

Regioselective Ring Opening of Enantiomerically Enriched Epoxides via Catalysis with Chiral (Salen)Cr(III) Complexes

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Received 2 February 2001

Dedicated with respect and admiration to Professor Ryoji Noyori.

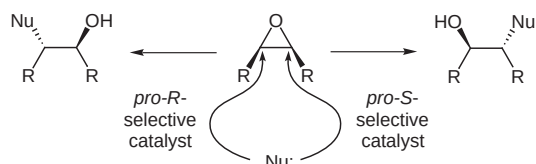
Abstract: Chiral (salen)chromium(III)N₃ complexes are demonstrated to be catalysts for the regioselective ring opening a variety of enantiomerically enriched epoxides. Selective nucleophilic attack at either epoxide carbon atom can be achieved by selection of the appropriate enantiomer of catalyst. A highly selective synthesis of norpseudoephedrine is described using this strategy.

Key words: regioselectivity, ring opening, (salen)Cr(III) complexes, epoxides

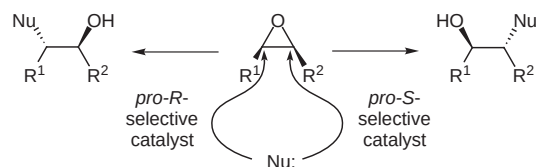
While the principal application of asymmetric catalysis is clearly toward enantioselective or diastereoselective reactions, the possibility also exists for a chiral catalyst to exert regiochemical control on a chiral substrate. This effect has been observed in a few cases in the context of parallel kinetic resolution reactions, wherein the two enantiomers of a racemate may be transformed to regioisomeric products.¹ A different manifestation of the same concept can be envisaged wherein the two enantiomeric partners of a chiral catalyst effect complementary regioselectivity on an enantioenriched substrate.² This principle is easily grasped if one considers the nucleophilic ring-opening of epoxides with a chiral catalyst (Scheme 1). Several examples have been uncovered of enantioselective nucleophilic ring-opening of meso epoxides,³ wherein catalyst enantioselectivity is manifested through selective nucleophilic attack at one of the enantiotopic C-O bonds. Naturally, the mirror-image catalyst reacts with the same selectivity at the other C-O bond, leading to the enantiomeric product in identical ee. In the case of an enantioenriched chiral epoxide wherein the heterotopic C-O bonds might be considered pseudo-enantiotopic, the same selectivity principles could result in enantiomeric catalysts affording regiocomplementary products. Such a process would constitute a peculiar example of "double asymmetric synthesis,"⁴ and on a practical level could define a novel strategy for effecting regioselective reactions of sterically and electronically unbiased substrates. We have explored this idea in the context of the (salen)Cr-catalyzed addition of TMSN₃ to epoxides,⁵ and describe our results herein.

Enantiomerically enriched *cis* dialkyl substituted epoxides, such as *cis*-2-heptene oxide and *cis*-2-octene oxide (**3** and **4**) bearing what may be viewed as "pseudoenantiotopic" C-O bonds, were evaluated first for regioselective epoxide ring opening in the (salen)CrN₃-catalyzed asymmetric ring opening (ARO) reaction. The

meso epoxide:



enantioenriched, chiral epoxide:



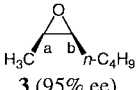
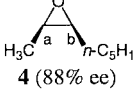
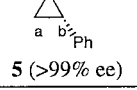
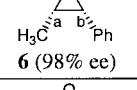
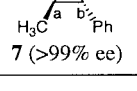
Scheme 1

enantioenriched epoxides were accessed by asymmetric epoxidation of the corresponding alkenes catalyzed by the enzyme chloroperoxidase using hydrogen peroxide.⁶ The achiral (salen)CrN₃ catalyst (**1**) effected ring-opening of (2*R*,3*S*)-**3** and (2*R*,3*S*)-**4** with no measurable regioselectivity, affording the ring-opened products in a 1:1 ratio (Table). Ring-opening with catalyst (*R,R*)-**2** provided a modest 2:1 regioselectivity, while use of the enantiomeric (*S,S*)-**2** led to a reversal in selectivity in both cases to afford a 1:4 and 1:3 ratio of regioisomers. Thus, while chiral (salen)CrN₃ catalyst **2** exerted only marginal control over the regioselectivity of epoxide ring opening, these examples provided a clear proof-of-principle of the desired effect.

More significant levels of catalyst control were revealed in the ring opening of styrene oxide derivatives. Three enantioenriched epoxides, (*R*)-styrene oxide (**5**), *cis*- β -methylstyrene oxide (**6**), and *trans*- β -methylstyrene oxide (**7**) were examined.⁸ Epoxides **5** and **7** were obtained in highly enantiomerically enriched form (>99% ee) from commercial sources.⁹ Epoxide **6** was synthesized by asymmetric epoxidation using the previously reported low temperature conditions with (salen)MnCl catalysts.¹⁰

Treatment of (*R*)-styrene oxide (**5**) with 5 mol% achiral catalyst **1** and Me₃SiN₃ at 20 °C, afforded a 4:1 ratio of regioisomeric products with preferential azide attack at the less hindered β -terminal position. Use of the chiral catalyst (*S,S*)-**2** enhanced the substrate bias to provide an 18:1 ratio of products favoring β -substitution. The enantiomer-

Table Asymmetric Ring Opening (ARO) of Enantiomerically Enriched Epoxides.⁷

Entry	Epoxide	Catalyst ^a (0.13 M)	Regioselectivity ^b (Time, Yield ^c)
1	 3 (95% ee)	1 (<i>R,R</i>)- 2 (<i>S,S</i>)- 2	1:1 (44 h, 81) 2:1 (26 h, 79) 1:4 (15 h, 77)
2	 4 (88% ee)	1 (<i>R,R</i>)- 2 (<i>S,S</i>)- 2	1:1 (44 h, 73) 2:1 (23 h, 74) 1:4 (15 h, 71)
3	 5 (>99% ee)	1 (<i>R,R</i>)- 2 (<i>S,S</i>)- 2	4:1 (16 h, 88) 1:7 (23 h, 87) 18:1 (21 h, 87)
4	 6 (98% ee)	1 (<i>R,R</i>)- 2 (<i>S,S</i>)- 2	3:1 (30 h, 73) 1:4 (20 h, 85) 45:1 (27 h, 70)
5	 7 (>99% ee)	1 (<i>R,R</i>)- 2 (<i>S,S</i>)- 2	1:9 (16 h, 89) 1:1 (32 h, 85) 1:84 (16 h, 88)

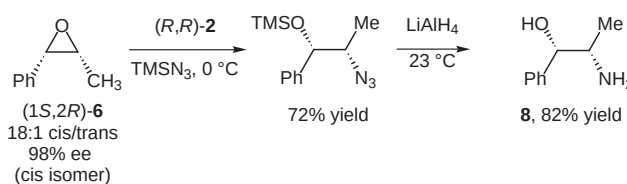
^a Catalyst concentrations were 0.12–0.13 M for substrates 5–7, and 0.06–0.08 M for **3** and **4**. ^b Selectivities are expressed as the ratio of products resulting from azide attack at positions a and b (a:b). Ratios were determined by GC analysis for styrene oxide and its derivatives, and by ¹H NMR for the aliphatic substrates. ^c Isolated yield of the regioisomeric mixture.

ic catalyst, (*R,R*)-**2**, overrode the substrate bias to afford a 1:7 ratio of products, the major isomer resulting from azide attack at the α -benzylic carbon atom. The enantiopurity of the two product regioisomers in the epoxide ring opening of **5** was conserved as determined by chiral gas chromatographic analysis.

The ring opening of *cis*- and *trans*- β -methylstyrene oxide (**6** and **7**) revealed similar profound matched and mismatched effects with **2** (Table, entries 4–5). In the case of **6**, the 3:1 substrate bias for β -substitution could be overcome to afford the α -benzylic substituted product, albeit with moderate 1:4 selectivity. The regioselectivity with *trans*-disubstituted **7** was 1:9 for α -benzylic substitution using achiral catalyst **1**, and the mismatched catalyst (*R,R*)-**2** effectively nullified this inherent bias to afford a 1:1 ratio of products. The tendency for *cis*- and *trans*-styrene oxide derivatives to display opposite regioselectivity in nucleophilic attack is well-documented, and may be explained by considering the difference in the stereoelectronic properties of the two disubstituted epoxides.¹¹ In *cis*-epoxide **6**, the phenyl group is rotated to avoid steric interactions with the methyl group, with the effect of blocking nucleophilic attack at the benzylic center. In contrast, the phenyl group of *trans* epoxide **7** is not subject to such a steric interaction and thus attack at the more electrophilic benzylic carbon atom is favored.

The new methodology was applied in a straightforward manner to the synthesis of (1*S*,2*S*)-norpseudoephedrine (**8**), a naturally occurring anorexiant found in several plant

species.¹² Sequential asymmetric epoxidation of *cis*- β -methylstyrene, selective ring opening as described above, and chromatographic purification afforded regioisomerically pure product in 51% overall yield. Azide reduction with LiAlH₄ provided **8** cleanly and in >99% ee.

**Scheme 2** Synthesis of norpseudoephedrine (**8**).

Acknowledgement

This work was supported by the National Institutes of Health (GM-43214) and by an Eli Lilly & Company-sponsored ACS Organic Division Graduate Fellowship to B. D. B.

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Article Identifier:

1437-2096,E;2001,0,SI,1013,1015,ftx,en;Y04401ST.pdf