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Palladium-Catalyzed C−H Arylation Using Phosphoramidate as a Directing Group at Room Temperature

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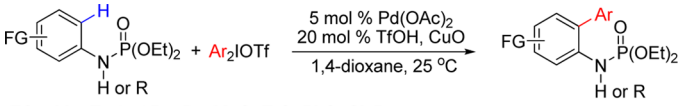
ABSTRACT



This communication describes the first phosphoramidate directing group for synthetically useful arylation. Remarkably, the nature of a new directing group drives selective C−H bond activation to afford diverse *N*-aryl phosphoramidates in good to excellent yields at room temperature.

The development of methods for new C−C and C−heteroatom bond formation is a critical challenge in organic chemistry, and in this regard, a C−H bond activation reaction represents one of the most promising approaches over the past few years.[1] In order for a C−H bond activation reaction to be of a general synthetic nature, the desired C−H bond in an organic molecule must be selectively activated over all the C−H bonds present in the molecule. Especially in benzene derivatives, because there is a slight difference in reactivity between the C−H bonds, a system to control regioselectivity is highly necessary. To overcome uncontrolled site selectivity, a number of examples of C−C and C−heteroatom bond forming reactions have been reported through introduction of a directing group in recent years. The most widely used directing groups in Pd(II)-catalyzed C−H activation

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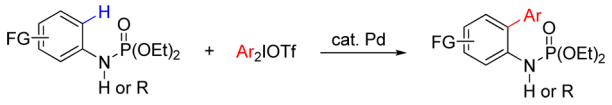
reactions utilize carboxylic derivatives[2−6] along with *N*-heterocycles[7] and aniline derivatives.[8] Although use of a directing group has become a practical strategy for allowing selective functionalization, the development of new practical directing groups is still a significant issue in the field of straightforward reactions.

Because the carbon species and their phosphorus counterparts have analogous characters regarding reactivity and biological activity,[9] we imagined that functionalization of *N*-aryl phosphoramidates *via* C−H bond activation would be an advantage over other methods. In addition, *N*-aryl phosphoramidates are among the most prominent synthetic derivatives due to versatile functionalities for further transformations.[10] Despite this interest in phosphoramidates, synthetic methods for *N*-aryl phosphoramidate derivatives are still limited.[11] A strategy using *N*-aryl phosphoramidates as a directing group for C−H bond activation, therefore, represents a relevant example for efficient synthesis of functional molecules which could be transformed into useful building blocks as well. As far as we know, *N*-aryl phosphoramidates have not been used in the transition-metal-catalyzed C−H activation reactions.[12]

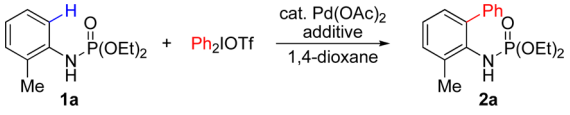
Recently, Pd-catalyzed arylation of aryl phosphates olefination of aryl hydrogen phosphates were reported.[13] Herein, we disclose the first protocol for the Pd(II)-catalyzed C−H arylation[14] of *N*-aryl phosphoramidates using di(aryl)-iodonium triflate (Ar_2IOTf) as an aryl reagent (Scheme 1).

Scheme 1. Pd-Catalyzed C−H Arylation Using Phosphoramidates



We initiated the study by examining the reaction between *N*-tolyl phosphoramidate **1a** and Ph_2IOTf in 1,4- dioxane at 60 °C (Table 1). The reaction was first carried out in the absence of additives which did not yield any desired product **2a** (Table 1, entry 1). Unfortunately, the arylation of **1a** did not proceed under both basic and solely acidic conditions, and **1a** remained quantitatively (entries 2−4). To trigger the reaction, we extensively tested various additives which are known to positively influence Pd-catalyzed C−H activation reactions (see the Supporting Information). However Ag_2CO_3 and $Cu(OAc)_2$ proved to be incompatible with the reaction conditions (entries 5 and 6). Gratifyingly, we observed that arylation of *N*-aryl phosphoramidate proceeded in the presence of catalytic amounts of both TfOH and Cu_2O (3 equiv), giving the arylated product **2a** in 25% yield in 1,4-dioxane at 60 °C after 16 h (entry 7). After surveying various copper salts to enhance the catalytic turnover, we found that CuO showed the highest efficiency (78%) compared with other salts (entry 9). The best result was obtained by using the catalyst $Pd(OAc)_2$ (5 mol %), TfOH (20 mol %), and CuO (3 equiv) in 1,4-dioxane at room temperature after 3 h,

Table 1. Optimization of the Pd-Catalyzed C−H Arylation[a]



entry	additive	temp (°C)	yield (%)
1	–	60	<1
2	NaOAc	60	<1
3	AcOH	60	<1
4	TfOH	60	<1
5	TfOH, Ag_2CO_3	60	<1
6	TfOH, $Cu(OAc)_2$	60	<1
7	TfOH, Cu_2O	60	25
8	TfOH, CuO	100	71
9	TfOH, CuO	60	78
10	TfOH, CuO	25	84[b]
11	TfOH, CuO	25	<1[c]

[a] Conditions: **1a** (0.3 mmol), 5 mol % $Pd(OAc)_2$, Ph_2IOTf (1.2 equiv), NaOAc, AcOH and TfOH (20 mol % each), Ag_2CO_3, $Cu(OAc)_2$, Cu_2O and CuO (3 equiv each), and 1,4-dioxane (1.2 mL), 16 h. [b] 3 h. [c] Reaction was carried out without $Pd(OAc)_2$ catalyst.

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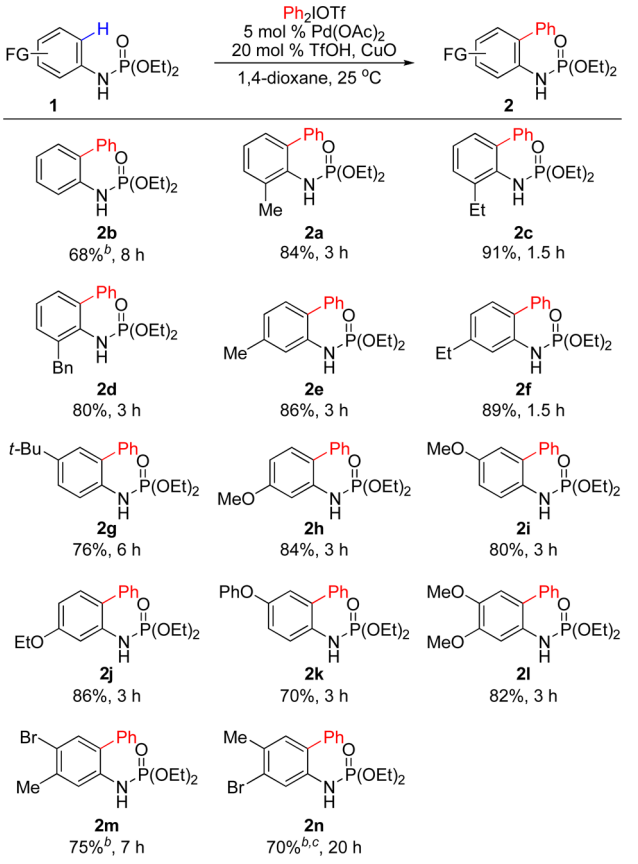
Scheme 2. Arylation of *N*-Aryl Phosphoramidates[a]



[a] Conditions: **1** (0.3 mmol), 5 mol % $Pd(OAc)_2$, Ph_2IOTf (1.2 equiv), 20 mol % TfOH, CuO (3 equiv), and 1,4-dioxane (1.2 mL). [b] 10 mol % $Pd(OAc)_2$ was used. [c] Reaction was carried out at 60 °C.

which gave rise to **2a** in 84% yield (entry 10). Notably, the arylation of phosphoramidates revealed that the reaction carried out at room temperature vs high temperatures provided a slightly higher yield (entries 8−10). A control reaction in the absence of the palladium catalyst was carried out with each reagent including the CuO additive and did not yield any arylated product (entry 11). When we complementarily examined iodobenzene and phenylboronic acid as aryl reagents, they provided none of the C−H activated product. In addition, diethyl phosphoramidate gave the best result among methyl, isopropyl, and cyclic phosphoramidates (see the Supporting Information).

As summarized in Scheme 2, various substrates were applied to the standard conditions to determine the scope and limitations of the present methodology. Arylation of electron-neutral substrate **1b** afforded the desired monophenylated product **2b** selectively. Phosphoramidate **1c** having an *ortho* ethyl group was converted to the corresponding C−H phenylated compound **2c** in 91% yield at room temperature. In the substrate containing a benzylic C−H bond site, this condition was selective for

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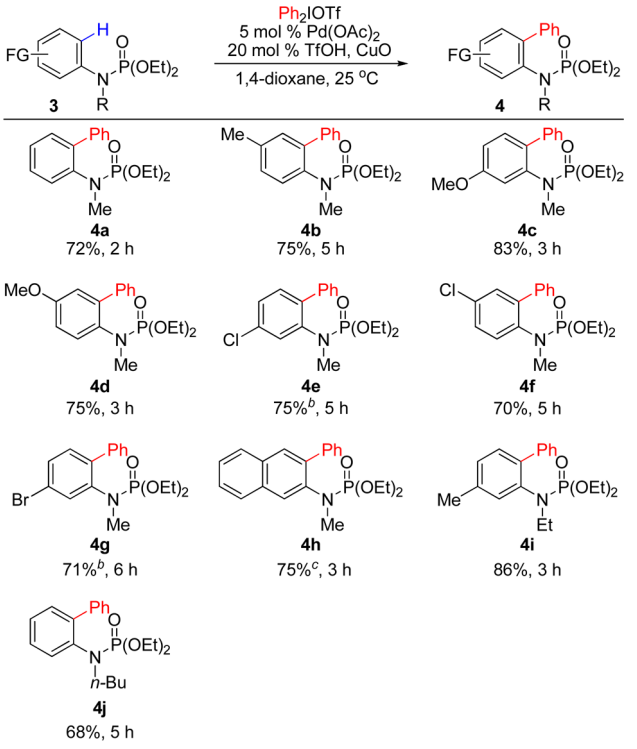
Scheme 3. Arylation of *N*-Alkyl-*N*-aryl Phosphoramidates[a]

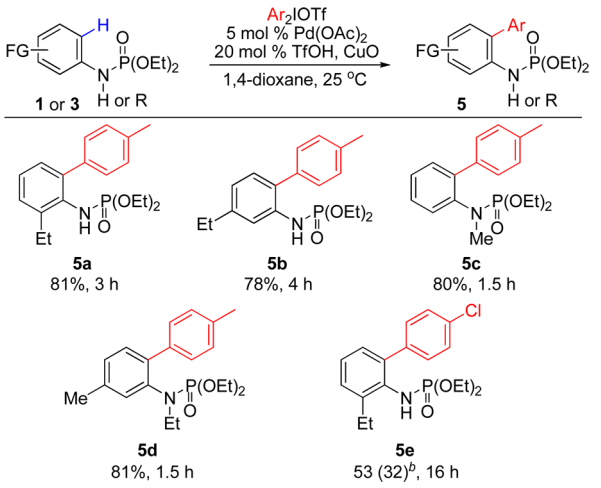


[a] Conditions: **3** (0.3 mmol), 5 mol % $Pd(OAc)_2$, Ph_2IOTf (1.2 equiv), 20 mol % TfOH, CuO (3 equiv), and 1,4-dioxane (1.2 mL). [b] 10 mol % $Pd(OAc)_2$ was used. [c] Reaction was carried out at 60 °C.

functionalization on the aromatic ring, which provided **2d** in 80% yield. The arylation of phosphoramidates (**1e** and **1f**) having an electron-donating methyl or ethyl group on the *meta* position of phenyl ring proceeded smoothly to give their corresponding products (**2e** and **2f**) in 86% and 89% yields, respectively. The 4-*tert*-butyl substituted substrate (**1g**) underwent monophenylation, which produced **2g** in 76% yield. Similar results were obtained for methoxy and ethoxy substituted arenes (**2h, 2i**, and **2j**). Moreover, subjecting the *meta* and *para* dimethoxy-substituted *N*-aryl phosphoramidate **1l** to the Pd catalyst afforded the desired C−H phenylated product **2l** in 82% yield. However, phenoxy-substituted substrate **1k** was less reactive and the phenylated product **2k** was isolated in 70% yield. The tolerance of the bromo group is especially useful due to further functionalization.

With these results in hand, we obtained Pd-catalyzed product **4a** selectively, indicating that a *N*-alkyl-*N*-aryl phosphoramidate was a good substrate for selective C−H bond functionalization (Scheme 3). Likewise, phosphoramidate **3b** having a *para* methyl group proceeded smoothly to give rise to the corresponding C−H phenylated compound **4b** in 75% yield. The phosphoramidates (**3c** and **3d**) with a methoxy group on the *meta* and *para* position of the phenyl ring furnished **4c** (83%) and **4d** (75%). *N*-Aryl-*N*-methyl phosphoramidates with a chloride or bromide group on the phenyl ring also afforded the desired products (**4e**, **4f**, and **4g**) in good yields. The halide

Scheme 4. Arylation of *N*-Aryl Phosphoramidate with Ar_2-IOTf[a]



[a] Conditions: **1** or **3** (0.3 mmol), 5 mol % $Pd(OAc)_2$, Ar_2IOTf (1.2 equiv), 20 mol % TfOH, CuO (3 equiv), and 1,4-dioxane (1.2 mL). [b] Recovery yield of starting material.

functionality affords a handle to introduce other groups on the phenyl ring *via* coupling reactions. The naphthalene-based substrate (**3h**) gave corresponding product **4h** in 75% yield without any difficulties as well albeit at 60 °C. Similarly, *N*-ethyl-*N*-(3-methylphenyl) phosphoramidate (**3i**) worked well. *N*-Butyl-*N*-phenyl phosphoramidate (**3j**) was also an efficient substrate toward the Pd-catalyzed arylation. These results suggested that the present method could be applied in not only *N*-aryl- but also *N*-alkyl-*N*-aryl-phosphoramidates.

Next, we evaluated the reactivity of this transformation with a couple of hypervalent iodine coupling partners (Scheme 4). The Ar_2IOTf containing electron-donating methyl substituent was observed to be compatible with the Pd-catalyzed C−H arylation of *N*-aryl phosphoamidates. Under the optimum reaction conditions, treatment of phosphoramidate **1c** and **1f** having an *ortho* or *meta* ethyl group with di-(4-methylphenyl)iodonium triflate afforded the desired product **5a** and **5b** in 81% and 78% yields, respectively. In addition, *N*-alkyl-*N*-aryl phosphoramidates were good substrates for selective C−H arylation. Exposure of **3a** and **3i** to the Pd catalyst in the presence of di-(4-methylphenyl)iodonium triflate (1.2 equiv) gave rise to **5c** and **5d** in 80% and 81% yields, respectively.

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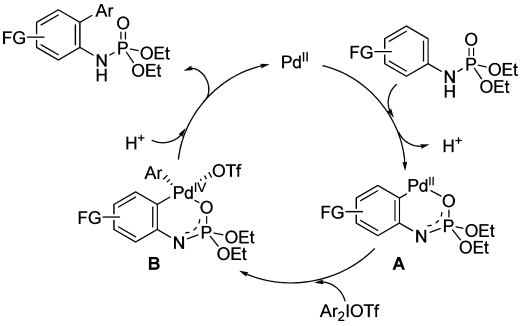
Scheme 5. A Plausible Mechanism



Remarkably, the chloride substituent was also well tolerated on the oxidant. Phosphoramidate **1c** was reacted with di-(4-chlorophenyl)iodonium triflate to provide **5e** in 53% yield together with the starting material (**1c**, 32%).

On the basis of the preliminary studies,[15] the mechanism of this catalysis is proposed as shown in Scheme 5. Coordination of *N*-aryl phosphoramidates to the Pd(II) catalyst and subsequent C−H activation form the six-membered palladacycle **A**. Then, the aryl Pd(II) intermediate (**A**) could be oxidized to the Pd(IV) species (**B**) by Ar_2IOTf. Although the precise role of the copper salt still remains to be elucidated, it may be reasonable to postulate that CuO plays a constructive role as a base for generation of intermediate **A**. It tentatively supports this possible pathway for which a stoichiometric amount of CuO is required to achieve full conversion; using 20 mol % of CuO gave only 22% desired product **2a** (see Supporting Information).

In summary, we have developed a novel protocol to effect C−H arylation that takes place at room temperature using synthetically useful *N*-aryl phosphoramidates as a new directing group with di(aryl)iodium triflate (Ar_2IOTf) for the first time. The present method also could be applied for *N*-alkyl-*N*-aryl phosphoramidates. A stoichiometric amount of CuO was crucial for efficient Pd(II) catalysis for the arylation of phosphoramidates.

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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.