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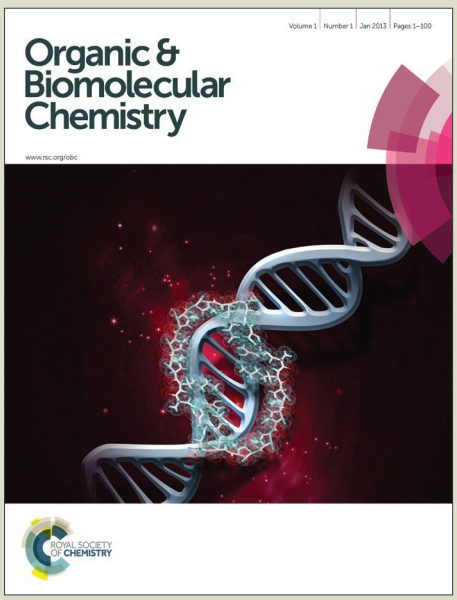

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Triflate-Functionalized Calix[6]arenes as Versatile Building-Blocks: Application to the Synthesis of an Inherently Chiral Zn(II) Complex

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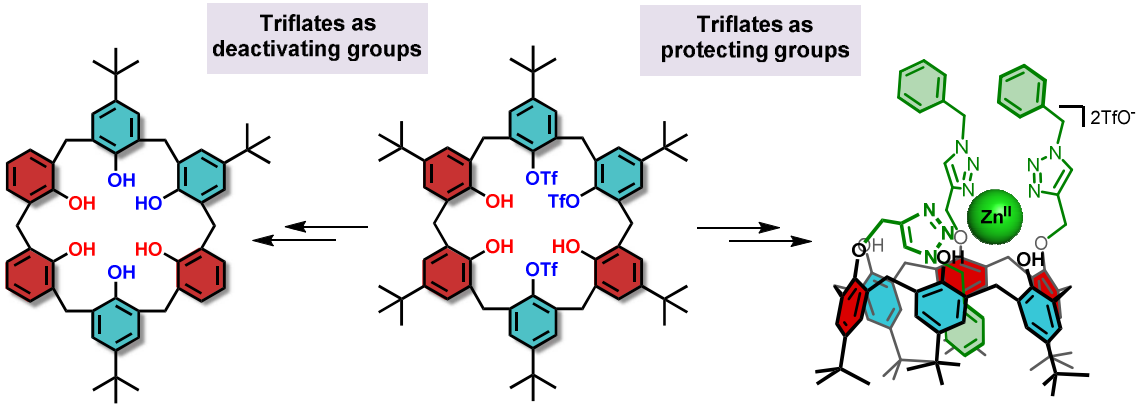
Graphical Abstract

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*-*t*Bu-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. $X_6H_4Tf_2$ **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, $X_6H_3Tf_3$ **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.[1] Indeed, such cavity-based metal complexes can find applications as selective catalysts[2] and can contribute to a better understanding of the mechanisms occurring at active sites of metallo-enzymes.[3] A possible strategy for the elaboration of these metal complexes is to combine a coordination core to concave macrocyclic platforms such as cyclodextrins,[4] hemicryptophanes,[5] resorcinarenes[6] or calixarenes.[3,4] In this regard, some of us have developed calix[6]arenes bearing three aza-coordinating arms such as *N*-methyl-imidazole (ImMe)[7] or 1,2,3-triazole (Triaz)[8] 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**7**[a] displayed in Figure 1). It was shown that the so-called *funnel complexes* nicely mimic the poly-imidazole sites found in the active site of many metallo-enzymes.[9] These C_{3v} symmetrical *N*-donor ligands were synthesized by functionalization of the 1,3,5-tris-methoxy-*p*-*t*Bu-calix[6]arene ($X_6H_3Me_3$) platform[10] (obtained itself from *p*-*t*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[11] (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[12] 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.[13]

As part of our continuous interest in the synthesis and study of calix[6]arene-based receptors for neutral[14] or charged species,[15] 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,[16] only one example of a calix[6]arene analogue has been reported.[17]

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.

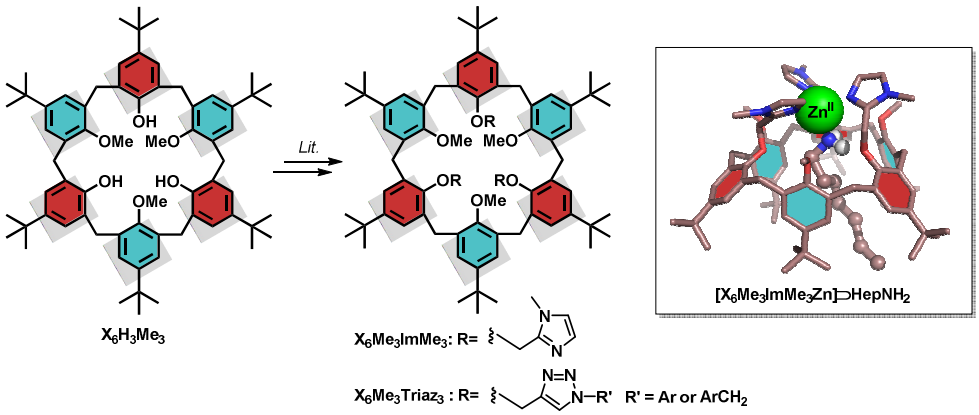
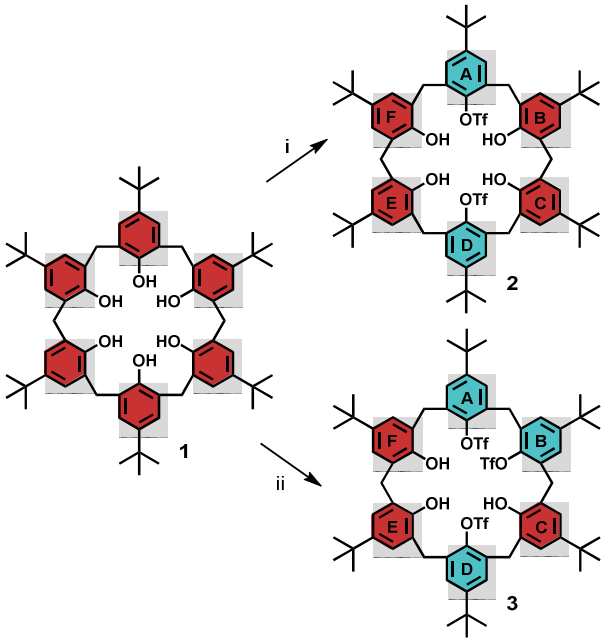


Figure 1. Synthesis of $X_6Me_3ImMe_3$ and $X_6Me_3Triaz_3$ from $X_6H_3Me_3$. Inset: X-ray structure of the funnel complex $[X_6Me_3ImMe_3Zn]\supset HepNH_2$.

Results and discussion

Direct introduction of triflate groups on the parent calix[6]arene X_6H_6 **1** was not reported, thus this reaction was first investigated by reacting **1** with triflic anhydride (Tf_2O) under various reaction conditions. The influence of the nature of the base (i.e. either DMAP, pyridine, K_2CO_3 or Cs_2CO_3 from 2.5 to 10 equiv.), the amount of Tf_2O (from 2.5 to 6 equiv.), the solvent (i.e. either CH_2Cl_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.[18] It was found that the use of Tf_2O (2.5 equiv.) in CH_2Cl_2 at 40 °C in the presence of either DMAP (2.5 equiv.) or Cs_2CO_3 (4 equiv.) allows, respectively, the formation of the bis-triflate or tris-triflate derivative (i.e. $X_6H_4Tf_2$ **2** or $X_6H_3Tf_3$ **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 $X_6H_4Tf_2$ **2** is fully regioselective as attested by TLC monitoring of the reaction and NMR analysis of the crude product. $X_6H_3Tf_3$ **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 Tf_2O 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 ^1H NMR signals in $CDCl_3$ at 25 °C but spectra suitable for signal assignment and structure characterization could be obtained by changing the solvent and/or the temperature.[18] The ^{13}C chemical shifts of the bridging methylene groups indicate that both compounds display a major cone-like conformation (31.5 ppm < δ $^{13}C_{ArCH2}$ < 32.8 ppm for **2** and 31.1 ppm < δ $^{13}C_{ArCH2}$ < 32.4 ppm for **3**).[19] 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 Ar*H* (1:1:1), $ArCH_2$ (2:1) and *t*Bu (2:1) ^1H 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 *t*Bu groups) and attest to an asymmetric substitution pattern at the small rim (Figure 2).[20]



Scheme 1. Synthesis of $X_6H_4Tf_2$ **2** and $X_6H_3Tf_3$ **3** from X_6H_6 **1**. i) Tf_2O (2.5 equiv.), DMAP (2.5 equiv.), CH_2Cl_2, 40 °C, 5h, 71%; ii) Tf_2O (2.5 equiv.), Cs_2CO_3 (4 equiv.), CH_2Cl_2, rt, 3h30, 37%.

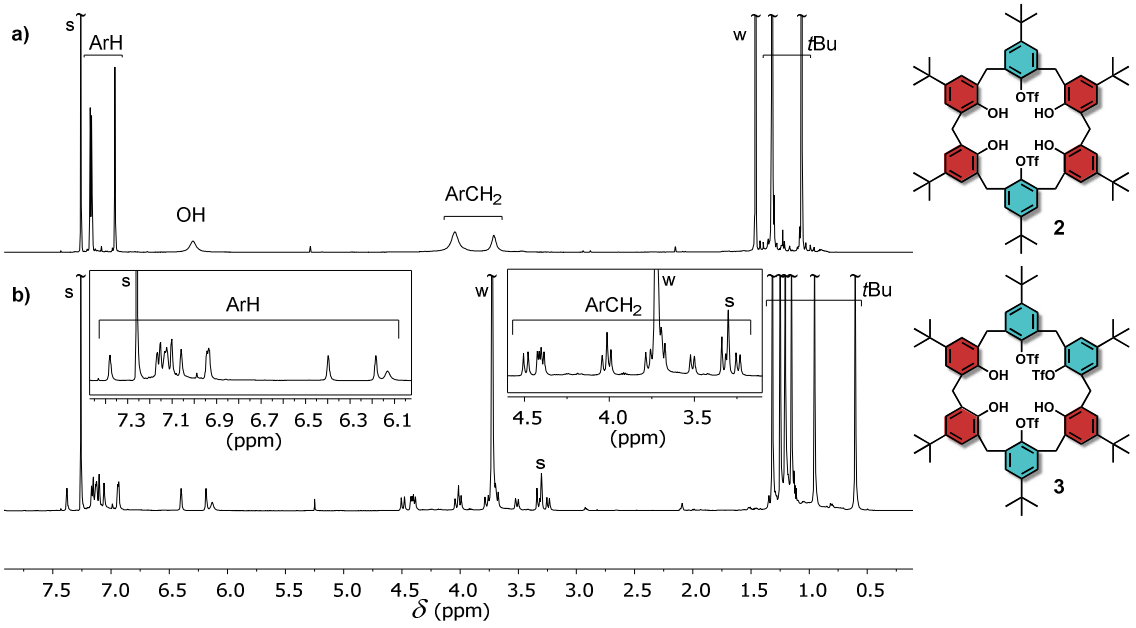


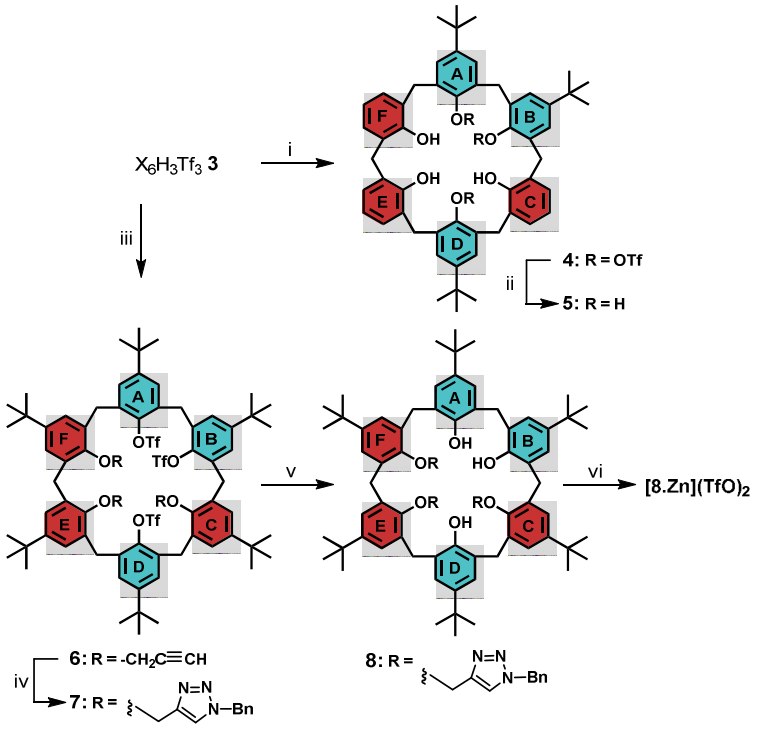
Figure 2. ^{1}H NMR spectra (600MHz) of a) $X_6H_4Tf_2$ **2** in $CDCl_3$ at 80 °C; b) $X_6H_3Tf_3$ **3** in $CDCl_3/CD_3OD$ (9:1) at 5 °C. s = residual solvents; w = residual water.

The synthetic potential of $X_6H_4Tf_2$ **2** and $X_6H_3Tf_3$ **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

(CH_2Cl_2, THF, DMF or 1,4-dioxane). Under all the basic conditions tested (i.e. K_2CO_3, NaH, NaOH, nBu$_4$NOH, 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 X_6H_6 **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, H_2SO_4, HNO_3 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 $AlCl_3$ 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-1*H*-imidazol-2-yl)methanol with **3** in presence of DIAD and PPh_3 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-1*H*-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[21] with BnN_3 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 N_3-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) $AlCl_3$ (12 equiv.), toluene, 40 °C, 10h, 80%; ii) NaOH (1M), 1,4-dioxane, rt, 4 days, 86%. iii) HC≡CCH_2OH (22 equiv.), DIAD (22 equiv.), PPh_2(*p*-PhOMe) (18 equiv.), THF/CH_2Cl_2 (4:1), rt, 36h, 80%; iv) BnN_3 (9 equiv.), $CuSO_4 \cdot 5H_2O$ (3.6 equiv.), sodium ascorbate (7.2 equiv.), CH_2Cl_2/H_2O (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 $CDCl_3$ showed that ligand **8** and the corresponding zinc complex **[8.Zn](TfO)$_2$** have similar diffusion coefficients,[18] 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 ^{1}H NMR spectra of **8** and **[8.Zn](TfO)$_2$** in $CDCl_3$ are rather crowded due to the asymmetric substitution pattern of the calixarene skeleton (Figure 3). Nevertheless, it was possible to assign all the ^{1}H signals through extensive analysis of the corresponding 2D NMR spectra (COSY, HSQC, HMBC).[18] 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).[18] 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 ^{13}C chemical shifts of the bridging methylene groups indicate that the calixarene cores display a major cone-like conformation (28.9 ppm < δ $^{13}C_{ArCH2}$ < 33.1 ppm for **8** and 28.8 ppm < δ $^{13}C_{ArCH2}$ < 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 (δ $^1H_{tBu}$ = 0.24 ppm). In contrast, it is the benzyl group of this unit that folds into the cavity of the complex **[8.Zn](TfO)$_2$** (δ $^1H_{ArH\text{-}Bn}$ = 6.86, 6.47 and 6.34 ppm). Most importantly, the significant down-field shifts observed for the C*H* signals of the triazole units attest to the coordination of the metal center ($\Delta\delta$ $^1H_{CH}$ = 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.[7] Interestingly, preliminary NMR studies showed that ligand **8** was also able to complex Pb^{2+} and Hg^{2+}.[18] Coordination to these metal ions as well as others, and the host-guest properties of the corresponding complexes are currently under investigation.

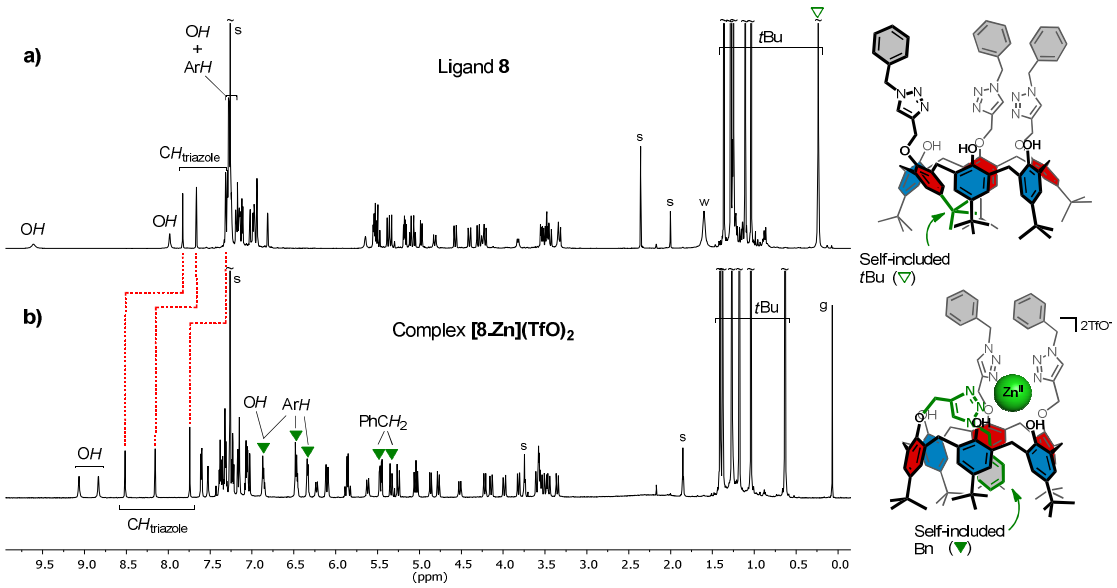


Figure 3. ^{1}H NMR spectra (600MHz, 25 °C) in $CDCl_3$ and of a) ligand **8**; b) complex **[8.Zn](TfO)$_2$** and 3D representation of their conformation in solution. s = residual solvents; w = residual water; g = grease.

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/benzophenone 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*-*t*Bu-calix[6]arene 2. Tf_2O (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_2Cl_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_2Cl_2. Combined organic layers were washed with water, filtrated over Wa filter and concentrated under reduced pressure. Purification by flash chromatography (cyclohexane/CH_2Cl_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_2Cl_2: 60/40). Mp > 260 °C (decomp.). IR (ATR) υ_{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, ArH_{OH}), 7.17 (s, 4H, ArH_{OH}), 6.97 (s, 4H, ArH_{OTf}), 6.30 (br(s), 4H, ArO*H*), 4.06 (br(s), 8H, Ar$_{OTf}$*C*H_2Ar$_{OH}$), 3.71 (br(s), 4H, Ar$_{OH}$*C*H_2Ar$_{OH}$), 1.32 (s, 36H, *t*Bu$_{OH}$), 1.06 (s, 18H, *t*Bu$_{OTf}$). ^{13}C{^{1}H} NMR (150

MHz, $CDCl_3$, 353K): δ (ppm) 151.64, 148.84, 144.83, 142.21, 133.31, 128.81, 128.59, 127.03, 126.34, 119.24 (q, *J* = 318 Hz, 2 CF_3), 34.62, 34.28, 32.96, 32.49, 31.74, 31.09.. HRMS (APCI-): calcd for $C_{68}H_{81}F_6O_{10}S_2$ $[M-H]^-$ 1235.5181, found 1235.5158.

1,2,4-tristriflate-*p*-*t*Bu-calix[6]arene 3. Tf_2O (1.28 mL, 7.70 mmol) was added dropwise to a solution of **1** (3.00 g, 3.08 mmol) and Cs_2CO_3 (4.02 g, 12.3 mmol) in dry CH_2Cl_2 (150 mL). The reaction mixture was then stirred for 3h30 at room temperature and an aqueous solution of HCl (60 mL, 1M) was added. The aqueous layer was extracted with CH_2Cl_2. Combined organic layers were washed with water, filtrated over Wa filter and concentrated under reduced pressure. Purification by flash chromatography (cyclohexane/CH_2Cl_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_2Cl_2; 60:40). Mp = 170 °C. IR (ATR) υ_{max} 2967, 1486, 1405, 1248, 1139, 1069, 874, 770, 663. ^{1}H NMR (600 MHz, $CDCl_3$/CD_3OD, 9:1, v/v, 278K): δ (ppm) 7.38 (s, 1H, Ar*H*), 7.17 (s, 1H, Ar*H*), 7.15 (s, 1H, Ar*H*), 7.13 (s, 1H, Ar*H*), 7.12 (s, 1H, Ar*H*), 7.10 (s, 1H, Ar*H*), 7.06 (s, 1H, Ar*H*), 6.94(3) (s, 1H, Ar*H*), 6.93(6) (s, 1H, Ar*H*), 6.40 (s, 1H, Ar*H*), 6.18 (s, 1H, Ar*H*), 6.13 (br(s), 1H, Ar*H*), 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, *t*Bu), 1.25 (s, 9H, *t*Bu), 1.21 (s, 9H, *t*Bu), 1.15 (s, 9H, *t*Bu), 0.95 (s, 9H, *t*Bu), 0.60 (s, 9H, *t*Bu). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$/CD_3OD, 9:1, v/v, 298K): δ(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, 125.20 (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 ^{13}C NMR signals, only 49 were observed due to some overlapping signals. HRMS (APCI-): calcd for $C_{69}H_{80}F_9O_{12}S_3$ $[M-H]^-$ 1368.4617, found 1368.4674.

1,2,4-tristriflate-1,2,4-tris-*p*-*t*Bu-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_2Cl_2. Combined organic layers were washed with water, filtrated over Wa filter and concentrated under reduced pressure. Purification by flash chromatography (cyclohexane/CH_2Cl_2: gradient from 90/10 to 50/50) afforded **4** (700 mg, 80%) as a pale pink solid. R_f: 0.30 (cyclohexane/CH_2Cl_2: 60/40). Mp = 138-139 °C. IR (ATR) υ_{max} 2965, 1470, 1400, 1212, 1136, 1072, 864, 754, 648, 609. ^{1}H NMR (400 MHz, $CDCl_3$, 298K): δ (ppm) 7.22 - 7.31 (m, Ar*H*, overlapping with residual $CHCl_3$ peak), 6.97-7.20 (m, 7H, Ar*H*), 6.80-6.97 (m, 6H, ArO*H*/Ar*H*), 6.65 (s, 1H, Ar*H*), 5.64 (s, 1H, Ar*OH*), 4.27 (s, 1H, Ar*OH*), 3.5-4.5 (m, 12H, ArCH_2), 1.13 (br(s), 9H, *t*Bu), 1.02 (s, 9H, *t*Bu), 0.97 (br(s), 9H, *t*Bu). HRMS (ESI+): calcd for $C_{57}H_{61}F_9NO_{12}S_3$ $[M+NH_4]^+$ 1218.3207, found 1218.3189.

1,2,4-tris-*p*-*t*Bu-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 CH_2Cl_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 **5** (290 mg, 0.360 mmol, 86% yield) as a pale pink solid. R_f: 0.30 (cyclohexane/CH_2Cl_2: 60/40). Mp = 246 °C. IR (ATR) υ_{max} 2964, 1485, 1468, 1362, 1258, 1205, 874, 751, 670, 638. ^{1}H NMR (300 MHz, $CDCl_3$, 298K): δ (ppm) 10.27-10.65 (m, 6H, ArO*H*), 7.07-7.21 (m, 12H, Ar*H*), 6.77-6.87 (m, 3H, Ar*H*), 3.6-4.2 (m, 12H, Ar*CH*$_2$), 1.19-1.33 (m, 27H, *t*Bu). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 298K): δ (ppm) 149.8, 147.5, 144.6, 129.6, 129.5, 127.8, 127.7, 127.6, 127.0, 126.8(4), 126.7(6), 126.5, 126.3, 121.9, 34.2, 33.0, 32.8, 32.7, 32.4, 31.7, 29.9. HRMS (APCI-): calcd for $C_{54}H_{59}O_6$ $[M-H]^-$ 803.4317, found 803.4269.

1,2,4-tristriflate-3,5,6-tris-propargyl-calix[6]arene 6. Diphenyl(2-methoxyphenyl)phosphine (2.70 g, 9.24 mmol) and DIAD (2.18 mL, 11.1 mmol) were added to a solution of **3** (700 mg, 0.51 mmol) in a dry mixture of THF/CH_2Cl_2 (15 mL, 4:1). After 10 min of stirring, propargyl alcohol was added (650 µL, 11.2 mmol) and the reaction mixture was further 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. 36h). The solvent was removed under reduced pressure and diethyl ether (15 mL) was added to the resulting crude residue in order to remove the diphenyl(2-methoxyphenyl)phosphine oxide that precipitates. The filtrate was concentrated under reduced pressure and the resulting residue was purified by flash chromatography (cyclohexane/CH_2Cl_2: 100/0 then 80/20) to afford **6** (605 mg, 0.408 mmol, 80% yield) as a white solid. R_f: 0.26 (cyclohexane/CH_2Cl_2: 80/20). Mp = 245 °C. IR (ATR) υ_{max} 2955, 1481, 1413, 1364, 147, 1139, 1112, 1068, 85, 770, 613. ^{1}H NMR (400 MHz, $CDCl_3$, 298K): δ (ppm) 7.66 (s, 1H, Ar*H*), 7.48 (s, 1H, Ar*H*), 7.47 (s, 1H, Ar*H*), 7.32 (s, 1H, Ar*H*), 7.30 (m, 2H, Ar*H*), 7.27 (s, 1H, Ar*H*), 7.20 (s, 1H, Ar*H*), 7.95 (s, 1H, Ar*H*), 7.93 (s, 1H, Ar*H*), 7.57 (s, 1H, Ar*H*), 7.56 (s, 1H, Ar*H*), 4.60 (d, 1H, OC*H*$_2$, *J* = 13.8 Hz), 4.27-4.45 (m, 8H, C*H*$_2$), 4.21 (d, 1H, ArC*H*$_2$, *J* = 13.5 Hz), 4.10 (d, 1H, ArC*H*$_2$, *J* = 14.1 Hz), 3.51-3.80 (m, 4H, C*H*$_2$), 3.44 (d, 1H, ArC*H*$_2$, *J* = 14.8 Hz), 3.21 (d, 1H, C*H*$_2$, *J* = 15.3 Hz), 2.89 (d, 1H, OC*H*$_2$, *J* = 14.5 Hz), 2.34-2.62 (m, 3H, C≡C*H*), 1.39 (s, 9H, *t*Bu), 1.38 (s, 9H, *t*Bu), 1.14 (s, 9H, *t*Bu), 1.13 (s, 9H, *t*Bu), 1.07(3) (s, 9H, *t*Bu), 1.06(8) (s, 9H, *t*Bu). HRMS (TOF LD+): calcd for $C_{78}H_{87}F_{90}NaO_{12}S_3$ $[M+Na]^+$ 1505.5108, found 1505.5114.

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 $CuSO_4{\cdot}5H_2O$ (300 mg, 1.20 mmol) was added to a stirred solution of **6** (500 mg, 0.337 mmol) and benzylazide (380 µL, 3.03 mmol) in CH_2Cl_2 (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 CH_2Cl_2 (20 mL) and an aqueous solution of NH_4OH (10 mL, 0.5%) was added. After extraction of the aqueous layer with CH_2Cl_2, the combined organic layers were washed with water, dried by filtration over Wa filter and concentrated under reduced pressure. Purification of the resulting residue by flash chromatography (CH_2Cl_2/MeOH: 100/0 then 98/2) afforded **7** (550 mg, 0.299 mmol, 89% yield). R_f: 0.31 (CH_2Cl_2/MeOH: 98/2). Mp = 135 °C. IR (ATR) υ_{max} 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 $C_{99}H_{109}F_9N_9O_{12}S_3$ $[M+H]^+$ 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_2Cl_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) υ_{max} 2954, 1482, 1362, 1202,, 1119, 991, 875, 818, 649, 628. ^{1}H NMR (600 MHz, $CDCl_3$, 298K): δ (ppm) 9.61 (br(s), 1H, ArO*H*), 7.98 (s, 1H, ArO*H*), 7.83 (s, 1H, CH_{tria}), 7.66 (s, 1H, CH_{tria}), 7.32 (s, 1H, CH_{tria}), 7.23-7.31 (m, ArO*H*/Ar*H,* overlapping with residual $CHCl_3$ peak), 7.13 - 7.21 (m, 4H, Ar*H*), 7.12 (d, 2H, Ar*H*, *J* = 7.2 Hz), 7.02 (d, 1H, Ar*H*, *J* = 2.1 Hz), 6.96-7.00 (m, 3H, Ar*H*), 6.94 (s, 2H, Ar*H*), 6.81 (d, 1H, Ar*H*, *J* = 2.2 Hz), 5.65 (s, 1H, Ar*H*), 5.50-5.57 (m, 3H, Ar*H*, NCH_2), 5.49 (d (AB), 1H, NCH_2, *J* = 14.9 Hz), 5.32-5.40 (m, 2H, NCH_2), 5.14-5.20 (m, 2H, OCH_2, NCH_2), 5.11 (d (AB), 1H, OCH_2, *J* = 11.9 Hz), 5.06 (d (AB), 1H, OCH_2, *J* = 11.9 Hz), 4.98 (d, 1H, OCH_2, *J* = 11.9 Hz), 4.82 (d, 1H, ArCH_2Ar, *J* = 15.2 Hz), 4.57 (d, 1H, ArCH_2Ar, *J* = 16.1 Hz), 4.40 (d, 1H, ArCH_2Ar, *J* = 16.9 Hz), 4.30 (d, 1H, ArCH_2Ar, *J* = 15.7 Hz), 4.19-4.27 (m, 2H, ArCH_2Ar), 3.82 (d, 1H, OCH_2, *J* = 9.8 Hz), 3.41-3.57 (m, 5H, ArCH_2Ar), 3.30-3.37 (m, 2H, ArCH_2Ar, OCH_2), 1.36 (s, 9H, *t*Bu), 1.28 (s, 9H, *t*Bu), 1.25 (s, 9H, *t*Bu), 1.11 (s, 9H, *t*Bu), 1.04 (s, 9H, *t*Bu), 0.24 (s, 9H, *t*Bu). HRMS (ESI+): calcd for $C_{96}H_{112}N_9O_6$ $[M+H]^+$ 1486.8730, found 1486.8626.

Zn-tristriazole-calix[6]arene complex [8.Zn](TfO)$_2$. Ligand **8** (50 mg, 0.034 mmol) was dissolved in dry THF (1.5 mL) and $Zn(OTf)_2$ (12.3 mg, 0.034 mmol) was added. After stirring for 1h at room temperature, pentane (15 mL) was added. The resulting white precipitate was isolated by centrifugation and then dried under vacuum to yield complex **[8.Zn](TfO)$_2$** quantitatively. Mp = 193 °C (decomp.). IR (ATR) υ_{max} 2955, 1482, 1363, 1281, 1226, 1175, 1030, 638, 575. ^{1}H NMR (600 MHz, $CDCl_3$, 298K): δ(ppm) 9.07 (s, 1H, ArO*H*), 8.84 (s, 1H, ArO*H*), 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, ArO*H*, 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_2Ar, *J* = 15.4 Hz), 4.22 (d, 1H , ArCH_2Ar, *J* = 13.0 Hz), 4.14 (d, 1H , ArCH_2Ar, *J* = 15.8 Hz), 3.99 (d, 1H, ArCH_2Ar, *J* = 17.7 Hz), 3.82 (d, 1H, ArCH_2Ar, *J* = 14.0 Hz), 3.52 - 3.62 (m, 4H, ArCH_2Ar), 3.50 (d, 1H, ArCH_2Ar, *J* = 16.1 Hz), 3.46 (d, 1H, ArCH_2Ar, *J* = 15.7

Hz), 3.35 (d, 1H, ArCH_2Ar, J = 14.1 Hz), 1.41 (s, 9H, *t*Bu), 1.38 (s, 9H, *t*Bu), 1.27 (s, 9H, *t*Bu), 1.18 (s, 9H, *t*Bu), 1.04 (s, 9H, *t*Bu), 0.63 (s, 9H, *t*Bu). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, 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, CF_3 from TfO^-), 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, 65.28, 56.27, 56.11, 34.66, 34.46, 34.34, 34.12, 34.08, 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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