

Synthesis and characterisation of calix[4]arene-based homogeneous catalysts

3.1 Introduction

Homogeneous catalysis has emerged as a potent synthetic tool, due to the well-defined nature of the catalysts. The idea of employing organic catalysts to promote asymmetric transformations is not new, during the past decade it has rapidly acquired interest among organic chemists. Homogeneous catalysts offer improved selectivity and increased activity. However homogeneous catalysts are difficult to recover as compared to heterogeneous catalysts. Nevertheless, the solvents could use a tunable phase behavior to achieve homogeneous catalysis with ease of separation (Fadhel et al., 2010). Calixarenes can provide variously substituted phenoxy and ether functionalities to a substituent attached to it that can serve as a phase transfer catalyst and organocatalysts. Their corresponding phenoxy units can be easily tuned to modify their steric environment and electronic effect

3.1.1 Background of calix[4]arene as organocatalysts

Organocatalysis has revolutionised organic chemistry and has shown to be a useful method for creating compounds with complex structures and the organocatalytic pathway includes organic molecules which can fasten up the chemical reactions. Recently, the importance of organocatalysis was recognized when Benjamin List and David MacMillan were awarded the Nobel Prize in Chemistry in 2021 for their contribution in the development of organocatalysis (MacMillan, 2008, List, 2007). A long-standing proposed use of supramolecular chemistry is the catalysis of organic reactions by macrocyclic molecules which makes use of non-covalent interactions in catalytic systems intending to achieve greater reaction rates, more selective catalysts or more ligands. The catalyst's selective binding to the substrate results in the creation of non-covalent interactions which increases selectivity and activity by converting the reactants into products. Particularly, the application of supramolecules in asymmetric catalysis has attracted substantial attention and shown tremendous achievement in recent years. A variety of supramolecular organocatalysts with exceptional activity and selectivity were created. Among these, calix[n]arenes i.e calix [4]arene have been explored extensively as organocatalysts for various organic reactions. Wang et al. reported the synthesis of a series of prolinamide and hydroxyprolinamide organocatalysts based on the calix[4]arene scaffold (Li et al., 2010). Organocatalytic behaviours of inherently chiral calix[4]arenes modified at the lower rim, Li et al. reported the synthesis of N,O-type enantiomers based on inherently chiral calix[4]arene their organocatalytic reaction can afford the desired products in excellent yields (up to 99%) but poor enantioselectivities (up to 7.5% ee). (Chang et al., 2017) Treatment of Boc-protected-L-proline or hydroxyproline with various aminocalix[4]arenes under one of the appropriate coupling conditions and subsequent deprotection of Boc group gave the target compound (ref 59) inherently chiral calixarenes bearing amino alcohol/phenol structure (Shirakawa and Shimizu, 2009b). To see the effect of the diarylmethanol moiety a novel class of calix[4]arene-based chiral primary amine-thiourea catalysts derived from p-tert-butylcalix[4]arene was synthesised and utilised for asymmetric Michael addition reaction (Durmaz and Sirit, 2013b). Genc et al. synthesised a series of calixarene-based chiral bifunctional thiourea organocatalysts and evaluated their catalytic efficacy to promote the aldol addition reaction between propanone and aromatic aldehydes (Genc and Sirit, 2016). Bifunctional catalytic scaffolds such as squaramide catalysts have emerged as an effective alternative to the urea/thiourea and guanidine catalysts as multiple hydrogen bond donors (Chauhan et al., 2015, Yang et al., 2020). Pan *et al.* studied the catalytic activity of an L-proline derivative attached to the lower rim of calix[4]arene developed

to catalyze the direct asymmetric aldol reaction (Li et al., 2009). Yilmaz et al. synthesised organocatalysts bearing L-proline derivatives with two prolinamide catalytic centres (Eymur et al., 2014, Uyanik et al., 2014). Calixarenes could be linked to Bronsted acids Manoury *et al* synthesised chiral calix[4]arene phosphonic acid and used as an organocatalyst in asymmetric aza-Diels-Alder reactions (Karpus et al., 2018b)

3.1.2 Background of calix[4]arene as Phase transfer catalysts

Reactions involving reactants that are present in two distinct phases are often inhibited because of their incapacity to interact with one another and to increase the pace of such reaction catalysts called phase transfer catalysts are used which eradicated the heterogeneity problem. Stark introduced the term "Phase-Transfer Catalysis" (PTC) to define and explain the required presence of tetraalkylammonium or phosphonium salts (in the form Q^+X^-) for promoting reactions between reagents located in immiscible phases (Starks, 1971). PTCs can be divided in two categories symmetric and asymmetric catalysis where tetraalkylammonium or phosphonium salts are mainly used to obtain achiral or racemic compounds. While asymmetric versions of PTCs are utilised in industries and research and for this purpose stereochemically modifiable ammonium salts are being utilised. The general mechanism of symmetric PTC is shown in Figure 3.1. The mechanism for asymmetric version of PTC is debatable because investigating biphasic systems is difficult. To explain asymmetric versions two mechanisms have been proposed Makosza's interfacial mechanism (Makosza, 1975), and Starks' extraction mechanism this is less accepted and applicable only to a few examples of PTC. According to the Makosza mechanism the inorganic base can access the interface between the two phases and it here directly deprotonates RH to give a metal-anion species MR. Subsequently, an ion exchange between MR and the chiral catalyst occurring at the interface, forms the chiral ion-pair Q^+R^- that can access the organic phase, where the reaction happens (Figure 3.2). The phase transfer catalysis (PTC) involves bringing together reactants-organic soluble components and anionic reactant-aqueous soluble reactant by utilizing a small amount of catalyst to move one reactant over the interface into the other phase and speed up the reaction rate. Calixarenes are essentially insoluble in water due to their aromatic nature, which increases their usefulness as Phase transfer reagents and some functionalised calixarenes have been used as PTC. Asymmetric PTC utilizing chiral quaternary ammonium salts has attracted great interest as a synthetic strategy since it provides quick access to a large number of enantiopure compounds employing only catalytic amounts of chiral phase-transfer agents (Shirakawa and Maruoka, 2013). The first asymmetric quaternary ammonium salts derived from cinchona alkaloids based on the calixarene skeleton (Srivastava and Srivastava, 2007b) Later in 2010, Shirakawa and Shimizu reported the synthesis of novel inherently chiral calix[4]arenes containing a quaternary ammonium moiety together with a hydroxymethyl and diarylmethanol moiety in an optically pure form. Chiral calix[4]arene-bearing secondary amides at the lower rim have been designed as phase-transfer catalysts in the asymmetric alkylation of N-(diphenylmethylene)- glycine esters. (De Simone et al., 2017b)

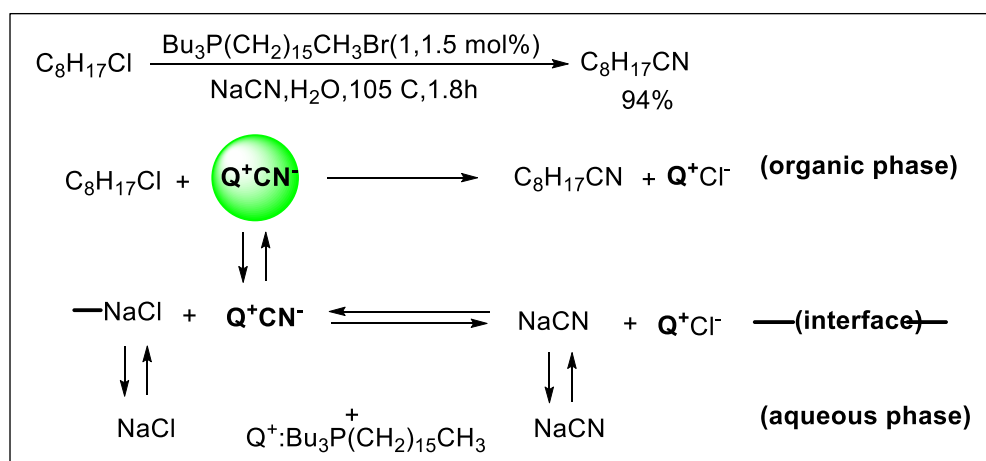


Figure 3.1 Representation of symmetric PTC mechanism (Ooi and Maruoka, 2007)

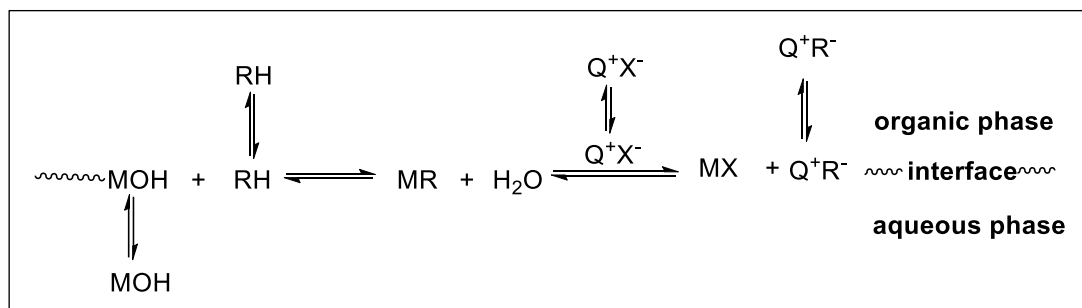


Figure 3.2 Representation of Makosza's interfacial mechanism for PTC.

3.2 Synthesis of calixarene catalysts

A series of catalysts based on calixarene skeleton have been reported. The calix [4] arene-based crown has also been synthesized by capping 1,3-arms. Therefore, the synthesis of the catalyst has been grossly divided here into two sections, one concerned with the derivatives of calixarene and the other with calix[4]arene-crown-5 (Joseph and Rao, 2011b)

3.2.1 Cinchonidine appended calix[4]arene

Table 3.1 Information related to sample code, supplier, and specification

Sample	CAS/Product number	specification	Supplier
K ₂ CO ₃	0584-08-07	powder and chunks Melting point =891 °C	Fisher Scientific
Cinchonine	75-03-6	Melting point 258 - 264 °C, Spec. rotation=+218.0 - +222.0 ° (c=0.5 in methanol)	Spectrochem
(-)-Cinchonidine	485-21-2	White powder, Melting point 201-206 °C, specific rotation=-109.2° (c=1.5, Ethanol)	Alpha Aesar
Ethyl bromoacetate	105-36-2	Clear colorless liquid, Melting poin=-38 °C	Spectrochem
^t BuOK	865-17-4	Solid, melting point= 256 °C	Across Organics
BaO	1304-28-5	white or off-white fine powder with a melting point exceeding 1,800 °C	Aldrich
Ba(OH) ₂ .8H ₂ O	12230-71-6	powder, crystals or chunks melting point =78 °C	Fisher Scientific
tetraethylene glycol	112-60-7	transparent, colorless, odorless, low volatility, hygroscopic liquid soluble in ethyl alcohol and very soluble in water melting point =-5.6 °C	Qualigens
oxalyl chloride	79-37-8	Liquid, melting point =-10-8 °C	Across Organics

S- α -methylbenzylamine	2627-86-3	Boiling point=187 °C, specific rotation= -39°, (neat)	Across Organics
R- α -methylbenzylamine	3886-69-9	Liquid Clear colorless, melting point =-10 °C, specific rotation= +38°, (neat)	Across Organics
L-(-)-10-Camphorsulfonyl chloride	39262-22-1	specific rotation= $[\alpha]_{18/D} 33^\circ$, (c = 3 in chloroform), melting point=66-68 °C	TCI
D-(+)-10-Camphorsulfonyl chloride	21286-54-4	Crystalline Powder, melting point= 67-68 °C, specific rotation= $[\alpha]_{22/D} +33^\circ$, (c = 1 in chloroform)	TCI

3.2.2 Synthesis of Cinchona anchored calix[4]arene

Natural Cinchona moiety is selected that could be appended with calix[4]arene. *Cinchona* alkaloids can be extracted from the bark of the tree *Cinchona officinalis* and four out of thirty different compounds recovered represent the greatest amount they are quinine, cinchonidine, quinidine and cinchonine. calix[4]arene can be modified at the lower rim by various substituents. The hydroxyl groups present at the lower rim attributed to the easy substitution. The readily available substituents are the ones that contain donor groups, esters, ketones, or ether. The moieties containing O, N and S bring out the O-alkylation and O-Acylation easily at the lower rim. Substitution easily locks the conformation of a calix[4]arene and this can be obtained by etherification or esterification at the lower rim with a carbon chain three or more units in length. Since such chains cannot pass through the annulus of calix[4]arene these derivatives are conformationally stable even at higher temperatures (Gutsche and Levine, 1982). The exact conformation(s) produced in a given alkylation reaction is dependent on the groups which are appended. For example, the propyl ether is locked in the cone conformation. (Gutsche et al., 1983). Different electrophiles can be used for substitution at the 1,3 position of calix [4]arene. (Joseph and Rao, 2011a). Alkylation of calix[4]arene can be varied by varying bases, altering the base can result in either partial or full alkylation. By selecting a strong base sodium hydride, all four sites get deprotonated and hence alkylated with the use of an alkyl halide. (Gutsche et al., 1983). In contrast, using a weaker base such as sodium or potassium carbonate results in the 1 and 3 positions being deprotonated, leading to the formation of a 1,3-disubstituted calixarene. Bulky substituents are attached to prevent the interconversions between four conformations. (Arduini et al., 1995) Though dialkylation can occur in various regiochemistry to give either the distal 1,3-dialkylated compound or proximal 1,2-dialkylated (Gutsche, 1998). Distal alkylation is frequently observed because of ease in synthesis as for proximal alkylation strong base such as sodium hydride is used with a stoichiometric amount of alkylating agent (Brunink et al., 1992). Organocatalysts derived from Cinchona alkaloids are applied in various asymmetric reactions, including Michael addition, (Vakulya et al., 2005) Mannich reaction (Song et al., 2006) (Li et al., 2020), Aldol reaction (Singh et al., 2010, Sakai et al., 2017), Morita-Baylis-Hillman, (Iwabuchi et al., 1999, Liu et al., 2010) and dihydroxylation (Hentges and Sharpless, 1980, Tian et al., 2004, Li et al., 2022).

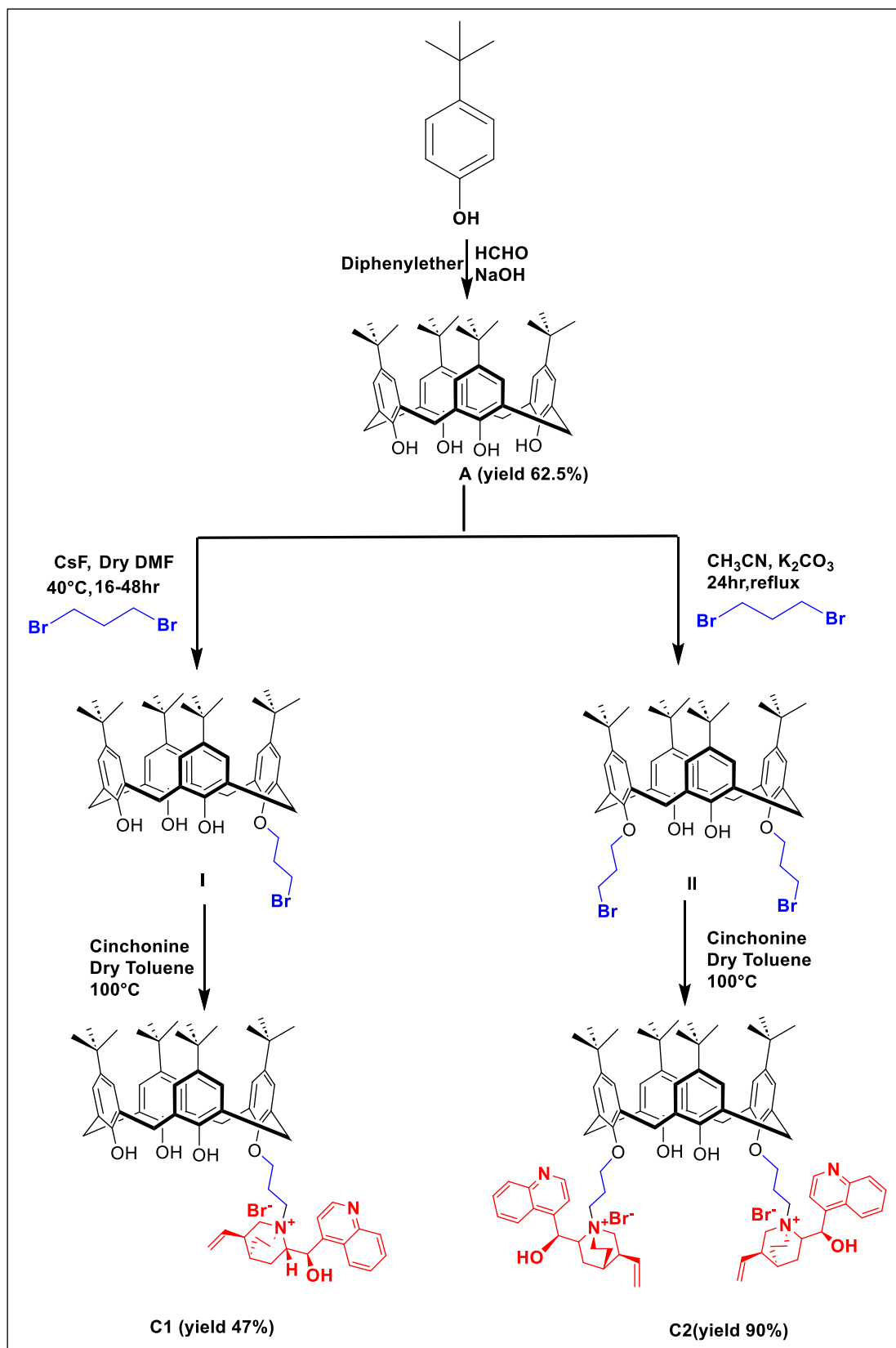


Figure 3.3 Synthesis of Cinchona anchored calixarene

3.2.3 Synthesis of Cinchona-Functionalized Crown Ether-Strapped Calixarene

Another important functionalisation of calix[4]arenes is the introduction of crown ether tethers. Crown ether and calix[4]arene subunits are linked by the phenolic oxygens of the calix components to form the receptor elements that distinguish calix[n]crown ether compounds from other macrocycles. Calixarenes are generally insoluble in water and many organic solvents, but it has been observed that esterification and etherification on the lower-rim, can improve their

solubility (Gutsche, 2008). The addition of ethylene glycol units ensures the rigidity with which the compound is held in the cone conformation, enforcing the cavity. The crown ether tether can bridge by either the 1,3-distal phenol units or 1,2- proximal phenol units respectively (Alfieri et al., 1983, Arduini et al., 1990, Arduini et al., 1997, Caccamese et al., 1999). Due to the challenges in the synthesis of 1,2- bridged calix[4]arene crowns there is not much research on it rather 1,3 bridged calix[4]arene crown is studied extensively. They have improved binding ability as well as selectivity to specific guest species such as cations, anions, or organic molecules. Usually, Calix[n]crowns are used as molecular scaffolds, where the functionalisation of calix[n]arene takes place at the distal phenolic oxygens with various poly(oxyethylene) chains. This polyether linkage with calix[n]arenes is very intriguing as these crowns can be used as complexing agents for alkali, alkaline earth metals and ammonium cations selectively and this leads to several applications. The first calixcrowns, 1,3-p-tert-butylcalix[4]crown-5 ethers were synthesised by reacting p-tert-butylcalix[4]arene with one equivalent of tetra- or penta-ethylene glycol ditosylate in the presence of two equivalents of t-BuOK in refluxing benzene. (Ungaro et al., 1984) Calix[4]arene and their derivatives provide a versatile platform of well-defined shape for the construction of sophisticated and functional structures. Calix[4]arene crowns can act as PTC for Fluorination (Lee et al., 2020, Jadhav et al., 2016), aromatic nucleophilic substitution reaction and benzyl nucleophilic substitution (Yang et al., 2010). One of the first reactions tested on calixarenes involved the esterification of the hydroxyl groups on the lower-rim. (See et al., 1991)

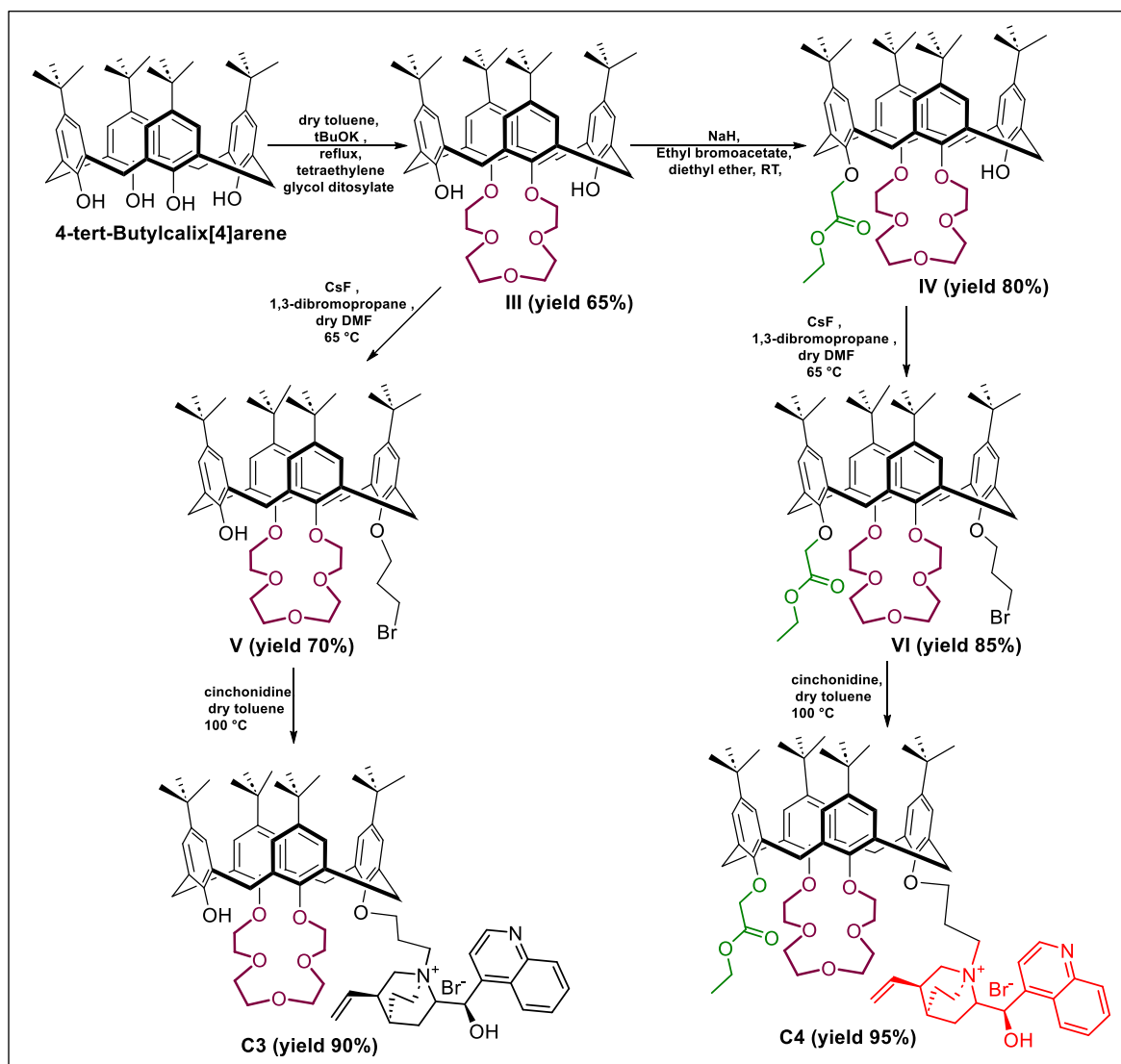


Figure 3.4 Synthesis of Cinchona -Functionalized Crown Ether-Strapped Calixarene

3.2.4 Synthesis of α -Methylbenzylamine functionalized calix[4]arene

Chiral inducers and auxiliaries frequently play a key role in the practical synthesis of enantiopure products. chiral 1-phenylethylamine (α -PEA) belongs to the ancillary compounds most often used for the synthesis of enantiomeric products. This primary amine is cheap and easily accessible in both enantiomeric forms which is capable of offering structural motifs. They are often used in the synthesis of chiral building blocks that are useful in asymmetric synthesis. Attributed to this application in various chiral recognition processes, α -PEA can be considered a privileged chiral inducer and auxiliary. Hence tethering α -Methylbenzylamine to calix[4]arene crown-5 gives a chiral catalyst.

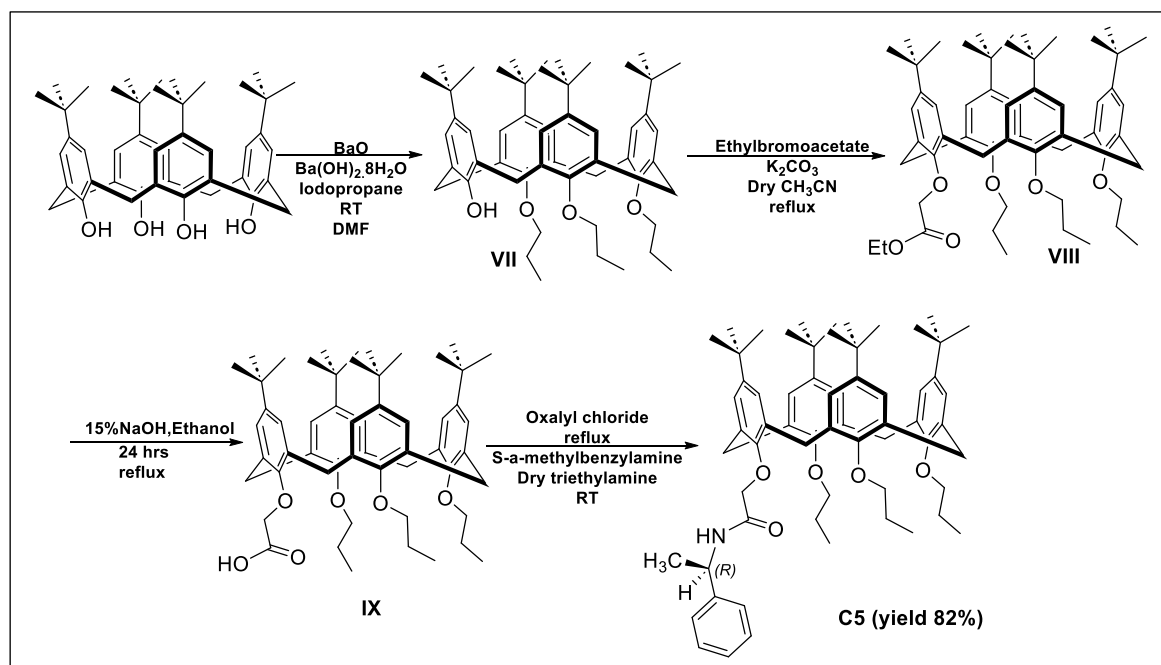


Figure 3.5 Synthesis of α -Methylbenzylamine functionalized calix[4]arene

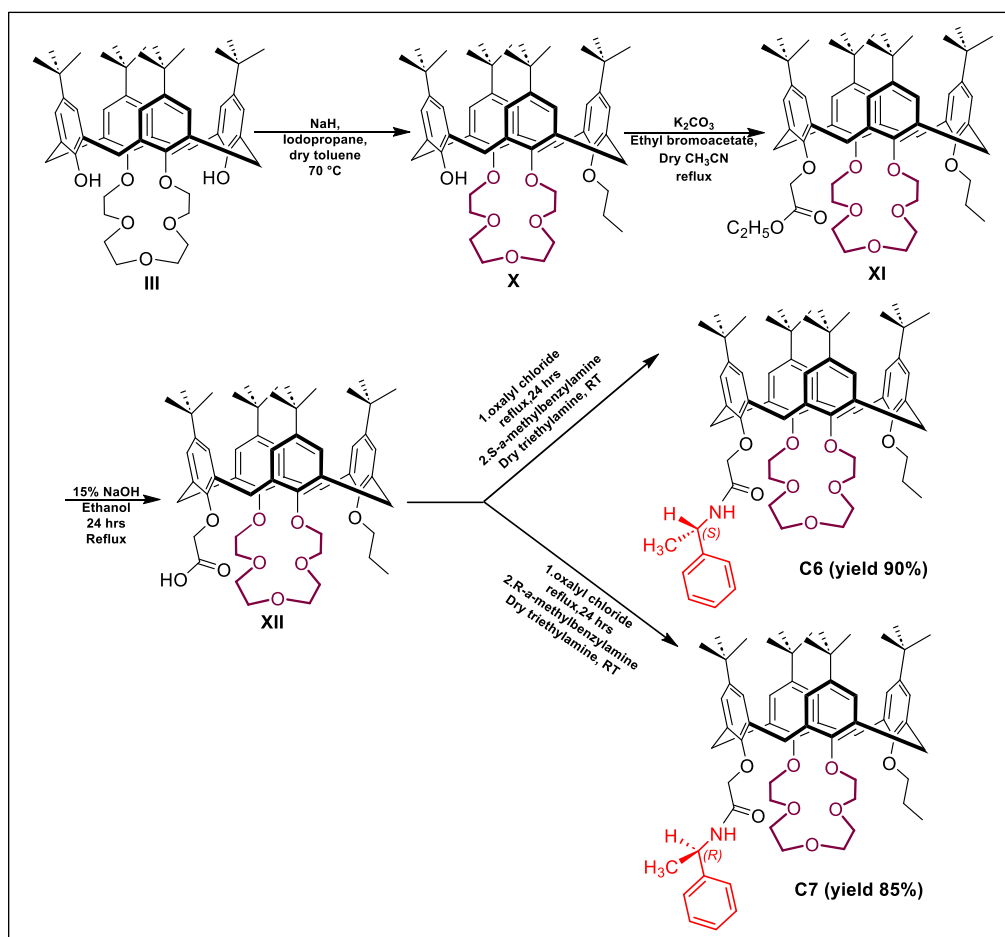


Figure 3.6 Synthesis of α -Methylbenzylamine functionalized crown-ether-appended calix[4]arene

3.2.5 Synthesis of camphor sulfonyl functionalised crown-ether-appended calix[4]arene

Camphor sulfonyl chloride has also been employed for the introduction of chirality into calixarenes. Kalchenko and co-workers have reported the preparation of chiral calix[4]arenes from the reaction of calix[4]arene monoalkyl ethers with 1(S)-camphor-10-sulfonyl chloride (Boyko et al., 2008) and (R)- or (S)-N-(1-phenylethyl)bromoacetamides (Boyko et al., 2006) and chiral 25-((1S)-10-camphorsulfonyl)-26-isopropoxy-27,28-dihydroxycalix[4]arene was obtained by asymmetrical lower rim (1S)-camphorsulfonylation of the monoisopropoxycalix[4]arene (Yakovenko et al., 2007). Shimizu et al. have prepared the chiral calix[4]arene derivatives and bearing a chiral residue (camphorsulfonyl group) for the optical resolution of racemic inherently chiral wide rim ABCD-type calix[4]arene fixed in a cone conformation and utilized it as an Organocatalyst on Enantioselectivity in Asymmetric Reactions. (Shirakawa et al., 2009b)

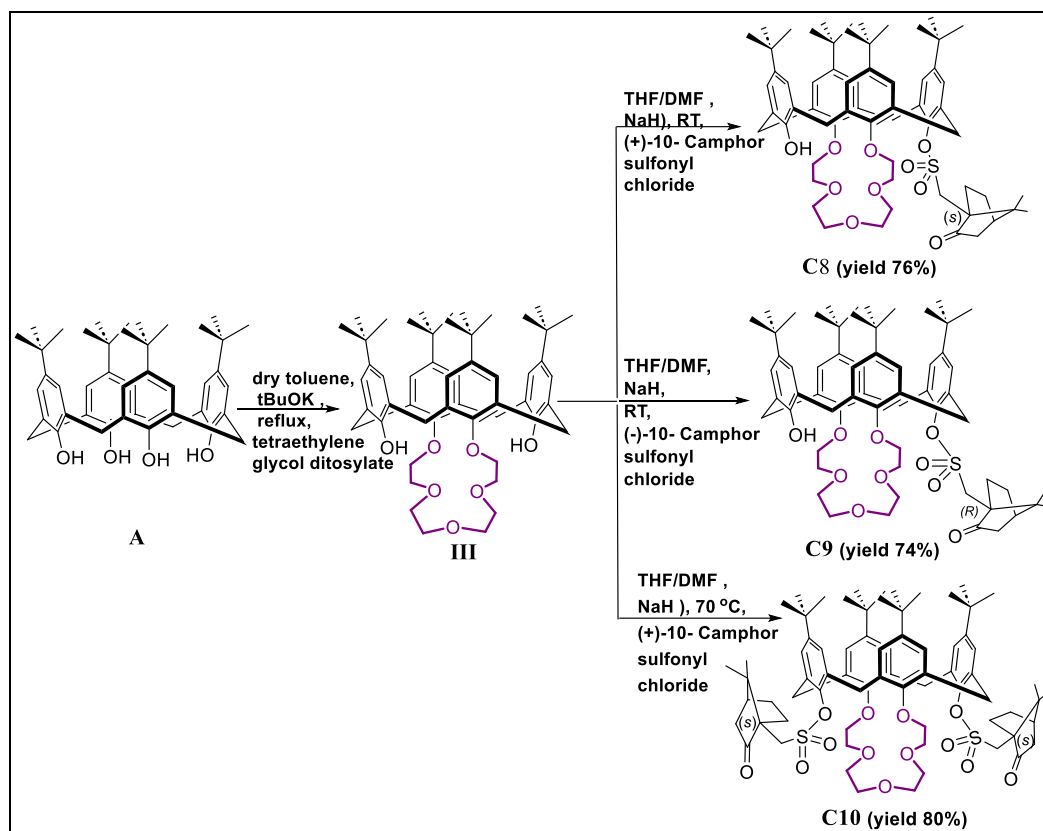
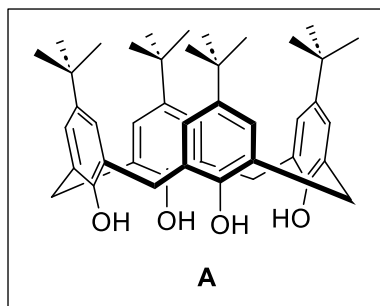


Figure 3.7 Synthesis of camphor sulfonyl functionalised crown-ether-appended calix[4]arene

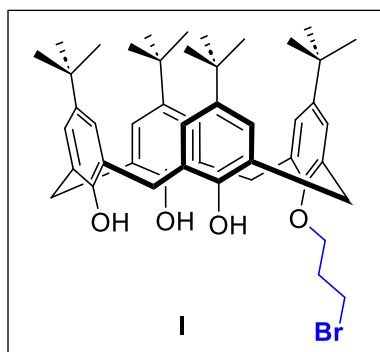
3.3 Experimental Section

General Remarks

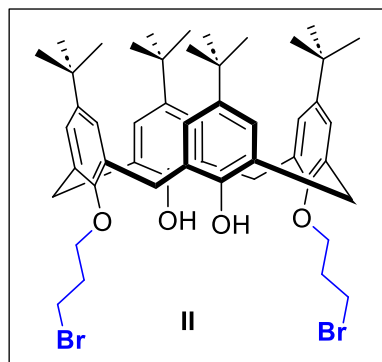
NMR spectra were recorded on a Bruker 500 spectrophotometer ^1H NMR, ^{13}C , ^{23}Na and ^{29}Si spectra were recorded on a 500, 126, 132, 500 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to the residual solvent peak (^1H CDCl_3 , $\delta = 7.26$; ^{13}C CDCl_3 , $\delta = 77.0$) Chemical shifts for ^1H NMR spectra are reported as in parts per million (ppm) downfield from SiMe and relative to the signal of chloroform-*d* (δ 7.26, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet) or m (multiplets). High resolution mass spectra (HRMS) were acquired using Agilent technologies model G6564 QTOF. The samples were ionized in positive ion mode using a MALDI or ESI ionization source. Infrared spectra were measured on a Bruker Vertex 70V spectrophotometer using KBr pellets at a room temperature range of 400-4000 cm^{-1} . Optical rotation was measured using a 1 mL cell with a 0.5 dm path length on a Rudolph Research Analytical Autopol II Automatic polarimeter. Optical rotation was measured using a 1 mL cell with a 0.5 dm path length on a Rudolph Research Analytical Autopol II Automatic polarimeter. Melting points were measured on a Buchi melting point apparatus M-565. Analytical thin layer chromatography was carried out on silica plates (SiO_2 , Merck 60 F254 Obtained from E. Merck chemical Co. Visualization of TLC plates was carried out using ultraviolet (UV) irradiation at 254 nm and/or by spraying 12-molybdo (VI)phosphoric acid ethanol solution. Dehydrated toluene, N,N-dimethylformamide (DMF), diethyl ether (Et_2O) and dichloromethane (CH_2Cl_2) and Dehydrated tetrahydrofuran (THF) were purchased from Alpha Aesar and hexane were purchased from Merck. Other reagents/solvents were purified by conventional methods. Catalysts were prepared under a nitrogen atmosphere, while Michael addition reactions were carried out in open-air. The enantiomeric excess of the Michael products was determined by HPLC measurements carried out using a Waters Model 2489 equipped with chiral columns DAICEL 4.6 mm $\times$ 250 mm Chiralpak IA, IB and AD-H, AS-H using condition *n*-Hexane/isopropanol solvent system and thermoscientific Vanquish detector Model: VC-D11-A equipped with chiral columns DAICEL 4.6 mm $\times$ 250 mm Chiralpak- AD-H



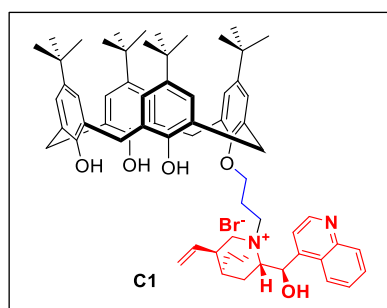
A-Formaldehyde (37%, aq solution) (6.2 ml) was added to a mixture of *p*-*tert*-butyl phenol (10 g, 0.06 mol) and NaOH (0.12 g, 0.003 mol). The solution was heated for 2 hrs at 110-120 °C using an oil bath. During this period, the clear solution became viscous and eventually turned into a thick golden solid. The reaction mixture was allowed to attain room temperature and diphenyl ether (100 mL) was added to dissolve the residue. A light-yellow color solution was obtained after 2-3 hrs. The contents of the above flask were heated slowly at 80-90 °C to remove water. If required, a stream of N₂ was blown over the reaction mixture for the removal of water. When the water was completely removed, the flask was fitted with a long condenser and the reaction mixture heated under reflux till a clear brown solution was obtained. The reaction mixture was cooled to room temperature and the product precipitated by the slow addition of ethyl acetate (150 mL) over a period of 1 hour. The precipitate was filtered and successively washed with ethyl acetate (20 mL), acetic acid (20 mL) and twice with water (10 mL) and twice with acetone (10 mL) to yield a light brown solid. The solid was dissolved in boiling toluene (100 mL) and the solution cooled to obtain *p*-*tert*-butyl calix[4]arene as a colourless crystalline solid. Yield = 6.74 g (62.5%). Melting Point -340-342 °C. ¹H NMR (500 MHz, Chloroform-*d*) δ 10.34 (s, 4H), 7.05 (s, 8H), 4.26 (d, *J* = 13.9 Hz, 4H), 3.49 (d, *J* = 12.6 Hz, 4H), 1.21 (s, 36H) ¹³C NMR (CDCl₃) δ; 147.06, 144.76, 128.08, 125.90, 34.40, 32.99, 31.79. (Iqbal, 1990)



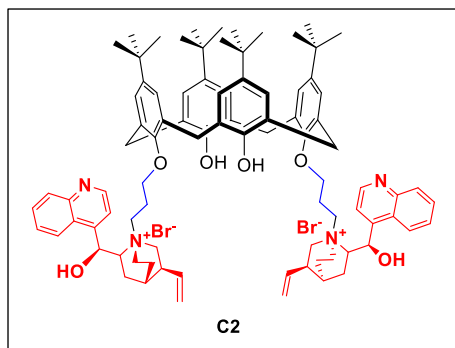
I-The *p*-*tert*-butyl calix-4-arene (A) (0.648g, 1mmol), cesium fluoride (0.182g, 1.2mmol), 1,3 dibromo-propane (0.167g, 10mmol) are added to a two neck round bottom flask containing 20ml dry DMF. The reaction mixture was stirred at 40° C for 48 hrs. The reaction was quenched with 2N HCl (20ml) and water. The product was extracted by DCM (2×20ml) using a separating funnel. The organic layer was dried over anhydrous Na₂SO₄. Removal of DCM gave white solid as a product ~700mg. ¹H NMR (500 MHz, CDCl₃) δ 10.08 (s, 1H), 9.44 (s, 2H), 7.09 (s, 2H), 7.07 (d, *J* = 2.5 Hz, 2H), 7.05 (s, 2H), 6.99 (d, *J* = 2.4 Hz, 2H), 4.35 (d, *J* = 13.0 Hz, 2H), 4.31 – 4.22 (m, 4H), 4.00 (t, *J* = 6.2 Hz, 2H), 3.45 (d, *J* = 13.5 Hz, 4H), 2.65 (p, *J* = 6.0 Hz, 2H), 1.23 – 1.18 (m, 36H). ¹³C NMR (126 MHz, CDCl₃) δ 148.71, 148.31, 147.41, 143.67, 143.11, 133.29, 128.24, 127.81, 127.28, 126.43, 125.81, 125.70, 125.60, 125.56, 74.27, 34.14, 33.90, 33.80, 32.87, 32.70, 32.01, 31.38, 31.34, 31.29, 31.10, 30.98, 30.15.



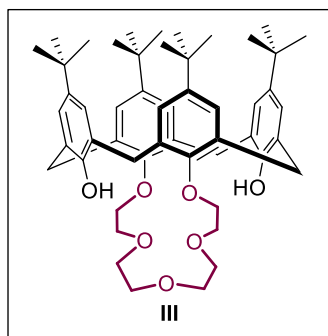
II- To a suspension of p-tert-butylcalix[4]arene (6.46 g, 10.0 mmol) in dry CH₃CN (250 mL) were added 1,3 dibromo propane (20.0 g, 0.10 mmol) and K₂CO₃ (3.45 g, 25.0 mmol). The reaction mixture was refluxed for 48 h. The solvent and unreacted dibromide were then removed in vacuo, and the residue was quenched with 5% HCL (100 mL) and CHCl₃ (200 mL). The organic phase was separated, washed with water, and dried. The solvent was then distilled off, and the oily residue was subjected to column chromatography (CH₂Cl₂-Petroleum ether (60-90 °C) 2:3) to give white, pure compound. (4.10 g, 70%). Melting point- 288-290 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.64 (s, 2H), 7.05 (s, 4H), 6.87 (s, 4H), 4.27 (d, J = 13.0 Hz, 4H), 4.12 (t, J = 5.5 Hz, 2H), 4.01 (t, J = 6.5 Hz, 2H), 3.35 (d, J = 13.0 Hz, 4H), 2.53 (p, J = 6.0 Hz, 2H), 1.28 (s, 18H), 1.02 (s, 18H). ¹³C NMR (126 MHz, CDCl₃) δ 150.99, 149.59, 147.69, 142.11, 133.19, 127.97, 126.10, 125.60, 73.75, 34.43, 34.22, 33.91, 32.27, 32.08, 31.45, 30.73, 30.11.



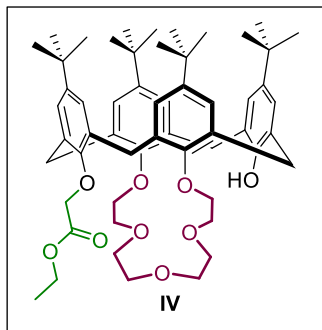
C1- A mixture of cinchonine (1.1 mmol) and compound I (0.5 mmol) was dissolved in 20ml dry toluene in two-neck round bottom flask. The reaction mixture stirred at 100 °C for 24hrs under nitrogen. After the completion of reaction (checked by TLC), solvent was evaporated to get a solid product which was recrystallized in diethyl ether and chloroform to give pure crystals White solid; 0.500 g, yield 47%. [α]₂₅^D = -100 (c = 0.1, CHCl₃); ¹H NMR (CDCl₃) δ: 8.85 (d, J = 4.4, 2H), 8.05 (d, J = 8.2, 2H), 7.94 (d, J = 8.4, 2H), 7.70 (d, J = 4.4, 2H), 7.48 (d, J = 8.1, 2H), 7.26–7.20 (m, 5H), 6.45 (s, 2H), 6.11–5.99 (m, 2H), 5.24–5.13 (m, 3H), 4.13 (d, J = 9.3, 2H), 3.27 (m, 6H), 3.02 (m, 2H), 2.50 (d, J = 8.9, 2H), 2.41–2.28 (m, 2H), 1.93 (s, 1H), 1.82 (s, 2H), 1.70–1.57 (m, 2H), 1.35 (s, 9H), 1.33 (s, 18H), 1.31 (s, 9H), 1.06 (s, 2H). ¹³CNMR: 149.9, 149.8, 149.7, 149.4, 146.9, 143.6, 142.6, 141.3, 137.6, 129.7, 129.5, 128.2, 127.6, 125.8, 125.0, 124.2, 123.8, 120.7, 115.7, 80.3, 65.9, 65.7, 63.9, 61.2, 53.3, 41.3, 38.9, 31.4, 30.5, 26.3, 23.9, 19.8; IR (KBr): 3430 (O-H), 2935 (C-Ar), 1585 (C=N), 1314, 895 cm⁻¹, HRMS (ESI) m/z [M+H₂O]⁺ calcd for C₆₆H₈₅O₆N₂Br 1081.5591, found 1081.5587; mp 203-204 °C (Decomp)



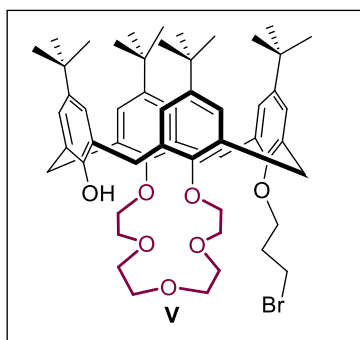
C2- A mixture of cinchonine (1.1 mmol) and compound II (0.5 mmol) was dissolved in 20 ml dry toluene in two neck round bottom flasks. The reaction mixture was stirred at 100°C for 24 hrs under nitrogen. After the completion of the reaction (checked by TLC), the solvent was evaporated to get a solid product which was recrystallized in diethyl ether and chloroform to give pure crystals White solid; 1.33 g, yield 90%. $[\alpha]_{25}^D = -85$ (c = 0.1, CHCl₃) ¹H NMR (CDCl₃) δ : 8.92 (d, 2H, J = 4.6 Hz), 8.05(d, 2H, J = 8.2 Hz), 7.91 (d, 2H, J = 4.6 Hz), 7.82(d, 2H, J = 8.4 Hz), 7.60–7.53 (m, 2H), 7.34 (t, 2H, J = 7.6 Hz), 7.09 (s, 4H), 7.00 (s, 2H), 6.77 (s, 4H), 6.59–6.55 (m, 2H), 6.37(d, 2H, J = 5.4 Hz), 5.44 (m, 2H), 5.02 (d, 2H, J = 17.3 Hz), 4.90 (d, 2H, J = 10.5 Hz), 4.59–4.48 (m, 4H), 4.43–4.36 (m, 2H), 4.18 (d, 4H, J = 13.1 Hz), 4.12–3.86 (m, 2H), 3.78–3.58 (m, 6H), 3.56 (t, 2H, J = 8.7 Hz), 3.43 (m, 2H), 3.34 (t, 4H, J = 13.0 Hz), 2.83 (br, 2H), 2.70–2.49 (m, 4H), 2.20–1.89 (m, 10H), 1.29 (s, 18H), 0.92 (s, 18H). ¹³C NMR (CDCl₃) δ : 151.6, 150.2, 149.7, 149.2, 148.0, 143.9, 141.9, 140.5, 129.8, 132.81, 13.11, 129.6, 127.7, 125.7, 125.2, 123.0, 120.9, 115.7, 80.4, 65.9, 65.7, 53.8, 41.6, 40.0, 39.2, 34.0, 33.64, 31.7, 30.8, 26.5, 24.3, 20.5; IR(KBr): 3400 (O-H), 2960 (C-Ar), 1487 (C=N), 1200, 1119, 1028 (C-N), 951, 871 cm⁻¹. HRMS (ESI) m/z [M + 2H₂O] + calcd for C₈₈H₁₁₄O₈N₄Br₂ 1514.6983, found 1514.6980; mp 240–245 °C (Decomp)



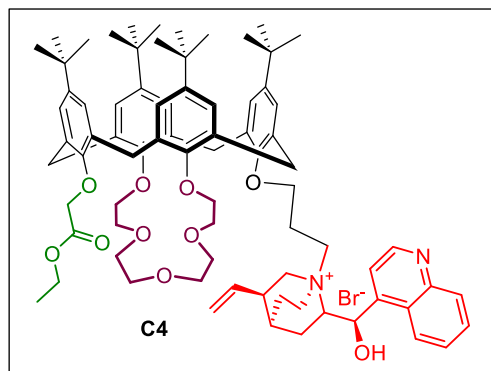
III- Synthesis of p-tert-butylcalix[4]arene-crown-5: A mixture of p-tert-butylcalix[4]arene (1.46 g, 2.25 mmol) and ^tBuOK (0.23 g, 2 mmol) in 50 mL of dry toluene was refluxed (using heating blocks) under nitrogen gas with stirring for 1.5 h, then tetraethylene glycol ditosylate (1.06 g, 2 mmol) was added. After refluxing for 24 h, a second portion of ^tBuOK (0.23 g, 2 mmol) was added, and the reaction mixture was refluxed for an additional 24 h. It was then cooled to room temperature, treated with 1 N HCl (125 mL), and extracted five or six times with 30 mL of diethyl ether each time. The combined organic layers were washed three times with water (100 mL each time), and the solvent was removed by rotary evaporation. The crude product was purified by column chromatography using silica gel as packing material and dichloromethane/ethyl acetate (4:1) as eluent gives white solid, 1.17 g, 65% yield of I, ¹H NMR (500 MHz, Chloroform-d) δ : 7.16 (s, 2H), 7.07 (s, 4H), 6.75 (s, 4H), 4.37 (d, J = 13.0 Hz, 4H), 4.07 (s, 8H), 3.97 (t, J = 5.5 Hz, 4H), 3.85 (d, J = 5.5 Hz, 4H), 3.29 (d, J = 13.0 Hz, 4H), 1.31 (s, 20 H), 0.91 (s, 16H). ¹³C NMR (126 MHz, Chloroform-d): 150.8, 149.8, 146.8, 141.2, 132.5, 129.8, 127.8, 125.4, 124.9, 71.0, 70.8, 70.3, 33.8, 31.7, 31.0



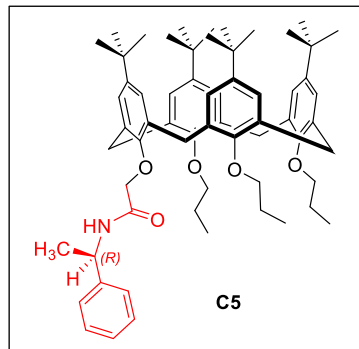
IV- Synthesis of p-tert-butylcalix[4]arene-crown-5 ester : Compound (III) (0.27 g, 0.3 mmol), NaH (0.04 g, 1.75 mmol) and ethyl bromoacetate (0.6 mL, 5.4 mmol) were taken in 70 mL diethyl ether and stirred at room temperature in an inert atmosphere for 72 h. After removing the solvent by rotavapour, the solid mass was treated with 10% HCl (50 mL) and extracted with dichloromethane (50 mL). The organic layer was washed twice with water (50 mL each time) and the solvent was removed by rotavapour. The product was purified by column chromatography using silica gel as packing material and ethyl acetate-hexane (1:5) as eluent. Initially, starting materials were eluted followed by desired ester. Removal of eluant gave white solid, 0.22g, 80 % yield. ^1H NMR (CDCl_3) δ : 7.64 (m, 1H), 7.05 (s, 4H), 6.87 (s, 4H), 5.36 (t, $J=5.5$ Hz, 2H), 4.27 (m, 6H), 4.12 (m, 8H), 4.00 (m, 4H), 3.88 (m, 4H), 3.36 (d, $J=12.0$ Hz, 4H), 1.52 (t, $J=5.2$ Hz, 3H), 1.27 (s, 18H), 1.01 (s, 18H). ^{13}C NMR (CDCl_3) δ : 169.8, 150.8, 149.8, 146.8, 141.2, 132.5, 129.8, 127.8, 125.4, 124.9, 71.0, 70.8, 70.3, 67.9, 33.8, 31.7, 30.9, 25.6



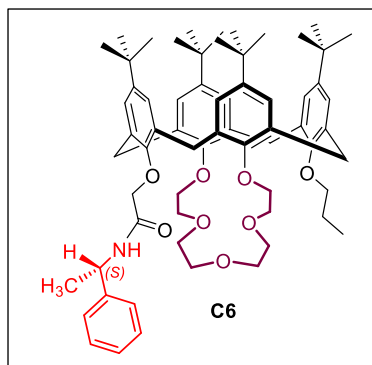
V-Synthesis of bromopropyl p-tert-butylcalix[4]arene-crown-5: To a solution of CsF (0.18 g, 1.2 mmol) in dry DMF (20 mL), p-tert-butylcalix[4]arene-crown-5 (III, 0.81 g, 1 mmol) and 1,3-dibromopropane (1.02 mL, 10 mmol). The reaction mixture was stirred at 40 °C (water bath) for 48 h. TLC followed the progress of the reaction, and after completion the reaction was quenched with 2N HCl (40 mL). The reaction mixture was extracted with CH_2Cl_2 , (2 x 20 mL). The combined organic layers were washed with water (2 x 25 mL) and dried with anhydrous MgSO_4 . After evaporation of the solvent, the remaining crude product was recrystallized in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (1:1) to afford white crystals 0.65g, 70% yield, ^1H NMR (500 MHz, Chloroform- d) δ : 7.64 (s, 1H), 7.05 (s, 4H), 6.87 (s, 4H), 4.27 (m, 6H), 4.12 (s, 8H), 3.99 (t, $J = 5.5$ Hz, 4H), 3.88 (m, 4H), 3.61 (m, 2H), 3.33 (d, $J = 13.0$ Hz, 4H), 2.22 (m, 2H), 1.27 (s, 18 H), 1.01 (s, 18H). ^{13}C NMR (126 MHz, Chloroform- d): 150.8, 149.8, 146.8, 141.2, 132.5, 129.8, 127.8, 125.4, 124.9, 71.0, 70.8, 70.3, 67.9, 33.8, 31.7, 30.9, 25.6.



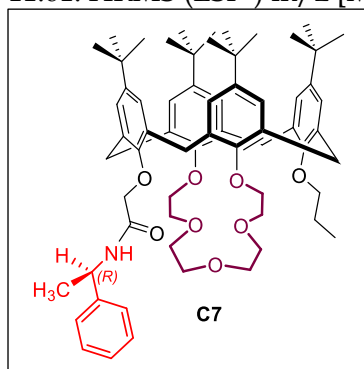
C4- Synthesis of C4: In a two-neck round bottom flask, a mixture of cinchonidine (0.12 g, 0.40 mmol) and compound (VI, 0.40 g, 0.39 mmol) was dissolved in 20 ml of dry toluene. In an inert environment, the reaction mixture was stirred at 100°C (using a heating block) for 24 h. After the completion of the reaction (monitored by TLC), a solid off-white product was obtained by evaporating the solvent. Pure product was obtained to obtain White crystalline compound, 0.49 g; 95% yield, $[\alpha]_{28}^D = +95^\circ$ (c 1, CHCl₃); ¹H NMR (CDCl₃) δ : 8.89 (d, J = 4.4, 2H), 8.12 (d, J = 8.2, 2H), 7.99 (d, J = 8.4, 2H), 7.68 (t, 2H), 7.61 (d, J = 8.1, 2H), 7.05 (t, 2H), 7.02 (s, 4H), 6.86 (s, 4H), 6.00 (m, 2H), 5.77 (d, 2H), 5.05–5.01 (m, 3H), 4.26 (d, 4H), 4.11 (m, 2H), 3.98 (m, 1H), 3.96 (d, 1H), 3.64 (m, 2H), 3.38 (t, 7H), 3.32 (m, 3H), 3.10 (m, 3H), 2.98 (m, 2H), 2.7 (m, 1H), 2.48 (m, 2H), 2.26 (m, 3H), 2.06 (m, 4H), 1.75 (m, 3H), 1.38 (m, 5H), 1.25 (s, 5H), 1.19 (s, 20H), 1.01 (s, 16H). ¹³C NMR (126 MHz, Chloroform-d): 150.2, 140.2, 130.4, 129.0, 126.6, 125.7, 125.2, 123.0, 118.3, 114.8, 71.6, 60.1, 50.0, 49.5, 39.8, 34.0, 33.8, 31.9, 31.7, 31.0, 29.7, 29.6, 28.1, 26.2, 21.2, 14.1; HRMS (ESI) m/z [M] + calcd for C₇₈H₁₀₂O₁₀N₂Br 1306.6796, found 1306.6795; mp 194–197°C (decomp)



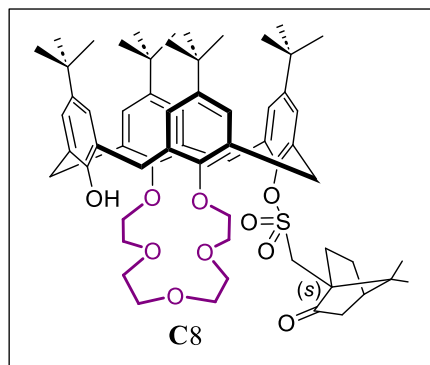
C5-Synthesis of Catalyst C5: Oxalyl chloride (0.522g, 4.12 mmol) was slowly added to a stirred solution of VIII (0.267g, 0.32 mmol) in 15 mL of dry CHCl₃ at 0°C. The reaction mixture was refluxed under nitrogen atmosphere for 24 h, then was cooled at room temperature and the solvent was removed under reduced pressure to give a white solid. The crude product was dissolved in 6 mL of dry CHCl₃ and added dropwise to a stirred solution of (S)-α-methylbenzylamine (0.0387g, 0.32 mmol) and Et₃N (0.0323g, 0.32 mmol) in 3 mL of dry CHCl₃ at 0°C. The reaction mixture was stirred for 24 h at room temperature under nitrogen atmosphere followed by washing with a 1N aqueous solution of HCl (2 × 5 mL). The aqueous phase was extracted with CHCl₃ (3 × 5 mL). The collected organic layers were washed with H₂O (10 mL), dried over Na₂SO₄, and evaporated. The crude product was purified by column chromatography (SiO₂, CH₂Cl₂) to afford catalyst C5 as a white solid (0.294g, 82 %): mp 120–121 °C; $[\alpha]_{20}^D = -40 \pm 0.8$ (c = 1.00, CHCl₃); ¹H NMR (500 MHz, Chloroform-d) δ 8.48 (s, 1H), 7.90 (s, 1H), 7.14 (s, 1H), 7.04 (s, 4H), 6.86 (s, 3H), 6.54–6.48 (m, 2H), 5.60 (s, 2H), 4.30 (d, J = 13.1 Hz, 4H), 3.95 (t, J = 6.4 Hz, 3H), 3.81–3.70 (m, 3H), 3.31 (d, J = 12.9 Hz, 4H), 2.06–2.00 (m, 3H), 1.72 (d, J = 6.8 Hz, 3H), 1.66 (d, J = 7.0 Hz, 1H), 1.60 (d, J = 6.8 Hz, 1H), 1.27 (s, 27H), 1.01 (s, 12H), 0.82 (s, 9H). ¹³C NMR (126 MHz, Chloroform-d) δ 152.37, 149.25, 148.38, 145.12, 139.68, 131.31, 127.94, 127.50, 126.19, 125.45, 123.91, 123.48, 123.40, 123.19, 123.09, 76.51, 50.38, 30.13, 29.52, 28.14, 21.87, 21.83, 12.57. HRMS (ESI+) m/z [M + H]⁺ calcd for C₆₃H₈₅NO₅, 935.6402; found 935.6406.



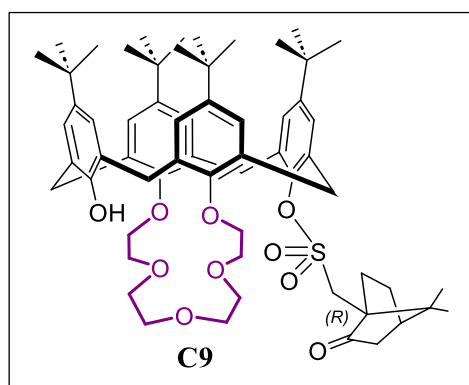
C6-Synthesis of Catalyst C6: Oxalyl chloride (0.393 g, 3.1 mmol) was slowly added to a stirred solution of IX (0.485g, 0.4 mmol) in 10 mL of dry CHCl_3 at 0°C . The reaction mixture was refluxed under nitrogen atmosphere for 24 h, then was cooled at room temperature and the solvent was removed under reduced pressure to give a white solid. The crude product was dissolved in 6 mL of dry CHCl_3 and added dropwise to a stirred solution of (S)- α -methylbenzylamine (0.058 g, 0.4 mmol) and Et_3N (0.04 g, 0.4 mmol) in 3 mL of dry CHCl_3 at 0°C . The reaction mixture was stirred for 24 h at room temperature under a nitrogen atmosphere, then was washed with a 1N aqueous solution of HCl (2×5 mL). The aqueous phase was extracted with CHCl_3 (3×5 mL). The collected organic layers were washed with H_2O (10 mL), dried over Na_2SO_4 and evaporated. The crude product was purified by column chromatography (SiO_2 , CH_2Cl_2) to afford catalyst C6 as a white solid (0.485 g, 90 %): mp $106 - 107^\circ\text{C}$; $[\alpha]_D^{20} = +30 \pm 0.8$ ($c = 1.00$, CHCl_3); ^1H NMR (500 MHz, Chloroform- d) δ 7.33 (m, 1H), 7.12 (s, 4H), 7.01 (m, 2H), 6.43 (s, 4H), 5.01 (m, 1H), 4.36 (d, $J = 12.5$ Hz, 4H), 4.32 – 4.21 (m, 8H), 3.80 (d, $J = 11.7$ Hz, 8H), 3.69 (t, $J = 7.4$ Hz, 4H), 3.14 (d, $J = 12.6$ Hz, 4H), 1.98 – 1.92 (m, 4H), 1. (s, 2H), 1.34 (s, 18H), 0.92 (m, 4H), 0.81 (s, 18H). ^{13}C NMR (126 MHz, Chloroform- d) δ 152.49, 151.52, 142.43, 141.41, 136.76, 132.88, 123.01, 121.89, 116.35, 111.55, 75.20, 74.75, 74.50, 74.24, 70.00, 69.34, 68.79, 67.54, 31.55, 31.03, 29.39, 29.22, 28.60, 28.49, 26.85, 20.99, 11.61. HRMS (ESI+) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{65}\text{H}_{87}\text{NO}_8$, 1009.6409; found 1009.6410.



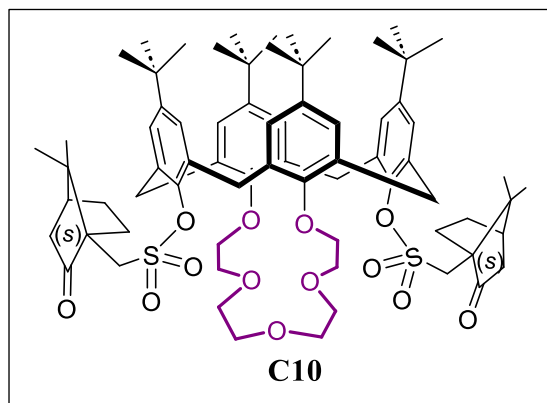
C7: Catalyst was synthesized with the same procedure for catalyst C6. The crude product was purified by column chromatography (SiO_2 , CH_2Cl_2) to afford C7 as a white solid (0.458g, 85 %): mp $106 - 107^\circ\text{C}$; $[\alpha]_D^{20} = -31 \pm 0.8$ ($c = 1.00$, CHCl_3); NMR (500 MHz, Chloroform- d) δ 7.32 (m, 1H), 7.12 (s, 6H), 7.02 (m, 2H), 6.43 (s, 4H), 5.01 (m, 1H), 4.36 (d, $J = 12.5$ Hz, 4H), 4.29 (d, $J = 3.4$ Hz, 4H), 4.27 – 4.21 (m, 4H), 3.82 (d, $J = 4.5$ Hz, 4H), 3.78 (d, $J = 4.8$ Hz, 4H), 3.69 (t, $J = 7.4$ Hz, 4H), 3.14 (d, $J = 12.6$ Hz, 4H), 1.96 (d, $J = 7.4$ Hz, 3H), 1.47 – 1.41 (m, 3H), 1.34 (s, 16H), 1.05 (t, $J = 7.4$ Hz, 3H), 0.81 (s, 20H). ^{13}C NMR (126 MHz, CDCl_3) δ 167.08, 153.99, 151.38, 143.94, 142.92, 134.38, 130.68, 124.51, 123.39, 71.51, 70.85, 70.30, 69.05, 30.72, 30.10, 29.99, 28.68, 22.50, 13.11. HRMS (ESI+) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{65}\text{H}_{87}\text{NO}_8$, 1009.6412; found 1009.6414



C8: To a solution of calix[4]crown-5 (**III**) (1.2g, 1.5 mmol) in Dry THF/DMF mixture (16/1), a 60% suspension of sodium hydride in mineral oil was added (0.06g, 1.62 mmol). After stirring the reaction mixture at room temperature for 2 hours, (+)-10-camphor sulfonyl chloride (0.40g, 1.65 mmol) in THF (2.5 mL) was added. The reaction mixture was stirred at ambient temperature for 18h. The solvent was removed under vacuum and the oily residue was dissolved into chloroform and washed with saturated NH_4Cl solution. Then the organic layer was dried over Na_2SO_4 . The residue was further purified through column chromatography $\text{CH}_2\text{Cl}_2/\text{MeOH} = 95/5$ to 60/40 as eluent to afford **C8** as a white crystalline solid (1.14 g, 76%); $[\alpha]^{28}_{\text{D}} = +52^\circ$ (c 1, CHCl_3); ^1H NMR (500 MHz, Chloroform-*d*) δ 7.19 (s, 1H), 7.07 (s, 4H), 6.75 (s, 4H), 4.60 (m, 1H), 4.37 (d, $J = 13.0$ Hz, 4H), 4.08 (s, 8H), 3.97 (t, $J = 5.3$ Hz, 4H), 3.84 (t, $J = 5.5$ Hz, 4H), 3.29 (d, $J = 13.0$ Hz, 4H), 3.18 (s, 1H), 2.06 – 1.94 (m, 3H), 1.31 (s, 18H), 1.19 (s, 3H), 1.11 (s, 3H), 1.04 (d, $J = 7.4$ Hz, 6H), 0.91 (s, 18H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 214.73, 214.17, 150.82, 149.82, 146.85, 141.23, 135.12, 134.93, 134.83, 134.30, 134.24, 132.51, 127.85, 125.56, 125.35, 125.01, 124.96, 71.26, 71.07, 70.90, 70.69, 70.37, 70.06, 58.66, 58.39, 47.81, 47.70, 43.37, 43.11, 42.49, 33.89, 33.85, 31.68, 31.34, 31.04, 30.97, 20.35, 20.17, 20.07, 19.96, 19.78. HRMS (ESI+) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{62}\text{H}_{84}\text{O}_{10}\text{S}$, 1020.5800; found 1020.5805



C9: The synthetic procedure is the same as catalyst **C8** using (-)-10-camphor sulfonyl chloride; The residue was purified through column chromatography $\text{CH}_2\text{Cl}_2/\text{MeOH} = 95/5$ to 60/40 as eluent to afford **C9** as a white crystalline solid (1.11 g, 74%); $[\alpha]^{28}_{\text{D}} = -50^\circ$ (c 1, CHCl_3); ^1H NMR (500 MHz, Chloroform-*d*) δ 7.29 (s, 1H), 7.07 (s, 4H), 6.75 (s, 4H), 4.60 (m, 1H), 4.37 (d, $J = 13.0$ Hz, 4H), 4.07 (s, 8H), 3.96 (t, $J = 5.4$ Hz, 4H), 3.84 (d, $J = 5.4$ Hz, 4H), 3.29 (d, $J = 13.1$ Hz, 4H), 3.18 (m, 1H), 2.00 (m, 1H), 1.31 (s, 20H), 1.11 (s, 4H), 1.04 (s, 4H), 1.03 (s, 4H), 0.91 (s, 16H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 213.73, 213.17, 149.82, 148.82, 145.85, 140.23, 131.511, 126.85, 124.56, 124.35, 124.01, 123.96, 57.66, 57.39, 46.81, 46.70, 46.26, 42.37, 41.49, 32.89, 32.86, 30.88, 30.68, 30.35, 29.97, 18.96, 18.87. HRMS (ESI+) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{62}\text{H}_{84}\text{O}_{10}\text{S}$, 1020.5800; found 1020.5803



C10: To a solution of calix[4]crown-5 **III** (1.2g, 1.5 mmol) in DryTHF/DMF mixture (16/1), a 60% suspension of sodium hydride in mineral oil was added (0.14g, 6.0 mmol). After stirring the reaction mixture at room temperature for 2 hours, D-(+)-10-camphor sulfonyl chloride (1.50g, 8.0 mmol) in THF (2.5 mL) was added. The reaction mixture was stirred at ambient temperature for 5h followed by heating at 70 °C for 12h. Reaction was monitored via TLC. After completion of reaction, reaction mixture was cooled to room temperature and solvent was removed under vacuum and the oily residue was dissolved into chloroform and washed with saturated NH₄Cl solution. Then the organic layer was dried over Na₂SO₄. The residue was further purified through column chromatography CH₂Cl₂/MeOH = 95/5 to 60/40 as eluent to afford **C10** as a white crystalline solid (1.47 g, 80%); [α]_D²⁸ = +78° (c 1, CHCl₃); ¹H NMR (600 MHz, Chloroform-*d*) δ 7.07 (s, 4H), 6.75 (s, 4H), 4.38 (d, *J* = 13.0 Hz, 4H), 4.37-4.25 (m, 2H), 4.10 – 4.06 (m, 4H), 3.96 (d, *J* = 5.4 Hz, 4H), 3.85 (d, *J* = 5.4 Hz, 4H), 3.30 (d, *J* = 13.1 Hz, 4H), 2.83 (s, 2H), 2.17 – 1.90 (m, 2H), 1.78 (s, 4H), 1.34 (s, 2H), 1.31 (s, 20H), 1.21 (s, 4H), 0.94 (s, 4H), 0.91 (s, 16H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 214.41, 214.15, 150.82, 149.81, 146.85, 141.22, 132.51, 127.84, 125.44, 124.97, 71.07, 70.90, 70.37, 43.26, 42.82, 42.52, 42.4, 37.12, 34.15, 33.92, 33.89, 33.85, 33.82, 33.06, 31.76, 31.50, 31.35, 31.27, 31.04, 30.99, 29.72, 26.90, 24.93, 22.72, 20.25, 20.25, 19.86, 19.71, 14.14. HRMS (ESI+) *m/z* [M + H]⁺ calcd for C₇₂H₉₈O₁₃S₂ 1234.6400; found 1234.6406