Highly Enantioselective Oxidation of *cis*-Cyclopropylmethanols to Corresponding Aldehydes Catalyzed by Chloroperoxidase

Shanghui Hu and Jonathan S. Dordick*

Department of Chemical Engineering, Rensselaer Polytechnic Institute, Troy, New York 12180

dordick@rpi.edu

Received September 30, 2001

Abstract: Chloroperoxidase (CPO) catalyzes the enantioselective oxidation of cyclopropylmethanols, such as 2-methylcyclopropylmethanol, to cyclopropyl aldehydes using *tert*-butyl hydroperoxide as the terminal oxidant. In all cases, CPO oxidation of *cis*-cyclopropanes shows much higher enantioselectivity than with the trans isomers, although CPO gives similar catalytic activity on both isomers. This presents the first example for a heme enzyme that catalyzes the enantioselective oxidation of cyclopropylmethanols. This finding enables a novel route to the synthesis of optically active cyclopropane derivatives, which occur widely in natural products and compounds of pharmaceutical interest. In addition, chiral cyclopropane molecules may be useful model substrates to investigate reaction mechanisms of CPO and the related cytochromes P450.

The chiral cyclopropyl substructure occurs widely in natural products and compounds of pharmaceutical interest.[1] Two strategies for their synthesis have been advanced: (i) catalytic transition-metal-based carbene transformation[2] and (ii) the asymmetric Simmons−Smith reaction via zinc-mediated cyclopropanation of allylic alcohols.[3] However, each method has some clear limitations. The first approach requires diazo carbonyl compounds as precursors of the putative carbenes and is successful only in generating optically active carboxylated cyclopropanes. In most cases, the products are a mixture of two diastereomers with the trans isomer predominating.[2] The second approach is effective in producing chiral cyclopropylmethanol analogues; however, stoichiometric quantities of chiral auxiliary, modifiers, or promoters are typically required to obtain high enantioselectivity (>90% ee).[3]

Enzymatic methods have also been used to prepare optically active cyclopropanes; however, the substrate range is limited.[4] For example, alcohol dehydrogenase has been used to catalyze the enantioselective oxidation of *cis*-1,2-bis(hydroxymethyl)cyclopropane with 100% ee.[4a] Esterase- and lipase-catalyzed hydrolysis of dimethyl *cis*-cyclopropane-1,2-dicarboxylate and *cis*-1,2-bis(butyryloxymethyl)cyclopropane have also been reported with 94% and 99% ee, respectively, yet this is a two-step process that involves initial chemical esterification followed by enantioselective enzymatic hydrolysis of the resulting esters. Because chiral cyclopropyl aldehydes represent useful functionalized subunits for the construction of complex natural products and compounds of pharmaceutical interest containing cyclopropyl groups,[3a,4c] we sought an alternative, highly selective, single-step enzymatic procedure to yield these compounds from corresponding cyclopropyl carbinols. To that end, we chose chloroperoxidase (CPO) from the fungus *Caldariomyces fumago* as the biocatalyst. CPO is a versatile heme enzyme that catalyzes a variety of oxidative reactions,[5,6] including asymmetric epoxidation of alkenes, allylic, benzylic, and propargylic hydroxylations, and sulfoxidations.[7] CPO normally oxidizes allylic, benzylic and propargylic alcohols to the corresponding aldehydes.[8] Because of its unique stereoelectronic effects,[9] the cyclopropane ring behaves in many ways such as an alkene. Thus we speculated that CPO could oxidize a variety of cyclopropylmethanols to the corresponding aldehydes.[10]

We have found that CPO can catalyze the enantioselective oxidation of cyclopropylmethanols to aldehydes using *tert*-butylhydroperoxide (TBHP) as the terminal oxidant. To investigate the enantioselectivity of CPO-catalyzed oxidation of racemic cyclopropylmethanols, in each case we proceeded to ca. 50% conversion of alcoholic substrate. Under the appropriate conditions, the oxidation of *trans*-2-phenylcyclopylmethanol **1** provided the respective aldehyde with relatively high reaction turn-

* To whom correspondence should be addressed. Phone: (518) 276-2899. Fax: (518) 276-2207.

(1) For selected examples, see: (a) Ashton, W. T.; Meurer, L. C.; Cantone, C.; Field, A. K.; Hannah, J.; Karkas, J. D.; Liou, R.; Patel, G. F.; Perry, H. C.; Wagner, A. F.; Walton, E.; Tolman, R. L. *J. Med. Chem.* **1988**, *31*, 2304−2315. (b) Dappen M. S.; Pellicciari, R.; Natalini, B.; Monahan, J. B.; Chiorri, C.; Cordi, A. A. *J. Med. Chem.* **1991**, *34*, 161−168. (c) White J. D.; Kim, T.-S.; Nambu, M. *J. Am. Chem. Soc.* **1995**, *117*, 5612−5613.

(2) (a) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726−728. (b) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911−935. (c) Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 10270−10271.

(3) (a) Yamamoto, H.; Arai, I.; Mori, A.*J. Am. Chem. Soc.* **1985**, *107*, 8254−8255. (b) Charette, A. B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651−2652. (c) Denmark, S. E.; O'Connor, S. P. *J. Org. Chem.* **1997**, *62*, 584−594. (d) Charette, A. B.; Juteau, H.; Lebel, H.; Molinaro, C. *J. Am. Chem. Soc.* **1998**, *120*, 11943−11952.

(4) (a) Jakovac, I. J.; Goodbrand, H. B.; Lok, K. P.; Jones, J. B. *J. Am. Chem. Soc.* **1982**, 104, 4659−4665. (b) Scheneider, M.; Engel, N.; Boensmann, H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 67. (c) Grandjean, D.; Pale, P. Chuche, J. *Tetrahedron* **1991**, *47*, 1215−1230.

(5) (a) Shaw, P. D.; Hager, L. P. *J. Biol. Chem.* **1961**, *236*, 1626−1630. (b) Morris, D. R.; Hager, L. P. *J. Biol. Chem.* **1966**, *241*, 1763−1768.

(6) (a) Blanke, S. R.; Yi, S.; Hager, L. P. *Biotechnol. Lett.* **1989**, *11*, 769−774. (b) van Deurzen, M. P. J.; van Rantwijk, F.; Sheldon, R. A. *Tetrahedron* **1997**, *53*, 13183−13220.

(7) (a) Allain, E. J.; Hager, L. P.; Deng, L.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1993**, *115*, 4415−4416. (b) Zaks, A.; Dodds, D. *J. Am. Chem. Soc.* **1995**, *117*, 10419−10424. (c) Dexter, A. F.; Lakner, F. J.; Campbell, R. A.; Hager, L. P. *J. Am. Chem. Soc.* **1995**, *117*, 6412−6413. (d) Lakner, F. J.; Cain, K. P.; Hager, L. P. *J. Am. Chem. Soc.* **1997**, *119*, 443−444. (g) Hu, S.; Hager, L. P. *Tetrahedron Lett.* **1999**, 1641−1644. (h) Hu, S.; Hager, L. P. *J. Am. Chem. Soc.* **1999**, *121*, 872−873. (i) Colonna, N.; Casella, L.; Carrea, G.; Pasta, P. *Tetrahedron*: *Asymmetry* **1992**, *3*, 95−106.

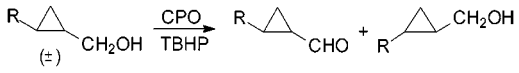
(8) (a) Geigert, J.; Dalietos, D. J.; Neidelman, S. L.; Lee, T. D.; Wadsworth, J. *Biochem. Biophys. Res. Commun.* **1983**, *114*, 1104−1108. Aliphatic primary alcohols are poor substrates for CPO oxidation. (b) Miller, V. P.; Tschirret-Guth, R. A.; Ortiz de Montillano, P. R. *Arch. Biochem. Biophys.* **1995**, *319*, 333−340. (c) Hu, S. H.; Hager, L. P. *Biochem. Biophys. Res. Commun.* **1998**, *253*, 544−546. (d) Kiljunen, E.; Kanerva, L. T. *Tetrahedron*: *Asymmetry* **1999**, *10*, 3529−3535.

(9) *The Chemistry of the cyclopropyl group*; Rappoport, Z., Ed.; John Wiley & Sons: Chichester, 1987; Part 1.

(10) (a) Newcomb, M.; Letadicbiadatti, F. H.; Chestney, D. L.; Roberts, E. S.; Hollenberg, P. F. *J. Am. Chem. Soc.* **1995**, *117*, 12085−12091. (b) Toy, P. H.; Newcomb, M.; Hollenberg, P. F. *J. Org. Chem.* **1997**, *62*, 9114−9122. (c) Toy, P. H.; Newcomb, M.; Hollenberg, P. F. *J. Am. Chem. Soc.* **1998**, *120*, 7719−7729. (d) Toy, P. H.; Newcomb, M.; L. P. Hager. *Chem. Res. Toxicol.* **1998**, *11*, 816−823.

10.1021/jo016161i CCC: $22.00
Published on Web 12/08/2001

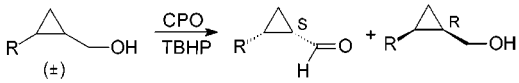
Table 1. Chloroperoxidase-Catalyzed Oxidation of *trans*-Cyclopropylcarbinols



		aldehyde		alcohol				
entry	R	yield[a] (%)	ee[b] (%)	yield[a] (%)	ee[b] (%)	turnover[c]	conversion[d] (%)	E[e]
1	Ph	34	3[f]	60	15	2,400	40	1.2
2	$AcOCH_2$	39	-	57	20	2,200	59	1.6
3	$BrCH_2CH_2$	48	18	31	21	2,500	62	1.7
4	$BrCH_2CH_2CH_2$	33	31	46	22	1,500	60	2.3

[a] Isolated yields. [b] Determined by ^{1}H NMR of the Mosher ester of the corresponding alcohol. [c] Number of enzyme turnovers as defined in ref 11. [d] Determined by GC analysis. [e] *E* value was calculated using the equation in ref 12. [f] Determined by chiral GC using α-Dex column.

Table 2. Chloroperoxidase-Catalyzed Enantioselective Oxidation of *cis*-Cyclopropylcarbinols



		aldehyde		alcohol				
entry	R	yield[a] (%)	ee[b] (%)	yield[a] (%)	ee[b] (%)	turnover[c]	conversion[d] (%)	E[e]
5	Ph	7[d]	65	>90	18[f]	40	8	6.0
6	$PhCH_3$	32	66[b]	45	95	432	54	35
7	CH_3	37[d]	90	60	37[f]	988	38	27
8	CH_3CH_2	30	89	57	57	2,340	39	30
9	$CH_3CH_2CH_2$	44	82[b]	42	93	2,052	54	34
10	$AcOCH_2$	40	92	57	57[f]	1,722	41	44
11	$BrCH_2CH_2$	35	91[b]	50	83	1,170	45	60

[a] Isolated yields. [b] Determined by ^{1}H NMR of the Mosher ester of the corresponding alcohol. [c] Number of enzyme turnovers as defined in ref 11. [d] Determined by GC analysis. [e] *E* value was calculated using the equation in ref 12. [f] Determined by chiral GC using α-Dex column.

over number[11] but poor enantioselectivity (Table 1). We also investigated a number of other functionalized *trans*-cyclopropylmethanols **2**−**4** as substrates for CPO. In all cases, the resulting aldehydes and the unreacted alcohols were obtained as the sole products (Table 1). Although CPO-catalyzed oxidation of these *trans*-cyclopropylmethanols shows high reaction turnover numbers, the enantioselectivities of CPO on these trans isomers were low (E[12] = 1.2−2.3) (Table 1).

When compared with the trans isomer, CPO catalyzes the oxidation of *cis*-2-phenylcyclopropylmethanol **5** with ca. 60-fold lower reactivity (as reflected in the diminished reaction turnover number). Despite this lower reactivity, the enzyme displayed substantially greater enantioselectivity. The *E* value increased from 1.2 for **1** to 6.0 for **5**. When the phenyl group is extended to benzyl (**6**), the enantioselectivity and reactivity of CPO dramatically increased, as did both enantioselectivity and enzymic reactivity for all other larger substrates tested (Table 2). This included straight-chain cyclopropylcarbinol derivatives, as well as acetoxy and brominated derivatives. When conversions were maintained below 50%, aldehydes having >90% ee were obtained.

In all cases, the CPO-catalyzed oxidation of cyclopropanes showed much higher enantioselectivity toward the cis isomers than toward the trans isomers. Among cis-2-substituted cyclopylcarbinols, CPO preferentially oxidized the enantiomer having the *S* configuration at C-1. This appears to be independent of the nature of the substituents on the cyclopropane ring. Thus, the enzyme's intrinsic enantioselectivity must be controlled by the unique active-site structure of CPO. Recent studies of the prochiral selectivity of CPO-catalyzed oxidation of arylalkanols to aldehydes have shown that cleavage of the *pro*-S C−H bond predominates over cleavage of the *pro*-R C−H bond.[13] Analogous stereoselectivity has also been observed for CPO-catalyzed epoxidation of alkenes and propargylic hydroxylations.[7] Thus, chiral cyclopropane molecules may serve as useful model substrates to investigate of the mechanism of enantioselective oxidation catalyzed by CPO as well as related P450 enzymes.

Despite numerous studies of the P450 catalyzed oxidation of cyclopropylmethanes, an enantioselective version has not been reported.[10] In contrast, CPO readily utilizes TBHP instead of oxygen as the terminal oxidant, and does not require cofactors. Our findings provide a novel route for the synthesis of natural products and the compounds of pharmaceutical interest containing chiral cyclopropyl groups.

Experimental Section

General Methods for Preparation of Racemic Cyclopropylmethanols. Cyclopropanation of cinnamyl alcohol, *cis*-

(11) Defined as mol of product produced per mole of enzyme added.

(12) To more conveniently compare kinetic resolutions, the inherent enantioselectivity, called the enantiomeric ratio, *E*, measures the ability of the enzyme to distinguish between enantiomers. To calculate *E*, one must measure two of the three variables: enantiomeric purity of the starting material (ee_s), enantiomeric purity of the product (ee_p), and extent of conversion (*c*). Often, enantiomeric purities are more accurately measured than conversion; in these cases, the following equation is employed:

$$E = \ln\left[\frac{(1 - ee_s)}{\left(1 + \left(ee_s/ee_p\right)\right)}\right] / \ln\left[\frac{(1 + ee_s)}{\left(1 + \left(ee_s/ee_p\right)\right)}\right]$$

(a) Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294−7299. (b) Chen, C.-S., Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1987**, *109*, 2812−2817.

(13) Baciocchi, E.; Fabbrini, M.; Lanzalunga, O.; Manduchi, L.; Pochetti, G. *Eur. J. Biochem.* **2001**, *268*, 665−672.

3-phenyl-2-propen-1-ol, *cis*-2-buten-1-ol, *cis*-2-penten-1-ol, and *cis*-2-hexen-1-ol with diethylzinc and diiodomethane yielded the corresponding cyclopropyl methanols **1**, **5**, **7**, **8**, and **9** in yields of 60−98%.[3] Cyclopropanation of allylbenzene, 4-bromo-1-butene, and 5-bromo-1-pentene with diazoacetate in the presence of catalytic rhodium(II) diacetate or cupric sulfate gave pure *cis*- and *trans*-cyclopropyl carboxylates after flash chromatography with EtOAc/hexane (20:1).[2] Treatment of the above carboxylates with $LiAlH_4$ afforded cyclopropyl alcohols **3**, **4**, **6,** and **11**, respectively in yields of 80−95%. The cyclopropyl alcohols **2** and **10** were obtained in yields of 72% and 40%, respectively by $LiAlH_4$ reduction of *trans* and *cis*-dimethylcyclopropane dicarboxylates,[3] and monoacetylation with Ac_2O/DMAP in dichloromethane. Oxidation of the racemic cyclopropyl alcohols with pyridinium chlorochromate provided the corresponding racemic aldehydes, which were used as standards for gas chromatography, NMR, and TLC analysis.

Mosher ester synthesis was performed as follows:[3a,14] (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (1.1 equiv) was added to a solution of alcohol (0.02 mmol), DMAP (1.2 equiv), and triethylamine (7 equiv) in CH_2Cl_2. After 5 h, the mixture was filtered through a short plug of silica gel eluted with EtOAc/hexane (1:4) and concentrated in vacuo. The enantiomeric excess (ee) was determined by ^1H NMR through the relative integration of the multiplets of the corresponding Mosher esters from two enantiomers of the alcohols.

General Procedure for Chloroperoxidase-Catalyzed Oxidation. Chloroperoxidase (1400 units/mg) was obtained from Chirazyme, Inc. (Urbana, IL). Cyclopropylmethanol (0.3 mmol) and CPO (0.05−0.6 μmol) were stirred vigorously with TBHP (0.6 mmol) in the presence of 1% (v/v) of polyethylenimine[5] in 5.0 mL of 50 mM sodium citrate buffer, pH 5.5. The reaction vial was capped, and the mixture was stirred for 1 h at room temperature. Sodium hydrosulfite was then added, and the mixture was extracted twice with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, and the products were purified by flash chromatography (CH_2Cl_2/acetone). Quantitative gas chromatography (GC) was performed with dodecane as an internal standard. The conversion of the reaction was evaluated by GC analysis using the corresponding aldehydes and alcohols as authentic samples.

(1*S*,2*R*)-1-Formyl-2-phenylcyclopropane (5): 7% yield determined by GC, 8% conversion; 65% ee determined by gas chromatography using a chiral α-Dex column (100 °C, 10 min, 100 → 150 °C, 1.5 °C/min; t_R = 38.3. min, minor isomer; 38.6 min, major isomer); ^1H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, J = 7.0 Hz, 1H), 7.33−7.21 (m, 5H), 2.83 (q, J = 8.5 Hz, 1H), 2.17−2.10 (m, 1H), 1.88 (dt, J = 7.5, 13.5 Hz, 1H), 1.59 (dt, J = 5.5, 8.0 Hz, 1H).

(1*R*,2*S*)-2-Phenylcyclopropylmethanol (5): >90% isolated yield; 18% ee determined by gas chromatography using a chiral α-Dex column (100 °C, 10 min, 100 → 150 °C, 1.5 °C/min; t_R = 38.3. min, major isomer; 38.6 min, minor isomer).^1H and ^{13}C NMR spectral data match literature data.[3] The absolute configuration was assigned on the basis of the analogue to alcohol **6**.

(1*S*,2*R*)-(+)-2-Benzyl-1-formylcyclopropane (6): 32% isolated yield, 54% conversion; 66% ee determined by ^1H NMR analysis of MTPA ester of the corresponding alcohol obtained from $LiAlH_4$ reduction of aldehydes **6** (4.56 ppm, major; 4.52 ppm, minor); ^1H NMR (500 MHz, $CDCl_3$) δ 9.58 (d, J = 5.0 Hz, 1H), 7.32−7.20 (m, 5H), 2.94 (q, J = 7.5 Hz, 1H), 2.82 (q, J = 7.5 Hz, 1H), 2.08−2.02 (m, 1H), 1.83−1.76 (h, J = 7.5 Hz, 1H), 1.41−1.37 (m, 1H), 1.32 (dt, J = 5.0, 8.0 Hz, 1H). The absolute configuration was determined by ^1H NMR analysis of MTPA ester of the corresponding alcohol obtained from $LiAlH_4$ reduction of aldehyde **6**.

(1*R*,2*S*)-(+)-2-Benzylcyclopropylmethanol (6): 45% isolated yield; 95% ee determined by ^1H NMR analysis of MTPA ester (4.56 ppm, minor; 4.52 ppm, major); $[\alpha]^{25}_D$ +15.4° (*c* 0.22, CH_2Cl_2). ^1H and ^{13}C NMR spectral data match the literature data. The absolute configuration was determined by comparing the optical rotation with literature data.[2]

(1*S*,2*R*)-(−)-2-Methyl-1-formylcyclopropane (7): 37% yield determined by GC and 38% conversion of the racemic alcohol **5**, determined by GC analysis; 90% ee determined by chiral gas chromatography analysis of the corresponding alcohol obtained by $LiAlH_4$ reduction of aldehyde **7** (chiral α-Dex column, 60 °C, t_R = 10.8 min, minor isomer; 11.3 min, major isomer); ^1H NMR (500 MHz, $CDCl_3$) δ 9.38 (d, J = 6.0, 1H), 1.89−1.83 (m,1H), 1.57−1.49 (m, 1H), 1.27 (d, J = 6.5 Hz, 3 H), 1.25−1.21 (m, 1H), 1.18−1.14 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.37, 28.31, 18.85, 15.94, 13.54. The absolute configuration was determined by chiral GC analysis of the corresponding alcohol obtained by $LiAlH_4$ reduction of aldehyde **7**.

(1*R*,2*S*)-(+)-2-Methylcyclopropanemethanol (7): 60% isolated yield; 37% ee determined by gas chromatography using chiral α-Dex column (60 °C, t_R = 10.8 min, major isomer; 11.3 min, minor isomer); $[\alpha]^{25}_D$ +19.0° (*c* 0.19, CH_2Cl_2). ^1H and ^{13}C NMR spectral data are identical to the literature data. The absolute configuration was determined by comparing the optical rotation with literature data.[3]

(1*S*,2*R*)-(−)-2-Ethyl-1-formylcyclopropane (8): 35% isolated yield; 56% conversion; 59% ee determined by gas chromatography using a chiral α-Dex column (50 °C, 10 min, 50 → 90 °C, 2 °C/min; t_R = 18.6 min, major isomer; 18.9 min, minor isomer); $[\alpha]^{25}_D$ −9.8° (*c* 0.60, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 9.36 (d, J = 5.5 Hz, 1H), 1.89−1.58 (m, 2H), 1.53−1.41 (m, 2H), 1.25−1.17 (m, 2H), 0.97 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.13, 28.04, 26.84, 21.78, 14.92, 14.41. The absolute configuration was determined by chiral GC analysis of the corresponding alcohol obtained by $LiAlH_4$ reduction of aldehyde **8**.

(1*R*,2*S*)-(+)-2-Ethylcyclopropylmethanol (8): 40% isolated yield; 92% ee determined by ^1H NMR analysis of MTPA ester (4.45 ppm, major; 4.50 ppm, minor); $[\alpha]^{25}_D$ +29.2° (*c* 0.37, CH_2Cl_2). ^1H and ^{13}C NMR spectral data match the literature data. The absolute configuration was determined by comparing the optical rotation with literature data.[3]

(1*S*,2*R*)-(−)-1-Formyl-2-propylcyclopropane (9): 44% isolated yield; 54% conversion; 82% ee determined by ^1H NMR analysis of MTPA ester (4.43 ppm, minor; 4.48 ppm, major); $[\alpha]^{25}_D$ −13.8° (*c* 0.39, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 9.34 (d, J = 6.0 Hz, 1H), 1.88−1.83 (m, 1H), 1.67−1.31 (m, 5H), 1.26−1.16 (m, 2H), 0.91 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.16, 30.43, 27.94, 24.72, 23.27, 14.89, 13.91. The absolute configuration was determined by chiral GC analysis of the corresponding alcohol obtained by $LiAlH_4$ reduction of aldehyde **9**.

(1*R*,2*S*)-(+)-2-Propylcyclopropylmethanol (9): 42% isolated yield; 93% ee determined by ^1H NMR analysis of MTPA ester (4.43 ppm, major; 4.48 ppm, minor); $[\alpha]^{25}_D$ +27.9° (*c* 0.20, CH_2Cl_2). ^1H and ^{13}C NMR spectral data match the literature data. The absolute configuration was determined by comparing the optical rotation with literature data.[3]

(1*S*,2*R*)-2-Acetoxymethyl-1-formylcyclopropane (10): 40% isolated yield; 41% conversion; 92% ee determined by gas chromatography using chiral α-Dex column (100 °C, t_R = 22.4 min, major isomer; 22.0 min, minor isomer); ^1H NMR (500 MHz, $CDCl_3$) δ 9.54 (d, J = 4.0 Hz, 1H), 4.50 (q, J = 6.5 Hz, 1H), 3.94 (dd, J = 9.0, 12.0 Hz, 1H), 2.12−2.05 (m, 1H), 2.04 (s, 3H), 1.91−1.81 (m, 1H), 1.36−1.24 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.29, 171.11, 62.66, 26.82, 21.07, 12.94.

(1*R*,2*S*)-(−)-2-Acetoxymethylcyclopropylmethanol (10): 57% isolated yield; 57% ee determined by ^1H NMR analysis of MTPA ester (4.53 ppm, minor; 4.48 ppm, major); $[\alpha]^{25}_D$ −10.0° (*c* 0.55, CH_2Cl_2). ^1H and ^{13}C NMR spectral data match the literature data. The absolute configuration was determined by comparing the optical rotation with the literature data.[4c]

(1*S*,2*R*)-(+)-2-Bromoethyl-1-formylcyclopropane (11): 35% isolated yield; 45% conversion; 91% ee determined by ^1H NMR analysis of MTPA ester of the corresponding alcohol obtained from $LiAlH_4$ reduction of **11a** (4.05 ppm, minor; 4.01 ppm, major): $[\alpha]^{25}_D$ +32.0° (*c* 0.27, CH_2Cl_2). ^1H and ^{13}C NMR spectral data match the literature data. Excess $LiAlH_4$ reduction of aldehyde **11** afforded alcohol **11** and alcohol **8** (~5:1). The absolute configuration was determined by ^1H NMR analysis of

(14) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1982**, *109*, 5765−5780.

MTPA ester of the corresponding alcohol **8** obtained from $LiAlH_4$ reduction of aldehyde **11** (4.45 ppm, minor; 4.50 ppm, major).

(1*R*,2*S*)-(+)-2-Bromoethylcyclopropylmethanol (11b): 50% isolated yield; 83% ee determined by ^1H NMR analysis of MTPA ester (4.05 ppm, major; 4.01 ppm, minor); $[\alpha]^{25}_D$ +13.0° (*c* 0.13, CH_2Cl_2). ^1H and ^{13}C NMR spectral data match literature data.[1b] The absolute configuration was determined by ^1H NMR analysis of MTPA ester of the corresponding alcohol **8** obtained from $LiAlH_4$ reduction of aldehyde **11** (4.45 ppm, major; 4.50 ppm, minor).

Acknowledgment. We thank Dr. L. Hager for his helpful comments. This work was supported by the U.S. Department of Energy (DE-FC07-98CH10948).

Supporting Information Available: The details of characterization of aldehydes and alcohols **1**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO016161I