CATALYTIC ASYMMETRIC SYNTHESIS OF 2- AND 3-FURYLCARBINOLS

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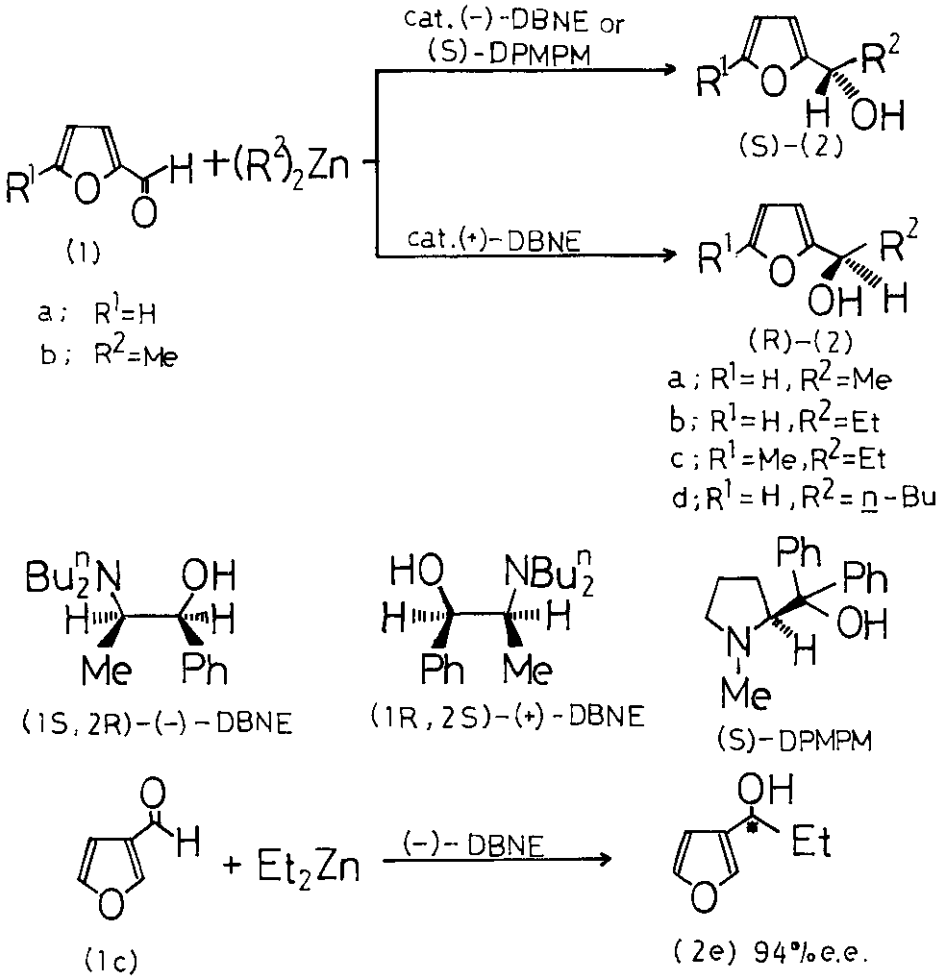
Abstract---Optically active 2- and 3-furylcarbinols were synthesized in high enantiomeric excesses (up to 94% e.e.) by the enantioselective addition of dialkylzinc reagents to 2- or 3-furaldehydes using N,N-dibutylnorephedrine and (S)-diphenyl(1-methylpyrrolidin-2-yl)methanol as chiral catalysts.

Optically active furylcarbinols (**2**) form an important class of compounds, because furyl group is recognized as substrate for the facile introduction of further functionalities.[1,2a,4b] Thus asymmetric synthesis of (**2**) is of current interest. Recently Sammes and Thetford prepared (S)-1-(2-furyl)ethanol (**2a**), a key intermediate of L-daunosamine,[2a] by asymmetric reduction of 2-acetylfuran using chiral reducing reagent [lithium borohydride - (S,S')-N,N'-dibenzoylcystine-tert-butyl alcohol].[3] However, (**2**) which is prepared by either chemical[2] and biochemical[4] asymmetric reduction has only limited structure. On the other hand, kinetic resolutions of racemic furylcarbinols often suffer from the low yields of the product (in principle below 50%) or the destruction of the starting material of undesired configuration.[4, 5]

We report asymmetric synthesis of (**2**) by catalytic asymmetric carbon - carbon bond forming reaction. When 2-furaldehyde (**1a**) was treated with diethylzinc (Et_2Zn) in hexane at 0 °C using 5 mol % of (1S, 2R)-(-)-N,N-dibutylnorephedrine (DBNE),[6] (S)-(-)-1-(2-furyl)propanol (**2b**) was obtained in 83% isolated yield and in 89% enantiomeric excess (e.e.). E.e. was determined with hplc analysis using chiral column. One of the advantages of the present chemical method over biochemical method is the easier access to the opposite enantiomer of (**2**). Thus by using (1R, 2S)-(+)-DBNE instead of (1S, 2R)-(-)-DBNE, (R)-(+)-(**2b**) was obtained in 88% e.e.



It was also found that (S)-diphenyl(1-methylpyrrolidin-2-yl)methanol (DPMPM)[7] and its lithium salt are efficient chiral catalysts in the ethylation of (**1a**) to afford (S)-(**2b**) in 88 - 92% e.e. Butylation of (**1a**) with n-Bu_2Zn occurred in 90% e.e.

On the other hand, reaction of 3-furaldehyde (**1c**) with Et_2Zn using (1S, 2R)-(-)-DBNE (5 mol%) afforded (**2e**) in 94% e.e.

As described, synthetically useful (**2**) of either enantiomers were conveniently prepared in high e.e.'s from (**1**) and $(R^2)_2Zn$ using DBNE or DPMPM as chiral catalysts.

Table 1. Catalytic asymmetric synthesis of furylcarbinols (2).

Entry[a]	(1)	R^2	Catalyst	(2)			
					$[\alpha]_D$(temp /°C, c, $CHCl_3$)	Yield/%	E.e./%[b]	Config.
1	**a**	Me	(S)-DPMPM	**a**	-17.8° (28, 7.1)	53	70	S
2	**a**	Et	(S)-DPMPM	**b**	-15.5° (23, 1.2)	94	88	S[c]
3[d]	**a**	Et	(S)-DPMPM	**b**	-21.5° (27, 1.1)	58	92	S
4	**a**	Et	(S)-DPMPM[e]	**b**	-15.7° (32, 1.2)	67	90	S
5	**a**	Et	(-)-DBNE	**b**	-16.8° (27, 2.0)	83	89	S
6[f]	**a**	Et	(-)-DBNE	**b**	-16.1° (27, 1.1)	64	90	S
7	**a**	Et	(+)-DBNE	**b**	+17.0° (33, 1.1)	74	88	R
8	**b**	Et	(-)-DBNE	**c**	-10.2° (29, 1.3)	79	87	S[c]
9	**a**	n-Bu	(-)-DBNE	**d**	-16.7° (24, 1.2)	58	90[g]	-[h]
10	**c**	Et	(-)-DBNE	**e**	-17.0° (30, 1.1)	52	94	-[h]

[a] Unless otherwise noted, reactions were run in hexane at 0 °C for 15 - 37 h. Molar ratio, (1) : catalyst : $(R^2)_2Zn$ = 1.0 : 0.04 - 0.05 : 2.0. [b] Based on hplc analyses using chiral column (Daicel chiralcel OD, 250 mm; 200-nm UV detector). Eluent 0.25% 2-propanol in hexane. Flow rate (ml / min), retention time (min); for (S)-(**2a**), 0.4, 205.8 (minor isomer), 218.5 (major isomer), for (S)-(**2b**), 0.4, 164.2 (minor isomer), 175.1 (major isomer), for (S)-(**2c**), 0.5, 79.4 (minor isomer), 88.0 (major isomer), for (**2e**), 0.4, 122.8 (minor isomer), 129.1 (major isomer). [c] Absolute configurations were determined by the correlation with the corresponding (S)-(-)-α-acetoxybutanoic acid [F. Bohlmann and G. Grau, Chem. Ber., 1965, **98**, 2608.] prepared by the following sequence: (i) Ac_2O, C_5H_5N; (ii) $NaIO_4$, cat. $RuCl_3$ xH_2O, $CCl_4/MeCN/H_2O$ (2 : 2 : 3) (Ref. 5a and references cited therein). [d] Molar ratio, (**1a**) : cat. : Et_2Zn = 1.0 : 0.05 : 3.0. [e] Lithium salt of DPMPM (prepared *in situ* by the reaction with n-butyllithium) was used. [f] Mixed solvent (toluene / hexane, 1 / 1.5, v/v) was used. [g] Determined by ^1H nmr (100 MHz) analysis of the corresponding acetate using chiral shift reagent [Eu(hfc)$_3$]. [h] Not determined.

EXPERIMENTAL

Typical procedure is exemplified as follows (Table 1, Entry 3). A solution of (**1a**) (121.5 mg, 1.26 mmol) and (S)-DPMPM (15.8 mg, 0.059 mmol) in hexane (2 ml)

was stirred for 8 min at 0 oC, then 2.6 ml of 1.0 M hexane solution of Et_2Zn (2.6 mmol) was added during the period of 3 min. After the mixture was stirred for 26 h at 0 °C, 10 ml of water were added to quench the reaction. The white precipitate was filtered off through a pad of Celite. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (5 x 6 ml). The combined organic layer was washed with saturated aqueous sodium chloride and dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the residue was purified by silica gel tlc (eluent, $CHCl_3$ / AcOEt, 8 / 1, v/v) to afford (S)-(**2b**) (150.2 mg, 1.19 mmol) in 94% yield.

(S)-(-)- and (R)-(+)-1-(2-Furyl)propan-1-ol (2b): Ir (neat) 3350, 2950, 2920, 2860, 1500, 1455, 1140 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.90 (t, J = 7.0 Hz, 3H), 1.50 - 2.16 (m, 2H), 2.50 (s, 1H), 4.53 (t, J = 7.0 Hz, 1H), 6.00 - 6.53 (m, 2H), 7.35 (S, 1H); M^+ calcd for $C_7H_{10}O_2$: 126.0681. Found: 126.0674.

(S)-(-)-1-(5-Methyl-2-furyl)propan-1-ol (2c): Ir (neat) 3350, 2960, 2930, 2870, 1560, 1450, 1220, 1015, 780 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.93 (t, J = 7.0 Hz, 3H), 1.50 - 2.13 (m, 2H), 2.23 (s, 3H), 2.50 (s, 1H), 4.45 (t, J = 6.6 Hz, 1H), 5.85 (br s, 1H), 6.02 (d, J = 3.2 Hz, 1H); M^+ calcd for $C_8H_{12}O_2$: 140.0838. Found: 140.0845.

(-)-1-(2-Furyl)pentan-1-ol (2d): Ir (neat) 3400, 2970, 2950, 2880, 1510, 1470, 1155, 1020, 740 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.65 - 2.16 (m, 9H), 2.83 (s, 1H), 4.60 (t, J = 6.0 Hz, 1H), 6.07 - 6.53 (m, 2H), 7.30 (s, 1H); M^+ calcd for $C_9H_{14}O_2$: 154.0994. Found: 154.0997.

(-)-1-(3-Furyl)propan-1-ol (2e): Ir (neat) 3370, 2960, 2930, 2870, 1500, 1160, 1020, 870, 790 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.90 (t, J = 6.6 Hz, 3H), 1.26 - 2.10 (m, 2H), 3.00 (s, 1H), 4.47 (t, J = 6.0 Hz, 1H), 6.33 (br s, 1H), 7.28 (s, 2H); M^+ calcd for $C_7H_{10}O_2$: 126.0681. Found: 126.0679.

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