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Highly Enantioselective Synthesis of β-Hydroxy Nitriles by the Cyanomethylation of Aldehydes using DPMPM as a Chiral Catalyst or Ligand

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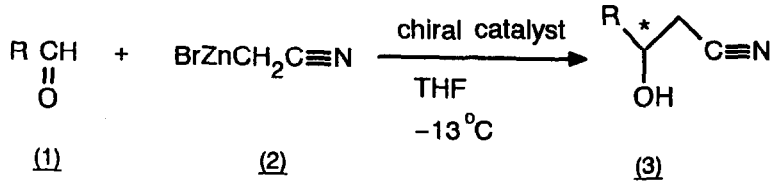
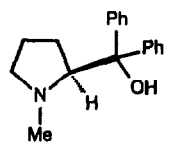
Abstract: Optically active β-hydroxy nitriles in up to 93% e.e. were obtained by the enantioselective addition of cyanomethylzinc bromide to aldehydes using DPMPM as a chiral catalyst or ligand.

Optically active β-hydroxy nitriles (3) are important compounds because cyano group can be converted into amino or carbonyl compounds.[1] However, there have been only a few reports on the preparation of optically active 3 by chemical[2] and biochemical[3] methods. We previously reported the first enantioselective addition of cyanomethyllithium to benzaldehyde using an aminoalcohol as chiral ligand.[2] However, a stoichiometric amount of the chiral ligand was required and the e.e. of the obtained β-hydroxy nitrile was moderate (40% e.e.).

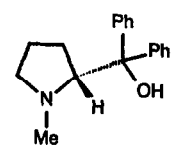


(1) (2) (3)

a; R=Ph
b; R=4-MeO-C_6H_4
c; R=2-Naphthyl
d; R=$PhCH_2CH_2$
e; R=(E)-PhCH=CH



(S)-(+)-DPMPM(4)



(R)-(-)-DPMPM(4)

Although the enantioselective addition of simple dialkylzincs to aldehydes using chiral catalysts are reported,[4] enantioselective addition of organozinc reagents with functional groups other than alkyls is a challenging problem.[5]

We report here a highly enantioselective cyanomethylation of aldehydes (1) with cyanomethylzinc bromide (2)[6] using diphenyl(1-methyl-2-pyrrolidinyl)methanol (DPMPM)(4)[7] as a chiral catalyst or ligand.

When benzaldehyde (1a) was reacted with cyanomethylzinc bromide (2) in the presence of 1 mol equiv. of (S)-(+)-4 in THF at -13 °C, (S)-(-)-3-hydroxy-3-phenylpropiononitrile (3a) with 93% e.e. was obtained in 76% yield (Table, entry 1). E.e. was determined by HPLC analysis using a chiral column. The result shows that the reagent 2 attacked from the Si face of the aldehyde (1). This stereochemical course is the same with that of dialkylzincs.[7] On the other hand, in the presence of (R)-(-)-4, (R)-(-)-3a with 93% e.e. was obtained (entry 2). Other aryl aldehydes (1b and 1c) were also cyanomethylated in 87-88% e.e.'s (entries 5 and 6). The reaction with 3-phenylpropionaldehyde (1d) (phenyl substituted aliphatic aldehyde) afforded (R)-(+)-3d with 74% e.e. (entry 7). The reaction with cinnamaldehyde (1e) (α,β-unsaturated aldehyde) afforded (S)-(-)-(3) (1,2-addition product) with 78% e.e. (entry 8).

Increasing interest has been centered on catalytic asymmetric synthesis.[8] Because cyanomethylzinc bromide adds to aldehydes without catalyst,[6] it was a question whether a catalytic amount of DPMPM (4) affords optically active 3. It was found that even the catalytic amount (0.3 mol equiv.) of (S)-(+)-4 afforded optically active (S)-(-)-3a with 78% e.e. (entry 3). Thus, the role of 4 is not only a chiral ligand but a chiral catalyst.

A typical procedure is as follows: (i) Preparation of cyanomethylzinc bromide (2)[6]: A THF solution (2 ml) of bromoacetonitrile (0.480g, 4 mmol) was added to a Zn-Cu couple (Zn content 91%), and the mixture was stirred for 1 h at room temperature. (ii) Enantioselective cyanomethylation: A THF solution (1 ml) of (S)-(+)-4 was added to 2 and the mixture was stirred for 1 h. The mixture was cooled to -13 °C in ethylene glycol bath and benzaldehyde (1a) (0.106g, 1 mmol) was added. The reaction mixture was stirred at -13 °C for 16 h, and was quenched with 1 M HCl. The mixture was extracted with ethyl acetate, and the extract was dried over anhydrous Na_2SO_4, and the solvent was evaporated under a reduced pressure. The residue was purified by silica gel TLC [developing solvent: hexane-AcOEt 2:1 (v/v) then di-

Table. Enantioselective Synthesis of β-Hydroxy Nitriles (3) by the Cyanomethylation of Aldehydes (1) using DPMPM (4) as a Chiral Catalyst or Ligand.

				3		
Entry[a]	RCHO(1)	(4)(Molar ratio 4/1)	Time (h)	Yield(%)	E.e.(%)[b]	Config.
1	1a	(S)-(+) (1.0)	16	76	93	S
2	1a	(R)-(-) (1.0)	16	77	93	R
3[c]	1a	(S)-(+) (0.3)	17	45	78	S
4[d]	1a	(S)-(+) (0.3)	16	61	75	S
5	1b	(S)-(+) (1.0)	17	70	88	
6	1c	(S)-(+) (1.0)	15	82	87	
7	1d	(S)-(+) (1.0)	16	58	74	R
8	1e	(S)-(+) (1.0)	16	59	78	S

[a] Unless otherwise noted, molar ratio 2/1 = 4.0.

[b] Determined by HPLC analyses using a chiral column (Chiralcel OF).

[c] Molar ratio 2/1 = 2.4.

[d] Molar ratio 2/1 = 3.0.

chloromethane]. (S)-(-)-3a was obtained in 76%.

As described above, highly enantioselective cyanomethylation of aldehydes was achieved using 4 as a chiral catalyst or ligand. Optically active β-hydroxy nitriles (3) are obtained in high e.e.'s. Either enantiomer of 3 of the desired configuration can be synthesized using the appropriate enantiomer of chiral 4.[9]

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9. Compound (4) is commercially available in either enantiomeric form from Tokyo Kasei Inc.