JOC The Journal of Organic Chemistry
Article
pubs.acs.org/joc

Tailored Functionalization of Polyphenol-Based Molecular Platforms

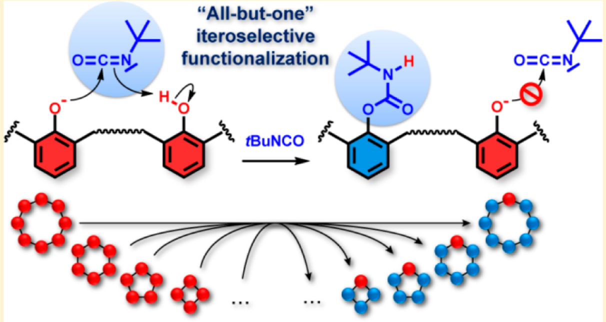
Roy Lavendomme,[†,‡] Axel Leroy,[†,‡] Michel Luhmer,[‡] and Ivan Jabin*[,†]

[†]Laboratoire de Chimie Organique, Université Libre de Bruxelles (ULB), Avenue F.D. Roosevelt 50, CP160/06, B-1050 Brussels, Belgium

[‡]Laboratoire de Résonance Magnétique Nucléaire Haute Résolution, Université Libre de Bruxelles (ULB), Avenue F.D. Roosevelt 50, CP160/08, B-1050 Brussels, Belgium

S Supporting Information

ABSTRACT: General and efficient methods for selective modification of macrocyclic oligomers are rare, mostly because restricting a reaction to a defined number of identical functional groups is difficult to achieve. This work describes a unique, general, and rational methodology for the iteroselective functionalization of polyphenolic platforms by *N-tert*-butylaminocarbonyl (Bac) groups. The methodology consists of reacting the oligomeric platform with *t*-BuNCO and an inorganic base in an apolar solvent. This very simple one-step procedure has been applied to various calix[4, 5, 6, and 8]arenes, and in all cases, calixarenes with a single leftover phenolic moiety were isolated in high yields (>90%). Interestingly, this so-called "all-but-one" methodology gives a straightforward access to calixarenes displaying inherent chirality. It is also shown that the Bac group can be used as a protective group. Thus, the all-but-one methodology has been used for the efficient monofunctionalization of a key precursor platform, illustrating its huge potential for the tailored synthesis of sophisticated macrocyclic oligomers.



■ INTRODUCTION

Macrocyclic oligomers such as cyclodextrins,[1] cucurbiturils,[2] resorcinarenes,[3] pillararenes,[4] and calixarenes[5] are widely used as molecular platforms in supramolecular chemistry and in particular for the design of sensors,[6] catalysts,[7] multivalent systems,[8] biomimetic receptors,[9] etc. In general, the synthesis of such supramolecular systems requires the controlled introduction of functional groups on the precursor platform. However, the development of efficient methods for selective modification of macrocyclic oligomers remains extremely challenging. Indeed, in addition to the control of the classical chemo-, regio-, and stereoselectivities, the reaction of a defined number of identical functional groups is a key issue that must be solved. By analogy with iterative processes, we propose to name "iteroselectivity" such a selectivity that concerns the formation of products (i.e., iteromers) differing by the number of repeating chemical transformations they underwent. High iteroselectivity is often crucial for the functionalization of large oligomers since numerous iteromers can otherwise be formed and their separation by traditional techniques may be precluded. Surprisingly, if examples of iteroselective functionalization of macrocycles have been described,[10] it seems that each type of molecular platform, or even each oligomer of a same family, needs specific considerations. The lack of general methodology is in part due to the lack of electronic and/or spatial couplings which are required to achieve iteroselectivity. In addition, rationalization of the factors governing the selectivity appears to be difficult, preventing the development of general strategies. As an exception, a general and rational tool for the selective monofunctionalization of molecular receptors through an intramolecular thermal Huisgen reaction has been described recently.[11] This iteroselective methodology is based on the recognition ability of a host decorated with azido groups toward an alkynyl guest. This elegant methodology is limited, however, to concave macrocyclic platforms able to encapsulate organic guests.

Herein, we describe a general strategy for the iteroselective modification of all but one phenolic unit of calix[*n*]arenes and propose a rationale for this process. The huge potential of this novel synthetic strategy is illustrated by the monofunctionalization of a key precursor platform which has been achieved efficiently through a straightforward three-step sequence.

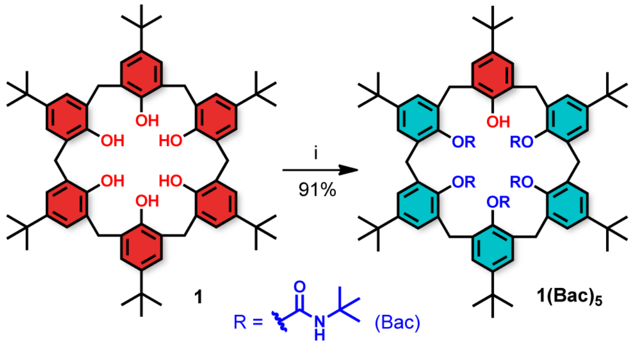
■ RESULTS AND DISCUSSION

In the course of developing new molecular boxes for neutral guests,[12] we were interested in preparing a calix[6]arene perfunctionalized by *N-tert*-butylaminocarbonyl groups (i.e., Bac groups) at the small rim. Hence, *p-tert*-butylcalix[6]arene (**1**) was reacted at room temperature (rt) with an excess of *tert*-butyl isocyanate (*t*-BuNCO) and $Ba(OH)_2$ in CH_2Cl_2. TLC analysis revealed the presence of a single new product besides a degradation product of *t*-BuNCO (i.e., *N,N′*-di-*tert*-butylurea). ESI-MS analysis confirmed the formation of a single iteromer as ultimate product, which surprisingly, was found to be the

Received: May 11, 2014
Published: June 23, 2014

pentafunctionalized derivative **1(Bac)**$_5$. Even after the addition of a larger excess of *t*-BuNCO (up to 21 equiv) and prolonged reaction time (95 h), no trace of the perfunctionalized compound **1(Bac)**$_6$ could be detected by ESI-MS or by ^{1}H NMR analysis of the crude reaction mixture. Similar results were obtained using $Ba(OH)_2 \cdot 8H_2O$ or other inorganic bases (KOH, K_2CO_3) as well as another apolar solvent (toluene). Optimization of the reaction conditions allowed the efficient synthesis of **1(Bac)**$_5$ on a gram scale and in high yield (91%) after purification by flash chromatography (FC) on silica gel (Scheme 1). Because of the coexistence of multiple conformations in slow exchange on the NMR chemical shift time scale, calix[6]arene **1(Bac)**$_5$ displays a complex ^{1}H NMR pattern in apolar solvents ($CDCl_3$, C_6D_6, toluene-d_8, CD_2Cl_2 and $(CDCl_2)_2$ were tested), even at high *T*.[13] However, upon the addition of a few equivalents of DMSO, a well-defined NMR signature corresponding to the host−guest complex **DMSO@1(Bac)**$_5$ was observed and this complex was thoroughly and unambiguously characterized through 1D and 2D NMR studies.[14]

Scheme 1. Highly Iteroselective Synthesis of 1(Bac)$_5$[a]



[a]Key: (i) *t*-BuNCO (18 equiv), $Ba(OH)_2 \cdot 8H_2O$ (2 equiv), CH_2Cl_2, rt, 24 h. Bac = *N*-*tert*-butylaminocarbonyl.

In a further series of experiments, we evaluated the possibility of extending this remarkably iteroselective reaction to other calixarenes. Several oligomers, i.e., calix[4, 5, 6, and 8]arenes **3**−**9**, were tested under similar reaction conditions [i.e., $Ba(OH)_2 \cdot 8H_2O$ (2 equiv), *t*-BuNCO (≥3 equiv/ArOH), CH_2Cl_2, rt] (Scheme 2). *p*-*tert*-Butylcalix[4]arene and its 1,3-dimethylated derivative **2** showed poor solubility under these conditions; however, the reaction could be run with **2** in the presence of NaOH (1.2 equiv) in place of $Ba(OH)_2$.

To our delight, iteroselective functionalization of all but one phenolic moieties of the calix[n]arenes **2**−**9** was readily achieved. Indeed, **2(Bac)**, **3(Bac)**$_3$, **4(Bac)**$_4$, **5(Bac)**$_2$, **6(Bac)**, **7(Bac)**, **8(Bac)**, and **9(Bac)**$_7$ were obtained in high yield as ultimate products (>90% after FC purification).[15] Remarkably, except the perfunctionalized derivative **9(Bac)**$_8$ which was observed at the level of trace by ESI-MS, in all other cases, the perfunctionalized derivative was not detected at all through careful ESI-MS and NMR analysis of the crude reaction mixture. All of the final compounds were successfully characterized by NMR spectroscopy, although, here as well, slow exchange between several conformations was sometimes responsible for intricate spectra.[14] In the case of **3(Bac)**$_3$ and **4(Bac)**$_4$, it was shown by NMR or LC−MS analyses that the reaction yields a mixture of two atropisomers.[14]

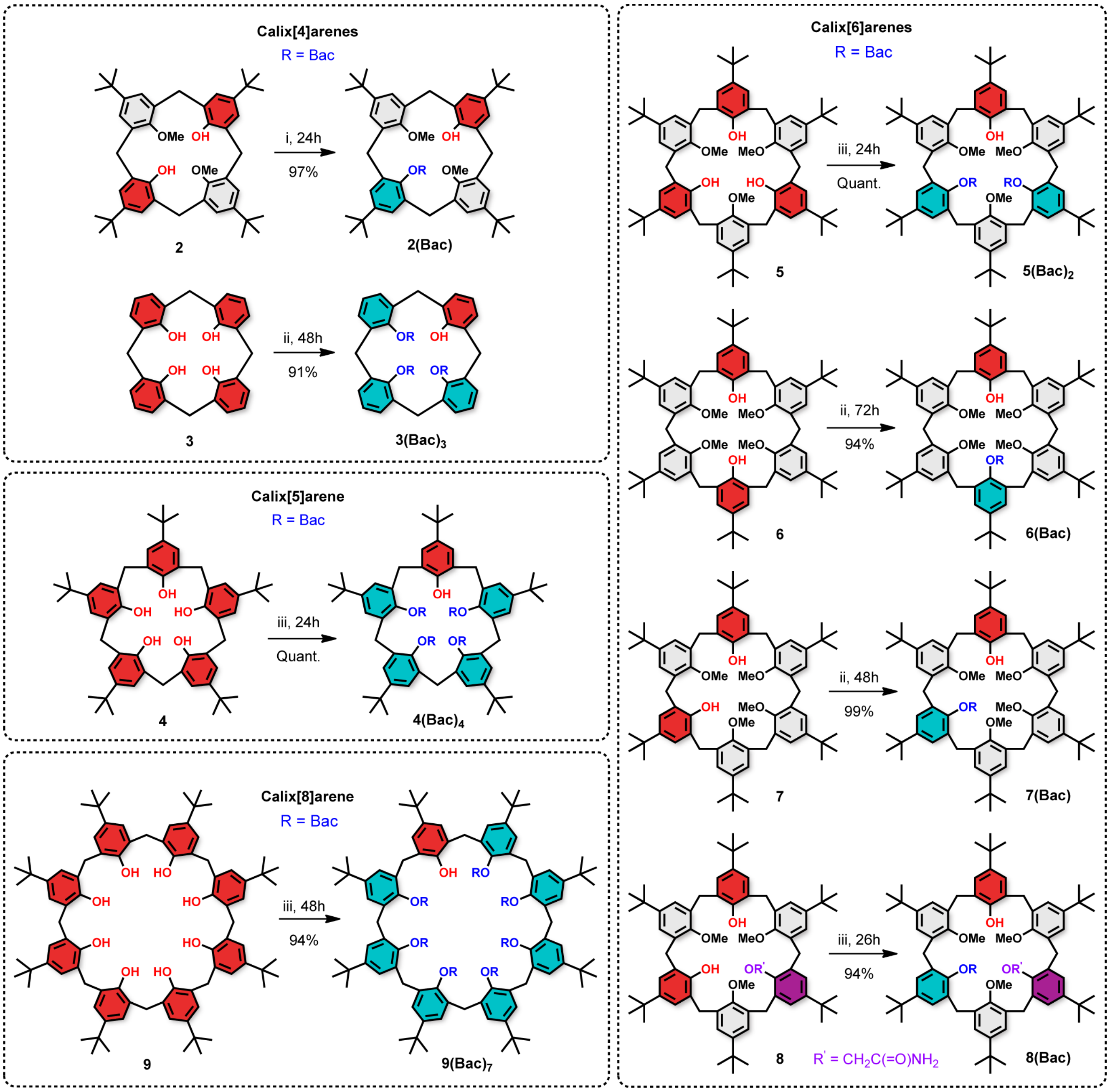
In a second step, experiments were run in order to gain insights into the factors that govern the remarkable selectivity of our "all-but-one" methodology. First, it is noteworthy that the monofunctionalization of 1,3-dialkylcalix[4]arenes with very reactive acyl isocyanates has been described previously.[10d] The selectivity of this reaction was rationalized by a particular conformation of the monocarbamate 1,3-dialkylcalix[4]arene product that involves specific intramolecular H-bonding interactions. Indeed, in this conformation, the remaining hydroxy group is sterically shielded by the bulky acylcarbamate group and thus presents a low reactivity. In good accordance with this explanation, the authors showed that the selective monofunctionalization by acyl isocyanates is specific to 1,3-dialkylcalix[4]arenes, and therefore, the all-but-one selectivity herein described is not expected to share the same grounds.[16] Actually, we propose the iteroselectivity of the all-but-one methodology to be due to a mechanism that involves a concerted proton transfer from the acidic hydroxy group of a phenolic moiety to the isocyanate reacting with a phenolate moiety on the same calixarene (Figure 1). Indeed, if such an internal proton transfer is mandatory, the addition of a phenolate moiety on *t*-BuNCO can take place only if an unreacted phenolic unit is still present on the macrocyclic platform. Hence, the last OH group remains unreacted, leading to the observed iteroselective functionalization of all but one phenolic unit.

This proton assisted mechanism is supported by the following arguments: (i) In apolar solvents such as CH_2Cl_2 or toluene, the development of charges in the transition state at the level of the carbamate group should be highly unfavorable. In such solvents, the internal concerted proton transfer is thus expected to significantly reduce the activation energy of the addition reaction. (ii) The conjugate acids (i.e., H_2O or $KHCO_3$) formed by deprotonation of the calixarene by either $Ba(OH)_2$, KOH, NaOH, or K_2CO_3 are poorly soluble in apolar solvents, and thus, except for the calixarene itself, no other proton donor is present in significant amount in the reaction mixture. Moreover, because of steric effects, the intermolecular proton transfer between two macrocyles is highly disfavored. The important steric hindrance of *t*-BuNCO is also expected to prevent the approach of an external proton donor. (iii) Calixarenes **1**−**9** as well as the intermediates formed in the course of the reaction are macrocyclic platforms displaying multiple H-bond donor groups in close proximity. The binding of the H-bond acceptor *t*-BuNCO might precede the addition reaction, giving the process an intramolecular character.

Actually, the factors that govern the observed iteroselectivity share similarities with those operating in enzymatic systems. To some extent, the calixarene can be seen as a biomimetic macrocyclic platform that can recognize and transform the isocyanate in a rather confined and isolated environment thanks to the assistance of an internal concerted proton transfer.

Additional experiments were carried out to test the proposed mechanism. First, calix[6]arene **1** was reacted under the same conditions as previously described except that MeOH (20 equiv) was added after the formation of **1(Bac)**$_5$. In this case, a small amount of the perfunctionalized derivative **1(Bac)**$_6$ was observed by ESI-MS after 3 h.[14] Another experiment was conducted with **1** in CH_2Cl_2 using EtNCO in place of the bulky *t*-BuNCO. After 7 h, the iteromer **1(Eac)**$_5$ (Eac = *N*-ethylaminocarbonyl) was observed as the major product, but prolonged reaction time (24 h) led ultimately to the formation of the perfunctionalized derivative **1(Eac)**$_6$ (Scheme 3). These

Scheme 2. Extension of the Iteroselective Methodology to Calix[*n*]arenes 2–9[a]



[a]Key: (i) *t*-BuNCO (3 equiv/ArOH), NaOH (1.2 equiv), CH_2Cl_2, rt; (ii) *t*-BuNCO (5 equiv/ArOH), $Ba(OH)_2 \cdot 8H_2O$ (2 equiv), CH_2Cl_2, rt; (iii) *t*-BuNCO (3 equiv/ArOH), $Ba(OH)_2 \cdot 8H_2O$ (2 equiv), CH_2Cl_2, rt. Bac = *N*-*tert*-butylaminocarbonyl.

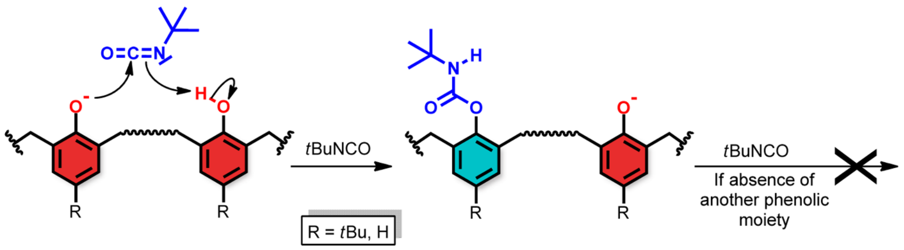
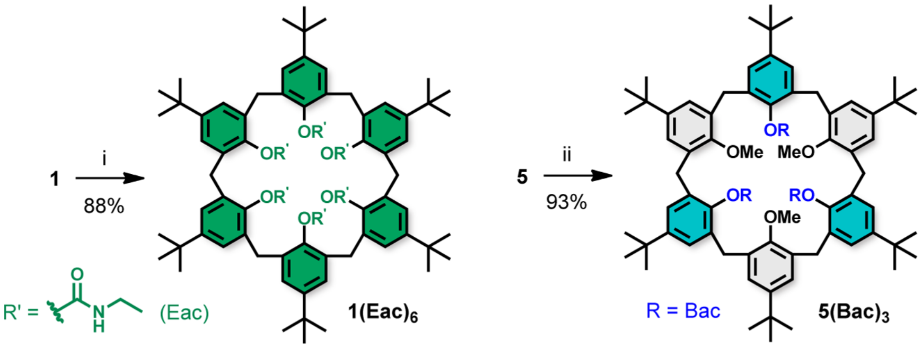


Figure 1. Rationalization of the iteroselectivity of the reaction between calixarenes and *t*-BuNCO.

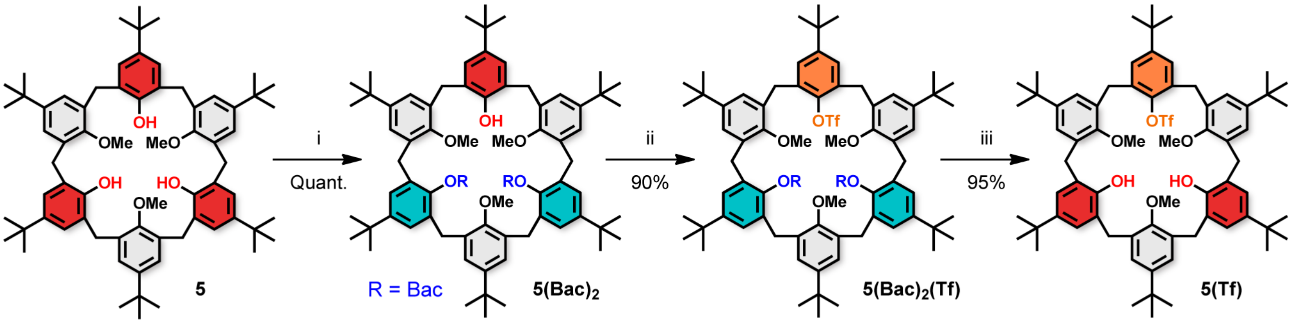
two experiments strongly suggest that the pentafunctionalized compound is first formed through an internal proton assisted mechanism and that the much slower last addition reaction is likely assisted by an external proton donor (i.e., MeOH or

Scheme 3. Perfunctionalization of 1 and 5[a]



[a]Key: (i) EtNCO (18 equiv), $Ba(OH)_2{\cdot}8H_2O$ (2 equiv), CH_2Cl_2, rt, 24 h; (ii) *t*-BuNCO (9 equiv), KOH (1 equiv), DMF, rt, 3 h. Bac = *N*-*tert*-butylaminocarbonyl, Eac = *N*-ethylaminocarbonyl.

Scheme 4. Efficient and Selective Monofunctionalization of 5 through the Three-Step Sequence Consisting of the All-but-One Protection/Functionalization/Deprotection[a]



[a]Key: (i) *t*-BuNCO (9 equiv), $Ba(OH)_2{\cdot}8H_2O$ (2 equiv), CH_2Cl_2, rt, 24 h; (ii) Tf_2O (3 equiv), pyridine (6 equiv), CH_2Cl_2, rt, 5 h; (iii) $MeSO_3H$ (11 equiv), CH_2Cl_2, rt, 20 h. Bac = *N*-*tert*-butylaminocarbonyl.

residual water). It also indicates that the use of a bulky isocyanate is mandatory in order to prevent the protonation by an external proton donor. Finally, calix[6]arene **5** was reacted with *t*-BuNCO under classical conditions [i.e., KOH (1 equiv) or $Ba(OH)_2{\cdot}8H_2O$ (2 equiv), rt] except that the reaction was conducted in anhydrous DMF.[17] As expected, in this polar solvent, the perfunctionalized compound **5(Bac)**$_3$ was isolated in high yield (Scheme 3), highlighting the crucial role played by the solvent.

These results show that the all-but-one methodology can be considered as a general, efficient, and very simple tool for the iteroselective functionalization of calixarenes. Very interestingly, it gives an easy access to calixarenes presenting three different groups (ABC pattern) on the narrow rim, thus of inherent chirality[18] (e.g., **7(Bac)** and **8(Bac)** in Scheme 2). Such chiral calixarenes are currently the subject of intensive studies and their selective synthesis is generally a quite difficult task.[19] Furthermore, using the Bac group as a protecting group, the methodology could be exploited for the selective monofunctionalization of macrocyclic platforms. Indeed, the all-but-one methodology leaves a single unreacted phenolic moiety that can be functionalized in a further step. The subsequent removal of the Bac groups would yield a macrocyclic platform that has been selectively monofunctionalized in a three-step sequence. Moreover, repeating this three-step sequence several times should allow the selective introduction of different functional groups, opening the way to the tailored synthesis of very sophisticated macrocyclic compounds.

The first challenge was to see if a Bac group can be easily removed from a phenolic moiety. For this, the pentafunctionalized derivative **1(Bac)**$_5$ dissolved in CH_2Cl_2 was treated with an excess of various acids or bases, and the formation of the deprotected calix[6]arene **1** was monitored by TLC, ^1H NMR, and ESI-MS analyses. It was found that all of the Bac groups can be cleaved efficiently either in strong basic (MeOK or TBAOH in $MeOH/CH_2Cl_2$, DBU in CH_2Cl_2) or acidic (Tf_2NH, $MeSO_3H$, or TfOH in CH_2Cl_2) conditions. In contrast, the Bac group resists weaker bases (DMAP, TEA, or DIPEA in CH_2Cl_2, and K_2CO_3 in acetone/CH_2Cl_2 or H_2O/CH_2Cl_2) and weaker acids (TFA in CH_2Cl_2). The feasibility of the three-step sequence, i.e., all-but-one protection/functionalization/deprotection, was then evaluated with the 1,3,5-trismethylated calix[6]arene **5** (Scheme 4). It is worth mentioning that only rare examples of monofunctionalization of this key calix[6]arene[20] were described in the literature, and in all cases, the reported methodology was moderately iteroselective.[21] To illustrate the monofunctionalization of **5**, we chose to introduce a triflate group because it can be converted afterward in a large variety of other functional groups.[22] First, the synthesis of **5(Tf)** through the direct reaction of **5** with Tf_2O (pyridine, CH_2Cl_2) was tested but, as expected, a lack of itereroselectivity was observed through ESI-MS monitoring of the reaction. On the contrary, reaction of **5(Bac)**$_2$ with Tf_2O led to **5(Bac)**$_2$**(Tf)** in high yield, and the subsequent removal of the Bac groups by $MeSO_3H$ afforded the desired monofunctionalized calix[6]arene **5(Tf)** in 95% yield after FC purification. **5(Tf)** was thus produced from **5** in an impressive overall yield of 86%, highlighting the efficiency of the three-step sequence and the huge synthetic potential of the all-but-one methodology.

■ CONCLUSION

In conclusion, we have developed a unique and general methodology for the efficient functionalization of all but one phenolic moieties of calixarenes by *N*-*tert*-butylaminocarbonyl (Bac) groups. Remarkably, in all cases, the perfunctionalized products were either not observed or detected in trace quantities. The all-but-one iteroselectivity can be rationalized by an internal proton assisted mechanism which is supported by the results of two complementary experiments. It is noteworthy that such a mechanism is reminiscent of those encountered in natural systems. The methodology can give a straightforward access to calixarenes displaying inherent chirality. Moreover, it was shown that the Bac group can be used as a protective group and thus the methodology constitutes an unrivalled general strategy for the highly selective monofunctionalization of calixarenes. Current efforts are directed toward the extension of the methodology to other polyphenolic platforms (e.g., heteracalixarenes, resorcinarenes, pillararenes, etc.).

■ EXPERIMENTAL SECTION

The reactions were not performed under inert atmosphere unless otherwise stated. Solvents were distilled prior to use. Commercial anhydrous DMF was used. Anhydrous dichloromethane was obtained from distillation over CaH_2. Silica gel (230−400 mesh) was used for flash chromatography. NMR spectra were recorded either at 7.0, 9.4, or 14.1 T. Traces of residual solvents were used as internal standards for ^1H (7.16 ppm for C_6D_5H, 7.26 ppm for $CHCl_3$, and 6.00 ppm for $CDCl_2CHCl_2$) and ^{13}C (128.06 ppm for C_6D_6, 77.16 ppm for $CDCl_3$ and 73.78 ppm for $(CDCl_2)_2$) chemical shift referencing. $CFCl_3$ (0.00 ppm) was used as internal standard for ^{19}F chemical shift referencing. Abbreviations: s, singlet; d, doublet; t, triplet; br, broad signal; m, massif; mult, multiplet. The high-resolution mass spectra were recorded with either TOF or Q-TOF ESI+ spectrometers. Electrospray ionization (ESI) mass spectra and LC−MS chromatograms were recorded with an ESI-MS apparatus coupled with an HPLC and equipped with an ion-trap using the following settings: spray voltage: 5 kV, capillary temperature: 160 °C, capillary voltage: 46 V, tube lens offset voltage: 30 V. C18 HPLC column was used for LC−MS analyses. Melting points (mp) are uncorrected. ATR-FTIR spectra were recorded at room temperature. The starting calixarenes were either commercial (**1**, **3**, **4**, **5**, and **9**) or synthesized according to procedures described in the literature (**2**,[23] **6**,[10a] **7**,[24] and **8**[21c]). Reactions involving *t*-BuNCO led to the formation of *N*,*N*′-di-*tert*-butylurea (identified by NMR spectroscopy), which was separated from the desired product by flash chromatography.

***p-tert*-Butylcalix[6]arene-penta-Bac (1(Bac)$_5$).** Crushed $Ba(OH)_2{\cdot}8H_2O$ (701 mg, 2.22 mmol) was added to a solution of calixarene **1** (1.08 g, 1.11 mmol) in CH_2Cl_2 (55 mL), and the mixture was stirred at room temperature. After 30 min, *t*-BuNCO (2.29 mL, 20.1 mmol) was added, and the mixture was stirred at room temperature for 24 h. CH_2Cl_2 (40 mL) was added, and the mixture was washed with $HCl_{(aq)}$ (0.1 M, 50 mL). The aqueous phase was extracted twice with CH_2Cl_2 (2 × 10 mL). The combined organic layers were concentrated under vacuum. The crude product was purified by flash chromatography [CH_2Cl_2/AcOEt (98:2, v/v)], affording calixarene **1(Bac)**$_5$ (1.49 g, 1.01 mmol) as a white solid. Yield: 91%. R_f [CH_2Cl_2/AcOEt (98:2, v/v)] = 0.43. Mp = 210 °C dec. IR (ATR) ν (cm^{-1}) = 2964, 1749, 1454, 1170. ^1H NMR (600 MHz, C_6D_6/DMSO (99:1, v/v), 298 K) δ (ppm) = 8.72 (s, 1H, $\mathrm{O}H$), 8.00 (s, 1H, $\mathrm{N}H$), 7.59 (d, ^4J = 2.4 Hz, 1H, $\mathrm{Ar}H$), 7.58 (d, ^4J = 2.4 Hz, 1H, $\mathrm{Ar}H$), 7.29 (d, ^4J = 1.8 Hz, 1H, $\mathrm{Ar}H$), 7.28 (d, ^4J = 1.8 Hz, 1H, $\mathrm{Ar}H$), 7.18−7.21 (m, 3H, $\mathrm{Ar}H$), 7.10 (d, ^4J = 2.4 Hz, 1H, $\mathrm{Ar}H$), 7.04 (d, ^4J = 1.8 Hz, 1H, $\mathrm{Ar}H$), 6.92 (d, ^4J = 1.8 Hz, 1H, $\mathrm{Ar}H$), 6.88 (d, ^4J = 1.8 Hz, 1H, $\mathrm{Ar}H$), 6.75 (d, ^4J = 1.8 Hz, 1H, $\mathrm{Ar}H$), 5.19 (s, 1H, $\mathrm{N}H$), 5.15 (s, 1H, $\mathrm{N}H$), 5.11 (s, 1H, $\mathrm{N}H$), 5.06 (s, 1H, $\mathrm{N}H$), 4.78 (d, ^2J = 15.0 Hz, 1H, $\mathrm{ArC}H_2$), 4.48 (d, ^2J = 16.8 Hz, 1H, $\mathrm{ArC}H_2$), 4.36 (d, ^2J = 17.4 Hz, 1H, $\mathrm{ArC}H_2$), 4.30 (d, ^2J = 14.4 Hz, 1H, $\mathrm{ArC}H_2$), 4.01 (d, ^2J = 13.2 Hz, 1H, $\mathrm{ArC}H_2$), 3.96 (d, ^2J = 13.2 Hz, 1H, $\mathrm{ArC}H_2$), 3.88 (d, ^2J = 16.8 Hz, 1H, $\mathrm{ArC}H_2$), 3.85 (d, ^2J = 13.2 Hz, 1H, $\mathrm{ArC}H_2$), 3.83 (d, ^2J = 13.2 Hz, 1H, $\mathrm{ArC}H_2$), 3.79 (d, ^2J = 17.4 Hz, 1H, $\mathrm{ArC}H_2$), 3.49 (d, ^2J = 15.0 Hz, 1H, $\mathrm{ArC}H_2$), 3.33 (d, ^2J = 14.4 Hz, 1H, $\mathrm{ArC}H_2$), 1.60 (s, 9H, N-*t*-Bu), 1.49 (s, 9H, N-*t*-Bu), 1.46 (s, 9H, N-*t*-Bu), 1.44 (s, 9H, Ar-*t*-Bu), 1.37 (s, 9H, Ar-*t*-Bu), 1.30 (s, 9H, N-*t*-Bu), 1.26(4) (s, 9H, Ar-*t*-Bu), 1.26(0) (s, 9H, N-*t*-Bu), 1.13 (s, 9H, Ar-*t*-Bu), 1.07 (s, 9H, Ar-*t*-Bu), 1.06 (s, 9H, Ar-*t*-Bu), 0.26 (br, 3H, 1 Me $\mathrm{DMSO_{in}}$), −0.21 (br, 3H, 1 Me $\mathrm{DMSO_{in}}$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$/DMSO (99:1, v/v), 298 K) δ (ppm) = 154.1, 153.2, 152.6, 151.8(4), 151.7(6), 149.6, 147.9, 147.7, 147.0, 146.9, 146.8, 146.7, 145.6, 145.4, 144.9, 144.7, 141.6, 135.4, 135.2, 133.6, 133.3, 133.1, 132.6, 132.5, 132.0, 131.6, 130.1, 128.8, 128.7, 128.2, 127.9, 127.8, 127.7, 126.5, 125.9, 125.7, 124.3, 124.2, 123.9, 123.2, 122.7, 51.5, 51.2, 51.0, 50.9, 50.2, 35.4, 35.3, 34.6, 34.5, 34.2(4), 34.1(6), 34.1(4), 34.1(0), 31.8(8), 31.8(5), 31.8, 31.7, 31.6, 31.3, 29.8, 29.5, 29.1, 29.0, 28.6. HRMS (ESI+): calcd for $C_{91}H_{129}N_5O_{11}Na$ $[M + Na]^+$ 1490.9586, found 1490.9586.

***p-tert*-Butylcalix[6]arene-hexa-Eac (1(Eac)$_6$).** Crushed $Ba(OH)_2{\cdot}8H_2O$ (65.4 mg, 0.207 mmol) was added to a solution of calixarene **1** (99.7 mg, 0.102 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred at room temperature. After 30 min, EtNCO (146 μL, 1.84 mmol) was added, and the mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated under vacuum. The crude product was purified by flash chromatography [CH_2Cl_2/AcOEt (3:1, v/v)] affording calixarene **1(Eac)**$_6$ (126 mg, 0.0900 mmol) as a white solid. Yield: 88%. R_f [CH_2Cl_2/AcOEt (3:1, v/v)] = 0.30. Mp = 236 °C dec. IR (ATR) ν (cm^{-1}) = 2956, 1732, 1479, 1187. ^1H NMR (600 MHz, $CDCl_3$, 248 K) δ (ppm) = 7.42 (s, 2H, $\mathrm{Ar}H$), 7.24−7.32 (m, 4H, $\mathrm{Ar}H$), 6.62 (s, 2H, $\mathrm{Ar}H$), 6.58 (s, 2H, $\mathrm{Ar}H$), 6.46 (s, 2H, $\mathrm{Ar}H$), 6.16 (s, 2H, $\mathrm{N}H$), 5.31 (s, 2H, $\mathrm{N}H$), 5.07 (s, 1H, $\mathrm{N}H$), 4.24 (d, ^2J = 15.8 Hz, 2H, $\mathrm{ArC}H_2$), 4.03 (d, ^2J = 14.9 Hz, 2H, $\mathrm{ArC}H_2$), 3.97 (d, ^2J = 15.7 Hz, 2H, $\mathrm{ArC}H_2$), 3.22−3.57 (m, 10H, $\mathrm{ArC}H_2$ and $\mathrm{NC}H_2$), 2.90 (t, ^3J = 5.9 Hz, 1H, $\mathrm{N}H$), 1.41 (t, ^3J = 7.1 Hz, 6H, $\mathrm{NCH_2C}H_3$), 1.39 (s, 9H, *t*-Bu), 1.33 (s, 18H, *t*-Bu), 1.17−1.22 (m, 9H, $\mathrm{NCH_2C}H_3$), 1.07 (mult., 2H, $\mathrm{NC}H_2$), 0.81 (s, 18H, *t*-Bu), 0.76 (s, 9H, *t*-Bu), −1.65 (mult., 3H, $\mathrm{NCH_2C}H_3$). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, 298 K) δ (ppm) = 155.2, 155.1, 154.5, 154.4, 148.2, 147.6, 145.6, 144.4, 133.4, 132.4, 132.2, 132.1, 131.6, 129.4, 128. 4, 127.5, 124.7, 123.3, 121.9, 36.4, 35.3, 34.7, 34.5, 34.2, 31.7, 31.2, 31.1, 29.6, 28.9, 16.0, 15.3, 12.8. HRMS (ESI+): calcd for $C_{84}H_{114}N_6O_{12}Na$ $[M + Na]^+$ 1421.8392, found 1421.8429.

***p-tert*-Butylcalix[4]arene-1,3-dimethyl-2-mono-Bac (2(Bac)).** Freshly crushed NaOH (10 mg, 0.25 mmol) was added to a solution of calixarene **2** (138 mg, 0.204 mmol) in CH_2Cl_2 (10 mL) and the mixture was stirred at room temperature. After 30 min, *t*-BuNCO (139 μL, 1.22 mmol) was added and the mixture was stirred at room temperature for 24h. The reaction mixture was concentrated under vacuum. The crude product was purified by flash chromatography [CH_2Cl_2/AcOEt (98:2, v/v)] affording calixarene **2(Bac)** (154 mg, 0.198 mmol) as a white solid. Yield: 97%. R_f [CH_2Cl_2/AcOEt (98:2, v/v)] = 0.48. Mp = 229−240 °C (sublimation). IR (ATR) ν (cm^{-1}) = 2962, 1739, 1483, 1183. ^1H NMR (600 MHz, $CDCl_3$, 298 K) δ (ppm) = 7.18 (s, 2H, $\mathrm{Ar}H$), 7.10 (s, 2H, $\mathrm{Ar}H$), 6.99 (s, 1H, $\mathrm{O}H$), 6.66 (s, 1H, $\mathrm{N}H$), 6.55 (d, ^4J = 2.1 Hz, 2H, $\mathrm{Ar}H$), 6.54 (d, ^4J = 2.1 Hz, 2H, $\mathrm{Ar}H$), 4.26 (d, ^2J = 13.4 Hz, 2H, $\mathrm{ArC}H_2^{ax}$), 4.23 (d, ^2J = 13.0 Hz, 2H, $\mathrm{ArC}H_2^{ax}$), 3.82 (s, 6H, OMe), 3.31 (d, ^2J = 13.4 Hz, 2H, $\mathrm{ArC}H_2^{eq}$), 3.25 (d, ^2J = 13.0 Hz, 2H, $\mathrm{ArC}H_2^{eq}$), 1.55 (s, 9H, N-*t*-Bu), 1.34(4) (s, 9H, Ar-*t*-Bu), 1.33(7) (s, 9H, Ar-*t*-Bu), 0.81 (s, 18H, Ar-*t*-Bu). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, 298 K) δ (ppm) = 154.0, 152.1, 150.7, 147.8, 146.1, 145.4, 141.6, 135.86, 131.95, 131.80, 128.16, 125.46, 125.41, 125.25, 125.05, 62.95, 49.83, 34.41, 34.00, 33.85, 31.90, 31.77, 31.50, 31.21, 31.10, 29.27. HRMS (ESI+): calcd for $C_{51}H_{70}NO_5$ $[M + H]^+$ 776.5254, found 776.5258.

Calix[4]arene-tris-Bac (3(Bac)$_3$). Crushed $Ba(OH)_2{\cdot}8H_2O$ (190 mg, 0.602 mmol) was added to a solution of calixarene **3** (125 mg, 0.294 mmol) in CH_2Cl_2 (6 mL), and the mixture was stirred at room temperature. After 30 min, *t*-BuNCO (688 μL, 6.02 mmol) was added, and the mixture was stirred at room temperature for 48 h. The mixture was washed with HCl_{aq} (0.1 M, 15 mL). The aqueous phase was washed twice by CH_2Cl_2 (2x 2 mL). The combined organic layers were concentrated under vacuum. The crude product was purified by flash chromatography [CH_2Cl_2/AcOEt (98:2 then 96:4, v/v)], affording two atropisomers of calixarene **3(Bac)$_3$** as white solids, i.e., **3(Bac)$_3$-cone** (44.1 mg, 0.0611 mmol, yield 21%) and **3(Bac)$_3$-partial-cone** (150 mg, 0.208 mmol, yield 70%).

3(Bac)$_3$-cone. R_f [CH_2Cl_2/AcOEt (98:2, v/v)] = 0.26. Mp = 270–285 °C (sublimation). IR (ATR) ν (cm^{-1}) = 1731, 1532, 1456, 1187. ^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ (ppm) = 7.25 (d, ^3J = 7.7 Hz, 2H, Ar*H*), 7.08–7.12 (m, 3H, Ar*H*), 6.77 (t, ^3J = 7.5 Hz, 1H, Ar*H*), 6.74 (br, 2H, Ar*H*), 6.63–6.70 (m, 4H, Ar*H*), 6.18 (br, 2H), 5.44 (br, 1H), 5.28 (s, 1H, O*H*), 4.05 (d, ^2J = 14.0 Hz, 2H, ArCH_2^{ax}), 4.04 (d, ^2J = 13.5 Hz, 2H, ArCH_2^{ax}), 3.47 (d, ^2J = 14.0 Hz, 2H, ArCH_2^{eq}), 3.38 (d, ^2J = 13.5 Hz, 2H, ArCH_2^{eq}), 1.46 (s, 9H, *t*-Bu), 1.43 (s, 18H, *t*-Bu). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 298 K) δ (ppm) = 153.4, 153.2, 153.0, 147.2, 145.1, 136.0, 133.8, 132.7, 130.0, 129.6, 128.9, 128.7, 128.2, 126.8, 125.7, 120.3, 51.2, 50.8, 32.2, 31.2, 29.3, 28.9. HRMS (ESI+): calcd for $C_{43}H_{51}N_3O_7Na$ $[M + Na]^+$ 744.3619, found 744.3615.

3(Bac)$_3$-partial-cone. R_f [CH_2Cl_2/AcOEt (98:2, v/v)] = 0.17. Mp = 215–220 °C. IR (ATR) ν (cm^{-1}) = 1738, 1455, 1174. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 7.21 (d, ^3J = 7.5 Hz, 2H, Ar*H*), 7.05–7.11 (m, 3H, Ar*H*), 6.96–7.03 (m, 4H, Ar*H*), 6.88 (t, ^3J = 7.5 Hz, 2H, Ar*H*), 6.76 (t, ^3J = 7.5 Hz 1H, Ar*H*), 5.24 (s, 1H, O*H*), 5.10 (s, 2H, N*H*), 3.83 (d, ^2J = 14.5 Hz, 2H, ArCH_2^{ax}), 3.81 (d, ^2J = 15.6 Hz, 2H, ArCH_2), 3.76 (d, ^2J = 15.6 Hz, 2H, ArCH_2), 3.67 (s, 1H, N*H*), 3.53 (d, ^2J = 14.5 Hz, 2H, ArCH_2^{eq}), 1.41 (s, 18H, *t*-Bu), 1.33 (s, 9H, *t*-Bu). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 298 K) δ (ppm) = 152.7, 151.6, 151.0, 148.5, 146.8, 135.3, 134.3, 133.4, 129.7, 129.5, 129.3, 129.1, 128.0, 125.1, 124.0, 119.6, 50.8, 50.5, 37.7, 33.2, 29.1, 29.0. HRMS (ESI+): calcd for $C_{43}H_{52}N_3O_7$ $[M + H]^+$ 722.3800, found 722.3796.

***p-tert*-Butylcalix[5]arene-tetra-Bac (4(Bac)$_4$).** Crushed Ba(OH)$_2$·8H_2O (168 mg, 0.536 mmol) was added to a solution of calixarene **4** (220 mg, 0.271 mmol) in CH_2Cl_2 (13 mL), and the mixture was stirred at room temperature. After 30 min, *t*-BuNCO (456 μL, 4.00 mmol) was added, and the mixture was stirred at room temperature for 24 h. CH_2Cl_2 (7 mL) was added, and the mixture was washed by $HCl_{(aq)}$ (0.1 M, 10 mL). The aqueous phase was washed twice by CH_2Cl_2 (2 × 5 mL). The combined organic layers were concentrated under vacuum. The crude product was purified by flash chromatography [CH_2Cl_2/AcOEt (98:2, v/v)], affording calixarene **4(Bac)$_4$** (326 mg, 0.270 mmol) as a white solid in quantitative yield. It is noteworthy to mention that the isolated product **4(Bac)$_4$** is actually a 72:28 mixture of two atropisomers according to LC–MS analysis (Figure S92, Supporting Information). The major one corresponds to the cone atropisomer and has been fully characterized by NMR spectroscopy, while the minor one could not be characterized. R_f [CH_2Cl_2/AcOEt (98:2, v/v)] = 0.44. Mp = 191–196 °C. IR (ATR) ν (cm^{-1}) = 2963, 1746, 1478, 1177. ^{1}H NMR (600 MHz, $CDCl_3$, 323 K) δ (ppm) (cone atropisomer) = 7.23 (s, 2H, Ar*H*), 7.21 (d, ^4J = 2.2 Hz, 2H, Ar*H*), 7.17 (s, 2H, Ar*H*), 6.69 (s, 2H, Ar*H*), 6.60 (s, 2H, Ar*H*), 5.48 (s, 2H, N*H*), 5.23 (s, 2H, N*H*), 4.38 (s, 1H, O*H*), 4.14 (d, ^2J = 15.4 Hz, 2H, ArCH_2^{ax}), 4.10 (d, ^2J = 14.3 Hz, 2H, ArCH_2^{ax}), 3.95 (d, ^2J = 14.2 Hz, 1H, ArCH_2^{ax}), 3.45 (d, ^2J = 15.4 Hz, 2H, ArCH_2^{eq}), 4.38 (d, ^2J = 14.3 Hz, 2H, ArCH_2^{eq}), 3.27 (d, ^2J = 14.2 Hz, 1H, ArCH_2^{eq}), 1.47 (s, 18H, N-*t*-Bu), 1.37–1.39 (m, 27H, N-*t*-Bu and Ar-*t*-Bu), 1.27 (s, 18H, Ar-*t*-Bu), 0.72 (s, 18H, Ar-*t*-Bu). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 298 K) δ (ppm) (cone atropisomer) = 153.0, 150.2, 148.0, 147.9, 144.5, 143.4, 143.1, 133.9, 133.2, 133.0, 132.0, 127.1, 127.0, 126.3, 126.2, 124.7, 124.0, 51.0, 50.9, 34.4, 34.2, 34.1, 31.8, 31.5, 31.4, 31.1, 29.9, 28.9, 28.8. HRMS (ESI+): calcd for $C_{75}H_{107}N_4O_9$ $[M + H]^+$ 1207.8038, found 1207.8059.

***p-tert*-Butylcalix[6]arene-1,3,5-trimethyl-2,4-di-Bac 5(Bac)$_2$.** Crushed Ba(OH)$_2$·8H_2O (735 mg, 2.33 mmol) was added to a solution of calixarene **5** (1.19 g, 1.17 mmol) in CH_2Cl_2 (50 mL), and the mixture was stirred at room temperature. After 30 min, *t*-BuNCO (1.20 mL, 10.5 mmol) was added, and the mixture was stirred at room temperature for 24 h. CH_2Cl_2 (50 mL) was added, and the mixture was washed by $HCl_{(aq)}$ (0.1 M, 50 mL). The aqueous phase was washed twice by CH_2Cl_2 (2 × 10 mL). The combined organic layers were concentrated under vacuum. The crude product was purified by flash chromatography [CH_2Cl_2/AcOEt (98:2, v/v)], affording calixarene **5(Bac)$_2$** (1.42 g, 1.17 mmol) as a white solid. Quantitative yield. R_f [CH_2Cl_2/AcOEt (98:2, v/v)] = 0.51. Mp = 196–200 °C. IR (ATR) ν (cm^{-1}) = 2961, 1746, 1481, 1174. ^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ (ppm) = 8.54 (s, 1H, O*H*), 7.22 (s, 2H, Ar*H*), 7.18 (s, 2H, Ar*H*), 7.12 (d, ^4J = 2.2 Hz, 2H, Ar*H*), 7.05 (d, ^4J = 1.9 Hz, 2H, Ar*H*), 6.78 (s, 2H, Ar*H*), 6.12 (s, 2H, Ar*H*), 5.45 (s, 2H, N*H*), 4.25 (d, ^2J = 13.8, 2H, ArCH_2^{ax}), 4.18 (d, ^2J = 15.3, 2H, ArCH_2^{ax}), 4.10 (d, ^2J = 15.2, 2H, ArCH_2^{ax}), 3.72 (s, 3H, OMe), 3.53 (d, ^2J = 15.2, 2H, ArCH_2^{eq}), 3.46 (d, ^2J = 15.3, 2H, ArCH_2^{eq}), 3.41 (d, ^2J = 13.8, 2H, ArCH_2^{eq}), 2.81 (s, 6H, OMe), 1.46 (s, 18H, N-*t*-Bu), 1.26 (s, 18H, Ar-*t*-Bu), 1.22 (s, 18H, Ar-*t*-Bu), 1.03 (s, 9H, Ar-*t*-Bu), 0.20 (s, 9H, Ar-*t*-Bu). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 298 K) δ (ppm) = 153.8, 153.3, 149.7, 148.3, 146.9, 145.6, 145.4, 142.3, 134.3, 133.9, 133.5, 132.0, 127.1, 126.6, 126.3, 126.1, 124.7, 124.1, 61.3, 60.8, 50.9, 34.6 (2), 34.5 (9), 34.2, 33.8, 31.8 (2), 31.7 (6), 31.7 (3), 31.6 (8), 31.0, 30.9, 29.3. HRMS (ESI+): calcd for $C_{79}H_{108}N_2O_8Na$ $[M + Na]^+$ 1235.8003, found 1235.8004.

***p-tert*-Butylcalix[6]arene-1,3,5-trimethyl-2,4,6-tri-Bac (5(Bac)$_3$).** Freshly crushed KOH (6.0 mg, 0.11 mmol) and calixarene **5** (103 mg, 0.101 mmol) were solubilized in anhydrous DMF (5.5 mL) under inert atmosphere, and the mixture was stirred at room temperature. After 30 min, *t*-BuNCO (105 μL, 0.920 mmol) was added, and the mixture was stirred at room temperature for 3 h. Water (5 mL) was added, and the mixture was filtered. The resulting precipitate was dried under vacuum and purified by flash chromatography [CH_2Cl_2/acetone (99:1, v/v)], affording calixarene **5(Bac)$_3$** (124 mg, 0.0945 mmol) as a white solid. Yield: 94%. R_f [CH_2Cl_2/acetone (98:2, v/v)] = 0.36. Mp = 209–213 °C. IR (ATR) ν (cm^{-1}) = 2963, 1748, 1480, 1173. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 7.29 (s, 6H, Ar*H*), 6.67 (s, 6H, Ar*H*), 5.15 (s, 3H, N*H*), 4.31 (d, ^2J = 15.4 Hz, 6H, ArCH_2^{ax}), 4.43 (d, ^2J = 15.4 Hz, 6H, ArCH_2^{eq}), 2.23 (s, 9H, OMe), 1.39 (s, 27H, N-*t*-Bu), 1.37 (s, 27H, Ar-*t*-Bu), 0.80 (s, 27H, Ar-*t*-Bu). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 298 K) δ (ppm) = 154.2, 152.8, 147.5, 146.5, 143.7, 133.7, 132.8, 128.3, 123.6, 60.5, 50.9, 34.4, 34.2, 31.7, 31.2, 29.6, 29.0. HRMS (ESI+): calcd for $C_{84}H_{118}N_3O_9$ $[M + H]^+$ 1312.8863, found 1312.8831.

***p-tert*-Butylcalix[6]arene-1,3,5-trimethyl-2,4-di-Bac-6-mono-triflyl (5(Bac)$_2$(Tf)).** Pyridine (97 μL, 1.2 mmol) and triflic anhydride (101 μL, 0.603 mmol) were added to a solution of calixarene **5(Bac)$_2$** (243 mg, 0.200 mmol) in anhydrous CH_2Cl_2 (10 mL), and the mixture was stirred at room temperature for 5 h. The mixture was washed with $HCl_{(aq)}$ (0.1 M, 30 mL), and the organic layer was concentrated under vacuum to afford 276 mg of an orange solid. Further purification is not required to proceed to the next step to synthesize calixarene **5(Tf)**. Purification of a fraction (30.2 mg) of this solid was done by flash chromatography [CH_2Cl_2] affording calixarene **5(Bac)$_2$(Tf)** (26.5 mg, 0.0197 mmol) as a white solid. Yield: 90%. R_f [CH_2Cl_2/AcOEt (98:2, v/v)] = 0.70. Mp = 189–192 °C. IR (ATR) ν (cm^{-1}) = 2962, 1748, 1481, 1212, 1173. ^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ (ppm) = 7.33 (s, 2H, Ar*H*), 7.28 (s, 2H, Ar*H*), 7.25–7.27 (signal masked by residual $CHCl_3$, Ar*H*), 6.75 (s, 2H, Ar*H*), 6.69 (s, 2H, Ar*H*), 6.66 (s, 2H, Ar*H*), 5.19 (s, 2H, N*H*), 4.45 (d, ^2J = 15.6 Hz, 2H, ArCH_2^{ax}), 4.26–4.32 (m, 4H, ArCH_2^{ax}), 3.62 (d, ^2J = 15.6 Hz, 2H, ArCH_2^{eq}), 3.45 (d, ^2J = 15.9 Hz, 2H, ArCH_2^{eq}), 3.42 (d, ^2J = 15.8 Hz, 2H, ArCH_2^{eq}), 2.33 (s, 6H, OMe), 2.18 (s, 3H, OMe), 1.39 (s, 18H, N-*t*-Bu), 1.38 (s, 18H, Ar-*t*-Bu), 1.35 (s, 9H, Ar-*t*-Bu), 0.81 (s, 18H, Ar-*t*-Bu), 0.79 (s, 9H, Ar-*t*-Bu). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 298 K) δ (ppm) = 154.4, 154.2, 152.8, 150.4, 147.5, 146.7, 146.4, 143.8, 134.5, 133.8, 133.4, 133.0, 132.8, 131.8, 129.0, 128.1, 125.3, 123.8, 123.1, 60.4, 60.3, 50.9, 34.5, 34.4, 34.2, 31.7, 31.2, 31.0, 30.8, 29.7, 29.4, 28.9. ^{19}F NMR (376 MHz, $CDCl_3$, 298 K) δ (ppm) = −73.71.

HRMS (ESI+): calcd for $C_{80}H_{107}F_3N_2O_{10}SNa$ $[M + Na]^+$ 1367.7491, found 1367.7488.

***p-tert*-Butylcalix[6]arene-1,3,5-trimethyl-2-monotriflyl (5(Tf)).** Methanesulfonic acid (56 μL, 0.86 mmol) was added to a solution of crude **5(Bac)$_2$(Tf)** (115 mg) in CH_2Cl_2 (4 mL), and the mixture was stirred at room temperature for 20 h. The mixture was washed with $K_2CO_{3(aq)}$ (1 M, 5 mL), and the organic phase was concentrated under vacuum. The mixture was purified by flash chromatography [CH_2Cl_2] affording calixarene **5(Tf)** (82.4 mg, 0.0718 mmol) as a white solid. Yield: 95%. Overall yield from **5(Bac)$_2$**: 86%. R_f [CH_2Cl_2/AcOEt (98:2, v/v)] = 0.70. Mp = 152−156 °C. IR (ATR) ν (cm^{-1}) = 2961, 1483, 1210. ^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ (ppm) = 7.07 (s, 2H, Ar*H*), 7.06 (d, ^4J = 2.0 Hz, 2H, Ar*H*), 6.98 (s, 2H, Ar*H*), 6.97 (d, ^4J = 1.9 Hz, 2H, Ar*H*), 6.93−6.95 (m, 4H, Ar*H*), 6.89 (s, 2H, O*H*), 3.69−4.50 (br/m, 12H, ArCH_2), 3.64 (s, 6H, OMe), 3.05 (br, 3H, OMe), 1.21 (s, 18H, *t*-Bu), 1.15 (s, 9H, *t*-Bu), 1.12 (s, 9H, *t*-Bu), 1.03 (s, 18H, *t*-Bu). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 298 K) δ (ppm) = 152.8, 152.7, 151.3, 150.0, 147.0, 146.9, 142.4, 142.2, 134.0, 132.9, 132.6, 132.0, 127.0, 126.8, 126.5, 126.1(4), 126.0(8), 126.0(6), 125.9, 125.7, 61.3, 61.2, 34.5, 34.3, 34.2, 34.0, 31.7, 31.6, 31.4, 31.3, 31.2, 31.1. ^{19}F NMR (376 MHz, $CDCl_3$, 298 K) δ (ppm) = −74.00. HRMS (ESI+): calcd for $C_{70}H_{90}F_3O_8S$ $[M + H]^+$ 1147.6303, found 1147.6306.

***p-tert*-Butylcalix[6]arene-1,2,4,5-tetramethyl-3-mono-Bac (6(Bac)).** First, starting material **6** has been recrystallized from chloroform/methanol in order to improve its solubility in CH_2Cl_2. Crushed $Ba(OH)_2\cdot 8H_2O$ (64.3 mg, 0.204 mmol) was added to a solution of calixarene **6** (104 mg, 0.101 mmol) in CH_2Cl_2 (3 mL), and the mixture was stirred at room temperature. After 30 min, *t*-BuNCO (116 μL, 1.02 mmol) was added, and the mixture was stirred at room temperature for 72 h. The reaction mixture was washed with HCl_{aq} (0.1 M, 5 mL), and the organic layer was concentrated under vacuum. The crude product was purified by flash chromatography [CH_2Cl_2/acetone (98:2, v/v)], affording 107 mg of a 93:7 mixture of calixarene **6(Bac)** (0.0887 mmol) and starting material **6** (0.0067 mmol) as a white solid. Further separation of these two compounds could not be achieved. Yield: 94% based on the conversion of **6**. R_f [CH_2Cl_2/acetone (98:2, v/v)] = 0.38. Mp = 169−178 °C (mixture). IR (ATR) ν (cm^{-1}) = 2960, 1747, 1481, 1174. ^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ (ppm) = 7.68 (s, 1H, O*H*), 7.04−7.07 (m, 4H, Ar*H*), 6.95 (s, 2H, Ar*H*), 6.94 (d, ^4J = 1.7 Hz, 2H, Ar*H*), 6.89 (s, 2H, Ar*H*), 6.88 (s, 2H, Ar*H*), 5.37 (s, 1H, N*H*), 4.25 (d, ^2J = 14.9 Hz, 2H, ArCH_2^{ax}), 4.15 (d, ^2J = 14.8 Hz, 2H, ArCH_2^{ax}), 4.06 (d, ^2J = 14.8 Hz, 2H, ArCH_2^{ax}), 3.64 (d, ^2J = 14.9 Hz, 2H, ArCH_2^{eq}), 3.63 (d, ^2J = 14.8 Hz, 2H, ArCH_2^{eq}), 3.48 (d, ^2J = 14.8 Hz, 2H, ArCH_2^{eq}), 3.24 (s, 6H, OMe), 2.90 (s, 6H, OMe), 1.37 (s, 9H, N-*t*-Bu), 1.15 (s, 18H, Ar-*t*-Bu), 1.14 (s, 18H, Ar-*t*-Bu), 1.13 (s, 9H, Ar-*t*-Bu), 0.99 (s, 9H, Ar-*t*-Bu). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 298 K) δ (ppm) = 154.4, 153.1, 149.7, 147.2, 146.7, 145.9, 144.7, 142.0, 133.8(4), 133.7(8), 133.4, 132.7(0), 132.6(8), 127.1, 126.6, 126.5, 126.3, 125.7, 124.9, 124.8, 61.2, 60.8, 50.6, 34.3 (0), 34.2 (6), 34.2, 34.0, 31.6 (2), 31.5 (6), 31.5, 31.3, 31.2, 30.7, 29.0. HRMS (ESI+): calcd for $C_{75}H_{102}NO_7$ $[M + H]^+$ 1128.7651, found 1128.7625.

***p-tert*-Butylcalix[6]arene-1,2,3,5-tetramethyl-3-mono-Bac (7(Bac)).** Crushed $Ba(OH)_2\cdot 8H_2O$ (63.9 mg, 0.203 mmol) was added to a solution of calixarene **7** (104 mg, 0.101 mmol) in CH_2Cl_2 (3 mL), and the mixture was stirred at room temperature. After 30 min, *t*-BuNCO (116 μL, 1.02 mmol) was added, and the mixture was stirred at room temperature for 48 h. The reaction mixture was washed with HCl_{aq} (0.1 M, 5 mL), and the organic layer was concentrated under vacuum. The crude product was purified by flash chromatography [CH_2Cl_2/acetone (98:2, v/v)], affording calixarene **7(Bac)** (113 mg, 0.100 mmol) as a white solid. Yield: 99%. R_f [CH_2Cl_2/acetone (98:2, v/v)] = 0.35. Mp = 168−172 °C. IR (ATR) ν (cm^{-1}) = 2961, 1748, 1481, 1174. ^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ = 7.69 (s, 1H, O*H*), 7.17 (s, 1H, Ar*H*), 7.13 (s, 1H, Ar*H*), 7.10 (d, ^4J = 2.2 Hz, 1H, Ar*H*), 7.04 (s, 1H, Ar*H*), 7.03 (s, 1H, Ar*H*), 7.01 (s, 1H, Ar*H*), 6.98 (s, 2H, Ar*H*), 6.93 (d, ^4J = 2.0 Hz, 1H, Ar*H*), 5.40 (s, 1H, N*H*), 4.23−4.31 (m, 2H, ArCH_2^{ax}), 4.18 (d, ^2J = 14.4 Hz, 1H, ArCH_2^{ax}), 4.11 (d, ^2J = 14.8 Hz, 1H, ArCH_2^{ax}), 4.04 (d, ^2J = 14.7 Hz, 1H, ArCH_2^{ax}), 3.96 (d, ^2J = 15.4 Hz, 1H, ArCH_2^{ax}), 3.65−3.71 (m, 2H, ArCH_2^{eq}), 3.60−3.65 (m, 4H, OMe + ArCH_2^{eq}), 3.57 (d, ^2J = 15.4 Hz, 1H, ArCH_2^{eq}), 3.53 (d, ^2J = 14.4 Hz, 1H, ArCH_2^{eq}), 3.44 (d, ^2J = 14.8 Hz, 1H, ArCH_2^{eq}), 3.36 (s, 3H, OMe), 2.91 (s, 3H, OMe), 2.60 (s, 3H, OMe), 1.43 (s, 9H, N-*t*-Bu), 1.28 (s, 9H, Ar-*t*-Bu), 1.18 (s, 9H, Ar-*t*-Bu), 1.16(3) (s, 9H, Ar-*t*-Bu), 1.15(5) (s, 9H, Ar-*t*-Bu), 1.11 (s, 9H, Ar-*t*-Bu), 0.72 (s, 9H, Ar-*t*-Bu). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 298 K) δ (ppm) = 154.8, 153.7, 153.6, 153.3, 152.7, 149.7, 147.7, 146.8, 146.5, 146.1, 145.3, 145.1, 142.0, 134.0, 133.8, 133.7, 133.4, 133.1, 132.6, 132.4, 132.2, 127.3, 127.0, 126.9, 126.6, 126.3, 125.9, 125.7, 125.5, 125.1, 125.0, 124.8, 124.6, 61.3, 60.9, 60.8, 60.6, 50.6, 34.4, 34.3 (4), 34.3 (2), 34.2 (8), 33.9 (9), 33.9 (6), 31.9, 31.8, 31.7, 31.5 (9), 31.5 (6), 31.5, 31.2, 31.1, 31.0, 30.3, 29.0. HRMS (ESI+): calcd for $C_{75}H_{101}NO_7Na$ $[M + Na]^+$ 1150.7476, found 1150.7474.

***p-tert*-Butylcalix[6]arene-1,3,5-trimethyl-2-monoamide-4-mono-Bac (8(Bac)).** Crushed $Ba(OH)_2\cdot 8H_2O$ (33.0 mg, 0.105 mmol) was added to a solution of calixarene **8** (54.6 mg, 0.0509 mmol) in CH_2Cl_2 (2.5 mL), and the mixture was stirred at room temperature. After 1 h, *t*-BuNCO (35 μL, 0.30 mmol) was added, and the mixture was stirred at room temperature for 26 h. The reaction mixture was concentrated under vacuum. The crude product was purified by flash chromatography [CH_2Cl_2/AcOEt (4:1, v/v)], affording calixarene **8(Bac)** (56.4 mg, 0.0481 mmol) as a pale orange solid. Yield: 94%. R_f [CH_2Cl_2/AcOEt (19:1, v/v)] = 0.41. Mp = 190 °C dec. IR (ATR) ν (cm^{-1}) = 2961, 1683, 1481, 1200. ^{1}H NMR (600 MHz, $(CDCl_2)_2$, 353 K): δ (ppm) = 7.34 (d, ^4J = 2.0 Hz, 1H, Ar*H*), 7.27 (d, ^4J = 2.3 Hz, 1H, Ar*H*), 7.21−7.25 (m, 2H, Ar*H*), 7.15 (d, ^4J = 2.2 Hz, 1H, Ar*H*), 7.14 (s, 1H, O*H*), 7.12 (d, ^4J = 2.1 Hz, 1H, Ar*H*), 7.08 (d, ^4J = 2.1 Hz, 1H, Ar*H*), 6.96 (br, 1H, Ar*H*), 6.60 (br, 1H), 6.53 (s, 1H, Ar*H*), 6.39 (br, 1H, Ar*H*), 6.32 (br, 1H, Ar*H*), 6.09 (br, 1H, Ar*H*), 4.72 (br, 2H), 4.37 (d, ^2J = 16.2 Hz, 1H, ArCH_2), 4.16 (d, ^2J = 15.8 Hz, 1H, ArCH_2), 4.12 (d, ^2J = 14.3 Hz, 1H, ArCH_2), 4.11 (d, ^2J = 15.9 Hz, 1H, ArCH_2), 4.05 (d, ^2J = 16.3 Hz, 1H, ArCH_2), 3.94 (s, 3H, OMe), 3.87 (d, ^2J = 15.8 Hz, 1H, ArCH_2), 3.76 (br, 3H, OMe), 3.67 (d, ^2J = 14.4 Hz, 1H, ArCH_2), 3.65 (d, ^2J = 16.4 Hz, 1H, ArCH_2), 3.60 (d, ^2J = 16.4 Hz, 1H, ArCH_2), 3.57 (d, ^2J = 15.9 Hz, 1H, ArCH_2), 3.52 (s, 3H, OMe), 3.20 (br, 2H, OCH_2C(O)N), 1.42 (s, 9H, Ar-*t*-Bu), 1.40 (s, 9H, Ar-*t*-Bu), 1.38 (s, 9H, N-*t*-Bu), 1.35 (s, 9H, Ar-*t*-Bu), 1.06−1.11 (m, 18H, Ar-*t*-Bu), 0.75 (s, 9H, Ar-*t*-Bu).^{13}C{^{1}H} NMR (100 MHz, $(CDCl_2)_2$, 353 K) δ (ppm) = 170.8, 153.6, 153.4, 153.1, 152.9, 149.8, 147.4, 147.2, 147.0, 146.1, 145.6, 145.5, 142.5, 134.6, 133.6, 133.5, 133.1, 132.7, 132.6, 132.4, 132.0, 131.4, 131.3, 128.1, 128.0, 127.4, 126.7, 126.4, 125.9, 125.6, 125.3, 125.1 (1), 125.0 (6), 124.1, 124.0, 123.9, 71.7, 61.2, 59.8, 58.8, 50.0, 34.0, 33.9, 33.8, 33.6 (6), 33.6 (5), 31.5, 31.4, 31.3, 31.1, 31.0, 30.8, 29.5, 28.7. HRMS (ESI+): calcd for $C_{76}H_{103}N_2O_8$ $[M + H]^+$ 1171.7714, found 1171.7711.

***p-tert*-Butylcalix[8]arene-hepta-Bac 9(Bac)$_7$.** Crushed $Ba(OH)_2\cdot 8H_2O$ (62.1 mg, 0.197 mmol) was added to a solution of calixarene **9** (127 mg, 0.0979 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred at room temperature. After 1 h, *t*-BuNCO (268 μL, 2.35 mmol) was added, and the mixture was stirred at room temperature for 48 h. The reaction mixture was concentrated under vacuum. The crude product was purified by flash chromatography [CH_2Cl_2/AcOEt (99:1, v/v)], affording calixarene **9(Bac)$_7$** (184 mg, 0.0924 mmol) as a white solid. Yield: 94%. R_f [CH_2Cl_2/AcOEt (99:1, v/v)] = 0.30. Mp = 221 °C (dec). IR (ATR) ν (cm^{-1}) = 2967, 1748, 1456, 1174. ^{1}H NMR (400 MHz, $(CDCl_2)_2$, 398 K) δ (ppm) = 7.18 (s, 2H, Ar*H*), 6.96−7.07 (m, 10H, Ar*H*), 6.90−6.96 (m, 4H, Ar*H*), 5.67 (s, 1H, O*H*), 4.89 (s, 2H, N*H*), 4.86 (s, 2H, N*H*), 4.79 (s, 1H, N*H*), 4.77 (s, 2H, N*H*), 3.76−3.87 (m, 16H, ArCH_2), 1.39 (s, 9H, *t*-Bu), 1.38 (s, 18H, *t*-Bu), 1.35 (s, 9H, *t*-Bu), 1.34 (s, 18H, *t*-Bu), 1.32 (s, 18H, *t*-Bu), 1.18−1.21 (m, 45H, *t*-Bu), 1.13 (s, 18H, *t*-Bu). HRMS (ESI+): calcd for $C_{123}H_{175}N_7O_{15}Na$ $[M + Na]^+$ 2013.3044, found 2013.3051.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

1D and 2D NMR spectra of all new compounds; LC−MS and ESI−MS analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ijabin@ulb.ac.be.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

R.L. is a Ph.D. student granted by the Fonds pour la Formation à la Recherche dans l'Industrie et dans l'Agriculture (FRIA-FRS, Belgium). This research was supported by the Fonds de la recherche scientifique-FNRS (FRFC 2.4.617.10.F project), the COST Action 1005 "Supramolecular Chemistry in Water", and the Université Libre de Bruxelles (ULB).

■ REFERENCES

(1) Szejtli, J. *Chem. Rev.* **1998**, *98*, 1743−1753.

(2) Lagona, J.; Mukhopadhyay, P.; Chakrabarti, S.; Isaacs, L. *Angew. Chem. Int. Ed.* **2005**, *44*, 4844−4870.

(3) Timmerman, P.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1996**, *52*, 2663−2704.

(4) (a) Ogoshi, T.; Kunai, S.; Fujinami, S.; Yamagishi, T.; Nakamoto, Y. *J. Am. Chem. Soc.* **2008**, *130*, 5022−5023. (b) Xue, M.; Yang, Y.; Chi, X.; Zhang, Z.; Huang, F. *Acc. Chem. Res.* **2012**, *45*, 1294−1308.

(5) Gutsche, C. D. In *Calixarenes: An introduction, 2nd Ed., Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 2008.

(6) (a) de Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515−1566. (b) *New Trends in Fluorescence Spectroscopy: Applications to Chemical and Life Sciences*; Valeur, B., Brochon, J.-C., Eds., Springer: Berlin, 2001.

(7) (a) Vriezema, D. M.; Cormelass Aragonés, M.; Elemans, J. A. A. W.; Cornelissen, J. J. L. M.; Rowan, A. E.; Nolte, R. J. M. *Chem. Rev.* **2005**, *105*, 1445−1489. (b) *Supramolecular Catalysis*; Van Leeuwen, P. W. N. M., Ed.; Wiley-VCH: Weinheim, 2008. (c) Nandi, P.; Tang, W.; Okrut, A.; Kong, X.; Hwang, S.-J.; Neurock, M.; Katz, A. *Proc. Natl. Acad. Sci. U.S.A.* **2013**, *110*, 2484−2489.

(8) (a) Badjić, J. D.; Nelson, A.; Cantrill, S. J.; Turnbull, W. B.; Stoddart, J. F. *Acc. Chem. Res.* **2005**, *38*, 723−732. (b) Ludden, M. J. W.; Reinhoudt, D. N.; Huskens, J. *Chem. Soc. Rev.* **2006**, *35*, 1122−1134. (c) Baldini, L.; Casnati, A.; Sansone, F.; Ungaro, R. *Chem. Soc. Rev.* **2007**, *36*, 254−266.

(9) *Bioinspiration and Biomimicry in Chemistry*; Swiegers, G., Ed.; Wiley-VCH: Weinheim, 2012.

(10) (a) Janssen, R. G.; Verboom, W.; Reinhoudt, D. N.; Casnati, A.; Freriks, M.; Pochini, A.; Ugozzoli, F.; Ungaro, R.; Nieto, P. M.; Carramolino, M.; Cuevas, F.; Prados, P.; De Mendoza, J. *Synthesis* **1993**, *1993*, 380−386. (b) Irwin, J. L.; Sherburn, M. S. *J. Org. Chem.* **2000**, *65*, 602−605. (c) Narumi, F.; Morohashi, N.; Matsumura, N.; Nobuhiko, I.; Kameyama, H.; Miyano, S. *Tetrahedron Lett.* **2002**, *43*, 621−625. (d) Yakovenko, A. V.; Boyko, V. I.; Kushnir, O. V.; Tsymbal, I. F.; Lipkowski, J.; Shivanyuk, A.; Kalchenko, V. I. *Org. Lett.* **2004**, *6*, 2769−2772. (e) Bistri, O.; Sinaÿ, P.; Sollogoub, M. *Chem. Commun.* **2006**, 1112−1114. (f) Le Gac, S.; Marrot, J.; Jabin, I. *Chem.—Eur. J.* **2008**, *14*, 3316−3322. (g) Itzhak, N.; Biali, S. E. *J. Org. Chem.* **2010**, *75*, 3437−3442. (h) Gomez-Biagi, R.; Nitz, M. *Chem. Commun.* **2011**, *47*, 8614−8616. (i) Slavik, P.; Dudic, M.; Flidrova, K.; Sykora, J.; Cisarova, I.; Bohm, S.; Lhotak, P. *Org. Lett.* **2012**, *14*, 3628−3631. (j) Galli, M.; Berrocal, J. A.; Di Stefano, S.; Cacciapaglia, R.; Mandolini, L.; Baldini, L.; Casnati, A.; Ugozzoli, F. *Org. Biomol. Chem.* **2012**, *10*, 5109−5112. (k) Jouffroy, M.; Armspach, D.; Matt, D.; Toupet, L. *Org. Biomol. Chem.* **2013**, *11*, 3699−3705. (l) Iwamoto, K.; Yanagi, A.; Araki, K.; Shinkai, S. *Chem. Lett.* **1991**, 473−476.

(11) (a) Colasson, B.; Reinaud, O. *J. Am. Chem. Soc.* **2008**, *130*, 15226−15227. (b) Menard, N.; Reinaud, O.; Colasson, B. *Chem.—Eur. J.* **2013**, *19*, 642−653. (c) Inthasot, A.; Dang Thy, M.-D.; Lejeune, M.; Fusaro, L.; Reinaud, O.; Luhmer, M.; Colasson, B.; Jabin, I. *J. Org. Chem.* **2014**, *79*, 1913−1919.

(12) Ménand, M.; Leroy, A.; Marrot, J.; Luhmer, M.; Jabin, I. *Angew. Chem., Int. Ed.* **2009**, *48*, 5509−5512.

(13) **1(Bac)**$_5$ is quasi-insoluble in standard polar solvents.

(14) See the Supporting Information.

(15) The separation of calixarenes **6** and **6(Bac)** by FC could not be achieved, and **6(Bac)** was isolated in presence of 7% of **6** (see the Supporting Information). The reported yield (94%) was calculated by taking into account the actual conversion of **6** (93%).

(16) We nevertheless ran experiments to check if the conditions reported for the selective monofunctionalization of 1,3-dialkylcalix[4]arenes could lead to a selective functionalization with a larger oligomer. Thus, calix[6]arene **5** was reacted with trichloroacetyl isocyanate (9 equiv) in the presence of Et_3N (cat.) in benzene at rt. Unsurprisingly, these reaction conditions led to the perfunctionalization of compound **5** (ESI-MS analysis). Furthermore, no reaction took place when trichloroacetyl isocyanate was replaced by *t*-BuNCO [*t*-BuNCO (9 equiv), Et_3N (cat.), benzene, rt]. These results clearly show that the selectivity of our all-but-one methodology and the selectivity of the previously reported monofunctionalization of 1,3-dialkylcalix[4]arenes have distinct origins.

(17) Because of solubility problems, the experiments in DMF were conducted with calix[6]arene **5** in place of **1**.

(18) Dalla Cort, A.; Mandolini, L.; Pasquini, C.; Schiaffino, L. *New J. Chem.* **2004**, *28*, 1198−1199.

(19) (a) Szumna, A. *Chem. Soc. Rev.* **2010**, *39*, 4274−4285. (b) Li, S.-Y.; Xu, Y.-W.; Liu, J.-M.; Su, C.-Y. *Int. J. Mol. Sci.* **2011**, *12*, 429−455. (c) Zheng, Y.-S.; Luo, J. *J. Inclusion Phenom. Macrocycl. Chem.* **2011**, *71*, 35−56.

(20) (a) Arduini, A.; Credi, A.; Faimani, G.; Massera, C.; Pochini, A.; Secchi, A.; Semeraro, M.; Silvi, S.; Ugozzoli, F. *Chem.—Eur. J.* **2008**, *14*, 98−106. (b) Ménand, M.; Jabin, I. *Org. Lett.* **2009**, *11*, 673−676. (c) Ménand, M.; Jabin, I. *Chem.—Eur. J.* **2010**, *16*, 2159−2169. (d) Bistri, O.; Colasson, B.; Reinaud, O. *Chem. Sci.* **2012**, *3*, 811−818. (e) Mattiuzzi, A.; Marcélis, L.; Jabin, I.; Moucheron, C.; Kirsch-De Mesmaeker, A. *Inorg. Chem.* **2013**, *52*, 11228−11236.

(21) (a) Sénèque, O.; Reinaud, O. *Tetrahedron* **2003**, *59*, 5563−5568. (b) Rondelez, Y.; Li, Y.; Reinaud, O. *Tetrahedron Lett.* **2004**, *45*, 4669−4672. (c) Darbost, U.; Zeng, X.; Giorgi, M.; Jabin, I. *J. Org. Chem.* **2005**, *70*, 10552−10560.

(22) For leading examples in the field of calixarenes, see: (a) Al-Saraierh, H.; Miller, D. O.; Georghiou, P. *J. Org. Chem.* **2005**, *70*, 8273−8280. (b) Molad, A.; Goldberg, I.; Vigalok, A. *J. Am. Chem. Soc.* **2012**, *134*, 7290−7292.

(23) Wang, W.-G.; Zheng, Q.-Y.; Huang, Z.-T. *Synth. Commun.* **1999**, *29*, 3711−3718.

(24) Otsuka, H.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1994**, *59*, 1542−1547.