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OXIDATIVE DESYMMETRIZATION OF *MESO*-CYCLIC ETHERS (2): RECOGNITION OF THE CORE STRUCTURE OF SUBSTRATES OF THE Mn(SALEN) CATALYST

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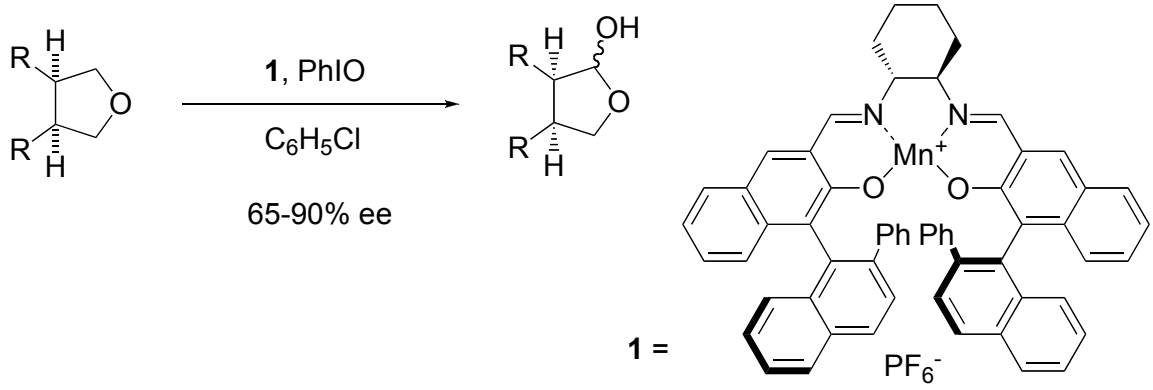
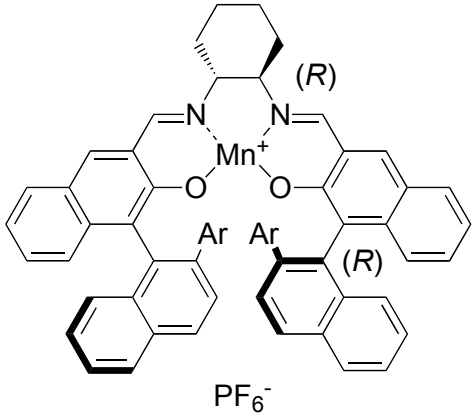
Abstract – Mn(salen) complexes bearing a binaphthyl chiral unit serve as catalysts for oxidative desymmetrization of *meso*-cyclic ethers. This study revealed that chiral recognition by the complex is strongly influenced by the core structure of substrates and this recognition is adjusted by an appropriate modification of the binaphthyl unit.

C-H bond oxidation is a straightforward method for preparing alcohols[1] and much effort has been directed to asymmetric catalytic C-H hydroxylation;[1b,c] however, highly enantioselective oxidation has been largely limited to the oxidation of benzylic and allylic C-H bonds.[2] We and others reported that chiral Mn(salen) complexes served as catalysts for asymmetric benzylic C-H oxidation.[2d,2l,2m,2n,2s,2t] We also found that Mn(salen) complex **1** catalyzed highly enantiotopos-selective α-hydroxylation of *meso*-tetrahydrofuran[3] (Scheme 1) and *meso*-pyrrolidine derivatives.[4]



Scheme 1. Desymmetrization of *meso*-tetrahydrofurans

On the other hand, we recently found that a Zr(salen) complex bearing the same salen ligand as complex **1** catalyzed highly enantiospecific Baeyer-Villiger (B-V) oxidation of racemic bicyclic[n.2.0] ketones (regiodivergent parallel kinetic resolution);[5] however, this B-V oxidation showed substrate specificity that is reminiscent of the lock and key model in biological reactions, suggesting that the Zr(salen) complex exerted strict molecular recognition. Substrate specificity seemed to be strongly affected by the core structure of the substrates. Thus, we expected that complex **1** could also recognize a core structure. If this is the case, enantioselectivity of the hydroxylation of a series of *meso*-cyclic ethers of the common core structure should be improved by the appropriate modification of complex **1**. Based on the structural studies of metallosalen complexes,[6] we revealed that the binaphthyl unit of the salen ligand plays a principal role in its molecular recognition. An important feature of metallosalen complexes is the ease of their synthesis in a modular fashion and various aryl substituents can be introduced via a cross-coupling reaction into the binaphthyl chiral unit, in place of the phenyl group. In order to explore the above possibility, we synthesized complexes (**2**-**9**) and examined the desymmetrization of two types of *meso*-cyclic ethers, 8-oxabicyclo[4.3.0]nonanes **10** and 3-oxabicyclo[3.3.0]octanes **12**.



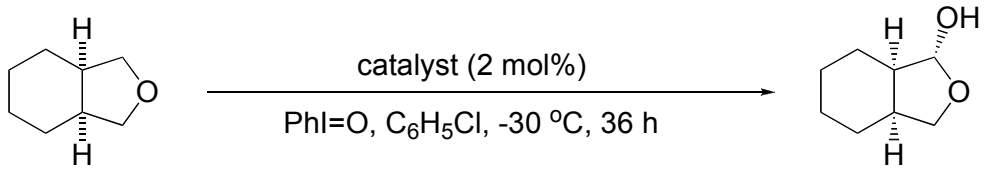
2 : Ar = 3,5-F_2-4-MeC_6H_2 **3** : Ar = 3,5-Cl_2-4-$TMSC_6H_2$

4 : Ar = 3,5-F_2-C_6H_3 **5** : Ar = 3,5-$Cl_2C_6H_3$

6 : Ar = 3,5-$(CF_3)_2$-C_6H_3 **7** : Ar = 3,5-$(MeO)_2$-C_6H_3

8 : Ar = 4-$TMSC_6H_4$ **9** : Ar = 3,5-F_2-4-$TMSC_6H_2$

We first examined desymmetrization of *meso*-8-oxabicyclo[4.3.0]nonane **10a** in chlorobenzene at -30 °C by using iodosylbenzene as the oxidant. Although we could not find any clear trend in the electronic and steric effects of the aryl substituents on enantioselectivity, complexes (**2**, **4**, and **9**) with a fluoro-substituent at the meta-carbons exhibited better enantioselectivity (93-94% ee) than complex **1**, though the reaction with **2** was relatively slow (entries 2, 4 and 9). To our knowledge, this is the highest enantioselectivity observed in desymmetrization via C-H hydroxylation.



10a **11a**

Table 1. Desymmetrization of **10a** with Mn(salen) complexes as catalysts

Entry	Catalyst	Yield/%[a]	Ee/%[b]	Confign[c]
1[d]	**1**	61	90	(1*R*,6*S*)
2	**2**	47	93	(1*R*,6*S*)
3	**3**	54	78	(1*R*,6*S*)
4	**4**	62	93	(1*R*,6*S*)
5	**5**	46	78	(1*R*,6*S*)
6	**6**	47	72	(1*R*,6*S*)
7	**7**	53	81	(1*R*,6*S*)
8	**8**	71	82	(1*R*,6*S*)
9	**9**	75	94	(1*R*,6*S*)

a) Isolated yield.

b) Determined by GLC analysis using optically active column (SUPELCO-BETA-DEX-225) after it was converted into the corresponding lactone by its treatment with pyridinium dichromate in CH_2Cl_2.

c) Absolute configuration of lactol **11a** was determined to be 1*R*,6*S* by the comparison of the specific rotation of the lactone with the reported one (Ref. 7).

d) Taken from reference 3b.

Thus, we examined desymmetrization of several other *meso*-8-oxabicyclo[4.3.0]nonane derivatives (**10b**-**10e**) with complexes **1**, **4** and **9** as the catalyst under the same conditions (Table 2). Of the complexes, **4** induced higher enantioselectivity in all the reactions than **1** and gave better yields, excepting the oxidation of *meso*-8-oxabicyclo[4.3.0]non-3-ene **10e**, which had a slow rate (entry 4). This suggests

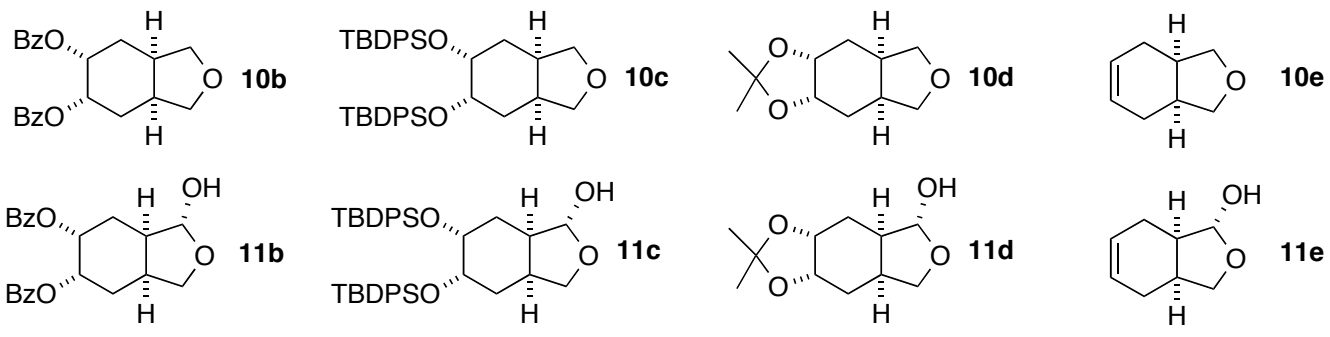


Table 2. Desymmetrization of *meso*-8-oxabicyclo[4.3.0]nonane derivatives (**10b**-**10e**) with **1**, **4** or **9** as the catalyst

Entry	Substrate	Product	Catalyst	Yield/%[a]	Ee/%
1	**10b**	**11b**[b]	**1**	58	87[c]
2	**10b**	**11b**[b]	**4**	66	90[c]
3	**10b**	**11b**[b]	**9**	35	86[c]
4	**10c**	**11c**[d]	**1**	37	56[e]
5	**10c**	**11c**[d]	**4**	56	86[e]
6	**10c**	**11c**[d]	**9**	21	76[e]
7	**10d**	**11d**[f]	**1**	55	65[c]
8	**10d**	**11d**[f]	**4**	66	69[c]
9	**10d**	**11d**[f]	**9**	33	43[c]
10	**10e**	**11e**[g]	**1**	19	75[h]
11	**10e**	**11e**[g]	**4**	17	86[h]
12	**10e**	**11e**[g]	**9**	21	81[h]

a) Isolated yield.

b) *Exo*-*endo* ratio was determined to be 76 : 24 by ^{1}H-NMR spectroscopy (400 MHz).

c) Determined by HPLC using optically active column (DAICEL CHIRALCEL OD-H, hexane/2-propanol = 90:10) after benzylacetalization.

d) *Exo*-*endo* ratio was determined to be 69 : 21 by ^{1}H-NMR spectroscopy (400 MHz).

e) Determined by HPLC using optically active column (DAICEL CHIRALCEL OD-H, hexane/2-propanol = 99.9:0.1) after 3,5-dinitrobenzoylation.

f) *Exo*-*endo* ratio was determined to be 75 : 25 by ^{1}H-NMR spectroscopy (400 MHz).

g) Product is a single isomer.

h) Determined by GLC analysis using optically active column (SUPELCO-BETA-DEX-225) after it was converted into the corresponding lactone by its treatment with pyridinium dichromate in CH_2Cl_2.

that complex **4** recognizes the 8-oxabicyclo[4.3.0]nonane core system better than **1**. The products **11b**-**11e** were equilibrium mixtures of two diastereomers at the anomeric carbon. Although the configuration of the anomeric carbon was not determined, it was considered that the major products have an *exo*-configuration at the carbon for steric reason.

We next examined desymmetrization of *meso*-3-oxabicyclo[3.3.0]octane derivatives (**12a** and **12b**) with complexes **1**, **4** and **9** as catalysts (Table 3). In contrast to the above results, complex **1** was a superior catalyst to complexes **4** and **9** for the reaction of this class of compounds.[8]

Table 3. Desymmetrization of *meso*-3-oxabicyclo[3.3.0]octane derivatives (**12a** and **12b**) with **1**, **4** or **9** as the catalyst[a]

Entry	Substrate	Product	Catalyst	Yield/%[b]	Ee%
1	**12a**	**13a**[c]	**1**	59	82[d]
2	**12a**	**13a**[c]	**4**	67	75[e]
3	**12a**	**13a**[c]	**9**	61	56[e]
4	**12b**	**13b**[f]	**1**	46	84[d]
5	**12b**	**13b**[f]	**4**	14	67[g]
6	**12b**	**13b**[f]	**9**	13	67[g]

a) Reactions were carried out at -30 °C for 36 h, unless otherwise mentioned

b) Isolated yield.

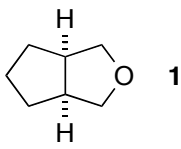
c) Product is a single isomer.

d) Taken from reference 3b. Reaction had been carried out for 65 h.

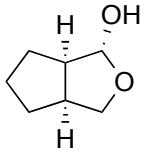
e) Determined by GLC analysis using optically active column (SUPELCO-BETA-DEX-225) after it was converted into the corresponding lactone by its treatment with pyridinium dichromate in CH_2Cl_2..

f) Product is a 90 : 10 mixture of *exo*- and *endo*-isomers. The ratio was determined by ^{1}H-NMR spectroscopy (400 MHz).

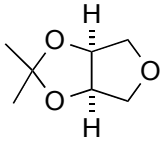
g) Determined by HPLC using optically active column (DAICEL CHIRALCEL OD-H, hexane/2-propanol = 50:50) after 3,5-dinitrobenzoylation.



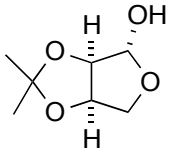
12a



13a



12b



13b

The typical experimental procedure is exemplified by oxidative desymmetrization of *meso*-8-oxabicyclo[4.3.0]nonane **10a** with complex **4** as the catalyst. Complex **4** (3.4 mg, 3.1 μmol) was added to a solution of **10a** (19.7 mg, 0.16 mmol) in chlorobenzene (1 mL) under nitrogen and the whole mixture was stirred for 10 min at -30 °C. Iodosylbenzene (37.8 mg, 0.17 mmol) was added to the mixture and the reaction mixture was stirred at -30 °C for 36 h. The mixture was quenched by adding several drops of dimethyl sulfide and allowed to warm to room temperature. The solution was directly chromatographed on silica gel (pentane/ether=5/2) to give the corresponding lactol (13.8 mg) in 62% yield. The enantiomeric excess of the lactol was determined as described in the footnote to Table 1.

In conclusion, we were able to demonstrate that Mn(salen) complex **4** is a superior catalyst for desymmetrization of *meso*-tetrahydrofurans possessing bicyclic [4.3.0] core structure, while complex **1** is a catalyst of choice for that of *meso*-tetrahydrofurans possessing [3.3.0] core structure. This study

indicated that optimizing a chiral catalyst for each substrate core structure is a promising approach for development of a highly enantioselective reaction, though the substrate scope might be moderate.

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REFERENCES AND NOTES

1. a) S. V. Ley, (ed), Comprehensive Organic Synthesis, Pergamon Press, Oxford New York Seoul Tokyo. 1991, *7*, chap 1 and 2. b) T. Katsuki, In *Comprehensive Asymmetric Catalysis,* ed. by E. N. Jacobsen, A. Pfaltz, H. Yamamoto, Springer (1999), Vol. II, Chap. 21. 791. c) G. B. Shu'pin, In *Transition Metals for Organic Synthesis*, ed by M. Beller, C. Bolm, Wiley-VCH (2nd Edition, 2004), 215.
2. a) J. T. Groves and P. Viski, *J. Am. Chem. Soc*., 1989, **111**, 8537. b) J. T. Groves and P. Viski, *J. Org. Chem.*, 1990, **55**, 3628. c) J. Muzart, *J. Mol. Catal*., 1991, **64***,* 381. d) J. F. Larrow and E. N. Jacobsen, *J. Am. Chem. Soc*., 1994, **116**, 12129. e) A. S. Gokhale, A. B. E. Minidis, and A. Pfaltz, *Tetrahedron Lett*., 1995, **36***,* 1831. f) A. Levina and J. Muzart, *Tetrahedron: Asymmetry,* 1995, **6**, 147. g) M. B. Andrus, A. B. Argade, X. Chen, and M. G. Pamment, *Tetrahedron Lett*., 1995, **36**, 2945. h) K. Kawasaki, S. Tsumura, and T. Katsuki, *Synlett*, 1995, 1245. i) M. T. Rispens, C. Zondervan, and B. L. Feringa, *Tetrahedron: Asymmetry,* 1995, **6**, 661. j) C. Zondervan and B. L. Feringa, *Tetrahedron: Asymmetry,* 1996, **7**, 1895. k) A. DattaGupta and V. K. Singh, *Tetrahedron Lett*., 1996, **37**, 2633. l) K. Hamachi, R. Irie, and T. Katsuki, *Tetrahedron Lett*., 1996, **37**, 4979. m) T. Hamada, J. Mihara, K. Hamachi, R. Irie, and T. Katsuki, *Tetrahedron*., 1998, **54**, 10017. n) N. Komiya, S. Noji, and S.-I. Murahashi, *Tetrahedron Lett*., 1998, **39**, 7921. o) R. Zhang, W.-Y. Yu, T.-S. Lai, and C.-M. Che, *Chem. Commun*., 1999, 1791. p) Y. Kohmura and T. Katsuki, *Tetrahedron Lett*., 2000, **41**, 3941. q) M. B. Andrus and J. C. Lashley, *Tetrahedron*., 2002, **58**, 845. r) M. B. Andrus and Z. Zhou, *J. Am. Chem. Soc*., 2002, **124**, 8806. s) S.-I. Murahashi, S. Noji, and N. Komiya, *Adv. Synth. Catal*., 2004, **346**, 195. t) S.-I. Murahashi, S. Noji, T. Hirabayashi, and N. Komiya, *Tetrahedron*: Asymmetry, 2005, **16**, 3527.
3. a) A. Miyafuji and T. Katsuki, *Synlett*, **1997**, 836. b) A. Miyafuji and T. Katsuki, *Tetrahedron*, 1998, **54**, 10339.
4. a) T. Punniyamurthy, A. Miyafuji, and T. Katsuki, *Tetrahedron Lett.*, 1998, **39,** 8295. b) T. Punniyamurthy and T. Katsuki, *Tetrahedron*, 1999, **55**, 9439.
5. A. Watanabe, T. Uchida, R. Irie, and T. Katsuki, *Proc. Natl. Acad. Sci. USA,* 2004, **101**, 5737.

6. T. Katsuki, *Adv. Synth. Catal.*, 2002, **34**, 131.
7. I. J. Jakovac, G. Ng, K. P. Lok, and J. B. Jones, *J. Chem. Soc., Chem. Commun.,* **1980**, 515.
8. Complexes (**2**, **3**, **5**, **6**, **7**, and **8**) were also inferior to complex **1**.