JOC Article

Effect of Additives on Chemoselectivity and Diastereoselectivity in the Catalytic Epoxidation of Chiral Allylic Alcohols with Hydrogen Peroxide and Binuclear Manganese Complexes

Hamdullah Kilic,*[,†] Waldemar Adam,[‡] and Paul L. Alsters[§]

Faculty of Science, Department of Chemistry, Ataturk University, 25240 Erzurum, Turkey, Institut für Organische Chemie, Universität Würzburg, Am Hubland, D-97074 Würzburg, Germany and Department of Chemistry, FB-110, University of Puerto Rico, RIO PIEDRAS, Puerto Rico 00931, and DSM Pharma Products, Innovative Synthesis and Catalysis, and Development, P.O. Box 18, 6160 MD Geleen, The Netherlands

hkilic@atauni.edu.tr

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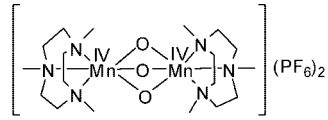

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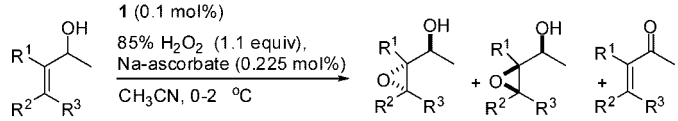

The catalytic oxidations of chiral allylic alcohols **2** by manganese complexes of the cyclic triamine 1,4,7-trimethyl-1,4,7-triazacyclononane (tmtacn) **1** and hydrogen peroxide as oxygen donor in the presence of co-catalyst are investigated to understand the factors that affect the catalyst selectivity. Chemoselectivity and diastereoselectivity of catalyst **1** are significantly affected by the structure of the allylic alcohol and the nature and amount of co-catalyst. More pronounced is the influence of the amount of added molar equivalents of H_2O_2 (20−110 mol % with respect to the substrate). Our present results reflect the complex redox chemistry of the Mn catalyst **1**/H_2O_2/co-catalyst system in the early phase of the alkene oxidation.

Introduction

The oxidation of olefins to the corresponding epoxides is of great synthetic value, from both an academic and an industrial research point of view.[1] Of special interest are catalytic procedures, because they allow economic use of the employed resources.[2] Numerous catalytic systems are known to utilize transition metal catalysts such as titanium, vanadium, rhenium, and manganese.[3] The epoxides, which are widely used in the fine chemicals industry, may be readily prepared by the stoichiometric oxidation of alkenes with peracids such as peracetic and *m*-chlorobenzoic acids.[4] The use of peracids is, however, not an environmentally friendly method because an equivalent amount of acid waste is produced. As an alternative approach, much effort in this field has been directed toward the efficient use of hydrogen peroxide as the oxygen source, since it is relatively cheap, environmentally benign, and readily available.[5] The only byproduct is water, which makes this reagent undoubtedly appealing for synthetic applications; un-

[†] Ataturk University.
[‡] Universität Würzburg and (present address) University of Puerto Rico.
[§] DSM Pharma Products.

(1) (a) Sheldon, R. A.; Kochi, J. K. *Metal Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981. (b) Lane, B. S.; Burgess, K *Chem Rev* **2003**, *103*, 2457–2474.

(2) (a) Sheldon, R. A *Top. Curr. Chem.* **1993**, *164*, 23–43. (b) Sobkowiak, A.; Tung, H.; Sawyer, D. T. *Prog. Inorg. Chem.* **1992**, *40*, 291–352.

(3) (a) Adam, W.; Corma, A.; Reddy, T. I.; Renz, M. *J. Org. Chem.* **1997**, *62*, 3631–3637. (b) Rossiter, B. E.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, *19*, 4733–4736. (c) Adam, W.; Mitchell, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 533–535. (d) Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; Chapter 4.2.

(4) Shapless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63–74.

(5) (a) Sato, K.; M.; Ogawa, M.; Hashimoto, T.; Noyori, R *J. Org. Chem.* **1996**, *61*, 8310–8311. (b) Hermann, W. A.; Fischer, R. W.; Marz, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1683–1641. (c) Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem.* **1994**, *59*, 1939–1942. (d) Lane, B. S.; Burgess, K. *J. Am. Chem. Soc.* **2001**, *123*, 2933–2934.

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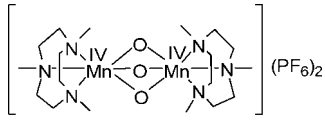
fortunately, hydrogen peroxide requires efficient activation for oxygen transfer, advantageously by catalysis.



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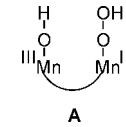
Manganese complexes of cyclic amines such as 1,4,7-trimethyl-1,4,7-triazacyclononane, abbreviated as Mn-tmtacn **1**, were reported to catalyze styrene epoxidation with hydrogen peroxide in methanol−carbonate buffers.[6] Because of the extensive oxidant decomposition that such catalysts cause, oxidant-to-substrate ratios of at least 100 need to be applied, which cause highly dilute product mixtures. In the presence of the alkene substrate, the balance between oxidant decomposition and epoxidation may be shifted in favor of the latter, when appropriate reaction conditions are chosen, e.g., acetone as solvent. Although the peroxide decomposition is suppressed, undesirable radical reactions take place.[7]

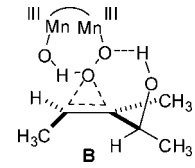
Recent studies have shown that the catalytic activity of manganese complexes **1** is strongly enhanced when carboxylic acids such as oxalic acid, ascorbic acid, and their salts are employed as co-ligands.[8] Besides the readily oxidized phenols and sulfides, even alkanes have been oxyfunctionalized with the catalyst **1**.[9] A spectroscopic examination has shown that complex **1** undergoes complex redox chemistry in contact with H_2O_2.[10,8d,e] A very recent detailed study of the alkene oxidations catalyzed by **1** plus carboxylic acid co-catalysts has revealed that in the presence of H_2O_2, **1** is transformed into catalytically active bis(μ-carboxylato)-Mn^{III}_2 complex **A** (Figure 1) during an initial lag period before the onset of alkene oxidation.[8d]

Manganese complexes Mn-tmtacn **1** have so far not been employed for the epoxidation of chiral allylic alcohols **2**. The set of stereochemically labeled alcohols **2** in Table 2 not only



A

FIGURE 1. H_2O_2-activated bis(μ-carboxylato)-Mn^{III}_2 complex **A**.



B

FIGURE 2. Proposed transition-state structure for the epoxidation of *Z*-**2c** by catalyst **1**.

constitutes a valuable mechanistic probe for the elucidation of oxygen-transfer processes but also offers the opportunity to test the chemoselectivity of the oxidation in terms of epoxide versus enone formation, that is, the insertion of an oxygen atom into the CC double bond or into the allylic CH bond.

We report herein the oxidation of allylic alcohols **2** with the Mn-tmtacn catalyst **1** and hydrogen peroxide as the oxygen source. The oxidative activity of catalyst **1**, its chemoselectivity, and stereoselectivity have been investigated in the presence of various co-catalysts. The present results display that the chemoselectivity and stereoselectivity of the oxidation of the chiral allylic alcohols **2** depend not only on the nature and amount of the carboxylic acid co-catalyst but also on the molar equivalents of added H_2O_2 (20−110 mol % with respect to the substrate).

Results

The Mn-tmtacn catalyst[11] **1** and the chiral allylic alcohols **2a**−**f** were prepared according to literature procedures.[12] The oxidations were conducted with a catalytic amount of Mn-tmtacn **1** and 1.1 equiv of hydrogen peroxide in the presence of a co-catalyst. A general procedure is given in the Experimental Section.

The allylic alcohol **2e** with $A^{1,3}$ strain was used as the model substrate to test the reactivity (% conversion of the allylic alcohol **2e**), chemoselectivity (allylic CH oxidation versus epoxidation), and stereoselectivity (*threo* versus *erythro* diastereomers) of the catalyst **1** in the presence of a variety of co-catalysts. In the absence of either the catalyst Mn-tmtacn **1** or the co-catalyst, the allylic alcohol **2e** remained unchanged even after 9 h of exposure to the oxidation conditions. The results for the co-catalysts oxalic acid and ascorbic acid and oxalate and ascorbate buffers are shown in Table 1. The allylic alcohols **2** without allylic strain, with $A^{1,2}$ or $A^{1,3}$ strain, and with both are given in Table 2, for the best set of oxidation conditions determined in Table 1. We shall now briefly focus on the important findings in Tables 1 and 2, by separately considering the reactivity, chemoselectivity, and diastereoselectivity of this oxidation system.

(6) Hage, R.; Iburg, J. E.; Kerschner, J.; Koek, J. E.; Lempers, E. L. M.; Martens, R. J.; Racheria, U. S.; Russell, S. W.; Swathoff, T.; van Vliet, M. R. P.; Warnaar, J. B.; van der Wolf, L.; Krijnen, B. *Nature* **1994**, *369*, 637–639.

(7) (a) De Vos, D.; Bein, T. *J. Chem. Soc., Chem. Commun.* **1996**, *91*, 7–918. (b) De Vos, D.; Bein, T. *J. Organomet. Chem.* **1996**, *520*, 195–200.

(8) (a) De Vos, D. E.; Sels, B. F.; Reynaers, M.; Subba Rao, Y. V.; Jacobs, P. A. *Tetrahedron Lett.* **1998**, *39*, 3221–3224. (b) Berkessel, A.; Sklorz, C. A. *Tetrahedron Lett.* **1999**, *40*, 7965–7968. (c) De Boer, J. W.; Brinksma, J.; Browne, W. R.; Meetsma, A.; Alsters, P. L.; Hage, R.; Feringa, B. L. *J. Am. Chem. Soc.* **2005**, *127*, 7990–7991. (d) De Boer, J. W.; Browne, W. R.; Brinksma, J.; Alsters, P. L.; Hage, R.; Feringa, B. L. *Inorg. Chem.* **2007**, *46*, 6353–6372. (e) De Boer, J. W.; Alsters, P. L.; Meetsma, A.; Hage, R.; Browne, W. R.; Feringa, B. L. *Dalton Trans.*, accepted for publication.

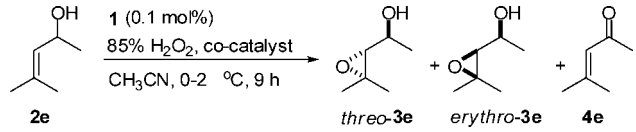
(9) (a) Smith, J. R. L.; Shul'pin, G. B *Tetrahedron Lett.* **1998**, *39*, 4909–4912. (b) Barton, D. H. R.; Choi, S.-Y.; Hu, B.; Smith, J. A. *Tetrahedron* **1998**, *54*, 3367–3378. (c) Barton, D. H. R.; Li, W.; Smith, J. A. *Tetrahedron Lett.* **1998**, *39*, 7055–7058. (d) Shul'pin, G. B.; Süss-Fink, G.; Lindsay Smith, J. R. *Tetrahedron* **1999**, *55*, 5345–5358. (e) Nizova, G. V.; Bolm, C.; Ceccarelli, S.; Pavan, C.; Shul'pin, G. B. *Adv. Synth. Catal.* **2002**, *344*, 899–905. (f) Nizova, G. V.; Shul'pin, G. B. *Tetrahedron* **2007**, *63*, 7997–8001. (g) dos Santos, V. A.; Shul'pina, L. S.; Veghini, D.; Mandelli, D.; Shul'pin, G. B. *React. Kinet. Catal. Lett.* **2006**, *88*, 339–348. (h) Shul'pin, G. B.; Matthes, M. G.; Romakh, V. B.; Barbosa, M. I. F.; Aoyagi, J. L. T.; Mandelli, D. *Tetrahedron* **2008**, *64*, 2143–2152. (i) Shul'pin, G. B.; Süss-Fink, G.; Shul'pina, L. S. *J. Mol. Catal., A: Chem.* **2001**, *170*, 17–34. (k) Woitiski, C. B.; Kozlov, Y. N.; Mandelli, D.; Nizova, G. V.; Schuchardt, U.; Shul'pin, G. B. *J. Mol. Catal. A: Chem.* **2004**, *222*, 103–119. (l) Shul'pin, G. B.; Nizova, G. V.; Kozlov, Y. N.; Arutyunov, V. S.; dos Santos, A. C. M.; Ferreira, A. C. T.; Mandelli, D. *J. Organomet. Chem.* **2005**, *690*, 4498–4504. (m) Mandelli, D.; Steffen, R. A.; Shul'pin, G. B. *React. Kinet. Catal. Lett.* **2006**, *88*, 165–173. (n) Romakh, V. B.; Therrien, B.; Süss-Fink, G.; Shul'pin, G. B. *Inorg. Chem.* **2007**, *46*, 1315–1331. (o) Sibbons, K. F.; Shastri, K.; Watkinson, M. *J. Chem. Soc., Dalton Trans.* **2006**, 645–661. (p) Smith, J. R. L.; Murray, J.; Walton, P. H.; Lowdon, T. R. *Tetrahedron Lett.* **2006**, *47*, 2005–2008. (r) Tanese, S.; Bouwman, E. *Adv. Inorg. Chem.* **2006**, *58*, 29–75.

(10) Gilbert, B. C.; Kamp, N; W, J.; Smith, J. R. L.; Oakes, J. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2161–2165.

(11) Wieghardt, K.; Bossek, U.; Nuber, B.; Weiss, J.; Bonvoisin, J.; Corbella, M.; Vitols, S. E.; Girerd, J. *J. Am. Chem. Soc.* **1988**, *110*, 7398–7411.

(12) (a) Morgan, B.; Oehlshläger, A. C.; Stokes, T. M. *J. Org. Chem.* **1992**, *57*, 3231–3236. (b) Renz, M. Ph.D. Thesis, University of Würzburg, 1996. (c) Adam, W.; Mitchell, C. M.; Paredes, R.; Smerz, A. K.; Veloza, L. A. *Liebigs Ann./Recl.* **1997**, 1365–1369. (d) Fatiadi, A. J. *Synthesis* **1976**, 65–92. (e) House, H. O.; Wilkins, J. M. *J. Org. Chem.* **1978**, *43*, 2443–2454. (f) Chamberlain, P.; Roberts, M. L.; Witham, G. H. *J. Chem. Soc. B* **1970**, 1374–1381. (g) Ho, N. H.; le Noble, W. L. *J. Org. Chem.* **1989**, *54*, 2018–2021. (h) Schalley, C. A.; Schröder, D.; Schwarz, H. *J. Am. Chem. Soc.* **1994**, *116*, 11089–11097.

TABLE 1. Catalytic Oxidation of the Allylic Alcohol 2e by the Mn-tmtacn Catalyst 1 with Hydrogen Peroxide As Oxygen Source in the Presence of Various Co-catalysts[a]



					selectivity[b]	
entry	co-catalyst	H_2O_2 [mol %]	convn[b] [%]	mb[c] [%]	chemo **3**: **4**	diastereo *threo*:*erythro*
1	ascorbic acid	110	66	60	88:12	85:15
2	oxalic acid	110	48	66	91:09	75:25
3	Na ascorbate	110	45	89	91:09	83:17
4	ascorbic acid/Na ascorbate	110	69	60	92:08	85:15
5	oxalic acid/ Na oxalate	110	65	70	91:09	64:35
6[d]	Na ascorbate	110	75	81	92:08	70:30
7	Na ascorbate	50	25	90	54:46	57:43
8	Na ascorbate	20	10	90	40:60	40:60

[a] Stoichiometric amounts: allylic alcohol **2e** (0.67 mmol); catalyst **1** (0.67 μmol, 67 μL of a 0.01 M stock solution in CH_3CN); 85% H_2O_2 (mol % specified in the third column), diluted with 0.4 mL of CH_3CN; co-catalyst (0.225 mol %) in 25 μL of water and 0.5 mL of CH_3CN. [b] Conversion of the allylic alcohol **2e** after complete consumption of the H_2O_2 (determined by the peroxide test). An aliquot was taken of the crude reaction mixture and the conversions and **3**:**4** product ratios were assessed by ^{1}H NMR analysis with 1,3-dichlorobenzene as internal standard; error $\approx \pm 5\%$ of the stated values. [c] Mass balance refers to the characterized products **3** and **4** and recovered allylic alcohol **2e**. [d] A 3-fold amount (0.675 mol %) of the co-catalyst was employed in entry 6, compared to 0.225 mol % used in the other entries.

Reactivity. The catalytic reactivity of the **1**−H_2O_2 system for the oxidation of the allylic alcohol **2e** was studied in the presence of oxalic acid, ascorbic acid, and oxalate and ascorbate buffers as co-catalysts. The results in Table 1 show that the Mn-tmtacn **1**/co-catalyst/hydrogen peroxide combination affords the epoxy alcohol **3e** as a major product. The reactivity of the catalytic system, measured in terms of allylic alcohol conversion, gave at complete H_2O_2 consumption the following order for the various co-catalysts: Na ascorbate (entry 3) ≤ oxalic acid (entry 2) < ascorbic acid (entry 1) ≈ oxalic acid/Na oxalate (entry 5) ≤ ascorbic acid/Na ascorbate (entry 4). Under these conditions, the highest reactivity is displayed by the ascorbic acid/Na ascorbate buffer (69% convn, entry 4), the lowest one by Na ascorbate alone (45% convn, entry 3). An increased catalytic activity was obtained when a 3-fold amount of sodium ascorbate was employed as the co-catalyst (75% convn, entry 6). When, however, the amount of H_2O_2 was reduced (entries 3, 7, and 8), expectedly the % convn dropped drastically.

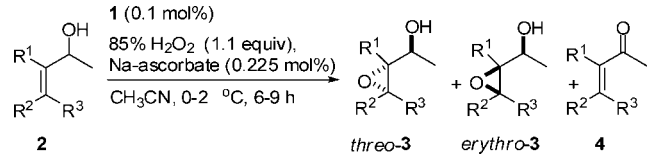
The optimized co-catalyst conditions (Table 1, entry 3) were then applied to the set of allylic alcohols **2a**−**f** (Table 2) to assess the structural effects on the reactivity of the present catalytic system. Depending on the degree and pattern of substitution of allylic alcohols **2a**−**f**, the conversions vary from 40% to 80%. The reactivity of the catalytic system decreases with the degree of substitution of the double bond, e.g., **2f** ≈ **2e** < **2d** ≈ **2c** < **2b** ≈ **2a**. Thus, the higher its degree of methyl substitution, the less reactive the allylic alcohol **2**, with the trimethyl derivative **2f** the least (40% convn, entry 8) and the unsubstituted substrate **2a** the most reactive (80% convn, entry 1). The most pronounced difference in the substitution pattern is exhibited for the monosubstituted pair **2b** (85% convn, entry 2) and **2c** (60% convn, entries 3 and 4).

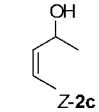
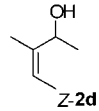
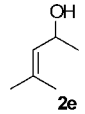
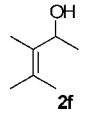
Chemoselectivity. The data reveal a relatively small effect on the chemoselectivity, measured in terms of the **3**:**4** product ratio, in regard to the co-catalyst choice (Table 1) and the structural variation of the allylic alcohols **2** (Table 2). For the model substrate **2e**, the ratio extends from 88:12 for ascorbic acid (Table 1, entry 1) to 92:8 for the ascorbic acid/Na ascorbate buffer (Table 1, entry 4), which is hardly significant since it lies essentially within the experimental error. It should be pointed out, however, that the **3**:**4** product ratio does not remain constant during the progress of the reaction. This is best exemplified by the results for Na ascorbate as co-catalyst (Table 1, entries 3, 7, and 8), in which the initial amount (mol %) of H_2O_2 was varied. Whereas for 100 mol % H_2O_2 (entry 3) the chemoselectivity is 91:9, for 50 mol % (entry 7) it is only 54:46, and for 20 mol % H_2O_2 (entry 8) the ratio even inverts to 40:60. Clearly, the chemoselectivity is a function of the initial amount of H_2O_2 used and, thus, on the reaction progress.

The dependence of the chemoselectivity on the structural variation of the allylic alcohols **2** (Table 2) shows that the corresponding epoxy alcohols **3a**−**f** are formed preferentially in this Mn-catalyzed oxidation of the allylic alcohols **2a**−**f** with H_2O_2; the exception is substrate *E*-**2c** (Table 2, entry 3), for which enone **4** is favored. In this context, mechanistically quite significant is the monosubstituted pair of double-bond diastereomers *E*-**2c** and *Z*-**2c**, for which the *E* isomer selects the *E*-**4c** enone product (entry 3), whereas the *Z* isomer favors in much higher predominance the *threo*-**3c** epoxy alcohol (entry 4). This trend of dependence on the double-bond geometry is also manifested for the diastereomeric pair of disubstituted substrates *E*-**2d** (entry 5) and *Z*-**2d** (entry 6) but is much less pronounced. In fact, the highest chemoselectivity (95:5) is observed for the *Z*-**2d** diastereomer (entry 6).

Diastereoselectivity. The type and amount of co-catalyst (Table 1) affects substantially the diastereoselectivity. The highest *threo*:*erythro* ratio (85:15) in favor of the *threo* diastereomer was obtained for ascorbic acid (entry 1) and the ascorbic acid/Na ascorbate buffer (entry 4) Thus, if *threo* selectivity is desired, of all the co-catalysts examined herein, ascorbic acid or the ascorbic acid/Na ascorbate buffer are the most effective. The *threo* selectivity drops substantially (70:30) when a 3-fold amount of sodium ascorbate (entry 6) is employed. Exceedingly disadvantageous for achieving a high *threo* selectivity is to conduct this oxidation at lower than stoichiometric initial amounts of H_2O_2, (Table 1) as shown in entry 7 (50 mol % H_2O_2) and entry 8 (20 mol % H_2O_2); in fact, the *erythro* isomer is selected in modest preference (40:60) in entry 8.

TABLE 2. Catalytic Oxidation of the Allylic Alcohol 2 by the Mn-tmtacn Catalyst 1 with Hydrogen Peroxide As Oxygen Source in the Presence of Sodium Ascorbate As Co-catalyst[a]

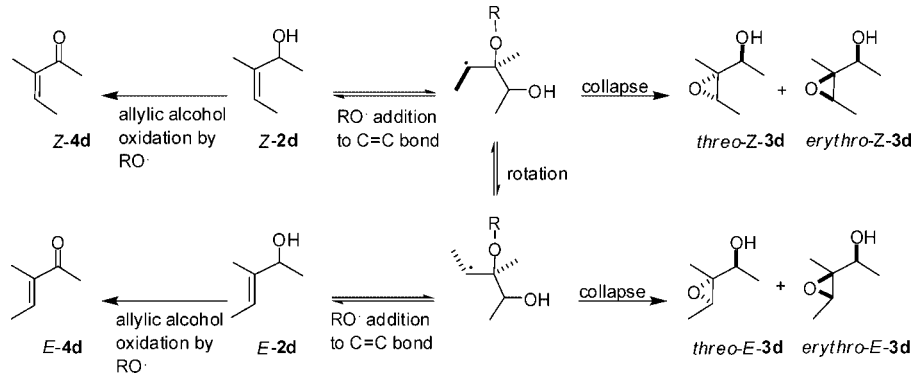


entry	substrate	convn[b] [%]	mb[c] [%]	selectivity[b] chemo **3** : **4**	selectivity[b] diastereo *threo*:*erythro*
1	 **2a**	80	90	80:20	50:50
2	 **2b**	85	95	87:13	50:50
3[d]	 *E*-**2c**	60	79	40:60	45:55
4[e]	 *Z*-**2c**	60	76	90:09	65:35
5[f]	 *E*-**2d**	65	95	81:19	55:45
6[g]	 *Z*-**2d**	55	87	95:05	65:35
7	 **2e**	45	89	91:09	83:17
8	 **2f**	40	85	n.d	83:17

[a] Stoichiometric amounts: allylic alcohol **2** (0.67 mmol); catalyst **1** (0.67 μmol, 67 μL of a 0.01 M stock solution in CH_3CN); 85% H_2O_2 (0.740 mmol), diluted with 0.4 mL of CH_3CN; co-catalyst (0.225 mol %) in 25 μL of water and 0.5 mL of CH_3CN. [b] Conversion of the allylic alcohol **2** after complete consumption of the H_2O_2 (determined by the peroxide test). An aliquot was taken of the crude reaction mixture and the conversions and **3**:**4** product ratios were assessed by ^{1}H NMR analysis with 1,3-dichlorobenzene as internal standard; error $\approx \pm 5\%$ of the stated values. [c] Mass balance refers to the characterized products **3** and **4** plus recovered allylic alcohol **2**. [d] Isomerization (9%) to the epoxy alcohols *threo*-*Z*-**3c** and *erythro*-*Z*-**3c** was observed; the epoxy alcohols **3c** and **3d** are not isomerized under the reaction conditions but are oxidized to the corresponding epoxy enones. [e] Isomerization (3%) to the epoxy alcohols *threo*-*E*-**3c** and *erythro*-*E*-**3c** was observed. [f] Isomerization (11%) to the epoxy alcohols *threo*-*Z*-**3d** and *erythro*-*Z*-**3d** was observed and their subsequent CH oxidation to the ketone *Z*-**4d**. [g] Isomerization (16%) to the epoxy alcohols *threo*-*E*-**3d** and *erythro*-*E*-**3d** was observed.

The structural variation, especially the substitution pattern, discloses a pronounced effect on the diastereoselectivity in the oxidation of the allylic alcohols **2a**−**f** (Table 2). The *threo*:*erythro* ratio varies from 50:50 (no diastereoselection) for the unsubstituted substrate **2a** (entry 1) to a high of 83: 17 for the most substituted derivatives **2e** (entry 7) and **2f** (entry 8), when the oxidation was conducted with sodium ascorbate as co-catalyst. In the latter two cases, the substrates **2e** and **2f** possess allylic strain, namely, $A^{1,3}$ strain for **2e** and both $A^{1,2}$ and $A^{1,3}$ strain for **2f**. Since for both substrates the *threo*:*erythro* ratio is the same (83:17), it is evident that $A^{1,2}$ strain is ineffective in the control of diastereoselection. This stereochemical trend is also displayed by the derivatives **2b** (entry 2, ratio 50: 50) and *E*-**2d** (entry 5, ratio 55: 45) with $A^{1,2}$ but no $A^{1,3}$ strain, since their diastereoselectivity is negligible. Also the diastereomeric pair *E*-**2d** (entry 5, 55: 45) and *Z*-**2d** (entry 6, 65: 35) confirms that $A^{1,2}$ strain is ineffective. The pair of diastereomers *E*-**2c** (entry 3, 45: 55)

SCHEME 1. Proposed Mechanism for the Isomerization of the *E*/*Z*-2d Allylic Alcohols and Formation of the *erythro*/*threo*-*E*/*Z*-3d Epoxy Alcohols and *E*/*Z*-4d Enones



and *Z*-**2c** (entry 4, 65: 35) corroborate these findings, but the control by $A^{1,3}$ strain is modest.

Discussion

The prominent trend displayed in Tables 1 and 2 is the fact that the conversion of the allylic alcohols decreases while the diastereoselectivity rises with the degree of substitution of electron-donating methyl groups at the double bond. Clearly, the allylic alcohols **2e** and **2f**, the most electron-rich substrates, show a lower reactivity. Bein[7] has reported the epoxidation of a series of alkenes with catalyst **1** and hydrogen peroxide and showed that the alkene structure plays an important role in the oxidation rate. For example, 1-methylcyclohexene is known to be more reactive than cyclohexene in the peracid epoxidation, but with the Mn-tmtacn complex **1** and hydrogen peroxide, the reactivity order is reversed. These results show that the more accessible but less electron-rich double bond is more readily oxidized. Presumably, steric repulsion between the catalytically active Mn complexes and the double-bond substituents hinders the transfer of the oxygen atom. Although it is often assumed that the nature of the catalytically active Mn species is of the high-valent oxo-Mn type,[13] recent work on the present system, namely, the combination Mn-tmtacn **1**/carboxylic acid co-catalyst/hydrogen peroxide, has convincingly demonstrated the role of the catalytically active bis(μ-carboxylato)-Mn^{III}_2 complex **A** (see Figure 1).[8c−e] This also holds for the ascorbate and oxalate co-catalysts, both of which not only allow in situ generation of bis(μ-carboxylato)-Mn^{III}_2 complex **A** but also are likely to facilitate reduction of catalyst **1**. Thereby, the catalyst is activated toward ligand exchange to form the catalytically active state.[8e]

The fact that *cis*/*trans* isomerization is observed in the epoxidation of the allylic alcohols *E*-**2c**, *Z*-**2c**, *E*-**2d**, and *Z*-**2d** indicates that at least part of the oxygen-atom transfer proceeds through radical intermediates. The oxygen-atom transfer from H_2O_2, catalyzed by the aforementioned bis(μ-carboxylato)-Mn^{III}_2 complex **A**, is a concerted process without *cis*/*trans* isomerization.[8c−e] It is, thus, likely that the *cis*/*trans* isomerization occurs in the initial phase of the reaction, during which catalyst **1** is transformed into the bis(μ-carboxylato)-Mn^{III}_2 complex **A** by a poorly understood reaction, in which presumably oxyl (RO•) radicals are generated from hydrogen peroxide as active oxygen species. At this point, we have no direct experimental evidence (e.g., EPR spectroscopy) as to the nature of the RO• radicals. We speculate that metal-free (e.g., HOO•) species might intervene as active oxygen entities. Alternatively, high-valent manganese oxo complexes may also be involved in the initial stage of the reaction, en route to the bis(μ-carboxylato)-Mn^{III}_2 formation. As mechanistically implicated in Scheme 1, the intervening substrate-derived C-centered radicals possess sufficient lifetime for substantial C−C bond rotation prior to collapse to the epoxide ring.[14]

We propose that the lack of chemo- and diastereoselectivity, observed initially at low conversion of substrate **2e** (Table 1, entries 7 and 8), may derive from unselective reactions mediated by RO• radicals in this phase of the allylic alcohol oxidation. Once catalyst **1** has been efficiently transformed into bis(μ-carboxylato)-Mn^{III}_2 complex **A**, a selective epoxidation dominates, catalyzed by the latter species. This accounts for the much higher selectivities observed at high conversion of substrate **2e** (see Table 1, entry 3 versus entries 7 and 8). The fact that the diastereoselectivity for the substrate **2e** varies with different carboxylate co-catalysts (Table 1) is in line with the role of bis(μ-carboxylato)-Mn^{III}_2 complex **A** as catalytically active species.

Hard to rationalize are the widely varying chemo- and diastereoselectivities as a function of the allylic alcohol structure. The fact, nevertheless, that the *threo* diastereoselectivity dominates in the epoxidation of the allylic alcohols *Z*-**2c** and *Z*-**2d** indicates that hydrogen bonding operates between the allylic hydroxy group and the manganese complex in the oxygen-transfer process. Therefore, in the absence of any further experimental evidence, we suggest the transition-state geometry **B** (Figure 2) for the oxygen transfer from complex **A** (Figure 1) to the allylic alcohol *Z*-**2c**, to account for the observed *threo* selectivity.

Conclusion

The current experimental results in Tables 1 and 2 reveal that the chemo- and diastereoselectivities in the epoxidation of

(13) (a) Smith, J. R. L.; Gilbert, B. C.; Mairata i Payeras, A.; Murray, J.; Lowdon, T. R.; Oakes, J.; Pons i Prats, R.; Walton, P. H. *J. Mol. Catal. A: Chem.* **2006**, *251*, 114–122. (b) Groves, J. T.; Lee, J.; Marla, S. S. *J. Am. Chem. Soc.* **1997**, *119*, 6269–6273. (c) Bennur, T. H.; Srinivas, D.; Sivasanker, S.; Puranik, V. G. *J. Mol. Catal. A: Chem.* **2004**, *219*, 209–216. (d) Bennur, T. H.; Sabne, S.; Deshpande, S. S.; Srinivas, D.; Sivasanker, S. *J. Mol. Catal. A: Chem.* **2002**, *185*, 71–80. (e) Gilbert, B. C.; Smith, J. R. L.; Mairata i Payeras, A.; Oakes, J. *Org. Biomol. Chem.* **2004**, *2*, 1176–1180.

(14) (a) Jacobsen, E. N.; Deng, L.; Furukawa, Y.; Martinez, L. E. *Tetrahedron* **1994**, *50*, 4323–4334. (b) McGarrigle, E. M.; Gilheany, D. C. *Chem. Rev.* **2005**, *105*, 1563–1602.

chiral allylic alcohols **2** with hydrogen peroxide as oxygen donor, catalyzed by the Mn-tmtacn catalyst **1** plus carboxylic acid co-catalysts, vary during the course of the reaction. Moreover, the observed diastereoselectivity for the substrates with 1,3-allylic strain depends on the amount and nature of the co-catalyst. We postulate that the enhanced selectivities with progressing conversion arises from the transformation of catalyst **1** into the more selective bis(μ-carboxylato)-Mn^{III}_2 complex **A**. In the initial phase, this process is accompanied by the generation of oxygen-centered radical species, which are responsible for the less selective oxidations. Additional experiments should be helpful in clarifying our mechanistic speculations, especially the involvement of radicals. Further mechanistic understanding of the various selectivities would enable optimizing the synthetic value of this attractive catalytic oxidation.

Experimental Section

Typical Procedure for the Catalytic Epoxidation of the Allylic Alcohols Manganese Complexes 1 and Hydrogen Peroxide. Into a 5-mL, two-necked, round-bottomed flask equipped with a thermostat and magnetic stirrer were placed 0.5 mL of CH_3CN, 0.67 mmol allylic alcohol, 76.3 μL (0.67 mmol) of 1,3-dichlorobenzene (as internal standard), 67 μL of stock solution of catalyst **1** (1 μmol/100 μL in CH_3CN), and co-catalyst as specified in Tables 1 and 2 in 25 μL of water. The reaction was initiated by addition of 0.4 mL of CH_3CN containing hydrogen peroxide (85%, 20 μL, 0.737 mmol) with the aid of a syringe within the time specified in Tables 1 and 2 at 0−2 °C, while the reaction progress was monitored by peroxide test (KI/AcOH). After completion of the reaction, the reaction mixture was diluted with 3 mL of CH_2Cl_2, dried over Na_2SO_4, and passed through a short silica gel column (150 mg). The solvent was removed under reduced pressure (25 °C, 450 Torr), and the conversion, mass balance, and chemo- and diastereoselectivities were determined by ^{1}H NMR analysis directly on the crude mixture (Tables 1 and 2). The epoxy alcohols **3a**−**f** and ketones **4a**−**f** are literature known and have been identified on the basis of their NMR data.

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Supporting Information Available: Characterization data for the epoxy alcohols **3a**−**f** and structure matrix. This material is available free of charge via the Internet at http://pubs.acs.org.

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