Published in final edited form as:

Chem Commun (Camb). 2017 April 20; 53(33): 4609–4611. doi:10.1039/c7cc02063e.

Palladium-Catalyzed, Aminoquinoline-Directed Arylation of Phosphonamidate and Phosphinic Amide sp^3 C-H Bonds

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Abstract

Aminoquinoline-directed, palladium-catalyzed sp^3 C-H bond arylation in phosphonamidates and phosphinic amides is reported. The reaction employs $\text{Pd}(\text{OAc})_2$ catalyst at 10 mol % loading and cesium phosphate or potassium carbonate base in 1,2-dichlorobenzene solvent. Directing group can be removed under basic conditions to afford phosphonic acid esters. The chemistry described here is the first example of unactivated sp^3 C-H bond arylation by using a phosphorus-containing directing group.

Directed functionalization of sp^3 carbon-hydrogen bonds has been extensively investigated in last years.¹ While many carboxamides are capable of facilitating C-H functionalization, the use of phosphorus-containing directing groups is rare.² Nearly all of these examples involve functionalization of sp^2 C-H bonds. Rhodium and palladium-catalyzed couplings of phosphonic acid and phosphinamide derivatives with alkenes and alkynes have been disclosed.^{2a–g} Several examples of inter- and intramolecular arene arylation by employing phosphorus-containing directing groups have been reported.^{2g–n} Intramolecular, cobalt porphyrin-catalyzed amination of benzylic and alkane C-H bonds^{3a} as well as palladium-catalyzed intramolecular oxygenation of benzylic C-H bonds have been disclosed.^{3b} Notably, there are no examples of unactivated sp^3 C-H bond arylation by using phosphorus-containing directing groups.

Phosphorus-containing compounds are crucial components of pesticides and organocatalysts, and find use in materials chemistry.⁴ Consequently, we decided to investigate C-H bond functionalization of phosphinamides possessing an aminoquinoline directing group. We have reported a method for cobalt-catalyzed, aminoquinoline-directed coupling of phosphinic amide sp^2 C-H bonds with alkynes, alkenes, and allyl pivalate (Scheme 1).^{5a} Since palladium-catalyzed arylation of aminoquinoline amide sp^3 C-H bonds is well-established,^{5b–e} similar arylations of aminoquinoline phosphinamides should be feasible. We report here a method for palladium-catalyzed arylation of aminoquinoline phosphinamides with aryl iodides.

The reaction optimization was carried out by taking into account previous aminoquinoline-directed, palladium acetate-catalyzed C-H bond arylations (Table 1).^{5a–d} Phosphonamidate

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Electronic Supplementary Information (ESI) available: Detailed experimental procedures and characterization data for new compounds. See DOI: 10.1039/x0xx00000x

1 did not react with *p*-tolyl iodide in the absence of base or in the presence of AgOAc (entries 1 and 2). Use of cesium phosphate base, which was successful in previously reported arylations,^{5c,d} afforded 60% yield of product in 1,2-dichlorobenzene solvent (entry 4). Addition of cesium acetate increased the yield to 73% (entry 4). Other solvents, such as toluene, were inefficient (entry 5). Use of a more electrophilic palladium trifluoroacetate catalyst resulted in a lower yield (entry 6). Control experiment without palladium gave no product (entry 7). If one equivalent of aryl iodide was used, product was obtained in 36% yield (entry 8).

The reaction scope with respect to aryl iodides is presented in Table 2. Simple alkylsubstituted aryl iodides give products in good yields (entries 1 and 2). Electron-rich substituents such as methoxy (entry 4), *t*-butyldimethylsilyloxy (entry 5), and pivaloylamido (entry 7) are tolerated well and arylations occur efficiently. Electron-poor aryl iodides possessing *p*-chloro (entry 3), ester (entry 6), and 3,5-bis-trifluoromethyl substituents (entry 8) are reactive and afford products in acceptable to good yields. Heterocycle-containing aryl iodides are also compatible with the reaction conditions. Thus, five-membered ring heterocycles such as thiophene (entry 9) and *N*-tosylindole (entry 10) could be reacted with **1** to give the corresponding functionalized products. Six-membered ring heterocyclic iodides could be used as well (entry 11).

Reaction scope with respect to phosphoramidates and phosphinic amides is presented in Scheme 2. Benzyloxy and alkyne-containing substrates are arylated in acceptable to good yields (**4** and **6**). Phosphinic amide **7** was reactive, affording arylation product in 62% yield (**7** to **8**). Diethyl phosphinic amide **9** gave a mixture of mono- and diarylation products in 49 and 27% yields, respectively. Furthermore, alkenylation of sp^3 C–H bonds is possible as shown in Scheme 3. Thus, phosphoramidate **1** was reacted with an aryl-substituted vinyl iodide affording **12** in 47% yield. An aromatic bromide is compatible with the reaction conditions, and could be used for further functionalization of the product.

Directing group can be removed by a two-step procedure. Alkylation by methyl iodide followed by base hydrolysis gave phosphonic acid ester **14** in 54% overall yield. Phosphonic acids are carboxylic acid isosteres.⁶ New methods for phosphonic acid preparation could be useful for facilitating carboxylate analog design and synthesis.

In conclusion, we have shown that aminoquinoline can direct palladium-catalyzed unactivated sp^3 C–H bond arylation in phosphoramidates and phosphinic amides. The reaction employs Pd(OAc)₂ catalyst at 10 mol % loading, cesium phosphate or potassium carbonate base, and proceeds in 1,2-dichlorobenzene solvent. Removal of directing group affords phosphonic acid esters. These arylations are the first examples of transition-metal catalyzed unactivated sp^3 C–H bond functionalization by using a phosphorus-containing directing group. At this point, reaction is limited to arylation of primary C–H bonds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the Welch Foundation (Chair E-0044) and NIGMS (Grant No. R01GM077635) for supporting this research.

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Scheme 1.
Aminoquinoline Phosphinamide Functionalization

Scheme 2.
Phosphonamidate and Phosphinic Amide Arylation

Scheme 3.
Alkenylation of **1**

Scheme 4.
Directing Group Removal

Table 1

Optimization of arylation^a

entry	catalyst	base	yield of 2 , %
1	Pd(OAc) ₂	none	NR
2	Pd(OAc) ₂	AgOAc	NR
3	Pd(OAc) ₂	Cs ₃ PO ₄	60
4 ^b	Pd(OAc) ₂	Cs ₃ PO ₄	73
5 ^c	Pd(OAc) ₂	Cs ₃ PO ₄	45
6	Pd(OCOCF ₃) ₂	Cs ₃ PO ₄	10
7	none	Cs ₃ PO ₄	NR
8 ^d	Pd(OAc) ₂	Cs ₃ PO ₄	36

^a Amide **1** (0.1 mmol), 4-iodotoluene (0.3 mmol), catalyst (0.01 mmol), base (0.3 mmol), 1,2-dichlorobenzene (0.5 mL). Yields were determined by ¹H NMR of reaction mixture, 1,1,2-trichloroethane as internal standard.

^b Cesium acetate (0.05 mmol) added.

^c Toluene solvent. Q = 8-quinoliny.

^d One equiv ArI used.

Table 2

Reaction Scope with Respect to Aryl Iodides^a

$ \begin{array}{c} \text{EtO} \quad \text{O} \\ \diagup \quad \diagdown \\ \text{P} \\ \\ \text{Me}-\text{CH}_2-\text{CH}_2-\text{N}-\text{Q} \\ \text{H} \\ \mathbf{1} \end{array} \xrightarrow[\substack{\text{ArI, CsOAc} \\ \text{1,2-dichlorobenzene,} \\ \text{130 } ^\circ\text{C, 24 h}}]{\substack{\text{Pd(OAc)}_2 \text{ (10 mol\%)} \\ \text{Cs}_3\text{PO}_4 \text{ (3 equiv)}}} \begin{array}{c} \text{EtO} \quad \text{O} \\ \diagup \quad \diagdown \\ \text{P} \\ \\ \text{Ar}-\text{CH}_2-\text{CH}_2-\text{N}-\text{Q} \\ \text{H} \end{array} $			
entry	Ar	product	yield, %
1	4-MeC ₆ H ₄		71
2	3-MeC ₆ H ₄		63
3	4-ClC ₆ H ₄		54
4	4-MeOC ₆ H ₄		68
5	4-TBSOC ₆ H ₄		45
6 ^b	4-EtO ₂ CC ₆ H ₄		62
7	4- <i>t</i> BuCONHC ₆ H ₄		70
8	3,5-(CF ₃) ₂ C ₆ H ₃		58
9	2-thiophenyl		61

^aPhosphonamidate (0.5 mmol), Pd(OAc)₂ (0.05 mmol), Cs₃PO₄ (1.5 mmol), CsOAc (0.25 mmol), 1,2-dichlorobenzene (2.5 mL), 130 °C, 24 h. Yields are isolated yields. Please see Supporting Information for details.

^bNo CsOAc.