Organic LETTERS

Letter

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Copper-Catalyzed Intermolecular Cyanotrifluoromethylation of Alkenes

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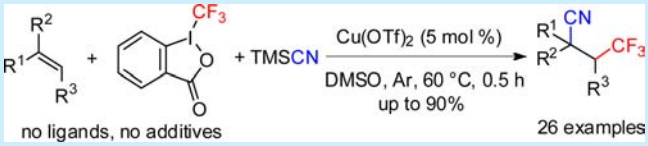
Supporting Information

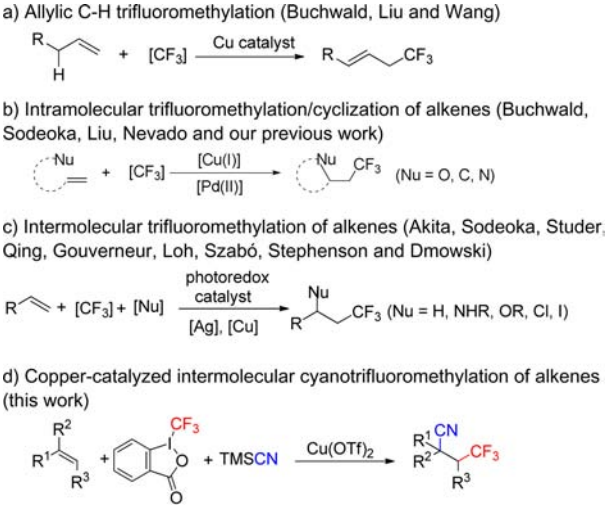
ABSTRACT: A novel and highly practical reaction for the copper-catalyzed intermolecular cyanotrifluoromethylation of alkenes is presented here. This methodology provides a general and straightforward way to synthesize a variety of useful CF_3-containing nitriles, which can be used for further preparation of pharmaceutically and agrochemically important compounds in synthetic organic chemistry.



Organic compounds bearing trifluoromethyl groups have attracted ever-increasing interest of chemists due to potential improvement in lipophilicity and bioactivity, and a series of trifluoromethylated derivatives have been prepared as pharmaceuticals, agrochemicals, and functional materials.[1,2] As a powerful synthetic tool in this area, transition-metal-mediated or -catalyzed trifluoromethylation reactions have provided a number of useful methods to construct a C−CF_3 bond from aryl,[3] aryl halides,[4] alkynes,[5] and the corresponding boronic acids.[6] In recent years, the trifluoromethylation of alkenes, especially unactivated alkenes, has become a research hotspot and effective methods have been studied intensively.[7] In 2011, the Buchwald, Liu, and Wang groups reported the copper-catalyzed electrophilic allylic trifluoromethylation of alkenes (Scheme 1a).[8] Furthermore, our group, as well as those of Buchwald, Sodeoka, Liu, and Nevado, independently demonstrated the trifluoromethylation of alkenes which involves a pattern of intramolecular cyclization in the presence of a copper catalyst (Scheme 1b).[9] However, the work for the trifluoromethylation of alkenes based on the intermolecular difunctionalization strategy is quite rare,[10] and most of these three-component reactions require photoredox catalyst (Scheme 1c).[11] Thus, the introduction of a CF_3 group synchronously with another important functional group into alkenes is highly desirable.

In this context, we were interested in the use of a copper catalyst for directed cyanotrifluoromethylation of alkenes. Nitriles, holding the post of remarkably versatile building blocks in numerous organic transformations such as carboxylic acids, amines, amides, ketones, and aldehydes,[12] are widely known as an important class of organic compounds, which are found in a number of pharmaceuticals, agricultural chemicals, and optoelectronic materials.[13] Since the unique role of the cyano group, its introduction into organic molecules, particularly by a catalytic protocol, is an important topic in synthetic chemistry. Due to our ongoing interest in the synthesis of CF_3-containing compounds, we envisioned that the intermolecular difunctionalization of alkenes which involves the C−CN and C−CF_3 bond formations could be achieved concurrently in one pot. Herein, we reported a new powerful protocol for the cyanotrifluoromethylation of alkenes with the use of a hypervalent iodine reagent and trimethylsilyl cyanide (TMSCN) as the cyano source under copper catalysis (Scheme 1d). It should be indicated that, at the same time as we finished this work, Szabó and co-workers reported the cyanotrifluoromethylation of styrenes with an electron-deficient double bond in the presence of CuCN.[14] Nevertheless, the reaction

Scheme 1. Previous and Present Works



Received: November 13, 2013
Published: December 13, 2013

   dx.doi.org/10.1021/ol403263c | *Org. Lett.* 2014, 16, 270−273

requires stoichiometric amounts of CuCN and has a low substrate scope.

At the outset of our studies, we chose styrene **1a** as the model substrate to optimize the reaction conditions (Table 1).

Table 1. Optimization of the Reaction Conditions[a]

1a 2 3a

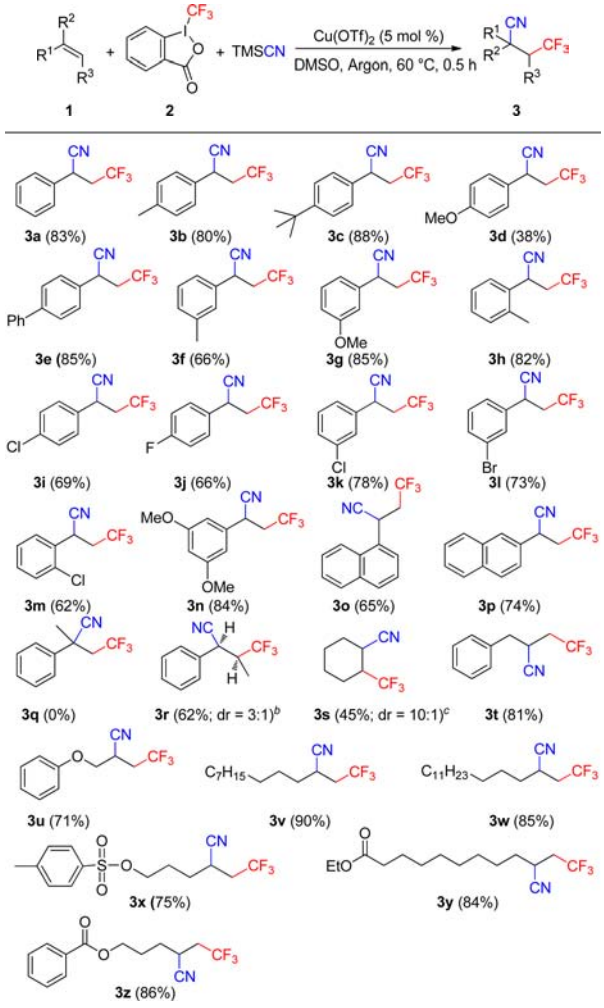
entry	catalyst (mol %)	solvent	t (h)	yield (%)[b]
1	CuCl (10)	DMF	1.0	34
2	CuI (10)	DMF	1.0	35
3	CuCN (10)	DMF	1.0	38
4	CuF_2 (10)	DMF	1.0	30
5	$Cu(OAc)_2$ (10)	DMF	1.0	28
6	$Cu(MeCN)_4PF_6$ (10)	DMF	1.0	36
7	$Cu(OTf)_2$ (10)	DMF	1.0	61
8	$Cu(OTf)_2$ (10)	CH_3CN	1.0	25
9	$Cu(OTf)_2$ (10)	DCM	1.0	20
10	$Cu(OTf)_2$ (10)	1,4-dioxane	1.0	23
11	$Cu(OTf)_2$ (10)	DMSO	1.0	79
12	$Cu(OTf)_2$ (20)	DMSO	1.0	69
13	$Cu(OTf)_2$ (5)	DMSO	1.0	82
14	**$Cu(OTf)_2$ (5)**	**DMSO**	**0.5**	**83**
15[c]	–	DMSO	0.5	NR

[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.24 mmol), TMSCN (0.3 mmol), copper catalyst, solvent (2.0 mL), 60 °C, under argon. [b]Isolated yield. [c]Without $Cu(OTf)_2$.

Initially, the reaction was carried out with TMSCN (1.5 equiv) and Togni's reagent **2**[15] (1.2 equiv) in the presence of 10 mol % CuCl in DMF at 60 °C for 1.0 h. Gratifyingly, the desired cyanotrifluoromethylation product 4,4,4-trifluoro-2-phenylbutanenitrile (**3a**) was isolated in 34% yield (Table 1, entry 1). Inspired by this result, different copper complexes, such as CuI, CuCN, CuF_2, $Cu(OAc)_2$, $Cu(MeCN)_4PF_6$, and $Cu(OTf)_2$, were applied into the reaction separately (Table 1, entries 2−7). It showed that $Cu(OTf)_2$ performed well and increased the yield to 61% (Table 1, entry 7). Meanwhile, screening of solvents revealed that DMSO was the best for the reaction (Table 1, entries 8−11). The loading of the catalyst and the reaction time were evaluated as well, and we obtained the best result as an 83% yield under the optimized conditions by using 5 mol % $Cu(OTf)_2$, TMSCN (1.5 equiv) and Togni's reagent **2** (1.2 equiv) in DMSO at 60 °C for 0.5 h (Table 1, entry 14).[16] The controlled experiments indicated the copper reagent was essential in catalyzing the reaction (Table 1, entry 15).

With the optimized conditions in hand (Table 1, entry 14), we next investigated the scope of alkenes in the cyanotrifluoromethylation process. As shown in Table 2, in most cases, alkenes **1a−1z** proceeded smoothly to transform into the cyanotrifluoromethylation products **3a−3z** in moderate to good yields, and the substrates bearing electron-donating groups gave higher yields than those containing electron-withdrawing groups on the aromatic rings. The halogen substituents, including fluoro, chloro, and bromo, were found to be tolerated under the optimized reaction conditions. Naphthalenes bearing vinyl groups at positions 1 and 2 afforded the desired products in 65% (**3o**) and 74% (**3p**) yield, respectively. No reaction occurred in the case of α-methylstyrene **1q**, which is likely due to the difficulty in

Table 2. Copper-Catalyzed Cyanotrifluoromethylation of Various Alkenes[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), TMSCN (0.3 mmol), $Cu(OTf)_2$ (0.01 mmol), DMSO (2.0 mL), 60 °C, 0.5 h, under argon, isolated yield. [b]Structure of the major diastereomer is shown. [c]The ratio of diastereomers was determined by crude ^{19}F NMR.

forming the iodo(III) cyclopropane **B** due to the effect of steric hindrance. However, 1,2-disubstituted alkenes were found to undergo the desired transformation and gave a mixture of diastereoisomers **3r** (dr = 3:1) and **3s** (dr = 10:1).

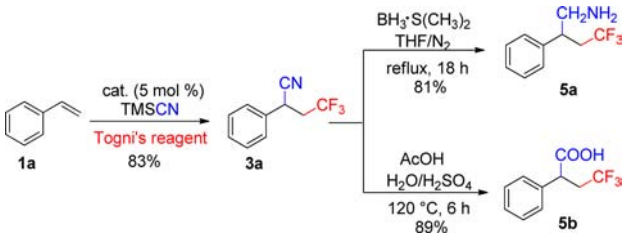
Encouraged by these promising results, we next applied the cyanotrifluoromethylation process to examine some linear olefins. The reactions of simple alkenes proceed smoothly, which gave the corresponding products in excellent yields (**3v** and **3w**). The NMR-based structure was further confirmed by X-ray crystallography of **3x**, which was obtained when **1x** was used as the substrate. Terminal olefins bearing a benzoate group was also well tolerated in this reaction, with the desired product being obtained in 86% yield (**3z**). The scope of alkenes demonstrated the wide compatibility of this new methodology in organic synthesis.

As alluded to earlier, the produced cyanotrifluoromethylation products are versatile synthetic intermediates, and they could be used to generate CF_3-containing products resulting from reaction of the cyano group. For instance, the CN group in the product **3a** was readily reduced to the CF_3-containing amine **5a** in the presence of $BH_3{\cdot}SMe_2$ as a reductant, while the

dx.doi.org/10.1021/ol403263c | Org. Lett. 2014, 16, 270−273

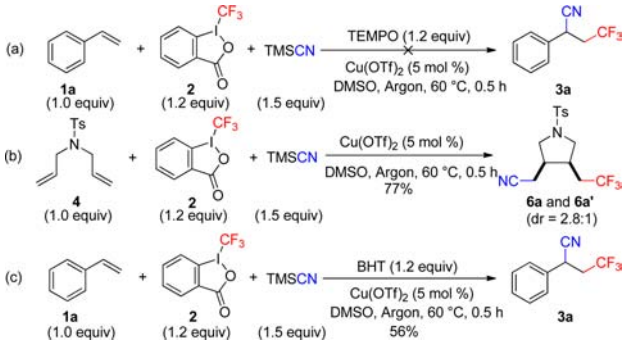
cyanotrifluoromethylation product **3a** could also convert to the CF_3-containing carboxylic acid **5b** in an excellent yield of 89% easily (Scheme 2). Thus, the copper-catalyzed intermolecular cyanotrifluoromethylation reaction proved to be synthetically useful in organic chemistry.

Scheme 2. Further Synthetic Transformation



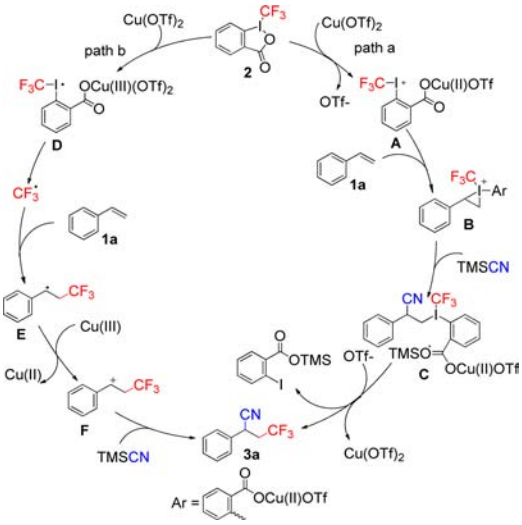
To gain further understanding about the reaction mechanism, inhibition experiments were conducted. When 1.2 equiv of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was added into the reaction system, the desired transformation was found to be completely inhibited and only a small amount of the TEMPO−CF_3 adduct was detected (Scheme 3a). Furthermore,

Scheme 3. Trapping Experiments (Ts = 4-Methylbenzenesulfonyl)



additional direct evidence for the radical mechanism was the reaction of *N,N*-diallyl-4-methylbenzenesulfonamide **4** under the standard reaction conditions, which gave a cyclization of cyanotrifluoromethylation product **6** in 77% yield (dr = 2.8:1) (Scheme 3b). However, when BHT (2,6-di-*tert*-butyl-4-methylphenol) was added as a radical scavenger, to our surprise, the desired product was obtained with a decreased yield (56%) (Scheme 3c), which was different from the result of TEMPO. We hypothesized that TEMPO on one hand was the effect of a radical scavenger, and on the other hand it might destroy Togni's reagent or interact with Cu(II). According to the experimental results and related published research studies in this field, we proposed two probable mechanisms (Scheme 4).[8,9c,10c,17] In path a, a copper catalyst activates Togni's reagent **2**, leading to the cationic active species **A**, which reacts with the styrene **1a** resulting in the iodo(III) cyclopropane **B**. Then the iodo(III) cyclopropane **B** is trapped by TMSCN to generate the intermediate **C**; after reductive elimination from **C**, the cyanotrifluoromethylation product **3a** is obtained. In path b, Togni's reagent **2** undergoes copper-assisted single-electron-transfer (SET) oxidation to generate the CF_3-containing radical species **D**. The CF_3 radical, which is released from decomposition of the radical species **D**, reacts with the styrene **1a** leading to the radical intermediate **E**. The radical

Scheme 4. Proposed Mechanism



intermediate **E** can be further oxidized to the cationic intermediate **F**, and then the cationic intermediate **F** is attacked by TMSCN to deliver the final cyanotrifluoromethylation product **3a**.

In summary, we have developed a copper-catalyzed intermolecular cyanotrifluoromethylation of alkenes based on the difunctionalization strategy. This methodology allows a broad substrate scope, including styrene derivatives and aliphatic olefins with a catalytic amount of copper. The highly practical reaction provides access to a variety of useful CF_3-containing nitriles, which can be used as remarkably versatile building blocks in synthetic organic chemistry. Further investigations of the mechanistic details and applications of this reaction are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, spectral data for all new compounds, crystallographic data, and CIF information for **3x** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation (NSF21072081) and the National Basic Research Program of China (973 Program) 2010CB8-33203 for financial support. We also acknowledge support from the "111" Project and Program for Changjiang Scholars and innovative Research Team in University (IRT1138).

■ REFERENCES

(1) (a) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3. (b) Kirsch, P. In *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, Germany, 2004. (c) Uneyama, K. In *Organofluorine Chemistry*; Blackwell: Oxford, U.K., 2006. (d) Ojima, I. In *Fluorine in Medicinal Chemistry and*

Chemical Biology; Wiley-Blackwell: Chichester, U.K., 2009. (e) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (f) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.

(2) (a) Smart, B. E. *Chem. Rev.* **1996**, *96*, 1555. (b) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214. (c) Hird, M. *Chem. Soc. Rev.* **2007**, *36*, 2070. (d) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. (e) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. (f) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470.

(3) (a) Grushin, V. V.; Marshall, W. J. *J. Am. Chem. Soc.* **2006**, *128*, 12644. (b) Shimizu, R.; Egami, H.; Nagi, T.; Chae, J.; Hamashima, Y.; Sodeoka, M. *Tetrahedron Lett.* **2010**, *51*, 5947. (c) Wiehn, M. S.; Vinogradova, E. V.; Togni, A. *J. Fluorine Chem.* **2010**, *131*, 951. (d) Wang, X.; Truesdale, L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3648. (e) Ball, N. D.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 2878. (f) Ball, N. D.; Gary, J. B.; Ye, Y.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 7577. (g) Ye, Y.; Lee, S. H.; Sanford, M. S. *Org. Lett.* **2011**, *13*, 5464. (h) Tomashenko, O. A.; Escudero-Adan, E. C.; Belmonte, M. M.; Grushin, V. V. *Angew. Chem., Int. Ed.* **2011**, *50*, 7655. (i) Danoun, G.; Bayarmagnai, B.; Grünberg, M. F.; Goossen, L. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 7972.

(4) (a) Oishi, M.; Kondo, H.; Amii, H. *Chem. Commun.* **2009**, *45*, 1909. (b) Cho, E. J.; Senecal, T. D.; Zhang, T. Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328*, 1679. (c) Mu, X.; Chen, S.; Zhen, X.; Liu, G. *Chem.—Eur. J.* **2011**, *17*, 6039. (d) Morimoto, H.; Tsubogo, T.; Litvinas, N. D.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 3793.

(5) (a) Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2010**, *132*, 7262. (b) Luo, D.-F.; Xu, J.; Fu, Y.; Guo, Q.-X. *Tetrahedron Lett.* **2012**, *53*, 2769. (c) Weng, Z.; Li, H.; He, W.; Yao, L.-F.; Tan, J.; Chen, J.; Yuan, Y.; Huang, K.-W. *Tetrahedron* **2012**, *68*, 2527. (d) Jiang, X.; Chu, L.; Qing, F.-L. *J. Org. Chem.* **2012**, *77*, 1251.

(6) (a) Chu, L.; Qing, F.-L. *Org. Lett.* **2010**, *12*, 5060. (b) Senecal, T. D.; Parson, A. T.; Buchwald, S. L. *J. Org. Chem.* **2011**, *76*, 1174. (c) Liu, T.-F.; Shen, Q.-L. *Org. Lett.* **2011**, *13*, 2342. (d) Xu, J.; Luo, D. F.; Xiao, B.; Liu, Z.-J.; Gong, T.-J.; Fu, Y.; Liu, L. *Chem. Commun.* **2011**, *47*, 4300. (e) Ye, Y.; Sanford, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 9034. (f) Novak, P.; Lishchynskyi, A.; Grushin, V. V. *Angew. Chem., Int. Ed.* **2012**, *51*, 7767.

(7) (a) Chu, L.; Qing, F.-L. *Org. Lett.* **2012**, *14*, 2106. (b) Shimizu, R.; Egami, H.; Hamashima, Y.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 4577. (c) Gao, P.; Yan, X.-B.; Tao, T.; Yang, F.; He, T.; Song, X.-R.; Liu, X.-Y.; Liang, Y.-M. *Chem.—Eur. J.* **2013**, *19*, 14420.

(8) (a) Parsons, A. T.; Buchwald, S. L. *Angew. Chem.* **2011**, *123*, 9286; *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.

(9) (a) Mu, X.; Wu, T.; Wang, H.; Guo, Y.; Liu, G. *J. Am. Chem. Soc.* **2012**, *134*, 878. (b) Zhu, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012**, *134*, 12462. (c) Egami, H.; Shimizu, R.; Kawamura, S.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 4000. (d) Kong, W.; Casimiro, M.; Merino, E.; Nevado, C. *J. Am .Chem. Soc.* **2013**, *135*, 14480. (e) He, Y.-T.; Li, L.-H.; Yang, Y.-F.; Wang, Y.-Q.; Luo, J.-Y.; Liu, X.-Y.; Liang, Y.-M. *Chem. Commun.* **2013**, *49*, 5687. (f) Kim, E.; Choi, S.; Kim, H.; Cho, E. J. *Chem.—Eur. J.* **2013**, *19*, 6209.

(10) (a) Ignatowska, J.; Dmowski, W. *J. Fluorine Chem.* **2007**, *128*, 997. (b) Yajima, T.; Nagano, H.; Saito, C. *Tetrahedron Lett.* **2003**, *44*, 7027. (c) Zhang, C.-P.; Wang, Z.-L.; Chen, Q.-Y.; Zhang, C.-T.; Gu, Y.-C.; Xiao, J.-C. *Chem. Commun.* **2011**, *47*, 6632. (d) Feng, C.; Loh, T.-P. *Chem. Sci.* **2012**, *3*, 3458. (e) Janson, P. G.; Ghoneim, I.; Ilchenko, N. O.; Szabó, K. J. *Org. Lett.* **2012**, *14*, 2882. (f) Li, Y.; Studer, A. *Angew. Chem.* **2012**, *124*, 8345; *Angew. Chem., Int. Ed.* **2012**, *51*, 8221. (g) Egami, H.; Shimizu, R.; Sodeoka, M. *Tetrahedron Lett.* **2012**, *53*, 5503. (h) Lu, D.-F.; Zhu, C.-L.; Xu, H. *Chem. Sci.* **2013**, *4*, 2478. (i) Wu, X.; Chu, L.; Qing, F.-L. *Angew. Chem., Int. Ed.* **2013**, *52*, 2198. (j) Egami, H.; Kawamura, S.; Miyazaki, A.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 7841.

(11) (a) Nguyen, J. D.; Tucker, J. W.; Konieczynska, M. D.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2011**, *133*, 4160. (b) Yasu, Y.; Koike, T.; Akita, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9567. (c) Yasu, Y.; Koike, T.; Akita, M. *Org. Lett.* **2013**, *15*, 2136. (d) Mizuta, S.; Verhoog, S.; Engle, K. M.; Khotavivattana, T.; O'Duill, M.; Wheelhouse, K.; Rassias, G.; Médebielle, M.; Gouverneur, V. *J. Am. Chem. Soc.* **2013**, *135*, 2505.

(12) (a) Larock, R. C. In *Comprehensive Organic Transformations*; Wiley-VCH: New York, 1989; p 819. (b) Fleming, F. F.; Zhang, Z. *Tetrahedron* **2005**, *61*, 747.

(13) (a) Murdoch, D.; Keam, S. J. *Drugs* **2005**, *65*, 2379. (b) Ozoe, Y.; Ishikawa, S.; Tomiyama, S.; Ozoe, F.; Kozaki, T.; Scott, J. G. *ACS Symp. Ser.* **2007**, *948*, 39.

(14) Ilchenko, N. O.; Janson, P. G.; Szabó, K. J. *J. Org. Chem.* **2013**, *78*, 11087.

(15) (a) Eisenberger, P.; Gischig, S.; Togni, A. *Chem.—Eur. J.* **2006**, *12*, 2579. (b) Niedermann, K.; Fruh, N.; Vinogradova, E.; Wiehn, M. S.; Moreno, A.; Togni, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 1059.

(16) See the Supporting Information for detailed data.

(17) (a) Kamigata, N.; Fukushima, T.; Yoshida, M. *Chem. Lett.* **1990**, 649. (b) Liu, W.; Huang, X.; Cheng, M.-J.; Nielsen, R. J.; Goddard, W. A., III; Groves, J. T. *Science* **2012**, *337*, 1322. (c) Yasu, Y.; Koike, T.; Akita, M. *Chem. Commun.* **2013**, *49*, 2037. (d) Pair, E.; Monteiro, N.; Bouyssi, D.; Baudoin, O. *Angew. Chem., Int. Ed.* **2013**, *52*, 5346. (e) Liu, X.; Xiong, F.; Huang, X.; Xu, L.; Li, P.; Wu, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 6962. (f) Xu, C.; Liu, J.; Ming, W.; Liu, Y.; Liu, J.; Wang, M.; Liu, Q. *Chem.—Eur. J.* **2013**, *19*, 9104.