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Unexpected Copper-Catalyzed Aerobic Oxidative Cleavage of $C(sp^3)-C(sp^3)$ Bond of Glycol Ethers

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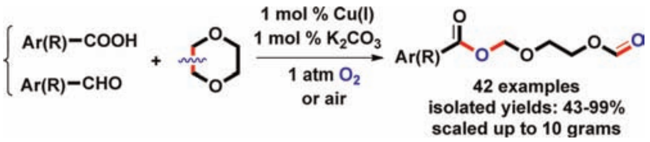
ABSTRACT



An unexpected Cu-catalyzed oxidative cleavage of the $C(sp^3)-C(sp^3)$ bond in glycol ethers by using air or molecular oxygen as the terminal stoichiometric oxidant is demonstrated. As a result, the corresponding α-acyloxy ethers and formates of 1,2-ethanediol are formed by direct coupling of carboxylic acids and aldehydes with glycol ethers under the reaction conditions. This method represents the first example of Cu-catalyzed aerobic cleavage of saturated C–C bond in ethers.

The transition-metal-catalyzed selective cleavage of C–C bonds is of fundamental interest and plays a great role in the chemical industry.[1] In the past decades, a variety of catalytic systems involving activation of C–C bonds have been developed.[2] However, there are only a few examples of catalytic cleavage of inert C–C bonds by using oxygen or air as the ultimate stoichiometric oxidant.[3] To the best of our knowledge, no examples have been described in the literature of catalytic aerobic cleavage of the $C(sp^3)-C(sp^3)$ bonds of ethers.[4] We report herein a highly selective Cu-catalyzed aerobic cleavage of the $C(sp^3)-C(sp^3)$ bond in glycol ether molecules. This system would represent the first example of Cu-catalyzed aerobic cleavage of the saturated C–C bond in ethers, which could be applied to degrade plastics and polymers made by glycol. Additionally, it could also provide an efficient and convenient protocol to synthesize α-acyloxy ethers by a coupling reaction of carboxylic acids and aldehydes with glycol ethers under mild conditions.

α-Acyloxy ethers are widely appearing substructures occurring in various pharmaceuticals such as Artemisinin, Sanguiin H-5, Candesartan Cilexetil, Fosinopril Sodium, etc. Generally, these compounds are synthesized via nucleophilic substitution of α-halo ethers by acid,[5] addition of alkenyl ethers with acid,[6] esterification of hemiacetals,

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(1) (a) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245. (b) Rybtchinski, B.; Milstein, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 870. (c) Jun, C.-H *Chem. Soc. Rev.* **2004**, *33*, 610.

(2) (a) Murakami, M.; Takahashi, K.; Amii, H.; Ito, Y. *J. Am. Soc. Chem.* **1997**, *119*, 9307. (b) Chatani, N.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Am. Soc. Chem.* **1999**, *121*, 8645. (c) Bart, S. C.; Chirik, P. J. *J. Am. Soc. Chem.* **2003**, *125*, 886. (d) Gunay, A.; Jones, W. D. *J. Am. Soc. Chem.* **2007**, *129*, 8729. (e) Mecinović, J.; Hamed, R. B.; Schofield, C. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2796. (f) Lai, T. H.; Chan, K. S. *Organometallics* **2009**, *28*, 6845. (g) He, C.; Guo, S.; Huang, L.; Lei, A. W. *J. Am. Soc. Chem.* **2010**, *132*, 8273.

(3) (a) Murahashi, S.-I.; Komiya, N.; Hayashi, Y.; Kumano, T. *Pure Appl. Chem.* **2001**, *73*, 311. (b) Sheldon, R. A.; Arends, I. W. C. E.; Brink, G.-J.; Dijksman, A. *Acc. Chem. Res.* **2002**, *35*, 774. (c) Mallat, T.; Baiker, A. *Chem. Rev.* **2004**, *104*, 3037. (d) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400. (f) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005**, *105*, 2329. (g) Piera, J.; Bäckvall, J. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3506. (h) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062. (i) Stahl, S. S. *Acc. Chem. Res.* **2012**10.1021/ar2002045. (j) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381.

(4) (a) Barker, M. W.; Perumal, S. I. *Tetrahedron Lett.* **1976**, *17*, 349. (b) Dugal, M.; Sankar, G.; Raja, R.; Thomas, J. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2310. (c) Wang, A. Z.; Jiang, H. F. *J. Am. Soc. Chem.* **2008**, *130*, 5030. (d) Chiba, S.; Zhang, L.; Ang, G. Y.; Hui, B. W. *Org. Lett.* **2010**, *12*, 2052. (e) Song, R. J.; Liu, Y.; Hu, R. X.; Liu, Y. Y.; Wu, J. C.; Yang, X. H.; Li, J. H. *Adv. Synth. Catal.* **2011**, *353*, 1467.

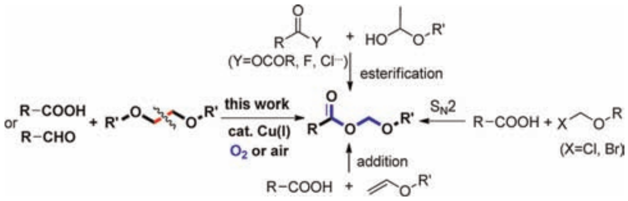
(5) Summerbell, R. K.; Lunk, H. E. *J. Am. Soc. Chem.* **1958**, *80*, 604.

(6) (a) Woods, G. F.; Kramer, D. N. *J. Am. Soc. Chem.* **1947**, *69*, 2246. (b) Croxall, W. J.; Glavis, F. J.; Neher, H. T. *J. Am. Soc. Chem.* **1948**, *70*, 2805.

10.1021/ol301220s

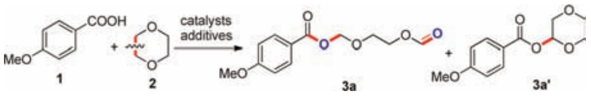
or more complex routes.[7] Very recently, Wan et al. reported a Bu_4NI-catalyzed method to form α-acyloxy ethers by an oxidative coupling reaction of acid with ethers using *tert*-butyl hydroperoxide (TBHP) as the terminal oxidant.[8] We report here a novel protocol to prepare α-acyloxy ethers by an oxidative coupling reaction of ethers with carboxylic acids and aldehydes catalyzed by Cu(I) with O_2 as an environmentally benign oxidant (Scheme 1).

Scheme 1. Methods for Preparation of α-Acyloxy Ethers



Initially, we chose *p*-anisic acid and 1,4-dioxane as the model substrates to optimize suitable conditions for this reaction (Table 1). It was found that the catalyst, base, and oxidant affect the reaction efficiency critically. The catalysts were screened, and it was found that Cu_2O was more efficient than others (entries 1−4). The oxidant Ag_2CO_3 was better than other Ag(I) salts (entries 5 and 6). Surprisingly, molecular oxygen can be used as a terminal oxidant in this reaction (entry 7). The yields increased significantly when the concentration of the reaction mixture decreased (entry 8). Air can also act as an effective oxidant (entry 9). Finally, the desired products could be nearly quantitatively isolated by using O_2 as the oxidant catalyzed by 1 mol % of Cu_2O and 1 mol % of K_2CO_3 (entries 10−16).

Table 1. Modification of the Typical Reaction Conditions[a]



entry	catalyst (mol %)	additive (equiv)	yield of **3a** (%)[b]	yield of **3a′** (%)[b]
1	CuI (10)	Ag_2CO_3 (2)	35	31
2	$CuBr_2$ (10)	Ag_2CO_3 (2)	16	19
3	Cu_2O (10)	Ag_2CO_3 (2)	55	40
4	Fe_2O_3 (10)	Ag_2CO_3 (2)	21	14
5	Cu_2O (10)	Ag_2O (2)	20	18
6	Cu_2O (10)	Ag_2SO_4 (2)	40	12
7	Cu_2O (5)	Ag_2CO_3 (0.1) + 1 atm O_2	48	35
8[c]	Cu_2O (5)	Ag_2CO_3 (0.1) + 1 atm O_2	78	21
9[c]	Cu_2O (5)	Ag_2CO_3 (0.1) + 1 atm Air	55	43
10[c]	Cu_2O (5)	Ag_2CO_3 (0.05) + 1 atm O_2	70	28
11[c]	**Cu_2O (1)**	**Ag_2CO_3 (0.01) + 1 atm O_2**	**76**	**23**
12[c]	**Cu_2O (1)**	**K_2CO_3 (0.01) + 1 atm O_2**	**80**	**19**
13[c]	Cu_2O (1)	KOH (0.01) + 1 atm O_2	68	16
14[c]	Cu_2O (1)	NaOAc (0.01) + 1 atm O_2	29	13
15[c]	Cu_2O (1)	1 atm O_2	0	0
16[c]	–	K_2CO_3 (0.01) + 1 atm O_2	0	0

[a] Reaction conditions: *p*-anisic acid (1.0 mmol), 1,4-dioxane (3 mL) as solvent, 110 °C, 5−22 h, unless otherwise noted. [b] Crude ^1H NMR yields using 4-bromobenzaldehyde as an internal standard. [c] 1,4-Dioxane (20 mL).

Various carboxylic acids involving aromatic and benzylic carboxylic acids were very effective substrates in this system (Figure 1). Aromatic carboxylic acids with either electron-donating or -withdrawing groups gave good yields of the products (**3b**−**3g**). As a result, the electronic effect of the substituents in aromatic carboxylic acids is not obvious. The *ortho*-substituted benzoic acids were also effective substrates (**3h** and **3i**). The amide group was tolerated in this reaction (**3j**), and the corresponding product **3j** was isolated as a white solid and its structure was confirmed by X-ray diffraction analysis. Naphthoic acid gave a 75% yield of the desired product (**3k**). It is noteworthy that heterocyclic carboxylic acids such as indole, pyrole, benzofuran, etc. gave good yields of the products (**3l**−**3n**). Benzylic acids were also effective substrates (**3o** and **3p**).

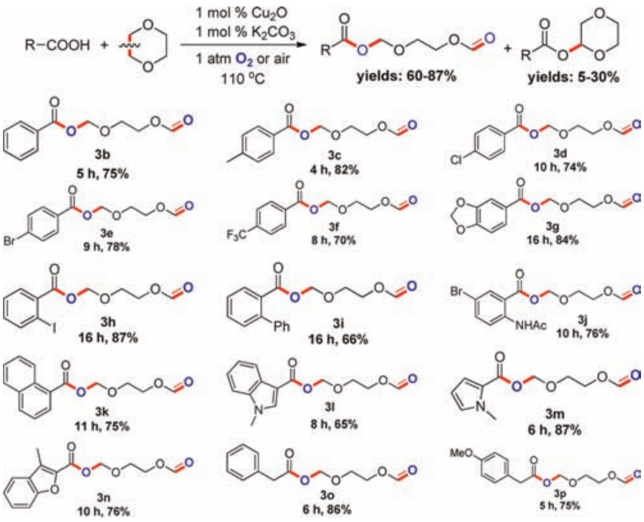


Figure 1. Reactions of various carboxylic acids with 1,4-dioxane. Reaction conditions: Carboxylic acid (1.0 mmol), Cu_2O (0.01 mmol), K_2CO_3 (0.01 mmol), 1,4-dioxane (20 mL), 1 atm O_2, 110 °C. Reaction times, indicated by TLC and isolated yields are shown. For **3l**, the same reaction conditions are used except Ag_2CO_3 (0.01 mmol) was used instead of K_2CO_3 (0.01 mmol).

A series of linear glycol ethers were found to react well with carboxylic acids under the conditions. The methoxymethyl 4-methoxybenzoate **3q** was isolated as the major product in 70% yield by reaction of glycol dimethyl ether with *p*-anisic acid (eq 1). Glycol diethyl ether gave the corresponding product **3r** in 43% yield (eq 2). Interestingly, 2-methoxyethyl ether gave two products by cleavage of different C−C bonds, a 50% yield of **3q** and 35% yield of **3q″**, respectively (eq 3), which might potentially be

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(7) (a) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, *65*, 191. (b) Zhang, Y.; Rovis, T. *Org. Lett.* **2004**, *6*, 1877.

(8) Chen, L.; Shi, E.; Liu, Z.; Chen, S.; Wei, W.; Li, H.; Xu, K.; Wan, X. B. *Chem.—Eur. J.* **2011**, *17*, 4085.

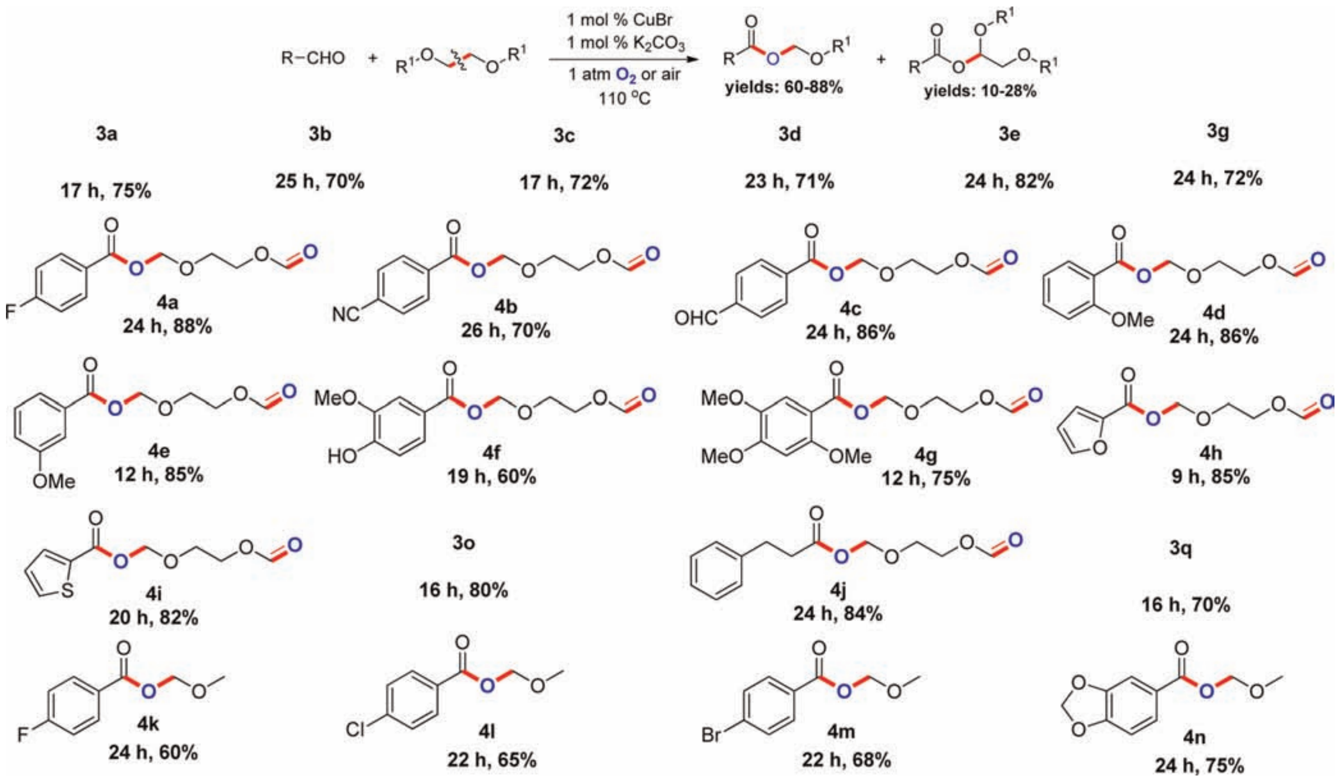
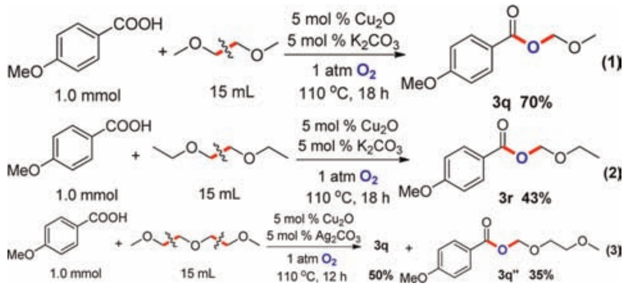


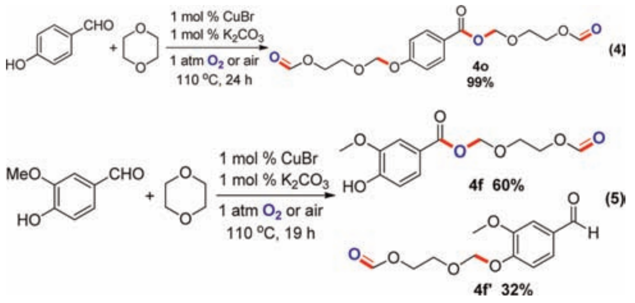
Figure 2. Reactions of various aldehydes with glycol ethers. Reaction conditions: Aldehyde (1.0 mmol), CuBr (0.01 mmol), K_2CO_3 (0.01 mmol), 1,4-dioxane (20 mL), 1 atm O_2, 110 °C. Reaction times and isolated yields are shown. For **3q** and **4k**–**m**, glycol dimethyl ether (15 mL) was used instead of 1,4-dioxane.

applied to the degradation of plastics and polymers made by glycol.



Under similar reaction conditions, a variety of aromatic aldehydes and an aliphatic aldehyde were very effective substrates in this system (Figure 2). Aromatic aldehydes with either electron-donating or -withdrawing groups gave good yields of the products (**3a**–**3g**, **4a**, and **4b**). The product **4c** with retention of one aldehyde group was isolated in 86% yield by reaction of 1,4-phthalaldehyde with dioxane (**4c**). The *ortho*, *meta*, and polysubstituted benzaldehydes were also effective substrates (**4d**–**4g**). It is noteworthy that heterocyclic aldehydes such as furfural and 2-thienylaldehyde gave 85% and 82% yields of the corresponding products, respectively (**4h** and **4i**). Benzylic aldehyde and the phenylpropyl aldehyde were also effective substrates (**3o** and **4j**). Other glycol ethers such as glycol dimethyl ether and glycol diethyl ether were found to react smoothly with various aldehydes under the typical reaction conditions (**3q**, **4k**–**4n**).

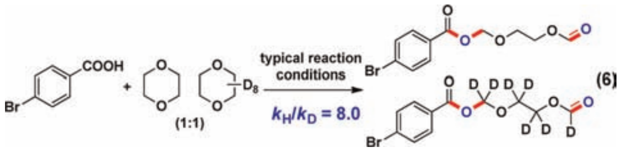
As demonstrated in the following equations, it is very interesting that the copper-catalyzed aerobic C–C bond cleavage of glycol ethers could also be successfully achieved by coupling of some phenols with 1,4-dioxane under the typical conditions (eqs 4 and 5). The product **4o** was isolated in almost quantitative yield by reaction of 4-hydroxybenzaldehyde with 1,4-dioxane (eq 4). The 3-methoxy-4-hydroxybenzaldehyde (vanillin) gave a 60% yield of **4f** and a 32% yield of **4f** (eq 5). Further studies on the coupling reactions of phenols with glycol ethers are ongoing in this laboratory. This protocol could be used as a novel strategy for the protection of phenols in synthetic chemistry.



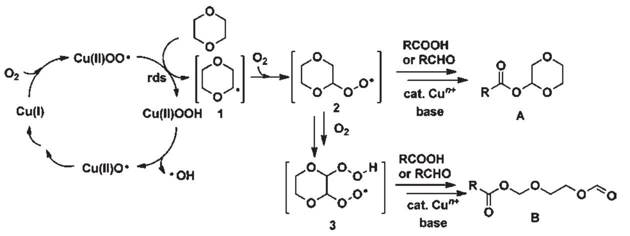
Additionally, this Cu-catalyzed aerobic cleavage of the C–C bond reaction could be scaled up. For example, a mixture of *p*-anisic acid (10.102 g, 0.066 mol), Cu_2O

(0.019 g, 0.13 mmol), K_2CO_3 (0.046 g, 0.33 mmol), and 1,4-dioxane (100 mL) was heated under reflux at 110 °C. Molecular oxygen or air was bubbled into the system for 70 h. When the reaction was finished as indicated by TLC, the solvent was evaporated under vacuum for reusing, and the residue was purified by flash column chromatography (petroleum ether/ethyl acetate) to afford the desired product **3a** (8.1 g, 48%) and **3a** (3.48 g, 22%). Moreover, the results showed that the turnover number (TON) increases with the increasing amount of the substrate (see Supporting Information). It indicates that this process might be conveniently scaled up in industry.

To gain mechanistic insight, a competing kinetic isotope effect (KIE) experiment was carried out (eq 6). As a result, a significant KIE was observed with the $k_H/k_D = 8.0$ (see Supporting Information). It suggests that the C−H bond cleavage should be the rate-determining step of this procedure. Furthermore, 1,4-dioxane gave 1,4-dioxan-2-ol as a major product along with the mono- and diformates of 1,2-ethanediol as minor products without carboxylic acid in this system, which is similar to the results given by Jewett and Lawless[9] that autoxidation of *p*-dioxane gave formate esters of 1,2-ethanediol. The addition of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) does not trap any radical intermediate but stops the reaction. No reactions occur when 4-methylmorpholine replaces dioxane. These two experiments indicate that the copper catalyst may be deactivated by coordination with a N-atom, which was further confirmed by addition of several nitrogen ligands such as *N,N*-dimethylethylenediamine (DMEDA), *N,N,N,N*-tetramethylethylenediamine (TMEDA), and 1,10-phenanthroline giving the same results as above. The minor product cannot give the open-chain product by further reaction with dioxane under the typical conditions. With the experimental data and literature precedent in hand, a plausible mechanism for this catalytic aerobic cleavage of C−C bonds is depicted in Scheme 2. This procedure is most likely a copper-catalyzed autoxidation rather than the copper-O_2 pathways in some enzymes such as tyrosinase and catechol oxidase.[10] Radical intermediate **1** would be formed by hydrogen abstraction from dioxane with a copper(II) peroxide radical, which could be generated by a combination of molecular oxygen with copper(I),[11] and the C−H bond cleavage should be the rate-determining-step. Auto-oxidation via reaction of radical **1** with O_2[12] could generate peroxide radical **2** which would give product **A**, another peroxide radical **3**, and product **B** followed by a series of electron transfer and Cu-promoted homolysis of activated C−H and C−C bonds in glycol ethers. This process should be far more complicated than the present primary mechanism which would be the subject of our future investigations.



Scheme 2. Possible Mechanism



In conclusion, this work demonstrates an unexpected Cu-catalyzed oxidative cleavage of the $C(sp^3)-C(sp^3)$ bond of glycol ether by using air or molecular oxygen as the terminal stoichiometric oxidant. As a result, the corresponding α-acyloxy ethers and formates of 1,2-ethanediol are formed by direct coupling of carboxylic acids and aldehydes with glycol ethers under the reaction conditions. This system would represent the first example of Cu-catalyzed aerobic cleavage of the saturated C−C bond in ethers, which could be potentially applied to the degradation of plastics and polymers made by glycol. Additionally, it could also provide an efficient and convenient protocol for large-scale preparation of various valuable pharmaceuticals containing an α-acyloxy ether subunit by simply coupling carboxylic acids and aldehydes with glycol ethers under mild conditions. Moreover, this process not only could be conveniently scaled up but also is atom-efficient and environmentally benign. This novel system may draw much attention from scientists focused on oxidation chemistry and copper enzymes in biology. Further studies of this system on the mechanism and expansion of the substrate scope are underway in our laboratory.

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Supporting Information Available. Full experimental details and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Jewett, D.; Lawless, J. G. *Bull. Environ. Contam. Toxicol.* **1980**, *25*, 118.

(10) (a) Solomon, E. I.; Sundaram, U. M.; Machonkin, T. E. *Chem. Rev.* **1996**, *96*, 2563. (b) Solomon, E. I.; Chen, P.; Metz, M.; Lee, S.-K.; Palmer, A. E. *Angew. Chem., Int. Ed.* **2001**, *40*, 4570. (c) Gamez, P.; Aubel, P. G.; Driessen, W. L.; Reedijk, J. *Chem. Soc. Rev.* **2001**, *30*, 376. (d) Lewis, E. A.; Tolman, W. B. *Chem. Rev.* **2004**, *104*, 1047.

(11) (a) Cramer, C. J.; Tolman, W. B. *Acc. Chem. Res.* **2007**, *40*, 601. (b) Arends, I.; Gamez, P.; Sheldon, R. A. *Adv. Inorg. Chem.* **2006**, *58*, 235. (c) Que, L., Jr.; Tolman, W. B. *Nature* **2008**, *455*, 333. (d) Wang, Y.; DuBios, J. L.; Hedman, B.; Hodgson, K. O.; Stack, T. D. P. *Science* **1998**, *279*, 537. (e) Prigge, S. T.; Eipper, B. A.; Mains, R. E.; Amzel, L. M. *Science* **2004**, *304*, 864. (f) Mirica, L. M.; Vance, M.; Rudd, D. J.; Hedman, B.; Hodgson, K. O.; Solomon, E. I.; Stack, T. D. P. *Science* **2005**, *308*, 1890. (g) Rolff, M.; Schottenheim, J.; Decker, H.; Tuczek, F. *Chem. Soc. Rev.* **2011**, *40*, 4077.

(12) (a) Walling, C. In *Active Oxygen in Chemistry*; Foote, C. S., Valentine, J. S., Greenberg, A., Liebman, J. F., Eds.; Blackie: 1995; pp 24−65. (b) Chudasama, V.; Fitzmaurice, R. J.; Caddick, S. *Nat. Chem.* **2010**, *2*, 592.

The authors declare no competing financial interest.