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Silver-Catalyzed Decarboxylative Alkynylation of Aliphatic Carboxylic Acids in Aqueous Solution

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Supporting Information

ABSTRACT: C(sp^3)−C(sp) bond formations are of immense interest in chemistry and material sciences. We report herein a convenient, radical-mediated and catalytic method for C(sp^3)−C(sp) cross-coupling. Thus, with $AgNO_3$ as the catalyst and $K_2S_2O_8$ as the oxidant, various aliphatic carboxylic acids underwent decarboxylative alkynylation with commercially available ethynylbenziodoxolones in aqueous solution under mild conditions. This site-specific alkynylation is not only general and efficient but also functional group compatible. In addition, it exhibits remarkable chemo- and stereoselectivity.

Alkynes are not only important tools and structural elements in material sciences and chemical biology but also versatile building blocks in organic synthesis.[1] The introduction of an alkynyl group into a molecule, in particular C-alkynylation, has thus drawn considerable attention. Enormous progress has been achieved in the Sonogashira reaction, which provides a convenient entry to C(sp^2)−C(sp) bond formations.[2] Significant efforts have also been made in C(sp^3)−C(sp) coupling reactions in the past decade. Fu et al. first extended the Sonogashira reaction to the use of primary alkyl halides as the electrophiles.[3] A number of transition-metal-catalyzed cross-coupling reactions were later developed for the C(sp^3)−C(sp) bond formation.[4−6] Nevertheless, these methods are mainly restricted to primary or secondary alkyl−alkynyl cross coupling while the tertiary alkyl−alkynyl coupling remains a difficult task. More recently, electrophilic C(sp^3)-alkynylation[7] with the use of ethynylbenziodoxolones was reported by Waser et al.[8] and found an immediate application in the total synthesis of drimane-type sesquiterpenoids by Yang and co-workers.[9] However, this method requires the use of active methylene compounds as nucleophiles. The development of more general and efficient methods for C(sp^3)−C(sp) bond formation is thus of great importance.

Compared to nucleophilic or electrophilic alkynylation, radical alkynylation reactions have received much less attention (Figure 1). Russell et al. first studied the radical alkynylation reactions of alkylmercury halides with various alkynes.[10] Fuchs et al. successfully developed the metal-free radical alkynylation of C−H bonds via reaction with acetylenic triflones.[11] This method was then extended to the chemospecific alkynylation of alkyl iodides.[12] Renaud and co-workers nicely introduced the alkynylation of *B*-alkylcatecholboranes with alkynyl sulfones, thus allowing the hydroalkynylation of alkenes to proceed in a one-pot procedure with the use of catecholborane.[13] Landais et al. extended this method to radical carboalkynylation of olefins.[14] Nevertheless, these radical methods rely heavily on the use of alkynyl sulfones as alkynylating agents.[15] In view of the excellent functional group compatibility and mild reaction conditions for radical reactions, it is highly desirable to develop new radical strategies for more convenient and efficient C(sp^3)−C(sp) bond formations. Herein we report the silver-catalyzed decarboxylative alkynylation of aliphatic carboxylic acids with ethynylbenziodoxolones in aqueous solution.

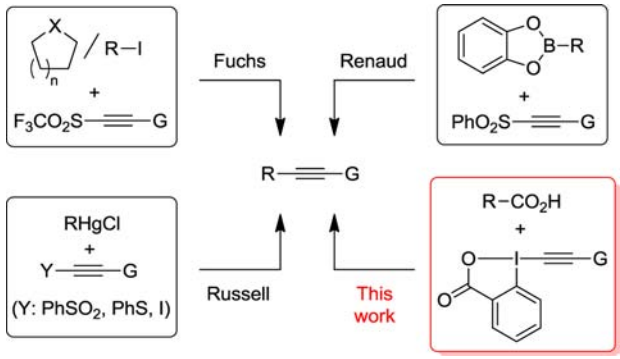

Figure 1. Overview of radical C-alkynylation reactions.

The ready availability, high stability, and low cost of carboxylic acids make them extremely promising raw materials for chemical synthesis.[16] We recently reported the silver-catalyzed oxidative decarboxylative chlorination and fluorination of aliphatic carboxylic acids.[17] We were then interested in whether the alkyl radical generated by oxidative decarboxylation could be efficiently trapped by a suitable alkynylating agent. Thus, with $K_2S_2O_8$ (1 equiv) as the oxidant and $AgNO_3$ (10 mol %) as the catalyst,[18] the reactions of adamantane-1-carboxylic acid (**A-1**) with a number of alkynylating agents were tested (Scheme 1). The reactions with phenylacetylene, phenylethynyl bromide, or phenyl phenylethynyl sulfone in various solvents gave either no or a very low yield (<5%) of the expected alkynylation product **1**, the major products being adamantane or adamantan-1-ol. We then turned to electrophilic alkynylating agents for help. The use of phenylethynyl phenyliodonium triflate did not show any improvement. However to our delight, when phenylethynylbenziodoxolone (**I-1**)[19] was employed, the reaction with **A-1** in aqueous DMF

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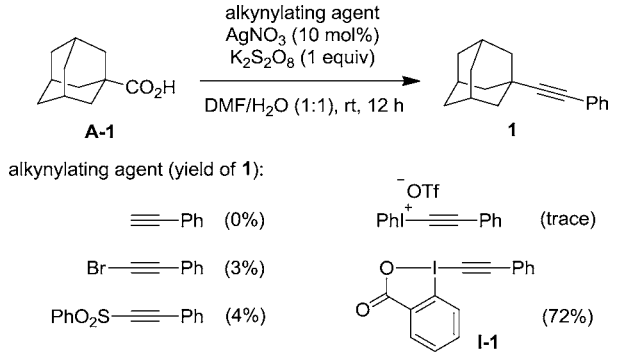
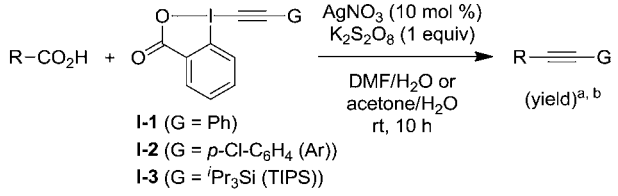
Scheme 1. Decarboxylative Phenylethynylation of Adamantane-1-carboxylic Acid

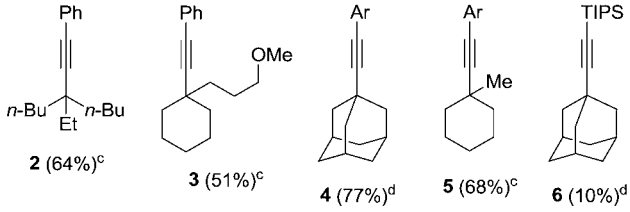


(or acetone) solution proceeded smoothly at room temperature, furnishing the expected alkyne **1** in 72% yield. In addition, 2-iodobenzoic acid was also isolated in >70% yield. Since 2-iodobenzoic acid serves as the starting material for the preparation of the benziodoxolone,[19] this catalytic alkynylation method is thus highly sustainable. To the best of our knowledge, this is the first example of alkynyliodine(III) compounds serving as radical acceptors.[20]

The above alkynylation reaction with **I-1** was then extended to other tertiary alkyl carboxylic acids without further optimization. As shown in Scheme 2, tertiary alkyl–phenyl-

Scheme 2. Decarboxylative Alkynylation of Tertiary Alkyl Acids in Aqueous Solution



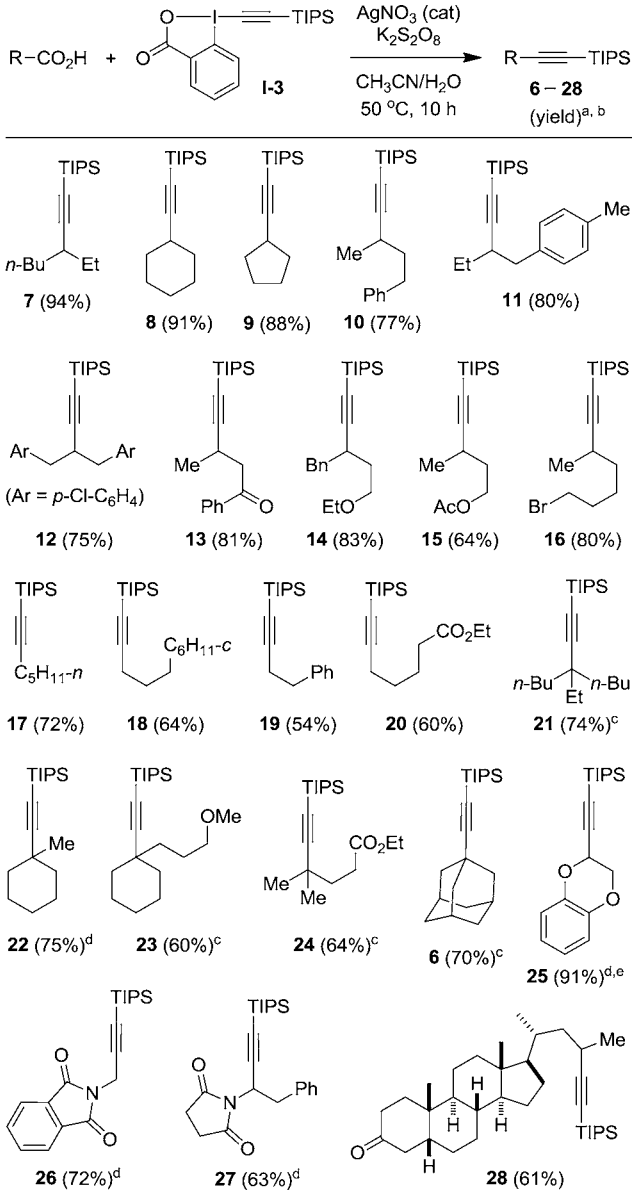


[a]Reaction conditions: acid (0.3 mmol), $AgNO_3$ (0.03 mmol), $K_2S_2O_8$ (0.3 mmol), alkynylating agent (0.45 mmol), DMF or acetone (3 mL), H_2O (3 mL), rt, 10 h. [b]Isolated yield based on the starting acid. [c]Solvent: acetone/H_2O. [d]Solvent: DMF/H_2O.

ethynyl coupling products **2** and **3** were achieved in good yields in acetone/water solution. *p*-Chlorophenylethynylbenziodoxolone (**I-2**) exhibited the reactivity similar to **I-1**, as evidenced by the synthesis of **4** and **5**. On the other hand, triisopropylsilyl (TIPS)-substituted ethynylbenziodoxolone **I-3** afforded the expected product **6** in only 10% yield.

The low product yield in the reaction of **I-3** indicated above urged us to optimize the experimental conditions. Our extensive study using 2-ethylhexanoic acid as the model substrate revealed that, in the presence of $AgNO_3$ (30 mol %) and $K_2S_2O_8$ (3 equiv), the reaction of **I-3** with 2-ethylhexanoic acid in CH_3CN/H_2O (1:1, v:v) solution at 50 °C for 10 h led to the clean formation of the expected alkyne product **7** in 94% isolated yield. The control experiments indicated that both $AgNO_3$ and $K_2S_2O_8$ were essential for the decarboxylation. Other Ag(I) salts such as $AgBF_4$ and AgOTf exhibited behavior similar to that of $AgNO_3$. Various aliphatic carboxylic acids were then tested under the optimized conditions, and the results are summarized in Scheme 3. The

Scheme 3. Silver-Catalyzed Decarboxylative Alkynylation of Aliphatic Acids in CH_3CN/H_2O



[a]Reaction conditions: carboxylic acid (0.3 mmol), $AgNO_3$ (0.09 mmol), **I-3** (0.45 mmol), $K_2S_2O_8$ (0.9 mmol), CH_3CN (3 mL), H_2O (3 mL), 50 °C, 10 h. [b]Isolated yield based on the corresponding carboxylic acid. [c]20 mol % $AgNO_3$ was used. [d]10 mol % $AgNO_3$ was used. [e]Reaction time: 1 h.

decarboxylative alkynylation proceeded smoothly for all the primary, secondary, and tertiary alkyl acids, and the corresponding products **6**–**24** were achieved in good to excellent yields. For tertiary alkyl acids and α-heteroatom-substituted alkyl acids, the amount of the catalyst $AgNO_3$ could be reduced to 10 or 20 mol %. Note that alkyne **6** was now

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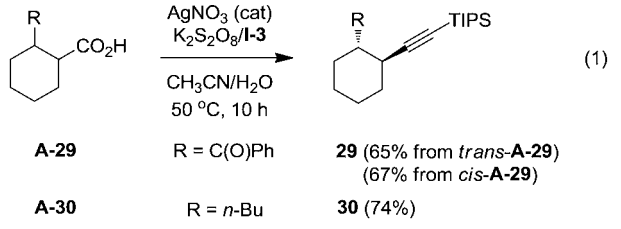
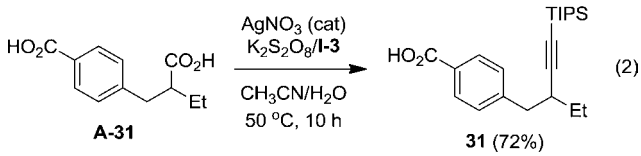
obtained in 70% yield. The catalytic processes enjoy the tolerance of a variety of functional groups, including amide, ester, carbonyl, halide, ether, aryl, etc., which encourages their application to more complexed organic molecules. For example, alkyne **28** was obtained in 61% yield as a 1:2 mixture of two diastereoisomers from the corresponding dehydrolithocholic acid derivative. It is interesting to note that this reaction was in fact diastereoselective. To explore the stereoselectivity of alkynylation, acid **A-29** was employed as the probe. Indeed, both *trans*-**A-29** and *cis*-**A-29** led to the exclusive formation of *trans*-substituted product **29** (eq 1). Similarly, acid **A-30** as the mixture of two stereoisomers yielded the *trans*-configured product **30** only (eq 1). Nevertheless, racemic product **27** was obtained from the reaction of optically pure N-protected (*S*)-phenylalanine.

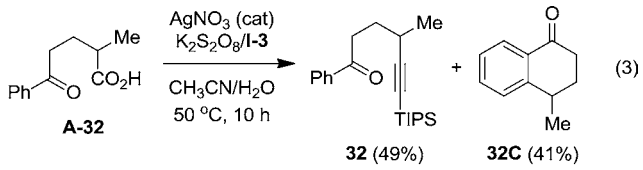


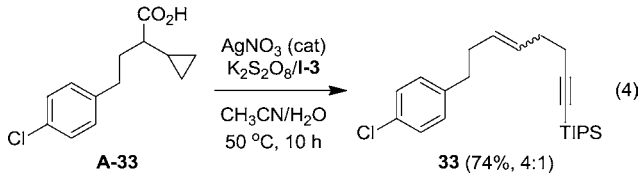


Unlike aliphatic acids, aromatic acids such as 4-chlorobenzoic acid or 2-nitrobenzoic acid failed to give any desired products under the above experimental conditions, while all the starting acids were recovered. This allows the successful implementation of chemoselective alkynylation. As illustrated in eq 2, the alkylic carboxyl group in diacid **A-31** was selectively removed to provide alkyne **31** while the benzoic carboxyl group remained intact.

The above results have clearly demonstrated the generality of decarboxylative alkynylation. Moreover, the TIPS group in the products (such as **13** and **25**) can be easily removed by treatment with tetrabutylammonium fluoride to give the terminal alkynes (see the Supporting Information), which can be utilized for further transformations such as the Sonogashira cross-coupling.

The radical mechanism can also be inferred from the above experiments. A more direct evidence was the reaction of acid **A-32** in which the alkynylation product **32** (49%) was accompanied by the cyclization product **32C** (41%), as indicated in eq 3. To provide solid evidence on the radical mechanism, cyclopropylacetic acid **A-33** was designed as the radical probe.[21] The reaction of **A-33** with **I-3** under the optimized conditions gave the ring-opening product **33** in 74% yield as a 4:1 mixture of two stereoisomers determined by HPLC (eq 4). These two experiments strongly support the involvement of free radical mechanism in the decarboxylative alkynylation.





On the basis of the above results, a plausible mechanism was proposed for the catalytic decarboxylative alkynylation (Figure 2). Oxidation of Ag(I) by persulfate generates the Ag(II)

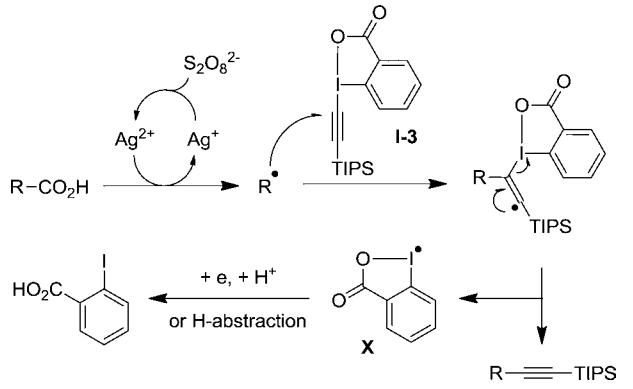
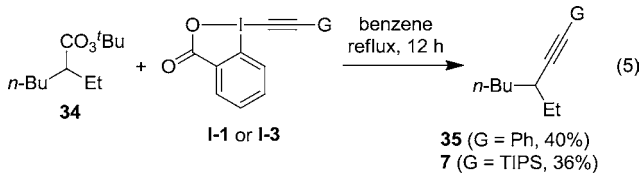


Figure 2. Proposed mechanism of decarboxylative alkynylation.

intermediate, which then undergoes single electron transfer with a carboxylate to produce the carboxyl radical.[18] Fast decarboxylation of the carboxyl radical gives the corresponding alkyl radical. Addition of the alkyl radical to the triple bond of **I-3** followed by subsequent β-elimination of the adduct radical affords the final product alkyne along with the formation of benziodoxolonyl radical (**X**). 2-Iodobenzoic acid is then produced from the benziodoxolonyl radical via either H-abstraction or reduction–protonation sequence.

To provide further evidence on the above mechanism, *tert*-butyl 2-ethylhexaneperoxoate (**34**) was used as the alkyl radical precursor (via O–O bond cleavage followed by decarboxylation).[17b] The reactions of **34** with **I-1** or **I-3** in refluxing benzene for 12 h afforded the corresponding alkynylation product **35** or **7** in around 40% yield (eq 5). This result



supports our hypothesis in Figure 2, i.e., once the alkyl radical is generated, $Ag^{+}/S_2O_8^{2-}$ is unlikely to be involved in the subsequent processes. Further mechanistic investigations are certainly required to understand the interaction of alkyl radicals with ethynylbenziodoxolones.

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In conclusion, we have developed the decarboxylative alkynylation of aliphatic carboxylic acids in aqueous solution with $AgNO_3$ as the catalyst and the commercially available ethynylbenziodoxolones as alkynylating agents. This radical-mediated C(sp^3)−C(sp) cross-coupling is not only efficient and general but also functional group compatible. In addition, it also exhibits remarkable chemo- and stereoselectivity. In view of the mild experimental conditions and ready availability of both substrates and reagents, this convenient and site-specific alkynylation method should find practical applications in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details, characterization of new compounds, and ^1H and ^{13}C NMR spectra. 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.

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■ REFERENCES

(1) Diederich, F.; Stang, P. J.; Tykwinski, R. R. *Acetylene Chemistry: Chemistry, Biology and Material Science*; Wiley-VCH: Weinheim, 2005.

(2) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874.

(3) Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642.

(4) (a) Altenhoff, G.; Würtz, S.; Glorius, F. *Tetrahedron Lett.* **2006**, *47*, 2925. (b) Vechorkin, O.; Barmaz, D.; Proust, V.; Hu, X. *J. Am. Chem. Soc.* **2009**, *131*, 12078.

(5) (a) Yang, L.-M.; Huang, L.-F.; Luh, T.-Y. *Org. Lett.* **2004**, *6*, 1461. (b) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2006**, *8*, 3093. (c) Zhao, Y.; Wang, H.; Hou, X.; Hu, Y.; Lei, A.; Zhang, H.; Zhu, L. *J. Am. Chem. Soc.* **2006**, *128*, 15048. (d) Nicolai, S.; Erard, S.; González, D. F.; Waser, J. *Org. Lett.* **2010**, *12*, 384. (e) Cahiez, G.; Gager, O.; Buendia, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 1278. (f) Chen, M.; Zheng, X.; Li, W.; He, J.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 4101. (g) Nicolai, S.; Piemontesi, C.; Waser, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 4680. (h) Vechorkin, O.; Godinat, A.; Scopelliti, R.; Hu, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 11777. (i) Hatakeyama, T.; Okada, Y.; Yoshimoto, Y.; Nakamura, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 10973. (j) Ye, F.; Ma, X; Xiao, Q.; Li, H.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2012**, *134*, 5742.

(6) (a) Rayabarapu, D. K.; Tunge, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13510. (b) Bi, H.-P.; Zhao, L.; Liang, Y.-M.; Li, C.-J. *Angew. Chem., Int. Ed.* **2009**, *48*, 792. (c) Zhang, W.-W.; Zhang, X.-G.; Li, J.-H. *J. Org. Chem.* **2010**, *75*, 5259.

(7) Brand, J. P.; Waser, J. *Chem. Soc. Rev.* **2012**, *41*, 4165.

(8) González, D. F.; Brand, J. P.; Waser, J. *Chem. −Eur. J.* **2010**, *16*, 9457.

(9) Shi, H.; Fang, L.; Tan, C.; Shi, L.; Zhang, W.; Li, C.-c.; Luo, T.; Yang, Z. *J. Am. Chem. Soc.* **2011**, *133*, 14944.

(10) (a) Russell, G. A.; Ngoviwatchai, P. *Tetrahedron Lett.* **1986**, *27*, 3479. (b) Russell, G. A.; Ngoviwatchai, P.; Tashtoush, H. I.; Pla-Dalmau, A.; Khanna, R. K. *J. Am. Chem. Soc.* **1988**, *110*, 3530. (c) Russell, G. A.; Ngoviwatchai, P. *J. Org. Chem.* **1989**, *54*, 1836.

(11) (a) Gong, J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1996**, *118*, 4486. (b) Xiang, J.; Jiang, W.; Fuchs, P. L. *Tetrahedron Lett.* **1997**, *38*, 6635.

(12) Xiang, J.; Fuchs, P. L. *Tetrahedron Lett.* **1998**, *39*, 8597.

(13) Schaffner, A.-P.; Darmency, V.; Renaud, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 5847.

(14) Liautard, V.; Robert, F.; Landais, Y. *Org. Lett.* **2011**, *13*, 2658.

(15) Copper- or silver-catalyzed oxidative C(sp^3)−H alkynylation with alkynes was reported by Li et al. The mechanism is likely the oxidation of radical intermediates followed by nucleophilic alkynylation. See: (a) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810. (b) Correia, C. A.; Li, C.-J. *Heterocycles* **2010**, *82*, 555.

(16) Gooßen, L. J.; Rodríguez, N.; Gooßen, K. *Angew Chem., Int. Ed.* **2008**, *47*, 3100.

(17) (a) Wang, Z.; Zhu, L.; Yin, F.; Su, Z.; Li, Z.; Li, C. *J. Am. Chem. Soc.* **2012**, *134*, 4258. (b) Yin, F.; Wang, Z.; Li, Z.; Li, C. *J. Am. Chem. Soc.* **2012**, *134*, 10401.

(18) (a) Anderson, J. M.; Kochi, J. K. *J. Am. Chem. Soc.* **1970**, *92*, 1651. (b) Anderson, J. M.; Kochi, J. K. *J. Org. Chem.* **1970**, *35*, 986.

(19) Zhdankin, V. V.; Kuehl, C. J.; Krasutsky, A. P.; Bolz, J. T.; Simonsen, A. J. *J. Org. Chem.* **1996**, *61*, 6547.

(20) For selected reviews on the chemistry of hypervalent iodine compounds, see: (a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123. (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (c) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299.

(21) Newcomb, M. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. *1*, pp 317−336.