JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

University of Sussex

Subscriber access provided by University of Sussex Library

Communication

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

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/ja310203c • Publication Date (Web): 27 Nov 2012

Downloaded from http://pubs.acs.org on November 30, 2012

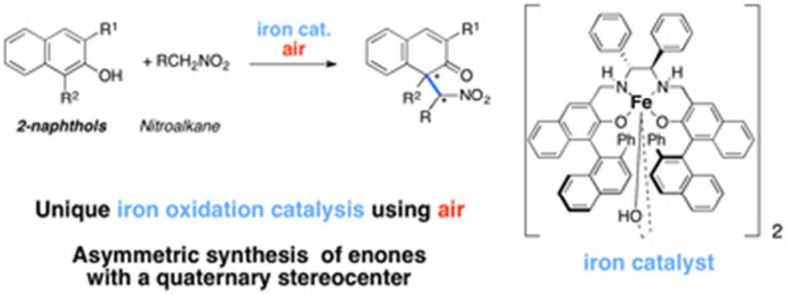
Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a free service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are accessible to all readers and citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.

ACS Publications
High quality. High impact.

Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.



Graphic for TOC
33x12mm (300 x 300 DPI)

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

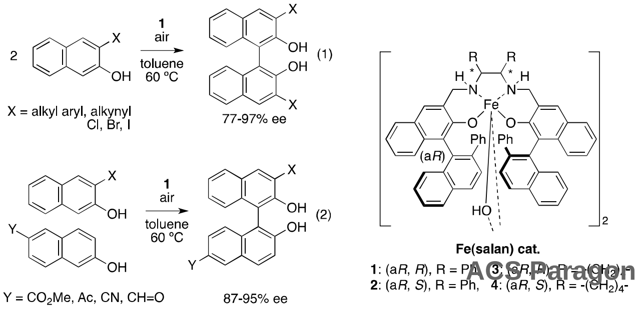
Takuya Oguma, Tsutomu Katsuki*

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.

Supporting Information Placeholder

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

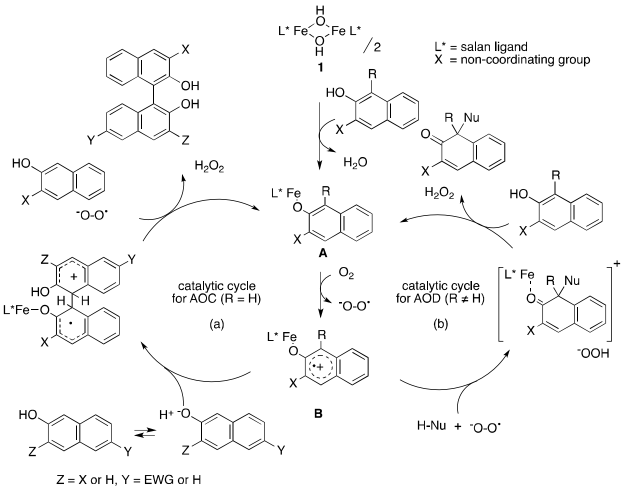
Aromatic compounds are abundant in the biological sphere as well as in petroleum feedstocks. From a synthetic viewpoint, the development of enantioselective methods for dearomatization is a topic of growing interest. Among the methods, asymmetric oxidative dearomatization (AOD) of hydroxy aromatic compounds 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] chiral iodine(III) species in the presence of *m*-CPBA,[2c,d,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 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 oxidative dearomatization could 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 oxidant.[5] Iron is the most abundant transition metal in the earth's crust[6] and dioxygen is a clean oxidant.[7]



Scheme 1. Iron-catalyzed AOC of 2-Naphthols

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.

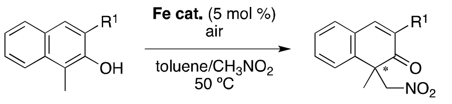
We recently developed iron(salan) complex-catalyzed asymmetric aerobic oxidative coupling (AOC) of 2-naphthols and kinetic resolution of secondary alcohols.[8] *Homo*- and *cross*-AOC of 2-naphthols afford highly enantioenriched C_2- and C_1-symmetric BINOLs, respectively (Scheme 1).[8a,b] Based on the mechanistic studies, we have proposed a radical/anion mechanism[9] via a radical cation **B** [Scheme 2, catalytic cycle for AOC (a)], which is attacked by naphthoxide anion to give the BINOL, for the AOC.[8b,c] The 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 of appropriate pKa [*cf.* 2-naphthol, pKa = 17.1 (in DMSO)] would react with **B** (R≠H), which should be reluctant to couple with the 2-naphthoxide anion due to the steric hindrance by the C1 substituent, to give an oxidative dearomatization product that has a stereogenic quaternary carbon center in a catalytic and enantioselective manner [catalytic cycle for AOD (b)].[10,11]



Scheme 2. The Proposed Mechanism for AOC of 2-Naphthols and a Possible Approach toward Exploring Asymmetric Dearomatization

Since the pKa of nitroalkane is ca. 17, we anticipated that nitroalkane would be a suitable nucleophile for enantioselective AOD. Thus, we examined oxidative dearomatization 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 with high yield (90%) and enantioselectivity (90% ee) (Table 1, entry 1). Inferior results were obtained using other complexes (**2**-**4**) as catalysts (entries 2-4). Thus, we optimized the reaction condition for asymmetric AOD using **1** as the catalyst. It is noteworthy that the reaction proceeded at 25 °C with high enantioselectivity (93% ee), while the reaction was slow (entry 5). Use of nitromethane as a solvent diminished the enantioselectivity and yield (entry 6). Thus, the reaction was further optimized at 50 °C in toluene/nitromethane (9:1). The best result was obtained when the reaction was performed on a 0.5 mmol scale with 4 mol % of **1** for 48 h (entry 7). The reaction using degassed solvent under argon atmosphere did not proceed, confirming that dioxygen is crucial for this reaction (entry 8). The reaction of 1-methyl-2-naphthol, which has no substituent at C3 position, also proceeded but the enantioselectivity was modest (entry 9).

Table 1. Fe(salan) Catalyzed Oxidative Dearomatization of 2-Naphthols Using Nitromethane as Nucleophile



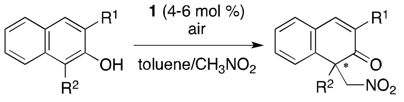
5a: R¹ = Me, **5b**: R¹ = H **6a**: R¹ = Me, **6b**: R¹ = H

entry	R¹	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 toluene/CH_3NO_2 (9/1, 0.1 M) with iron catalyst (5 mol %) on a 0.1 mmol scale under air, unless otherwise mentioned. [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 optical rotation is shown in the parentheses. [d] Run at 25 ºC. [e] Run in CH_3NO_2 (0.1 M). [f] Run with 4 mol % iron catalyst for 48 h on a 0.5 mmol scale. [g] Isolated yield. [h] Run under argon atmosphere. [i] A racemic O-C(1) coupled dimer (**8**, R^2 = Me) was also produced in 5% yield (Ref. 11).

Under these conditions, we examined oxidative dearomatization 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 with high yield and selectivity (entry 1). 3-Phenyl, 3-phenylethynyl-, and 3-(3,5-dichlorophenyl)-substituted substrates were also suitable substrates for this reaction (entries 2-4, **6d**-**f**). The reactions of 3-chloro-, 3-bromo- and 3-iodo-1-methyl-2-naphthols proceeded with high enantioselectivity of 94-96% ee to give 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 such as ethyl and *n*-hexyl groups 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 the 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.

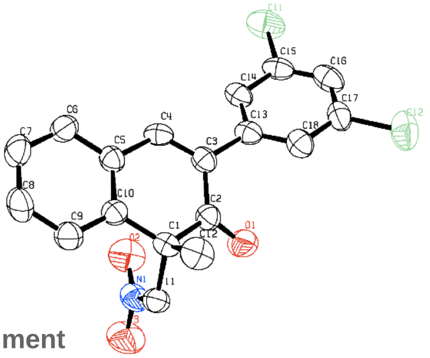
Table 2. Asymmetric Dearomatization of 1,3-Disubstituted-2-naphthols with Nitromethane[a]



5 **6**

entry	R¹	R²	temp. (ºC)	yield[b] (%)	ee[c] (%)
1	Allyl	Me	60	92 (**6c**)	90 (+)
2	Ph	Me	60	82 (**6d**)	93 (+)
3[d]	PhC≡C	Me	60	91 (**6e**)	89 (+)
4	3,5-$Cl_2C_6H_3$	Me	60	81 (**6f**)	96 (+)[e]
5[d]	Cl	Me	60	83 (**6g**)	94 (+)
6[d]	Br	Me	60	84 (**6h**)	95 (+)
7[d]	I	Me	60	87 (**6i**)	96 (+)
8	Me	Et	50	87 (**6j**)	88 (+)
9	Me	*n*-Hex	50	75 (**6k**)	89 (+)
10[d]	Cl	*c*-Hex	60	43 (**6l**)	96 (+)

[a] Reaction was performed using **5** (0.5 mmol) and **1** (4 mol %) in toluene/nitromethane (9/1, 0.1 M) for 48 h on a 0.5 mmol scale, unless otherwise mentioned. [b] Isolated yield. [c] Determined by Chiral HPLC, see SI in detail. The sign of optical rotation is given in the parentheses. [d] Run using **1** (6 mol %)

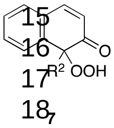


for 72 h. [e] Absolute configuration was determined to be *S* by X-ray analysis (see, Figure 1).

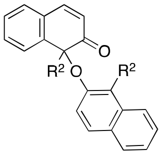
The oxidative dearomatization product (**6f**) gave a single crystal suitable for X-ray crystallographic analysis, and the analysis unambiguously determined its absolute configuration as *S* (Figure 1).[14]

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

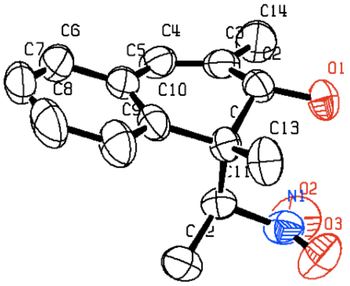
Moreover, 1,3-dimethyl-2-naphthol **5a** reacted with 1-nitro-*n*-alkane such as nitroethane and 1-nitropropane to give the dearomatization products **9a** and **9b** in a good diastereo- and highly enantioselective manner (eq. 3).

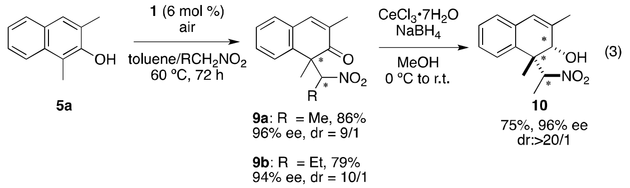


7



8



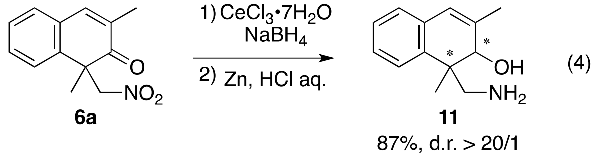


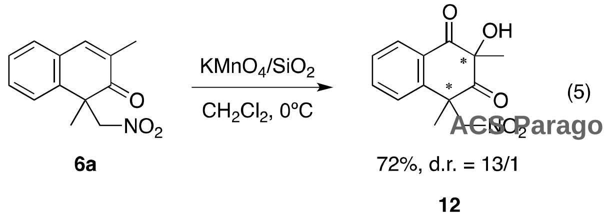
Compound **9a** could be reduced under Luche condition to give the alcohol **10** with high diastereoselectivity of >20/1. The relative stereochemistry of **10** was determined by X-ray analysis (Figure 2).[14] We also examined AOD of **5a** using 2-nitropropane; however, the reaction did not proceed, probably because of the steric hindrance of the isopropyl group.

Figure 2. ORTEP view of compounds **10** (50% probability). Hydrogen atoms have been omitted for clarify.

We also examined 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%).

Dearomatized compound **6a** could be converted with high diastereoselectivity into amino alcohol **11** (87%) in the following sequence: i) $NaBH_4$ reduction under Luche condition and ii) indium reduction of the resulting nitro ketone (eq. 4). On the other hand, the reaction of **6a** using SiO_2-supported $KMnO_4$ gave a 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 assumes that this AOD is facilitated by coordination of nitro compound in nitro or aci form to the radical cationic species **B** that should have a highly asymmetric coordination sphere,[8b] and the subsequent intramolecular carbon-carbon bond formation proceeds smoothly with high enantioselectivity. Thus, the radical cationic **B** must have an open-coordination site for 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.

In summery, we were able to achieve iron-catalyzed asymmetric oxidative dearomatization of 1,3-disubstituted-2-naphthols using nitroalkanes as nucleophile, in which all-carbon quaternary stereocenter was formed with high enantioselectivity of 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/asymmetric construction of an all-carbon quaternary stereocenter in an intermolecular manner.[16] Further study on the mechanism of this oxidative dearomatization is in progress.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures; 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

ACKNOWLEDGMENT

We thank Dr. Kenji Matsumoto, Kochi University, for help with X-ray analysis. Financial support from Nissan Chemical Industries, Ltd., the International Institute for Carbon-Neutral Energy Research (WPI-I2CNER), and JSPS KAKENHI Grant No. 23245009 from MEXT, Japan is gratefully acknowledged. T.O. is grateful for the JSPS Research Fellowships for Young Scientists.

REFERENCES

(1) Reviews on oxidative dearomatization; (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, though 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 on iron-catalyzed reaction; (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) For reviews on the use of O_2 as the oxidant, see: (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, 2003, p123.

(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. *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) For recent selected examples of asymmetric construction of all carbon quaternary center via *non-oxidative* dearomatization, see; (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 and OD/asymmetric Michael reaction tandems provide a product having all carbon quaternary center with high enantioselectivity (Ref. 2b and 2g).

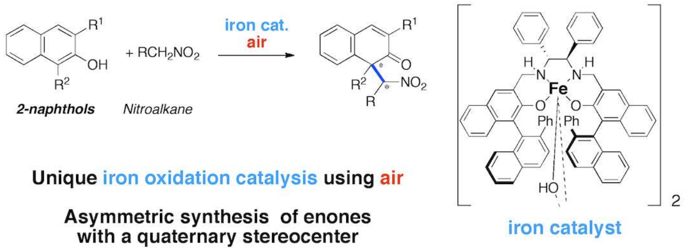
(12) *Metal-Catalyzed Cross-coupling Reactions,* Ed by Diederich, F.; Stang, P. J. Wiley-VCH, Weinheim, 1997.

(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**. 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 SI.

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



Unique iron oxidation catalysis using air

Asymmetric synthesis of enones with a quaternary stereocenter