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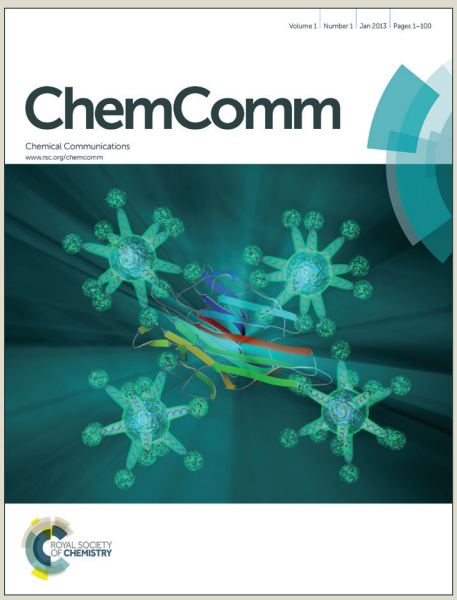

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Iron-Catalysed Asymmetric Tandem Spiro-Cyclization Using Dioxygen in Air as Hydrogen Acceptor

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Takuya Oguma[a,b] and Tsutomu Katsuki*[b,c,d]

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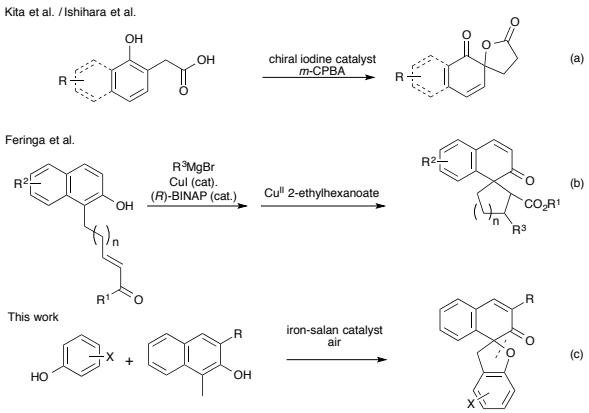
A tandem combination of *ortho*-quinone methide (*o*-QM) formation/Michael addition/asymmetric dearomatization, which is catalysed by iron-salan complex in air with high enantioselectivity, provides an efficient method for spirocyclic (2*H*)-dihydro-benzofuran synthesis from 2-naphthols and phenols. The key to the success of the tandem synthesis is the development of aerobic oxidative *o*-QM formation.

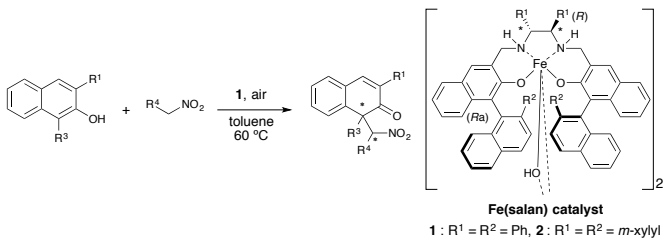
Spirocyclic frameworks are found in many biologically active products and are used for developing a novel class of chiral auxiliaries.[1] Various enantioselective methods for the intra- and intermolecular synthesis of spirocyclic compounds have been reported.[2,3] However, the substrates of intermolecular reactions are mostly limited to structurally similar cyclic α-keto, α-alkylidene, and α-hydroxy lactones or lactams.[3] Thus, new strategies for asymmetric intermolecular spirocyclization using different classes of starting materials have been required.



Scheme 1. Asymmetric oxidative dearomatization strategies for cons tructing chiral spirocyclic frameworks.

Oxidative dearomatization of *o*-substituted arenols is an efficient approach for the synthesis of spiroenone derivatives. For example, Kita et al. and Ishihara et al. have been reported chiral hypervalent iodine catalysed intramolecular spirolactonization using *m*-CPBA as the terminal oxidant (Scheme 1, a).[4,5] On the other hand, Feringa et al. developed one pot, two step spirocyclization involving enantioselective Michael addition and subsequent oxidative dearomatization of 2-naphthols using stoichiometric copper(II) as the oxidant (b).[6] In this paper, we describe enantioselective intermolecular spirocyclic (2*H*)-dihydrobenzofuran synthesis utilizing iron catalyst and dioxygen in air as the oxidant, from two different arenols, 1-methyl-2-naphthols and phenols (c).

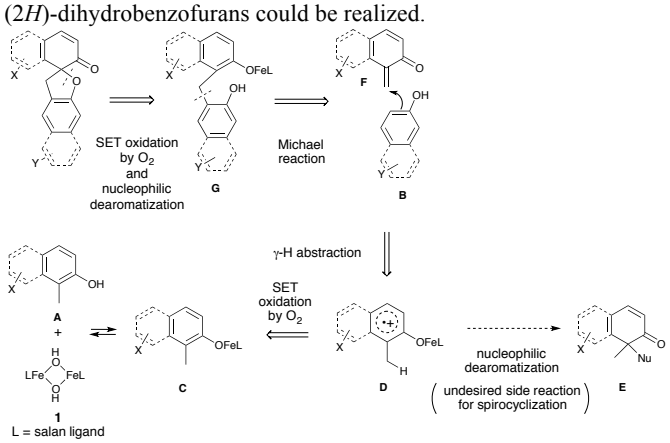
We recently reported that (di-μ-hydroxo)iron-salan dimer **1** catalyses asymmetric aerobic oxidative dearomatization of 1-substituted 2-naphthols in the presence of nitroalkanes (Scheme 2).[7,8]



Scheme 2. Iron-catalysed asymmetric aerobic oxidative dearomatiza tion.

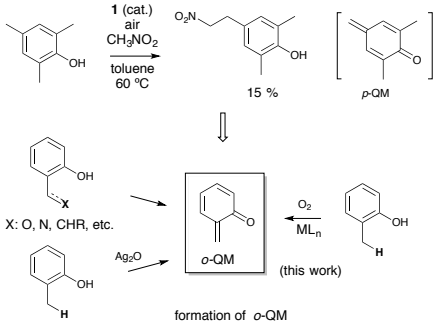
This dearomatization reaction has been thought to proceed through a radical cation species **D** that is attacked by the anion species *in situ* generated from nitroalkane under the reaction conditions to give the dearomatized product **E** (Scheme 3). On the other hand, chiral spirocyclic (2*H*)-dihydrobenzofuran would be prepared by asymmetric intramolecular oxidative dearomatization of methylenebis(arenol) **G**, which could in turn be prepared by Michael addition of arenolate anion to *o*-QM **F**, which is a strong Michael

acceptor.[9,10] Thus, if radical cationic species **D** can be transformed in the presence of a nucleophile that cannot attack the cationic aromatic ring but serves as a Michael donor, to **F** under the reaction conditions and conversion of **D** to **E** (undesired dearomatization process) can be suppressed, a simple tandem approach to spirocyclic (2*H*)-dihydrobenzofurans could be realized.



Scheme 3. Retro-synthetic analysis for oxidative spirocyclic dihydro benzofuran synthesis from two different arenols (**A** and **B**).

Oxidative transformation of *o*-substituted phenol to the *o*-QM has been achieved using silver oxide as an oxidant[11,12] but aerobic oxidative transformation has not been reported. However, while studying aerobic oxidative dearomatization,[7] we happened to find an interesting result that might be a clue for achieving the tandem synthesis (Scheme 4). The treatment of 2,4,6-timethylphenol with nitromethane in the presence of complex **1** in air gave 2,6-dimethyl-4-(2-nitroethyl)phenol. This result suggests that arenol can be dehydrogenated to QM *via* a radical cationic species and the QM can serve as a Michael acceptor under the reaction conditions.

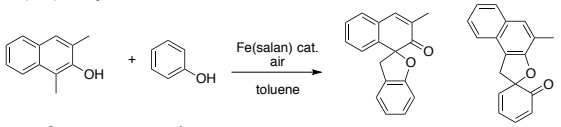


Scheme 4. A clue toward tandem synthesis of oxidative spirocyclic (2*H*)-dihydrobenzofuran: aerobic oxidative *o*-QM formation.

Thus, aerobic oxidation of 1-methyl-2-naphthols and phenols was expected to give the desired spirocyclic (2*H*)-dihydrobenzofurans in a tandem manner for the following reasons; i) phenolate anion serves as a Michal donor;[13] ii) the pKa (18 in DMSO) of phenol is similar to that of nitroalkane (17 in DMSO) and phenol is expected to generate the phenolate anion under the reaction conditions; and iii) naphthol is more easily oxidized than phenol,[14] and 2-naphthol (or its unit) should be selectively oxidized in the two steps (**A** to **D** and **G** to the product).

Based on this expectation, we examined the oxidation of a mixture of 1,3-dimethyl-2-naphthol **3a** and phenol **4a** in air at 90 °C in the presence of **1** (Table 1). As anticipated, spirocyclic (2*H*)-dihydrobenzofuran **5a** was exclusively obtained with high enantioselectivity,[15] albeit with moderate yield, and the formation of **6** was not observed (entry 1). The reaction did not proceed at 25 ºC (entry 2), and the reaction in O_2 reduced the yield, likely because compound **3a** suffers autoxidation under this condition[16] (entry 3). The use of excess amount of substrate (**3a** or **4a**) did not increase the yield, and the formation of some unidentified products was observed (entries 4 and 5). Use of 10 mol% of the catalyst improved the yield to 54% (entry 6). To further increase enantioselectivity, we surveyed iron-salan catalysts (See E.S.I. for additional catalyst optimization) and found that complex **2** bearing 3,5-dimethylphenyl substituents at its ethylendiamine and binaphthyl moieties showed higher enantioselectivity of 92% ee (entry 7). The yield was improved to 86% by adding 0.5 equiv. of **3a** at 24 h and extending the reaction time to 48 h (entry 8).

Table 1. Development of iron-catalysed asymmetric tandem synthesis of spir ocyclic (2*H*)-dihydrobenzofuran **5a**[a].



3a + **4a** → **5a** + **6**

Entry	Catalyst	ºC	**3a** : **4a**	Oxidant	Yield **5a** (%)[b]	Ee **5a** (%)[c]
1	**1**	90	1 : 1	air	36	86
2	**1**	25	1 : 1	air	nr	nd
3	**1**	90	1 : 1	O_2	12	82
4	**1**	90	1 : 2	air	38	83
5	**1**	90	2 : 1	air	30	84
6[d]	**1**	90	1 : 1	air	54	84
7[d]	**2**	90	1 : 1	air	57	92
8[d,e]	**2**	90	1.5 : 1	air	86[f]	91

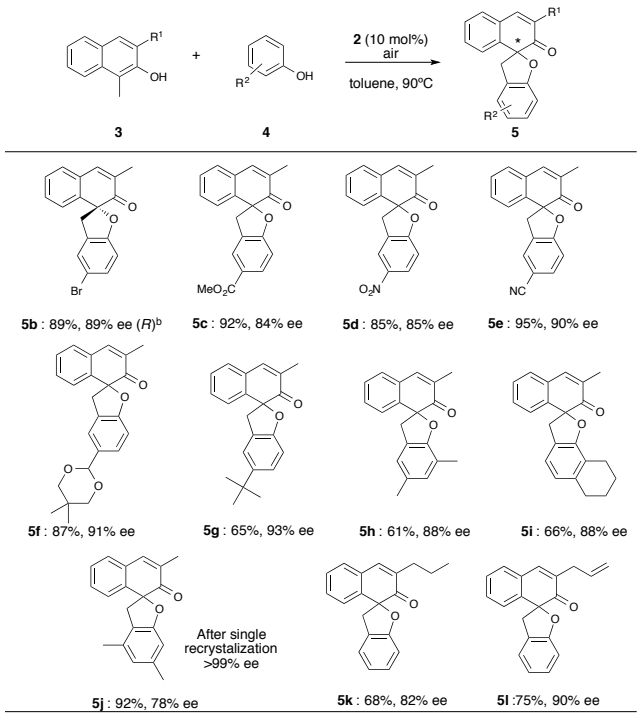
[a]Reactions were run on a 0.1 mmol scale in toluene for 24 h using 5 mol% of iron-salan catalyst (1 or 2) under air, unless otherwise noted. [b]Determined by ^{1}H NMR analysis using phenanthrene as an internal standard. [c]Determined by HPLC analysis on a chiral stationary phase column. [d]10 mol% of catalyst was used. [e]Run on a 0.4 mmol scale for 48 h. 0.5 equiv. of 3a was added at 24 h. [f]Isolated yield.

With complex **2** as the catalyst, we further examined the reactions between 1,3-dimethyl-2-naphthol and substituted phenols (Table 2). High enantioselectivity (84-93% ee) has been achieved irrespective of location of the substituents, except that the reaction of 3,5-dimethylphenol afforded **5j** with a somewhat diminished enantioselectivity (78% ee). Fortunately, enantiopure **5j** was obtained by a single recrystallization from dichloromethane/*n*-hexane. Moreover, a broad functional group compatibility was observed; halo, ester, nitro, and cyano groups withstood the reaction conditions, and only the formyl group, which decomposed under the reaction condition, did not. However, the corresponding acetal group was tolerant of the conditions and compound **5f** was obtained with high enantioselectivity and yield. Recrystallization of **5b** from dichloromethane/*n*-hexane gave a single crystal that is suitable for crystallographic analysis, and its absolute configuration was determined to be *R*.[17]

The reactions of 1-methyl-3-(*n*-propyl)-2-naphthol and 3-allyl-1-methyl-2-naphthol with phenol also proceeded with high enantioselectivity of 82 and 90% ees, respectively, to give **5k** and **5l**, respectively. It is noteworthy that the reaction of 3-allyl-1-methyl-2-naphthol gave only the spirocyclic product **5l** formed *via* a 1,2-naphthoquinone methide intermediate. No product was detected *via* a 2,3-naphthoquinone methide intermediate. On the other hand, the reaction of 1-ethyl-3-methyl-2-naphthol with phenol did not proceed. Although the reason for this is unclear, the formation of Michael addition product (**G** in Scheme 3) was not detected and either γ-

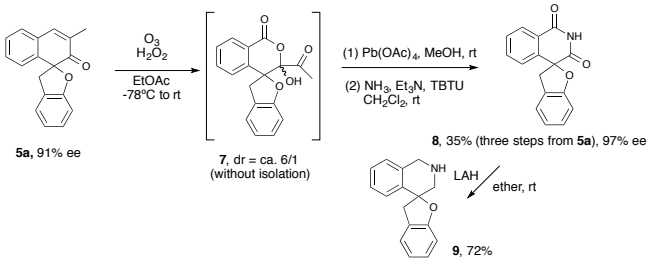
hydrogen abstraction or Michael addition step is not likely to proceed.

Table 2. Asymmetric tandem synthesis of spirocyclic (2*H*)-dihydrobenzofurans[a]



[a]Reactions were run at 90 °C in toluene with a molar ratio (**3** : **4** = 1 : 1) for 24 h using iron-salan catalyst **2** in air on 0.4 mmol scale and further run for 24 h after 0.5 eq. of **3** was added. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase column. All yields are isolated ones. [b]Determined by X-ray crystallographic analysis.

Spiro(benzofuranazaalkane)s show unique biological activity.[18] To explore the utility of the present reaction, we examined the conversion of **5a** to spiro[benzofuranisoquinoline] **9**, a class of spiro(benzofuranazaalkane)s (Scheme 5). Its derivatives show biological activity such as diuretic, antihypertensive, and anticonvulsant activities. Thus, **5a** was submitted to ozonolysis with oxidative workup to give lactone **7** as an equilibrium mixture of two diastereomers, which was further converted without isolation to **8**; i) $Pb(OAc)_4$ oxidation and ii) imidation with aqueous ammonia in the presence of *O*-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (TBTU). Fortunately, when the obtained **8** was ultrasonicated in ethyl acetate/MeOH (1/2), most of **8** was dissolved and the concentration of the solution gave a highly enantioenriched **8** (97% ee). The ee of a small amount of undissolved **8** was 11%. The enantioenriched **8** was reduced by LAH to afford **9**. **5a** was converted in four steps into **9** in a total yield of 25%.



Scheme 5. Transformation of 5a to 9.

In conclusion, we have developed an iron-catalysed oxidative *o*-QM formation/Michael addition/asymmetric oxidative dearomatization tandem strategy for the synthesis of spirocyclic compounds, which was inspired by the discovery of in situ aerobic oxidative *o*-QM formation. This strategy enables a facile synthesis of useful spirocyclic (2*H*)-dihydrobenzofurans with air as the hydrogen acceptor from 1-methyl-2-naphthol and phenol derivatives. By utilizing the tandem synthesis as a key step, a core structure **9** of biologically active spiro[benzofuranisoquinoline]s was constructed in only five steps from easily available 1,3-dimethyl-2-naphthol and phenol in a highly enantioselective manner.

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Notes and references

[a] Department of Chemistry, Graduate School of Science, Kyushu University, Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan.
[b] International Institute for Carbon-Neutral Research (WPI-I2CNER), Kyushu University, Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan.
[c] Institute for Advanced Study, Kyushu University, Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan.
[d] JST, ACT-C, Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan.

Electronic Supplementary Information (ESI) available: [experimental and spectral data, and crystallographic data]. See DOI: 10.1039/c000000x/

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