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Aerobic oxidative desymmetrization of *meso*-diols with bifunctional amidoiridium catalysts bearing chiral *N*-sulfonyldiamine ligands

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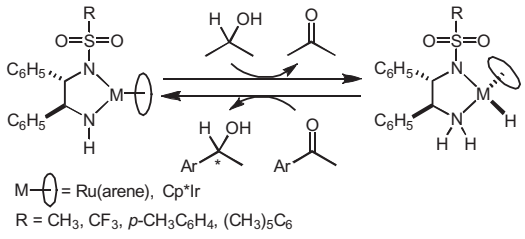
ABSTRACT

Asymmetric aerobic oxidation of a range of *meso*- and prochiral diols with chiral bifunctional Ir catalysts is described. A high level of chiral discrimination ability of Cp*Ir complexes derived from (*S*,*S*)-1, 2-diphenylethylenediamine was successfully demonstrated by desymmetrization of secondary benzylic diols such as *cis*-indan-1,3-diol and *cis*-1,4-diphenylbutane-1,4-diol, providing the corresponding (*R*)-hydroxyl ketones with excellent chemo- and enantioselectivities. Enantiotopic group discrimination in oxidation of symmetrical primary 1,4- and 1,5-diols gave rise to chiral lactones with moderate ees under similar aerobic conditions.

Oxidation of alcohols is a fundamental and useful transformation in synthetic organic chemistry. Most of the processes are carried out by using stoichiometric or overstoichiometric oxidants, resulting in the formation of undesirable waste materials.[1] In light of environmental sustainability and atom-economy, catalytic dehydrogenative oxidation of alcohols using clean hydrogen acceptors has been widely investigated to overcome some drawbacks of the conventional methods using hazardous or toxic reagents. After our original works on chiral bifunctional Ru(η^6-arene) complexes bearing chelating chiral amine ligands including Tsdpen (*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) as one of the most efficient catalysts for hydrogen transfer reactions between secondary alcohols and ketones, isoelectronic Cp*Rh and Cp*Ir (Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl) variants have been also realized.[2,3] During the interconversion between the amido and hydrido(amine) complexes based on the metal/ligand bifunctionality as shown in Scheme 1, both chiral catalysts efficiently promote asymmetric transfer hydrogenation of aromatic ketones using 2-propanol as a hydrogen donor as well as the reverse asymmetric oxidation of secondary alcohols using acetone as a hydrogen acceptor.[4]

As an extensive study of this redox transformation, Rauchfuss and we independently disclosed the reaction of hydrido(amine) Ir complexes with molecular oxygen to give amido complexes and water.[5] We also reported that the chiral Cp*Ir complexes bearing chiral diamines efficiently catalyze enantioselective oxidation of *rac*-secondary benzylic alcohols using molecular oxygen as an oxidant. Thanks to the excellent enantiomer discrimination ability of the chiral catalysts toward the racemic substrates, the unreacted chiral alcohols were enantiomerically enriched (with a maximum k_f/k_s ratio of >100) even at the ambient temperature under atmospheric pressure of air without any additives; however, theoretical yield of optically active products can never exceed a limit of 50% while asymmetric hydrogenation of the corresponding ketones can give optically active alcohols in 100% yield.

On the other hand, asymmetric desymmetrization of *meso*- or prochiral molecules offers potentially useful access to chiral compounds theoretically in 100% yield.[6] Among them, various enzymatic and chemical catalysts have been explored for the desymmetrization of *meso*-diols through enantioselective acylation.[7] Oxidative desymmetrization of *meso*-diols was also attainable in catalytic asymmetric hydrogen transfer reactions using ketones as hydrogen acceptors. Ikariya and Noyori demonstrated



Scheme 1. Interconversion between amido and hydrido-Ir complexes.

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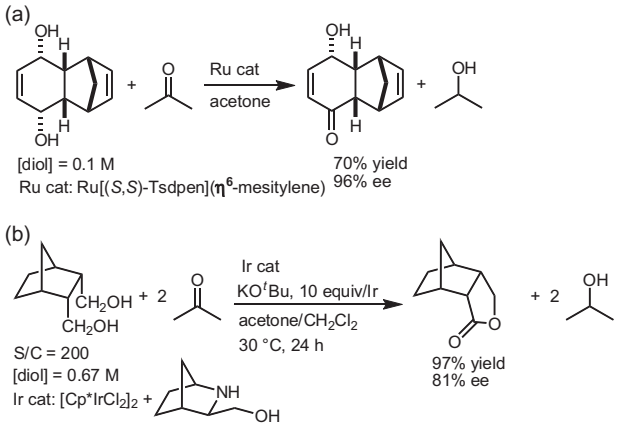
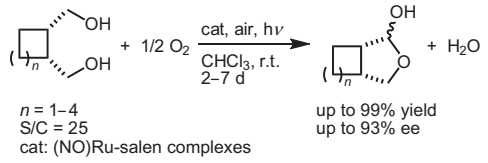
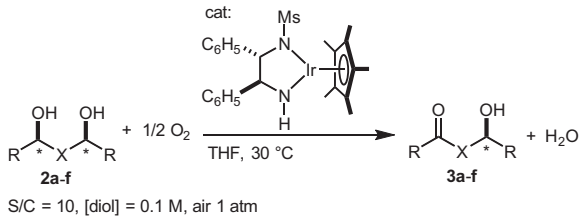


Scheme 2. Oxidative desymmetrization of *meso*-diols with bifunctional catalysts.



Scheme 3. Asymmetric oxidation of primary *meso*-diols.



Scheme 4. Asymmetric oxidation of secondary *meso*-diols.

that Ru[(*S*,*S*)-Tsdpen](η^6-mesitylene) promotes dehydrogenative oxidation via desymmetrization of a secondary *meso*-diol to give the corresponding hydroxy-enone in 70% yield and 96% ee as shown in Scheme 2(a).[4a] Suzuki reported the related Ir-catalyzed desymmetrization in which cyclic or acyclic secondary diols[8] were oxidized to hydroxyl ketones in good yields with high chemo- and enantioselectivities of up to >99% ee, whereas primary *meso*-1,2-cyclohexanedimethanol analogs afforded chiral lactones with up to 81% ee (Scheme 2b).[9]

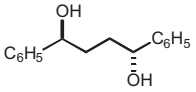
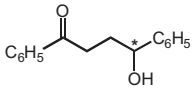
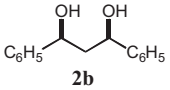
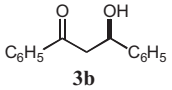
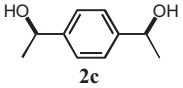
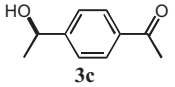
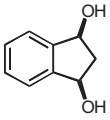
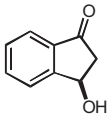
Asymmetric aerobic oxidation via desymmetrization of *meso*-diols is also possible with a chiral Pd-sparteine catalyst, which has been developed independently by Sigman and Stoltz; however, the scope of the reaction was limited to linear secondary 1,3- or 1,7-diols and 1,2,3,4-tetrahydronaphthalene-1,4-diol.[10] Katsuki et al. have developed Ru(salen) catalysts for the aerobic oxidation of *meso*-diols to afford the corresponding hydroxyl ketones or lactols as shown in Scheme 3.[11] Herein, we disclose asymmetric desymmetrization of secondary and primary symmetrical diols via aerobic oxidation catalyzed by the well-defined bifunctional Ir catalysts, Cp*Ir[(*S*,*S*)-Msdpen] (**1a**, Msdpen = *N*-(methanesulfonyl)-1,2-diphenylethylenediamine) and Cp*Ir[(*S*,*S*)-Tsdpen] (**1b**).

Inspired by our earlier success with asymmetric oxidation of 1-phenylethanol derivatives,[5] we initially examined the aerobic asymmetric oxidation of acyclic *meso*-diols having secondary benzylic alcohol groups as represented in Scheme 4, and the results are listed in Table 1. The reactions using the amido–Ir complex, (*S*,*S*)-**1a**, with a substrate/catalyst molar ratio (S/C) of 10 were conducted in THF (0.1 M) under air (balloon) at 30 °C, according to the reaction conditions reported in our previous work.[5]

A partial dehydrogenation of *meso*-1,4-diol (**2a**) was accomplished within 48 h to give a hydroxyl ketone in 70% yield with 90% ee (entry 1), and a trace amount of over-oxidation product, diketone was observed. The reaction of 1,3-diol (**2b**) gave an unsatisfactory result, the product yield being 31% even after the 96 h reaction, possibly due to its relatively strong chelating interaction between two hydroxyl groups and the metal center (entry 2). Asymmetric oxidation of *meso*-α,α′-dimethyl-(1,4-benzene)dimethanol (**2c**) proceeded smoothly, affording the desired *R*-product in 62% yield with a high ee of 94% (entry 3).

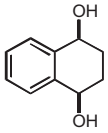
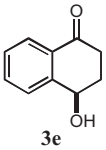
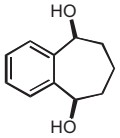
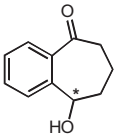
The chiral Ir catalyst exhibited an excellent catalytic performance in the oxidative desymmetrization of cyclic secondary *meso*-diols. The oxidation of *cis*-indan-1,3-diol (**2d**) and 1,2,3,4-tetrahydronaphthalene-1,4-diol (**2e**) gave the corresponding oxidation products, (*R*)-hydroxyl ketones (**3d** and **3e**) with 95% and

Table 1
Catalytic asymmetric aerobic oxidation of secondary *meso*-diols **2**

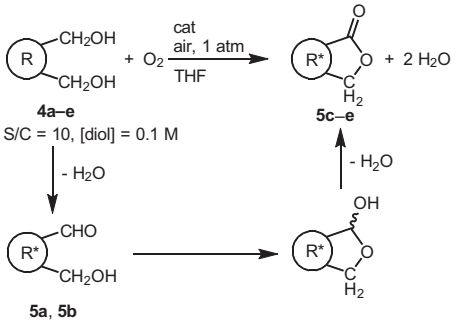
Entry	Substrate	Product	Time (h)	% Conversion[a]	% Yield[a,b]	% ee[c]
1	 **2a**	 **3a**	48	76	70 (1)	90 (+)
2	 **2b**	 **3b**	96	40	31	90 (*R*)
3	 **2c**	 **3c**	48	68	62 (4)	94 (*R*)
4	 **2d**	 **3d**	48	99	99	95 (*R*)

(*continued on next page*)

Table 1 (*continued*)

Entry	Substrate	Product	Time (h)	% Conversion[a]	% Yield[a,b]	% ee[c]
5	 **2e**	 **3e**	48	99	93 (2)	99 (*R*)
6	 **2f**	 **3f**	96	46	40 (1)	85 (+)

[a] Determined by ^{1}H NMR analysis.
[b] Yield of diketones is given in the parenthesis.
[c] Determined by HPLC analysis.

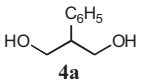
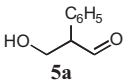
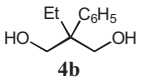
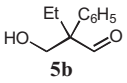
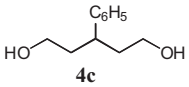
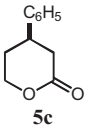
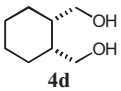
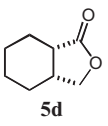
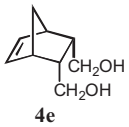
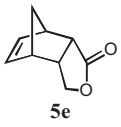


Scheme 5. Asymmetric oxidation of symmetrical primary diols.

99% ees, respectively (entries 4 and 5). As notable applications of the oxidation products, (*R*)-**3e** can be transformed to the antidepressant sertraline, and enantiomerically pure (*S*)-**3e** shows significant anti-tubercular activity (MIC 50 μg/ml).[12,13] The reaction of a seven-membered diol (**2f**) gave a moderate yield (40%; entry 6).[14]

To expand the substrate scope and to improve the practicality of the chiral amido complex, the aerobic oxidation of symmetrical primary diols (**4**) to chiral lactones was also tested as outlined in Scheme 5.[15] In similar to the secondary diols, the outcome of the reaction was influenced by the structure of substrates. When 2-phenyl-1,3-propanediols (**4a** and **4b**) were used as the prochiral substrate, the reactions gave rise to only a trace or small amount formation of hydroxyl aldehydes (**5a** and **5b**) without providing the corresponding lactols or lactones (Table 2 entries 1 and 2). The oxidation of 3-phenyl-1,5-pentanediol (**4c**) with (*S*,*S*)-**1b** gave a 6-membered (*R*)-lactone (**5c**) with only 25% ee in 30% yield (entry 3). The chiral catalyst differentiates the enantiotopic hydroxy groups on the substrate to give δ-hydroxyl aldehyde and the subsequent formation of hemiacetal allows the oxidative lactonization. Because of the facile latter process, the hydroxyl aldehyde

Table 2
Catalytic asymmetric aerobic oxidation of symmetrical primary diols **4**

Entry	Cat.	Substrate	Product	Time (h)	% Conversion[a]	% Yield[a]	% ee[b]
1	**1b**	 **4a**	 **5a**	24	12	0	––
2	**1a**	 **4b**	 **5b**	48	35	8	––
3	**1b**	 **4c**	 **5c**	24	38	30	25 (*R*)
4	**1a**	 **4d**	 **5d**	24	70	64	34 (1*R*,6*S*)
5	**1b**	 **4e**	 **5e**	120	77	72	50 (2*S*,3*R*)

[a] Determined by ^{1}H NMR analysis.
[b] Determined by HPLC analysis.

intermediate was not obtained. In contrast to 6-membered lactone formation, the reaction of primary *meso*-1,4-diols proceeded smoothly to give 5-membered chiral γ-lactones in reasonably good yields. When the oxidation of *cis*-cyclohexane-1,2-dimethanol (**4d**) was conducted under the standard conditions, (1*R*,6*S*)-lactone (**5d**) was obtained in 64% yield with 34% ee (entry 4). While a prolonged reaction time to 120 h was required, the dehydrogenation of *cis-endo*-5-norbornene-2,3-dimethanol (**4e**) by using the catalyst **1b** displayed an improved enantioselectivity of 50% (entry 5). These results suggest that although poor to moderate enantioselectivity in the present aerobic oxidative lactonization, our bifunctional chiral catalyst could potentially discriminate enantiotopic groups on the prochiral substrates after further tuning of chiral molecular catalysts.

In summary, we have demonstrated that the structurally well-defined amidoiridium complexes **1** serve as an efficient catalyst toward asymmetric oxidative desymmetrization of various symmetrical diols with molecular oxygen even under mild and neutral conditions. By using this method, up to >99% ee of hydroxyl ketones and 50% ee of lactones were furnished from the oxidation of secondary and primary diols, respectively. The use of non-toxic and non-hazardous air as the oxidant should offer the unique and promising catalytic method in accordance with the guiding principles of atom economy and environmental benignity. Further investigation of the substrate scope and development of more robust and long-lived catalysts under aerobic atmosphere are underway.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.103.

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