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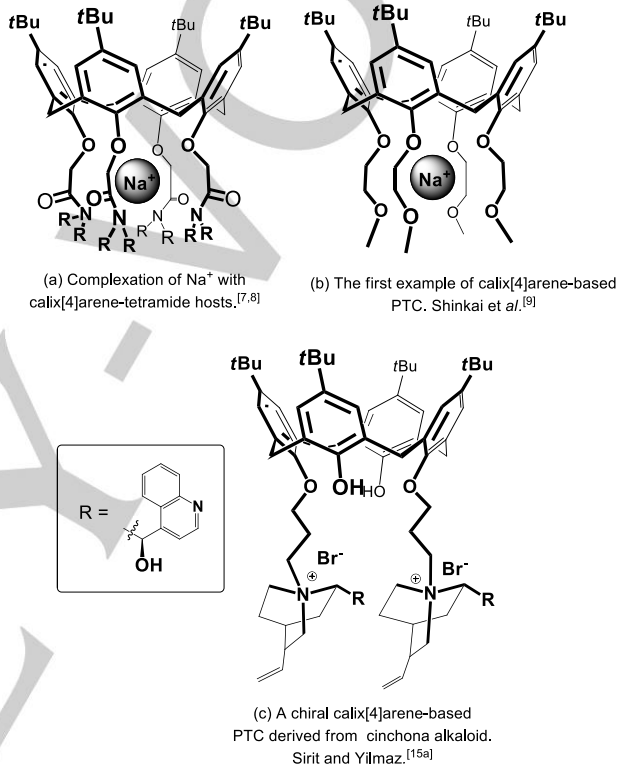
# Directing the Cation Recognition Ability of Calix[4]arenes Toward Asymmetric Phase-Transfer Catalysis

Nicola Alessandro De Simone,[a] Rosaria Schettini,[a] Carmen Talotta,[a] Carmine Gaeta,[a] Irene Izzo,[a] Giorgio Della Sala,*[a] and Placido Neri*[a]

**Abstract:** The recognition abilities of chiral calixarene hosts toward alkali cation guests have been exploited for the first time in asymmetric phase-transfer catalysis. The binding affinities of a series of chiral α-methylbenzylamine-derived calix[4]arene-amides toward $Na^+$ guest have been determined by $^1H$ NMR titration experiments. The good apparent association constant values are consistent with the macrocycles' catalytic efficiency in the asymmetric alkylation of *N*-(diphenylmethylene)-glycine esters under phase-transfer conditions.

## Introduction

Calix[*n*]arenes[1] are a well-known class of macrocyclic compounds which have been largely exploited in the last decades due to their particular three-dimensional shape and ease of functionalization.[2] The synthetic versatility of calixarene macrocycles makes them suitable for a wide range of applications including molecular recognition and sensing,[3] synthesis of interpenetrated architectures,[4] biomolecular recognition,[5] and catalysis.[6] It has long been known that calix[4]arene-amide hosts show a high affinity towards alkali metal cations.[7,8] The studies conducted by Arnaud-Neu *et al.*[8] showed that, among the alkali metal cations series, $Na^+$ was the best extracted cation (Figure 1a).[7] These cation-recognition abilities of calixarene-amides have been particularly exploited in sensing devices[7a,c-e] for the detection of metal ions and for the extraction of alkali picrates,[8] whereas their employment in phase transfer catalysis has surprisingly remained elusive. About thirty years ago, in pioneering works, Shinkai[9] and Taniguchi[10] reported some examples of PTC[11] exploiting the cation-complexing abilities of calixarene-ether derivatives (Figure 1b). Since then, however, this approach has been neglected.[12] Surprisingly, even if calix[4]arene-tetramides are better hosts for alkali-metal cations with respect to calixarene-ethers,[7,8] the PTC abilities of calix-amide derivatives have been totally disregarded.




(a) Complexation of $Na^+$ with calix[4]arene-tetramide hosts.[7,8]

(b) The first example of calix[4]arene-based PTC. Shinkai et *al.*[9]

(c) A chiral calix[4]arene-based PTC derived from cinchona alkaloid. Sirit and Yilmaz.[15a]

**Figure 1.** Examples of calix[4]arene-based phase-transfer catalysts.

Recently, through a different approach, some examples of calixarene-based PTC have been proposed,[6b,13] in which the macrocycle acts as a scaffold bearing quaternary ammonium groups, that are the actual phase-transfer catalysts (Figure 1c).[13a-f]

The development of enantioselective reactions using a PTC protocol is a task of great importance because of the possibility to obtain optically active molecules of biological and pharmaceutical interest.[14] In this regard, the synthesis of optically active α-amino acids via an asymmetric PTC protocol with chiral calixarene-ammonium catalysts has been investigated in the last decade.[15] Thus, Sirit[15a] and co-workers designed a chiral calix[4]arene, bearing at the lower rim two ammonium pendant groups derived from cinchona alkaloid, as a phase–transfer catalyst for the enantioselective synthesis of α-amino acids. Analogously, Su[15d] and Shimizu[15b,c] reported calix[4]arene-based phase-transfer catalysts, bearing cationic pendant groups at the lower and the upper rim respectively, for the enantioselective α-functionalization of glycine. Surprisingly, no examples of asymmetric phase-transfer catalysis exploiting

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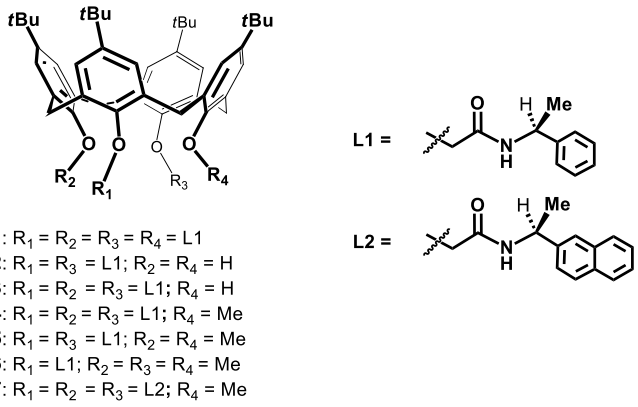
the cation-recognition abilities of chiral calixarene-amide hosts have been reported to date.




**1**: $R_1 = R_2 = R_3 = R_4 = L1$
**2**: $R_1 = R_3 = L1$; $R_2 = R_4 = H$
**3**: $R_1 = R_2 = R_3 = L1$; $R_4 = H$
**4**: $R_1 = R_2 = R_3 = L1$; $R_4 = Me$
**5**: $R_1 = R_3 = L1$; $R_2 = R_4 = Me$
**6**: $R_1 = L1$; $R_2 = R_3 = R_4 = Me$
**7**: $R_1 = R_2 = R_3 = L2$; $R_4 = Me$

**Figure 2.** Calix[4]arene-amides employed in this study.

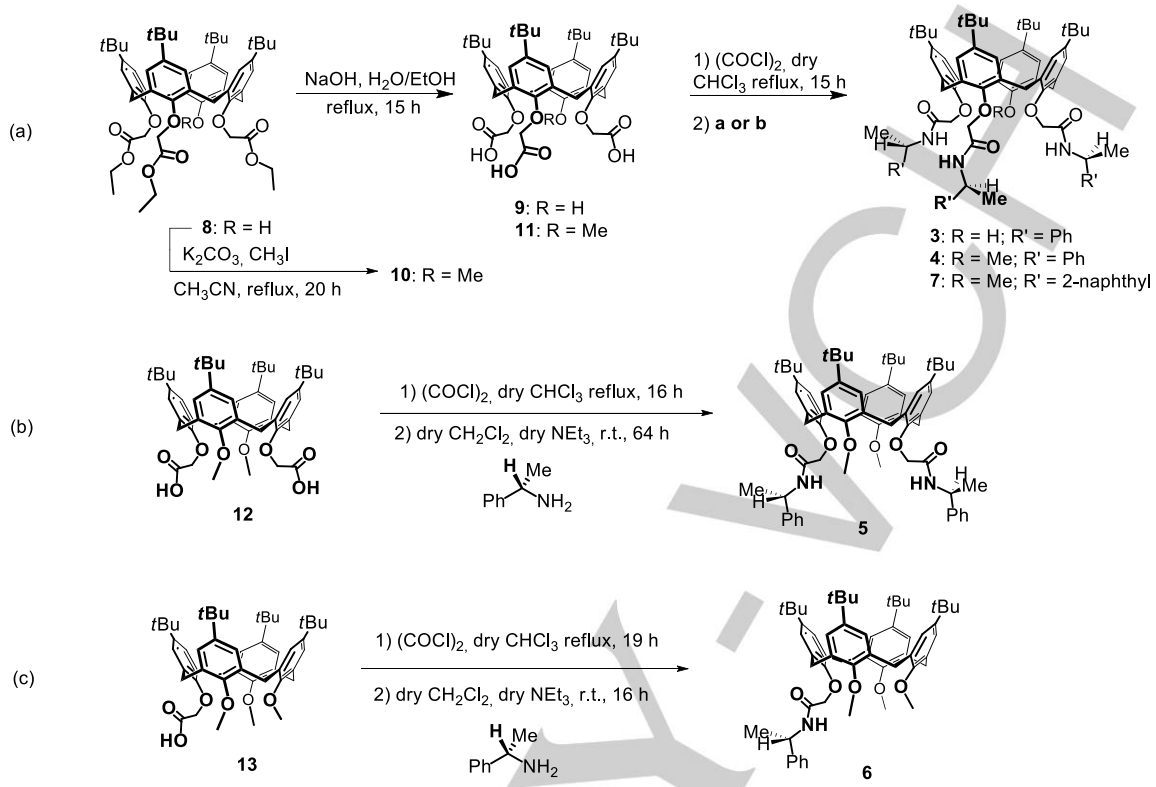
Prompted by these considerations we designed chiral calix[4]arene-amides **1-7** (Figure 2) and, in continuation of our research on macrocycle catalyzed phase-transfer reactions,[16] we wish to report here on their abilities as phase-transfer catalysts in the asymmetric alkylation of *N*-(diphenylmethylene)-glycine esters. In particular, in all cases we have designed calixarenes catalysts **1**–**7** bearing secondary amides at lower rim thanks to their ease of synthesis and good complexing abilities.

## Results and Discussion

**Synthesis of calix[4]arene-amides 1-7.** Calixarene-amide derivatives **1** and **2** (Figure 2) were obtained following the procedures reported by Stibor and coworkers.[17] Calixarene-monohydroxy-triamide **3** (Figure 2) was obtained following the procedure reported in Scheme 1a. In details, the known calix[4]arene-tri-carboxylic acid **9**[18] was converted into the corresponding acyl chloride and then coupled with (*S*)-α-methylbenzylamine to give **3** in 20 % yield, which was characterized by HR ESI(+)-MS, $^1$H and $^{13}$C NMR spectroscopy.[19]

Calixarene-monomethoxy-triamide **4** was obtained following a synthetic route similar to **3** (Scheme 1a). The methylation of the free OH group of **8** in the presence of potassium carbonate afforded 25-methoxy-26,27,28-tris-((ethoxycarbonyl)methoxy)-5,11,17,23-tetra-*tert*-butyl-calix[4]arene **10**[20] in 70 % yield. Derivative **10** was suspended in a mixture of EtOH/$H_2O$ and hydrolyzed in the presence of NaOH to give triacid **11**[20] in 96 % yield, which was converted into the corresponding acyl chloride and coupled with (*S*)-α-methylbenzylamine to give **4**[19] in 57 % yield.

The synthesis of calix-dimethoxy-diamide **5** is outlined in Scheme 1b. The known diacid derivative **12**[21] was converted into the corresponding diacyl chloride and then directly coupled with (*S*)-α-methylbenzylamine to give **5** in 80 % yield, which was characterized by HR ESI(+)-MS, $^1$H and $^{13}$C NMR spectroscopy.[19] Calix-trimethoxy-monoamide **6** was easily obtained (Scheme 1c) by transformation of the known monoacid derivative **13**[22] into the corresponding acyl chloride by treatment with oxalyl chloride, and subsequent coupling with (*S*)-α-methylbenzylamine to give **6** in 60 % yield**.**[19] Finally, calix-monomethoxy-naphthyl-triamide **7** was obtained in 76 % yield, by coupling the acyl chloride of **11** (Scheme 1a) with (*S*)-1-(2-naphthyl)ethylamine.[19]




**Scheme 1.** Synthesis of derivatives **3**-**6.** Conditions a): dry $CH_2Cl_2$, dry $NEt_3$, (*S*)-α-methylbenzylamine, 15 h, room temperature. Conditions b): dry $CH_2Cl_2$, dry $NEt_3$, (*S*)-1-(2-naphthyl)ethylamine, 3 d (63 h), room temperature.

**Asymmetric PTC Catalysis.** With the calix[4]arene-amides **1-7** in our hands we decided to test their catalytic performances in the phase-transfer alkylation of *N*-(diphenylmethylene)-glycine *t*-butyl ester **14** with benzyl bromide in a liquid-liquid system NaOH 50 %/toluene at 0 °C, with a catalyst loading of 5 mol-% (Table 1, entries 1-7). The alkylation catalyzed by tetramide **1** led to the (*R*)-benzylated product **15a** with a good yield but with disappointing enantioselectivity (Table 1, entry 1). Comparable yields and faster reactions were obtained with phenolic amides **2** and **3**, but the resulting enantioselectivities were even lower (Table 1, entries 2 and 3).

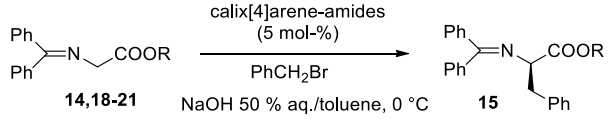
As the phenolic groups on the lower rim might be involved in side alkylation reactions leading to the transformation of the catalyst during the process,[23] we directed our attention to calix-methoxy-amides **4-6**. A significant improvement of both yield and enantioselectivity was achieved with triamide **4** (Table 1, entry 4); enantioselectivities decreased by reducing the number of chiral amide appendages (entries 5 and 6). Scarce catalytic activity and enantioselectivity are especially shown by monoamide **6**, which led to racemic product and incomplete conversion even after 20 h; in this case, presumably, the presence of only one chiral amide group results in reduced cation-complexing and stereodifferentiating abilities. The introduction of (*S*)-α-methylnapthylamine residues in place of (*S*)-α-methylbenzylamine slowed down the reaction and led to a decrease in enantioselectivity (Table 1, entry 7).

A comparison of the yields obtained in the presence of calixarene-amides **1-7** with the low conversion observed in the uncatalyzed reaction (8 % yield after 24 h, Scheme 2a) confirmed the catalytic activity of these macrocycles. In order to assess the effect of calixarene scaffold on catalytic activity and enantioselectivity, we conducted the reaction in the presence of chiral monoamide **16** (0.20 equiv., Scheme 2b). Racemic benzylated product **15a** was obtained in 9 % yield, presumably as a result of the background reaction. The achiral tetramide **17**, albeit less active than its chiral analogue **1**, also showed a moderate catalytic activity (5 mol-% cat., 40 % yield, Scheme 2c). We assumed that the calixarene scaffold plays an essential role in phase-transfer catalysis activity by preorganizing and orienting properly the amide groups in such a way as to favor the complexation of $Na^+$ cation. To support this hypothesis, the recognition abilities of calix[4]arene amides toward $Na^+$ cation were then assessed (see the next section).

Successively, we evaluated the effect of the ester group in the substrate, using the best catalyst **4**. As expected,[16a,24a,25] the presence of less hindered ester groups, such as ethyl and benzyl, proved to be detrimental for the stereoselectivity of

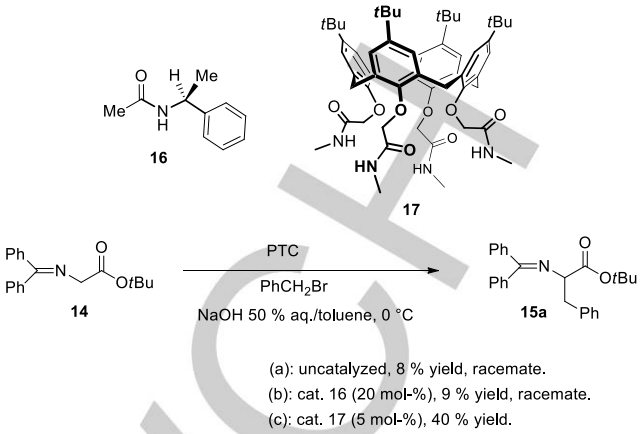
alkylation (Table 1, entries 8 and 9). Slightly lower *ee* was achieved starting from cumyl ester **20** (Table 1, entry 10). A disappointing result was also observed with the benzhydryl ester **21**, with an unexpected inversion of enantioselectivity (Table 1, entry 11).

**Table 1.** Phase-transfer benzylation of *N*-(diphenylmethylene)-glycine esters promoted by calix[4]arene-amides **1-7**.[a]




| Entry | Catalyst | Substrate | Time [h] | Yield[b] [%] | *ee*[c,d] [%] |
|---|---|---|---|---|---|
| 1 | **1** | *t*Bu– (**14**) | 20 | 77 | 13 |
| 2 | **2** | *t*Bu– (**14**) | 4 | 71 | 7 |
| 3 | **3** | *t*Bu– (**14**) | 4 | 83 | 5 |
| 4 | **4** | *t*Bu– (**14**) | 5 | 92 | 28 |
| 5 | **5** | *t*Bu– (**14**) | 4 | 92 | 13 |
| 6 | **6** | *t*Bu– (**14**) | 20 | 48 | rac |
| 7 | **7** | *t*Bu– (**14**) | 20 | 97 | 9 |
| 8 | **4** | Et– (**18**) | 3 | 77 | 4 |
| 9 | **4** | Bn– (**19**) | 7 | 80 | rac |
| 10 | **4** | $Ph(Me)_2C$– (**20**) | 6 | 84 | 24 |
| 11 | **4** | $Ph_2CH$– (**21**) | 5 | 74 | 6 (*S*) |

[a] All reactions were performed in a liquid-liquid system with 0.08 mmol of substrate **14**,**18**-**21**, benzyl bromide (1.2 equiv.), and catalyst (5 mol-%) in toluene (0.8 mL) and NaOH 50 % aq (0.5 mL). [b] Isolated yields. [c] Determined by HPLC using a Chiralcel OD-H chiral stationary phase. [d] The absolute configuration of the products were determined by comparison of the HPLC retention times and optical rotations with literature values.[15a,16a,24]




**Scheme 2.** Phase-transfer benzylation of *N*-(diphenylmethylene)-glycine *t*-butyl ester **14** catalyzed by amide **16** and calixarene-tetramide **17**. Comparison with the uncatalyzed process.

After screening of the catalysts and the ester groups of the the substrates, our attention was directed towards examining the effect of other parameters, such as solvent, base, catalyst loading, and temperature, on the benzylation of *t*-butyl ester **14**. Good yields but poor enantioselectivities were obtained in different reaction media such as chlorinated solvents, ether, chlorobenzene, and xylenes (Table 2, entries 2-8). Gratifyingly, a significant improvement, up to 35 % *ee*, was achieved in mesitylene (Table 2, entry 9). A decrease of *ee* was observed with a 10 mol-% amount of $CH_2Cl_2$ in mesitylene (Table 2, entry 10). The use of inorganic bases other than aqueous NaOH 50 % resulted in low values and a startling inversion of the enantioselectivity (Table 2, entries 11-14). By replacing sodium with the larger potassium or cesium cation, a change of the host-guest tridimensional structure is anticipated, with specific reference to the cation position into the binding site. This may affect the mode of association with the carbanion and hence the reaction enantioselectivity.[26] At -20 °C the reaction proceeded slowly and, even after prolonged reaction time, low conversion and enantioselectivity resulted (Table 2, entry 15). Lower enantioselectivities were also obtained with smaller or higher catalyst loadings (Table 2, entries 16 and 17). While examples erosion of enantioselectivity with increasing amount of catalyst has been frequently described,[27,28] much less common is the opposite effect.[29] Presumably, at higher concentrations, aggregation of the host-guest complex can explain the influence on enantioselectivity.

**Table 2.** Optimization of phase-transfer benzylation of **14** promoted by calix[4]arene-triamide **4**.[a]

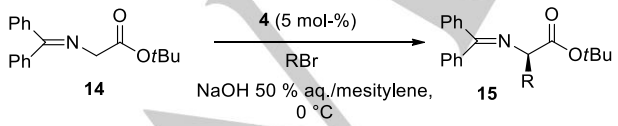

| Entry | Solvent | Base | Time | Yield[b] | *ee*[ [c,d] |
|---|---|---|---|---|---|

| | | | [h] | [%] | [%] |
|---|---|---|---|---|---|
| 1 | toluene | NaOH 50 % aq. | 5 | 92 | 28 |
| 2 | $Et_2O$ | NaOH 50 % aq. | 5 | 87 | 4 |
| 3 | $CH_2Cl_2$ | NaOH 50 % aq. | 7 | 83 | 6 |
| 4 | $CHCl_3$ | NaOH 50 % aq. | 30 | 78 | 5 |
| 5 | chlorobenzene | NaOH 50 % aq. | 5 | 90 | rac |
| 6 | *m*-xylene | NaOH 50 % aq. | 20 | 82 | 3 |
| 7 | *p*-xylene | NaOH 50 % aq. | 7 | 84 | rac |
| 8 | *o*-xylene | NaOH 50 % aq. | 5 | 88 | 17 |
| 9 | mesitylene | NaOH 50 % aq. | 7 | 86 | 35 |
| 10 | mesitylene/ $CH_2Cl_2$ 9:1 | NaOH 50 % aq. | 6 | 89 | 26 |
| 11 | mesitylene | NaOH (s) | 92 | 75 | 4 (*S*) |
| 12 | mesitylene | KOH 50 % aq. | 92 | 76 | 10 (*S*) |
| 13 | mesitylene | KOH (s) | 44 | 79 | 15 (*S*) |
| 14 | mesitylene | CsOH (s) | 44 | 72 | 11 (*S*) |
| 15 [e] | mesitylene | NaOH 50 % aq. | 92 | 12 | 14 |
| 16 [f] | mesitylene | NaOH 50 % aq. | 7 | 73 | 28 |
| 17 [g] | mesitylene | NaOH 50 % aq. | 20 | 73 | 13 |

[a] Reactions were performed in a liquid-liquid system with 0.08 mmol of **14**, benzyl bromide (1.2 equiv.), and catalyst (5 mol-%) in toluene (0.8 mL) and NaOH 50 % aq (0.5 mL), except where otherwise noted. [b] Isolated yields. [c] Determined by HPLC using a Chiralcel OD-H chiral stationary phase. [d] The absolute configuration of the product was determined by comparison of the HPLC retention time and optical rotation with literature values.[24a] [e] Reaction performed at -20 °C. [f] 10 mol-% of catalyst loading was used. [g] 2.5 mol-% of catalyst loading was used.

Finally, we carried out this calix[4]arene-amide catalysed reaction with other alkylating agents, under optimized conditions (NaOH 50 % aq., 5 mol-% of triamide **4**, in mesitylene, Table 3). Good yields of alkylated products were obtained in all cases. Higher enantioselectivities were achieved with *p*-alkyl substituted benzyl substrates (Table 3, entries 2 and 3), whereas with a *ortho*-substituted substrate and with allyl bromide a 15 % *ee* resulted (Table 3, entries 4 and 5).

**Table 3.** Phase-transfer alkylation of **14** promoted by calix[4]arene-triamide **4**.[a]




| Entry | R | Product | Time [h] | Yield[b] [%] | *ee*[c,d] [%] |
|---|---|---|---|---|---|
| 1 | benzyl | **15a** | 7 | 86 | 35 |
| 2 | 4-methylbenzyl | **15b** | 7 | 85 | 47 |
| 3 | 4-(*t*-butyl)benzyl | **15c** | 20 | 79 | 44 |
| 4 | 2-methylbenzyl | **15d** | 7 | 75 | 15 |
| 5 [e] | allyl | **15e** | 20 | 75 | 15 |

[a] All reactions were performed in a liquid-liquid system with 0.08 mmol of **14**, benzyl bromide (1.2 equiv.), and catalyst (5 mol-%) in toluene (0.8 mL) and NaOH 50 % aq (0.5 mL). [b] Isolated yields. [c] Determined by HPLC using a Chiralcel OD-H chiral stationary phase. [d] The absolute configuration of the product was determined by comparison of the HPLC retention time and optical rotation with literature values.[16b,24a,28,30] [e] 1.5 equiv. of allyl bromide were used.

**Recognition abilities of calix[4]arene-amides toward $Na^+$ cation**. The complexation of $Na^+$ by calix[4]arene-amide catalyst is a requisite step in the phase-transfer alkylation of glycine ester **14** with benzyl bromide (see Schemes in Tables 1-3). With the aim to explore the recognition abilities of the most active calix[4]arene-amides catalysts toward $Na^+$ guest we performed $^1$H NMR titration experiments[31] of a solution of host in $CDCl_3$ with $Na^+$ as the $TFPB^-$ [tetrakis[3,5-bis(trifluoromethyl)phenyl]borate][32] salt. The hydrophobic $TFPB^-$, that is known to be a weakly coordinating anion,[32a] was chosen as counteranion due to the good solubility of its sodium salt in organic solvents.[32b] As previously shown by us,[3a,4b,c] the good solubility of the $TFPB^-$ salts in $CDCl_3$ enable the determination of the apparent association constant of the complex by direct integration of its $^1$H NMR signals with respect to those of the free host.

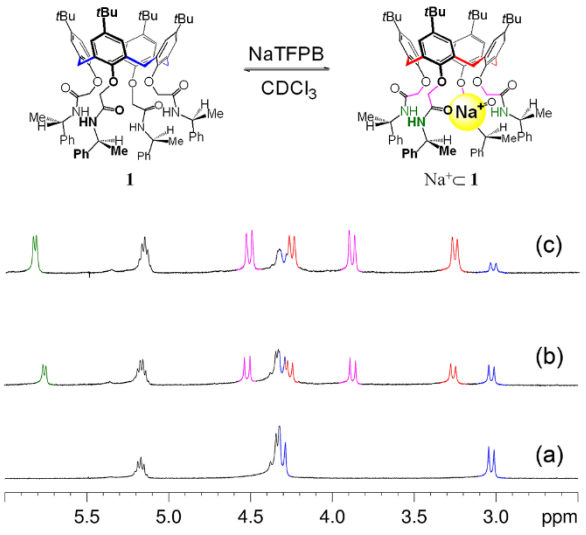



**Figure 3.** Expansion of the $^1$H NMR spectra (400 MHz, $CDCl_3$, 298 K) of: (a) tetramide **1** (1.9 mM) (b) a mixture of **1** (1.0 equiv., 1.9 mM) and **NaTFPB** (0.5 equiv., 0.95 mM) after mixing; (c) an equimolar solution (1.9 mM) of **1** and **NaTFPB** after equilibration for 3 d at 298 K.

Initially, we studied the recognition abilities of calixarene-tetramide **1** toward NaTFPB in $CDCl_3$. The $^1H$ NMR spectrum of **1** in $CDCl_3$ (Figure 3a) undergoes drastic changes after addition of NaTFPB. After the addition of 0.5 equiv of NaTFPB, a new AX system (4.25 and 3.26 ppm, $J$ = 12.0 Hz) emerged in the $^1H$ NMR spectrum (in red in Figure 3b), which was attributable to the $ArCH_2Ar$ groups of the $Na^+\subset$**1** complex in slow exchange with those of the free host **1** on the NMR time scale. The $OCH_2$ protons of the free host **1**, which resonate in $CDCl_3$ at 4.33 ppm (AB system), form a new AX system (4.52 and 3.89 ppm, $J$ = 13.2 Hz) after complexation with $Na^+$ (in magenta in Figure 1b). After a further addition of 0.5 equiv of NaTFPB, the $Na^+\subset$**1** complex was formed in 74 % after 3 d at 298 K, as determined by $^1H$ NMR signal integration of both complexed and free host **1** (Figure 3c; the NMR signal areas were obtained by using a fitting program, see supporting information for further details). From the percentage of formation of the $Na^+\subset$**1** complex an apparent association constant of $1.22\pm0.04\times10^4$ $M^{-1}$ was obtained.

Successively, we studied the binding affinity of calixarene-monomethoxy-triamide **4** toward NaTFPB in $CDCl_3$ (Figure 4). Free **4** adopts a cone conformation in $CDCl_3$ as indicated by the presence in its $^1H$ NMR spectrum ($CDCl_3$, 298 K) of four AX systems at 4.49/3.24, 4.31/2.94, 4.11/3.24, and 4.08/3.24 ppm (COSY spectrum, see supporting information) which correlate in the HSQC spectrum with $CH_2$ carbon signals at 31.6, 31.5, and 31.8 (x2) ppm, respectively. By the known Gutsche's and de Mendoza's rules,[33] these data were only compatible with a cone conformation of **4.** In addition, the presence in the $^1H$ NMR spectrum of **4** in $CDCl_3$ (600 MHz, 298 K) of shielded aromatic signals in the 6.40-6.47 ppm region (integrating for 4 H) evidenced that the calixarene skeleton of **4** adopts a pinched conformation. The pinched-cone conformation adopted by **4** in solution was studied by DFT calculations at the B3LYP/6-31G(d,p) level of theory and by 1D and 2D NMR spectroscopy. A close inspection of the DFT-optimized structure of **4 (**Figure 5) reveals the presence of two intramolecular H-bonding interactions between amide groups at the lower rim, which stabilize the pinched conformation of **4**.

When NaTFPB salt (0.5 equiv) was added to a $CDCl_3$ solution of **4** a new set of signals emerged in the $^1H$ NMR spectrum attributable to the formation of the $Na^+\subset$**4** complex, which was in slow exchange on the NMR time scale (Figure 4b). After a further addition of 0.5 equiv of NaTFPB salt, the formation of the $Na^+\subset$**4** complex was complete after 3 d (72 h) at 298 K ($^1H$ NMR analysis; Figure 4c).

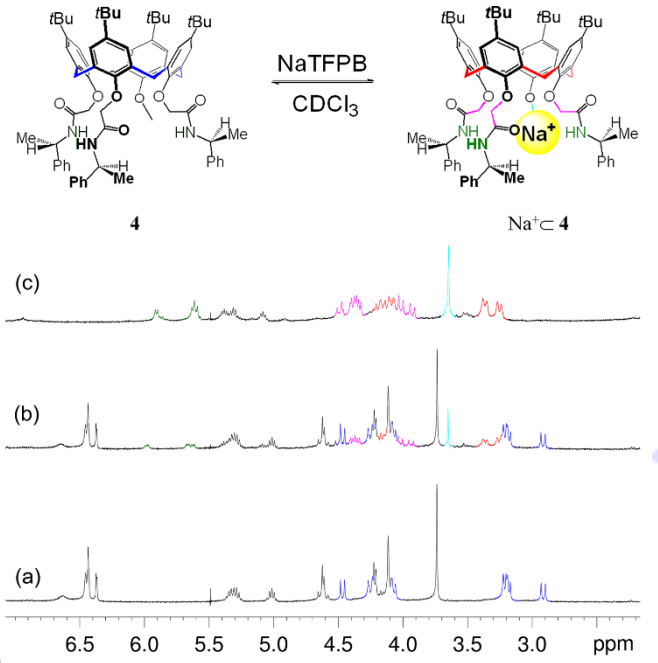



**Figure 4.** $^1H$ NMR spectra (400 MHz, $CDCl_3$, 298 K) of: (a) triamide **4** (1.9 mM) (b) an equimolar solution (1.9 mM) of **4** and **NaTFPB** after mixing; (c) an equimolar solution (1.9 mM) of **4** and **NaTFPB** after equilibration for 3 d (72 h) at 298 K.

At this point the 1:1 stoichiometry of the $Na^+\subset$**4** complex was determined by spectral integration (with respect to the $TFPB^-$ArH signal), while the assignment of its $^1H$ and $^{13}C$ NMR spectra was obtained by means of 1D and 2D NMR studies (2D HSQC and COSY spectra; 600 MHz, $CDCl_3$).[19] Interestingly, the formation of the $Na^+\subset$**4** complex was easily followed by the disappearence of the $^1H$ NMR ArH signals of **4** between 6.40-6.47 ppm, which are attributable to the aromatic rings of the pinched-cone inwardly oriented with respect to the calix-cavity. This result clearly indicated that upon $Na^+$ complexation, **4** switches from the pinched-cone to a cone conformation in which the ArH resonate between 7.01 and 7.39 ppm. After the formation of the $Na^+\subset$**4** complex, the destruction of the intramolecular H-bonds between amide groups occurs, which was evidenced by the upfield shift (see green signals in Figures 2b and 2c) of the N-H signals. The analysis of the complexation induced shifts of $^1H$ NMR signals of **4**, clearly showed that the $Na^+$ cation is encapsulated inside the cavity delimited by the oxygen atoms at the lower rim to establish ion-dipole interactions. Thus, the $^1H$ NMR signals attributable to the $OCH_2$ groups at the lower rim of **4** are downfield shifted upon complexation of $Na^+$, whereas the singlet at 3.74 ppm attributable to the $OCH_3$ group of **4** is upfield shift at 3.65 ppm. A close inspection of the DFT-optimized structure of the $Na^+\subset$**4** complex at the B3LYP/6-31G(d,p) theory level, indicates that the $OCH_3$ group is positioned right at the top of a close phenyl ring to establish a C-H$\cdots\pi$ interaction, with a C-H$\cdots\pi^{centroid}$ distance of 2.81 Å (Figure 5*). This result is fully in accord with the $^1H$

NMR upfield shift observed for the OMe signal of **4** in the $Na^+\subset$ **4** complex against the trend observed for the other $OCH_2$ groups at the lower rim of **4**.

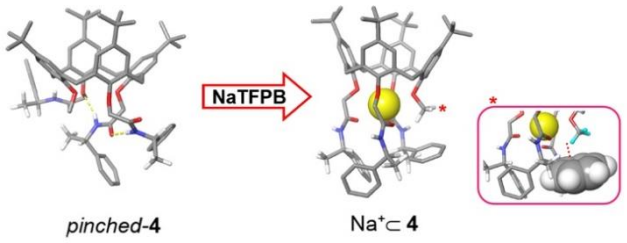



**Figure 5.** DFT-optimized structures of free **4**, in the pinched-cone conformation, and $Na^+\subset$**4** complex at the B3LYP/6-31G(d,p) theory level (some H atoms have been omitted for clarity). Dotted lines in yellow indicate intramolecular H-bonds stabilizing the pinched conformation (average N-H···O=C distance 2.87 Å). Inset (*): particular of the C-H···π interaction between methyl group and phenyl ring in the $Na^+\subset$**4** complex.

In a similar way, when NaTFPB (0.5 equiv) was added to a $CDCl_3$ solution of naphthyl-triamide **7**, a new set of signals emerged. In particular, four new AX systems (4.04 and 3.19 ppm, $J$ = 11.8 Hz; 4.14 and 3.30 ppm, $J$ = 11.8 Hz; 4.17 and 3.37 ppm, $J$ = 12.4 Hz; 4.21 and 3.22 ppm, $J$ = 12.0 Hz) which was attributable to $ArCH_2Ar$ groups of $Na^+\subset$**7** complex in slow exchange on the NMR time scale. In addition, three AX systems (4.33 and 3.85 ppm, $J$ = 14.8 Hz; 4.37 and 4.05 ppm, $J$ = 11.6 Hz and 4.60 and 4.44 ppm, $J$ = 13.6 Hz) were attributable to the $OCH_2$ groups of $Na^+\subset$**7** complex. Finally, the $OCH_3$ group was present as a singlet at 3.60 ppm. Upon a further addition of 0.5 equiv of NaTFPB salt, the formation of the $Na^+\subset$**7** complex was complete ($^1$H NMR analysis) after equilibration for 3 d (72 h) at 298 K. A percentage of formation of 78 % was calculated by integration of the OC$H_3$ singlets for free and complexed **7**, which gave an apparent association constant of $9.16\pm0.04\times10^3$ $M^{-1}$. Also in this case the NMR signal areas were obtained by using a fitting program (see supporting information for further details).

The apparent association constant of the $Na^+\subset$ **4** complex could not be determined by direct signal integration because the intensities of the $^1$H NMR signals (Figure 4c) of the free host **4** were below the reliable 10 % limit. Therefore, $K_{ass}$ evaluation was carried out by means of a competition experiment[31] between calix-triamides **4** and **7**[19] by mixing them with NaTFPB in a 1:1:1 ratio. After equilibration for 3 d (72 h), the $Na^+\subset$**4** complex was preferentially formed over the $Na^+\subset$**7** one with a percentage of formation of 56 and 44 %, respectively. From these data, an apparent association constant of $1.26\pm0.09\times10^4$ $M^{-1}$ was calculated for the formation of $Na^+\subset$**4** complex in $CDCl_3$. Interstingly when the competition experiment was carried out between hosts **4** and **1** for NaTFPB guest**,** the calculated association constant value of $1.30\pm0.06\times10^4$ $M^{-1}$ was consistent with previously determined value**.**

VT $^1$H NMR studies showed that calix-dimethoxy-diamide **5** adopts in solution a cone conformation. In fact, its $^1$H NMR spectrum at 233 K reveals the presence of an AX system at 4.12 and 3.20 ppm, attributable to $ArCH_2Ar$ groups, which correlates in the 2D HSQC spectrum with a signal at 31.2 ppm. From the known Gutsche's and de Mendoza's rules,[33] these data were only compatible with a cone conformation of **5**. Upon addition of NaTFPB (1 equiv) to a $CDCl_3$ solution of **5** at 298 K, a new set of slowly exchanging signals attributable to the $Na^+\subset$**5** complex emerged in the $^1$H NMR spectrum. A close inspection of the 1D and 2D NMR spectra of the NaTFPB/**5** mixture (1:1 in $CDCl_3$, 298 K) revealed the presence of two $Na^+\subset$**5** complexes in which the two calix[4]arene macrocycles adopted different conformations (Figure 6). In details, four doublets were present at 4.06, 3.95, 3.33, and 3.31 ppm which correlated with carbon resonances at 29.8 and 30.0 ppm, attributable to $ArCH_2Ar$ groups between *syn* oriented Ar-rings, and compatible with a calixarene in a cone conformation ($Na^+\subset$**5**$^{cone}$). In addition, the $OCH_2$ groups belonging to the $Na^+\subset$**5**$^{cone}$ complex were observed at 4.52 and 4.40 ppm, while the $OCH_3$ singlet was present at 3.52 ppm. Surprisingly, a close inspection of the 1D and 2D NMR spectra revealed the presence of a $Na^+\subset$**5** complex in which the calixarene adopts a partial-cone conformation ($Na^+\subset$**5**$^{paco}$) in a 1:1 ratio with respect to $Na^+\subset$**5**$^{cone}$ complex (by integration of the $^1$H NMR signlas). In fact, two AB systems at 3.76 and 3.82 ppm, which correlated with carbon resonances at 37.5 and 37.9 ppm, were indicative of $ArCH_2Ar$ groups between *anti* oriented Ar-rings. In addition, two AB systems attributable to $OCH_2$ groups were observed at 4.51/4.26 and 4.60/4.28 ppm. Finally, a singlet attributable to $OCH_3$ group of the $Na^+\subset$**5**$^{paco}$ complex was present at 3.30 ppm, while the $OCH_3$ group belonging to the inverted Ar-ring was found at 1.97 ppm.

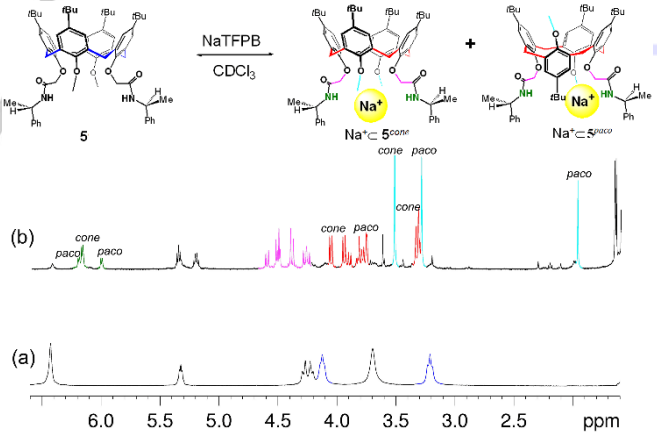



**Figure 6.** Expansion of the $^1$H NMR spectra (400 MHz, $CDCl_3$, 298 K) of: (a) derivative **5** (1.9 mM) (b) an equimolar solution (1.9 mM) of **5** and **NaTFPB** after equilibration for 3 d at 298 K.

The good binding affinities determined for calix[4]arene-amides **1**, **4**, and **7** toward $Na^+$ guest support a phase-transfer catalytic role for these macrocycles. We suggest a mechanism involving the interfacial formation of a tight ion pair between $Na^+\subset$calixarene-amide complex and the enolate anion generated

after deprotonation of **14**. The chiral lipophilic ion pair can diffuse into the organic layer and undergo enantioselective alkylation.[34]

## Conclusions

For the first time, the cation recognition abilities of chiral calix-amide hosts have been exploited in asymmetric phase transfer catalysis. In particular, α-methylbenzylamine and 1-(2-naphthyl)ethylamine-derivatives **1**-**7** turned out to be effective catalysts in the asymmetric alkylation of *N*-(diphenylmethylene)-glycine esters under PTC conditions. The recognition abilities of catalysts **1**, **4**, **5**, and **7** toward $Na^+$ guest have been investigated by $^1$H NMR titration experiments. The good calculated apparent association constant values for $Na^+\subset$**X** (**X** = **1**, **4**, and **7**) complexes are consistent with the remarkable catalytic activity exhibited by calixarene-amides **1**-**7** in the above-mentioned PTC process. This finding opens up new scenarios in phase-transfer catalysis, with the view to designing novel macrocyclic catalysts based on calixarene scaffolds decorated with chiral cation-coordinating moieties. Further studies developing this concept are in progress and will be reported in due course.

## Experimental Section

**General Information.** HR MALDI mass spectra were acquired on a FT-ICR mass spectrometer equipped with a 7T magnet. All chemicals were reagent grade and were used without further purification. Compounds **16**[35] and **17**[36] were prepared as reported in the literature. Anhydrous solvents were used as purchased from the supplier. When necessary compounds were dried *in vacuo* over $CaCl_2$. Reaction temperatures were measured externally. Reactions were monitored by TLC silica gel plates (0.25 mm) and visualized by UV light, or by spraying with $H_2SO_4$-$Ce(SO_4)_2$. Flash chromatography was performed on silica gel 60 (particle size: 0.040−0.063 mm) and the solvents employed were of analytical grade. Enantiomeric excesses of products **15a-e** were determined by chiral HPLC using Chiralcel OD-H columns with an UV detector set at 260 nm. Optical rotation values were measured at λ = 589 nm, corresponding to the sodium D line, at the temperatures indicated. NMR spectra were recorded on a 600 [600 ($^1$H) and 150 MHz ($^{13}$C)], 400 MHz spectrometer [400 ($^1$H) and 100 MHz ($^{13}$C)] or 300 MHz spectrometer [300 ($^1$H) and 75 MHz ($^{13}$C)]. Chemical shifts are reported relative to the residual solvent peak ($CHCl_3$: *δ* 7.26, $CDCl_3$: *δ* 77.23; TCDE: *δ* 6.0, TCDE: *δ* 74.0). Standard pulse programs, provided by the manufacturer, were used for 2D COSY and 2D HSQC experiments. One-dimensional $^1$H and $^{13}$C spectra, and two-dimensional COSY-45 and heteronuclear single quantum correlation (HSQC) were used for NMR peak assignment. COSY-45 spectra were taken using a relaxation delay of 2 s with 30 scans and 170 increments of 2048 points each. HSQC spectra were performed with gradient selection, sensitivity enhancement, and phase-sensitive mode using Echo/Antiecho-TPPI procedure. A typical experiment comprised 20 scans with 113 increments of 2048 points each.

**Compound 3.** Oxalyl chloride (0.88 mL, 10 mmol) was slowly added to a stirred solution of **9**[18] (0.22 g, 0.27 mmol) in 10 mL of dry $CHCl_3$ at 0 °C. The reaction mixture was refluxed under nitrogen atmosphere for 15 h, then was cooled at room temperature and the solvent was removed under reduced pressure to give a dark solid. The crude product was dissolved in 5 mL of dry $CHCl_3$ and added dropwise to a stirred solution of (S)-α-methylbenzylamine (0.10 mL, 0.80 mmol) and dry $Et_3N$ (0.11 mL, 0.80 mmol) in 10 mL of dry $CHCl_3$ at 0 °C. The reaction mixture was stirred for 15 h at room temperature under nitrogen atmosphere, then was washed with a 1N aqueous solution of HCl (2 × 5 mL). The aqueous phase was extracted with $CHCl_3$ (3 × 5 mL). The collected organic layers were washed with $H_2O$ (10 mL), dried over $Na_2SO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography ($SiO_2$, $CHCl_3$) to give the compound **3** as a white solid (0.060 g, 20 % yield): mp 126−128 °C; $[\alpha]_D^{20}$ = −38.5±0.7 (*c* = 0.100, $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$, 298 K): *δ* 8.06 (d, *J* = 8.2 Hz, N*H*, 1H), 7.48 – 7.07 (overlapped Ar*H* + N*H*, 21H), 6.79 (d, *J* = 8.2 Hz, N*H*, 1H), 6.52 (s, Ar*H*, 1H), 6.51 (s, ArH, 1H), 6.48 (s, Ar*H*, 1H), 6.44 (s, Ar*H*, 1H), 5.31 – 5.28 (*overlapped*, *CH*PhCH$_3$ + O*H*, 3H), 5.09 (m, *CH*PhCH$_3$, 1H), 4.66 (d, *J* = 14.6 Hz, OC*H*$_2$CO, 1H), 4.37 (d, *J* = 13.8 Hz, OC*H*$_2$CO, 1H), 4.29 (d, *J* = 13.3 Hz, ArC*H*$_2$Ar, 1H), 4.23 (d, *J* = 14.6 Hz, OC*H*$_2$CO, 1H), 4.19 (d, *J* = 13.1 Hz, ArC*H*$_2$Ar, 1H), 4.14 (d, *J* = 13.8 Hz, OC*H*$_2$CO, 1H), 4.07 (d, *J* = 12.9 Hz, ArC*H*$_2$Ar, 1H), 3.75 (d, *J* = 13.1 Hz, ArC*H*$_2$Ar, 1H), 3.50 (d, *J* = 13.7 Hz, OC*H*$_2$CO, 1H), 3.38 (d, *J* = 13.3 Hz, ArC*H*$_2$Ar, 1H), 3.17 (d, *J* = 13.1 Hz, ArC*H*$_2$Ar, 2H), 3.12 (d, *J* = 13.7 Hz,, OC*H*$_2$CO, 1H) 3.03, (d, *J* = 12.9 Hz, ArC*H*$_2$Ar, 1H), 1.74 (d, *J* = 7.0 Hz, CHPhC*H*$_3$, 3H), 1.67 (d, *J* = 7.0 Hz, CHPhC*H*$_3$, 3H), 1.58 (d, *J* = 6.9 Hz, CHPhC*H*$_3$, 3H), 1.37 (*s*, C(C*H*$_3$)$_3$, 9H), 1.36 (*s*, C(C*H*$_3$)$_3$, 9H), 0.83 (*s*, C(C*H*$_3$)$_3$, 9H), 0.77 (*s*, C(C*H*$_3$)$_3$, 9H). **$^{13}$C NMR** (100 MHz, $CDCl_3$, 298 K): *δ* 168.9, 167.9, 167.5, 151.9, 151.6, 151.5, 149.8, 147.6, 146.7, 146.5, 143.3, 143.0, 142.8, 142.7, 135.4, 135.2, 131.6, 131.1, 130.8, 130.4, 128.9, 128.8, 128.7, 128.4, 128.3, 128.0, 127.8, 127.6, 126.9, 126.7, 126.6, 125.8, 125.7, 125.5, 125.5, 125.3, 75.8, 75.7, 74.0, 49.5, 49.0, 48.9, 34.4, 34.2, 33.9, 33.8, 32.1, 31.9, 31.8, 31.5, 31.3, 31.1, 21.9, 21.3, 20.1. IR (KBr): ṽ = 2962, 2868, 1657, 1538, 1480, 1454, 1393, 1362, 1300, 1219, 1196, 1123, 1048, 872, 771, 699 cm$^{-1}$. HRMS (ESI+) *m*/*z* $[M]^+$ calcd for $C_{74}H_{90}N_3O_7$, 1132.6773; found 1132.6778.

**Compound 4.** Oxalyl chloride (1.5 mL, 18 mmol) was slowly added to a stirred solution of **11** (0.38 g, 0.46 mmol) in 20 mL of dry $CHCl_3$ at 0 °C. The reaction mixture was refluxed under nitrogen atmosphere for 13 h, then was cooled at room temperature and the solvent was removed under reduced pressure to give a dark solid. The crude product was dissolved in 13 mL of dry $CHCl_3$ and added dropwise to a stirred solution of (S)-α-methylbenzylamine (0.18 mL, 1.4 mmol) and dry $Et_3N$ (0.19 mL, 1.4 mmol) in 23 mL of dry $CHCl_3$ at 0 °C. The reaction mixture was stirred for 22 h at room temperature under nitrogen atmosphere, then was washed with a 1N aqueous solution of HCl (2 × 15 mL). The aqueous phase was extracted with $CHCl_3$ (3 × 10 mL). The collected organic layers were washed with $H_2O$ (20 mL), dried over $Na_2SO_4$ and evaporated. The crude product was purified by column chromatography ($SiO_2$, $CHCl_3$/hexane from 6/4 to 9/1 (*v*/*v*)) to give the derivative **4** as a white solid (0.22 g, 57 %): mp 140 −143 °C; $[\alpha]_D^{20}$ = − 26.4 ± 0.4 (*c* = 1.00, $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$, 298 K): *δ* 7.73 (broad, NH, 1H), 7.70 (d, *J* = 8.4 Hz, N*H*, 1H), 7.46 (d, *J* = 7.2 Hz, Ar*H*, 2H), 7.40 (d, *J*, = 7.2 Hz, Ar*H*, 2H), 7.28 – 7.02 (overlapped, Ar*H*, 15H), 6.78 (broad, N*H*, 1H), 6.47 – 6.45 (overlapped, Ar*H*, 3H), 6 40 (s, Ar*H*, 1H), 5.35 – 5.27 (m NC*H*PhCH$_3$, 2H), 5.04 – 5.00 (m, NC*H*PhCH$_3$, 1H), 4.69 – 4.60 (overlapped, OC*H*$_2$CO, 2H), 4.49 (d, *J* = 13.2 Hz, ArC*H*$_2$Ar, 1H), 4.30 (d, *J* = 13.2 Hz, ArC*H*$_2$Ar, 1H), 4.22 (s, OC*H*$_2$CO, 2H), 4.13 (s, OC*H*$_2$CO, 2H) 4.11 (d, *J* = 12.4 Hz, ArC*H*$_2$Ar, 1H), 4.08 (d, *J* = 12.4 Hz, ArC*H*$_2$Ar, 1H), 3.74 (s, OC*H*$_3$, 3H), 3.24 (overlapped, ArC*H*$_2$Ar, 3H), 2.94 (d, *J* = 13.2 Hz ArC*H*$_2$Ar, 1H), 1.65 (d, *J* = 6.8 Hz, CHPhC*H*$_3$, 3H), 1.58 (d, *J* = 7.2 Hz, CHPhC*H*$_3$, 3H), 1.41 (d, *J* = 6.8 Hz, CHPhC*H*$_3$, 3H), 1.34 (s, C(C*H*$_3$)$_3$, 9H), 1.33 (s, C(C*H*$_3$)$_3$, 9H), 0.86 (s, C(C*H*$_3$)$_3$, 9H), 0.85 (s, C(C*H*$_3$)$_3$, 9H). **$^{13}$C NMR** (100 MHz, $CDCl_3$, 298 K): δ 168.33, 168.28, 168.1, 154.9, 153.1, 152.0, 145.8, 145.6, 145.2, 145.1, 143.3, 143.1, 142.8, 134.9, 134.7, 134.7, 131.3, 131.3, 130.8, 128.5, 128.4, 127.2, 126.5, 126.3, 126.2, 126.1, 125.8, 125.1, 124.7, 124.6, 74.7, 74.6, 60.2, 48.7, 48.5, 48.3, 34.1, 33.6, 31.6, 31.5, 31.2, 31.0, 21.8, 21.5, 21.2. IR (KBr): ṽ = 3286, 3036, 2963, 2868, 1659, 1544, 1480, 1393, 1362, 1300, 1219,

1195, 1124, 1047, 1021, 949, 871, 772, 698 $cm^{-1}$. HRMS (ESI+) *m*/*z* [M + Na]$^+$ calcd for $C_{75}H_{91}N_3NaO_7$, 1168.6749; found 1168.6756.

**Compound 5.** Oxalyl chloride (0.27 mL, 3.2 mmol) was slowly added to a stirred solution of **12** (0.097 g, 0.12 mmol) in 5 mL of dry $CHCl_3$ at 0 °C. The raction mixture was refluxed under nitrogen atmosphere for 16 h, then was cooled at room temperature and the solvent removed under reduced pressure to give a white solid. The crude product was dissolved in 1 mL of dry $CHCl_3$ and added dropwise to a stirred solution of (S)-α-methylbenzylamine (0.03 mL, 0.2 mmol) and dry $Et_3N$ (0.03 mL, 0.2 mmol) in 3 mL of dry $CHCl_3$ at 0 °C. The reaction mixture was stirred for 64 h at room temperature under nitrogen atmosphere, then was washed with a 1N aqueous solution of HCl (2 × 5 mL). The aqueous phase was extracted with $CHCl_3$ (3 × 5 mL). The collected organic layers were washed with $H_2O$ (5 mL), dried over $Na_2SO_4$ and evaporated. The crude product was purified by column chromatography ($SiO_2$, $CHCl_3$) to afford **5** as a white solid (0.096 g, 80 % ): mp 237-239 °C; $[\alpha]_D^{20}$ = − 34.68 ± 0.04 (*c* = 0.997, $CHCl_3$); **$^1$H NMR** (600 MHz, $CDCl_3$, 298 K): *δ* 7.30 – 7.20 (overlapped, N*H* + Ar*H*, 12H), 7.12 (s, Ar*H*, 4H), 6.42 (s, Ar*H*, 4H), 5.31 (overlapped, CO*CH*PhCH$_3$, 2H), 4.27-4.21 (overlapped, OC$H_2$CO, 4H), 4.11 (broad, Ar*CH*$_2$Ar, 4H), 3.69 (s, OC$H_3$, 6H), 3.20 (broad, Ar*CH*$_2$Ar, 4H), 1.49 (d, *J* = 6.6 Hz, CHPh*CH*$_3$, 6H), 1.32 (s, C(C$H_3$)$_3$, 18H), 0.81 (s, C(C$H_3$)$_3$, 18H). **$^{13}$C NMR** (150 MHz, $CDCl_3$, 298 K): *δ* 168.4, 154.8, 146.3, 145.5, 142.6, 135.3, 131.1, 131.0, 128.9, 127.7, 126.1, 125.0, 74.3, 60.3, 48.0, 34.3, 33.7, 31.8, 31.1, 21.7. IR (KBr): ṽ = 3414, 3201, 3032, 2962, 2868, 2819, 1671, 1603, 1525, 1480, 1455, 1393, 1362, 1301, 1282, 1241, 1218, 1210, 1197, 1122, 1051, 1021, 955, 912, 871, 833, 815, 771, 699 $cm^{-1}$. HRMS (ESI+) *m*/*z* [M+H]$^+$ calcd for $C_{66}H_{83}N_2O_6$, 999.6246; found 999.6260.

**Compound 6.** Oxalyl chloride (0.26 mL, 3.1 mmol) was slowly added to a stirred solution of **13** (0.18 g, 0.24 mmol) in 10 mL of dry $CHCl_3$ at 0 °C. The reaction mixture was refluxed under nitrogen atmosphere for 19 h, then was cooled at room temperature and the solvent was removed under reduced pressure to give a white solid. The crude product was dissolved in 6 mL of dry $CHCl_3$ and added dropwise to a stirred solution of (S)-α-methylbenzylamine (0.03 mL, 0.2 mmol) and $Et_3N$ (0.03 mL, 0.2 mmol) in 3 mL of dry $CHCl_3$ at 0 °C. The reaction mixture was stirred for 16 h at room temperature under nitrogen atmosphere, then was washed with a 1N aqueous solution of HCl (2 × 5 mL). The aqueous phase was extracted with $CHCl_3$ (3 × 5 mL). The collected organic layers were washed with $H_2O$ (10 mL), dried over $Na_2SO_4$ and evaporated. The crude product was purified by column chromatography ($SiO_2$, $CH_2Cl_2$) to afford **6** as a white solid (0.12 g, 60 %): mp 106 −107 °C; $[\alpha]_D^{20}$ = − 15.4 ± 0.8 (*c* = 1.00, $CHCl_3$); **$^1$H NMR** (600 MHz, TCDE, 353 K): *δ* 7.22 (s, Ar*H*, 5H), 7.13 (s, N*H*, 1H), 6.94 – 6.87 (overlapped, Ar*H*, 4H), 6.65 (s, Ar*H*, 2H), 6.51 (s, Ar*H*, 2H), 5.16 (broad, CO*CH*PhCH$_3$, 1H), 4.15 (broad, OC$H_2$CO, 2H), 4.00 (broad, ArC$H_2$Ar, 2H), 3.88 (broad, Ar*CH*$_2$Ar, 4H), 3.33 (s, OCH$_3$, 3H), 3.20 (s, OCH$_3$, 6H), 3.14 (broad, ArC$H_2$Ar, 2H), 1.45 (broad, CHPh*CH*$_3$, 3H), 1.17 (s, C(C$H_3$)$_3$ 9H), 1.14 (s, C(C$H_3$)$_3$, 9H), 0.98 (s, C(C$H_3$)$_3$, 9H), 0.83 (s, C(C$H_3$)$_3$, 9H). **$^{13}$C NMR** (150 MHz, TCDE, 353 K): *δ* 168.5, 155.1, 154.8, 152.0, 145.3, 144.3, 143.0, 134.6, 134.3, 132.7, 131.7, 128.7, 127.4, 126.2, 126.1, 125.5, 125.4, 125.3, 74.2, 60.4, 60.1, 49.6, 48.3, 34.0, 34.0, 33.7, 33.7, 31.7, 31.6, 31.4, 31.2, 29.7, 21.3. IR (KBr): ṽ = 2961, 2928, 2867, 2819, 1734, 1684, 1659, 1653, 1540, 1521, 1507, 1481, 1458, 1447, 1392, 1362, 1300, 1219, 1122, 1048, 1023, 847, 870, 772 $cm^{-1}$. HRMS (ESI+) *m*/*z* [M + Na]$^+$ calcd for $C_{57}H_{73}NNaO_5$, 874.5381; found 874.5391.

**Compound 7.** Oxalyl chloride (0.78 mL, 9.3 mmol) was slowly added to a stirred solution of **11** (0.20 g, 0.24 mmol) in 10 mL of dry $CHCl_3$ at 0 °C. The reaction mixture was refluxed under nitrogen atmosphere for 15 h, then was cooled at room temperature and the solvent was removed under reduced pressure to give a white solid. The crude product was dissolved in 7 mL of dry $CHCl_3$ and added dropwise to a stirred solution of (S)-1-(2-naphthyl)ethylamine (0.22 g, 1.3 mmol) and dry $Et_3N$ (0.18 mL, 1.3 mmol) in 13 mL of dry $CHCl_3$ at 0 °C. The reaction mixture was stirred for 63 h at room temperature under nitrogen atmosphere, then was washed a 1N aqueous solution of HCl (2 × 10 mL). The aqueous phase was extracted with $CHCl_3$ (3 × 10 mL). The collected organic layers were washed with $H_2O$ (25 mL), dried over $Na_2SO_4$ and evaporated. The crude product was purified by column chromatography ($SiO_2$, $CH_2Cl_2$/$Et_2O$ 96/4 (*v*/*v*)) to afford compound **7** as white solid (0.24 g, 76 %): mp 138-139 °C; $[\alpha]_D^{20}$ = − 424 ± 4 (*c* = 0.0938, $CHCl_3$); **$^1$H NMR** (600 MHz, $CDCl_3$, 298 K): δ 7.88 (s, Ar*H*, 1H), 7.85 (broad, N*H*, 1H), 7.83 (broad, N*H*, 1H), 7.81 (s, Ar*H*, 1H), 7.75 – 7.63 (overlapped, Ar*H*, 7H), 7.58 (s, Ar*H*, 1H), 7.57 (s, Ar*H*, 1H), 7.51 (s, Ar*H*, 1H), 7.50 (s, Ar*H*, 1H), 7.47 (broad, N*H*, 1H), 7.55 – 7.37 (overlapped, Ar*H*, 6H), 7.13 (d, *J* = 1.8 Hz, Ar*H*, 1H), 7.12 (d, *J* = 1.8 Hz, Ar*H*, 1H), 7.09 (s, Ar*H*, 2H), 7.06 (d, *J* = 2.4 Hz, Ar*H*, 1H), 6.94 (d, *J* = 2.4 Hz, Ar*H*, 1H), 6.50 (broad, Ar*H*, 1H), 6.47 (broad, Ar*H*, 1H), 6.45 (d, *J* = 2.4 Hz, Ar*H*, 1H), 6.36 (d, *J* = 1.8 Hz, Ar*H*, 1H), 5.49 – 5.43 (overlapped, CO*CH*PhCH$_3$, 2H), 5.11 – 5.08 (*m*, CO*CH*PhCH$_3$, 1H), 4.75-4.71 (overlapped, OC$H_2$CO, 2H), 4.53 (d, *J* = 13.2 Hz, Ar*CH*$_2$Ar, 1H), 4.34 (d, *J* = 12.6 Hz, Ar*CH*$_2$Ar, 1H), 4.25 (broad, OC$H_2$CO, 2H), 4.17 – 4.12 (overlapped, OC$H_2$CO, 2H), 4.10 – 4.06 (overlapped, Ar*CH*$_2$Ar, 2H), 3.73 (*s*, OCH$_3$, 3H), 3.23 – 3.21 (overlapped, Ar*CH*$_2$Ar, 2H), 3.17 (*d*, *J* = 13.2 Hz, Ar*CH*$_2$Ar, 1H), 2.87 (*d*, *J* = 12.6 Hz, Ar*CH*$_2$Ar, 1H), 1.74 (*d*, *J* = 7.2 Hz, CHPh*CH*$_3$, 3H), 1.60 (*d*, *J* = 7.2 Hz, CHPh*CH*$_3$, 3H), 1.39 (*d*, *J* = 6.6 Hz, CHPh*CH*$_3$, 3H), 1.31 (*s*, CCH$_3$, 9H), 1.30 (*s*, CCH$_3$, 9H), 0.87 (*s*, CCH$_3$, 9H), 0.84 (*s*, CCH$_3$, 9H). **$^{13}$C NMR** (150 MHz, $CDCl_3$, 298 K): δ 168.6, 155.1, 152.3, 145.4, 145.2, 140.9, 140.6, 140.3, 134.8, 134.6, 133.4, 133.3, 132.8, 132.7, 131.5, 131.1, 128.5, 128.4, 128.3, 128.1, 128.0, 128.0, 127.7, 127.7, 126.2, 126.1, 126.0, 125.9, 125.8, 125.4, 125.2, 125.0, 124.9, 124.8, 74.8, 60.4, 48.8, 48.6, 34.2, 34.2, 33.8, 33.7, 31.7, 31.2, 21.8, 21.4, 21.3. IR (KBr): ṽ = 3282, 3055, 2963, 2868, 1652, 1602, 1543, 1480, 1393, 1362, 1299, 1219, 1195, 1124, 1050, 1019, 949, 871, 855, 816, 772 $cm^{-1}$. HRMS (ESI+) *m*/*z* [M + Na]$^+$ calcd for $C_{87}H_{98}N_3NaO_7$, 1319.7297; found 1319.7256.

**Compound 10.**[20] $CH_3I$ (0.38 mL, 6.09 mmol) was added to a suspension of **8** (0.55 g, 0.61 mmol) and $K_2CO_3$ (0.34 g, 2.44 mmol) in $CH_3CN$ (15 mL) at 0 °C. The reaction mixture was refluxed for 15 h. The solvent was evaporated under reduced pressure and the crude product was suspended in $CH_2Cl_2$ (30 mL) and washed with a 1N aqueous solution of HCl (2 × 15 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL). The collected organic layers were washed with $H_2O$, dried over $Na_2SO_4$ and evaporated. The crude product was triturated with methanol, filtered and the solid was washed with cold methanol to give the derivative **10** as a white solid (0.39 g, 70 % yield). Spectroscopic data were consistent with those previously reported:[20] mp >250 °C dec; **$^1$H NMR** (600 MHz, TCDE, 353 K): *δ* 6.96 (s, Ar*H*, 2H), 6.88 (s, Ar*H*, 2H), 6.64 (broad, Ar*H*, 1H), 6.48 (broad, Ar*H*, 1H), 6.43 (s, Ar*H*, 2H), 4.64 – 4.62 (overlapped, OC$H_2$ + Ar*CH*$_2$Ar, 4H), 4.54 (d, *J* = 12.6 Hz, Ar*CH*$_2$Ar, 2H), 4.37 (s, OC$H_2$CO, 2H), 4.29 (s, OC$H_2$CO, 2H), 4.12 (q, *J* = 7.2 Hz, OC$H_2$CH$_3$, 4H), 4.00 (q, *J* = 7.2 Hz, OC$H_2$CH$_3$, 2H), 3.65 (s, OC$H_3$, 3H), 3.05 (d, *J* = 12.6 Hz, Ar*CH*$_2$Ar, 4H), 1.18 – 1.16 (overlapped, C(C$H_3$)$_3$, + OCH$_2$*CH*$_3$, 24H), 1.09 (t, *J* = 6.6 Hz, OCH$_2$*CH*$_3$, 3H), 0.81 (s, C(C$H_3$)$_3$, 18H). **$^{13}$C NMR** (150 MHz, TCDE, 353 K): δ 171.0, 169.7, 156.2, 156.1, 153.4, 145.5, 145.2, 135.1, 133.7, 132.5, 132.1, 132.0, 126.0, 125.7, 125.5, 125.3, 74.5, 72.3, 71.8, 60.7, 60.2, 51.5, 34.2, 34.1, 33.8, 32.4, 31.8, 31.6, 31.5, 14.4, 14.3, 14.3. (ESI+) *m*/*z* [M+Na]$^+$: 943.5 Anal. Calcd for $C_{57}H_{76}O_{10}$: C, 74.32; H, 8.32. Found: C, 74.30; H, 8.34.

**Compound 11.** [20] A suspension of NaOH (0.57 g, 14 mmol) in EtOH (4 mL) and $H_2O$ (3 mL) was added to a solution of **10** (0.44 g, 0.47 mmol) in EtOH (14 mL). The reaction mixture was refluxed for 14 h. Then the solvent was evaporated under reduced pressure and the crude product

was triturated with a 1N aqueous solution of HCl, filtered and the solid washed with cold $H_2O$ and dried in vacuo to give the derivative **11** as a white solid (0.38 g, 96 %). Spectroscopic data were consistent with those previously reported:[20] mp 248 −250 °C; **$^1$H NMR** (400 MHz, $CDCl_3$, 298 K): *δ* 9.06 (broad, COO*H*, 3H), 7.16 (overlapped, ArH, 4H), 6.61 (overlapped, ArH, 4H), 4.86 – 4.75 (overlapped, Ar$CH_2$Ar + O$CH_2$COOH, 6H), 4.56 (broad s, O$CH_2$COOH, 2H), 4.28 (d, *J* = 12.8 Hz, Ar$CH_2$Ar, 2H), 3.79 (s, $OCH_3$, 3H), 3.28 – 3.21 (overlapped, Ar$CH_2$Ar, 4H), 1.32 (s, C($CH_3$)$_3$, 18H), 0.85 (s, C($CH_3$)$_3$, 18H). **$^{13}$C NMR** (100 MHz, $CDCl_3$, 298 K): *δ* 173.4, 171.0, 151.0, 149.7, 147.0, 146.3, 145.8, 134.5, 134.1, 132.9, 131.9, 131.7, 125.9, 125.8, 125.4, 125.2, 72.0, 71.7, 63.3, 34.0, 33.6, 31.5, 31.3, 31.2, 30.9, 30.9, 30.5. HRMS (ESI+) *m*/*z* $[M + K]^+$ calcd for $C_{51}H_{64}NaO_{10}$, 859.3818; found 859.4391.

**General procedure for the phase-transfer alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester (14) catalyzed by chiral calix[arene]-amide 4.** To a solution of *N*-(diphenylmethylene)glycine *tert*-butyl ester **14** (148 mg, 0.50 mmol) and chiral catalyst **4** (28.8 mg, 0.025 mmol) in mesitylene (5.0 mL) under inert athmosphere, the alkyl bromide (1.2-1.5 equiv.) was added. The mixture was degassed and then brought to 0° C. Degassed 50 % aqueous NaOH (0.5 mL) was then added. The reaction mixture was stirred at 0 °C until TLC disappearance of the starting material. Then the suspension was diluted with $CH_2Cl_2$ (25 mL) and water (15 mL), and the organic layer was taken. The aqueous layer was extracted twice with $CH_2Cl_2$ (25 mL × 2) and the combined organic phases were dried over $Na_2SO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (petroleum ether−ethyl acetate: 98:2 to 90:10) afforded the pure alkylated products. The characterization data of the known products **19a-e** matched those previously reported.[24a,28,30]

**General procedure for the preparation of $Na^+\subset$X (X = 1, 4, and 7) complexes**. The calixarene-amide derivative (1.9 mM) and the sodium TFPB salt (1.9 mM) were dissolved in $CDCl_3$ (0.5 mL). Each solution was sonicated for 15 min at room temperature and then was transferred into a NMR tube for 1D and 2D NMR spectra acquisition. The $K_{assoc}$ values have been determined by integration of $^1$H NMR signals of free and complexed host, as reported in SI (Figures S54-S56). The errors reported for the determination of the association constant values were all obtained by three separate measurements.

**Determination of $K_{assoc}$ value $Na^+\subset$4 complex by competition experiment.** $^1$H NMR competition experiments were carried out on a 1:1:1 mixture of hosts **4** ($1.9\times10^{-3}$ $M^{-1}$), **7** ($1.9\times10^{-3}$ $M^{-1}$) and guest **NaTFPB** ($1.9\times10^{-3}$ $M^{-1}$) in $CDCl_3$. The mixture was equilibrated for 3 days at 298 K. Accordingly, a $K_a$ value of $1.06\pm0.06\times10^4$ $M^{-1}$ was calculated for **$Na^+\subset$4** complex following a recently reported procedure (see supporting information for further details).

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[1] a) P. Neri, J. L. Sessler, M.-X. Wang B., Eds., *Calixarenes and Beyond*, Springer, Dordrecht, **2016**; b) C. D. Gutsche, *Calixarenes, An Introduction*, Royal Society of Chemistry, Cambridge, UK, **2008**; c) Z. Asfari, V. Böhmer, J. Harrowfield, J. Vicens, Eds., *Calixarenes 2001*, Kluwer, Dordrecht, **2001**; d) J. Vicens, J. Harrowfield, Eds., *Calixarenes in the Nanoworld*, Springer, Dordrecht, **2007**.

[2] a) S. Shinkai, H. Koreishi, K. Ueda, T. Arimura, O. Manabe, *J. Am. Chem. Soc.* **1987**, *109*, 6371-6376; b) C. D. Gutsche, L.-G. Lin, *Tetrahedron* **1986**, *42*, 1633-1640; c) W. Verboom, A. Durie, R. J. M. Egberink, Z. Asfari, D. N. Reinhoudt, *J. Org. Chem.* **1992**, *57*, 1313-1316; d) C. D. Gutsche, P. F. Pagoria, *J. Org. Chem.* **1985**, *50*, 5795-5802; e) A. Arduini, S. Fanni, G. Manfredi, A. Pochini, R. Ungaro, A. R. Sicuri, F. Ugozzoli, *J. Org. Chem.* **1995**, *60*, 1448-1453; f) A. Casnati, Y Ting, D. Berti, M. Fabbi, A. Pochini, R. Ungaro, D. Sciotto, G. G. Lombardo, *Tetrahedron* **1993**, *49*, 9815-9822; g) M. De Rosa, A. Soriente, G. Concilio, C. Talotta, C. Gaeta, P. Neri, *J. Org. Chem.* **2015** 80, 7295-7300.

[3] a) C. Gaeta, C. Talotta, F. Farina, M. Camalli, G. Campi, P. Neri, *Chem. Eur. J.* **2012**, *18*, 1219-1230; b) F. Troisi, L. Mogavero, C. Gaeta, E. Gavuzzo, P. Neri, *Org. Lett.* **2007**, *9*, 915-918; c) N. Dozova, R. Kumar, T. Pradhan, F. Lacombat, B. Valeur, J. S. Kim, P. Plaza, *Chem. Commun.* **2015**, *51*, 14859-14861; d) E. Brunetti, S. Moerkerke, J. Wouters, K. Bartik, I. Jabin, *Org. Biomol. Chem.* **2016**, *14*, 10201-10207; e) G. De Leener, F. Evoung-Evoung, A. Lascaux, J. Mertens, A. G. Porras-Gutierrez, N. Le Poul, C. Lagrost, D. Over, Y. R. Leroux, F. Reniers, P. Hapiot, Y. Le Mest, I. Jabin, O. Reinaud, *J. Am. Chem. Soc.* **2016**, *138*, 12841-12853.

[4] a) A. Arduini, R. Bussolati, A. Credi, A. Secchi, S. Silvi, M. Semeraro, M. Venturi, *J. Am. Chem. Soc.* **2013**, *135,* 9924-9930; b) C. Gaeta, C. Talotta, L. Margarucci, A. Casapullo, P. Neri, *J. Org. Chem.* **2013**, *78*, 7627-7638; c) C. Talotta, C. Gaeta, T. Pierro, P. Neri, *Org. Lett.* **2011**, *13*, 3104-3107.

[5] a) M. Giuliani, I. Morbioli, F. Sansone, A. Casnati, *Chem. Commun*. **2015**, *51*, 14140-14159; b) S. Tommasone, C. Talotta, C. Gaeta, L. Margarucci, M. C. Monti, A. Casapullo, B. Macchi, S. P. Prete, A. L. De Araujo, P. Neri, *Angew. Chem. Int. Ed.* **2015**, *54*,15405-15409; *Angew. Chem.* **2015**, *127*, 15625-15629.

[6] a) D. H. Homden, C. Redshaw, *Chem. Rev.* **2008**, *108*, 5086-5130; b) M. Yilmaz, S. Sayin in *Calixarenes and Beyond* (Eds: P. Neri, J. L. Sessler, M.–X. Wang), Springer, Dordrecht, **2016,** pp. 719-741; c) M. Durmaz, A. Tataroglu, H. Yilmaz, A. Sirit, *Tetrahedron: Asymmetry* **2016**, *27*, 148-156; d) A. Soriente, M. De Rosa, M. Fruilo, L. Lepore, C. Gaeta, P. Neri, *Adv. Synth. Catal*. **2005**, *347*, 816-824; e) M. De Rosa, P. La Manna, A. Soriente, C. Gaeta, C. Talotta, P. Neri, *RSC Adv.* **2016**, *6*, 91846-91851.

[7] a) P. L. H. M. Cobben, R. J. M. Egberink, J. G. Bomer, P. Bergveld, W. Verboom, D. N. Reinhoudt, *J. Am. Chem. Soc.* **1992**, *114*, 10573-10582; b) F. Arnaud-Neu, M. A. McKervey, J. Schwing-Weill in *Calixarenes 2001* (Eds.: Z. Asfari, V. Böhmer, J. Harrowfield, J. Vicens) Kluwer, Dordrecht, **2001**, pp. 385-406; c) S. Amemiya, *Anal. Chem.* **2016**, *88*, 8893-8901; d) P. J. Greenawalt, S. Amemiya, *Anal. Chem.* **2016**, *88*, 5827-5835; e) F. Cadogan, K. Nolan, D. Diamond in *Calixarenes 2001* (Eds.: Z. Asfari, V. Böhmer, J. Harrowfield, J. Vicens) Kluwer, Dordrecht, **2001**, pp. pp. 627-641.

[8] a) F. Arnaud-Neu, G. Barrett, S. Fanni, D. Marrs, W. McGregor, A. M. McKervey, M.-J. Schwing-Weill, V. Vetrogon, S. Wechsler, *J. Chem. Soc., Perkin Trans. 2* **1995**, 453-461; b) F. Arnaud-Neu, S. Barboso, F. Berny, A. Casnati, N. Muzet, A. Pinalli, R. Ungaro, M.-J. Schwing-Weill, G. Wipff, *J. Chem. Soc., Perkin Trans. 2* **1999**, 1727-1738; c) F. Arnaud-Neu, S. Barboso, S. Fanni, M.-J. Schwing-Weill, *Ind. Eng. Chem. Res.* **2000,** *39,* 3489-3492.

[9] K. Araki, A. Yanagi, S. Shinkai, *Tetrahedron* **1993**, *49*, 6763-6772.

[10] a) H. Taniguchi, E. Nomura, *Chem. Lett.* **1988**, *20*, 1773-1776; b) E. Nomura, H. Taniguchi, K. Kawaguchi, Y. Otsuji, *J. Org. Chem.* **1993**, *58*,

4709-4715; c) E. Nomura, H. Taniguchi, K. Kawaguchi, Y. Otsuji, *Chem. Lett.* **1991**, *20*, 2167-2170.

[11] a) M. Mąkosza, M. Fedoryński, *Curr. Catal.* **2012**, *1*, 79-87; b) M. Mąkosza, *Pure Appl. Chem.* **2000**, *72*, 1399-1403; c) C. M. Starks, C. L. Liotta, M. Halpern, *Phase-Transfer Catalysis*, Chapman & Hall, New York, **1994**.

[12] F. Yang, Y. Wang, H. Guo, J. Xie, Z. Liu, *Can. J. Chem.* **2010**, *88*, 622-627.

[13] a) S. Shimizu, K. Kito, Y. Sasaki, C. Hirai, *Chem. Commun.* **1997**, 1629-1630; b) S. Shimizu, S. Shirakawa, T. Suzuki, Y. Sasaki, *Tetrahedron* **2001**, *57*, 6169-6173; c) S. Shimizu, S. Shirakawa, Y. Sasaki, C. Hirai, *Adv. Synth. Catal*. **2002**, *344*, 370-378; d) P. Srivastava, R. Srivastava, *Tetrahedron Lett.* **2007**, *48*, 4489-4493; e) E. Akceylan, M. Yilmaz, *Tetrahedron* **2011**, *67*, 6240-6245; f) S. Sayin, M. Yilmaz, *RSC Adv.* **2014**, *4*, 2219-2225; g) S. Shimizu, N. Shimada, Y. Sasaki, *Green Chem.* **2006**, *8,* 608-614; h) F. Yang, H. Guo, Z. Jiao, C. Li, J. Ye, *J. Iran. Chem. Soc.* **2012**, *9*, 327-332; i) Y. Xie, L. Mao, L. Li, *J. Chem. Res.* **2013**, 476-479.

[14] a) S. Shirakawa, K. Maruoka, *Angew. Chem. Int. Ed*. **2013**, *52*, 4312-4348; *Angew. Chem.* **2013**, *125*, 4408-4445; b) T. Ooi, K. Maruoka, *Angew. Chem. Int. Ed.* **2007**, *46*, 4222-4266; *Angew. Chem.* **2007**, *119*, 4300-4345; c) S.-s. Jew, H.-g. Park, *Chem. Commun.* **2009**, 7090-7103; d) J. Tan, N. Yasuda, *Org. Process Res. Dev.* **2015**, *19*, 1731-1746; e) S. Kaneko, Y. Kumatabara, S. Shirakawa, *Org. Biomol. Chem.* **2016**, *14*, 5367-5376.

[15] a) S. Bozkurt, M. Durmaz, M. Yilmaz, A. Sirit, *Tetrahedron: Asymmetry* **2008**, *19*, 618-623; b) S. Shimizu, S. Shirakawa, *Eur. J. Org. Chem.* **2009**, 1916-1924; c) S. Shirakawa, S. Shimizu, *New J. Chem*. **2010**, *34*, 1217-1222; d) W. Su, C. Jin, L. Huang, *J. Chem. Res.* **2012**, *36*, 532-535.

[16] a) R. Schettini, F. De Riccardis, G. Della Sala, I. Izzo, *J. Org. Chem.* **2016**, *81*, 2494-2505; b) R. Schettini, B. Nardone, F. De Riccardis, G. Della Sala, I. Izzo, *Eur. J. Org. Chem.* **2014**, 7793-7797; c) R. Schettini, A. D'Amato, F. De Riccardis, G. Della Sala, I. Izzo, *Synthesis* **2017**, 1319-1326; d) G. Della Sala, B. Nardone, F. De Riccardis, I. Izzo, *Org. Biomol. Chem.* **2013**, *11*, 726-731.

[17] I. Stibor, M. Růžičková, R. Krátký, M. Vindiš, J. Havlíček, E. Pinkhassik, P. Lhoták, A. R. Mustafina, Y. E. Morozova, E. K. Kazakova, V. P. Gubskaya, *Collect. Czech. Chem. Commun.* **2001**, *66*, 641-662.

[18] a) J. Kulesza, M. Guzinski, M. Bochenska, V. Hubscher-Bruder, F. Arnaud-Neu, *Polyedron*, **2014**, *77*, 89-95; b) K. Iwamoto, S. Shinkai, *J. Org. Chem.* **1992**, *57*, 7066-7073.

[19] See Supporting Information for further details.

[20] The derivatives **10** and **11** has been reported by Ungaro and coworkers through a different synthetic route, see: A. Arduini, A. Casnati, M. Fabbi, P. Minari, A. Pochini, A. R. Sicuri, R. Ungaro, *Supramol. Chem.* **1992**, *1*, 235-246.

[21] N. Sabbatini, A. Casnati, C. Fischer, R. Girardini, I. Guardigli, I. Manet, G. Sarti, R. Ungaro, *Inorg. Chim. Acta* **1996**, *252*, 19-24.

[22] V. S. Talanov, H.-S. Hwang, R. A. Bartsch, *J. Chem. Soc., Perkin Trans. 2,* **2001**, 1103-1108.

[23] For selected examples of alkylation of phenols under PTC conditions see: a) S. E. Denmark, R. C. Weintraub, N. D. Gould, *J. Am. Chem. Soc.* **2012**, *34*, 13415-13429; b) M. T. Coleman, G. LeBlanc, *Org. Process Res. Dev.* **2010**, *14*, 732-736; c) A. E. Jones, H. K. Wilson, P. Meath, X. Meng, D. W. Holt, A. Johnston, M. Oellerich, V. W. Armstrong, A. V. Stachulski, *Tetrahedron Lett.* **2009**, *50*, 4973-4977; d) J. D. Thomas, K. B. Sloan, *Tetrahedron Lett.* **2007**, *48*, 109-112; e) G. D. Yadav, N. M. Desai, *Org. Process Res. Dev.* **2005**, *9*, 749-756; f) G. D. Yadav, P. M. Bisht, *Ind. Eng. Chem. Res.* **2005,** *44,* 1273-1283; g) J. J. Vanden Eynde, I. Mailleux, *Synth. Commun.* **2001**, *31*, 1-7; h) refs. [13c,d].

[24] a) T. Ooi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **2003**, *125*, 5139-5151; b) B. Lygo, B. Allbutt, *Synlett* **2004**, 326-328; c) O. Lanitou, D. Dimotikali, E. Yannakopoulou, K. Papadopoulos, *Chem. Eng. J.* **2007**, *134*, 72-77.

[25] M. J. O'Donnell, W. D. Bennett, S. Wu, *J. Am. Chem. Soc.* **1989**, *111*, 2353-2355; T. Ooi, Y. Uematsu, K. Maruoka, *Tetrahedron Lett.* **2004**, *45*, 1675-1678.

[26] For other examples of inversion of enantioselectivity by changing the cation in PTC see: a) G. Guillena, R. Kreiter, R. van de Coevering, R. J. M. K. Gebbink, G. van Koten, P. Mazón, R. Chinchilla, C. Nájera, *Tetrahedron: Asymmetry* **2003**, *14*, 3705-3712; b) P. Mazón, R. Chinchilla, C. Nájera, G. Guillena, R. Kreiter, M. K. Gebbink, G. van Koten, *Tetrahedron: Asymmetry* **2002**, *13*, 2181-2185; c) T.-S. Kim, Y.-J. Lee, B.-S. Jeong, H.-g. Park, S.-s. Jew*, J. Org. Chem.* **2006**, *71*, 8276-8278; d) E. Brunet, A. M. Poveda, D. Rabasco, E. Oreja, L. M. Font, M. S. Batra, J. C. Rodríguez-Ubiz, *Tetrahedron: Asymmetry* **1994**, *5*, 935-948.

[27] a) S.-s. Jew, Y.-J. Lee, J. Lee, M. J. Kang, B.-S. Jeong, J.-H. Lee, M.-S. Yoo, M.-J. Kim, S.-h. Choi, J.-M. Ku, H.-g. Park, *Angew. Chem. Int. Ed.* **2004**, *43*, 2382-2385; *Angew. Chem.* **2004**, *116*, 2436-2439; b) M. Kitamura, S. Shirakawa, Y. Arimura, X. Wang, K. Maruoka, *Chem. Asian J.* **2008**, *3*, 1702-1714; c) M. Waser, K.Gratzer, R. Herchl, N. Müller, *Org. Biomol. Chem.* **2012**, *10*, 251-254.

[28] X. Wang, L. Yin, T. Yang, Y. Wang, *Tetrahedron: Asymmetry* **2007**, *18*, 108-114.

[29] For selected examples of improvement in the enantioselectivity with lower catalyt's loading see: a) F. Fini, G. Micheletti, L. Bernardi, D. Pettersen, M. Fochi, A. Ricci, *Chem. Commun.* **2008**, 4345-4347; b) T. B. Poulsen, L. Bernardi, M. Bell, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2006**, *45*, 6551-6554; *Angew. Chem.* **2006**, *118*, 6701-6704; c) ref. [16a].

[30] A. Siva, E. Murugan, *Synthesis* **2005**, 2927-2933.

[31] a) K. Hirose, *J. Inclusion Phenom. Macrocyclic Chem.* **2001**, 39, 193-209; b) K. Hirose in *Analytical Methods in Supramolecular Chemistry* (Ed.: C. A. Schalley), Wiley-VCH, Weinheim, **2007**, Chapter 2, pp. 17-54; c) S. Braun, H.-O. Kalinowsky, S. Berger, Eds., *150 and More Basic NMR experiments: A Pratical Course*, Wiley-VCH, Weinheim, **1996**, pp. 232-233.

[32] a) S. H. Strauss, *Chem Rev.* **1993**, *93*, 927-942; b) H. Nishida, N. Takada, M. Yoshimura, T. Sonoda, H. Kobayashi, *Bull. Chem. Soc. Jpn* **1984**, *57*, 2600-2604; for recent examples on the use of TFPB superweak anion in supramolecular chemistry, see: c) C. Li, X. Shu, J. Li, J. Fan, Z. Chen, L. Weng, X. Jia, *Org. Lett.* **2012**, *14*, 4126-4129; d) B. A. Blight, A. Camara-Campos, S. Djurdjevic, M. Kaller, D. A. Leigh, F M. McMillan, H. Mc Nab, A. M. Slawin, *J. Am. Chem. Soc.* **2009**, *131*, 14116-14122; e) H. Hou, K. C.-F. Leung, D. Lanari, A. Nelson, J. F. Stoddart, R. H. Grubbs, *J. Am. Chem. Soc.* **2006**, *128*, 13358-13359; for a review on counterion effects in supramolecular chemistry, see: f) T B. Gasa, C. Valente, J. F. Stoddart, *Chem. Soc. Rev.* **2011**, *40*, 57-78.

[33] a) C. Jaime, J. de Mendoza, P. Prados, P. M. Nieto, C. Sanchez, *J. Org. Chem.* **1991**, *56*, 3372-3376; b) J. O. Magrans, J. de Mendoza, M. Pons, P. Prados, *J. Org. Chem.* **1997**, *62*, 4518-4520; c) G. Bifulco, L. Gomez-Paloma, R. Riccio, C. Gaeta, F. Troisi, P. Neri, *Org. Lett.* **2005**, *7*, 5757-5760; d) G. Bifulco, R. Riccio, C. Gaeta, P. Neri, *Chem. Eur. J.* **2007**, *13*, 7185-7194.

[34] An analogous mechanism has been suggested for PTC reactions promoted by crown-ethers: a) A. Gobbi, D. Landini, A. Maia, S. Petricci, *J. Org. Chem.* **1998**, *63*, 5356-5361; b) L. Xia, Y. Jia, S. Tong, J. Wang, G. Han, *Kinet. Catal.* **2010**, *51*, 69-74.

[35] T. Nakamura, K. Tateishi, S. Tsukagoshi, S. Hashimoto, S. Watanabe, V. A. Soloshonok, J. L. Aceña, O. Kitagawa, *Tetrahedron* **2012**, *68*, 4013-4017.

[36] B. König, T. Fricke, K. Gloe, C. Chartroux, *Eur. J. Inorg. Chem.* **1999**, 1557-1562.

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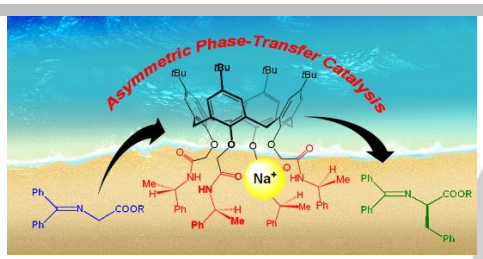
## Entry for the Table of Contents

# FULL PAPER

The recognition abilities of chiral calixarenes hosts toward alkali cation guests have been exploited for the first time in asymmetric phase-transfer catalysis. The binding affinities of a series of α-methylbenzylamine-derived calix[4]arene-amides toward $Na^+$ guest are consistent with their catalytic efficiency in the asymmetric alkylation of *N*-(diphenylmethylene)-glycine esters under phase-transfer conditions.




**Supramolecular catalysis**

*Nicola Alessandro De Simone, Rosaria Schettini, Carmen Talotta, Carmine Gaeta, Irene Izzo, Giorgio Della Sala,* and Placido Neri**

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**Directing the Cation Recognition Ability of Calix[4]arenes Toward Asymmetric Phase-Transfer Catalysis**