Regio- and Diastereoselective Epoxidation of Chiral Allylic Alcohols Catalyzed by Manganese(salen) and Iron(porphyrin) Complexes

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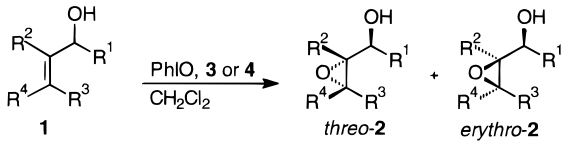
Abstract: Chiral acyclic allylic alcohols **1** have been chemo-, regio-, and diastereoselectively epoxidized to the corresponding epoxy alcohols **2** by catalysis with the achiral manganese(salen) and iron(porphyrin) complexes **3** and **4** and iodosyl benzene as oxygen donor. The *threo* diastereoselectivities establish that hydrogen bonding accounts for the observed hydroxy-group directivity. The dramatically reduced stereoselection in the protic methanol and the opposite sense in the diastereoselectivity (*erythro* instead of *threo*) for the ether and ester derivatives **5** of the allylic alcohol **1f** confirm that hydrogen bonding between the allylic alcohol and the oxo−metal complex operates in this oxygen-transfer process, with 1,3-allylic strain as the conformationally controlling feature. That metal−alcoholate bonding does not apply is displayed by the regioselectivities obtained in the epoxidation of 1-methylgeraniol (**1h**). By comparison of the diastereo- and regioselectivities with those of mechanistically defined catalytic and stoichiometric metal and nonmetal oxidants, we propose likely transition-state structures **A** and **B** for the present epoxidation.

Introduction

The catalytic and selective oxyfunctionalization of organic compounds for the preparation of optically active products is a subject of current interest and intensive study.[1] Catalysis is desirable for the preservation of natural resources and environmental compatibility, selectivity a necessity for the synthesis of complex natural products and biologically active compounds.

Undoubtedly, among such oxidations the catalytic and stereoselective epoxidations present still a challenging goal.[2] Catalysis is achieved by means of transition-metal complexes with common oxygen sources, while the stereoselectivity may be controlled either by an optically active oxidizing species[3] or by a chiral substrate.[4] Prominent examples are the Sharpless−Katsuki epoxidation of allylic alcohols[3a] and the Jacobsen−Katsuki epoxidation of unfunctionalized alkenes,[3b−d] both utilizing optically active metal complexes. Stereocontrol by the substrate, however, has been successfully applied in the diastereoselective epoxidation of chiral allylic alcohols. These compounds have proven to be useful mechanistic stereochemical probes for the investigation of the transition-state structures. Several catalytic [Ti(O*i*-Pr)$_4$/TBHP,[5] Ti-zeolite/H_2O_2,[6] $VO(acac)_2$/TBHP,[7] methyltrioxorhenium/UHP[8]] and noncatalytic (DMD,[9] *m*-CPBA[7]) methods have already been extensively studied and valuable information on the geometry of the oxygen-transfer process have been aquired. The mentioned catalytic oxidants include peroxy− and peroxo−metal complexes; however, the well-known oxo−metal-mediated oxidations, catalyzed by metal(salen)[10] or metal(porphyrin) complexes,[11] have not yet been subjected to this stereochemical scrutiny. Presumably, this omission rests on the literature claim that allylic CH insertion to afford α,β-enones overrides epoxidation, a preferred reaction path that erases all stereochemical information.[12]

We report herein the chemo-, regio-, and diastereoselective epoxidation of the chiral allylic alcohols **1** to the corresponding epoxy alcohols by the Mn(salen) and Fe(porphyrin) complexes **3** and **4** (eq 1). The synergistic interplay between 1,3-allylic



(eq 1)

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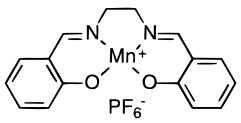
strain and hydroxy directivity was probed with the chiral



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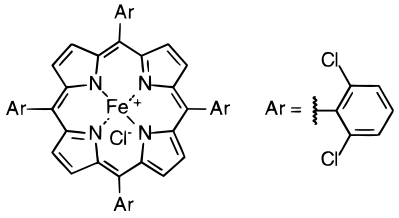

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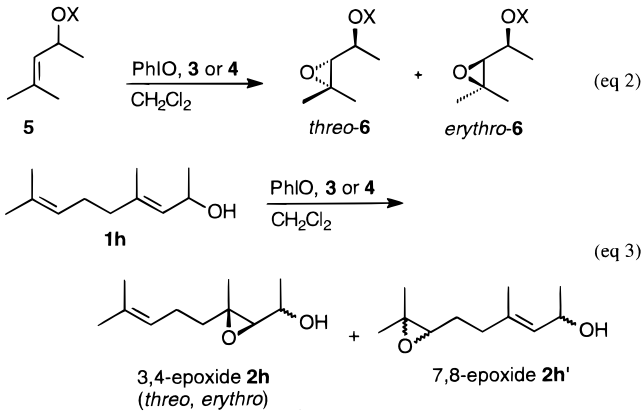
hydroxy-capped allylic derivatives **5** to afford the corresponding epoxides **6** (eq 2) and the regioselectivity was examined with the geraniol derivative **1h** (eq 3).



Results

The Mn(salen) and Fe(porphyrin) complexes **3** and **4**, the chiral allylic alcohols **1**, and their derivatives **5** (for structures see tables) were synthesized according to literature procedures (see Supporting Information). The epoxy alcohols **2** were formed preferentially in the metal-catalyzed oxidation of chiral allylic alcohols **1** with iodosyl benzene as the oxygen source, only for derivative **1b** some enone was observed. Conversions and mass balances were high to excellent in every case (see Supporting Information).

The allylic alcohols **1a**,**b** with no allylic strain were epoxidized nondiastereoselectively by the Mn(salen) **3** and in a low but insignificant *erythro* selectivity by the Fe(porphyrin) catalyst **4** (Table 1, entries 1,2). For the substrates **1c**,**d** (Table 1, entries 3,4) with 1,2-allylic strain, also a low, insignificant diastereoselectivity (slight *threo* preference for **1d**) was found. Clearly, 1,2-allylic strain does not play a significant role in this oxo−metal-mediated epoxidation of chiral allylic alcohols.

The allylic alcohols **1e**,**f** possess 1,3-allylic strain and their epoxidation in the nonpolar CH_2Cl_2 proceeded with high *threo* diastereoselectivity (Table 1, entries 5,6). In the polar protic methanol, however, the *threo* selectivity dropped drastically, as is shown for the allylic alcohol **1f** (Table 1, entry 6).

Substrate **1g** contains both 1,2- and 1,3-allylic strain and serves, therefore, as a stereochemical mechanistic probe to assess which type of allylic strain dominates for a particular oxidant.[7b] Since in the epoxidation of **1g** the *threo* diastereoselectivity decreased only slightly (Table 1, entry 7), 1,3-allylic strain dominates the stereochemical outcome of these oxo−metal-mediated reactions.

Table 1. Diastereoselectivities for the Epoxidation of Chiral Allylic Alcohols **1**

		catalyst:	**3**(Mn)[a,b]	**4**(Fe)[b]	$VO(acac)_2$[c]	$Ti(O^iPr)_4$[d]		
		[O] donor:	PhIO	PhIO	TBHP	TBHP	*m*-CPBA[e]	DMD[f]
		solvent:	CH_2Cl_2	CH_2Cl_2	CH_2Cl_2	$CDCl_3$	CH_2Cl_2	acetone
entry	substrate				*threo* : *erythro*[g]			
1		**1a**	54 : 46	45 : 55	20 : 80	71 : 29	60 : 40	50 : 50
2		**1b**	52 : 48[h]	37 : 63[h]	29 : 71	66 : 34	64 : 36	64 : 36
3		**1c**	48 : 52	42 : 58	05 : 95	22 : 78	45 : 55	56 : 44
4		**1d**	61 : 39	70 : 30	10 : 90	24 : 76	48 : 52	51 : 49
5		**1e**	89 : 11	89 : 11	71 : 29	91 : 09	95 : 05	67 : 33
6		**1f**	91 : 09 (57 : 43)[i]	84 : 16	86 : 14	95 : 05	95 : 05	76 : 24
7		**1g**	81 : 19	81 : 19	33 : 67	83 : 17	90 : 10	87 : 13

[a] 0.30 equiv of 4-phenylpyridine *N*-oxide (PPNO) as additive. [b] Conversions and mass balances were higher than 80% in most cases (see Supporting Information for exact values). [c] Entries 1−3, 5, 6 (ref 7a,b); entry 4 (ref 7c); entry 7 (ref 7d). [d] Reference 5. [e] Entries 1−3, 5, 6 (ref 7a,b); entry 4 (ref 7c); entry 7 (ref 7d). [f] Entries 1−3, 5−7 (ref 14); entry 4 (ref 7c). [g] Diastereomeric ratios (dr) determined by ^{1}H-NMR analysis of characteristic epoxide signals directly on the crude reaction mixture; error ±5% of the stated values. [h] Also ketone (∼15%) was observed. [i] Methanol as solvent.

Table 2. Diastereoselectivities of the Metal-Catalyzed Epoxidation of Chiral Oxyfunctionalized Substrates **5**

			threo:*erythro*[c]	
entry	substrate	X	**3**(Mn)[a,b]	**4**(Fe)[b]
1	**5a**	Me	39:61 (72)	22:78 (n.d.)[d]
2	**5b**	^{t}BuMe$_2$Si	14:86 (59)	04:96 (44)
3	**5c**	Ac[e]	36:64 (56)	10:90 (35)
4	**1f**	H	91:09 (95)	84:16 (91)

[a] 0.30 equiv of 4-phenylpyridine *N*-oxide (PPNO) as additive. [b] Mass balances were ≥80% in every case (see Supporting Information for exact values); conversions (%) are given in parentheses. [c] Diastereomeric ratios (dr) determined by ^{1}H-NMR analysis of characteristic epoxide signals directly on the crude reaction mixture; error ±5% of the stated values. [d] Not determined because of severe signal overlap in the ^{1}H-NMR spectrum. [e] ^{1}H-NMR spectral data for the epoxy acetates **6c** have been inadvertently switched in ref 14; for chemical correlation see Supporting Information.

The hydroxy-protected derivatives **5a**−**c** displayed a reversed diastereoselectivity (*erythro*) in these metal-catalyzed epoxidations (Table 2). For these substrates the *erythro* diastereoselectivity is significantly higher with the Fe(porphyrin) **4** than the Mn(salen) **3** catalyst and the differences in the magnitudes of the stereoselectivities are much more pronounced than those for the allylic alcohols **1**. A striking example is the acetate **5c** (Table 2, entry 3), which is epoxidized in low selectivity by the Mn(salen) **3**, but with high *erythro* selectivity by the Fe(porphyrin) **4** catalyst. Steric effects are responsible for this pronounced *erythro* selectivity. The highest *erythro* selectivity

Table 3. Diastereo- and Regioselectivities in the Epoxidation of 1-Methylgeraniol (**1h**)

			selectivities	
entry	oxidant	solvent	diastereo[a,b] *threo*: *erythro*	regio[b,c] 3,4:7,8
1	**3**(Mn)/PhIO[d]	CH_2Cl_2	94:06	47:53
2	**4**(Fe)/PhIO	CH_2Cl_2	88:12	27:73
3	Ti(O*i*-Pr)$_4$/TBHP[e]	CH_2Cl_2	98:02	95:05
4	VO(acac)$_2$/TBHP[e]	CH_2Cl_2	89:11	95:05
5	*m*-CPBA[e]	CCl_4	90:10	49:51
6	DMD[e]	acetone	84:16	16:84

[a] Diasteromeric ratios (dr) of the 3,4 epoxides; for the 7,8 epoxides the dr values are 50:50. [b] Determined by ^{1}H-NMR analysis of characteristic epoxide signals directly on the crude reaction mixture; error ±5% of the stated values. [c] Regioselectivity of the 3,4 and 7,8 epoxides. [d] 0.30 equiv of 4-phenylpyridine *N*-oxide (PPNO) as additive. [e] Reference 13.

was observed for the bulky silyl-protecting group in derivative **5b** (Table 2, entry 2).

The mechanistic probe 1-methylgeraniol (**1h**), which has been recently established by us,[13] was applied to assess the regio- as well as stereochemistry of the present metal-catalyzed epoxidations. As expected, analogous to the related 1,3-allylically strained alcohol **1f** (Table 1, entry 6), also a very high *threo* diastereoselectivity was obtained for the 3,4 epoxides **2h** (Table 3, entries 1 and 2).

In regard to the regioselectivity (Table 3, entries 1 and 2), for the Mn(salen) **3** catalyst both the 3,4 and 7,8 epoxides are formed in nearly equal amounts, while for the Fe(porphyrin) **4** catalyst the 7,8 epoxide is favored.

Discussion

The present results demonstrate, despite literature claims,[12a] that allylic alcohols may be effectively epoxidized by Mn(salen) and Fe(porphyrin) complexes with iodosyl benzene as the oxygen source. CH insertion to form α,β-unsaturated ketones was observed only to a minor extent for substrate **1b** (Table 1, entry 2).

For mechanistic scrutiny, our data establish unequivocally the hydroxy-directing effect in this oxo−metal-mediated epoxidation on three counts: (i) 1,3-Allylically strained alcohols afford *threo* epoxy alcohols with high (d.r. ca. 90:10) diastereoselectivity in the aprotic CH_2Cl_2 solvent (Table 1), (ii) in the protic MeOH, the diastereoselectivity drops to 57:43 (Table 1, entry 6), and (iii) when the hydroxy functionality is protected with an alkyl, silyl, or acyl group, *erythro* selectivity applies due to repulsive steric interactions (Table 2). These experimental findings support hydrogen bonding between the allylic hydroxy group and the oxo−metal intermediate as attractive interaction. That metal−alcoholate bonding does not operate in this metal-catalyzed oxygen transfer comes from the regioselectivities observed with the 1-methylgeraniol (**1h**) as probe (Table 3). For comparison, previously we have established[13] that oxidants such as Ti(O*i*-Pr)$_4$/TBHP and VO(acac)$_2$/TBHP (entries 3 and 4), typical for metal−alcoholate bonding, afford with high preference (95:5) the 3,4 epoxide, while the characteristic hydrogen-bonding systems *m*-CPBA and dimethyldioxirane (entries 5 and 6) favor the 7,8 regioisomer. The fact that the oxo−metal catalysts **3** and **4** lead to proportionally more of the 7,8 epoxide (entries 1 and 2) than the titanium and vanadium catalysts (entries 3 and 4) substantiates that the hydrogen-bonding mechanism rather than metal−alcoholate formation applies. The higher regioselectivity in favor of the 7,8 epoxide for the iron-catalyzed reaction versus that of manganese reveals that hydrogen bonding is less effective for the Fe−oxo than for the Mn−oxo intermediate and less of the 3,4 epoxide is formed.

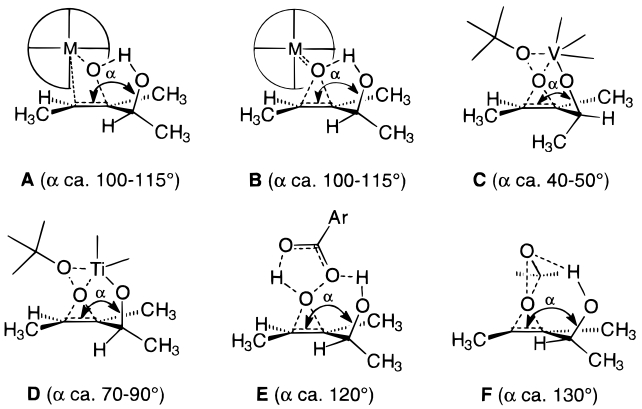


Figure 1. Transition-state structures for the epoxidation catalyzed by the manganese(salen) and iron(porphine) complexes (**A**, **B**), VO(acac)$_2$/TBHP (**C**), Ti(O^{i}Pr)$_4$/TBHP (**D**), *m*-CPBA (**E**), and DMD (**F**).

Now that hydrogen bonding has been established to be responsible for the observed hydroxy-directed *threo* selectivity in the present metal-catalyzed epoxidation, an unprecedented fact for oxo−metal complexes with valuable mechanistic information, it remains to inquire about the transition-state structure of this oxygen-transfer process. Decisive for this purpose is the dihedral angle O−C−C═C (α) between the π plane of the double bond and the hydroxy group of the allylic system (Figure 1), which assumes characteristic values for catalytic and stoichiometric epoxidations of chiral allylic alcohols with allylic strain. For the established oxidants (Figure 1), optimal dihedral angles (O−C−C═C) have been estimated to be 40−50° for VO(acac)$_2$/TBHP[7] (structure **C**), 70−90° for Ti(O*i*-Pr)$_4$/TBHP[5] (structure **D**), ca. 120° for *m*-CPBA[7] (structure **E**), and ca. 130° for DMD[14] (structure **F**) to rationalize the observed diastereoselectivities. Inspection of the complete set of *threo*:*erythro* diastereoselectivities in Table 1, which serves as a stereochemical fingerprint for the transition-state structure, suggests that the dihedral angles for the oxo−metal oxidants **3**/PhIO and **4**/PhIO fit qualitatively best between that for Ti(O*i*-Pr)$_4$/TBHP (70−90°) and *m*-CPBA (120°), more closely to the latter, and may be assigned to be 100−115°. The match is not perfect, but most indicative in this stereochemical comparison are the 1,3-allylically strained substrates **1e** and **1f**. Since metal−alcoholate bonding, as is the case for Ti(O-*i*Pr)$_4$/TBHP (structure **D**), is not involved for the oxo−metal complexes **3** and **4**, a hydrogen-bonded transition-state structure similar to that of *m*-CPBA (structure **E**) applies.

We propose the transition states **A** or **B** (Figure 1) to account for the stereochemical results of the oxo−metal-mediated epoxidation of chiral allylic alcohols. 1,3-Allylic strain provides the required conformational alignment and hydrogen bonding with the incoming oxidant the necessary attractive interaction for the preferred *threo* π-facial attack. In the absence of 1,3-strain, e.g. substrates **1a**,**b**, or for the 1,2-allylically strained derivatives **1c**,**d** (the influence of 1,2-allylic strain is negligible), low if any *threo* selectivity is found, which is in good accord

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with the proposed transition-state structures **A** and **B**. This favorable hydroxy-directing effect accelerates the reaction rate because the hydroxyl-protected derivatives **5** (Table 2) are less efficiently epoxidized than the parent allylic alcohol **1f**. Moreover, the substrates **5** possess no hydrogen-bonding donors and, hence, since there is no hydroxy-group directivity, steric effects promote *erythro* diastereoselectivity, as convincingly manifested in the case of the ^{t}BuMe$_2$Si-protected derivative **5b** (Table 2, entry 2). As for the proposed hydrogen bond between the oxo functionality of the oxo−metal complexes derived from the catalysts **3** and **4** and the hydroxy group of the allylic alcohols **1,** Jørgensen et al.[15] have reported computational results which show that the oxygen atom of an oxo−metal complex bears a partially negative charge despite its electrophilic character. Thus, the Mn(salen) and Fe(porphyrin) oxo complexes should be capable of hydrogen bonding. Moreover, the nucleophilic behavior of higher valent oxo−metal complexes is demonstrated by examples of electrophilic silylation.[16] Presumably, this hydrogen bonding to the oxo−metal complex activates the electrophilic character of the metal center and, consequently, enhances its reactivity. This would favor the metallaoxetane mechanism (structure A) through the well-established side-on attack[17] on the CC double bond by the oxo−metal functionality. However, our stereochemical data (Table 1), from which a dihedral angle of 100−115° has been extracted, are also consistent with the direct three-centered transition-state structure B for this oxygen-transfer process. For the time being, both transition states **A** and **B** (Figure 1) apply, but previous experimental[18] and computational[19] results favor the metallaoxetane option **A**, although the mechanism is still under debate.[18b,c,20]

These novel results establish that the hydroxy-directed epoxidation of chiral allylic alcohols may be effectively catalyzed by achiral manganese(salen) and iron(porphyrin) complexes. The highly *threo*-diastereoselective epoxide formation is controlled by the synergistic combination of 1,3-allylic strain and hydrogen bonding.

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Supporting Information Available: Experimental details and structure matrix (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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