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Continuous Flow Palladium(II)-Catalyzed Oxidative Heck Reactions with Arylboronic Acids

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Palladium(II)-catalyzed oxidative Heck reactions were investigated under continuous flow conditions. Selective, fast and convenient protocols for the coupling of arylboronic acids with electron-rich and electron-poor olefins were developed by using a commercially available flow reactor.

Introduction

The synthetic chemists of today are increasingly being expected to quickly deliver target products, at different scales, in good yield and high purity. Hence, new synthetic methods and purification strategies are urgently required to reach quality and productivity goals.[1,2] Within the pharmaceutical and fine chemistry communities, the use of emerging synthetic technologies such as microwave heating[3,4] and continuous flow processing[5–14] have attracted considerable interest. Key advantages associated with continuous flow protocols in comparison with traditional batch techniques include the ability to independently control, and directly evaluate, reaction parameters such as stoichiometry, temperature, pressure and flow rate.[15,16] In addition, flow techniques provide unique possibilities for facilitated and straightforward scale-up.[5,17]

Palladium(II)-catalyzed reactions with arylboronic acids constitute a group of recently developed synthetic methods that, in batch mode, typically afford high yields and selectivities, provided an efficient palladium(II) regeneration takes place after each catalytic turnover.[18–23] We are currently developing new oxidative palladium(II)-catalyzed coupling reactions to increase the number of available transformations starting from arylboron substrates.[24] Whereas related palladium(0)-catalyzed coupling reactions with organohalides (or halide surrogates) have been previously investigated under continuous flow conditions,[25–29] the palladium(II)-catalyzed counterparts remain unexplored. Consequently, for the mild palladium(II)-catalyzed methodologies to become an industrial alternative to palladium(0)-catalyzed coupling reactions, efficient processing protocols must be developed. In this short article, we present the successful continuous flow development, using a commercially available reactor, of various palladium(II)-catalyzed Heck reactions with arylboronic acids.

Results and Discussion

The first aim of this investigation was to develop a fast and convenient continuous flow method for the vinylation of arylboronic acids. Our previously employed vinylation conditions [2 mol-% $Pd(OAc)_2$ and 2.2 mol-% 1,3-bis(diphenylphosphanyl)propane, dppp] with the use of 4-acetylboronic acid (**1j**, Table 1) were used as a starting point for reaction parameter optimization.[30] In our straightforward experimental set-up, the two reactor sample loops were loaded with a reactant solution containing **1j** (0.5 M) and vinyl acetate (VA, 5 M) in DMF and a catalytic solution consisting of $Pd(OAc)_2$ (0.01 M) and dppp (0.011 M) in DMF. The solutions were then simultaneously pumped through a T-inlet and into a preheated PFTE reaction chamber (2 mL, 1 mm inner diameter). Optimization of residence time and reaction temperature revealed that full conversion of **1j** was reliably achieved after only 2 min of heating at 150 °C, providing desired styrene **2j** in 86% isolated yield (Table 1, Entry 10).[31] Furthermore, no trace amounts of acetophenone, resulting from deborylation of **1j**, or the corresponding stilbene were detected, suggesting that a continuous flow reaction format may provide additional benefits over comparable batch techniques.[32]

Next, to investigate the generality of this protocol, the vinylation of a range of arylboronic acids (Table 1) was conducted. As can be seen from Table 1, all the reactions proceeded smoothly, providing moderate to good isolated yields (42–86%) of the desired styrenes. Electron-rich (Table 1, Entries 1–7) and electron-poor arylating agents (Table 1, Entries 8–13) were all well tolerated. Marginally lower yields were observed upon the introduction of an *or-*

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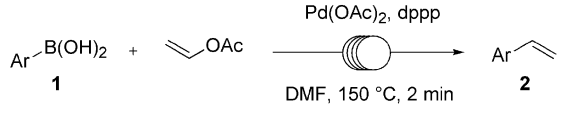
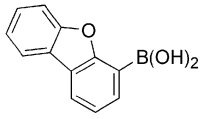
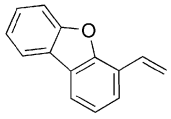
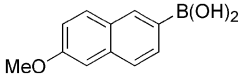
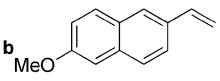
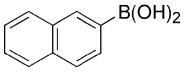
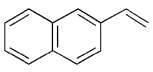
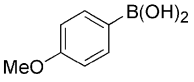
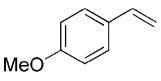
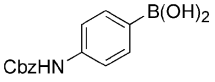
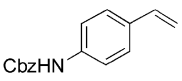
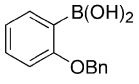
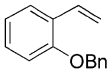
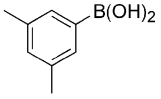
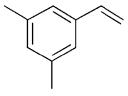
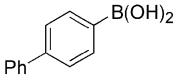
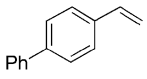
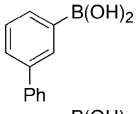
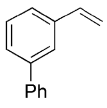
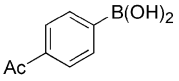
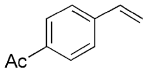
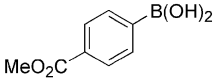
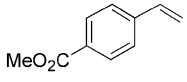
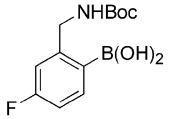
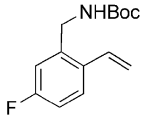
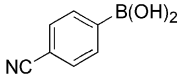
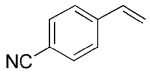
Table 1. Continuous flow vinylation of arylboronic acids **1**.[a]



Entry	Boronic acid	Product	Yield [%][b]
1	 **1a**	 **2a**	69
2	 **1b**	 **2b**	71
3	 **1c**	 **2c**	71
4	 **1d**	 **2d**	80 77[c]
5	 **1e**	 **2e**	63
6	 **1f**	 **2f**	62
7	 **1g**	 **2g**	42
8	 **1h**	 **2h**	68
9	 **1i**	 **2i**	86
10	 **1j**	 **2j**	86
11	 **1k**	 **2k**	79
12	 **1l**	 **2l**	55
13	 **1m**	 **2m**	80

[a] Reaction conditions: Boronic acid (1 mmol, 0.5 M), VA (10 mmol, 5 M), $Pd(OAc)_2$ (0.02 mmol, 0.01 M), dppp (0.022 mmol, 0.011 M) in DMF, 150 °C, residence time 2 min. [b] Isolated yields with purity >95% (LC–MS and ^1H NMR spectroscopy). [c] Reaction carried out on a 10-mmol scale.

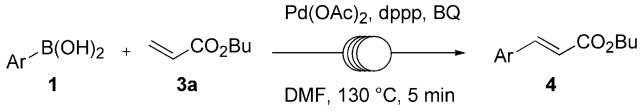
tho substituent (Table 1, Entries 1, 6 and 12) presumably due to unfavourable steric interactions and/or palladium chelation. 6-Methoxy-2-naphthylboronic acid also performed well, providing styrene **2b**, an intermediate in the synthesis of naproxen, in good yield (71%; Table 1, Entry 2). The modest yield afforded by 3,5-dimethylphenylboronic acid (**1g**) can be attributed to the volatile nature of the styrene product (42%; Table 1, Entry 7). Rewardingly, the potentially labile Cbz and Boc amino protecting groups both remained intact (Table 1, Entries 5 and 12) despite the presence of the palladium catalyst and the relatively high reaction temperature. Finally, a successful 10 mmol scale-out reaction on **1d** was performed, affording **2d** in 77% isolated yield after only 20 min of flow processing.

Having demonstrated the wide substrate scope and functional group compatibility of our continuous flow vinylation protocol, we next turned our attention to the oxidative Heck arylation of electron-poor and electron-rich olefins. Again, we used batch conditions previously developed in our laboratory [2 mol-% $Pd(OAc)_2$, 2.2 mol-% 2,9-dimethyl-1,10-phenanthroline, dmphen][33] and *p*-benzoquinone (BQ, 1 equiv.) together with **1j** and *n*-butyl acrylate (**3a**) as a point of departure for our investigation.[34] Encouraged by the modest amounts of deborylation observed in the vinylation reactions, we decided to use the boronic acid as the limiting reactant. This is in contrast to our previously reported oxidative Heck protocols, where the boronic acid (or equivalent) has been used in excess.[30,34] Thus, a secondary aim of our investigation became the development of a more economical and process friendly protocol. Initially, the two sample loops were loaded with a reactant solution containing **1j** (0.25 M) and **3a** (0.5 M) in DMF and a catalytic solution consisting of $Pd(OAc)_2$ (0.005 M), dmphen (0.0055 M) and BQ (0.25 M) in DMF. Test reactions at 150 °C and a residence time of 5 min revealed a working protocol; however, the stock catalytic solution was unstable and could not be stored for more than a few hours at room temperature. To our delight, exchanging dmphen for dppp provided a stable catalytic system capable of promoting the arylation of **3a**. A time/temperature optimization showed that full conversion of **1j** was accomplished after only 5 min of heating at 130 °C, affording desired acrylate **4j** in 85% yield (Table 2, Entry 8).

To further enhance the scope of this methodology, **3a** was arylated with a variety of arylboronic acids under the optimized continuous flow reaction conditions (Table 2). Rewardingly, the reactions performed well with both electron-rich (Table 2, Entries 1–5) and electron-poor (Table 2, Entries 6–9) boronic acids, furnishing *E* products **4** in moderate to good yields. Full chemoselectivity was observed in the reaction between bromine-containing **1p** and **3a**, with no trace amounts of side products resulting from bromine activation detected by LC–MS (Table 2, Entry 7). Once again, palladium(0)-labile, Cbz-protected aniline **1e** proved to be a useful substrate, providing 81% of the desired acrylate product (Table 2, Entry 3).

Next, the electron-rich olefin *n*-butyl vinyl ether (**3b**) and a small number of arylboronic acids were coupled under our continuous flow conditions (Table 3). As expected, these reactions were highly regiospecific, providing the internally arylated products, which were hydrolyzed and iso-

Table 2. Continuous flow arylation of *n*-butyl acrylate (**3a**) with arylboronic acids **1**.[a]

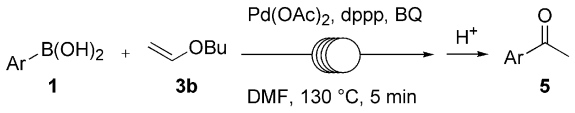


Entry	Boronic acid	Olefin	Product	Yield [%][b]
1	**1a**	**3a**	**4a**	62
2	**1n**	**3a**	**4n**	85
3	**1e**	**3a**	**4e**	81
4	**1d**	**3a**	**4d**	56
5	**1o**	**3a**	**4o**	60
6	**1h**	**3a**	**4h**	68
7	**1p**	**3a**	**4p**	89
8	**1j**	**3a**	**4j**	85
9	**1k**	**3a**	**4k**	67

[a] Reaction conditions: Boronic acid (0.5 mmol, 0.25 M), **3a** (1 mmol, 0.5 M), BQ (0.5 mmol, 0.25 M), $Pd(OAc)_2$ (0.01 mmol, 0.005 M), dppp (0.011 mmol, 0.055 M) in DMF, 130 °C, residence time 5 min. [b] Isolated yields with purity >95% (LC–MS and ^{1}H NMR spectroscopy).

lated as the corresponding methyl ketones **5**.[20,34–37] Most of the reactions proceeded smoothly, delivering modest to good yields of the desired products. Unfortunately, the reaction between **1p** and **3b** (Table 3, Entry 4) was extremely sluggish and doubling the residence time gave only a slight improvement in isolated yield (31 vs. 43%).

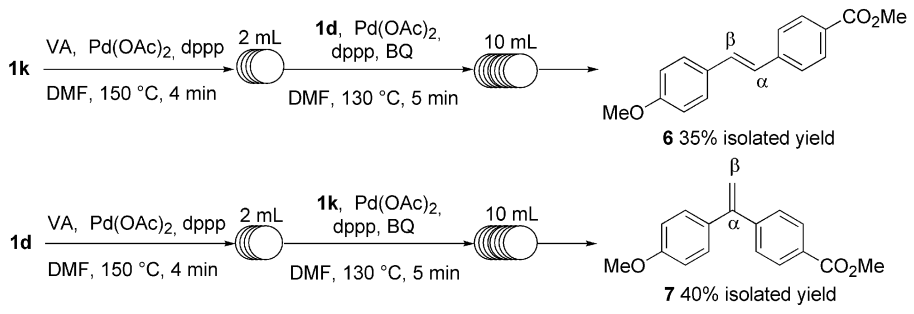
Table 3. Continuous flow arylation of *n*-butyl vinyl ether (**3b**) with arylboronic acids **1**.[a]



Entry	Boronic acid	Olefin	Product	Yield [%][b]
1	**1n**	**3b**	**5n**	85
2	**1e**	**3b**	**5e**	82
3	**1h**	**3b**	**5h**	77
4	**1p**	**3b**	**5p**	31 43[c]
5	**1j**	**3b**	**5j**	66

[a] Reaction conditions: Boronic acid (0.5 mmol, 0.25 M), **3b** (1 mmol, 0.5 M), BQ (0.5 mmol, 0.25 M), $Pd(OAc)_2$ (0.01 mmol, 0.005 M), dppp (0.011 mmol, 0.055 M) in DMF, 130 °C, residence time 5 min. Then hydrolysis with 1 M HCl (aq.). [b] Isolated yields with purity >95% (LC–MS and ^{1}H NMR spectroscopy). [c] Residence time 10 min.

Finally, we were intrigued by the prospect of synthesizing disubstituted styrenes, from arylboronic acids, by a sequential two-step vinylation–arylation continuous flow process. To this end, two different reaction schemes were designed,



Scheme 1. Two-step vinylation/arylation process.

incorporating both an electron-rich and an electron-poor intermediate styrene (Scheme 1). We reasoned that the excess amount of VA, present after the vinylation step, may compete with the styrene during the subsequent arylation step. Thus, the vinylation protocol was tuned and it was found that full conversion of **1k** was achieved, at 150 °C, when 4 equivalents of VA were employed with a residence time of 4 min. In the two-step protocol, $Pd(OAc)_2$ (2 mol-%), BQ (1 equiv.) and **1d** (1 equiv.) were added to the output of this reaction, and the solution passed through a second 10-mL PFTE reaction chamber at 130 °C for 5 min. This reaction gave a 1:9 mixture of α/β regioisomers and terminal *E* β-product **6** was isolated in 35% yield. When the process was reversed (i.e., vinylation of **1d** and arylation with **1k**) a decrease in β-selectivity was observed (α/β, 1:1) and internal α-arylated styrene **7** could be isolated in 40% yield. These results are in good agreement with the expected regioselectivity for styrene arylation under cationic conditions.[35,38]

Conclusions

We have developed the first continuous flow methods for the palladium(II)-catalyzed vinylation of arylboronic acids and the oxidative Heck arylation of electron-rich and electron-poor olefins. Compared to the previously reported batch protocols, this continuous flow protocol not only increases the reaction speed but also makes it possible to perform direct scale-up (or scale-out). Moreover, for the first time, we were able to utilize the more expensive arylboronic acid as the yield-determining reagent. Furthermore, a continuous flow two-step vinylation–arylation protocol was developed and an investigation into the scope of this methodology is currently underway in our laboratory. In view of the large number of commercially available boronic acids, we anticipate that our work will increase the utilization of continuous flow palladium(II)-catalyzed transformations in various applications related to fine and pharmaceutical chemistry.

Experimental Section

Typical Procedure for the Preparation of Styrenes 2: Two stock solutions were prepared. A reagent solution containing the boronic acid (1 mmol, 0.5 M) and vinyl acetate (10 mmol, 5 M) and a catalytic solution containing $Pd(OAc)_2$ (0.02 mmol, 0.01 M) and dppp (0.022 mmol, 0.011 M) in DMF. These solutions were loaded into separate 2-mL sample loops and simultaneously pumped through a T-inlet and into a PFTE reaction chamber (volume 2 mL) preheated to 150 °C at a constant flow rate of 1 mL min^{-1} (residence time 2 min). The output of the reaction was collected and diluted with EtOAc, filtered through a syringe filter and washed with NaOH (0.1 M aq.) and then with a 1:1 mixture of NH_4Cl (10% aq.) and NaCl (30% aq.). The organic phase was dried (phase separator) and concentrated in vacuo. The crude mixture was purified by silica chromatography (10 g silica, 0–20% EtOAc in heptane) to afford **2**.

Typical Procedure for the Preparation of 4 and 5: Two stock solutions were prepared. A reagent solution containing the boronic acid (0.5 mmol, 0.25 M) and **3a** or **3b** (1 mmol, 0.5 M) and a catalytic solution containing $Pd(OAc)_2$ (0.01 mmol, 0.005 M), dppp (0.0011 mmol, 0.0055 M) and BQ (0.5 mmol, 0.25 M) in DMF. These solutions were loaded into separate 2-mL sample loops and simultaneously pumped through a T-inlet and into a PFTE reaction chamber (volume 2 mL) preheated to 130 °C at a constant flow rate of 0.4 mL min^{-1} (residence time 5 min). The output of the reaction was collected and diluted with EtOAc filtered through a syringe filter and washed with NaOH (0.1 M aq.) and if **3b** was used HCl (1 M, aq.) and then with a 1:1 mixture of NH_4Cl (10% aq.) and NaCl (30% aq.). The organic phase was dried (phase separator) and concentrated in vacuo. The crude mixture was purified by silica chromatography (10 g silica, 0–20% EtOAc in heptane) to afford **4** or **5**.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization details for compounds **2g**, **2l**, **4a**, **4e** and **6** as well as ^1H and ^{13}C NMR spectra for all products.

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