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Cross-Coupling

Mild and Rapid Pd-Catalyzed Cross-Coupling with Hydrazine in Continuous Flow: Application to the Synthesis of Functionalized Heterocycles**

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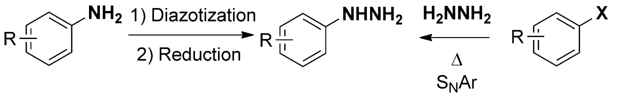
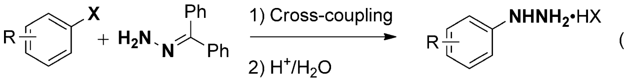
Functionalized arylhydrazines are of widespread importance as intermediates in the syntheses of nitrogen-containing heterocycles.[1] In this regard, indoles,[1,2] arylpyrazoles/pyrazolones,[1,3] and aryltriazoles,[1,4] among others,[1] can be efficiently generated from arylhydrazines. These heterocyclic motifs are prevalent structural elements in numerous compounds of significant biological/medicinal value.[5] Among current strategies to generate arylhydrazines, nucleophilic aromatic substitution to an aryl halide (ArX)[6] or diazotization of an aniline followed by reduction of the diazonium salt[7] have long been preparative methods of choice [Eq. (1)]. However, the former method typically requires an arene activated by electron-withdrawing groups, while the diazotization/reduction sequence is redox-exhaustive and involves the generation of unstable diazonium intermediates.



(1)

Modern cross-coupling technology has provided chemists with powerful tools to construct carbon–nitrogen bonds,[8] and thus presents an alternative method of synthesizing aryl hydrazines.[9] Accordingly, several such cross-coupling strategies have been reported utilizing hydrazine equivalents[10] such as benzophenone hydrazone [Eq. (2)].[10a–f] The only example of direct C–N cross-coupling with hydrazine was recently reported by Stradiotto et al.[11] While this method represented a notable advance, the reactions were set up in a nitrogen-filled glovebox and required relatively high catalyst loading (3–10 mol% Pd). More importantly, significant safety issues exist with the use of hydrazine in the presence of transition metals, particularly with heating; many metal–hydrazine complexes are known to be powerful explosives.[12] We have recently demonstrated the feasibility of C–N cross-coupling reactions in continuous flow,[13] and this strategy represents an attractive solution to minimizing the hazards associated with hydrazine/transition metal mixtures.[14,15] Described herein is a mild and potentially scalable method for the direct cross-coupling of aryl chlorides with hydrazine through the use of continuous flow technology [Eq. (3)], and the application of this technology to the rapid construction of a range of heterocyclic scaffolds.



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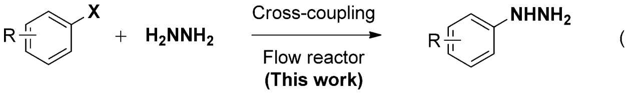

(3)

We began our investigation by carrying out several small-scale (≤ 0.20 mmol) batch experiments to identify suitable reaction conditions; the cross-coupling reaction of 4-chlorotoluene and a commercially available 1.0 M solution of hydrazine in THF (2.0 equiv) was selected for optimization (Table 1). A screen of precatalysts[16] revealed *t*BuXPhos (**L2**) and BrettPhos (**L3**) as efficient ligands in promoting the desired monoarylation of hydrazine with 3 mol% catalyst loading at 60 °C for 1 h. Under these conditions, 4-tolylhydrazine **1** was formed in high yield with high selectivity over diarylated products **2** and **3** (entries 2–4).[17,18] We subsequently found that the BrettPhos-based catalyst was extremely active as it provided **1** in 84% yield with 1.2 equiv of hydrazine at room temperature in only 3 min, albeit with slightly decreased selectivity over diarylation (entry 6). Interestingly, the effect of the stoichiometry of hydrazine on the selectivity over diarylation was not dramatic. While a ratio of 96:2:2 of **1**:**2**:**3** was observed with 2.0 equiv of hydrazine at room temperature (entry 10), good selectivity (92:5:3) for arylation of the more nucleophilic hydrazine was still achieved using only 1.2 equiv (entry 6). Further studies were conducted using 1.6 equiv (entry 8), as slightly better selectivity (95:2.5:2.5) was observed compared to using less hydrazine (entries 6 and 7), while increasing the amount of hydrazine provided no significant advantage (entries 9 and 10).

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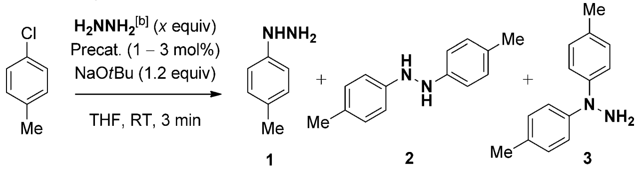
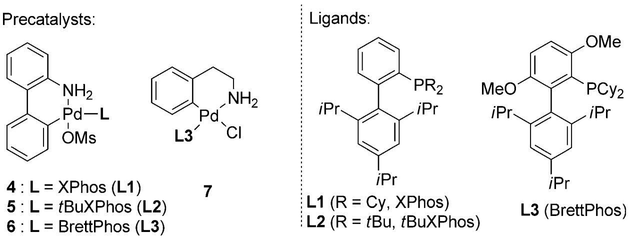
Table 1: Optimization of reaction conditions.[a]



Entry	Precat. [mol%]	H_2NNH_2[b] [equiv]	Yield of **1** [%][c]	Ratio (1:2:3)[c]
1[d]	**4** (3)	2.0	40	100:0:0
2[d]	**5** (3)	2.0	90	95:2.5:2.5
3[d]	**6** (3)	2.0	87	97:1.5:1.5
4[d]	**7** (3)	2.0	92	95:3:2
5	**5** (1)	1.2	24	100:0:0
6	**7** (1)	1.2	84	92:5:3
7	**7** (1)	1.4	86	92:4.5:3.5
8	**7** (1)	1.6	87	95:2.5:2.5
9[e]	**7** (1)	1.8	89	95:2.5:2.5
10[e]	**7** (1)	2.0	89	96:2:2

[a] Reaction conditions: 4-chlorotoluene (0.2 mmol), hydrazine (x equiv), precatalyst (x mol%), NaOtBu (1.2 equiv), THF (≈0.3 M). [b] 1.0 M solution in THF. [c] Determined by ^1H NMR analysis of the crude reaction mixture using trimethoxybenzene as an internal standard. See Supporting Information for additional attempts and complete details. [d] Run for 60 min at 60 °C. [e] Run for 10 min at RT (see Supporting Information for details).



We next turned our attention to developing a continuous flow process based on our batch-optimized reaction conditions. To this end, a microfluidic system was assembled as shown in Figure 1. Our group recently demonstrated that clogging issues resulting from solid formation associated with aryl amination reactions can be addressed by ultrasonication in flow,[13] and a similar system for hydrazine arylation was implemented. Additionally, we decided to trap the arylhydrazine intermediates as benzaldehyde hydrazones to avoid the isolation and storage of sensitive arylhydrazines.[19] Thus, THF solutions of precatalyst **7**, ArCl, hydrazine, and NaOtBu were consecutively merged and introduced into **R1** (submerged in a sonication bath) with a residence time (t_R) of 3 min at room temperature. Upon exiting **R1**, the reaction mixture was met with a stream of aqueous TFA which served a dual purpose: a) it dissolved solid NaCl formed following the cross-coupling reaction, and b) it acidified the reaction mixture to catalyze the hydrazone formation. The reaction mixture was finally merged with a solution of benzaldehyde and introduced into **R2**, which was submerged in an oil bath at 60 °C. Following fraction collection and offline workup and purification, hydrazone **8a** was isolated in 87% yield.

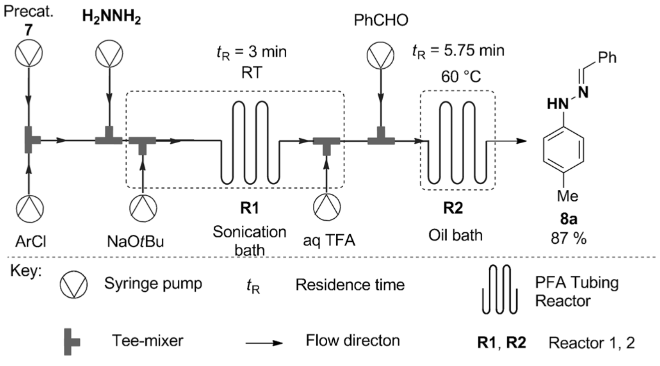
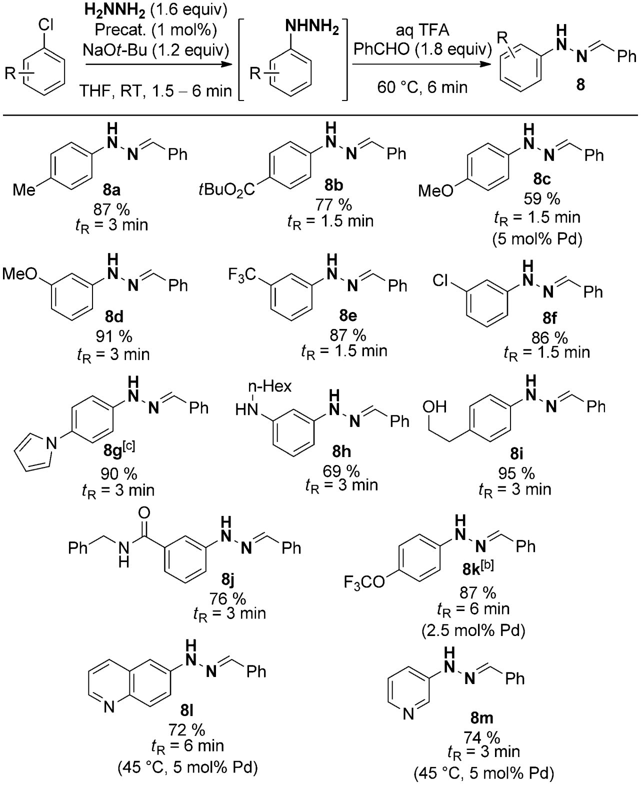


Figure 1. Experimental setup for continuous flow hydrazine arylation/hydrazone formation.[21] TFA = trifluoroacetic acid.

The scope of this transformation was then explored, and the results are summarized in Table 2. Good to excellent yields (59–95%) were obtained across a broad array of substrates. Both electron-neutral and electron-deficient aryl chlorides were coupled efficiently with 1 mol% catalyst loading and short reaction times (1.5–6 min). 1-Chloro-4-trifluoromethoxybenzene as well as electron-rich 4-chloroanisole could also be productively coupled, albeit with higher catalyst loadings (Table 2, entries **8c**, **8k**). Several functional groups were well tolerated including *tert*-butyl ester (**8b**), OCF_3 (**8k**), CF_3 (**8e**), halogen (**8f**), pyrrole (**8g**), primary alcohol (**8i**), as well as free N−H-bearing functional groups

Table 2: Continuous flow Pd-catalyzed cross-coupling of aryl chlorides with hydrazine/hydrazone formation.[a]

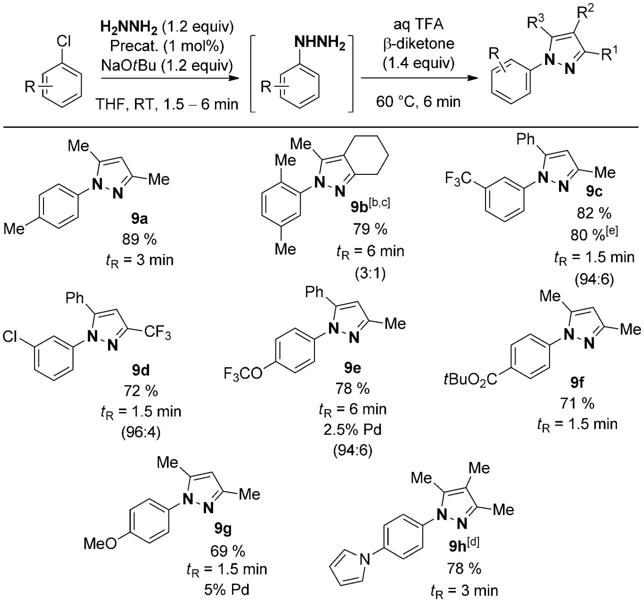


[a] Yields of isolated products on a 1.0 mmol scale (average of two runs). [b] 2.0 Equiv of hydrazine used. [c] Hydrazone formation performed offline in a batch reactor due to the insolubility of the $ArNHNH_2\cdot TFA$ salt.

such as an aniline (**8h**) or amide (**8j**). Reactions with heterocyclic aryl chlorides such as 6-chloroquinoline and 3-chloropyridine (**8l**, **8m**) were also successful with 5 mol% catalyst loading and a slightly elevated temperature (45 °C).[20]

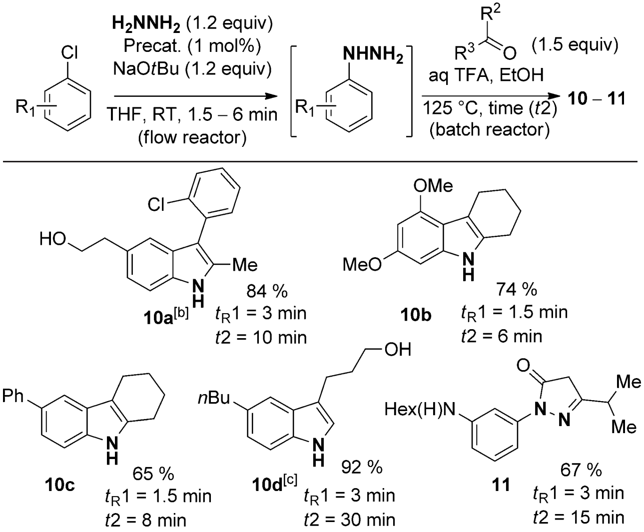
An additional advantage of continuous flow technology is the ability to integrate multistep syntheses into a single operation.[14d] Given the synthetic utility of arylhydrazines, we sought to develop tandem flow processes for the direct formation of interesting heterocycles. By introducing readily available β-diketones into the system following hydrazine arylation and subsequent acidification, cyclocondensation cleanly took place to furnish aryl pyrazole derivatives **9** in good to high yield over two steps (Table 3).[21,22] The amount of hydrazine used was reduced to 1.2 equivalents so as to not consume a large quantity of diketone by the formation of undesired N–H pyrazole side product. Unsymmetrically substituted diketones, which can often give rise to mixtures of regioisomers,[23] were efficient reaction partners providing aryl pyrazoles with high regioselectivity (entries **9c–e**). The exception was in the formation of **9b**, which was formed in good yield (79%) but modest regioselectivity (3:1). The formation of compound **9b** also demonstrates the tolerance of *ortho*-substitution in the cross-coupling reaction. To demonstrate the potential scalability of this process, the reaction to generate **9c** was performed on a 5 mmol scale: on this scale, the product was obtained in 80% yield.

Table 3: Continuous flow synthesis of aryl pyrazoles via cross-coupling of aryl chlorides with hydrazine.[a]



[a] Yields of isolated products on a 1.0 mmol scale (average of two runs). Numbers in parenthesis refer to the regioisomer ratios as determined by GC analysis of the crude reaction mixtures. [b] Pyrazole formation was more conveniently performed offline in a batch reactor due to longer required residence time. Pyrazole formation was run for 18 min. [c] Isolated as a mixture of regioisomers; **9b** is the major regioisomer. [d] Second step performed offline in a batch reactor due to the insolubility of the $ArNHNH_2$·TFA salt. [e] Yield of isolated product on a 5.0 mmol scale (average of 2 runs).

Table 4: Tandem hydrazine arylation/heterocycle synthesis.[a]



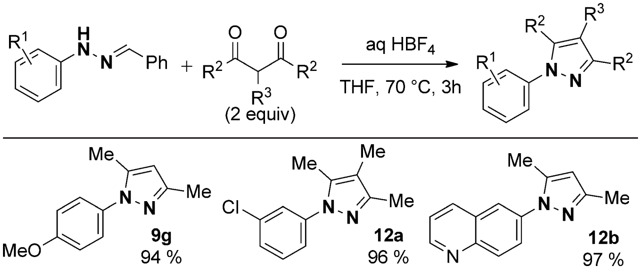
[a] Yields of isolated products on a 1.0 mmol scale (average of two runs). [b] *p*-Toluenesulfonic acid (*p*-TsOH) used. [c] 1.2 Equiv of 3,4-dihydro-2*H*-pyran used.

Indoles **10** as well as pyrazolone **11** could also be generated in multistep sequences (Table 4). Thus, following the acidification of the crude aryl hydrazine and introduction of a carbonyl compound (or equivalent), the crude reaction mixture was collected into a batch reactor and heated to 125 °C;[21] these reactions were complete in 6–30 min. Good yields over two steps of 2,3-disubstituted indoles were achieved using 2-chlorophenylacetone (entry **10a**) and cyclohexanone (entries **10b** and **10c**), as well with as 3,4-dihydro-3*H*-pyran to form 2-unsubstituted indole **10d**.[24] Cyclocondensation was also successful with ethyl isobutyrylacetate to give aryl pyrazolone **11** in 67% yield.

To demonstrate the competency of *N*-aryl benzaldehyde hydrazones **8** as arylhydrazine equivalents, **8c**, **8f**, and **8l** were treated with β-dicarbonyl compounds in the presence of aqueous acid (Table 5). The hydrazones smoothly underwent an in situ hydrolysis/cyclocondensation sequence to furnish *N*-aryl pyrazole products **9g** and **12a**–**12b** with excellent yields (94–97%).

In summary, a highly efficient and chemoselective method for the construction of arylhydrazines via a C–N cross-

Table 5: Use of *N*-aryl benzaldehyde hydrazones as arylhydrazine equivalents in aryl pyrazole synthesis.[a,b]



[a] Hydrazone (1 equiv), β-diketone (2.0 equiv), HBF_4 (10 equiv), THF (0.17 M), 70 °C, 3 h. [b] Yields of isolated products on a 0.50 mmol scale (average of two runs).

coupling reaction featuring a broad scope of aryl/heteroaryl chlorides has been developed. By taking advantage of the benefits of continuous flow, the hazards associated with the use of hydrazine in the presence of transition metals have been decreased, providing a convenient and potentially scalable cross-coupling method to access aryl/heteroarylhydrazines. Furthermore, the cross-coupling reactions are exceptionally rapid as they are complete in minutes at or slightly above room temperature. Multistep processes for the direct conversion of arylhydrazine intermediates into *N*-aryl pyrazoles and indoles have also been described.

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[1] a) A. R. Katritzky, A. F. Pozharskii, *Handbook of Heterocyclic Chemistry*, 2nd ed., Pergamon, New York, **2000**; b) T. Eicher, S. Hauptmann, *The Chemistry of Heterocycles*, 2nd ed., Wiley-VCH, Weinheim, **2003**; c) J. A. Joule, K. Mills, *Heterocyclic Chemistry*, 5th ed., Wiley, Chichester, **2010**.

[2] a) D. F. Taber, P. K. Tirunahari, *Tetrahedron* **2011**, *67*, 7195; b) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875.

[3] S. Fustero, M. Sánchez-Roselló, P. Barrio, A. Simón-Fuentes, *Chem. Rev.* **2011**, *111*, 6984.

[4] K. T. Potts, *Chem. Rev.* **1961**, *61*, 87.

[5] P. Ertl, S. Jelfs, J. Mühlbacher, A. Schuffenhauer, P. Selzer, *J. Med. Chem.* **2006**, *49*, 4568.

[6] Selected examples, see a) S. D'Andrea, Z. B. Zheng, K. DenBleyker, J. C. Fung-Tomc, H. Yang, J. Clark, D. Taylor, J. Bronson, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2834; b) M. Schlosser, T. Rausis, C. Bobbio, *Org. Lett.* **2005**, *7*, 127; c) V. A. Kuznetsov, K. M. Shubin, A. A. Schipalkin, F. S. Teplyakov, M. L. Petrov, *Russ. J. Org. Chem.* **2008**, *44*, 731; d) C. F. H. Allen, *Org. Synth.* **1933**, *13*, 36.

[7] a) G. H. Coleman, *Org. Synth.* **1922**, *2*, 71; b) A. S. Zentiva, M. Voslar, M. Zatopkova, L. Ridvan, T. Pekarek, WO Pat. 2008/104134, **2008**; c) J. P. Koilpillai, M. Subramanian, U. Mallela, V. B. Boddu, R. Dandala, S. Meenakshisunderam, WO Pat. 2008/075163, **2008**; d) R. Baker, V. G. Matassa, L. J. Street, US Pat. 5,298,520, **1994**; For a continuous flow-based approach, see e) D. L. Browne, I. R. Baxendale, S. V. Ley, *Tetrahedron* **2011**, *67*, 10296.

[8] Selected reviews: a) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27; b) D. S. Surry, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 6438; *Angew. Chem. Int. Ed.* **2008**, *47*, 6338; c) J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534; d) E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Angew. Chem.* **2007**, *119*, 2824; *Angew. Chem. Int. Ed.* **2007**, *46*, 2768; e) N. Marion, S. P. Nolan, *Acc. Chem. Res.* **2008**, *41*, 1440; f) H. Li, C. C. C. J. Seechurn, T. J. Colacot, *ACS Catal.* **2012**, *2*, 1147.

[9] S. L. Buchwald, S. Wagaw, O. Geis, US Pat. 6,465,693, **2002**.

[10] Selected examples using hydrazones: a) S. Wagaw, B. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 6621; b) S. Wagaw, B. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 10251; c) J. F. Hartwig, *Angew. Chem.* **1998**, *110*, 2249; *Angew. Chem. Int. Ed.* **1998**, *37*, 2090; d) V. Lefebvre, T. Cailly, F. Fabis, S. Rault, *J. Org. Chem.* **2010**, *75*, 2730; e) C. Mauger, G. Mignani, *Adv. Synth. Catal.* **2005**, *347*, 773; f) A. Klapars, J. C. Antilla, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7727; selected examples using hydrazides: g) A. Reichelt, J. R. Falsey, R. M. Rzasa, O. R. Thiel, M. M. Achmatowicz, R. D. Larsen, D. Zhang, *Org. Lett.* **2010**, *12*, 792; h) J. Chae, S. L. Buchwald, *J. Org. Chem.* **2004**, *69*, 3336; i) X. Xiong, Y. Jiang, D. Ma, *Org. Lett.* **2012**, *14*, 2552; j) L. Jiang, X. Lu, H. Zhang, Y. Jiang, D. Ma, *J. Org. Chem.* **2009**, *74*, 4542; k) M. R. Rivero, S. L. Buchwald, *Org. Lett.* **2007**, *9*, 973; l) M. Wolter, A. Klapars, S. L. Buchwald, *Org. Lett.* **2001**, *3*, 3803; m) R. Martín, M. R. Rivero, S. L. Buchwald, *Angew. Chem.* **2006**, *118*, 7237; *Angew. Chem. Int. Ed.* **2006**, *45*, 7079.

[11] R. L. Lundgren, M. Stradiotto, *Angew. Chem.* **2010**, *122*, 8868; *Angew. Chem. Int. Ed.* **2010**, *49*, 8686.

[12] Selected examples: a) A. Wojewódka, J. Belzowski, *Chemik* **2011**, *65*, 20; b) A. Wojewódka, J. Belzowski, Z. Wilk, J. Staś, *J. Hazard. Mater.* **2009**, *171*, 1175; c) S. Zhu, Y. Wu, W. Zhang, J. Mu, *Propellants Explos. Pyrotech.* **1997**, *22*, 317.

[13] a) T. Noël, J. R. Naber, R. L. Hartman, J. P. McMullen, K. F. Jensen, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 287; b) R. L. Hartman, J. R. Naber, N. Zaborenko, S. L. Buchwald, K. F. Jensen, *Org. Process Res. Dev.* **2010**, *14*, 1347.

[14] For discussions on the benefits of chemistry in continuous flow, see: a) T. Noël, S. L. Buchwald, *Chem. Soc. Rev.* **2011**, *40*, 5010; b) R. L. Hartman, J. P. McMullen, K. F. Jensen, *Angew. Chem.* **2011**, *123*, 7642; *Angew. Chem. Int. Ed.* **2011**, *50*, 7502; c) N. G. Anderson, *Org. Process Res. Dev.* **2012**, *16*, 852; d) D. Webb, T. F. Jamison, *Chem. Sci.* **2010**, *1*, 675; e) J. Wegner, S. Ceylan, A. Kirschning, *Adv. Synth. Catal.* **2012**, *354*, 17; f) P. B. Palde, T. F. Jamison, *Angew. Chem.* **2011**, *123*, 3587; *Angew. Chem. Int. Ed.* **2011**, *50*, 3525.

[15] For examples of the use of continuous flow for handling hydrazine, see: a) J. R. Breen, G. Sandford, D. S. Yufit, J. A. K. Howard, J. Fray, B. Patel, *Beilstein J. Org. Chem.* **2011**, *7*, 1048; b) E. Garcia-Egido, V. Spikmans, S. Y. F. Wong, B. H. Warrington, *Lab Chip* **2003**, *3*, 73; c) C. Wiles, P. Watts, S. J. Haswell, *Org. Process Res. Dev.* **2004**, *8*, 28; d) R. Eluri, B. Paul, *J. Nanopart. Res.* **2012**, *14*, 800; e) D. Cantillo, M. Baghbanzadeh, C. O. Kappe, *Angew. Chem.* **2012**, *124*, 10337; *Angew. Chem. Int. Ed.* **2012**, *51*, 10190.

[16] a) N. C. Bruno, M. T. Tudge, S. L. Buchwald, *Chem. Sci.* **2013**, *4*, 216; b) B. P. Fors, D. A. Watson, M. R. Biscoe, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 13552.

[17] The first- (**7**) and second-generation (**6**) BrettPhos precatalysts were found to be interchangeable, however, **7** has greater solubility in THF relative to **6** and was used throughout the remainder of the study.

[18] Analogous reactions at 60°C with 4-bromotoluene, 4-iodotoluene, and 4-methylphenyltosylate were less successful (63%, 30%, and 0% ^{1}H NMR yields of **1** were observed, respectively).

[19] Hydrazone formation has previously been shown to be a convenient method for the storage of arylhydrazines. See Refs. [10a–e] and Ref. [11].

[20] Known limitations: Under conditions similar to those described in Table 1, entry 8, low conversion was observed with 2-chloro-*m*-xylene, 4-chlorobenzamide, 4-chlorobenzenesulfonamide, 5-chloroindole, and 5-chloro-2-methylbenzothiazole. Low ^{1}H NMR yields of aryl hydrazine products were observed with 4-chlorobenzonitrile (50%) and 4-chlorobenzotrifluoride (16%).

[21] See Supporting Information for details regarding the experimental setup.

[22] For examples in flow, see: D. Obermayer, T. N. Glasnov, C. O. Kappe, *J. Org. Chem.* **2011**, *76*, 6657, and Refs. [15a–c].

[23] a) S. Fustero, R. Román, J. F. Sanz-Cervera, A. Simón-Fuentes, A. C. Cuñat, S. Villanova, M. Murguía, *J. Org. Chem.* **2008**, *73*, 3523; b) F. Gosselin, P. D. O'Shea, R. A. Webster, R. A. Reamer, R. D. Tillyer, E. J. J. Grabowski, *Synlett* **2006**, 3267.

[24] K. R. Campos, J. C. S. Woo, S. Lee, R. D. Tillyer, *Org. Lett.* **2004**, *6*, 79, and references therein.