The Reactions of Optically Pure Menthyloxymethylphenylphosphine-Borane with Organolithium Reagents

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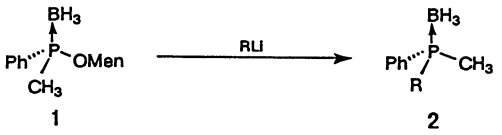
Synopsis. The reactions of (R_P)-menthyloxymethylphenylphosphine-borane with several organolithium reagents are described. Less sterically hindered reagents such as *m*-anisyllithium and *p*-anisyllithium react with the phosphine-borane to afford the corresponding substitution products with high stereochemical integrity with inversion of configuration. On the other hand, *o*-substituted phenyllithiums lead to products possessing very low optical purities.

Optically active organophosphorus compounds with a chiral center at phosphorus occupy a central position in the study of dynamic stereochemistry of phosphorus.[1] The utility of these compounds has also been proven in the area of catalytic asymmetric synthesis.[2-4] In previous publications,[5,6] we described that optically active tertiary phosphines, including chiral phosphine ligands, can be synthesized via phosphine-boranes. Based on these results, we intended to study the nucleophilic substitution reaction of optically active menthyloxymethylphenylphosphine-borane (**1**) with organolithium reagents, since the reaction was anticipated to provide optically active phosphine-boranes (**2**) which are key intermediates to homochiral bis-phosphinoethanes.



1 **2**

Compound **1**, whose chirality at phosphorus is (*R*), was prepared from dichlorophenylphosphine according to the procedure described in the previous paper.[6] This compound was allowed to react with several organolithium reagents under various conditions. Our initial trial was conducted with the reaction of **1** with *o*-anisyllithium. No trace of the expected substitution product was produced at room temperature even after 24 h (Entries 1 and 2 in Table 1). When the reagent was added to a solution of **1** in benzene, tetrahydrofuran (THF), or 1,2-dimethoxyethane (DME) at reflux, the substitution reaction occurred with inversion of configuration, although the enantiomeric excess of the product was significantly low (Entries 4, 5, and 6).[7] Under similar conditions, *m*-

Table 1. Reaction of Menthyloxymethylphenylphosphine-Borane with Organolithium Reagents

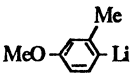
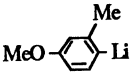
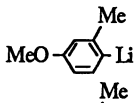
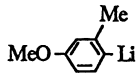
Entry	Lithium reagent	Solvent	Reac. cond.		Prod.	
			Temp/°C	Time/h	Yield/%	ee/%
1	*o*-$MeOC_6H_4Li$	Benzene	25	24	0	—
2	*o*-$MeOC_6H_4Li$	DME	25	24	0	—
3	*o*-$MeOC_6H_4Li$	Benzene	25—80	3	0	—
4	*o*-$MeOC_6H_4Li$	Benzene	80	0.5	65	2
5	*o*-$MeOC_6H_4Li$	THF	66	0.5	34	13
6	*o*-$MeOC_6H_4Li$	DME	83	0.5	47	12
7	*o*-$MeOC_6H_4Li$	DME-HMPA	83	3	0	—
8	*m*-$MeOC_6H_4Li$	Benzene	80	0.5	48	82
9	*m*-$MeOC_6H_4Li$	DME	83	0.5	57	95
10	*p*-$MeOC_6H_4Li$	Benzene	80	0.5	54	88
11	*p*-$MeOC_6H_4Li$	DME	83	0.5	54	99
12		Benzene	80	0.5	31	2
13		DME	83	0.5	0	—
14	*o*-$MeOC_6H_4Li$	DME	25	24	0	—
15	*o*-$MeOC_6H_4Li$	Benzene	25	24	0	—
16	*o*-$MeOC_6H_4Li$	THF	25	24	0	—
17	*o*-$MeOC_6H_4Li$	DME	83	2	0	—
18	1-Naphthyllithium	DME	25—83	3	0	—
19	1-Naphthyllithium	DME	83	3	0	—
20	*t*-C_4H_9Li	DME	25	3	0	—
21	*t*-C_4H_9Li	DME	83	1	0	—

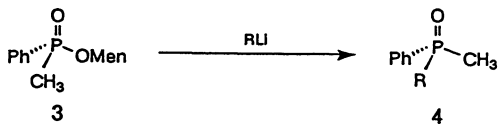
Table 2. Reaction of Menthylphenylphosphinate with Organolithium Reagents

Entry	Lithium reagent	Solvent	Reac. cond.		Prod.	
			Temp/°C	Time/h	Yield/%	ee/%
1	*o*-$MeOC_6H_4Li$	Benzene	25—80	3	0	—
2	*o*-$MeOC_6H_4Li$	Benzene	80	0.5	76	95
3	*o*-$MeOC_6H_4Li$	DME	83	0.5	70	94
4	*m*-$MeOC_6H_4Li$	Benzene	80	0.5	95	100
5	*m*-$MeOC_6H_4Li$	DME	83	0.5	88	100
6	*p*-$MeOC_6H_4Li$	Benzene	80	0.5	82	91
7	*p*-$MeOC_6H_4Li$	DME	83	0.5	78	93
8		Benzene	80	0.5	8	23
9		DME	83	0.5	0	—

and *p*-anisyllithiums reacted with **1** to afford the corresponding substitution products in moderate yields (entries 8—11). It is noted that the reactions proceeded with high stereospecificity, particularly in a polar solvent such as DME.

The reactions of **1** with some other sterically hindered lithium reagents were attempted. Unfortunately, however, they were severely subjected to steric hindrance and the expected products were not obtained except in the case of 4-methoxy-2-methylphenyllithium (Entry 12).

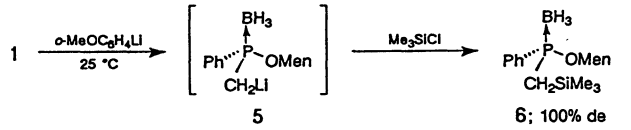
It is interesting to compare the reactivities of **1** with those of menthyl methylphenylphosphinate (**3**) whose structure resembles **1**. We have examined the reactions of **3** with anisyllithiums in benzene or DME at reflux.[8] The results are summarized in Table 2. The reactions gave rise to the corresponding substitution products (**4**) in both higher chemical and optical yields than in the case of the reactions of **1**. It is noted that the reaction of **3** with *o*-anisyllithium afforded a product possessing excellent enantiomeric excess (Entries 2 and 3).



3 4

We have been interested in the reaction of **1** with *o*-anisyllithium, which provided a product having a significantly low enantiomeric excess. There exist the following three conceivable factors to account for the loss of stereospecificity: 1) epimerization of the starting material **1** in the presence of *o*-anisyllithium, 2) racemization of the product under the reaction conditions, and 3) stereomutation of an intermediate pentacoordinate phosphorus compound or a radical species which may be generated by the one electron transfer from the organolithium reagent to compound **1**. Following additional experiments were carried out in order to obtain some mechanistic insight.

Compound **1** was treated with *o*-anisyllithium in benzene at room temperature and quenched with water. The recovered compound was found to be diastereomerically pure by ^1H NMR (500 MHz) analysis. Quenching with chlorotrimethylsilane provided compound **6** which was also diastereomerically pure. These results clearly indicate that an intermediate **5** was generated by proton abstraction with *o*-anisyllithium and that it was not epimerized under these conditions.[11]



5 6; 100% de

Optically active (*R*)-*o*-anisylmethylphenylphosphine-borane with 94%ee[12] was treated with 3 equiv of *o*-anisyllithium in benzene at 80 °C for 30 min. Enantiomeric excess of the recovered phosphine-borane was 94%ee; no racemization occurred under these conditions.

These results demonstrate that loss of stereospecificity is not ascribed to either epimerization of the starting material or racemization of the substitution product under the reaction conditions. We do not have any other evidence, but suspect that the loss of stereospecificity is ascribed to the stereomutation of the phosphoranyl radical intermediate.[13,14]

Experimental

1-Bromo-4-methoxy-2-methylbenzene. *N*-Bromosuccinimide (5.3 g, 29.5 mmol) was added to *m*-methylanisole (3.6 g, 29.5 mmol) in dichloromethane (40 mL) at −78 °C. The cooling bath was removed and the mixture was stirred for 1 h at room temperature. The mixture was washed with water and dried over $CaCl_2$. The solvent was removed, and the residual oil was distilled under reduced pressure. Yield 4.7 g (79%); bp 70—73 °C/133 Pa (lit,[15] 108.5 °C/156.0 Pa).

Reactions of 1 with Aryllithium Reagents (General Procedure). Aryl bromide (3 mmol) was added to *t*-butyllithium (3.7 mL of 1.7 mol dm^3 pentane solution) at −78 °C, and the temperature was elevated to room temperature during 30 min. The solution was added in one portion to a refluxing solution of **1** (1 mmol). The reaction mixture was refluxed for 30 min. The mixture was cooled to 0 °C and hydrolyzed with hydrochloric acid (1 mol dm^{-3}). The organic layer was separated, and the aqueous layer was extracted with

ether. The purification was performed by preparative TLC (benzene/hexane 2:1), and its enantiomeric excess was determined by HPLC analysis (column, Daicel Chemical Industries, Ltd. CHIRALCEL OJ; eluent, hexane/2-propanol 9:1; flow rate, 1.0 mL min^{-1}; detection, 254 nm light).

(*S*)-*m*-Anisylmethylphenylphosphine-Borane. Oil; $[\alpha]_D^{27}$ −5.56° (*c* 0.98, CH_3OH) (95%ee);, IR (Neat) 2350, 1590, 1480, 1250, and 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.86 (d, *J*=10 Hz, 3H), 3.84 (5, 3H), and 7.01—8.01 (m, 9H); MS *m/z* 230 (M^+-BH_3). Anal. Found: C, 69.08; H, 7.40%. Calcd for $C_{14}H_{18}OBP$: C, 68.89; H, 7.43%.

(*S*)-*p*-Anisylmethylphenylphosphine-Borane. Oil; $[\alpha]_D^{26}$ −2.91° (*c* 0.88, CH_3OH) (99%ee); IR (Neat) 2320, 1590, 1500, 1260, and 900 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.80 (d, *J*=9.9 Hz, 3H), 3.77 (s, 3H), and 6.75—7.70 (m, 9H); MS *m/z* 230 (M^+-BH_3). Anal. Found: C, 68.84; H, 7.34%. Calcd for $C_{14}H_{18}OBP$: C, 68.89; H, 7.43%.

(4-Methoxy-2-methylphenyl)methylphenylphosphine-Borane. Oil; IR (Neat) 2920, 2320, 1590, 1300, 1240, 1070, and 900 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.82 (d, *J*=9.0 Hz, 3H), 2.15 (s, 3H), 3.79 (5, 3H), and 6.60—7.75 (m, 8H); MS *m/z* 254 (M^+-BH_3) Anal. Found: C, 69.72; H, 7.71%. Calcd for $C_{15}H_{20}OBP$: C, 69.80; H, 7.81%.

Reactions of 3 with Aryllithium Reagents (General Procedure). A solution of aryllithium reagent (3 mmol) in pentane was prepared by the same procedure as described above. The solution was added in one portion to a refluxing solution of **3** (1 mmol). After refluxing for 30 min, the mixture was treated with hydrochloric acid (1 mol dm^{-3}) and extracted with chloroform. The product was separated by preparative TLC (ethyl acetate/methanol 10:1), and its enantiomeric excess was determined by HPLC analysis (column, Daicel Chemical Industries, Ltd. CHIRALCEL OJ or CHIRALCEL OD ((4-methoxy-2-methylphenyl)-methylphenylphosphine oxide); eluent, hexane/ethanol 9:1; flow rate, 0.2 mL min^{-1}; detection, 254 nm light).

(*R*)-*m*-Anisylmethylphenylphosphine Oxide. Oil; $[\alpha]_D^{27}$ −7.86° (*c* 1.03, CH_3OH) (100%ee); IR, (Neat) 3370, 1590, 1420, 1250, 1180, and 900 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.02 (d, *J*=9.5 Hz, 3H), 3.87 (s, 3H), and 7.03—7.99 (m, 9H).

(*R*)-*p*-Anisylmethylphenylphosphine Oxide. Oil (lit,[9] mp 120—121 °C); $[\alpha]_D^{27}$+7.07° (*c* 0.99, CH_3OH), $[\alpha]_D^{27}$+4.63° (*c* 1.00, C_6H_6), $[\alpha]_D^{29}$+2.19° (*c* 1.00, $CHCl_3$) (93%ee); IR (Neat) 3350, 1590, 1440, 1300, and 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.00 (d, *J*=13 Hz, 3H), 3.88 (s, 3H), and 6.94—7.98 (m, 9H).

(*R*)-(4-Methoxy-2-methylphenyl)methylphenylphosphine Oxide. Mp 140.0—140.5 °C; $[\alpha]_D^{26}$+1.75° (*c* 0.92, CH_3OH) (23%ee); IR (KBr) 2950, 1600, 1300, 1240, and 1180 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.01 (d, *J*=10.0 Hz, 3H), 2.37 (s, 3H), 3.86 (s, 3H), 6.71—8.18 (m, 8H). Anal. Found: C, 68.83; H, 6.38%. Calcd for $C_{15}H_{17}O_2P$: C, 69.22; H, 6.58%.

Compound 6. A solution of *o*-anisyllithium (3 mmol) in pentane was added to a solution of **1** (278 mg, 1 mmol) in benzene (5 mL) at room temperature. After stirring for 30 min, the mixture was treated with chlorotrimethylsilane (0.25 mL). The usual work up, followed by preparative TLC (benzene/hexane 1:5) afforded **5** (245 mg, 67%) as a colorless oil. $[\alpha]_D^{26}$−17.1° (*c* 1.00, C_6H_6); IR (Neat) 2910, 2350, 1440, 1370, 1250, 1000, and 850 cm^{-1}; ^{1}H NMR (500 MHz) ($CDCl_3$) δ=−0.11—0.05 (m, 9H), 0.70—1.64 (m, 10H), 0.71 (d, *J*=6.6 Hz, 3H), 0.85 (d, *J*=6.87 Hz, 3H), 0.94 (d, *J*=7.15 Hz, 3H), 2.13—2.17 (m, 1H), 4.09—4.13 (m, 1H), 7.35—7.51 (m, 3 H), and 7.79—7.84 (m, 2H); MS *m/z* 350 (M^+-BH_3). Anal. Found: C, 66.15; H, 10.36%. Calcd for $C_{20}H_{38}OBPSi$: C, 65.92; H, 10.51%.

References

1) For representative reviews, see: M. Mikolajczyk, *Pure Appl. Chem.*, **52**, 959 (1980); D. J. H. Smith, "Comprehensive Organic Chemistry," ed by I. O. Sutherland, Pergamon Press Ltd., Oxford (1979), Vol. 2, p. 1121—1187; R. S. Edmundson, *ibid.*, Vol. 2, p. 1257—1300.

2) For representative reviews, see: "Asymmetric Synthesis," ed by J. D. Morrison, Academic Press, New York (1985), Vol. 5, Chaps. 1—6; I. Ojima, N. Clos, and C. Bastos, *Tetrahedron*, **45**, 6901 (1989); H. B. Kagan and M. Sasaki, "The Chemistry of Organophosphorus Compounds," ed by F. R. Hartley, John Wiley & Sons Ltd., London (1990), Vol. 1, Chap. 3.

3) B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, and D. J. Weinkauff, *J. Am. Chem. Soc.*, **99**, 5946 (1977).

4) C. R. Johnson and T. Imamoto, *J. Org. Chem.*, **52**, 2170 (1987).

5) T. Imamoto, T. Kusumoto, N. Suzuki, and K. Sato, *J. Am. Chem. Soc.*, **107**, 5301 (1985).

6) T. Imamoto, T. Oshiki, T. Onozawa, T. Kusumoto, and K. Sato, *J. Am. Chem. Soc.*, **112**, 5244 (1990).

7) *o*-Anisylmagnesium bromide did not react with **1** in benzene at reflux.

8) Many substitution reactions of **3** with the Grignard reagents or organolithium reagents have been reported.[9] However, the reactions of **3** with anisyllithiums under these conditions have not yet been described in literature.

9) O. Korpium, R. A. Lewis, J. Chickos, and K. Mislow, *J. Am. Chem. Soc.*, **90**, 4842 (1968).

10) R. A. Lewis and K. Mislow, *J. Am. Chem. Soc.*, **91**, 7009 (1969); R. A. Lewis, K. Naumann, K. E. DeBruin, and K. Mislow, *J. Chem. Soc., Chem. Commun.*, **1969**, 1010; A. Nudelman and D. J. Cram, *J. Org. Chem.*, **36**, 335 (1971); W. S. Knowles, M. J. Sabacky, and B. D. Vineyard, "Homogeneous Catalysis II," *Adv. Chem. Ser.*, **132**, 274 (1972).

11) No substitution reaction occurred at 25 °C through to 80 °C (Entry 3) may be ascribed to the preferential proton abstraction with *o*-anisyllithium, since the generated anion may not undergo nucleophilic substitution.

12) Preparation of this compound by another method was described in Ref 6.

13) W. G. Bentrude, *Acc. Chem. Res.*, **15**, 117 (1982).

14) We suspect that the substitution reaction of **1** with *o*-anisyllithium or 4-methoxy-2-methylphenyllithium involves predominantly electron transfer process rather than direct S_N2 process. One electron is transferred from the organolithium reagent to the phosphine-borane **1** to generate a phosphoranyl radical intermediate. The intermediate is rapidly epimerized by pseudorotation[13] and eventually leads to a substitution product possessing a very low optical purity.

15) "Dictionary of Organic Compounds," ed by J. Buckingham, Chapman and Hall, New York (1982), Vol. 1, p. 837.