Remarkable Rate Enhancement Effect of the *o*-Methoxy Group in the Nucleophilic Substitution Reactions at the Phosphorus of Phosphine–Boranes

Tsuneo Imamoto* and Hideyuki Tsuruta
Department of Chemistry, Faculty of Science, Chiba University, Yayoi-cho, Inage-ku, Chiba 263

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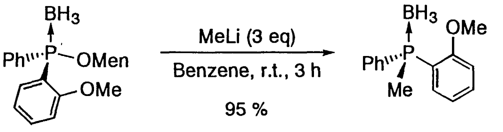
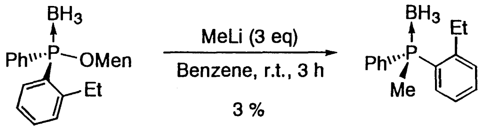
A remarkable rate enhancement effect of the *o*-methoxy group is observed in the nucleophilic substitution reactions at the phosphorus of phosphine–boranes.

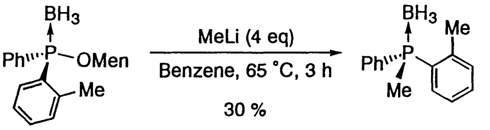
Previously, we reported that (S_P)-*l*-menthyloxyl(*o*-methoxyphenyl)phenylphosphine–borane (**1**) reacted with methyllithium in benzene at room temperature to give (*R*)-(*o*-methoxyphenyl)-methylphenylphosphine–borane (**2**) in 95% yield (Eq. 1).[1] Based on the result, we examined the reaction of (S_P)-(*o*-ethylphenyl)(*l*-menthyloxyl)phenylphosphine–borane (**3**) with methyllithium to obtain (*R*)-(*o*-ethylphenyl)methylphenylphosphine–borane (**4**). However, reaction difficulties arose under the same conditions and the desired product was obtained in only 3% yield (Eq. 2).[2] Reaction of another phosphine–borane **5**, that possesses an *o*-methyl group, with methyllithium at room temperature also proved difficult; it reacted sluggishly at 65 °C to afford the product in moderate yield (Eq. 3).



1 **2** (1)



3 **4** (2)



5 (3)

These facts suggest that the *o*-methoxy group significantly accelerates the substitution reaction. This rate enhancement may be explained by considering the coordination of the methoxy oxygen to the lithium ion. Thus, as is illustrated in Figure 1, the coordinative interaction attracts the reagent methyllithium closely to the reaction site to promote the substitution reaction at the phosphorus.

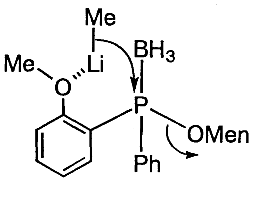
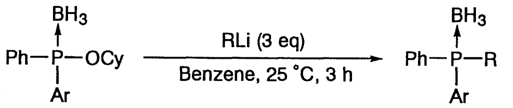


Figure 1.

Although there have been reported numerous examples of coordination- or chelation-controlled reactions,[3] this type of rate enhancement effect has scarcely appeared in the literature. Therefore, in order to demonstrate the generality of this rate enhancement effect, we examined the effects of substituents on the benzene ring using (cyclohexyloxy)phenyl(*o*- or *p*-substituted phenyl)phosphine–boranes as the model substrates. All reactions were carried out in benzene at 25 °C for 3 h (Eq. 4). The results are summarized in Table 1.[4]



(4)

6: Ar = *o*-$MeOC_6H_4$
7: Ar = *m*-$MeOC_6H_4$
8: Ar = *p*-$MeOC_6H_4$
9: Ar = *o*-MeC_6H_4
10: Ar = *p*-MeC_6H_4
11: Ar = *o*-$BnOC_6H_4$
12: Ar = *p*-$BnOC_6H_4$

13a: Ar = *o*-$MeOC_6H_4$, R = Me
13b: Ar = *o*-$MeOC_6H_4$, R = ^{n}Bu
14a: Ar = *m*-$MeOC_6H_4$, R = Me
14b: Ar = *m*-$MeOC_6H_4$, R = ^{n}Bu
15a: Ar = *p*-$MeOC_6H_4$, R = Me
15b: Ar = *p*-$MeOC_6H_4$, R = ^{n}Bu
16a: Ar = *o*-MeC_6H_4, R = Me
16b: Ar = *o*-MeC_6H_4, R = ^{n}Bu
17a: Ar = *p*-MeC_6H_4, R = Me
17b: Ar = *p*-MeC_6H_4, R = ^{n}Bu
18a: Ar = *o*-$BnOC_6H_4$, R = Me
18b: Ar = *o*-$BnOC_6H_4$, R = ^{n}Bu
19a: Ar = *p*-$BnOC_6H_4$, R = Me
19b: Ar = *p*-$BnOC_6H_4$, R = ^{n}Bu

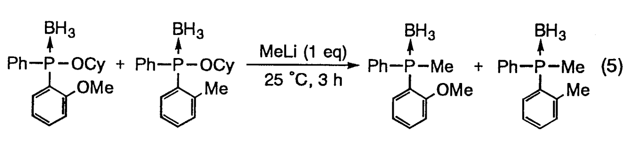
Table1. Reactions of phosphine–boranes with alkyllithiums

Entry	Substrate	RLi	Product	Yield / %^{a,b}
1	**6**	MeLi	**13a**	99
2	**6**	^{n}BuLi	**13b**	99
3	**7**	MeLi	**14a**	84 (15)
4	**7**	^{n}BuLi	**14b**	82 (12)
5	**8**	MeLi	**15a**	82 (18)
6	**8**	^{n}BuLi	**15b**	75 (24)
7	**9**	MeLi	**16a**	32 (59)
8	**9**	^{n}BuLi	**16b**	23 (77)
9	**10**	MeLi	**17a**	90 (8)
10	**10**	^{n}BuLi	**17b**	84 (14)
11	**11**	MeLi	**18a**	76 (16)
12	**11**	^{n}BuLi	**18b**	57^c
13	**12**	MeLi	**19a**	74 (12)
14	**12**	^{n}BuLi	**19b**	63 (10)

^{a}Isolated Yield. ^{b}The numbers in parentheses indicate recovery yields. ^{c}Butyl(*o*-hydroxyphenyl)phenylphosphine–borane (**18c**) was obtained in 34% yield.

It is noted that compound **6** reacted most smoothly with methyllithium or butyllithium to give the substitution products in 99% yield (Entries 1 and 2). In sharp contrast, compound **9** hardly reacted and the yields of the products were low (Entries 7 and 8). These results, together with those of the reactions of compound **10**, indicate that the low reactivity of compound **9** is largely ascribed to the steric hindrance of the *o*-methyl group. The reactions of compounds **11** and **12** are also worth mentioning. Each compound gave the substitution products in comparative yields (Entries 11–14). These facts suggest that the *o*-benzyloxy group also plays a role in the rate acceleration by coordinative interaction with alkyllithiums.

Competitive reactions between compounds **6** and **9** were carried out by changing the solvent with a view to obtaining further evidence of the *o*-methoxy effect (Eq. 5). The results are summarized in Table 2.



6 (1 eq) **9** (1 eq) **13a** **16a**

Table 2. Competitive reactions between compounds **6** and **9**

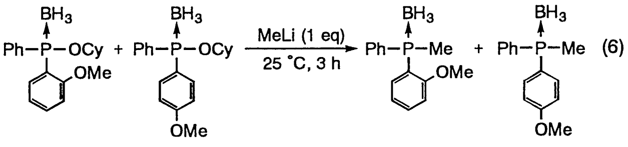
Entry	Solvent	Yield / %[a]	13a : 16a[b]
1	Benzene[c]	65	93 : 7
2	Ether	83	85 : 15
3	THF[c]	68	46 : 54
4	Benzene–TMEDA[c,d]	63	49 : 51

[a]Based on MeLi. [b]The ratio was determined by ^{1}H NMR. [c]The solvent contained 8% (v/v) ether. [d]TMEDA:MeLi = 1:1.

The reaction in benzene afforded compounds **13a** and **16a** in a high product ratio. Use of ether as the solvent resulted in a somewhat decreased product ratio, and use of THF provided compound **16a** predominantly rather than compound **13a**. The reaction in benzene in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) resulted in the formation of almost equal amounts of the two products.

A similar tendency was also observed in the competitive reactions between compounds **6** and **8** (Eq. 6, Table 3). It is noted that reaction in THF or in benzene–TMEDA afforded compound **15a** as the major product.

These results are reasonably interpreted by considering the coordination ability of the solvent or the additive (TMEDA). Thus, in a solvent of low coordinative ability, methyllithium interacts with the *o*-methoxy group to promote the substitution reactions. On the contrary, THF or TMEDA well coordinates to methyllitium,[5] and hence in these mediums the *o*-methoxy group does not promote the reactions but it rather retards them owing to the steric hindrance.



6 (1 eq) **8** (1 eq) **13a** **15a**

Table 3. Competitive reactions between compounds **6** and **8**

Entry	Solvent	Yield / %[a]	13a : 15a[b]
1	Benzene[c]	67	83 : 17
2	Ether	85	74 : 26
3	THF[c]	75	30 : 70
4	Benzene–TMEDA[c,d]	61	30 : 70

[a]Based on MeLi. [b]The ratio was determined by ^{1}H NMR. [c]The solvent contained 8% (v/v) ether. [d]TMEDA:MeLi = 1:1.

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References and Notes

1 T. Oshiki and T. Imamoto, *Bull. Chem. Soc. Jpn.*, **63**, 3714 (1990); T. Imamoto, T. Oshiki, T. Onozawa, M. Matsuo, T. Hikosaka, and M. Yanagawa, *Heteroatom Chem.*, **3**, 563 (1992); T. Imamoto, M. Matsuo, T. Nonomura, K. Kishikawa, and M. Yanagawa, *Heteroatom Chem.*, **4**, 475 (1993).

2 The reaction at refluxing temperature for 8 h using 4 equivalents of MeLi provided the product in 68% yield.

3 For recent representative examples of coordination- or chelation-controlled reactions, see the following: W. C. Still and J. H. McDonald, III, *Tetrahedron Lett.*, **21**, 1031 (1980); W. C. Still and J. A. Schneider, *Tetrahedron Lett.*, **21**, 1035 (1980); K. C. Nicolaou, D. A. Claremon, and W. E. Barnett, *J. Am. Chem. Soc.*, **102**, 6611 (1980); M. Kitamura, M. Isobe, Y. Ichikawa, and T. Goto, *J. Org. Chem.*, **49**, 3517 (1984); M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, **23**, 556 (1984); P. Beak and V. Snieckus, *Acc. Chem. Res.*, **15**, 306 (1982); H. W. Gschwend and H. R. Rodriguez, *Org. React.*, **26**,1 (1979); V. Snieckus, *Chem. Rev.*, **90**, 879 (1990); V. Snieckus, *Pure Appl. Chem.*, **66**, 2155 (1994).

4 All new compounds prepared afforded satisfactory spectral data (^{1}H NMR, IR). Melting points of the solid materials are as follow: **6**: 92–93 °C (MeOH), **8**: 77.5–78.5 °C (MeOH), **9**: 73–74 °C (MeOH), **10**: 53.5–54.0 °C (MeOH), **11**: 88.5–89.5 °C (EtOH), **13b**: 76.5–77.5 °C (MeOH), **18a**: 87.0–87.5 °C (^{i}PrOH), **18b**: 117.5–118.5 °C (MeOH–^{i}PrOH), **18c**: 119.0–120.5 °C (MeOH). Compounds **7**, **12**, **14b**, **15b**, **16a**, **16b**, **17a**, **17b**, **19a** and **19b** were obtained as pasty oil.

5 B. J. Wakefield, "Organolithium Methods," Academic Press, London (1988).