2

Literature review

2.1 Calixarene-based catalysts in a wide range of applications

Calix[4]arenes are macromolecular compounds having cone-shaped arene cavity. When properly derivatized, the bottom annulus and the upper part can both be utilized for host-guest interactions, and recognition of ions and molecular species. They have gained tremendous attention because of their utilization in supramolecular chemistry. After their functionalization calixarenes have been developed as new phase-transfer agents for normal PTC reactions and gene delivery, in catalysis, cation receptors, metal ion complexes of calix-conjugates, quaternized nitrogen center-based calix[4]arene conjugate, and many more. Alkylation reactions of active methylene compounds, alcohols and phenols with alkyl halides in aqueous NaOH solution can be carried out without the need for any added organic solvents in most cases. The water-soluble calix[n]arenes, which contain trimethylammoniomethyl groups on the upper rim, were used as inverse phase-transfer catalysts, resulting in the corresponding alkylated products in good to high yields.(Shimizu et al., 1997)(Figure 2.1)

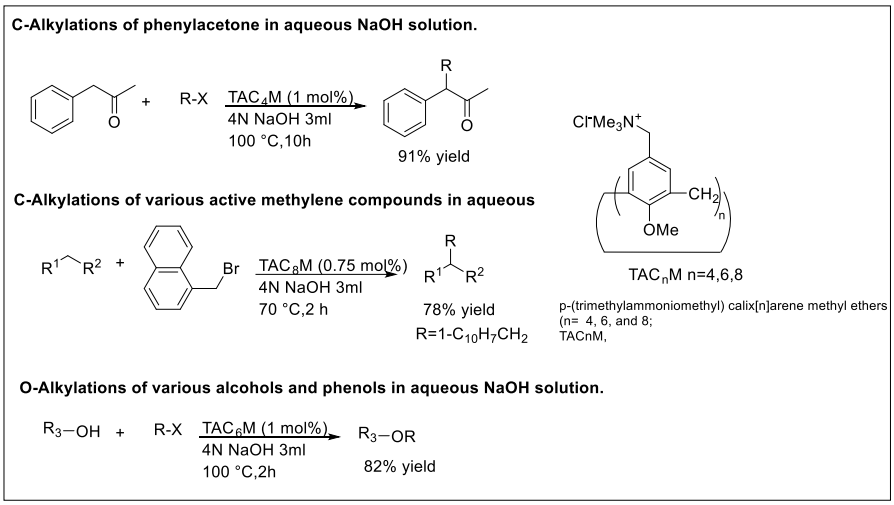


Figure 2.1 Alkylation reactions of active methylene compounds, alcohols, and phenols with alkyl halides in aqueous NaOH solution

Metal-based calixarenes like Ti(IV)/calixarene complexes can be used as efficient catalysts in the aldol reaction of Chans silyloxydiene with a range of aldehydes(Soriente et al., 2005b) (Figure 2.2)

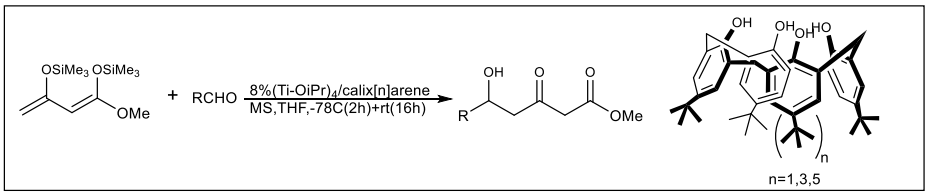


Figure 2.2 Aldol reaction of Chans silyloxydiene

The catalytic activity of calix[4]-arene-based quaternary ammonium salts was investigated for the Darzens condensation, O/N-alkylation reactions, and ethylbenzene oxidation.(Srivastava and Srivastava, 2007a) (Figure 2.3)

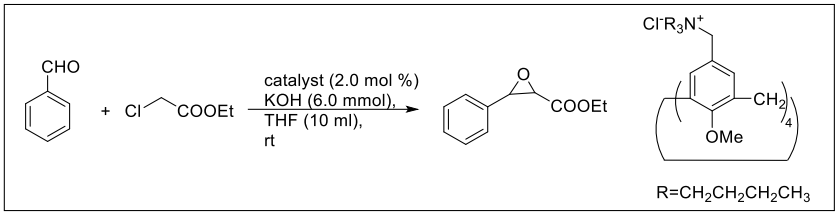


Figure 2.3 Darzens condensation, O/N-alkylation reactions

Another metal-based calixarene catalyst chlorotitanium calix[4]arene a complex was used as the catalyst for the polymerization of L- and rac-lactide under solvent-free conditions. The catalysts' high activity depended on the monomer-to-catalyst molar ratio and led to highly isotactic PLLA.(Massa et al., 2001b)(Figure 2.4)

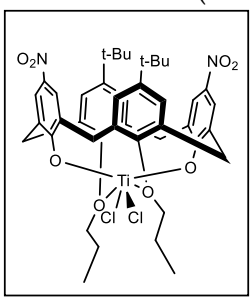


Figure 2.4 Chlorotitanium calix[4]arene complex

Surfactant-type Bronsted acid catalysts were synthesised from Calix[*n*]arene sulfonic acids that had aliphatic chains for allylic alkylation that yielded (60–94%).(Liu et al., 2008b)(Figure 2.5) and Dehydrative amination of alcohols in water using a water-soluble calix[4]resorcinarene sulfonic acid as a reusable multifunctional catalyst(Shirakawa and Shimizu, 2008b) (Figure 2.6)

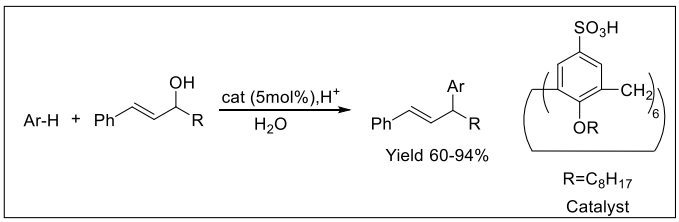


Figure 2.5 Allylic alkylation with allyl alcohols in water

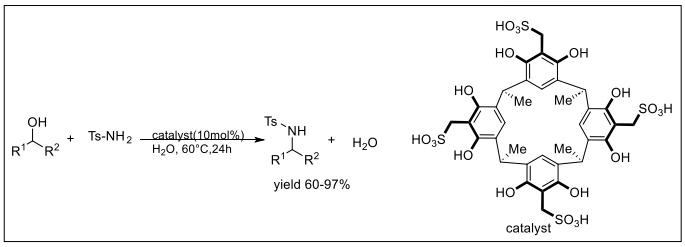


Figure 2.6 Dehydrative amination of alcohols

p-sulfonic acid calixarenes as organocatalysts was utilized for obtaining 3,4-dihydropyrimidin-2(1H)-ones/-thiones through Biginelli reactions. Many aromatic aldehydes as well as urea or thiourea can be employed for successfully synthesizing the corresponding Biginelli adducts.(da Silva et al., 2011)(Figure 2.7)

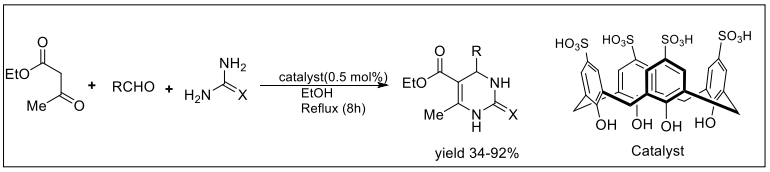


Figure 2.7 Biginelli reaction utilizing p-sulfonic acid calixarenes

The first examples of calixarene ionic liquids with 3D-shaped cavities. The phase transfer catalysis in water showed that they possessed excellent catalytic properties of aromatic nucleophilic substitution reaction and benzyl nucleophilic substitution. The optimized yields of product in the catalytic reaction were as high as approximately 97%.(Yang et al., 2012)(Figure 2.8)

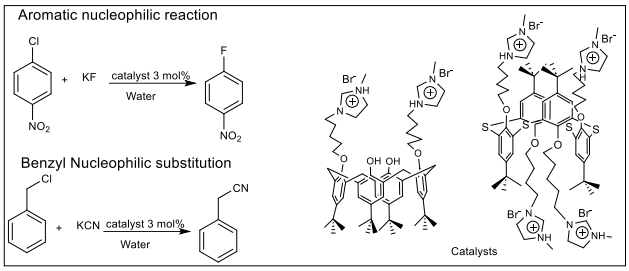


Figure 2.8 Aromatic nucleophilic substitution reaction and benzyl nucleophilic substitution catalysed by calixarene ionic liquid.

Piperidine derivatives can be synthesized via pseudo-five component, one-pot domino reaction through a combination of β-ketoesters, aromatic aldehydes, and various amines using p-sulfonic acid calix[n]arenes as catalysts(Palermo et al., 2016). (Figure 2.9)

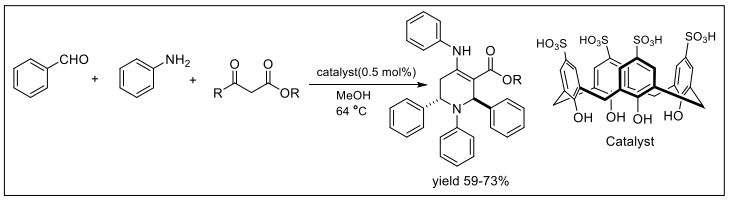


Figure 2.9 Synthesis of piperidine derivatives using p-sulfonic acid calix[n]arenes

Thioureido-calixarenes were utilized for a rate acceleration for the Vinylogous Mukaiyama Aldol Reaction (VMAR). The ability of the calixarene catalyst to accelerate the VMAR under on-water conditions is closely related to its hydrophobicity and to its recognition abilities toward the substrate.(De Rosa et al., 2016) (Figure 2.10)

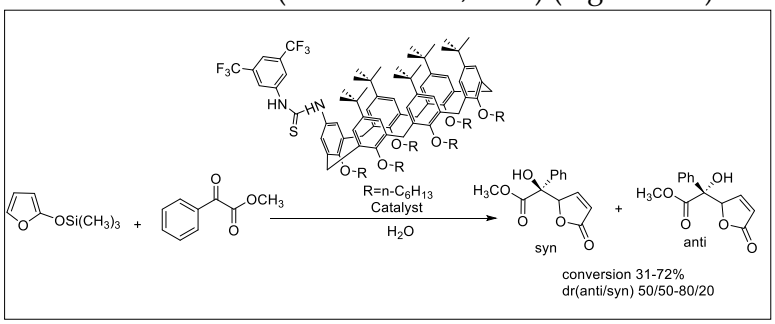


Figure 2.10 Vinylogous Mukaiyama Aldol Reactions

A facile method for the preparation of enantiomerically pure inherently chiral calix[4]arene phosphonic acid. The first tests of this unique calixarene Bronsted acid with inherent chirality in organocatalysis of the aza-Diels−Alder reaction of imines with Danishefsky's diene and epoxide ring opening by benzoic acid were performed. The calixarene phosphonic acid shows good catalytic activities(De Rosa et al., 2016) (Figure 2.11)

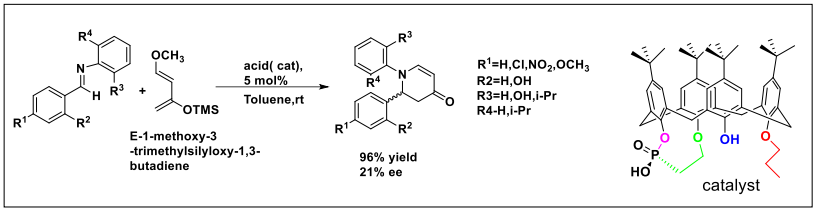


Figure 2.11 Calixarene-based organophosphorus Brönsted acids with inherent chirality

Table2.1 Various applications of calix[4]arene -based catalysts

S.no	Catalysts	Applications	result	references
1	Water-soluble calix[n]arenes 1n (n = 4, 6 and 8) containing trimethylammoniomethyl groups	nucleophilic substitution reaction of alkyl and arylalkyl halides with nucleophiles in water.	higher activity than CDs	(Shimizu et al., 1997)
2	Barium salt of p-tert-butylcalix[4]arene-crown-5	methanolysis of aryl acetates	The turnover frequency 3.8×10^{-4} min^{-1} to 7.4×10^{-3} min^{-1}	(Baldini et al., 2000)
3	1,2-alternate, Me_2Si-bridged p-tert-butylcalix[4]arene	[2 + 2 + 2] cycloaddition of terminal alkynes	first-order dependence 98% conversion	*(Ozerov et al., 2000)*
4	Ti(IV)–calix[4]arenes	epoxidation of allylic alcohols	95% yield	(Massa et al., 2001a)
5	Calix[*n*]arenes, which contain trimethylammoniomethyl groups on the upper rim	Aldol-type condensation and Michael addition reactions of activated methyl and methylene compounds	84% yield	(Shimizu et al., 2001)
6	Water-soluble calix[*n*]arenes, which contain trimethylammoniomethyl groups on the upper rim	alkylation reactions of active methylene compounds, alcohols, and phenols with alkyl halides	85 % yield	(Shimizu et al., 2002)
7	1,3-dimethoxy-*p*-Bu^t calix[4]arene titanium dichloride	ethylene polymerization		(Capacchione et al., 2003)
8	Ti(IV)/calixarene complexes	aldol reaction of Chans silyloxydiene with a range of aldehydes	91% yield	(Soriente et al., 2005a)
9	Calix[4]resorcinarene sulfonic acid	Mannich reaction benzaldehyde was treated with o-anisidine and 1-phenyl-1-(trimethylsiloxy)ethene	81% yield.	(Shimizu et al., 2006)

10	Calix[4]arene scaffold based quaternary ammonium salts	Darzens condensation benzaldehyde with α-chloroester	72% yield (O/N-alkylation) (yield 98%) and ethylbenzene oxidation	(Srivastava and Srivastava, 2007a)
11	Chlorotitanium calix[4]arene	polymerization of L- and rac-lactide	>99% monomer conversion	*(Frediani et al., 2008)*
12	Sulfonated-calixarene	alkylation of allylic alcohols with Indols	60–94% yields	(Liu et al., 2008a)
13	Water-soluble calix[4]resorcinarene sulfonic acid	dehydrative amination of alcohols.	97% yield	(Shirakawa and Shimizu, 2008a)
14	Inherently chiral calix[4]arenes containing quinolin-2-yl-methanol	catalytic asymmetric addition of diethylzinc to benzaldehyde	80% yield 17.9 %.ee	(Miao et al., 2009)
15	Titanacalixarenes	ethylene Polymerisation	Activity=350	(Espinas et al., 2010)
16	*p*-sulfonic acid calix[4]arene	4-(Methylthio)benzaldehydewas combined with3ethylacetoacetate and urea	92% yield	(da Silva et al., 2011)
17	5,11,17,23-tetrabutyl-25-[2-(diphenylphosphino)benzoate]-26,27,28-trihydroxycalix-[4]arene	Aza-Morita-Baylis-Hillman (aza-MBH) reaction of N-sulfonated imines with methyl vinyl ketone.	96% yield	(Shen et al., 2012)
18	Calixarene ionic liquids	aromatic nucleophilic substitution reaction and benzyl nucleophilic substitution.	97% yield	(Yang et al., 2012)
19	Tripropoxy-p-tert-butylcalix[4]arene and di-n-butylmagnesium	ring-opening polymerization of rac-Lactide	99% conversion in 5 minutes	(Walton et al., 2014)
20	*p*-sulfonic acid calix[*n*]arenes	methyl acetoacetate, benzaldehyde, and aniline	73% yield	(Palermo et al., 2016)
21	Thioureido-calixarenes	vinylogous Mukaiyama Aldol Reaction 2-(trimethylsiloxy)furan with	77% yield	(De Rosa et al., 2016)

		methylbenzoylformate		
22	Chiral calix[4]arene phosphoric acid	(a) aza-Diels–Alder reaction of imines with Danishefsky's diene (b) epoxide ring opening by benzoic acid	(a) 72% yield and 21 % ee (b) 75% yield; 11% ee	*(Karpus et al., 2018a)*
23	*p*-sulfonic acid calix[4]arene	Povarov reaction 4-bromoaniline, formaldehyde, and 2,3-dihydrofuran	94% yield	(Abranches et al., 2018)
24	Monometallic Zinc complex of oxygen depleted bis(pyrazole)-p-tert-butylcalix[4]arene	acetylation of alcohols and lactide polymerization	100% conversion	(Sinha et al., 2019)
25	Methylated bis-triethylene glycolic crown-5-calix[4]arene	as a phase-transfer catalyst in the nucleophilic aromatic ^{18}F - fluorination	95.2%	(Lee et al., 2020)

2.2 Asymmetric Michael Addition reaction utilizing calix[4]arene based catalysts and brief literature review

In synthetic organic chemistry, creating new chemical transformations for the effective and useful synthesis of complex structures has become the primary goal. The stereo-controlled synthesis of various significant scaffolds has been made possible by exploring several organic reactions for this aim. The asymmetric Michael reaction has been utilized extensively to produce important building block natural products also it is one of the most effective techniques for the production of carbon-carbon bonds.(Scheffler and Mahrwald, 2013, Zhang and Wang, 2012). Michael adducts could be synthesized by various Michael donors and acceptors, including chiral substrates. More recently asymmetric organocatalysis has emerged as a new, powerful, and effective methodology (Dalko and Moisan, 2001). Inherently chiral calix[4]arenes containing an amino alcohol structure or a quaternary ammonium moiety. These optically pure chiral calix[4]arenes were applied to asymmetric reactions as organocatalysts(Shirakawa and Shimizu, 2010a)(Figure 2.12). Calix[4]arene-based chiral bifunctional primary amine–thiourea catalysts as efficient organocatalysts for the asymmetric Michael addition of isobutyraldehyde and cyclopentanecarboxaldehyde to nitroalkenes. The reactions proceeded to give high yields (up to 95%) and (ee up to 99%)(Durmaz and Sirit, 2013b) (Figure 2.13)

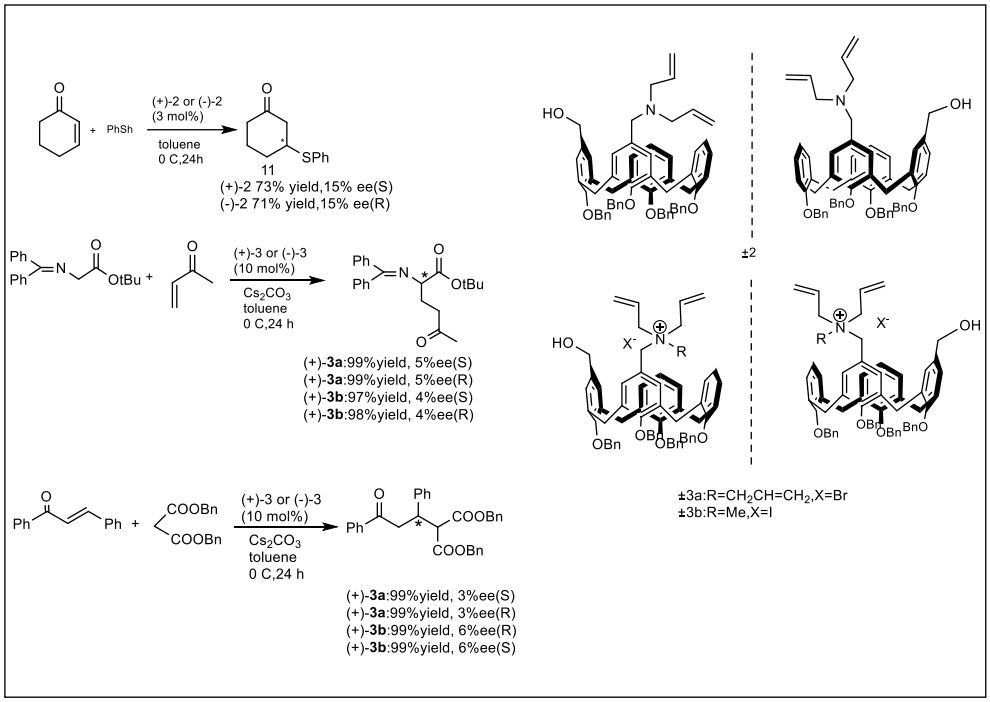


Figure 2.12 Inherently chiral calix[4]arene amino acid catalysed reactions

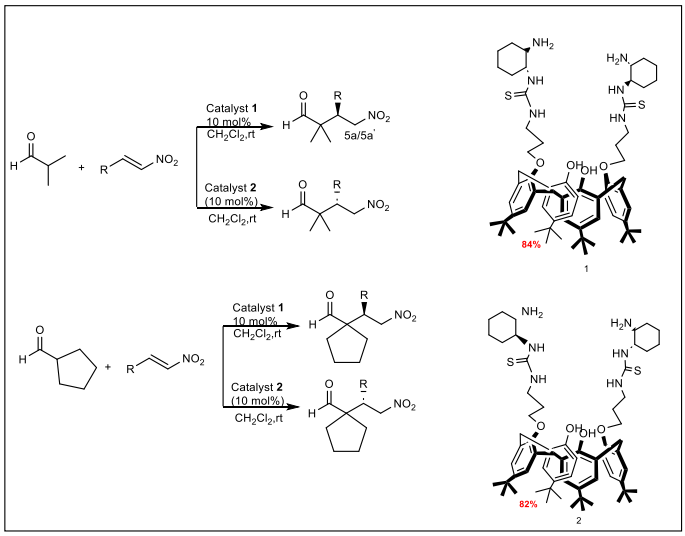


Figure 2.13 Asymmetric Michael addition of isobutyraldehyde and cyclopentanecarboxaldehyde to nitroalkenes

Another organocatalyst for asymmetric Michael addition of aldehydes to maleimides is calix[4]arene-based chiral bifunctional primary amine–thiourea catalysts 3a and 3b The reactions proceeded smoothly to give high yields (up to 99%) and *ee* (up to 98%)(Durmaz and Sirit, 2013a) (Figure 2.14)

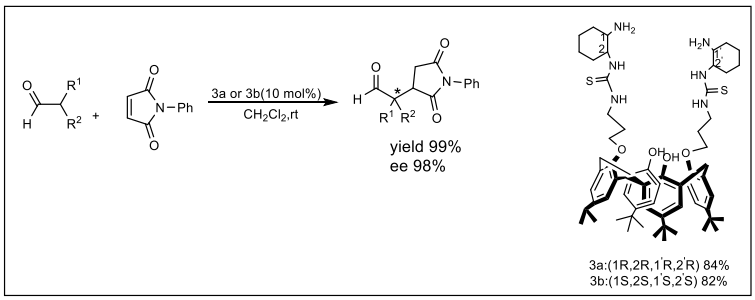


Figure 2.14 Asymmetric Michael addition of aldehydes to maleimides

chiral calix[4]arene with bis-squaramide moieties as bifunctional organocatalyst to catalyze the enantioselective conjugate addition of acetylacetone to various nitroolefins at room temperature(Vural et al., 2016)(Figure 2.15)

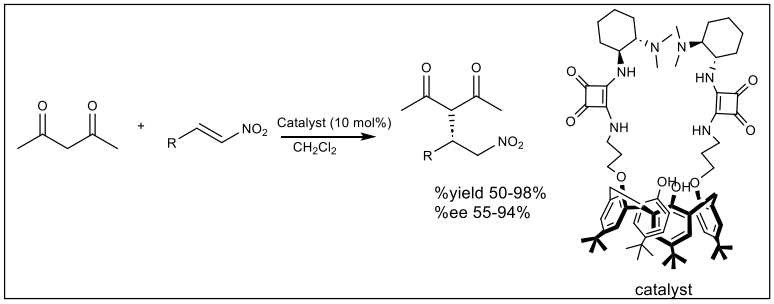


Figure 2.15 Conjugate addition of acetylacetone

Bifunctional chiral thiourea-tertiary amines bearing a calix[4]arene scaffold were synthesized and applied in catalytic asymmetric Michael addition of acetyl acetone and dimethyl malonate to nitroolefins.The corresponding adducts were obtained in excellent yields (up to 99%) and with high enantioselectivities (up to 94% ee)(Durmaz et al., 2016).Figure 2.16)

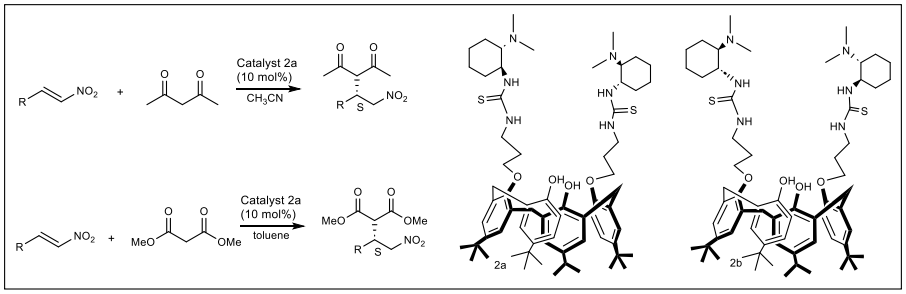


Figure 2.16 Michael addition of acetyl acetone and dimethyl malonate to nitroolefins

Table 2.2 The homogeneous Michael addition reaction is examined using previously reported chiral catalysts. The relevant literature studies are tabulated in table

S.No	Catalyst	Substrate	% yield and %ee	References
1	Inherently chiral calix[4]arene amino acid	(a) Thiophenol (b) glycine derivative (c) malonate	(a)73% yield ;15% ee (b)99% yield;5% ee (c) 99% yield;6% ee	(Shirakawa and Shimizu, 2009a)
2	Inherently chiral ABCD-type calix[4]arenes	Enones Thiophenol	99% yield; 30% ee	(Shirakawa et al., 2009a)
3	Chiral calix[4]arenes bearing a tertiary amine or a quaternary ammonium m oiety, together with a diarylmethanol moiety	Michael addition reaction of thiophenol	81% yield; 23% ee	(Shirakawa and Shimizu, 2010a)
4	Chiral calix[4]arene – thiourea catalysts	isobutyraldehyde to *trans*-β-nitrostyrene	95% yield; 99% ee	(Durmaz and Sirit, 2013b)

5	Calix[4]arene-based chiral bifunctional primary amine–thiourea catalysts	Aldehydes with maleimides	99% yield; 98% ee	(Durmaz and Sirit, 2013a)
6	Calix[4]arene-based chiral bifunctional primary amine–thiourea catalyst	Michael addition of aldehydes with nitroalkenes	95% yield ;99% ee	(Durmaz and Sirit, 2013b)
7	Chiral calix[4]arene with bis-squaramide	acetylacetone to β-nitrostyrenes	99% yield;94% ee	(Vural et al., 2016)
8	Calix[4]arene-based chiral bifunctional tertiary amine–thiourea catalysts	Michael additions of acetyl acetone and dimethyl malonate to nitroolefins	99 % yield; 94% ee	(Durmaz et al., 2016)
9	Upper-rim functionalized calix[4]arene-based thiourea installed onto the (R,R)-1,2-cyclohexane diamine scaffold	(a) Isobutyraldehyde and *N*-Phenylmaleimide (b) Isobutyraldehyde and β-Nitrostyrenes	(a) 98% yield;88% ee (b) 98% yield;93% ee	(De Simone et al., 2018)
10	Bifunctional calixarene thiourea organocatalysts	asymmetric Michael addition of acetylacetone to various nitroolefins	97% yield; 92% *ee*	(Genc and Sirit, 2018)
11	Upper rim-functionalized calix[4]thiourea cyclohexanediamine derivatives	*trans*-β-nitrostyrene and acetylacetone	99% yield;94% ee	(Li et al., 2018)
12	Chiral secondary amines bearing a tetraoxacalix[2] arene[2] triazine	Michael reaction of anthrone with nitroalkenes	82%-98% yield;75%-98% ee.	(Genc, 2019)

2.3 Asymmetric Alkylation reaction utilizing Calix[4]arene based chiral catalysts brief literature review

The synthesis of optically active α-Amino acids utilizing an easy-to-scale process is still a significant synthetic issue today, as α-Amino acids are important naturally occurring amino acids that assemble into polypeptides with a wide range of vital biological roles. Using asymmetric phase transfer catalysis, glycine imine esters are asymmetrically alkylated to produce natural or synthetic amino acids with desired enantioselectivity.(Sasson and Neumann, 2012) (O'Donnell, 2004). The Homogeneous Phase transfer alkylation reaction of esters is examined using various calix[4] arene-based catalysts. The recognition abilities of chiral calixarene hosts toward alkali cation guests have been exploited for the first time in asymmetric phase-transfer catalysis. catalytic efficiency in the asymmetric alkylation of *N*-(diphenylmethylene)-glycine esters under phase-transfer conditions.(De Simone et al., 2017b)(Figure 2.17)A novel catalyst consisting of two parts, one component being a quinoline alkaloid as the functional chiral phase transfer catalyst,

and the other the scaffold of calixarene, as an achiral phase transfer catalyst.(Huang et al., 2012) (Figure 2.18) The relevant literature studies are tabulated in Table 2.3.

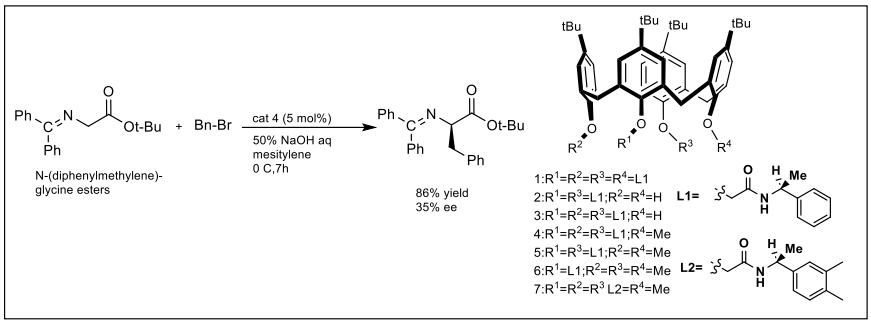


Figure 2.17 Asymmetric alkylation of N-(di-phenylmethylene)glycinetert-butyl ester with benzyl bromide

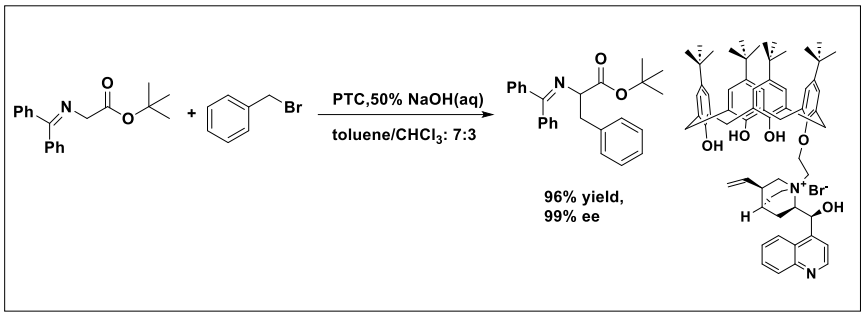


Figure 2.18 Asymmetric alkylation of N-(di-phenylmethylene)glycinetert-butyl ester with benzyl bromide with phase transfer catalyst

Inherently chiral calix[4]arenes containing a diarylmethanol structure. Calix[4]arenes 3b were applied to asymmetric reactions as a chiral base catalyst and as a chiral phase transfer catalyst, respectively. The effect of the diaryl group of 3b in the asymmetric reactions was examined, and a positive effect on enantioselectivity was observed.(Shirakawa and Shimizu, 2010a)(Figure 2.19)

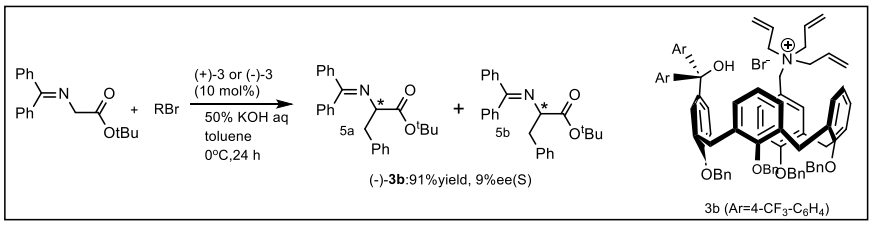


Figure 2.19 Asymmetric alkylations of a glycine derivative catalyzed by 3 under phase-transfer conditions.

Table 2.3 Literature review of asymmetric alkylation of glycine esters utilizing calixarene scaffold catalysts

S.No	Catalyst	substrate	ee	references
1	*p-tert*-butylcalix[4]arene-based chiral phase-transfer catalysts derived from cinchona alkaloids	ethylglycine ester with benzyl bromide.	yields 95% 57% ee.	(Bozkurt et al., 2008)
2	Calix[4]arene-amide	N-(di-phenylmethylene)glycinetert-butyl ester with benzyl bromide	86% Yield 35% ee	(De Simone et al., 2017b)

3	Chiral calix[4]arenes bearing a tertiary amine or a quaternary ammoniu m moiety, together with a diarylmethanol moiety	asymmetric alkyl ation of a glycine derivative with b enzyl bromide	91% yield 9% ee	(Shirakawa and Shimizu, 2010b)
4	Quaternary ammonium Cinchona-functionalized crown ether-strapped calix[4]arene phase-transfer catalysts	α-alkylation of glycine imines with benzyl bromide.	98% yield 99.9% ee	*(Malik et al., 2023)*

2.4 Asymmetric Henry reaction utilizing Calix[4]arene based chiral catalysts brief literature review

Nitroaldol or Henry reaction is a potent C-C bond-forming reaction. It is the addition reaction between nitroalkanes and carbonyl compounds that yields nitroalcohol. It provides important functionalized structural motifs like 1,2-amino alcohols amino sugars, nitro ketones, nitro alkenes, ketones, and other important compounds and α-hydroxy carboxylic acids. The importance of controlling the absolute stereochemistry of β -nitroalcohols is necessary but it is limited to organocatalytic methods and the reaction still presents some limitations. The key catalysts used are Cinchona alkaloids, phase transfer catalysts, thioureas, and guanidines. Najera et al in 1994 were the first to publish the organocatalytic Henry reaction affording enantiomeric excess up to 54%(Chinchilla et al., 1994). Further Murphy *et al*. synthesised chiral guanidines which were used in diastereoselective Henry reaction that gave moderate enantioselectivity in 2005 (Allingham et al., 2003, Ma et al., 2002). Nawasaga *et al*. developed a novel bifunctional catalyst for catalyzing the reaction of nitromethane with α-branched aldehydes reaching enantioselectivities up to 88%(Sohtome et al., 2005). Axially chiral guanidine bases were synthesised and utilized by Terada *et al* and afforded 89% ee (Ube and Terada, 2009). Furthermore, Maruoka *et al*.applied *N*-spiro C_2-symmetric chiral quaternary ammonium bifluoride as an efficient phase transfer catalyst in the reaction of silyl nitronates with aldehydes to give 95% ee (Ooi et al., 2003). Organocatalyst derived from suitably substituted cinchona moiety promoted the direct enantioselective nitroaldol reaction that gave up to 92% ee (Marcelli et al., 2006b). Shi *et al*. also utilised axially chiral bis(arylthiourea)-based organocatalyst in the enantioselective Henry reaction that provided the product with good yields and moderate enantioselectivities up to 72%(Liu et al., 2007). A pair of *N*,*O*-type enantiomers based on inherently chiral calix[4]arenes substituted at the lower rim were synthesized and applied to catalyze Henry reaction between aromatic aldehydes and nitromethane. 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).(Figure 2.20) Bridging chiral *p*-*t*butylcalix[4]arene tetrahydroisoquinolines as chiral organocatalysts for Henry reaction giving enantioselectivity up to 13.4% and 96% yield)(Ma et al., 2019).(Figure 2.21)

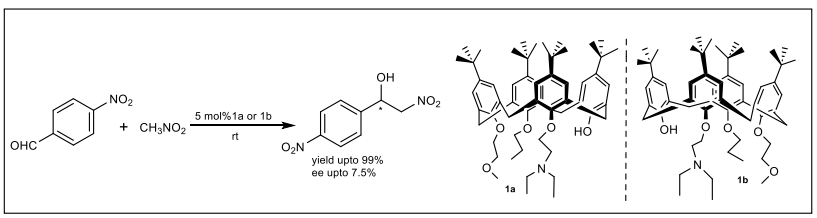


Figure 2.20 Henry reaction of nitromethane

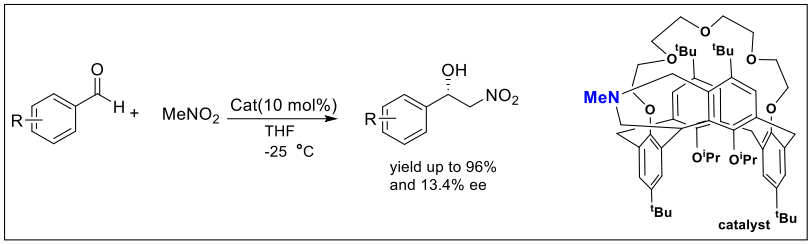


Figure 2.21 Amino-functionalized calixarenes as catalysts for the Henry reaction

Table 2.4 Literature review of asymmetric Henry reaction utilizing calixarene scaffold

S.No	Catalyst	substrate	ee	references
1	*N,O*-type enantiomers based on inherently chiral calix[4] arenes substituted at the lower rim	Aldehydes and nitromethane	99% yields 7.5% ee.	(Chang et al., 2017)
2	Bridging chiral *p*-t-butylcalix[4]arene tetrahydroisoquinolines	Aldehydes and nitromethane	96% yield 13.4% *ee*	(Ma et al., 2019)
3	Mononitration of a Calix[4]arene Methylene Bridge	Aldehydes and nitromethane	95% yield 22.3% ee	(Peng et al., 2021a)

2.5 Asymmetric Strecker reaction- Brief literature review

The synthesis of α-amino nitriles from aldehydes or ketones using alkaline cyanides and amine salts is a well-known traditional method known as the Strecker synthesis. The first amino acid synthesis was reported in 1850 by Strecker Synthesis. *a*-amino nitriles can be easily transformed into 1,2-diamines and 2-amino alcohols, all are important precursors for the synthesis of biologically active compounds. Consequently, emphasis has been paid to stereoselective Strecker reactions resulting in α-amino nitriles with high enantiopurity. To achieve this, chiral catalysts have been developed as organocatalysts. Surprisingly little attention has been paid to calixarene-derived enantioselective organocatalytic one-pot Strecker reaction and is virtually absent in the literature. The first successful catalytic three-component Strecker reaction was described with a chiral zirconium catalyst, although high enantioselectivities are realized at a long reaction time and sub-zero temperature (-45 ^{o}C)(Shinohara et al., 2019). To the best of our knowledge, the only organocatalytic report pertaining to the one-pot three-component Strecker reaction reported by Zhang et.*al* using Brønsted acids with moderate yields and low ee (40%)(Zhang et al., 2010) (Figure 2.22)

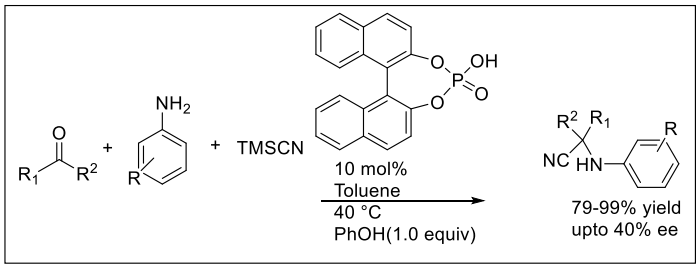


Figure 2.22 Three component Strecker Reaction

3
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 homogenous catalysts are difficult to recover as compared to heterogenous catalysts. Nevertheless, the solvents could use a tunable phase behavior to achieve homogenous 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* synthesized 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)

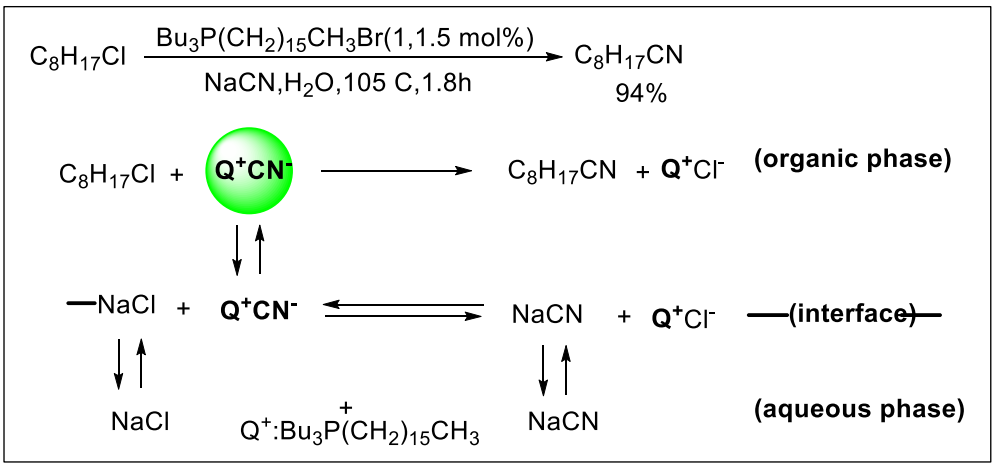


Figure 3.1 Representation of symmetric PTC mechanism(Ooi and Maruoka, 2007)

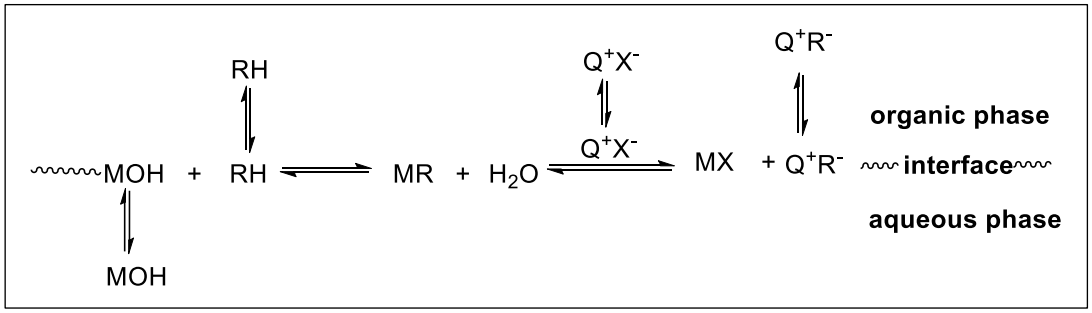


Figure 3.2 Representation of Makosza's interfacial mechanism for PTC.

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_2CO_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
$Ba(OH)_2.8H_2O$	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= [α]18/D 33°, (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= [α]22/D +33°,(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).

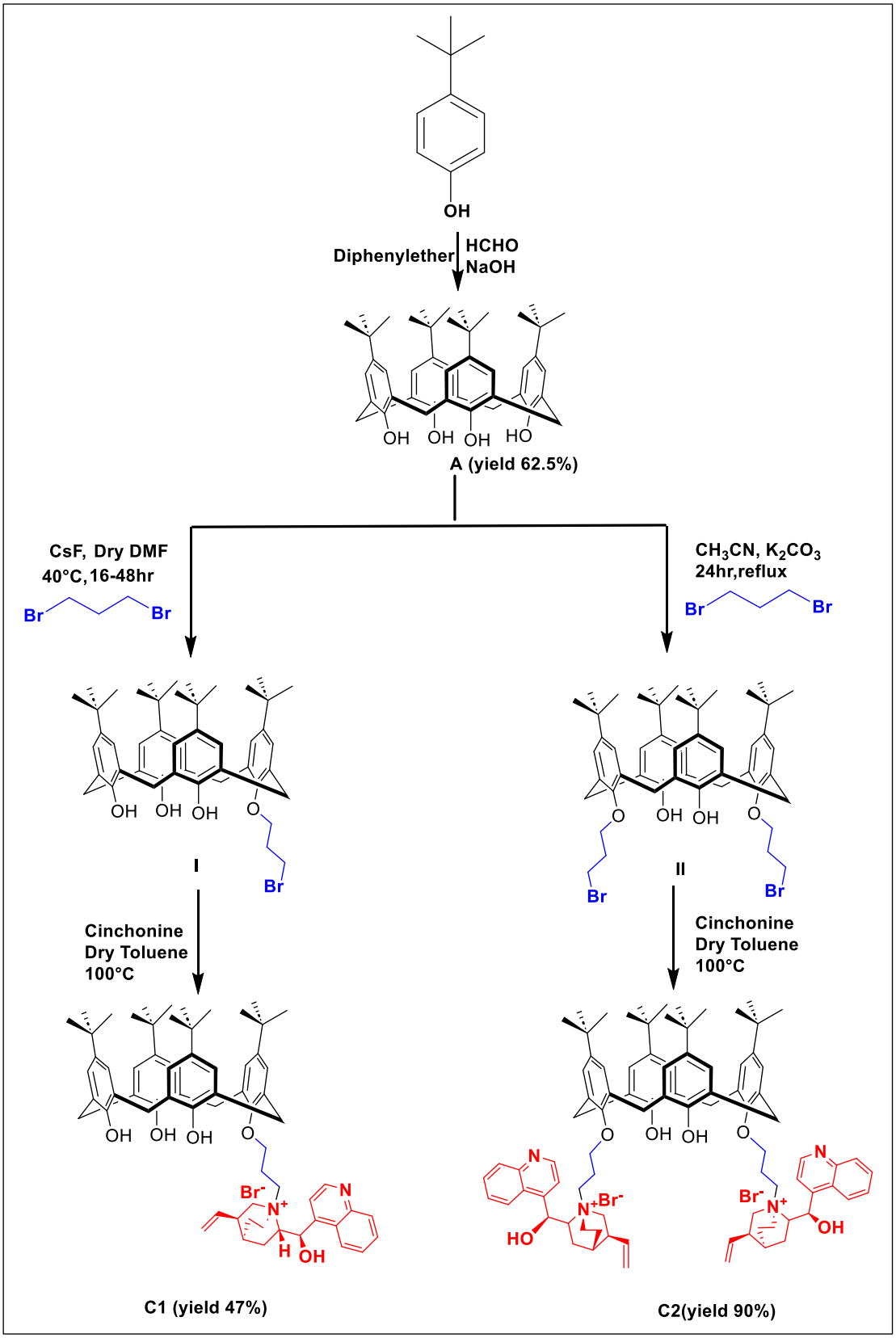


Figure 3.3 Synthesis of Cinchona anchored calixarene

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)

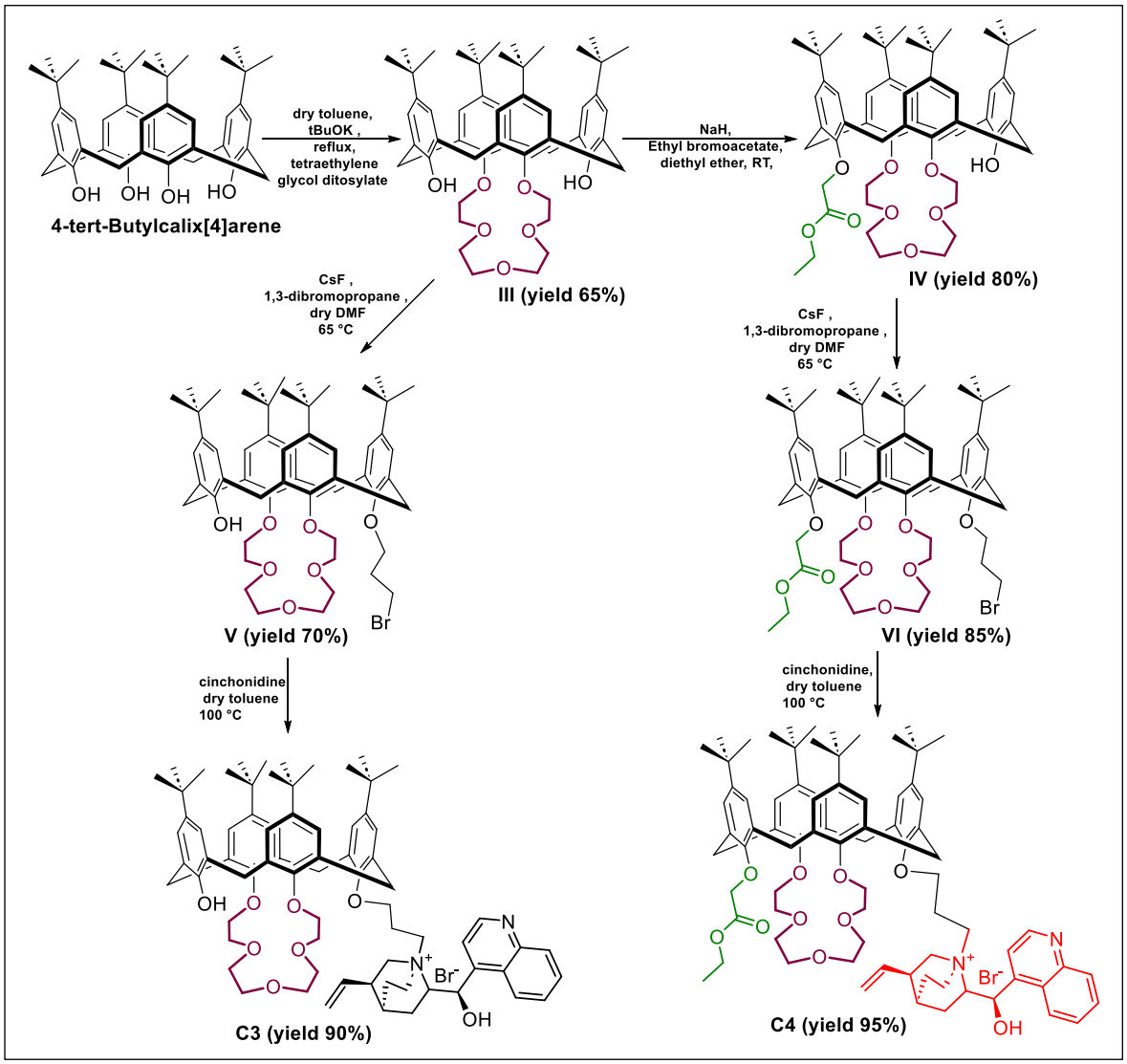


Figure 3.4 Synthesis of Cinchona -Functionalized Crown Ether-Strapped Calixarene

3.2.4 Synthesis of α-Methylbenzylamine functionalized crown-ether-appended 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.

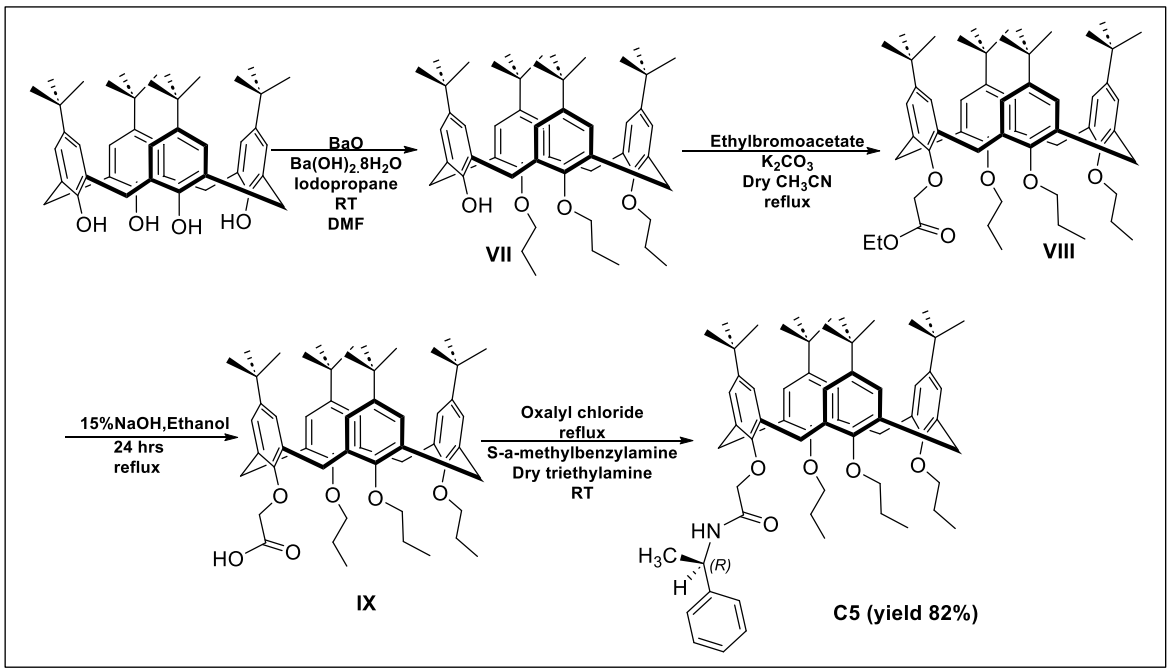


Figure 3.5 Synthesis of α-Methylbenzylamine functionalized calix[4]arene

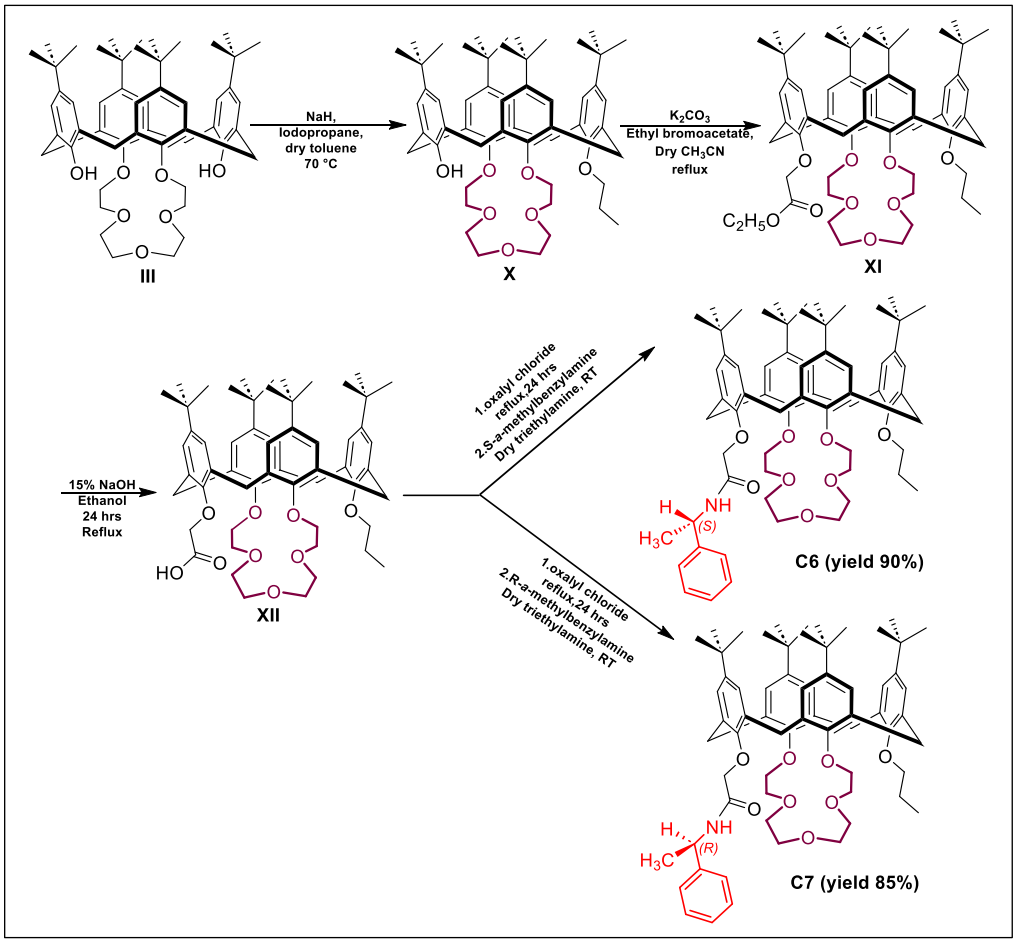


Figure 3.6 Synthesis of α-Methylbenzylamine functionalized crown-ether-appended calix[4]arene

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-((1*S*)-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)

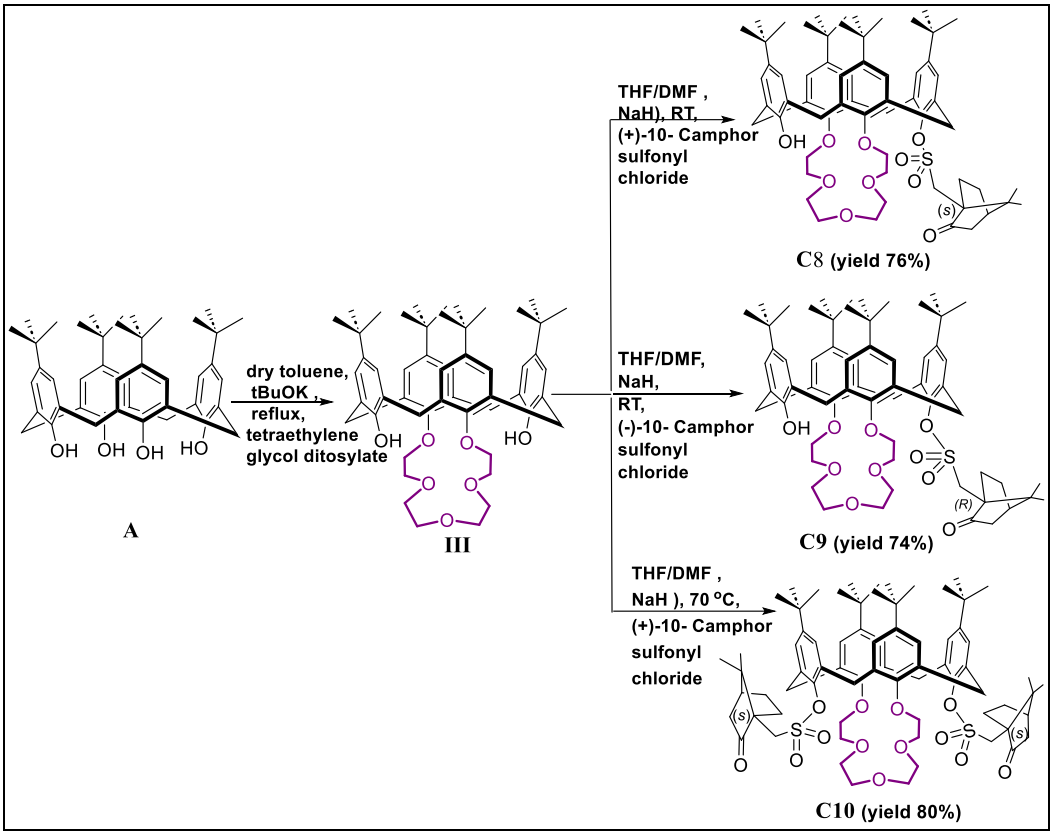
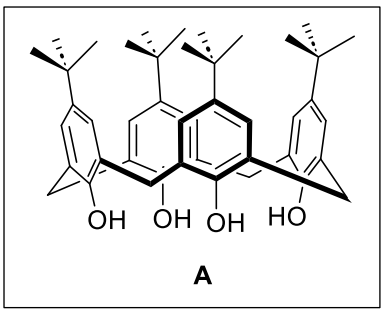


Figure 3.7 Synthesis of camphor sulfonyl functionalised crown-ether-appended calix[4]arene

3.3 Experimental Section

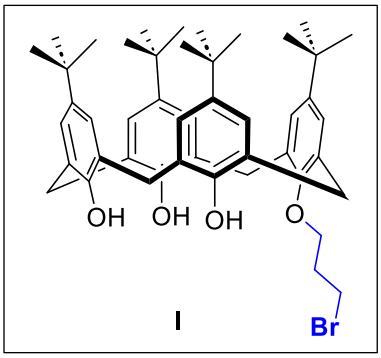
General Remarks

NMR spectra were recorded on a Bruker 500 spectrophotometer ^{1}H 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 (^{1}H $CDCl_3$, δ = 7.26; ^{13}C $CDCl_3$, δ = 77.0) Chemical shifts for ^{1}H 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,Ndimethylformamide (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 × 250 mm Chiralpak IA, IB and AD-H, AS-H using condition n-Haxane/isopropanol solvent system and thermoscientific Vanquish detector Model: VC-D11-A equipped with chiral columns DAICEL 4.6 mm × 250 mm Chiralpak- AD-H



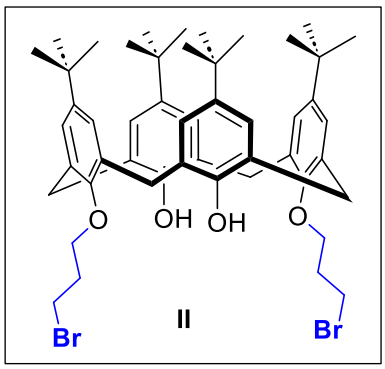
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A-Formaldehyde (37%, aq solution) (6.2 ml) was added to a mixture of *p-tert*-butyl phenol (10 g,0.06 mol) and NaOH (0.12 g,0.003 mol). The solution was heated for 2 hrs at 110-120 ^{o}C using an oil bath. During this period, the clear solution became 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 ^{o}C to remove water. If required, a stream of N_2 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 (100mL) 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 ^{o}C. ^{1}H 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) ^{13}C NMR ($CDCl_3$) δ; 147.06, 144.76, 128.08, 125.90, 34.40, 32.99, 31.79.(Iqbal, 1990)

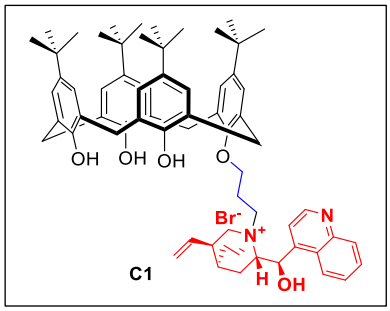


I

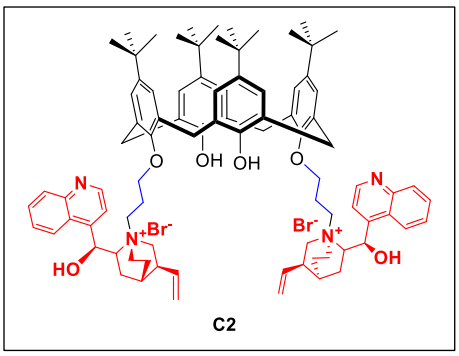
I-The p-tert-butyl calix-4-arene (A) (0.648g, 1mmol), cesium fluoride (0.182g, 1.2mmol), 1,3 dibromo-propane (0.167g, 10mmol) are added to a two neck round bottom flask containing 20ml dry DMF. The reaction mixture was stirred at 40° C for 48 hrs. The reaction was quenched with 2N HCl (20ml) and water. The product was extracted by DCM (2×20ml) using a separating funnel. The organic layer was dried over anhydrous Na_2SO_4. Removal of DCM gave white solid as a product ~700mg. 1H NMR (500 MHz, $CDCl_3$) 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).^{13}C NMR (126 MHz, $CDCl_3$) 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 CH_3CN (250 mL) were added 1,3 dibromo propane (20.0 g, 0.10 mmol) and K_2CO_3 (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 $CHCl_3$ (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 (CH_2Cl_2-Petroleum ether (60-90 ^oC) 2:3) to give white, pure compound. (4.10 g, 70%). Melting point- 288-290 ^oC.^1H NMR (500 MHz, $CDCl_3$) 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). ^{13}C NMR (126 MHz, $CDCl_3$) 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.

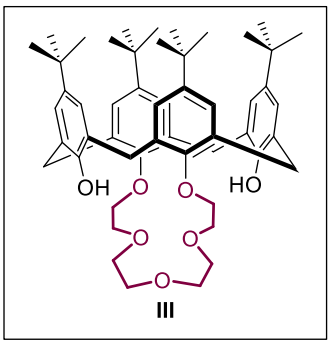


C1- A mixture of cinchonine (1.1 mmol) and compound I (0.5 mmol) was dissolved in 20ml dry toluene in two-neck round bottom flask. The reaction mixture stirred at 100°C for 24hrs under nitrogen. After the completion of reaction (checked by TLC), solvent was evaporated to get a solid product which was recrystallized in diethyl ether and chloroform to give pure crystals White solid; 0.500 g, yield 47%. $[\alpha]_{25}^{D}$ = -100 (c = 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) 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). ^{13}CNMR: 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+H_2O]+ calcd for $C_{66}H_{85}O_6N_2Br$ 1081.5591, found 1081.5587; mp 203-204 °C(Decomp)



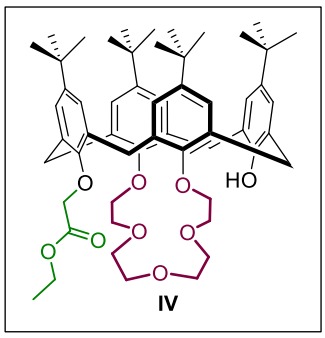
C2

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, $CHCl_3$) ^{1}H NMR ($CDCl_3$) 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). ^{13}C 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+ $2H_2O$] + calcd for $C_{88}H_{114}O_8N_4Br_2$ 1514.6983, found 1514.6980; mp 240-245 °C (Decomp)



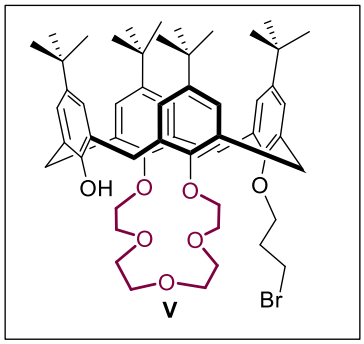
III

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 ^{t}BuOK (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 ^{t}BuOK (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, ^{1}H 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). ^{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, 33.8, 31.7, 31.0



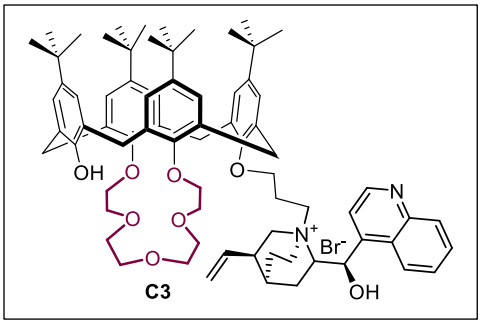
IV

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 was eluted followed by desired ester. Removal of eluant gave white solid, 0.22g, 80 % yield. ^{1}H 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=12.0Hz, 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, 31.7.0, 30.9, 25.6



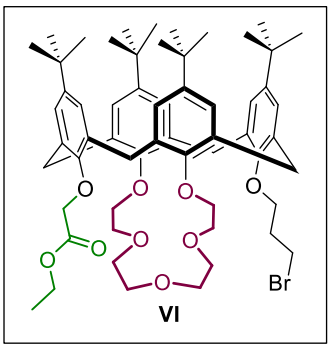
V

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]arenecrown-5 (III, 0.81 g, 1 mmol) and 1,3-dibromopropane (1.02 mL, 10 mmol). The reaction mixture was stirred at 40 ^{o}C (water bath) for 48 h. TLC followed the progress of the reaction, and after completion the reaction was quenched with 2N HCI (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 CH_2Cl_2/MeOH (1:1) to afford white crystals 0.65g, 70% yield, ^{1}H 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.



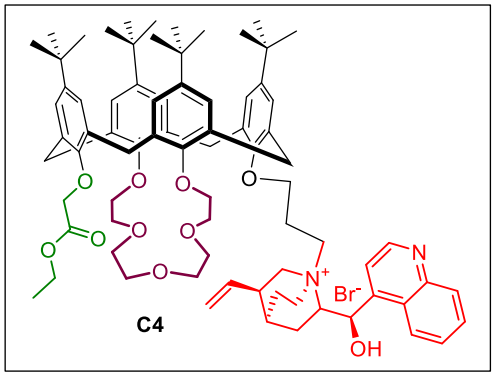
C3

C3- Synthesis of Catalyst C3: In a two-neck round bottom flask, a mixture of cinchonidine (0.15 g, 0.51 mmol) and compound (V, 0.47g, 0.5 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. The pure product was obtained by recrystallizing the crude in diethyl ether and chloroform (1:1) to give a white crystalline solid, 0.56 g; 90% yield of VI. $[\alpha]_{28}^{D}$ = +139° (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, Chloroform-d) δ: 8.94 (d, J = 4.4, 2H), 8.13 (d, J =8.2, 2H), 8.02 (d, J=8.4, 2H), 7.70 (t, 2H), 7.60 (d, J = 8.1, 2H), 7.54 (t, 1H), 7.04 (s, 5H), 6.67 (s, 4H), 6.00 (m, 2H), 5.71 (s, 2H), 5.04 (m, 4H), 4.24 (m, 2H), 4.13 (m, 4H), 4.01 (m, 1H) , 3.99 (m, 1H), 3.70 (t, 5H), 3.57 (t, 7H), 3.35 (d, 4H), 3.25 (d, 2H), 3.11 (m, 3H), 2.90 (m, 4H), 2.80 (m, 2H), 2.78 (m, 1H), 2.74 (m, 1H), 2.35 (m, 1H), 1.52 (s, 8H), 1.42 (s, 16H), 1.02 (s, 12H). ^{13}C NMR (126 MHz, Chloroform-d): 150.5, 150.2, 148.7, 148.2, 147.3, 141.7, 140.4, 132.8, 130.4, 129.0, 128.2, 127.5, 126.6, 125.7, 125.2, 123.0, 118.2, 114.6, 72.3, 72.0, 60.1, 50.1, 49.5, 42.6, 39.9, 37.1, 34.8, 32.7, 31.9, 31.9, 31.8, 31.6, 31.0, 30.3, 30.0, 29.9, 29.3, 28.1, 27.1, 26.4, 22.7, 14.1; HRMS (ESI) m/z [M+H]+ calcd for $C_{74}H_{96}O_8N_2Br$ 1221.6579, found 1221.6580; mp 215-220 °C (decomp)

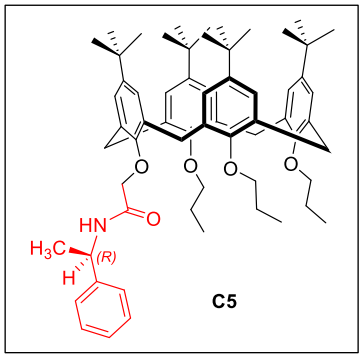


VI

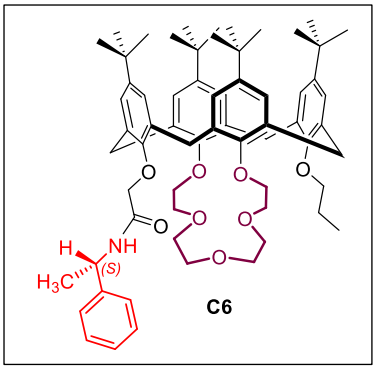
VI- Synthesis of bromopropyl p-tert-butyl Calix [4] arene crown-5 ester: To a solution of 4(0.50 g, 0.56 mmol) and CsF (0.10 g, 0.67 mmol) in dry DMF (20 mL), and 1,3-dibromopropane (1.12 g, 0.57 mL, 5.6 mmol). The reaction mixture was stirred at 40 °C (water bath) for 48 h. TLC followed the progress of the reaction, and after completion the reaction was quenched with 2N HCI (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 CH_2Cl_2/MeOH (1:1) to afford off white solid with 0.48 g, 85% yield, ^{1}H NMR (500 MHz, Chloroform-d) δ 7.05 (s, 4H), 6.87 (s, 4H), 5.36 (dd, J = 13.0, 4.7 Hz, 2H), 4.27 - 4.13 (m,8H), 4.15 – 4.09 (m, 8H), 4.00 (td, J = 6.5, 2.8 Hz, 4H), 3.61 (t,,J=6.1 Hz, 2H), 3.34 (d, J = 13.0 Hz, 4H), 2.43 (t, J = 6.1 Hz, 3H), 2.02 – 1.99 (m, 3H), 1.27 (s, 19H), 1.01 (s, 17H). ^{13}C NMR (126 MHz, Chloroform-d) δ 169.6, 151.9, 145.2, 144.4, 135.3, 135.2, 131.6,127.8, 124.6, 73.4, 72.5, 66.9, 60.1, 34.1, 33.8, 33.6, 31.7, 31.1, 31.0, 29.7, 14.1.



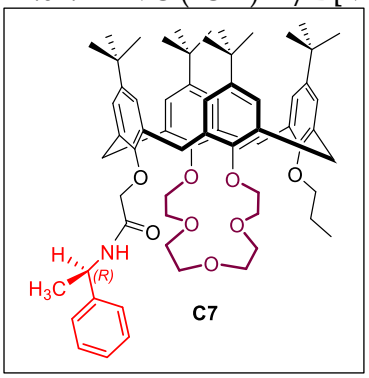
C4- Synthesis of C4: In a two-neck round bottom flask, a mixture of cinchonidine (0.12 g, 0.40 mmol and compound (VI, 0.40 g, 0.39 mmol) was dissolved in 20 ml of dry toluene. In an inert environment, the reaction mixture was stirred at 100°C (using a heating block) for 24 h. After the completion of 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° (c 1, $CHCl_3$); ^1H NMR ($CDCl_3$)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). ^{13}C 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 $C_{78}H_{102}O_{10}N_2Br$ 1306.6796, found 1306.6795; mp 194-197°C (decomp)



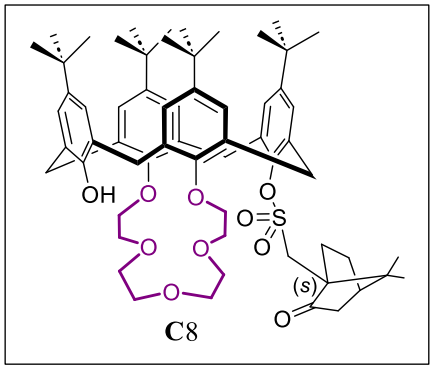
C5-Synthesis of Catalyst C5: Oxalyl chloride (0.522g, 4.12 mmol) was slowly added to a stirred solution of VIII (0.267g,0.32 mmol) in 15 mL of dry $CHCl_3$ at 0°C. The reaction mixture was refluxed under nitrogen atmosphere for 24 h, then was cooled at room temperature and the solvent was removed under 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 (0.0387g,0.32 mmol) and Et_3N (0.0323g,0.32 mmol) in 3 mL of dry $CHCl_3$ 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 $CHCl_3$ (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 **C5** as a white solid (0.294g, 82 %): mp 120 −121 °C; $[\alpha]^{D}_{20}$ = − 40 ± 0.8 (c = 1.00, $CHCl_3$); ^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). ^{13}C 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 $C_{63}H_{85}NO_5$, 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 °C; $[\alpha]^{D}_{20}$ = + 30 ± 0.8 (c = 1.00, $CHCl_3$); ^{1}H 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) δ152.49,151.52 ,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 $[M + H]^+$ calcd for $C_{65}H_{87}NO_8$, 1009.6409; found 1009.6410.

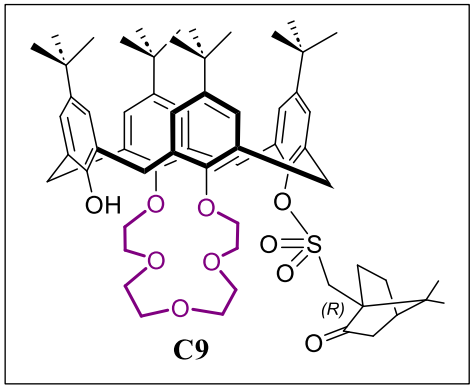


C7: Catalyst was synthesized with the same procedure for catalyst C6. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2) to afford C7 as a white solid (0.458g, 85 %): mp 106 −107 °C; $[\alpha]^{D}_{20}$ = - 31 ± 0.8 (c = 1.00, $CHCl_3$); NMR (500 MHz, Chloroform-d) δ 7.32 (m, 1H), 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 $[M + H]^+$ calcd for $C_{65}H_{87}NO_8$, 1009.6412; found 1009.6414



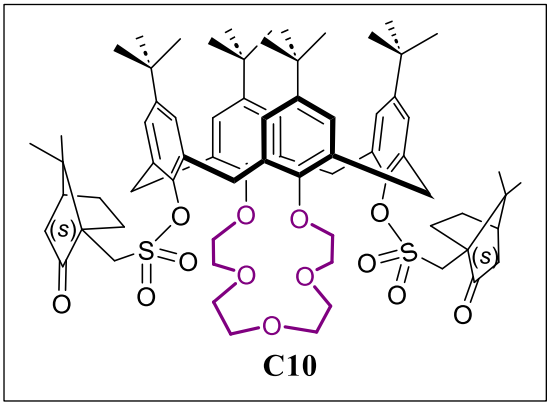
C8

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 CH_2Cl_2/MeOH = 95/5 to 60/40 as eluent to afford **C8** as a white crystalline solid (1.14 g, 76%); $[\alpha]^{28}_D$ = +52° (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, Chloroform-*d*) δ7.19 (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 [M + H] $^+$ calcd for $C_{62}H_{84}O_{10}S$, 1020.5800; found 1020.5805



C9

C9: The synthetic procedure is the same as catalyst **C8** using (-)-10-camphor sulfonyl chloride; The residue was purified through column chromatography CH_2Cl_2/MeOH = 95/5 to 60/40 as eluent to afford C9 as a white crystalline solid (1.11 g, 74%); $[\alpha]^{28}_D$ = - 50° (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, Chloroform-*d*) δ7.29(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 [M + H] $^+$ calcd for $C_{62}H_{84}O_{10}S$, 1020.5800; found 1020.5803



C10

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 ^{o}C for 12h. Reaction was monitored via TLC. After completion of reaction, reaction mixture was cooled to room temparture and 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 CH_2Cl_2/MeOH = 95/5 to 60/40 as eluent to afford **C10** as a white crystalline solid (1.47 g, 80%); $[\alpha]^{28}_D$ = +78^{o} (c 1, $CHCl_3$); ^{1}H 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). ^{13}C 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 $C_{72}H_{98}O_{13}S_2$ 1234.6400; found 1234.6406