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Oxidative Palladium Catalysis in S_NAr Reactions Leading to Heteroaryl Ethers from Pyridotriazol-1-yloxy Heterocycles with Aryl Boronic Acids

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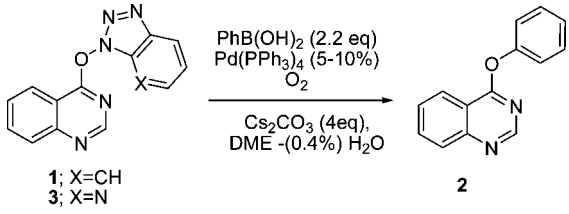
Palladium-catalyzed coupling reactions have proven to be valuable in aryl−aryl bond-forming reactions.[1−4] Our recent interest in synthetic applications of phosphonium and benzotriazol-1-yloxy (*O*Bt) heterocycles[5,6] as versatile electrophilic intermediates in S_NAr reactions prompted us to explore the latter in palladium-catalyzed coupling to form aryl−aryl products. This hypothesis seemed to be an attractive undertaking because certain phosphonium heterocycles[7] have recently been reported to undergo aryl−aryl coupling despite being less stable than their *O*Bt counterparts.[6]

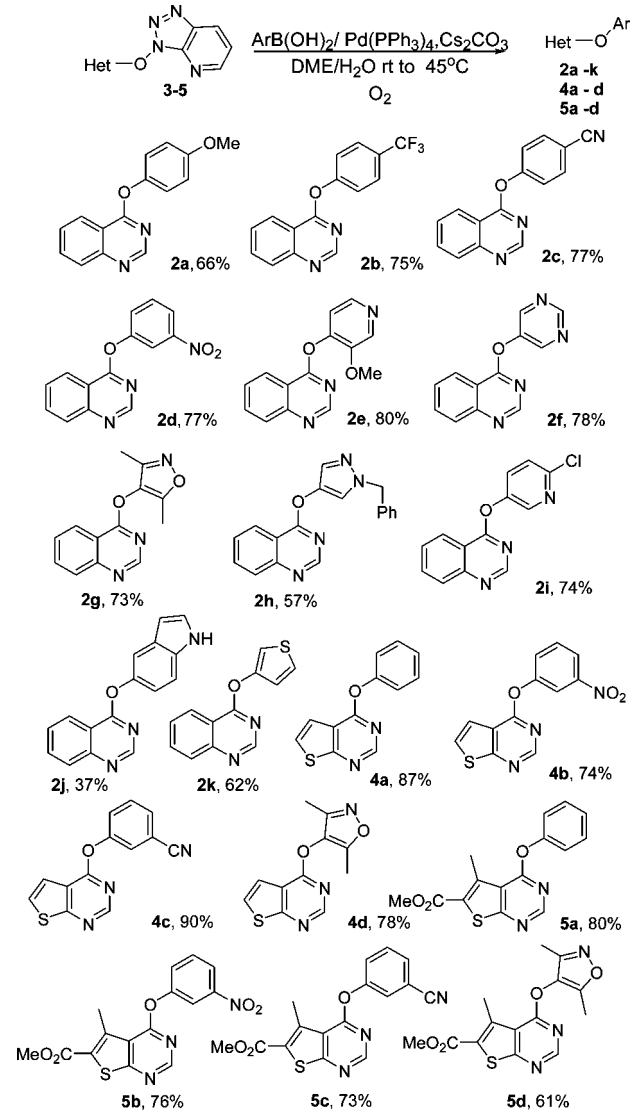
Initial extensive optimization was conducted on 4-(1*H*-benzo[*d*][1,2,3]triazol-1-yloxy)quinazoline (**1**) and phenylboronic acid by evaluating various metals, ligands, solvents, and bases. Unexpectedly, the 4-phenoxyquinazoline product **2** instead of 4-phenylquinazoline was formed with Pd-based catalysts such as $Pd(PPh_3)_4$ in DME (0.4−0.8% water content) under air or oxygen atmosphere (Scheme 1). After considerable experimentation and elimination of the undesired byproduct, improvement of yields (45 to 80%) was eventually accomplished by replacing the *O*Bt moiety in **1** with the more reactive *N*-hydroxypyridotriazole (*O*Pt) derived from the coupling of quinazolin-4-one with PyAOP.[8,9] Quinazolin-4-one itself was refractory to cross-coupling with aryl boronic acids under the reaction conditions, suggesting an alternative pathway to the copper-promoted Chan−Lam−Evans C−O coupling reaction.[10] Performing the reaction under inert atmosphere without oxygen or air suppressed the formation of heteroaryl ethers. Triphenylphosphine oxide was also produced in these oxygen- or air-mediated reactions.

Scheme 1. Cross-Coupling of **1** and **3** with Phenylboronic Acid



A number of structurally and electronically diverse aryl boronic acids were then evaluated (Table 1). While isolated yields of **2a**−**k** were generally high for both aryl and heteroaryl boronic acids, several 2-heteroaryl boronic acids, such as 2-furyl boronic acid, 2-thiophene boronic acid, their benzo derivatives, and 2-indole boronic acids were rather refractory to coupling with **3**. Boronic acids with both electron-withdrawing and -donating groups gave excellent isolated yields of the corresponding quinazolines. Heteroaryl boronic acids derived from π-deficient heterocycles proved to be efficient cross-coupling partners. Of interest is the chemoselectivity in 2-chloropyridine coupling to give **2i**, which occurs without any interference from the chloro moiety. Neither proximal substitution effects, as in the five-membered azoles **2g** and **2h**, nor the free NH moiety in indole **2j** posed any issue.

Table 1. Heteroaryl Ethers from Aryl Boronic Acids and O_2 with **3**



The competence of this new ether-forming reaction was further demonstrated in privileged heterocyclic systems such as the *O*Pt thienopyrimidines **4** and **5** with a representative set of boronic acids under oxidative Pd(0) catalysis (Table 1). The desired O-arylated heterocycles **4a**−**d** and **5a**−**d** were produced in excellent yields comparable to those for quinazolines. The impact of steric hindrance due to the peri effect in thienopyrimidine **5** proved to be

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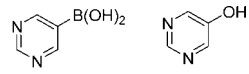
inconsequential in this case. Importantly, in each of these reactions, we did not detect any C−C or C−N coupling products by LC−MS techniques, while all of the boronic acid was consumed during the reaction.

Preliminary mechanistic studies regarding the origin of the ether oxygen and the possible intermediacy of phenols suggested complex reaction pathways. ESI/LC−MS techniques were employed to monitor the kinetics of disappearance of **3** and pyrimidine-5-boronic acid **6** and the appearance of ether **2f** and 5-hydroxypyrimidine **7**. The choice of **6** for mechanistic studies was specifically made on the basis of the ease of ionization and detection of both **6** and **7** by ESI techniques.



6 7

First, when dioxygen was replaced by $^{18}O_2$, the level of ^{18}O incorporation into **2f** and **7** after 21 h amounted to 42 and 32%, respectively, with 55% total conversion to **2f** (Table 2). To investigate the formation of ^{16}O in **2f** and **7**, the reaction was conducted with dioxygen and $H_2{}^{18}O$. In this case, no ^{18}O incorporation was detected in either **2f** or **7** (Table 2), suggesting that $^{18}O_2$

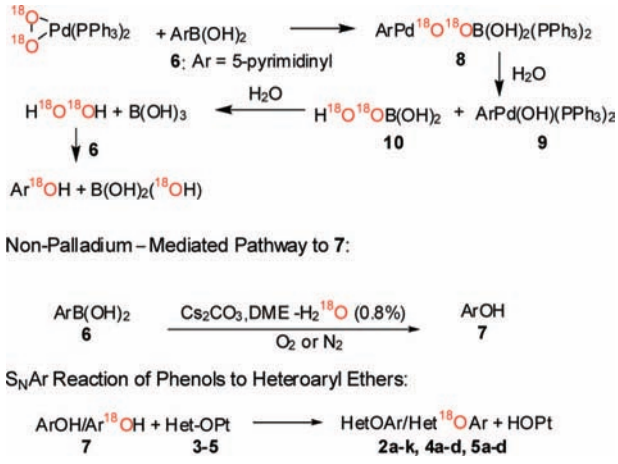
Table 2. $^{18}O/^{16}O$ Ratios in **7** and **2f** at Various Reaction Times

cmpd	conditions[a]	1 min	1 h	2.5 h	21 h
7	$^{18}O_2$, H_2O	6:94	12:88	17:83	32:68
2f	$^{18}O_2$, H_2O	1<:99	12:88	25:75	42:58
7	O_2, $H_2{}^{18}O$	0:100	0:100	0:100	0:100
2f	O_2, $H_2{}^{18}O$	Trace	0:100	0:100	0:100

[a] **6** (2.2 equiv), 15% $Pd(PPh_3)_4$, DME, Cs_2CO_3 (4 equiv).

is partially the source of oxygen in **2f**. Second, performing the reaction without **3** under the standard conditions in DME/$H_2{}^{18}O$ (0.8%) confirmed the disappearance of boronic acid **6** and the formation of unlabeled **7** (83%, 20 h). Pyrimidine **7** was also detected (39%, 20 h) in the absence of **3** and $Pd(PPh_3)_4$. Unexpectedly, **7** was also formed (32%, 20 h) from **6** when dioxygen was replaced by nitrogen in DME/$H_2{}^{18}O$ (0.8%). These experiments suggest that an alternative non-palladium-mediated pathway competes with the oxidative pathway to produce **7** (Scheme 2).

Scheme 2. Proposed Mechanistic Oxidative Pathway to **7**



It is therefore proposed[11] that $ArPd^{18}O^{18}OB(OH)_2(PPh_3)_2$ (**8**, Ar = 5-pyrimidinyl), formed from **6** and (η^2-$^{18}O_2$)$Pd(PPh_3)_2$,[11−15] is a plausible intermediate that upon hydrolysis produces $ArPd(OH)(PPh_3)_2$ (**9**) and $H^{18}O^{18}OB(OH)_2$ (**10**).[11] Further hydrolysis of **10** affords $H_2{}^{18}O_2$, which then reacts with **6** to generate $Ar^{18}OH$[15] (Scheme 2).

We therefore conclude that the oxygen ether in these compounds is derived from two sources: an oxidative pathway (H_2O_2 via O_2) catalyzed by palladium and a non-palladium-mediated reaction involving Cs_2CO_3 (Scheme 2). In these transformations, the *O*Pt heterocycles **3**−**5** serve as efficient trapping agents of phenols generated in situ in an S_NAr fashion.[5b,6]

In summary, a new method based on a three-component reaction for the C−O coupling of pyrido- and benzotriazol-1-yloxyquinazolines and -thienopyrimidines with aryl boronic acids and molecular oxygen for the preparation of heteroaryl ethers has been described. The scope of this Pd-catalyzed S_NAr reaction is broad, particularly when phenols are not readily available or are unstable (Table 1, entries **2e**, **2g**, **2h**, **2k**, **4d**, and **5d**). Additionally, this method avoids the lack of N- versus O-chemoselectivity observed in palladium-catalyzed O-arylation of heterocyclic amides.[16] Expansion to other heterocycles is under investigation. The results demonstrate excellent O-chemoselective control[16] under mild conditions and have important fundamental and practical implications in broadening the scope and versatility of palladium-mediated coupling reactions.

Acknowledgment. This work is dedicated in memory of Hassan Elokdah, Ronald Magolda, and John Morin.

Supporting Information Available: Experimental details and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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