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Continuous Flow

Packed-Bed Reactors for Continuous-Flow C–N Cross-Coupling**

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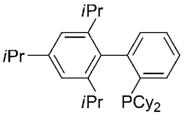
Continuous-flow technology, already firmly establishd on very large scale in the petrochemical industry, is becoming a point of emphasis for many companies in the pharmaceutical industry as the push for lean manufacturing intensifies.[1,2] The decrease in the number of isolated intermediates, the reduction of the capital equipment footprint, and better control over the production line are some of the key benefits of these methods. The use of microfluidic systems with small channels can provide fast mixing and efficient mass transfer for homogeneous reactions. However, as is the case in batch reactions, mixing and mass transfer are major issues in flow reactions involving multiple phases (liquid/liquid or liquid/gas). As a result of these issues, a large number of reactions that are vital to the preparation of pharmaceuticals require significant modification to be run in flow, and practical methods are required to overcome these obstacles.[3]

Microfluidics have found considerable application in this area of research, as the ability to perform a large number of reactions without the need for a large amount of reagents and solvents is desirable for research on a laboratory scale. The ability to perform a large number of reactions allows for thorough optimization of the reaction conditions and can also allow for studies of the reaction kinetics to aid in the transition from laboratory scale to production scale.[4]

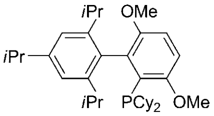
The palladium-catalyzed amination reaction of aryl halides is a widely utilized transformation in the pharmaceutical industry,[5] and thus a general method for performing this reaction in flow[6] would greatly aid in the development of flow syntheses of active pharmaceutical ingredients (APIs). However, while a great deal of research has been devoted to the development of highly active catalyst systems that can facilitate the coupling of a wide range of aryl electrophiles with a host of amine nucleophiles, the vast majority of these methods involve insoluble inorganic bases and/or form insoluble salt by-products.[7] Moreover, attempts to use soluble organic bases in these reactions have seen limited success.[8]

We postulated that a biphasic system with an organic solvent and water could solubilize both the organic and inorganic components of these reactions and could be a general solution to the formation of solids in flow.[9,10] Biphasic amination reactions that employ hydroxide bases, which could provide significant economic savings,[11] have been already reported.[12] The first report of palladium-catalyzed C–N bond formation using NaOH as a base was reported by Boche and co-workers in 1998.[12a] In 2001, Grasa et al. reported the coupling of aryl bromides with indoles using an N-heterocyclic carbene (NHC) ligand and NaOH as the base, with the reaction being performed in 1,4-dioxane.[12b] Similar conditions were later reported by Gooβen et al.[12c] Hartwig and co-workers have examined the use of hydroxide bases more thoroughly, and in 2002 they reported a method that employs KOH or NaOH, an equimolar amount of water, and a phase-transfer catalyst (PTC).[12d] Similar conditions were later reported by Urgaonkar and Verkade.[12e] Reactions using KOH in *tert*-butyl alcohol, as well as the first examples of amination performed in water without a cosolvent were reported by Huang et al. in 2003.[12f] Additional studies include the use of KOH in water with small amounts of *t*BuOH by Gong and Xu,[12g] the use of toluene and highly concentrated KOH under microwave conditions by Van Baelen and Maes,[12h] and reactions carried out in water with KOH and PTC by Lipshutz et al.[12i] However, a general method that allows for the complete solubility of all of the components of the reaction, which would be imperative for flow synthesis, remains an elusive goal.

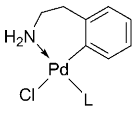
These previous methods fall into two categories: those that used very small amounts of water in an organic solvent, and those that used water as the solvent. For our study, it was decided to work with equal volumes of water and organic solvent to ensure complete solubility of both the organic and inorganic reagents and products. Initial studies were performed using the XPhos precatalyst (**3**)[13] with toluene as a solvent and aqueous KOH as the base, and were performed under batch conditions. The reaction of 4-chloroanisole and aniline in the presence of **3** (1 mol%) at 80°C for one hour resulted in only a 32% yield (Table 1, entry 1).



XPhos **1**



BrettPhos **2**



3; L = **1**
4; L = **2**

Since phase-transfer catalysts had been shown to accelerate similar coupling reactions, in which KOH was used as the base, a selection of these catalysts was examined. Tetrabutylammonium salts (Table 1, entries 2–4) provided an increase in yield, with the bromide giving the best result at 73% (Table 1, entry 2). Other quaternary ammonium bromides and a phosphonium bromide were also examined, but gave decreased yields in all cases (Table 1, entries 5–7). Next,

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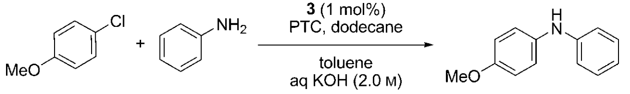
Table 1: Batch optimization of the phase-transfer catalyst (PTC) for the biphasic, palladium-catalyzed, C–N cross-coupling.[a]



Entry	PTC	PTC [%]	T [°C]	t [min]	**Yield [%]**[b]
1	none	–	80	60	32
2	$Bu_4N^+Br^-$	10	80	60	73
3	$Bu_4N^+OAc^-$	10	80	60	42
4[c]	$Bu_4N^+OH^-$	–	80	60	51
5	$Me_3NBn^+Br^-$	10	80	60	10
6	$Et_3NOct^+Br^-$	10	80	60	18
7	$Ph_4P^+Br^-$	10	80	60	22
8	$Bu_4N^+Br^-$	1	80	120	99
9	"	5	80	120	99
10	"	10	80	120	99
11	"	50	80	120	27
12	"	1	100	60	99

[a] Reaction conditions: Solution 1 (0.5 mL), ArCl (2 M), $ArNH_2$ (2.4 M), dodecane (2.4 M) in toluene; solution 2 (0.5 mL), **3** (0.02 M) in toluene; solution 3 (1.0 mL), base (2 M) in water; PTC added as a solid. [b] GC yield. [c] 1.0 mL of a 2.0 M solution of $Bu_4N^+OH^-$ in water was used in place of KOH.

the effect of the amount of tetrabutylammonium bromide (TBAB) was investigated: No difference in yield was observed when it was used between 1 and 10 mol% (Table 1, entries 8–10). However, when the quantity was increased to 50 mol% a drastic decrease in yield was observed (Table 1, entry 11).

During the course of these optimization reactions it was observed that the efficiency of the reaction was strongly influenced by the effectiveness of the mixing. As seen in Figure 1, the stirring rate was found to be directly proportional to the reaction yield; an increase of the stirring rate from 60 rpm to 900 rpm resulted in an increase in the yield of desired product from 13% to 60%.

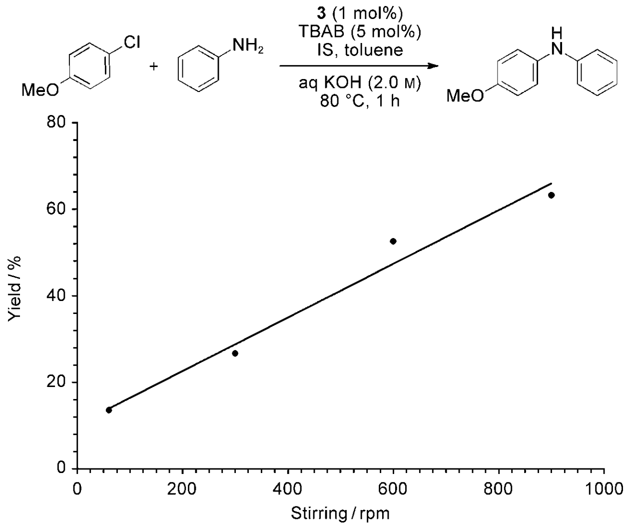
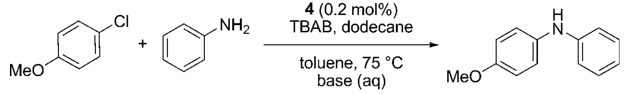


Figure 1. Stirring-rate dependence in batch. Reaction conditions: ArCl (1.0 mmol), $ArNH_2$ (1.2 mmol), **3** (1 mol%), TBAB (5 mol%), internal standard (biphenyl, 20 mol%), toluene (1 mL), 2.0 M KOH (aq) (1 mL).

Table 2: Batch optimization of the C–N cross-coupling.[a]



Entry	PTC [mol%]	Base	Base [M]	t [min]	**Yield [%]**[b]
1	–	KOH	2.0	17	12
2	1	KOH	2.0	17	24
3	5	KOH	2.0	17	63
4	10	KOH	2.0	17	74
5	5	KOH	2.0	10	50
6	5	K_3PO_4	2.0	10	14
7	5	Cs_2CO_3	2.0	10	20
8	5	K_2CO_3	2.0	10	30
9[c]	5	KOH	2.0	10	14
10[d]	5	KOH	1.0	20	51
11	5	KOH	2.0	20	78
12[e]	5	KOH	4.0	20	90

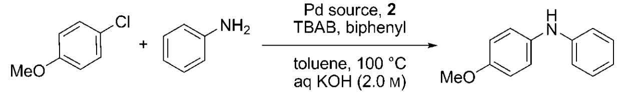
[a] Reaction conditions: Solution 1 (0.5 mL), ArCl (2 M), $ArNH_2$ (2.4 M), TBAB, dodecane (0.4 M) in toluene; solution 2 (0.5 mL), **6** (0.004 M) in toluene; solution 3 (1.0 mL), base (2 M) in water. [b] GC yield. [c] 1,4-Dioxane used in place of toluene. [d] 2.0 mL of 1.0 M KOH. [e] 0.5 mL of 4.0 M KOH.

In addition to these initial studies that were performed with **1** as the supporting ligand, experiments were also performed using **2**, which gives rise to a more active catalyst but is also more expensive than **1**.[14,15] When reactions were performed using a reduced loading of **4**, it was found that the effect of the PTC loading was more evident, with higher amounts, resulting in increased yields of the cross-coupled product (Table 2, entries 1–4). While 10 mol% of TBAB gave the highest yield, it was found to be above the solubility limit of TBAB in toluene. Thus, 5 mol% TBAB was used for the remainder of the study. Several other inorganic bases besides KOH were also investigated; however, only moderate levels of conversion were observed when K_3PO_4, Cs_2CO_3, or K_2CO_3 were employed (Table 2, entries 5–8).

With the base and PTC chosen, an experiment was performed using 1,4-dioxane in place of toluene to determine whether increasing the miscibility of the two phases would increase the efficiency of the reaction (Table 2, entry 9). This solvent change resulted in a decreased yield of product; therefore, toluene was used as the organic solvent for the remainder of our study. Next, the effect of the concentration of the base on these reactions was explored (Table 2, entries 10–12). The use of a more concentrated base gave a higher yield. However, as the method was being developed for use in flow, the increase was not sufficient to compensate for the increased viscosity of the base, which would lead to an unacceptable pressure drop when the reaction was performed under flow conditions.

Lastly, we examined the long-term stability of the catalyst precursors used for these experiments. In the same way that solubility was important to facilitate use in flow, it was essential to have reagents and catalysts that could be stored as solutions for the duration of an experiment. While large-scale flow equipment often incorporates a dissolution step to minimize the time spent in solution, laboratory-scale experiments require solutions which can be loaded onto pumps at the beginning of the experiment. This requirement resulted in a test being performed where the three solutions used in these experiments were prepared and then stored under argon in sealed volumetric flasks for 24 hours. In the case of **4** (Table 3, entries 1 and 2), the activity of the catalyst decreased from 88% to 70% over the course of the 24 hours of storage. Performing the same experiment with allylpalladium chloride dimer (**5**) and **2** gave a 45% yield for both the freshly made and the aged catalyst solutions. The yield was lower with **5**, which is attributable to slower activation of the catalyst, but once the active catalyst was formed, both reactions provided excellent yields (Table 3, entries 3 and 6).

Table 3: Batch optimization of the catalyst for the C–N cross-coupling.[a]



Entry	Pd source	Pd [mol%]	L [mol%]	Aging [h][b]	t [min]	**Yield [%]**[c]
1	**4**	0.5	0.1	0	3	88
2	**4**	0.5	0.1	24	3	70
3	**4**	0.5	0.1	24	6	96
4	**5**	0.5	0.6	0	3	45
5	**5**	0.5	0.6	24	3	45
6	**5**	0.5	0.6	24	6	94

[a] Reaction conditions: Solution 1 (0.5 mL), ArCl (2 M), $ArNH_2$ (2.4 M), TBAB (0.1 M), biphenyl (0.4 M) in toluene; solution 2 (0.5 mL), Pd (0.01 M), ligand (0.012 M) in toluene; solution 3 (1.0 mL), 2 M KOH in water. [b] Time between preparation and use of solution 2. [c] GC yield.

We next applied our optimized reaction conditions to experiments in flow. The strong influence on the efficiency of the mixing that was observed for the batch reactions was also observed when the reaction was performed in continuous flow. The use of immiscible liquid phases leads to segmented flow, which does not provide the same kind of mixing that is possible in a mechanically stirred reaction. We found that when the optimized (in batch) reaction conditions were transferred to a flow system, the reaction proceeded with greatly reduced efficiency. A variety of approaches were examined, including modification of the flow reactor (tubing) dimensions and changes in the microfluidic connections, in an attempt to overcome this mixing issue. However, all initial efforts resulted in only minor increases in the reaction efficiency.

As a consequence of the observed influence of mixing on the reaction proficiency, we tested the effect of a commercially available microfluidic mixing tee on this reaction. The mixing tee provided efficient mixing, but the two phases quickly separated to segmented flow upon exiting the mixer and no improvement in the reaction was observed. This result suggested that a more continuous source of mixing was required. It was found that the use of tube reactors packed with stainless-steel spheres could provide both the appropriate reactor volumes and the required biphasic mixing necessary for these reactions. This finding was in agreement with the elegant work recently reported by Bogdan and McQuade.[16]

As seen in Figure 2, when the reaction of ethyl 2-aminobenzoate and 2-chloroanisole was run in 0.04 inch PFA tubing (56 cm, 448 μL), less than 20% of the product was observed for residence times of 2–10 minutes. When the tubing reactor was replaced with a packed-bed reactor (100 mm × 3.8 mm ID tubing, 60–125 μm packing, 448 μL void volume), the same reaction gave full conversion after a residence time of 6 minutes. These results clearly demonstrate the importance of effective mixing for these reactions. Additionally, a sample was collected for 71 minutes (2.0 mmol, 8 minutes residence time, 56 μL min^{-1} total flow rate, 14 μL min^{-1} for solution 2). This sample provided 530 mg of isolated product, which corresponds to 98% yield, and was in agreement with the yields obtained by gas chromatography (GC). This result shows that the combination of a toluene/water biphasic system and the packed-bed reactor results in an effective protocol for palladium-catalyzed amination reactions of aryl halides in flow.

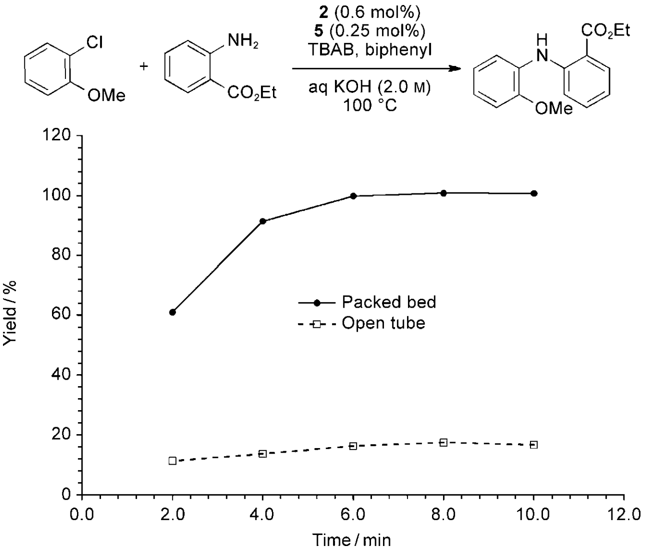


Figure 2. Comparison between a packed bed and an open tube. Reaction conditions: ArCl (1.0 equiv), $ArNH_2$ (1.2 equiv), **2** (0.6 mol%), **5** (0.25 mol%), TBAB (5 mol%), internal standard (biphenyl, 20 mol%), toluene (1 mL), 2.0 M KOH (aq, 1 mL).

We next wanted to examine the range of reaction conditions that could be used for this biphasic reaction. The results in Figure 3 demonstrate the effect of reactor size on the yield of the reaction. The reactions in Figure 3 were performed using a series of four packed beds of different sizes. In the largest packed bed, the results tracked very closely with the results obtained for this reaction in the batch process with high stirring rates. In addition to the samples collected for GC analysis, one sample was collected for 46 minutes (2.0 mmol, 10 min residence time, 87 μL min^{-1} total flow rate, 22 μL min^{-1} for solution 2). This sample provided 374 mg (94%) of isolated product. As the size of the packed bed was

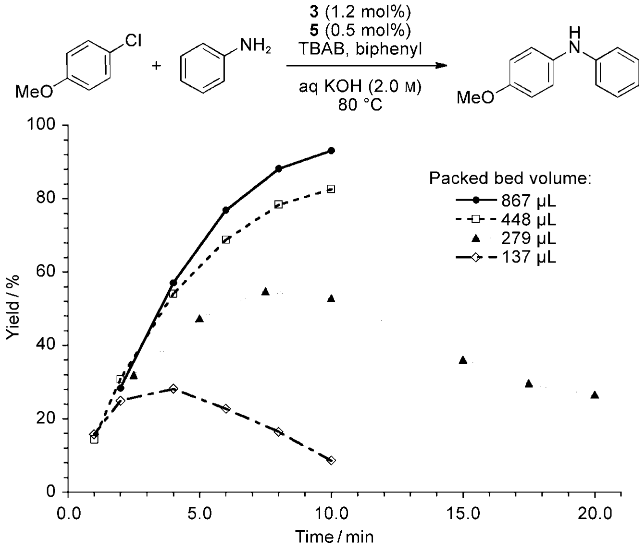


Figure 3. Comparison of different sized packed beds. Reaction conditions: ArCl (1.0 equiv), $ArNH_2$ (1.2 equiv), **2** (1.2 mol%), **5** (0.5 mol%), TBAB (5 mol%), internal standard (biphenyl, 20 mol%), toluene (1 mL), 2.0 M KOH (aq, 1 mL).

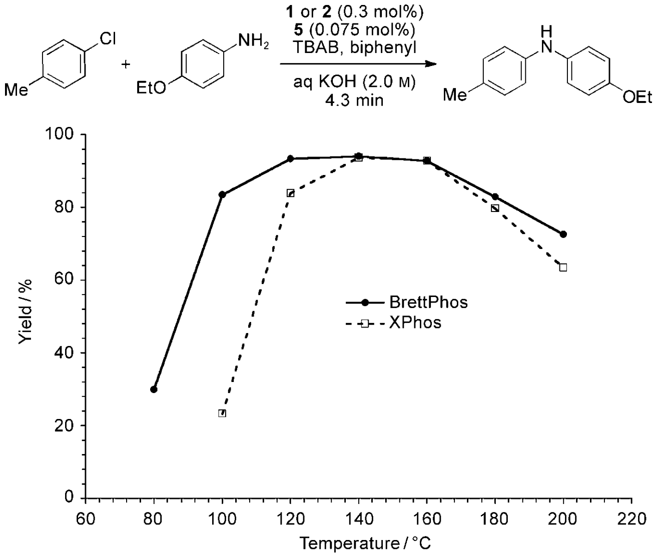


Figure 4. High temperature experiments. Reaction conditions: ArCl (1.0 equiv), $ArNH_2$ (1.2 equiv), **1** or **2** (0.3 mol%), **5** (0.075 mol%), TBAB (5 mol%), internal standard (biphenyl, 20 mol%), toluene (1 mL), 2.0 M KOH (aq, 1 mL).

decreased, the yield of the reaction was also decreased. Interestingly, it was found with the two smallest packed beds that after a certain point the reaction yield began to decrease with increased residence time (decreased flow rate). The reaction conversion was in agreement with the reaction yield, thereby implying that the product was not degrading over time. It was postulated that the mixing in the packed beds was related to the flow rate of the two reaction streams. Such a postulation suggested that the biphasic amination method presented herein would be most effective for fast reactions where moderate flow rates can be maintained. Further studies to quantify the hydrodynamic parameters of the packed beds are underway.

One important benefit of continuous-flow chemistry is the ability to access reaction conditions that are either difficult to achieve or unsafe in standard batch systems. The most common example of this is the use of high temperatures and pressures. We thought that increasing the temperature above the boiling point of the two solvents in the biphasic amination system could allow for the reduction of the reaction time, thereby increasing the number of possible reactions that could be performed efficiently using this method.

Figure 4 shows the effect of increasing the temperature and pressure for a palladium-catalyzed amination reaction performed in toluene. In this experiment a 1000 psi back-pressure regulator was used to inhibit solvent vaporization, and HPLC pumps were used to overcome this pressure drop. The reaction time was held constant and the temperature was systematically increased from 80 °C to 200 °C. The reaction rate was greatly enhanced by the increased temperature, to a point where catalyst decomposition began to take place. Gratifyingly, a reaction that only proceeded to approximately 30% yield under the standard conditions was driven to complete conversion at the increased temperature. One sample was collected at the 120 °C conditions for 20 minutes (2.0 mmol, 4.3 min residence time, 200 $\mu L\,min^{-1}$ total flow rate, 50 $\mu L\,min^{-1}$ for solution 2), and the product was isolated in 90% yield (409 mg). This result suggests that a wide range of reactions could be performed by using this method by optimizing catalyst loading, reaction time, and reaction temperature. In addition to the ability to push difficult reactions to completion with increased temperature, this approach can also be used to decrease the amount of catalyst needed for these reactions, as shown in Figure 4, where only 0.15 mol% Pd was used. Another benefit of the ability to perform flow reactions under forcing conditions is the potential to use less-expensive supporting ligands to form the catalysts for these reactions. As can be seen in Figure 4, although **2** provided the most active catalyst, it was possible to achieve the same levels of reactivity using **1**, which at present is considerably cheaper.[15]

In conclusion, conditions have been developed for palladium-catalyzed C–N bond-forming reactions carried out in a continuous-flow manner. The optimized conditions involve the use of aqueous KOH, toluene as a reaction solvent, TBAB as a phase-transfer catalyst, and a packed-bed microreactor. Moderate flow rates ($>40\,uL\,min^{-1}$) are necessary for efficient mixing. High temperature and pressure reaction conditions are easily accessed, and lead, in some cases, to greatly enhanced reaction rates.

Experimental Section

Materials: Endcaps from standard 1/4 inch HPLC columns were recycled for the preparation of the packed beds used in this study. Sintered stainless-steel (SS) frits (0.189 inch diameter and 10 µm pore size) were purchased from IDEX Health and Science (formerly Upchurch Scientific). Nuts and ferrule sets (1/4 inch SS) were purchased from Swagelok. The tubing (SS, 0.25 inch OD x 0.21 inch ID) was purchased from McMaster Carr and was cut to length. Microspheres (SS, 60–125 µm) were purchased from Duke Scientific, a subsidiary of Thermo Fisher. Microfluidic connections were made with standard Upchurch fittings (IDEX Health and Science), either 10–32 coned fittings, or 1/4–28 flat-bottomed fittings for 1/16 inch OD tubing.

Procedure for the reaction reported in Figure 1: An oven-dried screw-top volumetric flask (5.00 mL), equipped with a stir bar and a teflon screw-cap septum, was charged with **2** (32.2 mg, 0.06 mmol) and **5** (9.2 mg, 0.025 mmol). The vessel was evacuated and back-filled with argon (this process was repeated a total of 3 times) and toluene (ca. 5 mL) was added to make the solution up to volume. Solution 1 was stirred for 5 min to allow complete dissolution of the solid reagents. A second flask (5.00 mL), equipped in the same manner, was charged with biphenyl (308 mg, 2.0 mmol) and TBAB (161 mg, 0.5 mmol). The vessel was evacuated and back-filled with argon (this process was repeated a total of 3 times), and then 2-chloroanisole (1.21 mL, 10.0 mmol) and ethyl 2-aminobenzoate (1.77 mL, 12.0 mmol) were added, with toluene used to make the solution up to volume. Solution 2 was stirred to allow the dissolution of the solid reagents. Solutions 1 and 2 were loaded into plastic syringes and fitted to syringe pumps as described in the Supporting Information (448 µL packed bed). Three other syringes were filled separately with KOH (2 M), ethyl acetate and water, and were fitted to the remaining syringe pumps. The reagents were flowed through the packed-bed reactor at the appropriate flow rates to give residence times of 2–10 min. Samples were collected, diluted with ethyl acetate and water, mixed vigorously, and an aliquot of the organic layer was filtered through a plug of silica, eluting with ethyl acetate, and the sample was analyzed by GC.

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Keywords: amination · continuous flow · cross-coupling · packed-bed reactors · palladium

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[1] For references on lean manufacturing, see: a) T. Ohno, *Toyota Production System: Beyond Large-Scale Production*, Productivity Press University Park, Portland, OR, **1988**; b) J. P. Womack, D. T. Jones, D. Roos, *The Machine That Changed the World: The Story of Lean Production*, HarperCollins, New York, **1991**; c) J. M. Gross, K. R. McInnis, *Kanban Made Simple*, American Management Association, New York, **2003**.

[2] For an application of Lean Manufacturing to the drug industry, see: H. N. Weller, D. S. Nirschl, E. W. Petrillo, M. A. Poss, C. J. Andres, C. L. Cavallaro, M. M. Echols, K. A. Grant-Young, J. G. Houston, A. V. Miller, R. T. Swann, *J. Comb. Chem.* **2006**, *8*, 664–669.

[3] a) D. M. Roberge, L. Ducry, N. Bieler, P. Cretton, B. Zimmermann, *Chem. Eng. Technol.* **2005**, *28*, 318–323; b) R. W. Dugger, J. A. Ragan, D. H. B. Ripin, *Org. Process Res. Dev.* **2005**, *9*, 253–258; c) G. N. Doku, W. Verboom, D. N. Reinhoudt, A. van der Berg, *Tetrahedron* **2005**, *61*, 2733–2742; d) J. Yoshida, A. Nagaki, T. Iwasaki, S. Suga, *Chem. Eng. Technol.* **2005**, *28*, 259–266; e) J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* **2006**, *4*, 2337–2347; f) J. Kobayashi, Y. Mori, S. Kobayashi, *Chem. Asian J.* **2006**, *1–2*, 22–35; g) T. Fukuyama, T. Rahman, M. Sato, I. Ryu, *Synlett* **2008**, *2*, 151–163.

[4] a) K. F. Jensen, *Chem. Eng. Sci.* **2001**, *56*, 293–303; b) P. D. I. Fletcher, S. J. Haswell, E. Pombo-Villar, B. H. Warrington, P. Watts, S. Y. F. Wong, X. L. Zhang, *Tetrahedron* **2002**, *58*, 4735–4757; c) K. Jahnisch, V. Hessel, H. Lowe, M. Baerns, *Angew. Chem.* **2004**, *116*, 410–451; *Angew. Chem. Int. Ed.* **2004**, *43*, 406–446; d) H. Pennemann, P. Watts, S. J. Haswell, V. Hessel, H. Lowe, *Org. Process Res. Dev.* **2004**, *8*, 422–439; e) V. Hessel, H. Lowe, *Chem. Eng. Technol.* **2005**, *28*, 267–284; f) P. Watts, S. J. Haswell, *Chem. Soc. Rev.* **2005**, *34*, 235–246; g) K. Geyer, J. D. C. Codee, P. H. Seeberger, *Chem. Eur. J.* **2006**, *12*, 8434–8442; h) K. F. Jensen, *MRS Bull.* **2006**, *31*, 101–107; i) A. J. deMello, *Nature* **2006**, *442*, 394–402; j) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107*, 2300–2318; k) B. Ahmed-Omer, J. C. Brandt, T. Wirth, *Org. Biomol. Chem.* **2007**, *5*, 733–740; l) P. Watts, C. Wiles, *Chem. Commun.* **2007**, 443–467; m) P. Watts, C. Wiles, *Chem. Eng. Technol.* **2007**, *30*, 329–333; n) R. L. Hartman, K. F. Jensen, *Lab Chip* **2009**, *9*, 2495–2507; o) W. Ehrfeld, V. Hessel, H. Lowe, *Microreactors: New Technology for Modern Chemistry*, Wiley-VCH: Weinheim, **2000**; p) K. F. Jensen, in *New Avenues to Effcient Chemical Synthesis: Emerging Technologies* (Eds.: P. H. Seeberger, T. Blume), Springer, Heidelberg, **2007**, pp 57–76; q) V. hessel, J. C. Schouten, A. Renken, J.-I. Yoshida, *Handbook of Micro Reactors*, Wiley-VCH, Weinheim, **2009**.

[5] For a selection of recent papers that use palladium-catalyzed aminations to make biologically active compounds, see: a) F. W. Goldberg, R. A. Ward, S. J. Powell, J. E. Debreczeni, R. A. Norman, N. J. Roberts, A. P. Dishington, H. J. Gingell, K. F. Wickson, A. L. Roberts, *J. Med. Chem.* **2009**, *52*, 7901–7905; b) S. Guo, Y. Song, Q. Huang, H. Yuan, B. Wan, Y. Wang, R. He, M. G. Beconi, S. G. Franzblau, A. P. Kozikowski, *J. Med. Chem.* **2010**, *53*, 649–659; c) V. Sandanayaka, B. Mamat, R. K. Mishra, J. Winger, M. Krohn, L.-M. Zhou, M. Keyvan, L. Enache, D. Sullins, E. Onau, J. Zhang, G. Halldorsdottir, H. Sigthorsdottir, A. Thorlaksdottir, G. Sigthorsson, M. Thorsteinnsdottir, D. R. Davies, L. J. Stewart, D. E. Zembower, T. Andresson, A. S. Kiselyov, J. Singh, M. E. Gurney, *J. Med. Chem.* **2010**, *53*, 573–585; d) M. Decker, Y.-G. Si, B. I. Knapp, J. M. Bidlack, J. L. Neumeyer, *J. Med. Chem.* **2010**, *53*, 402–418.

[6] For references pertaining to palladium-catalyzed amination reactions in microflow, see: a) C. Mauger, O. Buisine, S. Caravieilhes, G. Mignani, *J. Organomet. Chem.* **2005**, *690*, 3627–3629; b) D. Popa, R. Marcos, S. Sayalero, A. Vidal-Ferran, M. A. Pericàs, *Adv. Synth. Catal.* **2009**, *351*, 1539–1556; c) G. Shore, S. Morin, D. Mallik, M. G. Organ, *Chem. Eur. J.* **2008**, *14*, 1351–1356; d) R. L. Hartman, J. R. Naber, N. Zaborenko, S. L. Buchwald, K. F. Jensen, *Org. Proc. Res. Dev.* early view; e) P. Bazinet, J. P. McMullen, J. R. Naber, A. Musacchio, K. F. Jensen, S. L. Buchwald, *Org. Proc. Res. Dev.* (submitted).

[7] For recent reviews of palladium-catalyzed aminations, see: a) D. S. Surry, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 6438–6461; *Angew. Chem. Int. Ed.* **2008**, *47*, 6338–6361; b) S. L. Buchwald, L. Jiang, in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: A. deMeijere, F. Diederich), Wiley-VCH, Weinheim, **2004**, p 699; c) J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534–1544; d) N. Marion, S. P. Nolan, *Acc. Chem. Res.* **2008**, *41*, 1440–1449.

[8] a) R. E. Tundel, K. W. Anderson, S. L. Buchwald, *J. Org. Chem.* **2006**, *71*, 430–433; b) E. R. Murphy, J. R. Martinelli, N. Zaborenko, S. L. Buchwald, K. F. Jensen, *Angew. Chem.* **2007**, *119*, 1764–1767; *Angew. Chem. Int. Ed.* **2007**, *46*, 1734–1737.

[9] For a reviews of metal-catalyzed reactions in water, see: a) M. Carril, R. SanMartin, E. Dominguez, *Chem. Soc. Rev.* **2008**, *37*, 639–647; b) K. H. Shaughnessy, *Chem. Rev.* **2009**, *109*, 643–710.

[10] a) A. S. Dallas, K. V. Gothelf, *J. Org. Chem.* **2005**, *70*, 3321–3323; b) S. R. Stauffer, M. A. Steinbeiser, *Tetrahedron Lett.* **2005**, *46*, 2571–2575.

[11] B. Schlummer, U. Scholz, *Adv. Synth. Catal.* **2004**, *346*, 1599–1626.

[12] a) G. Wullner, H, Jansch, S. Kannenberg, F. Schubert, G. Boche, *Chem. Commun.* **1998**, 1509–1510; b) G. A. Grasa, M. S. Viciu, J. Huang, S. P. Nolan, *J. Org. Chem.* **2001**, *66*, 7729–7737; c) L. J. Goossen, J. Paetzold, O. Briel, A. Rivas-Nass, R. Karch, B. Kayser, *Synlett* **2005**, 275–278; d) R. Kuwano, M. Utsunomiya, J. F. Hartwig, *J. Org. Chem.* **2002**, *67*, 6479–6486; e) S. Urgaon-

kar, J. G. Verkade, *J. Org. Chem.* **2004**, *69*, 9135 – 9142; f) X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 6653 – 6655; g) C. Xu, J.-F. Gong, Y.-J. Wu, *Tetrahedron Lett.* **2007**, *48*, 1619 – 1623; h) G. Van Baelan, B. U. W. Maes, *Tetrahedron* **2008**, *64*, 5604 – 5619; i) B. H. Lipshutz, D. W. Chung, B. Rich, *Adv. Synth. Catal.* **2009**, *351*, 1717 – 1721.

[13] M. R. Biscoe, B. P. Fors, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 6686 – 6687.

[14] B. P. Fors, D. A. Watson, M. R. Biscoe, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 13552 – 13554.

[15] Prices from the Strem Chemicals online catalog: XPhos [564483–18–7] $36 g based on price for 10 grams, BrettPhos [N/A] $264 g.

[16] A. Bogdan, D. T. McQuade, *Beilstein J. Org. Chem.* **2009**, *5*, No. 17.