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Multifunctional Crown-5-calix[4]arene-based Phase-Transfer Catalysts for Aromatic ^{18}F-Fluorination

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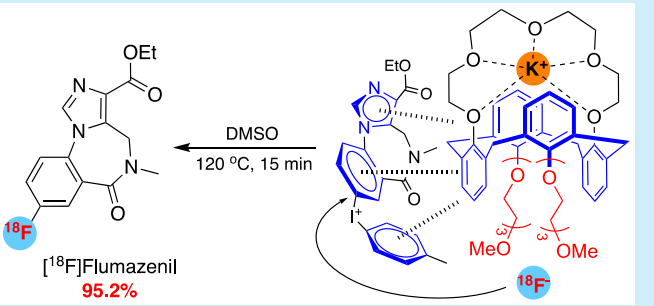
ABSTRACT: Methylated bis-triethylene glycolic crown-5-calix[4]arene (M-BTC5A) as a phase-transfer catalyst showed the best performance among other analogues and even conventional Kryptofix 222 in the nucleophilic aromatic ^{18}F-fluorination of diaryliodonium tosylate precursors owing to (i) the efficient release of reactive "naked" [^{18}F]fluoride, (ii) the high stabilization of the precursor in the reaction, and, presumably, (iii) the ease of access between the precursor and the K^{18}F/M-BTC5A complex facilitated by $\pi-\pi$ interactions. [^{18}F]Flumazenil was produced in high radiochemical yield using M-BTC5A.



Fluorine-containing arenes are attractive for the development of new materials or technologies in diverse research fields.[1−4] The introduction of fluorine into bioactive molecules enhances their potency and bioavailability by modulating conformational and stereoelectronic properties such as the polarity, lipophilicity, and pK_a.[5−7] The radioisotope fluorine-18 (^{18}F) has also been extensively used to produce radiopharmaceuticals for positron emission tomography (PET).[8,9] Because of the relatively high in vivo stability of a C_{Ar}−F bond compared with a C(sp^3)−F bond, the introduction of ^{18}F into an aromatic ring of a radiopharmaceutical candidate increases the metabolic stability of ^{18}F in the parent molecule.[10,11]

Nucleophilic aromatic substitution (S_NAr) with [^{18}F]-fluoride has been commonly used to generate ^{18}F-labeled radiotracers considering the operational simplicity, high molar activity, and selectivity.[12] The introduction of no-carrier-added (n.c.a.) ^{18}F into arenes via S_NAr generally requires a polar aprotic solvent and high temperature.[13] Furthermore, the S_NAr ^{18}F-labeling reaction needs sufficient activation of the aromatic ring from ortho or para electron-withdrawing groups.[14] These restrictions therefore limit the options for developing fluorine-substituted arenes and radiotracers in which the late introduction of [^{18}F]fluoride is desired, prompting research groups to explore new types of precursors and transition-metal catalysts to attain a versatile S_NAr ^{18}F-labeling strategy.[15−23] Indeed, such new approaches have led to the spectacular growth of aromatic ^{18}F-fluorination in recent years. Despite these new strategies showing promising results, the archetypal Kryptofix 222 (K_{222}) is still used for numerous investigations as a phase-transfer catalyst (PTC), which is one of the primary components in aliphatic and aromatic ^{18}F-labeling.[8] Therefore, we aimed to develop an effective aromatic ^{18}F-fluorination strategy using novel PTCs and apply this strategy to the practical synthesis of a known ^{18}F-labeled radiotracer.

In our previous study, we reported that fluoride could be effectively introduced into an aliphatic position using a bis-triethylene glycolic crown-5-calix[4]arene (BTC5A). The BTC5A consists of two polyethers to initially attract metal fluorides and a crown-5-calix[4]arene subunit capable of capturing an alkali metal cation, ultimately exhibiting excellent PTC behavior toward nucleophilic fluorination.[24]

On the basis of the success of aliphatic fluorination using BTC5A,[24−29] we anticipate that the application of BTC5A to aromatic ^{18}F-fluorination will be promising; besides trapping an alkali metal ion, it is expected that the crown-calix[4]arene subunit containing four aromatic rings will also interact with precursors via $\pi-\pi$ interactions[30,31] to further facilitate approaching each other. Because of these $\pi-\pi$ interactions, we surmise that ^{18}F will have more opportunities to participate in aromatic ^{18}F-fluorination with the help of BTC5A. To elucidate the effect of the polyether moiety and the terminal methyl group, methylated bis-triethylene glycolic crown-5-calix[4]arene (M-BTC5A), which has polyether tails the same length as BTC5A, and bis-methylated crown-5-calix[4]arene (BMC5A) without polyether tails were also evaluated for aromatic ^{18}F-fluorination (Figure 1). Herein we investigated various reaction conditions using K_{222} and three BTC5A-based

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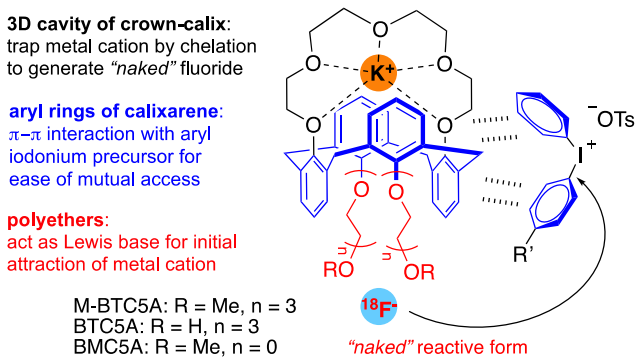


Figure 1. Structure and concept of BTC5A-based phase-transfer catalysts for the aromatic ^{18}F-fluorination of a diaryliodonium salt precursor.

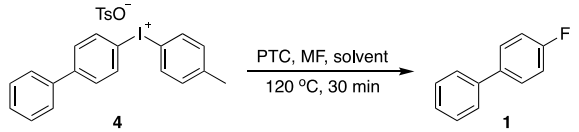
PTCs to validate the capability of each PTC as an organic promoter to enhance the rate of fluorination.

The influence of different solvents, PTCs, and fluoride sources was first explored to optimize the aromatic fluorination of diaryliodonium tosylate **4** to produce **1** (Table 1). Aprotic solvents (except *N*-methyl-2-pyrrolidone (NMP)) generally improved the yield of **1** using KF in the presence of M-BTC5A (Table 1, entries 1−5). When DMF or CH_3CN was used with M-BTC5A, the aromatic fluorination of **4** resulted in reasonable yields of **1**, similar to our previous results.[15,16] Notably, M-BTC5A resulted in the highest yield of **1** in DMSO (Table 1, entry 5); the same conditions using the conventional K_{222} instead of M-BTC5A resulted in a ∼13-fold decreased yield (Table 1, entry 6). The other BTC5A-based PTCs (BTC5A and BMC5A) also provided good yields of **1** in DMSO (Table 1, entries 7 and 8), but they were not superior to M-BTC5A. To explore fluoride sources in addition to KF, CsF and *n*-Bu_4NF were also investigated with **4** and M-BTC5A. As expected, CsF, which is relatively inappropriate in size for cation capture in the crown-calix subunit of M-BTC5A, exhibited slightly reduced fluoride incorporation (Table 1, entry 9). When using *n*-Bu_4NF, the yield was approximately half of that obtained with KF, even though fluoride from *n*-Bu_4NF was already in the reactive "naked" and "free" form (Table 1, entry 10).

To demonstrate whether **4** is affected by PTCs, the instability of **4** was measured in the presence of either K_{222} or M-BTC5A (Table 2). DMSO was the desired solvent for the efficient fluorination of **4** to **1** with fewer decomposed products (**2** and **3**) under basic conditions compared with DMF (Table 2, entries 1 and 4 versus Table 1, entries 3 and 5). TEMPO is a well known radical scavenger that is a common component in the ^{18}F-fluorination reaction containing a diaryliodonium salt precursor because it can reduce the generation of aromatic hydrocarbons via radical-induced decomposition.[32−35] Therefore, we added TEMPO to the reaction medium in the presence of K_{222}, showing that TEMPO increased the stability of **4** to 69% (37% without TEMPO). The addition of TEMPO to BTC5A and M-BTC5A-treated groups improved the stability of **4** as well, but to a lesser extent (Table 2, entries 3 and 4). In particular, M-BTC5A not only gave the highest stability to **4** under S_NAr but also reduced the proportion of hydrogenated **2**. Therefore, it is reasonable to speculate that BTC5A-based PTCs could be instrumental in the stabilization of precursor **4** without the aid of TEMPO. It is beneficial to obtain a relatively low proportion of hydrogenated products in the reaction mixture to facilitate the isolation of pure ^{18}F-labeled products.

From these results, we demonstrated that our protocol using BTC5A-based PTCs is more effective than K_{222} in at least three aspects. (i) BTC5A-based PTCs capture the alkali metal cation to enhance the nucleophilicity of fluoride more than with K_{222} (Table 1, entries 5, 7, and 8 versus Table 1, entry 6). (ii) Related to the stability, the diaryliodonium tosylate precursor **4** is more highly stabilized in the presence of the BTC5A-based PTCs, and more opportunities to participate in the reaction are available (Table 2, entries 3 and 4 versus Table 2, entry 2). Therefore, minimizing the decomposition of **4** using BTC5A-based PTCs significantly increases the yield of **1**, unlike with K_{222} (Table 1, entries 5−7). (iii) It is also hypothesized that the ease of access between the precursor and metal fluoride/BTC5A-based PTC complexes by $\pi-\pi$ interactions may increase the fluoride incorporation in **4** to yield **1**. In contrast, the metal fluoride/K_{222} complex, which does not contain any aromatic rings, inherently lacks the ability

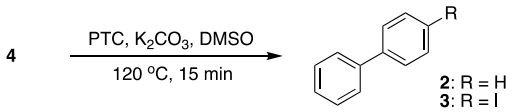
Table 1. Nucleophilic Aromatic Fluorination of Diaryliodonium Tosylate 4 under Various Reaction Conditions[a]



entry	PTC	MF	solvent	yield (%)[b]
1	M-BTC5A	KF	NMP	0
2	M-BTC5A	KF	DMA	7.6 ± 1.6
3	M-BTC5A	KF	DMF	9.1 ± 2.3
4	M-BTC5A	KF	CH_3CN	29.2 ± 7.3
5	M-BTC5A	KF	DMSO	79.7 ± 0.5
6	K_{222}	KF	DMSO	6.1 ± 1.9
7[c]	BTC5A	KF	DMSO	63.8 ± 3.4
8	BMC5A	KF	DMSO	68.7 ± 3.8
9	M-BTC5A	CsF	DMSO	65.6 ± 3.1
10	M-BTC5A	*n*-Bu_4NF	DMSO	39.4 ± 4.8

[a]All reactions were performed using KF (4 equiv), PTC (1.1 equiv), and **4** (4 μmol) in solvent (0.3 mL) at 120 °C for 30 min. [b]Yield obtained from HPLC (n = 3). [c]n = 5.

Table 2. Instability of 4 in the Presence of Different PTCs with or without TEMPO[a]



entry	PTC	remaining % of **4** (with TEMPO)	ratio of 2/3 (with TEMPO)
1[b]	M-BTC5A	51 ± 1.1%	0.43
2	K_{222}	37 ± 4.0% (69 ± 4.0%)	0.64 (0.24)
3	BTC5A	66 ± 2.0% (74 ± 2.9%)	0.35 (0.16)
4	M-BTC5A	68 ± 0.8% (78 ± 0.9%)	0.30 (0.14)

[a]All reactions were performed using 4 μmol of **4** with K_2CO_3 (0.8 equiv) and PTC (1.1 equiv) in DMSO (0.3 mL) at 120 °C for 15 min (n = 3). [b]DMF used instead of DMSO. Instability represents the percentage of decomposed products (**2** and **3**) compared with the concentration of **4** using HPLC. Results using 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO, 1 mg, 6.4 μmol) are given in parentheses.

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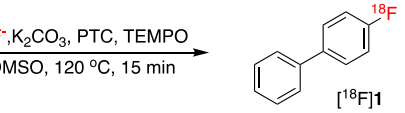
to introduce $\pi-\pi$ interactions with the precursor (Table 1, entry 6). Considering the size of the n-Bu_4N^+ cation, it is likely that fluoride from n-Bu_4NF may not form the F^-/M-BTC5A complex, and n-Bu_4NF/M-BTC5A performed poorly compared with KF/M-BTC5A, despite the use of highly reactive n-Bu_4NF (Table 1, entry 10). The comparison of entries 5 and 7 in Table 1 indicates that M-BTC5A is more efficient than BTC5A. We propose the following plausible explanations: (i) The terminal hydroxyl groups in BTC5A can interact with fluoride by hydrogen bonding to generate "flexible" fluoride,[36] which relatively reduces the reactivity of fluoride compared the "naked" fluoride generated from M-BTC5A, and (ii) the diaryliodonium tosylate precursor **4** is slightly more unstable in the presence of BTC5A, containing more reactive terminal hydroxyl groups than that of M-BTC5A (Table 2, entries 3 and 4). In addition, we conducted a kinetic study under optimized conditions and identified that the micromole-scale S_NAr reactions were completed within 15−30 min (Figure 1S).

Table 3 summarizes the results of the aromatic ^{18}F-fluorination of **4** using different PTCs. We found that M-

Table 3. ^{18}F-Fluorination with Different PTCs[a]



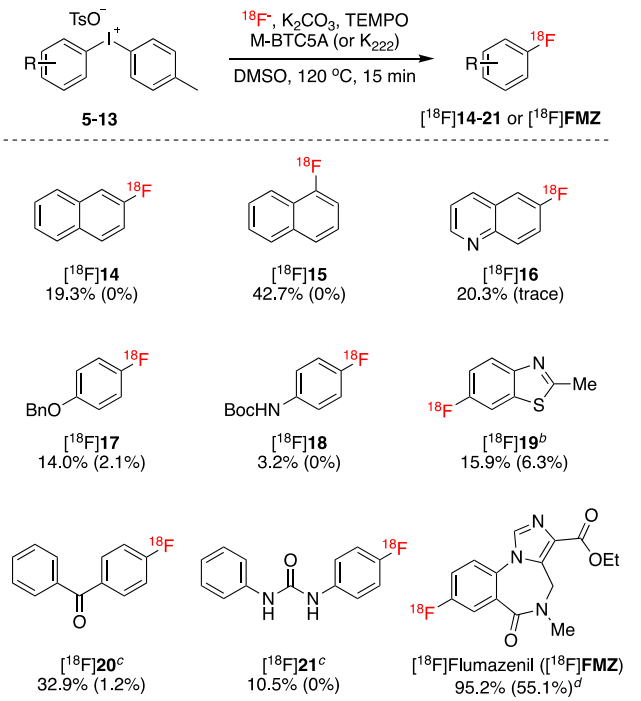
entry	PTC	equiv of PTC	yield (%)[b]
1	K_{222}	0.55	28.8 ± 5.3
2	BTC5A	1.1	42.6 ± 3.8
3	BTC5A	0.55	59.2 ± 2.3
4	BMC5A	0.55	38.8 ± 5.6
5	M-BTC5A	1.1	61.5 ± 8.8
6	M-BTC5A	0.55	82.3 ± 5.7
7	M-BTC5A	0.27	79.6 ± 2.1
8	M-BTC5A	0.1	41.1 ± 6.1
9[c]	M-BTC5A	0.55	75.7 ± 5.9

[a]All reactions were performed using **4** (4 μmol) and K_2CO_3 (0.8 equiv) in the presence of 1 mg of TEMPO in DMSO (0.3 mL) at 120 °C for 15 min. [b]Radiochemical yield was obtained by radio-TLC analysis (n = 3). [c]TEMPO was not used.

BTC5A showed the best PTC activity to obtain **1** among the PTCs studied, including conventional K_{222} (Table 3, entries 1−6). To optimize M-BTC5A for aromatic ^{18}F-fluorination, we performed radiolabeling reactions by changing the amount of M-BTC5A and then determining the radiochemical yield (RCY) of [^{18}F]**1** (Table 3, entries 5−8). The highest RCY of [^{18}F]**1** was obtained with 0.55 equiv of M-BTC5A (~82%; Table 3, entry 6). Even when only 0.1 equiv of M-BTC5A was used, the RCY was ~41%. Interestingly, the use of M-BTC5A in the absence of TEMPO resulted in only a slight reduction in the RCY of [^{18}F]**1** (Table 3, entry 9), but it was considerably sufficient for aromatic ^{18}F-fluorination.

The optimized ^{18}F-labeling conditions in the presence of M-BTC5A were applied to various diaryliodonium tosylate precursors (**4**−**13**) and compared with the conventional labeling protocol using K_{222} (Scheme 1). The ^{18}F-labeling reaction proceeded in moderate to high RCY using diaryliodonium tosylate with diverse electron densities and chemical conformations. Our ^{18}F-labeling protocol using M-BTC5A produced some ^{18}F-labeled products (e.g., [^{18}F]**17**, [^{18}F]**19**, and [^{18}F]Flumazenil ([^{18}F]**FMZ**)) in up to three times higher

Scheme 1. Substrate Scope of ^{18}F-Labeled Arenes[a]



[a]All reactions were carried out on a 3 to 4 μmol scale of the precursor with ^{18}F (~11 MBq), K_2CO_3 (0.8 equiv), and TEMPO (1 mg, 6.4 μmol) in the presence of M-BTC5A (0.55 equiv) in DMSO (0.3 mL) at 120 °C for 15 min. Yields in parentheses were obtained using K_{222} (5.5 mg, 14.6 μmol) instead of M-BTC5A. Radiochemical yield was measured by radio-TLC. [b]In CH_3CN. [c]In DMF. [d]Reported yield in ref 16.

RCY compared with the conventional method. Furthermore, whereas [^{18}F]**14**−**16** and [^{18}F]**18**−**21** were difficult to obtain following the method using K_{222},[13,37−40] they could be synthesized in significantly or relatively high RCY from our protocol using M-BTC5A. ([^{18}F]**14**, [^{18}F]**15**, and [^{18}F]**20** were also prepared in 14−59% RCY from oxidized iodoarenes.[41,42]) These results indicate that our M-BTC5A-catalyzed S_NAr ^{18}F-fluorination method is vital for the efficient synthesis of a number of ^{18}F-labeled radiopharmaceuticals. For example, [^{18}F]**FMZ**, a representative ^{18}F-labeled radiopharmaceutical, was successfully prepared using our ^{18}F-labeling protocol with M-BTC5A from the corresponding diaryliodonium salt in significantly high RCY (~95%) compared with the conventional labeling method employing K_{222} (~55%).[16] The molar activity (A_M) of [^{18}F]**FMZ** when starting with 16.2 GBq of ^{18}F was 316.7 GBq·μmol^{-1}, which is similar to the previously reported value, thus indicating that aromatic ^{18}F-fluorination with M-BTC5A does not adversely affect the A_M of [^{18}F]**FMZ**.

In conclusion, we demonstrated that BTC5A-based PTCs (i.e., BTC5A, BMC5A, and M-BTC5A) could act as highly efficient PTC systems for the nucleophilic aromatic ^{18}F-fluorination of various diaryliodonium tosylate precursors to prepare the corresponding ^{18}F-labeled arenes ([^{18}F]**1**, [^{18}F]**14**-**21**, or [^{18}F]**FMZ**). In this method, M-BTC5A performed better in the ^{18}F-labeling reaction than the conventional PTCs studied owing to (i) the efficient capture of the alkali metal cation to release the reactive "naked" [^{18}F]fluoride, (ii) the desirable high stability of diaryliodonium tosylates in the presence of M-BTC5A, and (iii) the ease of access between the

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precursor and the K[18]F/M-BTC5A complex probably facilitated by $\pi-\pi$ interactions. It is notable that the PET radiopharmaceutical [^{18}F]**FMZ** was successfully prepared in high RCY by the M-BTC5A-catalyzed nucleophilic aromatic ^{18}F-fluorination protocol. These results suggest that this ^{18}F-labeling protocol using M-BTC5A has much potential in radiopharmaceutical science.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03604.

Experimental procedures and characterization data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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