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Enantioenriched Synthesis of C_1-Symmetric BINOLs: Iron-Catalyzed Cross-Coupling of 2-Naphthols and Some Mechanistic Insight

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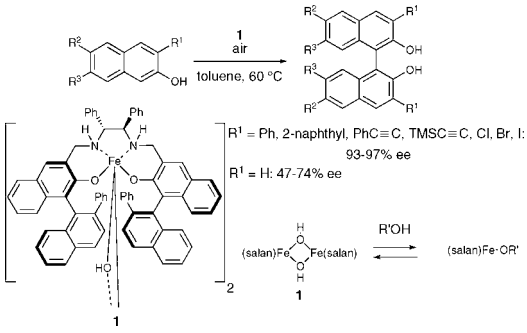
Abstract: Highly enantioselective aerobic oxidative cross-coupling of 2-naphthols with broad substrate scope was achieved using an iron(salan) complex as the catalyst. Enantiomeric excesses of the products ranged from 87 to 95%. The scope of the cross-coupling reaction was found to be different from that of the homocoupling reaction under the same reaction conditions.

C_2-symmetric BINOL derivatives have been widely used as chiral auxiliaries.[1] Recent studies have further disclosed that 3,3′-disubstituted BINOLs have potential for application to various asymmetric catalyses.[2] Asymmetric aerobic oxidative coupling of 2-naphthols is the most atom-economical method for their synthesis,[3−6] but its application has been mostly limited to simple BINOLs, with a few exceptions involving copper-mediated coupling of 2-naphthols bearing an electron-withdrawing group such as an ester or acyl group at C3.[3d−f,h,j] In the course of our studies of the development of asymmetric oxidation reactions that do not rely on the use of rare-metal-based catalysts, we discovered that iron(salan) complex **1** catalyzes the aerobic oxidative coupling of 3-substituted 2-naphthols ($R^1 \neq H$) with high enantioselectivities of up to 97% ee (Scheme 1).[7] 2-Naphthols substituted at either or any of C3, C6, or C7 undergo the coupling regardless of the electronic nature of the substituents, with the exception of chelating substrates (R^1 = ester). C_1-symmetric BINOLs are also deemed to be efficient chiral auxiliaries, and recent seminal studies have given glimpses of their potential.[1a,8] However, these substances remain largely unstudied because of difficulties in their synthesis.[8a] Although asymmetric aerobic oxidative cross-coupling between two different 2-naphthols should be a simple and direct method, limited successes have been obtained by the extension of the known homocoupling reactions because of their narrow scopes. One of a few examples is a copper-mediated oxidative coupling that preferentially provides a cross-coupling product and shows high enantioselectivity in the coupling of 2-naphthols bearing an electron-withdrawing group such as an ester or acyl group at C3.[3e,f,i,j] Although asymmetric oxidative cross-coupling is under development, the experimental results have generally shown that the cross-coupling is favored for those coupling partners having sufficiently different redox potentials.[8a]

On the basis of the asymmetric catalysis of aerobic oxidative homocoupling by the iron(salan) complex, we were intrigued by the possibility of developing a cross-coupling reaction with a broad substrate scope and shedding light on the mechanism governing the iron-mediated oxidative coupling reaction. Several mechanisms, typically radical−radical and radical−anion couplings, have been proposed for oxidative coupling,[3b,4e,g,6b,9] and the latter is considered to be a more plausible mechanism for the cross-coupling reaction.[8a,9]

The radical−anion coupling can accommodate either a first- or second-order dependence of the rate on substrate concentration. To facilitate the design of proper reaction conditions for the cross-coupling reaction, we embarked on the study of the kinetics of this iron-mediated aerobic oxidative coupling using **1** as the catalyst. The dependence of the rate on substrate concentration was found to be first-order (Figure 1). No oxidative coupling occurred in the absence of molecular oxygen. Treatment of 2-naphthol with stoichiometric **1** did not give the coupling product under an argon atmosphere.

Scheme 1. Iron(salan)-Catalyzed Asymmetric Aerobic Oxidative Coupling of 2-Naphthols



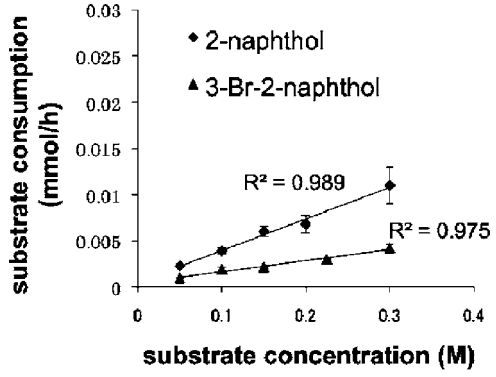


Figure 1. Dependence of the rate on substrate concentration.

These results suggested that complex **1**, a di-μ-hydroxo dimer,[10] dissociates into a monomeric species prior to the oxidative coupling event (Scheme 1). Hence, the relationship between the enantiomeric excesses of the product and the catalyst was investigated, and a linear relationship was observed (Figure 2), which was interpreted as evidence of the possible participation of a monomeric complex (Scheme 1).[11] In agreement with this interpretation, mixing complex **1** and 3-bromo-2-naphthol at room temperature immediately produced the new species **2**, which was determined to be a monomeric iron(salan)(3-bromo-2-naphthoxo) complex by X-ray structure analysis (Figure 3).[12] It is noteworthy that complex **2** showed asymmetric catalysis of aerobic oxidative couplings identi-

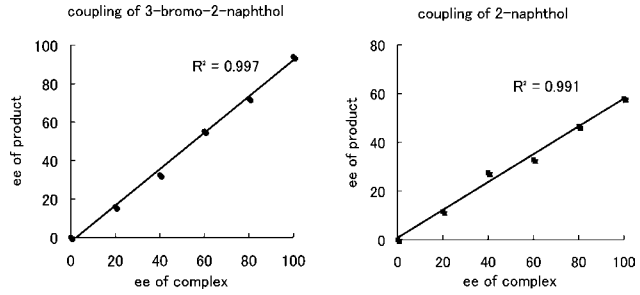


Figure 2. Relationship between the enantiomeric excesses of catalyst **1** and the coupling product.

cal to that of **1**, indicating that complexes **1** and **2** come into rapid equilibrium with each other. Moreover, it was found that the dependence of the rate on the partial pressure of O_2 is also first-order (Figure S1 in the Supporting Information).[13] These results suggested that a monomeric iron(salan)(2-naphthoxo) intermediate and molecular oxygen participate in the rate-determining step of this iron-catalyzed oxidative coupling.

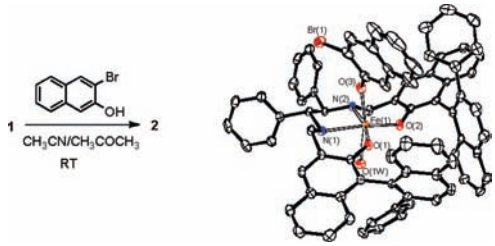


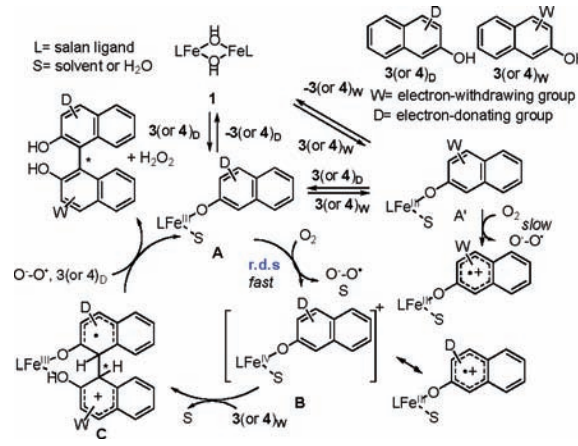
Figure 3. Preparation of iron(salan)(2-naphthoxo) complex **2** and its ORTEP view (50% probability). Hydrogen atoms and solvent molecules have been omitted for clarity.

The results described above seem to be reasonably explained by the mechanism shown in Scheme 2. (Di-μ-hydroxo)iron(salan) complex **1** is in equilibrium with monomeric species **A** and **A′** in the presence of 2-naphthols. Of these species, **A** is more rapidly oxidized than **A′** to give **B**, and a more acidic 2-naphthol (**3**$_W$ or **4**$_W$) preferentially binds to **B** after dissociation and gives **C**, in which a phenolic proton shifts between the two phenolic oxygen atoms, preferentially.[3b] **C** can be converted to **A** via proton and hydrogen atom abstraction and subsequent ligand exchange. On the basis of the kinetic studies, the first-order dependence of the rate on substrate and oxygen concentration, and the fact that species **A** is isolable, the rate-determining step of this oxidation is the most likely to be the step from **A** to **B**, and the conformation of **B** seems to play a crucial role in the determination of the stereochemistry of this coupling.

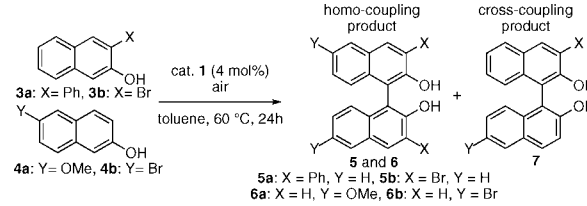
On the basis of mechanistic considerations as well as previous results,[7,8a,9] we expected that a combination of a 2-naphthol bearing a substituent at C3 and a less electron-rich 2-naphthol either with or without a substituent at C3 would undergo highly enantioselective cross-coupling in the presence of **1**. To confirm this expectation, we explored the coupling reaction between the two naphthols **3a** and **4b** and that between the two naphthols **3b** and **4a** (Scheme 3). As anticipated, both reactions preferentially gave the cross-coupling product. The enantiomeric excess of the cross-coupling product **7a**, in which the C3 substituent exists in the electron-rich naphthol moiety, was as high as 90%, while the enantiomeric excess of the cross-coupled product **7b** having no C3 substituent in the electron-rich naphthol moiety was moderate.

We envisioned that this conception could generally be applied to the cross-coupling reactions between 3-substituted 2-naphthols

Scheme 2. Possible Explanation of the Cross-Coupling between Electron-Rich and -Poor 2-Naphthols



Scheme 3. Cross-Selective Iron(salan)-Catalyzed Asymmetric Aerobic Oxidative Coupling of 2-Naphthols



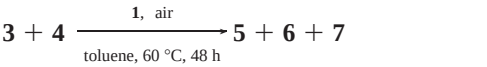
entry	X	Y	ee of **5**	ee of **6**	ee of **7**[a]	**5** : **6** : **7** (molar ratio)[b]
1	Ph	Br	**93**% ee (**5a**)	**17**% ee (**6a**)	90% ee (**7a**)	3 : 1 : 5
2	Br	OMe	94% ee (**5b**)	42% ee (**6b**)	60% ee (**7b**)	1 : 2 : 3

[a] Isolated yields were 42% for **7a** and 36% for **7b**.
[b] The molar ratio was estimated by ^{1}H NMR analysis.

and less electron-rich 2-naphthols. Indeed, the cross-coupling products between the two types of 2-naphthols were obtained with high enantiomeric excesses ranging from 87 to 95% (Table 1). The reactions between slightly electron-rich and electron-poor substrates (**3c** with **4b** and **3d** with **4b**) gave mixtures of cross- and homocoupling products, as the homocoupling of **4b** occurred under the conditions (entries 1 and 2). On the other hand, 6-methoxycarbonyl-2-naphthol **4c** did not undergo the homocoupling reaction under the present conditions but was found to undergo the cross-coupling reaction with more electron-rich **3a** (entry 3). This means that **4c** cannot be oxidized under these conditions but can react with the radical cation species derived from **3a**: **4c**, which bears an electron-withdrawing ester group, is more acidic and more readily dissociates to give an anionic alkoxide than an electron-rich substrate such as **3a.**[3b,6] The alkoxide is coordinated with the radical cation species and undergoes the cross-coupling in an intramolecular manner.[3f] This result is compatible with the proposed radical−anion mechanism. Since electron-rich **3a** should be more oxidizable than **4c**, **3a** should be consumed more rapidly than **4c** in the coupling of **3a** and **4c**, and the cross/homo ratio (**7f**/**5a**) should increase as the molar ratio (**4c**/**3a**) increases. Indeed, the reaction with a **4c**/**3a** molar ratio of 2:1 showed a higher cross/homo ratio of 11:2 when **3a** was added in three parts (entry 4). This type of reaction is of high synthetic value. Thus, we investigated the effect of various groups at C6 and found that acetyl, formyl, and nitrile groups efficiently suppress the homocoupling without disturbing the cross-coupling (entries 5−7). On the other hand, a trimethylsilylethynyl group can be used as the C3 substituent (entry 8). It is noteworthy that weakly electron-withdrawing groups such as bromo and iodo groups are also available as the C3 substituent. Adequate cross-selectivity as well as high enantioselectivity can be obtained

in these reactions (entries 4−10). Moreover, the products **7k** and **7l** obtained from 3-bromo- and 3-iodo-2-naphthols **3b** and **3f**, respectively, can be converted to various C_1-symmetric BINOLs via a cross-coupling reaction.

Table 1. Asymmetric Oxidative Cross-Coupling of Various 2-Naphthols[a]

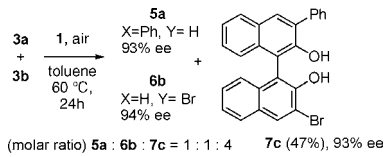


			5		7		
entry	X	Y	yield (%)[b]	ee (%)[c]	yield (%)[b]	ee (%)[c]	5/6/7[d]
1[e]	2-naphthyl	Br	42	90	52	89	2:2:5
	(**3c**)	(**4b**)	(**5c**)		(**7d**)		
2[e]	PhC≡C	Br	34	96	44	88	4:3:9
	(**3d**)	(**4b**)	(**5d**)		(**7e**)		
3[f]	Ph	CO_2Me	41	90	52	90	2:0:5
	(**3a**)	(**4c**)	(**5a**)		(**7f**)		
4[f,g]	Ph	CO_2Me	25	90	70	90	2:0:11
	(**3a**)	(**4c**)	(**5a**)		(**7f**)		
5[f,g]	Ph	Ac	17	90	65	88	2:0:15
	(**3a**)	(**4d**)	(**5a**)		(**7g**)		
6[f,g]	Ph	CHO	20	90	60	88	1:0:6
	(**3a**)	(**4e**)	(**5a**)		(**7h**)		
7[g,h]	Ph	CN	14	90	68	87	1:trace:10
	(**3a**)	(**4f**)	(**5a**)		(**7i**)		
8[f,g]	TMSC≡C	CO_2Me	10	96	53	93	2:0:21
	(**3e**)	(**4c**)	(**4e**)		(**7j**)		
9[f,i]	Br	CO_2Me	7	93	54	93	1:0:15
	(**3b**)	(**4c**)	(**5a**)		(**7k**)		
10[f,i]	I	CO_2Me	5	95	50	95	1:0:20
	(**3f**)	(**4h**)	(**5a**)		(**7l**)		

[a] The coupling reactions were carried out in toluene with a **3**/**4** molar ratio of 1:1 by using **1** (4 mol %) for 48 h on a 0.5 mmol scale under aerobic conditions, unless otherwise mentioned. [b] Isolated yield. The theoretical maximum (100%) yields of the cross-coupling and homocoupling products correspond to the formation of 0.5 and 0.25 mmol of products, respectively. [c] Determined by HPLC analysis on a chiral stationary phase column. [d] Molar ratio of respective BINOL products. [e] The ee value of homocoupling product **6b** was 18% ee. [f] No homocoupling product derived from **4** was obtained. [g] Using 2 equiv of **4**, with **3** added in three batches over 9 h. [h] A trace amount of the homocoupling product derived from **4f** was detected. [i] Run for 96 h using 6 mol % **1** and 2 equiv of **4**, with **3** added in three batches over 24 h.

This concept can be successfully applied to the coupling between the electron-rich and -poor 2-naphthols with a C3 substituent (Scheme 4).

Scheme 4. Cross-Coupling of Two 3-Substituted 2-Naphthols



In summary, we were able to propose a possible mechanism for aerobic oxidative coupling of 2-naphthols using iron(salan) complex **1** as the catalyst on the basis of studies of the kinetics and the relationship between product ee and catalyst ee for the coupling, and this enabled us to establish a highly enantioselective aerobic oxidative cross-coupling method for the preparation of C_1-symmetric BINOLs. This cross-coupling reaction possesses a wider substrate scope than the previously reported enantioselective cross-coupling oxidation.[3e,f,i,j] Moreover, the present study's disclosure that the scope of the cross-coupling reaction is different from that of the homocoupling is noteworthy. For example, the presence of two C3 substituents is not essential for obtaining high enantioselectivity in the oxidative coupling process if the less electron-deficient naphthyl moiety has a C3 substituent, and 6-methoxycarbonyl-2-naphthol **4c**, which cannot undergo a homocoupling reaction under the present aerobic oxidation conditions, can undergo a cross-coupling reaction. Investigation of the detailed stereochemical course of this reaction is in progress.

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Supporting Information Available: Experimental procedures, spectral data for binaphthols, HPLC conditions, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) In our previous report (ref 7), we proposed that complex **1** is a μ-oxo dimer on the basis of its IR spectrum. However, its structure was revealed to be a di-μ-hydroxo dimer by X-ray crystallography. For the X-ray crystallography, see Figure S2.
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(12) The supplementary crystallographic data for **2** have been deposited with The Cambridge Crystallographic Data Centre (CCDC) under entry code CCDC 771569. These data can be obtained free of charge from the CCDC via www.ccdc.ac.jk/data_request.cif.
(13) See the Supporting Information for details.

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