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Simple and Sustainable Iron-Catalyzed Aerobic C−H Functionalization of *N*,*N*-Dialkylanilines

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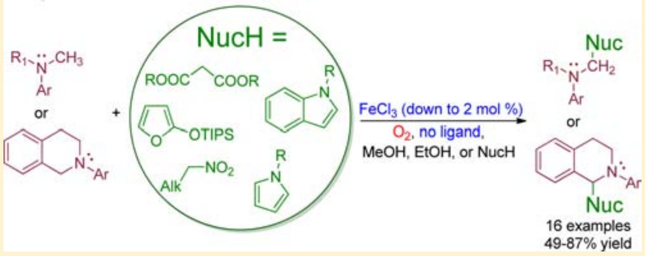
Ⓢ *Supporting Information*

ABSTRACT: Iron(III) chloride catalyzes the aerobic oxidation of tertiary anilines, including tetrahydroisoquinolines, to form reactive iminium ion intermediates that undergo Mannich reactions with silyloxyfurans, nitroalkanes, and other nucleophiles to give the corresponding butenolides, nitro compounds, and α-substituted tetrahydroisoquinolines, respectively, in good to excellent yields.

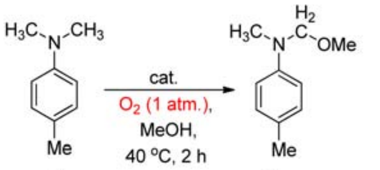


INTRODUCTION

Because of its natural abundance and electrochemical properties, iron as a catalyst is a desired goal for oxidative chemistry.[1] Yet, despite its dominance in biological oxidations,[2] iron catalysts have been shadowed for many years by precious metals in performance-driven catalytic oxidations of aliphatic C−H bonds,[3] and these oxidations have commonly used peroxides[4] rather than dioxygen. Although many oxidative processes are of interest, the oxidation of C−H bonds adjacent to nitrogen is one of the most important and useful strategies for C−H functionalization because this process forms iminium ions, substrates of Mannich reactions,[4f,5] that are widely used for the syntheses of natural products and pharmaceuticals.[6] The most efficient oxidative Mannich reactions were developed for catalysis with ruthenium(II)[7] and dirhodium(II)[8] complexes and have relied on *tert*-butyl hydroperoxide (TBHP) as the oxidant. Copper-based methods with TBHP are mainly limited to oxidative reactions with tetrahydroisoquinoline derivatives.[4c,9] Here we report facile vinylogous oxidative Mannich, aza-Henry reactions, and other reactions of iminium ions with carbon nucleophiles catalyzed by common ferric chloride in the absence of any additional ligands with O_2 as the oxidant.

Copper(I) salts have been employed in catalytic aerobic oxidative functionalizations by indoles, nitroalkanes, and isocyanides, but they have been generally limited to reactions that occur at the 1-position of tetrahydroisoquinolines.[4c−f,10] Iron(0) and iron(II) complexes were used as reagents[11] or catalysts[12] in cytochrome P-450-inspired demethylation[2a,13] of tertiary amines. Iron(II) and iron(III) salts were investigated for the oxidative Mannich reactions of *N*,*N*-dialkylanilines and tetrahydroisoquinolines with carbon nucleophiles, but they were only reported to be effective with TBHP[14] or di-*tert*-butylperoxide[15] as the oxidant. Our recent investigations of oxidative Mannich reactions[8a] with TBHP that included those catalyzed by CuBr, $FeCl_3 \cdot 6(H_2O)$, and $Co(OAc)_2$ suggested that 4-substituted *N*,*N*-dimethylanilines could undergo oxidation in methanol to the corresponding methoxy hemiaminals by O_2. Hemiaminals are iminium ion reservoirs in Mannich reactions.[8a] Hence, we inquired if CuBr, $FeCl_3$, or $Co(OAc)_2$ could catalyze oxidative functionalization of an aliphatic C−H bond adjacent to nitrogen of *N*,*N*-dialkylanilines in the most atom economical fashion in the presence of a nucleophile.

Initial investigations were carried out with 4-methyl-*N*,*N*-dimethylaniline (**1**) in methanol under one atmosphere of O_2. The catalyst loading, solvent, concentration, temperature, and the reaction time were kept the same as they were for the oxidative Mannich reaction with TBHP.[8a] Evaluation of CuBr-, $FeCl_3 \cdot 6(H_2O)$-, and $Co(OAc)_2$-catalyzed oxidations of **1** by O_2 showed that ferric chloride outperformed the other metal compounds, forming the corresponding methoxy hemiaminal **2** in 50% yield (eq 1). Furthermore, ferric chloride showed the highest catalytic activity among the studied metallic compounds reaching 71% conversion with just 2.0 mol % (eq 1). Presumably, a reduction potential of Fe(III)/Fe(II) redox pair (+0.77 V vs NHE) matching a potential of **1** (+0.97 V vs NHE)[16] enables iron to shuttle electrons to dioxygen better than Cu(II)/Cu(I) (+0.15 V vs NHE) or Co(III)/Co(II) (+1.82 V vs NHE) redox pairs. Ferric chloride was chosen for oxidative Mannich reactions with dioxygen.



1 **2** (1)

CuBr (5.0 mol %)	75% conv., 32% yield
$Co(OAc)_2$ (10.0 mol %)	61% conv., 42% yield
$FeCl_3 \cdot 6(H_2O)$ (2.0 mol %)	**71% conv., 50% yield**

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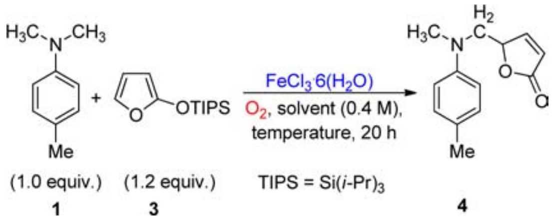
With $FeCl_3$ as the catalyst, siloxyfuran **3**, a known precursor of γ-butyrolactones,[17] was chosen as a nucleophile for the oxidative vinylogous Mannich reaction. The ubiquitous γ-butyrolactone fragments are widely used in synthesis[18] and appear in pharmaceuticals,[19] natural products,[20] and biomass processing.[21] The Mannich adduct **4** was isolated in 70% yield using just 1.2 equiv of **3**, with one atmosphere of O_2, and 2.0 mol % of $FeCl_3 \cdot 6(H_2O)$ (eq 2).

(2)

This initial success prompted elaboration of reaction conditions suitable for a large scope of *N,N*-dialkylanilines in the ferric chloride oxidative Mannich reaction by O_2 (Table 1).

Table 1. Optimization of Conditions of the $FeCl_3$-Catalyzed Oxidative Vinylogous Mannich Reaction with Siloxyfuran 3



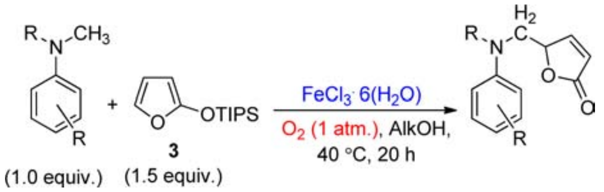
entry	cat. load, mol %	oxidant	solvent	*T*, °C	conv., %[a]	yield, %[b,c]
1	2.0	O_2	MeOH	40	92	70
2	**5.0**	$\mathbf{O_2}$	**MeOH**	**40**	**96**	**72**
3	10.0	O_2	MeOH	40	94	10
4	2.0	O_2	MeOH	65	60	5
5	2.0	air	MeOH	40	76	36
6	**2.0**	$\mathbf{O_2}$	**EtOH**	**40**	**80**	**94**
7	5.0	O_2	EtOH	40	100	5
8[d]	10.0	O_2	EtOH	40	<5	–
9[e]	10.0	O_2	EtOH	40	<5	–

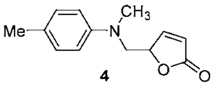
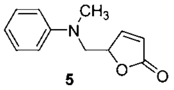
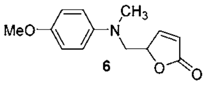
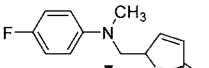
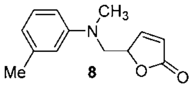
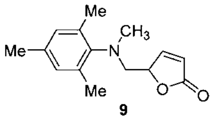
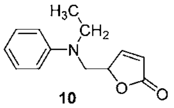
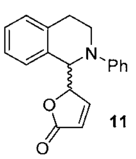
[a] Determined by ^1H NMR spectroscopy from the ratio of the absorption (2.89 ppm, s, 6H) corresponding to **1** and that of biphenyl (7.60 ppm, d, *J* = 7.2 Hz, 4H) that was used as an internal standard. [b] Isolated yield after column chromatography on silica gel. [c] Yield calculated on the basis of the amount of consumed **1**. [d] 99.99% pure $FeCl_2$ (10.0 mol %) was used instead of $FeCl_3 \cdot 6H_2O$. [e] 99.99% pure $FeCl_2$ (10.0 mol %) and $FeCl_3 \cdot 6H_2O$ (1.0 mol %) was used instead of $FeCl_3 \cdot 6H_2O$.

Optimization of $FeCl_3$ loading for the oxidative vinylogous Mannich reaction of **1** and **3** in methanol showed that conversions above 90% could be achieved with just 2.0 mol % of ferric chloride (entries 1 and 2). The yield of **4** remained around 70% in the presence of 2.0 and 5.0 mol % of $FeCl_3$ but fell to 10% with 10.0 mol % loading of $FeCl_3$ (entries 1–3), presumably because of a more rapid alcoholysis of **3**. Refluxing methanol decreased conversion of **4** to 60% (entry 4). The use of air as the oxidant furnished **4** in only 36% yield compared to 70% yield with only dioxygen (entry 5). In ethanol the oxidative Mannich reaction of **1** with **3** catalyzed by 2.0 mol % of $FeCl_3$ afforded an 80% conversion and a 94% isolated yield of **4** based on consumed **1** (entry 6). The use of 5.0 mol % of $FeCl_3$ furnished **4** in only 5% yield because of rapid ethanolysis of siloxyfuran **3** (entry 7); that oxidation must be significantly faster than alcoholysis of the silyloxyfuran, which is also catalyzed by ferric chloride, is evident in this result. When soluble $FeCl_2$ was used in place of $FeCl_3$ or with $FeCl_2$:$FeCl_3$ in a 10:1 ratio under the same conditions, the oxidative Mannich product **4** was formed in less than 5% yield, and a majority of the unoxidized **1** was recovered (entries 8–9). This latter result suggests that dioxygen bound to iron(II) does not initiate the oxidative Mannich reaction.

The scope of the oxidative vinylogous Mannich reaction was examined under the optimized conditions with representative *N,N*-dialkylanilines which afforded butenolide products in

Table 2. Substrate Scope of the $FeCl_3$-Catalyzed Aerobic Oxidative Vinylogous Mannich Reaction of *N,N*-Dialkylanilines with Siloxyfuran 3

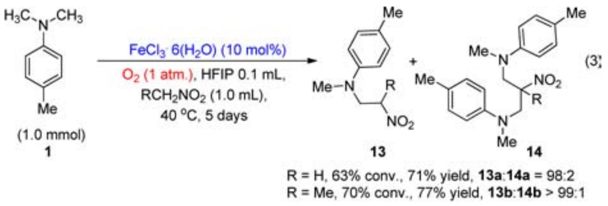


entry	method[a]	product	isolated yield, %[b]
1	A	 **4**	85
2	A	 **5**	87
3	A	 **6**	84
4	B	 **7**	66
5	B	 **8**	72
6	A	 **9**	66
7	A	 **10**	49
8	A	 **11**	50[c]

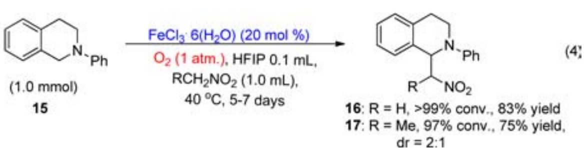
[a] **Method A:** 2.0 mol % of $FeCl_3 \cdot 6H_2O$ in ethanol. **Method B:** 5.0 mol % of $FeCl_3 \cdot 6H_2O$ in methanol. [b] Isolated yield after column chromatography on silica gel. [c] Diastereomer ratio is 3:1.

49–87% yield (Table 2). Electron-rich *N,N*-dimethylanilines formed Mannich adducts in greater than 84% yield (entries 1–3). The moderately electron-deficient 4-fluoro-*N,N*-dimethylaniline afforded **7** in 66% yield (entry 4). In the presence of two methyl groups in the ortho positions of the aromatic ring of aniline, butenolide **9** was obtained in 66% yield (entry 6). Unsymmetrical *N*-methyl-*N*-ethylaniline underwent selective reaction at only the *N*-methyl group (entry 7), and the oxidative Mannich reaction of *N*-phenyltetrahydroisoquinoline **15** occurred as expected at the 1-position with **11** isolated in 50% yield. These observations and results are not unlike those found with TBHP as the oxidant under $Rh_2(cap)_4$ catalysis.[8b]

The generality of ferric chloride for catalysis of the oxidative functionalization of C–H bonds adjacent to nitrogen with O_2 as the oxidant (Table 2) was assessed with nitromethane for the aza-Henry reaction. Prior studies of TBHP or photolytic catalytic oxidation reported efficient functionalization with *N*-aryltetrahydroisoquinolines but only limited success with dialkylanilines.[23] Consistent with this limitation, treatment of **1** in nitromethane as solvent under the optimized conditions described for aerobic oxidation with silyloxyfuran **3** in Table 2 gave no aza-Henry or double addition products even with 10 mol % of the iron(III) catalyst. Further increases in catalyst loading returned only trace amounts of **13a**, and addition of 0.5 mL of methanol to the reaction mixture with stirring for 1–2 h led to the quantitative recovery of **1**. The absence of oxidation of *N,N*-diallkylaniline **1** indicated catalyst inhibition by the reactant amine. However, performing the same reaction in ethanol as solvent using 10 equiv of nitromethane gave 44% conversion and a 32% isolated yield of **13a** within 24 h. Efforts to trigger the iron-catalyzed reaction with various additives in nitromethane as solvent revealed that weak acids promoted the oxidation to give the desired product, whereas organic bases did not (see Supporting Information). With the addition of only a 1.0 equiv of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), the oxidative aza-Henry product **13a** was obtained in 71% yield based on consumed **1** (eq 3, R = H), and these conditions were optimal for the aza-Henry reaction.[24] Formation of the double addition product **14a**, which was as high as 2:98 for **14a**:**13a** in reactions with HFIP, was successfully minimized under these conditions.[25]



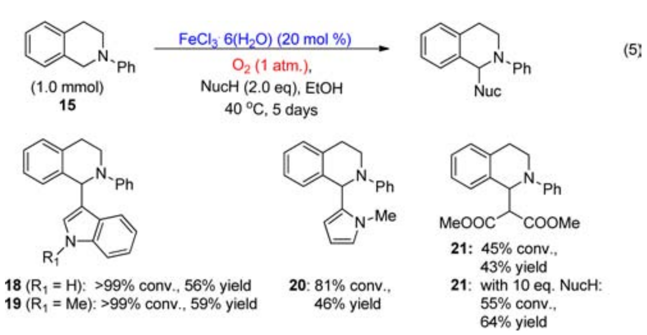
R = H, 63% conv., 71% yield, **13a**:**14a** = 98:2
R = Me, 70% conv., 77% yield, **13b**:**14b** > 99:1



16: R = H, >99% conv., 83% yield
17: R = Me, 97% conv., 75% yield, dr = 2:1

The acid-promoted Fe(III)/O_2 conditions of the oxidative Mannich (aza-Henry) reaction were also effective for reaction of dimethylaniline **1** with nitroethane (eq 3, R = Me). Further investigations of this transformation with *N*-phenyltetrahydroisoquinoline (**15**) and nitromethane, as well as nitroethane, showed higher reactivity for this reactant compared to *N,N*-dialkylanilines, and the Mannich adducts **16** and **17** were formed with high conversion in 83% and 75% isolated yield, respectively, under optimized conditions (eq 4). Addition of HFIP minimized oxidation of **15** to the corresponding amide formed by oxidation at the α position. The diastereomeric ratio for **17** was 2.0, which is between those reported for the copper(I) bromide-catalyzed oxidation by TBHP[23a] and the iridium(III) photoredox catalysis of the same reaction.[23b]

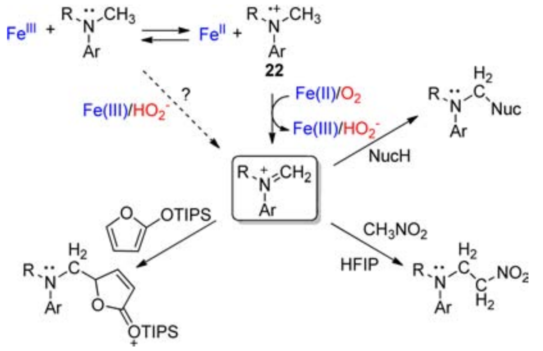
To ascertain that this iron-catalyzed aerobic C–H functionalization is generally applicable to a broad range of nucleophiles, we examined the oxidative transformation of *N*-phenyltetrahydroisoquinoline (**15**) in the presence of representative nucleophiles whose coupling reactions due to TBHP oxidations of **15** have been widely reported.[4c,f,7,9] As noted in eq 5, reactions with indole, 1-methyl indole, and 1-methylpyrrole occurred under the standard conditions employed for the oxidative vinylogous Mannich reaction to give high conversions but moderate yields of the coupled products. Dimethyl malonate gave moderate conversion and moderate isolated yield based on consumed **15** even with 10 equiv of the nucleophile. Reactions performed in the presence of HFIP resulted in the same percentage of conversions and isolated yields as those performed in the absence of HFIP (see Supporting Information). Oxidation of *N*-phenyltetrahydroisoquinoline **15** to form the corresponding amide was a competing reaction, and the yield of this product increased with increasing water content. As is also evident from prior investigations with TBHP,[9] phenylacetylene does not undergo coupling with **15** under the mild conditions employed for iron(III)-catalyzed aerobic oxidations.



18 (R_1 = H): >99% conv., 56% yield
19 (R_1 = Me): >99% conv., 59% yield
20: 81% conv., 46% yield
21: 45% conv., 43% yield
21: with 10 eq. NucH: 55% conv., 64% yield

Consistent with the compatibility of ferric chloride with tertiary anilines and tetrahydroisoquinolines, as well as with the previously established mechanism for the oxidative Mannich reactions of these amines,[8a] the initiation step is proposed to be electron transfer between ferric chloride and the amine to produce radical cation **22** and iron(II) chloride (Scheme 1). This proposal is compatible with the potentials of the Fe(III)/Fe(II) (+0.77 V vs NHE) and amine/radical cation redox pairs (+0.79 V/+1.08 V vs NHE).[26] The fate of the amine radical cation in arriving at the iminium ion product is less certain, but hydrogen atom abstraction from the radical cation that produces the iminium ion directly is plausible, either directly[27] or through iron(II)-bound dioxygen.[1g] The resulting peroxo species could then enter Haber–Weiss or Fenton-like chemistry to complete the process.[28] The requirement of mild acid to effect the oxidative aza-Henry reaction, either to inhibit coordination of iron(III) with the amine reactant or to activate the nitroalkane, suggests that these conditions may make possible a variety of other oxidative Mannich reactions that have previously been reported using TBHP.[4c–f,7a,9,14,29]

Scheme 1. Plausible Mechanism for Ferric Chloride-Catalyzed Aerobic Oxidative C−H Functionalization Reactions



The oxidative protocol that we have reported allows facile functionalization of an aliphatic C−H bond adjacent to nitrogen with siloxyfuran, nitroalkanes, and other nucleophiles using a commodity catalyst ($FeCl_3$) and an atom-efficient oxidant (O_2). Given the exceptional simplicity of the reported procedure, we anticipate that ligand free $FeCl_3$-catalyzed oxidations by O_2 will be applied to a wide range of transformations, as we have illustrated with indols, pyrroles, and methyl malonate, and will be considered as possible pathways of corrosive degradations.[30]

■ EXPERIMENTAL SECTION

General Procedure for $FeCl_3$-Catalyzed Oxidative Vinylogous Mannich Reactions of *N,N*-Dialkylanilines with Silyloxyfuran 3 in Ethanol. To a solution of the *N,N*-dialkylaniline (0.5 mmol) and siloxyfuran **3** (0.25 mmol, 0.5 equiv, 60 mg) in ethanol (1.5 mL) was added $FeCl_3 \cdot 6(H_2O)$ (10 μmol, 2.0 mol %, 2.7 mg) at room temperature. The vial was equipped with a balloon containing only O_2, and the resulting solution was stirred at 40 °C for 5 h. A second portion of siloxyfuran **3** (0.50 mmol, 1 equiv, 120 mg) was added to the solution, and the reaction mixture was stirred overnight at 40 °C under the atmosphere of O_2. The reaction mixture was then concentrated under reduced pressure, and the reaction product was isolated by column chromatography on silica gel.

General Procedure for the $FeCl_3$-Catalyzed Oxidative Mannich Reaction of *N,N*-Dimethylanilines and 2-Phenyl-1,2,3,4-tetrahydroisoquinoline in Nitroalkanes. To an oven-dried flask containing a magnetic stirring bar were added the amine (1.0 mmol), $FeCl_3 \cdot 6(H_2O)$ (20 mol %, 54.0 mg), nitroalkane (1.0 mL), and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP, 0.1 mL) in sequence. The vial was equipped with a balloon containing only O_2, and the resulting solution was stirred at 40 °C for 5 days. The reaction mixture was then quenched with Et_3N (0.3 mL) and concentrated under reduced pressure, and the reaction product was isolated by column chromatography on silica gel. The reactions of nitroethane and **15** were run for 7 days; and other reactions with nitroalkanes were run for 5 days.

General Procedures for the $FeCl_3$-Catalyzed Oxidative Mannich Reactions of 2-Phenyl-1,2,3,4-tetrahydroisoquinoline with Representative Nucleophiles in Ethanol. To a solution of 2-phenyl-1,2,3,4-tetrahydroisoquinoline (1.0 mmol, 209 mg) and nucleophiles (2.0 mmol, 2.0 equiv) in ethanol (2.0 mL), $FeCl_3 \cdot 6(H_2O)$ (20 mol %, 54.0 mg), was added at room temperature. The vial was equipped with a balloon containing only O_2, and the solution was stirred at 40 °C for 5 days. The reaction mixture was then quenched with Et_3N (0.3 mL) and concentrated under reduced pressure, and the reaction product was isolated by column chromatography on silica gel.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General procedures, summary of conditions for optimization, and spectral characterization of previously unknown substrates. 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) Rosenzweig, A. C.; Frederick, C. A.; Lippard, S. J.; Nordlund, P. *Nature* **1993**, *366*, 537. (b) Feig, A. L.; Lippard, S. J. *Chem. Rev.* **1994**, *94*, 759. (c) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (d) Park, J. S.; Karnas, E.; Ohkubo, K.; Chen, P.; Kadish, K. M.; Fukuzumi, S.; Bielawski, C. W.; Hudnall, T. W.; Lynch, V. M.; Sessler, J. L. *Science* **2010**, *329*, 1324. (e) Chen, M. S.; White, M. C. *Science* **2010**, *327*, 566. (f) Beal, E. J.; House, C. H.; Orphan, V. J. *Science* **2009**, *325*, 184. (g) Mayer, A. C.; Bolm, C. In *Iron Catalysis in Organic Chemistry*; Plietker, B., Ed.; Wiley-VCH: Weinheim, Germany, 2008. (h) Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783. (i) Zhao, M.; Helms, B.; Slonkina, E.; Friedle, S.; Lee, D.; DuBois, J.; Hedman, B.; Hodgson, K. O.; Frechet, J. M. J.; Lippard, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 4352.

(2) (a) Yi, C.; Jia, G.; Hou, G.; Dai, Q.; Zhang, W.; Zheng, G.; Jian, X.; Yang, C.-G.; Cui, Q.; He, C. *Nature* **2010**, *468*, 330. (b) Meunier, B.; de Visser, S. P.; Shaik, S. *Chem. Rev.* **2004**, *104*, 3947.

(3) (a) Wu, W.; Jiang, H. *Acc. Chem. Res.* **2012**, *45*, 1736. (b) Campbell, A. N.; Stahl, S. S. *Acc. Chem. Res.* **2012**, *45*, 851. (c) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005**, *105*, 2329. (d) Mallat, T.; Baiker, A. *Chem. Rev.* **2004**, *104*, 3037.

(4) (a) RatnikovM. O.DoyleM. P.*e-EROS Encyclopedia of Reagents for Organic Synthesis*; John Wiley and Sons: New York, 2012; 10.1002/047084289X.r385 (b) Company, A.; Lloret, J.; Gomez, L.; Costas, M. In *Alkane C-H Activation by Single-Site Metal Catalysis*; Pérez, P. J., Ed.; Springer: Dordrecht, Netherlands, 2012. (c) Boess, E.; Schmitz, C.; Klussmann, M. *J. Am. Chem. Soc.* **2012**, *134*, 5317. (d) Yang, F.; Li, J.; Xie, J.; Huang, Z.-Z. *Org. Lett.* **2010**, *12*, 5214. (e) Xie, J.; Huang, Z.-Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 10181. (f) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (g) McLaughlin, E. C.; Choi, H.; Wang, K.; Chiou, G.; Doyle, M. P. *J. Org. Chem.* **2009**, *74*, 730. (h) Murahashi, S.-I.; Zhang, D. *Chem. Soc. Rev.* **2008**, *37*, 1490.

(5) (a) Murahashi, S.-i.; Komiya, N. In *Modern Oxidation Methods*, 2nd ed.; Baeckvall, J.-E., Ed.; Wiley-VCH: Weinheim, Germany, 2010. (b) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1045.

(6) (a) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076. (b) Toure, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439.

(7) (a) Wang, M.-Z.; Zhou, C.-Y.; Wong, M.-K.; Che, C.-M. *Chem.—Eur. J.* **2010**, *16*, 5723. (b) Murahashi, S.-I.; Nakae, T.; Terai, H.; Komiya, N. *J. Am. Chem. Soc.* **2008**, *130*, 11005.

(8) (a) Ratnikov, M. O.; Doyle, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 1549. (b) Catino, A. J.; Nichols, J. M.; Nettles, B. J.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 5648.

(9) Li, Z.; Bohle, D. S.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8928.

(10) (a) Boess, E.; Sureshkumar, D.; Sud, A.; Wirtz, C.; Fares, C.; Klussmann, M. *J. Am. Chem. Soc.* **2011**, *133*, 8106. (b) Shen, Y.; Li, M.; Wang, S.; Zhan, T.; Tan, Z.; Guo, C.-C. *Chem. Commun.* **2009**, 953.

(11) (a) Kok, G. B.; Scammells, P. J. *Aust. J. Chem.* **2011**, *64*, 1515. (b) Nakano, Y.; Savage, G. P.; Saubern, S.; Scammells, P. J.; Polyzos, A. *Aust. J. Chem.* **2013**, *66*, 178.

(12) (a) Narog, D.; Lechowicz, U.; Pietryga, T.; Sobkowiak, A. *J. Mol. Catal. A Chem.* **2004**, *212*, 25. (b) Li, Y.; Jia, F.; Li, Z. *Chem.—Eur. J.* **2013**, *19*, 82. (c) Li, H.; He, Z.; Guo, X.; Li, W.; Zhao, X.; Li, Z. *Org. Lett.* **2009**, *11*, 4176.

(13) Baciocchi, E.; Lanzalunga, O.; Lapi, A.; Manduchi, L. *J. Am. Chem. Soc.* **1998**, *120*, 5783.

(14) (a) Liu, P.; Zhou, C.-Y.; Xiang, S.; Che, C.-M. *Chem. Commun.* **2010**, *46*, 2739. (b) Kumaraswamy, G.; Murthy, A. N.; Pitchaiah, A. *J. Org. Chem.* **2010**, *75*, 3916. (c) Han, W.; Ofial, A. R. *Chem. Commun.* **2009**, 5024.

(15) Volla, C. M. R.; Vogel, P. *Org. Lett.* **2009**, *11*, 1701.

(16) Goto, Y.; Watanabe, Y.; Fukuzumi, S.; Jones, J. P.; Dinnocenzo, J. P. *J. Am. Chem. Soc.* **1998**, *120*, 10762.

(17) (a) Martin, S. F.; Barr, K. J.; Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc.* **1999**, *121*, 6990. (b) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895.

(18) (a) Trost, B. M.; Burns, A. C.; Bartlett, M. J.; Tautz, T.; Weiss, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 1474. (b) Chen, W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 15249. (c) Singh, R. P.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2010**, *132*, 9558.

(19) Seitz, M.; Reiser, O. *Curr. Opin. Chem. Biol.* **2005**, *9*, 285.

(20) Takano, E. *Curr. Opin. Microbiol.* **2006**, *9*, 287.

(21) Delhomme, C.; Weuster-Botz, D.; Kuehn, F. E. *Green Chem.* **2009**, *11*, 13.

(22) Presumably, the concentration of O_2 was reduced in methanol at the boiling point, while methanolysis of siloxyfuran **3** was facilitated with higher temperature.

(23) (a) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672. (b) Condie, A. G.; Gonzalez-Gomez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464. (c) Arrayas, R. G.; Carretero, J. C. *Chem. Soc. Rev.* **2009**, *38*, 1940.

(24) When benzoic acid derivatives and *p*-toluenesulfonic acid are used as additives instead of HFIP, either lower or no conversionis detected (see Supporting Information for details).

(25) Noble, A.; Anderson, J. C. *Chem. Rev.* **2013**, *113*, 2887.

(26) Dombrowski, G. W.; Dinnocenzo, J. P.; Zielinski, P. A.; Farid, S.; Wosinska, Z. M.; Gould, I. R. *J. Org. Chem.* **2005**, *70*, 3791.

(27) (a) Hao, W.; Parker, V. D. *J. Org. Chem.* **2012**, *77*, 9286. (b) Kulszewicz-Bajer, I.; Zagorska, M.; Wielgus, I.; Pawlowski, M.; Gosk, J.; Twardowski, A. *J. Phys. Chem. B* **2007**, *111*, 34. (c) Cho, J.; Jeon, S.; Wilson, S. A.; Liu, L. V.; Kang, E. A.; Braymer, J. J.; Lim, M. H.; Hedman, B.; Hodgson, K. O.; Valentine, J. S.; Solomon, E. I.; Nam, W. *Nature* **2011**, *478*, 502. (d) Friedle, S.; Reisner, E.; Lippard, S. J. *Chem. Soc. Rev.* **2010**, *39*, 2768. (e) Ensing, B.; Buda, F.; Gribnau, M. C. M.; Baerends, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 4355. (f) Merkx, M.; Kopp, D. A.; Sazinsky, M. H.; Blazyk, J. L.; Muller, J.; Lippard, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 2782. (g) Chen, K.; Que, L., Jr. *J. Am. Chem. Soc.* **2001**, *123*, 6327.

(28) (a) Brillas, E.; Sires, I.; Oturan, M. A. *Chem. Rev.* **2009**, *109*, 6570. (b) Wang, B.; Yin, J.-J.; Zhou, X.; Kurash, I.; Chai, Z.; Zhao, Y.; Feng, W. *J. Phys. Chem. C* **2013**, *117*, 383.

(29) Ghobrial, M.; Schnuerch, M.; Mihovilovic, M. D. *J. Org. Chem.* **2011**, *76*, 8781.

(30) Keenan, C. R.; Sedlak, D. L. *Environ. Sci. Technol.* **2008**, *42*, 1262.