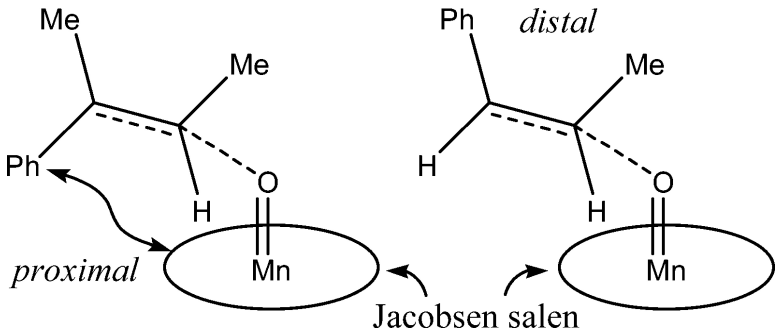
Article

Probing Competitive Enantioselective Approach Vectors Operating in the Jacobsen–Katsuki Epoxidation: A Kinetic Study of Methyl-Substituted Styrenes

Peter Fristrup, Brian B. Dideriksen, David Tanner, and Per-Ola Norrby

J. Am. Chem. Soc., **2005**, 127 (39), 13672-13679• DOI: 10.1021/ja051851f • Publication Date (Web): 13 September 2005



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 2 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
ARTICLES
Published on Web 09/13/2005

Probing Competitive Enantioselective Approach Vectors Operating in the Jacobsen−Katsuki Epoxidation: A Kinetic Study of Methyl-Substituted Styrenes

Peter Fristrup, Brian B. Dideriksen, David Tanner, and Per-Ola Norrby*

Contribution from the Department of Chemistry, Technical University of Denmark, Building 201 Kemitorvet, DK-2800 Kgs. Lyngby, Denmark

Received March 23, 2005; E-mail: pon@kemi.dtu.dk

Abstract: This paper describes a study of reactivity and enantioselectivity for a series of methyl-substituted styrenes in the Jacobsen−Katsuki (Mn(salen)-catalyzed) epoxidation reaction. Competition experiments provided kinetic data for the reactivity of the seven possible methyl-substituted styrenes (mono-, di- and trisubstituted) relative to styrene itself, ee values were measured by chiral GC, and absolute configurations were secured by chemical correlation. Of particular interest was the switch in absolute configuration at the benzylic position of the epoxides derived from (*Z*)- and (*E*)-α,β-dimethylstyrene, respectively. The results could be rationalized in terms of an approach vector with the phenyl substituent proximal to the salen. As opposed to alkyl groups, a proximal phenyl group has very little effect on the rate of the reaction. Consideration of distal vs proximal approach allows prediction of absolute stereochemistry as a function of alkene substitution pattern. Trisubstituted alkenes with one phenyl group cis to the alkene hydrogen can be identified as a favored substrate class in the title reaction, with both rate and selectivity close to the classic (*Z*)-β-substituted styrene substrates.

Introduction

Epoxides have fittingly been described as being "one of the main muscles" of organic synthesis,[1] since a wide range of regio- and stereoselective ring opening reactions are available[2] for the conversion of epoxides to useful (chiral) intermediates. In addition, the epoxide ring is an important structural element in the pharmacophores of certain bioactive natural products, e.g., dynemicin A,[3] neocarzinostatin,[4] and the epothilones.[5] Practical and general methods for the enantioselective epoxidation of prostereogenic alkenes are thus highly desirable, and the first major breakthrough came in the early 1980s with the discovery and development of the Sharpless titanium-catalyzed asymmetric epoxidation of allylic alcohols.[6] This prompted an ongoing search for other catalyst systems capable of the enantioselective epoxidation of "nonfunctionalized" alkenes, i.e., substrates lacking a functional group capable of preorganizing the catalyst. Significant recent advances toward this challenging goal include the development of chiral (salen)-metal[7] or chiral (porphyrin)-metal catalyst systems,[8] as well as methodology based on chiral dioxiranes.[9] Of these methods, the Jacobsen−Katsuki [Mn-(salen)]-catalyzed epoxidation reaction in particular has enjoyed increasing use in target-oriented synthesis.[10] As for any catalytic system, rational development of even better protocols for enantioselective epoxidation will rely, at least in part, on information garnered from mechanistic[11,12] and theoretical

(1) Seebach, D.; Weidmann, B.; Wilder, L. In *Modern Synthetic Methods, 1983*; Scheffold, R., Ed.; Otto Salle Verlag: Frankfurt, 1983; p 323.
(2) For reviews, see: (a) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421. (b) Taylor, S. K. *Tetrahedron* **2000**, *56*, 1149. (c) Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437. (d) Pfenninger, A. *Synthesis* **1986**, 89. (e) Behrens, C. H.; Sharpless, K. B. *Aldrichimica Acta* **1983**, *16*, 67.
(3) Tokiwa, Y.; Miyoshi-Saitoh, M.; Kobayashi, H.; Sunaga, R.; Konishi, M.; Oki, T.; Iwasaki, S. *J. Am. Chem. Soc.* **1992**, *114*, 4107.
(4) Edo, K.; Mizugaki, M.; Koide, Y.; Seto, H.; Furihata, K.; Otake, N.; Ishida, N. *Tetrahedron Lett.* **1985**, *26*, 331.
(5) Höfle, G.; Bedorf, N.; Steinmetz, H.; Schomburg, D.; Gerth, K.; Reichenbach, H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1567.
(6) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) For a review, see: Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 6A.
(7) (a) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (b) Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron Lett.* **1990**, *31*, 7345. (c) Katsuki, T. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 6B. (d) Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: 1999; Chapter 18.2.
(8) (a) Collman, J. P.; Zhang, X. M.; Lee, V. J.; Uffelman, E. S.; Brauman, J. I. *Science* **1993**, *261*, 1404. (b) Groves, J. T.; Viski, P. *J. Org. Chem.* **1990**, *55*, 3628.
(9) (a) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488. (b) Adam, W.; Saha-Möller, C. R.; Zhao, C.-G. *Org. React.* **2002**, *61*, Chapter 2.
(10) For examples, see (a) Nicolaou, K. C.; Safina, B. S.; Funke, C.; Zak, M.; Zécri, F. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1937. (b) Yoshida, M.; Ismail, M. A.-H.; Nemoto, H.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2629. (c) Chen, Y.; Evarts, J. B., Jr.; Torres, E.; Fuchs, P. L. *Org. Lett.* **2002**, *4*, 3571. (d) Coleman, R. S.; Garg, R. *Org. Lett.* **2001**, *3*, 3487.
(11) (a) Engelhardt, U.; Linker, T. *Chem. Commun.* **2005**, 1152. (b) Linde, C.; Koliai, N.; Norrby, P. O.; Åkermark, B. *Chem.—Eur. J.* **2002**, *8*, 2568. (c) Adam, W.; Roschmann, K. J.; Saha-Moller, C. R.; Seebach, D. *J. Am. Chem. Soc.* **2002**, *124*, 5068. (d) Adam, W.; Mock-Knoblauch, C.; Saha-Moller, C. R.; Herderich, M. *J. Am. Chem. Soc.* **2000**, *122*, 9685. (e) Palucki, M.; Finney, N. S.; Pospisil, P. J.; Guler, M. L.; Ishida, T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 948. (f) Linde, C.; Arnold, M.; Norrby, P. O.; Åkermark, B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1723. (g) Finney, N. S.; Pospisil, P. J.; Chang, S.; Palucki, M.; Konsler, R. G.; Hansen, K. B.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1720. (h) Feichtinger, D.; Plattner, D. A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1718. (i) Jacobsen, E. N.; Deng, L.; Furukawa, Y.; Martinez, L. E. *Tetrahedron* **1994**, *50*, 4323.
(12) (a) Brandt, P.; Norrby, P. O.; Daly, A. M.; Gilheany, D. G. *Chem.—Eur. J.* **2002**, *8*, 4299. (b) Feichtinger, D.; Plattner, D. A. *Chem.—Eur. J.* **2001**, *7*, 591.

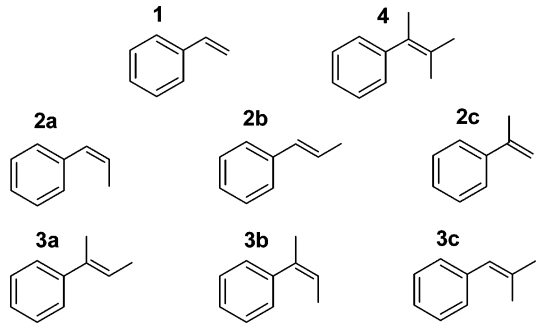
10.1021/ja051851f CCC: $30.25

Table 1. Relative Kinetics in the Jacobsen−Katsuki Epoxidation for the Eight Alkenes under Investigation along with Measured Enantio- and Diastereoselectivities

entry	alkene	major product	relative reactivity[a]	ee epoxide	absolute configuration[b]	diastereomeric ratio (dr)
1	**1**	**5**	1.00	53%	(*R*)	
2	**2a**	**6a**	0.75	89%	(*R*)	10.3[c]
3	**2b**	**6b**	0.39	25%	(*R*)	72.2[d]
4	**2c**	**6c**	0.63	54%	(*S*)	
5	**3a**	**7a**	0.67	73%	(*S*)	∼500[e]
6	**3b**	**7b**	0.100	71%	(*R*)	5.3[f]
7	**3c**	**7c**	0.059	61%	(*R*)	
8	**4**	*g*	0.079[g]	<5%		

[a] The correlation coefficient was larger than 0.995 in all cases. [b] At the benzylic position the presence or absence of a methyl group in the α-position does not change the sequence in the Cahn−Ingold−Prelog system, so (*R*) indicates the same sense of chirality throughout. [c] The ee of the diastereomeric epoxide **6b** was 73%, and the configuration was (*S*). [d] The high dr resulted in very small amounts of the diastereomeric epoxide, and the ee could not be determined accurately. [e] Only the major enantiomer of the diastereomeric epoxide was detected. [f] The ee of the diastereomeric epoxide **7a** was 31%, and the configuration was (*S*). [g] Mostly to non-epoxide products.

Chart 1. Structures of the Eight Styrenes Investigated



studies.[12,13] In this paper, we present the results of a reactivity/selectivity investigation of the Jacobsen−Katsuki epoxidation, based on kinetic studies of a series of methyl-substituted styrenes, as part of an effort to understand the factors responsible for the orientation of the substrate in the proposed transition state for the reaction.

Our starting point was the large difference in enantioselectivity observed (see ref 7a and Table 1, entries 2 and 3) for the epoxidation of (*Z*)- and (*E*)-*β*-methylstyrene, respectively. We therefore chose to investigate the set of eight alkenes shown in Chart 1, to systematically probe the effects of methyl substitution by determination of (i) reactivity relative to that of styrene itself in competition experiments, (ii) enantioselectivity and absolute configuration, and (iii) diastereoselectivity in cases where epimerization could be observed (**2a,b**, **3a,b**).

Results and Discussion

All the alkenes **1**−**4** could be separated using GC (for retention times, see Supporting Information, Table S1), allowing determination of the relative concentrations at various levels of conversion in competition experiments. With the concentrations of styrene and the relevant methyl-substituted styrene in hand, the relative reactivity of the two substrates could be determined, assuming a first-order reaction in each styrene and identical reaction orders in other reactants (eq 1; A and B are the concentrations of the two competing substrates, with subscript "0" indicating initial concentration).

$$\ln\left(\frac{A_0}{A}\right) = k_{\text{rel}} \ln\left(\frac{B_0}{B}\right) \tag{1}$$

Each reaction was first performed on the isolated alkene, and the formation of epoxide was followed by chiral GC using *n*-decane as internal standard. After workup, pure epoxides were obtained by flash chromatography. Racemic epoxides were synthesized separately (see Experimental Section), and the GC burn ratios compared to *n*-decane were established. In this way the selectivity of the epoxidation could be determined for each alkene individually (Table 1).

The GC conditions used (see Experimental Section for details) also allowed an estimation of the mass balance during the competition experiments. The initial competition experiments were performed under conditions identical to those of the preparative reactions, except for the use of equimolar quantities of styrene and the alkene under investigation. Of the eight alkenes (Chart 1), styrene was the fastest reacting substrate and its relative reactivity was set to unity. This first set of competition experiments gave satisfactory results for all three monomethyl-substituted alkenes **2a**−**c** and one of the dimethyl-substituted alkenes (**3a**). The data from these kinetic experiments were plotted according to eq 1, yielding a straight line for each competition experiment, as expected (Figure 1).

As shown in Table 1 (entries 2−4) the relative reactivities of **2a**−**c** were 0.75, 0.39, and 0.63, respectively, and in all three cases the correlation was excellent, with $r^2 > 0.999$. Interestingly, the dimethyl-substituted **3a** was the third-fastest reacting alkene (relative reactivity 0.67, $r^2 = 0.997$) of all the substrates tested (Table 1, entry 5).

The two remaining dimethyl-substituted styrenes **3b** and **3c** were subjected to identical competition experiments with styrene, and the initial results obtained within 30 min indicated relative reactivities of 0.10 and 0.06, respectively. However, the plot was not linear during the entire run, and both compounds were therefore subjected to new competition experiments involving the slower-reacting **2b**. The measured slopes were 0.26 and 0.15, and correcting for the reactivity of **2b** itself, one again obtains relative reactivities of 0.10 and 0.06 for **3b** and **3c**, respectively, but now with increased accuracy (Table 1, entries 6 and 7; $r^2 = 0.997$ and 0.996, respectively).

Tetrasubstituted alkene **4** was very unreactive in the standard preparative asymmetric epoxidation procedure (only 24% conversion after 3 h), and only minor amounts of the epoxide could be isolated, due to degradation of the reactant and product under the reaction conditions. In the competition experiment, **4** was epoxidized together with **2b** and the reactivity of **4** relative to styrene was calculated to 0.09 with $r^2 = 0.995$ (Table 1, entry 8), but again only minor amounts of the epoxide could be detected. The plot for epoxidation of alkenes **3b**, **3c**, and **4** in competition with **2b** is shown in Figure 2.

The relative rates, *ee* values for the major product from each run (except for epoxidation of styrene **4**), and diastereomeric ratios for nonstereospecific reactions are collected in Table 1.

(13) (a) Cavallo, L.; Jacobsen, H. *Inorg. Chem.* **2004**, *43*, 2175. (b) Abashkin, Y. G.; Burt, S. K. *Org. Lett.* **2004**, *6*, 59. (c) Khavrutskii, I. V.; Musaev, D. G.; Morokuma, K. *J. Am. Chem. Soc.* **2003**, *125*, 13879. (d) Cavallo, L.; Jacobsen, H. *J. Org. Chem.* **2003**, *68*, 6202. (e) Jacobsen, H.; Cavallo, L. *Chem.—Eur. J.* **2001**, *7*, 800. (f) El Bahraoui, J.; Wiest, O.; Feichtinger, D.; Plattner, D. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2073. (g) Cavallo, L.; Jacobsen, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 589. (h) Abashkin, Y. G.; Collins, J. R.; Burt, S. K. *Inorg. Chem.* **2001**, *40*, 4040. (i) Strassner, T.; Houk, K. N. *Org. Lett.* **1999**, *3*, 419.

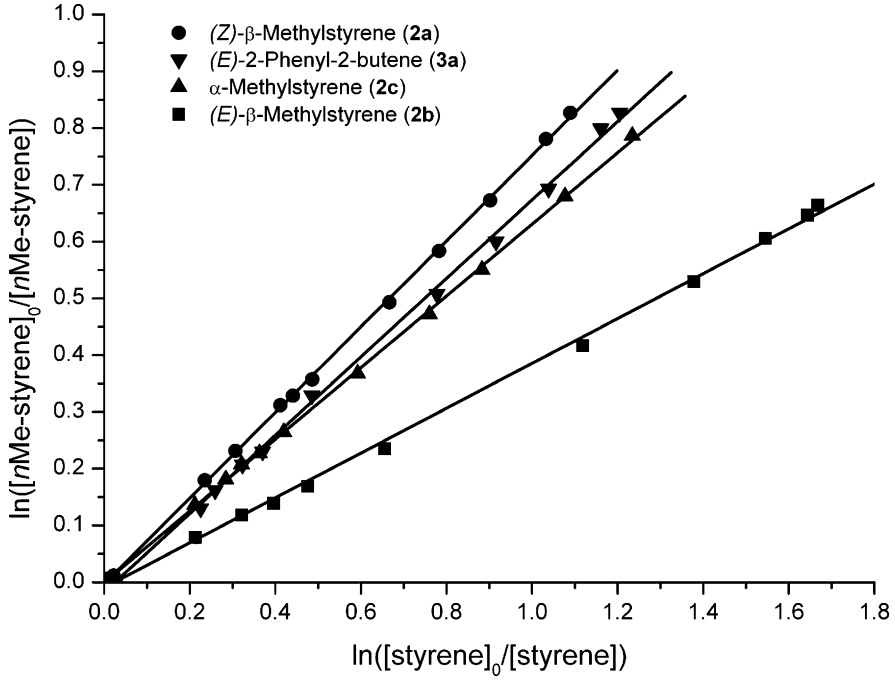


Figure 1. Results from the epoxidations of **2a**−**c** and **3a** in competition with styrene.

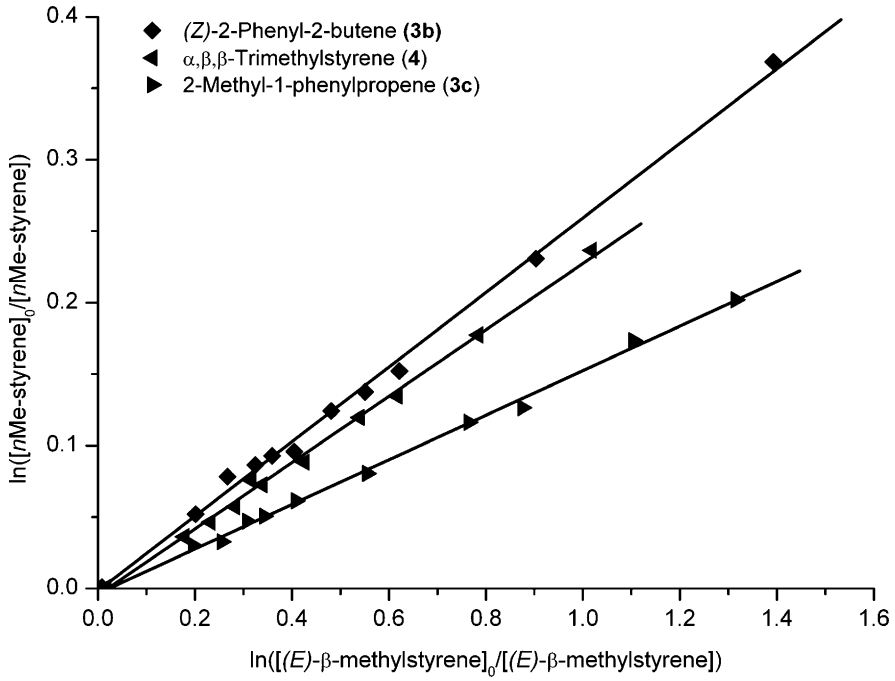


Figure 2. Results from the epoxidations of **3b**−**c** and **4** in competition with (*E*)-*β*-methylstyrene (**2b**).

With these data in hand, our next task was assignment of the absolute configuration of the major products **5**−**7** (Chart 2). For **5**, absolute configuration was assigned by comparison with a commercially available sample (Sigma-Aldrich), while **6a** could be assigned by comparison with literature data (see ref 7a). For **6b**, **6c**, and **7b** we relied on chemical correlation with epoxides derived from chiral 1,2-diols which were themselves the products of Sharpless asymmetric dihydroxylation of alkenes **2b**, **2c**, and **3a**, respectively (see Experimental Section for details). Finally, the absolute configurations of **7a** and **7c** were assigned by comparison with the products of Shi asymmetric epoxidation[14] of alkenes **3a** and **3c**, respectively.

From the results in Table 1, no simple correlation between reactivity and selectivity is immediately obvious, and no trends could be discerned in a plot of selectivity (measured as % *ee* for the major product) as a function of relative rate in competition with styrene (Figure 3). However, we note that if the classical side-on approach vector is postulated,[15] the major enantiomer always comes from an approach where at least one alkene hydrogen points toward the salen ligand.[16] For the trisubstituted substrates **3a**−**c** as well as the *cis*-disubstituted

(14) Tu, Y.; Wang, Z. X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806.
(15) Groves, J. T.; Nemo, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 5786.
(16) Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378.

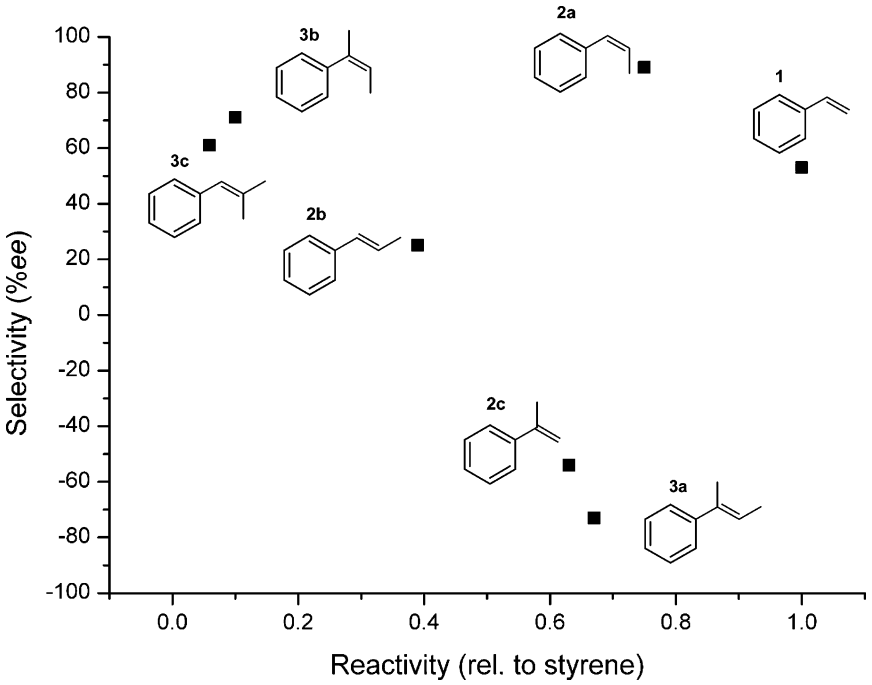
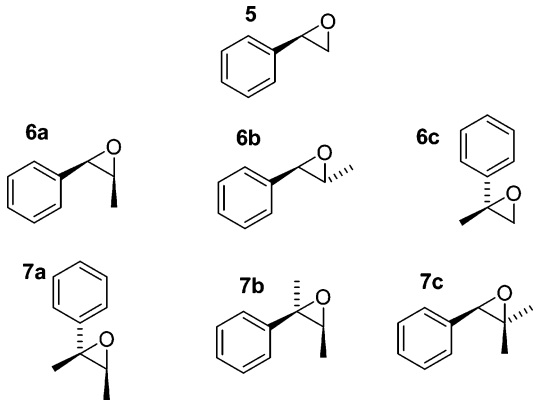


Figure 3. Selectivity (measured as %ee) plotted against the relative reactivity (measured in competition with styrene). Positive ee values denote formation of the (*R*)-configuration at the benzylic position as the major product, and negative ee values, the (*S*)-configuration.

Chart 2. Seven Epoxides Detected as the Expected Major Products from the Epoxidation Reaction of Alkenes **1**−**3** with the (*R,R*)-Configured Jacobsen's Catalyst[a]



[a] Trimethylstyrene (**4**) did not yield significant amounts of epoxide under these reaction conditions.

substrate **2a** (Table 1, entries 2 and 5−7), this condition is sufficient to predict the absolute sense of chirality, as already shown for related systems by the groups of Jacobsen[16] and of Katsuki.[17] However, the relative *reactivity* of the substrates is still puzzling. In the earlier studies, trisubstituted alkenes were assumed to be less reactive than *cis*-disubstituted ones,[16,17] whereas, in the current study, the rate of epoxidation of substrate **3a** is comparable to that of the favored substrate **2a** (Table 1, entries 2 and 5). Furthermore, the switch in absolute sense of chirality between **2b** and **2c** (Table 1, entries 3 and 4), which both would be required to point either a methyl group or a phenyl group toward the salen, requires a more detailed consideration of the steric influences of the substituents on the possible approach vectors. New trends become apparent if the data from Table 1 are converted to rankings of relative rates for formation of the (*R*) and (*S*) configuration, respectively, at the benzylic position of each chiral epoxide (see Table 2).

From the selectivities and reactivities shown in Table 1 and Figure 3, the isolated reactivity leading to the two enantiomeric products can be calculated as follows (ee in %, $-100 \leq \text{ee} \leq 100$):

$$r_{tot} = r_R + r_S$$

$$r_R = r_{tot}(100 + \text{ee})/200$$

$$r_S = r_{tot} - r_R$$

In Table 2 we have listed the isolated reactivities to either enantiomer for each substrate, relative to the total reactivity for styrene.

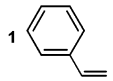
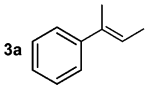
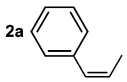
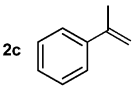
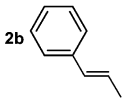
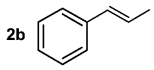
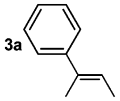
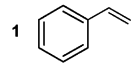
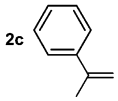
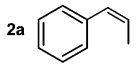
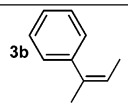
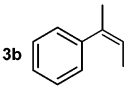
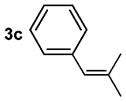
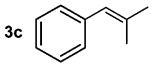
On the basis of the data shown in Tables 1 and 2, we will now attempt to reconcile our results with previous mechanistic suggestions concerning the Jacobsen−Katsuki reaction, with particular emphasis on the mode of approach of the alkene to the chiral metal-oxo complex. It is now generally accepted[18,19] that the Jacobsen−Katsuki epoxidation can proceed by at least two competing pathways (concerted or radical, the latter being invoked to explain the nonstereospecificity observed for a number of substrates); however, irrespective of the pathway taken, the transition state is held to be asynchronous,[11b] with an initial reaction at the β-carbon of styrene derivatives. High steric bulk at the β-position (dimethyl-substitution) would thus be expected to retard the rate irrespective of which enantiomer of the epoxide is being formed (Table 1, entry 7; Table 2, entries 7 and 14).

Several approach vectors have been suggested in the literature, differing in which part of the salen ligand is interacting with the substrate.[7c,d,13,20,21] The various suggestions have been

(17) Fukuda, T.; Irie, R.; Katsuki, T. *Synlett* **1995**, 197.

(18) For a review, see: Limberg, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5932.
(19) McGarrigle, E. M.; Gilheany, D. G. *Chem. Rev.* **2005**, *105*, 1563.

Table 2. Isolated Reactivities Leading to Either (*R*)- or (*S*)-configuration at the Benzylic Position

Entry	Structure	Rate to *(R)*-enantiomer	Entry	Structure	Rate to *(S)*-enantiomer
1		0.77	8		0.58
2		0.71	9		0.30
3		0.39	10		0.24
4		0.09	11		0.24
5		0.09	12		0.04
6		0.09	13		0.01
7		0.05	14		0.01

evaluated in a recent review.[19] The common denominator, derived from earlier work using porphyrin ligands,[15] is that the alkene approaches side-on, which in combination with the requirement of initial attack at the β-position yields four possible orientations for styrenes (Figure 4). Of these, the large majority

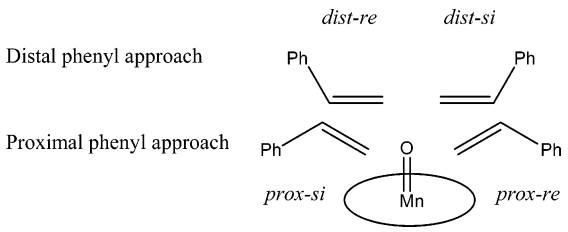


Figure 4. Illustration of the distal phenyl and proximal phenyl approach vectors.

of published approach vectors have used the orientation that we term "distal", but both of the groups of Jacobsen[16] and Katsuki[17] have also suggested that trisubstituted alkenes can add with a phenyl substituent pointing toward the salen (here termed "proximal" approach) when such an approach avoids the more serious penalty of pointing two substituents toward the salen.

Separating the approaches into "distal" and "proximal" paths, we can see that the enantioselectivity is dependent on the preference for either of these paths, as well as on the inherent selectivity of each path. With the enantiomer of the metal-oxo complex employed here the paths to the right in Figure 4 are disfavored, so that the distal path leads predominantly to the (*R*)-configuration at the benzylic position of the epoxide. This approach can be highly enantioselective (Table 1, entry 2) but can be blocked to a large extent by an α-methyl substituent (Table 2, entries 4−6). A β-methyl substituent has negligible effect on the distal approach when pointing away from the salen (cis to the phenyl substituent) but reduces the reaction rate by approximately a factor of 2 when pointing toward the salen (trans). For substrates with an α-methyl, further methyl substitution at the β-position seems to have very little effect (Table 2, entries 4 and 6).

The proximal phenyl path has previously only been considered as a least-hindered approach for trisubstituted alkenes in catalytic epoxidation,[16,17] but the importance of stabilizing interactions between two aryl moieties for the selectivity in catalytic oxidations has been amply demonstrated for the Sharpless asymmetric dihydroxylation reaction.[22] Assuming that the approach orientation of the alkene itself is similar to that for the distal vector, the proximal vector should lead predominantly to the (*S*)-configuration at the benzylic position of the

(20) Dalton, C. T.; Ryan, K. M.; Wall, V. M.; Bousquet, C.; Gilheany, D. G. *Top. Catal.* **1998**, *5*, 75.
(21) Katsuki, T. *Adv. Synth. Catal.* **2002**, *344*, 131.
(22) (a) Fristrup, P.; Tanner, D.; Norrby, P. O. *Chirality* **2003**, *15*, 360. (b) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278.

epoxide, in good agreement with the data in Table 2. We propose that this path is essentially blocked (sterically) for substrates such as **2a** and **3b** with a β-methyl cis to the phenyl (Table 2, entries 12 and 13) but is the major or even exclusive pathway for substrate **3a**, where the opposite alkene side is blocked by two substituents (Table 2, entry 8). If it is assumed that **2a** reacts exclusively by the distal phenyl path, and **3a** exclusively by the proximal path, the ee values in Table 1 (entries 2 and 5) can be taken as a measure of the "inherent" enantioselectivity of each pathway (89% for distal vs 73% for proximal). Styrene itself should be able to react via both pathways, and the data in Table 2 (entries 1 and 11) indicate an approximately 3-fold difference in rate, in favor of the distal approach. A β-methyl substituent trans to the phenyl group has no measurable effect on the proximal path (Table 2, entries 10 and 11) but provides a weak inhibition of the distal phenyl path (Table 2, entries 1 and 3), leading to an almost complete loss of enantioselectivity for **2b** in the traditional Jacobsen system (Table 1, entry 3).[7a]

The Mn(salen)-catalyzed epoxidation is known to be a strongly electrophilic reaction[7c,7d,11b,e,g,h] and, thus, would be expected to be accelerated by the electron-donating methyl substituents. For the distal path, the observed effect is instead a retardation, due either to the steric blocking that has already been discussed or to loss of conjugation, which penalizes the transition state more than the ground state. The latter effect is implied from the result for **2a** (Table 2, entry 2), which reacts slightly slower than styrene itself (Table 2, entry 1), despite the higher electron density. For the proximal path on the other hand, it is clear that α-methyl substitution increases the reactivity (Table 2, entries 8 and 9), probably due to a pure inductive effect and lack of steric blocking. The inductive effect is strong enough to overcome most of the penalty incurred by a proximal phenyl group. As a result, the dimethyl-substituted styrene **3a** reacts through the proximal path with a rate rivaling the two substrates that are unhindered in the distal path, **1** and **2a**, whereas the two trisubstituted alkenes that have to react with a methyl group pointing toward the salen are much slower (**3b** and **3c**, Table 1, entries 6 and 7).

The epoxidation reaction is fairly stereospecific under the conditions employed here, in no case yielding more than 20% epimerized product. There is a clear consensus that epimerized products are produced through bond rotation in a radical intermediate,[7c,d] strongly supported by the observation that epimerization is completely suppressed in substrates substituted with a radical trap.[11f] There are also strong indications that the radical intermediate is produced as a side path and that the main reaction under the conditions employed here proceeds through a concerted, asynchronous TS.[11b,f] However, for the part of the reaction proceeding through a radical intermediate, the epoxide ring formation can occur either with or without epimerization of the benzylic stereocenter. For the four substrates where we can measure epimerization, the β-monomethyl-substituted styrenes **2a**−**b** and **3a**−**b**, the diastereomeric ratios can be used to judge the relative propensity of the radical intermediates for bond rotation. For (*Z*)-β-methyl styrene (**2a**), bond rotation in the radical leads to the (*E*)-configured intermediate, which is favored energetically, and this accounts for the observed high degree of epimerization, approximately 10%. In the case of (*E*)-β-methylstyrene (**2b**) the radical would isomerize to a less favored intermediate, and in this case the stereospecificity is high, ca. 70:1. For the two dimethyl-substituted styrenes (**3a** and **3b**), the difference in energy between (*E*)- and (*Z*)-configuration is much smaller (the β-methyl is cis to either a methyl or a phenyl), so for these substrates the stabilization of the radical by noncovalent interactions with the salen is expected to be more important. For substrate **3a** the intermediate radical is already stabilized in the proximal phenyl approach, and consequently the propensity to isomerization is low, resulting in our highest observed stereospecificity, about 500:1. For alkene **3b** both possible approaches are subject to steric hindrance, but entry through the distal path followed by isomerization in the intermediate radical can provide stabilization by orienting the phenyl in a position proximal to the salen, leading to our highest observed epimerization, almost 20% (5:1).

Summary and Conclusions

Differences in selectivity and reaction rate in the Jacobsen−Katsuki epoxidation of a range of methyl-substituted styrenes have been rationalized as arising from a competition of approach vectors with opposite enantiomeric preference at the benzylic position. One vector (termed "distal") corresponds to most earlier proposals of approaches, whereas a less frequently invoked approach with the phenyl group coming in close to the salen is termed "proximal". The effect of styrene substitution on the rate through each of these vectors has been elucidated.

The current results also allow identification of the factors needed for vector switching in the epoxidation reaction. Styrenes with (*E*)-α,β-dialkyl substitution will not be able to react via a distal approach and will therefore give high selectivities, but with an opposite sense of chiral induction at the benzylic center relative to that expected for the "classical" (*Z*)-β-alkyl-styrene substrates and with a comparable rate. For a styrene to be a favored substrate in the Jacobsen−Katsuki epoxidation, in the sense that it should react both fast and with high enantioselectivity, one side must be blocked by two substituents, whereas the other side can accept a phenyl but not an alkyl substituent. All styrene substitution patterns except the two favored ones give either lower selectivity, lower reactivity, or both.

Experimental Section

Glassware was dried in an oven at 140 °C. Dichloromethane, *n*-hexane, and *n*-pentane were purchased from LabScan (HPLC grade) and were used as received. Diethyl ether was from Bie & Berntsen and used as received. (*R*,*R*)-(−)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride, α-methylstyrene, (*E*)-β-methylstyrene, styrene oxide, (*R*)-(+)-styrene oxide, 2-bromo-3-methyl-2-butene, and *n*-decane were purchased from Aldrich and used as received. (*Z*)-β-Methylstyrene was purchased from TCI (Japan) and used as received. GC was performed on a Shimadzu GC-2010 equipped with an AOC-20i autosampler for 12 samples. Procedure A: Chrompack CP Chirasil-Dex CB 0.25 mm × 25 m column and temperature program, which was 90 °C for 20 min followed by a ramp (20 °C/min) to 180 °C which was kept for 15.50 min. Styrene oxide and α-methylstyrene oxide were analyzed using procedure B: Supelco β-Dex 120 0.25 mm × 30 m column and temperature program was 100 °C for 20 min followed by a ramp (20 °C/min) to 180 °C which was kept for 15.50 min.

General Procedure for Preparative Epoxidations: The olefin under investigation (1.0 mmol) and *n*-decane (0.5 mmol, 71 mg) were dissolved in dichloromethane (1 mL) and cooled to 0 °C. After mixing, the first sample (20 μL) was withdrawn and diluted to 1.5 mL with

diethyl ether. (*R*,*R*)-(−)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride (0.04 mmol, 26 mg) was added to the reaction vessel, and a precooled (0 °C) aqueous solution of NaOCl (∼0.55 M, 3.5 mL) was added. 20 μL samples of the organic phase were withdrawn after 1, 30, 60, 120, and 180 min, each time with stirring stopped briefly to allow phase separation. The sample was filtered through 1 cm of silica using 1.5 mL of diethyl ether and analyzed by chiral GC. After 3 h the reaction mixture was diluted with hexane (25 mL), and the phases separated. The organic phase was washed once with H_2O (30 mL) and twice with brine (30 mL), then dried over Na_2SO_4, filtered, and evaporated to give a yellow oil. The crude product was purified by flash chromatography (5% ether in pentane). The products were characterized by ^{1}H NMR spectroscopy (see below) and analyzed by chiral GC.

General Procedure for Competitive Epoxidations: Styrene (0.5 mmol, 51 mg), *n*-decane (0.5 mmol, 71 mg), and the olefin under investigation (0.5 mmol) were dissolved in dichloromethane (1 mL) and cooled to 0 °C. After mixing, the first sample (20 μL) was withdrawn and diluted to 1.5 mL with diethyl ether. (*R*,*R*)-(−)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese-(III) chloride (0.04 mmol, 26 mg) was added to the reaction vessel, and a sample (20 μL) was withdrawn and filtered through 1 cm of silica using 1.5 mL of diethyl ether. A precooled (0 °C) aqueous solution of NaOCl (∼0.55 M, 3.5 mL) was added with rapid stirring. 20 μL samples of the organic phase were withdrawn after 2.5, 5, 7.5, 10, 15, 30, 45, 60, 90, and 120 min and filtered as mentioned above, each time stopping the stirring for 10 s to allow phase separation. All samples were analyzed by chiral GC using the appropriate general temperature program.

The competitive epoxidations of compounds **3b**−**c** and **4** were performed using (*E*)-β-methylstyrene (0.5 mmol, 56 mg) instead of styrene as the only change.

Dimethyl-substituted styrenes **3** were synthesized according to literature procedures.[22a] α,β,β-Trimethylstyrene was synthesized via a similar Suzuki coupling procedure with 2-bromo-3-methyl-2-butene as the bromide coupling partner. The reaction gave the desired product in 87% yield (4.74 g) after chromatography (pentane).

^{1}H NMR (300 MHz, $CDCl_3$, δ):1.58 (br s, 3H), 1.80 (br s, 3H), 1.95 (br s, 3H), 7.06−7.33 (m, 5H).[23] ^{13}C NMR ($CDCl_3$, 75.4 MHz, δ): 20.8, 21.1, 22.3, 54.7, 126.0, 127.5, 128.2, 128.7, 130.3, 145.6.

Racemic (*E*)-β-Methylstyrene oxide was synthesized using a one-pot procedure developed by Kolb and Sharpless.[24] The desired epoxide **6b** was isolated as a clear oil in 60% overall yield (2.15 g). GC retention times were 13.8 min and 14.0 min, respectively, for the two enantiomers (procedure A).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.45 (br d, 5.4 Hz, 3H), 3.04 (qd, 2.1 Hz, 5.4 Hz, 1H), 3.58 (br d, 2.1 Hz, 1H), 7.23−7.38 (m, 5H).[25] ^{13}C NMR (75.4 MHz, $CDCl_3$, δ): 16.9, 58.0, 58.5, 124.5, 127.0, 127.4, 136.7.[25]

The racemic epoxides **6a**, **6c**, **7a**−**c**, and **8** were all synthesized according to this general procedure: The alkene (1.0 equiv, 20 mmol) was dissolved in CH_2Cl_2 (100 mL), and the solution was cooled to 0 °C (ice-bath). MCPBA (1.1 equiv, 22 mmol, 4.93 g) was added slowly with stirring. The reaction mixture was left stirring for 2 h and then transferred to a separatory funnel with CH_2Cl_2 (20 mL). *n*-Pentane (500 mL) was added, and the organic phase was extracted twice with saturated aqueous $NaHCO_3$ (100 mL) and then saturated aqueous NaCl (100 mL) and dried over $MgSO_4$. The solvent was removed on a rotary evaporator (12 mmHg, 25 °C), and the crude product was purified by flash column chromatography (5% ether in pentane). A solution of phosphomolybdic acid (12 g) in ethanol (250 mL) was used to visualize the product on TLC.

(*Z*)-β-Methylstyrene oxide was isolated as a clear oil in 86% yield (2.31 g). GC retention times were 15.8 min and 18.4 min, respectively, for the two enantiomers (procedure A).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.09 (dd, 5.4 Hz, 0.9 Hz, 3H), 3.31−3.39 (m, 1H), 4.07 (d, 4.2 Hz, 1H), 7.25−7.39 (m, 5H).[26] ^{13}C NMR (75.4 MHz, $CDCl_3$, δ): 12.79, 55.38, 57.77, 126.81, 127.71, 128.24, 135.75.[27]

α-Methylstyrene oxide was isolated as a clear oil in 77% yield (1.03 g, 10 mmol scale). GC retention times were 18.4 min and 18.8 min, respectively, for the two enantiomers (procedure B).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.72 (s, 3H), 2.80 (d, 5.4 Hz, 2H), 2.97 (d, 5.4 Hz, 2H), 7.21−7.40 (m, 5H).[28] ^{13}C NMR (75.4 MHz, $CDCl_3$, δ): 21.77, 56.73, 57.05, 125.25, 127.42, 128.30, 141.10.[29]

β,β-Dimethylstyrene oxide was isolated as a clear oil in 81% yield (2.41 g). GC retention times were 14.7 min and 15.0 min, respectively, for the two enantiomers (procedure A).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.08 (s, 3H), 1.49 (s, 3H), 3.87 (s, 1H), 7.24−7.39 (m, 5H).[30] ^{13}C NMR (75.4 MHz, $CDCl_3$, δ): 18.2, 25.0, 61.3, 64.8, 126.6, 127.6, 128.3, 136.8.[30]

(*E*)-α,β-Dimethylstyrene oxide was isolated as a clear oil in 55% yield (1.64 g). GC retention times were 17.3 min and 17.6 min, respectively, for the two enantiomers (procedure A).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.43 (d, 5.4 Hz, 3H), 1.67 (s, 3H), 2.95 (q, 5.5 Hz, 1H), 7.22−7.38 (m, 5H).[31] ^{13}C NMR (75.4 MHz, $CDCl_3$, δ): 14.7, 17.6, 60.6, 62.8, 125.3, 127.4, 128.5, 143.3.

(*Z*)-α,β-Dimethylstyrene oxide was isolated as a clear oil in 79% yield (2.29 g). GC retention times were 12.8 min and 13.8 min, respectively, for the two enantiomers (procedure A).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 0.98 (dd, 5.4 Hz, 0.9 Hz, 3H), 1.64 (s, 3H), 3.17 (q, 5.4 Hz, 1H), 7.23−7.38 (m, 5H).[32] ^{13}C NMR (75.4 MHz, $CDCl_3$, δ): 14.7, 24.8, 61.5, 62.9, 126.8, 127.3, 128.3, 139.9.

α,β,β-Trimethylstyrene oxide (5 mmol scale) was isolated as a clear oil in 87% yield (0.71 g). GC retention times were 14.2 min and 15.6 min, respectively, for the two enantiomers (procedure A).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 0.97 (s, 3H), 1.48 (s, 3H), 1.62 (s, 3H), 7.20−7.38 (m, 5H).[33] ^{13}C NMR (75.4 MHz, $CDCl_3$, δ): 21.0, 21.6, 21.9, 64.0, 66.8, 126.3, 127.0, 128.2, 142.5.

Synthesis of enantioenriched epoxides a by three-step procedure (dihydroxylation, tosylation, and ring-closure):

α-Methylstyrene (10 mmol, 1.18 g) was added to 100 mL of a solution of $K_2OsO_2(OH)_4$ (0.05 mmol, 18 mg), $(DHQD)_2PHAL$ (0.10 mmol, 78 mg), $K_3Fe(CN)_6$ (30 mmol, 9.88 g), and K_2CO_3 (30 mmol, 4.14 g) in *t*-BuOH/H_2O, 1:1 cooled to 0 °C. The resulting mixture was stirred at 0 °C overnight and then quenched by addition of $Na_2S_2O_3$ (10 g). The phases were separated and the water phase was extracted three times with EtOAc (100 mL). The combined organic phases were washed with 5% H_2SO_4 (20 mL), saturated aqueous $NaHCO_3$ (60 mL), and then saturated aqueous NaCl (60 mL), dried over $MgSO_4$, and purified by flash chromatography on silica gel (40% EtOAc in heptane) to give the diol in quantitative yield (1.52 g).

The diol (1 mmol, 152 mg) was dissolved in CH_2Cl_2 (2 mL), and 1 equiv of TsCl (192 mg) was added followed by the addition of 2 equiv of Et_3N. The solution was stirred at rt overnight. Pentane (∼50 mL)

(23) Berthiol, F.; Doucet, H.; Santelli, M. *Eur. J. Org. Chem.* **2003**, *6*, 1091.
(24) Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515.
(25) Besse, P.; Renard, M. F.; Veschambre, H. *Tetrahedron: Asymmetry* **1994**, *7*, 1249.
(26) Sasaki, H.; Irie, R.; Hamada, T.; Suzuki, K.; Katsuki, T. *Tetrahedron* **1994**, *50*, 11827.
(27) Monti, J. P.; Faure, R.; Sauleau, A.; Sauleau, J. *Magn. Reson. Chem.* **1986**, *24*, 15.
(28) Archelas, A.; Furstoss, R. *J. Org. Chem.* **1999**, *64*, 6112.
(29) Concellón, J. M.; Cuervo, H.; Fernández-Fano, R. *Tetrahedron* **2001**, *57*, 8983.
(30) Pedragosa-Moreau, S.; Archelas, A.; Furstoss, R. *Tetrahedron* **1996**, *52*, 4593.
(31) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *46*, 11224.
(32) Satoh, T.; Kobayashi, S.; Nakanishi, S.; Horiguchi, K.; Irisa, S. *Tetrahedron* **1999**, *55*, 2515.
(33) Yamamoto, H.; Miura, M.; Nojima, M.; Kusabayashi, S. *J. Chem. Soc., Perkin Trans. 1* **1986**, 173.

was added, and the mixture was washed with saturated aqueous NaCl (5 mL). The crude epoxide was purified by flash chromatography on silica gel (1% Et_3N, 10% ether in pentane) to give **3c** in 23% yield. The enantiomeric excess was determined to be 95% by chiral GC using procedure B.

(*E*)-α,*β*-Dimethylstyrene (5 mmol, 661 mg) was added to a solution of $K_2OsO_2(OH)_4$ (0.025 mmol, 9 mg), $(DHQD)_2PHAL$ (0.05 mmol, 39 mg), $K_3Fe(CN)_6$ (15 mmol, 4.94 g), and K_2CO_3 (15 mmol, 2.07 g) in *t*-BuOH/H_2O, 1:1 (50 mL) cooled to 0 °C. The resulting mixture was stirred at 0 °C overnight and then quenched by addition of 5 g of $Na_2S_2O_3$. The phases were separated, and the water phase was extracted three times with EtOAc (50 mL). The combined organic phases were washed with 5% H_2SO_4 (10 mL), saturated aqueous $NaHCO_3$ (30 mL), and then saturated aqueous NaCl (30 mL), dried over $MgSO_4$, and purified by flash chromatography on silica gel (40% EtOAc in heptane) to give the diol in 66% yield (547 mg).

The diol (0.5 mmol, 83 mg) was dissolved in CH_2Cl_2 (5 mL), and 1 equiv of TsCl (95 mg) was added followed by the addition of Et_3N (1 mL). The solution was refluxed overnight and became yellow, but TLC showed only limited conversion of the diol. A small (∼5 mg) amount of DMAP was added, and after refluxing for 96 h the reaction was worked up. The reaction mixture was transferred to a separatory funnel with CH_2Cl_2 (10 mL), diluted with pentane (100 mL), and washed with saturated aqueous NaCl (10 mL). The crude epoxide was purified by flash chromatography on silica gel (1% Et_3N, 10% ether in pentane) to give **7b** in 54% yield. The enantiomeric excess was determined to be 95% by chiral GC using procedure A.

Acknowledgment. We wish to thank Professor Declan Gilheany for illuminating discussions. Professor Saverio Florio kindly provided suggestions for the chiral analysis of α-methylstyrene oxide. Financial support from the Danish Technical Sciences Research Council and the Technical University of Denmark is gratefully acknowledged.

Supporting Information Available: GC retention times for alkenes, epoxides, and byproducts. This material is available free of charge via the Internet at http://pubs.acs.org.

JA051851F