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Continuous-Flow Microreactor Chemistry under High-Temperature/Pressure Conditions

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High-temperature organic synthesis can be performed under continuous-flow conditions in a stainless steel microtubular flow reactor capable of achieving temperatures of 350 °C and 200 bar. Under these extreme experimental environments transformations normally performed in a high-boiling solvent at reflux temperature – or under sealed-vessel microwave conditions – can be readily converted to a flow regime by using lower boiling solvents in or near their supercritical state.

The use of microreactors has opened up new horizons for synthetic organic chemistry[1,2] and the chemical manufacturing industry.[3] Microreaction technology is generally defined as the continuous-flow processing of reactions within structured channels of less than 1000 μm diameter. Because of the high surface/volume ratio in microchannels of this type, heat transfer is very efficient and reaction temperatures in microreactors can be changed efficiently by application or removal of heat.[1,2] Traditionally, most synthetic transformations performed in microreactors have involved ambient or even low-temperature conditions in order to safely conduct highly exothermic reactions.[1–4] More recently, processes at elevated-temperature conditions in sealed microreaction devices[5] (and related continuous-flow reactors[6–8]) have been reported, although the number of publications describing synthetically valuable transformations in a genuine high-temperature and high-pressure (>200 °C/>50 bar) flow regime is rather limited, with most applications focusing on the generation of high-temperature or supercritical water (scH$_2$O).[9,10]

High-temperature processing offers many distinct advantages as demonstrated by the recent success of microwave-assisted organic synthesis.[11] In microwave chemistry, reaction times can often be reduced from hours to minutes by efficient and rapid direct dielectric heating of the reaction mixture in a sealed vessel to temperatures far above the boiling point of the solvent under atmospheric conditions.[11] Because of the comparatively low pressure limit of most commercially available microwave reactors (ca 20 bar),[12] genuine high-temperature/pressure processing is generally not possible. This precludes the possibility to work with and exploit the unique reactivity of solvents in their near- or super-critical state.[13] In addition, microwave chemistry is difficult so scale due to the limited penetration depth of microwave irradiation into absorbing media.[14] Therefore, translating high-temperature microwave chemistry to scalable continuous-flow processes is becoming increasingly important. Herein we describe the use of a stainless steel microreactor capable of operating at temperatures up to 350 °C and pressures of up to 200 bar for performing organic synthesis. We demonstrate that high-speed microwave chemistry can be performed with equal efficiency in a conventionally heated flow system where the rapid heating and high-temperature conditions achieved in a microwave reactor can be adequately mimicked.

The microreactor system used for our studies is a high-temperature/high-pressure microtubular flow unit that can be used for processing homogeneous reaction mixtures (Figure 1).[15] The reactor uses stainless steel coils (i.d. 1000 μm) of variable length (4, 8 and 16 mL volume) that can be directly heated across their full length by electric resistance heating to temperatures up to 350 °C. The reaction mixture is introduced to the reactor block containing the steel coils and a heat exchanger through one (or more) standard HPLC pumps (flow rate: 0.01–10.0 mL min^{-1}). The system pressure valve sets and stabilizes the set pressure value in a pressure range of 50–200 bars. The temperature is measured/controlled on the outside of the coil at three positions with the aid of thermocouples and reflects the reaction temperature inside the coil.[16]

Our initial experiments involved the Diels–Alder reaction of 2,3-dimethylbutadiene (**1**) and acrylonitrile (**2**) to provide the cyclohexene adduct **3** (Scheme 1, Reaction 1). Under

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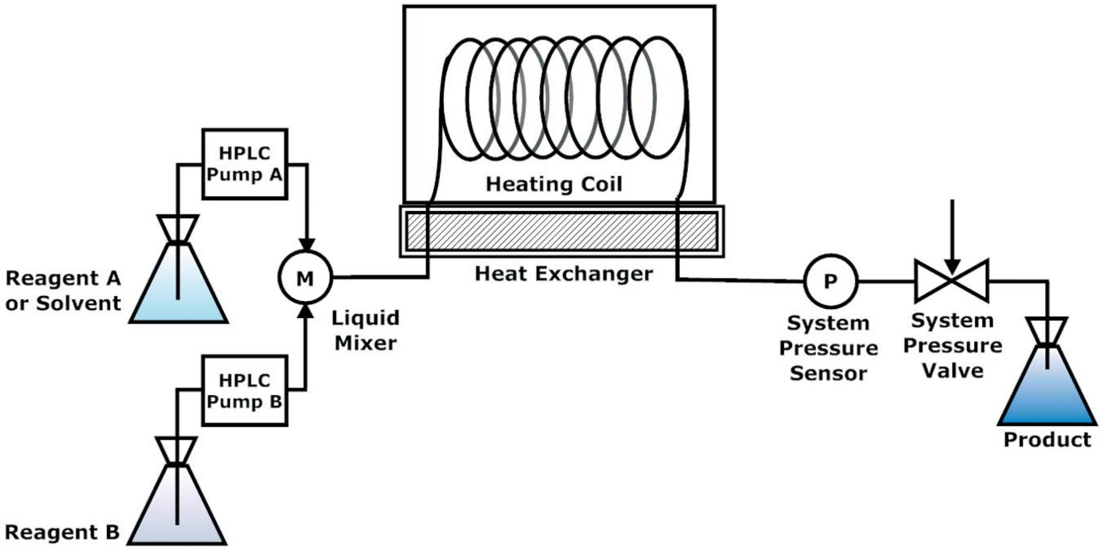
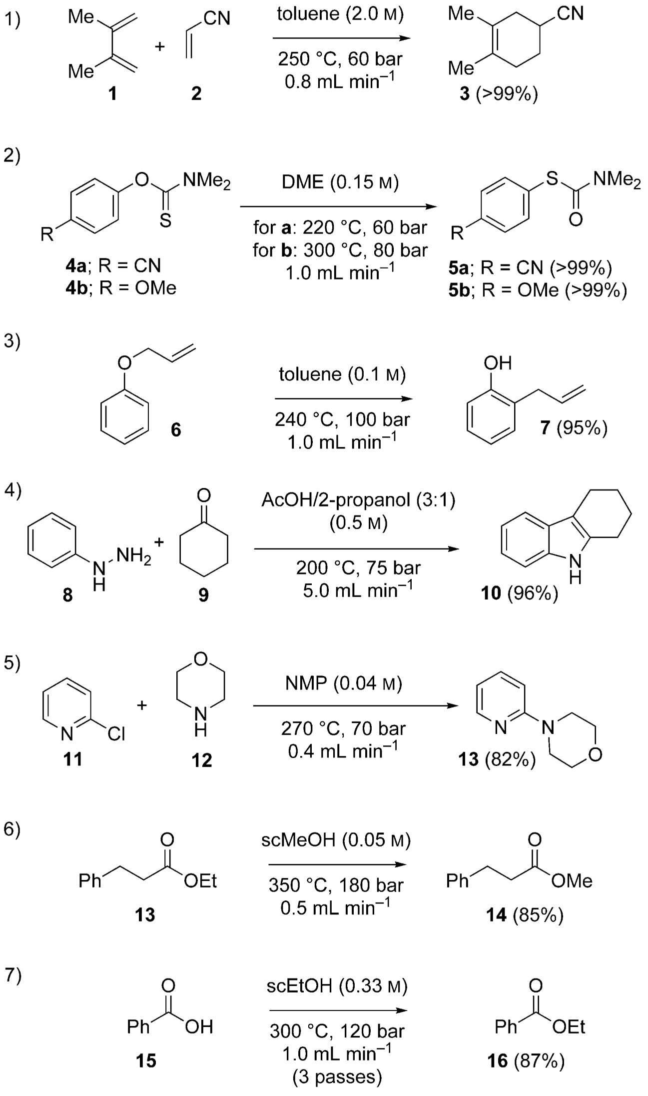


Figure 1. High-temperature/pressure microtube flow reactor (schematic).

sealed-vessel batch microwave conditions the normally required quite long reaction times for this cycloaddition process could be reduced to 20 min at 240 °C (or 10 min at 250 °C) by using toluene as solvent.[17] In the high-temperature/pressure flow reactor these conditions could easily be mimicked and full conversion accompanied by a near quantitative isolated product yield was obtained at 250 °C (60 bar set pressure) at a flow rate of 0.8 mL min^{-1}. By applying the 4 mL stainless steel coil this corresponds to a residence time inside the heated coil of ca. 5 min, correlating with the reported reaction times under the batch microwave conditions. Lower reaction temperatures or higher flow rates led to incomplete conversions. Since the flow reactor can operate under significantly higher pressure (200 bar) compared to standard batch microwave systems (20 bar),[12] we were able to perform the cycloaddition at the same temperature also in lower boiling solvents such as MeCN (autogenic pressure 36 bar), THF (42 bar) and 1,2-dimethoxyethane (33 bar) to give identical results.

Another high-temperature chemistry example involves the Newman-Kwart rearrangement, a valuable synthetic method for converting phenols to thiophenols via their *O*- and *S*-thiocarbamates.[18] This rearrangement proceeds via an *O*- to *S*-aryl migration which has a high activation energy, and therefore many synthetically useful examples of this rearrangement require temperatures of 200–300 °C.[18] Detailed studies by Moseley at al. have recently shown that Newman-Kwart rearrangements can be efficiently carried out under high-temperature microwave conditions in *N*-methylpyrrolidone (NMP) or related high-boiling solvents.[14,19] Whereas for the electronically activated substrate **4a** reaction temperatures of 220 °C were sufficient, a deactivated substrate such as *O*-thiocarbamate **4b** required a rearrangement temperature of ≥300 °C.[19] In our hands, flow processing of **4a** in NMP at 200 °C (1.0 mL min^{-1} flow rate, 4 mL coil) led to full and clean conversion to **5a**, whereas for substrate **4b** the temperature had to be increased to 280 °C in order to still obtain a full conversion to **5b** at a 1.0 mL min^{-1} flow rate (residence time 4 min) (Figure 2).[20] In order to avoid an aqueous/extractive workup required for Newman-Kwart rearrangements carried out in NMP (b.p. 202 °C),[18,19] we have repeated both rearrangements by using DME (b.p. 85 °C) as solvent under similar reaction conditions (Scheme 1, Reaction 2). Despite the high reaction temperatures, both transformations were very clean with no byproducts being observed by HPLC, GC, and ^{1}H NMR monitoring and provided nearly quantitative isolated product yields by simple evaporation of DME from the reaction mixture. It should be noted that for the rearrangement **4b** → **5b** performed at 300 °C and 80 bar of pressure, DME should be considered to be in a supercritical state (T_c = 263 °C; P_c = 39 bar).[13]

A more challenging case proved to be the Claisen rearrangement of allyl phenyl ether (**6**) (Scheme 1, Reaction 3). Under batch microwave conditions this transformation requires 1–2 h reaction time, even at 250 °C (toluene, 13 bar).[17] Our carefully optimized flow conditions utilized toluene as solvent at 240 °C and 100 bar reactor pressure. Applcation of a flow rate of 1.0 mL min^{-1} in the 4 mL stainless steel coil provided the desired rearranged product **7** in high purity and yield, with only small amounts (<5%) of undesired byproducts being formed. In fact, the Claisen rearrangement **6** → **7** proved to be rather sensitive to changes in temperature: at <230 °C incomplete conversion was obtained, whereas at higher reaction temperatures numerous side products were formed, therefore not allowing a further reduction in the reaction time by increasing the temperature (see Supporting Information). Here, the advantage of being



Scheme 1. Continuous-flow synthesis under high-temperature/pressure conditions with a stainless steel based flow reactor (Figure 1). For details on reaction optimization and experimental conditions see the Supporting Information.

able to change the reaction temperature "on-the-fly" in the flow experiment proved extremely helpful in optimizing reaction conditions.

In order to evaluate potential differences between microwave and conventionally heated flow systems, we have investigated the Fischer indole synthesis of tetrahydrocarbazole **10** (Scheme 1, Reaction 4). This reaction was recently performed by Bagley et al. using a microwave-heated flow reactor.[21] By applying identical reaction conditions (AcOH, 150 °C, 4 min residence time) isolated product yields very similar to those reported by Bagley were obtained (ca. 90%). In an effort to prepare tetrahydrocarbazole **10** on scale in the flow reactor, we have reoptimized the reaction conditions to increase the throughput. Carrying out the Fischer indole synthesis at 200 °C (75 bar) at a flow rate of 5.0 mL min^{-1} in a 16 mL stainless steel coil (residence time ca. 3 min) allowed the generation of 25 g of indole product within 1 h of flow processing.

Another classic and synthetically valuable high-temperature transformation is the nucleophilic aromatic substitution (S_NAr) of 2-halopyridines with amines. Typically, reaction times of several days are required for unactivated substrates such as 2-chloropyridine, even at high temperatures.[22] For the direct amination of 2-chloropyridine with morpholine (Scheme 1, Reaction 5) in NMP as solvent full conversion was achieved at 270 °C and 70 bar pressure under flow conditions with the 4 mL coil. The choice of solvent for this transformation was governed by the solubility of the formed morpholinium hydrochloride byproduct, allowing processing in a fully homogeneous fashion throughout the reaction.[23]

In some of the examples described above the use of a supercritical solvent allows the convenience of a simplified reaction workup since the (low boiling) solvent can be readily removed by evaporation. For the catalyst-free transesterification (Scheme 1, Reaction 6) and esterification (Reaction 7) the use of the appropriate alcohol in a supercritical state is a requirement, with little or no reaction occurring below 200 °C for both processes.[24,25] Due to the high ionic product of supercritical methanol (T_c = 239 °C; P_c = 81 bar) and ethanol (T_c = 268 °C; P_c = 61 bar), the solvent acts as an acidic catalyst itself and promotes the reaction under these extreme conditions.[13] For the transesterification (Reaction 6) full conversion was achieved at 350 °C at a 0.5 mL min^{-1} flow rate (8 min residence time). In case of the esterification (Reaction 7) a lower temperature of 300 °C was chosen in order to prevent decomposition of the benzoic acid material. In order to attain complete conversion, the reaction mixture was processed three times through the 4 mL heated steel coil at a flow rate of 1 mL min^{-1} (12 min residence time).

In summary, we have demonstrated that synthetic transformations requiring high temperatures can be conveniently performed in a high-temperature/high-pressure flow reactor that is based on standard HPLC-type equipment. Homogeneous reactions conducted under batch microwave conditions can rapidly be translated to a flow format. Because of efficient heat transfer through the thin steel reactor coil, rapid heating and cooling of the reaction mixture can be achieved. Taking advantage of the rapid cooling at the end of the reaction, the technology is somewhat related to flash vacuum pyroylsis where reactive intermediates may be trapped on a cold surface.[26] Since the flow reactor allows processing at significant pressure (200 bar), the unique reactivity and physical properties of solvents in their supercritical state can be exploited. High-temperature/high-pressure flow processing thus combines many of the features attributed to microwave chemistry, with the advantages of flow synthesis and serves as a convenient technique for process intensification. A particularly important advantage of flow chemistry is direct scalability, a critical problem in microwave-assisted batch transformations.[27] We believe that this technology will be particularly useful not only for organic

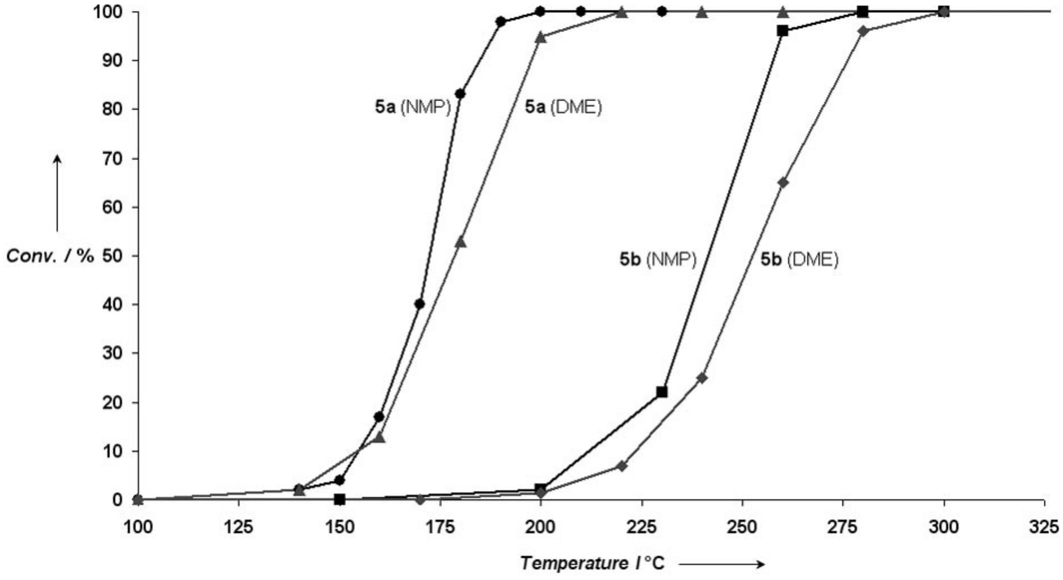


Figure 2. Conversion at different temperatures/online reaction optimization for the Newman-Kwart rearrangement of *O*-thiocarbamate **4a** and **4b** in NMP and DME as solvents (Scheme 1, Reaction 2). Flow processing (100–330 °C, 60–80 bar), 1 mL min^{-1} flow rate, 4 mL stainless steel coil, residence time 4 min.

synthesis,[28] but also for other areas where high reaction temperatures and controlled rapid heating are often a prerequisite such as, for example, the generation of high-quality nanocrystals.[29]

Supporting Information (see footnote on the first page of this article): Detailed experimental descriptions of flow reactions.

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[1] For recent reviews, see: a) C. Wiles, P. Watts, *Eur. J. Org. Chem.* **2008**, 1655; b) T. Fukuyama, M. T. Rahman, M. Sato, I. Ryu, *Synlett* **2008**, 151; c) B. Ahmed-Omer, J. C. Brandt, T. Wirth, *Org. Biomol. Chem.* **2007**, *5*, 733; d) P. Watts, C. Wiles, *Chem. Commun.* **2007**, 433; e) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107*, 2300.

[2] a) *Microreactors in Organic Synthesis* (Ed.: T. Wirth), Wiley-VCH, Weinheim, **2008**; b) *Handbook of Micro Reactors* (Eds.: V. Hessel, J. C. Schouten, A. Renken, Y. Wang. J.-i. Yoshida), Wiley-VCH, Weinheim, **2009**.

[3] a) D. M. Roberge, B. Zimmermann, F. Rainone, M. Gottsponer, M. Eyholzer, N. Kockmann, *Org. Process Res. Develop.* **2008**, *12*, 905; b) H. Pennemann, P. Watts, S. J. Haswell, V. Hessel, H. Löwe, *Org. Process Res. Develop.* **2004**, *8*, 422; c) V. Hessel, S. Hardt, H. Löwe, *Micro Chemical Process Engineering*, Wiley-VCH, Weinheim, **2004**.

[4] a) J.-i. Yoshida, A. Nagaki, T. Yamada, *Chem. Eur. J.* **2008**, *14*, 7450; b) J.-i. Yoshida, *Flash Chemistry – Fast Organic Synthesis in Microsystems*, Wiley-VCH, Weinheim, **2008**.

[5] a) E. R. Murphy, J. R. Martinelli, N. Zaborenko, S. L. Buchwald, K. F. Jensen, *Angew. Chem.* **2007**, *119*, 1764; *Angew. Chem. Int. Ed.* **2007**, *46*, 1734; b) P. W. Miller, N. J. Long, A. J. De Mello, R. Vilar, H. Audrain, D. Bender, J. Passchier, A. Gee, *Angew. Chem.* **2007**, *119*, 2933; *Angew. Chem. Int. Ed.* **2007**, *46*, 2875; c) B. C. Hamper, E. Tesfu, *Synlett* **2007**, 2257; d) K. Tanaka, S. Motomatsu, K. Koyama, S. Tanaka, K. Fukase, *Org. Lett.* **2007**, *9*, 299; e) O. Flögel, J. D. C. Codée, D. Seebach, P. H. Seeberger, *Angew. Chem.* **2006**, *118*, 7157; *Angew. Chem. Int. Ed.* **2006**, *45*, 7000; f) S. Liu, T. Fukuyama, M. Sato, I. Ryu, *Org. Process Res. Develop.* **2004**, *8*, 477; g) E. Garcia-Egido, S. Y. F. Wong, B. H. Warrington, *Lab Chip* **2002**, *2*, 31.

[6] For reactions performed in microwave-heated glass microcapillaries, see: a) E. Comer, M. G. Organ, *J. Am. Chem. Soc.* **2005**, *127*, 8160; b) G. Shore, S. Morin, D. Mallik, M. G. Organ, *Chem. Eur. J.* **2008**, *14*, 1351.

[7] For reactions performed in fluorinated polymer tubings, see: a) M. Baumann, I. R. Baxendale, S. V. Ley, N. Nikbin, C. D. Smith, J. Tierney, *Org. Biomol. Chem.* **2008**, *6*, 1577; b) C. J. Smith, F. J. Iglesias-Sigüenza, I. R. Baxendale, S. V. Ley, *Org. Biomol. Chem.* **2007**, *5*, 2758; c) C. H. Hornung, M. R. Mackley, I. R. Baxendale, S. V. Ley, *Org. Process Res. Dev.* **2007**, *11*, 399.

[8] For heterogeneously catalyzed reactions in flow reactors, see: a) S. Ceylan, C. Friese, C. Lammel, K. Mazac, A. Kirschning, *Angew. Chem.* **2008**, *120*, 9083; *Angew. Chem. Int. Ed.* **2008**, *47*, 8950; b) K. Mennecke, R. Cecilia, T. N. Glasnov, S. Gruhl, C. Vogt, A. Feldhoff, M. A. L. Vargas, C. O. Kappe, U. Kunz, A. Kirschning, *Adv. Synth. Catal.* **2008**, *350*, 717; c) K. Mennecke, W. Solodenko, A. Kirschning, *Synthesis* **2008**, 1589; d) N. Nikbin, M. Ladlow, S. V. Ley, *Org. Process Res. Develop.* **2007**, *11*, 458; e) I. R. Baxendale, C. M. Griffith-Jones, S. V. Ley, G. K. Tranmer, *Chem. Eur. J.* **2006**, *12*, 4407.

[9] a) H. Kawanami, K. Matsushima, M. Sato, Y. Ikushima, *Angew. Chem.* **2007**, *119*, 5221; *Angew. Chem. Int. Ed.* **2007**, *46*, 5129; b) C. Yan, J. Fraga-Dubeuil, E. Garcia-Verdugo, P. A. Hamley, M. Poliakoff, I. Pearson, A. Suart Coote, *Green Chem.* **2008**, *10*, 98; c) Y. Ikushima, K. Hatakeda, M. Sato, O. Sato,

M. Arai, *Chem. Commun.* **2002**, 2208; d) J. O. Metzger, F. Bangert, *Chem. Ber.* **1994**, *127*, 673.

[10] For a review on high-pressure microreactor chemistry, see: F. Benito-López, R. J. M. Egberink, D. N. Reinhoudt, W. Verboom, *Tetrahedron* **2008**, *64*, 10023.

[11] a) C. O. Kappe, *Chem. Soc. Rev.* **2008**, *37*, 1127; b) C. O. Kappe, *Angew. Chem.* **2004**, *116*, 6408; *Angew. Chem. Int. Ed.* **2004**, *43*, 6250, and references therein.

[12] C. O. Kappe, D. Dallinger, S. S. Murphree, *Practical Microwave Synthesis for Organic Chemists – Strategies, Instruments, and Protocols*, Wiley-VCH, Weinheim, **2009**.

[13] a) *Chemical Synthesis Using Supercritical Fluids* (Eds.: P. G. Jessop, W. Leitner), Wiley-VCH, Weinheim, **1999**; b) *High Pressure Chemistry – Synthetic, Mechanistic and Supercritical Applications* (Eds.: R. van Eldik, G. Klärner), Wiley-VCH, Weinheim, **2002**; Y. Arai, T. Sako, Y. Takebayashi, *Supercritical Fluids: Molecular Interactions, Physical Properties, and New Applications*, Springer, Berlin-Heidelberg, **2002**.

[14] J. D. Moseley, P. Lenden, M. Lockwood, K. Ruda, J.-P. Sherlock, A. D. Thomson, J. P. Gilday, *Org. Process Res. Dev.* **2008**, *12*, 30 and references cited therein.

[15] The flow reactor (X-Cube Flash) is available from Thales Nanotechnology Inc. (Budapest), Hungary. For further information, please refer to http://www.thalesnano.com.

[16] The accurate monitoring of temperature inside a microreactor is a nontrivial affair. The temperature can be estimated by indirect chemical methods. For details, see: T. Iwasaki, J.-i. Yoshida, *Macromolecules* **2005**, *38*, 1159.

[17] J. M. Kremsner, C. O. Kappe, *J. Org. Chem.* **2006**, *71*, 4651.

[18] G. C. Lloyd-Jones, J. D. Moseley, J. S. Renny, *Synthesis* **2008**, 661.

[19] a) J. D. Moseley, R. F. Sankey, O. N. Tang, J. P. Gilday, *Tetrahedron* **2006**, *62*, 4685; b) J. D. Moseley, P. Lenden, *Tetrahedron* **2007**, *63*, 4120.

[20] For an example of a Newman-Kwart rearrangement performed in a microreactor at 170 °C, see: X. Zhang, S. Stefanick, F. J. Villani, *Org. Process Res. Develop.* **2004**, *8*, 455.

[21] M. C. Bagley, R. L. Jenkins, M. Caterina Lubinu, C. Mason, R. Wood, *J. Org. Chem.* **2005**, *70*, 7003.

[22] S. Narayan, T. Seelhammer, R. E. Gawley, *Tetrahedron Lett.* **2004**, *45*, 757.

[23] The results presented here are in good agreement with previous studies on the flow amination of 2-chloropyridine in NMP as solvent under low-pressure flow conditions. See ref.[5c] for details.

[24] a) S. Saka, D. Kusdiana, *Fuel* **2001**, *80*, 225; b) G. Socher, R. Nussbaum, K. Rissler, E. Lankmayr, *Fresensius J. Anal. Chem.* **2001**, *371*, 369.

[25] J. Geuens, J. M. Kremsner, B. A. Nebel, S. Schober, R. A. Dommisse, M. Mittelbach, S. Tavernier, C. O. Kappe, B. U. W. Maes, *Energy Fuels* **2008**, *22*, 643.

[26] a) R. F. C. Brown, *Eur. J. Org. Chem.* **1999**, 3211; b) V. M. Tsefrikas, L. T. Scott, *Chem. Rev.* **2006**, *106*, 4868.

[27] Several flow reactors heated by microwave irradiation have been disclosed in the literature. Because of limitations in the materials used for the construction of these devices, reactors suitable for high-pressure processesing have not been described. For reviews, see: a) I. R. Baxendale, J. J. Hayward, S. V. Ley, *Comb. Chem. High Throughput Screening* **2007**, *10*, 802; b) T. N. Glasnov, C. O. Kappe, *Macromol. Rapid Commun.* **2007**, *28*, 395.

[28] For a recent application of the X-Cube Flash reactor for Mizoroki–Heck reactions at <200 °C, see: T. N. Glasnov, S. Findenig, C. O. Kappe, *Chem. Eur. J.* **2009**, *15*, 1001.

[29] J. A. Gerbec, D. Magana, A. Washington, G. F. Strouse, *J. Am. Chem. Soc.* **2005**, *127*, 15791.

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