JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Iron-Catalyzed Dioxygen-Driven C−C Bond Formation: Oxidative Dearomatization of 2-Naphthols with Construction of a Chiral Quaternary Stereocenter

Takuya Oguma[†] and Tsutomu Katsuki*[,†,‡]

[†]Department of Chemistry, Graduate School of Science, and International Institute for Carbon-Neutral Energy Research (WPI-I2CNER), Kyushu University, Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan

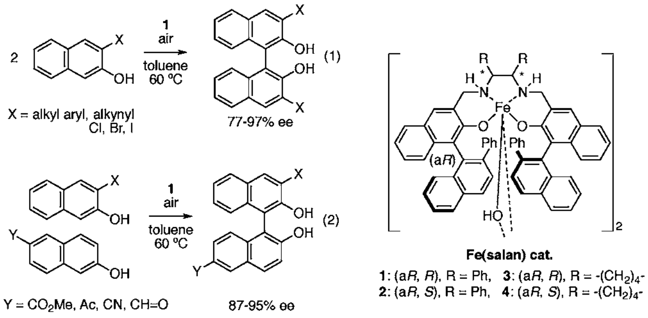
[‡]JST, ACT-C, Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan

Supporting Information

ABSTRACT: Iron(salan) complex **1** was found to catalyze the oxidative dearomatization of 1-substituted 2-naphthols with the formation of an all-carbon quaternary stereocenter in air in the presence of nitroalkanes, to afford the corresponding cyclic enones with high enantioselectivity of 88−96% ee.

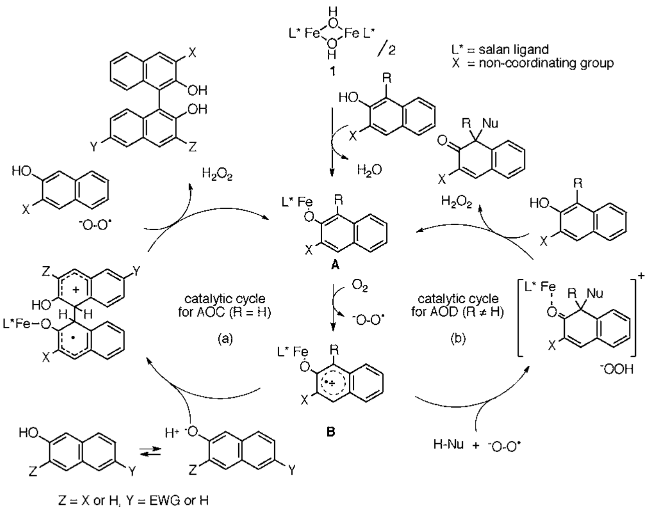
Aromatic compounds are abundant in the biological sphere as well as in petroleum feedstocks. From a synthetic viewpoint, the development of enantioselective methods for dearomatization is a topic of growing interest. Among such methods, asymmetric oxidative dearomatization (AOD) of hydroxy aromatic compounds provides useful multifunctional cyclic enone derivatives, which are versatile chiral building blocks in asymmetric synthesis.[1] Thus, AOD has been intensively studied. AOD is classified into two types: (1) C−X (X = O, N, F) bond-forming AOD and (2) C−C bond-forming AOD. AOD of type 1 (X = O) has been achieved using either a stoichiometric Cu(I)/sparteine/O_2/base system,[2a,b] a chiral iodine(III) species in the presence of *m*-CPBA,[2c−e] or a stoichiometric chiral iodine(V) reagent.[2c,f] AOD of type 1 (X = O, N, F) has also been achieved using a combination of oxidative dearomatization (OD) and enantioselective Michael reaction.[2g,3] AOD using a chiral lactate as a chiral auxiliary has also been reported.[2h] AOD of type 2, which provides unique spirocyclic compounds, has been achieved using a combination of asymmetric Michael reaction and C−C bond-forming OD.[4] These seminal studies proved that OD can be achieved in a highly enantioselective manner under mild conditions. On the other hand, several dearomatizing enzymes contain iron active species and use dioxygen as the oxidant.[5] Iron is the most abundant transition metal in the earth's crust,[6] and dioxygen is a clean oxidant.[7] Hence, we were intrigued to investigate iron-catalyzed AOD using dioxygen or air as the oxidant, which should provide a more ecologically benign and atom-efficient method.

Scheme 1. Fe(salan)-Catalyzed AOC of 2-Naphthols



We recently developed an iron(salan) complex-catalyzed asymmetric aerobic oxidative coupling (AOC) of 2-naphthols and kinetic resolution of secondary alcohols.[8] Homo- and cross-AOC of 2-naphthols afford highly enantioenriched C_2- and C_1-symmetric BINOLs, respectively (Scheme 1).[8a,b] On the basis of mechanistic studies, we proposed that the AOC proceeds via a radical/anion mechanism[9] involving radical cation **B** (Scheme 2a, catalytic cycle for AOC), which is attacked by naphthoxide anion to give the BINOL.[8b,c] X-ray analysis of **A** (X = Br, R = H) revealed that one side of the naphthoxo unit faces an open space.[8b] Thus, we expected that a nucleophile with an appropriate pK_a (e.g., 2-naphthol, pK_a = 17.1 in DMSO) would react with **B** (R ≠ H), which should be

Scheme 2. Proposed Mechanism for AOC of 2-Naphthols and a Possible Approach for Exploring AOD



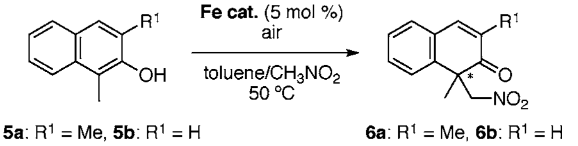
Received: October 16, 2012
Published: November 27, 2012

dx.doi.org/10.1021/ja310203c | *J. Am. Chem. Soc.* 2012, 134, 20017−20020

reluctant to couple with the 2-naphthoxide anion because of the steric hindrance by the C1 substituent, to give an OD product containing a stereogenic quaternary carbon center in a catalytic and enantioselective manner (Scheme 2b, catalytic cycle for AOD).[10,11]

Since the pK_a's of nitroalkanes are ca. 17, we anticipated that nitroalkanes would be suitable nucleophiles for AOD. Thus, we examined the OD of 1,3-dimethyl-2-naphthol (**5a**) with nitromethane in the presence of 5 mol % iron(salan) complex **1** at 50 °C under air, and the dearomatized product **6a** was obtained in high yield (90%) and enantioselectivity (90% ee) (Table 1, entry 1). Inferior results were obtained using complexes **2**−**4** as catalysts (entries 2−4). Thus, we optimized the reaction conditions for AOD using **1** as the catalyst. It is noteworthy that although the reaction proceeded at 25 °C with high enantioselectivity (93% ee), it was slow (entry 5). Using nitromethane as the solvent diminished the enantioselectivity and yield (entry 6). Thus, the reaction was further optimized at 50 °C in 9:1 toluene/nitromethane. The best result was obtained when the reaction was performed on a 0.5 mmol scale with 4 mol % **1** for 48 h (entry 7). The reaction using degassed solvent under an argon atmosphere did not proceed, confirming that dioxygen is crucial for this reaction (entry 8). The reaction also proceeded with 1-methyl-2-naphthol (**5b**), which has no substituent at the C3 position, but the enantioselectivity was modest (entry 9).

Table 1. Fe(salan)-Catalyzed AOD of 2-Naphthols Using Nitromethane as the Nucleophile[a]

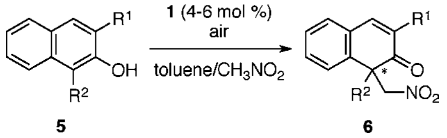


entry	R^1	cat.	yield (%)[b]	ee (%)[c]
1	Me	**1**	90	90 (+)
2	Me	**2**	trace	n.d.
3	Me	**3**	61	80 (+)
4	Me	**4**	48	84 (−)
5[d]	Me	**1**	54	93 (+)
6[e]	Me	**1**	70	84 (+)
7[f]	Me	**1**	93[g]	90 (+)
8[h]	Me	**1**	n.r.	−
9	H	**1**	23[i]	34 (+)

[a] Reactions were run at 50 °C for 24 h in 9:1 toluene/CH_3NO_2 (0.1 M) with catalyst (5 mol %) on a 0.1 mmol scale under air, unless otherwise noted. [b] Determined by ^1H NMR analysis using phenanthrene as an internal standard. [c] Determined by HPLC analysis on a chiral stationary phase column. The sign of the optical rotation is shown in parentheses. [d] Run at 25 °C. [e] Run in CH_3NO_2 (0.1 M). [f] Run with 4 mol % catalyst for 48 h on a 0.5 mmol scale. [g] Isolated yield. [h] Run under an argon atmosphere. [i] A racemic O−C1-coupled dimer (**8**, R^2 = Me) was also produced in 5% yield (see ref 13).

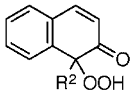
Under these conditions, we examined the OD of various 1,3-disubstituted 2-naphthols (Table 2). The reaction of 3-allyl-1-methyl-2-naphthol was slow at 50 °C but gave the corresponding enone **6c** at 60 °C in high yield and selectivity (entry 1). 3-Phenyl-, 3-phenylethynyl-, and 3-(3,5-dichlorophenyl)-substituted substrates were also suitable for this reaction, affording **6d**−**f**, respectively (entries 2−4). The reactions of 3-chloro-, 3-bromo-, and 3-iodo-1-methyl-2-naphthols proceeded with high enantioselectivity of 94−96% ee to give the corresponding α-halogen-substituted enones **6g**−**i**, which could be good substrates for cross-coupling reactions (entries 5−7).[12] It is noteworthy that 2-napthols bearing a *n*-alkyl substituent (e.g., ethyl, *n*-hexyl) at the C1 position, which is attacked by nucleophile, also underwent the dearomatization with high enantioselectivity (entries 8 and 9). Dearomatization of 1-cyclohexyl-3-chloro-2-naphthol, which has a bulky secondary alkyl group at C1, proceeded slowly but with high enantioselectivity (entry 10). Autoxidation products (**7** and/or **8**)[13] were not detected in the dearomatization of 1,3-disubstituted 2-naphthols in air.

Table 2. AOD of 1,3-Disubstituted 2-Naphthols with Nitromethane[a]

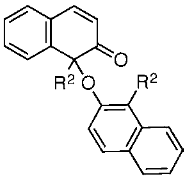


entry	R^1	R^2	*T* (°C)	**6**, yield (%)[b]	ee (%)[c]
1	allyl	Me	60	**6c**, 92	90 (+)
2	Ph	Me	60	**6d**, 82	93 (+)
3[d]	PhC≡C	Me	60	**6e**, 91	89 (+)
4	3,5-$Cl_2C_6H_3$	Me	60	**6f**, 81	96 (+)[e]
5[d]	Cl	Me	60	**6g**, 83	94 (+)
6[d]	Br	Me	60	**6h**, 84	95 (+)
7[d]	I	Me	60	**6i**, 87	96 (+)
8	Me	Et	50	**6j**, 87	88 (+)
9	Me	*n*-Hex	50	**6k**, 75	89 (+)
10[d]	Cl	*c*-Hex	60	**6l**, 43	96 (+)

[a] Reactions were run using **5** (0.5 mmol) and **1** (4 mol %) in 9:1 toluene/nitromethane (0.1 M) for 48 h on a 0.5 mmol scale, unless otherwise noted. [b] Isolated yields. [c] Determined by chiral HPLC (see the Supporting Information for details). The sign of the optical rotation is given in parentheses. [d] Run using **1** (6 mol %) for 72 h. [e] The absolute configuration of **6f** was determined to be *S* by X-ray analysis (Figure 1).

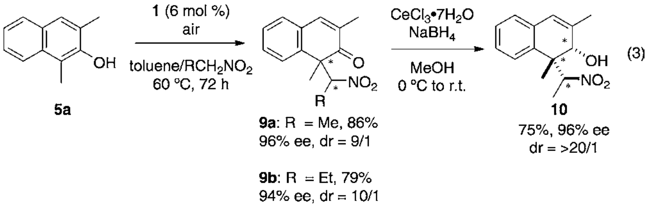


7



8

The AOD product **6f** gave a single crystal suitable for X-ray crystallographic analysis, which unambiguously determined its absolute configuration to be *S* (Figure 1).[14] Moreover, **5a** reacted with nitroethane and 1-nitropropane to give the dearomatization products **9a** and **9b**, respectively, with good diastereoselectivity in a highly enantioselective manner (eq 3).



Compound **9a** could be reduced under Luche conditions to give alcohol **10** with a high diastereoselectivity of >20/1. The

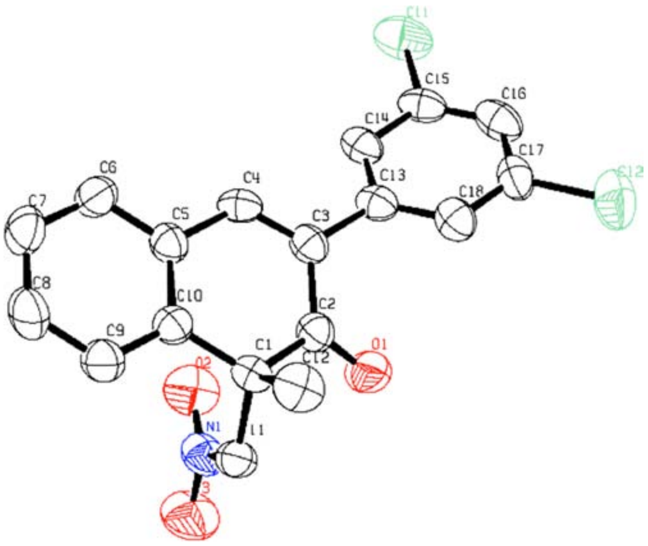


Figure 1. ORTEP view of compound **6f** (50% probability ellipsoids). H atoms have been omitted for clarity.

relative stereochemistry of **10** was determined by X-ray analysis (Figure 2).[14] We also examined the AOD of **5a** using 2-nitropropane; however, the reaction did not proceed, probably because of steric hindrance by the isopropyl group.

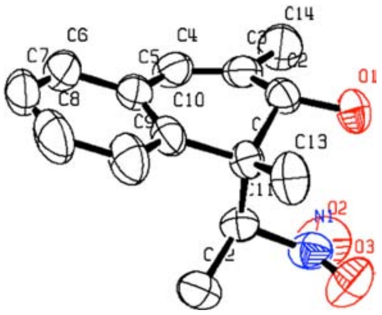
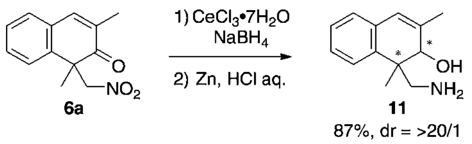


Figure 2. ORTEP view of compound **10** (50% probability ellipsoids). H atoms have been omitted for clarity.

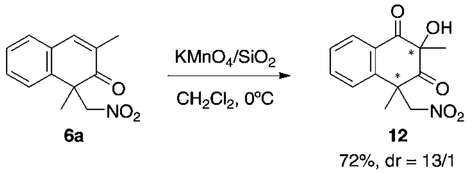
We also examined the AOD of two 1-naphthol and two phenol derivatives under the same conditions in the presence of nitromethane, but the desired dearomatized products were not obtained.[15] However, it is interesting to note that the reaction of 2,4,6-trimethylphenol gave 2,6-dimethyl-4-(2-nitroethyl)-phenol as a major product, albeit in low yield (ca. 15%).

The dearomatized compound **6a** could be converted into amino alcohol **11** (87% yield) with high diastereoselectivity by the following sequence: (i) $NaBH_4$ reduction under Luche conditions and (ii) zinc reduction of the resulting nitroalcohol (eq 4). On the other hand, the reaction of **6a** using SiO_2-supported $KMnO_4$ gave highly functionalized naphthalene-1,3-dione **12** in 72% yield (eq 5). These examples demonstrate the synthetic utility of the present AOD.

Although the detailed mechanism of asymmetric induction is unclear at present, we assume that this AOD is facilitated by coordination of the nitro compound in nitro or aci form to radical cation **B**, which should have a highly asymmetric coordination sphere,[8b] and the subsequent intramolecular C−C bond formation proceeds smoothly with high enantioselectivity. Thus, radical cation **B** must have an open coordination site for the nitro group. In accord with this assumption, chelating substrates such as 1-methyl-3-methoxy-2-naphthol and 1-methyl-3-methoxycarbonyl-2-naphthol did not undergo the reaction.



(4)



(5)

In summary, we were able to achieve iron-catalyzed asymmetric oxidative dearomatization of 1,3-disubstituted 2-naphthols using nitroalkanes as nucleophiles, leading to the formation of an all-carbon quaternary stereocenter with high enantioselectivity (88−96% ee). This reaction is driven by oxygen reduction and is highly atom-efficient and ecologically benign. To the best of our knowledge, this is the first example of simultaneous oxidative dearomatization and asymmetric construction of an all-carbon quaternary stereocenter in an intermolecular manner.[16] Further studies of the mechanism of this oxidative dearomatization are in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures 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

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Dr. Kenji Matsumoto (Kochi University) for help with X-ray analysis. Financial support from Nissan Chemical Industries, Ltd.; and MEXT, Japan (WPI-I2CNER; and JSPS KAKENHI Grant 23245009) is gratefully acknowledged. T.O. is grateful for the JSPS Research Fellowships for Young Scientists.

■ REFERENCES

(1) Reviews of OD: (a) Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383. (b) Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235. (c) Roche, S. P.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2011**, *50*, 4068.

(2) Selected examples of C−X (X = O, N, F) bond-forming AOD: (a) Zhu, J.; Grigoriadis, N. P.; Lee, J. P.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2005**, *127*, 9342. (b) Dong, S.; Zhu, J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2008**, *130*, 2738. (c) Dohi, T.; Maruyama, A.; Takenaga, N.; Senami, K.; Minamitsuji, Y.; Fujioka, H.; Caemmerer, S. B.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3787. (d) Quideau, S.; Lyvinec, G.; Marguerit, M.; Bathany, K.; Ozanne-Beaudenon, A.; Buffeteau, T.; Cavagnat, D.; Chénedé, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4605. (e) Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2175. (f) Boppisetti, J. K.; Birman, V. B. *Org. Lett.* **2009**, *11*, 1221. (g) Vo, N. T.; Pace, R. D. M.; O'Hara, F.; Gaunt, M. J. *J. Am. Chem.*

Soc. **2008**, *130*, 404. (h) Mejorado, L. H.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2006**, *128*, 15625.

(3) Anodic oxidative aromatic ring umpolung/asymmetric Michael addition has been reported, although the products are aromatic compounds. See: Jensen, K. L.; Franke, P. T.; Nielsen, L. T.; Daasbjerg, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 129.

(4) Rudolph, A.; Bos, P. H.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 5834.

(5) (a) Boll, M. *J. Mol. Microbiol. Biotechnol.* **2005**, *10*, 132. (b) Ferraro, D. J.; Gakhar, L.; Ramaswamy, S. *Biochem. Biophys. Res. Commun.* **2005**, *338*, 175.

(6) Reviews of iron-catalyzed reactions: (a) Correa, A.; Mancheño, O. G.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108. (b) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217.

(7) Reviews of the use of O_2 as an oxidant: (a) Podgoršek, A.; Zupan, M.; Iskra, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 8424. (b) Sheldon, R. A.; Arends, I. W. C. E. In *Advances in Catalytic Activation of Dioxygen by Metal Complexes*; Simandi, L. I., Ed.; Kluwer Academic: Dordrecht, The Netherlands, 2003; p 123.

(8) (a) Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2009**, *131*, 6082. (b) Egami, H.; Matsumoto, K.; Oguma, T.; Kunisu, T.; Katsuki, T. *J. Am. Chem. Soc.* **2010**, *132*, 13633. (c) Matsumoto, K.; Egami, H.; Oguma, T.; Katsuki, T. *Chem. Commun.* **2012**, *48*, 5823. (d) Kunisu, T.; Oguma, T.; Katsuki, T. *J. Am. Chem. Soc.* **2011**, *133*, 12937.

(9) (a) Hovorka, M.; Günterová, J.; Závada, J. *Tetrahedron Lett.* **1990**, *31*, 413. (b) Hovorka, M.; Závada, J. *Tetrahedron* **1992**, *48*, 9517.

(10) Recent selected examples of asymmetric construction of all-carbon quaternary centers via nonoxidative dearomatization: (a) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314. (b) García-Fortanet, J.; Kessler, F.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 6676. (b) Rousseaux, S.; García-Fortanet, J.; Del Aguila Sanchez, M. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 9282. (c) Wu, Q.-F.; He, H.; Liu, W.-B.; You, S.-L. *J. Am. Chem. Soc.* **2010**, *132*, 11418. (d) Leon, R.; Jawalekar, A.; Redert, T.; Gaunt, M. J. *Chem. Sci.* **2011**, *2*, 1487. (e) Wu, Q.-F.; Liu, W.-B.; Zhuo, C.-X.; Rong, Z.-Q.; Ye, K.-Y.; You, S.-L. *Angew. Chem., Int. Ed.* **2011**, *50*, 4455. (f) Wu, K.-J.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2012**, *14*, 3772. (g) Qi, J.; Beeler, A. B.; Zhang, Q.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2010**, *132*, 13642. (h) Yoshida, M.; Nemoto, T.; Zhao, Z.; Ishige, Y.; Hamada, Y. *Tetrahedron: Asymmetry* **2012**, *23*, 859.

(11) It has been reported that AOD/[4 + 2] dimerization tandem provides product having an all-carbon quaternary center with high enantioselectivity (see ref 2b).

(12) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1997.

(13) It has been reported that 1-alkyl-2-naphthols undergo autoxidation in air or oxygen at room temperature to give **7** and/or **8**. See: Carnduff, J.; Leppard, D. G. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2570.

(14) CCDC 904096 for **6f** and 904097 for **10** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(15) For details, see the Supporting Information.

(16) For an intramolecular version, see ref 4.