# New One-pot Cross-coupling Reaction between Grignard Reagents and Alkoxymethyldiphenylphosphonium Iodides in situ-Formed from Alcohols, Chlorodiphenylphosphine and Iodomethane

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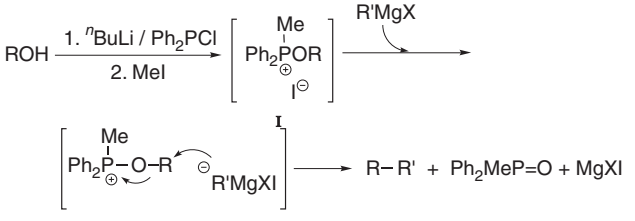
A new one-pot cross-coupling reaction between Grignard reagents and alkoxymethyldiphenylphosphonium iodides, which were in situ-formed from $^n$BuLi-treated alcohols, chlorodiphenylphosphine and iodomethane, proceeded smoothly to afford the corresponding coupling products in good to high yields.

There are a number of reactions reported concerning Grignard reagents and phosphorus compounds such as phosphorus trichloride, trialkyl phosphate, triaryl phosphate and alkyl diphenylphosphinate etc.[1,2] Since Grignard reagents generally attack on phosphorus atom, therefore, phosphine or oxophosphorane derivatives are formed in the main. Among the few examples of *C*-alkylation reaction with hindered Grignard reagents having mesityl or trityl groups and phosphates having trimethyl or geranyl diethyl groups,[3] no successful *C*-alkylation using Grignard reagents and alkoxydiphenylphosphines was reported to date. In our previous paper,[4] alkylations of various carboxylic acids[5,6] or phenols[7] with alkoxydiphenylphosphonium salt in situ-formed from alcohols, chlorodiphenylphosphine and 2,6-dimethyl-1,4-benzoquinone were presented as a new-type of oxidation–reduction condensation. Alkoxydiphenylphosphines having a primary, secondary or tertiary alkoxy group, oxidizing agent such as 2,6-dimethyl-1,4-benzoquinone, and carboxylic acids or phenols afforded the alkylated products in good to high yields. In our point of view, alkoxydiphenylphosphines behaved more effectively in the formation of important intermediate phosphonium salt since the alkoxy part had been introduced to phosphine in advance. In order to expand the idea of this type of reaction, *C*-alkylation reaction using Grignard reagents and alkoxymethyldiphenylphosphonium iodides in situ-formed from $^n$BuLi-treated alcohols, chlorodiphenylphosphine and iodomethane were tried and the corresponding cross-coupling products were obtained in good to high yields along with methyl(diphenyl)phosphine oxide (Scheme 1).

In the first place, *C*-alkylation of 1 equivalent of PhMgBr with 1 equivalent of *p*-methoxybenzyloxydiphenylphosphine ($Ph_2POPMB$), in situ formed from $^n$BuLi-treated *p*-methoxybenzyl alcohol (PMBOH) and chlorodiphenylphosphine, was tried (Table 1, entry 1). When PhMgBr and the phophonium salt were allowed to react at 100 °C for 0.5 h, the desired 1-benzyl-4-methoxybenzene was obtained in 10% yield along with triphenylphosphine (53% yield) which was formed by direct attack of Grignard reagent on phosphorus atom. Interestingly, the desired product was obtained in 38% yield when the reaction was carried out using benzyl bromide at 50 °C for 2 h (Table 1, entry 4) while the desired product was not obtained when mild oxidant such as 2,6-dimethyl-1,4-benzoquinone was used at −78 °C for 3 h (Table 1, entry 3).

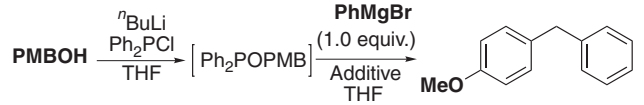



**Scheme 1.**

After screening several types of alkylating reagents shown in Table 2, the desired product was obtained in 59% yield and no triphenylphosphine was observed when phosphonium salt formed by treating alkoxydiphenylphosphine with iodomethane at rt for 1 h was used (Table 2, entry 8). Generally, monoalkylphosphonic esters are known to be formed by the reaction of trialkyl phosphites with alkyl halides (Michaelis–Arbuzov reaction).[8,9] However, the above reaction did not take place in the case of using alkoxydiphenylphosphine and iodomethane even when they were heated at 100 °C, therefore, higher temperature (150–250 °C) should be needed. Since then, iodomethane was used as the most preferable reagent for a complete formation of alkoxyalkyldiphenylphosphonium salts from alkoxydiphenylphosphines and alkylating reagents as shown in Table 2. In the above reaction, Grignard reagents coupled with iodide anion of the phosphonium salts forming an intermediate ate complex **I** which was in turn decomposed to procedure cross-coupling product together with $Ph_2MeP{=}O$ and MgXI. Similarly, alkoxydiphenylphosphonium salts were formed easily in case of using anion such as $^-OTf$ or $BF_4^-$ while the coupling reaction hardly proceeded because Grignard reagents did not form the corresponding ate complex **I** with phosphonium triflate or tetrafluoroborate. Actually, corresponding alcohol and $Ph_2MeP{=}O$ were detected after quenching the reaction with saturated aq $NH_4Cl$.

When 2.0 or 3.0 equivalents of PhMgBr were allowed to re-

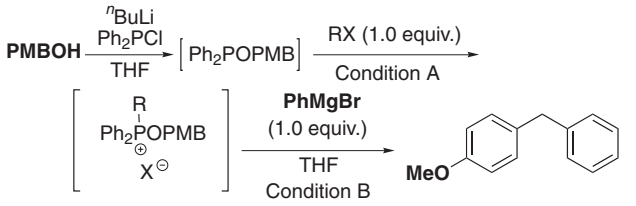
**Table 1.** Cross-coupling reaction between PhMgBr and alkoxydiphenylphosphonium salt in situ-formed from PMBOH, $Ph_2PCl$ and Additive




| Entry | Additive | Condition | Yield/% | Yield/%[a] |
|---|---|---|---|---|
| 1 | None | 100 °C, 0.5 h | 10 | 53 |
| 2[b] | None | 100 °C, 0.5 h | 10 | — |
| 3 | 2,6-Dimethyl-1,4-benzoquinone | −78 °C, 3 h | N.D. | |
| 4 | BnBr | 50 °C, 2 h | 38 | Trace |

[a]Yields of by-product ($PPh_3$). [b]5 equivalent of PhMgBr was used.

**Table 2.** Cross-coupling reaction between PhMgBr and *p*-methoxydiphenylphosphonium salt in situ-formed from PMBOH, $Ph_2PCl$ and alkylating reagents




| Entry | Alkylating reagents | Condition A | Condition B | Yield[a]/% |
|---|---|---|---|---|
| 1 | BnBr | 50 °C, 1 h | 50 °C, 2 h | 38 |
| 2 | BnBr | rt, 1 h | 50 °C, 1 h | 48 |
| 3 | BnCl | 100 °C, 1 h | 50 °C, 2 h | 19 |
| 4 | BnI | rt, 1 h | rt, 1 h | 52 |
| 5 | EtOTs | 50 °C, 1 h | 50 °C, 1 h | 22 (22) |
| 6 | $HBF_4$ | rt, 0.5 h | rt, 1 h | N.D. |
| 7 | $Et_3O^+BF_4^-$ | 50 °C, 1 h | 50 °C, 1 h | N.D. |
| 8 | MeI | rt, 1 h | rt, 1 h | 59 |
| 9 | EtI | rt, 1 h | 50 °C, 1 h | 32 (3) |
| 10 | $^n$BuI | rt, 1 h | rt, 3 h | 29 (12) |
| 11 | $^t$BuI | rt, 1 h | rt, 3 h | 17 (19) |
| 12 | MeOTf | rt, 1 h | rt, 1 h | 6 |
| 13 | $BnB(C_6F_5)_4$ | rt, 1 h | rt, 1 h | N.D. |

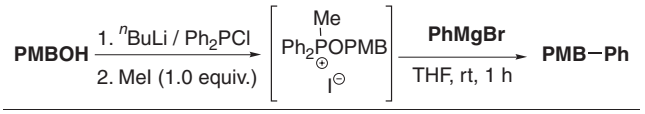
[a]Yields of parenthesis are ones of by-product ($Ph_3P$).

act with one molar each of $Ph_2POPMB$ and iodomethane at room temperature, the desired cross-coupling product was obtained in quantitative yields (Table 3, entries 4 and 5).

Next, the cross-coupling reaction by using various Grignard reagents and alkoxymethyldiphenylphosphonium iodides in situ-formed from $^n$BuLi-treated several alcohols, chlorodiphenylphosphine and iodomethane were tried (Table 4). When benzyl alcohols having electron-donating or electron-withdrawing groups and aliphatic or phenyl Grignard reagents having electron-donating or electron-withdrawing groups were used, the corresponding coupling products were obtained in good to high yields (Table 4, entries 1–14). On the other hand, the desired product was obtained in 30% yield when secondary Grignard reagent such as cyclohexylmagnesium bromide was used (Table 4, entry 8). When tertiary Grignard reagent such as $^t$BuMgCl was treated with the phosphonium salt formed from $Ph_2POPMB$ and iodomethane, the desired product was not formed. Also, in the case of using primary alcohols such as hexyl alcohol or pentanol, the reaction proceeded smoothly to afford the cross-coupling products in good yields. When isopropyl alcohol or *tert*-butyl alcohol was used, no *C*-alkylation reaction took place at all.

Typical experimental procedure is as follows: under argon atmosphere, a solution of magnesium (0.9 mmol) and bromobenzene (0.9 mmol) in THF (3 mL) was stirred for 1 h at room

**Table 3.** Cross-coupling reaction between PhMgBr and *p*-methoxybenzyloxymethyldiphenylphosphonium iodide in situ-formed from PMBOH, $Ph_2PCl$ and MeI




| Entry | PhMgBr/equiv. | Yield/% | Entry | PhMgBr/equiv. | Yield/% |
|---|---|---|---|---|---|
| 1 | 1.0 | 59 | 4 | 2.0 | quant. |
| 2 | 1.3 | 75 | 5 | 3.0 | quant. |
| 3 | 1.5 | 97 | | | |

**Table 4.** Various cross-coupling reaction between Grignard reagents and alkoxymethyldiphenylphosphonium iodide in situ-formed from ROH, $Ph_2PCl$ and MeI




| Entry | ROH | R′MgBr | equiv. | Yield/% |
|---|---|---|---|---|
| 1 | *p*-MeO-$C_6H_4CH_2OH$ | PhMgCl | 2 | quant. |
| 2[a] | | PhMgBr | 2 | quant. (99) |
| 3[b] | | PhMgI | 2 | 30 |
| 4 | | *p*-MeO-$C_6H_4MgBr$ | 2 | 98 |
| 5 | | *p*-$CF_3$-$C_6H_4MgBr$ | 2 | 96 |
| 6 | | $PhCH_2MgBr$ | 2 | 92 |
| 7 | | $CH_3(CH_2)_5MgBr$ | 3 | 90 |
| 8 | | cyclohexyl-MgBr | 2 | 30 |
| 9[b] | | $^t$BuMgCl | 3 | N.R. |
| 10 | BnOH | *p*-MeO-$C_6H_4MgBr$ | 3 | 94 |
| 11 | | $CH_3(CH_2)_5MgBr$ | 3 | 89 |
| 12 | p-Cl-$C_6H_4CH_2OH$ | *p*-MeO-$C_6H_4MgBr$ | 3 | 86 |
| 13[a] | | $PhCH_2MgBr$ | 3 | 82(81) |
| 14 | | $CH_3(CH_2)_3MgBr$ | 3 | 76 |
| 15 | $CH_3(CH_2)_5OH$ | $PhCH_2MgBr$ | 3 | 80 |
| 16[a] | $CH_3(CH_2)_4OH$ | $PhCH_2CH_2MgBr$ | 3 | 78(79) |
| 17 | $^i$PrOH | *p*-MeO-$C_6H_4MgBr$ | 3 | N.R. |
| 18 | $^t$BuOH | PhMgBr | 3 | N.R. |

[a]Yields in the parenthesis are those carried out by one-pot procedure and the same results were obtained without removing lithium chloride. [b]Grignard reagent in $Et_2O$ solution.

temperature and then was refluxed for 1 h. The dark brown mixture was transferred via cannula to an addition funnel, and was slowly added at 0 °C to a mixture of alkoxydiphenylphosphine[10] (0.6 mmol) and iodomethane (0.6 mmol), and the solution was stirred for 1 h at room temperature. After completion of the reaction (detected by TLC), it was quenched with saturated aq $NH_4Cl$ and the mixture was extracted with $Et_2O$. The organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by preparative TLC to afford the desired products.

Thus, a new and efficient method for one-pot cross-coupling reaction by using Grignard reagents and alkoxymethyldiphenylphosphonium iodides, in situ formed from alcohols, chlorodiphenylphosphine and iodomethane, proceeded smoothly to afford the corresponding cross-coupling products in good to high yields. Further study on this type of condensation reaction is now in progress.

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