Asymmetric Catalysis in Water

Chiral-Mn(Salen)-Complex-Catalyzed Kinetic Resolution of Secondary Alcohols in Water**

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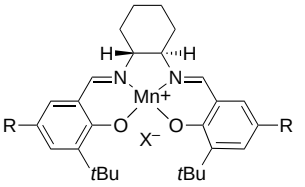
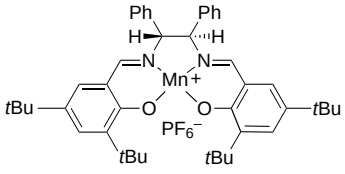
The development of efficient catalytic asymmetric reactions is currently one of the most challenging tasks in synthetic chemistry. Many efforts have been devoted to the creation of chiral metal complexes for use in advanced asymmetric catalysis.[1] Salen ligands are now recognized as efficient auxiliaries and many metallosalen complexes have been found to serve as excellent catalysts for various asymmetric reactions, such as epoxidation, aziridination, cyclopropanation, and Diels–Alder reactions, for kinetic resolution of racemic epoxides, and for asymmetric ring opening of meso epoxides.[2,3] In particular, the pioneering studies of Jacobsen and co-workers and Katsuki and co-workers have led to the development of a variety of chiral Mn(salen) catalysts that epoxidize alkenes with high enantioselectivity.[2d]

Recently, we found that Mn(salen) complexes were effective catalysts for the oxidation of secondary alcohols to ketones in the presence of the cooxidant diacetoxyiodobenzene ($PhI(OAc)_2$).[4] We became interested in extending the scope of this potentially useful reaction to asymmetric catalysis and envisaged applying it to the oxidative kinetic resolution of secondary alcohols, the kinetic resolution of which has previously been accomplished through acylation[5,6] and oxidation.[7] Katsuki and co-workers have reported the use of binol-derived Ru(salen) complexes as catalysts in the photoinduced aerobic oxidation of racemic secondary alcohols. In spite of the high enantioselectivities reported, the reaction times for Katsuki's catalyst under photolytic conditions are generally long.[7a] Asymmetric oxidation of alcohols in the presence of catalytic binol-derived Mn(salen) complexes with PhIO as the cooxidant were also reported by Katsuki and co-workers; however only low yields and moderate enantioselectivities were observed.[7b] Herein we report a convenient, mild, enantioselective oxidation of alcohols catalyzed by chiral Mn(salen) complexes in water, with $PhI(OAc)_2$ as the cooxidant.

Water is the basis and bearer of life in Nature. Numerous biochemical organic reactions (and inorganic reactions) within living systems inevitably occur in aqueous media. On the other hand, most laboratory and industrial organic reactions are carried out in organic solvents. In recent decades, chemists have begun to investigate the possibility of using water as a solvent for organic reactions, with sometimes surprising and unforeseen results.[8] In initial investigations, we studied the oxidative kinetic resolution of α-methylbenzyl alcohol catalyzed by the Mn(salen) complex **1b**, with $PhI(OAc)_2$ as the cooxidant (Table 1). When the reaction was carried out in CH_2Cl_2 only 2% *ee* was attained (Table 1, entry 1). When water was used instead of CH_2Cl_2, 8.9% *ee* was observed (Table 1, entry 2). As the substrate and catalyst were insoluble in water, the phase-transfer catalyst (PTC) tetraethylammonium bromide was then included in the aqueous system, and the product was formed with an unexpected 84.1% *ee* (Table 1, entry 3). Further optimization of the reaction conditions resulted in 51.7% conversion and 85.2% *ee* (Table 1, entry 4). This excellent result led us to believe that water is important for the reaction. The use of water as the solvent is also advantageous in other respects, for example in terms of environmental considerations.



1a: R=*t*Bu, X=Cl; **1b**: R=*t*Bu, X=PF_6
2: R=Me, X=PF_6



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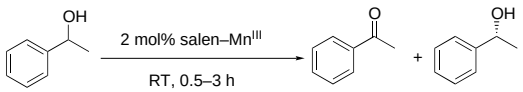
Effective stereochemical communication between substrate and catalyst is essential for attaining high enantioselectivities in reactions involving an asymmetric catalyst.[9] Thus, we examined a selection of catalysts for the oxidative kinetic resolution of alcohols. When the *tert*-butyl groups at the 5,5′-positions in complex **1a** were replaced by methyl

Table 1: Initial experiments.[a]



Entry	Cat.	Additive	*t* [h]	Conv. [%][b]	*ee* [%][c]	k_{rel}
1[d]	**1b**	–	3	55.5	2.0	<1.1
2	**1b**	–	2	25.0	8.9	1.9
3	**1b**	$N(C_2H_5)_4Br$	2	63.4	84.1	7.2
4	**1b**	$N(C_2H_5)_4Br$	1	51.7	85.2	23.7
5	**1b**	$N(C_2H_5)_4Br$	0.5	48.1	71.9	16.8
6	**1a**	$N(C_2H_5)_4Br$	1	51.5	80.1	17.3
7	**2**	$N(C_2H_5)_4Br$	1	42.5	19.1	<1.1
8	**3**	$N(C_2H_5)_4Br$	0.5	62.5	88.1	8.9

[a] Reaction was carried out at room temperature (20°C) with catalyst (2 mol%), $N(C_2H_5)_4Br$ (8 mol%), α-methylbenzyl alcohol (0.25 mmol), $PhI(OAc)_2$ (0.175 mmol), and H_2O (1 mL). [b] Conversion determined by GC using an internal standard. [c] Determined by GC on a CP-Chirasil-Dex CB capillary column. [d] Reaction was carried out in CH_2Cl_2.

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substituents (complex **2**), low enantioselectivity in the kinetic resolution of α-methylbenzyl alcohol was observed (Table 1, entry 7). Hence, it appeared that the steric hindrance at the 5,5′-positions was favorable for the enantioselectivity of the reaction. The Mn(salen) complex **3,** derived from (*R,R*)-diphenylethylenediamine, was more efficient than the Mn(salen) complex **1b**. Jacobsen's catalyst **1a** (a good catalyst for epoxidation reactions) also gave good results (Table 1).

Next, the substrate scope of the oxidative kinetic resolution was evaluated (Table 2). It can be seen that α-methylbenzyl alcohols with a substituent at the 4-position are generally good substrates for oxidative kinetic resolution with high k_{rel} values.[10] However, when the R^1 group of the substrate was changed from methyl to ethyl, or to even bulkier substituents, the enantioselectivity of the reaction decreased sharply (Table 2, entries 12 and 13). In the case of α-methylbenzyl alcohol (Table 2, entries 1 and 2) and 1-phenyl-2-propanol (Table 2, entries 10 and 11), the Mn(salen) complex **3** was more effective in distinguishing between the enantiomers of the substrate than complex **1b**. However, for the other substrates with substituents on the aromatic ring, use of the complex **1b** gave rise to higher enantioselectivities. The results showed that electronic cooperation between the catalyst and the substrate had a strong influence on the enantioselectivity of the reaction.

In conclusion, a mild, convenient method for the enantioselective kinetic resolution of secondary alcohols in the presence of Mn(salen) catalysts has been discovered. Water can be used successfully as a benign solvent in this reaction system. The use of water makes the reaction more significant in terms of potential industrial applications. Further studies into the mechanism and other potential catalysts are now underway in our laboratory.

Experimental Section

General procedure for the Mn(salen)-complex-catalyzed kinetic resolution of secondary alcohols in water.

A mixture of the substrate (0.25 mmol), catalyst (0.005 mmol), tetraethylammonium bromide (0.02 mmol) and water (1 mL) was stirred in a 5-mL tube for a few minutes at room temperature. The cooxidant, $PhI(OAc)_2$ (0.175 mmol), was then added and the reaction system was stirred for a further 0.5–1 h. The products were extracted with diethyl ether when the reaction was complete. The conversion and *ee* values were determined by GC.

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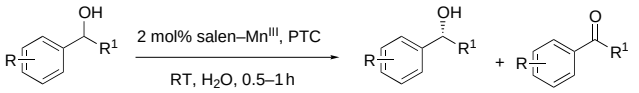
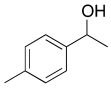
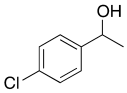
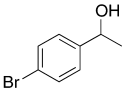
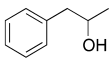
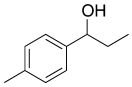
Table 2: Asymmetric kinetic resolution of secondary alcohols.[a]



Entry	Substrate	Cat.	*t* [h]	Conv. [%][b]	*ee* [%][c]	k_{rel}
1		**1b**	1	51.7	85.2	23.7
2		**3**	0.5	62.5	88.1	8.9
3		**1b**	1	67.7	90.0	7.0
4		**3**	0.5	61.9	55.4	3.4
5		**1b**	1	61.1	97.8	18.2
6		**3**	0.5	56.7	90.5	16.6
7		**1b**	1	12.3	3.0	1.6
8		**1b**	1	65.9	96.8	11.3
9		**3**	0.5	60.4	79.5	7.4
10		**1b**	1	56.3	73.0	7.6
11		**3**	0.5	60.0	80.1	7.7
12		**1b**	1	64.8	5.4	1.1
13		**1b**	1	67.7	23.9	1.5

[a] Reaction carried out at room temperature (20 °C) with catalyst (2 mol%), $N(C_2H_5)_4Br$ (8 mol%), substrate (0.25 mmol), $PhI(OAc)_2$ (0.175 mmol), and H_2O (1 mL). [b] Conversion determined by GC using an internal standard. [c] Determined by GC on a CP-Chirasil-Dex CB capillary column.

[1] R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1993**.

[2] For a review, see: a) T. Katsuki, *Coord. Chem. Rev.* **1995**, *140*, 189; b) T. Katsuki, *J. Mol. Catal. A* **1996**, *113*, 87; c) Y. N. Ito, T. Katsuki, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 603; d) E. N. Jacobsen, M. H. Hu in *Comprehensive Asymmetric Catalysis, Vol. 2* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, p. 649; e) T. Katsuki in *Comprehensive Asymmetric Catalysis, Vol. 2* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, p. 791; f) J. M. Keith, J. F. Larrow, E. N. Jacobsen, *Adv. Synth. Catal.* **2001**, *343*, 5.

[3] a) M. Tokunaga, J. F. Larrow, F. Kakiuchi, E. N. Jacobsen, *Science* **1997**, *277*, 936; b) D. A. Annis, E. N. Jacobsen, *J. Am. Chem. Soc.* **1999**, *121*, 4147; c) L. E. Martinez, J. L. Leighton, D. H. Carsten, E. N. Jacobsen, *J. Am. Chem. Soc.* **1995**, *117*, 5897; d) S. E. Schaus, J. F. Larrow, E. N. Jacobsen, *J. Org. Chem.* **1997**, *62*, 4197; e) J. F. Larrow, E. N. Jacobsen, *J. Am. Chem. Soc.* **1996**, *118*, 7420; f) E. N. Jacobsen, F. Kakiuchi, R. G. Konsler, J. F. Larrow, M. Tokunaga, *Tetrahedron Lett.* **1997**, *38*, 773; g) M. Wu, E. N. Jacobsen, *J. Org. Chem.* **1998**, *63*, 5252; h) J. A. Miller, W. Jin, S. T. Nguyen, *Angew. Chem.* **2002**, *114*, 3077; *Angew. Chem. Int. Ed.* **2002**, *41*, 2953.

[4] W. Sun, H. W. Wang, C. G. Xia, P. Q. Zhao, unpublished results.

[5] Catalytic acylation: a) E. Vedejs, J. A. MacKay, *Org. Lett.* **2001**, *3*, 535; b) E. Vedejs, O. Daugulis, *J. Am. Chem. Soc.* **1999**, *121*, 5813; c) E. Vedejs, O. Daugulis, S. T. Diver, *J. Org. Chem.* **1996**, *61*, 430; d) S. J. Miller, G. T. Copeland, N. Papaionnou, T. E. Horstmann, E. M. Ruel, *J. Am. Chem. Soc.* **1998**, *120*, 1629; e) J. C. Ruble, H. A. Latham, G. C. Fu, *J. Am. Chem. Soc.* **1997**, *119*, 1492; f) J. C. Ruble, J. Tweddell, G. C. Fu, *J. Org. Chem.* **1998**, *63*, 2794; g) C. E. Garrett, M. M.-C. Lo, G. C. Fu, *J. Am. Chem. Soc.* **1998**, *120*, 7479; h) B. Tao, J. C. Ruble, D. A. Hoic, G. C. Fu, *J. Am. Chem. Soc.* **1999**, *121*, 5091; i) T. Kawabata, M. Nagato, K. Takasu, K. Fuji, *J. Am. Chem. Soc.* **1997**, *119*, 3169; j) T. Oriyama, Y. Hori, K. Imai, R. Sasaki, *Tetrahedron Lett.* **1996**, *37*, 8543; k) T. Sano, K. Imai, K. Ohashi, T. Oriyama, *Chem. Lett.* **1999**, 265.

[6] Enzymatic acylation: a) J. H. Choi, Y. H. Kim, S. H. Nam, S. T. Shin, M.-J. Kim, J. Park, *Angew. Chem.* **2002**, *114*, 2479; *Angew.*

Chem. Int. Ed. **2002**, *41*, 2373; b) A. L. E. Larsson, B. A. Persson, J.-E. Bäckvall, *Angew. Chem.* **1997**, *109*, 1256; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1211; c) B. A. Persson, A. L. E. Larsson, M. L. Ray, J.-E. Bäckvall, *J. Am. Chem. Soc.* **1999**, *121*, 1645; d) B. A. Persson, F. F. Huerta, J.-E. Bäckvall, *J. Org. Chem.* **1999**, *64*, 5237; e) F. F. Huerta, J.-E. Bäckvall, *Org. Lett.* **2001**, *3*, 1209; f) P. C. D. Jesus, M. C. Rezende, M. D. G. Nascimento, *Tetrahedron: Asymmetry* **1995**, *6*, 63.

[7] For the oxidative kinetic resolution of secondary alcohols, see: a) K. Masutani, T. Uchida, R. Irie, T. Katsuki, *Tetrahedron Lett.* **2000**, *41*, 5119; b) T. Hamada, R. Irie, J. Mihara, K. Hamachi, T. Katsuki, *Tetrahedron* **1998**, *54*, 10017; c) I. Nishibayashi, I. Takei, S. Uemura, M. Hidai, *Organometallics* **1999**, *18*, 2291; d) S. Hashiguchi, A. Fujii, K. J. Haack, K. Matsumura, T. Ikariya, R. Noyori, *Angew. Chem.* **1997**, *109*, 300; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 288; e) E. M. Ferreira, B. M. Stoltz, *J. Am. Chem. Soc.* **2001**, *123*, 7725; f) D. R. Jensen, J. S. Pugsley, M. S. Sigman, *J. Am. Chem. Soc.* **2001**, *123*, 7475; g) J. A. Mueller, D. R. Jensen, M. S. Sigman, *J. Am. Chem. Soc.* **2002**, *124*, 8202.

[8] For a recent review, see: a) U. M. Lindström, *Chem. Rev.* **2002**, *102*, 2751; b) C. J. Li in *Green Chemistry: Frontiers in Benign Chemical Syntheses and Processes*, (Eds.: P. T. Anastas, T. C. Williamson), Oxford, New York, **1998**, chap. 14, p. 234.

[9] M. Palucki, N. S. Finney, P. J. Pospisil, M. L. Güler, T. Ishida, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 948.

[10] $k_{rel} = \ln[(1-C)(1-ee)]/\ln[(1-C)(1+ee)]$, where C is the conversion and ee is the enantiomeric excess; for an excellent discussion of kinetic resolution, see: H. B. Kagan, J. C. Fiaud, Kinetic Resolution, *Top. Stereochem.* **1988**, *18*, 249.

  0044-8249/03/11509-1074 $ 20.00+.50/0