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Suzuki–Miyaura Cross-Coupling of Heteroaryl Halides and Arylboronic Acids in Continuous Flow

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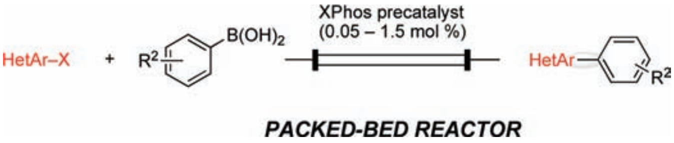
ABSTRACT



General continuous-flow conditions for the Suzuki–Miyaura cross-coupling of heteroaryl halides and (hetero)arylboronic acids have been developed. A wide range of heterobiaryl products is obtained in excellent yields (20 examples) employing low catalyst loadings (0.05–1.5 mol % Pd).

Heterobiaryl compounds are a prevalent structural motif in many pharmaceuticals and other biologically active molecules.[1] The palladium-catalyzed Suzuki–Miyaura cross-coupling reaction (SMC) is arguably the most versatile method to construct such C–C bonds,[2] since it facilitates the efficient coupling of (hetero)aryl halides and pseudohalides with (hetero)arylboronic acids. Recently, considerable attention has been focused on the development of continuous-flow versions of the SMC reaction.[3,4] Continuous-flow microreactors offer several advantages as compared to traditional batch reactors, such as enhanced heat and mass transfer, precise control over residence/reaction times, and the typically facile transition between laboratory and production scale processes in flow.[4,5] Despite a number of reports in this area, the use of heterocyclic coupling partners has been largely neglected.[3] This may be in part due to the fact that cross-coupling reactions with heteroaryl substrates have proven challenging as compared to the analogous couplings of simpler substrates and thus typically require the use of highly active catalyst systems.[6,7] Furthermore, it is known that five-membered 2-heteroarylboronic acids are prone to rapid decomposition *via* protodeboronation under aqueous

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basic conditions.[7a] Moreover, heterocyclic compounds are highly polar and thus poorly soluble in most organic solvents, which is a concern in microfluidic systems since significant amounts of precipitate are difficult to introduce in flow systems and can cause the reactor to clog. Given these potential challenges, particularly with regards to boronic acid stability, we felt that the rapid and efficient generation of the catalytically active $L_1Pd(0)$ species was crucial to the success of the SMC of heteroaryls in flow. To this end, Buchwald has reported the use of dialkylbiaryl monophosphine-ligated palladacycles **P1**–**4**, which can be quickly and efficiently activated in the presence of a base (Figure 1).[7,8] Herein, we report the development of general conditions for the continuous-flow SMC coupling of heteroaryl halides and pseudohalides with (hetero)arylboronic acids using these palladacycles at low catalyst loadings.

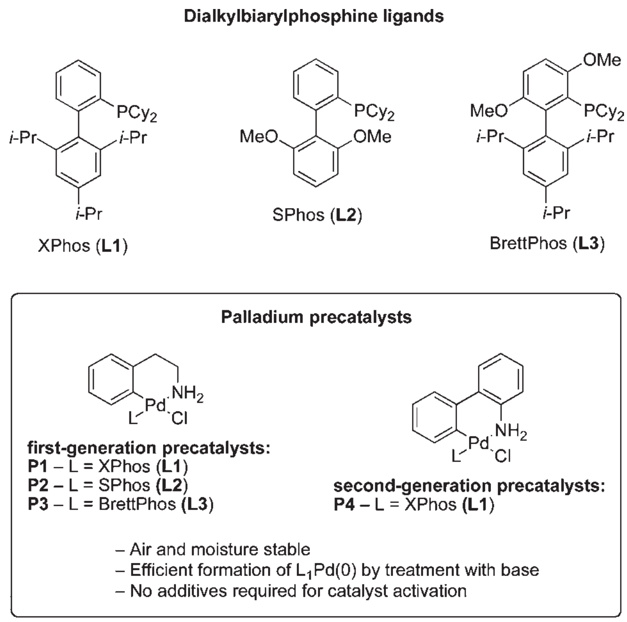
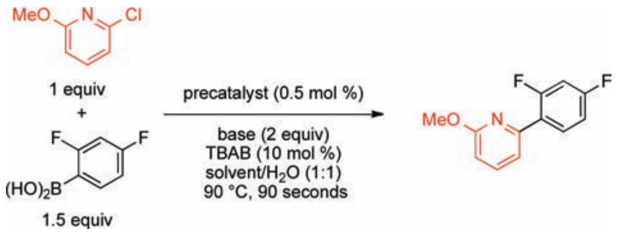


Figure 1. Dialkylbiarylphosphine ligands and palladium precatalysts used in this study.

We initiated our investigation by examining the reaction of 2-chloro-6-methoxypyridine with 2,4-difluorophenylboronic acid under batch conditions (Table 1). We anticipated that a biphasic solvent system, which ensures a complete dissolution of both inorganic and organic solids, would be highly preferable in a continuous-flow setting to avoid clogging. Using 0.5 mol % XPhos precatalyst **P1**, K_3PO_4 as a base, tetrabutylammonium bromide (TBAB) as a phase transfer catalyst in NMP/H_2O (1:1), and 2-chloro-6-methoxypyridine was successfully coupled with 2,4-difluorophenylboronic acid (Table 1, entry 1). When precatalysts **P2** and **P3** (with SPhos and BrettPhos as ligands) were employed, incomplete conversion was obtained after 90 s (Table 1, entries 2 and 3).[9] With second generation XPhos precatalyst **P4**, full conversion was also obtained in 90 s (Table 1, entry 1). We chose to use this second generation XPhos precatalyst (**P4**) because it is readily synthesized in a one-pot procedure from commercially available starting materials and can be easily activated with weak bases at room temperature.[7a] Further reaction optimization studies revealed that K_3PO_4 was optimal as compared to other weak bases (Table 1, entries 5 and 6). While the use of toluene, *t*-BuOH, and dioxane as solvents provided product in excellent yields, highly polar boronic acids were insoluble in these solvents, making it incompatible with continuous flow (Table 1, entries 7–9).

Table 1. Optimization of the Suzuki–Miyaura Reaction of 2-Chloro-6-methoxypyridine with 2,4-Difluorophenylboronic Acid in Batch[a]



entry	precatalyst	solvent	base	yield (GC)[b]
1	**P1**	NMP	K_3PO_4	98
2	**P2**	NMP	K_3PO_4	35
3	**P3**	NMP	K_3PO_4	0
4	**P4**	NMP	K_3PO_4	99
5	**P4**	NMP	Cs_2CO_3	43
6	**P4**	NMP	K_2CO_3	9
7	**P4**	toluene	K_3PO_4	98
8	**P4**	*t*-BuOH	K_3PO_4	99
9	**P4**	dioxane	K_3PO_4	99

[a] Reaction conditions: HetArCl (0.5 mmol), $ArB(OH)_2$ (0.75 mmol), precatalyst (0.5 mol %), solvent (1 mL), 4 M aq base solution (0.5 mL), 0.1 M aq TBAB (0.5 mL) at 90 °C for 90 s. [b] GC yield, using biphenyl as an internal standard.

With optimized batch conditions in hand, a microfluidic system was assembled as shown in Figure 2. A solution of

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heteroaryl halide, arylboronic acid, and XPhos precatalyst **P4** in NMP was combined with aqueous streams of TBAB and K_3PO_4, respectively. This biphasic mixture was subsequently introduced in a 400 μL packed-bed reactor (stainless steel spheres, 60−125 μm packing), which has been shown to improve the interfacial contact between the two immiscible phases.[8b] Upon exiting the packed-bed reactor, the reaction mixture was quenched with water and ethyl acetate (EtOAc). When NMP/H_2O (1:1) was used as the solvent system in continuous flow, we observed that, upon combining the organic stream and the water stream, arylboronic acid precipitated out of the solution, which caused instant clogging of the microreactor. However, by employing an NMP/toluene/H_2O (4:1:5) mixture, the organic phase was sufficiently apolar to decrease the solubility of H_2O in NMP and thus prevent precipitation of arylboronic acid.

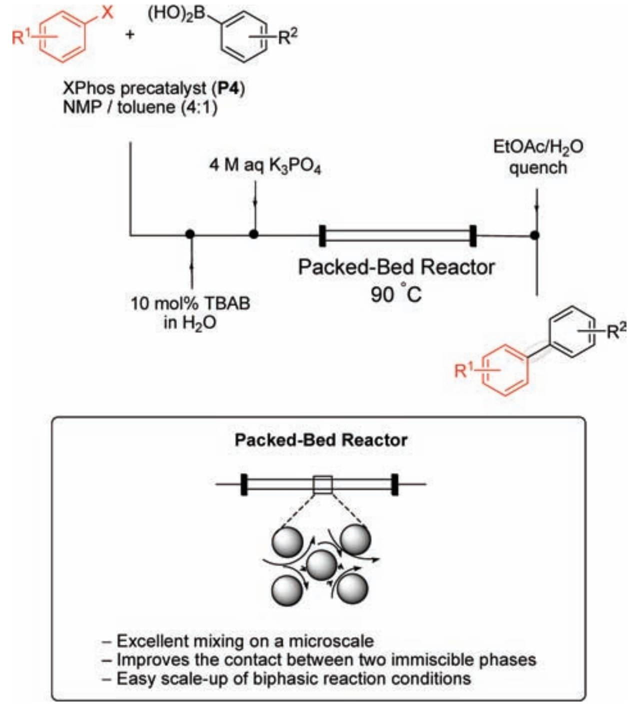


Figure 2. Schematic representation of the microreactor setup for continuous-flow palladium-catalyzed Suzuki−Miyaura cross-coupling reactions employing heteroaryl halides and (hetero)arylboronic acids.

Next, we set out to explore the scope of this SMC reaction in continuous flow (Figure 3). A wide array of heterocyclic aryl chlorides and bromides, including 2-pyridyl, 3-pyridyl, 6-quinolinyl, 1-isoquinolinyl, 5-pyrimidinyl, 2-pyrimidinyl, 2-pyrazinyl, 3-thiophenyl, 4-pyrazolyl, and 5-benzoxazolyl halides, could be efficiently coupled with a broad range of arylboronic acids within a 3 min residence time in good to excellent isolated yields. It is noteworthy that many of these examples involve the SMC coupling between a heteroaryl halide and a heteroarylboronic acid.

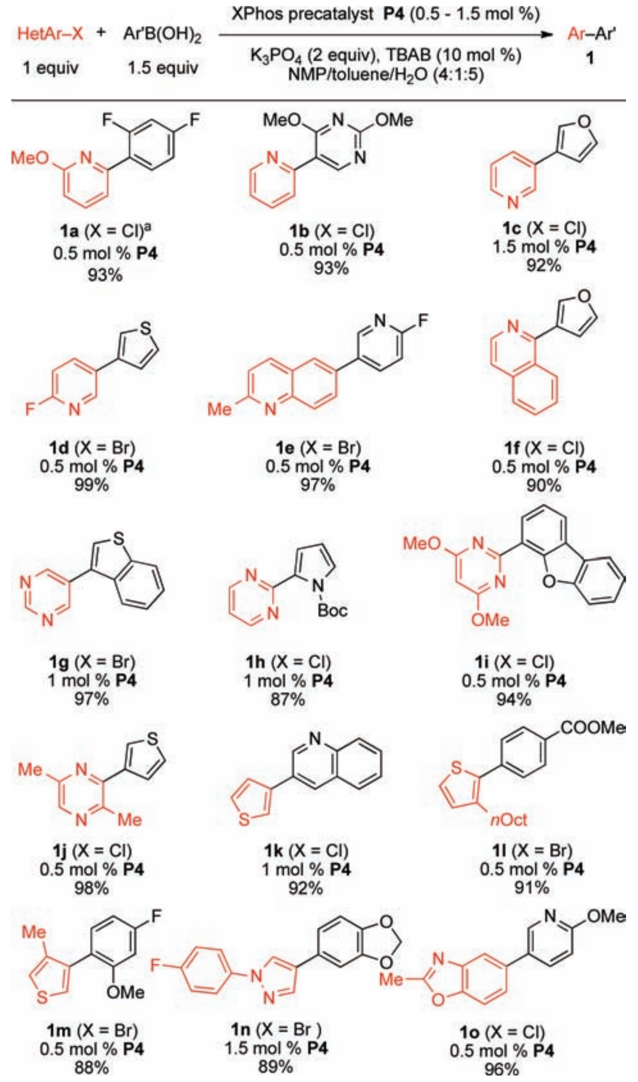
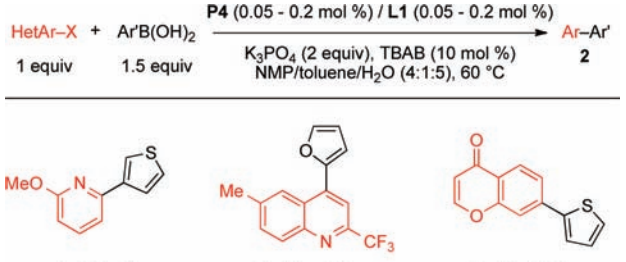


Figure 3. Substrate scope of the continuous-flow Suzuki−Miyaura cross-coupling of heteroaryl halides and (hetero)-arylboronic acids. Reaction conditions: ArX (1.0 equiv), $ArB(OH)_2$ (1.5 equiv), precatalyst **P4** (x mol %), NMP/toluene (4:1), 4 M aq K_3PO_4, 0.1 M aq TBAB at 90 °C, 3 min residence time. Isolated yield on a 2 mmol scale. Note: (a) 40 s residence time.

We then focused our attention on the development of continuous-flow protocols employing particularly low catalyst loadings (Figure 4). The ability to perform SMC reactions in flow with low catalyst loadings is of great importance for process development since it significantly reduces the palladium cost and simplifies removal of palladium residues from the target molecule. For the reaction between 2-chloro-6-methoxypyridine and 3-thienylboronic acid, incomplete conversion to heterobiaryl **2a** was observed at 90 °C in the presence of 0.05 mol % of XPhos precatalyst **P4**. Having observed during optimization studies that higher temperatures led to lower conversions, we surmised that competitive protodeboronation was problematic. Indeed, by lowering the temperature to 60 °C and employing a reaction time of 5 min, there was a decrease in the quantity of protodeboronation observed and, hence, heterobiaryl **2a** could be obtained in excellent isolated yield. It should be noted that this result represents the lowest palladium loading that has been reported for an SMC reaction carried out under continuous-flow conditions.[10] Having addressed the problem of protodeboronation, we wondered if we could utilize five-membered 2-heteroarylboronic acids. These boronic acids are known to quickly protodeboronate at elevated temperatures when employing aqueous bases.[7a] In our microfluidic system, successful coupling was obtained with only 0.2 mol % of XPhos precatalyst **P4** at 60 °C and a 5 min residence time.



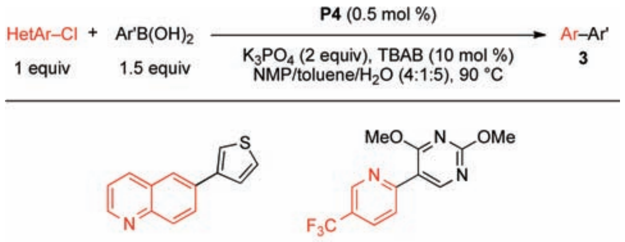
2a (X = Cl)
0.05 mol % **P4**
0.05 mol % **L1**
99%

2b (X = OTf)
0.2 mol % **P4**
0.2 mol % **L1**
82%

2c (X = OTf)
0.2 mol % **P4**
0.2 mol % **L1**
84%

Figure 4. Formation of heterocyclic biaryls using low catalyst loadings and unstable 2-heteroarylboronic acids. Reaction conditions: HetArX (1.0 equiv), ArB(OH)$_2$ (1.5 equiv), precatalyst **P4** (*x* mol %), XPhos **L1** (*x* mol %), NMP/toluene (4:1), 4 M aq K$_3$PO$_4$, 0.1 M aq TBAB at 60 °C, 5 min residence time. Isolated yield on a 2 mmol scale.

The efficiency of a biphasic reaction in a batch reactor is highly dependent on the effectiveness of the mixing process. To scale up such a process in batch, these reaction conditions require advanced and specialized mixing devices, such as special designs in agitator blades or the installation of baffles in the reactor. However, with our microfluidic system, we were able to scale up the reaction conditions very efficiently just by extending the operating time of the device (Figure 5). We were able to run SMC coupling reactions for 5 h without any interruption to collect 10 mmol of the corresponding biaryl heterocycles.



3a
5 hours
1.95 g
92% isolated yield

3b
5 hours
2.77 g
97% isolated yield

Figure 5. Formation of heterocyclic biaryls on a 10 mmol scale. Reaction conditions: HetArCl (1.0 equiv), ArB(OH)$_2$ (1.5 equiv), precatalyst **P4** (0.5 mol %), NMP/toluene (4:1), 4 M aq K$_3$PO$_4$, 0.1 M aq TBAB at 90 °C, 3 min residence time. Isolated yield on a 10 mmol scale.

In summary, we have developed a general continuous-flow process for the Suzuki–Miyaura cross-coupling of heteroaryl halides and (hetero)arylboronic acids. A wide range of heterobiaryl components could be obtained in good to excellent yields. Noteworthy are the use of low catalyst loadings, unstable 2-heteroarylboronic acids, and the possibility to scale up the reaction very efficiently. Key to the success of this process was (i) the use of an XPhos precatalyst (**P4**), which guarantees fast activation of the catalytically active species; (ii) the use of a biphasic solvent system, which ensures good solubility of both organic and inorganic solids; and (iii) the use of a packed-bed reactor, which improves the contact between the immiscible phases.

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Supporting Information Available. Details on the equipment setup, experimental procedures, and spectral data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[10] For an example that utilizes 0.25 mol % Pd(PPh$_3$)$_4$ for the SMC coupling between nonheteroaryl coupling partners: see ref 3b.