Flow Chemistry

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Continuous-Flow Synthesis of Biaryls Enabled by Multistep Solid-Handling in a Lithiation/Borylation/Suzuki–Miyaura Cross-Coupling Sequence**

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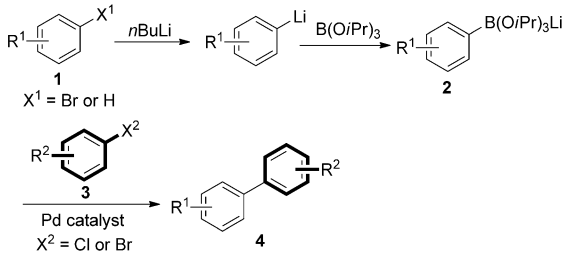
Continuous-flow methods have gained considerable interest over the last decade since they offer several advantages over traditional batch manufacturing processes.[1,2] Recently, the scope of continuous-flow processes has expanded to include multistep synthetic transformations, which are attractive in that they can result in less waste due to fewer purification steps and less manipulation of compounds. Yet, the development of multistep continuous-flow syntheses remains a particularly difficult challenge due to increased complexity as compared to single step processes. Flow-rate synergy, solvent compatibility, and the effect of by-products and impurities must be considered and optimized in downstream reactions.[3] In addition, a major challenge for the development of multistep syntheses in continuous flow is the handling of the solids, which usually leads to irreversible clogging. Although ultrasonication has been used to address this problem in one-step continuous-flow methodologies,[4] to the best of our knowledge, no examples of multistep continuous-flow methods including a solid-forming reaction have been disclosed.

Palladium-catalyzed C–C bond-forming reactions serve as useful methods in the synthesis of functionalized materials and biologically active compounds.[5] The Suzuki–Miyaura coupling reaction (SMC) can be regarded as one of the most important reactions for these bond-forming processes.[6,7] In general, organoboron reagents are prepared via lithium[8] or magnesium organometallic compounds in a two-step process.[9,10] Given the significance of biaryls in the pharmaceutical industry, we anticipated that the preparation of a boronate reagent,[11] immediately followed by a Suzuki–Miyaura cross-coupling reaction in one single streamlined process would be of great interest for the chemical community.[12] Herein, we report the three-step synthesis of biaryls from the lithiation of aryl halides/heteroarenes, followed by borylation and Suzuki–Miyaura coupling under continuous-flow conditions. Notably, this process was made possible through efficient handling of solids under multistep conditions with the aid of acoustic irradiation (Scheme 1). After the completion of our work, the one-pot preparation of magnesium di(hetero)aryl- and magnesium dialkenylboronates for Suzuki–Miyaura coupling reactions was reported by Knochel et al.[13]



Scheme 1. Biaryl synthesis in continuous flow by a lithiation/borylation/Suzuki–Miyaura cross-coupling sequence.

We started our investigation by examining the lithiation of 4-bromoanisole by *n*-butyllithium (2.5 M in hexanes) in THF at room temperature under flow conditions (Figure 1), which we found to be completed in only two seconds. Unfortunately,

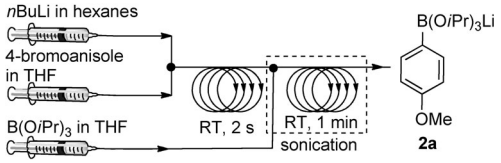


Figure 1. Continuous-flow setup for the room-temperature lithiation/borylation of 4-bromoanisole.

when the lithiation reaction was quenched by a stream of $B(OiPr)_3$ (0.33 M in THF, 200 μL min^{-1}), lithium triisopropyl(4-methoxyphenyl)borate (**2a**) precipitated from the solution, blocking the reactor tubing. We isolated **2a** and tested its solubility in various solvents including THF, 1,4-dioxane, NMP, acetone, DMF, DMSO, and water; little solubility of **2a** was seen in any case. However, we found that when the stream exiting from the first reactor was quenched with a more dilute $B(OiPr)_3$ solution (0.05 M, flow rate = 1 mL min^{-1}) with acoustic irradiation, the lithiation/borylation reaction could proceed smoothly.

We next focused on the coupling reaction of aryl halides with **2a**, generated in flow as above. We examined the reaction of **2a** with 4-bromo-3-fluorobenzonitrile (**3a**) in

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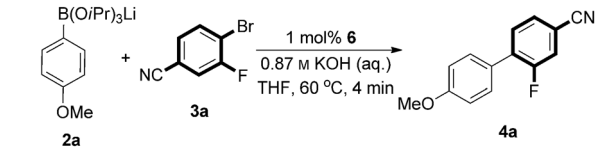
batch employing our recently developed second-generation palladium precatalysts **6** (Figure 2).[14] When this reaction was carried out in THF at 60 °C for 4 min, it was found that only precatalysts bearing SPhos or XPhos as ligand could facilitate full conversion of the aryl halide, affording the desired product **4a** in 72 % and 98 % GC yield, respectively (Figure 2).



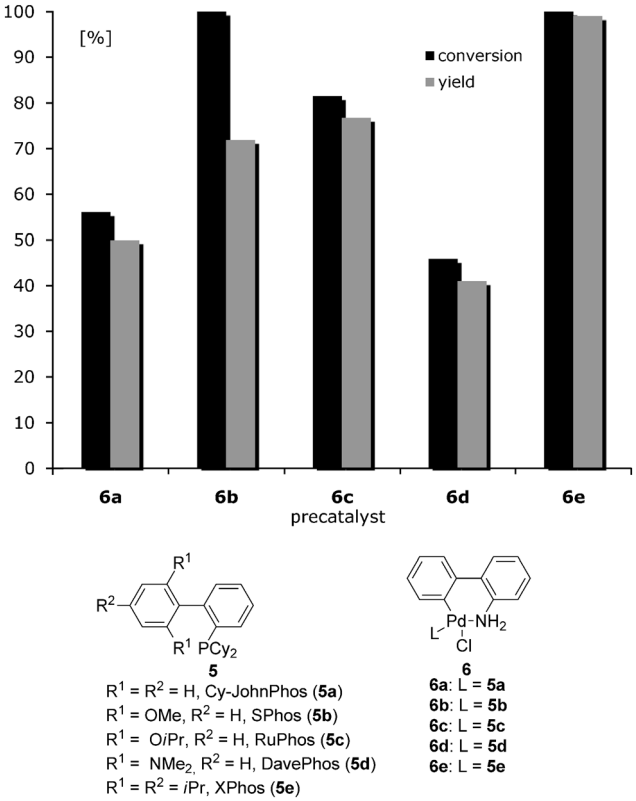


Figure 2. Precatalysts **6** with different biaryl phosphine ligands.

With good conditions in hand, a microfluidic system was assembled as shown in Figure 3. Solutions of aryl bromides in tetrahydrofuran and *n*-butyllithium in hexanes (1.6 M or 2.5 M) were loaded into syringes and introduced into a reactor made of a PFA (perfluoroalkoxyalkane) tubing (0.04″ inner diameter) at room temperature. Upon exiting the first reactor, the stream was mixed with a $B(OiPr)_3$ solution at a T mixer, and the combined streams were subsequently introduced into another PFA-tubing reactor (0.04″ inner diameter). After exiting the second reactor, the reaction stream was combined with, respectively, an aqueous KOH solution (0.87 M) and a solution of aryl halide and precatalyst **6e** in THF. This solution was introduced into a third PFA-tubing reactor (0.04″ inner diameter). In order to avoid reactor clogging and

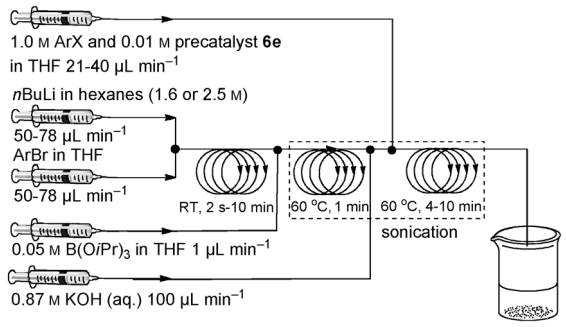
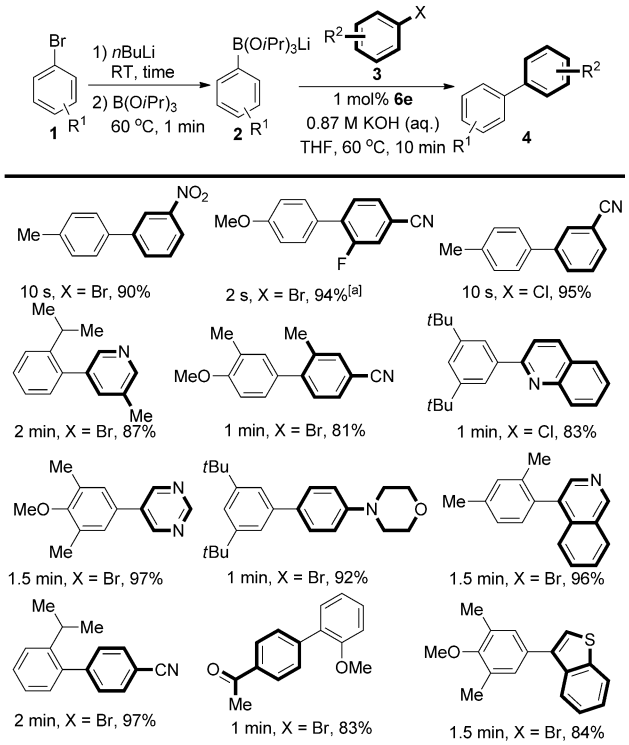


Figure 3. Continuous-flow setup for the lithiation/borylation/Suzuki–Miyaura cross-coupling sequence of two aryl halides.

ensure a good mixing of the three-phase SMC reaction stream, the second and third reactors were placed in a sonication bath. Finally, the product stream was collected upon exiting the third reactor.

Next, we set out to explore the scope of this three-step triphasic flow system using various aryl halides (Scheme 2). Using the setup as shown in Figure 3, various aryl bromides could be lithiated at room temperature. The reaction sequence could be successfully carried out with *para*-, *meta*-, *ortho*-, and multi-substituted aryl bromides. In the third step, a broad range of aryl bromides and chlorides could be applied to this process. Aryl halides with both electron-withdrawing and electron-donating substituents were well tolerated under



Scheme 2. Substrate scope of the lithiation/borylation/Suzuki–Miyaura cross-coupling sequence of two organic halides (yield of isolated product based on **3**). For details, see Supporting Information. [a] The Suzuki–Miyaura cross-coupling reaction was finished in 4 min.

the optimal reaction conditions; notably, various heteroaromatic halides, such as quinoline, isoquinoline, pyrimidine, and benzothiophene, could also be employed in this lithiation/borylation/Suzuki–Miyaura cross-coupling reaction, affording the corresponding biaryls in good to excellent yields.

We next applied this protocol to the lithiation/borylation/Suzuki–Miyaura cross-coupling of heteroarenes with aryl halides. It is known that five-membered 2-heteroaromatic boronic acids are unstable at room temperature and are especially challenging coupling partners for Suzuki–Miyaura reactions due to quick decomposition under basic aqueous conditions.[15] The realization of a lithiation/borylation/Suzuki–Miyaura cross-coupling of heteroarenes with functionalized aryl or heteroaryl halides would be of great interest for the synthesis of pharmaceuticals and agrochemicals. Thus, we chose thiophene and 3-bromoisoquinoline as coupling partners to investigate this process. It was found that thiophene could be deprotonated at room temperature with *n*-butyllithium (1.6 M) in four minutes. Keeping the instability of 2-heteroaromatic boron reagents and the insolubility of lithium triisopropyl(thiophen-2-yl)borate in mind, we modified our standard setup by quenching the lithiation reaction at room temperature and reducing the residence time in the second reactor to 6 seconds (Figure 4).

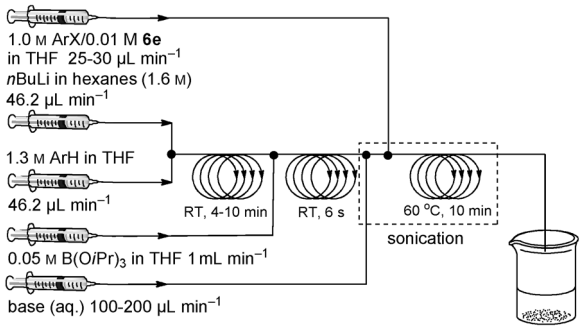
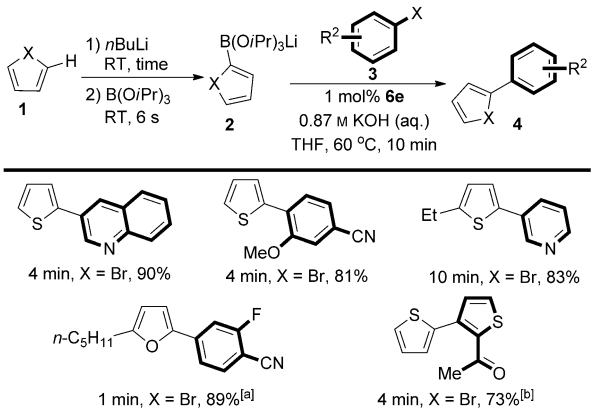


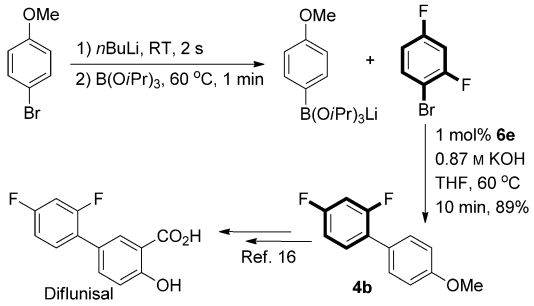
Figure 4. Continuous-flow setup for the lithiation/borylation/Suzuki–Miyaura cross-coupling sequence of heteroarenes with aryl halides.

Next, we evaluated the scope of lithiation/borylation/Suzuki–Miyaura cross-coupling reactions of heteroarenes with aryl halides. Thiophenes and furans could be deprotonated smoothly at room temperature and followed by a borylation and a Suzuki–Miyaura cross-coupling reaction with *ortho*-substituted aryl or heteroaromatic halides, yielding the desired products in good yields (Scheme 3). It is noteworthy that by using this protocol, low-cost heteroarenes can be implemented directly, without using unstable 2-heteroaromatic boronic acids or more expensive 2-heteroaromatic bromides.

To further demonstrate the potential applications of this flow system, we synthesized **4b** by lithiation/borylation of 4-bromanisole, followed by Suzuki–Miyaura coupling with 1-bromo-2,4-difluorobenzene using the setup in Figure 3. **4b** is a key intermediate for the synthesis of Diflunisal,[16] a non-steroidal anti-inflammatory drug with analgesic and anti-pyretic effects[17] (Scheme 4).



Scheme 3. Lithiation/borylation/Suzuki–Miyaura cross-coupling of heteroarenes with aryl halides (yield of isolated product based on **3**). [a] 0.44 M NaF aqueous solution was used instead of KOH. [b] 0.87 M KF aqueous solution was used instead of KOH.



Scheme 4. Synthesis of **4b** in continuous flow.

In summary, we have demonstrated an efficient and modular synthesis of biaryls from aryl halide substrates by a lithiation/borylation/Suzuki–Miyuara cross-coupling sequence in continuous flow. In the case of heteroarenes, direct lithium–proton exchange allows the use of heteroarenes in this three-step flow strategy. Significantly, this protocol represents the first example of a three-phase flow process with an efficient solid handling in multistep syntheses under acoustic irradiation, which features easy operation, ambient conditions, and inexpensive starting materials. Of importance is that the lithiation is conducted at room temperature using commercially available *n*-butyllithium solutions, which greatly enhances the synthetic utility of this process.

Experimental Section

General procedure: A THF solution of aryl bromides or heteroarenes was loaded into a plastic syringe, and *n*-butyllithium solution (1.6 M or 2.5 M in hexanes) was loaded into a second plastic syringe. These two solutions were mixed at a T mixer and delivered to the first microreactor made of PFA tubing (0.04″ inner diameter) using a Harvard Apparatus syringe pump. A second syringe pump was used to pump $B(OiPr)_3$ (0.05 M in THF) and mix it with the stream exiting the first reactor at a scecond T mixer. The mixed stream was introduced into the second microreactor (PFA tubing, 0.04″ inner diameter). The base solution was loaded into a fourth plastic syringe

and pumped into the system using a third Harvard Apparatus syringe pump. Sequentially, the solution of aryl halides and XPhos precatalyst **6e** in THF was loaded into the fifth plastic syringe, which was merged with the combined stream of base solution and the mixture from the second reactor using a fourth Harvard Apparatus syringe pump. The combined mixture was introduced into the third microreactor (PFA tubing, 0.04″ inner diameter). Upon exiting the reactor, the mixture was collected. Further details on the flow setup and workup procedures can be found in the Supporting Information.

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