Enantioface-Differentiating (Asymmetric) Addition of Alkyllithium and Dialkylmagnesium to Aldehydes by Using (2*S*,2′*S*)-2-Hydroxymethyl-1-[(1-alkylpyrrolidin-2-yl)-methyl]pyrrolidines as Chiral Ligands

Teruaki Mukaiyama,* Kenso Soai, Toshio Sato, Hisashi Shimizu, and Keisuke Suzuki

Contribution from the Department of Chemistry, Faculty of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan. *Received July 28, 1978*

Abstract: Asymmetric addition of alkyllithium and dialkylmagnesium to aldehydes was investigated by using the chiral amino alcohols **2**, derived easily from (*S*)-proline, as ligands. High optical yields (45–95%) of secondary alcohols were achieved by the reaction of alkyllithium (alkyl = ethyl, *n*-propyl, and *n*-butyl) and aldehydes in a 1:1 mixture of dimethoxymethane and dimethyl ether at −123 °C. In the reaction of methyllithium and benzaldehyde, bulkiness of the substituents, R^1 and R^2, in the ligand **2** remarkably affected the optical purity, and 1-phenylethanol was obtained in 86% optical yield by employing **2d** (R^1 = H; R^2 = *n*-Pr) as a chiral ligand. Similarly, (*R*)-alcohols were obtained in 22–92% optical yields by the reaction of dialkylmagnesium and aldehydes in toluene at −110 °C.

Introduction

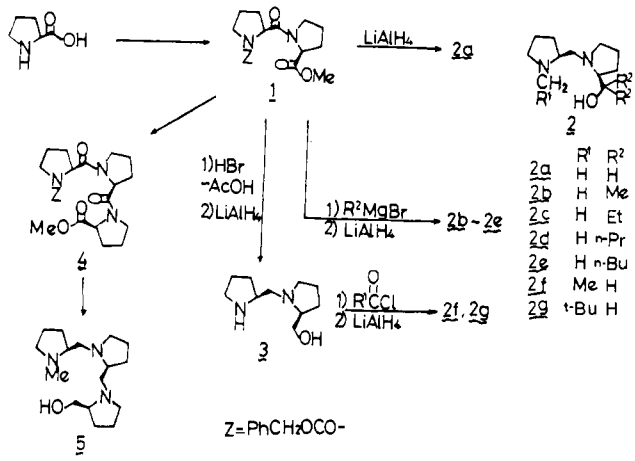
Over the years there have been a number of studies on the synthesis of optically active secondary alcohols from achiral carbonyl compounds via asymmetric induction.[1] Asymmetric reduction of ketones has been most widely investigated and relatively high optically pure alcohols have been obtained by the following methods: (a) the reduction of ketones with chiral aluminum alkoxides, magnesium alkoxides,[1] or Grignard reagent;[1] (b) the reduction of ketones with chiral metal hydride reagents;[2] (c) the hydrogenation[3] or the hydrosilylation[4] of ketones by using a chiral rhodium(I) complex as a catalyst. On the other hand, the optical yields of secondary alcohols derived from aldehydes by the asymmetric addition of organometallic reagents[5–9] in a chiral solvent, or by using a chiral ligand such as (−)-spartein,[5b,c,7] (−)-*N*-methylephedrine,[7,9] D-glucofuranose,[6c,7] tartaric acid derivative,[5d,e,8] or oxazoline derivative,[6d] are generally low (~40%).

Recently, we reported that (*S*)-2-(anilinomethyl)pyrrolidine is a very efficient ligand for the asymmetric reduction of various aryl ketones with $LiAlH_4$.[2b] This prompted us to study the exploration of a new and useful ligand for the asymmetric addition of organometallic reagents to aldehydes. It was found that (2*S*,2′*S*)-2-hydroxymethyl-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine (**2a**) is a quite efficient ligand for the asymmetric addition of *n*-butyllithium to benzaldehyde, and (*S*)-1-phenyl-1-pentanol with 95% optical purity was obtained as briefly reported in the previous communication.[10b] We now wish to describe the scope and limitations of this method.

Chiral Ligands

All of the chiral ligands employed in the present study were derived from a readily available chiral amino acid, (*S*)-proline; that is, (2*S*,2′*S*)-2-hydroxymethyl-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine (**2a**) was obtained in 81% yield by the reduction of *N*-[(*N*-benzyloxycarbonyl)prolyl]proline methyl ester (**1**), prepared in 92% yield from (*S*)-proline methyl ester and (*S*)-*N*-benzyloxycarbonylproline. (2*S*,2′*S*)-2-(1,1-Dialkyl-1-hydroxymethyl)-1-[(1-methylpyrrolidin-2-yl)methyl]-pyrrolidines (**2b–e**) were prepared by successive treatment of **1** with Grignard reagents and $LiAlH_4$. The dipeptide **1** was treated with HBr–AcOH, followed by reduction with $LiAlH_4$ to afford the amino alcohol (**3**). (2*S*,2′*S*)-2-Hydroxymethyl-1-[(1-alkylpyrrolidin-2-yl)methyl]pyrrolidines (**2f,g**) were provided by the reduction of the corresponding amide of **3** with $LiAlH_4$. (2*S*,2′*S*,2″*S*)-2-Hydroxymethyl-1-{[1-(1-methylpyrrolidin-2-yl)methyl]pyrrolidin-2-yl}methylpyrrolidine (**5**) was prepared by the reduction of the tripeptide (**4**) with $LiAlH_4$.

Scheme I



These ligands could be easily separated from the product by washing the reaction mixture with aqueous hydrochloric acid and recovered in over 80% yield without any loss of optical purity.

Results and Discussion

In the first place, we examined the detailed reaction conditions such as molar ratio of reactants, temperature, and solvent in the asymmetric addition of *n*-butyllithium to benzaldehyde using **2a** as a chiral ligand (see Table I). The molar ratio of the aldehyde:*n*-butyllithium:**2a** was found to be optimum at 1.0:6.7:4.0, respectively. The effect of solvents was remarkable, and after screening various solvents at a temperature of −78 °C, the best result was obtained when the addition reaction was carried out in dimethoxymethane (entry 11). It is apparent that lowering the temperature increased the degree of asymmetric induction (entries 2, 3, 11, and 12). In order to carry out the reaction at −123 °C, a mixed solvent of dimethoxymethane with a solvent of low melting point (methyl ether or pentane, entries 13 and 14) was employed, and (*S*)-1-phenyl-1-pentanol was obtained in 95% optical yield by using a 1:1 mixture of dimethoxymethane and methyl ether as the solvent.

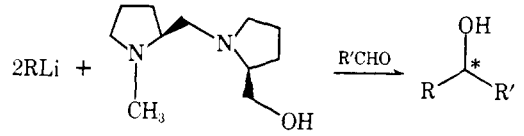
Further, the asymmetric addition of various alkyllithiums to benzaldehyde and an aliphatic aldehyde was carried out in

0002-7863/79/1501-1455$01.00/0 © 1979 American Chemical Society

Table I. Asymmetric Addition of *n*-Butyllithium to Benzaldehyde Using the Ligand **2a**[a]

entry	solvent	temp, °C	1-phenyl-1-pentanol yield,[b] %	1-phenyl-1-pentanol opt purity,[c] %
1	hexane	−78	49	20
2	Me_2O	−78	80	53
3	Me_2O	−123	80	82
4	Et_2O	−78	76	44[d]
5	Et_2O	−78	60	49[e]
6	Et_2O	−78	57	55
7	Et_2O	−123	60	72
8	*n*-Pr_2O	−78	83	31
9	THF	−78	80	48
10	DME[f]	−78	94	53
11	DMM[g]	−78	67	72
12	DMM	−100	77	87
13	DMM–pentane (1:1)	−123	57	77
14	DMM–Me_2O (1:1)	−123	77	95

[a] **2a** was treated with *n*-butyllithium at 0 °C for 30 min and cooled to the indicated temperature. Benzaldehyde was added and the reaction mixture was stirred for 1 h. The molar ratio of benzaldehyde: *n*-butyllithium:**2a** was 1.0:6.7:4.0, unless otherwise noted. [b] Isolated yields. [c] Optical purity was calculated from optical rotation based upon the highest value available, $[\alpha]_D$ +31.3° (*c* 3, benzene). See ref 5. All of the alcohols had the *S* configuration. [d] The molar ratio of benzaldehyde:*n*-butyllithium:**2a** was 1.0:7.2:3.6. [e] The molar ratio of benzaldehyde:*n*-butyllithium:**2a** was 1.0:6.3:3.6. [f] 1,2-Dimethoxyethane. [g] Dimethoxymethane.



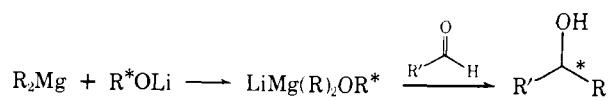
2a

the presence of **2a** as a chiral ligand, and the results are summarized in Table II. The chiral ligand **2a** was very effective, and much higher optical yields were achieved in comparison with the previous methods, and even in the case of the reaction of an aliphatic aldehyde, the corresponding alcohol was obtained in high optical yield (entry 8). It should be noted that the configuration of the alcohol obtained in the addition of ethyllithium to benzaldehyde depended on the solvent employed (entries 3 and 4).

Besides alkyllithium, there are various organometallic reagents, such as Grignard reagents, dialkylmagnesium, alkylcopper, dialkylzinc, or trialkylaluminum, which may be applicable to the synthesis of optically active alcohols by the asymmetric addition to aldehydes because of their strong affinities to the heteroatoms of the present chiral ligands to form the key complexes.

Various organometallic compounds were screened by employing the lithium salt of **2a** as a chiral ligand in the reaction with benzaldehyde, and it was found that dialkylmagnesium was much more effective than Grignard reagents, dialkylzinc, alkylcopper, or trialkylaluminum, as shown in Table III.

Further, the effects of both solvent and temperature were studied in the reaction of dibutylmagnesium with benzaldehyde in the presence of the lithium salt of **2a.** Greater optical purity was exhibited at lower temperature (entries 5, 6, 11, and 12 in Table III) and toluene was found to be better than ether type solvents in contrast with the solvent effect observed in the reaction by using alkyllithium (see Table I).



R*OH:**2a**

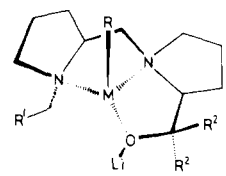
Various dialkylmagnesiums were employed for the reaction with benzaldehyde, and the results are listed in Table IV. All of the alcohols thus obtained possessed the *R* configuration, whereas the alcohols, obtained in the similar reaction of alkyllithiums, possessed the *S* or *R* configuration, depending upon the size of alkyllithiums.

As shown in Tables II and IV, 1-phenyl-1-propanol, 1-phenyl-1-butanol, and 1-phenyl-1-pentanol were obtained in high optical yields by the reaction of the corresponding alkyllithiums or dialkylmagnesiums with benzaldehyde, but the optical purity of 1-phenylethanol was lower than that of the other secondary alcohols. Then, in order to increase the optical purity of 1-phenylethanol, we attempted to modify the chiral ligand **2a** either by replacing the hydroxymethyl group with disubstituted hydroxymethyl groups (**2b–e**) or by changing the *N*-methyl group to more bulky alkyl groups (**2f,g**).

The lithium salts of ligands **2e,f** were employed for the reaction of either methyllithium or dimethylmagnesium with benzaldehyde, and it was found that 86% optical yield was attained by using **2d** (R^1 = H; R^2 = *n*-Pr) as a chiral ligand in the reaction of methyllithium (entry 4 in Table V).

The ligands **2b–f** were also employed for the reaction of *n*-butyllithium and benzaldehyde, and it was observed that the formation of the alcohol possessing the *R* configuration was preferred by employing the ligands with larger substituents, R^1 and R^2 (see Table V). In addition, it should be noted that (*R*)-1-phenyl-1-pentanol was obtained in 68% optical yield by using **5** as a chiral ligand which has three pyrrolidine moieties (entry 15).

As reported previously,[10a] when 2-hydroxymethyl-1-methylpyrrolidine or (2*S*,2′*S*)-2-methoxymethyl-**1**-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine was employed for the reaction of *n*-butyllithium with benzaldehyde, the optical yield of the (*S*)-alcohol was only 14% in both cases (see the Experimental Section). These results indicate that two pyrrolidine moieties[11] and the lithiated hydroxymethyl group[12] are essential for the asymmetric induction. A rigid complex **7** might be formed by virtue of the coordination of oxygen and



7 RM = Alkyllithium or Dialkylmagnesium

two nitrogen atoms to alkylmetal providing an effective chiral environment for asymmetric induction.

As shown in Table I, with respect to solvent effects in the reaction using *n*-butyllithium, dimethoxymethane was the superior medium, while the use of *n*-propyl ether and hexane gave poor optical purity of alcohols. On the contrary, the use of toluene in the reaction using dialkylmagnesium gave higher optical yield than that of ether-type solvents.

Another important fact is that the use of methyllithium, prepared from methyl bromide and lithium metal, in the reaction with benzaldehyde gave only 6% optical purity of the (*R*)-alcohol, while the use of methyllithium prepared from methyl iodide and lithium metal gave 86% optical purity of the (*R*)-alcohol (entry 4 in Table V). These results indicate that the interaction of iodide ion[13] with metallic species in the complex formed between methyllithium and the ligand **2d** may contribute to the effective asymmetric induction.

Moreover, the size of alkylmetal and the bulkiness of the

Table II. Asymmetric Addition of Alkyllithium to Aldehydes Using **2a**:[a] $R^1Li + R^2CHO \xrightarrow{\mathbf{2a}} R^1R^2\overset{*}{C}HOH$

entry	R^1	R^2	solvent	temp, °C	alcohol yield,[b] %	alcohol [α]D (c, solvent)	alcohol opt purity,[c] %	alcohol config.[d]
1	Me	Ph	Et_2O	0[e]	82	$[\alpha]^{26}_D$ +9.2° (6.00, cyclopentane)	21[f]	*R*
2	Me	Ph	DMM[g]	0[e]	81	$[\alpha]^{24}_D$ +16.7° (6.11, cyclopentane)	40	*R*
3	Et	Ph	Et_2O	−123	32	$[\alpha]^{27}_D$ +17.5° (0.86, $CHCl_3$)	39[h]	*R*
4	Et	Ph	DMM	−100	59	$[\alpha]^{23}_D$ −24.7° (5.15, $CHCl_3$)	54	*S*
5	Et	Ph	DMM-Me_2O (1:1)	−123	70	$[\alpha]^{21}_D$ −20.6° (5.15, $CHCl_3$)	45	*S*
6	*n*-Pr	Ph	DMM-Me_2O (1:1)	−123	64	$[\alpha]^{18}_D$ −27.7° (5.93, benzene)	60[i]	*S*
7	*n*-Bu	Ph	DMM-Me_2O (1:1)	−123	77	$[\alpha]^{22}_D$ −29.8° (3.02, benzene)	95	*S*
8	*n*-Bu	*i*-Pr	DMM-Me_2O (1:1)	−123	57	$[\alpha]^{25}_D$ −22.1° (9.27, EtOH)	80[j]	*S*

[a] The molar ratio of aldehyde:alkyllithium:**2a** is 1.0:6.7:4.0. [b] Isolated yields. [c] Optical purity was calculated from optical rotation based upon the highest value available. [d] Absolute configurations are based on the literature. [e] When the reaction was carried out at lower temperature, the optical purity decreased. [f] Based on $[\alpha]^{21}_D$ 43.1° (*c* 7.19, cyclopentane). See ref 14. [g] Dimethoxymethane. [h] Based on $[\alpha]_D$ +45.45° (*c* 5.15, $CHCl_3$). See ref 15. [i] Based on $[\alpha]_D$ +45.9° (*c* 6, benzene). See ref 16. [j] Based upon $[\alpha]_D$ +27.67° (*c* 10, EtOH). See ref 17.

Table III. Addition of Alkylmetals to Benzaldehyde Using the Lithium Salt of **2a**[a]

entry	alkylmetal	solvent	temp, °C (time, h)	alcohol yield, %[b]	alcohol opt purity,[c] %
1	*n*-BuCu	Et_2O	−78 (1)	22	0
2	Et_2Zn	Et_2O	−78 → 0 (3)	76	0
3	Et_3Al	Et_2O	r.t. (6)	*d*	
4	*n*-BuMgBr	Et_2O	−78 (1)	90	47
5	*n*-Bu_2Mg	Et_2O	−78 (1)	93	68
6	*n*-Bu_2Mg	Et_2O	−123 (1)	89	73
7	*n*-Bu_2Mg	Me_2O	−123 (1)	84	43
8	*n*-Bu_2Mg	THF	−110 (1)	91	59
9	*n*-Bu_2Mg	DMM[e]	−78 (1)	87	51
10	*n*-Bu_2Mg	DME[f]	−78 (1)	96	28
11	*n*-Bu_2Mg	toluene	−78 (1)	93	60
12	*n*-Bu_2Mg	toluene	−110 (1)	94	88

[a] The molar ratio of benzaldehyde:alkylmetal:the lithium salt of **2a** was 1:4:4, and this ratio was optimum. [b] Isolated yields. [c] Optical purity was calculated from optical rotation. 1-Phenyl-1-pentanol obtained had the *R* configuration. [d] Benzyl alcohol was obtained in 28% yield. [e] Dimethoxymethane. [f] Dimethoxyethane.

Table IV. Asymmetric Addition of Dialkylmagnesium to Aldehydes Using the Lithium Salt of **2a**[a]

$$R^1{}_2Mg + R^2CHO \rightarrow R^1R^2\overset{*}{C}HOH\ (R)\text{-}(+)$$

entry	R^1	R^2	yield, %[b]	alcohols [α]D (c, solvent)	alcohols opt purity,[c] %
1	Me	Ph	56	$[\alpha]^{25}_D$ +14.7° (4.21, cyclopentane)	34
2	Et	Ph	74	$[\alpha]^{26}_D$ +41.8° (5.19, chloroform)	92
3	*n*-Pr	Ph	90	$[\alpha]^{24}_D$ +32.3° (6.03, benzene)	70
4	*i*-Pr	Ph	59	$[\alpha]^{26}_D$ +19.2° (4.78, ether)	40[d]
5	*n*-Bu	Ph	94	$[\alpha]^{22}_D$ +27.5° (2.98, benzene)	88
6	*i*-Bu	Ph	81	$[\alpha]^{25}_D$ +13.6° (15.2, heptane)	42[e]
7	*n*-Bu	*i*-Pr	70	$[\alpha]^{22}_D$ +6.0° (10.0, ethanol)	22

[a] The reaction was carried out in toluene at −110 °C for 1 h. The molar ratio of aldehyde:dialkylmagnesium:the lithium sals of **2a** was 1:4:4. All alcohols possesses the *R* configuration. [b] Isolated yields. [c] Optical purity was calculated by optical rotation. See footnotes in Table II. [d] Based upon $[\alpha]^{20}_D$ +47.7° (*c* 7, Et_2O). See ref 18. [e] Based upon $[\alpha]^{26}_D$ +32.3° (*c* 16.6, heptane) see ref 14.

substituents, R^1 and R^2, of the ligands seem to play an important role for the asymmetric induction. In the reaction of alkyllithiums and benzaldehyde in ether, the formation of the (*S*)-alcohols was preferred by employing *n*-butyl- or *n*-propyllithium, while the (*R*)-alcohols were formed by employing ethyl- or methyllithium (Table II). The optical purity of the (*R*)-alcohol, derived from the reaction of *n*-butyllithium and benzaldehyde, was increased by using the ligands with larger substituents, R^1 and R^2 (Table V).

In conclusion, it is noted that the ligand **2**, easily prepared from (*S*)-proline, is very efficient for the asymmetric addition of alkyllithium and dialkylmagnesium to aldehydes, and higher optical yields of either (*S*)- or (*R*)-alcohols were achieved in comparison with the previous methods.

Experimental Section

General. Melting points and boiling points are uncorrected. NMR spectra were taken on a Hitachi R-24 spectrometer. Infrared spectra were taken on a Hitachi EPI-G2 spectrometer. Optical rotation was taken on a Jasco DIP-SL automatic polarimeter. THF, dimethoxy-

Table V. Effect of the Substituents, R^1 and R^2, in **2**:[a] $PhCHO \rightarrow PhR\overset{*}{C}HOH$

entry	ligand	alkylmetal	alcohol yield,[b] %	alcohol opt purity,[c] %	alcohol config[d]
1	**2b** (R^1 = H; R^2 = Me)	MeLi	62	5	*R*
2	**2b**	Me_2Mg	82	43	*R*
3	**2c** (R^1 = H; R^2 = Et)	MeLi	79	77	*R*
4	**2d** (R^1 = H; R^2 = *n*-Pr)	MeLi	82	86	*R*
5	**2d**	Me_2Mg	77	21	*R*
6	**2e** (R^1 = H; R^2 = *n*-Bu)	MeLi	69	70	*R*
7	**2f** (R^1 = Me; R^2 = H)	MeLi	61	17	*R*
8	**2g** (R^1 = *t*-Bu; R^2 = H)	MeLi	79	20	*R*
9	**2a** (R^1 = H; R^2 = H)	BuLi	60	72	*S*
10	**2b**	BuLi	77	0	
11	**2c**	BuLi	80	11	*R*
12	**2e**	BuLi	85	23	*R*
13	**2f**	BuLi	78	5	*S*
14	**2g**	BuLi	85	54	*R*
15	**5**	BuLi	80	68	*R*

[a] In the case of the reaction using alkyllithium, the molar ratio of benzaldehyde:alkyllithium:**2** was 1.0:6.7:4.0, and the reaction was carried out in Et_2O at −123 °C for 1 h. In the case of the reaction using dimethylmagnesium, the molar ratio of benzaldehyde:dimethylmagnesium:the lithium salt of **2** was 1:4:4, and the reaction was carried out in toluene at −110 °C for 1h. [b] Isolated yields. [c] Optical purity was calculated by optical rotation. [d] Absolute configurations are based on the literature values.

ethane, dimethoxymethane, ethyl ether, and *n*-propyl ether were distilled from $LiAlH_4$ prior to use. Methyl ether was dried by passing the gas through a tube packed with calcium chloride. Pentane and hexane were dried over molecular sieves 4A. Toluene was dried over sodium wire. Reactions involving air-sensitive compounds were carried out under an atmosphere of argon. For evaporative bulb-to-bulb distillation, a Büchi Kugelrohrofen was used.

Materials. Methyllithium was prepared from methyl iodide and lithium metal in ether according to the general procedure.[19] Ethyl- and *n*-propyllithium were prepared from the corresponding alkyl bromide and lithium metal in pentane.[20] A hexane solution of *n*-butyllithium and a hexane solution of triethylaluminum were supplied from Tokyo Kasei Co. Ltd. Diethylzinc was prepared from zinc and ethyl iodide.[21] *n*-Butylcopper was prepared in situ from butyllithium and cuprous iodide in ether at −20 °C. Ethereal dialkylmagnesium solution was prepared by treating alkylmagnesium bromide with equimolar amounts of dioxane in ether at room temperature for 12 h.

(2*S*,2′*S*)-*N*-(*N*-Benzyloxycarbonylprolyl)proline Methyl Ester (1). To a stirred mixture of dicyclohexylamine salt of (*S*)-*N*-benzyloxycarbonylproline[22] (21.5 g, 50 mmol) and (*S*)-proline methyl ester hydrochloride[23] (8.3 g, 50 mmol) in chloroform (150 mL) was added a chloroform (50 mL) solution of dicyclohexylcarbodiimide (10.4 g, 50 mmol) at 0 °C; the mixture was stirred at 0 °C for 3 h, and then at room temperature overnight. After evaporation of chloroform, ethyl acetate (200 mL) was added. Insoluble dicyclohexylurea and dicyclohexylamine hydrochloride were removed by filtration. The filtrate was washed successively with 10% citric acid (100 mL), water (100 mL), 4% sodium bicarbonate (100 mL), and water (100 mL), and dried over anhydrous sodium sulfate. The ethyl acetate solution was concentrated to give **1** (16.5 g, 92%) as a viscous oil which crystallized on standing: mp 77–78 °C (ethyl acetate–hexane) (lit.[24] 76–78 °C); $[\alpha]^{26}_D$ −116° (*c* 1, MeOH) [lit.[24] $[\alpha]^{20}_D$ −120° (*c* 1, MeOH)]; IR (neat) 1740, 1700, 1650 cm^{-1}; NMR ($CDCl_3$) δ 1.45–2.55 (m, 8 H), 3.15–4.20 (m, 7 H), 4.30–4.80 (m, 2 H), 5.10 (s, 2 H), 7.33 (s, 5 H). Anal. ($C_{19}H_{24}O_5N_2$) C, H, N.

(2*S*,2′*S*)-2-Hydroxymethyl-1-[(1-methylpyrrolidin-2-yl)methyl]-pyrrolidine (2a). A THF (50 mL) solution of **1** (16.5 g, 46 mmol) was added to a stirred suspension of $LiAlH_4$ (6.08 g, 160 mmol) in THF (200 mL) at 0 °C, and then the reaction mixture was heated to reflux for 3 h. Aqueous sodium sulfate was added dropwise to the reaction mixture, after it was cooled to 0 °C. The resulting white precipitate was removed by filtration. The filtrate was dried over anhydrous potassium carbonate, and concentrated. Distillation gave **2a** (7.34 g, 81%) as a colorless oil: bp 112 °C (4.5 mm); $[\alpha]^{28}_D$ −130° (*c* 0.36, EtOH); IR (neat) 3360, 2950, 2875, 2775, 1450, 1345, 1205, 1155, 1105, 1080, 1050, 910 cm^{-1}; NMR ($CDCl_3$) δ 1.4–2.8 (m, 11 H), 2.32 (s, 3 H), 2.85–3.33 (m, 2 H), 3.43 (d of d, *J* = 4.5 Hz, 2 H), 4.72 (s, 1 H). Anal. ($C_{11}H_{22}ON_2$) C, H, N.

(2*S*,2′*S*)-2-(1-Hydroxy-1-methylethyl)-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine (2b). To a THF (65 mL) solution of **1** (13.9 g, 38 mmol) was added a THF (100 mL) solution of methylmagnesium bromide (93 mmol) at −20 °C; the mixture was stirred at 0 °C for 1 h. The reaction mixture was poured into cold, aqueous ammonium chloride, and the organic layer was extracted with ether. The ethereal extract was dried over anhydrous sodium sulfate and concentrated. The resulting solid was dissolved in THF (50 mL), and the THF solution was added to a suspension of $LiAlH_4$ (9.79 g, 258 mmol) in THF (200 mL) at 0 °C, and then heated to reflux for 3 h. Similar workup as described in the preparation of **2a** gave **2b** as a colorless oil: bp 85 °C (1 mm); $[\alpha]^{19}_D$ −50.8° (*c* 1, EtOH); IR (neat) 3350, 2930, 2860, 2775, 1445, 1360, 1175, 1130, 935 cm^{-1}; NMR ($CDCl_3$) δ 1.10 (s, 6 H), 1.23–2.15 (m, 8 H), 2.22–3.45 (m, 9 H), 2.30 (s, 3 H). Anal. ($C_{13}H_{26}ON_2$) C, H, N.

(2*S*,2′*S*)-2-(1-Ethyl-1-hydroxypropyl)-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine (2c). To a THF (60 mL) solution of **1** (18 g, 50 mmol) was added a THF (150 mL) solution of ethylmagnesium bromide (127 mmol) at −20 °C; the mixture was stirred at room temperature overnight. The reaction mixture was poured into cold, aqueous ammonium chloride. The organic layer was extracted with ether. The ethereal extract was dried over anhydrous sodium sulfate and concentrated. The residual, viscous oil was dissolved in THF (100 mL), and the THF solution was added to a suspension of $LiAlH_4$ (11.4 g, 300 mmol) in THF (250 mL) at 0 °C, and then heated to reflux for 3 h. After we cooled the reaction mixture to 0 °C, aqueous sodium sulfate was added dropwise. The resulting white precipitate was removed by filtration. The filtrate was dried over anhydrous potassium carbonate and concentrated. The residue was chromatographed on an alumina column. Elution with methylene chloride–ethyl acetate gave **2c** (12.7 g, 56%): bp 95 °C (1 mm); $[\alpha]^{22}_D$ −88.7° (*c* 1, EtOH); IR (neat) 3400, 2950, 2860, 2775, 1450, 1355, 1205, 1160, 1130, 1070, 1040, 955 cm^{-1}; NMR ($CDCl_3$) δ 0.65–1.15 (m, 6 H), 1.15–2.0 (m, 12 H), 2.0–3.95 (m, 9 H), 2.35 (s, 3 H). Anal. ($C_{15}H_{30}ON_2$) C, H, N.

(2*S*,2′*S*)-2-(1-Hydroxy-1-propylbutyl)-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine (2d) and (2*S*,2′*S*)-2-(1-butyl-1-hydroxypentyl)-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine (2e) were prepared in an identical procedure as that described for **2c**. **2d** (33%): bp 110 °C (0.7 mm); $[\alpha]^{26}_D$ −70.3° (*c* 1, EtOH); IR (neat) 3360, 3125, 2930, 2840, 2770, 1430, 1125, 1035, 990 cm^{-1}; NMR (CCl_4) δ 0.7–2.05 (m, 22 H), 2.05–3.60 (m, 8 H), 2.37 (s, 3 H), 4.45 (s, 1 H, exchange with D_2O). Anal. ($C_{17}H_{34}ON_2$) C, H, N. **2e** (21%): bp 120 °C (0.8 mm); $[\alpha]^{24}_D$ −60.6° (*c* 1, EtOH); IR (neat) 3180, 2950, 2860, 2775, 1455, 1445, 1370, 1355, 1205, 1130, 1040 cm^{-1}; NMR ($CDCl_3$) δ 0.63–1.08 (m, 6 H), 1.08–2.05 (m, 20 H), 2.05–3.24 (m, 9 H), 2.50 (s, 3 H). Anal. ($C_{19}H_{38}ON_2$) C, H, N.

2-Hydroxymethyl-1-[(pyrrolidin-2-yl)methyl]pyrrolidine (3). To an acetic acid (170 mL) solution of **1** (21.6 g, 60 mmol) was added 25

mL of 30% HBr–acetic acid; the mixture was stirred for 1 h. Acetic acid was removed as the heptane azeotrope at room temperature under reduced pressure. The residue was washed three times with ether (100 mL) by decantation, and the solvent was removed under reduced pressure. To the residue was added THF (160 mL), and the powder of $LiAlH_4$ (17 g, 450 mmol) was slowly added at −10 °C. The reaction mixture was stirred overnight at room temperature and heated to reflux for 3 h. Similar workup as described in the preparation of **2a** gave **3** (6.72 g, 62%) as a colorless oil: bp 115 °C (0.9 mm); $[\alpha]^{28}_D$ −52.8° (*c* 1.01, EtOH); IR (neat) 3330, 1400, 1065, 1045 cm^{-1}; NMR ($CDCl_3$) δ 3.80 (s, 2 H), 3.45 (d, 2 H), 3.34–2.15 (m, 8 H), 2.09 (m, 8 H). Anal. ($C_{10}H_{20}ON_2$) C, H, N.

2-Hydroxymethyl-1-[(1-ethylpyrrolidin-2-yl)methyl]pyrrolidine (2f). To an acetonitrile (50 mL) solution of **3** (5.52 g, 30 mmol) was added an acetonitrile (10 mL) solution of acetyl chloride (2.59 g, 33 mmol) at 0 °C; the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated in vacuo. The resulting solid was treated with 10% NaOH (20 mL), and extracted with ether. The ethereal extract was dried over anhydrous potassium carbonate and concentrated to give the crude amide. A THF (50 mL) solution of the crude amide was added to a stirred suspension of $LiAlH_4$ (2.0 g, 53 mmol) in THF (50 mL) at 0 °C and heated to reflux for 1 h. Similar workup as described in the preparation of **2a** gave **2d** (4.45 g, 70%) as a colorless oil: bp 102 °C (0.8 mm); $[\alpha]^{26}_D$ −103.2° (*c* 1, EtOH); IR (neat) 3360, 2950, 2875, 2775, 1450, 1345, 1205, 1155, 1105, 1080, 1050, 910 cm^{-1}; NMR (CCl_4) δ 1.06 (t, J = 6 Hz, 3 H), 1.35–3.60 (m, 20 H), 4.44 (s, 1 H, exchange with D_2O). Anal. ($C_{12}H_{24}ON_2$) C, H, N.

(2*S*,2′*S*)-2-Hydroxymethyl-1-[(1-neopentylpyrrolidin-2-yl)methyl]pyrrolidine (2g) was prepared in 72% yield from pivaloyl chloride and **3** according to the procedure for **2f**: bp 114 °C (0.6 mm); $[\alpha]^{32}_D$ −163° (*c* 1.02, EtOH); IR (neat) 3400, 2945, 2860, 2780, 1470, 1450, 1390, 1355, 1195, 1110, 1035 cm^{-1}; NMR (CCl_4) δ 1.83 (s, 9 H), 1.4–2.8 (m, 18 H) 2.8–3.6 (m, 3 H). Anal. ($C_{15}H_{30}ON_2$) C, H, N.

(2*S*,2′*S*,2″*S*)-2-Hydroxymethyl-1-{1-[(1-methylpyrrolidin-2-yl)-methyl]pyrrolidin-2-yl}methylpyrrolidine (5). To a methanol (150 mL) solution of **1** (37.4 g, 100 mmol) was added 1 N NaOH (110 mL); then DMF was added (100 mL). After being stirred at room temperature overnight, the reaction mixture was concentrated in vacuo. To the residue was added 4% $NaHCO_3$ solution (100 mL); the mixture was washed with ethyl acetate. The aqueous solution was acidified with 5 N HCl to pH 3, and the resulting white precipitate, *N*-(*N*-benzyloxycarbonylprolyl)proline, was collected by vacuum filtration and washed successively with water (30 mL), ethanol (50 mL), and ether (50 mL), and then dried in vacuo. To a mixture of the precipitate (27.9 g), dicyclohexylamine (14.5 g, 80.5 mmol), and (*S*)-proline methyl ester hydrochloride (13.2 g, 80.5 mmol) in $CHCl_3$ (200 mL) was added a chloroform (70 mL) solution of dicyclohexylcarbodiimide (16.7 g, 80.5 mmol) at 0 °C; the mixture was stirred at 0 °C for 3 h and then kept at room temperature overnight. Similar workup as described in the preparation of **1** gave the crude tripeptide **4** as a vitreous solid (26.9 g): mp 109–110 °C (ethyl acetate–hexane); $[\alpha]^{28}_D$ −157.6° (*c* 1.01, EtOH): IR (KBr) 1745, 1690, 1645 cm^{-1}; NMR ($CDCl_3$) δ 1.6–2.4 (m, 12 H), 3.25–3.90 (m, 9 H), 4.23–4.83 (m, 3 H), 5.03 (m, 2 H), 7.20 (s, 5 H). Anal. ($C_{24}H_{31}O_6N_3$) C, H, N.

To a suspension of $LiAlH_4$ (12 g, 316 mmol) in THF (70 mL) was added a THF (20 mL) solution of **4** (26.9 g, 70 mmol) at 0 °C; the mixture was heated to reflux for 8 h. Similar workup as described in the preparation of **2a** gave **5** as a viscous oil (17.1 g, 61%): bp 135 °C (0.6 mm); $[\alpha]^{24}_D$ −200° (*c* 0.5, EtOH); IR (neat) 3350, 2960, 2860, 2775, 1450, 1355, 1345, 1205, 1130, 1110, 1080, 1045, 910 cm^{-1}; NMR ($CDCl_3$) δ 1.3–2.2 (m, 12 H), 2.2–2.9 (m, 10 H), 2.33 (s, 3 H), 2.0–3.9 (m, 6 H). Anal. ($C_{16}H_{31}ON_3$) C, H, N.

Asymmetric Addition of Alkyllithium to an Aldehyde in Ether. To an ether (18 mL) solution of **2** (4.05 mmol) was added alkyllithium (6.75 mmol) at 0 °C under an argon atmosphere. After 30 min, the reaction mixture was cooled to −123 °C. An ether solution (2 mL) of an aldehyde (1 mmol) was added, and the mixture was stirred for 1 h at −123 °C. The reaction was quenched with 3 N hydrochloric acid, and the product was extracted with ether. The ethereal extract was dried over anhydrous sodium sulfate and concentrated. The alcohol was separated by silica gel TLC using methylene chloride as a developing solvent and the isolated product was further purified by bulb-to-bulb distillation. The product was identified by NMR, IR, and VPC analyses, and optical purity was calculated by optical rotation.

In a similar manner, asymmetric addition of alkyllithium to an aldehyde in various solvents, such as hexane, *n*-propyl ether, THF, dimethoxymethane, or dimethoxyethane was carried out. In the case of using methyl ether, the preparation of the lithium salt of **2** was carried out at −78 °C.

Asymmetric Addition of Alkyllithium to an Aldehyde in a 1:1 Mixture of Dimethoxymethane and Methyl Ether. Immediately after evaporation of a solution of alkyllithium (6.75 mmol) in vacuo at 0 °C, dimethoxymethane (10 mL) and **2** (4.05 mmol) in 2.5 mL of dimethoxymethane were added successively at −78 °C under an argon atmosphere. The reaction mixture was stirred for 30 min, and 13 mL of methyl ether was introduced. After cooling the reaction mixture to −123 °C, a dimethoxymethane (0.5 mL) solution of an aldehyde (1 mmol) was added. After stirring for 1 h at −123 °C, the reaction was quenched with 3 N hydrochloric acid, and the product was extracted with ether. Similar workup as described above gave the corresponding pure alcohol.

Asymmetric Addition of Various Organometallic Reagents (Except Alkyllithium) to Benzaldehyde in Ether. A mixture of an organometallic reagent (4 mmol) and the lithium salt of **2** (4 mmol) in ether (18 mL) was stirred for 30 min and then cooled. An ether (2 mL) solution of benzaldehyde (0.106 g, 1 mmol) was added and stirred for 1 h. Similar workup described above gave the corresponding pure alcohol.

Asymmetric Addition of Dialkylmagnesium to an Aldehyde in Toluene. To an ether (7 mL) solution of **2** (4 mmol) was added *n*-butyllithium (4 mmol), followed by addition of an ether solution of dialkylmagnesium (4 mmol) at 0 °C. The solvent was removed by evaporation first with aspirator pressure and then with the vacuum pump (1 mm) at room temperature for 20 min, and then toluene (18 mL) was added. After the reaction mixture was cooled to −110 °C, a toluene (2 mL) solution of an aldehyde was added dropwise, and the stirring was continued for 1 h at −110 °C. The reaction was quenched with 3 N hydrochloric acid. Similar workup as described above gave the pure alcohol.

Recovery of Chiral Amino Alcohols 2. The acidic solution from above was neutralized with solid $NaHCO_3$ and then concentrated in vacuo. The residue was treated with a small amount of 10% NaOH and the crude amino alcohols were extracted with ether. The ethereal extracts were dried over anhydrous potassium carbonate, and concentrated. Distillation afforded the pure amino alcohols in over 80% recovery and examination of the $[\alpha]_D$ values indicated, in every case, that no racemization had occurred.

2-Methoxymethyl-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine. A THF (40 mL) solution of **2a** (3.75 g, 18.9 mmol) was added to a stirred suspension of potassium hydride (0.81 g, 20 mmol) in THF (10 mL) at room temperature and stirred for an additional hour. A THF (20 mL) solution of methyl iodide (2.68 g, 18.9 mmol) was added dropwise over 3 h and stirred overnight. The reaction mixture was poured into cold saturated brine (50 mL), extracted with ether, dried with anhydrous potassium carbonate, and concentrated. Distillation gave 2.59 g (60%) of a clear oil: bp 75 °C (0.6 mm); $[\alpha]^{30}_D$ −156.3° (*c* 1.027, EtOH); IR (neat) 3400, 2960, 2875, 2780, 1455, 1350, 1200, 1157, 1130 cm^{-1}; NMR (CCl_4) δ 2.2 (s, 3 H), 1.0–2.7 (m, 14 H), 3.2 (s, 3 H), 2.7–3.4 (m, 4 H). Anal. ($C_{12}H_{24}ON_2$) C, H, N.

Reaction of *n*-Butyllithium with Benzaldehyde in the Presence of 2-Methoxymethyl-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine. To an ether (18 mL) solution of 2-methoxymethyl-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine (0.849 g, 4.0 mmol) was added *n*-butyllithium (2.75 mmol) at 0 °C. After 30 min, the reaction mixture was cooled to −123 °C. An ether (2 mL) solution of benzaldehyde (0.106 g, 1 mmol) was added and stirred for 1 h at −123 °C. The usual workup gave (*S*)-1-phenyl-1-pentanol (0.106 g, 65%): $[\alpha]^{29}_D$ −4.3° (*c* 3.01, benzene) (14%, optical purity).

2-Hydroxymethyl-1-methylpyrrolidine. A THF (100 mL) solution of *N*-*tert*-butyloxycarbonylproline[25] (21.50 g, 100 mmol) was added to a stirred suspension of $LiAlH_4$ (15.18 g, 400 mmol) in THF (100 mL) at 0 °C and then heated to reflux for 16 h. Similar workup as described in the preparation of **2a** gave 9.94 g (87%) of a colorless oil: bp 94 °C (48 mm); $[\alpha]^{28}_D$ −50.7° (*c* 1.021, EtOH); IR (neat) 3360, 2950, 2875, 2775, 1450, 1345, 1205, 1155, 1105, 1080, 1050, 910 cm^{-1}; NMR (CCl_4) δ 1.4–2.5 (m, 6 H), 2.3 (s, 3 H), 2.7–3.15 (m, 1 H), 3.40 (d, J = 2 Hz, 2 H), 4.70 (s, 1 H). Anal. ($C_6H_{13}ON$) C, H, N.

Reaction of *n*-Butyllithium with Benzaldehyde in the Presence of 2-Hydroxymethyl-1-methylpyrrolidine. To an ether (18 mL) solution

of 2-hydroxymethyl-1-methylpyrrolidine (0.466 g, 4.05 mmol) was added *n*-butyllithium (6.75 mmol) at 0 °C. After 30 min, the reaction mixture was cooled to −123 °C. An ether (2 mL) solution of benzaldehyde (0.106 g, 1 mmol) was added and stirred for 1 h at −123 °C. The usual workup gave (*S*)-1-phenyl-1-pentanol (0.146 g, 89%): $[\alpha]^{24}_D$ −4.3° (*c* 2.99, benzene) (14%, optical purity).

Acknowledgment. The authors wish to thank the Ministry of Education, Japan, for a grant-in-aid.

References and Notes

(1) (a) Morrison, J. D.; Mosher, H. S. "Asymmetric Organic Reactions", Prentice-Hall: Englewood Cliffs, N.J., 1971; pp 160–218, 415–419; (b) Izumi, Y.; Tai, A.; Hirota, K.; Harada, T. *Kagaku Sosetsu* **1971**, 85–151.

(2) Chiral lithium hydride reagents: (a) Brinkmeyer, R. S.; Kapoor, V. M. *J. Am. Chem. Soc.* **1977**, *99*, 8339–8341; (b) Asami, M.; Ohno, H.; Kobayashi, S.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1869–1873, and references cited therein. Chiral borohydrides: Brown, H. C.; Mandal, A. K. *J. Org. Chem.* **1977**, *42*, 2996–2999, and references cited therein.

(3) (a) Levi, A.; Modena, G.; Scorrano, G. *J. Chem. Soc., Chem. Commun.* **1975**, 6–7; (b) Heil, B.; Torös, S.; Vastag, S.; Morko, L. *J. Organomet. Chem.* **1975**, *94*, C47–48.

(4) Ojima, I.; Kogure, T.; Nagai, Y. *J. Organomet. Chem.* **1976**, *122*, 83–97.

(5) (a) Seebach, D.; Geiss, K.-H. "New Application of Organometallic Reagents in Organic Synthesis"; Seebach, D., Ed.; Elsevier: Amsterdam, 1976; pp 54–58; (b) Nozaki, H.; Aratani, T.; Toraya, T. *Tetrahderon Lett.* **1968**, 4097–4098; (c) Nozaki, H.; Aratani, T.; Toraya, T.; Noyori, R. *Tetrahedron* **1971**, *27*, 905–913; (d) Seebach, D.; Dörr, H.; Bastani, B.; Ehrig, V. *Angew. Chem.* **1969**, *81*, 1002–1003; (e) Seebach, D.; Kalinowski, H.; Bastani, B.; Grass, G.; Daum, H.; Dörr, H.; DuPreez, N. P.; Ehrig, V.; Langer, W.; Nüssler, C.; Oei, H.-A., Schmidt, M. *Helv. Chim. Acta* **1977**, *60*, 301–325.

(6) (a) Blomberg, C.; Coops, J. *Recl. Trav. Chim. Pays-Bas* **1964**, *83*, 1083–1092; (b) French, W.; Wright, G. F. *Can. J. Chem.* **1964**, *42*, 2474–2479; (c) Inch, T. D.; Lewis, C. J.; Sainsbury, G. L.; Sellers, D. J. *Tetrahedron Lett.* **1969**, 3657–3600; (d) Meyers, A. I.; Ford, M. E. *Tetrahedron Lett.* **1974**, 1341–1344; (e) Iffland, D. C.; Davis, J. E. *J. Org. Chem.* **1977**, *42*, 4150–4151.

(7) Zweig, J. S.; Luche, J. L.; Barreriro, E.; Crabbé, P. *Tetrahedron Lett.* **1975**, 2355–2358.

(8) Bruer, H.-J.; Haller, R. *Tetrahedron Lett.* **1972**, 5227–5230.

(9) Boireau, G.; Abenhaim, D.; Bourdais, J.; Henry-Bash, E. *Tetrahedron Lett.* **1976**, 4781–4782.

(10) Reported in preliminary form: (a) Mukaiyama, T.; Soai, K.; Kobayashi, S. *Chem. Lett.* **1978**, 219–222; (b) Soai, K.; Mukaiyama, T. *Chem. Lett.* **1978**, 491–492; (c) Sato, T.; Soai, K.; Suzuki, K.; Mukaiyama, T. *Chem. Lett.* **1978**, 601–604.

(11) Alkyllithium is known to form a tight complex with a bidentate diamine such as *N,N,N′,N′*-tetramethylethylenediamine. See Peterson, D. J. *J. Org. Chem.* **1967**, *32*, 1717–1720.

(12) Meyers reported the similar effect of metal salt; the magnesium salt of 4-hydroxymethyl-2-methyl-5-phenyl-2-oxazoline was more effective as a ligand for the asymmetric addition of Grignard reagents to carbonyl compounds than 4-methoxymethyl-2-methyl-5-phenyl-2-oxazoline. See ref 6d.

(13) The content of iodide ion in the ether solution of methyllithium was determined by means of volumetric analysis using potassium periodate, and the ratio of **2d**:iodide ion was 1:0.8.

(14) Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870–1877.

(15) Pickard, H. L.; Kenyon, J. *J. Chem. Soc.* **1914**, 1115–1131.

(16) Mislow, K.; Hamermesh, C. L. *J. Am. Chem. Soc.* **1955**, *77*, 1590–1594.

(17) Pickard, H. L.; Kenyon, J. *J. Chem. Soc.* **1913**, 1923–1959.

(18) MacLeod, R.; Welch, F. J.; Mosher, H. S. *J. Am. Chem. Soc.* **1960**, *82*, 876–880.

(19) Wittig, G.; Hesse, A. *Org. Syn.* **1970**, *50*, 66–72.

(20) Gillman, H.; Moore, F. W.; Baine, O. *J. Am. Chem. Soc.* **1941**, *63*, 2479–2482.

(21) Noller, C. R. "Organic Syntheses"; Wiley: New York, 1948; Collect. Vol. II, pp 184–187.

(22) Klieger, E.; Schroder, E.; Gibian, H. *Justus Liebigs Ann. Chem.* **1961**, *640*, 157–167.

(23) Guttman, S. *Helv. Chim. Acta.* **1961**, *44*, 721–744.

(24) Martinez, J.; Winternitz, F. *Bull. Soc. Chim. Fr.* **1972**, 4707–4709.

(25) Nagasawa, T.; Kuroiwa, K.; Narita, K.; Isowa, Y. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1269–1272.

Oxyphosphorane and Monomeric Metaphosphate Ion Intermediates in Phosphoryl Transfer from 2,4-Dinitrophenyl Phosphate in Aprotic and Protic Solvents

Fausto Ramirez*[1] and James F. Marecek

Contribution from the Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794. *Received September 7, 1978*

Abstract: The reactions of 2,4-dinitrophenyl dihydrogen phosphate, $ArPH_2$, and of salts of type $(ArPH)^-(R_4N)^+$, $(ArPH)^-(R_3NH)^+$, $(ArP)^{2-}(R_4N)^+(R_3NH)^+$, and $(ArP)^{2-}2(R_3NH)^+$, where R_4N^+ = $(n\text{-}C_4H_9)_4N^+$ and R_3N = $(i\text{-}C_3H_7)_2C_2H_5N$, have been studied in aprotic and protic solvents, in the absence and in the presence of alcohols or water, ROH, following the release of phenol and the fate of the phosphorus. The results are interpreted as follows. (1) The *acid* and the *monoanion* react via oxyphosphorane intermediates, P(5). (2) The *dianion* reacts via a monomeric metaphosphate ion intermediate, PO_3^-. In the absence of ROH, acid, monoanion, and dianion generate cyclic trimetaphosphoric acid or its salts, $(CP_3)^{3-}$ in aprotic solvents. Phosphoryl transfer to ROH by the P(5) mechanism proceeds at a relatively slow rate, the rate depends on alcohol size, and the reaction does not generate *tert*-butyl phosphate from *tert*-butyl alcohol. Rates are faster and independent of alcohol size, and *tert*-butyl phosphate is formed from *tert*-butyl alcohol by the PO_3^- mechanism. Formation of $(CP_3)^{3-}$ is not an indication of PO_3^- intermediacy in phosphorylation. The conclusions are limited to aminium salts of $ArPH_2$ where the amine is sterically hindered.

This work is concerned with the mechanisms by which phosphomonoesters transfer their phosphoryl group to nucleophiles in solutions:

$$XP(O)(OH)_2 + ROH \rightarrow ROP(O)(OH)_2 + XH \quad (1)$$

We have studied the behavior of anhydrous 2,4-dinitrophenyl phosphate[2] in aprotic and protic media, in the absence of bases and in the presence of one or more molar equivalents of the sterically hindered diisopropylethylamine, and have compared the results with those obtained utilizing the anhydrous monotetra-*n*-butylammonium salt of the acid, $(ArPH)^-(R_4N)^+$. From such studies, we have obtained compelling evidence for the participation of oxyphosphorane, P(5), and of monomeric metaphosphate ion, PO_3^-, intermediates in these reactions, depending on experimental conditions.

The participation of P(5) intermediates in reactions of phosphotriesters and phosphodiesters is widely accepted.[3-9] The intervention of PO_3^- intermediates in the hydrolysis of *alkyl* phosphates was proposed to account for a maximum reaction rate at the pH which corresponds to a maximum concentration of monoanion, $(RPH)^-$[10-13] (eq 2).[10-11]

Aryl phosphates, $XP(O)(OH)_2$, derived from phenols, XH,

0002-7863/79/1501-1460$01.00/0 © 1979 American Chemical Society