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Low pressure Pd-catalyzed carbonylation in an ionic liquid using a multiphase microflow system†

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A low pressure microflow system was developed for palladium-catalyzed multiphase carbonylation reactions in an ionic liquid. The microflow system resulted in superior selectivity and higher yields in carbonylative Sonogashira coupling and amidation reactions of aryl iodides compared to the conventional batch system.

The benefits of having an exceedingly high surface-to-volume ratio and efficient heterogeneous mass-transfer in microchannels have led many researchers to study continuous flow systems using microreactors for heterogeneous catalytic reactions.[1,2] We previously reported that a continuous microflow system can be quite useful for the catalytic reactions, which employ ionic liquids (IL) as the reaction medium and catalyst-support.[3] Thus, Pd-catalyzed cross-coupling reactions, such as the Sonogashira reaction[3a] and the Mizoroki–Heck reaction[3b] can be carried out with efficient catalyst recycling in a continuous microflow system. In this communication, we report on the successful application of catalytic microflow reactions to Pd-catalyzed carbonylation reactions using CO gas under pressurized conditions. We found that Pd-catalyzed carbonylation reactions in ionic liquids, when conducted in conjunction with a microreactor, proceeded efficiently, even at low CO pressures.

Using the microflow system outlined in Fig. 1, we examined the Pd-catalyzed carbonylation of iodoarenes in an ionic liquid. The microflow system used in this study consists of two T-shaped micromixers (T-1 and T-2) and a stainless tube reactor as well as equipment designed to ensure the pressurized microflow of CO. This continuous microflow approach involves the mixing of an ionic liquid containing the Pd-catalyst with CO and the substrates, successively, in different micromixers and then passing the multiphase (ionic liquid–substrate–CO) through a heated capillary tube reactor acting as a residence time unit to give the desired products.

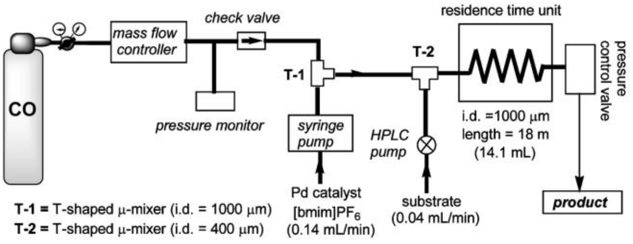
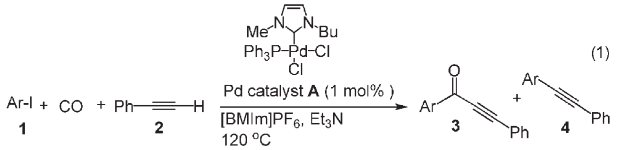


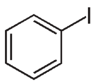
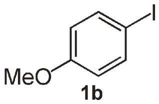
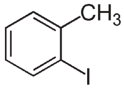
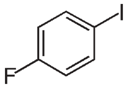
Fig. 1 Schematic diagram of the microflow system.

We carried out a Pd-catalyzed carbonylative Sonogashira coupling of aryl iodides **1** and phenylacetylene (**2**) in [BMIm]PF_6, as the first model reaction (eqn (1)).[4] For example,

Table 1 Pd-catalyzed carbonylative three-component coupling of **1** and **2**[a]



(1)

Entry	1	CO pressure	System/Product/Yield[b]		
1	 **1a**	5 atm	Microflow	**3a** (83%)	**4a** (—)
2			Batch	**3a** (25%)	**4a** (60%)
3	**1a**	3 atm	Microflow	**3a** (80%)	**4a** (—)
4			Batch	**3a** (14%)	**4a** (65%)
5	 **1b**	5 atm	Microflow	**3b** (77%)	**4b** (—)
6			Batch	**3b** (67%)	**4b** (21%)
7	**1b**	3 atm	Microflow	**3b** (77%)	**4b** (—)
8			Batch	**3b** (44%)	**4b** (39%)
9	 **1c**	5 atm	Microflow	**3c** (92%)	**4c** (—)
10			Batch	**3c** (36%)	**4c** (37%)
11	 **1d**	5 atm	Microflow	**3d** (72%)	**4d** (—)
12			Batch	**3d** (65%)	**4d** (16%)

[a] Reaction conditions. *Microflow*: **1** (7 mmol), **2** (8.4 mmol, 1.2 equiv.), Et_3N (25.2 mmol, 3.6 equiv.), CO (5 or 3 atm), Pd-cat. (1 mol%), [BMIm]PF_6 (17 mL); flow rates: mixture of **1**, **2** and Et_3N (0.04 mL min^{-1}), Pd/[BMIm]PF_6 (0.14 mL min^{-1}), CO (1.0 mL min^{-1}); 120 °C; residence time: 12 min. *Batch*: **1** (1.0 mmol), **2** (1.2 equiv), Et_3N (3.6 equiv.), Pd-cat. (1 mol%), [BMIm]PF_6 (3.0 mL), CO (5 or 3 atm); 120 °C, reaction time: 1 h. [b] Yields were determined from ^1H NMR.

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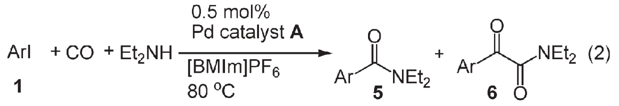
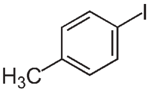
Table 2 Pd-catalyzed single/double carbonylation of aryl iodides[a]



Entry	Substrate	CO	System/Products/Yields[b]			
1	**1a**	20 atm	Microflow	**5a** (6%)	**6a** (80%)	**1a** (—)
2			Batch	**5a** (11%)	**6a** (63%)	**1a** (22%)
3	 **1e**	20 atm	Microflow	**5e** (5%)	**6e** (85%)	**1a** (—)
4			Batch	**5e** (4%)	**6e** (70%)	**1e** (17%)
5	**1e**	15 atm	Microflow	**5e** (10%)	**6e** (68%)	**1a** (—)
6			Batch	**5e** (11%)	**6e** (52%)	**1e** (17%)

[a] Reaction conditions. *Microflow*: **1** (14.0 mmol), Et_2NH (70 mmol, 5.0 equiv.), CO (20 or 15 atm), Pd-cat. (0.5 mol%) in $[BMIm]PF_6$ (17 mL); flow rates: mixture of **1** and Et_2NH (0.04 mL min^{-1}), Pd/$[BMIm]PF_6$ (0.14 mL min^{-1}), CO (0.25 mL min^{-1}); 80 °C; residence time: 34 min. *Batch*: **1** (2.66 mmol), Et_2NH (5.0 equiv.), Pd-cat. (0.5 mol%), $[BMIm]PF_6$ (2.0 mL), CO (20 or 15 atm), 80 °C, reaction time: 5 h. [b] Yields were determined from ^1H NMR.

at a CO pressure of 20 atm, a batch reaction gave α,β-acetylenic ketone **3a** as the sole product in 83% yield, whereas when the reaction was conducted at 5 atm of CO, the Sonogashira coupling product **4a** was produced in 60% yield as the dominant product over the desired product **3a** (25%) (Table 1, entry 2). In sharp contrast, the use of the microflow system gave **3a** (83%) exclusively, even at 5 atm of CO pressure, and the formation of non-carbonylation product **4a** was not observed (entry 1). By further lowering the CO pressure to 3 atm, the microflow system still yielded **3a** (80%) exclusively (entry 3), whereas in the batch reaction, carbonylation selectivity further diminished giving **3a** in only 14% (entry 4). This tendency generally holds for other substrates, **1b**, **1c** and **1d**, as well (entries 5–12).[5] Thus the microflow system showed excellent performance in producing solely the acetylenic ketones **3**, even under reduced CO pressures, without the formation of the Sonogashira byproduct **4**.

Given the remarkably high efficiency of a microflow system for carbonylative-Sonogashira coupling reactions, we examined the applicability of our system for the Pd-catalyzed carbonylation of aromatic iodides in the presence of a secondary amine, which is being extensively investigated with regard to single/double carbonylation selectivity (eqn (2)).[6,7] Thus, when we carried out the carbonylation of iodobenzene (**1a**) in the presence of Et_2NH at a CO pressure of 20 atm, the microflow system produced the α-keto amide **6a** in 80% yield along with 6% of amide **5a** in 34 min (Table 2, entry 1), while a batch reaction suffered from a low conversion of **1a**, consequently resulting in an inferior yield of **6a** (63%) even after 5 h (entry 2). Similarly, taking another substrate, 4-iodotoluene (**1e**), and carrying out the reactions at various CO pressures (20 and 15 atm), the yields of the α-keto amide **6e** were higher in the case of the microflow system than that in a batch system for all cases examined (entries 3–6).

Since CO exhibits low solubility in highly viscous ionic liquids,[8] carbonylation selectivity is presumed to be controlled by the diffusion efficiency of CO. The extent of CO diffusion into the bulk of IL in a batch reactor can be altered by varying (i) the CO pressure and/or (ii) the surface-to-area ratio by taking different amounts of IL.

This hypothesis was tested by carrying out carbonylative-coupling reactions of **1d** with **2** under 5 atm of CO pressure with variable volumes of $[BMIm]PF_6$ with a constant IL/CO surface area using an autoclave (Fig. 2a). The results showed that the selectivity for carbonylation increased with increasing value of the IL/CO surface area-to-IL volume ratio (Fig. 2b).

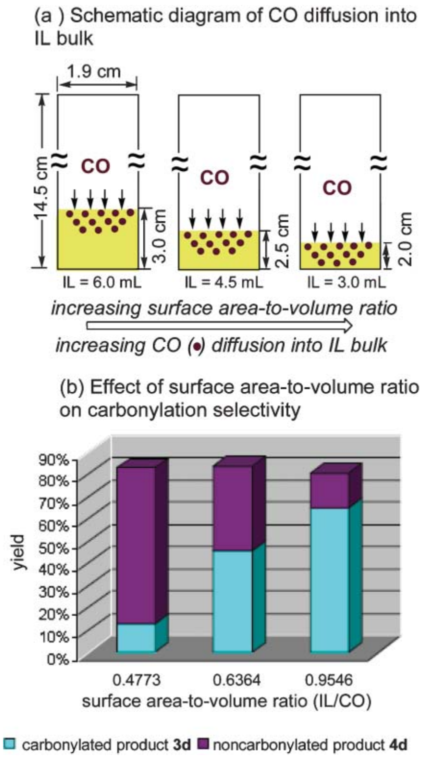
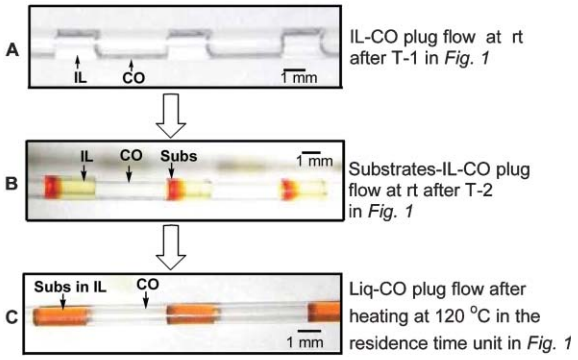


Fig. 2 Controlled carbonylation experiment taking different volumes of IL in a 50 mL autoclave reactor and using the same molar concentrations of **1d** (0.33 M), **2** (0.40 M), Et_3N (1.19 M) and Pd-catalyst A (1.0 mol%) in each run.



IL-CO plug flow at rt after T-1 in *Fig. 1*

Substrates-IL-CO plug flow at rt after T-2 in *Fig. 1*

Liq-CO plug flow after heating at 120 °C in the residence time unit in *Fig. 1*

Fig. 3 Photographic images of the flow regime inside the capillary tube (id = 1000 μm).

To obtain a better understanding of the higher efficiency of our microflow system over the batch reactor, we decided to visualize the real time microflow patterns using transparent capillary tubes. The photographic images revealed the occurrence of a segmented plug-flow inside the microscale channels (Fig. 3). When the IL and CO were mixed in the first T-shaped μ-mixer (T-1), a segmented IL–CO plug flow resulted (Photo A) which, after mixing with the substrates (**1b**, **2** and Et_3N) at the second T-mixer (T-2), again gave an alternate IL–substrate–CO plug flow (Photo B). When this IL–substrate–CO flow was fed into the residence time unit (temperature 120 °C), the substrate-phase dissolved in the IL-phase giving a liquid–gas segmented flow regime (Photo C). Thus, the superior efficiency of the microflow system over the batch reactor can be attributed to the occurrence of plug flow, because, this type of flow regime might have provided a large specific interfacial area between the CO and liquid phase[9] and facilitated the diffusion of CO into the thin IL (approximately 2.0 mm) plugs. On the contrary, for batch reactions, such a large interfacial area-to-volume ratio or efficient CO diffusion through IL cannot be obtained because mechanical stirring is the only means for multiphase mixing.

In summary, palladium-catalyzed carbonylation reactions in a microflow system were carried out in an ionic liquid, which can function as a recyclable reaction media and catalyst support. The results clearly demonstrate that liquid–gas segmented microflow offered excellent selectivity and high yields for carbonylation reactions even when conducted at relatively lower CO pressures. Additional studies suggest that at low pressure, the diffusivity of CO into the ionic liquid bulk is a limiting factor for determining the carbonylation/non-carbonylation selectivity ratio in a batch system.

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Notes and references

1 For recent reviews on microchemical technology in synthesis, see: (*a*) W. Ehrfeld, V. Hessel and H. Lehr, *Top. Curr. Chem.*, 1998, **194**, 233; (*b*) W. Ehrfeld, V. Hessel and H. Löwe, in *Microreactor: New Technology for Modern Chemistry*, WILEY-VCH, Weinheim, 2000; (*c*) P. D. I. Fletcher, S. J. Haswell, E. Pombo-Villar, B. H. Warrington, P. Watts, S. Y. F. Wong and X. Zhang, *Tetrahedron*, 2002, **58**, 4735; (*d*) K. Jähnisch, V. Hessel, H. Löwe and M. Baerns, *Angew. Chem., Int. Ed.*, 2004, **43**, 406; (*e*) P. Watts and S. J. Haswell, *Chem. Soc. Rev.*, 2005, **34**, 235.

2 For recent reviews on microreactors in heterogeneous catalysis, see: (*a*) A. Kirschning and G. Jas, *Top. Curr. Chem.*, 2004, **242**, 209; (*b*) G. N. Doku, W. Verboom, D. N. Reinhoudt and A. V. D. Berg, *Tetrahedron*, 2005, **61**, 2733; (*c*) L. Kiwi-Minsker and A. Renken, *Catal. Today*, 2005, **110**, 2; For recent studies also see: (*d*) J. Kobayashi, Y. Mori, K. Okamoto, R. Akiyama, M. Ueno, T. Kitamori and S. Kobayashi, *Science*, 2004, **304**, 28; (*e*) R. Abdallah, V. Meille, J. Shaw, D. Wenn and C. de Bellefon, *Chem. Commun.*, 2004, 372; (*f*) N. Yoswathananont, K. Nitta, Y. Nishiuchi and M. Sato, *Chem. Commun.*, 2004, 40; (*g*) D. I. Enache, G. H. Hutchings, S. T. Taylor, R. Natividad, S. Raymahasay, J. K. Winterbottom and E. H. Stitt, *Inds. Eng. Chem. Res.*, 2005, **44**, 6295; (*h*) Y. Oenal, M. Lucas and P. Claus, *Chem.-Ing.-Tech.*, 2005, **77**, 101.

3 (*a*) T. Fukuyama, M. Shinmen, S. Nishitani, M. Sato and I. Ryu, *Org. Lett.*, 2002, **4**, 1691; (*b*) S. Liu, T. Fukuyama, M. Sato and I. Ryu, *Org. Process Res. Dev.*, 2004, **8**, 477.

4 We recently reported on the autoclave version of this reaction in IL: T. Fukuyama, R. Yamaura and I. Ryu, *Can. J. Chem.*, 2005, **83**, 711.

5 When DMF was used as the reaction medium instead of an ionic liquid, no such difference between the microflow system and the batch system was observed.

6 (*a*) F. Ozawa, H. Soyama, H. Yanagihara, I. Aoyama, H. Takino, K. Izawa, T. Yamamoto and A. Yamamoto, *J. Am. Chem. Soc.*, 1985, **107**, 3235; (*b*) E. Mizushima, T. Hayashi and M. Tanaka, *Green Chem.*, 2001, **3**, 76.

7 *cf.* P. W. Miller, N. J. Long, A. J. de Mello, R. Vilar, J. Passchier and A. Gee, *Chem. Commun.*, 2006, 546.

8 At 295 K and 1.0 bar CO solubility in $[BMIm]PF_6$ is 1.47 mM, whereas for toluene it is 7.3 mM. For details see: C. A. Ohlin, P. J. Dyson and G. Laurenczy, *Chem. Commun.*, 2004, 1070.

9 B. K. H. Yen, A. Günther, M. A. Schmidt, K. F. Jensen and M. G. Bawendi, *Angew. Chem., Int. Ed.*, 2005, **44**, 5447.