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Flow Chemistry **Hot Paper**

Rapid and Efficient Copper-Catalyzed Finkelstein Reaction of (Hetero)Aromatics under Continuous-Flow Conditions**

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Abstract: *A general, rapid, and efficient method for the copper-catalyzed Finkelstein reaction of (hetero)aromatics has been developed using continuous flow to generate a variety of aryl iodides. The described method can tolerate a broad spectrum of functional groups, including N-H and O-H groups. Additionally, in lieu of isolation, the aryl iodide solutions were used in two distinct multistep continuous-flow processes (amidation and Mg–I exchange/nucleophilic addition) to demonstrate the flexibility of this method.*

Aryl and heteroaryl iodides are valuable building blocks widely used in organic synthesis. Their versatility stems, in part, from their higher reactivity when compared to the corresponding aryl chloride/bromide, particularly with respect to transition-metal-catalyzed carbon–carbon and carbon–heteroatom bond-forming reactions.[1] Aryl iodides have also found applications in hypothyroidism and myxedema coma treatment,[2] anticancer therapy,[3] and X-ray contrast imaging.[4] Because of their importance in both industrial and academic settings, several synthetic methods have been developed to access (hetero)aryl iodides.[5,6] However, these processes usually require the use of either a stoichiometric amount of a transition-metal reagent, or highly polar solvents; many others have a limited substrate scope.[6] The use of these methods may also be hampered by incomplete conversion, and/or generate side products that are chromatographically inseparable from the desired product. In addition, the preparation of functionalized (hetero)aromatic iodides is usually not trivial.[6]

In recent years, improvements in reactions to effect aromatic iodination have been made, particularly by Yu,[7] Sanford,[8] Hayashi,[9] and others.[10] These methods have the advantage of being simple and high yielding, although the use of directing groups, or long reaction times may be required. Considering our previous work on the copper-catalyzed halogen-exchange reaction of aryl halides[10a] and continuous-flow manufacturing,[11–14] we felt that the Finkelstein reaction of aromatics could be effectively accelerated under flow conditions by precise control over residence time at elevated temperatures and pressures. Moreover, the exceedingly low solubility of anhydrous sodium iodide in the nonpolar solvents that we previously utilized could be an advantage in flow.[10a] This is because a sodium iodide packed-bed reactor would provide efficient mixing and enhanced mass and heat transfer to further improve the efficiency of the proposed transformation. Herein, we describe the development of a rapid and efficient copper-catalyzed Finkelstein reaction of (hetero)aromatics in flow. The reaction was then applied to two distinct, multistep continuous-flow processes, including either a halogen exchange/C–N bond-forming sequence or a halogen exchange/Mg–I exchange/nucleophilic addition sequence, thus further demonstrating the flexibility of the methodology.

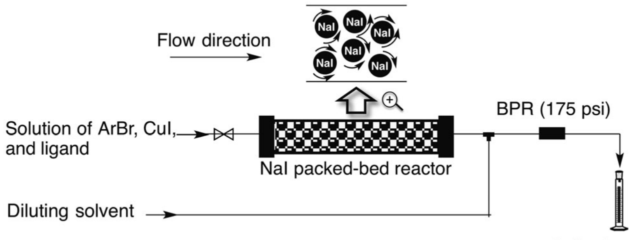

Figure 1. Experimental setup for the copper-catalyzed Finkelstein reaction of aromatics in flow. See the Supporting Information for details.

During our preliminary investigation using batch conditions, we found that while reactivity improved by increasing the reaction temperature from 90 °C to 130 °C, increasing the loading of the "I^-" source had no effect on the conversion of the electrophile (see the Supporting Information). An increase of the reaction temperature beyond 130 °C resulted in inconsistent conversions and yields.[15] Considering the difficulties of handling superheated reaction mixtures, a flow process would be a good alternative to mitigate potential safety hazards, prevent the vaporization of volatile components, and maintain uniform heating.[13,14] Therefore, we designed a sodium iodide packed-bed reactor for further investigations under flow conditions (Figure 1). Although sodium iodide is highly hygroscopic, the reactor and all reagent solutions were easily prepared on the bench top and the reagents were subsequently introduced to the reactor using syringe pumps. As shown in Table 1, by using **L1** as the ligand, 68 % conversion of **1a** was achieved at 160 °C with a 30 min residence time (entry 4). A further increase of the reaction temperature to 180 °C afforded 95 % conversion (entry 5). After evaluating several diamine ligands, **L1** proved to be the most effective. By increasing the catalyst loading of CuI to 7 mol %, more than 99 % conversion was achieved

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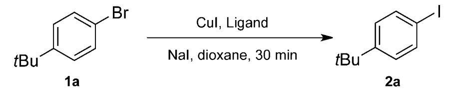
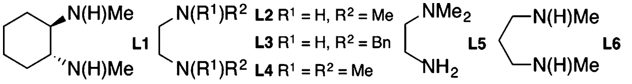
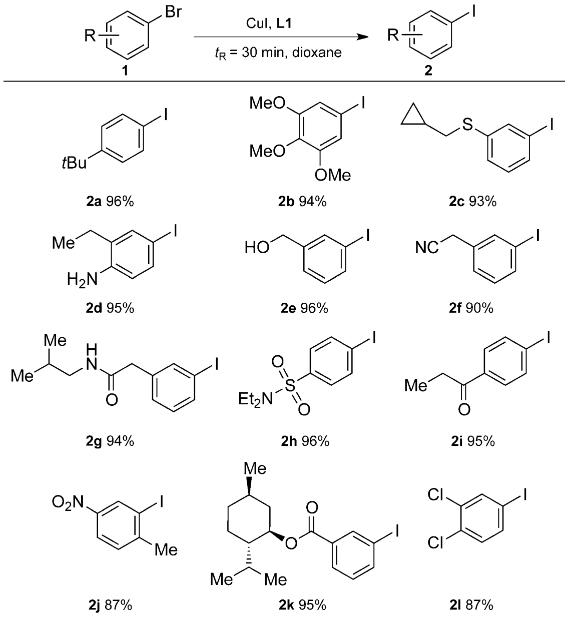
Table 1: Optimization of the copper-catalyzed Finkelstein reaction of aromatics under batch and flow conditions.[a]



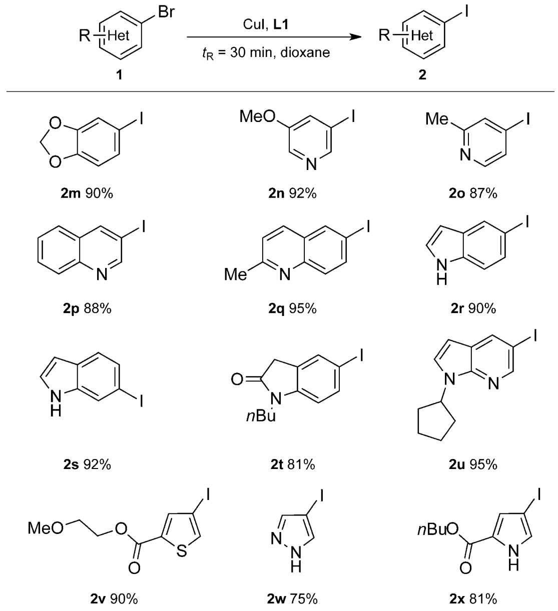
Entry	CuI [mol %]	Ligand [mol %]	Temp. [°C]	Conversion [%]	Yield [%]
Under Batch Conditions					
1	5	**L1** (10)	90	5	<5
2	5	**L1** (10)	110	18	18
3	5	**L1** (10)	130	34	34
Under Flow Conditions					
4	5	**L1** (10)	160	68	68
5	5	**L1** (10)	180	95	94
6	5	**L2** (10)	180	85	84
7	5	**L3** (10)	180	67	66
8	5	**L4** (10)	180	5	5
9	5	**L5** (10)	180	59	59
10	5	**L6** (10)	180	23	23
11	7	**L1** (10)	180	>99	98
12	10	**L2** (20)	180	>99	96

[a] Conversions and yields were determined by GC analysis of the crude reaction mixture. See the Supporting Information for details.





Scheme 1. Substrate scope of the copper-catalyzed conversion of aryl bromides to aryl iodides using continuous flow. Yields of isolated products based on a 1 mmol scale are reported as an average of two runs. See the Supporting Information for details.



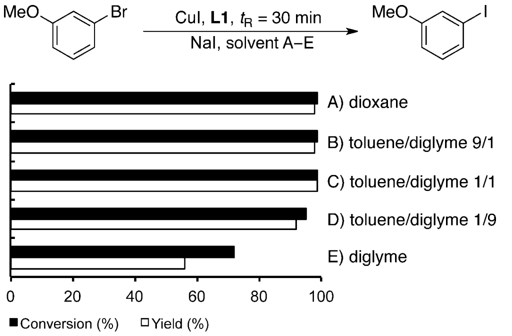
Scheme 2. Substrate scope of the copper-catalyzed conversion of heteroaryl bromides to heteroaryl iodides using continuous flow. Yields of isolated products based on a 1 mmol scale are reported as an average of two runs. See the Supporting Information for details.

(entry 11). Interestingly, the less expensive diamine ligand **L2** could also be used, although a higher catalyst loading (10 mol %) was required to achieve satisfactory conversion (entry 12).

Having established efficient flow conditions, the substrate scope was investigated (Scheme 1) using the experimental setup shown in Figure 1. The copper-catalyzed Finkelstein reaction of aromatics could be successfully carried out with *para*-, *meta*-, and *ortho*-substituted aryl substrates. In addition, electron-rich, electron-neutral, and electron-deficient bromoarenes all represented excellent substrates. Moreover, the flow conditions tolerated a variety of sensitive functional groups, such as nitrile (**2f**), amide (**2g**), sulfonamide (**2h**), enolizable ketone (**2i**), ester (**2j**), nitro (**2k**), and chlorine (**2l**). Notably, acidic functional groups, including free NH_2 (**2d**) and OH (**2e**), groups could also be successfully transformed without the formation of N- or O-arylation side products.

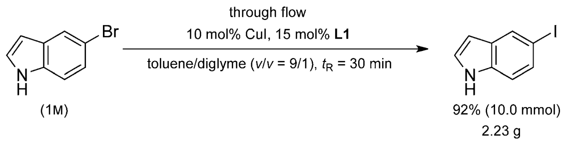
We next focused on expanding the scope of this method to include heteroaryl substrates. As summarized in Scheme 2, a variety of heterocyclic compounds, including benzodioxole (**2m**), pyridine (**2n** and **2o**), quinoline (**2p** and **2q**), indole (**2r** and **2s**), oxindole (**2t**), azaindole (**2u**), thiophene (**2v**), pyrazole (**2w**), and pyrrole (**2x**), could be efficiently transformed into heteroaryl iodides using the developed flow conditions. Unprotected heterocycles, such as indole (**2r** and **2s**), pyrazole (**2w**), and pyrrole (**2x**), could also be directly employed as substrates to prepare the iodides in good to excellent yields without competitive N-arylation.

Next, a range of solvents suitable for the copper-catalyzed Finkelstein reaction of aromatics was evaluated under flow conditions. As shown in Scheme 3, when dioxane was used as the solvent, more than 99% conversion (>98% yield) of ArBr was detected. When the solubility of the NaI salts was improved by increasing the diglyme/toluene ratio, the conversion of ArBr remained fast, more than 95% conversion of ArBr was afforded in all cases examined (A–D).



Scheme 3. Copper-catalyzed halogen-exchange reactions in different solvents under flow conditions.

We next successfully performed the copper-catalyzed Finkelstein reaction of aromatics using flow conditions on a 10 mmol scale. As shown in Scheme 4, we were able to generate 2.23 g of 5-iodoindole in 250 min collection time using a toluene/diglyme mixture as the solvent.



Scheme 4. Copper-catalyzed Finkelstein reaction of 5-bromoindole on a 10 mmol scale. See the Supporting Information for details.

In light of the synthetic versatility of aryl iodides and the outstanding efficiency of multistep continuous-flow processes, we decided to assemble subsequent steps in-line to utilize the crude aryl iodide solutions generated with our method. Although significant improvements have been made to copper-catalyzed amidation, aryl bromides still exhibit lower reactivities than iodides for such coupling processes.[16] With the optimized Finkelstein reaction in hand, we designed a two-step flow process to realize a formal copper-catalyzed amidation of aryl bromides in a highly efficient fashion. As shown in the flow setup (Figure 2, Path A), after the halogen-exchange reaction was complete, the resulting mixture was mixed with an amide solution. Then, without further addition of any catalyst or ligand, the combined solution was directly introduced into a second Cs_2CO_3 packed-bed reactor at 120 °C to perform the copper-catalyzed Goldberg coupling reaction. Finally, the resulting mixture was collected and purified to afford the corresponding products. As shown in Scheme 5, lactam (**3a**, **3e**), primary amide (**3b**), benzamide (**3d**), and carbamate (**3c**) could be successfully employed as nucleophiles in this two-step continuous-flow process (through Path A). Notably, only 30 min residence times were required in the second step to ensure complete conversions of the aryl iodides.[17]

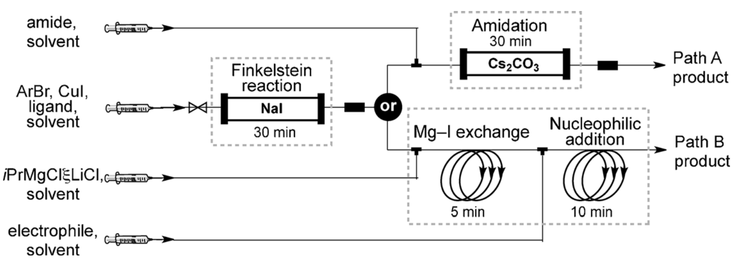
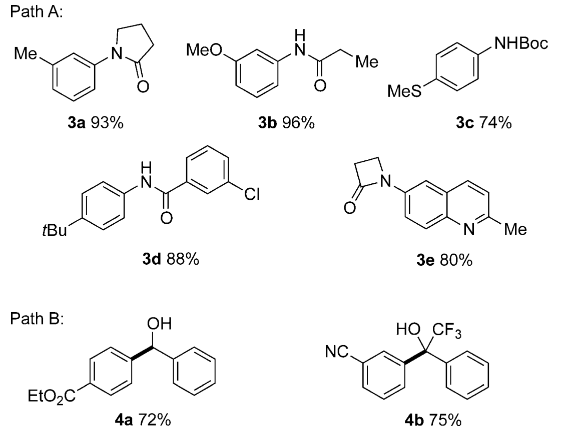


Figure 2. Continuous-flow setups for both a halogen exchange/C–N bond formation and a halogen exchange/Mg–I exchange/nucleophilic addition sequence. For more details, please see the Supporting Information.



Scheme 5. Continuous-flow synthesis through a halogen exchange/amidation (Path A) or a halogen exchange/I–Mg exchange/nucleophilic addition sequence (Path B). Yields of isolated products based on a 1 mmol scale are reported as an average of two runs. For more details, please see the Supporting Information.

For metal–halogen exchange reactions, aryl iodides manifest higher reactivity and better functional-group tolerance than the corresponding bromides.[1a,18,19] Thus, we saw the opportunity to apply our method to a three-step continuous-flow process comprised of a halogen exchange/Mg–I exchange followed by a nucleophilic addition. As shown in Figure 2 Path B), a solution of an aryl iodide was mixed with a solution of iPrMgCl·LiCl at 0 °C. After the Mg–I exchange reaction was completed, the resulting solution was mixed with a stream of the electrophile to effect the nucleophilic addition. It is noteworthy that Grignard reagents containing an ethyl ester (**4a**) or a nitrile (**4b**) could be successfully generated through Mg–I exchange at 0 °C (5 min), which normally requires lower temperatures (−40 to −20 °C) and longer reaction times (30–60 min) under batch conditions.[18,19]

In conclusion, we have developed a general and efficient flow process to access aromatic and heteroaromatic iodides from the corresponding bromides through a copper-catalyzed halogen-exchange reaction. This method represents the first example of a copper-catalyzed Finkelstein reaction conducted in flow, using a sodium iodide packed-bed reactor. The proper choice of the reaction medium, which has exceedingly low solubility for salts, is of importance to afford a satisfactory conversion for this reaction. In addition, two multistep continuous-flow processes, including a halogen exchange/amidation and a halogen exchange/Mg–I exchange/nucleophilic addition sequence were established to further demonstrate the utility and efficiency of this flow method. With these two sequences, a rapid and efficient copper-catalyzed amidation or a functional-group-tolerable Mg–I exchange under mild conditions could be realized.

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Keywords: copper · cross-coupling · flow chemistry · synthetic methods

[1] For selected examples of the application of (hetero)aryl iodides in organic synthesis, see: a) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem. Int. Ed.* **2003**, *42*, 4302; *Angew. Chem.* **2003**, *115*, 4438; b) O. A. Tomashenko, E. C. Escudero-Adán, M. M. Belmonte, V. V. Grushin, *Angew. Chem. Int. Ed.* **2011**, *50*, 7655; *Angew. Chem.* **2011**, *123*, 7797; c) C. Uyeda, Y. Tan, G. C. Fu, J. C. Peters, *J. Am. Chem. Soc.* **2013**, *135*, 9548; d) S. Bontemps, J. S. Quesnel, K. Worrall, B. A. Arndtsen, *Angew. Chem. Int. Ed.* **2011**, *50*, 8948; *Angew. Chem.* **2011**, *123*, 9110; e) I. Popov, S. Lindeman, O. Daugulis, *J. Am. Chem. Soc.* **2011**, *133*, 9286.

[2] a) R. Bunevičius, G. Kažanavičius, R. žalinkevičius, A. J. Prange, Jr., *N. Engl. J. Med.* **1999**, *340*, 424; b) I. Klein, K. Ojamaa, *N. Engl. J. Med.* **2001**, *344*, 501.

[3] L. C. Cerchietti, E. C. Lopes, S. N. Yang, K. Hatzi, K. L. Bunting, L. A. Tsikitas, A. Mallik, A. I. Robles, J. Walling, L. Varticovski, R. Shaknovich, K. N. Bhalla, G. Chiosis, A. Melnick, *Nat. Med.* **2009**, *15*, 1369.

[4] F. Hallouard, N. Anton, P. Choquet, A. Constantinesco, T. Vandamme, *Biomaterials* **2010**, *31*, 6249.

[5] For reviews see: a) E. B. Merkushev, *Synthesis* **1988**, 923; b) T. D. Sheppard, *Org. Biomol. Chem.* **2009**, *7*, 1043.

[6] a) K. Takagi, N. Hayama, S. Inokawa, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3691; b) T. T. Tsou, J. K. Kochi, *J. Org. Chem.* **1980**, *45*, 1930; c) G. Meyer, Y. Rollin, J. Perichon, *Tetrahedron Lett.* **1986**, *27*, 3497; d) J. H. Clark, C. W. Jones, *J. Chem. Soc. Chem. Commun.* **1987**, 1409; e) S. H. Yang, C. S. Li, C. H. Cheng, *J. Org. Chem.* **1987**, *52*, 691; f) K.-I. Yamashita, M. Tsuboi, M. S. Asano, K.-I. Sugiura, *Synth. Commun.* **2012**, *42*, 170.

[7] a) T.-S. Mei, R. Giri, N. Maugel, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2008**, *47*, 5215; *Angew. Chem.* **2008**, *120*, 5293; b) X.-C. Wang, Y. Hu, S. Bonacorsi, Y. Hong, R. Burrell, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 10326.

[8] D. Kalyani, A. R. Dick, W. Q. Anani, M. S. Sanford, *Org. Lett.* **2006**, *8*, 2523.

[9] Y. Imazaki, E. Shirakawa, R. Ueno, T. Hayashi, *J. Am. Chem. Soc.* **2012**, *134*, 14760.

[10] a) A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 14844; b) A. S. Dudnik, N. Chernyak, C. Huang, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2010**, *49*, 8729; *Angew. Chem.* **2010**, *122*, 8911; c) S. G. Newman, J. K. Howell, N. Nicolaus, M. Lautens, *J. Am. Chem. Soc.* **2011**, *133*, 14916; d) A. A. Cant, R. Bhalla, S. L. Pimlott, A. Sutherland, *Chem. Commun.* **2012**, *48*, 3993; e) A. Casitas, M. Canta, M. Solà, M. Costas, X. Ribas, *J. Am. Chem. Soc.* **2011**, *133*, 19386; f) A. C. Bissember, M. G. Banwell, *J. Org. Chem.* **2009**, *74*, 4893.

[11] For selected recent examples in our group, see: a) A. DeAngelis, D.-H. Wang, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 3434; *Angew. Chem.* **2013**, *125*, 3518; b) M. Chen, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 4247; *Angew. Chem.* **2013**, *125*, 4341; c) N. Chernyak, S. L. Buchwald, *J. Am. Chem. Soc.* **2012**, *134*, 12466; d) T. Noël, T. J. Maimone, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 8900; *Angew. Chem.* **2011**, *123*, 9062.

[12] For selected reviews of organic synthesis in flow, see: a) J. C. Pastre, D. L. Browne, S. V. Ley, *Chem. Soc. Rev.* **2013**, *42*, 8849; b) J. Wegner, S. Ceylan, A. Kirschning, *Adv. Synth. Catal.* **2012**, *354*, 17; c) D. T. McQuade, P. H. Seeberger, *J. Org. Chem.* **2013**, *78*, 6384; d) U. Hintermair, G. Franciò, W. Leitner, *Chem. Commun.* **2011**, *47*, 3691; e) K. S. Elvira, X. C. i Solvas, R. C. R. Wootton, A. J. deMello, *Nat. Chem.* **2013**, *5*, 905; f) C. Wiles, P. Watts, *Green Chem.* **2014**, *16*, 55; g) K. Booker-Milburn, *Nat. Chem.* **2012**, *4*, 433; h) C. G. Frost, L. Mutton, *Green Chem.* **2010**, *12*, 1687; i) J. Yoshida, Y. Takahashi, A. Nagaki, *Chem. Commun.* **2013**, *49*, 9896; j) T. Chinnusamy, S. Yudha, M. Hager, P. Kreitmeier, O. Reiser, *ChemSusChem* **2012**, *5*, 247.

[13] For reviews of handling high-temperature conditions in flow, see: a) T. N. Glasnov, C. O. Kappe, *Chem. Eur. J.* **2011**, *17*, 11956; b) V. Hessel, D. Kralisch, N. Kockmann, T. Noël, Q. Wang, *ChemSusChem* **2013**, *6*, 746; c) N. Kockmann, D. M. Roberge, *Chem. Eng. Technol.* **2009**, *32*, 1682.

[14] For examples of handling high-temperature conditions in flow, see: a) C. Battilocchio, B. J. Deadman, N. Nikbin, M. O. Kitching, I. R. Baxendale, S. V. Ley, *Chem. Eur. J.* **2013**, *19*, 7917; b) A. G. O‘Brien, Z. Horváth, F. Lévesque, J. W. Lee, A. Seidel-Morgenstern, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2012**, *51*, 7028; *Angew. Chem.* **2012**, *124*, 7134; c) J. Baek, P. M. Allen, M. G. Bawendi, K. F. Jensen, *Angew. Chem. Int. Ed.* **2011**, *50*, 627; *Angew. Chem.* **2011**, *123*, 653; d) B. Gutmann, J.-P. Roduit, D. Roberge, C. O. Kappe, *Angew. Chem. Int. Ed.* **2010**, *49*, 7101; *Angew. Chem.* **2010**, *122*, 7255; e) D. R. Snead, T. F. Jamison, *Chem. Sci.* **2013**, *4*, 2822; f) F. Ullah, Q. Zang, S. Javed, P. Porubsky, B. Neuenswander, G. H. Lushington, P. R. Hanson, M. G. Organ, *Synthesis* **2012**, *44*, 2547; g) H. Kawanami, K. Matsushima, M. Sato, Y. Ikushima, *Angew. Chem. Int. Ed.* **2007**, *46*, 5129; *Angew. Chem.* **2007**, *119*, 5221; h) M. Chen, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 11628; *Angew. Chem.* **2013**, *125*, 11842; i) J. G. Stevens, R. A. Bourne, M. V. Twigg, M. Poliakoff, *Angew. Chem. Int. Ed.* **2010**, *49*, 8856; *Angew. Chem.* **2010**, *122*, 9040.

[15] GC conversions of **1a** ranging from 33% to 73% were obtained under batch conditions (5 mol% CuI, 10 mol% **L1**, 1.0 M in dioxane, 180°C, 30 min).

[16] a) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2010**, *1*, 13; b) S. V. Ley, A. W. Thomas, *Angew. Chem. Int. Ed.* **2003**, *42*, 5400; *Angew. Chem.* **2003**, *115*, 5558; c) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054.

[17] When mixed solutions of aryl bromides and catalysts were used to perform the same cross-coupling reaction under flow conditions, less than 5% conversion of aryl bromides was observed in all examples.

[18] For examples of Mg–I exchange under batch conditions, see: a) L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, *37*, 1701; *Angew. Chem.* **1998**, *110*, 1801; b) M. Rottländer, L. Boymond, G. Cahiez, P. Knochel, *J. Org. Chem.* **1999**, *64*, 1080.

[19] For examples of metal–halogen exchange under flow conditions, see: a) D. L. Browne, M. Baumann, B. H. Harji, I. R. Baxendale, S. V. Ley, *Org. Lett.* **2011**, *13*, 3312; b) A. Nagaki, H. Kim, J. Yoshida, *Angew. Chem. Int. Ed.* **2009**, *48*, 8063; *Angew. Chem.* **2009**, *121*, 8207; c) A. Nagaki, H. Kim, Y. Moriwaki, C. Matsuo, J. Yoshida, *Chem. Eur. J.* **2010**, *16*, 11167; d) H. Kim, A. Nagaki, J. Yoshida, *Nat. Commun.* **2011**, *2*, 1264.