

Suzuki–Miyaura Cross-Coupling Reactions in Flow: Multistep Synthesis Enabled by a Microfluidic Extraction**

Timothy Noël, Simon Kuhn, Andrew J. Musacchio, Klavs F. Jensen,* and Stephen L. Buchwald*

The synthesis of complex organic molecules typically involves multiple reaction steps and requires the isolation and purification of reaction intermediates. As a result, synthetic chemistry is a very labor-intensive and time-consuming undertaking. Several strategies have been developed in order to increase the efficiency of multistep syntheses, such as, protecting group free syntheses,^[1] one-pot syntheses,^[2] cascade reactions,^[3] and multicomponent reactions.^[4]

In the last decade, the use of continuous-flow reactors for multistep syntheses has gained a considerable amount of interest because they allow for integration of the individual reaction steps and subsequent separations in one single streamlined process. These microreactors provide several advantages compared to traditional batch reactors, for example, enhanced heat- and mass-transfer, safety of operation, precise control over residence (reaction) time, isolation of sensitive reactions from air and moisture, and the ease of scale-up or operating several devices in parallel (numbering up).^[5,6] Several approaches have been developed in order to combine multiple reaction steps in one single continuous operation. One strategy involves the use of telescoping reactions in which reagents are added consecutively in order to achieve further transformations of a given starting product without the use of intermediate purifications. This technique has proven very effective for multistep flow chemistry because it simplifies the microfluidic setup dramatically.^[7] However, excess reagents and by-products formed during the reaction can negatively affect the downstream reactions which significantly limits the generality of this method. Another approach has been the use of immobilized reagents, catalysts and scavengers in order to achieve multistep syntheses in flow.^[8]

Although this method has allowed the construction of complex molecules without the need for purification and isolation of intermediates, swelling of certain polymer supports, deposition of products and by-products, catalyst leaching,^[9] and the necessity to periodically replace the cartridges limit the practicality of these systems. Lastly, several unit operations have been developed in order to achieve separations and purifications in a continuous fashion, such as, a single-step liquid–liquid microextraction^[10] and a microfluidic distillation.^[11] These unit operations have successfully been implemented in continuous-flow syntheses.^[12,13]

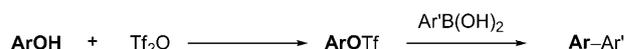
Cross-coupling reactions serve as powerful methods to construct carbon–carbon and carbon–heteroatom bonds in a variety of biologically active molecules.^[14,15] The Suzuki–Miyaura cross-coupling reaction (SMC) can be regarded as one of the most important of these bond-forming processes.^[16,17] This method allows for the coupling of aryl halides/pseudo halides with aryl boronic acids or aryl boronates. Notably, aryl triflates have been shown to be one of the most efficient coupling partners. However, the lack of commercially available triflates and their instability requires their preparation prior to their use in the SMC reaction and makes them less attractive for SMC reactions. These are central reasons why synthetic chemists try to circumvent the use of aryl triflates and employ the commercially available aryl halides. Nevertheless, the use of phenols would be of high interest because of their availability and low cost. Here, we describe a microfluidic system that is suitable to transform phenols into their corresponding aryl triflates, which are, subsequently, transformed into biaryls by means of a SMC reaction (Scheme 1). This process possesses a unique chemical

[*] Dr. T. Noël, A. J. Musacchio, Prof. Dr. S. L. Buchwald
 Department of Chemistry
 Massachusetts Institute of Technology
 77 Massachusetts Avenue, Cambridge, MA 02139 (USA)
 Fax: (+1) 617-253-3297
 E-mail: sbuchwal@mit.edu
 Homepage: <http://mit.edu/chemistry/buchwald/>

Dr. S. Kuhn, Prof. Dr. K. F. Jensen
 Department of Chemical Engineering
 Massachusetts Institute of Technology
 77 Massachusetts Avenue, Cambridge, MA 02139 (USA)
 E-mail: kfjensen@mit.edu

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Scheme 1. Synthesis of biaryls starting from substituted phenols.

challenge because by-products formed in the first reaction can negatively affect the downstream reaction. Moreover, since catalytic reactions are very sensitive to small amounts of impurities an effective strategy to remove these by-products needs to be utilized.

A microfluidic system was assembled as shown in Figure 1. The first reaction, the formation of aryl triflate, was carried out in a 100 μL reactor made of PFA (perfluoroalkoxyalkane) tubing (0.02" inner diameter, 50 cm length) at room temperature. Solutions of triflic anhydride (Tf_2O), as well as phenol and triethylamine in toluene were loaded into syringes and introduced into the microfluidic system through syringe pumps. The triflic anhydride and reagent streams

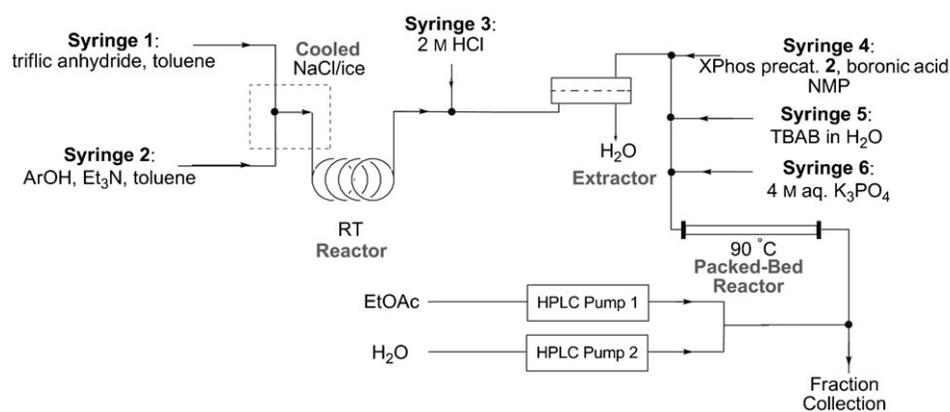


Figure 1. Microreactor setup for the continuous-flow synthesis of palladium-catalyzed Suzuki–Miyaura cross-coupling reactions starting from substituted phenols.

were combined in a T-mixer. This T-mixer was cooled in a NaCl/ice bath in order to effectively dissipate the heat generated by the exothermic triflate formation. Although quantitative yields were obtained for the intermediate triflate, without cooling, poor and irreproducible overall yields for the SMC-coupled product were obtained. We hypothesize that a side product is formed which cannot be efficiently extracted out of the organic stream and inhibits the catalyst in the SMC reaction. Upon exiting the first reactor, the reaction was quenched with 2 M hydrochloric acid (HCl) establishing a slug-flow regime. This enabled the extraction of triethylamine and other salts through convective mass transfer between the two phases. Next, the two phases were separated in a phase separation device by using a thin porous fluoropolymer membrane that selectively wets the organic phase (Figure 2). This selective wetting of the membrane by the organic phase facilitates the separation process based on the capillary

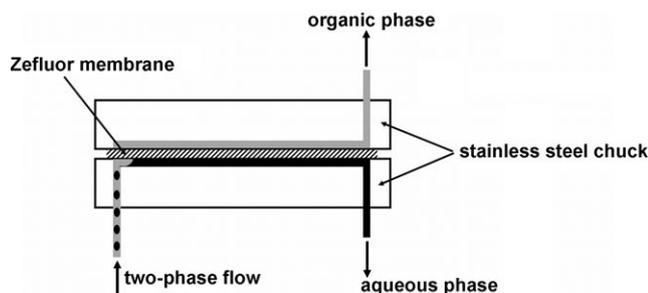
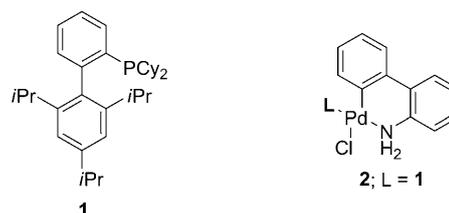


Figure 2. Sketch of the phase separation device.

pressure difference.^[10a] To successfully operate the separation device the combined fluidic resistance from the separated organic stream needs to be less than the separated aqueous stream. In addition, the pressure difference between the organic and the aqueous side across the membrane needs to be less than the capillary pressure difference. Since the second reaction step involves the use of a packed-bed reactor with an associated increase in pressure drop, the aforementioned two criteria were met by adding backpressure to the aqueous side of the separator. The organic phase was combined with solutions of second-generation XPhos precat. 2

(Scheme 2) and the corresponding boronic acid, tetrabutylammonium bromide (TBAB) as a phase transfer catalyst, and aqueous K_3PO_4 . This biphasic mixture was next introduced into a 400 μ L packed-bed reactor filled with stainless steel spheres (60–125 μ m packing) reactor which was placed in a 90 °C oil bath. These dramatically enhance the mixing in biphasic mixtures by improving the contact between the two phases.^[15b] Stainless steel spheres are an inert and com-



Scheme 2. XPhos ligand **1** and second-generation XPhos precat. **2** used in the palladium-catalyzed Suzuki–Miyaura cross-coupling reactions.

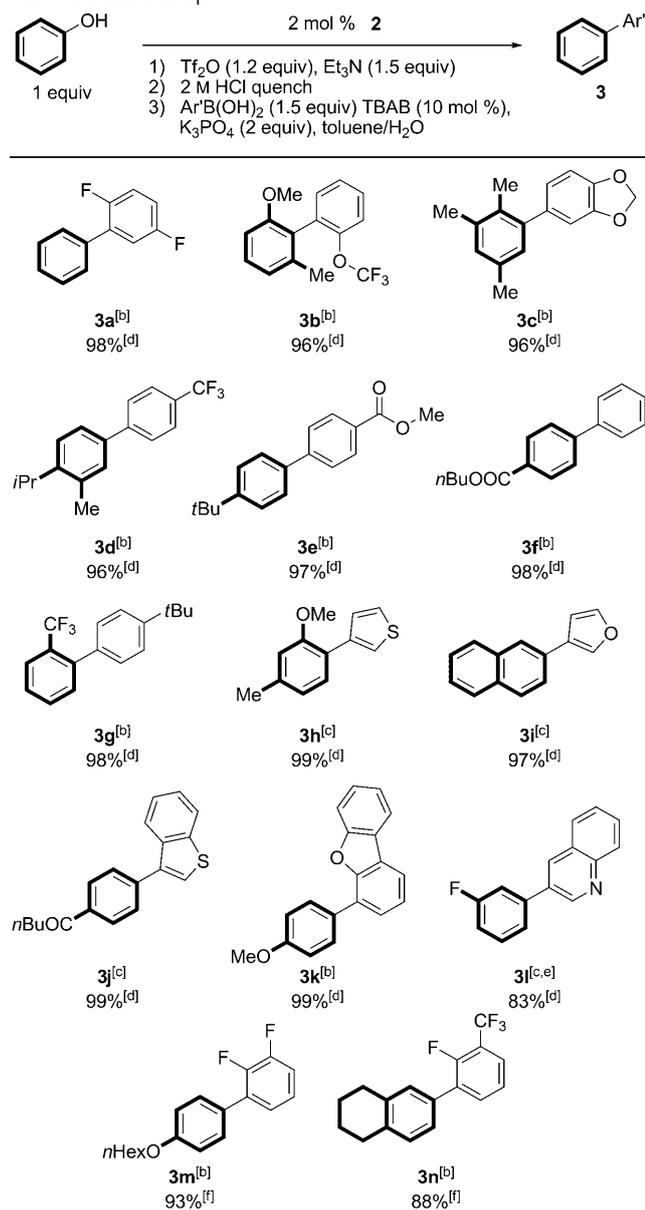
mercially available material, which exhibits an excellent chemostability, a high tolerance towards basic solutions, and a good thermal conductivity,^[18] which makes these beads an ideal choice for use as a packing material. Finally, the product stream was merged with a quench of water and ethyl acetate (EtOAc).

Our initial investigation focused on finding a solvent that was compatible with both steps of the process. Ethereal solvents proved to be ideal for the SMC reaction,^[19] however, these were not compatible with triflic anhydride. Moreover, the by-products formed during the triflate formation reaction completely shut down the SMC reaction even in the presence of a continuous liquid–liquid extraction step. Toluene was found to be the optimal solvent for both steps. The by-products formed in the first reaction could be efficiently removed by continuous extraction and allowed the SMC reaction to proceed. We observed that complete conversion of phenol and quantitative yields for the corresponding triflate could be obtained in a matter of seconds using 1.2 equivalents of triflic anhydride (see the Supporting Information). After exiting the separation device, the organic phase was combined with boronic acid and 2 mol % XPhos precat. **2** dissolved in 1-methyl-2-pyrrolidinone (NMP), aqueous TBAB, and aqueous K_3PO_4 . It is worth mentioning that this second-generation XPhos precat. **2** is easily obtained in a one-pot procedure starting from commercially available chemicals and generates the catalytically active L_1Pd^0 species quickly and efficiently.^[19,20] These advantages make this class of precat. **2** ideally suited for continuous-flow reactions

where scalability and fast initiation of the catalyst are required.

This process could be applied to the cross-coupling of various phenols with a wide range of arylboronic acids (Table 1). Under optimized conditions, most reactions could be finished with residence times of 152 s in the first reactor and 240 s in the packed-bed reactor. Typically, isolated yields of more than 95% yield were obtained. Both electron-rich and electron-deficient phenols could be used. Also phenols bearing *ortho* substituents could be efficiently employed in

Table 1: Suzuki–Miyaura cross-coupling of ArOH and Ar'B(OH)₂ using the microfluidic setup.^[a]



[a] 1) ArOH (1.0 equiv), Tf₂O (1.2 equiv), Et₃N (1.5 equiv), toluene, room temperature. 2) 2 M HCl. 3) Ar'B(OH)₂ (1.5 equiv), XPhos precatalyst **2** (2 mol %), NMP, TBAB (10 mol %) in H₂O, aq. K₃PO₄. [b] Residence time reactor 1 = 152 s; residence time reactor 2 = 240 s. [c] Residence time reactor 1 = 203 s; residence time reactor 2 = 320 s. [d] Yield of isolated product on a 1 mmol scale. [e] 3 mol % of **2** was used. [f] Yield of isolated product on a 5 mmol scale.

our two-step protocol (Table 1, examples **3b** and **3c**). Both electron-rich and electron-deficient boronic acids appeared to be efficient coupling partners (Table 1). Heteroaromatic boronic acids underwent the SMC reaction to form the desired products in excellent overall yields (Table 1, substrates **3h–l**). For most heteroaromatic boronic acids, longer reaction times were required to obtain a full conversion of the aryl triflate (residence time reactor 1 = 203 s; residence time reactor 2 = 320 s) (Table 1, substrates **3h**, **3i**, **3j**, and **3l**). For substrate **3l**, 3 mol % of precatalyst **2** was required in order to obtain complete conversion.

The use of a continuous liquid–liquid extraction device, a packed-bed reactor and the ease with which our microfluidic setup could be stabilized were key requisites for the successful formation of C–C coupled products starting from phenols. To further demonstrate the robustness of our system, we were able to run experiments for more than 4 h without any interruption to collect in total 5 mmol of product (Table 1, substrates **3m** and **3n**). This result demonstrates one of the major advantages of flow chemistry, which is the ease to scale-up reactions and, more specifically, biphasic reactions. In batch, biphasic conditions require advanced and expensive mixers, using baffles or special designs in agitator blades.

In conclusion, we have developed a continuous-flow microfluidic system that can efficiently transform phenols into their corresponding aryl triflates and, subsequently, convert the intermediate triflates into biaryls by means of a Suzuki–Miyaura cross-coupling reaction. Key for the success in this multistep synthesis was the use of a microfluidic extraction operation to remove impurities generated in the first reaction and a packed-bed reactor to increase the mixing efficiency of the biphasic Suzuki–Miyaura cross-coupling reaction. It is noteworthy that the start-up and steady-state of this microfluidic system was easily achieved and, as a result, the cross-coupling of various phenols with a wide range of arylboronic acids was possible (14 examples). Excellent results were obtained in all cases.

Experimental Section

A toluene solution of the phenol substrate (1.0 M) and triethylamine (1.5 M) was loaded into a SGE glass syringe (5 mL) and a toluene solution of triflic anhydride (1.2 M) was loaded into a second glass SGE syringe (5 mL). These two solutions were delivered to the first microreactor (100 μL volume) using a single Harvard Apparatus syringe pump (20 μL min⁻¹). A second syringe pump was used to pump 2 M HCl (80 μL min⁻¹) and mix it with the triflate stream exciting the first reactor. This stream was delivered to a continuous liquid–liquid extraction device. An NMP solution of boronic acid (1.5 M) and XPhos precatalyst **2** (0.02 M) was loaded in a fourth syringe (5 mL Normject plastic syringe), an aq. TBAB solution (0.1 M) was loaded in a fifth syringe (5 mL Normject plastic syringe) and aq. K₃PO₄ (4 M) was loaded in a sixth syringe (5 mL Normject plastic syringe). These three solutions were merged with the organic phase coming from the extraction device and delivered to a packed-bed reactor (400 μL, packed with 60–125 μm stainless steel spheres) at 90 °C using two additional syringe pumps (20 μL min⁻¹). Upon exiting the reactor, the reaction was quenched with EtOAc (200 μL min⁻¹) and H₂O (200 μL min⁻¹). The flow rates and pressures were allowed to stabilize to a steady state. Next, a sample was collected in order to obtain exactly 1 mmol of product. Further details on the equipment

setup and workup procedures can be found in the Supporting Information.

Sample analysis: GC analysis was used to determine the conversions. NMR spectroscopy and IR spectroscopy were used to identify the products.

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