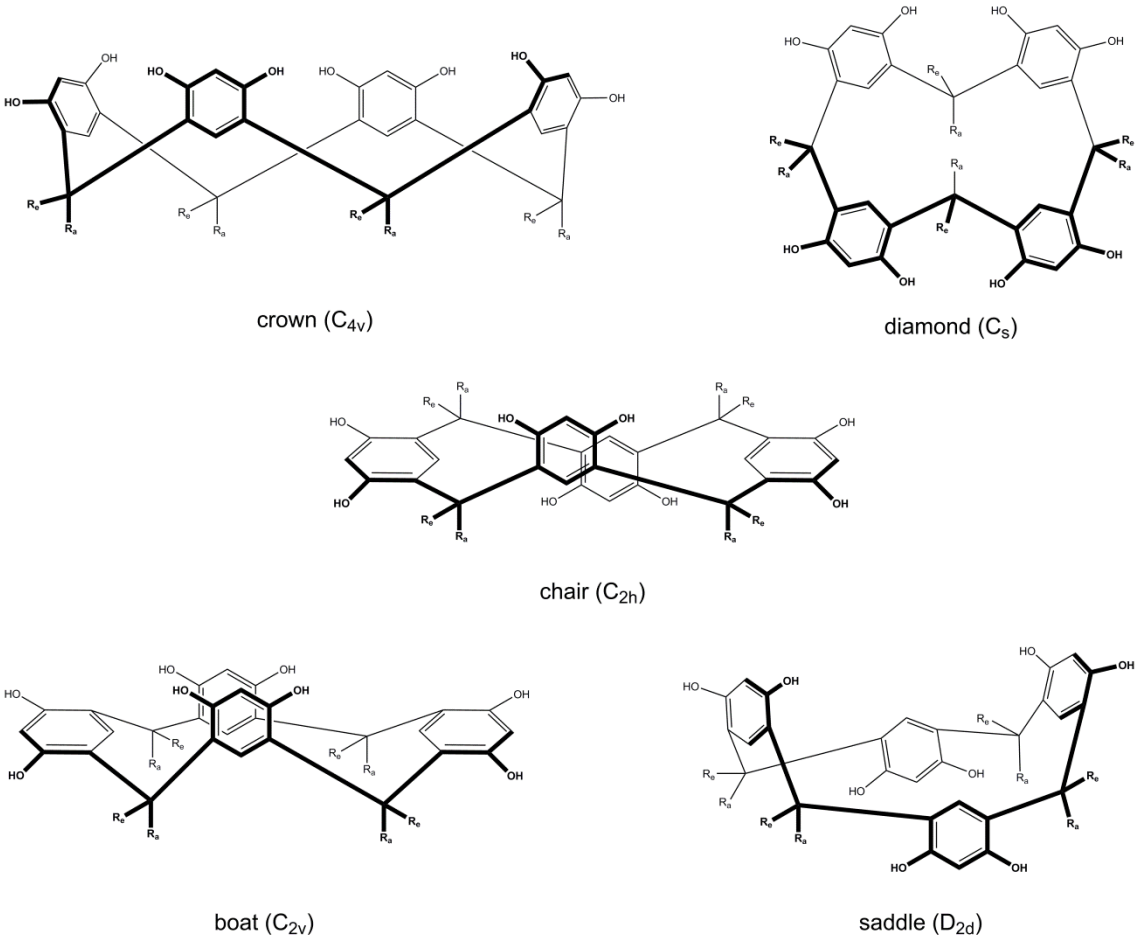


Figure 1.5. Conformation of the resorcin[4]arene macrocyclic ring, reproduced from *Timmerman et al*.[22]

2. The *relative configuration of the substituents at the methylene bridges*: all-cis (ccc), cis-cis-trans (cct), cis-trans-trans (ctt), and trans-cis-trans (tct) arrangement (**Fig. 1.6.**).

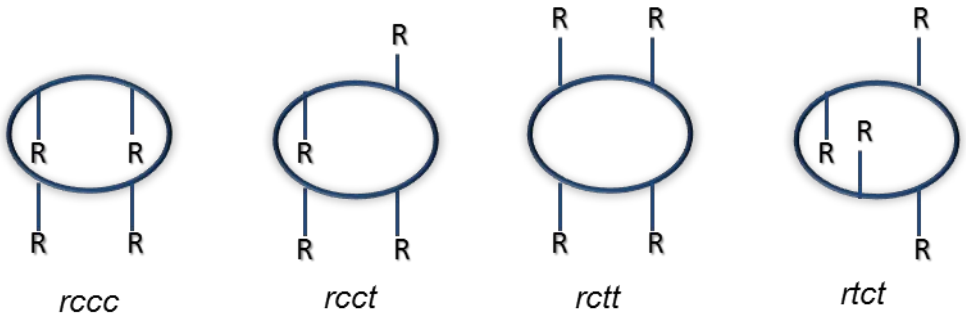


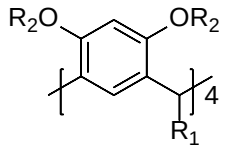
Figure 1.6. Relative configuration of the substituents at the methylene bridges.

3. The *individual conformation of the substituents at the methylene bridges*, which may be either pseudo-axial or pseudo-equatorial.

Combining these stereochemical elements a vast number of possible stereoisomers can be obtained. However, only a limited number have been reported experimentally. All diastereoisomers can be produced during the synthesis, but, the ratios can be manipulated by modifying the reaction conditions, such as: choice of solvent (solubility), dilution, reaction time and temperature (stability of the different isomers).[34]

In 1996, *Timmerman*[22] publishes "*Resorcinarene*" where the group analyses a study by *Weinel* and *Schneider*[34], in which the diastereoisomers formation ratio is manipulated by experimental modification of the reaction conditions. The results of the study are presented below:

1. *Thermodynamics*: the product ratio is mainly determined by the thermodynamic stability of the different isomers, because the condensation reaction is reversible under such conditions. Weinelt and Schneider[34] published in 1991 "*Mechanisms of Macrocycle Genesis. The Condensation of Resorcinol with Aldehydes*", in which they carried out an isomerization experiment in order to study the thermodynamic stability of the different isomers (**Fig. 1.7.**).



a = boat conformation; **b** = chair conformation;

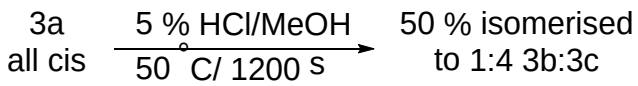
c = diamond conformation; **d** = saddle conformation.

Compound **3**: R_1=CH_3, R_2=H

Compound **4**: R_1=C_6H_5, R_2=H

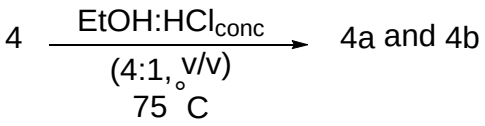
Figure 1.7. Isomerization study by *Winelt and Schneider*.[34]

The experiment concluded that at 50 °C the boat (ccc) isomer **3a** is slightly more stable than the diamond isomer **3c** (ctt), leaving the chair isomer **3b** (ctt) as the least stable (**Scheme 1.**).



Scheme 1. Resorcinarene isomerization temperature study results by *Winelt and Schneider*.[34]

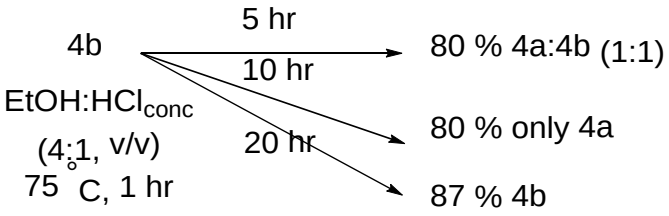
2. *Solubility in the reaction solvent*: if in the reaction one or more products precipitate out, the product ratio at the equilibrium is determined by the relative solubilities of the different isomers in the reaction solvent (**Scheme 2.**).



Scheme 2. Resorcinarene isomerization solvent study results by *Winelt and Schneider*.[34]

During the experiment, only isomers **4a** and **4b** were obtained due to precipitation in the solvent system; **4c** was not detected.

3. *Reaction time*: isomers can form or degrade with time (**Scheme 3.**).



Scheme 3. Resorcinarene isomerization time study results by *Winelt and Schneider*.[34]

These results conclude that precipitation of the least soluble isomer serves as a thermodynamic sink.

4. *Functional groups, intra- and intermolecular interactions*: for example, if R_1 is a long chain, that increases the solubility, than precipitation of products will be affected. When the upper rim is functionalized with free hydroxyl groups, the ratio of isomers can be affected by the solvent, which influences the formation of intra- and intermolecular hydrogen bonds.

1.2.2 Synthesis and formation mechanism.

Resorcinarenes are conveniently synthesized in high yields from the one step acid catalysed reaction of resorcinol or resorcinol ethers with various aldehydes.[32, 33] A reaction scheme outlining the preparation of resorcinarenes is shown in **Fig. 1.8**.

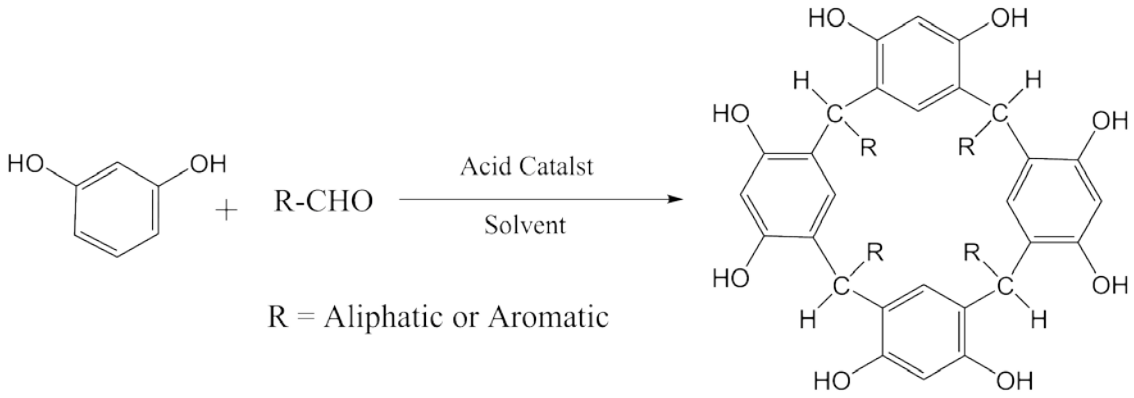


Figure 1.8. General scheme for acid catalysed condensation of resorcinol and aldehydes to afford resorcin[4]arene.[35, 36]

This condensation reaction can be carried out in the presence of a solvent (generally alcohols such as methanol and ethanol) and an acid catalyst. Reaction mixtures are heated under reflux for 30 min to several hours and the products formed are crystallized out from the solution on cooling.[35, 37]

"Macrocyclization is favored by the following: (a) fast degradation of oligomers, (b) fast ring closure of tetramers, as well as (c) fast chain growth to these in comparison to ring opening."[34]

Resorcinarenes obtained from the resorcinol-aliphatic or aromatic aldehydes reactions (**Fig. 1.9.)** are presented in **Table 1**.

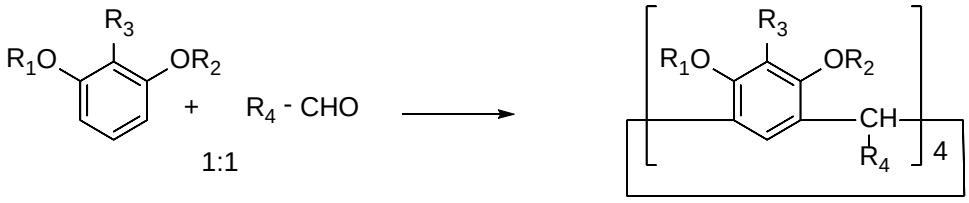


Figure 1.9. General scheme resorcin[4]arene synthesis.[1, 37]

Table 1. Influence of substituents on the yield of resorcinarene synthesis, in a study by *Tunstad*[35] and *Hogberg.*[1, 37]

Entry	R_1	R_2	R_3	R_4	Yield (%)
1	H	H	H	CH_3	88
2	H	CH_3	H	CH_3	2
3	CH_3	CH_3	H	CH_3	0.2
4	H	H	H	Ph*	90
5	H	H	H	2-OH-Ph	78
6	H	H	H	4-OH-Ph	91
7	H	H	H	4- CH_3-Ph	94

The results in **Table 1** show that, when the hydroxyl groups of resorcinol are substituted with methyl ether groups, then the resorcinarene formation yields are very low. This indicates that the activation of benzene ring positions in the resorcinol molecule by the hydroxyl groups is important for the reaction of the aldehydes to form the cyclic structures. With the unsubstituted resorcinol, resorcinarenes were produced in good yields with aliphatic and aromatic aldehydes.[1,37]

The resorcinarenes were found to be higher melting solids. In order to determine the effect of alkyl chain length of an aliphatic aldehyde on the physical properties of resorcinarenes, compounds were made using different aldehydes. The results are presented in **Table 2**.[1,37]

Table 2. Resorcinarenes: effect of varying alkyl chain length of aldehydes, data from *Tunstad*[35] and *Hogberg*.[1, 37]

Entry	R – CHO; R =	Yield (%)	m.p. (°C)
1	CH_3	60	> 360
2	$CH_2 – CH_3$	88	> 360
3	$(CH_2)_2CH_3$	92	> 360
4	$(CH_2)_3CH_3$	89	344 – 345
5	$(CH_2)_4CH_3$	77	329 – 330
6	$(CH_2)_{10}CH_3$	68	285

From this study (**Table 2.**) it was clear that, when the aldehyde alkyl chain length was increased, the resorcinarenes produced were observed to be more soluble in hexane, benzene and chloroform solvents. In addition, the melting points were found to decrease with increase in chain length of the aldehydes.[1, 35, 37]

Weinelt and *Schneider*[1, 34] studied the resorcinarene formation mechanism and, using ^{1}H NMR spectroscopy, they concluded that the mechanism is a step-wise condensation to give the linear tetramer **5**, which undergoes a fast cyclization due to H bonding formation, to give the cyclized tetramer **6**.

A mechanism proposed for the formation of resorcinarene from the hydrochloric acid catalysed condensation of resorcinol with acetaldehyde in the presence of methanol solvent is shown below (**Fig. 1.10.**).[34]

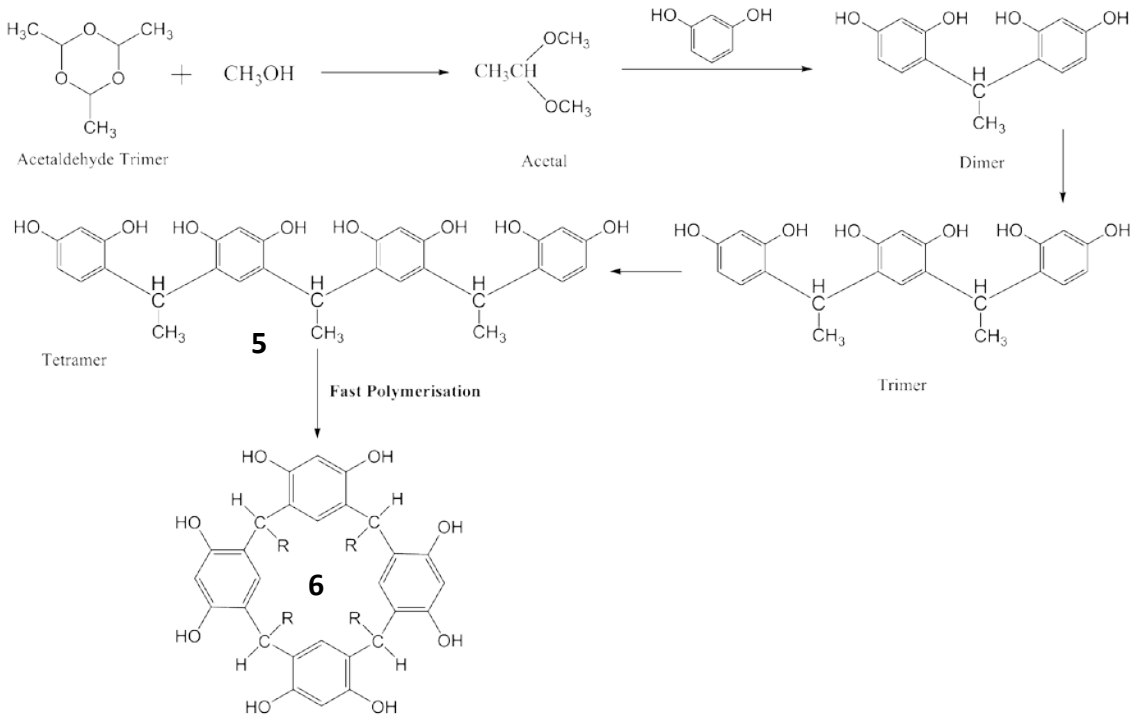


Figure 1.10. Mechanism of resorcinarene formation from resorcinol and aldehyde, proposed by *Weinelt* and *Schneider*.[1, 34]

1.3 Resorcinarenes – Applications.

The 8 hydroxyl groups present in the structure give them the possibility to form complexes with organic molecules such as neutral molecules, metals and ammonium cations. Resorcinarene complexes may serve as *enzyme metalosite models, redox sensors, selective extractants for radioactive ions and molecular magnetic materials.*[1] Significant industrial applications for resorcinarenes have been reported.[2] Current interests in the possible applications include *binding and incorporation of guest compounds.*[3, 4]

Nanoparticles are used to develop new generations of stronger materials for applications ranging from the medical to aerospace. These particles are often fragile and unstable. When their surfaces are touched, they may lose their properties and structure. Resorcinarene molecules have bowl-shaped heads which can enable them to adhere readily to the surface of nanoparticles. Gold nanoparticles (10-20 nanometers diameter) were successfully encapsulated with resorcinarene.[38] By this

process, a polymer cage was created around the surface of gold particles by chemically stitching the resorcinarene together. The porous coating of gold nanoparticles then permits them to interact with the substances outside the coating but prevented them from touching each other. This process has significant impact on the physical properties and stability of nanoparticles. Potential uses of nanoparticles with resorcinarenes could be, for example, in the *drug delivery* applications. This method can be employed to stabilize nanoparticles with magnetic properties that may be used in the development of *microelectronic devices and magnetic sensors*.

Resorcinarenes and structurally similar macrocyclics have drawn much attention in the last years, which saw *Jean-Marie Lehn* win the Nobel prize in 1987 for his work in the area. The chemistry of these large oligomeric species is best known for '***host-guest***' interactions, otherwise known as ***supramolecular chemistry***. Defined by *Lehn* as the "*chemistry of molecular assemblies and of the intermolecular bond*", supramolecular chemistry encompasses the non-covalent interactions between 'host' and 'guest' molecules, autonomous processes such as 'self-assembly' and 'self-organization' of molecular devices and systems and recognition between molecular systems, functions that recall with those of complex proteins and their intermolecular interactions.[39, 40]

In typical molecular chemistry, individual precursors react chemically, resulting in direct bonding and interactions driven by factors such as activation energies of the precursors, their chirality and rotation of groups around bonds. The overall resulting species is permanently distinct from any of its parent species; chirality may have been changed or removed, the shape may be unique to the molecules and the chemical reactivity and energies will differ.[39, 40, 41]

With supramolecular interactions, a large 'host' species with a complementary cavity or hole available for binding (i.e. a macrocyclic oligomer) interacts with a smaller 'guest' molecule, typically a monoatomic ion, larger ion or sometimes a more sophisticated species (a chemical substrate, hormone etc.) , forming a *'host-guest complex' or 'supermolecule'* (**Fig. 1.11.**).[41]

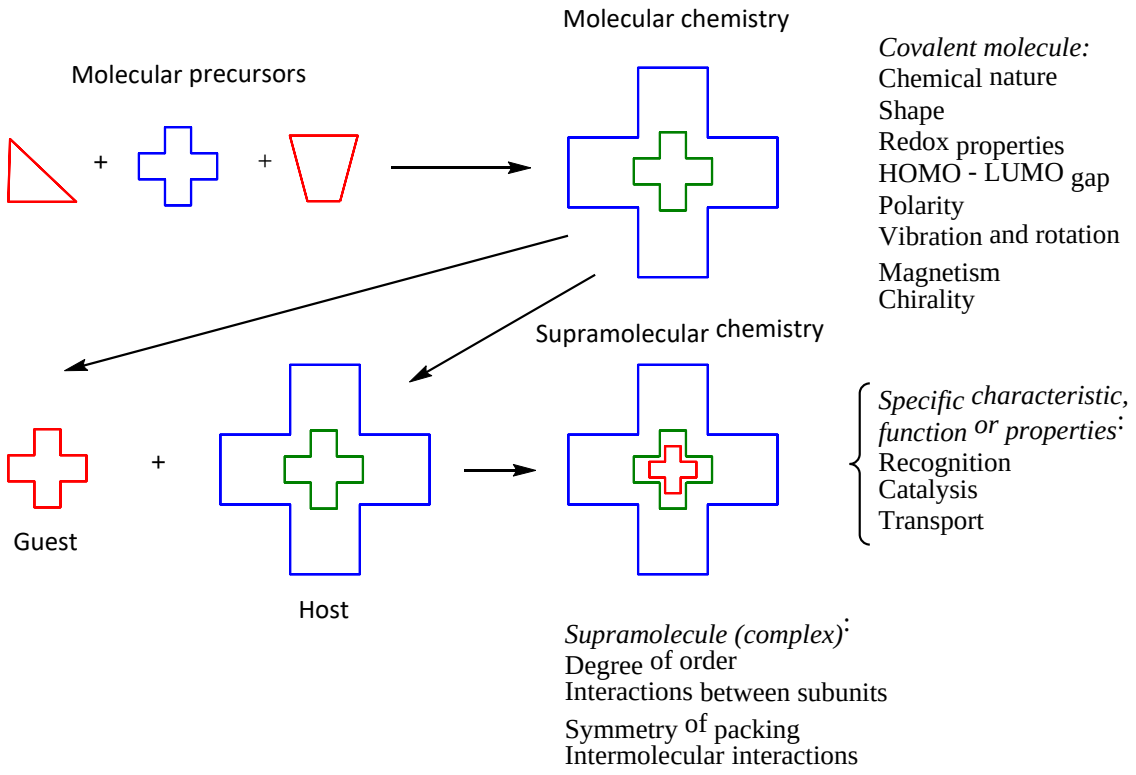


Figure 1.11. Comparison between the scope of molecular and supramolecular chemistry according to *Lehn*.[40]

The host-guest complex is typically stabilized by interactions between binding sites, such as hydrogen bond donors, electron pair donors, and binding sites, such as a Lewis acidic cation, a halide anion/hydrogen bond acceptor. Some examples of host-guest pairs are described in **Table 3**.[42]

Table 3. Classification of common host-guest compounds of neutral hosts.[42]

Host	Guest	Interaction	Class	Example
Crown ether	Metal cation	Ion – dipole	Complex (cavitand)	$[K^+([18]crown-6)]$
Spherand	Alkyl ammo-nium cation	Hydrogen bonding	Complex (cavitand)	Spherand . $(CH_3NH_3^+)$
Cyclodextrin	Organic molecule	Hydrophobic / van der Waals	Cavitate	(α-cyclodextrin) (p-hydroxybenzoic acid)
Water	Organic molecule, halogen etc.	Van der Waals / crystal packing	Clathrate	$(H_2O)_6$. (CH_4)

Table 3. Continuation.

Host	Guest	Interaction	Class	Example
Calixaarene	Organic molecule	Van der Waals / crystal packing	Cavitate	(p-t-butylcalix[4]arene) . (toluene)
Cyclotriveratrylene (CTV)	Organic molecule	Van der Waals / crystal packing	Clathrate	(CTV) 0.5 (acetone)

Macrocycles are very useful in *supramolecular chemistry*, as they provide whole cavities that can completely surround guest molecules and may be chemically modified to provide targeted properties.[43]

In the case of resorcinarenes, cavitands are synthesized by the covalent linking of neighbouring resorcinolic hydroxyl groups as shown in **Fig. 1.12**.[44] Cavitands are extremely rigid molecules, but the possibility of multifunctionalization may make them suitable candidates for synthetic enzymes for example. Two cavitands are covalently linked *via* their upper rims to form the carcerands.[5]

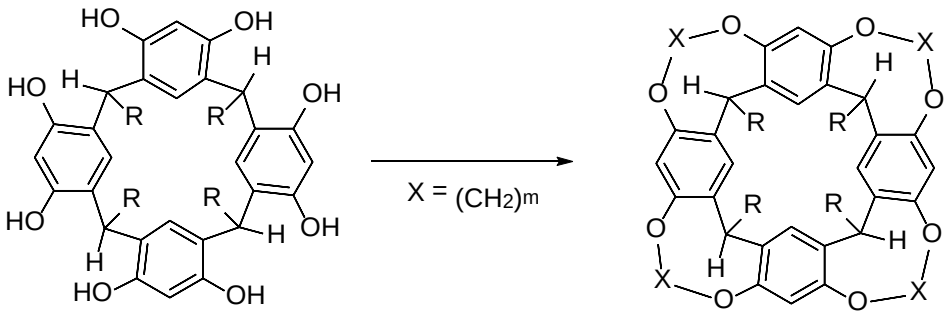


Figure 1.12. Cavitands forming process, starting from resorcinarenes.

Common metallacycle shapes in these types of applications include triangles, squares, and pentagons, each bearing functional groups that connect the pieces by self-assembly.[43] An example of this kind of host-guest system is presented in **Fig. 1.13**.

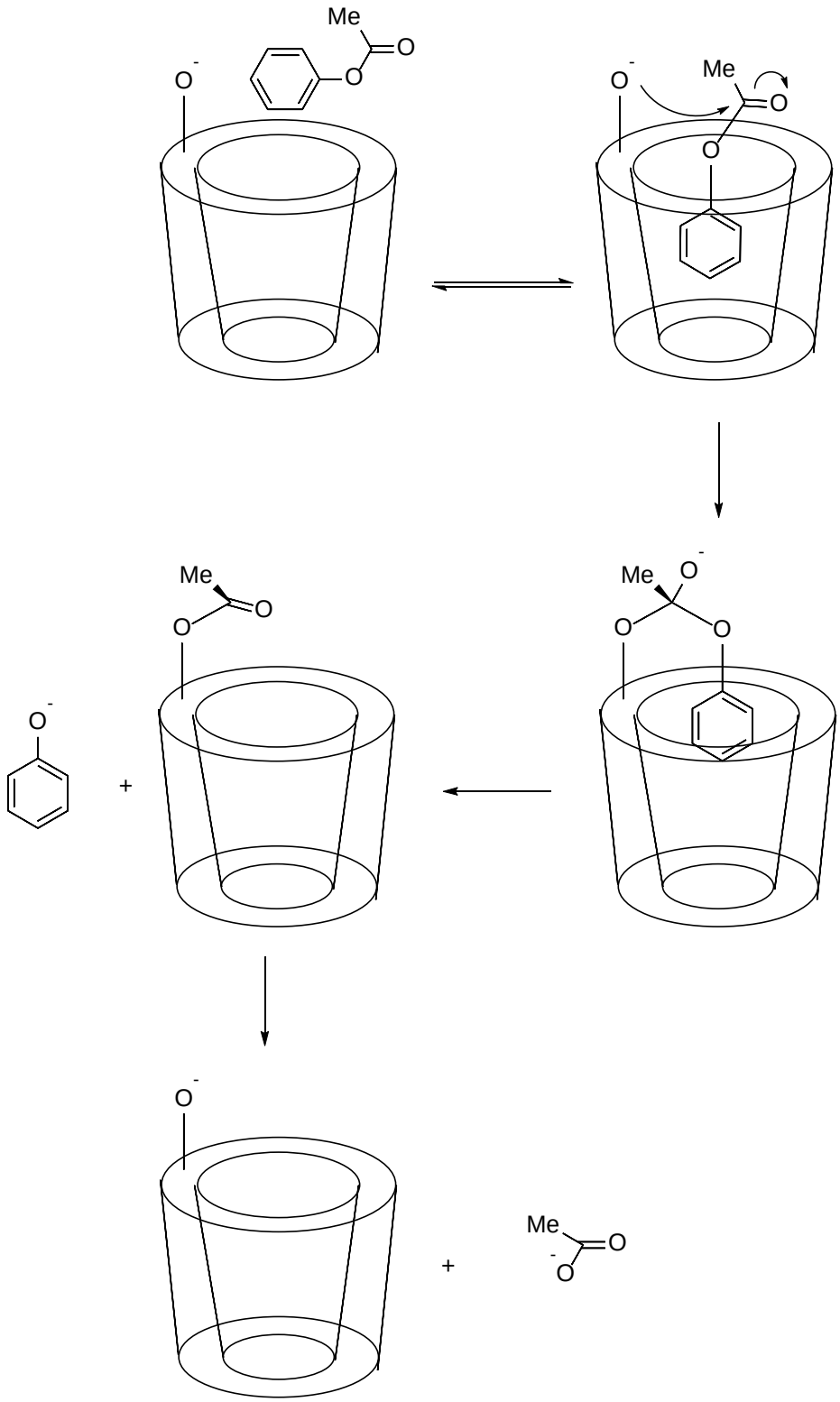


Figure 1.13. Mechanism of ester hydrolysis by ß-evelodextrin, after *Diederich*.[39]

"Due to the shape and functionalization, resorcinarenes are perfect carcerand hosts. Intracavity inclusion of a wide range of aromatic guest molecules in a 1:1 fashion has been observed for numerous calix[n]arenes. A wide range of ***inclusion complexes*** *are formed by both calix[4]arenes and [4]resorcinarenes with aromatic and aliphatic guests (haloalkanes, acetone, DMD, DMSO, etc.), generally stabilized by a range of weak interactions of the C – H - - - π type. Calix[5]arenes also possess a well-defined cavity and form similar complexes, whereas the higher calixarenes such as calix[6]arenes and calix[8]arenes form much less well defined cavities and do not exhibit the formation of such well-defined encapsulated species."*[39]

Another interesting species are the carcerand hosts, which are not limited to resorcinarene derivatives. *Timmerman*[22] prepared the mixed [4]resorcin – calix[4]arene host (**Fig. 1.14.**) arasing from face-to-face coupling of the two different bowl-shaped macrocyclic hemispheres.

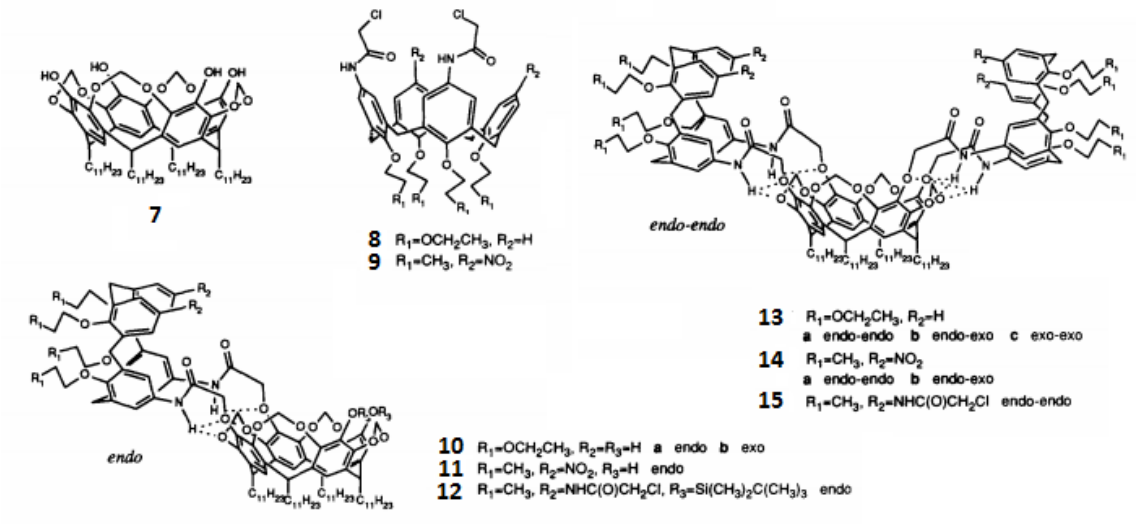


Figure 1.14. Synthesis of mixed carcerands, reproduced from *Timmerman*.[22]

While resorcinarene carcerands are essentially spherical or elongated curved-ended cylinders, the cavity in the compounds in **Fig. 1.14.** are more egg-shaped, making it highly unsymmetrical, with the wider, shallower resorcinarene cavity forming the base of the egg and the deeper, narrower calix[4]arene forming the tip. Furthermore, the carcerand cavity can be used as micro-reaction vessels, that isolates and protects the hosts from the outside medium.

Catalysis is a major application of supramolecular chemistry. Because their unique shape and functionalities, these compounds bind reactants into conformations suitable for reaction, thus lowering the transition state energy of the reaction.

Supramolecular chemistry is also important in the **pharmaceutical industry** and research, as these types of compounds can *encapsulate* and have a *targeted release mechanism.*

Other applications of resorcinarenes include: ion chromatography columns[5], dyes[6], membranes/films[7], supported liquid membrane (SLM)[8], polymer inclusion membranes (PIM)[9], biomimetic membranes[10], ligands in metal chemistry[11], chiral NMR solvating agent[12], detecting electrodes[13], biomimetic and biomedical applications[14], biopharmaceutical applications[15], chromatographic separation and analysis[16], chemosensors[17], electrical and optical applications[18], electrochemical sensors[19], chemical imaging[20], data storage and amperometric detectors[21].

1.4 Aim and Project Strategy.

Resorcinarenes are widely used in many fields, including as synthetic enzymes. They behave as cavitands, hosting H_2O molecules or metal ions, for metabolic reactions catalysis. Thus there is a need for further investigation into how these molecules can mimic enzymes. The cavitands add a recognition element to this and can discriminate between differently sized molecules that display the same functionality; something for which small-molecule catalysts are ill suited.[45]

Calixarenes are bowl-shaped molecules, well known as hosts for small molecules and ions. One type of calix[4]resorcinarenes[46], is easily prepared, and the three-dimensional shapes and efficacy as hosts of these materials has been thoroughly studied.[47]

Resorcinarenes have several factors that make them suitable for being artificial enzymes: they are easily prepared in high yields, from cheap material, they have a cone shape, mimicking the inner enzyme binding sites/cavities, and they have

functionalities that can be easily derivatised into targeted functionalities that resemble the ones of the enzymes.[48]

The aim of the project is to design and synthesize new molecules, "calyxzymes" that can function in a similar way to enzymes, by providing a binding pocket coupled with functionality for catalysis, but with the additional facility to catalyse two or more sequential reactions.

First objective was to monofunctionalize with the desired groups: amines, esters, ethers, carboxylic acids, alcohols, boronic acids; subsequent step was to try to couple them and ad two or more functionalities on the same rim, step which was found challenging due to steric hindrance and low reactivity of the monosubstituted derivatives, all reactions taking long time or high temperature and/or pressure.

A challenge in the design of enzymes is that multiple properties, including substrate binding, transition state stabilization and product release, must be simultaneously optimized.

So this project counts on the resorcinarenes properties such as flexibility, their versatility as scaffolds and host molecules, to generate structures that function in selective molecular catalysis of several sequential processes. The long-term vision is that this work will open new possibilities for the design and synthesis of molecules that can function as artificial enzymes for the catalysis of a wide range of chemical and biochemical processes.

Below are listed a few literature examples, in which resorcinarenes upper rim is functionalized in such way that they act as enzymes, being able to catalyse different reactions.

In 2004, *Rebek*[49] published "*A Functionalized, Deep Cavitand Catalyzes the Aminolysis of a Choline Derivative*", where he attaches a pyridone moiety on a resorcinarene cavitand **16** (**Fig. 1.15.**) which catalyses the aminolysis of choline derivative. In this case, the resorcinarene substrate acts as an esterase, providing a cavity, binding sites and rotation of the pyridone into and out of the cavity, which is restricted by steric clashes with the neighbouring amides.

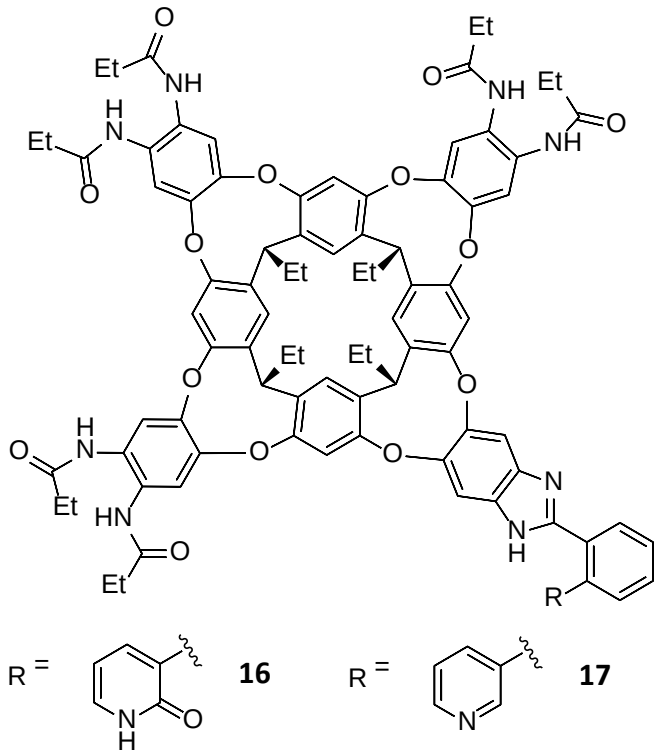
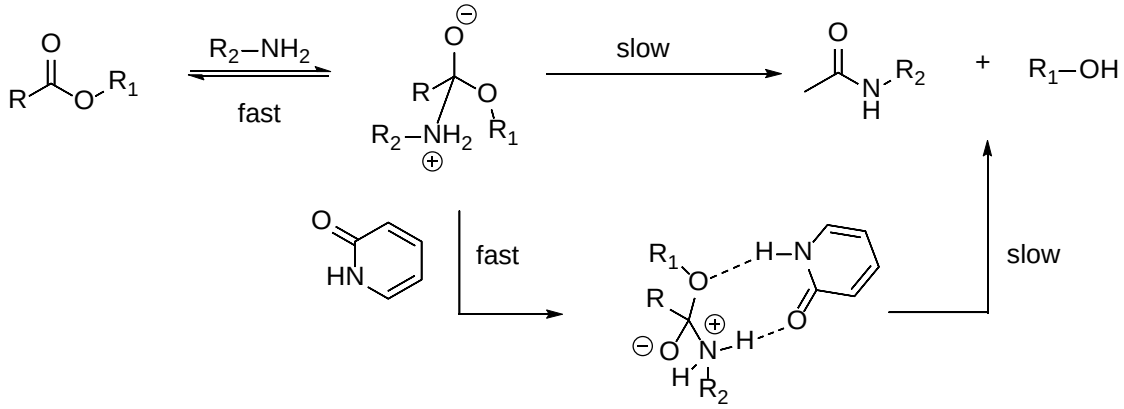


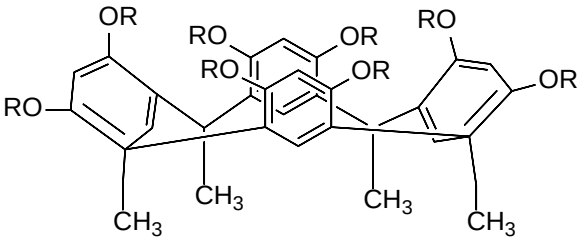
Figure 1.15. *Rebek's* calyxzyme.[49]

A proposed mechanism for the pyridone-catalysed aminolysis of esters is sketched in (**Scheme 4.**).



Scheme 4. *Pyridone* – catalysed aminolysis of esters, reaction pathway proposed by *Rebek*.[49]

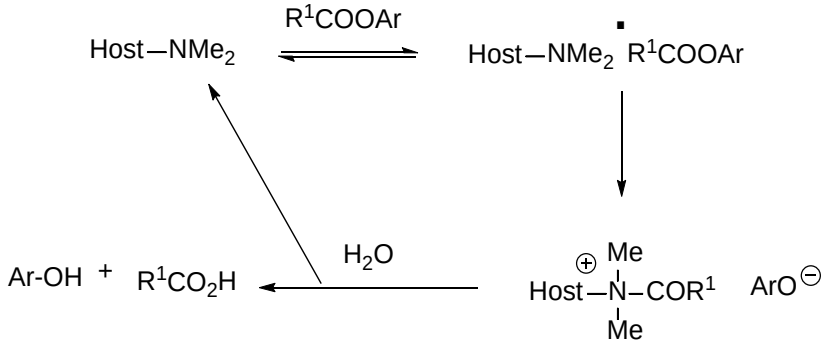
Another interesting example is reported by *Williams*[48] in which an octa(dimethylaminopropyl)calix[4]arene is a primitive artificial estearase for 4-nitrophenyl esters (**Fig. 1.16.**).



18a R = H
18b R = CH_2COOEt
18c R = $CH_2CONH(CH_2)_3N(CH_3)_2$

Figure 1.16. *Williams's* artificial estearase, based on resorcinarenes °C substrate.[48]

These resorcinarene-based compounds offer both binding site and catalytic function within the same molecule, making them candidates for artificial enzymes. A proposed mechanism for the catalysed reaction is shown in (**Scheme 5.**).

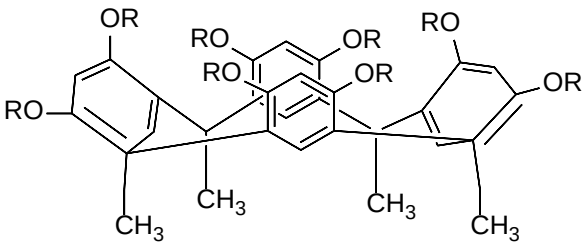


Scheme 5. Proposed catalytic reaction scheme of resorcinarene catalyst, by *Williams*.[48]

In 2006, *Cevasco*[50] published "*Catalysis and inhibition of ester hydrolysis in the presence of resorcinarene hosts functionalized with dimethylamino groups*" in which the research group builds water soluble N,N-dimethylamino functionalized resorcinarenes frameworks (**Fig. 1.17.** – compounds **19-23**), which are further used to

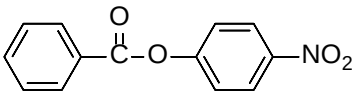
catalyse in the hydrolysis of carboxylate and sulfonate esters of 4-nitrophenol and 2,4-dinitrophenol (**24**, **25**, **26**). The resorcinarene-based structures are good candidates for synthetic enzymes, due to their concave regions for substrate complexation and functionalities that are potential nucleophilic catalysts.

Catalysts:



Compounds for hydrolysis:

19 R = H
20 R = $CH_2CO_2C_2H_5$
21 R = $CH_2CONH(CH_2)_3N(CH_2)_2$
22 R = $(CH_2)_3CO_2C_2H_5$
23 R = $(CH_2)_3CONH(CH_2)_3N(CH_3)_2$



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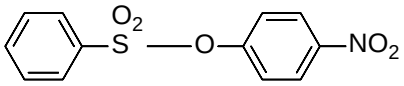

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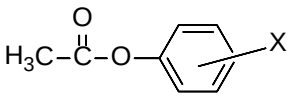

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Figure 1.17. Structures of N,N-dimethylamino functionalized resorcinarenes catalysts by *Cevasco*.[48]

Calixarene-related research has previously been centred largely on the synthesis of achiral molecules, and on simple complexation phenomena, mostly with metal ion and simple molecules such as amines and their salts. This project, in contrast, seeks to take advantage of the resorcinarene scaffold to build catalyst molecules designed for a range of reaction types. It brings together three strands of knowledge: of the synthesis and functionalization of the resorcinarenes, of their special shape selectivity and binding properties for organic molecules and of multifunctional catalysis. Further, the potential of bifunctional catalysis in particular has been recognised[51], with aminoboronic acids being promising green, non-transition-metal catalysts.[52]

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CHAPTER II: Results and Discussions.

2.1 Synthesis of resorcin[4]arene starting material 38.

Interest in resorcinarene chemistry has increased in the last years, as they provide a diverse range of molecular assemblies that have significant pharmaceutical properties and applications in industry and synthesis. As well as their importance to science they are conveniently and easily prepared in high yields from the one step acid catalysed reaction of resorcinol or resorcinol ethers with various aldehydes, making these type of structures accessible.[1,2]

In 2012, *Sardjonoa*[3] published "*Green Synthesis of Some Calix[4]resorcinarene under Microwave Irradiation*", in which he reported a green synthetic procedure for the preparation of some calix[4]resorcinarenes from vanillin (**Fig. 2.1.**), cinnamaldehyde (**Fig. 2.2**) and anisaldehyde (**Fig. 2.3**), using a household microwave. This method is a very rapid heating alternative to the conventional method that involves very long reaction times (from 20-24 hr in conventional heating to 5-8 min in microwave irradiation), as well as a green method because of the minimum amount of solvents used.[3]

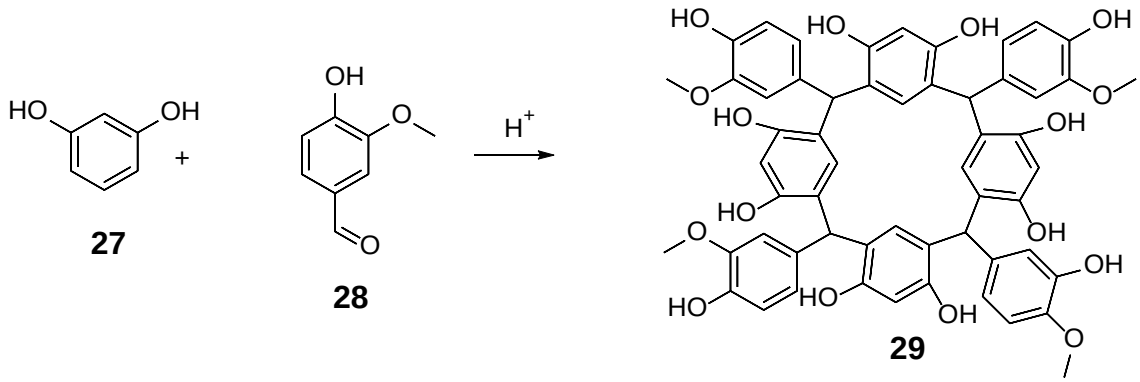


Figure 2.1. Resorcinarene synthesis from resorcinol and vanillin, protocol by *Sardjonoa*.[3]

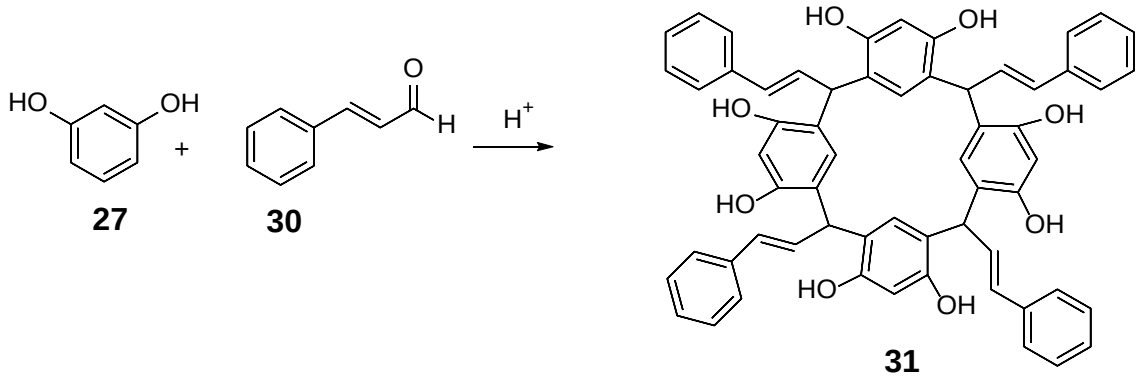


Figure 2.2. Resorcinarene synthesis from resorcinol and cinnamaldehyde, protocol by *Sardjonoa*.[3]

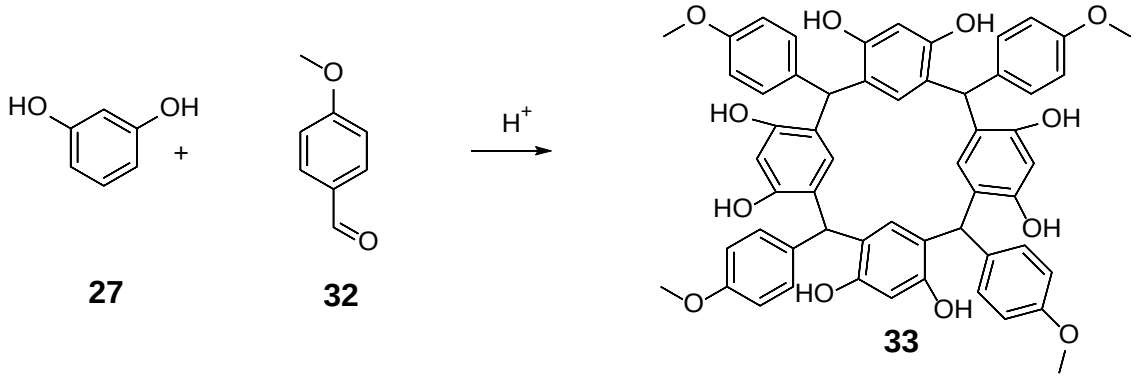
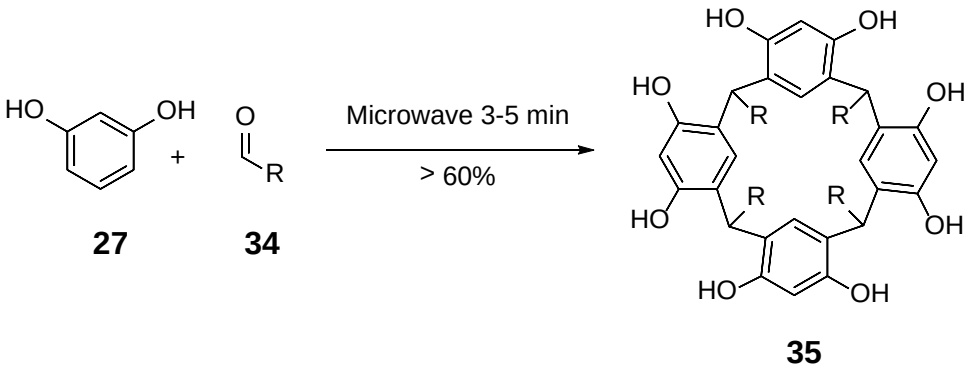


Figure 2.3. Resorcinarene synthesis from resorcinol and anisaldehyde, protocol by *Sardjonoa*.[3]

In 2006, *Hedidi* published "*Microwave-assisted synthesis of calix[4]resorcinarenes*" in which the group reported a green efficient pathway for resorcin[4]arenes with both aliphatic and aromatic aldehydes (**Fig. 2.4**).[4]



27 **34** **35**

Figure 2.4. Synthesis of resorcinarene by cyclocondensation of resorcinol and aldehydes, protocol by *Hedidi*.[4]

In the cited work,[4] the group compared the times between the microwave-assisted reaction and the classical heating reaction. They use catalytic amounts of TPA or HCl, reaction which takes 3 to 5 min to reach completion using the microwave-assisted protocol, but using the classical method it takes between 3 and 5 hours, depending on the substrates.

The substrates, reaction times and yields are recorded in the table below, and according to the group's findings, the acid plays a crucial role during the dehydration step, as very low yields were obtained when reactions were carried out without it (**Table 4**).

Table 4. Microwave – assisted cyclocondensation of resorcinol and aldehydes, study by *Hedidi*.[4]

	Conditions				
R -	**Power (W)**	**Time (min)**	**T (°C)**	**Yield (%)**	**m.p. (°C)**
p-But-*O*-C_6H_4	---	600	80	85	> 300
	100	3	80	96	
	---	300	80	78	
	300	5	108	91	
CH_3	---	600	80	60	> 300
	100	3	80	88	
	---	300	80	67	
	300	5	108	89	
$CH_3(CH_2)_3$	---	600	80	69	> 300
	100	3	80	82	

Table 4. Continuation

	Conditions				
R -	**Power (W)**	**Time (min)**	**T (°C)**	**Yield (%)**	**m.p. (°C)**
$CH_3(CH_2)_3$	---	300	80	91	
	300	5	108	88	
$CH_3(CH_2)_4$	---	600	80	87	> 300
	100	3	80	95	
	---	300	80	88	
	300	5	108	91	
$CH_3(CH_2)_6$	---	600	80	79	> 300
	100	3	80	93	
	---	300	80	84	
	300	5	108	91	
$CH_3(CH_2)_7$	---	600	80	82	280
	100	3	80	96	
	---	300	80	91	
	300	5	108	90	
$CH_3(CH_2)_8$	---	600	80	84	295
	100	3	80	93	
	---	300	80	87	
	300	5	108	89	
$CH_3(CH_2)_{10}$	---	600	80	85	285
	100	3	80	93	
	---	300	80	---	
	300	5	108	90	
C_6H_5	---	600	80	88	300
	100	3	80	94	
	---	300	80	78	
	300	5	108	95	

"The difference between reaction times can be explained by the fact that the conventional heating is an inward heat transfer, while in the case of microwave irradiation, the thermal energy is generated in situ due to the interaction of polar molecules or ionic species with the electric field. Physical acceleration (higher temperature) or chemical activation (enhancement of dipole moment) could happen using microwaves, which reduces reaction times and enhance yields in comparison with conventional reflux reaction conditions."[4] Although improved times for resorcin[4]arene synthesis have been reported by using microwave protocols, a classical method was chosen for this project, as similar yields are obtained and this makes it possible to scale-up the reaction.

In this project, 3-methoxyphenol was chosen as the resorcinol starting material unit, in the conditions described by *Mocerino*[5] leaving one hydroxyl group free on each aromatic ring. Hexanal was chosen for the condensation, forming the desired bowl-shape lower rim and as well contributing to a good solvation in organic solvents. The condensation reaction was carried out in DCM as solvent, being easy to remove, in the presence of $BF_3.OEt_2$ as the Lewis acid of choice, giving the desired chiral tetramer characterized by hydrogen bonding between the rings. A reaction scheme outlining the preparation of resorcinarene **38** is shown in (**Fig. 2.5**). Representation **38(a)** depicts the fact that, under the used conditions, a racemic mixture of resorcin[4]arene is obtained. In this reaction, the product that is obtained is **38(b)**, which adopts a crown conformation due to the hydrogen bonding. Structure **38(c)**, adopting a boat conformation, can be achieved by modifying the reaction conditions, such as temperature (thermodynamic stability of a certain isomer) and choice of solvent (solubility and interference with the hydrogen bonding), and is accessible in some of the later reactions, where this product is used.

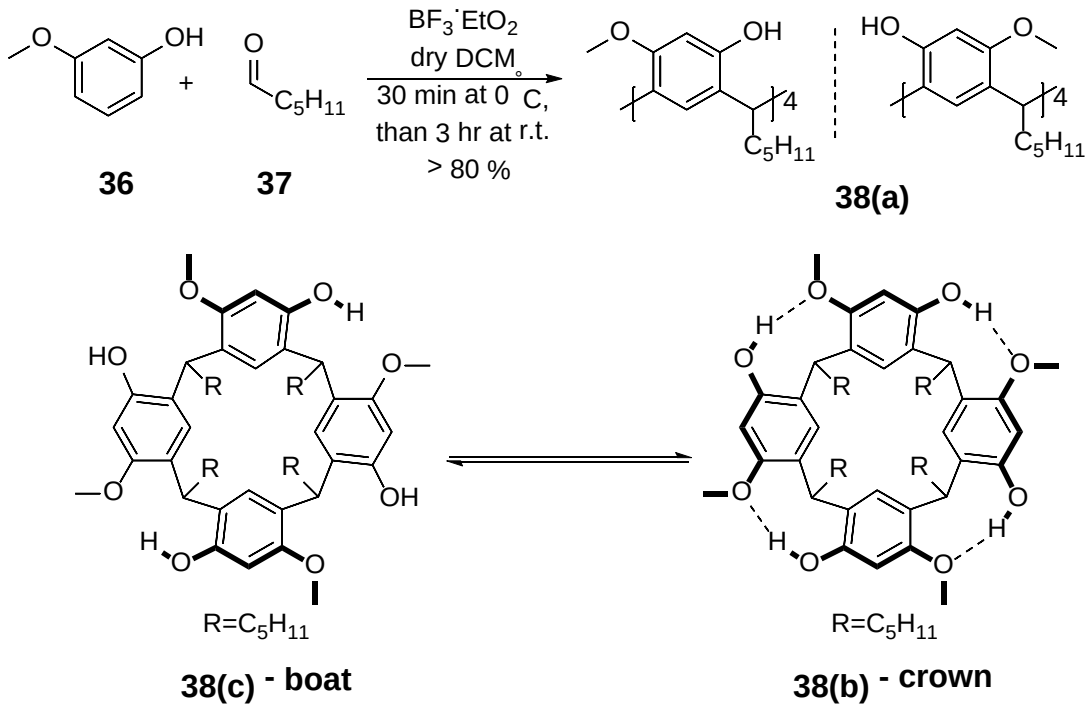


Figure 2.5. Synthesis of resorcinarene racemic mixture- **38a**; representation of hydrogen bonding interaction between hydroxyl groups- **38b, 38c**.

2.2 Monofunctionalization of resorcinarene 38 at the phenolic OH.

As discussed in Chapter I, the first step in this project's strategy was to attach different functional groups on the upper rim, functionalization occurring either on the ortho position (position 2) or at the phenolic OH group (position 1); followed by bifunctionalization as shown in (**Fig. 2.6**).

We were interested in preparing resorcinarene derivatives that are axially chiral and nitrogen-substituted on the upper rim. For our substrate this can happen either on the ortho position (the method for which is described in the following subchapter), or at the phenolic OH.

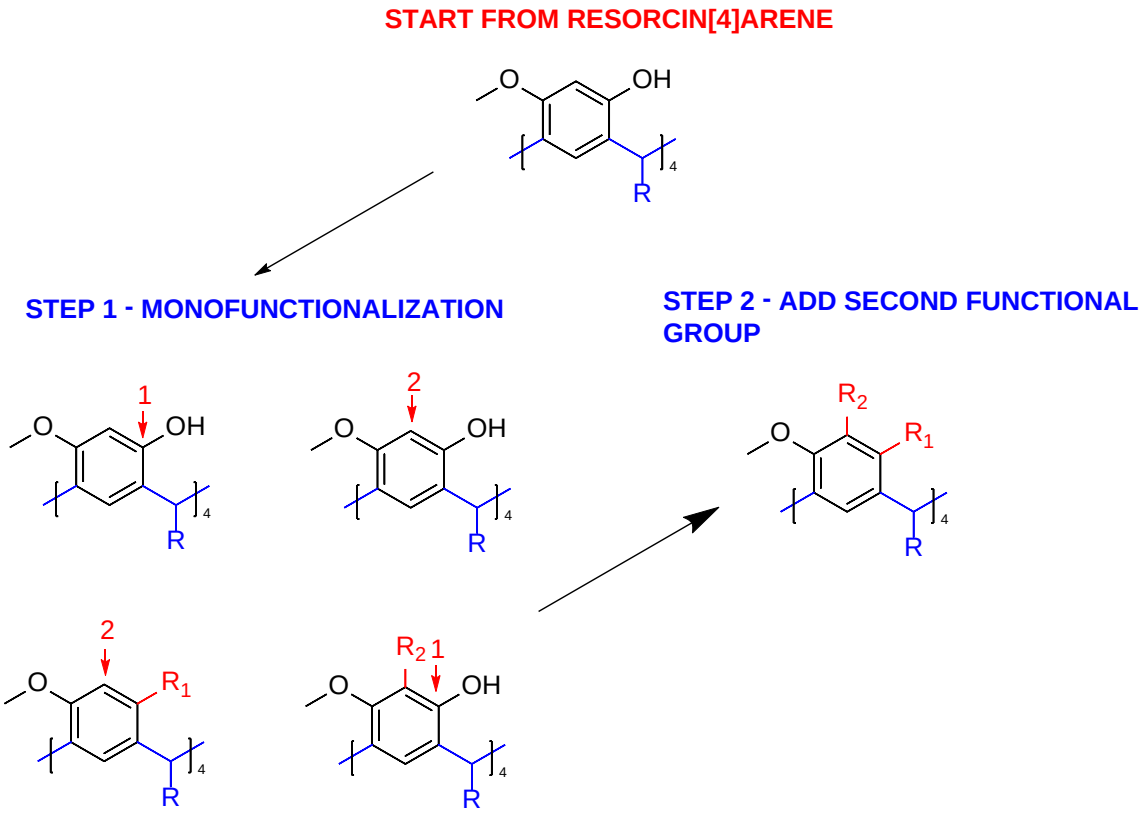


Figure 2.6. Multifunctionalization strategy.

Amination of aromatic compounds has been intensely studied in the last few years and has been achieved using a variety of different methods.[6] We searched for methods that use substrates similar to our starting material that gave good results in terms of yields and lack of secondary products.

In 2011, *Page*[7] published "*C4-Symmetric Alkoxyresorcin[4]arene Triflates: The Use of Palladium-Catalyzed Reactions in the Synthesis of Axially Chiral Derivatives with Amino- and/or Alkoxy-Substituents*", in which he reported a route that involved a triflate transformation of the phenolic hydroxyl group, followed by a palladium-catalysed Buchwald–Hartwig amination, giving the aminated resorcinarenes in good yields.[7]

2.2.1 Triflate protection of the phenolic OH of resorcinarene 38.

At this stage in the synthesis, two routes are possible to obtain the desired triflate intermediate. The first method is a one-pot reaction that allowed us to scale up the reaction having the downside of long reaction times (up to 12 hr).[7]

Compound **38** was treated with triethylamine and trifluoromethanesulfonicanhidride in dry DCM under nitrogen at -78 °C. After 15 minutes, the reaction mixture was allowed to reach room temperature and was then stirred overnight. Extraction and column chromatography separation afforded the desired compound **39** in good yields (89 %) (**Fig. 2.7.**).

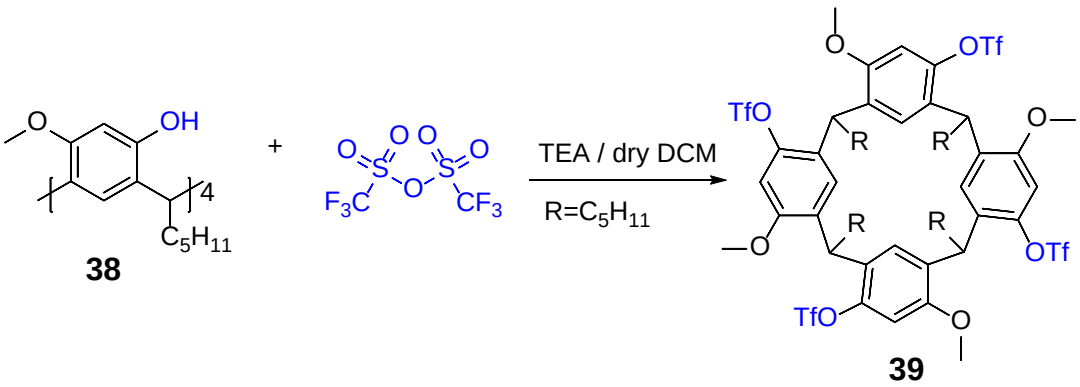


Figure 2.7. Triflation of resorcinarene using trifluoromethanesulfonicanhidride.

A more rapid route to triflate derivatives of phenols using *N*-phenylbis(trifluoromethanesulfonimide) and microwave irradiation has been reported[7], this microwave assisted method having improved times (5-20 min) but involving small scale reaction and less desirable yields.

Compound **38** was treated with K_2CO_3 and *N*-phenyl-bis(trifluoromethanesulfonimide) in dry MeCN under nitrogen. The reaction mixture was submitted to microwave

irradiation for five minutes, followed by extraction and crystallization, giving the desired compound **39** in lower yields (42 %) (**Fig. 2.8.**).

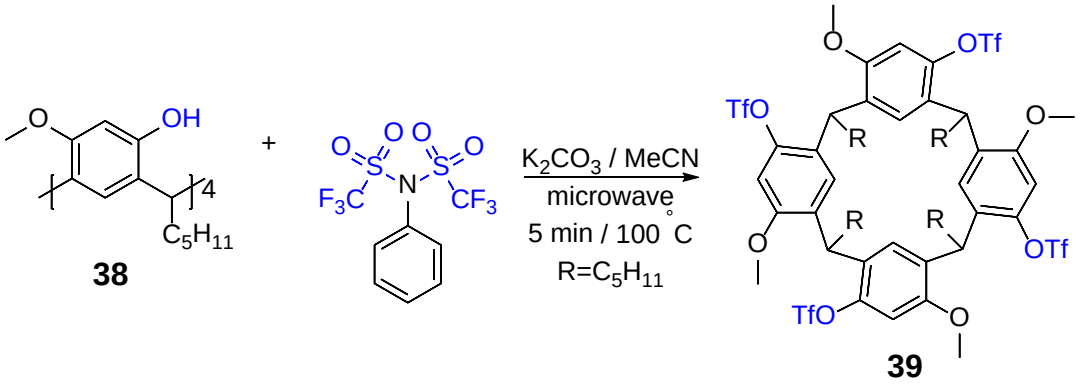


Figure 2.8. Triflation of resorcinarene **38** using *N*-phenyl-bis(trifluoromethanesulfonimide), to afford compound **39**.

2.2.2 Buchwald-Hartwig palladium-catalysed amination of triflated resorcinarene 39.

Formation of carbon-heteroatom bonds is widely used in synthetic chemistry.[8] The process involves the reaction of aryl halides/triflates with a palladium/phosphine complex.

In 1997, *Buchwald*[8] published "*Palladium-Catalysed Amination of Aryl Triflates*", where the research group proposed a plausible catalytic cycle for amination of aryl triflates, shown in (**Fig. 2.9.**).

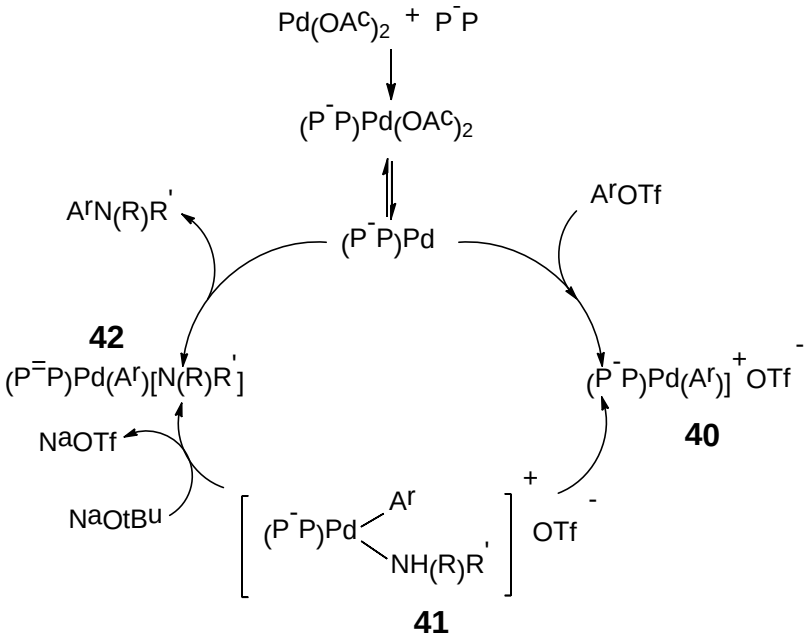


Figure 2.9. Proposed catalytic cycle for aryl triflate palladium-catalysed amination, by *Buchwald*.[8]

The proposed catalytic cycle consists of:[8]

a) In the first step, the two reagents $Pd(OAc)_2$ and bis-phosphine (P-P) react, forming the $[(P\text{-}P)Pd(OAc)_2]$complex. This complex is reduced to a Pd(0) species [(P-P)Pd].

b) Oxidative addition of aryl triflate forms the palladium aryl cation species **40** $(P\text{-}P)Pd(Ar)]^{+}OTf^{-}$.

c) Amine coordination follows to give complex **41**, where Pd is coordinated to both the aromatic moiety and the amine.

d) Complex **41** is deprotonated by $NaO^{t}Bu$ to afford palladium amido complex **42** (P-P)Pd(Ar)[N(R)R'].

e) Reductive elimination of complex **42** yields the arylamine and regenerates the Pd(0) catalyst.

Different protocols were investigated by *Page*,[7] our best results in the case of resorcinarenes being obtained by using a standardized protocol that involved racemic

(±)-BINAP, tris(dibenzylideneacetone)dipalladium and caesium carbonate in degassed toluene, outlined in (**Fig. 2.10.**).

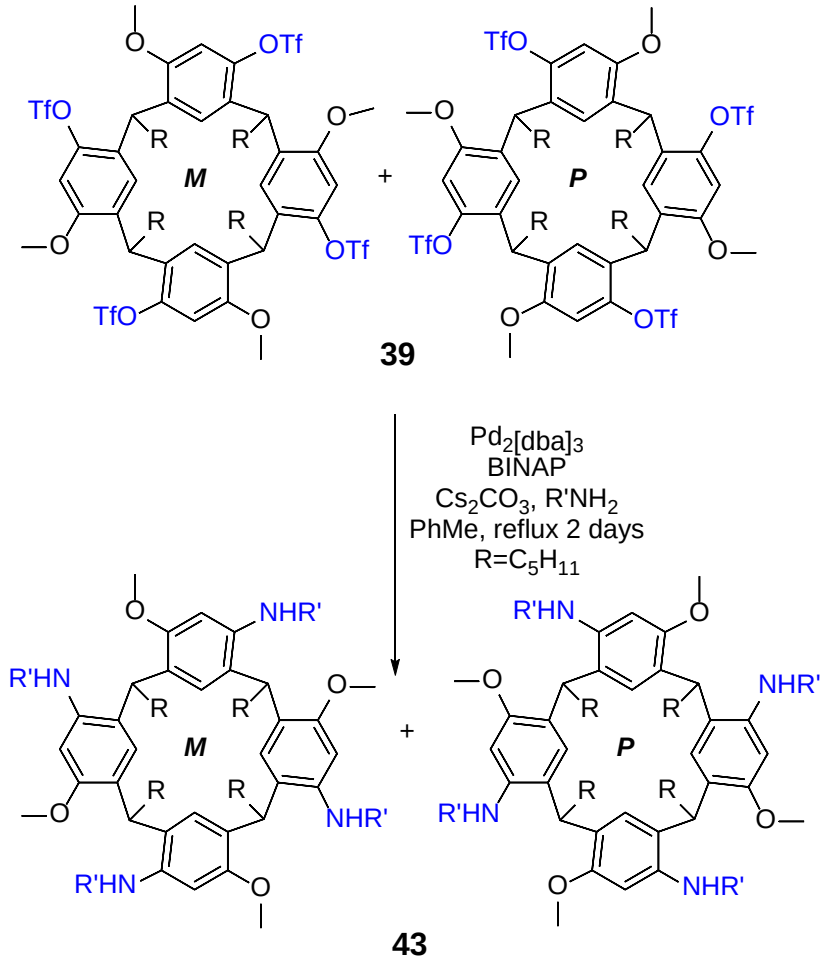


Figure 2.10. Pretaration of diastereoisomeric aminoalkoxycalix[4]arenes from resorcin[4]arene tetrakis(triflates), protocol by *Page*.[7]

Using this method, we chose different amines which gave the better yields and that allowed us to avoid steric hindrance, as this factor is an issue when working with resorcinarenes. In **Table 5** are shown the different amines used by the group which successfully gave the desired amine derivatives of resorcinarenes in good yields (> 43 %).

Table 5. Palladium-catalysed reactions of triflates with primary amines, study by *Page*.[7]

R′	Primary amine	Yield (%)
n-C_5H_{11}	aniline	70
n-C_5H_{11}	aniline	92
n-C_5H_{11}	2-isopropylaniline	46
n-C_5H_{11}	2-isopropylaniline	92
n-C_5H_{11}	2,5-dimethylaniline	65
n-C_5H_{11}	2-fluoroaniline	72
n-C_5H_{11}	2,6-dimethylaniline	72
2-methylpropyl	2-isopropylaniline	43
n-$C_{11}H_{23}$	aniline	94
n-$C_{11}H_{23}$	2-isopropylaniline	69
n-C_5H_{11}	aniline	47
n-$C_{11}H_{23}$	cyclohexylamine	63

The next step in our synthesis was the introduction of carboxylic acid moiety. In order to achieve this, we first have to generate an ester unit which can be easily hydrolysed to carboxylic acid.

2.2.3 Alkylation of the phenolic OH of resorcinarene 38.

Following a procedure by *Mori*[9], the phenolic groups were converted to the corresponding ethers using a Williamson synthesis. Treatment of compound **38** with

K_2CO_3, methyl bromoacetate in dry MeCN under reflux for 8 hours gave compound **44** in good yields (> 85 %).

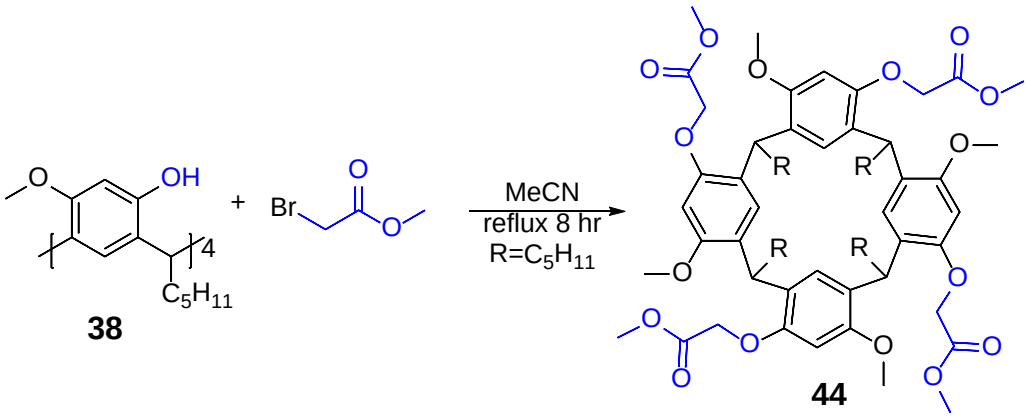


Figure 2.11. Alkylation of resorcinarene with methyl bromoacetate.

2.2.4 Saponification of the ester moiety of resorcinarene 44.

Compound **44** was hydrolysed to the corresponding carboxylic derivative **45** following a standard procedure: LiOH was added to a solution of the starting material in THF:H_2O (20:20 ml). The mixture was stirred for 2 hr at r.t. and then acidified with 1 M HCl to reduce the pH below 3.5. Compound **45** was obtained by crystallization from the reaction mixture upon cooling in MeOH in quantitative yields (> 95 %).

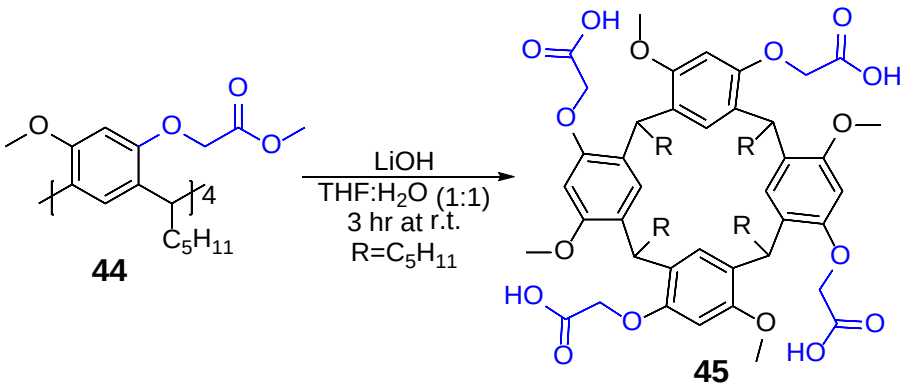


Figure 2.12. Saponification of compound **44**.

Next we decided to introduce an alkene moiety to the ring, as this group can be easily converted into other functional groups of interest.

2.2.5 Allylation of the phenolic OH of resorcinarene 38.

In the table below are listed some literature procedures for allylation of a phenolic OH group using allyl bromide.

Table 6. Allylation of phenolic OH groups – some literature procedures.

Ref.	Base	Solvent	Conditions and reagents *	Yield (%)
10	K_2CO_3	Me_2CO	reflux	97
11	K_2CO_3	DMF	24 hr r.t.	94
12	Bu_4NOH	H_2O	15 min r.t., than 85 min at 50 °C	86
13	KOH	X	TBAI 5 %, 14 hr r.t.	89
14	NaOH	H_2O	MJOD reactor system, 55 min at 35 °C	60
15	CsF-Celite	MeCN	reflux	77
16	K_2CO_3	EtOH	Reflux 5 hr	63
17	DBU, K_2CO_3 or strong base ion exchange resin Amberlyst A26	BuOH	PhCN, 4 min at 0 °C	67

"Potassium carbonate is the preferred base of choice in laboratory synthesis when performing nucleophilic substitution reactions. Commonly, it is stirred to form a suspension, where the K_2CO_3 transforms after the reaction into the (also insoluble) salt KBr, H_2O and CO_2."[17]

We decided to use potassium carbonate as the base with it being cheap, readily available and strong enough to react with our substrates in low quantities.

Next step was to choose the solvent system. Looking at solvents that other groups have used in these types of phenolic alkylation processes using allyl bromide, we decided upon MeCN because it is cheap and available, it has a low boiling point, our

starting material has a good solubility in this solvent and K_2CO_3 remains as a precipitate, being easy to remove by simple filtration.

Figure 2.13 shows the reaction scheme of the allylation of our substrate. Treatment of compound **38** with allyl bromide and K_2CO_3 in MeCN under reflux gave compound **46** upon crystallization from cold MeOH, in quantitative yields (~100 %).

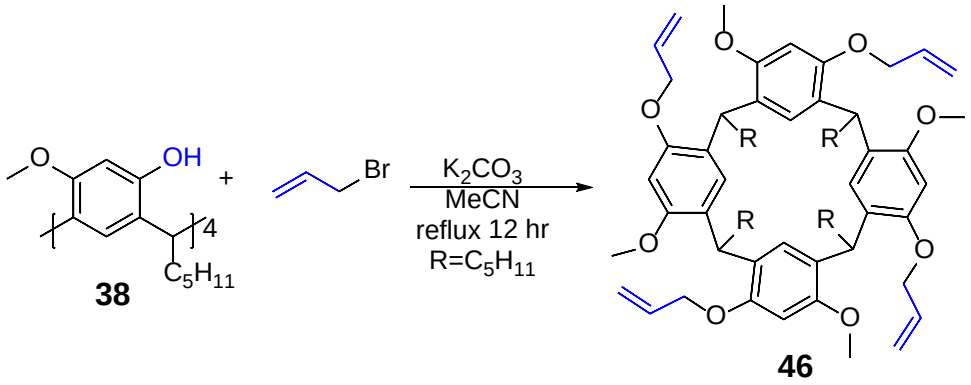


Figure 2.13. Allylation of resorcinarene **38** with allyl bromide.

We were happy to be able to apply the allylation reaction to our substrate as compound **46** was not reported in the literature, as far as we know. The structure was confirmed by IR, ^{1}H NMR, ^{13}C NMR, COSY, HSQC. This compound exhibited a C_4 symmetry in solution in deuterated chloroform as judged from its ^{1}H NMR spectroscopic data.

Crystals of resorcinarene **46** were obtained by slow crystallisation from DCM/methanol at room temperature, and followed by analysis using single crystal x-ray diffraction (**Fig. 2.14**). X-ray details are listed in **Appendix 14**. The resorcinarene **46** in the solid state is isolated as the rccc (all four substituents in the resorcinarene fragment are mutually cis) alternate boat conformer.[18]

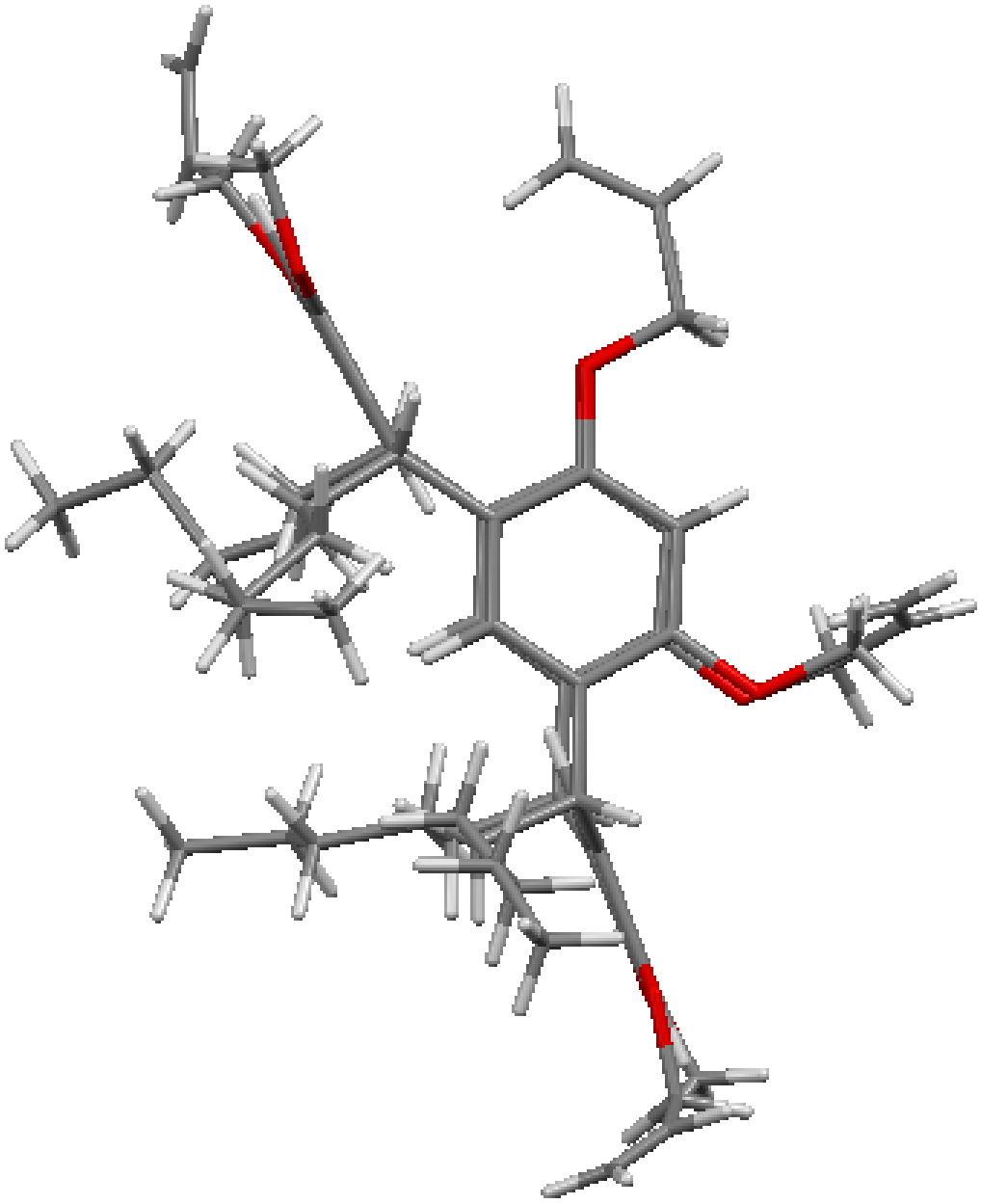


Figure 2.14-A. Crystal structure of resorcinarene **46** – side view, showing the overlaping of the distal aromatic rings, and the boat conformation adopted by this compound.

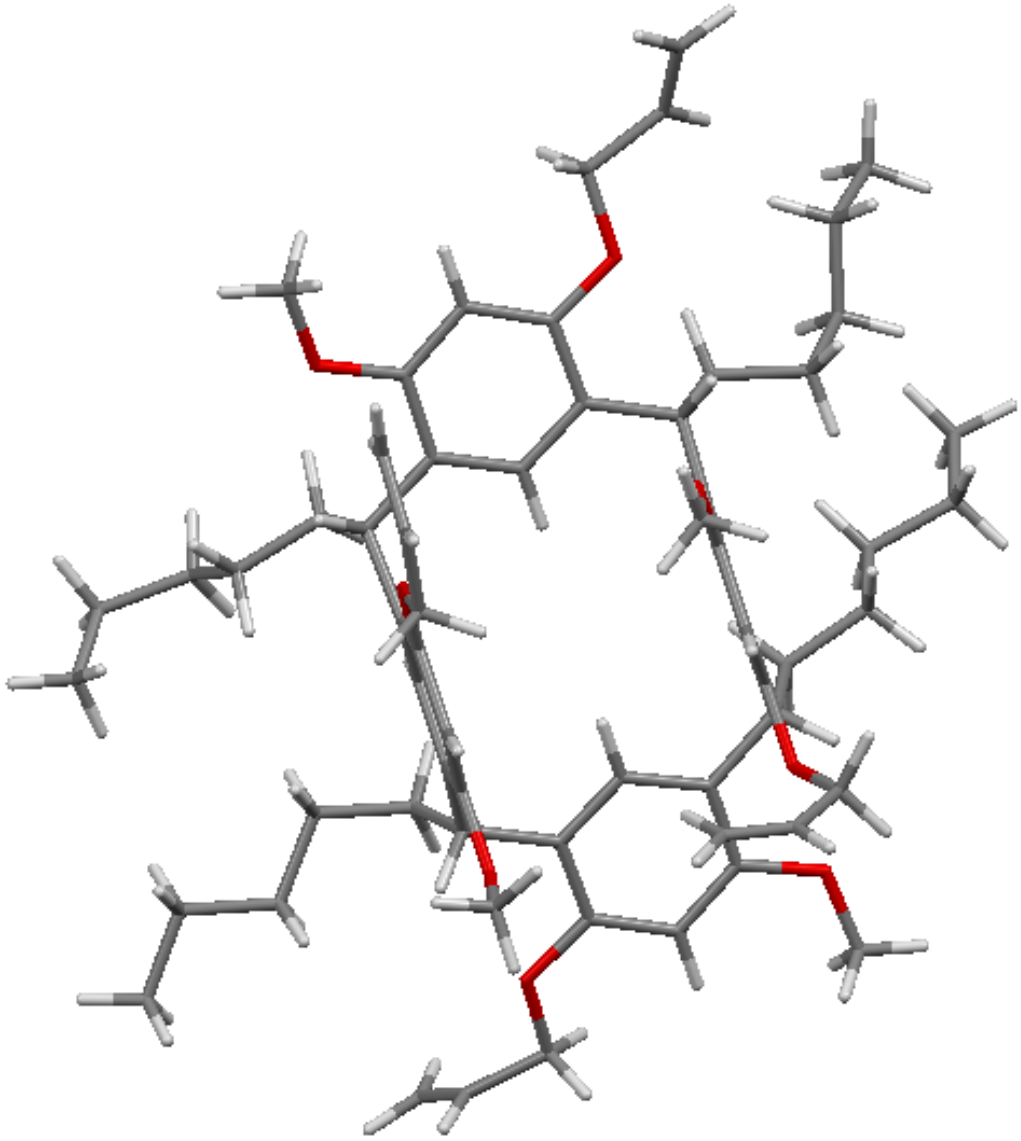


Figure 2.14-B. Crystal structure of resorcinarene **46** – top view, showing the lower rim C_5H_{11} chains pointing away.

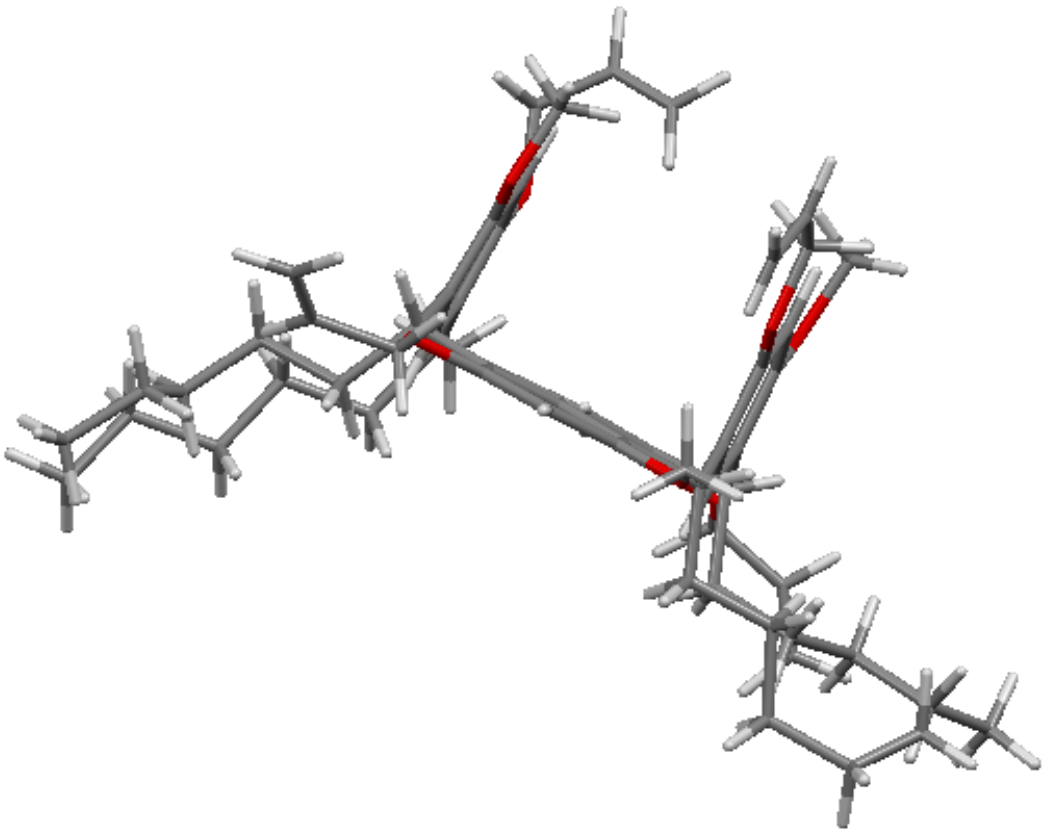


Figure 2.14-C. Crystal structure of resorcinarene **46** – side view, showing that one allyl moiety is pointing inside the cavity, while the rest point outside the cavity.

The crystal structure shows that in solid state all four methoxy groups seem to be in the same plane with the aromatic rings. Three of the allyl units point outside the cavity, as expected, as in this form the lowest energy/repulsion is achieved, but strangely enough, one allyl unit points inside the cavity. Interestingly we noticed that the alkyl chains point further away from the core structure comparing to the crystal structure of the starting material **38.** The geometry of the lower rim of the resorcinarene is less organised; the alkyl groups exhibit small differences in arrangement.

2.2.6 Ozonolysis of the alkene groups of resorcinarene 46.

Ozonolysis is a well-documented reaction that allows the cleavage of alkene double bonds by reaction with ozone. Depending on the work up, different products may be isolated: reductive work-up gives either alcohols or carbonyl compounds, while oxidative work-up leads to carboxylic acids or ketones. [18, 19]

We had hoped to use this reaction to obtain compound **47** as shown in (**Fig. 2.15**). The reaction conditions used for ozonolysis were taken from reports for a simple allyl phenol ether.[20]

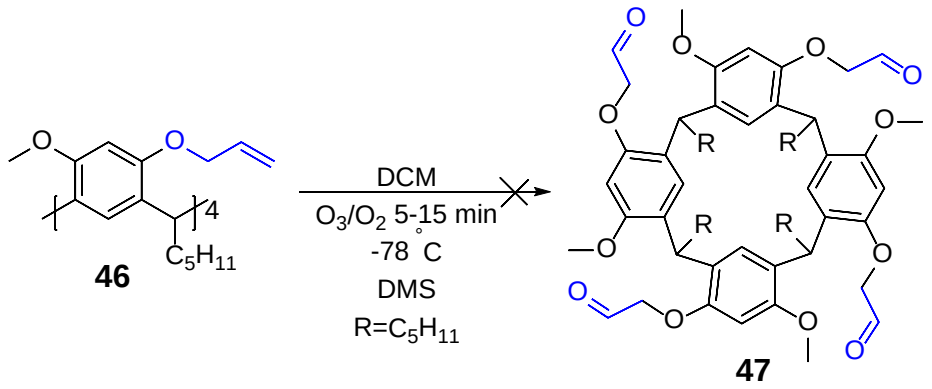


Figure 2.15. Ozonolysis of the alkene functional groups of resorcinarene **46**.

The alkene substrate **46** was dissolved in dry DCM in a flame-dried flask under N_2. The solution was cooled to -78 °C and submitted to a stream of O_3/O_2, the colour of the reaction mixture changing to blue, which indicated the success of the reaction. After all the starting material was consumed, the reaction mixture was quenched with DMS.

Unfortunately, this reaction was not successful. Although all starting material was consumed after 15 min, the desired product was not observed. TLC analysis showed the consumption of the entire starting material but, ^{1}H NMR spectrum indicated the degradation/fragmentation of the substrate (**Fig. 2.16**).

In the proton NMR we would expect a triplet in the region of 9-10 ppm and a doublet in the region of 5 ppm, but neither was observed. [21]

More interestingly we saw the disappearance of a very distinctive peak around 3.5 ppm, corresponding to the methoxy moieties in the structure.

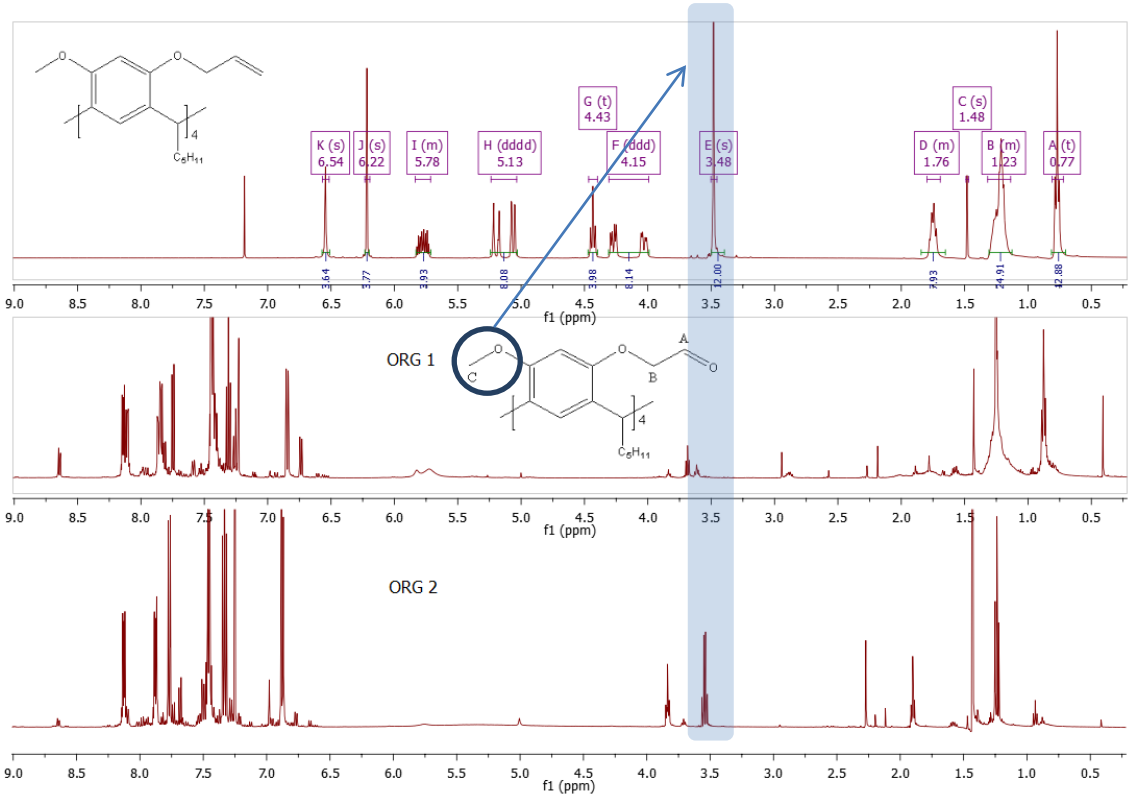


Figure 2.16. ^{1}H NMR spectra comparing resorcinarene **46** and **47**.

We thought that perhaps the reaction time was too long and the reaction conditions too harsh, and so we repeated the procedure but this time leaving it only 5 minutes. Similar results were obtained, so we concluded that the substrate is fragmented when undergoing ozonolysis.

2.3 Monofunctionalization of resorcinarenes 38, 46 and 60 at the ortho position.

2.3.1 Mannich reaction of resorcinarene 38.

One of the project's objectives was to attach amines on the upper rim of the resorciarenes. In 2006, *Page*[19] published "*Mannich and O-Alkylation Reactions of Tetraalkoxyresorcin[4]arenes*" where the group investigated microwave-assisted reactions in order to improve reaction times and yields, and to obtain cleaner products.

Following their protocol, resorcinarene **38** was treated with bis(dimethylamino)-methane and microwaved for 10 min at 110 °C and 300 W, giving compound **48** in 83 % yield (**Fig. 2.17**).

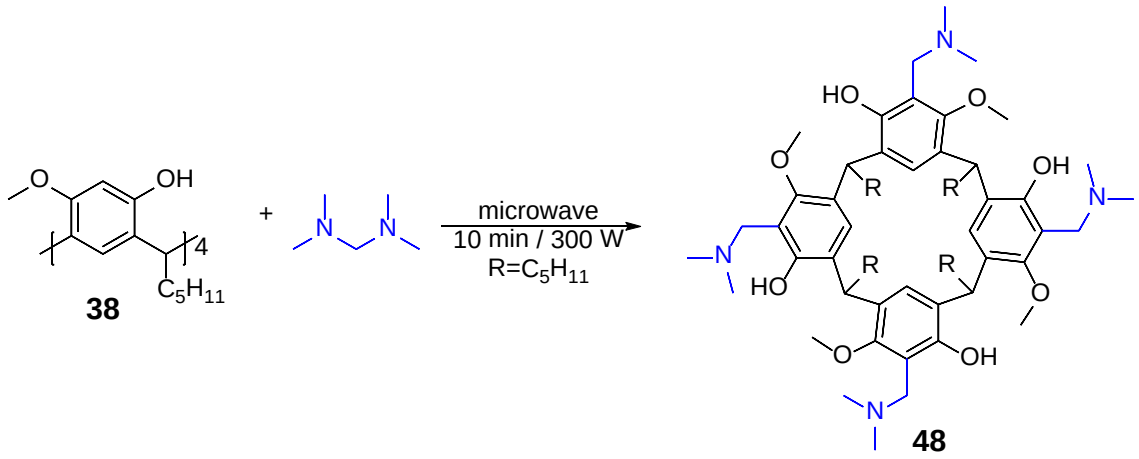


Figure 2.17. Mannich reaction of resorcinarene **38** with bis(dimethylamino)methane using microwave irradiation.

Following a procedure by *Page*[5], we also managed to attach an amine functional group at the ortho position.

A solution of bis(dimethylamino)methane together with a 30 fold excess of anhydrous potassium carbonate was stirred in dichloromethane; this was followed by the

addition of acetyl chloride. The tetramethoxyresorcinarene **38** was then added after 30 min and the mixture was stirred at room temperature for up to 5 days, giving a very pure crystalline racemic product **48** in 98 % yield (**Fig. 2.18**).

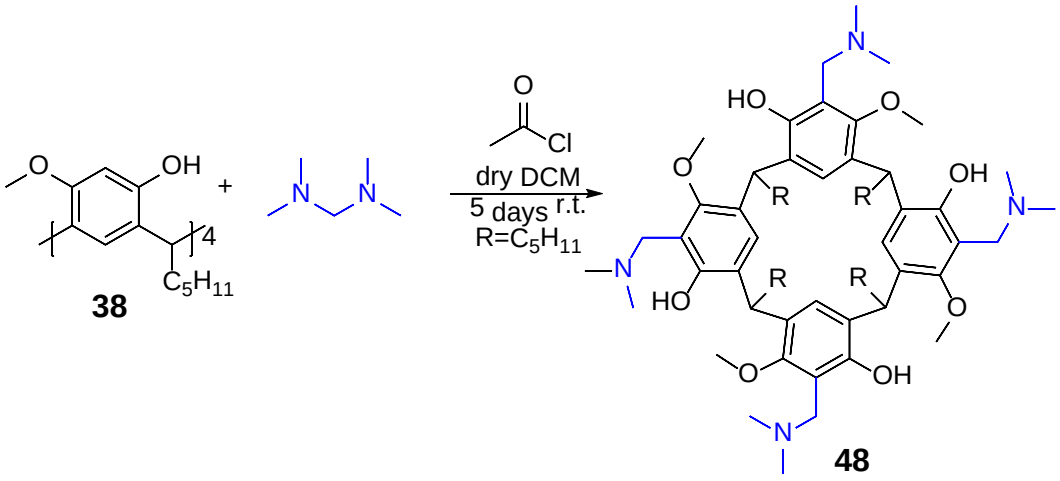


Figure 2.18. Formation of Mannich Base **48**.

Comparing the two methods we determined that similar yields were obtained, the microwave-assisted reaction has better reaction times, whereas the method used by *Page* allows scaling up the reaction.

2.3.2 Claisen rearrangement of resorcinarene 46.

A Claisen rearrangement of substrate **46** was also attempted. The Claisen rearrangement was discovered in 1912, and since then it has been in the spot light for a wide range of synthetic applications.[22] The Claisen rearrangement is popular for carbon–carbon bond forming reactions in organic synthesis and occurs *via* a concerted [3-3]-sigmatropic rearrangement of allyl vinyl ethers to give ɣ,δ-unsaturated carbonyls.[23]

The aromatic Claisen rearrangement is intramolecular and is generally a thermally initiated reaction. The mechanism occurs *via* the formation of a cyclized activated complex and an intermediate dienone through a [3,3]-rearrangement of the allyl ether.

The *ortho*-dienone usually rapidly enolizes to the stable product, an o-allylphenol (ortho Claisen rearrangement) (**Fig. 2.19.**).[21, 23]

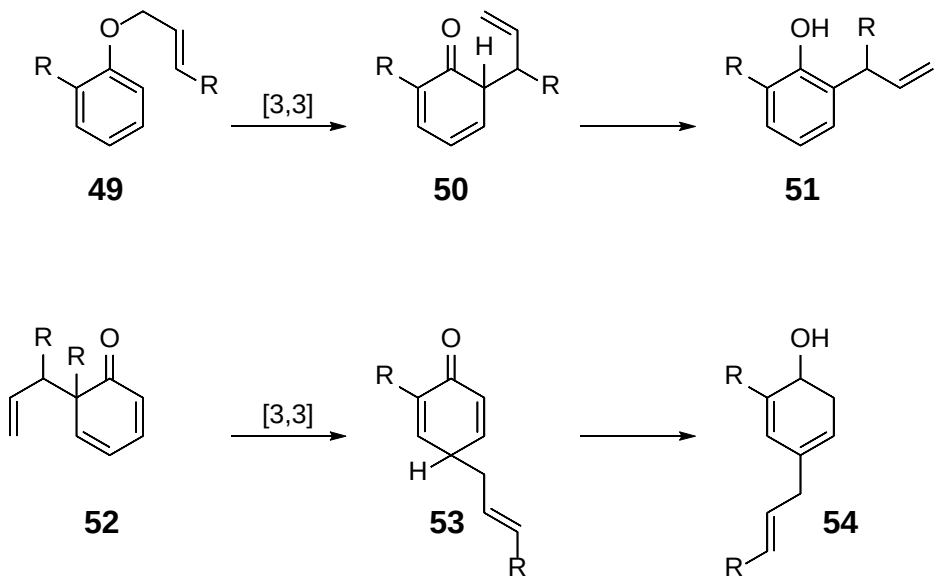


Figure 2.19. Mechanism pathways for the Claisen rearrangement of aromatic allyl ethers.[21, 23]

However, if the *ortho* position is substituted, a second [3,3] step takes place, followed by enolization leading to the *para*-product (*para*-Claisen rearrangement). When the *ortho* position is substituted, rearomatization cannot take place, thus the allyl group must first undergo a Cope rearrangement to the *para* position before tautomerisation is possible.[23]

In general the transition state geometry is a chair-like arrangement in preference to a boat. This may change when the substrate is sterically hindered or inhibited, in which case the reaction can occur partly or totally through a boat-like conformation (**Fig. 2.20**).[24]

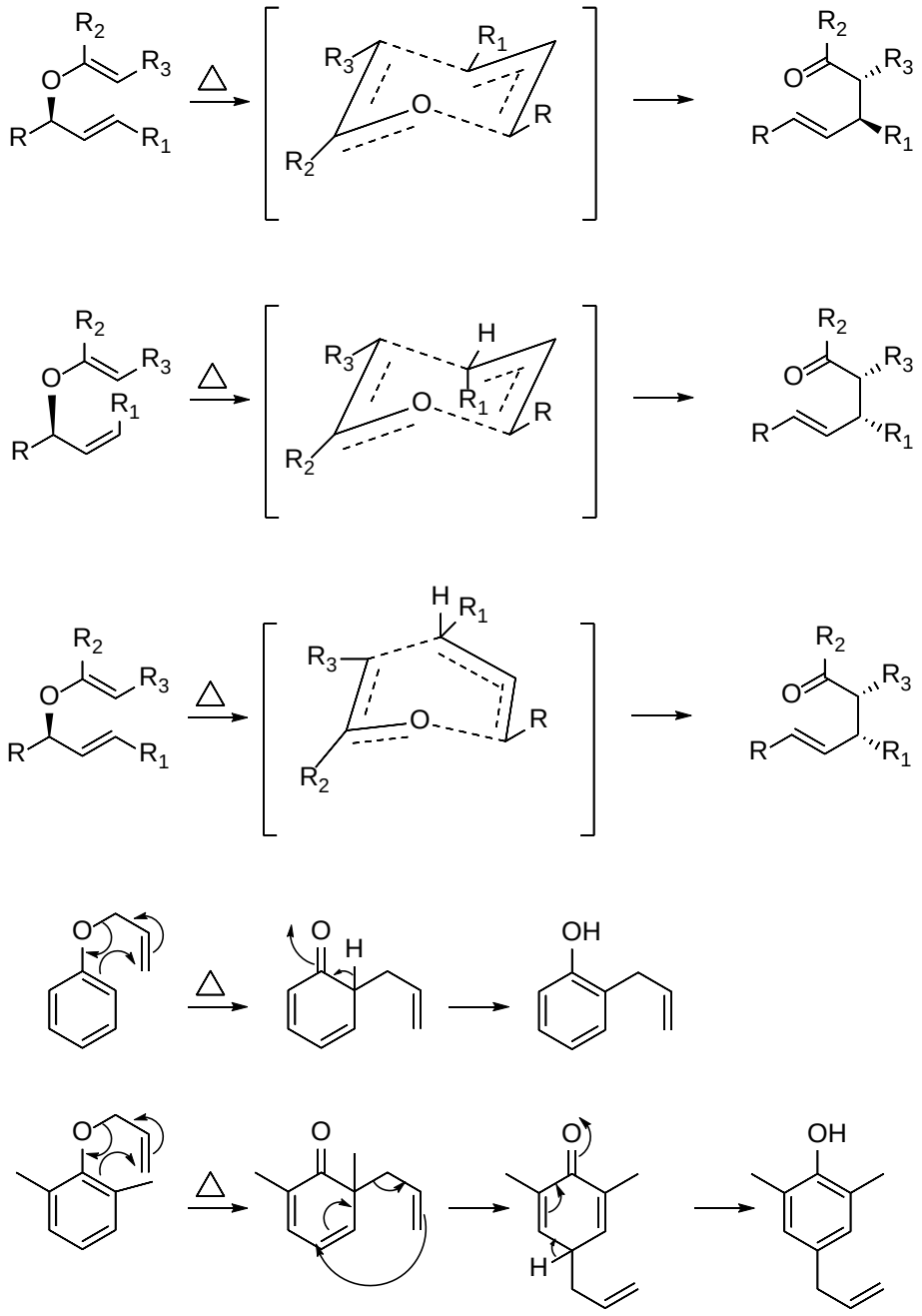


Fig 2.20. Transition states for the Claisen rearrangement.[24]

The Claisen rearrangement is a thermal reaction, although in some cases it can occur through a radical intermediate as stated in "*The photochemical rearrangement of aromatic ethers. A review of the Photo-Claisen reaction*" by *Galindo*[25] (**Fig. 2.21**).

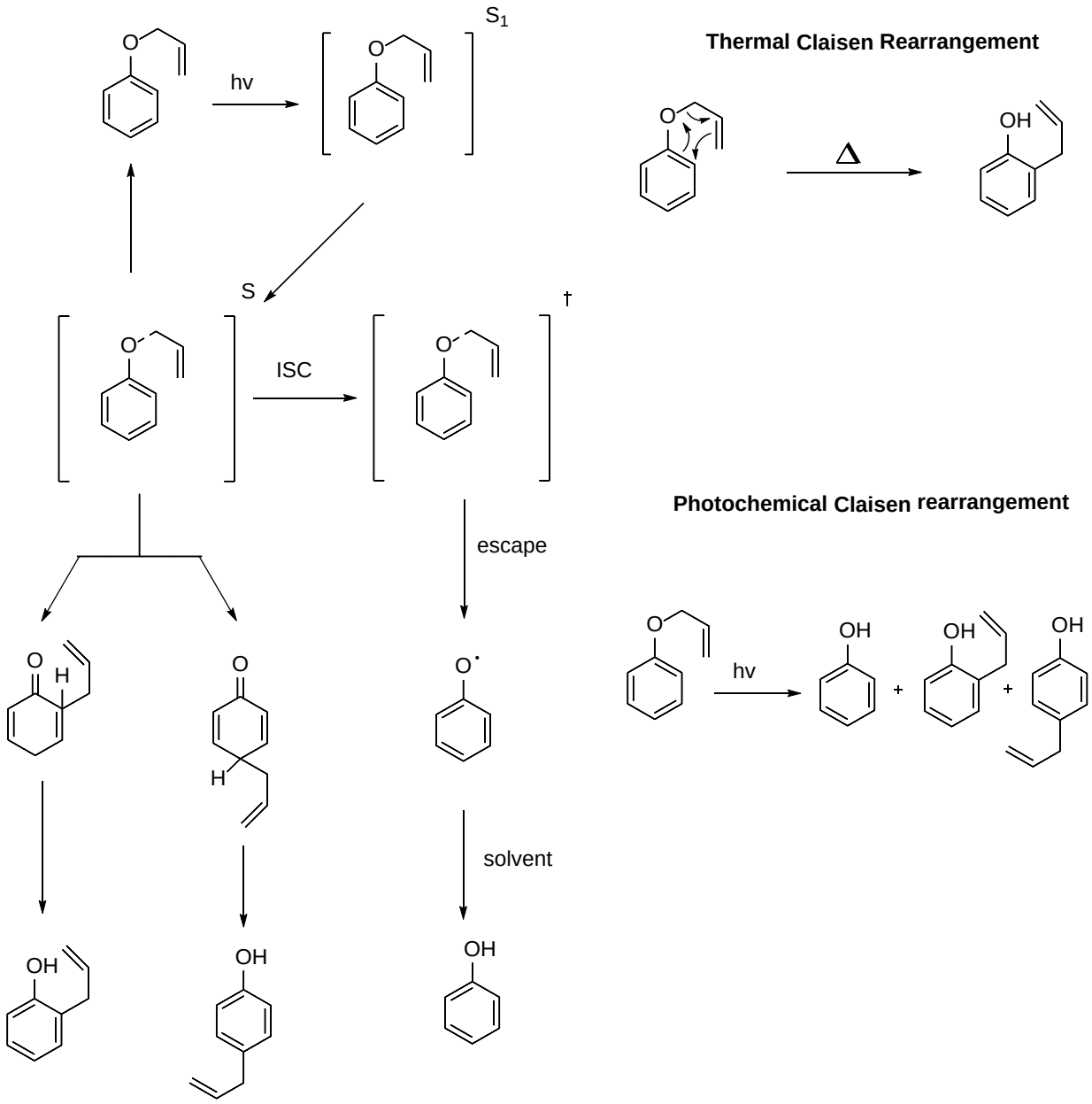


Figure 2.21. Photo-Claisen Rearrangement and thermal Claisen rearrangement mechanism, by *Galindo*.[25]

The thermal reaction gives in almost all cases the *ortho*-product as it undergoes a [3,3] sigmatropic rearrangement, going through a six membered ring transition state. On the other hand, the photochemical reaction gives both *para*- and *ortho*- products and the parent phenol, as it is a stepwise pathway.[25, 26]

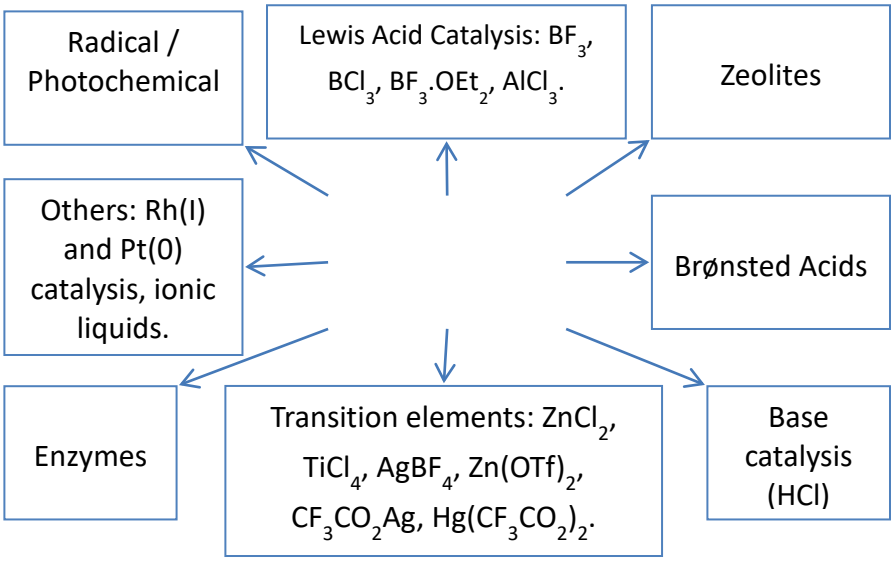
There is a number of literature reports of this type of reaction performed on substrates similar to ours (**Table 7**).

Table 7. Literature protocols for the Claisen rearrangement.[24, 27-32]

Ref.	Solvent	T (°C)	Time/ Yield	Other
27	Dry toluene	70	16 hr / 71 %	Substrate: substituted aromatic allyl ethers
28	DMF	120	8-20 hr / 89 %	Substrate: 1-bromonaphtyl allyl ethers derivatives, Used 3 equiv. K_2CO_3, Dry conditions
24	PhCl	-40-0	0.2-2 hr / 85 %	Substrate: allyl phenyl ethers i) 1.3 equiv. BCl_3, ii) H_2O
29	H_2O	> 265 / 5MPa	< 1 min / 98 %	Substrate: aromatic allyl ethers HPHT-H_2O micro reactor
30	Toluene	150	7 hr / 96 %	Substrate: *O*-allyl kojates Microwave
31	DEA	150	20 min / 85 %	Substrate: naphtyl 2-propynyl ethers Cat. CsF, Microwave
32	DMF	300-315	6 min / 92 %	Substrate: aromatic allyl ethers

A variety of procedures for the Claisen rearrangement have been reported in the literature, as well as catalysed methodologies designed to activate the reaction and to promote a "*greener process by the reduction of energy consumption, reaction time and waste production*".[22]

A series of methods for promoting and optimizing the Claisen reaction are presented in **Scheme 6**.[24, 32, 33-37]



Scheme 6. Types of optimization procedures for the Claisen rearrangement.

The reaction has been proven to be influenced by many factors such as: steric hindrance, temperature, time, types of substituents (EWG/EDG), catalysts and solvent systems.

We first tried a classical method, consisting of heating the starting material at high temperature. According to literature[38] it was observed that the reaction rate increases with the production of phenol derivatives, so addition of phenolic compounds result in the enhancement of the reaction rate. In addition, the polarity of the solvent plays an important role. In protic solvents, the reaction is faster than in aprotic solvents.[32]

A number of solvents were screened under varying conditions (**Table 8**): DMF, MeCN, THF, EtOH:H_2O (28.5 % and 85 %), phenol, p-chlorophenol and diphenyl ether. Unfortunately, in all cases full recovery of the starting material was obtained, excepting entry *8*. When refluxing in xylene for 8 days, although starting material was still present in high percentage (TLC analysis), some product spots started appearing, but were hard to separate and in very low yields, so the reaction was abandoned.

Table 8. Attempted conditions for the Claisen rearrangement.

Entry	Solvent	Time	Tempera-ture (°C)	Yield (%)	Method
1.	DMF	20-40 min	180-190	N/A	µW *
2.	Xylene	12 days	160	SM and fragments	Reflux
3.	DMF	30-60 min	170-210	N/A	µW
4.	DMF	2-5 hr	250	SM +UM**	µW
5.	MeCN	90-120 min	120-200	N/A	µW
6.	Xylene	5 min – 3 hr	120-160	SM +UM	µW
7.	Xylene	3 hr	170	24 %, all SM consumed but many side products	µW
8.	Xylene	3 hr	180	<30 %, all SM consumed but many side products	µW
9.	THF	40-120 min	55	N/A	Oil bath
10.	Xylene	3 days	reflux	N/A	Heat plate
11.	EtOH:H_2O (28.5 % or 85 %)	30-90 min	reflux	N/A	Heat plate
12.	DCM	4 hr	-40 °C to r.t.	N/A	
13.	No solvent	13 hr	230	94 %	µW

* µW = microwave irradiation, **UM = inseparable mixture

Secondly, among the protocols reported in literature, many use a variety of transition metal catalysts, having advantageously short reaction times and high yields but with the downsides of high costs and the difficulty of removing transition metal impurities.[28]

We chose one of the smallest transitional metals mentioned in literature as being a good catalyst for this type of reaction: Zn.

Following a procedure published by *Gupta*,[39] "*Zinc Catalyzed Claisen Rearrangement of Allyl Aryl Ethers to o-Allylated Phenols in Liquid Phase*", **substrate 46** was dissolved in THF and charged with zinc powder (2.5 mol %). The reaction mixture was stirred in an oil-bath at 55 °C for the required time and monitored by TLC (visualization in iodine vapours). The zinc powder was removed by simple vacuum filtration. Despite our expectations, the reaction did not take place under the conditions used and recovery of starting material was observed.

From previous reported reactions it became clear that both reaction time and temperature were significant factors in the success of this reaction, so we chose a higher boiling point solvent, xylene, we increased the Zn equivalents to 10 mol %, and refluxed the reaction mixture for three days, but, unfortunately this still resulted in the recovery of the starting material.

Next we tried to catalyse our reaction using a Lewis acid. An example of a Claisen rearrangement when Lewis acid BCl_3 is used as catalyst is represented below (**Fig.2.22**) along with the various competing processes that can rationalize observed side reactions.[40, 41]

The Lewis acid BCl_3 and the substrate form an ether-BCl_3 complex and from here, there are two possible pathways. The complex can cleave to form cleaved phenols and allyl cations which leads to intramolecular allyl transfers. The second pathway considers a [3,3] rearrangement through a charge-delocalized transition state, **56,** to the ortho dienone intermediate, **57.** Preferentially, the deprotonation of **57** to the boron ester will take place, unless the [3,3] migration terminus does not bear a hydrogen, in which case the substrate will undergo a [3,3], [1,2], or [3,4] rearrangement giving side products.[24]

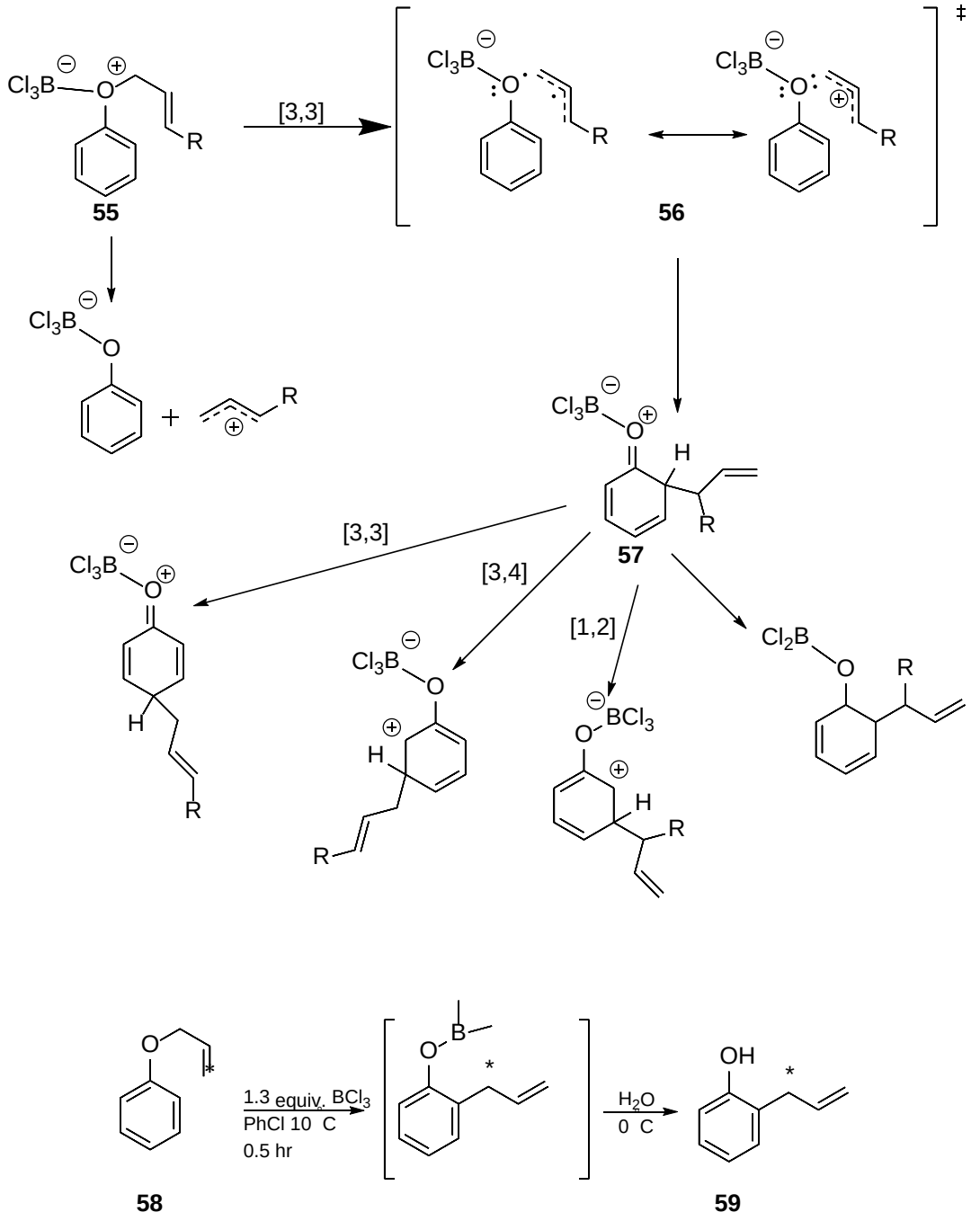


Figure 2.22. Claisen rearrangement mechanism in the presence of Lewis acid BCl_3.[40, 41]

Substrate **46** was treated with $BF_3.OEt_2$ at −40 °C in dry DCM. The reaction mixture was stirred at −40 °C for one hour, than at room temperature for three hours. The reaction mixture was monitored by TLC (visualization in p-anisaldehyde), extracted in DCM, washed with water and brine, and dried over $MgSO_4$. TLC showed a mixture of blue-coloured spots that could indicate the formation of B-O complexes. Unfortunately, workup afforded only starting material and some degradation products.

Subsequently, our attention was turned towards microwave irradiation. Microwave radiation has two components: electric field and magnetic field. The electric field will interact with any molecule that has a dipole or that is ionic. At any given point in time, the electric field is constantly oscillating, from positive to negative and back. These oscillations cause the molecules to rotate such that the appropriate pole will be aligned with the changing field. As the molecules move, they generate thermal energy, leading to a rapid temperature rise. The more polar the solvent is or the stronger its dipole moment, the more rotation and movement take place, thus generating more heat.

Substrate **46** was placed into a dry microwave vial, dissolved in the chosen solvent (DMF, MeCN, Xylene) and microwaved between 80 °C and 250 °C for 5 min – 48 hours (**Table 8**).

Solvent: xylene took up to 10 min to reach 190 °C and could not easily reach higher temperatures, so we decided upon the solvent system xylene:DMF (95:5). Using this solvent system, high temperatures were reached in a matter of seconds, and furthermore all starting material was consumed after 2 hours and a half (for quantities between 0.01 - 0.5 g).

Temperature: we screened a range of temperature values for the microwave reaction and we saw that below 170 °C, starting material and small degradation fragments are isolated. Between 200 °C and 230 °C the best reaction yields were achieved (< 35 %), whereas for any temperatures over 230 °C more side products were formed.

Time: when trying to scale up the reaction, using exactly same reaction conditions the yield decreased dramatically, so we screened the reaction times and found out that the reaction times increase with the increase of the quantity of starting material (**Fig. 2.23**). Although the starting material is consumed faster, using ^{1}H NMR spectroscopy we calculated the time corresponding to the maximum obtained yields. It was disappointing to find that any attempts to carry out the reaction on a scale bigger than 1 g resulted in a decrease of the yield. This could be a result of side product formation or degradation, information supported by TLC analysis, as the number of spots on the TLC increase with time.

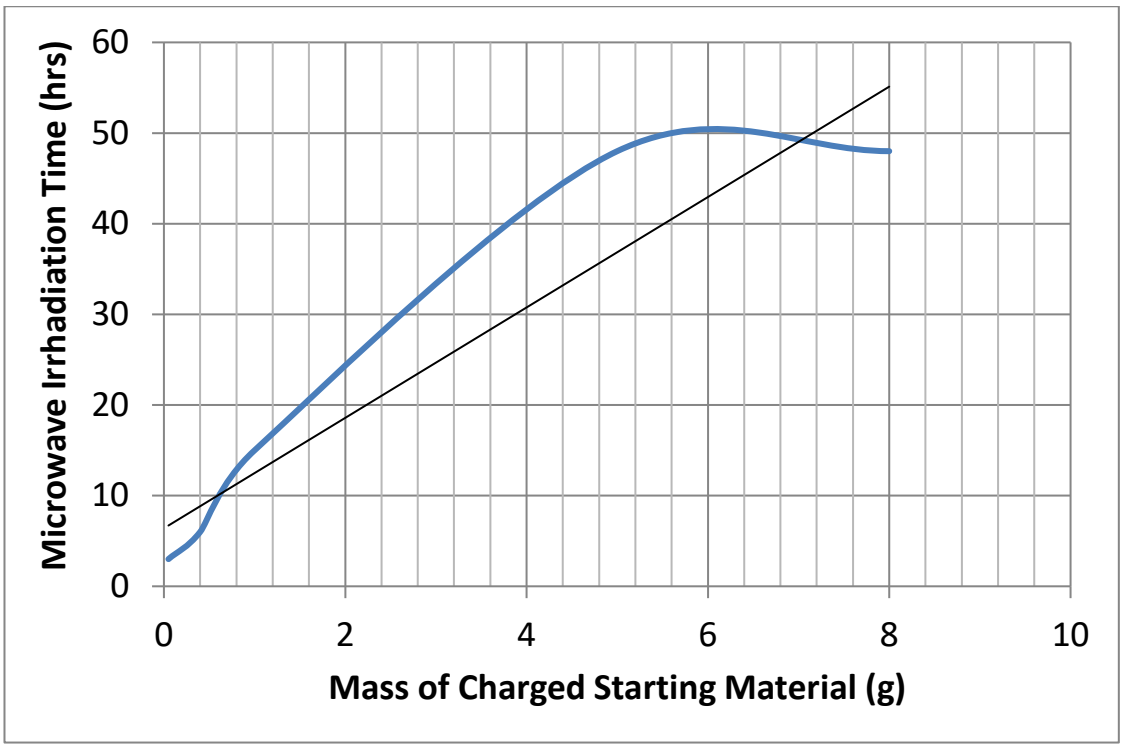


Figure 2.23. Correlation between the mass of starting material and reaction time.

Furthermore, we observed that the increase of the reaction time results in side reactions and decreasing yields of the expected product. The side products were very difficult to separate from the rearrangement product by flash chromatography, which made the isolation and purification process difficult.

Finally, we managed to obtain the desired tetra-substituted resorcinarene, although in low yields (< 35 %), and we were happy to be able to apply the Claisen reaction to our substrate (**Fig. 2.24**) as compound **60** was not reported in literature. The structure was confirmed by multiple spectroscopic techniques including IR, ^{1}H NMR, ^{13}C NMR, COSY, HSQC, and HRMS. This compound exhibited a C_4 symmetry in solution, in deuterated chloroform, as judged from its ^{1}H NMR spectroscopic data.

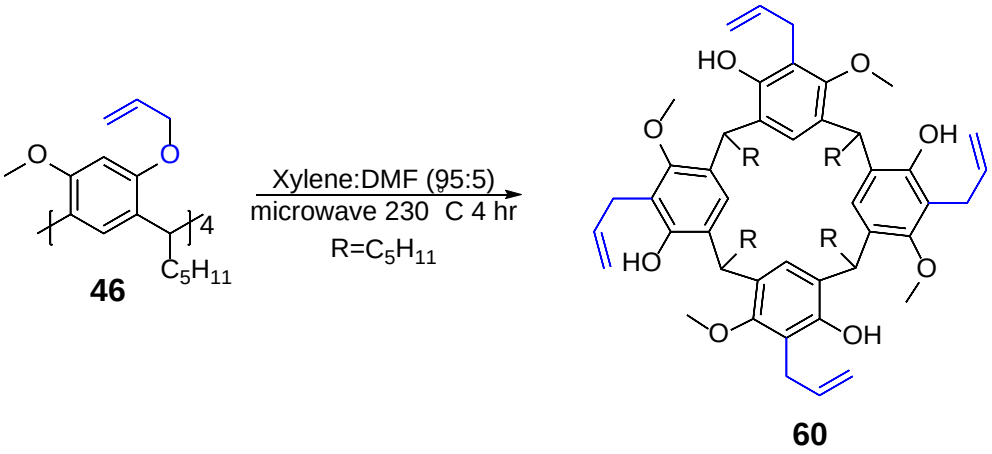


Figure 2.24. Claisen rearrangement of compound **46**.

Crystals of resorcinarene **60** were obtained by slow crystallisation from cold methanol at room temperature.

The resorcinarene **60** in the solid state is isolated as the rccc crown conformer (**Fig. 2.25**).[18] X-ray details are listed in **Appendix 15**. The crystal structure shows that in solid state all four methoxy groups point outside the ring, and all propenyl units point outside the cavity, as expected, as in this adopted form the lowest energy/repulsion is achieved. The alkyl chains point away from the core structure, the geometry of the lower rim of the compound is less organized; the alkyl groups exhibit small differences in arrangement.

Comparing the crystal structures of the starting material **46** and compound **60**, we observe the following:

- **Conformation**: compound **46** exhibits a boat conformation, while compound **60** adopts a crown geometry, similar to that of the starting material **38**;

- **Methoxy groups**: in compound **46**, the methoxy units appear to be in the same plane with the aromatic rings, while in compound **60**, they point outside the ring;

- **Lower rim chain**: in the case of compound **46**, the C_5H_{11} chain points away from the core structure, while in compound **60**, the chain points downwards, along the central axis of the structure;

- **Allylic moieties**: compound **60** has the allylic units situated on the ortho positions, allowing the formation of hydrogen bonds (between the OMe and phenolic OH groups) between neighbouring aromatic rings, thus giving a crown conformation, and pushing down the lower rim C_5H_{11} chains. In the case of compound **46**, the allylic moieties are attached on the phenolic OH, hydrogen bonds are not allowed to form and don't hold the structure together. Due to repulsion between rings, two distal aromatic units will adopt a perpendicular position to the other two rings, allowing the lower rim C_5H_{11} chains to push away from each other.

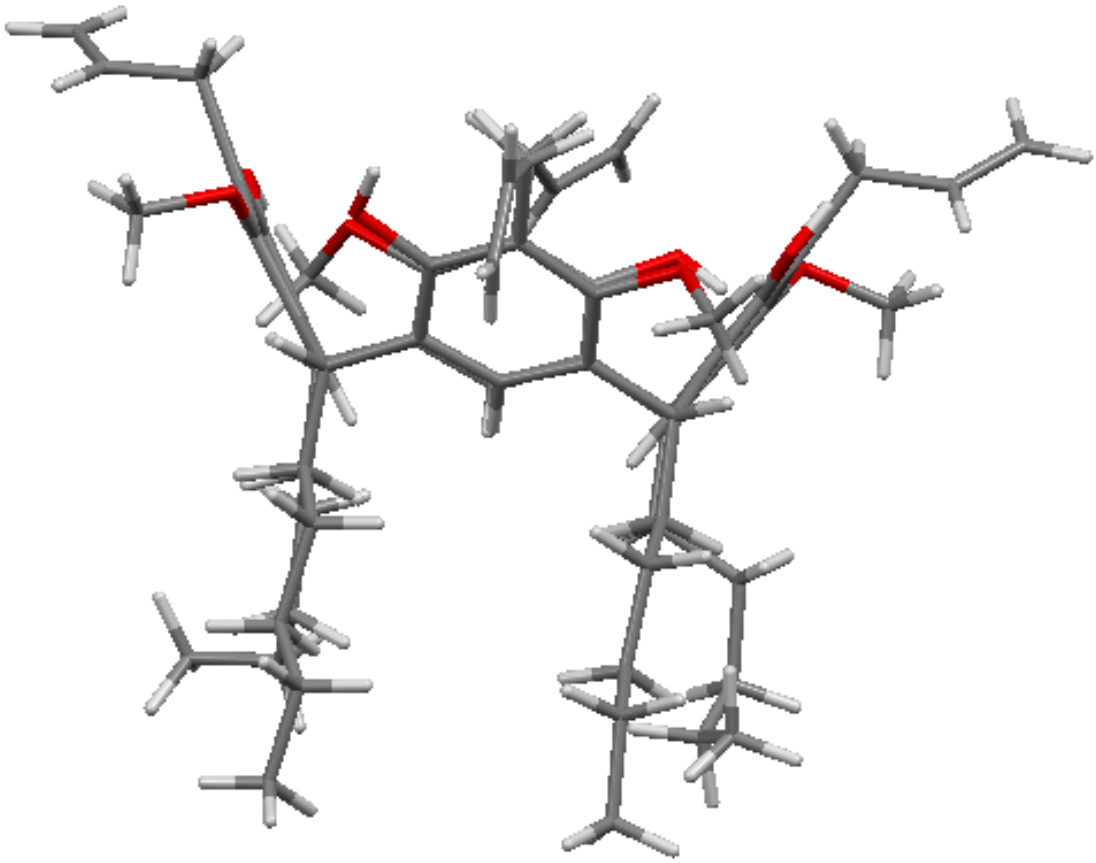


Figure 2.25-A. Crystal structure of resorcinarene **60** – side view, showing the overlapping of the distal aromatic rings, and the crown conformation adopted by this compound.

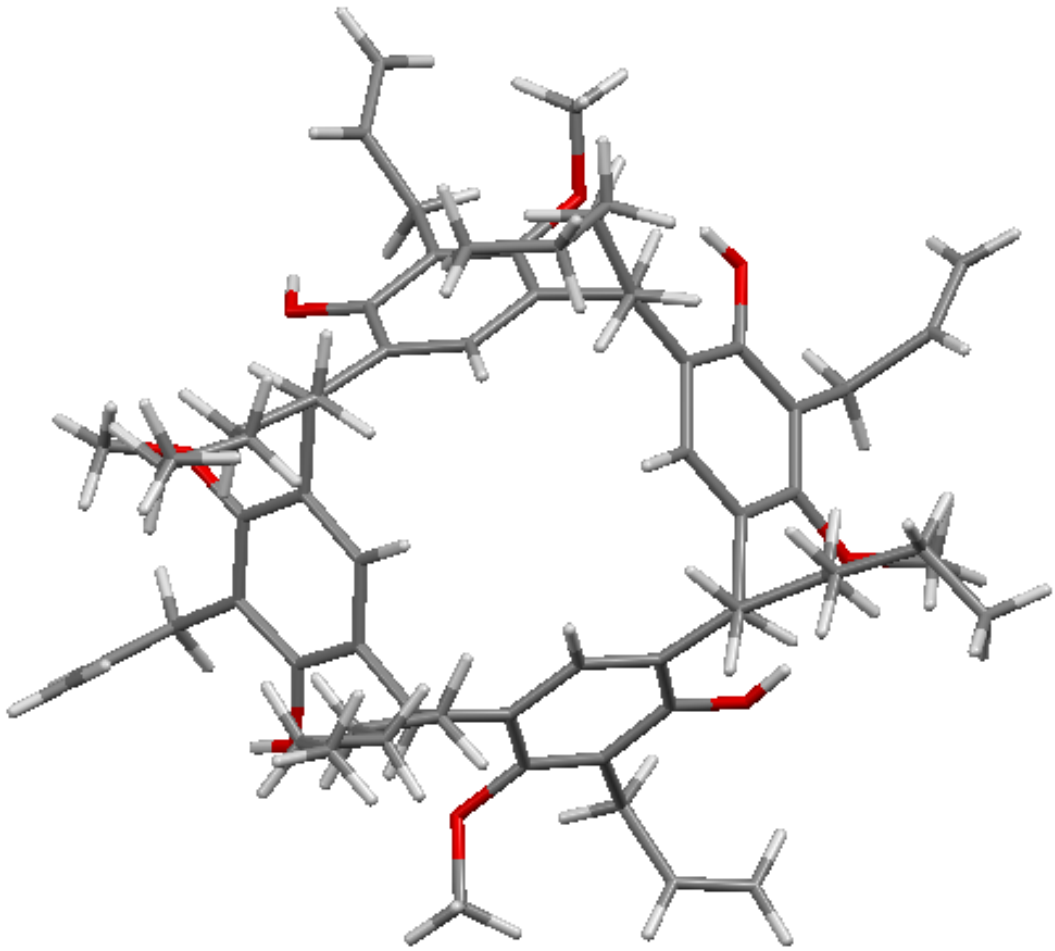


Figure 2.25-B. Crystal structure of resorcinarene **60** – bottom view, showing the lower rim C_5H_{11} chains pointing downwards from the cavity.

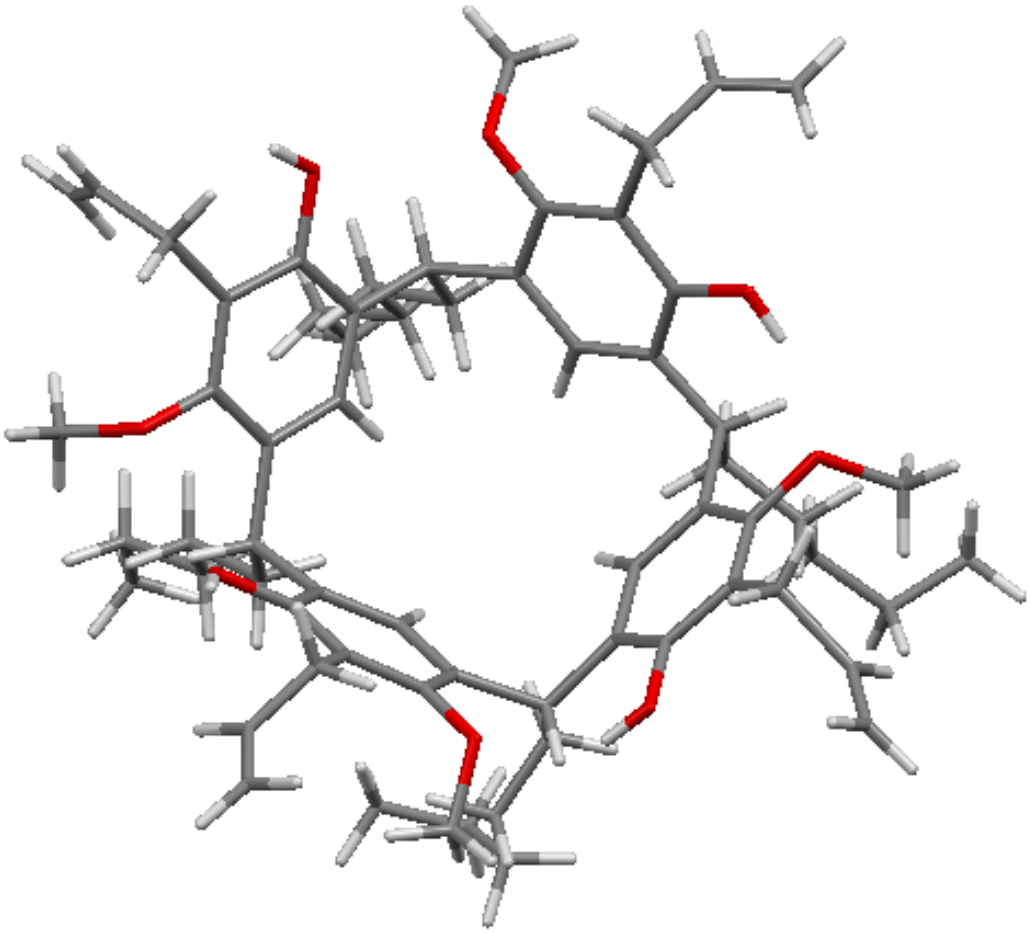


Figure 2.25-C. Crystal structure of resorcinarene **60** – top view, showing that all allyl moieties are pointing outside the cavity.

Neat reaction- in 2007, *Majumdar*[32] published "*Catalysis of the Claisen rearrangement*" in which he reported that the Claisen rearrangement can be carried out by microwave irradiation in the absence of a solvent. Furthermore, the group concluded that "*in the absence of a solvent, the Claisen rearrangement (in the solid*

phase) took a longer irradiation time to obtain comparable yields with the same reaction in a solvent".

Although our reaction was successful, the yield was unsatisfactory. To improve the reaction we tried the reaction neat (no solvent) using microwave irradiation. We had a breakthrough, as after 13 hours of irradiation at 230 °C (for 0.3 g of starting material), we were able to isolate up to 90 % yield after chromatographic purification. Unfortunately, when scaling up, the microwave vials could not withstand the temperature and pressure and fractured, so this procedure needs adjustments.

Yields: low yields were still obtained, despite all our efforts to optimize. In **Table 8** are listed some attempted reaction conditions.

There are several possible explanations for the low reactivity of our substrate. At first we thought it could be steric hindrance, as the allylic groups are attached to a crowded cavitand, with all other positions substituted, and it was our concern that it could be for this reason that the transition states were not favoured, even at high temperatures. Then, looking at the reaction mechanism, if we were forming the tetra-substituted resorcinarene, that would mean that all four rings would have to lose aromaticity to form the dienone intermediates, a process that is not energetically favoured, thus cannot occur concomitantly. We think that one ring unit reacts first, than the second in different rings, and so on, giving in the end a complex mixture of mono-, bi-, tri- and tetra-substituted derivatives. This idea was supported by IR and ^{1}H NMR data: IR spectroscopy shows the presence of both OH and alkene functionalities, and in the ^{1}H NMR spectra, characteristic peaks of the methoxy and alkene groups are present with small difference in chemical shifts.

As future work: in order to improve the yields of the Claisen rearrangement, the regular solvent systems could be substituted with ionic liquids as they are known for their "*nonvolatility, nonflammability, stability and ease of recyclability*".[41]

In 2005, *Armstrong*[41] published "*Using Geminal Dicationic Ionic Liquids as Solvents for High-Temperature Organic Reactions*" in which the group reports a series of dicationic ionic liquids with high thermal stabilities (degradation/volatization onset temperatures

ranged from 330 to > 400 °C) used for isomerization reactions, Claisen rearrangements and Diels-Alder reactions.

The rearrangement of *m*-methoxy allyl phenyl ether, similar to our core fragment, showed the highest regioselectivity in the $C_9(mpy)_2$-NTf_2 ionic liquid.

2.3.3 Ozonolysis of the alkene groups of resorcinarene 60.

Having this new compound **60**, we tried an ozonolysis reaction, hoping to obtain the corresponding ketones as shown in (**Fig. 2.26**).

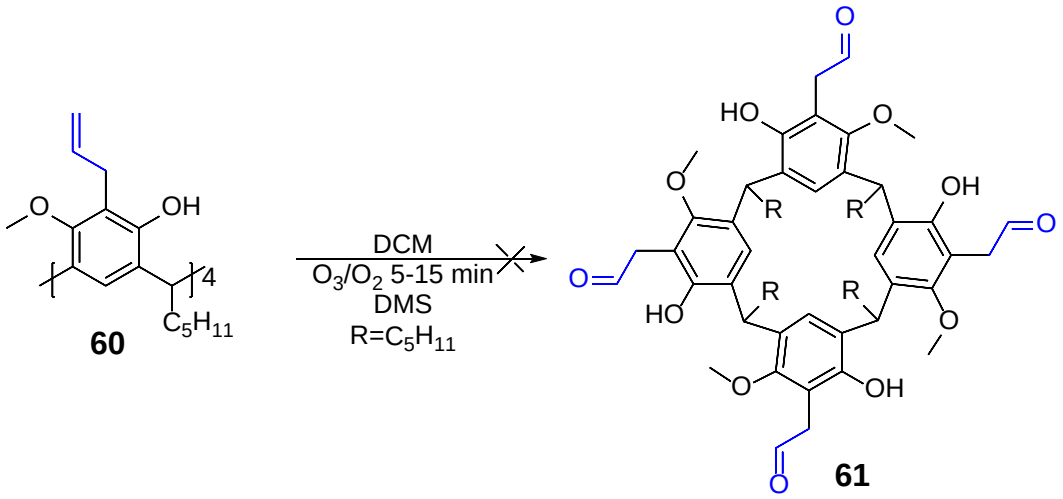


Figure 2.26. Ozonolysis of the alkene functional groups of resorcinarene **60**.

Following a procedure similar for compound **46**, the alkene substrate **60** was dissolved in dry DCM in a flame-dried flask under N_2. The solution was cooled to −78 °C and submitted to a stream of O_3/O_2, the colour of the reaction mixture changing to blue. After all the starting material was consumed, the reaction mixture was quenched with DMS.

Unfortunately, this reaction was not successful. Although all starting material was consumed after 15 min, the desired product was not observed. TLC analysis showed the consumption of the entire starting material, but ^{1}H NMR analysis indicates degradation/fragmentation of the substrate (**Fig. 2.27**).

In the proton NMR spectrum we would expect a triplet in the 9-10 ppm region and a doublet in the 4 ppm region, but neither was observed. The lack of any peak in the 9-10 ppm region indicates the absence of any aldehyde (RCHO) functionality.[42]

As in the case of compound **46**, we see the disappearance of a very distinctive peak around 3.5 ppm, peak C, corresponding to the methoxy moiety in the structure, as well as the disappearance of the peaks corresponding to the alkene group: 3.24 (ddd, "-CH_2-"), 4.91 (dd, "=CH_2"), 5.95 (dddd, "=CH-") ppm.

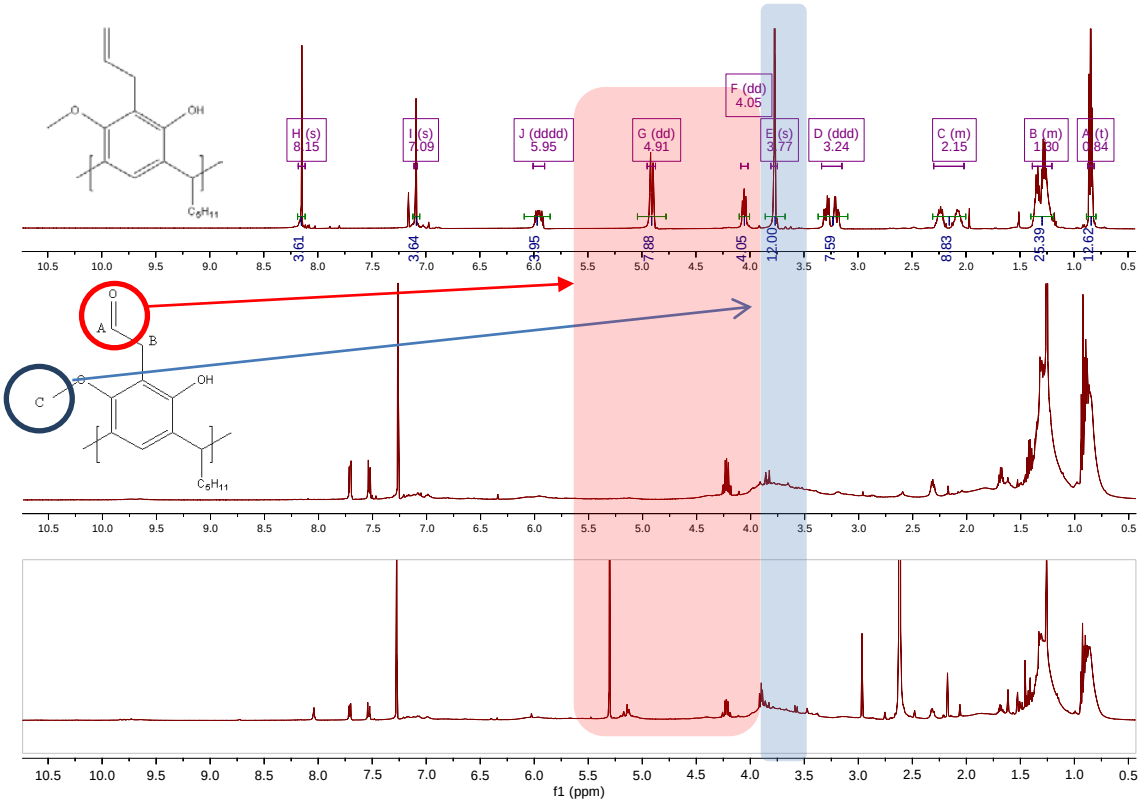


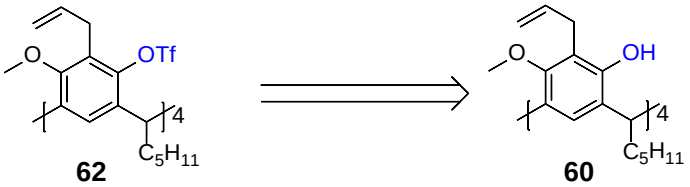
Figure 2.27. ^{1}H NMR spectrums comparing resorcinarene **60** and **61**.

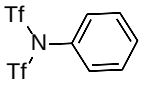
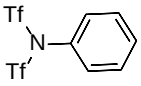
The reaction time was shortened to 5 min, but similar results were obtained, and we concluded that the substrate is fragmented when undergoing ozonolysis.

2.3.4 Triflation of resorcinarene 60.

Next we tried to triflate the phenolic OH of substrate **60**. In **Table 9** are listed the procedures that were applied.

Table 9. Tried procedures for the triflation of compound **60**.



	Triflation reagent	Base	Conditions	Results
a)		K_2CO_3	microwave / MeCN, 42 hr / 100 °C	SM + decomposition
b)	OTf_2	Pyridine	i) SM / dry DCM ii) OTf_2 / dry DCM, 0 °C iii) Py, overnight r.t.	SM + decomposition
c)	OTf_2	TEA	i) SM / dry DCM ii) TEA, OTf_2 / -78 °C ii) 8 days / r.t.	SM + fragmentation
d)	OTf_2	DMAP / 2,6-lutidine	i) SM, DMAP, lutidine, 10 - 15 min / -78 °C ii) OTf_2, overnight / r.t.	SM + fragmentation
e)	OTf_2	*n*-BuLi	i) DIPA / dry THF, 10 - 15 min / -78 °C ii) *n*-BuLi, 30 min / -78 °C iii) SM / dry THF, 30 min / -78 °C iv) OTf_2, overnight / r.t.	SM + fragmentation
f)	OTf_2	TEA / DMAP	i) SM / dry DCM, TEA, DMAP 10 - 15 min / -78 °C ii) OTf_2 at -78 °C ii) overnight / r.t.	SM + fragmentation
g)	OTf_2	*i*-Pr_2NEt or K_2CO_3	i) SM / dry DCM, base 10 - 15 min / -78 °C ii) OTf_2 at -78 °C ii) overnight / r.t.	SM + fragmentation
h)		*i*-Pr_2NEt	SM, $PhN(OTf)_2$, base / MeCN overnight / r.t.	SM + decomposition
i)	OTf_2	Pyridine	i) SM / dry pyridine ii) OTf_2 at 0 °C ii) 2 days / reflux iv) HCl	> 89%

SM = starting material
DIPA = Diisopropyl amine

After many tries with no success, we managed to synthesize compound **62**, following the next procedure: trifluoromethanesulfonic anhydride was added dropwise over a solution of **60** in anhydrous pyridine at 0 °C, under an atmosphere of N_2, colour changing to yellow. The reaction mixture was refluxed for two days under N_2, colour changing to dark brown. After the reaction has finishes, the reaction mixture was diluted with EtOAc, washed with HCl at 0 °C, with water, than brine, dried on $MgSO_4$ and filtered, yielding a colourless solid (yield > 89 %) (**Fig. 2.28**).

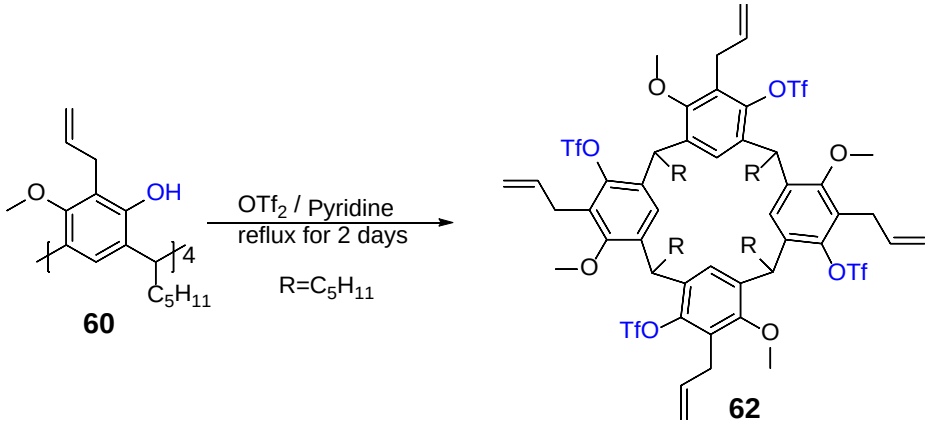


Figure 2.28. Triflation of compound **60** to afford compound **62**.

We were happy to be able to triflate substrate **60**, as the new product **62** was not reported in the literature, as far as we know. The structure was confirmed by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, COSY, HSQC, MS.

2.3.5. Alkylation of the phenolic OH of resorcinarene 60.

Following a procedure by *Mori*[9], like in the case of compound **44**, the phenolic groups were converted to the corresponding ethers using a Williamson synthesis. Treatment of compound **60** with K_2CO_3, methyl bromoacetate in MeCN under reflux for 48 hours gave compound **60-B** in good yields (87 %). The evolution of the reaction was followed by TLC, and the completion required a longer time (48 hr) than in the case of compound **44** (8 hr), due to steric hindrance. We were happy to be able to alkylate substrate **60**, as compound **60-B** was not reported in literature, as far as we know. Unfortunately, the structure was only analysed by ^{1}H NMR.

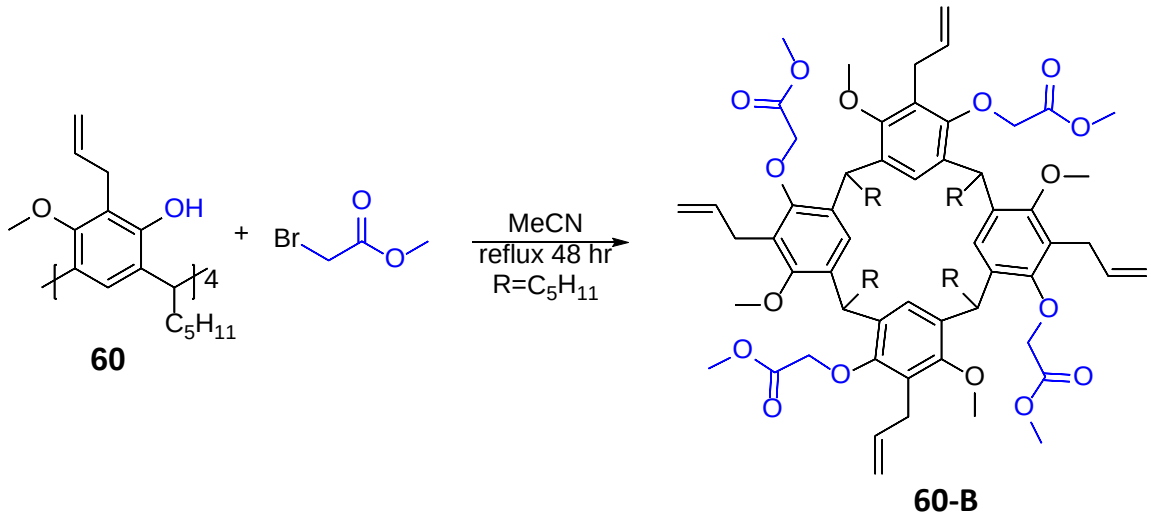


Figure 2.29. Alkylation of resorcinarene **60** with methyl bromoacetate.

2.4. Epoxidation of the alkene moiety of resorcinarenes 46 and 60.

Epoxides (oxiranes) are 3-membered heterocycles (cyclic ethers) formed from one O atom and two C atoms, that due to their polarity and ring/angle strain, are very reactive towards a ring opening (**Fig 2.30**).

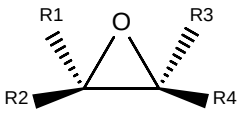
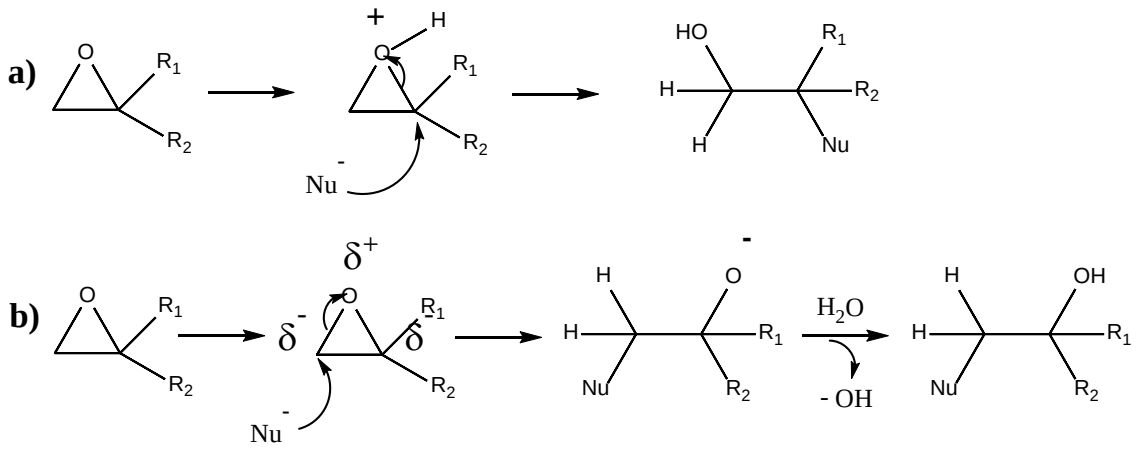


Figure 2.30. General epoxide moiety.

Because of that, these chemical species can react with a wide number of reagents, such as nucleophiles, electrophiles, acids, bases, reducing and oxidizing agents. (**Scheme 7**).[43]



Scheme 7. Nucleophilic addition to an epoxide: a) Acid-catalysed; b) Base-catalysed.[43]

These compounds are important as this structure is encountered in many natural and biologically active compounds, and they can be useful intermediates/building blocks in organic synthesis (**Fig. 2.31**).[44-46]

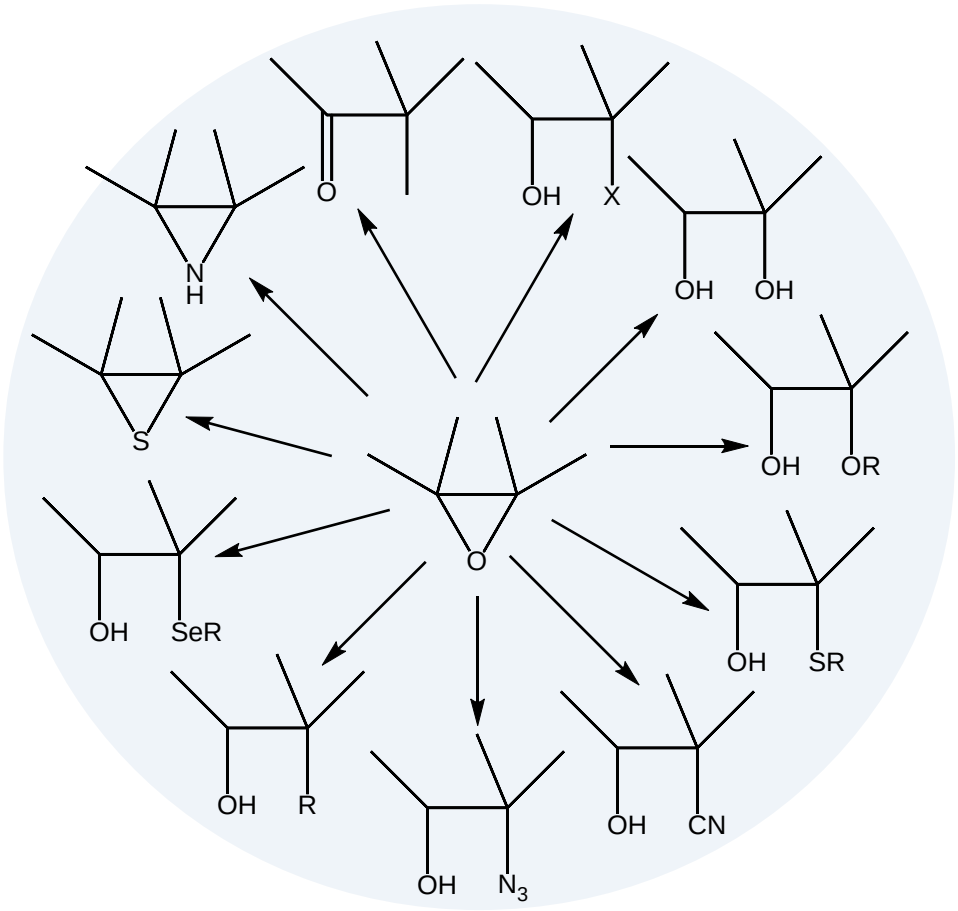


Figure 2.31. Epoxide reaction roadmap.[43]

In the table below are presented some methods used in literature for alkenes and aromatic alkene epoxidations.

Table 10. Epoxidation conditions found in the literature.

Ref.	Substrate	Reagents	Yield (%)	Conditions
47	Olefins	Oxaziridinium-mediated epoxidation, oxone	90	r.t. 2-6 hr
48	Substituted aromatic olefins	First generation-type manganese salen catalyst, benzotrifluoride, cat. 0.39 mol %, PhIO	50-100	r.t. 10 min
49	Substituted alkenes	DMDO/acetone	85-95	-78 to 56 °C, 0.1-12 hr
50	Unfunctionalized aryl alkenes	Oxone / Na_2CO_3, MeCN:H_2O 1:1, 5-10 mol % iminium salt catalyst	Up to 100	0 °C, < 45 min
51	Simple alkenes	Chiral ketones, HSO_5^- ,CH_2Cl_2-H_2O pH 7-8, potassium peroxomonosulphate	60-92	5-25 min
52	Aromatic alkenes	0.96 mol % catalyst (iron, picH, Me-picH complex), 35 % H_2O_2, MeCN	69-98	25 °C, 5 min
53	Alkenes	m-CPBA, $NaHCO_3$, CH_2Cl_2	Up to 100 % depending on substrate	r.t., 16-20 hr
53	Alkenes	Oxone ®, trifluoroacetone, Na_2.EDTA, MeCN-water, $NaHCO_3$,	Up to 100 % depending on substrate	0 °C, 2-3 hr

As we were working on a new compound, we had to take in consideration some influential factors that affect this type of reaction such as: solvent system, temperature, oxidant and catalyst.

m-CPBA is one of the most used peroxyacid for oxidation reactions. So, our first choice was a classical method, in which our substrate (**60**) was reacted in DCM with m-CPBA at 0 °C, in an attempt to prepare the tetra-substituted resorcinarene (**63**) (**Fig. 2.32.**).

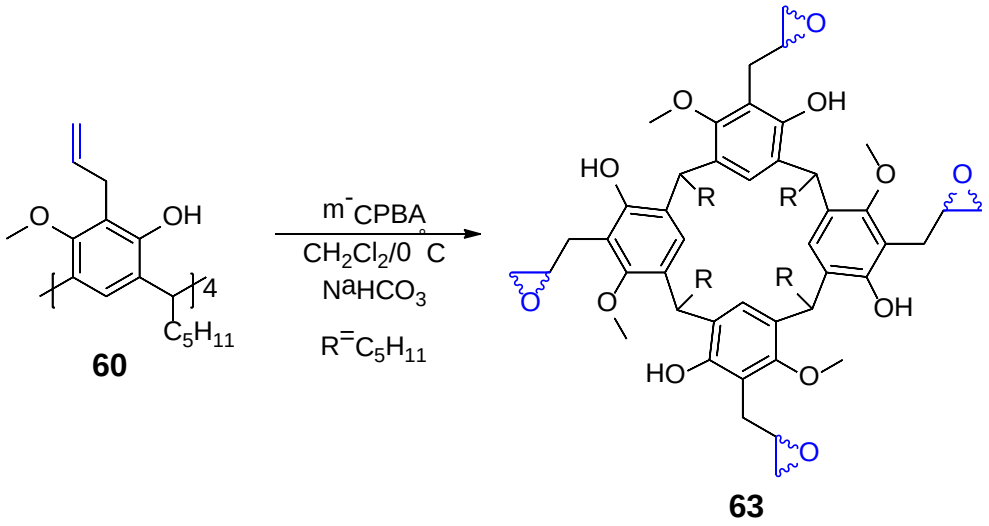


Figure 2.32. Epoxidation of compound **60** using *m*-CPBA.

During the reaction we observed (using TLC) that using less than 9 equivalents of *m*-CPBA, took 50 min, at 0 °C, for all the starting material to be consumed, and multiple spots arose on the TLC. However increasing the *m*-CPBA equivalents to 20, the starting material was consumed in 5-10 min, but still multiple spots were observed on the TLC.

It became clear that reaction time and quantities of reagents are significant factors in the success of this reaction. Unfortunately, we could not separate the spots using column chromatography.

Our concern was that, as the reaction moves forward, acids and water are formed as side products and could interfere with the reaction, and so we repeated the reaction using 1.5 equivalents of base (Na_2CO_3) for each equivalent of *m*-CPBA, but no major differences were observed by TLC. We know the starting material is consumed, but,

unfortunately, the IR and ^{1}H NMR spectra were inconclusive. This can be due to the fact that from this reaction, several products can be formed. Each ring in the product has an epoxide group that can be present in one of the two diastereoisomeric forms, giving a range of possible conformations and arrangements (**Fig 2.33**).

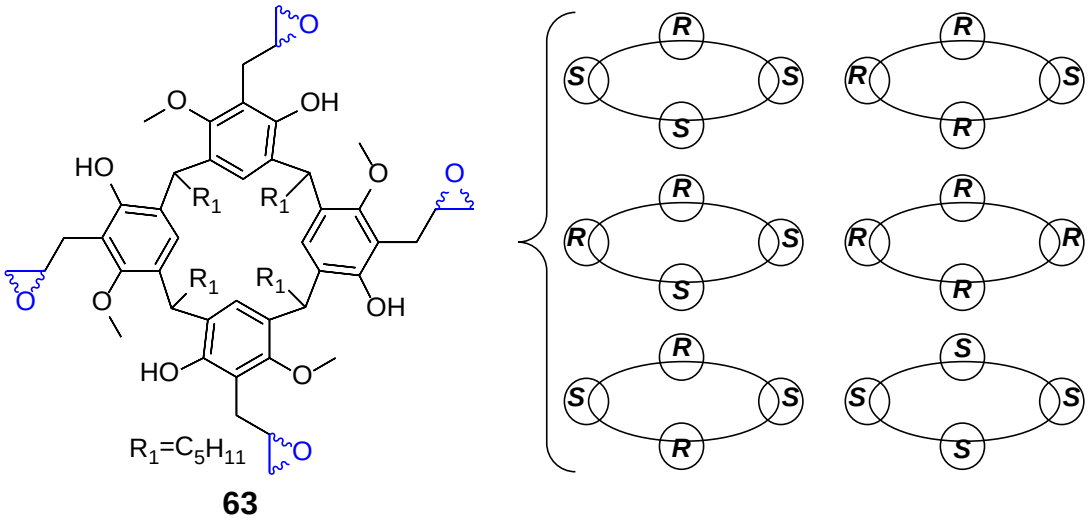


Figure 2.33. Possibilities of *S* and *R* combinations.

We can observe (**Fig. 2.34**) from the ^{1}H NMR spectrum that the multiplet characteristic for C15 and the dd corresponding to C16 disappear, concluding that the double bond is broken. As well, a very distinctive peak is the singlet around 3.5-4 ppm corresponding to C7, and we can see that after the reaction, instead of a singlet, we observe a multiplet in the expected region, with the correct number of protons as we would expect. This could indicate that several products are formed.

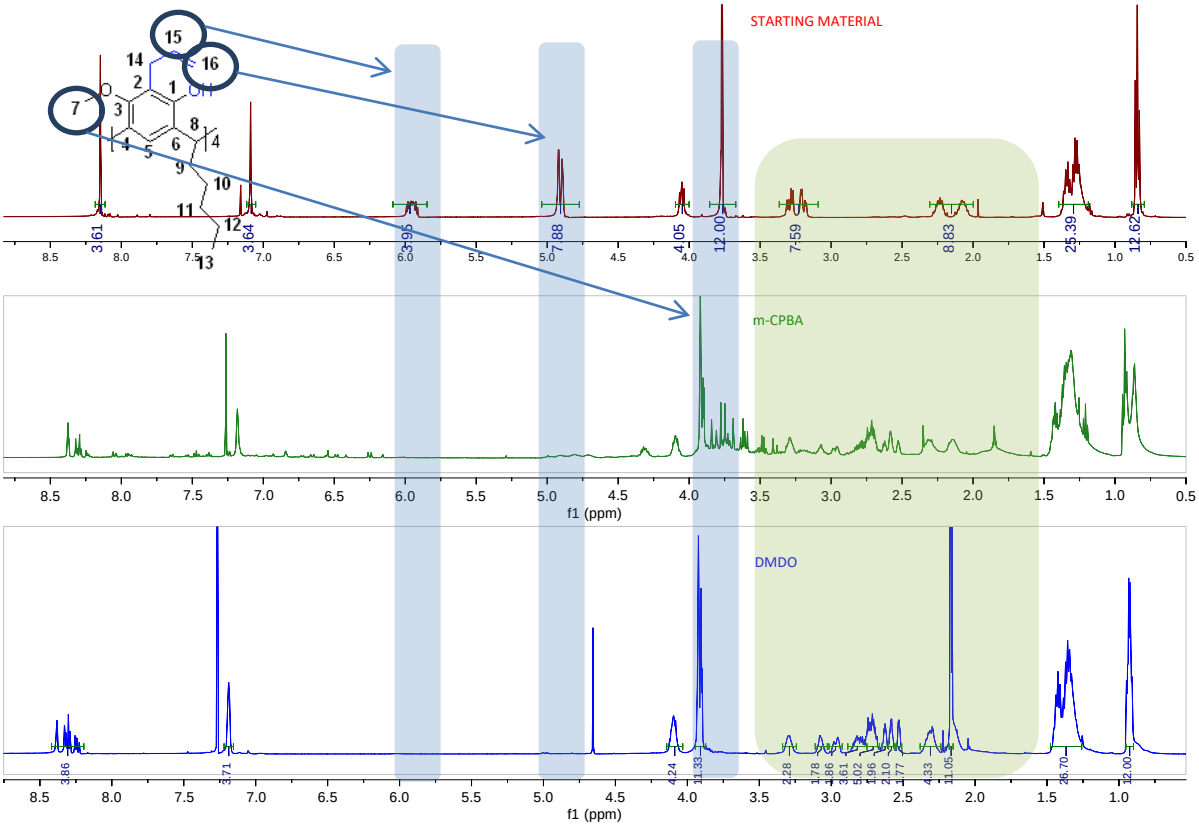


Figure 2.34. ^{1}H NMR comparison between the starting material **60** and the NMRs of the epoxidation reaction using *m*-CPBA or DMDO.

To investigate further, we next tried an epoxidation of compound **60** using DMDO/acetone (**Fig. 2.35**), which is a useful oxidant for a variety of oxyfunctionalizations.[49]

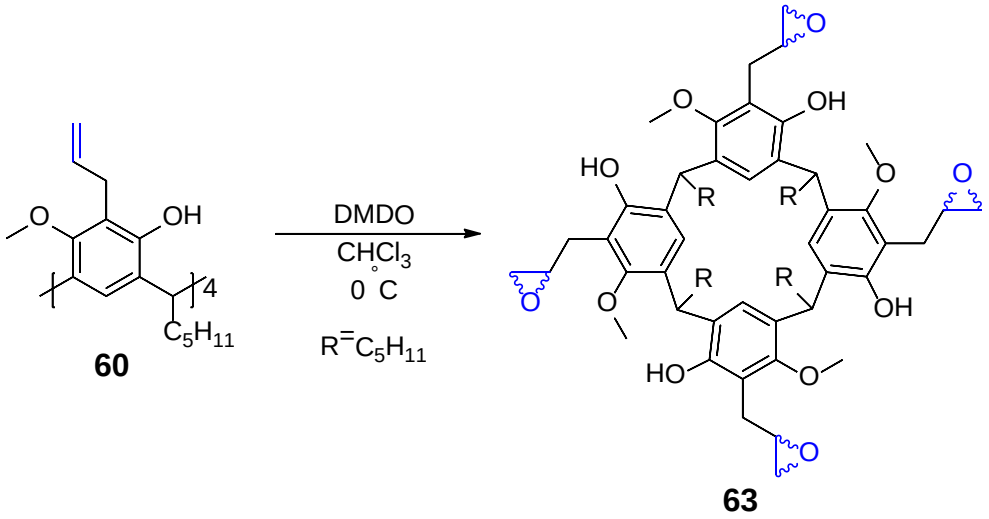


Figure 2.35. Epoxidation of compound **60** using DMDO.

The starting material **60** was dissolved in chloroform and the reaction mixture was cooled to 0 °C. A 0.03 M solution of DMDO/acetone was added to the mixture and the reaction was monitored by TLC. The DMDO/acetone solution was freshly prepared before each epoxidation. In this case, we can see that the ^{1}H NMR spectrum is much cleaner. The same observations were made as in the case of the *m*-CPBA. Looking at the 2-3.5 ppm region (**Fig. 2.36**), there are several possibilities: either the peaks correspond to the different epoxide diastereoisomers, or maybe there was a ring closure, or the epoxide rings opened giving different alcohols, or we obtained a mixture of epoxides and alcohols on different positions.

In 1984, *Gorzynski*[45] published "*Synthetically Useful Reactions of Epoxides*" in which an interesting remark was made. According to their studies, epoxides can be ring opened by neighbouring functionalities on the same structure, in an intramolecular fashion, generating carbocycles. This can happen either in the presence of a strong base or an olefin in the presence of a Lewis acid.[45]

Unfortunately, the IR and ^{1}H NMR spectra were inconclusive. This could be due to the fact that from this reaction, several products could be formed.

Using DMDO, only 9 equivalents were required to consume all starting material in 30 min. The TLC indicated multiple spots. As in the case of *m*-CPBA, many product spots are observed. Moreover, purification of this product proved extremely challenging.

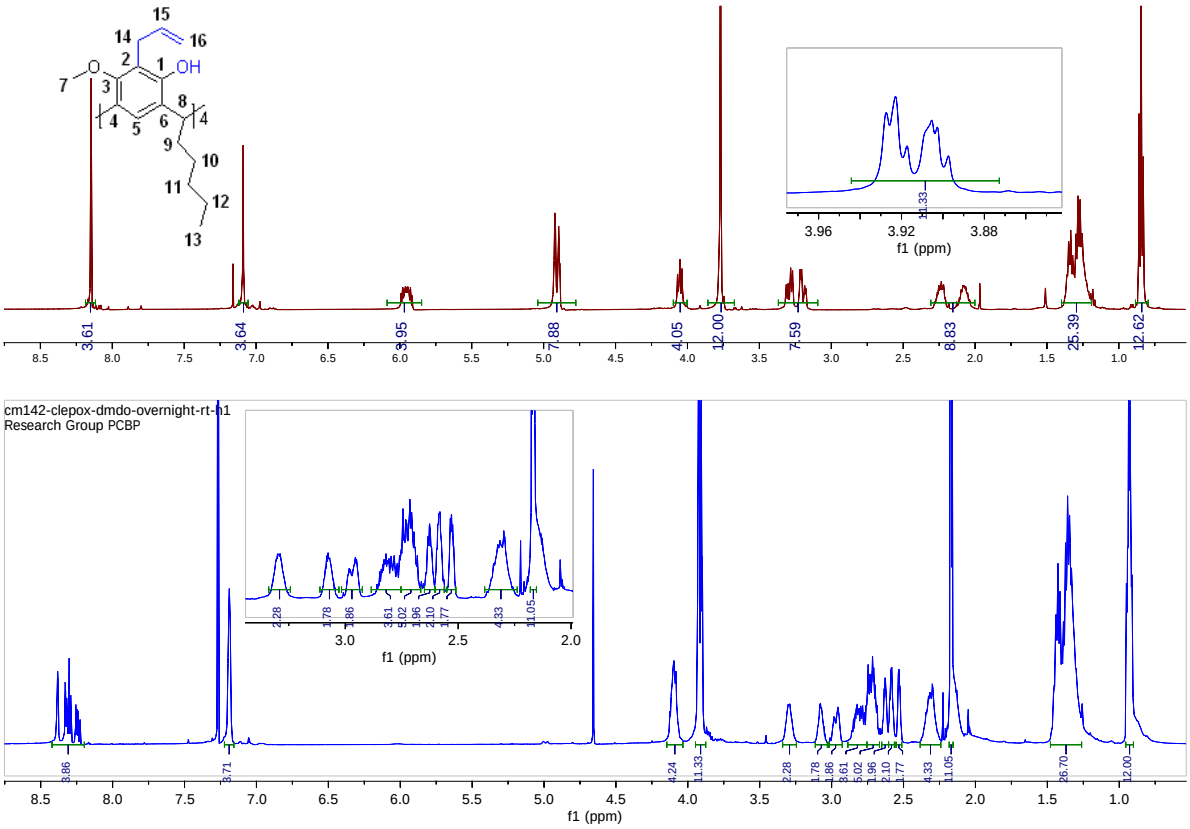


Figure 2.36. NMR spectra comparison between the starting material **60** and compound **63**.

We turned our attention towards catalysis; in this case, our concern was high steric hindrance.

Epoxidation catalysis can either be carried out by the usual transition-metal catalysts, having the drawback of oxidative degradation, or by using metal-free organic catalysts. In 2001, *Adam*[54] published the review "*Synthetic Applications of Nonmetal Catalysts for Homogeneous Oxidations*" in which he presents some popular organic catalysts (**Fig. 2.37**).

Lately many groups have shown an interest in iminium salt catalysed epoxidation, using Oxone as primary oxidant. In 2006, *Page*[55] published "*Non-aqueous iminium salt mediated catalytic asymmetric epoxidation*" in which the research group reported a new method, involving iminium salt-catalysed epoxidation in non-aqueous conditions, which eliminates the use of water and base, having TPPP as oxidant (**Fig. 2.38**).

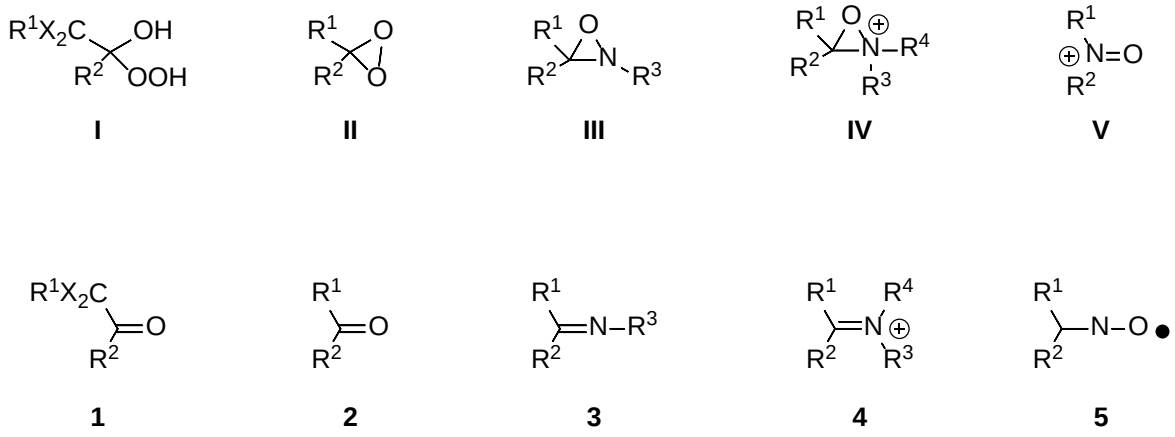


Figure 2.37. Nonmetal catalysts used for homogenous oxidations, by *Adams*.[54]

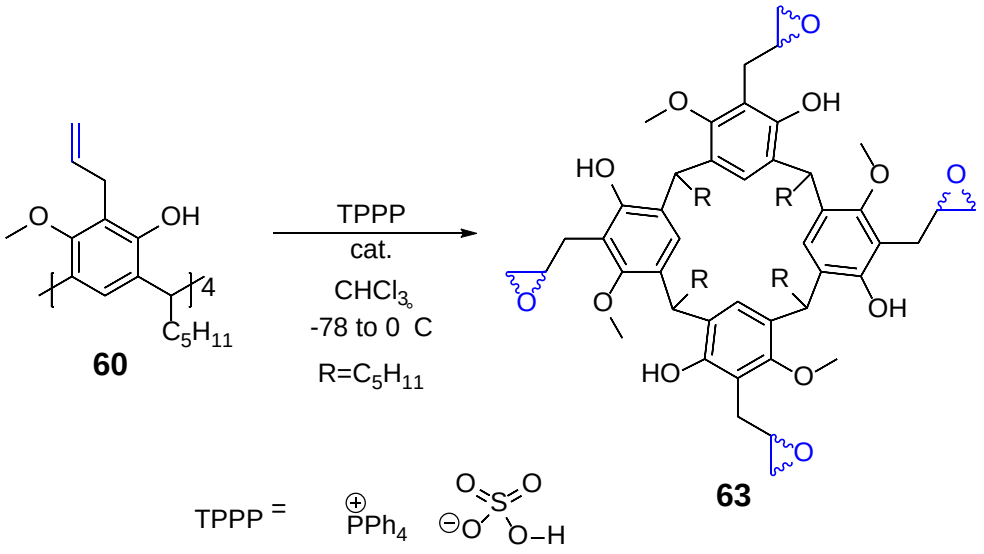


Figure 2.38. Iminium salt-catalysed epoxidation of compound **60**.

Following the cited procedure, resorcinarene **60** was treated with a solution of TPPP and iminium salt in $CHCl_3$ or DCM at low temperature (-78 to 0 °C) and stirred for 15-20 min, hoping to achieve the tetra-substituted product **63**. Unfortunately, this approach was not successful, although the substrate showed some reactivity. Modifications of the reaction time, reaction temperature and reagents equivalents failed to provide positive results. We presume this low reactivity is due to steric hindrance.

The lack of results provided by TLC, IR and NMR, led us to investigate further using MALDI. Crude mixtures were used and major spectroscopy peaks were recorded, as we can see in (**Fig. 2.39 – 2.42**).

We were pleased to find the expected values corresponding to our tetra-substituted resorcinarene.

Table 11 – expected values for MALDI analysis for compounds.

Compound no.	***m/z* SM***	***m/z* Product (tetra-epoxide)***
46/60	984.65	1048.63
46/60 + K^+	1023.61	1087.59
46/60 + Na^+	1007.64	1071.62

* Required values calculated in ChemDraw

Figure 2.39. MALDI spectra (without Matrix) for the epoxidation of **60** using *m*-CPBA.

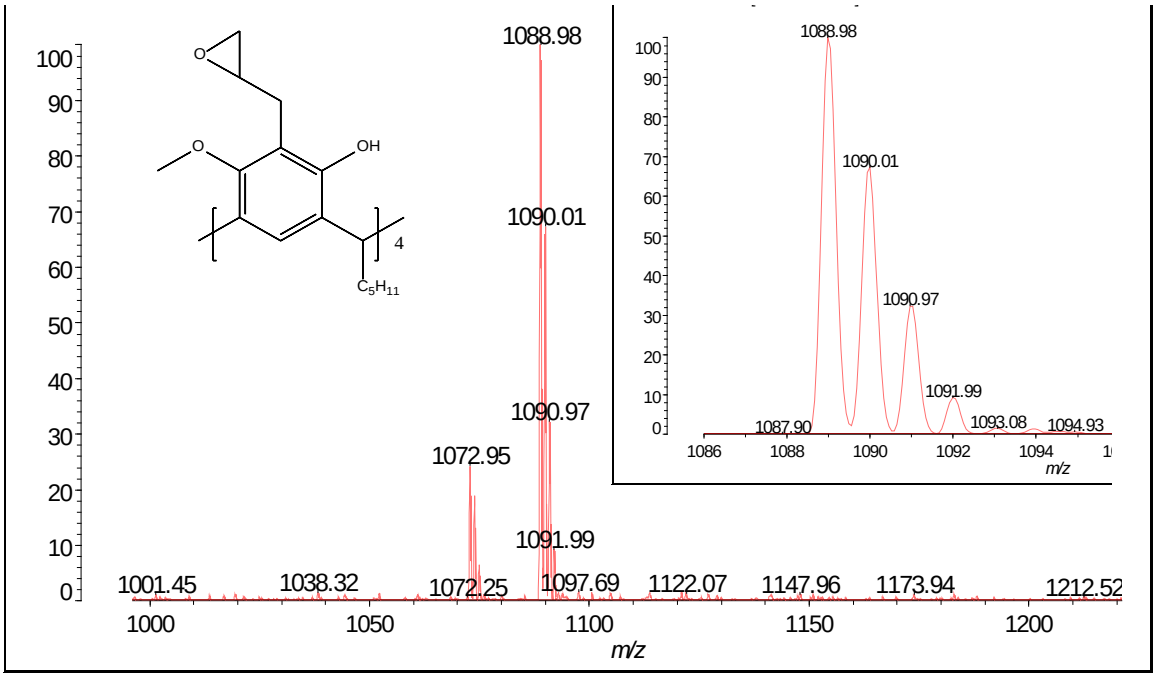


Figure 2.40. MALDI spectra (with Matrix) for the epoxidation of **60** using *m*-CPBA.

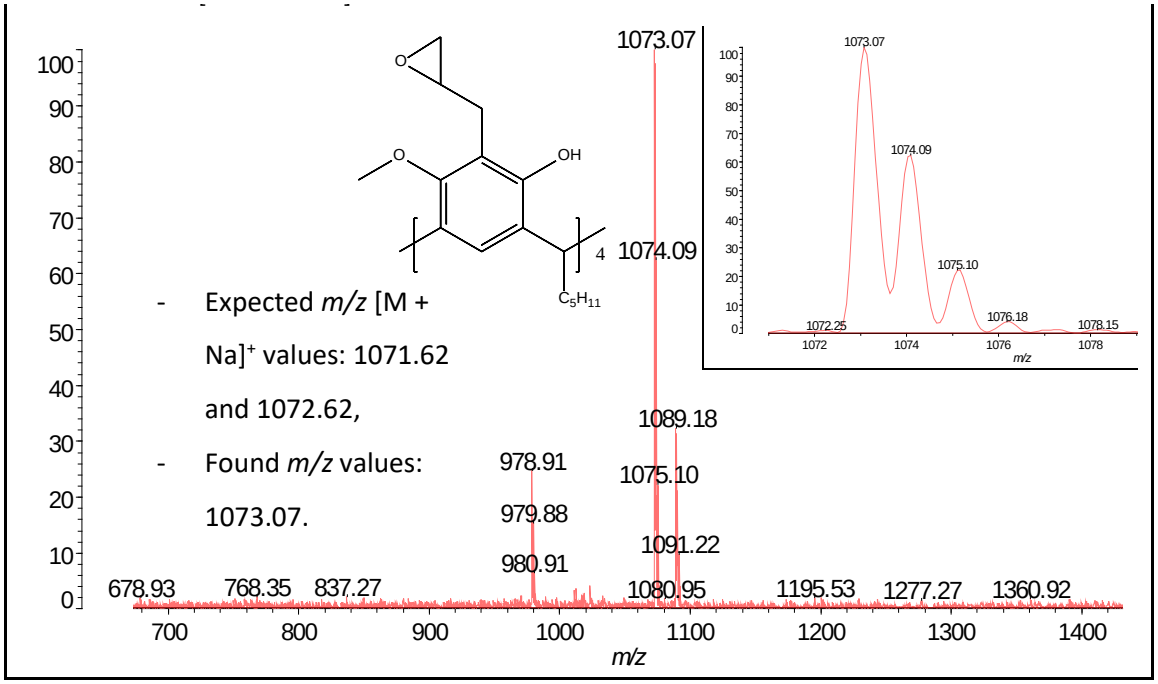


Figure 2.41. MALDI spectra (without Matrix) for the epoxidation of **60** using DMDO.

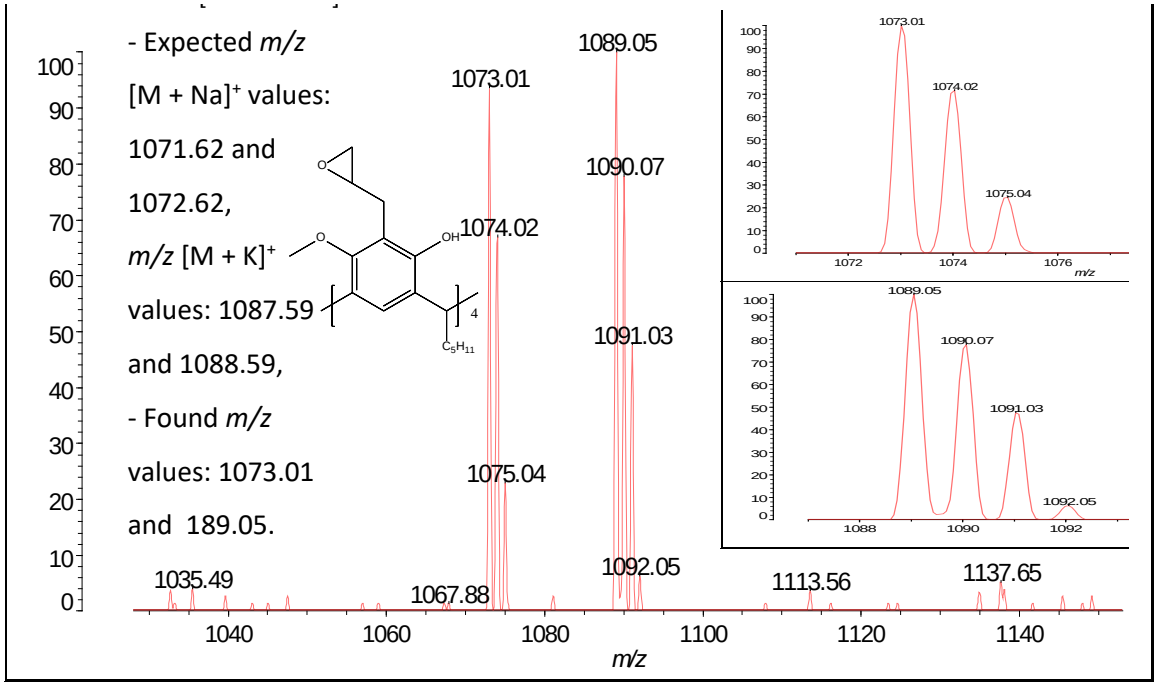
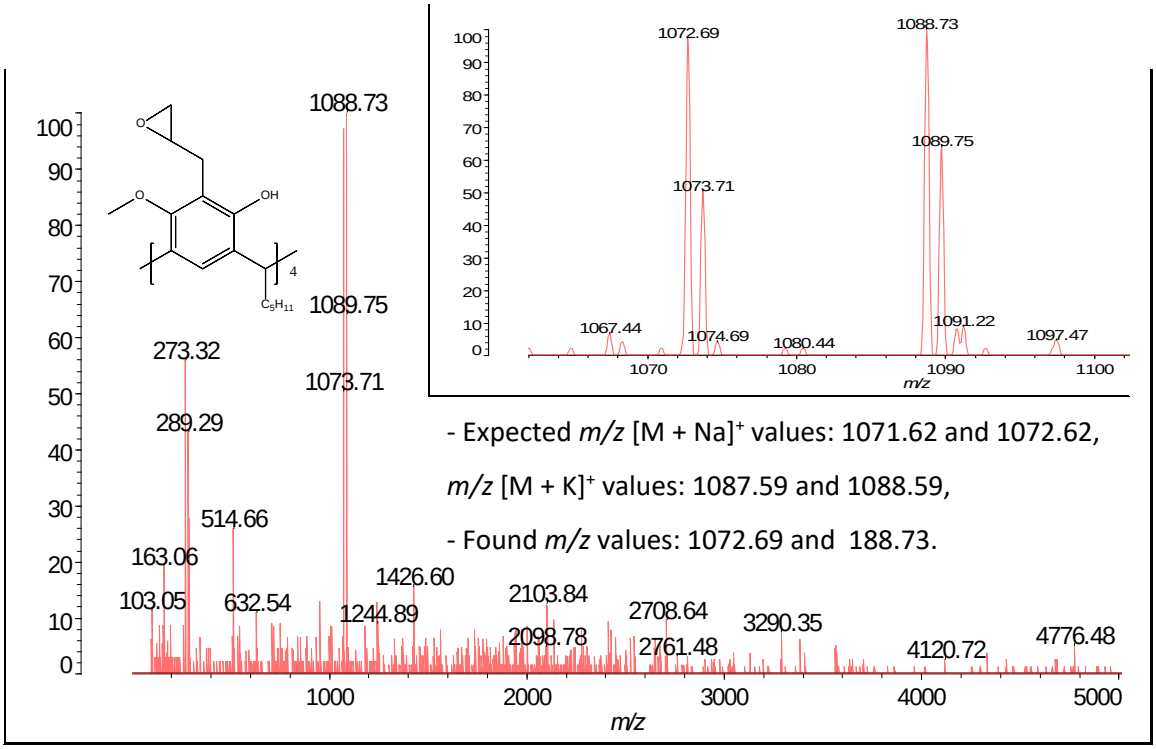


Figure 2.42. MALDI spectra (with Matrix) for the epoxidation of **60** using DMDO



Similar procedures were attempted on substrate **46**, and similar results were obtained (**Fig. 2.43 – 2.48**).

Substrate **46** was also reacted in DCM with m-CPBA at 0 °C, in an attempt to produce the tetra-substituted resorcinarene **64** (**Fig. 2.43.**).

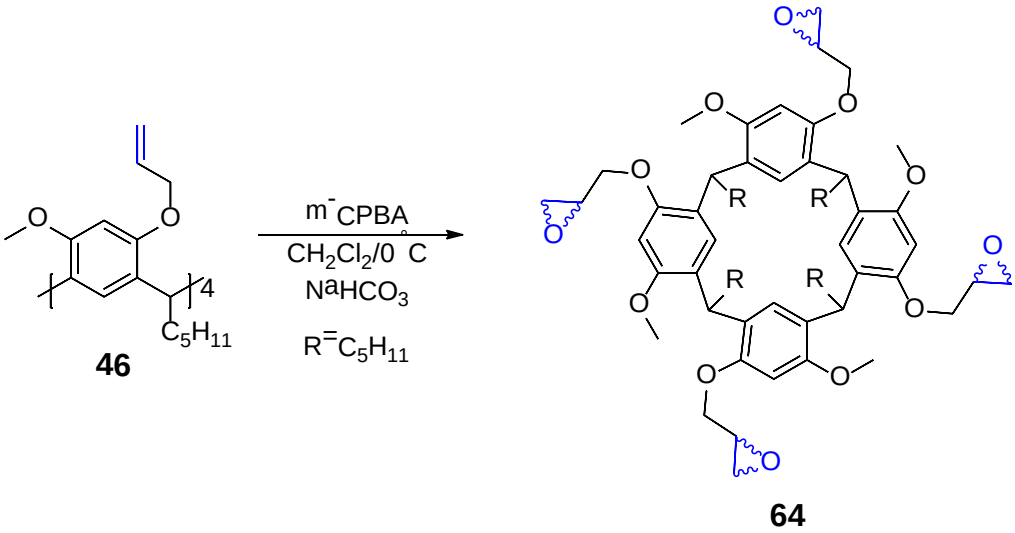


Figure 2.43. Epoxidation of compound **46** using *m*-CPBA.

The starting material **46** was dissolved in chloroform and the reaction mixture was cooled down to 0 °C. A 0.03 M solution of DMDO/acetone was added to the mixture and the reaction was monitored by TLC (**Fig. 2.44.**).

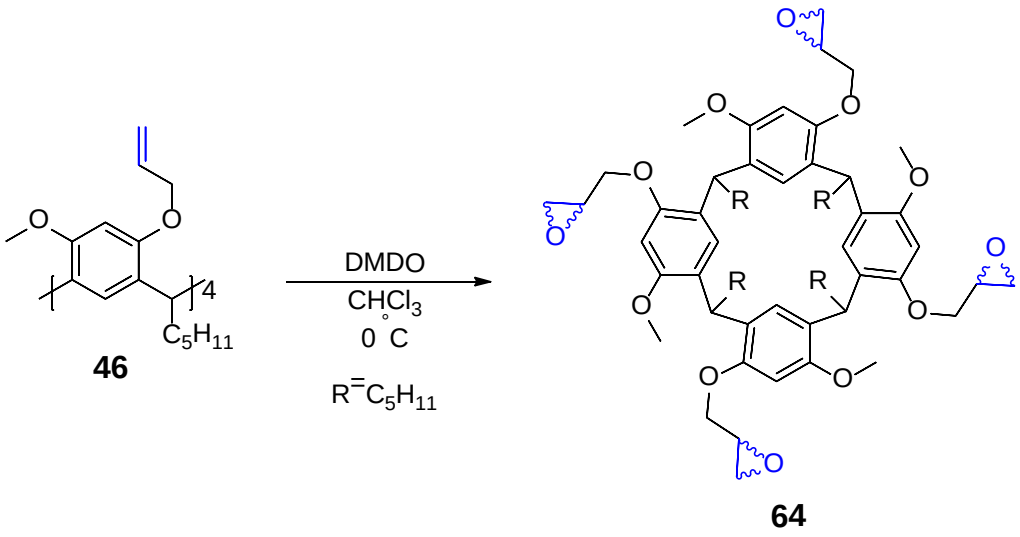


Figure 2.44. Epoxidation of compound **46** using DMDO.

Resorcinarene **46** was treated with a solution of TPPP and iminium salt in $CHCl_3$ or DCM at low temperature (-78 to 0 °C) and left stirring for 15-20 min, hoping to achieve the tetra-substituted product **64** (**Fig. 2.45**).

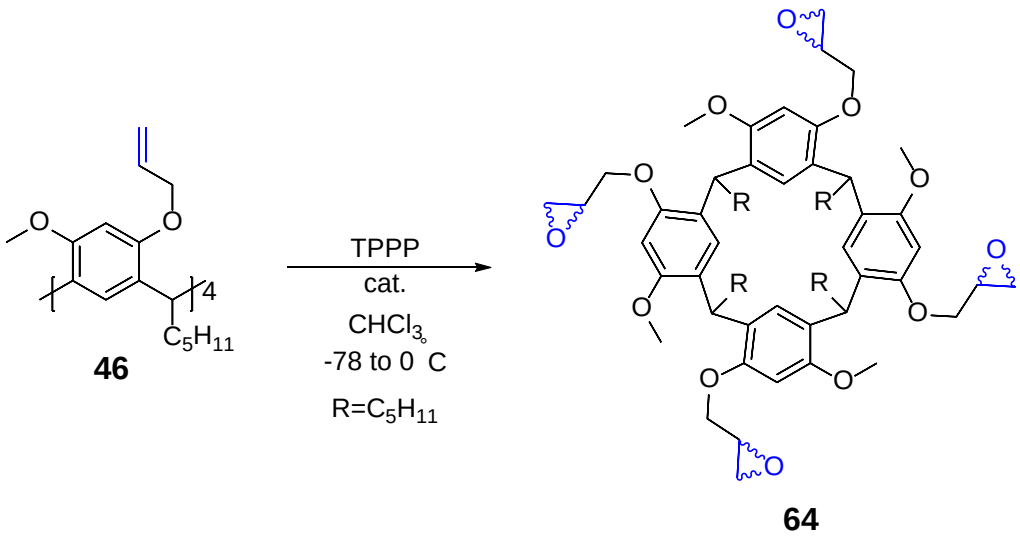


Figure 2.45. Iminium salt-catalyzed epoxidation of compound **46**.

46-*m*-CPBA-without Matrix

46-*m*-CPBA-with Matrix

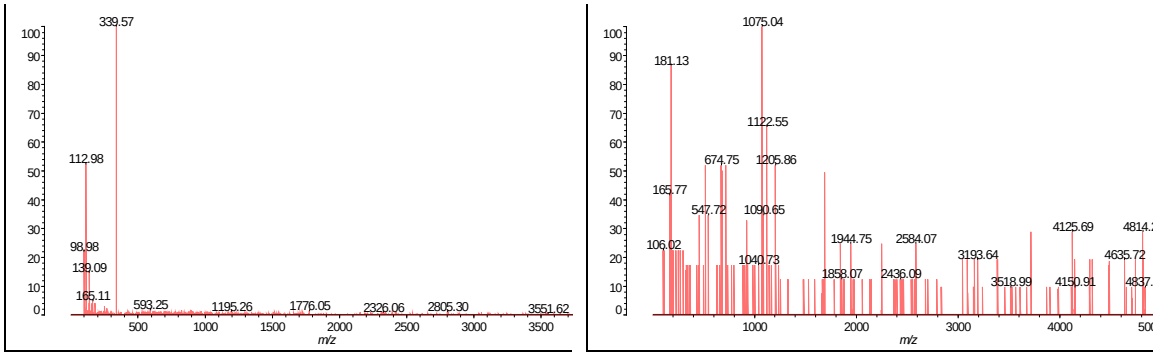


Figure **2.46**. MALDI spectra for the epoxidation of **46** using m-CPBA.

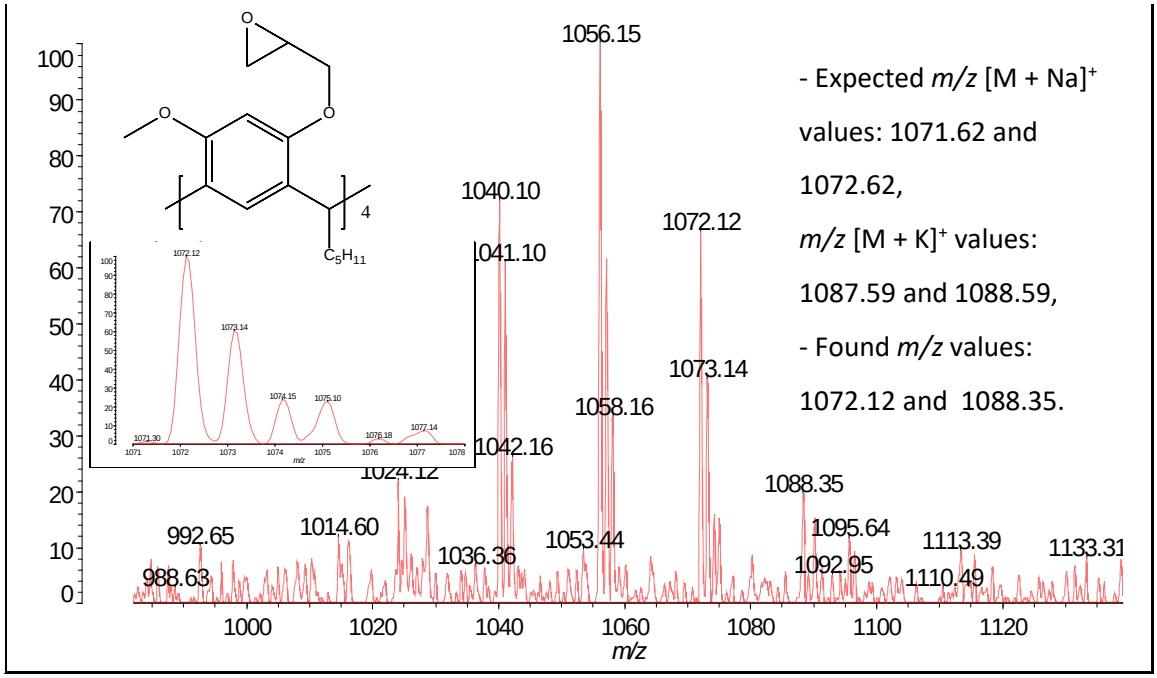


Figure **2.47**. MALDI spectra (without Matrix) for the epoxidation of **46** using DMDO.

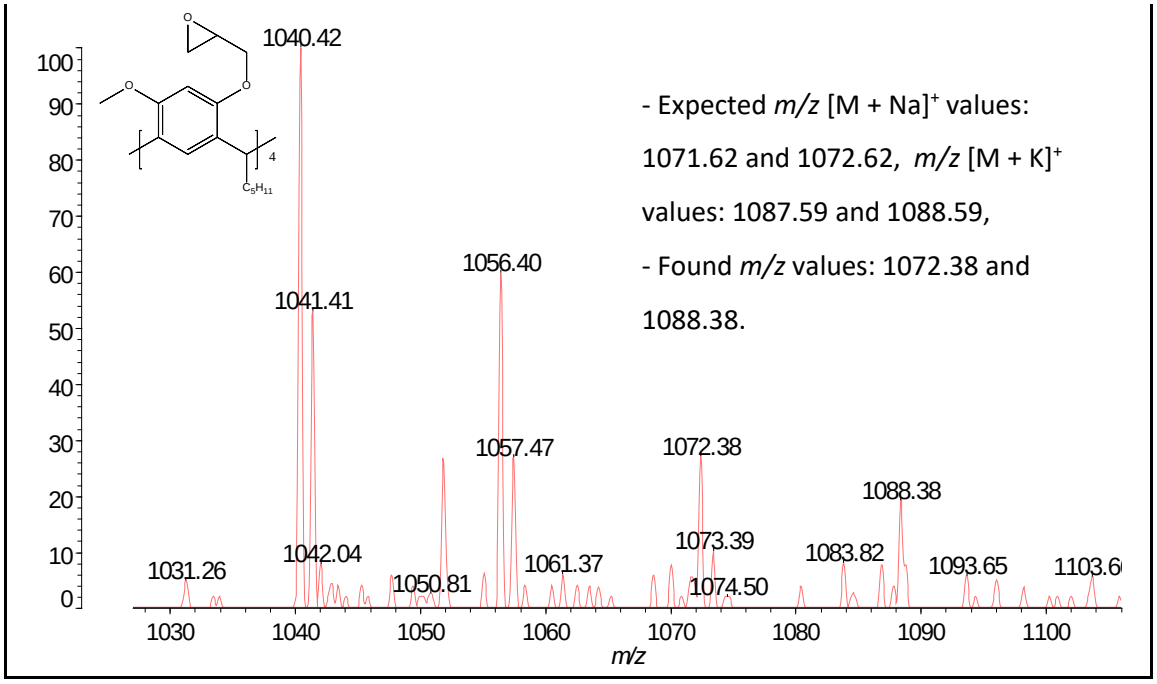


Figure **2.48**. MALDI spectra (with Matrix) for the epoxidation of **46** using DMDO.

We can see that for substrate **60** we have identified the desired *m/z* values for both methods, using *m*-CPBA and using DMDO, but in the case of substrate **46**, we could not identify the desired values when using *m*-CPBA, but we were glad to obtain positive results using the DMDO method.

As future work for this type of reaction, a preparative TLC might be used to separate the various spots, and then use MALDI for analysis.

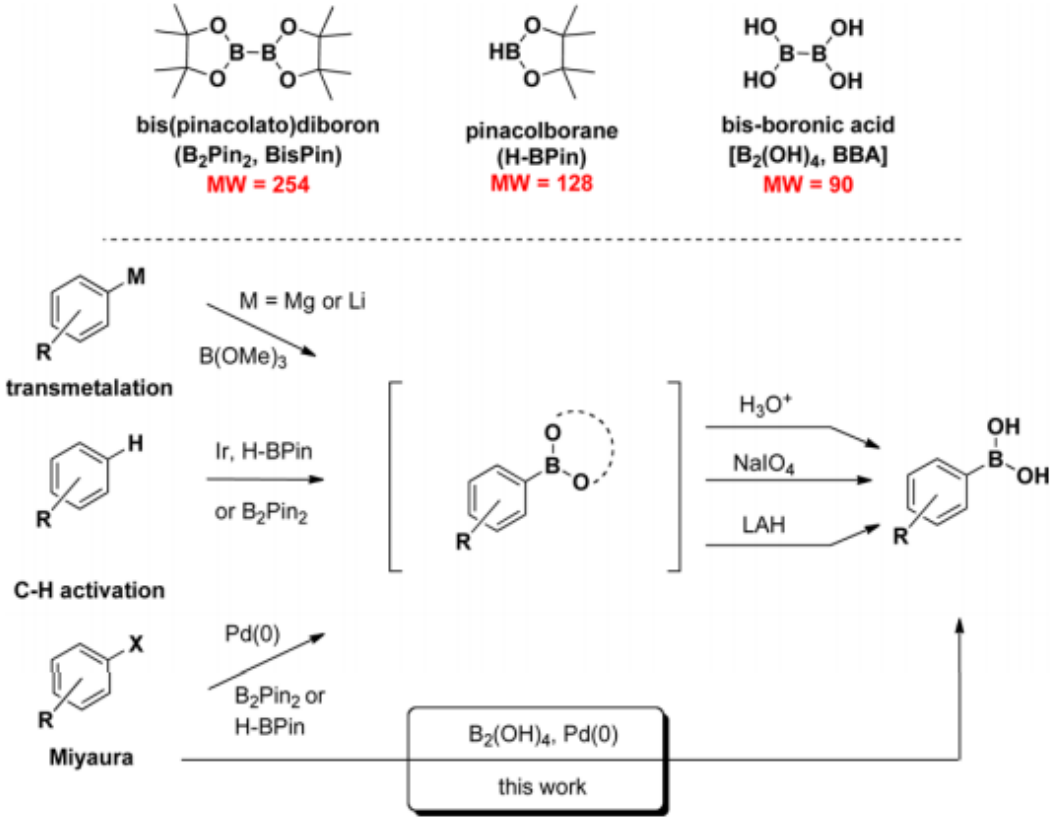
2.5. Hydroboration and Borylation of resorcinarenes 39, 46, 60 and 62.

Organoboron systems are important in synthetic chemistry, as precursors to introducing new functionalities as well as for medicinal and biological applications. These compounds have been used to prepare enzyme inhibitors, drug delivery compounds and antibody mimics.[56-59]

Boronic esters and acids are generally prepared as shown in **scheme 8**[56, 60] via:

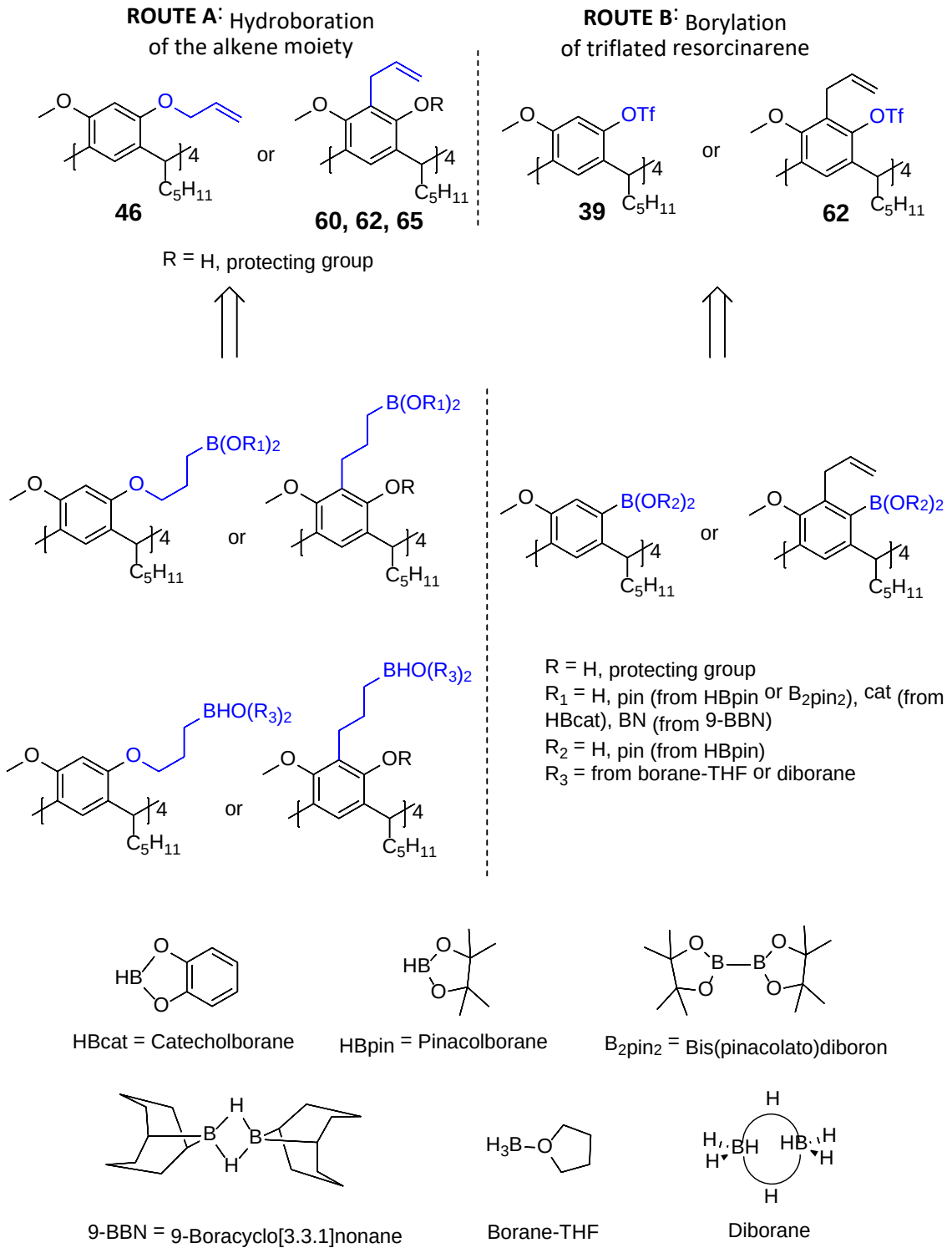
a) transmetalation (Grignard or lithiation) with an excess of trialkylborate – protocol that involves the preparation of organometallic species, which can tolerate few functional groups;

b) C-H activation or palladium catalysed borylation – procedures more tolerant to functionality but, using B_2pin_2 generate unwanted byproducts that are hard to hydrolyse or remove; there are high costs of the catalysts, there are catalyst decomposition and heavy metal impurities.



Scheme 8. Methods for boronic esters and acids synthesis, reproduced from.[60]

Looking at our structure we can see that, in order to attach a boron moiety, there are two possible routes: the first possibility involves a hydroboration of the alkene moiety (**Scheme 9 – Route A**), while the second route involves a catalysed aryl borylation of our triflated resorcinarenes (**Scheme 9 – Route B**).



Scheme 9. Proposed strategies for resorcinarene borylation or hydroboration.

We first attempted a classical approach (**Fig. 2.49.**). Borane in THF was added to substrate **46** or **60** and refluxed for one week. The substrate did not appear reactive enough under the conditions used and recovery of starting material was obtained (**Table 12 – entries 1 and 5**).

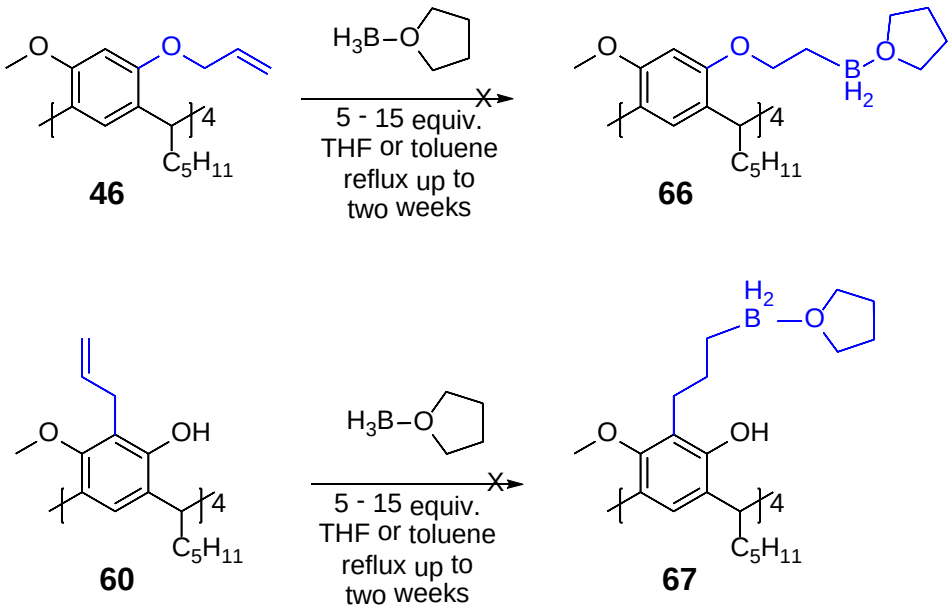
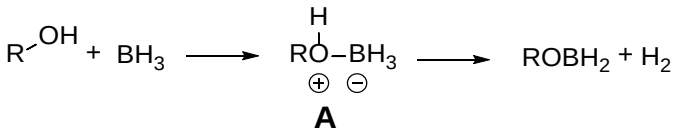


Figure 2.49. Hydroboration of the resorcinarene alkene moiety using borane-THF.

In 1976, *Clinton*[61] published "*Reduction of Organic Compounds with Diborane*" in which he stated that the BH_3-THF reacts relatively slowly with phenolic OH, thus, in the case of compound **60**, could be a competing reaction. The BH_3 "*reacts with the alkoxy oxygen to give intermediate **A**, which decomposes with evolution of hydrogen*" (**scheme 10**).



Scheme 10. General reaction of BH_3 with alcohols.[61]

In an attempt to optimize this reaction, we increased the amount of boron-THF, we changed the solvent to toluene, in order to increase the temperature, and we increased the reaction time to up to 2 weeks, but all reactions gave a recovery of the starting material (**Table 12 – entry 9**). When using substrate **60**, the analysis of ^{1}H NMR spectrum indicated decomposition products (**Table 12 – entry 13**).

In 1981, *Brown*[62] published "*Hydroboration. 57. Hydroboration with 9-Borabicyclo[3.3.1]nonane of Alkenes Containing Representative Functional Groups*", in which the group used 9-BBN to perform hydroborations on terminal alkenes. 9-BBN

presents a series of advantages: is soluble in most organic solvents, is stable in inert conditions, it hydroborates preferably the terminal carbon and it tolerates many functional groups. The disadvantage when applying this protocol to our hindered substrates is its bulky nature.

Compounds **46, 60** and **62** were treated with 9-BBN in THF at 0 °C and stirred at this temperature for 1.5 hr and then for 1 hr at room temperature (**Fig. 2.50.**).

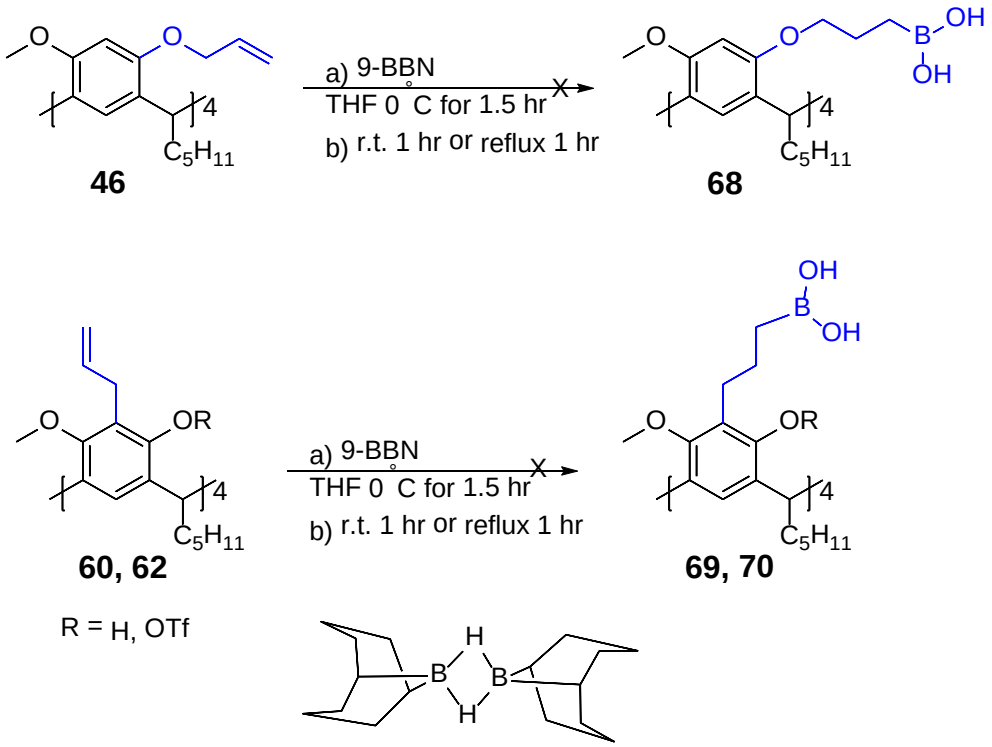


Figure 2.50. Hydroboration of the resorcinarene alkene moiety using 9-BBN.

As monitoring by TLC did not indicate any reactivity, we increased the temperature and left the reaction mixture under reflux for one hour. Unfortunately, we recovered the majority of the starting material alongside with degradation fragments (**Table 12 – entries 20 and 21**).

Interestingly, when applying the protocol to substrate **62**, the TLC analysis showed that all starting material is consumed, but no desired products were observed by ^{1}H NMR spectroscopy (**Table 12 – entry 22**).

Next we changed the boron source, and the hydroboration reaction was performed using bis(pinacolato)diboron (**Fig. 2.51.**) but similar results were obtained and starting material was recovered (**Table 12 – entries 2, 6, 10 and 14**).

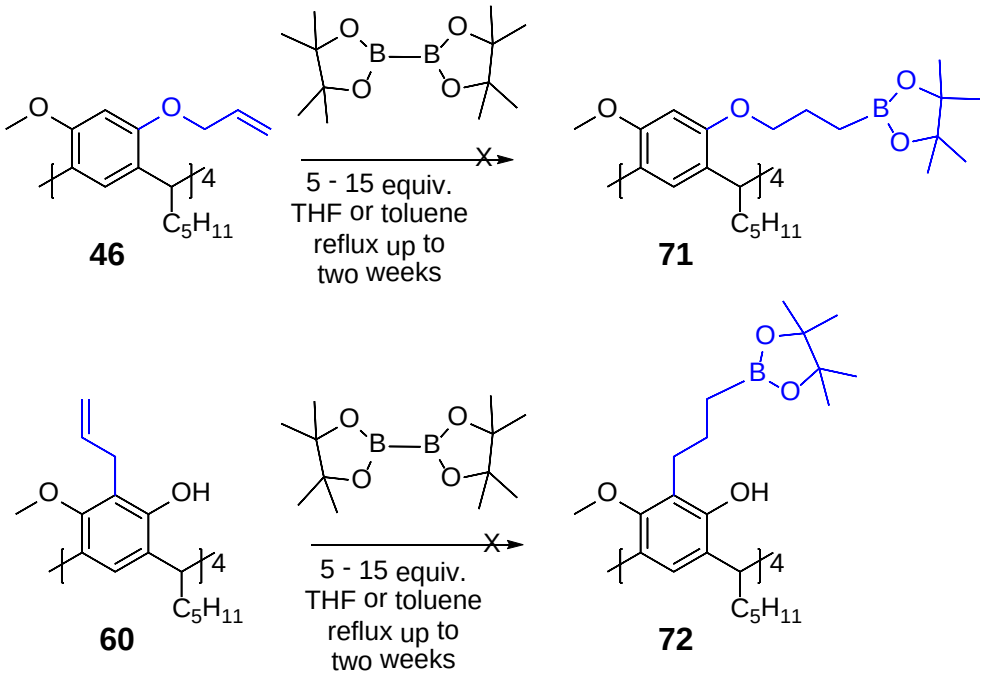


Figure 2.51. Hydroboration of the resorcinarene alkene moiety using Bis(pinacolato)diboron.

When treating substrates **46** and **60** with HBpin (**Fig. 2.52.**), alongside the recovery of the majority of the starting material we detected side products (**Table 12 – entries 3, 7 and 11**), that might be attributed to decomposition or byproducts arising from the HBpin reagent.

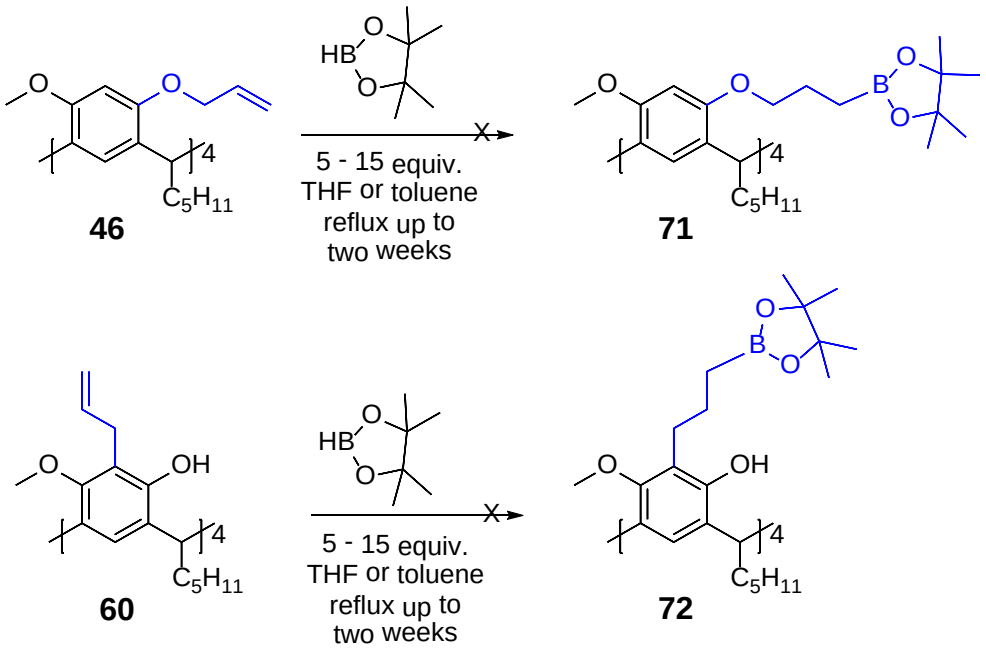


Fig. 2.52. Hydroboration of the resorcinarene alkene moiety using HBpin.

Interestingly, after treatment of **60** with HBpin at reflux over two weeks, the ^{1}H NMR spectrum showed only decomposition fragments (**Table 12 – entry 15**).

Cathecolborane (HBcat) proved to be unreactive under the reaction conditions (**Fig. 2.53**) and the starting material was recovered alongside with degradation fragments (**Table 12 – entries 4, 8, 12 and 16**).

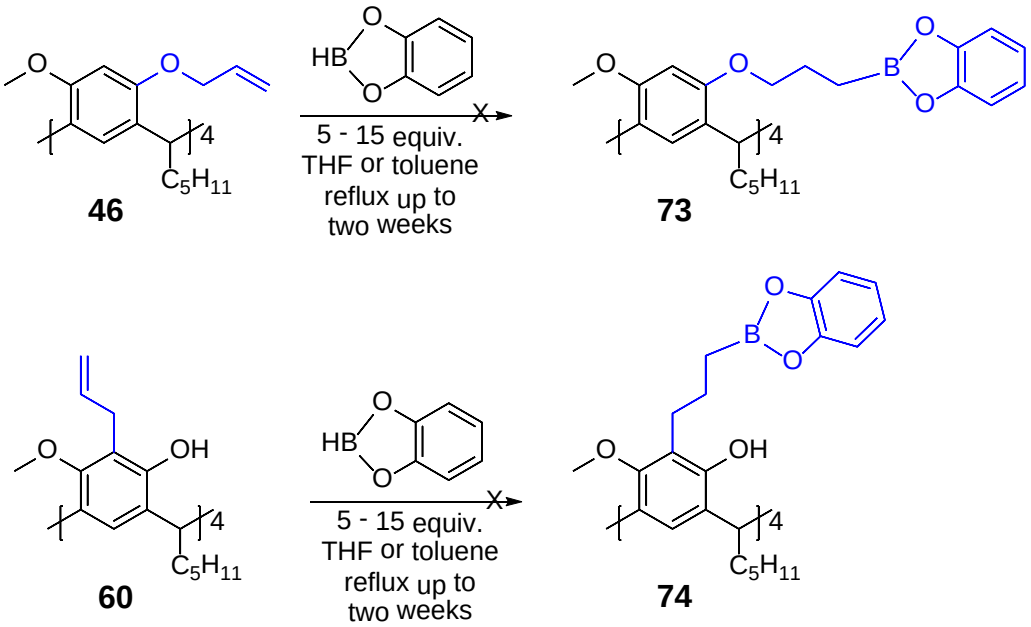
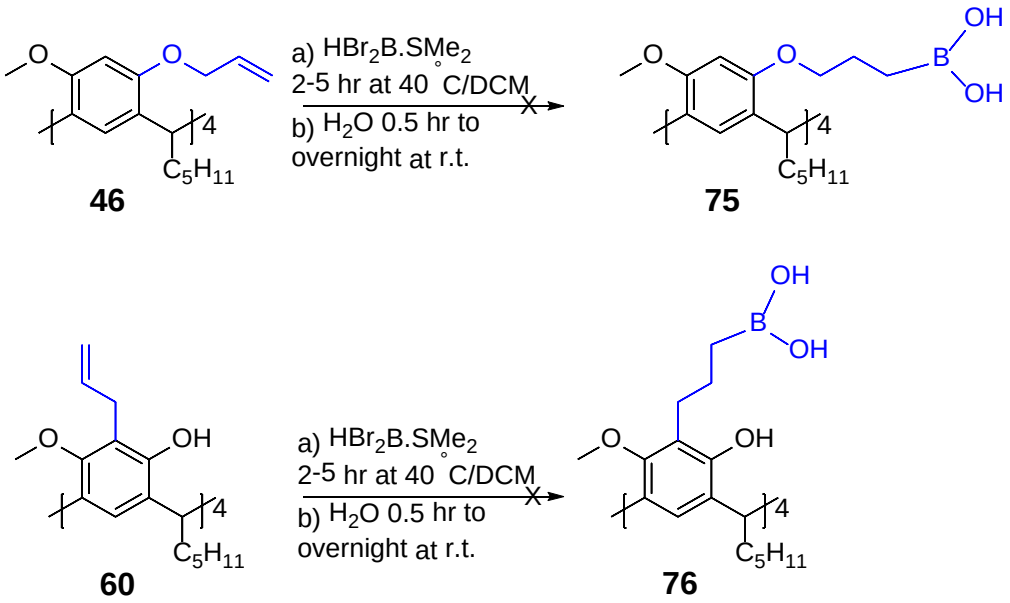


Figure 2.53. Hydroboration of the resorcinarene alkene moiety using HBcat.

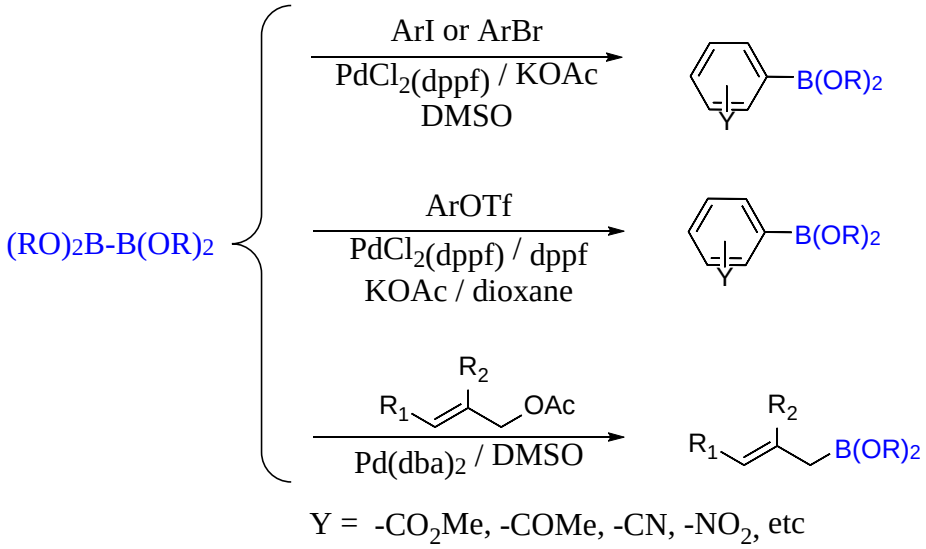
Following the reported procedure by Brown,[63] compounds **60** and **46** were treated with $HBr_2B.Sme_2$ in DCM, and the mixture was refluxed for 2-5 hr, forming an alkyl dibromoborane dimetlylsulfide intermediate. This complex is decomposed by water into the corresponding boronic acids: the reaction mixture was treated with H_2O and the reaction was stirred overnight at room temperature (**Fig. 2.54.**). Various conditions were screened (**Table 12 – entries 17, 18 and 19**), and TLC indicated no starting material, but unfortunately the desired compound was not achieved.



$$RCH{=}CH_2 + HBr_2B.Sme_2 \rightarrow RCH_2CH_2BBR_2.Sme_2 + 2H_2O \rightarrow RB(OH)_2 + HBr$$

Figure 2.54. Hydroboration of the resorcinarene alkene moiety using $HBr_2B.Sme_2$.

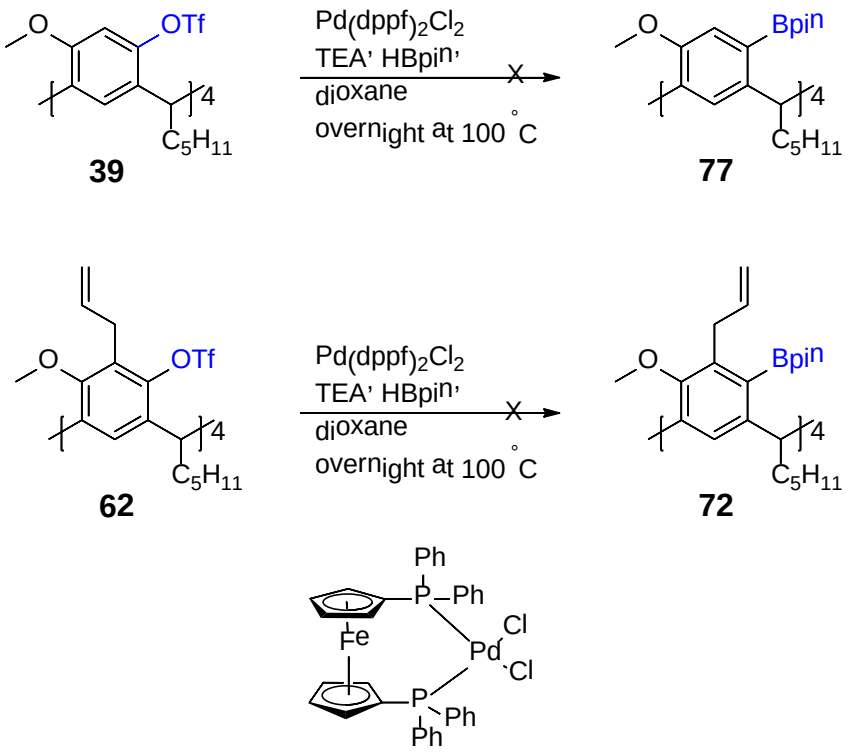
As we were interested in aryl substrates, we were happy to find a paper by *Miyaura,*[64] in which the group describes a palladium-catalysed method to obtain arylboronates from aryl halides, aryl triflates and aryl acetates, coupled with bis(pinacolato)diboron, as shown in **Scheme 11**.



Scheme 11. Synthesis of arylboronates from aryl halides, aryl triflates and aryl acetates through palladium-catalysed cross-coupling with bis(pinacolato)diboron by *Miyaura* et al.[64]

A similar protocol was published by *Murata*[65] in 2000, in "*Palladium-Catalyzed Borylation of Aryl Halides or Triflates with Dialkoxyborane: A Novel and Facile Synthetic Route to Arylboronates*". Following the cited procedure, the starting material (compounds **39** and **62**), TEA and HBpin were added to a solution of $PdCl_2(dppf)_2$ in dioxane, and the reaction mixture was heated at 100 °C overnight (**Fig. 2.55.**).

Unfortunately, TLC and ^{11}B NMR spectroscopy showed that the reaction was unsuccessful and the starting material was recovered (**Table 12 – entry 24**).



$Pd(dppf)_2Cl_2$ = [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)

Figure 2.55. Palladium-catalysed hydroboration of resorcinarene **62**.

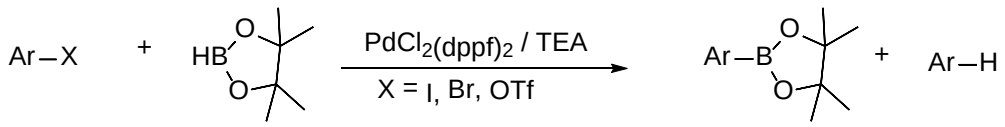
The proposed catalytic cycle (**Scheme 12**) for the palladium catalysed borylations consists of:[65]

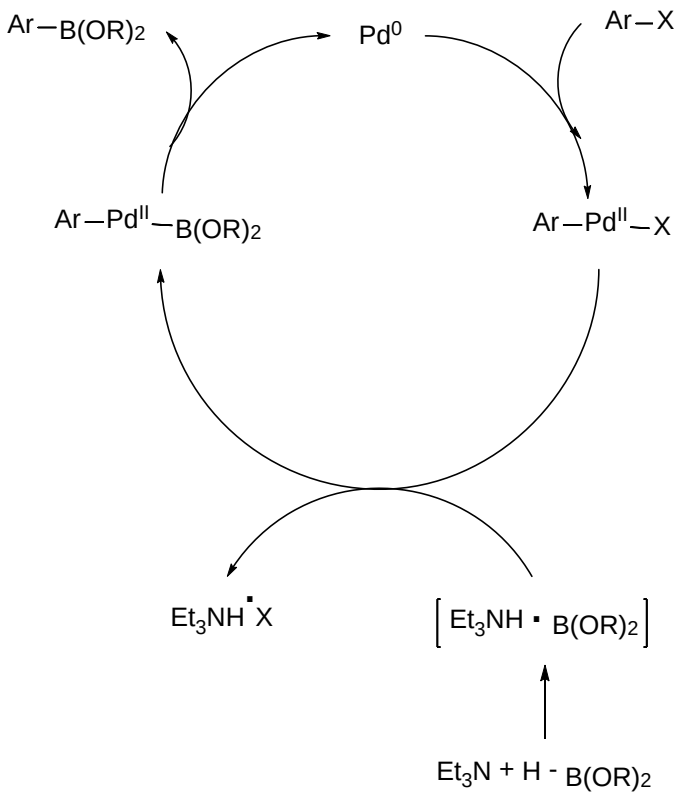
a) *Oxidative addition* of Ar – X to the Pd catalyst to give Ar – Pd^{II} – X (arylpalladium) species;

b) *Ligand exchange* between the X of Ar – Pd^{II} – X and the boryl anion, giving Ar – Pd^{II} – $B(OR)_2$ intermediate and Et_3 – NH**.**X;

c) *Reductive elimination* gives the arylboronate Ar – $B(OR)_2$ and regeneration of the catalyst.

General reaction scheme:





Scheme 12. Proposed catalytic cycle for Pd-catalysed borylation, by *Masuda*.[65]

Another procedure that was attempted is pictured in **Fig. 2.56.**[66] The starting material (**comp 46, 60** and **62**) was added to a stirred solution of CuCl, xantphos, NaO^{t}Bu and B_2pin_2 in anhydrous THF, and stirred at room temperature for 5 min. Dried MeOH was added and the reaction mixture was stirred overnight at room temperature to 40 °C.

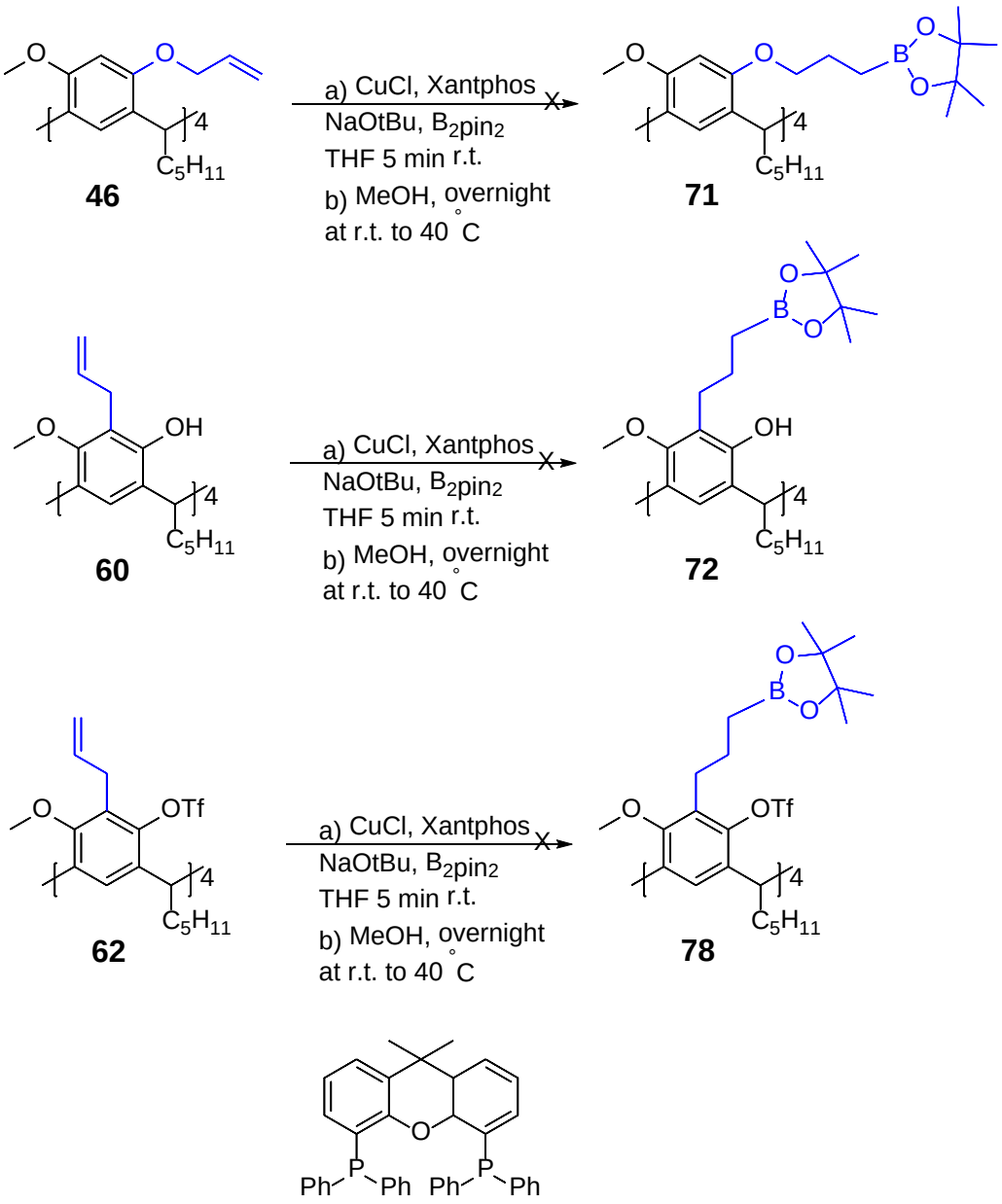


Figure 2.56. CuCl catalysed hydroboration of the resorcinarene alkene moiety.

When applying the cited procedure on compound **60**, the TLC, ^{1}H NMR and ^{11}B NMR spectroscopy indicated recovery of the starting material (**Table 12 – entry 26**).

When the protocol was applied to compound **46**, the crude ^{1}H NMR spectrum showed some signs of reactivity alongside with starting material. The same peak pattern is multiplied and shifted both upfield and downfield of the original starting material peak, a fact which would indicate that on some rings the functionality has changed. Unfortunately, the ^{11}B NMR indicated that no desired product was formed. The

spectrum (**Fig. 2.57.**) showed three signals: a singlet at +22 ppm, corresponding to the hydrolysed B_2pin_2, one at +30 ppm, for a $O[B(R)OH]_2$ species and a peak at + 33 ppm, indicating a $RB(OH)_2$ species. Unfortunately no desired compounds were observed. In an attempt to push the reaction forward, we increased the temperature and stirred the reaction mixture at 40 °C overnight. Unfortunately, similar results were obtained (**Table 12 – entry 25**).

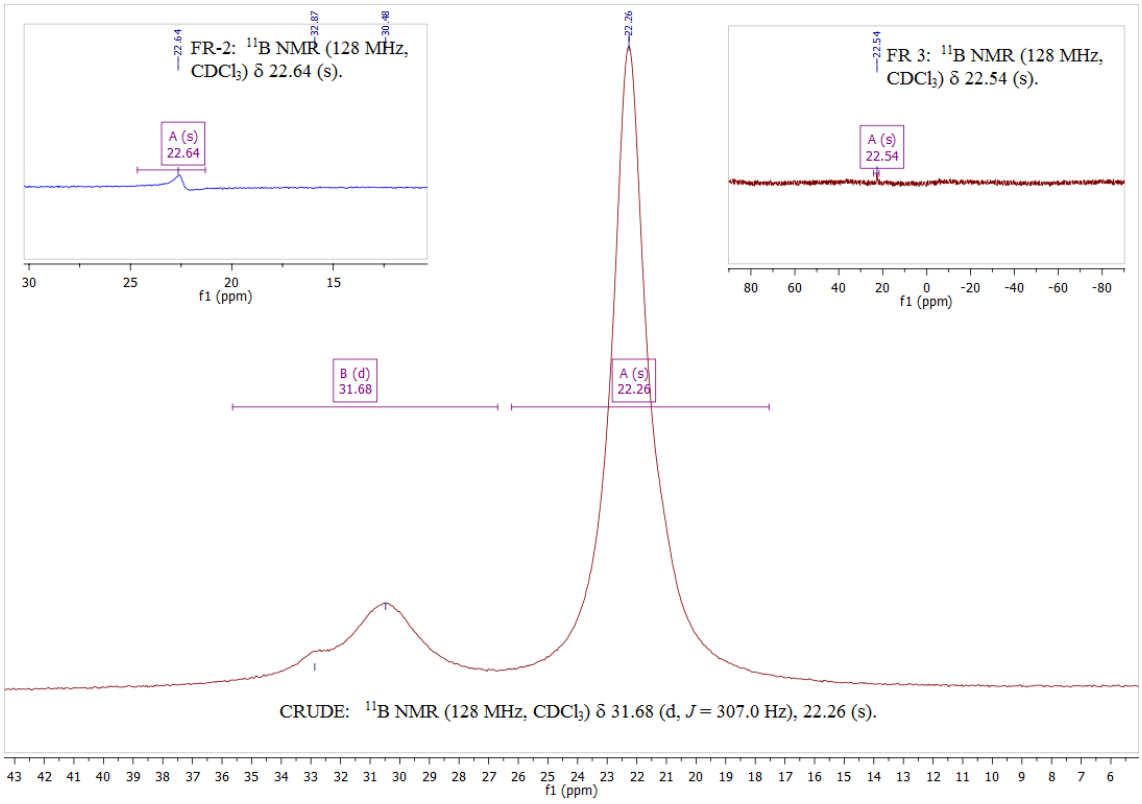


Figure 2.57. ^{11}B NMR of compound **71**.

We separated the reaction mixture into 3 fractions by column chromatography. The first fraction was starting material, but for the second and third fractions, the ^{1}H NMR spectrum showed no signs of starting material. Moreover, the ^{11}B NMR spectrum of the two fractions have a small signal at +22 ppm. We looked at the ^{11}B NMR spectrum of B_2pin_2 and HBpin, and we saw the same signal around +22 ppm, similar to the signal in fraction 2 and 3. We concluded that the signals at +22 ppm are just degradation products resulting from the B_2pin_2 reagent.

We also screened the procedure with our substrate **62**. To our surprise, similar results to compound **46** were observed. ^{1}H NMR spectroscopy showed the majority of the

starting material, while in the ^{11}B NMR spectrum two peaks appear: one at +22 ppm, belonging to the non-reacted B_2pin_2 and a singlet at +31 ppm, indicating the formation of a boronate species. In this case, increasing the temperature gave similar results. We concluded that the substrate is not reactive enough under the applied conditions, but shows some signs of reactivity (**Table 12 – entry 25**).

Finally we tried a protocol by *Heddenham*[57] in which $PdCl_2$ was added to a solution of starting material (compounds **39 and 62**), TPP and TEA, and the mixture was stirred at room temperature for 5 min. $LiH_3BN(^iPr)_2$ (LAB) (freshly prepared using a protocol by *Pasumansky*[67]) was added and the reaction mixture was refluxed for 12 hr. MeOH was added at 0 °C and the mixture was stirred at this temperature for 15 min (**Fig. 2.58.**). The solvent was removed in *vacuo*, NaOH was added, and the mixture was washed with hexanes. The aqueous layer was cooled to 0 °C and acidified to a pH lower than 1 with conc. HCl. The aqueous layer was washed with diethyl ether and the combined organic layers were dried over $MgSO_4$.

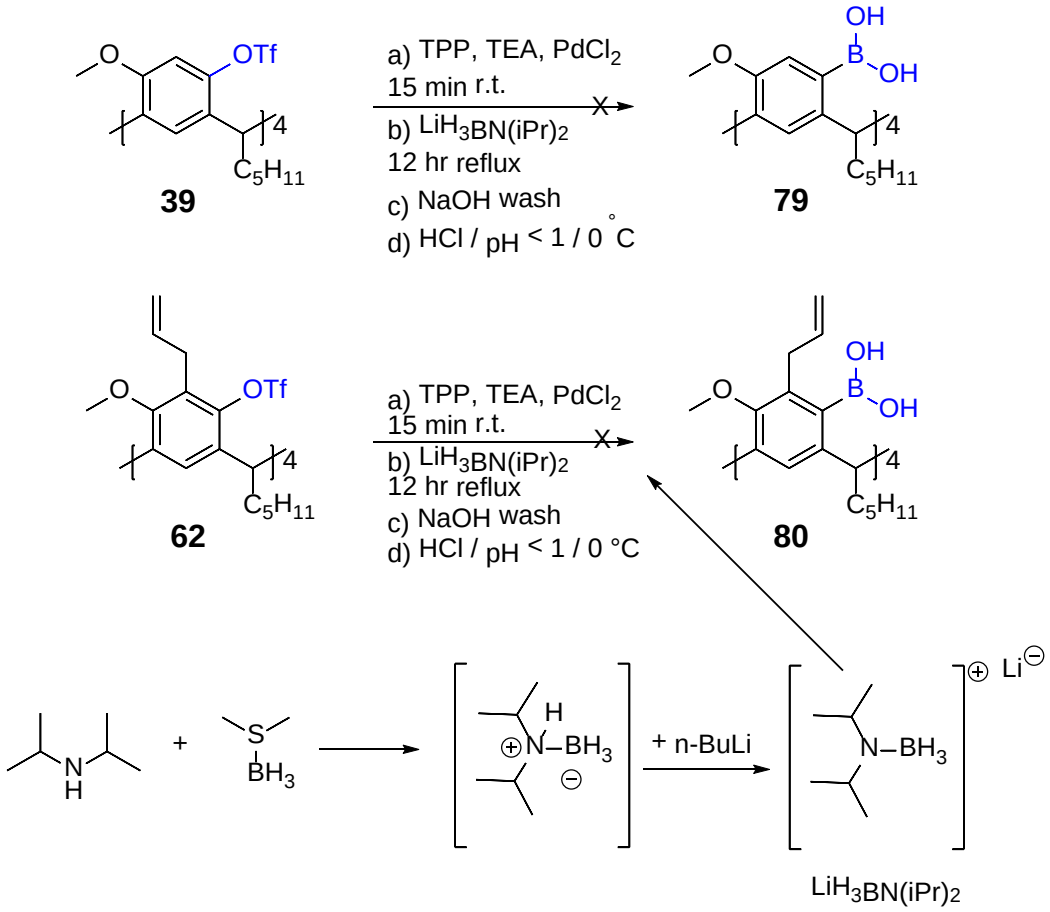


Figure 2.58. Palladium-catalysed hydroboration of the triflate-protected resorcinarene using LAB (Lithium Amino Borane).

The $LiH_3BN(^iPr)_2$ was prepared as follows:[67] borane dimethylsulfide was added dropwise over a solution of diisopropylamine in anhydrous THF at 0 °C and stirred one hour at the mentioned temperature, to give the diisopropylamine borane complex. *n*-BuLi was added and the reaction mixture was stirred for further 1 hour at 0 °C to give the lithium diisopropylaminoborohydride complex.

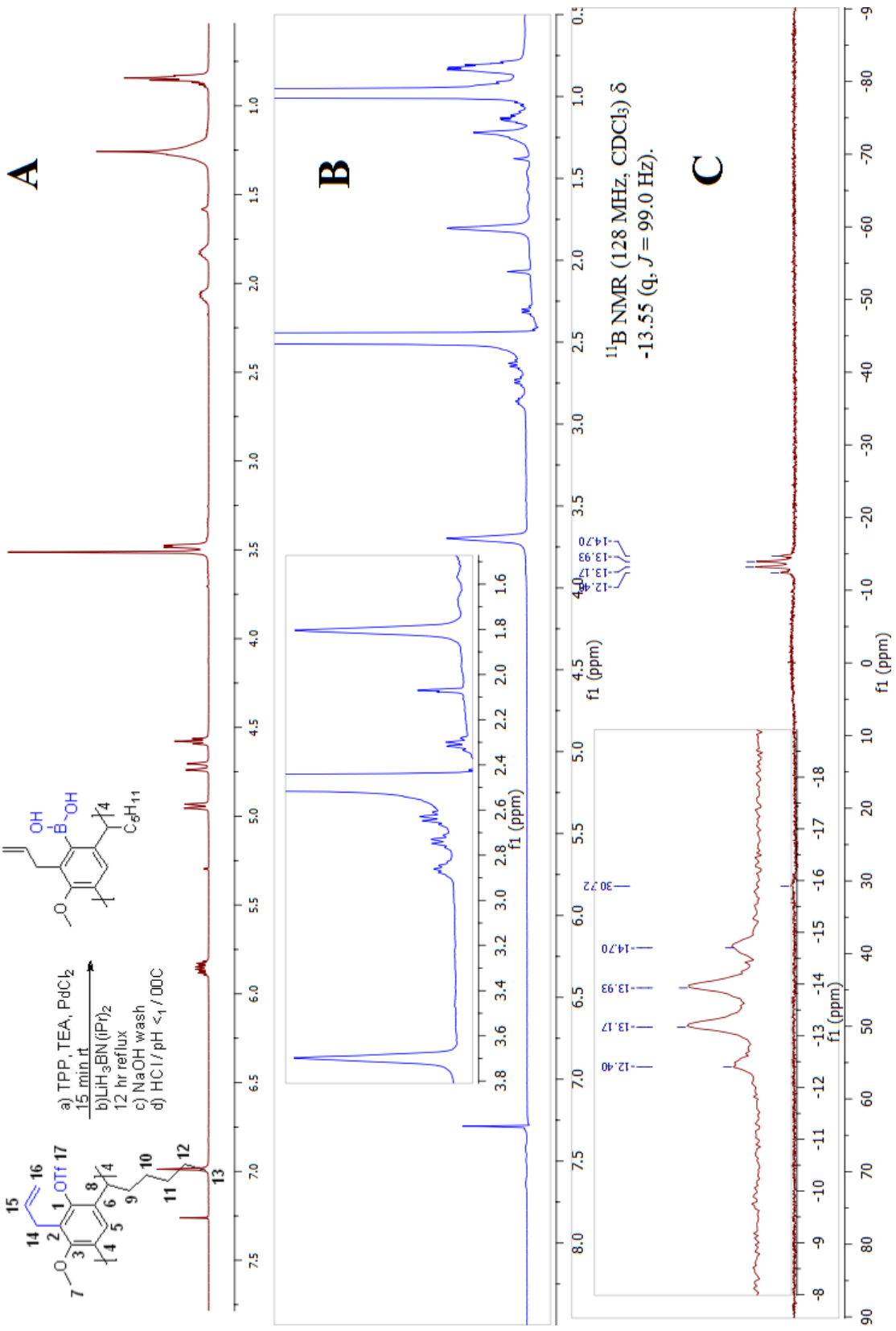


Figure 2.59. Spectroscopic data of the palladium-catalysed hydroboration of the triflate-protected resorcinarene **62** using LAB a) ^{1}H NMR of starting material **62**, b) ^{1}H NMR of the reaction mixture, c) ^{11}B NMR of the reaction mixture.

When applying this protocol to substrate **62**, the spectroscopic data reveals something interesting (**Table 12 – entry 23**). In the ^{1}H NMR spectrum the peaks corresponding to the alkene moiety (**Fig. 2.59. – A**) disappear completely, or they shift so upfield (from 5.85, 4.83 and 3.48 ppm to under 3 ppm) that they overlap with other signals, but such big shift is highly improbable. As well, the triplet corresponding to C8 (4.58) ppm disappears.

Unfortunately, the quadruplet at -13.55 ppm from the ^{11}B NMR indicates the unreacted *i*PrN-$B^{-}H_3$ compound.

When performing the hydroboration on substrate **39**, In the ^{11}B NMR spectrum the same quadruplet signal appears at -14 ppm, together with two other signals, one at +30 ppm (corresponding to a boronate: RB $(OR')_2$) and one small signal at +40 ppm that could indicate the presence of a (BR_2 OR) species (**Fig. 2.60.**). Unfortunately, no desired compounds were observed and we concluded that the substrate is unreactive.

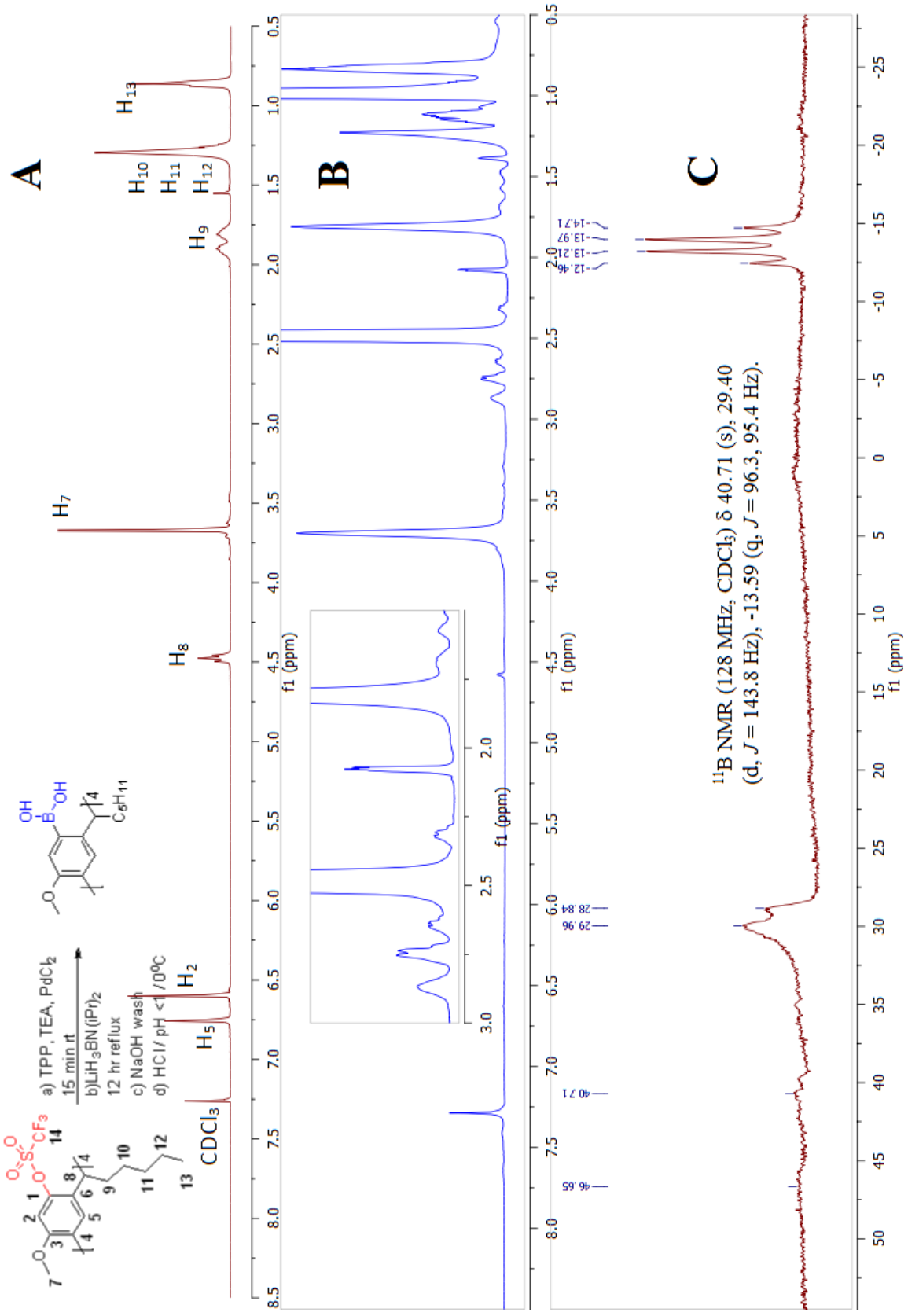


Figure 2.60. Spectroscopic data of the palladium-catalysed hydroboration of the triflate-protected resorcinarene **39** using LAB a) ^{1}H NMR of starting material **39**, b) ^{1}H NMR of the reaction mixture, c) ^{11}B NMR of the reaction mixture.

Table 12. Investigation into the borylation and hydroboration of resorcinarenes.

Entry	SM	Borane source	Solvent	Conditions	Results
1	46	Borane/THF 4 – 15 equiv.	THF	reflux 4 days	SM
2		Bis(pinacolato)diborane 5 – 15 equiv.			SM
3		HBpin 5 – 15 equiv.			SM + byproducts
4		HBcat 5 – 15 equiv.			SM
5	60	Borane/THF 4 – 15 equiv.	THF	reflux 1 week	SM
6		Bis(pinacolato)diborane 5 – 15 equiv.			SM
7		HBpin 5 – 15 equiv.			SM + byproducts
8		HBcat 5 – 15 equiv.			SM
9	46	Borane/THF 4 – 15 equiv.	Toluene	reflux 2 weeks	SM
10		Bis(pinacolato)diborane 5 – 15 equiv.			SM
11		HBpin 5 – 15 equiv.			SM + byproducts
12		HBcat 5 – 15 equiv.			SM
13	60	Borane/THF 4 – 15 equiv.	Toluene	reflux 2 weeks	decomposition products
14		Bis(pinacolato)diborane 5 – 15 equiv.			SM
15		HBpin 5 – 15 equiv.			No SM, decomposition products
16		HBcat 5 – 15 equiv.			SM

Table 12. Continuation

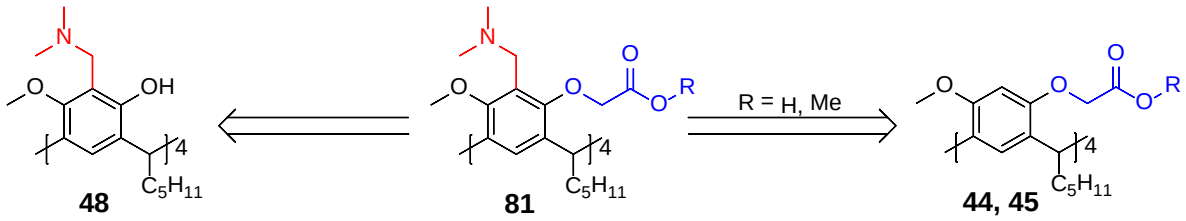
Entry	SM	Borane source	Solvent	Conditions	Results
17	46, 60	$HBr_2B.Sme_2$ 4 – 12 equiv.	DCM	2-5 hr / 40 °C, than H_2O / 0.5 hr to overnight / r.t.	No SM, byproducts
18		$HBr_2B.Sme_2$ 10 equiv.		6 days / 0 °C	
19		$HBr_2B.Sme_2$ 10 equiv.		45 min / -78 °C	
20	46 60	9-BBN 3 equiv.	THF	1.5 hr /0 °C, than 1 hr / r.t	SM + decomposition products
21				1 hr reflux	
22	62	9-BBN 3 equiv.	THF	5 days reflux	No SM, degradation products
23	39 62 46	LAB	-	TPPP, TEA, $PdCl_2$ / 15 min r.t., than LAB / 12 hr reflux	Shows reactivity, but no desired products obsered
24	39 62	HBpin 6.25 equiv.	dioxane	$Pd(dppf)Cl_2$, TEA, 4 hr to overnight / 100 °C	SM
25	46 62	B_2pin_2 4 equiv. THF	CuCl, xantphos, NaO^tBu / 5-10 min r.t., than MeOH, overnight r.t. to 40 °C		Shows reactivity, but no desired products obsered
26	60				SM

* LAB = Lithium Amino Borane

2.6 Multifunctionalization of the upper rim.

Below are presented a few schemes and tables of different tries of multifuntionalization of the upper rim, that unfortunately concluded in either recovery of the starting material or in the recovery of part/majority of the starting material alongside with fragmentation/decomposition products.

Table 13. Atempts to attach an ester/carboxylic acid unit and an amine unit, starting either from the aminated resorcinarene **48**, or from the resorcinarene that has an ester/carboxilix acid unit already attached **44**, **45**.



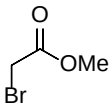
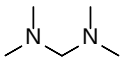
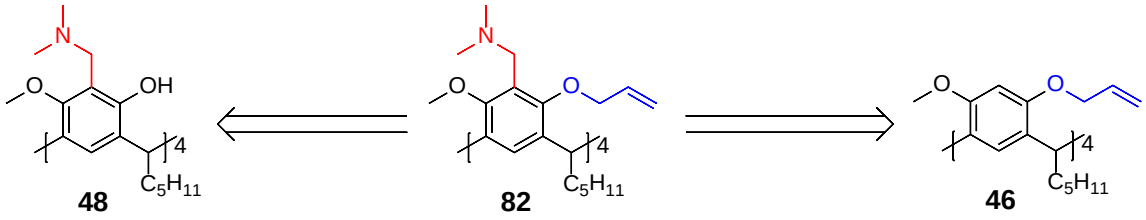
Reagent	Base	Conditions	Results	Reagent	Conditions	Results
 **A**	K_2CO_3	8 hr reflux/MeCN	SM + decompozition	 **B**	microwave 10-30 min 300 W	SM
	K_2CO_3	microwave 2 hr 165 °C/DMF 300 W	SM + decompozition - shows reactivity		 K_2CO_3 / DCM 5 days / r.t.	SM
	Pyridine	i) 2 days reflux ii) HCl / 30 min / r.t.	SM + decompozition - shows reactivity			
	n-BuLi	i) THF / 1 hr -78 °C to r.t. ii) A, 12 hr / r.t. iii) HCl / pH < 7	SM + decompozition			

Table 14. Attempts to attach an alkene moiety and an amine unit, starting either from the aminated resorcinarene **48**, or from the resorcinarene that has an allylic unit already attached **46**.



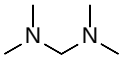
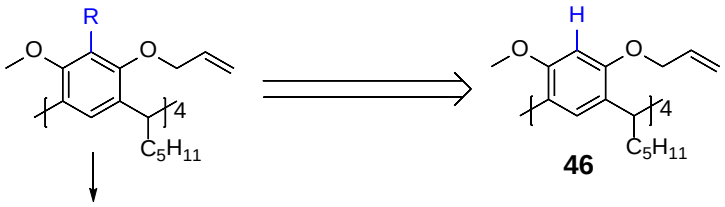
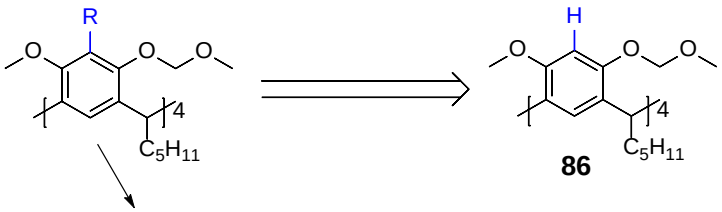
Reagent	Base	Conditions	Results	Reagent	Conditions	Results
	K_2CO_3	24 hr reflux/MeCN	SM + fragmentation	 **B**	microwave 10-30 min 300 W	SM
	n-BuLi	overnight reflux MeCN	SM + decompozition			SM
	Pyridine	i) 8 hr reflux ii) HCl / 30 min / r.t.	SM + fragmentation		K_2CO_3 / DCM 5 days / r.t.	

Table 15. Deprotonation study carried at the ortho position of substrate **46**.



Compound	R	Conditions	Results
83		 *n*-BuLi / THF 1.5 hr / r.t.	decompozition + polimerization
84	Me	i) *n*-BuLi / THF 3-5 hr / -78 °C ii) overnight / 0 °C iii) MeI 5-10 min / -78 °C	SM + decompozition
85	D	i) *n*-BuLi / THF 3-5 hr / -78 °C ii) overnight / 0 °C iii) D_2O 5-10 min / -78 °C	SM + decompozition

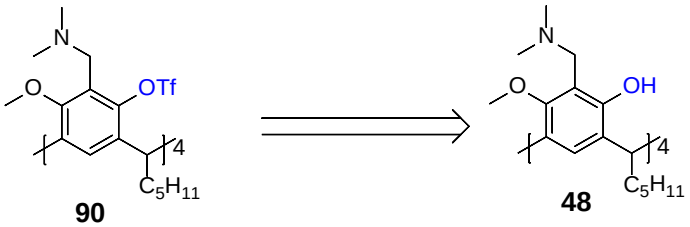
Table 16. Deprotonation study carried at the ortho position of substrate **86**.

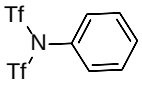


86

Compound	R	Conditions	Results
87		 *n*-BuLi / THF 1.5 hr / r.t.	SM
88	Me	i) *n*-BuLi / THF 20 min / -78 °C ii) MeI 10 min / 0 °C to r.t.	SM
89	D	i) *n*-BuLi / THF 20 min / -78 °C ii) D_2O 10 min / 0 °C to r.t.	SM

Table 17. Triflation of the phenolic OH of substrate **48**.



Reagent	Base	Conditions	Results
	K_2CO_3	microwave / MeCN 5-30 min / 120 °C	SM
OTf_2	TEA	i) TEA, OTf_2 -78 °C / DCM ii) 7 days / r.t.	SM + decompozition
OTf_2	TEA	i) TEA, OTf_2 -78 °C / DCM ii) overnight / reflux	SM + fragmentation
OTf_2	Pyridine	i) OTf_2 / 0 °C ii) 2-5 days / reflux iii) HCl	SM + fragmentation
OTf_2	DMAP / 2,6-lutidine	DCM 5 days / r.t.	no SM fragmentation
OTf_2	i) 1:1 toluene:30% aq.H_3PO_4, 5 min <10 °C ii) 30 min / r.t.		SM + decompozition

2.7. References Chapter II:

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CHAPTER III: Experimental section.

3.1. General.

Commercially available reagents were used as supplied, without further purification, unless stated otherwise and stored according to the manufacturer's recommendations.

When purified, THF, Et_2O were freshly distilled from sodium benzophenone ketyl radical, toluene, DCM, MeCN, and DMF were distilled from CaH_2. Petrol refers to the fraction of petroleum ether boiling in the range 40-60 °C. Solvents were removed using a Büchi rotary evaporator (water bath temperature approx. 40 °C) or a high *vacuum* pump between room temperature and 60 °C. All non-aqueous reactions were carried out under oxygen-free nitrogen or argon, and the glassware and needles were either flame-dried or dried in an oven (150 °C) for at least 2 hours and then allowed to cool under a stream of nitrogen immediately prior to use. Sensitive liquid reagents were added via syringe or cannula.

Flash column chromatography was carried out on Davisil® chromatographic silica media LC60Å 40-63 µm (amorphous silicon dioxide). Thin layer chromatography was carried on commercially available Kieselgel aluminium backed plates. Plates were looked at under UV light and developed by staining using aqueous potassium permanganate, ethanolic phosphomolybdic acid or *p*-Anisaldehyde followed by heating.

Melting points were recorded on a Büchi B-545 Melting Point apparatus and are uncorrected.

Infra-red spectra were recorded in the range 4000-400 cm^{-1} on a Perkin-Elmer 1720X FT-IR spectrophotometer as thin films on NaCl plates or as solid samples on diamond windows.

All NMR spectra were recorded in deuteriochloroform solution unless otherwise stated using a Bruker Avance III 2 channel 500 MHz spectrometer equipped with a multinuclear 1H/15N-31P broad band direct detect. Chemical shifts were recorded in parts per million (ppm) and are referenced to either tetramethylsilane, or the residual protons of the deuterated solvents used. Abbreviations used are as follows: s (singlet), d (doublet), t (triplet), q (quartet), sept (septet), m (multiplet) and br (broad).

Mass spectra were determined at the EPSRC Mass Spectrometry Unit, Swansea.

Microwave reactions were carried out on a Biotage Initiator Robot Sixty with auto sampler.

3.2. Numbering used in this work.

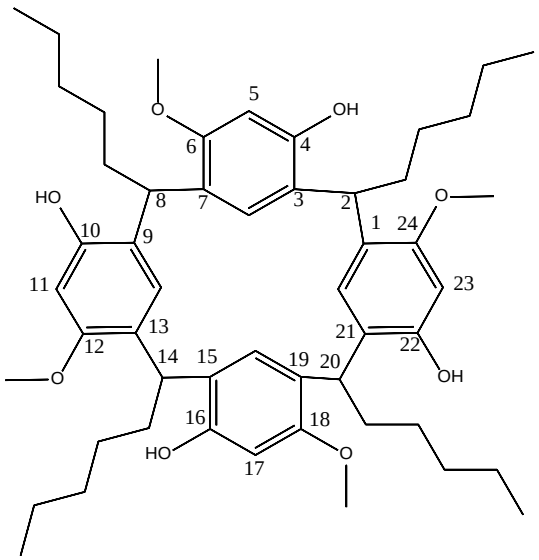
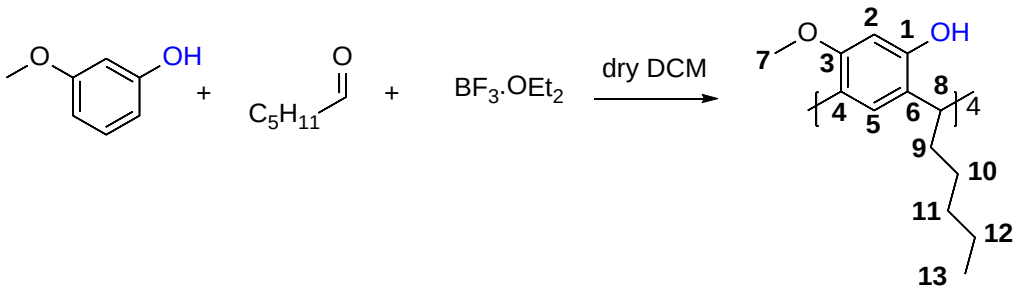


Figure 3.1. General numbering used for nomenclature of starting material (**38**) 2,8,14,20-Tetrapentyl-4,10,16,22-tetrahydroxy-6,12,18,24-tetramethoxyresorcinarene**.**

3.3. Experimental.

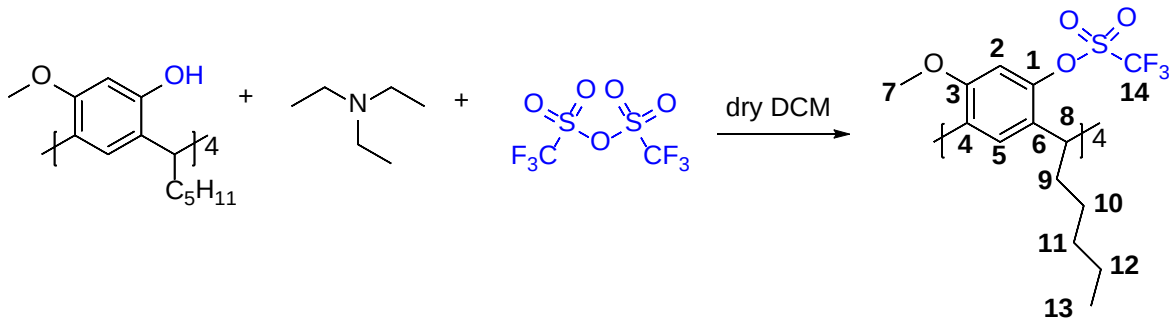
COMPOUND **38**: 2,8,14,20-Tetrapentyl-4,10,16,22-tetrahydroxy-6,12,18,24-tetramethoxyresorcinarene.[1]



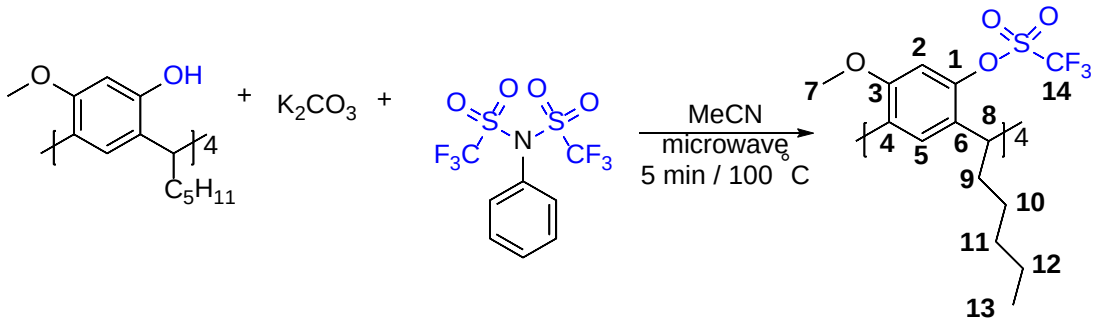
Hexanal (8.07 g, 81.0 mmol) was added to a solution of 3-methoxy-phenol (10 g, 81.0 mol) in dry DCM (100 ml) under nitrogen. $BF_3.OEt_2$ (22.87 g, 16.0 mol) was added over a period of 30 minutes to the reaction mixture at 0 °C the colour shifting to red wine. The reaction mixture was allowed to reach room temperature, stirred for another 3 hours, washed with water (3 x 50 ml). The aqueous layer was extracted with DCM (10 ml). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure and the residue was recrystallised in cold methanol to give the *title compound* as a colourless solid (14.8 g, 89 %). **m.p.** 229-232 °C; **ν_{max}/cm^{-1}** 3401 (OH, stretching), 2853, 2929 and 2858 (C-H, stretching), 1620, 1589 (C=C, stretching), 1496 (C-H, bending), 1337 (Ar-OH, bending), 1239 (C-O, stretching); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.21 (4H, s, H_5), 6.34 (4H, s, H_2), 4.26 (4H, t, *J* = 7.8 Hz, H_8), 3.82 (12H, s, H_7), 2.28 – 2.06 (8H, m, H_9), 1.43 – 1.18 (24H, m, H_{10}, H_{11} and H_{12}), 0.89 (12H, t, *J* = 7.0 Hz, H_{13}) ppm; **^{13}C NMR** (400 MHz, in $CDCl_3$): δ = 153.78 (C_3 or C_1), 153.11 (C_3 or C_1), 124.89 (C_5), 124.79 (C_4 or C_6), 123.84 (C_4 or C_6), 100.18 (C_2), 56.07 (C_7), 34.14 (C_9), 33.33 (C_8), 32.20 (C_{10}), 28.01 (C_{11}), 22.93 (C_{12}), 14.38 (C_{13}) ppm.

Data are in agreement with those previously reported.[1]

COMPOUND **39**: 2,8,14,20-Tetrapentyl-4,10,16,22-tetratriflate-6,12,18,24-tetramethoxyresorcinarene.[2]



Procedure A: Triethylamine (0.98 g, 9.71 mmol) was added to a solution of **38** (1 g, 1.21 mmol) in dry DCM (25 ml) under nitrogen. Trifluoromethanesulfonic anhidride (2.74 g, 9.71 mmol) was added drop wise at -78 °C the colour shifting to yellow. After 15 minutes, the reaction mixture was allowed to reach room temperature (colour shifting to brown), stirred overnight and then washed with water (3 x 10 ml). The aqueous layer was extracted with DCM (10 ml), the combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and filtered through a pad of silica. The solvents were removed under reduced pressure and the residue was recrystallised from cold MeCN to give the *title compound* as a colourless solid (1.03 g, 89 %).

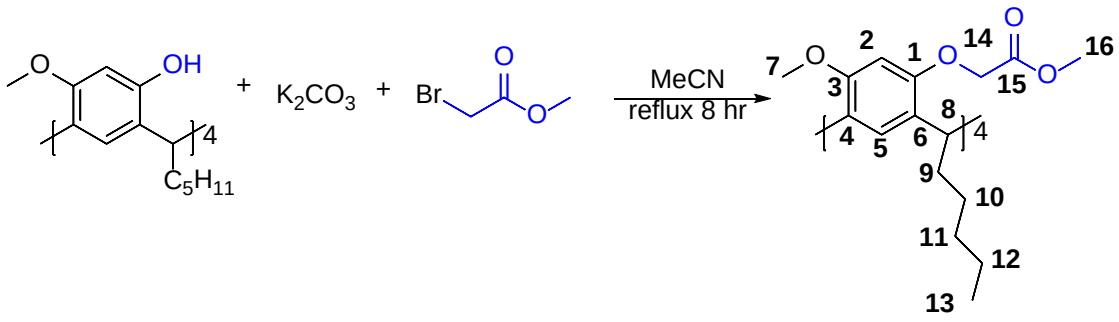


Procedure B: **38** (0.5 g, 0.61 mmol), K_2CO_3 (0.5 g, 3.64 mmol) and *N*-phenyl-bis(trifluoromethanesulfonimide) (0.65 g, 1.81 mmol) were dissolved in dry MeCN (1.5 ml) under nitrogen. The reaction mixture was then submitted to microwave irradiation for five minutes (100 °C, 300 W). Water and DCM were then added to the reaction mixture; the organic phase was separated, washed with water

and brine, and dried over anhydrous Na_2SO_4. The solvent was removed in *vacuum* and the residue was recrystallised from cold MeCN to give the *title compound* as a colourless solid (0.44 g, 42 %). **m.p.** 126-128 °C; **ν_{max}/cm^{-1}** 2857, 2933 and 2861 (C-H, stretching), 1618, 1584 (C=C, stretching), 1498 (C-H, bending), 1349 (S=O, stretching), 1246, 1210, 1059 (C-O, stretching); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.76 (4H, s, H_5), 6.60 (4H, s, H_2), 4.48 (4H, t, *J* = 7.4 Hz, H_8), 3.67 (12H, s, H_7), 1.99 – 1.69 (8H, m, H_9), 1.30 (24H, s, H_{10}, H_{11} and H_{12}), 0.86 (12H, t, *J* = 6.1 Hz, H_{13}) ppm; **^{13}C NMR** (400 MHz, in $CDCl_3$): δ = 156.12 (C_3 or C_1), 147.00 (C_3 or C_1), 132.04 (C_5), 127.31 (C_4 or C_6), 126.73 (C_4 or C_6), 118.47 (q, *J* = 319 Hz, C_{14}), 103.48 (C_2), 55.52 (C_7), 36.24 (C_9), 34.86 (C_8), 32.01 (C_{10}), 27.62 (C_{11}), 22.75 (C_{12}), 14.24 (C_{13}) ppm; **^{19}F NMR** (471 MHz, $CDCl_3$): δ = -74.57 (s) ppm.

Data in agreement with those previously reported.[2]

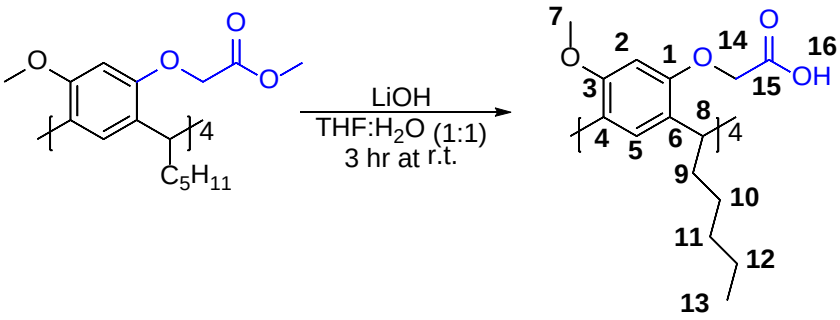
COMPOUND **44**: 2,8,14,20-Tetrapentyl-4,10,16,22-tetraacetyl-6,12,18,24-tetramethoxyresorcinarene.[3]



K_2CO_3 (1.68 g, 12.1 mmol) was added to a solution of **38** (1.0 g, 1.21 mmol) in dry MeCN (20 ml) and then methyl bromoacetate (1.15 ml, 12.1 mmol) was added. The reaction mixture was refluxed for 8 hours and monitored by TLC. When the reaction has come to completion, the MeCN was removed in *vacuum*. The reaction mixture was then washed with water (3 x 10 ml) and the aqueous layer was extracted with DCM (3 x 10 ml). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (DCM/EtOAc, 9:1). The product was recrystallised from cold MeOH to give the *title compound* as a colourless solid

(1.16 g, 86 %). **m.p** 98-100 °C; **ν_{max}/cm^{-1}** 2953, 2930 and 2857 (C-H, stretching), 1762, 1739 (C=O, stretching), 1610, 1584 (C=C, stretching), 1304, 1212, 1194 and 1177 (C-O, stretching); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.62 (4H, s, H_5), 6.29 (4H, s, H_2), 4.51 (4H, t, *J* = 7.4 Hz, H_8), 4.12 (4H, d, *J* = 15.9 Hz, H_{14a}), 4.03 (4H, d, *J* = 15.9 Hz, H_{14b}), 3.77 (12H, s, H_7), 3.62 (12H, s, H_{16}), 1.87 – 1.75 (8H, m, H_9), 1.39 – 1.21 (24H, m, H_{10}, H_{11} and H_{12}), 0.85 (12H, t, *J* = 6.9 Hz, H_{13}) ppm; **^{13}C NMR** (400 MHz, in $CDCl_3$): δ = 170.07 (C_{15}), 155.56 (C_3 or C_1), 155.88 (C_3 or C_1), 128.29 (C_5), 127.52 (C_4 or C_6), 126.31 (C_4 or C_6), 99.60 (C_2), 68.28 (C_{14}), 55.51 (C_7), 51.91 (C_{16}), 35.46 (C_9), 34.63 (C_8), 32.13 (C_{10}), 27.67 (C_{11}), 22.65 (C_{12}), 14.15 (C_{13}) ppm.

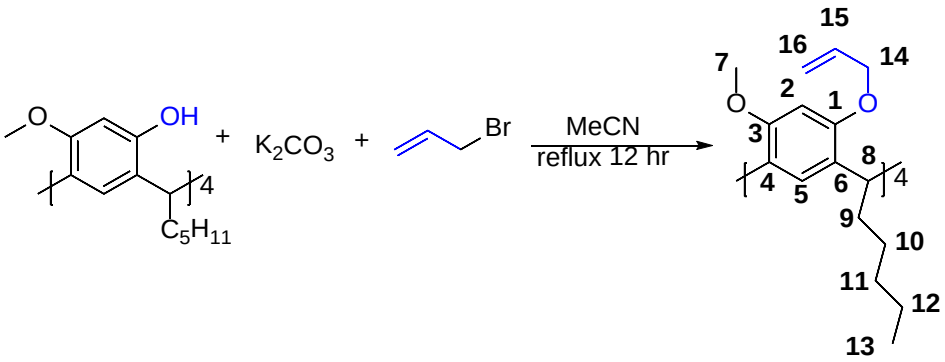
COMPOUND **45**: 2,8,14,20-Tetrapentyl-4,10,16,22-tetracarboxyl-6,12,18,24-tetramethoxyresorcinarene.



LiOH (0.09 g, 3.6 mmol) was added to a solution of **44** (2 g, 1.8 mmol) in THF:H_2O (20:20 ml). The mixture was stirred for 2 hours at r.t. and then acidified with 1M HCl to pH lower than 3.5. Then the reaction mixture was washed with water (3 x 5 ml). The aqueous layer was extracted with DCM (5 ml). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4.The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (Petrol/EtOAc, 1:1). The product was recrystallised from cold MeOH to give the *title compound* as a colourless solid (1.77 g, 93 %). **m.p** 78-90 °C; **ν_{max}/cm^{-1}** 3415 – 2998 (O-H, stretching), 2953, 2929 and 2858 (C-H, stretching), 1757, 1735 (C=O, stretching), 1611, 1585 (C=C, stretching), 1298 (C-O, stretching); **^{1}H NMR** (400 MHz, DMSO): δ = 6.58 (4H, s, H_5), 6.36 (4H, s, H_2), 4.46 (4H, dist. t, *J* = 7.3 Hz, H_8), 4.41 (4H, d, *J* = 16.0 Hz, H_{14a}), 4.23 (4H, d, *J* = 16 Hz, H_{14b}) 3.54 (12H, s, H_7), 2.46 (12H, s, H_{13}), 1.77 – 1.61 (8H, m, H_9), 1.24 – 1.09 (24H, dist. m, H_{10}, H_{11} and H_{12}), 0.85 (12H, dist. t, *J* = 5.6

Hz, H_{13}) ppm; **^{13}C NMR** (126 MHz, in $CDCL_3$): δ = 171.30 (C_{15}), 155.18 (C_3 or C_1), 153.38 (C_3 or C_1), 127.59 (C_5), 126.92 (C_4 or C_6), 126.32 (C_4 or C_6), 98.02 (C_2), 66.49 (C_{14}), 56.13 (C_7), 35.33 (C_9), 34.49 (C_8), 32.02 (C_{10}), 27.41 (C_{11}), 22.62 (C_{12}), 14.12 (C_{13}) ppm; **HRMS**: calc. for $C_{60}H_{80}O_{16}$ (*m/z*) 1056.54, found 1055.53 $(M - H)^-$.

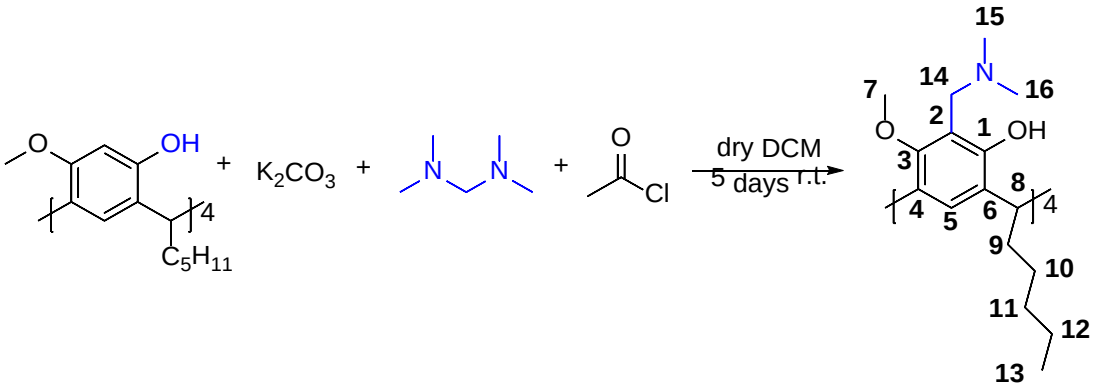
COMPOUND **46**: 2,8,14,20-Tetrapentyl-4,10,16,22-tetraoxyallyl-6,12,18,24-tetramethoxyresorcinarene.



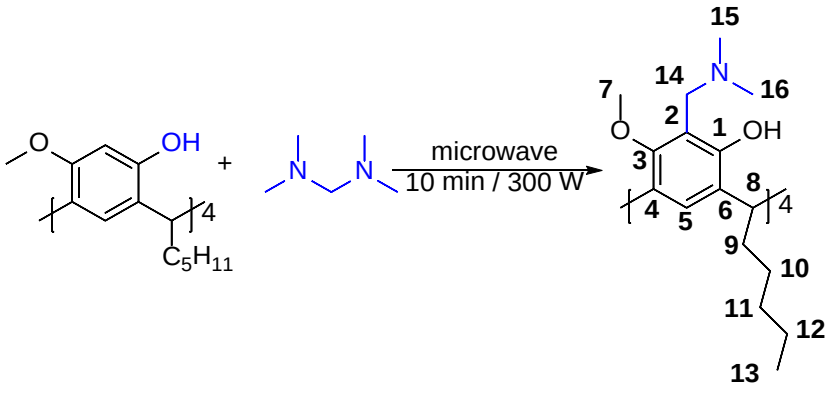
Allyl bromide (0.44 g, 3.64 mmol) was added to a solution of **38** (0.5 g, 0.61 mmol) and K_2CO_3 (0.5 g, 3.64 mmol) in MeCN (15 ml) and the mixture was refluxed overnight. After evaporating the MeCN under reduced pressure, the reaction mixture was washed with water (3 x 5 ml) and the aqueous layer was extracted with DCM (2 X 5 ml). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and filtered through a pad of silica. The solvents were removed under reduced pressure and the residue was recrystallised from MeOH to give the *title compound* as a colourless solid (quantitative). **m.p.** 137-139 °C; **ν_{max}/cm^{-1}** 3080 (=C-H, stretch), 2953, 2929 and 2857 (C-H, stretching), 1610, 1582 (C=C, stretching), 1497, 1464,1444 and 1422 (C-H, bending), 1300 (C-O, stretching), 1194 (C-O, stretching); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.54 (4H, s, H_5), 6.22 (4H, s, H_2), 5.78 (4H, m, H_{15}), 5.20 (4H, dd, *J* = 17.3, 1.65 Hz, H_{16a}), 5.06 (4H, dd, *J* = 10.5, 1.65 Hz, H_{16b}), 4.43 (4H, t, *J* = 7.4 Hz, H_8), 4.27 (4H, dd, *J* = 12.8, 4.7 Hz, H_{14a}), 4.03 (4H, dd, *J* = 12.8, 5.2 Hz, H_{14b}), 3.48 (12H, s, H_7), 1.80 – 1.69 (8H, m, H_9), 1.32 – 1.14 (24H, m, H_{10}, H_{11} and H_{12}), 0.77 (12H, t, *J* = 6.9 Hz, H_{13}) ppm; **^{13}C NMR** (126 MHz, in $CDCl_3$): δ = 155.56 (C_3 or C_1), 154.98 (C_3 or C_1), 134.17 (C_{15}), 126.77 (C_4 or C_6), 126.67 (C_4 or C_6), 116.12 (C_{16}), 98.44

(C_2), 70.23 (C_{14}), 55.68 (C_7), 35.57 (C_8), 34.65 (C_8), 32.22 (C_{10}), 27.93 (C_{11}), 22.67 (C_{12}), 14.17 (C_{13}) ppm; **HRMS**: calc. for $C_{64}H_{88}O_8$ (*m/z*) 984.64, found 1002.68 $(M + NH_4)^+$.

COMPOUND **48**: 2,8,14,20-Tetrapentyl-5,11,17,23-tetra(dimethylmethylene)-6,12,18,24-tetramethoxyresorcinarene.[4]



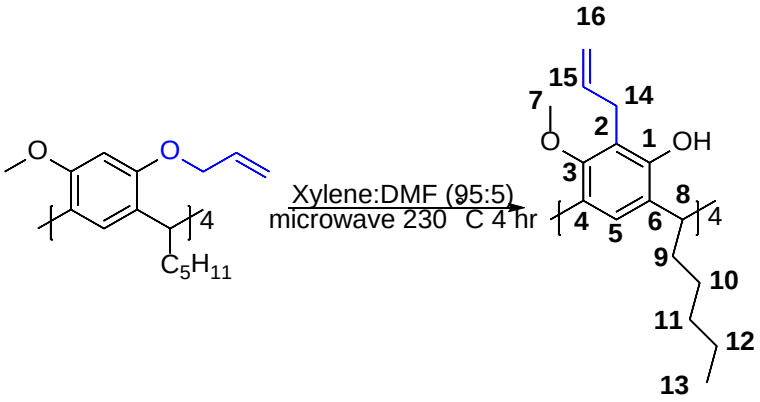
Procedure A: A mixture of K_2CO_3 (2.5 g, 18.2 mmol) and dry DCM (50 ml) was treated with tetramethyldiaminomethane (0.68 g, 6.68 mmol) under nitrogen. Acetyl chloride (0.5 g, 6.38 mmol) was added drop wise and then the reaction mixture was stirred for 30 minutes at r.t. A solution of **38** (0.5 g, 0.61 mmol) in dry DCM (10 ml) was added drop wise into the first solution and then the reaction mixture was left for 5 days stirring at r.t. The reaction mixture was filtered to remove the solid impurities and then washed with water (10 ml). The aqueous layer was extracted with diethyl ether (3 x 10 ml). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4.The solvent was removed under reduced pressure and the residue was recrystallised from cold MeCN to give the *title compound* as a colourless solid (0.48 g, 89 %).



Procedure B: (0.5 g, 0.61 mmol) of **38** were added into a microwave vial under a N_2 atmosphere and dissolved in (0.62 g, 6.06 mmol) Bis(dimethylamino)methane. The mixture was microwaved for 10 minutes, at 300 W and 13-15 bar. The reaction mixture was extracted with DCM (3 X 10 ml), washed with water (3 X 5 ml) and brine and dried over anhydrous Na_2SO_4. The solvent was removed in *vacuum* and the residue was recrystallised from MeCN to give the *title compound* as a colourless solid (0.44 g, 83 %). **m.p** 186-190 °C; $\boldsymbol{\nu_{max}/cm^{-1}}$ 2952, 2930 and 2856 (C-H, stretching), 1595 (C=C, stretching), 1460 (C-H, stretching), 1303, 1224 and 1086 (C-N, stretch); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.73 (4H, s, H_5), 4.49 (4H, t, *J* = 7.4 Hz, H_8), 3.67 (4H, d, *J* = 13.7 Hz, H_{14a}), 3.54 (4H, d, *J* = 13.7 Hz, H_{14b}), 3.42 (12H, s, H_7), 2.22 (24H, s, H_{15}, H_{16}), 1.98 – 1.72 (8H, m, H_9), 1.39 – 1.21 (24H, m, H_{10}, H_{11} and H_{12}), 0.83 (12H, t, *J* = 6.8 Hz, H_{13}) ppm; **^{13}C NMR** (400 MHz, in $CDCl_3$): δ = 154.53 (C_3 or C_1), 154.35 (C_3 or C_1), 128.05 (C_4 or C_6), 127.68 (C_4 or C_6), 125.83 (C_2), 113.72 (C_5), 61.28 (C_7), 56.44 (C_{14}), 44.54 (C_{15},C_{16}), 36.09 (C_9), 32.49 (C_8), 31.16 (C_{10}), 28.38 (C_{11}), 22.98 (C_{12}), 14.38 (C_{13}) ppm.

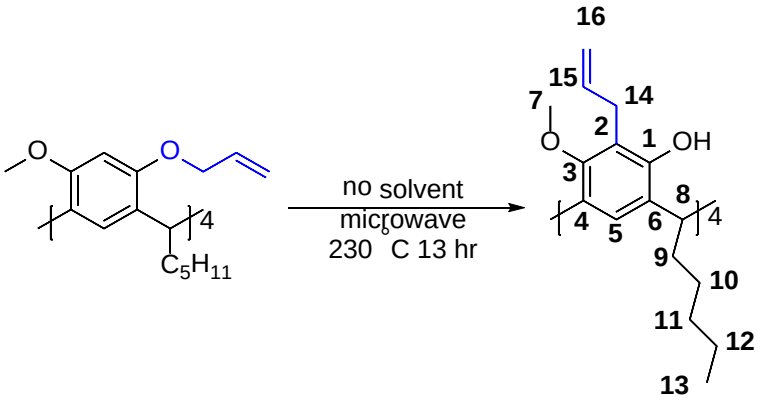
Data are in agreement with those previously reported[4] with one exception. Although in the cited reference the signal for C_{10} was reported at a shift of 35.9 ppm, and in this work it appears at 31.16 ppm, the compound was confirmed by HSQC.

COMPOUND **60**: 2,8,14,20-Tetrapentyl-4,10,16,22-tetrahydroxy-5,11,17,23-tetraallyl-6,12,18,24-tetramethoxyresorcinarene.



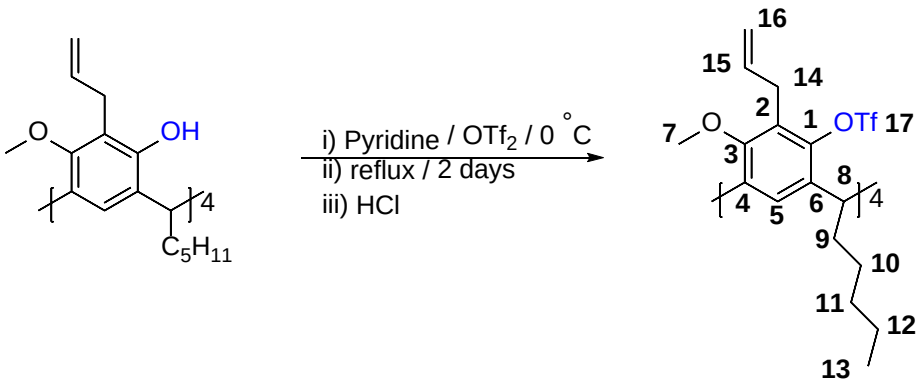
PROCEDURE A: (0.5 g, 0.51 mmol) **46** were added to a solution of (4 ml) xylene:DMF (95:5). The reaction mixture was microwaved for 4 hr at 230 °C and then extracted

with DCM (3 X 5 ml), washed with water and brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (Petrol/EtOAc, 86:14). The product was recrystallised from cold MeOH to give the *title compound* as a colourless solid (0.18 g, < 36 %).



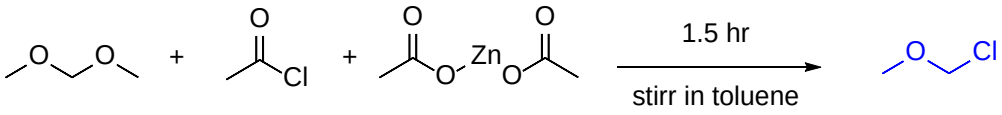
PROCEDURE B: (0.3 g, 0.3 mmol) **46** were microwaved, in neat conditions (no solvent), for 13 hr at 230 °C, extracted with DCM (3 X 5 ml), washed with water and brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (Petrol/EtOAc, 86:14). The product was recrystallised from cold MeOH to give the *title compound* as a colourless solid (0.27 g, 90 %). Unfortunately, when scaling up, the microwave vials could not withstand the temperature and pressure and fractured, so this procedure needs adjustments. **m.p.** 188-190 °C; **ν_{max}/cm^{-1}** 3305 (O-H, stretching), 3075 (=C-H, stretch), 2953, 2930 and 2859 (C-H, stretching), 1637, 1591 (C=C, stretching), 1467 (C-H, bending), 1294 (C-O, stretching); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.09 (4H, s, H_5), 6.00 – 5.90 (4H, m, H_{15}), 4.92 (4H, dd, *J* = 3.5, 1.8 Hz, H_{16a}), 4.89 (4H, dd, *J* = 3.9, 1.8 Hz, H_{16b}), 4.05 (4H, dist. t, *J* = 6.2 Hz, H_8), 3.77 (12H, s, H_7), 3.29 (4H, dd, *J* = 15.3, 6.6 Hz, H_{14a}), 3.19 (4H, dd, *J* = 15.3, 5.1 Hz, H_{14b}), 2.30 – 2.02 (8H, m, H_9), 1.38 – 1.20 (24H, m, H_{10}, H_{11} and H_{12}), 0.84 (12H, t, *J* = 7.2 Hz, H_{13}) ppm; **^{13}C NMR** (126 MHz, in $CDCl_3$): δ = 153.01 (C_3 or C_1), 151.79 (C_3 or C_1), 137.28 (C_{15}), 129.49 (C_4 or C_6), 127.76 (C_4 or C_6), 120.99 (C_5), 120.58 (C_2), 114.58 (C_{16}), 63.08 (C_7), 35.53 (C_9), 33.91 (C_8), 32.16 (C_{10}), 29.49 (C_{14}), 28.24 (C_{11}), 22.74 (C_{12}), 14.19 (C_{13}) ppm; **HRMS**: calc. for $C_{64}H_{88}O_8$ (MH+) 985.6557, found 985.6535.

COMPOUND **62**: 2,8,14,20-Tetrapentyl-4,10,16,22-tetratriflate-5,11,17,23-tetrapropenyl-6,12,18,24-tetramethoxyresorcinarene.



Trifluoromethanesulfonic anhydride (0.23 g, 0.82 mmol) was added dropwise over a solution of **62** (0.1 g, 0.11 mmol) in anhydrous pyridine (1 ml / 0.1 g) at 0 °C under an atmosphere of N_2, colour changing to yellow. The reaction mixture was refluxed for two days under N_2, colour changing to dark brown. After the reaction has finishes, the reaction mixture was diluted with EtOAc, washed with HCl at 0 °C, with water, than brine, dried on $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the residue was recrystallised from cold MeOH to give the *title compound* as a colourless solid (yield > 89 %). **m.p.** 112-115 °C; **ν_{max}/cm^{-1}** 2963, 2931 and 2871 (C-H, stretching), 1639 (C=C, stretching), 1405 (C-H bending – methyl group), 1214 (C-F stretching), 1139 (S=O, stretching), 1039 (C-O, stretching); **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 6.99 (4H, s, H_5), 5.85 (4H, m, H_{15}), 4.94 (4H, dd, *J* = 10.3, 1.45 Hz, H_{16a}), 4.72 (4H, dd, *J* = 17.2, 1.45 Hz, H_{16b}), 4.58 (4H, dist. t, *J* = 7.3 Hz, H_8), 3.51 (12H, s, H_7), 3.48 (8H, d, *J* = 5.3 Hz, H_{14}), 2.11 – 1.77 (8H, m, H_9), 1.35 – 1.15 (24H, m, H_{10}, H_{11} and H_{12}), 0.91 – 0.79 (12H, m, H_{13}) ppm; **^{13}C NMR** (126 MHz, in $CDCl_3$): δ = 156.57 (C_3 or C_1), 144.47 (C_4 or C_6), 134.86 (C_{15}), 125.84 (C_5), 120.31 (q, *J* = 317 Hz, C_{17}), 115.23 (C_{16}), 61.63 (C_7), 38.50 (C_8), 36.66 (C_9), 31.75 (C_{10}), 28.98 (C_{14}), 27.55 (C_{11}), 22.54 (C_{12}), 14.03 (C_{13}) ppm; **^{19}F NMR** (471 MHz, in $CDCl_3$): δ = -73.52 ppm; **HRMS**: calc. for $C_{68}H_{84}F_{12}O_{16}S_4$ $(M + H)^+$ 1512.45, found 1530. 47 $(M + NH_4)^+$.

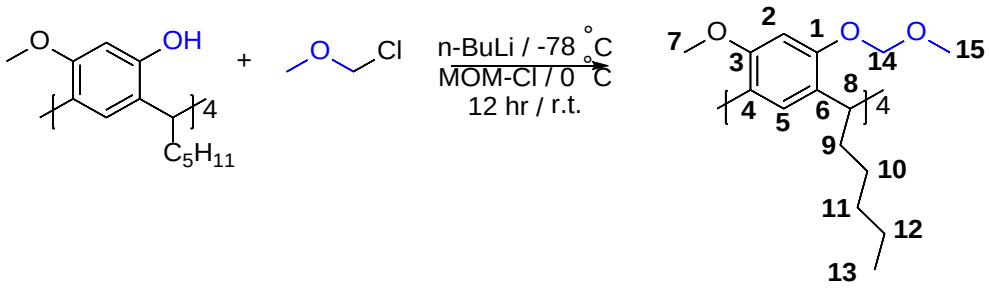
Methylchloromethyl ether (**MOM-Cl**).[5]



A three-neck 500 ml flask fitted with a thermocouple thermometer, reflux condenser, and addition funnel was charged with dimethoxymethane (44.25 ml, 0.50 mol), toluene (133 ml), and $Zn(OAc)_2$ (9.2 mg, 0.01 %). Acetyl chloride (35.5 ml, 0.50 mol) was placed in the addition funnel, and was then introduced into the reaction mixture at a constant rate over 5 min. The $Zn(OAc)_2$ dissolved shortly after addition of the AcCl was started. During the next 15 min, the reaction mixture warmed slowly to 45 °C, and then cooled to ambient temperature over 3 hr, at which time analysis of an aliquot of the reaction mixture by NMR indicated complete consumption of DMM. Solutions of MOMCl in toluene prepared using this stoichiometry have a density of 0.91 g/ml and approximately 2.1 M (18 % w/w). **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 5.40 (2H, s, MOMCl), 3.63 (3H, s, MeOAc), 3.46 (3H, s, MOMCl), 2.01 (3H, s, MeOAc) ppm.

Data are in agreement with those previously reported.[5]

COMPOUND **86**: 2,8,14,20-Tetrapentyl-4,10,16,22-tetramethoxymethyl-6,12,18,24-tetramethoxyresorcinarene.[1,4]

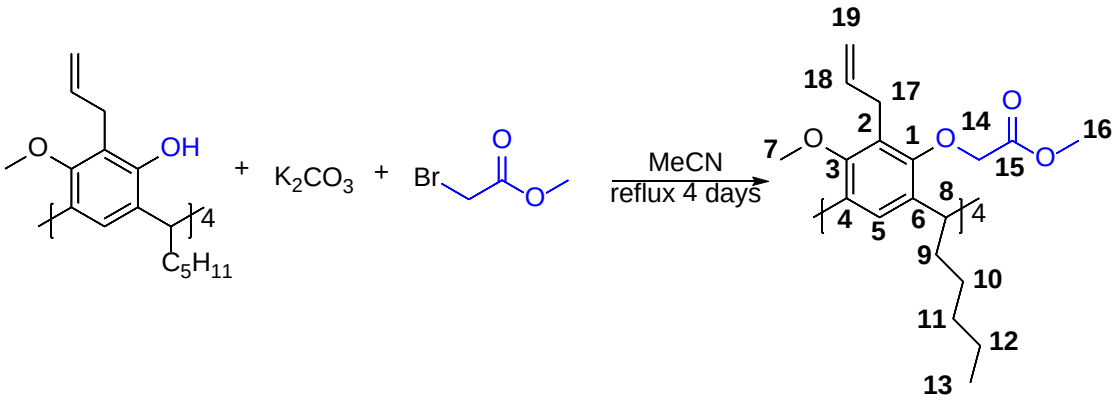


38 (0.5 g, 0.6 mmol) was dissolved in dry THF (20 ml) in a dried rbf under nitrogen and the solution was cooled at -78 °C. *n*-BuLi in hexanes (2.0 ml, 4.9 mmol) was slowly added to the solution and the reaction mixture was stirred for 30 minutes. The reaction was then allowed to warm up to 0 °C. Methoxymethyl chloride (370 µl, 4.9 mmol) was then added to the reaction mixture.the mixture was allowed to warm

to r.t and was stirred for 12 hr. Brine (20 ml) was then added and the phases were separated. The aqueous phase was extracted with diethyl ether (3 x 10 ml). The combined organic phases were washed with brine dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (Petrol/EtOAc, 85:15) to give the *title compound* as a colourless foam (0.6 g, 86 %). **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 6.65 (4H, s, H_2), 6.48 (4H, s, H_5), 4.84 (4H, d, *J* = 6.4 Hz, H_{14a}), 4.73 (4H, d, *J* = 6.4 Hz, H_{14b}), 4.49 (4H, t, *J* = 7.5 Hz, H_8), 3.62 (12H, s, H_7), 3.34 (12H, s, H_{15}), 1.86 – 1.79 (8H, m, H_9), 1.37 – 1.23 (24H, m, H_{10}, H_{11} and H_{12}), 0.85 (12H, t, *J* = 6.8 Hz, H_{13}) ppm.

Data are in agreement with those previously reported.[1, 4]

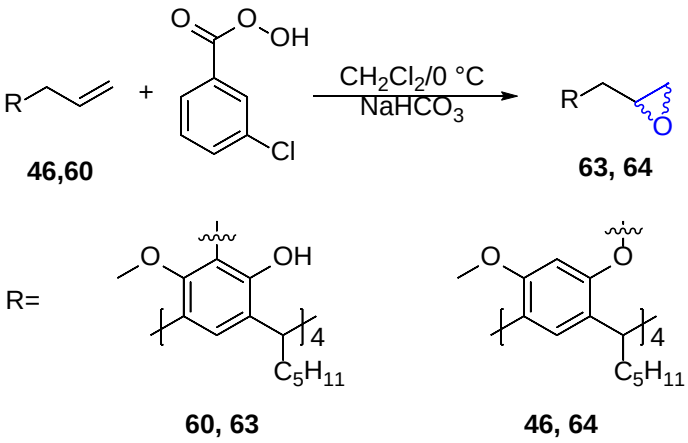
COMPOUND **60-B**: 2,8,14,20-Tetrapentyl-4,10,16,22-tetraacetyl-5,11,17,23-tetrapropenyl-6,12,18,24-tetramethoxyresorcinarene (The reaction conditions used for MOM protection were taken from reports for a simple phenol).[3]



To a stirred solution of **60** (0.4 g, 0.41 mmol) in MeCN (20 ml/ 1 g of SM) were added methyl bromoacetate (0.4 ml, 4.07 mmol) and K_2CO_3 (0.57 g, 4.07 mmol), and the resulting mixture was refluxed for 48 hr. After cooling, the reaction mixture was diluted with DCM, and filtered by celite pad. The filtrate was evaporated, and the residue was chromatographed on silica gel (DCM/EtOAc, 9:1). The product was recrystallised from cold MeOH to give the *title compound* as a whit colourless solid (0.45 g, 87 %). **m.p.** 83-85 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.16 (4H, s, H_5), 6.08 – 5.96 (4H, m, H_{15}), 4.98 (8H, m, H_{16}), 4.12 (4H, dd, *J* = 8.8, 6.9 Hz, H_8), 3.84 (24H, d, *J* =

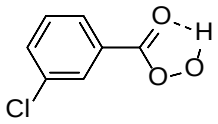
1.5 Hz, H_7, H_{17}), 3.79 (8H, s, H_{19}), 3.31 (8H, ddd, *J* = 20.4, 15.3, 5.9 Hz, H_{14}), 2.38 – 2.08 (8H, m, H_9), 1.46 – 1.24 (24H, m, H_{10}, H_{11} and H_{12}), 0.92 (12H, t, *J* = 7.2 Hz, H_{13}) ppm.

General Procedure for the Preparation of Racemic Epoxides using meta-Chloroperoxybenzoic acid (m-CPBA),[6] used for compounds **63** and **64**.



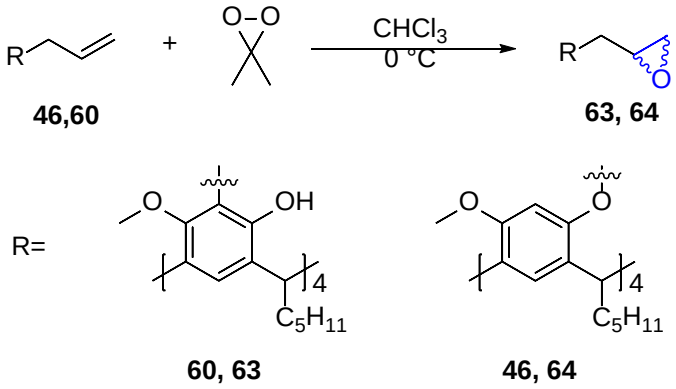
The alkene was dissolved in CH_2Cl_2 (10 ml/g) and the solution cooled using an ice bath. A solution of *m*-CPBA (2 equiv. per alkene) in CH_2Cl_2 (10 ml/g, pre-dried over $MgSO_4$) was added. The reaction was allowed to reach ambient temperature and stirred until complete consumption of the substrate was observed by TLC. Saturated aqueous $NaHCO_3$ (10 ml/g) was added and the layers were separated. The organic layer was washed with saturated aqueous NaOH (1.0 M, 10 ml/g) and dried ($MgSO_4$). The solvents were removed under reduced pressure and the residue purified by column chromatography, typically eluting with EtOAc/Petrol (1:99), to give the pure epoxide.

Purification of *m*-CPBA.[7]



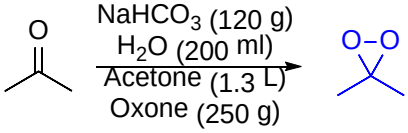
Commercial *m*-CPBA contains ~77 % *m*-CPBA, he rests are acids and water. To get a 99 % *m*-CPBA, 35 g *m*-CPBA (Aldrich 57–86 %) was dissolved in 250 ml Et_2O and washed with 3 × 150 ml buffer solution (410 ml 0.1 M NaOH, 250 ml 0.2 M KH_2PO_4 made up to 1 L, pH 7.5). The ether layer was dried over $MgSO_4$ and carefully evaporated under reduced pressure to give ca. 17 g pure *m*-CPBA (CAUTION! potential explosive).

General Procedure for the Preparation of Racemic Epoxides using Dimethyldioxirane (DMDO),[6, 8] used for compounds **63** and **64**.



To a solution of an alkene in $CHCl_3$ (2 ml per 0.1 g alkene) which was cooled at 0 °C, the DMDO solution in acetone (0.03 M, 1.5 equiv. per alkene group) was gradually added. After 5 min of stirring, the reaction progress was checked by TLC. After the reaction has come to completion, the solvent was removed under reduced pressure at room temperature. The crude was purified by column chromatography.

Preparation of Dimethyldioxirane (**DMDO**) – large scale.[8]



A 2-L, three-necked, round-bottom flask containing a mixture of water, acetone and $NaHCO_3$, is equipped with a large magnetic stirring bar and connected via a U-tube to a *vacuum* distilling adapter and a receiver, which was cooled at -78 °C. The mixture of

water, acetone and $NaHCO_3$ was cooled to 5-10 °C. While cooling and stirring vigorously, Oxone© was added in 5 portions in 30 min intervals. The reaction was left stirred for 15 min then a moderate *vacuum* was applied. The DMDO/acetone solution was distilled and collected in the cooled at (-78 °C) receiver. The DMDO solution was dried over anhydrous K_2CO_3 and filtered into a pre-cooled 1 L round bottom flask. The solution was flushed with Ar, stoppered with glass stopper and stored in the freezer (-20 °C) over molecular sieves (4 Å). (DMDO is slowly decomposed by K_2CO_3, therefore storage on K_2CO_3 should be avoided).

Preparation of Dimethyldioxirane (**DMDO**) – small scale.[9]

Distilled H_2O (20 ml), acetone (30 ml) and $NaHCO_3$ (24 g, 0.285 mol) were combined in a 1-L round bottom flask and chilled in an ice/water bath and stirred for 20 min. After 20 min, stirring is halted and Oxone© (25 g, 0.164 mol) was added in a single portion. The flask was loosely covered and the slurry was stirred vigorously for 15 min while still submerged in the ice bath. After 15 min, the stirr bar was removed from the reaction flask and rinsed with a small portion of distilled water.

The flask containing the reaction slurry was then attached to a rotary evaporator with the water bath set at room temperature. The pump bulb (250 ml) was chilled in a dry ice/acetone bath and a *vacuum* of 155 mmHg was applied *via* a benchtop diaphragm pump accompanied in-line *vacuum* regulator. During this process, the flask was rotated vigorously (210 rpm) to prevent the slurry from bumping into the trap. After 15 min, the bath temperature was gradually raised to 40 °C over the course of 10 min. When the bath temperature reached 40 °C, the distillation was halted immediately by releasing the *vacuum* and raising the flask from the heated water bath.

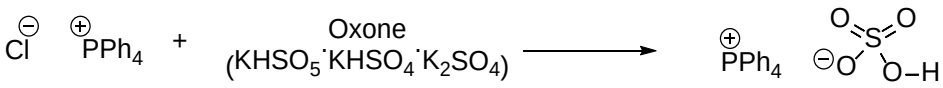
The pale yellow solution of DMDO was decanted from the pump bulb directly into a graduated cylinder to measure the total volume of the solution (an average of 25 ml) and the solution was dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and rinsed with 10 ml acetone.

DMDO concentration determination - iodometric titration.[9]

The concentration of DMDO was determined by iodometric titration as follows: 25 ml of 0.02 M aqueous solution of sodium thiosulfate (496 mg $Na_2S_2O_3.5H_2O$ in 100 ml H_2O) was placed in a 25 ml graduated burette. A 100 ml Erlenmeyer flask was charged with water (20 ml), glacial acetic acid (1 ml), a freshly prepared solution of sodium iodide (10 ml) (10 g NaI in 50 ml H_2O) and then the DMDO solution (2 ml) was added. The solution was titrated rapidly with 0.02 M sodium thiosulfate until the disappearance of the yellow iodine colour. The concentration was calculated according to the following equation:

$$DMDO_{concentration} = \frac{Molarity\ of\ titrant\ x\ ml\ of\ titrant}{ml\ of\ DMDO\ solution\ x\ 2}$$

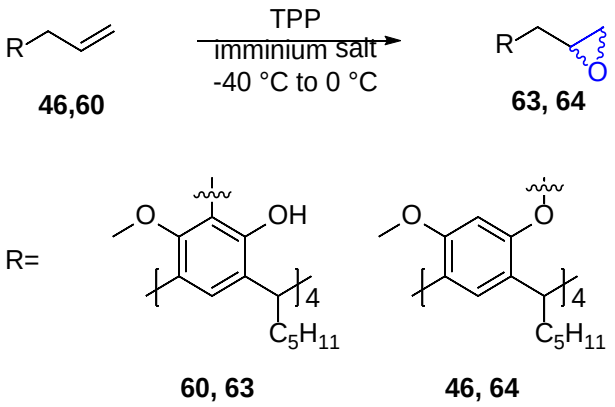
Preparation Tetraphenylphosphonium monoperoxysulfate (TPPP).[10]



Oxone (15 g, 48.8 mmol) was dissolved in deionised water (300 ml) at 10 °C, and to the stirring solution tetraphenylphosphonium chloride (15 g, 40.0 mmol) dissolved in CH_2Cl_2 (300 ml) was added. The remaining solution was left to stir for ½ hour. Extraction of the organic layer was followed by removal of remaining CH_2Cl_2 under reduced pressure. The white solid was washed with distilled water (2 x 75 ml) and then dissolved in CH_2Cl_2 (200 ml), and dried ($MgSO_4$). To the CH_2Cl_2 solution, hexane (50 ml) was added, and left at –20 °C for 24 hours. The cloudy solution was filtered, and any remaining solvents removed under reduced pressure to yield white crystalline TPPP (12.506 g, 70 %). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.19 (1H, s, OH), 7.87 – 7.80 (4H, m, 4x para H on Ph), 7.75 – 7.68 (8H, m, 8x ortho H on Ph), 7.62 – 7.54 (8H, m, 8x meta H on Ph) ppm.

Data are in agreement with those previously reported.[10]

General Procedure for Catalytic Asymmetric Epoxidation of Alkenes Mediated by Imminium Salts using TPPP,[10] used for compounds **63** and **64**.



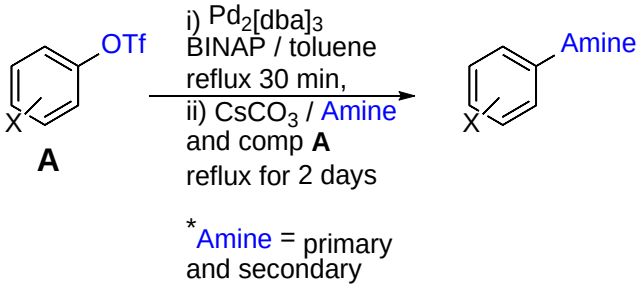
Tetraphenylphosphonium monoperoxysulfate (2 equiv. per each alkene group) was dissolved in the desired solvent (2 ml per 0.1 g oxidant) and the solution cooled to the required temperature. To this was added the iminium salt as a solution (0.5 ml per 0.1 g oxidant). This iminium salt solution was cooled to the same temperature as the solution containing the oxidant and added dropwise to it over 15-20 min; the temperature of the reaction vessel was monitored to minimise increase in the temperature during the addition. A solution of the alkene in the reaction solvent (0.5 ml per 0.1 g oxidant) was added dropwise. The mixture was stirred at the reaction temperature until the alkene was completely consumed according to TLC. Et_2O (pre-cooled to the reaction temperature) (20 ml per 0.1 g oxidant) was added to induce precipitation of the remaining oxidant and the mixture filtered through Celite. The solvents were removed, Et_2O (40 ml) was added to the residue and the solution was passed through a short pad of silica gel to remove catalyst residues. The solvents were removed to give the epoxide. If the reaction does not reach to completion then the epoxide can be separated from the alkene by column chromatography.

The lack of results provided by TLC, IR and NMR, led us to investigate further using MALDI. Crude mixtures were used and major spectroscopy peaks were recorded, as we can see in (**Fig. 2.34, 2.36, 2.39 – 2.42, 2.46 – 2.48**) in the "Results and Discussions" chapter. Using MALDI, we were pleased to find the expected values corresponding to our tetra-substituted resorcinarene.

COMPOUND **64**: expected *m/z* $[M + Na]^+$: 1072.62 and *m/z* $[M + K]^+$: 1088.59; found *m/z* values: 1072.38 and 1088.38.

COMPOUND **63**: expected *m/z* $[M + Na]^+$: 1072.62 and *m/z* $[M + K]^+$: 1087.59 and 1088.59; found *m/z* values: 1072.69 and 188.73.

General Procedure for the **Buchwald-Hartwig Coupling**.[2]

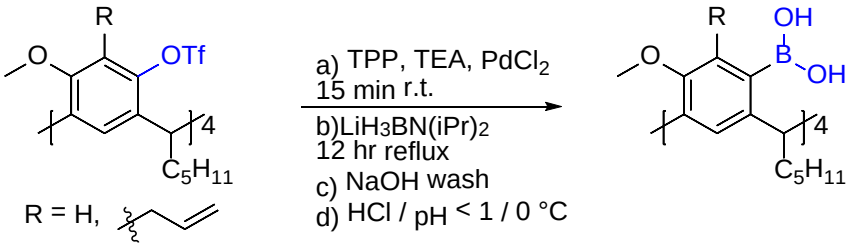


$Pd_2[dba]_3$ (0.2 equiv.) and (±)-BINAP (0.4 equiv.) were dissolved in degassed toluene (10 ml) in a 25 ml flame-dried round-bottomed flask. The mixture was heated under reflux for 30 min. Starting material (1 equiv.), caesium carbonate (12 equiv.) and the corresponding amine (12 equiv.) were added to the mixture. The mixture was then heated under reflux for 2 days until no starting material remained. The mixture was allowed to cool to room temperature, filtered through a pad of silica/celite and washed with ethyl acetate. The solution was concentrated under reduced pressure and the residue was then purified using column chromatography using Petrol/EtOAc (95:5) as the eluent giving the desired product.

General Procedure for ozonolysis (The reaction conditions used for ozonolysis were taken from reports for a simple allyl phenol ether).[11]

Ozonolysis in the presence of pyridine: The alkene substrate (1-3 mmol) and dry pyridine (3-9 mmol) were dissolved in dry CH_2Cl_2 (15-20 ml) in a flame-dried flask under N_2. The solution was cooled to -78 °C, at which point a stream of O_3/O_2 (~ 1 mmol/min of O_3) was introduced through a disposable pipet for a period that varied with the amount of alkene (~ 1 min/mmol). Once complete, the crude reaction mixture was diluted with CH_2Cl_2 (10 ml) and sat. aq. $NaHCO_3$ (15 ml). The aqueous layer was extracted (3 x 5 ml) with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4 and filtered through a cotton plug. The residue obtained upon concentration was purified via flash chromatography with ethyl acetate/hexanes to furnish the aldehyde or ketone.

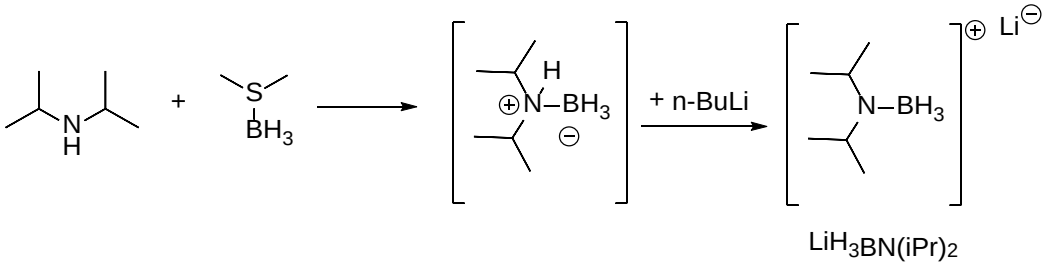
General procedure for the synthesis of an **aryl boronic acid** from the reaction of aryl triflates with $BH_2N(i\text{-}Pr)_2$ in the presence of a palladium catalyst.[12]



Triphenylphosphene (0.53 g, 2 mmol, 80 mol %), starting material (2.5 mmol), and triethylamine (7.2 ml, 20 mmol) were added to a 50 ml round-bottomed flask equipped with a sidearm, condenser, and stir bar. This solution was then degassed by alternating *vacuum* and argon three times. Palladium dichloride (0.092 g, 0.52 mmol, 20 mol %) was then added under positive argon pressure. After stirring at room temperature for 15 min, diisopropylaminoborane (20 ml, 1 M solution in THF, 20 mmol) was added and the reaction mixture was degassed again by alternating *vacuum* and argon three times. The reaction solution was then heated to reflux. After 12 hr of reflux the reaction was cooled to 0 °C and methanol (6 ml) was added through

the condenser slowly. After 15 min of stirring all the solvent was removed under reduced pressure to yield a black solid. This solid was dissolved with sodium hydroxide (8 ml, 3 M) and subsequently washed with hexanes (310 ml). The aqueous layer was then cooled to 0 °C (ice bath) and acidified to pH 1 with concentrated HCl, with the boronic acid usually precipitating out as a white solid. The aqueous fraction was then extracted with diethyl ether 10 ml). The organic fractions were combined, dried with magnesium sulfate and filtered. The solvent was then removed under reduced pressure.

General Procedure for the Preparation of **LAB** Reagent 1 M Solution in THF.[13]



Diisopropylamine (5.00 g, 7 ml, 50 mmol, 1 equiv.) was mixed with anhydrous THF (18 ml) in a 100-ml, round-bottom flask. The solution was cooled to 0 °C (ice bath), and borane dimethylsulfide (5 ml, 10 M, 50 mmol, 1 equiv.) was added dropwise via syringe; the mixture stirred for 1 hr at 0 °C and was analyzed by ^{11}B NMR: the analysis showed the solution to be diisopropylamine borane complex: **^{11}B NMR** (160 Hz, d-THF): δ = -21.18 (q, *J* = 97.2 MHz) ppm. Then, n-butyl lithium in hexanes (20 ml, 2.5 M, 50 mmol, 1 equiv.) was measured in an oven-dried graduated cylinder and was added dropwise via cannula needle to the solution of amine borane at 0 °C (CAUTION: Hydrogen evolution). After stirring at 0 °C for 1 hr, an aliquot was taken and analyzed by ^{11}B NMR which showed the solution to be lithium diisopropylaminoborohydride: **^{11}B NMR** (160 MHz, d-THF): δ = -23.44 (q, *J* = 85.6 Hz) ppm. LAB reagent was transferred to an oven-dried, nitrogen-cooled, ampule via a cannula needle. LAB reagents can be stored in an ampule under nitrogen without decomposition for at least 6 months.

Data are in agreement with those previously reported.[13]

3.2. References Chapter III.

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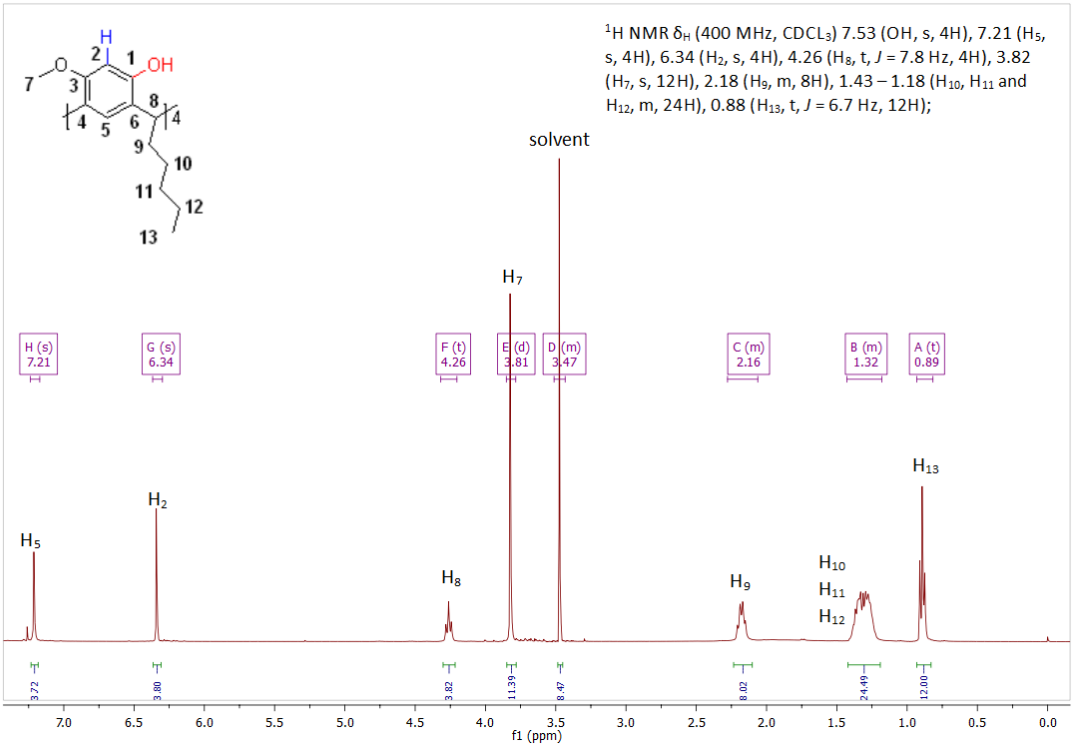
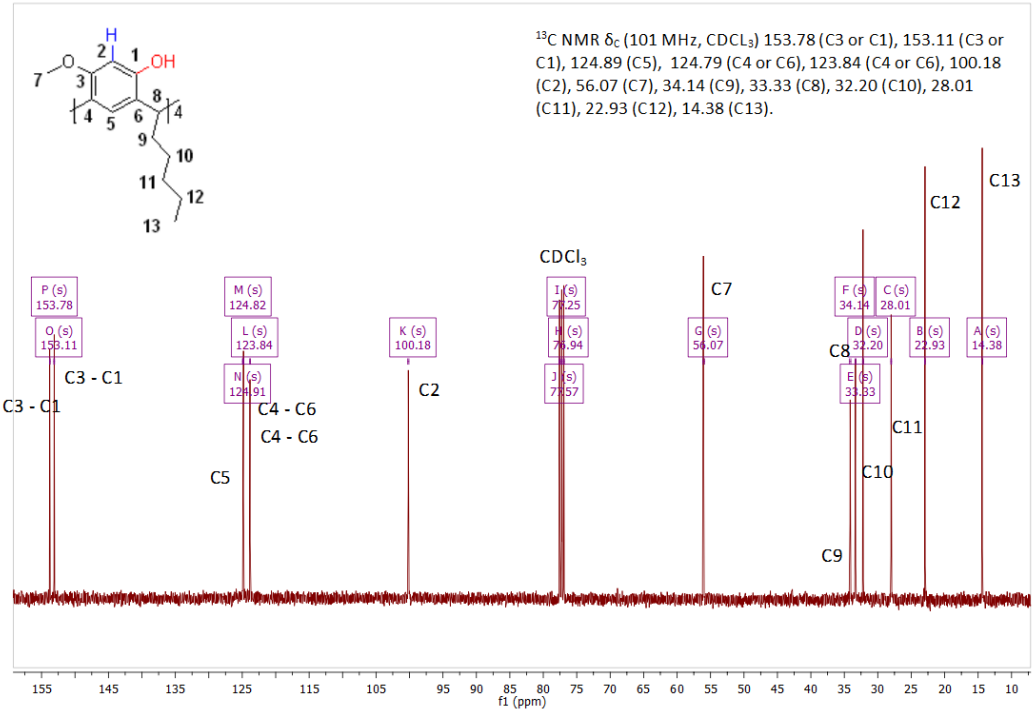
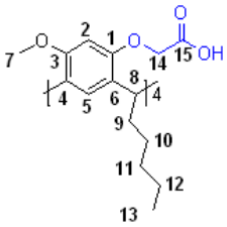
Appendix 1. ^{1}H NMR spectrum for compound **38**.



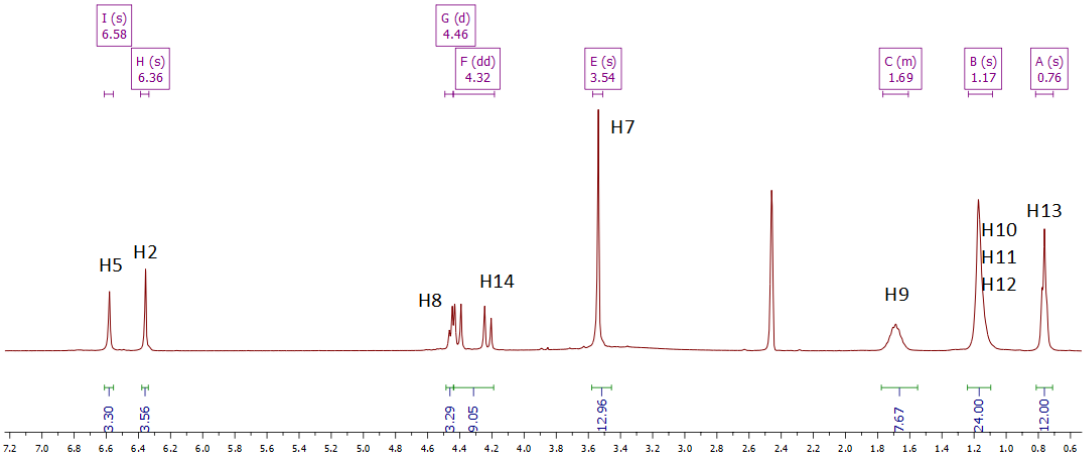
Appendix 2. ^{13}C NMR spectrum for compound **38**.



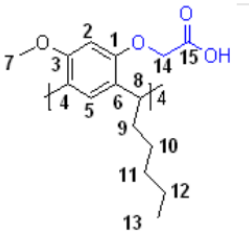
Appendix 3. ^{1}H NMR spectrum for compound **45**.



^{1}H NMR (400 MHz, DMSO) δ 6.58 (s, 1H), 6.36 (s, 1H), 4.46 (d, *J* = 7.3 Hz, 1H), 4.32 (dd, *J* = 74.7, 16.0 Hz, 1H), 3.54 (s, 1H), 2.46 (s, 1H), 1.77 – 1.61 (m, 1H), 1.17 (s, 2H), 0.76 (s, *J* = 5.7 Hz, 1H).

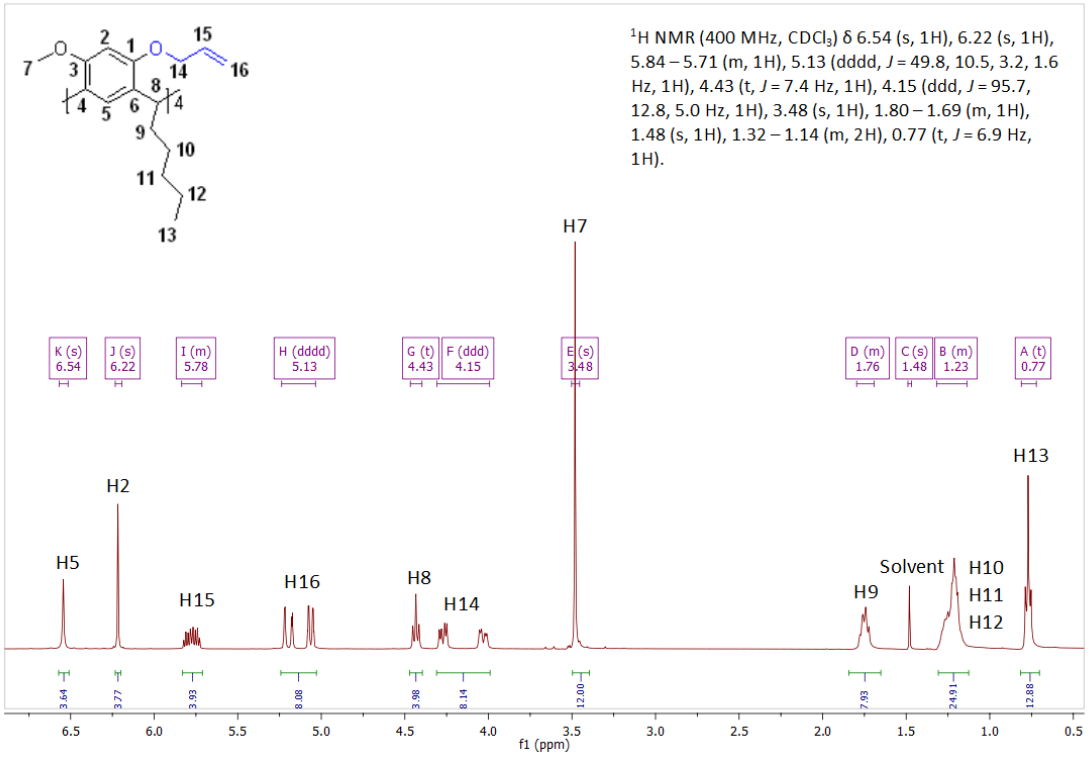


Appendix 4. ^{13}C NMR spectrum for compound **45**.

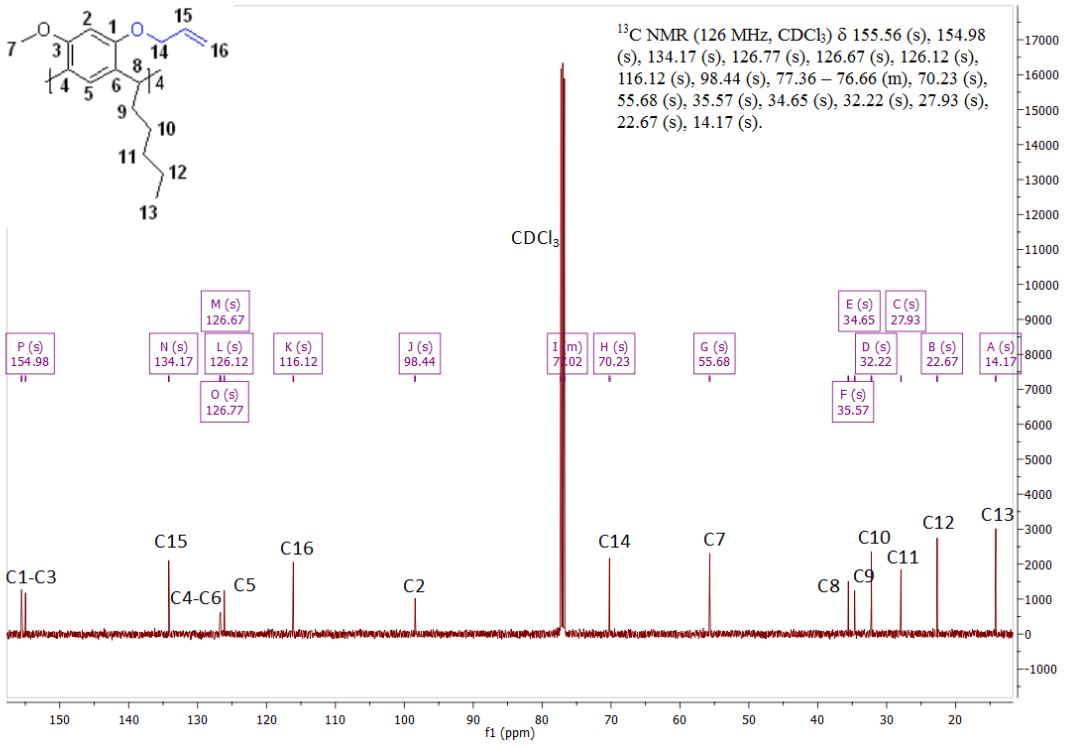


^{13}C NMR (126 MHz, $CDCl_3$) δ 171.30 (s), 155.18 (s), 153.38 (s), 127.59 (s), 126.92 (s), 126.32 (s), 98.02 (s), 77.32 – 76.70 (m), 66.49 (s), 56.13 (s), 35.33 (s), 34.49 (s), 32.02 (s), 27.41 (s), 22.62 (s), 14.12 (s).

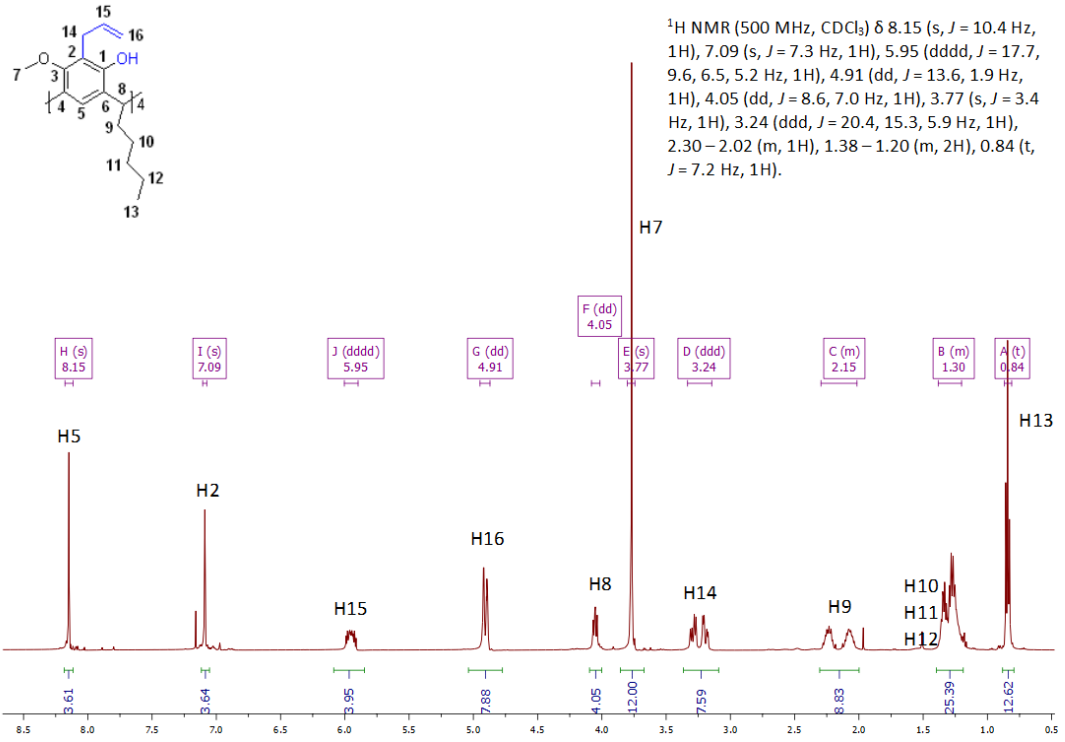
Appendix 5. ^{1}H NMR spectrum for compound **46**.



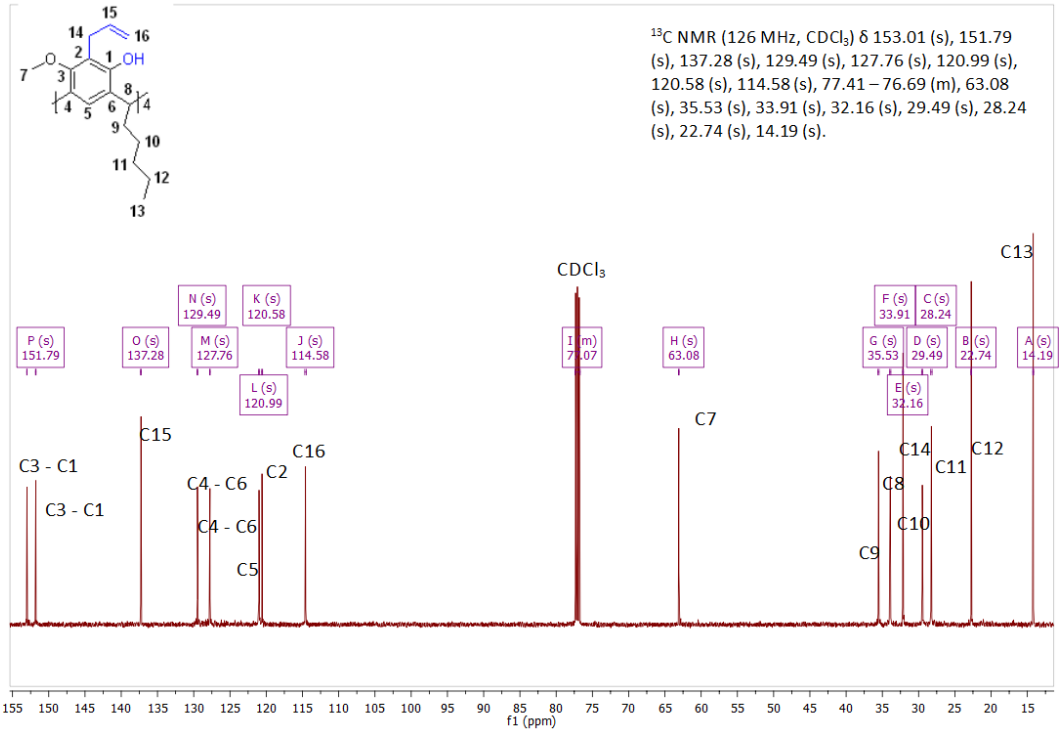
Appendix 6. ^{13}C NMR spectrum for compound **46**.



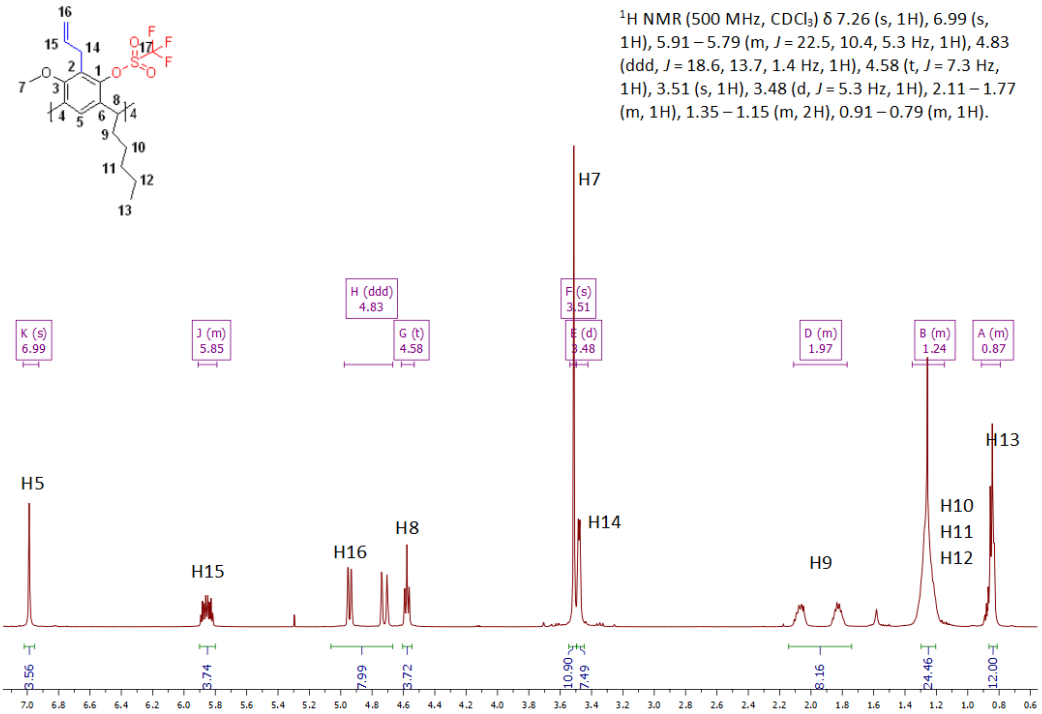
Appendix 7. ^{1}H NMR spectrum for compound **60**.



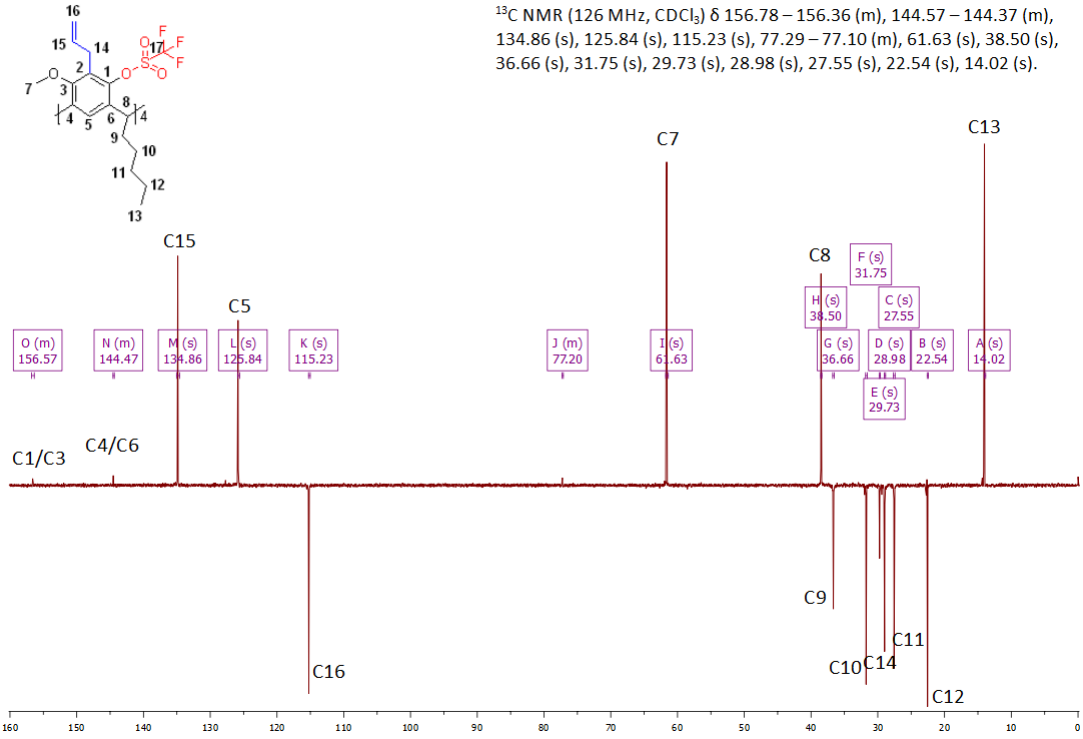
Appendix 8. ^{13}C NMR spectrum for compound **60**.



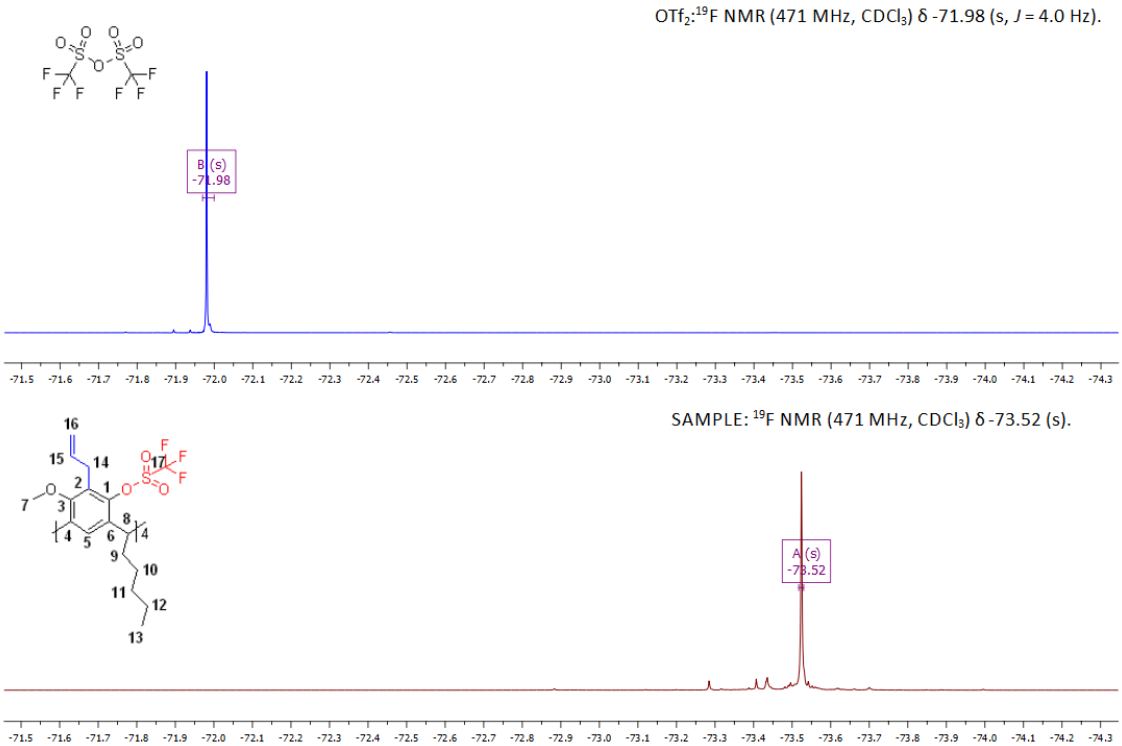
Appendix 9. ^{1}H NMR spectrum for compound **62**.



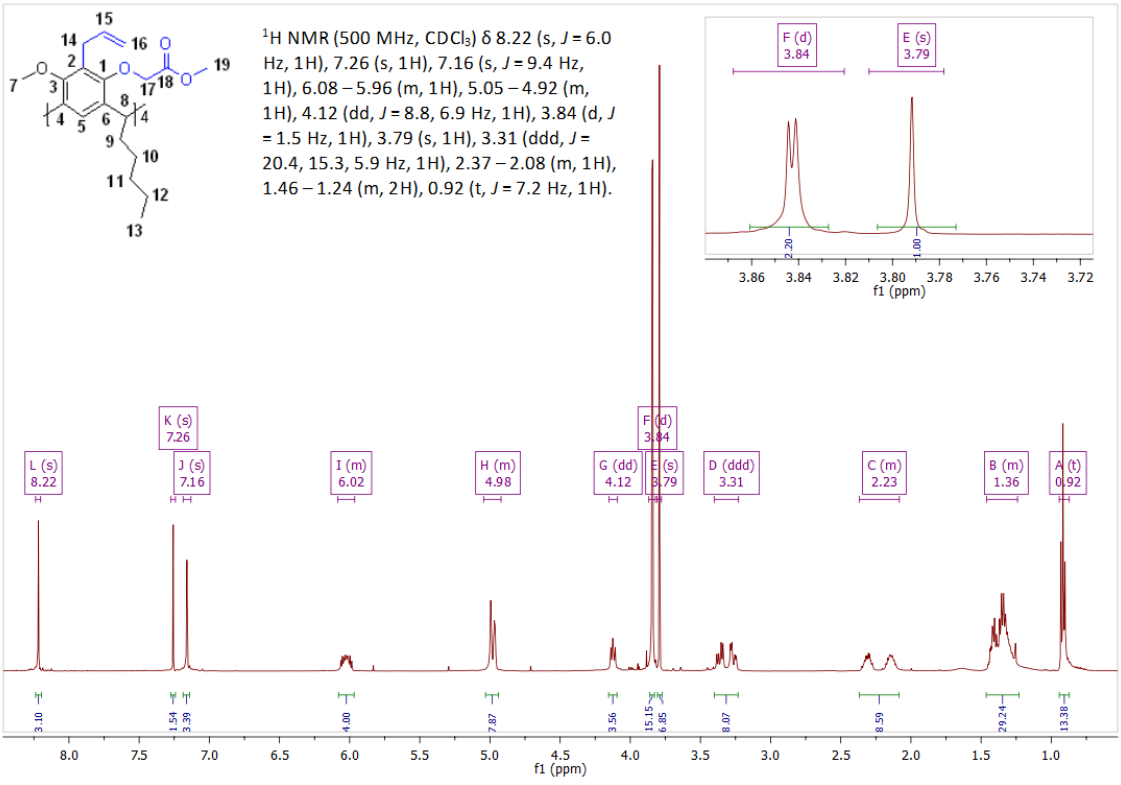
Appendix 10. ^{13}C NMR spectrum for compound **62**.



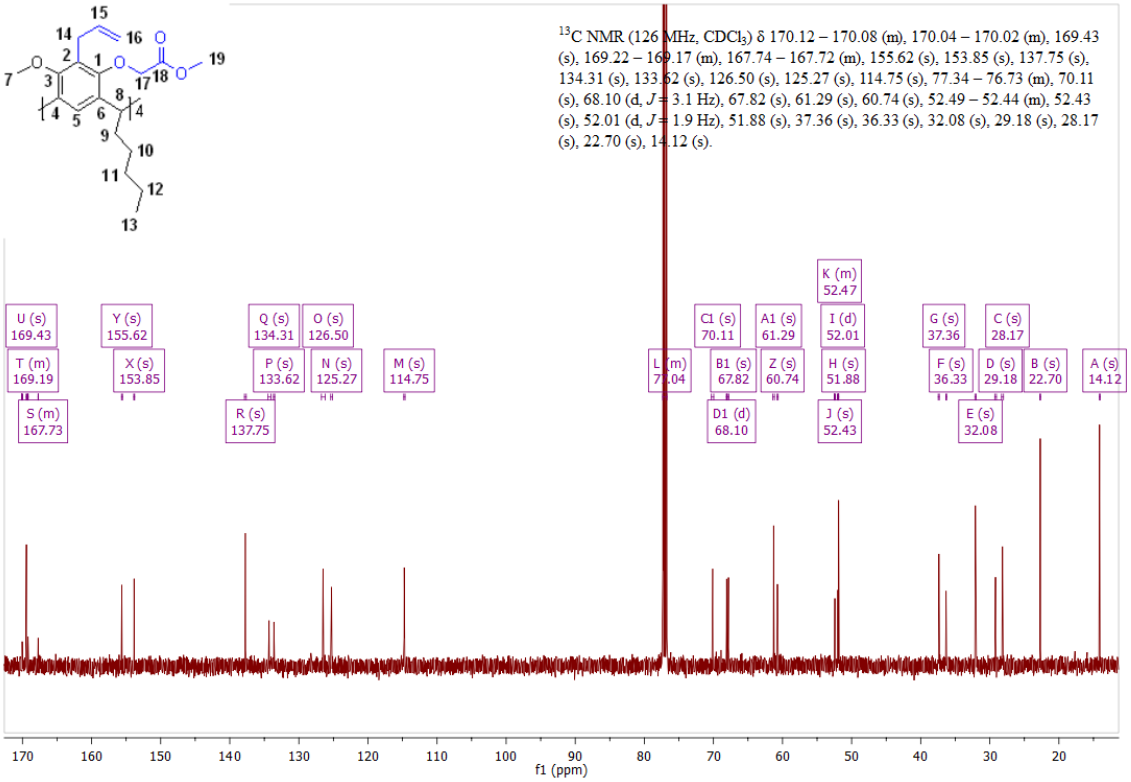
Appendix 11. ^{19}F NMR spectrum for compound **62**.



Appendix 12. ^{1}H NMR spectrum for compound **60-B**.



Appendix 13. ^{13}C NMR spectrum for compound **60-B**.



Appendix 14. Crystal structure experimental data for compound **46**.

The data were collected at a temperature of -148 ± 1°C to a maximum 2θ value of 137.3°.

Appendix 14.A. Crystal Data

Empirical Formula	$C_{64}H_{88}O_8$
Formula Weight	985.39
Crystal Color, Habit	colorless, prism
Crystal Dimensions	0.120 X 0.120 X 0.120 mm
Crystal System	monoclinic
Lattice Type	Primitive

Lattice Parameters	a = 18.665(2) Å, b = 16.490(2) Å, c = 19.264(2) Å,
	β = 99.364(2)°, V = 5850.2(11) Å^3
Space Group	$P2_1/n$ (#14)
Z value	4
D_{calc}	1.119 g/cm^3
F_{000}	2144.00
μ(CuKα)	5.646 cm^{-1}

Appendix 14.B. Intensity Measurements

Diffractometer	XtaLAB P200
Radiation	CuKα (λ = 1.54187 Å), multi-layer mirror monochromated
Voltage, Current	40kV, 30mA
Temperature	-148.0°C
Detector Aperture	83.8 x 70.0 mm
Data Images	3112 exposures
ω oscillation Range (χ=60.0, ϕ=-45.0)	-125.0 - 55.0°
Exposure Rate	10.0 sec./°
Detector Swing Angle	-34.88°
ω oscillation Range (χ=30.0, ϕ=90.0)	-108.0 - -48.0°
Exposure Rate	10.0 sec./°

Detector Swing Angle -34.88°

ω oscillation Range (χ=60.0, ϕ=-90.0) -173.5 - -10.0°

Exposure Rate 10.0 sec./°

Detector Swing Angle -99.88°

ω oscillation Range (χ=30.0, ϕ=45.0) -187.0 - -40.0°

Exposure Rate 10.0 sec./°

Detector Swing Angle -99.88°

ω oscillation Range (χ=60.0, ϕ=-180.0) -165.0 - -10.0°

Exposure Rate 10.0 sec./°

Detector Swing Angle -99.88°

ω oscillation Range (χ=60.0, ϕ=135.0) -190.0 - -127.5°

Exposure Rate 10.0 sec./°

Detector Swing Angle -99.88°

ω oscillation Range (χ=60.0, ϕ=0.0) -165.0 - -19.0°

Exposure Rate 10.0 sec./°

Detector Swing Angle -99.88°

ω oscillation Range (χ=30.0, ϕ=135.0) -152.5 - -44.5°

Exposure Rate 10.0 sec./°

Detector Swing Angle -99.88°

ω oscillation Range (χ=60.0, ϕ=90.0) -174.0 - -114.0°

Exposure Rate 10.0 sec./°

Detector Swing Angle -99.88°

ω oscillation Range (χ=30.0, ϕ=0.0) -70.0 - -10.0°

Exposure Rate 10.0 sec./°

Detector Swing Angle -99.88°

ω oscillation Range (χ=30.0, ϕ=-90.0) -190.0 - -10.0°

Exposure Rate 10.0 sec./°

Detector Swing Angle -99.88°

ω oscillation Range (χ=60.0, ϕ=45.0) -174.0 - -10.0°

Exposure Rate 10.0 sec./°

Detector Swing Angle -99.88°

ω oscillation Range (χ=60.0, ϕ=-135.0) -190.0 - -120.0°

Exposure Rate 10.0 sec./°

Detector Swing Angle -99.88°

Detector Position 31.97 mm

Pixel Size 0.172 mm

$2\theta_{max}$ 137.3°

No. of Reflections Measured Total: 65360, Unique: 10701 (R_{int} = 0.0561)

Corrections Lorentz-polarization, Absorption, (trans. factors: 0.763 - 0.934)

Appendix 14.C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR2011)
Refinement	Full-matrix least-squares on F^2
Function Minimized	Σ w $(Fo^2 - Fc^2)^2$
Least Squares Weights	$w = 1/ [\sigma^2(Fo^2) + (0.1629 \cdot P)^2, + 2.4948 \cdot P]$, where $P = (Max(Fo^2,0) + 2Fc^2)/3$
$2\theta_{max}$ cutoff	137.3°
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (All reflections)	10701
No. Variables	657
Reflection/Parameter Ratio	16.29
Residuals: R1 (I>2.00σ(I))	0.0801
Residuals: R (All reflections)	0.0867
Residuals: wR2 (All reflections)	0.2521
Goodness of Fit Indicator	1.062
Max Shift/Error in Final Cycle	0.005
Maximum peak in Final Diff. Map	1.55 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.64 $e^-/Å^3$

Appendix 14.D. Table showing bond lengths (Å)

atom	atom	distance	atom	atom	distance	atom	atom	distance
O2	C2	1.381(2)	O2	C13	1.431(3)	O4	C4	1.384(2)
O4	C16	1.426(3)	O19	C19	1.371(3)	O19	C35	1.422(3)
O22	C22	1.377(2)	O22	C38	1.413(3)	O40	C40	1.374(3)
O40	C45	1.431(3)	O42	C42	1.379(3)	O42	C48	1.395(3)
O56	C56	1.377(2)	O56	C61	1.406(4)	O58	C58	1.373(3)
O58	C64	1.419(3)	C1	C2	1.404(3)	C1	C6	1.391(3)
C1	C7	1.523(3)	C2	C3	1.390(3)	C3	C4	1.392(3)
C4	C5	1.400(3)	C5	C6	1.391(3)	C5	C17	1.522(3)
C7	C8	1.539(3)	C7	C59	1.519(3)	C8	C9	1.531(3)
C9	C10	1.523(4)	C10	C11	1.497(4)	C11	C12	1.525(6)
C13	C14	1.488(3)	C14	C15	1.312(4)	C17	C18	1.523(3)
C17	C24	1.540(3)	C18	C19	1.397(3)	C18	C20	1.396(3)
C19	C23	1.392(3)	C20	C21	1.391(3)	C21	C22	1.397(3)
C21	C29	1.523(3)	C22	C23	1.393(3)	C24	C25	1.527(3)
C25	C26	1.509(5)	C26	C27	1.535(8)	C27	C28	1.342(13)
C29	C30	1.544(3)	C29	C39	1.526(3)	C30	C31	1.524(3)
C31	C32	1.499(4)	C32	C33	1.523(4)	C33	C34	1.496(5)
C35	C36	1.491(3)	C36	C37	1.313(4)	C39	C40	1.400(3)

C39	C44	1.390(3)	C40	C41	1.397(3)	C41	C42	1.387(3)
C42	C43	1.398(3)	C43	C44	1.393(3)	C43	C49	1.519(3)
C45	C46	1.466(5)	C46	C47	1.110(9)	C49	C50	1.542(3)
C49	C55	1.519(3)	C50	C51	1.519(3)	C51	C52	1.517(4)
C52	C53	1.520(4)	C53	C54	1.513(4)	C55	C56	1.396(3)
C55	C60	1.393(3)	C56	C57	1.396(3)	C57	C58	1.393(3)
C58	C59	1.396(3)	C59	C60	1.391(3)	C61	C62	1.364(6)
C62	C63	1.122(9)	C3	H3	0.950	C6	H6	0.950
C7	H7	1.000	C8	H8A	0.990	C8	H8B	0.990
C9	H9A	0.990	C9	H9B	0.990	C10	H10A	0.990
C10	H10B	0.990	C11	H11A	0.990	C11	H11B	0.990
C12	H12A	0.980	C12	H12B	0.980	C12	H12C	0.980
C13	H13A	0.990	C13	H13B	0.990	C14	H14	0.950
C15	H15A	0.950	C15	H15B	0.950	C16	H16A	0.980
C16	H16B	0.980	C16	H16C	0.980	C17	H17	1.000
C20	H20	0.950	C23	H23	0.950	C24	H24A	0.990
C24	H24B	0.990	C25	H25A	0.990	C25	H25B	0.990
C26	H26A	0.990	C26	H26B	0.990	C27	H27A	0.990
C27	H27B	0.990	C28	H28A	0.980	C28	H28B	0.980
C28	H28C	0.980	C29	H29	1.000	C30	H30A	0.990
C30	H30B	0.990						

C31	H31A	0.990	C31	H31B	0.990	C32	H32A	0.990
C32	H32B	0.990	C33	H33A	0.990	33	H33B	0.990
C34	H34A	0.980	C34	H34B	0.980	C34	H34C	0.980
C35	H35A	0.990	C35	H35B	0.990	C36	H36	0.950
C37	H37A	0.950	C37	H37B	0.950	C38	H38A	0.980
C38	H38B	0.980	C38	H38C	0.980	C41	H41	0.950
C44	H44	0.950	C45	H45A	0.990	C45	H45B	0.990
C46	H46	0.950	C47	H47A	0.950	C47	H47B	0.950
C48	H48A	0.980	C48	H48B	0.980	C48	H48C	0.980
C49	H49	1.000	C50	H50A	0.990	C50	H50B	0.990
C51	H51A	0.990	C51	H51B	0.990	C52	H52A	0.990
C52	H52B	0.990	C53	H53A	0.990	C53	H53B	0.990
C54	H54A	0.980	C54	H54B	0.980	C54	H54C	0.980
C57	H57	0.950	C60	H60	0.950	C61	H61A	0.990
C61	H61B	0.990	C62	H62	0.950	C63	H63A	0.950
C63	H63B	0.950	C64	H64A	0.980	C64	H64B	0.980
C64	H64C	0.980						

Appendix 14.E. Table showing bond angles (°)

atom	atom	atom	angle	atom	atom	atom	angle
C2	O2	C13	117.17(15)	C4	O4	C16	117.41(16)
C19	O19	C35	118.46(16)	C22	O22	C38	117.92(17)
C40	O40	C45	118.45(18)	C42	O42	C48	119.2(2)
C56	O56	C61	118.76(19)	C58	O58	C64	117.91(16)
C2	C1	C6	117.15(18)	C2	C1	C7	119.39(17)
C6	C1	C7	123.46(17)	O2	C2	C1	115.17(17)
O2	C2	C3	123.57(17)	C1	C2	C3	121.26(18)
C2	C3	C4	119.38(18)	O4	C4	C3	122.82(17)
O4	C4	C5	115.74(17)	C3	C4	C5	121.44(18)
C4	C5	C6	117.06(18)	C4	C5	C17	119.97(17)
C6	C5	C17	122.96(17)	C1	C6	C5	123.69(17)
C1	C7	C8	110.95(17)	C1	C7	C59	112.31(16)
C8	C7	C59	114.28(17)	C7	C8	C9	114.44(19)
C8	C9	C10	113.2(2)	C9	C10	C11	113.9(3)
C10	C11	C12	111.7(4)	O2	C13	C14	107.81(17)
C13	C14	C15	123.7(2)	C5	C17	C18	113.30(16)
C5	C17	C24	110.83(17)	C18	C17	C24	113.86(17)
C17	C18	C19	119.61(18)	C17	C18	C20	123.3(2)
C19	C18	C20	117.07(18)	O19	C19	C18	115.37(17)

O19	C19	C23	123.3(2)	C18	C19	C23	121.34(19)
C18	C20	C21	123.8(2)	C20	C21	C22	116.92(19)
C20	C21	C29	123.1(2)	C22	C21	C29	120.03(18)
O22	C22	C21	115.77(19)	O22	C22	C23	122.6(2)
C21	C22	C23	121.59(19)	C19	C23	C22	119.3(2)
C17	C24	C25	112.55(19)	C24	C25	C26	117.1(3)
C25	C26	C27	115.9(5)	C26	C27	C28	120.4(7)
C21	C29	C30	113.97(16)	C21	C29	C39	111.99(17)
C30	C29	C39	109.32(18)	C29	C30	C31	115.4(2)
C30	C31	C32	114.3(2)	C31	C32	C33	115.0(2)
C32	C33	C34	113.5(3)	O19	C35	C36	108.94(19)
C35	C36	C37	126.2(3)	C29	C39	C40	119.87(18)
C29	C39	C44	122.76(17)	C40	C39	C44	117.32(19)
O40	C40	C39	115.45(18)	O40	C40	C41	123.41(19)
C39	C40	C41	121.1(2)	C40	C41	C42	119.5(2)
O42	C42	C41	123.15(19)	O42	C42	C43	115.69(19)
C41	C42	C43	121.1(2)	C42	C43	C44	117.57(19)
C42	C43	C49	119.39(19)	C44	C43	C49	122.96(17)
C39	C44	C43	123.27(18)	O40	C45	C46	105.7(2)
C45	C46	C47	138.2(5)	C43	C49	C50	108.49(18)
C43	C49	C55	112.91(17)	C50	C49	C55	114.24(16)

C49	C50	C51	113.72(19)	C50	C51	C52	113.51(19)
C51	C52	C53	112.4(2)	C52	C53	C54	112.9(2)
C49	C55	C56	119.98(18)	C49	C55	C60	123.4(2)
C56	C55	C60	116.60(19)	O56	C56	C55	115.84(19)
O56	C56	C57	122.3(2)	C55	C56	C57	121.82(18)
C56	C57	C58	119.1(2)	O58	C58	C57	123.4(2)
O58	C58	C59	115.43(17)	C57	C58	C59	121.15(19)
C7	C59	C58	119.43(18)	C7	C59	C60	123.18(19)
C58	C59	C60	117.39(17)	C55	C60	C59	123.8(2)
O56	C61	C62	119.9(4)	C61	C62	C63	125.1(5)
C2	C3	H3	120.3	C4	C3	H3	120.3
C1	C6	H6	118.2	C5	C6	H6	118.2
C1	C7	H7	106.2	C8	C7	H7	106.2
C59	C7	H7	106.2	C7	C8	H8A	108.7
C7	C8	H8B	108.6	C9	C8	H8A	108.6
C9	C8	H8B	108.7	H8A	C8	H8B	107.6
C8	C9	H9A	108.9	C8	C9	H9B	108.9
C10	C9	H9A	108.9	C10	C9	H9B	108.9
H9A	C9	H9B	107.8	C9	C10	H10A	108.8
C9	C10	H10B	108.8	C11	C10	H10A	108.8
C11	C10	H10B	108.8	H10A	C10	H10B	107.7

C10	C11	H11A	109.3	C10	C11	H11B	109.3
C12	C11	H11A	109.3	C12	C11	H11B	109.3
H11A	C11	H11B	107.9	C11	C12	H12A	109.5
C11	C12	H12B	109.5	C11	C12	H12C	109.5
H12A	C12	H12B	109.5	H12A	C12	H12C	109.5
H12B	C12	H12C	109.5	O2	C13	H13A	110.2
O2	C13	H13B	110.1	C14	C13	H13A	110.1
C14	C13	H13B	110.1	H13A	C13	H13B	108.5
C13	C14	H14	118.1	C15	C14	H14	118.1
C14	C15	H15A	120.0	C14	C15	H15B	120.0
H15A	C15	H15B	120.0	O4	C16	H16A	109.5
O4	C16	H16B	109.5	O4	C16	H16C	109.5
H16A	C16	H16B	109.5	H16A	C16	H16C	109.5
H16B	C16	H16C	109.5	C5	C17	H17	106.1
C18	C17	H17	106.0	C24	C17	H17	106.0
C18	C20	H20	118.1	C21	C20	H20	118.1
C19	C23	H23	120.4	C22	C23	H23	120.4
C17	C24	H24A	109.1	C17	C24	H24B	109.1
C25	C24	H24A	109.1	C25	C24	H24B	109.1
H24A	C24	H24B	107.9	C24	C25	H25A	108.0
C24	C25	H25B	108.0	C26	C25	H25A	108.0

C26	C25	H25B	108.0	H25A	C25	H25B	107.3
C25	C26	H26A	108.3	C25	C26	H26B	108.3
C27	C26	H26A	108.3	C27	C26	H26B	108.3
H26A	C26	H26B	107.4	C26	C27	H27A	107.2
C26	C27	H27B	107.2	C28	C27	H27A	107.2
C28	C27	H27B	107.2	H27A	C27	H27B	106.9
C27	C28	H28A	109.5	C27	C28	H28B	109.5
C27	C28	H28C	109.5	H28A	C28	H28B	109.5
H28A	C28	H28C	109.5	H28B	C28	H28C	109.5
C21	C29	H29	107.1	C30	C29	H29	107.1
C39	C29	H29	107.1	C29	C30	H30A	108.4
C29	C30	H30B	108.4	C31	C30	H30A	108.4
C31	C30	H30B	108.4	H30A	C30	H30B	107.5
C30	C31	H31A	108.7	C30	C31	H31B	108.7
C32	C31	H31A	108.7	C32	C31	H31B	108.7
H31A	C31	H31B	107.6	C31	C32	H32A	108.5
C31	C32	H32B	108.5	C33	C32	H32A	108.5
C33	C32	H32B	108.5	H32A	C32	H32B	107.5
C32	C33	H33A	108.9	C32	C33	H33B	108.9
C34	C33	H33A	108.9	C34	C33	H33B	108.9
H33A	C33	H33B	107.7	C33	C34	H34A	109.5

C33	C34	H34B	109.5	C33	C34	H34C	109.5
H34A	C34	H34B	109.5	H34A	C34	H34C	109.5
H34B	C34	H34C	109.5	O19	C35	H35A	109.9
O19	C35	H35B	109.9	C36	C35	H35A	109.9
C36	C35	H35B	109.9	H35A	C35	H35B	108.3
C35	C36	H36	116.9	C37	C36	H36	116.9
C36	C37	H37A	120.0	C36	C37	H37B	120.0
H37A	C37	H37B	120.0	O22	C38	H38A	109.5
O22	C38	H38B	109.5	O22	C38	H38C	109.5
H38A	C38	H38B	109.5	H38A	C38	H38C	109.5
H38B	C38	H38C	109.5	C40	C41	H41	120.3
C42	C41	H41	120.3	C39	C44	H44	118.4
C43	C44	H44	118.4	O40	C45	H45A	110.6
O40	C45	H45B	110.6	C46	C45	H45A	110.6
C46	C45	H45B	110.6	H45A	C45	H45B	108.7
C45	C46	H46	110.9	C47	C46	H46	110.9
C46	C47	H47A	120.0	C46	C47	H47B	120.0
H47A	C47	H47B	120.0	O42	C48	H48A	109.5
O42	C48	H48B	109.5	O42	C48	H48C	109.5
H48A	C48	H48B	109.5	H48A	C48	H48C	109.5
H48B	C48	H48C	109.5	C43	C49	H49	106.9

C50	C49	H49	106.9	C55	C49	H49	106.9
C49	C50	H50A	108.8	C49	C50	H50B	108.8
C51	C50	H50A	108.8	C51	C50	H50B	108.8
H50A	C50	H50B	107.7	C50	C51	H51A	108.9
C50	C51	H51B	108.9	C52	C51	H51A	108.9
C52	C51	H51B	108.9	H51A	C51	H51B	107.7
C51	C52	H52A	109.1	C51	C52	H52B	109.1
C53	C52	H52A	109.1	C53	C52	H52B	109.1
H52A	C52	H52B	107.8	C52	C53	H53A	109.0
C52	C53	H53B	109.0	C54	C53	H53A	109.0
C54	C53	H53B	109.0	H53A	C53	H53B	107.8
C53	C54	H54A	109.5	C53	C54	H54B	109.5
C53	C54	H54C	109.5	H54A	C54	H54B	109.5
H54A	C54	H54C	109.5	H54B	C54	H54C	109.5
C56	C57	H57	120.4	C58	C57	H57	120.4
C55	C60	H60	118.1	C59	C60	H60	118.1
O56	C61	H61A	107.3	O56	C61	H61B	107.3
C62	C61	H61A	107.3	C62	C61	H61B	107.3
H61A	C61	H61B	106.9	C61	C62	H62	117.4
C63	C62	H62	117.5	C62	C63	H63A	120.0
C62	C63	H63B	120.0	H63A	C63	H63B	120.0

O58	C64	H64A	109.5	O58	C64	H64B	109.5
O58	C64	H64C	109.5	H64A	C64	H64B	109.5
H64A	C64	H64C	109.5	H64B	C64	H64C	109.5

Appendix 15. Crystal structure experimental data for compound **60**.

Appendix 15.A. Crystal Data

Empirical Formula	$C_{64}H_{88}O_8$
Formula Weight	985.39
Crystal Color	colorless
Lattice Parameters	a = 13.3100(13) Å, b = 17.7240(17) Å, c = 24.752(2) Å,
	α = 90.000°, β = 93.4(7) °, γ 90.000°, v = 5828.88 $Å^3$
Space group	$P2_1/c$
Z value	4

Appendix 15.B. Table showing bond lengths (Å)

atom	atom	atom	angle	atom	atom	atom	angle
C2	O2	C7	110(1)	C38	C39	C40	123(2)
H4	O4	C4	109.5	H39	C39	C40	119
C12	O12	C17	113.6(4)	C39	C40	H40A	120
H14	O14	C14	109.5	C39	C40	H40B	120
C22	O22	C27	115.5(7)	H40A	C40	H40B	120

H24	O24	C24	109.5	C1	C41	C35	111.4(9)
C32	O32	C37	113.7(5)	C1	C41	H41	107.4
H34	O34	C34	109.4	C1	C41	C42	110.8(9)
C2	C1	C6	117.5(9)	C35	C41	H41	107
C2	C1	C41	122.3(9)	C35	C41	C42	112.4(9)
C6	C1	C41	120.1(8)	H41	C41	C42	107
O2	C2	C1	116(1)	C41	C42	H42A	109
O2	C2	C3	120(1)	C41	C42	H42B	109
C1	C2	C3	124(1)	C41	C42	C43	112(1)
C2	C3	C4	117.6(9)	H42A	C42	H42B	108
C2	C3	C8	122.8(9)	H42A	C42	C43	109
C4	C3	C8	119.4(9)	H42B	C42	C43	109
O4	C4	C3	116.6(7)	C42	C43	H43A	108
O4	C4	C5	120.2(6)	C42	C43	H43B	108
C3	C4	C5	123.2(7)	C42	C43	C44	117(2)
C4	C5	C6	116.5(7)	H43A	C43	H43B	107
C4	C5	C47	124.2(6)	H43A	C43	C44	108
C6	C5	C47	119.3(6)	H43B	C43	C44	108
C1	C6	C5	121.3(8)	C43	C44	H44A	107
C1	C6	H6	119.4	C43	C44	H44B	107
C5	C6	H6	119.4	C43	C44	C45	122(2)

O2	C7	H7A	110	H44A	C44	H44B	107
O2	C7	H7B	110	H44A	C44	C45	107
O2	C7	H7C	109	H44B	C44	C45	107
H7A	C7	H7B	109	C44	C45	H45A	108
H7A	C7	H7C	109	C44	C45	H45B	109
H7B	C7	H7C	109	C44	C45	C46	115(2)
C3	C8	H8A	109.7	H45A	C45	H45B	107
C3	C8	H8B	109.6	H45A	C45	C46	108
C3	C8	C9	110.1(9)	H45B	C45	C46	108
H8A	C8	H8B	108	C45	C46	H46A	110
H8A	C8	C9	109.6	C45	C46	H46B	110
H8B	C8	C9	109.6	C45	C46	H46C	110
C8	C9	H9	116	H46A	C46	H46B	109
C8	C9	C10	127(1)	H46A	C46	H46C	109
H9	C9	C10	117	H46B	C46	H46C	109
C9	C10	H10A	120	C5	C47	C11	110.8(5)
C9	C10	H10B	120	C5	C47	H47	105.8
H10A	C10	H10B	120	C5	C47	C48	114.6(5)
C12	C11	C16	117.3(5)	C11	C47	H47	105.8
C12	C11	C47	121.1(5)	C11	C47	C48	113.1(5)
C16	C11	C47	121.5(5)	H47	C47	C48	105.9

O12	C12	C11	119.7(5)	C47	C48	H48A	108.5
O12	C12	C13	116.3(5)	C47	C48	H48B	108.4
C11	C12	C13	123.9(6)	C47	C48	C49	115.3(6)
C12	C13	C14	117.3(6)	H48A	C48	H48B	107.5
C12	C13	C18	122.4(6)	H48A	C48	C49	108.4
C14	C13	C18	120.3(6)	H48B	C48	C49	108.5
O14	C14	C13	116.0(7)	C48	C49	H49A	107.8
O14	C14	C15	123.7(7)	C48	C49	H49B	107.8
C13	C14	C15	120.3(7)	C48	C49	C50	118.1(8)
C14	C15	C16	119.0(6)	H49A	C49	H49B	107.1
C14	C15	C53	118.8(7)	H49A	C49	C50	107.8
C16	C15	C53	122.0(6)	H49B	C49	C50	107.8
C11	C16	C15	122.0(6)	C49	C50	H50A	107
C11	C16	H16	119.1	C49	C50	H50B	107
C15	C16	H16	118.9	C49	C50	C51	122(1)
O12	C17	H17A	109.5	H50A	C50	H50B	107
O12	C17	H17B	109.4	H50A	C50	C51	107
O12	C17	H17C	109.5	H50B	C50	C51	107
H17A	C17	H17B	109.5	C50	C51	H51A	106
H17A	C17	H17C	109.5	C50	C51	H51B	106
H17B	C17	H17C	109.4	C50	C51	C52	125(1)

C13	C18	H18A	108.3	H51A	C51	H51B	106
C13	C18	H18B	108.3	H51A	C51	C52	106
C13	C18	C19	116.5(7)	H51B	C51	C52	106
H18A	C18	H18B	107.2	C51	C52	H52A	109
H18A	C18	C19	108.1	C51	C52	H52B	109
H18B	C18	C19	108.1	C51	C52	H52C	110
C18	C19	H19	118	H52A	C52	H52B	109
C18	C19	C20	123(1)	H52A	C52	H52C	110
H19	C19	C20	118	H52B	C52	H52C	109
C19	C20	H20A	120	C15	C53	C21	108.3(6)
C19	C20	H20B	120	C15	C53	H53	106.9
H20A	C20	H20B	120	C15	C53	C54	113.8(7)
C22	C21	C26	115.8(7)	C21	C53	H53	106.9
C22	C21	C53	122.4(7)	C21	C53	C54	113.5(7)
C26	C21	C53	121.8(7)	H53	C53	C54	107
O22	C22	C21	118.7(7)	C53	C54	H54A	108.6
O22	C22	C23	117.3(7)	C53	C54	H54B	108.6
C21	C22	C23	123.9(7)	C53	C54	C55	114.3(8)
C22	C23	C24	116.6(6)	H54A	C54	H54B	107.6
C22	C23	C28	125.4(6)	H54A	C54	C55	108.8
C24	C23	C28	117.9(6)	H54B	C54	C55	108.7

O24	C24	C23	117.3(5)	C54	C55	H55A	109
O24	C24	C25	121.0(5)	C54	C55	H55B	109
C23	C24	C25	121.7(6)	C54	C55	C56	113.0(9)
C24	C25	C26	116.6(6)	H55A	C55	H55B	108
C24	C25	C59	121.0(5)	H55A	C55	C56	109
C26	C25	C59	122.4(6)	H55B	C55	C56	109
C21	C26	C25	125.2(6)	C55	C56	H56A	109
C21	C26	H26	117.4	C55	C56	H56B	109
C25	C26	H26	117.4	C55	C56	C57	112(1)
O22	C27	H27A	109	H56A	C56	H56B	108
O22	C27	H27B	109	H56A	C56	C57	109
O22	C27	H27C	110	H56B	C56	C57	109
H27A	C27	H27B	109	C56	C57	H57A	109
H27A	C27	H27C	110	C56	C57	H57B	109
H27B	C27	H27C	109	C56	C57	C58	111(1)
C23	C28	H28A	107.4	H57A	C57	H57B	108
C23	C28	H28B	107.4	H57A	C57	C58	109
C23	C28	C29	119.5(7)	H57B	C57	C58	109
H28A	C28	H28B	107	C57	C58	H58A	110
H28A	C28	C29	107.5	C57	C58	H58B	109
H28B	C28	C29	107.4	C57	C58	H58C	109

C28	C29	H29	118.4	H58A	C58	H58B	109
C28	C29	C30	123(1)	H58A	C58	H58C	110
H29	C29	C30	118	H58B	C58	H58C	109
C29	C30	H30A	120	C25	C59	C31	111.8(5)
C29	C30	H30B	120	C25	C59	H59	107.4
H30A	C30	H30B	120	C25	C59	C60	119.7(5)
C32	C31	C36	117.2(6)	C31	C59	H59	107.5
C32	C31	C59	119.5(6)	C31	C59	C60	102.3(5)
C36	C31	C59	123.2(6)	H59	C59	C60	107.5
O32	C32	C31	118.7(6)	C59	C60	H60A	109.6
O32	C32	C33	118.7(7)	C59	C60	H60B	109.6
C31	C32	C33	122.3(7)	C59	C60	C61	110.1(6)
C32	C33	C34	115.8(8)	H60A	C60	H60B	108.2
C32	C33	C38	125.6(8)	H60A	C60	C61	109.6
C34	C33	C38	118.5(9)	H60B	C60	C61	109.7
O34	C34	C33	111.4(9)	C60	C61	H61A	110.3
O34	C34	C35	125(1)	C60	C61	H61B	110.2
C33	C34	C35	123(1)	C60	C61	C62	107.5(7)
C34	C35	C36	116.8(9)	H61A	C61	H61B	108.5
C34	C35	C41	118.1(9)	H61A	C61	C62	110.1
C36	C35	C41	125.1(9)	H61B	C61	C62	110.2

C31	C36	C35	124.2(8)	C61	C62	H62A	109.9
C31	C36	H36	117.9	C61	C62	H62B	110
C35	C36	H36	117.9	C61	C62	C63	108.7(8)
O32	C37	H37A	109.6	H62A	C62	H62B	108.3
O32	C37	H37B	109.4	H62A	C62	C63	109.8
O32	C37	H37C	109.6	H62B	C62	C63	110.1
H37A	C37	H37B	109.5	C62	C63	H63A	110
H37A	C37	H37C	109.3	C62	C63	H63B	110
H37B	C37	H37C	109.5	C62	C63	C64	108(1)
C33	C38	H38A	108	H63A	C63	H63B	108
C33	C38	H38B	108	H63A	C63	C64	110
C33	C38	C39	115(1)	H63B	C63	C64	110
H38A	C38	H38B	108	C63	C64	H64A	110
H38A	C38	C39	108	C63	C64	H64B	109
H38B	C38	C39	109	C63	C64	H64C	109
C38	C39	H39	119	H64A	C64	H64B	109
H64B	C64	H64C	109	H64A	C64	H64C	110

Appendix 15.C. Table showing bond angles (°)

Atom	atom	distance	atom	atom	distance
O2	C2	1.39(1)	C20	H20A	0.95
O2	C7	1.51(2)	C20	H20B	0.95
O4	H4	0.84	C21	C22	1.38(1)
O4	C4	1.37(1)	C21	C26	1.38(1)
O12	C12	1.403(9)	C21	C53	1.55(1)
O12	C17	1.419(9)	C22	C23	1.39(1)
O14	H14	0.841	C23	C24	1.41(1)
O14	C14	1.35(1)	C23	C28	1.50(1)
O22	C22	1.39(1)	C24	C25	1.40(1)
O22	C27	1.43(1)	C25	C26	1.37(1)
O24	H24	0.84	C25	C59	1.50(1)
O24	C24	1.387(8)	C26	H26	0.95
O32	C32	1.38(1)	C27	H27A	0.98
O32	C37	1.44(1)	C27	H27B	0.98
O34	H34	0.84	C27	H27C	0.98
O34	C34	1.41(1)	C28	H28A	0.988
C1	C2	1.38(2)	C28	H28B	0.991
C1	C6	1.37(1)	C28	C29	1.45(1)
C1	C41	1.54(2)	C29	H29	0.95

C2	C3	1.38(2)	C29	C30	1.31(2)
C3	C4	1.37(1)	C30	H30A	0.95
C3	C8	1.52(2)	C30	H30B	0.95
C4	C5	1.38(1)	C31	C32	1.40(1)
C5	C6	1.45(1)	C31	C36	1.40(1)
C5	C47	1.51(1)	C31	C59	1.54(1)
C6	H6	0.949	C32	C33	1.39(1)
C7	H7A	0.98	C33	C34	1.43(2)
C7	H7B	0.98	C33	C38	1.66(2)
C7	H7C	0.98	C34	C35	1.40(2)
C8	H8A	0.99	C35	C36	1.35(1)
C8	H8B	0.99	C35	C41	1.51(2)
C8	C9	1.60(2)	C36	H36	0.951
C9	H9	0.95	C37	H37A	0.98
C9	C10	1.33(1)	C37	H37B	0.98
C10	H10A	0.95	C37	H37C	0.98
C10	H10B	0.95	C38	H38A	0.99
C11	C12	1.36(1)	C38	H38B	0.99
C11	C16	1.40(1)	C38	C39	1.42(2)
C11	C47	1.53(1)	C39	H39	0.95
C12	C13	1.38(1)	C39	C40	1.32(2)

C13	C14	1.42(1)		C40	H40A	0.95
C13	C18	1.55(1)		C40	H40B	0.95
C14	C15	1.39(1)		C41	H41	1
C15	C16	1.38(1)		C41	C42	1.52(2)
C15	C53	1.55(1)		C42	H42A	0.99
C16	H16	0.95		C42	H42B	0.99
C17	H17A	0.98		C42	C43	1.52(2)
C17	H17B	0.98		C43	H43A	0.99
C17	H17C	0.979		C43	H43B	0.99
C18	H18A	0.99		C43	C44	1.47(3)
C18	H18B	0.99		C44	H44A	0.99
C18	C19	1.40(1)		C44	H44B	0.99
C19	H19	0.95		C44	C45	1.48(3)
C19	C20	1.32(1)		C45	H45A	0.99
C45	C46	1.44(4)	x	C55	H55B	0.99
C45	H45B	0.99		C55	C56	1.55(2)
C46	H46A	0.98		C56	H56A	0.99
C46	H46B	0.98		C56	H56B	0.99
C46	H46C	0.98		C56	C57	1.53(2)
C47	H47	1		C57	H57A	0.99
C47	C48	1.548(9)		C57	H57B	0.99

C48	H48A	0.989	C57	C58	1.53(2)
C48	H48B	0.99	C58	H58A	0.98
C48	C49	1.49(1)	C58	H58B	0.98
C49	H49A	0.99	C58	H58C	0.98
C49	H49B	0.99	C59	H59	1
C49	C50	1.52(1)	C59	C60	1.522(8)
C50	H50A	0.99	C60	H60A	0.99
C50	H50B	0.99	C60	H60B	0.99
C50	C51	1.28(2)	C60	C61	1.51(2)
C51	H51A	0.99	C61	H61A	0.991
C51	H51B	0.99	C61	H61B	0.99
C51	C52	1.40(2)	C61	C62	1.57(1)
C52	H52A	0.98	C62	H62A	0.99
C52	H52B	0.98	C62	H62B	0.99
C52	H52C	0.98	C62	C63	1.55(2)
C53	H53	1	C63	H63A	0.99
C53	C54	1.51(1)	C63	H63B	0.99
C54	H54A	0.99	C63	C64	1.49(2)
C54	H54B	0.99	C64	H64A	0.979
C54	C55	1.51(2)	C64	H64B	0.98
C55	H55A	0.99	C64	H64C	0.98