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Radical (Phenylsulfonyl)difluoromethylation of Isocyanides with $PhSO_2CF_2H$ under Transition-Metal-Free Conditions

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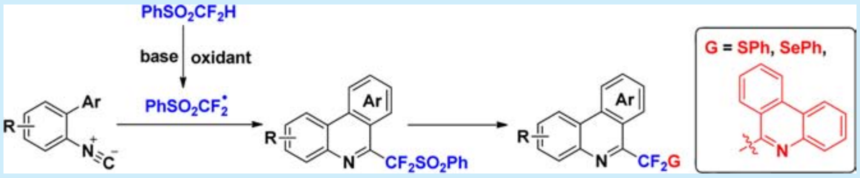
Supporting Information

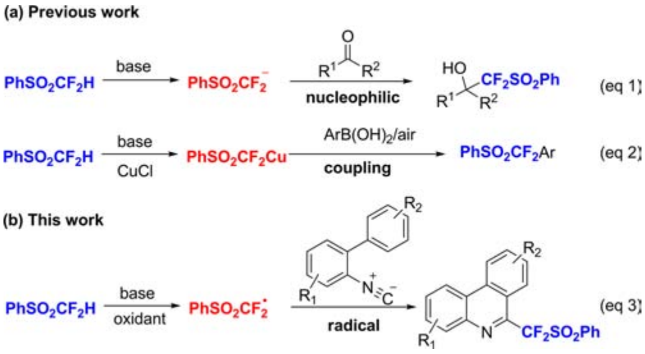


ABSTRACT: An atom-economical method for radical (phenylsulfonyl)difluoromethylation of isocyanides with $PhSO_2CF_2H$ under transition-metal-free conditions has been developed. A $PhSO_2CF_2$ radical is generated through the oxidation of $PhSO_2CF_2^-$ after the deprotonation of $PhSO_2CF_2H$ in one pot. The reaction exhibits excellent functional-group tolerance and the resulting products can be further modified with the removal of a $PhSO_2$ group to give other CF_2-containing compounds.

The phenanthridine core is an important substructure existing in various natural products which possess a wide range of biological activities and applications.[1] Selective introduction of fluorine-bearing motifs into organic molecules, including the above-mentioned phenanthridine derivatives, may effectively enhance the latters' biological activity due to the increased lipophilicity and metabolic stability.[2] Therefore, it is highly desirable to develop efficient methods for the incorporation of fluorinated moieties into diverse organic structures. Among various fluoroalkyl groups, the *gem*-difluoroalkyl group has attracted particular interest, since the CF_2 moiety is known to be isosteric to the ethereal oxygen atom.[3] In this respect, the $PhSO_2CF_2$ group is appealing based on the fact that it is a versatile functional group that can be converted to other highly useful difluorinated moieties such as difluoromethyl ($-CF_2H$), difluoromethylene ($-CF_2-$), and difluoromethylidene ($=CF_2$) groups.[4] Over the past decades, nucleophilic (phenylsulfonyl)difluoromethylation of a variety of electrophiles with $PhSO_2CF_2H$ has proved to be a powerful strategy for the synthesis of fluorinated compounds.[5,6] For example, α-difluoromethyl alcohols can be readily prepared by nucleophilic difluoromethylation of carbonyl compounds with its anion $PhSO_2CF_2^-$ (Scheme 1, eq 1).[6] In addition, a method for copper-mediated aerobic (phenylsulfonyl)difluoromethylation of arylboronic acids with $PhSO_2CF_2H$ has been developed that proceeds via the in situ generated $PhSO_2CF_2Cu$ species (Scheme 1, eq 2).[7]

As very important reactive intermediates, fluoroalkyl radicals have attracted much attention in recent years,[8] and many reagents, including the Langlois reagent,[9] the Togni reagent,[10] the Umemoto reagent,[11] the Ruppert–Prakash reagent,[12] and fluoroalkyl halides,[5c,13] have been used for the radical fluoroalkylation. However, to the best of our knowledge, there is no report on the direct radical fluoroalkylation with the readily available $PhSO_2CF_2H$ reagent.[5c] Considering that the generation of $PhSO_2CF_2$ radical by the homolytic cleavage of the F_2C-H bond of $PhSO_2CF_2H$ is a formidable challenge, we envisioned that the radical could be generated through the oxidation of $PhSO_2CF_2^-$ after the deprotonation of $PhSO_2CF_2H$ in one pot. We realized that the difficulty in this chemistry lies in how to find suitable oxidants and strong bases and how to make them well compatible in the same reaction system. Recently, $PhI(OAc)_2$-mediated radical fluoroalkylation of arenes,[12d] unactivated alkenes[12c,14] or isocyanides[12e] under silver-mediated, -catalyzed or -free conditions has been developed, which inspired us to develop an atom-economical method for radical (phenylsulfonyl)difluoromethylation with

Scheme 1. (Phenylsulfonyl)difluoromethylation of Organic Molecules with $PhSO_2CF_2H$



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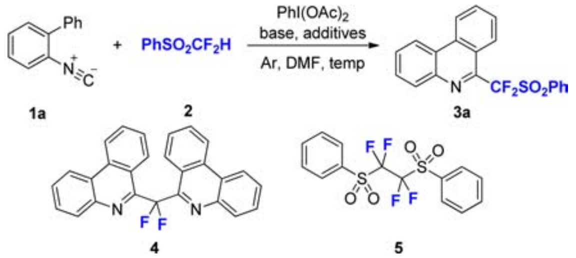
$PhSO_2CF_2H$ using $PhI(OAc)_2$ as a mild oxidant under transition-metal-free conditions (Scheme 1, eq 3).

At the onset of our investigation, isocyanide **1a** was used as a model substrate, LiHMDS/THF as a base, and $PhI(OAc)_2$ as an oxidant and DMF as solvent, respectively, for the radical (phenylsulfonyl)difluoromethylation with $PhSO_2CF_2H$ (Table 1, entry 1). We were pleased to find that the desired product **3a** was formed in 13% yield. Further optimization of the reaction conditions showed that *t*-BuONa/DMF solution (2.0 M) gave a higher yield than other bases (Table 1, entries 1–4). It was noteworthy that no desired product **3a** could be detected when mixing *t*-BuONa (solid) and $PhI(OAc)_2$ together before the addition of **2** (Table 1, entry 5), indicating that charging sequence is very important. The reaction was quite sensitive to temperature, and the yield was gradually increased as the temperature decreased; we found that −50 °C was the optimal temperature for the reaction (Table 1, entries 4 and 6–10). At the same time, we found that although the side product **4** can be diminished at low temperatures, another side product **5** (via homocoupling of the radical intermediate) was increasingly formed (for details, see the Supporting Information). The yield was further improved effectively by increasing the amount of $PhI(OAc)_2$ and *t*-BuONa/DMF to 6.0 equiv and adding some additives (Table 1, entries 11–20), which turned out to be useful to inhibit the generation of side product **5** to some extent (for details, see the SI). Furthermore, the addition of weak bases could increase the conversion of $PhSO_2CF_2H$ (Table 1, entries 12–15 and 18–20), and the reaction could be further promoted in the presence of I_2 (Table 1, entries 17, 18, and 20). Finally, the optimal yield of **3a** (78% yield) was obtained when employing Cs_2CO_3 (1.0 equiv) as a base and I_2 (0.2 equiv) as an additive (Table 1, entry 18).

With the optimized reaction conditions in hand, we further investigated the substrate scope of the current method and found that a variety of isocyanides **1** could be transformed into the corresponding products **3** in moderate to good yields (Scheme 2). Both electron-withdrawing groups (**3b–f**) and electron-donating groups (**3g,h**) on the *para*-position of the R^2-substituted phenyl ring were compatible under the reaction

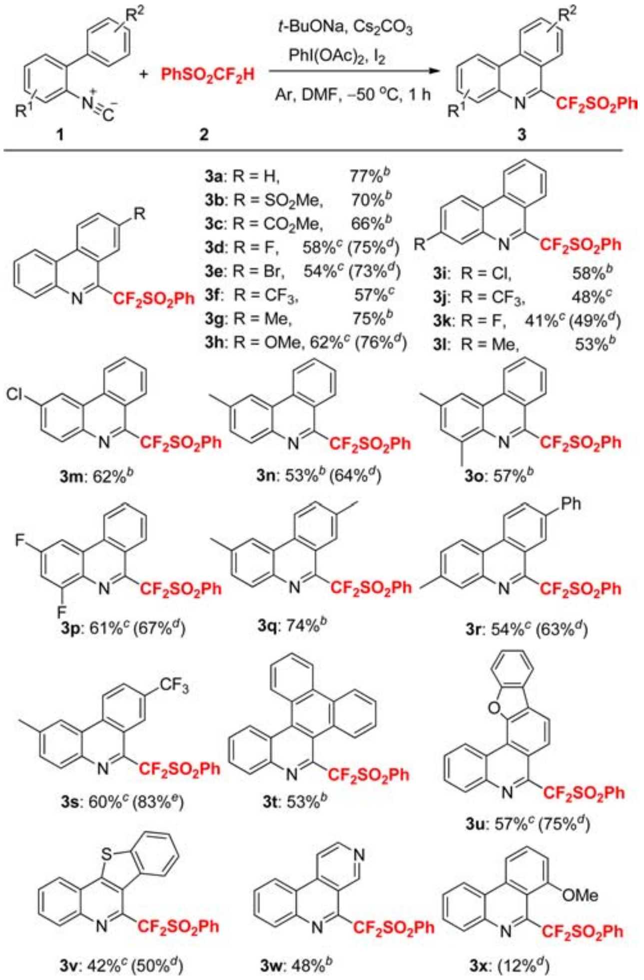
Table 1. Optimization of Reaction Conditions[a]



entry	base	additive (1.0 equiv)	temp (°C)	**3a**, yield[b] (%)
1	LiHMDS		−50	13
2	NaHMDS		−50	7
3	*t*-BuOK		−50	19
4	*t*-BuONa		−50	41
5[c]	*t*-BuONa		−50	0
6	*t*-BuONa		−60	39
7	*t*-BuONa		−40	39
8	*t*-BuONa		−30	34
9	*t*-BuONa		−10	21
10	*t*-BuONa		rt	5
11[d]	*t*-BuONa		−50	54
12[d]	*t*-BuONa	$NaHCO_3$	−50	58
13[d]	*t*-BuONa	Na_2CO_3	−50	61
14[d]	*t*-BuONa	Cs_2CO_3	−50	70
15[d]	*t*-BuONa	K_3PO_4	−50	62
16[d]	*t*-BuONa	BQ[e]	−50	58
17[d]	*t*-BuONa	I_2[e]	−50	67
18[d]	***t*-BuONa**	$\mathbf{Cs_2CO_3/I_2}$[e]	**−50**	**78**
19[d]	*t*-BuONa	K_3PO_4/BQ[e]	−50	66
20[d]	*t*-BuONa	Na_2CO_3/I_2[e]	−50	74

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2** (2.0 equiv), $PhI(OAc)_2$ (4.0 equiv), base (4.0 equiv), DMF (1.0 mL), Ar, 1 h. [b] Yields were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. [c] *t*-BuONa (solid) and $PhI(OAc)_2$ were mixed together before the addition of **2**. [d] $PhI(OAc)_2$ (6.0 equiv) and *t*-BuONa/DMF (2.0 mol/L, 6.0 equiv) were used. [e] 0.2 equiv of additive was added.

Scheme 2. Radical (Phenylsulfonyl)difluoromethylation of Isocyanides[a]

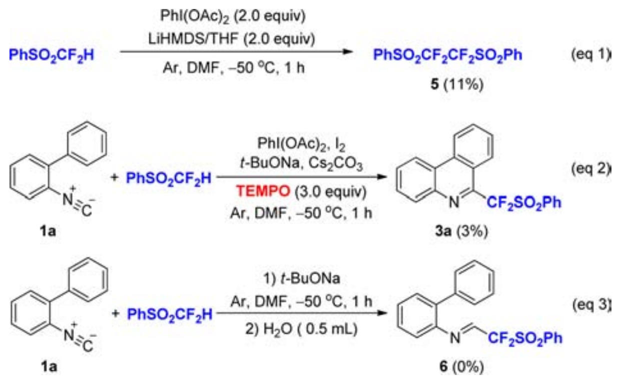


[a] General conditions: isocyanides 1 (0.2 mmol), $PhSO_2CF_2H$ (0.4 mmol), $PhI(OAc)_2$ (1.2 mmol), *t*-BuONa/DMF (2.0 M, 0.6 mL), Cs_2CO_3 (0.2 mmol) and I_2 (0.04 mmol) in 1.3 mL of DMF at −50 to −60 °C for 1 h. [b] Isolated yields were given by column chromatography on silica. [c] Isolated yields were given by recrystallization. [d] Yields were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. [e] Yields were determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

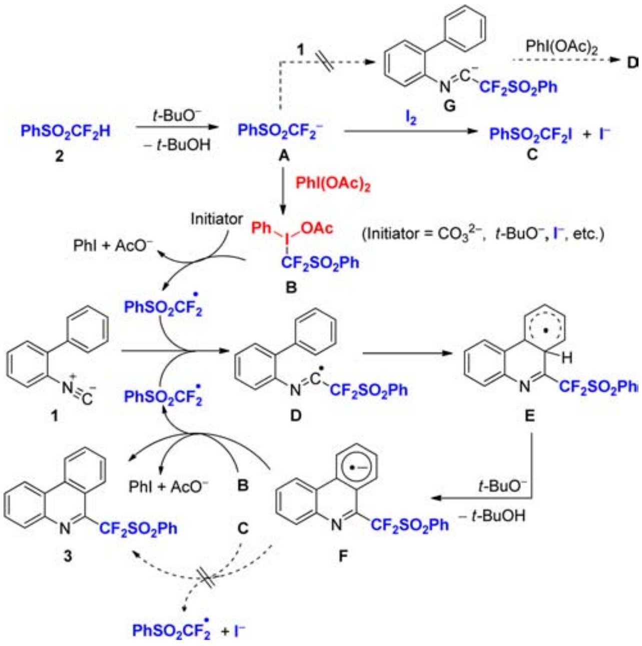
conditions, with no significant influence on the yields of products. In the case of R^1-substituted isocyanides, the desired products were obtained in slightly lower yields when the substituents were on the *meta*- or *para*-positions (**3i**−**n**). Those with two substituents in the same or different aromatic rings gave good yields of products (**3o**−**s**). In addition to biphenyl derivatives, those fused to other aryl (**3t**,**u**) and heteroaryl (**3v**,**w**) moieties also worked well in the reaction, albeit providing the products in moderate yields. Compared with **3h**, the 2-methyloxy-substituted isocyanide **1x** was transformed to product **3x** in poor yield (12%), which might be because only one reactive site was available on the aryl ring. It was noteworthy that under optimized conditions the reaction can be easily scaled up; for example, when 10 mmol of **1a** (1.79 g) was used, 54% of isolated yield of **3a** (1.99 g) could be obtained after repeated recrystallization.

To gain more insights into this transition-metal-free radical (phenylsufonyl)difluoromethylation reaction, we carried out some control experiments. First, in the absence of isocyanide **1a**, the homocoupling product $PhSO_2CF_2CF_2SO_2Ph$ (**5**) was formed in 11% yield, and a peak at −111.1 ppm was observed in a crude sample by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard (Scheme 3, eq 1). Second, the inhibition experiment of **1a** with TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, 3.0 equiv), which is known as an efficient radical scavenger, was conducted under the standard reaction conditions, and the reaction was almost shut down (Scheme 3, eq 2). Similarly, when 3.0 equiv of 1,3-dinitrobenzene, which easily undergoes one electron reduction,[15] was added into the standard reaction system, no desired product **3a** could be detected. Third, a large amount of PhI was obtained by column chromatography on silica gel when the desired products were isolated, indicating that $PhI(OAc)_2$ was reduced. Fourthly, the attempt to capture the protonated product (**6**) of the intermediate **G** failed (Scheme 3, eq 3, and Scheme 4), thus ruling out the path of the oxidation of **G**. These experiments support the involvement of a $PhSO_2CF_2$ radical species in the current fluoroalkylation reaction. Finally, we probed the role of the additive I_2 in this reaction. Because a trace amount of $PhSO_2CF_2I$ was detected after the completion of the reaction, we initially thought that $PhSO_2CF_2I$ could serve as a $PhSO_2CF_2$ radical source in this reaction and the formation of $PhSO_2CF_2I$ via iodination of $PhSO_2CF_2$ anion by I_2 could improve the generation of $PhSO_2CF_2$ radical. In fact, when I_2 was replaced by $PhSO_2CF_2I$ (0.2 equiv), the consumption of the latter resulted in a relatively low yield (53%), even lower than that in the absence of I_2, which suggested that $PhSO_2CF_2I$ might not participate in the reaction. Therefore, we propose that the iodide ion formed from the reaction between $PhSO_2CF_2$ anion and I_2 may serve as an additional initiator to promote the generation of $PhSO_2CF_2$ radical from the hypervalent iodine intermediate **B** (Scheme 4).

Scheme 3. Control Experiments



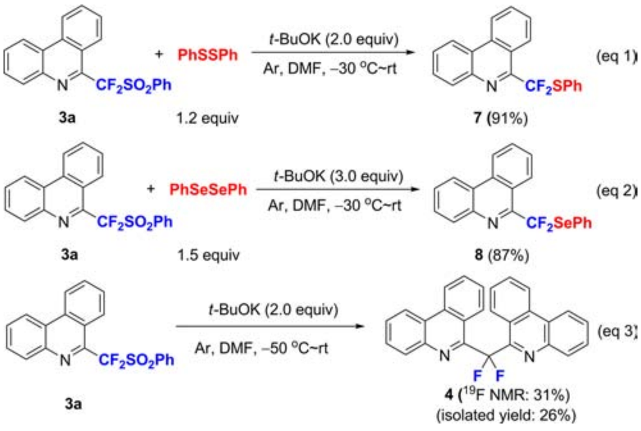
Scheme 4. Plausible Reaction Mechanism



Based on the aforementioned results, a plausible reaction mechanism is proposed in Scheme 4. After the deprotonation of $PhSO_2CF_2H$, the hypervalent iodine intermediate **B** is generated from $PhSO_2CF_2$ anion (**A**) and $PhI(OAc)_2$. Single-electron transfer (SET) from an initiator (such as the iodide ion in situ produced from **A** and I_2) to **B** gives $PhSO_2CF_2$ radical and thus initiates the reaction. Then the $PhSO_2CF_2$ radical adds to **1** to give the imidoyl radical **D**, which subsequently undergoes intramolecular radical cyclization to afford the radical intermediate **E**. Deprotonation of **E** by *t*-BuO$^-$ provides radical anion **F**,[10a,13b,16] which reacts with intermediate **B** through a SET process to generate product **3** and to regenerate $PhSO_2CF_2$ radical. A secondary path that involves the generation of $PhSO_2CF_2$ radical from $PhSO_2CF_2I$ is less likely due to the inhibition effect of $PhSO_2CF_2I$ on the reaction.

It was reported that the $PhSO_2$ group in some fluoroalkyl sulfones could be removed by the nucleophilic attack of alkoxide or hydroxide, and the generated fluoroalkyl anions were able to react with different electrophiles such as carbonyl compounds and disulfides.[6b,17] We assumed that a similar type of S−C bond cleavage could occur with our products **3**. As expected, the transformation of $PhSO_2$ group to PhS and PhSe group was accomplished successfully (Scheme 5, eqs 1 and 2). Furthermore, in the absence of other electrophiles, **3a** could react with another molecule of itself to give rise to a structurally symmetrical product **4** (Scheme 5, eq 3), which is the side product observed during our optimization of reaction conditions (see Table 1 and the SI). The formation of **4** from **3a**/*t*-BuOK/DMF is intriguing and needs further study to understand its reaction mechanism.

Scheme 5. Transformation of $PhSO_2$ Group to Other Functionalities



In summary, we have developed an atom-economical method for radical (phenylsulfonyl)difluoromethylation of isocyanides with $PhSO_2CF_2H$ reagent under transition-metal-free conditions. This new strategy shows an unusual role of $PhSO_2CF_2H$, from which a $PhSO_2CF_2$ radical is formed in the presence of $PhI(OAc)_2$. The reaction tolerates many functional groups, and the transformation of $PhSO_2$ group to other groups mediated by *t*-BuOK is accomplished. Further exploration of the synthetic applications of fluoroalkyl sulfones is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03013.

Experimental procedures and characterization data for products (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Phillips, S. D.; Castle, R. N. *J. Heterocycl. Chem.* **1981**, *18*, 223. (b) Ishikawa, T. *Med. Res. Rev.* **2001**, *21*, 61. (c) Abdel-Halim, O. B.; Morikawa, T.; Ando, S.; Matsuda, H.; Yoshikawa, M. *J. Nat. Prod.* **2004**, *67*, 1119. (d) Zhu, S.; Ruchelman, A. L.; Zhou, N.; Liu, A. A.; Liu, L. F.; LaVoie, E. J. *Bioorg. Med. Chem.* **2005**, *13*, 6782. (e) Sripada, L.; Teske, J. A.; Deiters, A. *Org. Biomol. Chem.* **2008**, *6*, 263. (f) Bernardo, P. H.; Wan, K.-F.; Sivaraman, T.; Xu, J.; Moore, F. K.; Hung, A. W.; Mok, H. Y. K.; Yu, V. C.; Chai, C. L. L. *J. Med. Chem.* **2008**, *51*, 6699. (g) Dubost, E.; Dumas, N.; Fossey, C.; Magnelli, R.; Butt-Gueulle, S.; Ballandonne, C.; Caignard, D. H.; Dulin, F.; Santos, J. S. d.-O.; Millet, P.; Charnay, Y.; Rault, S.; Cailly, T.; Fabis, F. *J. Med. Chem.* **2012**, *55*, 9693.

(2) (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (c) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (d) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308.

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

(4) (a) Prakash, G. K. S.; Hu, J.; Olah, G. A. *J. Org. Chem.* **2003**, *68*, 4457. (b) Prakash, G. K. S.; Hu, J.; Mathew, T.; Olah, G. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 5216. (c) Prakash, G. K. S.; Hu, J.; Wang, Y.; Olah, G. A. *Org. Lett.* **2004**, *6*, 4315. (d) Prakash, G. K. S.; Hu, J.; Wang, Y.; Olah, G. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5203. (e) Ni, C.; Hu, J. *Tetrahedron Lett.* **2005**, *46*, 8273. (f) Surya Prakash, G. K.; Hu, J.; Wang, Y.; Olah, G. A. *Eur. J. Org. Chem.* **2005**, *2005*, 2218. (g) Zhu, J.; Wang, F.; Huang, W.; Zhao, Y.; Ye, W.; Hu, J. *Synlett* **2011**, *2011*, 899. (h) Li, X.; Zhao, J.; Hu, M.; Chen, D.; Ni, C.; Wang, L.; Hu, J. *Chem. Commun.* **2016**, *52*, 3657.

(5) (a) Prakash, G. K. S.; Hu, J. *Acc. Chem. Res.* **2007**, *40*, 921. (b) Hu, J.; Zhang, W.; Wang, F. *Chem. Commun.* **2009**, 7465. (c) Hu, J. *J. Fluorine Chem.* **2009**, *130*, 1130. (d) Ni, C.; Hu, J. *Synlett* **2011**, *2011*, 770.

(6) (a) Stahly, G. P. *J. Fluorine Chem.* **1989**, *43*, 53. (b) Prakash, G. K. S.; Hu, J.; Mathew, T.; Olah, G. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 5216. (c) Liu, J.; Ni, C.; Li, Y.; Zhang, L.; Wang, J.; Hu, J. *Tetrahedron Lett.* **2006**, *47*, 6753.

(7) Li, X.; Zhao, J.; Hu, M.; Chen, D.; Ni, C.; Wang, L.; Hu, J. *Chem. Commun.* **2016**, *52*, 3657.

(8) (a) Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8950. (b) Koike, T.; Akita, M. *Top. Catal.* **2014**, *57*, 967. (c) Alonso, C.; Martinez de Marigorta, E.; Rubiales, G.; Palacios, F. *Chem. Rev.* **2015**, *115*, 1847. (d) Belhomme, M. C.; Besset, T.; Poisson, T.; Pannecoucke, X. *Chem. - Eur. J.* **2015**, *21*, 12836. (e) Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2015**, *115*, 683. (f) Ni, C.; Hu, M.; Hu, J. *Chem. Rev.* **2015**, *115*, 765. (g) Ni, C.; Zhu, L.; Hu, J. *Huaxue Xuebao* **2015**, *73*, 90. (h) Zhang, B.; Studer, A. *Chem. Soc. Rev.* **2015**, *44*, 3505.

(9) (a) Wilger, D. J.; Gesmundo, N. J.; Nicewicz, D. A. *Chem. Sci.* **2013**, *4*, 3160. (b) Cui, L.; Matusaki, Y.; Tada, N.; Miura, T.; Uno, B.; Itoh, A. *Adv. Synth. Catal.* **2013**, *355*, 2203.

(10) (a) Zhang, B.; Mück-Lichtenfeld, C.; Daniliuc, C. G.; Studer, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 10792. (b) Tomita, R.; Yasu, Y.; Koike, T.; Akita, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 7144.

(11) (a) Yasu, Y.; Koike, T.; Akita, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9567. (b) Tomita, R.; Koike, T.; Akita, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 12923.

(12) (a) Ye, Y.; Lee, S. H.; Sanford, M. S. *Org. Lett.* **2011**, *13*, 5464. (b) Hafner, A.; Bräse, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3713. (c) Wu, X.; Chu, L.; Qing, F.-L. *Angew. Chem., Int. Ed.* **2013**, *52*, 2198. (d) Seo, S.; Taylor, J. B.; Greaney, M. F. *Chem. Commun.* **2013**, *49*, 6385. (e) Wang, Q.; Dong, X.; Xiao, T.; Zhou, L. *Org. Lett.* **2013**, *15*, 4846.

(13) (a) Sun, X.; Yu, S. *Org. Lett.* **2014**, *16*, 2938. (b) Zhang, B.; Studer, A. *Org. Lett.* **2014**, *16*, 3990. (c) Gu, J. W.; Min, Q. Q.; Yu, L. C.; Zhang, X. *Angew. Chem., Int. Ed.* **2016**, *55*, 12270.

(14) Ma, G.; Wan, W.; Li, J.; Hu, Q.; Jiang, H.; Zhu, S.; Wang, J.; Hao, J. *Chem. Commun.* **2014**, *50*, 9749.

(15) Kornblum, N. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 734.

(16) Rong, J.; Deng, L.; Tan, P.; Ni, C.; Gu, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 2743.

(17) (a) Prakash, G. K. S.; Hu, J.; Olah, G. A. *Org. Lett.* **2003**, *5*, 3253. (b) Li, X.; Zhao, J.; Zhang, L.; Hu, M.; Wang, L.; Hu, J. *Org. Lett.* **2015**, *17*, 298.