

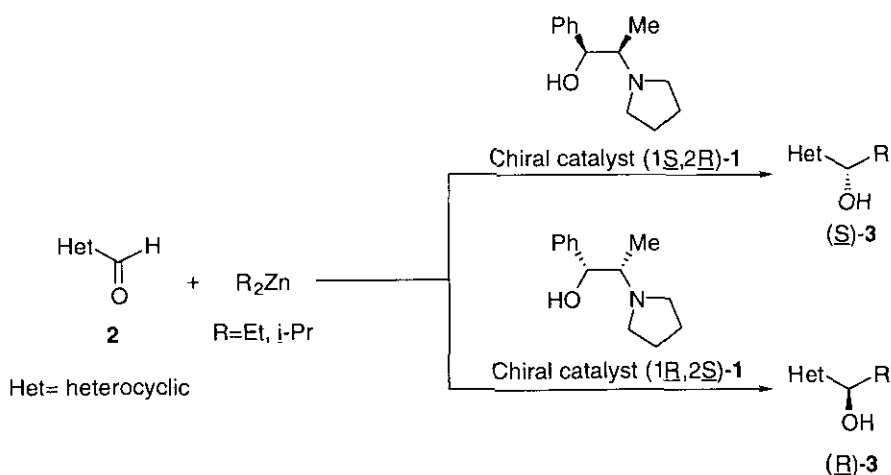
1-PHENYL-2-(1-PYRROLIDINYL)-1-PROPANOL AS A CHIRAL CATALYST FOR THE HIGHLY ENANTIOSELECTIVE ADDITION OF DIALKYLZINCS TO FIVE-MEMBERED HETEROCYCLIC ALDEHYDES

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Abstract - (1*S*,2*R*)- and (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol catalyze the enantioselective addition of dialkylzincs to furfuraldehydes, thiophenecarbaldehydes, and 1-(*p*-tosyl)-2-pyrrolecarbaldehyde to afford the corresponding enantiomerically enriched *sec*-alcohols with up to 87% enantiomeric excess.

Chiral β -amino alcohols have been widely utilized as chiral ligands and chiral catalysts for the enantioselective additions of organometallic reagents to aldehydes and ketones.¹ During our continuing study on the enantioselective addition of dialkylzincs to aldehydes,² we found that 2-pyrrolidinyl-1-phenylpropanol (**1**) is an efficient chiral catalyst for the enantioselective addition of dialkylzincs to aliphatic^{3a} and aromatic^{3b} aldehydes. Recently, (1*R*,2*S*)-**1** was applied as an efficient chiral ligand to the highly enantioselective addition of alkynyllithium to a ketone in asymmetric synthesis of HIV reverse transcriptase inhibitor, Efavirenz.⁴

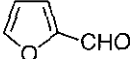
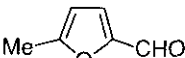
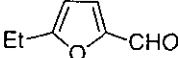
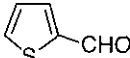
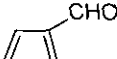
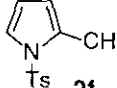


Scheme 1. Catalytic enantioselective addition of dialkylzincs to heterocyclic aldehydes (**2**) using **1**.

On the other hand, chiral furylcarbinols serve as useful synthetic intermediates for the asymmetric synthesis of natural products⁵ such as L-daunosamine^{5c} and γ -lactone^{5b} isolated from *Streptomyces griseus*.

With the interest in the enantioselective alkylation of heterocyclic aldehydes,⁶ we report herein the catalytic enantioselective addition of dialkylzincs to furaldehydes, thiophenecarbaldehydes, and 1-(*p*-tosyl)-2-pyrrolicarbaldehyde using **1** (Scheme 1). The results are shown in Table 1. When 2-furaldehyde (**2a**) was

Table 1. Enantioselective Addition of Dialkylzincs to Heteroaromatic Aldehydes Using **1** as a Chiral Catalyst.

Entry ^a	Aldehydes	R	Config. of 1	Alcohol 3			
				Yield (%)	E.e. (%)	Config.	
1 ^b		Et	(1R,2S)	3a	71	79	R
2	2a	Et	(1S,2R)	3a	66	77	S
3 ^c		Et	(1R,2S)	3a	54	76	R
4		<i>i</i> -Pr	(1R,2S)	3b	76	86	R
5		Et	(1R,2S)	3c	88	70	R
6	2b	<i>i</i> -Pr	(1R,2S)	3d	70	80	ND ^d
7		Et	(1R,2S)	3e	55	74	ND ^d
8	2c	<i>i</i> -Pr	(1R,2S)	3f	78	76	ND ^d
9		Et	(1S,2R)	3g	75	81	S
10 ^b	2d	<i>i</i> -Pr	(1S,2R)	3h	85	80	S
11 ^b		Et	(1S,2R)	3i	55	81	S ^e
12 ^b	2e	<i>i</i> -Pr	(1S,2R)	3j	65	87	S ^e
13 ^b		Et	(1S,2R)	3k	67	86	ND ^d

^a Reaction was performed in toluene at 0 °C in the presence of 10 mol% of **1** using 2.2 molar equiv. of dialkylzinc. ^b 3.3 molar equiv. of dialkylzinc was used. ^c 20 mol% of **1** was used. ^d Not determined.

^e The configuration was determined by modified Mosher method.⁷

treated with Et_2Zn in the presence of ($1\text{R}, 2\text{S}$)-**1** (10 mol%) in toluene at $0\text{ }^\circ\text{C}$ for 20 h, (R)-1-(2-furyl)-1-propanol (**3a**) with 79% e.e. was obtained in 79% yield (Entry 1). The relationship between the configuration of obtained carbinol and the catalyst (**1**) used was matched to those of the aliphatic and aromatic aldehydes.³ Use of 20 mol% of **1** afforded **3a** with 76% e.e. (Entry 3). When $i\text{-Pr}_2\text{Zn}$ was used as alkylating reagent, the corresponding alcohols (**3b**, **3d** and **3f**) were obtained with relatively high e.e.s (Entries 4, 6, and 8). 2-Thiophencarbaldehyde (**2d**) was reacted with Et_2Zn and $i\text{-Pr}_2\text{Zn}$ to give the corresponding 2-thienylcarbinols (**3g**) and (**3h**) in 81 and 80% e.e., respectively (Entries 9, 10). Enantioselective addition of Et_2Zn and $i\text{-Pr}_2\text{Zn}$ to 3-thiophencarbaldehyde (**2e**) gave 3-thienylcarbinols (**3i**) and (**3j**) with 81 and 87% e.e., respectively (Entries 11, 12). Thus, thiophencarbaldehydes were alkylated enantioselectively regardless of the position of aldehydes. 1-(*p*-Tosyl)-2-pyrrolicarbaldehyde (**2f**) afforded the corresponding alcohol with 86% e.e.

In conclusion, ($1\text{S}, 2\text{R}$)- and ($1\text{R}, 2\text{S}$)-1-phenyl-2-(1-pyrrolidiny)-1-propanols (**1**) catalyze the enantioselective addition of dialkylzincs to furaldehydes, thiophencarbaldehydes, and 1-(*p*-tosyl)-2-pyrrolicarbaldehyde to afford enantiomerically enriched *sec*-alcohols with moderate to high e.e.s.

EXPERIMENTAL

General: Optical rotation was measured by Jasco DIP-1000 polarimeter. IR spectra were recorded with Horiba FT210 spectrophotometer. ^1H and ^{13}C NMR spectra were measured with Bruker DPX300 spectrometer using tetramethylsilane as an internal standard and CDCl_3 was used as solvent. High resolution mass spectra (HRMS) were obtained with JEOL JMS-SX102A mass spectrometer. Toluene was distilled from calcium hydride and dried over molecular sieves 4A.

General procedure for the enantioselective alkylation of aldehydes (2) using ($1\text{S}, 2\text{R}$)- or ($1\text{R}, 2\text{S}$)-1-phenyl-2-(1-pyrrolidiny)-1-propanol (1) as a chiral catalyst. To a toluene solution (4 mL) of the chiral catalyst ($1\text{S}, 2\text{R}$)- or ($1\text{R}, 2\text{S}$)-**1** (20.5 mg, 0.1 mmol, 10 mol %) and aldehyde (**2a-f**) (1 mmol) was added dialkylzinc (2.2 mL of a 1 M toluene solution, 2.2 mmol) at $0\text{ }^\circ\text{C}$. The reaction mixture was stirred for 20 h at $0\text{ }^\circ\text{C}$, then it was quenched by the addition of water. The mixture was filtered using Celite and the filtrate was extracted with dichloromethane. The combined extract was dried over MgSO_4 and evaporated to dryness under reduced pressures. Purification of the residue on silica gel chromatography gave alcohols (**3a-k**). (S)-Alcohols (**3**) were obtained by using ($1\text{S}, 2\text{R}$)-**1** and (R)-alcohols (**3**) were obtained by using ($1\text{R}, 2\text{S}$)-**1**.

(R)-1-(2-Furyl)-2-methyl-1-propanol (3b) The e.e. was determined to be 86% e.e. by HPLC analysis using a chiral column (Daicel Chiralcel OB-H: 4 x 250 mm, 220 nm UV detector, room temperature, eluent: 3% 2-propanol in hexane, flow rate: 0.4 mL/min, retention time (min) 36 for the major R isomer, 40 for the minor S isomer). $[\alpha]_{\text{D}}^{18} +18.1^\circ$ (c 1.0, CHCl_3); ^1H NMR and IR spectra were accorded with those in the literature.⁸

(R)-1-[2-(5-Methylfuryl)]-1-propanol (3c) The e.e. was determined to be 70% e.e. by HPLC analysis using a chiral column (Daicel Chiralcel OD-H: 4 x 250 mm, 220 nm UV detector, room temperature, eluent: 0.25% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time (min) 34 for the major R isomer, 40 for the minor S isomer). $[\alpha]_{\text{D}}^{20} +7.6^\circ$ (c 1.0, CHCl_3); ^1H NMR and IR spectra were

accorded with those in the literature.^{6a}

(R)-1-[2-(5-Methylfuryl)]-2-methyl-1-propanol (3d) (1R,2S)-**1** was used as chiral catalyst. The e.e. was determined to be 70% e.e. by HPLC analysis using a chiral column (Daicel Chiralcel AS: 4 x 500 mm, 220 nm UV detector, room temperature, eluent: 0.4% 2-propanol in hexane, flow rate: 0.4 mL/min, retention time (min): 40 for the major R isomer, 44 for the minor S isomer). Colorless oil. $[\alpha]_D^{20} +18.6^\circ$ (c 1.0, CHCl_3); $^1\text{H NMR } \delta$ 0.85 (3H, d, $J=6.8$ Hz), 1.03 (3H, d, $J=6.8$ Hz), 1.81 (1H, d, $J=4.0$ Hz), 2.07 (1H, dq, $J=6.8, 6.8, 6.8$ Hz), 2.27 (3H, s), 4.28 (1H, dd, $J=6.8, 4.0$ Hz), 5.89 (1H, d, $J=3.0$ Hz), 6.09 (1H, d, $J=3.0$ Hz); $^{13}\text{C NMR ppm}$ 13.4, 18.3, 18.8, 33.0, 73.4, 105.8, 107.2, 151.2, 154.2; IR (neat: NaCl) 3363, 2960, 2925, 2873, 1566, 1469 cm^{-1} ; HRMS found m/z 154.0987, calcd for $\text{C}_9\text{H}_{14}\text{O}_2$: 154.0994.

(+)-1-[2-(5-Ethylfuryl)]-1-propanol (3e) (1R,2S)-**1** was used as chiral catalyst. The e.e. was determined to be 74% e.e. by HPLC analysis (chiral column: Daicel Chiralcel OD: 4 x 250 mm, 220 nm UV detector, room temperature, eluent: 1% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time (min) 14 for the major enantiomer and 16 for the minor enantiomer). Colorless oil: $[\alpha]_D^{20} +7.3^\circ$ (c 1.0, CHCl_3); $^1\text{H NMR } \delta$ 0.96 (3H, t, $J=7.4$ Hz), 1.21 (3H, t, $J=7.5$ Hz), 1.84 (2H, d, $J=7.5$ Hz), 1.92 (1H, d, $J=7.5$ Hz), 2.64 (qd, $J=7.5, 0.8$ Hz, 1H), 4.54 (1H, q, $J=7.5$ Hz), 5.91 (1H, dt, $J=7.5, 0.8$ Hz), 6.12 (1H, d, $J=3.0$ Hz); $^{13}\text{C NMR ppm}$ 10.0, 12.0, 21.3, 28.4, 69.1, 104.2, 106.4, 154.7, 157.2; IR (neat: NaCl): 3290, 2970, 2940, 2880, 1560, 1460 cm^{-1} ; HRMS, (M^+): found m/z 154.0997, calcd for $\text{C}_9\text{H}_{14}\text{O}_2$ 154.0994.

(+)-1-[2-(5-Ethylfuryl)]-2-methyl-1-propanol (3f) (1R,2S)-**1** was used as chiral catalyst. The e.e. was determined to be 76% e.e. by HPLC analysis using a chiral column (Daicel Chiralcel AS: 4 x 250 mm, 220 nm UV detector, room temperature, eluent: 0.4% 2-propanol in hexane, flow rate: 0.4 mL/min, retention time (min) 20 for the major isomer, 23 for the minor isomer). Colorless oil. $[\alpha]_D^{20} +19.4^\circ$ (c 1.0, CHCl_3); $^1\text{H NMR } \delta$ 0.86 (3H, d, $J=6.8$ Hz), 1.02 (3H, d, $J=6.7$ Hz), 1.21 (3H, t, $J=7.5$ Hz), 1.80 (1H, d, $J=5.2$ Hz), 2.10 (1H, dq, $J=7.2, 6.8, 6.7$ Hz), 2.62 (2H, qd, $J=7.5, 0.8$ Hz), 4.29 (1H, dd, $J=7.2, 5.2$ Hz), 5.90 (1H, dt, $J=3.0, 0.8$ Hz), 6.10 (1H, d, $J=3.0$ Hz); $^{13}\text{C NMR ppm}$ 12.0, 18.3, 18.8, 21.3, 33.1, 73.5, 104.1, 107.0, 154.1, 157.0; IR (neat: NaCl) 3400, 2970, 2940, 2880, 1560, 1460 cm^{-1} ; HRMS found m/z 168.1155, calcd for $\text{C}_{10}\text{H}_{16}\text{O}_2$: 168.1150; Anal. Calcd for $\text{C}_{10}\text{H}_{16}\text{O}_2$: C, 71.39; H, 9.59. Found C, 71.07; H, 9.70.

(S)-1-(2-Thienyl)-1-propanol (3g) The e.e. was determined to be 81% e.e. by HPLC analysis using a chiral column (Daicel Chiralcel OD: 4 x 250 mm, 254 nm UV detector, room temperature, eluent: 0.25% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time (min) 62 for the minor R isomer, 69 for the major S isomer). $^1\text{H NMR}$ and IR spectra were accorded with those in the literature.⁹

(S)-1-(2-Thienyl)-2-methyl-1-propanol (3h) The e.e. was determined to be 81% e.e. by HPLC analysis using a chiral column (Daicel Chiralcel OD: 4 x 250 mm, 254 nm UV detector, room temperature, eluent: 1.0% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time (min) 22 for the major S isomer, 26 for the minor R isomer). $^1\text{H NMR}$ and IR spectra were accorded with those in the literature.¹⁰

(S)-1-(3-Thienyl)-1-propanol (3i) The e.e. was determined to be 81% e.e. by HPLC analysis using a chiral column (Daicel Chiralcel OJ: 4 x 250 mm, 254 nm UV detector, room temperature, eluent: 1.0% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time (min) 23 for the major S isomer, 27 for the minor R isomer). Colorless oil. $[\alpha]_D^{19} -27.9^\circ$ (c 1.0, CHCl₃); ¹H NMR δ 0.94 (3H, t, J=7.4 Hz), 1.80 (1H, s), 1.83 (2H, qd, J=7.4, 6.5 Hz), 4.71 (1H, t, J=6.5 Hz), 7.08 (1H, dd, J=5.0, 1.2 Hz), 7.19 (1H, dd, J=3.0, 1.2 Hz), 7.31 (1H, dd, J=5.0, 3.0 Hz); ¹³C NMR ppm 10.4, 31.5, 72.2, 121.0, 126.2, 126.2, 146.4; IR (neat: NaCl) 3320, 2964, 2835, 1459, 1417 cm⁻¹; HRMS found m/z 142.0443, calcd for C₇H₁₀OS: 142.0452.

(S)-1-(3-Thienyl)-2-methyl-1-propanol (3j) The e.e. was determined to be 87% e.e. by HPLC analysis using a chiral column (Daicel Chiralcel OD: 4 x 250 mm, 254 nm UV detector, room temperature, eluent: 1.0% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time (min) 17 for the major S isomer, 23 for the minor R isomer). Colorless oil. $[\alpha]_D^{18} -28.5^\circ$ (c 1.0, CHCl₃); ¹H NMR δ 0.84 (3H, d J=6.8 Hz), 0.99 (3H, d, J=6.7 Hz), 1.80 (1H, d, J=3.5 Hz), 1.98 (1H, qqd, J=6.8, 6.7, 6.5 Hz), 4.51 (1H, dd, J=6.5, 3.5 Hz), 7.05 (1H, dd, J=5.0, 1.2 Hz), 7.16 (1H, dd, J=3.0, 1.2 Hz), 7.30 (1H, dd, J=5.0, 3.0 Hz); ¹³C NMR ppm 18.5, 19.2, 35.2, 76.5, 121.5, 126.0, 126.4, 145.5; IR (neat: NaCl) 3388, 2960, 2871, 1467 cm⁻¹; HRMS found m/z 156.0602, calcd for C₈H₁₂OS: 156.0609.

(+)-1-[2-(N-Tosylpyrrolyl)]-1-propanol (3k) (1S,2R)-1 was used as chiral catalyst. The e.e. was determined to be 86% e.e. by HPLC analysis using a chiral column (Daicel Chiralcel OD-H: 4 x 250 mm, 254 nm UV detector, room temperature, eluent: 1.0% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time (min) 28 for the minor isomer, 34 for the major isomer). Colorless oil. $[\alpha]_D^{22} +39.0^\circ$ (c 0.53, CHCl₃); ¹H NMR δ 0.84 (3H, d J=7.4 Hz), 1.77 (2H, qd, J=7.4, 6.4 Hz), 2.34 (3H, s), 2.70 (1H, s), 4.67 (1H, t, J=6.4 Hz), 6.1-6.2 (2H, m), 7.1-7.4 (3H, m), 7.61 (2H, m); IR (neat: NaCl) 3542, 3433, 2968, 2933, 2877, 1597, 1490, 1363 cm⁻¹; HRMS found m/z 279.0922, calcd for C₁₄H₁₇NO₃S: 279.0929.

ACKNOWLEDGMENT

Partial financial support from the Ministry of Education, Science, Sports and Culture is gratefully acknowledged.

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Received, 21st June, 1999