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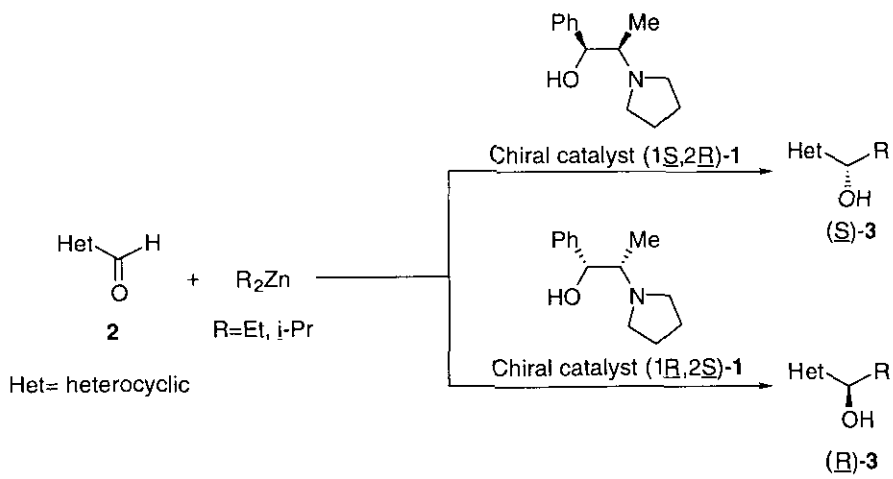
Abstract - (1S,2R)- and (1R,2S)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol catalyze the enantioselective addition of dialkylzincs to furaldehydes, thiophenecarbaldehydes, and 1-(p-tosyl)-2-pyrrolecarbaldehyde to afford the corresponding enantiomerically enriched sec-alcohols with up to 87% enantiomeric excess.

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, (1R,2S)-**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]

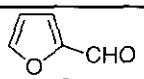
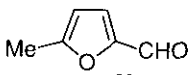
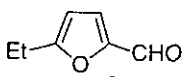
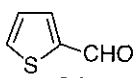
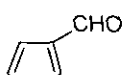
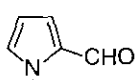


Scheme 1. Catalytic enantioselective addition of dialkylzincs to heterocyclic aldehydes (**2**) using **1**.

On the other hand, chiral furylcarbinols serve as useful synthetic intermediates for the asymmetric synthesis of natural products[5] 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-pyrrolecarbaldehyde 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]	 **2a**	Et	(1R,2S)	**3a**	71	79	R
2		Et	(1S,2R)	**3a**	66	77	S
3[c]		Et	(1R,2S)	**3a**	54	76	R
4		i-Pr	(1R,2S)	**3b**	76	86	R
5	 **2b**	Et	(1R,2S)	**3c**	88	70	R
6		i-Pr	(1R,2S)	**3d**	70	80	ND[d]
7	 **2c**	Et	(1R,2S)	**3e**	55	74	ND[d]
8		i-Pr	(1R,2S)	**3f**	78	76	ND[d]
9	 **2d**	Et	(1S,2R)	**3g**	75	81	S
10[b]		i-Pr	(1S,2R)	**3h**	85	80	S
11[b]	 **2e**	Et	(1S,2R)	**3i**	55	81	S[e]
12[b]		i-Pr	(1S,2R)	**3j**	65	87	S[e]
13[b]	 **2f**	Et	(1S,2R)	**3k**	67	86	ND[d]

[a] Reaction was performed in toluene at 0 ℃ 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 (1R,2S)-**1** (10 mol%) in toluene at 0 ℃ 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-Pr_2Zn 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-Pr_2Zn 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-Pr_2Zn to 3-thiophencarbaldehyde (**2e**) gave 3-thienylcarbinols (**3i**) and (**3j**) with 81 and 87% e.e., respectively (Entries 11, 12). Thus, thiophenecarbaldehydes were alkylated enantioselectively regardless of the position of aldehydes. 1-(p-Tosyl)-2-pyrrolecarbaldehyde (**2f**) afforded the corresponding alcohol with 86% e.e.

In conclusion, (1S,2R)- and (1R,2S)-1-phenyl-2-(1-pyrrolidinyl)-1-propanols (**1**) catalyze the enantioselective addition of dialkylzincs to furaldehydes, thiophenecarbaldehydes, and 1-(p-tosyl)-2-pyrrolecarbaldehyde 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 (1S,2R)- or (1R,2S)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol (1) as a chiral catalyst. To a toluene solution (4 mL) of the chiral catalyst (1S,2R)- or (1R,2S)-**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 ℃. The reaction mixture was stirred for 20 h at 0 ℃, 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 (1S,2R)-**1** and (R)-alcohols (**3**) were obtained by using (1R,2S)-**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). $[\alpha]_D^{18}$ +18.1° (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). $[\alpha]_D^{20}$ +7.6° (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° (c 1.0, $CHCl_3$); ^1H NMR δ 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, dqq, 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}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 $C_9H_{14}O_2$: 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° (c 1.0, $CHCl_3$); ^1H NMR δ 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}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 $C_9H_{14}O_2$ 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° (c 1.0, $CHCl_3$); ^1H NMR δ 0.86 (3H, d, J=6.8 Hz), 1.02 (3H, d, J=6.7Hz), 1.21 (3H, t, J=7.5 Hz), 1.80 (1H, d, J=5.2 Hz), 2.10 (1H, dqq, J=7.2, 6.8, 6.7 Hz), 2.62 (2H, qd, J=7.5, 0.8Hz), 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}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 $C_{10}H_{16}O_2$: 168.1150; Anal. Calcd for $C_{10}H_{16}O_2$: 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). ^1H 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). ^1H 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° (c 1.0, $CHCl_3$); ^{1}H 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); ^{13}C 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 $C_7H_{10}OS$: 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° (c 1.0, $CHCl_3$); ^{1}H 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); ^{13}C 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 $C_8H_{12}OS$: 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° (c 0.53, $CHCl_3$); ^{1}H 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 $C_{14}H_{17}NO_3S$: 279.0929.

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