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Borate-mediated aryl polyfluoroalkoxylation under transition-metal-free conditions†

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We describe the transition-metal-free coupling for polyfluoroalkoxy arenes using polyfluoroalkoxy borates, which serve as counterions to diaryliodonium salts and transferring mediators of polyfluoroalkoxy groups. This strategy demonstrates high functional group compatibility owing to the low nucleophilicity of the borate mediator, thus offering a practical approach for synthesizing diverse polyfluoroalkoxy arenes.

Owing to the unique properties of fluorine atoms and fluorinated functional groups, fluorine-containing molecules have been utilized across a wide range of chemical industries, including pharmaceuticals, agrochemicals, and functional organic materials.[1] Modification of bioactive compounds with fluorine functional groups would provide more efficient ADME (absorption, distribution, metabolism, and excretion) properties relative to non-fluorinated parent compounds.[2] Fluoroalkoxy groups are a widely introduced functional group in pharmaceuticals and agrochemicals.[3] For instance, trifluoroethyl aryl ethers are found in numerous drug molecules and agrochemicals (Fig. 1a). In addition, the replacement of non-fluorinated alkoxy groups in bioactive compounds with polyfluorinated counterparts enhances lipophilicity (Fig. 1b).[4] Therefore, incorporating polyfluorinated alkoxy groups is an effective strategy in drug design; thus, synthetic methods for polyfluoroalkoxylation have attracted much attention.[5]

Trifluoroethyl aryl ethers have been constructed via the Williamson ether synthesis using the corresponding phenols and trifluoroethyl sources bearing leaving groups, which require the superior ability to the trifluoromethyl group (Fig. 2a).[6] *Ipso* substitutions of arene derivatives bearing appropriate leaving groups, such as aromatic nucleophilic substitution (S_NAr)[7] and ligand coupling of diaryliodonium salts,[8] are also efficient approaches (Figs. 2b and 2c). However, the low nucleophilicity

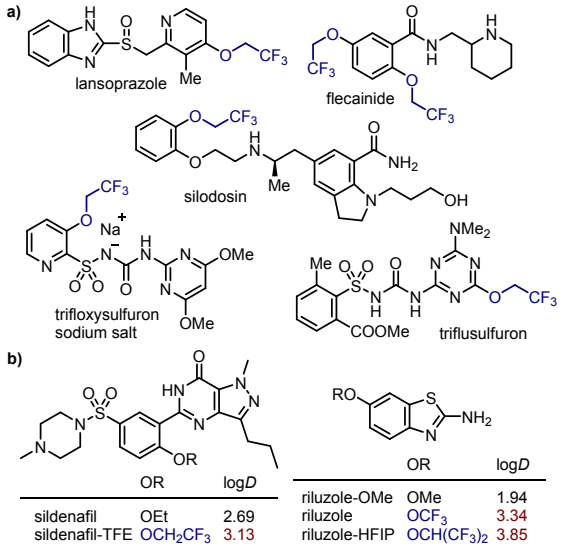

Fig. 1 a) Bioactive compounds bearing trifluoroethyl aryl ethers. b) Lipophilicity control by introduction of fluoroalkoxy group.

of fluorinated alcohols limits substrate variation; the former requires highly electron-deficient aryl groups, whereas the latter requires strong bases, such as NaH or lithium hexamethyldisilazide (LHMDS), which limits the number of substrate examples. Oxidative activation of arenes enables C-H bond fluoroalkoxylation, although the reaction proceeds only with anilide derivatives.[9] In addition, transition-metal-catalyzed coupling using aryl halides or boronates produces a wide variety of trifluoroethyl aryl ethers,[4a,10] and combination with a

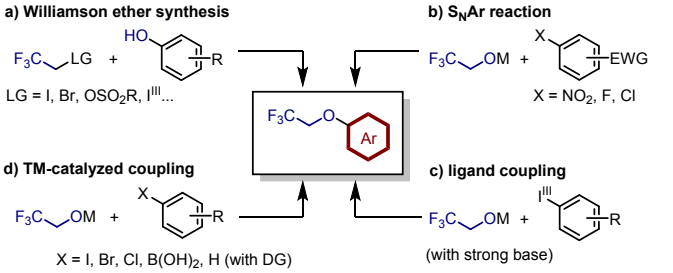

Fig. 2 Reported synthetic approaches to trifluoroethyl aryl ethers.

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directing group on the arenes induces C-H bond fluoroalkoxylation (Fig. 2d).[11] Nevertheless, the use of transition metal catalysts is a major drawback for the industrial production of pharmaceuticals and agrochemicals. In comparison with the trifluoroethoxy group, highly fluorinated alkoxides, such as hexafluoroisopropoxide, generally show lower reactivity owing to their strong inductive effect.[12] Therefore, versatile synthetic methods for polyfluoroalkoxy arenes bearing a wide variety of polyfluoroalkyl and aryl groups without the use of transition metal or strong base are highly desirable.

To synthesize a wide variety of polyfluoroalkoxy arenes under transition-metal-free conditions, we focused on a boron-intermediary ligand-transfer strategy employing diaryliodonium salts, which are efficient arylating reagents based on hypervalent iodine. Various nucleophiles react with diaryliodonium salts to afford the corresponding arylation products in the absence or presence of transition metal catalysts.[13] Among the aryl group variations, easily accessible and bench-stable aryl(trimethoxyphenyl)iodonium (TMP-iodonium) salts enable unified selective aryl transfer for various nucleophiles, as has been demonstrated by several groups including ours.[14,15] The transition-metal-free arylation using diaryliodonium salts proceeds via ligand exchange of the counter anion of the diaryliodonium salts with the nucleophiles and subsequent ligand coupling between the nucleophile and the aryl group (Fig. 3a). Thus, the nucleophile acts as the reaction site for ligand exchange, while simultaneously serving as a coupling partner. To enhance the reactivity of the first step, an appropriate strong base is required to activate the nucleophile leading to sufficient nucleophilicity, which frequently limits the substrate scope due to its high basicity exemplified by the above-mentioned trifluoroethoxylation.[16] Our group demonstrated the decarboxylative coupling of α,α-difluoro-β-ketoacid salts with TMP-iodonium salt generating aryl difluoromethyl ketones, wherein the carboxylate moiety coordinates to an iodine(III) center facilitating ligand exchange and eliminating carbon dioxide during ligand coupling.[17] This successive transformation encouraged us to develop a new type of ligand coupling strategy for the polyfluoroalkoxylations. We assumed that the borate anion serves as the transferring mediator to facilitate ligand exchange despite its low nucleophilicity, forming stable diaryliodonium salts and

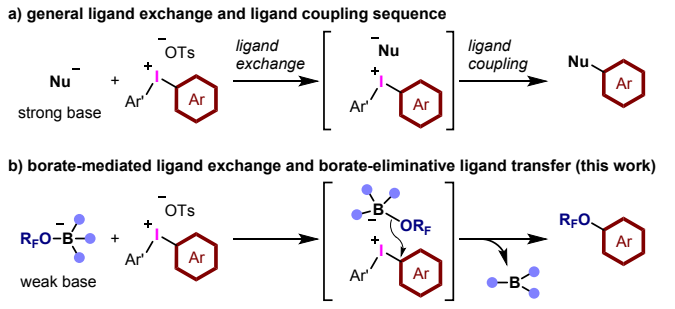
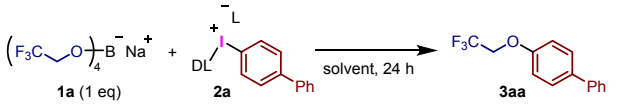


Fig. 3 a) General ligand exchange and ligand coupling sequence. b) Borate-mediated ligand exchange and borate-eliminative ligand transfer (this work).

Table 1 Optimization of reaction conditions for trifluoroethoxylation [a]



Entry	DL	L	Solvent	Temp.	Yield of **3aa**
1	TMP	OTs	toluene	100 °C	35%
2	TMP	OTs	toluene/H_2O (4:1)	100 °C	>99%
3	TMP	OTs	AcOEt/H_2O (4:1)	100 °C	9%
4	TMP	OTs	DME/H_2O (4:1)	100 °C	20%
5	TMP	OTs	hexane/H_2O (4:1)	100 °C	70%
6	TMP	OTs	toluene/H_2O (4:1)	70 °C	96%
7 [b]	TMP	OTs	toluene/H_2O (4:1)	70 °C	>99% (94%) [c]
8 [b]	TMP	OAc	toluene/H_2O (4:1)	70 °C	96%
9 [b]	DMP	OTs	toluene/H_2O (4:1)	70 °C	>99%
10 [b]	Mes	OTs	toluene/H_2O (4:1)	70 °C	66%

[a] Reaction conditions: **1a** (1 eq) and **2a** (0.20 mmol) in solvent (2 mL) for 24 h. ^{19}F NMR yield. [b] 2 eq of **1a** was employed. [c] Isolated yield. DL = dummy ligand. TMP = 2,4,6-trimethoxyphenyl. DMP = 2,4-dimethoxyphenyl. Mes = mesityl. DME = 1,2-dimethoxyethane.

sequentially leading to indirect ligand transfer accompanied by the elimination of neutral borate (Fig. 3b). Herein, we describe the additive-free polyfluoroalkoxylation of TMP-iodonium salts using polyfluoroalkoxy borate salt.

The investigation commenced with the coupling reaction of 4-phenylphenyl(TMP)iodonium tosylate (**2a-TMP-OTs**) with tetrakis(trifluoroethoxy)borate salt (**1a**),[4a,18] which is bench-stable and easily accessible from $NaBH_4$ and trifluoroethyl alcohol (Table 1). The reaction in toluene solvent at 100 °C afforded the corresponding trifluoroethyl aryl ether **3aa** in 35% yield (entry 1). Considering the solubilities of these starting materials, a biphasic solvent consisting of toluene and water in an optimal ratio (4:1) was employed to generate **3aa** quantitatively (entry 2). The combination of other organic solvents, such as EtOAc, 1,2-dimethoxyethane, or hexane, with water decreased the reaction yield (entries 3–5). The desired compound **3aa** was obtained in 96% yield, even at a lower temperature of 70 °C (entry 6). The use of 2 equiv. of **1a** resulted in a quantitative yield (entry 7). Iodonium salts that have 1,3-dimethoxyphenyl or mesityl ligands, as well as acetate anion, produced **3aa** in moderate to high yields (entries 8–10).

Based on the optimization of the reaction conditions, the trifluoroethoxylation of TMP-iodonium tosylates **2-TMP-OTs** bearing various functional groups was examined to afford the corresponding coupling products, which have high volatilities that decreased the isolated yields (Fig. 4a). Trifluoroethyl aryl ethers bearing ester (**3ab**), nitro (**3ac**), cyano (**3ad**), and acetyl (**3ae**) groups were obtained in moderate to high yields. The halogen atoms attached to the aryl group (**3af**), the reactive points in the transition-metal-catalyzed cross-coupling, were intact under the present reaction conditions. TMP-iodonium tosylates bearing hydrocarbons and alkoxy groups also underwent trifluoroethoxylation to afford the corresponding ethers (**3ag–3ak**). In addition, chloropyridine with a trifluoroethoxy group (**3al**) was synthesized. However, this method is not applicable to polyalkoxy arenes and certain

heteroarenes, such as indole and benzofuran, due to the difficulty of synthesizing the corresponding TMP-iodonium salts.

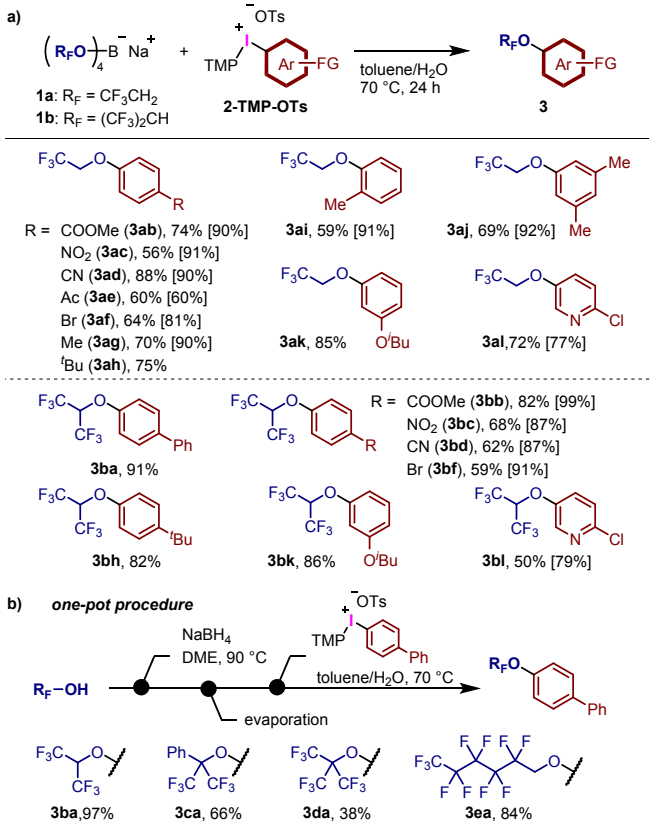


Fig. 4 Substrate scope for various polyfluoalkyl aryl ethers. Reaction conditions: a) fluoroalkoxyborate (**1a**: 0.40 mmol, **1b**: 0.29 mmol) and TMP-iodonium tosylate (**2-TMP-OTs**, 0.20 mmol) in toluene/H_2O (4:1, 4 mL) at 70 °C for 24 h. b) Rf-OH (4.0 mmol) and $NaBH_4$ (1.0 mmol) in DME at 90 °C for 4 h; evaporation; **2a-TMP-OTs** (0.50 mmol) in toluene/H_2O (4:1, 10 mL) at 70 °C for 24 h. Isolated yield [19F NMR yield] are described.

We also examined the introduction of hexafluoroisopropoxy group under additive-free conditions. Various aryl groups bearing electron-withdrawing (**3ba–3bd**, **3bf**) and -donating (**3bh** and **3bk**) groups, as well as heteroarenes (**3bl**), afforded the corresponding hexafluoroisopropyl aryl ethers. The borate-mediated polyfluoroalkoxylation of TMP-iodonium salts was applied to a one-pot reaction starting from a polyfluorinated alcohol (Fig. 4b). Hexafluoroisopropyl alcohol was treated with $NaBH_4$. Then the concentrated residue was reacted with TMP-iodonium salt in toluene/water mixed solvent at 70 °C for 20 h to afford **3ba** in 97% yield. This protocol synthesized aryl ethers bearing various polyfluoroalkyl groups, such as sterically crowded (**3ca** and **3da**) and long-chain polyfluoroalkyl groups (**3ea**).

This borate-mediate method was compared with the previously reported approach using diaryliodonium salt (Fig. 5a); the reaction of **2e-TMP-OTs** with trifluoroethyl alcohol and NaH resulted in a low yield of **3ae**,[8a] because undesirable reactions presumably occurred due to the high basicity and/or

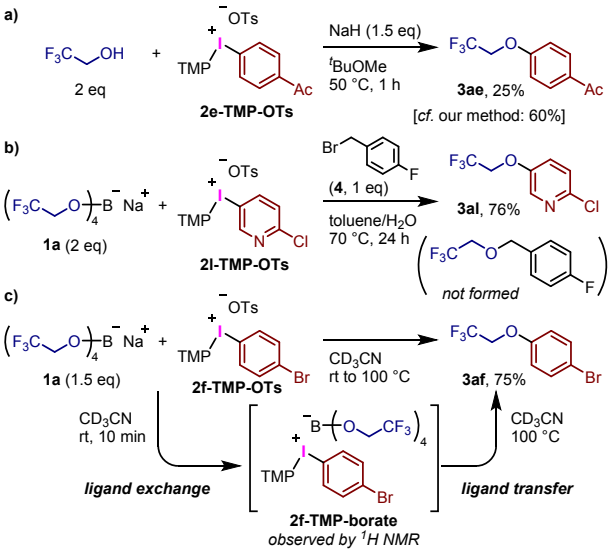


Fig. 5 a) Comparison with the reported method. b) Competitive reaction. c) NMR monitoring of trifluoroethoxylation.

nucleophilicity of alkoxide. Meanwhile, our method afforded **3ae** in 60% yield. Owing to the less nucleophilicity of polyfluoroalkoxy borate salts, the present protocol induces chemoselective polyfluoroalkoxylation; treatment of **1a** with **2l-TMP-OTs** in the presence of benzyl bromide **4** produced **3al** in 76% yield, wherein neither the S_NAr reaction with the chlorine atom nor the S_N2 reaction with the bromine atom proceeded even in the presence of 2 equiv. of **1a** (Fig. 5b).[19] In contrast, sodium trifluoroethoxide reacted with benzyl bromide to generate the corresponding dialkyl ether.[16] Next, the reaction of **1a** with **2f-TMP-OTs** in CD_3CN was monitored by ^1H NMR spectroscopy, which indicated that the iodonium borate intermediate **2f-TMP-borate** was generated at room temperature after 10 min (Fig. 5c and S1). Subsequent heating of the reaction mixture at 100 °C afforded the coupling product in 75% yield. We propose that the present polyfluoroalkoxylation starts with a quick ligand exchange of the tosylate anion in the TMP-iodonium salt with a polyfluoroalkoxy borate anion. Then, the polyfluoroalkoxy group is transferred intramolecularly to the aryl group to afford the polyfluoroalkoxy arene along with borate elimination.

In conclusion, we developed a transition-metal-free method for the synthesis of polyfluoroalkoxy arenes using diaryliodonium and polyfluoroalkoxy borate salts. This innovative approach addresses the limitations of traditional methods, which require strong bases or transition metal catalysts to enhance functional group compatibility. This additive-free protocol demonstrated selective polyfluoroalkoxylation under mild conditions and can be applied to the synthesis of various polyfluoroalkoxy arenes. Our findings contribute significantly to the field of drug design and agrochemicals, offering an efficient and versatile strategy for incorporating fluorinated functional groups into bioactive compounds.

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Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (a) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881−1886; (b) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320−330; (c) *Fluorine in Pharmaceutical and Medicinal Chemistry: From Biophysical Aspects to Clinical Applications*; Eds. V. Gouverneur and K. Müller, Imperial College Press, 2012 (d) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications, 2nd ed.*; Wiley-VCH, 2013; (e) *Frontiers of Organofluorine Chemistry*; Ed. I. Ojima, World Scientific, 2019.

2 *Prodrugs and Targeted Delivery: Towards Better ADME Properties*; Ed. J. Rautio, Wiley-VCH, 2011.

3 (a) A. Tlili, F. Toulgoat and T. Billard, *Angew. Chem. Int. Ed.*, 2016, **55**, 11726–11735; (b) G. Landelle, E. Schmitt, A. Panossian, J.-P. Vors, S. Pazenok, P. Jeschke, O. Gutbrod and F. R. Leroux, *J. Fluorine Chem.*, 2017, **203**, 155–165.

4 (a) B. Pethő, M. Zwillinger, J. T. Csenki, A. E. Káncz, B. Krámos, J. Müller, G. T. Balogh and Z. Novák, *Chem. –Eur. J.*, 2017, **23**, 15628–15632; (b) J. Su, K. Chen, Q.-K. Kang and H. Shi, *Angew. Chem. Int. Ed.*, 2023, **62**, e202302908.

5 B. Pethő and Z Novák, *Asian J. Org. Chem.*, 2019, **8**, 568 –575.

6 Selected examples, see: (a) T. Nakai, K. Tanaka and N. Ishikawa, *J. Fluorine Chem.*, 1977, **9**, 89–93; (b) F. Camps, J. Coll, A. Messeguer and M. A. Pericàs, *Synthesis*, 1980, **1980**, 727–728; (c) T. Umemoto and Y. Gotoh, *J. Fluorine Chem.*, 1986, **31**, 231–236; (d) X. Shen, C. N. Neumann, C. Kleinlein, N. W. Goldberg and T. Ritter, *Angew. Chem. Int. Ed.*, 2015, **54**, 5662 –5665; (e) S. K. Mangawa, C. Sharma, A. K. Singh and S. K. Awasthi, *RSC Adv.*, 2015, **5**, 35042–35045.

7 (a) J. T. Gupton, J. P. Idoux, C. Colon and R. Rampi, *Synth. Commun.* 1982, **12**, 695–700; (b) J. P. Idoux, J. T. Gupton, C. K. McCurry, A. D. Crews, C. D. Jurss, C. Colon and R. C. Rampi, *J. Org. Chem.*, 1983, **48**, 3771–3773; (c) J. P. Idoux, M. L. Madenwald, B. S. Garcia, D. L. Chu and J. T. Gupton, *J. Org. Chem.*, 1985, **50**, 1876–1878; (d) K. Kubo, K. Oda, T. Kaneko, H. Satoh and A. Nohara, *Chem. Pharm. Bull.*, 1990, **38**, 2853–2858.

8 (a) S. K. Sundalam and D. R. Stuart, *J. Org. Chem.* 2015, **80**, 6456−6466; (b) E. Lindstedt, E. Stridfeldt and B. Olofsson, *Org. Lett.*, 2016, **18**, 4234−4237; (c) R. T. Gallagher, S. Jha, B. E. Metze and D. R. Stuart, *Synlett*, 2024, **35**, 889–894.

9 (a) S. Maiti, T. Alam and P. Mal, *Asian J. Org. Chem.*, 2018, **7**, 715–719; (b) Z.-Y. Mo, X.-Y. Wang, Y.-Z. Zhang, L. Yang, H.-T. Tang and Y.-M. Pan, *Org. Biomol. Chem.*, 2020, **18**, 3832–3837.

10 Selected early examples, see: (a) H. Suzuki, T. Matuoka, I. Ohtsuka and A. Osuka, *Synthesis*, 1985, **1985**, 499–500; (b) M. A. Keegstra, T. H. A. Peters and L. Brandsma, *Tetrahedron*, 1992, **48**, 3633–3652; (c) T. D. Quach and R. A. Batey, *Org. Lett.*, 2003, **5**, 1381−1384; (d) D. Vuluga, J. Legros, B. Crousse and D. Bonnet-Delpon, *Eur. J. Org. Chem.*, 2009, 3513–3518; (e) X. Wu, B. P. Fors and S. L. Buchwald, *Angew. Chem. Int. Ed.*, 2011, **50**, 9943–9947; (f) R. Huang, Y. Huang, X. Lin, M. Rong and Z. Weng, *Angew. Chem. Int. Ed.*, 2015, **54**, 5736–5739; (g) K. Zhang, X.-H. Xu and F.-L. Qing, *J. Fluorine Chem.*, 2017, **196**, 24–31.

11 Selected early examples, see: (a) A. R. Dick, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2004, **126**, 2300–2301; (b) J. Roane and O. Daugulis, *Org. Lett.*, 2013, **15**, 5842–5845; (c) L.-B. Zhang, X.-Q. Hao, S.-K. Zhang, Z.-J. Liu, X.-X. Zheng, J.-F. Gong, J.-L. Niu and M.-P. Song, *Angew. Chem. Int. Ed.*, 2015, **54**, 272–275; (d) X.-K. Guo, L.-B. Zhang, D. Wei and J.-L. Niu, *Chem. Sci.*, 2015, **6**, 7059–7071. For a review, see: (e) L. Monsigny, F. Doche and T. Besset, *Beilstein J. Org. Chem.*, 2023, **19**, 448–473.

12 Transition-metal-catalyzed hexafluoroisopropoxylation of aryl chlorides was recently achieved, see ref. 4b.

13 (a) P. J. Stang and V. V. Zhdankin, *Chem. Rev.*, 1996, **96**, 1123–1178; (b) E. A. Merritt and B. Olofsson, *Angew. Chem. Int. Ed.*, 2009, **48**, 9052– 9070; (c) B. Olofsson, *Top. Curr. Chem.*, 2015, **373**, 135–166; (d) K. Aradi, B. L. Tóth, G. L. Tolnai and Z. Novák, *Synlett*, 2016, **27**, 1456–1485; (e) K. Kikushima, E. E. Elboray, J. O. C. Jiménez-Halla, C. R. Solorio-Alvarado and T. Dohi, *Org. Biomol. Chem.*, 2022, **20**, 3231–3248; (f) P. Villo and B. Olofsson, *Arylations Promoted by Hypervalent Iodine Reagents. In Patai's Chemistry of Functional Groups*; John Wiley & Sons, Ltd, 2018.

14 (a) J. Malmgren, S. Santoro, N. Jalalian, F. Himo and B. Olofsson, *Chem. –Eur. J.*, 2013, **19**, 10334–10342; (b) T. L. Seidl, S. K. Sundalam, B. McCullough and D. R. Stuart, *J. Org. Chem.*, 2016, **81**, 1998–2009; (c) A. H. Sandtorv and D. R. Stuart, *Angew. Chem. Int. Ed.*, 2016, **55**, 15812–15815; (d) T. L. Seidl and D. R. Stuart, *J. Org. Chem.*, 2017, **82**, 11765–11771; (e) D. R. Stuart, *Chem. –Eur. J.*, 2017, **23**, 15852–15863; (f) S. Basu, A. H. Sandtorv and D. R. Stuart, *Beilstein J. Org. Chem.*, 2018, **14**, 1034–1038; (g) R. T. Gallagher, S. Basu and D. R. Stuart, *Adv. Synth. Catal.*, 2020, **362**, 320–325.

15 (a) T. Dohi, D. Koseki, K. Sumida, K. Okada, S. Mizuno, A. Kato, K. Morimoto and Y. Kita, *Adv. Synth. Catal.*, 2017, **359**, 3503–3508; (b) K. Kikushima, M. Miyamoto, K. Watanabe, D. Koseki, Y. Kita and T. Dohi, *Org. Lett.*, 2022, **24**, 1924−1928. (c) K. Kikushima, A. Morita, E. E. Elboray, T. Bae, N. Miyamoto, Y. Kita and T. Dohi, *Synthesis*, 2022, **54**, 5192−398; (d) E. E. Elboray, T. Bae, K. Kikushima, Y. Kita and T. Dohi, *Adv. Synth. Catal.*, 2023, **365**, 2703−2710; (e) K. Kikushima, K. Komiyama, N, Umekawa, K. Yamada, Y. Kita and T. Dohi, *Org. Lett.*, 2024, **26**, 5347–5352.

16 Q. Yang and J. T. Njardarson, *Tetrahedron Lett.*, 2013, **54**, 7080–7082.

17 K. Kikushima, K. Yamada, N. Umekawa, N. Yoshio, Y. Kita and T. Dohi, *Green Chem.*, 2023, **25**, 1790−1796.

18 (a) G. L. Tolnai, B. Pethő, P. Králl and Z. Novák, *Adv. Synth. Catal.*, 2014, **356**, 125–129; (b) B. Pethő, D. Vangel, J. T. Csenki, M. Zwillinger and Z. Novák, *Org. Biomol. Chem.*, 2018, **16**, 4895–4899.
The reaction of **1a** with (4-bromomethylphenyl)(TMP)-iodonium tosylate also proceeded chemoselective trifluoroethoxylation to afford the corresponding 4-trifluoroethoxybenzyl bromide in 68% yield. See, Scheme S1.

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

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