Organic LETTERS

Letter

pubs.acs.org/OrgLett

Metal-Free, Efficient Oxyfluorination of Olefins for the Synthesis of α-Fluoroketones

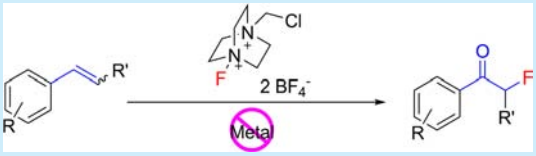
Qiang Yang,[†] Liu-Liang Mao,[†] Bin Yang,[†] and Shang-Dong Yang*[,†,‡]

[†]State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. China

[‡]State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, P. R. China

Supporting Information

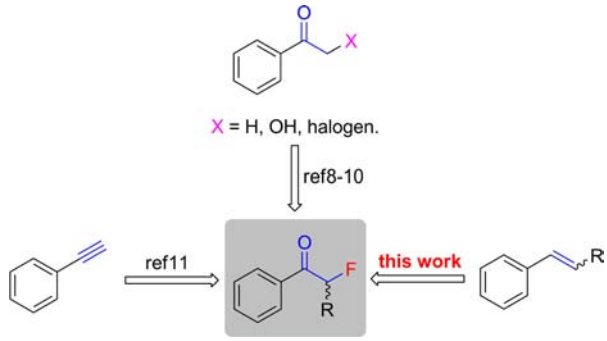
ABSTRACT: A novel oxyfluorination of olefin reactions has been developed. The reactions involve a metal-free and green catalytic system for the synthesis of α-fluoroketones which is an important building block for organic synthesis. Moreover, this reaction system exhibits great functional group tolerance.



At present, fluorinated organic compounds have been extensively used as pharmaceuticals, agrochemicals, fine chemicals, and material science.[1] In particular, approximately 20% of medicinal compounds contain fluorine.[1b,2] When the fluorine element is introduced into organic compounds, it exhibits some unique and excellent properties: inductance conformation changes, pK_a, and dipole moments are altered, and lipophilicity is increased.[1e,3] As a consequence, the development of new and efficient methods to synthesize organic fluorides has become a hot topic in organic synthesis.[4] α-Fluoroketones are extremely valuable building blocks in medicinal and biological chemistry and can be easily transformed into chiral α-fluoroethylamines[5] and α-fluoroethylhydroxys[6,10b] and a large number of interesting molecules.[7] Generally, α-fluoroketones are prepared from α-hydroxy-substituted ketones,[8] phenylketones,[9] α-haloketones,[9b,c,10] or phenylacetylene[11] (Scheme 1) and other methods.[12,16a] However, most of the methods suffer from limitations such as environmental unfriendliness, low atom economy, and complicated procedures. Therefore, an effective and especially environmentally friendly method is still required. Recently, transformations that result in the difunctionalization of alkenes[13,14] provide a powerful strategy for the synthesis of various multifunctionalized organic compounds for the difunctionalization step and atom economy. Thus, difunctionalization of alkenes has made tremendous contributions to organic synthesis. Herein we wish to report an efficient and direct approach to α-fluoroketones by olefin difunctionalization under metal-free conditions. In this transformation, molecular oxygen as a co-oxidant is used.[15] In addition, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) is a stable, mild, and effective source of electrophilic fluorinating reagents.[16]

Initially, we began our study with the reaction of styrene (**1a**) and Selectfluor (**2a**) in the presence of 2 equiv of $K_2S_2O_8$ to provide **3a** in 9% yield under an Ar atmosphere (Table 1, entry 1). Then a number of peroxides were examined first; *tert*-butyl hydroperoxide (TBHP, 70% in water) was found to be the most effective oxidant to generate the desired product **3a** in 26% yield (Table 1, entry 2). When TBHP reacted under an oxygen atmosphere, it gave the desired product **3a** in 36% yield (Table 1, entry 3). Different additives including bases and acids were also examined (Table 1, entries 4−10); the results show that acetic acid had a better effect on the reactant and gave the desired product **3a** in 44% yield (Table 1, entry 8). While the role of acetic acid remains unclear, it might be to adjust the pH of the reaction system and promote the production of fluorine free radicals.[14j] The amount of acetic acid was also very crucial to the reaction (Table 1, entries 11−13); which could give the desired product **3a** in 48% yield in the presence of 0.4 equiv of CH_3COOH. Surprisingly, using 2-iodoxybenzoic acid (IBX) instead of TBHP at a 0.2 M concentration afforded **3a** in an excellent yield of 68% (Table 1, entry 14). We found that increasing the concentration decreased the yield of **3a** (Table 1, entries 15−16). In addition, using 1 equiv instead of 2 equiv of IBX gave the product **3a** in 74% yield (Table 1, entry 17). Different fluorine sources were also evaluated, but only

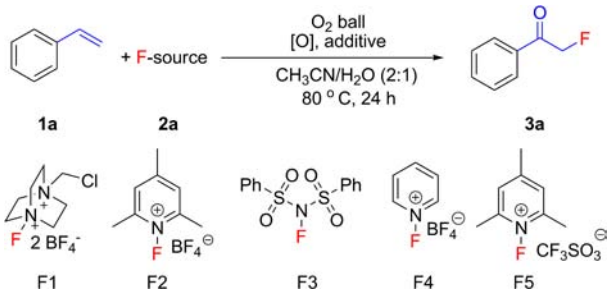
Scheme 1. Strategies for Synthesis of α-Fluoroketones



Received: May 12, 2014
Published: June 5, 2014

   dx.doi.org/10.1021/ol501357w | *Org. Lett.* 2014, 16, 3460−3463

Table 1. Optimization of Reaction Conditions[a]



entry	F-source (equiv)	oxidant (equiv)	additive (equiv)	concn (mol/L)	yield (%)[b]
1[c]	F1 (2.0)	$K_2S_2O_8$ (2.0)	–	0.4	9
2[c]	F1 (2.0)	TBHP[d] (2.0)	–	0.4	26
3	F1 (2.0)	TBHP[d] (2.0)	–	0.4	36
4	F1 (2.0)	TBHP[d] (2.0)	pyridine (1.5)	0.4	3
5	F1 (2.0)	TBHP[d] (2.0)	NaO^{t}Bu	0.4	6
6	F1 (2.0)	TBHP[d] (2.0)	$NaHCO_3$ (1.5)	0.4	3
7	F1 (2.0)	TBHP[d] (2.0)	HCOOH (1.5)	0.4	29
8	F1 (2.0)	TBHP[d] (2.0)	CH_3COOH (1.5)	0.4	44
9	F1 (2.0)	TBHP[d] (2.0)	HCl (1.5)	0.4	20
10	F1 (2.0)	TBHP[d] (2.0)	KH_2PO_4 (1.5)	0.4	35
11	F1 (2.0)	TBHP[d] (2.0)	CH_3COOH (0.2)	0.4	39
12	F1 (2.0)	TBHP[d] (2.0)	CH_3COOH (0.3)	0.4	44
13	F1 (2.0)	TBHP[d] (2.0)	CH_3COOH (0.4)	0.4	48
14	F1 (2.0)	IBX (2.0)	CH_3COOH (0.4)	0.2	68
15	F1 (2.0)	IBX (2.0)	CH_3COOH (0.4)	0.4	58
16	F1 (2.0)	IBX (2.0)	CH_3COOH (0.4)	0.6	47
17	F1 (2.0)	IBX (1.0)	CH_3COOH (0.4)	0.2	74(63)[e]
18	F2 (2.0)	IBX (1.0)	CH_3COOH (0.4)	0.2	n.d.
19	F3 (2.0)	IBX (1.0)	CH_3COOH (0.4)	0.2	n.d.
20	F3 (2.0)	IBX (1.0)	CH_3COOH (0.4)	0.2	n.d.
21	F4 (2.0)	IBX (1.0)	CH_3COOH (0.4)	0.2	n.d.
22	F5 (2.0)	IBX (1.0)	CH_3COOH (0.4)	0.2	n.d.
23	**F1 (1.7)**	**IBX (1.0)**	**CH_3COOH (0.4)**	**0.2**	**75(65)[e]**
24[c]	F1 (1.7)	IBX (1.0)	CH_3COOH (0.4)	0.2	34[e]

[a]Reaction conditions: **1a** (0.5 mmol), Selectfluor, [O], additive, CH_3CN/H_2O (2:1 v/v), O_2 (balloon), 24 h. [b]GC yields based on **1a**. [c]Under Ar atmosphere. [d]*tert*-Butyl hydroperoxide (TBHP, 70% in water). [e]Value in parentheses reflects isolated yield.

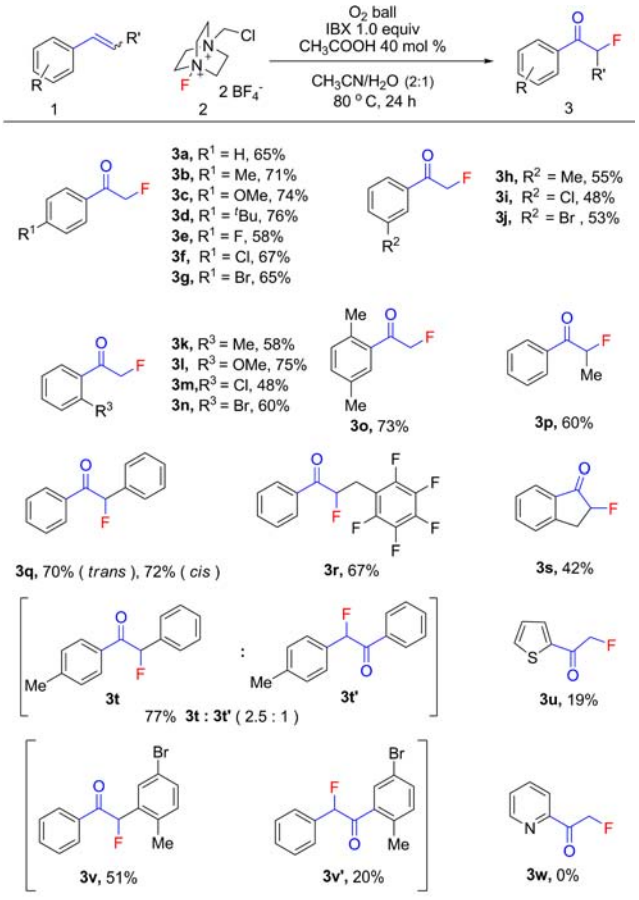
Selectfluor could obtain the product (Table 1, entries 18−22). With further optimization, the best yield (75%) was achieved under the standard reaction conditions with styrene (1.0 equiv), Selectfluor (1.7 equiv), and acetic acid (0.4 equiv) in CH_3CN/H_2O at a 0.2 M concentration under an oxygen atmosphere (Table 1, entry 23). It is worthy to note that the reaction could also proceed under an Ar atmosphere with optimized conditions to afford **3a** in 34% yield (Table 1, entry 24).

Having the optimized conditions in hand, the substrate scope of the oxyfluorination reaction was investigated with a variety of vinyl arenes. As shown in Scheme 2, the method tolerates various types of functional groups including both electron-rich and -deficient CH_3, CH_3O, *t*-Bu, F, Cl, and Br groups which were obtained in moderate to good yields (**3a**−**3n**). It is noteworthy that 2,5-dimethylstyrene was utilized to also obtain α-F-substituted ketone **3o** in 73% yield. Notably the nonterminal alkenes were also tolerated in the reaction, thus resulting in the desired products in moderate to good yields (**3p**, **3q**, and **3s**) under the standard reaction conditions. Compound **3r** which has good medicinal value as well as other applications[17] could also be formed by this method in 67% yield. Other unsaturated olefins, such as **1t** and **1v** with some complex substituent, generated products **3t**/**3t′** and **3v**/**3v′**, exhibiting regioselectivity. A heteroaromatic alkene such as 2-vinylthiophene also worked well and gave the α-F-substituted ketone **3u** in relatively low yield, while 2-vinylpyridine had no desired product for the oxyfluorination reaction. When we tried to use the 1-dodecene as the substrate, we did not obtain a single product, because the free radical transition state is very active in changing its position.

In order to explore the possible mechanism, various control experiments were carried out as described in Scheme 3. A radical verification experiment (Scheme 3, eqs 1−2) suggested that the reaction was likely to form a radical.[18] In this transformation, an oxygen source was a key issue in investigating whether the O_2 or H_2O provided the oxygen for the final products, and an ^{18}O-labeling experiment (Scheme 3, eqs 3−5) was performed. When $H_2{}^{18}O$ was added into the reaction, 82% ^{18}O-labeled product was obtained (Scheme 3, eq 3).[19] Under the $^{18}O_2$ atmosphere, we could hardly detect the ^{18}O-labeled product in the standard reaction conditions (Scheme 3, eq 4). With 10% H_2O in the reaction system, we could detect 23% of the ^{18}O-labeled product in the standard reaction conditions under a

dx.doi.org/10.1021/ol501357w | *Org. Lett.* 2014, 16, 3460−3463

Scheme 2. Synthesis of α-Fluoroketones from Olefins[a,b]



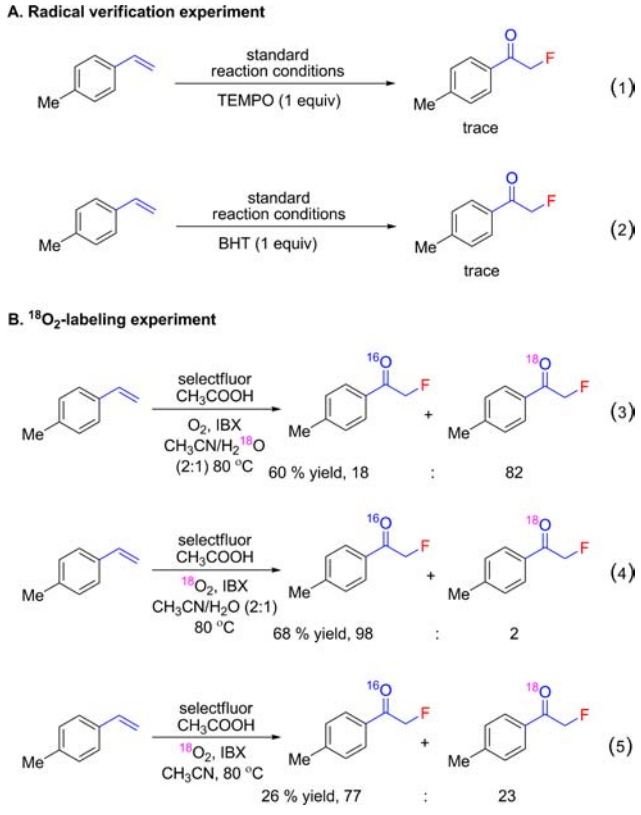
[a]Reaction conditions: Olefins (0.5 mmol), Selectfluor (0.85 mmol), IBX (0.5 mmol), CH_3COOH (0.2 mmol), CH_3CN/H_2O (2:1 v/v), Concn = 0.2 M, O_2 (balloon), 80 °C, 24 h. [b] Isolated yield.

$^{18}O_2$ atmosphere (Scheme 3, eq 5). These results indicated that H_2O and O_2 competed to provide an oxygen source. In addition, the presence of H_2O in the reaction prompted the dissolution of Selectfluor and IBX and the improvement of the reaction efficiency.

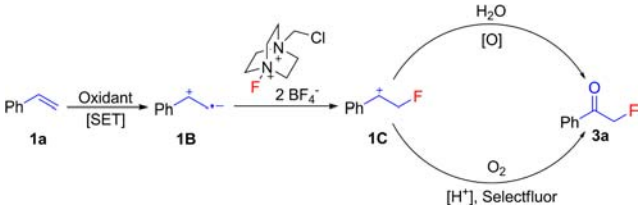
Although the detailed mechanism remains unclear, a plausible mechanism is proposed on the basis of the above results and is shown in Scheme 4. The alkene of **1a** first generates a benzylic carbonium radical (**1B**) by single-electron transfer [SET] under the oxidative conditions.[20] This nucleophilic **1B** reacts with selectfluor to form the β-fluorinated benzylic carbocation (**1C**) which is attacked by H_2O and further oxidized to afford the α-fluoroketone product of **3a**. On the other hand, we also could not exclude another pathway; the β-fluorinated benzylic carbocation could be oxidized by molecular dioxygen and selectfluor directly under acidic conditions in the absence of IBX to obtain the α-fluoroketones product.

In conclusion, we have successfully developed a metal-free, efficient acylfluorination method to access α-fluoroketones. Inexpensive and easily available unsaturated olefins, wide functional-group tolerance, and atom economical conditions are key features of the reaction. Moveover, this method produced not only important building blocks of ketones but also a wide range of applications in medicinal and agrochemical research of the C_{sp3}–F bond that will be applied to other organic syntheses. Further studies on the reaction detail mechanism and applications are ongoing in our laboratory.

Scheme 3. Experiments for Mechanistic Studies



Scheme 4. Plausible Mechanistic Pathway



■ ASSOCIATED CONTENT

Supporting Information

Experimental details and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

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

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the NSFC (Nos. 21272100) and Program for New Century Excellent Talents in University (NCET-11-0215 and lzujbky-2013-k07) financial support.

REFERENCES

(1) (a) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (c) Böhm, H. J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637. (d) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (e) Jeschke, P. *ChemBioChem* **2004**, *5*, 571. (f) Jeschke, P. *Science* **2010**, *66*, 10. (g) Kirsch, P.; Bremer, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4216.

(2) Thayer, A. M. *Chem. Eng. News* **2006**, *84*, 15.

(3) Morgenthaler, M.; Schweizer, E.; Hoffmann-Röder, A.; Benini1, F.; Martin, R. E.; Jaeschke, G.; Wagner, B.; Fischer, H.; Bendels, S.; Zimmerli, D.; Schneider, J.; Diederich, F.; Kansy, M.; Müller, K. *ChemMedChem* **2007**, *2*, 1100.

(4) (a) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2004**, *44*, 214. (b) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134. (c) Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2008**, *130*, 10060. (d) Furuya, T.; Strom, A. E.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 1662. (e) Wang, X.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520. (f) Furuya, T.; Ritter, T. *Org. Lett.* **2009**, *11*, 2860. (g) Ball, N. D.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 3796. (h) Ye, Y.; Schimler, S. D.; Hanley, P. S.; Sanford, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 16292. (i) Xia, J. B.; Zhu, C.; Chen, C. *J. Am. Chem. Soc.* **2013**, *135*, 17494. (j) Sibi, M. P.; Landais, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 3570. (k) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214. (l) Emer, E.; Pfeifer, L.; Brown, J. M.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2014**, *53*, 4181. (m) Gao, B.; Zhao, Y.; Ni, C.; Hu, J. *Org. Lett.* **2014**, *16*, 102. (n) Braun, M.-G.; Doyle, A. G. *J. Am. Chem. Soc.* **2013**, *135*, 12990. (o) McMurtrey, K. B.; Racowski, J. M.; Sanford, M. S. *Org. Lett.* **2012**, *14*, 4094. (p) Ye, Y.; Sanford, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 4648. (q) Yin, F.; Wang, Z.; Li, Z.; Li, C. *J. Am. Chem. Soc.* **2013**, *134*, 10401. (r) Ichiishi, N.; Canty, A. J.; Yates, B. F.; Sanford, M. S. *Org. Lett.* **2013**, *15*, 5134. (s) Browne, D. L. *Angew. Chem., Int. Ed.* **2014**, *53*, 1482. (t) Liu, Q.; Wu, Y.; Chen, P.; Liu, G. *Org. Lett.* **2013**, *15*, 6210. (u) Hu, M.; He, Z.; Gao, B.; Li, L.; Ni, C.; Hu, J. *J. Am. Chem. Soc.* **2013**, *135*, 17302. (v) Zhang, Z.; Wang, F.; Mu, X.; Chen, P.; Liu, G. *Angew. Chem., Int. Ed.* **2013**, *52*, 7549.

(5) (a) Thvedt, T. H. K.; Fuglseth, E.; Sundby, E.; Hoff, B. H. *Tetrahedron* **2010**, *66*, 6733. (b) Malamakal, R. M.; Hess, W. R.; Davis, T. A. *Org. Lett.* **2010**, *12*, 2186.

(6) (a) Borzecka, W.; Lavandera, I.; Gotor, V. *J. Org. Chem.* **2013**, *78*, 7312. (b) Mohanta, P. K.; Davis, T. A.; Gooch, J. R.; Flowers, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 11896. (c) Matsuda, T.; Harada, T.; Nakamura, K. *Chem. Commun.* **2000**, *46*, 1367. (e) Ramachandran, P. V.; Teodorovic, A. V.; Gong, B.; Brown, H. C. *Tetrahedron: Asymmetry* **1994**, *5*, 1075.

(7) (a) He, Y.; Zhang, X.; Shen, N.; Fan, X. *J. Fluorine Chem.* **2013**, *156*, 9. (b) Lawrence, N. J.; Patterson, R. P.; Ooi, L. L.; Cook, D.; Ducki, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5844. (c) Yoon, S. C.; Cho, J.; Kim, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 109. (d) Heinrich, M. R. *Tetrahedron Lett.* **2007**, *48*, 3895.

(8) Kim, K.-Y.; Kim, B. C.; Lee, H. B.; Shin, H. *J. Org. Chem.* **2008**, *73*, 8106.

(9) (a) Middleton, W. J.; Bingham, E. M. *J. Am. Chem. Soc.* **1980**, *102*, 4845. (b) Fuglseth, E.; Thvedt, T. H. K.; Møll, M. F.; Hoff, B. H. *Tetrahedron* **2008**, *64*, 7318. (c) Chen, Z.; Zhu, W.; Zheng, Z.; Zou, X. *J. Fluorine Chem.* **2010**, *131*, 340. (d) Stavber, S.; Zupan, M. *Tetrahedron Lett.* **1996**, *37*, 3591. (e) Stavber, S.; Jereb, M.; Zupan, M. *Chem. Commun.* **2000**, *46*, 1323.

(10) (a) Tenza, K.; Northen, J. S.; O'Hagan, D.; Slawin, A. M. Z. *J. Fluorine Chem.* **2004**, *125*, 1779. (b) Fuglseth, E.; Sundby, E.; Hoff, B. H. *J. Fluorine Chem.* **2009**, *130*, 600.

(11) Haro, T.; de; Nevado, C. *Adv. Synth. Catal.* **2010**, *352*, 2767.

(12) (a) Bélanger, É.; Cantin, K.; Messe, O.; Tremblay, M.; Paquin, J.-F. *J. Am. Chem. Soc.* **2007**, *129*, 1034. (b) Kumar, M.; Scobie, M.; Mashuta, M. S.; Hammond, G. B.; Xu, B. *Org. Lett.* **2013**, *15*, 724. (c) Takeuchi, Y.; Suzuki, T.; Satoh, A.; Shiragami, T.; Shibata, N. *J. Org. Chem.* **1999**, *64*, 5708. (d) Yang, X.; Phipps, R. J.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5225. (e) Lubin, H.; Dupuis, C.; Pytkowicz, J.; Brigaud, T. *J. Org. Chem.* **2013**, *78*, 3487. (f) Hoffman, R. V.; Tao, J. *J. Org. Chem.* **1999**, *64*, 126. (g) Kwiatkowski, P.; Beeson, T. D.; Conrad, J. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 1738. (h) Wang, W.; Jasinski, J.; Hammond, G. B.; Xu, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 7247. (i) Suzuki, T.; Hamashima, Y.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 5435. (j) Enders, D.; Potthoff, M.; Raabe, G.; Runsink, J. *Angew. Chem. Int. Ed.* **1997**, *36*, 2362.

(13) Reviews for the difunctionalization of alkenes: (a) Sibbald, P. A. *Palladium-catalyzed oxidative difunctionalization of alkenes: New reactivity and new mechanisms*; ProQuest, UMI Dissertation Publishing: 2011. (b) Jacques, B.; Muñiz, K. In *Catalyzed Carbon-Heteroatom Bond Formation*; Yudin, A. K., Ed.; Wiley-VCH: 2011; p 119. (c) Muñiz, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9412. (d) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981. (e) Chemler, S. R. *Org. Biomol. Chem.* **2009**, *7*, 3009. (f) Kotov, V.; Scarborough, C. C.; Stahl, S. S. *Inorg. Chem.* **2007**, *46*, 1910. (g) Jensen, K. H.; Sigman, M. S. *Org. Biomol. Chem.* **2008**, *6*, 4083. (h) Li, G.; Kotti, S. R. S. S.; Timmons, C. *Eur. J. Org. Chem.* **2007**, 2745.

(14) For the metal-free difunctionalization of alkenes: (a) Lovick, H. M.; Michael, F. E. *J. Am. Chem. Soc.* **2010**, *132*, 1249. (b) Schmidt, V. A.; Alexanian, E. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 4491. (c) Pandit, P.; Gayen, K. S.; Khamarui, S.; Chatterjee, N.; Maiti, D. K. *Chem. Commun.* **2011**, *47*, 6933. (d) Schmidt, V. A.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 11402. (e) Röben, C.; Souto, J. A.; González, Y.; Lishchynskyi, A.; Muñiz, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 9478. (f) Zhang, C. P.; Wang, Z. L.; Chen, Q. Y.; Zhang, C. T.; Gu, Y. C.; Xiao, J. C. *Chem. Commun.* **2011**, *47*, 6632. (g) Farid, U.; Wirth, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 3462. (h) Lu, Q.; Zhang, J.; Wei, F.; Qi, Y.; Wang, H.; Liu, Z.; Lei, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 7156. (i) Li, Y.-M.; Wei, X.-H.; Li, X.-A.; Yang, S.-D. *Chem. Commun.* **2013**, *49*, 11701. (j) Li, Z.; Zhang, C.; Zhu, L.; Liu, C.; Li, C. *Org. Chem. Front.* **2014**, *1*, 100.

(15) (a) Stahl, S. S. *Science* **2005**, *309*, 1824. (b) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400. (c) Schultz, M. J.; Sigman, M. S. *Tetrahedron* **2006**, *62*, 8227. (d) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (e) Muzart, J. *Chem.—Asian J.* **2006**, *1*, 508. (f) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381. (g) Piera, J.; Bäckvall, J. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3506.

(16) (a) Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737. (b) Nyffeler, P. T.; Duron, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 192. (c) Banks, R. E.; Mohialdin-Khaffaf, S. N.; Lal, G. S.; Sharifa, l.; Syvret, R. G. *J. Chem. Soc., Chem. Commun.* **1992**, *8*, 595. (d) Singh, R. P.; Shreeve, J. M. *Acc. Chem. Res.* **2004**, *37*, 31.

(17) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359.

(18) (a) Rueda-Becerril, M.; Sazepin, C. C.; Leung, J. C. T.; Okbinoglu, T.; Kennepohl, P.; Paquin, J.-F.; Sammis, G. M. *J. Am. Chem. Soc.* **2012**, *134*, 4026. (b) Barker, T. J.; Boger, D. L. *J. Am. Chem. Soc.* **2012**, *134*, 13588. (c) Sibi, M. P.; Landais, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 3570.

(19) For details, see the Supporting Information.

(20) (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2001**, *123*, 3183. (b) Nicolaou, K. C.; Baran, P. S.; Kranich, R.; Zhong, Y.-L.; Sugita, K.; Zou, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 207.

NOTE ADDED AFTER ASAP PUBLICATION

References 9d,e and 12j were added on June 13, 2014.