Continuous Suzuki–Miyaura Reactions with Novel Ce–Sn–Pd Oxides and Integrated Crystallization as Continuous Downstream Protocol

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An integrated process including continuous-flow syntheses directly coupled to product isolation via continuous crystallization is presented. For the synthesis part, $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$ was used as heterogeneous catalyst in a custom-made packed-bed reactor (the so-called "Plug and Play" reactor) for continuous Suzuki–Miyaura cross-couplings of various *para*- and *ortho*-substituted bromoarenes with phenylboronic acid using environmentally friendly aqueous ethanolic mixtures as reaction solvents. The reactions were stable for up to 30 h without any detectable catalyst deactivation. The desired biaryl products were obtained in gram scale with good to excellent yields and high selectivity. For three methyl-, ketyl-, and nitrile-functionalized biphenyl products, isolation was done using water as antisolvent in an integrated crystallization process as continuous downstream protocol. The desired products could be isolated with high purity and with yields of up to 95% for the overall process.

Keywords: integrated continuous processes, flow chemistry, Suzuki–Miyaura reaction, heterogeneous catalysis, continuous crystallization

1. Introduction

Over the last years, continuous-flow processes, traditionally applied for the production of petrochemicals, bulk chemicals, and polymers at large scales, have gained more and more attention also for the production of fine chemicals, active pharmaceutical ingredients (APIs), and agrochemicals [1, 2]. Several examples for continuous multistep API syntheses or even end-to-end manufacturing plants have been reported [3–9] and reflect the great effort which has been done to establish suitable continuous protocols for the primary and secondary manufacturing of APIs. Although the advantages of continuous processes are well-known [10, 11] (e.g., increased throughput, reduced waste, simplified scale-up or improved safety, especially when hazardous reagents are used [12]), the application of continuous processes is not yet standard practice in pharmaceutical manufacturing, despite the effort of the Federal Drug Administration (FDA) [13, 14]. Economic concerns and the lack of adequately educated personnel, technical challenges (insufficient reliability, leaking), and equipment for production at larger scales are hurdles for the implementation of continuous processes in industry [11]. Thus, the development of stable and reliable continuous synthesis and downstream protocols has an extraordinary high potential as pharmaceutical manufacturing is, despite all difficulties, clearly transitioning toward continuous manufacturing.

We present here a novel continuous setup for an integrated synthesis-crystallization process in flow. In particular, continuous Suzuki–Miyaura reactions were carried out in a packed-bed reactor and the product isolation was done by continuous antisolvent crystallization. Continuous crystallization is a common unit operation for the purification of organic compounds because of its high efficiency, and the low capital and operational costs [15]. In addition to large-scale batch and continuous crystallizers, numerous small-scale semibatch and continuous setups with high-intensity mixers and impeller jets have been reported in literature [16]. Furthermore, particle formation in flow-through devices with inner diameters of few centimeters has been reported. Our group published several studies focusing on the controlled growth of crystals by selecting precise cooling trajectories in continuous-flow crystallizers [15–18].

The coupling of a chemical reaction in flow with a continuous purification is a step further in the development of completely continuous end-to-end manufacturing and has become more and more popular in recent years [9, 19]. Probably the most well-known example is the work by the MIT–Novartis Center for the end-to-end manufacturing of the API aliskiren hemifumarate [8].

In our work, $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$ was used as heterogeneous catalyst in a custom-made packed-bed reactor (the so-called "Plug and Play" reactor) for continuous Suzuki–Miyaura cross-couplings of various *para*- and *ortho*-substituted bromoarenes with phenylboronic acids. The synthesis setup was directly coupled to a continuous crystallization process to obtain the crystalline products with high purity.

Palladium-substituted cerium and mixed cerium–tin oxides can be prepared by the solution combustion technique [20]. Using this method, palladium-substituted ceria and ceria composites can be synthesized at the gram scale, out of inexpensive precursors, in an easy and rapid manner (within a few hours) with standard laboratory equipment and without specialized working techniques. Furthermore, due to the homogeneous mixing of the catalyst precursors at the molecular level and the high combustion temperature (>900 °C) [21], this method guarantees high crystallinity, high purity, large specific surface areas, and precise elemental and phase composition of the resulting mixed oxides [22]. Initially developed as catalysts for gas-phase oxidation reactions [23], catalysts of this type also proved to be highly active and reusable ligand-free catalysts for Heck-type C–C coupling reactions [24].

Palladium catalyzed cross-coupling reactions, used for the formation of carbon–carbon and carbon–heteroatom bonds, are an indispensable synthetic tool for organic chemists and are widely used in the production of fine chemicals, APIs, and agrochemicals [25–27]. Among the different types of cross-coupling reactions, the Suzuki–Miyaura reaction is by far the most popular reaction in terms of publications and patents [28]. Initially published by Miyaura and Suzuki in 1979 [29], this reaction involves the coupling of organoborons with organic halides, catalyzed by palladium and with the aid of an adequate base. To benefit from the numerous advantages of heterogeneously catalyzed processes, especially the easy separation of the palladium containing catalyst from the reaction solution, a high number of heterogeneous catalysts has been developed and applied in Suzuki–Miyaura cross-coupling reactions [30]. Commonly used solid supports for the immobilization of palladium on organically modified and ligand-

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free systems include silica, polymers beads, monolithic supports, and PdEnCatTM [31]. Although many of these systems show good activity and recyclability when used in batch processes, such heterogeneous catalysts often suffer from rapid deactivation and significant palladium leaching into the solution when used in continuous-flow packed-bed reactors [32]. This phenomenon is attributed to a homogeneous mechanism of the cross-coupling reaction, involving soluble Pd(II) species during the oxidative addition step. The good recyclability in batch reactions is assigned to a readsorption of palladium on the solid support upon completion of the reaction (assuming the solid support as reservoir for catalytically active palladium) [33–36]. Using continuous-flow packed-bed reactors, soluble palladium will migrate through the packed catalyst bed (as in chromatography), which leads to elution of palladium into the reaction solution, contamination of the product and finally to catalyst deactivation [37, 38]. Hence, some authors propagate the use of homogeneous catalytic systems in continuous flow, combined with appropriate catalyst recycling strategies [39] or recirculating reactors [40] rather than packed-bed flow reactors [32, 37, 38]. Nevertheless, Pandarus et al. [41] reported the use of Sol–Gel Entrapped SiliaCat DPP-Pd as suitable heterogeneous catalyst for Suzuki–Miyaura cross-coupling reactions in a continuous packed-bed reactor. In this study, continuous processes for the synthesis of unsymmetrical biaryls with moderate to high yields and low palladium contents in the isolated product, which were stable for up to 40 h, could be established. Thus, the realization of stable continuous processes using packed-bed reactors with heterogeneous palladium catalysts appears to be principally possible when the appropriate catalyst–solvent–base systems are used.

2. Results and Discussion

2.1. Continuous-Flow Process Design. The continuous Suzuki–Miyaura reactions were carried out in the so-called "Plug and Play" reactor, which was developed by us together with OneA Engineering [42, 43]. This novel reaction device (Figure 1) includes three modules arranged in a sandwich approach: at the bottom and the top, two heating modules, and in the middle, the reaction module. The reaction module includes two openings in which commercial high-performance liquid chromatography (HPLC) columns ($L \times D$: 40 mm × 8.0 mm) filled with the catalyst particles can be introduced.

The reaction mixtures were premixed and pumped through the reactor using an HPLC pump. First, the media were preheated in the heating modules. They include U-shaped tubes (1 mm inner diameter) that are embedded in six channels (Figure 1, right) filled with thermostatic oil in order to allow rapid heat transfer. The reaction media enters then the catalyst bed in the HPLC columns via an isolated capillary that connects the heating module with the reaction modules (not shown in Figure 1).

The use of this reaction setup enables a significant variation of reaction parameters. The HLPC pump allows flow rates of the reaction solution between 0.1 mL/min and (theoretically) 50 mL/min. The amount of catalyst can be adjusted to the desired synthesis by using larger HPLC columns or by employment of multiple reaction modules in line. The reactor itself allows reaction temperatures of up to 200 °C and a pressure of up to 40 bar. Flow rates, temperature, and the pressure inside the system were continuously monitored using the software LabView.

2.2. Continuous Suzuki–Miyaura Reaction. The continuous Suzuki–Miyaura reactions were carried out using a bed of the $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$ particles in the HPLC columns.

Figure 2a shows the reaction progress of 4-bromotoluene vs. time for the continuous synthesis of 4-methylbiphenyl using one reaction module (1.10 g catalyst) at a flow rate of 0.45 mL/min and a temperature of 86 °C. The conversion profiles using $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$ as catalyst in continuous flow generally show an initial phase, which is characterized by a rapid decrease of substrate conversion. After this initial phase, the process enters a phase of constant substrate conversion and product yield (with an average conversion of 50.6% of 4-bromotoluene during the period between 120 and 930 min). The initial phase is also characterized by a visually recognizable, significant loss of palladium by leaching into the reaction solution. This was confirmed using inductively coupled plasma optical emission spectrometry (ICP-OES) analysis. As expected, the first fraction, deriving from the initial phase (120 min), showed a very high content of palladium (13.5 g/kg dried solid). However, the Pd content of the fractions taken from the period of constant conversion (120–930 min) was below the limit of quantitation of the applied analytic method (<10 mg/kg dried solid) in every sample.

Figure 2b shows the same reaction, using two reaction modules (2.41 g catalyst) at the same flow rate (0.45 mL/min). Due to the limited solubility of the product 4-methylbiphenyl in the applied reaction solvent (EtOH–H_2O = 6:4 *v*/*v*), the concentration of the substrate 4-bromotoluene had to be reduced from 58 mmol/L to 47 mmol/L to prevent precipitation of the product and subsequent blocking of the system at the reactor outlet at higher conversion. The use of a third reaction module (3.67 g catalyst) and an increase of temperature to 91 °C led to an almost complete conversion of 4-bromotoluene (93.2% average conversion in the period between 120 and 450 min, Figure 2c). In this experiment, also higher flow rates were applied (450–750 min: 0.675 ml/min, average conversion: 91.1%, 750–1050 min: 0.9 mL/min, average conversion: 90.0%). Due to the higher temperature of 91 °C, product solubility in the outlet stream could be enhanced and system blocking did not occur even at high conversion rates. In each experiment depicted in Figure 2, a stable process without observable catalyst deactivation could be established for at least 15 h using various substrate concentrations, flow rates, and temperatures.

In order to test the performance of the catalyst at high conversion levels for a longer period, a long-time experiment using three reaction modules at 91 °C was performed (Figure 3).

In this case, the flow rate was reduced after 120 min from 0.45 mL/min to 0.225 mL/min. Using these reaction conditions,

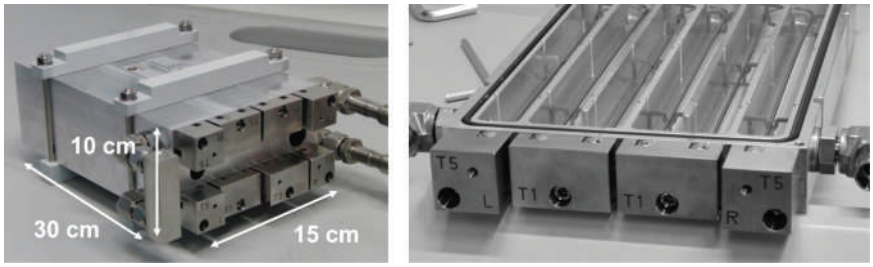


Figure 1. Pictures of the "Plug and Play" reactor. Left: The reactor with the heating modules (top and bottom) and the reaction module in the middle. Right: Inner view of the heating modules that include U-shaped tubes in which the reaction media is preheated

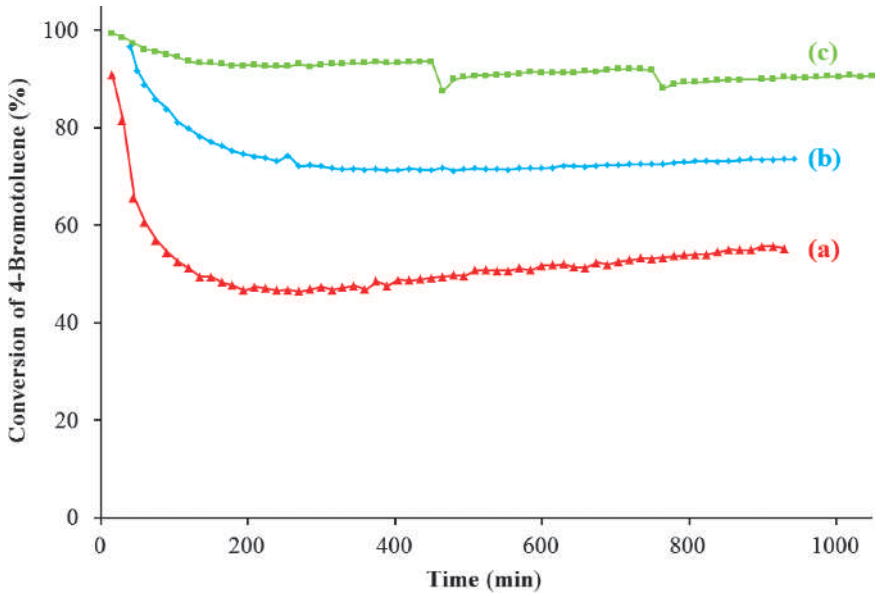


Figure 2. Continuous synthesis of 4-methylbiphenyl out of 4-bromotoluene and phenylboronic acid using one (a), two (b), and three (c) reaction modules at different flow rates, substrate concentrations, and temperatures

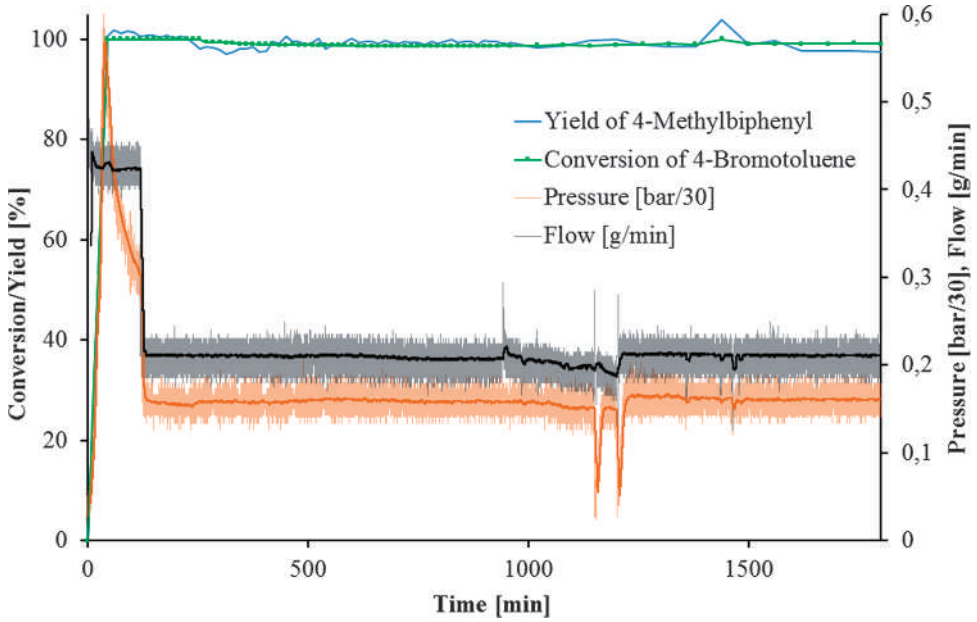


Figure 3. Continuous synthesis of 4-methylbiphenyl out of 4-bromotoluene and phenylboronic acid: long-time experiment (30 h) using three reaction modules, flow rate of 0.225 mL/min

an average conversion of 99% could be reached for more than 30 h. The time scale of the performed continuous reaction experiments was chosen based on other studies for continuous Pd-catalyzed C–C coupling reactions (Suzuki, Heck, and Negishi couplings) in single-pass packed-bed flow reactors (2 and 40 h) [41, 44–47]. To the best of our knowledge, Pandarus et al. [41] set the benchmark for a stable single-pass packed-bed flow process with 30 for the synthesis of 4-methoxybiphenyl. In order to reach this benchmark in terms of stability, our long-time experiments were performed for a period of 30 h. Since rapidly deactivating catalysts for Suzuki and Heck reactions can undergo dramatic loss of reactivity in less than 2 h [48], the experiments using other substrates than 4-bromotoluene were performed with reaction times of 15 and 9 h, respectively. In all these experiments, no deactivation of the catalyst was observed. Future work will concentrate on studying the overall life time of the catalytic material.

Figure 3 also shows, in addition to the substrate conversion vs. time, the measured mass flow and the obtained system pressure, as well as the product yield over time. As can be seen, the yield of 4-methylbiphenyl, also determined by HPLC analysis, equaled the measured conversion of 4-bromotoluene to the greatest extent within the error limits of the HPLC method. Together with the low amounts of homocoupling side products biphenyl (originating from the homocoupling of phenylboronic acid, average concentration of 0.17 mmol/L) and 4,4′-dimethylbiphenyl (homocoupling product of 4-bromotoluene, average concentration of 0.024 mmol/L) and the complete absence of other side products (protodeboronation product benzene, boronic acid oxidation product phenol, and dehalogenation product toluene) in the chromatograms, this proves the extraordinarily high selectivity of the process (99.6% in the period between 120 and 1800 min).

Another important feature, which illustrates the high robustness of the process, is the constant system pressure over time, which indicates the absence of precipitating products or side products inside the catalyst bed. During the experiment depicted in Figure 3, flushing of the HPLC with pure reaction solvent was necessary twice due to decreasing mass flow rates (indicated by the sudden drop of system pressure after 1150 and 1200 min). However, these short interruptions of the process did not lead to any observable change of the catalyst performance regarding substrate conversion, product yield, or pressure in the subsequent process period.

In further experiments, the catalyst performance for the reaction of different 2- and 4-substituted bromoarenes with phenylboronic acid was tested for the synthesis of 4-methylbiphenyl, biphenyl-4-carbonitrile, biphenyl-4-methanol, and 4-phenylphenol, using approximately 1.25 g of catalyst (1 reaction module) at a flow rate of 0.45 mL/min and a temperature of 90 °C.

The initial concentration of the aryl-bromide varied between 40 and 50 mmol/L, dependent on the solubility of the reaction educts and products in the applied reaction solvent. Furthermore, 2-bromobenzonitrile and 5-bromo-1-indanone were reacted with phenylboronic acid in shorter experiments (9 h). The applied reaction parameters and the observed product yields, selectivities, and turnover frequencies for each reaction are summarized in Table 1. Detailed illustrations including conversions, yields, system pressure, and flow rates of each reaction are given in Supporting Information.

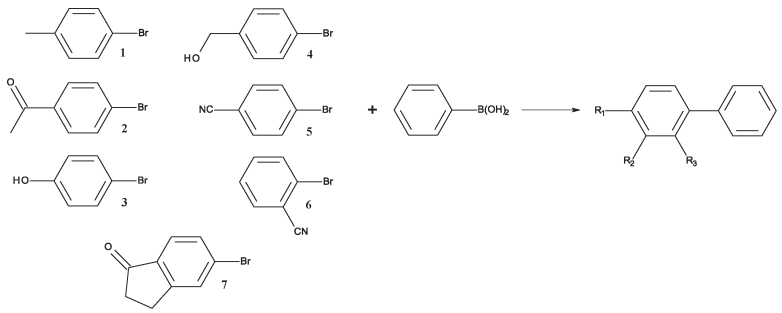
In all experiments, except for the synthesis of 4-phenylphenol, stable processes without any observable deactivation of the catalyst after the initial phase could be established (Figure 4). Preliminary experiments have shown that the catalyst lifetime is massively influenced by the choice of the reaction solvent, i.e., in this study especially the ratio of ethanol and water as the solvent mixture. In general, higher ratios of water lead to improved catalyst stability but decrease the solubility of the arylbromides as well as the solubility of the biphenyl products. When 4-bromophenol was used as a substrate, a slight but continuous decrease of product yield could be observed (from 77% after 120 min to 68% after 900 min), although a higher ratio of water in the reaction solvent was used for the synthesis of 4-phenylphenol (EtOH–H_2O = 1:1 *v*/*v*, compared to EtOH–H_2O = 6:4 in all other experiments). Nevertheless, we assume that a further optimization of the reaction solvent could be a suitable strategy to enhance catalyst stability also in this reaction.

As expected, bromoarene substrates bearing electron withdrawing groups in *para*-position (4-bromoacetophenone, 4-bromobenzonitrile, 5-bromo-1-indanone) showed higher reactivity than substrates with more electron releasing substituents (4-bromotoluene, 4-bromophenol, 4 bromobenzyl alcohol). The lowest reaction rates were observed for the coupling reaction of the sterically more demanding 2-bromobenzonitrile with phenylboronic acid. Nevertheless, also biphenyl-2-benzonitrile could be synthesized with 78 mg/h and with yields >80%.

In general, the described method using $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$ as heterogeneous catalyst in a fixed-bed reactor proved to be a convenient, uncomplicated, and reliable procedure for the synthesis of substituted biphenyls at good to excellent yields and extraordinarily high selectivities on a scale of up to 10 g per day.

2.3. Continuous Crystallization. In order to continuously separate the reaction product from the reaction solvent, a continuous crystallization unit was attached to the reactor outlet. The integrated synthesis and crystallization process is illustrated in a flow sheet in Figure 5. To show the flexibility of the setup,

Table 1. Continuous Suzuki–Miyaura cross-coupling reaction of phenylboronic acid with various bromoarenes, using $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$ as catalyst and K_2CO_3 as base: reaction parameters and summarized results



Entry	Bromide	Conc. (mmol/L)	Solvent H_2O–EtOH[a]	Cat. (g)[b]	*T* (°C)	Flow (mL/min)	t^R (min)[c]	Yield (%)[d]	Sel. (%)[e]	Prod. (mg/h)	TOF (h^{-1})[f]
1	**1**	58.5	6:4	1.09	86	0.45	4	51.8	99.6	138	12.1
2		46.8	6:4	2.41	86	0.45	8	73.1	99.8	155	6.2
3		46.8	6:4	3.72	91	0.225	24	99.1	99.5	105	2.7
4		46.8	6:4	3.67	91	0.45	12	93.2	99.8	198	5.2
5						0.675	9	91.1	99.8	290	7.6
6						0.90	6	90.1	99.8	383	10.0
7	**2**	40	6:4	1.22	90	0.45	4	97.7	99.7	207	13.9
8	**3**	50	1:1	1.28	90	0.45	4	74.8	98.7	172	12.7
9	**4**	45	6:4	1.27	90	0.45	4	74.3	99.8	166	11.5
	5	45	6:4	1.26	90	0.45	4	93.6	99.6	204	14.6
11	**6**	40	6:4	4.06	90	0.225	24	80.9[g]	99.2	78	1.7
12	**7**	35	6:4	1.28	90	0.45	4	93.4	99.6	184	11.1

[a] Solvent ratios in *v*/*v*.
[b] 1 g of catalyst corresponds to 6.6 mg or 0.062 mmol palladium.
[c] Residence time in the reaction modules.
[d] Average yields, determined by HPLC analysis after the initial process phase (120 min) or at constant process yield (entries 5 and 6).
[e] Calculated as $c_{\text{Heterocoupling Product}}/(c_{\text{Heterocoupling Product}} + c_{\text{Homocoupling Products}})$, averages after the initial process phase (120 min) or at constant process yield (entries 5 and 6).
[f] Turnover frequencies were calculated from the volumetric flow rate, u_V (L/h); the product yield, *Y* (%); the concentration of arylbromide substrate, c_{ArX} (mol/L); the catalyst mass, m_{Cat} (g); and the palladium content of the catalyst, $c_{Pd,Cat}$ (mol/g), using the equation: $\text{TOF} = \frac{u_V * Y * c_{ArX}}{m_{Cat} * c_{Pd,\,Cat}}$.
[g] Initial phase: 180 min.

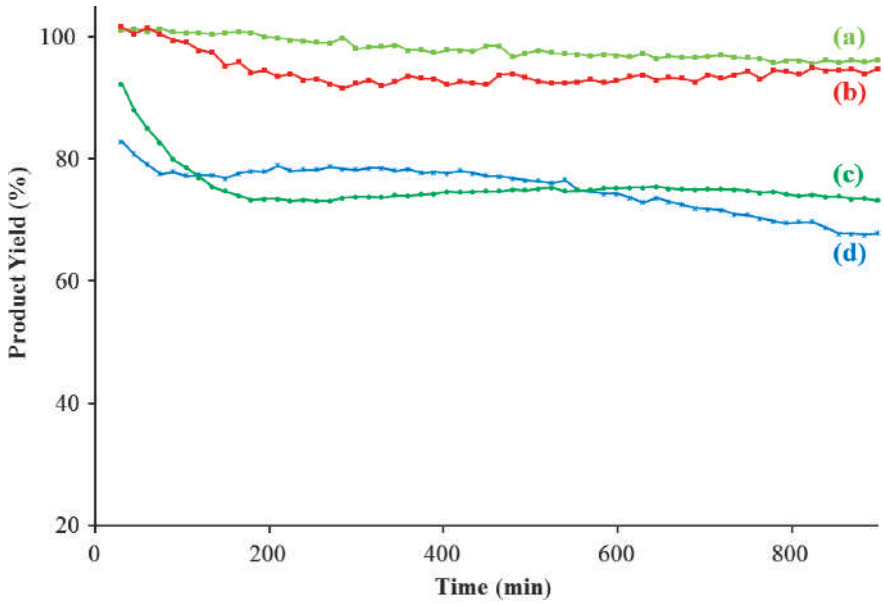


Figure 4. Continuous synthesis of 4-acetylbiphenyl (a), biphenyl-4-carbonitrile (b), biphenyl-4-methanol (c), and 4-phenylphenol (d). Product yields were determined by HPLC analysis

continuous crystallization was carried out for three reaction products: 4-methylbiphenyl, 4-acetylbiphenyl, and biphenyl-4-carbonitrile. A summary of all reaction and crystallization conditions is given in Table 2.

Crystallization of the product was achieved by addition of water as antisolvent and subsequent cooling of the reaction mixture. In preliminary experiments, the biphenyl products bearing hydroxyl groups (4-phenylphenol and biphenyl-4-methanol) showed considerable solubility in the ethanol–water mixtures, indicating that the use of water as antisolvent is not the ideal separation strategy for hydroxyl-functionalized biphenyls. In contrast, methyl-, ketyl-, and nitrile-functionalized biphenyls proved to be more suitable substances for crystallization using water as antisolvent. In this study, three products, which represent examples for each of these functional groups (4-methylbiphenyl, 4-acetylbiphenyl, and biphenyl-4-carbonitrile representatively for methyl-, ketyl-, and nitrile-functionalized biphenyls) were isolated in an integrated continuous crystallization process directly after synthesis. The amount of added antisolvent as well as the temperature during crystallization was adapted for each product in order to maximize the yield of the crystallized product but, at the same time, to minimize the product agglomeration in the crystallization tube and to prevent system clogging.

The crystallization was carried out under ultrasonic irradiation at temperatures between 8 and 20 °C. The addition of the antisolvent was done via a Y junction, which was placed directly in the cooled ultrasonic bath for the crystallization of 4-acetylbiphenyl. For the crystallization of biphenyl-4-benzonitrile and 4-methylbiphenyl, the reaction solvent as well as the antisolvent was preheated before mixing. Both preheating and crystallization under ultrasonic irradiation were done to prevent precipitation of the product inside the Y junction and product agglomeration in the crystallization tube which would decrease product yields and/or to clogging of the crystallization system. The crystallized product was finally separated from the reaction solvent by filtration using a glass frit.

To guarantee practically full conversion of the substrates, two reaction modules filled with catalyst were used for the synthesis of 4-acetylbiphenyl and biphenyl-4-carbonitrile. After the

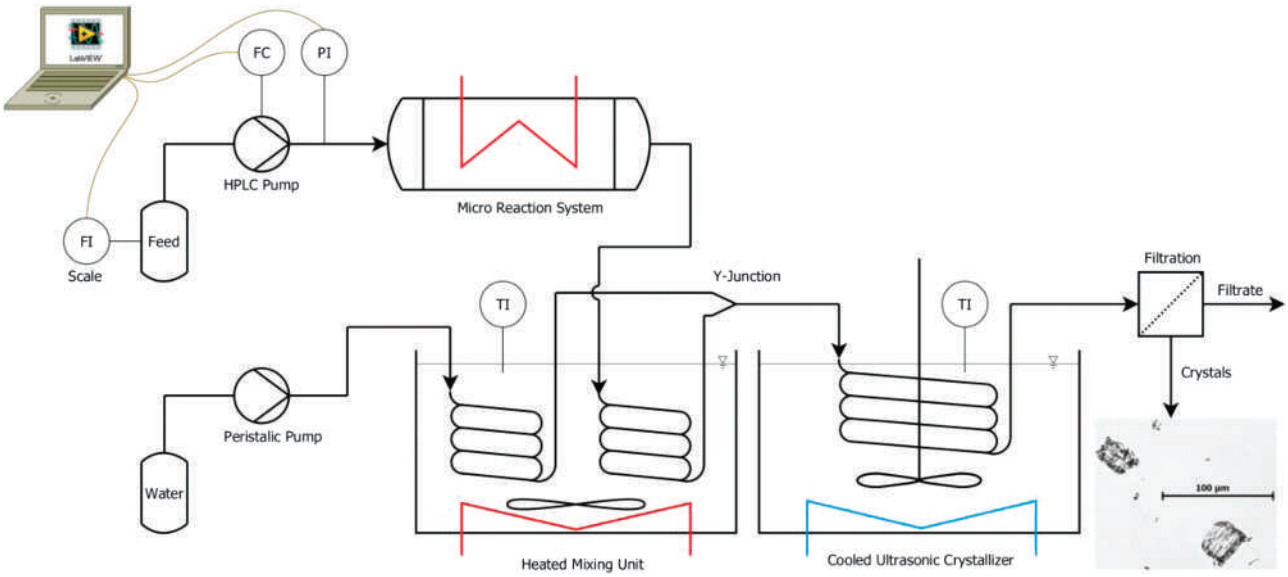
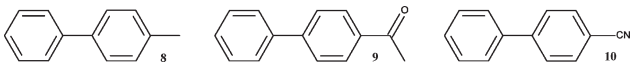


Figure 5. Integrated process for the continuous synthesis and subsequent continuous crystallization of 4-acetylbiphenyl, biphenyl-4-carbonitrile, and 4-methylbiphenyl

Table 2. Process parameters and summarized results for the integrated continuous synthesis and crystallization of 4-methylbiphenyl (**8**), 4-acetylbiphenyl (**9**), and biphenyl-4-carbonitrile (**10**)



Entry	Bromide	$c_{Bromide}$ (mmol/L)	Product	T_R[a] (°C)	m_{Cat} (g)	Flow RS[b] (mL/min)	Flow AS[c] (mL/min)	T_{Mix}[d] (°C)	T_{Cry}[e] (°C)	$Y_{Syn.}$[f] (%)	Y[g] (%)	Prod. (mg/h)
1	**1**	50	**8**	90	3.59	0.45	0.3	70	20	>99	67	151
2	**2**	40	**9**	90	2.70	0.45	0.1	RT	8	>99	89	189
3							0.3	RT	8	>99	92	194
4							0.5	RT	8	>99	96	204
5	**5**	45	**10**	90	2.40	0.45	0.3	80	8	>99	91	198

[a] Temperature for the continuous synthesis reaction.
[b] Flow rate of the reaction solvent during biphenyl synthesis.
[c] Flow rate of the antisolvent (water).
[d] Temperature at the mixing point (Y junction).
[e] Crystallization temperature in the cooled ultrasonic bath.
[f] Yield of the continuous synthesis process, determined by HPLC analysis.
[g] Yield of the overall process, determined gravimetrically after drying of the product in a desiccator at reduced pressure.

abovementioned initial phase (120 min) of considerable palladium leaching, the continuous synthesis unit was connected with the crystallization unit. During crystallization of 4-acetylbiphenyl (entries 2–4), three different operating points, characterized by three different flow rates of the antisolvent (0.1, 0.3, and 0.5 mL/min) were examined successively in a single experiment. For each operating point, the flow rate of antisolvent was kept constant for 3 h. After increasing the flow rate, the system was allowed to equilibrate for half an hour. Product collection was started after the equilibration time again and was continued for another 3 h. Thus, the overall process was run for 13 h (crystallization process: 11 h) at excellent yields of the isolated product (89–96%). During this time, no considerable pressure increase or visually recognizable clogging could be observed.

Biphenyl-4-carbonitrile was continuously crystallized using one operating point (flow of antisolvent: 0.3 mL/min) for a period of 5 h. Due to product precipitation at the mixing point (Y junction), when water was added at room temperature, the reaction solution as well as the antisolvent had to be preheated before mixing. Using preheated solvents, clogging of the Y junction and pressure increase could be avoided and biphenyl-4-carbonitrile could be isolated with high yield (91%).

The lowest overall product yields were obtained for the crystallization of 4-methylbiphenyl. At low temperatures, product deposition at the walls of the crystallization tube was observed despite ultrasonic irradiation. Hence, the crystallization temperature had to be increased to 20 °C at an antisolvent flow rate of 0.3 mL/min. Under these conditions, the product could not be quantitatively crystallized from the reaction mixture. However, an overall process yield of 67% could be achieved.

The amount of side products in the crystallized products was determined by means of HPLC measurements. Besides the desired product peak, only one peak, which was assigned to the boronic acid homocoupling product biphenyl, could be observed in the chromatograms of all tested final products. Phenylboronic acid, arylbromide substrates, or other side products could not be detected. Hence, the crystallization process not only acts as separation process for the organic compounds but also represents a purification process, especially for reactions, where a complete conversion of the bromide substrate cannot be achieved (as it was the case for the synthesis of 4-methylbiphenyl). The degree of contamination of the final products with the catalyst metals cerium, tin, and palladium was analyzed by means of ICP-MS. The amounts of residual metal in the low ppm range prove the high stability and leaching resistance of the employed catalyst. The results of these analyses are summarized in Table 3.

The particle size distribution of the crystallized products was analyzed using laser diffraction (HELOS Sympatec). All obtained crystals are plate shaped (see Figure 5 for an example of a 4-methylbiphenyl crystal). For 4-methylbiphenyl, the largest particles were obtained (x_{10}: 14 μm, x_{90}: 100 μm), the other products have a particle size in the range of ~3 μm (x_{10}) to ~30–46 μm (x_{90}) (Table 4) and a monomodal q_3 density distribution (Figure 6). As described above, 4-acetylbiphenyl (**9**) was crystallized using three different operation parameters (antisolvent flow rates from 0.1 to 0.5 mL/min); however, these parameters did not notably influence the particle size of the crystals.

3. Conclusions

In this study, seven different substituted arylbromides were coupled with phenylboronic acid in a continuous-flow packed-bed reactor using the Suzuki–Miyaura cross-coupling reaction. The palladium-substituted mixed cerium–tin oxide $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$ catalyst did not show any deactivation

Table 3. Amounts of the side-product biphenyl and the catalyst metals cerium, tin and palladium in the final product

Entry	Product	Biphenyl (g/kg)[a]	Ce (mg/kg)[b]	Sn (mg/kg)[b]	Pd (mg/kg)[b]
1	**8**	2.0	1.9 ± 1.1	0.39. ± 0.25	1.1 ± 0.1
2	**9.1**	0.4	0.12 ± 0.01	0.20 ± 0.05	0.28 ± 0.01
3	**9.2**	0.7	0.83 ± 0.03	0.19 ± 0.04	0.96 ± 0.1
4	**9.3**	0.4	0.17 ± 0.08	0.21 ± 0.05	0.59 ± 0.04
5	**10**	3.6	0.54 ± 0.07	0.26 ± 0.06	2.1 ± 0.1

[a] Determined by HPLC analysis.
[b] Determined by ICP–MS analysis.

Table 4. Characteristic mean diameters x_{10}, x_{50}, and x_{90} of the obtained crystals

Entry	Product	x_{10} (μm)	x_{50} (μm)	x_{90} (μm)
1	**8**	13.9	41.7	100.3
2	**9.1**[a]	3.0	14.5	46.5
3	**9.2**[b]	2.8	11.8	37.0
4	**9.3**[c]	2.7	15	46.4
5	**10**	2.7	11.1	32.6

[a] Flow rate of antisolvent: 0.1 mL/min (operating point 1).
[b] Flow rate of antisolvent: 0.3 mL/min (operating point 2).
[c] Flow rate of antisolvent: 0.5 mL/min (operating point 3).

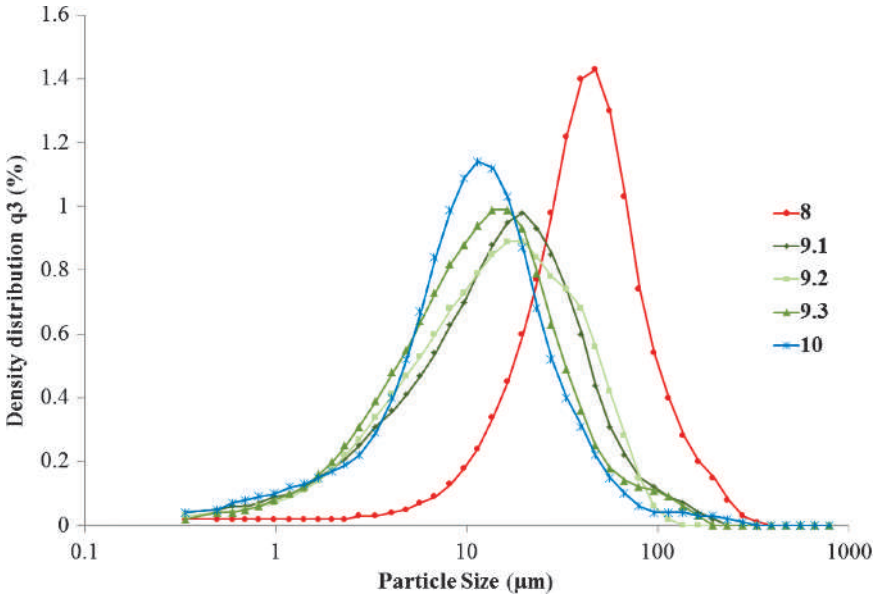


Figure 6. Particle size distribution of the obtained crystals

over 30 h. The desired biphenyls could be synthesized in good to high yields and very high selectivities on a scale of 78–383 mg/h, depending on the reaction partners and the applied reaction conditions. Three continuously synthesized biphenyls (4-methylbiphenyl, 4-acetylbipheny, and biphenyl-4-carbonitrile) were isolated out of the reaction solution using a directly coupled continuous crystallization process. Continuous crystallization of the products was achieved by addition of water as antisolvent and subsequent cooling of the mother liquor in an ultrasonic bath. Using the integrated continuous synthesis/crystallization process, overall process yields of up to 96% on a scale of 151–204 mg/h (up to ~5 g/day) were achieved.

All in all, the described process allows the easy and reliable continuous production and isolation of various substituted biphenyls at excellent yields and high purities. Minimal amounts of metals, especially palladium in the final product at the low ppm level, indicate the high stability and good leaching resistance of the employed inorganic catalyst. Furthermore, the use of the "green solvents" ethanol and water throughout the whole synthesis and crystallization procedure can be seen as main advantage of the described process and indicates the potential for an application on a larger scale.

4. Experimental

All chemicals were purchased from commercial suppliers and used as received, except for phenylboronic acid, which was recrystallized from water prior to use.

4.1. Catalyst Synthesis. $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$ was synthesized using a modification of the solution combustion method reported by Baidya et al. For the production of 3 g of $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$, 5.000 g ammonium cerium(IV) nitrate, 1.861 g tin(II) oxalate, 0.033 g palladium(II) chloride, and 3.294 g glycine (fuel) were thoroughly mixed by grinding the components using mortar and pestle. The solid mixture was suspended in 2 mL of water in a borosilicate dish with 600 mL capacity. The suspension was treated in an ultrasonic bath, until a viscous but clear solution was formed. The mixture was placed in a muffle furnace at 350 °C, which led to an ignition of the redox mixture within less than 5 min. The resulting spongiform, voluminous, and porous solid was ground with mortar and pestle and was heated for another 5 h at 350 °C. After that procedure, the synthesized oxide was directly usable as catalyst. The catalyst itself appears as porous, light brown, and powderly solid with a particle size of ~190 µm (x_{10} = 5.5 µm, x_{50} = 33.8 µm, x_{90} = 189.4 µm). The X-ray diffraction (XRD) spectra of the particles clearly show that PdO or metallic Pd species could not be observed and a cubic/tetragonal mixed phase structure was observed.

4.2. Continuous Suzuki–Miyaura Reaction. For continuous Suzuki–Miyaura reactions, the arylbromide (35–50 mmol/L, depending on the solubility of the arylbromide and the corresponding biphenyl product), 1.5 molecular equivalents of phenylboronic acid, 1.5 molecular equivalents of base (potassium carbonate), and anisole (internal standard for the HPLC analysis, 1 g/L) were dissolved in the reaction solvent (EtOH–water = 6:4 *v*/*v*, except for the synthesis of 4-phenylphenol, where a reaction solvent of EtOH–water = 1:1 *v*/*v* was used) and degassed in an ultrasonic bath for 30 min. Pumping of the reaction mixture through the Plug and Play reactor was done using an HPLC pump (Knauer, Azura P4.1 S) at flow rates between 0.225 and 0.9 mL/min. The pressure inside the system was monitored via the internal pressure sensor of the HPLC pump. The mass flow was observed using a balance (Kern EWJ600-2 M), which was connected via a serial RS-232 to a PC. The acquisition of the observed data (pressure, system pressure) was done using the software LabView. The reactor was externally heated using a Lauda P10 Proline thermostat and Lauda Ultra 350 as heating medium. The temperature was monitored using a K-type thermocouple attached to the outside of the HPLC column.

To monitor the reaction progress, HPLC samples were drawn at an interval of 15 min from the outlet of the reactor. The samples were analyzed using an Agilent 1100 Series HPLC, equipped with a Poroshell 120 EC-C18 separation column. Mixtures of ultrapure water, methanol, and orthophosphoric acid were used as mobile phase for HPLC analysis. Detailed descriptions of the applied HPLC methods are given in Supporting Information.

In this study, the amount of catalyst was generally adjusted to the synthetic problem by employing one, two or three standard HPLC columns ($L \times D$: 40 mm × 8.0 mm), each filled with approximately 1.25 g of catalyst (corresponding to 6.7 mg or 0.08 mmol palladium), as reaction modules.

4.3. Continuous Crystallization. Continuous crystallization of the synthesized product was done by addition of antisolvent (water) and a subsequent cooling of the mother liquor. The crystallization was done in a polyfluorethylenpropylene (FEP) tube (length: 4 m, I.D.: 2 mm, O.D.: 4 mm), which was immersed in an ultrasonic bath (Elma Transsonic 780). A Lauda Alpha RA 12 was used as external cryostat to cool the ultrasonic bath. The addition of water (antisolvent) via a polypropylene Y junction was done using an Ismatec Regio Digital MS-4/6-100 peristaltic pump. For the crystallization of 4-methylbiphenyl and biphenyl-4-carbonitrile, the antisolvent as well as the reaction solvent had to be preheated before mixing to avoid product precipitation in the Y junction. This was done in a water bath which was heated by a Heidolph MR 3001 K magnetic stirrer. At the outlet of the crystallization unit, the solid product was separated from the mother liquor by filtration using a glass frit connected to a water aspirator. After separation, the solid product was dried in a desiccator at room temperature under reduced pressure for several days.

ICP-MS measurements were performed on an Agilent 7500ce ICP-MS after microwave-assisted acidic digestion of the samples.

The particle size measurements were conducted with a HELOS/KR (Sympatec) Laser diffraction sensor. For the measurements, the particles were suspended in a water solution containing Tween 20 as tenside.

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Supporting Information

Electronic Supplementary Material (ESM) is available in the online version at doi: 10.1556/1846.2016.00021.

References

1. Wiles, C.; Watts, P. *Green Chem.* **2014**, *16*, 55–62.
2. Newman, S. G.; Jensen, K. F. *Green Chem.* **2013**, *15,* 1456–1472.
3. Hopkin, M. D.; Baxendale, I. R.; Ley, S. V. *Org. Biomol. Chem.* **2013**, *11,* 1822–1839.
4. Hartwig, J.; Ceylan, S.; Kupracz, K.; Coutable, K.; Kirschning, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 9813–9817.
5. Snead, D. R.; Jamison, T. F. *Chem. Sci.* **2013**, *4*, 2822–2827.
6. Bogdan, A. R.; Poe, S. L.; Kubis, D. C.; J. Broadwater, S. J.; McQuade, D. T. *Angew. Chem., Int. Ed.* **2009**, *48*, 8547–8550.
7. Heider, P. L.; Born, S. C.; Basak, S.; Benyahia, B.; Lakerveld, R.; Zhang, H.; Hogan, R.; Buchbinder, L.; Wolfe, A.; Mascia, S.; Evans, J. M. B.; Jamison, T. F.; Jensen, K. F. *Org. Process Res. Dev.* **2014**, *18*, 402–409.
8. Mascia, S.; Heider, P. L.; Zhang, H.; Lakerveld, R.; Benyahia, B.; Barton, P. I.; Braatz, R. D.; Cooney, C. L.; Evans, J. M. B.; Jamison, T. F.; Jensen, K. F.; Myerson, A. S.; Trout, B. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 12359–12363.
9. Adamo, A.; Beingessner, R. L.; Behnam, M.; Chen, J.; Jamison, T. F.; Jensen, K. F.; Monbaliu, J-.C. M.; Myerson, A. S.; Revalor, E. M.; Snead, D. R.; Stelzer, T.; Weeranoppanant, N.; Wong, S. Y.; Zhang, P. *Science* **2016**, *352*, 61–67.
10. Poechlauer, P.; Colberg, J.; Fisher, E.; Jansen, M.; Johnson, M. D.; Koenig, S. G.; Lawler, M.; Laporte, T.; Manley, J.; Martin, B.; O'Kearney-McMullan, A. *Org. Process Res. Dev.* **2013**, *17*, 1472–1478.
11. Poechlauer, P.; Manley, J.; Broxterman, R.; Gregertsen, B.; Ridemark, M. *Org. Process Res. Dev.* **2012**, *16*, 1586–1590.
12. Gutmann, B.; Cantillo, D.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2015**, *54*, 6688–6728.
13. Chatterjee, S. *IFPAC Annu. Meet.* **2012**.
14. PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, Guidance for Industry, Food and Drug Administration, Silver Spring, MD 2004.
15. Besenhard, M. O.; Neugebauer, P.; Ho, C-.D.; Khinast, J. G. *Cryst. Growth Des.* **2015**, *15*, 1683–1691.
16. Eder, R. J. P.; Schrank, S.; Besenhard, M. O.; Roblegg, E.; Gruber-Woelfler, H.; Khinast, J. G. *Cryst. Growth Des.* **2012**, *12*, 4733–4738.
17. Eder, R. J. P.; Radl, S.; Schmitt, E.; Innerhofer, S.; Maier, M.; Gruber-Woelfler, H.; Khinast, J. G. *Cryst. Growth Des.* **2010**, *10*, 2247–2257.
18. Neugebauer, P.; Khinast, J. G. *Cryst. Growth Des.* **2015**, *15*, 1089–1095.
19. Johnson, M. D.; May, S. A.; Calvin, J. R.; Remacle, J.; Stout, J. R.; Diseroad, W. D.; Zaborenko, N.; Haeberle, B. D.; Sun, W.-M.; Miller, M. T.; Brennan, J. *Org. Process Res. Dev.* **2012**, *16*, 1017–1038.
20. Baidya, T.; Gupta, A.; Deshpandey, P. A.; Madras, G.; Hegde, M. S. *J. Phys. Chem. C* **2009**, *113*, 4059–4068.
21. Dinka, P.; Mukasyan, A. S. *J. Phys. Chem. B* **2005**, *109*, 21627–21633.
22. Deshpande, P. A.; Aruna, S. T.; Madras, G. *Catal. Sci. Technol.* **2011**, *1*, 1683–1691.
23. Hegde, M. S.; Madras, G.; Patil, K. C. *Acc. Chem. Res.* **2009**, *42*, 704–712.
24. Sanjaykumar, S. R.; Mukri, B.; Patil, S.; Madras, G.; Hegde, M. S. *J. Chem. Sci.* **2011**, *123*, 47–54.
25. Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451–3479.
26. Magano, J.; Dunetz, J. R. *Chem. Rev.* **2011**, 2177–2250.
27. Biajoli, A. F. P.; Schwalm, C. S.; Limberger, J.; Claudino, T. S.; Monteiro, A. L. *J. Braz. Chem. Soc.* **2014**, *25*, 2186–2214.
28. Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062–5085.
29. Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, *19*, 866–867.
30. Molnár, Á. *Chem. Rev.* **2011**, *111*, 2251–2320.
31. Noel, T.; Buchwald, S. L. *Chem. Soc. Rev.* **2011**, *40*, 5010–5029.
32. Cantillo, D.; Kappe, C. O. *ChemCatChem* **2014**, *6*, 3286–3305.
33. Kazmaier, U.; Hähn, S.; Weiss, T. D.; Kautenburger, R.; Maier, W. F. *Synlett* **2007**, *16*, 2579–2583.
34. Amoroso, F.; Colussi, S.; Del Zotto, A.; Llorca, J.; Trovarelli, A. *J. Mol. Catal. A Chem.* **2010**, *315*, 197–204.
35. Richardson, J.; Jones, C. *J. Catal.* **2007**, *251*, 80–93.
36. Gruber-Woelfler, H.; Radaschitz, P. F.; Feenstra, P. W.; Haas, W.; Khinast, J. G. *J. Catal.* **2012**, *286*, 30–40.
37. Cantillo, D.; Kappe, C. O. *Chim. Oggi* **2015**, *33*, 6–11.
38. Greco, R.; Goessler, W.; Cantillo, D.; Kappe, C. O. *ACS Catal.* **2015**, *5*, 1303–1312.
39. Peeva, L.; Arbour, J.; Livingston, A. *Org. Process Res. Dev.* **2013**, *17*, 967–975.
40. Pavia, C.; Ballerini, E.; Bivona, L. A.; Giacalone, F.; Aprile, C.; Vaccaro, L.; Gruttadauria, M. *Adv. Synth. Catal.* **2013**, *355*, 2007–2018.
41. Pandarus, V.; Gingras, G.; Béland, F.; Ciriminna, R.; Pagliaro, M. *Org. Process Res. Dev.* **2014**, *18*, 1550–1555.
42. Lichtenegger, G. J.; Gruber-Woelfler, H. *Chim. Oggi* **2015**, *33*, 12–18.
43. Gruber-Woelfler, H.; Schnitzer, H.; Narodoslawsky, M.; Khinast, J. G. *Green Process. Synth.* **2015**, *4*, 51–55.
44. Egle, B.; Muñoz, J.; Alonso, N.; De Borggraeve, W.; de la Hoz, A.; Díaz-Ortiz, A.; Alcázar, J. *J. Flow Chem.* **2013**, *4*, 22–25.
45. Martinez, A.; Krinsky, J. L.; Penafiel, I.; Castillon, S.; Loponov, K.; Lapkin, A.; Godard, C.; Claver, C. *Catal. Sci. Technol.* **2015**, *5*, 310–319.
46. Mateos, C.; Rincón, J. A.; Martín-Hidalgo, B.; Villanueva, *Tetrahedron Lett.* **2014**, *55*, 3701–3705.
47. Phan, N. T. S.; Khan, J.; Styring, P. *Tetrahedron* **2005**, *61*, 12065–12073.
48. Greco, R.; Goessler, W.; Cantillo, D.; Kappe, C. O. *ACS Catal.* **2015**, *5*, 1303–1312.