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Continuous Flow Sonogashira C–C Coupling Using a Heterogeneous Palladium–Copper Dual Reactor

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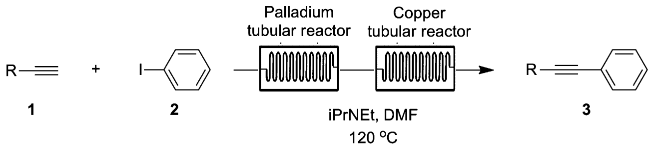
ABSTRACT



We report the development of a heterogeneous catalyst system on continuous flow chemistry. A palladium (Pd) coated tubular reactor was placed in line with copper (Cu) tubing using a continuous flow platform, and a Sonogashira C–C coupling reaction was used to evaluate the performance. The reactions were favorably carried out in the Cu reactor, catalyzed by the traces of leached Pd from the Pd reactor. The leached Pd and Cu were trapped with a metal scavaging resin at the back-end of the continuous flow system, affording a genuine approach toward green chemistry.

Microreactor and tubular reactor technologies in continuous flow are particularly advantageous as they improve heat transfer and atom economy through better reaction control.[1] Recent trends have shown an increase in the use of metal tubular reactors as a catalytic source to promote green chemistry.[2] The Cu tubular reactor has been shown to be effective in catalyzing the click reactions from simple starting materials using the one-pot methodology, employing conventional heating and ultrasound as additional sources of energy.[3] Commercially available Cu tube flow reactor has also been used to carry out several synthetic transformations in good yields.[4] Kawanami et al. developed a Pd–Cu alloy on the inner surface of the tubular reactor and investigated Sonogashira C–C coupling under elevated temperature and pressure.[5] Despite the tedious Pd coating, the use of water as a reaction solvent, the short

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(1) For a few selected reviews and examples of continuous flow chemistry, see: (a) Kirschning, A.; Jas, G. In *Applications of Immobilized Catalysts in Continuous Flow Processes*; Topics in Current Chemistry, Vol. 242; Springer-Verlag: Berlin Heidelberg, 2004; p 209. (b) Watts, P.; Wiles, C. *J. Chem. Res.* **2012**, *36*, 181–193. (c) van den Broek, S. A. M. W.; Leliveld, J. R.; Becker, R.; Delville, M. M. E.; Nieuwland, P. J.; Koch, K.; Rutjes, F. P. J. T. *Org. Process Res. Dev.* **2012**, *16*, 934–938. (d) Calabrese, G. S.; Pissavini, S. *AIChE J.* **2011**, *5*, 828–834. For a few examples on using microreactors and tubular reactors in continuous flow chemistry, see: (e) Razzaq, T.; Kappe, O. C. *Chem.—Asian J.* **2010**, *5*, 1274. (f) Hartman, R.; McMullen, J.; Jensen, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 7502–7519. (g) Yoshida, J. I.; Kim, H.; Nagaki, A. *ChemSusChem* **2011**, *4*, 331–340.

(2) Mason, B. P.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. *Chem. Rev.* **2007**, *107*, 2300–2318.

(3) For some selected examples using Cu tubular reactor, see: (a) Bogdan, A. R.; Sach, N. W. *Adv. Synth. Catal.* **2009**, *351*, 849–854. (b) Bogdan, A. R.; James, K. *Chem.—Eur. J.* **2010**, *16*, 14506–14512. (c) Bogdan, A. R.; James, K. *Org. Lett.* **2011**, *13*, 4060–4063. (d) Tu, N. P.; Hochlowski, J. E.; Djuric, S. W. *Mol. Diversity* **2012**, *16*, 53–58.

(4) Zhang, Y.; Jamison, T. F.; Patel, S.; Mainolfi, N. *Org. Lett.* **2011**, *13*, 280–283.

(5) (a) Javaid, R.; Kawanami, H.; Chatterjee, M.; Ishizaka, T.; Suzuki, A.; Suzuki, T. M. *Chem. Eng. J.* **2011**, *167*, 431–435 and references cited therein. (b) Kawanami, H.; Matsushima, K.; Sato, M.; Ikushima, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 5129–5132.

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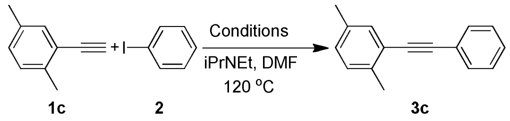
residence time, and the nonleaching nature of the system promoted green chemistry efforts.

Pd is a precious metal of relatively low abundance, high toxicity, and higher risk to sustainable sourcing.[6] Many cross-couplings are carried out with the use of Pd catalysis.[7] There is a great need to further reduce the amount of Pd used for practical applications. In this paper, a dual Pd−Cu inline tubular reactor was reported. A Pd coated tubular reactor was placed in line with a Cu tubing, providing facile access to a wide range of Sonogashira coupling products from moderate to good yields under ambient conditions, while utilizing only a minimal amount of Pd. An in-line scavenger resin column easily removed the minute amount of leached Pd and Cu.

Our initial setup showed good conversions when a homogeneous Pd catalyst was used in a Cu reactor (Table 1, entries 1−3).[8] Notably, the efficiency was maintained at a low catalyst loading (0.1 mol %). It has been widely reported that a quasi-homogeneous mechanism takes place in a heterogeneous Pd reaction where the leached Pd(II) from solid supports catalyzes the reaction.[9] To explore a new Pd-source, we chose a Pd tubular reactor and carried out the same reaction without any homogeneous Pd catalyst[10] where 47% of the desired product was observed (Table 1, entry 4). Leaching of 3785 ppb of Pd occurred from the Pd reactor, and we assume this to be the standard catalytic amount needed for this transformation. The amount of Pd leached is equivalent to about 0.5 mol % of the homogeneous Pd system. We also noticed that a negligible amount (~6 ppb) of Pd is leached out when only solvent is flowing through the Pd tube. Apparently, the Pd was leached out during oxidative addition in Cycle A (Scheme 1).

Table 1. Sonogashira Coupling Reactions between **1c** and **2a** Showing the Efficiency of the Palladium−Copper Dual Reactor

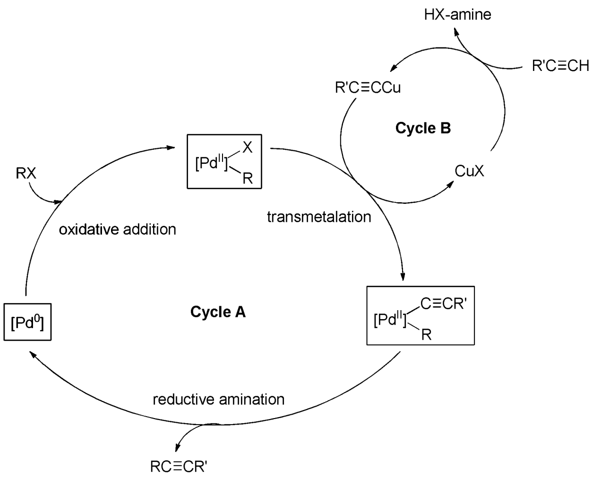


entry[a]	reaction conditions	yield[b] (%)	Pd collected[c] (ppb)
1	$Pd(Cl_2)(PPh_3)_2$ (1 mol %)[d]	quant	102.9 (7601)[e]
2	$Pd(Cl_2)(PPh_3)_2$ (0.5 mol %)[d]	95	78.9 (3801)
3	$Pd(Cl_2)(PPh_3)_2$ (0.1 mol %)[d]	90	65.7 (760.1)
4	Pd reactor	47	3785 (NA)
5	Pd−Cu dual reactor	quant	51.7 (3785)
6	Cu−Pd dual reactor	60	− (NA)
7	Pd−PFA dual reactor	0	− (NA)
8	Pd−SS dual reactor	10	− (NA)

[a] 0.6 mL/min flow rate and residence times of 2 min (Cu reactor), 2.67 min (Pd reactor), 3.67 min (PFA reactor), and 6.83 min (stainless steel reactor) where applicable. [b] Normalized GC yield. [c] Palladium collected was analyzed using ICP-OES for entries 1−5 only. [d] Reaction was carried out using homogeneous catalyst in a Cu reactor. [e] Amount of Pd introduced into the reaction.

We then decided to place the Pd reactor in line with a Cu reactor where the former may provide the required catalytic amount of leached Pd for the Sonogashira reaction. Indeed, the reaction with the Pd−Cu flow reactor afforded the desired product in quantitative conversions (Table 1, entry 5). Notably, the Pd collected from the Pd−Cu dual reactor was much lower (51.7 ppb) than the single Pd reactor (3785 ppb),[11] probably due to the redeposition of Pd particles on the Cu reactor.[12] The deposition of the Pd catalyst was also observed for the homogeneous system.

Scheme 1. Outline of the Reaction Mechanism for Sonogashira C−C Coupling Reaction[14]



The sequence and the presence of Cu from the Pd−Cu dual reactor are crucial to the overall efficiency. Low conversions were obtained when (i) the sequence was reversed (Table 1, entry 6) and (ii) Cu was absent (Table 1, entries 4, 7, and 8).[13] These investigations revealed that the heterogeneous Pd−Cu dual reactor follows the Sonogashira mechanism, where the transmetalation in Cycle B with Cu occurs after the oxidative addition in Cycle A (Scheme 1).[14] The close proximity of the Pd catalyst with Cu during transmetalation probably aids the redeposition of the Pd on the Cu tubing.

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(6) (a) Price of Pd was US $690/oz on January 12, 2012. (b) Oral exposure limit is 10 ppm based on Specific Limits for Residues of Metal Catalysts, accessed May 13, 2012. (c) Supply risk index is 8.5, based on "*British Geological Survey: Risk List 2011*", accessed May 13, 2012.

(7) (a) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062–5085. (b) Magano, J.; Dunetz, J. R. *Chem. Rev.* **2011**, *111*, 2177–2250.

(8) Refer to Supporting Information for more homogeneous Pd catalysis in Cu reactor. In this study, we found out that the optimum (where highest yield of the products were obtained) concentration of reactants and flow rate are 0.05 M and 0.6 mL/min respectively. We decided to use these conditions for the rest of our experiments.

(9) Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133–173 and references cited therein.

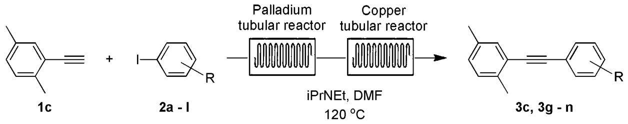
(10) The Pd tubular reactor was purchased from Autochem Pte Ltd., and according to the vendor, the metal was coated onto Cu tubing using conventional electroplating methods.

(11) Leached Pd(II) was collected at two different points: at the exits of the Pd and the Cu reactors, measured using the inductively coupled plasma optical emission spectrophotometer (ICP-OES).

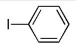
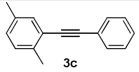
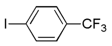
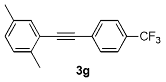
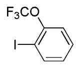
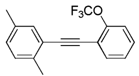
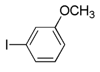
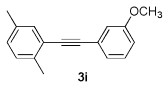
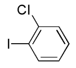
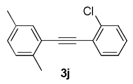
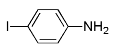
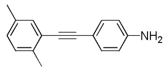
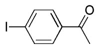
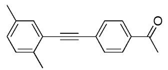
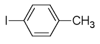
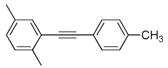
(12) Zhao, F.; Bhanage, B. M.; Shirai, M.; Arai, M. *Chem.—Eur. J.* **2000**, *6*, 843–848.

(13) Pd-Perfluoroalkoxy (Pd-PFA) and Pd-Stainless steel (Pd-SS) flow reactors.

Table 2. Sonogashira C$-$C Coupling Using the Pd$-$Cu Flow Reactor



1c + 2a - l → 3c, 3g - n

entry[a]	aryl iodide **2**	product **3**	yield[b]
1	 2a	 3c	98
2	 2b	 3g	84
3	 2c	 3h	88
4	 2d	 3i	78
5	 2e	 3j	82[c]
6	 2f	 3k	41
7	 2g	 3l	quant
8	 2h	 3m	75[c]

[a] Flow rates for selected entries were set at 0.6 mL/min to give a residence time of 2.83 min in the Pd reactor and 2 min in the Cu reactor, with reagent concentrations at 0.05 M. [b] Normalized GC yield. [c] Flow rates were set at 0.1 mL/min with a lower reagent concentration (0.025 M).

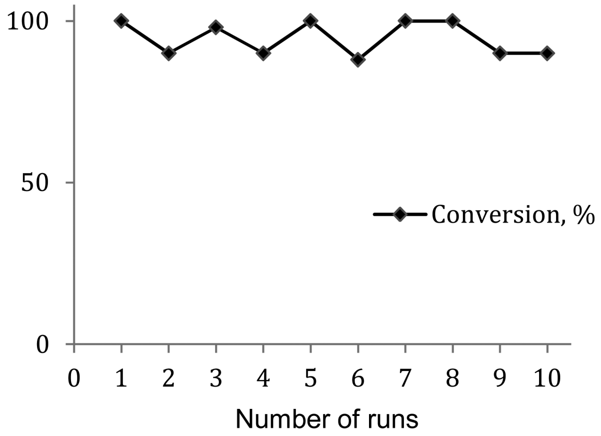


Figure 1. Performance of the Pd$-$Cu dual reactor during a continuous run of 10 cycles of the Sonogashira C$-$C coupling reaction.

Having developed the optimal conditions for this Pd$-$Cu dual reactor, we then extended this methodology to a range of commercially available substituted iodobenzenes. The range of substitution patterns and functionalities that were tested using this setup is shown in Table 2. From the results shown, substrates with both electron-withdrawing and -donating substituting groups afforded the diarylalkynes through coupling with the terminal alkyne and the conversions range from 40% to 98%. Generally, substrates with electron-withdrawing groups afforded a higher conversion due to the ease of oxidative addition. The unsatisfactory conversion for 4-iodoaniline (Table 2, entry 6) could be attributed to the coordination of the amino group to the Pd particles to form a Pd complex, thereby deactivating the catalytic system in the Pd reactor.[15] Although the Cu reactor has shown to be an effective scavenger by facilitating the redeposition of Pd particles, the backend of the continuous flow was fitted with a chromatographic column, packed with metal scavenging resin (QuadraPure TU). Trace amounts of Pd and Cu were effectively trapped with less than 20 ppb of these metals detected using ICP-OES.

Most of the continuous flow reactors with prepacked catalysts usually require postloading after extended usage. For our Pd$-$Cu dual reactor, the performance was maintained even after a continuous run of 10 cycles (Figure 1). Since only a minute amount of Pd is used in each cycle, the Pd tube provides a quasi-unlimited source of Pd catalyst.

In conclusion, we have established the first continuous flow Sonogashira C$-$C coupling reaction on a heterogeneous Pd$-$Cu dual reactor, through a quasi-homogeneous type mechanism. The Pd reactor can serve as a Pd source, and the catalytic amount can be reduced significantly with no loss of reaction efficiency. The following advantages strongly increase the appeal of this method: (i) ease of setting up and carrying out the reactions; (ii) promoters such as phosphines are not needed; (iii) only the required amount of Pd is leached out from the Pd tubing through oxidative addition; (iv) traces of leached Pd can be removed effectively with the Cu reactor and, subsequently, the metal scavenging resins at the backend of the flow setup; (v) the performance can be maintained after several catalytic cycles. Subsequent applications of this method on the large-scale synthesis of chemicals will be reported in due course.

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Supporting Information Available. Experimental procedures and full characterization (^{1}H and ^{13}C NMR data and spectra, and GCMS) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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