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SHORT COMMUNICATION

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General Suzuki Coupling of Heteroaryl Bromides by using Tri-*tert*-butylphosphine as a Supporting Ligand

Yinjun Zou,[a] Guizhou Yue,[b] Jianwei Xu,[c] and Jianrong (Steve) Zhou*[a]

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A general procedure for the fast Suzuki coupling of major families of heteroaryl bromides was realized by using $Pd(OAc)_2$/P*t*Bu_3 as the catalyst. Many couplings were finished within minutes at room temperature in *n*-butanol. Different from previous studies, three typical heteroaryl bromides were systematically examined in couplings of various heteroaryl and aryl boronic acids.

Introduction

The coupling of heteroaryl groups is indispensable in today's synthesis of medicines and advanced materials.[1] For this purpose, Suzuki coupling is routinely used to forge these $C(sp^2)$–$C(sp^2)$ single bonds.[2] For instance, Suzuki coupling has been employed in the large-scale synthesis of the Sartan family of antihypertensive drugs and the agrochemical Boscalid.[3] Organoboronic acids and esters are bench-top-stable, and the byproducts after reactions are nontoxic. Furthermore, many functionalized organoboron reagents now can be easily accessed through metal-catalyzed borylation of arenes[4] and aryl halides.[5]

In the past decade, many efforts have been devoted to the Suzuki coupling of challenging substrates such as heteroaryl chlorides,[6] tosylates, and mesylates.[7] Couplings of heteroaryl bromides, in comparison, are considered to be easier, and thus, they are actually more frequently used in synthesis. For example, Suzuki couplings of pyridyl,[8] thienyl,[9] and indolyl bromides[10] were used to prepare medicinally active entities. In other applications, oligo- and polythiophenes are frequently used in organic conducting materials and in photovoltaic cells.[11] In reality, each new set of coupling partners requires optimization of the palladium catalysts. A general Pd-catalyzed Suzuki coupling for heteroaryl bromides has been lacking.[12]

[a] Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University
21 Nanyang Link, Singapore 637371
E-mail: jrzhou@ntu.edu.sg
http://www.spms.ntu.edu.sg/cbc/FacultyResearch/Individual%20Faculty/SZhou.html
[b] College of Basic Sciences, Sichuan Agricultural University
Ya'an, Sichuan, China 625014
[c] Institute of Materials Research and Engineering, Agency for Science, Technology and Research
3 Research Link, Singapore 117602

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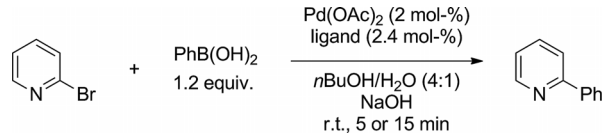
Results and Discussion

Initially, we chose 2-bromopyridine and phenylboronic acid as substrates to search for highly active catalysts. Arylpyridines are often used in drug discovery. Under many reported conditions, the model coupling was very slow, <10% yield after 1 h at room temperature. After extensive research, we found that $Pd(OAc)_2$ and P*t*Bu_3 formed an exceptionally active catalyst. Almost quantitative yield was observed after 5 min (Table 1, Entry 1). Furthermore, a 0.1 mol-% loading of a Pd catalyst can still give 95% yield after 5 min. The air-stable P*t*Bu_3·HBF_4 salt has been used to release the free phosphine P*t*Bu_3 under basic conditions. Other ligands are less active. For example, $P(1\text{-Ad})_2Bu$ (Ad = adamantyl) gave 74% yield under similar conditions (Table 1, Entry 2). 2-(Dicyclohexylphosphino)-2′,4′,6′-triisopropylbiphenyl (XPhos) provided 33% yield after 15 min (Table 1, Entry 8). Free N-heterocyclic carbenes such as 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) and 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes) showed

Table 1. The effect of ligands and Pd complexes on model Suzuki coupling.



Entry	Ligand	5 min		15 min	
		Conv. [%]	Yield [%]	Conv. [%]	Yield [%]
1	P*t*Bu_3	100	98	100	99
2	$P(1\text{-Ad})_2Bu$	74	65	82	74
3	$P(1\text{-Ad})_2Bn$	15	6	29	17
4	PCy_3	14	4	18	9
5	PPh_3	9	5	14	9
6	P(*o*-Tol)$_3$	3	2	10	6
7	SPhos	12	3	16	6
8	XPhos	30	18	45	33

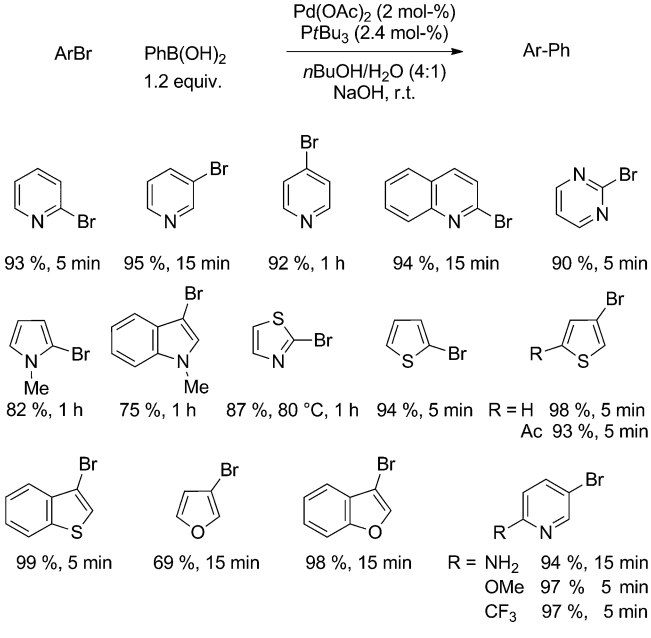
poor reactivity. 1,3-Bis(diphenylphosphino)propane (dppp), 1,1′-bis(diphenylphosphino)ferrocene (dppf), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos), and one of the Josiphos ligands gave <10% yield after 1 h (see the Supporting Information). $Pd(PtBu_3)_2$ was as active as $Pd(OAc)_2/PtBu_3$.

We found that strong bases of alkali hydroxides and *tert*-butoxides were very important for the fast coupling. In contrast, weaker bases of carbonates and acetates caused much slower coupling (see the Supporting Information). A high concentration of hydroxide anion is known to accelerate transmetalation through the intermediacy of palladium hydroxide complexes.[13]

The use of aqueous alcohols was a prerequisite for the fast coupling. For example, in pure MeOH, EtOH *n*BuOH, and *i*PrOH, the yields were only 30–66% after 5 min (see the Supporting Information). In comparison, if water was included as a minor cosolvent, almost full conversion was observed in 5 min in most solvents. Certainly, good solubility of the hydroxide base and $PhB(OH)_2$ in aqueous alcohols accelerated the transmetalation and contributed to fast overall coupling. Faster transmetalation can also lead to fast formation of active LPd^0 catalysts from $Pd(OAc)_2$ through double transmetalation and reductive elimination of biphenyl.[14] Biphenyl was detected in the reaction mixture after 1 min by GC.

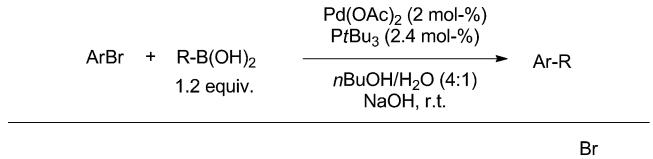
The new method can be applied to many families of heteroaryl bromides (Scheme 1). Most examples finished the reaction within a few minutes at room temperature. The only one exception was 2-bromothiazole, which needed heating at 80 °C. The observed fast couplings of many heterocycles confirmed the legitimacy of the model reaction in Table 1.

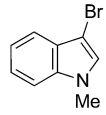
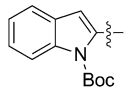
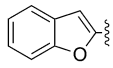
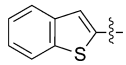
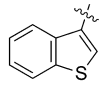
Next, we explored the coupling efficiency of various heteroaryl boronic acids, together with three model heteroaryl bromides of pyridine, thiophene, and indole (Table 2). Pyridine and indole are electron-poor and electron-rich azacycles, respectively, that are widely used in drug discovery. Many couplings of 2-bromopyridine and 2-bromothiophene proceeded smoothly in aqueous *n*-butanol. In other cases that did not give good yields, the use of *n*-butanol or dioxane solved the problem. Five-membered 2-heteroaryl boronic acids of furan, thiophene, pyrrole, and indole underwent either fast hydrolysis with water or protodeborylation. *N*-Methyl-3-bromoindole was deliberately chosen to test the reactivity boundary of a very electron-rich azacycle. These types of *N*-alkylindolyl halides without activation by electron-withdrawing groups have rarely been used in



Scheme 1. Fast couplings of heteroaryl bromides with $PhB(OH)_2$.

Table 2. Coupling of major families of heteroarylboronic acids.[a]



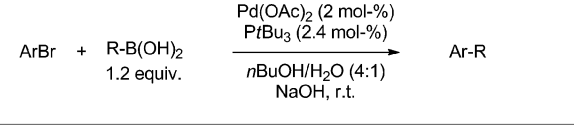
Entry	R-B(OH)$_2$			
1		95 % 6 h, 80 °C *n*BuOH	50 %, Pd (5 mol-%) 24 h, 100 °C CsOH, *t*BuOH	89 % 7 h, 100 °C $EtMe_2COH/H_2O$ (4:1)
2		95 % 2 h, 80 °C *n*BuOH	90 % 5 min, *n*BuOH	95 % 80 °C, 2 h *n*BuOH
3		96 % 2 h, 80 °C *n*BuOH	88 % 2 h, 50 °C dioxane	96 % 2 h, 50 °C dioxane
4		86 % 15 min, *n*BuOH	77 % 15 min, *n*BuOH	81 % 15 min, *n*BuOH
5		97 %, 15 min, *n*BuOH	91 % 5 min	83 % 1 h, *n*BuOH
6		92 % 1 h	97 % 5 min	85 % 6 h, 80 °C dioxane
7		81 % 5 min, *n*BuOH	92 % 5 min	96 % 10 h, 80 °C dioxane
8		92 % 5 min	96 % 5 min	66 % 10 h, 80 °C dioxane
9		95 % 5 min	95 % 5 min	70 % 1 h, *n*BuOH
10		94 % 15 min	93 % 5 min	95 % 8 h, dioxane

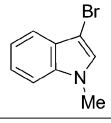
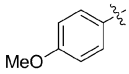
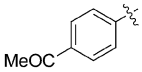
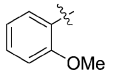
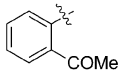
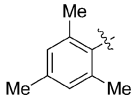
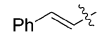
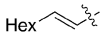
[a] Boc = *tert*-butoxycarbonyl.

Suzuki couplings.[15] Under standard conditions in aqueous *n*-butanol, the main side reactions were the hydrolysis of the aryl boronic acids and reduction of the C–Br bond. Logically, the use of dry *n*-butanol and dioxane solvents solved these problems in most cases. In the coupling with the 3-pyridylboron reagent,[16] 2-methylbutan-2-ol was used to minimize the reduction of the C–Br bond.

Similarly, couplings of the three heteroaryl bromides were conducted with various aryl- and alkenylboronic acids (Table 3). Most couplings were finished after a few minutes at room temperature. Electron-donating and electron-withdrawing groups could be present on the aryl rings. Again, *N*-methyl-3-bromoindole coupled very slowly, and in some examples, dioxane was used to prevent hydrolysis of the arylboronic acids. Couplings of 3-bromoindole carrying no electron-withdrawing groups were generally more difficult than couplings of the other two bromides. Hindered 2-mesitylboronic acid underwent efficient coupling if the base and solvent were changed.

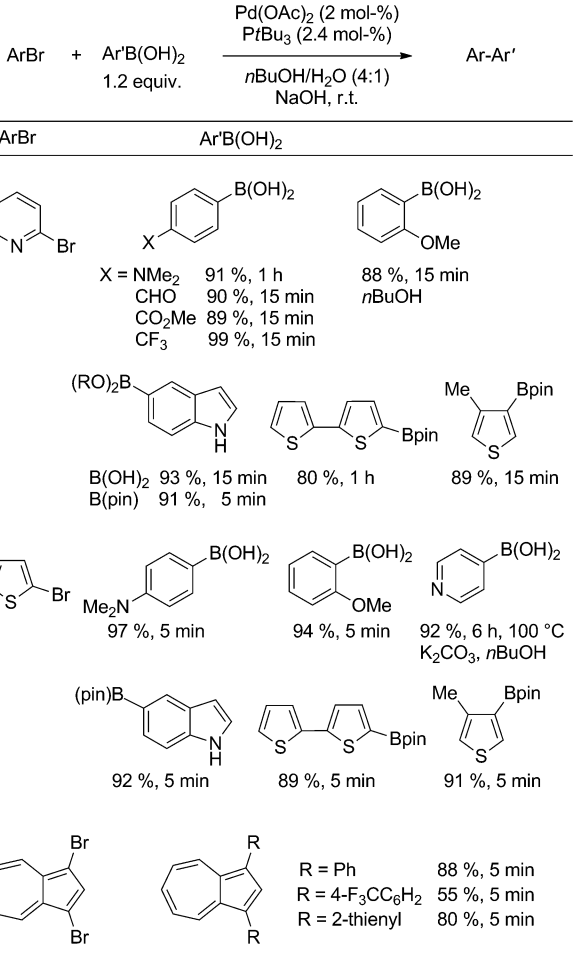
Table 3. Couplings of aryl- and vinylboronic acids.



Entry	R-B(OH)$_2$			
1		93 % 5 min	94 % 5 min	75 % 1 h
2		93 % 5 min	88 % 5 min	92 % 8 h, 80 °C dioxane
3		90 % 15 min	89 % 5 min	90 % 16 h, 80 °C dioxane
4		92 % 15 min, *n*BuOH	91 % 5 min	93 % 15 min
5		95 % 2 h, 80 °C dioxane/H$_2$O (4:1)	94 % 1 h	77 % 10 h, 80 °C dioxane
6		88 % 24 h, K$_3$PO$_4$ dioxane/H$_2$O (4:1)	82 % 1 h dioxane/H$_2$O (4:1)	93 %, Pd (5 mol-%) 100 °C, 6 h NaO*t*Bu, EtMe$_2$COH
7		91 % 5 min, *n*BuOH	87 % 5 min, *n*BuOH	91 % 1 h
8		95 % 5 min	95 % 5 min	83 % 15 min

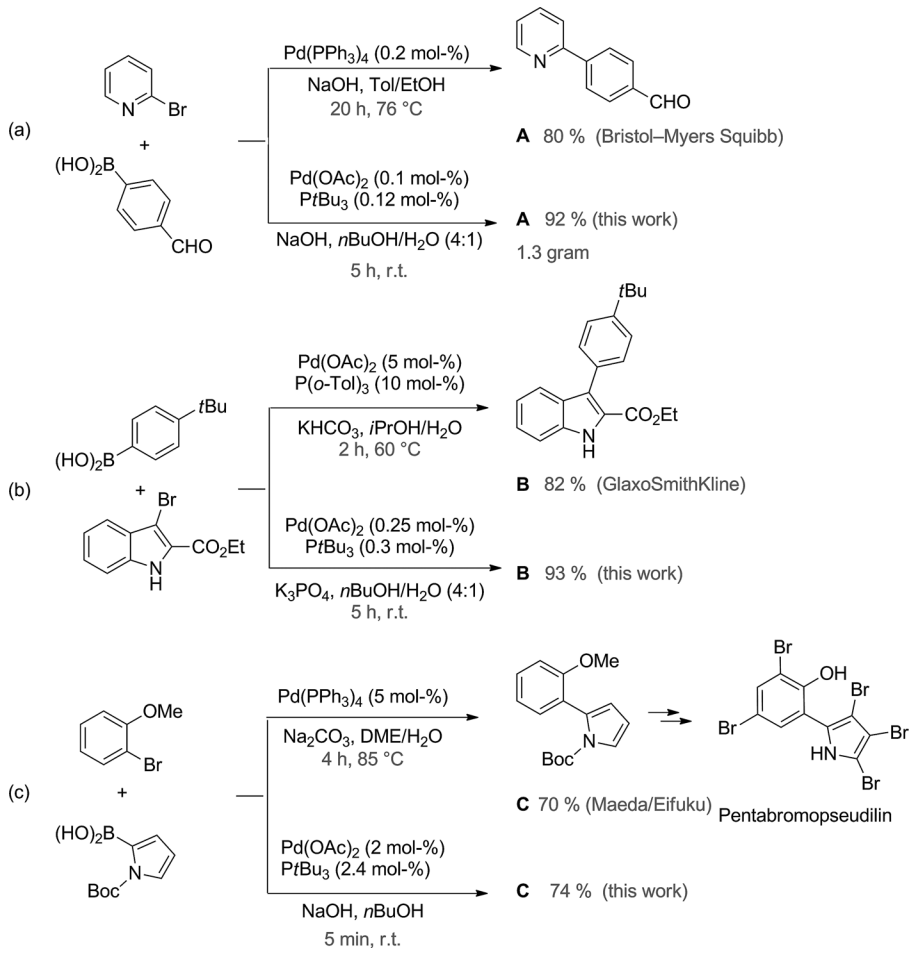
2-Bromopyridine and 2-bromothiophene coupled very efficiently with many other organoboronic acids (Table 4). Notably, some boron pinacolates of indole, thiophene, and dithiophene reacted well. Some 1,3-diarylazulenes were used as advanced materials.[17] Our method allowed efficient diarylation of 1,3-dibromoazulene. All products were formed within minutes at room temperature without further optimization of the conditions. The new method proved superior to existing procedures.[18] In one example, coupling of electron-poor *p*-$F_3CC_6H_4B(OH)_2$ led to 55% yield of the product, and the main byproduct was by monoarylation (ca. 30%).

Table 4. Additional examples of Suzuki couplings.



[a] pin = pinacolate.

Suzuki coupling has been used to prepare the biaryl motif in an HIV protease inhibitor. The reaction proceeded at 80 °C and required two loadings of $Pd(PPh_3)_4$ (Scheme 2a).[8a] In comparison, our method allowed the coupling to proceed at room temperature with a Pd loading of 0.1 mol-%. In a second comparison, a 3-arylindole derivative has been shown to enhance insulin sensitivity in the treatment of type-2 diabetes. It was previously synthesized through Suzuki coupling at 60 °C by using $Pd(OAc)_2$/P(*o*-Tol)$_3$ (Scheme 2b).[19] Under our conditions, the same coupling could be performed at room temperature with a Pd loading of 0.25 mol-%. The third example is pentabromopseudilin, a natural product with interesting antibiotic and antitumor activities.[20] In a report by Maeda and



Scheme 2. Applications of the new Suzuki method.

Eifuku, the $Pd(PPh_3)_4$ catalyst required heating at 85 °C (Scheme 2c).[21] Our procedure furnished the coupling product in 5 min.

Conclusions

We developed a general method for the Suzuki coupling of heteroaryl bromides by using one single catalyst formed from $Pd(OAc)_2$ and $PtBu_3$. In many cases, extremely fast couplings were observed at room temperature, which proved more effective than many existing procedures.[22]

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization of new compounds, and copies of the ^1H NMR and ^{13}C NMR spectra.

Acknowledgments

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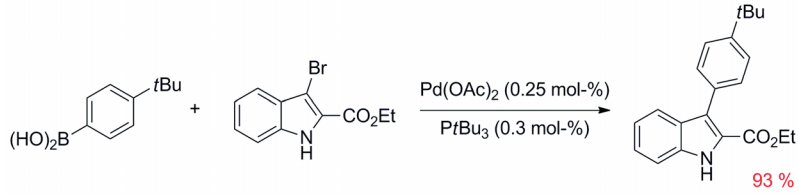
Suzuki Coupling



A fast, general coupling of heteroaryl bromides is realized by using a single palladium catalyst supported by tri-*tert*-butylphosphine.

Keywords: Cross-coupling / Palladium / Heterocycles / Transmetalation / Fused-ring systems

