

(Salen)ruthenium-catalyzed Desymmetrization of *meso*-Diols (2). Apical Ligand Effect on Enantioselectivity

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(Received February 14, 2003; CL-030126)

Enantiotopos-selectivity of aerobic oxidation of *meso*-diols using chiral (nitrosyl)Ru(salen) complexes as catalyst was found to be dependent on the nature of their apical ligand. The oxidation with complex **5** possessing an apical hydroxo ligand as the catalyst showed moderate to good enantioselectivity (up to 80% ee).

Optically active lactols occur in many natural products as subunits. Among various methods for the synthesis of optically active lactols, desymmetrization (enantiotopos-selective oxidation) of *meso*-diols is an attractive one from the synthetic point of view, because various *meso*-diols are readily available. Horse liver alcohol dehydrogenase is well known to undergo highly selective desymmetrization of *meso*-diols;¹ however, the products are not lactols but lactones. Amongst chemical methods,^{2,3} electrooxidation of prochiral or *meso*-diols is highly enantioselective, but the products are also lactones.³ Thus, for the transformation of *meso*-diols to chiral lactols, a catalyst showing not only enantiotopos selectivity but also chemoselectivity is required.

We have recently demonstrated that a chiral (nitrosyl)(salen)-ruthenium complex [hereafter denoted as (ON)Ru(salen)] is an efficient catalyst for enantiomer-differentiating aerobic oxidation of racemic secondary alcohols under photo-irradiation,^{4,5} and (ON)Ru(salen) bearing tetramethylethylenediamine as its diamine unit catalyzes chemoselective aerobic oxidation of 1,*n*-diols to give the corresponding lactols also under photo-irradiated conditions.⁶ Based on these results, we expected that desymmetrization of *meso*-1,4-diols giving the corresponding optically active lactols would be realized by using a chiral (ON)Ru(salen) bearing chiral quaternary carbons at its ethylenediamine unit as the catalyst. Indeed, the oxidation of

Table 1. Desymmetrization of various *meso*-diols using **3** as catalyst^a

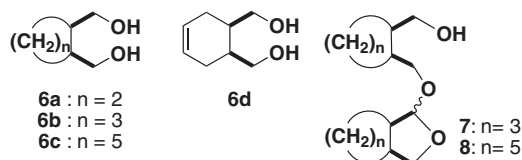
Entry	Substrate	Time/d	Yield/% ^b	% ee ^c	(% ee) ^d	Confgn ^e
1	1	2.5	28	70	(67)	1 <i>R</i> , 6 <i>S</i> ^f
2	6a	3	32	66	(59)	1 <i>R</i> , 4 <i>S</i> ^g
3	6b	3	34	64	(65)	1 <i>R</i> , 5 <i>S</i> ^g
4	6c	3	30	62	(63)	— ^h
5	6d	3	25	71	(66)	1 <i>R</i> , 6 <i>S</i> ⁱ

^aTwo mol% of the catalyst was used. ^bIsolated yield of lactol.

^cDetermined by GLC analysis using optically active column (SUPELCO BETA-DEX-225) after its conversion to the corresponding lactone.

^dThe enantioselectivity observed with complex **2** (abstracted from Ref. 7). ^eDetermined by comparison of the specific rotation after its conversion to the corresponding lactone.

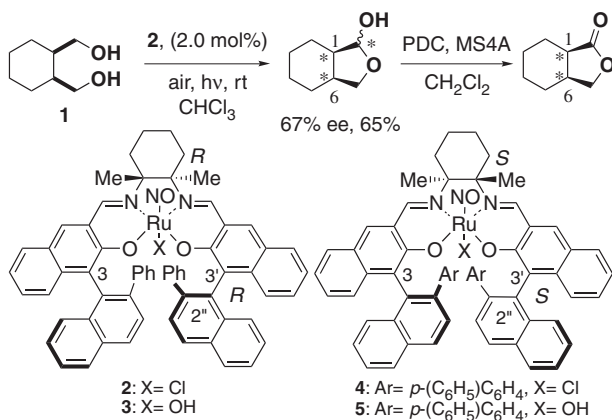
^fRef. 10a. ^gRef. 10b. ^hThe absolute configuration has not been determined. ⁱRef. 10c.



1,2-bis(hydroxymethyl)cyclohexane **1** using complex **2** as the catalyst showed moderate enantioselectivity (Scheme 1).⁷

We recently found that complex **2** was converted into complex **3** bearing an apical hydroxo ligand upon its exposure to silica gel (FL100B, FUJI SILYSIA CHEMICAL LTD).⁸ Thus, we examined desymmetrization of a series of 1,4-*meso*-diols with **3** as catalyst. The reactions were slow, but it is noteworthy that complex **3** showed a slightly better enantioselectivity in the oxidation of *meso*-diols (**1**, **6a**, and **6d**) than complex **2**, while both **2** and **3** showed a similar level of enantioselectivity in the oxidation of **6b** and **6c** (Table 1). Upon the oxidation of **6b** and **6c**, the formation of a trace amount of mixed acetals (**7** and **8**) was observed.⁹

In these aerobic oxidations, the alkyl moiety of the diol coordinated to the ruthenium ion was considered to be directed toward the space around C3 or C3'.^{6a} Therefore, we expected that (ON)Ru(salen) bearing a bulkier substituent at C2'' would show higher asymmetric induction. Thus, we synthesized complex **4**. During chromatography on silica gel, complex **4** was found to be partly transformed to hydroxo complex **5**.⁸ Oxidation of diol **1** was examined by using **4** as the catalyst (Table 2). Contrary to our expectation, the reaction with complex **4** showed slightly diminished enantioselectivity together with low chemical yield (Entry 1). In contrast, the reaction with **5** showed better enantioselectivity of 81% ee (Entry 2), albeit with low chemical yield. Use of 4 mol% of **5** improved the chemical yield ca. twice as many (Entry 3), and prolonged reaction time gave an accep-



Scheme 1.

Table 2. Desymmetrization of *meso*-diol **1** with **4** or **5** as catalyst

Entry	Catalyst ^a	Time/d	Yield/% ^b	% ee	Confgn
1	4	2.5	9	62	1 <i>S</i> , 6 <i>R</i>
2	5	2.5	14	81	1 <i>S</i> , 6 <i>R</i>
3	5 ^c	2.5	33	82	1 <i>S</i> , 6 <i>R</i>
4	5 ^c	7	80	80	1 <i>S</i> , 6 <i>R</i>

^aThe catalyst (2 mol%) was used, unless otherwise mentioned.^bIsolated yield of lactol. ^cFour mol% of the catalyst was used.**Table 3.** Desymmetrization of various *meso*-diols using **5** as catalyst^a

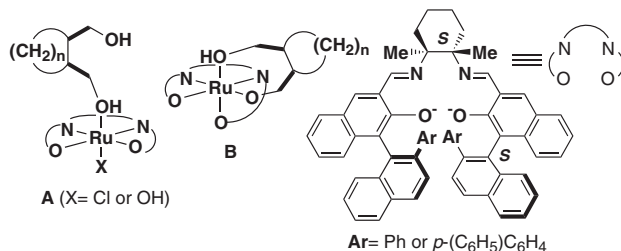
Entry	Substrate	Time/d	Yield/% ^b	% ee	Confgn
1	6a	7	64	74	1 <i>S</i> , 4 <i>R</i>
2	6b	7	78	66	1 <i>S</i> , 5 <i>R</i>
3	6c	7	80	63	- ^c
4	6d	7	68	75	1 <i>S</i> , 6 <i>R</i>

^aFour mol% of the catalyst was used. ^bIsolated yield of lactol.^cThe absolute configuration has not been determined.

table chemical yield without reducing enantioselectivity (Entry 4).¹¹

Thus, we examined the oxidation of other *meso*-diols with complex **5** as the catalyst (Table 3). The same trend in enantioselectivity as observed in the reaction with **3** was again observed: the oxidations of diols **6a** and **6d** proceeded with better enantioselectivity than that with complex **2**, while the oxidations of diols **6b** and **6c** showed a similar level of selectivity to that with **2** or **3**.

Although the mechanism of asymmetric induction of the oxidations is unclear at present, we were intrigued by the above-described trend in enantioselectivity of the reactions with (hydroxo)(ON)Ru(salen) complexes (**3** and **5**) as the catalyst. It is known that hydroxo and alkoxo ligands are readily exchangeable with alcohol, and metallosalen complexes bearing such an exchangeable ligand readily adopt a *cis*- β structure when a bidentate ligand is coordinated.^{12,13} We have proposed that the reactions using complex **2** as the catalyst proceed via intermediate **A** (X = Cl).⁷ We speculated that some *meso*-diols (**6b** and **6c**) would coordinate to the metal center through one hydroxy group to give an intermediate **A** (X = OH), while other *meso*-diols (**1**, **6a**, and **6d**) would make chelates (**B**) (Figure 1). It was considered that the reactions through intermediate **A** would show a similar level of enantioselectivity irrespective of the salen and apical ligands of the catalysts: because of high conformational freedom of the coordinated diol, a slight modification of the salen ligand had minimal effect on the enantioselectivity. On the other hand, the reaction via **B** was considered to show better enantioselectivity when the coordination sphere of the ruthenium ion is asymmetrically well defined, because the chelated diol is conformationally restricted. These considerations agree with the experimental results, but it is unclear at present

**Figure 1.**

what factor determines the coordinating behavior of each *meso*-diol.

In conclusion, we were able to achieve good to high enantioselective aerobic oxidation of *meso*-diols by using an (ON)(hydroxo)(salen)ruthenium complex as the catalyst under photo-irradiation. The nature of the apical ligand was found to influence the reaction pathway of the present aerobic oxidation. Further study on the mechanism of the present aerobic oxidation is in progress.

References and Notes

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- Complexes **2** and **4** were completely converted into complexes **3** and **5**, respectively, when they were exposed to silica gel for 12 h. On the other hand, treatment of **3** and **5** with trimethylsilyl chloride gave **2** and **4**, respectively: Complexes **2-5** gave satisfactory ¹H NMR and IR spectra, respectively. IR spectra of **3** and **5** showed the absorption at ca. 3540 cm⁻¹ characteristic to OH group, while those of **2** and **4** did not show such absorption.
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- Typical experimental procedure is exemplified by the desymmetrization of *meso*-diol **1**: **1** (14.4 mg, 0.1 mmol) and **5** (4.6 mg, 4.0 mol%) were dissolved in anhydrous CHCl₃ (0.5 mL). The solution was stirred under irradiation with a halogen lamp in air for 7 days at ambient temperature. The mixture was directly chromatographed on silica gel (hexane/ethyl acetate = 1/1) to give the corresponding lactol (11.4 mg, 80%). To a suspension of the lactol and molecular sieves 4 Å (120 mg) in anhydrous CH₂Cl₂ (0.5 mL) was added pyridinium dichromate (60 mg, 0.16 mmol). The mixture was stirred overnight at room temperature, diluted with hexane/EtOAc (4/1) and filtered through a pad of silica gel. The filtrate was concentrated under reduced pressure. The ee of the resulting lactone was determined by GLC analysis.
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