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# High Enantioselectivities in an (*E*)-Alkene Epoxidation by Catalytically Active Chromium Salen Complexes. Insight into the Catalytic Cycle

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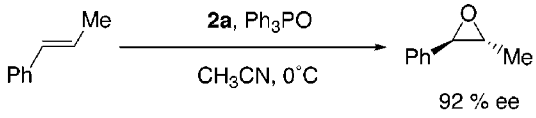
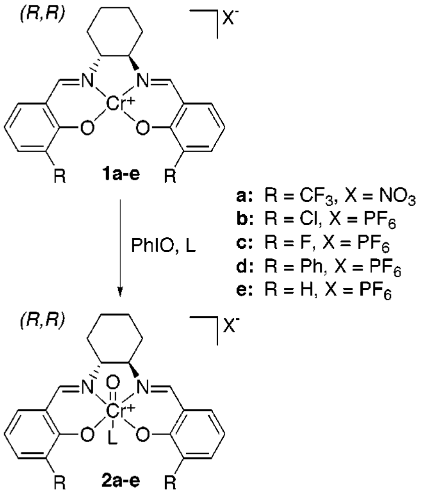
## ABSTRACT



**The epoxidation of (*E*)-*β*-methylstyrene mediated by an oxochromium salen complex yields the epoxide in 92% ee in stoichiometric mode, the highest ee yet reported for a metal-mediated epoxidation of an (*E*)-alkene. The effect of added donor ligands, previously substantial, has reached a ceiling with this complex. In catalytic mode a slightly reduced ee and higher yield is obtained, indicating both the presence of a second oxidation cycle and that the major oxidant reacts with its reduced form.**

There continues to be great interest in the development of general reagents for catalytic asymmetric alkene epoxidation,[1] the most notable successes being the systems of Sharpless, Jacobsen/Katsuki, and Shi.[2] For some time we have been working on the development of catalysts based on a chromium salen template such as **1**.[3−6] Part of our rationale for studying the chromium series was the availability of the stoichiometric variant of the reaction, since unlike the manganese salen system the oxochromium(V) complexes (e.g., **2**) are stable[7] and can be prepared from the corresponding Cr(III) species (e.g., **1**) using iodosylbenzene (Scheme 1). This provides an opportunity to study the

**Scheme 1.** Chromium Oxo-Salen Complexes



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(1) Dalton, C. T.; Ryan, K. M.; Wall, V. M.; Bousquet, C.; Gilheany, D. G. *Top. Catal.* **1998**, *5*, 71−90.

(2) (a) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed; Wiley-VCH: New York, 2000; Chapter 6A. (b) Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer, New York, 1999; Chapter 18.2, pp 649−677. (c) Katsuki, T. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed; Wiley-VCH: New York, 2000; Chapter 6B. (d) Wang, Z.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 2328−2329.

(3) Bousquet, C.; Gilheany, D. G. *Tetrahedron Lett.* **1995**, *36*, 7739−7742.

(4) Dalton, C. T.; Ryan, K. M.; Coyne, E. J.; Wall, V. M.; Bousquet, C.; Gilheany, D. G. *Abstracts of Papers*; 211th National Meeting of the American Chemical Society, New Orleans, LA.; American Chemical Society: Washington, DC, 1996; ORGN 161−165.

(5) Ryan, K. M.; Bousquet, C.; Gilheany, D. G. *Tetrahedron Lett.* **1999**, *40*, 3613−3616.

(6) Daly, A. M.; Dalton, C. T.; Renehan, M. F.; Gilheany, D. G. *Tetrahedron Lett.* **1999**, *40*, 3617−3620.

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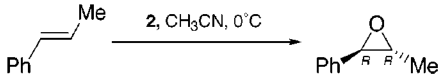
stereoselection in the absence of factors related to the catalytic cycle. Our best reported ee to date is 86% in the epoxidation of ($E$)-$\beta$-methylstyrene,[5] using complex **2b** in stoichiometric mode. This value is approached but not equalled in catalytic (10 mol %) mode with iodosylbenzene.

The most notable aspect of our system is that ($E$)-alkenes give much better selectivity than that of ($Z$)-alkenes, which is in contrast to the manganese salen based system of Jacobsen[2b] and indeed nearly all other metal oxo based oxidants.[8] This observation called into question the previously widely accepted side-on approach mechanism for epoxidation,[9] and an explanation based on the presumed greater degree of twist in the chromium salen complexes compared to that of their manganese counterparts was proposed by ourselves[1,4,6] and others.[10,11] Another notable aspect of the system is the role of the extra ligand L, usually an oxo-donor such as, e.g., phosphine or amine oxide, the presence of which can change the ee by >30%.[3,5]

We now report that, as a further development of our extensive study of the variation of ee with substitution on the salen ring,[5] we have succeeded in raising the ee to above 90%, again in stoichiometric mode. We had previously observed that although all positions on the salen ring have an effect on the ee, the 3,3′-positions (R in **1**) were of paramount importance. In addition we found that electron-withdrawing groups were necessary for short reaction time. This led us to synthesize the trifluoromethyl-substituted analogue **1a** and the derived oxo species **2a**. The latter, on stoichiometric reaction with ($E$)-$\beta$-methylstyrene in the presence of triphenylphosphine oxide over 90 min, gave the corresponding epoxide in 92% ee and 45% yield. With this good result in hand, the best ee value for an ($E$)-alkene using a metal-based reagent,[2d,8,12] we felt it appropriate to study both the stoichiometric and catalytic system in greater detail. This has resulted in a number of mechanistic and preparative insights.

**Stoichiometric Studies.** Table 1 (entries 1−4) shows the effect on epoxide ee of the use of some of our usual L for **2a**, in the stoichiometric epoxidation of ($E$)-$\beta$-methylstyrene. It can be seen that they have either a minimal or detrimental effect on ee. This is in contrast to our previous results[3,5] using other salen complexes, a selection of which are also given in Table 1 (entries 5−8). A trend emerges that the more enantioselective the system is without L, the less the benefit derived on addition of L. This "ceiling effect" is more than a manifestation of the changing value of $\Delta\Delta H^{\ddagger}$ with increasing ee. We believe the stereoselection in the system is due to a twist in the complex (vide supra) and that this twist can be affected by the donor ligand L. We propose that in complex **2a** the conformation without L reaches an optimum and that the effect of coordination of L on the complex conformation, and thus the ee, is minimal.

**Table 1.** Variation of Donor Ligand L in **2**

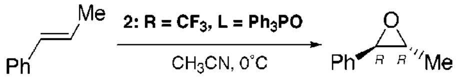


| entry | complex | L | ee %$^{a,b}$ | Δee$^{c}$ |
|---|---|---|---|---|
| 1 | **2a** | Ph$_3$PO | 92 | +2 |
| 2 | **2a** | pyridine N-oxide | 85 | −5 |
| 3 | **2a** | DMF | 67 | −23 |
| 4 | **2a** | DMSO | 86 | −4 |
| 5$^{d}$ | **2b** | Ph$_3$PO | 86 | +6 |
| 6$^{d}$ | **2c** | Ph$_3$PO | 86 | +16 |
| 7$^{d}$ | **2d** | Ph$_3$PO | 85 | +19 |
| 8$^{d}$ | **2e** | Ph$_3$PO | 72 | +14 |

$^{a}$ For experimental procedure, see Supporting Information. $^{b}$ Epoxide is obtained in 40−60% yield in all cases. $^{c}$ Δee = (ee with L) − (ee without L). $^{d}$ Results taken from ref 5.

Nonnucleophilic counterions X (to chromium in **1** and **2**) are required for successful epoxidation,[7] and a variety were examined (Table 2). Nitrate was found to give the highest ee. The others showed only small effects with the exception of BARF, whose behavior is anomalous in that it shows an ee improvement of 50% on addition of Ph$_3$PO. The BARF complex also yields an appreciable quantity of *cis*-epoxide from ($E$)-$\beta$-methylstyrene, a very unexpected observation. It is known however that tetraarylborates are susceptible to one-electron oxidation,[13] which in our system would generate a Cr(IV)═O species that could well exhibit significantly

**Table 2.** Variation of Counterion in **2**



| entry | counterion X | ee %$^{a,b}$ | Δee$^{c}$ |
|---|---|---|---|
| 1 | NO$_3$ | 92 | +2 |
| 2 | PF$_6$ | 88 | +2 |
| 3 | OTf | 88 | +16 |
| 4 | BF$_4$ | 87 | +13 |
| 5 | BARF$^{d}$ | 88 | +50 |

$^{a}$ For experimental procedure, see Supporting Information. $^{b}$ There is no significant yield variation between different counterions. $^{c}$ Δee = (ee with L) − (ee without L). $^{d}$ BARF: [B(3,5-bis-CF$_3$-phenyl)$_4$].

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(7) Samsel, E. G.; Srinivasan, K.; Kochi, J. K. *J. Am. Chem. Soc.* **1985**, *107*, 7606−7617.

(8) A ruthenium salen complex has recently been shown to catalyse the epoxidation of *E*,*Z* and terminal alkenes in 80−90% ee: Takeda, T.; Irie, R.; Shinoda, Y.; Katsuki, T. *SynLett* **1999**, 1157−1159.

(9) Collman, J. P.; Zhang, X.; Lee, V. J.; Uffelman, E. S.; Brauman, J. I. *Science* **1993**, *263*, 1404−1411. Groves, J. T.; Nemo, T. E. *J. Am Chem. Soc*. **1983**, *105*, 5786−5791.

(10) Houk, K. N.; DeMello, N. C.; Condroski, K.; Fennen, J.; Kasuga, T. Origins of Stereoselecivity in Jacobsen Epoxidations. *Electronic Conference on Heterocyclic Chemistry*, *ECHET96*, 24/6−22/7 1996; Rzepa, H. S., Snyder, J. P., Leach, C., Eds.; London; http://www.ch.ic.ac.uk/ectoc/echet96/.

(11) Hamada, T.; Fukuda, T.; Imanishi, H.; Katsuki, T. *Tetrahedron* **1996**, *52*, 515−530. Ito, Y. N.; Katsuki, T. *Tetrahedron Lett.* **1998**, *39*, 4325. Irie, R.; Hashihayata, T.; Katsuki, T.; Akita, M.; Moro-oka, Y. *Chem. Lett.* **1998**, 1041−1042.

(12) Very recently the use of a Mn(salen) complex to epoxidize *E*-alkenes in good ee was reported: Nishikori, H.; Ohta, C.; Katsuki, T. *SynLett* **2000**, 1557−1560.

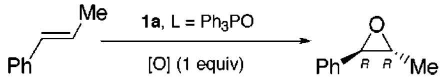
(13) Murphy, S. T.; Zou, C.; Miers, J. B.; Ballew, R.; Dlott, D.; Schuster, G. B. *J. Phys. Chem.* **1993**, *97*, 13152−13157.

different reactivity.[14] When no donor ligand is used with X = BARF, the *trans:cis* ratio of epoxide is 1:1, but this increases to 3:1 when L = $Ph_3PO$. The phosphine oxide, by accelerating epoxidation,[7] may inhibit reduction of Cr(V) to Cr(IV) by BARF, thereby decreasing the amount of *cis*-epoxide produced.

We also tested a number of different substrates, but the selectivity was found to be poorer for other *E* substrates such as (*E*)-stilbene (58% ee) and (*E*)-3-hexene (33% ee). (*Z*)-Alkenes, e.g,. (*Z*)-$\beta$-methylstyrene, also result in poor enantioselectivity ($<$30%); however, it is notable that the *E* isomer of epoxide is also obtained although in low ee (22%). This observation of epimerization is significant for the mechanism of oxygen transfer and strongly suggests the presence of a discrete intermediate at some point along the reaction path.

To investigate the efficiency of various oxidants we carried out epoxidations of (*E*)-$\beta$-methylstyrene in the presence of $Ph_3PO$ with a stoichiometric quantity of **1a** and 1.2 equiv of each of the oxidants listed in Table 3. In each case the typical literature procedures were used and the reaction was carried out at 0 °C. We have found iodosylbenzene to be the only satisfactory oxidant. Both tetrabutylammonium persulfate[15a] and hydrogen peroxide[15b] produce tiny yields of epoxide, even when a stoichiometric amount of chromium complex is used (Table 3). Use of bleach,[15c] which is highly desirable, produced only low selectivity and favored the opposite enantiomer than with iodosylbenzene. This, along with the fact that the characteristic deep green color of the iodosylbenzene-derived (salen)Cr(V)=O species **2** is not observed when using bleach, suggests that the bleach and iodosylbenzene systems follow different pathways.

**Table 3.** Variation of Oxidant



| entry | oxidant [O] | ee % | yield % |
|---|---|---|---|
| 1 | PhIO$^a$ | 92 | 45 |
| 2 | NaOCl$^b$ | −21 | 33 |
| 3 | $H_2O_2$$^c$ | 0 | 2 |
| 4 | $^n$Bu$_4$NHSO$_5$$^d$ | 0 | 3 |

$^a$ For experimental procedure, see Supporting Information. $^b$ See ref 15c. $^c$ See ref 15b. $^d$ See ref 15a.

**Catalytic Studies.** Given the high ee's observed in the stoichiometric system we then undertook an investigation of the catalytic variant of the reaction. Reactions were carried out using **1a** as catalyst, PhIO as oxygen source, and (*E*)-$\beta$-methylstyrene as substrate. In general catalytic reactions gave lower ee's and higher yields; e.g., 10 mol % **1a** gave 82% ee and 71% yield after 24 h. This corresponds to a turnover frequency of approximately 0.4. Use of less catalyst results in extended reaction time and further reduction in ee; e.g., 5 mol % **1a** gave 77% ee and 28% yield after 24 h. Such catalytic performance is not exceptional and also not unusual for similar chromium systems;[7] however, some significant conclusions about the reaction mechanism and catalytic cycle may be drawn from these results.

The observation of a lower ee in the catalytic system strongly indicates the presence of more than one oxidizing species in solution. Katsuki and Imanishi, in experiments with chromium salen complexes, suggested that an adduct of PhIO with the chromium salen complex could be responsible for certain effects they observed.[16] This could be possible in our case and similar species have been observed by Plattner and co-workers for the Mn series.[17] Also Collman and co-workers have very recently reported evidence for the existence of differing active oxidizing species when different iodosylarenes are used as the oxygen source in competitive oxidations of alkane substrates catalyzed by an Fe-porphyrin species.[18] The suggestion of adduct formation is therefore not unreasonable. However, previous work in this laboratory has shown that portionwise addition of iodosylbenzene did not effect the ee.

Valentine and co-workers studied the oxidation of alkenes by iodosylbenzene in the presence of iron(III) and aluminum(III) salts.[19] They suggested a nonredox mechanism leading to epoxide, which if operational in our system would be likely to lead to low selectivity since the first bond-forming step takes place some distance from the metal center. It is thus a possibility for a minor pathway to epoxide. Another possible species would be a (salen)Cr(IV)=O complex, but this, as suggested above, would be likely to lead to the production of *cis* epoxide from (*E*)-alkene. This was not observed. Catalyst decomposition is also unlikely since the ee remains constant throughout the reaction. Without the ability to examine the reactive intermediates in detail it is difficult to decide which is the correct analysis.

The increased yield in the catalytic reaction led us to further investigate the yields obtained in the stoichiometric system. The previously suggested catalytic cycle for metal salen and metal porphyrin catalyzed oxidations is shown in Figure 1, pathway a. We propose that in a stoichiometric reaction, where (salen)Cr(III) cannot be reoxidized to (salen)Cr(V)=O, the Cr(III) species reacts with the Cr(V) species as shown in Figure 1, pathway b, removing it from the system. This removal of the active oxidant could account, at least in part,[20] for the decreased yield in the stoichiometric reaction. In the catalytic system, such an interaction is much less likely, especially in the early stages of the reaction when

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(14) Groves, J. T.; Kruper, W. J.; Haushalter, R. C. *J. Am. Chem. Soc.* **1980**, *102*, 6377−6380.

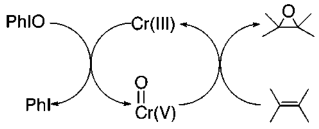
(15) (a) Pietikäinen, P. *Tetrahedron* **2000**, *56*, 417−424. (b) Irie, R.; Hosoya, N.; Katsuki, T. *Synlett* **1994**, 255−256. (c) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063−7064.

(16) Katsuki, T.; Imanishi, H. *Tetrahedron Lett.* **1997**, *38*, 251−254.

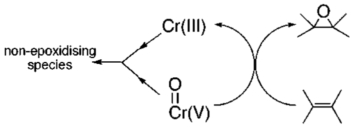
(17) Plattner, D. A.; Feichtinger, D. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1718−1719. Plattner, D. A.; Feichtinger, D.; El-Bahraoui, J.; Wiest, O. *Int. J. Mass. Spectrom.* **2000**, *195/196*, 351−362. Feichtinger, D.; Plattner, D. A. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1023−1028.

(18) Collman, J. P.; Chien, A. S.; Eberspacher, T. A.; Brauman, J. I. *J. Am. Chem. Soc.* **2000**, *122*, 11098−11100.

(19) Yang, Y.; Diederich, F.; Valentine, J. S. *J. Am. Chem. Soc.* **1991**, *113*, 7195−7205.



(a) Catalytic reaction



(b) Stoichiometric reaction

**Figure 1.** Reaction cycles.

a large excess of PhIO is present and a higher yield is thus obtained. We have accumulated a number of pieces of experimental evidence for this hypothesis. By adding (salen)Cr(III) to a (salen)Cr(V)=O solution, we have observed that (salen)Cr(III) can cause the decomposition of (salen)Cr(V)=O on the time scale of the epoxidation. This cannot occur under catalytic conditions. Further evidence includes (a) increased yield in the stoichiometric reaction with increased amounts of oxidant (1 equiv PhIO, 22% yield; 2 equiv, 45% yield), (b) reduction of the yield by one-third with the addition of excess Cr(III) to the reaction, and (c) increase in the yield by one-half with the use of an excess of pre-prepared Cr(V)=O in the stoichiometric reaction. The identity of the species produced on interaction of (salen)Cr(III) and (salen)Cr(V)=O is unfortunately not clear. We believe that oxidation of the salen ligands at the imine sites is unlikely, since we are able to recycle material from the epoxidation reaction quantitatively and reuse it in a further reaction without loss of activity or selectivity.

An alternative is conproportionation of (salen)Cr(V)=O and (salen)Cr(III) to form a $\mu$-oxo Cr(IV) dimer.[21] A similar $\mu$-oxo Mn(IV) dimer has been postulated to be in equilibrium with (salen)Mn(V)=O in the catalytic manganese system.[17,22] To investigate this idea an electrospray mass spectrum of a typical stoichiometric reaction mixture was obtained 10 min after the alkene substrate was added. This showed the presence of the (salen)Cr(III) species **1a** (*m*/*z* 508, relative intensity 72) along with its acetonitrile adduct (*m*/*z* 548, 32). Also present was the derived (salen)Cr(V)=O complex **2a** (*m*/*z* 534, 100) as well as a peak at *m*/*z* 1032 (40) and one at 1072 (27). The peak at *m*/*z* 1032 may be assigned the $\mu$-oxo Cr(IV) dimer structure and the peak at *m*/*z* 1072 to the acetonitrile adduct of this species. This entity does not survive to the material recovered from the reaction mixture, since a mass spectrum of the recovered material shows no evidence of a peak at *m*/*z* 1032. We would suggest therefore that the interaction of (salen)Cr(V)=O and (salen)Cr(III) yields a $\mu$-oxo Cr(IV) dimer. This dimeric species does not subsequently regenerate (salen)Cr(V)=O. Instead it reacts in a pathway that does not lead to epoxide. Thus it acts as a sink for (salen)Cr(V)=O rather than a reservoir as in the manganese-based system.

In summary, we have developed a new reagent (**2a**) for the stoichiometric epoxidation of (*E*)-$\beta$-methylstyrene in $>$90% ee. The reduced form (**1a**) can be used as a catalyst in the same tranformation, albeit affording slightly lower ee. Variation of the donor ligand suggests a selectivity ceiling has been reached for this type of ligand. Comparison of the catalytic and stoichiometric reactions indicates that in the stoichiometric system the oxidant reacts with its reduced form, thereby lowering the yield. Further efforts to optimize the system, as well as a computational and experimental investigation of the reaction mechanism, are ongoing.

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**Supporting Information Available:** Experimental procedures for the synthesis of complex **2a** and for asymmetric epoxidation. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Initially we ascribed the lower yield to epoxide decomposition catalyzed by Cr(salen) complex, a known reaction (K. B. Sharpless, private communication); however, control experiments showed this not to be a significant factor. In a typical case the yield of epoxide is 45% with 20% unreacted alkene and 5% byproducts (benzyl methyl ketone and benzaldehyde), which does not complete the mass balance of the reaction. Given that no other epoxide rearrangement products are observed, alkene must be consumed by another pathway. This has been suggested by Kochi and co-workers to be polymerization.[7]

(21) Woo, L. K. *Chem. Rev.* **1993**, *93*, 1125. Parkin, G. *Prog. Inorg. Chem.* **1998**, *47*, 1.

(22) Srinivasan, K.; Michaud, P.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309−2320.