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# In Situ Generation of Phosphoryl Alkylindiums and Their Synthetic Application to Arylalkyl Phosphonates via Palladium-Catalyzed Cross-Coupling Reactions

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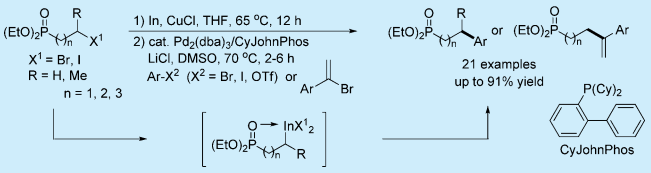
Supporting Information

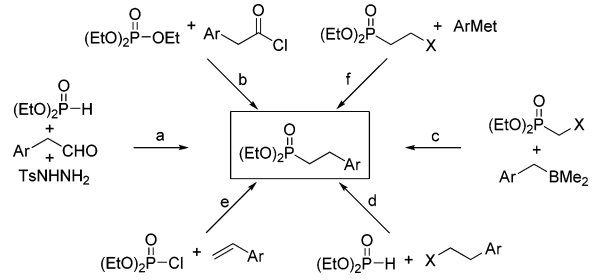
**ABSTRACT:** Phosphoryl alkylindium reagents are generated in situ from the direct insertion of indium with bromoalkyl phosphonates in the presence of CuCl, and their synthetic application to arylalkyl phosphonates is reported via a Pd-catalyzed cross-coupling reaction with tolerance of a diversity of functional groups including ester, ketone, aldehyde, nitrile, nitro, trifluoromethyl, chloride, methoxy, hydroxy, and amino.




Organophosphonate is an essential functional group in synthetic as well as biological chemistry.[1] In synthetic chemistry, it is a starting material for the preparation of alkenes via the Horner−Wadsworth−Emmons reaction.[2] In biological chemistry, their distinctive structure and polarity provide them a significant function in pharmaceuticals and agrochemicals.[3] Therefore, a wide range of synthetic intermediates and precursors and biologically active compounds require introduction of a phosphonate group to the molecule. To date, the most conventional approaches for the formation of the P−C ($sp^3$) bond are the Michaelis−Arbuzov[4] and Michaelis−Becker reactions.[5] Despite its prevalence, the trivalent phosphorus compounds employed in the Michaelis−Arbuzov reaction have normally low stability and effuse a repulsive odor. The Michaelis−Becker reaction occasionally needs long reaction times and a strong base. Thus, we envisioned that if organometallic reagents having a phosphonate group can be successfully prepared, it will be an efficient synthetic method of functionalized organophosphonates via C−C bond-forming reaction.

Because 2-aryl phosphonate derivatives have been known to be inhibitors of the human low molecular weight protein tyrosine phosphatase (HCPTP),[6] synthesis of these compounds from easily accessible precursors has been continuously investigated (Scheme 1): Cu-catalyzed synthesis of alkylphosphonates from *H*-phosphonates and *N*-tosylhydrozones (a),[7] the reductive deoxygenation of acyl phosphonates (b),[8] reaction of phosphorus-containing carbenoids with organoboranes (c),[9] $Cs_2CO_3$-promoted synthesis of phosphonates (d),[10] and reaction of zirconocene−alkene complexes with chlorophosphate (e).[11] As shown in Scheme 1, all of these reactions were achieved via the formation of the P−C ($sp^3$) bond. In contrast, Takagi and co-workers recently reported a Rh-catalyzed cross-coupling reaction of arylzinc reagent with 2-iodoethyl phosphonate, leading to 2-aryl phosphonates via the formation of a C−C bond (f).[12] However, as far as we are aware, there are no synthetic methods for 2-aryl phosphonates via the cross-coupling

**Scheme 1. Previously Reported Synthetic Methods of 2-Aryl Phosphonates**




reaction of electrophilic coupling partners with 2-phosphoryl organometallic compounds, which are the polarity-inversed method of pathway (f).

This has triggered intensive investigations on the polarity-inversed synthetic method of 2-aryl phosphonates. Such a reaction would enable 2-aryl phosphonates to be easily obtained from 2-halo phosphonates and aryl halides. In continuing efforts to develop a synthetic method of organophosphorus compounds[13] and organoindium reagents,[14,15] we describe herein in situ generation of phosphoryl alkylindium reagents from the reaction of bromoalkyl phophonates with indium and their synthetic application to arylalkyl phosphonates via Pd-catalyzed cross-coupling reactions (Scheme 2).

Initially, diethyl 2-bromoethylphosphonate (**1a**) obtained from triethyl phosphite and 1,2-dibromoethane was selected as the substrate to explore in situ generation of 2-phosphoryl indium reagent **2a**. After many attempts, it was found that the insertion took place smoothly in the presence of indium (1.4 equiv) and CuCl (1.4 equiv) in refluxing THF for 12 h, providing quantitatively the $\beta$-phosphoryl indium reagent **2a** (Figure 1). However, In/LiCl, In/CuI/LiCl, In/CuI, In/$InCl_3$, and $InCl_3$

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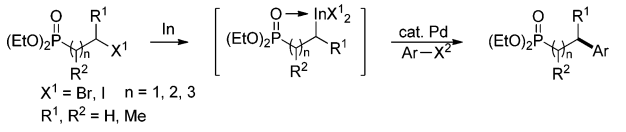
**Scheme 2. In Situ Preparation of Phosphoryl Alkylindiums and Their Synthetic Application to Arylalkyl Phosphonates**



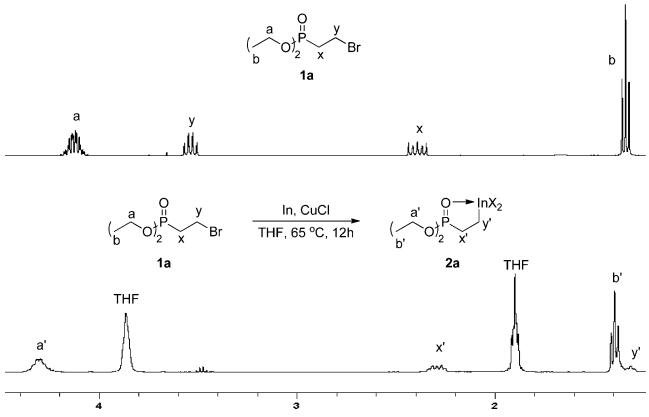
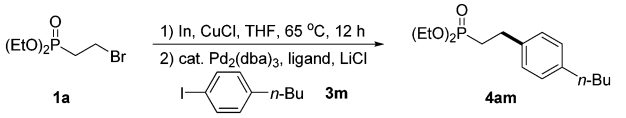




**Figure 1.** In situ generation of 2-phosphoryl indium reagents.

were not effective for the insertion (see the Supporting Information).[15]

Encouraged by this promising result, we investigated a Pd-catalyzed cross-coupling reaction of 2-phosphoryl indium **2a** with 4-iodobutylbenzene (**3m**) (Table 1). When $Pd_2(dba)_3$ and

**Table 1. Pd-Catalyzed Cross-Couplings Using 2-Phosphoryl Indiums**[a]

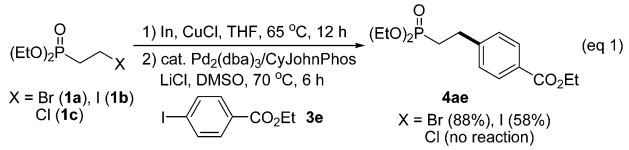



| entry | ligand | solvent | temp (°C) | time (h) | yield[b] (%) |
|---|---|---|---|---|---|
| 1 | $(4\text{-}CF_3C_6H_4)_3P$ | DMA | 80 | 2 | 12 (48) |
| 2 | $(4\text{-}CF_3C_6H_4)_3P$ | NMP | 80 | 5 | 21 (60) |
| 3 | $(4\text{-}CF_3C_6H_4)_3P$ | DMF | 80 | 5 | 13 (41) |
| 4 | $(4\text{-}CF_3C_6H_4)_3P$ | DMSO | 80 | 5 | 34 (38) |
| 5[c] | $(4\text{-}CF_3C_6H_4)_3P$ | DMSO | 70 | 3 | 15 (41) |
| 6[d] | $(4\text{-}CF_3C_6H_4)_3P$ | DMSO | 70 | 5 | N.R. |
| 7 | $(4\text{-}MeOC_6H_4)_3P$ | DMSO | 70 | 5 | 1 (76) |
| 8 | DPPP | DMSO | 70 | 5 | 2 (84) |
| 9 | DPPE | DMSO | 70 | 5 | N.R. |
| 10 | DPPF | DMSO | 70 | 5 | 7 (64) |
| 11 | DPEphos | DMSO | 70 | 1 | 14 (52) |
| 12 | Xantphos | DMSO | 70 | 6 | 6 (37) |
| 13 | $(C_6F_5)_3P$ | DMSO | 70 | 4 | 28 (42) |
| 14 | $(2\text{-furyl})_3P$ | DMSO | 70 | 2 | 14 (54) |
| 15 | CyJohnphos | DMSO | 70 | 6 | 76 (70)[e] |

[a]Indium reagent was prepared in situ from **1a** (0.5 mmol), In (1.0 mmol), and CuCl (1.0 mmol) in THF (1.5 mL) at 65 °C for 12 h. After removal of THF, indium reagent was treated with $Pd_2(dba)_3$ (5 mol %), CyJohnphos (20 mol %), LiCl (0.5 mmol), and **3m** (0.35 mmol, 1 equiv) in DMSO (1 mL). [b]NMR yield using mesitylene as an internal standard. Numbers in parentheses indicate yield of 4,4′-*n*-butyl-1,1′-biphenyl. [c]CuBr was used instead of CuCl. [d]CuI was used instead of CuCl. [e]Isolated yield.

$(4\text{-}CF_3C_6H_4)_3P$ in the presence of LiCl were used as catalyst, DMSO provided 2-(4-butylphenyl)phosphonate (**4am**) in 34% yield (entry 4, see the Supporting Information). DMA, NMP, and DMF are less effective (entries 1, 2, and 3). Among the copper salts examined, CuCl is superior to CuBr and CuI (entries 4−6). Next, a myriad of ligands such as $(4\text{-}MeOC_6H_4)_3P$, DPPP, DPPE, DPPF, DPEphos, Xantphos, $(C_6F_5)_3P$, and $(2\text{-furyl})_3P$ were screened, and thus, sterically bulky CyJohnphos gave the best result (76% yield) in DMSO at 70 °C for 6 h (entry 15).

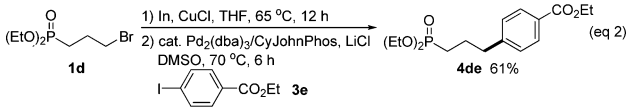
Next, 2-phosphoryl indium reagents derived from diethyl 2-haloethylphosphonates were employed in the coupling reaction with ethyl 4-iodobenzoate (**3e**) under the optimum reaction conditions (eq 1). Although diethyl 2-chloroethylphosphonate




(**1c**) was totally ineffective, the corresponding bromide and iodide gave the desired coupling product **4ae** in 88% and 58% yields, respectively.

Inspired by these results, a wide range of aryl iodides **3** were examined to demonstrate the scope and limitation of the coupling reaction using the 2-phosphoryl ethylindium reagents **2a** (Scheme 3). When iodobenzene and 1-iodonaphthalene were treated with 2-phosphoryl indium, the desired 2-aryl phosphonates **4aa** and **4ab** were obtained in good yields. Electronic variation of substituents at the arene moiety of aryl iodides had little effect on the reaction efficiency. It is noteworthy that electron-withdrawing groups such as ethoxycarbonyl, acetyl, formyl, nitrile, nitro, trifluoromethyl, and chloride are tolerable in the cross-coupling reaction, which makes the present method useful. Aryl iodides having electron-withdrawing ethoxycarbonyl groups at the *meta* and *para* position underwent the cross-coupling reaction in high yield. However, an *o*-ethoxycarbonyl substituent lowered the reactivity, probably due to steric reasons (**4ac**). Also, the cross-coupling reactions of 2-phosphoryl indium reagent **2a** with aryl iodides bearing an electron-donating methyl, butyl, and methoxy group proceeded smoothly to deliver the desired compounds in good yields ranging from 78% and 82%. An unmasked hydroxyl group was compatible with the present reaction conditions, affording the desired product **4ao** in 76% yield. 3-Iodoaniline was also converted to 2-(3-aminophenyl) phosphonate **4ap** without protection albeit in slightly low yield. 1,4-Diiodobenzene was effectively coupled with 2-phosphoryl indium reagent **2a** (3 equiv), producing diphosphate **4aq** in 66% yield.

Upon increasing the chain length between the bromide and the phosphoryl group, yields of the corresponding (4-(ethoxycarbonyl)phenyl)alkyl phosphonates **4de** and **4ee** were remarkably diminished (eqs 2 and 3). These results indicate




that the directing effect is induced by the phosphoryl group and are in contrast to the reactivity of homologues of ester-containing indium homoenolates.[15d]

Next, a variety of electrophilic coupling partners, including aryl and vinyl bromides and aryl triflate, were investigated (Table 2).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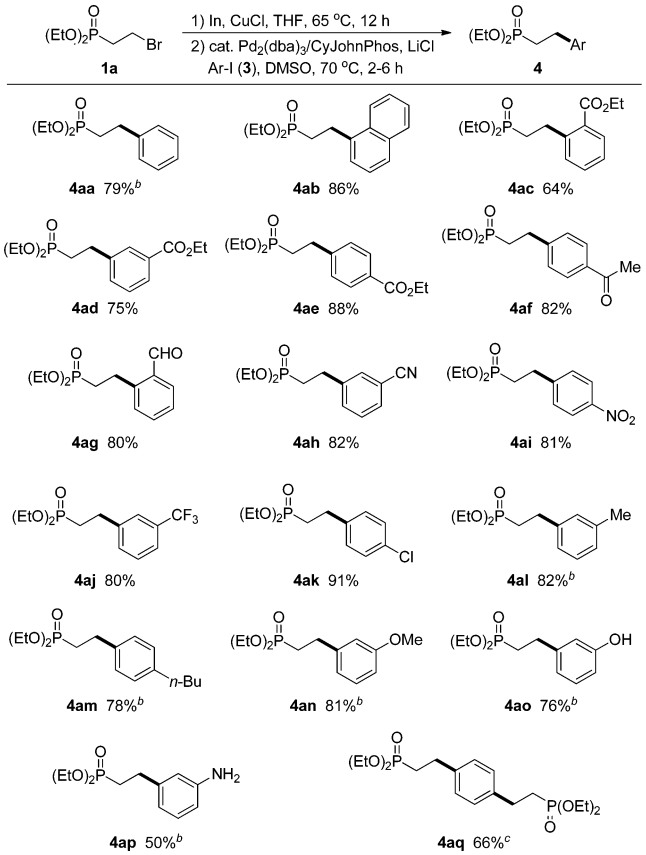
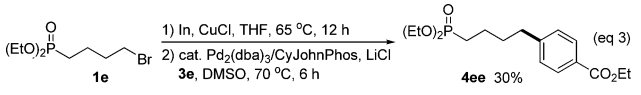
**Scheme 3. Pd-Catalyzed Cross-Couplings of 2-Phosphoryl Ethylindiums with Aryl Iodides[a]**

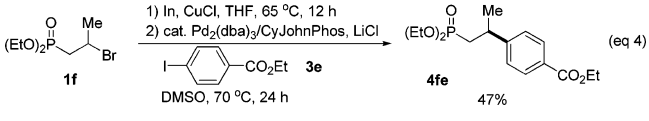



[a]Indium reagent was prepared in situ from **1a** (0.5 mmol), In (1.0 mmol), and CuCl (1.0 mmol), in THF (1.5 mL). [b]Indium reagent was prepared in situ from **1a** (0.7 mmol), In (1.4 mmol), and CuCl (1.4 mmol) in THF (3.0 mL). [c]**1a** (1.05 mmol), In (1.47 mmol), CuCl (1.47 mmol), and **3q** (0.35 mmol) were used.



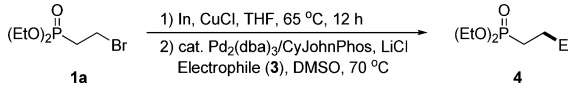

The coupling reaction of 2-phosphoryl indium with ethyl 4-bromobenzoate (**3r**) proceeded smoothly at 70 °C to produce **4ae** in 94% yield after 5 h. 4-Ethoxycarbonylphenyl trifluoromethanesulfonate (**3s**) was compatible with these reaction conditions (entry 3). α-Bromostyrene (**3t**) was readily converted to γ-phenyl phosphonate **4ar** in good yield (entry 4).

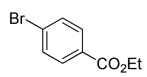
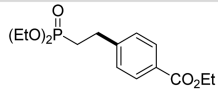
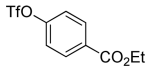
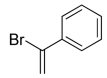
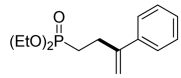
Because direct preparation of organoindium reagent from secondary alkyl bromide is generally difficult,[15b] the insertion reaction followed by coupling reaction is a current challenge. Reaction of ethyl 4-iodobenzoate (**3e**) with 2-phosphorylindium reagent derived from diethyl 2-bromopropyl phosphonate (**1f**) gave the desired product **4fe** in acceptable yield (eq 4). However, diethyl 2-bromo-2-methylethyl phosphonate (**1g**) is totally ineffective (eq 5).



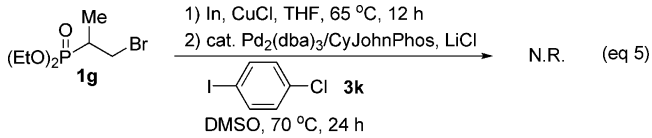

In summary, we have developed in situ preparation of phosphoryl alkylindiums from the direct insertion of indium with bromoalkyl phosphonates in the presence of CuCl. The Pd-catalyzed cross-coupling reaction of the phosphoryl alkylindium reagents with a number of aryl iodides, bromides, and triflates and vinyl bromide proceeded smoothly to provide the functionalized arylalkyl phosphonates in good to excellent yields. A wide range of functional groups, including ester, ketone, aldehyde, nitrile, nitro, trifluoromethyl, chloride, methoxy, hydroxy, and amino, are tolerable in the cross-coupling reactions. Upon increasing the chain length between the bromide and the phosphoryl group, the directing effect by the phosphoryl group is observed.

**Table 2. Pd-Catalyzed Cross-Couplings of 2-Phosphoryl Indiums with Aryl Bromide and Triflate and Alkenyl Bromide[a]**




| entry | electrophile (**3**) | product | time (h) | yield (%) |
|---|---|---|---|---|
| 1 |  |  | 22 | 63 |
| 2[b] | **3r** | **4ae** | 5 | 94 |
| 3 |  | **4ae** | 5 | 90 |
| | **3s** | | | |
| 4[b,c] |  |  | 5 | 62 |
| | **3t** | **4ar** | | |

[a]Indium reagent was prepared in situ from **1a** (0.5 mmol), In (1.0 mmol), and CuCl (1.0 mmol) in THF (1.5 mL). [b]Indium reagent was prepared in situ from **1a** (0.7 mmol), In (1.4 mmol), and CuCl (1.4 mmol) in THF (3.0 mL). [c]50 °C.




## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, characterization data, and $^{1}H$ and $^{13}C$ NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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