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1,1-Difluoroethyl chloride (CH_3CF_2Cl), a novel difluoroalkylating reagent for 1,1-difluoroethylation of arylboronic acids†

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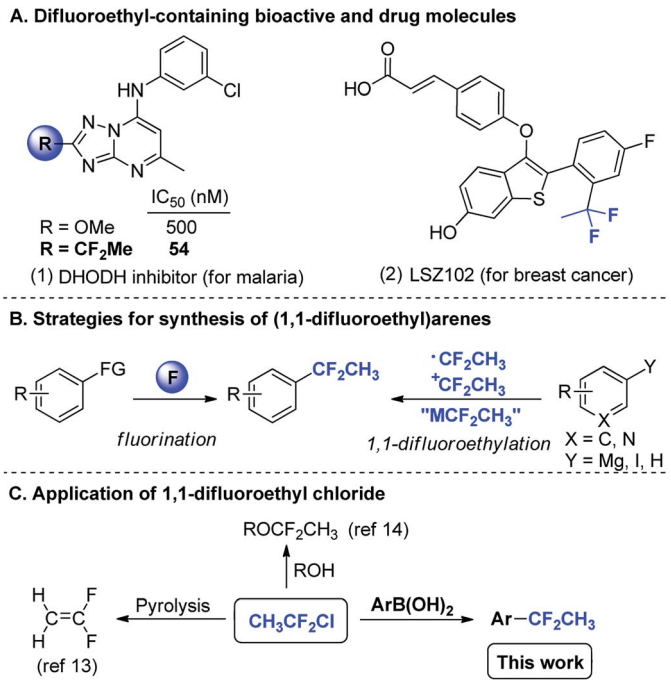
1,1-Difluoroethylated aromatics are of great importance in medicinal chemistry and related fields. 1,1-Difluoroethyl chloride (CH_3CF_2Cl), a cheap and abundant industrial raw material, is viewed as an ideal 1,1-difluoroethylating reagent, but the direct introduction of the difluoroethyl (CF_2CH_3) group onto aromatic rings using CH_3CF_2Cl has not been successfully accomplished. Herein, we disclose a nickel-catalyzed 1,1-difluoroethylation of arylboronic acids with CH_3CF_2Cl for the synthesis of (1,1-difluoroethyl) arenes.

Organic fluorine compounds have attracted extensive attention in recent years, since the introduction of fluorine atom(s) into organic molecules often results in dramatic changes in physical, chemical and biological properties.[1,2] Among them, aromatic compounds containing the difluoroethyl (CF_2CH_3) group are of great importance, because it mimics the steric and electronic features of a methoxy group, which makes it a significant group for drug design.[3] For instance, a triazolopyrimidine-based dihydroorotate dehydrogenase (DHODH) inhibitor[4] shows remarkable advantage in terms of potency due to the replacement of a methoxy group by a difluoroethyl group (Scheme 1A). LSZ102,[5] a clinical agent, is currently applied in phase I/Ib trials for the treatment of estrogen receptor alpha-positive breast cancer (Scheme 1A). Thus, the invention of reagents or methods for the synthesis of (1,1-difluoroethyl)arenes is a very appealing and pretty meaningful task.

The synthesis of such compounds are generally accomplished by two strategies:[6] one is the transformation of a functional group to a difluoromethylene (CF_2) group or a CF_2CH_3 moiety, such as nucleophilic fluorination of ketones or their derivatives,[7] dihydrofluorination of terminal arynes,[8] and benzylic C–H fluorination;[9] the other is the direct introduction of a CF_2CH_3 moiety onto aromatic rings, including nucleophilic,[10] electrophilic[11] and radical 1,1-difluoroethylation[12] (Scheme 1B). In spite of these important accomplishments, it is still a key challenge to develop low-cost and easily available difluoroalkylating reagents for synthesis of (1,1-difluoroethyl) arenes.

1,1-Difluoroethyl chloride (CH_3CF_2Cl; HCFC-142b; bp = −9.5 °C), a cheap and abundant industrial raw material used for vinylidene fluoride (VDF),[13] is viewed as an ideal source to prepare difluoroethylated derivatives.[14] We envisioned that the direct introduction of CF_2CH_3 onto aromatic rings could be



Scheme 1 (A) Difluoroethyl-containing bioactive and drug molecules; (B) strategies for synthesis of (1,1-difluoroethyl)arenes. M = metal; (C) application of 1,1-difluoroethyl chloride.

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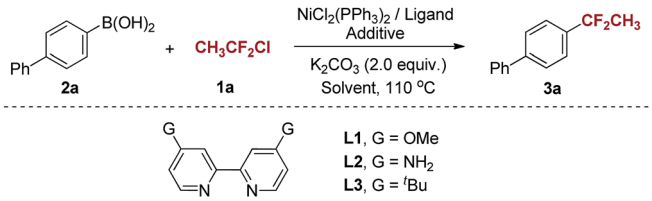
through transition-metal-catalyzed 1,1-difluoroethylation of arylboronic acids with CH_3CF_2Cl (Scheme 1C). Although transition-metal-catalyzed difluoroalkylation of aromatics using activated difluoroalkyl halides (RCF_2X, R = π system) has been successfully reported,[15] the use of unactivated RCF_2X (R = alkyl) for synthesis of difluoroalkylarenes was rarely reported.[11,16] To the best of our knowledge, the use of CH_3CF_2Cl to prepare Ar–CF_2CH_3 compounds through a Suzuki-type cross-coupling reaction has not been reported and remains challenges because of the difficulties in activating the inert C–Cl bond of CH_3CF_2Cl and in suppressing homo-coupling and deboronation of arylboronic acids. Herein, we wish to disclose a nickel-catalyzed 1,1-difluoroethylation of arylboronic acids with CH_3CF_2Cl.

At the onset of our investigation, 4-biphenylboronic acid (**2a**) was chosen as the model substrate for the nickel-catalyzed 1,1-difluoroethylation reaction (Table 1). To our delight, the product **3a** was obtained in 5% yield in the presence of $NiCl_2(PPh_3)_2$ (5 mol%), 2,2′-bipyridine (5 mol%), K_2CO_3 (2.0 equiv.) in DME at 110 °C (Table 1, entry 1). The low yield should be due to the residual **2a** and the formed homo-coupling and deboronation of **2a** (determined by GC-MS). To improve the reaction efficiency, different diamine ligands were examined (Table 1, entries 2–5). As a result, diOMe-bpy (**L1**) improved the yield of **3a** to 15% (Table 1, entry 2), while diNH_2-bpy (**L2**) and di^{t}Bu-bpy (**L3**) gave poor yields of **3a** (Table 1, entry 3 and 4). 1,10-Phenanthroline (phen), commonly used in copper-catalyzed reactions, led to a negative result in current reaction (Table 1, entry 5). With the optimal combination of Ni and ligand established (for details, see ESI†), we next investigated the influence of additives and solvent. As previously reported,[16,17] pyridine derivatives could promote Ni-catalyzed Suzuki–Miyaura cross-coupling reactions. Thus, we attempted the current reaction in the presence of pyridine and its derivatives. As expected, the use of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) afforded a higher yield of **3a** (Table 1, entry 8), while pyridine (Py) and 4-cyanopyridine (4-CNPy) proved to be ineffective for the reaction (Table 1, entry 6 and 7). To improve the yield of **3a**, we increased the loading of DMAP to 50 mol% and the yield was correspondingly enhanced to 49% (Table 1, entry 9). Consequently, the use of 70 mol% of DMAP provided the desired product in 61% yield (Table 1, entry 10). In addition, when 3 mol% of $NiCl_2(PPh_3)_2$ and ligand were employed in the reaction, the yield of **3a** was increased to 70% and did little change by prolonging reaction time (Table 1, entry 12). However, only trace of the product was formed in the absence of ligand **L1** (Table 1, entry 13), indicating that the diamine ligand is essential in the Ni-catalyzed 1,1-difluoroethylation of arylboronic acids. For further insight the reactivity of other ligands in the presence of DMAP, we conducted the reactions with ligands **L2** and **L3** under the optimized conditions (Table 1, entry 14 and 15). The results showed that the combination of ligand **L2** with DMAP offered a low yield of 24% due to the residue of **2a**, and ligand **L3** gave a yield of 61% because of a little more deboronation of **2a**. For solvent screening (for details, see ESI†), it was found that 1,4-dioxane and DMF were inferior to DME (Table 1, entry 16 and 17).

Table 1 Optimization of reaction conditions[a]

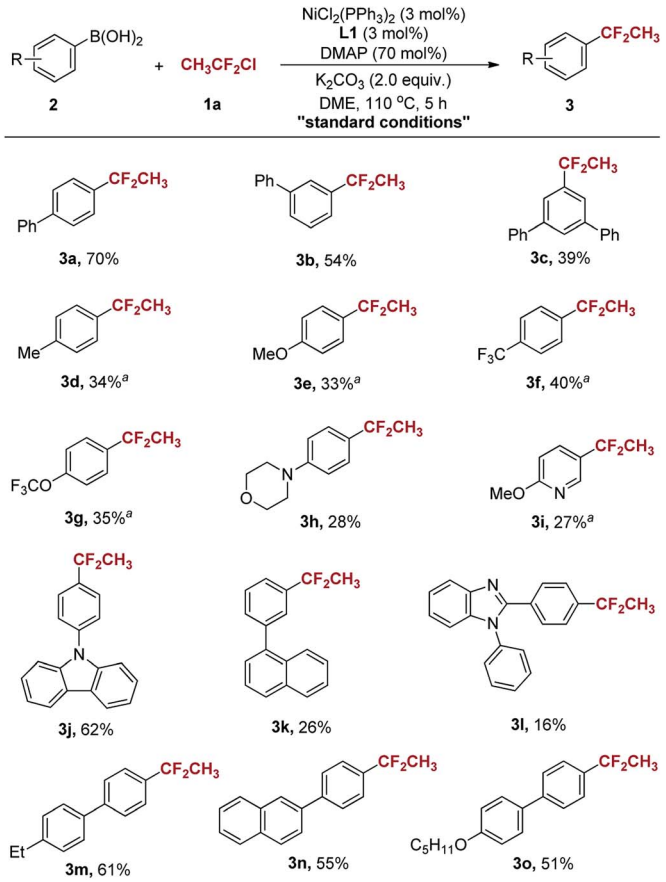


Entry	Ligand (mol%)	Additive (mol%)	Solvent	Yield[b] (%)
1	bpy (5)	—	DME	5
2	**L1** (5)	—	DME	15
3	**L2** (5)	—	DME	7
4	**L3** (5)	—	DME	7
5	Phen (5)	—	DME	Trace
6	**L1** (5)	Py (10)	DME	Trace
7	**L1** (5)	4-CNPy (10)	DME	Trace
8	**L1** (5)	DMAP (10)	DME	30
9	**L1** (5)	DMAP (50)	DME	49
10	**L1** (5)	DMAP (70)	DME	61
11	**L1** (5)	DMAP (100)	DME	59
12[c]	**L1** (3)	DMAP (70)	DME	70 (69)[d]
13[c]	—	DMAP (70)	MME	Trace
14[c]	**L2** (3)	DMAP (70)	DME	24
15[c]	**L3** (3)	DMAP (70)	DME	61
16[c]	**L1** (3)	DMAP (70)	1,4-Dioxane	31
17[c]	**L1** (3)	DMAP (70)	DMF	21

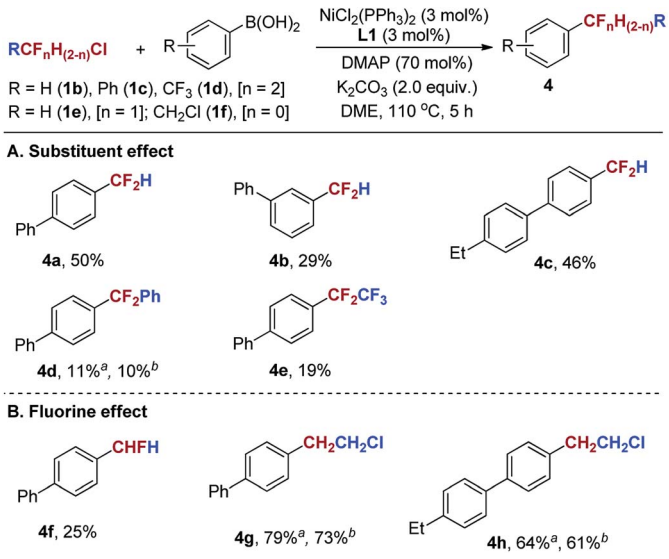
[a] Reaction conditions: **2a** (0.2 mmol, 1.0 equiv.), **1a** (2.0–2.6 mmol), $NiCl_2(PPh_3)_2$ (5 mol%), K_2CO_3 (2.0 equiv.), solvent (2 mL), 110 °C, N_2, 5 h. [b] Isolated yield. [c] $NiCl_2(PPh_3)_2$ (3 mol%). [d] The reaction was conducted for 12 h. bpy = 2,2′-bipyridine, phen = 1,10-phenanthroline, DME = 1,2-dimethoxyethane, DMAP = 4-(*N*,*N*-dimethylamino)pyridine.

With the optimised conditions in hand, we further explored the substrate scope of the 1,1-difluoroethylation of arylboronic acids with CH_3CF_2Cl (Scheme 2). The reaction can tolerate a variety of functional groups, such as methyl, methoxyl, trifluoromethyl, trifluoromethoxy and substituted morpholine (Scheme 2, **3d–3h**). Generally, the substituent group of arylboronic acids with π-system showed good reactivity toward CH_3CF_2Cl, affording the desired product in moderate to good yields (Scheme 2, **3a**, **3b**, **3m–3o**). It was found that the reaction afforded slightly low yields with sterically hindered arylboronic acids under the standard conditions (Scheme 2, **3c**, **3k**, **3l**). In addition, this transformation was also applicable to 4-(9*H*-carbozol-9-yl)phenylboronic acid and the 1,1-difluoroethylated product was obtained in 62% yield (Scheme 2, **3j**).

To investigate the substituent effect of fluoroalkyl chlorides on the Suzuki-type reaction, we conducted comparative experiments using HCF_2Cl (**1b**), $PhCF_2Cl$ (**1c**) and CF_3CF_2Cl (**1d**) under the standard conditions (Scheme 3A). When arylboronic acids and **1b** were subjected to the standard conditions, the reaction provided difluoromethylated products (**4a–4c**) in moderate yields. However, the use of **1c** and **1d** gave poor yields of the corresponding products **4d** and **4e**, respectively. These results indicate that the reactivity of RCF_2Cl in the reaction with **2a** decreases in the following order: CH_3CF_2Cl > HCF_2Cl >



Scheme 2 Scope of 1,1-difluoroethylation of arylboronic acids with CH_3CF_2Cl. Reaction conditions (unless otherwise specified): **2** (0.2 mmol, 1.0 equiv.), **1a** (1.3 M in DME, 2.6 mmol, 13.0 equiv.), DME (2 mL), 110 °C, N_2, 5 h. Isolated yields. [a]Yields were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard.



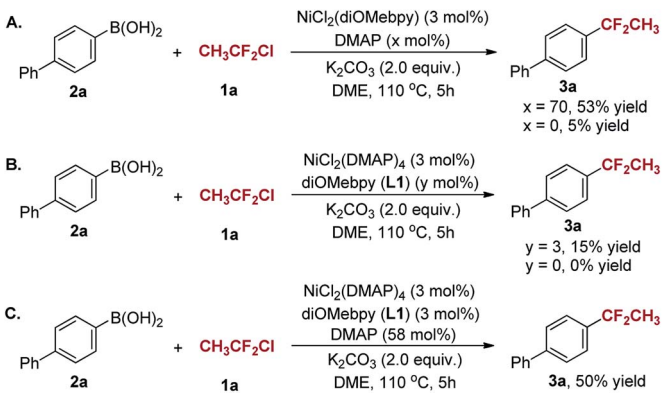
Scheme 3 Ni-catalyzed cross-coupling of arylboronic acids with alkyl halides. Reaction conditions: **2** (0.2 mmol, 1.0 equiv.), **1** (2.0 mmol, 10 equiv.), DME (2 mL). Isolated yields. [a]**1** (1.0 mmol, 5.0 equiv.). [b]**1** (0.2 mmol, 1.0 equiv.), **2** (0.3 mmol, 1.5 equiv.).

$CF_3CF_2Cl \approx PhCF_2Cl$. Next, we intended to explore the fluorine effect on the reaction. Comparative experiments by the use of H_2CFCl (**1e**) and $ClCH_2CH_2Cl$ (**1f**) were conducted under the standard conditions (Scheme 3B). It was found that the reaction of **1e** with **2a** afforded monofluoromethylated product **4f** in a low yield, while β-chloroethylarenes (**4g**, **4h**) were obtained in good yields under the standard conditions. These results indicate that the reactivity of RCl in the reaction with **2a** decreases in the following order: $ClCH_2CH_2Cl \approx CH_3CF_2Cl > H_2CFCl$.

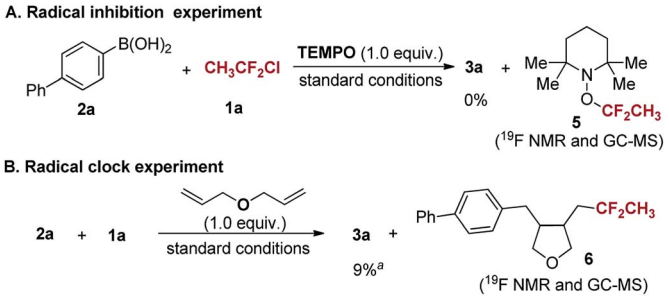
To examine the role of DMAP in the reaction, we prepared nickel complexes $NiCl_2$(diOMebpy) and $NiCl_2(DMAP)_4$. Both of them could serve as precatalysts and offered **3a** in 50% and 15% yield, respectively (Scheme 4A and B). However, $NiCl_2$(diOMebpy) provided **3a** in a low yield (5%) in the absence of DMAP (Scheme 4A) and the use of $NiCl_2(DMAP)_4$ resulted in no product without diOMebpy (Scheme 4B). It was noted that the additional DMAP did enhance the yield from 15% to 50% (Scheme 4C). These results demonstrate that one of the roles of DMAP may function as a co-ligand in the Ni-catalyzed reaction. Apparently, the combination of diOMebpy as a bidentate ligand with 70 mol% of DMAP facilitates the Ni-catalyzed 1,1-difluoroethylation of arylboronic acids with CH_3CF_2Cl.

In order to obtain some insight into the mechanism of the current reaction, radical inhibition and radical clock experiments were conducted (Scheme 5). In the presence of 2,2,6,6-tetramethylpiperidine-1-oxy (TEMPO) as a radical scavenger, the reaction was readily inhibited and compound **5** was detected by ^{19}F NMR and GC-MS. Furthermore, when diallyl ether was added to the reaction under the standard conditions, a ring-closing product **6** was formed (determined by ^{19}F NMR and GC-MS), along with 9% yield of **3a** (for details, see ESI†). These results demonstrate that a 1,1-difluoroethyl radical is indeed generated in the reaction.

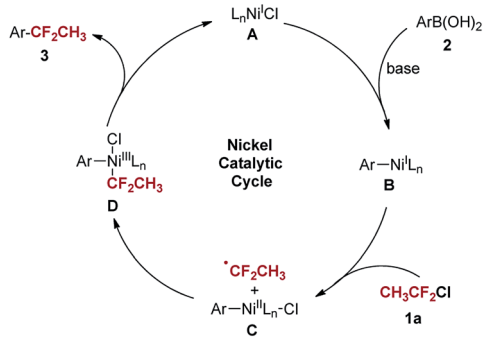
On the basis of these results and previous reports,[16,18] a plausible mechanism involving Ni(I)/Ni(III) catalytic cycle was proposed for the 1,1-difluoroethylation reaction (Scheme 6). The $L_nNi(I)Cl$ intermediate (**A**) is supposed to be generated *via* the comproportionation of initially formed $L_nNi(0)$ species and the remaining $L_nNi(II)Cl_2$,[19] followed by transmetalation with arylboronic acids. The formed $L_nNi(I)Ar$ species (**B**) reacts with CH_3CF_2Cl through a SET pathway to produce 1,1-difluoroethyl



Scheme 4 The role of DMAP. Isolated yields.



Scheme 5 Radical trapping experiments. [a]The yield was determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard.



Scheme 6 Proposed reaction mechanism.

radical and $L_nNi(II)(Ar)(Cl)$ species (**C**). Subsequently, the resulting $L_nNi(III)(Ar)(CF_2CH_3)(Cl)$ species (**D**) undergoes reductive elimination to give the coupling product **3** and regenerates $L_nNi(I)Cl$ to complete the catalytic cycle. It is noted that DMAP may not only function as a co-ligand to coordinated to the nickel center,[16,20] but also activate the arylboronic acids to facilitate the transmetalation.[17a]

In conclusion, the first transition-metal-catalyzed 1,1-difluoroethylation of arylboronic acids with the cheap and easily available CH_3CF_2Cl has been successfully developed. This method can tolerate methyl, methoxyl, trifluoromethyl and heteroarenes, affording 1,1-difluoroethylated products in moderate to good yields. The reactivity of different alkyl chlorides in the reaction was also investigated. Initial mechanism study showed the nickel-catalyzed 1,1-difluoroethylation probably involves a $Ni^{I/III}$ process. Current efforts are to develop catalytic system for improving yields and novel reactions with CH_3CF_2Cl as cheap fluorine source.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 (*a*) J.-P. Bégué and D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley, Hoboken, NJ, 2008; (*b*) K. Uneyama, *Organofluorine Chemistry*, Blackwell, Oxford, U.K., 2006; (*c*) D. A. Nagib and D. W. C. MacMillan, *Nature*, 2011, **480**, 224; (*d*) T. Furuya, A. S. Kamlet and T. Ritter, *Nature*, 2011, **473**, 470; (*e*) Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herlé, N. Sach, M. R. Collins, Y. Ishihara and P. S. Baran, *Nature*, 2012, **492**, 95.

2 For reviews, see: (*a*) M. Schlosser, *Angew. Chem., Int. Ed.*, 2006, **45**, 5432; (*b*) D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308; (*c*) T. Furuya, J. E. M. N. Klein and T. Ritter, *Synthesis*, 2010, 1804; (*d*) O. A. Tomashenko and V. V. Grushin, *Chem. Rev.*, 2011, **111**, 4475; (*e*) X.-F. Wu, H. Neumann and M. Beller, *Chem.–Asian J.*, 2012, **7**, 1744; (*f*) F.-L. Qing, *Chin. J. Org. Chem.*, 2012, **32**, 815; (*g*) C. Ni, M. Hu and J. Hu, *Chem. Rev.*, 2015, **115**, 765.

3 (*a*) P. Kirsch, *Modern fluoroorganic chemistry: synthesis, reactivity, applications*, Wiley-VCH, Weinheim, 2013; (*b*) G. M. Blackburn, D. E. Kent and F. J. Kolkmann, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1119; (*c*) D. B. Berkowitz and M. Bose, *J. Fluorine Chem.*, 2001, **112**, 13; (*d*) D. O'Hagan, Y. Wang, M. Skibinski and A. M. Z. Slawin, *Pure Appl. Chem.*, 2012, **84**, 1587.

4 M. O. Anderson, J. Zhang, Y. Liu, C. Yao, P.-W. Phuan and A. S. Verkman, *J. Med. Chem.*, 2012, **55**, 5942.

5 G. S. Tria, T. Abrams, J. Baird, H. E. Burks, B. Firestone, L. A. Gaither, L. G. Hamann, G. He, C. A. Kirby, S. Kim, F. Lombardo, K. J. Macchi, D. P. McDonnell, Y. Mishina, J. D. Norris, J. Nunez, C. Springer, Y. Sun, N. M. Thomsen, C. Wang, J. Wang, B. Yu, C.-L. Tiong-Yip and S. Peukert, *J. Med. Chem.*, 2018, **61**, 2837.

6 For a review, see: X. Li, J. Liu, X. Li, H. Liu, H. Liu, Y. Li, Y. Liu and Y. Dong, *J. Fluorine Chem.*, 2018, **216**, 102.

7 (*a*) L. N. Markovskij, V. E. Pashinnik and A. V. Kirsanov, *Synthesis*, 1973, 787; (*b*) G. S. Lal, G. P. Pez, R. J. Pesaresi and F. M. Prozonic, *Chem. Commun.*, 1999, 215; (*c*) C. York, G. K. S. Prakash and G. A. Olah, *Tetrahedron*, 1996, **52**, 9.

8 O. E. Okoromoba, J. Han, G. B. Hammond and B. Xu, *J. Am. Chem. Soc.*, 2014, **136**, 14381.

9 (*a*) J.-B. Xia, C. Zhu and C. Chen, *J. Am. Chem. Soc.*, 2013, **135**, 17494; (*b*) P. Xu, S. Guo, L. Wang and P. Tang, *Angew. Chem., Int. Ed.*, 2014, **53**, 5955; (*c*) J. Ma, W. Yi, G. Lu and C. Cai, *Org. Biomol. Chem.*, 2015, **13**, 2890; (*d*) A. M. Hua, D. N. Mai, R. Martinez and R. D. Baxter, *Org. Lett.*, 2017, **19**, 2949.

10 X. Li, J. Zhao, Y. Wang, J. Rong, M. Hu, D. Chen, P. Xiao, C. Ni, L. Wang and J. Hu, *Chem.–Asian J.*, 2016, **11**, 1789.

11 (*a*) Y. Ohtsuka and T. Yamakawa, *J. Fluorine Chem.*, 2016, **185**, 96; (*b*) L. An, Y.-L. Xiao, S. Zhang and X. Zhang, *Angew. Chem., Int. Ed.*, 2018, **57**, 6921.

12 (*a*) Q. Zhou, A. Ruffoni, R. Gianatassio, Y. Fujiwara, E. Sella, D. Shabat and P. S. Baran, *Angew. Chem., Int. Ed.*, 2013, **52**, 3949; (*b*) J. Rong, L. Deng, P. Tan, C. Ni, Y. Gu and J. Hu, *Angew. Chem., Int. Ed.*, 2016, **55**, 2743.
13 F. B. Downing, A. F. Benning, and R. C. McHarness, *US Pat.*, US 2551573, 1945.
14 A. L. Henne and M. A. Smook, *J. Am. Chem. Soc.*, 1950, **72**, 4378.
15 (*a*) Z. Feng, Q.-Q. Min, Y.-L. Xiao, B. Zhang and X. Zhang, *Angew. Chem., Int. Ed.*, 2014, **53**, 1669; (*b*) Q.-Q. Min, Z. Yin, Z. Feng, W.-H. Guo and X. Zhang, *J. Am. Chem. Soc.*, 2014, **136**, 1230; (*c*) Y.-L. Xiao, W.-H. Guo, G.-Z. He, Q. Pan and X. Zhang, *Angew. Chem., Int. Ed.*, 2014, **53**, 9909.
16 Y.-L. Xiao, Q.-Q. Min, C. Xu, R.-W. Wang and X. Zhang, *Angew. Chem., Int. Ed.*, 2016, **55**, 5837.
17 (*a*) L. An, Y.-L. Xiao, Q.-Q. Min and X. Zhang, *Angew. Chem., Int. Ed.*, 2015, **54**, 9079; (*b*) X.-P. Xia, Y.-L. Xiao and X. Zhang, *Chin. J. Chem.*, 2018, **36**, 143.
18 S. L. Zultanski and G. C. Fu, *J. Am. Chem. Soc.*, 2013, **135**, 624.
19 J. Cornella, E. Gómez-Bengoa and R. Martin, *J. Am. Chem. Soc.*, 2013, **135**, 1997.
20 C. Xu, W.-H. Guo, X. He, Y.-L. Guo, X.-Y. Zhang and X. Zhang, *Nat. Commun.*, 2018, **9**, 1170.