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Synthesis, Resolution, Structure, and Racemization of Inherently Chiral 1,3-Alternate Azacalix[4]pyrimidines: Quantification of Conformation Mobility

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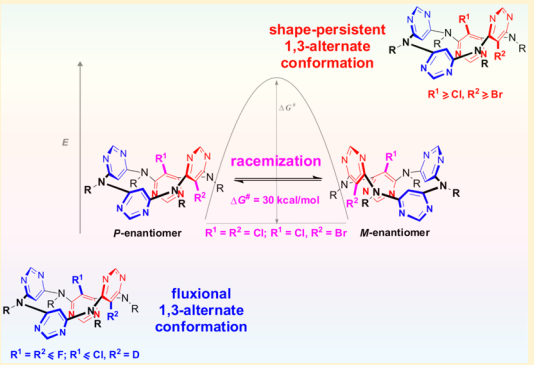
Supporting Information

ABSTRACT: The synthesis, resolution, structure, and racemization of inherently chiral 1,3-alternate azacalix[4]pyrimidine macrocycles are reported. Site-selective halogenations of monohalo-substituted azacalix[4]pyrimidines with NBS, NCS, and NFSI produced a number of the lower-rim dihalogenated 1,3-alternate azacalix[4]pyrimidines. 1,3-Alternate azacalix[4]pyrimidines bearing two proximal substituents were AABB-type and ABCC-type inherently chiral macrocycles, and three pairs of conformationally stable *P* and *M* enantiomers with >99.5% ee were obtained from the resolution of racemic samples by chiral HPLC. Absolute configurations were determined by X-ray crystallography and were correlated with their CD spectra. The rate constants for racemization of macrocycles were measured, and enthalpies ($\Delta H^{\ddagger}$) and entropies ($\Delta S^{\ddagger}$) of activation were determined by the Eyring plot method. The present study revealed that a combination of two proximal substituents larger than the van der Waals radii r_w = 1.75 Å (such as chlorine) and r_w = 1.47 Å (such as fluorine) at the lower rim was the minimum steric requirement for the resolution and isolation of conformationally stable inherently chiral enantiomers of 1,3-alternate azacalix[4]pyrimidines at room temperature, while a combination of two substituents larger than the van der Waals radii r_w = 1.75 Å (such as chlorine) and r_w = 1.85 Å (such as bromine) gave rise to an immobilized 1,3-alternate conformation up to 180 °C.



INTRODUCTION

As a new generation of synthetic macrocyclic host molecules in supramolecular chemistry, heteracalixaromatics, or heteroatom-bridged calix(het)arenes, have attracted great attention because of their easy accessibility, structure diversity, and versatile molecular recognition properties.[1−6] By means of the fragment coupling strategy[7,8] and the one-pot reaction approach,[9] a wide variety of parent and functionalized heteracalixaromatics that contain different heteroatom linkages and varied (het)arenes have been constructed from commercially available materials.[10−12] Many functionalized heteracalixaromatics have also been synthesized on the basis of chemical manipulations of the parent macrocycles.[8,13,14] Introduction of heteroatoms into the methylene bridges of the conventional calixarenes has rendered heteracalixaromatics unique structural characteristics. One of the salient structural features is the self fine tuning of the conformations and the cavity sizes of the macrocycles, because bridging heteroatoms such as nitrogen can adopt different electronic configurations and form various conjugation systems with their adjacent aromatic rings.[1−4,7,8,13d,15] The interplay between induction and conjugation effects of bridging heteroatoms also results in the variation of electron density and the quadruple moment of aromatic rings, regulating the noncovalent bonding ability of macrocyclic hosts.[1,2] As a consequence, azacalix[*n*]pyridines act as powerful and selective receptors for metal ions,[10h,i,16,17] organometallic clusters[18] and fullerenes,[7,10g,19] while oxacalix[2]arene[2]triaiznes are able to recognize anions of varied geometries and shapes through anion−π interactions.[20]

Because of the intramolecular hydrogen bond interactions between the lower-rim phenolic hydroxy groups, classic calix[4]arenes adopt stable cone, partial cone, 1,3-alternate, and 1,2-alternate conformations. The interconversions of conformational structures in solution are readily and elegantly studied by variable-temperature ^{1}H NMR techniques simply by monitoring the change in signals of bridging methylene protons.[21] In contrast, most of the heteroatom-bridged calix[4](het)arenes do not contain phenolic hydroxy groups as conventional calixarenes, and they adopt dominantly the 1,3-alternate conformation[1−4] in the solid state due to probably dipole−dipole repulsion of the proximal aromatic rings.[22] In

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solution, they may also exist as 1,3-alternate conformers or a mixture of conformers which undergo very rapid conformational interconversions. Since heteracalixaromatics do not contain characteristic methylenes either as do conventional calixarenes, the investigation of conformational behaviors of these macrocycles in solution has remained a formidable task until now.[1−4] To solve this intriguing and frustrating problem, we envisioned that enantiomerically pure inherently chiral heteracalixaromatics would provide useful tools. If the process of racemization of an inherently chiral macrocycle can be followed, for instance, interconversions of conformers could be probed and quantified.

Inherently chirality is a unique feature associated with heteracalixaromatics. Although applications of these inherently chiral macrocyclic hosts have been speculated for years, the progress of research appears slow.[1−3] This is mainly due to the difficulty in obtaining the desired enantiopure heteracalixaromatics.[23] It is particularly true in comparison to the synthesis of enantiopure inherently chiral calix[4]arene derivatives.[24−26] For example, a few attempts have been made to synthesize inherently chiral heteroatom-bridged calix[4](het)arenes; however, successful resolution of racemic mixtures into enantiopure compounds has been scarce.[23c] Conformational mobility has been proposed to account for the fast racemization of inherently chiral macrocycles. It becomes evident that comprehension of conformational structures of heteracalixaromatics in solution is paramount in the design and synthesis of enantiopure inherently chiral macrocycles. In turn, an understanding of the process of racemization of a set of enantiopure inherently chiral heteracalixaromatics would provide a unique method to establish the thermodynamic and kinetic aspects of interconversion between macrocyclic conformers.

Previous studies have implied that the presence of substituents on both rims of heteracalixaromatics is important in immobilizing macrocyclic conformations.[1,2,23a,c,27] To elucidate the steric effect of the substituents at the lower rim on the conformational behaviors of heteracalixaromatics, we designed a series of halogenated azacalix[4]pyrimidines. It was envisioned that the size or the volume of halogen atoms could serve as a steric metric, allowing us to define quantitatively the steric requirements for the stabilization of enantiopure inherently chiral heteracalixaromatics. We report herein a systematic study of the synthesis, resolution, and structure of inherently chiral azacalix[4]pyrimidine derivatives. The conformational mobility of heteracalixaromatics was investigated quantitatively by an examination of the kinetics of racemization of enantiopure 1,3-alternate azacalix[4]pyrimidines.

RESULTS AND DISCUSSION

Synthesis of Halogenated Azacalix[4]pyrimidines. We discovered previously that bromination of tetramethylazacalix[4]pyrimidine (**1**) by *N*-bromosuccinimide (NBS) under controlled conditions affords selectively mono- and distally di- and tribrominated products in moderate to good yields.[10e] In order to synthesize chloro-substituted analogues, the chlorination reaction of **1** was conducted (Scheme 1). As summarized in Table 1, treatment of macrocycle **1** with equimolar *N*-chlorosuccinimide (NCS) in glacial acetic acid at ambient temperature for 3 days led to the formation of a mixture of monochlorinated azacalix[4]-pyrimidine **2** (22%), proximally dichlorinated azacalix[4]-pyrimidine **3** (14%), and a trace amount of distally dichlorinated azacalix[4]pyrimidine **4** and trichlorinated

Scheme 1. Chlorination of Azacalix[4]pyrimidine 1

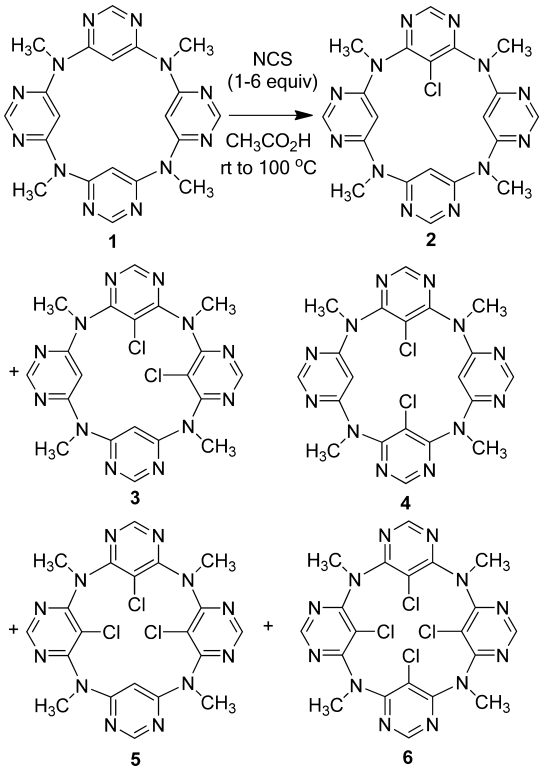

Table 1. Selective Synthesis of Chloro-Substituted Azacalix[4[pyrimidines

				yield (%)				
entry	amt of NCS (equiv)	T (°C)	t (h)	**2**	**3**	**4**	**5**	**6**
1	1	room temp	72	22	14	<1	<1	
2	1	70	12	32	16	<1	<1	
3	1	70	24	29	18	<1	<1	
4	1	95	12	29	20	<1	<1	
5	2.5	70	12	20	23	5	5	
6	3.5	100	12				100	
7	6.0	100	12					100

azacalix[4]pyrimidine **5** (entry 1, Table 1). The reaction was facilitated when the temperature was increased to 70 °C, giving products **2** and **3** in yields of 32% and 16%, respectively (entry 2, Table 1). Elongating the time or further increasing the temperature did not markedly influence the reaction outcomes (entries 3 and 4, Table 1). The use of 2.5 equiv of NCS under identical conditions afforded a mixture of **2** and **3** in moderate yields. In addition, a small amount of **4** (5%) and trichlorinated product **5** (5%) were also isolated (entry 5, Table 1). When 3.5 or 6 equiv of NCS was employed, the reaction proceeded smoothly at 100 °C to furnish the formation of tri- and tetrachlorinated azacalix[4]pyrimidines **5** and **6** as the sole product quantitatively (entries 6 and 7, Table 1). It is interesting to note that, while bromination reactions under various conditions did not give proximal dibromo azacalix[4]-pyrimidine,[10e] virtually no distal dichloro azacalix[4]pyrimidine **4** was obtained from the chlorination of **1**.

To prepare fluoro-substituted azacalix[4]pyrimidines, an electrophilic aromatic fluorination reaction was attempted using *N*-fluorobenzenesulfonimide (NFSI) as a fluorinating

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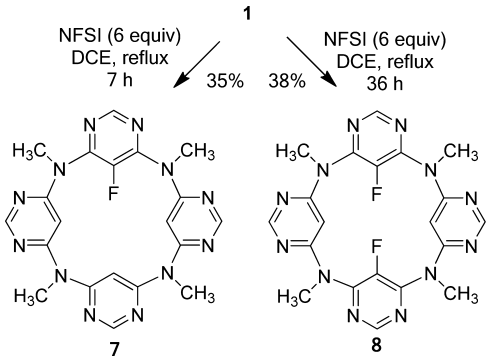
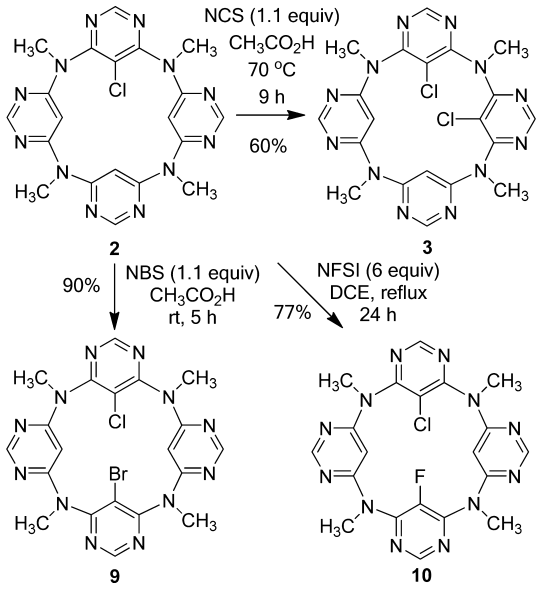
reagent. In refluxing 1,2-dichloroethane, macrocycle **1** reacted with excess NFSI (6 equiv) to give the monofluoro azacalix[4]pyrimidine product **7** in 35% yield in 7 h. When the reaction mixture was refluxed for an additional period, difluorination occurred at the lower-rim position of opposing pyrimidine rings to afford product **8** in 38% yield (Scheme 2). Although a mixture of very polar and nonseparable byproducts was observed, no other di-, tri-, and tetrafluorinated products were isolated.

Scheme 2. Fluorination of Azacalix[4]pyrimidine 1



The different site selectivity observed for dihalogenation was intriguing. To shed light on the selectivity and also to synthesize different dihalogenated macrocycles, halogenation reactions were examined using monohalo-substituted azacalix[4]pyrimidines as reactants. As illustrated in Scheme 3, chlorination of **2** by NCS in warm acetic acid produced

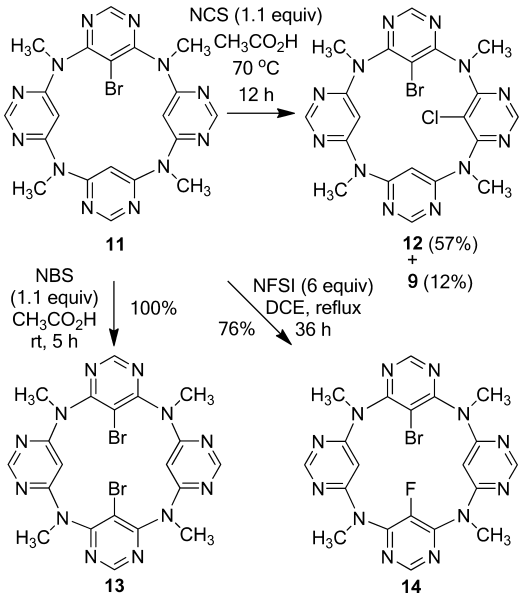
Scheme 3. Chlorination, Bromination, and Fluorination of Monochloro Azacalix[4]pyrimidine 2



exclusively proximally dichlorinated product **3** in 60% yield, while bromination took place site-selectively on the distal pyrimidine ring to afford product **9** in an almost quantitative yield. Similar to bromination, fluorination occurred on the pyrimidine ring opposite the chloropyrimidine of **2** upon treatment with 6 equiv of NFSI, with product **10** being isolated in 77% yield.

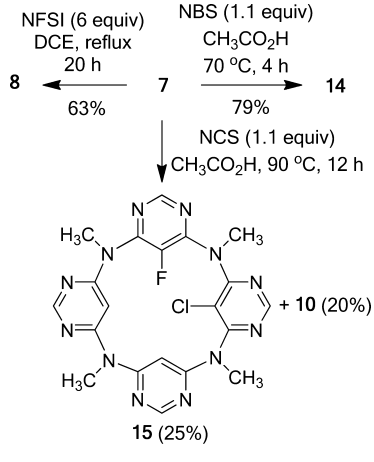
In the case of monobromo-substituted azacalix[4]pyrimidine **11**, which was obtained in 85% yield from the reaction of **1** with NBS,[10e] further bromination and fluorination proceeded site specifically at the distal pyrimidine ring to afford products **13** and **14** in 100% and 76% yields, respectively. Notably, however, compound **11** underwent a chlorination reaction site selectively to give a mixture of proximally and distally chlorinated products **12** and **9**, with the former being the major product in 57% yield (Scheme 4).

Scheme 4. Chlorination, Bromination, and Fluorination of Monobromo Azacalix[4]pyrimidine 11



When bromination and fluorination were applied to monofluoro-containing azacalix[4]pyrimidine **7**, we observed again site-specific reactions which generated distally brominated and fluorinated products **14** and **8**, respectively, in good yields. Under chlorinating reaction conditions, compound **7** was converted into the proximally dihalogenated macrocyclic product **15** in 25% yield. The distal dihalo product **10** was also formed in moderate yield (Scheme 5).

Scheme 5. Chlorination, Bromination, and Fluorination of Monofluoro Azacalix[4]pyrimidine 7



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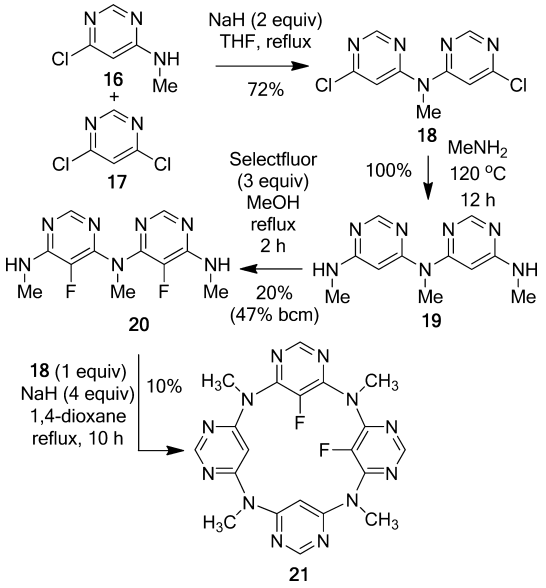
It is very interesting to address that while bromination and fluorination of monohalogenated azacalix[4]pyrimidines occurred regiospecifically on the opposite or distal pyrimidine ring, the chlorination reaction took place regioselectively on the proximal pyrimidine ring. Although further study was needed to clarify the mechanism, different site selectivities between chlorination and bromination of monohalogenated azacalix[4]-pyrimidines were probably the reflection of different reaction pathways when NCS and NBS were used respectively as halogenating reagents. Indeed, when 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO), a widely used radical trap, was added to the reaction mixture, the chlorination reaction was inhibited overwhelmingly.

Aiming to delineate the steric effect of the substituents at the lower rim of two neighboring pyrimidine rings on the conformational structure, we required difluorinated azacalix[4]-pyrimidine **21**. Since it cannot be synthesized from fluorination of compound **7**, a [2 + 2] fragment coupling approach was utilized alternatively. As shown in Scheme 6, a condensation

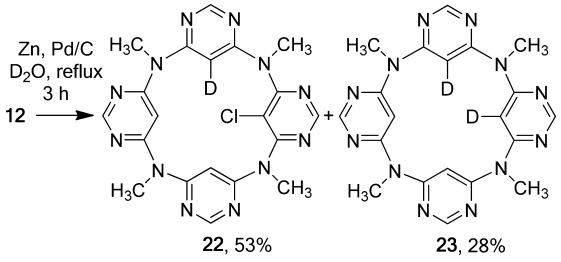
Scheme 6. Synthesis of Proximally Difluoro Substituted Azacalix[4]pyrimidine 21



reaction between methylaminopyrimidine **16** and dichloropyrimidine **17** in the presence of NaH gave a 72% yield of product **18**, which underwent an amination reaction with methylamine at 120 °C in a sealed tube to afford product **19** quantitatively. Difluorination of **19** was not trivial, however, as many attempts met with failure (see the Supporting Information). Finally, we chose Selectfluor as a fluorinating reagent. In refluxing methanol for 2 h, the desired product **20** was obtained in 20% yield (47% based on consumed starting material), with a large amount of starting material **19** being recovered. Either lengthening the reaction time or increasing the reaction temperature led to the formation of messy byproducts. A macrocyclic condensation reaction between **20** and **18** appeared challenging as well. To merely obtain the target molecule for structure study, we did not optimize the reaction conditions. Thus, with the aid of NaH as a base, the reaction of **20** with **18** in refluxing 1,4-dioxane for 10 h gave product **21**, albeit in low yield.

Having proximally dihalogenated azacalix[4]pyrimidine **12** in hand, we then tested the synthesis of deuterated compound **22**, an inherently chiral azacalix[4]pyrimidine compound containing even smaller substituents on the low rim. Sasson[28] reported in 2000 a catalytic system which is able to effect the deuteration of bromobenzene. Following this protocol, we found compound **12** was transformed into the desired product **22** in 53% yield when it was refluxed in a mixture of zinc, palladium/carbon, and D_2O. In addition to the reduction of the C−Br bond which gave product **22**, deuteration of the C−Cl bond was also observed, leading to the formation of dideuterated azacalix[4]pyrimidine **23** in 28% yield (Scheme 7).

Scheme 7. Synthesis of Deuterated Azacalix[4]pyrimidines 22 and 23



Structures of Halogenated Azacalix[4]pyrimidines. Structures of all synthesized halogenated azacalix[4]-pyrimidines, including deuterated species, were elucidated on the basis of spectroscopic data and microanalysis. To understand the conformational structures of these macrocycles at the molecular level, single crystals were cultivated by slow evaporation of the solvent from solution. The molecular structures of **3**, **6**, **10**, and **14** in the solid state were determined by X-ray crystallography.

At first glance of the molecular structures illustrated in Figures 1−4, both distally and proximally dihalogenated azacalix[4]pyrimidines such as **3**, **10**, and **14** and tetrachloro-substituted azacalix[4]pyrimidine **6** generally adopt a 1,3-alternate conformation in the crystalline state. Careful examination of the structures revealed that the parent macrocyclic ring of the proximal dichloro-bearing product **3** was nearly symmetric, having a C_{2v} symmetry, while the other products **6**, **10**, and **14** existed as slightly distorted 1,3-alternate conformers. Further scrutiny of the bond lengths, bond angles, and planarity of the bridging nitrogen atoms (see captions in Figures 1-4) indicated that each nitrogen atom adopted an sp^2 electronic configuration and formed strong conjugation with one of its adjacent pyrimidine rings and partial conjugation with the other.

It is important to emphasize that all azacalix[4]pyrimidine products synthesized gave only one set of distinct proton and carbon resonance signals in their ^1H and ^{13}C NMR spectra. As one of the representative examples, Figure 5 shows the ^1H and ^{13}C NMR spectra of **3** at room temperature. Interestingly and notably, there were three different methyl groups. The NMR spectra indicated clearly that azacalix[4]pyrimidine derivatives existed either as the shape-persistent 1,3-alternate conformers that assembled the structures observed in the solid state or as equilibrium mixtures in which various 1,3-alternate conformers underwent rapid interconversions relative to the NMR time scale.

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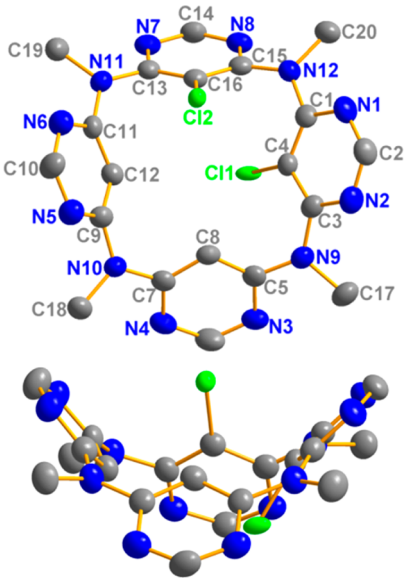

Figure 1. X-ray molecular structure of racemic **3** with top (top) and side (bottom) views. Bond lengths (Å): C(1)−N(12), 1.401; C(3)−N(9), 1.398; C(5)−N(9), 1.388; C(7)−N(10), 1.394; C(9)−N(10), 1.388; C(11)−N(11), 1.406; C(13)−N(11), 1.385; C(15)−N(12), 1.397.

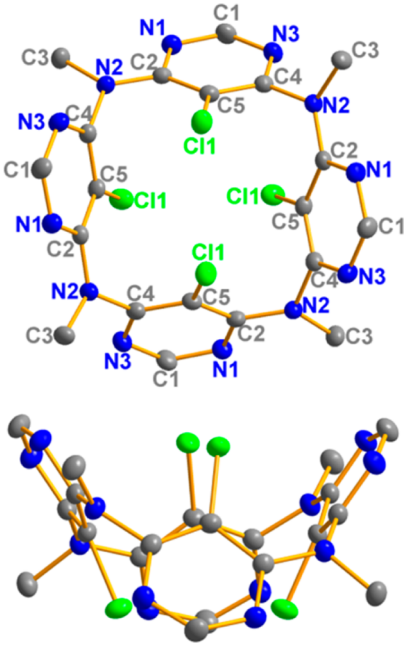

Figure 2. X-ray molecular structure of **6** with top (top) and side (bottom) views. Bond lengths (Å): C(2)−N(2), 1.367; C(4)−N(2), 1.425.

Resolution and Structure of Inherently Chiral Azacalix[4]pyrimidines. Inspired by the observation of 1,3-alternate conformation of proximal dichloro azacalix[4]-pyrimidine **3** in the X-ray molecular structure and of one single set of proton and carbon resonance signals in its ^{1}H and ^{13}C NMR spectra, we assumed compound **3**, an AABB-type inherently chiral macrocycle, would adopt the same 1,3-alternate conformation in solution and its interconversion or macrocyclic ring inversion through the rotations of aromatic rings around the meta−meta axes or through the macrocyclic annulus would be prohibited due to the presence of two proximal chloro substituents at the lower rim. If that were the case, 1,3-alternate conformers of lower-rim proximally disubstituted azacalix[4]pyrimidines, depending on the steric effect of the substituent, would most likely exist as conformationally stable and resolvable inherently chiral macrocycles.

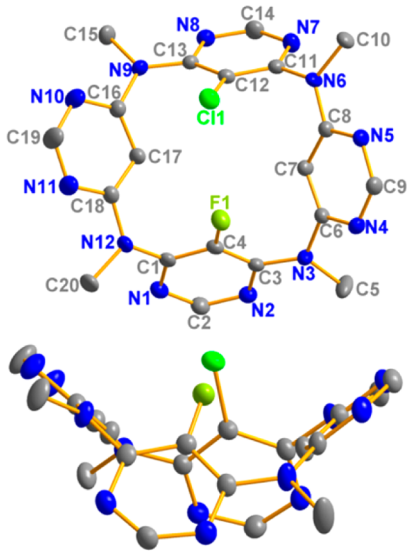

Figure 3. X-ray molecular structure of **10** with top (top) and side (bottom) views. Bond lengths (Å): C(1)−N(12), 1.414; C(3)−N(3), 1.370; C(6)−N(3), 1.414; C(8)−N(6), 1.373; C(11)−N(6), 1.405; C(13)−N(9), 1.371; C(16)−N(9), 1.408; C(18)−N(12), 1.376.

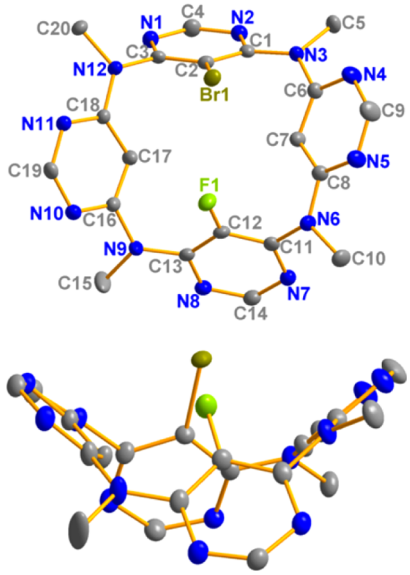

Figure 4. X-ray molecular structure of **14** with top (top) and side (bottom) views. Bond lengths (Å): C(1)−N(3), 1.374; C(6)−N(3), 1.415; C(8)−N(6), 1.372; C(11)−N(6), 1.415; C(13)−N(9), 1.374; C(16)−N(9), 1.414; C(18)−N(12), 1.366; C(3)−N(12), 1.413.

To test our hypothesis, HPLC analysis using columns packed with chiral stationary phases was utilized to resolve the racemic sample of **3**. We were very pleased to find out that racemic compound **3** was readily resolved into two fractions of different retention times at ambient temperature on an amylose tris(3,5-dimethylphenylcarbamate) immobilized silica gel HPLC column (Chiralpak IA) eluted with a mixture of hexane, Et_2NH, and $CHCl_3$. As shown in Figure 6, the circular

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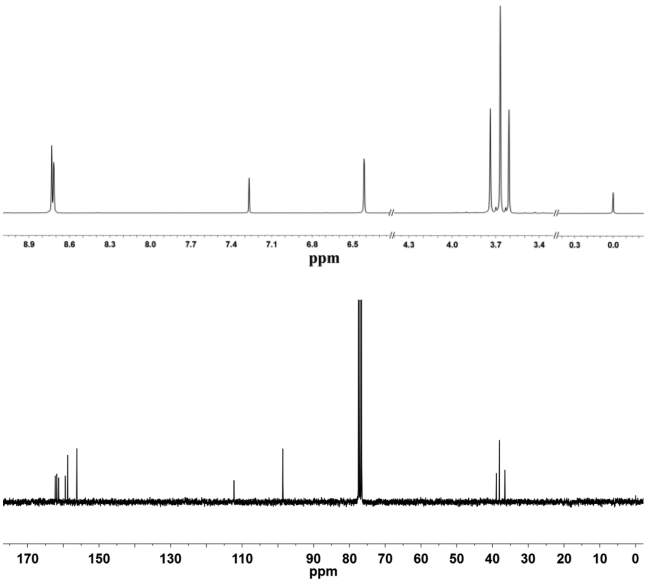

Figure 5. ^{1}H (top) and ^{13}C (bottom) NMR spectra of **3**.

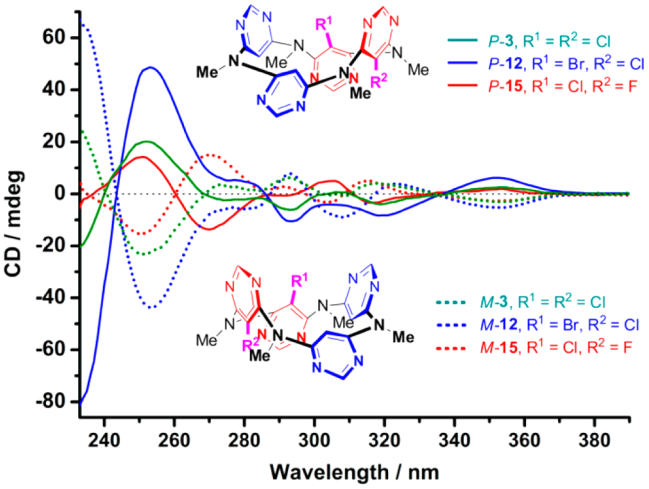

Figure 6. CD spectra of *P* and *M* enantiomers of inherently chiral azacalix[4]pyrimidines **3**, **12**, and **15**.

dichroism (CD) spectra of two resolved fractions collected from HPLC analysis show a perfect mirror image, indicating distinct enantiotropy of two resolved fractions.

Encouraged by the successful resolution of inherently chiral dichloro-substituted azacalix[4]pyrimidine **3**, all other racemic samples of ABCC- and AABB-type inherently chiral azacalix[4]pyrimidine derivatives **12**, **15**, and **21**–**23** were subjected to resolution. As we anticipated, the steric effect of the substituents at the lower rim played a critical role in dictating the resolution of enantiomerically pure inherently chiral azacalix[4]pyrimidine derivatives. For example, when one of the chlorine substituents of **3** was replaced by bromine, a sterically larger atom, racemic macrocycle **12** underwent nice resolution to afford a pair of enantiomers. On a decrease in steric bulkiness of one of the two chlorine atoms of **3** to fluorine, racemic azacalix[4]pyrimidine **15** was also resolved, and a pair of antipodes was obtained. Figure 6 shows the excellent mirror image of CD curves of enantiomers of **12** and **15**. However, a further decrease in steric effect by changing one chlorine of **3** into deuterium led to the inability to resolve racemic azacalix[4]pyrimidine **22**. We also found that difluorinated and dideuterated racemic azacalix[4]pyrimidines **21** and **23**, the inherently chiral macrocycles that contain the smallest substituents, were not resolvable under the identical conditions of chiral HPLC analysis.

To our delight, both *P* and *M* antipodes of **15** gave high-quality single crystals. X-ray molecular structures, depicted in Figure 7, revealed that the macrocyclic skeleton adopts a highly symmetric 1,3-altenate conformation. As illustrated explicitly in Figure 7, *P*-**15** and *M*-**15** are mirror images of one another, but they cannot be superimposed. It is worth mentioning that the *P* enantiomer of **15** gave a CD curve showing a maximum positive peak at 251 nm, while the *M* enantiomer gave a maximum negative peak at 251 nm. This is the first example of correlation of absolute configurations of inherently chiral heteracalixaromatics with CD spectra. Since both antipodes of **6** and of **12** exhibited CD curves similar to those of *P*-**15** and *M*-**15**, we assigned samples giving positive and negative peaks at around 252 nm as *P* and *M* enantiomers, respectively (Figure 6).

Racemization of Inherently Chiral Azacalix[4]-pyrimidines—Quantification of Conformational Mobility. Although the unsuccessful resolution of racemic inherently chiral azacalix[4]pyrimidines **21**–**23** might result from inefficient chiral recognition by the chiral stationary phases of HPLC columns, it is most likely, we considered, that the fast racemization of these macrocycles accounts for the unsuccessful separation and isolation of conformationally stable *P* and *M* enantiomers. Since racemization of inherently chiral azacalix[4]pyrimidines proceeded through a macrocyclic ring inversion mechanism, viz. rotation of aromatic rings around the meta–meta axes or through the macrocyclic annulus, the introduction of large substituents such as two chlorine atoms (**3**), one chlorine and one bromine atom (**12**), or one chlorine and one fluorine atom (**15**) on the lower rim could hinder the macrocyclic ring inversion, giving isolable enantiomers of inherently chiral azacalix[4]pyrimidine compounds. In contrast, because two proximally substituted fluorine atoms (**21**), two deuterium atoms (**23**), and a combination of one chlorine and one deuterium atom (**22**) imposed very small steric hindrance, inversion of the macrocyclic ring could take place easily, leading to rapid racemization. On the other hand, the rate of inversion of macrocyclic conformation, namely the conformation mobility, should be temperature dependent. To shed light on the conformational structures in solution, the kinetics of racemization of enantiomers at different temperatures was measured.

Scheme 8 shows the racemization of inherently chiral azacalix[4]pyrimidines in which *k* is the rate constant. Following Blakemore's study of racemization of 7,7′-dihydroxy-8,8′-biquinolyl,[29] it was assumed that racemization of inherently chiral azacalix[4]pyrimidines is a first-order reaction. Derivation of the first-order rate law for this racemization resulted in the equation $\ln(ee_0/ee_t) = 2kt$, where ee_0 and ee_t are enantiomeric excess values of inherently chiral azacalix[4]-pyrimidines at the beginning of the reaction and at a specified reaction time, respectively.

To measure the kinetics of a racemization process, the enantiopure azacalix[4]pyrimidine sample **3**, **12** ,or **15** in *o*-dichlorobenzene solution was heated to different temperatures. At a specific temperature, enantiomeric excess values were determined at various time intervals by means of chiral HPLC analysis. Illustrated in Figure 8 is the change of enantiomeric

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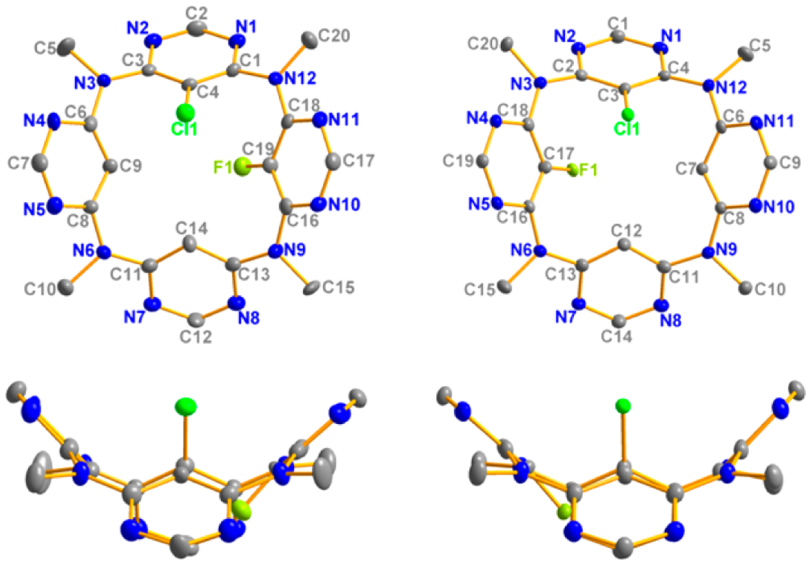
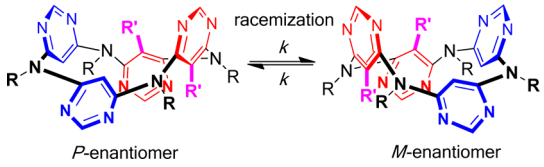


Figure 7. X-ray molecular structures of the *P* enantiomer (left) and *M* enantiomer (right) of azacalix[4]pyrimidine **15** with top (top) and side (bottom) views. Selected bond lengths (Å) of *P*-**15**: C(1)−N(12), 1.401; C(3)−N(3), 1.380; C(6)−N(3), 1.399; C(8)−N(6), 1.404; C(11)−N(6), 1.401; C(13)−N(9), 1.402; C(16)−N(9), 1.382; C(18)−N(2), 1.390. Selected bond lengths (Å) of *M*-**15**: C(2)−N(3), 1.394; C(4)−N(12), 1.380; C(6)−N(12), 1.391; C(8)−N(9), 1.394; C(11)−N(9), 1.390; C(13)−N(6), 1.396; C(16)−N(6), 1.387; C(18)−N(3), 1.397.

Scheme 8. Racemization of Inherently Chiral Azacalix[4]pyrimidines



excess of enantiopure **3** against time at 363 K. Apparently, enantiopure *P*-**3** was able to undergo racemization gradually. The plot of $\ln(ee_0/ee_t)$ against time gave a straight line, and the rate constant (k) for racemization at 363 K was obtained from the slope (Figure 8). Figure 9 summarizes the rate constants at 368−383 K (see Figures S14−S17 in the Supporting Information). Expectedly, racemization was accelerated upon an increase in the reaction temperature: the higher the temperature, the faster the racemization. On the basis of the Eyring equation $\ln(k/T) = \Delta S^{\ddagger}/R - \ln(h/k_B) - \Delta H^{\ddagger}/RT$, the activation enthalpy ($\Delta H^{\ddagger}$) and entropy ($\Delta S^{\ddagger}$) were obtained respectively from the slope and intercept of the plot of $\ln(k/T)$ against $1/T$ (Figure 9). It should be noted that a similar temperature-dependent racemization process was evidenced for enantiopure chloro- and fluoro-bearing azacalix[4]pyrimidine **15** (see Figures S19−S23 in the Supporting Information). In contrast, the macrocyclic analogue *P*-**12**, which bears a relatively larger bromo group in addition to a chloro substituent, appeared very stable, and it was reluctant to undergo macrocyclic ring inversion. Even when it was heated to an elevated temperature such as 453 K (180 °C), only a marginal degree of racemization was observed (ee decreases from >99.5% to 88.3% in 13 h) (see Figures S47 and S48 in the Supporting Information).

As shown in Figure 9, the entropy of activation $\Delta S^{\ddagger}$ for the racemization of **3** or **15** was almost negligible, an indication of the unimolecular macrocyclic ring inversion process. The enthalpies of activation $\Delta H^{\ddagger}$ obtained for racemization of **3** and **15** were 30.6 ± 2.3 and 30.3 ± 2.3 kcal/mol, respectively.

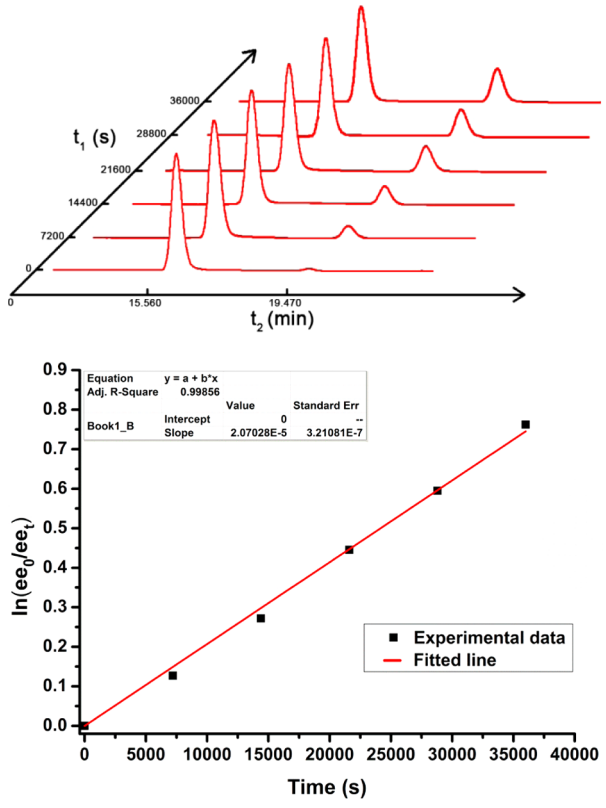


Figure 8. Racemization of enantiopure *P*-**3** at 363 K in *o*-dichlorobenzene: (a) HPLC chromatograms of the racemization process, with retention times (t_2) for *P*-**3** and *M*-**3** of 15.56 and 19.47 min, respectively; (b) plot of $\ln(ee_0/ee_t)$ against time (t_1).

Racemization of azacalix[4]pyrimidines **3** and **15** thus requires activation free energies $\Delta G^{\ddagger}$ at 298 K of 30.4 and 30.3 kcal/mol, respectively. The slightly lower $\Delta G^{\ddagger}$ and $\Delta H^{\ddagger}$ values for **15** in comparison to those for **3** are in agreement with the fact that the former macrocycle contains fluorine and chlorine atoms, whereas the latter bears two chlorine atoms. Taking the

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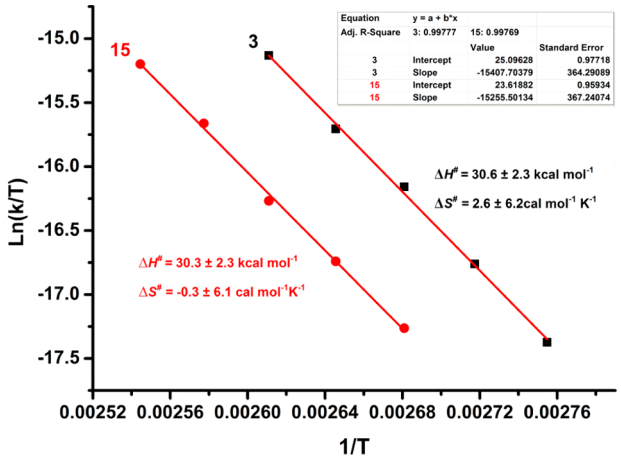

T (K)	363	368	373	378	383
k (10^{-5}, s^{-1}) for **3**	1.035	1.933	3.583	5.709	10.272
T (K)	373	378	383	388	393
k (10^{-5}, s^{-1}) for **15**	1.188	2.029	3.299	6.121	9.850

Figure 9. Eyring plots and rate constant data for the racemization of **3** and **15** in *o*-dichlorobenzene. Eyring equation: $\ln(k/T) = \Delta S^{\ddagger}/R - \ln(h/k_b) - \Delta H^{\ddagger}/RT$. Errors in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are expressed as 95% confidence limits.

aforementioned outcomes of resolution and racemization of all proximally disubstituted azacalix[4]pyrimidine derivatives into consideration, it is evident that the steric effect originating from two proximal substituents at the lower rim is pivotal in stabilizing conformationally enantiopure inherently chiral 1,3-alternate azacalix[4]pyrimidines. As estimated from the van der Waals radii of halogens,[30] a combination of two substituents with r_w = 1.75 Å (van der Waals radius of chlorine) and r_w = 1.47 Å (van der Waals radius of fluorine) was the minimum steric requirement for the resolution and isolation of conformationally stable inherently chiral enantiomers of heteracalixaromatics at room temperature. To prevent the macrocyclic ring inversion of heteracalixaromatics up to 180 °C, the introduction of two groups which have, respectively van der Waals radii *greater than* 1.75 Å (van der Waals radius of chlorine) and 1.85 Å (van der Waals radius of bromine) was necessary.

CONCLUSION

We have developed facile methods for the synthesis of diverse lower-rim halogenated azacalix[4]pyrimidine compounds. Under controlled mild conditions, the reaction of azacalix[4]-pyrimidine with NCS afforded selectively monochlorinated and proximally di-, tri-, and tetrachlorinated products, while fluorination of azacalix[4]pyrimidine with NFSI yielded monofluoro-substituted and distally difluoro-substituted compounds. When monohalogenated azacalix[4]pyrimidine compounds were treated with NBS and NFSI, further halogenation occurred site specifically on the opposite pyrimidine ring to form the corresponding dismally dihalogenated macrocyclic products. Reaction of monohalo-substituted azacalix[4]-pyrimidines with NCS, however, led to the selective formation of proximally chlorinated products. All halogenated azacalix[4]-pyrimidines adopt 1,3-alternate conformations, with the bridging nitrogen atoms having an sp^2 electronic configuration to form conjugation with one of their adjacent pyrimidine rings.

Among the synthesized compounds, six azacalix[4]-pyrimidines which contained two proximal substituents, either identical or different, were AABB-type and ABCC-type inherently chiral macrocycles due to their 1,3-alternate conformational structures. Depending on the combined steric effects of two substituents, dichloro-substitued, chloro-/fluoro-substituted, and bromo-/chloro-substituted macrocycles were resolved into three pairs of conformationally stable *P* and *M* enantiomers with >99.5% ee at ambient temperature under conditions of chiral HPLC analysis. Absolute configurations were determined by X-ray crystallography, and they were correlated with their circular dichroism (CD) spectra. The kinetics of racemization of enantiomers of both dichloro-substituted and chloro-/fluoro-substituted azacalix[4]-pyrimidines were measured at different temperatures, indicating ca. 30 kcal/mol free energy of activation for racemization at 298 K.

It was concluded that 1,3-alternate conformations, such as those assembled in the solid state, are the most populated structures of azacalix[4]pyrimidines in solution. However, without any substitution or with sterically small substituents on the lower rim, 1,3-alternate azacalix[4]pyrimidines undergo free and very rapid macrocyclic ring inversion at ambient temperature relative to the time scale of analytical methods. In the case of proximally disubstituted azacalix[4]pyrimidines, the presence of two substituents larger than the van der Waals radii r_w = 1.75 Å (such as chlorine) and r_w = 1.47 Å (such as fluorine), respectively, at the lower rim is able to immobilize conformational mobility at room temperature. A minimum amount of activation free energy of 30 kcal/mol is required when these macrocycles undergo conformation interconversions. A combination of two groups larger than the van der Waals radii r_w = 1.75 Å (such as chlorine) and r_w = 1.85 Å (such as bromine), respectively, is necessary to prevent the macrocyclic ring inversion, yielding a shape-persistent 1,3-alternate conformation in solution up to 180 °C. The present study has provided for the first time the quantification of conformational mobility that will serve as an important guideline in the design of conformationally stable heteracalix-aromatics.

EXPERIMENTAL SECTION

General Procedure for the Reaction of Azacalix[4]pyrimidne 1 with NCS. A mixture of **1** (107 mg, 0.25 mmol) and NCS (34−200 mg, 0.25−1.5 mmol) in glacial acetic acid (10 mL) was stirred at a specific temperature for a period of time (see Table 1). The solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane (50 mL). The organic solution was washed with saturated aqueous Na_2CO_3 solution (30 mL) and dried over with anhydrous $MgSO_4$. After removal of solvent, the residue was chromatographed on a silica gel column (200−300) with a mixture of dichloromethane and acetone as the mobile phase to give pure products **2**−**6**.

2 (23 mg, 20%, see entry 5, Table 1): white needles; mp >300 °C; IR (KBr) ν 1589, 1526, 1482, 1433, 1218 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.77 (s, 1H), 8.73 (s, 2H), 7.05 (s, 1H), 6.21 (s, 2H), 3.65 (s, 6H), 3.58 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 162.0, 161.8, 160.6, 160.0, 159.2, 157.0, 115.7, 101.2, 96.1, 37.2, 35.9; EI-MS *m*/*z* 464 $[M + 2]^+$, 462 $[M]^+$, 427 $[M - Cl]^+$. Anal. Calcd for $C_{20}H_{19}N_{12}Cl$: C, 51.89; H, 4.14; N, 36.31. Found: C, 51.53; H, 4.08; N, 36.31.

3 (29 mg, 23%, see entry 5, Table 1): white needles; mp 286−287 °C; IR (KBr) ν 1597, 1569, 1525, 1429, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.73 (s, 2H), 8.72 (s, 2H), 6.42 (s, 2H), 3.74 (s, 3H), 3.67 (s, 6H), 3.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2,

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161.8, 161.3, 159.5, 158.7, 156.2, 112.3, 98.6, 38.9, 38.1, 36.5; EI-MS m/z 500 $[M + 4]^+$, 498 $[M + 2]^+$, 496 $^{M+}$, 463 $[M - Cl + 2]^+$, 461 $[M - Cl]^+$, 425 $[M - 2Cl]^+$. Anal. Calcd for $C_{20}H_{18}N_{12}Cl_2$: C, 48.30; H, 3.65; N, 33.80. Found: C, 48.17; H, 3.63; N, 33.55.

4 (6 mg, 5%, see entry 5, Table 1): white needles; mp >300 °C; IR (KBr) ν 1590, 1562, 1535, 1483, 1427 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.81 (s, 2H), 8.72 (s, 2H), 5.35 (s, 2H), 3.61 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 161.1, 158.3, 157.3, 119.2, 93.4, 37.3; EI-MS m/z 500 $[M + 4]^+$, 498 $[M + 2]^+$, 496 $^{M+}$, 463 $[M - Cl + 2]^+$, 461 $[M - Cl]^+$, 425 $[M - 2Cl]^+$. Anal. Calcd for $C_{20}H_{18}N_{12}Cl_2$: C, 48.30; H, 3.65; N, 33.80. Found: C, 48.44; H, 3.62; N, 33.52.

5 (132 mg, 100%, see entry 6, Table 1): white needles; mp 263–264 °C; IR (KBr) ν 1561, 1473, 1430, 1119 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.71 (s, 2H), 8.70 (s, 1H), 5.78 (s, 1H), 3.70 (s, 6H), 3.63 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2, 162.0, 160.7, 160.0, 158.2, 156.1, 156.0, 115.3, 110.2, 96.3, 39.1, 38.1; EI-MS m/z 536 $[M + 6]^+$, 534 $[M + 4]^+$, 532 $[M + 2]^+$, 530 $[M]^+$, 499 $[M - Cl + 4]^+$, 497 $[M - Cl + 2]^+$, 495 $[M - Cl]^+$, 459 $[M - 2Cl]^+$. Anal. Calcd for $C_{20}H_{17}N_{12}Cl_3$: C, 45.17; H, 3.22; N, 31.61. Found: C, 45.27; H, 3.22; N, 31.40.

6 (141 mg, 100%, see entry 7, Table 1): white needles; mp >300 °C; IR (KBr) ν 1556, 1477, 1421, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.70 (s, 4H), 3.65 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 155.9, 113.1, 39.4; MALDI-TOF-MS m/z 567 $[M + H]^+$, 531 $[M - Cl]^+$. Anal. Calcd for $C_{20}H_{16}N_{12}Cl_4$: C, 42.42; H, 2.85; N, 29.68. Found: C, 42.22; H, 2.86; N, 29.39.

General Procedure for the Reaction of Azacalix[4]pyrimidne 1 with NFSI. A mixture of **1** (86 mg, 0.2 mmol) and NFSI (378 mg, 1.2 mmol) in DCE (20 mL) was refluxed for 7 or 36 h. The reaction mixture was cooled to room temperature and filtered through a Celite pad. The filtrate was placed under vacuum to remove solvent. The residue was dissolved in dichloromethane (50 mL), washed with a saturated aqueous Na_2CO_3 (30 mL) solution, and dried over anhydrous $MgSO_4$. After removal of solvent, the residue was chromatographed on a silica gel column (200–300) with a mixture of dichloromethane and acetone as the mobile phase to give pure **7** (31 mg, 35%) or **8** (35 mg, 38%).

7: white solid; mp >300 °C; IR (KBr) ν 1589, 1532, 1508, 1474, 1441, 1396, 1320, 1232, 1119 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.72 (s, 2H), 8.58 (s, 1H), 7.06 (s, 1H), 6.46 (s, 2H), 3.63 (s, 6H), 3.58 (s, 6H);^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 162.2, 162.0, 160.0, 159.0, 154.3 (d), 150.3 (d), 141.2 (d), 100.0, 97.0, 36.5, 35.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −131.8 (s, 1F); ESI-MS m/z 447.3 $[M + H]^+$. Anal. Calcd for $C_{20}H_{19}FN_{12}$: C, 53.81; H, 4.29; N, 37.65. Found: C, 53.76; H, 4.33; N, 37.91.

8: white solid; mp >300 °C; IR (KBr) ν 1591, 1532, 1475, 1442, 1397, 1342, 1257 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 2H), 8.60 (s, 2H), 5.86 (t, J = 3.1, 2H), 3.63 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 158.0, 154.3, 150.5 (d), 142.0(d), 94.8, 36.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −129.6 (s, 1F); ESI-MS m/z 465.3 $[M + H]^+$ Anal. Calcd for $C_{20}H_{18}F_2N_{12}$: C, 51.72; H, 3.91; N, 36.19. Found: C, 51.61; H, 3.90; N, 36.20.

General Procedure for Chlorination of Monohalogenated Azacalix[4]pyrimidines 2, 7, and 11. A mixture of **2** (47 mg, 0.1 mmol) and NCS (15 mg, 0.11 mmol) in glacial acetic acid (5 mL) was stirred at 70 °C for 9 h. The resulting mixture was worked up by following the aforementioned procedure used for the reaction between **1** and NCS to give pure product **3** (30 mg, 60%). The same reaction between **7** (111 mg, 0.25 mmol) and NCS (38 mg, 0.275 mmol) or between **11** (127 mg, 0.25 mmol) and NCS (38 mg, 0.275 mmol) afforded products **15** (30 mg, 25%) and **10** (24 mg, 20%) or products **12** (77 mg, 57%) and **9** (16 mg, 12%).

9: white solid; mp 264–265 °C; IR (KBr) ν 1592, 1561, 1483, 1423 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.80 (s, 1H), 8.71 (s, 2H), 5.33 (s, 2H), 3.59 (s, 6H), 3.58 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 162.0, 161.8, 161.1, 158.8, 158.4, 157.2, 119.1, 111.3, 93.6, 37.1, 37.0; CI-MS m/z 541 $[M + 1]^+$, 507 $[M - Cl]^+$, 461 $[M - Br - Cl]^+$. Anal. Calcd for $C_{20}H_{18}BrClN_{12}$: C, 44.34; H, 3.35; N, 31.02. Found: C, 44.31; H, 3.35; N, 30.70.

10: white solid; mp >300 °C; IR (KBr) ν 1593, 1554, 1534, 1488, 1444, 1423, 1397, 1246, 1121, 984 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.71 (s, 2H), 8.60 (s, 1H), 5.63 (d, J = 2.8 Hz), 3.63 (s, 6H), 3.61 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 161.7 (d), 161.0, 158.3, 157.0, 154.3 (d), 150.6 (d), 142.4 (d), 118.0, 94.3, 37.3, 36.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −129.2 (s, 1F); ESI-MS m/z (%) 481.2 $[M + H]^+$ (100), 483.2 $[M + 3]^+$ (35); HRMS (FTMS-APCI) $C_{20}H_{18}ClFN_{12}$ requires 481.15207 $[M + H]^+$, found 481.15227 $[M + H]^+$.

12: white solid; mp 289–290 °C; IR (KBr) ν 1657, 1461, 1428, 1114 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.76–8.71 (m, 4H), 6.45 (s, 1H), 6.43 (s, 1H), 3.73 (s, 3H), 3.661 (s, 3H), 3.657 (s, 3H), 3.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 162.3, 162.2, 161.9, 161.8, 161.5, 161.3, 159.6, 158.9, 158.8, 157.1, 156.2, 112.2, 103.3, 98.9, 98.6, 38.9, 38.1, 36.5; CI-MS m/z 541 $[M + 1]^+$, 507 $[M - Cl]^+$, 461 $[M - Br - Cl]^+$. Anal. Calcd for $C_{20}H_{18}BrClN_{12}$: C, 44.34; H, 3.35; N, 31.02. Found: C, 44.40; H, 3.35; N, 30.95.

15: white solid; mp 266–267 °C; IR (KBr) ν 1589, 1574, 1523, 1477, 1437, 1396, 1323, 1221, 1118, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.713 (s, 1H), 8.708, (s, 1H), 8.54 (d, J = 1.6 Hz, 1H), 6.55 (t, J = 2.7 Hz, 1H), 6.33 (d, J = 0.8 Hz, 1H), 3.72 (s, 3H), 3.67 (s, 3H), 3.64 (s, 3H), 3.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 162.5, 162.1, 162.0, 161.8, 161.1, 159.5, 158.8, 158.7, 155.9, 153.6 (d), 151.1 (d), 149.0 (d), 140.2 (d), 112.9 (d), 99.6 (d), 97.2, 38.2, 37.7, 37.0, 36.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −137.9 (s, 1F); ESI-MS m/z (%) 481.2 $[M + H]^+$ (100), 483.2 $[M + 3]^+$ (35). Anal. Calcd for $C_{20}H_{18}ClFN_{12}$: C, 49.95; H, 3.77; N, 34.95. Found: C, 50.23; H, 3.87; N, 34.82.

General Procedure for Bromination of Monohalogenated Azacalix[4]pyrimidines 2, 7, and 11. A mixture of **2** (47 mg, 0.1 mmol) and NBS (20 mg, 0.11 mmol) in glacial acetic acid (5 mL) was stirred at room temperature for 5 h. After workup as mentioned for the reaction between **1** and NCS, pure product **9** (49 mg 90%) was obtained. The same reaction between **7** (67 mg, 0.15 mmol) and NBS (30 mg, 0.17 mmol) or between **11** (76 mg, 0.15 mmol) and NBS (30 mg, 0.17 mmol) for a period of time (see Schemes 5 and 4) afforded **14** (62 mg, 79%) or **13**[10e] (88 mg, 100%).

14: white solid; mp >300 °C; IR (KBr) ν 1593, 1553, 1536, 1486, 1444, 1423, 1398, 1346, 1305, 1244, 1121, 985 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.71 (s, 2H), 8.60 (s, 1H), 5.59 (d, J = 3.6 Hz, 2H), 3.62 (s, 6H), 3.61 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 161.9, 161.7, 158.5, 158.1, 154.4 (d), 150.6 (d), 141.2 (d), 110.0, 94.2 (d), 37.1, 36.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −129.1 (s, 1F); ESI-MS m/z (%) 525.1 $[M + 1]^+$ (100), 526.1 $[M + 2]^+$ (30), 527.1 $[M + 3]^+$ (100). Anal. Calcd for $C_{20}H_{18}BrFN_{12}$: C, 45.73; H, 3.45; N, 31.99. Found: C, 45.45; H, 3.32; N, 31.64.

General Procedure for Fluorination of Monohalogenated Azacalix[4]pyrimidines 2, 7, and 11. A mixture of **2** (93 mg, 0.2 mmol) and NFSI (378 mg, 1.2 mmol) in DCE (20 mL) was refluxed for 24 h. After workup as mentioned for the synthesis of **7**, pure product **10** (76 mg 77%) was obtained. The same reaction between **7** (44 mg, 0.1 mmol) and NFSI (267 mg, 0.6 mmol) or between **11** (76 mg, 0.15 mmol) and NFSI (284 mg, 0.9 mmol) gave, after a period of time (see Schemes 5 and 4), product **8** (29 mg, 63%) or **14** (60 mg, 76%).

Synthesis of 21. *Synthesis of 18.* To a solution of **16**[31] (7.15 g 50 mmol) in dry THF (300 mL) was added NaH (2.4 g, 100 mmol) slowly at room temperature. After the resulting mixture was refluxed for 12 h, reactant **17** (14.8 g 100 mmol) was added slowly. The reaction mixture was refluxed for another 12 h and was then cooled to room temperature. The reaction was quenched by adding a small amount of water. The solvents were removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (200 mL). The organic solution was washed three times with brine (100 mL) and dried over anhydrous $MgSO_4$. After removal of solvent, the residue was chromatographed on a silica gel column (100–200) with a mixture of dichloromethane and ethyl acetate as the mobile phase to give pure product **18** (9.18 g, 72%) as a white solid: mp 171–172 °C; IR (KBr) ν 1587, 1557, 1520, 1454, 1392, 1356, 1316, 1121, 1099 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.739 (s, 1H), 8.737 (s, 1H), 7.56 (s, 1H),

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7.55 (s, 1H), 3.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 161.3, 157.8, 110.5, 35.0; CI-MS m/z (%) 255.0 $[M]^+$ (100), 253.9 $[M - 1]^+$ (29), 256 $[M + 1]^+$ (47), 257 $[M + 2]^+$ (47). Anal. Calcd for $C_9H_7Cl_2N_3$: C, 42.21; H, 2.76; Cl, 27.69; N, 27.35. Found: C, 42.16; H, 2.98; N, 27.31.

Synthesis of ***19***. A mixture of **18** (2.04 g, 8 mmol), aqueous methylamine solution (32 mL, 33% in water), and water (50 mL) was stirred at 120 °C in a sealed tube for 12 h. After the mixture was cooled to room temperature, water (100 mL) was added and the mixture was extracted three times with CH_2Cl_2 (100 mL). The combined organic phase was washed with brine (100 mL × 3) and dried over anhydrous $MgSO_4$. After removal of solvent, the residue was chromatographed on a silica gel column (100−200) with a mixture of dichloromethane and acetone as the mobile phase to give pure product **19** (1.96 g, 100%) as a white solid: mp 158−189 °C; IR (KBr) ν 3251, 3113, 3001, 1636, 1575, 1432, 1405, 1313, 1256, 1230, 1088 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (s, 2H), 6.29 (s, 2H), 5.09 (bs, 2H), 3.55 (s, 3H), 2.92 (d, J = 5.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 161.9, 157.6, 89.9, 34.9, 28.3; ESI-MS m/z (%) 246.3 $[M + H]^+$ (100), 268.1 $[M + 23]^+$ (30); HRMS (FTMS-ESI) $C_{11}H_{15}N_7$ requires 246.14617 $[M + H]^+$, found 246.14631 $[M + H]^+$.

Synthesis of ***20***. A mixture of **19** (123 mg, 0.5 mmol) and Selectfluor (3 equiv) in methanol (20 mL) was refluxed for 2 h. After workup as mentioned for the synthesis of **7**, starting material **19** (70 mg, 57%) and product **20** (28 mg, 20%) were isolated. On the basis of the consumed starting material, the chemical yield of **20** was 47%. **20**: white solid; mp 122−124 °C; IR (KBr) ν 3266, 3174, 3036, 2930, 1624, 1581, 1527, 1477, 1439, 1402, 1359, 1327, 1286, 1267, 1209, 1182, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (s, 2H), 4.89 (bs, 2H), 3.57 (s, 3H), 3.06 (d, J = 4.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4 (d), 152.3 (t), 146.6 (d), 135.8 (dd), 35.8 (t), 27.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −160.7 (s, 1F); ESI-MS m/z (%) 274.3 $[M - 7]^+$ (100), 282.1 $[M + 1]^+$ (30), 262.2 $[M - 19]^+$ (30). Anal. Calcd for $C_{11}H_{13}F_2N_7$: C, 46.97; H, 4.66; N, 34.86. Found: C, 46.64; H, 4.70; N, 34.69.

Synthesis of ***21***. To a solution of **20** (70 mg 0.25 mmol) in dry 1,4-dioxane (10 mL) at room temperature was added NaH (24 mg, 1 mmol) slowly. After the mixture was refluxed for 12h, **18** (63 mg, 0.25 mmol) was added slowly. The reaction mixture was refluxed for another 12 h. After workup as mentioned for the synthesis of **18**, product **21** (12 mg, 10%) was obtained as a white solid: mp >300 °C; IR (KBr) ν 1591, 1532, 1475, 1442, 1397, 1342, 1257 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (s, 2H), 8.52 (s, 2H), 6.56 (s, 2H), 3.70 (s, 3H), 3.65 (s, 6H), 3.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 162.5, 162.3, 158.8, 153.3, 151.3, 149.3, 140.7 (d), 98.3, 37.4, 36.8, 36.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −139.5 (s, 1F); ESI-MS m/z 465.2 $[M + H]^+$; HRMS (FTMS-ESI) $C_{20}H_{18}F_2N_{12}$ requires 465.18182 $[M + H]^+$, found 465.18184 $[M + H]^+$.

Synthesis of Deuterated Azacalix[4]pyrimidines 22 and 23. Under argon protection, a mixture of **12** (81 mg, 0.15 mmol), zinc powder (98 mg, 1.5 mmol), and Pd/C (10%, 20 mg) in D_2O (10 mL) was refluxed for 3 h. After removal of solid residues by filtration, the filtrate was extracted with dichloromethane (10 mL × 3). The combined organic phase was washed with brine (20 mL × 3) and dried over anhydrous $MgSO_4$. After removal of solvent, the residue was chromatographed on a silica gel column (100−200) with a mixture of dichloromethane and acetone as the mobile phase to give pure products **22** (37 mg, 53%) and **23** (18 mg, 28%).

22: white solid; mp >300 °C; IR (KBr) ν 1587, 1523, 1483, 1432, 1396, 1219, 1123 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.768 (s, 1H), 8.765 (s, 1H), 8.73 (s, 1H), 7.05 (d, J = 0.8 Hz, 1H), 6.22 (d, J = 0.8 Hz, 1H), 3.64 (s, 6H), 3.57 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 162.0 (d), 161.8 (d), 160.6, 160.0 159.2, 157.0, 115.7, 101.2, 96.1, 37.2, 36.0; ESI-MS m/z (%) 464.3 $[M + H]^+$ (100), 466.3 $[M + 3]^+$ (33); HRMS (FTMS-ESI) $C_{20}H_{18}DClN_{12}$ requires 464.16797 $[M + H]^+$, found 464.16739 $[M + H]^+$.

23: white solid; mp >300 °C; IR (KBr) ν 1584, 1523, 1475, 1438, 1394, 1213, 1118 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 4H), 6.99 (s, 2H), 3.56 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4 (d), 160.2, 98.9, 35.6; ESI-MS m/z 431.3 $[M + H]^+$; HRMS (FTMS-ESI) $C_{20}H_{18}D_2N_{12}$ requires 431.21322 $[M + H]^+$, found 431.21292 $[M + H]^+$.

Resolution of Enantiomers of 3, 12, and 15. Using the HPLC method, racemic samples **3**, **12**, and **15** were resolved on an amylose tris(3,5-dimethylphenylcarbamate) immobilized silica gel HPLC column (Chiralpak IA). Mobile phase used for **3** and **12**: hexane/Et_2NH/$CHCl_3$ = 50/0.1/50, 0.5 mL/min, 25 °C. Mobile phase used for **15**: hexane/Et_2NH/CH_2Cl_2/*i*-PrOH = 70/0.1/20/10. 0.5 mL/min, 25 °C. Two fractions at retention times 15.87 and 19.78 min for **3**, at retention times 14.70 and 18.17 min for **12**, and retention times 38.50 and 42.77 min for **15** were separately collected. The enantiomeric excess (ee) of resolved components was >99.5% on the basis of chiral HPLC analysis. CD spectra obtained showed the mirror images of resolved enantiomers.

Measurement of Kinetics of Racemization of Enantiomers of 3 and 15. A solution of enantiopure **3** or **15** (ee >99.5%) in *o*-dichlorobenzene (1.5×10^{-3} mol/L) was kept in an isotherm bath in the range 363−393 K. At a specific temperature, a very small amount of sample was pipetted in at different time intervals and the enantiomeric excess value (ee_t) was analyzed by chiral HPLC analysis. A plot of $\ln(ee_o/ee_t)$ against time gave a straight line, and a rate constant (k) for racemization was obtained from the slope. After rate constants were measured at different temperatures, the Eyring plot of $\ln(k/T)$ against $1/T$ gave the enthalpy ($\Delta H^{\ddagger}$) and entropy ($\Delta S^{\ddagger}$) of activation for racemization.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, tables, figures, and CIF files giving detailed experimental procedures, characterization data for all products, X-ray crystallographic data for **3**, **6**, **10**, **14**, *P*-**15**, and *M*-**15**, ^{1}H and ^{13}C NMR spectra of the products, and kinetics of racemization of enantiomers **3** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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