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Catalytic Asymmetric Synthesis of Optically Active Secondary Alcohols Deuterated on the Secondary Carbon by the Enantioselective Alkylation of Aldehydes

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Synopsis. Optically active secondary alcohols deuterated on the secondary carbon were obtained in high enantiomeric excesses from the enantioselective addition of dialkylzincs to aldehyde-*formyl-d*'s using chiral catalysts.

Optically active deuterated alcohols (**3**) have been used for studies concerning the mechanism of chemical reactions and biochemical transformations.[1] However, the methodology for the asymmetric synthesis of (**3**) has been limited to the synthesis of 1-deuterated primary alcohols by enantioselective biological[2] and chemical reductions.[3−6]

Recently the enantioselective addition of dialkylzincs to aldehydes was reported.[7] We have reported the enantioselective addition of organozinc reagents to aldehydes using *N*,*N*-dibutylnorephedrine (DBNE),[8] and (*S*)-(+)-diphenyl(1-methyl-2-pyrrolidinyl)methanol (DPMPM)[9] as chiral catalysts.

We report here on the first highly enantioselective synthesis of optically active deuterated secondary alcohols by the enantioselective addition of dialkylzincs (**2**) to aldehyde-*formyl-d*'s (**1**)[10] using DBNE and DPMPM as chiral catalysts.

When benzaldehyde-*formyl-d* was treated with diethylzinc in hexane at 0 °C in the presence of (1*S*, 2*R*)-(−)-DBNE (6 mol%), optically active (*S*)-(−)-1-phenyl-1-propan-1-*d*-ol was obtained in 92% yield and 94% enantiomeric excess (e.e.) (Table 1, Entry 1). The

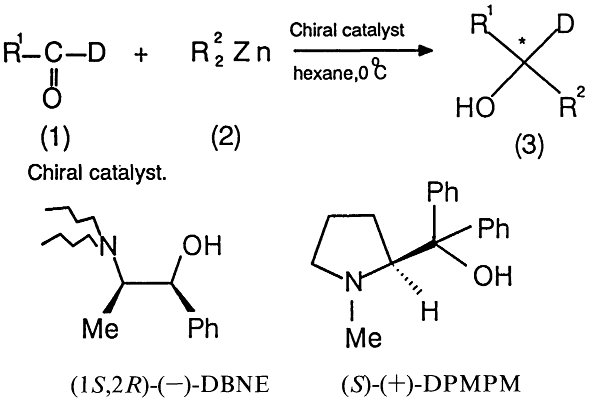

Fig. 1.

Table 1. Asymmetric Synthesis of Optically Active Deuterated Secondary Alcohols

Entry[a]	(1) R^1	(2)[b] R^2	Chiral catalyst	Time / h	Alcohol (3) $[\alpha]_D$/° (*c*, temp, $CHCl_3$)	Yield[c] / %	E.e.[d] / %	Config.[4]
1	C_6H_5-	Et	(−)-DBNE	22	−41.5 (5.0, 25)	92	94	*S*
2	C_6H_5-	Et	(+)-DBNE	22	+47.0 (4.4, 25)	88	95	*R*
3	C_6H_5-	Et	(+)-DPMPM	22	−40.3 (4.7, 25)	86	91	*S*
4	C_6H_5-	Me	(−)-DBNE	144	−37.3 (3.2, 28)	74	80	*S*
5	$CH_3(CH_2)_5$-	Et	(−)-DBNE	15	+8.4 (5.0, 25)	79	84	*S*

a) Solvent was hexane and the reaction temperature was 0 °C. b) Molar ratio, **1**:**2**:catalyst =1:2.2:0.06. c) Isolated yields. d) Determined by HPLC analyses using chiral column. For Entries 1—4, Chiralpak OB was used. For Entry 5, after converting 3-nonan-3-*d*-ol to the corresponding benzoate, Chiralpack OT(+) was used [eluent: MeOH; flow rate: 1.0 ml min^{-1}; temperature: 0 °C; retention time for the major isomer: 5.3 min.; retention time for the minor isomer: 11.1 min]. e) Tentatively assigned based on the sense of the asymmetric induction of the addition of dialkyl-zincs to aldehydes using DBNE[8] and DPMPM.[9] In addition, the ^{19}F NMR spectrum of (*S*)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) ester of (−)-1-phenylethan-1-*d*-ol (80% e.e., Entry 4) showed that the major peak appears at the down field by 0.20 ppm than the minor peak. Based on the empirical rule of the correlation of configuration and ^{19}F NMR chemical shifts of MTPA esters [G. R. Sullivan, J. A. Dale, and H. S. Mosher, *J. Org. Chem.*, **38**, 2143 (1973)], the configuration of the major enantiomer of (−)-1-phenylethan-1-*d*-ol, (Entry 4) was considered to be *S*. In a similar manner, the configuration of (−)-1-phenyl-1-propan-1-*d*-ol (Entry 1) was estimated as *S*. For estimating the configuration of (+)-3-nonan-3-*d*-ol (Entry 5), the benzoate of (*S*)-(+)-3-nonanol (without deuterated hydrogen atom)) with 52% e.e. was analyzed by HPLC under the same conditions as described in footnote d. The retention times of the major and minor isomers were 5.1 and 10.3 min, respectively. This order of the retention times was the same with that of (+)-3-nonan-3-*d*-ol (Entry 5). Thus, the configuration of (+)-3-nonan-3-*d*-ol (Entry 5) was estimated as being *S*.

opposite (*R*)-(+)-enantiomer of the alcohol with 95% e.e. was synthesized using (1*R*, 2*S*)-(+)-DBNE instead of (−)-DBNE. It was also found that (*S*)-(+)-DPMPM was effective to afford (*S*)-(−)-1-phenyl-1-propan-1-*d*-ol in 91% e.e. (Entry 3).

On the other hand, treatment of Me_2Zn with benzaldehyde-*formyl-d* at 0 °C in the presence of 6 mol% of (1*S*, 2*R*)-(−)-DBNE in hexane afforded optically active 1-phenylethan-1-*d*-ol in 80% e.e. (Entry 4).

The method was also applicable to the asymmetric synthesis of optically active *aliphatic* deuterated secondary alcohol. Thus, the enantioselective addition of Et_2Zn to heptanal-1-*d* using 6 mol% of (1*S*, 2*R*)-(−)-DBNE afforded the optically active 3-nonan-3-*d*-ol in 84% e.e. (Entry 5). This type of *aliphatic* deuterated secondary alcohols is not considered to be synthesized in high e.e. by the asymmetric reduction of aliphatic ketones, because the e.e.'s of asymmetric reduction of aliphatic ketones with straight chains are usually low.

As described, optically active deuterated secondary alcohols (**3**) were obtained in high e.e.'s by the enantioselective addition of dialkylzincs (**2**) to aldehyde-*formyl-d*'s (**1**) using DBNE and DPMPM as chiral catalysts.[11]

Experimental

All reactions were carried out under an argon atmosphere. Aldehyde-*formyl-d*'s (**1**) were synthesized from the Grignard reagents and pentacarbonyliron according to methods described in the literature.[10] The hexane solution of diethylzinc was purchased from Kanto Chemical Inc. ^1H NMR spectra and ^{19}F NMR spectra were taken on a Hitachi R-1200 (TMS as the internal reference) and JEOL JNM-EX270L, respectively. The IR spectra were recorded on a Hitachi 260-10 spectrometer. Measurements of mass spectra were carried out on a Hitachi RMU7M spectrometer.

Typical Procedure (Table 1, Entry 1): To a solution of (1*S*, 2*R*)-(−)-DBNE (6 mol%, 0.06 mmol) in hexane (1.0 ml) was added benzaldehyde-*formyl-d* (1.0 mmol in 1.0 ml hexane). The mixture was stirred at room temperature for 20 min; Et_2Zn (2.2 mmol, 2.2 ml of 1 M hexane solution, 1 M=1 mol dm^{-3}) was then added at 0 °C. The reaction mixture was stirred at 0 °C for 22 h, and then quenched with 1 M HCl. The mixture was extracted with dichloromethane; the extract was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel TLC [hexane–AcOEt 4 : 1(v/v) as developing solvents]. Enantiomeric excesses were determine by HPLC analyses using a chiral column (see footnote e in Table 1). (*S*)-1-phenyl-1-propan-1-*d*-ol (configuration tentatively assigned according to footnote e in Table 1) with 94% e.e. was obtained in 92% yield; ^1H NMR ($CDCl_3$) $\delta=0.91$ (t, 3H, $J=7.3$ Hz) , 1.61—1.89 (3H, m), and 7.33 (s, 5H) IR (neat) 3350, 2960, 2925, 1600, and 1445 cm^{-1}; Found: *m/z* 137.0951. Calcd for $C_9H_{11}DO$: M, 137.0951.

(*S*)-1-Phenylethanol-1-*d* (Table 1, Entry 4): Yield 74%; 80% e.e.; ^1H NMR ($CDCl_3$) $\delta=1.41$ (s, 1H), 2.53 (s, 1H) and 7.30 (s, 6H); IR (neat) 3350, 2960, 2925, 1600, and 1445 cm^{-1}; Found: *m/z* 123.0793. Calcd for C_8H_9DO: M, 123.0795.

(*S*)-3-Nonan-3-*d*-ol (Table 1, Entry 5): Yield 79%; 84% e.e.; ^1H NMR ($CDCl_3$) $\delta=0.70$—1.12 (m, 6H) and 1.12—1.83 (m, 13H) IR (neat) 3350, 2970, 2935, and 1465 cm^{-1}; Found: *m/z* 145.1569. Calcd for $C_9H_{19}DO$: M, 145.1578.

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