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Mn-promoted Aerobic Oxidative C−C Bond Cleavage of Aldehydes with Dioxygen Activation: A Simple Synthetic Approach to Formamides

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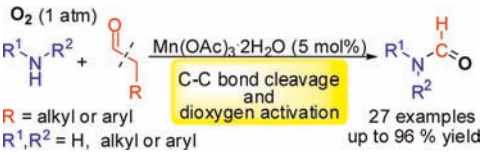
ABSTRACT



A novel Mn-promoted aerobic oxidative C−C bond cleavage of aldehydes with dioxygen activation has been developed. The usage of molecular oxygen (1 atm) as oxidant, reactant, and an initiator to trigger this transformation makes this transformation very green and practical. A plausible radical process is proposed on the basis of mechanistic studies. Furthermore, this method provides a practical, neutral, and mild synthetic approach to formamides, which are important units in biologically active molecules.

The cleavage of the carbon−carbon bond has attracted much attention and emerged as a tremendous challenge in past years.[1] Recently, numerous unique and useful carbon−carbon bond cleavage procedures have been developed.[2−7] Among these procedures, three general strategies have been extensively studied: (1) chelation assistance;[2] (2) the release of strain energy;[3] and (3) cleavage of functionalized substrates with the functional fragment as the leaving group such as carbonyls,[4] nitriles,[5] carboxylic acids,[1c,6] or others.[7] Therefore, the discovery of new processes to achieve carbon−carbon bond cleavage with

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(1) For some reviews, see: (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. (d) Tobisu, M.; Chatani, N. *Chem. Soc. Rev.* **2008**, *37*, 300. (e) Jun, C.-H.; Park, J.-W. *Top. Organomet. Chem* **2007**, *24*, 117.

(2) Sattler, A.; Parkin, G. *Nature* **2010**, *463*, 523.

(3) For some reviews, see: (a) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (b) de Meijere, A. *Chem. Rev.* **2003**, *103*, 931 and reviews in this issue. For some recent examples, see: (c) Seiser, T.; Cramer, N. *J. Am. Chem. Soc.* **2010**, *132*, 5340. (d) Jiang, M.; Liu, L.-P.; Shi, M.; Li, Y. *Org. Lett.* **2010**, *12*, 116. (e) Chen, Z.; Lai, W.; Zhang, J. *Org. Lett.* **2011**, *13*, 1170. (f) Lin, M.; Li, F.; Jiao, L.; Yu, Z.-X. *J. Am. Chem. Soc.* **2011**, *133*, 1690.

(4) (a) 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. (b) Chiba, S.; Zhang, L.; Ang, G. Y.; Hui, B. W.-Q. *Org. Lett.* **2010**, *12*, 2052. (c) Mecinovic, J.; Hamed, R. B.; Schofield, C. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2796. (d) He, C.; Gou, S.; Huang, L.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 8273.

(5) (a) Tobisu, M.; Kinuta, H.; Kita, Y.; Rémond, E.; Chatani, N. *J. Am. Chem. Soc.* **2012**, *134*, 115. (b) Hirata, Y.; Yada, A.; Morita, E.; Nakao, Y.; Hiyama, T.; Ohashi, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2010**, *132*, 10070.

(6) (a) Hu, P.; Zhang, M.; Jie, X.; Su, W. *Angew. Chem., Int. Ed.* **2012**, *51*, 227. (b) Shang, R.; Fu, Y.; Li, J.-B.; Zhang, S.-L.; Guo, Q.-X.; Liu, L. *J. Am. Chem. Soc.* **2009**, *131*, 5738. (c) Pusterla, I.; Bode, J. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 513. (d) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 5776. (e) Cicchillo, R. M.; Zhang, H.; Blodgett, J. A. V.; Whitteck, J. T.; Li, G.; Nair, S. K.; Donk, W. A.; Metcalf, W. W. *Nature* **2009**, *459*, 871. (f) Gooβen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662.

(7) (a) Li, H.; Li, W.; Liu, W.; He, Z.; Li, Z. *Angew. Chem., Int. Ed.* **2011**, *50*, 2975. (b) Waibel, M.; Cramer, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 4455. (c) Li, H.; Li, Y.; Zhang, X.-S.; Chen, K.; Wang, X.; Shi, Z.-J. *J. Am. Chem. Soc.* **2011**, *133*, 15244. (d) Baidya, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2011**, *133*, 13880. (e) Gunay, A.; Jones, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 8729. (f) Jones, W. D. *Nature* **1993**, *364*, 676. (g) Chen, C.; Kehr, G.; Frohlich, R.; Erker, G. *J. Am. Chem. Soc.* **2010**, *132*, 13594. (h) During the preparation of this manuscript, a elegant metal-free oxidative C−C bond cleavage with a similar process was reported; see:Tiwari, B.; Zhang, J.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 1911.

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unactivated fragments as the leaving group still remains a big challenge. Herein, we disclose a novel Mn-promoted aerobic oxidative C−C bond cleavage of value for formamide synthesis (Figure 1). The significance of this present finding is 3-fold: (1) the method realizes C−C σ-bond cleavage with an unactivated alkyl chain fragment as the leaving group; (2) environmentally friendly molecular oxygen is used as the primary oxidant[8,9] and the C−C bond cleavage proceeds via a superoxide radical pathway; (3) the chemistry provides a practical, neutral, and mild synthetic approach to formamides, which are important units in biologically active molecules of wide substrate scope.[10]

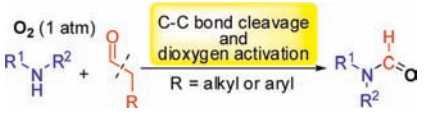


Figure 1. Simple synthetic approach to formamides.

Our studies commenced with the reactions of 4-aminobenzonitrile (**1a**) and hexanal (**2a**) using toluene as solvent at 90 °C under O_2 (1 atm). Interestingly, *N*-(4-cyanophenyl)formamide was produced in 69% yield (entry 1, Table S1 Supporting Information). Further studies indicated that transition metals could benefit this transformation. Among these metal salts, $Mn(OAc)_3 \cdot 2H_2O$ was the most effective, promoting the yield of **3aa** to 84% (entry 5, Table S1, Supporting Information).

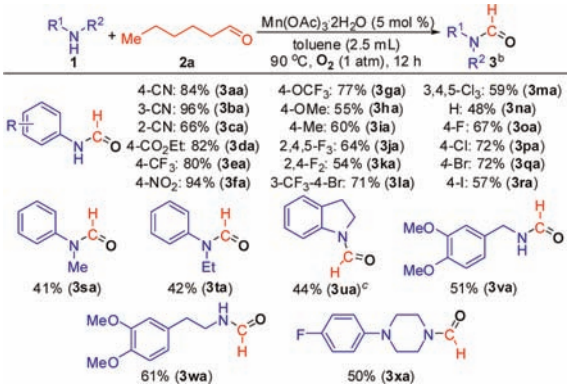
Under these optimized conditions, the scope of substituted amine (**1**) was investigated (Scheme 1). Our results indicate that anilines with both electron-donating and electron-withdrawing groups operate well in this reaction, giving moderate to excellent yields. Furthermore, substituents at different positions of the arene group (*para-*, *meta-*, and *ortho*-position) do not affect its efficiency. Notably, even when chloro-, bromo-, and iodo-substituted aniline were employed as substrates, the desired formamides **3pa**, **3qa**, and **3ra** were formed in 72%, 72%, and

(8) Dioxygen has been used as an ideal oxidant; for some reviews, see: (a) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005**, *105*, 2329. (b) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400. (c) Sigman, M. S.; Jensen, D. R. *Acc. Chem. Res.* **2006**, *39*, 221. (d) Gligorich, K. M.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 6612. (e) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062. (f) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381.

(9) For some selected reactions on dioxygen activation in recent years, see: (a) Chiba, S.; Zhang, L.; Lee, J.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 7266. (b) Wang, H.; Wang, Y.; Liang, D.; Liu, L.; Zhang, J.; Zhu, Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 5678. (c) Wang, J.; Wang, J.; Zhu, Y.; Lu, P.; Wang, Y. *Chem. Commun.* **2011**, *47*, 3275. (d) King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 12068. (e) Decharin, N.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 5732. (f) Campbell, A. N.; White, P. B.; Guzei, L. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 15116. (g) Du, F.-T.; Ji, J.-X. *Chem. Sci* **2012**, *3*, 460. (h) Rolff, M.; Schottenheim, J.; Peters, G.; Tuczek, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 6438. (i) Schröder, K.; Join, B.; Amali, A. J.; Junge, K.; Ribas, X.; Costas, M.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 1425. (j) Zhang, C.; Xu, Z.; Zhang, L.; Jiao, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 11088.

(10) (a) Miyauchi, M.; Endoh, Y.; Uematsu, T. *Bull. Environ. Contam. Toxicol.* **1995**, *55*, 446. (b) Yuta, K.; Jurs, P. C. *J. Med. Chem.* **1981**, *24*, 241. (c) Popoff, I. C.; Singhal, G. H.; Engle, A. R. *J. Med. Chem.* **1971**, *14*, 550.

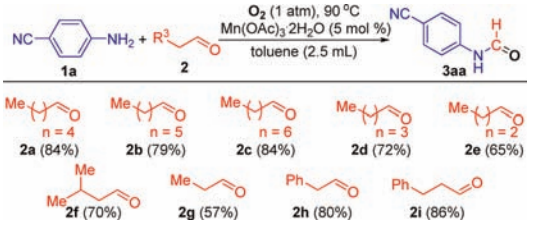
Scheme 1. Aerobic Oxidation of Different Amines (**1**) with **2a**[a]



[a] Standard reaction conditions; see entry 5, Table S1. [b] Isolated yields; the conversions are nearly 100%. [c] The standard reaction conditions without $Mn(OAc)_3 \cdot 2H_2O$.

57% yield, respectively. The structure of **3qa** was further confirmed by single-crystal X-ray analysis (see Figure S1, Supporting Information). It is noteworthy that *N*-substituted anilines such as *N*-methyl- and *N*-ethylanilines could be smoothly transformed into the desired products (**3sa** and **3ta**, Scheme 1). Under metal-free conditions, indoline could be converted into the desired product in moderate yield (**3ua**, Scheme 1). Interestingly, alkylamines also worked well under the standard reaction conditions (**3va**, **3wa**, and **3xa**, Scheme 1). Furthermore, the conversions of all the substituted amines are 100%.

Scheme 2. Aerobic Oxidation of **1a** with Different Aldehydes (2)[a]



[a] Standard reaction conditions; see entry 5, Scheme 1. [b] Isolated yields.

The scope of the aerobic C−C bond oxidative cleavage to obtain formamides was further expanded to a variety of substituted aldehydes (**2**) (Scheme 2). Our results indicated that the aldehydes with longer alkyl chains tended to afford higher yields of product (**2a**−**2g**, Scheme 2). Interestingly, substrates with steric hindrance did not lower the efficiency of this transformation (**2f**, Scheme 2). Furthermore, when the leaving group was an aryl these substrates also worked well (**2h** and **2i**, Scheme 2).

As formamides are ubiquitous structural motifs that can be found in many bioactive compounds,[10] the present method provides a simple and easy practical protocol for the construction of some bioactive compounds under neutral

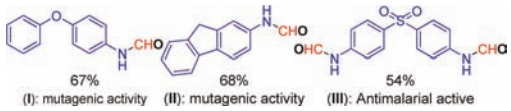


Figure 2. Biologically active molecules.

conditions from simple and readily available starting materials (Figure 2 and Supporting Information). For example, **I**[10a] and **II**[10b] are reported as mutagenic active molecules, which can be easily synthesized from the corresponding simple starting materials. Furthermore, **III**[10c] is reported as an antimalarial active molecule, which can be constructed in one step by the present protocol (Figure 2 and Supporting Information).

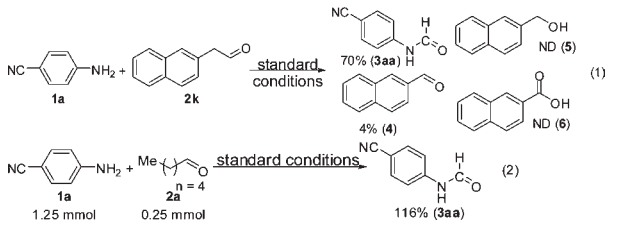


Figure 3. Control experiments to detect the byproducts.

To analyze the aldehyde fragmentation products, **1a** was reacted with 2-(naphthalen-2-yl)acetaldehyde (**2k**) under standard reaction conditions (1, Figure 3). From the reaction system, the desired product **3aa** and 2-naphthaldehyde (**4**) were obtained in 70% and 4% yields, respectively. Other conceivable byproducts such as naphthalen-2-ylmethanol (**5**) and 2-naphthoic acid (**6**) were not detected by GC−MS (1, Figure 3). Many unknown byproducts were isolated that might be polymers of the fragments.

When 5 equiv of **1a** was employed in the reaction with **2a**, the desired product **3aa** was obtained in 116% yield (2, Figure 3). The isolated yield was calculated on the basis of substrate **2a**. This fact provides additional evidence that other additional aldehydes could be formed in this transformation. It is also concluded that the aldehyde is not the sole byproduct; otherwise, the higher yield could be achieved in this control reaction.

To further probe the reaction mechanism, the reaction of **1a** with carbon monoxide under the standard conditions was investigated (1, Figure 4). However, the desired product **3aa** was not obtained. This result might exclude carbon monoxide as the intermediate of this aerobic oxidative C−C bond cleavage transformation. The reaction of **1a** and **2a** in the presence of $^{18}O_2$ (1 atm) generated ^{18}O labeling product ***[18]O*-3aa** in 80% yield (2, Figure 4, determined by HRMS, see the Supporting Information), which indicates that the oxygen atom of the formamide product originated from molecular oxygen.

On the basis of the above results, a plausible mechanism for this aerobic oxidative C−C bond cleavage is illustrated

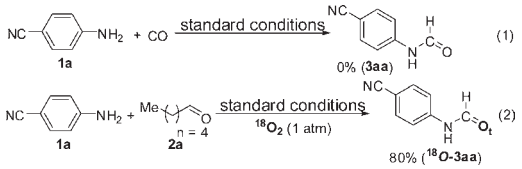
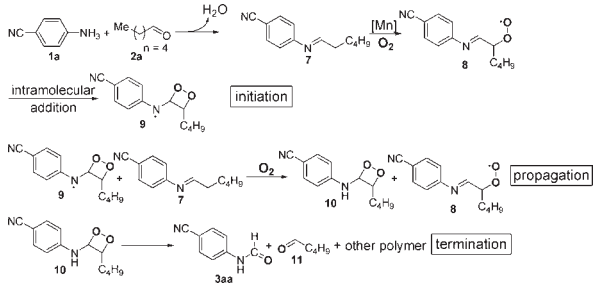


Figure 4. Origination of oxygen atom.

in Scheme 3. 4-Aminobenzonitrile (**1a**) and hexanal (**2a**) initially dehydrate to form imine (**7**).[11] Imine (**7**) could be oxidized to superoxide radical (**8**) by a radical pathway

Scheme 3. Proposed Mechanism



under O_2.[12] Further intramolecular radical addition to the imine generates the radical intermediate (**9**).[13] Mn(III) salt may assist the above two steps via a single electron-transfer process.[14] Under O_2 conditions, **9** could react with the imine (**7**) to form intermediates **10** and **8**.[12] Then **8** could produce the intermediate **9** to realize the propagation. Finally, the fragmentation of **10** would produce the desired

(11) (a) Shiraishi, Y.; Ikeda, M.; Tsukamoto, D.; Tanaka, S.; Hirai, T. *Chem. Commun.* **2011**, *47*, 4811. (b) Casey, C. P.; Johnson, J. B. *J. Am. Chem. Soc.* **2005**, *127*, 1883. (c) Mannathusamy, G.; Purushothaman, S.; Vijayakumar, K.; Jeyaraman, T.; Ramalingam, G. *J. Chem. Res.* **2005**, *5*, 299.

(12) (a) Rieche, A.; Hoeft, E.; Schultze, H. *Chem. Ber.* **1964**, *97*, 195. (b) *Science of Synthesis. Compounds with One Saturated Carbon-Heteroatom Bond. Peroxides*; Berkessel, A., Ed.; Thieme: Stuttgart, 2009; Vol. 38, pp 9−141. (c) Simándi, L.; Simándi, T. M.; May, Z.; Besenyei, G. *Coord. Chem. Rev.* **2003**, *245*, 85. (d) Schank, K.; Beck, H.; Werner, F. *Helv. Chim. Acta* **2000**, *83*, 1611. (e) Davies, A. G.; Foster, R. V.; Nery, R. *J. Chem. Soc.* **1954**, 2204. (f) Yamamoto, H.; Akutagawa, M.; Aoyama, H.; Omote, Y. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2300. (g) Nakamura., H.; Goto, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3776. (h) Wang, A.; Jiang, H. *J. Am. Chem. Soc.* **2008**, *130*, 5030. (i) Zhang, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 28.

(13) (a) Sequeira, F. C.; Turnpenny, B. W.; Chemler, S. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 6365. (b) Zeng, W.; Chemler, S. R. *J. Am. Chem. Soc.* **2007**, *129*, 12948. (c) Fuller, P. H.; Kim, J.-W.; Chemler, S. R. *J. Am. Chem. Soc.* **2008**, *130*, 17638. (d) Semmelhack, M. F.; Schmid, C. R.; Cortés, D. A.; Chou, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 3374. (e) Gamez, P.; Arends, I. W. C. E.; Reedijk, J.; Sheldon, R. A. *Chem. Commun.* **2003**, 2414. (f) Maeda, Y.; Nishimura, T.; Uemura, S. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2399. (g) Semmelhack, M. F.; Schmid, C. R.; Cortes, D. A.; Chou, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 3374. (h) Dijksman, A.; Arends, I. W. C. E.; Sheldon, R. A. *Org. Biomol. Chem.* **2003**, *1*, 3232.

(14) (a) Wu, X.; Seo, M. S.; Davis, K. M.; Lee, Y.-M.; Chen, J.; Cho, K.-B.; Pushkar, Y. N.; Nam, W. *J. Am. Chem. Soc.* **2011**, *133*, 20088. (b) Yu, X.; Liu, C.; Jiang, L.; Xu, Q. *Org. Lett.* **2011**, *13*, 6184. (c) Wang, Y.-F.; Toh, K. K.; Chiba, S.; Narasaka, K. *Org. Lett.* **2008**, *10*, 5019. (d) Chan, W.-K.; Ho, C,-M.; Wong, M.-K.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 14796.

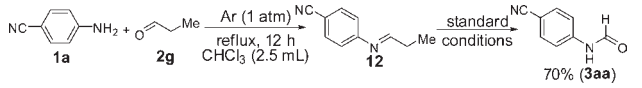


Figure 5. Reaction of imine intermediate.

formamide (**3aa**), aldehyde (**11**), and some unknown polymer byproduct.

To prove that imines play a role as key intermediates in this transformation, imine intermediate **12** was employed under the standard reaction conditions (Figure 5 and Supporting Information). After 12 h, the desired product **3aa** was obtained in 70% yield (Figure 5 and Supporting Information). These results illustrate that imines can serve as the key intermediates in this transformation.

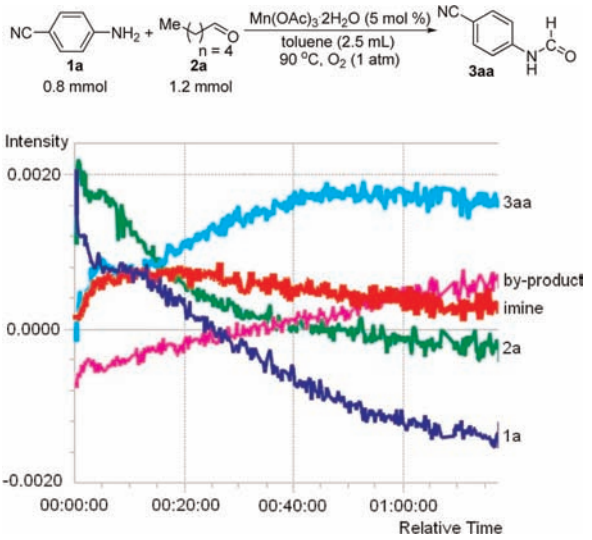


Figure 6. Data of in situ FT-IR analysis during the reaction of **1a** and **2a**.

The presence of imine (1654 cm^{-1}: C=N stretching vibration) was also supported by the data of in situ FT-IR analysis (Figure 6; for more details, see the Supporting Information). As shown in Figure 2, the concentration of imine increased quickly at the initial stage of this transformation. After that, the signal of imine decreased slowly under the same reaction conditions. These facts not only prove the presence of imine (**7**) but also indicate that the dehydration to form imines (**7**) is not the rate-determining step. Furthermore, from the in situ FT-IR data, we could also detect the presence of the byproduct which may be the polymer (Figure 6).

To probe the mechanism of this transformation, we tried to catch some intermediates by EPR. In the EPR spectra monitored with the addition of the radical trap 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO), the signal

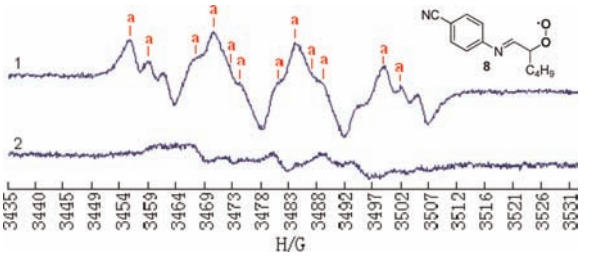


Figure 7. Electron paramagnetic resonance (EPR) spectra: (1) reaction mixture in the presence of the radical trap DMPO (2.5×10^{-2} M); (2) reaction mixture in the presence of the SOD ($2.5 \times 10-3$ M) and the radical trap DMPO ($1.25 \times 10-2$ M).

corresponding to (DMPO−OO(H) has been identified.[12i] (See the "a" peaks in (1), Figure 7. There are 12 classical peaks. The calculated hyperfine splittings are g_0 (2.050), α_N (14.3 G), α^{β}_H (15.2 G), and α^{γ}_H (2.6 G).) The above signal disappeared with the addition of the superoxide dismutase (SOD) ((2), Figure 7). These data (for more details, see the Supporting Information) indicate that the superoxide radical **8** may play a role as a key intermediate in this transformation (Scheme 3 and Figure 7). Furthermore, there were no radical signals detected when the reaction was carried out under Ar (1 atm) (see the Supporting Information). This result proves that molecular oxygen is not only the oxidant but also the initiator to trigger this radical process.

In conclusion, we have demonstrated a novel Mn-promoted aerobic oxidative C−C bond cleavage of aldehydes with dioxygen activation. This chemistry realizes the aerobic oxidative cleavage of a carbon−carbon σ-bond with an inert alkyl chain fragment as the leaving group. The use of molecular oxygen (1 atm) as the oxidant, reactant, and initiator to trigger this radical process under mild conditions makes this transformation green and practical. This method provides a practical, neutral, and mild synthetic approach to formamides of wide structural variety. A plausible radical process is proposed on the basis of mechanistic studies. Further studies to clearly understand the reaction mechanism and the synthetic applications are ongoing in our laboratory.

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Supporting Information Available. Experimental details and NMR spectral analysis of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.