Asymmetric Epoxidation

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Asymmetric Counteranion-Directed Transition-Metal Catalysis: Enantioselective Epoxidation of Alkenes with Manganese(III) Salen Phosphate Complexes**

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Dedicated to Professor Eric N. Jacobsen on the occasion of his 50th birthday

Inspired by pioneering contributions on chiral Brønsted acid mediated reactions[1] and our own studies in aminocatalysis,[2] we are currently exploring asymmetric counteranion-directed catalysis (ACDC) as a general strategy for asymmetric synthesis.[3] According to this concept, catalytic reactions that proceed via cationic intermediates can be performed highly enantioselectively by the incorporation of a chiral counteranion into the catalyst. After our initial proof of concept with organocatalytic transfer hydrogenations and epoxidations,[3,4] ACDC has recently been extended to transition-metal catalysis with Toste's gold-catalyzed allene cyclizations,[5] and our palladium-catalyzed Tsuji–Trost-type α-allylation of aldehydes.[6] The further exploration of the potential of ACDC in transition-metal catalysis, especially applied to redox reactions, is of great interest and significance.[7] Here we report a highly enantioselective epoxidation of olefins that is catalyzed by a chiral ion pair consisting of an achiral Mn^{III}–salen cation and a chiral phosphate counteranion.

Stimulated by an important contribution from Kochi et al., Jacobsen and Katsuki have significantly advanced the catalytic asymmetric epoxidation of unfunctionalized alkenes by introducing chiral Mn^{III}–salen catalysts.[8,9] These complexes display a broad substrate scope although certain olefin classes still fail to be converted with high enantioselectivity. Interestingly, cationic Mn–salen complexes are C_2-symmetrical and inherently chiral—even when the salen ligand itself is achiral. In case of the Jacobsen–Katsuki epoxidation, the chiral backbone of the salen ligand fixes the complex in one of the two enantiomorphic confirmations. The neutral donor ligands typically added increase reactivity and enantioselectivity by displacing the apically coordinated anion of the Mn complex.[9e,10] Chiral neutral donor ligands such as sparteine and chiral N-oxides have been used in combination with an achiral Mn–salen complex and shown to shift the equilibrium of enantiomeric conformational isomers of the cationic metal complex to one side. Reasonably good enantioselectivities have been achieved in the corresponding epoxidations.[11]

We hypothesized that a chiral counteranion should also be able to induce a preference for one of the two enantiomorphic conformations. Specifically, chiral binol-derived phosphate anions are ideally suited for our purposes, because in addition to possibly inducing one enantiomorphic conformation of the cationic complex, these ions may also amplify the chiral microenvironment around the metal center with suitable substituents at the 3,3′-positions (Figure 1). Overall, this may lead to a new type of chiral Mn–salen catalyst with unique properties.

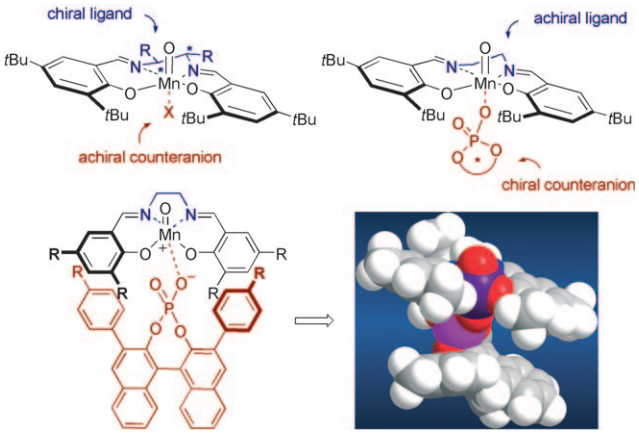

Figure 1. Design principle and modeling of a chiral ion-pair epoxidation catalyst (R = CH_3 in 3D model).

We initially combined the achiral Mn–salen cation **1a** with different binol-derived phosphates **2**. The ion-pair catalysts form quickly when the corresponding phosphoric acids and the Mn–salen chloride complex are mixed in the presence of 1 equivalent of aq. NaOH, and can be used directly. Chromene **3** was chosen as a model substrate because it is particularly suited for Jacobsen–Katsuki-type epoxidations and its product is of potential value as a pharmaceutical intermediate.[12] In the presence of 10 mol% of the ion-pair catalyst and 1.2 equivalents of iodosobenzene (PhIO) as the oxidant, the epoxidation of chromene **3** proceeded highly effectively in benzene at room temperature (see Table 1).

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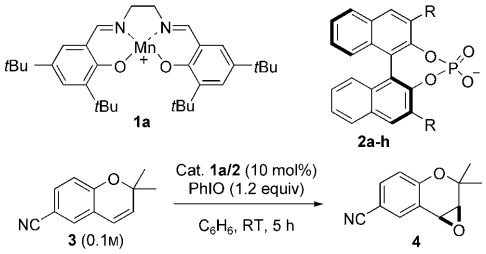
Table 1: Conversions and enantioselectivities for the epoxidation of **3** catalyzed by the achiral Mn–salen cation **1a** and different chiral phosphates **2**.



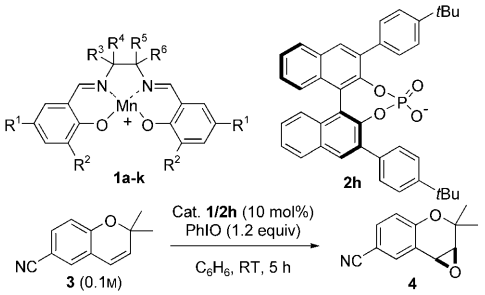
Entry	R	Cat.	Conv. [%][a]	e.r.[b]
1	Ph (**2a**)	**1a/2a**	89	54:46
2	2,4,6-(iPr)$_3$-C$_6$H$_2$ (**2b**)	**1a/2b**	>99	69:31
3	3,5-(CF$_3$)$_2$-C$_6$H$_3$ (**2c**)	**1a/2c**	>99	75:25
4	4-biphenyl (**2d**)	**1a/2d**	87	79:21
5	2-naphthyl (**2e**)	**1a/2e**	>99	75:25
6	9-anthryl (**2f**)	**1a/2f**	83	56:44
7	9-phenanthryl (**2g**)	**1a/2g**	>99	74:26
8	4-tBu-C$_6$H$_4$ (**2h**)	**1a/2h**	>99	95:5

[a] Determined by GC-MS. [b] Determined by HPLC analysis on a chiral stationary phase.

Phosphates **2a**–**2d** (entries 1–4, Table 1), which have substituents at different positions of the 3,3′-phenyl groups were investigated first. Of those, anion **2d** gave the highest enantioselectivity (79:21 e.r.). Chiral binol-derived phosphates with other aromatic substituents were also studied but did not lead to improved enantioselectivity (entries 5–7, Table 1). Reasoning that *p*-substitution at the 3,3′-aryl groups may be critical in extending the remote axial chirality of the binaphthyl into close vicinity to the presumed Mn^{V}–oxo reaction center, possibly preventing certain olefin trajectories, we also synthesized the 4-*tert*-butylphenyl-substituted phosphate **2h**. To our delight, catalyst **1a**/**2h** promoted the epoxidation smoothly and in excellent enantioselectivity of 95:5 e.r. (entry 8, Table 1). With this catalyst the olefin was completely consumed after 30 min and epoxide **4** was isolated in nearly quantitative yield (98%).

Since **2h** stood out as the best chiral phosphate, we next examined the combination of this anion with different cationic Mn–salen complexes **1a–k** under the same conditions (Table 2). Tuning of the Mn–salen complex by changing the 5,5′-substituents of **1** (R^1) revealed that the enantioselectivity depends not only on the electronics of the substituent but also on its size (Table 2, entries 1 and 2, Table 2). It had been shown earlier that Jacobsen catalysts give higher enantioselectivities with electron-donating substitutents,[13] but this trend was not observed in our system. For example, the methoxy-substituted catalyst **1c**/**2h** gave lower enantioselectivity than the bromine-substituted complex **1e**/**2h** (entries 2 and 4, Table 2). Some variations of the diamine bridge of the salen ligand were also explored (entries 7–10, Table 2). However, ethylenediamine proved to be optimal. In addition, several different solvents were tested, and it was found that more polar solvents lead to diminished enantioselectivity. Further optimizations, which included lowering the substrate concentration to 50 mM and the catalyst loading to 5 mol%,

Table 2: Conversions and enantioselectivities for the epoxidation of **3** catalyzed by different combinations of achiral Mn^{III}–salen cations and chiral phosphate **2h**.



Entry	R^1	R^2	R^3, R^4 R^5, R^6	Cat.	Conv. [%][a]	e.r.[b]
1	OSi(iPr)$_3$	tBu	H	**1b/2h**	90	82:18
2	OMe	tBu	H	**1c/2h**	>99	68:32
3	H	tBu	H	**1d/2h**	>99	83:17
4	Br	tBu	H	**1e/2h**	>99	82:18
5	NO$_2$	tBu	H	**1f/2h**	>99	71:29
6	tBu	H	H	**1g/2h**	>99	57:43
7	tBu	tBu	Me	**1h/2h**	>99	57:43
8	tBu	tBu		**1i/2h**	>99	71:29
9	tBu	tBu		**1j/2h**	>99	79:21
10	tBu	tBu		**1k/2h**	>99	46:54
11[c]	tBu	tBu	H	**1a/2h**	>99	97:3

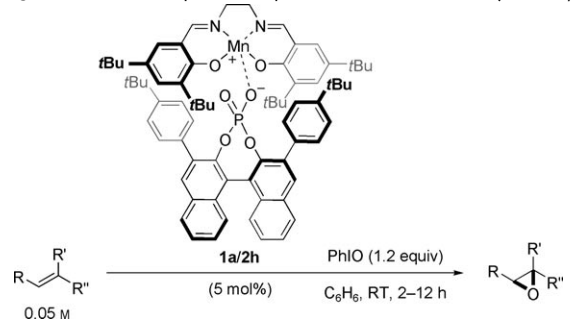
[a] Determined by GC-MS. [b] Determined by HPLC analysis on a chiral stationary phase. [c] Conditions: 0.05 M, 5 mol% catalyst **1a**/**2h**.

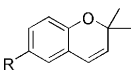
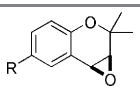
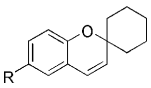
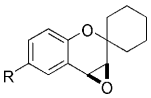
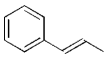
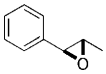
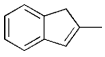
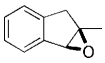
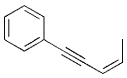
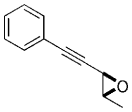
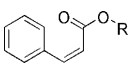
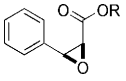
finally resulted in the formation of product **4** in essentially quantitative yield and with an improved e.r. of 97:3 (entry 11, Table 2).

The substrate scope was evaluated next. As shown in Table 3, different types of olefins can be epoxidized efficiently within short reaction times, providing the corresponding chromene- (entries 1–12), acyclic *cis*-alkene- (entries 14 and 17), and cinnamate-derived epoxides (entries 18 and 19, Table 3) in high yields and enantioselectivities (92:8 to 98:2 e.r.). Various functional groups such as ether, nitro, ester, and nitrile are tolerated. Overall, the extent of enantioselectivity we observe with various substrates using our ion-pair catalyst **1a**/**2h** closely resembles that obtained with the Jacobsen catalyst, although in the case of electron-deficient alkenes (entries 6, 18, and 19) and with styrene (entry 13), slightly higher enantioselectivities are achieved with our catalyst.[10b,12]

The absolute configuration of epoxide **4** was determined to be *S*,*S* when ion pair **1a**/(*S*)-**2h** was used, by comparison of the HPLC retention times and the optical rotation with literature values.[11b] The observed absolute configuration is consistent with our conformational analysis of the ion-pair catalyst. Accordingly, the *S*-configured phosphate **2h** stabilizes one enantiomorphic conformation of the cationic Mn complex. This specific "absolute conformation" is apparently identical with that of the *S*,*S* Jacobsen catalyst where it is induced from the chiral salen backbone. In a sense, the role of

Table 3: Substrate scope in epoxidations with catalyst **1a/2h**.



Entry	Alkene	Product	Yield [%][a] (d.r.)[b]	e.r.[c]
				
1	R = CN		98	97:3
2	R = OMe		83	96:4
3	R = Me		81	95:5
4	R = Br		88	96:4
5	R = Ph		97	95:5
6	R = NO_2		98	98:2
7	6-NHAc, 7-NO_2		98	95:5
				
8	R = H		93	97:3
9	R = CN		99	97:3
10	R = NO_2		99	98:2
11	7-NO_2		98	97:3
12	R = COOMe		97	97:3
13			80	85:15
14[d]			81 (6:1)	94:6
15			90	66:34
16			92	92:8
17[e]			97 (1:3)	96:4
				
18[f]	R = Et		92 (3:1)	97:3
19[g]	R = *i*Pr		93 (4:1)	98:2

[a] Yield of isolated product. [b] The d.r. value refers to the ratio of *cis*/*trans* epoxides. [c] Determined by GC or HPLC on a chiral stationary phase. [d] e.r. of the *trans* product 76:24. [e] e.r. of the *cis* product 78:22. [f] e.r. of the *trans* product 90:10. [g] e.r. of the *trans* product 95:5.

the anion in our system can be compared to that of a hand holding a tool. By virtue of the chirality of the hand, the entire assembly becomes chiral. Similarly, the role of the chiral anion is to freeze out a chiral conformation of the cationic catalyst, which can then act as an enantioselective catalyst. The exact trajectory of the olefin towards the Mn–oxo center is of great interest, and the structural characterization of our ion-pair catalyst is currently being pursued with great intensity.[14]

Another noteworthy aspect of our catalyst is that it is so reactive that no additional neutral ligand is required to increase the reactivity. In fact, adding such a ligand (*N*-methylmorpholine *N*-oxide, NMO) to our reaction mixture results in a dramatically reduced enantioselectivity and reactivity, as expected. The strong activity of our ion-pair catalyst may result from the weakened covalent character of the sterically overloaded ("frustrated")[15] manganese–phosphate Lewis pair. This situation increases the cationic character of the Mn complex, presumably a requirement for its activity. Obviously, there is a lot of work to be done on mechanistic and structural aspects of our reaction and catalyst.

In summary, the ion-pair epoxidation catalyst **1a/2h**, which consists of an achiral Mn–salen complex and a chiral phosphate counteranion, represents another powerful application of the concept of asymmetric counteranion-directed catalysis. The unique role of the counteranion in stabilizing an enantiomorphic conformation of a cationic catalyst is remarkable and currently inspires mechanistic studies and the design of catalysts for other reactions in our group.

Experimental Section

6-Cyano-2,2-dimethylchromene (**3**, 18 mg, 0.1 mmol), freshly prepared iodosobenzene (26 mg, 0.12 mmol), and catalyst **1a/2h** (0.005 mmol, 5 mol%) were dissolved in anhydrous benzene (2 mL). The resulting mixture was stirred at room temperature for 2 h. The solvent was then removed and the residue was purified by column chromatography on silica gel (hexane/EtOAc 10:1) to afford pure epoxide (*S*,*S*)-**4** (20 mg, 0.098 mmol, 98%) with 97:3 e.r. as determined by HPLC analysis.

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