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# Osmium-Catalyzed Asymmetric Dihydroxylation of Cyclic *Cis*-Disubstituted Olefins

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*Summary:* A new class of *cis*-disubstituted olefins has been found to give good enantioselectivities in the asymmetric dihydroxylation reaction using the standard PHAL and PYR ligands, all the olefins are conjugated, and the reacting double bond is endocyclic in a 5-, 6-, 7-, or 8-membered ring.

As a result of continuous refinements and improvements, the asymmetric dihydroxylation (AD) process now achieves fair to excellent ee for five of the six possible olefin substitution types (i, ii, iii, v, vi,[1] Figure 1), while using only two ligand classes: PHAL[2] and PYR[3] (Figure 1). *Cis*-olefins (iv, Figure 1) are usually very poor substrates for these ligands, with *cis*-allylic and homoallylic alcohols being an exception.[4] Only with a unique ligand (IND-,[5] Figure 1) is good enantioselectivity realized for some unfunctionalized *cis*-olefins, yet with no example exceeding 80% ee. We report here that the PHAL and PYR ligands are surprisingly successful for a variety of synthetically important, cyclic *cis*-disubstituted olefins.

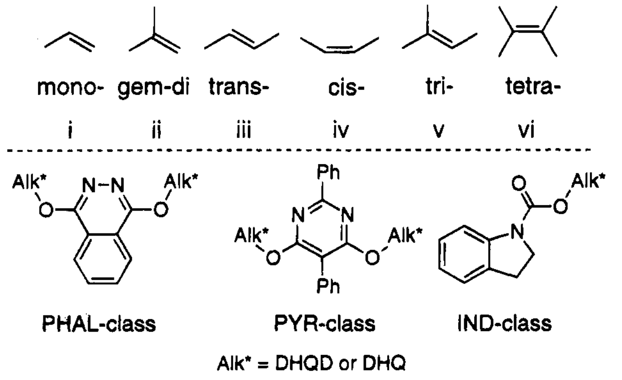

**Figure 1.**

The results for AD of 23 cyclic *cis*-disubstituted olefins, all are conjugated and some are dienes and trienes, are summarized in Table 1. Previous studies have revealed that *cis*-olefins tend to react slowly.[6] We addressed the rate problem by raising the potassium osmate level to 1 mol % and by using the additive $MeSO_2NH_2$.[7] In some difficult cases 5 mol % of potassium osmate was used, e.g., in entries 9−11.

For entries 1−5 and 8−16, the PHAL−ligand class renders the highest ee. With the spiro bicyclic dienes (entries 6 and 7), little change in enantioselectivity is noted across the three ligand classes. The PYR-ligand class seems to be the best for chromenes (entries 17−21). Entries 1−4 show that an increase in the ring size leads to a drop in ee. For the unsymmetrical conjugated dienes in entries 8−12 and 16, AD occurs preferentially at the more electron-rich double bond (as indicated by MOPAC calculations), with the 1,2-disubstituted diol as the main product in each case. This regioselectivity in favor of a *cis*- over a trisubstituted olefin contrasts with our earlier results for nonconjugated acyclic olefins where a trisubstituted olefin is preferred over a *cis*-disubstituted olefin.[8] However the present results are not really unexpected since they are consonant with the general preference for osmylation to occur at the more electron-rich double bond.[9]

The enantioselectivity trends for AD of the 6-substituted 2,2-dimethylchromenes (entries 18−21) suggest that an electronic factor plays a role in the selectivity, as the electron-donating substituent (Et) results in the highest ee and the electron-withdrawing groups ($CF_3$, Br and CN) lead to lower ee's.

For entries 9 and 10, in the presence of excess co-oxidant [$K_3Fe(CN)_6$], kinetic resolution occurs due to AD of the remaining double bond. This has the effect of raising the ee since the major enediol enantiomer from AD of the first double bond is the slow-reacting enediol enantiomer for AD of the second double bond. For example, in the presence of 3 equiv of $K_3Fe(CN)_6$, the diene in entry 10 gives 92% ee while with 3.3 equiv of $K_3Fe(CN)_6$ it affords 99% ee. When a racemic sample of the ene-3,4-diol product in entry 10 was subjected to AD with AD-mix-$\beta$, the slow-reacting (3*S*,4*R*)-diol was recovered in 35% ee at 35% conversion ($k_{rel}$ = ca. 6.5).

Of the 23 enantiomerically enriched diols produced in this study, the absolute configurations have been rigorously established for only six entries (2,[11] 12,[12] 17,[14] 18,[13]

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⊗ Abstract published in *Advance ACS Abstracts,* November 1, 1994.

[1] Morikawa, K.; Park, J.; Andersson, P. G.; Hashiyama, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 8463.

[2] Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.

[3] Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785.

[4] VanNieuwenhze, M. S.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 843.

[5] Wang, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7568.

[6] Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 7047.

[7] The general experimental procedure for AD of these cyclic *cis*-olefins was as follows: To a stirred reaction mixture maintained at 0 °C and consisting of ligand (5 mol % for entries 1−12 or 1 mol % for entries 16−23), $K_2OsO_2(OH)_4$ (2.35 mg, 1 mol %), $K_3Fe(CN)_6$ (988 mg, 3 mmol), $K_2CO_3$ (415 mg, 3 mmol), $MeSO_2NH_2$ (190 mg, 2 mmol), and 10 mL of *t*-BuOH−$H_2O$ (1:1), 5 mL of each, was added 1 mmol of the olefin. After the reaction was complete (TLC), 1.5 g of $Na_2SO_3$ was added and the mixture was stirred for 30 min while warming to room temperature. The workup was as previously reported,[2] and the crude diol was purified by flash chromatography on a silica gel column.

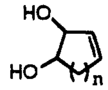
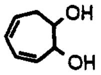
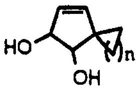
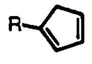
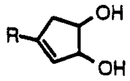
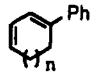
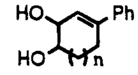
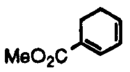
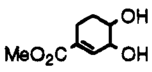
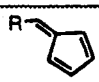
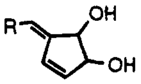
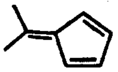
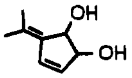
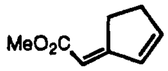
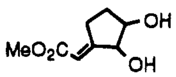
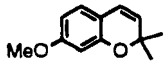
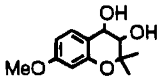
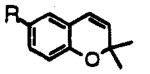
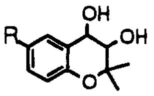
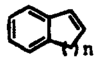
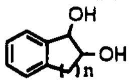
[8] Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570.

[9] For these conjugated cyclic olefins, molecular mechanics calculations with MOPAC (using AM1 semiempirical Hamiltonians: Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902) indicated that the *cis*-disubstituted double bond is more electron rich than the trisubstituted double bond.

[10] AD of the fulvenes (entries 13−15) was performed at room temperature in the presence of 5 mol % of ligand and 2.5 mol % of potassium osmate and otherwise as in ref 7. The regioselectivity as well as ee observed in the AD of unsymmetrical fulvenes (entries 13 and 14) is dependent on the choice of ligand. When using $(DHQD)_2$−PHAL for entry 14, oxidation of the *cis*-disubstituted double bond *anti* to the *t*-Bu group is the main pathway with an *anti:syn* diol product ratio of 4:1 (83% ee for the anti diol). Surprisingly with $(DHQD)_2$−PYR, almost no enantioselectivity or regioselectivity is observed. The DHQD−IND ligand gives moderate regio- and enantioselectivities. With all three ligand classes, no diol from AD of the trisubstituted double bond is detected.

0022-3263/94/1959-6895$04.50/0

**Table 1. AD[a] of Cyclic *Cis*-Disubstituted Olefins (ee's[b] and Absolute Configurations[c])**

| Entry | | | (DHQD)$_2$-PHAL | (DHQD)$_2$-PYR | (DHQ)$_2$-PYR | DHQD-IND | Products |
|---|---|---|---|---|---|---|---|
| 1 |  | n = 1 | 38% (3*S*, 4*R*) | 7% (3*S*, 4*R*) | | 29% (3*S*, 4*R*) |  |
| 2 | | n = 2 | 37% (3*S*, 4*R*) | 23% (3*S*, 4*R*) | | 24% (3*S*, 4*R*) | |
| 3 | | n = 3 | 30% (3*S*, 4*R*) | 21% (3*S*, 4*R*) | | 1%(3*S*, 4*R*) | |
| 4 | | n =4 | 5% (3*S*, 4*R*) | | | | |
| 5 |  | | 16% (3*S*, 4*R*) | 24% (3*S*, 4*R*) | | 11% (3*S*, 4*R*) |  |
| 6 |  | n =1 | 53% (3*S*, 4*R*) | 55% (3*S*, 4*R*) | | 50% (3*S*, 4*R*) |  |
| 7 | | n =3 | 70% (3*S*, 4*R*) | 70% (3*S*, 4*R*) | | 73%(3*S*, 4*R*) | |
| 8 |  | R = Me | 56% (3*S*, 4*R*) | 8% (3*S*, 4*R*) | | 31% (3*S*, 4*R*) |  |
| 9 | | R = Ph | 99% (3*S*, 4*R*) | 97% (3*S*, 4*R*) | | 95% (3*S*, 4*R*) | |
| 10 |  | n = 1 | 91% (3*S*, 4*R*) | 10% (3*S*, 4*R*) | | |  |
| 11 | | n = 2 | 41% (3*S*, 4*R*) | | | | |
| 12 |  | | 31% (3*S*, 4*R*) | | | |  |
| 13[d] |  | R = <br>n-C$_7$H$_{15}$ | 80%(3*S*, 4*R*) | | | |  |
| 14[d] | | R = t-Bu | 83% (3*S*, 4*R*) | 1% (3*S*, 4*R*) | | 61% (3*S*, 4*R*) | |
| 15[d] |  | | 30% (3*S*, 4*R*) | | | |  |
| 16 |  | | 47% (2*S*, 3*R*) | | | |  |
| 17 |  | | 21% (3*S*, 4*S*) | 67% (3*S*, 4*S*) | 67 (3*R*, 4*R*) | 32% (3*S*, 4*S*) |  |
| 18 |  | R = CN | | 58% (3*S*, 4*S*) | 63% (3*R*, 4*R*) | |  |
| 19 | | R = Br | | 59% (3*S*, 4*S*) | 74% (3*R*, 4*R*) | | |
| 20 | | R = CF$_3$ | | 66% (3*S*, 4*S*) | 74% (3*R*, 4*R*) | | |
| 21 | | R = Et | | 76% (3*S*, 4*S*) | 84% (3*R*, 4*R*) | | |
| 22 |  | n = 1 | 42% (1*R*, 2*S*) | 35% (1*R*, 2*S*) | | |  |
| 23 | | n = 2 | 15% (1*R*, 2*S*) | 7% (1*R*, 2*S*) | | 16% (1*R*, 2*S*) | |

[a] The isolated yields of diols were 30–97% for unsubstituted cyclic dienes (entries 1–5), 34–84% for substituted cyclic dienes (entries 6–12 and 16), 50–60% for fulvenes (entries 13–15), and 70–90% for cyclic olefins (entries 17–23). [b] Enantiomeric excesses were determined by HPLC analysis of MTPA esters (entries 1–6), benzoyl esters (entries 7 and 8), and free diols (entries 9–23); see supplementary material. [c] The absolute configurations of the diols were assigned as described in the text (only those for entries 2, 12, 17, 18, 22, and 23 have been proved by direct correlation). For the fulvene-derived diols the absolute configurations are tentatively assigned following the AD face-selection mnemonic. [d] See ref 10 for reaction conditions.

22,[15] and 23[15b–d],[16]). The configuration of entry 10 was assigned using Mosher's $^1$H NMR method.[17] The configurations of the 16 remaining diols are tentatively assigned using our mnemonic device (Figure 2) in which the sp$^2$ substituent on the reacting cis-double bond always occupies the northwest quadrant, while the sp$^3$ substituent on the same double bond resides in the

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(11) Takano, S.; Yoshimitsu, T.; Ogasawara, K. *J. Org. Chem.* **1994**, *59*, 54. All configurational assignments are reversed in this publication.

(12) Pansegrau, P. D.; Anderson, K. S.; Widlanski, T.; Ream, J. F.; Sammons, R. D.; Sikorski, J. A.; Knowles, J. R. *Tetrahedron Lett.* **1991**, *32*, 2589.

(13) Lee, N. H.; Muci, A. R.; Jacobsen, E. N. *Tetrahedron Lett.* **1991**, *32*, 5055.

(14) (a) Halpin, R. A.; El-Naggar, S. F.; McCombe, K. M.; Vyas, K. P.; Boyd, D. R.; Jerina, D. M. *Tetrahedron Lett.* **1982**, *23*, 1655. (b) Jennings, R. C. *Tetrahedron Lett.* **1982**, *23*, 2693.

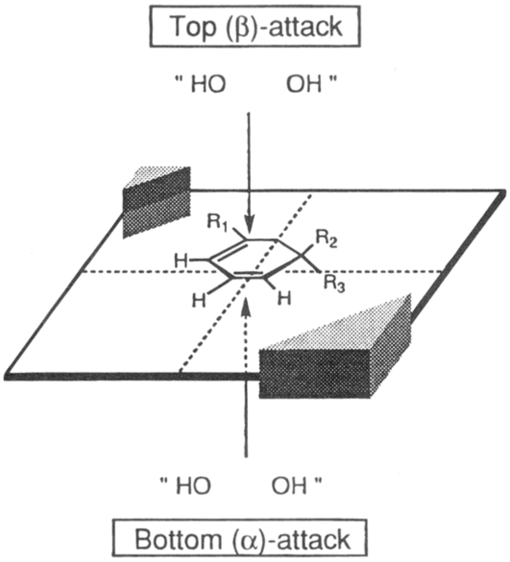


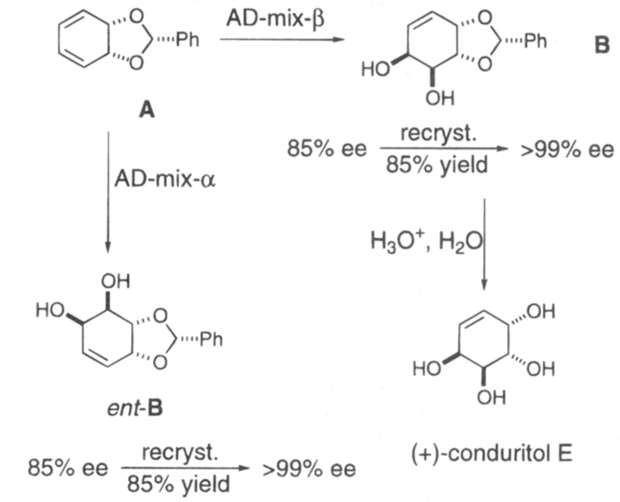
**Figure 2.**

northeast quadrant. In these latter cases the assignment was also supported by comparison (e.g., sign of rotation and order of elution from chiral HPLC) with the diols of analogous structure and known configuration (see supplementary material for details).

The above mnemonic device has proven quite dependable for this class of substrates. For example, when we applied it to the recently published results[11] for AD of prochiral diene **A** it predicted the opposite enantiofacial selectivities to those reported. Indeed, as the authors now realize,[18] all the absolute configurations in their paper are reversed due to comparison with an incorrect literature assignment for conduritol.[19a] Their excellent AD results for diene **A** are shown in Scheme 1 with the correct absolute configurations.

In conclusion, this study extends the AD to a new class of synthetically useful olefins.[20]

**Scheme 1**



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**Note added in proof**: Catalytic enantioselective epoxidations of cyclic 1,3-dienes were reported early this year by the Jacobsen group [Chang, S.; Heid, R. M.; Jacobsen, E. N. *Tetrahedron Lett.* **1994**, *35*, 669].

**Supplementary Material Available:** Characterization data for all the diols, as well as the methods for their ee determination and for establishing their absolute configurations (14 pages). This material is contained in 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.

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(15) (a) Kabato, K.; Ziffer, H. *J. Org. Chem.* **1975**, *40*, 3467. (b) Imute, M.; Ziffer, H. *J. Am. Chem. Soc.* **1979**, *101*, 3990. (c) Kasai, M.; Kawai, K.; Imute, M.; Ziffer, H. *J. Org. Chem.* **1984**, *49*, 675. (d) Boyd, D. R.; McMordie, R. A. S.; Sharma, N. D.; Dalton, H.; Williams, P.; Jenkins, R. O. *J. Chem. Soc., Chem. Commun.* **1989**, 339.

(16) Imute, M.; Ziffer, H. *J. Org. Chem.* **1978**, *43*, 4540.

(17) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *103*, 4092.

(18) Personal communication from Professors K. Ogasawara and S. Takano.

(19) (a) Hudlicky, T.; Price, J. D.; Olivo, H. F. *Synlett* **1991**, 645. (b) This assignment was corrected in: Carless, H. A. J. *Tetrahedron: Asymmetry* **1992**, *3*, 795. See also: Hudlicky, T.; Luna, H.; Olivo, H. F.; Anderson, C.; Nugent, T.; Price, J. D. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2907.

(20) While a lot of the ee's are not yet in the useful range, a number of them are. In addition, some of the diols are crystalline and reach high enantiopurity after recrystallization (e.g., entries 12, 17, 19, 20, and 21).