Versatile Chiral Reagent for the Highly Enantioselective Synthesis of Either Anti or Syn Ester Aldols

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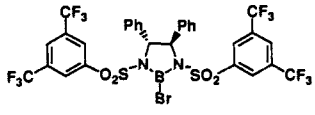
A highly effective chiral reagent (**1**) has been developed for promoting enantioselective aldol reactions of an achiral propionate ester with an achiral aldehyde to give either syn or anti aldol products with excellent diastereo- and enantioselectivity. The chiral controller unit in **1** is readily available and recoverable. A mechanistic explanation is also presented herein for the selective formation of either *E* or *Z* ester enolate intermediates, depending on reactant structure, which provides a coherent picture of aldol diastereoselectivity in both this and previous research.[1,2]



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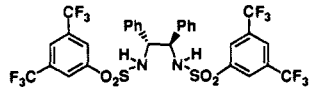

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The *R,R* reagent **1** was prepared starting from (*R,R*)-1,2-diamino-1,2-diphenylethane,[3] 3,5-bis(trifluoromethyl)benzenesulfonyl chloride,[4] 3 equiv of triethylamine, and 0.1 equiv of 4-(dimethylamino)pyridine in CH_2Cl_2 at 0 °C to give bis(sulfonamide) **2**, mp 155–156 °C, $[\alpha]^{20}_D$ +83.7° (*c* = 1, $CHCl_3$), in >90% yield after recrystallization from CH_2Cl_2–hexane. Reaction of **2** with 2 equiv of boron tribromide in CH_2Cl_2 at reflux for 3 h and subsequent removal of solvent and excess BBr_3 in vacuo provided reagent **1** as a colorless solid (moisture sensitive), ^{11}B NMR peak at δ +26.4 (relative to external $BF_3{\cdot}Et_2O$).[5] The reaction of **1** (designated below as R^*_2BBr), *tert*-butyl propionate, and triethylamine (TEA) in 1:2 toluene–hexane or CH_2Cl_2 as solvent at −78 °C for 4 h produced selectively the boron enolate in which methyl and OB substituents are trans ("transoid enolate", **3**), as shown by the reaction with a variety of aldehydes (−78 °C, 2 h) to form anti aldol products (**4**) selectively (see Scheme I). Table I summarizes the results of a number of experiments. Excellent enantioselectivity was observed except for the case of cyclohexanecarboxaldehyde, in which the enantioselection was only 87:13. However, as shown in Table I, the use of the propionate ester of (+)-menthol with cyclohexanecarboxaldehyde leads to formation of the desired aldol product in 96% de and 94% ee with CH_2Cl_2 as solvent.[6] Equally good results were obtained with 3-phenylpropanal and (+)-menthyl propionate (Table I), demonstrating the generality of high stereoselectivity for a range of conjugated and nonconjugated aldehyde structures.

Scheme II outlines the method by which reagent **1** promotes the formation of syn aldol products. In general, the reaction of reagent **1** with the phenylthio ester of propionic acid in the presence of diisopropylethylamine (DPEA) in CH_2Cl_2 (preferred solvent) at −40 °C for 2 h led cleanly to formation of "cisoid" enolate **5** as shown by the further reaction with various aldehydes (2 h at −78 °C) to form syn aldol products **6**. For example, benzaldehyde and cyclohexanecarboxaldehyde were converted to syn aldols in 93% yield, 97% ee, and 99:1 syn:anti ratio and in 86% yield, 91% ee and 98:2 syn:anti ratio, respectively (for product analysis see ref 3). In the case of 3-phenylpropanal the syn aldol was obtained in 79% yield and 83% ee with a syn:anti ratio of 98:2.

The above described results show that the reagent **1** allows the highly selective conversion of *tert*-butyl or (+)-menthyl propionate and various aldehydes to anti aldols and also the transformation of the same aldehydes to syn aldols with *S*-phenyl thiopropionate.[3] The divergence in stereochemistry of enolate formation from **1** as a function of ester structure may be due to a fundamental mechanistic dichotomy. The initial complex of **1** with *S*-phenyl thiopropionate (**7**) may undergo sulfur-promoted dissociation of bromide ion in the solvent CH_2Cl_2 to form ion pair **8** more rapidly than direct deprotonation by the hindered base DPEA. Deprotonation of **8** in the conformation shown would then favor the "cisoid" enolate **5**. Support of this proposal has been obtained from the experimental finding that the reaction of *S*-phenyl thiopropionate and **1** with TEA in 1:2 toluene–hexane produces cisoid and transoid enolates in a ratio of 55:45. This result is predicted from Scheme II since the less polar solvent should slow the dissociation of **7** to ion pair **8** while the sterically smaller TEA (relative to DPEA) should accelerate the direct deprotonation of **7** to form the transoid enolate.[7] On the other hand, the initial complex of **1** with *tert*-butyl propionate (**9**), in the favored conformation shown, can be expected to lose bromide ion slowly compared to deprotonation by TEA, to form the transoid enolate, because the bulky *tert*-butyl group prefers an out-of-plane orientation which disfavors ionization to **10**.[8]

The above argument involving E1- and E2-like mechanisms for boron enolate formation also provides a simple explanation for Brown's finding[2] that propiophenone is converted to the transoid boron enolate by dicyclohexylboron chloride–TEA (99:1 selectivity, E2-like mechanism) and to the cisoid boron enolate by dicyclohexylboron triflate–DPEA (99:1 selectivity, E1-like mechanism).[9] Clearly, the better triflate leaving group should favor the two-step, E1-like mechanism for which the more hindered amine DPEA is also advantageous.[10]

(1) The references that follow document the major advances of the past years on the synthetic refinement of the aldol process. (a) Fenzl, W.; Köster, R. *Justus 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.; Goodman, J. M. *Tetrahedron Lett.* **1989**, *30*, 997.

(2) Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 3441.

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

(4) 3,5-Bis(trifluoromethyl)benzenesulfonyl chloride was synthesized in 81% yield from commercially available 3,5-bis(trifluoromethyl)aniline by 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: Mrozik, H. H. U.S. Patent 4,005,199, Jan 25, 1977; *Chem. Abstr.* **1977**, *86*, P171112t. Reaction of 1,3-bis(trifluoromethyl)-benzene with chlorosulfuric acid gave mainly *m*-(trifluoromethyl)benzenesulfonyl chloride.

(5) The solubility of **1** in nonpolar solvents such as toluene and the Lewis acidity of **1** are both greater than observed for the sulfonamide reagents used in earlier work.[3]

(6) Use of the propionate ester of (−)-menthol with reagent **1**, triethylamine, and cyclohexanecarboxaldehyde led to a less stereoselective aldol reaction and a poor anti:syn ratio (88:12).

(7) A number of experiments confirm that TEA favors transoid enolate relative to DPEA and that increasing solvent polarity favors cisoid enolate. The ratio of cisoid to transoid enolate was determined by reaction with benzaldehyde at −78 °C and analysis of the resulting syn–anti aldol mixture.

(8) Support for this argument has been obtained from the finding that the reaction of **1**, *S*-*tert*-butyl thiopropionate, and triethylamine in 1:2 toluene–hexane generates the transoid boron enolate with a selectivity of 92:8. Trityl propionate is also converted to the transoid enolate under these conditions.

(9) It has been known for some time that the reaction of *S*-phenyl thiopropionate with 9-borabicyclononane (9-BBN) triflate and DPEA leads selectively to the formation of the cisoid boron enolate. See: Hirama, M.; Garvey, D. S.; Lu, L. D.-L.; Masamune, S. *Tetrahedron Lett.* **1979**, *20*, 3937.

(10) The formation of cisoid enolates from both 9-BBN triflate and 9-BBN chloride[2] may be a consequence of strong steric acceleration of the E1 pathway in the 9-BBN system regardless of whether the leaving group is halide or triflate.

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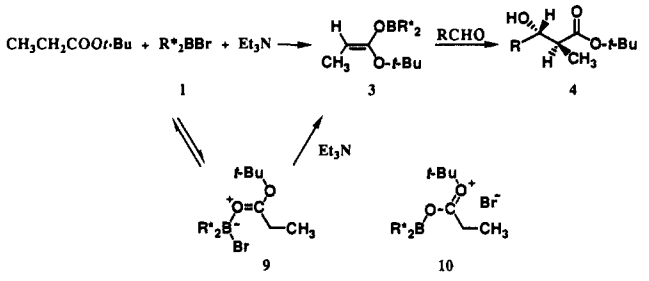
Table I. Reaction of Aldehydes with Propionate Esters Promoted by Bromoborane 1 and Triethylamine To Form Anti Aldols (for Example, 4)[a]

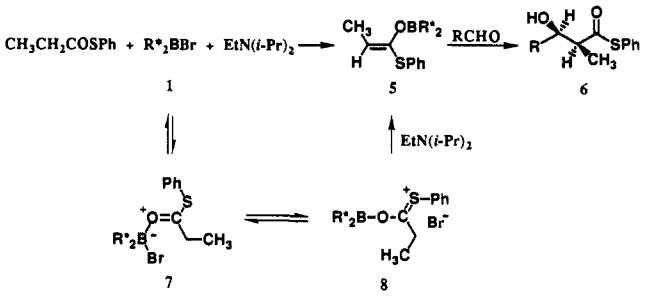
RCHO R	propionate ester	solvent	% yield of aldol	anti:syn	% ee[e]
C_6H_5	*t*-Bu	1:2 toluene–hexane	93	98:2[b]	94
C_6H_5	*t*-Bu	CH_2Cl_2	90	96:4[b]	89
(*E*)-C_6H_5CH=CH	*t*-Bu	1:2 toluene–hexane	81	99:1[b]	98
(*E*)-C_6H_5CH=CH	*t*-Bu	CH_2Cl_2	91	96:4[b]	97
cyclohexyl	*t*-Bu	1:2 toluene–hexane	82	94:6[b]	75
cyclohexyl	(+)-menthyl	1:2 toluene–hexane	91	99:1[c]	87
cyclohexyl	(+)-menthyl	CH_2Cl_2	86	98:2[c]	94
$C_6H_5CH_2CH_2$	(+)-menthyl	1:2 toluene–hexane	83	99:1[d]	95
$C_6H_5CH_2CH_2$	(+)-menthyl	CH_2Cl_2	80	97:3[d]	96

[a] Conditions as in text and ref 11. [b] Anti:syn ratios and % ee were determined by HPLC analysis using a chiral Daicel OD column. [c] Analysis by reduction to the corresponding diol mixture with $LiAlH_4$, conversion to the bis MTPA esters, and measurement of 500-MHz ^1H NMR spectra. [d] Anti:syn and de ratios determined by HPLC analysis using a Du Pont Zorbax silica gel column. [e] Absolute configuration, in each case, was determined for the predominating enantiomer (2*S*) by optical rotation and/or comparison with an authentic sample; see: (a) Reference 11. (b) Kim, B. Ph.D. Dissertation, Massachusetts Institute of Technology, Feb 1988.

Scheme I



Scheme II



We believe that the methodology outlined herein will prove to be of considerable utility in synthesis.[11] The reagent **1** and its enantiomer are also highly selective in other enantioselective constructions, e.g., carbonyl allylation.[12]

Supplementary Material Available: Experimental procedures for the preparation of compounds **1**, **2**, **4** (R = C_6H_5), and **6** (R = C_6H_5), as well as key ^1H NMR data for anti aldol products **4** and syn aldol products **6** (5 pages). Ordering information is given on any current masthead page.

(12) This research was assisted financially by the National Science Foundation and the National Institutes of Health.

(11) The following procedure for an enantioselective aldol reaction is illustrative. ***tert*-Butyl (2*S*,3*R*)-(+)-2-Methyl-3-hydroxy-3-phenylpropionate (4, R = C_6H_5).** The (*R*,*R*)-(+)-bis[3,5-bis(trifluoromethyl)benzenesulfonamide] **2** (184 mg, 0.24 mmol) dissolved in dry CH_2Cl_2 (3 mL) under argon at 0 °C was treated with BBr_3 (1 M solution in dichloromethane, 480 μL, 0.48 mmol). The stirred sqlution was heated to 45 °C for 3 h and concentrated under vacuum. Dry dichloromethane (1 mL) was added and evaporated under vacuum. Dry toluene (8 mL) was added, and the resulting mixture was warmed to effect complete solution and then diluted with 16 mL of hexane. The homogeneous solution of bromoborane **1** was cooled to −78 °C, then treated with *tert*-butyl propionate (31 mg, 36 μL, 0.24 mmol), and stirred for 1 min. The resulting solution was treated with triethylamine (27 mg, 37 μL, 0.26 mmol) and stirred for 3.5 h at −78 °C. Benzaldehyde (23 mg, 22 μL, 0.22 mmol) in toluene (0.5 mL) was added over 5 min. The reaction was allowed to proceed for 1.5 h at −78 °C, then quenched by addition of methanol (0.5 mL) at −78 °C followed by dilution with 5 mL of pH 7 buffer. Extractive isolation (ether) afforded the anti aldol **4**, R = C_6H_5, along with the syn diastereoisomer in a ratio of 98:2 as determined by 500-MHz ^1H NMR measurement. Final purification and recovery of (*R*,*R*)-bis(sulfonamide) **2** (92%) were effected by silica gel chromatography (hexane–ethyl acetate, 5:1) to afford **4**, R = C_6H_5 (48.3 mg, 0.20 mmol, 93% yield, 94% ee), as a colorless liquid: $[\alpha]^{20}_D$ +54.66 (*c* 0.73, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.02 (d, *J* = 7 Hz, 3 H), 1.44 (s, 9 H), 2.71 (dt, *J* = 15, 7.5 Hz, 1 H), 3.19 (d, *J* = 4.8 Hz, 1 H), 4.70 (dd, *J* = 8.5, 4.5 Hz, 1 H), 7.26–7.35 (m, 5 H); 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), and 107 (8).

Zinc(II) Complexes and Aluminum(III) Porphyrin Complexes Catalyze the Epoxidation of Olefins by Iodosylbenzene

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Iodosylbenzene, OIPh, has been used as a single oxygen atom transfer reagent in a wide variety of studies, usually with the intention of generating reactive intermediates analogous to those occurring naturally in metalloenzyme-catalyzed reactions.[1] In several instances, it has been possible to observe directly high-valent oxo complexes prepared by using iodosylbenzene.[2-4] In the vast majority of cases, however, the intermediacy of high-valent metal oxo intermediates in metal complex catalyzed oxygenations of organic substrates by iodosylbenzene has been assumed or has been asserted on the basis of indirect evidence.[1j-l,3]

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