Kinetic Resolution of 1,2-Dihydronaphthalene Oxide and Related Epoxides via Asymmetric C–H Hydroxylation

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The ability of monooxygenase enzymes to effect highly selective oxidations of organic compounds has prompted widespread research efforts to craft well-defined small-molecule catalysts that display similar reactivity.[1] From a synthetic standpoint, the possibility of mimicking the enantioselectivity of such enzymatic systems is particularly attractive. In this context, considerable progress has been made recently in the design and development of synthetic monooxygenase mimics that catalyze enantioselective epoxidation of unsaturated hydrocarbons.[2] In contrast, the enantioselective oxidation of saturated C–H bonds, another monooxygenase-induced reaction pathway with considerable synthetic potential, has proven substantially more difficult to accomplish with synthetic catalysts. In fact, with the exception of the seminal work by Groves and Viski using chiral porphyrin-based catalysts,[3] there are no reported examples of asymmetric catalytic alkane hydroxylation. Since chiral (salen)Mn-based complexes have been demonstrated to be the most effective catalysts discovered thus far for asymmetric olefin epoxidation,[2,4] the possibility arises that intermolecular C–H hydroxylation may be accomplished with similar catalysts. We report here our initial findings in this area, with the observation that chiral (salen)Mn complexes do indeed catalyze asymmetric hydroxylation of chiral epoxides bearing benzylic C–H bonds.[5]

During the course of experiments on the asymmetric epoxidation of 1,2-dihydronaphthalene with catalyst **2**, it was observed that the enantiomeric excess of the product epoxide increased with time at the expense of product yield (Figure 1). This behavior was suggestive of a secondary kinetic resolution process;[6] indeed, when racemic epoxide was subjected to reaction with NaOCl in the presence of **2**, kinetic resolution occurred in such a manner that the slower reacting enantiomer was also the major enantiomer produced by epoxidation of 1,2-dihydronaphthalene. The major primary resolution product was isolated and identified as the *syn*-epoxy alcohol **4** (Scheme 1).[7]

The generality of the kinetic resolution phenomenon was addressed by studying the reactivity of a series of benzocyclic epoxides with varying ring size and substituents on the epoxide substrate. All epoxides examined were found to undergo kinetic resolution, although the degree and even absolute enantioselectivity were substrate-dependent (Table 1). The efficient kinetic resolution of **5** ($k_{rel} = 28$) indicated that high asymmetric induction is possible in C–H hydroxylation reactions catalyzed by complexes such as **2**.

The study of the hydroxylation of the diastereomeric epoxides **9a** and **9b** served to shed light on the basis for stereoselection in these reactions. The racemic syn isomer **9a** was unreactive

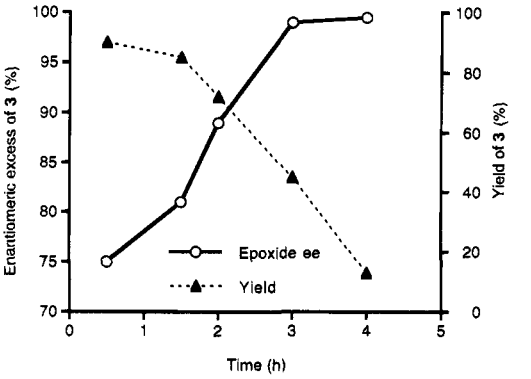
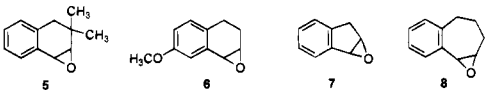


Figure 1. Epoxidation of 1,2-dihydronaphthalene with NaOCl catalyzed by **2**, showing increasing enantiomeric excess of the epoxide product with time. Yields were determined by GC analysis using an internal standard.

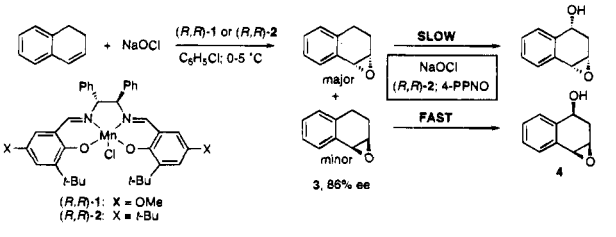
Table 1. (salen)Mn-Catalyzed Kinetic Resolution of Benzocyclic Epoxides



epoxide	epoxidation ee (%)[a]	kinetic resolution, k_{rel}[b]	configuration of unreacted epoxide
3	86 (1*R*,2*S*)	4.8	1*R*,2*S*
5	92 (1*R*,2*S*)	28	1*R*,2*S*
6	89 (1*R*,2*S*)	3.0	1*R*,2*S*
7	87 (1*R*,2*S*)	3.5	1*S*,2*R*
8	92 (1*R*,2*S*)	2.6	1*S*,2*R*

[a] Epoxidation with catalyst (*R*,*R*)-**1**. Enantiomeric excess was determined by capillary GLC analysis using a chiral Cyclodex B column (J.T. Baker), except for **7**, which was analyzed by HPLC using a Chiracel OB column (Daicel). In all cases, epoxide ee values were invariant until olefin consumption was complete. The configuration is given for each in parentheses. [b] Kinetic resolutions were performed on racemic epoxides using (*R*,*R*)-**2**. The values for k_{rel} were calculated according to the equation $k_{rel} = \ln[(1 - c)(1 - ee)]/\ln[(1 - c)(1 + ee)]$, where c is conversion and ee is the enantiomeric excess of the remaining epoxide (ref 6a).

Scheme 1



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(7) Compound **4** is an unstable colorless liquid that darkened upon standing in neat form even when stored at −20 °C: ^{1}H-NMR δ 7.53–7.33 (m, 4H), 4.65 (dt, J = 11.7, 2.0 Hz, 1H), 4.08 (d, J = 4.1 Hz, 1H), 3.94 (m, 1H), 2.94 (d, J = 11.7 Hz, 1H), 2.76 (dt, J = 15.6, 2.3 Hz, 1H), 1.97 (dd, J = 15.6, 4.1 Hz, 1H); ^{13}C-NMR δ 138.2, 132.3, 129.8, 129.7, 129.4, 128.4, 68.1, 55.6, 53.9, 29.8; IR (NaCl, cm^{-1}) 3508 (br); GC/MS (EI) *m/z* 162 (calcd for M$^+$ 162).

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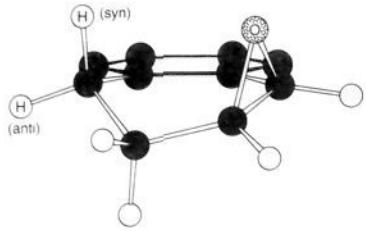
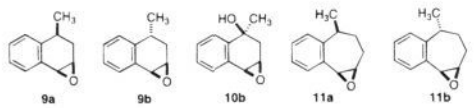


Figure 2. Calculated ground state structure (6-311G** basis set) of dihydronaphthalene oxide (**3**) illustrating the pseudoaxial orientation of H_{syn} and the pseudoequatorial relationship of H_{anti} benzylic hydrogens.

to NaOCl in the presence of **2** and led to no detectable hydroxylation products. In contrast, the anti isomer **9b** reacted smoothly within hours and underwent efficient kinetic resolution ($k_{rel} = 10$). The major resolution product from the reaction of **9b** was isolated and determined to be a diastereomerically pure epoxy alcohol (>96% pure by GC analysis of crude reaction mixtures). Comparison of ^{1}H-NMR difference NOE measurements of **9a** and **9b** with those of the resolution product provided conclusive evidence that the hydroxylation occurred with retention of configuration to afford **10b**.[8]



The dramatic difference in reactivity between **9a** and **9b** indicated that the hydroxylation in the latter substrate might be occurring via a directed reaction involving precoordination of the catalyst to the epoxide. However, this simple interpretation was ruled out with the observation that the analogous diastereomeric 7-membered ring derivatives **11a** and **11b** underwent hydroxylation at similar rates. Analysis of epoxides **3** and **5**−**8** by ^{1}H-NMR difference NOE and computer modeling suggested an alternative explanation for the diastereoselectivity of hydroxylation based on the stereoelectronic properties of the C−H bonds undergoing reaction. In the ground state conformation of the 6-membered ring epoxides **3**, **5**, **6**, and **9**, the benzylic substituent located syn to the epoxide group resides in a pseudoaxial orientation (Figure 2). In contrast, the substituent anti to the epoxide group orients pseudoaxially in the 5- and 7-membered ring epoxides **7** and **8**. Thus, the difference in reactivity between the diastereomeric epoxides **9a** and **9b** and the reversal in kinetic resolution selectivity between the 6-membered and the 5- and 7-membered ring compounds may be ascribed to a stereoelectronically-controlled selectivity for oxygen insertion into an axial C−H bond (Figure 3). Such selectivity is fully consistent with a stepwise radical mechanism for C−H hydroxylation in which hydrogen atom abstraction by a high-valent metal oxo intermediate is followed by oxygen rebound.[3a] The pseudoaxial C−H bond in these benzocyclic systems enjoys better overlap with the π-system of the aromatic ring and is therefore kinetically more reactive toward H atom abstraction.

The synthetic utility of this kinetic resolution process was addressed in the context of a one-pot tandem asymmetric epoxidation/kinetic resolution process as a viable route to highly

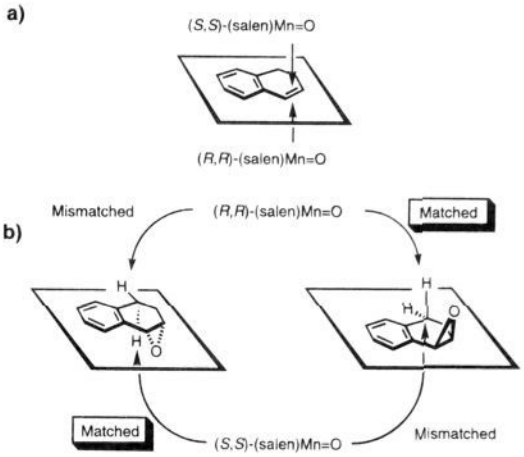


Figure 3. Stereoselectivity mnemonics for (a) the epoxidation of dihydronaphthalene and (b) the kinetic resolution of dihydronaphthalene oxide with chiral (salen)Mn catalysts.

enantiomerically enriched epoxides. A two-catalyst system was employed utilizing a highly enantioselective catalyst (**1**) for the epoxidation step and a more reactive catalyst (**2**) for the resolution step.[9] In this manner, the dihydronaphthalene derivatives **3** and **5** were produced in ≥98% ee in moderate to good isolated yield (53% and 79%, respectively).[10]

In conclusion, we have demonstrated that stereoselective oxidation of benzylic C−H bonds is possible utilizing readily-available[11] chiral (salen)Mn complexes, thereby expanding the scope of reactivity attainable with these catalysts. Efforts are underway to extend this stereoselective hydroxylation reaction to prochiral substrates.

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(8) Compound **10b** was isolated as a colorless liquid which also darkened upon standing: ^{1}H-NMR δ 7.58 (d, J = 8.0 Hz, 1H), 7.51 (dd, J = 1.3, 7.3 Hz, 1H), 7.42 (dt, J = 1.4, 7.6 Hz, 1H), 7.34 (dt, J = 1.2, 7.5 Hz, 1H), 4.10 (d, J = 4.1 Hz, 1H), 3.94 (m, 1H), 3.62 (s, 1H), 2.62 (dd, J = 2.8, 15.4 Hz, 1H), 1.99 (d, J = 15.4 Hz, 1H), 1.66 (s, 3H); ^{13}C-NMR δ 148.3, 131.7, 130.3, 129.6, 127.8, 125.1, 68.6, 55.3, 54.5, 36.3, 26.2; HRMS (CI) m/z 194.1177 (calcd for $[M + NH_4]^+$ 194.1180).

(9) A 50 mL round-bottomed flask equipped with a magnetic stir bar and a rubber septum was charged with 1,2-dihydronaphthalene (1.36 g, 10 mmol), 4-PPNO (170 mg, 10 mol %), (*R,R*)-**1** (72 mg, 1 mol %), and chlorobenzene (10 mL). The mixture was purged of air, cooled in an ice bath, and stirred under positive N_2 pressure. Precooled, purged, buffered NaOCl solution (30 mL, 1.8 equiv) was added via syringe, and the mixture was stirred for 2 h. At this point, (*R,R*)-**2** (37 mg, 0.5 mol %) in chlorobenzene (1 mL) was added, and the mixture was stirred for an additional 2 h. Heptane (10 mL) and Celite (0.5 g) were added with stirring, and the mixture was filtered through Celite. The filtrate was washed with water (2 × 30 mL) and then saturated aqueous $NaHCO_3$ (30 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (EtOAc/hexanes 1:7). Epoxide **3** was isolated as a crystalline solid, mp 45−46 °C (0.784 g, 98% ee).

(10) 1,2-Dihydronaphthalene is widely used as model substrate for studies on asymmetric epoxidation catalysis, and it has been reported to undergo epoxidation with unusually high enantioselectivity relative to other substrates with certain catalyst systems. Since the secondary kinetic resolution pathways outlined in this study are likely to be accessible to other chiral oxo-transfer catalysts, enantioselectivities obtained in the epoxidation of this olefin should be interpreted with caution unless the participation of secondary resolution processes has been conclusively ruled out. Cf. ref 4d and (a) Yamada, T.; Imagawa, K.; Nagata, T.; Mukaiyama, T. *Chem. Lett.* **1992**, 2231. (b) Mukaiyama, T.; Yamada, T.; Nagata, T.; Imagawa, K. *Chem. Lett.* **1993**, 327. (c) Collman, J. P.; Lee, V. J.; Zhang, X.; Ibers, J. A.; Brauman, J. I. *J. Am. Chem. Soc.* **1993**, *115*, 3834. (d) Veryat, M.; Maury, O.; Faverjon, F.; Over, D. E.; Ramasseul, R.; Marchon, J.-C.; Turowska-Tyrk, I.; Scheidt, W. R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 220.

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