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

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Supporting Information

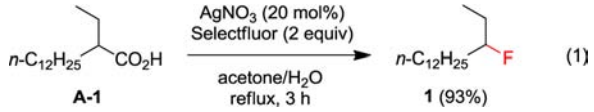
ABSTRACT: Although fluorinated compounds have found widespread applications in the chemical and materials industries, general and site-specific C(sp^3)−F bond formations are still a challenging task. We report here that with the catalysis of $AgNO_3$, various aliphatic carboxylic acids undergo efficient decarboxylative fluorination with SELECTFLUOR® reagent in aqueous solution, leading to the synthesis of the corresponding alkyl fluorides in satisfactory yields under mild conditions. This radical fluorination method is not only efficient and general but also chemoselective and functional-group-compatible, thus making it highly practical in the synthesis of fluorinated molecules. A mechanism involvinig Ag(III)-mediated single electron transfer followed by fluorine atom transfer is proposed for this catalytic fluorodecarboxylation.

The introduction of fluorine atoms into organic molecules significantly changes their physical, chemical, and biological properties, and thus, fluorinated compounds have found widespread applications in almost all aspects of the chemical industry ranging from materials to agrochemicals and pharmaceuticals.[1] Moreover, ^{18}F-labeled organic compounds are clinically used as contrast agents for positron emission tomography.[2] However, despite fluorine's importance, C−F bond formation, especially site-specific monofluorination of complex molecules, is still challenging.[3,4] In particular, methods for the general and site-specific formation of C(sp^3)−F bonds are limited, contrast to the recent significant progress in the formation of aromatic C(sp^2)−F bonds[4,5] led by the Buchwald group[5a] and the Ritter group.[5b,c]

Alkyl fluorides are mainly accessed by either nucleophilic or electrophilic substitution reactions. However, the weak nucleophilicity of fluoride ions limits access to C−F bonds via direct nucleophilic substitution reactions.[6] The conversion of alkyl alcohols to alkyl fluorides using (diethylamino)sulfur trifluoride (DAST) or [bis(2-methoxyethyl)amino]sulfur trifluoride (Deoxo-Fluor® reagent) is a common method for site-specific monofluorination, but it often suffers from the competing dehydration and rearrangement processes.[7,8] The C(sp^3)−F reductive elimination from alkylgold(III) fluoride complexes also proceeds via carbocation-like rearrangements, as reported by Mankad and Toste.[9] Electrophilic fluorination using fluorine reagents such as 1-chloromethyl-4-fluorodiazoniabicyclo[2.2.2]-octane bis(tetrafluoroborate) (SELECTFLUOR® reagent, Air Products and Chemicals, Inc.)[10] or *N*-fluorobis-(benzenesulfonyl)imide (NFSI) provides a convenient entry to site-selective monofluorination and can be highly enantioselective under transition-metal catalysis or organocatalysis.[11,12] Nevertheless, the method is mainly restricted to the synthesis of α-fluoro carbonyl compounds. The development of more general and practical methods for site-specific C(sp^3)−F bond formation is certainly highly desirable.

In comparison with nucleophilic or electrophilic fluorination, radical fluorination is far less explored. Not only its synthetic potential but also the detailed mechanisms remain unclear. While radical intermediates might be involved in the fluorodecarboxylation of carboxylic acids with F_2[13] or XeF_2,[14] these reactions suffer from low efficiency and limited substrate scope. Furthermore, the high toxicities and instabilities of these two reagents prevented practical applications of these methods. Very recently, Sammis and co-workers reported the fluorination of alkyl radicals via the decomposition of *tert*-butyl peresters of carboxylic acids with NFSI and SELECTFLUOR® reagent.[15] However, this method requires the prior conversion of carboxylic acids to peresters, and the reported efficiency for the fluorination of primary alkyl radicals is low. In addition, the generality of this method is unclear, and the simultaneous generation of highly reactive *tert*-butoxyl radicals in this system is undesirable.

Herein we report that the silver-catalyzed decarboxylative fluorination of aliphatic carboxylic acids with SELECTFLUOR® reagent in aqueous solution provides a convenient, general, and efficient method for site-specific C(sp^3)−F bond formation. Our extensive study using 2-ethyltetradecanoic acid (**A-1**) as the model substrate revealed that with the catalysis of $AgNO_3$ (20 mol %), the reaction of **A-1** with SELECTFLUOR® reagent in 1:1 (v:v) acetone/H_2O solution at refluxing temperature (method A) for 3 h leads to the clean formation of the expected product 3-fluoropentadecane (**1**) in 93% isolated yield (eq 1).



(1)

No decarboxylative hydrogenation or hydroxylation product (pentadecane or pentadecan-3-ol) could be detected. Other Ag(I) salts, such as $AgBF_4$, AgOAc, and AgOTf, exhibited almost the same catalytic behavior as $AgNO_3$, while no reaction occurred

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without the presence of a Ag(I) salt. On the other hand, bidentate silver complexes such as $Ag(Phen)_2OTf$ (Phen = 1,10-phenanthroline) or $Ag(BPy)_2OTf$ (BPy = 2,2′-bipyridine) failed to initiate the fluorodecarboxylation. Switching the fluorine source from SELECTFLUOR® reagent to NFSI led to no reaction at all. In addition to Ag(I) ions, water also proved to be essential. No decarboxylation occurred in any of the anhydrous organic solvents screened, including acetone, *N*,*N*-dimethylformamide, and dimethyl sulfoxide, even with the catalysis of $AgBF_4$, which has better solubility than $AgNO_3$ in these solvents. The fluorodecarboxylation was slightly slower in CH_3CN/H_2O solution and did not proceed in biphasic systems such as C_6H_6/H_2O or $ClCH_2CH_2Cl/H_2O$.

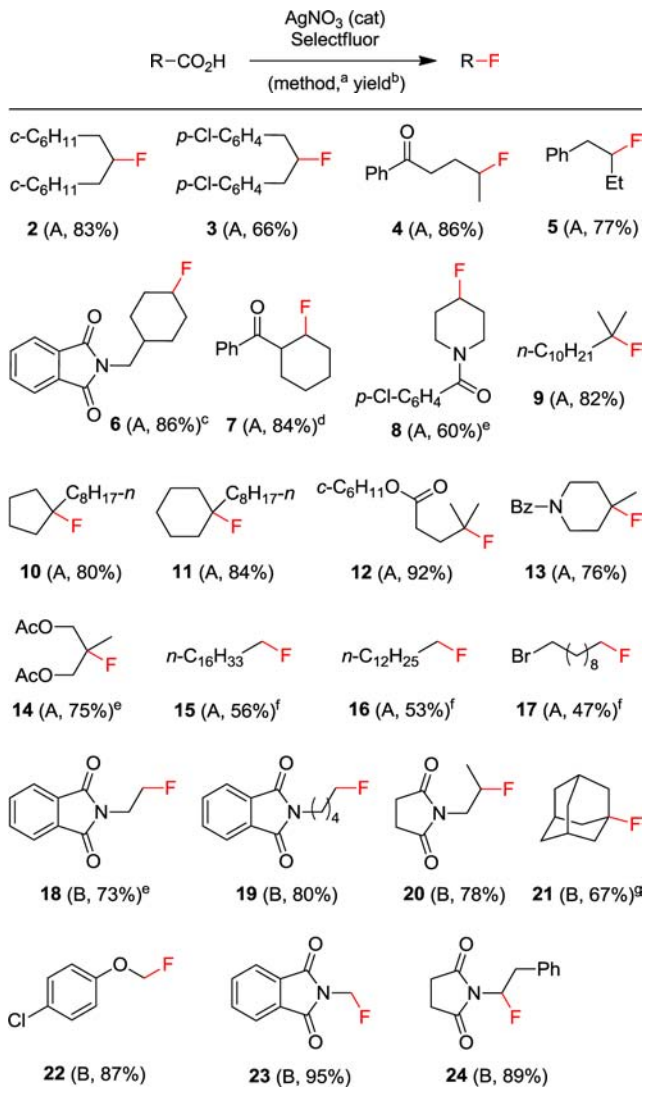
With the optimized conditions (eq 1) in hand, we then set out to explore the scope and limitations of the above method, and the results are summarized in Table 1. Secondary alkyl carboxylic acids underwent efficient decarboxylative fluorination to afford the corresponding products **2**–**8**. Both *cis*- and *trans*-2-benzoylcyclohexanecarboxylic acid led to the formation of the same fluoride **7** as a 1:1 mixture of two stereoisomers under the same reaction conditions, implying that the two reactions proceeded via the same intermediate. Tertiary alkyl carboxylic acids were more reactive than secondary ones, and their reactions proceeded smoothly even at room temperature, as exemplified by the synthesis of fluorides **9**–**14** in high yields. In comparison, primary alkyl carboxylic acids were less reactive. For example, the reaction of stearic acid at refluxing temperature gave the expected product **15** in only 20% yield, while about 70% of the stearic acid was recovered. Nevertheless, increasing the amount of SELECTFLUOR® reagent to 4 equiv increased the yield to 37%. Further adjustment of the water/acetone ratio allowed fluoride **15** to be isolated in 56% yield, the major byproduct being the decarboxylative hydrogenation product heptadecane, as indicated by GC–MS. In a similar fashion, fluorides **16** and **17** were obtained in moderate yields. On the other hand, for substrates having better solubility in water, the reaction could be performed in pure water (method B). Thus, the reactions of N-protected 3-aminopropanoic acid and 6-aminohexanoic acid with SELECTFLUOR® reagent proceeded smoothly and cleanly in warm water (~55 °C), leading to the high-yield production of functionalized primary alkyl fluorides **18** and **19**, respectively. No decarboxylative hydrogenation products could be observed in these two cases. The use of water alone as the solvent also proved advantageous in cases where the fluorinated products were sensitive toward SELECTFLUOR® reagent.[16] For example, the fluorodecarboxylation of adamantane-1-carboxylic acid in water/acetone solution at room temperature gave 1-fluoroadamantane (**21**) in only 22% yield along with the formation of di- and trifluorinated adamantanes in comparable amounts. However, when the reaction was carried out in water, the expected product **21** was obtained in 67% yield. Similarly, α-heteroatom-substituted alkyl fluorides **22**–**24** were synthesized in much higher yields in water than in water/acetone. Presumably, the poor water solubility of the product fluorides inhibits their further reaction with SELECTFLUOR® reagent in water.

Unlike aliphatic carboxylic acids, aromatic acids such as benzoic acid, 4-chlorobenzoic acid, and 2-nitrobenzoic acid failed to give any desired products under the above experimental conditions, with all of the starting acid being recovered in each case.

The above results clearly demonstrate the generality of this new method. The catalytic processes enjoy the tolerance of a variety of functional groups, including amide, ester, carbonyl, halide, ether, and aryl, which in turn encourages their application to more complex organic molecules. For example, dehydrolithocholic acid derivatives **A-25** and (+)-**A-26** underwent decarboxylative fluorination to give the corresponding products **25** and (+)-**26** in high yields (eq 2).

It can also be inferred from Table 1 that the reactivity of carboxylic acids decreases in the order tertiary > secondary > primary ≫ aromatic. This reactivity pattern thus allows the successful implementation of chemoselective fluorodecarboxylation. For example, 2,2-dimethylpentanedioic acid (**A-27**) underwent chemoselective decarboxylation to give the tertiary alkyl fluoride **27** in almost quantitative yield (eq 3). Similarly, the alkylic carboxyl groups in diacids **A-28** and **A-29** were selectively

Table 1. $AgNO_3$-Catalyzed Decarboxylative Fluorination of Carboxylic Acids



[a]Method A: acid (0.2 mmol), SELECTFLUOR® reagent (0.4 mmol), $AgNO_3$ (0.04 mmol), acetone (2 mL), H_2O (2 mL), 10 h; reaction temperature: reflux for **1**–**7** and **15**–**17**, 45 °C for **8** and **14**, rt for **9**–**13**. Method B: acid (0.2 mmol), SELECTFLUOR® reagent (0.4 mmol), $AgNO_3$ (0.04 mmol), H_2O (2 mL), 55 °C, 1–10 h. [b]Isolated yields based on the starting acid. [c]Two stereoisomers in 72:28 ratio. [d]cis/trans = 50:50. [e]30 mol % $AgNO_3$ was used. [f]4 equiv of SELECTFLUOR® reagent was used, and the acetone/H_2O ratio was adjusted to 4:1. [g]1 equiv of SELECTFLUOR® reagent was used.

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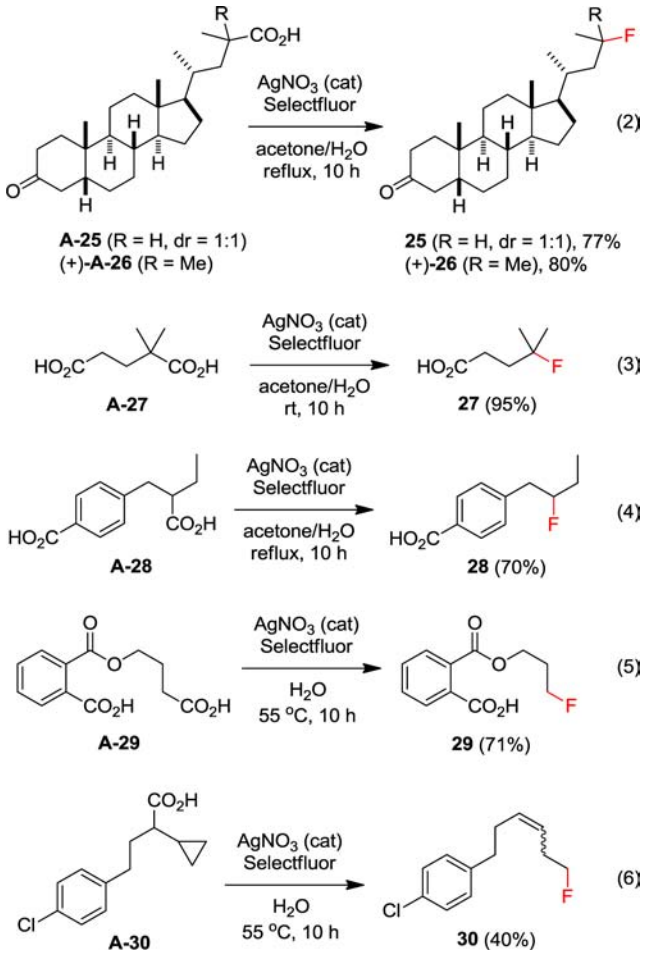


removed while the benzoic carboxyl groups remained intact, providing alkyl fluorides **28** and **29**, respectively (eqs 4 and 5).

The above relative reactivities of carboxylic acids strongly suggest that the reaction proceeds by an oxidative radical decarboxylation mechanism. To provide further evidence of the radical mechanism, cyclopropylacetic acid **A-30** was designed as a radical probe.[17] The silver-catalyzed reaction of **A-30** with SELECTFLUOR® reagent in water afforded the ring-opening product **30** in 40% yield as a 4:1 mixture of two stereoisomers along with the recovery of **A-30** in 21% yield (eq 6). No corresponding fluoromethylcyclopropane derivative could be detected by ^{1}H NMR analysis. This result strongly supports the involvement of a free radical mechanism in the silver-catalyzed fluorodecarboxylation.

Although the detailed mechanism is still not clear, a tentative one can be proposed (Figure 1). The oxidation of Ag(I) by SELECTFLUOR® reagent generates an Ag(III)−F intermediate, presumably via oxidative insertion. The trivalent silver species then undergoes single electron transfer (SET) with a carboxylate anion to give the divalent silver intermediate Ag(II)−F and a carboxyl radical. The fast decarboxylation of the carboxyl radical provides the corresponding alkyl radical, which then abstracts the fluorine atom of the adjacent Ag(II)−F to afford the alkyl fluoride product and regenerate the Ag(I) catalyst. Thus, the silver-catalyzed decarboxylative fluorination likely involves SET followed by fluorine atom transfer. The inactiveness of NFSI in the fluorodecarboxylation might be ascribed to its failure to generate the high-valent silver species, as NFSI is a much weaker oxidant than SELECTFLUOR® reagent.

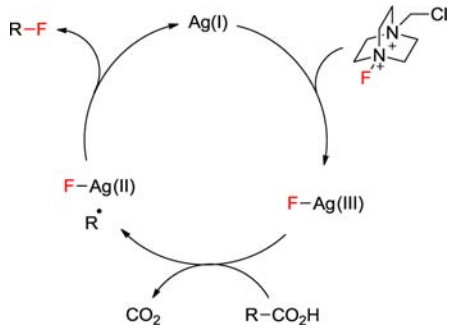
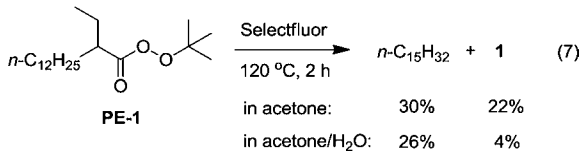


Figure 1. Proposed Mechanism of Silver-Catalyzed Decarboxylative Fluorination.

The Ag(II)- or Ag(III)-mediated decarboxylation of carboxylic acids is well-documented.[18,19] It is reasonable to assume that Ag(III)−F has a reactivity similar to that of Ag(II) in decarboxylation since the Ag−F bonding is substantially covalent in Ag(III) and Ag(II) fluorides.[20] While the fluorine atom transfer from Ag(II)−F to an alkyl radical is unprecedented, transition-metal-assisted halogen (Cl or Br) atom transfer, that is, trapping of an alkyl radical by a complexed metal halide in a higher oxidation state ($M^{n+1}L_mX$) to give the alkyl halide and the metal ion in a lower oxidation state (M^nL_m), is well-known.[21] An alternative explanation for the fluorine transfer would be an SET mechanism involving oxidation of the alkyl radical to a carbocation by Ag(II) with subsequent capture of the carbocation by a fluoride anion. However, this is unlikely because solvated F^- is much less nucleophilic than H_2O.

Another possibility for the fluorination would be fluorine transfer from SELECTFLUOR® reagent to an alkyl radical. To test this hypothesis, we designed the following experiments. When 1-adamantanecarboxylic acid was treated with Ag(BPy)$_2$S$_2$O$_8$ (200 mol %) and SELECTFLUOR® reagent (200 mol %) in acetone/H_2O at room temperature, decarboxylation occurred. However, only a trace amount of 1-fluoroadamantane could be detected by GC−MS, as the major product was adamantan-1-ol in 43% yield. This showed that the oxidation of adamantyl radical by the Ag(II) complex is much faster than the fluorine transfer to the adamantyl radical from SELECTFLUOR® reagent. In another set of experiments, *tert*-butyl 2-ethyltetradecaneperoxoate (**PE-1**), the perester of acid **A-1**, was used as the radical precursor (eq 7). The reaction of **PE-1** with



SELECTFLUOR® reagent (200 mol %) in dry acetone was carried out in a sealed tube at 120 °C. All of the **PE-1** was consumed within 2 h. The ^{1}H NMR and GC-MS analyses of the resulting mixture showed the formation of pentadecane (30%) and fluoride **1** (22%) along with a number of unidentified byproducts, implying that the rate of F abstraction from SELECTFLUOR® reagent is comparable to that of H abstraction from the solvent acetone for secondary alkyl radicals. When the same reaction was carried out in the 1:1 (v:v) acetone/water solution, pentadecane was obtained in 26% yield, but only a 4% yield of fluoride **1** was observed. Instead, pentadecan-3-ol was formed in 7% yield as determined by GC−MS (see the

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Supporting Information). These results are in sharp contrast to the outcome depicted in eq 1, indicating that the mechanism of fluorine transfer from SELECTFLUOR® reagent to alkyl radicals is unlikely to be involved in the above silver-catalyzed processes. Furthermore, the solvent effects in eq 7 strongly suggest the SET mechanism for the reaction of alkyl radicals with SELECTFLUOR® reagent, which in turn supports our hypothesis of a concerted fluorine atom transfer mechanism in the silver-catalyzed fluorodecarboxylation.

An alternative mechanism for the fluorodecarboxylation would be the involvement of divalent silver species such as Ag(II)−F−Ag(II) rather than Ag(III)−F.[22] To check on this possibility, a mixture of acid **A-1**, $AgNO_3$ (20 mol %), $K_2S_2O_8$ (200 mol %) and KF (100 mol %) in acetone/H_2O was refluxed for 10 h. No expected fluorinated product **1** could be detected, whereas the H-abstraction product pentadecane was obtained in ∼80% yield. The reaction of **A-1a** with AgF (100 mol %) and $K_2S_2O_8$ (200 mol %) afforded the same result. It is known that the interaction of $AgNO_3$ with $K_2S_2O_8$ results in the formation of Ag(II) intermediates.[18] Thus these experiments do not support Ag(II) intermediacy. Further mechanistic investigations are certainly required to reveal the nature of the high-valent silver intermediates in the above decarboxylative fluorination.

In conclusion, we have developed a novel decarboxylative fluorination of aliphatic carboxylic acids that uses SELECTFLUOR® reagent as the fluorine source and $AgNO_3$ as the catalyst. The ready availability and low cost of the safe fluorine reagent and catalyst, the mild experimental conditions, the remarkable chemoselectivity, and the wide functional group compatibility render this new radical fluorination method of practical value in the synthesis of fluorinated molecules.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full experimental details; characterizations of new compounds; and copies of ^1H, ^{13}C and ^{19}F 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) (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (d) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305.

(2) Miller, P. W.; Long, N. J.; Vilar, R.; Gee, A. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 8998.

(3) Furuya, T.; Kuttruff, C. A.; Ritter, T. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 803.

(4) (a) Grushin, V. V. *Acc. Chem. Res.* **2010**, *43*, 160. (b) Furuya, T.; Klein, J. E. M. N.; Ritter, T. *Synthesis* **2010**, 1804. (c) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470.

(5) (a) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; García-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661. (b) Tang, P.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 12150. (c) Lee, E.; Kamlet, A. S.; Powers, D. C.; Neumann, C. N.; Boursalian, G. B.; Furuya, T.; Choi, D. C.; Hooker, J. M.; Ritter, T. *Science* **2011**, *334*, 639.

(6) Selected examples: (a) Young, S. *J. Chem. Soc.* **1881**, *39*, 489. (b) Kim, D. W.; Song, C. E.; Chi, D. Y. *J. Am. Chem. Soc.* **2002**, *124*, 10278. (c) Kim, K.-Y.; Kim, B. C.; Lee, H. B.; Shin, H. *J. Org. Chem.* **2008**, *73*, 8106.

(7) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.

(8) (a) Singh, R. P.; Shreeve, J. M. *Synthesis* **2002**, 2561. (b) Sutherland, A.; Vederas, J. C. *Chem. Commun.* **1999**, 1739.

(9) Mankad, N. P.; Toste, F. D. *Chem. Sci.* **2012**, *3*, 72.

(10) (a) Singh, R. P.; Shreeve, J. M. *Acc. Chem. Res.* **2004**, *37*, 31. (b) Nyffeler, P. T.; Durón, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2005**, *44*, 192.

(11) Hamashima, Y.; Sodeoka, M. *Synlett* **2006**, 1467.

(12) Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science* **2011**, *334*, 1681.

(13) Grakauskas, V. *J. Org. Chem.* **1969**, *34*, 2446.

(14) (a) Patrick, T. B.; Johri, K. K.; White, D. H. *J. Org. Chem.* **1983**, *48*, 4158. (b) Patrick, T. B.; Johri, K. K.; White, D. H.; Bertrand, W. S.; Mokhtar, R.; Kilbourn, M. R.; Welch, M. J. *Can. J. Chem.* **1986**, *64*, 138. (c) Patrick, T. B.; Khazaeli, S.; Nadji, S.; Hering-Smith, K.; Reif, D. *J. Org. Chem.* **1993**, *58*, 705. (d) Ramsden, C. A.; Shaw, M. M. *Tetrahedron Lett.* **2009**, *50*, 3321.

(15) 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.

(16) Chambers, R. D.; Parsons, M.; Sanford, G.; Bowden, R. *Chem. Commun.* **2000**, 959.

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

(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) Kouadio, I.; Kirschenbaum, L. J.; Mehrotra, R. N.; Sun, Y. *J. Chem. Soc., Perkin Trans. 2* **1990**, 2123.

(20) Grochala, W.; Hoffmann, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2742.

(21) (a) Clark, A. J. *Chem. Soc. Rev.* **2002**, *31*, 1. (b) Severin, K. *Curr. Org. Chem.* **2006**, *10*, 217. (c) Pintauer, T. *Eur. J. Inorg. Chem.* **2010**, 2449. (d) Li, C. In *Encyclopedia of Radicals in Chemistry, Biology and Materials*; Chatgilialoglu, C., Studer, A., Eds.; Wiley: Chichester, U.K., 2012; pp 943−964.

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