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Continuous Flow Coupling and Decarboxylation Reactions Promoted by Copper Tubing

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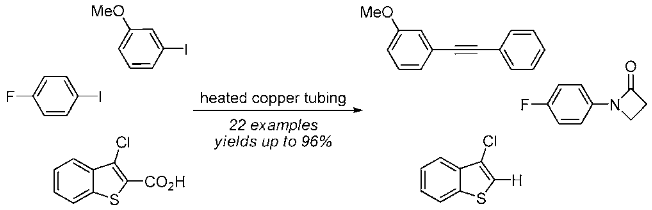
ABSTRACT



A convenient and efficient flow method for Ullmann condensations, Sonogashira couplings, and decarboxylation reactions using a commercially available copper tube flow reactor (CTFR) is described. The heated CTFR effects these transformations without added metals (e.g., Pd), ligands, or reagents, and in greater than 90% yield in most cases examined.

In recent years organic synthesis has been impacted greatly by the rapid growth of innovative technologies such as microwave-assisted heating,[1] polymer-supported reagents/catalysts,[2] and continuous flow processes. Among these developments, continuous flow chemical synthesis has emerged as an important alternative to traditional batch synthesis and enjoyed considerable use in both academic and industrial laboratories.[3] Compared to batch, flow offers several distinct benefits including efficient mixing, precisely controlled reaction parameters, automated reaction processes, the ability to perform reactions at high temperatures and high pressures, and ease of scale-up. Many previously challenging or hazardous reactions can now be safely and efficiently conducted in flow.[4] In addition, flow synthesis methods can be combined with other enabling technologies to improve efficiency and productivity significantly.[5] As part of our efforts to develop methods of chemical synthesis in flow,

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[†] Novartis Institutes for Biomedical Research.

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(1) Caddick, S.; Fitzmaurice, R. *Tetrahedron* **2009**, *65*, 3325.

(2) Solinas, A.; Taddei, M. *Synthesis* **2007**, *16*, 2409.

(3) Recent reviews: (a) Razzaq, T.; Kappe, O. C. *Chem. Asian J.* **2010**, *5*, 1274. (b) McMullen, J. P.; Jensen, K. F. *Annu. Rev. Anal. Chem.* **2010**, *3*, 19. (c) Geyer, K.; Gustafsson, T.; Seeberger, P. H. *Synlett* **2009**, *15*, 2382. (d) Jones, R. V.; Csajagi, C.; Szekelyhidi, Z.; Kovacs, I.; Borcsek, B.; Urge, L.; Darvas, F. *Chim. Oggi* **2008**, *26*, 10. (e) LaPorte, T. L.; Wang, C. *Curr. Opin. Drug Discovery Dev.* **2007**, *10*, 738. (f) Wild, G. P.; Wiles, C.; Watts, P. *Lett. Org. Chem.* **2006**, *3*, 419.

(4) Recent examples: (a) Bedore, M. W.; Zaborenko, N.; Jensen, K. F.; Jamison, T. F. *Org. Process Res. Dev.* **2010**, *14*, 432. (b) O'Brien, M.; Baxendale, I. R.; Ley, S. V. *Org. Lett.* **2010**, *12*, 1596. (c) Grafton, M.; Mansfield, A. C.; Fray, J. M. *Tetrahedron Lett.* **2010**, *51*, 1026. (d) Kulkarni, A. A.; Kalyani, V. S.; Joshi, R. A.; Joshi, R. R. *Org. Process Res. Dev.* **2009**, *13*, 999. (e) Baumann, M.; Baxendale, I.; Martin, L. J.; Ley, S. V. *Tetrahedron* **2009**, *65*, 6611. (f) Malet-Sanz, L.; Madrzak, J.; Holvey, R. S.; Underwood, T. *Tetrahedron Lett.* **2009**, *50*, 7263.

(5) (a) Baxendale, I. R.; Hayward, J. J.; Ley, S. V. *Comb. Chem. High Throughput Screening* **2007**, *10*, 802. (b) Bogdan, A. R.; Mason, B. P.; Sylvester, K. T.; McQuade, T. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 1698. (c) Baxendale, I. R.; Hayward, J. J.; Lanners, S.; Ley, S. V.; Smith, C. D. *Microreact. Org. Synth. Catal.* **2008**, 84. (d) Lee, J.-K.; Fuchter, M. J.; Williamson, R. M.; Leeke, G. A.; Bush, E. J.; McConvey, I. F.; Saubern, S.; Ryan, J. H.; Holmes, A. B. *Chem. Commun.* **2008**, *39*, 4780.

10.1021/ol1026848

we now report a simple and expeditious means for conducting a variety of useful copper-promoted reactions[6] using a commercially available copper tube reactor.[7]

The copper tube flow reactor (CTFR) that we employed is made of a coil of copper tubing with 1.0 mm i.d. (inner diameter) (Figure 1A). The coil is wound around an open mesh support and, when inserted into a glass jacket, can be heated by circulated air to 150 °C by using a standard Vaportec R4 heating module. The copper tubing can be heated safely up to 250 °C when a metal jacket is used (Figure 1, parts B and C). We envisioned that these reactors would offer unique advantages of performing copper-promoted reactions, i.e., by simply flowing substrates/reagents into the heated coil without any additional catalysts (copper or otherwise). Herein we report the first use of a CTFR for Ullmann couplings (no added ligands), Sonogashira couplings (no added Pd), and high-temperature protiodecarboxylation reactions.

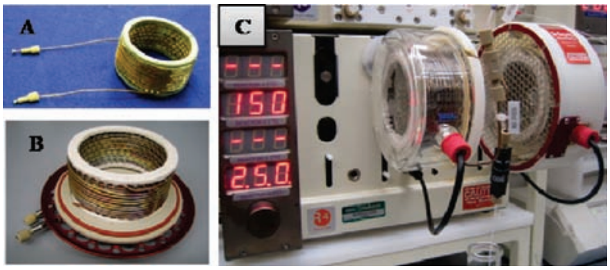
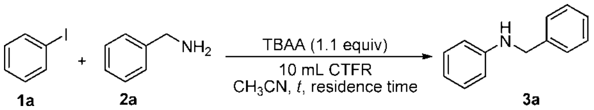


Figure 1. (A) A copper flow coil. (B) A high-temperature CTFR with the top metal jacket removed (1.0 mm i.d. tubing). (C) Heated CTFRs using a standard Vaportec R4 heating module.

Ullmann condensation of aryl halides and amines is a very useful strategy to obtain aryl and biaryl *N*-containing compounds, which occur in numerous natural products, pharmaceuticals, and polymers.[8] The traditional conditions used for this chemistry require high temperature, high copper loading, and long reaction times. Spectacular improvements have been made in the past decade, particularly rendering the reaction conditions much milder by using suitable ligands.[9] However, methods that do not use added ligands, such as that described below, can generally be more attractive.[10]

Our investigations began with the coupling of iodobenzene (**1a**) and benzylamine (**2a**). After evaluating various conditions in CTFR using the Vaportec R4/R2 system, we found that with tetra-*n*-butylammonium acetate[11] (TBAA) as base and acetonitrile[10e] as solvent, coupling of **1a** and **2a** was achieved without the use of any other ligands or catalysts (Table 1; see the Supporting Information for details). No product formation was observed when the same conditions were applied to experiments carried out in a PFA (perfluoroalkoxyalkane) tube reactor heated to the same temperature (entry 3), suggesting that the copper tubing was promoting the reaction. Other parameters were then quickly tuned in flow, and the optimal conditions are shown in entry 2. The CTFR approach was more efficient than microwave and batch reactions with traditionally used catalysts (entries 4−6).

Table 1. Ullmann Coupling of **1a** and **2a**



1a + **2a** → **3a**

entry[a]	method	*t* (°C)	residence time (min)	flow rate (mL/min)	conversion (%)[b]
1	copper tube	150	30	0.33	65
2[c]	copper tube	150	120	0.17	100
3	PFA tube	150	30	0.33	0
4[d]	microwave	150	30		50
5[e]	microwave	150	30		31
6[f]	oil bath	90	960		40

[a] Flow conditions: **1a** (2.0 mmol, 1.0 M), **2a** (2.4 mmol, 1.2 M). [b] Conversion is based on ^{1}H NMR analysis of crude materials. [c] Two 10 mL CTFRs were connected in series. [d] Microwave, 400 W, CuI (10 mol %), CH$_3$CN (1.0 M). [e] Microwave, 400 W, Cu powder (10 mol %), CH$_3$CN (1.0 M). [f] Sealed tube was used.

We then applied this protocol to couplings of several aryl halides and amines. In general, a 250 psi backpressure regulator was used to ensure that acetonitrile could be safely heated well above its boiling point without flashing. The trace amounts of copper[12] leached from the tubing were efficiently removed with Quadrapure Thiourea[13] (QP-TU). As illustrated in Table 2, both alkyl amines and *N*-containing heterocycles were effective coupling partners. Reactions using less reactive aryl bromides proceeded smoothly (entries 1 and 6). These conditions were also effective for the Ullmann−Goldberg[14] amide synthesis (entries 7 and 8).

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(6) Previous reports of copper flow technology: (a) Ceylan, S.; Klande, T.; Vogt, C.; Friese, C.; Kirschning, A. *Synlett* **2010**, *13*, 2009. (b) Bogdan, A. R.; Sach, N. W. *Adv. Synth. Catal.* **2009**, *351*, 849. (c) Bogdan, A. R.; James, K. *Chem.—Eur. J.* 2010ASAP.

(7) Copper tube flow reactors are available from Vapourtec Ltd.: www.vapourtec.co.uk.

(8) (a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382. (b) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 853. Reviews: (c) Lindley, J. *Tetrahedron* **1984**, *40*, 1433. (d) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (e) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954. (f) Das, P.; Sharma, D.; Kumar, M.; Singh, B. *Curr. Org. Chem.* **2010**, *14*, 754.

(9) (a) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2010**, *1*, 13. (b) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450. (c) Ley, S. V.; Thomas, A. W. *Ang. Chem. Int. Ed.* **2003**, *42*, 5400. (d) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581.

(10) Selected examples (batch): (a) Truong, V.; Morrow, M. *Tetrahedron Lett.* **2010**, *51*, 758. (b) Colacino, E.; Villebrun, L.; Martinez, J.; Lamaty, F. *Tetrahedron* **2010**, *66*, 3730. (c) Zhang, J.; Zhang, Z.; Wang, Y.; Zheng, X.; Wang, Z. *Eur. J. Org. Chem.* **2008**, *30*, 5112. (d) Yang, X.-D.; Li, L.; Zhang, H.-B. *Helv. Chim. Acta* **2008**, *91*, 1435. (e) Zhu, R.; Xing, L.; Wang, X.; Cheng, C.; Su, D.; Hua, Y. *Adv. Synth. Catal.* **2008**, *350*, 1253. (f) Correaa, A.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349*, 2673. (g) Zhao, Y.; Wang, Y.; H.Sun, H.; Li, L.; Zhang, H. *Chem. Commun.* **2007**, 3186.

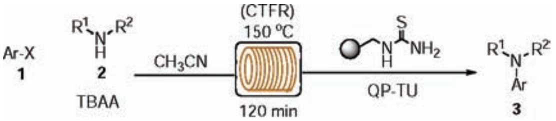
(11) Yang, C.-T.; Fu, Y.; Huang, Y.-B.; Yi, J.; Guo, Q.-X.; Liu, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 7398.

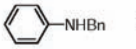
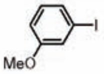
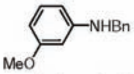
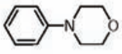
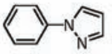
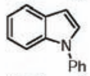
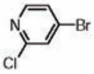
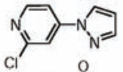
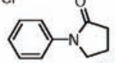
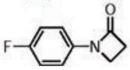
(12) See the Supporting Information for trace copper analyses.

(13) QP-TU was purchased from Aldrich (product no. 655422).

(14) Goldberg, *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691.

Table 2. Synthesis of Arylamines in CTFR

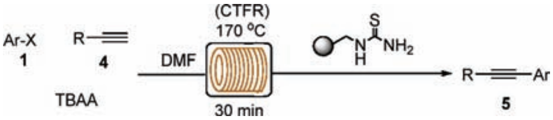


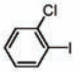
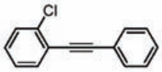
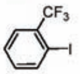
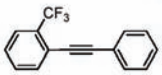
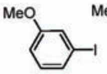
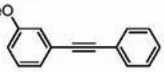
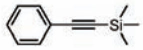
entry[a]	aryl halide	product		conversion[c]	yield[d]
1	Ph-X **1a**: X=I **1b**: X=Br **1c**: X=Cl		**3a**	X=I, 100% X=Br, 100% X=Cl, 0%	74%
2			**3b**	83%	78%
3	**1a**		**3c**	80%	76%
4[b]	**1a**		**3d**	100%	92%
5[b]	**1a**		**3e**	90%	83%
6			**3f**	82%	53%
7	**1a**		**3g**	98%	95%
8			**3h**	95%	85%

[a] Reaction conditions: A solution of **1** (1.0 M), **2** (1.20 M), and TBAA (1.10 M) in CH_3CN was injected from pump at 0.17 mL/min, two 10 mL CTFR were connected using a standard PFA tubing (1.0 mm i.d.). [b] 0.1 mL/min flow rate, 200 min residence time. [c] Conversion is based on ^1H NMR analysis of crude materials. [d] Isolated yields after flash chromatography on silica gel.

Encouraged by the preliminary results, we next turned our attention to the Sonogashira cross-coupling reaction,[15] particularly methods in which Pd was not used.[16] After some experimentation in heated CTFR, we learned that solvent choice was a key paramter in flow. DMF was found to be appropriate, but other solvents such as CH_3CN, THF, EtOAc, and EtOH resulted in precipitation and subsequent system blockage during the reaction. We found that TBAA, the organic ionic base also used for the Ullmann-type reactions (vide supra), was again more effective than other commonly used bases (e.g., Et_3N, Hünig's base, Et_2NH, n-$BuNH_2$; see the Supporting Information for details). A general protocol was thus developed, and a range of arylalkynes were constructed in good yields (Table 3). When less reactive substrates such as bromobenzene (entry 1) or trimethylsilyl acetylene (entry 5) were employed the reaction required a catalytic amount of palladium. Notably Hay−Glaser coupling[17] byproducts (symmetrical 1,3-diynes) were not observed in any case, possibly attributable to the flow reaction format (rate of alkyne addition and short residence time).[18]

Table 3. Synthesis of Arylalkynes in CTFR



entry[a]	aryl halide	product		conversion[c]	yield[d]
1	**1a** **1b**		**5a**	**1a**: 96% **1b**: 100%[b]	90%
2			**5b**	95%	90%
3			**5c**	100%	92%
4			**5d**	90%	87%
5[b]	**1a**		**5e**	100%	94%
6	**1a**		**5f**	87%	78%

[a] Reaction conditions: A solution of **1** (1.0 M), **4** (1.20 M) in DMF, and a stock solution of TBAA (1.10 M) in DMF was mixed through pumps into a T-mixer at a total flow rate of 0.33 mL/min. [b] 0.50 mol % $Pd(PPh_3)_2Cl_2$ was added, reaction was heated at 120 °C. The palladium catalyst and leached trace amount of copper were removed with QP-TU. [c] Conversion is based on ^1H NMR analysis of crude materials. [d] Isolated yields after flash chromatography on silica gel.

We also examined the use of high-temperature CTFR for protiodecarboxylation reactions.[19] Traditional batch processes involve the use of copper powder or copper(I) salts at elevated temperatures and, in some cases, even above 250 °C.[20] Moreover, the release of CO_2 gas generated in the reaction at such temperatures raises significant safety concerns, particularly when carrying out large scale syntheses in batch. We speculated that flow reactors would provide us with a more controlled process because only a small amount of gas would be generated and liberated from the system at any given time. As illustrated in Table 4, decarboxylation reactions of many aromatic and heteroaromatic substrates were successfully achieved at 250 °C in CTFR without any additional catalysts, ligands, or additives. In the case of 5-fluoroindole-2-carboxylic acid, 2.0 equiv of quinoline and longer reaction time were required (entry 6).

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(15) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. Recent reviews: (b) Chinchilla, R.; Najera, C. *Chem. Rev.* **2007**, *107*, 874. (c) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46.

(16) Selected examples (batch): (a) Jiang, H.; Fu, H.; Qiao, R.; Jiang, Y.; Zhao, Y. *Synthesis* **2008**, *15*, 2417. (b) Monnier, F.; Turtaut, F.; Duroure, L.; Taillefer, M. *Org. Lett.* **2008**, *10*, 3203. (c) Tambade, P. J.; Patil, Y. P.; Nandurkar, N. S.; Bhanage, B. M. *Synlett* **2008**, *6*, 886. (d) Biffis, A.; Scattolin, E.; Ravasio, N.; Zaccheria, F. *Tetrahedron Lett.* **2007**, *48*, 8761. (e) Chen, G.; Zhu, X.; Cai, J.; Wan, Y. *Synth. Commun.* **2007**, *37*, 1355.

(17) (a) Hay, A. S. *J. Org. Chem.* **1960**, *25*, 1275. (b) Hay, A. S. *J. Org. Chem.* **1962**, *27*, 3320. (c) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2633.

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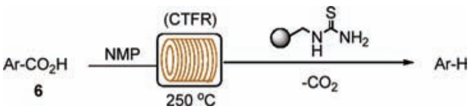
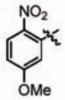
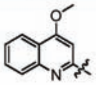
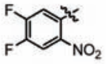
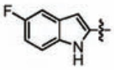
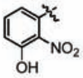
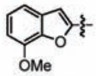
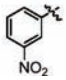
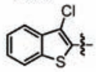
(19) Recent reports: (a) Goossen, L. J.; Rodriguez, N.; Linder, C.; Lange, P.; Fromm, A. *ChemCatChem* **2010**, *2*, 430. (b) Goossen, L. J.; Manjolinho, F.; Khan, B. A.; Rodriguez, N. *J. Org. Chem.* **2009**, *74*, 2620. (c) Goossen, L. J.; Thiel, W. R.; Rodriguez, N.; Linder, C.; Melzer, B. *Adv. Synth. Catal.* **2007**, *349*, 2241.

(20) (a) He, M.; Zhang, F. *J. Org. Chem.* **2007**, *72*, 442. (b) Molina, P.; Fresneda, P. M.; Garcia-Zafra, G.; Almendros, P. *Tetrahedron Lett.* **1994**, *35*, 8851. (c) Atwell, G. J.; Baguley, B. C.; Denny, W. *J. Med. Chem.* **1989**, *32*, 396.

Table 4. High-Temperature Protiodecarboxylation Reactions



entry[a]	Ar	Rt (min)[b]	yield[c]	entry[a]	Ar	Rt (min)[b]	yield[c]
1		15	96%	5		50	90%
2		30	94%	6[d]		240	96%
3		30	98%	7		50	92%
4		30	93%	8		50	92%

[a] Reaction conditions: A solution of **6** (1.0 M in NMP) was injected from pump. [b] Residence time. [c] Isolated yields with purity >95% (^{1}H NMR spectroscopy). [d] 2.0 equiv of quinoline was added; the experiment was set up in recycling mode at 1.0 mL/min flow rate.

In summary, we have demonstrated the effectiveness of commercially available CTFR for several important copper-mediated transformations including Ullmann condensations (no added supporting ligand), Sonogashira couplings (no added Pd), and protiodecarboxylation reactions by way of a simple and more environmentally benign procedure. The reactor itself acts as a source of fresh copper metal and can be safely heated at high temperatures and high pressures. When experiments were performed under the same conditions in PFA or stainless steel tube reactors, reactions failed to give any desired products, suggesting a promoting effect of the copper tubing. In many cases, the crude reaction products can be used further in multistep processes without additional purification.

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Supporting Information Available: Complete experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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