

# Multistep Microchemical Synthesis Enabled by Microfluidic Distillation\*\*

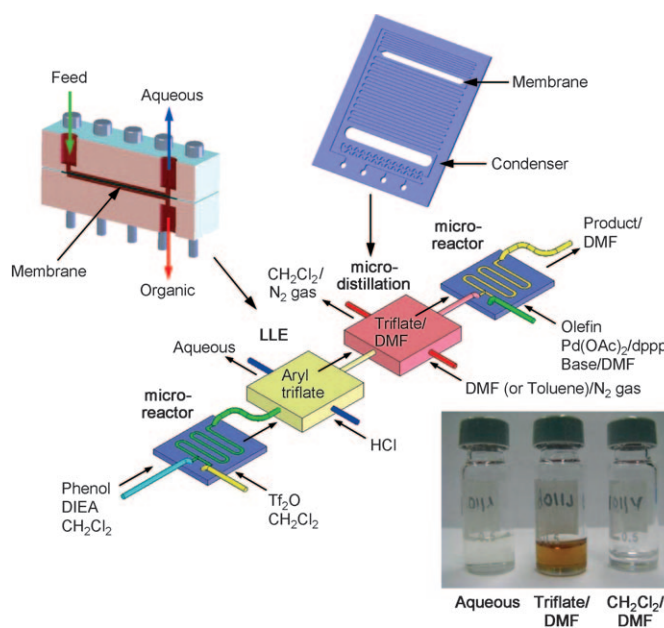
Ryan L. Hartman, John R. Naber, Stephen L. Buchwald,\* and Klavs F. Jensen\*

Complex organic molecules, such as active pharmaceutical ingredients, are synthesized by multiple reactions, which require a workup and isolation of the intermediates. Recent interest in microfluidic systems for continuous-flow synthesis has motivated the integration of multiple chemical reactions and separations in an attempt to streamline the process.<sup>[1–4]</sup> Microreactor networks provide advantages for chemical synthesis such as enhanced heat and mass-transfer characteristics, safety of operation, isolation of sensitive reactions from air or moisture, and a reduction of hazardous waste, while potentially providing a fundamental understanding of how production scale processes operate.<sup>[5–16]</sup> Nevertheless, studies combining multiple steps in a flow system are relatively limited.<sup>[1–3,17–25]</sup> Recently, multiple reaction steps were combined with intermediate liquid–liquid extractions to provide a continuous-flow synthesis of carbamates, which proceeded via a Curtius rearrangement of organic azides and subsequent reaction of the isocyanate with an alcohol.<sup>[1]</sup> This example illustrates the advantage of forming and immediately using small quantities of potentially hazardous intermediates (organic azides) in continuous flow systems. By taking advantage of the high interfacial area in microscale multiphase flow systems, intermediate extraction steps allowed completion of three sequential reaction steps.<sup>[1]</sup> Other reports have combined reactions with a liquid–liquid extraction for Co<sup>II</sup> wet analysis,<sup>[3]</sup> multiple reaction steps without intermediate separations,<sup>[19,22]</sup> multiple steps with off-line workups using reagents and catalysts on solid supports,<sup>[17,21]</sup> and solvent exchange by evaporation through porous poly(dimethylsiloxane).<sup>[18]</sup> The integration of reactions with analysis on a chip has also advanced the field of micro total analysis systems ( $\mu$ TAS).<sup>[20,26,27]</sup> These studies underscore the importance of integrating different unit operations to perform synthetic transformations.

A typical batch synthesis requires a variety of reactions, separation techniques and purifications. Separations are

equally essential for continuous-flow chemistry, with single-step liquid–liquid extraction<sup>[28–30]</sup> and microevaporation<sup>[18,31–35]</sup> having already been demonstrated. Distillation is an important method for separating liquid mixtures and can allow both purification and solvent exchange. Distillation processes operate by exploiting the difference in volatility between the components in a liquid mixture. Microfluidic distillation, based exclusively on boiling point differences, is challenging because surface forces dominate over gravitational forces at these micro-scale. By using gas–liquid segmented flow in conjunction with gas–liquid separators, limitations were overcome to enable the separation of binary solvent mixtures.<sup>[36]</sup> Combining microfluidic distillation with multiple reaction steps would offer a tool for synthetic organic chemistry and would provide a deeper understanding of how multistep microfluidic processes operate. In the current work, we present the first example of a multistep chemical synthesis employing a microfluidic distillation to exchange reaction solvents (Figure 1).

The Heck reaction is a versatile transformation in organic chemistry<sup>[37,38]</sup> which finds applications in the production of active pharmaceutical ingredients,<sup>[39]</sup> natural product synthesis,<sup>[40,41]</sup> and fine chemical production.<sup>[42]</sup> In addition to aryl halides, aryl triflates and nonaflates can be used as coupling partners to extend the scope of the reaction to a wider range of starting materials and to access regioisomeric products.<sup>[43]</sup>



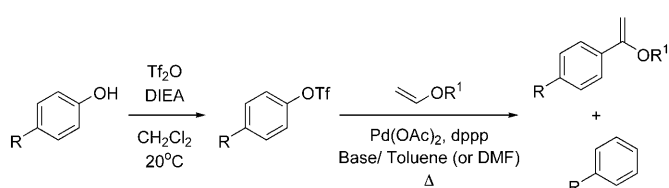
**Figure 1.** Reaction and separation scheme for continuous-flow synthesis involving solvent switch using microfluidic distillation.

[\*] R. L. Hartman, Prof. K. F. Jensen  
Department of Chemical Engineering  
Massachusetts Institute of Technology  
77 Massachusetts Ave., Cambridge, MA 02139 (USA)  
Fax: (+1) 617-258-8992  
E-mail: k Jensen@mit.edu  
Homepage: <http://web.mit.edu/jensenlab>  
J. R. Naber, Prof. S. L. Buchwald  
Department of Chemistry, Massachusetts Institute of Technology  
77 Massachusetts Ave., Cambridge, MA 02139 (USA)  
E-mail: sbuchwal@mit.edu

[\*\*] K.F.J. and S.L.B. thank the Novartis International AG for funding.  
Supporting information for this article is available on the WWW  
under <http://dx.doi.org/10.1002/anie.200904634>.

Because of this, examples of Heck reactions with aryl triflates are common; however, the almost complete lack of commercial availability of aryl triflates necessitates their preparation prior to their use in Heck reactions.<sup>[44–48]</sup>

Triflates are commonly prepared, in chlorinated solvents, from phenols and trifluoromethanesulfonic anhydride using stoichiometric amine bases. After the reaction, a general work-up procedure can include removal of the chlorinated solvent and addition of another solvent such as ethyl acetate (EA) to facilitate the workup. Further steps involve liquid–liquid extraction of the reaction mixture sequentially with aqueous acid, base, and brine to remove salt byproducts and excess reagents, subsequent removal of the solvent, and often purification of the triflate. In the second reaction step, the purified triflate, alkene coupling partner, amine base, palladium precatalyst and ligand are combined in a polar aprotic solvent, such as DMF, and heated to 100 °C or higher for the duration of the reaction (Scheme 1).



**Scheme 1.** Model chemistry for continuous-flow solvent exchange. DIEA = diisopropylethylamine, Tf = trifluoromethanesulfonyl, dppp = 1,3-bis(diphenylphosphino)propane, DMF = *N,N*-dimethylformamide.

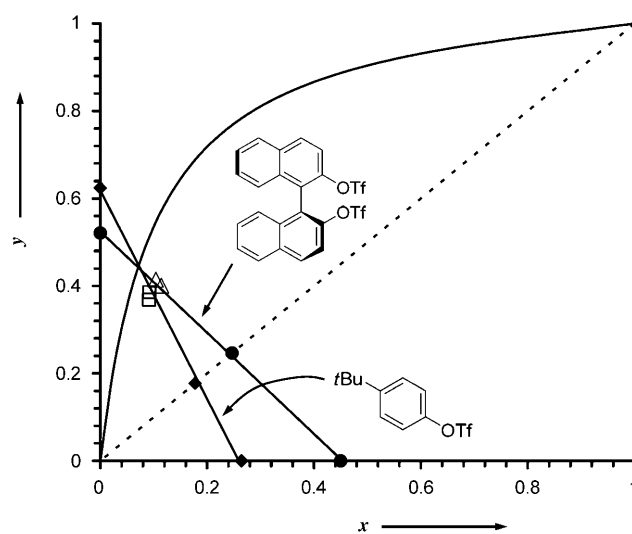
In the continuous-flow process, we wanted to take advantage of both the glassware-like compatibility and excellent heat transfer properties of silicon based microreactors to perform the chemistry, and the high interfacial area that results from micron length scales to increase the efficiency of the liquid–liquid extraction.<sup>[28]</sup> The first reaction step, the synthesis of an aryl triflate from a phenol and triflic anhydride (see Scheme 1), was carried out in a microreactor as illustrated in Figure 1. The syntheses of two different aryl triflates were investigated at 20 °C: 4-*tert*-butylphenyl trifluoromethanesulfonate and (*S*)-1,1'-binaphthyl-2,2'-diyl bis(trifluoromethanesulfonate). Upon exiting the microreactor, the product was combined with 2.0 M hydrochloric acid (HCl) and segmented flow was established.<sup>[49–51]</sup> Side-by-side contact of HCl slugs with the organic phase enhanced mass transport of DIEA to the aqueous droplets, making possible a single-stage liquid–liquid extraction.<sup>[1,28,49–51]</sup>

As shown in the reaction sequence of Figure 1, purified aryl triflate exiting the liquid–liquid extraction was combined with pure toluene (or DMF). The resulting stream (with a dichloromethane-to-toluene volumetric ratio of 1:4) was then delivered to the microfluidic distillation device (Figure 1). Gas–liquid segmented flow was established by combining nitrogen gas with the liquid stream, which enabled controlled flashing. The temperature of the distillation device (70 °C) was maintained above the boiling point of CH<sub>2</sub>Cl<sub>2</sub> (i.e., 40 °C) yet below the boiling point of toluene (i.e., 110 °C) or DMF (i.e., 153 °C). Consequently, the vapor phase was enriched with CH<sub>2</sub>Cl<sub>2</sub> while the liquid phase was comprised mostly of

toluene (or DMF) and aryl triflate. The liquid and vapor phases were additionally separated by exploiting the differences in their surface tensions. The device was designed such that the liquid (i.e., reaction products and solvent) flowed through an integrated PTFE membrane (0.5 μm pore size) whereas the vapor did not. Detailed pressure drop calculations, device fabrication, and theory of operation have been previously reported.<sup>[36]</sup>

In addition to the multistep experiments, samples of the aqueous phase, vapor condensate, and product streams were collected after the distillation stage for analysis. A photograph of a set of these samples is shown in Figure 1. It can be seen in this Figure that the distillate appeared to be colorless while the product stream was orange-brown in color. NMR analysis confirmed that the triflate remained in the liquid product stream in the case of dichloromethane-to-toluene solvent exchange, and that the starting material was converted into the triflate in 91–95 % yield. The analysis also identified that 93 % of the DIEA was extracted into the aqueous phase whereas the remaining 7 % was in the liquid product stream. The vapor condensate exiting the distillation stage was exclusively comprised of CH<sub>2</sub>Cl<sub>2</sub> and toluene as confirmed by NMR analysis.

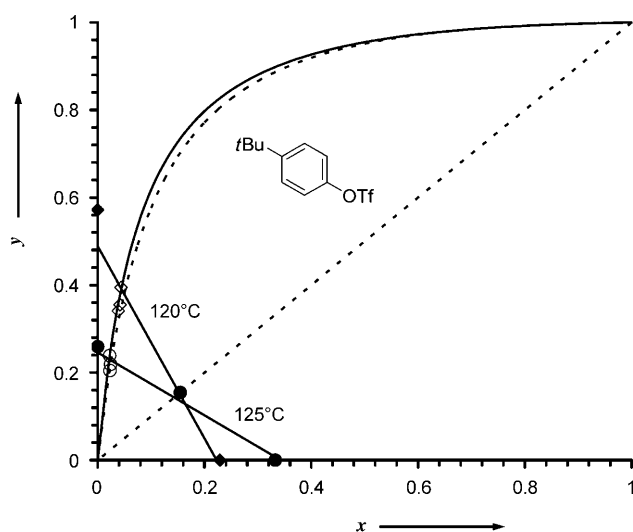
When a liquid mixture is comprised of two or more components with different volatilities, a phase equilibrium of the varying compositions exists and can be represented by a McCabe–Thiele diagram (see the Supporting Information for more details).<sup>[52,53]</sup> Figure 2 shows the McCabe–Thiele diagram for the CH<sub>2</sub>Cl<sub>2</sub>–toluene solvent exchange that was studied. In Figure 2, the theoretical equilibrium of a CH<sub>2</sub>Cl<sub>2</sub>/toluene binary mixture (at 70.0 °C) is shown by the curved line. The solid straight lines are described by Equation S3 (see the Supporting Information) and represent the mass balance during the separation of CH<sub>2</sub>Cl<sub>2</sub> and toluene for both triflate syntheses. Details on how these operating lines were obtained can be found in the Supporting Information section. For the synthesis of (*S*)-1,1'-binaphthyl-2,2'-diyl bis(trifluoromethanesulfonate) (binol triflate), we observed that CH<sub>2</sub>Cl<sub>2</sub> compo-



**Figure 2.** Mole fraction of CH<sub>2</sub>Cl<sub>2</sub> in the liquid product (*x*) and vapor condensate (*y*) streams for the separation of CH<sub>2</sub>Cl<sub>2</sub>/toluene at 70 °C.

sitions of  $(0.11 \pm 0.01)$  [liquid product stream] and  $(0.41 \pm 0.01)$  [vapor condensate stream] were close to those predicted by the equilibrium diagram ( $\Delta$  in Figure 2). Similarly, values of  $(0.09 \pm 0.01)$  [liquid product stream] and  $(0.38 \pm 0.01)$  [vapor condensate stream] were measured during the synthesis and separation of 4-*tert*-butylphenyl triflate ( $\square$  in Figure 2). Careful analysis of Figure 2 also shows that the  $\text{CH}_2\text{Cl}_2$  content of the feed stream was reduced from 0.2 (or 0.25 for binol triflate) to 0.1 mol fraction. Therefore, diluting the product stream from the first reaction step and carrying out one distillation step resulted in a switch of the solvent composition from 100%  $\text{CH}_2\text{Cl}_2$  to 90:10 toluene/ $\text{CH}_2\text{Cl}_2$ .

The synthesis of 4-*tert*-butylphenyl trifluoromethanesulfonate and subsequent solvent exchange from  $\text{CH}_2\text{Cl}_2$  to DMF was also investigated (Figure 3). We observed that



**Figure 3.** Mole fraction of  $\text{CH}_2\text{Cl}_2$  in the liquid product ( $x$ ) and vapor condensate ( $y$ ) streams for the separation of  $\text{CH}_2\text{Cl}_2$ /DMF at 120 and 125°C. The curved dashed line represents the change in equilibrium.

increasing the distillation temperature from 120°C to 125°C resulted in a fundamental change in operation. At 120°C, the slope of the operating line (i.e., the ratio of molar flow rate of liquid stream to vapor condensate) was greater than one, however, at 125°C the slope was less than one. Such control over flow rates is advantageous for continuous-flow chemical processes. Adjusting temperature alone can potentially change the entire outcome of the downstream microchemical process. Trace amounts of aryl triflate ( $< 0.3$  mol%) were found in the vapor condensate collected during solvent exchange from  $\text{CH}_2\text{Cl}_2$  to DMF, implying that operation at higher temperatures resulted in product vaporization. Calculation of the total molar flow rates through the system revealed that the mole fraction of aryl triflate vaporized,  $f$ , ranged from 0.07 to 0.22. Loss of product in a chemical process is undesirable, but can potentially be minimized using a more selective separation process. For example, multistage distillation would enable lower operating temperatures, maximizing solvent separation, and minimizing product losses.

In the final reaction step (see Scheme 1), a palladium-catalyzed coupling of 4-*tert*-butylphenyl triflate with *n*-butyl vinyl ether was carried out by combining the product stream exiting the microfluidic distillation stage with the other reagents and a catalyst in a downstream microreactor at 125°C (see Figure 1). Analysis of the samples exiting the microreactor elucidated the extent of the reaction. Table 1 shows the residence time,  $\text{CH}_2\text{Cl}_2$  composition, conversion of aryl triflate, and yield of the Heck product with increasing distillation stage temperature.

**Table 1:** Residence time ( $t$ ),  $\text{CH}_2\text{Cl}_2$  composition, conversion, and yield as a function of distillation temperature.

| $T$ [°C] | $t$ [min] | $\text{CH}_2\text{Cl}_2$ [vol %] | Conv. $\pm$ s.d. [%] <sup>[a]</sup> | Yield $\pm$ s.d. [%] <sup>[a]</sup> |
|----------|-----------|----------------------------------|-------------------------------------|-------------------------------------|
| 110      | 5.1       | 9.6                              | $47.1 \pm 8.7$                      | $42.8 \pm 5.9$                      |
| 120      | 5.5       | 7.1                              | $67.6 \pm 4.5$                      | $57.5 \pm 4.1$                      |
| 125      | 8.1       | 6.0                              | $96.3 \pm 0.4$                      | $76.8 \pm 0.7$                      |

[a] s.d. = standard deviation for three samples.

Increasing the temperature increases the amount of volatile solvent separated from the product stream, which decreased the volume fraction of  $\text{CH}_2\text{Cl}_2$ , increased the concentration of the triflate, and decreased the flow rate of the product stream. Concentrating the aryl triflate entering the final reactor increased the reaction rate while decreasing the total flow rate resulted in a longer residence time for the reaction (Table 1). Batch experiments were performed to elucidate the influence of residual  $\text{CH}_2\text{Cl}_2$  on the Heck reaction. Figure S1 in the Supporting Information shows that the reaction was most efficient in pure DMF and increasing the fraction of  $\text{CH}_2\text{Cl}_2$  decreased the product yield, which was in agreement with the results in flow. As shown in Scheme 1, reduction of the triflate was also observed during the Heck reaction. The selectivity for the Heck product relative to the reduced product remained constant and was estimated to be approximately 15:1.

The preparation of an aryl triflate and a subsequent Heck reaction of this triflate represented a case study for multistep synthesis with integrated microfluidic distillation. Continuous operation of the scheme presented in this paper could produce uninterrupted quantities of 1-(1-butoxyvinyl)-4-*tert*-butyl benzene. Based on data reported in Table 1 and the residence times investigated, approximately  $32 \text{ mg h}^{-1}$  (or  $0.135 \text{ mmol h}^{-1}$ ) of product could be synthesized. To test this, an experiment was repeated using the conditions from line 3 of Table 1 and Table S1 (see the Supporting Information), and the product stream was collected for 5.5 hours. As described in the Supporting Information, the product was hydrolyzed to the methyl ketone,<sup>[54]</sup> which was isolated in a 69% yield. Just as importantly, the working principles can be applied to other chemical reactions to achieve continuous-flow syntheses. For example, toluene could be removed to concentrate the isocyanate intermediated in the flow synthesis of carbamates without the need for a collection/boiling tank.<sup>[1]</sup> In addition to performing manipulations with solvents during a synthesis, microfluidic distillation can potentially be used as a product

purification process or as a separation step to facilitate reagent recycling.

In conclusion, we have designed a microfluidic distillation operation which exploits differences in volatility between components in liquid mixtures. Microfluidic distillation was used to allow the completion of a microchemical synthesis involving multiple reaction and separation steps. A triflate was synthesized in  $\text{CH}_2\text{Cl}_2$ , after which the solvent was switched to either toluene or DMF, and a palladium-catalyzed Heck reaction was performed. Microfluidic distillation offers new opportunities for continuous-flow chemical syntheses that require a separation between the reaction steps. Moving forward, however, is not without challenges. Strategies for handling solids in microchemical systems will enable multi-step synthesis using solid reagents or catalysts, or when solid by-products or products are formed. Furthermore, the integration of multiple distillation stages promises more selective separations.

### Experimental Section

A  $\text{CH}_2\text{Cl}_2$  solution of the substrate (1.0M), base (1.5M DIEA), and internal standard (0.2M) was loaded into a syringe and a  $\text{CH}_2\text{Cl}_2$  solution of  $\text{TiF}_4$  (1.2M) was loaded into a separate syringe (Hamilton Gastight 2.5 mL) and delivered to the first microreactor (see Figure 1) using a Harvard Apparatus syringe pump (3 to  $4\ \mu\text{L}\cdot\text{min}^{-1}$ ). Two additional pumps and five separate syringes were used to deliver 2.0M HCl ( $24\ \mu\text{L}\cdot\text{min}^{-1}$ ), pure toluene or DMF ( $24\ \mu\text{L}\cdot\text{min}^{-1}$ ), and DMF solutions of 4.0M *n*-butyl vinyl ether, 4.0M base, and 0.033M  $\text{Pd}(\text{OAc})_2/0.050\text{M}$  dppp (all at  $2\ \mu\text{L}\cdot\text{min}^{-1}$ ) in subsequent steps according to Figure 1. Nitrogen gas was delivered to the microdistillation stage directly from a gas tank fitted with a regulator. The three inlets and outlet of each microreactor were cooled ( $20^\circ\text{C}$ ) using chucks that have been described previously,<sup>[36]</sup> whereas the main reaction channels were heated using cartridge heaters in conjunction with proportional-integral-derivative (PID) controllers and aluminium chucks. Further details on the equipment setup and work-up procedures can be found in the Supporting Information.

Sample analysis: NMR spectroscopy was used to identify the product and quantify concentrations of  $\text{CH}_2\text{Cl}_2$ , toluene, and DMF in all streams. GC analysis was used to quantify concentrations of the reagents and products in all streams.

Received: August 20, 2009

Revised: November 19, 2009

Published online: December 18, 2009

**Keywords:** Heck reaction · microfluidic distillation · microreactors · palladium · synthetic methods

- [1] H. R. Sahoo, J. G. Kralj, K. F. Jensen, *Angew. Chem.* **2007**, *119*, 5806; *Angew. Chem. Int. Ed.* **2007**, *46*, 5704.
- [2] H. Song, J. D. Tice, R. F. Ismagilov, *Angew. Chem.* **2003**, *115*, 792; *Angew. Chem. Int. Ed.* **2003**, *42*, 768.
- [3] M. Tokeshi, T. Minagawa, K. Uchiyama, A. Hibara, K. Sato, H. Hisamoto, T. Kitamori, *Anal. Chem.* **2002**, *74*, 1565.
- [4] R. L. Hartman, K. F. Jensen, *Lab Chip* **2009**, *9*, 2495–2507.
- [5] A. J. deMello, *Nature* **2006**, *442*, 394.
- [6] P. D. I. Fletcher, S. J. Haswell, E. Pombo-Villar, B. H. Warrington, P. Watts, S. Y. F. Wong, X. L. Zhang, *Tetrahedron* **2002**, *58*, 4735.
- [7] V. Hessel, H. Lowe, *Chem. Eng. Technol.* **2005**, *28*, 267.
- [8] K. Jähnisch, V. Hessel, H. Lowe, M. Baerns, *Angew. Chem.* **2004**, *116*, 410; *Angew. Chem. Int. Ed.* **2004**, *43*, 406.
- [9] K. F. Jensen, *Chem. Eng. Sci.* **2001**, *56*, 293.
- [10] K. F. Jensen, *MRS Bull.* **2006**, *31*, 101.
- [11] B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107*, 2300.
- [12] H. Pennemann, P. Watts, S. J. Haswell, V. Hessel, H. Lowe, *Org. Process Res. Dev.* **2004**, *8*, 422.
- [13] P. Watts, C. Wiles, *Chem. Commun.* **2007**, 443.
- [14] P. Watts, C. Wiles, *Chem. Eng. Technol.* **2007**, *30*, 329.
- [15] N. Wang, T. Matsumoto, M. Ueno, H. Miyamura, S. Kobayashi, *Angew. Chem.* **2009**, *121*, 4838; *Angew. Chem. Int. Ed.* **2009**, *48*, 4744.
- [16] J. Kobayashi, Y. Mori, K. Okamoto, R. Akiyama, M. Ueno, T. Kitamori, S. Kobayashi, *Science* **2004**, *304*, 1305.
- [17] I. R. Baxendale, J. Deeley, C. M. Griffiths-Jones, S. V. Ley, S. Saaby, G. K. Tranmer, *Chem. Commun.* **2006**, 2566.
- [18] C. C. Lee, G. D. Sui, A. Elizarov, C. Y. J. Shu, Y. S. Shin, A. N. Dooley, J. Huang, A. Daridon, P. Wyatt, D. Stout, H. C. Kolb, O. N. Witte, N. Satyamurthy, J. R. Heath, M. E. Phelps, S. R. Quake, H. R. Tseng, *Science* **2005**, *310*, 1793.
- [19] H. Usutani, Y. Tomida, A. Nagaki, H. Okamoto, T. Nokami, J. Yoshida, *J. Am. Chem. Soc.* **2007**, *129*, 3046.
- [20] D. Belder, M. Ludwig, L. W. Wang, M. T. Reetz, *Angew. Chem.* **2006**, *118*, 2523; *Angew. Chem. Int. Ed.* **2006**, *45*, 2463.
- [21] I. R. Baxendale, C. M. Griffiths-Jones, S. V. Ley, G. K. Tranmer, *Synlett* **2006**, 427.
- [22] D. Grant, R. Dahl, N. D. P. Cosford, *J. Org. Chem.* **2008**, *73*, 7219.
- [23] W. Li, H. H. Pharn, Z. Nie, B. MacDonald, A. Guenther, E. Kumacheva, *J. Am. Chem. Soc.* **2008**, *130*, 9935.
- [24] C. Wiles, P. Watts, S. J. Haswell, *Lab Chip* **2007**, *7*, 322.
- [25] I. R. Baxendale, S. V. Ley, A. C. Mansfield, C. D. Smith, *Angew. Chem.* **2009**, *121*, 4077; *Angew. Chem. Int. Ed.* **2009**, *48*, 4017.
- [26] O. Trapp, S. K. Weber, S. Bauch, T. Backer, W. Hofstadt, B. Spliethoff, *Chem. Eur. J.* **2008**, *14*, 4657.
- [27] O. Trapp, S. K. Weber, S. Bauch, W. Hofstadt, *Angew. Chem.* **2007**, *119*, 7447; *Angew. Chem. Int. Ed.* **2007**, *46*, 7307.
- [28] J. G. Kralj, H. R. Sahoo, K. F. Jensen, *Lab Chip* **2007**, *7*, 256.
- [29] M. Tokeshi, T. Minagawa, T. Kitamori, *J. Chromatogr. A* **2000**, *894*, 19.
- [30] A. Aota, M. Nonaka, A. Hibara, T. Kitamori, *Angew. Chem.* **2007**, *119*, 896; *Angew. Chem. Int. Ed.* **2007**, *46*, 878.
- [31] D. A. Boyd, J. R. Adleman, D. G. Goodwin, D. Psagtis, *Anal. Chem.* **2008**, *80*, 2452.
- [32] A. Hibara, K. Toshin, T. Tsukahara, K. Mawatari, T. Kitamori, *Chem. Lett.* **2008**, *37*, 1064.
- [33] B. H. Timmer, K. M. van Delft, W. Olthuis, P. Bergveld, A. van den Berg, *Sens. Actuators B* **2003**, *91*, 342.
- [34] R. C. R. Wootton, A. J. deMello, *Chem. Commun.* **2004**, 266.
- [35] Y. Zhang, S. Kato, T. Anazawa, *Chem. Commun.* **2009**, 2750.
- [36] R. L. Hartman, H. R. Sahoo, B. C. Yen, K. F. Jensen, *Lab Chip* **2009**, *9*, 1843.
- [37] I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009.
- [38] F. Alonso, I. P. Beletskaya, M. Yus, *Tetrahedron* **2005**, *61*, 11771.
- [39] P. Mahavir, *Topics in Organometallic Chemistry*, Vol. 6, Springer, Berlin, **2004**, p. 181.
- [40] K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4516; *Angew. Chem. Int. Ed.* **2005**, *44*, 4442.
- [41] A. B. Dounay, L. E. Overman, *Chem. Rev.* **2003**, *103*, 2945.
- [42] J. G. de Vries, *Can. J. Chem.* **2001**, *79*, 1086.
- [43] W. Cabri, I. Candiani, *Acc. Chem. Res.* **1995**, *28*, 2.
- [44] A. L. Hansen, T. Skrydstrup, *J. Org. Chem.* **2005**, *70*, 5997.
- [45] S. R. Gilbertson, Z. Fu, *Org. Lett.* **2001**, *3*, 161.
- [46] K. Olofsson, M. Larhed, A. Hallberg, *J. Org. Chem.* **2000**, *65*, 7235.

- [47] W. Cabri, I. Candiani, A. Bedeschi, R. Santi, *J. Org. Chem.* **1992**, 57, 3558.
  - [48] W. Cabri, I. Candiani, A. Bedeschi, S. Penco, R. Santi, *J. Org. Chem.* **1992**, 57, 1481.
  - [49] A. Günther, K. F. Jensen, *Lab Chip* **2006**, 6, 1487.
  - [50] A. Günther, M. Jhunjhunwala, M. Thalmann, M. A. Schmidt, K. F. Jensen, *Langmuir* **2005**, 21, 1547.
  - [51] A. Günther, S. A. Khan, M. Thalmann, F. Trachsel, K. F. Jensen, *Lab Chip* **2004**, 4, 278.
  - [52] W. L. McCabe, E. W. Thiele, *Ind. Eng. Chem.* **1925**, 17, 605.
  - [53] P. C. Wankat, *Equilibrium-Staged Separations—Separations in Chemical Engineering*, Prentice Hall PTR, Englewood Cliffs, **1988**.
  - [54] W. Cabri, I. Candiani, A. Bedeschi, *J. Org. Chem.* **1990**, 55, 3654.
-