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Ir-Catalyzed Oxidative Desymmetrization of *meso*-Diols

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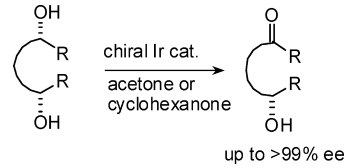
ABSTRACT



The catalytic oxidative desymmetrization of *meso*-diols was realized using a chiral iridium catalyst. In particular, the reaction is effective for the cyclic diols to give the corresponding hydroxy ketones in high chemical yields with high ee's. With this reaction as a key step, a short-step synthesis of common intermediate of ottelione and scyphostatin was achieved.

Desymmetrization of *meso* compounds is an efficient strategy for the synthesis of chiral complex molecules. Oxidative desymmetrization of diols has been achieved by using metal catalysts, organocatalysts, electrooxidations, and enzymatic methods.[1] Recently, we have succeeded in developing several kind of oxidation by an Ir catalyst.[2] Among them, Ir-catalyzed oxidative desymmetrization of primary diols has been found to be useful for the synthesis of chiral lactones (Scheme 1, eq 1).[2c] Herein, we describe the Ir-catalyzed oxidative desymmetrization of secondary diols (Scheme 1, eq 2). So far there are several reports for the oxidative desymmetrization of secondary diols. In 1997, Noyori et al. reported excellent ee's with unsaturated diols using a Ru catalyst (56−70%, 87−96% ee).[1c] The Sigman[1h,j,k] and Stoltz groups[1i] have succeeded in aerobic oxidative desymmetrization with Pd−sparteine catalysts, respectively (69−79%, 76−95% ee). Katsuki et al. have developed the aerobic reaction using a Ru(salen) complex (69%, 77% ee for 1,3-indandiol).[1f] Onomura et al. reported the oxidation of 1,2-diols such as *meso*-hydrobenzoin using NBS in the presence of chiral Cu complex to give 97% yield with 76% ee.[1l] Despite these efforts, there is no report which achieved both high yields and high ee's.

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Scheme 1. Two Types of Oxidative Desymmetrization

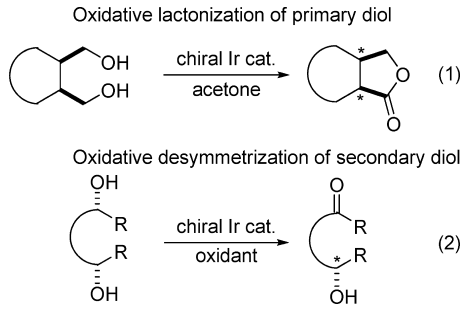
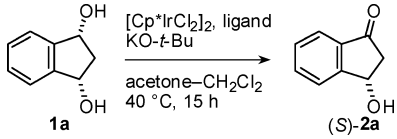
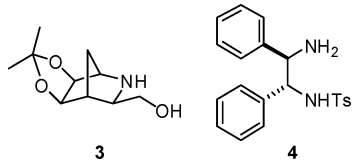


Table 1. Ligand Screening for the Oxidative Desymmetrization of *meso*-Indan-1,3-diol[a]



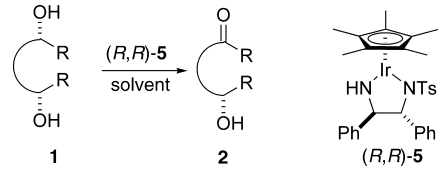
entry	ligand[b]	yield (%)	ee (%)
1	(1*S*,3*R*,4*R*)-2-azanorbornyl methanol[3]	13	73[c]
2	(1*R*,2*R*,6*S*,7*R*,9*R*)-**3**[4]	95	95[c]
3	(1*S*,2*R*)-*cis*-1-amino-2-indanol	25	71
4	(*R*)-phenylglycinol	22	55
5	(1*R*,2*R*)-diphenylethanolamine	34	51
6	(*R*,*R*)-**4**	54	>99

[a] The reaction was conducted using 0.133 mmol of **1a** in 1:2 acetone−CH_2Cl_2 mixed solvent (0.67 M) containing 1 mol % of the catalyst. [b] For ligand structures, see the Supporting Information. [c] (*R*)-**2a** was obtained.



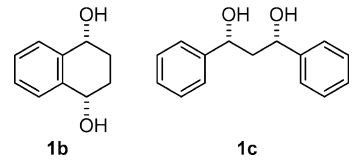
Initial screening of several chiral ligands was carried out using *meso*-indan-1,3-diol (**1a**) as a substrate. Stirring a mixture of $[Cp^*IrCl_2]_2$ with chiral ligand and *t*-C_4H_9OK (1:2:10 molar ratio) in CH_2Cl_2 at room temperature for 10 min under argon gave a dark red suspension. The soluble portion of this mixture was used as a catalyst for oxidative desymmetrization of *meso*-diols (Table 1). When the Ir catalyst with ligand **3**[4] in 2:1 acetone−CH_2Cl_2 was stirred at 40 °C for 15 h (**1a**/acetone/Ir = 1:7:0.01 molar ratio), β-hydroxy ketone **2a** was obtained in 95% yield with 95% ee (entry 2). The ligands which are effective in the asymmetric oxidative lactonization gave lower selectivities (entries 1 and 4). The other amino alcohol ligands also afforded **2a** in moderate ee's (entries 3 and 5). Finally, TsDPEN ligand (TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) was found to be the optimum ligand in selectivity (>99% ee, entry 6).

Table 2. Oxidative Desymmetrization of *meso*-Diols



entry	diol	solvent	concn of **1** (M)	time (h)	yield (%)	ee (%)
1[a]	**1a**	A[e]	2	14	97	91
2[a]	**1a**	C[f]	2	14	95	>99
3[b]	**1b**	A	2	5	92	93
4[b]	**1b**	C	2	4	92	>99
5[c]	**1c**	C	2	24	32	95
6[c]	**1c**	C	0.5	24	70	90
7[c,d]	**1c**	C[g]	0.1	10	91	−71

[a] With 1 mol % of catalyst at 30 °C. [b] With 1 mol % of catalyst at 40 °C. [c] With 10 mol % of catalyst at 60 °C. [d] The catalyst prepared from **3** was used instead of **5**. [e] A = acetone. [f] C = cyclohexanone. [g] Cyclohexanone/CH_2Cl_2 = 1:20.



Since ligand **4** showed the best selectivity, next we examined the substrate generality of the oxidative desymmtrization with preformed Ir complex **5**.[5] The reaction in higher concentration increased the yield (Table 2, entry 1). Cyclohexanone, which has higher oxidation potential than acetone, afforded >99% ee with 95% yield (entry 2). It is noteworthy that we did not observe the overoxidation product (1,3-indandione) in this system. Moreover, the treatment of **2a** under the same conditions for 14 h gave no diketone but **2a** without losing the optical purity. Similarly, the reaction of **1b** proceeded smoothly in cyclohexanone (entry 4). However, the reaction of acyclic 1,3-diol **1c** needed higher catalyst loading, and the 1,3-diphenyl-1-propanone was obtained as byproduct in 21% yield with higher concentration conditions (entry 5).[6] Decreasing the concentration suppressed the byproduct formation to give moderate yield and ee (entry 6). The catalyst prepared from ligand **3** gave 91% yield and moderate ee (entry 7). However, application of the same conditions of entry 6 to the reaction of 1,2-diols such as *meso*-hydrobenzoin gave unsatisfactory results (23% ee).

Oxidation of *meso*-diols could include the kinetic resolution pathway as shown in Scheme 2. To gain mechanistic

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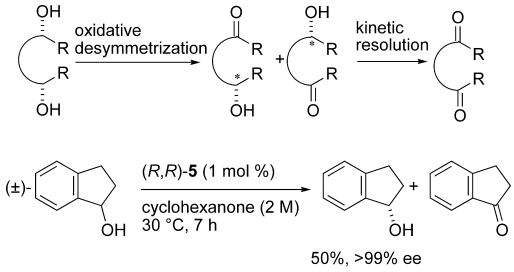
(6) Although the mechanism for the formation of 1,3-diphenyl-1-propanone is not clear, initial oxidation and following dehydration could give α,β-unsaturated ketone. The reduction of the double bond could afford the saturated ketone. See: Fujita, K.; Asai, C.; Yamaguchi, T.; Hanasaka, F.; Yamaguchi, R. *Org. Lett.* **2005**, *7*, 4017–4019.

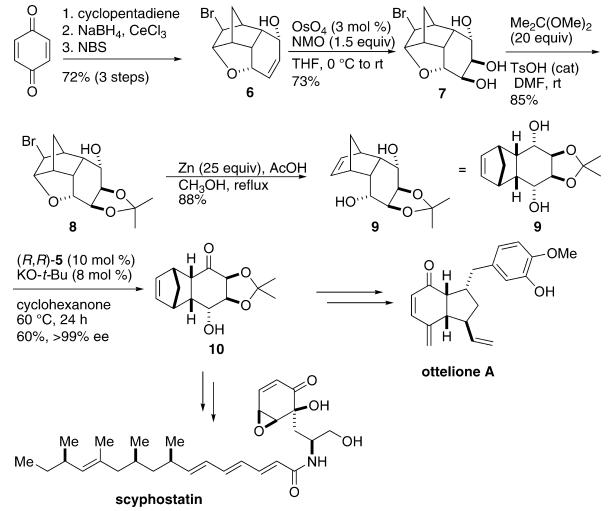
insight into the present reaction, oxidative kinetic resolution of 1-indanol was carried out.[7] The reaction of racemic 1-indanol with (*R*,*R*)-**5** in cyclohexanone proceeded at 30 °C for 7 h, and (*S*)-indanol was recovered with 50% yield and >99% ee.

Scheme 2. Oxidative Kinetic Resolution



With the efficient catalytic oxidative desymmetrization of *meso*-diols in hand, we attempted the catalytic asymmetric preparation of the common synthetic intermediate **10** for scyphostatin[8] and ottelione[9] (Scheme 3). Scyphostatin is the most potent and specific sphingomyelinase inhibitor, and otteliones are expected as new leads for cancer chemotherapeutic agents. In the previous synthetic route, the corresponding TBDMS-protected compound was synthesized from (−)-quinic acid in 10 steps.[8] The requisite *meso*-diol was prepared from *p*-benzoquionone in six steps. The allyl alcohol **6**[10] was treated with 3 mol % of OsO_4 and NMO (*N*-methylmorpholine *N*-oxide), affording the triol **7** in 73% yield. After protection of the *cis*-diol moiety of **7**, reductive

Scheme 3. Catalytic Asymmetric Synthesis of the Synthetic Intermediate of Ottelione A and Scyphostatin



cleavage of cyclic bromo ether gave the *meso*-diol **9**. The oxidative desymmterization of **9** successfully proceeded in the presence of KO-*t*-Bu (60%, >99% ee).[11]

In conclusion, we have demonstrated the efficient Ir-catalyzed oxidative desymmetrization of *meso*-diols. This method might be useful for the synthesis of other complex molecules.

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Supporting Information Available: Experimental details and characterization of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) For an example of Ir-catalyzed oxidative kinetic resolution, see: Arita, S.; Koike, T.; Kayaki, Y.; Ikariya, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 2447–2449.

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(11) The *trans*-diol was obtained as a byproduct (13% NMR yield, >99% ee). See the Supporting Information.The details will be discussed in an upcoming paper.