Highly Enantioselective Alkynylation of Aldehydes Promoted by Chiral Oxazaborolidines

E. J. Corey* and Karlene A. Cimprich

Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138

Received January 12, 1994

The nucleophilic alkynylation of carbonyl compounds is an important synthetic method whose utility would be considerably enhanced if practical enantioselective versions were available. Current methodology is far from ideal, suffering from both moderate enantioselectivity and limited scope.[1] In contrast, considerable progress has been made with the enantioselective addition of dialkyl- and alkenylzinc compounds to aldehydes using chiral amino alcohols as ligands.[2,3] Herein we describe the use of chiral oxazaborolidines as catalysts for the enantioselective addition of alkynylboranes to aldehydes in a manner analogous to the asymmetric reduction of ketones with borane or catecholborane mediated by proline-derived oxazaborolidines.[4]

The rationale for the new enantioselective alkynylation process is outlined in Scheme 1. The alkynylation reagent is the dimethylborane **2** generated in situ from bromodimethylborane and the corresponding alkynylstannane.[5-7] In the presence of a stoichiometric amount of **1**, R = *n*-Bu,[8-10] the addition of **2** to an aldehyde is accelerated and controlled sterically to form propargyl carbinols **3** with excellent enantioselectivity. Oxazaborolidine **1**, R = Ph, efficiently promotes the alkynylation reaction of some substrates in substoichiometric quantities.

A typical procedure involves addition of a solution of bromodimethylborane[11] in methylcyclohexane (1 equiv) to a solution of the alkynylstannane (1.3–1.5 equiv) in toluene at −78 °C. A solution of the oxazaborolidine (0.25–1.0 equiv in toluene) is added after 30 min, and after an additional 15 min, the aldehyde is added. The reactions are generally complete after 8–24 h at −78 °C, and the chiral ligand is readily recovered as the hydrochloride salt, making the reaction practical even when a stoichiometric amount of the oxazaborolidine is required.

Scheme 1

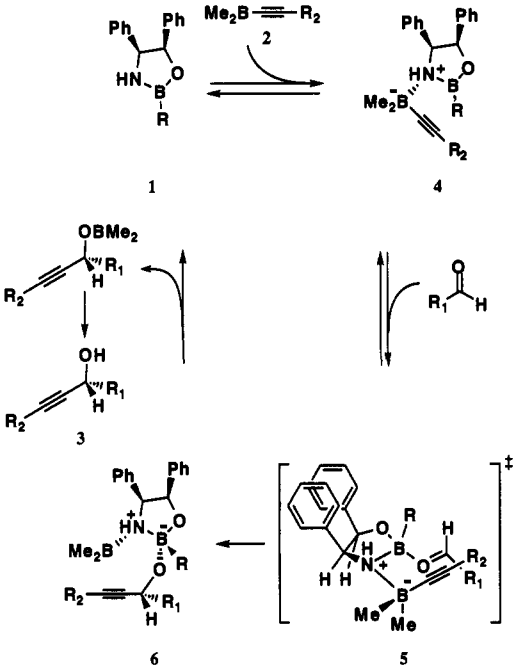
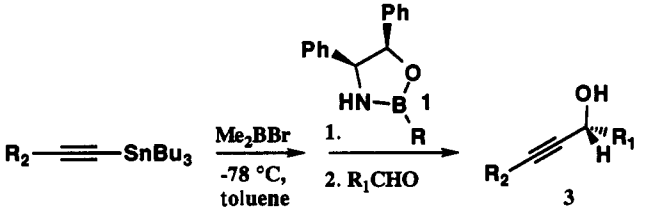


Table 1. Enantioselective Alkynylation of Aldehydes[a]



R_1	R_2	1, R (equiv)	yield of 3 (%)	rotn (+ or −)	ee (%) (config)
c-C_6H_{11}	Ph	Bu (1.0)	96	−	90[b]
c-C_6H_{11}	*n*-C_5H_{11}	Bu (1.0)	82	−	95 (*R*)[c,e]
Ph	Ph	Bu (1.0)	78	+	96 (*R*)[b,d]
Ph	*n*-C_5H_{11}	Bu (1.0)	28	+	94 (*R*)[c,f]
n-C_5H_{11}	Ph	Bu (1.0)	90	−	96 (*R*)[b,e]
n-C_5H_{11}	*n*-C_5H_{11}	Bu (1.0)	80	+	96[c]
c-C_6H_{11}	Ph	Me (1.0)	95	−	90[b]
t-Bu	Ph	Bu (1.0)	71	+	97 (*R*)[b,d]
n-C_5H_{11}	Ph	Ph (0.25)	77	−	93 (*R*)[b,e]
Ph	Ph	Ph (0.25)	72	+	97 (*R*)[b,d]
c-C_6H_{11}	Ph	Ph (0.25)	80	−	85[b]
p-$MeOCOC_6H_4$	Ph	Me (1.0)	80	+	96[b]
p-$NO_2C_6H_4$	Ph	Ph (1.0)	86	+	96[b]

[a] All reactions were run at −78 °C in toluene. [b] Enantiomeric excess was determined by HPLC analysis (Daicel Chiracel OD column) of the alcohol. [c] Enantiomeric excess was determined by HPLC analysis (Daicel Chiracel OD column) of the benzoate ester. [d] Absolute configuration is based on measurement of the optical rotation and comparison with the literature, see: Tombo, G. M. R.; Didier, E.; Loubinoux, B. *Synlett* **1990**, 547–548. See also: Ramachandran, P. V.; Teodorovic, A. V.; Rangaishenvi, M. V.; Brown, H. C. *J. Org. Chem.* **1992**, *57*, 2379–2386. [e] Absolute configuration was determined by measuring the rotation of the hydroxy ester formed on benzoylation (PhCOCl, pyridine, DMAP), oxidative cleavage (catalytic $RuCl_3$–H_2O, $NaIO_4$), hydrolysis (LiOH), and esterification (CH_2N_2) of the resulting hydroxy acid, see: Ko, K.-Y.; Frazee, W. J.; Eliel, E. L. *Tetrahedron* **1984**, *40*, 1333–1343. See also: Grieco, P. A.; Takigawa, T.; Vedananda, T. R. *J. Org. Chem.* **1985**, *50*, 3111–3115. [f] Absolute configuration was determined by conversion to *O*-acetylmandelic acid (Ac_2O, pyridine, DMAP; $RuCl_3$–H_2O, $NaIO_4$; CH_2N_2) and determination of optical rotation.

Representative results are summarized in Table 1. The propargylic alcohols were formed with excellent enantioselectivity in every case. Better yields were obtained with less hindered

(1) (a) Mukaiyama, T.; Suzuki, K.; Soai, K.; Sato, T. *Chem. Lett.* **1979**, 447–448. (b) Mukaiyama, T.; Suzuki, K. *Chem. Lett.* **1980**, 255–256. (c) Niwa, S.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 937–943. (d) Tombo, G. M. R.; Didier, E.; Loubinoux, B. *Synlett* **1990**, 547–548.

(2) For recent reviews of this area, see: (a) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833–856. (b) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49–69.

(3) (a) Oppolzer, W.; Radinov, R. N. *Helv. Chim. Acta* **1992**, *75*, 170–173. (b) Oppolzer, W.; Radinov, R. N. *J. Am. Chem. Soc.* **1993**, *115*, 1593–1594.

(4) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925–7926. (c) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611–614. (d) Corey, E. J.; Link, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 1906–1908.

(5) Wrackmeyer, B.; Nöth, H. *Chem. Ber.* **1977**, *110*, 1086–1094.

(6) *B*-1-Alkynyl-9-borabicyclo[3.3.1]nonanes have been shown to readily undergo addition to aldehydes and ketones, affording the racemic propargylic alcohols in good yields: (a) Brown, H. C.; Molander, G. A.; Singh, S. M.; Racherla, U. S. *J. Org. Chem.* **1985**, *50*, 1577–1582. (b) Evans, J. C.; Goralski, C. T.; Hasha, D. L. *J. Org. Chem.* **1992**, *57*, 2941–2943.

(7) For preparation of the related vinylborane, see: Singleton, D. A.; Martinez, J. P.; Ndip, G. M. *J. Org. Chem.* **1992**, *57*, 5768–5771.

(8) See also: Quallich, G. J.; Woodall, T. M. *Tetrahedron Lett.* **1993**, *34*, 4145–4148.

(9) Oxazaborolidines **1** (R = *n*-Bu and R = Ph) were prepared by azeotropic removal of water (4-A molecular sieves, Dean–Stark trap, 18 h) from a mixture of (1*R*,2*S*)-(−)-2-amino-1,2-diphenylethanol and *n*-butylboronic acid or triphenylboroxine in refluxing toluene.

(10) For the preparation of (1*R*,2*S*)-(−)-2-amino-1,2-diphenylethanol, see: (a) Weijlard, J.; Pfister, K., III.; Swanezy, E. F.; Robinson, C. A.; Tishler, M. *J. Am. Chem. Soc.* **1951**, *73*, 1216–1218. (b) Lyle, G. G.; Lacroix, W. *J. Org. Chem.* **1963**, *28*, 900–901. (c) Saigo, K.; Ogawa, S.; Kikuchi, S.; Kasahara, A.; Nohira, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1568–1573.

(11) Guindon, Y.; Yoakim, C.; Morton, H. E. *J. Org. Chem.* **1984**, *49*, 3912–3920.

0002-7863/94/1516-3151$04.50/0 © 1994 American Chemical Society

aliphatic aldehydes, and, in addition, aryl acetylenes gave slightly higher yields than their aliphatic counterparts.

The high degree of enantioselectivity attained in these reactions and the observed preference for the formation of (*R*)-carbinols merit comment. The transition-state model **5** shown in Scheme 1 can explain this preference. Shielding of one face of the oxazaborolidine ring by the phenyl substituents favors coordination of the alkynylborane to nitrogen on the opposite face of the ring. Coordination of the aldehyde to the oxazaborolidine *syn* to the alkynylborane and *via* the lone pair *anti* to the large alkyl group would then lead to the observed aldehyde facial selectivity *via* transition-state assembly **5**. Subsequent loss of product as the borinate releases the oxazaborolidine for repetition of the catalytic cycle. This model is consistent with the observed absolute stereochemical selectivity and is analogous to that proposed for the oxazaborolidine-catalyzed reduction of ketones.[12]

The ability of oxazaborolidine **1**, R = Ph, to promote the reaction in substoichiometric quantities, in contrast to the butyl analog, may be a consequence of phenyl enhancement of the dissociation of $R_2C{\equiv}CCHR_1OBMe_2$ from **6** with regeneration of catalyst **1** relative to other processes. The greater Lewis acidity of **1**, R = Ph, relative to **1**, R = *n*-Bu, may serve to compensate for the greater bulk of phenyl with regard to the binding of RCHO. It is noteworthy that the oxazaborolidine derived from (1*R*,2*S*)-(−)-2-amino-1,2-diphenylethanol and tris(*p*-trifluoromethyl)-phenylboroxine enhances the rate of alkynylation noticeably but provides the propargyl carbinol with decreased enantioselectivity (<80%).[13]

The nature of the substituent on nitrogen also appears significant as replacement of the hydrogen by an alkyl group prohibits reaction.[14] Alkynyldimethylboranes are sterically demanding, and it is possible that coordination of the alkynylborane is impeded in these cases, preventing further reaction. The sensitivity of this reaction to steric effects may be partly responsible for the problems encountered in transferring (trimethylsilyl)-acetylene. The desired product is obtained in low yield (<30%, 84% ee) even when a more Lewis acidic oxazaborolidine is used (**1**, R = *p*-CF_3-C_6H_4). The proximity of R_1 of the aldehyde and R_2 of the acetylene in the transition-state assembly **5** may account for this observation. Further evidence for steric hinderance is provided by the reaction of *tert*-butylacetylene with hexanal, which proceeds relatively slowly and in only 56% yield (91% ee) with 1 equiv of oxazaborolidine **1**, R = *p*-CF_3-C_6H_4.

In conclusion, this paper describes a new methodology for the enantioselective alkynylation of aldehydes. Oxazaborolidine **1**, which is available in either enantiomeric form, can be used in stoichiometric or catalytic amounts to promote the formation of propargylic alcohols with unprecedented enantioselectivity, in good yield and with predictable absolute configuration. In addition, the commercially available chiral amino alcohol can be recovered efficiently for reuse. We believe that the methodology described herein will prove to have many applications and that further improvements are likely.

The following experimental procedures illustrate the details of catalyst formation and aldehyde alkynylation.

Preparation of Oxazaborolidine 1, R = Ph. A 25-mL round-bottom flask containing (1*R*,2*S*)-(−)-2-amino-1,2-diphenylethanol (Aldrich) (0.2268 g, 1.06 mmol) and triphenylboroxine (0.1215 g, 0.39 mmol) was fitted with a Dean–Stark trap containing 4-A molecular sieves in the side arm. The system was evacuated and purged with argon three times, charged with toluene (20 mL), and heated at reflux for 18 h. After concentration of the reaction mixture to approximately 3 mL by distillation at 1 atm, the Dean–Stark apparatus was replaced with a three-way stopcock capped with a rubber septum and then connected to a vacuum line. Complete removal of toluene *in vacuo* and addition of 3.5 mL of toluene under argon provided a 0.3 M solution of **1**, R = Ph: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87–7.85 (m, 2H), 7.52–7.44 (m, 3H), 7.04–6.94 (m, 10 H), 5.94 (d, J = 8.4 Hz, 1H), 5.15 (d, J = 8.4 Hz, 1 H), 4.16 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.6, 138.9, 134.0, 130.7, 127.9, 127.6, 127.4, 127.0, 126.8, 126.5, 84.5, 64.8; ^{11}B NMR (160 MHz, $CDCl_3$) δ 33.0 (s).

Preparation of (*R*)-Methyl 4-(1-Hydroxy-3-phenyl-2-propynyl)benzoate. A flame-dried 10-mL Schlenk flask containing (phenylethynyl)tri-*n*-butyltin (316 μL, 0.90 mmol) was evacuated and purged with argon five times and then charged with dry toluene (1.5 mL, distilled from Na^0). The solution was cooled to −78 °C in a dry ice–acetone bath, and a solution of bromodimethylborane[11] (0.76 mmol, 1.11 M) in methylcyclohexane was added dropwise with a gas-tight syringe. After 20 min at −78 °C, freshly prepared oxazaborolidine **1**, R = Me, (0.73 mmol, 0.49 M in toluene) was added dropwise along the wall of the flask, and 20 min later a solution of 4-(methoxycarbonyl)benzaldehyde (0.114 g, 0.69 mmol) in toluene (1.5 mL) was added over 5 min *via* cannula. The reaction was quenched with 0.8 mL of 1 M methanolic HCl after 18 h at −78 °C, warmed to 23 °C, and filtered to remove (1*R*,2*S*)-(−)-2-amino-1,2-diphenylethanol–HCl. The filtrate was washed with distilled water and then brine, dried ($MgSO_4$), and concentrated to afford the crude alcohol. Purification by silica gel chromatography (50% Et_2O in hexane) provided 148.7 mg (0.56 mmol, 80%) of the pure alcohol as a colorless oil. Enantiomeric excess was determined to be 96% by HPLC analysis: $[\alpha]^{23}_D$ +7.56° (c = 1.5, $CHCl_3$); FTIR (thin film) 3428, 2951, 2234, 1721 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.3 Hz, 2H), 7.46 (m, 2H), 7.32 (m, 3H), 5.75 (br s, 1H), 3.93 (s, 3H), 2.41 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 145.4, 131.7, 130.0, 129.9, 128.8, 128.3, 126.6, 122.1, 88.1, 87.1, 64.6, 52.2; EIMS m/e 267 [M + H$^+$]; HRMS calcd for $[C_{17}H_{14}O_3]^+$ 266.0943, found 266.0947; HPLC (Chiracel OD, 25% *i*-PrOH in hexane, 254 nm), t_R 7.7 (major), 16.8 (minor); TLC R_f 0.44 (50% Et_2O in hexanes).[15]

Supplementary Material Available: Experimental procedures and spectral data for propargylic alcohol and oxazaborolidines (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(12) (Phenylethynyl)dimethylborane, generated by treatment of Me_2BBr with lithium phenylacetylide in toluene, transferred phenylacetylene to cyclohexanecarboxaldehyde in the presence of **1** (R = *n*-Bu, 1.0 equiv) in 72% yield and 88% ee, suggesting that Bu_3SnBr is not participating in the alkynylation reaction. However, this method of generating the alkynylborane is restricted to those lithium acetylides which are soluble in toluene.

(13) This catalyst was tested using (phenylethynyl)tri-*n*-butyltin and cyclohexanecarboxaldehyde as substrates.

(14) Oxazaborolidines derived from *n*-butylboronic acid and (*S*)-(−)-α,α-diphenyl-2-pyrrolidinemethanol, (1*R*,2*S*)-(−)-2-(*N*-methylamino)-1,2-diphenylethanol, or (−)-ephedrine did not promote the transfer of an alkynyl group to an aldehyde.

(15) This research was assisted financially by grants from the National Institutes of Health and a grant from Eli Lilly Corporation to K.A.C.