Pergamon

Tetrahedron Letters 41 (2000) 2769–2772

TETRAHEDRON LETTERS

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

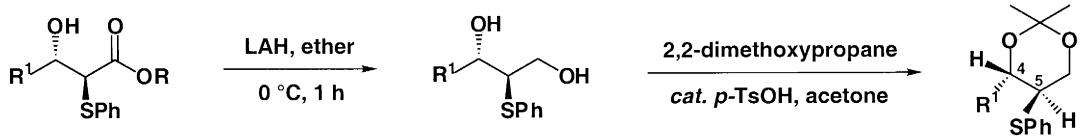
Received 18 January 2000; accepted 16 February 2000

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.

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 aldehydes[1] 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 CH_2Cl_2 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]



3 **4** **5**

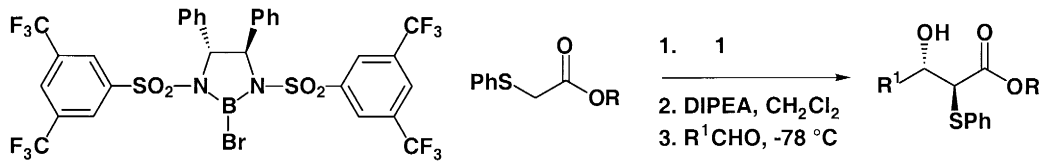
[R^1=Ph, *t*-Bu; R=Me_2CH, *t*-Bu]

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.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00302-6

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

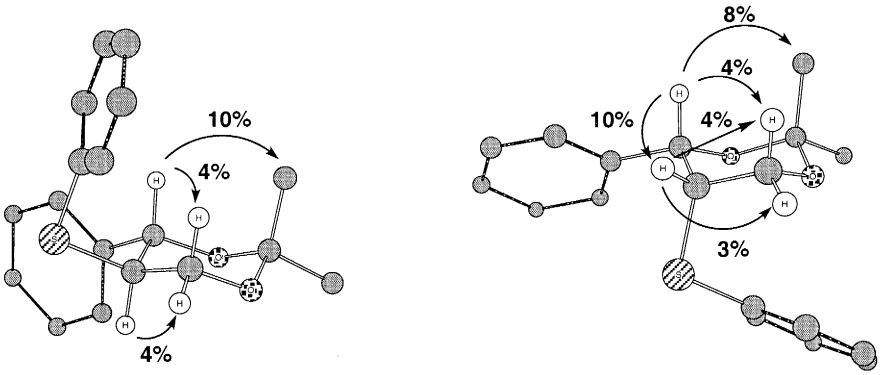


1 **2** **3**

Entry	R of Ester	R^1 of R^1CHO	Yield (%)	*anti* : *syn*[a]	ee (%)[b] of *anti*
1	*t*-Bu	C_6H_5	97	98 : 2	90
2	*t*-Bu	*(E)*-C_6H_5CH=CH	79	97 : 3	94
3	*t*-Bu	*t*-Bu	83	98 : 2	63[c]
4	*t*-Bu	Me_2CH	75	91 : 9	99
5	Me_2CH	C_6H_5	44	95 : 5	90
6	Me	C_6H_5	45	9 : 1	87

[a] Analysis by measurement of ^{1}H 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, R^1=C_6H_5), 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]

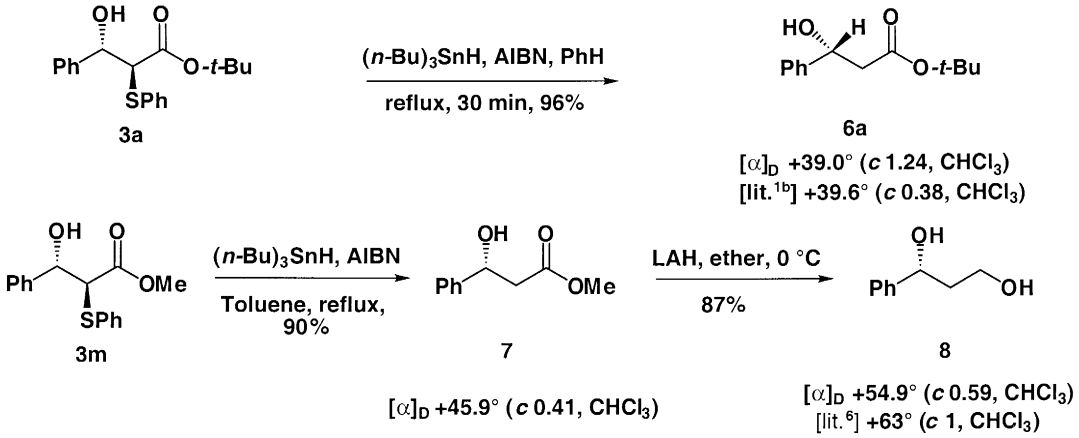


***anti* diastereomer of 5a** ***syn* diastereomer of 5a**

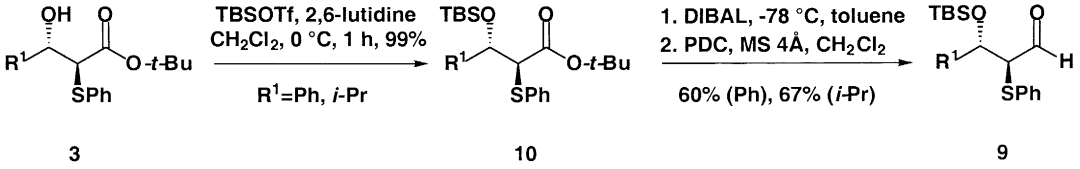
Fig. 1. Selected NOE enhancements of 1,3-dioxane **5a**

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, R^1=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**: $[\alpha]_D^{23}$ +39.0 (*c* 1.24, $CHCl_3$)). Methyl 3-hydroxy-3-phenyl-2-thiophenoxypropionate

3m (Table 1, entry 6) was transformed into diol **8** to verify its absolute configuration {**7**: $(n\text{-Bu})_3SnH$, AIBN, toluene, 90% yield, $[\alpha]_D^{23}$ +45.9 (*c* 0.41, $CHCl_3$); **8**: LAH, ether, 0°C, 87% yield, $[\alpha]_D^{23}$ +54.9 (*c* 0.59, $CHCl_3$)}.



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 CH_2Cl_2 led quantitatively to the silyl ethers **10**. Reduction of the silyl ether **10** (diisobutylaluminum hydride, −78°C, toluene) followed by pyridinium dichromate oxidation[8] (molecular sieve 4 Å, 23°C, CH_2Cl_2) furnished the aldehydes **9**.[9]



3 **10** **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 diastereoslective aldol step.

(3*S*,2*S*)-(−)-*t*-Butyl 3-hydroxy-3-phenyl-2-thiophenoxypropionate (**3a**) (R^1=Ph, R=*t*-Bu); the diazaborolidine **1*R*** (1.0 equiv.) prepared from the (*R*,*R*)-(+)-bis-3,5-di(trifluoromethyl)benzene-sulfonamide (320 mg, 0.419 mmol) and 0.5 M BBr_3 in CH_2Cl_2 (1.68 mL, 0.838 mmol),[1a] was dissolved in CH_2Cl_2 (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 $MgSO_4$, 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, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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: ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C 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]

References

1. (a) Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976. (b) Corey, E. J.; Choi, S. *Tetrahedron Lett.* **1991**, *32*, 2857.
2. (a) Corey, E. J.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 1229. (b) Corey, E. J.; Lee, D.-H. *J. Am. Chem. Soc.* **1991**, *113*, 4026.
3. (a) Sato, T.; Okazaki, H.; Otera, J.; Nozaki, H. *J. Am. Chem. Soc.* **1988**, *110*, 5209. (b) Sato, T.; Otera, J.; Nozaki, H. *J. Org. Chem.* **1990**, *55*, 6116.
4. (a) Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P. G.; Consolandi, E. *J. Org. Chem.* **1992**, *57*, 456. (b) Sugano, Y.; Naruto, S. *Chem. Pharm. Bull.* **1988**, *36*, 4619. (b) Youn, J.-H.; Herrmann, R.; Ugi, I. *Synthesis* **1987**, 159. (c) Poli, G.; Belvisi, L.; Manzoni, L.; Scolastico, C. *J. Org. Chem.* **1993**, *58*, 3165. (d) Enders. D.; Schäfer, T. Piva, O.; Zamponi, A. *Tetrahedron* **1994**, *50*, 3349. (e) Chibale, K.; Warren, S. *Tetrahedron Lett.* **1994**, *35*, 3991.
5. Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1984**, 753.
6. Kim, B. PhD dissertation, Department of Chemistry, M.I.T., Feb. 1988.
7. *anti* Aldol adduct **3** was separated from its *syn* diastereomer by flash chromatography on silica gel.
8. Furber, M.; Mander, L. N. *J. Am. Chem. Soc.* **1987**, *109*, 6389.
9. A small amount of the α-epimeric diastereomer was formed in this process. (a) R^1=Ph, *anti*:*syn*=93:7; *anti* Aldehyde: $[\alpha]_D^{23}$ +82.2 (*c* 3.13, $CHCl_3$); ^{1}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}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 [$C_{21}H_{28}SO_2Si$] *m/e* 390 ($M+NH_4^+$); R_f=0.47 (10% ethyl acetate in hexane). *syn* Aldehyde: ^{1}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*-Pr, *anti*:*syn*=97:3; *anti* Aldehyde: $[\alpha]_D^{23}$ +35.9 (*c* 0.56, $CHCl_3$); ^{1}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}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 [$C_{18}H_{30}SO_2Si$] *m/e* 356 ($M+NH_4^+$); R_f=0.49 (10% ethyl acetate in hexane). *syn* Aldehyde: ^{1}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).

10. This research was assisted financially by a grant from the National Institutes of Health.