Editor's Choice

Iron-catalyzed Selective Oxidation of α,β-Unsaturated Aldehydes to α,β-Unsaturated Carboxylic Acids by Molecular Oxygen

Shinji Tanaka, Yoshihiro Kon, Yumiko Uesaka, Ryo Morioka, Masanori Tamura, and Kazuhiko Sato*

Interdisciplinary Research Center for Catalytic Chemistry, National Institute of Advanced Industrial Science and Technology (AIST), Central 5, Higashi 1-1-1, Tsukuba

(E-mail: k.sato@aist.go.jp)

Selective oxidation of α,β-unsaturated aldehydes to α,β-unsaturated carboxylic acids was performed using O_2 as the oxidant in the presence of a simple iron catalyst. The addition of an alkali metal carboxylate as a cocatalyst enhanced the selectivity for the desired product. Redox tuning of the iron catalyst via association with the alkali metal led to a controlled radical generation during the catalytic O_2 oxidation.

Molecular oxygen (O_2) is a readily available, inexpensive oxidant and is regarded as a promising natural resource for oxygen-containing chemical products.[1,2] Conventional chemical processes including oxidations often use stoichiometric amounts of hazardous oxidants, leading to the formation of equimolar amounts of a by-product as waste. Although oxidation by O_2 would proceed with 100% atom efficiency under ideal conditions and thus generate no waste, such dioxygenase-type reactions have been reported less frequently than monooxygenase- and oxidase-type oxidation reactions, in which only one O atom of O_2 incorporates into substrate and O_2 is consumed by re-oxidation of catalyst, respectively.[3] In particular, the synthesis of value-added chemical products should be replaced by dioxygenase-type reactions to reduce waste generated during multistep reactions.

α,β-Unsaturated carboxylic acids are among the most valuable intermediates and precursors for chemical production and pharmaceuticals.[4] Although the oxidation of aliphatic aldehyde into carboxylic acids proceeds by O_2 even without a catalyst,[5,6] several methods have been developed for the preparation of α,β-unsaturated carboxylic acids from their aldehyde derivatives, requiring severe and complex reaction conditions.[7] Recently, N-heterocyclic carbene (NHC)-catalyzed O_2 oxidation reactions of α,β-unsaturated aldehyde were developed by several groups, yet more than equimolar amounts of base were essential for good reaction yields.[8] From the standpoint of green-sustainable chemistry, catalytic oxidation using O_2 without large amounts of base is promising even if an organocatalyst could be employed.[9] Nobile et al. reported a Fe catalyst bearing 2-(acetoacetoxy)ethyl methacrylate ligand-catalyzed O_2 oxidation of trans-2-hexenal; however, substrates were limited and a halogenated solvent was required.[10] Mukaiyama et al. proposed the effectiveness of β-diketonate ligand to activate metal-catalyzed oxidation.[11] More useful methods and systems to activate a base-metal complex must be developed to realize practical O_2 oxidation for the production of valuable fine chemicals.

It is widely accepted that non-redox metal ions have considerable effect on the redox state of redox-active metal, promoting electron-transfer reactions[12] as well as catalytic reactions.[13] An appropriate combination of redox-active and non-redox-active base metals might act as simpler catalysts exhibiting enhanced activity in oxidation reactions. Herein, we report the preparation of α,β-unsaturated carboxylic acids from α,β-unsaturated aldehydes using a combination of O_2 and a Fe catalyst whose catalytic activity was induced by the simple addition of alkali metal carboxylate.

During our study on oxidation of allylic alcohols by Fe catalyst,[14] we found that some product aldehydes oxidized into carboxylic acid under air after standing a long time, without the use of β-diketonate metal complex, which is a highly reactive catalyst.[11] Stimulated by this unexpected finding, we carried out catalytic O_2 oxidation of α,β-unsaturated aldehyde by simple Fe salt, using trans-2-decenal (**1a**) as a model substrate (Table 1). **1a** was treated with 0.01 equiv of $Fe(NO_3)_3 \cdot 9H_2O$ in EtOAc solution at 25 °C under atmospheric pressure of O_2, resulting in the full conversion of the substrate and the formation of trans-2-decenoic acid (**2a**) in 49% yield (Entry 2). ^{1}H NMR of the product mixture indicated the presence of trans-2-perdecenoic acid (25%), and octanoic acid (12%) as by-products, which have been generated by undesired oxidation of the olefin part.[6c] No oxidation occurred in the absence of the catalyst (Entry 1). When 0.2 equiv of CH_3COONa was added in this catalysis, product yield and selectivity were improved to 76% and 77%, respectively (Entry 3), while other sodium salts, $NaNO_3$ and NaOTf, were less effective (Entries 4 and 5).[15] For other Fe salts, [Fe(acac)$_3$] catalyzed the oxidation to yield **2a** in 55% yield with 56% selectivity (Entry 6), and $Fe(OAc)_2$ did not show catalytic activity due to low solubility (Entry 7). CF_3COONa, a more electronegative carboxylate salt, increased product yield and selectivity (Entry 8), and thus trifluoroacetic acid and its salts were screened as additives. Interestingly, higher yields and selectivity were achieved when salts containing larger mono-cations were added (Entries 8, 10, 11, and 12), whereas the addition of acid (Entry 9) or Zn salt (Entry 13) was less effective. A higher substrate concentration (2 M) induced higher yield and selectivity of **2a** in the presence of Na and K salts (Entries 14 and 15). Selective oxidation proceeded even under air, giving **2a** in 72% yield with 86% selectivity (Entry 17). Moreover, **2a** was not generated under Ar (Entry 18).

After optimization of catalysis conditions, we screened the substrates (Table 2). α,β-Unsaturated aldehydes having linear alkyl groups, such as crotonaldehyde (**1b**), trans-2-pentenal (**1c**), and trans-2-hexenal (**1d**), were oxidized to corresponding carboxylic acids in good yields with high selectivity (Entries 1–3). 3-Methyl-2-butenoic acid (**2e**), which includes reactive trisubstituted olefin, was obtained at lower yield (Entry 4). For aromatic aldehydes, benzaldehyde (**1f**) and 2-thiophenecarboxaldehyde (**1g**) were oxidized into corresponding acids **2f** and **2g** in moderate-to-high yields though oxidation of **1g** required longer reaction time (Entry 6). Aldehydes having an alkyne

Table 1. Oxidation of *trans*-2-decenal under various conditions[a]

Fe(NO$_3$)$_3$·9H$_2$O (0.01 equiv)
Additive (0.2 equiv)
O$_2$ (1 atm)

n-C$_7$H$_{15}$ —CHO (**1a**) → EtOAc, 25 °C, 16 h → n-C$_7$H$_{15}$—COOH (**2a**)

Entry	Additive	Conv. /%[b]	Yield /%[b]	Selec. /%[b]
1[c]	none	0	0	0
2	none	98	48	49
3	CH$_3$COONa	99	76	77
4	NaNO$_3$	98	58	59
5	NaOTf	96	67	70
6[d]	none	>99	55	56
7[e]	none	0	0	0
8	CF$_3$COONa	98	77	79
9	CF$_3$COOH	97	49	51
10	CF$_3$COOLi	>99	70	70
11	CF$_3$COOK	94	86	91
12	CF$_3$COOCs	93	83	89
13	(CF$_3$COO)$_2$Zn	58	45	78
14[f]	CF$_3$COONa	89	86 (82)[g]	97
15[f]	CF$_3$COOK	93	85	91
16[f]	CF$_3$COOCs	90	81	90
17[f,h]	CF$_3$COONa	84	72	86
18[f,i]	CF$_3$COONa	5	0	0

[a]Reaction conditions: *trans*-2-decenal (1 mmol), Fe(NO$_3$)$_3$·9H$_2$O (0.01 mmol), additive (0.2 mmol), EtOAc (1.0 mL), O$_2$ balloon (1 atm), 25 °C, 16 h, unless otherwise stated. [b]Determined by ^{1}H NMR using biphenyl as internal standard. Selec. = Yield/Conv. × 100. Yields of isolated product were shown in parentheses. [c]Without Fe(NO$_3$)$_3$·9H$_2$O. [d][Fe(acac)$_3$] was used instead of Fe(NO$_3$)$_3$·9H$_2$O. [e]Fe(OAc)$_2$ was used instead of Fe(NO$_3$)$_3$·9H$_2$O. [f]EtOAc (0.50 mL). [g]Gram scale (25 mmol of substrate). [h]Under Air. [i]Under Ar.

Table 2. Scope and limitation of the aldehydes[a]

Entry	Substrate	Product	Conv. /%[b]	Yield/%[b]	Selec. /%[b]
1[c]	1b	2b	99	84	85
2	C$_2$H$_5$ 1c	C$_2$H$_5$ 2c	99	86 (85)[d,e]	87
3	n-C$_3$H$_7$ 1d	n-C$_3$H$_7$ 2d	>99	87 (88)[f]	87
4	1e	2e	92	49 (38)[f]	53
5	Ph 1f	Ph 2f	98	97 (90)[f]	99
6[e,f]	1g	2g	95	75 (74)	79
7[f]	n-C$_5$H$_{11}$ 1h	n-C$_5$H$_{11}$ 2h	88	78 (82)	89
8	Me$_3$Si 1i	Me$_3$Si 2i	96	84 (69)[f]	88
9[c]	1j	2j	76	32	42

[a]Reaction conditions: aldehyde (1 mmol), Fe(NO$_3$)$_3$·9H$_2$O (0.01 mmol), CF$_3$COONa (0.2 mmol), EtOAc (0.50 mL), O$_2$ balloon (1 atm), 25 °C, 16 h, unless otherwise stated. [b]Determined by ^{1}H NMR using biphenyl or hexamethylbenzene as internal standard. Selec. = Yield/Conv. × 100. Yields of isolated product were shown in parentheses. [c]Determined by GC using biphenyl as internal standard. [d]Gram scale (25 mmol of substrate). [e]40 h. [f]5 mmol scale.

moiety at the α,β-position are also less reactive towards oxidation in the absence of catalyst.[6c] In this catalysis, carboxylic acids having alkyne moiety at the α,β-position, **2h** and **2i**, were obtained in better yields and selectivity (Entries 7 and 8) compared with those of reported catalytic O$_2$ oxidations.[8c,16] Oxidations of acrolein **1j** were less selective, giving acrylic acid **2j** in 32% (Entry 9).
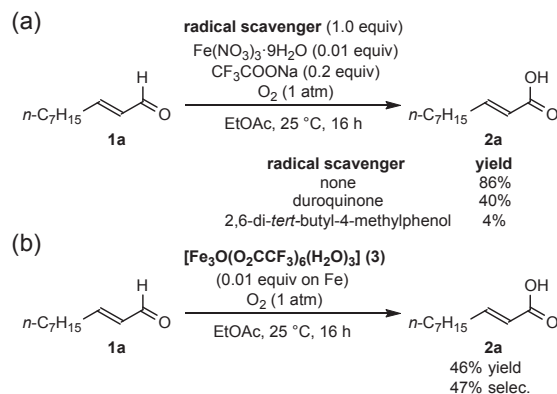
To demonstrate the practical applicability of our proposed method, gram-scale (25 mmol of substrate) reactions were attempted for several substrates. 3.5 g of *trans*-2-decenoic acid (**2a**) and 2.1 g of *trans*-2-pentenoic acid (**2c**) were isolated successfully (Table 1, Entry 14; Table 2, Entry 2).

Control experiments were conducted to elucidate the reaction mechanism. Generally, aerobic oxidation of aldehydes was initiated by the generation of acyl radical from aldehyde, followed by radical coupling with O$_2$.[5] The resulting acylperoxo radical species was reduced to percarboxylic acid via H atom abstraction or reduction by metal catalyst, and finally the reaction between percarboxylic acid and aldehyde gave two carboxylic acids (Scheme S1). In fact, radical scavengers such as duroquinone and 2,6-di-*tert*-butyl-4-methylphenol diminished the yield of product (Scheme 1a). Although aliphatic aldehydes are oxidized under O$_2$ even without a catalyst,[5] in the present

(a)
radical scavenger (1.0 equiv)
Fe(NO$_3$)$_3$·9H$_2$O (0.01 equiv)
CF$_3$COONa (0.2 equiv)
O$_2$ (1 atm)

n-C$_7$H$_{15}$ —CHO (**1a**) → EtOAc, 25 °C, 16 h → n-C$_7$H$_{15}$—COOH (**2a**)

radical scavenger	yield
none	86%
duroquinone	40%
2,6-di-*tert*-butyl-4-methylphenol	4%

(b)
[Fe$_3$O(O$_2$CCF$_3$)$_6$(H$_2$O)$_3$] (**3**)
(0.01 equiv on Fe)
O$_2$ (1 atm)

n-C$_7$H$_{15}$ —CHO (**1a**) → EtOAc, 25 °C, 16 h → n-C$_7$H$_{15}$—COOH (**2a**)
46% yield
47% selec.

Scheme 1. Control experiments.

reaction a metal catalyst was necessary for the activation of the aldehyde due to the stabilization effect of the unsaturated part. Catalytic activity for metal-catalyzed aerobic oxidation is highly

dependent on the redox potential of the catalyst.[15] For example, a nickel complex bearing electron-donating β-diketonate ligands showed high catalytic activity.[17] Nevertheless, an electron-deficient additive enhanced selectivity for the product in this catalysis. A possible catalyst generated in the reaction mixture was $[Fe_3O(O_2CCF_3)_6(H_2O)_3]$ (**3**).[18] The catalytic oxidation of **1a** by **3**, however, afforded **2a** with only 47% selectivity, indicating that **3** is not an active catalyst (Scheme 1b). Thus, we postulated that an iron-carboxylate complex associated with alkali metal might be the active catalyst for this reaction. This assumption was consistent with the fact that selectivity relied on the kind of alkali metal of carboxylate salt (Table 1, Entries 8, 10, 11, and 12).

The incorporation of non-redox-active metal lowered the redox potential of the redox-active metal center in some complexes.[12] Electrochemical analysis of $Fe(NO_3)_3 \cdot 9H_2O$ in EtOAc exhibited a redox wave due to Fe^{3+}/Fe^{2+} at -2 mV vs. FcH. Upon the addition of CF_3COONa, a reduction wave was observed as a shoulder at a potential lower than that of $Fe(NO_3)_3 \cdot 9H_2O$ itself, and was negatively shifted as larger amounts of CF_3COONa were added (Figure S1 and Table S2). The re-oxidation wave also shifted negatively, suggesting that the accumulation of alkali metal carboxylate stabilized Fe at a higher oxidation state. Based on this observation, the Fe(III)-assisted generation of acyl radical from aldehyde was controlled to remain at a low concentration. In addition, the reduction of acylperoxo radical into percarboxylic acid was facilitated by the iron catalyst, inhibiting the side reactions of the radical species at the olefin moiety as well as the generation of acyl radical via a chain reaction. Altogether, a low concentration of the radical species was maintained throughout the catalytic reaction, leading to higher selectivity for the product.

A variety of polynuclear 3d transition metal complexes containing alkali metal was known.[19] Thereby, we attempted to isolate the Fe–Na complex by a reaction of $Fe(NO_3)_3 \cdot 9H_2O$ with an excess amount of CF_3COONa in EtOAc under O_2. A red compound was obtained, exhibiting peaks assignable to $[Fe_3\text{-}Na(CF_3COO)_{10}(EtOAc)]^-$ and $[Fe_3Na_2(CF_3COO)_{11}(EtOAc)]^-$ at m/z 1408 and 1544 in ESI-MS spectra, respectively (Figure S2). Catalysis on oxidation of **1a** using this compound gave **2a** in 82% yield.

In summary, we achieved selective oxidation of α,β-unsaturated aldehyde into α,β-unsaturated carboxylic acid by O_2, using an iron catalyst. The alkali metal carboxylate additive played a key role in the enhancement of selectivity. Although additional experiments are necessary to clarify the mechanism underlying this reaction, it is clear that Fe-alkali metal species having lower redox potential efficiently controlled the radical reaction between the organic compound and O_2. The development of such a redox catalyst enabling a controlled O_2 oxidation reaction is under way in our laboratory.

References and Notes

1 *Modern Oxidation Methods*, 2nd ed., ed. by J.-E. Bäckvall, Wiley-VCH, Weinheim, **2011**. doi:10.1002/9783527632039.

2 a) T. Punniyamurthy, S. Velusamy, J. Iqbal, *Chem. Rev.* **2005**, *105*, 2329. b) R. Irie, T. Uchida, K. Matsumoto, *Chem. Lett.* **2015**, *44*, 1268.

3 Recent reports for O_2 oxidation: a) A. Gonzalez-de-Castro, C. M. Robertson, J. Xiao, *J. Am. Chem. Soc.* **2014**, *136*, 8350. b) G. J. Chuang, W. Wang, E. Lee, T. Ritter, *J. Am. Chem. Soc.* **2011**, *133*, 1760. c) V. A. Schmidt, E. J. Alexanian, *Angew. Chem., Int. Ed.* **2010**, *49*, 4491.

4 J. K. Augustine, Y. A. Naik, A. B. Mandal, N. Chowdappa, V. B. Praveen, *J. Org. Chem.* **2007**, *72*, 9854, and references cited therein.

5 M. B. Smith, J. March, in *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th ed., Wiley, New York, **2007**, p. 1769.

6 Recent reports for aerobic oxidation of aldehydes: a) C. Marteau, F. Ruyffelaere, J.-M. Aubry, C. Penverne, D. Favier, V. Nardello-Rataj, *Tetrahedron* **2013**, *69*, 2268. b) N. Shapiro, A. Vigalok, *Angew. Chem., Int. Ed.* **2008**, *47*, 2849. c) V. Chudasama, A. R. Akhbar, K. A. Bahou, R. J. Fitzmaurice, S. Caddick, *Org. Biomol. Chem.* **2013**, *11*, 7301.

7 a) C. W. Smith, R. T. Holm, *J. Org. Chem.* **1957**, *22*, 746. b) H. Rapoport, W. Nilsson, *J. Org. Chem.* **1962**, *27*, 629. c) A. Nishihara, I. Kubota, *J. Org. Chem.* **1968**, *33*, 2525.

8 a) O. Bortolini, C. Chiappe, M. Fogagnolo, P. P. Giovannini, A. Massi, C. S. Pomelli, D. Ragno, *Chem. Commun.* **2014**, *50*, 2008. b) M. Yoshida, Y. Katagiri, W.-B. Zhu, K. Shishido, *Org. Biomol. Chem.* **2009**, *7*, 4062. c) P.-C. Chiang, J. W. Bode, *Org. Lett.* **2011**, *13*, 2422. d) L. Möhlmann, S. Ludwig, S. Blechert, *Beilstein J. Org. Chem.* **2013**, *9*, 602.

9 a) B. M. Trost, *Science* **1991**, *254*, 1471. b) R. A. Sheldon, *Chem. Ind.* **1992**, 903.

10 R. Giannandrea, P. Mastrorilli, C. F. Nobile, G. P. Suranna, *J. Mol. Catal.* **1994**, *94*, 27.

11 T. Mukaiyama, T. Yamada, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 17.

12 a) J. S. Kanady, E. Y. Tsui, M. W. Day, T. Agapie, *Science* **2011**, *333*, 733. b) F. Li, K. M. Van Heuvelen, K. K. Meier, E. Münck, L. Que, Jr., *J. Am. Chem. Soc.* **2013**, *135*, 10198. c) Y. J. Park, S. A. Cook, N. S. Sickerman, Y. Sano, J. W. Ziller, A. S. Borovik, *Chem. Sci.* **2013**, *4*, 717. d) Y. Morimoto, H. Kotani, J. Park, Y.-M. Lee, W. Nam, S. Fukuzumi, *J. Am. Chem. Soc.* **2011**, *133*, 403.

13 a) R. Giri, N. Maugel, J.-J. Li, D.-H. Wang, S. P. Breazzano, L. B. Saunders, J.-Q. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 3510. b) L. J. Clouston, V. Bernales, R. K. Carlson, L. Gagliardi, C. C. Lu, *Inorg. Chem.* **2015**, *54*, 9263. c) R. Zeng, H. Sheng, Y. Zhang, Y. Feng, Z. Chen, J. Wang, M. Chen, M. Zhu, Q. Guo, *J. Org. Chem.* **2014**, *79*, 9246.

14 S. Tanaka, Y. Kon, T. Nakashima, K. Sato, *RSC Adv.* **2014**, *4*, 37674.

15 Optimization of conditions such as an amount of additive, other additives, and solvents were listed in Table S1 of Supporting Information.

16 S. Sakaguchi, T. Takase, T. Iwahama, Y. Ishii, *Chem. Commun.* **1998**, 2037.

17 T. Yamada, O. Rhode, T. Takai, T. Mukaiyama, *Chem. Lett.* **1991**, 5.

18 A. E. Tapper, J. R. Long, R. J. Staples, P. Stavropoulos, *Angew. Chem., Int. Ed.* **2000**, *39*, 2343.

19 a) J. Zhang, P. Teo, R. Pattacini, A. Kermagoret, R. Welter, G. Rogez, T. S. A. Hor, P. Braunstein, *Angew. Chem., Int. Ed.* **2010**, *49*, 4443. b) N. Hoshino, A. M. Ako, A. K. Powell, H. Oshio, *Inorg. Chem.* **2009**, *48*, 3396.