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Triflate-Functionalized Calix[6]arenes as Versatile Building-Blocks:
Application to the Synthesis of an Inherently Chiral Zn(II) Complex

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Graphical Abstract
The regioselective synthesis of two calix[6]arenes bearing triflate groups is described. These
compounds constitute versatile molecular platforms that allow the elaboration of sophisticated
calixarene-based systems selectively functionalized at the large and/or at the small rim.

Abstract
Cavity-based metal complexes can find many applications notably in the fields of catalysis
and biomimicry. In this context, it was shown that metal complexes of calix[6]arenes bearing
three aza-coordinating arms at the small rim provide excellent structural models of the poly-
imidazole sites found in the active site of many metallo-enzymes. All these N-donor ligands
were synthesized from the 1,3,5-tris-methoxy-p-tBu-calix[6]arene platform, which presents
some limitations in terms of functionalization. Therefore, there is a need for the development
of new calix[6]arene-based building-blocks selectively protected at the small rim. Herein we
describe the regioselective one step synthesis of two calix[6]arenes decorated with triflate
groups, i.e. $X_6H_3Tf_2$ 2 and $X_6H_3Tf_3$ 3, from the parent calix[6]arene $X_6H_6$ 1. It is shown that
the triflate groups can either act as protecting or deactivating groups, allowing the elaboration
of sophisticated calixarene-based systems selectively functionalized at the large and/or at the small rim. In addition, $X_6H_3Tf_3$ is functionalized on the A, B, and D rings and thus gives access to inherently chiral compounds, as demonstrated by the synthesis of a rare example of inherently chiral cavity-based metal complex.

**Keywords:** Calixarenes – Supramolecular chemistry – Inherent Chirality – NMR – Zn complex

**Introduction**

The design of metal complexes associated to a cavity has emerged as a research field of significant importance. Indeed, such cavity-based metal complexes can find applications as selective catalysts and can contribute to a better understanding of the mechanisms occurring at active sites of metallo-enzymes. A possible strategy for the elaboration of these metal complexes is to combine a coordination core to concave macrocyclic platforms such as cyclodextrins, hemicryptophanes, resorcinarenes or calixarenes. In this regard, some of us have developed calix[6]arenes bearing three aza-coordinating arms such as $N$-methyl-imidazole (ImMe) or 1,2,3-triazole (Triaz) units at the small rim (Figure 1). These calix[6]arene-based tridentate $N$-donor ligands can complex metal ions (e.g. Zn$^{2+}$, Cu$^+$. or Cu$^{2+}$) to yield mononuclear complexes with a labile neutral guest such as an alcohol or an amine coordinated within the cavity (see the X-ray structure displayed in Figure 1). It was shown that the so-called funnel complexes nicely mimic the polyimidazole sites found in the active site of many metallo-enzymes. These $C_{3v}$ symmetrical $N$-donor ligands were synthesized by functionalization of the 1,3,5-tris-methoxy-$p$-Bu-calix[6]arene ($X_6H_3Me_3$) platform (obtained itself from $p$-Bu-calix[6]arene in ca. 30% yield). Actually, the protecting methyl groups present in these ligands turned out to be quite difficult to remove (and thus to replace) selectively. Moreover, 1,2,4-tris-substituted $N$-donor ligands would be particularly interesting to study since they could lead to inherently chiral complexes. However, such asymmetrically functionalized ligands cannot be prepared from the $X_6H_3Me_3$ platform and no calix[6]arene-based precursor 1,2,4-tris-functionalized by substituents that could be potentially used as protecting groups are available in good yield.

As part of our continuous interest in the synthesis and study of calix[6]arene-based receptors for neutral or charged species, we wanted to develop a new family of $N$-donor ligands that could be easily functionalized at the small rim in order to vary the proximal environment of the coordinated metal ion. Another goal was to develop an access to inherently chiral funnel complexes. With these objectives in mind, we envisioned the use of calix[6]arenes selectively functionalized by triflate groups as starting platforms. Indeed, such groups were a priori good candidates for the further functionalization of the calixarene based-ligands either at the small or the large rim. Provided that we could find conditions which could enable the selective synthesis of triflate-substituted calix[6]arenes, the resulting building-blocks should have a great potential for the synthesis of calix[6]arenes possessing substitution patterns that could be hardly prepared otherwise. However, even though calix[4]arenes decorated by triflate groups have already been well-described, only one example of a calix[6]arene analogue has been reported.
Herein, we report the synthesis of calix[6]arenes selectively functionalized by two or three triflate groups at the small rim, the study of the synthetic potential of such building-blocks and their use for the design of a new family of inherently chiral metal complexes.

Figure 1. Synthesis of $X_6\text{Me}_3\text{ImMe}_3$ and $X_6\text{Me}_3\text{Triaz}_3$ from $X_6\text{H}_3\text{Me}_3$. Inset: X-ray structure of the funnel complex $[X_6\text{Me}_3\text{ImMe}_3\text{Zn}]\cdot\text{HepNH}_2$.

Results and discussion

Direct introduction of triflate groups on the parent calix[6]arene $X_6\text{H}_6$ 1 was not reported, thus this reaction was first investigated by reacting 1 with triflic anhydride ($\text{Tf}_2\text{O}$) under various reaction conditions. The influence of the nature of the base (i.e. either DMAP, pyridine, $\text{K}_2\text{CO}_3$ or $\text{Cs}_2\text{CO}_3$ from 2.5 to 10 equiv.), the amount of $\text{Tf}_2\text{O}$ (from 2.5 to 6 equiv.), the solvent (i.e. either $\text{CH}_2\text{Cl}_2$, acetone or acetonitrile) and the temperature (25 °C or 40 °C) was evaluated and all reactions were monitored by ESI-MS and TLC analyses. It was found that the use of $\text{Tf}_2\text{O}$ (2.5 equiv.) in $\text{CH}_2\text{Cl}_2$ at 40 °C in the presence of either DMAP (2.5 equiv.) or $\text{Cs}_2\text{CO}_3$ (4 equiv.) allows, respectively, the formation of the bis-triflate or tris-triflate derivative (i.e. $X_6\text{H}_4\text{Tf}_2$ or $X_6\text{H}_3\text{Tf}_3$) as the main product. Compounds 2 and 3 were isolated in 71% and 37% yields after flash chromatography (Scheme 1). It is noteworthy that the formation of $X_6\text{H}_4\text{Tf}_2$ 2 is fully regioselective as attested by TLC monitoring of the reaction and NMR analysis of the crude product. $X_6\text{H}_3\text{Tf}_3$ 3 being the sole tris-triflate regioisomer that can be formed from 2, this compound was also selectively obtained. Actually, the 37% yield in the case of 3 is due to the recovery of a significant amount of the intermediate 2 (31% yield). Attempts to increase this yield by prolonging the reaction time and/or increasing the amount of $\text{Tf}_2\text{O}$ led to the formation of a mixture of regioisomeric tetra-triflate calix[6]arenes that were difficult to separate from 3. Both compounds 2 and 3 display broad and poorly resolved $^1\text{H}$ NMR signals in $\text{CDCl}_3$ at 25 °C but spectra suitable for signal assignment and structure characterization could be obtained by changing the solvent and/or the temperature. The $^{13}\text{C}$ chemical shifts of the bridging methylene groups indicate that both compounds display a major cone-like conformation (31.5 ppm < $\delta^{13}\text{C}_{\text{ArCH}_2}$ < 32.8 ppm for 2 and 31.1 ppm < $\delta^{13}\text{C}_{\text{ArCH}_2}$ < 32.4 ppm for 3). The NMR measurements also show that the triflate groups of calix[6]arenes 2 and 3 were selectively introduced on the A, D and A, B, D aromatic units, respectively (Scheme 1). In the case of 2, the patterns of the $\text{ArH}$ (1:1:1), $\text{ArCH}_2$ (2:1) and $t\text{Bu}$ (2:1) $^1\text{H}$ signals are indeed characteristic of a $C_{2v}$-symmetrical compound while, in the case of 3, the overall NMR profile is much more complex (e.g. six...
singlet signals for the tBu groups) and attest to an asymmetric substitution pattern at the small rim (Figure 2).^{20}

Scheme 1. Synthesis of X₆H₄Tf₂ 2 and X₆H₃Tf₃ 3 from X₆H₆ 1. i) Tf₂O (2.5 equiv.), DMAP (2.5 equiv.), CH₂Cl₂, 40 °C, 5h, 71%; ii) Tf₂O (2.5 equiv.), Cs₂CO₃ (4 equiv.), CH₂Cl₂, rt, 3h30, 37%.

Figure 2. ¹H NMR spectra (600MHz) of a) X₆H₄Tf₂ 2 in CDCl₃ at 80 °C; b) X₆H₃Tf₃ 3 in CDCl₃/CD₃OD (9:1) at 5 °C. s = residual solvents; w = residual water.

The synthetic potential of X₆H₄Tf₂ 2 and X₆H₃Tf₃ 3 was then evaluated. Most of the functionalization reactions of phenolic moieties proceeding either under acidic or basic conditions, the resistance of 2 and 3 to acids and bases was first studied in various solvents
(CH₂Cl₂, THF, DMF or 1,4-dioxane). Under all the basic conditions tested (i.e. K₂CO₃, NaH, NaOH, nBu₄NOH, DBU and tBuOK), the cleavage of the triflate groups and the recovery of the phenol moieties was observed by TLC analysis. In particular, the use of NaH in DMF led to the quantitative formation of calix[6]arene X₆H₆ 1 after a few hours at rt. In strong contrast, 2 and 3 were found to be particularly stable in the presence of strong acids such as concentrated solutions of HCl, H₂SO₄, HNO₃ and TFA. On one hand, these results indicate that functionalization of the building-blocks 2 and 3 should be achieved under neutral or acidic conditions. On the other hand, the easy removal of the triflate groups under basic conditions is particularly interesting in the perspective of using these groups as protecting groups.

First, the deactivation of the aromatic units bearing the triflate groups toward electrophilic reagents was evaluated through an 

*ipso*-substitution reaction at the large rim of calixarene 3. To our delight, when 3 was treated with AlCl₃ in toluene, detertiobutylation proceeded selectively on the phenol moieties that are not deactivated by the triflate groups, producing 4 in 80% yield (Scheme 2). A subsequent cleavage of the triflate groups under basic conditions afforded calix[6]arene 5 whose tBu groups have been selectively removed from the aromatic units C, E and F. This two-step sequence nicely illustrates the possibility of tuning the large rim substitution pattern through the selective introduction of triflate groups at the small rim. It is noteworthy that calix[6]arene 5 also displays an asymmetric substitution pattern at the large rim and thus constitutes an interesting building-block for the elaboration of inherently chiral calix[6]arene-based receptors.

With building-block 3 in hands, we next moved to the synthesis of a new family of N-donor ligands that could give access to inherently chiral funnel complexes. The first challenge was to find a synthetic pathway for the introduction of three chelating arms at the small rim of 3. Indeed, classical alkylation of the phenol moieties was proscribed due to the instability of the triflate groups under basic conditions. A Mitsunobu reaction was thus envisaged for the alkylation of the phenol units. Unfortunately, reaction of (1-methyl-1H-imidazol-2-yl)methanol with 3 in presence of DIAD and PPh₃ led to a partial removal of the triflate groups and to the formation of a complex mixture of products. A possible explanation for the cleavage of the triflate groups may lie in the basicity of the imidazole reagent. This hypothesis was confirmed by the replacement of (1-methyl-1H-imidazol-2-yl)methanol with the non-basic propargyl alcohol, which led to the tris-etherified calix[6]arene 6 in 80% yield (Scheme 2). Further CuAAC click reaction with BnN₃ afforded the tris-triazole 7 in 89% yield and final removal of the triflate groups under basic conditions gave the desired compound 8 in 63% overall yield from 3. It is noteworthy that 8 constitutes a unique calix[6]arene-based ligand since it displays: i) an asymmetric substitution pattern that can potentially be exploited for intra-cavity chiral recognition, ii) a tridentate N₃-coordination site (i.e. the three triazole units) in close proximity to three phenolic donor groups whose coordination properties can be modulated by their protonation state, iii) three phenolic positions that can be easily modified in order to append additional functional subunits. To illustrate the chelating potential of the ligand 8, the synthesis of the corresponding inherently chiral Zn(II) complex [8.Zn](TfO)₂ was achieved in quantitative yield through reaction with 1 equiv. of Zn(OTf)₂ (Scheme 2).
Scheme 2. Synthesis of compounds 4-8 and complex [8.Zn](TfO)₂. i) AlCl₃ (12 equiv.), toluene, 40 °C, 10h, 80%; ii) NaOH (1M), 1,4-dioxane, rt, 4 days, 86%. iii) HC≡CCH₂OH (22 equiv.), DIAD (22 equiv.), PPh₂(p-PhOMe) (18 equiv.), THF/CH₂Cl₂ (4:1), rt, 36h, 80%; iv) BnN₃ (9 equiv.), CuSO₄.5H₂O (3.6 equiv.), sodium ascorbate (7.2 equiv.), CH₂Cl₂/H₂O (1:1), rt, 6 days, 89%; v) NaOH (1M), 1,4-dioxane, rt, 6 days, 88%; vi) Zn(OTf)₂ (1 equiv.), THF, rt, 1h, quant.

DOSY experiments in CDCl₃ showed that ligand 8 and the corresponding zinc complex [8.Zn](TfO)₂ have similar diffusion coefficients, indicating that the complex is composed of a single calixarene subunit and thus corresponds to a mononuclear species with a 1:1 zinc/ligand ratio. The ¹H NMR spectra of 8 and [8.Zn](TfO)₂ in CDCl₃ are rather crowded due to the asymmetric substitution pattern of the calixarene skeleton (Figure 3). Nevertheless, it was possible to assign all the ¹H signals through extensive analysis of the corresponding 2D NMR spectra (COSY, HSQC, HMBC). The three-dimensional structures of 8 and [8.Zn](TfO)₂ are schematized in Figure 3, they were mainly deduced from chemical shift data and the structure of [8.Zn](TfO)₂ was then confirmed by the detection of nuclear Overhauser effects (2D ROESY spectrum). In both cases, the presence of three signals corresponding to the OH protons show that 8 and [8.Zn](TfO)₂ are not deprotonated. The ¹³C chemical shifts of the bridging methylene groups indicate that the calixarene cores display a major cone-like conformation (28.9 ppm < δ¹³C₆CH₂ < 33.1 ppm for 8 and 28.8 ppm < δ¹³C₆CH₂ < 33.4 ppm for [8.Zn](TfO)₂). The poly-aromatic cavity of 8 is filled by a self-included t-Bu group, which belongs to the functionalized unit C (δ¹H₆t-Bu = 0.24 ppm). In contrast, it is the benzyl group of this unit that folds into the cavity of the complex [8.Zn](TfO)₂ (δ¹H₆Ar-Bn = 6.86, 6.47 and 6.34 ppm). Most importantly, the significant down-field shifts observed for the CH signals of the triazole units attest to the coordination of the metal center (Δδ¹H₆CH = 0.69, 0.50 and 0.43 ppm, Figure 3b). Thus, all these NMR data confirm the formation of the inherently chiral Zn
Complex [8.Zn](TfO)$_2$ with a coordination of the metal center to the three chelating triazole arms. By analogy to closely related funnel complexes in chloroform, either water molecule(s) or a phenol moiety may likely complete the coordination sphere of the Lewis acidic metal ion. Interestingly, preliminary NMR studies showed that ligand 8 was also able to complex Pb$^{2+}$ and Hg$^{2+}$. Coordination to these metal ions as well as others, and the host-guest properties of the corresponding complexes are currently under investigation.

**Figure 3.** $^1$H NMR spectra (600MHz, 25 °C) in CDCl$_3$ and of a) ligand 8; b) complex [8.Zn](TfO)$_2$ and 3D representation of their conformation in solution. s = residual solvents; w = residual water; g = grease.

**Conclusion**

The regioselective synthesis of two calix[6]arenes bearing triflate groups, i.e. $X_6H_4TF_2$ 2 and $X_6H_3TF_3$ 3, was achieved successfully from the parent calix[6]arene $X_6H_6$ 1. These compounds constitute rare examples of calix[6]arenes decorated with triflate groups. Very interestingly, the building-block 3 is functionalized on the A, B, and D rings and thus gives access to inherently chiral calix[6]arenes. It is shown that the triflate groups can be easily removed under basic conditions and can therefore act as protecting groups for the elaboration of sophisticated calixarene-based systems. Besides, the triflate groups deactivate the corresponding aromatic units toward electrophilic reagents and, consequently, allow the transfer of the functionalization pattern of the small rim to the large rim. Therefore, as demonstrated by the synthesis of 5, calix[6]arenes with an asymmetric substitution pattern at the large rim can be easily obtained from building-block 3. While this route was not explored in the framework of this study, the triflate groups could be also exploited as activating groups for metal-catalyzed coupling reactions. The synthetic potential of $X_6H_3TF_3$ 3 was further illustrated by the synthesis of the inherently chiral Zn-complex [8.Zn](TfO)$_2$. All in all, 2 and 3 can be seen as versatile molecular platforms that can be selectively functionalized at the large and/or at the small rim. Removal of the triflate groups then provides additional possibilities of tailored functionalization. This work opens the route to a large variety of...
calixarene-based ligands whose properties can be finely tuned by the functionalization pattern.

**Experimental Section**

**General experimental methods.** All reactions using dry solvents were conducted under argon atmosphere employing standard techniques. All solvents were reagent grade. Tetrahydrofuran and dichloromethane were respectively freshly distilled from sodium/benzophene and calcium hydride under argon. Toluene (99.9%, Extra Dry over Molecular Sieve, Stabilized, AcroSeal) was purchased from ACROS Organics. Reactions were magnetically stirred and monitored by thin layer chromatography using Merck-Kiesegel 60F254 plates or Macherey-Nagel Pre Coated TLC-sheets Alugram® Xtra Sil/UV254. Flash chromatography was performed with silica gel 60 (particle size 35-70 µm) supplied by Merck. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. All organic layers were dried over Wa filters (hydrophobic phase separation papers, MN 616 WA (1/4)) supplied by Macherey-Nagel.

$^1$H NMR spectra were recorded at 300, 400 or 600 MHz. $^{13}$C NMR spectra were recorded at 75, 100 or 150 MHz. Traces of residual solvents were used as internal standard for $^1$H (7.26 ppm for CHCl$_3$) and for $^{13}$C (77.16 ppm for CDCl$_3$). CDCl$_3$ was filtered through a short column of basic alumina to remove traces of DCl. Most of the $^1$H NMR spectra signals were assigned on the basis of 2D NMR analyses (COSY, ROESY, HSQC, HMBC). Despite extensive signal averaging (thousands of scans), most $^{13}$C NMR spectra showed poor signal-to-noise ratio because of the asymmetric functionalization pattern of the compounds and thus cannot be described (see Supplementary Information). Chemical shifts are quoted on the δ scale, coupling constants ($J$) are expressed in Hertz (Hz). Abbreviations: s for singlet; d for doublet; t for triplet; br for broad signal; m for massif. Melting points were recorded on a Stuart Scientific Analogue SMP11 or Büchi Melting Point B-545. IR analyses were performed with a FT-IR spectrometer using ATR (Attenuated Total Reflectance) method. ESI-MS and HRMS analyses were performed using methanol as solvent. Low resolution mass spectra were recorded with an ESI-MS spectrometer equipped with an ion-trap. High-resolution mass-spectra were obtained on Quadrupole Time of Flight (QTOF) 6520 series from Agilent Technologies, used in 4 GHz mode (High resolution mode), source was an electrospray ionization source (ESI), Multimode source (used in APCI mode) or a (MALDI-TOF MS LD+).

**1,4-bistriflate-p-tBu-calix[6]arene 2.** Tf$_2$O (425 µL, 2.57 mmol) was added dropwise to a solution of 1 (1.00 g, 1.03 mmol) and DMAP (314 mg, 2.57 mmol) in dry CH$_2$Cl$_2$ (30 mL). The reaction mixture was then stirred for 5h at 40 °C and an aqueous solution of HCl (20 mL, 1M) was added. The aqueous layer was extracted with CH$_2$Cl$_2$. Combined organic layers were washed with water, filtrated over Wa filter and concentrated under reduced pressure. Purification by flash chromatography (cyclohexane/CH$_2$Cl$_2$; 70:30, then 65:35) afforded 2 (900 mg, 0.727 mmol, 71% yield) as a white solid. R$^f$ 0.22 (cyclohexane/CH$_2$Cl$_2$; 60/40). Mp > 260 °C (decomp.). IR (ATR) $\nu$ max 2963, 1486, 1364, 1248, 1213, 1184, 1138, 1073, 912, 871, 641, 617. $^1$H NMR (600 MHz, CDCl$_3$, 353K): δ (ppm) 7.18 (s, 4H, Ar$_2$OH), 7.17 (s, 4H, Ar$_2$OH), 6.97 (s, 4H, Ar$_2$OTf), 6.30 (br(s), 4H, ArOH), 4.06 (br(s), 8H, Ar$_2$OTfCH$_2$Ar$_2$OH), 3.71 (br(s), 4H, Ar$_2$OHCH$_2$Ar$_2$OH), 1.32 (s, 36H, tBu$_2$OH), 1.06 (s, 18H, tBu$_3$OTf). $^{13}$C{${^1}$H} NMR (150
HRMS (APCI+): calcd for C_{69}H_{33}F_{13}O_{13}S_{2} [M-H]^- 1235.5181, found 1235.5185.

1,2,4-tristriflate-p-tBu-calix[6]arene 3. TfO (1.28 mL, 7.70 mmol) was added dropwise to a solution of 1 (3.00 g, 3.08 mmol) and Cs_{2}CO_{3} (4.02 g, 12.3 mmol) in dry CH_{2}Cl_{2} (150 mL). The reaction mixture was then stirred for 3h at room temperature and an aqueous solution of HCl (60 mL, 1M) was added. The aqueous layer was extracted with CH_{2}Cl_{2}. Combined organic layers were washed with water, filtered over Wa filter and concentrated under reduced pressure. Purification by flash chromatography (cyclohexane/CH_{2}Cl_{2}: 70/30), then 65/35 afforded 3 (1.56 g, 1.14 mmol, 37% yield) as a white solid and 2 (1.2 g, 0.97 mmol, 31% yield). R_{f}: 0.36 (cyclohexane/CH_{2}Cl_{2}, 60:40). Mp = 170 °C. IR (ATR) \nu_{max} 2967, 1486, 1405, 1248, 1139, 1069, 874, 770, 663. ^{1}H NMR (600 MHz, CDCl_{3}/CD_{3}OD, 9:1, v/v, 278K): \delta (ppm) 7.38 (s, 1H, ArH) 7.17 (s, 1H, ArH), 7.15 (s, 1H, ArH), 7.13 (s, 1H, ArH), 7.12 (s, 1H, ArH). 7.04 (s, 1H, ArH). 6.93 (s, 1H, ArH), 6.40 (s, 1H, ArH), 6.18 (s, 1H, ArH). 6.13 (brs), 1H, ArH), 4.49 (d, 1H, ArCH_{2}, J = 16.4 Hz), 4.37 - 4.44 (m, 2H, ArCH_{2}), 3.97 - 4.06 (m, 2H, ArCH_{2}), 3.65 - 3.83 (m with residual solvent, 4H, ArCH_{2}), 3.51 (d, 1H, ArCH_{2}, J = 13.7 Hz), 3.29-3.35 (m with residual solvent, 1H, ArCH_{2}), 3.24 (d, 1H, ArCH_{2}, J = 13.8 Hz), 1.32 (s, 9H, tBu), 1.25 (s, 9H, tBu), 1.21 (s, 9H, tBu), 1.15 (s, 9H, tBu), 0.95 (s, 9H, tBu), 0.60 (s, 9H, tBu). \^13C (^1H) NMR (100 MHz, CDCl_{3}/CD_{3}OD, 9:1, v/v, 298K): \delta (ppm) 151.04, 150.76, 150.67, 150.59, 150.40, 148.97, 148.00 (br), 145.23 (br), 143.86 (br), 143.49, 142.41, 141.94 (br), 135.83 (br), 133.27, 132.49, 132.06 (br), 131.83, 130.75 (br), 130.05 (br), 128.51 (br), 128.22, 127.79, 127.41, 127.21, 126.91, 126.71, 126.57, 126.35, 126.04, 125.80 (br), 124.94 (br), 124.74, 121.98 (br), 118.73 (q, J = 318 Hz, 2 CF_{3}), 118.54 (q, J = 318 Hz, CF_{3}), 34.47, 34.39, 34.24 (br), 34.21, 33.98, 33.93, 32.69 (br), 32.03 (br), 31.63, 31.58, 31.52, 31.10 (br), 30.86, 30.81. Note that out of the 57 expected \^13C NMR signals, only 49 were observed due to some overlapping signals. HRMS (APCI+): calcd for C_{69}H_{33}F_{13}O_{13}S_{2} [M-H]^- 1368.4674, found 1368.4674.

1,2,4-tristriflate-1,2,4-tris-p-tBu-calix[6]arene 4. Anhydrous AlCl_{3} (1.17 g, 8.77 mmol) was added to a solution of 3 (1.00 g, 0.73 mmol) in dry toluene (12 mL). The reaction mixture was then stirred at 40 °C. The reaction was monitored by ESI-MS and TLC and was stopped after the complete consumption of the starting material and intermediate products (c.a. 10h). An aqueous solution of HCl (20 mL, 1M) was then added and the aqueous layer was extracted with CH_{2}Cl_{2}. Combined organic layers were washed with water, filtered over Wa filter and concentrated under reduced pressure. Purification by flash chromatography (cyclohexane/CH_{2}Cl_{2}: gradient from 90/10 to 50/50) afforded 4 (700 mg, 80%) as a pale pink solid. R_{f}: 0.30 (cyclohexane/CH_{2}Cl_{2}, 60/40). Mp = 138-139 °C. IR (ATR) \nu_{max} 2965, 1470, 1400, 1212, 1136, 1072, 864, 754, 648, 609. \^1H NMR (400 MHz, CDCl_{3}, 298K): \delta (ppm) 7.22 - 7.31 (m, ArH, overlapping with residual CHCl_{3} peak), 6.97-7.20 (m, 7H, ArH), 6.80-6.97 (m, 6H, ArOH/ArH), 6.65 (s, 1H, ArH), 5.64 (s, 1H, ArOH), 4.27 (s, 1H, ArOH), 3.5-4.5 (m, 12H, ArCH_{2}), 1.13 (brs), 9H, tBu), 1.02 (s, 9H, tBu), 0.97 (brs), 9H, tBu). HRMS (ESI+): calcd for C_{75}H_{39}F_{26}O_{15}N_{12} [M+NH_{4}]^{+} 1218.3207, found 1218.3199.

1,2,4-tris-p-tBu-calix[6]arene 5. An aqueous solution of NaOH (8 mL, 1M) was added to a solution of 4 (500 mg, 0.416 mmol) in 1,4-dioxane (6 mL). The reaction mixture was then vigorously stirred at room temperature. The reaction was monitored by ESI-MS and TLC and...
was stopped after the complete consumption of the starting material and intermediate products (c.a. 4 days). An aqueous solution of HCl (10 mL, 1M) was then added and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were then washed with water and dried by filtration over Na₂SO₄ filter. Removal of the solvent under reduced pressure afforded 5 (290 mg, 0.360 mmol, 86% yield) as a pale pink solid. Rf 0.30 (cyclohexane/CH₂Cl₂: 40/60). Mp = 246 °C. IR (ATR) ʋmax 2964, 1485, 1468, 1362, 1258, 1205, 874, 751, 670, 638. ¹H NMR (300 MHz, CDCl₃, 298K): δ (ppm) 10.27-10.65 (m, 6H, ArOH), 7.07-7.21 (m, 12H, ArH), 6.77-6.87 (m, 3H, C≡C-tBu), 1.07 (s, 9H, C(tBu)), 1.19-1.33 (m, 3H, CH₂(tBu)), 3.6-4.2 (m, 12H, ArCH₂). ¹³C (¹H) NMR (75 MHz, CDCl₃, 298K): δ (ppm) 149.8, 147.5, 144.6, 129.6, 129.5, 127.8, 127.7, 127.6, 126.8, 126.7, 126.5, 126.3, 121.9, 34.2, 33.0, 32.8, 32.7, 32.4, 31.7, 29.9. HRMS (APCI⁺): calcd for C₅₄H₅₉O₆ [M+H]⁺ 803.4317, found 803.4269.

1,2,4-tristriflate-3,5,6-tris-propargyl-calix[6]arene 6. Diphenyl(2-methoxyphenyl)phosphine oxide (2.70 g, 9.24 mmol) and DIAD (2.18 mL, 11.1 mmol) were added to a solution of 1,2,4-tristriflate-3,5,6-tris-benzyltriazole-calix[6]arene 7. An aqueous solution (8 mL) containing sodium ascorbate (480 mg, 2.42 mmol) and CuSO₄·5H₂O (300 mg, 1.20 mmol) was added to a stirred solution of 6 (500 mg, 0.337 mmol) and benzylazine (380 µL, 3.03 mmol) in CH₂Cl₂ (8 mL). The biphasic mixture was then vigorously stirred at room temperature. The reaction was monitored by ESI-MS and TLC and was stopped after the complete consumption of the starting material and intermediate products (c.a. 6 days). The reaction mixture was then diluted with CH₂Cl₂ (20 mL) and an aqueous solution of NH₄OH (10 mL, 0.5%) was added. After extraction of the aqueous layer with CH₂Cl₂, the combined organic layers were washed with water, dried by filtration over Na₂SO₄ filter and concentrated under reduced pressure. Purification of the resulting residue by flash chromatography (CH₂Cl₂/MeOH: 100/0 then 98/2) afforded 7 (550 mg, 0.299 mmol, 89% yield). Rf 0.31 (CH₂Cl₂/MeOH: 98/2). Mp = 135 °C. IR (ATR) ʋmax 2963, 1457, 1364, 1211, 1137, 1067,
859, 769, 625. $^1$H NMR (300 MHz, CDCl$_3$, 298K): the spectrum shows the presence of multiple conformers in slow exchange rate and thus cannot be interpreted, see the Supplementary information. HRMS (ESI+): calcd for C$_{99}$H$_{100}$F$_3$N$_9$O$_{12}$S$_3$ [M+H]$^+$ 1883.7242, found 1883.7115.

1,2,4-tris-benzyltriazole-calix[6]arene 8. An aqueous solution of NaOH (3 mL, 1M) was added to a solution of 7 (100 mg, 0.0543 mmol) in 1,4-dioxane (3 mL). The reaction mixture was then vigorously stirred at room temperature. The reaction was monitored by ESI-MS and TLC and was stopped after the complete consumption of the starting material and intermediate products (c.a. 6 days). An aqueous solution of HCl (4 mL, 1M) was then added and the aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic layers were then washed with water and dried by filtration over WA filter. Removal of the solvent under reduced pressure afforded 8 (69 mg, 0.048 mmol, 88%). Mp = 136 °C. IR (ATR) $\nu_{\max}$ 2955, 1482, 1363, 1281, 1226, 1175, 1030, 638, 575. $^1$H NMR (600 MHz, CDCl$_3$, 298K): $\delta$ (ppm) 9.07 (s, 1H, ArOH), 8.84 (s, 1H, ArOH), 8.52 (s, 1H, CH$_{tria}$), 8.16 (s, 1H, CH$_{tria}$), 7.74 (s, 1H, CH$_{tria}$), 7.61 (d, 2H, ArH$_{Bn}$, $J = 7.3$ Hz), 7.53 (s, 1H, ArH$_{calix}$), 7.38 (t, 2H, ArH$_{Bn}$, $J = 7.6$ Hz), 7.35 (s, 1H, ArH$_{calix}$), 7.29 - 7.34 (m, 3H, ArH$_{calix}$, ArH$_{Bn}$), 7.27 (s, 1H, ArH$_{calix}$), 7.23 (t, 2H, ArH$_{Bn}$, $J = 7.7$ Hz), 7.17 (d, 1H, ArH$_{calix}$, $J = 2.1$ Hz), 7.14 - 7.16 (m, 2H, ArH$_{calix}$), 7.07 (d, 2H, ArH$_{Bn}$, $J = 7.3$ Hz), 7.05 (d, 1H, ArH$_{calix}$, $J = 2.0$ Hz), 7.03 (d, 1H, ArH$_{calix}$, $J = 2.1$ Hz), 6.83 - 6.89 (m, 2H, ArOH, ArH$_{Bn}$), 6.44 - 6.50 (m, 3H, ArH$_{calix}$, ArH$_{Bn}$), 6.34 (d, 2H, ArH$_{Bn}$, $J = 7.3$ Hz), 6.23 (d, 1H, OCH$_2$, $J = 11.9$ Hz), 6.12 (s, 1H, ArH$_{calix}$), 6.09 (s, 1H, ArH$_{calix}$), 5.88 (d (AB), 1H, NCH$_2$, $J = 14.3$ Hz), 5.84 (d (AB), 1H, NCH$_2$, $J = 14.6$ Hz), 5.62 (d, 1H, OCH$_2$, $J = 13.5$ Hz), 5.43 - 5.49 (m, 2H, NCH$_2$), 5.34 (d, 1H, NCH$_2$, $J = 15.1$ Hz), 5.25 (d, 1H, NCH$_2$, $J = 14.3$ Hz), 5.01 - 5.07 (m, 2H, OCH$_2$), 4.87 (d, 1H, OCH$_2$, $J = 12.1$ Hz), 4.77 (d, 1H, OCH$_2$, $J = 13.9$ Hz), 4.52 (d, 1H, ArCH$_2$Ar, $J = 15.4$ Hz), 4.22 (d, 1H, ArCH$_2$Ar, $J = 13.0$ Hz), 4.14 (d, 1H, ArCH$_2$Ar, $J = 15.8$ Hz), 3.99 (d, 1H, ArCH$_2$Ar, $J = 17.7$ Hz), 3.82 (d, 1H, ArCH$_2$Ar, $J = 14.0$ Hz), 3.52 - 3.62 (m, 4H, ArCH$_2$Ar), 3.50 (d, 1H, ArCH$_2$Ar, $J = 16.1$ Hz), 3.46 (d, 1H, ArCH$_2$Ar, $J = 15.7$ Hz).
Hz), 3.35 (d, 1H, ArCH₂Ar, J = 14.1 Hz), 1.41 (s, 9H, tBu), 1.38 (s, 9H, tBu), 1.27 (s, 9H, tBu), 1.18 (s, 9H, tBu), 1.04 (s, 9H, tBu), 0.63 (s, 9H, tBu).

$^{13}$C{¹H} NMR (150 MHz, CDCl₃, 298K): δ(ppm) 152.15, 151.04, 150.36, 149.56, 149.10, 148.61, 148.07, 147.51, 144.62, 144.50, 143.33, 143.24, 141.77, 133.75, 133.60, 133.50, 133.21, 132.91, 132.00, 131.78, 129.84, 129.81, 129.72, 129.62, 129.51, 129.44, 129.40, 128.97, 128.86, 128.72, 127.80, 127.71, 120.84 (q, J = 318 Hz, CF₃ from TfO$^{-}$U$^{+}$), 127.15, 127.07, 126.96, 126.90, 126.87, 126.81, 126.69, 126.60, 126.56, 126.43, 125.33, 124.82, 124.57, 124.32, 123.29, 122.85, 121.24, 67.61, 67.09, 56.27, 56.11, 34.66, 34.46, 34.34, 34.12, 33.69, 33.35, 32.98, 31.83, 31.66, 31.55, 31.42, 31.24, 31.20, 28.80. Note that out of the 79 expected $^{13}$C NMR signals, only 70 were observed due to some overlapping signals.

**Supplementary Information:** 1D and 2D NMR spectra of all new compounds, ROESY spectrum of [8.Zn](TfO)$_2$, DOSY spectrum of a mixture of 8 and [8.Zn](TfO)$_2$, NMR complexation studies with Pb$^{2+}$ and Hg$^{2+}$ salts, reaction conditions that were tested for the synthesis of 2 and 3.

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**Notes and References**


It is noteworthy that in the case of the asymmetrically functionalized compounds 3-8, racemization occurs through the cone-cone inversion process, preventing any separation of the two enantiomers at room temperature. In contrast, it may be possible, in principle, to separate the two enantiomers of the rigidified Zn(II) complex [8.Zn(TfO)]$_2$. 

See the Supplementary Information.