Asymmetric Cyclization *via* Oxygen Cation Radical: Enantioselective Synthesis of *cis*-4b,9b-Dihydrobenzofuro[3,2-b]benzofurans

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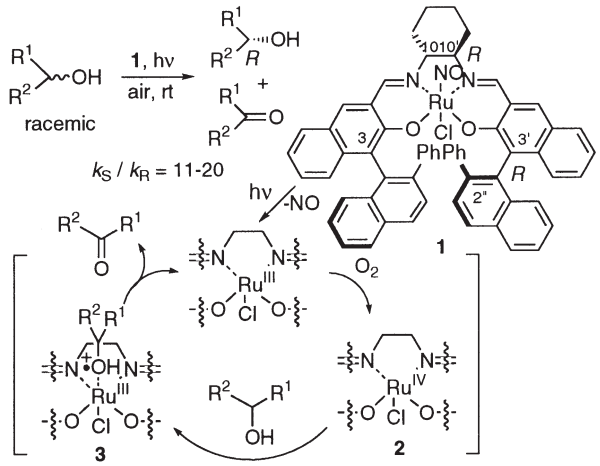
Aerobic oxidative cyclization of 2,2′-dihydroxystilbenes *via* oxygen cation radical to give *cis*-4b,9b-dihydrobenzofuro[3,2-b]benzofurans was carried out in an enantioselective manner (up to 89% ee) by using (nitrosyl)Ru(salen) **10** as the catalyst under photo-irradiated conditions.

Catalytic asymmetric reaction promoted by molecular oxygen is one of the goals of organic synthesis because of its high atom economy and environmental benignancy.

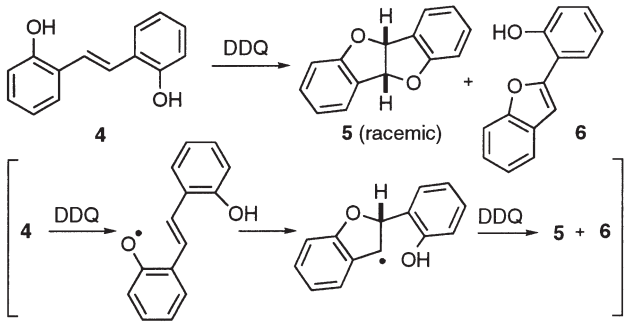
We recently demonstrated that (ON)Ru(salen) **1** catalyzed enantiomer-differentiating aerobic oxidation of racemic secondary alcohols under photo-irradiated conditions. Photo-irradiation has been considered to promote dissociation of the nitrosyl ligand to give a coordinatively unsaturated Ru(III) species that is oxidized to Ru(IV) species **2** by oxygen. Alcohol is coordinated to **2** and undergoes single electron transfer to give a cation radical intermediate **3** that gives ketone *via* hydrogen atom and proton abstraction (Scheme 1).[1] This reaction mechanism was supported by the fact that β-naphthols underwent oxidative coupling under the same conditions.[2,3]

On the other hand, radical cyclization is an important tool for construction of cyclic compounds[4] and oxygen radical cyclization is also a useful method for the formation of cyclic ethers.[5] However, its synthetic application is rather limited.[6] Although several diastereoselective oxygen radical cyclizations have been reported,[5a–c] few study on enantioselective cyclization has been reported.[7] Thus, we studied Ru(salen)-catalyzed enantioselective cyclization of an oxygen cation radical.

In 1975, Cardillo et al. reported that oxidative cyclization of 2,2′-dihydroxystilbene **4** provided a mixture of *cis*-4b,9b-dihydrobenzofuro[3,2-b]benzofuran **5** and 2-(2-hydroxyphenyl)-benzofuran **6** (Scheme 2).[5d]



Scheme 1.



Scheme 2.

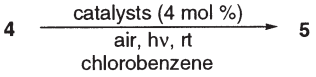
We expected that asymmetric version of this unique bicyclization reaction could be achieved by using (ON)Ru(salen) complex as the catalyst which would promote aerobic oxidation *via* a cation radical (*vide supra*).[8,9] Thus, we examined oxidative cyclization of **4** in the presence of **1** in chlorobenzene (Table 1, entry 1). The desired cyclization proceeded smoothly to give the desired **5** of 34% ee accompanied with **6** (14%).

Although the transition state structure of this reaction is unclear at present, the resulting phenol cation radical is considered to reside on the ruthenium ion and close to the 2″-phenyl group, and the other hydroxyphenyl group to be located close to the ethylenediamine. This spatial arrangement of the intermediate suggests that enantioselectivity of the reaction would be affected by the steric repulsion between the substrate and the 2″- and 10′-substituents of the catalyst.

Accordingly, we examined the oxidative cyclization of **4** with various Ru(salen)s **7-11** as the catalyst (Table 1). As expected, enantioselectivity of the reactions depended on the catalyst used. (*R*, *R*)-**1** showed slightly better enantioselectivity than its (*R*, *S*)-diastereomer **7** (entries 1 and 2). Replacement of the 2″-phenyl group of **1** with biphenylyl group resulted in a small improvement of enantioselectivity (entry 3). The remarkable improvement was brought by the modification of the diamine moiety: the complex **10** bearing 1,2-diphenylethylenediamine as its diamine unit induced high enantioselection of 81% ee (entry 5). On the other hand, the catalyst **11** showed poor enantioselectivity (entry 6).

We next examined the effect of solvent on enantioselectivity (Table 2). Clear relationship was not observed between solvent polarity and enantioselectivity. Amongst the reactions examined, the highest enantioselectivity (89% ee) was achieved when *t*-BuOH was used as the solvent (entry 1), though the chemical yield was modest. The yield of **6** was low (2%). The reaction in toluene gave better chemical yield, but enantioselectivity was slightly diminished (entry 3). Thus, use of mixed solvent was examined

Table 1. Asymmetric aerobic oxidative cyclization of 2,2′-dihydroxystilbene **4** using Ru(salen) as catalyst[a]



Entry	Catalyst	Yield of **5** / %	% ee[b]
1	**1**	85	34
2	**7**	83	26
3	**8**	72	57
4	**9**	62	42
5	**10**	79	81
6	**11**	76	<1

[a]Reaction was carried out for 4 h under irradiation using a halogen lamp as the light source. [b]Determined by HPLC analysis using optically active column (DAICEL CHIRALCEL OD-H, hexane/2-propanol = 100/1).

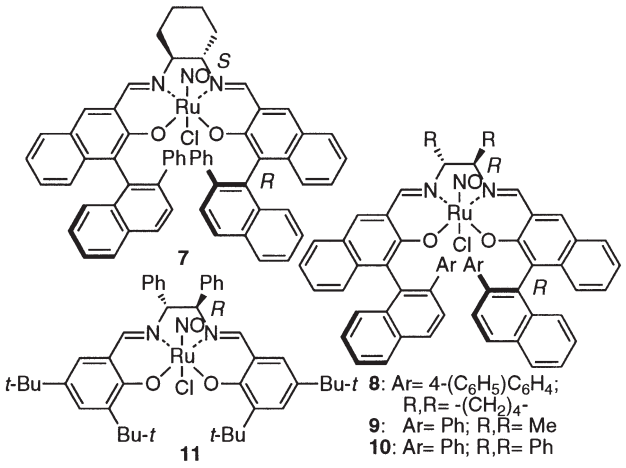


Table 2. Solvent effect on asymmetric oxidative cyclization of **4** using **10** as the catalyst[a]

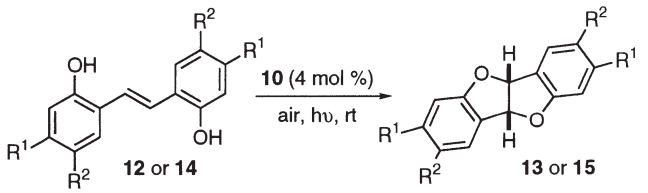
Entry	Solvent	Yield of **5** / %	% ee[b]
1	*t*-BuOH	23	89
2	*i*-Pr_2O	12	85
3	toluene	78	82
4	toluene-*t*-BuOH (2:3)	87	86

[a]Reaction was carried out under irradiation using a halogen lamp as the light source. [b]Determined by HPLC analysis using optically active column (DAICEL CHIRALCEL OD-H, hexane/2-propanol = 100/1).

and acceptable enantioselectivity and chemical yield were achieved by using mixed toluene-*t*-butyl alcohol (2 : 3) (entry 4), though a small amount of **6** (13%) was formed.[10]

To understand the mechanism of asymmetric induction by **10**, we next examined the reactions of substituted 2,2′-dihydroxystilbenes (Scheme 3). From the proposed arrangement of the intermediate (*vide supra*), the introduction of the substituents onto the benzene ring of the substrate is considered to cause the undesired steric repulsion with the 2″- and 10′-substituent and to lower the enantioselectivity. Indeed, the reaction of 4,4′-dimethyl derivative **12** proceeded with moderate enantioselectivity of 66% ee (Scheme 3). The reaction of 5,5′-dimethyl derivative **14** showed further reduced enantioselectivity of 10% ee. Use of diisopropyl ether as the solvent improved enantioselectivity of both the reactions, though the chemical yields were insufficient.

In conclusion, we were able to achieve high enantioselectivity in the cyclization of an oxygen cation radical for the first time, though there is still a room for improvement. Further study is in progress in our laboratory.



Scheme 3.

Dedicated with respect and admiration to Professor Teruaki Mukaiyama on the occasion of his 75th birthday.

References and Notes

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7 To our knowledge, asymmetric oxygen radical cyclization (1.3% ee) using copper-amine complex as the oxidant has been reported: B. Feringa and H. Wynberg, *Bioorg. Chem.*, **7**, 397 (1978).
8 A possibility that the cation radical species undergoes deprotonation and the resulting radical species undergoes cyclization can not be removed.
9 During the reviewing process, one referee suggested that the present reaction might proceed *via* Michael-type addition of phenol to mesomeric radical enone. Indeed, Wallis have reported that 2,4′-dihydroxystilbene derivative cyclizes *via* Michael-type addition of phenol to mesomeric dienone.[11] We, however, believe that the present cyclization occurs in the vicinity of the metal center from its moderate to high enantioselectivity and proceeds through intramolecular addition of phenoxy radical to olefin as proposed by Cardillo et al. (Scheme 2).
10 Experimental procedure for oxidative cyclization of **4**:[12] **4** (21.2 mg, 0.1 mmol) and **11** (4.4 mg, 4 mol%) were dissolved in *t*-BuOH (1.2 ml) and toluene (0.8 ml). The solution was stirred under irradiation with a halogen lamp in air for 1 h at room temperature and kept stirred for 3 h without irradiation. The procedure was further repeated seven times. Then, the mixture was chromatographed on silica gel (hexane : ethyl acetate = 9 : 1) to give **5** (17.0 mg, 81%) of 84% ee and **6** (2.0 mg, 10%).
11 A. F. A. Wallis, *Aust. J. Chem.*, **25**, 1529 (1972).
12 Experiments described in Tables 1 and 2 and Scheme 3 were carried out in 25 μmol scale and irradiation was continued during the reactions. The exemplified experiment was performed in 0.1 mmol scale (Ref. 10) and irradiated every four hours to avoid temperature-rising.