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Calixarenes |*Hot Paper*|

Bis-*tert*-Alcohol-Functionalized Crown-6-Calix[4]arene: An Organic Promoter for Nucleophilic Fluorination

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Abstract: A bis-*tert*-alcohol-functionalized crown-6-calix[4]arene (BACCA) was designed and prepared as a multifunctional organic promoter for nucleophilic fluorinations with CsF. By formation of a CsF/BACCA complex, BACCA could release a significantly active and selective fluoride source for S_N2 fluorination reactions. The origin of the promoting effects of BACCA was studied by quantum chemical methods. The role of BACCA was revealed to be separation of the metal fluoride to a large distance (>8 Å), thereby producing an essentially "free" F^-. The synergistic actions of the crown-6-calix[4]arene subunit (whose O atoms coordinate the countercation Cs^+) and the terminal *tert*-alcohol OH groups (forming controlled hydrogen bonds with F^-) of BACCA led to tremendous efficiency in S_N2 fluorination of base-sensitive substrates.

Introduction

Calixarenes comprise an extensively studied class of macrocyclic compounds that are usually associated with host–guest chemistry.[1] Several remarkable applications of calixarene derivatives have been devised, including their uses as platforms for shape-selective catalysts, efficient sensors, highly selective extractants, enzyme mimics, precursors of capsules, molecular glue for multimetal assemblies, building blocks for nanoporous materials, and sophisticated auxiliaries in separation science.[1,2] Among various calixarene derivatives, calix[4]arene is the simplest member of this family of compounds, which is easily accessible in large quantities as a very convenient building block.[3] There have been many reports on the complexation properties of calix[4]arene derivatives as potential ionophores with metal cations or counter anions.[3,4] In particular, Sessler et al. reported that a crown ether-strapped calix[4]arene-capped calix[4]pyrrole showed good performance as an ion-pair receptor for solvent-separated CsF ions by the binding of cesium cation to the crown ether-strapped calix[4]arene subunit together with complexation of fluoride anion within the calix[4]pyrrole core.[5]

Over the last several decades, the synthesis of fluorinated biomolecules has attracted much attention from the scientific community as a result of the importance of these compounds in the pharmaceutical sciences and in fluorine-18 labeling chemistry for applications in positron emission tomography (PET) molecular imaging studies.[6] Among the strategies for their preparation, nucleophilic fluorination of various alkyl sulfonate or halide substrates by using alkali metal fluorides (MFs) is a traditional approach because of the wide availability of these substrates and easy access to MFs as fluoride sources.[7] However, the strong Coulombic influence of the alkali metal cation (M^+) on fluoride makes MFs inactive toward nucleophilic fluorination, and MFs are also insoluble in organic media.[7,8] To solve these problems, crown ether derivatives have been widely used as phase-transfer catalysts (PTCs) to enhance both the reactivity and solubility of MFs by forming MF–crown ether complexes (Figure 1 A).[9] It is well known that selective solvation of the alkali metal cation through crown ether complexation in polar aprotic solvents (e.g., CH_3CN and DMF) generates a highly reactive "naked" fluoride source for S_N2 fluorination reactions.[10] However, the "naked" fluoride can cause various

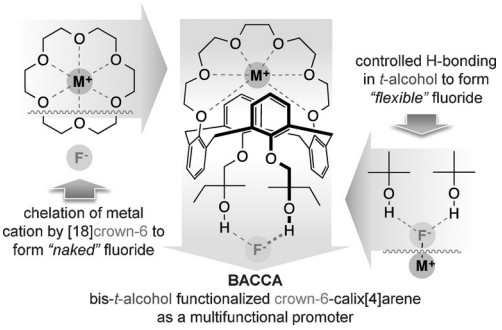

Figure 1. Concept of bis-*tert*-alcohol-functionalized crown-6-calix[4]arene (BACCA) as a multifunctional organic promoter.

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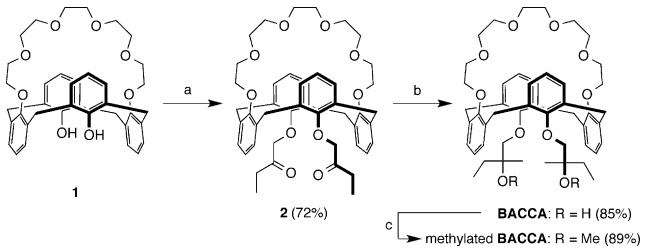
side reactions, such as elimination and/or hydroxylation, in nucleophilic fluorinations due to its strong basicity.[11]

In recent advances, we found that bulky protic *tert*-alcohol solvents such as *t*BuOH and *tert*-amyl alcohol—including oligoethylene glycols—can increase the reactivity of MFs by forming coordinated fluoride complexes (which we termed "flexible" fluoride) through controlled hydrogen bonding between the *tert*-alcohol solvent and MF (Figure 1C).[12,13] Moreover, the reduced basicity of this "flexible" fluoride allowed the S_N2 fluorination to proceed selectively while suppressing side reactions.[12] Such controlled H-bonding is also known to play a crucial role in an enzymatic nucleophilic fluorination system using a fluorinase.[14] Thus, based on a combination of the two concepts mentioned above—the crown ether-strapped calix[4]arene ion-pair receptor and *tert*-alcohol coordinated "flexible" fluoride—we designed a bis-*tert*-alcohol-functionalized crown-6-calix[4]arene (BACCA) as a new type of multifunctional organic promoter for highly efficient nucleophilic fluorination with an alkali metal fluoride (Figure 1B). In these types of promoter systems, it was expected that both the Lewis base and Lewis acid parts would cooperate to produce the "flexible" and active nucleophiles. The O atoms in the crown ether-strapped calix[4]arene subunit of BACCA can bind to M^+ (in particular, Cs^+),[5] whereas the *tert*-alcohol OH groups can act as anchors for the nucleophile (in particular, F^-)[12,13b] in a fluoride recognition site of initial interaction by hydrogen bonding to provide rate enhancement. Herein, we describe the preparation of BACCA and demonstrate its strong promoting effects for S_N2 type fluorinations with high chemoselectivity. We also examined the origin of the rate acceleration by quantum chemical methods, which showed that the crown ether and *tert*-alcohol moieties in the promoter act on Cs^+ and F^-, respectively, to separate CsF and thus produce an essentially "free" nucleophile.

Results and Discussion

The BACCA promoter was prepared as shown in Scheme 1. First, a crown-6-calix[4]arene (**1**) was prepared from the commercially available calix[4]arene according to a previously reported procedure.[4e] *O*-alkylation of the two remaining phenolic OH groups of **1** using 1-bromo-2-butanone in the presence of Cs_2CO_3 at reflux for 24 h then afforded the bis-keto intermediate **2** in 72% yield. Subsequent reaction of **2** with Grignard reagent CH_3MgBr successfully gave the BACCA in 85% yield. Finally, methylated BACCA was prepared by *O*-methylation of the two terminal OH groups using methyl iodide in order to investigate the role of the terminal *tert*-alcohol subunits of BACCA in S_N2 fluorination reactions.



Scheme 1. Synthesis of bis-*tert*-alcohol-substituted crown-6-calix[4]arene. Reagents: a) $BrCH_2COCH_2CH_3$, Cs_2CO_3, CH_3CN, reflux, 24 h; b) CH_3MgBr, THF, 0 °C to room temp, 3 h; c) CH_3I, NaH, 60 °C, 24 h.

In the present study, we used CsF as the alkali metal fluoride source, considering the three-dimensional cavity generated by the crown-6-calix[4]arene subunit on the upper rim of BACCA, which is known to have a high affinity for Cs^+. Initially, to investigate the promoter activity of BACCA, S_N2 fluorination of the model compound 2-(3-methanesulfonyloxypropoxy)naphthalene (**3**) was carried out by using 3 equivalents of CsF in the presence of BACCA (1.0 equiv) at 100 °C for 6 h in polar aprotic CH_3CN. The result of this reaction was compared with that of the same reaction in the absence of any promoter or in the presence of methylated BACCA, in which the two terminal *tert*-alcohol groups were methylated to prevent H-bonding with the fluoride of CsF (Figure 2). Fluorination in the absence of

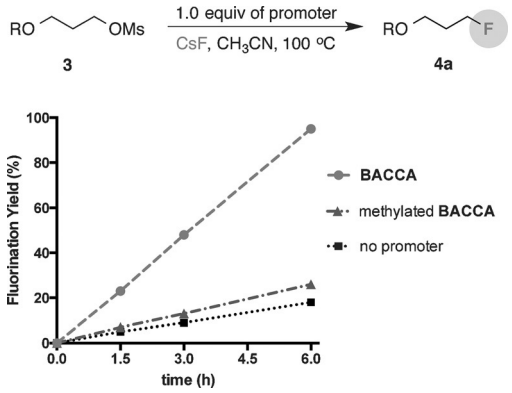
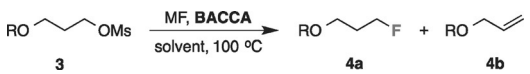


Figure 2. Nucleophilic fluorination reaction using CsF with BACCA, methylated BACCA, or without any promoter. The quantity of product was determined by ^1H NMR spectroscopy. R = naphthyl.

any promoter hardly proceeded, whereas the same reaction in the presence of BACCA proceeded smoothly and was complete within 6 h. This result showed that BACCA had very good promoter activity for S_N2 fluorination. To clarify the influence of the two terminal *tert*-alcohols of BACCA, the same reaction was performed in the presence of the dimethylated BACCA promoter, which exhibited significantly lower promoter activity in the S_N2 fluorination reaction compared to BACCA. This result suggests that controlled H-bonds between F^- and BACCA play a crucial role in enhancing the nucleophilicity of CsF by producing the "flexible" fluoride effect,[12] as well as affording fluoride recognition for the initial interaction in more effectively forming the CsF–BACCA complex (Figure 1B).[13]

To determine the optimal reaction conditions and to further study the properties of BACCA under various conditions, S_N2 fluorination reactions were performed with various alkali metal fluorides in the presence of BACCA (different molar ratios: 1.0, 0.5, or 0.25 equiv) in a range of solvent systems (Table 1). As expected, fluorination in the presence of larger amounts of BACCA proceeded faster while suppressing the competing β-

Table 1. Fluorination of mesylate **3** with alkali metal fluoride (MF) in the presence of BACCA.[a]



3 **4a** **4b**

Entry	BACCA [equiv]	Solvent	MF	*t* [h]	Yield [%][b] 4a	4b
1	1.0	CH_3CN	CsF	6	95 (91)[c]	trace
2	0.5	CH_3CN	CsF	12	90	7
3	0.25	CH_3CN	CsF	24	87	9
4	1.0	CH_3CN	RbF	16	88	10
5	1.0	CH_3CN	KF	24	42[d]	trace
6	1.0	CH_3CN	NaF	24	–[e]	–
7	1.0	*t*-amyl alcohol	CsF	1	96 (93)[c]	–
8	1.0	DMF	CsF	1.5	81	17

[a] Reaction conditions: Mesylate **3** (1.0 mmol), MF (3.0 equiv) in solvent (4.0 mL) at 100 °C; [b] yields determined by ^{1}H NMR spectroscopy; [c] yield of isolated product in parentheses; [d] 46% of starting material remained; [e] no reaction. R = naphthyl.

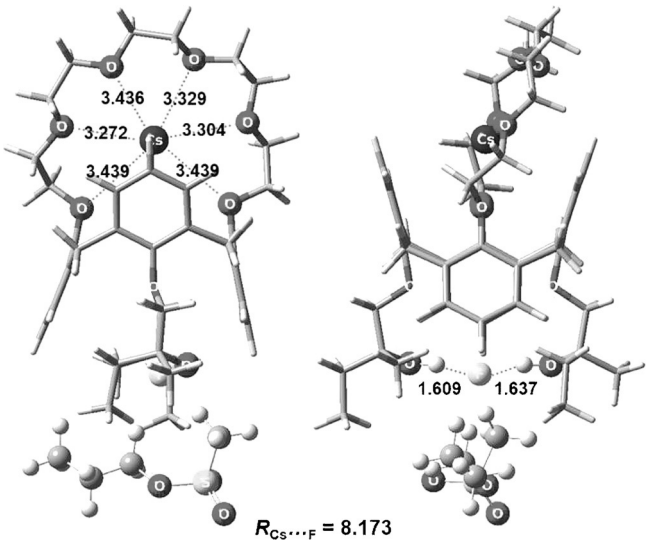


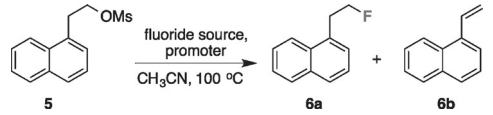
Figure 3. Two views of the pre-reaction complex.

elimination compared to the same reaction using catalytic amounts (0.5 and 0.25 equiv; Table 1, entries 1–3). Next, the efficiency of BACCA was examined with various alkali metal fluorides, such as NaF, KF, and RbF (Table 1, entries 4–6); NaF was inactive in the reaction despite the use of BACCA, whereas BACCA did not show good efficiency with either KF or RbF compared to CsF. Considering the three-dimensional cavity of BACCA and the strong electrostatic interaction of small size MFs, it may be difficult for such MFs to form a stable MF–BACCA complex that would generate a reactive fluoride during the reaction.[5] Furthermore, solvent effects with different types of solvents, such as *tert*-amyl alcohol, DMF, and 1,4-dioxane, were investigated in BACCA-promoted nucleophilic fluorination with CsF (Table 1, entries 7–9). In a bulky protic solvent, *tert*-amyl alcohol, the fluorination had a significantly faster reaction rate (within 1 h; entry 7), affording the desired fluorinated product **4a** in excellent yield without the formation of byproducts (e.g. alkenes). It seems that a synergistic effect of the *tert*-alcohol medium and BACCA promoter allowed the formation of a tetra-*tert*-alcohol-coordinated fluoride complex with BACCA.[12,15] In a polar aprotic solvent, DMF (entry 8), even though the fluorination reaction proceeded relatively quickly, a large amount of alkene byproduct (17%) was formed. Presumably, BACCA acts solely as a phase-transfer catalyst by selective solvation of the BACCA–Cs^+ complex in DMF because the O atom in DMF is a strong H-bond acceptor that competes with fluoride for interaction with the bis-terminal *tert*-alcohol subunit, thus preventing formation of the BACCA–F^- complex.

To clarify the role of BACCA for promoting the S_N2 fluorination presented in Figure 2 and Table 1, we examined the structure of the calculated pre-reaction complex (B3LYP/6-31G**[16]/LANL2DZ(Cs)[17] SCRF = SMD method with the SMD technique[18] for the solvent continuum, as implemented in the Gaussian 09 suite of programs[19]) for the reaction in CH_3CN (Figure 3). Bulky substrate **3** was modeled as C_3H_7–OMs, to simplify the computational effort. The most striking feature was the extremely large distance (> 8 Å) between the counter cation Cs^+ and the nucleophile F^-. The Cs···F distance in the ion pair CsF was 2.347 Å,[20] which indicates that BACCA essentially dissociates CsF. Figure 3 also shows that this very desirable capability of BACCA was achieved by two cooperating effects: the oxygen atoms in the crown-6-calix[4]arene subunit strongly coordinate to the counter cation Cs^+, and the two terminal *tert*-alcohols form hydrogen bonds with F^-. Although the presumed role of crown ethers for promoting S_N2 reactions by separating the metal cation from the nucleophile was considered dubious in recent investigations,[21] here the crown ether clearly performs this important function with the help of the OH groups. These two factors exert a strong synergistic influence to overcome the powerful Coulombic attraction between Cs^+ and F^- and to thereby separate the ions. The substrate is situated in such a manner that the nucleophilic F^- may easily attack the close-lying electropositive carbon center of the substrate by interactions of F^- with the electropositive carbon atom and the methyl hydrogen atoms. These intricate interactions among Cs^+, F^-, BACCA, and the substrate function to form a pre-reaction complex in a configuration that is extremely favorable for S_N2 fluorination.

Our study further focused on the influence of BACCA on the chemoselectivity of the S_N2 fluorination reaction. For this purpose, S_N2 fluorinations were conducted with the base-sensitive substrate 1-(2-methanesulfonylethyl)naphthalene (**5**) under a range of conditions (Table 2). S_N2 fluorinations of mesylate **5** using "naked" fluoride sources generated from conventional PTC systems, such as tetrabutylammonium fluoride (TBAF) and CsF/18-crown-6 complex in CH_3CN, predominantly afforded styrene **6b** (88% and 81%, respectively; Table 2, entries 1 and 2), with the corresponding fluorinated product **6a** formed in only 12% and 19% yield, respectively. The use of CsF in the absence of any PTC system in the same reaction gave a very low reaction rate, as well as poor chemoselectivity (Table 2, entry 3). Gratifyingly, the BACCA promoter not only increased the nucleophilicity of CsF but also significantly enhanced the chemoselectivity, even in a polar aprotic medium (CH_3CN) compared with conventional PTCs, and this fluorination reac-

Table 2. Chemoselective fluorination of base-sensitive substrate **5** in the presence of BACCA.[a]



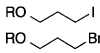
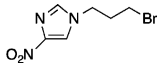
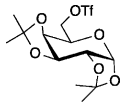
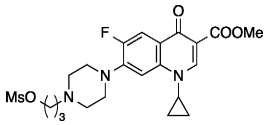
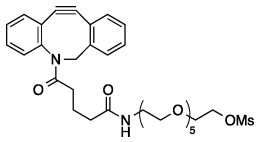
Entry	Fluoride source with or without promoter	*t* [h]	Yield [%][b]	
			6a	**6b**
1	TBAF	0.5	12	88
2	CsF/18-crown-6	1	19	81
3	CsF	5	10[c]	17
4	CsF/BACCA	5	81	19
5	CsF/methylated BACCA	5	9	91
6	CsF/BACCA in *tert*-amyl alcohol[d]	1	92 (90)[e]	8

[a] Reaction conditions, unless otherwise indicated: **5** (1.0 mmol), fluoride source (3.0 equiv) with or without promoter (1.0 equiv) in CH_3CN (4.0 mL) at 100 °C; [b] yields determined by ^{1}H NMR spectroscopy; [c] 73% of the starting material remained; [d] reaction performed in 4.0 mL of *tert*-amyl alcohol instead of CH_3CN; [e] yield of isolated product in parentheses.

tion afforded product **6a** in 81% yield along with only 19% styrene **6b** (Table 2, entry 4). Interestingly however, the same reaction in the presence of methylated BACCA showed quite poor chemoselectivity, providing predominantly the styrene byproduct **6b** (91%) with only 9% of the fluorinated product **6a** (Table 2, entry 5), which suggests that methylated BACCA has only a PTC-like property. This result shows that the bis-*tert*-alcohol subunit of BACCA is a very important site in the reaction process both for chemoselectivity and for promoter activity. In particular, these observations (entries 4 and 5) were highly consistent with our hypothesis that the bis-*tert*-alcohol subunit of BACCA interacts with F^- to generate a less basic but active *tert*-alcohol-coordinated "flexible" fluoride and provide a "protic" environment[12] in the reaction medium by controlled H-bonding, which is similar to the enzymatic fluorination system associated with fluorinase.[14] Next, we investigated the synergistic effect between the BACCA promoter and *tert*-alcohol medium in the fluorination of base-sensitive substrate **5** (Table 2, entry 6). Gratifyingly, as expected, this BACCA-promoted fluorination reaction in *tert*-amyl alcohol provided the best performance, with much higher selectivity and a faster reaction rate, to afford **6a** in 92% yield with only 8% styrene **6b**.

We also examined the scope of this BACCA-promoted fluorination in *tert*-alcohol medium with a variety of substrates (Table 3). Secondary alkyl bromides are known to be another representative group of base-sensitive substrates for which it is difficult to obtain secondary alkyl fluorides by nucleophilic fluorination with TBAF, even in protic *tert*-alcohol media (Table 3, entries 3 and 4, respectively). Moreover, fluorination in *tert*-alcohol by using CsF is also not efficient for producing *sec*-alkyl fluorides, due to the extremely slow reaction rate (Table 3, entry 2). Notably, the *sec*-alkyl fluoride was readily produced by this BACCA-promoted fluorination in *tert*-alcohol medium (Table 3, entry 1) compared with other fluorination procedures developed to date, such as KF in triethylene glycol[13a] and polystyrene-supported pentaethylene glycol-promoted fluorination with CsF in *tert*-alcohol[13b] (Table 3, entries 5 and 6, respectively). The *sec*-alkyl fluoride was also obtained from the corresponding *sec*-alkyl tosylate by the BACCA-promoted fluorination reaction in *tert*-alcohol in excellent yield (90%; Table 3, entry 7). The fluorination of *primary* iodo- and bromoalkanes in the presence of BACCA in *tert*-amyl alcohol proceeded highly selectively, affording **6a** in good yields (83% and 91%; Table 3, entries 8 and 9, respectively). Interestingly, a primary bromoalkyl nitroimidazole was converted into the corresponding fluorinated product in 85% yield with an unexpectedly fast reaction rate ($t = 45$ min; Table 3, entry 10), compared with that of the bromoalkane ($t = 9$ h; entry 9) under the same fluorination conditions. Presumably, strong H-bonding interactions between the CsF/BACCA complex and the N and O atoms of the nitroimidazole substrate as H-bond acceptors may facilitate their close proximity, thereby increasing the reaction rate. 3-Fluoro-picoline-*N*-oxide was obtained from 3-chloro-picoline-*N*-oxide in 78% yield by using

Table 3. BACCA-promoted S_N2 fluorination of various substrates with CsF in *tert*-alcohol medium.

Entry	Substrate	Method[a]	*t* [h]	*T* [°C]	Yield [%][b]	
					Product	Alkene
1		A	12	100	86	12
2[c]		B	12[d]	100	28	16
3[c]		C	3	100	8	92
4[c]		D	3	100	19	81
5[c]		E	4	100	59	23
6[c]		F	3	100	80	17
7		A	3	100	90	8
8[d]		A	5	100	83	17
9[d]		A	8	100	91	9
10		A	45 min	90	85	7
11		A	5	100	78	–
12		A	1	80	96	–
13		A	5	100	97	–
14		A	5	100	93	–

[a] Method A: substrate (1.0 mmol), CsF (3.0 equiv), BACCA (1.0 equiv) in *tert*-amyl alcohol (4.0 mL); method B: with CsF in *tert*-amyl alcohol; method C: with TBAF in CH_3CN; method D: with TBAF in *tert*-amyl alcohol; method E: with KF (5.0 equiv) in triethylene glycol; method F: with CsF and polymer-supported pentaethylene glycol (1.0 equiv) in *tert*-amyl alcohol; [b] yield of isolated product; [c] reference [13b]; [d] yields determined by ^{1}H NMR spectroscopy.

this method (Table 3, entry 11) and the fluorination of a sugar triflate proceeded at 80 °C within 1 h, to provide the corresponding fluoro-sugar product in 96% yield (Table 3, entry 12). A fluoropropyl ciprofloxacin,[22] which has antibacterial activity, was produced in 97% yield by reaction with the corresponding mesylate precursor (Table 3, entry 13). Finally, considering the importance of azadibenzocyclooctyne (ADIBO) derivatives in copper-free "click chemistry" for diverse applications of fluorine-18 labeling chemistry,[23] a fluorinated ADIBO derivative was prepared in 93% yield from the corresponding mesylate precursor by using our fluorination protocol (Table 3, entry 14).

Conclusion

In conclusion, we have prepared BACCA as a new type of multifunctional organic promoter designed for S_N2 fluorination with CsF. In this reaction, BACCA showed a PTC effect by binding of Cs^+ to its crown-6-calix[4]arene subunit, thus dissociating CsF in solution with the release of an essentially "free" fluoride. Moreover, the bis-terminal *tert*-alcohol subunit of BACCA played crucial roles in enhancing the nucleophilicity of CsF and in reducing the formation of byproducts by generating *tert*-alcohol-coordinated "flexible" fluoride from controlled H-bonding between the F^- nucleophile and the *tert*-alcohol groups of BACCA, as established in a quantum chemical study. In particular, the BACCA-promoted fluorination in *tert*-alcohol medium exhibited tremendous efficiency in the S_N2 fluorination of base-sensitive substrates, allowing reactions to proceed with much higher chemoselectivity and at a significantly faster rate due to the synergistic effects of BACCA and the *tert*-alcohol solvent. Our current work is focused on developing more efficient calix[4]arene based multifunctional promoters through structural modifications and also on PET applications of the synthetic protocols for rapid ^{18}F labeling of radiopharmaceuticals.

Experimental Section

1,3-Alternate 25,27-Bis(propionylmethoxy)-26,28-calix[4]crown-6 (2): A solution of crown-6-calix[4]arene(**1**, 1.0 g, 1.59 mmol), 1-bromo-2-butanone (961 mg, 6.37 mmol), and Cs_2CO_3 (1.04 g, 3.18 mmol) in CH_3CN (35 mL) was heated at reflux for 24 h under a nitrogen atmosphere. After the reaction mixture had cooled to room temperature, the solvent was removed under reduced pressure. To the resulting brownish solid, 5% aqueous HCl (35 mL) and CH_2Cl_2 (25 mL) were added, and the organic layer was separated, washed by water (35 mL), and dried over anhydrous sodium sulfate. After removal of the solvent, flash column chromatography (EtOAc/hexane; 1:3) gave **2** (881 mg, 1.15 mmol, 72%) as a white solid: M.p. 113–117 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.13$ (t, $J = 7.2$ Hz, 6H), 2.62 (q, $J = 7.2$ Hz, 4H), 3.18 (d, $J = 13.6$ Hz, 4H), 3.50–3.75 (m, 12H), 4.01 (t, $J = 6.8$ Hz, 4H), 4.27 (t, $J = 6.4$ Hz, 4H), 4.36–4.48 (m, 8H), 6.14 (d, $J = 7.2$ Hz, 4H), 6.27 (t, $J = 7.2$ Hz, 2H), 6.86 (t, $J = 7.6$ Hz, 2H), 7.02 ppm (d, $J = 7.6$ Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 7.4$, 31.1, 32.7, 69.8, 70.8, 70.9, 71.0, 73.1, 78.9, 122.4, 123.0, 128.0, 129.2, 133.2, 136.3, 154.6, 157.9, 207.1 ppm; HRMS (FAB TOF): *m/z* calcd for $C_{46}H_{55}O_{10}$ $[M+H]^+$ 767.3795; found 767.3798.

Bis-*tert*-alcohol-functionalized crown-6-calix[4]arene (BACCA): Under nitrogen, to a solution of compound **2** (850 mg, 1.10 mmol) in anhydrous THF (25 mL) was added CH_3MgBr in THF solution (3 M, 2.2 mL, 6.6 mmol) dropwise at 0 °C. The reaction mixture was stirred for 3 h and then quenched by slow addition of 5% aqueous HCl (20 mL). The organic layer was extracted with EtOAc (3× 30 mL), dried over sodium sulfate, and concentrated under reduced pressure on a rotary evaporator. Flash column chromatography (EtOAc/hexane; 1:3) afforded BACCA (743 mg, 0.93 mmol, 85%) as a white solid: M.p. 354–358 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.00$ (t, $J = 7.6$ Hz, 6H), 1.34 (s, 6H), 1.74 (q, $J = 7.6$ Hz, 4H), 3.19 (d, $J = 14.0$ Hz, 4H), 3.47–3.76 (m, 16H), 4.00 (t, $J = 6.8$ Hz, 4H), 4.27 (t, $J = 6.4$ Hz, 4H), 4.45 (d, $J = 13.2$ Hz, 4H), 5.97 (d, $J = 7.6$ Hz, 4H), 6.18 (t, $J = 7.6$ Hz, 2H), 6.95 (t, $J = 7.6$ Hz, 2H), 7.12 ppm (d, $J = 7.6$ Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 8.4$, 23.5, 30.8, 31.9, 70.1, 70.2, 70.8, 71.0, 72.5, 82.5, 122.2, 122.8, 127.7, 129.4, 132.8, 132.9, 136.8, 136.9, 154.6, 158.0 ppm; HRMS (FAB TOF): *m/z* calcd for $C_{48}H_{63}O_{10}$ $[M+H]^+$ 799.4421, found 799.4423.

Methylated BACCA: Under nitrogen, methyl iodide (1.78 g, 12.52 mmol) was added to a suspension of NaH (60% in mineral oil, 336 mg, 8.4 mmol) and BACCA (500 mg, 0.63 mmol) in DMF (15 mL), and stirred for 1 h at room temperature and then for 24 h at 60 °C. After DMF was removed under reduced pressure, EtOAc (15 mL) and water (35 mL) were added to the crude product. Then, the aqueous layer was extracted with EtOAc (3×20 mL) and the combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. Flash column chromatography EtOAc/hexane; 1:3) gave the methylated BACCA (462 mg, 0.56 mmol, 89%) as a slightly yellow oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.95$ (t, $J = 8$ Hz, 6H), 1.38 (s, 4H), 1.70–190 (m, 4H), 3.19 (d, $J = 14$ Hz, 2H), 3.23 (s, 6H), 3.59 (d, $J = 6.8$ Hz, 2H), 3.61–3.85 (m, 10H), 3.96 (t, $J = 8$ Hz, 4H), 4.24 (t, $J = 8$ Hz, 2H), 4.40–4.52 (m, 4H), 5.96 (d, $J = 7.6$ Hz, 4H), 6.08 (t, $J = 7.6$ Hz, 2H), 6.96 (t, $J = 7.2$ Hz, 2H), 7.12 ppm (d, $J = 7.2$ Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 8.0$, 20.8, 27.9, 31.1, 49.5, 49.5, 69.5, 70.9, 71.2, 71.4, 72.4, 76.9, 78.7, 122.2, 122.6, 127.7, 129.5, 132.9, 132.9, 132.9, 133.0, 137.0, 155.4, 158.3 ppm; HRMS (FAB TOF): *m/z* calcd for $C_{15}H_{28}N_2O_6$ $[M]^+$ 826.4656; found 826.4658.

Typical procedure for BACCA-promoted fluorination in CH_3CN (Table 1, entry 1): CsF (456 mg, 3 mmol) was added to the mixture of mesylate **3** (281 mg, 1.0 mmol) and BACCA (799 mg, 1.0 mmol) and CH_3CN (4 mL) in a reaction vial. The reaction mixture was stirred for 6 h at 100 °C. The reaction time was determined by monitoring with TLC. The reaction mixture was filtered and the solid was washed with diethyl ether (20 mL). The solvent was removed from the filtrate under reduced pressure. Flash column chromatography (10% EtOAc/hexanes) of the residue afforded 2-(3-fluoropropoxy)naphthalene (**4a**) as a colorless oil (186 mg, 0.91 mmol, 91%). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.14$–2.39 (m, 2H), 4.24 (t, $J = 6.2$ Hz, 2H), 4.72 (dt, $J = 46.8$, 5.8 Hz, 2H), 7.16–7.22 (m, 2H), 7.34–7.53 (m, 2H), 7.76–7.83 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 30.4$ (d, $J = 20.1$ Hz), 63.6 (d, $J = 25.3$ Hz), 80.8 (d, $J = 163.9$ Hz), 106.8, 118.8, 123.6, 126.4, 126.7, 127.6, 129.1, 129.4, 134.6, 156.7 ppm; MS (EI) *m/z* 204 (M^+); HRMS (EI): *m/z* calcd for $C_{13}H_{13}FO$ $[M]^+$ 204.0950; found 204.0932. Registry No. provided by the author: 398–53–8.

Typical procedure for BACCA-promoted fluorination in *tert*-alcohol medium (Table 2, entry 6): CsF (456 mg, 3 mmol) was added to the mixture of mesylate **5** (250 mg, 1.0 mmol), BACCA (799 mg, 1.0 mmol) and *tert*-amyl alcohol (4 mL) in a reaction vial. The reaction mixture was stirred for 1 h at 100 °C. The reaction time was determined by monitoring with TLC. The reaction mixture was filtered and the solid was washed with diethyl ether (20mL). The sol-

vent was removed from the filtrate under reduced pressure. Flash column chromatography (10% EtOAc/hexanes) of the residue afforded 1-(2-fluoroethyl)naphthalene (**6a**) as a colorless oil (157 mg, 0.90 mmol, 90%). ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 3.44$ (dt, $J = 13.7$, 6.9 Hz, 2H), 4.75 (dt, $J = 47.5$, 6.9 Hz, 2H), 7.30–7.37 (m, 2H), 7.41–7.49 (m, 2H), 7.70 (d, $J = 8.2$ Hz, 1H), 7.80 (d, $J = 8.2$ Hz, 1H), 7.95 ppm (d, $J = 8.2$ Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 33.9$ (d, $J = 20.1$ Hz), 83.6 (d, $J = 168.0$ Hz), 123.4, 125.6, 125.7, 126.3, 127.3, 127.7, 128.9, 132.0, 132.8 (d, $J = 8.5$ Hz), 133.9 ppm; MS (EI): *m/z* 174 $[M]^+$, 141 (100); elemental analysis calcd (%) for $C_{12}H_{11}F$: C 82.73, H 6.36; found: C 82.63, H 6.34. Registry No. provided by the author: 693785–25–0.

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