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Aerobic Oxidative Kinetic Resolution of Secondary Alcohols with Naphthoxide-Bound Iron(salan) Complex

Takashi Kunisu, Takuya Oguma, and Tsutomu Katsuki*

Department of Chemistry, Faculty of Science, Graduate School, and International Institute for Carbon-Neutral, Energy Research, Kyushu University, Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan

S *Supporting Information*

ABSTRACT: The first general method for iron-catalyzed aerobic oxidative kinetic resolution of secondary alcohols was achieved with good to high enantiomeric differentiation (k_{rel} = 7−50). Although iron(salan) complex **1** does not catalyze alcohol oxidation, the naphthoxide-bound iron(salan) complex does.

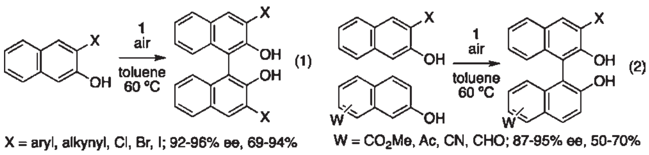
Advances in organic synthesis in the last several decades have benefitted from the development of asymmetric catalysis by transition metal complexes, especially with rare metals such as Pd, Rh, Ru, etc. However, the reserves of rare metals are scarce, and depletion is possible in the near future. Thus, much effort has recently been directed to development of asymmetric catalysis with abundant transition metals, i.e., iron, which is the second most abundant metal in the earth's crust.[1] Another important issue in organic synthesis is further development of ecologically benign reactions.

In this context, we were interested in iron-catalyzed asymmetric oxidation using molecular oxygen, a green oxidant.[2] We explored aerobic oxidative coupling of 2-naphthols using di-μ-hydroxo iron(salan) complex **1** as the catalyst in air and achieved a highly enantioselective homocoupling reaction of 3-substituted 2-naphthols (Scheme 1, eq 1).[3a] The subsequent kinetic and X-ray studies indicated that the coupling reaction proceeds through an iron(salan)(2-naphthoxo) complex **A** according to a radical anion mechanism (Scheme 2) and leads to development of an enantioselective oxidative cross-coupling reaction affording C_1-BINOLs (Scheme 1, eq 2).[3b] Intermediate **A** also catalyzes the coupling of 2-naphthols with nearly identical enantioselectivity to complex **1**. Coordination of the naphthoxo ligand may facilitate the single electron transfer.

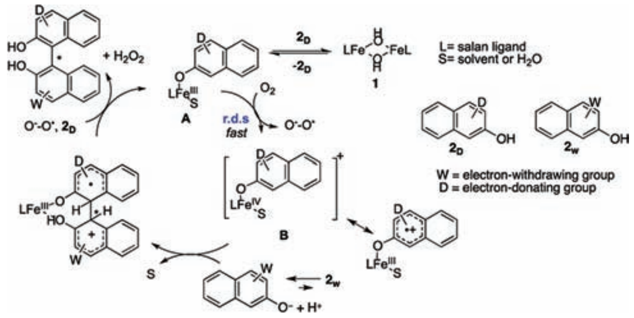
We expected that if the aerobic oxidation stops at the cationic radical species (**B**) in the reaction cycle, we could use it as a catalyst for alcohol oxidation. Thus, we examined aerobic oxidative kinetic resolution (OKR) of secondary alcohols in the presence of various aromatic alcohols, which are reluctant to undergo oxidative coupling.[3b] Although various metal complexes have been used as catalysts for OKR,[2,4] no general method of OKR using iron as a catalyst has been reported.[5] Herein, we communicate an efficient iron-catalyzed OKR using air as an oxidant.

The expected OKR of (±)-1-phenylethanol proceeded in the presence of 2-naphthol with k_{rel} value of 24 at 50 °C,[6] albeit slowly (Table 1, entry 1). The oxidative homocoupling of 2-naphthol also proceeded under the conditions.

Scheme 1. Aerobic Oxidative Coupling of 2-Naphthols Using Complex 1 as a Catalyst



Scheme 2. Proposed Mechanism for Asymmetric Aerobic Oxidative Cross-Coupling of 2-Naphthols



Thus, we screened various 2-naphthols in search of an anti-coupling additive. Addition of 1-methyl-2-naphthol **4** also promoted oxidation but enantiomer differentiation decreased (entry 2). Oxidation did not occur in the presence of 3-methoxycarbonyl-2-naphthol **5** with a chelating property (entry 3). 6-Methoxycarbonyl-2-naphthol **6** was a poor additive (entry 4). Oxidation was slightly accelerated by 4-*tert*-butylphenol **7**, but little enantiomer differentiation was observed (entry 5). To our delight, 1-naphthol **8** was found to enhance the oxidation rate and the enantioselectivity (k_{rel} = 35) without undergoing undesired coupling (entry 6). These results indicate that coordination of an electron-donating and nondimerizable naphthol is essential for this approach.[7] Oxidation at 25 °C was slow and much less selective (entry 7). Oxidation was best performed using 3 mol % of catalyst and 8 mol % of additive at 50 °C, after optimization (entry 8). We also examined other iron(salan) complexes (**9**−**11**) in the presence of **8**, but they did not show any catalysis of alcohol oxidation (entries 9−11). Of note, complex **1** did not

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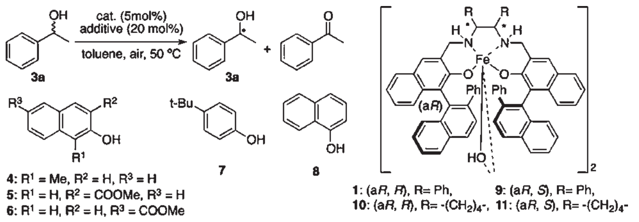
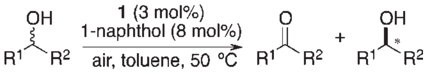
Table 1. Kinetic Resolution of 1-Phenylethanol Using Iron(salan) Catalysts[a]



entry	cat.	additive	time (h)	conv. (%)[b]	ee (%)[b]	config.[c]	k_{rel}
1	**1**	$\mathbf{2_H}$[d]	48	50	81	(*R*)	24
2	**1**	**4**	48	26	22	(*R*)	5
3	**1**	**5**	48	nr	nd	nd	nd
4	**1**	**6**	48	26	24	(*R*)	7
5	**1**	**7**	48	9	2	(*R*)	2
6	**1**	**8**	12	54	95	(*R*)	35
7[e]	**1**	**8**	48	11	6	(*R*)	3
8[f]	**1**	**8**	24	55 (41)[g]	98	(*R*)	41
9	**9**	**8**	12	nr	nd	nd	nd
10	**10**	**8**	12	trace	nd	nd	nd
11	**11**	**8**	12	nr	nd	nd	nd

[a] Reactions were run in toluene (0.1 M) with iron catalyst (5 mol %) and additive (20 mol %) on a 0.1 mmol scale under air, unless otherwise mentioned. [b] Determined by GC analysis on a chiral capillary column using bicyclohexyl as an internal standard. See SI. [c] Determined by comparison of the optical rotation with the literature value. [d] $\mathbf{2_H}$ = 2-naphthol. [e] Run at 25 °C. [f] Run on a 0.5 mmol scale (0.5 M) in the presence of 3 mol % of **1** and 8 mol % of **10**. [g] The number in parentheses refers to recovered **3a**.

Table 2. Aerobic OKR of Secondary Alcohols Using 1 as a Catalyst in the Presence of 1-Naphthol[a]



entry	R^1	R^2	time (h)	conv. (%)[b]	ee (%)[b,c]	yield (%)[d]	k_{rel}
1	*p*-$MeOC_6H_4$	Me	24	60	97 (*R*)	37 (**3b**)	19
2	*p*-$Me_2NC_6H_4$	Me	19	54	96 (*R*)	46 (**3c**)	39
3[e]	*p*-NCC_6H_4	Me	24	56	92 (*R*)	42 (**3d**)	20
4	*p*-ClC_6H_4	Me	26	56	91 (*R*)	43 (**3e**)	19
5[e]	*p*-$CF_3C_6H_4$	Me	22	53	90 (*R*)	37 (**3f**)	27
6	2-naphthyl	Me	18	52	94 (*R*)	46 (**3g**)	50
7[e]	phenyl	Et	40	54	73 (*R*)	42 (**3h**)	9
8	1-hydroxyindan		23	55	67 (*R*)	45 (**3i**)	7
9	1-hydroxytetralin		19	53	82 (*R*)	46 (**3j**)	16
10[e]	1-hydroxybenzosuberan		36	57	88 (*R*)	42 (**3k**)	14
11	(*E*)-PhCH=CH	Me	36	54	90 (*R*)	41 (**3l**)	23
12[e]	$Ph(CH_2)_2$	Me	25	57	86 (*R*)	41 (**3m**)	13
13[e]	*c*-pentyl	Me	24	62	99 (*R*)	35 (**3n**)	20

[a] Reactions were run in toluene (0.5 M) with iron catalyst **1** (3 mol %) and 1-naphthol (8 mol %) on a 0.5 mmol scale under air, unless otherwise mentioned. [b] Conversion and ee values were determined by GC or HPLC analysis on chiral stationary phase column using bicyclohexyl or phenanthrene as an internal standard. See SI. [c] Determined by comparison of the optical rotation with the literature value. [d] Recovered **3**. [e] Run with iron catalyst **1** (4 mol %) and 1-naphthol (12 mol %).

catalyze aerobic oxidation of 1-phenylethanol **3a** in the absence of 1-naphthol.

Under the optimized conditions, we examined OKR of other secondary carbinols (Table 2).

Regardless of the electronic nature of aryl substituents (methoxy, cyano, chloro, and trifluoromethyl groups), a series of secondary benzylic alcohols were enantiomerically differentiated with good selectivity (k_{rel} = 19−39). It is noteworthy that the basic dimethylamino group did not disturb oxidation (entry 2). 1-(2-Naphthyl)ethanol was an excellent substrate (k_{rel} = 50) (entry 6). 1-Phenylpropanol was also oxidized, but the enantioselectivity was moderate (entry 7). Cyclic carbinols were also oxidized, although enantioselectivity was dependent on ring size (entries 8−10). The reactions of alkenyl carbinols were also highly enantioselective (entry 11). It should be noted that nonactivated alcohols **3m** and **3n** were also available as substrates (entries 12 and 13).

In summary, we demonstrated that the catalytic activity of iron(salan) complexes can be enhanced by coordination of a naphthoxide ligand and this modified complex catalyzes aerobic kinetic resolution of secondary alcohols. Further investigation of iron-catalyzed oxidation is in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Experimental procedures; GC and HPLC conditions. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

katsuscc@chem.kyushu-univ.jp

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■ REFERENCES

(1) Reviews on iron-catalyzed reactions: (a) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217–6254. (b) Correla, A.; Mancheño., O. G.; Bolm., C. *Chem. Soc. Rev.* **2008**, *37*, 1108–1117. (c) Gaillard, S.; Renaud, J.-L. *ChemSusChem* **2008**, *1*, 505–509. (d) Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3317–3321.

(2) Reviews on oxidation using molecular oxygen: (a) Bäckvall, J.-E. *Modern Oxidation Methods*; Wiley-VHC: Weinheim, 2004. (b) Beller, M. *Adv. Synth. Catal.* **2004**, *346*, 107–108. (c) Irie, R.; Katsuki, T. *Chem. Records* **2004**, *4*, 96–109. (d) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400–3420. (e) Schultz, M. J.; Sigman, M. S. *Tetrahedron* **2006**, *62*, 8227–8241.

(3) (a) Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2009**, *131*, 6082–6083. (b) Egami, H.; Matsumoto, K.; Oguma, T.; Kunisu, T.; Katsuki., T. *J. Am. Chem. Soc.* **2010**, *132*, 13633–13635.

(4) Selected reports of OKR of secondary alcohols using molecular oxygen: (a) Masutani, K.; Uchida, T.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 5119–5123. (b) Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475–7476. (c) Mueller, J. A.; Cowell, A.; Chandler, B. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 14817–14824. (d) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725–7726. (e) Ebner, D. C.; Bagdanoff, J. T.; Ferreira, E. M.; McFadden, R. M.; Caspi, D. D.; Trend, R. M.; Stoltz, B. M. *Chem. Eur,*

J. **2009**, *15*, 12978–12992. (f) Radosevich, A. T.; Musich, C.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 1090–1091. (g) Pawar, V. D.; Bettigeri, S.; Weng, S.-S.; Kao, J.-Q.; Chen, C.-T. *J. Am. Chem. Soc.* **2006**, *128*, 6308–6309. (h) Chen, T.; Jiang, J.-J.; Xu, Q.; Shi, M. *Org. Lett.* **2007**, *9*, 865–868. (i) Arita, S.; Koike, T.; Kayaki, Y.; Ikariya, T. *Angew. Chem., Int. Ed.* **2008**, *49*, 2447–2449. (j) Tomizawa, M.; Shibuya, M.; Iwabuchi, Y. *Org. Lett.* **2009**, *11*, 1829–1831.

(5) Recently, Sekar et al. reported iron-catalyzed OKR using O_2 as the terminal oxygen, but the substrate was limited to benzoines, and a catalytic amount of TEMPO was necessary, see: Muthupandi, P.; Alamsetti, S. K.; Sekar, G. *Chem. Commun.* **2009**, 3288–3290.

(6) For determination of k_{rel}, see: Balavoine, G.; Moradpour, A.; Kagan, H. B. *J. Am. Chem. Soc.* **1974**, *96*, 5152–5158.

(7) For the behavior of 1-naphthol during the oxidation, see Supporting Information.