α-Hydroxy Ketones in High Enantiomeric Purity from Asymmetric Dihydroxylation of Enol Ethers

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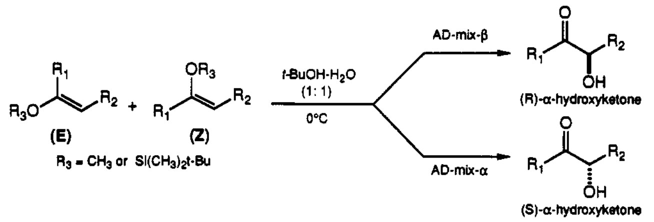
Summary: Highly enantioselective construction of α-hydroxy ketones by the osmium-catalyzed asymmetric dihydroxylation of the corresponding enol ethers has been achieved.

Chiral α-hydroxy ketones are important building blocks for the asymmetric synthesis of natural products[3] and medicines.[4] Consequently, numerous studies have aimed at their stereoselective synthesis.[5] Recently, Davis et al.[5] reported that α-hydroxy carbonyl compounds are obtained with good enantioselectivities by asymmetric oxidation of ketone enolates using an enantiomerically pure oxaziridine. In our efforts to extend the scope of the asymmetric dihydroxylation (AD),[6] we have now found that enol ethers are excellent substrates, giving α-hydroxy ketones in high enantiomeric purity. Both alkyl and silyl enol ethers were examined.

Except for entries 6 and 7, all the AD experiments reported in Table I were performed on the crude *E*/*Z* mixture of enol ether isomers produced by either the Wohl[8] or Ireland[9] methods. α-Hydroxy ketones were isolated in 68–95% yields and with good to excellent enantiomeric excesses. As shown in Scheme I, (*R*)-α-hydroxy ketones result when AD-mix-β[10] is employed and (*S*)-α-hydroxy ketones arise using AD-mix-α-.[10] Comparable isolated yields and ee's were obtained from both AD-mixes. One can easily obtain the *Z*-rich, trisubstituted methyl enol ethers from aliphatic ketones, and these *Z*-trisubstituted enol ethers are expected to give high enantioselectivity in the AD process.[11] Indeed, these methyl enol ethers of saturated ketones gave high ee's (entries 1 and 2). On the other hand, aryl ketones gave methyl enol ethers with substantial *E*-isomer content; nevertheless, they too gave good to excellent ee's (entries 3–5). Methyl enol ethers of aryl alkyl ketones appear to give better ee's with a longer alkyl chain (cf. entries 3 and 5). Surprisingly, the *E* methyl enol ether of deoxybenzoin gave 90% ee (entry 7). *Z*-Rich silyl enol ethers of aryl alkyl and aryl aryl ketones gave excellent ee's (97–99 % ee) (entries 10–13).

Scheme I



It is noteworthy that a poor *Z*/*E* ratio in the preparation of an enol ether is not necessarily damning with regard to the enantioselectivity realized upon AD of the *E*/*Z* mixture. For example, the results in entries 3, 4, 5, 7, and 8 reveal that the *E*-isomer gives the same ketol enantiomer as the *Z*-isomer, albeit in somewhat lower ee. In fact, only the *E*-isomer of methyl enol ethers derived from saturated ketones (i.e., entries 1 and 2) gave poor ee's.[12] Fortunately, this particular class of enol ethers is readily produced with high *Z*-isomer content.

Enol ethers are relatively easy to prepare and the AD is so simple and convenient to perform that this new approach should in many cases offer the best route available to chiral α-hydroxy ketones. However, certain aspects of these results, especially those for aryl-substituted methyl enol ethers (e.g., entries 5 and 7), appear to violate our proposed selectivity mnemonic by placing a phenyl substituent in the quadrant where the smallest non-hydrogen substituent should lie. These puzzling observations provide ideas and impetus for our ongoing mechanistic studies of the AD process.

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[1] On leave from Tanabe Seiyaku Co. LTD.

[2] On leave from Showa Denko K. K.

[3] Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon Press: New York, 1983; Chapter 2.

[4] (a) Girijavallabhan, V. M.; Ganguly, A. K.; Pinto, P. A.; Sarre, O. Z. *BioMed. Chem. Lett.* **1991**, *1*, 349. (b) Konosu, T.; Miyaoka, T.; Tajima, Y.; Oida, S. *Chem. Pharm. Bull.* **1991**, *39*, 2241.

[5] Davis, F. A.; Sheppard, A. C.; Chen, B.-C.; Haque, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6679 and references cited therein.

[6] (a) Sharpless, K. B.; Amberg, W.; Beller, M.; Chen. H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585. (b) 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 and references cited therein.

[7] (a) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324. (b) Uijttewaal, J. A.; Jonkers, F. L.; van der Gen, A. *J. Org. Chem.* **1979**, *44*, 3157.

[8] Wohl, R. A. *Synthesis* **1974**, 38. We obtained highly *Z*-rich methyl enol ethers from aliphatic ketones (entries 1 and 2) without any special efforts, and the same procedures gave methyl enol ethers with poor *Z*/*E* ratios from aryl ketones (entries 3–7). The typical procedure is described in the supplementary material.

[9] Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. The presence of HMPA results in high *Z*-selectivity.

[10] The AD-mix-β or AD-mix-α, 1.4 g, necessary for the conversion of 1 mmol of olefin contains 0.980 g of $K_3Fe(CN)_6$ (3 mmol), 0.410 g of K_2CO_3 (3 mmol), 0.0078 g of $(DHQD)_2$-PHAL (for AD-mix-β) or $(DHQ)_2$-PHAL (for AD-mix-α) (0.01 mmol), and 0.00074 g of $K_2OsO_2(OH)_4$ (0.002 mmol). These two AD-mixes are now available from Aldrich.

[11] We have reported a mnemonic device which predicts that the trisubstituted *Z*-enol ethers from ketones will give better ee's than their *E* counterparts. See ref 6.

[12] The AD of a 15*E*/85*Z* mixture of the methyl enol ether of 2,6-dimethyl-4-heptanone using AD-mix-β gives the α-hydroxy ketone in 86% ee. Therefore, by comparison with the result in entry 2 (in this AD both *E*- and *Z*-isomers reacted completely) we can estimate that the *E*-isomer gives less than 40% ee.

[13] **A Typical Procedure.** To a well-stirred mixture of AD-mix-β (1.4 g) and $CH_3SO_2NH_2$ (0.095 g, 1 mmol) in *tert*-butyl alcohol-water (5 mL/5 mL) at 0 °C was added (*Z*)-1-(4-methoxyphenyl)-1-(*tert*-butyldimethylsiloxy)-1-propene (entry 11) (0.278 g, 1 mmol). The reaction mixture was stirred for 16 h at 0 °C. Solid sodium sulfite (1 g) was added and the mixture was stirred for an additional hour. Methylene chloride (30 mL) was added to the reaction mixture and after separation of the layers, the aqueous phase (lower layer) was further extracted with CH_2Cl_2 (30 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated to give an oil, which was purified by flash chromatography to afford pure (*R*)-2-hydroxy-1-(4-methoxyphenyl)propanone as a colorless oil (0.172 g, 94%). This ketol was fully characterized by ^1H NMR, IR, and HRMS. The ee was determined to be 99% by HPLC (Daicel Chiralcel OB); $[\alpha]^{25}_D$ +32.8° (*c* 1.36, MeOH). Tsuchihashi; et al. [*Bull. Chem. Soc. Jpn.* **1987**, *60*, 1027] reported $[\alpha]^{20}_D$ −33.4° (*c* 1.05, MeOH) for the *S*-isomer.

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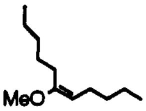
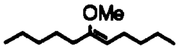
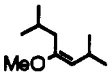
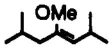
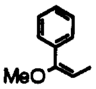
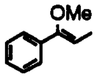
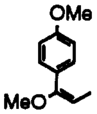
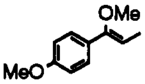
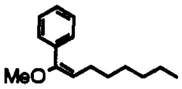
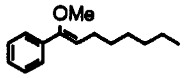
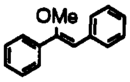
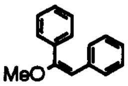
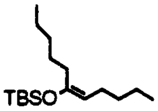
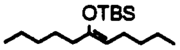
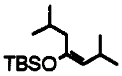
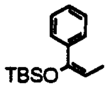
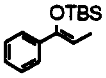
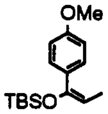
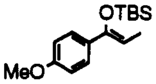
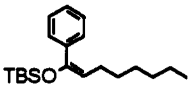
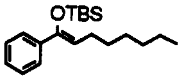
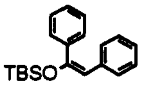
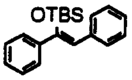
Table I. Enantiomeric Excess (% ee) of the α-Hydroxy Ketones Resulting from Catalytic Asymmetric Dihydroxylation (AD) of Enol Ethers

	enol ether[a]			AD-mix-β		AD-mix-α	
entry	*E*	*Z*	ratio of E/Z	% ee[b]	confign[c]	% ee[b]	confign[c]
1			4/96	95	(*R*)[d]	96	(*S*)[d]
2			6/94	91	(*R*)[d]	93	(*S*)[d]
3			33/67	85	*R*	84	*S*
4			42/58	87	*R*	87	*S*
5			33/67	94	(*R*)[d]	92	(*S*)[d]
6[e]			1/>99	99	*R*	98	*S*
7[f]			>99/1	90	*R*		
8			25/75	89	(*R*)[d]	86	(*S*)[d]
9			12/88	79	(*R*)[d]		
10			1/>99	97	*R*		
11			1/>99	99	*R*	97	*S*
12			1/>99	99	(*R*)[d]	99	(*S*)[d]
13			<3/>97	97	*R*		

[a] Assignments of *E*- and *Z*-isomers of enol ethers were made by ^{1}H NMR,[7] and the *E*/*Z* ratio was also determined by ^{1}H NMR analysis. [b] Enantiomeric excesses were determined by HPLC analysis (see supplementary material). [c] Absolute configurations were determined by comparison of optical rotations with literature values. [d] Absolute configurations were not determined in these cases. They are tentatively assigned by (1) analogy to the sign of the rotation for similar ketols of known configuration, (2) and adhering to the AD face selection rule. [e] The pure *Z*-isomer was obtained by crystallization. [f] The pure *E*-isomer was obtained by flash chromatography on silica.

to undertake this study based on his own successful results in the AD of enol ethers at Sepracor.

Supplementary Material Available: General experimental procedures for the preparation of methyl enol ethers and for the AD of enol ethers, as well as spectral data for starting materials and products, details for determination of enantiomeric excesses and absolute configurations of α-hydroxy ketones (5 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.