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Pd(II)-Catalyzed *ortho*-Arylation of Aryl Phosphates and Aryl Hydrogen Phosphates with Diaryliodonium Triflates

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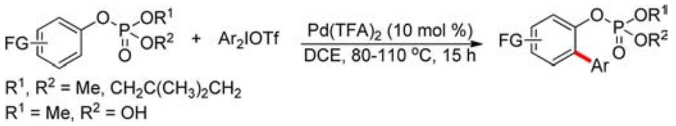
ABSTRACT



Functionalized biaryl compounds were successfully synthesized using phosphates as the *ortho*-directing group in the Pd(II)/Pd(IV) catalytic cycle.

Pd-catalyzed C–H activation reactions have attracted a great deal of attention and demonstrated their synthetic usefulness for *ortho* C–H functionalizations by not only C–C bond but also C–heteroatom bond formation.[1] Nitrogen-containing directing groups such as amides,[2] imines,[3] and *N*-heterocycles[4] are most commonly used. In recent years, C–H activation using carboxyl and hydroxyl directing groups has been extensively studied.[5,6]

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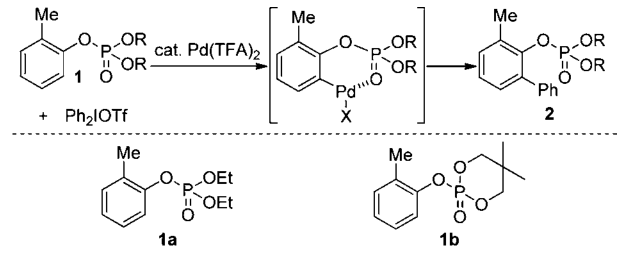
Scheme 1. Arylation of Organophosphates



Nonetheless, there is still a need to search for new efficient functional groups to direct *ortho*-selective C–H cleavage, which will make a considerable impact in synthetic applications. As such, our group has recently focused on utilizing organophosphates as the directing group in C–H activation reactions.[7]

Organophosphates are the main building block in DNA and RNA. They are also important constituents in many cofactors that are essential for life and biological activities, as well as the basis of many agrochemicals such as insecticides and herbicides. Moreover, they are very useful functional groups in organic synthesis,[8] given their numerous synthetic applications, especially in the area of cross-coupling.[9] Additionally, we have also been interested in the possibility of Pd insertion to the C—H bond via the chelation of a P=O bond with Pd(II) through weak coordination. By utilizing this property, we hope to synthesize biaryl compounds, well-known to be major moieties in natural products.

The common pathway for such C–C bond formations to produce biaryl compounds generally included the Pd(II)/Pd(0) catalytic cycle, and thus often required the presence of an oxidant to regenerate the catalyst.[1i] Recent studies using Ar_2IOTf or Ar_2IBF_4 suggested the use of iodonium salts as a great alternative for such reactions.[5f,10] In this case, the iodonium salt can serve as the arylating agent as well as the oxidant, whereby the reaction intermediate will then go through a Pd(II)/Pd(IV) catalytic pathway. Herein, we report the development of the organophosphates as the *ortho*-directing group for C–H activated arylation via Pd(II)/Pd(IV) catalysis (Scheme 1).

Table 1. Optimizing Reaction Conditions with **1a** and **1b**[a]

entry	substrate	base	temp (°C)	solvent	conv (%)[b]
1	**1a**	–	90	DCE	72 (52)[c]
2	**1a**	Li_2CO_3	90	DCE	0
3	**1a**	Cs_2CO_3	90	DCE	0
4	**1a**	K_3PO_4	90	DCE	0
5	**1a**	Na_2CO_3	90	DCE	88 (55)[c]
6	**1a**	Na_2CO_3	90	DCE	0[d]
7	**1a**	Na_2CO_3	90	dioxane	16
8	**1a**	Na_2CO_3	90	$PhCF_3$	0
9	**1a**	Na_2CO_3	90	DMF	0
10	**1a**	Na_2CO_3	90	xylene	0
11	**1b**	–	110	DCE	59 (57)[c]
12	**1b**	Na_2CO_3	110	DCE	61 (60)[c]
13	**1b**	Na_2CO_3	110	dioxane	14
14	**1b**	Na_2CO_3	110	toluene	16
15	**1b**	Na_2CO_3	110	^{t}BuOH	0

[a] Conditions: 0.15 mmol of **1**, 2 equiv of Ph_2IOTf, 10 mol % of $Pd(TFA)_2$, 1.5 equiv of base in 1 mL of solvent for 15 h. [b] Conversion of starting material **1**, based on crude NMR. [c] Isolated yield. [d] 20 mol % of DMSO was added.

We began our studies with diethyl *o*-tolyl phosphate (**1a**) as the substrate, which can be easily synthesized from commercially available *o*-cresol and diethyl chlorophosphate. As shown, when **1a** was reacted with Ph_2IOTf (2 equiv) using $Pd(TFA)_2$ (10 mol %) in 1,2-dichloroethane at 90 °C for 15 h, 72% of the starting material was reacted to give the phenylated product **2a** along with unidentified side products (Table 1, entry 1). As such, a low isolated yield of only 52% was obtained. In the presence of various bases such as Li_2CO_3, Cs_2CO_3, or K_3PO_4, the reaction did not occur (entries 2–4). The introduction of Na_2CO_3 (entry 5) not only increased the conversion to 88% but also greatly reduced the side reactions as studied in the crude NMR analysis. However, the isolated yield of **2a** gave only an unsatisfactory 55% yield. The addition of 20 mol % DMSO to stabilize the Pd catalyst also did not help (entry 6).[11] Changing the solvent to 1,4-dioxane, trifluorotoluene, DMF, or xylene only worsened the reaction (entries 7–10). We then proposed a more bulky phosphate **1b**, hoping that the substrate will be thermally more stable toward the reaction than the diethyl phosphate derivatives. Indeed, **1b** proved to be more stable with almost quantitative isolated yield for each reaction. Nonetheless, the reaction of **1b** was relatively slow with low conversion of the starting material even at 110 °C (entries 11–15). Further attempts to change $Pd(TFA)_2$ to $Pd(OTf)_2$, $PdCl_2$, and other Pd catalysts were also unsuccessful.

As further exemplified in Table 2, a few examples of *ortho*- or *meta*-alkyl substituted phosphates were

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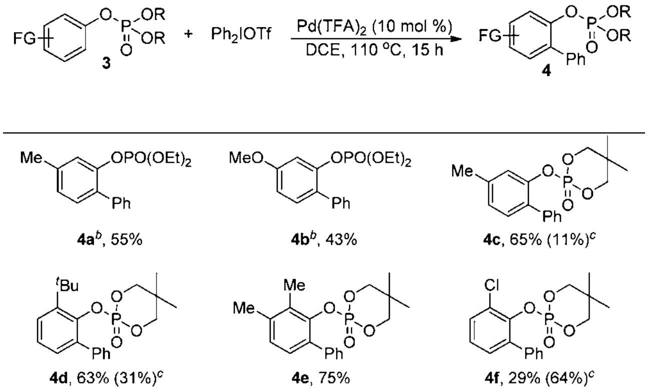
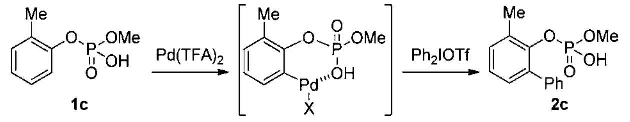
Table 2. Initial Studies of *ortho*-Arylation Using Organophosphates **3**[a]



[a] Conditions: 0.15 mmol of **3**, 2 equiv of Ph$_2$IOTf, 10 mol % of Pd(TFA)$_2$, in 1 mL of 1,2-dichloroethane at 110 °C for 15 h. [b] Reaction was carried out in 90 °C with 1.5 equiv of Na$_2$CO$_3$. [c] Recovery yield of starting material **3**.

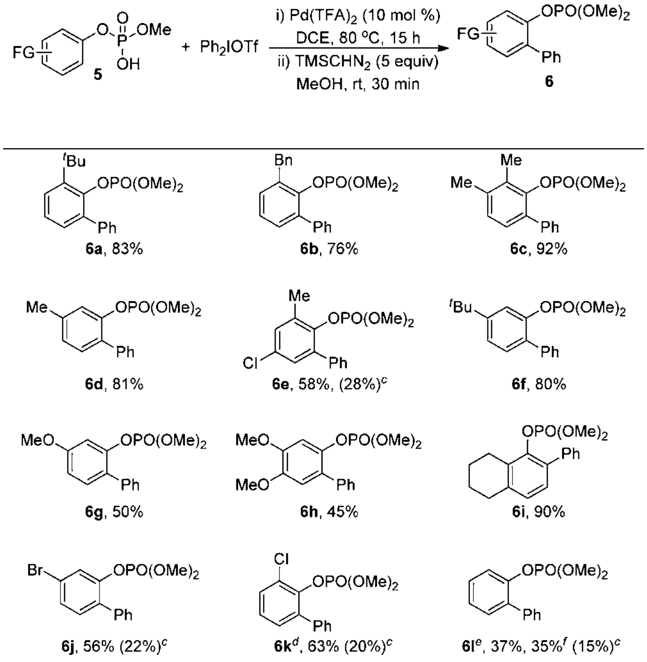
Table 3. Optimizing Reaction Conditions[a]



entry	base	temp (°C)	solvent	conv (%)[b]
1	Na$_2$CO$_3$	rt	DCE	messy
2	–	rt	DCE	27[c]
3	–	rt	DCE	54
4	–	80	DCE	95 (85)[d]
5	–	80	DME	50
6	–	80	dioxane	messy
7	–	110	DCE	messy

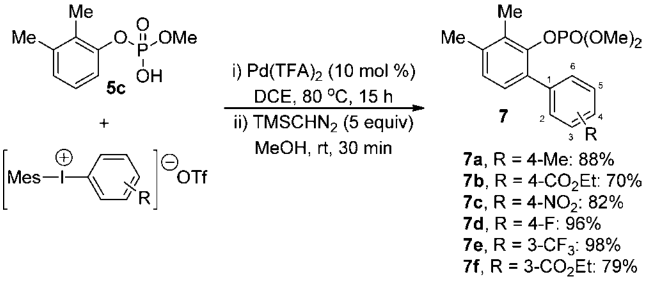
[a] Conditions: 0.15 mmol of **1**, 2 equiv of Ph$_2$IOTf, 10 mol % of Pd(TFA)$_2$, 1.5 equiv of base in 1 mL of solvent for 15 h. [b] Conversion of starting material **1c**, based on crude NMR. [c] 10 mol % of Pd(OAc)$_2$ was used instead. [d] Isolated yield after methylation with TMSCHN$_2$.

Table 4. Substrate Scope for *ortho*-Selective Arylation via a Monophosphoric Acid Directing Group[a,b]



[a] Conditions: (i) 0.15 mmol of **5**, 2 equiv of Ph$_2$IOTf, 10 mol % of Pd(TFA)$_2$, in 1 mL of 1,2-dichloroethane at 80 °C for 15 h. (ii) 5 equiv of TMSCHN$_2$ in 0.5 mL of MeOH at rt for 30 min. [b] Isolated yield is based on the yield over two steps. [c] Recovery yield of methylated starting material **5**. [d] Reaction was carried out at 110 °C. [e] 1.2 equiv of Ph$_2$IOTf was used instead. [f] Yield of diarylated product.

Scheme 2. Arylation of Monophosphoric Acid **5c** with Various Aryl Iodonium Salts



demonstrated (**3a**–**3f**), which reacted to give moderate yields of the phenylated products. The initial studies of *ortho*-arylation were not as satisfactory, as the reaction was slow with the recovery of a substantial amount of the starting material in nearly all cases. Nevertheless, these results strongly suggest the presence of the chelation of the P=O bond with a Pd(II)-catalyst which promotes *ortho*-arylation.

We next turned our attention to monophosphoric acid as the directing group for C–H activated alkenylation and started our studies using methyl *o*-tolyl hydrogen phosphate (**1c**) as a model compound. To our delight, the reactivity was increased significantly, as the reaction can proceed even at ambient temperature (entries 2, 3) as shown in Table 3. The presence of Na$_2$CO$_3$ was unnecessary (entry 1), and a more reactive Pd(TFA)$_2$ proved to be a better catalyst as compared to Pd(OAc)$_2$ (entries 2, 3). **1c** was shown to work best at 80 °C in 1,2-dichloroethane (entries 4–6) with high conversion (95%) and good isolated yield (85%). However, decomposition was observed when the reaction was carried out at 110 °C (entry 7).

Table 4 summarized the substrate scope for *ortho*-arylation under the standard optimized conditions. For facile purification, the crude arylated monophosphoric acids were first methylated using TMS-diazomethane to afford the respective methyl phosphate esters **6a**–**6l**. As seen, substrates **6a**–**6f**, bearing alkyl at the *ortho*- or *meta*-position, significantly facilitate arylation. For *meta*-substituted substrates, arylation occurred at the less hindered position as predicted. When the reaction was performed with alkoxyl substituents, substrates **6g** and **6h** were too reactive and gave low isolated yields. Although substrates **6e**, **6j**, and **6k** with electron-withdrawing halogens are tolerant toward the standard conditions, the reaction rate is relatively slower. The selectivity for unsubstituted **6l** was not well-controlled as well.

Even so, the reaction can be further expanded by introducing a diverse range of functionalized aryl derivatives just by varying the iodonium salts. As shown in Scheme 2, **5c** reacted cleanly with a list of [Mes–I–Ar]OTf iodonium salts to furnish the desired products **7a**–**7f** in high yields.[5f,10] Various functional groups such as ester, fluoride, and amide are also compatible. The regioselectivity is noteworthy especially for aryl iodonium salts that contained a *para*- or *meta*-substituent.

In conclusion, we have developed simple yet efficient reaction conditions for introducing different functionalized aryl groups at the *ortho*-position via the use of monophosphoric acid as the directing group.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.