Organic LETTERS

Letter

pubs.acs.org/OrgLett

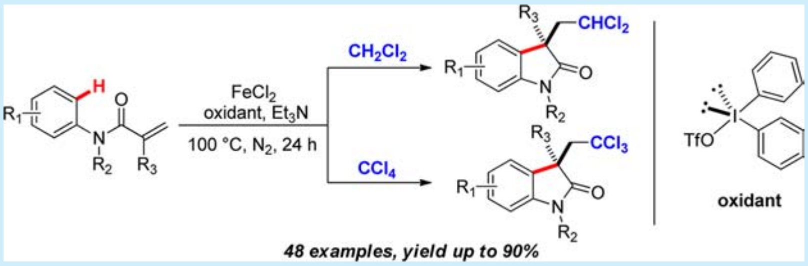
Iron-Catalyzed Cascade Carbochloromethylation of Activated Alkenes: Highly Efficient Access to Chloro-Containing Oxindoles

Ming-Zhu Lu[†] and Teck-Peng Loh*[,†,‡]

[†]Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei, 230026, China

[‡]Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

Supporting Information



ABSTRACT: An iron-catalyzed carbodi- and trichloromethylation of activated alkenes with readily available dichloro- and tetrachloromethane has been developed. A diaryliodonium salt is used as an efficient oxidant in this transformation. This reaction tolerates a variety of functional groups and allows for a highly efficient synthesis of various chloro-containing oxindoles.

More than 5000 natural products containing one or more carbon−halogen bonds have been discovered and isolated in past decades.[1] Hence, halogen-containing organic molecules are prevalent in natural sources.[2] Chlorinated natural products containing di- or trichloromethyl groups are an important subclass of these compounds that exhibit excellent biological activity (Figure 1). They include molecules such as dysithiazolamide,[3] sintokamide,[4] dysamide,[5] barbamide,[6] and muironolide.[7] The development of efficient methods for the introduction of di- or trichloromethyl functional groups into organic compounds is therefore of great importance and has attracted considerable attention. An elegant method for the halogenation of unactivated aliphatic carbon centers, catalyzed by novel halogenating enzymes, was reported by Walsh et al.[8] Recently, Zakarian et al. reported an efficient and stereoselective chloroalkylation reaction of *N*-acyl oxazolidinones by dual Ti−Ru catalysis.[9] Although these advances have been made in recent years, straightforward methods for the incorporation of chloroinated moieties are still lacking.[10] Therefore, pratical and efficient strategies are highly desirable in this field.

The oxindole motif is widely recognized as an important nitrogen-containing heterocycle found in many pharmaceuticals and biologically active compounds.[11] Over the past few years, oxidative intramolecular difunctionalization of alkenes has attracted the interest of synthetic chemists and has been efficiently applied to the synthesis of functionalized oxindoles.[12] In this context, considerable efforts have been focused on the direct oxidative C−H functionalization/cyclization of activated alkenes for construction of functionalized oxindoles. Liu et al. reported an impressive example of arylalkylation of *N*-aryl acrylamide derivatives with acetonitriles using a Pd catalyst.[13] Duan[14a] and Li[14b] independently established the Cu-catalyzed and Lewis acid facilitated 1,2-benzylarylation of activated alkenes with benzylic C_{sp3}−H bonds and aryl C_{sp2}−H bonds. In addition, Duan also demonstrated a metal-free cascade radical addition/cyclization reaction of activated alkenes with alcohols to deliver

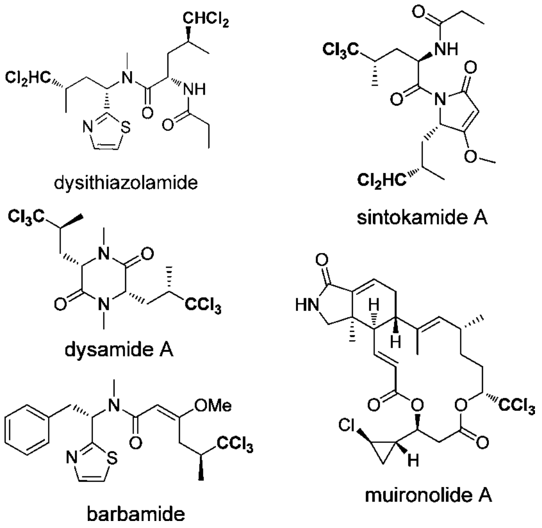


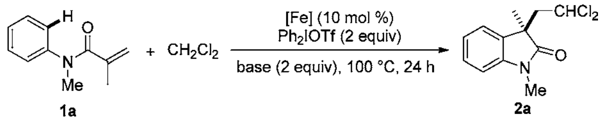
Figure 1. Important di- and trichloromethylated natural products.

Received: June 18, 2014
Published: September 9, 2014

hydroxyl-containing oxindoles.[14c] More recently, Li et al. reported an iron-catalyzed direct oxidative 1,2-alkylarylation of alkenes with a C_{sp3}–H bond adjacent to a heteroatom.[14d] However, a cascade carbodichloromethylation of alkenes to prepare more valuable chloro-containing oxindoles has never been reported and, thus, remains a major challenge. To solve this problem, we envisaged that dichloromethyl-containing oxindoles could be potentially accessed by direct addition of dichloromethyl radicals to *N*-arylacrylamides followed by cyclization and loss of a proton induced by electron transfer to an Fe(III) intermediate. We herein describe a new protocol for the environmentally benign iron-catalyzed cascade di- or trichloromethyl/cyclization of activated alkenes with CH_2Cl_2 and CCl_4 to construct chloro-containing oxindoles.

We commenced our investigation by using the readily available *N*-methyl-*N*-phenylmethacrylamide (**1a**) as the model substrate with CH_2Cl_2 in the presence of 10 mol % $FeCl_2$ as a catalyst, 2 equiv of $PhI(OAc)_2$ as an oxidant, and 2 equiv of triethylamine as a base at 100 °C to test our hypothesis. Gratifyingly, the desired dichloromethylated oxindole (**2a**) could be obtained in a modest 33% yield after 24 h (Table 1, entry 1). To our surprise, we were pleased to find that a significantly increased 80% yield was obtained when we used Ph_2IOTf instead of $PhI(OAc)_2$ as the oxidant (Table 1, entry 2). Diaryliodonium salts indeed have been extensively studied as a powerful arylation reagent catalyzed by Pd,[15a−c] Cu,[15d,e] Ru,[15f] and even *N*-heterocyclic carbene (NHC)[15g] catalysts. We herein demonstrate that diaryliodonium salts also can be employed as the oxidant for iron-catalyzed carbodichloromethylation of activated alkenes.[16] No reaction was observed in the absence of this iodonium salt (Table 1, entry 3). Among the bases screened, *i*-Pr_2NEt also delivered the corresponding product, albeit in 55% yield (Table 1, entry 7). Surprisingly, the use of 2 equiv of pyridine completely inhibited this reaction (Table 1, entry 8). It is noteworthy that iron(III) catalysts were also effective for this transformation, delivering the product in modest yield (Table 1, entries 9−11). $FeBr_2$ showed similar efficiency with a slight decrease in isolated yield (Table 1, entry 12). Lowering the temperature to 80 °C only gave the product in 42% yield (Table 1, entry 13). Finally, control experiments clearly demonstrated that either $FeCl_2$ or Et_3N alone failed to promote this kind of transformation (Table 1, entries 14−15).

Table 1. Optimization of Reaction Conditions[a]

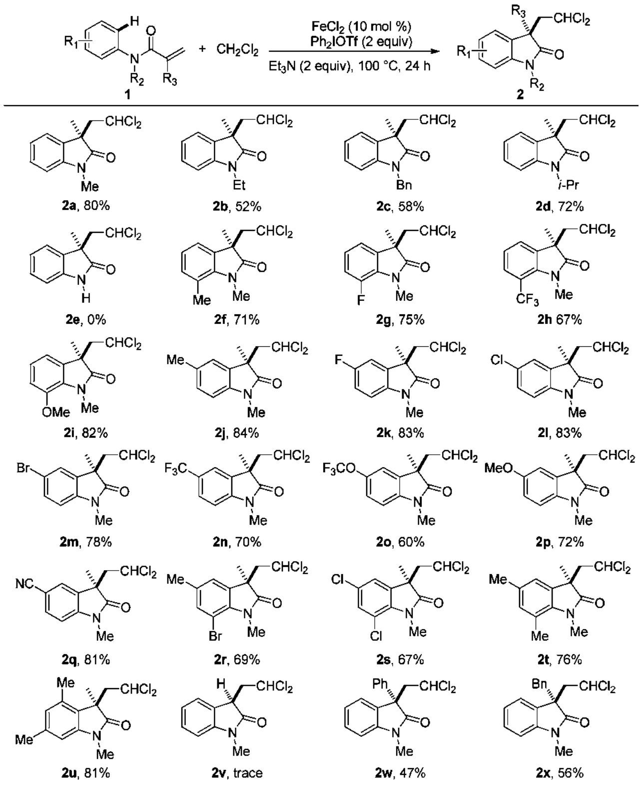


entry	[Fe]	base	temp (°C)	yield[b] (%)
1[c]	$FeCl_2$	Et_3N	100	33
2	$FeCl_2$	Et_3N	100	80
3[d]	$FeCl_2$	Et_3N	100	0
4	$FeCl_2$	DABCO	100	17
5	$FeCl_2$	DBU	100	44
6	$FeCl_2$	DMAP	100	14
7	$FeCl_2$	*i*-Pr_2NEt	100	55
8	$FeCl_2$	pyridine	100	0
9	$FeBr_3$	Et_3N	100	56
10	$FeCl_3$	Et_3N	100	52
11	$Fe(acac)_3$	Et_3N	100	56
12	$FeBr_2$	Et_3N	100	77
13	$FeCl_2$	Et_3N	80	42
14	$FeCl_2$		100	0
15		Et_3N	100	0

[a]Reaction conditions: **1a** (0.2 mmol), [Fe] (10 mol %), Ph_2IOTf (2 equiv), base (2 equiv), CH_2Cl_2 (2 mL), 24 h, under N_2. [b]Isolated yields. [c]2 equiv of $PhI(OAc)_2$ was used. [d]No Ph_2IOTf.

With the optimized conditions in hand (Table 1, entry 2), we next turned our attention to evaluate the scope of activated alkenes in this reaction. Various *N*-arylacrylamides were investigated as depicted in Scheme 1. Substrates with different *N*-protection groups showed that the electron-donating groups were appropriate for this reaction, providing the products in moderate yield (**2b**−**2d**). However, no product was obtained when a free *N*-H acrylamide was employed (**2e**). *N*-Arylacrylamides bearing both electron-donating and -withdrawing substituents at the *ortho*-position could successfully give the desired oxindoles (**2f**−**2i**) in good yields (67−82%). The reaction of various *para*-substituted *N*-arylacrylamides with CH_2Cl_2 also proceeded smoothly to furnish the corresponding products in good-to-excellent yield (**2j**−**2q**). It is worth noting that halogen atoms (F, Cl, and Br) were well tolerated under the typical conditions, enabling further functionalization of the corresponding dichloromethylated oxindoles at the halogenated positions by conventional cross-coupling reactions. Furthermore, substrates bearing two substituents on the aryl ring were also good for this reaction and provided the corresponding oxindoles (**2r**−**2u**) in good yield. However, the unsubstituted arylacrylamide was inefficient in this system (**2v**). Finally, the

Scheme 1. Iron-Catalyzed Carbodichloromethylation of Activated Alkenes[a]

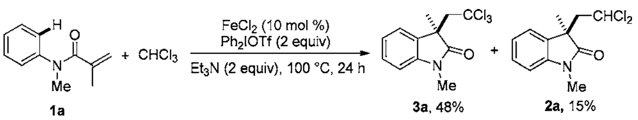


[a]Reaction conditions: **1a** (0.3 mmol), $FeCl_2$ (10 mol %), Ph_2IOTf (2 equiv), Et_3N (2 equiv), CH_2Cl_2 (3 mL), 24 h, under N_2.

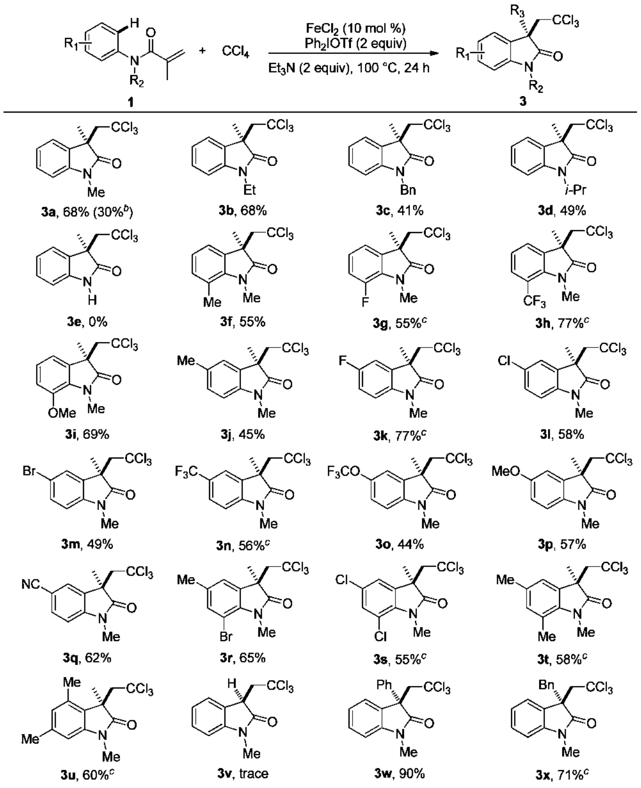
desired 3-phenyl and benzyl analogues (**2w** and **2x**) were obtained in modest yield.

Since we had demonstrated an efficient method of iron-catalyzed carbodichloromethylation of activated alkenes to prepare valuable dichloromethylated oxindoles, it was reasonable to expect that trichloromethylated oxindoles might be simply accessed if we used chloroform ($CHCl_3$) instead of dichloromethane as the solvent. The experiments were next conducted in chloroform under the forementioned conditions. As expected, the trichloromethylated oxindole (**3a**) was isolated in 48% yield (Scheme 2). Much to our surprise, the dichloromethylated product (**2a**) was also obtained in 15% yield with similar polarity to **3a**. Obviously, a C−Cl bond was being cleaved in the formation of **2a** by this process. Inspired by this result, we reasoned that a trichloromethylation reaction may be possible if a C−Cl bond from readily available tetrachloromethane (CCl_4) could be efficiently cleaved in the reaction, exclusively giving the single product **3a**. Encouragingly, we found that a good yield (68%) could be obtained when we used CCl_4 as the solvent under the standard conditions (Scheme 3). This yield dramatically dropped to 30% when the iodonium oxidant was removed from the reaction system. Similar to the results summarized in Scheme 1, substrates bearing electron-donating groups on the N-atom were also good for this reaction (**3b**−**3d**). Again, unsubstituted *N*-arylacrylamide did not give the product under the conditions. Various substituted *N*-arylacrylamides proceeded smoothly and delivered the corresponding trichloromethylated oxindoles in moderate-to-good yield regardless of electron-donating or -withdrawing substituents on the *ortho*-position or *para*-position (**3f**−**3q**). Multisubstituted arylacrylamides were also efficient under the optimized conditions and afforded the oxindoles in modest yields (55−65%). Finally, α-substituted arylacrylamides, such as phenyl (**3w**) and benzyl (**3x**), reacted well in this process and delivered the products in 90% and 71% yields, respectively.

Scheme 2. Iron-Catalyzed Chloromethylation of 1a with Chloroform



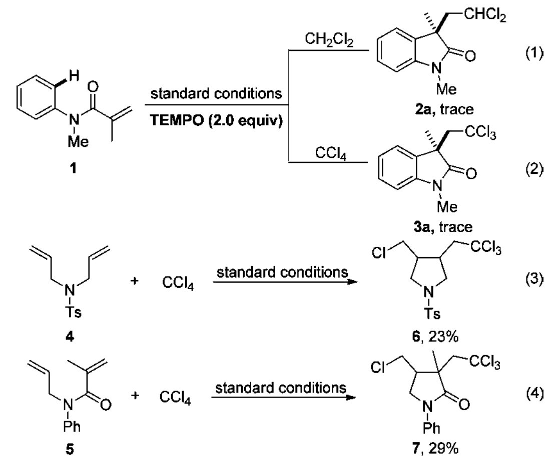
Scheme 3. Iron-Catalyzed Carbotrichloromethylation of Activated Alkenes[a]



[a]Reaction conditions: **1a** (0.3 mmol), $FeCl_2$ (10 mol %), Ph_2IOTf (2 equiv), Et_3N (2 equiv), CCl_4 (3 mL), under N_2 for 24 h. [b]No oxidant. [c]At 120 °C.

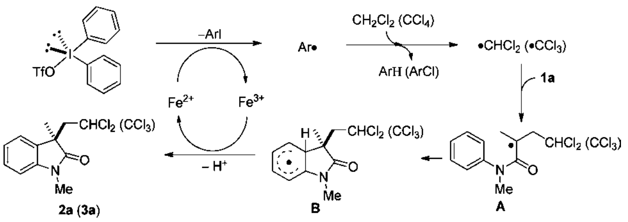
To gain insights into the mechanism of this process, several radical-trapping experiments were carried out. First, when the reactions were conducted in the presence of 2.0 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as the radical scavenger, only trace amounts of the desired products were detected (eqs 1−2, Scheme 4). Moreover, when the 1,6-diene substrates **4** and **5** were used, the cyclization products **6** and **7** were obtained in 23 and 29% yields, respectively (eqs 3−4, Scheme 4).[17] All these results reveal that di- or trichloromethyl radicals are probably involved in this process.

Scheme 4. Radical Trapping Experiments



While the detailed reaction mechanism of this transformation is not yet known, a plausible mechanism is proposed on the basis of these results and previous studies (Scheme 5). This process is likely to be initiated by generation of the aryl radical from the diaryliodonium salt by the iron catalyst.[18] Subsequently, selective hydrogen-atom abstraction from CH_2Cl_2 or chlorine-atom abstraction from CCl_4 by the aryl radical generates the corresponding dichloromethyl radical (·$CHCl_2$) or trichloro-

Scheme 5. Proposed Reaction Mechanism



methyl radical ($\cdot CCl_3$), followed by addition to the C═C bond of *N*-methyl-*N*-phenylmethacrylamide (**1a**) affording the radical intermediate **A**. Then, intramolecular cyclization of intermediate **A** with the aromatic ring results in the formation of aryl radical intermediate **B**. Finally, single-electron transfer (SET) from the Fe(III) intermediate to intermediate **B** and further proton abstraction with the assistance of base provide the corresponding dichloromethylated oxindole **2a** or trichloromethylated oxindole **3a**.

In summary, we have developed an efficient iron-catalyzed di- and trichloromethylation of activated alkenes using the iodonium salt as the oxidant. Readily available CH_2Cl_2 and CCl_4 are employed as the chloromethyl sources, and various chloro-containing oxindoles are prepared in good-to-excellent yield. This protocol tolerates a wide range of functional groups and could see broad synthetic appeal for the preparation of bioactive chloro-containing oxindoles.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectral data for all new compounds (^1H NMR, ^{13}C NMR, HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: teckpeng@ntu.edu.sg.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the financial support from the National Natural Science Foundation of China (No. 21372210) and the Singapore Ministry of Education Academic Research Fund (MOE 2011-T2-1-013, ETRP 1002 111, and MOE2010-T2-2-067) for the funding of this research. The authors are grateful to Professor Roderick Bates of Nanyang Technological University for his careful proofreading of this manuscript.

■ REFERENCES

(1) Gribble, G. W. *Heterocycles* **2012**, *84*, 157.

(2) (a) Gribble, G. W. *Acc. Chem. Res.* **1998**, *31*, 141. (b) Kahne, D.; Leimkuhler, C.; Lu, W.; Walsh, C. *Chem. Rev.* **2005**, *105*, 425. (c) Vaillancourt, F. H.; Yeh, E.; Vosburg, D. A.; Garneau-Tsodikova, S.; Walsh, C. T. *Chem. Rev.* **2006**, *106*, 3364. (d) Paul, C.; Pohnert, G. *Nat. Prod. Rep.* **2011**, *28*, 186.

(3) (a) Ardá, A.; Rodríguez, J.; Nieto, M. I.; Bassarello, C.; Gomez-Paloma, L.; Bifulco, G.; Jiménez, C. *Tetrahedron* **2005**, *61*, 10093. (b) Ardá, A.; Soengas, R. G.; Nieto, M. I.; Jiménez, C.; Rodríguez, J. *Org. Lett.* **2008**, *10*, 2175.

(4) (a) Sadar, M. D.; Williams, D. E.; Mawji, N. R.; Patrick, B. O.; Wikanta, T.; Chasanah, E.; Irianto, H. E.; Soest, R. V.; Andersen, R. J. *Org. Lett.* **2008**, *10*, 4947. (b) Gu, Z. H.; Zakarian, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 9702.

(5) Durow, A. C.; Long, G. C.; O'Connell, S. J.; Willis, C. L. *Org. Lett.* **2006**, *8*, 5401.

(6) (a) Nguyen, V.-A.; Willis, C. L.; Gerwick, W. H. *Chem. Commun.* **2001**, 1934. (b) Orjala, J.; Gerwick, W. H. *J. Nat. Prod.* **1996**, *59*, 427. (c) Sitachitta, N.; Rossi, J.; Roberts, M. A.; Gerwick, W. H.; Fletcher, M. D.; Willis, C. L. *J. Am. Chem. Soc.* **1998**, *120*, 7131.

(7) (a) Flores, B.; Molinski, T. F. *Org. Lett.* **2011**, *13*, 3932. (b) Xiao, Q.; Young, K.; Zakarian, A. *Org. Lett.* **2013**, *15*, 3314.

(8) (a) Vaillancourt, F. H.; Yeh, E.; Vosburg, D. A.; O'Connor, S. E.; Walsh, C. T. *Nature* **2005**, *436*, 1191. (b) Vaillancourt, F. H.; Yin, J.; Walsh, C. T. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 10111. (c) Galonić, D. P.; Vaillancourt, F. H.; Walsh, C. T. *J. Am. Chem. Soc.* **2006**, *128*, 3900.

(9) (a) Beaumont, S.; Ilardi, E. A.; Monroe, L. R.; Zakarian, A. *J. Am. Chem. Soc.* **2010**, *132*, 1482. (b) Gu, Z. H.; Herrmann, A. T.; Zakarian, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 7136.

(10) (a) Li, Y.; Cao, Y. L.; Gu, J. Y.; Wang, W.; Wang, H.; Zheng, T.; Sun, Z. H. *Eur. J. Org. Chem.* **2011**, 676. (b) Li, D. S.; Li, Y.; Chen, Z. Q.; Shang, H. Q.; Li, H. S.; Ren, X. F. *RSC Adv.* **2014**, *4*, 14254.

(11) For selected reviews on oxindoles: (a) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (b) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (c) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381. (d) Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *132*, 6104. (e) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003.

(12) (a) Wu, T.; Zhang, H.; Liu, G. S. *Tetrahedron* **2012**, *68*, 5229. (b) Xie, J.; Xu, P.; Li, H. M.; Xue, Q. C.; Jin, H. M.; Cheng, Y. X.; Zhu, C. J. *Chem. Commun.* **2013**, *49*, 5672. (c) Li, Z. J.; Zhang, Y.; Zhang, L. Z.; Liu, Z.-Q. *Org. Lett.* **2014**, *16*, 382. (d) Dai, Q.; Yu, J. T.; Jiang, Y.; Guo, S. J.; Yang, H. T.; Cheng, J. *Chem. Commun.* **2014**, *50*, 3865. (e) Fu, W. J.; Xu, F. J.; Fu, Y. Q.; Zhu, M.; Yu, J. Q.; Xu, C.; Zou, D. P. *J. Org. Chem.* **2013**, *78*, 12202. (f) Zhou, B.; Hou, W.; Yang, Y. X.; Feng, H. J.; Li, Y. C. *Org. Lett.* **2014**, *16*, 1322. (g) Li, Y.-M.; Wei, X.-H.; Li, X.-A.; Yang, S.-D. *Chem. Commun.* **2013**, *49*, 11701. (h) Shen, T.; Yuan, Y. Z.; Jiao, N. *Chem. Commun.* **2014**, *50*, 554. (i) Yuan, Y. Z.; Shen, T.; Wang, K.; Jiao, N. *Chem.—Asian J.* **2013**, *8*, 2932. (j) Wei, X.-H.; Li, Y.-M.; Zhou, A.-X.; Yang, T.-T.; Yang, S.-D. *Org. Lett.* **2013**, *15*, 4158. (k) Matcha, K.; Narayan, R.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2013**, *52*, 7985. (l) Mu, X.; Wu, T.; Yang, H.-Y.; Guo, Y.-L.; Liu, G. S. *J. Am. Chem. Soc.* **2012**, *134*, 878. (m) Xu, P.; Xie, J.; Xue, Q. C.; Pan, C. D.; Cheng, Y. X.; Zhu, C. J. *Chem.—Eur. J.* **2013**, *19*, 14039. (n) Lu, Q. Q.; Liu, C.; Peng, P.; Liu, Z. L.; Fu, L. J.; Huang, J. G.; Lei, A. W. *Asia J. Org. Chem.* **2014**, *3*, 273. (o) Yang, F.; Klumphu, P.; Liang, Y.-M.; Lipshutz, B. H. *Chem. Commun.* **2014**, *50*, 936. (p) Kong, W. Q.; Casimiro, M.; Fuentes, N.; Merino, E.; Nevado, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 13086. (q) Wang, J.-Y.; Su, Y.-M.; Yin, F.; Bao, Y.; Zhang, X.; Xu, Y.-M.; Wang, X.-S. *Chem. Commun.* **2014**, *50*, 4108.

(13) Wu, T.; Mu, X.; Liu, G. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 12578.

(14) (a) Zhou, S.-L.; Guo, L.-N.; Wang, H.; Duan, X.-H. *Chem.—Eur. J.* **2013**, *19*, 12970. (b) Zhou, M.-B.; Wang, C.-Y.; Song, R.-J.; Liu, Y.; Wei, W.-T.; Li, J.-H. *Chem. Commun.* **2013**, *49*, 10817. (c) Meng, Y.; Guo, L.-N.; Wang, H.; Duan, X.-H. *Chem. Commun.* **2013**, *49*, 7540. (d) Wei, W.-T.; Zhou, M.-B.; Fan, J.-H.; Liu, W.; Song, R.-J.; Liu, Y.; Hu, M.; Xie, P.; Li, J.-H. *Angew. Chem., Int. Ed.* **2013**, *52*, 3638.

(15) For selected examples, see: (a) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (b) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972. (c) Xiao, B.; Fu, Y.; Xun, J.; Gong, T.-J.; Dai, J.-J.; Yi, J.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 486. (d) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. (e) Duong, H. A.; Gilligan, R. E.; Cooke, M. L.; Phipps, R. J.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 463. (f) Ho, J. S.; Castro, L. C. M.; Aihara, Y.; Tobisu, M.; Chatani, N. *Asia J. Org. Chem.* **2014**, *3*, 48. (g) Toh, Q. Y.; McNally, A.; Vera, S.; Erdmann, N.; Gaunt, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 3772.

(16) The Li group reported the diarylation of alkenes using diaryliodonium triflates as arylation reagents; see ref 12f.

(17) The cyclization of 1,6-dienes with alkylchlorides by a photoredox catalyst was reported very recently; see: Liu, Y.; Zhang, J.-L.; Song, R.-J.; Li, J.-H. *Eur. J. Org. Chem.* **2014**, 1177.

(18) For selected examples of aryl radicals generated from diaryliodonium salts by photoredox catalysts, see: (a) Neufeldt, S. R.; Sanford, M. S. *Adv. Synth. Catal.* **2012**, *354*, 3517. (b) Fumagalli, G.; Boyd, S.; Greaney, M. F. *Org. Lett.* **2013**, *15*, 4398.