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[[(Ethoxycarbonyl)difluoromethyl]thio]phthalimide: A Shelf-Stable, Electrophilic Reagent with a Convertible Group for the Synthesis of Diversified Fluoroalkylthiolated Compounds

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Supporting Information

ABSTRACT: A shelf-stable and easily convertible reagent for the preparation of diversified fluoroalkylthiolated compounds, [[(ethoxycarbonyl)difluoromethyl]thio]phthalimide, was developed. [[(Ethoxycarbonyl)difluoromethyl]thio]phthalimide is an efficient electrophilic fluoroallylthiolating reagent that reacted with electron-rich heteroarenes/arenes, β-ketoesters, oxindoles, benzofuranones, and thiols. More importantly, the ethoxycarbonyl group of the resulting fluoroalkylthiolated compounds could be easily converted into various other functional groups such as chloride, alkynyl, hydrocarbonyl, carbomoyl, hydromethyl, or heteroaryl groups.

Recently, there has been widespread and rapidly increasing interest in two fluoroalkyl groups, trifluoromethylthio ($-SCF_3$) and difluoromethylthio ($-SCF_2H$),[1] mainly owing to their unique properties including the high lipophilicity[2] and strong electron-withdrawing induction effect, as well as promising applications in the improvement of the pharmacokinetics of lead compounds for new drug discovery. As a result, in the past several years, a number of shelf-stable, highly reactive electrophilic trifluoromethylthiolating[3,4] or difluoromethylthiolating[5,6] reagents that allow the efficient incorporation of both groups under mild conditions have been successfully developed. From the viewpoint of medicinal chemists, these reagents offer powerful and operationally simple tools to facilitate the preparation of structural analogues of the target molecule for structure–activity relationship studies (SAR). However, the SAR studies could be more effective if compounds with other valuable fluoroalkylthiolated groups $-SCF_2FG$ (FG = functional group) could be conveniently available since subtle changes in the structure of the lead compound often allow for fine-tuning of the desired pharmacokinetic properties and thus considerably streamline the search for the drug molecule. In this respect, two electrophilic fluoroalkylthiolating reagents $PhNHSCF_2SO_2Ph$ (**1a**)[7] and $MesNHSCF_2PO(OEt)_2$ (Mes = mesityl) (**1b**)[8] have emerged very recently, which provided straightforward access to compounds with $-SCF_2SO_2Ph$ or $-SCF_2PO(OEt)_2$ moieties (Figure 1). However, while serving as a proof-of-concept, these reagents were inherently limited in a lack of diversity of the functional groups that could be installed because both the sulfonyl and phosphonate groups cannot be easily converted to other functional groups.

To avoid this limitation, we questioned that if an electrophilic fluoroalkylthiolating reagent with a readily convertible group can be invented and if such a group can be efficiently transformed into various other functional groups after the functionalized fluoroalkylthiolating moiety is delivered to the target molecule, a promising and practical strategy to access diversified fluoroalkylthiolated derivatives for SAR studies could be developed. Herein, we report the design and preparation of [[(ethoxycarbonyl)difluoromethyl]thio]-phthalimide (**1c**), which is an efficient electrophilic fluoroalkylthiolating reagent, as demonstrated by its reactions with electron-rich heteroarenes/arenes, β-ketoesters/oxindoles/benzofuranones, and thiols. More importantly, the ethoxycarbonyl group of the resulting fluoroalkylated compounds was successfully further converted into various other functional groups such as chloride, alkynyl, hydrocarbonyl, carbomoyl, hydromethyl, or heteroaryl.

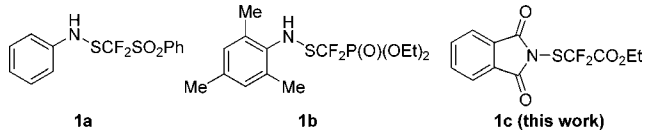

Figure 1. Electrophilic fluoroalkylthiolating reagents.

[[(Ethoxycarbonyl)difluoromethyl]thio]phthalimide (**1c**) can be readily synthesized by treatment of easily available *N*-(chlorosulfenyl) phthalimide[9] with in situ generated $AgCF_2CO_2Et$ at −40 °C for 2 h. The reaction can be easily scaled up to 30 mmol, and compound **1c** was obtained in 67% yield (Figure 2, route 1). Alternately, compound **1c** can be prepared in two steps starting from commercially available reagents benzenemethanethiol, ethyl bromodifluoroacetate, and potassium phthalimide. Following a literature reported procedure, ethyl 2-(benzylthio)-2,2-difluoroacetate was ob-

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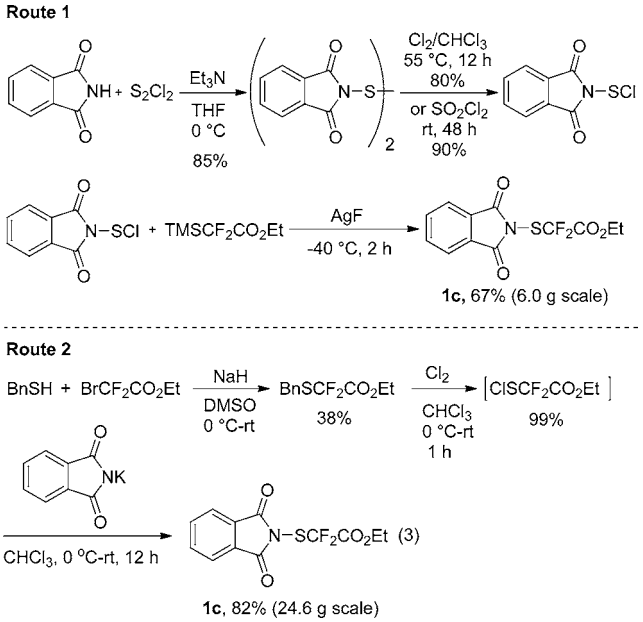


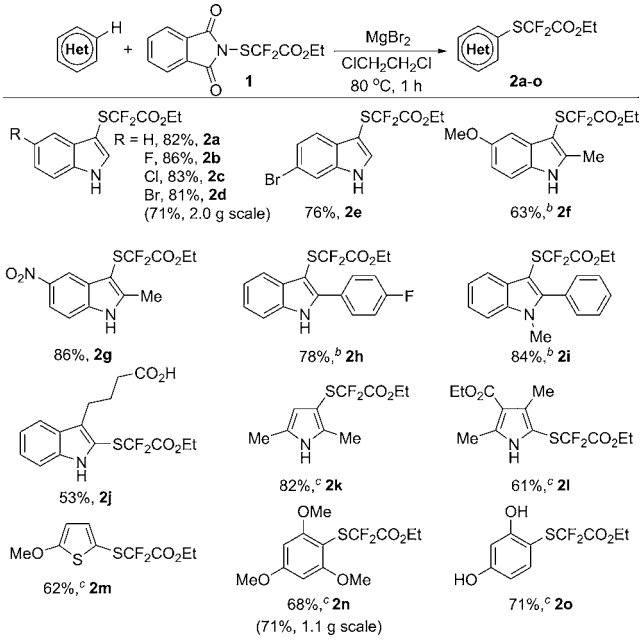
Figure 2. Methods for the preparation of [[(ethoxycarbonyl)-difluoromethyl]thio]phthalimide (**1c**).

tained in 38% yield by reaction of sodium benzenemethanethiolate with ethyl bromodifluoroacetate in DMSO.[10] Upon treatment with a saturated solution of chlorine in $CHCl_3$ at 0 °C for 1.0 h, ethyl 2-(benzylthio)-2,2-difluoroacetate was quantitatively converted into [(ethoxycarbonyl)difluoromethyl]sulfenyl chloride. Without isolation, the in situ formed [(ethoxycarbonyl)difluoromethyl]sulfenyl chloride was allowed to react with potassium phthalimide at room temperature for 12 h to generate the desired compound **1c** in 82% yield (Figure 2, route 2). Even though the yield of the first step of the preparation was slightly low, the chemicals involved in this synthetic route are cheap, thus allowing for scale up. As a matter of fact, 24.6 g of compound **1c** can be produced when the reaction was conducted on a 100 mmol scale. Compound **1c** was fully characterized by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopies, and the structure of compound **1c** was unambiguously confirmed by X-ray analysis of its single crystals (see the Supporting Information for details). Compound **1c**, a white solid with a melting point 88–89 °C, is not air, moisture, or light sensitive. No detectable decomposition was observed after more than one month of shelf storage at ambient temperature.

With this new reagent in hand, we first examined its electrophilicity by reactions of reagent **1c** with indole under the conditions for Friedel–Crafts-type trifluoromethylthiolation/difluoromethylthiolation of electron-rich arenes. It was found that reactions of indole with reagent **1c** in the presence of 1.5 equiv of Lewis acids[4g] such as Me_3SiCl or $BF_3{\cdot}Et_2O$ occurred in less than 11% yields after 8 h at 80 °C. Likewise, reactions in the presence of Brønsted acids[11] such as triflic acid, *p*-toluenesulfonic acid, or camphorsulfonic acid occurred in low yields as well. Interestingly, the reactions underwent effective Friedel–Crafts-type fluoroalkylthiolation when Lewis acids such as LiBr, nBu_4NBr, or $MgBr_2$ were used as activators.[12] Further optimization of the conditions showed that reaction in the presence of 1.5 equiv of $MgBr_2$ in 1,2-dichloroethane or THF occurred to full conversion after 1.0 h at 80 °C to give the desired 3-[[(ethoxycarbonyl)difluoromethyl]thio]indole in 84% and 83% yield, respectively (see Table S1 in the Supporting Information for details). Elongating the reaction time resulted in lower yields of the products due to slow decomposition of the products in the reaction mixture. Although details of the role of $MgBr_2$ are not yet clear, we postulate that $MgBr_2$ may activate as Lewis acid to interact with both carbonyl groups of the phthalimide moiety and the [(ethoxycarbonyl)difluoromethyl]thio moiety. The Lewis acid–Lewis base interaction may enhance the electrophilicity of the [(ethoxycarbonyl)difluoromethyl]thio moiety, thus promoting the Friedel–Crafts-type fluoroalkylthiolation.

In general, reactions of a variety of indoles with electron-donating or -withdrawing groups occurred in good to excellent yields under the optimized conditions (Scheme 1, **2a–f**).

Scheme 1. $MgBr_2$-Mediated Fluoroalkylthiolation of Heteroarenes or Arenes with Reagent 1c[a]



[a]Reaction conditions: arene (0.3 mmol), reagent **1c** (0.36 mmol), $MgBr_2$ (0.45 mmol) in 2.0 mL of 1,2-dichloroethane at 80 °C for 1 h; isolated yields. [b]THF was used as the solvent. [c]Reaction conducted with arene (0.5 mmol), reagent **1c** (0.6 mmol), and $MgBr_2$ (0.75 mmol) in 3.0 mL of 1,2-dichloroethane at 80 °C for 1 h; isolated yields. THF = tetrahydrofuran.

Reactions of 2-substituted indoles also underwent efficient [(ethoxycarbonyl)difluoromethyl]thiolation (Scheme 1, **2g–i**). Likewise, indole with a substituent at 3-position also reacted to give the corresponding products in high yield (Scheme 1, **2j**). Not only indoles but also other electron-rich heteroarenes such as pyrroles or thiophenes underwent efficient [(ethoxycarbonyl)difluoromethyl]thiolation in high yields under mild conditions (Scheme 1, **2k–m**). Furthermore, electron-rich arenes such as 1,3,5-trimethoxybenzene or resorcinol reacted with reagent **1c** under slightly modified conditions to give the corresponding [(ethoxycarbonyl)difluoromethyl]thiolated arenes in high yields (Scheme 1, **2n,o**). Importantly, functional groups such as fluoride, chloride, bromide, ester, carboxylic acid, or nitro were compatible with the reaction conditions (Scheme 1, **2b–e,g–h,j,l**). Moreover, the gram-scale reactions were also effective (Scheme 1, **2d,n**).

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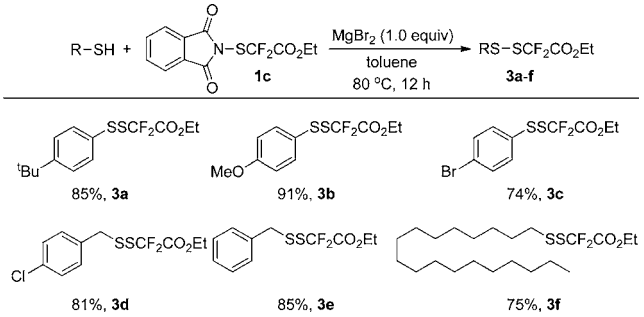
To expand the scope of the reactions of the electrophilic reagent **1c**, we studied its reaction with thiols. It was discovered that reactions of thiols with reagent **1c** in toluene occurred smoothly after 12 h at 80 °C to give the unsymmetric fluoroalkylated disulfides in high yields when $MgBr_2$ was used as activator. Not only aryl thiols but also alkyl thiols reacted effectively to provide the corresponding fluoroalylated disulfides in good to excellent yields (Scheme 2, **3a–f**).

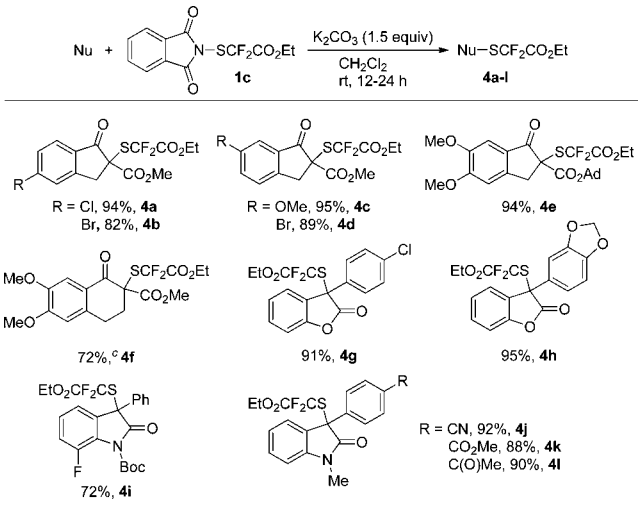
Scheme 2. $MgBr_2$-Mediated Fluoroalkylthiolation of Thiols with Reagent 1c[a,b]



[a]Reaction conditions: thiol or thiophenol (0.5 mmol), reagent **1c** (0.6 mmol), $MgBr_2$ (0.5 mmol) in 3.0 mL of toluene at 80 °C for 12 h. [b]Isolated yields.

To further extend the synthetic utility of reagent **1c**, we studied its reaction with other nucleophiles such as β-ketoesters, oxindoles, and benzofuranones. A brief screening of the bases and solvents revealed that the use of a combination of K_2CO_3 as the base and CH_2Cl_2 as the solvent was suitable for this system. The method was successfully applied to the [(ethoxycarbonyl)difluoromethyl]thiolation of β-ketoesters, oxindoles, and benzofuranones to furnish the corresponding [(ethoxycarbonyl)difluoromethyl]thiolated compounds in good yields (**4a–l**), as summarized in Scheme 3. For example, reactions of β-ketoesters derived from 5-chloro or 5-bromoindanones with [ethoxycarbonyl(difluoromethyl)]-thiolated products in 94% and 82% yield, respectively (Scheme 3, **4a**,**b**). Likewise, reaction of 3-(4-cyanophenyl)-2-benzofuranone with reagent **1c** occurred smoothly to give the desired product in 91% yield (Scheme 3, **4j**). Notably, the resulting products from these reactions bear a quaternary carbon center, which would be otherwise difficult to access.

Scheme 3. Scope for the Reaction of β-Ketoesters, Oxindoles, and Benzofuranones with Reagent 1c[a,b]



[a]Reaction conditions: nucleophile (0.5 mmol), reagent **1c** (0.6 mmol), K_2CO_3 (0.75 mmol) in 3.0 mL of dichloromethane at room temperature for 12 h; [b]Isolated yields [c]Twenty-four h.

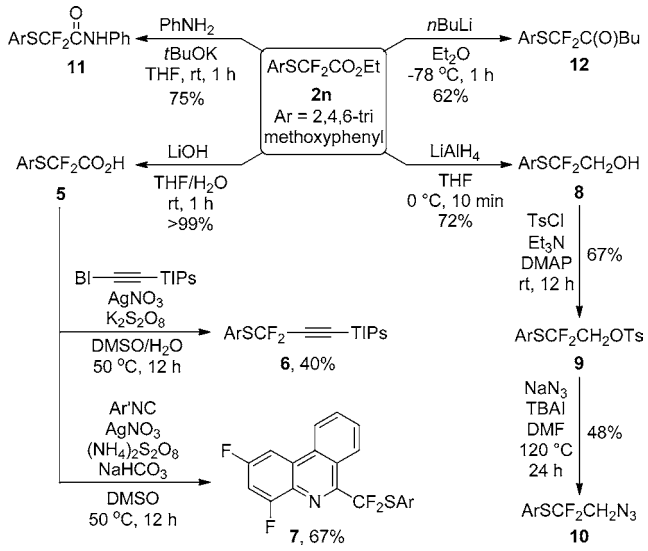
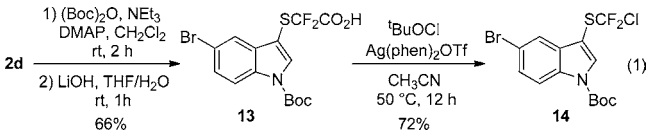


Figure 3. Functional group transformation of the [(ethoxycarbonyl)-difluoromethyl]thio group in compound **2n**.

of compound **2n** under alkaline conditions generated compound **5**, which can be easily converted into compound **6** and **7** via silver-catalyzed Hunsdiecker type-decarboxylative coupling with 1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one[13] or 3,5-difluoro-2-isocyano-1,1′-biphenyl.[14] Likewise, a Boc-protected derivative of compound **2d** underwent decarboxylative chlorination in the presence of 5.0 mol % of $Ag(Phen)_2OTf$ and 2.0 equiv of ^{t}BuOCl to give chlorodifluoromethylthiolated indole **14** in good yield (eq 1).[15]



Furthermore, compound **2n** can be easily converted into amide **11** and ketone **12** in good yields (Figure 3). Alternatively, the ester group of compound **5** can be readily reduced into alcohol **8**. Compound **8** could be further converted into alkyl azide **10**, which is an important intermediate that allows for further transformation including the Click reaction.[16] Thus, the current method provides a general approach for the preparation of fluoroalkylthiolated alkylazide, which may have potential applications in the field of chemical biology.

In summary, a new, easily scalable, shelf-stable reagent [[(ethoxycarbonyl)difluoromethyl]thio]phthalimide (**1c**) was successfully developed. Reagent **1c** is an efficient electrophilic fluoroalkylthiolating reagent, as demonstrated by its reactions

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with electron-rich heteroarenes/arenes, β-ketoesters/oxindoles/benzofuranones, and thiols. More importantly, the ethoxycarbonyl group of resulting fluoroalkylated compounds was successfully further converted into various other functional groups such as chloride, alkynyl, hydrocarbonyl, carbomoyl, hydromethyl, or heteroaryl. The versatility of functional transformations from the ethoxycarbonyl group of the resulting fluoroalkylated compounds clearly highlights the unique capabilities of reagent **1c** in enabling a broad range of functional groups availability for SAR studies. The studies for further applications of reagent **1c** are undergoing currently 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.7b00010.

Synthesis, analytical data, computational details, NMR data of compounds **1c**, **2a−o**, **3a−f**, **4a−l**, and **5−14**, X-ray crystallographic data of **1c** (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (b) Landelle, G.; Panossian, A.; Leroux, F. R. *Curr. Top. Med. Chem.* **2014**, *14*, 941. (c) Manteau, B.; Pazenok, S.; Vors, J.-P.; Leroux, F. R. *J. Fluorine Chem.* **2010**, *131*, 140. (d) Xu, X.-H.; Matsuzaki, K.; Shibata, N. *Chem. Rev.* **2015**, *115*, 731. (e) Ni, C.-F.; Hu, M.-Y.; Hu, J.-B. *Chem. Rev.* **2015**, *115*, 765.

(2) (a) Rico, I.; Wakselhan, C. *Tetrahedron Lett.* **1981**, *22*, 323. (b) Fujita, T.; Iwasa, J.; Hansch, C. *J. Am. Chem. Soc.* **1964**, *86*, 5175. (c) Landelle, G.; Panossian, A.; Leroux, F. R. *Curr. Top. Med. Chem.* **2014**, *14*, 941.

(3) Reviews for electrophilic trifluoromethylating reagents: (a) Boiko, V. N. *Beilstein J. Org. Chem.* **2010**, *6*, 880. (b) He, W.-M.; Weng, Z.-Q. *Prog. Chem.* **2013**, *25*, 1071. (c) Tlili, A.; Billard, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 6818. (d) Toulgoat, T.; Alazet, S.; Billard, T. *Eur. J. Org. Chem.* **2014**, *2014*, 2415. (e) Shao, X.-X.; Xu, C.-F.; Lu, L.; Shen, Q. *Acc. Chem. Res.* **2015**, *48*, 1227. (f) Chachignon, H.; Cahard, D. *Chin. J. Chem.* **2016**, *34*, 445. (g) Barata-Vallejo, S.; Bonesi, S.; Postigo, A. *Org. Biomol. Chem.* **2016**, *14*, 7150.

(4) Selected examples for the development of electrophilic trifluoromethylthiolating reagents: (a) Munavalli, S.; Rohrbaugh, D. K.; Rossman, D. I.; Berg, F. J.; Wagner, G. W.; Durst, H. D. *Synth. Commun.* **2000**, *30*, 2847. (b) Ferry, A.; Billard, T.; Langlois, B. R.; Bacqué, E. *J. Org. Chem.* **2008**, *73*, 9362. (c) Alazet, S.; Zimmer, L.; Billard, T. *Chem. - Eur. J.* **2014**, *20*, 8589. (d) Yang, Y.-D.; Azuma, A.; Tokunaga, E.; Yamasaki, M.; Shiro, M.; Shibata, N. *J. Am. Chem. Soc.* **2013**, *135*, 8782. (e) Shao, X.-X.; Wang, X.-Q.; Yang, T.; Lu, L.; Shen, Q. *Angew. Chem., Int. Ed.* **2013**, *52*, 3457. (f) Vinogradova, E. V.; Müller, P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2014**, *53*, 3125. (g) Xu, C.; Ma, B.; Shen, Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 9316. (h) Zhang, P.-P.; Li, M.; Xue, X.-S.; Xu, C.-F.; Zhao, Q.-C.; Liu, Y.-F.; Wang, H.-Y.; Guo, Y.-L.; Lu, L.; Shen, Q. *J. Org. Chem.* **2016**, *81*, 7486. Bu, M.-J.; Lu, G.-P.; Cai, C. *Org. Chem. Front.* **2016**, *3*, 630.

(5) Reviews for the preparation of difluoromethylthiolated compounds: Brahms, D. L. S.; Dailey, W. P. *Chem. Rev.* **1996**, *96*, 1585. (b) Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996**, *52*, 8619. (c) Hu, J.-B.; Zhang, W.; Wang, F. *Chem. Commun.* **2009**, 7465. (d) Xiong, H.-Y.; Pannecoucke, X.; Besset, T. *Chem. - Eur. J.* **2016**, *22*, 16734.

(6) Selected examples for difluoromethylthiolation: (a) Zhang, W.; Zhu, J.-M.; Hu, J.-B. *Tetrahedron Lett.* **2008**, *49*, 5006. (b) Wu, J.; Gu, Y.; Leng, X.-B.; Shen, Q. *Angew. Chem., Int. Ed.* **2015**, *54*, 7648. (g) Wu, J.; Liu, Y.-F.; Lu, C.-H.; Shen, Q. *Chem. Sci.* **2016**, *7*, 3757. (h) Arimori, S.; Matsubara, O.; Takada, M.; Shiro, M.; Shibata, N. *R. Soc. Open Sci.* **2016**, *3*, 160102. (j) Han, J.-B.; Qin, H.-L.; Ye, S.-H.; Zhu, L.; Zhang, C.-P. *J. Org. Chem.* **2016**, *81*, 2506. (k) Lin, Y.-M.; Yi, W.-B.; Shen, W.-Z.; Lu, G.-P. *Org. Lett.* **2016**, *18*, 592. (l) Howard, J. L.; Schotten, C.; Alston, S. T.; Browne, D. L. *Chem. Commun.* **2016**, *52*, 8448. (k) Zhu, D.-H.; Shao, X.-X.; Hong, X.; Lu, L.; Shen, Q. *Angew. Chem., Int. Ed.* **2016**, *55*, 15807.

(7) Ismalaj, E.; Le Bars, D.; Billard, T. *Angew. Chem., Int. Ed.* **2016**, *55*, 4790.

(8) Xiong, H.-Y.; Bayle, A.; Pannecoucke, X.; Besset, T. *Angew. Chem., Int. Ed.* **2016**, *55*, 13490.

(9) (a) Zibarev, A. V.; Miller, A. O.; Gatilov, Y. V.; Furin, G. G. *Heteroat. Chem.* **1990**, *1*, 443. (b) Hutchinson, S. A.; Baker, S. P.; Linden, J.; Scammells, P. J. *Bioorg. Med. Chem.* **2004**, *12*, 4877.

(10) Eto, H.; Kaneko, Y.; Takeda, S.; Tokizawa, M.; Sato, S.; Yoshida, K.; Namiki, S.; Ogawa, M.; Maebshi, K.; Ishida, K.; Matsumoto, M.; Asaoka, T. *Chem. Pharm. Bull.* **2001**, *49*, 173.

(11) Ma, B.-Q.; Shao, X.-X.; Shen, Q. *J. Fluorine Chem.* **2015**, *171*, 73.

(12) Honeker, R.; Ernst, J. B.; Glorius, F. *Chem. - Eur. J.* **2015**, *21*, 8047.

(13) Chen, F.; Hashmi, A. S. K. *Org. Lett.* **2016**, *18*, 2880.

(14) Wan, W.; Ma, G.-B.; Li, J.-L.; Chen, Y.-R.; Hu, Q.-Y.; Li, M.-J.; Jiang, H.-Z.; Deng, H.-M.; Hao, J. *Chem. Commun.* **2016**, *52*, 1598.

(15) Wang, Z.-T.; Zhu, L.; Yin, F.; Su, Z.-Q.; Li, Z.-D.; Li, C.-Z. *J. Am. Chem. Soc.* **2012**, *134*, 4258.

(16) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.

■ NOTE ADDED AFTER ASAP PUBLICATION

Scheme 1 was corrected on February 20, 2017.

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