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Chiral diazaborolidine-mediated enantioselective aldol reactions of phenylthioacetate esters

E. J. Corey* and Soongyu Choi

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138, USA

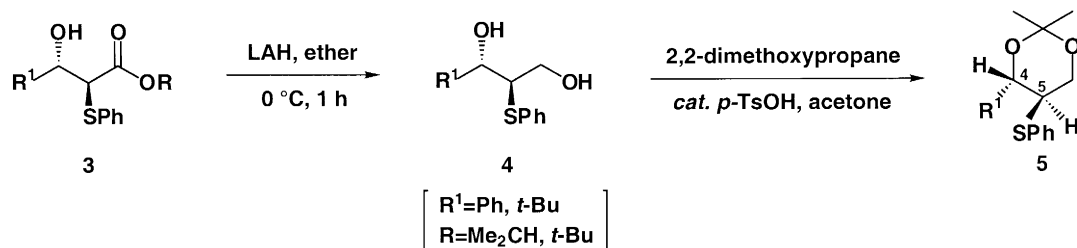
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Abstract

Methodology is described for the enantioselective conversion of achiral aldehydes by *anti*-selective aldol reaction to chiral β -hydroxy- α -phenylthio esters and aldehydes. © 2000 Elsevier Science Ltd. All rights reserved.

The chiral diazaborolidine **1** is an exceedingly useful reagent for a number of boron enolate-mediated enantioselective reactions, including *anti*- and *syn*-selective aldol reactions of esters with aldehydes¹ and enantioselective Ireland–Claisen rearrangements.² Reported herein is the extension of this methodology to the enantioselective synthesis of β -hydroxy- α -phenylthio esters and aldehydes, versatile intermediates which have received limited attention thus far.^{3,4}

The reaction of the boron reagent **1** (*R,R*-form) with phenylthioacetate esters (**2**) and diisopropylethylamine in CH₂Cl₂ at –78°C produced the (*Z*)-boron enolate (OBR*₂ and SPh *trans*). The aldol reactions between the (*Z*)-enolate and four different aldehydes at –78°C afforded *anti*- β -hydroxy- α -phenylthio esters **3**, with efficient recovery of the chiral ligand. As listed in Table 1, isolated yields, diastereoselectivities and enantioselectivities were generally good and comparable to those of the *t*-butyl bromoacetate.^{1b}



The stereochemistry of the aldol products **3** was established by ¹H NMR NOE analysis (Fig. 1) of the corresponding 1,3-dioxane derivatives **5**, which were prepared by lithium aluminum hydride reduction (ether, 0°C, 1 h) and subsequent ketalization of the diols **4** (2,2-dimethoxypropane, cat. *p*-toluenesulfonic

* Corresponding author.

Table 1
Reactions of **1**, phenylthioacetate esters and aldehydes

Entry	R of Ester	R ¹ of R ¹ CHO	Yield (%)	<i>anti</i> : <i>syn</i> ^a	ee (%) ^b of <i>anti</i>
1	<i>t</i> -Bu	C ₆ H ₅	97	98 : 2	90
2	<i>t</i> -Bu	(<i>E</i>)-C ₆ H ₅ CH=CH	79	97 : 3	94
3	<i>t</i> -Bu	<i>t</i> -Bu	83	98 : 2	63 ^c
4	<i>t</i> -Bu	Me ₂ CH	75	91 : 9	99
5	Me ₂ CH	C ₆ H ₅	44	95 : 5	90
6	Me	C ₆ H ₅	45	9 : 1	87

^a Analysis by measurement of ¹H NMR Spectrum (500MHz). ^b % ee were determined by HPLC analysis using a Daicel Chiralcel OD column, except as noted. ^c A Daicel Chiralpak AD column was used for HPLC analysis. ^d Authentic samples of racemic compounds were prepared from LDA enolate of the corresponding ester and aldehyde in ether.

acid, acetone, 23°C). In the case of **5a** from **3a** (R=*t*-Bu, R¹=C₆H₅), the coupling constant between H-4 and H-5 of the major diastereomer was 10.8 Hz (a typical value for vicinal diaxial hydrogens of a 1,3-dioxane) and that of the minor diastereomer was 2.3 Hz (typical of the *cis* stereorelationship of H-4 and H-5).^{4b,5}

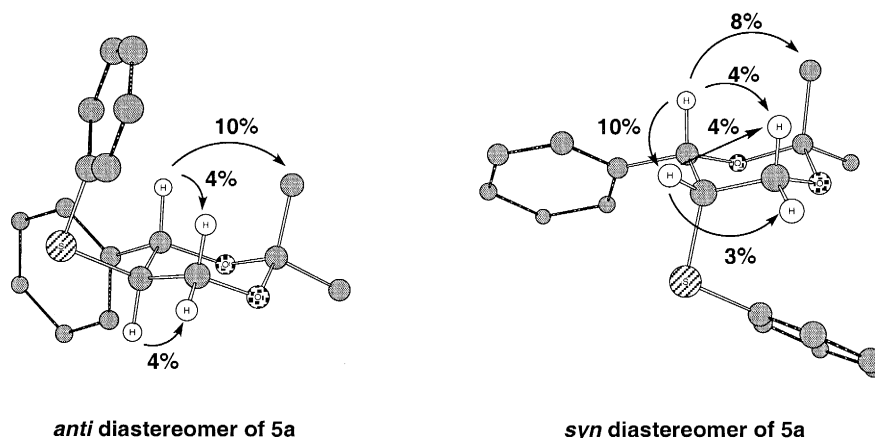
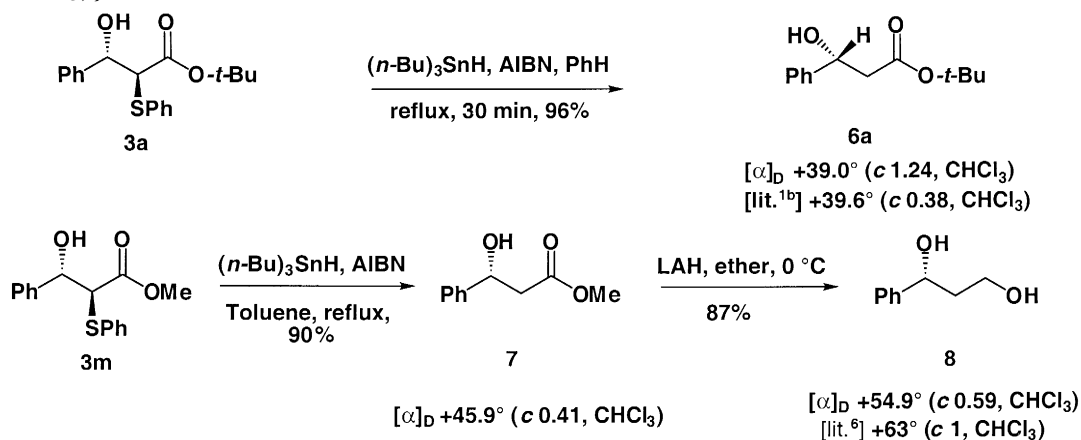


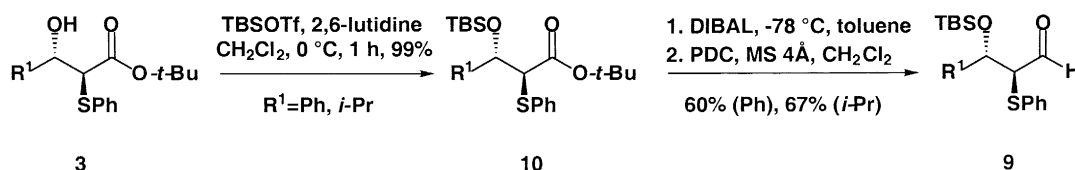
Fig. 1. Selected NOE enhancements of 1,3-dioxane **5a**

The major diastereomer of the aldol product **3** was confirmed to be the *anti* aldol diastereomer through NOE measurements (Fig. 1) as well as from coupling constant data. The absolute configuration of the hydroxy group in β-hydroxy-α-phenylthio ester **3a** was established by conversion to the corresponding diol **8** and comparison of the specific rotation with literature values. To arrive at the β-hydroxy ester **6a**, the aldol product **3a** (R=*t*-Bu, R¹=Ph: 90.3% ee) was treated with tributyltin hydride and a catalytic amount of azobis-isobutyronitrile (AIBN) in benzene at reflux for 30 min (96% yield). The resulting (3*R*)-3-hydroxy-3-phenyl-propionate (**6a**), which had previously been prepared from tributyltin hydride reduction of (2*S*,3*S*)-*t*-butyl 2-bromo-3-hydroxy-3-phenylpropionate,^{1b} was identical with the known compound; (for **6a**: [α]_D²³ +39.0 (*c* 1.24, CHCl₃)). Methyl 3-hydroxy-3-phenyl-2-thiophenoxypropionate

3m (Table 1, entry 6) was transformed into diol **8** to verify its absolute configuration {**7**: (*n*-Bu)₃SnH, AIBN, toluene, 90% yield, $[\alpha]_D^{23} +45.9$ (*c* 0.41, CHCl₃); **8**: LAH, ether, 0 °C, 87% yield, $[\alpha]_D^{23} +54.9$ (*c* 0.59, CHCl₃)}.



The synthesis of β -hydroxy- α -phenylthio aldehydes **9** from *anti* aldol adducts **3** was demonstrated as follows.⁷ Treatment of esters **3** with *t*-butyl-dimethylsilyl trifluoromethanesulfonate in CH₂Cl₂ led quantitatively to the silyl ethers **10**. Reduction of the silyl ether **10** (diisobutylaluminum hydride, -78 °C, toluene) followed by pyridinium dichromate oxidation⁸ (molecular sieve 4 Å, 23 °C, CH₂Cl₂) furnished the aldehydes **9**.⁹



In summary, the transformations described above provide a new route to a variety of chiral intermediates which are useful in synthesis. The following procedure is illustrative of the enantio- and diastereoselective aldol step.

(3*S*,2*S*)-(-)-*t*-Butyl 3-hydroxy-3-phenyl-2-thiophenoxypropionate (**3a**) (*R*¹=Ph, *R*=*t*-Bu); the diazaborolidine **1R** (1.0 equiv.) prepared from the (*R,R*)-(+)-bis-3,5-di(trifluoromethyl)benzene-sulfonamide (320 mg, 0.419 mmol) and 0.5 M BBr₃ in CH₂Cl₂ (1.68 mL, 0.838 mmol),^{1a} was dissolved in CH₂Cl₂ (8 mL) at 23 °C and cooled to -78 °C. The solution was treated with *t*-butyl thiophenoxyacetate (94.0 mg, 0.419 mmol) and diisopropylethylamine (108.3 mg, 0.838 mmol) at -78 °C. The reaction mixture was stirred for 5 h at -78 °C and then treated with benzaldehyde (40.0 mg, 0.377 mmol) in dichloromethane (3 mL). After stirring for an additional 30 min, the reaction was quenched with MeOH (3 mL) and water (8 mL) at -78 °C. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The collected organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to afford the crude product. Final purification of the crude product by silica gel chromatography gave the alcohol **3a** (120.2 mg, 97% yield, *anti*:*syn*=98:2, *anti* 90% ee, *syn* 43% ee). *anti* Product: $[\alpha]_D^{23} -76.8$ (*c* 1.76, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.39–7.24 (m, 10H), 5.01 (dd, *J*=6.7, 6.5 Hz, 1H), 3.88 (d, *J*=6.7 Hz, 1H), 3.54 (d, *J*=6.5 Hz, 1H), 1.29 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 170.9, 140.7, 133.6, 133.1, 128.9, 128.4, 128.1, 127.9, 126.7, 82.5, 74.4, 58.2, 27.8; FTIR (thin film, cm⁻¹) 3475, 3458, 2977, 1724, 1368; *R*_f=0.33 (17% ethyl acetate in hexane). *syn* Product: ¹H NMR (500 MHz, CDCl₃) δ 7.46–7.25 (m, 10H), 4.98 (d, *J*=7.5 Hz, 1H), 3.76 (d, *J*=7.5 Hz, 1H), 3.47 (s, 1H), 1.23 (s, 9H); ¹³C NMR (100 MHz,

CDCl_3) δ 170.0, 139.6, 133.3, 129.0, 128.3, 128.1, 127.1, 82.1, 72.9, 60.5, 27.6; $R_f=0.35$ (17% ethyl acetate in hexane).¹⁰

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9. A small amount of the α -epimeric diastereomer was formed in this process. (a) $R^1=\text{Ph}$, *anti:syn*=93:7; *anti* Aldehyde: $[\alpha]_D^{23} +82.2$ (*c* 3.13, CHCl_3); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.53 (d, $J=5.7$ Hz, 1H), 7.34–7.19 (m, 10H), 5.03 (d, $J=7.0$ Hz, 1H), 3.71 (dd, $J=7.0, 5.7$ Hz, 1H), 0.87 (s, 9H), 0.08 (s, 3H), -0.22 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 193.8, 141.0, 132.7, 132.1, 129.1, 128.5, 127.8, 126.9, 75.1, 66.6, 64.7, 25.7, 18.2, -4.5 , -5.0 ; FTIR (thin film, cm^{-1}) 2954, 2890, 1722, 1470; LRMS (CI) for $[\text{C}_{21}\text{H}_{28}\text{SO}_2\text{Si}] m/e$ 390 ($\text{M}+\text{NH}_4^+$); $R_f=0.47$ (10% ethyl acetate in hexane). *syn* Aldehyde: $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.50 (d, $J=4.5$ Hz, 1H), 7.42–7.2 (m, 10H), 5.20 (d, $J=5.1$ Hz, 1H), 3.71 (dd, $J=5.1, 4.5$ Hz, 1H), 0.91 (s, 9H), 0.08 (s, 3H), -0.14 (s, 3H). (b) $R^1=i\text{-Pr}$, *anti:syn*=97:3; *anti* Aldehyde: $[\alpha]_D^{23} +35.9$ (*c* 0.56, CHCl_3); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.47 (d, $J=5.8$ Hz, 1H), 7.39–7.25 (m, 5H), 4.02 (dd, $J=5.8, 4.3$ Hz, 1H), 3.59 (dd, $J=4.7, 4.4, 4.3$ Hz, 1H), 2.03 (qd, $J=6.7, 4.7$ Hz, 1H), 0.97 (d, $J=6.7$ Hz, 3H), 0.96 (d, $J=6.7$ Hz, 3H), 0.92 (s, 9H), 0.16 (s, 3H), 0.10 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 194.7, 132.6, 132.3, 129.3, 127.9, 77.8, 60.1, 33.5, 26.0, 18.4, 17.6, -3.9 , -4.0 ; FTIR (thin film, cm^{-1}) 3061, 2959, 2886, 1718, 1583, 1470, 1440; LRMS (CI) for $[\text{C}_{18}\text{H}_{30}\text{SO}_2\text{Si}] m/e$ 356 ($\text{M}+\text{NH}_4^+$); $R_f=0.49$ (10% ethyl acetate in hexane). *syn* Aldehyde: $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.55 (d, $J=4.4$ Hz, 1H), 7.4–7.3 (m, 5H), 3.94 (dd, $J=4.9, 4.4$ Hz, 1H), 3.7 (dd, $J=6.8, 4.4$ Hz, 1H), 1.83 (qd, $J=6.8, 4.9$ Hz, 1H), 1.0 (d, $J=6.8$ Hz, 3H), 0.95 (d, $J=6.8$ Hz, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.02 (s, 3H).
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