

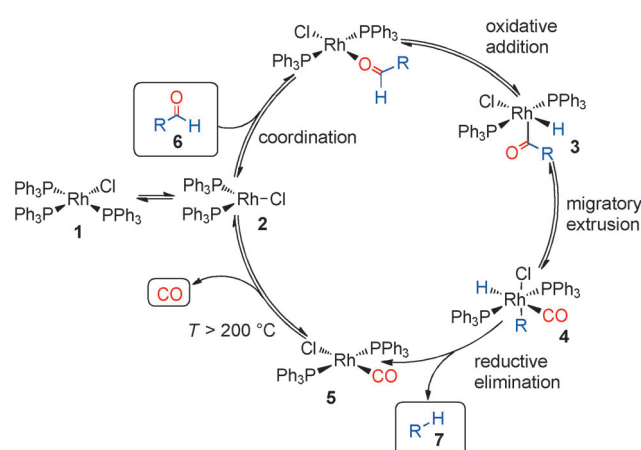
Shifting Chemical Equilibria in Flow—Efficient Decarbonylation Driven by Annular Flow Regimes**

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Abstract: To efficiently drive chemical reactions, it is often necessary to influence an equilibrium by removing one or more components from the reaction space. Such manipulation is straightforward in open systems, for example, by distillation of a volatile product from the reaction mixture. Herein we describe a unique high-temperature/high-pressure gas/liquid continuous-flow process for the rhodium-catalyzed decarbonylation of aldehydes. The carbon monoxide released during the reaction is carried with a stream of an inert gas through the center of the tubing, whereas the liquid feed travels as an annular film along the wall of the channel. As a consequence, carbon monoxide is effectively vaporized from the liquid phase into the gas phase and stripped from the reaction mixture, thus driving the equilibrium to the product and preventing poisoning of the catalyst. This approach enables the catalytic decarbonylation of a variety of aldehydes with unprecedented efficiency with a standard coil-based flow device.

The decarbonylation of aldehydes with stoichiometric amounts of the Wilkinson complex ($[\text{RhCl}(\text{PPh}_3)_3]$) was reported by Tsuji and Ohno in 1965.^[1–3] The reaction proceeds at or near room temperature and generates the decarbonylated product along with the stable inorganic complex *trans*- $[\text{RhCl}(\text{CO})(\text{PPh}_3)_2]$. Early studies by Walborsky and Allen as well as others demonstrated that the reaction occurs with a high degree of stereoselectivity and with overall retention of the configuration of the carbon atom attached to the aldehyde group.^[4] Stereospecific decarbonylation has since matured into a key strategic element in the synthesis of complex natural products.^[5]

Computational and experimental studies indicate that the decarbonylation reaction starts with the dissociation of a phosphine ligand from the square-planar rhodium complex **1** to generate a coordinatively unsaturated d^8 complex **2** (Scheme 1).^[6] The coordinatively unsaturated species subse-



Scheme 1. Catalytic cycle for the rhodium-mediated decarbonylation of aldehydes.^[1,6]

quently reacts by a rapid, reversible oxidative addition into the C(O)–H bond of the aldehyde to form an acyl rhodium(III) hydride complex **3**.^[6] The reaction then proceeds by a rate-limiting migratory extrusion of CO to give the 16e alkyl or aryl rhodium(III) hydride **4**, and finally produces the 16e carbonyl complex *trans*- $[\text{RhCl}(\text{CO})(\text{PPh}_3)_2]$ (**5**) and the decarbonylated product **7** by an irreversible reductive elimination (Scheme 1).^[6]

Early attempts to make the system catalytic failed because the electronically depleted Rh–CO complex **5** does not participate in the oxidative addition into the aldehyde C–H bond, and loss of the CO ligand to regenerate the active species does not proceed at preparatively useful reaction rates at temperatures below 220 °C.^[1] Indeed, even heating of the $[\text{RhCl}(\text{CO})(\text{PPh}_3)_2]$ complex to temperatures as high as 260 °C with an excess of triphenylphosphane failed to convert the rhodium carbonyl complex back into the tris(triphenylphosphine)rhodium species.^[1c] Significant progress toward a more efficient decarbonylation reaction was made by the introduction of cationic rhodium complexes of chelating bisphosphines, such as $[\text{Rh}(\text{dppp})_2]\text{Cl}$ (dppp = 1,2-bis(diphenylphosphanyl)propane).^[7] These complexes are less electron rich and, accordingly, bind CO less strongly owing to decreased Rh–CO π -back-bonding. More recently, a convenient procedure for the decarbonylation of aldehydes was reported for which the active catalyst was prepared in situ from commercially available $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ and the dppp ligand.^[8] The reaction was performed under an argon atmosphere and required a reaction time of 16 h with catalyst loadings of 0.4–10 mol% in boiling diglyme as the solvent

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(b.p. 162 °C).^[8,9] However, harsh conditions and extended reaction times, together with the requirement for high-boiling solvents, which are difficult to remove from the product after the reaction, make catalytic decarbonylation reactions generally incompatible with a high-yielding and sustainable reaction procedure. Therefore, the majority of decarbonylation protocols for the synthesis of complex molecules still rely on stoichiometric or near-stoichiometric amounts of a rhodium complex.^[5]

Herein, we describe a unique biphasic gas–liquid continuous-flow decarbonylation protocol that enables the efficient decarbonylation of aldehydes in the presence of a catalytic amount of a rhodium precursor within only 8–25 min. This otherwise very challenging transformation is made possible by inducing an annular flow regime in a coil-based micro-reactor by using nitrogen as an inert carrier gas, which efficiently removes CO from the equilibrium.

We chose 4-cyanobenzaldehyde (**6a**) as the model substrate for initial optimization experiments (for optimization details, see the Supporting Information). As it was clearly evident from previously reported studies that a fast, catalytic decarbonylation reaction would have to involve a high-temperature regime, controlled sealed-vessel microwave heating was used for process optimization.^[10] The active $[\text{Rh}(\text{dppp})]^+$ catalyst could be generated in situ from dppp and various Rh sources, such as $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ or $\text{Rh}(\text{OAc})_2$ (see Table S1 in the Supporting Information). Initial optimization of the reaction conditions provided best results with 4 mol % of $\text{Rh}(\text{OAc})_2$ and 8 mol % of dppp in aprotic, inert solvents, such as toluene. The reaction was remarkably clean (ca. 95 % according to GC with a flame ionization detector, GC–FID), and the only detectable side product was 4,4'-dicyanobenzophenone, formed by a decarbonylative homocoupling of 4-cyanobenzaldehyde.^[11]

Our initial batch experiments confirmed that the rhodium-catalyzed decarbonylation of aromatic aldehydes requires fairly high temperatures for a reaction to occur at reasonable rates, or for the catalytic cycle to be completed at all. Furthermore, even though a clean decarbonylation was possible at reaction temperatures of around 200 °C by sealed-vessel microwave heating, the reaction rate greatly depended on the scale on which the experiments were performed. With increasing filling volume and consequently decreasing available headspace in the sealed vessel, the reaction rate decreased markedly. Whereas full conversion was observed on a 0.6 mmol scale in a 10 mL microwave vial after 15 min at 180 °C, the conversion gradually decreased to 26 % when the scale was increased to 1.4 mmol (see Table S4). Similarly, conversions were around only 30 % for initial continuous-flow experiments in pressurized coil reactors, in which the headspace is essentially eliminated.^[12] Only when the back

pressure of the flow system was reduced, and the pressure approached the vapor pressure of the solvent, did the conversion increase from 30 to around 70 % (see Table S5). These experiments clearly demonstrate that the lack of a headspace in the closed flow system, and the consequently high concentration of CO in the liquid phase, inhibits the decarbonylation reaction and prevents genuine catalysis. It is well-known that, depending on temperature and the partial pressure of CO, rhodium forms a range of different carbonyl complexes, and the electronically depleted carbonyl compounds generally do not participate in the decarbonylation reaction.^[1,13]

To prevent the poisoning of the catalyst by carbon monoxide, we envisaged stripping the CO from the reaction mixture with a stream of an inert gas fed into the flow system (Figure 1).^[14,15] Indeed, when N_2 was fed into the flow reactor, the conversion increased strikingly and approached or even surpassed the results obtained under microwave batch conditions on a small scale. Optimization of the process parameters clearly illustrates that operation at the highest temperature and lowest pressure is desired—namely, slightly above the vapor pressure of the solvent at a given temperature, to avoid its vaporization (Table 1; see also Tables S9–S12).^[14,16] Under such conditions, the experimentally determined residence time of the reaction mixture in the flow

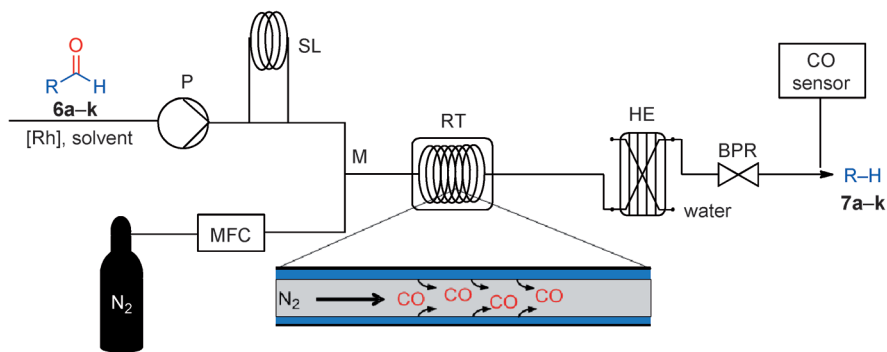


Figure 1. Gas–liquid continuous-flow decarbonylation of aldehydes with N_2 as a stripping gas. P = HPLC pump, SL = sample loop (poly(tetrafluoroethylene), 0.8 mm inside diameter), M = mixer (1.0 mm i.d.), RT = residence tube (stainless steel, 1 mm i.d.), HE = heat exchanger (stainless steel, 1 mm i.d.), BPR = back-pressure regulator.

Table 1: Continuous-flow decarbonylation reactions at different temperatures and N_2 flow rates (Figure 1; flow rate of liquid feed: 0.5 mL min^{-1}).^[a]

T/p [°C]/[bar]	N_2 [mL min^{-1}] ^[b]		
	8	15	25
180/6.8	65 %	72 %	89 %
200/9.1	89 %	93 %	95 % ^[c]
220/12.5	92 %	93 %	

[a] The percentages given are the conversion of **6a** into **7a** under the specified conditions of temperature, pressure, and nitrogen flow rate, as determined by GC–FID. Flow reactions were performed in a 20 mL stainless-steel reactor with a 0.2 M solution of 4-cyanobenzaldehyde (**6a**) in toluene (2 mL), $\text{Rh}(\text{OAc})_2$ (4 mol %), and dppp (8 mol %). [b] Gas flow in mL min^{-1} under normal conditions ($T_n = 0^\circ\text{C}$ and $p_n = 1 \text{ atm}$). [c] The pressure was increased from 9.1 to 9.7 bar.

system was essentially independent of the flow rate of the gaseous feed, the back pressure, and the reaction temperature. With flow rates of $15 \text{ mL}_\text{N} \text{ min}^{-1}$ for the N_2 feed and 0.5 mL min^{-1} for the liquid feed at 180°C and a back pressure of around 6 bar, carbon monoxide could be detected at the outlet of the tubing already 3 to 4 min after the reaction mixture had been injected, whereas the product left the reactor after roughly 8 to 9 min (see Table S9 and Figure S6 in the Supporting Information). This result indicates that the liquid travels as an annular film on the channel wall, whereas the carbon monoxide is carried with the stream of nitrogen through the center of the tubing (annular flow).^[16] With an increasing flow rate of the gaseous feed, as well as with increasing temperature and/or decreasing pressure, a transition from annular flow or annular-dispersed flow (gas core contains entrained liquid droplets) to dispersed flow was apparent. In the case of dispersed flow, the gas core contains the volatile liquid, and the nonvolatile catalyst is deposited on the wall of the capillary (dry-out).^[16]

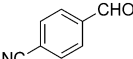
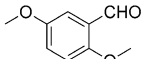
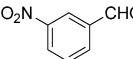
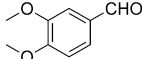
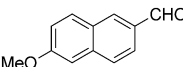
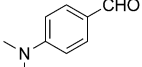
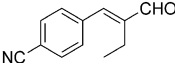
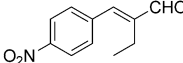
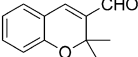
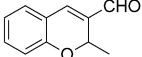
Essentially full conversion of 4-cyanobenzaldehyde (**6a**) into benzonitrile (**7a**) was observed on a 2 mmol scale with $\text{Rh}(\text{OAc})_2$ (4 mol %) and dppp (8 mol %) at 200°C and flow rates of 0.5 mL min^{-1} for the liquid feed and $25 \text{ mL}_\text{N} \text{ min}^{-1}$ for the N_2 feed. Pure benzonitrile was isolated in 84 % yield after column chromatography (Table 2). As expected, benzaldehydes lacking electron-withdrawing groups reacted significantly slower than cyanobenzaldehyde. With 2,5-dimethoxybenzaldehyde (**6b**), conversions of $> 90\%$ were observed after the flow rate of the liquid feed was decreased to 0.3 mL min^{-1} , and the pure product was isolated as described above in 87 % yield. The scale of this reaction was then

increased to 10 mmol (20 mL) to simulate steady-state operation (the volume of the reaction mixture was about 5 times the effective residence volume). The decarbonylated product **7b** was formed with essentially identical conversion on this scale (93 % according to GC–FID), and the product was isolated in 82 % yield, thus demonstrating that the CO is effectively removed from the reaction space. For some of the other tested aromatic aldehydes, **6d–f**, full conversion did not readily occur under these conditions, and conversions could not be improved by simply increasing the reaction time or by increasing the reaction temperature above 200°C . Thus, the catalyst loading was increased to 8 mol % to promote high conversion. Generally, the reactions were very clean and the decarbonylated compounds were the only products detected in the reaction mixtures.

The stereospecific decarbonylation of α -alkyl *trans*-cinnamaldehydes to give the corresponding *cis* alkenes has been reported previously.^[1b,4] Since the *trans*-cinnamaldehydes can be readily prepared by an aldol condensation of benzaldehyde and an enolizable aliphatic aldehyde, the condensation/decarbonylation sequence might constitute an attractive two-step synthesis of *cis* alkenes. The flow-decarbonylation procedure gave complete conversion of 4-cyano- and 4-nitro- α -ethyl-*trans*-cinnamaldehyde (**6g** and **6h**) into the decarbonylated products **7g** and **7h** at temperatures as low as 180°C (Table 2). With both substrates, a roughly 10:90 mixture of the *cis* and the *trans* alkene was obtained, with the *trans* compound as the major component (Table 2). Similarly, α -methyl-*trans*-cinnamaldehyde gave a roughly 30:70 mixture of *cis*- and *trans*- β -methylstyrene. Furthermore, 2-methylindanone was formed in significant amounts from the α -methylcinnamaldehyde by an intermolecular hydroacylation (see the Supporting Information). Additionally, decarbonylation of the aliphatic aldehyde 3-phenylpropionaldehyde with $\text{Rh}(\text{OAc})_2/\text{dppp}$ gave a 1:1 mixture of ethylbenzene and styrene (see Table S15). The Wilkinson complex generally affords the respective alkanes from the aliphatic aldehydes selectively.^[1]

The efficiency of this novel flow protocol was then highlighted by the synthesis of various chromenes by decarbonylation of the corresponding 2-formylchromenes. Chromenes constitute an important class of natural products and are key intermediates in the synthesis of many natural products, including cannabinoids, anthocyanins, and flavones.^[9] A two-step synthesis of chromenes by a Michael addition/aldol condensation of a salicylaldehyde and an acrylaldehyde, followed by subsequent rhodium-catalyzed decarbonylation, was utilized by Bräse and co-workers for the

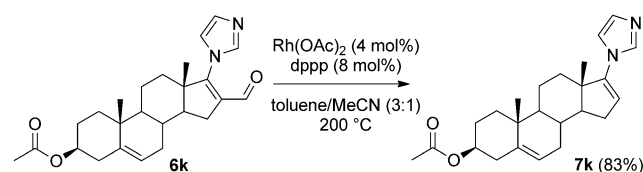
Table 2: Decarbonylation of aldehydes under continuous-flow conditions (Figure 1).^[a]

R-CHO 6a-j		$\text{Rh}_2(\text{OAc})_4$, dppp toluene, 200 °C	R-H 7a-j
Substrate	Conversion [%] (yield [%]) ^[b]	Substrate	Conversion [%] (yield [%]) ^[b]
6a ^[c] 	94 (84)	6b 	92 (87)
6c 	85 (71)	6d ^[d] 	88 (82)
6e ^[d] 	95 (76)	6f ^[d] 	69 (53)
6g ^[e] 	100 (83) <i>cis/trans</i> 11:89	6h ^[e] 	100 (61) <i>cis/trans</i> 9:91
6i 	100 (84)	6j 	100 (85)

[a] Flow reactions were performed at 200°C in a 25 mL stainless-steel reactor with 4 mL of a 0.5 M solution of aldehydes **6a–j**, $\text{Rh}(\text{OAc})_2$ (4 mol %), and dppp (8 mol %) in toluene as the solvent; the pressure was adjusted to approximately 10 bar, and the flow rates of the liquid and gaseous feed were 0.3 and 25 mL min^{-1} , respectively (residence time: 8–15 min). [b] The conversion was determined by GC–FID. The yield of the isolated product is given in parentheses. [c] The reaction was performed in a 20 mL stainless-steel coil with flow rates of 0.5 and 25 mL min^{-1} for the liquid and gaseous feed, respectively. [d] The reaction was performed with $\text{Rh}(\text{OAc})_2$ (8 mol %) and dppp (16 mol %). [e] The reaction was performed at 180°C and 7 bar.

synthesis of eulatachromene and various related chromene derivatives.^[9] The decarbonylation reaction was performed by a procedure developed by Madsen and co-workers ($\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ (5 mol %), dppp (10 mol %), 16 h at the reflux temperature of diglyme).^[8] Our flow decarbonylation protocol provided complete decarbonylation of 2-substituted formylchromenes in residence times of around 10 min at a reaction temperature of 200 °C. The 2-methyl- and 2,2-dimethyl-2H-chromenes **6j** and **6i** were formed with good selectivity and isolated by chromatography in 85 and 84 % yield, respectively (Table 2).

Finally, we performed the decarbonylation of the 16-formylandrosta-5,16-diene derivative **6k** to yield the C17-heteroaryl steroidal CYP17 inhibitor/antiandrogen **7k** (Scheme 2). This and related compounds are experimental



Scheme 2. Synthesis of the C17-heteroaryl steroidal CYP17 inhibitor/antiandrogen **7k**.

drugs for the treatment of prostate cancer and are currently under clinical development.^[17] A scalable and cost-efficient protocol for the generation of these compounds is therefore of utmost importance. The C17-heteroaryl 6-formylandrosta-diene can readily be synthesized in two steps by the Vilsmeier–Haack formylation of commercially available dehydroisoandrosterone 3-acetate and subsequent nucleophilic replacement of the C17 chloride substituent with imidazole.^[17] Continuous-flow decarbonylation under the conditions outlined above with toluene/MeCN (3:1) as the solvent proceeded with remarkable selectivity, and no sign of double-bond isomerization was apparent. With a catalyst loading of 4 mol % of $\text{Rh}(\text{OAc})_3$ at a reaction temperature of 200 °C, the desired target compound **7k** was formed as virtually the sole product after a residence time of about 25 min. The product **7k** was isolated by elution through a short column of silica gel in 83 % yield (1 mmol scale).

In conclusion, we have developed an efficient catalytic high-temperature/high-pressure continuous-flow Tsuji–Wilkinson decarbonylation protocol that can be applied to a variety of aldehydes. The carbon monoxide released during the reaction was removed from the reaction mixture by a continuous stream of N_2 as a stripping gas, thus driving the equilibrium to the product and preventing poisoning of the catalyst. Separation techniques involving mass transfer (e.g. distillation, stripping, and absorption) are common for the selective removal of components from a reaction mixture and shifting of an equilibrium in the desired direction.^[14] In a batch mode, this operation would have to be performed under reflux conditions in a high-boiling solvent, and thus under complex reaction conditions that are difficult to scale up. In the flow mode, the use of a falling-film reactor or

a CSTR cascade may be feasible, but would significantly increase complexity if operated under pressure. In this study, these principles have been implemented in a novel continuous-flow high-temperature/high-pressure process in a standard coil-based microreactor environment.^[18] The unique transport capabilities at these scales (i.e., large interfacial areas and short diffusion paths) and the corresponding efficient gas–liquid interaction enabled the desired transformation to be performed with exceptional efficiency.

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- [1] a) J. Tsuji, K. Ohno, *Tetrahedron Lett.* **1965**, 6, 3969–3971; b) J. Tsuji, K. Ohno, *Tetrahedron Lett.* **1967**, 8, 2173–2176; c) K. Ohno, J. Tsuji, *J. Am. Chem. Soc.* **1968**, 90, 99–107.
- [2] For a recent review on the rhodium-catalyzed decarbonylation, see: A. Korotvicka, D. Necas, M. Kotora, *Curr. Org. Chem.* **2012**, 16, 1170–1214.
- [3] For examples of palladium- and iridium-catalyzed decarbonylation reactions, see: Pd: a) D. Maiti, *Green Chem.* **2012**, 14, 2314–2320; b) A. Modak, A. Deb, T. Patra, S. Rana, S. Maity, D. Maiti, *Chem. Commun.* **2012**, 48, 4253–4255; c) S. Dahoah, Z. Nairoukh, M. Fanun, M. Schwarze, R. Schomäcker, J. Blum, *J. Mol. Catal. A* **2013**, 380, 90–93; Ir: d) T. Iwai, T. Fujihara, Y. Tsuji, *Chem. Commun.* **2008**, 6215–6217; e) E. P. K. Olsen, R. Madsen, *Chem. Eur. J.* **2012**, 18, 16023–16029.
- [4] a) H. M. Walborsky, L. E. Allen, *Tetrahedron Lett.* **1970**, 11, 823–824; b) H. M. Walborsky, L. E. Allen, *J. Am. Chem. Soc.* **1971**, 93, 5465–5468.
- [5] For selected examples of rhodium-catalyzed decarbonylation as part of multistep syntheses of complex molecules, see: a) C.-M. Zeng, M. Han, D. F. Covey, *J. Org. Chem.* **2000**, 65, 2264–2266; b) T. Kato, M. Hoshikawa, Y. Yaguchi, K. Izumi, Y. Uotsu, K. Sakai, *Tetrahedron* **2002**, 58, 9213–9222; c) B. J. Morgan, C. A. Mulrooney, M. C. Kozlowski, *J. Org. Chem.* **2010**, 75, 44–56; d) R. M. Wilson, R. K. Thalji, R. G. Bergman, J. A. Ellman, *Org. Lett.* **2006**, 8, 1745–1747; e) J. P. Malerich, T. J. Maimone, G. I. Elliott, D. Trauner, *J. Am. Chem. Soc.* **2005**, 127, 6276–6283; f) M. Harmata, S. Wacharasindhu, *Org. Lett.* **2005**, 7, 2563–2565; g) H. Zhang, A. Padwa, *Tetrahedron Lett.* **2007**, 47, 3905–3908.
- [6] P. Fristrup, M. Kreis, A. Palmelund, P.-O. Norrby, R. Madsen, *J. Am. Chem. Soc.* **2008**, 130, 5206–5215.
- [7] D. H. Doughty, L. H. Pignolet, *J. Am. Chem. Soc.* **1978**, 100, 7083–7085.
- [8] M. Kreis, A. Palmelund, L. Bunch, R. Madsen, *Adv. Synth. Catal.* **2006**, 348, 2148–2154.
- [9] M. C. Bröhmer, N. Volz, S. Bräse, *Synlett* **2009**, 1383–1386, and references therein.
- [10] T. N. Glasnov, C. O. Kappe, *Chem. Eur. J.* **2011**, 17, 11956–11968.
- [11] The rhodium-catalyzed decarbonylative homocoupling of benzaldehydes in the presence of an oxidant has been exploited for the preparation of benzophenones: L. Yang, T. Zeng, Q. Shuai, X. Guo, C.-J. Li, *Chem. Commun.* **2011**, 47, 2161–2163.
- [12] For a recent example highlighting the reverse effect of headspace in microwave batch versus flow experiments, see: N. Zaborenko, M. W. Bedore, T. F. Jamison, K. F. Jensen, *Org. Process Res. Dev.* **2011**, 15, 131–139.

- [13] a) F. Abu-Hasanayn, M. E. Coldman, A. S. Goldman, *J. Am. Chem. Soc.* **1992**, *114*, 2520–2524; b) T. C. Fessard, S. P. Andrews, H. Motoyoshi, E. M. Carreira, *Angew. Chem. Int. Ed.* **2007**, *46*, 9331–9334; *Angew. Chem.* **2007**, *119*, 9492–9495; c) E. Taarning, R. Madsen, *Chem. Eur. J.* **2008**, *14*, 5638–5644.
- [14] J. Benitez, *Principles and Modern Applications of Mass Transfer Operations*, 2nd ed Wiley, Hoboken, **2009**.
- [15] Besides thermal means to regenerate the catalytically active species, photochemical and chemical methods to remove CO from a carbonyl complex have been reported (see the Supporting Information for details).
- [16] Depending on the total flow rate and volumetric flow ratio, several gas–liquid flow patterns are possible; see: A. Faghri, Y. Zhang, *Transport Phenomena in Multiphase Systems*, Elsevier, Burlington, MA, **2006**.
- [17] a) V. C. O. Njar, K. Kato, I. P. Nnane, D. N. Grigoryev, B. J. Long, A. M. H. Brodie, *J. Med. Chem.* **1998**, *41*, 902–912; b) V. D. Handratta, T. S. Vasaitis, V. C. O. Njar, L. K. Gediya, R. Kataria, P. Chopra, D. Newman, Jr., R. Farquhar, Z. Guo, Y. Qiu, A. M. H. Brodie, *J. Med. Chem.* **2005**, *48*, 2972–2984; c) P. Purushottamachar, A. M. Godbole, L. K. Gediya, M. S. Martin, T. S. Vasaitis, A. K. Kwegyir-Afful, S. Ramalingam, Z. Ates-Alagoz, V. C. O. Njar, *J. Med. Chem.* **2013**, *56*, 4880–4898.
- [18] P. Plouffe, A. Macchi, D. M. Roberge in *Flow Chemistry, Vol. 1* (Eds.: F. Darvas, V. Hessel, G. Dorman), De Gruyter, Berlin, **2014**, pp. 139–152.