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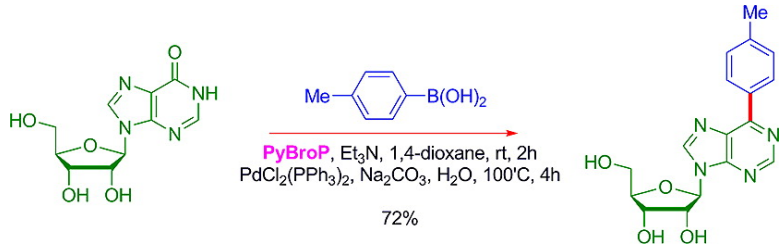

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Pd-Catalyzed Direct Arylation of Tautomerizable Heterocycles with Aryl Boronic Acids via C−OH Bond Activation Using Phosphonium Salts

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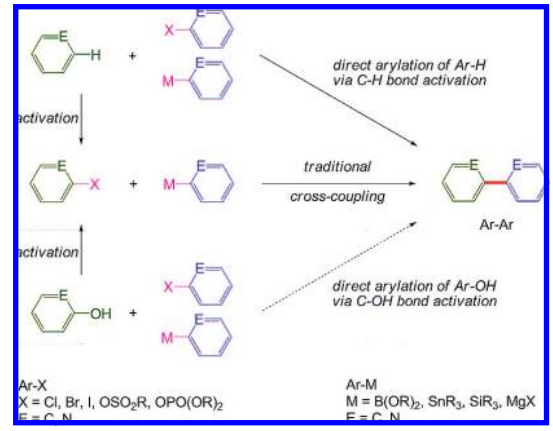
Biaryl compounds (Ar−Ar) have become increasingly important building blocks in materials and pharmaceuticals.[1] Transition-metal-catalyzed biaryl cross-coupling of arenes or heterocycles (Ar−H) have proven to be an exceedingly valuable process in contemporary organic synthesis developed in the past decades.[2] Traditional biaryl synthesis involves the coupling of activated Ar−H (Ar−X) and metalated Ar−H (Ar−M) (Scheme 1). Preparation of both coupling partners usually requires multisteps including protection of the sensitive functional groups in the substrates if necessary. This generates waste from reagents, solvents, and purifications. Direct arylation is a new type of cross-coupling between an *unactivated and unprotected* substrate and one of the traditional coupling partners (Ar−X or Ar−M). In recent years, direct arylation via C−H bond activation has emerged as an attractive alternative approach to traditional cross-coupling methods, and has led to a number of reactions that utilize directing groups, repulsive steric interactions, electron-rich substrates or C−H bond acidity, through the coupling of Ar−H with either Ar−X or Ar−M.[3]

Ar−H and Ar−OH are both synthetic precursors of Ar−X. Like Ar−H, Ar−OH is also widely available as arenols and tautomerizable heterocycles. Although direct arylation of Ar−H via C−H bond activation has enjoyed explosive growth in the past several years, direct arylation of Ar−OH via C−OH bond activation, either catalytically or stoichiometrically, has remained largely unknown.[4] An advantage of direct arylation of Ar−OH is that the C−OH bond activation and functionalization is regiospecific, while direct arylation of Ar−H via C−H bond activation and functionalization is known to suffer from overfunctionalization or regioselectivity issues.[5]

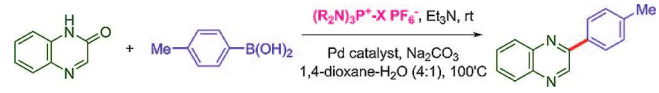
Phosphonium salts (PyBroP, PyBOP, BroP, BOP), uranium salts (TBTU, TATU) and carbodiimides (DCC, EDC) are well-known reagents for the coupling of carboxylic acids with amines to form amides and peptides. In 2004,[6] we first disclosed that, while uranium salts and carbodiimides were not effective, phosphonium salts showed excellent reactivity in the direct C−N, C−O, C−S, and C−C bond formations of tautomerizable heterocycles with various nucleophiles via the new phosphonium salt-mediated-tautomerization-activation-coupling process (phosphonium coupling). When considering the scope of this unprecedented, mild, efficient, and chemoselective phosphonium coupling as a new synthetic methodology,[7,8] we had predicted that these coupling conditions could be potentially applicable to other electron-deficient heterocyclic or aromatic systems.[6] Indeed, the utility and advantage of this new phosphonium coupling has been well demonstrated in recent rapidly growing applications along this line.[9] As part of our continued interest in this new phosphonium coupling methodology, herein we report the first Pd-catalyzed direct arylation via C−OH bond activation of tautomerizable heterocycles with aryl boronic acids using phosphonium salts.

The chemo-selective nature of the phosphonium salts that are bonded only to the acidic phenolic hydroxyl group in the electron-deficient tautomerizable heterocycles makes protection and deprotection of the sensitive functionalities in the substrates, such as the alcoholic hydroxyl group, unnecessary.[6] Synthesis without protecting groups is becoming

Scheme 1. Traditional Cross-Coupling versus Direct Arylation



Scheme 2. Pd-Catalyzed Direct Arylation via C−OH Bond Activation Using Phosphonium Salts



an attractive trend in modern synthetic organic chemistry.[10] We realized that this new phosphonium coupling was actually a combination of C−OH bond activation using a phosphonium salt and subsequent functionalization with a nucleophile in one step. We envisioned that under the Suzuki−Miyaura cross-coupling condition (Pd catalyst and aryl boronic acid), the resulting heterocycle-phosphonium salt might chemically behave like some of the known preactivated oxygen-containing cross-coupling partners, such as sulfonates[11] and phosphates.[12] This would undergo Pd-catalyzed direct arylation of the heterocycle with an aryl boronic acid to furnish the biaryl product with new C−C bond formation.

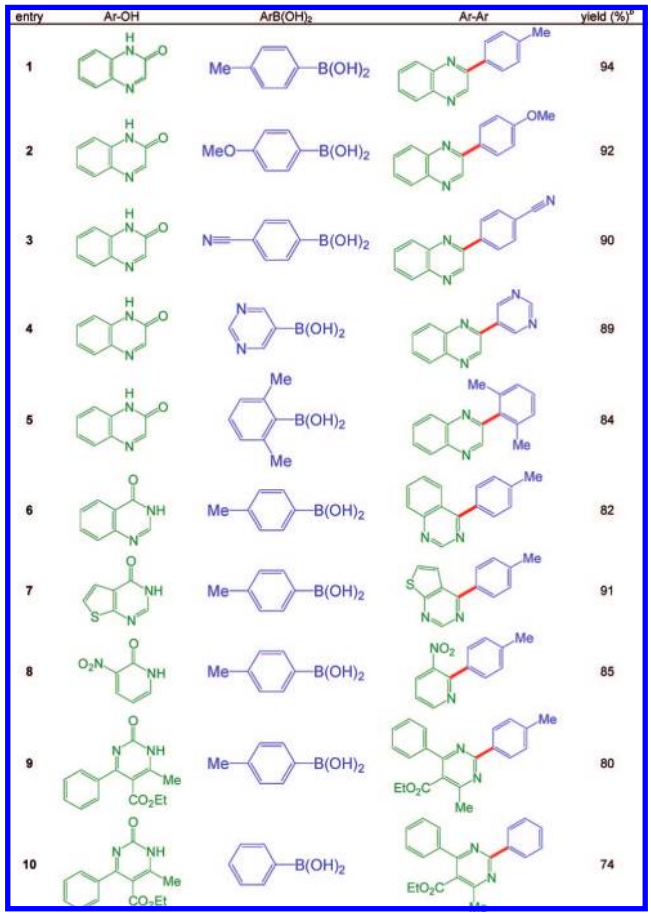
Table 1. Screening of Phosphonium Salts and Pd Catalysts[a]

Pd catalyst	phosphonium salt	yield (%)[b]
$Pd(PPh_3)_4$	PyBroP	82
$Pd(PPh_3)_4$	BroP	78
$Pd(PPh_3)_4$	PyBOP	26
$Pd(PPh_3)_4$	BOP	20
$Pd(OAc)_2$	PyBroP	35
$Pd(dppf)CH_2Cl_2$	PyBroP	42
$Pd(dba)CHCl_3$	PyBroP	trace
$PdCl_2(CH_3CN)_2$	PyBroP	11
$Pd(OAc)_2(PPh_3)_2$	PyBroP	79
$PdCl_2[P(o\text{-}Tol)_3]_2$	PyBroP	66
$PdCl_2(PPh_3)_2$	PyBroP	94

[a] Conditions: 2-quinoxalinone (0.5 mmol), phosphonium salt (1.2 equiv) and Et_3N (3 equiv) in 1,4-dioxane (4 mL) at room temp for 2 h; then, Pd catalyst (5 mol %), *p*-tolyl boronic acid (2 equiv), Na_2CO_3 (5 equiv) and water (1 mL) at 100 °C for 4 h. [b] Isolated yield.

10.1021/ja804804p CCC: $40.75

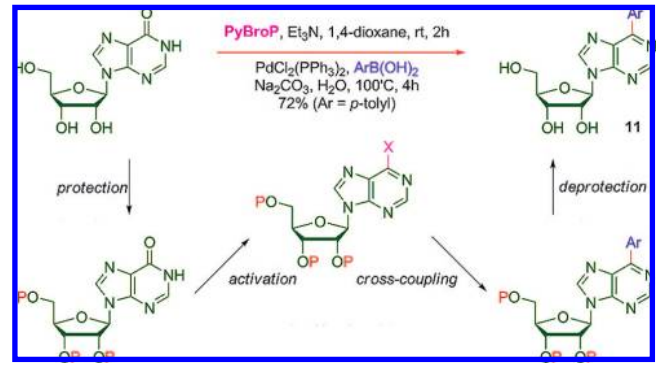
Table 2. Pd-Catalyzed Direct Arylation of Tautomerizable Heterocycles with Aryl Boronic Acids Using PyBroP[a]



[a] Conditions: Ar−OH (0.5 mmol), PyBroP (1.2 equiv) and Et_3N (3 equiv) in 1,4-dioxane (4 mL) at room temp for 2 h; then, $PdCl_2(PPh_3)_2$ (5 mol%), $ArB(OH)_2$ (2 equiv), Na_2CO_3 (5 equiv) and water (1 mL) at 100 °C for 4 h. [b] Isolated yield.

At the outset of the study, we investigated the direct arylation of 2-quinoxalinone with *p*-tolyl boronic acid by using a combination of two standard conditions: the phosphonium coupling condition[6] (PyBroP, Et_3N, 1,4-dioxane, room temp) and the Suzuki−Miyaura cross-coupling condition[2] ($Pd(PPh_3)_4$, Na_2CO_3, water, heating) (Scheme 2). A mixture of 2-quinoxalinone (0.5 mmol), PyBroP (1.2 equiv) and Et_3N (3 equiv) in 1,4-dioxane (4 mL) was stirred at room temp for 2 h. Then, $Pd(PPh_3)_4$ (5 mol%), *p*-tolyl boronic acid (2 equiv), Na_2CO_3 (5 equiv), and water (1 mL) were added, and the mixture was stirred in a sealed tube at 100 °C for 4 h. To our delight, the direct arylation proceeded successfully to produce the biaryl product in 82% yield (Table 1). For comparison purposes, other common phosphonium salts (PyBOP, BroP, and BOP) were also tested for the direct arylation reaction. As shown in Table 1, it was found that the Br-derived reagents (PyBroP and BroP) were far more effective than the OBt-derived reagents (PyBOP and BOP), probably because the latter simultaneously produced the heterocycle-OBt ether as the side product[6,8] that virtually shut down the cross-coupling reaction. With PyBroP as the best reagent of choice for the direct arylation, we then tried to improve the reaction condition by screening a variety of Pd catalysts. We soon found out that $PdCl_2(PPh_3)_2$ was the best catalyst that led to the biaryl product in 94% yield. As for the base involved in the direct arylation, it was observed that carbonates (Na, K, and Cs) were more effective than other bases such as DIPEA, DBU, DABCO, DMAP, CsF, NaOAc, K_3PO_4, NaOH, and NaOBu^t. In addition, the direct arylation appeared

Scheme 3. Multistep versus Single-Step Synthesis of 6-Arylpurine Ribonucleosides



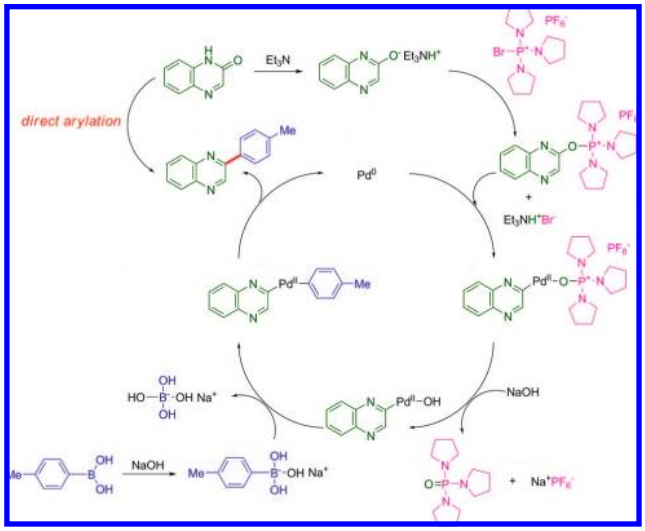
to be sluggish in the absence of water, and replacement of water with alkyl alcohols such as MeOH, EtOH, and *i*-PrOH resulted in slower reactions as well as formation of the alkyloxy-heterocycle ethers as side products.

With the optimized direct arylation conditions available, we embarked on an investigation of the reaction scope. A variety of tautomerizable heterocycles were examined for the Pd-catalyzed direct arylation via C−OH bond activation using PyBroP (Table 2). The Pd-catalyzed phosphonium coupling condition proved to be general for the direct arylation of these tautomerizable heterocycles with *p*-tolyl boronic acid. Complete conversion, and good to excellent isolated yields were observed for all the heterocycles employed.[13] Both electron-rich and electron-poor aryl boronic acids coupled well with the heterocycle-phosphonium salt to afford the biaryl products in excellent yields. Direct arylation using heteroaryl and sterically hindered aryl boronic acids also efficiently furnished the biaryl products in high yields. It should be pointed out that the cross-coupling of the heterocycle-phosphonium salts behaved in contrast to the cross-coupling of aryl phosphates, which was known to be severely impeded by both electronic and steric effects of the aryl boronic acids.[12]

One of the important applications to showcase such a mild, efficient, and chemo-selective direct arylation via C−OH bond activation is the cross-coupling of the purine ribonucleosides with aryl boronic acids to synthesize the biologically important 6-arylpurine ribonucleosides, which were known to display significant cytostatic and anti-HCV effects.[14] It generally takes four steps to prepare the 6-arylpurine nucleosides, including protection, activation (halogenation or sulfonylation), cross-coupling, and deprotection (Scheme 3). The preparation of these ribonucleosides has attracted considerable synthetic attention in recent years.[15] By using the Pd-catalyzed phosphonium coupling, the synthesis of the 6-arylpurine ribonucleoside can now be efficiently achieved in a single step in 72% yield from *unactivated and unprotected* inosine and an aryl boronic acid.

On the basis of the modified Suzuki−Miyaura catalytic cycle,[16] we propose the possible mechanism of the Pd-catalyzed direct arylation of 2-quinoxalinone that is shown in Scheme 4. It most likely proceeds through the following seven domino steps: (1) tautomerization of 2-quinoxalinone to 2-quinoxalinol in the presence of Et_3N; (2) activation of 2-quinoxalinol with PyBroP generating the heterocycle-phosphonium salt; (3) oxidative insertion of Pd(0) catalyst to the C−O bond of the heterocycle-phosphonium salt forming the heterocycle-Pd(II)−phosphonium species; (4) reaction with a base (e.g., NaOH) producing the heterocycle-Pd(II)−OH species; (5) activation of the aryl boronic acid with the base affording the aryl boron-ate complex; (6) transmetalation of the heterocycle-Pd(II)−OH species with the aryl boron-ate complex giving the heterocycle-Pd(II)−aryl species; and (7) reductive elimination of the biaryl product and regeneration of the Pd(0) catalyst.

Scheme 4. Possible Mechanism of the Pd-Catalyzed Direct Arylation via C−OH Bond Activation Using PyBroP



In conclusion, we have developed the first Pd-catalyzed direct arylation via C−OH bond activation of tautomerizable heterocycles with aryl boronic acids using phosphonium salts. The scope of the direct arylation has been shown to tolerate a variety of electron-deficient tautomerizable heterocycles and aryl boronic acids. The mechanism of the direct arylation is proposed to proceed via a domino seven-step process including the unprecedented heterocycle-Pd(II)−phosphonium species. Application of the Pd-catalyzed phosphonium coupling via C−OH bond activation leads to the most efficient synthesis of the biologically important 6-arylpurine ribonucleoside from *unactivated and unprotected* inosine in a single step. This direct arylation via C−OH bond activation using phosphonium salts could be potentially applicable to other transition-metal-catalyzed cross-coupling reactions, such as the Sonogashira and the Heck reactions, which will be reported in due course.

Acknowledgment. Dedicated to Professor William von E. Doering on the occasion of his 90th birthday. We thank Professor Daniel L. Comins for helpful discussions.

Supporting Information Available: Preparation of the biaryl ethers **9a** and **10a**, hydrogen−deuterium exchange experiment of **11**−**11a**, characterization data and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Interestingly, direct arylation of the multifunctionalized 2-pyrimidinone with aryl boronic acids produced the unexpected biaryl ethers (**9a** and **10a**) (C−O bond formation) as the minor side products along with the desired biaryl products (**9** and **10**). To confirm their structures, the identical biaryl ethers **9a** and **10a** were alternatively prepared via our previous phosphonium coupling for the direct C-O bond formation by using the corresponding phenols (see Supporting Information). The reason for the biaryl ether formation on this substrate was unclear, and neither C−C nor C−O bond formation was observed in the absence of PyBroP. For recent reviews on biaryl ether synthesis via Cu-mediated C−O bond formation using aryl boronic acids, see: (a) Ley, S. L.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (b) Frlan, R.; Kikelj, D. *Synthesis* **2006**, 2271.

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