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REVIEW ARTICLE

Inherently chiral calixarenes: a decade's review

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Abstract Inherently chiral calixarenes are receiving increasing attention due to their intriguing structures and potential applications in chemical, analytical, biological and material fields. This review mainly covers the advances in syntheses, structures, and applications of inherently chiral calixarenes which emerged later than 2000. Outlook on the development orientation of inherently chiral calixarenes is tentatively provided.

Keywords Calixarene · Inherently chiral · Optical resolution · Stereoselective synthesis · Organocatalyst · Enantioselective recognition

Introduction

Calixarenes as an excellent molecular scaffold have been extensively used in the construction of functionalized host molecules, which have found applications in various fields. The reasons underlying their versatility include (1) readiness of modification of the calixarene skeletons and (2) richness of their stereochemistry. The synthetic advances of calixarene chemistry have allowed the modification on the narrow rim, wide rim, *meta* position, bridging methylene, and outer-face (Fig. 1).

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Calixarenes have intriguing stereochemistry in terms of their rich conformational and configurational isomerisms. Calixarenes may adopt numerous conformations, which are defined by the relative orientation of the phenolate units in the macrocycles. For example, unmodified calix[4]arene may exist as four typical conformers called cone, partial cone, 1,2-alternate, and 1,3-alternate conformers. Configurational isomerism, including *cis*/*trans* and optical isomerism, may occur in calixarenes. It is well known that in the case of calix[4]arenes, four typical conformations can be locked by introduction of bulky substituents (R > Et) at the narrow rim. Strictly speaking, under the condition of restricted "oxygen-through-the-annulus", the four typical isomers are inconvertible under normal conditions and should belong to configurational isomers (*cis*/*trans* isomers or geometrical isomers as in substituted alkenes and cycloalkanes). However, for habitual and expedient reasons, they are referred to as conformational isomers. Another stereoisomerism, namely optical isomerism could also take place where generation of chiral species is involved.

Chirality could be effected in calixarenes both at the molecular level and at the supramolecular level. Calixarenes of "acquired chirality" and "inherent chirality" fall into the former category. Calixarenes with acquired chirality owe their chirality to at least one chiral subunit. A host of enantiomerically pure chiral calixarenes could be obtained by direct introduction of various foreign chiral sources such as amino acids, small peptides, carbohydrates, chiral epoxides, amino alcohols, BINOL etc. onto the reactive narrow/wide rims [1]. An alternative strategy makes bridging methylene carbon stereogenic, as has been newly exemplified by the work of Wulff's group [2, 3]. Calixarenes could also be endowed with "inherent chirality", the concept of which was first introduced by Böhmer

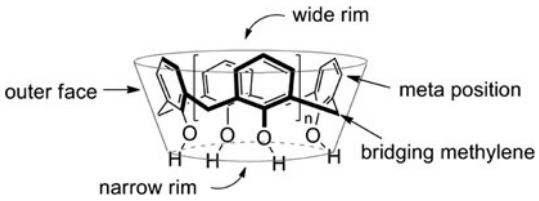


Fig. 1 Diagram of the structure of calixarenes

to describe chiral calixarenes which are not based on a chiral subunit but on the absence of a plane of symmetry or an inversion center in the molecule as a whole [4]. The term "inherent chirality" is now extended to describe a variety of chiral molecules whose chirality arises from the introduction of a curvature in an ideal planar structure that is devoid of perpendicular symmetry planes in its bidimensional representation [5, 6]. Access to inherently chiral calixarenes is usually not as straightforward as that of calixarenes with acquired chirality for two reasons: (1) regio-control and conformation-control problems are usually involved at the synthetic stage and (2) optical resolution process is indispensable for non-stereoselective synthetic methods where achiral reagents and achiral reaction conditions are used. Calixarenes could also be used as building blocks for the construction of systems with supramolecular chirality, which results from assemblies based on supramolecular interactions [7–11]. Calixarene-based systems with supramolecular chirality emerged relatively late compared with chiral species constructed at the molecular level.

Chemistry of chiral calixarenes is an important component of calixarene chemistry and is motivated by the prospect of chemical, analytical, biological and material applications as synzymes [12], enantioselective sensors [13], catalysts [14], chiral stationary phases for chromatography [15], chiral solvating agents for NMR [16], drug dispensers [17], and so on [18, 19], besides its theoretical significance. The study of chiral calixarenes has experienced the development stages of from species of acquired chirality to inherent chirality to supramolecular chirality, from concentrating on novel structures at the early stage to attaching importance to specific functions at the current stage.

Inherent chirality is peculiar in that it is associated with the absence of a plane of symmetry or an inversion center in the molecule as a whole, instead of being associated with a local stereogenic center. It is this stereochemical appeal that stimulates chemists to study the structures and functions of inherently chiral calixarenes. Excellent reviews on inherently chiral calixarenes were made by Böhmer [4], Shinkai et al. [20] at least a decade ago. However, the past decade witnessed rapid evolution of inherently chiral calixarenes on aspects of synthetic methodologies, structural diversity, and applications, which justifies this review. The current review focuses on the syntheses, structures, and applications of inherently chiral calixarenes which emerged later than 2000. Earlier examples, which were covered in previous reviews [4, 20, 21], are not to be detailed except for the considerations of significance and introductory integrity. Thiacalixarenes, resorcinarenes and related analogues are not covered in this review. Recent reviews relevant to inherently chiral species are also recommended for readers' reference [1, 6, 22, 23].

Non-stereoselective syntheses of inherently chiral calixarenes

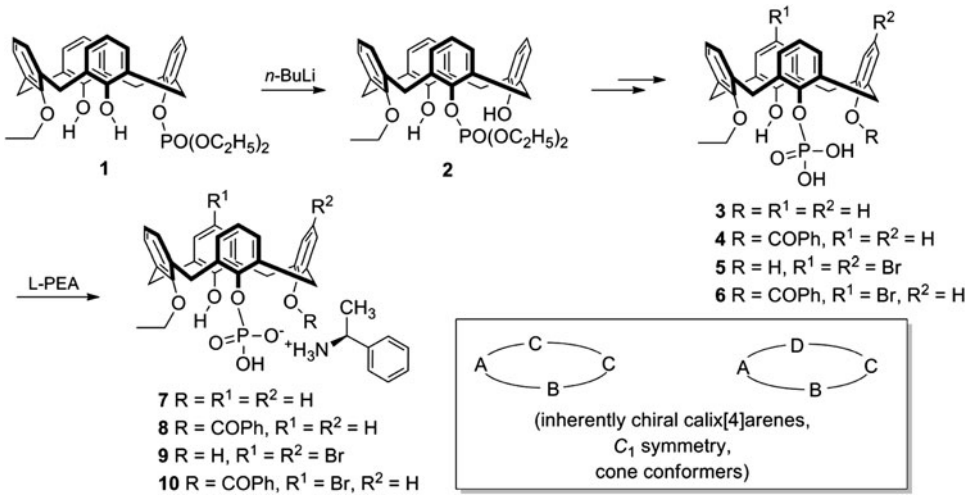
Non-stereoselective synthesis, where achiral reactants and conditions are used, gives racemic products. Thus, optical resolution process is necessary for obtaining enantiopure products. Compared with the method of fragment condensation which appeared at the early stage, direct modification of parent calixarene scaffolds is predominant in the syntheses of calixarene-based inherently chiral species and proves much more fruitful. The past decade witnessed concrete advances in optical resolution of inherently chiral calixarenes.

Of C_1 symmetry—substituted at the narrow/wide rim

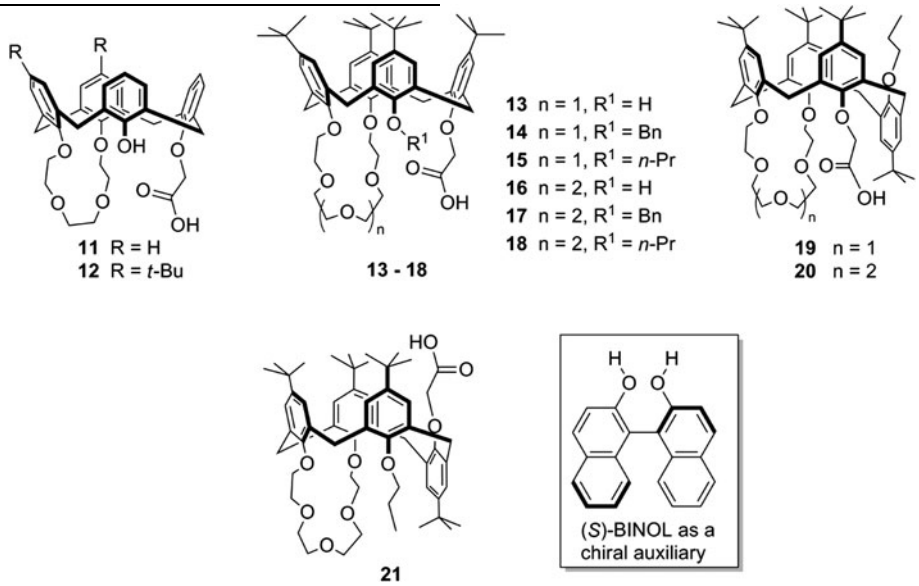
Inherently chiral calix[4]arenes of C_1 symmetry are among the earliest developed chiral calixarenes, with the first example, as a synthetic serendipity, dating back to as early as 1982 [24]. Ever since then, a few efforts have been devoted to seeking feasible synthetic protocols for inherently chiral calixarenes of diverse structures. However, before and in the early part of 2000s, optical resolution was usually realized by HPLC method with chiral column (for racemates) or nonchiral column (for diastereomeric derivatives). An example occurred in 2002 was provided by Kalchenko's group. By use of rearrangement of narrow-rim 1,3-disubstituted calix[4]arene **1** into its asymmetrical 1,2-regioisomer **2** under strongly basic condition and subsequent derivatization, racemic inherently chiral calix[4]-arene phosphoric acids **3–6** were synthesized. In an attempt to effect optical resolution, **3–6** were subjected to L-phenylethylamine in methanol solution to form diastereomeric salts **7–10**, which were easily separated by HPLC method on achiral columns [25] (Scheme 1).

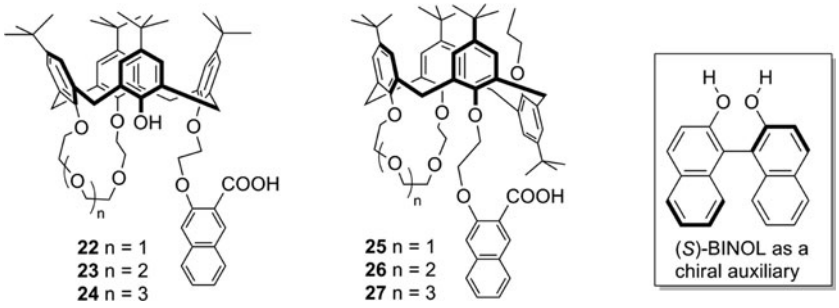
Obviously, it is preferable to achieve chemical resolution by easier operation such as conventional column chromatography, which allows scale preparation enantiopure species and facilitates their applications. The past decade has seen a breakthrough in optical resolution via chemical resolution, the curtain of which was first unveiled by the

Scheme 1 Preparation of inherently chiral calix[4]arene phosphoric acid cone conformers with C_1 symmetry



representative work of Huang's group, who reported the synthesis of a series of tri-*O*-alkylated and tetra-*O*-alkylated inherently chiral calix[4]crown derivatives in the cone and partial cone conformations by sequential alkylation of the 1,2-calix[4]crowns (Scheme 2). (*S*)-BINOL as an efficient chiral auxiliary was used to react with the carboxylic moiety attached on the calix[4]arenes to form diastereomers, which could be separated by preparative TLC in the cases of **11**–**13**, **19**, **20** and by conventional column chromatography on silica gel in the cases of **14**, **15**, **17**, **18**. Subsequent hydrolysis of the separated diastereomers gave corresponding enantiomers. The relationship between structure and optical resolution was discussed for this system: (1) for efficient resolution, the carboxylic group and crown ether moiety must be convergent (with **21** as a counter example); (2) increasing the size of the 1,2-crown loop disfavors optical resolution of tri-*O*-alkylated cone conformers; (3) complete alkylation, which accentuates the spatial congestion at the narrow rim, has a beneficial effect on optical resolution. It is justifiable that the significant steric effect of the BINOL motif plays an important role in the optical resolution process [26, 27].



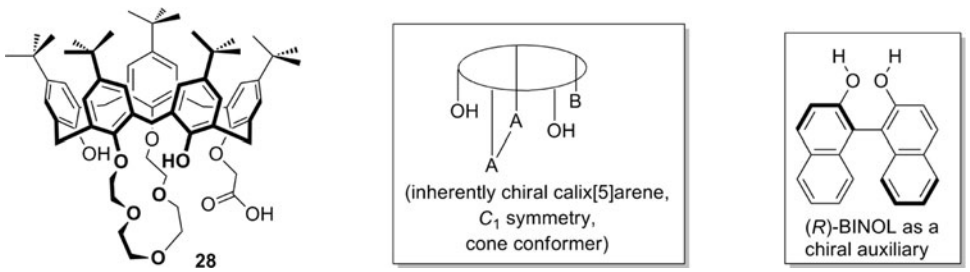


Along with this strategy, the same group has also synthesized and optically resolved a series of inherently chiral fluorescent calix[4]crown analogs, which consist of a crown ether moiety and a carboxyl group as potential recognition sites and a naphthyl as a fluorophore. Fluorescent titration experiments revealed that the tetra-*O*-alkylated crown-6 partial cone conformer **27** has considerable enantioselective recognition ability towards leucinol in CH_2Cl_2 [28].

Using (*R*)-BINOL as a chiral auxiliary, the same group has also efficiently resolved an inherently chiral calix[5]-crown-5 carboxylic acid **28** [29], which was first synthesized by Pappalardo and coworkers [30] as racemates. This is the first example of optical resolution of an inherently chiral calix[5]arene by chemical resolution method and may encourage further efforts on the studies of optical resolution and properties of inherently chiral calix[5]arenes.

36), as was deduced from relevant NMR spectra. This is a rare report on inherently chiral calix[4]arenes of C_1 symmetry in a definite 1,2-alternate conformation (not a *pure* inherent chirality in this case, of course) [31] (Scheme 4). Likewise, (*S*)-2′-methoxy-1,1′-binaphthalene-2-carboxylic acid was used as a chiral auxiliary for the optical resolution of **32** [32, 33]. The absolute configurations of **31** and **32** were determined by X-ray crystallographic analysis and CD spectra analysis.

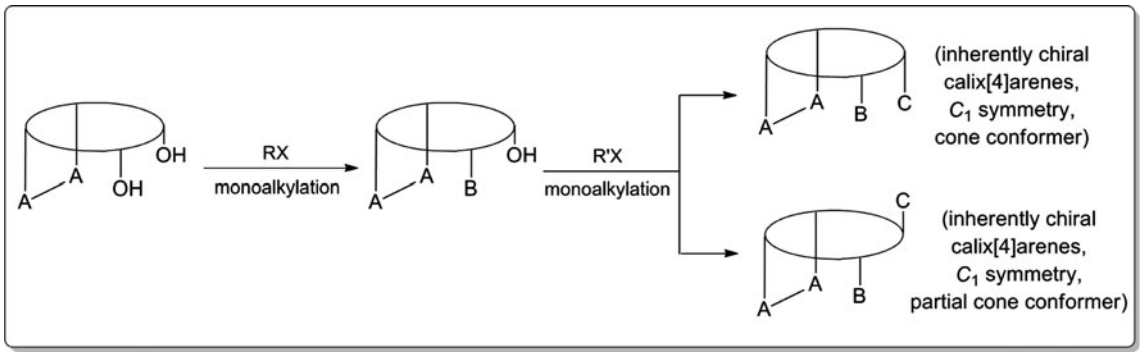
An unexpected single-step formation of a 1,2-*anti*-heterodisubstituted calix[4]arene in the partial cone conformation was discovered by de Mendoza et al. Benzylation of the paco tribenzoyl calix[4]arene **37** with 4-iodobenzyl bromide in the presence of NaH in DMF and subsequent work up under acidic conditions yielded the 1,2-*anti*-heterodisubstituted calix[4]arene **38** as a major product (Scheme 5). The process involves an in situ



Inherently chiral calix[4]arene partial cone conformers of A∀HH substitution pattern at the narrow rim has been synthesized by Narumi and Hattori's group. Dialkylation of the readily available 1,2-disiloxane bridged calix[4]arene **29** followed by desilylation provided an easy access to inherently chiral anti-*O*,*O*′-dialkylated calix[4]arenes **31** and **32** (Scheme 3). (*S*)-2-Methoxy-2-(naphthalene-1-yl)propionic acid was used as a chiral auxiliary to effect monoesterification with **31** in the presence of DCC, which led to the formation of a mixture of four diastereomers **33**–**36**. By repeated flash chromatography on silica gel, the mixture of **33**–**36** could be isolated and thus guaranteed the optical resolution of **31**. It is interesting to note that the diastereomeric intermediates exist as two pairs of diastereomers, namely a pair of partial cone conformers (**33**, **34**) and a pair of 1,2-alternate conformers (**35**,

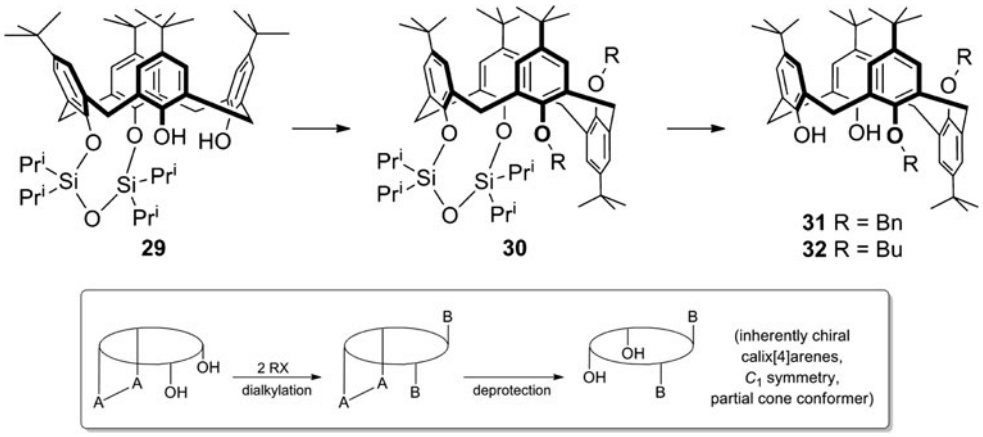
alkylation with simultaneous partial deacylation. The structure of **38** was confirmed by X-ray crystallography [34].

Compared with narrow-rim functionalization, selective functionalization at the wide rim is difficult. This accounts for the scarcity of wide-rim substituted inherently chiral calixarenes. Shimizu and coworkers have synthesized a series of inherently chiral calix[4]arene cone conformers featuring amino acid, aminoalcohol and aminophenol structures at the wide rim by multi-step sequences [35–39]. Efficient optical resolution of racemic **39** was achieved by direct recrystallization in the presence of enantiopure mandelic acid. In the optical resolution of racemic **43**, the wide-rim phenolic group was utilized to react with chiral auxiliary (*S*)-10-camphorsulfonyl chloride to form

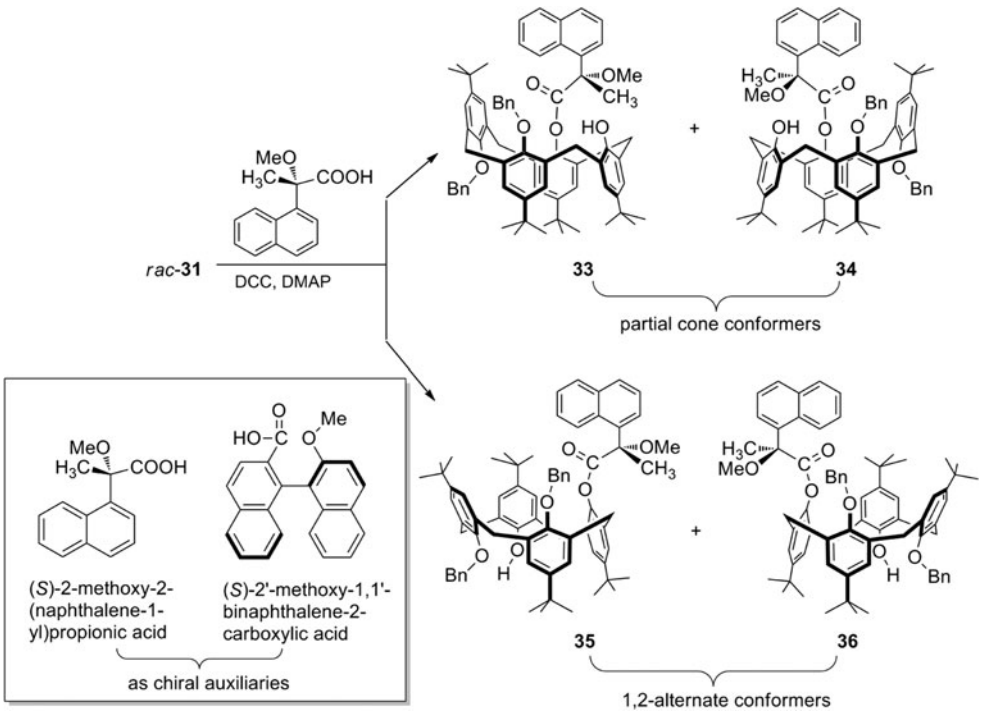


Scheme 2 Schematic representation of the synthesis of inherently chiral calix[4]arene cone conformers and partial cone conformers with C_1 symmetry by way of sequential alkylation of the 1,2-calix[4]crowns

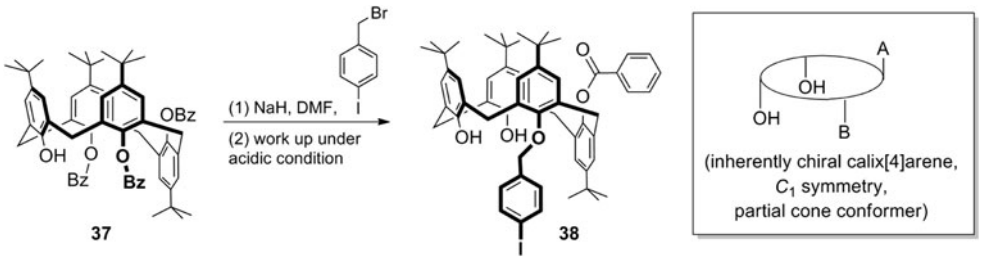
Scheme 3 A specific example and schematic representation of the synthesis of inherently chiral calix[4]arene partial cone conformers with C_1 symmetry by way of dialkylation and deprotection starting from 1,2-disiloxane bridged calix[4]arene



Scheme 4 Optical resolution of *rac*-**31** using two phenolic hydroxyls as resolving sites and a carboxylic acid as chiral auxiliary: simultaneous formation of two pairs of diastereomers as partial cone conformers and 1,2-alternate conformers

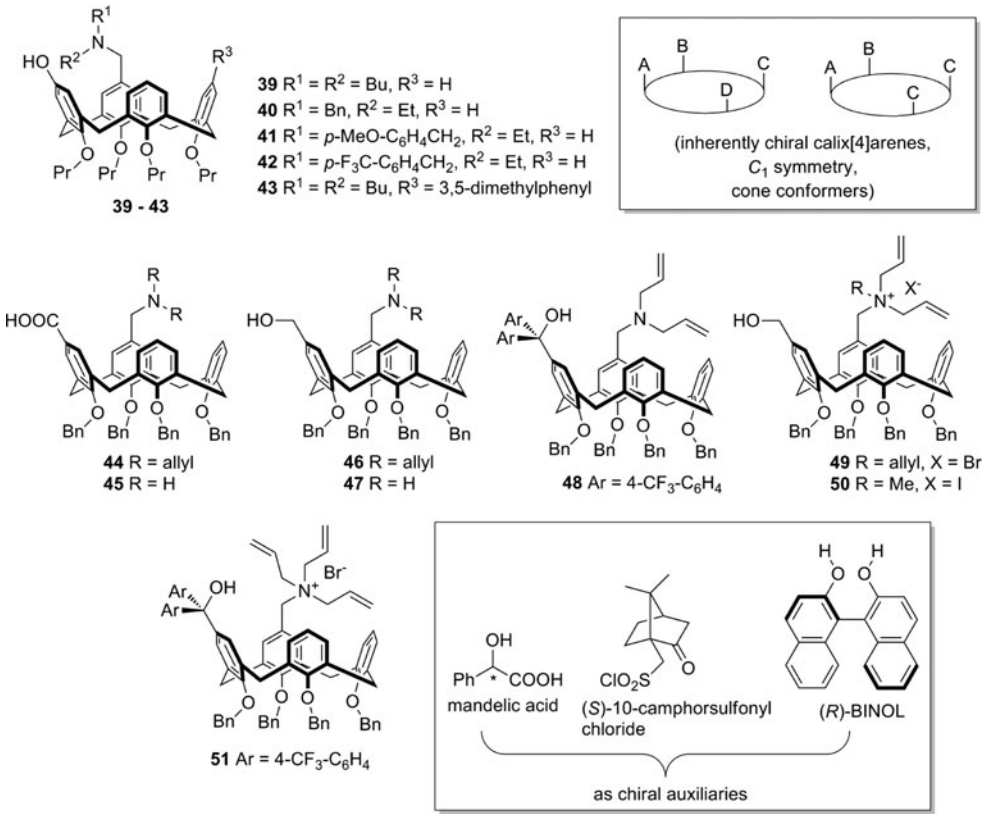


Scheme 5 An unexpected single-step formation of 1,2-*anti*-heterodisubstituted calix[4]arene partial cone conformer with C_1 symmetry



corresponding diastereomeric (1*S*)-camphorsulfonyl esters, which could be separated by preparative HPLC. Similarly, (*R*)-BINOL was used as a chiral auxiliary to react with carboxylic acid derivative **44**, followed by preparative HPLC separation of the resultant diastereomeric esters. Racemic calix[4]arenes **40–42** were resolved in optically pure forms by preparative chiral HPLC. It seems that chemical resolution of wide-rim substituted inherently chiral calixarenes is less efficient than that of narrow-rim substituted species. This reflects the fact that at the more spacious wide rim, the spatial interactions among various functionalities are weakened, which disfavors the differentiation of diastereomers. Based on the resolved calix[4]arenes or separated diastereomeric intermediates, inherently chiral amino acid, aminoalcohols and quaternary ammoniums derivatives (**45–51)** were synthesized.

^{1}H NMR titration experiments revealed that inherently chiral calix[4]arene aminophenol **39** may recognize enantiomers of mandelic acid discriminately and **39** could be used as a chiral NMR solvating agent to determine the enantiopurity of mandelic acid at ambient temperature. Such enantiomeric recognition was speculated to be associated with the cooperation of the amino and hydroxyl groups and the calixarene cavity. Since asymmetric Michael addition reaction of thiophenol is known to be catalyzed by chiral amino alcohols, the application of enantiopure **39** as a chiral organocatalyst was tested for the Michael addition of 2-cyclohexen-1-ones and thiophenols. High catalytic efficiencies with low enantioselectivities (ee $\leq$ 16%) were observed. Comparable enantioselectivities were also obtained with inherently chiral calix[4]arene aminoalcohol analog **47**. With **40–42**, only 3% ee values were observed. This preliminary results indicated that inherently chiral calixarenes as an organocatalyst definitely induced chirality in the products and encouraged the same group to improve chiral induction ability of the inherently

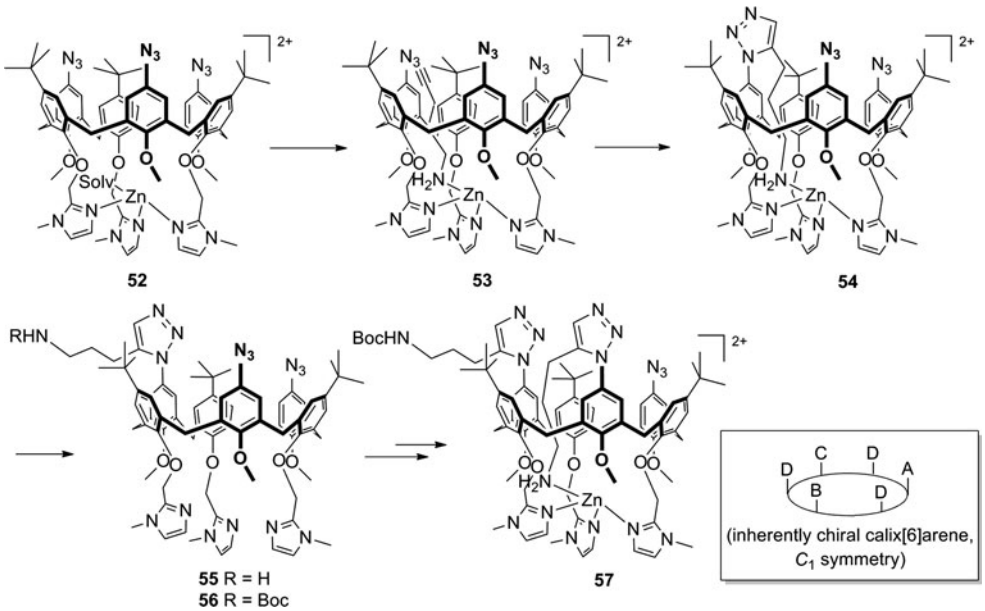


chiral calix[4]arenes by structural modification. By attachment of an additional bulky 3,5-dimethylphenyl group at the wide rim (**43**, as compared with **39**), higher enantioselectivities (up to 31%) were reached in the Michael addition reaction of 2-cyclohexen-1-one with thiophenols. Likewise, beneficial effect of the bulky diarylmethanol structure on enantioselectivity was also observed (compare **48** with **46**). Enantiopure **49–51** bearing quaternary ammonium moieties were used as chiral phase transfer catalysts to the asymmetric Michael addition reactions and low enantioselectivities (≤6%) were observed. Inherently chiral calix[4]arene amino acid **45** did not show catalytic activity for the asymmetric direct aldol reaction of acetone.

Selective modification of the higher analogues of calix[4]arenes, such as calix[6]arenes and calix[8]arenes is much more ticklish and this accounts for the relative sluggishness of the development of inherently chiral calix[5, 6, 8]arenes. However, in 2008, Reinaud and coworkers [40] offered an impressive perspective for the selective functionalization of the wide rim of a calix[6]-arene by use of host–guest chemistry as a synthetic tool, which also opened a route to inherently chiral calix[6]arenes. Firstly, the zinc complex of a tris(azido)-calix[6]arene (**52**) was reacted with 5-aminopentyne in the noncoordinating solvent THF to form a Zn complex intermediate with an encapsulated alkyne (**53**). The coordination of the amine to Zn (II) allows the preorganization of the alkyne substrate in the vicinity of the azido substituent for the host and the guest to react intramolecularly and selectively to afford the Huisgen 1,3-dipolar cycloaddition product **54**. Demetalation of the zinc-amine complex followed by *N*-Boc protection gave the calix[6]-arene derivative **56**, which is able to accommodate another reactive alkyne in the cavity. Another round of functionalization at the wide rim using 5-aminopentyne in THF yielded an inherently chiral calix[6]arene **57** with an ADBDCD substitution pattern at the wide rim (Scheme 6).

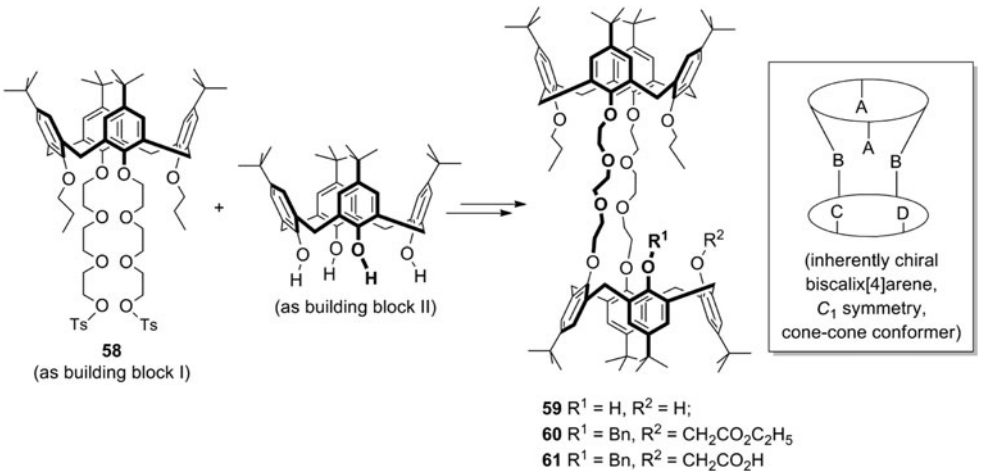
All the inherently chiral entities abovementioned are monocalixarene-based. Yet the versatility of calixarenes invokes chemists' imagination to design multicalixarene-based chiral molecules, for the prospect of exploiting the potential synergistic effect of the calix cavities for the chiral recognition/catalysis process. Recently, Chung et al. have devised a strategy for the synthesis of a structurally rigid inherently chiral biscalix[4]arene. Initial treatment of calix[4]arene ditosylate **58** (as building block I) with *p-tert*-butylcalix[4]arene (as building block II) in the presence of *t*-BuOK in toluene afforded a desirable biscalix[4]arene platform **59**. By sequential alkylation and hydrolysis, inherently chiral biscalix[4]arene **61** which is covalently assembled by two calix[4]arene building blocks in a 1,3-position linking with 1,2-position pattern was produced. Optical resolution of racemic **61** was achieved by semi-preparative chiral HPLC [41] (Scheme 7).

Inherently chiral calix[4]arene of C_1 symmetry adopting a 1,3-alternate conformation is still "the missing member" at the current stage.



Scheme 6 Selective functionalization of the wide rim of a calix[6]arene by use of host–guest chemistry as a synthetic tool to afford an inherently chiral calix[6]arene with an ADBDCD substitution pattern at the wide rim (C_1 symmetry)

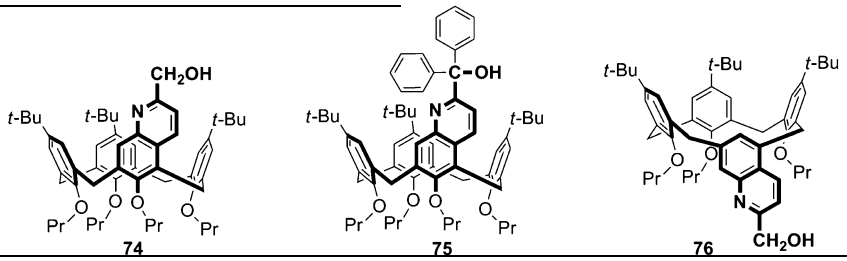
Scheme 7 Covalent assembly of two calix[4]arene building blocks in a 1,3-position linking with 1,2-position pattern to form inherently chiral biscalix[4]arenes in the cone–cone conformation



Of C_1 symmetry—substituted at the *meta* position

Inherent chirality of C_1 symmetry could also be generated by modification of the *meta* position of a phenolic unit (Fig. 2). Ring closure strategy, substitution reaction, addition reaction and rearrangement have been previously used for this purpose. Additional examples emerged in the past decade.

Starting with aminocalix[4]arene **62** and **63**, a series of inherently chiral calix[4]quinolines of C_1 symmetry in the cone and partial cone conformation were synthesized by Huang and Chen's group through ring closure strategy (Schemes 8, 9). By utilizing the carboxylic group on the newly formed ring as the resolving site and (*S*)-BINOL as the chiral auxiliary, **66** (cone conformer) and **71** (partial cone conformer), in which the carboxyls are located at the 3-position, could be easily resolved via column chromatography on silica gel, which allowed the gram-scale preparation of corresponding enantiomers. Racemic **67**, as the debutyl analog of **66**, was optically resolved using (*R*)-phenylglycinol as a chiral auxiliary via, however, preparative TLC. The positive effect of *t*-butyls at the wide rim on optical resolution may be attributable to the steric effect or rigidity they induce. For cone conformer **69**, in which the carboxyl is located at the 2-position, (*S*)-BINOL is also effective for optical resolution through preparative TLC. However, its partial cone counterpart **73** could not be optically resolved under similar condition. This result reveals that the position of the carboxyl as the resolving site is a key factor in efficient optical resolution [42].



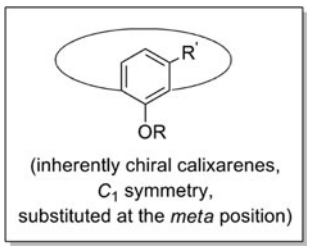
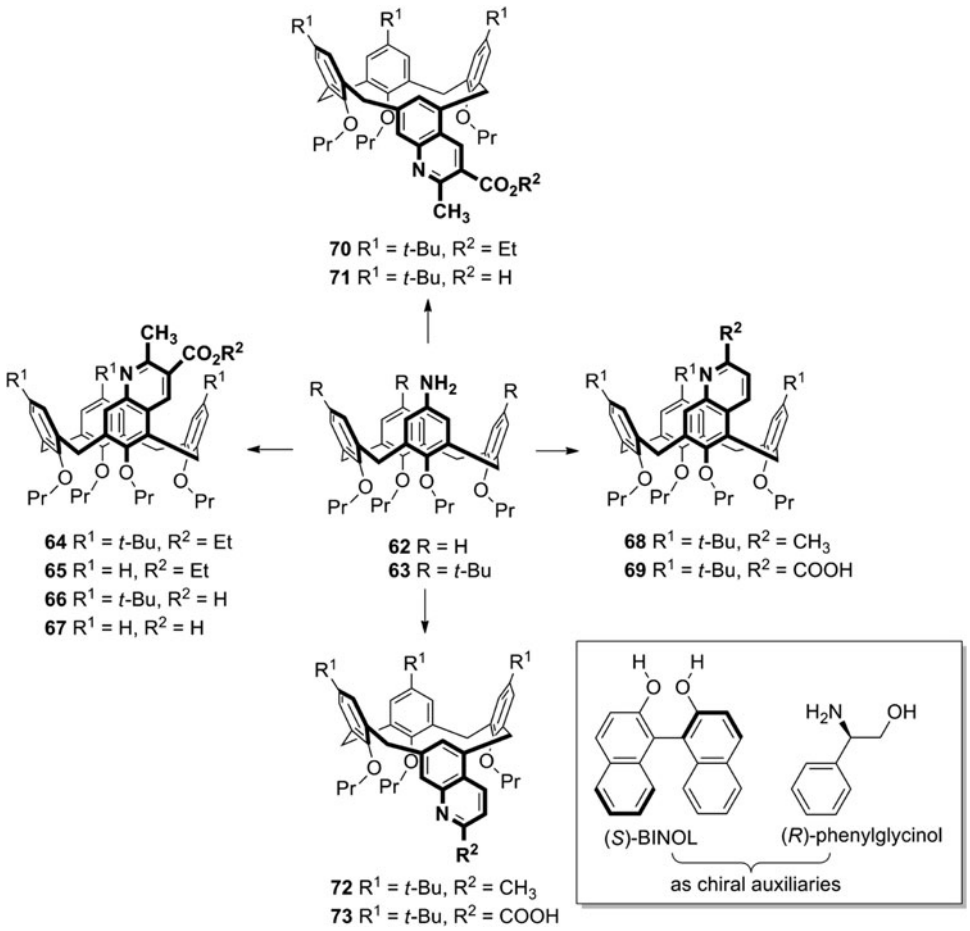


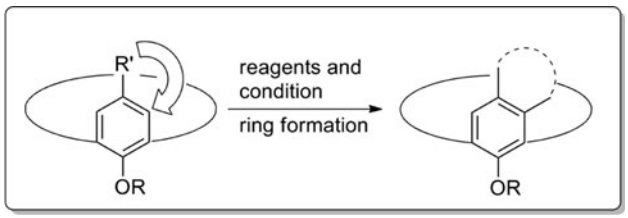
Fig. 2 Diagram of inherently chiral calixarenes with C_1 symmetry: substituted at the meta position

Enantiopure **66**, **71** and diastereomeric BINOL ester intermediates of **69** were further used to synthesize inherently chiral calix[4]arenes incorporating a quinolin-2-yl-methanol moiety (**74**–**76**), which were treated as *N*,*O*-type chiral ligands for the catalytic asymmetric addition of diethylzinc to benzaldehyde. Under the conditions tested, high catalytic efficiency and low enantioselectivity (ee $< 18\%$) were observed. This indicates that the enantioselectivity of the reaction is induced by the inherent chirality of the ligands via a remote stereocontrol [43].

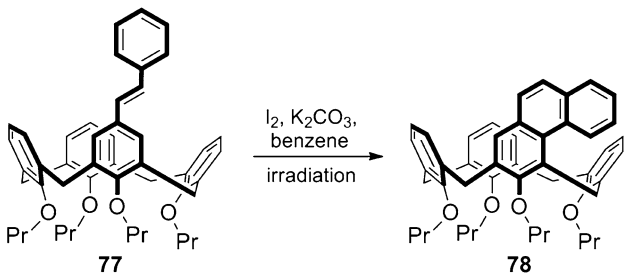
Oxidative photocyclization of *p*-styryl-substituted calix[4]arenes has been achieved for the synthesis of calix[4]phenanthrene **78** under optimal condition in high yields as racemates [44] (Scheme 10). This work may serve as the basis for the development of calix[4]phenanthrenes

Scheme 8 Use of aminocalix[4]arene **62** and **63** to synthesize a series of inherently chiral calix[4]quinonline cone and partial cone conformers with C_1 symmetry





Scheme 9 Schematic representation of the synthesis of *meta*-substituted inherently chiral calixarenes by ring closure strategy

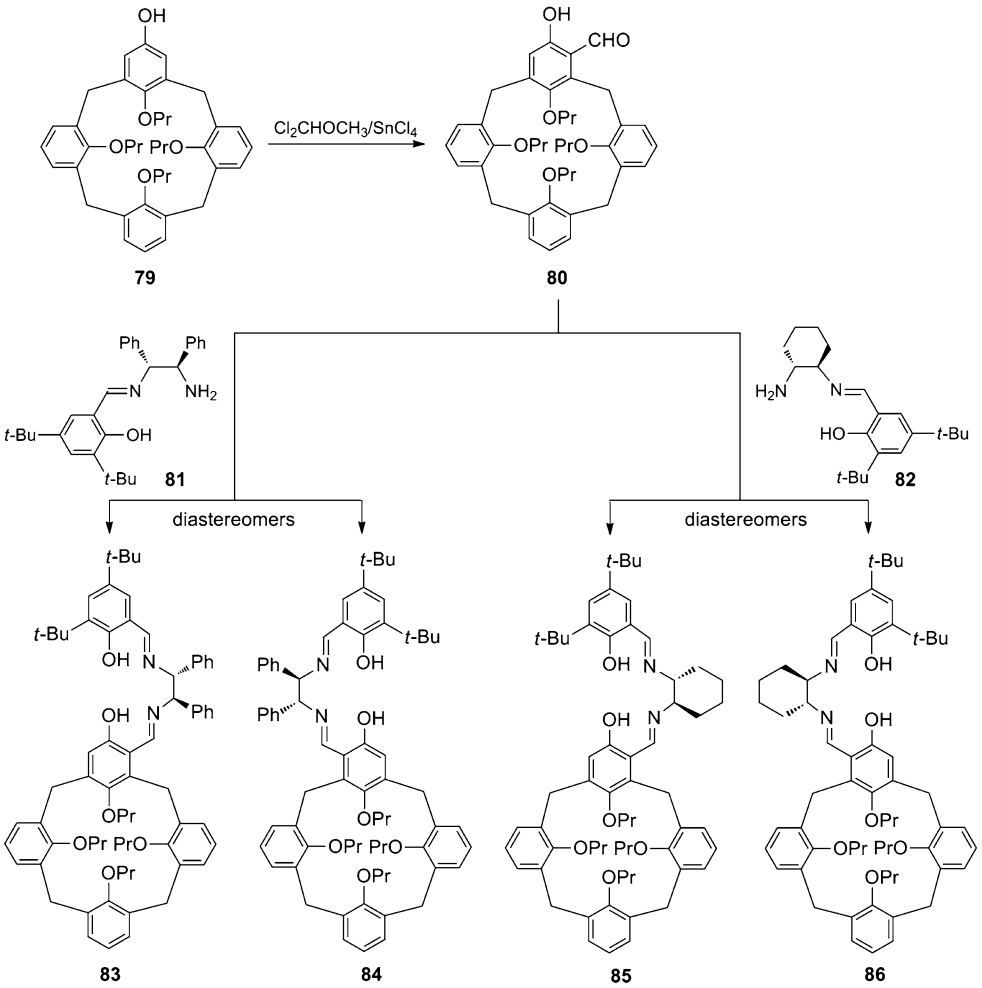


Scheme 10 Synthesis of a *meta*-substituted inherently chiral calixarene by oxidative photocyclization of *p*-styryl-substituted calix[4]arene

containing more phenanthrene units, which are a class of cavitands that possess deep cavities and have potential complexation properties for C_{60} and C_{70}.

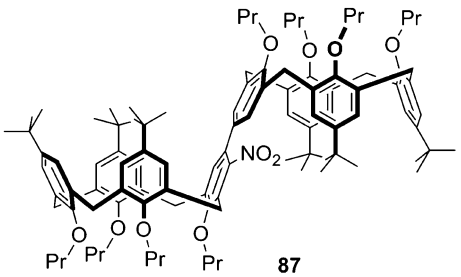
Electrophilic aromatic substitution was firstly demonstrated as an efficient synthetic method for *meta*-substituted inherently chiral calix[4]arenes by Reinhoudt and coworkers [45] in 1995, where acetoamido as an activating and directing group was introduced at the wide rim (*para*-position), followed by mono-bromination or mono-nitration at the *meta*-position to produce inherently chiral calix[4]arenes. *para*-Hydroxyl substituted calix[4]arene **79** has also been used to synthesize *meta*-substituted species, as was exemplified by the work of Tomaselli et al. Gross formylation of **79** afforded *meta*-substituted species **80** (as racemates), in which the calixarene moiety was incorporated a salicylaldehyde functionality. Reaction of **80** with suitable imino-amino intermediate (**81**, **82**) led to the formation of salen calix[4]arene diastereomeric pairs **83/84** and **85/86**, which could be isolated by preparative PLC (Schemes 11, 12). Calix-salens **83–86** were utilized as ligands to prepare corresponding uranyl (VI) and Mn(III) complexes. The chiral (salen)Mn^{III} complexes with a built-in calix[4]arene cavity were used as catalysts for enantioselective epoxidation

Scheme 11 Synthesis of chiral calix-salen ligands with a built-in calix[4]arene cavity

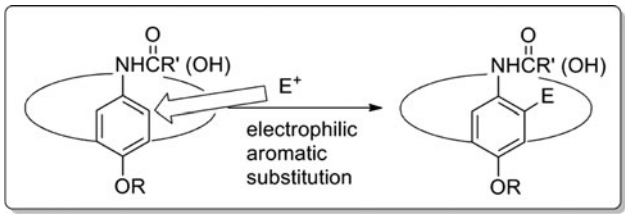


reactions of styrene, 1,2-dihydronaphthalene and some standard *cis*-*β*-alkylstyrenes. In the molecular design stage, the calixarene cavity was assumed to have the potential to recognize the alkene through the alkyl group and thus influence the alkene approach trajectory. However, it was observed that all the (salen)Mn^{III} complexes caused moderate and comparable ee values for all the substrates studied. Based on experimental data and conformational analysis which is facilitated by the single crystal structure of the UO_2-**83** complex, it cannot be concluded that the presence of the calix[4]arene cavity has the ability to induce a catalytic selectivity based on molecular recognition mechanism of the alkene to be oxidized [46].

Even an aromatic ring unit of a calix[4]arene could serve as an *ortho*-directing group for electrophilic aromatic substitution reaction. In 2005, Neri et al. discovered that reaction of *p*-*tert*-butyl-5,5-biscalix[4]arene under suitable nitration condition yielded a single mononitro derivative **87** in high yield. NMR and MS spectra confirmed its *ortho*-position to biphenyl linkage and therefore its inherent chirality [47]. This is another example of inherently chiral biscalix[4]arene.



Recently, Neri et al. have opened a new route for the synthesis of inherently chiral calix[4]arene substituted at the *meta*-position by rearrangement. The silver-mediated nucleophilic substitution on calix[4]arene *p*-bromodienone derivative **89** (the "*p*-bromodienone route") with activated aromatic substrates (e.g. resorcinol) allowed the introduction of aromatic moieties at the *meta*-position to form inherently chiral calixarene **91**, along with the achiral *para*-substituted de-*tert*-butylated product **92**. A dienone-phenol rearrangement is believed to be involved in the formation of **91** [48] (Scheme 13).



Scheme 12 Schematic representation of the synthesis of *meta*-substituted inherently chiral calixarenes by electrophilic aromatic substitution

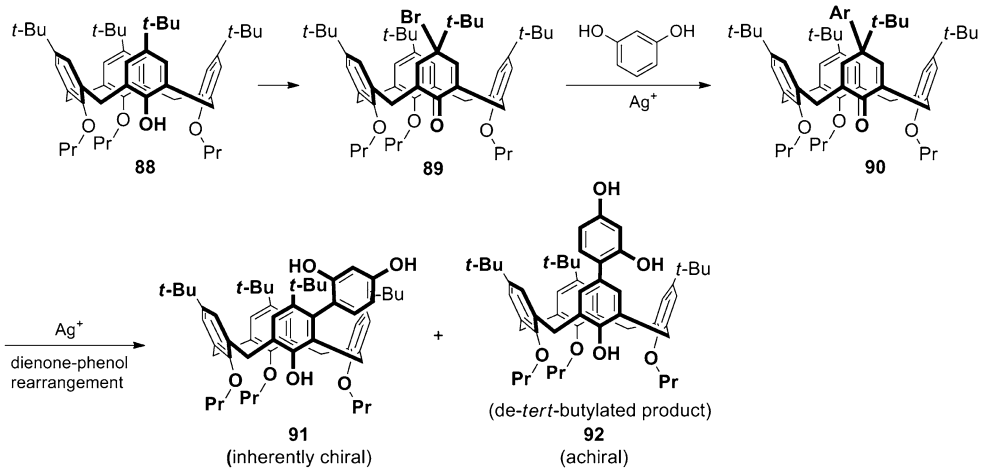
Of C_2 symmetry—substituted at the narrow/wide rim

For many asymmetric reactions, it has been observed that auxiliaries with C_2 symmetry elements provide higher levels of absolute stereochemical control than do the non-symmetric C_1 counterparts [49]. This (at least partially) justifies those efforts devoted to the design and synthesis of inherently chiral calixarenes with C_2 symmetry. Asymmetric substitution pattern could occur at the narrow rim, the wide rim or at both rims. Early examples (**93**–**98** as cone conformers) feature formation of two proximal bridges with opposite ring directionality [50–52] (Scheme 14). No new example of this design has emerged over the past decade.

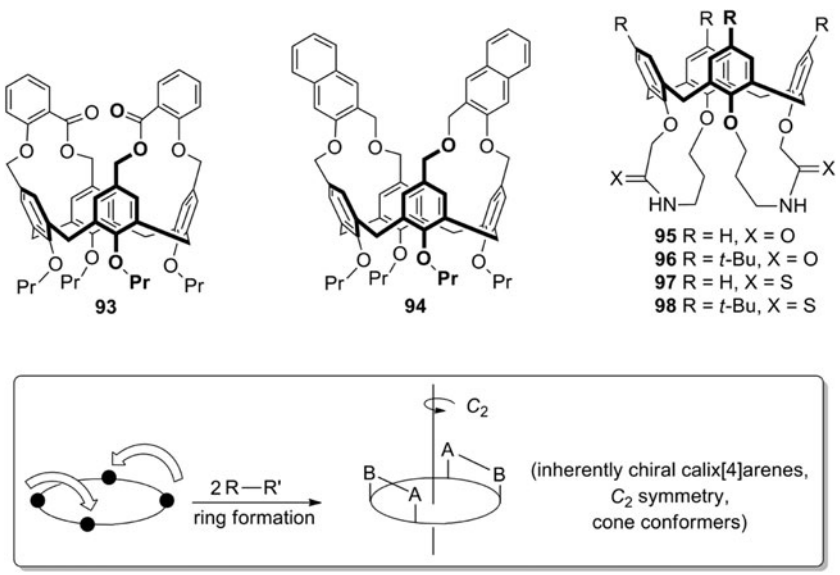
Inherently chiral 1,3-alternate conformers of C_2 symmetry has been demonstrated by Gutsche et al. in as early as 1999. Reaction of the S_4-symmetric bisanhydride 1,3-alternate conformer **99** with alcohols and amines gave corresponding C_2-symmetric half amides or half esters **100** in quantitative yields [53] (Schemes 15, 16).

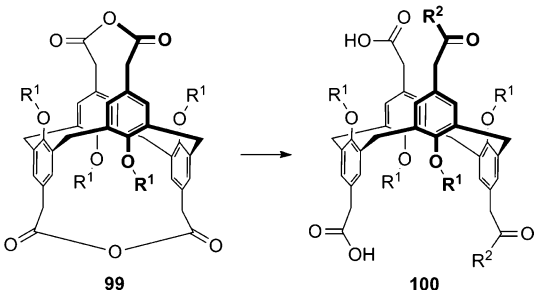
Compounds of similar structure have later been produced by de Mendoza et al. in an alternative way. The paco tribenzoyl calix[4]arene **37** was stirred for 15 min with an excess of sodium hydride in DMF at room temperature and subsequently quenched with cold HCl to yield the

Scheme 13 Synthesis of a *meta*-substituted inherently chiral calix[4]arene by dienone-phenol rearrangement



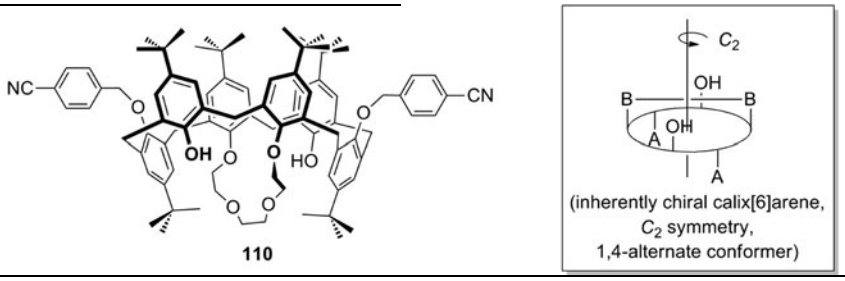
Scheme 14 Schematic representation of the synthesis of inherently chiral calix[4]arenes with C_2 symmetry by the formation of two proximal bridges with opposite ring directionality





Scheme 15 From the S_4-symmetric bisanhydride 1,3-alternate conformer **99** to inherently chiral 1,3-alternate conformers **100** with C_2 symmetry

An inherently chiral calix[6]arene in the rare 1,4-alternate conformation with a C_2-symmetric substitution pattern (**110**) was synthesized via a two step process starting from the parent *p-tert*-butylcalix[6]arene. The racemic **110** was effectively resolved by chiral HPLC method. X-ray diffraction and ^{1}H NMR study confirmed that **110** adopts a 1,4-alternate conformation both in the crystalline state and in solution [56].



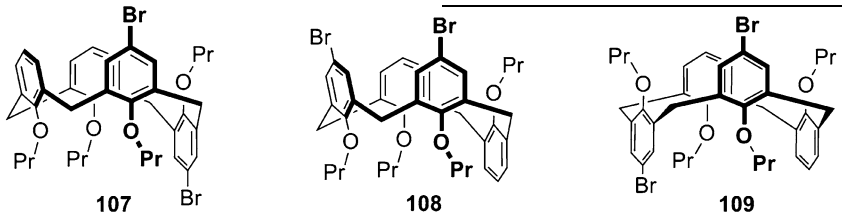
mono-deacylated intermediate **101**. For **101**, it is definite that the two benzoyl groups adopt the *anti* orientation, though its actual conformation remains unclear, due to the free rotation of the two free phenol rings. Subsequent alkylation with propyl iodide afforded corresponding inherently chiral 1,3-alternate conformer **102** of C_2 symmetry (Scheme 17). The formation of these structures is of widespread interest in that it may help the development of recognition systems with two complementary groups directly placed in close proximity and catalytic systems with the catalytic center flanked by recognition site [54]. However, for asymmetric application, the prerequisite of optical resolution still remains to be satisfied.

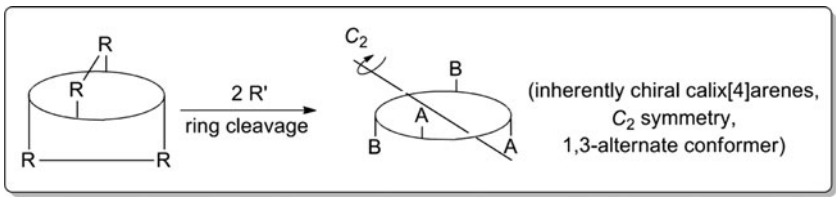
A rare example of inherently chiral 1,2-alternate conformer of C_2 symmetry as racemates (**106**) has been reported by Shimizu and coworkers [55] via a multiple-step sequence (Scheme 18). Two inherently chiral partial cone conformers (**107**, **108**) of C_1 symmetry and a 1,3-alternate conformer of C_2 symmetry (**109**) were also synthesized in this work.

Of C_2 and C_4 symmetry—substituted at the *meta* positions

Though *meta*-substituted chiral calix[4]arenes with C_2 and C_4 symmetry are aesthetically appealing because of high symmetry, their syntheses are by no means easy tasks (Fig. 3). Böhmer's 2 + 2 fragment condensation represented early efforts to generate such *meta*-substituted calix[4]arenes with C_2 symmetry (**112**, for example). An obvious advantage of this 2 + 2 fragment condensation lies in the definite style of the ring formation process. However, the overall yield is very low for this multiple-step synthesis [57] (Scheme 19).

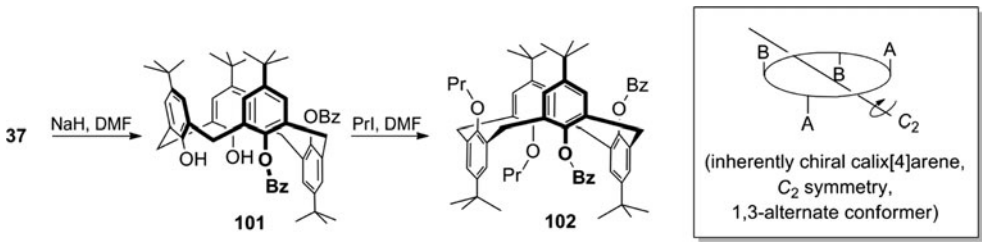
Inherently chiral calix[4]naphthalenes of C_2 symmetry in a *meta*-position plus narrow rim-substitution pattern were synthesized by Georghiou et al. in 2002. Acid or base-induced condensation reaction of **113** with aqueous formaldehyde afforded achiral C_2-symmetrical calix[4]naphthalene **114**. By subsequent 1,3-dialkylation under basic



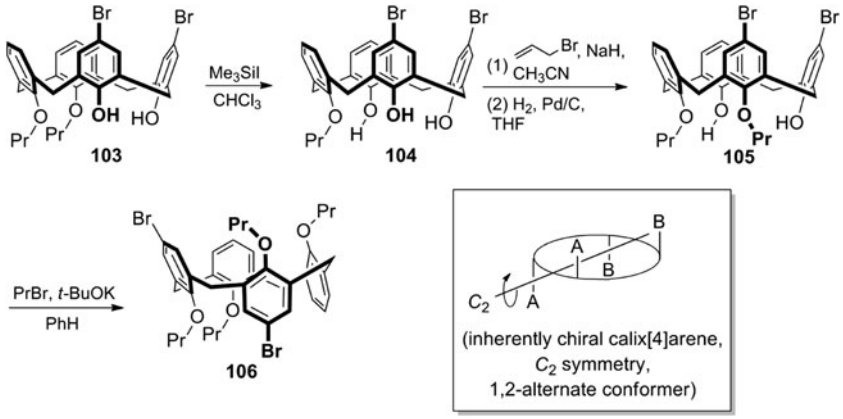


Scheme 16 Schematic representation of synthesis of inherently chiral 1,3-alternate conformers with C_2 symmetry by desymmetric ring cleavage of the S_4-symmetric bicyclic calix[4]arene in the 1,3-alternate conformation

Scheme 17 An alternative to an inherently chiral calix[4]arene 1,3-alternate conformer with C_2 symmetry



Scheme 18 Synthesis of an inherently chiral 1,2-alternate conformer with C_2 symmetry via a multiple-step sequence



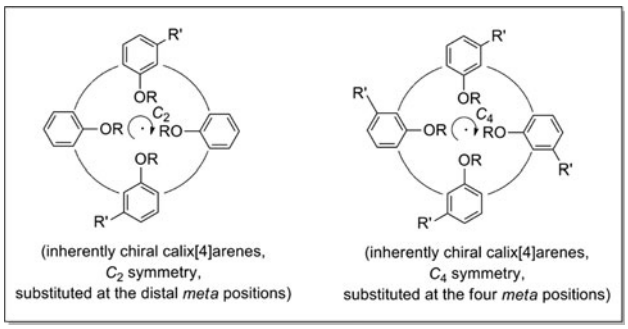
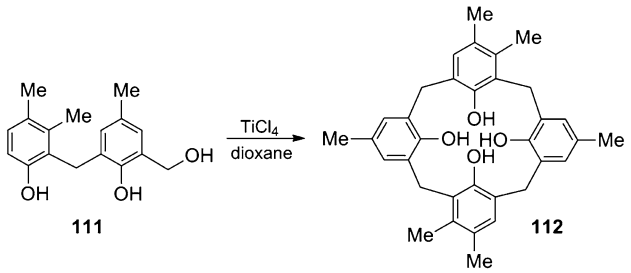


Fig. 3 Diagram of inherently chiral calix[4]arenes with C_2 and C_4 symmetry: substituted at the meta positions



Scheme 19 Synthesis of a *meta*-substituted inherently chiral calix[4]arene with C_2 symmetry by 2 + 2 fragment condensation

conditions, **114** was converted into inherently chiral species of C_2 symmetry **115**–**118** [58] (Scheme 20).

Generation of inherently chiral species of C_2 symmetry by virtue of direct modification of parent calixarenes, as was shown by a recent example (**122**) [59] (Scheme 21), is encumbered with an intrinsic disadvantage of the concomitant formation of the achiral regioisomer, which leads to low yields and possible separation problem. It is not surprising that the method of direct modification is particularly unsuitable for the synthesis of inherently chiral molecules of C_4 symmetry under normal conditions.

In general, the past decade did not see breakthrough in the synthetic methodologies of inherently chiral

calixarenes of C_2 and C_4 symmetry. Optical resolution of related racemic molecules is still a challenge.

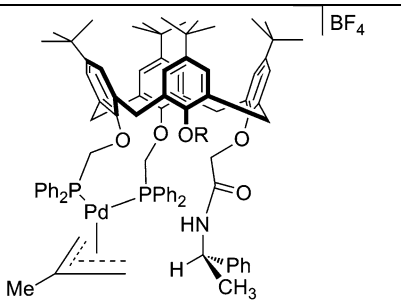
Efforts on stereoselective syntheses of inherently chiral calix[4]arenes

Stereoselective synthesis of inherently chiral calix[4]arenes, where chiral substrates, chiral reagents, or chiral catalysts are involved, is more intriguing than the non-stereoselective methods for its potential to obtain chiral calixarenes of high enantiomeric excesses (or diastereomeric excesses). All the examples reported so far are inherently chiral cone and partial cone conformers of C_1 symmetry.

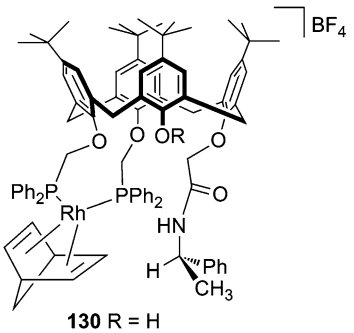
Using chiral reagent

The earliest endeavor was made by Matt et al. for the synthesis of inherently chiral calix[4]arene-based diphosphines. Monoalkylation of the 1,2-disubstituted precursor **124** with (*R*)-$BrCH_2CONHCHMePh$ in the presence of K_2CO_3 afforded a pair of diastereomers **125** and **126**, as a result of the coexistence of the chiral carbon atom introduced by the chiral reagent and the AABC asymmetrical substitution pattern of the calixarene platform (Scheme 22). Though no diastereoselectivity was observed for this reaction, diastereomers **125** and **126** could readily be separated by column chromatography. The absolute configuration of **126** was determined by single crystal X-ray diffraction study.

Palladium complexes **127**–**129** and rhodium complexes **130**–**132** were prepared from **126** via multiple steps and were used as chiral catalysts in the asymmetrical alkylation of 1,3-diphenylprop-2-enyl acetate and hydrogenation of dimethyl itaconate, respectively. Low to moderate enantioselectivities (ee 25–67%) were observed for these inherently chiral calix[4]arene-based chelate complexes (**127**, **128**, **130**, **131**), in contrast to zero ee value observed for **129** and **132** which lack an inherently chiral calixarene skeleton. These results indicate that the inherently chiral calix[4]arene skeleton has the ability to transfer its chiral information to the catalytic centre [60].

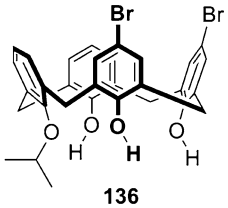


127 R = H
128 R = $SiMe_3$
129 R = (*R*)-$CH_2CONHCHMePh$



130 R = H
131 R = $SiMe_3$
132 R = (*R*)-$CH_2CONHCHMePh$

Kalchenko et al. reported the diastereoselective (1*S*)-camphor sulfonylation as the shortest way to inherently chiral calix[4]arene. The reaction of monoether **133** with (1*S*)-camphor-10-sulfonyl chloride in the presence of NaH selectively gave the proximally heteroalkylated products **134** and **135** as diastereomers (de of **134** = 15%). By simple crystallization, **134** and **135** could be separated. The absolute configurations of **134** and **135** were determined by X-ray crystallography. Subjecting **134** to sequential dibromination and hydrolysis gave enantiopure inherently chiral calix[4]arene **136** as a cone conformer [61, 62] (Scheme 23). This synthesis is interesting in that it could afford a type of enantiopure inherently chiral calix[4]arenes such as **136** which are chiral by virtue of simultaneous substitution at both rims. In view of the three unmodified phenoxyls at the narrow rim, enantiopure **136** may offer an excellent platform for the construction of more sophiscated inherently chiral calix[4]arenes in all four conformations.



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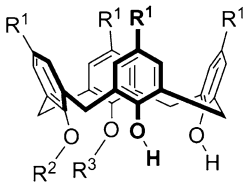


137 R^1 = *t*-Bu, R^2 = Me, R^3 = (*S*)-$CH_2CONHCHMePh$
138 R^1 = *t*-Bu, R^2 = *n*-Pr, R^3 = (*S*)-$CH_2CONHCHMePh$
139 R^1 = H, R^2 = Me, R^3 = (*R*)-$CH_2CONHCHMePh$
140 R^1 = H, R^2 = *n*-Pr, R^3 = (*R*)-$CH_2CONHCHMePh$

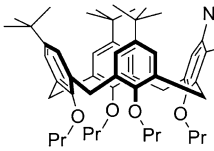
The same group also developed a series of diheteroalkylated inherently chiral calix[4]arenes **137**–**140** (and corresponding diastereomers) using similar synthetic strategy [63].

Using chiral substrate

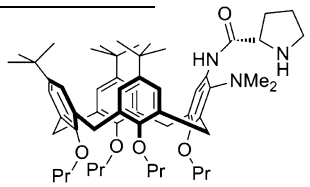
Kalchenko et al. reported the first diastereoselective synthesis of inherently chiral calix[4]carbamates by substrate control. 1,3-Heterosubstituted chiral calix[4]arene **141** was monoacylated with acylisocyanate, leading to the formation of diastereomeric **142** and **143** in a 4:1 ratio (60% de) (Scheme 24). Crystallization afforded enanitopure **142**, whose absolute structure was determined by X-ray crystallography. The diastereoselectivity is believed to be associated with the proximity of the chiral moiety to the reactive hydroxyl and the mild reaction condition (5 °C) in the acylation process [64].

The absolute configurations of both diastereomers were determined by X-ray crystallography. By sequential bromination and hydrolysis of **145** and **146** respectively, both enantiomers of inherently chiral calix[4]arene carboxylic acid **147** as cone conformers were obtained, which demonstrated chiral discrimination ability toward chiral α-phenylethylamine by ^{1}H NMR titration [65]. Calixarene **147** is another example of enantiopure inherently chiral calix[4]arene with a pattern of simultaneous substitution at both rims.

Huang, Chen et al. achieved the synthesis of *meta*-substituted inherently chiral species by the introduction of L-Boc prolinamide at the wide rim. Bromination and nitration of the chiral amidocalix[4]arene substrate **149** occurred at the *meta* position, giving corresponding diastereomers **150**/**151** and **152**/**153**, respectively (Scheme 26). Though no diastereoselectivity was observed in this system, the pairs of diastereomers could be separated by preparative TLC (for



154 R = Br
155 R = NO_2
156 R = Cl
157 R = CN
158 R = Ph
159 R = NH_2



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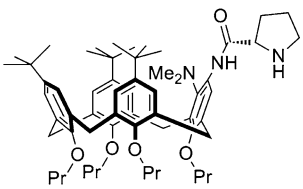

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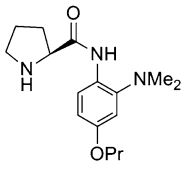

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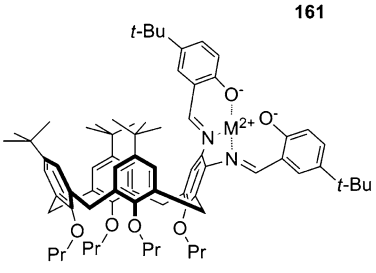

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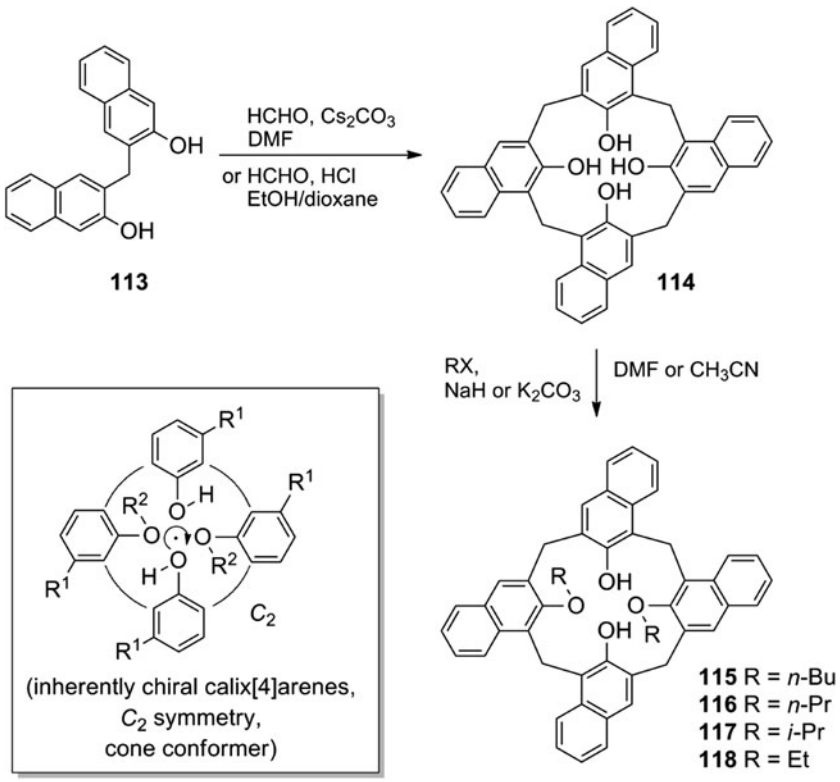
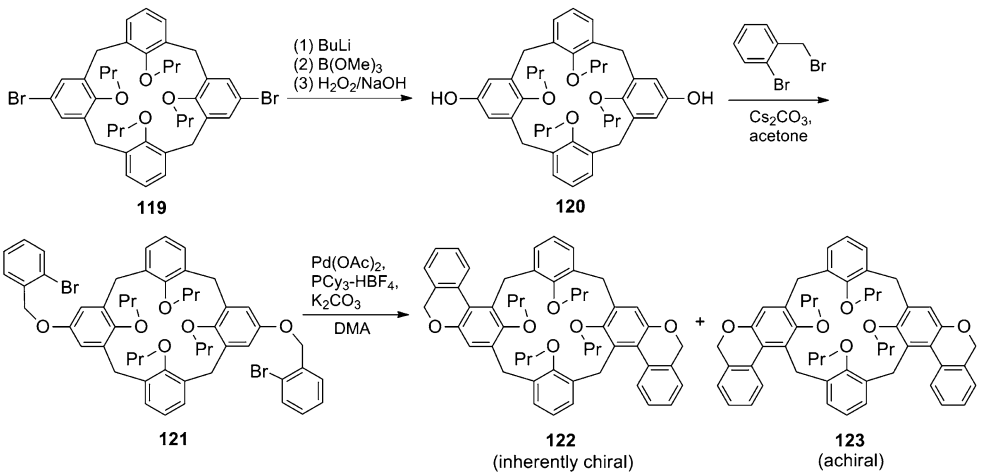
Likewise, the 1,3-heterosubstituted chiral calix[4]arene **144** was monobenzoylated to afford diastereomers **145** and **146** (de of **145** = 10%) as partial cone conformers, which were separated by column chromatography (Scheme 25). bromination products) or by column chromatography (for nitration products). The L-Boc prolinamide moiety had dual functions of activation and chiral auxiliary. Hydrolysis of the diastereomers afforded enantiopure

Scheme 20 Synthesis of inherently chiral calix[4]arene cone conformers with C_2 symmetry by a combination of *meta*-substitution and narrow rim substitution



Scheme 21 A synthetic case of generation of an inherently chiral calix[4]arene with C_2 symmetry by direct modification of the parent calixarene platform

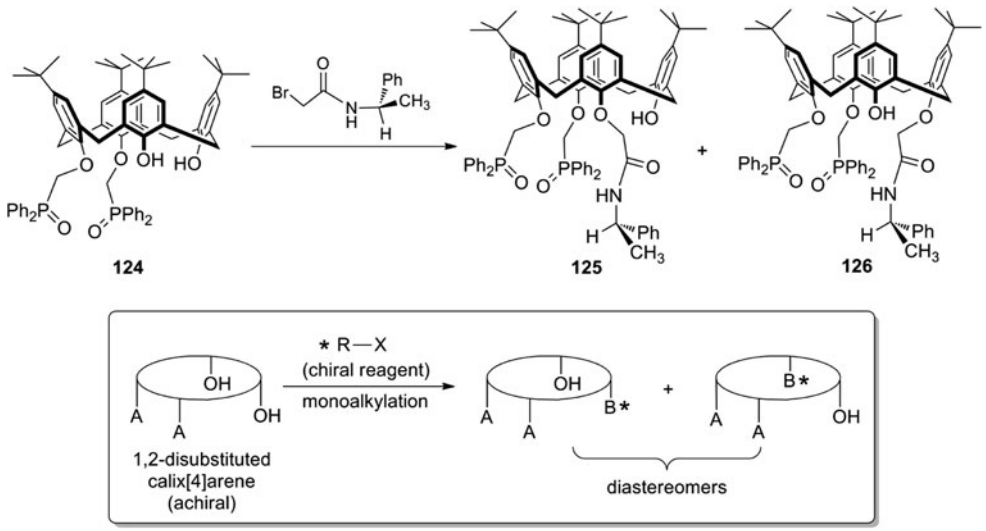


meta-substituted inherently chiral calix[4]arenes **154** and **155** [66].

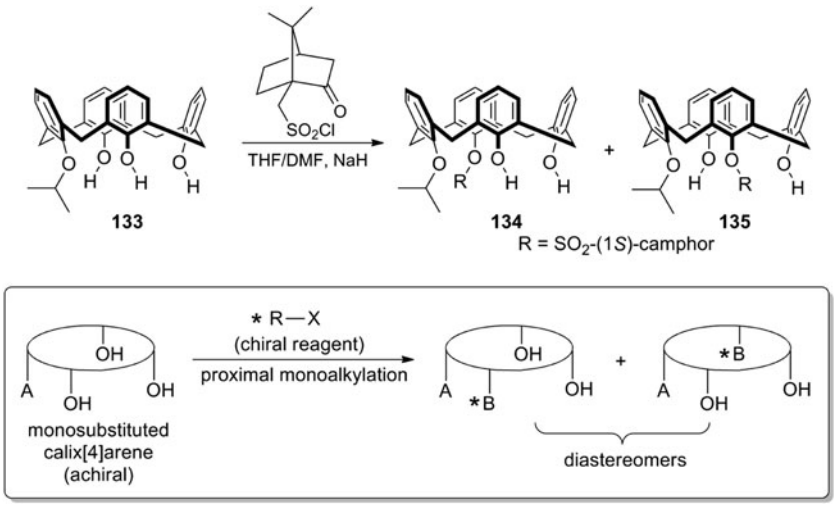
Interestingly, further study by the same group revealed that L-Boc proline could also serve as a chiral acylating reagent for the nonenzymatic kinetic resolution of the racemic **155** [67]. A series of enantiopure *meta*-substituted inherently chiral aminocalix[4]arene derivatives **156–158** have also been synthesized in further study [68].

Enantiopure *meta*-substituted inherently chiral L-prolinamidocalix[4]arene diastereomers **160** and **161** were synthesized and applied as bifunctional organocatalysts in the enantioselective aldol reaction. The results suggested that they could promote the aldol reaction between aromatic aldehydes and ketones in high yields and good enantioselectivity (in terms of *anti* products) in some cases. Notably, for the reaction of 4-nitrobenzaldehyde and cyclohexanone at −20 °C catalyzed by **160–162**, the enantioselectivity (*anti* products) decreased in order of **160**, **162** and **161**, indicating that the inherently chiral skeleton may influence the stereocontrol of the reaction [69]. Starting from enantiopure inherently chiral diaminocalix[4]arene **159** (and its enantiomer), the same group has also produced three pairs of chiral salphen-based metal (Zn^{2+}, Ni^{2+}, and Cu^{2+}) complexes (**163** and corresponding

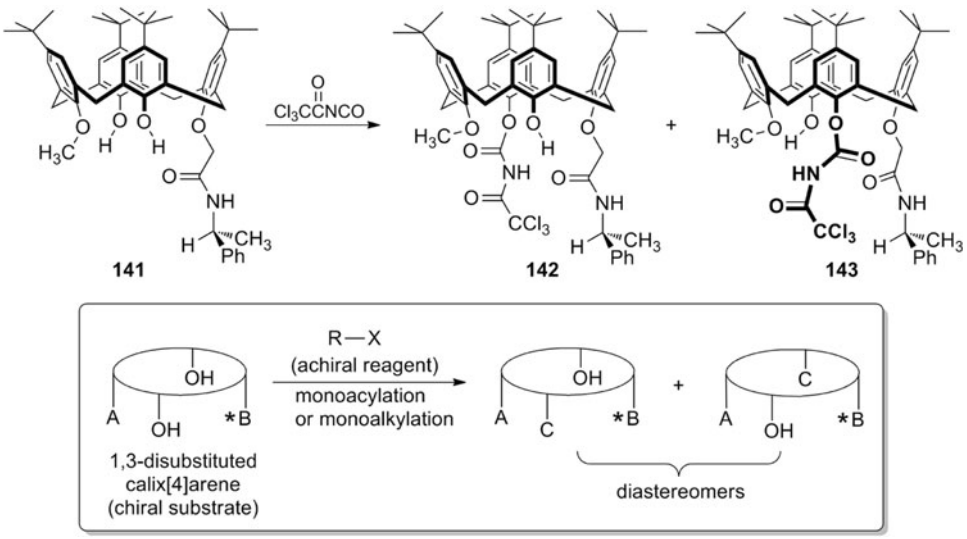
Scheme 22 A specific example and schematic representation of the synthesis of inherently chiral calix[4]arenes by use of chiral reagent: monoalkylation of an achiral 1,2-disubstituted calix[4]arene with a chiral reagent

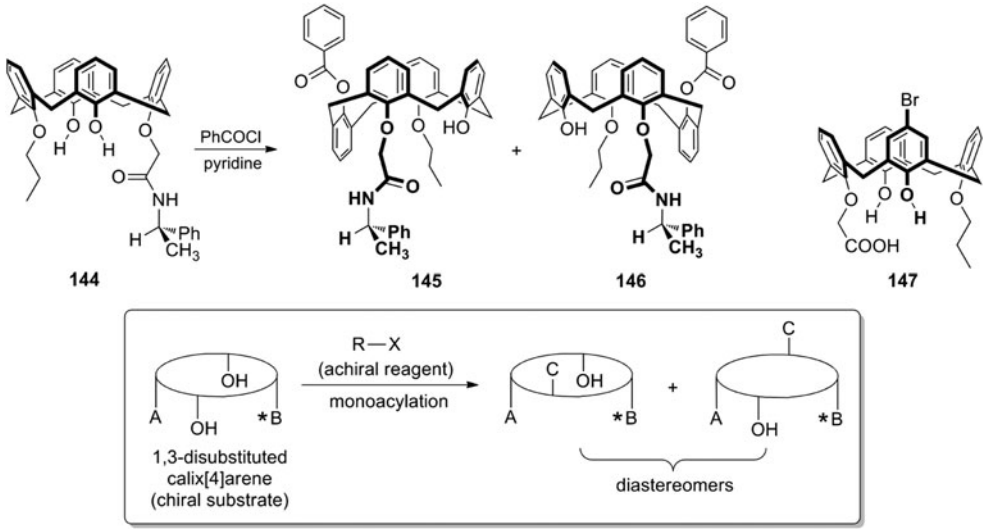


Scheme 23 A specific example and schematic representation of the synthesis of inherently chiral calix[4]arenes by use of chiral reagent: proximal monoalkylation of an achiral monosubstituted calix[4]arene with a chiral reagent

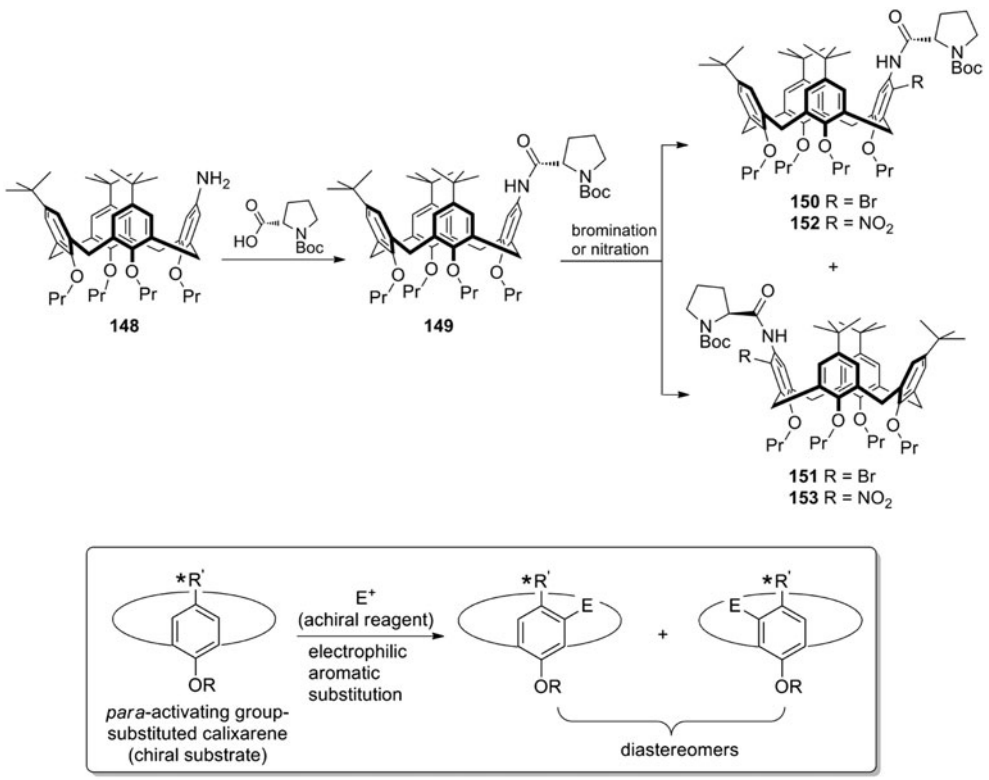


Scheme 24 A specific example and schematic representation of the synthesis of inherently chiral calix[4]arene cone conformers by use of chiral calixarene substrate: monoacylation or monoalkylation of a chiral 1,3-disubstituted calix[4]arene with an achiral reagent





Scheme 25 A specific example and schematic representation of the synthesis of inherently chiral calix[4]arene partial cone conformers by use of chiral calixarene substrate: monoacylation of a chiral 1,3-disubstituted calix[4]arene with an achiral reagent

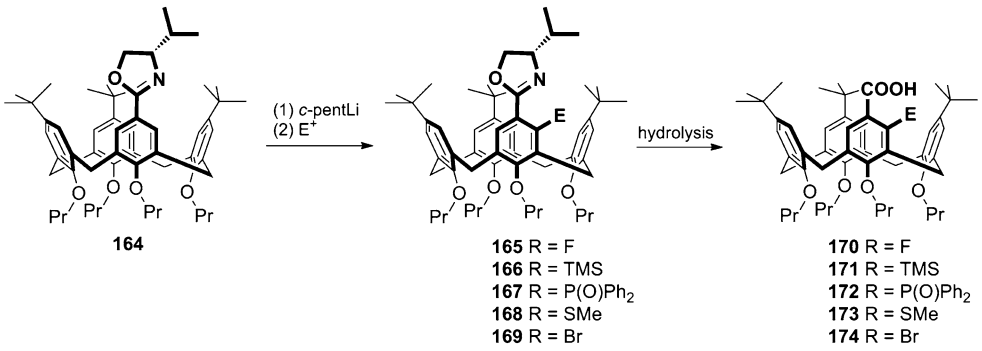


Scheme 26 A specific example and schematic representation of the synthesis of inherently chiral calix[4]arenes by use of chiral calixarene substrate: electrophilic aromatic substitution of a chiral *para*-activating group-substituted calix[4]arene with an achiral electrophile

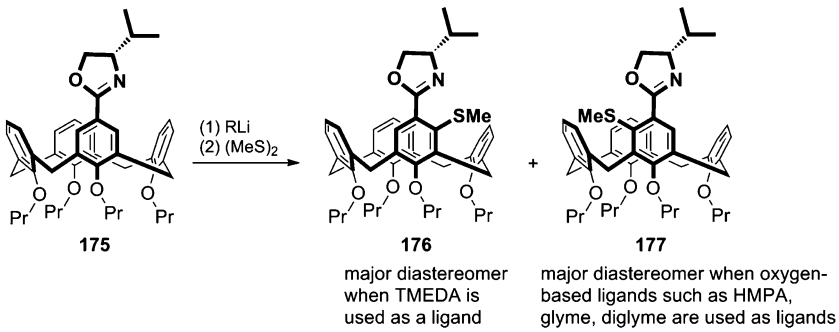
enantiomer), the asymmetric catalytic ability of which being still awaiting test [70].

In contrast to the efforts previously introduced, where moderate to ignorable stereoselectivity was observed, a practical synthesis of inherently chiral calix[4]arenes with high enantiomeric excesses has been developed very recently by Arnott et al. using a chiral oxazoline moiety at the wide rim as an ortholithiation directing group to induce high de values. Ortholithiation of chiral substrate **164** with cyclopentyllithium in the presence of TMEDA as an additive, followed by quenching with a series of electrophiles (electrophilic aromatic substitution) afforded the

Scheme 27 A practical diastereoselective synthesis of inherently chiral calix[4]arenes by use of a chiral oxazoline moiety at the wide rim as an ortholithiation directing group to induce high de values



Scheme 28 Reversal of diastereoselectivity by a choice of ligand



meta-substituted calix[4]arene derivatives **165–169** in high de values of >92%. Removal of the oxazoline chiral auxiliary by microwave-assisted hydrolysis led to the formation of the *meta*-substituted inherently chiral calix[4]arene carboxylic acids **170–174**, whose ee values should be equal to the de values of corresponding precursors. The absolute configuration of the major diastereomer was unambiguously confirmed by the X-ray crystal structure of a related derivative [71] (Scheme 27).

Further study revealed that diastereoselectivity could be reversed by a choice of ligand for a given reaction system with the debutylated analogue of **164** (**175**) as a reactant and dimethyl disulfide as an electrophile. When TMEDA is used as a ligand, the major diastereomers have *cR* chirality as is shown by **176**. However, oxygen-based ligands such as HMPA, glyme, and diglyme tend to cause a reversal in the diastereoselectivity. Based on the experimental results and DFT calculation, the authors suggested a mechanism for this stereocontrol through ligand choice [72] (Scheme 28).

Apart from its practicability of direct obtaining inherently chiral calixarenes of high ee values that avoids resolution techniques, this work has demonstrated the potential of using calixarene as a model to investigate the general mechanism of a specific reaction.

Conclusions and outlook

The study of inherently chiral calixarenes has attracted enduring attention over the past decade and advances have been made on aspects of structure diversity, synthetic methodologies, and applications. However, there is still more to be expected for the decade to come. On the aspect of enriching structural diversity, inherently chiral calix[4]arenes in the 1,2-alternate conformation and in the 1,3-alternate conformation are to be enriched; selective modification of bridging methylenes [73–76] or outer face [77, 78] could provide additional possibilities for the construction of novel inherent chirality; the construction of inherently chiral biscalixarenes and multiple calixarenes is intriguing; aggregate systems with supramolecular chirality may be built on inherently chiral calixarene components. Concerning synthetic methodologies, an efficient synthetic method of inherently chiral calixarene with C_2, especially C_4 symmetry by direct modification of the parent calixarenes is highly demanded, which may involve a suitable template to control the directionality; understanding of the relationship between structure and optical resolution is to be extended and deepened; advantageous utilization of inclusion ability to realize regioselective functionalization is an excellent strategy especially suitable for calix[5, 6, 8]arenes to build inherent chirality; asymmetric synthesis of inherently chiral calixarenes by substrate control, reagent control, and especially catalyst control is a promising strategy for direct access to enantiopure products. More applications of inherently chiral calixarenes in realms of chemistry, biology and material are envisioned to emerge in the next decade. So far, the inherently chiral calixarenes used as chiral sensors and chiral catalysts have demonstrated efficiency that is encouraging but far from

being satisfactory. This could partially be attributed to the limited systems studied. Meanwhile, a question naturally arises as to the criticality of the role played by inherent chirality. It is a challenge for researchers to find an appropriate niche for the application of specific inherently chiral calixarenes as well as to design and synthesize inherently chiral calixarenes aimed at performing specific functions.

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