Enantioselective Epoxidation with Chiral Mn^{III}(salen) Catalysts: Kinetic Resolution of Aryl-Substituted Allylic Alcohols

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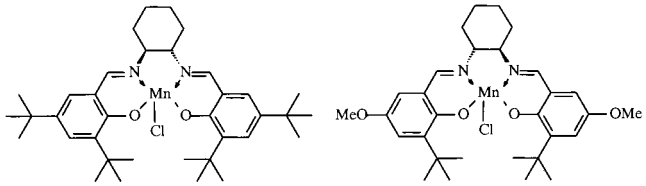
A set of aryl-substituted allylic alcohols *rac*-**2** has been epoxidized by chiral Mn(salen*) complexes **1** as the catalyst and iodosyl benzene (PhIO) as the oxygen source. Whereas one enantiomer of the allylic alcohol **2** is preferentially epoxidized to give the *threo*- or *cis*-epoxy alcohol **3** (up to 80% ee) as the main product (dr up to >95:5), the other enantiomer of **2** is enriched (up to 53% ee). In the case of 1,1-dimethyl-1,2-dihydronaphthalen-2-ol (**2c**), the CH oxidation to the enone **4c** proceeds enantioselectively and competes with the epoxidation. The absolute configurations of the allylic alcohols **2** and their epoxides **3** have been determined by chemical correlation or CD spectroscopy. The observed diastereo- and enantioselectivities in the epoxidation reactions are rationalized in terms of a beneficial interplay between the hydroxy-directing effect and the attack along the Katsuki trajectory.

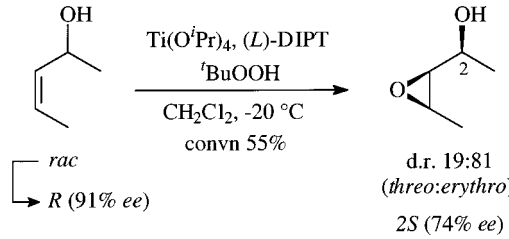
Introduction

Optically active epoxy alcohols are valuable building blocks for the asymmetric synthesis of biologically active molecules; for example, the β-blockers Propanolol and Falintolol have been prepared from (*R*)-propenol oxide.[1] For such enantioselective transformation, the Sharpless−Katsuki epoxidation represents one of the most efficient routes to optically active epoxy alcohols from primary allylic alcohols.[2] When a racemic allylic alcohol is used as substrate, kinetic resolution is a necessary consequence, in which one enantiomer is epoxidized preferably to the corresponding *erythro*-epoxy alcohol, while the other enantiomer of the allylic alcohol is enriched (Scheme 1).[2] Recently we have reported that secondary allylic alcohols are epoxidized in high *threo* diastereoselectivity by an achiral Mn^{III}(salen) complex with iodosyl benzene as oxygen source.[3] This raises the question whether racemic allylic alcohols may be enantioselectively epoxidized with chiral Mn^{III}(salen*) catalysts **1** through kinetic resolution. Although optically active Mn^{III}(salen*) complexes have already been used in the kinetic resolution of unfunctionalized olefins,[4] the use of such Jacobsen's catalysts in the enantioselective epoxidation of functionalized alkenes such as allylic alcohols appears to have not been attempted to date. Of course, for this purpose racemic aryl-substituted substrates should be employed, since these are destined to work best in the asymmetric Jacobsen−Katsuki epoxidation.[5]



S,S-**1a** *R,R*-**1b**

Scheme 1. Kinetic Resolution of a Chiral Allylic Alcohol in the Sharpless−Katsuki Epoxidation



Results

The allylic alcohols *rac*-**2a**−**f** (for structures, see Table 1) were synthesized according to literature methods.[6−11]

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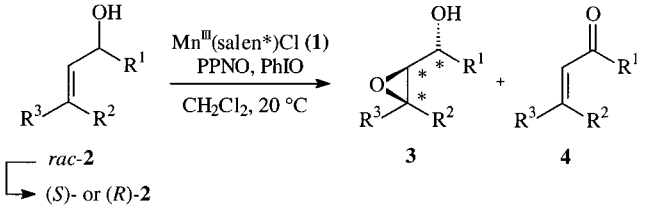
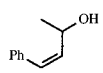
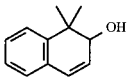
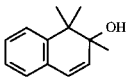
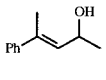
Table 1. Enantioselective Epoxidation of the Racemic Allylic Alcohols 2a–f



entry	substrate	catalyst[b] (10 mol %)	convn (%)	mb[c] (%)	selectivities[a] chemo 3 : 4	diastereo[d] 3	enantio (% *ee*) 3 (major)	3 (minor)	2	k_{rel}[e]
1	 **2a**	(*S,S*)-**1a**	21 (37)[f]	61	>95: 5	>95: 5	73 [2*S*(+)][g] 80 [2*S*(+)][h]	--	46 [*R*(-)]	12.9
2		(*R,R*)-**1b**	20 (41)[f]	73	>95: 5	>95: 5	69 [2*R*(-)][g] 80 [2*R*(-)][h]	--	53 [*S*(+)]	12.5
3	 **2b**	(*S,S*)-**1a**	51	90	89:11	90:10	66 [1*R*(+)]	81 [1*S*(-)]	36 [*R*(-)]	2.9
4		(*R,R*)-**1b**	48	>95	86:14	93: 7	56 [1*S*(-)]	82 [1*R*(+)]	43 [*S*(+)]	4.1
5	 **2c**	(*S,S*)-**1a**	47	>95	45:55	83:17	47 [2*S*(-)]	32 [2*S*(+)]	19 [*R*(+)]	1.8
6		(*R,R*)-**1b**	37	>95	43:57	80:20	56 [2*R*(+)]	20 [2*R*(-)]	11 [*S*(-)]	1.6
7	 **2d**	(*S,S*)-**1a**	37	>95	--	>95: 5	6 (-)	--	9 (+)	1.5
8		(*R,R*)-**1b**	23	>95	--	>95: 5	32 (+)	--	6 (-)	1.6
9	 **2e**	(*S,S*)-**1a**	54	66	>95: 5	93: 7	38 [2*S*(-)]	52 [2*R*(+)]	22 [*R*(+)]	1.8
10		(*R,R*)-**1b**	38	70	>95: 5	92: 8	51 [2*R*(+)]	56 [2*S*(-)]	21 [*S*(-)]	2.5
11	 **2f**	(*S,S*)-**1a**	13	>95	90:10	88:12	19 (+)	--	8 (-)	3.6
12		(*R,R*)-**1b**	11	>95	92: 8	95: 5	0	--	4 (+)	2.0

[a] Determined by ^{1}H NMR spectroscopy of the crude product (error ± 5%) or by chiral HPLC analysis (error ± 2%). [b] Molar ratio of **2**/**1**/PPNO (4-phenylpyridine *N*-oxide)/PhIO = 1.0:0.1:0.2:0.6. [c] Mass balance. [d] *cis*:*trans* or *threo*:*erythro* ratio. [e] Calculated according to $k_{rel} = \ln(1 - \text{conv})[1 - \text{ee}(\mathbf{2})]/\ln(1 - \text{conv})[1 + \text{ee}(\mathbf{2})]$. [f] Calculated according to conv = ee(**2a**)/[ee(**2a**) + ee(**3a**)]. [g] 50:50 mixture of *cis*- and *trans*-epoxides **3a**, ee of *cis*-**3a**. [h] ee of *trans*-**3a**.

Racemic samples of both diastereomers of the epoxides **3a,b,d,e,f** were prepared by dimethyldioxirane (DMD) epoxidation of the corresponding allylic alcohols **2**, while epoxy alcohol **3c** (*cis*:*trans* = 67:33) was obtained by oxidation of **2c** with PhIO, catalyzed by an achiral Mn^{III}-(salen) complex.

The manganese-catalyzed asymmetric epoxidation of the allylic alcohols **2** was carried out with 10 mol % of catalyst **1**, 20 mol % of 4-phenylpyridine *N*-oxide (PPNO) as additive, and 0.6 equiv of iodosyl benzene (PhIO) as oxygen source. The results are summarized in Table 1.

Since it is well-known[5] that the Jacobsen–Katsuki epoxidation works best for *cis*-disubstituted olefins with aryl groups, the substrates **2a–c** were employed first. The acyclic allylic alcohol **2a** was epoxidized in excellent chemo- and diastereoselectivity (>95:5, entries 1 and 2) to afford the corresponding *threo*-configured epoxy alcohol **3a** as a 50:50 mixture of the *cis*- and *trans*-epoxides *threo*-**3a**. Such *cis*/*trans* isomerization has been observed in the Jacobsen–Katsuki epoxidation of *cis*-*β*-methylstyrene and *cis*-stilbene[5] and may be suppressed (*cis*:*trans* = 90:10, data not shown) by the use of the Mn^{III}(salen*) catalyst with PF_6^- as counterion.[12] At about 20% conversion (observed) in the kinetic resolution of (*Z*)-4-phenyl-3-buten-2-ol (**2a**) with the catalyst (*S,S*)-**1a** (entry 1), the unreacted (*R*)-configured allylic alcohol **2a** was obtained in 46% ee, while the (*S*) enantiomer was epoxidized to the (2*S*,3*R*,4*S*)-*cis*-epoxide **3a** (73% ee) and the (2*S*,3*R*,4*R*)-*trans*-epoxide **3a** (80% ee). From these enantioselectivities a conversion of 37% is calculated; this discrepancy may be explained in terms of the low mass balance (61%). Complementary results were observed for the substrate **2a** with the (*R,R*)-**1b** catalyst (entry 2), except that now preferentially the (*R*)-**2a** enantiomer was epoxidized.

Under the same reaction conditions, the indenol **2b** (entries 3 and 4) was converted to the epoxy-alcohols **3b** in good chemoselectivity (epoxide/enone 89:11) and diastereoselectivity (90:10), with *cis*-**3b** as the main product. At a conversion of 51% with the (*S,S*)-**1a** catalyst (entry 3), the (1*R*)-*cis*-epoxide was formed in 66% ee and the (1*S*)-*trans*-epoxide in 81% ee, while (*R*)-indenol [(*R*)-**2b**] was enantiomerically enriched (36% ee). Again, complementary results were obtained for the (*R,R*)-**1b** catalyst (entry 4), for which expectedly the optically active (*S*)-**2b** enantiomer was left behind. Also minor (11–14%)

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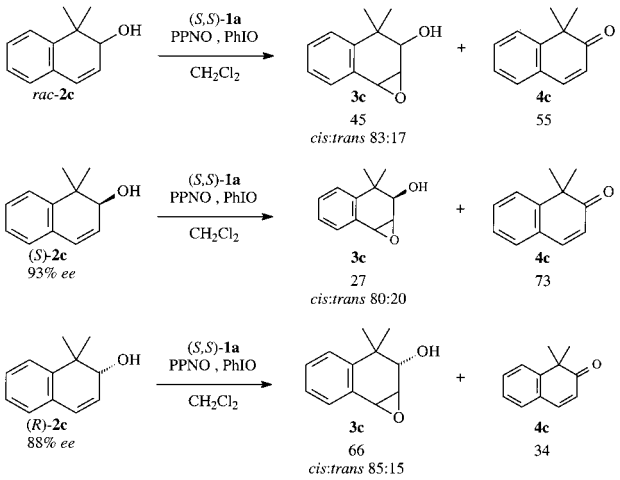
Scheme 2. Oxidation of Racemic and Enantiomerically Enriched Allylic Alcohol 2c by the (*S,S*)-1a Catalyst



amounts of CH oxidation to the enone **4b** took place (entries 3 and 4).

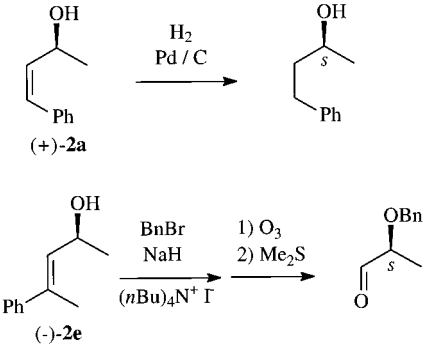
When 1,1-dimethyl-1,2-dihydronaphthalen-2-ol (**2c**) was submitted to the Mn^{III}(salen*)Cl/PPNO/PhIO oxidation (entries 5 and 6), the corresponding enone **4c** (allylic CH oxidation) was the main product; epoxidation occurred only in 45% and 43% yields. As in the case of the indenol **2b**, the *cis*-**3c** epoxide was formed as the major diastereomer (entry 5), but in slightly reduced (83:17) diastereoselectivity. Also, the ee values of the remaining allylic alcohol **2c** were substantially lower, that is, 19% (*R*) for the (*S,S*)-**1a** catalyst (entry 5) and 11% (*S*) for (*R,R*)-**1b** (entry 6). The best enantioselectivity for the epoxy-alcohol *cis*-**3c** (56% ee) was obtained with the (*R,R*)-**1b** catalyst (entry 6).

The possibility of an enantioselective CH oxidation was examined next. For this purpose, enantiomerically enriched allylic alcohol **2c** [the ee values were 92% (*S*) and 88% (*R*), Scheme 2] was treated with the (*S,S*)-**1a** catalyst and iodosyl benzene. While the (*S*)-**2c** enantiomer was oxidized preferentially to the enone **4e** (27:73 chemoselectivity), the (*R*)-**2c** enantiomer was epoxidized more readily (66:34 chemoselectivity). For comparison, the chemo- and diastereoselectivity of the reaction with *rac*-**2c** and (*S,S*)-**1a** (Table 1, entry 5) are also shown in Scheme 2.

Since in 1,1,2-trimethyl-1,2-dihydronaphthalen-2-ol (**2d**) the CH oxidation is totally suppressed, this tertiary allylic alcohol was examined to assess the enantioselectivity of the epoxidation (entries 7 and 8). While the diastereoselectivity of the epoxidation was excellent (>95:5), the epoxide *cis*-**3d** was formed in a rather poor enantioselectivity [6% ee with catalyst (*S,S*)-**1a** and 32% ee with (*R,R*)-**1b**]. Consequently, essentially no enantiomeric enrichment (<10% ee) of the remaining allylic alcohol **2d** was observed.

The diastereomeric, trisubstituted 4-phenyl-3-penten-2-ols **2e,f** were examined to determine the steric effects on the various selectivities. The (*E*)-diastereomer **2e** (entries 9 and 10) was epoxidized in excellent chemoselectivity (>95:5) and diastereoselectivity (93:7), to afford the corresponding *threo*-configured epoxy-alcohol **3e**. Unlike (*Z*)-4-phenyl-3-buten-2-ol (**2a**), no *cis*/*trans* isomerization was detected. At a conversion of 54% with the (*S,S*)-**1a** catalyst (entry 9), the (2*S*)-*threo* epoxide **3e**

Scheme 3. Assignment of the Absolute Configurations of the Allylic Alcohols 2a,e by Chemical Correlation



was formed in 38% ee and the (2*R*)-*erythro*-epoxide **3e** in 52% ee, while (*R*)-(*E*)-4-phenyl-3-penten-2-ol (**2e**) was moderately enantiomerically enriched (22% ee). Complementary results were found for the (*R,R*)-**1b** catalyst (entry 10).

When the diastereomeric (*Z*)-4-phenyl-3-penten-2-ol (**2f**) was submitted to the Mn^{III}(salen*)Cl/PPNO/PhIO oxidation (entries 11and 12), analogous to its (*E*)-diastereomer **2e** (entry 9), the *threo*-**3f** epoxide was formed as the major diastereomer, but in slightly reduced (90:10) chemoselectivity (entry 11). Also, no *cis*/*trans* isomerization occurred. The ee values of the *threo*-epoxy alcohol **3f** were substantially lower, that is, 19% for the (*S,S*)-**1a** catalyst (entry 11), and for (*R,R*)-**1b** merely racemic epoxy alcohol **3f** was obtained (entry 12). Consequently, there was essentially no enantiomeric enrichment of the remaining allylic alcohol **2f**.

The absolute configurations of the acyclic allylic alcohols **2a** and **2e** were determined by chemical correlation, as outlined in Scheme 3. Thus, (+)-(*Z*)-4-phenyl-3-buten-2-ol (**2a**) was converted to the known (*S*)-phenylbutan-2-ol[13] by catalytic hydrogenation, which establishes that the (+)-**2a** enantiomer possesses the (*S*) configuration. The (−)-(*E*)-4-phenyl-3-penten-2-ol (**2e**) was first benzylated and then cleaved by ozonolysis to the known (*S*)-2-benzyloxypropanal,[14] which allowed assignment of the (*S*) configuration to the (−)-**2e** enantiomer.

To determine the absolute configuration of the cyclic allylic alcohol **2c**, circular-dichroism (CD) spectroscopy was employed. After enzymatic kinetic resolution of *rac*-**2c** [(+) alcohol 81% ee, (−) acetate 92% ee at 47% conversion] with the lipase from *Burkholderia* sp. (CHIRAZYME L-1), the required second chromophore in the enantiomerically enriched (+)-**2c** was introduced by treatment with benzoyl chloride in pyridine to give the optically active benzoate of **2c** (data not shown). Its CD and UV spectra are given in Figure 1.

A word of caution must be expressed, in view of the fact that the 1,2-dihydronaphthalene chromophore shows itself a large Cotton effect at about 260 nm [cf. CD spectrum of the acetate, light line]. This peak must be ignored, because it does not arise from the coupling of the two chromophores. Thus, the negative Cotton effect observed at 228 nm allows one to infer the (*R*) configuration for the parent alcohol (+)-**2c**.

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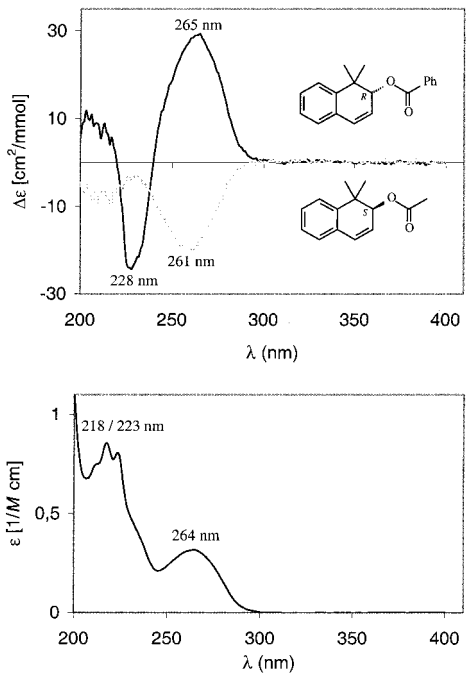

Figure 1. CD (upper) and UV (lower) spectra of the benzoate (dark line) and acetate (light line) derivatives of the allylic alcohol **2c**.

Since the manganese-catalyzed epoxidation of the substrates **2d** and **2f** were poorly selective (cf. Table 1, entries 7, 8, 11, and 12), the absolute configurations of the allylic alcohols **2d,f** and their epoxides **3d,f** were not determined. The enantiomerically enriched allylic alcohols **2a**−**c,e** (20−53% ee), whose absolute configurations are known, were epoxidized to give both diastereomers of the epoxy-alcohols **3a**−**c,e**. By comparison of HPLC retention times and the signs of optical rotation (see Supplementary Information), the absolute configurations of the epoxy alcohols **3a**−**c,e** were assessed.

Discussion

As shown in the Results section, when the model substrate (*Z*)-4-phenyl-3-buten-2-ol (**2a**) was allowed to react with the (*S*,*S*)-**1a** catalyst under the standard conditions, the (*S*)-**2a** enantiomer was epoxidized to the *threo*-configured *cis*-(2*S*,3*R*,4*S*)-epoxide **3a** (73% ee) and the *trans*-(2*S*,3*R*,4*R*)-epoxide **3a** (80% ee), while the (*R*)-configured allylic alcohol **2a** was enantiomerically enriched up to 46% ee (Table 1, entry 1). The diastereo- and enatioselectivity of this manganese-catalyzed epoxidation may be rationalized in terms of the synergistic interplay between the hydroxy-directing effect[3,15] and the attack along the Katsuki trajectory[5] (Figure 2). On the basis of 1,3-allylic strain ①, the preferred conformer is given in Figure 2, in which the hydrogen atom at the C-2 position of the substrate points toward the phenyl ring. Favorable hydrogen bonding ② between the hydroxy functionality of substrate **2a** and the Mn(V)oxo functionality obliges attack from that π face of the double bond such that the oxygen transfer leads to the *threo*-epoxides **3a** as the main diastereomer. Thus, the observed *threo* diastereoselectivity (Table 1, entries 1 and 2) underlies hydroxy-directivity control, in which conformational alignment through 1,3-allylic strain and hydrogen bonding between substrate and reagent cooperate.

To rationalize the observed enantioselectivity, the Katsuki trajectory ③ needs to be examined in more detail.[5] Katsuki postulated that the allylic alcohol **2a** should approach the Mn(V)oxo functionality of the (*S*,*S*)-Mn(V)oxo species as shown in Figure 2, that is, the substrate should come from the right side and the phenyl group should point away from the right-hand aryl group of the salen ligand to avoid $\pi-\pi$ interaction. Since along this attack only the (*S*) enantiomer of allylic alcohol **2a** may hydrogen-bond ② effectively, the (*S*)-**2a** enantiomer is oxidized preferentially to the *threo*-configured (2*S*,3*R*,4*S*)-*cis*-epoxide **3a** and the (2*S*,3*R*,4*R*)-*trans*-epoxide **3a**, while the (*R*)-**2a** enantiomer is enriched. In this way, the enantioselectivity displayed in the manganese-catalyzed kinetic resolution of allylic alcohol **2a** may be accounted for in terms of the mutual assistance of the hydroxy-directing effect and the attack along the Katsuki trajectory.

While this rationale also applies to the substrates **2b** (Table 1, entries 3 and 4) and **2e,f** (entries 9−12), the stereochemical results (entries 5 and 6) for 1,1-dimethyl-1,2-dihydronaphthalen-2-ol (**2c**) cannot be explained in this way. According to the Katsuki rationale, the epoxidation of the cyclic allylic alcohol **2c** with the (*S*,*S*)-**1a** catalyst should preferentially lead to the (2*R*)-configured epoxide *cis*-**3c**; however, the opposite enantiomer, namely, (2*S*)-*cis*-**3c**, is observed (Table 1, entry 5). This discrepancy may be explained in terms of the allylic CH oxidation of substrate *rac*-**2c**, which constitutes the main reaction pathway. Thus, the kinetic resolution in this step rather than in the epoxidation is responsible for the observed enantioselectivity. Indeed, in a control experiment with the enantiomerically enriched allylic alcohol **2c** (cf. Results section, Scheme 2), it was shown that the (*S*)-**2c** enantiomer was oxidized preferentially to the enone **4c** by the (*S*,*S*)-**1a** catalyst (**3c**:**4c** = 27:73), while the (*R*)-**2c** enantiomer was epoxidized more readily (**3c**:**4c** = 66:34). If the enantioselectivity in the CH oxidation were the same for both enantiomers (*S*)-**2c** and (*R*)-**2c**, the kinetic resolution of allylic alcohol *rac*-**2c** would be dictated by the asymmetric epoxidation and not by the enantioselective enone formation. Consequently, when a racemic mixture of the allylic alcohol *rac*-**2c** and the catalyst (*S*,*S*)-**1a** is subjected to the standard reaction conditions, the (*S*)-**2c** enantiomer is oxidized preferentially to the enone **4c** rather than being epoxidized to the (2*R*)-configured *cis*-**3c** epoxy alcohol, and therefore, the (*R*)-**2c** enantiomer is enriched by the former reaction mode. The epoxidation of the substrate **2c** to the epoxy alcohols **3c** could also proceed enantioselectively, but that this is evidently not the case is already suggested by the fact that (2*R*)-*cis*-**3c** should be formed preferentially according to the Katsuki rationale. More significant, the manganese-catalyzed epoxidation of the methyl derivative **2d**, which is prohibited to undergo CH oxidation, proceeded in poor enantioselectivity (Table 1, entries 7 and 8). Thus, the (*R*)-**2c** enantiomer, which was enriched by enantioselective CH oxidation, is epoxidized to the (2*S*)-*cis*- and (2*S*)-*trans*-**3c** epoxy alcohols without substantial additional kinetic resolution (Table 1, entries 5 and 6).

It remains to explain why (*E*)-4-phenyl-3-penten-2-ol (**2e**) is epoxidized selectively (up to 51% ee), while its (*Z*)-diastereomer **2f** is not (Table 1, entries 9−12). As shown

(15) Adam, W.; Wirth, T. *Acc. Chem. Res.* **1999**, *32*, 703−710.

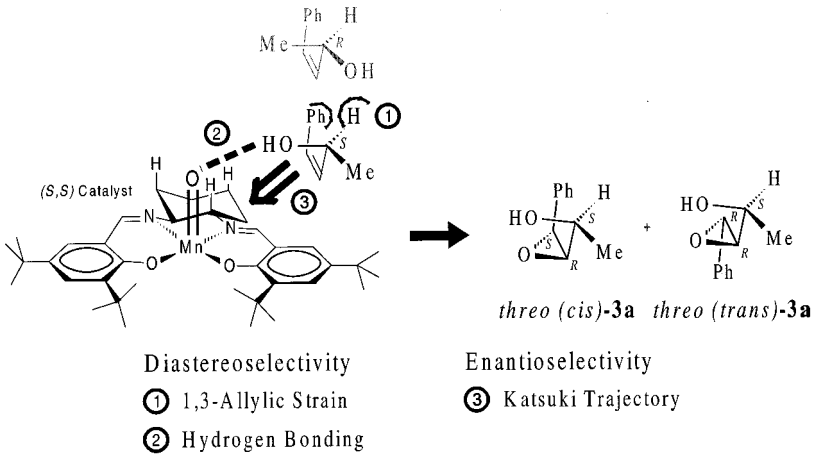

Figure 2. Controlling factors on the diastereo- and enantioselectivity in the epoxidation of the chiral allylic alcohol **2a**.

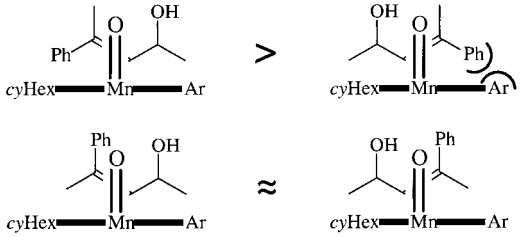

Figure 3. Steric effects in the epoxidation of substrates **2e** (top) and **2f** (bottom), viewed along the Katsuki trajectory.

in Figure 3, the diastereomeric allylic alcohols **2e,f** may orientate themselves along the Katsuki trajectory in two different ways toward the Mn(V)oxo functionality of the (*S,S*)-**1a** catalyst. For the substrate **2e**, the upper right-hand approach is disfavored, since its phenyl group would be placed proximate to the aryl group of the salen ligand and $\pi-\pi$ repulsion would be expected to build up. Thus, the asymmetric epoxidation of the **2e** diastereomer occurs in good enantioselectivity along the upper left-hand approach. Contrarily, the phenyl group of the **2f** diastereomer points away almost perpendicularly from the plane of the salen ligand, and thus, $\pi-\pi$ repulsion is minimized such that both attacks become energetically equal. Expectedly, the epoxidation of the *Z*-configured allylic alcohol **2f** is not enantioselective.

In conclusion, the kinetic resolution of aryl-substituted allylic alcohols **2** in the enantioselective epoxidation by the chiral Mn^{III}(salen*) catalysts **1** provides a promising alternative to the established Sharpless–Katsuki epoxidation for the synthesis of optically active *threo*- or *cis*-configured epoxy alcohols **3**. As a bonus, enantiomerically enriched allylic alcohols **2** are obtained. The stereochemical control in this asymmetric oxidation is accounted for in terms of the beneficial interplay between the hydroxy-directing effect and the attack along the Katsuki trajectory.

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Supporting Information Available: Experimental details of the epoxidation reactions mentioned in the text; analytical and spectral characterization data of the alcohols **2**, the epoxides **3** and the enones **4**; experimental details of the chemical correlation of the alcohols **2a,c,e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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