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Catalytic Enantioselective Synthesis and Switchable Chiroptical Property of Inherently Chiral Macrocycles

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ABSTRACT: We report herein a strategy to construct enantiopure inherently chiral macrocycles, ABCD-type heteracalix[4]aromatics, through a catalytic enantioselective intramolecular C-N bond forming reaction. A chiral ligand-palladium complex was found to efficiently induce the inherent chirality of molecules during macrocyclization process with *ee* values up to >99%. The resulting ABCD-type heteracalix[4]aromatics displayed excellent and *p*H-triggered switchable electronic circular dichroism and circularly polarized luminescence properties.

Molecular chirality defines the non-superimposability of three-dimensional molecules onto their mirror images. Since enantiomers often display drastically different effects on biological systems, there has been continuous research interest in the synthesis of enantiopure small organic molecules[1] to meet the demand of the discovery and the development of chiral drugs[2]. On the other hand, small chiral molecules provide unique platforms for the fabrication of chiral functional materials and devises. However, this fascinating aspect of small molecular chirality remains largely unexplored[3]. One of the current focuses of the study is the chiroptical properties such as circularly polarized luminescence (CPL) of enantiomerically enriched or pure small molecules[4] and molecular assemblies[5].

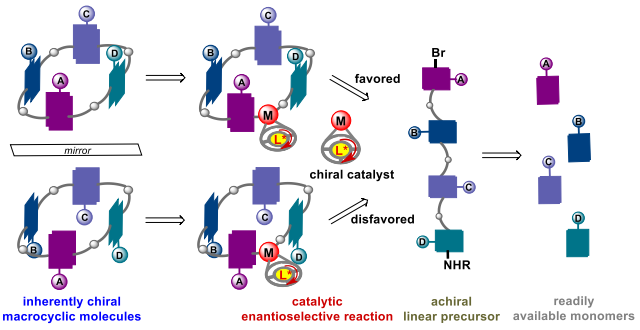


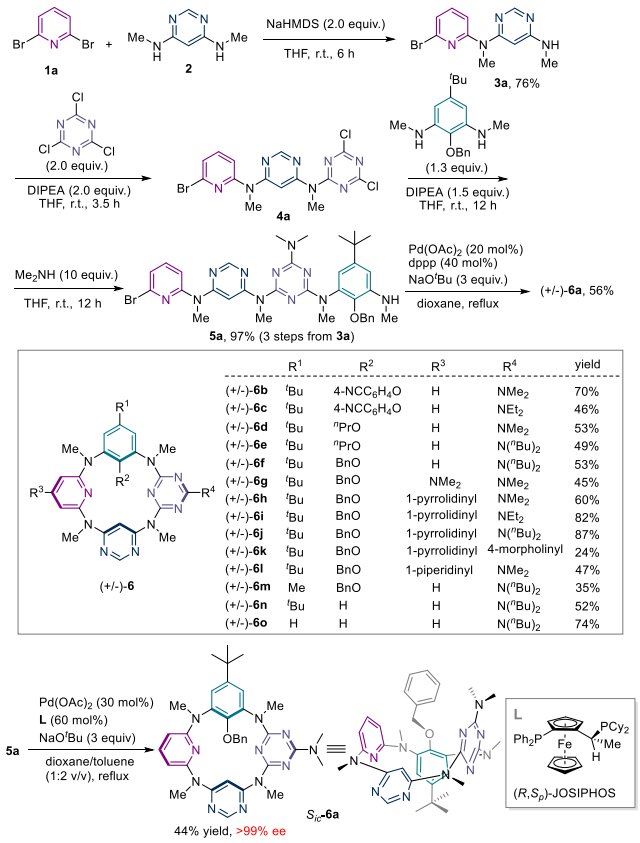
Figure 1. Schematic presentation of mirror image of inherently chiral macrocycles and a strategy of catalytic asymmetric synthesis

Molecular chirality is classified generally into point, axial, planar, and helical chirality based on stereogenic elements. In 1994, Böhmer[6,7] coined inherently chiral calixarenes to describe calixarenes devoid of any symmetry elements except a C_1 asymmetry axis (Figure 1). In other words, ring opening of an inherently chiral calixarene macrocyclic structure leads to an achiral linear molecule. The term of inherent chirality has now been accepted by macrocyclic and supramolecular chemistry community to differentiate a special collection of chiral macrocycles from other well-known central, axial, planar and helical molecules. It is noteworthy that while synthesis and application of conventional types of chiral molecules have reached a highly sophisticated level[1], catalytic synthesis of enantiomerically pure inherently chiral molecules remains a formidable challenge. Resolution of racemic samples using analytic HPLC with columns coated with chiral stationary phase is the most frequently way so far to obtain a tiny amount of enantiomers[8]. There were only two attempts to synthesize inherently chiral macrocycles by means of enantioselective catalysis. In the presence of cross-linked crystals of *Aspergillus niger* lipase, a tris(*O*-2-hydroxyethyl)-substituted calixarene derivative underwent mono acetylation to afford an enantiopure macrocycle in 19% yield[9]. The other example was a $Pd(dba)_2$/(*R*)-SEGPHOS-catalyzed intramolecular cross coupling reaction which produced an azacalix[4]arene product in 78% yield with 35% *ee*[10]. The inaccessibility of inherently chiral macrocycles has unfortunately hampered the investigation of the chiroptical properties such as CPL activity of this class of chiral molecules[11].

We report herein the first catalytic enantioselective synthesis and switchable electronic circular dichroism (ECD) and CPL properties of ABCD-type heteracalix[4]aromatics. Heteracalix[4]aromatics are a unique type of synthetic macrocycles widely used in molecular recognition, fabrication of sophisticated (supra)molecular architectures[12,13], and the exploration of high valent organocopper chemistry[14-16]. Evidently, assembly of four different aromatic rings into heteracalix[4]aromatics would generate novel inherently chiral macrocycles (ABCD-type, Figure 1). The facile catalytic synthesis of enantiomerically pure heteracalix[4]aromatics would significantly expand applications of this already-useful type of host molecules. More importantly, comprehension of correlation between inherent chirality and chiroptical properties will open an avenue to new chiral science and technology. It should be noted that inherently chiral heteracalix[4]aromatics do not necessarily contain four completely different aromatic

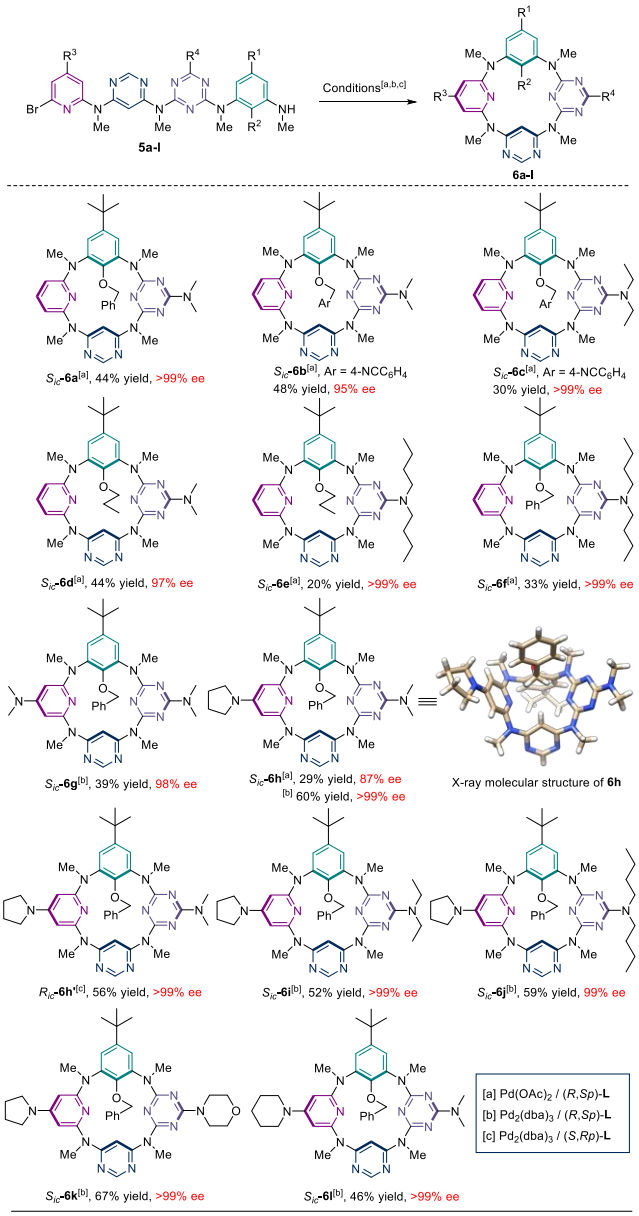
subunits[6,7]. Even the AABB-type macrocycles such as the proximally dechlorinated 1,3-alternate tetraazapyrimidine is resolvable into a pair of enantiomers[17]. To showcase the potential of fragment coupling strategy to create diverse inherently chiral structures, and also to construct the inherently chiral cavity surrounded by aromatic rings of different electronic features, we concentrated on tetraazacalix[4]aromatics which contain benzene, pyridine, pyrimidine and triazine rings. We envisioned the use of a chiral ligand in Pd-catalyzed intramolecular C_{aryl}-N bond forming reaction[18,19] would induce the inherent chirality. In other word, the transfer or the expression of chirality of a homochiral catalyst or a ligand to a macrocyclic skeleton was expected during macrocyclization process (Figure 1).

Scheme 1. Reaction design and optimized reaction conditions.



As a prelude of enantioselective catalysis, we examined the synthesis of racemic tetraazacalix[4]aromatics (+/-)-**6** by means of a fragment coupling strategy (Scheme 1). Condensation between 2,6-dibromopyridine **1a** and 4,6-di(methylamino)pyrimidine **2** afforded 4-methylamino-6-((6-bromopyridin-2-yl)(methyl)amino)pyrimidine **3a**. The resulting AB segment **3a** underwent facile nucleophilic aromatic substitution with cyanuric chloride to form intermediate **4a**, which, without isolation and purification, reacted consecutively with 2-(benzyloxy)-5-(*tert*-butyl)-N^1,N^3-dimethylbenzene-1,3-diamine and methylamine to produce an ABCD-type linear tetramer **5a** efficiently in an overall yield of 97%. Pleasingly, $Pd(OAc)_2$/dppp-catalyzed intramolecular Buchwald-Hartwig reaction[20] furnished 16-membered macrocycle **6a** in 56% yield. The method was found very general, and a number of racemic ABCD-type tetraazacalix[4]aromatics **6b-o** were synthesized successfully (Scheme 1). Substantiated by spectroscopic data and single-crystal X-ray structure of **6b** (Supporting Information), **6** adopt 1,3-altenate conformation. Encouragingly, except for **6m-o**, all

Table 1. Catalytic enantioselective synthesis of **6**.



[a]**5** (0.1 mmol), $Pd(OAc)_2$ (30 mol%), (*R*,*Sp*)-**L** (60 mol%), NaO^{t}Bu (3 equiv.), dioxane/toluene (*v*/*v* = 1/2, *c* 3.3 mM), reflux; [b]$Pd_2(dba)_3$ was used as a catalyst; [c](*S*,R_p)-**L** was used as a chiral ligand.

ABCD-type macrocycles were resolved into a pair of enantiomers by chiral HPLC (Supporting Information). The outcomes also showed clearly that removal of a sterically bulky group from either upper or lower rim position of benzene ring, macrocycles **6n** and **6o** became very fluxional conformationally. Even in the case of **6m**, a methyl group on the benzene ring appeared not large enough to prevent racemization of the inherently chiral macrocycle.

To develop a synthetic method for enantiopure inherently chiral heteracalixaromatics, we commenced with Pd-catalyzed cyclization reaction of linear tetramer **5a** using a chiral ligand. Gratefully, after screening only a handful of chiral ligands, (R,S_p)-JOSIPHOS (**L**) stood out as the best one to afford macrocycle **6a** with >99% *ee* albeit in a low yield. The reaction conditions were optimized (Supporting Information) and both a good yield (44%) and outstanding enantioselectivity (>99% *ee*) were achieved when the reaction was refluxed in a dioxane/toluene mixture (1:2 v/v) in the presence of $Pd(OAc)_2$ (0.3 equiv.), **L** (0.6 equiv.), and NaO^{t}Bu (3 equiv.) (Scheme 1).

The catalytic enantioselective reaction provided a very general method for the synthesis of diverse inherently chiral tetraazacalix[4]aromatics **6** (Table 1). The substrates **5b-c**, which contained the palladium-coordinating cyano group[21], were transformed equally efficiently into the inherently chiral products **6b-c**. When the benzyl group at the lower rim was replaced by *n*-propyl, the least alkyl group able to inhibit the flip of *para*-*t*-butylphenyl ether subunit around the annulus of macrocyclic ring[22], macrocycles **6d-e** were obtained similarly with 97% and >99% *ee*s, respectively. Notably, the same catalytic system was found to tolerate the amino group on the pyridine nucleus, however with decreased enantioselectivity of 87% *ee* (**6h**). The use of a combination of $Pd_2(dba)_3$ (15 mol%) with **L** (60 mol%) as a catalyst further improved the yield of **6h** to 60% with >99% *ee* (Supporting Information). Under the modified catalysis, a number of macrocycles (**6g-l**), which contained an enhanced Lewis basic pyridine moiety[23] such as *N*,*N*-dimethylamino, 1-pyrrolidinyl and 1-piperidinyl were prepared in good yields with excellent enantiomeric purity. The method also enabled the construction of inherently chiral tetrazacalix[4]aromatics which bear different *N*,*N*-dialkylamino substituents including a 4-morpholinyl group (**6k**) on the triazine subunit. The absolute configuration was assigned based on the molecular structure of (S_{ic})-**6h**, which was determined unambiguously with single-crystal X-ray diffraction experiment (Table 1). Conceivably, macrocyclic compound (R_{ic})-**6h'**, the enantiomer of (S_{ic})-**6h**, was synthesized in 56% yield with >99% *ee* using *ent*-**L** as ligand. Noteworthily, heating an *o*-dichlorobenzene solution of enantioenriched **6h** at 150 °C for 20 h did not cause racemization, indicating the high stability of its inherent chirality or 1,3-altenate conformation due to the steric effect of bulky substituents on benzene unit (Supporting Information).

The extraordinarily high-level induction of inherent chirality by a chiral JOSIPHOS-ligated palladium complex was unprecedented and intriguing. To have a deeper insight into the chirality expression from a chiral catalyst to inherently chiral macrocycles, we conducted DFT calculations at the M06/6-311+g(d,p)/SDD//M06/6-31g(d)/SDD level of theory. Two pairs of probable transition states (Figures 2 and S53) of the Buchwald-Hartwig amination leading to a pair of enantiomers were computed according to literature.[24] The calculations indicated that the activation free energy of the transition state (**TS-1**) leading to the major enantiomer was the lowest compared to that of others. This was in agreement with the excellent enantioselectivities observed in the experiments. Analysis of the transition states also revealed the origin of the enantiocontrol. In **TS-2** which leads to R_{ic} enantiomer, two cyclohexyl groups on phosphine experience substantial steric repulsion with pyridine ring and the N-Me group, respectively. By contrast, the repulsion between the cyclohexyl ring and the N-Me group in **TS-1** is reduced. More importantly, there is non-covalent C-H···π attraction between the C-H bond of a cyclohexyl group and pyridine ring. It is therefore the favorable C-H···π interaction and reduced steric repulsion between substituents on ligand and fragments of substrate that lower the activation energy of **TS-1** and consequently lead to high enantioselectivity.

The acquired enantiopure macrocycles **6** exhibited excellent ECD and CPL properties and most excitingly an unusual chiroptical switching effect (Figure 3). Recorded in acetonitrile, ECD spectra of (S_{ic})-**6h** showed two negative Cotton effects at 268 and 316 nm and two positive ones at 284 and 300 nm. Being the enantiomer of (S_{ic})-**6h**, (R_{ic})-**6h'** gave the expected mirror-imaged ECD spectra. Compounds (S_{ic})-**6h** and (R_{ic})-**6h'** were fluorescent, giving a broad emission band centered at 479 nm upon excitation at 310 nm. Notably, (S_{ic})-**6h** and (R_{ic})-**6h'** showed strong CPL activity with emission maxima consistent with those observed in their fluorescent spectra. Upon UV irradiation at 310 nm in acetonitrile for instance, (S_{ic})-**6h** and (R_{ic})-**6h'** gave complementary CPL spectra with large luminescence dissymmetry values of $|g_{lum}| = 2\times10^{-3}$ at 500 nm. The same signs of ECD and CPL spectra observed indicated no significant difference between the ground-state and excited-state conformations.

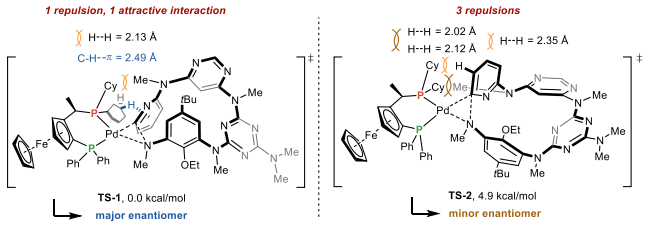


Figure 2. Computed transition states **TS-1** and **TS-2**.

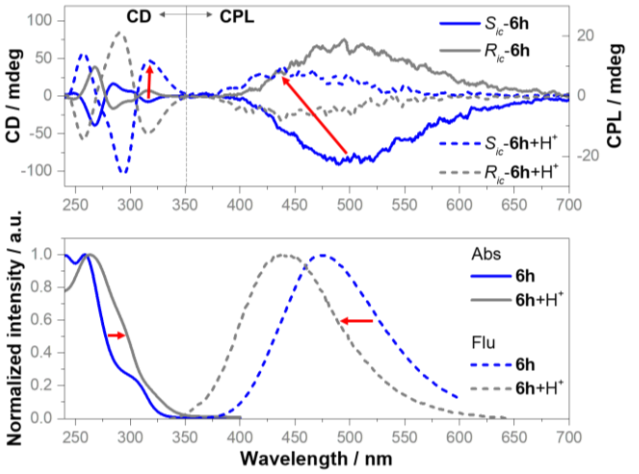


Figure 3. ECD (top left, 2×10^{-5} M), CPL (top right, 1×10^{-4} M, λ_{ex} = 310 nm), UV/vis (bottom left, 1×10^{-5} M), and fluorescence (bottom right, 1×10^{-6} M, λ_{ex} = 310 nm) spectra of (S_{ic})-**6h** and (R_{ic})-**6h'** in the absence and presence of CF_3CO_2H (10 equiv) in CH_3CN.

All products were able to undergo regiospecific protonation on the nitrogen atom of the pyridine subunit because of its highest basicity among aza-arenes within macrocycle (Supporting Information). Surprisingly, titration of (S_{ic})-**6h** and (R_{ic})-**6h'** with CF_3CO_2H led to the complete inversion of all Cotton effects. While the bond at 268 nm was blue-shifted to 252 nm, two weak absorption bands between 284 and 300 nm were emerged to give a strong peak at 298 nm. It was remarkable that the switching effect was also observed in CPL spectra. As a consequence of the interaction of (S_{ic})-**6h** and (R_{ic})-**6h'** with CF_3CO_2H, for instance, the CPL emission band was reversed entirely with the concomitant hypsochromic shift from 500 nm to 450 nm (Figure 3). Slightly decreased $|g_{lum}|$ value (1×10^{-3}) was obtained for protonated macrocycles. Macrocycles (S_{ic})-**6g-l** which contain an electron-donating group on the pyridine subunit displayed almost the same chiroptical properties including CPL reversal upon interaction with an acid. In the case of products (S_{ic})-**6a** and (S_{ic})-**6f** devoid of an electron-donating group on the pyridine ring, however, their CPL activities were quenched by an acid. No CPL reversal was observed (Supporting Information). The CPL switch was also reversible. Deprotonation of [(S_{ic})-**6**-H]$^+$ with ^{n}Bu$_4$NOH resulted in the recovery of ECD and CPL of (S_{ic})-**6**. No appreciable decay of the intensity of the signals were observed

after three cycles of chiroptical switching triggered by protonation and deprotonation (Supporting Information). To the best of our knowledge, chiral molecules exhibited both the sign inversion and the blueshift of CPL upon interaction with stimulus are unprecedented[25,26]. Though the mechanism of this unusual CPL switching effect displayed by inherently chiral tetraazacalix[4]aroamtics awaits an in-depth study,[27] the complete sign inversion of CPL was not resulted from the inversion of absolute configuration of the macrocycles because of the stability of 1,3-alternate conformation of **6** (*vide supra*). Inversion of macrocyclic conformation would lead to racemization. It was most probably attributable to the reversal of the order of polarity of constitutional aromatic rings of macrocyclic skeleton. In other words, after protonation, pyridine subunit become the most electron-deficient moiety instead of triazine ring, reversing the handedness of macrocyclic molecule. The blueshift of CPL was likely owing to switching of fluorophore from pyridine to pyrimidine after protonation of pyridine moiety.

In conclusion, we have developed a Pd-catalyzed highly enantioselective synthesis of ABCD-type inherently chiral tetraazacalix[4]aromatics. The fascinating chirality expression from catalyst to inherently chiral macrocycles stemmed most probably from the formation of an energetically favorable diastereomeric intermediate in which the chiral ligand dictated the handedness of organometallic macrocycle prior to reductive elimination. The outcomes opened a new avenue to access various enantiopure inherently chiral molecules with ease in an asymmetric catalytic fashion. The acquired enantiopure inherently chiral tetraazacalix[4]aromatics were excellent chiroptical molecules, displaying a unique *p*H-triggered chiroptical switching effect. We believe that the inherently chiral macrocycles would expand extraordinarily the chiral chemical space leading to the great opportunity both in the development of stereochemistry and in the discovery of chiral medicines and materials. The acknowledged versatile molecular recognition properties of heteracalix[4]aromatics would render the resulting inherently chiral macrocycles a unique guest-responsive chiroptical system.

ASSOCIATED CONTENT

Supporting Information.
Experimental details and data for compound characterization, crystal data, photophysical and chiroptical properties, and theoretical calculations. The Supporting Information is available free of charge on the ACS Publications website.
Crystallographic data for (S_{ic})-**6h** and (+/-)-**6b** (CIF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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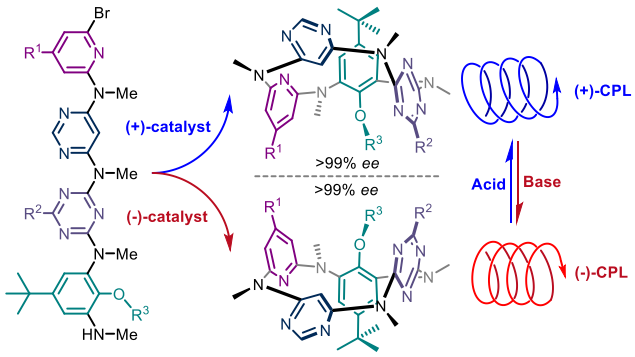
Br
R1
N–Me
N–Me
R2
N–Me
HN–Me
(+)-catalyst
(-)-catalyst
>99% ee
>99% ee
(+)-CPL
Acid
Base
(-)-CPL

TOC