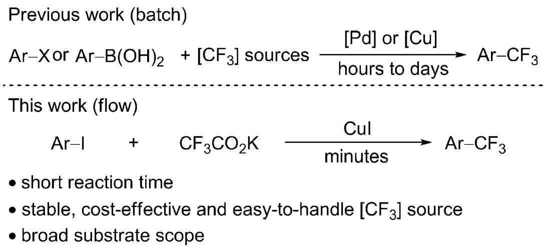
Cross-Coupling

DOI: 10.1002/ange.201306094

Rapid and Efficient Trifluoromethylation of Aromatic and Heteroaromatic Compounds Using Potassium Trifluoroacetate Enabled by a Flow System**

*Mao Chen and Stephen L. Buchwald**

The development of synthetic methods to introduce trifluoromethyl groups into aromatic and heteroaromatic compounds is of considerable interest as CF_3-substituted molecules often possess improved physical and chemical properties.[1] As a result, a variety of synthetic methods have been developed to accomplish this task.[2,3] Nagib and MacMillan[4] and Baran and co-workers[5] reported elegant examples of (hetero)-aromatic trifluoromethylation reactions by CF_3 radical processes. These have the advantage of being simple and high yielding, though a lack of regiocontrol is observed with certain classes of substrates. Although palladium and copper systems have been developed for the trifluoromethylation of (hetero)aromatic precursors, the scope of heterocyclic substrates handled by these methods is limited (Scheme 1).[3] In addition, they usually necessitate the use of an excess of expensive or gaseous CF_3 reagents (the latter which are more difficult to handle in normal laboratory settings) and have reaction times ranging from hours to days. Thus, it would be desirable to devise a rapid and efficient method which can be applied to a broad range of substrates and employs a low-cost CF_3 source.



Scheme 1. Aromatic trifluoromethylation under batch and flow conditions.

Since the pioneering work by Wiemers and Burton,[6] a great deal of effort has been expended to devise convenient means of generating a $[CuCF_3]$ species, which is the presumed key intermediate in many copper-mediated trifluoromethylation processes.[3,7–10] In 2008, Vivic and co-workers disclosed that $[CuCF_3]$ could be stabilized with NHC ligands,[11] and the resulting complexes were applied to the room temperature transformation of aryl iodides into aryl trifluoromethyl compounds. Amii and co-workers then reported the first copper-catalyzed aromatic trifluoromethylation process utilizing Et_3SiCF_3.[3b] The subsequent use of the isolated $[(phen)CuCF_3]$ reagent by Hartwig and co-workers allowed the successful transformation of a variety of aryl halides and several heteroaryl iodides into trifluoromethyl (hetero)arenes.[3g]

Among the various trifluoromethylating reagents, fluoroform and trifluoroacetate salts are stable and low priced, and thus represent attractive CF_3 sources for many applications. Seminal work by Grushin and co-workers demonstrated the viability of fluoroform in trifluoromethylation processes.[3h,12] While a major step forward, the need to manipulate gaseous CF_3H is inconvenient for some applications. Because of the ease of handling and low cost, trifluoroacetate salts have been used by Matsui and co-workers and others in the trifluoromethylation of aryl halides.[8–10] Only a limited number of heterocycles have been successfully furnished under batch conditions. In those processes, up to 10 equivalents of sodium trifluoroacetate were used, and mixtures of $Ar-CF_3$, $Ar-C_2F_5$, and $Ar-H$ were usually obtained during reaction times of several hours. The separation of $Ar-CF_3$ from these side products is usually difficult because of their similar physical properties. Given our experience in both flow and trifluoromethylation chemistry,[3a,13] we wondered if a method combining the two would be advantageous. Herein, we report an efficient aromatic trifluoromethylation process conducted under flow conditions. With this operationally simple method, a broad spectrum of trifluoromethylated aromatic and heteroaromatic compounds can be prepared from the corresponding aryl iodides in a protocol requiring only minutes of residence time, and using CF_3CO_2K as the CF_3 source.

Early in our work, in studies carried out under batch conditions, we found that the rate of the decarboxylation of CF_3CO_2K could be substantially accelerated by increasing the reaction temperature from 160 °C to 200 °C in the presence of copper iodide.[14] In principle, this rapid decarboxylation process could facilitate the generation of the desired $[CuCF_3]$ intermediate. While the high temperature and the increased pressure which occurs during decarboxylation[15] can present problems under batch conditions, especially on a larger scale,

---

[*] Dr. M. Chen, Prof. Dr. S. L. Buchwald
Department of Chemistry, Room 18-490
Massachusetts Institute of Technology
Cambridge, MA 02139 (USA)
E-mail: sbuchwal@mit.edu

[**] We thank Novartis International AG and the National Institutes of Health for financial support (GM46059). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. We thank Dr. John R. DeBergh and Dr. Christine Nguyen for assistance with the preparation of this manuscript.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201306094.

flow processes are able to readily manage reaction parameters such as temperature, pressure, and residence times.[16–18]

The handling of solids under flow conditions can be problematic. Considering the low solubility of CuI in NMP, we first examined a number of ligands, such as 1,10-phenanthroline, 2,2′-bipyridine, TMEDA, DMEDA, and pyridine, to establish suitable reaction conditions. Pyridine proved to be the optimal ligand, thus furnishing a homogenous solution in combination with CuI. The CuI (2.0 equiv)/pyridine (2.4 equiv) combination was applied to a mixture of CF_3CO_2K (2.0 equiv) and 4-iodobipenyl (1.0 equiv) at 200°C for 15 minutes to provide an excellent yield of 4-trifluoromethylbiphenyl (95% as determined by ^{19}F NMR spectroscopy). Only trace amounts of the reduced product (biphenyl) or double insertion product (4-pentafluoroethyl biphenyl), were detected (< 2% as judged by GC analysis). Interestingly, when CF_3CO_2K was replaced with CF_3CO_2Na under otherwise identical reaction conditions, only a 40% yield of the desired product was realized.[19]

We next adapted our process to flow conditions. A solution of CF_3CO_2K, CuI, and pyridine in NMP was mixed with a solution of 4-trifluoromethylbiphenyl in NMP and introduced into a stainless steel tube reactor submerged in a preheated 200°C bath using an optimized 16 minute residence time (Figure 1). At this point the mixture was diluted with a stream of ethyl acetate (controlled with back-pressure regulators). Finally, the resulting mixture was collected and subsequently purified in a standard fashion by column chromatography to afford **2a** in 87% yield upon isolation (Table 1).

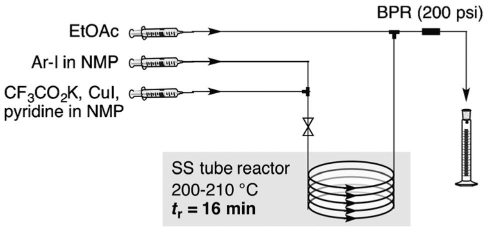
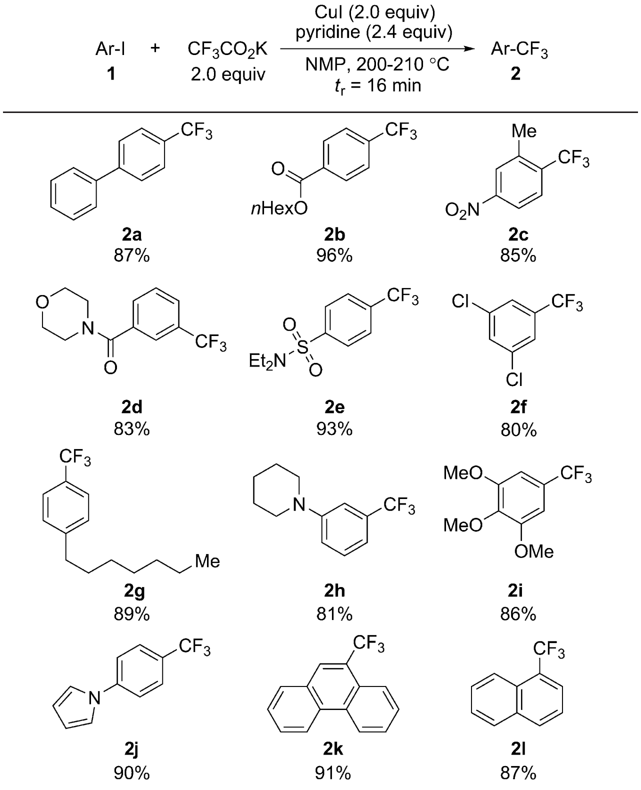


Figure 1. Flow setup for the aromatic trifluoromethylation. See the Supporting Information for details. NMP = *N*-methylpyrrolidone.

Having established efficient flow conditions, the substrate scope was investigated (Table 1) using the flow setup shown in Figure 1. All of the substrates underwent complete conversion using a 16 minute residence time, thus affording products in good to excellent yields and in over 95% purity. The high selectivity for trifluoromethylation further enhances the efficiency of this method, since the separation of Ar–H, a typical side product of trifluoromethylation processes, from Ar–CF_3 can often be difficult. The aromatic trifluoromethylation reaction could be successfully carried out with *para*-, *meta*-, and *ortho*-substituted aryl substrates. In addition, electron-deficient, electron-neutral, and electron-rich iodoarenes are all suitable substrates. As illustrated in Table 1, the flow conditions tolerate ester- (**2b**), nitro- (**2c**), amide- (**2d**), sulfonamide- (**2e**), and chloro-substituted (**2f**) aryl compounds as well.

Table 1: Substrate scope of the trifluoromethylation of aromatic compounds under flow conditions.[a]

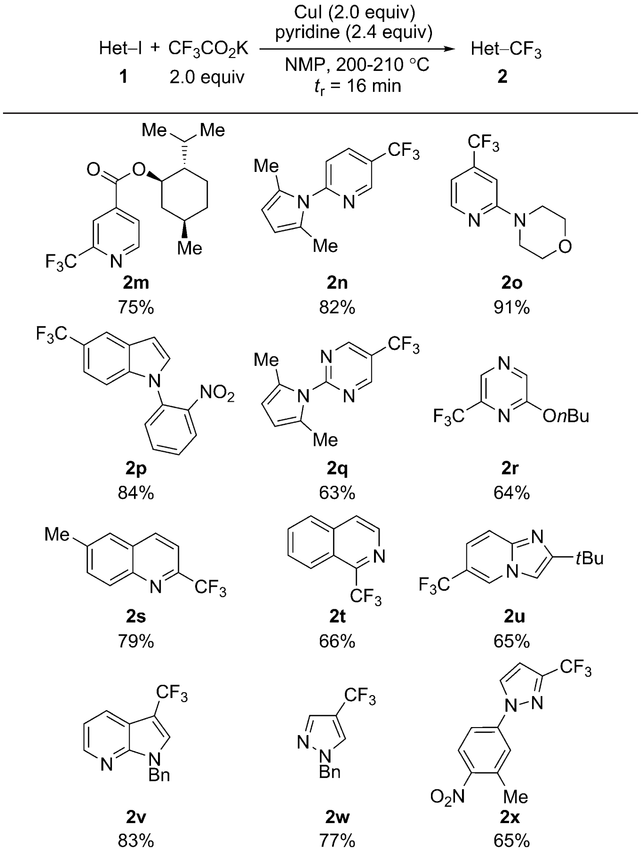


[a] Yields of isolated products (average of two runs) based on 1 mmol scale are shown. See the Supporting Information for details.

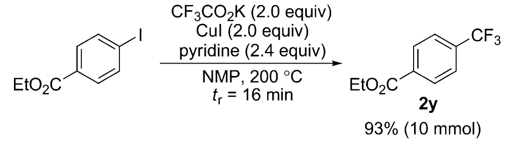
In light of the above results, we next focused on expanding the scope of this method to heteroaryl substrates (Table 2).[8b] Nitrogen-containing heterocycles are known to coordinate with copper species, and thus represent a challenging class of substrates for copper-catalyzed processes. As shown in Table 2, a variety of heterocyclic compounds including pyridines (**2m**, **2n**, and **2o**), indole (**2p**), pyrimidine (**2q**), pyrazine (**2r**), quinoline (**2s**), isoquinoline (**2t**), imidazopyridine (**2u**), and pyrrolopyridine (**2v**) substrates could be efficiently coupled with the trifluoromethyl group under the flow conditions. Trifluoromethylpyrazole is the core unit of many pharmaceuticals, agrochemicals, and potential drug candidates (e.g., Celecoxib, Mavacoxib, Razaxaban, SC-560),[20] but these five-membered heterocycles are poor substrates for palladium-catalyzed processes.[21] However, by using this flow method, both 2- and 3-trifluoromethyl-substituted pyrazoles (**2w** and **2x**) could be prepared in good yields.

One of the major advantages of flow chemistry involves the ease-to-scale-up reactions. To further demonstrate the robustness of our flow system, we successfully performed the trifluoromethylation of ethyl 4-iodobenzoate under flow conditions on a 10 mmol scale (Scheme 2). In a period of 208 minutes, we were able to generate two grams (10 mmol) of product.

Table 2: Substrate scope of the trifluoromethylation of heteroaromatic compounds under flow conditions.[a]



[a] Yields of isolated products (average of two runs) based on 1 mmol scale are shown. See the Supporting Information for details.



2y
93% (10 mmol)
2.0 g

Scheme 2. Trifluoromethylation of ethyl 4-iodobenzoate on 10 mmol scale. See the Supporting Information for details.

To probe the mechanism of this reaction, we performed a Hammett study. Because of the small size of microflow reactors, an advantage of their use is their efficient mass and heat transfer with short reaction times which are difficult to control in a batch reactor.[16] Accordingly, a flow system with the same setup as shown in Figure 1 was used to conduct the kinetic study. All experiments were performed under reaction conditions under a 1 minute residence time at 200°C. In competition experiments, an excess of the equimolar mixture of 3- or 4-substituted aryl iodides and iodobenzene relative to CF_3CO_2K was used. The relative rates of different reactions were extracted from the product distributions after reaching a steady state. As shown in Figure 2, a linear correlation (R^2 = 0.98) with a slope of 0.52 was observed using this flow method. The positive ρ value is consistent with the presence of a nucleophilic $[CuCF_3]$ species which undergoes oxidative addition with aryl iodides, and slightly favors substrates with electron-withdrawing groups. The ρ value observed here was similar to that obtained from other copper-catalyzed or copper-mediated processes in our group.[22]

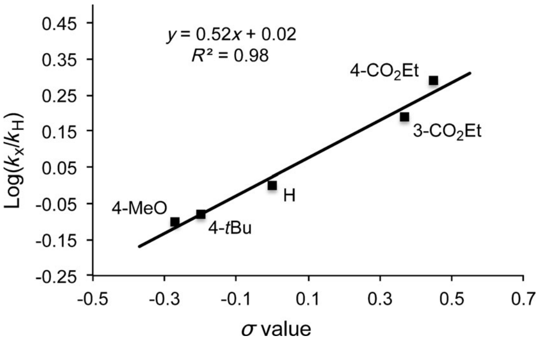


Figure 2. Hammett plots of competition experiments. See the Supporting Information for details.

In conclusion, we have developed a simple, scalable, and efficient technique to introduce a trifluoromethyl group into aromatic and heteroaromatic compounds by copper-mediated cross-coupling reactions. This method represents the first example of aromatic trifluoromethylation conducted in flow, using stable, cost-effective, and easy-to-handle CF_3CO_2K as the CF_3 source. Of importance, very short reaction times (minutes) are required to achieve full conversion of (hetero)-aryl starting materials in this process. To increase the practicality of the protocol, all components used to assemble our reactors are available from commercial sources. Moreover, we have also successfully performed a Hammett study using a 1 minute residence time at 200°C by employing flow techniques, thus providing a reliable method of studying the reaction under "hot and fast", and synthetically relevant reaction conditions.

Experimental Section

General procedure: A solution of aryl iodide (0.6 M) in NMP was loaded into a stainless steel syringe and a solution of CuI (0.8 M), CF_3CO_2K (0.8 M) and pyridine (0.96 M) in NMP was loaded into a second stainless steel syringe. The flow rates of two solutions were 40 μL/min and 60 μL/min separately delivering with two Harvard Apparatus syringe pumps. After mixing with a T-mixer, the resulting mixture was delivered into the stainless steel reactor (1/16 inch OD, 0.046 inch ID, 1.6 mL volume) at 200–210°C (Caution: Hot! A suitable bath oil should be used[23]). Upon exiting the reactor, the reaction was quenched with EtOAc (100 μL/min). Next, after reaching steady state, the sample was collected in order to obtain exactly 1 mmol of product. Further safety information as well as details of the flow setup and workup procedures can be found in the Supporting Information.

Sample analysis: NMR and IR spectroscopies were used to identify the products.

Received: July 12, 2013

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

[1] a) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881; b) M. Schlosser, *Angew. Chem.* **2006**, *118*, 5558; *Angew. Chem. Int. Ed.* **2006**, *45*, 5432; c) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320; d) C. Isanbor, D. O'Hagan, *J. Fluorine Chem.* **2006**, *127*, 303; e) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis Reactivty, Applications*, Wiley-VCH, Weinheim, **2004**; f) T. Umemoto, *Chem. Rev.* **1996**, *96*, 1757; g) S. G. K. Prakash, A. K. Yudin, *Chem. Rev.* **1997**, *97*, 757; h) B. R. Langlois, T. Billard, *Synthesis* **2003**, 185; i) M. A. McClinton, D. A. McClinton, *Tetrahedron* **1992**, *48*, 6555; j) R. P. Singh, J. M. Shreeve, *Tetrahedron* **2000**, *56*, 7613; k) I. Kieltsch, P. Eisenberger, K. Stanek, A. Togni, *Chima* **2008**, *62*, 260.

[2] For recent reviews of trifluoromethylation, see: a) O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475; b) J.-A. Ma, D. Cahard, *J. Fluorine Chem.* **2007**, *128*, 975; c) R. J. Lundgren, M. Stradiotto, *Angew. Chem.* **2010**, *122*, 9510; *Angew. Chem. Int. Ed.* **2010**, *49*, 9322; d) S. Roy, B. T. Gregg, G. W. Gribble, V.-D. Le, S. Roy, *Tetrahedron* **2011**, *67*, 2161; e) X.-F. Wu, H. Neumann, M. Beller, *Chem. Asian J.* **2012**, *7*, 1744; f) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470.

[3] For selected recent examples, see: a) E. J. Cho, T. D. Senecal, T. Kinzel, Y. Zhang, D. A. Watson, S. L. Buchwald, *Science* **2010**, *328*, 1679; b) M. Oishi, H. Kondo, H. Amii, *Chem. Commun.* **2009**, 1909; c) N. D. Ball, J. B. Gary, Y. Ye, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 7577; d) X.-G. Zhang, H.-X. Dai, M. Wasa, J.-Q. Yu, *J. Am. Chem. Soc.* **2012**, *134*, 11948; e) Y. Ye, M. S. Sanford, *J. Am. Chem. Soc.* **2012**, *134*, 9034; f) T. Knauber, F. Arikan, G.-V. Röschenthaler, L. J. Gooßen, *Chem. Eur. J.* **2011**, *17*, 2689; g) H. Morimoto, T. Tsubogo, N. D. Litvinas, J. F. Hartwig, *Angew. Chem.* **2011**, *123*, 3877; *Angew. Chem. Int. Ed.* **2011**, *50*, 3793; h) P. Novák, A. Lishchynskyi, V. V. Grushin, *Angew. Chem.* **2012**, *124*, 7887; *Angew. Chem. Int. Ed.* **2012**, *51*, 7767; i) M. M. Kremlev, W. Tyrra, A. I. Mushta, D. Naumann, Y. L. Yagupolskii, *J. Fluorine Chem.* **2010**, *131*, 212; j) C. P. Zhang, Z. L. Wang, Q. Y. Chen, C. T. Zhang, Y. C. Gu, J. C. Xiao, *Angew. Chem.* **2011**, *123*, 1936; *Angew. Chem. Int. Ed.* **2011**, *50*, 1896; k) M. Döbele, M. S. Wiehn, S. Bräse, *Angew. Chem.* **2011**, *123*, 11737; *Angew. Chem. Int. Ed.* **2011**, *50*, 11533; l) T. Liu, X. Shao, Y. Wu, Q. Shen, *Angew. Chem.* **2012**, *124*, 555; *Angew. Chem. Int. Ed.* **2012**, *51*, 540; m) L. Chu, F.-L. Qing, *J. Am. Chem. Soc.* **2012**, *134*, 1298; n) Z. Weng, R. Lee, W. Jia, Y. Yuan, W. Wang, X. Feng, K. W. Huang, *Organometallics* **2011**, *30*, 3229; o) J.-J. Dai, C. Fang, B. Xiao, J. Yi, J. Xu, Z.-J. Liu, X. Lu, L. Liu, Y. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 8436; p) G. Danoun, B. Bayarmagnai, M. F. Grünberg, L. J. Gooßen, *Angew. Chem.* **2013**, *125*, 7972; *Angew. Chem. Int. Ed.* **2013**, *52*, 7972.

[4] D. A. Nagib, D. W. C. MacMillan, *Nature* **2011**, *480*, 224.

[5] Y. Ji, T. Brueckl, R. D. Baxter, Y. Fujiwara, I. B. Seiple, S. Su, D. G. Blackmond, P. S. Baran, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 14411.

[6] D. M. Wiemers, D. J. Burton, *J. Am. Chem. Soc.* **1986**, *108*, 832.

[7] a) G. K. S. Prakash, R. Krishnamurti, G. A. Olah, *J. Am. Chem. Soc.* **1989**, *111*, 393; b) G. P. Stahly, D. R. Bell, *J. Org. Chem.* **1989**, *54*, 2873; c) A. Kruse, G. Siegemund, D. C. A. Schumann, I. Ruppert, Ger. Offen. DE3805534, **1988**.

[8] For examples of using CF_3CO_2Na as CF_3 sources, see: a) K. Matsui, E. Tobita, M. Ando, K. Kondo, *Chem. Lett.* **1981**, 1719. b) This paper investigated the reactions of heteroaryl substrates: G. E. Carr, R. D. Chambers, T. F. Holmes, *J. Chem. Soc. Perkin Trans. 1* **1988**, 921; c) Y. Li, T. Chen, H. Wang, R. Zhang, K. Jin, X. Wang, C. Duan, *Synlett* **2011**, 1713.

[9] For examples using CF_3CO_2Me, see: a) B. R. Langlois, N. Roques, *J. Fluorine Chem.* **2007**, *128*, 1318; b) T. Schareina, X. F. Wu, A. Zapf, A. Cotte, M. Gotta, M. Beller, *Top. Catal.* **2012**, *55*, 426.

[10] For examples of using CF_3CO_2K as CF_3 sources, see R. W. Lin, R. I. Davidson, U.S. Patent 4808748, **1989**.

[11] G. G. Dubinina, H. Furutachi, D. A. Vicic, *J. Am. Chem. Soc.* **2008**, *130*, 8600.

[12] A. Zanardi, M. A. Novikov, E. Martin, J. Benet-Buchholz, V. V. Grushin, *J. Am. Chem. Soc.* **2011**, *133*, 20901.

[13] For selected recent examples, see: a) A. DeAngelis, D.-H. Wang, S. L. Buchwald, *Angew. Chem.* **2013**, *125*, 3518; *Angew. Chem. Int. Ed.* **2013**, *52*, 3434; b) M. Chen, S. L. Buchwald, *Angew. Chem.* **2013**, *125*, 4341; *Angew. Chem. Int. Ed.* **2013**, *52*, 4247; c) N. Chernyak, S. L. Buchwald, *J. Am. Chem. Soc.* **2012**, *134*, 12466.

[14] See Figure S-1 in the Supporting Information for details.

[15] When 10 mmol CF_3CO_2K is decarboxylated in a 20 mL sealed flask at 200 °C, the pressure increases to about 15 atm according to the ideal gas law.

[16] For selected reviews in flow chemistry, see: a) S. V. Ley, *Chem. Rec.* **2012**, *12*, 378; b) J. Wegner, S. Ceylan, A. Kirschning, *Chem. Commun.* **2011**, *47*, 4583; c) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107*, 2300; d) J.-i. Yoshida, A. Nagaki, T. Yamada, *Chem. Eur. J.* **2008**, *14*, 7450; e) C. Wiles, P. Watts, *Chem. Commun.* **2011**, *47*, 6512; f) A. Cukalovic, J. C. M. R. Monbaliu, C. V. Stevens, *Top. Heterocycl. Chem.* **2010**, *23*, 161; g) T. Fukuyama, M. T. Rahman, M. Sata, I. Ryu, *Synlett* **2008**, 151.

[17] a) W. Ehrfeld, V. Hessel, H. Löwe, *Microreactors: New Technology for Modern Chemistry*, Wiley-VCH, Weinheim, **2000**; b) P. H. Seeberger, T. Blume, *New Avenues to Efficient Chemical Synthesis-Emerging Technologies*, Springer, Berlin, **2007**; c) T. Wirth, *Microreactors in Organic Synthesis and Catalysis*, Wiley-VCH, Weinheim, **2008**.

[18] For examples of handling high-temperature conditions in flow, see: a) J. Sedelmeier, I. R. Baxendale, S. V. Ley, *Green Chem.* **2009**, *11*, 683; b) I. R. Baxendale, C. M. Griffiths-Jones, S. V. Ley, G. K. Tranmer, *Chem. Eur. J.* **2006**, *12*, 4407; c) N. Zaborenko, M. W. Bedore, T. F. Jamison, K. F. Jensen, *Org. Process Res. Dev.* **2011**, *15*, 131; d) A. G. O'Brien, Z. Horváth, F. Lévesque, J. W. Lee, A. Seidel-Morgenstern, P. H. Seeberger, *Angew. Chem.* **2012**, *124*, 7134; *Angew. Chem. Int. Ed.* **2012**, *51*, 7028; e) M. G. Organ, P. R. Hanson, A. Rolfe, T. B. Samarakoon, U. Farman, *J. Flow Chem.* **2011**, *1*, 32; f) Y. Zhang, T. F. Jamison, S. Patel, N. Mainolfi, *Org. Lett.* **2011**, *13*, 280; g) D. Cantillo, H. Sheibani, C. O. Kappe, *J. Org. Chem.* **2012**, *77*, 2463; h) H. Kawanami, K. Matsushima, M. Sato, Y. Ikushima, *Angew. Chem.* **2007**, *119*, 5221; *Angew. Chem. Int. Ed.* **2007**, *46*, 5129; i) J. G. Stevens, R. A. Bourne, M. V. Twigg, M. Poliakoff, *Angew. Chem.* **2010**, *122*, 9040; *Angew. Chem. Int. Ed.* **2010**, *49*, 8856; j) B. Gutmann, J.-P. Roduit, D. Roberge, C. O. Kappe, *Angew. Chem.* **2010**, *122*, 7255; *Angew. Chem. Int. Ed.* **2010**, *49*, 7101; k) J. Baek, P. M. Allen, M. G. Bawendi, K. F. Jensen, *Angew. Chem.* **2011**, *123*, 653; *Angew. Chem. Int. Ed.* **2011**, *50*, 627.

[19] See Table S-1 in the Supporting Information for details.

[20] a) C. Lamberth, *Heterocycles* **2007**, *71*, 1467; b) J. Elguero, A. M. S. Silva, A. C. Tomé in *Modern Heterocyclic Chemistry* (Eds.: J. Alvarez-Builla, J. J. Vaquero, J. Barluenga), Wiley-VCH, Weinheim, **2011**, pp. 635–725.

[21] Y. Ye, M. S. Sanford, *Synlett* **2012**, 2005.

[22] E. R. Strieter, B. Bhayana, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 78.

[23] For example, the silicone oil from Alfa Aesar, catalogue number 45896, with a temperature range of 25–250 °C.