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Continuous-Flow Synthesis of Monoarylated Acetaldehydes Using Aryldiazonium Salts

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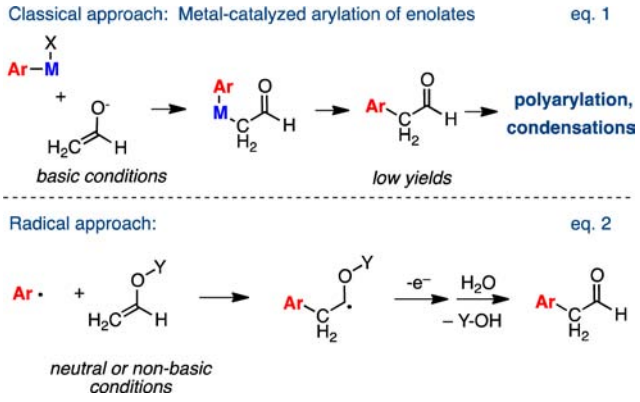
Supporting Information

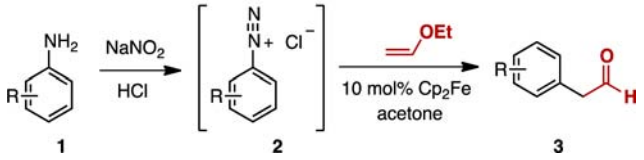
ABSTRACT: Anilines and ethyl vinyl ether can be used as precursors for a process that is the synthetic equivalent of the α-arylation of acetaldehyde enolate. The reaction manifests a high level of functional group compatibility, allowing the ready preparation of a number of synthetically valuable compounds.

Transition-metal-catalyzed α-arylation of carbonyl compounds and their equivalents has seen increased use over the past 15 years.[1,2] Extensive research in this field has resulted in the development of a variety of direct metal-catalyzed enolate arylation methods for aldehydes,[2a−d] ketones,[2l,i,j] acetate esters,[2e,g,h] and amides.[2l] In addition, efficient enantioselective arylation reactions of carbonyl compounds have been demonstrated.[3] Yet, despite the significant progress in this field, the selective arylation of simple acetaldehyde still remains a challenge. This problem arises from the intrinsic sensitivity of acetaldehyde and its arylation products toward the typically basic reaction conditions as well as the tendency of the initially formed products to undergo further arylation (eq 1).[2a−d]



Radical processes often can provide a feasible alternative to metal-catalyzed anionic reactions. Among these, the Meerwein arylation represents an attractive, synthetically equivalent method to access α-arylated carbonyl compounds (eq 2).[4] This process employs aryldiazonium salts as effective sources of reactive aryl radicals. One of the versions of this reaction proceeds via the addition of an aryl radical across the double bond of an enol derivative to produce an alkyl radical intermediate. The latter is converted into the corresponding arylated carbonyl compound upon a single-electron oxidation/hydrolysis sequence (eq 2). The relatively high reaction rates of addition of aryl radicals to unsaturated bonds allow these reactions to proceed rapidly and with high functional group compatibility under *nonbasic* reaction conditions at low temperatures. In addition, a wide range of commercially available anilines, along with several methods reported for their diazotization, render these compounds particularly attractive alternatives to aryl halides as the aryl group donor sources. However, despite these perceived advantages, the application of the Meerwein arylation reaction to the synthesis of arylacetaldehydes remains largely underdeveloped.[5] A significant drawback of this arylation methodology is the generation of highly reactive, thermo- and shock-sensitive aryldiazonium salts. These issues raise significant safety concerns and impose very stringent procedures and regulations on the use of these materials in large-scale reactions.[6] It has previously been demonstrated that continuous-flow manufacturing can provide a solution for the efficient and safe handling of highly reactive intermediates on a variable scale.[7] In this communication, we report a method for the synthesis of monoarylacetaldehydes **3** via a ferrocene-catalyzed Meerwein arylation reaction of ethyl vinyl ether with aryldiazonium chlorides **2** generated in situ from anilines **1** using a continuous flow technique (Scheme 1).

Scheme 1. Meerwein Arylation Reaction Approach toward Monoarylacetaldehydes



One of the major prerequisites for an efficient flow process is the homogeneity of the reaction conditions. Thus, small-scale batch optimizations were initially performed to establish suitably *homogeneous* Meerwein arylation conditions.[8] Accordingly, *p*-chlorophenyl diazonium salt intermediates **2a** were generated in situ with acid and sodium nitrite and subsequently allowed to react with a 10-fold excess of ethyl vinyl ether in the presence of either copper or iron salts (Table 1). The use of *p*-chlorophenyl diazonium chloride in the presence of CuCl as either a catalyst (entry 1) or a promoter (entry 2) resulted in rapid decomposition of the aryldiazonium salt, furnishing

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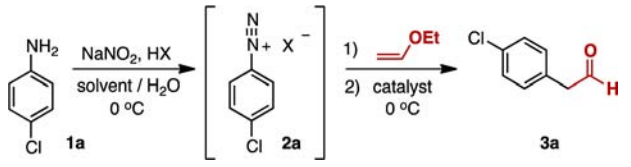
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst [mol %]	HX	solvent/H_2O[b]	yield (%)[c]
1	CuCl [5]	HCl	MeCN/H_2O	32
2	CuCl [100]	HCl	MeCN/H_2O	52
3	CuCl [100]	H_2SO_4	MeCN/H_2O	60
4	$FeSO_4·7H_2O$ [10]	H_2SO_4	DMSO/H_2O	71
5	$FeSO_4·7H_2O$ [10]	HCl	DMSO/H_2O	43
6	$FeSO_4·7H_2O$ [10]	HCl	acetone/H_2O	32
7	Cp_2Fe [10]	H_2SO_4	acetone/H_2O	65
8	Cp_2Fe [10]	H_2SO_4	DMSO/H_2O	63
9	Cp_2Fe [10]	HCl	acetone/H_2O	80
10	Cp_2Fe [10]	HCl	MeCN/H_2O	79

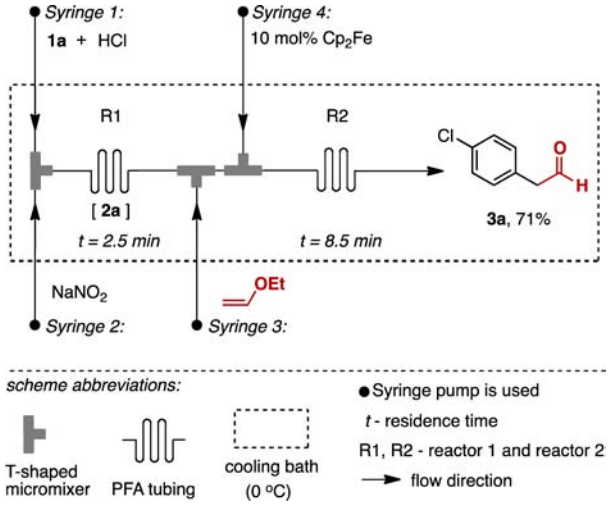
[a]Optimization of the reaction conditions was conducted on a 60 μmol scale. See the Supporting Information for details. [b]3:1 solvent/water mixture. [c]Determined by GC analysis versus a calibrated internal standard.

moderate yields of the aldehyde product **3a**. Switching to an aryldiazonium salt possessing the less nucleophilic hydrosulfate counterion led only to a moderate improvement in the reaction yield (entry 3). Interestingly, the use of aryldiazonium hydrosulfate in the presence of stoichiometric amounts of a water-soluble $FeSO_4·7H_2O$ promoter in a mixture of dimethyl sulfoxide (DMSO) and H_2O provided **3a** in good yield. The identity of the diazonium salt counterion was crucial, as switching to the more reactive diazonium chloride resulted in decreased product yields (entries 5 and 6).

Encouraged by these results with iron salts, we next chose to explore the use of ferrocene (Cp_2Fe), which is soluble in most organic solvents, as a catalyst for this transformation.[9] We found that both in situ-generated diazonium chloride and hydrosulfate salts reacted well in the presence of 10 mol % ferrocene. When the solvent was changed to an acetone/water mixture, the desired product **3a** was obtained in 80% yield (Table 1, entry 9). Similar results were achieved by using an acetonitrile/water mixture as the solvent (entry 10). Notably, the ferrocene-catalyzed Meerwein arylation reaction occurred rapidly, with full conversions achieved in 8.5−10 min in all cases.

Next, we focused on translating these promising batch results into a continuous-flow process.[10] The flow setup for the diazotization/arylation sequence was assembled as shown in Scheme 2. Diazotization of aniline **1a** was carried out at 0 °C in the first reactor (R1 in Scheme 2) for 2.5 min by mixing an acidic solution of **1a** (syringe 1) with a stream of sodium nitrite solution (syringe 2). The resultant solution of aryldiazonium chloride **2a** (Scheme 2) was then mixed with a stream of a solution of ethyl vinyl ether (10 equiv) in acetone from syringe 3. Finally, a solution of ferrocene from syringe 4 was introduced into the system, and the reaction mixture was then allowed to flow through the second reactor (R2 in Scheme 2) at 0 °C, after which it was collected in a precooled (0 °C) flask under an inert atmosphere. Following aqueous workup and purification, the corresponding arylacetaldehyde product **3a** was obtained in 71% isolated yield.[11]

Scheme 2. Continuous-Flow Setup for the Diazotization/Arylation Sequence[12]



With the optimized conditions in hand, the scope of this transformation with various anilines was investigated using the continuous-flow setup outlined in Scheme 2 (Table 2). Most of the anilines examined underwent efficient diazotization in 0.6−3 min in the first reactor followed by a facile Meerwein arylation reaction in 8.5 min in the second reactor. We found that a wide range of anilines possessing both strongly electron-withdrawing substituents and mildly electron-donating groups underwent the Meerwein arylation quite efficiently (entries **3a−x**). Notably, with this method, a number of monoaryl-acetaldehydes possessing a variety of functional groups (F, Cl, Br, I, CN, NO_2, CF_3, OCF_3, and CO_2t-Bu) were obtained in good to high yields. In addition, we found that polyhalogenated anilines could efficiently serve as aryl group donors, furnishing the corresponding aldehydes as useful building blocks possessing multiple sites for further modular functionalizations of the benzene ring (entries **3d−g**, **3o**, and **3s−u**). These polyhalogenated derivatives would be challenging to access via the existing transition-metal-catalyzed methodologies. Furthermore, *o*-nitroaniline derivatives also reacted readily to provide *o*-nitro-substituted arylacetaldehydes **3p−r**, which are important precursors for the synthesis of indole derivatives. Finally, heterocyclic amines, such as 3-aminopyridines, could successfully be employed in this reaction to access the corresponding heteroarylated acetaldehydes **3v−x** in good yields (Table 2).

A plausible mechanism for this process is depicted in Scheme 3.[13] A single-electron reduction of the aryldiazonium salt intermediate with the ferrocene catalyst produces the corresponding aryl radical **4** and ferrocenium cation. Next, radical arylation of ethyl vinyl ether leads to alkyl radical intermediate **5**. A single-electron oxidation of the latter with ferrocenium ion affords acylium cation intermediate **6** and regenerates the ferrocene catalyst. Finally, hydrolysis of **6** provides arylacetaldehyde product **3** (Scheme 3).

Considering the high synthetic value of arylacetaldehydes, we decided to demonstrate the utility of the crude monoarylacetaldehyde products obtained using our continuous-flow method by using them to synthesize several important molecules (Scheme 4). β-Phenethylamines represent an important class of compounds possessing a wide range of pharmaceutically important properties. Accordingly, reductive amination of crude **3** with *p*-anisidine in the presence of $NaBH(OAc)_3$

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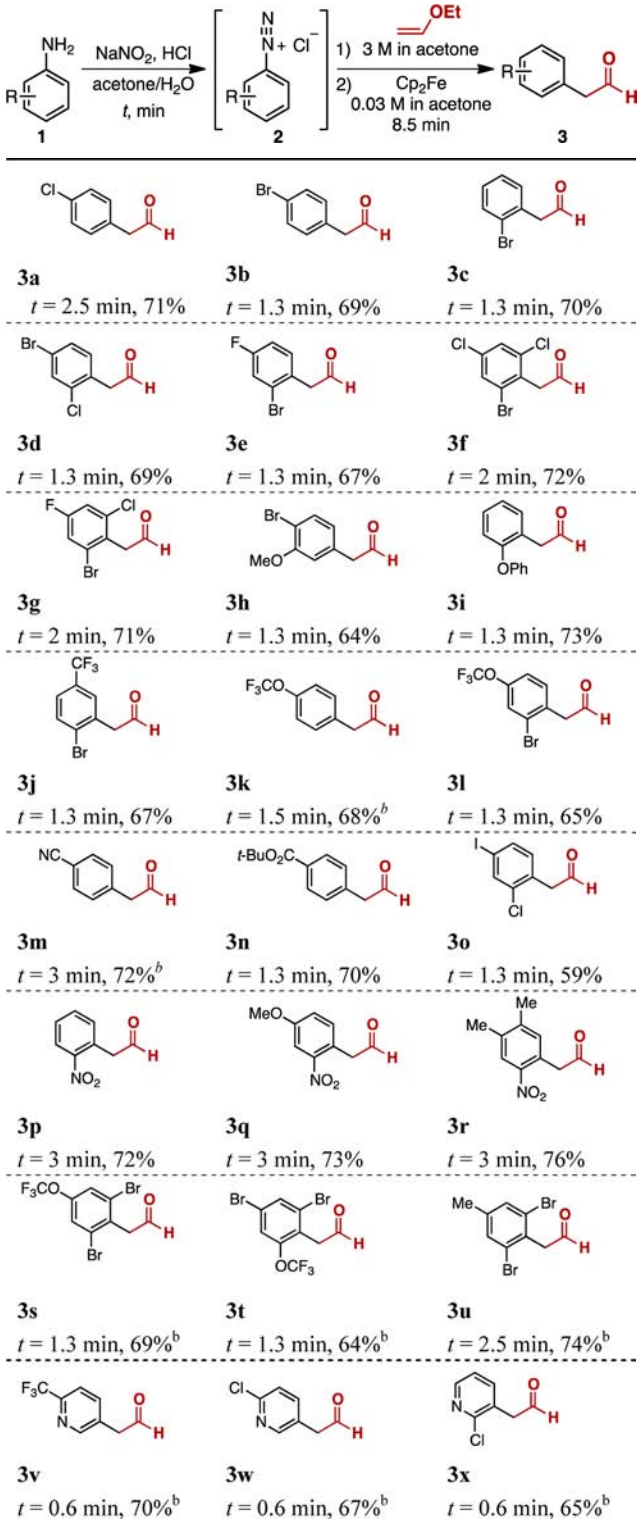
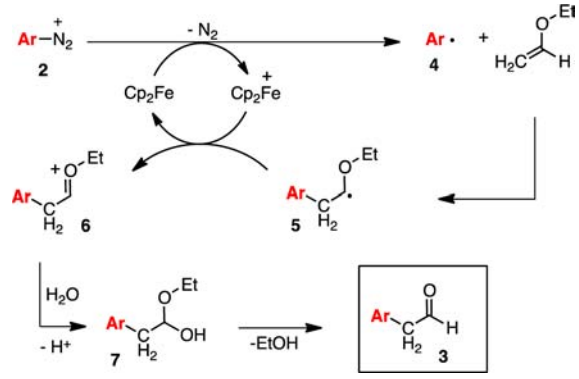
Table 2. Continuous-Flow Synthesis of Monoarylacetaldehydes[a]



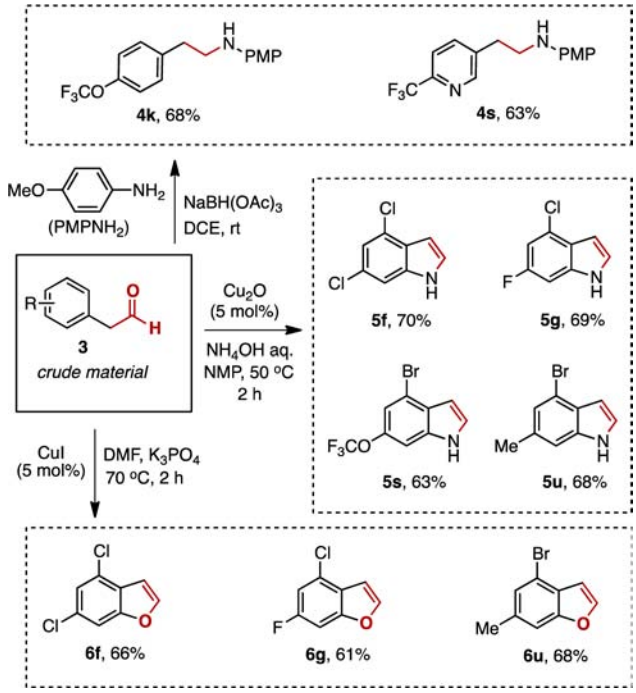
[a]Isolated yields (averages of two runs) are shown. See the Supporting Information for details. [b]Isolated as the corresponding alcohol after reduction of the crude reaction mixture with $NaBH_4$.

provided easy access to *N*-PMP-protected *β*-phenethylamine derivatives **4k** and **4s** in good yields (Scheme 4; PMP = *p*-methoxyphenyl). Next, we explored the possibility of synthesizing polyhalogenated heterocycles, which could be valuable

Scheme 3. Plausible Catalytic Cycle for Meerwein Arylation Reaction



Scheme 4. Further Transformations of Arylacetaldehydes 3 Obtained via the Continuous-Flow Method[15]



building blocks for organic synthesis and medicinal chemistry. We envisioned that polyhalogenated aldehydes **3f**, **3g**, **3s**, and **3u** (Table 2) could serve as suitable precursors for their synthesis. Thus, a Cu_2O-catalyzed amination/condensation of these crude polyhalogenated aldehydes furnished the corresponding indole derivatives **5f**, **5g**, **5s**, and **5u** in good overall yields. Finally, a Cu(I)-catalyzed cyclization of *o*-bromoarylacetaldehydes **3f**, **3g**, and **3u** under basic reaction conditions afforded the corresponding 4,6-dichloro- (**6f**), 4-chloro-6-fluoro- (**6g**), and 4-bromo-6-methyl-substituted (**6u**) benzofurans in good yields via a three-step sequence starting from the corresponding anilines **1** (Scheme 4).[14]

In summary, we have demonstrated an efficient continuous-flow process for the synthesis of monoarylated acetaldehydes featuring the Meerwein arylation reaction as a synthetic equivalent of the direct *α*-arylation of acetaldehyde enolate. Notably, the mild reaction conditions of this process, particularly the absence of base, allow for high functional group tolerance and enable the ready preparation of an array of

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synthetically valuable compounds. The use of anilines as aryl group donors in this reaction provides a facile entry into a wide range of polyhalogenated products, thus addressing the shortcomings of traditional transition-metal-catalyzed enolate arylation methodologies relying on aryl halides. Importantly, the continuous-flow method provides a general solution for the efficient and safe generation of a range of unstable aryldiazonium salts, enabling a scalable synthesis of arylacetaldehydes. Additional efforts to expand further the scope of this transformation are currently underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For recent reviews of metal-catalyzed α-arylation of carbonyl compounds, see: (a) Johansson, C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676. (b) Bellina, F.; Rossi, R. *Chem. Rev.* **2009**, *110*, 1082.

(2) (a) Terao, Y.; Fukuoka, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2002**, *43*, 101. (b) Martín, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7236. (c) Vo, G. D.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 2127. (d) Martín, R.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 4561. (e) Biscoe, M. R.; Buchwald, S. L. *Org. Lett.* **2009**, *11*, 1773. (f) Liu, P.; Lanza, T. J.; Jewell, J. P.; Jones, C. P.; Hagmann, W. K.; Lin, L. S. *Tetrahedron Lett.* **2003**, *44*, 8869. (g) Jórgensen, M.; Lee, S.; Liu, X.; Wolkowski, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 12557. (h) Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996. (i) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360. (j) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473. (k) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546. (l) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108.

(3) (a) Harvey, J. S.; Simonovich, S. P.; Jamison, C. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 13782. (b) Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 4260. (c) Lundin, P. M.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11027. (d) Lou, S.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 1264. (e) Conrad, J. C.; Kong, J.; Laforteza, B. N.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 11640. (f) Dai, X.; Strotman, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 3302. (g) Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594.

(4) For selected reviews of the Meerwein arylation reaction, see: (a) Heinrich, M. R. *Chem.—Eur. J.* **2009**, *15*, 820 and references therein. For representative examples of the synthesis of monoarylcarbonyl compounds via the Meerwein arylation reaction, see: (b) Kralj, A.; Wetzel, A.; Mahmoudian, S.; Stamminger, T.; Tschammer, N.; Heinrich, M. R. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5446. (c) Maligres, P. E.; Humphrey, G. R.; Marcoux, J.-F.; Hillier, M. C.; Zhao, D.; Krska, S.; Grabowski, E. J. J. *Org. Process Res. Dev.* **2009**, *13*, 525. (d) Molinaro, C.; Mowat, J.; Gosselin, F.; O'Shea, P. D.; Marcoux, J.-F.; Angelaud, R.; Davies, I. W. *J. Org. Chem.* **2007**, *72*, 1856. (e) Naidan, V. M.; Fesak, A. Y. *Russ. J. Gen. Chem.* **2003**, *73*, 1419. (f) Mella, M.; Coppo, P.; Guizzardi, B.; Fagnoni, M.; Freccero, M.; Albini, A. *J. Org. Chem.* **2001**, *66*, 6344. (g) Cardwell, K.; Hewitt, B.; Ladlow, M.; Magnus, P. *J. Am. Chem. Soc.* **1988**, *110*, 2242. (h) Kikukawa, K.; Matsuda, T. *Chem. Lett.* **1977**, 159.

(5) (a) Minisci, F.; Coppa, F.; Fontana, F.; Pianese, G.; Zhao, L. *J. Org. Chem.* **1992**, *57*, 3929. (b) Raucher, S.; Koolpe, G. A. *J. Org. Chem.* **1983**, *48*, 2066.

(6) (a) Nielsen, M. A.; Nielsen, M. K.; Pittelkow, T. *Org. Process Res. Dev.* **2004**, *8*, 1059. (b) Fortt, R.; Wootton, R. C. R.; de Mello, A. J. *Org. Process Res. Dev.* **2003**, *7*, 762.

(7) For selected reviews of continuous-flow processes, see: (a) Marion, R.; Muthusamy, G.; Geneste, F. *J. Catal.* **2012**, *286*, 266. (b) Palde, P. B.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 3525. (c) Noel, T.; Buchwald, S. L. *Chem. Soc. Rev.* **2011**, *40*, 5010. (d) Hartman, R. L.; McMullen, J. P.; Jensen, K. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 7502.

(8) Caution! Diazonium salts are unstable and dangerously explosive intermediates. *All* diazonium salts used for optimizations in batch *were generated in situ at 0 °C on a 60 μmol scale*. Every batch experiment was neutralized at low temperature with an excess of aqueous solution of inorganic base ($NaHCO_3$) to quench potentially remaining generated diazonium salt.

(9) (a) Connelly, N. G.; Geiger, W. E. *Chem. Rev.* **1996**, *96*, 877. (b) Beckwith, A. L. J.; Jackson, R. A.; Longmore, R. W. *Aust. J. Chem.* **1992**, *45*, 857. (c) Freidlina, R. K.; Kandror, I. I.; Gasanov, R. G.; Kopylova, B. V.; Bragina, I. O.; Yashkina, L. V. *Russ. Chem. Bull.* **1984**, *33*, 758.

(10) (a) Sedelmeier, J.; Ley, S. V.; Baxendale, I. R.; Baumann, M. *Org. Lett.* **2010**, *12*, 3618. (b) Horie, T.; Sumino, M.; Tanaka, T.; Matsushita, Y.; Ichimura, T.; Yoshida, J.-i. *Org. Process Res. Dev.* **2010**, *14*, 405. (c) Hartman, R. L.; Naber, J. R.; Zaborenko, N.; Buchwald, S. L.; Jensen, K. F. *Org. Process Res. Dev.* **2010**, *14*, 1347.

(11) (a) Sedelmeier, J.; Ley, S. V.; Baxendale, I. R.; Baumann, M. *Org. Lett.* **2010**, *12*, 3618. (b) Horie, T.; Sumino, M.; Tanaka, T.; Matsushita, Y.; Ichimura, T.; Yoshida, J.-i. *Org. Process Res. Dev.* **2010**, *14*, 405. (c) Hartman, R. L.; Naber, J. R.; Zaborenko, N.; Buchwald, S. L.; Jensen, K. F. *Org. Process Res. Dev.* **2010**, *14*, 1347.

(12) See the Supporting Information for details.

(13) (a) Kochi, J. K. *J. Am. Chem. Soc.* **1955**, *77*, 5090. (b) Kochi, J. K. *J. Am. Chem. Soc.* **1955**, *77*, 5274.

(14) For selected examples of the Cu-catalyzed synthesis of benzofurans via a intramolecular cyclization reaction of carbonyl derivatives, see: (a) Carril, M. N.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Org. Lett.* **2006**, *8*, 1467. (b) Ackermann, L.; Kaspar, L. T. *J. Org. Chem.* **2007**, *72*, 6149. (c) Tadd, A. C.; Fielding, M. R.; Willis, M. C. *Tetrahedron Lett.* **2007**, *48*, 7578. (d) Lu, B.; Wang, B.; Zhang, Y.; Ma, D. *J. Org. Chem.* **2007**, *72*, 5337. (e) Chen, C.-y.; Dormer, P. G. *J. Org. Chem.* **2005**, *70*, 6964.

(15) Yields of products are based on the starting aniline.