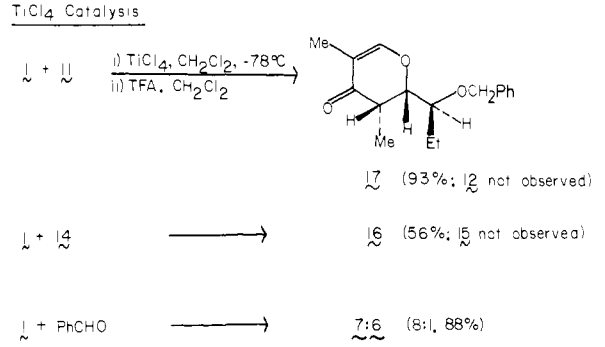
respectively. It is interesting to note that with the nonchelatable benzaldehyde, under these same conditions, the topology of the process is changed, affording an 8:1 ratio of the trans and cis pyrones **7** and **6**, respectively.



In summary, the following stereochemical relationships can now be built into the cyclocondensation reaction with alkoxyaldehydes With magnesium bromide, strict chelation control is coupled to the exo pericyclic mode, leading to trans dihydropyrones. With titanium tetrachloride, strict chelation control is coupled to erythro stereochemistry in a Mukaiyama[1] aldol process, leading to cis dihydropyrones. Since the dihydropyrones are themselves amenable to the installation of additional chirality in a systematic fashion, a new strategy for asymmetric synthesis is at hand.

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Sulfoxide-Mediated Intramolecular Hydroxylation of a Remote Olefin in an Acyclic System

Frank M. Hauser*† and Suzanne R. Ellenberger

Department of Chemistry and Biochemical Sciences
Oregon Graduate Center
Beaverton, Oregon 97006

Jon C. Clardy and Lawrence S. Bass

Baker Laboratory, Cornell University
Ithaca, New York 14853

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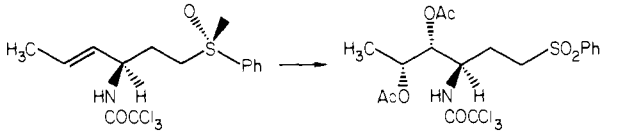
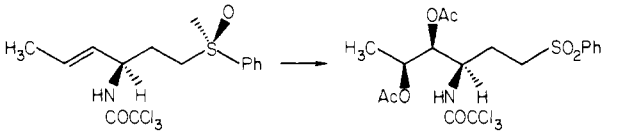
The development of procedures for diastereo- and enantioselective functionalization of acyclic olefinic systems has greatly facilitated the synthesis of complex natural products.[1-7] A criterion for successful use of this methodology is that participating functionality be proximate, i.e., allylic or homoallylic to the olefinic center.

In conjunction with our program to develop methods for stereoselective synthesis of biologically important amino hexoses from noncarbohydrate precursors,[7] we have found an example of stereospecific hydroxylation of an olefinic center in an acyclic system that is guided by a sulfoxide functionality more remote than homoallylic.[8]

Treatment of separate diastereoisomeric sulfoxides **1** and **3** with a catalytic amount of osmium tetroxide (3-5 mol %) and trimethylamine *N*-oxide[9] (3 equiv) furnished, after acetylation, the diastereoisomeric diacetate sulfones **2** (96%, mp 134-136 °C) and **4** (93%, mp 149-150 °C), respectively, as the sole products of



1 **2**

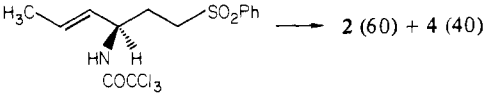


3 **4**

the individual reactions. The stereochemistry in **2** and **4** was tentatively assigned by observation of the acetate methyl absorptions in the ^{1}H NMR spectra. The acetate methyls in **2** were closely-spaced singlets (δ 1.74 and 1.71) whereas in **4** they were well-separated singlets (δ 1.87 and 1.74).[10] This difference was attributed to the fact that in the chain-extended configuration of **4**, hydrogen bonding between the amide proton and the carbonyl oxygen of the neighboring acetate generates a seven-membered ring in which the alkyl substituents are equatorial.

Initially, the stereochemistry of the individual sulfoxides **1** and **3** was assigned by assuming that a complexation between the oxygen of the sulfoxide and the osmium had occurred prior to hydroxylation of the olefin.[11] This supposition was subsequently confirmed by hydroxylation of the olefinic sulfone **5** and by X-ray analysis of the sulfoxide **1**.

In order to establish if the olefinic sulfone **5** was an intermediate and to assess the role of the amide functionality in determining the stereochemical outcome, **5** was independently prepared and hydroxylated under the same conditions. After acetylation, a 60:40 ratio of diacetate sulfones **2** and **4** was obtained in a 94% yield.



5

This result demonstrates that while the amide exerts a modest steric effect favoring formation of the anti (relative to the amide) hydroxylation product, complexation of the amide with the osmium is not occurring.[12] Furthermore, the fact that hydroxylation of

† Recipient of a Career Development Award, 1978-1983, from the National Cancer Institute (CA 00486).

(1) For a recent review, see: Bartlett, P. A. *Tetrahedron* **1980**, 2, and references therein.

(2) For the (a) diastereo- and (b) enantiospecific epoxidation of allyl alcohols, see: (a) Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1957**, 1958. Pierre, J.-L.; Chautempts, P.; Arnaud P. *Bull. Soc. Chim. Fr.* **1969**, 1317. Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136. Tanaka, S.; Yamamoto, H.; Nozaki, H.; Sharpless, K. B.; Michaelson, R. C.; Cutting, J. D. *Ibid.* **1974**, *96*, 5254. Chautemps, T.; Pierre, J.-L. *Tetrahedron* **1976**, 549. Rossiter, B. E.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, *20*, 4733. Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63. Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S. *J. Chem. Soc.* **1979**, *101*, 159. (b) Yamada, S.; Mashiko, T.; Terashima, S. J. *Ibid.* **1977**, *99*, 1988. Michaeslon, R. C.; Palermo, R. E.; Sharpless, K. B. *Ibid.* **1977**, *99*, 1980. Katsuki, T.; Sharpless, K. B. *Ibid.* **1980**, *102*, 5974.

(3) For the diastereoselective epoxidation of homoallylic alcohols, see: Barlett, P. A.; Jernstedt, K. K. *J. Am. Chem. Soc.* **1977**, *99*, 4828.

(4) For the diastereoselective halo-hydroxylation of allyl and homoallyl amides, see: Wang, Y.-F.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1982**, *104*, 6465. Parker, K. A.; O'Fee, R. *Ibid.* **1983**, *105*, 654.

(5) For the enantioselective hydroxylation of olefins with osmium tetroxide, see: Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263.

(6) For the diastereoselective hydroxylation of allyl alcohols with osmium tetroxide, see: Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943; **1983**, 3947. Stork, G.; Kahn, M. *Ibid.* **1983**, *24*, 3951.

(7) For the diastereoselective hydroxylation of an allyl amide with osmium tetroxide, see: Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1981**, *46*, 227.

(8) Johnson and co-workers have found that a sulfoximine group will guide the stereospecific hydroxylation of an adjacent olefinic center. Johnson, C. R.; Barbachyn, M. R. *J. Am. Chem. Soc.*, following paper in this issue.

(9) Ray, R.; Matteson, D. S. *Tetrahedron Lett.* **1980**, *21*, 449.

(10) Spectra were determined in benzene-d_6.

(11) This assumption was based on the fact that both Os^{8+} and the sulfoxide oxygen are hard species.

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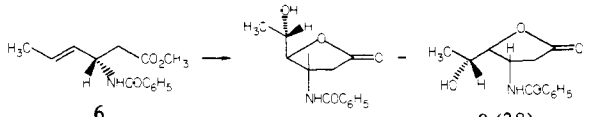
the sulfoxides is stereospecific and that of the sulfone is not demonstrates that oxidation of the sulfoxide to a sulfone does not take place prior to hydroxylation of the olefin. Additional evidence which indicates that a complex initially forms between the osmium and the sulfoxide group was derived from a study of the hydroxylation of **1** and **3** with 2 or less equiv of TMNO. In every instance, only the diol sulfones **2** and **4** and the respective starting materials were isolated. No products of incomplete oxidation or hydroxylation such as the diol sulfoxide or olefinic sulfone **5** were found.[13] Apparently, once complexation of the osmium occurs, complete conversion to products results.

Further studies have been initiated to establish the generality of this methodology and to extend it to achieve diastereo- and enantioselective total syntheses of natural products.

Acknowledgment. We express our appreciation to Drs. Richard Finke and John Baldwin (University of Oregon) and G. Doyle Daves, Jr. (Lehigh University), for their comments. This work was generously supported by the National Institutes of Health of the Department of Health, Education and Welfare (GM 26754 and CA 24487).

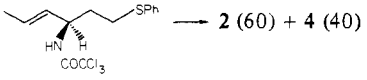
Supplementary Material Available: An ORTEP drawing and tables of fractional coordinates, bond distances, and bond angles (6 pages). Ordering information is given on any current masthead page.

(12) In related work, hydroxylation of the allyl amide **6** gave a 62:38 ratio of lactones **7** and **8**.[7] A parallel explanation accounts for this result.



6 7 (62) 8 (38)

(13) Upon hydroxylation of the olefinic sulfide **9** (catalytic OsO_4, 4 equiv of TMNO) and subsequent acetylation, a 60:40 ratio of the diacetate sulfones



2 and **4** were obtained as the only products of reaction. The relative rate of oxidation is: sulfone > sulfoxide ≫ sulfide.

Sulfoximine-Directed Osmylation: Synthesis of Enantiomerically Pure Dihydroxycycloalkanones

Carl R. Johnson* and Michael R. Barbachyn

Department of Chemistry, Wayne State University
Detroit, Michigan 48202

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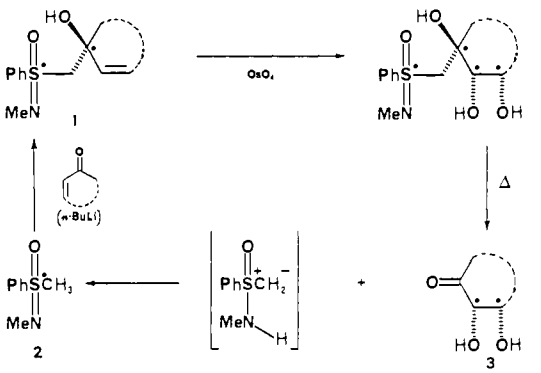
Of the existing methods for the conversion of alkenes to *cis*-1,2-diols, the most reliable method continues to be the reaction of alkenes with osmium tetroxide in either catalytic[1a] or stoichiometric[1b,2] modes. The stereochemical outcome of alkene osmylations with respect to existing substituents in the substrate is dependent on several factors. Steric considerations are of demonstrated importance.[3] The importance of allylic

Scheme I



substituents—especially heteroatom-containing groups such as hydroxyl or alkoxyl—in the determination of diastereoface selectivity has also become evident.[4-7]

Osmium tetroxide is known to reversibly form stable adducts with basic ligands such as pyridine[1b] and quinuclidine.[8] Behrman and co-workers[9] have invoked this complexation to account for a sequence-selective osmylation in polynucleotides in which the cyclosine residues are modified by attaching an osmiophilic diamino residue. We anticipated that the methylimino group of adducts **1**[10] of *N*,*S*-dimethyl-*S*-phenylsulfoximine (**2**) and cycloalkenones would facilitate and direct[14] osmylation of the adjacent carbon–carbon double bond. Furthermore, the antiperiplanar effect[7] of the allylic hydroxyl group should provide a synergistic enhancement of the diastereoface selectivity. A novel dihydroxy ketone optical activation method was envisioned involving (1) directed osmylation and (2) thermal reversal[12] of the sulfoximine addition to afford optically pure dihydroxy ketones **3** and the recyclable resolving agent **2** (Scheme I).

As an initial probe of this concept, (*S*)-**2** was added to 3,5,5-trimethyl-2-cyclohexenone and the resulting diastereomers **4** were separated by silica gel chromatography using ethyl acetate/hexanes as eluent.[10,12] Treatment of the individual diastereomers[13] in water/tetrahydrofuran solutions containing trimethylamine *N*-oxide dihydrate (1.5 equiv) with solutions of osmium tetroxide (5 mol %) in tetrahydrofuran for 24–72 h at room temperature afforded crude triols. In each case, analytical HPLC revealed a single diastereomeric product, which was isolated in 78% yield after flash chromatography as a white amorphous solid. Stoi-

(1) (a) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973. Ray R.; Matteson, D. S. *Ibid.* **1980**, 449. (b) Criegee, R. *Justus Liebigs Ann. Chem.* **1936**, *522*, 75. Criegee, R.; Marchand, B.; Wannowius, H. *Ibid.* **1942**, *550*, 99.

(2) Schroder, M. *Chem. Rev.*, **1980**, *80*, 187.

(3) Danishefsky, S.; Hirama, M.; Gombatz, K.; Harayama, T.; Berman, E.; Schuda, P. *J. Chem. Soc.* **1978**, *100*, 6536; *Ibid.* **1979**, *101*, 7020. (b) Smith, A. B., III; Boschelli, D. *J. Org. Chem.* **1983**, *48*, 1217. For a related result, see: Kon, K.; Isoe, S. *Tetrahedron Lett.* **1980**, *3399*.

(4) For a discussion of factors affecting the stereochemistry of osmylations of allylic alcohol systems, see: (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, 3943, 3947. (b) Stork, G.; Kahn, M. *Ibid.* **1983**, 3951.

(5) Smith, A. B., III; Branca, S. J.; Pilla, N. N.; Guaciara, M. A. *J. Org. Chem.* **1982**, *47*, 1855.

(6) Posternak, T.; Friedli, H. *Helv. Chim. Acta* **1953**, *36*, 251.

(7) For a discussion of the "antiperiplanar effect" and its role in controlling the stereochemistry of additions to allylic systems see: Caramella, P.; Rondan, N. G.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2438. Paddon-Row, M. N. Rondan, N. G., Houk, K. N. *Ibid.* **1982**, *104*, 7162. Houk, K. N. *Pure Appl. Chem.* **1983**, *55*, 277. See also: Franck, R. W.; John, T. V.; Olejniczak, K.; Blount, J. F. *J. Am. Chem. Soc.* **1982**, *104*, 1106.

(8) Cleare, M. J.; Hydes, P. C.; Griffith, W. P.; Wright, M. J. *J. Chem. Soc., Dalton Trans.* **1977**, 941.

(9) Ford, H.; Chang, C.-H.; Behrman, E. *J. J. Am. Chem. Soc.* **1979**, *101*, 2251; **1981**, *103*, 7773.

(10) Johnson, C. R.; Barbachyn, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 4290. This paper describes the preparation of enantiomerically pure cyclopropyl ketones utilizing the hydroxyl group of enantiomerically pure β-hydroxysulfoximines of type **1** to provide diastereoface selection in the Simmons–Smith reaction.

(11) The directive effect of a basic group in this reaction could be the result of guidance of the reagent to one diastereoface of the alkene or of nucleophilic triggering of osmate ester formation from equilibrating oxametallacyclobutane intermediates. For recent discussions of osmium tetraoxide mechanisms, see: Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263. Sharpless, K. B.; Teranishi, A. Y.; Backvall, J.-E. *Ibid.* **1977**, *99*, 3120. Casey, C. P. *J. Chem. Soc., Chem. Commun.* **1983**, *126*. Schroder, M.; Constable, E. C. *Ibid.* **1982**, 734.

(12) Johnson, C. R.; Zeller, J. R. *J. Am. Chem. Soc.* **1982**, *104*, 4021; *Tetrahedron*, in press.

(13) In some cases it was found to be more expedient to osmylate the mixture of diastereomers **1** and then separate the triol diasteromers by chromatography.

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