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Copper-mediated N- and O-arylations with arylboronic acids in a continuous flow microreactor: a new avenue for efficient scalability

Brajendra K. Singh [a,c], Christian V. Stevens [b,*], Davy R. J. Acke [b], Virinder S. Parmar [c], Erik V. Van der Eycken [a,*]

[a] Laboratory for Organic and Microwave-Assisted Chemistry (LOMAC), Department of Chemistry, University of Leuven, Celestijnenlaan 200F, B-3001 Heverlee, Leuven, Belgium
[b] Research group SynBioC, Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure links 653, B-9000 Gent, Belgium
[c] Bioorganic Laboratory, Department of Chemistry, University of Delhi, Delhi 110 007, India

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ABSTRACT

A continuous flow procedure has been elaborated for the copper(II)-mediated N- and O-arylation of a range of compounds with arylboronic acids using a commercial microreactor setup. The compounds could be continuously generated in good yields paving the way for efficient scalability.

Among the C-heteroatom bond forming reactions, the copper-mediated heteroatom arylation has gained increasing importance. Independently reported by the groups of Chan,[1] Evans[2] and Lam[3] in 1998, this cross-coupling procedure resolved the long-standing problem of the simple and mild formation of C(aryl)–O and C(aryl)–N bonds using an arylboronic acid as the aryl donor in combination with a base and copper acetate as the catalyst, as these reactions can be conducted at room temperature in air, providing a practical advantage over the Buchwald–Hartwig cross-coupling reaction.[4] The method has proven to be applicable to a wide range of nucleophilic reaction partners including phenols, amines, anilines, amides, imides, ureas, carbamates, and sulfonamides. Also, aromatic heterocycles as imidazoles, pyrazoles, triazoles, tetrazoles, benzimidazoles, and indazoles participate efficiently in this copper(II)-mediated reaction.[5] The scope of the procedure was expanded by the potential of a catalytic variant using less than stoichiometric amounts of $Cu(OAc)_2$ employing oxygen as oxidant or TEMPO/air, pyridinium N-oxide/air or $[\{Cu(\mu\text{-}OH)(tmeda)\}_2]Cl_2$/oxygen in the presence of $Cu(OAc)_2$ as the Cu(II)-source.[6]

We recently reported the usefulness of this copper(II)-mediated cross-coupling protocol for the N-arylation of the 2(1*H*)-pyrazinone scaffold in solution phase[7] and on solid support.[8] As 2(1*H*)-pyrazinones have received considerable interest due to their valuable application as scaffolds for the generation of a diverse array of biologically interesting compound libraries,[9] we were keen to know whether this cross-coupling protocol could be run in a continuous flow set up paving the way for efficient scalability. Microreactor technology is a rather new type of technology, which has gained high interest during the last two decades. The first literature related to chemistry in microstructured devices appeared in 1986 in a German patent that described how a microreactor should be built.[10] Since then the interest in the application of microreactors is growing steadily.[11,12] The main scale-up problems of organic reactions are associated with heat and mass transport, and shortcomings can lead to thermal runaway reactions. Microreactors should guarantee a better mass transfer, a safer handling of reactions, and a higher selectivity.[13] However, the major advantage of this technology is the scalability.[14] A classic scale-up is a time-consuming and expensive process. By contrast, once a process is optimized under microreactor conditions, there is no need anymore to scale up the reactor. Instead several microreactors are placed in parallel to produce higher quantities. Using this method, no modifications of the labscale conditions are necessary anymore.

Despite the large interest in copper-mediated heteroatom arylation during the last years,[5] to our knowledge no studies are performed yet on the use of microreactors for this purpose. The microreactor that is used in our study is a commercially available

* Corresponding authors. Tel.: +32 16 327406.
E-mail addresses: chris.stevens@ugent.be (C. V. Stevens), erik.vandereycken@chem.kuleuven.be (E. V. Van der Eycken).

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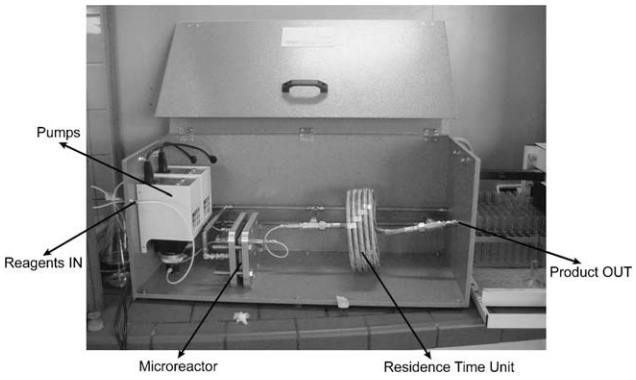


Figure 1. The applied microreactor: a CYTOS® College System, produced by CPC—Cellular Process Chemistry Systems GmbH; (1) input reagents via two pumps; (2) microreactor; (3) residence time unit; (4) output reaction mixture.

Table 1
Optimization of the flow rate for the N-arylation of pyrazinone **1** using microreactor technology

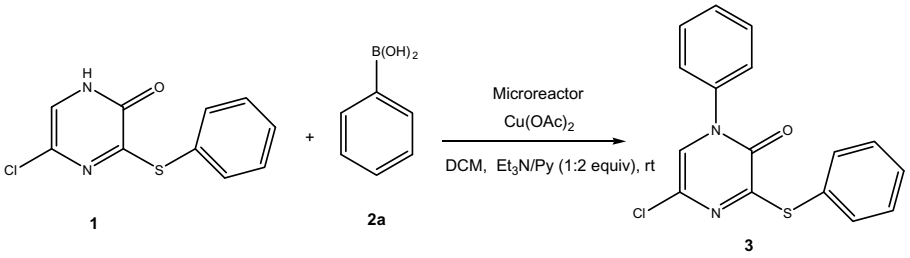
Entry[a]	Residence time (min)	Flow rate (ml/min)	Conversion[b] (%)
1	15	1.54	30
2	45	0.52	50
3	60	0.39	70
4	90	0.26	90
5	120	0.20	100[c]

[a] All optimization reactions were performed at 25 °C on a 1.0 mmol scale of pyrazinone **1**. The pyrazinone **1** and boronic acid **2a** (2 equiv) were dissolved in DCM (40 mL) and Et_3N (1.0 equiv), pyridine (2.0 equiv) and $Cu(OAc)_2$ (1.0 equiv) were separately dissolved in DCM (40 mL), and both mixtures were simultaneously brought into the microcapillary by the aid of two separate pumps (with the same pump rate).
[b] The conversion was estimated by quantitative TLC.
[c] This resulted in an isolated yield of 79%.

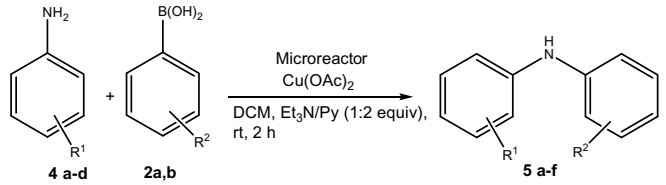
CYTOS® College System, produced by CPC—Cellular Process Chemistry Systems GmbH (Fig. 1).[15] The entire device consists of two piston pumps, the microreactor itself and a residence time unit (RTU). The microreactor consists of several stacked plates. In a number of these plates, a path is etched. After stacking the plates together, a fluid pathway is formed with dimensions in the submillimeter range. The microreactor has two inlets. Each inlet flow is divided into four parallel, flows which are one by one mixed together in an interdigital mixer. After passing through a mixing chamber, all parallel flows are once more divided in two flows each. Finally, all eight flows come together to leave the microreactor as one outlet flow (D).

Our initial investigations of this copper(II)-mediated cross-coupling in a microreactor setup were performed using pyrazinone **1** and phenylboronic acid (Scheme 1). For this purpose, a mixture of pyrazinone **1** (1 mmol, 238 mg) and boronic acid **2a** (2 mmol, 244 mg) in dichloromethane (DCM; 40 mL) was brought into the microreactor through one pump and a solution of $Cu(OAc)_2$ (1 mmol, 182 mg), Et_3N (1 mmol, 102 mg), and pyridine (2 mmol, 160 mg) in DCM (40 mL) through another pump allowing efficient mixing at rt in the microcapillary (Fig. 1). Different flow rates resulting in different residence times ranging from 15 to 120 min were applied (Table 1). When the reaction was performed using a relatively high flow rate of 1.54 mL/min, approximately 30% conversion to the desired N-arylated pyrazinone was obtained after 15 min (Table 1, entry 1). Prolonging the residence time to 45 min by lowering the flow rate to 0.52 mL/min resulted in an increased conversion of 50% (Table 1, entry 2). Consequently, when the reaction was carried out for 120 min, a 100% conversion was achieved delivering 79% of the desired N-arylated compound **3** after purification (Table 1, entry 5). This is much faster compared to the required 12 h under conventional conditions.[7] Alternative solvents were screened, but only DMF seemed to be as efficient as dichloroethane (DCE); acetonitrile and dioxane were unsuccessful to dissolve the copper acetate efficiently resulting in clogging problems of the microreactor. In DMF, the reaction was faster as compared to DCM as the reaction could be run at elevated temperature. When the reaction was performed at 130 °C for 30 min, a 100% conversion was achieved delivering compound **3** in 72% yield. However, isolation from the DMF mixture turned out to be difficult. Therefore, we decided to perform our further investigations using DCM at rt. We then gradually increased the concentration of different compounds to 5- and 10-fold, applying the optimized conditions, that is, a flow rate of 0.2 mg/mL in DCM at rt. Both reactions were running well without any problem. Applying the 10-fold concentration, that is, reaction on 10.0 mmol of pyrazinone **1**, we were able to continuously generate compound **3** in 21 mg (0.066 mmol) per minute, opening the way for its synthesis on a multigram scale. However, further increasing the concentration to a 15-fold (15 mmol of pyrazinone **1**) caused clogging problems of the microreactor due to the low solubility of $Cu(OAc)_2$ in DCM. To the best of our knowledge, copper(II)-mediated C–N coupling reactions have never been performed on a multigram scale applying microreactor technology.

After having established an efficient continuous flow microreactor protocol[16] for the N-arylation of pyrazinone **1**, we evaluated the applicability for differently substituted anilines (Scheme 2, Table 2). Thus, aniline **4a** (1.0 mmol, 93 mg) and phenylboronic acid **2a** (2.0 mmol, 244 mg) were dissolved in DCM (40 mL), and mixed in the microcapillary with a solution of $Cu(OAc)_2$ (1.0 mmol, 182 mg), Et_3N (1.0 mmol, 101 mg), and pyridine (2.0 mmol, 158 mg) in DCM (40 mL) applying both pumps with a flow rate of 0.2 mL/min and a residence time of 2 h. The reaction proceeded well yielding 71% of the N-arylated aniline **5a** (Table 2, entry 1). The concentration could easily be increased to 10-fold resulting in the formation of **5a** at a rate of 10 mg/min. As a proof of concept, when the reaction was run under conventional conditions applying the same parameters, the arylation of 1 g of aniline with phenylboronic acid yielded the N-arylated aniline in 67% in 24 h clearly indicating the usefulness of our microreactor protocol. However, upon further scale up to 10-fold, we noticed that the reaction could not



Scheme 1. N-Arylation of the pyrazinone **1** scaffold.



Scheme 2. N-Arylation of anilines using the continuous flow microreactor protocol.

Table 2
N-Arylation of differently substituted anilines

Entry	Product	R^1	R^2	Isolated (g)	Yield[a] (%)
1	**5a**[19]	H (**4a**)	H (**2a**)	1.2	71
2	**5b**[20]	H (**4a**)	3-OEt (**2b**)	1.5	73
3	**5c**[21]	4-Cl (**4b**)	H (**2a**)	1.3	67
4	**5d**[22]	4-Cl (**4b**)	3-OEt (**2b**)	1.7	69
5	**5e**	2,4,6-Cl (**4c**)	3-OEt (**2b**)	No reaction[b]	—
6	**5f**[23]	2,4-NO_2 (**4d**)	3-OEt (**2b**)	1.7	56

[a] All reactions were performed at 25 °C on a 10.0 mmol scale of the anilines **4a–d**. The aniline **4a–d** and boronic acid (2.0 equiv) were dissolved in DCM (40 mL) and Et_3N (1 equiv), pyridine (2.0 equiv) and $Cu(OAc)_2$ (1.0 equiv) were separately dissolved in DCM (40 mL), and both mixtures were simultaneously brought into the microcapillary by the aid of two separate pumps at a flow rate of 0.20 mL/min resulting in a residence time of 2 h.

[b] Only starting aniline was recovered.

finish even in 5 days, and the desired N-arylated aniline was isolated in a poor 51% yield next to some unidentified side products as was indicated by TLC. The optimized microreactor protocol was further applied to variously substituted anilines, and the corresponding N-arylated amines were isolated in gram quantities with moderate to good yields ranging from 56% to 73% (Table 2, entries 2–4 and 6) except for 2,4,6-trichloroaniline, which is probably too sterically encumbered (Table 2, entry 5).

The optimized protocol was also demonstrated to work well for the N-arylation of the aliphatic cyclohexyl amine with phenylboronic acid. Thus, upon mixing at rt in the microcapillary a solution of cyclohexyl amine (10 mmol, 990 mg) and phenylboronic acid (20 mmol, 2.44 g) in DCM (40 mL) with a mixture of $Cu(OAc)_2$ (10 mmol, 1.82 g), Et_3N (10 mmol, 1.01 g), and pyridine (20 mmol, 1.58 g) in DCM (40 mL) with a flow rate of 0.2 mL/min, the desired phenylated compound[17] was continuously delivered in 11 mg/min with an isolated 71% yield.

We could also broaden the scope of the protocol to amides. Thus, using the same procedure we were able to generate the N-phenylated caprolactam[18] on a 10 mmol scale (1.13 g). The desired compound was delivered in 83% yield at a rate of 13 mg/min.

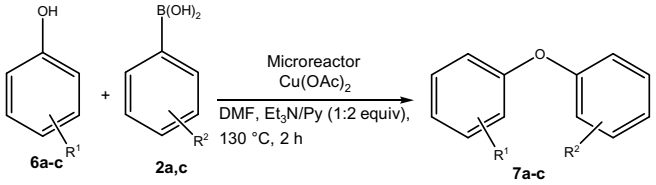
Finally, we examined the applicability of the optimized protocol for the O-arylation of some substituted phenols **6a–c**. To our disappointment, when the reaction was run with **6a** only a 60% conversion could be achieved even after a residence time of 2 h. However, when the reaction was performed in DMF at 130 °C in 2 h at a flow rate of 0.2 mL/min, 100% conversation were obtained, and the compounds **7a–c** were isolated in good yields in all the cases (Table 3) (see Scheme 3).

In conclusion, we have demonstrated that microreactor technology could be efficiently used for the copper(II)-mediated N- and O-arylation of various compounds with arylboronic acids. For the investigated N-arylations, best results were obtained when performing the reactions in DCM at rt for 2 h, where under conventional conditions these require 12–72 h.[1,3,7] However, for the O-arylation of the investigated phenols it has been proven that DMF at 130 °C is the condition of choice. These results are opening the way for efficient scalability of this type of reaction, avoiding tedious scaling-up procedures.

Table 3
O-Arylation of differently substituted phenols

Entry	Product	R^1	R^2	Isolated (g)	Yield[a] (%)
1	**7a**[24]	3-OCH_3	H	1.44	72
2	**7b**[25]	2-I	4-OMe	2.25	69
3	**7c**[26]	4-Et	4-OMe	1.59	70

[a] All reactions were performed at 130 °C on a 10.0 mmol scale of substituted phenol. Phenol **6a–c** and boronic acid **2a**,**c** (2.0 equiv) were dissolved in DMF (40 mL) and Et_3N (1.0 equiv), pyridine (2.0 equiv) and $Cu(OAc)_2$ (1.0 equiv) were separately dissolved in DMF (40 mL), and both mixtures were simultaneously brought into the microcapillary by the aid of two separate pumps at a flow rate of 0.20 mL/min resulting in a residence time of 2 h.



Scheme 3. O-Alkylation of substituted phenols.

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16. In a typical experiment, a solution of the pyrazinone **1**[7] (10 mmol, 2.13 g) and phenylboronic acid (20 mmol, 2.44 g) in DCM (40 mL) was allowed to mix with a solution of $Cu(OAc)_2$ (10 mmol, 1.82 g), Et_3N (10 mmol, 1.01 g), and pyridine (20 mmol, 1.58 g) in DCM (40 mL) using two separate pumps with a flow rate of 0.2 mL/min. At the outlet of the microreactor, the reaction mixture was collected with a flow rate of 0.4 mL/min, and the solvent was immediately removed under vacuum. The crude reaction mixture was passed through a pad of silica gel affording the desired N-arylated pyrazinone **3**[7] in 79% yield. The microreactor was consecutively flushed with DCM, concentrated acetic acid, and DCM to prevent deposition of $Cu(OAc)_2$ in microcapillary.
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26. *1-(4-Ethylphenoxy)-4-methoxybenzene* (**7c**): It was obtained as viscous transparent oil in 70% yield. ^1H NMR (300 MHz, $CDCl_3$): δ 7.13–7.10 (d, 2H, J = 8.31 Hz), 6.97–6.93 (m, 2H), 6.90–6.82 (m, 4H), 3.79 (s, 3H), 2.64–2.57 (q, 2H, J = 7.59 Hz), 1.24–1.19 (t, 3H, J = 7.86 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 156.67, 156.05, 152.00, 151.06, 138.87, 129.31, 120.84, 119.94, 118.13, 115.17, 56.05, 28.51, 16.21 HRMS (EI): calcd for $C_{15}H_{16}O_2$: 228.1150, found: 228.1213.