Catalytic Asymmetric Induction. Highly Enantioselective Addition of Dialkylzincs to Aldehydes Using Chiral Pyrrolidinylmethanols and Their Metal Salts

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Abstract: A series of chiral pyrrolidinylmethanols were synthesized from (*S*)-proline. Optically active secondary alcohols (*R* and *S* enantiomers, respectively) in up to 100% enantiomeric excess (ee) were obtained in high yields from the enantioselective addition of dialkylzincs to aldehydes catalyzed by 2–5 mol % of chiral pyrrolidinylmethanols. The sense of the asymmetric induction and the degrees of enantioselectivities were highly dependent on the structure of the catalysts. (+)-DPMPM (**3**, tertiary amino tertiary alcohol) catalyzed the reaction of aryl, α,β-unsaturated, and aliphatic aldehydes to afford (*S*) alcohols in high ee's. When the lithium salt of **3** was employed as catalyst in the reactions of aryl and α,β-unsaturated aldehydes, the ee's of (*S*) alcohols reached 100%. On the other hand, (−)-*erythro*-PNPM (**10**, tertiary amino secondary alcohol) afforded (*R*) alcohols in high ee (100% ee). The steric course of the reaction is discussed.

Enantioselective addition of organometallic reagents to aldehydes using chiral ligands affords optically active secondary alcohols.[1] However, these processes require at least a stoichiometric amount of chiral source. The use of diamino alcohols as ligands in organolithium and dialkylmagnesium additions was pioneered by Professor T. Mukaiyama.[1a]

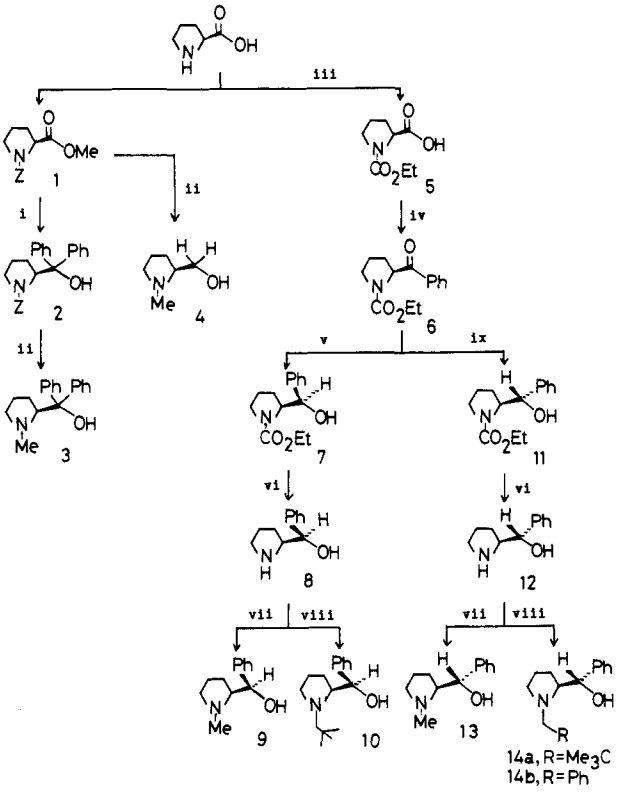
Increasing interest has been centered on the catalytic asymmetric induction in carbon–carbon bond-forming reactions.[2] Recently, a few reports appeared on the enantioselective addition of dialkylzincs to aldehydes using chiral amino alcohols (such as naturally occurring alkaloid) as catalysts.[3] (−)-3-*exo*-(Dimethylamino)isoborneol (alicyclic amino alcohol) was found to be an efficient catalyst for the formation of (*S*) alcohols.[3b] However, the enantioselectivity in the ethylation of aliphatic heptanal is moderate (61% ee).

We report highly enantioselective addition of dialkylzincs to aldehydes using artificial chiral pyrrolidinylmethanols (heterocyclic amino alcohols) as chiral catalysts.

Synthesis of Chiral Catalysts

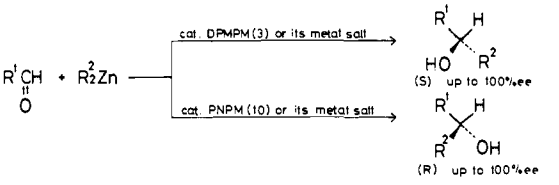
A series of chiral pyrrolidinylmethanols were derived from readily available (*S*)-proline as shown in Scheme I. (*S*)-(+)-Diphenyl(1-methylpyrrolidin-2-yl)methanol (DPMPM, **3**) was obtained in 83% yield from (*S*)-*N*-((benzyloxy)carbonyl)proline methyl ester (**1**) by reaction with phenylmagnesium bromide and subsequent reduction with lithium aluminum hydride. (1*R*,2′*S*)-Phenyl(1-methylpyrrolidin-2-yl)methanol (**9**, *erythro*-PMPM) and (1*S*,2′*S*)-phenyl(1-methylpyrrolidin-2-yl)methanol (**13**, *threo*-PMPM) were prepared by the N-methylation reaction of the corresponding **8** (100% ee, 100% de) and **12** (100% ee, 100% de),[4] respectively; *N*-(Ethoxycarbonyl)proline (**5**) was converted to the corresponding phenyl ketone (**6**), and the subsequent diastereoselective reductions with diisobutylaluminum (DIBAL) hydride and potassium tri(*sec*-butyl)borohydride afforded **7** and **11**, respectively, followed by the removal of the ethoxycarbonyl group. N-Methylation of amino alcohols **8** and **12** afforded respectively **9** (*erythro*-PMPM) and **13** (*threo*-PMPM). (1*R*,2′*S*)-Phenyl(1-neopentylpyrrolidin-2-yl)methanol (**10**, *er-*

Scheme I[a]



[a] (i) PhMgBr; (ii) $LiAlH_4$; (iii) $ClCO_2Et$, NaOH; (iv) (1) $(COCl)_2$, CH_2Cl_2, $HCONMe_2$, (2) $AlCl_3$, benzene, or (1) Ph_2POCl, (2) PhMgBr; (v) $(Me_2CHCH_2)_2AlH$; (vi) KOH, MeOH; (vii) HCHO, HCO_2H; (viii) (1) RCOCl, (2) $LiAlH_4$; (ix) KBH $(s\text{-}C_4H_9)_3$. Z = $PhCH_2OCO$–.

Scheme II



(1) (a) Mukaiyama, T.; Soai, K.; Kobayashi, S. *Chem. Lett.* **1978**, 219. Soai, K.; Mukaiyama, T. *Ibid.* **1978**, 491. Sato, T.; Soai, K.; Suzuki, K.; Mukaiyama, T. *Ibid.* **1978**, 601. Mukaiyama, T.; Soai, K.; Suzuki, K.; Sato, T. *Ibid.* **1979**, 447. Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455. Soai, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3371. (b) Mazaleyrat, J.-P.; Cram, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 4585. (c) Weidman, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 31. (d) Eleveld, M. B.; Hogeveen, H. *Tetrahedron Lett.* **1984**, *25*, 5187. (e) Tomioka, K.; Nakajima, M.; Koga, K. *Chem. Lett.* **1987**, 65.

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(3) (a) Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823. (b) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071. (c) Smaardijk, Ab. A.; Wynberg, H. *J. Org. Chem.* **1987**, *52*, 135.

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Table I. Asymmetric Addition of Dialkylzinc to Aldehydes Using Chiral Pyrrolidinylmethanols as Catalyst[a]

entry	aldehyde	dialkylzinc	catalyst	solvent[b]	yield,[c] %	$[\alpha]_D^{21}$, deg (c, solvent)	ee, %	config
1	benzaldehyde	Et_2Zn	**3**	H	100	−44.2 (5.0, $CHCl_3$)[i]	97[h]	*S*
2[d]	benzaldehyde	Et_2Zn	**3**	H	100	−40.9 (5.0, $CHCl_3$)[i]	90	*S*
3[e]	benzaldehyde	Et_2Zn	**3**	H	100	−35.52 (5.0, $CHCl_3$)[i]	78	*S*
4	benzaldehyde	Et_2Zn	**3**	CH–H	100	−40.4 (5.2, $CHCl_3$)[i]	89	*S*
5[e]	benzaldehyde	Et_2Zn	**3**	CH–H	100	−38.8 (5.0, $CHCl_3$)[i]	85	*S*
6	benzaldehyde	Et_2Zn	**10**	H	100	+47.17 (5.1, $CHCl_3$)[i]	100[h]	*R*
7[f]	benzaldehyde	Et_2Zn	**10**	H	100	+46.14 (5.1, $CHCl_3$)[i]	100[h]	*R*
8	benzaldehyde	Et_2Zn	**9**	H	100	+32.06 (4.6, $CHCl_3$)[i]	72	*R*
9	benzaldehyde	Et_2Zn	**9**	CH–H	100	+33.72 (5.1, $CHCl_3$)[i]	74	*R*
10	*p*-chlorobenzaldehyde	Et_2Zn	**3**	H	100	−23.11 (5.1, C_6H_6)[j]	98[h]	*S*
11	*p*-chlorobenzaldehyde	Et_2Zn	**3**	CH–H	100	−20.57 (5.0, C_6H_6)[j]	86	*S*
12	*p*-chlorobenzaldehyde	Et_2Zn	**10**	H	100	+28.59 (5.1, C_6H_6)[j]	100[h]	*R*
13	*p*-chlorobenzaldehyde	Et_2Zn	**9**	CH–H	100	+19.03 (5.0, C_6H_6)[j]	79	*R*
14	*p*-chlorobenzaldehyde	Et_2Zn	**9**	H	91	+16.83 (5.0, C_6H_6)[j]	70	*R*
15[f]	*p*-chlorobenzaldehyde	Et_2Zn	**9**	H	83	+5.13 (5.1, C_6H_6)[j]	21	*R*
16	*p*-methoxybenzaldehyde	Et_2Zn	**3**	H	100	−27.35 (5.1, C_6H_6)[k]	81	*S*
17	*p*-methoxybenzaldehyde	Et_2Zn	**3**	CH–H	100	−30.25 (5.1, C_6H_6)[k]	89	*S*
18[g]	*p*-methoxybenzaldehyde	Et_2Zn	**3**	CH–H	100	−30.96 (5.0, C_6H_6)[k]	92	*S*
19[e]	*p*-methoxybenzaldehyde	Et_2Zn	**3**	CH–H	100	−32.41 (5.0, C_6H_6)[k]	96[h]	*S*
20	*p*-methoxybenzaldehyde	Et_2Zn	**3**	CP–H	99	−29.07 (5.0, C_6H_6)[k]	86	*S*
21	*p*-methoxybenzaldehyde	Et_2Zn	**3**	Et_2O–H	93	−24.86 (5.0, C_6H_6)[k]	73	*S*
22	*p*-methoxybenzaldehyde	Et_2Zn	**3**	CH_2Cl_2–H	78	−26.46 (5.1, C_6H_6)[k]	78	*S*
23	*p*-methoxybenzaldehyde	Et_2Zn	**10**	H	100	+36.53 (5.1, C_6H_6)[k]	100[h]	*R*
24	*p*-methoxybenzaldehyde	Et_2Zn	**9**	CH–H	100	+25.42 (5.0, C_6H_6)[k]	75	*R*
25	*p*-methoxybenzaldehyde	Et_2Zn	**9**	H	97	+20.8 (5.0, C_6H_6)[k]	62	*R*
26	(*E*)-cinnamaldehyde	Et_2Zn	**3**	CH–H	100	−6.23 (2.6, $CHCl_3$)[l]	100 (71[l])	*S*
27	(*E*)-cinnamaldehyde	Et_2Zn	**3**	H	91	−5.74 (2.6, $CHCl_3$)[l]	97 (65[l])	*S*
28	(*E*)-cinnamaldehyde	Et_2Zn	**10**	H	89	+6.53 (3.2, $CHCl_3$)[l]	100 (89[l])	*R*
29	(*E*)-cinnamaldehyde	Et_2Zn	**9**	CH–H	100	+3.33 (2.9, $CHCl_3$)[l]	56 (38[l])	*R*
30	3-phenylpropanal	Et_2Zn	**3**	CH–H	100	+24.70 (5.0, EtOH)[m]	92	*S*
31	3-phenylpropanal	Et_2Zn	**10**	H	100	−20.23 (5.0, EtOH)[m]	86	*R*
32	3-phenylpropanal	Et_2Zn	**9**	CH–H	100	−15.37 (5.0, EtOH)[m]	57	*R*
33	heptanal	Et_2Zn	**3**	CH–H	96	+8.77 (8.3, $CHCl_3$)[n]	91	*S*
34	heptanal	Et_2Zn	**10**	H	100	−6.42 (8.3, $CHCl_3$)[n]	67	*R*
35	heptanal	Et_2Zn	**9**	CH–H	87	−4.93 (8.3, $CHCl_3$)[n]	57	*R*
36	cyclohexanecarboxaldehyde	Et_2Zn	**3**	CH–H	95	−3.11 (neat)[o]	38	*S*
37	cyclohexanecarboxaldehyde	Et_2Zn	**10**	H	100	+6.99 (neat)[o]	86	*R*
38	cyclohexanecarboxaldehyde	Et_2Zn	**9**	CH–H	91	+6.32 (neat)[o]	78	*R*
39	3-methylbutanal	Et_2Zn	**3**	CH–H	93	+21.23 (neat)[p]	73	*S*
40	3-methylbutanal	Et_2Zn	**9**	CH–H	79	−14.10 (neat)[p]	66	*R*
41	heptanal	Me_2Zn	**3**	CH–H	93	+6.92 (5.1, EtOH)[q]	69	*S*
42	heptanal	Me_2Zn	**9**	CH–H	83	−5.90 (4.8, EtOH)[q]	58	*R*

[a] Unless otherwise noted, aldehyde:dialkylzinc:catalyst molar ratio was 1:2.2:0.02 for the reaction using **3** as catalyst and 1:2.2:0.05 for the reaction using **9** or **10** as catalyst. Procedure was as follows. The mixture containing aldehyde (1 mmol), catalyst (0.02 or 0.05 mmol), and solvent (2.2 mL) was refluxed for 20 min, and then the mixture was cooled to 0 °C and dialkylzinc (2.2 mmol) in hexane (2.2 mL) was added. [b] H = hexane; CH = cyclohexane; CP = cyclopentane. [c] Isolated yield by preparative TLC. $[\alpha]_D$ was measured after the isolated product was further distilled. [d] Without reflux of a mixture of benzaldehyde, **3**, and hexane. [e] A mixture containing **3**, Et_2Zn, and solvent was refluxed for 20 min and then cooled to 0 °C, and aldehyde was added. [f] Aldehyde:Et_2Zn:**3** molar ratio = 1:2.2:0.02. [g] Aldehyde was added to an ice-cooled mixture of **3**, Et_2Zn, and cyclohexane. [h] Determined by HPLC analysis using a Bakerbond DNBPG chiral column. [i] Reported value for (*S*)-1-phenylpropanol is $[\alpha]_D$ −45.45° (*c* 5.15, $CHCl_3$): Pickard, R. H.; Kenyon, J. *J. Chem. Soc.* **1914**, 1115. [j] $[\alpha]_D$ −10.4° (*c* 5, C_6H_6) for (*S*)-1-(4-cyclophenyl)propanol in 43% ee: Capillon, J.; Guette, J. *Tetrahedron* **1979**, *35*, 1817. [k] $[\alpha]_D$ −17.2° (*c* 5, C_6H_6) for (*S*)-1-(4-methoxyphenyl)propanol in 51% ee: see footnote *j*. [l] $[\alpha]_D^{22}$ −5.7° ($CHCl_3$) for (*S*)-1-phenylpent-1-en-3-ol in 96% ee determined by HPLC using a chiral column: see ref 3b. Ee's in parentheses are based on $[\alpha]_D^{23}$ −6.6° (*c* 3.2, $CHCl_3$) in 75% ee: Sato, T.; Gotoh, Y.; Wakabayashi, Y.; Fujisawa, T. *Tetrahedron Lett.* **1983**, *24*, 4123. [m] $[\alpha]_D$ +26.8° (*c* 5.0, EtOH) for (*S*)-1-phenyl-3-pentanol: see ref in footnote *k* (Sato et al.). [n] $[\alpha]_D^{24}$ +9.6° (*c* 8.3, $CHCl_3$) for (*S*)-3-nonanol: Mukaiyama, T.; Hojo, K. *Chem. Lett.* **1976**, 893. [o] $[\alpha]_D^{30}$ −8.1° (neat) for (*S*)-1-cyclohexylpropanol: Levene, P. A.; Marker, R. E. *J. Biol. Chem.* **1932**, *97*, 379, 385. [p] $[\alpha]_D^{25}$ +21.23° (neat) for (*S*)-5-methylhexan-3-ol: Levene, P. A.; Marker, R. E. *J. Biol. Chem.* **1931**, *90*, 672. [q] $[\alpha]_D^{21}$ +10.1° (*c* 5.575, EtOH) for (*S*)-2-octanol: Hill, R. K. *J. Am. Chem. Soc.* **1958**, *80*, 1611.

ythro-PNPM), (1*S*,2′*S*)-*threo*-PNPM (**14a**), and (1*S*,2′*S*)-phenyl(1-benzylpyrrolidin-2-yl)methanol (**14b**) were prepared by the reduction of the corresponding amides.

Results and Discussion

Enantioselective Addition to Aldehydes (Scheme II). In order to examine the effect of the structure of the catalysts, enantioselective additions of diethylzinc to benzaldehyde were conducted at 0 °C in the presence of a catalytic amount (2 mol %) of various pyrrolidinylmethanols.[5] All catalysts except **14a** and **14b** afforded 1-phenylpropanol (**15**) in over 90% synthetic yields. Catalysts were easily removed from the reaction mixture by washing with 1 M hydrochloric acid. The relation between the enantiomeric excesses (ee) of the obtained 1-phenylpropanol (**15**) and the catalysts is shown in Scheme III and Table I. The effect of the structure of the alcohol moiety of pyrrolidinylmethanol was compared by using *N*-methyl derivatives (**3**, **9**, **13**, and **4**). (+)-DPMPM (**3**), possessing a tertiary alcohol, afforded (*S*)-1-phenylpropanol (**15**) in 97% ee (entry 1). On the other hand, *erythro*-PMPM (**9**), possessing a secondary alcohol, afforded (*R*)-**15** in 72% ee (entry 8), and *threo*-PMPM (**13**) afforded (*S*)-**15** in 31% ee. *N*-Methylprolinol (**4**), with a primary alcohol, failed to afford optically active **15**. Thus as the alcohol moiety became more bulky, the degree of asymmetric induction became higher. The sense of the asymmetric induction was reversed between **3** (and **13**) and **9** (and **10**). As to the effect of N substituents, bulky substituents favored *R* selectivity. Thus *erythro*-**10**, with an *N*-neopentyl substituent, afforded (*R*)-**15** in quantitative synthetic yield and in 100% ee (entries 6 and 7). In the threo series, the sense of the asymmetric induction was reversed according to the increase in the bulkiness of the N substituent (however, ee's of **15** were low).

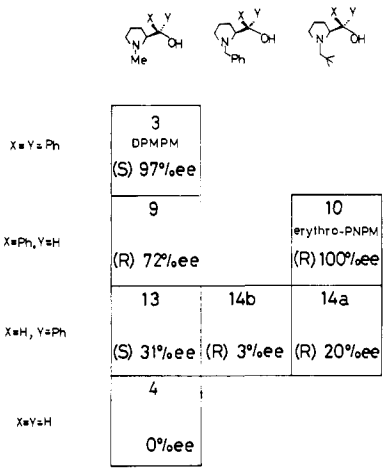
The complementary asymmetric induction between **3** and **9** (and **10**) is general in the enantioselective alkylations of aryl, α,β-un-

Table II. Effect of Metal Alkoxide of Chiral Pyrrolidinylmethanol[a]

entry	aldehyde	dialkylzinc	catalyst	solvent[b]	yield, %	$[\alpha]_D$, deg (*c*, solvent)[i]	ee, %	config
1	benzaldehyde	Et_2Zn	Li-**3**	H	100	−44.95 (5.1, $CHCl_3$)	99.5[c]	*S*
2	benzaldehyde	Et_2Zn	Li-**3**	CH–H	94	−44.16 (5.1, $CHCl_3$)	98[c]	*S*
3[d]	benzaldehyde	Et_2Zn	Li-**3**	H	100	−44.95 (5.1, $CHCl_3$)	99[c]	*S*
4[e,f]	benzaldehyde	Et_2Zn	Li-**3**	H	100	−42.9 (5.0, $CHCl_3$)	94	*S*
5[e]	benzaldehyde	Et_2Zn	Li-**3**	H	77	−40.0 (5.1, $CHCl_3$)	88	*S*
6	*p*-chlorobenzaldehyde	Et_2Zn	Li-**3**	CH–H	91	−24.56 (5.5, C_6H_6)	100[c]	*S*
7	*p*-methoxybenzaldehyde	Et_2Zn	Li-**3**	CH–H	96	−33.73 (5.0, C_6H_6)	100[c]	*S*
8[g]	*p*-methoxybenzaldehyde	Et_2Zn	Li-**3**	CH–H	98	−33.16 (5.0, C_6H_6)	98	*S*
9[h]	*p*-methoxybenzaldehyde	Et_2Zn	Li-**3**	CH–H	93	−31.50 (5.0, C_6H_6)	93	*S*
10	(*E*)-cinnamaldehyde	Et_2Zn	Li-**3**	H	94	−6.45 (3.2, $CHCl_3$)	100 (73)	*S*
11	(*E*)-cinnamaldehyde	Et_2Zn	Li-**3**	CH–H	93	−5.72 (3.2, $CHCl_3$)	96 (65)	*S*
12	benzaldehyde	Me_2Zn	Li-**3**	CH–H	63	−34.69 (7.1, c-C_5H_{10})[j]	80	*S*
13	(*E*)-cinnamaldehyde	Me_2Zn	Li-**3**	CH–H	47	−22.33 (5.2, $CHCl_3$)[k]	89	*S*
14	benzaldehyde	Et_2Zn	Li-**10**	H	100	+47.17 (5.1, $CHCl_3$)	100[c]	*R*
15	benzaldehyde	Et_2Zn	Li-**9**	CH–H	100	+34.75 (5.1, $CHCl_3$)	76	*R*
16	benzaldehyde	Et_2Zn	Li-**9**	T–H	100	+31.56 (5.0, $CHCl_3$)	69	*R*
17	benzaldehyde	Et_2Zn	Li-**9**	H	100	+25.33 (5.1, $CHCl_3$)	56	*R*
18	benzaldehyde	Me_2Zn	Li-**9**	CH–H	100	+24.99 (5.1, c-C_5H_{10})[j]	58	*R*
19	*p*-chlorobenzaldehyde	Et_2Zn	Li-**9**	CH–H	86	+20.17 (5.0, C_6H_6)	83	*R*
20	*p*-methoxybenzaldehyde	Et_2Zn	Li-**9**	CH–H	98	+17.95 (5.0, C_6H_6)	53	*R*
21	(*E*)-cinnamaldehyde	Me_2Zn	Li-**9**	CH–H	84	+16.91 (5.1, $CHCl_3$)[k]	68	*R*

[a] Unless otherwise noted, aldehyde:R_2Zn:catalyst molar ratio = 1:2.2:0.02 for the reaction using Li-**3** as catalyst and 1:2.2:0.05 for the reaction using Li-**9** or Li-**10** as catalyst. Procedure was as follows. *n*-BuLi (0.02 mmol) in hexane was added to a hexane solution of catalyst followed by the addition of aldehyde. Then the mixture was cooled to 0 °C and dialkylzinc was added. [b] See footnote *b* of Table I. T = toluene. [c] Determined by HPLC analysis using a chiral column. [d] *n*-BuLi (0.02 mmol) and Et_2Zn (2.2 mmol) were added to a hexane (2.2 mL) solution of **3** (0.02 mmol) in this order. The mixture was refluxed for 20 min and then cooled to 0 °C, and aldehyde (1 mmol) was added. [e] Aldehyde:Et_2Zn:catalyst molar ratio = 1:2.2:0.05. [f] *n*-BuLi (0.02 mmol) and aldehyde (1 mmol) were added to a hexane solution of **3** (0.05 mmol) in this order. The mixture was refluxed for 20 min and then cooled to 0 °C, and Et_2Zn (2.2 mmol) in hexane was added. [g] Reaction was carried out according to footnote *d* in Table I without reflux of the mixture. [h] Aldehyde:Et_2Zn:catalyst molar ratio = 1:1.2:0.02. [i] For the reported values, unless otherwise noted, see appropriate footnotes *i–l* in Table I. [j] $[\alpha]_D^{20}$ +43.1° (*c* 7.19, c-C_5H_{10}) for (*R*)-1-phenylethanol: Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870. [k] $[\alpha]_D$ +24.7° (*c* 5.0, $CHCl_3$) for (*R*)-4-phenylbut-3-en-2-ol: Kenyon, j.; Partridge, S. M.; Phillips, H. *J. Chem. Soc.* **1936**, 85.

Scheme III. Relation of the Catalyst and ee's of the Obtained 1-Phenylpropanol (**15**) in Enantioselective Addition of Diethylzinc to Benzaldehyde



saturated, and aliphatic aldehydes. Results are shown in Table I. Even aliphatic heptanal was ethylated in 91% ee when **3** was used as catalyst (entry 33). (*R*) alcohols of 100% ee were obtained respectively from *p*-chlorobenzaldehyde and *p*-methoxybenzaldehyde using **10** (entries 12 and 23).

The effect of solvent was examined in the reaction of *p*-methoxybenzaldehyde with Et_2Zn using 2 mol % of **3**. As shown in Table I (entries 16, 17, 20, 21, and 22), hydrocarbons such as hexane, cyclohexane, cyclopentane, or their mixed solvent were more suitable than ether–hexane and dichloromethane–hexane.

Lithium Alkoxide of Chiral Pyrrolidinylmethanol as Catalyst. In the alkylation of aryl and α,β-unsaturated aldehydes, better enantioselectivities were observed when the lithium salt of **3** (*tert*-alkoxide) was employed as catalyst than when **3** itself was employed. Results are summarized in Table II. Thus the reaction of *p*-chlorobenzaldehyde and Et_2Zn in cyclohexane–hexane using 2 mol % of Li salt of **3** afforded (*S*)-1-(4-chlorophenyl)propanol in 100% ee, which was determined by HPLC analysis using a

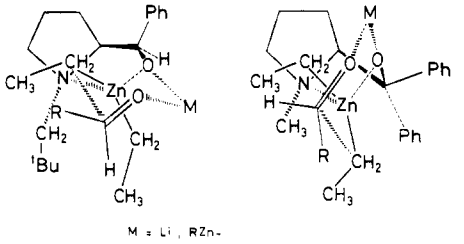


Figure 1.

chiral column (entry 6). Enantiomerically high (*S*) alcohols (99.5 and 100% ee) were also obtained from the reaction with benzaldehyde and *p*-methoxybenzaldehyde (entries 1 and 7).[6]

On the other hand, the lithium salt of **10** (*sec*-alkoxide) was found to complement the lithium salt of **3** and afforded (*R*)-**15** in 100% ee (entry 14). Thus, the enantioselectivities of the lithium salts of *erythro*-pyrrolidinylmethanols **9** and **10** were comparable with those of their parent **9** and **10**.

We postulate the reactive complexes shown in Figure 1. Dialkylzinc may be chelated to form a five-membered ring with nitrogen and oxygen atoms of lithium or the alkylzinc[7] salt of pyrrolidinylmethanols. In the case of **3** [(+)-DPMPM], aldehyde (RCHO) approaches from the direction so that the substituent (R) is far from the dialkylzinc–**3** complex. Thus (*S*) alcohol is formed. A six-center mechanism of the alkylation of aldehyde may be possible. In the case of the lithium salt of **3** (*tert*-alkoxide), lithium *sec*-alkoxide formed from aldehyde and zinc *tert*-alkoxide from **3** may kinetically form in the alkylation. However, these may easily change to the original lithium *tert*-alkoxide of **3** and

(5) Soai, K.; Ookawa, A.; Ogawa, K.; Kaba, T. *J. Chem. Soc., Chem. Commun.* **1987**, 467.

(6) In addition, ethylmagnesium alkoxide derived from **3** and diethylmagnesium catalyzed the addition of diethylzinc to benzaldehyde in toluene–hexane to afford (*S*)-1-phenylpropanol in 97% yield and in 99% ee (observation by S. Niwa in our group).

(7) Diethylzinc is known to react rapidly with primary, secondary, and tertiary alcohols to afford monoalkoxide. Further reaction of monoalkoxide with secondary and tertiary alcohols is slow. See: Ishimori, M.; Tsuruta, T. *Makromol. Chem.* **1963**, *64*, 190.

zinc *sec*-alkoxide formed from the alkylation of aldehyde, because the acidity of the tertiary alcohol of **3** with two electron-withdrawing phenyl groups[8] is stronger than that of the secondary alcohol. Thus the lithium salt of **3** may act as a catalyst.

The higher enantioselectivity of the lithium salt of **3** (*tert*-alkoxide) than **3** (zinc alkoxide) may be attributed to the different character of the metals (lithium and zinc) of the alkoxides. Lithium has a stronger hard acid character than zinc.[9] Thus it may more easily coordinate with the oxygen atom (hard base) of the approaching aldehyde than zinc does.[7] This coordination of the lithium cation may control the steric course of the reaction to afford higher ee's. On the other hand, zinc has borderline acid character;[9] therefore interaction of zinc with the oxygen atoms of the aldehyde may be weaker than that of the lithium cation.

On the other hand, in the case of metal salt of **9** [(−)-*erythro*-PNPM], the lower part of the complex is considered to be less hindered because there is no phenyl group in the lower part. Thus the aldehyde may approach from the lower part to afford (*R*) alcohol. A bulky neopentyl N substituent is considered to block effectively the approach of aldehyde from the rear. In the case of the lithium salt of **9** and **10** (*sec*-alkoxide), both kinetically formed zinc alkoxide of **9** or **10** and lithium alkoxide derived from aldehyde are secondary. Thus the original lithium alkoxide of **9** or **10** may change to zinc alkoxide. This may explain the comparable (but very high in **10**) enantioselectivities of the lithium salts of *erythro*-pyrrolidinylmethanols **9** and **10** with parent **9** and **10**.

Conclusion

In summary, chiral pyrrolidinylmethanols and their metal salts were efficient catalysts in the enantioselective addition of dimethyl- and diethylzincs to aldehydes. Optically active secondary alcohols were obtained in high synthetic yields and in high ee's (up to 100% ee) under mild reaction conditions. The structures of both the N substituent and the alcohol moiety of the catalysts were important factors in controlling the stereochemistry of the reaction. By employing pyrrolidinylmethanols or their metal salts of an appropriate structure derived from (*S*)-proline, both enantiomers of the secondary alcohols desired were obtained. It should be noted that the opposite enantiomers of secondary alcohols in high ee's should be obtained by using chiral pyrrolidinylmethanols derived from commercially available (*R*)-proline.

Experimental Section

Materials. Diethylzinc in hexane was purchased from Kanto Chemical Co.

Synthesis of (*S*)-(+)-Diphenyl(1-methylpyrrolidin-2-yl)methanol (3, DPMPM). PhMgBr (40 mmol) in THF (40 mL, 1 M solution) was added to a THF (20 mL) solution of (*S*)-*N*-((benzxyloxy)carbonyl)proline methyl ester[10] (2.63 g, 10 mmol) at 0 °C, and the mixture was stirred for an additional 4 h. Saturated aqueous ammonium chloride was added to quench the reaction, and the organic layer was separated. The precipitate in the aqueous layer was filtered off, and the filtrate was extracted with chloroform. The combined organic layers were dried and evaporated under reduced pressure. The resulting oil was used without further purification. The oil (3.95 g) was dissolved in THF (30 mL) and was cooled to 0 °C. Lithium aluminum hydride (0.759 g, 20 mmol) was added to the solution in several portions, and the mixture was refluxed for 2 h. After the mixture was cooled to 0 °C, water was added. The mixture was acidified to pH 3 with 1 M HCl, washed with ether, and made alkaline with concentrated aqueous NaOH. The precipitate was filtered off and washed with ethyl acetate. The organic layer was separated, and the filtrate was extracted with dichloromethane. The combined extract was dried and evaporated under reduced pressure. Compound **3** was obtained in 83% yield (2.21 g) and was recrystallized from hexane: mp 68.5–68.9 °C; $[\alpha]^{23}_D$ +57.0° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.4–2.0 (m, 7 H), 2.05–2.65 (m, 1 H), 2.85–3.30 (m, 1 H), 3.4–3.8 (t, 1 H), 3.8–4.7 (b, 1 H), 6.95–7.7 (m, 10 H); IR (KBr) 3300, 2980, 2950, 2820, 2800, 1500, 1455, 1035, 710 cm^{-1}; Anal. ($C_{18}H_{21}NO$) C, H, N.

Synthesis of (1*R*,2′*S*)-(−)-Phenyl(1-methylpyrrolidin-2-yl)methanol (9, *erythro*-PMPM). Formaldehyde (37% aqueous solution, 0.3 mL) was added to a refluxing mixture containing (1*R*,2′*S*)-phenyl(2′-pyrrolidinyl)methanol (**8**, 0.247 g, 1.4 mmol, 100% ee, 100% de, by the recrystallization of the hydrochloride from acetonitrile–diisopropyl ether),[4] 98% formic acid (0.4 mL), and water (0.09 mL) over a period of 5 min and reflux was continued for 4 h. The mixture was cooled and made alkaline to pH 11 with concentrated aqueous NaOH followed by the extraction with dichloromethane. The extract was dried and evaporated in vacuo. Distillation of the resulting oil by the bulb-to-bulb method (140 °C/2 mmHg) afforded **9** (0.254 g) in 95% yield: $[\alpha]^{24}_D$ −59.0° (*c* 0.73, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.97–2.0 (m, 4 H), 2.0–2.7 (m, 5 H), 2.95–3.30 (m, 1 H), 3.55 (s, 1 H), 4.83 (d, 2 H, *J* = 2.8 Hz), 7.23 (5 H); IR (neat) 3430, 2986, 2780, 1455, 710 cm^{-1}; M^+ calcd for $C_{12}H_{16}NO$: 190.1233. Found: 190.1246.

Synthesis of (1*S*,2′*S*)-(−)-Phenyl(1-methylpyrrolidin-2-yl)methanol (13, *threo*-PMPM). The title compound was prepared from (1*S*,2′*S*)-phenyl(2′-pyrrolidinyl)methanol (**12**, 100% ee, 100% de, by the recrystallization of its hydrochloride from acetonitrile–diisopropyl ether)[4] by the same procedure described for **9**. **13**: yield 97%; $[\alpha]^{25}_D$ +13.6° (*c* 0.95, MeOH), $[\alpha]^{25}_{365}$ +53.6° (*c* 0.95, MeOH); ^1H NMR ($CDCl_3$) δ 1.5–2.0 (4 H, m), 2.2 (3 H, s), 2.3–3.3 (3 H, m), 4.15 (1 H, b), 4.34 (1 H, d, *J* = 4.8 Hz), 7.27 (5 H, s); IR (neat) 2950, 2780, 1455, 1040, 760, 700 cm^{-1}; M^+ calcd for $C_{12}H_{16}NO$: 190.1233. Found: 190.1241.

(1*S*,2′*S*)-Phenyl(1-neopentylpyrrolidin-2-yl)methanol (14a, *threo*-PNPM). To the hydrochloride of **12** (3.0 mmol) in 1 M aqueous NaOH (10 mL) and ether (5 mL) was added pivaloyl chloride (4.5 mmol), and the mixture was stirred for 3.5 h at room temperature. 3-(Dimethylamino)propylamine (2.5 mmol) was added, and the mixture was stirred for 20 min. Ethyl acetate was added, and the organic layer was separated, washed successively with saturated aqueous sodium hydrogen carbonate, water, 1 M HCl, and saturated aqueous NaCl, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was reduced with lithium aluminum hydride (2 mol equiv) in tetrahydrofuran (10 mL) at reflux temperature for 5 h. After cooling of the mixture, 1 M hydrochloric acid was added. The mixture was adjusted to pH 10 by adding concentrated aqueous NaOH, and the precipitate was filtered off. The filtrate was extracted with ether, and the extract was dried over Na_2SO_4 and evaporated. The residue was purified by bulb-to-bulb distillation (170 °C/3 mmHg, bath temperature) to afford **14a** in 69% yield: $[\alpha]^{20}_D$ +37.50° (*c* 1.01, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.95 (s, 9 H), 1.40–2.00 (m, 4 H), 2.23 (s, 2 H), 2.30–3.35 (m, 3 H), 3.95–4.3 (m, *J* = 7 Hz, 2 H), 7.35 (m, 5 H); IR (neat) 3400, 2960, 2880, 1455, 1370, 705 cm^{-1}; M^+ calcd for $C_{16}H_{24}NO$: 246.1859. Found: 246.1863.

(1*S*,2′*S*)-Phenyl(1-benzylpyrrolidin-2-yl)methanol (14b) and (1*R*,2′*S*)-Phenyl(1-neopentylpyrrolidin-2-yl)methanol (10, *erythro*-PNPM). These were prepared in a manner similar to that described above.

Yield of **14b** was 92%: $[\alpha]^{20}_D$ +98.02° (*c* 1.03, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.45–2.0 (m, 4 H), 2.0–2.60 (m, 1 H), 2.60–3.15 (m, 2 H), 3.43 (q, *J* = 12 Hz, 2 H), 3.85 (broad, 1 H), 4.30 (d, *J* = 5.8 Hz, 2 H), 7.15 (s, 10 H); IR (KBr) 3150, 1440, 1060, 725, 690 cm^{-1}. Anal. ($C_{18}H_{21}NO$) C, H, N.

Yield of **10** was 87%: $[\alpha]^{20}_D$ −75.48° (*c* 1.03, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.00 (s, 9 H), 1.20–2.0 (m, 4 H), 2.05–3.0 (m, 4 H), 3.0–3.8 (m, 2 H), 4.7 (d, *J* = 3.0 Hz, 1 H), 7.2 (s, 5 H); IR (neat) 3450, 2950, 1300, 700 cm^{-1}. Anal. ($C_{16}H_{25}NO$) C, H, N.

General Procedure for the Enantioselective Alkylation of Aldehydes Using Pyrrolidinylmethanol as Catalyst. The mixture containing chiral pyrrolidinylmethanol (0.02 mmol, 2 mol %), aldehyde (1.0 mmol), and a solvent such as cyclohexane (2.5 mL) was refluxed for 20 min and was cooled to 0 °C. Dialkylzinc in hexane (1 M solution, 2.2 mL) was added to the ice-cooled mixture over a period of 5 min, and the mixture was stirred for an additional 4–24 h. HCl (1 M) was added to quench the reaction. The mixture was extracted with dichloromethane, and the extract was dried and evaporated under reduced (or atmospheric in the cases of low-boiling-point product) pressure. The residue was purified by silica gel TLC ($CHCl_3$ as developing solvent). The yield was calculated at this stage. Optical rotation was measured after the isolated product was further purified by bulb-to-bulb distillation. The product was identified by NMR, IR, and HPLC analyses, comparing with those of authentic samples. Ee's were determined by HPLC analyses using a chiral column and optical rotation. Conditions of HPLC analyses: chiral column, Bakerbond DNBPG covalent, 4.6 × 250 mm; detection, 254-nm UV light. For 1-phenylpropanol: eluent, 0.25% 2-propanol in hexane; flow rate, 0.6 mL/min; retention time (min), *S* isomer 45.2, *R* isomer 47.4. For 1-(*p*-chlorophenyl)propanol: 0.2% 2-propanol in hexane; flow

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rate, 0.8 mL/min; *S* isomer 37.8, *R* isomer, 39.9. For 1-(*p*-methoxyphenyl)propanol: 0.2% 2-propanol in hexane; flow rate 0.9 mL/min; *S* isomer 67.0, *R* isomer 70.3.

General Procedure for the Enantioselective Alkylation of Aldehydes Using the Lithium Salt of Pyrrolidinylmethanol as Catalyst. To a chiral pyrrolidinylmethanol (0.05 mmol, 2 mol %) in a suitable solvent such as cyclohexane (6.3 mL) was added 0.035 mL of *n*-butyllithium (0.05 mmol, 1.51 M hexane solution). After the mixture was stirred for 15 min, an aldehyde (2.5 mmol) in cyclohexane was added, and stirring was continued for an additional 20 min. Then the mixture was cooled to 0 °C, and 5.6 mL of dialkylzinc (5.6 mmol, 1 M hexane solution) was added. The mixture was stirred for 4–24 h, 1 M HCl (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (4 × 20 mL). The extract was dried over Na_2SO_4 and was evaporated. Purification, identification, and the determination of ee of the products were performed as described above.

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Registry No. 1 (Z = $PhCH_2OC(O)$), 5211-23-4; **3**, 110529-22-1; **8**, 74936-95-1; **9**, 110529-23-2; **10**, 110529-24-3; **12**, 74936-96-2; **12**·HCl, 110529-25-4; **13**, 74936-98-4; **14a**, 110529-26-5; **14b**, 110529-27-6; (*S*)-$PhCH(OH)CH_2CH_3$, 613-87-6; (*R*)-$PhCH(OH)CH_2CH_3$, 1565-74-8; (*S*)-*p*-$ClC_6H_4CH(OH)CH_2CH_3$, 73890-73-0; (*R*)-*p*-$ClC_6H_4CH(OH)CH_2CH_3$, 110611-21-7; (*S*)-*p*-$MeOC_6H_4CH(OH)CH_2CH_3$, 73854-04-3; (*R*)-*p*-$MeOC_6H_4CH(OH)CH_2CH_3$, 105836-14-4; (*S*)-(*E*)-$PhCH{=}CHCH(OH)CH_2CH_3$, 103729-97-1; (*R*)-(*E*)-$PhCH{=}CHCH(OH)CH_2CH_3$, 110611-22-8; (*S*)-$Ph(CH_2)_2CH(OH)CH_2CH_3$, 71747-37-0; (*R*)-$Ph(CH_2)_2CH(OH)CH_2CH_3$, 105836-17-7; (*S*)-$CH_3(CH_2)_5CH(OH)CH_2CH_3$, 61925-49-3; (*R*)-$CH_3(CH_2)_5CH(OH)CH_2CH_3$, 61925-50-6; (*S*)-$CH_3(CH_2)_5CH(OH)CH_3$, 6169-06-8; (*R*)-$CH_3(CH_2)_5CH(OH)CH_3$, 5978-70-1; (*S*)-c-$C_6H_{11}CH(OH)CH_2CH_3$, 110529-28-7; (*R*)-c-$C_6H_{11}CH(OH)CH_2CH_3$, 38636-38-3; (*S*)-$(CH_3)_2CHCH_2CH(OH)CH_2CH_3$, 93031-24-4; (*R*)-$(CH_3)_2CHCH_2CH(OH)CH_2CH_3$, 39003-07-1; (*S*)-$PhCH(OH)CH_3$, 1445-91-6; (*R*)-$PhCH(OH)CH_3$, 1517-69-7; (*S*)-(*E*)-$PhCH{=}CHCH(OH)CH_3$, 81176-43-4; (*R*)-(*E*)-$PhCH{=}CHCH(OH)CH_3$, 62413-47-2; benzaldehyde, 100-52-7; *p*-chlorobenzaldehyde, 104-88-1; *p*-methoxybenzaldehyde, 123-11-5; (*E*)-cinnamaldehyde, 14371-10-9; 3-phenylpropanal, 104-53-0; heptanal, 111-71-7; cyclohexanecarboxaldehyde, 2043-61-0; 3-methylbutanal, 590-86-3.

Ionization of 9-Cyano- and 9-(Carbomethoxy)fluorene in Dimethyl Sulfoxide–Water Mixtures. How Important Is Solvent Reorganization?[1]

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Abstract: Rate constants (k_1^B, k_{-1}^{BH}) for the reversible deprotonation of 9-cyanofluorene (Fl-CN) and 9-(carbomethoxy)fluorene (Fl-COOMe) by primary aliphatic amines and by piperidine and morpholine have been measured in 10%, 50%, and 90% aqueous Me_2SO at 20 °C. Intrinsic rate constants, defined as $k_0 = k_1^B/q = k_{-1}^{BH}/p$ at $\Delta pK + \log(p/q) = 0$, were calculated by suitable interpolation of Brønsted plots. Increased Me_2SO content of the solvent has virtually no effect on k_0 for Fl-CN and increases k_0 of Fl-COOMe by a very small amount. This contrasts with the large increase in k_0 reported by Ritchie for the ionization of Fl-COOMe by oxyanions when the reaction was conducted in Me_2SO instead of methanol. It also contrasts with the large increases in k_0 for similar solvent changes in the ionization of acetylacetone, 1,3-indandione, nitromethane, and phenylnitromethane by amines. A formalism which breaks down the solvent effect on k_0 into contributions from late solvation of the developing carbanion and late solvation of the developing ammonium ion (amine reaction) or early desolvation of the oxyanion (oxyanion reactions) accounts for these various observations quite well in a qualitative way. A more quantitative analysis indicates that an additional factor contributes significantly to the solvent effect, though. It is suggested that this factor represents solvent reorganization in the sense of a dynamic solvent effect. Rate constants for the reaction of Fl-CN with the anion of Fl-COOMe were also measured in 90% Me_2SO. The intrinsic rate constant for carbon to carbon proton transfer estimated from the results appears to be substantially higher than expected on the basis of the Marcus relation.

It is well-known that proton transfers to and from carbon are usually much slower than proton transfers to and from oxygen, nitrogen, and sulfur.[3] This is particularly true for systems in which the carbanion benefits extensively from resonance stabilization. Three main factors have variously been invoked as contributing to this behavior. (1) The poor hydrogen bonding capability of carbon acids and of the carbanionic carbon.[3a,d,4] (2) The need for structural reorganization which accompanies the delocalization of the negative charge.[3,4b,5] (3) The need for solvent reorganization.[4b,6-8]

The meaning of the term "solvent reorganization" or "solvent reorientation" has evolved over time and different authors use the term to describe different phenomena. One of the most influential early studies which led to the suggestion that solvent reorganization plays an important role in proton transfers was Ritchie's[7] investigation of the solvent effect on the ionization of aromatic hydrocarbons. Defining k at $\Delta pK = 0$ as the *intrinsic* rate constant, k_0, he found, for example, that k_0 for the deprotonation of 9-(carbomethoxy)fluorene by a series of benzoate ions in Me_2SO was approximately 100-fold higher than k_0 for the ionization of the same carbon acid by methoxide ion in methanol.

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