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Oxidation of aryl-substituted allylic alcohols by an optically active Fe(III)(porph*) catalyst: enantioselectivity, diastereoselectivity and chemoselectivity in the epoxide versus enone formation

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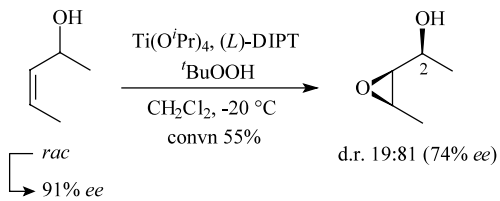
Abstract—A set of aryl-substituted allylic alcohols (±)-**2** was oxidized using the chiral Fe(porph*) complex **1** as the catalyst and iodosyl benzene (PhIO) as the oxygen source. Whereas one enantiomer of the allylic alcohol **2** is preferentially epoxidized to give the *threo*- or *cis*-epoxy alcohol **3** (up to 43% e.e.) as the main product (d.r. up to >95:5), the other enantiomer of **2** is enriched (up to 31% e.e.). Some non-stereoselective allylic oxidation to give the enone **4** also takes place. The observed diastereo- and enantioselectivities in the epoxidation reactions are rationalized in terms of a synergistic interplay between the hydroxy-directing effect and the steric interactions of the catalyst **1** and the substrate **2**.

1. 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 an 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). The efficiency of this kinetic resolution depends profoundly on the structure of the allylic alcohol employed, the e.e. values of the enriched alcohols range from 10 to >96%.[2]



Scheme 1. The kinetic resolution of a chiral allylic alcohol in the Sharpless–Katsuki epoxidation.

Recently we have reported that secondary allylic alcohols are epoxidized with high *threo* diastereoselectivity by an achiral Fe(III)(porph) complex with iodosyl benzene as oxygen source;[3] with an optically active Mn(III)-(salen*) catalyst, kinetic resolution takes place.[4] This raises the question as to whether these racemic allylic alcohols may also be enantioselectively epoxidized with a chiral Fe(III) (porph*) catalyst **1** (Fig. 1) through kinetic resolution. The catalyst **1** was recently described by Collman et al.[5] as a highly selective (e.e. up to 90%) and readily prepared Fe(III)(porph*) complex for the epoxidation of unfunctionalized olefins.

Although the enantioselective epoxidation by optically active Fe(III)(porph*) catalysts has been extensively investigated during the last decades,[6] their use in the enantioselective epoxidation of functionalized alkenes such as allylic alcohols appears not to have been attempted to date. Herein, we report the asymmetric epoxidation of acyclic and cyclic racemic allylic alcohols **2** by the Fe(III)(porph*) catalyst **1** under conditions of <50% conversion (Scheme 2). Since trisubstituted olefins had not been investigated by Collman et al.[5] for the catalyst **1**, the diastereomeric pair of trisubstituted racemic allylic alcohols **2e** and **2f** was also

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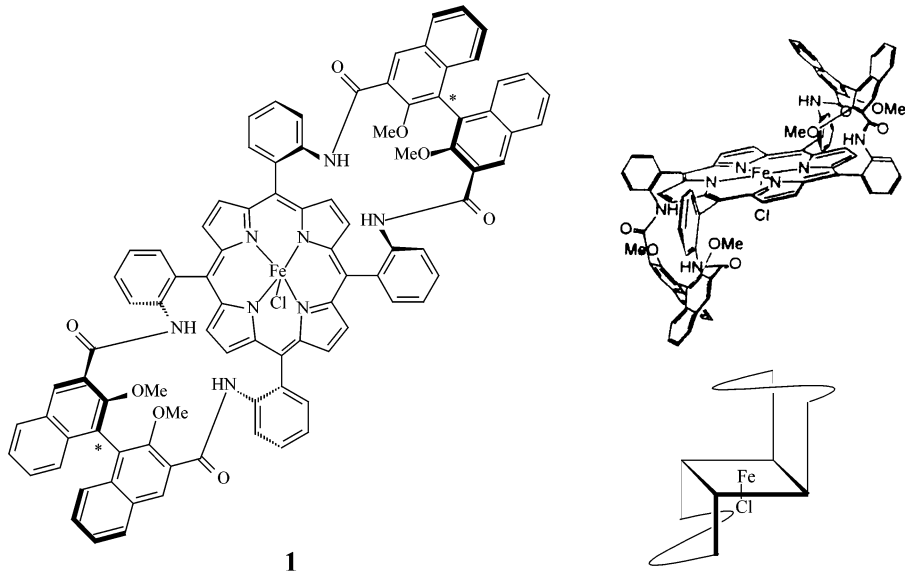
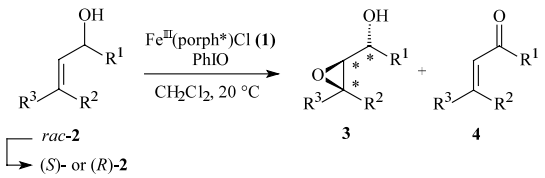


Figure 1. Structure of the chiral Fe(III)(porph*) catalyst **1**.



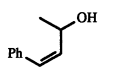
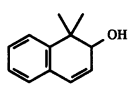
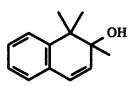
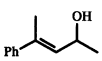
Scheme 2. Enantioselective epoxidation of the racemic allylic alcohols **2** with catalyst **1**.

examined. The diastereoselectivity and particularly the enantioselectivity, as well as the chemoselectivity between epoxide **3** and enone **4** formation were of interest in this study.

2. Results

The chiral Fe(porph*)Cl catalyst **1** was prepared as already described by Collman et al.[5,7] The allylic alco-

Table 1. Fe-catalyzed oxidation of allylic alcohols **2**

entry	substrate[b]		convn (%)	mb[c] (%)	selectivity[a] chemo 3 : 4	diastereo[d] 3	enantio (% e.e.) 3 (major)	3 (minor)	2	k_{rel}[e]
1		**2a**	33	88	95: 5	> 95: 5	23 [*2S*(+)][e]	—	11 [*R*(-)]	1.7
2		**2b**	48	>95	> 95: 5	90:10	43 [*1R*(+)]	48 [*1S*(-)]	31 [*R*(-)]	2.7
3		**2c**	34	>95	62:38	73:27	40 [*2S*(-)]	9 [*2R*(-)]	0	1.0
4		**2d**	27	>95	—	> 95: 5	2 (-)	—[f]	3 (+)	1.2
5		**2e**	32	>95	83:17	87:13	3 [*2R*(+)]	0	5 [*S*(-)]	1.3
6		**2f**	18	>95	93: 7	> 95: 5	6 (+)	—	1 (+)	1.1

a) Determined by ^{1}H-NMR spectroscopy of the crude product (error ±5%) for the chemo- and diastereoselectivities or by chiral HPLC analysis (error ±2%) for the enantiomeric excess (% e.e.); b) 1.0 : 0.05 : 0.8 molar ratio of **2** / **1** / PhIO; c) mb = mass balance; d) *cis* : *trans* or *threo* : *erythro* ratio; e) calculated according to k_{rel} = ln(1-conv)[1-e.e.(**2**)]/ln(1-conv)[1+e.e.(**2**)]; f) while *trans*-**3d** epoxide could not be detected by NMR, traces of it were seen in the HPLC analysis.

hols (±)-**2a**–**f** (for structures, see Table 1) were synthesized according to literature methods.[8–13] Racemic samples of diastereomers of the epoxides **3a**, **3b** and **3d**–**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 iron-catalyzed asymmetric epoxidation of the allylic alcohols **2** was carried out with 5 mol% of catalyst **1** and 0.8 equiv of iodosyl benzene (PhIO) as oxygen source. The results are summarized in Table 1; for comparison, the selectivity factors k_{rel} are also given.[14]

Since it is well known[15] that Fe(porph)-catalyzed epoxidations work best for *cis*-disubstituted olefins, the substrates **2a**–**d** were employed first. The phenyl-substituted acyclic allylic alcohol **2a** (entry 1) was epoxidized with excellent chemo- and diastereoselectivity (95:5) to afford the corresponding *threo*-configured epoxy alcohol **3a**. Unlike the manganese-catalyzed epoxidation,[4] no *cis*/*trans* isomerization was observed. At a conversion of 33%, the unreacted allylic alcohol **2a** was obtained in 11% e.e., with the (*R*)-enantiomer as the major isomer, while the (*S*) enantiomer was preferentially epoxidized to the (2*S*,3*R*,4*S*)-epoxide **3a** in 23% e.e.

When the indenol **2b** (entry 2) was subjected to the Fe(porph*)Cl/PhIO oxidation, no allylic CH oxidation to the enone **4b** took place (epoxide/enone >95:5) and the *cis*-configured epoxide **3b** was observed as the main product (dr 90:10). At 48% conversion, the kinetic resolution of indenol **2b** gave the (1*R*)-*cis*-epoxide in 43% e.e. and the (1*S*)-*trans*-epoxide in 48% e.e., while (*R*)-indenol (*R*)-**2b** was enriched to the extent of 31% e.e.

In the oxidation of the cyclic allylic alcohol 1,1-dimethyl-1,2-dihydronaphthalen-2-ol **2c**, only moderate chemoselectivity (62:38) and diastereoselectivity (73:27) was obtained (entry 3). While the major diastereomer *cis*-**3c** showed at 34% conversion an e.e. of 40% in favor of the (2*S*)-enantiomer, the enantiomeric excess of the other diastereomer (2*R*)-**3c** was rather low (9% e.e.) and of the remaining allylic alcohol **2c** none at all (0% e.e.).

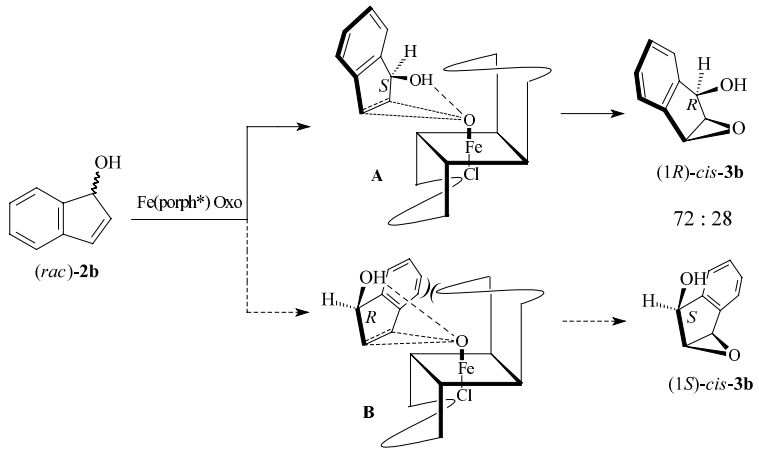
To account for the lack of resolution of the allylic alcohol **2c**, possibly the (*R*)-enantiomer of **2c** is preferentially epoxidized to the (2*S*)-**3c** epoxy alcohol, whereas the enantiomeric (*S*)-**2c** is more readily converted to the enone **4c** by allylic oxidation. If these two reaction modes were to occur to the same extent, the remaining alcohol **2c** would not be enantiomerically enriched. Indeed, a related case of such competitive oxidations has already been demonstrated in the manganese-catalyzed epoxidation of the allylic alcohol **2c**.[4] While (*S*)-**2c** was converted preferentially to the enone **4c** by the chiral (*S*,*S*)-Mn(III)(salen*) catalyst, the remaining (*R*)-**2c** enantiomer was epoxidized. To test such a possibility for the present case, the two enantiomers of the allylic alcohol **2c** [the e.e. values are 91% for the (*S*) and 88% for the (*R*)-enantiomer] were separately treated with catalyst **1** and iodosyl benzene to assess the effect of allylic oxidation on the enantioselectivity. The chemoselectivities are quite similar [the epoxide **3c**/enone **4c** ratios are 42:58 for (*S*)-**2c**, 62:38 for (*R*)-**2c** and 62:38 for (±)-**2c**], which implies that enone formation plays only a minor role in influencing the enantioselectivity of this asymmetric epoxidation. Furthermore, since both enantiomers of **2c** are oxidized to the enone **4c** with about equally efficiency, CH oxidation does not significantly contribute to the kinetic resolution of the allylic alcohol **2c**. Moreover, the conversion of the allylic alcohol **2c** is moderate (34%) such that only low e.e. values are expected. The combined effect of these factors may be responsible for the lack of kinetic resolution in the reaction of the allylic alcohol **2c**.

For the 1,1,2-trimethyl-1,2-dihydronaphthalen-2-ol **2d**, CH oxidation is not possible, and for this reason this tertiary alcohol was chosen to assess the enantioselectivity of the epoxidation (entry 4) without complications by competitive allylic oxidation. Whereas excellent diastereoselectivity (>95:5) was observed, the major epoxide *cis*-**3d** was formed as an essentially racemic mixture (2% e.e.), but for the minor epoxide *trans*-**3d** an e.e. of 48% was obtained. In view of these facts, essentially no enrichment (3% e.e.) of the remaining allylic alcohol **2d** was found.

To determine the steric effects on the various selectivities, the diastereomerically trisubstituted 4-phenyl-3-penten-2-ols **2e** and **2f** were examined. The (*E*)-diastereomer **2e** (entry 5) was epoxidized with good chemoselectivity (83:17) and diastereoselectivity (87:13) to afford the corresponding *threo*-configured epoxy alcohol **3e**. As in the case of (*Z*)-4-phenyl-3-buten-2-ol **2a**, no *cis*/*trans* isomerization was detected. The enantioselectivity was low [3% e.e. for (2*R*)-**3e**] and, therefore, allylic alcohol **2e** remained almost racemic (5% e.e.). When the diastereomeric (*Z*)-4-phenyl-3-penten-2-ol **2f** was submitted to the iron-catalyzed oxidation (entry 6), analogous to its (*E*)-diastereomer **2e** (entry 5), the *threo*-epoxide **3f** was formed as the major diastereomer. Although better chemoselectivity (93:7) and diastereoselectivity (>95:5) were achieved for the diastereomer **2f** compared to **2e**, essentially racemic epoxy alcohol **3f** (6% e.e.) and allylic alcohol **2f** (1% e.e.) were obtained. Due to the low e.e. values found for these trisubstituted allylic alcohols **2e** and **2f**, their enantioselectivity shall not be discussed in terms of a mechanistic rationale.

3. Discussion

The diastereo- and enantioselectivity of this iron-catalyzed epoxidation may be rationalized in terms of the synergistic interplay between the hydroxy-directing effect[3,16] and the steric interactions between the chiral Fe(porph*)oxo complex and the allylic alcohol **2**.[5] In Scheme 3 this is illustrated for the model substrate indenol **2b**, for which the chemoselectivity is excellent (exclusive epoxidation), the diastereoselectivity high (d.r. 90:10), and the enantioselectivity is the best [the



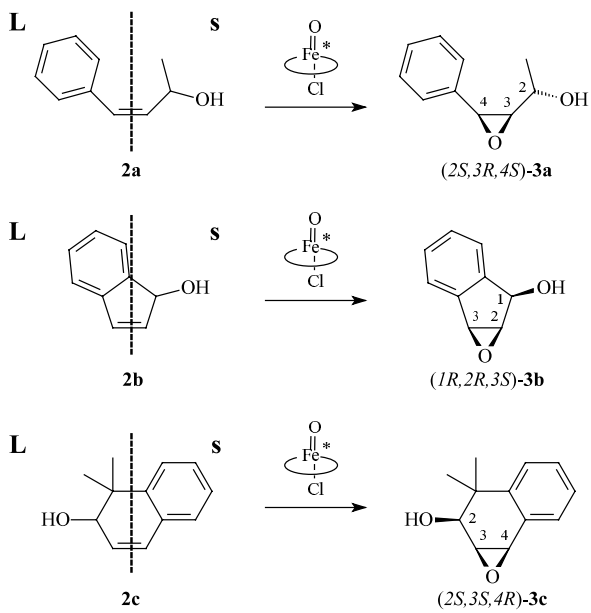
Scheme 3. Mechanistic rationale for the kinetic resolution in the catalytic epoxidation of indenol (±)-**2c** by the chiral Fe(porph*)oxo complex.

(*S*)-**2b** enantiomer is epoxidized to the *cis*-configured (1*R*)-epoxide **3b** (43% e.e.), whereas the (*R*)-configured allylic alcohol **2b** is enantiomerically enriched up to 31% e.e. (Table 1, entry 2)] for all the allylic alcohols **2** examined herein. Hydrogen bonding between the hydroxyl functionality of the allylic alcohol **2b** and the Fe(porph*)oxo oxidant favors attack onto the π face of the double bond *syn* to the hydroxy group, such that the oxygen transfer leads to the *cis*-epoxide **3b** as the main diastereomer. Thus, the observed *cis* diastereoselectivity (Table 1, entry 2) underlies hydroxy-directive control.[16]

To rationalize the observed enantioselectivity, the steric interactions between catalyst **1** and the substrate **2b** need to be examined in more detail. As already proposed by Collman et al.,[5] the binaphthyl bridge forms a chiral pocket around the Fe(porph*)oxo functionality. Consequently, the two diastereomeric catalyst-substrate complexes **A** and **B** shall be considered for the reaction of the racemic indenol (±)-**2b** with the oxidant. When the hydroxy-directed (*S*)-**2b** enantiomer approaches the Fe(porph*)oxo functionality as shown in complex **A**, the sterically more demanding aryl ring of the substrate fits into the available space away from the upper inwardly leaning binaphthyl lobe. In contrast, complex **B** is less favored since the aryl ring of the (*R*)-**2b** enantiomer interferes with the upper inwardly leaning binaphthyl lobe. Thus, the (*S*)-**2c** alcohol enantiomer is epoxidized preferentially to the (1*R*)-*cis*-**3b** epoxy alcohol, such that the (*R*)-**2b** enantiomer is enriched. Evidently, the steric interactions between the substrate and catalyst are relatively weak and, hence, the enantioselectivity is only moderate, i.e. the e.e. values fall between 40 and 50% for the allylic alcohol **2b** (Table 1, entry 2), the substrate with the best asymmetric control.

The mechanistic rationale in Scheme 3 also applies to the substrates **2a** and **2c**. While the diastereoselectivity in the epoxidation of allylic alcohols **2** implies hydroxy-directivity control,[16] the enantioselectivity is also directed by the steric demand of the substituents on the double bond of the substrate (Scheme 4). The sterically more demanding **L** part of the substrate avoids interaction with the upper, inwardly leaning lobe of the binaphthyl bridge, analogous to the indenol **2b** (Scheme 4), such that the type **A** structure is preferred over type **B**. For the allylic alcohols **2a** and **2b**, the aryl ring constitutes the **L** group and, consequently, the epoxides (2*S*,3*R*,4*S*)-**3a** and (1*R*,2*R*,3*S*)-**3b** are formed as the main enantiomers. In contrast, for the allylic alcohol **2c**, the *gem*-dimethyl substituent represents the **L** group and, thus, the (2*S*,3*S*,4*R*)-**3c** enantiomer is obtained preferentially on epoxidation.

The set of allylic alcohols **2a**–**f**, oxidized in this work by the chiral Fe(porph*) catalyst **1**, had already been examined in the Mn(salen*)-catalyzed enantioselective epoxidation.[4] Consequently, it is pertinent to compare the efficacy of these two catalytic oxidation systems in terms of chemo-, diastereo- and enantioselectivity. The



Scheme 4. Substrate-directed enantioselectivity in the asymmetric epoxidation of allylic alcohols **2a**, **2c** and **2d** by the chiral Fe(porph*)oxo complex (**L** = large, **s** = small).

epoxide **3**/enone **4** ratios are similar for both Fe(porph*) and Mn (salen*) complexes: Whereas the allylic alcohols **2a** (95:5 versus >95:5) and **2f** (93:7 versus 91:9) display almost the same high chemoselectivity in favor of epoxidation, more epoxide is produced in the iron-catalyzed oxidation of the substrates **2b** (>95:5 versus 87:15) and **2c** (62:38 versus 44:56); however, for the allylic alcohol **2e** (83:17 versus >95:5), epoxidation is favored by the Mn(salen*) complex. The diastereoselectivities, which range from 73:27 to >95:5, are about the same with both metals for all substrates **2a–f** within experimental error; thus, for both metal-oxo oxidants the hydroxy-directing effect operates with equal efficiency. The main discrepancy between the Fe(porph*) and Mn(salen*) catalysts concerns the enantioselectivity: Whereas the iron complex **1** displays only low selectivities with e.e. values from 2 to 43% (the k_{rel} values range from 1.0 to 2.7), e.e. values up to 80% (k_{rel} 12.9) may be obtained for the Mn(salen*) complex.

4. Conclusion

In summary, the racemic allylic alcohols **2** used in this study have been instructive in elucidating mechanistic details of the iron-catalyzed oxygen-transfer process. Evidently, the stereochemical control in this Fe(porph*)-catalyzed asymmetric oxidation is accounted for in terms of the synergistic interplay between the hydroxy-directing effect and the steric interactions between the substituents of the catalyst **1** and the substrate **2**.

5. Experimental

5.1. General procedure for the iron-catalyzed epoxidation of the allylic alcohols 2

A mixture of the Fe(porph*)Cl catalyst **1** (37.4 mg, 25.0 μmol, 5 mol%) and the appropriate allylic alcohol **2** (500 μmol) in CH_2Cl_2 (5 mL) was stirred for 2 min at rt (ca. 20°C). PhIO (88.0 mg, 400 μmol) was then added in small portions over 2 min and the resulting suspension was stirred for ca. 14 h until a clear purple solution was obtained. After removal of the solvent (20°C, 400 mbar), the residue was transferred onto a short column of silica gel (ca. 10 g) and eluted first with 100 mL of petroleum ether to remove iodobenzene, afterwards with 200 mL of a petroleum ether/diethyl ether mixture (1:1) to recover the oxidation products. After removal of the solvent (30°C, 10 mbar), the resulting colorless oil was analyzed by ^1H NMR spectroscopy and chiral HPLC; the mass balance was determined by the weight of the crude product and the products detected by NMR spectroscopy. The quantitative data are summarized in Table 1 (see main text).

Analytical and spectral characterization data of the alcohols **2**, the epoxides **3** and the enones **4** can be found in the Supporting Information of Ref. 4.

Acknowledgements

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