# *Communications*

Regioselective Carbomethoxylation of Chiral Epoxides: A New Route to Enantiomerically Pure β-Hydroxy Esters

Klaus Hinterding and Eric N. Jacobsen*

*Department of Chemistry and Chemical Biology, Harvard University, Cambridge, MA 02138*

An efficient method for the catalytic carbonylation of aliphatic, racemic epoxides has been reported in the recent patent literature using $Co_2(CO)_8$ (**1**) in the presence of 3-hydroxypyridine (**2**) as cocatalyst.[1] We became interested in the possibility of applying this reaction to the carbonylation of enantioenriched epoxides, as the coupling of such practical methodology to the recently developed co-catalyzed hydrolytic kinetic resolution (HKR) of terminal epoxides[2] (eq 1) could provide novel access to synthetically valuable β-hydroxy carbonyl derivatives in optically active form. We describe here the successful elaboration of this strategy.

(1)
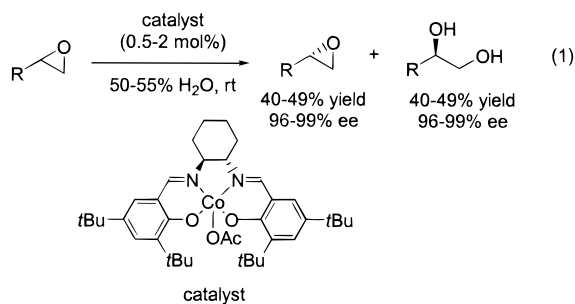
Under reducing conditions using CO/H_2, carbonylation of epoxides can lead directly to β-hydroxy carbonyl compounds in the aldol oxidation state.[3] Subjection of a series of optically pure terminal epoxides (**3a−h**) to CO/H_2 (1:1, 1000 psi) in the presence of **1** (5 mol %) led to dimeric aldol products. Treatment with 1,3-propane diol under acidic conditions provided the monomeric dioxolane derivatives (eq 2).

(2)
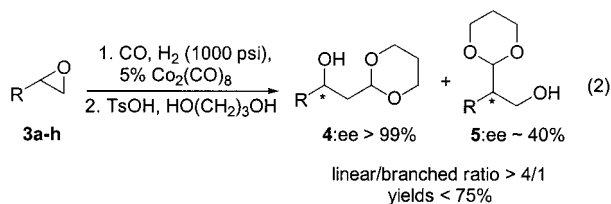
The stereochemical integrity of the reactants was preserved in the linear reaction products **4** (ee >99%). However, this procedure was found to suffer from formation of

Table 1. Carbomethoxylation of Enantiomerically Pure Terminal Epoxides

substrate		temperature (°C)[a]	yield (%)	ee[b] (%)
	3a	65	92	> 99
	3b	65	95	> 99
	3c	65	93	> 99
	3d	65	96	> 99
Cl—	**3e**	55	96	> 99
	3f	60	95	> 99
BnO—	**3g**	55	86	> 99
MeO—	**3h**	60	91	> 99

[a] All reactions were run on a 5 mmol scale in a 1/1 mixture of MeOH/THF at $[3a−h]_0 = 0.5$ M and a final pressure of 600 psi for 9 h, except for **3h**, which was run at 670 psi. [b] ee's were determined by chiral GC or by chiral HPLC using commercially available chiral columns. See the Supporting Information.

branched byproducts **5** (linear/branched = 50:1−4:1) and unsatisfactory yields (<75% for the two step process). In addition, partial racemization accompanied formation of the branched isomers, with ee's of ca. 40% measured for the isolated products.

In contrast, carbomethoxylation of highly enantioenriched epoxides with CO/MeOH according to the Drent protocol[1] proved to be high-yielding, highly regioselective, and stereoretentive. Reaction of methanolic solutions of epoxides **3a−h** in the presence of 5 mol % **1** and 10 mol % **2** proceeded under relatively mild conditions (600 psi CO, 55−65 °C) to furnish the 3-hydroxy esters **6a−h** in optically pure form (Table 1). The experimental protocol is remarkably simple: filtration of the crude reaction mixtures through silica gel to remove catalysts, followed by solvent evaporation, afforded the products in excellent yields and >95% purity as determined by ^{1}H NMR analysis.[4]

A range of functional groups on the epoxide are tolerated in the carbomethoxylation reaction. For example, no deleterious effects were observed in substrates bearing halide (**3e**),

(1) (a) Drent, E.; Kragtwijk, E. Eur. Pat. Appl. 577206, 30 Mar. 1994; *Chem Abstr.* **1994**, *120*, 191517c. (b) For earlier work, see: Eisenmann, J. L.; Yamartino, R. L.; Howard, J. F. *J. Org. Chem.* **1961**, *26*, 2102.
(2) (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (b) Brandes, B. D.; Jacobsen, E. N. *Tetrahedron: Asymmetry* **1997**, *8*, 3927. (c) Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 6776.
(3) (a) Yokokawa, C.; Watanabe, Y.; Takegami, Y. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 677. (b) Takegami, Y.; Yokokawa, C.; Watanabe, Y. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 935. (c) Roos, L.; Goetz, R.W.; Orchin, M. *J. Org. Chem.* **1965**, *30*, 3203. d) Rosenthal, A.; Kan, G. *Tetrahedron Lett.* **1967**, 477.

(4) **General Experimental Procedure for the Preparation of Hydroxy Esters 6a−h.** An autoclave was charged under air with **1** (0.25 mmol, 85 mg) and **2** (0.5 mmol, 48 mg). THF (5 mL) and MeOH (5 mL) were added, followed by epoxides **3a−h** (5 mmol). The reaction vessel was flushed three times with CO (15 psi) and then charged to a pressure of 600 psi (~40 bar). After being heated and stirred under the stated conditions (Table 1), the autoclave was cooled to room temperature, the excess gases were vented carefully, and the reaction mixture was poured into Et_2O (150 mL) to precipitate the catalysts. The suspension was stirred in air for 2 h and then filtered through a plug of silica gel. Solvents were removed in vacuo, affording the reaction products as colorless or slightly yellowish oils in >95% purity as determined by ^{1}H NMR.

alkenyl (**3f**),[5] benzyloxy (**3g**), or enolizable ester (**3h**) substituents. In general, carbonylation occurred selectively at the 1-position of the terminal epoxide; only in the case of propylene oxide (**3a**) could a branched isomer be detected by GC analysis (linear/branched > 50:1). However, terminal epoxides bearing sp[2] substituents (e.g., styrene oxide and 1,3-butadiene monoepoxide) underwent carbomethoxylation in low yield (10−15%) and with poor regioselectivity (linear/ branched ~1:1). The complete retention of the stereochemical integrity of the epoxide substrates in the β-hydroxy ester products is a key feature of this reaction and is most notable in the case of diester **6h**, which can undergo epimerization via enolization, and of chloro ester **6e**, given that the precursor epoxide epichlorohydrin is susceptible to racemization in the presence of nucleophiles.[6]

Application of two sequential cobalt-catalyzed reactions allows the synthesis of a range of enantiomerically enriched β-hydroxy esters from racemic epoxides. In most cases, the requisite epoxides are readily available, and both reactions are easily performed on a large scale.[7] In addition, the carbonylation methodology can be extended to afford direct access to different carbonyl derivatives including aldehydes (vide supra), carboxylic acids,[1] and Weinreb amides.[8,9] This strategy for the preparation of enantiopure β-hydroxy carbonyl building blocks thereby provides an interesting alternative to existing, highly effective reductive and aldol-type methods.[10]

Supporting Information Available: Chromatographic analyses of racemic and enantiomerically enriched β-hydroxy esters **6a**−**h**.

JO982336L

(5) Carboalkoxylations of olefins generally require much harsher conditions than those employed here. See, for example: Takeuchi, R.; Ishii, N.; Sugiura, M.; Sato, N. *J. Org. Chem.* **1992**, *57*, 4189. For reviews see: (a) Tkatchenko, I. In *Comprehensive Organometallic Chemistry;* Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, 1982; Vol. 8, pp 101−223. (b) Bates, R. W. In *Comprehensive Organometallic Chemistry II;* Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: Oxford, 1995, Vol. 12, pp 349−386.

(6) Schaus, S. E.; Jacobsen, E. N. *Tetrahedron Lett.* **1996**, *37*, 7937.

(7) The reaction was carried out on a 200 mmol scale for (*S*)-propylene oxide **3a** (65 °C, 600 psi, 24 h) using only MeOH (200 mL) as solvent. (*S*)-Methyl-3-hydroxybutyrate **6a** was obtained in 83% yield by distillation (regioselectivity: l/b > 60/1; no racemization detectable).
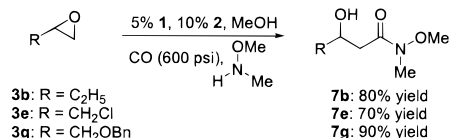
(8) Preliminary experiments indicate that performing the carbonylation reaction in the presence of *N,O*-dimethylhydroxylamine results in direct formation of β-hydroxy Weinreb amides in 70−90% yield:

3b: R = C$_2$H$_5$
3e: R = CH$_2$Cl
3g: R = CH$_2$OBn

7b: 80% yield
7e: 70% yield
7g: 90% yield

(9) Benzyl amides can also be prepared by an analogous procedure. See: Tsuji, Y.; Kobayashi, M.; Okuda, F.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 1253.

(10) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; Chapter 2, pp 28−55. For a leading reference on asymmetric catalytic aldol approaches to simple β-hydroxy carbonyl compounds, see: Carreira, E. M.; Singer, R. A.; Lee, W. S. *J. Am. Chem. Soc.* **1994**, *116*, 8837.