

Chiral Co(III)(salen)-catalysed hydrolytic kinetic resolution of racemic epoxides in ionic liquids

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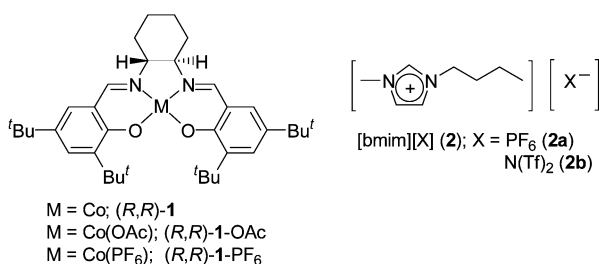
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In the chiral Co(III)(salen)-catalysed HKR of racemic epoxides, in the presence of ionic liquids, Co(II)(salen) complex is oxidised without acetic acid to catalytically active Co(III)(salen) complex during reaction and, moreover, this oxidation state is stabilised against reduction to Co(II) complex which enables the reuse of the recovered catalyst for consecutive reactions without extra reoxidation.

Hydrolytic kinetic resolution (HKR) of racemic epoxides using Jacobsen's chiral (salen)Co(III)(OAc) complex **1**-OAc as a catalyst is one of the most practical approaches towards the preparation of enantiopure terminal epoxides.¹ The chiral catalyst **1**-OAc is readily accessible, and displays high enantioselectivity. However, this catalyst provides relatively low turnover numbers and frequencies. Therefore, it would be highly desirable to develop a recyclable catalyst system to maximise the total turnover numbers. Attempts to anchor Jacobsen's catalyst onto insoluble supports have already been made for facilitation of catalyst separation and catalyst reuse.^{2,3} Although these heterogeneous analogues of **1**-OAc gave almost the same enantioselectivities as compared to those of the homogeneous one, complicated synthetic manipulations for their preparation was required. Moreover, during the reaction, these solid-bound catalysts^{2,3} as well as the homogeneous ones^{1a} are reduced to Co(II) complex **1** which is known to be inactive for HKR^{1a} and thus, they should be re-oxidised to Co(III) complex with acetic acid under air before use in the next run.



For catalyst recycling, a new approach has very recently been adopted in a number of catalytic reactions involving the use of room temperature ionic liquids (IL), in particular, consisting of 1,3-dialkylimidazolium cations and their counter anions.⁴ In these solvents, catalysts having polar or ionic character can be immobilised and thus the ionic solutions containing the catalyst can be easily separated from reagents and products. Moreover, switching from an organic solvent to an ionic liquid often results in improvement of catalytic performances (rate acceleration and selectivity improvement, etc.) due to its highly polar and ordered character.⁵ Here we wish to report another effect of ionic liquids on catalysis. In the chiral Co(III)(salen)-catalysed HKR of racemic epoxides, in the presence of ionic liquids, Co(II)(salen) complex **1** can be oxidised without use of acetic acid to catalytically active Co(III)(salen) complex during reaction which may not be possible in conventional organic

solvents. Moreover, the Co(III) oxidation state is maintained after reaction which enables the reuse of the recovered catalyst for the next runs without extra reoxidation.

To investigate the effect of ionic liquids on catalytic efficiencies, we first carried out the HKR of racemic epichlorohydrin (ECH) using catalytic amounts of (*R,R*)-Co(III)(salen) complex (*R,R*)-**1**-OAc in a mixture (4/1, v/v) of THF and an ionic liquid, [bmim][X] **2** (X = PF₆ (**2a**), NTf₂ (**2b**)), at 20 °C. After completion of the reaction, enantioenriched (*S*)-ECH was collected together with THF by vacuum distillation. From the residue, the produced (*R*)-diol was extracted with water remaining the ionic liquid phase in which Co(salen) complex was dissolved. THF was distilled off by rotary evaporation at below 20 °C affording the enantioenriched (*S*)-ECH, and the aqueous layer was concentrated *in vacuo* giving (*R*)-diol. As shown in Table 1, in the presence of 0.5 mol% of (*R,R*)-**1**-OAc (entries 1 and 4) or even using the reduced amounts (0.1 mol% in entry 2 and 0.025 mol% in entry 3) of (*R,R*)-**1**-OAc, all reactions in the ionic liquids **2** proceeded smoothly to afford the optically pure (*S*)-ECH (>99% ee). In HKR of other epoxides, the yields and enantiomeric excesses were also quite comparable to those^{1a} obtained without ionic liquids (entries 5–7).

More importantly, we found that the oxidation state of Co(salen) complex dissolved in the recovered ionic liquid phase was not +II, but +III. As mentioned above, in the case of using organic solvents as reaction media, Co(III) catalyst **1**-OAc is reduced to Co(II)-complex **1** during the HKR reactions.^{1a} The UV spectrum of the recovered ionic liquid phase containing

Table 1 Hydrolytic kinetic resolution of terminal epoxides using Co(III)(salen) catalyst (*R,R*)-**1**-OAc in the presence of an IL **2**.^a

Entry	R	IL	Catalyst (mol%)	Conversion (%) ^{b,c}	%ee of epoxide ^d	%ee of diol ^d
1	CH ₂ Cl	2a	0.5	52	>99	91.9
2	CH ₂ Cl	2a	0.1	52	>99	91.2
3 ^e	CH ₂ Cl	2a	0.025	55	>99	79.3
4	CH ₂ Cl	2b	0.5	53	>99	89.0
5	Me	2a	0.5	51	>99	94.1
6	<i>n</i> -Bu	2a	0.5	54	>99	84.9
7 ^f	Ph	2a	1.0	53	97.9	86.3

^a Unless indicated otherwise, the reactions were carried out on a 10 mmol scale of epoxide in a mixture of 2 mL of THF and 0.5 mL of **2** at 20 °C for 24 h. The molar ratio of epoxide:H₂O:(*R,R*)-**1**-OAc was 1:0.7:0.005.

^b Based on total racemic mixture. ^c Estimated based on the ee of recovered epoxide and diol product; see ref. 2. ^d Determined by chiral HPLC or GC.

^e The reactions were carried out on 100 mmol scale of ECH in the presence of 4 mL of THF and 0.05 mol% of **2a** at 20 °C for 60 h. The molar ratio of epoxide:H₂O:(*R,R*)-**1**-OAc was 1:2.0:0.00025. ^f The reaction was carried out for 48 h.

Co(salen) complex (from the reaction of entry 1 in Table 1) is the same as that of Co(III)(salen)(PF₆) complex **1**·PF₆.⁷ On the other hand, the UV spectrum of Co complex recovered after HKR carried out only in THF solvent is similar to that of Co(II) complex **1** (Fig. 1). In the XPS (X-ray Photoelectron Spectroscopy) spectrum of both the recovered Co(salen) complex and Co(III)(salen)(PF₆) complex **1**·PF₆, the Co 2p_{3/2} line appeared at ~780 eV, whereas XPS line of Co(II)(salen) complex **1** appeared at ~777 eV (Fig. 2). These results clearly indicate that the recovered cobalt complex has +III oxidation state.

Moreover, we also found that in the presence of the ionic liquid **2**, catalytically inactive Co(II)(salen) complex **1** instead of Jacobsen's chiral Co(III)(salen)·OAc catalyst **1**·OAc can be directly used as a catalyst precursor. The Co(II) complex **1** is oxidised without use of acetic acid to catalytically active Co(III) complex during HKR reactions. As shown in Table 2, all HKRs of racemic ECH using catalytic amounts of (*R,R*)-**1** proceeded smoothly, even using 0.025 mol% of (*R,R*)-**1**. It should be here noted again that Co(II) complex **1** can not catalyse HKR of racemic epoxide effectively in organic solvents.^{4b} Moreover, after work-up, the recovered ionic liquid phase containing Co(III)(salen) complex (recovered from the reaction of entry 1 in Table 2) was reused for successive reactions without an extra reoxidation step. This catalytic system involving the ionic liquid [bmim][NTf₂] **2b** was reused up to ten times without any loss of

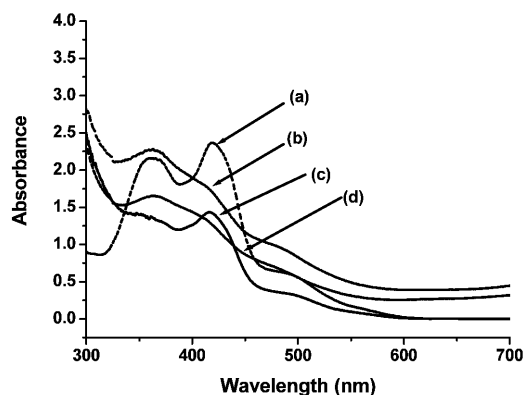


Fig. 1 UV Spectra of various Co(salen) complexes: (a) the Co(II) complex **1**, (b) the Co(III)(PF₆) complex **1**·PF₆, (c) the recovered Co(salen) complex after HKR of epichlorohydrin in THF, (d) the ionic liquid phase containing Co(salen) complex recovered from the reaction of entry 1 in Table 1.

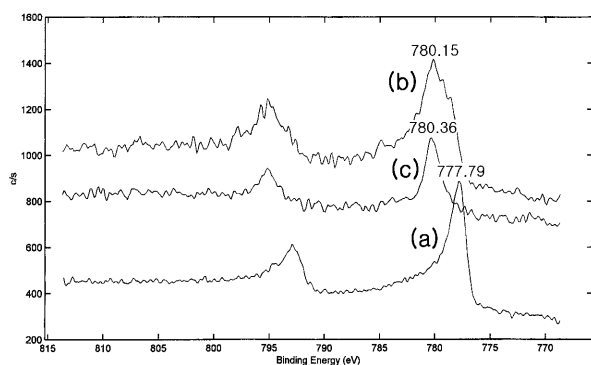


Fig. 2 XPS of various Co(salen) complexes: (a) Co(II)(salen) complex **1**, (b) Co(III)(salen) complex **1**·PF₆, (c) the recovered Co(salen) complex after HKR of epichlorohydrin in THF-[bmim][PF₆] **2a**.

Table 2 Hydrolytic kinetic resolution of ECH using Co(II)(salen) complex (*R,R*)-**1** and IL **2**.^a

Entry	IL ^b	Catalyst (mol%)	Time (h)	Conversion (%) ^{c,d}	% ee of epoxide ^e	% ee of diol ^e
1	2b	0.5	21	53	>99	86.0
2 ^f	2b	0.1	26	52	>99	91.2
3	2b	0.05	48	52	>99	90.3
4 ^f	2a	0.025	70	53	>99	88.0
5 ^g	2b	0.025	70	53	>99	87.1

^a The reactions were carried out on 100 mmol scale of ECH in the presence of 2.7 equiv. of H₂O in 10 mL of THF at 20 °C. ^b The molar ratio of IL **2** and catalyst (*R,R*)-**1** was 2:1. ^c Based on total racemic mixture. ^d Estimated based on the ee of recovered epoxide and diol product; see ref. 2.

^e Determined by chiral HPLC or GC. ^f The reactions were carried out on 1 mol scale of epichlorohydrin in the presence of 1.5 equiv. of H₂O in 10 mL of THF at 20 °C. ^g The reactions were carried out on 100 mmol scale of ECH in the presence of 2.0 equiv. of H₂O in 4 mL of THF at 20 °C.

activity and enantioselectivity (>99% ee). Very interestingly, the catalytic activity of the recovered ionic liquid phase increased upon reuse (reaction time; 22 h for the first run, 22 h for the second run, 15 h for the third run, 4 h for the fourth run, 3 h for the fifth run, 2 h for the sixth run, 2 h for the seventh run, 2 h for the eighth run, 2 h for the ninth run, 2 h for the tenth run). The reason for the increase in activity upon reuse can be ascribed to increasing concentration of catalytically active Co(III) complex in the reaction mixture. However, at the present time, it is not clear why, in the presence of an ionic liquid, Co(II) complex was oxidised without use of acetic acid to catalytically active Co(III) complex and this oxidation state was maintained. Studies to understand the above mentioned effects of the ionic liquids on Co(salen)-catalysed HKR reactions of racemic epoxides will be carried out.

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Notes and references

- (a) M. Tokunaga, J. F. Larrow, F. Kakiuchi and E. N. Jacobsen, *Science*, 1997, **277**, 936; (b) E. N. Jacobsen, *Acc. Chem. Res.*, 2000, **33**, 421; (c) E. N. Jacobsen and M. H. Wu, in *Comprehensive Asymmetric Catalysis*, eds.; E. N. Jacobsen, A. Pfaltz, H. Yamamoto, Springer, Berlin, 1999, **Vol. 3**, pp. 1309; (d) S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Togunaga, K. B. Hansen, A. E. Gould, M. E. Furrow and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 1307.
- D. A. Annis and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1999, **121**, 4147.
- G.-J. Kim and D.-W. Park, *Catal. Today*, 2000, **63**, 537.
- For recent reviews on ionic liquids: R. Sheldon, *Chem. Commun*, 2001, 2399; P. Wasserscheid and W. Keim, *Angew. Chem. Int. Ed.*, 2000, **39**, 3772; T. Welton, *Chem. Rev.*, 1999, **99**, 2071.
- Recent examples: C. E. Song, W. H. Shim, E. J. Roh and J. H. Choi, *Chem. Commun*, 2000, 1695; C. E. Song and E. J. Roh, *Chem. Commun*, 2000, 837; C. E. Song, W. H. Shim, E. J. Roh, J. H. Choi and S.-g. Lee, *Chem. Commun*, 2001, 1122; C. E. Song, D. Jung, E. J. Roh, S.-g. Lee and D. Y. Chi, *Chem. Commun*, 2002, 3038; D. W. Kim, C. E. Song and D. Y. Chi, *J. Am. Chem. Soc.*, 2002, **124**, 10278.
- 1-*n*-Butyl-3-methylimidazolium cation [bmim] and its counter anions, hexafluorophosphate [PF₆] and bis(trifluoromethanesulfonyl)imide [NTf₂], were used. Ionic liquids used in this study were chloride-free (< 5 ppm) and purchased from C-TRI Co., Ltd. (www.c-tri.com).
- Co(III)(salen)(PF₆) **1**·PF₆ was prepared by reaction of Co(II)(salen) complex **1** with (C₅H₅)₂Fe(PF₆) according to the following Katsuki's procedure: R. Irie, K. Noda, Y. Ito, N. Matsumoto and T. Katsuki, *Tetrahedron: Asymmetry*, 1991, **2**, 481.