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Catalytic Asymmetric Synthesis of Optically Active Alkynyl Alcohols

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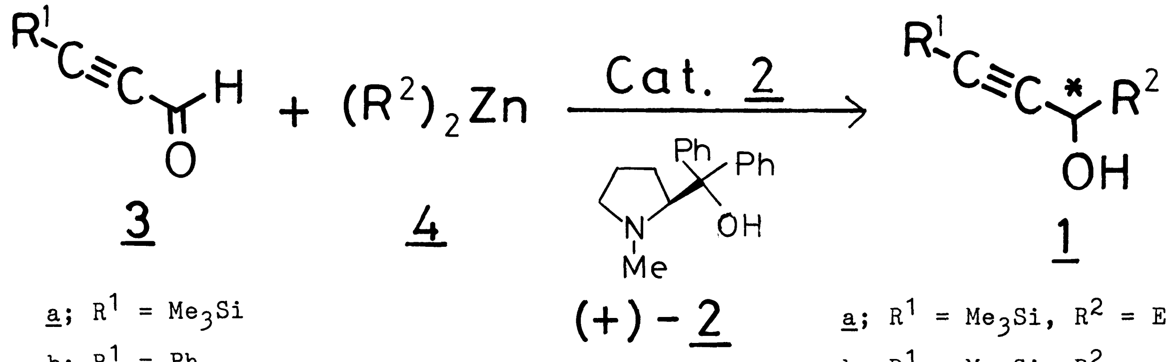
Enantioselective additions of dialkylzinc reagents to alkynyl aldehydes using (*S*)-(+)-diphenyl(1-methylpyrrolidin-2-yl)methanol as a chiral catalyst afford optically active *sec*-alkynyl alcohols in high enantiomeric excess.

Optically active *sec*-alkynyl alcohols (**1**) form an important class of compounds. They serve as intermediates of hydroxy carboxylic acids,$^{1)}$ and versatile natural products such as steroids,$^{2)}$ avenaciolide,$^{3)}$ vitamin E,$^{4)}$ prostaglandins,$^{5)}$ pheromones,$^{6)}$ tetrahydrocerulenin,$^{7)}$ and biologically active prostacyclin minetics.$^{8)}$ Conventional methods of the asymmetric synthesis of **1** require *stoichiometric amounts* of chiral auxiliaries in the reduction of acetylenic ketones,$^{9)}$ the alkynylation of aldehydes,$^{10)}$ and the reductive cleavage of acetylenic acetal.$^{11)}$

On the other hand, increasing interest has been directed to catalytic asymmetric carbon-carbon bond forming reactions.$^{12)}$

Nucleophilic addition of dialkylzincs to aldehydes is usually very sluggish.$^{13)}$ In 1978, Mukaiyama and his co-workers including one of the present authors (K. S.) found$^{14a)}$ that (2*S*,2'*S*)-2-hydroxymethyl-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine (chiral β-aminoalcohol derived from amino acid)$^{15)}$ catalyzes$^{16)}$ the enantioselective addition of diethylzinc to benzaldehyde. During our continuing study on the enantioselective addition of dialkylzincs to aliphatic



3 **4** (+)-**2** **1**

a; R^1 = Me_3Si
b; R^1 = Ph
c; R^1 = *n*-Bu

a; R^1 = Me_3Si, R^2 = Et
b; R^1 = Me_3Si, R^2 = *n*-Bu
c; R^1 = Ph, R^2 = Et
d; R^1 = Ph, R^2 = *n*-Bu
e; R^1 = *n*-Bu, R_2 = Et

Table 1. Catalytic Asymmetric Synthesis of Optically Active Alkynyl Alcohols(1)

	3	4	1				
Entry[a)]	R^1	R^2		$[\alpha]^{25}$ (*c*, solvent)	Yield/%	ee/%	Config.
1	Me_3Si	Et	a	$[\alpha]_{365}$ -5.16° (2.13, $CHCl_3$)	67	78[b)]	
2	Me_3Si	*n*-Bu	b	$[\alpha]_{365}$ -4.71° (2.00, $CHCl_3$)	54	72[b)]	
3	Ph	Et	c	$[\alpha]_D$ -13.7° (2.00, Et_2O)	70	70[c)](73[d)])	*S*
4	Ph	*n*-Bu	d	$[\alpha]_D$ +6.24° (1.33, $CHCl_3$)	61	67[c)]	
5	*n*-Bu	Et	e	$[\alpha]_{365}$ -5.90° (3.05, Et_2O)	71	64[e)]	

a) Reaction conditions; molar ratio of 2 : 3 : 4 = 0.05 : 1.0 : 2.0; 12-14 h at -20 °C. b) Based on HPLC analyses of the corresponding (-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) esters[19)] using chiral column (Daicel chiralcel OD, 250 mm; 254-nm UV detector). Eluent 0.01% 2-propanol in hexane; flow rate 0.5 ml/min; (-)-MTPA ester of 1a, retention time (min), 13.6 for major peak, 17.7 for minor peak. For (-)-MTPA ester of 1b, retention time (min), 12.8 for major peak, 16.0 for minor peak. c) Based on HPLC analyses using chiral column. For 1c, eluent 7% 2-propanol in hexane; flow rate 1.0 ml/min; retention time (min), 7.6 for minor peak, 17.0 for major peak. For 1d, eluent 5% 2-propanol in hexane; flow rate 1.0 ml/min; retention time (min), 9.3 for minor peak, 30.2 for major peak. d) Based on (*S*)-(+)-1-phenylpentan-3-ol which was obtained from 1c by the hydrogenation (10% Pd / C), [$[\alpha]_D^{25}$ +19.6° (*c* 2.43, EtOH), lit. (Ref. 22) value $[\alpha]_D$ +26.8° (*c* 5, EtOH)]. e) NMR (500 MHz) analysis of the MTPA ester.

aldehydes (A), aromatic aldehydes (B), α,β-unsaturated aldehydes (C), and formylesters (D), we have reported highly enantioselective reactions using chiral β-aminoalcohol derivatives as catalysts, i. e., chiral pyrrolidinylmethanols (for A, B, and C),[14b)] *N*,*N*-dibutylnorephedrine (DBNE) (for A, B, and D),[14c)] polymer-bound *N*-alkylnorephedrines (for A and B),[14d)] and an ephedrine derivative (for B).[14e)] We also reported dilithium salt of chiral piperazine as a highly enantioselective catalyst for B.[14f)] Recently Noyori and his co-workers have reported[17)] highly enantioselective addition of dialkylzincs to B and C using a catalytic amount of 3-*exo*-(dimethylamino)isoborneol (β-aminoalcohol).[18)]

We report here the catalytic asymmetric synthesis of alkynyl alcohols (1) using (*S*)-(+)-diphenyl(1-methylpyrrolidin-2-yl)methanol (2)[14b)] as chiral amino-alcohol auxiliary. Optically active secondary alkynyl alcohols were obtained in high enantiomeric excess by enantioselective addition of dialkylzincs to alkynyl aldehydes (3) using (+)-(2) as a chiral catalyst.

When 3-trimethylsilyl-2-propynal (3a) was treated with diethylzinc in toluene using (+)-2 (5 mol%), (-)-1-trimethylsilyl-1-pentyn-3-ol (1a) was obtained in 67% yield with 78% ee (the optical purity was determined on the basis of analysis of the corresponding (-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid ester[19)] using chiral HPLC column). Since various alkynyl aldehydes (3) can be easily prepared from ethyl formate and the corresponding alkynes,20) the present method can apply to the synthesis of various 1. In fact, reactions using 3 with aryl (3b) or aliphatic (3c) substituent afforded 1c-e in 64 - 73% ee (entries 3 - 5). In addition, trimethylsilyl group of 1a can be removed by treatment with methanolic NaOH,3) and further functional modification of acetylenic group is possible. Results of the catalytic asymmetric addition of dialkylzincs (4) to 3 are summarized in Table 1. The reactions using dibutylzinc gave comparable enantioselectivities with diethylzinc (67 - 72% ee, entries 2 and 4). The enantioselectivity changed by the selection of the catalyst. Lithium salt of (+)-2 showed almost the same enantioselectivity. On the other hand, (+)-2 showed higher enantioselectivity (1c, 70-73% ee, entry 3) than (1S,2R)-(-)-DBNE14c,21) (ee of 1c was 21%). The enantioselectivity obtained in hexane or cyclohexane as solvent was comparable with that obtained in toluene.

Typical experimental procedure is as follows. A mixture of 3a (0.126 g, 1.00 mmol) and (+)-2 (0.013 g, 0.05 mmol) in toluene (2 ml) was stirred at room temperature for 30 min, and then cooled to -20 °C. Diethylzinc (2 ml of 1 M solution in toluene; 2.0 mmol) was added during 10 min, and the reaction mixture was stirred at -20 °C for 12 h. The reaction was quenched with 1 M hydrochloric acid (5 ml), the organic layer was separated, and the aqueous layer was extracted with dichloromethane (10 ml x 3). The combined organic layer was dried (Na_2SO_4) and then evaporated under reduced pressure. The residue was purified by preparative TLC over silica gel (developing solvent $CHCl_3$/hexane = 4/1, v/v) to afford 1a (0.104 g, 0.67 mmol, 67%).

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