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NEW PROCESS FOR ENANTIOSELECTIVE NUCLEOPHILIC ADDITION TO ALDEHYDES TO FORM SECONDARY ALCOHOLS

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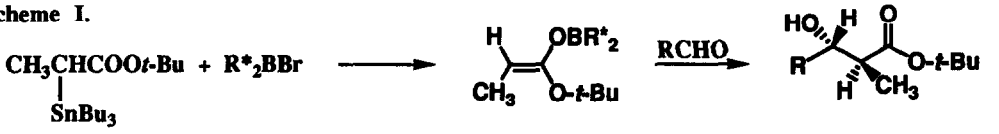
Summary: New methodology is described for the enantioselective conversion of aldehydes to *anti* aldols **4** and homoallylic alcohols **7**.

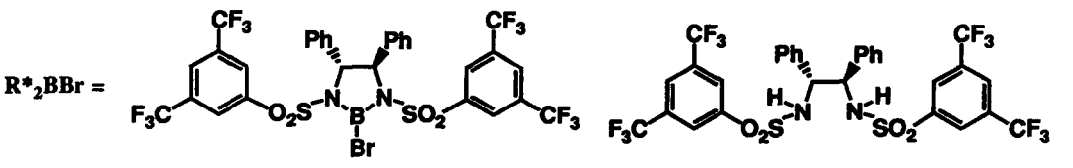
Previous studies in our laboratory have resulted in new methodology for enantioselective aldolization and allylation of aldehydes using recoverable reagents derived from (*R,R*)- or (*S,S*)-1,2-diamino-1,2-diphenylethane.[1] The aldol reaction between aldehydes and achiral propionate esters (particularly the phenylthio ester) could be controlled to produce *syn* aldols with excellent diastereo- and enantioselectivity, but no conditions were found for the efficient production of the diastereomeric *anti* aldols. This fact and the lack of highly efficient, direct *anti* aldolization procedures, despite much research in this area,[2] have encouraged us to search for new processes for enantioselective *anti* aldolization. Described herein is such a method. It is based on the use of the α-stannylated ester **1** and the boron reagent **2** to generate stereoselectively the boron enolate **3** which reacts with aldehydes to form *anti* aldols (**4**) (Scheme I). In addition we describe herein the application of the chiral boron reagent **2** to the enantioselective allylation and 2-chloroallylation of aldehydes.

The boron reagent **2** was produced from the (*R,R*)-bissulfonamide **5**[3] by reaction with BBr_3 in dry CH_2Cl_2.[4] Reaction of **2** in 1 : 2 toluene-hexane at -78°C with **1** for 5 h generated boron enolate **3**, which upon

Scheme I.



1 **2** **3** **4**



2 **5**

treatment with benzaldehyde at -78°C for 3 h afforded aldol **4**, R=C_6H_5, in 80% yield and 93% enantiomeric excess (ee), with an *anti* : *syn* ratio of 97 : 3.[5] The reaction of cinnamaldehyde with boron enolate **3** under the same conditions furnished **4**, R=*E*-C_6H_5CH=CH, in 89% yield and 96% ee, with an *anti* : *syn* ratio of 96 : 4. The aldol reaction of **3** and cinnamaldehyde could also be carried out stereoselectively in toluene or CH_2Cl_2 in 79-83% yield, 90-91% ee, and 94 : 6 to 98 : 2 *anti* : *syn* ratio. The reaction of cyclohexanecarboxaldehyde with enolate **3** in 1 : 2 toluene-hexane at -78°C afforded *anti* aldol **4**, R=chex, in 72% yield, 71% ee, and 92 : 8 *anti* : *syn* ratio. In each of these reactions the *anti* aldol product was readily obtained in pure form by silica gel chromatography and the bissulfonamide controller **5** was recovered efficiently for reuse.

The following procedures are illustrative.

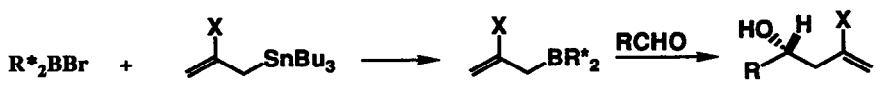
2-Tri(*n*-butyl)tin-*t*-butyl propionate. A solution of LDA (22 mmol) in tetrahydrofuran (80 mL) at -78°C was treated with *t*-butyl propionate (2.6 g, 3 mL, 20 mmol) in tetrahydrofuran (5 mL) over 10 min. The reaction mixture was stirred for 15 min at -78°C, and treated with tri(*n*-butyl)tin triflate (8.7 g, 20 mmol) (Aldrich Co.) in tetrahydrofuran (10 mL). The reaction was allowed to proceed for 1 h at 0°C and then quenched with aqueous buffer solution (pH 7, 10 mL). The aqueous layer was extracted with ethyl ether (100 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude 2-tri(*n*-butyl)tin-*t*-butyl propionate. Final purification was effected by silica gel chromatography (SiO_2, deactivated by 1%-triethylamine in hexane) or kugel-rohr vacuum distillation (150-155°C, 0.6 mm of Hg) to afford 2-tri(*n*-butyl)tin-*t*-butyl propionate (7.1 g, 17 mmol, 85% yield) as colorless liquid ; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, *J*=7.2 Hz, 9H), 0.90-0.98 (m, 6H), 1.27 (d, *J*=7.0 Hz, 3H), 1.28-1.37 (m, 6H), 1.42 (s, 9H), 1.45-1.63 (m, 6H), 2.26 (q, *J*=7.0 Hz, 1H); IR (film) 2957, 2928, 1704, 1143 cm^{-1}.

***t*-Butyl (2S,3R)-(+)-2-Methyl-3-hydroxy-3-phenylpropionate.** (+)-Bis-3,5-di(trifluoromethyl)benzenesulfonamide (184 mg, 0.24 mmol) was placed in a dry 50 mL round-bottom flask equipped with magnetic stir bar and sealed with a septum. The flask was evacuated and flushed with argon three times. Freshly distilled dichloromethane (3 mL) was added, and the homogeneous solution was cooled to 0°C and treated with BBr_3 (1 M solution in dichloromethane, 480 μL, 0.48 mmol). The solution was stirred at 0°C for 5 min, warmed to 45°C, kept at 45°C for 3 h, and concentrated under vacuum (*ca.* 2 mm of Hg) using a metal tube inserted through the septum. Dryness of the vacuum line was maintained with a drying tube containing NaOH pellets and $CaSO_4$ to prevent possible hydrolysis of bromoborane. Dry dichloromethane (1 mL) was added and evaporated under vacuum as above. Freshly distilled toluene (8 mL) was added and the resulting mixture was warmed to effect complete solution and then diluted with freshly distilled hexane (16 mL). The homogeneous solution of bromoborane was cooled to -78°C, and then treated with 2-tri(*n*-butyl)tin-*t*-butyl propionate (100 mg, 88 μL, 0.24 mmol) in toluene (0.5 mL), and stirred for 5 h at -78°C. Benzaldehyde (23 mg, 22 μL, 0.22 mmol) in toluene (0.5 mL) was added dropwise at -78°C over 5 min. The reaction was allowed to proceed for 3 h at -78°C and then quenched by addition of methanol (0.5 mL) and aqueous buffer solution (pH 7, 5 mL) at -78°C. The aqueous layer was extracted with ethyl ether (10 mL). The combined organic extracts were washed with aqueous KF (20%, 10 mL) and brine (10 mL). The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Final purification of *t*-butyl (2S,3R)-(+)-2-methyl-3-hydroxy-3-phenylpropionate and recovery of (R,R)-bissulfonamide were effected by silica gel chromatography (hexane-ethyl acetate, 5:1) to afford *t*-butyl (2S,3R)-(+)-2-methyl-3-hydroxy-3-phenylpropionate (42 mg, 0.18 mmol, 80% yield) as a colorless

liquid and (R,R)-bissulfonamide (170 mg, 92% recovery). Spectral data for *t*-butyl (2S,3R)-(+)-2-methyl-3-hydroxy-3-phenylpropionate: $[\alpha]_D^{20}$ = +54.66 (c 0.73, $CHCl_3$,); ^1H NMR (500 MHz, $CDCl_3$) δ 1.02 (d, *J*=7Hz, 3H), 1.44(s, 9H), 2.71(dq, *J*=8.5, 7Hz, 1H), 3.19(d, *J*=4.5Hz, 1H), 4.70(dd, *J*=8.5, 4.5Hz, 1H), 7.26~7.35(m, 5H); IR (film) 3448(br), 2976, 2930, 1725, 1368, 1154, 700 cm^{-1}; mass spectrum (FAB, 3-nitrobenzyl alcohol), m/e (relative intensity) 259(M^++Na^+, 100), 203(18), 198(7), 173(48), 119(7), 107(8).

Reaction of bromoborane **2** with allyltributylstannane in toluene at 23°C for 3 h resulted in transmetallation to give the allylborane **6**, X=H. Reaction of the toluene solution of **6**, X=H, at -78°C with benzaldehyde for 3 h afforded the (*R*)-homoallylic alcohol **7**, R=C_6H_5, X=H,[6] in 92% yield and 96% ee in addition to the recovered chiral controller **5**, as outlined in Scheme II.[7] Reaction of benzaldehyde with **6**, X=Cl (prepared in CH_2Cl_2 at 23°C for 20 h from the corresponding tributylstannane) in CH_2Cl_2 at -78°C for 3 h produced **7**, R=C_6H_5, X=Cl,[6] in 80% yield and 90% ee.[7] In a parallel way cyclohexanecarboxaldehyde was converted to **7**, R=chex, X=H,[6] in 84% yield and 92% ee and to **7**, R=chex, X=Cl,[6] in 76% yield and 88% ee.[7]

Scheme II.



2 **6** **7**

The following procedure illustrates the allylation process.

(R)-(+)-1-Phenyl-3-buten-1-ol. The (+)-bis-3,5-di(trifluoromethyl)benzenesulfonamide **5** (184 mg, 0.24 mmol) was converted to bromoborane **2** as described above. Freshly distilled toluene (8 mL) was added and the resulting mixture was warmed to effect complete solution. The homogeneous solution of bromoborane was cooled to 0°C and treated with allyl-tri(*n*-butyl)tin (79 mg, 74 μL, 0.24 mmol). The reaction mixture was stirred for 10 min at 0°C, and then allowed to warm to 23°C, and kept for 3 h at 23°C. The resulting solution was cooled to -78°C and a solution of benzaldehyde (23 mg, 22 μL, 0.22 mmol) in toluene (0.5 mL) was added dropwise over 5 min. The reaction was allowed to proceed for 3 h at -78°C and quenched by addition of aqueous buffer solution (pH 7, 5 mL) at -78°C. The aqueous layer was extracted with ethyl ether (10 mL). The combined organic extracts were washed with KF (20%, 10 mL) and brine (10 mL). The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Final purification of (R)-(+)-1-phenyl-3-buten-1-ol and recovery of (R,R)-bissulfonamide were effected by silica gel chromatography (hexane-ethyl acetate, 5:1) to afford (R)-(+)-1-phenyl-3-buten-1-ol (30 mg, 0.20 mmol, 92% yield) as a colorless liquid and the (R,R)-bissulfonamide **5** (170 mg, 92% recovery). Spectral data for (R)-(+)-1-phenyl-3-buten-1-ol: $[\alpha]_D^{20}$ = +45 (c 1.1, benzene); ^1H NMR (300 MHz, $CDCl_3$) δ 2.05 (d, *J*=3.0 Hz, 1H), 2.30-2.51 (m, 2H), 4.61-4.80 (m, 1H), 5.13-5.22 (m, 2H), 5.73-5.92 (m, 1H), 7.28-7.41 (m, 5H); IR (film) 3382, 3072, 2979, 2930, 1541, 1493, 1450, 1313, 1199, 1045, 995 cm^{-1}.

In this paper a novel enantioselective synthesis of *anti* aldols (**4**) is described from the α-tributylstannyl ester **1**,[8] aldehydes and the chiral borane **2**. This method can also be applied to the synthesis of the enantiomers of **4**, since the enantiomer of **2** is readily available.[1] This route to chiral *anti* aldols is especially useful because of the predictable[1] and high enantiopreference, the recoverability of the chiral reagent, and the ready execution. The allylation reactions using the highly reactive reagent **2** are also very enantioselective and practical.[9]

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(1) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493.

(2) See (a) Fenzl, W.; Köster, R. *Justis Liebigs Ann. Chem.* **1975**, 1322. (b) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (c) Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39. (d) Masamune, S.; Sato, T.; Kim, B.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279. (e) Ito, Y.; Sawamura, M; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405. (f) Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1985**, *26*, 5807. (g) Braun, M.; Devant, R. *Tetrahedron Lett.* **1984**, *25*, 5031. (h) Ambler, P. W.; Davies, S. G. *Tetrahedron Lett.* **1985**, *26*, 2129. (i) Paterson, I. *Chem. Ind.* (London) **1988**, 390. (j) Paterson, I.; Lister, M. A. *Tetrahedron Lett.* **1988**, *29*, 585. (k) Paterson, I.; Goodman, J. M. *Tetrahedron Lett.* **1989**, *30*, 997.

(3) Bissulfonamide **5** was prepared from (*R*,*R*)-1,2-diamino-1,2-diphenylethane[1] and 3,5-bistrifluoromethylbenzenesulfonyl chloride (2 equiv) by reaction in CH_2Cl_2 with triethylamine (3 equiv) and 4-dimethylaminopyridine (0.1 equiv) at 0°C for 2 h. The sulfonyl chloride was synthesized in 81% yield from commercially available 3,5-bistrifluoromethylaniline by diazotization in acetic acid (addition of aqueous sodium nitrite to a solution of the amine and hydrochloric acid in AcOH at 0°C) and subsequent addition of the diazonium salt to a saturated solution of sulfur dioxide in acetic acid containing 0.15 equiv of cupric chloride; see, H. H. Mrozik, U.S. Patent 4,005,199, Jan. 25, 1977; *Chem. Abst.*, **1977**, *86*, P171112 t.

(4) The bromoborane **2** is an extremely effective and useful chiral Lewis acid by virtue of its excellent solubility at low temperatures and strong Lewis acidity relative to many other bissulfonamide-derived bromoboranes studied to date.

(5) *Anti* : *syn* ratio and % ee determined by HPLC analysis using a Daicel OD column. Alternatively, ee values could also be determined by reduction of the aldol with $LiAlH_4$ in THF, conversion of the resulting diol to the bis-(*R*)-α-methoxy-α-trifluoromethylphenylacetate (MTPA) ester, and measurement of 500 MHz ^1H NMR spectra.

(6) Corey, E. J.; Yu, C.-M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495.

(7) The values of % ee were determined by 500 MHz ^1H NMR analysis of the MTPA ester and the absolute configuration was demonstrated by measurement of optical rotation.

(8) For earlier literature on the preparation of various tri-*n*-butylstannyl esters see Zapata, A.; Acuna A., C. *Synth. Commun.* **1984**, *14*, 27.

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