(Salen)ruthenium-Catalyzed Desymmetrization of *Meso*-Diols: Catalytic Aerobic Asymmetric Oxidation under Photo-Irradiation

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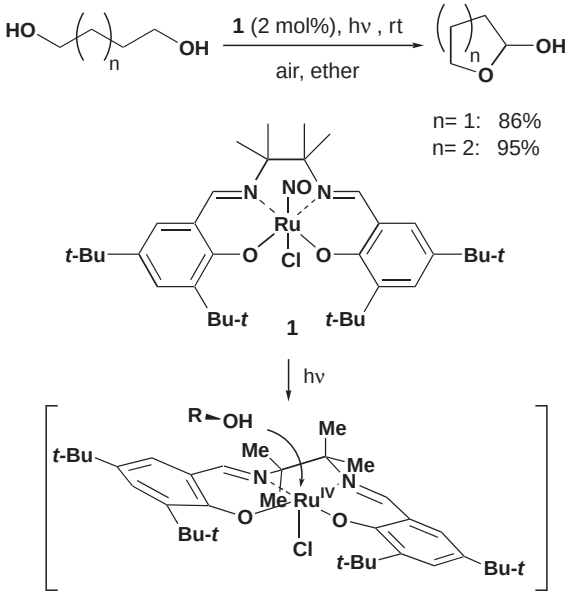
Catalytic aerobic oxidation of *meso*-diols using (nitrosyl)-Ru(salen) **7** as the catalyst under photo-irradiation proceeded with moderate enantioselectivity (up to 67% ee) to give the corresponding lactols.

Asymmetric oxidative desymmetrization of σ-symmetric diols is a useful method for the synthesis of optically active lactols that are important building blocks, and much effort has been directed toward this end. Although oxidizing enzyme such as horse liver alcohol dehydrogenase is well known to undergo highly enantiotopos-selective oxidation of *meso*-diols,[1] only a few chemical methods are available for this purpose but their enantioselectivity is insufficient.[2,3]

Recently, we demonstrated that (nitrosyl)(salen)ruthenium complex [hereafter denoted as (ON)Ru(salen)] **6** was an efficient catalyst for enantiomer-differentiating aerobic oxidation of racemic secondary alcohols under photo-irradiation.[4,5] Furthermore, it was revealed that (ON)Ru(salen) **1** bearing tetramethylethylenediamine as its diamine unit catalyzed chemo- and/or regio-selective aerobic oxidation of primary alcohols[6] and 1,n-diols[7] to give aldehydes and lactols, respectively, also under photo-irradiated conditions (Scheme 1). Irradiation is indispensable for the dissociation of the apical nitrosyl ligand to give the active Ru^{IV} species and the pseudo-axial methyl groups at the diamine unit plays an important role in discriminating steric bulkiness of alcohol. Based on these results, we expected that desymmetrization (enantiotopos-selective oxidation) of *meso*-1,4-diols would be realized by using a chiral (ON)Ru(salen) bearing chiral quaternary carbons at its ethylenediamine unit, as the catalyst.



Scheme 1.

We first examined desymmetrization of *meso*-1,2-di(hydroxymethyl)cyclohexane **2a** by using complexes **5–8** as the catalyst (Table 1). The reactions with **5** and **6** gave acceptable chemical yields, but enantioselectivities were low (entries 1 and 2). On the other hand, the reaction with **7** bearing axial methyl groups at the diamine unit[8] showed moderate enantioselectivity (55% ee) as expected, though the chemical yield was somewhat diminished (entry 3). Its diastereomer **8** was a poor catalyst, suggesting that (*R*)-binaphthyl unit and (*R*, *R*)-dimethylcyclohexane unit is a matched combination for inducing asymmetry in this reaction (entry 4). The absolute configuration of the products was determined by the specific rotation with the reported one,[9a] after they were oxidized to the corresponding lactones.

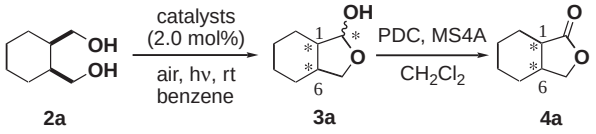


Table 1. Asymmetric aerobic oxidation of *meso*-diol **2a** using (ON)Ru(salen)s as catalyst[a]

Entry	Catalyst	Yield/%[b]	% ee[c]	Confign
1	**5**	81	4	1*R*, 6*S*
2	**6**	69	9	1*R*, 6*S*
3	**7**	53	55	1*R*, 6*S*
4	**8**	11	22	1*S*, 6*R*

[a]Reactions were carried out for 18 h under irradiation using a halogen lamp as the light source. [b]Isolated yield of lactol **3a**. [c]Determined by GLC analysis using optically active column (SUPELCO BETA-DEX-225) after its conversion to the corresponding lactone.

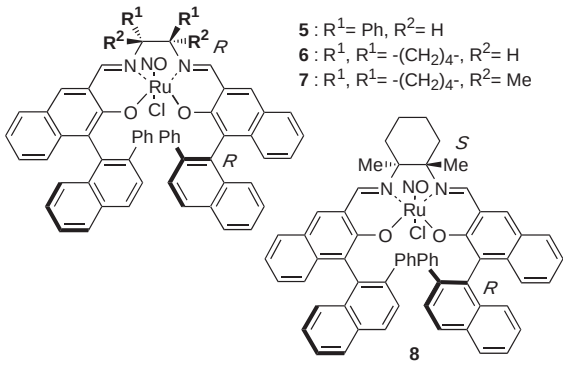


Table 2. Optimization of the reaction conditions for desymmetrization of **2a** using **7** as the catalyst[a]

Entry	Solvent	Time/d	Yield/%[b]	% ee[c,d]
1	benzene	1	64	55
2	THF	1	21	52
3	acetone	1	16	51
4	AcOEt	1	77	58
5	toluene	1	29	53
6	PhCl	1	33	55
7	CH_2Cl_2	1	35	65
8	$CHCl_3$	1	54	67
9	$(CH_2Cl)_2$	1	85	59
10	$(CHCl_2)_2$	1	32	62
11	$CHCl_3$	2.7	65	67

[a]Reactions were carried out under irradiation using a halogen lamp as the light source. [b]Isolated yield of lactol **3a**. [c]Determined by GLC analysis using optically active column (SUPELCO BETA-DEX-225) after its conversion to the corresponding lactone. [d]The absolute configuration of the product was 1*R*, 6*S*.

We next examined the effect of solvent on enantioselectivity (Table 2). Although the solvent effect was small, the reactions in halocarbons (entries 7–10) generally showed good enantioselectivity, and the best result was obtained when chloroform was used as the solvent (entry 8). The reaction was slow but elongation of the reaction time increased the chemical yield without changing enantioselectivity (entry 11).

Desymmetrization of a series of *meso*-1,2-di(hydroxymethyl)cycloalkanes (**2b–d**) was also examined under the optimized conditions (Table 3). The ring size of diols affects enantioselectivity of the reactions to a small extent (entries 1–3). Oxidation of *meso*-4,5-di(hydroxymethyl)cyclohexene **2e** exhibited a similar level of enantioselectivity (entry 4).[10] It is noteworthy that no epimerization was observed in these reactions.[11]

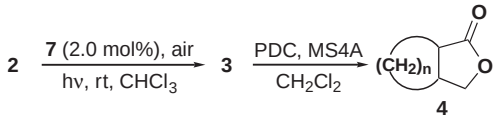
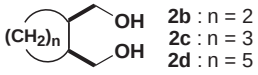
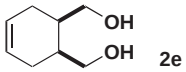


Table 3. Catalytic oxidative desymmetrization of various *meso*-diols **2** using **7** as the catalyst[a]

Entry	Substrate	Time/d	Yield/%[b]	% ee[c]	Config[d]
1	**2b**	2	49	59	1*R*, 4*S*[e]
2	**2c**	3	57	65	1*R*, 5*S*[f]
3	**2d**	2	64	63	—[g]
4	**2e**	3	66	66	1*R*, 6*S*[h]

[a]Reactions were carried out under irradiation using a halogen lamp as the light source. [b]Isolated yield of lactol **3**. [c]Determined by GLC analysis using optically active column (SUPELCO BETA-DEX-225) after its conversion to the corresponding lactone. [d]The absolute configuration of the product was determined by comparison of the specific rotation after its conversion to the corresponding lactone. [e]Ref. 9b. [f]Ref. 9b. [g]The absolute configuration has not been determined. [h]Ref. 9c.





In conclusion, we were able to demonstrate that enantiotopos-selective aerobic oxidation of *meso*-diols could be achieved by using (nitrosyl)(salen)ruthenium complex as the catalyst under photo-irradiation, though there is some room for improvement in enantioselectivity. Further study on aerobic asymmetric oxidation of *meso*-diols is in progress.

References and Notes

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10 Typical experimental procedure is exemplified by the oxidative desymmetrization of **2a**: *meso*-diol **2a** (14.4 mg, 0.1 mmol) and (ON)Ru(salen) **7** (2.0 mg, 2.0 mol%) were dissolved in anhydrous chloroform (0.5 mL). The solution was stirred under irradiation with a halogen lamp in air for 2.7 days at room temperature. The mixture was directly chromatographed on silica gel (hexane/ethyl acetate = 1/1) to give lactol **3a** (9.2 mg, 65%). To a suspension of lactol **3a** and 4 Å molecular sieves (100 mg) in anhydrous dichloromethane (0.5 mL) was added pyridinium dichromate (49 mg, 0.13 mmol). The mixture was stirred for 6 h at room temperature, diluted with hexane/ethyl acetate (4/1) and filtered through a pad of silica gel. The filtrate was concentrated under reduced pressure. The enantiomeric excess of the resulting lactone was determined by GLC analysis using optically active column (SUPELCO BETA-DEX-225).

11 All the lactones obtained in these reactions have the corresponding *cis*-bicyclo ring structures. The configuration of the lactone derived from **2d** was proven to be *cis* by the chemical correlation: LAH reduction of the lactone gave *meso*-diol **2d**.