Nonstereospecific Mechanisms in Asymmetric Addition to Alkenes Result in Enantiodifferentiation after the First Irreversible Step

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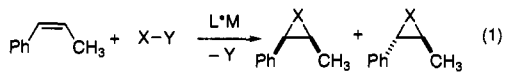
Enantioselectivity in a nonconcerted asymmetric reaction is not necessarily determined by the initial enantiodifferentiating event but rather by the relative energies of the diastereomeric transition states in the first irreversible step. Examples of such Curtin–Hammett control have been demonstrated in Rh-catalyzed asymmetric hydrogenation reactions.[4,5] A logical corollary to this principle specifies that events succeeding the first irreversible step should not influence the enantiomeric composition of the final product.[6]

The concept that "the die is cast"[6] in the first irreversible step of a multi-step reaction is indeed strictly true for stereospecific additions to olefins, which constitute the majority of known asymmetric catalytic alkene transformations.[7] However, we note here that a significant exception arises for nonstereospecific asymmetric reactions, wherein the relative configuration of the product is not predicated by the mechanism of the reaction. Two such enantioselective processes have recently been uncovered in our laboratories, (salen)Mn-catalyzed epoxidation[8] and (bisimine)Cu-catalyzed aziridination.[9] In both reactions, disubstituted acyclic cis alkenes are oxidized to afford mixtures of cis and trans disubstituted heterocycles with good-to-high enantioselectivity (eq 1). As illustrated below, the enantiomeric composition of the

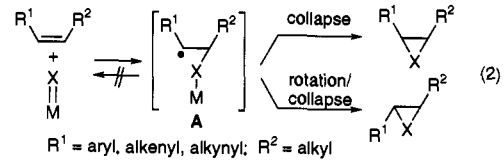


(1)

L*M = (salen)MnCl, X = O (Y = NaCl or ArI)
L*M = (bisimine)CuOTf, X = NTs (Y = ArI)

products can be profoundly influenced by events following the first irreversible step in these reactions.[10]

Nonstereospecificity in (Schiff base)metal-catalyzed epoxidations and aziridinations of conjugated alkenes is well-precedented and has generally been attributed to a stepwise mechanism involving a partially- or freely-rotating common radical intermediate (eq 2).[11,12] If the mechanism in eq 2 is assumed and the



(2)

R1 = aryl, alkenyl, alkynyl; R2 = alkyl

reactions leading to A were reversible, then cis–trans isomerization of alkene would be expected. However, for all substrates studied in our laboratories, olefin isomerization does not occur under conditions of asymmetric epoxidation or aziridination. Therefore, the first carbon–heteroatom bond-forming step is concluded to be irreversible and therefore turnover-limiting.[13]

Nonconjugated olefins are oxidized stereospecifically by a concerted or nearly concerted mechanism,[14] so it is reasonable to assume that generation of the radical intermediate A from conjugated alkenes occurs regiospecifically at the carbon bearing the conjugating group R^1.[15] On the basis of a simple analysis, it might be predicted that chiral catalysts functioning under such a mechanism should induce identical enantioselectivity in the cis and trans products, since the configuration at the carbon bearing R^2 is established in this first irreversible step that leads to the common intermediate. However, as shown in Table 1, the experimentally observed enantiomeric excesses of cis and trans epoxides or aziridines can be very different.[16] This apparent paradox may be attributed to the fact that with a chiral complex, the common intermediate is actually generated as a mixture of two diastereomers, A_1 and A_2 (Scheme 1). Each of these may partition to cis and trans products, but their diastereomeric relationship allows for the degree of partitioning to be different. As expressed in Scheme 1, this is the case if $[k_{major}]_{cis}/[k_{major}]_{trans} \neq [k_{minor}]_{cis}/[k_{minor}]_{trans}$.[17]

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(4) Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746.
(5) Other catalytic alkene addition mechanisms may also involve reversible addition of catalyst to the double bond prior to the selectivity-determining step, e.g.: (a) Sharpless, K. B.; Teranishi, A. Y.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1977**, *99*, 3120. (b) Sundermeyer, *J. Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1144. (c) Göbel, T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1329.
(6) Bosnich, B. In *Asymmetric Catalysis*; Bosnich, B., Ed.; Marinus Nijhoff: Boston, 1986; p 14.
(7) E.g.: (a) Epoxidation: Johnson, R. A.; Sharpless, K. B. Comprehensive Organic Synthesis, Vol. 7; Pergamon: New York, 1991; Chapter 3.2. (b) Dihydroxylation: Crispino, G. A.; Ho, P. T.; Sharpless, K. B. *Science (Washington, D.C.)* **1993**, *259*, 64. (c) Hydrogenation, hydrosilation, and hydrocyanation: Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; Chapter 10.
(8) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801.
(9) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326. See also: Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328.
(10) Recently, Scharf et al. have enunciated the "isoinversion principle", which describes the interesting consequences of a mechanism in which two diastereomeric intermediates are generated from a stereoselective event but wherein only one intermediate is formed reversibly (Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 477). The reactions discussed here do not belong to this surprisingly large class of reactions.
(11) (a) Lee, N. H.; Jacobsen, E. N. *Tetrahedron Lett.* **1991**, *32*, 6533. (b) Srinivasan, K.; Perrier, S.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309. (c) Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron Lett.* **1990**, *31*, 7345. (d) O'Connor, K. J.; Wey, S.-J.; Burrows, C. J. *Tetrahedron Lett.* **1992**, *33*, 1001.
(12) Groves and Stern have demonstrated through elegant isotope labeling studies that (tetramesitylporphinato)MnCl-catalyzed epoxidation of alkenes proceeds via two different Mn=O intermediates, only one of which effects epoxidation nonstereospecifically (Groves, J. T.; Stern, M. K. *J. Am. Chem. Soc.* **1987**, *109*, 3812). This possibility has not yet been addressed directly in the (salen)Mn- or (bisimine)Cu-catalyzed oxidations. However the high enantiomeric excesses obtained with these catalysts in the oxidation of cyclic cis alkenes (e.g., >98% ee with 2,2-dimethylchromene derivatives) render unlikely the participation of two independent oxidants, since both oxidants would be required to exert nearly absolute enantioselectivity.
(13) There exists a finite possibility that the initially-formed intermediate might reverse specifically to the cis olefin but not to the thermodynamically favored trans olefin. Although unlikely, this possibility cannot be ruled out completely. Under such conditions, the isoinversion principle[10] would apply. Similarly, a reversibly-formed intermediate may exist on the pathway to A (e.g., a charge transfer complex). The extent of reversibility in the formation of this intermediate could affect the facial selectivity in the formation of A, but it does not bear on the cis/trans partitioning in the product formation.
(14) Fu, H.; Look, G. C.; Zhang, W.; Jacobsen, E. N.; Wong, C.-H. *J. Org. Chem.* **1991**, *56*, 6497.
(15) In addition, the major enantiomers of the cis and trans products have been shown to be epimeric at the conjugating group R^1 for all substrates examined thus far.
(16) In all cases, enantiomeric excesses and cis/trans ratios of products remained constant during the course of the reactions. Control experiments also established that neither the cis nor the trans products were susceptible to isomerization under the reaction conditions.
(17) As noted by a referee, the reactions may be viewed as involving two stereoselective steps, each of which is irreversible. The selectivity in the second step sets the configuration at the carbon bearing R^1; it is determined by the stereocenter bearing R^2 and by the dissymmetry of the chiral ligand. It is the latter effect which gives rise to differences in the degree of cis/trans partitioning for the major and minor pathways.

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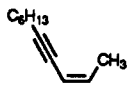
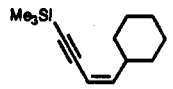
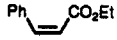
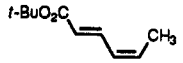
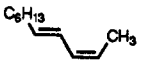
Table 1. Nonstereospecific, Enantioselective Oxidation of Cis Disubstituted Alkenes

entry	substrate	reaction[a]	ee_{cis} (%): ee_{trans} (%)	% cis/% trans	ee_{facial}[b]	$[cis/trans]_{major}/[cis/trans]_{minor}$[c]
1		E[d]	88:71	4.9	85	2.6
2		E[e]	43:90	0.62	72	0.13 (1:7.6)
3		E[e]	64:98	0.19	93	0.047 (1:21)
4		E[f]	92:64	4.0	86	5.3
5		E[e]	14:66	0.14	60	0.27 (1:3.7)
6		E[g]	55:92	0.91	74	0.14 (1:7.0)
7		A[h]	67:81	3.0	70	0.52 (1:1.9)

[a] E, epoxidation; A, aziridination. [b] Calculated using eq 3. [c] Calculated according to eq 6. [d] Zhang, W. Ph.D. Thesis, Univerisity of Illinois, 1991. [e] Reference 11a. [f] Jacobsen, E. N.; Deng, L.; Furukawa, Y.; Martínez, L. E. *Tetrahedron*, in press. [g] Chang, S. B.; Lee, N. H.; Jacobsen, E. N. *J. Org. Chem.*, in press. [h] Reference 9.

There are accordingly two independent factors that influence enantioselectivity in these stepwise additions: the facial selectivity in the first step (ee_{facial}, determined by k_{major} vs k_{minor}) *and* the relative diastereoselectivities of ring closure ($[k_{major}]_{cis}/k_{major}]_{trans}$ vs $[k_{minor}]_{cis}/[k_{minor}]_{trans}$). Assuming that both cis and trans products arise solely from irreversibly-formed common intermediates $\mathbf{A_1}$ and $\mathbf{A_2}$ and that the products are epimeric at R^2, the facial selectivity can be calculated by straightforward manipulation of the terms in Scheme 1 (eq 3):[18]

$$ee_{facial} = \frac{\mathbf{A_1} - \mathbf{A_2}}{\mathbf{A_1} + \mathbf{A_2}} = (ee_{cis} \times \%cis) + (ee_{trans} \times \%trans) \quad (3)$$

where ee_{cis} is the enantiomeric excess of cis product, and ee_{trans} is the enantiomeric excess of trans product.

The diastereoselectivity of ring closure, defined as the cis/trans partitioning of intermediates **A** and $\mathbf{A_2}$, can either be calculated (eqs 4 and 5)[18] or measured experimentally. The ratio of these diastereoselectivities (eq 6) provides a measure of the difference in cis/trans partitioning for the diastereomeric intermediates.

$$[cis]_{major}/[trans]_{major} = \left(\frac{\%cis}{\%trans}\right)\left(\frac{1 + ee_{cis}}{1 + ee_{trans}}\right) \quad (4)$$

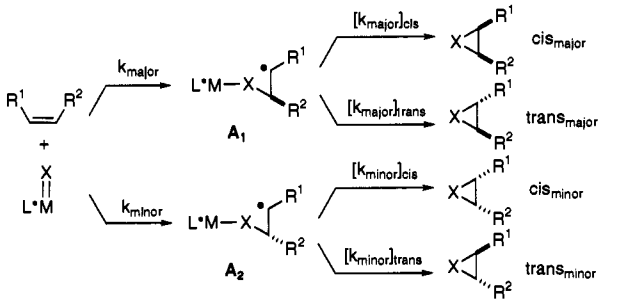
$$[cis]_{minor}/[trans]_{minor} = \left(\frac{\%cis}{\%trans}\right)\left(\frac{1 - ee_{cis}}{1 - ee_{trans}}\right) \quad (5)$$

$$\text{relative diastereoselectivity of ring closure} = \frac{[cis]_{major}/[trans]_{major}}{[cis]_{minor}/[trans]_{minor}} = \frac{(1 + ee_{cis})/(1 - ee_{cis})}{(1 + ee_{trans})/(1 - ee_{trans})} \quad (6)$$

As displayed in Table 1, significant divergence between the enantiomeric composition of the cis and trans products arises when the cis/trans partitioning (k_{cis}/k_{trans}) is very different for the major and the minor pathways. In the most extreme case examined thus far (entry 3), the diastereoselectivities of ring closure differ by a factor of 21. It is significant that, in most cases examined, the diastereoselectivity of cis/trans partitioning results in an *enhancement in the enantiomeric excess of the major product*. More important, very high enantioselectivity for either the cis or the trans product can be attained despite modest facial selectivity (ee_{facial}) in the first step (entries 2, 4, 6). This arises if the favored intermediate ($\mathbf{A_1}$ in Scheme 1) partitions selectively to the major diastereomer of the product, while the minor intermediate ($\mathbf{A_2}$) preferentially undergoes collapse to the minor diastereomer.

(18) Derivation of eqs 3–5 is provided as supplementary material.

Scheme 1



In summary, ligand dissymmetry in a chiral catalyst can strongly influence the reactivity of irreversibly-formed intermediates and effect a formal *enantioselectivity refinement* after the first irreversible step of a nonconcerted process. This constitutes a potentially controllable feature of asymmetric catalyst design, and our current efforts are directed toward elucidating the steric and electronic factors that influence the diastereoselectivity of ring closure in enantioselective atom- and group-transfer reactions.

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Supplementary Material Available: Derivation of eqs 3–5 (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.