Organic Letters
Letter
pubs.acs.org/OrgLett

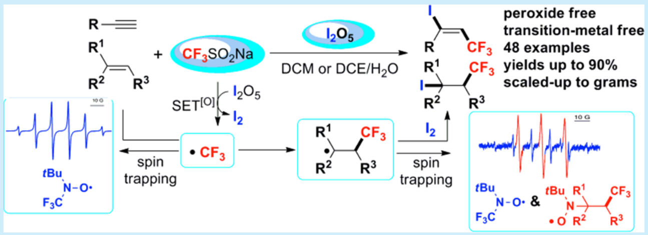
Iodotrifluoromethylation of Alkenes and Alkynes with Sodium Trifluoromethanesulfinate and Iodine Pentoxide

Zhaojia Hang, Zejiang Li, and Zhong-Quan Liu*

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, Gansu 730000, China

Ⓢ *Supporting Information*

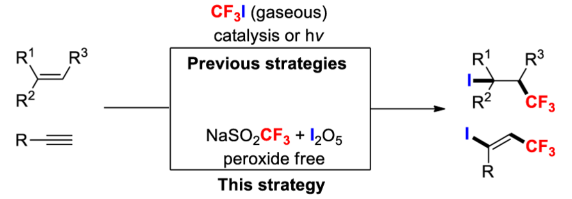
ABSTRACT: A scalable, selective, and operationally easy iodotrifluoromethylation of a wide range of alkenes and alkynes by using two simple and safe solids, sodium trifluoromethanesulfinate and iodine pentoxide, in aqueous medium has been developed. Mechanistic studies confirm that free-radical processes are involved in this system since the key radical intermediates such as CF_3 and β-CF_3 alkyl radicals have been clearly detected by spin trapping and electron spin resonance.



A variety of billion dollar pharmaceuticals, agrochemicals, and materials contain a trifluoromethyl (CF_3) group mainly because the electron-withdrawing nature, unique lipophilicity, and metabolic stability of this special substituent can dramatically modify their properties.[1] Hence, much effort has been made to explore new efficient strategies for introduction of the CF_3 group into organic molecules in the past decades.[2−4] Recently, strategies for difunctionalization-type trifluoromethylation of alkenes and alkynes have drawn considerable attention due to the convenient and versatile further functional group transformations of the products. For example, a wide range of CF_3-bearing building blocks such as carbocycles, aziridines, epoxides, and lactones can be easily prepared via the carbotrifluoromethylation,[5] aminotrifluoromethylation,[6] and oxytrifluoromethylation[7] of alkenes. Among these trifluoromethylation-involved difunctionalization of unsaturated bonds, halotrifluoromethylation, especially the iodotrifluoromethylation of olefins and alkynes, has attracted much attention in the past years.[8] Given the well-known nucleophilic substitution and cross-coupling importance and utility of iodides, it is not surprising that chemists have made great efforts to develop more efficient methods for incorporation of iodine and the CF_3 group into organic compounds in one step. However, almost all of these strategies for direct iodotrifluoromethylation of alkenes and alkynes are achieved by using CF_3I, which is a gas and makes the operation hard to handle (Scheme 1). Therefore, more safe and operationally easy iodotrifluoromethylation of alkenes and alkynes is highly desirable.

To solve the problems, we began to hypothesize that single-electron oxidation of a safe CF_3-derivatived anion (e.g., $CF_3SO_2^-$) by an inorganic hypervalent iodine oxidant would generate the CF_3 radical, which adds to the unsaturated bonds, followed by capture of the reducing substance iodine to form β-CF_3 iodides. It is known that the Langlois reagent, sodium trifluoromethanesulfinate ($NaSO_2CF_3$), can be used as an inexpensive and stable trifluoromethyl anion (CF_3^-) source,[9] which has been applied in oxidative free-radical trifluoromethylation of arenes,[9a] heterocycles,[9b,c] aryl boronic acids,[9d,e] and α,β-unsaturated acids.[9g] As our continuous studies on single-electron-transfer reactions, we find that several inorganic iodines such as iodic acid (HIO_3, IA) and iodine pentoxide (I_2O_5, IP) can act as safe and reliable single-electron oxidative surrogates for organic hypervalent iodines in some cases.[10] Although they are rarely used in organic synthesis,[11] IA and IP are extensively applied in industry due to their particular stability and low-cost.[12] Inspired by our previous work, we envisioned whether IA/IP could promote a free-radical iodotrifluoromethylation of alkenes and alkynes through oxidation of CF_3SO_2Na. If it did work, it would provide a novel and safe strategy for iodotrifluoromethylation of olefins and alkynes without using gaseous CF_3I. Fortunately, we successfully accomplished a safe, green, and scalable methodology for iodotrifluoromethylation of a wide range of alkenes and alkynes by using two simple, stable, and inexpensive solids CF_3SO_2Na and I_2O_5 in aqueous medium (Scheme 1).

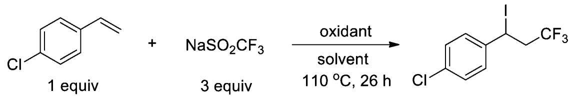
Scheme 1. Strategies for Iodotrifluoromethylation of Alkenes and Alkynes



Initially, various inorganic iodines as the potential single-electron oxidants to trigger the reaction of alkenes with CF_3SO_2Na have been screened (Table 1; see also the Supporting Information). We found that the oxidants and solvent critically affect the efficiency of the reaction. I_2O_5 was

Received: May 15, 2014

Table 1. Modification of the Typical Reaction Conditions[a]



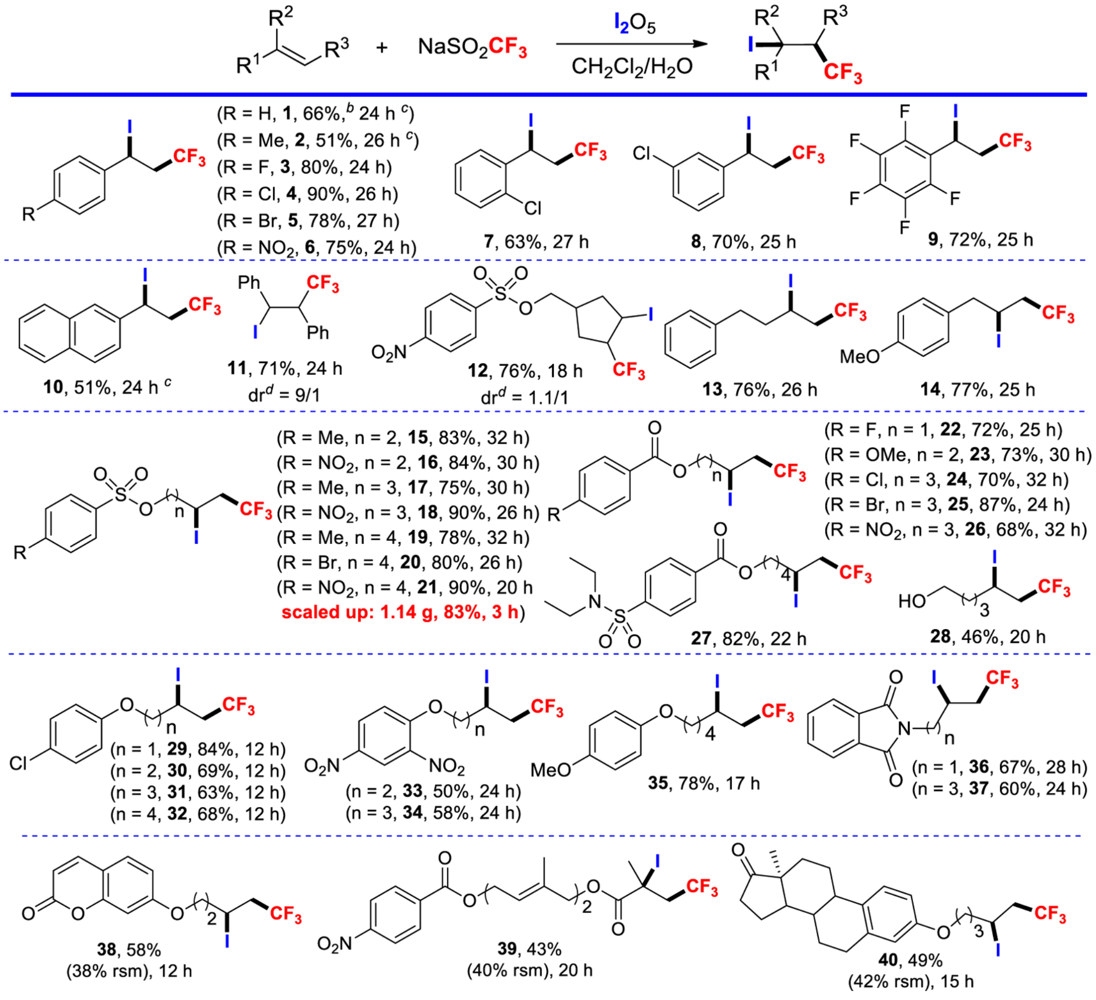
entry	oxidant (equiv)	solvent	yield (%)[b]
1	PhI(OAc)$_2$ (2)	CH_2Cl_2/H_2O (4/1, 4.5 mL)	
2	PhI(OCOCF$_3$)$_2$ (2)	CH_2Cl_2/H_2O (4/1, 4.5 mL)	5
3	IBX (2)	CH_2Cl_2/H_2O (4/1, 4.5 mL)	
4	DMP (2)	CH_2Cl_2/H_2O (4/1, 4.5 mL)	
5	HIO_3 (4)	CH_2Cl_2/H_2O (4/1, 4.5 mL)	53
6	**I_2O_5 (2)**	**CH_2Cl_2/H_2O (4/1, 4.5 mL)**	**90**
7	I_2O_5 (2)	CH_3CN/H_2O (4/1, 4.5 mL)	10
8	I_2O_5 (2)	t-BuOH/H_2O (4/1, 4.5 mL)	5
9	I_2O_5 (2)	CH_3COCH_3/H_2O (4/1, 4.5 mL)	
10	I_2O_5 (2)	$AcOH/H_2O$ (4/1,4.5 mL)	

[a] Reaction conditions: alkene (1 equiv, 0.2 mmol), $NaSO_2CF_3$ (3 equiv, 0.6 mmol), 110 °C, 26 h, sealed tube. [b] Isolated yields.

more efficient than organic hypervalent iodine compounds such as PhI(OAc)$_2$, PhI(OCOCF$_3$)$_2$, 2-iodoxybenzoic acid (IBX), Dess-Martin periodinane (DMP), and HIO_3 (Table 1, entries 1−6). A mixed solvent of CH_2Cl_2/H_2O was shown to be more effective than others such as CH_3CN/H_2O, *t*BuOH/H_2O, acetone/H_2O, and AcOH/H_2O (Table 1, entries 7−10).

With the optimized reaction conditions in hand, iodotrifluoromethylation of a broad range of olefins with CF_3SO_2Na and I_2O_5 was studied (Scheme 2). As depicted in Scheme 2, various aryl- and alkyl-substituted alkenes give *β*-CF_3 alkyl iodide as the major product in moderate to high yields under the typical reaction conditions. Diverse functional groups such as halogens (F, Cl, Br), NO_2, sulfonate, sulfamide, carboxylate, amide, ether, carbonyl, and hydroxyl can be well-tolerated in this system (**1**−**40**). Terminal and nonterminal alkenes are all compatible with this novel approach, but when both of the double bonds are in one substrate, the iodotrifluoromethylation selectively occurs at the terminal position (**38** and **39**). In addition, this reaction can be easily scaled up to gram level (**21**). Interestingly, the efficiency of the scaled-up reaction substantially increases (**21**, 0.2 mmol of alkene, 20 h, 90% yield; 4.0 mmol of alkene, 3 h, 83% yield), which suggests that this method could be potentially applied in the chemical industry. Furthermore, products *β*-CF_3 alkyl iodides are very useful synthons, which can be easily converted into various classes of compounds such as amine, alcohol, azide, ether, ester, cyanide,

Scheme 2. I_2O_5-Mediated Iodotrifluoromethylation of Alkenes[a]

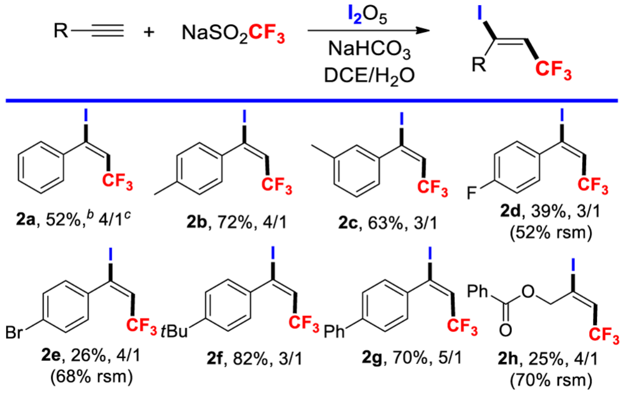


[a] Reaction conditions: alkene (1 equiv, 0.2 mmol), $NaSO_2CF_3$ (3 equiv, 0.6 mmol), I_2O_5 (2 equiv, 0.4 mmol), CH_2Cl_2/H_2O (4/1, 4.5 mL), 110 °C, sealed tube. [b] Isolated yields. [c] 90 °C. [d] Obtained as a mixture of diastereoisomers. The diastereomeric ratio determined by ^{19}F NMR spectroscopy.

and so on via the well-known nucleophilic substitution. In contrast to the previously reported strategies for alkene iodotrifluoromethylation that require gaseous CF_3I,[8] our strategy holds the advantages of easy operation and using safer and more easily handled CF_3 source ($NaSO_2CF_3$).

We next turned our attention to the iodotrifluoromethylation of alkynes by using this method. As illustrated in Scheme 3, various aryl- and alkyl-substituted alkynes are amenable to this novel protocol. A series of (*E*)-*β*-CF_3 alkenyl iodides were obtained by reaction of alkynes with CF_3SO_2Na/I_2O_5 with the assistance of $NaHCO_3$ (**2a**–**2h**). It is noteworthy that the CF_3-substituted vinyl iodides can serve as valuable synthetic building blocks in versatile coupling reactions. Notably, stereospecific reduction of the (*E*)-*β*-CF_3 alkenyl iodides allows CF_3-containing (*Z*)-olefins to be prepared (see Supporting Information). On the other hand, elimination reaction of *β*-CF_3 alkyl iodides with a base would selectively give the CF_3-substituted (*E*)-alkenes. The selective preparation of both *cis*- and *trans*-isomers of CF_3-bearing alkenes makes this system very attractive.

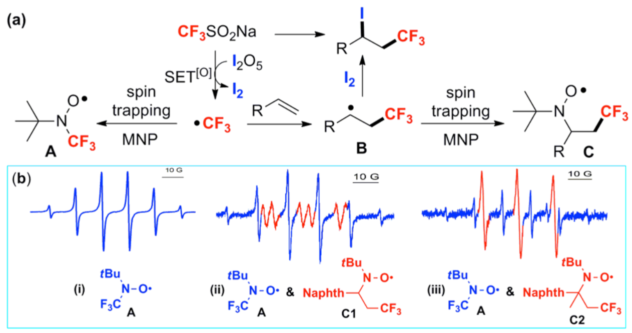
Scheme 3. I_2O_5-Mediated Iodotrifluoromethylation of Alkynes[a]



[a]Reaction conditions: alkyne (1 equiv, 0.2 mmol), $NaSO_2CF_3$ (3 equiv, 0.6 mmol), I_2O_5 (3 equiv, 0.6 mmol), $NaHCO_3$ (5 equiv, 1.0 mmol), and $ClCH_2CH_2Cl$ (DCE)/H_2O (4/1, 3.5 mL), 110 °C, 22 h, sealed tube. [b]Isolated yields. [c]Ratio of the *E*/*Z* isomers determined by ^{19}F NMR spectroscopy.

In order to confirm our hypothesis for this single-electron oxidative free-radical process, a series of mechanistic studies by electron spin resonance (ESR) have been carried out (Scheme 4). The ESR signals of CF_3 radical as well as *β*-CF_3 alkyl radicals were clearly observed by using 2-methyl-2-nitrosopropane (MNP) as a radical spin trap. As depicted in Scheme 4a, single-electron oxidation of $NaSO_2CF_3$ by I_2O_5 would generate CF_3 radical, which is quickly trapped by MNP to form the relatively stable trifluoromethyl *t*-butyl nitroxide radical **A** (Scheme 4b, (i), $g = 2.0061$, $a_N = a_F = 12.25$ G).[13] Subsequently, addition of the CF_3 radical to alkene would lead to *β*-CF_3 alkyl radical **B**, which adds to MNP forming radical **C**. It can be seen from Scheme 4b that the information on the key radical intermediates **A** and **C1** ($g = 2.0057$, $a_N = 14.75$ G, $a_H = 3.58$ G) in the iodotrifluoromethylation of 2-vinylnaphthalene has been recorded by ESR studies. To further confirm the generation of radicals **B** and **C**, iodotrifluoromethylation of 2-(prop-1-en-2-yl)naphthalene in the presence of MNP has been carried out. As shown in Scheme 4b (iii), radicals **A** and **C2** ($g = 2.0055$, $a_N = 15.46$ G) have also been detected by ESR through spin trapping technology. As expected, the signal of the *β*-CF_3 alkyl nitroxide radical changed from sextet to triplet without the *β*-hydrogen (**C1** vs **C2**). For the formation of the CF_3-substituted iodide product, the final step might involve the capture of radical **B** by I_2, which is formed from I_2O_5 via a multistep redox process. Although the mechanistic details of this process are not very clear now, the formation of I_2 has been confirmed by observation of a color change from red to deep blue when starch was added into the solution. Overall, this iodotrifluoromethylation of alkenes does involve an atom transfer process, which is supported by the ESR studies.

Scheme 4. (a) Proposed Mechanism and Spin Trapping of the Radical Intermediates and (b) ESR Spectra of Radicals



In summary, we have developed a safe, scalable, and operationally easy iodotrifluoromethylation of alkenes and alkynes by using two simple solids, $NaSO_2CF_3/I_2O_5$, in aqueous medium. This strategy allows convenient access to a series of useful CF_3-containing building blocks such as *β*-CF_3 alkyl iodides and *β*-CF_3 alkenyl iodides. Additionally, the key intermediates such as CF_3 and *β*-CF_3 alkyl radicals are clearly observed by spin trapping technology via ESR studies, which confirms that the free-radical process is involved in this system. This strategy is expected to be applicable to the trifluoromethylation of manifold biomolecules, pharmaceutical candidates, and materials. Further studies on this system are underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full experimental details and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: liuzhq@lzu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This project is supported by the National Science Foundation of China (No. 21272096). We also thank Professors Bo Zhou, Xiangfeng Shao, Wei Yu, and Long-Min Wu (State Key Laboratory of Applied Organic Chemistry, Lanzhou University, P.R. China) for helpful discussions.

REFERENCES

(1) (a) *Organofluorine Compounds: Chemistry and Applications*; Hiyama, T., Ed.; Springer: New York, 2000. (b) *Modern Fluoroorganic Chemistry: Synthesis Reactivity, Applications*; Kirsch, P., Ed.; Wiley-VCH: Weinheim, Germany, 2004. (c) *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; Wiley-Blackwell: Chichester, UK, 2009.

(2) For selected recent reviews on trifluoromethylation, see: (a) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (b) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. (c) Jin, Z.; Hammond, G. B.; Xu, B. *Aldrichimica Acta* **2012**, *45*, 67. (d) Ye, Y.; Sanford, M. S. *Synlett* **2012**, *23*, 2005. (e) Besset, T.; Schneider, C.; Cahard, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 5048. (f) Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8950. (g) Wang, X.; Zhang, Y.; Wang, J. *Sci. China: Chem.* **2012**, *42*, 1. (h) Barata-Callejo, S.; Postigo, A. *Coord. Chem. Rev.* **2013**, *257*, 3051. (i) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214. (j) Liu, H.; Gu, Z.; Jiang, X. *Adv. Synth. Catal.* **2013**, *355*, 617.

(3) For selected recent examples of transition-metal-catalyzed trifluoromethylation, see: (a) Parsons, A. T.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 9120. (b) Xu, J.; Fu, Y.; Luo, D.-F.; Jiang, Y.-Y.; Xiao, B.; Liu, Z.-J.; Gong, T.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 15300. (c) Wang, X.; Ye, Y.; Zhang, S.; Feng, J.; Xu, Y.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 16410. (d) Kawai, H.; Furukawa, T.; Nomura, Y.; Tokunaga, E.; Shibata, N. *Org. Lett.* **2011**, *13*, 3596. (e) Chu, L.; Qing, F. L. *J. Am. Chem. Soc.* **2012**, *134*, 1298. (f) Liu, T.; Shao, X.; Wu, Y.; Shen, Q. *Angew. Chem., Int. Ed.* **2012**, *51*, 540. (g) Hu, M.; Ni, C.; Hu, J. *J. Am. Chem. Soc.* **2012**, *134*, 15257. (h) Feng, C.; Loh, T.-P. *Angew. Chem., Int. Ed.* **2013**, *52*, 12414. (i) Dai, J.; Fang, C.; Xiao, B.; Yi, J.; Xu, J.; Liu, Z.-J.; Lu, X.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135*, 8436. (j) Wu, X.; Chu, L.; Qing, F.-L. *Angew. Chem., Int. Ed.* **2013**, *52*, 2198. (k) Wang, X.; Xu, Y.; Mo, F.; Ji, G.; Qiu, D.; Feng, J.; Ye, Y.; Zhang, S.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2013**, *135*, 10330. (l) Wang, X.; Ye, Y.; Ji, G.; Xu, Y.; Zhang, S.; Feng, J.; Zhang, Y.; Wang, J. *Org. Lett.* **2013**, *15*, 3730.

(4) For selected recent examples of trifluoromethylation by means of photoredox, see: (a) Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224. (b) Nguyen, J. D.; Tucker, J. W.; Konieczynska, M. D.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2011**, *133*, 4160. (c) Ye, Y.; Sanford, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 9034. (d) Iqbal, N.; Jung, J.; Park, S.; Cho, E. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 539. (e) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322.

(5) For selected recent carbotrifluoromethylation of alkenes, see: (a) Mu, X.; Wu, T.; Wang, H.-Y.; Guo, Y.-L.; Liu, G. *J. Am. Chem. Soc.* **2012**, *134*, 878. (b) Kong, W.; Casimiro, M.; Merino, E.; Nevado, C. *J. Am. Chem. Soc.* **2013**, *135*, 14480. (c) Kong, W.; Casimiro, M.; Fuentes, N.; Merino, E.; Nevado, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 13086. (d) Egami, H.; Shimizu, R.; Kawamura, S.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 4000. (e) Liu, X.; Xiong, F.; Huang, X.; Xu, L.; Li, P.; Wu, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 6962. (f) Chen, Z.-M.; Bai, W.; Wang, S.-H.; Yang, B.-M.; Tu, Y.-Q.; Zhang, F.-M. *Angew. Chem., Int. Ed.* **2013**, *52*, 9781.

(6) For selected recent aminotrifluoromethylation of alkenes, see: (a) Yasu, Y.; Koike, T.; Akita, M. *Org. Lett.* **2013**, *15*, 2136. (b) Egami, H.; Kawamura, S.; Miyazaki, A.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 7841. (c) Wang, F.; Qi, X.; Liang, Z.; Chen, P.; Liu, G. *Angew. Chem., Int. Ed.* **2014**, *53*, 1881.

(7) For selected recent oxytrifluoromethylation of alkenes, see: (a) Janson, P. G.; Ghoneim, I.; Ilchenko, N. O.; Szabó, K. J. *Org. Lett.* **2012**, *14*, 2882. (b) Zhu, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012**, *134*, 12462. (c) Yasu, Y.; Koike, T.; Akita, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9567. (d) Li, Y.; Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8221. (e) Zhu, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 12655. (f) Jiang, X.-Y.; Qing, F.-L. *Angew. Chem., Int. Ed.* **2013**, *52*, 14177.

(8) For selected reviews on iodoperfluoroalkylation of alkenes and alkynes, see: (a) Huang, W.-Y. *J. Fluorine Chem.* **1992**, *58*, 1. (b) Brace, N. O. *J. Fluorine Chem.* **1999**, *93*, 1. (c) Zhang, C.-P.; Chen, Q.-Y.; Guo, Y.; Xiao, J.-C.; Gu, Y.-C. *Chem. Soc. Rev.* **2012**, *41*, 4536. For selected examples of iodotrifluoromethylation of alkenes and alkynes by using CF_3I, see: (d) Tsuchii, K.; Imura, M.; Kamada, N.; Hirao, T.; Ogawa, A. *J. Org. Chem.* **2004**, *69*, 6658. (e) Itoh, Y.; Mikami, K. *Tetrahedron* **2006**, *62*, 7199. (f) Ignatowska, J.; Dmowski, W. *J. Fluorine Chem.* **2007**, *128*, 997. (g) Petrik, V.; Cahard, D. *Tetrahedron Lett.* **2007**, *48*, 3327. (h) Herrmann, A. T.; Smith, L. L.; Zakarian, A. *J. Am. Chem. Soc.* **2012**, *134*, 6976. (i) Xu, T.; Cheung, C.-W.; Hu, X. *Angew. Chem., Int. Ed.* **2014**, *53*, 4910.

(9) For selected examples of trifluoromethylation by using Langlois reagent, see: (a) Langlois, B. R.; Laurent, E.; Roidot, N. *Tetrahedron Lett.* **1991**, *32*, 7525. (b) Ji, Y.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 14411. (c) Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herlé, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. *Nature* **2012**, *492*, 95. (d) Ye, Y.; Künzi, S. A.; Sanford, M. S. *Org. Lett.* **2012**, *14*, 4979. (e) Li, Y.; Wu, L.; Neumann, H.; Beller, M. *Chem. Commun.* **2013**, *49*, 2628. (f) Deb, A.; Manna, S.; Modak, A.; Patra, T.; Maity, S.; Maiti, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 9747. (g) Li, Z.; Cui, Z.; Liu, Z.-Q. *Org. Lett.* **2013**, *15*, 406.

(10) (a) Chai, L.; Zhao, Y.; Sheng, Q.; Liu, Z.-Q. *Tetrahedron Lett.* **2006**, *47*, 9283. (b) Liu, Z.-Q.; Zhao, Y.; Luo, H.; Chai, L.; Sheng, Q. *Tetrahedron Lett.* **2007**, *48*, 3017.

(11) Nicolaou, K. C.; Montagnon, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1386.

(12) (a) Hiroto, U.; Keiji, N.; Katsumi, O. Patent No. JP 06040710; *Chem. Abstr.* **1994**, *120*, 326849. (b) Chandrasekhar, S.; Gopalaiah, K. *Tetrahedron Lett.* **2002**, *43*, 4023.

(13) Zhao, C.-X.; Peng, Y.-Y.; Qu, Y.-L.; Peng, H. *Chem. J. Chin. Univ.* **1992**, *13*, 1448.