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Electrochemical reduction of fluoroalkyl sulfones for radical fluoroalkylation of alkenes†

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Radical fluoroalkylation of alkenes has been developed by electrochemical reduction of fluoroalkyl sulfones. A series of electron-deficient alkenes readily undergo hydrofluoroalkylation in good to excellent yields. This chemistry represents the first example of electrochemical generation of fluoroalkyl radicals from sulfones, which are used for practical radical fluoroalkylation of organic compounds.

Fluorinated compounds have found wide applications in pharmaceuticals and agrochemicals due to the unique impact of fluorine substitution on their biological properties.[1] As a consequence, numerous methods have been developed for the incorporation of fluorine atoms or fluorinated moieties into organic molecules.[2] Among them, radical fluoroalkylation has been paid special attention because of its mild reaction conditions, broad functional group tolerance, and ability to modulate bioactive molecules at a late stage of synthesis.[3] However, most of the known methods generate fluoroalkyl radicals by visible light photoredox catalysis or by using stoichiometric amounts of redox agents.[4] On the other hand, organic electrochemistry, as a sustainable and green technique to generate radicals and radical ions,[5] has gained increasing attention in radical fluoroalkylation.[5b] In the past decades, R_fCOOH,[6] R_fSO_2M,[7] $R_fSO_2NHNHBoc$,[8] R_fSO_2Cl[9] and R_fX[10] have been exploited for radical tri- or difluoromethylation under electrochemical conditions. However, electrochemical radical fluoroalkylations with these reagents have some drawbacks, such as the lack of structural diversity in fluoroalkyl groups, as well as the requirement of specialized setups and transition metal catalysis.

Fluoroalkyl sulfones are a class of bench-stable and easily accessible organofluorine compounds, and have been well recognized as versatile fluoroalkylation reagents.[1f] In 2016, we reported the first example of using fluoroalkyl sulfones as modular fluoroalkyl radical precursors for efficient fluoroalkylation under visible-light photoredox catalysis (Scheme 1A).[11] In 2018, we reported an iron-catalyzed difluoromethylation of arylzincs using difluoromethyl 2-pyridyl sulfone as difluoromethyl radical precursor,[12] while the Baran group reported nickel-catalyzed fluoroalkylation of aryl zinc chlorides using 1-phenyl-1*H*-tetrazol-5-yl (PT) sulfones as radical fluoroalkylation reagents (Scheme 1B).[13] Very recently, iron-catalyzed radical fluoroalkylation of arylborates with sulfone reagents has been developed as an alternative for alkyl–aryl coupling, wherein the coordination between the iron catalyst and the sulfones plays an important role in overcoming the reduction potential limitation of sulfones in the intermolecular single-electron-transfer (SET) process.[14] Inspired by the excellent radical reactivity of fluorinated sulfones under either visible light photoredox catalysis or transition metal catalysis,[11–15] we envisioned that cathodic reduction of fluorinated sulfones would also be operable for the generation of fluoroalkyl radicals,[5] which can be useful for the electrochemical fluoroalkylation of challenging substrates by taking advantage of the reduction potential-tunable ability of sulfones.

Herein, we report our success in the generation of fluoroalkyl radicals from heteroaryl fluoroalkyl sulfones under direct cathodic reduction conditions. The synthetic utility of the so-generated fluoroalkyl radicals is demonstrated by the electrochemical hydro-fluoroalkylation of alkenes (Scheme 1C). Previously, selective electrochemical hydro-fluoroalkylation of alkenes had been a challenging task due to the unmatched reactivity between alkenes and available radical fluoroalkylation reagents.[16] Currently, the reaction can be carried out with inexpensive graphite electrodes under transition-metal-free conditions in aqueous medium and undivided cells. The easy availability of the sulfone reagents, the mildness of the reaction conditions, and the operational simplicity of the procedures make the method an attractive tool for the late-stage modification of bioactive complex molecules.

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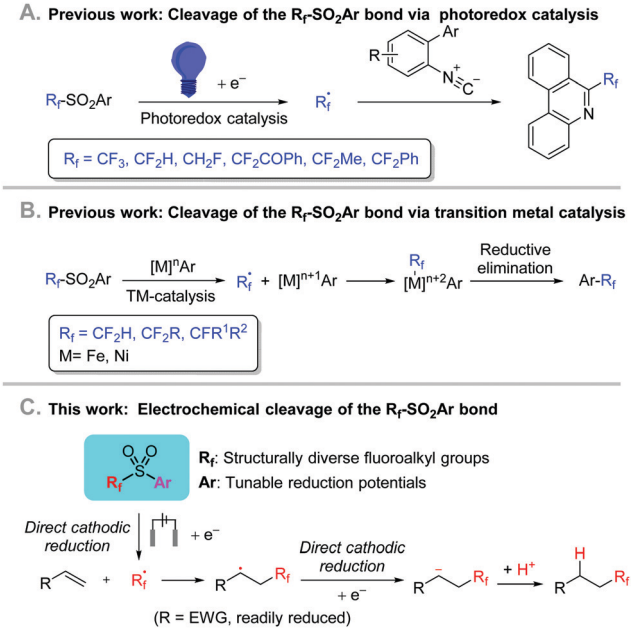
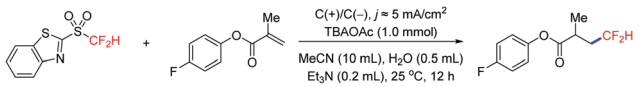


Scheme 1 Radical fluoroalkylation with fluoroalkyl sulfones.

We initially investigated the electroreductive hydrodifluoromethylation of methacrylate **2a** with several (hetero)aryl difluoromethyl sulfones in an undivided cell (a flask) equipped with a pair of graphite electrodes under constant current (Table 1). In a mixed solvent of acetonitrile and water (10 : 1, v/v) with TBAOAc as the electrolyte and Et_3N as an additive, the reaction with difluoromethyl benzo[*d*]thiazol-2-yl (2-BT) sulfone (**1a**) afforded the desired product **3a** in 90% ^{19}F NMR yield (Table 1, entry 1). Among the sulfone reagents tested, sulfone **1a**, which is of the highest reduction potential (E_{red} = −1.32 V *vs.* SCE),[15] gave **3a** in the highest yield (Table 1, entries 1–3). The low efficiency with 2-$PySO_2CF_2H$ (E_{red} = −1.83 V *vs.* SCE)[15] and $PhSO_2CF_2H$ (E_{red} = −2.07 V *vs.* SCE)[15] probably arises from the relatively rapid reduction of alkene **2a** (Table 1, entries 2 and 3). When only one equivalent of sulfone **1a** is used, a moderate yield of **3a** was obtained (Table 1, entry 4), implying the existence of the competitive consumption of the fluoroalkyl radicals. Control experiment in the absence of Et_3N indicates that a basic additive is necessary (Table 1, entry 5). When DBU was used instead of Et_3N, the yield was only slightly lower (Table 1, entry 6); however, the use of K_2CO_3 instead of Et_3N significantly reduced the yield (Table 1, entry 7). The additive probably serves as the sacrificial reductant to provide electrons for the simultaneous cathodic reduction. In view of the efficiency and the cost, Et_3N is the additive of choice and the optimal volume ratio of acetonitrile/Et_3N is 50 : 1 (Table 1, entry 8). Nevertheless, as indicated by the control experiment (Table 1, entry 9), electricity is required to promote the hydrofluoroalkylation reaction. The reaction was favorable in the presence of water, and the absence of additional water led to somewhat lower yield (Table 1, entry 10). A screen of other parameters revealed that acetonitrile is superior to other solvents (Table 1, entries 11–13) and TBAOAc is a good supporting electrolyte (Table 1, entries 14 and 15) for this hydrofluoroalkylation.

Table 1 Optimization of the reaction conditions

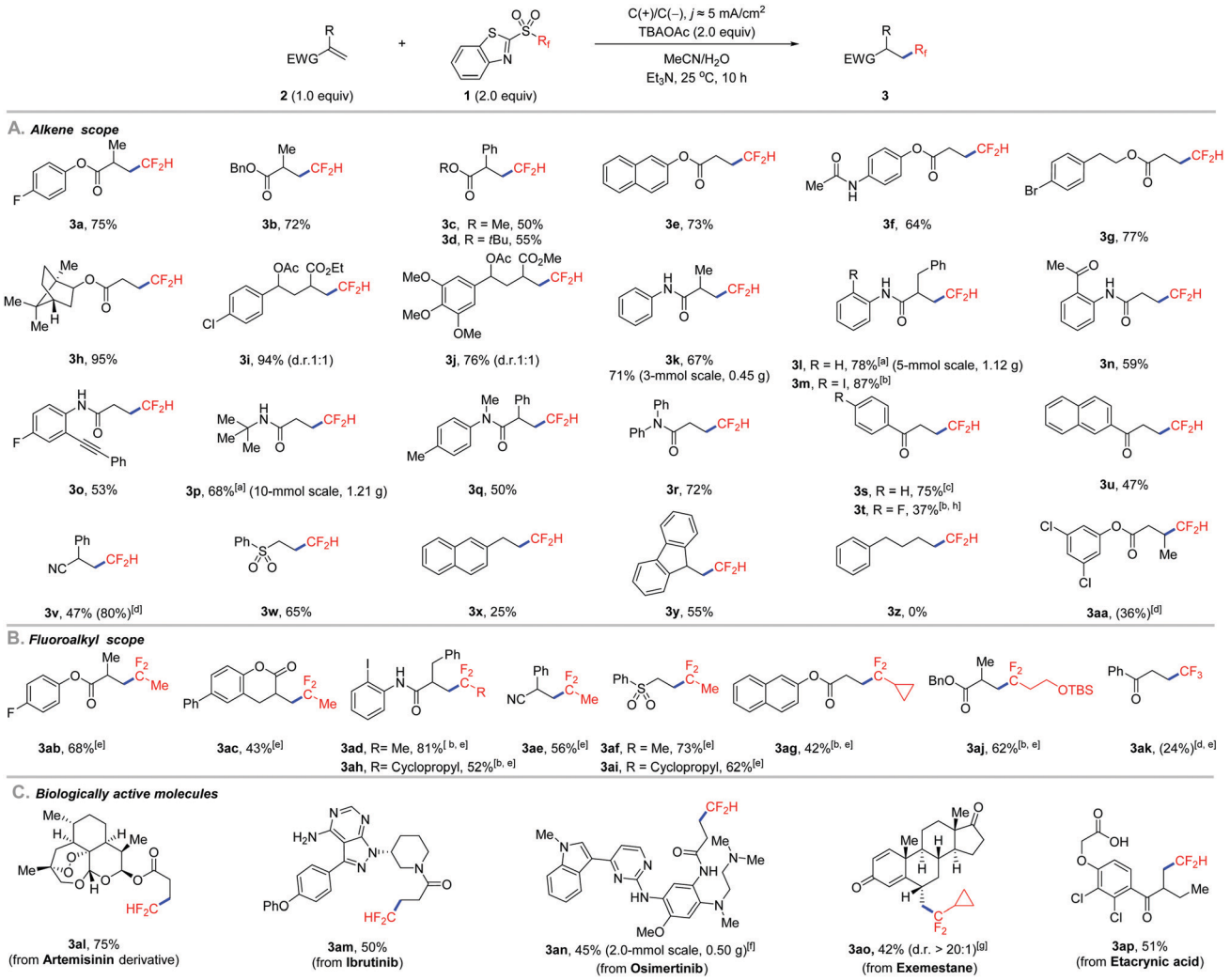


1a (1.0 mmol) **2a** (0.5 mmol) **3a**

Entry[a]	Deviation from standard conditions	Yield[b] [%]
1	None	90 (>99)[c]
2	2-$PySO_2CF_2H$ instead of **1a**	22 (>99)[c]
3	$PhSO_2CF_2H$ instead of **1a**	7 (28)[c]
4	1.0 equiv. of **1a**	54
5	Without Et_3N	49
6	DBU instead of Et_3N	85
7	K_2CO_3 instead of Et_3N	58
8	0.1 mL of Et_3N ($MeCN/Et_3N$, 100 : 1, v/v)	82
9	Without electricity	0
10	Without additional water	87
11	DMF instead of MeCN	86
12	MeOH instead of MeCN	69
13	DCM instead of MeCN	75
14	$TBAPF_6$ instead of TBAOAc	88
15	$TBABF_4$ instead of TBAOAc	80

[a] Reaction conditions: Undivided cell, graphite anode ($j \approx 5$ mA cm^{-2}), graphite cathode, **2a** (0.5 mmol), MeCN (10 mL), 25 °C, 3.8 F mol^{-1}, argon bubbled for 10 min initially. [b] Yield was determined by ^{19}F NMR spectroscopy using 1-fluoronapthalene as internal standard. [c] In parentheses: conversion of sulfone reagent.

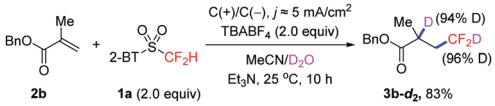
With the optimized conditions in hand (Table 1, entry 1), we investigated the scope of the electroreductive hydrofluoroalkylation reaction (Scheme 1). A range of alkenes were tested by using sulfone **1a** as the reagent (Scheme 2A). 1-Substituted and 1,2-disubstituted electron-deficient terminal alkenes including acrylic esters (**3b–3j**)/amides (**3k–3r**), acrylonitriles (**3v**), and vinyl ketones (**3s–3u**)/sulfones (**3w**) afforded the desired products in moderate to excellent yields. Fluoro (**3a**, **3o**), chloro (**3i**), bromo (**3g**), iodo (**3m**) and alkynyl (**3o**) groups on the aromatic ring are well tolerated. In the case of acrylic amides, both secondary (**3k–3o**) and tertiary (**3q–3r**) amides could undergo the reaction and no radical cyclization occurred on the *N*-aryl substituents. Other alkenes such as 1-substituted (**3x**) and 1,1-disubstituted styrenes (**3y**) as well as 1,2-disubstituted acrylic esters (**3aa**) are also viable substrates. However, only low yields were obtained with monosubstituted styrene (**3x**) and a 1,2-disubstituted alkene (**3aa**), which presumably arises from the relatively slow SET reduction of the new C-centered radical and the steric hindrance towards initial fluoroalkyl radical addition, respectively. Non-activated alkenes such as but-3-en-1-ylbenzene failed to take part in the reaction probably due to the unmatched electronic nature of the alkene and difluoromethyl radical under such conditions (**3z**). As shown in Scheme 2B, we also surveyed various fluoroalkyl benzo[*d*]thiazol-2-yl sulfones. The applicable fluoroalkyl group is not limited to CF_2H, and other α,α-difluoroalkyl groups such as CF_2CH_3, cyclopropyldifluoromethyl, and a functionalized difluoroalkyl group containing a protected hydroxyl group were also efficiently transferred to electron-deficient alkenes to give the hydro-difluoroalkylation products (**3ab–3aj**). The CF_3 group



Scheme 2 The reaction of sulfone **1** with alkenes. Reaction conditions: **1** (1.0 mmol), **2** (0.5 mmol), Tetrabutylammonium acetate (1.0 mol), Et_3N (0.2 mL) water (0.5 mL) in CH_3CN (10 mL) were conducted with the 5 mA constant current at room temperature for 10 hours under argon atmosphere. Yield of isolated product. [a] Reaction was conducted with a 20 mA constant current at room temperature for 20 hours. [b] Reaction was conducted for 12 hours. [c] Tetrabutylammonium hexafluorophosphate was used as electrolyte. [d] Yield was determined by ^{19}F NMR spectroscopy using 1-fluoronapthalene as internal standard and the value is in brackets. [e] Reaction was conducted with a 7 mA constant current at room temperature. [f] Zinc is used as the sacrificial anode. [g] The value of d.r. was determined by ^{19}F NMR spectroscopy. [h] 1-(4-Fluorophenyl)-3-chloro-1-propanone (0.5 mmol) was used as substrate.

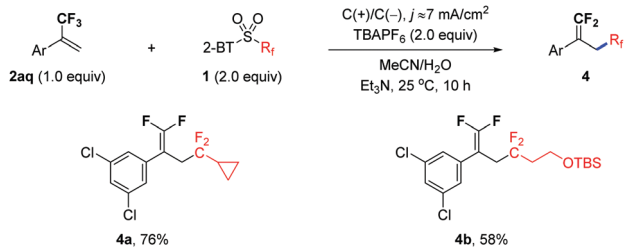
can also be incorporated, albeit the yield of the hydrotrifluoromethylation product was low due to the ready reduction of $^{\bullet}CF_3$ to CF_3^- under such conditions (**3ak**).[17,18] This protocol is suitable for the late-stage modification of biologically active molecules containing alkene functional groups (Scheme 2C). Hydro-difluoromethylated analogues of an Artemisinin derivative, Ibrutinib, Osimertinib, and Etacrynic acid were isolated in moderate to good yields (**3al–3ap**). Hydro-difluoroalkylation of Exemestane produced the corresponding product (**3ao**) in moderate yield, excellent diastereoselectivity and regioselectivity. The absolute configuration of the newly formed carbon center was determined by NOE experiment. Moreover, the practicability of this protocol is also demonstrated with the gram- or subgram-scale synthesis of several hydro-difluoromethylation products (**3k**, **3l**, and **3p**).

It is worth noting that when D_2O was used instead of H_2O as the additive, the reaction of 2-$BTSO_2CF_2H$ (**1a**) with alkene **2b** under similar conditions led to the deutero-deuterodifluoromethylation product (**3b**-d_2) with high deuterium incorporation (eqn (1)). Apparently, a fast deuteration of sulfone **1a** occurs first before its electroreduction (see Section 5.2 in ESI†). The high incorporation of the second deuterium atom indicates the feasibility of this protocol for deutero-difluoroalkylation with other sulfone reagents.



(1)

To figure out the possible pathway of his electroreductive hydrofluoroalkylation reaction, mechanistic studies were conducted.



Scheme 3 Probing the involvement of carbanion. The reaction of sulfone **1** with alkenes. Reaction conditions: **1** (1.0 mmol), **2aq** (0.5 mmol), tetrabutylammonium hexafluorophosphate (1.0 mmol), Et_3N (0.2 mL), water (0.5 mL) in CH_3CN (10 mL) were conducted with the 7 mA constant current for 10 hours.

^{19}F NMR spectroscopy analysis of the reaction mixture after the completion of the reaction showed that in addition to the desired product, difluoromethanesulfinate was also formed. The use of HCF_2SO_2Na instead of sulfone **1a** under our optimized conditions did not afford the desired product **3a** (see Section 5.1 in ESI†). These results suggest that the fluoroalkyl radical is generated *via* direct SET reduction of the fluoroalkyl sulfone. When an electron-deficient alkene, 2-trifluoromethylstyrene **2aq**, was used as the substrate, its reaction with fluoroalkyl sulfones **1c** and **1d** afforded 1,1-difluroalkenes as the major products (**4a** and **4b**) (Scheme 3). The formation of the β-fluoride elimination products strongly supports the involvement of α-trifluoromethylated carbanion as an intermediate (for a proposed mechanism, see Section 5.4 in ESI†).

In conclusion, we investigated the behavior of fluorinated sulfones under electrochemical conditions and applied difluoroalkyl and trifluoromethyl heteroaryl sulfones to electrochemical organic synthesis for the first time. The easy availability of the sulfone reagents, the mildness of the reaction conditions, and the operational simplicity of the procedures make this electrochemical method an attractive tool for the late-stage modification of bioactive complex molecules.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) R. D. Chambers, *Fluorine in Organic Chemistry*, Blackwell, Oxford, 2004; (*b*) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2004; (*c*) K. Uneyama, *Fundamentals in Organic Fluorine Chemistry*, Blackwell, Oxford, 2006; (*d*) L. Gregory, P. Armen and R. L. Frederic, *Curr. Top. Med. Chem.*, 2014, **14**, 941; (*e*) M. Inoue, Y. Sumii and N. Shibata, *ACS Omega*, 2020, **5**, 10633; (*f*) Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai and N. Shibata, *iScience*, 2020, **23**, 101467.
2 (*a*) T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem., Int. Ed.*, 2013, **52**, 8214; (*b*) V. Gouverneur and K. Seppelt, *Chem. Rev.*, 2015, **115**(2), 563; (*c*) R. Britton, V. Gouverneur, J.-H. Lin, M. Meanwell, C. Ni, G. Pupo, J.-C. Xiao and J. Hu, *Nat. Rev. Methods Primers*, 2021, **1**, 47.
3 S. Barata-Vallejo, M. V. Cooke and A. Postigo, *ACS Catal.*, 2018, **8**, 7287.
4 (*a*) T. Koike and M. Akita, *Top. Catal.*, 2014, **57**, 967; (*b*) M.-C. Belhomme, T. Besset, T. Poisson and X. Pannecoucke, *Chem. – Eur. J.*, 2015, **21**, 12836; (*c*) S. Liu, Y. Huang, F.-L. Qing and X.-H. Xu, *Org. Lett.*, 2018, **20**, 5497; (*d*) B. He, Q. Pan, Y. Guo, Q.-Y. Chen and C. Liu, *Org. Lett.*, 2020, **22**, 6552.
5 (*a*) M. Yan, Y. Kawamata and P. S. Baran, *Chem. Rev.*, 2017, **117**, 13230; (*b*) Z. Zou, W. Zhang, Y. Wang and Y. Pan, *Org. Chem. Front.*, 2021, **8**, 2786.
6 (*a*) C. J. Brookes, P. L. Coe, D. M. Owen, A. E. Pedler and J. C. Tatlow, *J. Chem. Soc., Chem. Commun.*, 1974, **39**, 323; (*b*) K. Uneyama and H. Nanbu, *J. Org. Chem.*, 1988, **53**, 4598; (*c*) K. Arai, K. Watts and T. Wirth, *ChemistryOpen*, 2014, **3**, 23.
7 A. M. A. G. OBrien, Y. Inokuma, M. Fujita, P. S. Baran and D. G. Blackmond, *Angew. Chem., Int. Ed.*, 2014, **53**, 111868.
8 (*a*) P. Xiong, H. H. Xu, J. Song and H. C. Xu, *J. Am. Chem. Soc.*, 2018, **140**, 2460; (*b*) H. H. Xu, J. Song and H. C. Xu, *ChemSusChem*, 2019, **12**, 3060.
9 (*a*) E. J. Horn, B. R. Rosen and P. S. Baran, *ACS Cent. Sci.*, 2016, **2**, 302; (*b*) S. Rodrigo, C. Um, J. C. Mixdorf, D. Gunasekera, H. M. Nguyen and L. Luo, *Org. Lett.*, 2020, **22**, 6719.
10 (*a*) C. P. Andrieux, L. Gelis and J.-M. Saveant, *Tetrahedron Lett.*, 1989, **30**, 4961; (*b*) V. G. Koshechko, L. A. Kiprianova, L. I. Fileleeva and Z. Z. Rozhkova, *J. Fluorine Chem.*, 1995, **70**, 277; (*c*) H. Asai and K. Uneyama, *Chem. Lett.*, 1995, 1123.
11 (*a*) J. Rong, L. Deng, P. Tan, C. Ni, Y. Gu and J. Hu, *Angew. Chem., Int. Ed.*, 2016, **55**, 2743; (*b*) J. Rong, C. Ni, Y. Wang, C. Kuang, Y. Gu and J. Hu, *Acta Chim. Sin.*, 2017, **75**, 105.
12 W. Miao, Y. Zhao, C. Ni, B. Gao, W. Zhang and J. Hu, *J. Am. Chem. Soc.*, 2018, **140**, 880.
13 R. R. Merchant, J. T. Edwards, T. Qin, M. M. Kruszyk, C. Bi, G. Che, D. H. Bao, W. Qiao, L. Sun, M. R. Collins, O. O. Fadeyi, G. M. Gallego, J. J. Mousseau, P. Nuhant and P. S. Baran, *Science*, 2018, **360**, 75.
14 Z. Wei, W. Miao, C. Ni and J. Hu, *Angew. Chem., Int. Ed.*, 2021, **60**, 13597–13602.
15 (*a*) W. Fu, X. Han, M. Zhu, C. Xu, Z. Wang, B. Ji, X. Q. Hao and M. P. Song, *Chem. Commun.*, 2016, **52**, 13413; (*b*) G. Zou and X. Wang, *Org. Biomol. Chem.*, 2017, **15**, 8748; (*c*) M. Zhu, W. Fu, Z. Wang, C. Xu and B. Ji, *Org. Biomol. Chem.*, 2017, **15**, 9057; (*d*) M. Zhu, Q. You and R. Li, *J. Fluorine Chem.*, 2019, **228**, 109391; (*e*) Y. Nakayama, G. Ando, M. Abe, T. Koike and M. Akita, *ACS Catal.*, 2019, **9**, 6555; (*f*) L. Trump, A. Lemos, B. Lallemand, P. Pasau, J. Mercier, C. Lemaire, A. Luxen and C. Genicot, *Angew. Chem., Int. Ed.*, 2019, **58**, 13149; (*g*) B. Josephson, C. Fehl, P. G. Isenegger, S. Nadal, T. H. Wright, A. W. J. Poh, B. J. Bower, A. M. Giltrap, L. Chen, C. Batchelor-McAuley, G. Roper, O. Arisa, J. B. I. Sap, A. Kawamura, A. J. Baldwin, S. Mohammed, R. G. Compton, V. Gouverneur and B. G. Davis, *Nature*, 2020, **585**, 530.
16 For selected examples on hydro-fluoroalkylation of alkenes under non electrochemical conditions, see Section S8 in ESI†.
17 2-$PySO_2CF_3$ that has a lower reduction potential than 2-$BTSO_2CF_3$ (see ref. 11*a*) can also be electrochemically reduced under such conditions; however, similar result was given.
18 Monofluoroalkyl and nonfluoroalkyl sulfones failed to undergo alkylation reactions (see Scheme S2 in ESI†).