OL | Organic Letters

Cite This: Org. Lett. XXXX, XXX, XXX–XXX

Letter

pubs.acs.org/OrgLett

Bis-triethylene Glycolic Crown-5-calix[4]arene: A Promoter of Nucleophilic Fluorination Using Potassium Fluoride

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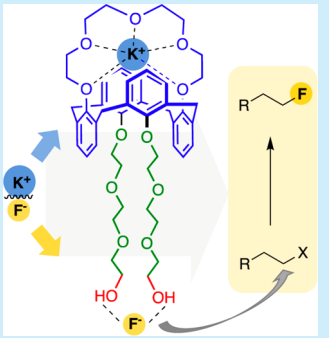
Supporting Information

ABSTRACT: We designed and synthesized a bis-triethylene glycolic crown-5-calix[4]arene (BTC5A) as a multifunctional promoter for nucleophilic fluorination using KF. The synergetic effect of the calix-crown moiety and ethylene glycols of BTC5A enabled KF to be easily dissolved in organic solvents and activated the fluoride in even nonpolar aprotic media. To validate its practicality, the S_N2 fluorinations including ^{18}F-fluorination of various substrates were successfully conducted using KF(or $[^{18}F]F^-$) in the presence of BTC5A.



Despite the low abundance of fluorine-containing organic compounds in nature, they are of considerable interest in the materials and pharmaceutical research areas, especially in radiopharmaceutical science in the context of fluorine-18 ($t_{1/2}$ = 110 min) use in positron emission tomography (PET).[1,2] Nucleophilic fluorination using a fluoride source in polar aprotic media (e.g., CH_3CN, DMF) is commonly used to prepare fluorinated organic molecules.[3] The use of potassium fluoride (KF) as a nucleophilic fluorine source is traditionally a priority consideration for this type of reaction due to its availability, low cost, and thermal stability.[4] However, the high lattice energy of KF results in low solubility and reactivity in reaction media, which restricts its wider applications for nucleophilic fluorination.[4,5] To overcome these issues, crown ether derivatives such as 18-crown-6 and Kryptofix 2.2.2 (K222) have been investigated as phase-transfer catalysts (PTCs) to render KF soluble and facilitate its reactivity by selective solvation of the K^+ cation in organic solvents.[6] Whereas 2D-structured 18-crown-6 inadequately activates KF, strong coordination between the K^+ cation and the 3D cavity of K222 results in the release of reactive "naked" fluoride as a strong nucleophile.[1,6,7] However, this reactive fluoride can also cause unexpected side reactions (e.g., β-elimination or hydroxylation) due to its also high basicity.[7] Furthermore, the nitrogen of K222 may attack substrate electron-deficient sites to cause *N*-alkylation.[8]

Protic solvents, such as tertiary alcohols and oligo-ethylene glycols, have recently been reported to be suitable for chemoselective nucleophilic fluorination using alkali metal fluorides.[1,9,10] In particular, oligo-ethylene glycols appear to provide a less basic but more reactive "*flexible*" fluoride from KF by controlled hydrogen-bonding between fluoride and their terminal alcohols ("*flexible*" fluoride makes S_N2 fluorination proceed selectively and suppress side reactions due to its low basicity and protic environment), and by selectively solvating K^+ with polyether, which can act as a Lewis base.[1,9,10] However, the high boiling points of these oligo-ethylene glycols restricts due to downstream separation issues.[11]

Calixarenes as macrocyclic oligomers have received a great deal of interest in host–guest chemistry as enzyme mimics, ion-pair receptors, extractants, catalyst platforms, and molecular recognition agents.[12,13] More recently, a bis-*tert*-alcohol-functionalized crown-6-calix[4]arene (BACCA) was devised as a PTC system for nucleophilic fluorination using CsF.[14] BACCA could facilitate the reactivity of CsF by selective binding of Cs^+ toward its crown-6-calix[4]arene moiety as well as the formation of "*flexible*" fluoride via the controlled hydrogen bonding between the fluoride and its *tert*-alcohol moiety with minimization of the β-elimination side reaction. Several calixarenes derivatives have been designed to bind specific alkali metals.[14,15] For example, crown-6-calix[4]arene and crown-5-calix[4]arene selectively bind Cs^+ and K^+, respectively, due to their geometries and crown-calix cavity sizes.[15]

In the present study, we designed and synthesized a nucleophilic fluorination promoter called bis-triethylene glycolic crown-5-calix[4]arene (BTC5A) for activation of KF (Figure 1). BTC5A possesses multiple subunits that weaken the strong ionic interaction of KF. We expected that oxygen atoms present in the crown-calix moiety act as a Lewis base and coordinate with K^+[10] and predicted two polyethers

Received: February 20, 2019

DOI: 10.1021/acs.orglett.9b00649
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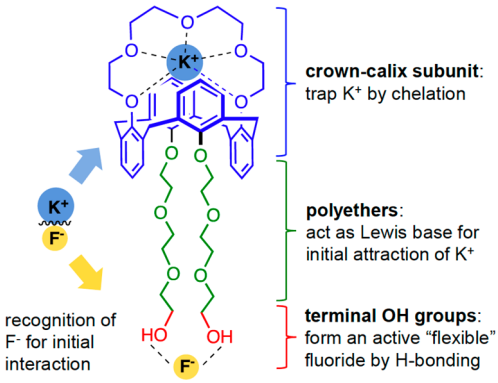
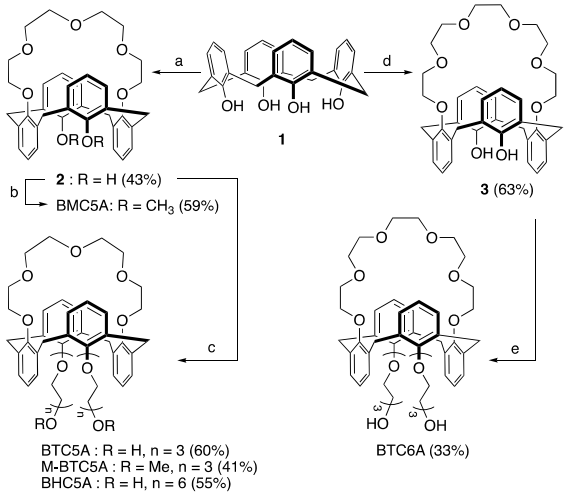


Figure 1. Bis-triethylene glycol-functionalized crown-5-calix[4]arene (BTC5A) as a promoter of S_N2 fluorination by KF.

containing oxygen atoms would attract K^+ and facilitate its approaching crown-calix cavities. In addition, we anticipated terminal OH groups would hydrogen bond with fluoride to make it *"flexible"* fluoride[9] with enhanced fluorination reactivity and selectivity. These cooperative activities were found to enhance the reactivity of KF and provide excellent fluorination efficiencies. In addition, rates of fluorination were markedly enhanced in different solvents, even in toluene (a nonpolar aprotic system), which is known to be unsuitable for the S_N2-type fluorination.

BTC5A and its derivatives were synthesized as shown in Scheme 1. Calix[4]arene (**1**), the catalyst platform, was

Scheme 1. Synthesis of Bis-oligothylene Glycolic Crown-calix[4]arenes[a]

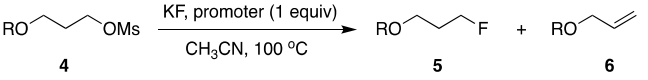


[a]Reagents: (a) $TsO(CH_2CH_2O)_3CH_2CH_2OTs$, K_2CO_3, CH_3CN, 130 °C, 3 h, microwave; (b) CH_3I, NaH, DMF, 30 °C, 3 h; (c) $TsO(CH_2CH_2O)_nR$, Cs_2CO_3, CH_3CN, 100 °C, 4 days; (d) $TsO(CH_2CH_2O)_4CH_2CH_2OTs$, K_2CO_3, CH_3CN, 100 °C, 4 days; (e) $TsO(CH_2CH_2O)_3H$, Cs_2CO_3, CH_3CN, 100 °C, 4 days.

prepared as previously described.[16] Crown-5-calix[4]arene (**2**) and crown-6-calix[4]arene (**3**) were prepared in slightly different manners. Compound **2** was prepared by the *O*-alkylation of **1** at two of its four phenolic OH groups using tetraethylene glycol ditosylate and K_2CO_3 in microwave synthesizer for 3 h, whereas **3** was prepared by the *O*-alkylation of calix[4]arene in the presence of pentaethylene glycol ditosylate and K_2CO_3 at 100 °C for 4 days. Next, *O*-alkylation of the remaining two OH groups of **2** or **3** in the presence of the corresponding ethylene glycol tosylate and Cs_2CO_3 at 110 °C for 4 days gave BTC5A, methylated bis-triethylene glycolic crown-5-calix[4]arene (M-BTC5A), bis-hexaethylene glycolic crown-5-calix[4]arene (BHC5A), and bis-triethylene glycolic crown-6-calix[4]arene (BTC6A). In addition, bis-methylated crown-5-calix[4]arene (BMC5A) was also prepared by *O*-methylation of the two phenolic OH groups of **2** with methyl iodide to validate the PTC effect of only 3D cavity of BMC5A toward KF in nucleophilic fluorination.

To investigate the catalytic ability of a part of BTC5A, 2-(3-methanesulfonyloxypropoxy)naphthalene (**4**) was subjected to nucleophilic fluorination using 3 equiv of KF in the presence of various promoters in acetonitrile (Table 1). S_N2 fluorination

Table 1. Nucleophilic Fluorination of Mesylate 4 in the Presence of Various Promoters[a]



4 5 6

			yield[b] (%)	
entry	promotor	time (h)	5	6
1	BMC5A	12	93	7
2	triethylene glycol (2 equiv)	12	22[c]	
3	BTC5A	6	97	3
4	BHC5A	6	97	3
5	BTC6A	24	97	2
6	M-BTC5A	9	93	6
7	18-crown-6	18	91	9
8	K222	3	88	11

[a]All reactions were carried out on a 0.05 mmol reaction scale of mesylate **4** with 3 equiv of KF in 0.2 mL of CH_3CN. [b]Yields were determined by ^1H NMR spectroscopy. [c]78% of starting material remained. R = 2-naphthyl.

using BMC5A, which has only a crown-5-calix[4]arene cavity, showed moderate fluorination activity and provided the fluorinated product **5** in 93% yield with 7% of **6** as an alkene byproduct (entry 1), whereas 2 equiv of triethylene glycol barely promoted the same reaction (entry 2). Notably, when two subunits (crown-5-calix[4]arene and triethylene glycols) were combined to make BTC5A, fluorination activity was obviously increased (entry 3). Furthermore, this result was superior to that obtained when 18-crown-6 was used as a conventional PTC in terms of reactivity and selectivity (entry 7). A comparison of entries 3 and 8 showed BTC5A provided less alkene than K222 because the two terminal hydroxy groups of BTC5A formed hydrogen bonding with fluoride to generate reactive but less basic *"flexible"* fluoride.[9] A comparison of entries 3 and 4 showed lengths of ethylene glycol did not influence fluorination activity. Because BTC5A has shorter ethylene glycol chains than BHC5A, and thus, generates less chemical waste, we decided to use BTC5A for further reaction studies. BTC6A, which has a larger cavity than BTC5A, was also evaluated as a promoter for KF (entry 5), but as was expected, the crown-6-calix[4]arene unit, which is known to be suitable for Cs^+, could did not efficiently coordinate with K^+ and fluorinations required considerably longer. Finally, in order to confirm the hydrogen bonding effect, which we consider enhances reactivity and selectivity, we synthesized M-BTC5A in which terminal hydroxy groups

DOI: 10.1021/acs.orglett.9b00649
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were blocked by methyl groups (entry 6). As has been previously reported,[6] blocking H-bonding between BTC5A and fluoride markedly reduced reactivity and selectivity.

We conducted a kinetic study to investigate the effects of solvent and of the terminal OH groups of BTC5A on fluorination (Figure 2) and compared reaction rates for

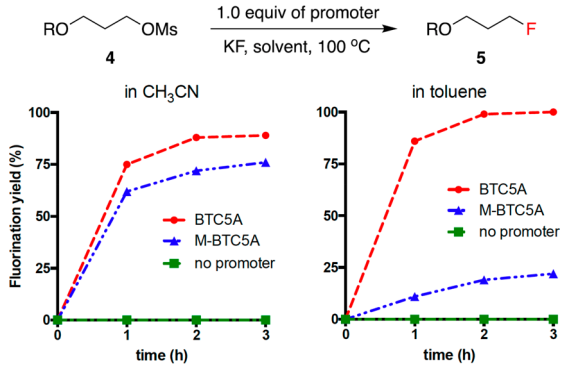
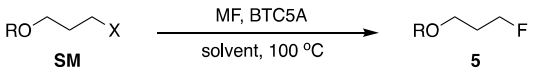


Figure 2. Catalytic activities of BTC5A and M-BTC5A on S_N2 fluorination by KF in CH_3CN or toluene reaction medium. Yields were determined by ^1H NMR spectroscopy. R = 2-naphthyl.

BTC5A, M-BTC5A, or without either in two solvent systems, that is, CH_3CN (a polar aprotic solvent) and toluene (a nonpolar aprotic solvent). Naturally, when an alkali metal salt is used for a S_N2 reaction polar aprotic solvents are more suitable than nonpolar aprotic solvents, as in polar aprotic solvents metal cations are selectively solvated by ion−dipole interactions resulting in an increase in nucleophilicity, whereas in nonpolar aprotic solvents the absence of a solvent dipole moment means that alkali metal salts are barely solvated.[3] As we expected, in both cases, fluorination reactions were more rapid in the presence of promoter. However, S_N2 fluorination of **4** in toluene proceeded more efficiently and faster than the same reaction in CH_3CN, which we suspect was caused by hydrogen bonding between the terminal OH groups of BTC5A and fluoride. We also performed the same reaction using M-BTC5A. Surprisingly, the fluorination activity of M-BTC5A in toluene (compared with CH_3CN) was drastically lower than that of BTC5A, indicating that hydrogen bonding between promoter hydroxy groups and fluoride plays an important role in the reaction. We consider that the terminal hydroxy groups in BTC5A could produce "*flexible*" fluoride[9] easily in toluene, but that in CH_3CN, the terminal hydroxy groups of BTC5A are partially inhibited by dipole−dipole interactions with CH_3CN, and thus, hydrogen bonding between the terminal hydroxy groups of BTC5A and fluoride did not efficiently produce "*flexible*" fluoride. Accordingly, the reaction rate was slower in CH_3CN than in toluene and rates were no different for BTC5A or M-BTC5A.

Inspired by the results of the kinetic study, we conducted nucleophilic fluorination in a range of solvents and using different alkali metals (Table 2). We confirmed toluene produced better fluorination rates than CH_3CN (Figure 2) and screened diverse aliphatic and aromatic hydrocarbon nonpolar aprotic solvents. Notably, all of these hydrocarbon nonpolar aprotic solvents greatly improved fluorination rates (3 h, 100%, entries 1−5). This result is contrary to the expectation that a nonpolar aprotic solvent is undesirable for nucleophilic displacement reactions. Next, the same reaction using 0.5 equiv of BTC5A showed a similar reaction rate (slightly slower, entry 6) to the reaction using 1.0 equiv of BTC5A. However, using 0.25 equiv of BTC5A required a more than 12 h reaction time (entry 7) to complete the fluorination. We also investigated the fluorination efficiency of BTC5A in the presence of NaF, RbF, and CsF (entries 8−10). NaF was

Table 2. Nucleophilic Fluorination in the Presence of BTC5A under Different Reaction Conditions[a]



entry	solvent	BTC5A (equiv)	X	MF	time (h)	yield[b] (%) SM	yield[b] (%) 5
1	toluene	1.0	OMs	KF	2.5		100 (95[c])
2	benzene	1.0	OMs	KF	3		100
3	xylene	1.0	OMs	KF	3		100
4	cyclohexane	1.0	OMs	KF	3		100
5	heptane	1.0	OMs	KF	3		100
6	toluene	0.5	OMs	KF	3	trace	98
7	toluene	0.25	OMs	KF	12	4	96
8	toluene	1.0	OMs	NaF	24	100	
9	toluene	1.0	OMs	RbF	12	6	94
10	toluene	1.0	OMs	CsF	1.5		100
11[d]	toluene	1.0	OMs	CsF	3	97	trace
12	DMF	1.0	OMs	KF	5		89[e]
13	1,4-dioxane	1.0	OMs	KF	12	11	88
14	*tert*-amyl alcohol	1.0	OMs	KF	0.5	trace	97
15	*tert*-amyl alcohol	1.0	OTs	KF	0.5	trace	97
16	*tert*-amyl alcohol	1.0	I	KF	3		71[f]
17	*t*-amyl alcohol	1.0	Br	KF	3		90[g]
18	*tert*-amyl alcohol	-	OMs	KF	12	96	4

[a]Unless otherwise indicated, all reactions were carried out with **SM** (0.05 mmol) and MF (3.0 equiv) in 0.2 mL of solvent. [b]Yields were determined by ^1H NMR spectroscopy. [c]Yield of isolated product obtained using 1.0 mmol of **4**. [d]BMC5A was used instead of BTC5A. [e]With 11% alcohol. [f]With 28% alkene. [g]With 10% alkene. R = 2-naphthyl.

DOI: 10.1021/acs.orglett.9b00649
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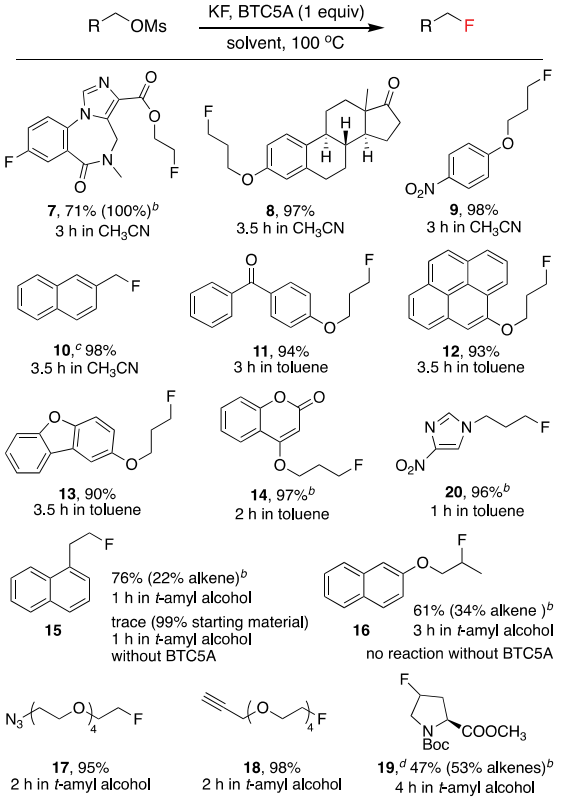
completely inactive. The reactions using RbF took a considerable time (~12 h) to convert **4** into **5** in 94% yield. Unexpectedly, although Cs^+ was not a suitable size for crown-5-calix[4]arene cavity,[15] the fluorination with CsF completed only in 1.5 h, which has faster reaction rate compared to the same reaction with KF and RbF (entries 1, 9, and 10). We offer two reasons for these results: (i) CsF has a weaker lattice energy than KF or RbF and (ii) the ethylene glycols play a crucial role in the activation of CsF. To clarify these results, we conducted fluorination with CsF in the presence of BMC5A promoter without an ethylene glycol subunit in toluene, and as was expected, the fluorination rate decreased noticeably (3 h, 3%, entry 11). Next, we investigated nucleophilic fluorination with BTC5A in polar aprotic solvents. In DMF, it took 5 h to complete the fluorination reaction, affording the fluoro product **5** in 89% yield with the 11% of alcohol byproduct (entry 12). In 1,4-dioxane, the reaction proceeded poorly (12 h, 88%, entry 13), presumably the two oxygen atoms of 1,4-dioxane acted formed hydrogen bonds and inhibited the formation of "*flexible*" fluoride by interacting with the terminal hydroxyls of BTC5A. We also evaluated fluorination reactions using model compounds with different leaving groups, such as halides and sulfonates, in *tert*-amyl alcohol, which is known to be a suitable solvent for this reaction (entries 14−17).[9] For mesylate and tosylate substrates, the reaction proceeded in excellent yields (both 97%) and was completed within 30 min (entries 14 and 15) in *tert*-amyl alcohol. However, iodo and bromo substrates were converted into the fluoro product **5** relatively slowly in lower yields (71 and 90%, respectively) and produced alkene byproducts (28 and 10%, entries 16 and 17, respectively). It is notable that KF was almost inactive even in *tert*-alcohol medium in the absence of BTC5A promoter (entry 18).

Having investigated the effectiveness of BTC5A, we explored substrate scope for the nucleophilic fluorinations of various substrates using KF in different solvent systems. The results are summarized in Scheme 2. Fluoroflumazenil (**7**) was successfully prepared in the presence of BTC5A in CH_3CN in 71% yield. A fluorinated estrone derivative **8** was synthesized in 97% yield from the corresponding mesylate, and **9** was obtained in 98% yield using the same fluorination protocol. 2-(Bromomethyl)naphthalene was successfully converted into **10** in 98% yield in CH_3CN. 4-(3-Fluoropropoxy)benzophenone (**11**) as photosensitizer was obtained from the corresponding mesylate in 94% yield in toluene. The fluorination of 1-(3-methanesulfonyloxypropoxy)pyrene in toluene provided 1-(3-fluoropropoxy)pyrene (**12**) in 93% yield, and 2-(3-fluoropropoxy)dibenzofuran (**13**) was also prepared in 90% yield. We also fluorinated a coumarin mesylate and a nitroimidazole mesylate in toluene and obtained **14** and **20** at good yields (97 and 96%, respectively). The fluorination of 1-(2-methanesulfonylethyl)naphthalene, which is known to be base sensitive, proceeded to afford **15** in *tert*-amyl alcohol solvent in a yield of 76%. Fluorination of secondary alkyl mesylate (another base-sensitive substrate) in *tert*-amyl alcohol produced the desired fluoro product **16** in a yield of 61%. However, these base-sensitive compounds **15** and **16** could not be obtained by the same reactions without BTC5A. For application of click chemistry, a fluoro azide **17** and a fluoro-alkyne **18** were synthesized from the corresponding mesylate using the same method at yields of 95 and 98%, respectively. A *sec*-fluoroproline derivative **19** was obtained in 47% yield using this BTC5A-promoted fluorination reaction using KF.

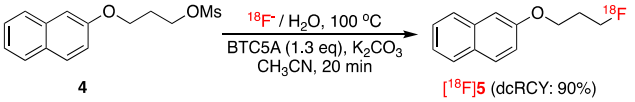
Scheme 2. BTC5A-Promoted S_N2 Fluorinations of the Various Substrates in the Presence of KF[a]



[a]All reactions were carried out using 0.18 mmol of substrate, KF (3.0 equiv), and BTC5A (1 equiv) in 0.7 mL of solvent at 100 °C. Yields of isolated products are indicated unless otherwise noted. [b]Yields were determined by ^1H NMR spectroscopy. [c]**10** was synthesized from 2-(bromomethyl)naphthalene. [d]**19** was prepared from the corresponding tosylate substrate.

In Scheme 3, we carried out ^{18}F-fluorination of **4** using no-carrier-added [^{18}F]fluoride generated from cyclotron for PET

Scheme 3. ^{18}F-Labeling Reaction with BTC5A



application of BTC5A. The desired ^{18}F-labeled product [^{18}F]**5** was obtained at a radiochemical yield (RCY) of 90% after reaction for only 20 min (radio TLC ratio 100%, total reaction time 35 min). After the ^{18}F-labeling reaction, BTC5A was successfully removed by short column chromatography.

In summary, we designed and prepared BTC5A as a PTC system and demonstrated its efficacy in nucleophilic fluorination using KF. BTC5A in the presence of KF was found to provide high fluorination rates. During reaction, oxygen atoms in crown-5-calix[4]arene subunit appeared to act as Lewis bases and coordinate K^+ to allow the fluoride to be "free" from K^+ cation. Furthermore, bis-ethylene glycols containing polyethers and terminal hydroxy groups seemed to play important roles in two ways: (i) polyethers attracted the K^+ cation to BTC5A and facilitate K^+ to crown-5-calix[4]arene complexation and (ii) terminal hydroxy groups formed the hydrogen bonding with fluoride to increase its

DOI: 10.1021/acs.orglett.9b00649
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reactivity and selectivity by forming "*flexible*" fluoride. In particular, the nucleophilic fluorination with BTC5A in nonpolar aprotic solvents (e.g., toluene, heptane, benzene) proceeded faster than in CH_3CN, which contradicted expectations; that is, a nonpolar aprotic solvent is inadequate for S_N2-type nucleophilic displacement reactions. This result suggests BTC5A may enable the use of nonpolar aprotic solvents for S_N2-type nucleophilic fluorination. We also observed good ^{18}F-labeling efficiency in the presence of BTC5A with [^{18}F]-fluoride.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00649.

Experimental procedures and characterization data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Basic Science Research Program (Grant No. 2017R1A2A2A10001451), funded by the Ministry of Science and ICT (MSIT), the MOTIE (Ministry of Trade, Industry & Energy), and KSRC (Korea Semiconductor Research Consortium) support program (Grant No. 10080450), Korea.

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DOI: 10.1021/acs.orglett.9b00649
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