Direct Catalytic Enantioselective Reduction of Achiral α,β-Ynones. Strong Remote Steric Effects Across the C−C Triple Bond

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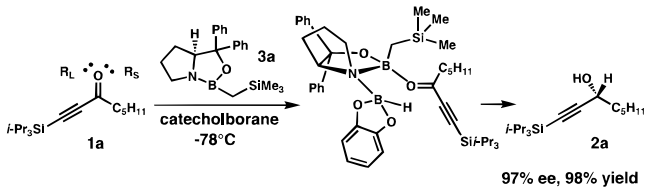
Chiral propargylic alcohols are extremely useful intermediates for the enantioselective synthesis of complex molecules, for example, eicosanoids,[1] macrolides,[2] and enediyne antibiotics.[3] There have been only two principal approaches to the enantioselective synthesis of propargylic alcohols: (1) enantioselective alkynylation of aldehydes[4] and (2) reduction of α,β-ynones[5] or their π-$Co_2(CO)_6$-protected derivatives.[6] Although the last method[6] is catalytic and quite effective, we sought a *more direct* catalytic synthesis. This research led to the discovery of a remarkable steric effect across the acetylenic linkage and a direct and highly effective catalytic enantioselective reduction of α,β-ynones.

Scheme 1



The example described in Scheme 1 is representative. Treatment of ketone **1a** and oxazaborolidine **3a** (0.05 equiv) with catecholborane (1.2 equiv) as the stoichiometric reductant at −78 °C in CH_2Cl_2 produced the (*R*)-acetylenic alcohol in 98% yield and 97% ee (66:1 enantiomer ratio (er)).[7−9] The acetylenic ketone undergoes enantioselective reduction in the sense expected for coordination of the catalyst at the carbonyl lone pair *anti* to the (triisopropylsilyl)ethynyl unit, which functions effectively as the larger carbonyl substituent (R_L) versus the *n*-pentyl group (R_S).[10] An indication of the scope of this reduction is provided by the examples shown in Table 1. The products are valuable synthetic building blocks; for example, **2a** for eicosanoid synthesis,[1,5b] **2c** for enediyne derivatives,[3] and **2d** for elaboration products of ethynyl oxiranes. It is noteworthy that for the reduction of ketone **1e** isopropyl corresponds to R_S and ethynyl to R_L. The previously unknown (triisopropylsilyl)acetylenic ketones **1a**−**e** were efficiently prepared via a novel and highly selective Friedel−Crafts acylation (RCOCl, $AlCl_3$, CH_2Cl_2, 0 °C) of (triisopropylsilyl)-(trimethylsilyl)acetylene.[11] A greater understanding of the factors responsible for the high enantioselectivity observed in the reduction of the α,β-ynones can be gained from the data shown in Tables 2−4. The results in Table 2 reveal a dramatic enhancement of the asymmetric induction as the distal group of the alkyne increases in size from *n*-pentyl (68% ee, 4:1 enantiomer ratio) to phenyl and trimethylsilyl (87% ee, 14:1 enantiomer ratio) to triisopropylsilyl (96% ee, 49:1 enantiomer ratio). A consistently greater remote steric effect of the triisopropylsilyl group relative to the trimethylsilyl group is documented in Table 3.[12] The dependence of the enantioselectivity of reduction of the (triisopropylsilyl)acetylenic ketones on the *alkyl group attached to the boron* atom of the catalyst is clearly shown by the data in Table 4. A systematic increase in the size of the boron substituent resulted in marked enhancement of the enantioselectivity of the reduction. Thus, in CH_2Cl_2, the percent ee observed increased from 60% (B−Me, catalyst **3c**) to 92% (B-*n*-Bu, catalyst **3b**) to 97% (B-CH_2SiMe_3, catalyst **3a**), whereas in toluene, the percent ee observed increased from 46% ((*S*)-enantiomer, **3c**) to 72% ((*R*)-enantiomer, **3b**) to 95% (**3a**).[13] It is interesting to note that the selectivity of the reduction varies with solvent for catalyst **3c** (CH_2Cl_2, 4:1

(1) (a) Nicolaou, K. C.; Webber, S. E. *J. Am. Chem. Soc.* **1984**, *106*, 5734. (b) Chemin, D.; Linstrumelle, G. *Tetrahedron* **1992**, *48*, 1943. (c) Corey, E. J.; Niimura, K.; Konishi, Y.; Hashimoto, S.; Hamada, Y. *Tetrahedron Lett.* **1986**, *27*, 2199.

(2) Roush, W. R.; Sciotti, R. J. *J. Am. Chem. Soc.* **1994**, *116*, 6457.

(3) Vourloumis, D.; Kim, K. D.; Petersen, J. L.; Magriotis, P. A. *J. Org. Chem.* **1996**, *61*, 4848.

(4) (a) Mukaiyama, T.; Suzuki, K.; Soai, K.; Sato, T. *Chem. Lett.* **1979**, 447. (b) Mukaiyama, T.; Suzuki, K. *Chem. Lett.* **1980**, 255. (c) Niwa, S.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 937. (d) Tombo, G. M. R.; Didier, E.; Loubinoux, B. *Synlett* **1990**, 547. (e) Corey, E. J.; Cimprich, K. A. *J. Am. Chem. Soc.* **1994**, *116*, 3151

(5) (a) Midland, M. M.; Kazubski, A. *J. Am. Chem. Soc.* **1982**, *47*, 2816. (b) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717. (c) Marshall, J. A.; Robinson, E. D.; Zapata, A. *J. Org. Chem.* **1989**, *54*, 5854. (d) Brown, H. C.; Ramachandran, P. V.; Weissman, S. A.; Swaminathan, S. *J. Org. Chem.* **1990**, *55*, 6328.

(6) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1995**, *36*, 9153.

(7) The absolute configuration of the product was determined by desilylation (1.1 equiv of tetrabutylammonium fluoride, THF, 23 °C) and comparison of the optical rotation with known (*R*)-1-octyn-3-o1; $[\alpha]_{D,25}$ +4.2 (*c* 0.55, CH_2Cl_2), $[\alpha]_{D,20}$ (lit.) +6.5 (*c* 2.0, CH_2Cl_2). The absolute configurations of the other (triisopropylsilyl)acetylenic alcohols (Table 1) were assigned by analogy.

(8) Catalyst **3a** was prepared using (*S*)-α,α-diphenyl-2-pyrrolidinemethanol and $Me_3SiCH_2B(OH)_2$. For the catalyst preparation procedure see the Supporting Information. Physical data for **3a**: ^{1}H NMR (400 MHz, $CDCl_3$ (distilled)) δ 7.52 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 7.9 Hz, 2H), 7.17−7.35 (m, 6H), 4.28 (dd, J = 5.6, 10.0 Hz, 1H), 3.34 (m, 1H), 3.04 (m, 1H), 1.76 (m, 2H), 1.58 (m, 1H), 0.79 (m, 1H), 0.08 (s, 3H), 0.05 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ (distilled)) δ 148.02, 144.34, 128.04, 127.06, 126.50, 126.39, 126.22, 87.31, 72.61, 43.39, 30.50, 25.95, 0.58, 0.50 ppm; ^{11}B NMR (96 MHz, $CDCl_3$ (distilled)) δ 35.12 (br s) ppm; MS (CI) $[M + H]^+$ (100%), M^+ (35%); HRMS (CI) calcd for $[C_{21}H_{29}BNOSi]$ 350.2111, found 350.2123. Reduction of 1a: Ketone **1a** (1.6 mmol, 449 mg) (azeotropically dried with toluene under an inert atmosphere) was treated with catalyst **3a** (0.05 equiv, 0.08 mmol, 400 μL of a 0.2 M toluene solution). The toluene was removed *in vacuo*, CH_2Cl_2 (4 mL) was added, and the solution was cooled to −78 °C. A solution of catecholborane (1.2 equiv, 1.9 mmol, 200 μL) in CH_2Cl_2 (800 μL) was then added dropwise over 10 min. After 5 h of stirring, MeOH (1 mL) was added, the solution was warmed to 23 °C, diluted with Et_2O, washed with 2:1 1 N NaOH-saturated $NaHCO_3$ until the aqueous layer was colorless, washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The addition of Et_2O (10 mL) followed by 0.5 M HCl in MeOH (0.05 equiv, 0.08 mmol, 160 μL) resulted in precipitation of the amino alcohol hydrochloride salt as a fine powder which was removed via filtration. The Et_2O was removed *in vacuo*, and the residue was passed through a short column of silica gel (30:1 to 15:1 hexanes−EtOAc) to provide 440 mg of **2a** as a clear oil (98% yield): $[\alpha]_{D,25}$ +12.1 (*c* 1.40, benzene); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.38 (m, 1H), 1.76 (d, J = 4.9 Hz, 1H), 1.71 (m, 2H), 1.46 (m, 2H), 1.31 (m, 4H), 1.01−1.29 (m, 21H), 0.89 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.99, 85.48, 63.12, 37.99, 31.49, 24.86, 22.63, 18.63, 14.01, 11.19 ppm; FT-IR (neat) 3407, 2957, 2942, 2893, 2865, 1464 cm^{-1}; MS (CI) 300 ($[M + NH_4]^+$, 100); HRMS (CI) calcd for $[C_{17}H_{38}NOSi]$ ($[M + NH_4]^+$) 300.2723, found 300.2736. The enantioselectivity of the reduction was determined by conversion of the alcohol to the *p*-nitrobenzoate and HPLC analysis (Chiralcel OD, 0.05% *i*-PrOH in hexanes, 0.5 mL/min, λ = 254 nm) which showed the product to be of 97% ee (t_R = 30.4 min, major; 26.0 min, minor).

(9) The reduction of ketone **1a** using 0.1 equiv of catalyst **3a** and 1.0 equiv of BH_3−Me_2S as the stoichiometric reductant in THF at 0 °C gave the enantiomer of **2a** in 40% ee and 88% yield.

(10) While this work was in progress, the stoichiometric and catalytic (0.5 mol equiv) asymmetric reduction of phenyl-substituted and terminal acetylenic ketones was reported (2 equiv of B−Me oxazaborolidine **3c**, 5 equiv of BH_3−Me_2S, THF, −30 °C). Under these conditions the acetylenic group is effectively R_S: Parker, K. A.; Ledeboer, M. W. *J. Org. Chem.* **1996**, *61*, 3214.

(11) (a) Prepared from (trimethylsilyl)acetylene (*n*-BuLi, THF, −78 °C) and triisopropylsilyl chloride (-78 to 23 °C) in 96% yield after distillation (bp 56−57 °C (0.25 mmHg)). For details see the Supporting Information. (b) For another selective reaction of (triisopropylsilyl)(trimethylsilyl)-acetylene, see: Stang, P. J.; Zhdankin, V. V.; Arif, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 8997.

(12) The (trimethylsilyl)acetylenic ketones were prepared according to established procedures: (a) Birkofer, L.; Ritter, A.; Uhlenbrauck, H. *Chem. Ber.* **1963**, *96*, 3280. (b) Walton, D. R. M.; Waugh, F. *J. Organomet. Chem.* **1972**, *37*, 45. (c) Newman, H. *J. Org. Chem.* **1973**, *38*, 2254. (d) Earl, R. A.; Vollhardt, K. P. C. *J. Org. Chem.* **1984**, *49*, 4786. (e) Reference 3.

(13) The enantioselectivity of the reduction of the π-$Co_2(CO)_6$ complex of 3-nonyn-2-one also increased with the size of the alkyl group on the boron atom: 87% ee, **3b**; 90% ee, B−*i*-Bu catalyst; 95% ee, **3a**. See ref 6.

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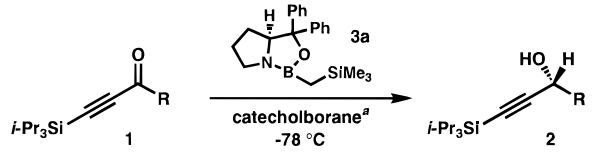
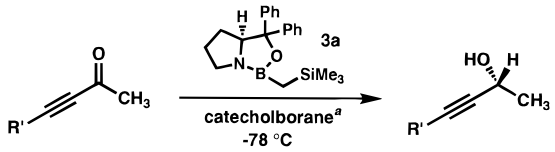
Table 1. Oxazaborolidine-Catalyzed Reduction of Acetylenic Ketones



entry	R	ee (%)	yield (%)
a	$CH_2(CH_2)_3CH_3$	97[b]	98
b	CH_3	95[b]	100
c	$CH_2CH_2CO_2Et$	90[c]	95
d	CH_2Cl	95[d]	97
e	$CH(CH_3)_2$	90[b,e]	91

[a] Reactions were run with 0.05 equiv of **3a** and 1.2 equiv of catecholborane in CH_2Cl_2. Use of higher temperatures resulted in lower enantioselectivity. [b] Percent ee determined by conversion to the p-nitrobenzoate and HPLC analysis (Chiralcel OD). [c] Percent ee determined by conversion to the benzoate and HPLC analysis (Chiralcel OD). [d] Percent ee determined by ^{1}H NMR analysis of the Mosher ester. [e] Catalyst **3b** (B−*n*-Bu) was used.

Table 2. Effect of Alkynyl Terminus on Enantioselectivity



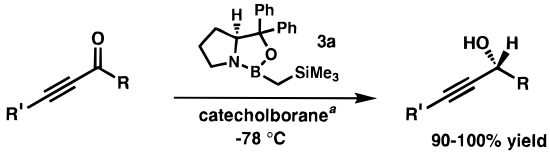
entry	R′	ee (in %) (er)[b]	yield (%)
a	$CH_3(CH_2)_3CH_2$	68[c] (5:1)	93
b	Ph	87[d] (14:1)	100
c	Me_3Si	87[e] (14:1)	92
d	*i*-Pr_3Si	96[f] (49:1)	95

[a] Reactions were run with 0.05 equiv of **3a** and 1.2 equiv of catecholborane in toluene. [b] Enantiomer ratio. [c] Percent ee determined by conversion to the benzoate and HPLC analysis (Chiralcel OD). [d] Percent ee determined by HPLC analysis (Chiralcel OD). [e] Percent ee determined by conversion to the *p*-nitrobenzoate and HPLC analysis (Whelk-O1). [f] Percent ee determined by conversion to the *p*-nitrobenzoate and HPLC analysis (Chiralcel OD).

enantiomer ratio; toluene, 1:3 enantiomer ratio) and catalyst **3b** (CH_2Cl_2, 24:1 enantiomer ratio; toluene, 6:1 enantiomer ratio) but not for catalyst **3a** which gave very high levels of enantioselectivity in both CH_2Cl_2 and toluene.[14] A very important feature of the CH_2SiMe_3 group is that it projects steric bulk far from the Lewis acidic boron atom of the catalyst, thereby providing an additional point of contact with alkynes possessing remote substituents. For these acetylenic ketones, the rigid linear nature of the alkyne positions the triisopropylsilyl group in proximity to the trimethylsilyl group of the catalyst for carbonyl binding *syn* to the acetylenic moiety. To avoid the latter unfavorable interaction, the ketone preferentially binds via the carbonyl lone pair *anti* to the alkyne to produce the (*R*)-propargylic alcohol. The results shown in Tables 2 and 3 are a consequence of such remote steric effects across the triple bond.

(14) In contrast to the other substrates studied, the reduction of ketone **1c** did show a considerable dependence upon the solvent used (product **2c** of 53% ee with catalyst **3a** in toluene). For other examples of significant solvent effects, see ref 6.

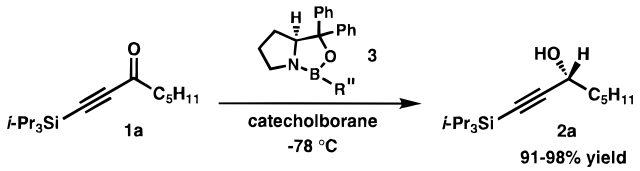
Table 3. Reduction of (Trialkylsilyl)acetylenic Ketones



entry	R	R′ = $SiMe_3$ ee (in %) (er)	R′ = Si(*i*-Pr)$_3$ ee (in %) (er)
a	$CH_2(CH_2)_3CH_3$	92[b] (24:1)	97 (66:1)
b	CH_3	87[b] (14:1)	95 (39:1)
c	$CH_2CH_2CO_2Et$	83[c,d] (11:1)	90 (19:1)

[a] Reactions were run with 0.05 equiv of **3a** and 1.2 equiv of catecholborane in CH_2Cl_2. [b] Percent ee determined by conversion to the *p*-nitrobenzoate and HPLC analysis (Whelk-O1). [c] Percent ee determined by conversion to the benzoate and HPLC analysis (Chiralcel OD). [d] Reduction of this substrate using 1 equiv of B−Me oxazaborolidine **3c** and 2.5 equiv of BH_3−Me_2S in THF at −30 °C provided the enantiomeric alcohol in 60% ee and 40% yield. See ref 10.

Table 4. Effect of Boron Substituent and Solvent on Enantioselectivity



		ee[b] (in %) (er)	
entry	R″[a]	CH_2Cl_2	toluene
a	CH_2SiMe_3	97 (66:1)	95 (39:1)
b	n-Bu	92 (24:1)	72 (6:1)
c	Me	60 (4:1)	46 (1:3)[c]

[a] Entries a and b (CH_2Cl_2) utilized 0.05 equiv of catalyst. Entries b (toluene) and c utilized 0.15 equiv of catalyst. No significant changes in enantiomeric excess were noted with different catalyst loads. [b] Percent ee determined by conversion to the *p*-nitrobenzoate and HPLC analysis (Chiralcel OD). [c] The major product is the (*S*)-enantiomer of **2a**.

In conclusion, the first catalytic enantioselective reduction of α,β-ynones described herein provides useful propargylic alcohols of very high optical purity in excellent yields. High enantioselectivity with catalyst **3a** is due to a novel remote steric effect across the C−C triple bond involving the distal *i*-Pr_3Si substituent[15] of the substrate and the Me_3SiCH_2 group on the boron atom of the catalyst **3a** which strongly disfavors the minor pathway.

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Supporting Information Available: Experimental procedures for the preparation of (triisopropylsilyl)(trimethylsilyl)acetylene, ketones **1a**−**e**, and catalysts **3a**−**c**, as well as complete physical data for the chiral alcohols in Tables 1−3 (8 pages). See any current masthead page for ordering and Internet access instructions.

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(15) (a) Rücker, Ch. *Chem. Rev.* **1995**, *95*, 1009. (b) Corey, E. J.; Rücker, Ch. *Tetrahedron Lett.* **1982**, *23*, 719. (c) Corey, E. J.; Cho, H.; Rücker, Ch.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.