HIGHLY ENANTIOSELECTIVE ADDITION OF DIALKYLZINCS TO AROMATIC ALDEHYDES USING 1-PHENYL-2-(1-PYRROLIDINYL)-1-PROPANOL AS A CHIRAL CATALYST

Kenso Soai,* Takashi Konishi, and Takanori Shibata

Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo, 162-8601 Japan

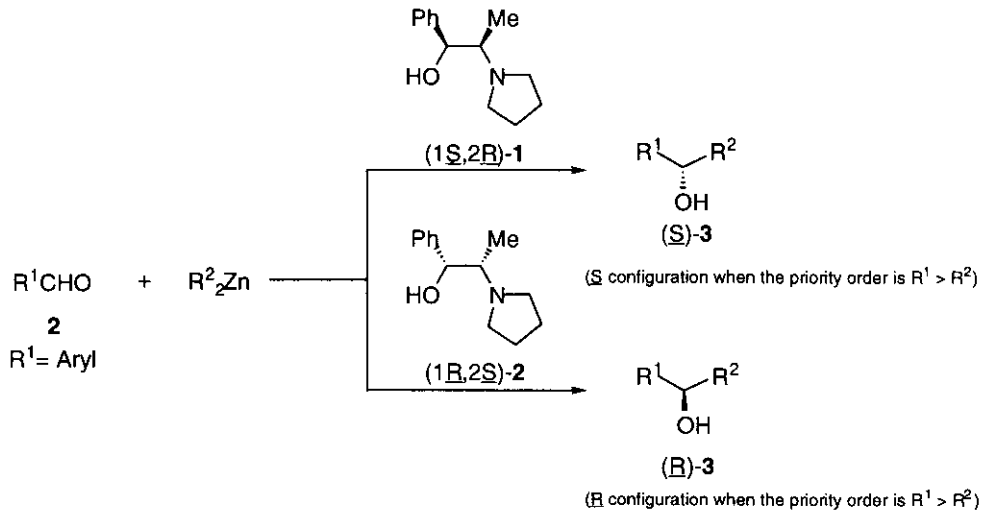
Asbtract - (1S,2R)- and (1R,2S)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol catalyzes the enantioselective addition of dialkylzincs to aromatic aldehydes to afford enantiomerically enriched aromatic sec-alcohols with up to 92% enantiomeric excess.

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] Mukaiyama *et al.* (including K.S.) reported highly enantioselective additions of alkyllithium,[2a] dialkylmagnesium[2b] and alkynyllithium[2c] to aldehydes in the presence of chiral β-amino alcohols possessing two pyrrolidine rings.[2d] Furthermore, the same group also reported the accelerated addition of diethylzinc to benzaldehyde in the presence of an amino alcohol.[2d] Then chiral β-amino alcohols have been used as chial catalysts in the enantioselective addition of dialkylzincs to aldehydes.[3]

During our continuous study on the enantioselective addition of dialkylzincs to aldehydes, we have devised diphenyl(1-methylpyrrolidin-2-yl)methanol (DPMPM),[3c,4] N,N-dialkylnorephedrines,[5] 2,5-diisopropylpiperazine[6] and polymer supported chiral amino alcohols[7] as chiral catalysts. Among chiral N,N-dialkylnorephedrines, 2-pyrrolidinyl-1-phenylpropanol (**1**)[5b] possessing a pyrrolidine ring was found to be an efficient chiral catalyst for the enantioselective addition of diethylzinc to aliphatic aldehydes such as nonanal and 3-methylbutanal.[5b]

As an example of the excellent practical use of chiral amino alcohol (**1**) which was originally synthesized by our group, synthesis of a potent HIV reverse transcriptase inhibitor Efavirentz (DMP-266)[8] can be mentioned. In a key step of asymmetric synthesis of Efavirentz, (1R,2S)-**1** was utilized as a chiral ligand for the highly enantioselective addition of alkynyllithium to trifluoromethyl ketone.

In order to seek another possible use of this chiral amino alcohol (**1**) as a chiral catalyst, we examined an



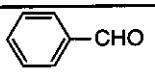
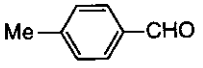
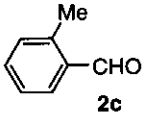
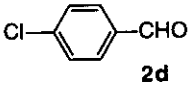
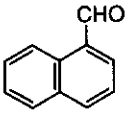
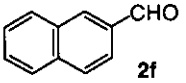
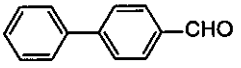
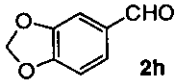
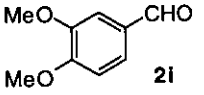
enantioselective addition of dialkylzincs to aromatic aldehydes using **1** as a chiral catalyst. Aromatic aldehydes were reacted with dialkylzincs using **1** as a chiral catalyst to afford enantiomerically enriched alcohols. The results are shown in Table 1. When benzaldehyde was treated with Et_2Zn in the presence of (1S,2R)-**1** (10 mol%) in hexane, (*S*)-1-phenylpropanol (**3a**) with 88% e.e. was obtained in 91% yield (Entry 1). Even 5 mol% of catalyst (**1**) was enough to obtain **3a** (Entry 2). Introduction of a methyl substituent at the 2 or 4 positions of the benzene ring of aldehyde did not change the e.e.s. Thus, enantioselective ethylation of *p*- and *o*-tolualdehydes afforded the corresponding alcohols with almost the same 88-89% e.e.s. (Entries 4 and 9). In a similar manner, aldehydes possessing chloro and phenyl substituents at the 4 position gave alcohols with 87-88% e.e.s (Entries 10 and 15). The enantioselectivity of the asymmetric ethylation to 1-naphthaldehyde (**2e**) was higher (92% e.e.) than to 2-naphthaldehyde (**2f**) (87% e.e.) (Entries 12 and 13). sec-Alcohols possessing methylenedioxy and dimethoxy moieties were also synthesized in high e.e.s (Entries 16 and 17).

Chiral amino alcohol (**1**) is easily prepared in either enantiomeric form. By using the appropriate enantiomer of **1**, chiral alcohol (**3**) possessing the desired configuration can be synthesized; (S)-**3c** with 88% e.e. was obtained in 93% yield using (1S, 2R)-**1** (Entry 4), and (R)-**3c** with the same 88% e.e. was obtained in 93% yield using (1R, 2S)-**1** (Entry 6).

Generality of the structure of dialkylzinc is exemplified by the enantioselective additions of di(n-butyl)zinc and diisopropylzinc to aldehyde (**2b**) affording the corresponding alcohols (**3d**) with 91% e.e. (Entry 7) and **3e** with 92% e.e. (Entry 8), respectively.

As described, (1S,2R)- and (1R,2S)-1-phenyl-2-(1-pyrrolidinyl)-1-propanols (**1**) catalyze the enantioselective addition of dialkylzincs to aromatic aldehydes to afford enantiomerically enriched aromatic sec-alcohols with high e.e.s.

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

Entry[a]	R^1CHO	R^2	Config. of **2**	Alcohol **3**			
				Yield (%)		E.e. (%)	Config.
1	 **2a**	Et	(1S,2R)	**3a**	91	88	S
2		Et	(1S,2R)[b]	**3a**	85	87	S
3[c]		n-Bu	(1S,2R)	**3b**	57	89	S
4	 **2b**	Et	(1S,2R)	**3c**	93	88	S
5		Et	(1S,2R)[b]	**3c**	87	92	S
6		Et	(1R,2S)	**3c**	93	88	R
7[c]		n-Bu[d]	(1S,2R)	**3d**	64	91	S[e]
8[c]		i-Pr	(1S,2R)	**3e**	71	92	S[e]
9	 **2c**	Et	(1S,2R)	**3f**	90	89	S
10	 **2d**	Et	(1S,2R)	**3g**	92	87	S
11[c]		Et	(1S,2R)	**3g**	93	88	S
12	 **2e**	Et	(1S,2R)	**3h**	86	92	S
13	 **2f**	Et	(1S,2R)	**3i**	94	87	S
14		Et	(1R,2S)	**3i**	99	86	R
15	 **2g**	Et	(1S,2R)	**3j**	97	88	S[e]
16	 **2h**	Et	(1S,2R)	**3k**	91	91	S[e]
17	 **2i**	Et	(1S,2R)	**3l**	96	88	S[e]

[a] Reaction was performed in hexane at 0 ℃ in the presence of 10 mol% of **1** using 2.2 Molar equiv. of dialkylzinc. [b] 5 mol% of **1** was used. [c] Toluene was used as a solvent. [d] 4.2 Molar equiv. of dibutylzinc was used. [e] The configuration was temporarily assigned by the configuration of the chiral catalyst used.

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. Hexane was distilled from calcium hydride and dried over molecular sieves 4A (MS 4A).

Experimental procedure for the enantioselective alkylation of aldehyde (2a-g) using amino alcohol (1) as a chiral catalyst (Entries 1-15). To a hexane solution (4 mL) of the chiral catalyst **1** (0.1 mmol, 10 mol %) and aldehyde **2a-g** (1 mmol) was added dialkylzinc (2.2 mL of a 1 M hexane solution, 2.2 mmol) at 0 °C. The reaction mixture was stirred for 20 h at 0 °C, then it was quenched by the addition of 1 M HCl and the mixture 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 thin-layer chromatography (TLC, developing solvent: hexane / EtOAc = 4 / 1) gave alcohol (**3a-g**).

Experimental procedure for the enantioselective alkylation of aldehydes (2h and 2i) using amino alcohol 1 as a chiral catalyst (Entries 16 and 17). To a hexane solution (4 mL) of the chiral catalyst (1S,2R)-**1** (0.1 mmol, 10 mol %) and aldehyde (**2h,i**) (1 mmol) was added dialkylzinc (2.2 mL of a 1 M hexane solution, 2.2 mmol) at 0 °C. The reaction mixture was stirred for 20 h at 0 °C, then it was quenched by the addition of water and the mixture was filtered using celite and the filtrate was extracted with ethyl acetate. The combined extract was dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressures. Purification of the residue using neutral silica gel column (eluent: hexane / EtOAc = 3 / 1) gave alcohol (**3h**) and (**3i**), respectively.

(S)-1-(4-Methylphenyl)-1-pentanol (3d) The enantiomeric excess was determined to be 91% e.e. by HPLC analysis using a chiral column (Daicel Chiralcel OB-H: 4 x 250 mm, 254 nm UV detector, rt, eluent: 3% 2-propanol in hexane, flow rate: 0.5 mL/min, retention time (min): 25 for the major S isomer, 35 for the minor R isomer). Colorless crystal. mp 29.0-30.0 °C; $[\alpha]_D^{24}$ –34.8° (c 2.3, C_6H_6); ^1H NMR δ (ppm) = 0.88 (t, 3H, J=7.0 Hz), 1.16-1.44 (m, 4H), 1.62-1.84 (m, 2H+1H), 2.34 (s, 3H), 4.61 (t, 1H, J=6.7 Hz), 7.15 (d, 2H, J=8.0 Hz), 7.23 (d, 2H, J=8.0 Hz); ^{13}C NMR δ=13.9, 21.0, 22.5, 27.9, 38.6, 74.3, 125.79, 128.9, 136.8, 141.9; IR(KBr disk) 3369 cm^{-1}; HRMS found m/z 178.1352, calcd for $C_{12}H_{18}O$: 178.1358.

2-Methyl-1-(4-methylphenyl)-1-propanol (3e)

The e.e. was determined to be 92% by HPLC analysis (chiral column: Daicel Chiralcel AD: 4 x 250 mm, 254 nm UV detector, rt, eluent: 3% 2-propanol in hexane, flow rate: 0.5 mL/min, retention time (min) 18 for the major R enantiomer and 21 for the S enantiomer). Colorless oil: $[\alpha]_D^{26}$ -30.9° (c 2.0, C_6H_6); ^1H NMR: δ (ppm) = 0.78(d, J=6.8 Hz, 3H), 1.00(d, J=6.8 Hz, 3H), 1.85(br, 1H), 1.94(dqq, $J_d=J_q=J_q=6.8$ Hz, 1H), 2.34(s, 3H), 4.30(d, J=6.8 Hz, 1H), 7.12-7.21(m, 4H), ^{13}C NMR: δ (ppm) = 18.36, 18.91, 21.09,

35.16, 79.91, 126.47, 128.83, 136.99, 140.64, IR (neat: NaCl): 3431 cm^{-1}; HRMS, (M^+): found m/z 164.1200, calcd for $C_{11}H_{16}O$ 164.1202.

(S)-1-(4- Biphenylyl)-1-propanol (3j) The e.e. was determined to be 88% e.e. by HPLC analysis using a chiral column (Daicel Chiralcel AD: 4 x 250 mm, 254 nm UV detector, rt, eluent: 3% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time (min) 15 for the major S isomer, 18 for the minor R isomer). Colorless crystal. mp 63.0-63.5 °C (89% e.e., recrystallized from hexane); $[\alpha]_D^{22}$ –18.6° (c 2.0, C_6H_6) for **3j** with 89% e.e.; ^1H NMR δ (ppm) = 0.93 (t, 3H, J=7.4 Hz), 1.69-1.91 (m, 2H), 2.07 (br, 1H), 4.60 (t, 1H, J=6.6 Hz), 7.03-7.45 (m, 5H), 7.55-7.59 (m, 4H); ^{13}C NMR δ (ppm) = 10.2, 31.8, 75.7, 126.4, 127.0, 127.1, 127.2, 128.7, 140.3, 140.8, 143.8; IR (KBr disk) 3369 cm^{-1}; HRMS found m/z 212.1197, calcd for $C_{15}H_{16}O$: 212.1202.

(S)-1-(3,4-Methylenedioxyphenyl)-1-propanol (3k) The e.e. was determined to be 91% e.e. by HPLC analysis using a chiral column (Daicel Chiralcel OB-H: 4 x 250 mm, 254 nm UV detector, rt, eluent: 20% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time (min) 15 for the major S isomer, 25 for the minor R isomer). Colorless oil. $[\alpha]_D^{24}$ –18.7° (c 2.1, C_6H_6). ^1H NMR and IR spectra were accorded with those in the literature.[9]

(S)-1-(3,4-Dimethoxyphenyl)-1-propanol (3l) The enantiomeric excess was determined to be 88% e.e. by HPLC analysis using a chiral column (Daicel Chiralcel OB-H: 4 x 250 mm, 254 nm UV detector, rt, eluent: 5% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time (min) 26 for the major S isomer, 34 for the minor R isomer). Colorless crystal. mp 42.5-43.5 °C (93% e.e., recrystallized from pentane-Et_2O) ; $[\alpha]_D^{24}$ –29.3° (c 2.0, C_6H_6) for **3l** with 93% e.e. ^1H NMR and IR spectra were accorded with those in the literature.[10]

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