A C-H Activation Route to Inherently Chiral Calix[4]Arenes

by

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Declaration

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Abstract

The unique three-dimensional structure of the calixarene molecule allows it to possess, what is known as, inherent chirality. The compound, therefore, has potential application in various host-guest chemistry interactions. Our group is interested in developing new methods of synthesizing *meta*-functionalized inherently chiral calix[4]arenes. Recently, it has been demonstrated that *ortho*-halogenated *N*-aryl methyl carbamates may be selectively synthesized in acidic conditions through a $Pd(OAc)_2$ assisted C-H activation. However, our research showed that when brominating a methyl (4-methoxyphenyl)carbamate without the inclusion of the catalyst, the regioselectivity of the reaction was not compromised. With this in mind, we investigated the role of the $Pd(OAc)_2$ and the carbamate directing group when synthesizing *meta*-brominated inherently chiral calix[4]arenes.

On a mono-substituted carbamate calix[4]arene system, we found that *meta*-brominated inherently chiral calix[4]arenes could be synthesized in high yields (85–90%), either through electrophilic aromatic substitution or C-H activation. After establishing the reaction conditions, we attempted to asymmetrically brominate the calix[4]arene by making use of a chiral 1(*S*)-(+)-menthyl carbamate directing group. For the reactions that included the catalyst, slightly higher yields were obtained compared to the reactions that did not. It was also found through alpha-D experiments that the $Pd(OAc)_2$ assisted reactions resulted in a higher specific rotation. Unfortunately, no further evidence of diastereoselectivity could be obtained as the respective ^1H NMR spectra showed no obvious differences and attempting to separate the diastereomers using HPLC proved unsuccessful.

We also demonstrate for the first time that *meta*-functionalized inherently chiral calix[4]arenes of C_4 symmetry can be synthesized through direct modification. This was achieved by making use of a methyl *N*-aryl carbamate directing group in an acid catalyzed electrophilic aromatic substitution. Purification was burdened with issues of isolating co-forming achiral stereoisomers, however, the desired inherently chiral calix[4]arene was finally isolated in yields as high as 40%.

Opsomming

Die unieke drie-dimensionele struktuur van die calixarene molekule stel dit in staat om te besit, wat bekend staan as inherente chiraliteit. Die molekule het dus potensiële toepassing in verskeie gasheer-gas chemiese interaksies. Ons groep is geïnteresseerd om nuwe metodes vir die sintetisering van *meta*-gefunksionaliseerde inherente chiral calix[4]arene te ontwikkel. Onlangs is dit gedemonstreer dat *orto*-gehalogeneerde *N*-arielmatielkarbamate selektief gesintetiseer kan word in suur toestande deur ‘n $Pd(OAc)_2$ assistente C-H aktivering. Ons navorsing het egter getoon dat by die brominering van 'n metiel (4-metoksifeniel)karbamaat sonder die insluiting van die katalisator die regioselektiwiteit van die reaksie nie gekompromiseer is nie. Met hierdie in gedagte het ons die rol van die $Pd(OAc)_2$ en die karbamaat-regerende groep in die sintese van *meta*-gebroomde inherente chiral calix[4]arene ondersoek.

Op 'n mono-gesubstitueerde karbamaat calix[4]arene stelsel het ons bevind dat *meta*-gebroomde inherente chirale calix[4]arene gesintetiseer kan word in hoë opbrengste (85-90%), óf deur elektrofiliese aromatiese substitusie of C-H aktivering. Nadat ons die reaksietoestande gevestig het, het ons probeer om die calix[4]arene asimmetries te bromineer deur gebruik te maak van 'n chirale 1(*S*)-(+)-mentielkarbamaat-regerende groep. Vir die reaksies wat die katalisator ingesluit het, is effens hoër opbrengste behaal in vergelyking met die reaksies wat dit nie gedoen het nie. Daar is ook deur alfa-D eksperimente gevind dat die $Pd(OAc)_2$ assistente reaksies tot 'n hoër spesifieke rotasie gelei het. Ongelukkig kan geen verdere bewys van diastereoselektiwiteit verkry word nie, aangesien die onderskeie ^1H NMR spektra geen duidelike verskille toon nie en pogings om die diastereomere met behulp van HPLC te skei, was onsuksesvol.

Ons demonstreer ook vir die eerste keer dat meta-funksionaliseerde inherente chirale calix[4]arene van C_4-simmetrie deur direkte modifikasie gesintetiseer kan word. Dit is behaal deur gebruik te maak van 'n metiel *N*-arylkarbamaat-regiegroep in 'n suur gekataliseerde elektrofiliese aromatiese substitusie. Suiwering is belas met die probleme van die isolering van ko-vormende achirale stereoisomere, maar die verlangde inherente chirale calix[4]arene is uiteindelik geïsoleer in opbrengste so hoog as 40%.

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Abbreviations

^{1}H NMR	Proton NMR
^{13}C NMR	Carbon NMR
COSY	Correlation spectroscopy
HSQC	Heteronuclear single-quantum correlation spectroscopy
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HPLC	High performance liquid chromatography
IR	Infrared spectroscopy
Mp	Melting point
MS	Mass spectrometry
R_f	Retention factor
TLC	Thin layer chromatography
PTSA	*p*-toluenesulfonic acid
NBS	N-bromosuccinamide
$Pd(OAc)_2$	Palladium acetate
RT	Room temperature
DCM	Dichloromethane
PET	Petroleum ether
EtOAc	Ethyl acetate
THF	Tetrahydrofuran

Contents

1. Chapter 1 – Introduction

1.1. Introduction

Calix[4]arenes are macrocyclic compounds consisting of four phenyl rings each attached by a single carbon that forms the methylene bridge.[1] They are a product of a hydroxyalkylation reaction between formaldehyde and *para*-substituted phenols and can form rings of various sizes depending on the number of arene subunits present in the macrocycle (Figure 1.1).[2] Calixarenes take on a molecular bucket or basket-like shape in a three-dimensional space, hence the name calixarene, where 'calix' refers to its chalice-like shape and 'arene' indicating the repeating aromatic building block.[3] Due to the molecule's unique bowl-like structure and hydrophobic cavity that can hold smaller ions or molecules, they have found application in various fields and are commonly used as chiral ligands in asymmetric catalysis,[4,5] chiral stationary phases,[6] chemosensors [7,8] and other applicable applications that involve host-guest chemistry.

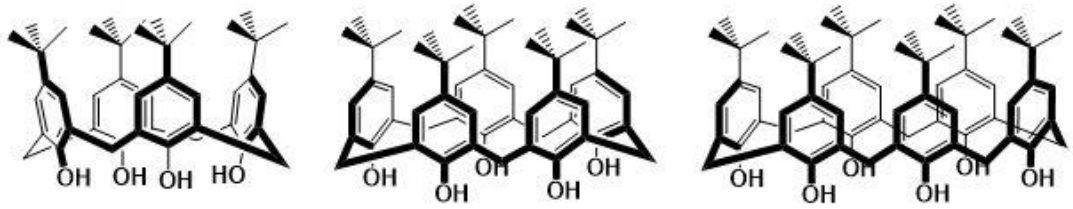


Figure 1.1: Calix[4]arene, calix[5]arene and calix[6]arene. Three of the different ring sizes a calixarene may possess.

1.2. History of Calix[4]arenes

The first reports of calixarene chemistry date back to 1872,[9,10] where Adolf von Baeyer was experimenting with acid catalysed reactions between phenol and various aldehydes in varying conditions. He noticed that in many of his reactions a thick resinous tar would form but he was never able to separate any pure material from the mixture and therefore, was unable to propose a possible structure for the substance.

It was only after the turn of the century where any material of commercial value could be obtained from the 'cement-like' product. In 1907, Leo Baekaland discovered that by using a small and controlled amount of base in the phenol-formaldehyde reaction, a commercially valuable material could be obtained and in 1909, he patented the process used to produce the

world's first synthetic plastic, Bakelite.[11] It was this revolutionary discovery that sparked worldwide scientific and industrial interest in the field of phenol and formaldehyde chemistry and since then, the Bakelite process has been described in over 400 patents.[3] However, the exact chemical structure of the material remained unknown.

It took just over 30 years until the next biggest discovery was made in the field of phenol/formaldehyde chemistry. During the 1940's, Alois Zinke, a professor at the University of Graz in Austria and his co-worker, Eric Ziegler, realized that by using *para*-substituted phenols in the condensation reaction, a degree of control could be achieved.[12,13] They understood that unsubstituted phenols could react at either the *ortho* or *para* positions, which would ultimately lead to a highly cross-linked polymer where the phenolic units can be connected to up to three other aryl subunits (Figure 1.2).[3]

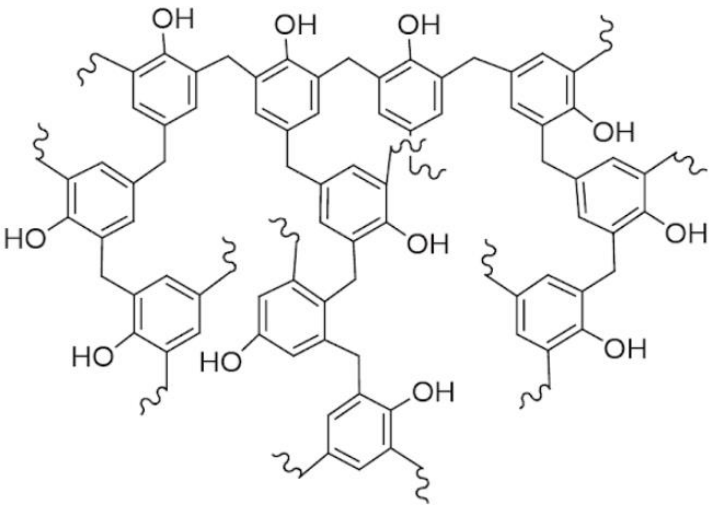


Figure 1.2: The reaction of unsubstituted phenols with formaldehyde forms a highly cross-linked polymer system.

The use of *para*-substituted phenols would limit the possible reaction sites and would leave only the *ortho* positions open to react. It took a while for Zinke to propose the cyclic nature of the high melting crystalline compound as he thought the cyclization of the oligomer was quite unlikely.[3] However, the idea of cyclization had been envisaged by a few other researchers earlier in 1940,[14] which encouraged Zinke to correctly propose the compound's structure which is depicted below in Figure 1.3.[13]

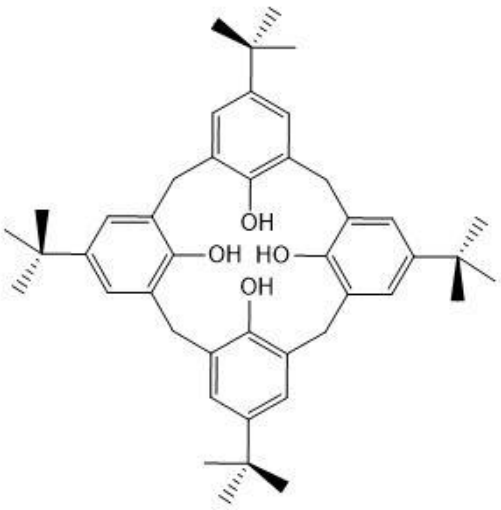


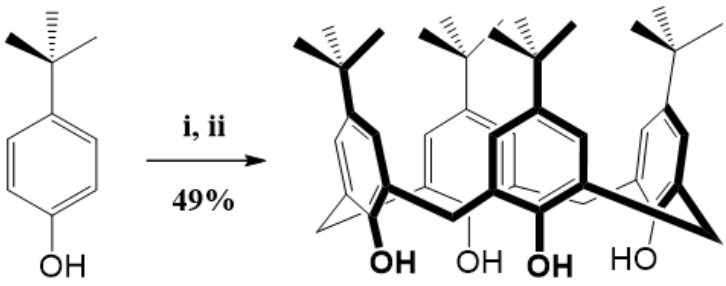
Figure 1.3: Zinke's proposed cyclic tetrameric structure for the base-induced condensation product of *p-tert*-butylphenol and formaldehyde.

Zinke was not able to prove the cyclic tetramer structure of the molecule and it was not until the development of more modern analytical tools that the structure was confirmed by several other chemists.[15-17]

Up until 1975, calixarenes were not called calixarenes. In fact, the compound had a variety of different names depending on which chemist was describing it.[15,16,18,19] David Gutsche, an American chemist at the University of Washington, was the one who coined the term calixarene.[20] He gained interest in Zinke's cyclic tetramers as potential molecular baskets when he embarked on the emerging field, at the time, of bioorganic chemistry relating to enzyme mimics in the early 1970's.[3] Gutsche ultimately became an extremely influential figure in calixarene chemistry. His research in the field spanned over three decades, where he developed synthetic strategies for selectively obtaining variously sized calixarene rings as well as pioneering the functionalization of the compound's skeleton at both narrow and wide rims.

1.3. Synthesis

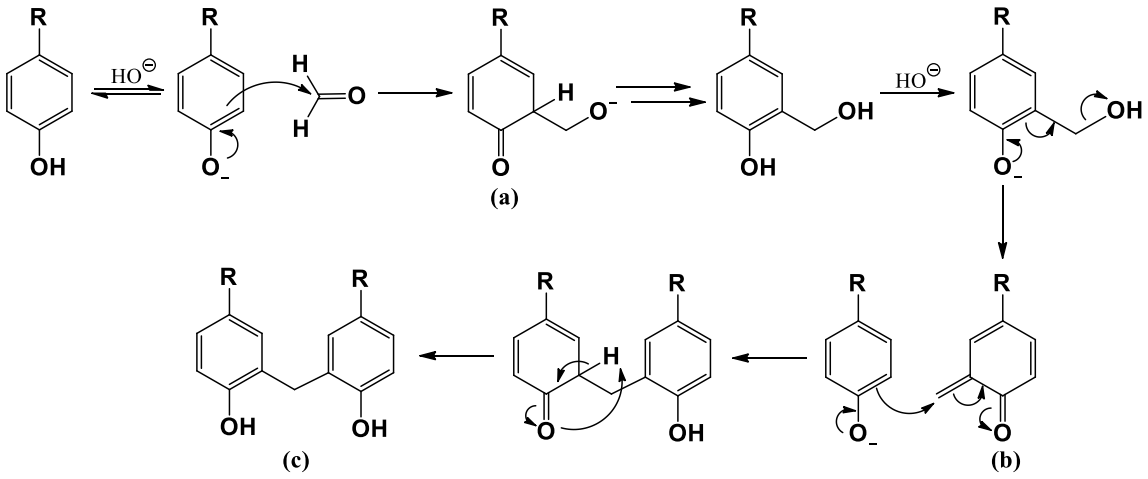
Since Zinke and Ziegler initially outlined the first synthetic procedure for the base-induced condensation reaction between formaldehyde and *para*-substituted phenols to produce the macrocyclic compound,[13] several chemists, including Cornforth[15] and Gutsche,[21] have modified the procedure to what is the most widely used strategy today. The scheme is outlined below (Scheme 1.1).



Scheme 1.1: Synthesis of *p-tert*-butylcalix[4]arene. i) CH_2O (1.25 eq.), NaOH (0.03 eq.), 120 °C, 30 minutes; ii) Ph_2O, reflux, 4 hrs.

Through a careful study done in Gutsche's laboratories, they discovered that the reproducibility of the calixarene synthesis is dependent on two main factors; firstly, the amount and type of base used (LiOH, NaOH, KOH, RbOH and CsOH) and secondly, the reaction conditions (i.e. temperature and duration of heating). [22,23] This study showed that when using the appropriate conditions, calixarenes of various ring sizes may be synthesized selectively in acceptable yields. For example, Gutsche and his co-workers realized that when increasing the molar equivalents of NaOH used from 0.03 eq to 0.3 eq the cyclic hexamer calix[6]arene was favoured over calix[4]arene.[22]

Currently the exact reaction mechanism of the base-induced oligomerization to form the cyclic calixarene structure is still under debate.[3] Considerable effort in the last century has been spent on determining the exact mode of action of the process and several mechanistic studies have been undertaken in order to try and understand the intricate details of the reaction. Scheme 1.2 below illustrates what today is, the most accepted proposed mechanism.



Scheme 1.2: Proposed base-induced oligomerization pathway.

The pathway is initiated by deprotonation of the phenol to afford the phenoxide that acts as a carbon nucleophile, which consequently reacts with the carbonyl of the formaldehyde through a nucleophilic addition to furnish compound **(a)**. To form the diarylmethyl compound, it is suspected that the hydroxymethyl phenol forms an *o*-quinone-methide intermediate **(b)** first, which would allow it to react with another phenoxide through a Michael-type process. Re-aromatization of the ring forms the diphenol compound **(c)**, which undergoes further oligomerization.

1.4. Structure and Conformations

The calixarene scaffold can be divided into three main subunits based on the potential areas of chemical manipulation. These three sites include, the wide rim, the narrow rim and the methylene bridge. These regions are highlighted below in Figure 1.4.

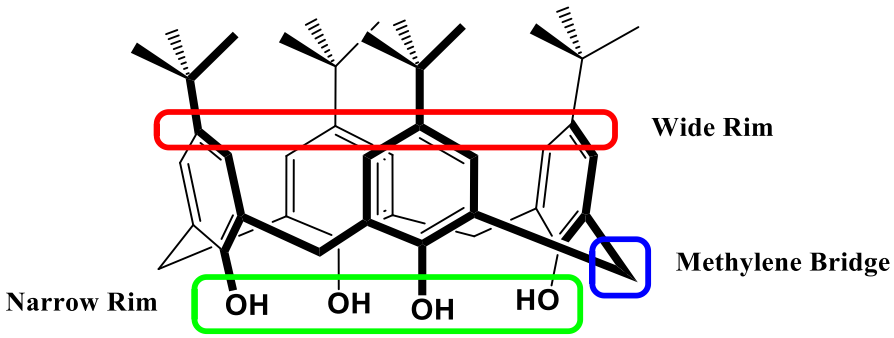


Figure 1.4: The three main regions on the calix[4]arene's structure.

Calixarenes may adopt numerous conformations that are defined by the relative orientation of the phenolate units within the macrocycle. In the solid state, hydrogen bonding between the hydroxyl groups of the narrow rim allow the alcohol moieties to bind, which locks the conformation of the molecule into its cone conformation, resulting in a near perfect C_4 symmetry.[19,24-26] This effect also adds to the compound's high melting point as well as its inability to dissolve in several organic solvents.[6,27,28] However, once in solution, the calix[4]arene skeleton has an increased degree of flexibility and the phenolic units can rapidly rotate using the methylene carbon as pivotal point.[17,25,27,29-31] Due to this phenomenon, known as 'oxygen-through-the-annulus', the two hydrogens attached to the bridging carbons interconvert between their respective equatorial and axial orientations, which can be seen below in Figure 1.5.

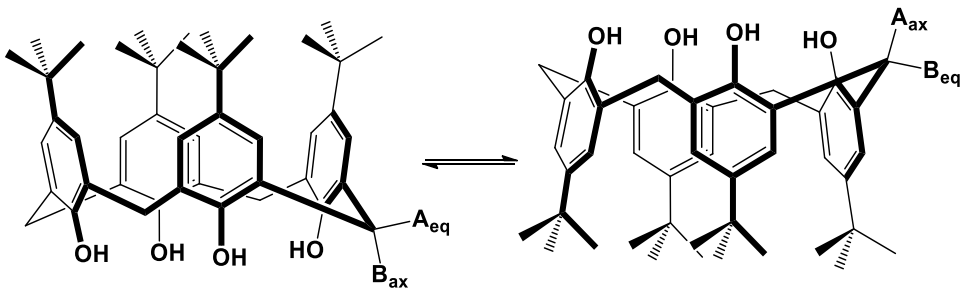


Figure 1.5: 'Oxygen through the annulus' rotation around the methylene bridge pivot.

At room temperature, these protons appear as broad signals in the compound's ^{1}H NMR spectrum, as the two different protons signals overlap owing to the rapid inversion. It is possible to prevent this rapid interconversion from occurring by functionalizing with bulky enough functionalities at the narrow rim, this is usually done through esterification or alkylation.[27,32] It was discovered by Shinkai *et al* that a propoxy functionality, was the smallest carbon chain needed to lock the skeleton in its cone conformation, thereby inhibiting its ability to flip.[33] Functionalization at the narrow rim also results in a break of the intramolecular hydrogen bonding forces experienced at the hydroxyl groups and allows for the molecule to possess a variety of different conformations.[32-35] With the aid of NMR spectroscopy, several chemists identified this property and were able to comfortably recognise four main conformations the calix[4]arene skeleton may possess.[3,27,36] The possible conformations are illustrated below (Figure 1.6).

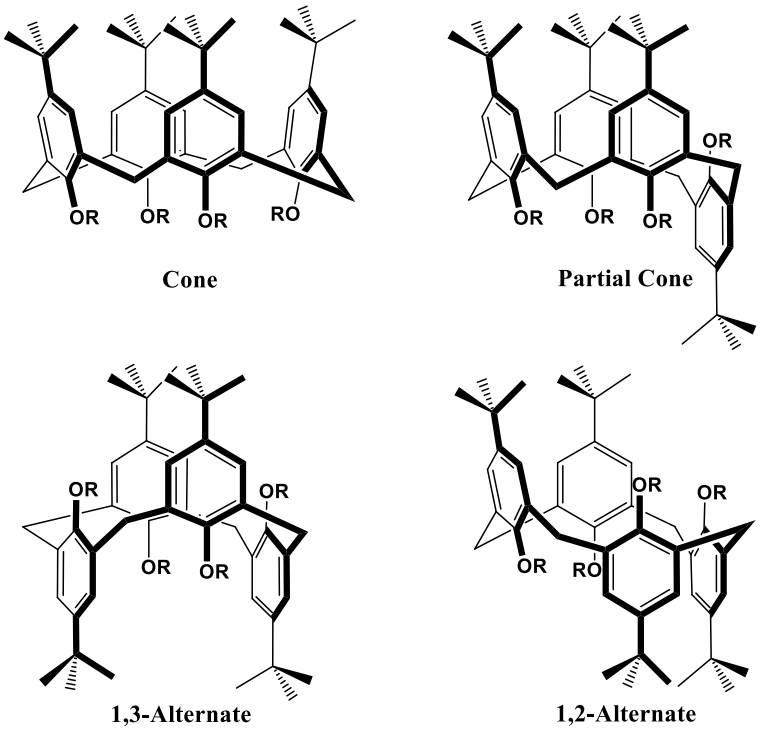


Figure 1.6: Four different isolatable conformations of calix[4]arene.

Finally, when functionalization at the wide rim is carried out, the calix[4]arene may adopt one more conformation, the pinched cone.[37,38] Although not as apparent as the previously mentioned conformations, the structural difference can still be observed in the compound's ^{1}H NMR spectrum. The added functional groups will push away from the remainder of the skeletons structure through electrostatic repulsion. The pinched cone conformation is depicted below in Figure 1.7.

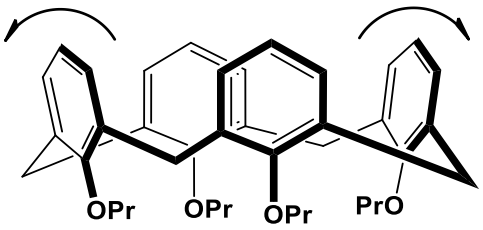


Figure 1.7: Pinched cone conformation of the calix[4]arene. A result of selectively functionalizing the wide rim of the molecule.

1.5. Calixarenes and Chirality

Since their discovery, chiral calixarenes have found application in numerous fields and dedicated research continues to broaden the horizon for this convenient molecular tool.[39,40] Most of these chiral calixarenes however, are considered to possess acquired chirality, meaning

they owe their chirality to at least one chiral stereogenic centre, the conventional point chirality. Synthesizing one of these chiral calixarenes is relatively simple and is done by functionalizing one of the reactive sites on the calixarene skeleton with a chiral moiety such as amino acids, small peptides or most natural product derivatives. One of the earliest examples of chiral calixarenes was synthesized by Shinkai and co-workers,[41] where they attached a (*S*)-2-methylbutoxy group to the narrow rim of a calix[6]arene-*p*-hexasulphonate (Figure 1.8).

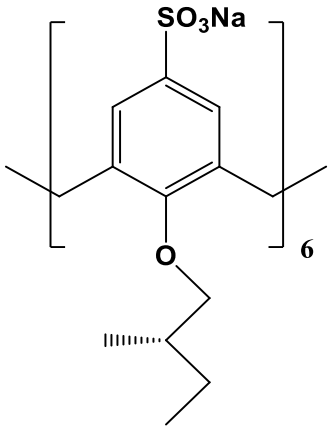


Figure 1.8: Narrow rim functionalized with a (*S*)-2-methylbutoxy group.

This proved to be an extremely efficient route towards producing chiral calixarenes and one could potentially produce a vast library of chiral calixarenes with a variety of chiral functional groups attached to the different reactive sites on the calixarene scaffold. It is obvious to note though, that the optical purity of these compounds is a result of the functionality attached to the calixarene skeleton rather than the calixarene itself. The calixarene can, however, possess its own form of chirality in the form of inherent chirality, a term coined by Böhmer in 1994 when describing calixarenes that are not based on a chiral subunit but on the absence of a plane of symmetry or an inversion centre in the molecule as a whole.[42] Schiaffino[43] and then Szumna[44] rephrased the definition to describe a variety of chiral molecules whose chirality "arises from the introduction of a curvature in an ideal planar structure that is devoid of perpendicular symmetry planes in its bidimensional representation."

Synthesizing enantiopure inherently chiral calixarenes is by no means an easy task and has been proven to be more than challenging over the years. So much so, that possible application studies for this group of compounds have been somewhat limited due to the difficulty in obtaining any significant amount of optically pure material. Inducing inherent chirality onto calixarenes may be achieved *via* careful modification of the compound at either the narrow rim, wide rim, methylene bridge or the *meta* position,[40] illustrated below in Figure 1.9.

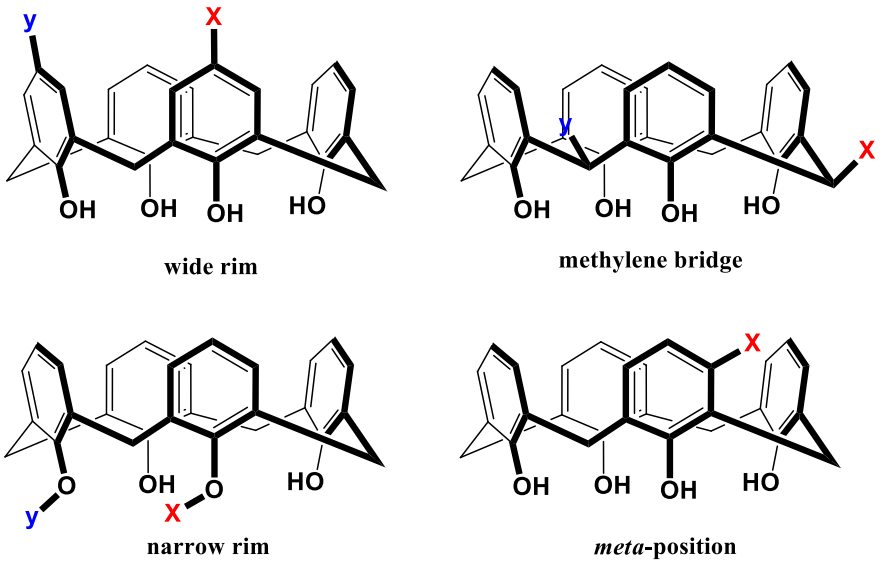
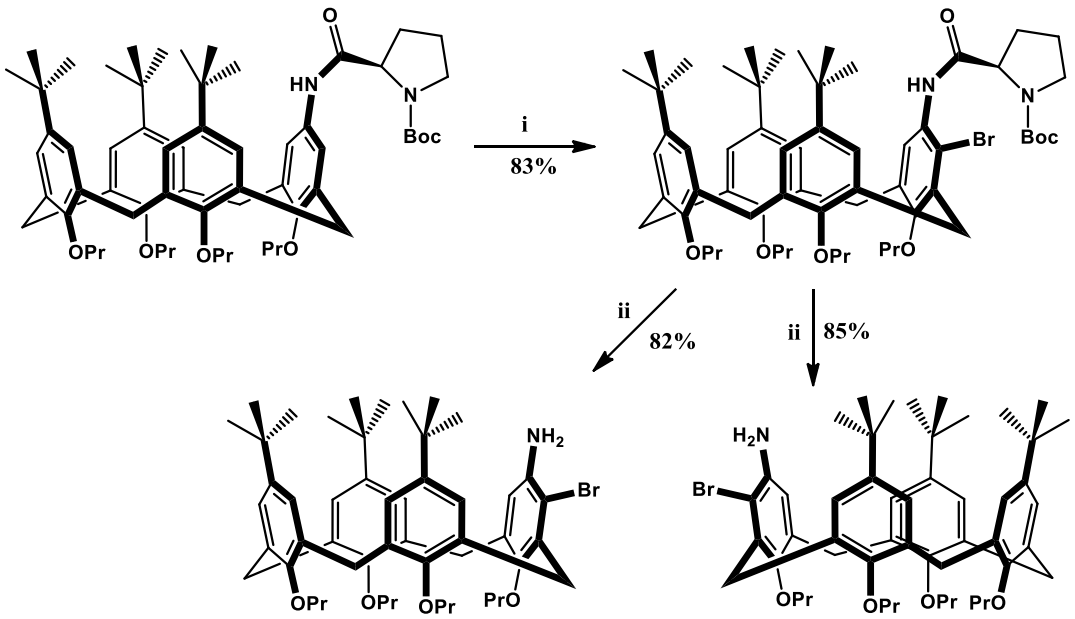


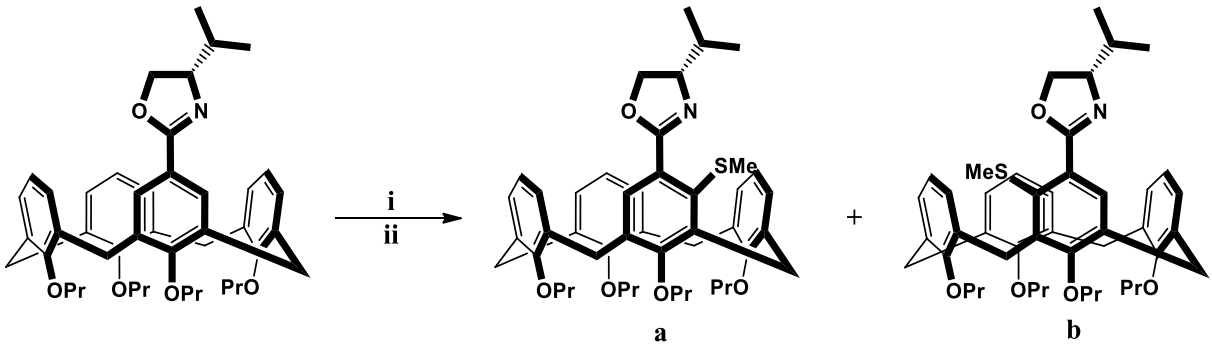
Figure 1.9: Four positions open for functionalization to produce inherently chiral calix[4]arenes.

Examples of *meta*-functionalized inherently chiral calixarenes remain relatively rare in comparison to its counterparts. This is mainly since the *meta* position on each of the phenolic units are not activated due to the electron donating nature of the alkoxy functionalities at the narrow rim. In the past, a variety of strategies have been employed to achieve functionalization at this position including, ring closure strategy,[45] electrophilic aromatic substitutions[46,47] and rearrangements,[48] each with their own merits and short comings. One such method that has proven to be a relatively efficient way of accessing these compounds is by making use of a directing group at the wide rim of the calixarene. When using a strong activating functionality as the directing group, it is possible to functionalize the *meta* position through electrophilic aromatic substitution. Reinhoudt and co-workers were the first to demonstrate this strategy in 1995 by making use of an activating acetoamido directing group at the *para* position for a mono-bromination or nitration at the desired *meta* position to produce inherently chiral calixarenes.[46] More recently, Huang and co-workers synthesized a pair of diasteromers *via* bromination of the *meta* position using a chiral *N*-Boc-(L)-proline as the activating group at the *para* position.[47] The diastereomers were then separated using preparative TLC before being hydrolysed to produce both inherently chiral calix[4]arene enantiomers. Scheme 1.3 below illustrates the procedure clearly.



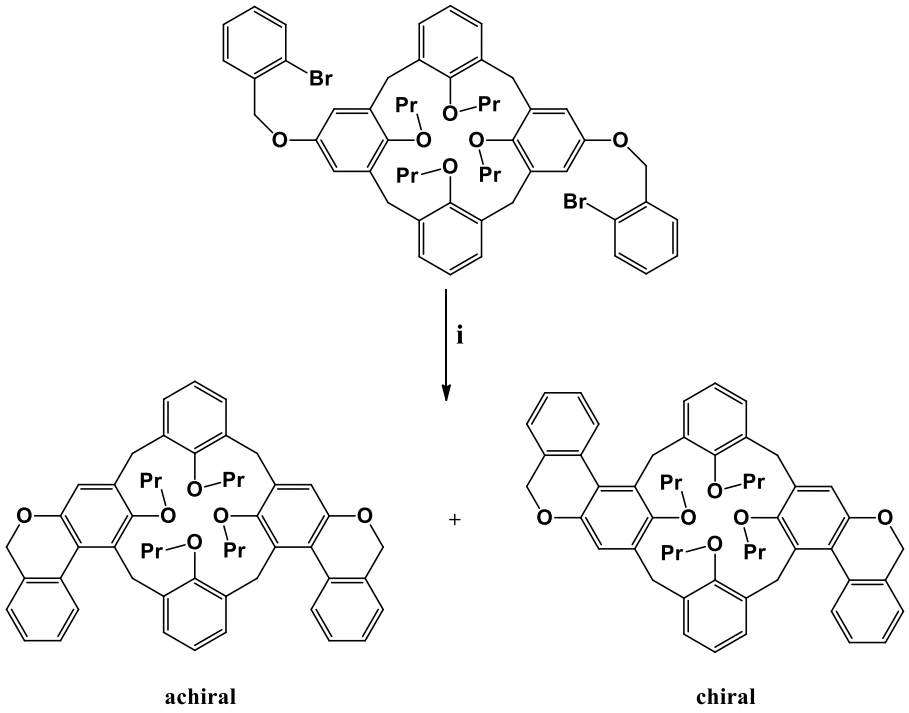
Scheme 1.3: *Meta*-bromination of a mono-functionalized chiral L-boc proline followed by hydrolysis of the amide to form the two inherently chiral enantiomers. i) NBS, 2-butanone, ii) $Ba(OH)_2$, *n*-BuOH/DMSO.

Although, Huang's work showed a high yielding method into accessing enantiopure inherently chiral calix[4]arenes, the tedious effort needed to separate the formed diastereomers cannot be overlooked. In 2009, our group was able to asymmetrically synthesize *meta*-functionalized inherently chiral calix[4]arenes in high diastereoselectivity by employing an *ortho*-lithiation strategy with an oxazoline directing group (Scheme 1.4).[49] Apart from achieving a diastereomeric excess over 90%, it was shown that by changing the ligand, the selectivity could be switched, allowing for the synthesis of either diastereomer.[50] This was an extremely useful strategy as it avoided the need for resolution of the isomers, the biggest hurdle currently in *meta*-functionalized inherently chiral calixarenes.



Scheme 1.4: Reversal of diastereoselectivity by choice of ligand through an *ortho*-lithiation strategy. Diastereomer **a** is favoured when TMEDA is used as the ligand and diastereomer **b** when oxygen-based ligands are used. i) *c*PentLi (5 eq), TMEDA (10 eq), Et_2O, –78 °C, 4.5 hrs, ii) Me_2S_2 (10 eq), –78 °C to RT, 12 hrs.

The above examples all possess C_1 symmetry; however, a few papers have demonstrated *meta*-functionalized inherently chiral calix[4]arenes with a higher degree of symmetry. Inherently chiral calix[4]arenes possessing C_2 or C_4 symmetry are attractive targets, but their synthesis, and especially their resolution, are particularly hard to come by. One of the initial attempts at synthesizing *meta*-substituted calix[4]arenes of C_2 and C_4 symmetry was a 2 + 2 fragment condensation done by Böhmer in 1990.[24] This method would ensure that the ring would possess the appropriate structure upon formation however, the multistep synthesis resulted in an extremely low overall yield. More recently Mattay and co-workers[51] have demonstrated that accessing C_2 inherently chiral calix[4]arenes could be done *via* direct modification of the parent calix[4]arene. A distal di-bromo propylated calix[4]arene was first subjected to lithiation, followed by arylboronate formation and finally oxidative carbon-boron bond cleavage to afford a dihydroxycalix[4]arene. Alkylation of the two alcohol moieties *via* a Williamson ether synthesis produced the dibenzyl ether calix[4]arene shown below (Scheme 1.5). The subsequent *meta*-functionalization was achieved by direct arylation using a protocol demonstrated by Fagnou and co-workers.[52] The diastereomers formed in a 1:1 ratio with a combined yield 94%, and could only be separated through multiple chromatography steps, including a final HPLC purification run. The final step of the synthesis is illustrated below in Scheme 1.5.



Scheme 1.5: Synthesis of C_2 chiral calix[4]arene *via* direct modification. i) $Pd(OAc)_2$, PCy_3-HBF_4, K_2CO_3, DMA.

Although the direct modification strategy shows the possibility of accessing these highly symmetrical *meta*-functionalized inherently chiral calix[4]arenes, the subsequent purification needed to separate the diastereomers formed is extremely painstaking and is a serious issue that needs to be overcome. When considering a C_4 system, the number of possibilities of the diastereomers that may form, raises the level of complexity significantly.

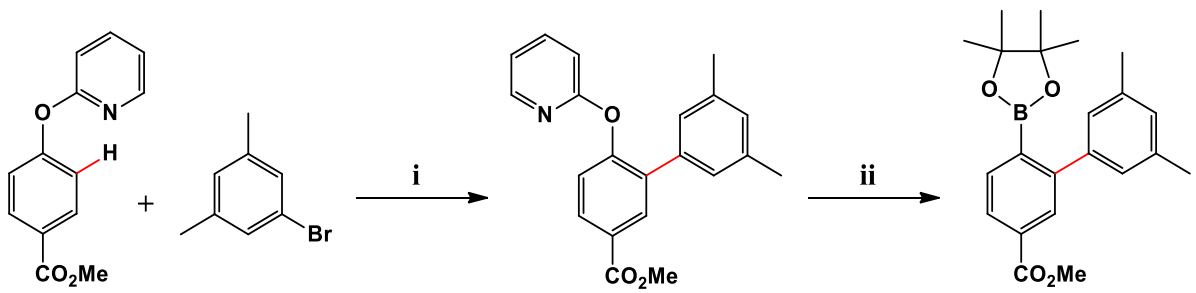
Since the success of using an *ortho*-lithiation strategy to access *meta*-functionalized inherently chiral calix[4]arenes in 2009, our group has actively investigated various other methods of synthesizing these compounds. Recently, C-H activation has shown promise in selectively functionalizing targeted C-H bonds and has, therefore, been considered as a viable approach in synthesizing *meta*-functionalized inherently chiral calix[4]arenes.

1.6. C-H Activation

C-H activation has proven to be one of the more useful tools in synthetic chemistry in the last few years. The scope of C-H activation has grown tremendously from initial attempts focused on functionalizing relatively simple hydrocarbons[53] to where the technique is now a viable strategy in late stage functionalization.[54] What is particularly attractive about C-H activation is

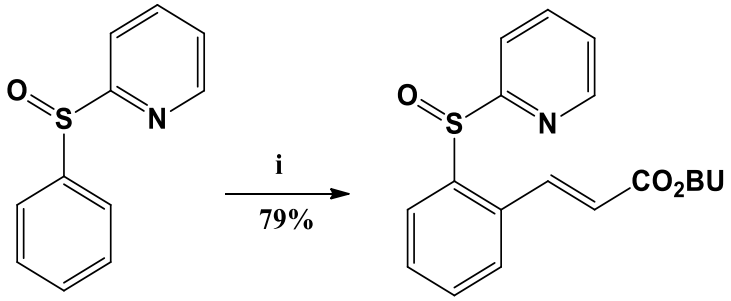
that relatively unreactive C-H bonds can be targeted and functionalized even in the presence of considerably more reactive functional groups.[55-59]

In the presence of a transition metal catalyst, previously considered non-activated C-H bonds may be transformed into C-C bonds or even C-heteroatom bonds that may undergo further manipulation. When considering molecular scaffolds that possess more than one C-H bond with similar chemical properties, being able to direct, or select, the exact C-H bonds that are to be functionalized is critical.[60] Murai and Chetani made massive advancements in controlled site-selectivity by employing directing groups.[61,62] Typically, these directing groups contain electron donating or π-donating functional groups that can coordinate to the chosen transition metal catalyst and form the cyclometalate.[63-68] Their ability to selectively activate a certain C-H bond depends on their proximity to the chosen site to be activated. Furthermore, the directing group may be part of the molecule's skeleton or have the sole purpose of directing the C-H activation and then being subsequently removed. These 'traceless' directing groups, a term used by Zhang and Spring in their 2014 paper,[69] are an extremely attractive prospect and many others including Tobisu and Chatani have taken on the challenge.[70] In their work, shown in Scheme 1.6 below, they made use of aryl 2-pyridyl ether as the directing group for a controlled C-H activation which was then followed by a catalytic borylative cleavage of the directing group leaving the versatile boryl functionality in its place.



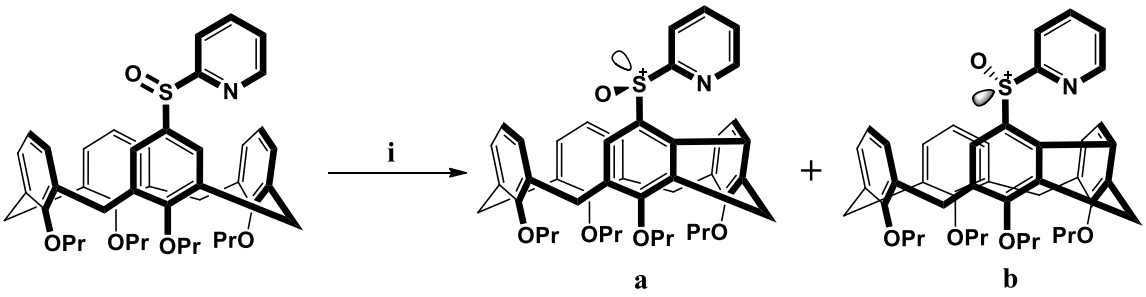
Scheme 1.6: C-H activation using an aryl 2-pyridyl ether as the directing group followed by a borylative cleavage. i) Ruthenium catalyst; ii) bis(pinocolato)diboron, $[RhCl(cod)]_2$, PCy_3.

Another example making use of a removable directing group was demonstrated in a 2011 paper by Carretero and co-workers.[71] Using 2-pyridyl sulfoxide as a directing group, they were able to *ortho*-alkenylate the phenyl sulfoxide selectively in the presence of $Pd(OAc)_2$ and $K_2S_2O_8$ as the oxidant (Scheme 1.7). The directing group could then be cleaved *via* a sulfoxide/lithium exchange using *n*Buli in THF at –98°C.



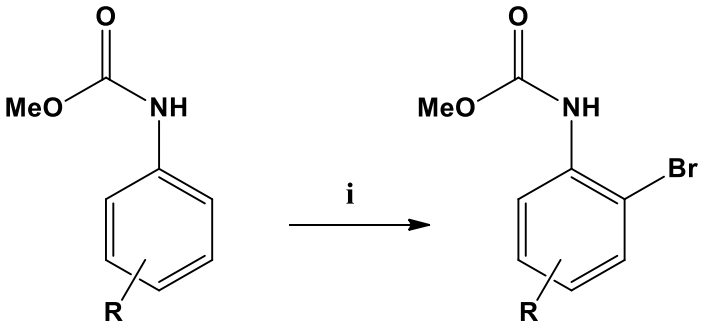
Scheme 1.7: A Pd^{II} catalysed monoolefination of phenyl 2-pyridyl sulfoxide. i) $Pd(OAc)_2$ (10 mol%), butyl acrylate (2 eq), $K_2S_2O_8$ (2 eq), DCE, 110 °C, 20 hrs.

Lhoták and co-workers also attempted to use a 2-pyridyl sulfoxide directing group in a palladium catalysed C-H activation on a calix[4]arene system.[72] They attempted to synthesize a *meta*-functionalized inherently chiral calix[4]arene by reacting the mono-substituted *para*-2-pyridyl sulfoxide calix[4]arene with methyl acrylate in the presence of Ag_2CO_3 and benzoquinone (Scheme 1.8 below). However, to their surprise, instead of the traditional *meta*-functionalized inherently chiral calix[4]arene they were after, an intramolecular bridge formed with the adjacent aryl to form a new class of inherently chiral calix[4]arenes. The two diastereomers formed, **a** and **b**, were separated *via* preparative TLC with a yield 43% and 29% respectfully.



Scheme 1.8: Synthesis of *meta*-bridged inherently chiral calix[4]arenes through a double C-H activation. i) Methyl acrylate, $Pd(OAc)_2$, Ag_2CO_3, benzoquinone, DCE-benzene, 100 °C, 16 hrs.[72]

Although there are many literature examples of C-H activation, a relatively recent publication by Moghaddam and co-workers published in 2016 stood out as it had the option of introducing chirality into the directing group.[73] They demonstrated that by making use of *N*-aryl carbamates as a removable directing group, they could *ortho*-halogenate a variety of phenolic compounds even in the presence of traditionally deactivating functionalities (Scheme 1.9 below).



Scheme 1.9: Moghaddam and co-workers' general reaction scheme for halogenation of *N*-arylcarbamates. i) $Pd(OAc)_2$, NBS, PTSA, DCE, 50 °C, 3-4 hrs. R = H, 3-Cl, 4-Cl, 4-NO_2, 4-OMe, 4-Me, 3-F, 2-Cl, 2-Me.[73]

They started out by establishing the optimal conditions needed for the reaction to proceed on a chosen model, methyl *N*-(*p*-tolyl)carbamate. After numerous optimization reactions, they managed to selectively synthesize their desired *ortho*-brominated product in yields exceeding 90%. A considerably commendable effort, as the yields reported in their initial attempts were as low as 15%. Once the optimal conditions were figured out, they subjected a variety of similar scaffolds to the said conditions and found that they could obtain very similar results.

Based upon the results of Moghaddam and co-worker's paper, carbamates posed as extremely efficient *ortho* directing groups when performing C-H functionalizations on sp^2 hybridized carbon atoms. Carbamates themselves contain the necessary π and electron donating elements in the form of the carbonyl oxygen atom and the ability to hydrolyse them back into their amine precursor poses them as one of the more attractive directing groups for C-H activation.

1.7. Project Proposal

Inspired by the work of Moghaddam and co-workers, the aim of this project is to synthesize *meta*-brominated inherently chiral calix[4]arenes by employing *N*-aryl carbamates as a directing group in a C-H activation reaction (see Figure 1.10 below).

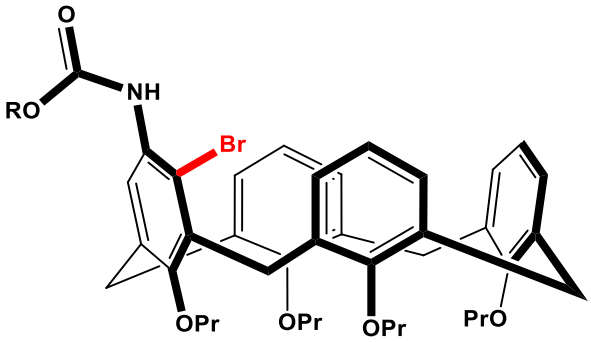


Figure 1.10: Proposed target molecule.

The first objective is to establish the chemistry on one of the smaller molecules used in Moghaddam's paper as part of a model study. The chemistry would then need to be tested on the calix[4]arene system. At first, a proof of concept would have to be carried out by making use of an achiral carbamate directing group. If successful, an appropriate chiral carbamate would then be utilized as a directing group to try and encourage a degree of stereoselectivity in the subsequent bromination. Furthermore, establishing whether the presence of the transition metal catalyst, $Pd(OAc)_2$ may also improve stereoselectivity, in the hopes of synthesizing *meta*-functionalized inherently chiral calix[4]arenes with a degree of diastereoselectivity.

Finally, the synthesis of *meta*-functionalized inherently chiral calix[4]arenes of C_4 symmetry will be attempted. Using the *ortho* directing properties of an achiral methyl carbamate and exploiting its ability to freely rotate around its aryl-*N* σ-bond, it is envisaged that a degree of control can be achieved when brominating each of the phenolic units of the calix[4]arene skeleton (Figure 1.11).

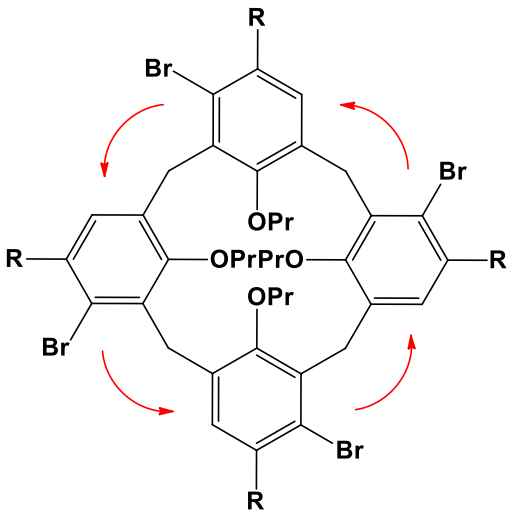


Figure 1.11: Target inherently chiral calix[4]arene displaying C_4 symmetry.

1.8. References

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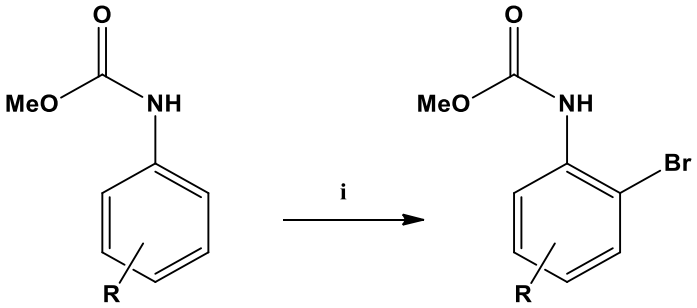
2. Chapter 2 – Model study of *ortho*-brominations of methyl (4-methoxyphenyl)carbamate

2.1. Introduction

A model study was first investigated to gain insight into the intricacies of C-H activation before trying to perform the reaction on the more structurally complex calix[4]arene scaffold. As previously mentioned in chapter 1, a paper by Moghaddam and co-workers,[1] Scheme 2.1, demonstrated a high yielding and selective method of halogenating variously substituted phenyl carbamates *via* a palladium assisted C-H activation. Previous studies[2–6] have shown that in order to activate specific C-H bonds, it is necessary to make use of a directing group that can form cyclometalated intermediates, a strategy that was popularized by Murai and Chatani.[7,8]



Scheme 2.1: Moghaddam and co-workers' general reaction scheme for halogenation of *N*-arylcarbamates. i) $Pd(OAc)_2$, NBS, PTSA, DCE, 50 °C, 3-4 hrs. R = H, 3-Cl, 4-Cl, 4-NO_2, 4-OMe, 4-Me, 3-F, 2-Cl, 2-Me.[1]

They started out by finding the optimal conditions needed for the reaction to proceed on a chosen model, methyl *N*-(*p*-tolyl)carbamate. They first set out to establish the dependence of the product formation on the presence and type of transition metal catalyst used. In acetonitrile, they found that $Pd(OAc)_2$ was the preferred catalyst, offering the highest yields. $Cu(OAc)_2$ and $PdCl_2$ resulted in lower yields, where completely excluding a catalyst the product yield was as low as 15% compared to the 62% obtained in the catalyzed conditions ($Pd(OAc)_2$ 5 mol %, MeCN, NBS, 100 °C, 2 h). They also managed to establish that when changing the solvent from MeCN to 1-4 dioxane or DCE, the yield would drop dramatically. However, in the presence of an acid additive, specifically PTSA (0.5 eq), the highest yield of 93% occurred in DCE. They finally tested if the reaction was temperature dependant and found that at temperatures lower than 60 °C the yield would decrease but at 60 °C they obtained a yield of 91%. With the optimal conditions established on the model compound they set out to test the

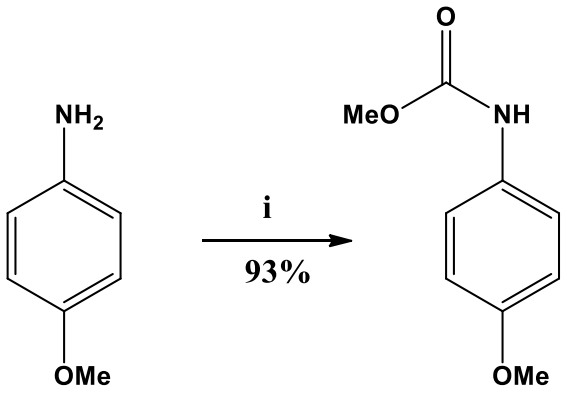
conditions on a variety of similar scaffolds and established that these conditions gave comparable results.

This posed as an extremely appealing method of C-H activation, as carbamates can be easily synthesized from their amine precursor and the relative ease of removing the functional group opens the door for further manipulation.[9] Furthermore, being able to halogenate aromatic compounds has long been considered one of the more valuable tools in organic synthesis, as halogenated aryl groups are often used in a wide variety of synthetic reactions.[10–12] Finally, as previously mentioned in chapter 1, *N*-substituted carbamates can possess a variety of R groups attached to the 'ether' oxygen atom. This is an important feature when taking the calix[4]arene into consideration. When trying to stereoselectively synthesize inherently chiral calixarenes, an element of chirality is needed in the reaction conditions or directing group itself. Therefore, being able to introduce a chiral R group onto the carbamate is a necessary feature.

For the aim of this model study, it was important to choose a structure that would represent one of the aryl subunits of the calix[4]arene skeleton. One compound fell into this category, methyl (4-methoxyphenyl)carbamate, as it possessed the activating methoxy moiety *para* to the carbamate directing group, much like the propoxy situated on the narrow rim of the calix[4]arene molecule.

2.2. Synthesis of (4-methoxyphenyl)carbamate (Compound **1**)

The starting material needed for the bromination study was synthesized from commercially available *p*-anisidine by reacting it with methyl chloroformate in the presence of pyridine, in accordance with reported literature.[13] This reaction was always high yielding (85-93%) and was always completed within half an hour. The crude product was purified *via* silica gel flash column chromatography and triturated from DCM and *n*-hexanes to produce a pale-yellow solid. The general procedure can be seen below in Scheme 2.2.



(1)

Scheme 2.2: Carbamate acylation of *p*-anisidine. i) Methyl chloroformate (1.5 eq), pyridine (1.5 eq), DCM, 0 °C – RT.[13]

Compound **1**'s ^{1}H NMR spectrum in $CDCl_3$ in Figure 2.1 below, shows the presence of the two methyl groups resonating as two singlets in close proximity at δ 3.78 ppm and δ 3.75 ppm. Further downfield, the broad singlet at δ 6.63 ppm, represents the nitrogen atom's single proton. The four hydrogen atoms attached to the aryl ring are split into two different signals. Highlighted in red, the signal for the protons *ortho* to the carbamate overlap with the $CDCl_3$ signal at δ 7.26 ppm and appear as a doublet, the multiplicity arising from their respective neighbouring hydrogen atoms at the *meta* position ($^{2}J_{HH}$ = 7.9 Hz). The remaining multiplet, around δ 6.84 ppm and integrating for two protons, signify the *meta* position protons. The newly synthesized aryl carbamate was then used in the following mechanistic study.

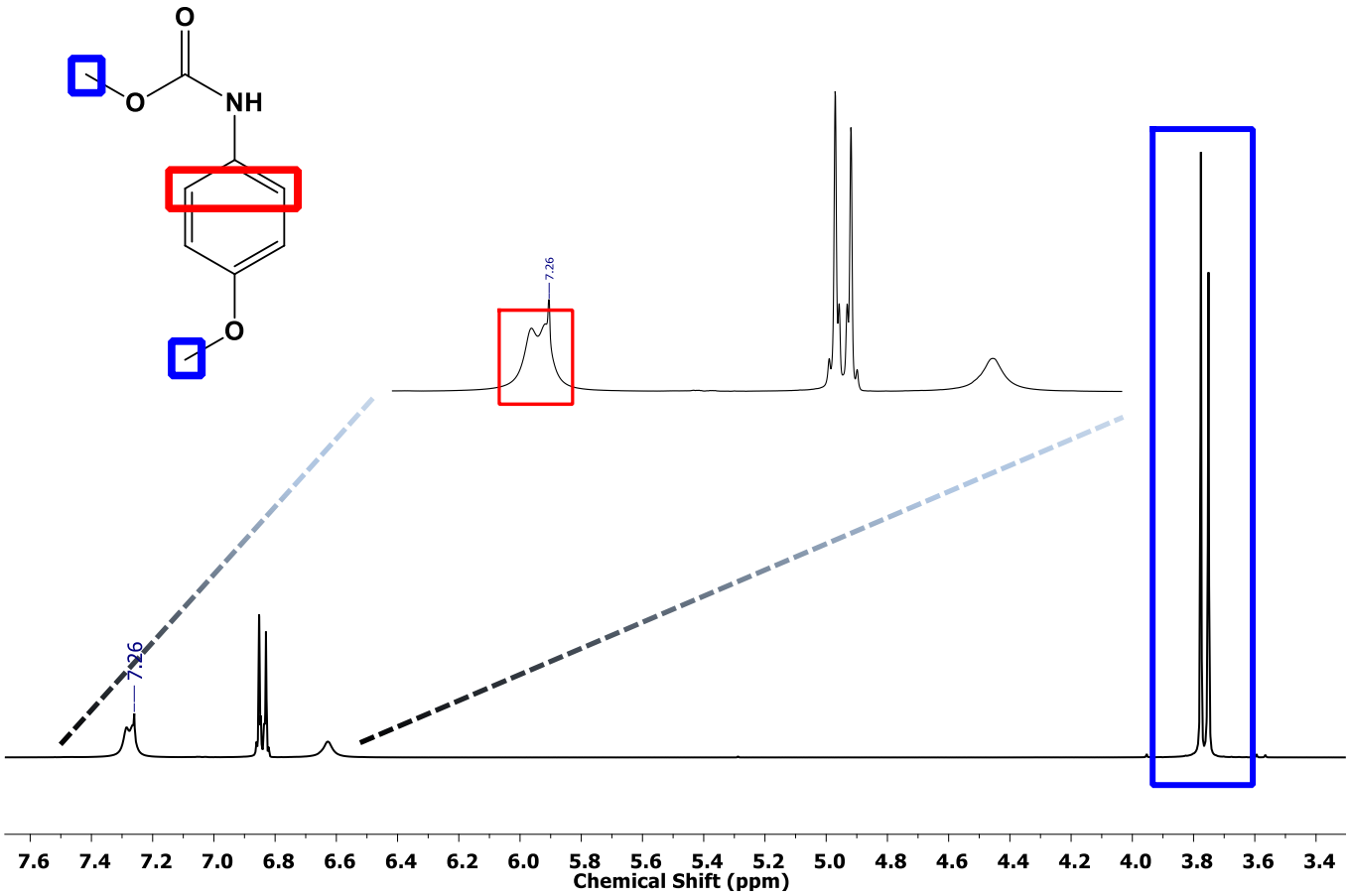
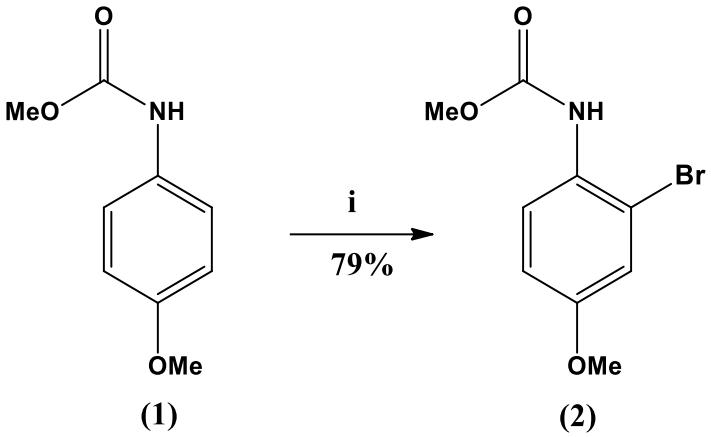


Figure 2.1: ^{1}H NMR spectrum ($CDCl_3$) of methyl (4-methoxyphenyl)carbamate **1**.

2.3. C-H activation

The following reaction outlined in Scheme 2.3, was no different to the conditions reported by Moghaddam and co-workers.[1] Before commencing with the reaction, it was important to ensure that the solvent was thoroughly degassed due to the presence of the $Pd(OAc)_2$ catalyst, by running it through at least five freeze pump thaw cycles. The reaction was then carried out in a Schlenk flushed with argon.



(1) (2)

Scheme 2.3: C-H activation of methyl (4-methoxyphenyl)carbamate **1**. i) NBS (1.1 eq), PTSA (0.5 eq), $Pd(OAc)_2$ (0.05 eq), DCE, 60 °C, 3.5 hrs.[1]

All four reagents were then added to the Schlenk charged with 2 mL of DCE and the mixture was left to stir for 2.5 hours at 60 °C. It was important to close the Schlenk once the reagents had been added in order to keep the pressure needed for the reaction to run to completion. After work-up and purification *via* silica gel flash column chromatography (EtOAc:hexanes 1:9), compound **2** was obtained in 79% yield. The slightly lower yield obtained compared to the reported literature may be a result of differing reaction pressures, as the reaction was performed in a Schlenk instead of a sealed tube.[1] The ^{1}H NMR spectra obtained for compound **2**, below in Figure 2.2, confirmed the structure and matched well with the literature.[1]

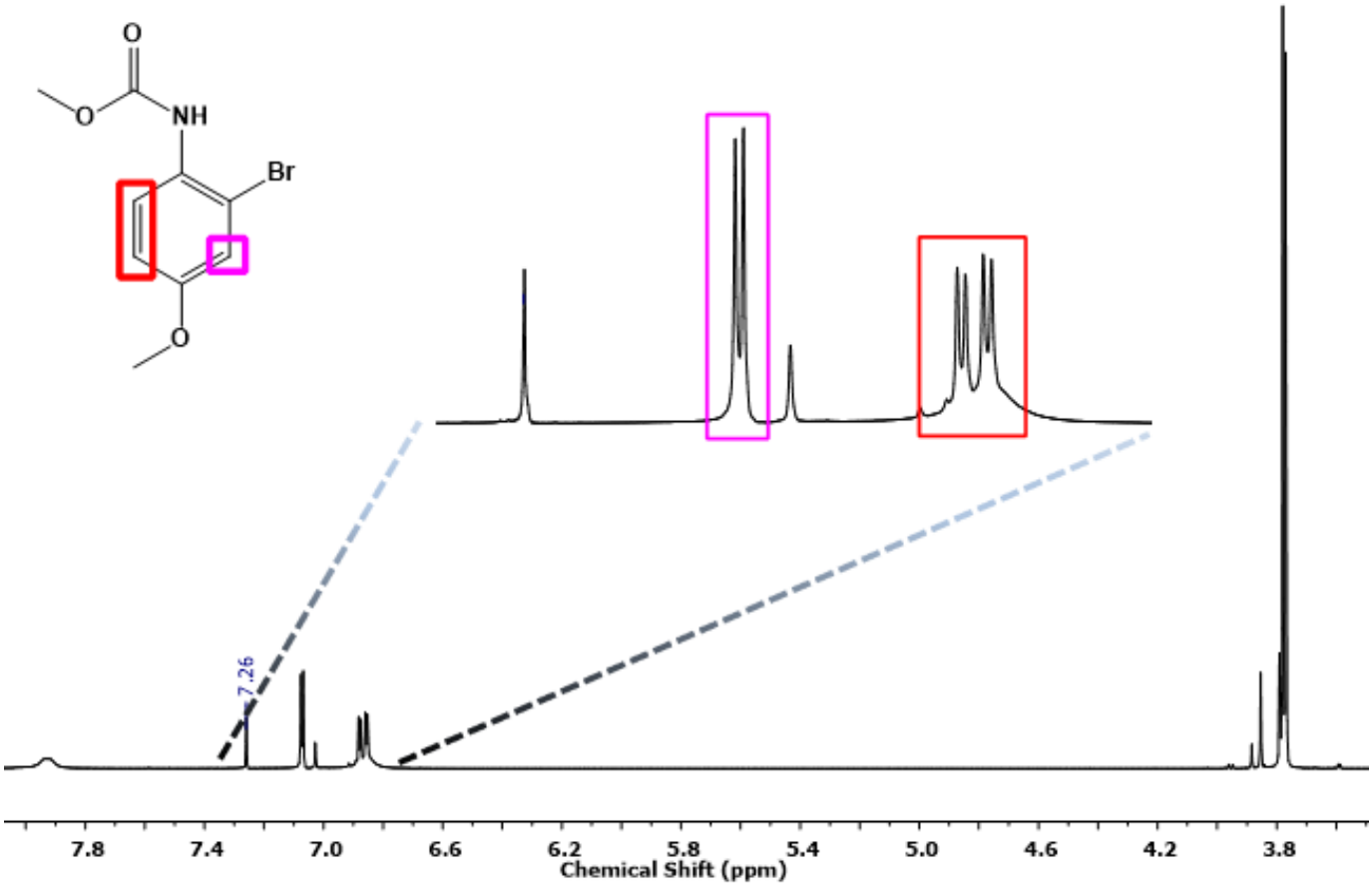


Figure 2.2:[1]H NMR spectrum ($CDCl_3$) of methyl (2-bromo-4-methoxyphenyl)carbamate **2**.

The introduction of the bromine atom at the *ortho* position, relative to the carbamate, causes a large downfield shift of the carbamate's N-H signal. The electronegativity of the bromine effectively pulls electron density away from the nitrogen causing the downfield shift. This effects the neighbouring *meta* hydrogen atom (highlighted in purple) in the same way. The signal shifts downfield from δ 6.84 ppm to δ 7.07 ppm and its multiplicity changes to a doublet with a coupling constant of 2.9 Hz, typical of *meta* couplings. Finally, the protons on the positions highlighted in red resonate as two different signals that overlap around δ 6.68 ppm, one a doublet and the other a doublet of a doublet. Both signals combined integrate for 2 hydrogen atoms.

In the proposed catalytic cycle (Figure 2.3),[1] Moghaddam and co-workers suggested that the palladium catalyst interchanges between its oxidation states, Pd^{II}/Pd^{IV}. The C-H activation is the initial step of the reaction whereby the $Pd(OAc)_2$ forms a cyclopalladate with the carbamate starting material, oxidizing the palladium from Pd^{II} to Pd^{IV}. The cyclic structure then collapses and reduces the metal back to Pd^{II} and gives off acetic acid as a by-product. Once the *ortho*

position has been activated, the NBS oxidatively inserts onto the metal, oxidizing it back to Pd^{IV}, before the final reductive elimination of the desired product and regeneration of the catalyst. According to the authors,[1] the PTSA in this reaction has a dual functionality, firstly protonating one of the carbonyl oxygens of the NBS to make '$^{+}$Br' more electrophilic and secondly, to help make the palladium catalyst more electrophilic.

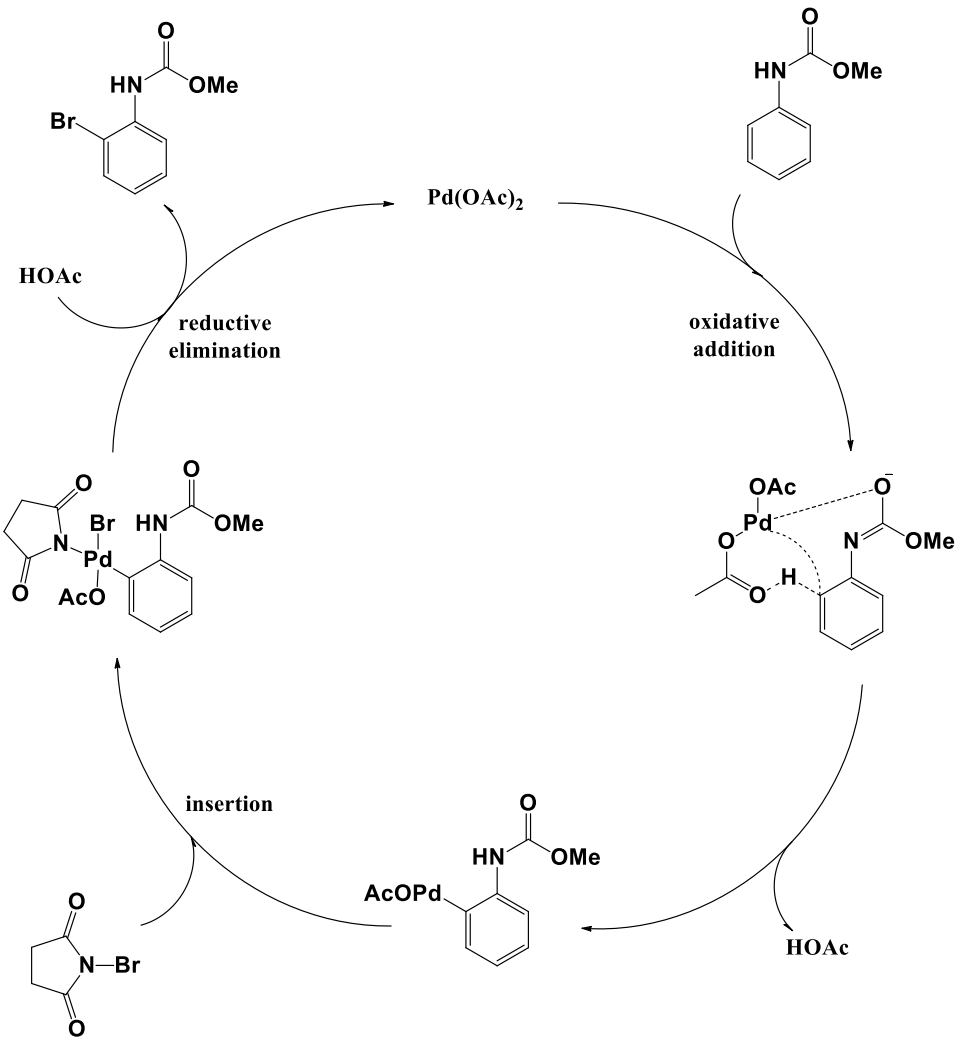
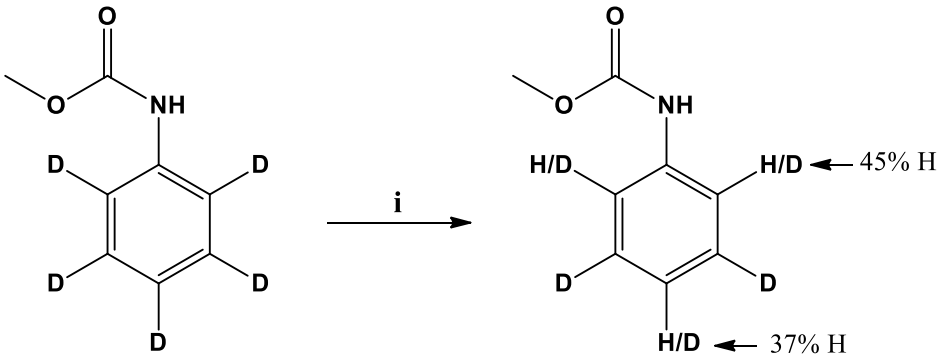


Figure 2.3: Problematic proposed catalytic cycle of the palladium mediated C-H Activation reaction of methyl (4-methoxyphenyl)carbamate.[1]

The proposed catalytic cycle in Figure 2.3 above, is not entirely accurate. The most obvious issue is that the nitrogen atom in the intermediate that forms after the oxidative addition step is deprotonated. This is very unlikely, considering that the reaction is performed in acidic conditions. A paper published by Li and Uhlig,[9] proposed a slightly different catalytic cycle for the palladium catalyzed carbamate directed *ortho* C-H activation. In their study, they investigated aniline carbamates as potential directing groups in palladium catalysed *ortho*-

arylations. Interestingly, they used the same molecule in their proposed cycle, methyl phenylcarbamate. Also under acidic conditions, using fluoroboric acid as the additive, the carbamate nitrogen in their intermediate after the first step still possessed its hydrogen atom and furthermore, the carbamate was not in its resonance form. The catalyst had simply coordinated to the lone pairs of the oxygen atom, therefore, the initial step was not an oxidative addition. This would mean that the catalyst would only be oxidized to Pd^{IV} after the oxidative insertion of the NBS.

Li and Uhlig also carried out several isotopic investigations to try and explain the reactivity of their substrates in differing reaction conditions. They found that when reacting a deuterated analogue of the methyl phenylcarbamate with HPF_6, H/D scrambling of the *ortho* and *para* positions was observed. However, no scrambling was seen when using KPF_6 or HBF_4. They also conducted the analysis in the presence of a palladium acetate catalyst and an arylating agent ($Ph_2I^+BF_4^-$) using HPF_6 as the additive and again they observed H/D scrambling at the *para* and remaining *ortho* position (the other *ortho* position had been successfully arylated). These results hint towards a competing electrophilic aromatic substitution that is dependent on the strength of the acid. The isotopic study can be seen below in Scheme 2.4.



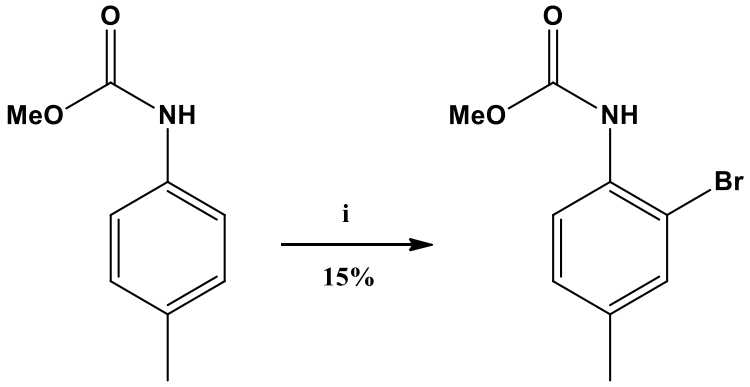
Scheme 2.4: Isotopic study showing the carbamate functional group activating the *ortho* and *para* position in the presence of a strong enough acid. i) HPF_6 (1 eq), toluene, 50 °C, 18 hrs.[9]

The results from this isotopic study questions the need for a transition metal catalyst when attempting to *ortho*-brominate the phenolic unit, especially when the *para* position is blocked. It is well known that amides are *ortho* and *para* directors when attached to the arene at the nitrogen atom, therefore, presuming that *N*-aryl carbamates behave the same is plausible. In the case of this work however, the aryl ring's *para* position is occupied by a methoxy group, another *ortho*/*para* directing group. If both functional groups are of equal strength in terms of

their directing properties, we can expect a mixture of both *ortho*- and *meta*-brominated products (relative to the carbamate) to form when performing the reaction without the catalyst. This prompted the following investigation of the necessity of the catalyst.

2.4. Electrophilic aromatic substitution

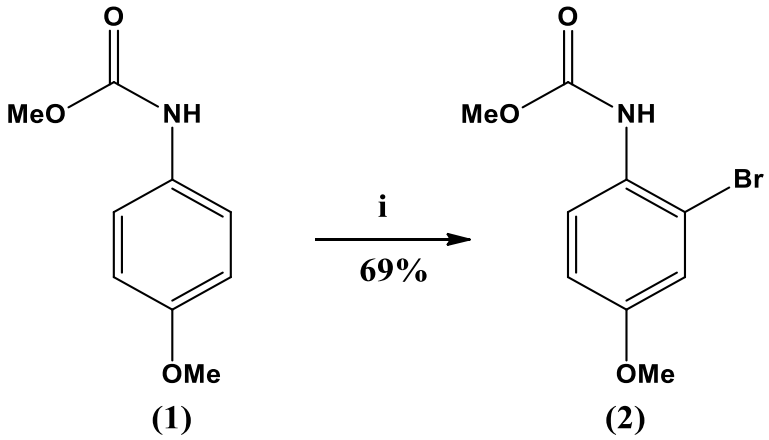
Li and Uhlig's isotopic study (Scheme 2.4) suggested that *N*-aryl carbamates act as *ortho* and *para* directors.[9] Therefore, the choice of a carbamate directing group for an *ortho*-functionalization makes the use of a catalyst somewhat unnecessary, especially if the *para* position is blocked. Therefore, the question had to be asked whether this reaction proceeds through the suggested C-H activation or was it simply an electrophilic aromatic substitution? Interestingly, in Moghaddam and co-workers' paper, the bromination of the methyl (4-methoxyphenyl)carbamate scaffold was never tested without the transition metal catalyst. In fact, only one reaction in the entire paper was performed without the presence of a transition metal catalyst, Scheme 2.5.



Scheme 2.5: Bromination of methyl (4-methoxyphenyl)carbamate. i) NBS (1.1 eq), MeCN (2 mL), 100 °C, 2 hrs.[1]

The conditions used in this reaction differed in several ways to the conditions outlined earlier in Scheme 2.1. Apart from the transition metal catalyst being omitted, there is no PTSA or any other acid additive and the reaction is carried out in a different solvent, which allowed them to perform the reaction at a higher temperature. Any of these two differences in the reaction conditions of Scheme 2.5 could attribute to the lower yield reported. It is more than likely however, that the lack of acid was to blame for the low reactivity, since Li and Uhlig demonstrated that the choice of acid played a pivotal role in activating the ring.

To answer the question of what mechanism was at play, the reaction procedure reported for Scheme 2.3 was repeated, but excluding $Pd(OAc)_2$ (Scheme 2.6).



Scheme 2.6: Electrophilic aromatic substitution of methyl (4-methoxyphenyl)carbamate **1**. i) NBS (1.1 eq), PTSA (0.5 eq), DCE, 60 °C, 3.5 hrs.

All three reagents were added to a Schlenk charged with DCE and heated to 60 °C. The solution was left to stir for three and a half hours. After the time had elapsed the solution was diluted with DCM and washed with a sat. $NaHCO_3$ solution and brine before being dried over $MgSO_4$ and concentrated. The crude product was purified using silica gel flash column chromatography to afford compound **2**. TLC analysis showed that compound **2** was the only product that had formed.

The fact that this reaction only yielded the *ortho*-brominated product indicates that the carbamate's directing properties are stronger than that of the methoxy's. More importantly it shows that for this reaction, the $Pd(OAc)_2$ is unnecessary, although a higher yield was reported when it was utilized. However, championing its ability in regioselectivity and preventing over bromination is misleading, as the same desired result can be accomplished in its absence. The reaction obviously needs no catalytic assistance in order for bromination to occur, therefore, the reaction outlined in Scheme 2.4 is more than likely to predominately follow an electrophilic aromatic substitution type mechanism rather than C-H activation. With only a catalytic amount of $Pd(OAc)_2$ present in the reaction, it is a strong possibility that only a small percentage of the starting material molecules may actually come into contact with the metal before being brominated.

To explain the low yield obtained in Moghaddam and co-workers work for the reaction where no catalyst was used (Scheme 2.5), it is likely a result of having no acid additive in the reaction. As previously mentioned, in that same paper they had mentioned that the PTSA had a dual function; increasing the reactivity of the $Pd(OAc)_2$ and protonating one of the carbonyl oxygens

of the NBS to make '$^{+}$Br' more electrophilic. The latter seems to be an important piece of information that was overlooked when optimizing the reaction conditions. Furthermore, as previously shown in Scheme 2.5, Li and Uhlig showed that the choice of acid had an effect on activating the aryl ring, therefore, increasing its susceptibility to electrophilic aromatic substitution.

Although the reaction conditions outlined in Scheme 2.6 prove that it is not necessary to make use of the palladium catalyst to achieve regioselective control, the higher yield obtained when it was included suggested that it does play a role in the reaction to some degree. Nevertheless, whether the catalyst was used or not, the strategy still posed as an effective method for selectively functionalizing *N*-phenylcarbamates at their *ortho* positions. When considering this on a calix[4]arene system, functionalization of the molecule at its *ortho* position relative to the directing group has proven to be more than challenging since its inception and therefore, this possible synthetic route is extremely attractive.

2.5. Conclusion

In conclusion, this model study demonstrated that by employing a carbamate functionality as either a directing group for C-H activation or simply as an activating group for an electrophilic aromatic substitution, it is possible to functionalize aryl compounds with an extremely high degree of regioselectivity. This study has also highlighted the pivotal role PTSA plays in the electrophilic aromatic substitution. Whether this would work on a calix[4]arene molecule would still need to be investigated but initial evidence gained from this model study suggests that this may be a viable strategy. Furthermore, the slightly improved yield when making use of $Pd(OAc)_2$ may indicate that the transition metal catalyst may be playing a small role in the reaction mechanism. This may prove to be significant when trying to stereoselectively *ortho*-functionalize the calix[4]arene scaffold when employing a chiral moiety as the directing group.

2.6. Experimental

2.6.1. General practices

The general practices described here also apply to the remaining synthetic work reported in other chapters, unless otherwise stated. All chemicals were purchased from Merck or Sigma-Aldrich. Dry toluene and tetrahydrofuran were distilled under nitrogen from sodium wire/sand and using benzophenone as an indicator. Dichloromethane was dried from calcium hydride under nitrogen. Other reagents that required purification were done so according to standard procedures.[14]

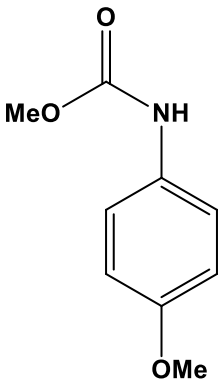
For syntheses performed under inert conditions the glassware was oven dried and then placed under vacuum of <0.5 mm Hg before being periodically flushed with argon/nitrogen until reaching room temperature. All reactions were performed under positive pressure of 2.8 kPa of 5.0 grade argon (Air Products). Low temperature reactions were performed in a Dewar containing ice and acetone (–15 °C), solid CO_2 and acetonitrile (–40 °C) or solid CO_2 and acetone (–78 °C).

Column chromatography was performed using 230 – 400 nm silica and thin layer chromatography (TLC) was performed using Macherey-Nagel DC-Fertigfolien ALUGRAM Xtra SIL G/UV254 TLC plates. Visualization of compounds on TLC plates was performed by using a UV lamp or using a cerium ammonium molybdate (CAM) solution followed by heating.

Both ^{1}H and ^{13}C NMR spectra were obtained using Varian 300 MHz VNMRS, Varian 400 MHz Unity INOVA and Varian 600 MHz Unity INOVA NMR instruments. Chemical shifts were recorded using the residual solvent peaks (chloroform-*d* or DMSO-d_6) and reported in ppm. Unless otherwise stated, NMR spectra was obtained at room temperature. All mass spectrometry spectra were obtained by Central Analytical Facility (CAF) at Stellenbosch University using a Waters API Q-TOF Ultima mass spectrometer. IR spectra were obtained using a Thermo Nicolet Nexus FTIR instrument using the ATR attachment. Melting points were obtained using a Gallenkamp Melting Point Apparatus.

2.6.2. Synthesis and characterization of model compounds

Methyl (4-methoxyphenyl)carbamate (1)[13]

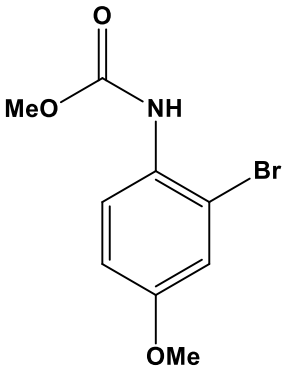


An oven dried 2-neck round-bottomed flask was charged with *p*-anisidine (200 mg, 1.62 mmol) dissolved in DCM (10 mL) and cooled to 0 °C. Pyridine (157 µL, 1.2 eq, 1.95 mmol) and methyl chloroformate (413 µL, 1.2 eq, 1.95 mmol) were subsequently added to the reaction. The solution was then allowed to warm to room temperature. After 15 mins, the contents of the flask were poured into H_2O (15 mL) and extracted with DCM (10 mL × 3). The organic layers were combined and was first washed with a 0.2 M HCl solution (20 mL) and finally with brine (20 mL) before being dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified *via* silica gel flash column chromatography (EtOAc:PET 10:90) before being triturated from DCM and *n*-hexanes to afford compound **1** in 93% yield as a pale-yellow solid (273 mg).

The characterisation data collected for this compound compared well to literature data.[15]

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.28 (br. d, $^2J_{HH}$ = 10.0 Hz, 2H, Ar*H*), 6.86 – 6.82 (m, 2H, Ar*H*), 6.63 (s, 1H, N*H*), 3.78 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3).

Methyl (2-bromo-4-methoxyphenyl)carbamate (2)[1]



An oven dried Schlenk equipped with a magnetic stir bar and flushed with argon was charged with **1** (100 mg, 0.552 mmol), NBS (108.5 mg, 1.1 eq), PTSA (48 mg, 0.5 eq), $Pd(OAc)_2$ (6.2 mg, 0.05 eq) and DCE (1.1 mL). The contents were then heated to 60 °C and left to stir for 2.5 hours. After 2.5 hours, the reaction contents were cooled to room temperature and then diluted with DCM (20 mL). The solution was then poured into H_2O (20 mL) after which the product was extracted with DCM (10 mL x 3). The organic layers were subsequently combined and washed with a 10% HCl solution (20 mL), followed by sat. $NaHCO_3$ (20 mL) solution and finally brine (20 mL). The solution was then dried over $MgSO_4$ and the solvent was removed *via* reduced pressure. Purification was achieved *via* silica gel flash column chromatography (EtOAc:PET 10:90) to obtain compound **2** as an orange solid in 79% yield (113 mg).

The characterisation data collected for this compound compared well to literature data.[1]

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.93 (br. s, 1H, N*H*), 7.07 (d, $^2J_{HH}$ = 2.9 Hz, 1H, Ar*H*), 6.87 (dd, $^2J_{HH}$ = 9.1, 2.8 Hz, 2H, Ar*H*), 3.78 (s, 3H, OCH_3) 3.77 (s, 3H, OCH_3).

2.7. References

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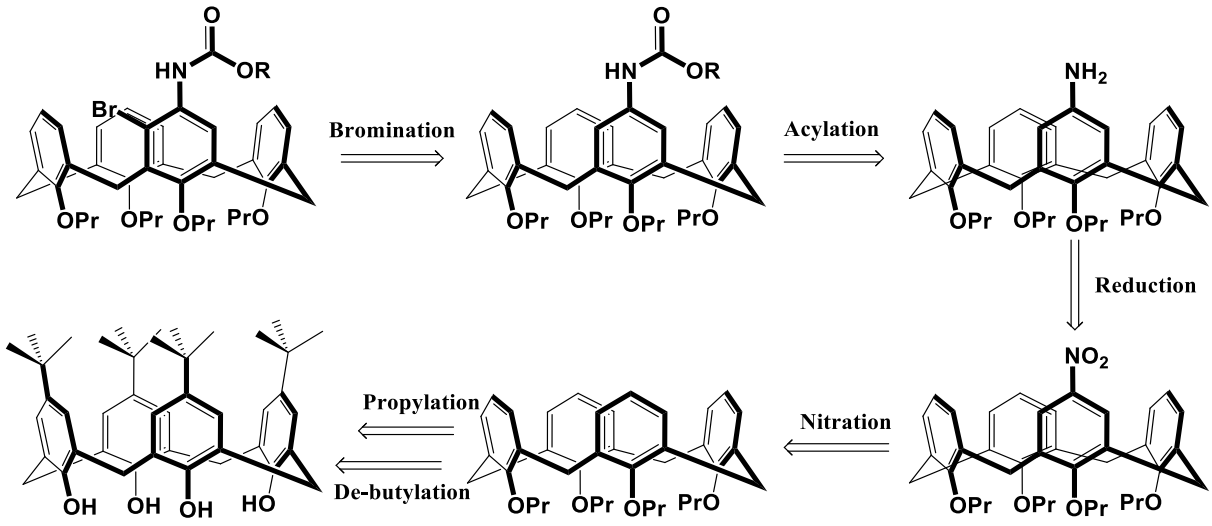
3. Chapter 3 – Mono-substituted carbamate calix[4]arenes

3.1. Introduction

The model study discussed earlier in chapter 2, showed that the presence of $Pd(OAc)_2$ catalyst improved the yield of the *ortho*-bromination reaction, although only by a small amount. Whether the same results would be obtained for the larger calix[4]arene scaffold needed to be evaluated. To obtain the mono-substituted carbamate calix[4]arene precursor, it was envisaged that it could be easily synthesized through an acylation reaction from an amine-functionalized calix[4]arene, identical to the model study in chapter 2. It was decided that the *para* position of the other three remaining aryl subunits of the calix[4]arene molecule should be vacant. Although these groups may be removed further along the synthetic process, with their absence, more information could be obtained from the nature of the carbamate functionality with regards to its ability to control the selectivity of the subsequent brominations. Furthermore, removing them all at once would reduce the number of steps needed to synthesize the final product. Therefore, the chosen synthetic route can be seen in the retrosynthetic analysis below (Scheme 3.1).



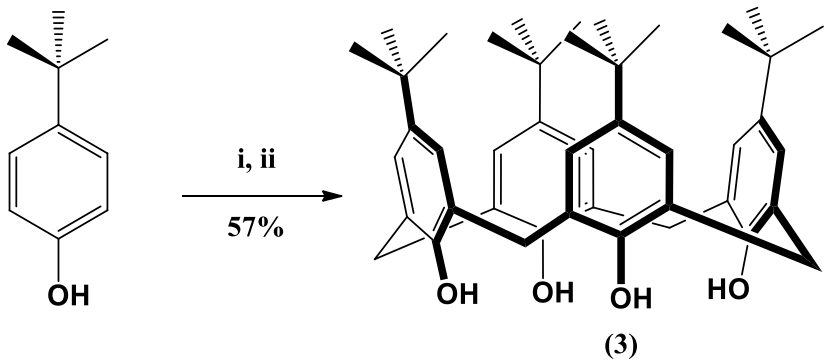
Scheme 3.1: Retrosynthetic analysis of the mono functionalized carbamate calix[4]arenes.

3.2. Synthesis of the mono-amino precursor

3.2.1. Parent calix[4]arene synthesis (**3**)

The synthesis of *p-tert*-butylcalix[4]arene has been modified several times since its initial discovery.[1–3] There are several procedures available in the literature for obtaining the macrocyclic compound but for this study, the synthetic procedure outlined by Gutsche was the

chosen route: a base induced condensation reaction of *p-tert*-butylphenol and 37% formaldehyde (Scheme 3.2).[3]



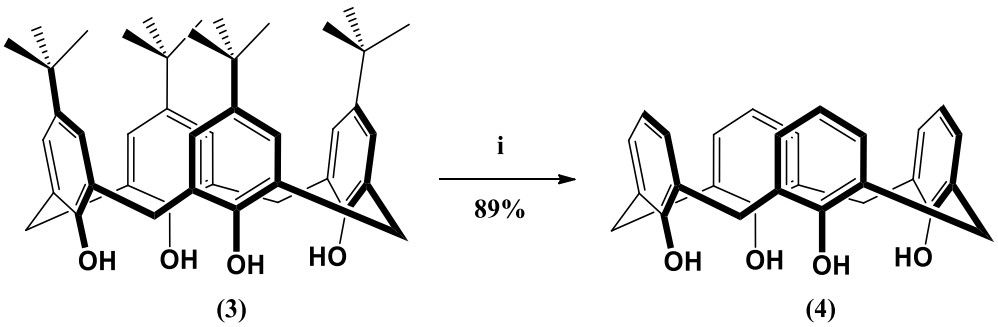
Scheme 3.2: Synthesis of *p-tert*-butylcalixarene **3**. i) CH_2O (1.25 eq.), NaOH (0.03 eq.), 120 °C, 30 min; ii) Ph_2O, reflux, 4 hrs.

The 37% formaldehyde solution and *p-tert*-butylphenol along with aqueous NaOH were stirred at 120 °C until the formation of a viscous yellow mass. After cooling to room temperature, Ph_2O and toluene were added to the reaction vessel. The contents were then heated to 180 °C to drive off water as a toluene/water azeotrope. Once the water had been driven off, the flask was flushed with N_2 and fitted with a reflux condenser before the reaction was heated to 270 °C and left under reflux for four hours. Once the time had elapsed the solution was cooled to room temperature and ethyl acetate was added and left to stir for a further 30 minutes. A white precipitate started to form, and the reaction was stopped and allowed to settle. The precipitate was filtered and washed successively with ethyl acetate, acetic acid and acetone. The solid was then dried to produce a white crystalline solid in yields between 55 and 60%. The ^{1}H NMR data obtained for the product matched well with reported literature and was sufficiently pure to continue to the next synthetic step (see experimental section 3.7).[4]

3.2.2. De-butylation of calixarene **3** (**4**)

The newly synthesized parent calixarene **3** was then subjected to a large scale debutylation of the *tert*-butyl functionalities at the wide rim of the macrocycle in a reverse Friedel–Crafts reaction (Scheme 3.3).[5] Using $AlCl_3$ as the Lewis acid, the parent calix[4]arene was stirred with phenol in toluene at room temperature for two hours under dry inert conditions. The mixture was then poured over crushed ice before being acidified with 1 M HCl. The organic layer was then separated and washed with water before being concentrated and dried. The off-white solid was finally purified *via* trituration and crystallization to afford calixarene **4** as a white solid in 89% yield. The proton NMR data obtained for the debutylated product matched

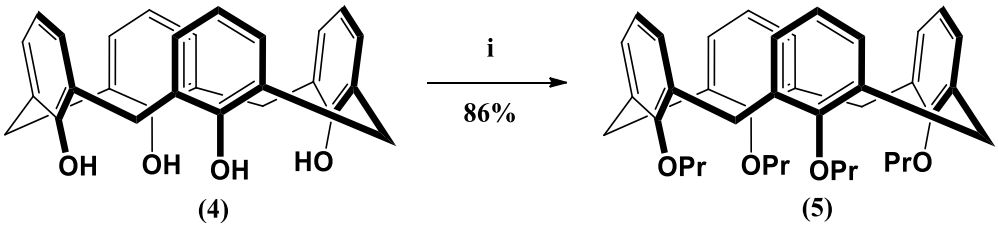
well with the reported literature and was ready for further functionalization (see experimental section 3.7).[5]



Scheme 3.3: Debutylation of **3** to yield calixarene **4**. i) $AlCl_3$ (4.9 eq.), PhOH (1.2 eq.), toluene, RT, 2 hrs.

3.2.3. Propylation (**5**)

In solution, the sp^3 hybridized carbons present at each methylene bridge allow for free rotation of the aryl subunits. This phenomenon allows for the possibility of several different conformations of the compound in solution. As previously discussed in chapter 1, Shinkai *et al.* demonstrated that by functionalizing the narrow rim of the compound would effectively lock the molecule into the cone conformation.[6] They found that the smallest chain needed for this was a propyl carbon chain. Calixarene **4** was therefore, propylated at the narrow rim following the procedure outlined by Dondoni and co-workers.[7]



Scheme 3.4: Synthesis of tetrapropoxy-calixarene **5**. i) NaH (17 eq.), 1-iodopropane (10 eq.), DMF, RT, 13 hrs.

Calixarene **4** was first reacted with excess NaH in dry DMF at 0 °C under argon in order for deprotonation to occur. Once the effervescence had finished, excess iodopropane was added and the reaction was allowedto warm to room temperature and left to stir overnight. The mixture was then cautiously acidified using a dilute solution of HCl to afford a yellow precipitate. The solid was then collected *via* filtration and purified using hot methanol. The

white crystalline solid was filtered and dried to afford calixarene **5** in good yield. Again, the ^{1}H NMR data obtained matched well with reported literature (Figure 3.1).[7]

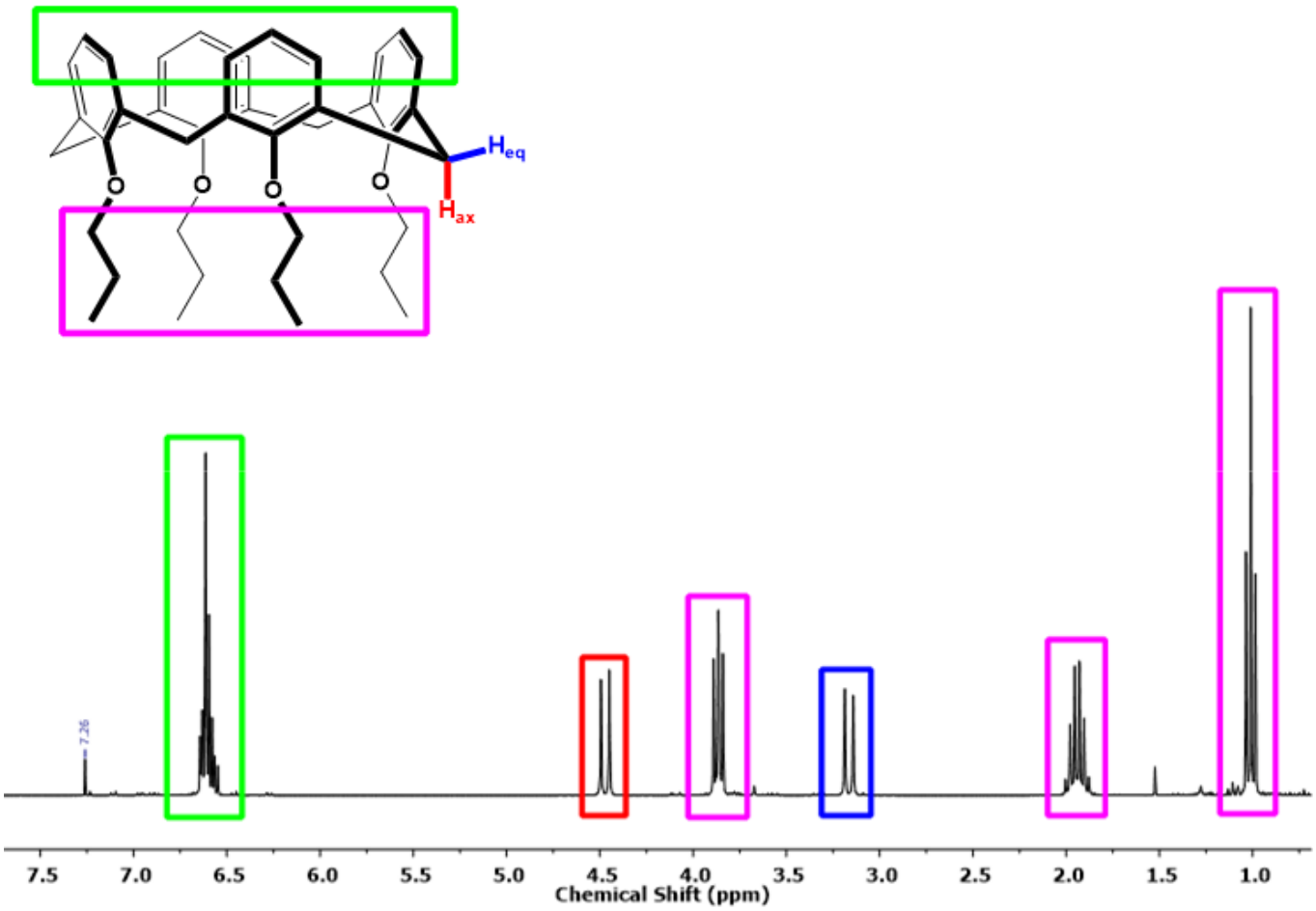


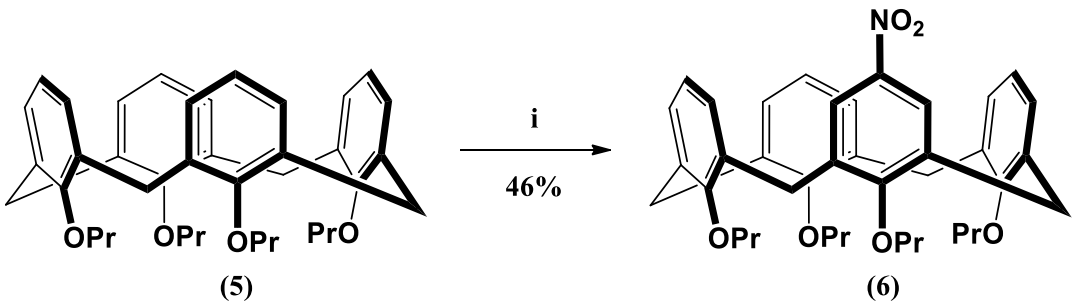
Figure 3.1: ^{1}H NMR ($CDCl_3$) spectrum of calixarene **5**.

All of the relevant signals are outlined above in calixarene **5**'s ^{1}H NMR spectrum. The addition of the propyl chains at the narrow rim of the calix[4]arene molecule gives rise to three distinct signals (outlined in purple). The signal resonating furthest downfield at δ 3.87 ppm, was assigned to the protons attached to the carbon closest to the oxygen atom of the propoxy chain. Moving away from the oxygen atom, the signals appear further upfield until the terminal carbon's protons, observed as a triplet at δ 1.01 ppm ($^{3}J_{HH}$ = 7.5 Hz). In the depiction of the calix[4]arene molecule, it can be seen that each methylene bridge carbon has two hydrogen atoms, one in the axial position (red) and one in the equatorial (blue). Each signal appears as a doublet with the equatorial protons resonating further upfield as they experience a shielding effect from the electron rich calix[4]arene macrocycle, whereas the axial protons experience a de-shielding anisotropic effect, hence, appearing further downfield at δ 4.47 ppm. Finally,

highlighted in green, are the aryl protons resonating around δ 6.60 ppm, integrating for the expected 12 hydrogen atoms.

3.2.4. Mono-nitration (**6**)

The following synthesis was rather low yielding and managing to obtain yields higher than 50% was almost impossible. When considering the other synthetic steps involved in obtaining the final inherently chiral calix[4]arene product, this step was by far the most limiting and significantly stunted the overall yield. The selective nitration of calixarene **5** to the mono nitrated product **6**, was governed by; molar equivalents of the nitrating agent (HNO_3), the temperature the reaction was performed at, and the reaction time. A strategy has been developed within our group for the mono-nitration of the tetrapropoxy-calix[4]arene in yields that exceed that reported previously.[8] It was, therefore, used as the chosen method to synthesize the mono-nitrated calixarene **6**. The procedure is illustrated in Scheme 3.5 below.



Scheme 3.5: Synthesis of the mono-nitrated calixarene **6**. i) HNO_3 (17 eq.), H_2SO_4 (10 eq.), DCM, 15 °C, 1 hr 20 minutes.

Calixarene **5**, dissolved in DCM, was first cooled to 0 °C before H_2SO_4 and a 70% solution of HNO_3 were added. Upon addition of the nitric acid, the contents of the flask would immediately darken from a clear solution to purple. As the reaction continued, the solution would gradually darken to almost black. After five minutes of stirring at 0 °C, the reaction was left to warm slowly to no more than 15 °C, after which the reaction continued for a further 80 minutes. When monitoring the progress of the reaction *via* TLC over 10-minute intervals, it was observed that before all the starting material had reacted, the over nitrated products; di- (proximal and distal), tri- and even the tetra-nitrated calix[4]arene started to form. It was found that if the reaction was allowed to continue until all the starting material had been used up, the yield for the mono-nitrated product would decrease significantly, from 46% to just below 40%. Therefore, it was deduced, that waiting for the starting material to be completely used up allowed more time for the already mono-nitrated products to continue to react with the highly

reactive nitronium ion. After the allotted time had run its course, the reaction was diluted with cold H_2O to prevent further nitration. The organic phase was washed with a mild basic solution and dried to produce an orange solid. Purification was achieved *via* silica gel flash chromatography to yield a pale-yellow solid. The compounds structure was confirmed using ^{1}H NMR spectroscopy (Figure 3.2) and matched well with that previously reported.[8]

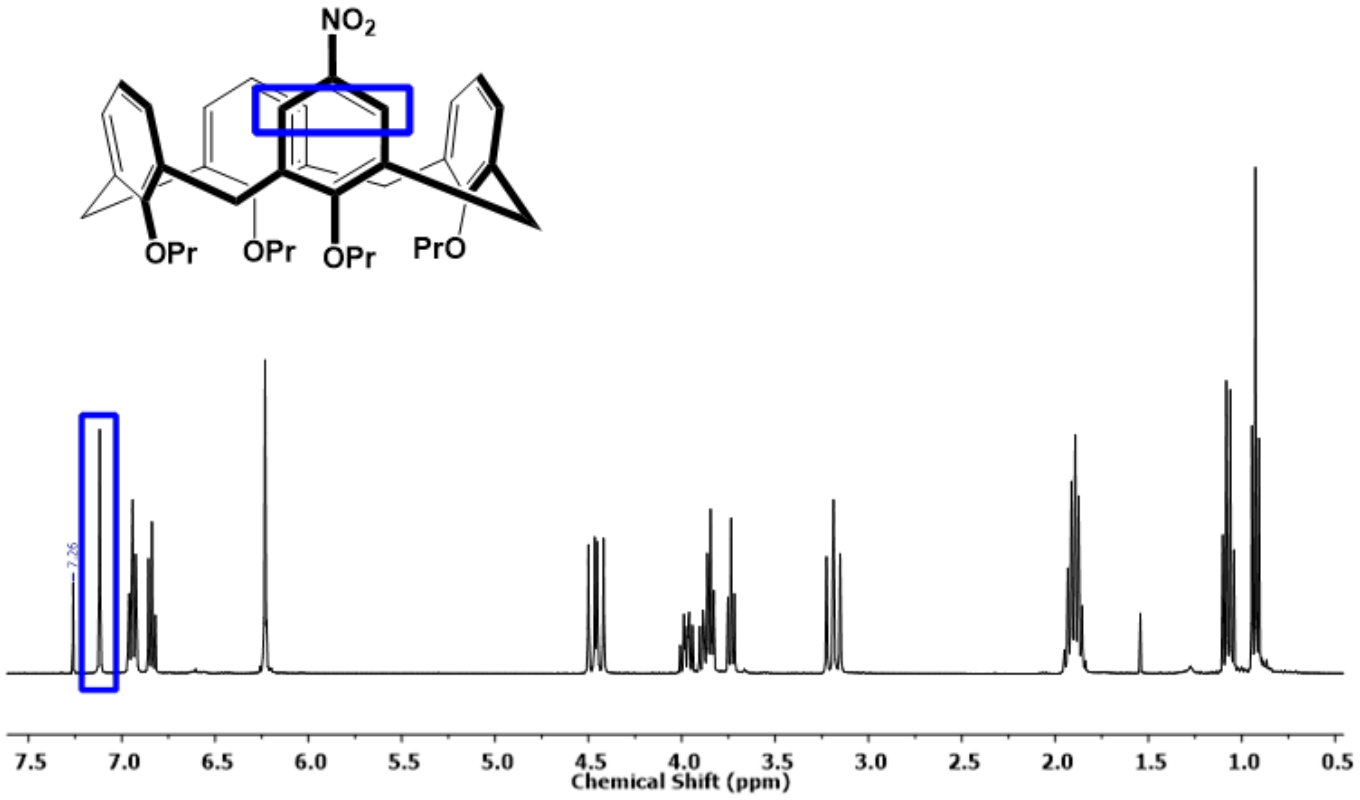


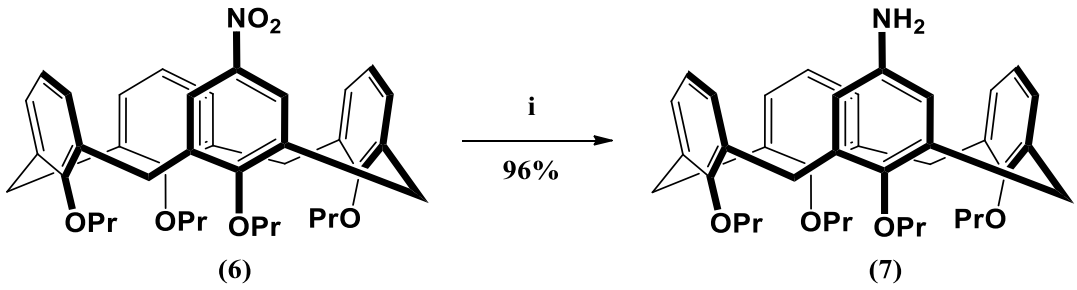
Figure 3.2: ^{1}H NMR ($CDCl_3$) spectrum for mononitro calixarene **6**.

Nitrating the calix[4]arene skeleton on only one of the aryl subunits had a profound effect on the compound's overall symmetry and the effects can be seen in the ^{1}H NMR spectrum. Furthest upfield, resonating around 1 ppm, the terminal carbons of the four propoxy groups' signal had split into three different signals, two of which overlap slightly at δ 1.06 ppm. Other areas where this splitting effect can also be seen are; the OCH_2CH_2 proton signals (δ 4.01 – δ 3.72 ppm), both signals for the axial and equatorial methylene protons (δ 4.46 ppm and δ 3.19 ppm respectfully), and in the aromatic region. Due to the deshielding effect of the nitro group, its two *ortho* hydrogens appear furthest downfield as singlet at δ 7.12 ppm, just upfield of the $CDCl_3$ signal at δ 7.26 ppm (outlined in blue). The other singlet in the aromatic region represents the three protons on the aryl ring distal to the nitrated ring. The upfield shift indicates that these hydrogen atoms are experiencing an anisotropic shielding effect, a result of the

calix[4]arene adopting a pinched cone conformation. This means that the nitrated ring and the ring that is distal to it, are orientated in a slightly more upright position compared to the rings that are adjacent.

3.2.5. Reduction of nitro group (7)

The newly synthesized mono-nitrated calixarene **6** was then reduced to its amine derivative in a near quantitative reaction, following a method previously described by Bitter and co-workers (Scheme 3.6 below).[9] Calixarene **6** was suspended in ethanol along with a catalytic amount of palladium on carbon and 5.2 molar equivalents of hydrazine hydrate. After 3 – 4 hours, the contents of the flask were cooled to room temperature before being filtered through a pad of Celite to obtain the white mono-amino product **7** as the sole product.



Scheme 3.6: Reduction of **6** to monoamino-calixarene **7**. i) 10% Pd/C (0.15 eq.), $NH_2NH_2 \cdot H_2O$ (5.2 eq.), EtOH, reflux, 3 hrs.

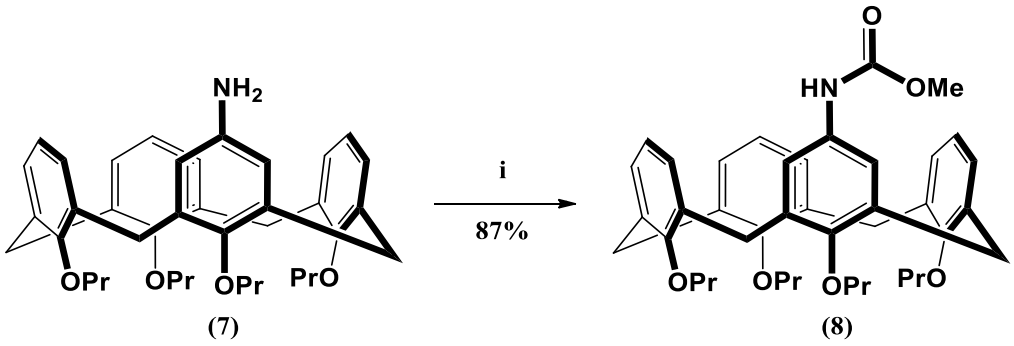
The ^{1}H NMR data obtained from the molecule indicated that the synthesis was successful and matched well with that already reported (see experimental section 3.7).[10] The only major difference to that of the mono-nitro precursor **6** was the large upfield shift of the singlet assigned to the protons *ortho* to the amine functional group from δ 7.12 ppm to δ 5.95 ppm. The added amine hydrogen atoms appeared as a broad singlet at δ 3.05 ppm.

3.3. Proof of concept *meta*-bromination

Before introducing a chiral directing group, the same achiral methyl carbamate used in the model study, was first attached to the mono-amino calix[4]arene skeleton. Due to the added complexities that the larger molecule would possess, it was important to limit any other factors that may interfere with the subsequent brominations. Therefore, the following section formed the proof of concept study for this project.

3.3.1. Methyl carbamate calix[4]arene synthesis (**8**)

Successful synthesis of the mono-amino calixarene **7** precursor, allowed for the calix[4]arene to be furnished with the targeted carbamate directing group. The carbamate acylation followed a similar procedure used in chapter 2 to synthesize compound **1**.[11]



Scheme 3.7: Acylation of **7** to produce the mono-functionalized methyl carbamate calixarene **8**. i) Methyl chloroformate (1.2 eq), pyridine (1.2 eq), DCM, RT, 15 minutes.

This reaction always produced the mono carbamate calix[4]arene as the sole product in very high yields. The high reactivity of the methyl chloroformate in the presence of pyridine resulted in the reaction running to completion within 15 minutes every time. The main function of the pyridine in this reaction was to mop up the resultant HCl by-product, however, since the base was used in slight excess, the remaining pyridine was neutralized and removed during the work-up by washing the organic phase with a very dilute acidic solution (0.2 M HCl). Further purification was achieved by silica gel flash column chromatography using a 5:95 EtOAc:PET solution as the eluent to produce the pure mono methyl carbamate calixarene **8** as an amorphous white glass.

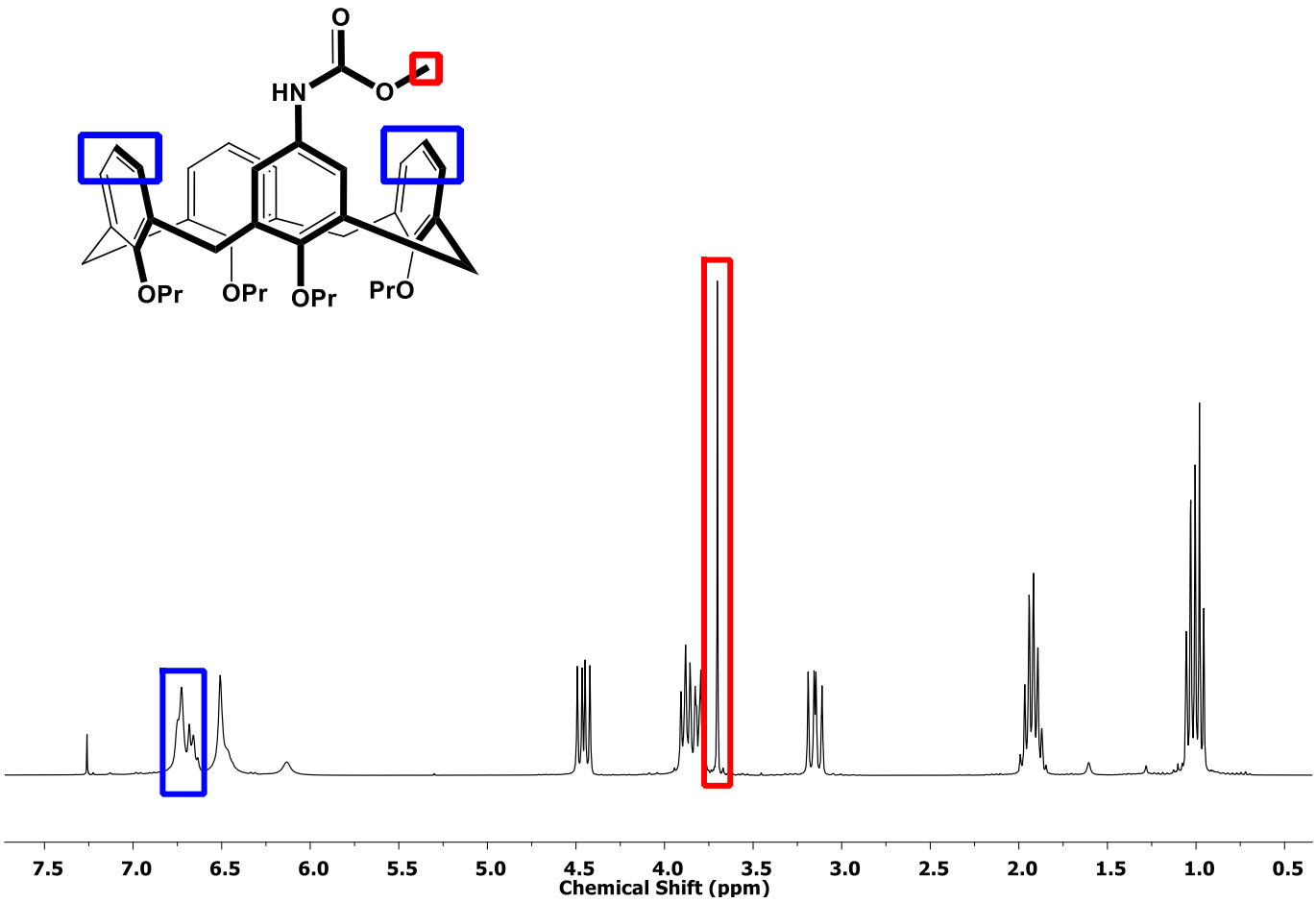


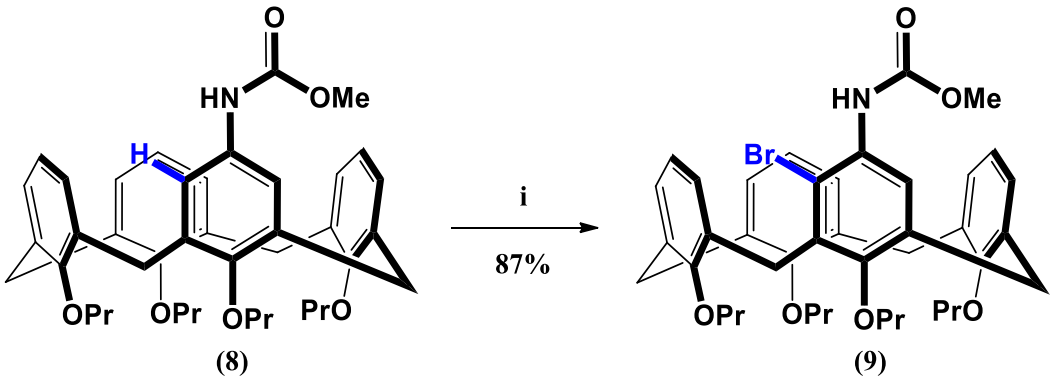
Figure 3.3: ^{1}H NMR ($CDCl_3$) spectra for mono methyl carbamate calix[4]arene, compound **8**.

The ^{1}H NMR spectrum obtained for this compound supported the formation of compound **8**. Again, as in the case of the mono nitro calixarene **6**, the break in symmetry of the compound resulted in a splitting of the aromatic protons. The multiplet furthest upfield, ranging from δ 6.76 to 6.61 ppm, integrated to a value of six. This array of signals was tentatively assigned to the six protons that are situated on the two aryl rings adjacent to the carbamate functionalized aryl subunit (outlined in blue). The remaining aryl protons, the two *ortho* hydrogens as well as the three that are distal to the carbamate, resonate further upfield at δ 6.46 ppm. The upfield shift of the distal and *ortho* protons can be explained by an anisotropic shielding effect from the calix[4]arene molecule, as was in the case of the mono-nitro calixarene **6**. This signal integrated to a value of five. The singlet resonating δ 3.69 ppm (highlighted in red) with an integration value of three matched the expected three protons attached to the methyl carbon of the carbamate functionality, the only three additional hydrogens present after attaching the carbamate moiety. Finally, the broad singlet observed at δ 6.07 ppm was assigned to the

remaining proton attached the nitrogen atom, which as expected, integrated to a value of one. Further proof of compound **8**'s synthesis was confirmed using ^{13}C NMR, mass spectrometry and IR analysis (see experimental section 3.7).

3.3.2. *Meta*-brominations (**9**)

As explained in chapter 1, inherent chirality may be introduced on a calix[4]arene skeleton by functionalization at the compound's *meta* position.[12] The study conducted in chapter 2 demonstrated the ability that the carbamate functionality had at directing both C-H activation and electrophilic aromatic substitutions to the directing group's relative *ortho* position. Although a higher yield was reported when the transition metal was included in the reaction, it was still not clear whether the reaction primarily proceeded through the proposed catalytic cycle. Li and Uhlig also suggested that there was a competing electrophilic aromatic substitution at play with their isotopic experiment.[13] The same procedure reported by Moghaddam and co-workers was used to synthesize the *meta*-bromo carbamate calixarene **9** (Scheme 3.8).[14]



Scheme 3.8: C-H activation of calixarene **8**. i) NBS (1.1 eq), PTSA (0.5 eq), $Pd(OAc)_2$ (0.05 eq), DCE (2 mL), 60 °C, 2.5 hrs.

As reported in the model chapter (chapter 2), the C-H activation was carried out in a closed Schlenk flushed with argon and equipped with a magnetic stir bar. All four reagents; calixarene **8**, PTSA, $Pd(OAc)_2$, and NBS along with the solvent, DCE, were heated up to 60 °C and left to stir for two and a half hours. Once the time had elapsed, the starting material had been used up and only one product had formed by TLC. With the three *para* positions of the other phenolic units open and available for functionalization (i.e. electrophilic bromination), it was an extremely pleasing result to see that only one product had formed. The reaction was worked-up using the same procedure outlined for compound **2** in chapter 2. The crude product was then purified using silica gel flash column chromatography (EtOAc:PET 1:9) to produce a racemic

mixture of the *meta*-functionalized inherently chiral calixarene **9**. The compound's ^{1}H NMR spectra strongly suggested that the desired *meta*-bromination had indeed occurred (Figure 3.4).

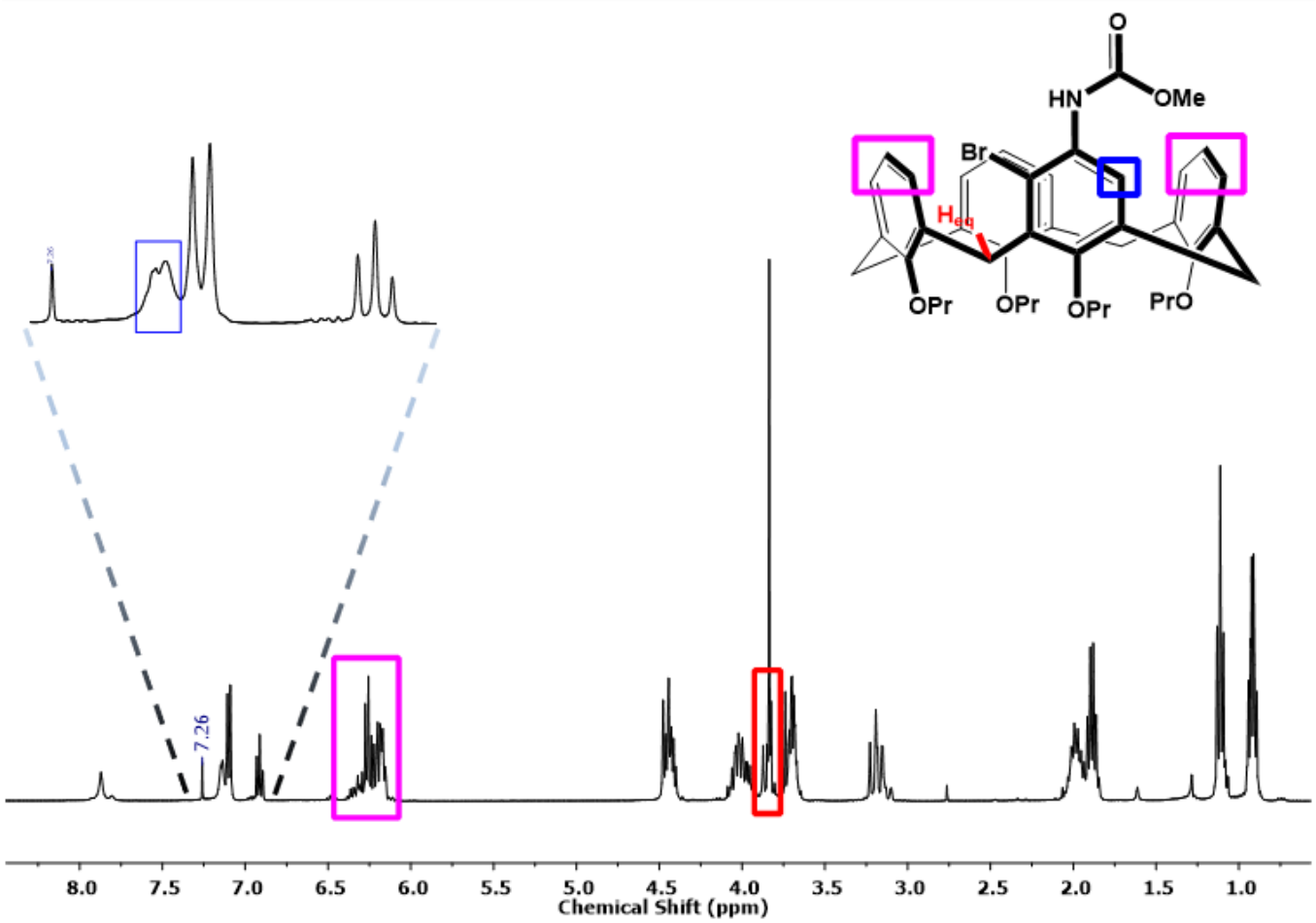


Figure 3.4: ^{1}H NMR spectra ($CDCl_3$) of calixarene **9**.

One of the clearer indications that the bromination had occurred at the *meta* position, is the downfield shift of only one of the methylene bridge's hydrogen atoms from δ 3.18 ppm to δ 3.84 ppm, overlapping with the carbamate's methyl signal. The proton depicted in red has its signal outlined in red. Thus, the remaining methylene bridges equatorial protons resonating at δ 3.18 ppm only integrate for three protons. Due to the bromine's high electronegativity, it deshields its neighbouring methylene bridge's equatorial hydrogen, causing the downfield shift. The aryl region shows four separate resonating signals. The multiplet furthest upfield (purple) integrated for six protons, which represent the protons of the aryl rings proximal to the directing group's ring (also highlighted in purple). Again, indicating that the calix[4]arene is adopting a pinched cone conformation. In the magnified section, the three signals represent the protons attached to the ring distal to the functionalized arene and the remaining hydrogen atom of the functionalized ring (outlined in blue). The apparent splitting of the signal can be

explained by a mixture of two rotational isomers that exist due to the restricted rotation around the carbamate bond. The two isomers experience slightly different environments and therefore result in two broad singlets that slightly overlap. The *para* proton on the distal ring resonates as a triplet at δ 6.91 ppm bridge ($^3J_{HH}$ = 7.4 Hz), with the remaining doublet at δ 7.10 ppm ($^2J_{HH}$ = 7.4 Hz) accounting for the hydrogen atoms adjacent to the *para* position. Finally, the last difference of the two spectra is the downfield shift of the amine signal, the broad singlet at δ 7.87 ppm. ^{13}C NMR, IR and MS spectrometry were used as further proof of structure.

The results obtained from the C-H activation reaction illustrated in Scheme 3.8 demonstrated an extremely efficient method of obtaining *meta*-functionalized inherently chiral calix[4]arenes in high yields. Not only was the reaction high yielding, the fact that only the desired compound was being synthesized was a huge bonus, as purification of the racemic mixture could be accomplished with minimal effort. However, as demonstrated in chapter 2, *ortho*-bromination of the smaller *para* methoxyphenylcarbamate could be achieved without the use of the catalyst. The ring activating properties of the carbamate functional group obviously rendered the *ortho* position active and therefore, promoted the selectivity of the substitution reaction. One aspect that needed to be considered however, was that in the model study the *ortho* position was the only site on the compound that would be activated. The other area that would normally be activated in the presence of an activating group (the *para* position) was blocked by the methoxy functionality. The same could be said for the calix[4]arene system but in this case, there are three other phenolic units with vacant *para* positions that are open for functionalization. With this logic, if the transition metal was playing a major role in the reaction, excluding it from the reaction could result in a loss of control and one would expect more than one product to form (i.e. brominations at the vacant *para* positions).

Attempting to ascertain whether the catalyst was playing a major role, the synthesis was attempted without the catalyst, as was shown in chapter 2. The same reaction conditions used in Scheme 3.8 were used, bar the $Pd(OAc)_2$. Again, the sole product that formed was the *meta*-brominated calixarene **9** in similar yields, differing only by a 5 – 10%. The ^{1}H NMR data obtained for this compound matched the spectrum generated from the C-H activation reaction (Figure 3.4).

This result strengthens the argument made in chapter 2 about the necessity of the catalyst. The fact that the reaction outcome is the same for both C-H activation and the electrophilic aromatic substitution, in both chapter 2 and here, indicates that the role $Pd(OAc)_2$ has on the end result

is minimal. Mechanistically, without the catalyst, the reaction definitely proceeds through the said electrophilic aromatic substitution. However, when including $Pd(OAc)_2$, it is more likely that only a certain percentage of the molecules actually come into contact with the catalyst, as only a catalytic amount of the transition metal was used. The molecules that are not initially in contact with the metal would probably already start reacting with the stoichiometric amount of NBS present in the reaction. In this instance, the catalyst is not needed for the desired result to occur.

The proof of concept study proved that when using a carbamate as a directing group for calix[4]arene *meta*-brominations, it was not necessary to incorporate $Pd(OAc)_2$ as a transition metal catalyst. However, this does not preclude the possibility that when it was incorporated, the molecules that encounter the metal may proceed through the catalytic cycle. If this is indeed the case, it may influence stereoselectivity when introducing a chiral aspect into the conditions. A chiral carbamate directing group may control the area to which the metal can approach in order to form the cyclometalate, which would in turn control which *meta* position of the calix[4]arene would be brominated. This concept was investigated and is discussed in the following section (chapter 3.4), whereby the chiral (1*S*)-(+)-menthyl carbamate directing group was the chosen candidate. Nonetheless, the proof of concept study has presented a new and highly efficient method in producing *meta*-functionalized inherently chiral calix[4]arenes, albeit racemic.

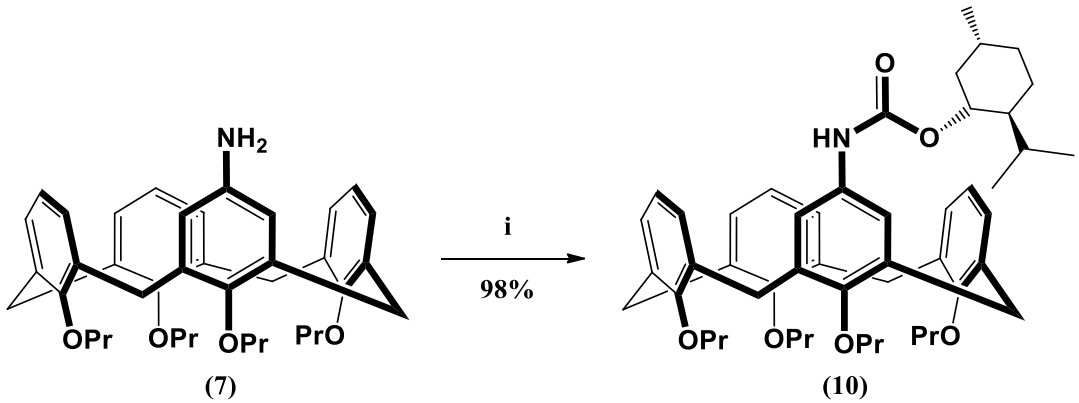
3.4. Stereoselective *meta*-bromination

Both the model study discussed previously in chapter 2, and the proof of concept discussed in chapter 3.3.2, confirmed that when attempting to *ortho*-brominate a *p*-substituted *N*-arylcarbamate, the same result can be obtained with or without $Pd(OAc)_2$. Furthermore, in the case of the calix[4]arene, the carbamate's activating properties alone prevent the vacant *para* positions of the other phenolic units from being brominated. The following study was conducted to determine whether a chiral directing group may influence the stereoselectivity of the brominations, and whether the catalyst may play a role in this regard.

3.4.1. Menthyl carbamate acylation (**10**)

Following the same protocol stated in section 3.3.1 above for the synthesis of the achiral methyl carbamate calix[4]arene,[11] a chiral menthyl carbamate calix[4]arene analogue was synthesized to introduce a stereochemical component to the system. (1*S*)-(+)-Menthyl chloroformate was

reacted with the mono-amino substituted calixarene **7** in the presence of pyridine to produce the desired chiral mono-substituted calixarene **10**, Scheme 3.9 below.



Scheme 3.9: Acylation of **7** to produce the mono-functionalized menthyl carbamate calixarene **10**. i) Menthyl chloroformate (1.2 eq), pyridine (1.2 eq), DCM, RT, 15 minutes.

Again, the reaction was facile giving yields in excess of 90%. Before adding the menthyl chloroformate to the reaction flask, which contained the mono-amino calixarene **7**, 1.2 eq of pyridine and DCM, the mixture was cooled to 0 °C. Upon addition of the menthyl chloroformate, the solution's colour changed from clear to a clear orange. The contents were then taken out of the ice bath, allowing it to warm to room temperature gradually. The colour of the solution gradually lightened and after approximately 10 minutes, it had a pale-yellow colour, a good indication that the reaction had run to completion. The same method of work-up and purification described for the synthesis of calixarene **8** was used to obtain calixarene **10** as an amorphous glass.

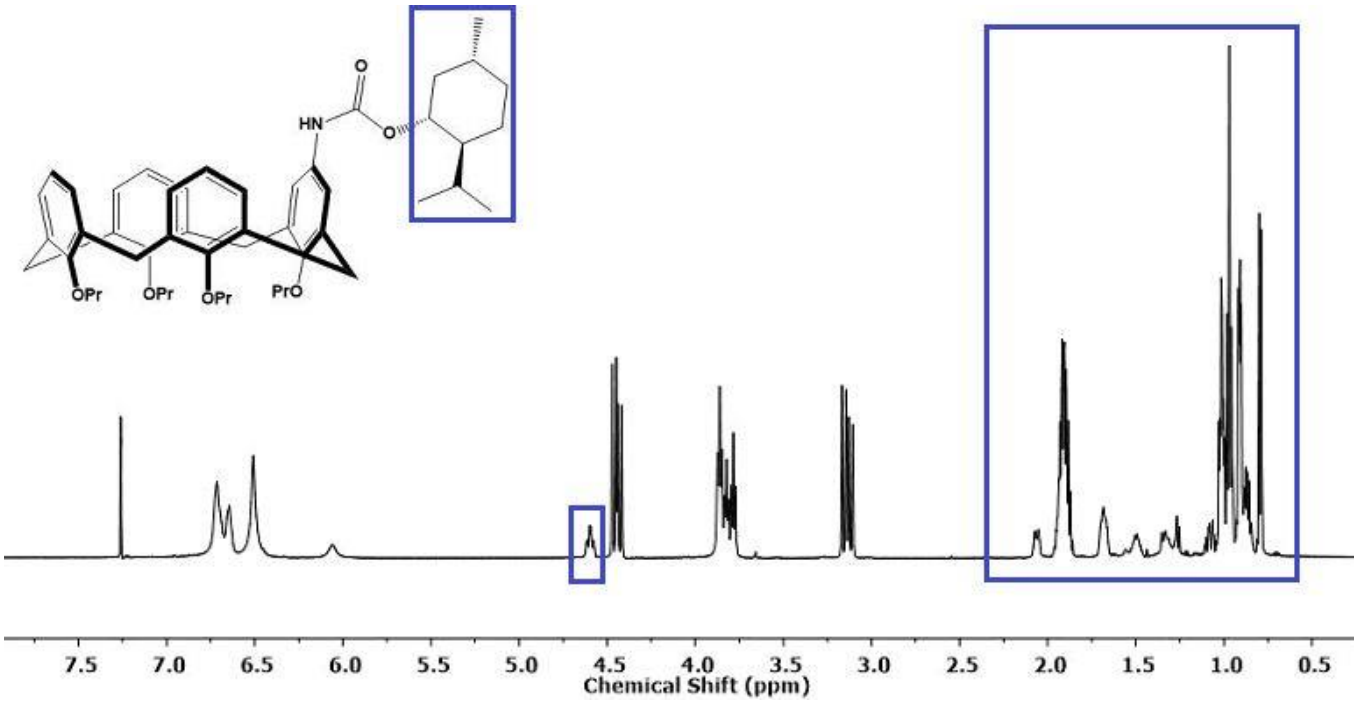


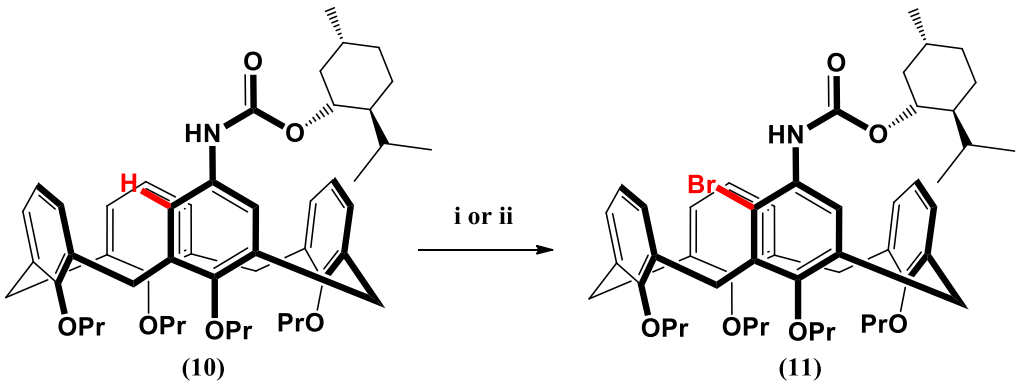
Figure 3.5: ^{1}H NMR ($CDCl_3$) spectra for mono menthyl carbamate calix[4]arene, compound **10**.

The ^{1}H NMR data obtained for calixarene **10** (Figure 3.5) confirmed the successful synthesis of the compound. The presence of the menthyl moiety added a layer of complexity to the signals present in the compound's ^{1}H NMR spectrum. The signals that emanate from the chiral menthyl group are outlined in blue (this also included the propyl groups' protons). Furthest upfield, resonating at δ 4.60 ppm as triplet of a doublet, lies the signal for the sole proton attached to the hexyl carbon connected to the oxygen of the carbamate. The remaining signals that stem from the menthyl substituent overlap with the terminal and middle carbon's hydrogen atoms of the propoxy groups on the calix[4]arene molecule, increasing the complexity of the compound's ^{1}H NMR spectrum. However, it was still quite easy to see that the attachment of the chiral menthyl moiety to the calix[4]arene was successful. ^{13}C NMR, IR and MS data was obtained for this compound.

3.4.2. Chiral menthyl carbamate calix[4]arene bromination (**11**)

The proof of concept study demonstrated that carbamates are more than an ideal candidate for activating the calix[4]arene's *meta* position, be it in the form of C-H activation or electrophilic aromatic substitution. However, it is still unclear as to whether the reaction does go through the cyclometallation step when incorporating the transition metal catalyst. Still, the high yielding method for accessing *meta*-functionalized inherently chiral calix[4]arenes was

extremely appealing. The newly synthesized chiral menthyl carbamate calixarene **10** was investigated as a possible chiral directing group in the hopes of inducing a degree of diastereoselectivity. Scheme 3.10 below shows the general conditions used for the synthesis of the inherently chiral calix[4]arenes.



(10) (11)

Scheme 3.10: *Meta*-bromination of calixarene **10** through either C-H activation (i) or electrophilic aromatic substitution (ii). i) NBS (1.1 eq), PTSA (0.5 eq), $Pd(OAc)_2$, DCM, 4h. ii) NBS (1.1 eq), PTSA (0.5 eq), DCM, 4 hrs.

For the electrophilic aromatic substitution, calixarene **10** and PTSA were added to a 5 mL Schlenk charged with DCM (1 mL). The reaction vessel was flushed with argon and then was set to the chosen temperature before the NBS was added. The Schlenk was then closed to maintain a constant pressure and the reaction was left to stir for four hours at the set temperature. It was found that if the vessel was not closed, there would still be unreacted starting material after the allotted time for both substitution and C-H activation reactions. After four hours, the contents of the flask were diluted with DCM and poured into H_2O and extracted with DCM. The organic layers were then combined and first washed with sat. $NaHCO_3$ and then brine before being dried over $MgSO_4$ and concentrated. Purification was achieved *via* silica gel flash column chromatography to afford calixarene **11** as a colourless glass in yields ranging from 82 – 86%.

The C-H activation procedure followed a similar protocol with just the addition of the $Pd(OAc)_2$ as the only new reagent. Before the catalyst and NBS were added, however, the contents of the vessel underwent at least five freeze pump thaw cycles in order to degas the solvent. The reaction was then flushed with argon and set to the desired temperature. Finally, the catalyst and NBS were added to the flask and the Schlenk was closed, as was done for the substitution reaction. NBS was only introduced after the catalyst was added in an attempt to try and promote the C-H activation route over the aromatic substitution. However, the catalyst

would only become activated once the NBS was added since it has a dual function acting as the bromine source and oxidant, oxidizing palladium from Pd^{II} to Pd^{IV}. Purification was achieved in similar manner as the substitution to afford the same product in yields ranging from 90 – 92%. Unfortunately, the two diastereomers formed possessed the same R_f value and therefore, could not be separated using conventional column chromatography.

A mini temperature-dependant study was conducted to determine whether the temperature of the reaction would promote selectivity of one of the stereoisomers. At each temperature two entries were made, one with the catalyst and one without (see Table 3.1).

Entry	Temperature (°C)	Catalyst	Brominating agent	Additive	Time	Yield (%)
1	25	$Pd(OAc)_2$	NBS	PTSA	4 hrs	90
2	25	-	NBS	PTSA	4 hrs	86
4	0	$Pd(OAc)_2$	NBS	PTSA	4 hrs	90
5	0	-	NBS	PTSA	4 hrs	82
6	–35	$Pd(OAc)_2$	NBS	PTSA	4 hrs	92
7	–35	-	NBS	PTSA	4 hrs	82

Table 3.1: *Meta*-brominations of calixarene **10** at various temperatures. NBS (1.1 eq), PTSA (0.5 eq) and $Pd(OAc)_2$ (0.05 eq).

Table 3.1 shows that the catalyst does increase the yield of the desired product, although only by a small magnitude. This suggests that the reaction does proceed, at least to some extent, through the C-H activation reaction pathway. The biggest difference in yield can be seen at the lowest temperature. As expected, the yield decreased slightly for the electrophilic aromatic substitutions when lowering the temperature, but this was not the case for the C-H activation, as the yields for the pair of diastereomers remained relatively constant. This is a promising outcome; as previously mentioned in the proof of concept study, the high reactivity of the substitution reaction would ultimately reduce the overall percentage of starting material that is exposed to the catalyst before bromination occurs. The ultimate goal would be to prevent the electrophilic aromatic substitution reaction from happening completely, this would ensure that all starting material would be subjected to the catalytic cycle and hopefully, induce a larger

diastereoselectivity for the bromination, assuming that there is no selectivity when electrophilic aromatic substitution occurs.

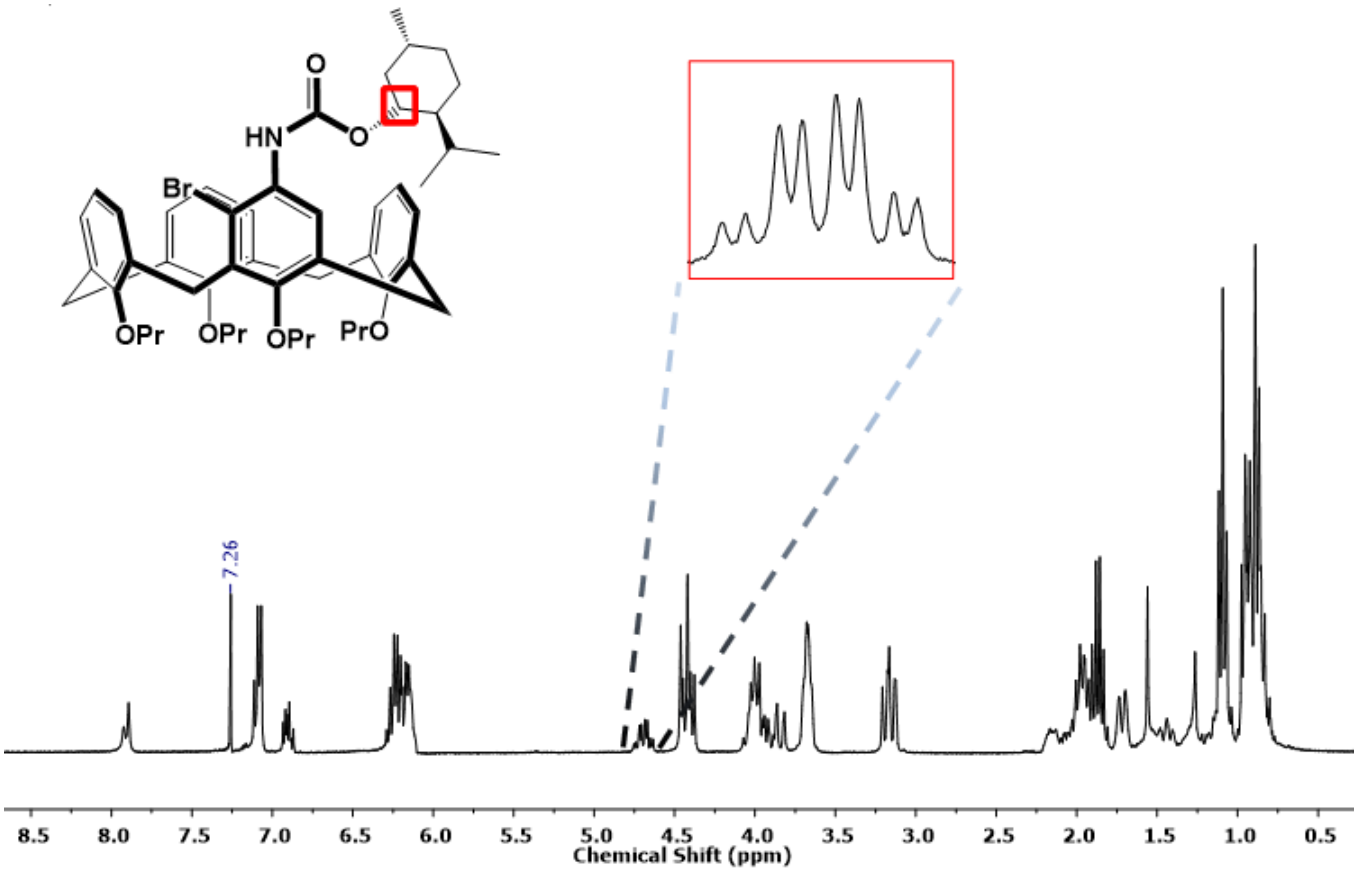


Figure 3.6: ^{1}H NMR spectra ($CDCl_3$) of calixarene **11**.

The compound's ^{1}H NMR spectra obtained from all reactions tested in the study (Table 3.1) were unfortunately all similar. It was hoped that some indication of diastereoselectivity would present itself in the various spectra. One of the possible signals where the selectivity could be observed would be the multiplet highlighted and magnified. It represented the proton attached to the chiral carbon closest to the calix[4]arene scaffold, hence, the most likely signal to be affected by the *meta*-functionalization of the calix[4]arene. Before bromination, the signal resonated as a triplet of a doublet (Figure 3.5). After bromination Figure 3.6 shows that the signal had been split in two that seemed to slightly overlap each other. The two overlapping signals can be interpreted as the pair of diastereomers formed. If they formed in a 1:1 ratio, one could expect the signal to appear symmetrical, however, the one half of the signal has a slightly stronger intensity. This may indicate a favour of the one isomer over the other. However, this interpretation is merely speculative, therefore, further evidence will need to be acquired. Furthermore, as previously mentioned, the same spectrum was observed for all entries made in

Table 3.1, suggesting that the use of the transition metal catalyst and colder temperatures do not have an effect on the selectivity. As in the case for calixarene **9**'s spectrum, the same trends were evident here; the downfield shift of the amine proton, the upfield shift of the proximal aryl protons, the splitting of the propoxy chains and the downfield shift of one of the equatorial methylene bridge protons. Again, ^{13}C NMR, IR and MS analytical techniques were used for further proof of structure.

3.5. Determining diastereoselectivity

After synthesizing the pair of diastereomers at various temperatures it was necessary to determine the selectivity of the *meta*-brominations. One method of determining the diastereoselectivity of the formed compounds would be through analysis of the ^{1}H NMR spectra but unfortunately, each spectrum generated for the reactions listed in Table 3.1 were identical. This can be explained by either of the two following hypotheses. One; the signals of the two different diastereoisomers are identical, and therefore, cannot be visualized in the ^{1}H NMR. Or two; there is no difference in selectivity at differing temperatures and the presence of the catalyst has no effect on the stereoselectivity of the reaction. The next method investigated was to separate the diastereomers using HPLC, which would allow for the calculation of the ratio between the two.[15] At first, the sample was passed through a normal phase column, using an IPA:Hexane mobile phase. Even after a number of adjustments made to the flow rate and solvent ratio, the diastereomers proved inseparable. We then turned our attention to a reverse phase column using a methanol:water eluent, but again, after several adjustments of parameters the experiment proved unsuccessful. It was finally decided that calculating the formed compounds' specific rotations could shed light on whether there was any selectivity at all.

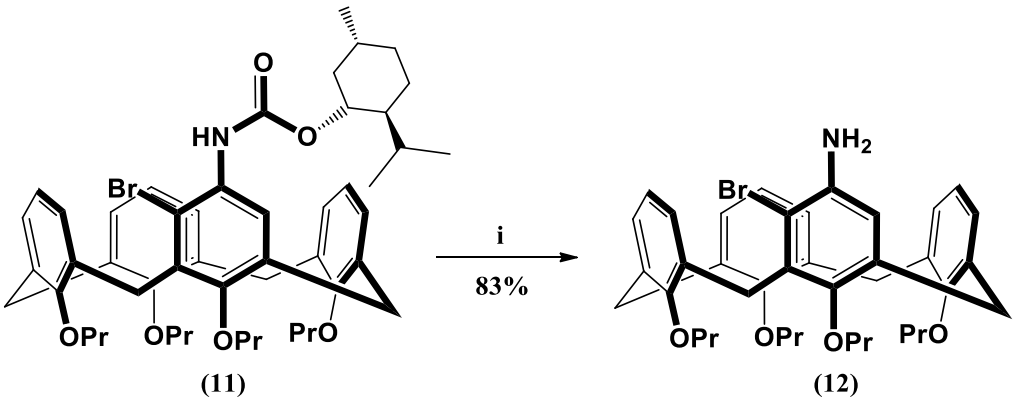
Alpha-D experiments are used to work out the specific rotation of chiral compounds using a polarimeter. Chiral compounds, which are optically active, rotate a beam of plane polarized light in either a clockwise or anticlockwise direction. Chiral compounds that rotate plane polarized light in a clockwise direction are considered dextrorotary and exhibit a positive specific rotation, whereas compounds that rotate the plane of polarization in anticlockwise direction are levorotatory and correspond with negative specific rotations.[16] One limitation for this technique, in the instance of this research project, is that the enantiomeric excess of the bromination reaction cannot be calculated as the specific rotation of the pure enantiomer must be known.[17] However, the results from this experiment will be able to clarify whether there is

a preference of one enantiomer over the other, since a racemic mixture would result in a specific rotation value of 0.

When considering the synthesized diastereoisomers from chapter 3.4.2, each of them have the chiral (1*S*)-(+)-menthyl carbamate attached at the wide rim. To get an accurate result of the specific rotation for the inherently chiral calix[4]arene molecule, this functional group must be removed since it has its own chiral signature and therefore, its own specific rotation. The removal of the carbamate functional group is discussed in the following section.

3.5.1. Synthesis of the brominated mono-amino enantiomers (**12**)

The chiral menthyl group had to be removed to produce the two different enantiomers. This was done *via* hydrolysis of the carbamate using TBAF. The reaction conditions are outlined in Scheme 3.11 below.



Scheme 3.11: Hydrolysis of carbamate directing group. i) TBAF (10 eq), THF, reflux, 36 hrs.

Several papers demonstrated that the hydrolysis of carbamates may be done using TBAF.[13,14,18] The fluorine anion attacks the electropositive carbonyl carbon breaking the bond between the nitrogen and carbonyl carbon.[18] The reaction was first tried at room temperature, however, after 24 hours no product spot had formed. Increasing the equivalents of TBAF also made no change to the reaction at room temperature. However, when attempting the reaction under reflux, the reaction moved forward and product started to form. 2 molar equivalents of TBAF was first used and although product began to form, the reaction never reached completion. Only after 10 equivalents of the reagent and enough time under reflux pushed the reaction to completion. Calixarene **11** was dissolved in THF and added to a 2-neck round-bottomed flask equipped with a reflux condenser. 10 equivalents of a 1 M solution of TBAF in THF was subsequently added and the reaction was left to proceed at reflux for 36 hours. After completion, the solvent

was removed *via* reduced pressure and then diluted with EtOAc. The solution was then washed with water at least six times to remove as much of the TBAF as possible. After attempting to purify the crude mixture using silica gel flash column chromatography, a stoichiometric amount of by-product, presumably menthyl fluoroformate, was still present. TLC analysis showed that the two compounds had the same R_f value, therefore, another method of purification was needed after chromatography. Realizing that the boiling point of menthyl chloroformate is 108-109 °C,[19] the contents were heated to 80 °C under reduced pressure for 8 hours. After heating, the ^{1}H NMR data (Figure 3.7 below) showed that the by-product had been removed which left the pure brominated mono-amino calixarene **12** as a colourless glass.

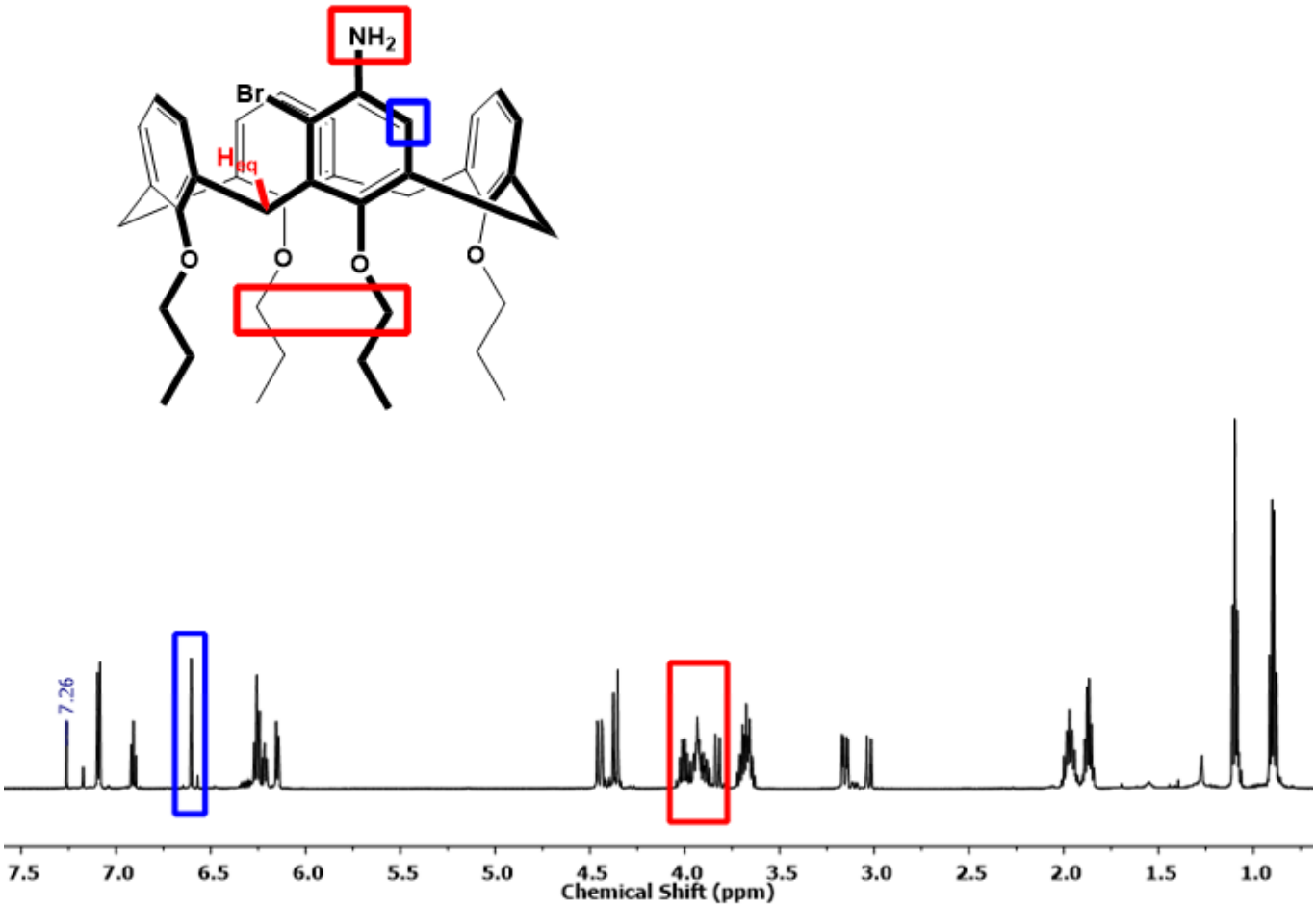


Figure 3.7: ^{1}H NMR spectra ($CDCl_3$) for calixarene **12**.

The first obvious difference between this spectrum and the one obtained for calixarene **11** is the absence of the menthyl signals. As in the case of the previous brominated calix[4]arenes, the equatorial methylene bridge proton closest to the bromine has shifted downfield and resonates in the area highlighted in red. Other hydrogen atoms that resonate in that area are the two amine protons and half of the protons attached to the carbon closest to the oxygen atom of

the propoxy chain. As expected, this area integrates for seven hydrogen atoms. In the aryl region, highlighted in blue is the non-brominated *meta* position's hydrogen atom with the aryl protons distal to the functionalized ring slightly downfield and the proximal signals resonate slightly upfield, again indicating the calix[4]arene adopting the pinched cone conformation (see experimental section for ^{13}C NMR, IR and MS data).

3.5.2. Alpha-D calculations

After unsuccessful attempts at determining the diastereoselectivity of the synthesis in Scheme 3.10, and with no apparent differences in the ^{1}H NMR data of the products produced in the differing conditions (Table 3.1), it was decided that Alpha-D experiments could help indicate whether there was any diastereoselectivity when using the chiral directing group, as previously discussed. The purified sample (calixarene **12**) was dissolved in DCM (10 mg/mL) and a monochromatic light was passed through the length of the sample. It was decided that only two samples needed to be analysed, therefore, products formed from entries 6 and 7 (Table 3.1) were chosen based on the following two parameters; temperature of the reaction conditions and determining the influence of the catalyst. Entries 6 and 7 had the coldest reaction conditions (–35 °C), therefore, the most likely conditions to induce diastereoselectivity. Furthermore, entry 6 used $Pd(OAc)_2$ in the reaction conditions whereas entry 7 did not. Comparing these two would help determine if the catalyst had an impact on the outcome of the reaction. The results are reported below.

The specific rotation for a sample can be determined by using the equation below.[20]

$$[\alpha]_D^T = \frac{\alpha_D^T}{c \times l}$$

Where:

$[\alpha]_D^T$ is the specific rotation in angular degrees per dm and per g/cm^3, at the temperature the measurement was taken and measured using a sodium 'D' light source.

α_D^T is the optical rotation in angular degrees at the temperature the measurement was taken and measured using a sodium 'D' light source.

c is the concentration in g/cm^3.

l is the length of the polarimeter tube in dm.

Both products for entries 6 and 7 were dissolved in DCM with a concentration of 10 mg/mL. A blank sample was first taken before each sample was added to the polarimeter tube. The results and calculations for the readings are shown below.

Entry 6 ($Pd(OAc)_2$):

$$[\alpha]_D^{23} = \frac{0.06_D^{23}}{0.01 \times 1}$$

$$[\alpha]_D^{23} = 6°$$

$\therefore [\alpha]_D^{23}$ +6°, *c* = 0.01 in dichloromethane

Entry 7 (no catalyst):

$$[\alpha]_D^{23} = \frac{0.03_D^{23}}{0.01 \times 1}$$

$$[\alpha]_D^{23} = 3°$$

$\therefore [\alpha]_D^{23}$ +3°, *c* = 0.01 in dichloromethane

The results above indicate that there was a slight increase in the specific rotation angle for the reaction that was performed with the catalyst. This suggests that the catalyst does impact the outcome of the reaction, albeit a relatively small influence. The small deviation further supports the previous notion that when the catalyst is included there is some aspect of C-H activation however, there is a competing electrophilic aromatic substitution which probably plays a larger role in brominating the *meta* position. In terms of the C-H activation reaction pathway, the chirality of the directing group forces the $Pd(OAc)_2$ to approach from a specific direction, hence, promoting one diastereomer to form over the other. In the case of the electrophilic aromatic substitution, however, the diastereoselectivity is most likely to arise from steric hindrance. This would be a much smaller effect due to the size of the brominating reagent, therefore, we would expect to see a smaller rotation angle, which is what was observed.

Both measurements resulted in positive specific rotation angles which is to be expected, as the same chiral directing group was used. The positive specific rotations mean that both can be considered dextrorotary. Unfortunately, without knowing what the specific optical rotation for an enantiopure product of calixarene **12** would be, the enantiomeric excess cannot be calculated. However, it can be seen that the $Pd(OAc)_2$ catalyst does play a small role in the

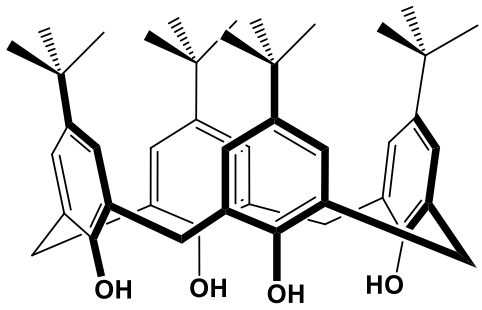
reaction with a larger rotation angle and slight increase in yields reported (Table 1). Lowering the reactivity of the electrophilic aromatic substitution could help in promoting a C-H activation reaction pathway.

3.6. Conclusion

The synthetic route taken to the target inherently chiral calix[4]arenes is an extremely facile and generally high yielding approach. Making use of the carbamate directing group has the advantage of being easily removed through TBAF hydrolysis as well as having the potential of hosting a wide variety of R groups, chiral or achiral. In terms of the carbamates directing properties, its ability to act as a directing group for C-H activation as well as a more than worthy *ortho* activator for electrophilic aromatic substitution, makes it a valuable strategy for the synthesis of *meta*-functionalized inherently chiral calix[4]arenes. Finally, we have shown that when utilizing the $Pd(OAc)_2$ in the bromination reactions, a marginally higher yield was reported and even a higher specific rotation angle, indicating that it does contribute slightly to the overall synthesis of the target compounds. Further improvement can be made for the diastereoselectivity of *meta*-functionalization by limiting the reactivity of the competing electrophilic aromatic substitution.

3.7. Experimental

5,11,17,23-tetra-*tert*-butyl-calix[4]arene (3)[3]



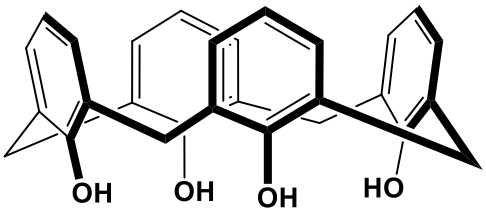
p-tert-Butyl phenol (66.0 g, 444 mmol), NaOH pellets (0.9 g, 20 mmol in 2 mL of H_2O) and a 37% formaldehyde solution (41.5 mL, 554 mmol, 1.3 eq) were added to a 2 L 3-neck round-bottomed flask equipped with a mechanical stirrer and mounted on a heating mantle. A steady flow of nitrogen was allowed to flow through the flask and the reaction was heated to 120 °C for at least 30 minutes until the formation of a yellow viscous substance occurred. Stirring of the reaction was stopped and left to cool to room temperature before diphenyl ether (550 mL) and toluene (50 mL) were added to the flask. The solution was then heated to 120 °C for 30 minutes to remove any residual H_2O. The contents were then first heated to 180 °C and then finally heated to reflux where the temperature was maintained for a further three hours. The contents were then cooled to room temperature and EtOAc (1 L) was added. The solution was left to stir at room temperature for a further 30 minutes and then left to stand overnight. The precipitate that formed was filtered

and washed with EtOAc (2 × 100 mL), acetic acid (2 × 100 mL) and acetone (2 × 100 mL). The white solid was dried under *vacuo* to produce calixarene **1** in 57% yield (40.94 mg).

^{1}H NMR collected for this compound compared well with literature data.[4]

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 10.36 (s, 4H, O*H*), 7.07 (s, 8H, Ar*H*), 4.28 (br. d, $^2J_{HH}$ = 13.2 Hz, 4H, ArC$H_{2(ax.)}$Ar), 3.51 (br. d, $^2J_{HH}$ = 13.3 Hz, 4H, ArC$H_{2(eq.)}$Ar), 1.23 (s, 36H, C(CH_3)$_3$).

25,26,27,28-Tetrahydroxycalix[4]arene (4)[5]

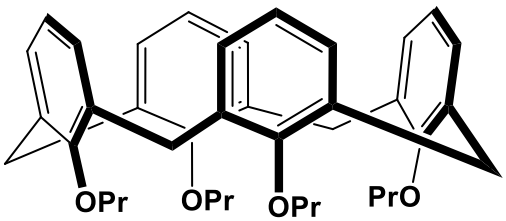


An oven dried 500 mL round-bottomed flask equipped with a magnetic stir bar and flushed with argon was charged with 10.0 g of compound **3** (15.4 mmol), phenol (2.90 g, 30.8 mmol) and dry toluene (100 mL). The solution was then cooled to 0 °C before $AlCl_3$ (9.86 g, 74.0 mmol) was added to the solution. The reaction was then allowed to warm to room temperature and was left to stir for a further two hours. The contents were then poured over crushed ice after which a 1 M HCl solution (100 mL) was added. The organic layer was then separated and first washed with H_2O (80 mL), then brine (80 mL), before being dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was then purified *via* trituration using hot methanol (50 mL) to produce a white precipitate that was filtered and dried under *vacuo* to yield compound **4** in 89% yield (5.83 g).

^{1}H NMR collected for this compound compared well with literature data.[5]

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 10.21 (s, 4H, O*H*), 7.07 (d, $^2J_{HH}$ = 7.6 Hz, 8H, Ar*H*), 6.74 (t, $^3J_{HH}$ = 7.5 Hz, 4H, Ar*H*), 4.27 (br. d, 4H, ArC$H_{2(ax.)}$Ar), 3.57 (br. d, 4H, ArC$H_{2(eq.)}$Ar).

25,26,27,28-Tetrapropoxycalix[4]arene (5)[7]



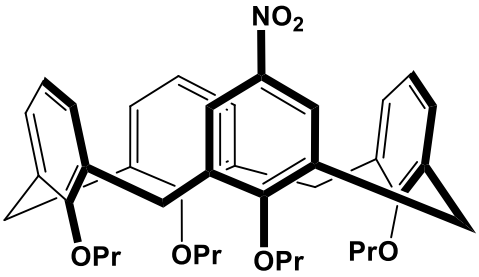
To an oven dried 3 neck round-bottomed flask equipped with a magnetic stir bar and flushed with argon, NaH in mineral oil (60%) (8.90 g, 17 eq) was suspended in *n*-hexanes (15 mL) and stirred for 10 minutes. The solvent was then subsequently removed using a syringe before of dry DMF (120 mL) was added to the flask. After cooling

the reaction to 0 °C, compound **4** (5.50 g) was added portionwise and left to stir for 30 minutes to allow for deprotonation to occur. Iodopropane (12.65 mL, 10 eq) was then added dropwise before the reaction was warmed to room temperature and left to stir overnight. A 1 M HCl solution (120 mL) was subsequently added to the reaction slowly to form a yellow precipitate. The precipitate was then filtered and washed with cold water. The precipitate was then stirred in hot methanol for a further 30 minutes before being cooled in a fridge for an additional three hours. The white solid was then filtered and dried under *vacuo* to afford compound **5** in 91% yield (6.99 g).

The characterisation data collected for this compound compared well to literature data.[7]

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 6.68 – 6.51 (m, 12H, Ar*H*), 4.47 (d, $^2J_{HH}$ = 13.3 Hz, 4H, ArC$H_{2(ax.)}$Ar), 3.91 – 3.81 (m, 8H, OCH_2CH_2), 3.16 (d, $^2J_{HH}$ = 13.4 Hz, 4H, ArC$H_{2(eq.)}$Ar), 2.06 – 1.85 (m, 8H, OCH_2CH_2CH_3), 1.01 (t, $^3J_{HH}$ = 7.5 Hz, 12H, OCH_2CH_2CH_3).

5-Nitro-25,26,27,28-tetrapropoxycalix[4]arene (6)[8]



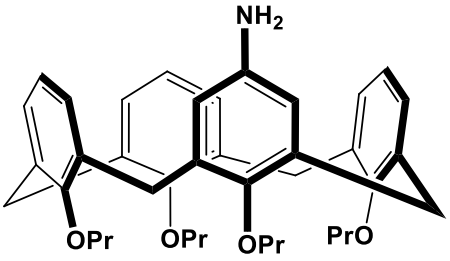
In a dry 2-necked round-bottomed flask equipped with a magnetic stir bar, a solution of compound **5** (2.00 g, 3.38 mmol) dissolved in DCM (200 mL) and H_2SO_4 (360 µL, 2 eq) was cooled to 0 °C. A 70% solution of nitric acid (215 µL, 1 eq) was then added at once and stirred for 5 minutes at 0 °C before being allowed to slowly warm to 15 °C. After 1 hour and 25 minutes the reaction was diluted with cold H_2O (200 mL). The product was extracted with DCM (80 mL x 3) after which the collected organic layers were combined and washed with sat. $NaHCO_3$ (100 mL x 3), brine (100 mL) and dried over $MgSO_4$ before removing the solvent *via* reduced pressure. The orange crude product was then purified using silica gel flash column chromatography (DCM:PET 25:75) to afford the mono-nitrated compound **6** as a pale-yellow solid in 46% yield (962 mg).

The characterisation data collected for this compound compared well to literature data.[8]

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.12 (s, 2H, Ar*H*), 6.94 (t, $^3J_{HH}$ = 7.4 Hz, 4H, Ar*H*), 6.84 (t, $^3J_{HH}$ = 7.4 Hz, 2H, Ar*H*), 6.25 – 6.20 (m, 3H, Ar*H*), 4.46 (dd, $^2J_{HH}$ = 18.6, 13.7 Hz, 4H, ArC$H_{2(ax.)}$Ar), 4.03 – 3.81 (m, 6H, OCH_2CH_2), 3.74 (t, $^3J_{HH}$ = 7.0 Hz, 2H, OCH_2CH_2), 3.19 (dd, $^2J_{HH}$ = 18.6, 13.7 Hz, 4H, ArC$H_{2(eq.)}$Ar), 1.98 – 1.82 (m, 8H,

$OCH_2CH_2CH_3$), 1.10 – 1.04 (m, 6H, $OCH_2CH_2CH_3$), 0.93 (t, $^3J_{HH}$ = 7.5 Hz, 6H, $OCH_2CH_2CH_3$).

5-Amino-25,26,27,28-tetrapropoxycalix[4]arene (7)[9]

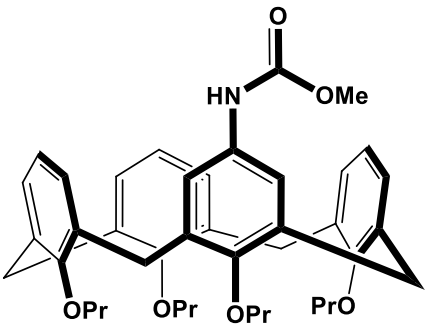


Compound **6** (350 mg, 0.549 mmol) and 10% palladium on carbon (87.6 mg, 0.15 eq) were suspended in 15 ml of EtOH (15 mL) in an oven dried 2-neck round-bottomed flask equipped with a reflux condenser and flushed with argon. The reaction was heated to reflux and left to stir for 30 minutes before hydrazine monohydrate (139 µL, 5.2 eq) was added to the flask and left to reflux for a further three hours. The reaction mixture was then cooled to room temperature before filtering the contents through a pad of Celite. The solvent was removed *via* reduced pressure to afford mono amino compound **7** as a white solid in nearly quantitative yield (327 mg, 98%).

The characterisation data collected for this compound compared well to literature data.[10]

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 6.72 – 6.52 (m, 9H, Ar*H*), 5.95 (s, 2H, Ar*H*), 4.43 (dd, $^2J_{HH}$ = 24.4, 13.3 Hz, 4H $ArCH_{2(ax.)}Ar$), 3.91 – 3.70 (m, 8H, OCH_2CH_2), 3.16 (d, $^2J_{HH}$ = 13.4 Hz, 2H, $ArCH_{2(eq.)}Ar$), 3.10 (s, 2H, NH_2), 3.03 (d, $^2J_{HH}$ = 13.3 Hz, 2H, $ArCH_{2(eq.)}Ar$), 2.05 – 1.79 (m, 8H, $OCH_2CH_2CH_3$), 1.02 – 0.96 (m, 12H, $OCH_2CH_2CH_3$).

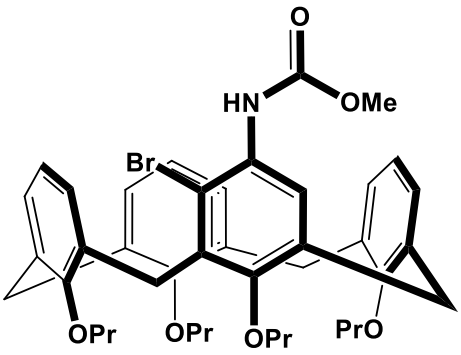
5-Methyl carbamate-25,26,27,28-tetrapropoxycalix[4]arene (8)[11]



To an oven dried 2-neck round-bottomed flask, compound **7** (375 mg) dissolved in DCM (20 mL) and pyridine (74.0 µL, 1.5 eq) was added. After cooling the mixture to 0 °C, methyl chloroformate (71.5 µL, 1.5 eq) was added. The reaction was then allowed to warm to room temperature and after 30 minutes the reaction had run to completion. H_2O (20 mL) was added to the reaction mixture and the product was subsequently extracted with DCM (10 mL x 3). The organic layers were combined and first washed with a dilute HCl solution (0.2 M, 25 mL) brine (25 mL) and dried over $MgSO_4$ before removing excess solvent under *vacuo*. The crude product was purified *via* silica gel flash column chromatography (EtOAc:PET 5:95) to afford compound **8** as a colourless glass (370 mg, 90%). R_f = 0.66 (10:90 EtOAc:PET) ; **Mp** = 124-128 °C; **IR (ATR, cm^{-1}):** 3374 (N-H),

2960 and 2873 (C-H)**,** 1727 (C=O), 1529 (arene), 1454 (C=C), 1211 and 1191 (C-O-C), 1005 and 966 (C-N), 757 (C-H); **^{1}H NMR (300 MHz, CHLOROFORM-*d*)** δ ppm 6.86 – 6.36 (m, 11H, Ar*H*), 6.13 (s, 1H, N*H*R), 4.46 (dd, 2H, $^{2}J_{HH}$ = 13.4, 8.1 Hz, ArC$H_{2(ax.)}$Ar), 3.92 – 3.76 (m, 8H, OCH_2CH_2), 3.70(s, 3H, OCH_3), 3.15 (dd, 2H, $^{2}J_{HH}$ = 13.4, 10.1 Hz, ArC$H_{2(eq.)}$Ar), 2.00 – 1.84 (m, 8H, CH_2CH_2CH_3), 1.08 – 0.94 (m, 12H, CH_2CH_2CH_3); **^{13}C{1H} (300 MHz, CHLOROFORM-*d*)** δ ppm 157.0 (Ar*C*), 156.5 (NH*C*OO), 153.0 (Ar*C*), 135.5 (Ar*C*), 135.3 (Ar*C*), 135.0 (Ar*C*), 131.5 (Ar*C*), 128.5 (Ar*C*), 128.4 (Ar*C*), 128.1 (Ar*C*), 122.1 (Ar*C*), 121.6 (Ar*C*), 119.4 (Ar*C*), 76.80 (O*C*H_2CH_2), 76.76 (O*C*H_2CH_2), 52.20 (O*C*H_3), 31.19 (Ar*C*H_2Ar), 31.12 (Ar*C*H_2Ar), 23.43 (OCH_2*C*H_2CH_3), 23.37 (OCH_2*C*H_2CH_3), 23.31 (OCH_2*C*H_2CH_3), 10.56 (OCH_2CH_2*C*H_3), 10.35 (OCH_2CH_2*C*H_3); **HRMS–Positive:** m/z $[M+NH_4]^+$ calcd. for $C_{42}H_{55}N_2O_6$: 683.406; found 683.405.

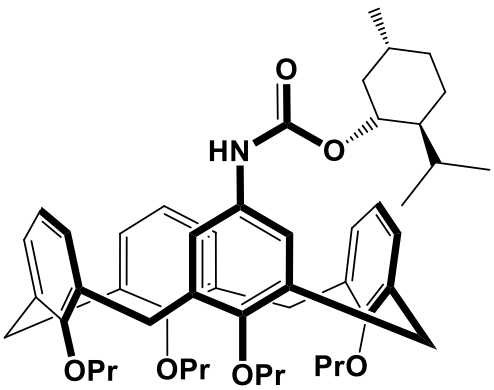
5-Methyl carbamate-6-bromo-25,26,27,28-tetrapropoxycalix[4]arene (9)[14]



A Shlenk equipped with a magnetic stir bar and flushed with argon was charged with compound **8** (97 mg, 0.146 mmol), NBS (28 mg, 0.157 mmol, 1.1 eq), PTSA (14 mg, 0.071 mmol, 0.5 eq) and $Pd(OAc)_2$ (1.6 mg, 0.007 mmol, 0.05 eq) in DCE (2 mL). The contents were heated to 60 °C and left to stir for two and a half hours. After the allotted time, the reaction was cooled to room temperature and diluted with DCM (5 mL) before being poured into H_2O (10 mL). The product was extracted with DCM (5 mL x 3) and the combined organic layers were subsequently washed with 10% HCl (10 mL), sat. $NaHCO_3$ (10 mL) and finally brine (10 mL). The solution was then dried over $MgSO_4$ and the solvent was removed *via* reduced pressure. Purification was achieved *via* silica gel flash column chromatography (2:98 EtOAc:PET) to yield compound **9** as an amorphous glass racemic mixture (90 mg, 82%). R_f = 0.7 (DCM); **Mp =** 174-184 °C; **IR (ATR, cm^{-1}):** 2957 and 2873 (C-H), 2365 (N-H), 1705 (C=O), 1455 (C=C), 1192 and 1087 (C-O-C), 1005 and 965 (C-N), 762 (C-H); **^{1}H NMR (300 MHz, CHLOROFORM-*d*)** δ ppm 7.86 (s, 1H, N*H*), 7.13 (d, 1H, $^{2}J_{HH}$ = 5.6 Hz, Ar*H*), 7.09 (d, 2H, $^{2}J_{HH}$ = 7.4 Hz, Ar*H*), (t, 1H, $^{3}J_{HH}$ = 7.4 Hz, Ar*H*) 6.40 – 6.09 (m, 6H, Ar*H*), 4.49 – 4.36 (m, 4H, ArC$H_{2(ax.)}$Ar), 4.11 – 3.81 (m, 4H, OCH_2CH_2 and 1H, ArC$H_{2(eq.)}$Ar), 3.83 (s, 3H, OCH_3), 3.74 – 3.63 (m, 4H, OCH_2CH_2), 3.27 – 3.06 (m, 3H, ArC$H_{2(eq.)}$Ar), 2.08 – 1.79 (m, 8H, CH_2CH_2CH_3), 1.13 – 1.07 (m, 6H, CH_2CH_2CH_3), 0.95 – 0.86 (m, 6H, CH_2CH_2CH_3); **^{13}C{1H} (300 MHz, CHLOROFORM-*d*)** δ ppm 158.0 (Ar*C*), 155.3 (NH*C*OO), 154.6 (Ar*C*),154.3

(Ar*C*), 137.6 (Ar*C*), 137.1 (Ar*C*), 137.0 (Ar*C*), 136.7 (Ar*C*), 135.5 (Ar*C*), 133.5 (Ar*C*), 132.4 (Ar*C*), 132.1 (Ar*C*), 130.2 (Ar*C*), 129.0 (Ar*C*), 128.9 (Ar*C*), 127.9 (Ar*C*), 127.8 (Ar*C*), 127.5 (Ar*C*), 126.6 (Ar*C*), 122.3 (Ar*C*), 122.3 (Ar*C*), 121.9 (Ar*C*), 121.0 (Ar*C*), 77.11 (O*C*H$_2$CH$_2$), 76.98 (O*C*H$_2$CH$_2$), 76.58 (O*C*H$_2$CH$_2$), 52.57 (O*C*H$_3$), 31.16 (ArCH$_2$Ar), 31.08 (Ar*C*H$_2$Ar), 31.04 (ArCH$_2$Ar), 30.24 (Ar*C*H$_2$Ar), 23.65 (OCH$_2$*C*H$_2$CH$_3$), 23.59 (OCH$_2$*C*H$_2$CH$_3$), 23.10 (OCH$_2$*C*H$_2$CH$_3$), 23.04 (OCH$_2$*C*H$_2$CH$_3$), 10.94 (OCH$_2$CH$_2$*C*H$_3$), 10.91 (OCH$_2$CH$_2$*C*H$_3$), 9.97 (OCH$_2$CH$_2$*C*H$_3$), 9.96 (OCH$_2$CH$_2$*C*H$_3$); **HRMS–Positive:** m/z [M+NH$_4$]$^+$ calcd. for C$_{42}$H$_{54}$BrN$_2$O$_6$: 761.317; found 761.316.

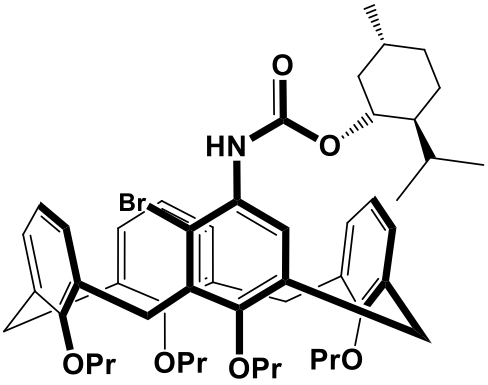
5-Menthyl carbamate-25,26,27,28-tetrapropoxycalix[4]arene (10)[11]



In an oven dried 2-neck round-bottomed flask, compound **9** (500 mg, 0.823 mmol) was dissolved in DCM (40 mL) and cooled to 0 °C. Pyridine (79.5 µL, 0.987 mmol, 1.2 eq) and menthyl chloroformate (209 µL, 0.987 mmol, 1.2 eq) were subsequently added and the mixture was warmed to room temperature. After 15 minutes, the contents of the flask were poured into H$_2$O (40 mL) and extracted with DCM (20 mL x 3). The organic layers were then combined and first washed once with dilute HCl solution (25 mL, 0.2 M) followed by brine (25 mL) and finally dried over MgSO$_4$. The solvent was removed under reduced pressure and the crude product was purified *via* silica gel flash column chromatography (3:97 EtOAc:PET) to afford compound **10** as a colourless glass (650 mg, 98%). ***R$_f$*** **=** 0.47 (10:90 EtOAc:PET) **Mp =** 68-72 °C **IR (ATR, cm^{-1}):** 2957, 2923 and 2872 (C-H), 1697 (C=O), 1454 (C=C), 1210 (C-O-C), 1006 and 966 (C-N), 757 (C-H); **^{1}H NMR (600 MHz, CHLOROFORM-*d*)** δ ppm 6.84 – 6.39 (m, 11H, Ar*H*), 6.06 (br. s, 1H, N*H*R), 4.60 (td, $^2J_{HH}$ = 10.8, 4.1 Hz, 1H, OC*H*hexyl) 4.44 (dd, $^2J_{HH}$ = 18.9, 13.4 Hz, 4H, ArC$H_{2(ax.)}$Ar), 3.91 – 3.75 (m, 8H, OCH_2CH$_2$), 3.14 (dd, $^2J_{HH}$ = 22.4, 13.5 Hz, 4H, ArC$H_{2(eq.)}$Ar), 2.06 (d, $^2J_{HH}$ = 11.8 Hz, 1H, C*H*C$_3$H$_7$), 1.97 – 1.85 (m, 8H, CH$_3$CH_2CH$_3$), 1.72 – 1.66 (m, 2H, hexyl*H*), 1.50 (tdd, $^3J_{HH}$ = 12.1, 6.7, 3.4 Hz, 1H, hexyl*H*), 1.38 – 1.29 (m, 1H, hexyl*H*), 1.12 – 0.83 (m, 3H, hexyl*H*), 1.03 – 0.95 (m, 12H, OCH$_2$CH$_2$CH_3), 0.91 (dd, $^2J_{HH}$ = 6.7, 3.3 Hz, 6H, CH(CH_3)$_2$), 0.79 (d, $^2J_{HH}$ = 7.0 Hz, 3H, CHCH_3). **^{13}C{1H} (400 MHz, CHLOROFORM-*d*)** δ ppm 157.0(Ar*C*), 156.5 (NH*C*OO), 152.7 (Ar*C*), 135.6 (Ar*C*), 135.3 (Ar*C*), 135.1 (Ar*C*), 132.0 (Ar*C*), 128.4 (Ar*C*), 128.4 (Ar*C*), 128.1 (Ar*C*), 122.1 (Ar*C*), 122.1 (Ar*C*), 121.7 (Ar*C*), 118.7 (Ar*C*) 76.81 (O*C*Hhexyl), 76.78 (O*C*H$_2$CH$_2$), 76.77 (O*C*H$_2$CH$_2$), 47.53 (hexyl*C*), 41.52

(hexyl*C*), 34.45 (hexyl*C*), 31.52 (Ar*C*H$_2$Ar), 31.24 (Ar*C*H$_2$Ar), 31.14 (Ar*C*H$_2$Ar), 26.38 (*C*H(CH$_3$)$_2$), 23.60 (hexyl*C*), 23.43 (hexyl*C*), 23.36 (OCH$_2$*C*H$_2$CH$_3$), 23.34 (OCH$_2$*C*H$_2$CH$_3$), 23.33 (OCH$_2$*C*H$_2$CH$_3$), 22.20 (CH(*C*H$_3$)$_2$), 21.00 (CH(*C*H$_3$)$_2$), 16.54 (hexyl*C*H$_3$), 10.57 (OCH$_2$CH$_2$*C*H$_3$), 10.56 (OCH$_2$CH$_2$*C*H$_3$), 10.37 (OCH$_2$CH$_2$*C*H$_3$). **HRMS–Positive:** m/z [M+NH$_4$]$^+$ calcd. for $C_{51}H_{71}N_2O_6$: 807.531; found 807.531.

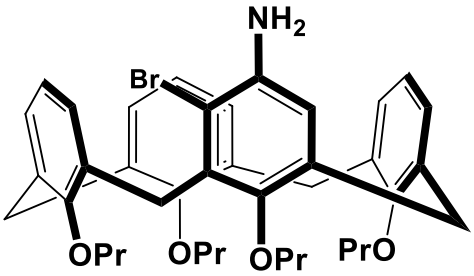
5-Menthyl carbamate-6-bromo-25,26,27,28-tetrapropoxycalix[4]arene (11)[14]



An oven dried 5 mL Schlenk equipped with a magnetic stir bar was charged with NBS (14.9 mg, 0.084 mmol, 1.1 eq), PTSA·H$_2$O (7.2 mg, 0.038 mmol, 0.5 eq), Pd(OAc)$_2$ (0.9 mg, 0.004 mmol, 0.05 eq) and DCM (1 mL). The reaction vessel was subjected to five freeze pump thaw cycles before being flushed with argon and cooled –35 °C. Once cooled, compound **10** (60 mg, 0.078 mmol) was added at once and the reaction was left to stir at –35 °C for a further four hours. After the time had elapsed, the reaction contents were diluted with DCM (10 mL) and washed with a 10% HCl solution (15 mL). The aqueous phase was extracted with DCM (10 mL × 3) before combining the organic phase and washing it once with sat. NaHCO$_3$ (20 mL) and finally brine (20 mL). The solution was finally dried over MgSO$_4$ and concentrated under *vacuo*. The crude product was then purified *via* silica gel flash column chromatography (1:99 EtOAc:PET) to produce compound **11** as a colourless glass (61 mg, 91%). ***R$_f$*** **=** 0.27 (4:96 EtOAc:PET); **Mp =** 74-84 °C; **IR (ATR, cm^{-1}):** 3411 (N-H), 2957, 2931 and 2872 (C-H), 1732 (C=O), 1509 (arene), 1455 (C=C), 1209 and 1187 (C-O-C), 1005 and 966 (C-N), 756 (C-H); **^{1}H NMR (600 MHz, CHLOROFORM-*d*)** δ ppm 7.91 (d, $^2J_{HH}$ = 9.2 Hz, 1H, N*H*), 7.15 – 7.03 (m, 3H, Ar*H*), 6.94 – 6.86 (m, 1H, Ar*H*), 6.34 – 6.09 (m, 6H, Ar*H*), 4.77 – 4.62 (m, 1H, OC*H*hexyl), 4.48 – 4.36 (m, 4H, ArC$H_{2(ax.)}$Ar), 4.10 – 3.79 (m, 4H, OCH_2CH$_2$ and 1H, ArC$H_{2(eq.)}$Ar), 3.72 – 3.61 (m, 4H, OCH_2CH$_2$), 3.24 – 3.09 (m, 3H, ArC$H_{2(eq.)}$Ar), 2.23 – 2.03 (m, 2H, hexyl*H*), 2.01 – 1.80 (m, 8H, CH$_3$CH_2CH$_3$), 1.72 (d, $^2J_{HH}$ = 11.6 Hz, 2H, hexyl*H*), 1.51 – 1.38 (m, 1H, hexyl*H*), 1.35 – 1.22 (m, 1H, hexyl*H*), 1.20 – 0.79 (m, 3H, hexyl*H*), 1.09 (t, $^3J_{HH}$ = 7.3 Hz, 6H, CH$_2$CH$_2$CH_3), 0.98 – 0.83 (m, 6H, CH$_2$CH$_2$CH_3, 6H, CH(CH_3)$_2$ and 3H, CHCH_3); **^{13}C{1H} (400 MHz, CHLOROFORM-*d*)** δ ppm 158.1 (Ar*C*), 158.1 (NH*C*OO), 155.3 (Ar*C*), 155.2 (Ar*C*), 137.2 (Ar*C*), 137.2 (Ar*C*), 137.1 (Ar*C*), 136.7 (Ar*C*), 133.5 (Ar*C*), 132.5 (Ar*C*), 130.6 (Ar*C*), 129.0 (Ar*C*), 129.0 (Ar*C*), 128.9 (Ar*C*), 127.9 (Ar*C*), 127.7 (Ar*C*), 127.5 (Ar*C*), 122.3 (Ar*C*), 121.9 (Ar*C*), 77.22 (O*C*Hhexyl), 77.01

(O*C*H$_2$CH$_2$), 76.99 (O*C*H$_2$CH$_2$), 76.59 (O*C*H$_2$CH$_2$), 75.55 (O*C*H$_2$CH$_2$), 47.42 (hexyl*C*), 47.35 (hexyl*C*), 41.45 (hexyl*C*), 31.64 (Ar*C*H$_2$Ar), 31.59 (Ar*C*H$_2$Ar), 31.19 (Ar*C*H$_2$Ar), 31.09 (Ar*C*H$_2$Ar), 26.52 (*C*H(CH$_3$)$_2$), 26.44 (*C*CH$_3$), 23.67 (OCH$_2$*C*H$_2$CH$_3$), 23.12 (OCH$_2$*C*H$_2$CH$_3$), 23.04 (OCH$_2$*C*H$_2$CH$_3$), 22.21 (OCH$_2$*C*H$_2$CH$_3$), 20.99 (CH(*C*H$_3$)$_2$), 20.93 (CH(*C*H$_3$)$_2$), 16.73 (hexyl*C*H$_3$), 10.94 (OCH$_2$CH$_2$*C*H$_3$), 10.93 (OCH$_2$CH$_2$*C*H$_3$), 9.99 (OCH$_2$CH$_2$*C*H$_3$), 9.98 (OCH$_2$CH$_2$*C*H$_3$); **HRMS–Positive:** m/z [M+NH$_4$]$^+$ calcd. for C$_{51}$H$_{70}$BrN$_2$O$_6$: 885.442; found 885.443.

5-Amino-6-bromo-25,26,27,28-tetrapropoxycalix[4]arene (12)[13,15,18]



In an oven dried 2-neck round-bottomed flask equipped with a reflux condenser and magnetic stir bar was charged with calixarene **11** (110 mg, 0.127 mmol), a 1 M solution of TBAF in THF, (1.27 mL, 10 eq) and THF (10 mL). The contents were heated to reflux and left to stir for 36 hours. After the time had elapsed, the solution was concentrated and then diluted with EtOAc (15 mL) before being washed with H$_2$O (10 mL × 6) and finally brine (10 mL). The liquid was dried over MgSO$_4$ and concentrated *via* reduced pressure. The crude product was then purified firstly *via* silica gel flash column chromatography (EtOAc:PET 1:9) and then heated at 80 °C under reduced pressure for eight hours to afford compound **12** as a yellow solid (72 mg, 83%). ***R$_f$*** **=** 0.33 (5:95 EtOAc:PET); **Mp =** 130-136 °C; **IR (ATR, cm^{-1}):** 1264 (C-N), 731 (C-H), 703 (C-H); **^{1}H NMR (400 MHz, CHLOROFORM-*d*)** δ ppm 7.10 (d, $^2J_{HH}$ = 7.4 Hz, 2H, Ar*H*), 6.91 (t, $^3J_{HH}$ = 7.4 Hz, 1H, Ar*H*), 6.61 (s, 1H, Ar*H*), 6.30 – 6.12 (m, 6H, Ar*H*), 4.49 – 4.32 (m, 4H, ArC*H*$_{2(ax.)}$Ar), 4.06 – 3.79 (m, 4H, OC*H*$_2$CH$_2$, 2H, N*H*$_2$ and 1H, ArC*H*$_{2(eq.)}$Ar), 3.75 – 3.62 (m, 4H, OC*H*$_2$CH$_2$), 3.21 – 3.00 (m, 3H, ArC*H*$_{2(eq.)}$Ar), 2.04 – 1.82 (m, 8H, CH$_3$C*H*$_2$CH$_3$), 1.10 (t, $^3J_{HH}$ = 7.4 Hz, 6H, CH$_2$CH$_2$C*H*$_3$), 0.96 – 0.84 (m, 6H, CH$_2$CH$_2$C*H*$_3$); **^{13}C{1H} (400 MHz, CHLOROFORM-*d*)** δ ppm 158.1 (Ar*C*), 155.3 (Ar*C*), 150.1 (Ar*C*), 139.0 (Ar*C*), 137.6 (Ar*C*), 137.3 (Ar*C*), 137.1 (Ar*C*), 136.6 (Ar*C*), 133.5 (Ar*C*), 133.3 (Ar*C*), 132.6 (Ar*C*), 129.0 (Ar*C*), 129.0 (Ar*C*), 127.7 (Ar*C*), 127.6 (Ar*C*), 127.3 (Ar*C*), 126.8 (Ar*C*), 122.2 (Ar*C*), 121.9 (Ar*C*), 115.7 (Ar*C*), 110.4 (Ar*C*), 77.06 (O*C*H$_2$CH$_2$), 76.95 (O*C*H$_2$CH$_2$), 76.55 (O*C*H$_2$CH$_2$), 31.18 (Ar*C*H$_2$Ar), 31.11 (Ar*C*H$_2$Ar), 30.89 (Ar*C*H$_2$Ar), 29.93 (Ar*C*H$_2$Ar), 23.66 (OCH$_2$*C*H$_2$CH$_3$), 23.62 (OCH$_2$*C*H$_2$CH$_3$), 23.10 (OCH$_2$*C*H$_2$CH$_3$), 22.97 (OCH$_2$*C*H$_2$CH$_3$), 10.95 (OCH$_2$CH$_2$*C*H$_3$), 10.94 (OCH$_2$CH$_2$*C*H$_3$), 10.01 (OCH$_2$CH$_2$*C*H$_3$), 9.99 (OCH$_2$CH$_2$*C*H$_3$). **HRMS–Positive:** m/z [M+H]$^+$ calcd. for C$_{40}$H$_{49}$BrNO$_4$: 686.284; found 686.285.

3.8. References

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F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Faldrich%2F378712%3Flang%3Den (accessed February 12, 2019).

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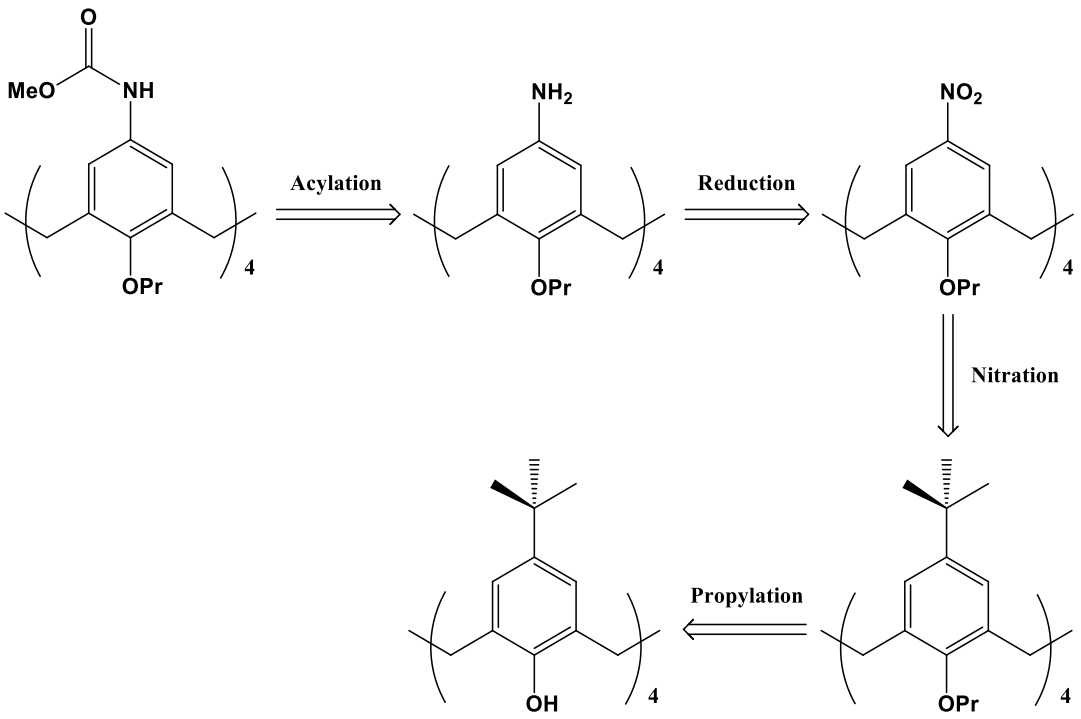
4. Chapter 4 – Tetra-substituted carbamate calix[4]arenes

4.1. Introduction

The mono-functionalized carbamate calix[4]arene, both chiral and achiral, showed that the carbamate functionality proved to be an efficient directing group for the *meta*-functionalization of the calix[4]arene molecule. Due to the functional group's *ortho* activating properties, it was shown that when synthesizing *meta*-functionalized inherently chiral calix[4]arenes, the need for $Pd(OAc)_2$ was not necessary. It proved to be a more than successful strategy in synthesizing these compounds in extremely mild conditions. Taking this into consideration, it seemed worthwhile to investigate whether this could be performed on a tetra-functionalized system, a prospect that was previously thought to be unlikely with no reported literature for generating inherently chiral calix[4]arenes of C_4 symmetry through direct modification.[1]

Considering the synthetic pathway chosen for the mono-carbamate calix[4]arenes, accessing the corresponding tetra-substituted analogue could be achieved in a similar manner. Previous work done by Reinhoudt and co-workers,[2] demonstrated that the tetranitro precursor could be synthesized through an *ipso*-nitration of a *tert*-butyl calix[4]arene. Therefore, this would eliminate the de-butylation synthetic step used in chapter 3. The retro-synthetic analysis is depicted below in Scheme 4.1.

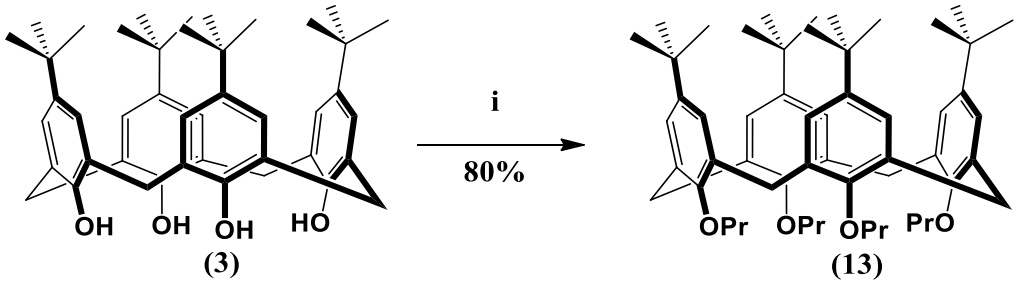


Scheme 4.1: Retrosynthetic analysis of the tetra-functionalized methyl carbamate calix[4]arene.

4.2. Synthesis of tetracarbamate calix[4]arene

4.2.1. Propylation of parent calix[4]arene (**13**)

As in the case of the mono-functionalized chapter, it was necessary to lock the calix[4]arene skeleton into its cone conformation by propylating the four hydroxy groups on the compound's narrow rim. However, keeping in mind that the following *ipso*-nitration required the *tert*-butyl groups to remain bonded to the calix[4]arene, the propylation was carried out on the parent calixarene **3** instead of its debutylated derivative **4**. Loosely following a procedure reported by Reinhoudt and co-workers,[3] the *tert*-butyl propylated calix[4]arene was synthesized in high yield without any complications. The conditions are outlined below in Scheme 4.2.

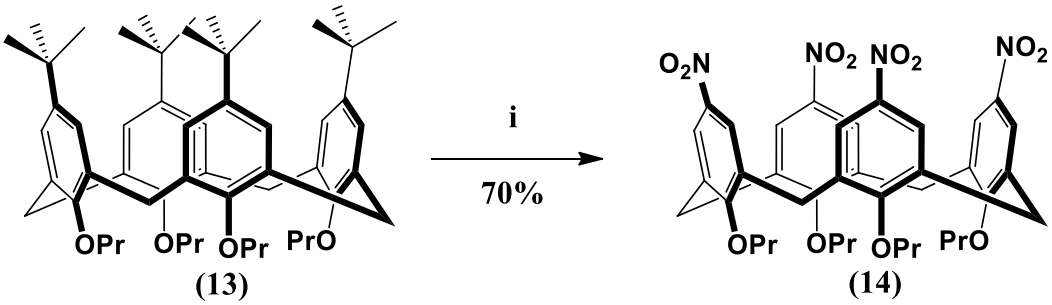


Scheme 4.2: Propylation of parent calixarene **3** to afford calixarene **13**. i) NaH (11 eq), iodo-propane (10 eq), DMF, RT, 12 hrs.

The synthesis was carried out in a dried round-bottom flask. The NaH in 60% mineral oil was suspended in 15 mL of *n*-hexanes and stirred for 15 minutes to strip the oil from the base. Once the 15 minutes had elapsed, the solvent was carefully removed *via* syringe while maintaining an inert atmosphere within the flask. Dry DMF was subsequently added to the base and the mixture was cooled to 0 °C. The parent calix[4]arene was then carefully added portionwise as the formation of H_2 gas evolved due to the base deprotonating the hydroxyl groups. After deprotonation, iodo-propane was added dropwise over 10 minutes to the cooled reaction before allowing the contents to slowly warm to room temperature. The reaction was then left to run overnight. The next morning, the now opaque yellow liquid, was cooled to 0 °C before adding a 2 M HCl solution carefully to precipitate the product. The yellow solid was then filtered and washed with cold methanol. The crude product was finally triturated in hot methanol and filtered to produce the propylated product **13** as a white solid. The ^{1}H NMR data obtained for the compound matched the reported literature data (see experimental section 4.8).[3]

4.2.2. *Ipso*-nitration (**14**)

Reinhoudt and co-workers demonstrated that the tetranitro calix[4]arene could be synthesized as the sole product in high yield (98%) by reacting a propylated *tert*-butyl calix[4]arene with trifluoroacetic acid and 100% HNO_3.[2] A similar approach was taken, however, a 70% solution of HNO_3 was used instead of the 100% solution, as it was readily available. Scheme 4.3 below outlines the conditions used.



Scheme 4.3: Synthesis of tetranitro calixarene **14**. i) 70% HNO_3 (20 eq), TFA (15 eq), DCM, RT, 4 hrs.

The synthesis was carried out in a round-bottomed flask at room temperature, unlike in the mono-nitration where carefully controlled temperatures were vital for maximizing the yield of the mono-functionalized product. Both acids were added to a well-stirred solution of the calix[4]arene starting material **13** in DCM at room temperature. Upon addition of the HNO_3 the solution would gradually darken until it appeared almost black with a slight purple tinge. The solution was left to stir for a further four hours, after which it had lightened to a red/orange colour, a good indication that the reaction had run to completion. The same procedure used in the mono-nitrated synthesis was followed for the work-up of this reaction. Purification was achieved by silica gel flash column chromatography (EtOAc:PET 2:8) and recrystallization using DCM as the solvent and *n*-hexanes as the anti-solvent. Due to the compounds highly symmetrical structure, the thin needle-like pale-yellow crystals would start to grow on the interface of the two solvents within a few minutes. Unlike in the case of Reinhoudt and co-workers' paper,[2] the tetra-nitrated calix[4]arene was never the sole product. TLC analysis showed the presence of, presumably, the di- and tri-nitrated products, but in trace amounts, not enough to isolate and characterize. Furthermore, the presence of the side products changed the approach of purification reported in Reinhoudt's paper. Instead of filtering the crude material through a short silica plug, a conventional column was needed. The difference in the obtained results can be attributed to the concentration of the HNO_3 solution used. Understandably, the

stronger 100% HNO_3 solution would have 'pushed' the reaction to completion quicker (a reaction time of 5-20 minutes was reported) and formed the desired product as the only compound, hence the reported 98% yield, compared to the yields obtained in this study ranging between 70 – 75%.

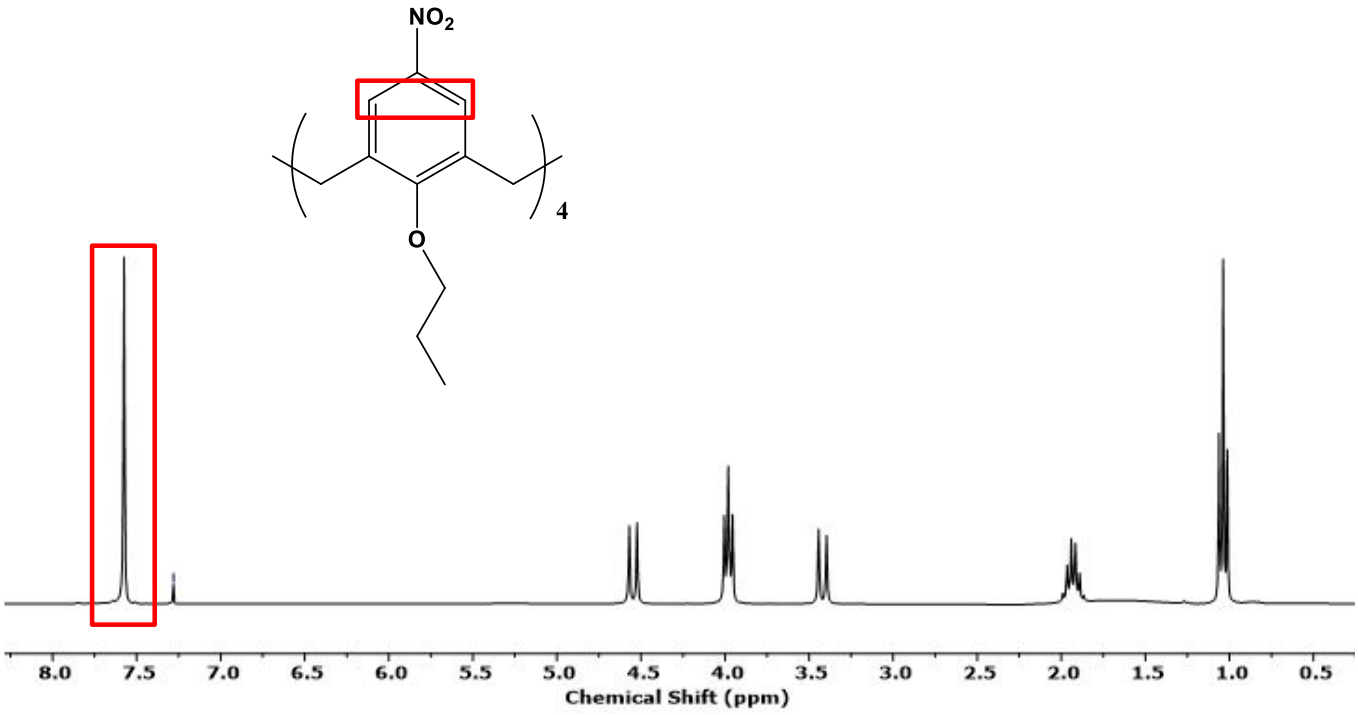
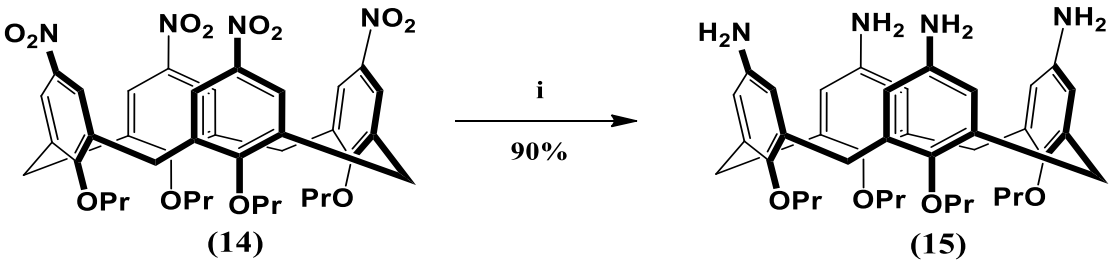


Figure 4.1: ^1H NMR spectra ($CDCl_3$) for tetranitro calixarene **14**.

The high degree of symmetry the pale-yellow solid possessed, resulted in a beautifully simple ^1H NMR spectrum (Figure 4.1). The aryl protons are represented by one singlet resonating at δ 7.55 ppm (highlighted in red), slightly downfield of the $CDCl_3$ solvent peak at δ 7.26 ppm. The downfield shift of these protons is owed to the electron withdrawing properties of the adjacent nitro groups, effectively pulling electrons out of their corresponding aromatic rings and deshielding their protons. The signals emanating from the propoxy chain of the molecule showed the compound's high symmetry perfectly. The splitting patterns of the three signals diligently followed the n + 1 rule. Firstly, at δ 3.96 ppm the hydrogen atoms of the carbon closest to the oxygen split into a triplet, secondly, at δ 1.91 ppm the equivalent protons of the centre carbon a sextet is observed and finally, at δ 1.02 ppm again we see a triplet for the protons attached to the terminal carbon.

4.2.3. Tetranitro reduction (**15**)

The reduction of the tetra-nitrated calixarene **14** to the amine was achieved in rather trying conditions. The synthetic procedure for the tetraamino calixarene **15** depicted below in Scheme 4.4, was a result of combining two different procedures described previously.[4,5] It proved to be an effective method for obtaining the compound, however, the success of this molecule's synthesis did not come as easily as was first envisaged. Before the reported method was chosen, several different reductive reaction procedures were attempted which included: making use of H_2 and palladium on carbon, Fe powder in combination with H_2O and glacial acetic acid and Raney nickel and hydrazine hydrate. All these attempts lead to a complex mixture of reduced and non-reduced calix[4]arene products that required purification using silica gel flash column chromatography. Although purification was possible, the yields obtained for the desired tetraamino calix[4]arene ranged between 30% and 60%, which were considered unsatisfactory, especially when taking into account the amount of overall mass lost.

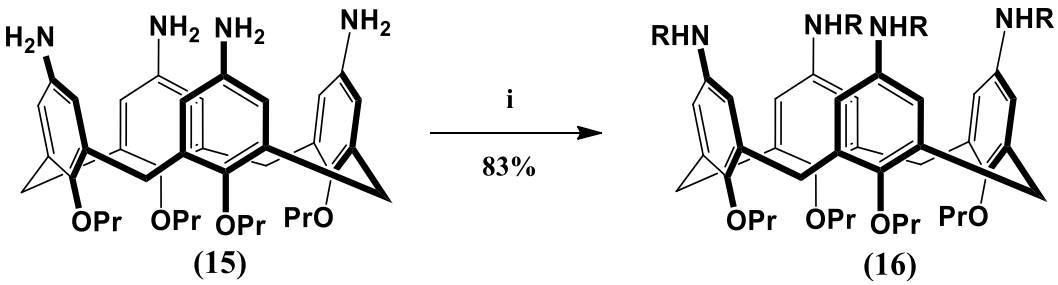


Scheme 4.4: Reduction of tetranitro calixarene **14** to tetraamino calixarene **15**. i) $NH_2NH_2{\cdot}H_2O$ (80 eq), Pd/C (0.15 eq), EtOH, reflux, 4 hrs.

The solution was found to be as follows: palladium catalyst and starting material were suspended in EtOH and heated to reflux before the hydrazine hydrate was added in one portion. After leaving the reaction to continue for a further three to four hours, the solution was cooled down to room temperature and subsequently filtered through Celite to afford the reduced product **15** as a white solid which needed no further purification. The amount of hydrazine appeared excessive, therefore, a few test reactions were carried out in order to see whether the amount of the reagent used could be lowered. However, even when up to 60 equivalents of hydrazine was used, the reaction yielded calix[4]arenes that still possessed the unreduced nitro groups. The ^{1}H NMR data obtained matched with the reported data perfectly (see experimental section 4.8).[4] Again, as in the case of the mono-amino calixarene **7**, there was an upfield shift for the aryl protons and the four amine's N-H signals appeared at the same frequency as the methylene bridge's equatorial protons.

4.2.4. Tetra-acylation (**16**)

Synthesizing the tetracarbamate calix[4]arene occurred with little to no trouble. Following a general procedure described in previous literature,[6] with slight adjustment, calixarene **16** was synthesized consistently in moderate to good yield (Scheme 4.5).



Scheme 4.5: Acylation of tetraamino calixarene **15** to form tetra-*N*-methyl carbamate calixarene **16**. i) Pyridine (12 eq), methyl chloroformate (12 eq), DCM, RT, 30 minutes. R = $COOCH_3$

The synthesis was carried out in a 2-neck round-bottomed flask charged with a well-stirred solution of calixarene **15** and pyridine in DCM. The solution was cooled to 0 °C before methyl chloroformate was injected. The solution colour would immediately change from a very pale peach-like colour to a more intense clear orange. The reaction was then allowed to warm up to room temperature and allowed to stir for a further 20 to 30 minutes, after which, from TLC evidence, the reaction had run to completion. The crude mixture, comprising of the desired product, unreacted methyl chloroformate and pyridine, was purified using silica gel flash column chromatography and recrystallization using a DCM and methanol mixture to produce beautiful needle-like crystals with a pale peach-like colour. The compound's ^{1}H NMR spectrum can be seen below in Figure 4.2.

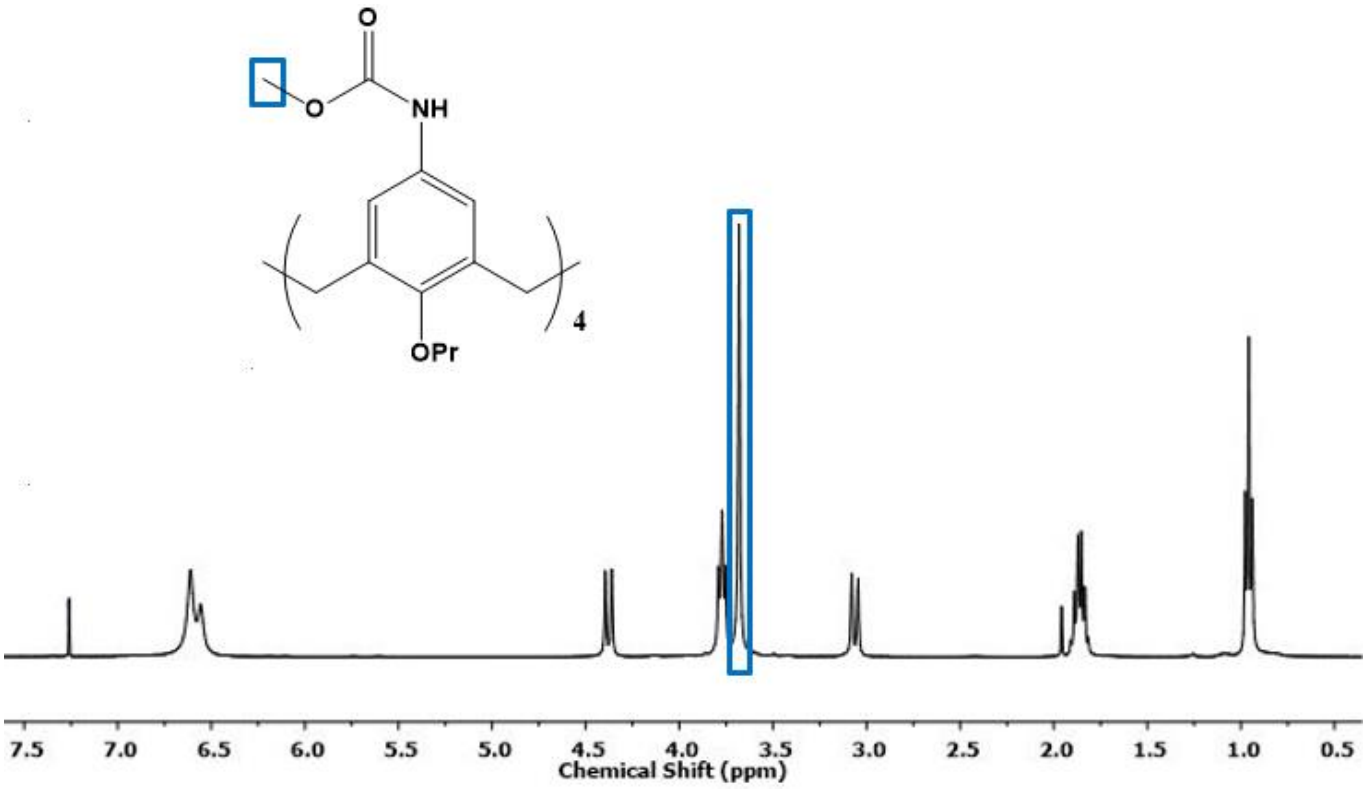
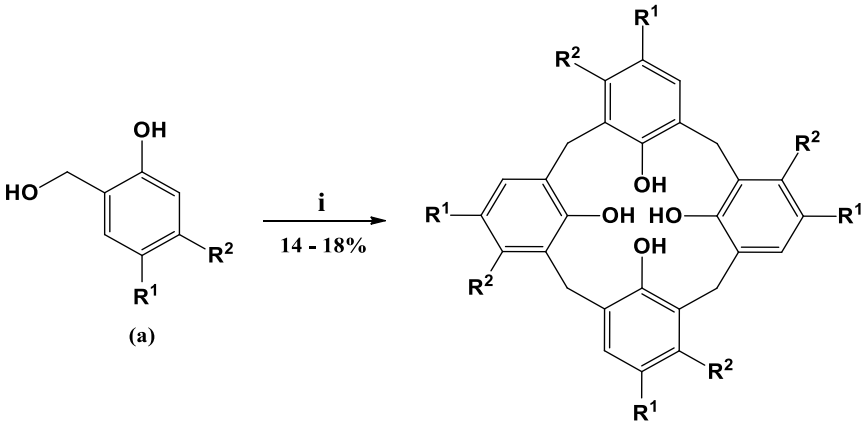


Figure 4.2: ^{1}H NMR spectra ($CDCl_3$) of tetra-methyl carbamate calixarene **16.**

The singlet resonating at δ 3.68 ppm (outlined in blue), which integrated to a value of 12, represented the four methyl hydrogen atoms attached to the carbamate, clear evidence of the successful synthesis of the desired calixarene **16**. Further proof of the compound's structure was the downfield shift of the nitrogen's hydrogen atoms to δ 6.56 ppm resonating as a broad singlet. Furthermore, the aryl proton's singlet resonated slightly upfield to the N-H proton at δ 6.61 ppm, also appearing as a broad singlet, which was undertaken as an indication of the carbamate's restricted rotation around its σ-bond. ^{13}C NMR, IR, and MS data further confirmed the compound's structure.

4.3. Bromination of tetra-carbamate calix[4]arene (**17**)

After establishing a successful and reproducible procedure for the synthesis of the tetracarbamate calix[4]arene in good yield, a *meta*-bromination study of the compound was conducted. Only one example of a C_4 *meta*-functionalized inherently chiral calix[4]arene has been reported in previous literature. Böhmer, successfully synthesized a *meta*-methyl functionalized inherently chiral calix[4]arene possessing C_4 symmetry by employing a 2 + 2 fragment condensation synthetic strategy (Scheme 4.6).[7] Although the synthesis of the compound was successful, the strategy only resulted in an overall yield below 10%.



Scheme 4.6: Condensation of compound **(a)** to afford the inherently chiral calix[4]arene. i) $TiCl_4$ (1 eq), dioxane, reflux, 40 hrs. R^1 = *t*-butyl, R^2 = methyl.[7]

With regards to accessing these compounds through direct modification of the calix[4]arene skeleton, only inherently chiral calix[4]arenes of C_2 symmetry have been reported.[8] Success, however, has been somewhat limited. The synthesis of these compounds has been riddled with complications, as along with the desired chiral product, the achiral isomer would form in tandem, which in turn, lead to poor yields and issues with separation. This was described previously in chapter 1.

The issue lies in selectively functionalizing the correct *meta* positions on the targeted aryl rings. For the calix[4]arene to be considered inherently chiral with C_4 symmetry, the R groups must point in the same direction. With this logic, it is easy to envisage other possible stereo arrangements that may arise that would result in an achiral molecule. In Figure 4.3 below, the four possible stereoisomers are illustrated. If one was to rotate calix[4]arene 'a' in Figure 4.3 90° in an anticlockwise direction, the compound would fit perfectly into itself. This action could be repeated another three times until it is back in its original position, with each 90° rotation fitting into its molecular stereo arrangement. However, if one of these R groups were to point in another direction, opposite to the other R groups, the compound would not possess its C_4 symmetry, and in the case of calix[4]arenes 'c' and 'd', it would be achiral. Although calix[4]arene 'b' has one of its R groups pointing in the opposite direction, it is still chiral, as its mirror image would be different and non-superimposable to the original compound. It is just not of C_4 symmetry.

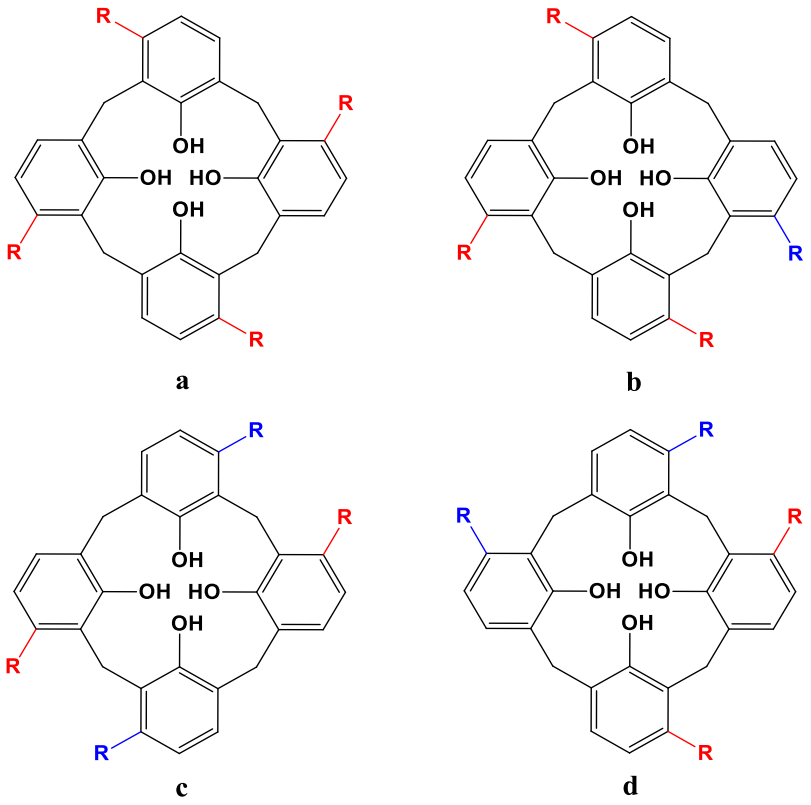


Figure 4.3: The four possible stereoisomers of tetra-substituted *meta*-functionalized calix[4]arenes.

Before embarking on the synthesis, it was realized that cooler conditions would be more likely to result in a uniform direction of brominations. In a high-energy environment, the bromination of the *meta* positions would occur too rapidly and therefore, limit the control of the selectivity of functionalization. This logic, however, presumes that the bromination of each of the aryl subunits occur one by one and not all at the same time. If this is indeed the case, would the bromination of one of the aryl rings influence the direction of the following brominations for its adjacent phenolic units? To determine this, a series of TLC investigations were carried out at timed intervals to determine the path of the reaction but first, the correct parameters and conditions needed to be established for the reaction.

The first attempt at the reaction was carried out at 0 °C instead of 60 °C as was reported in the previous chapters. At first, 5 molar equivalents of NBS and 2 equivalents of PTSA were used, with DCE as the choice of solvent. Within an hour, it appeared that the reaction had run its course, producing three compounds with very similar R_f values. At this stage, these three products could not be separated and therefore, were not characterized. Interestingly though, these three compounds were the only products that formed in temperatures ranging from 25 °C

to –35 °C in either DCE or DCM and using the same molar equivalents of reagents. At –78 °C however, the reaction would not move forward and after 6 hours, the starting material remained unreacted.

Performing the synthesis at –10 °C allowed the reaction to proceed slowly enough to monitor its progress *via* TLC in 10-minute intervals (Image 4.1). After the first 10 minutes, the starting material had already been used up and three new product spots had formed. After each 10 minutes, 2 – 3 new products would form at the expense of the previous ones until after about 50 minutes, the final three compounds had formed. This would suggest that the aryl subunits of the calix[4]arene were being brominated sequentially instead of all at once. This would perhaps explain why only three isomers are forming out of the possible four (Figure 4.3), as the aryl rings that are first functionalized may have an influence on the direction of the following brominations. This is of course assuming that the three compounds that were forming were isomers. However, this was only speculated, as the earlier formed compounds were never isolated and characterized.

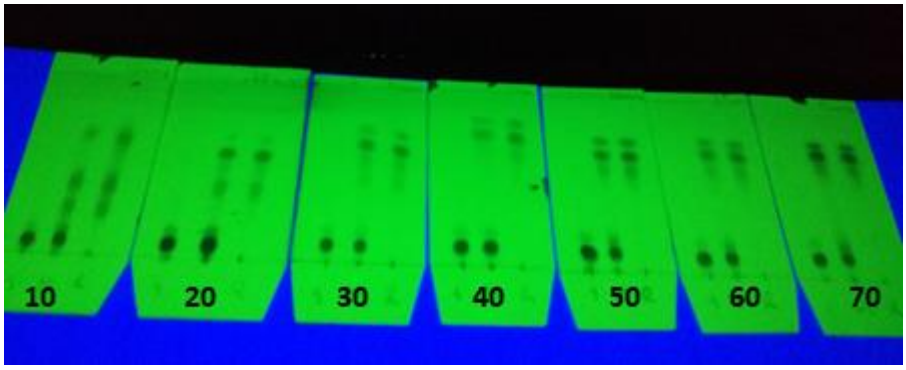


Image 4.1: TLC analysis taken at 10-minute intervals at –10 °C.

The only difference that could be observed in all the reactions is that when lowering the temperature of the reaction, the compound with the middle R_f value (the darker product spot in Image 4.1) would get increasingly more prominent on TLC. Furthermore, reactions with different molar equivalents of NBS were investigated to assess whether it influenced the products formed. Doubling the amount of NBS added had no real effect on the reaction outcome, however, on decreasing the equivalents to four, the compound with the lowest R_f value was only present in trace amounts, even after prolonged reaction time. This allowed for partial separation of the top two compounds and with great relief, both compounds were finally isolated.

Before obtaining enough pure material for ^{1}H NMR analysis, a sufficient amount was collected for mass spectrometry. As expected, both compounds possessed identical fragmentation patterns with base peak values of 1218.098 and 1218.099 (m/z $[M+NH_4]^+$). Not only did this confirm that the two compounds were isomers of one another, but also proved that each compound possessed only four bromine atoms, indicating that over or under bromination had not occurred. However, the structural arrangements of each compound were still uncertain and even more worrying, it was still unclear whether the desired inherently chiral calix[4]arene had been synthesized or not. Thankfully, the ^{1}H NMR data shed some light on this issue. Both spectra are shown below in Figures 4.4 and 4.5.

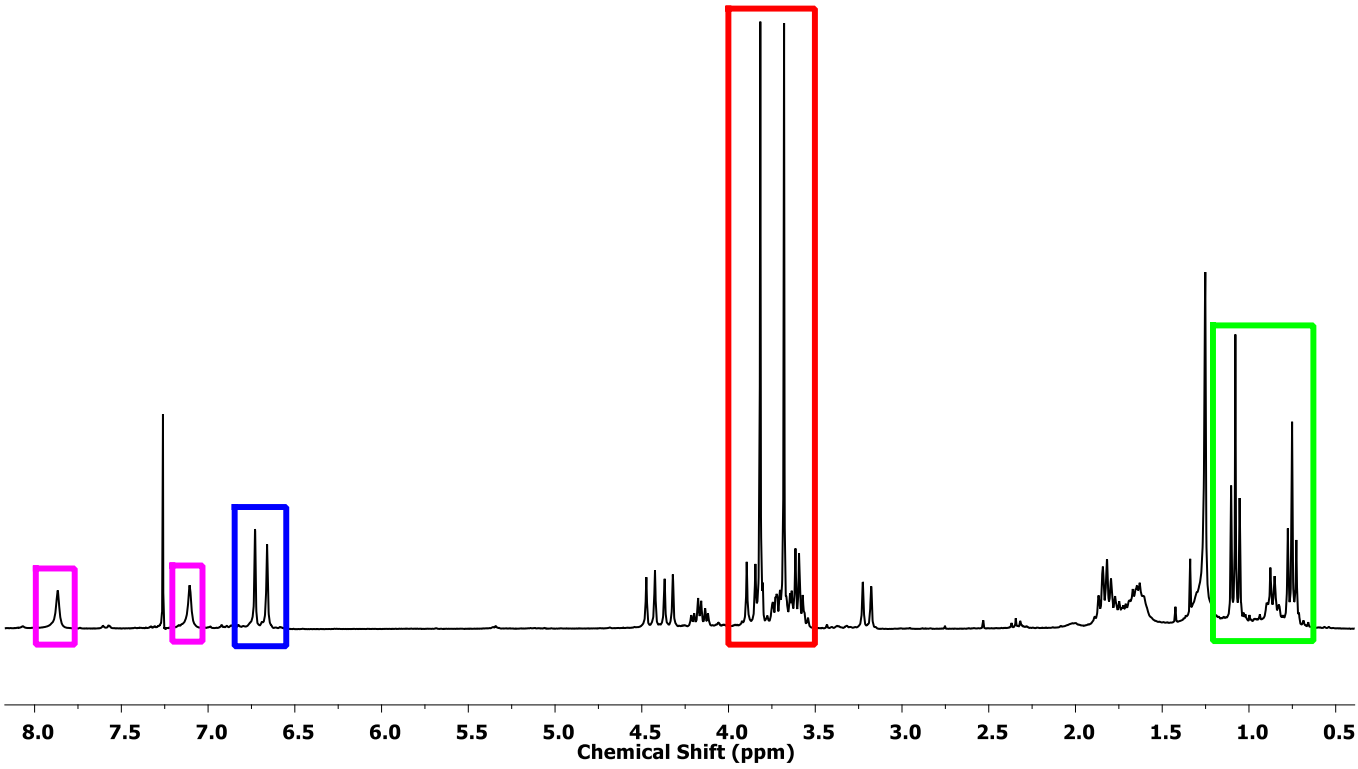


Figure 4.4: ^{1}H NMR spectrum ($CDCl_3$) for the achiral tetra brominated calix[4]arene.

The ^{1}H NMR spectrum displayed above in Figure 4.4 was acquired from the compound with the higher R_f value. Although the spectrum shows that compound was slightly impure, it could still be deduced that this calix[4]arene lacked C_4 symmetry. The signals outlined in purple, correspond to different N-H signals, both integrating for two protons. The two singlets outlined in blue, can be attributed to the four remaining aryl hydrogen atoms. These signals were the strongest indicator that this compound was not the target inherently chiral calix[4]arene. The inherently chiral calix[4]arene possesses C_4 symmetry, therefore, each of the four aryl rings

would be completely symmetrical which would result in one N-H signal and one aryl signal. The splitting of both N-H signals and aryl proton signals suggest that the isomer isolated was more likely to have two of its bromines pointing in one direction and the other bromines pointing in the opposite, much like the examples ‘c’ and ‘d’, illustrated in Figure 4.3 earlier. Furthermore, there were two methyl signals (outlined in red) that integrated for six protons each and there was also a splitting of the signal for the protons attached to the terminal carbon of the propoxy chain (outlined in green). It was hard to say whether this compound was arranged like ‘c’ or ‘d’ (Figure 4.3) from this ^{1}H NMR spectrum alone, but what was certain was that it was not the targeted inherently chiral calix[4]arene.

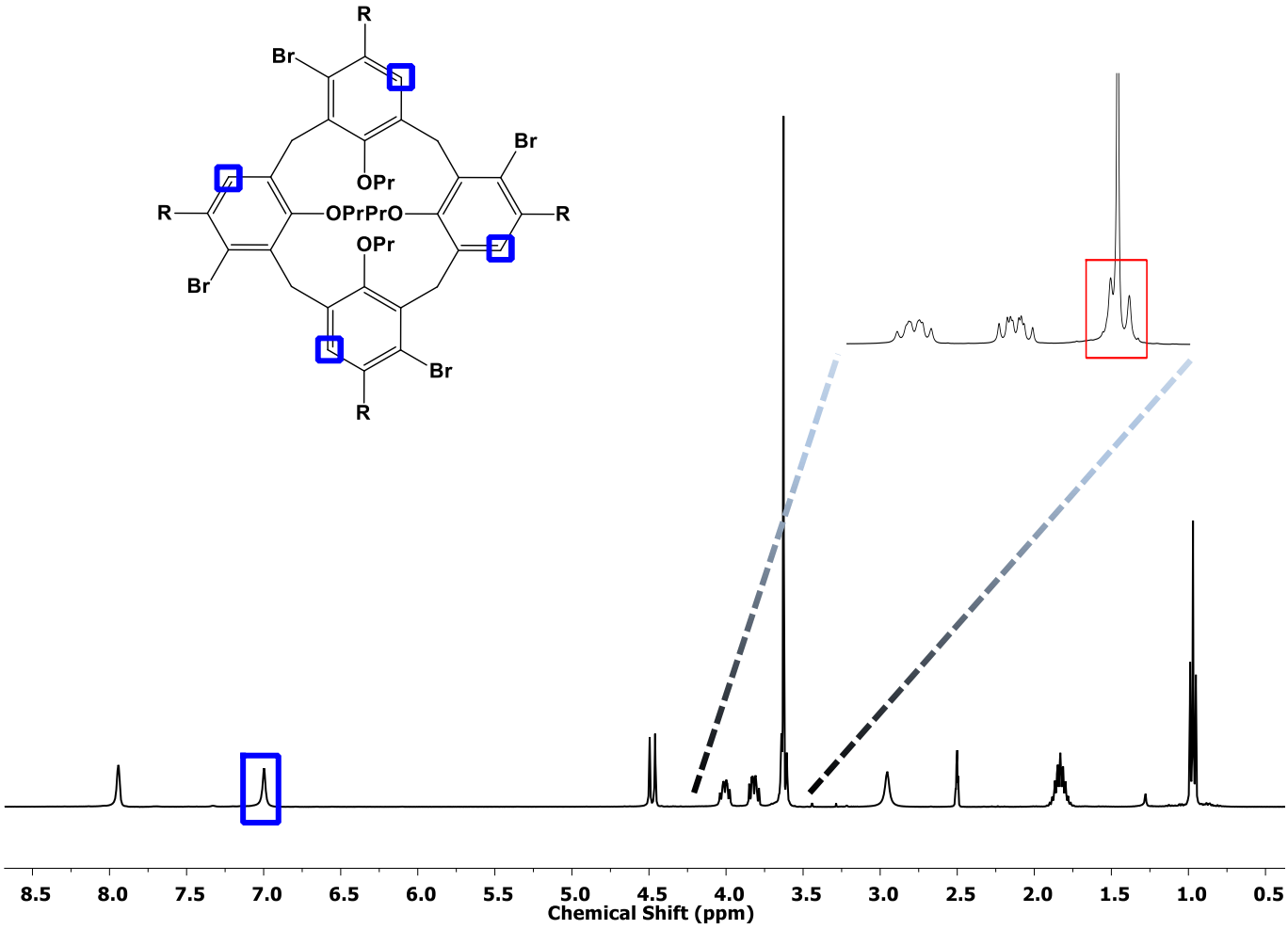
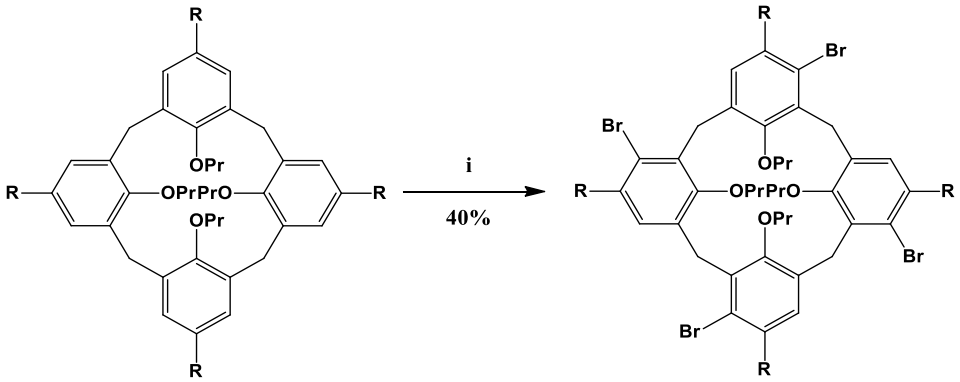


Figure 4.5: ^{1}H NMR spectrum for inherently chiral calixarene **18** with C_4 symmetry at 100 °C (DMSO-*6*). R = $NHCOOCH_3$

The ^{1}H NMR spectrum shown above in Figure 4.5 was taken at 100 °C for the more dominant product with the second highest R_f value. It was decided that in order to sharpen the peaks, the temperature should be increased to a point where the average signal would resonate. The

resultant spectrum came out beautifully. Furthest downfield, the N-H signals resonate at δ 7.94 ppm and at δ 7.00 ppm highlighted in blue, is the signal emanating from the aryl protons. The N-H and aryl protons integrate for four hydrogen atoms each. The 2D NMR data obtained confirmed that the N-H signal was indeed the one resonating furthest downfield. As in the case of all the other calix[4]arenes, the methylene bridge protons signals, appearing as AB doublets at δ 4.48 ppm (axial) and δ 3.63 ppm (equatorial). The equatorial methylene bridge hydrogens and the carbamate methyl protons, appearing as the large singlet, resonate at the same frequency and overlap one another. Both signals together integrate to a value of 16; 12 methyl protons and four methylene bridging hydrogens. The single singlets for both the N-H signals and aryl signals, was one of the biggest signs that the compound was completely symmetrical. Furthest upfield, at δ 0.96 ppm, the propoxy chain's terminal carbon's hydrogens resonate as a triplet ($^3J_{HH}$ = 7.4 Hz), another indication of the high degree of symmetry.

The final chosen reaction conditions are illustrated below in Scheme 4.7.



Scheme 4.7: Bromination of calixarene **16**. i) NBS (5 eq), PTSA (2 eq), DCM, –35 °C, 5 hrs. R = $NHCOOCH_3$

Calixarene **16** and PTSA were added to a 2-neck round-bottomed flask and dissolved in DCM before being cooled to –35 °C under argon. The contents were left to stir for 30 minutes to ensure that reaction contents had cooled to the desired temperature after which the NBS was added in one portion. The reaction was left to stir for a further 5 hours at –35 °C. Once the time had elapsed the reaction had run to completion. The solution was then added to H_2O and extracted with DCM. The organic layers were then combined and washed once with sat. $NaHCO_3$ and finally with brine. The orange solution was then dried over $MgSO_4$ and subsequently reduced to afford an orange crude product. Purification of the compounds were performed through multiple silica gel flash column chromatography runs. Along with the

previously mentioned ^{1}H NMR and MS data retrieved for this compound, IR, ^{13}C NMR, COSY, HSQC and HMBC data was also obtained.

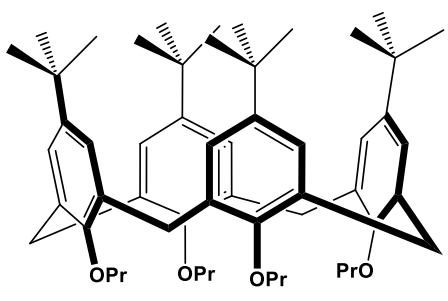
Only the main product, which was the desired inherently chiral calixarene **18**, could be purified sufficiently for full characterization as the other products would continuously co-elute. The compound with the highest R_f value was isolated in a very small amount, which allowed for a mass spectrometry and ^{1}H NMR analysis to be conducted. However, the ^{1}H NMR spectrum indicated that the achiral compound was not fully purified therefore, an accurate yield could not be determined.

4.4. Conclusion

For the first time it has been demonstrated that *meta*-functionalized inherently chiral calix[4]arenes of C_4 symmetry can be synthesized through direct modification of the calix[4]arene skeleton. The inherently chiral calix[4]arene was characterized using IR, MS, ^{1}H and ^{13}C NMR spectroscopy as well as 2D COSY, HSQC and HMBC experiments. Mass spectrometry proved that the two main compounds forming were isomers of one another. TLC evidence suggests that the bromination of one of the phenolic units may influence the direction of the subsequent brominations of its adjacent aryl rings, therefore, indicating that a degree of control can be achieved. The purification of these compounds however, as expected, proved to be quite challenging as only a pure sample could be obtained after multiple column chromatography runs. Finally, the activating properties of the carbamate functionality make it a more than efficient directing group for the synthesis of *meta*-functionalized calix[4]arenes.

4.5. Experimental

5, 11, 17, 23-tetra-*tert*-butyl-25, 26, 27, 28-tetrapropoxycalix[4]arene (13)[3]



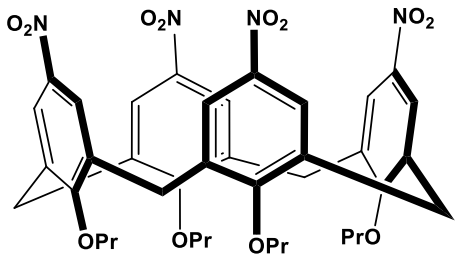
An oven dried 3-neck round-bottomed flask flushed with argon was charged with NaH (1.02 g, 42.4 mmol, 1.2 eq) and suspended in *n*-hexanes (15 mL). The suspension was stirred for 15 minutes to remove the mineral oil before the solvent was removed *via* syringe. Dry DMF (100 mL) was then added to the flask and was cooled to 0 °C before the parent calixarene **3** (2.50 g, 3.85 mmol) was added portionwise. To allow for deprotonation to occur, the reaction was left to stir for half an hour before iodopropane (3.76 mL, 38.5 mmol, 10 eq) was added and the mixture was left to slowly warm to room temperature and stirred

overnight (12 hours). A 2 M HCl solution (25 mL) was subsequently added dropwise to form a yellow precipitate. The precipitate was then filtered and washed with cold MeOH. The precipitate was then stirred in hot methanol for a further 30 minutes before being cooled in a fridge for three hours. The white precipitate was then filtered again and dried under *vacuo* to afford calixarene **13** in 84% yield (2.62 g).

The characterisation data collected for this compound compared well to literature data.[3]

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 6.79 (s, 8H, Ar*H*), 4.44 (d, $^2J_{HH}$ = 12.4 Hz, 4H, ArC$H_{2(ax.)}$Ar), 3.88 – 3.79 (m, 8H, OCH_2CH$_2$), 3.13 (d, $^2J_{HH}$ = 12.5 Hz, 4H, ArC$H_{2(eq.)}$Ar), 2.12 – 1.96 (m, 8H, OCH$_2$CH_2CH$_3$), 1.10 (s, 36H, C(CH_3)$_3$), 1.01 (t, $^3J_{HH}$ = 7.5 Hz, 12H, OCH$_2$CH$_2$CH_3).

5, 11, 17, 23-tetranitro-25, 26, 27, 28-tetrapropoxycalix[4]arene (14)[2]

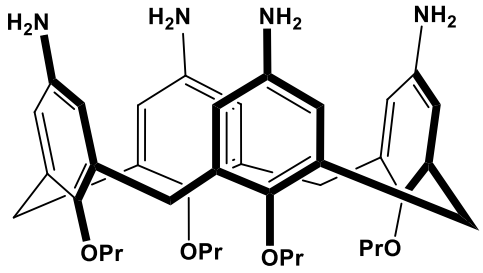


Calixarene **13** (1.00 g, 1.22 mmol) dissolved in DCM (20 mL) and TFA (1.50 mL, 19.6 mmol, 16 eq) was added to an oven dried 100 mL 2-neck round-bottomed flask equipped with a magnetic stir bar. A 70% HNO_3 solution (1.46 mL, 24.5 mmol, 20 eq) was subsequently added to the mixture. The solution was left to stir for one and a half hours. The contents were then poured over ice or cold water (20 mL) and extracted with DCM (15 mL × 3). The combined organic layers were then washed with sat. $NaHCO_3$ (25 mL × 3) and brine and dried over $MgSO_4$. Remaining solvent was removed under reduced pressure to afford an orange solid as the crude product. The crude was purified *via* silica flash gel column chromatography (EtOAc:PET 2:8) to yield compound **14** as a yellow solid (946 mg, 74%).

The characterisation data collected for this compound compared well to literature data.[9]

^{1}H NMR (600 MHz, CHLOROFORM-*d*) δ ppm 7.56 (s, 8H, Ar*H*), 4.53 (d, $^2J_{HH}$ = 14.0 Hz, 4H, ArC$H_{2(ax.)}$Ar), 4.02 – 3.91 (m, 8H, OCH_2CH$_2$), 3.40 (d, $^2J_{HH}$ = 14.1 Hz, 4H, ArC$H_{2(eq.)}$Ar), 1.95 – 1.87 (m, 8H, OCH$_2$CH_2CH$_3$), 1.02 (t, $^3J_{HH}$ = 7.4 Hz, 12H, OCH$_2$CH$_2$CH_3).

5, 11, 17, 23-tetraamine-25, 26, 27, 28-tetrapropoxycalix[4]arene (15)[4]

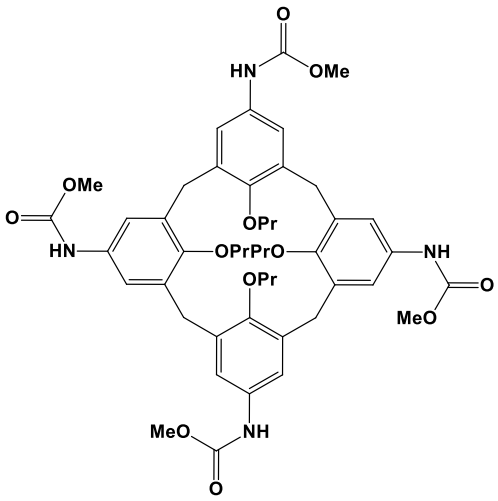


Calixarene **14** (652 mg, 0.844 mmol) and 5% platinum on carbon (494 mg, 0.127 mmol, 0.15 eq) were suspended in EtOH (40 mL) in an oven dried 2-neck round-bottomed flask equipped with a reflux condenser under argon. The reaction was then heated to reflux before hydrazine monohydrate (3.28 mL, 6.75 mmol, 80 eq) was added to the flask. The reaction was left to heat under reflux for a further four and a half hours. The reaction mixture was then cooled to room temperature before filtering the contents through Celite and removing the solvent *via* reduced pressure to afford tetraamino calixarene **15** as a white solid in near quantitative yield (551 mg, 95%).

The characterisation data collected for this compound compared well to literature data.[4]

^{1}H NMR (600 MHz, CHLOROFORM-*d*) δ ppm 6.05 (s, 8H, Ar*H*), 4.31 (d, $^2J_{HH}$ = 13.2 Hz, 4H, ArC$H_{2(ax.)}$Ar), 3.72 (t, $^3J_{HH}$ = 7.5, 8H, OCH_2CH$_2$), 2.94 (br. s, 8H, NH_2), 2.91 (d, $^2J_{HH}$ = 13.2 Hz, 4H, ArC$H_{2(eq.)}$Ar), 1.89 – 1.82 (m, 8H, OCH$_2$CH_2CH$_3$), 0.95 (t, $^3J_{HH}$ = 7.5 Hz, 12H, OCH$_2$CH$_2$CH_3).

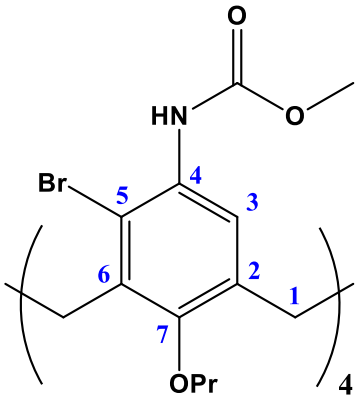
5, 11, 17, 23-tetra-methyl(carbamate)-25, 26, 27, 28-tetrapropoxycalix[4]arene (16)



In an oven dried 2-neck round-bottomed flask, calixarene **15** (350 mg, 0.536 mmol) was dissolved in DCM (20 mL). The reaction mixture was cooled to 0 °C after which pyridine (518 µL, 6.43 mmol) and methyl chloroformate (497 µL, 6.43, mmol) were added. The reaction was left to warm to room temperate and after 30 minutes, the mixture was washed with water (20 mL) and extracted with DCM (10 mL × 3). The organic layers were then combined washed with brine and dried over MgSO$_4$. Excess solvent was removed *via* reduced pressure before the crude product was purified *via* silica gel flash column chromatography (EtOAc:PET 1:1) to afford calixarene **16** as a pale orange solid (391 mg, 83%). R_f = 0.14 (EtOAc:PET 1:1); **Mp** = 228-232 °C; **IR (ATR, cm^{-1}):** 3313 (N-H) 2959 and 2874 (C-H) 1705 (C=O) 1600 (arene) 1537 and 1466 (C=C) 1212 (C-O-C) 995 and 964 (C-N) 768 (C-H); **^{1}H NMR (400**

MHz, CHLOROFORM-*d*) δ ppm 6.61 (br. s, 8H, Ar*H*), 6.56 (br. s, 4H, N*H*) 4.38 (d, $^{2}J_{HH}$ = 13.4 Hz, 4H, ArC$H_{2(ax.)}$Ar), 3.77 (t, $^{3}J_{HH}$ = 7.4 Hz, 8H, OCH_2CH$_2$), 3.68 (s, 12H, OCH_3), 3.06 (d, $^{2}J_{HH}$ = 13.5 Hz, 4H, ArC$H_{2(eq.)}$Ar), 1.93 – 1.80 (m, 8H, OCH$_2$CH_2CH$_3$), 0.96 (t, $^{3}J_{HH}$ = 7.4 Hz, 12H, OCH$_2$CH$_2$CH_3); **^{13}C{1H} (400 MHz, CHLOROFORM-*d*)** δ ppm 154.6 (Ar*C*), 153.0 (NH*C*OO), 135.3 (Ar*C*), 131.6 (Ar*C*), 119.7 (Ar*C*), 76.7 (O*C*H$_2$CH$_2$), 52.2 (O*C*H$_3$), 31.1 (Ar*C*H$_2$Ar), 23.1 (OCH$_2$*C*H$_2$CH$_3$), 10.3 (OCH$_2$CH$_2$*C*H$_3$); **HRMS–Positive:** m/z [M+NH$_4$]$^{+}$ calcd. for $C_{48}H_{60}N_4O_{12}$: 902.455; found 902.454.

4, 10, 16, 22-bromo-5, 11, 17, 23-tetra-methyl(carbamate)-25, 26, 27, 28-tetrapropoxycalix[4]arene (17)



In an oven dried 2-neck round-bottomed flask charged with a magnetic stir bar and flushed with argon, calixarene **16** (150 mg, 0.169 mmol) was dissolved in DCM (10 mL). PTSA was added and the contents were cooled to –35 °C. After 15 minutes, NBS (151 mg, 0.647 mmol, 5 eq) was added, afterwhich the reaction was left to stir at –35 °C for another five hours. Once complete, the reaction was diluted with H$_2$O (10 mL) and extracted with DCM (5 mL × 3). The organic layers were then combined and was first washed with sat. NaHCO$_3$ (15 mL) and then brine (15 mL), before being dried over MgSO$_4$ and concentrated under reduced pressure. The crude product was purified *via* 2 seperate silica gel flash column chromatography (EtOAc:PET 2:8) to produce calixarene **17** as a pale yellow glass (69 mg, 41 %). ***R$_f$*** **=** 0.28 (EtOAc:PET 4:6); **Mp =** 118-124 °C; **IR (ATR, cm^{-1}):** 3410 (N-H) 2959 and 2874 (C-H) 1732 (C=O) 1578 (arene) 1511 (C=C) 1215 and 1186 (C-O-C) 998 and 964 (C-N) 766 (C-H); **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ ppm 7.94 (s, 4H, N*H*), 7.00 (s, 4H, Ar*H*), 4.48 (d, $^{2}J_{HH}$ = 14.1 Hz, 4H, ArC$H_{2(ax.)}$Ar), 4.01 (ddd, $^{2}J_{HH}$ = 10.4, 8.6, 6.4 Hz, 4H, OCH_2CH$_2$), 3.82 (ddd, $^{2}J_{HH}$ = 10.4, 8.5, 6.2 Hz, 4H, OCH_2CH$_2$), 3.63 (s, 12H, OCH_3), 3.62 (d, 4H, $^{2}J_{HH}$ = 14.1 Hz, ArC$H_{2(eq.)}$Ar), 1.90 – 1.76 (m, 8H, OCH$_2$CH_2CH$_3$), 0.97 (t, $^{3}J_{HH}$ = 7.4 Hz, 12H, CH$_2$CH$_2$CH_3); **^{13}C{^{1}H} (400 MHz, DMSO-*d*$_6$)** δ ppm 154.3 (ArC_7), 153.9 (NH*C*OO), 133.4 (ArC_6), 131.2 (ArC_2), 130.0 (ArC_4), 127.0 (ArC_3), 118.8 (ArC_5), 76.24 (O*C*H$_2$CH$_2$), 51.08 (O*C*H$_3$), 30.63 (Ar*C*Ar), 21.72 (CH$_2$*C*H$_2$CH$_3$), 9.34 (CH$_2$*C*H$_3$); **^{1}H, ^{1}H GCOSY (400/400 MHz, DMSO-*d*$_6$)** δ ^{1}H/δ ^{1}H ppm 4.48 / 3.62 (ArC$H_{1(ax.)}$Ar / ArC$H_{1(eq.)}$Ar), 4.00 / 1.83 (OCH_2CH$_2$ / CH$_2$CH_2CH$_3$), 3.82 / 1.83 (OCH_2CH$_2$ / CH$_2$CH_2CH$_3$), 3.62 / 4.48 (ArC$H_{1(eq.)}$Ar / ArC$H_{1(ax.)}$Ar), 1.83 / 4.00, 3.82, 0.97 (CH$_2$CH_2CH$_3$ / OCH_2CH$_2$, OCH_2CH$_2$, CH$_2$CH$_2$CH_3), 0.97 / 1.83 (CH$_2$CH$_2$CH_3 / CH$_2$CH_2CH$_3$); **^{1}H,^{13}C GHSQC (400/400 MHz,**

DMSO-*d*$_6$) δ ^{1}H/δ ^{13}C ppm 7.00 / 127.0 (Ar*H*$_3$ / Ar*C*$_3$), 4.48 / 31.64 (ArC*H*$_{1(ax.)}$Ar / Ar*C*$_{1(ax.)}$Ar), 4.00 / 77.25 (OC*H*$_2$CH$_2$ / O*C*H$_2$CH$_2$), 3.82 / 77.25 (OC*H*$_2$CH$_2$ / O*C*H$_2$CH$_2$), 3.63 / 52.09 (OC*H*$_3$ / O*C*H$_3$) 3.62 / 31.64 (ArC*H*$_{1(eq.)}$Ar / Ar*C*$_{1ax.)}$Ar), 1.83 / 22.73 (CH$_2$C*H*$_2$CH$_3$ / CH$_2$*C*H$_2$CH$_3$), 0.97 / 10.35 (CH$_2$CH$_2$C*H*$_3$ / CH$_2$CH$_2$*C*H$_3$); **^{1}H,^{13}C GHMBC (400/400 MHz, DMSO-*d*$_6$)** δ ^{1}H/δ ^{13}C ppm 4.48 / 154.3, 133.4, 131.2, 127.0, 118.8 (ArC*H*$_{1(ax.)}$Ar / Ar*C*$_7$, Ar*C*$_6$, Ar*C*$_2$, Ar*C*$_3$, Ar*C*$_5$), 4.00 / 154.3, 9.34 (OC*H*$_2$CH$_2$ / Ar*C*$_7$, CH$_2$*C*H$_3$), 3.82 / 154.3, 9.43 (OC*H*$_2$CH$_2$ / Ar*C*$_7$, CH$_2$*C*H$_3$), 3.63 / 153.9 (OC*H*$_3$, NH*C*OO), 3.62 / 154.3, 133.4, 131.2, 127.0, 118.8 (ArC*H*$_{1(eq.)}$Ar / Ar*C*$_7$, Ar*C*$_6$, Ar*C*$_2$, Ar*C*$_3$, Ar*C*$_5$), 0.97 / 76.24, 21.72 (CH$_2$CH$_2$C*H*$_3$ / O*C*H$_2$CH$_2$, CH$_2$*C*H$_2$CH$_3$); **HRMS–Positive:** m/z [M+NH$_4$]$^{+}$ calcd. for C$_{49}$H$_{56}$Br$_4$N$_4$O$_{12}$: 1214.097; found 1214.107.

4.6. References

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5. Chapter 5 – Conclusion and future work

5.1. Conclusion

The main aim of this research project was to investigate and develop a new method in synthesizing *meta*-functionalized inherently chiral calix[4]arenes by using a carbamate functional group as a directing group for a controlled C-H activation. This method was inspired by work done by Moghaddam and co-workers where they demonstrated the ability the carbamate functional group at regioselectively directing the bromination of phenylcarbamates at their relative *ortho* positions.[1] Whether it would work on a calix[4]arene molecule, had to be investigated. The project also included a second study of synthesizing *meta*-functionalized inherently chiral calix[4]arenes of C_4 symmetry through direct modification. Again, the use of a carbamate was used at the wide rim of the calix[4]arene's scaffold to direct the subsequent *meta*-brominations. The concluding remarks of the project are reported below.

Before testing C-H activation on the calix[4]arene molecule, a model study was conducted. As previously mentioned, Moghaddam and co-workers demonstrated the ability carbamates had at directing $Pd(OAc)_2$ catalyzed C-H activation reactions on various phenylcarbamate derivatives. One of their studied compounds caught our attention in particular because of its structural similarities to that of a single phenolic unit of the calix[4]arene molecule, methyl (4-methoxyphenyl)carbamate. When replicating their reaction conditions, we obtained similar results in the C-H activation *ortho*-brominations, however, it was also found that the same compound could be synthesized without the use of the catalyst. Although these reactions resulted in lower yields, it suggested that there was a competing electrophilic aromatic substitution. The notion that *N*-substituted carbamates act as *ortho* and *para* directors was further substantiated by Li and Uhlig in their isotope exchange experiment (Scheme 2.4).[2]

Although the results obtained in the model study indicated that the role the catalyst played in the *ortho*-brominations of *para*-substituted *N*-arylcarbamates is relatively minimal, it still had to be tested on the larger calix[4]arene molecule. Before adding an element of chirality to the carbamate directing group, a proof of concept study was taken on, using the same methyl carbamate attached at the wide rim of the calix[4]arene. The synthetic route chosen to access the wide rim mono-functionalized carbamate calix[4]arene posed no issues at all and the carbamate calix[4]arenes, both chiral and achiral, were synthesized in good yields. The proof of concept study showed that the methyl carbamate directing group aided in the synthesis of the target *meta*-brominated inherently chiral calix[4]arene through either C-H activation or

electrophilic aromatic substitution. With all three of the other aryl rings' *para* positions vacant, it was expected that these positions would be brominated, especially in the absence of the transition metal catalyst. However, what was found was that the catalyst played no role in controlling the site of bromination. This study provided no evidence of C-H activation and it was assumed that the dominant mechanism at play was electrophilic aromatic substitution. The study did, however, provide a new method of synthesizing *meta*-functionalized inherently chiral calix[4]arenes.

In order to induce a degree of diastereoselectivity for the bromination reactions, the methyl group of the methyl carbamate was exchanged with 1(*S*)-(+)-menthyl. Synthesis of the chiral calix[4]arene followed the same protocol for the synthesis of the methyl carbamate calix[4]arene. A small study was performed to determine if there was any thermodynamic control. Each entry compared reactions that included $Pd(OAc)_2$ with ones that did not at different temperatures. The results showed that when decreasing temperatures from room temperature to –35 °C, the yields for the catalysed reactions remained consistent (90-92%). When the catalyst was excluded, the yields gradually decreased as the temperature was lowered. The thermodynamic study also showed that at every temperature, the reactions that included the catalyst resulted in higher yields, with the biggest difference of 10% recorded for the reactions performed at –35 °C. From these results it was deduced that the catalyst does play a role in the outcome of the reaction. However, it was theorised that the high reactivity of the electrophilic aromatic substitution probably resulted in most of the molecules reacting before they were exposed to the catalyst.

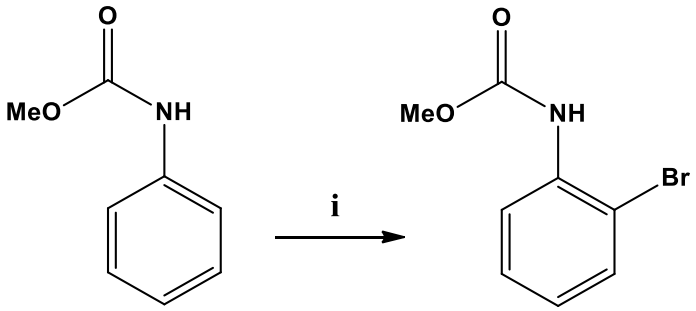
Determining the diastereoselectivity of the reported brominations proved to be quite challenging. At first, trying to distinguish if there were any difference in each of the entry's (Table 3.1) ^1H NMR spectra was investigated; unfortunately, no apparent discrepancies were observed. We then set out to see if a diastereomeric excess could be established using HPLC to separate the diastereomers that had formed. However, using both normal phase and reverse phase columns, the diastereomers could not be separated and therefore, no valuable information was obtained. It was then decided that alpha-D experiments would be able to give an idea of whether one stereoisomer was forming over the other. It was decided to test and compare the catalysed and non-catalysed reactions performed at the coldest temperatures (the most likely to show diastereoselectivity). For both entries, the chiral carbamates were first removed through TBAF hydrolysis to produce the corresponding enantiomers that needed to be analysed. It was found that at –35 °C, reactions that included $Pd(OAc)_2$ had a higher specific

rotation than those that did not include the catalyst by a magnitude of 3°. This further confirmed that the catalyst was having an impact on the reactions and that diastereoselectivity improved when the bromination occurred through the catalytic cycle.

Lastly, the tetra chapter (chapter 4) produced some very promising results. For the first time, we demonstrated that *meta*-functionalized inherently chiral calix[4]arenes could be synthesized through direct modification by using methyl carbamate as an electrophilic aromatic substitution *ortho* directing group. The synthetic route taken to reach the tetra methyl carbamate calix[4]arene only involved four high yielding reactions from the parent calix[4]arene. Bromination of the tetra carbamate calix[4]arene produced the same three compounds at various temperatures, two of which were successfully isolated and characterized. To our delight, the targeted inherently chiral calix[4]arene was the dominant product, obtained in yields close to 40%. A considerable achievement as the only other example of a *meta*-functionalized inherently chiral calix[4]arene of C_4 symmetry was synthesized *via* a 2 + 2 fragmentation procedure which resulted in overall yields below 10%.[3] Analytical techniques used to prove the compound's structure were, IR, MS, ^{1}H and ^{13}C NMR spectroscopy, as well as various 2D experiments which included COSY, GHMBC and GHSQC. Although there is more work to be done on this chapter, it shows that acquiring these compounds through direct modification is possible and should be further investigated.

5.2. Future Work

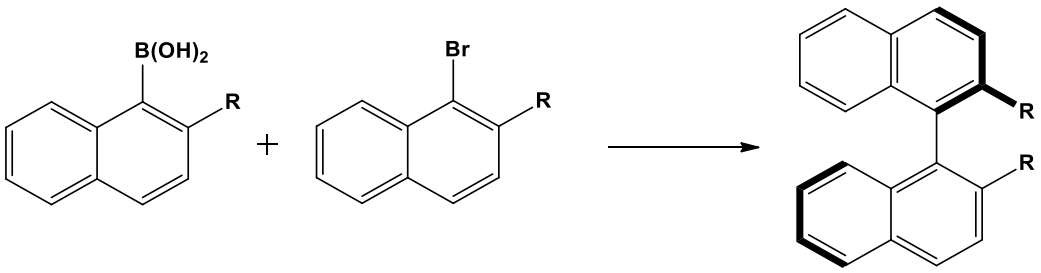
Each chapter left room for future work. With regards to the model chapter (chapter 2), the degree to which the carbamate acts as an electrophilic aromatic substitution *ortho*/*para* director still needs to be evaluated. We have demonstrated that when using NBS in acidic conditions, carbamates act as *ortho* directing groups in electrophilic aromatic substitution reactions, therefore, they can be considered as ring activators. One way to further substantiate the claim could be done by reacting the model compound with molecular bromine in the presence of $FeBr_3$, the more conventional method of brominating phenyls through electrophilic aromatic substitution. It would also be interesting to see whether there would be any control when utilizing the $Pd(OAc)_2$ in the bromination of a methyl phenylcarbamate with an open *para* position (Scheme 5.1). Although this compound was investigated in Moghaddam and co-workers' paper,[1] they again did not perform the reaction without the $Pd(OAc)_2$. This test reaction would, therefore, establish the ability the transition metal catalyst has at controlling the selectivity of the reaction.



Scheme 5.1: *Ortho*-bromination of methyl phenylcarbamate. i) $Pd(OAc)_2$, PTSA, NBS, DCE, 60 °C.

The work done in chapter 3 demonstrated an extremely facile method of synthesizing *meta*-functionalized inherently chiral calix[4]arenes. Determining the diastereoselectivity, however, proved to be quite challenging. This hurdle would, therefore, need to be overcome. Establishing the ideal parameters needed to separate the diastereomers through HPLC is one area that would provide more information on the selectivity. Once a diastereomeric excess is determined, improving the diastereoselectivity of the reaction would be the next investigation that would need to be undertaken. From the evidence gathered from chapter 3, it was clear that the C-H activation pathway resulted in a higher specific rotation compared to the electrophilic aromatic substitution mechanism. Therefore, reducing the competing electrophilic aromatic substitution may help with the selectivity of the brominations. There are several approaches that can be taken to address this issue. One way would be to reduce the reactivity of the substitution reaction, either by lowering the reaction temperature or by reducing the ring activating properties of the directing group. Li and Uhlig showed that the choice of acid influenced the ring activating properties of the carbamate.[2] Their results, therefore, provide a motive for investigation into the role that the additives play in the outcome of the reaction.

If enantiopure calix[4]arene material can be obtained, relevant application studies would then need to be undertaken. The palladium assisted Suzuki Coupling of axially chiral compounds is one such reaction that can be tested and has been investigated previously with several other chiral catalysts (Scheme 5.2).[4–7]



Scheme 5.2: Suzuki coupling. A potential application of inherently chiral calix[4]arene ligands in asymmetric catalysis.

With regards to the tetra system, adding a degree of chirality would be the next step. This may be done by making use of a chiral directing group as was done in chapter 3. Also trying to synthesize the desired product through a C-H activation route should be examined. One consideration that would need to be addressed for this reaction is whether all the targeted C-H bonds would need to be activated at once or sequentially. If they all need to be activated at once it would mean a stoichiometric amount of the catalyst would be needed. However, results obtained in chapter 4 show that one brominated ring may have an effect on the orientation of the subsequent brominations of the remaining phenolic units. Finally, even with the racemic compound, it's catalytic efficiency can be investigated through various application studies, such as the Suzuki coupling mentioned previously (Scheme 5.2).

5.3. References

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