

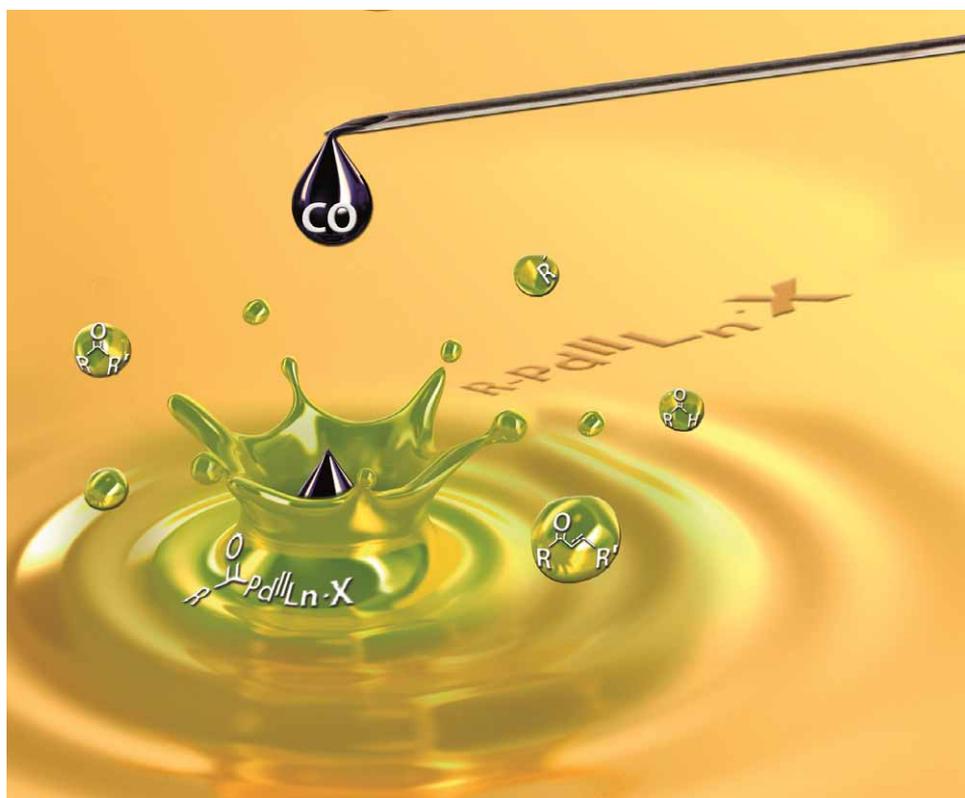
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Akira Suzuki

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CRITICAL REVIEW

Cross-coupling in flow†

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Until recently, cross-coupling reactions have been exclusively performed in batch processes. With the advent of microfluidics, significant effort has been devoted to develop a wide variety of continuous-flow techniques to facilitate organic synthesis. In this *critical review*, we attempt to give an overview of the different continuous-flow methodologies that have been developed and utilized for cross-coupling reactions. In addition, we attempt to point out the advantages of continuous-flow when compared with their batch counterparts (246 references).

1. Introduction

Since the early 1970s,^{1–3} cross-coupling chemistry has received significant attention.^{4,5} These transformations allow for the substitution of an aryl, vinyl and alkyl halide/pseudohalide by a nucleophile in the presence of a transition-metal catalyst. Typically, the mechanism of cross-coupling reactions is comprised of 3 steps: (i) oxidative addition, (ii) transmetalation and (iii) reductive elimination. Most commonly, these reactions involve the formation of a carbon–carbon bond utilizing

a range of different carbon nucleophiles, such as, aryl, vinyl and alkyl derivatives of magnesium (Kumada–Corriu),^{1,2} boron (Suzuki–Miyaura),^{6,7} zinc (Negishi),^{8,9} silicon (Hiyama),¹⁰ tin (Stille–Migita–Kosugi).^{11–14} More recently, the field of cross-coupling has been broadened to include carbon–heteroatom bond forming reactions; the most important of these involve the construction of C–N,^{15–17} C–O^{18,19} and C–S bonds.^{20,21}

The significance of cross-coupling reaction can hardly be overestimated. These methods have impacted the pharmaceutical and other industries, as well as the synthesis of natural products and other biologically active molecules.²² Moreover, they facilitate construction of building blocks for supramolecular chemistry, organic materials and polymers.^{23–25} The development of metal-catalyzed cross-coupling reactions continues to progress dramatically. Notable examples are the development of more active palladium catalysts which allow for lower catalyst loadings,^{26–33} the development of ‘green’ cross-coupling reactions, which involve the use of first-row

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transition metals^{34–37} and the use of water^{38–42} or ionic liquids^{43–44} as a reaction medium, and the employment of microwave technology for reaction rate acceleration.^{45–48}

In the last decade, continuous-flow microreactors have emerged as a new tool for both synthetic and process chemists.^{49–83} These microreactors provide several advantages compared to traditional batch reactors. For example, enhanced heat- and mass-transfer characteristics, safety of operation when using highly exothermic, explosive or toxic reagents, precise control over residence (reaction) time, isolation of sensitive reactions from air and moisture, high surface-to-volume ratio, the possibility of automation and the ease of scale-up or operating several devices in parallel (numbering up). In addition, these microreactors allow for integration of several reaction steps and subsequent separations in one single streamlined process, which results in a significant time-gain compared to traditional batch processes.

As a consequence of these advantages, the use of continuous-flow reactors has attracted a considerable amount of interest from the pharmaceutical industry.^{84,85} Currently, the pharmaceutical industry employs a batch-based manufacturing system, which is costly and time inefficient. Moreover, typical batch processes are carried out at different locations of a pharmaceutical plant resulting into many interruptions and requiring larger production facilities. In times of increasing environmental awareness and industrial efficiency, the implementation of continuous-flow technology is becoming a point of emphasis for many pharmaceutical companies.

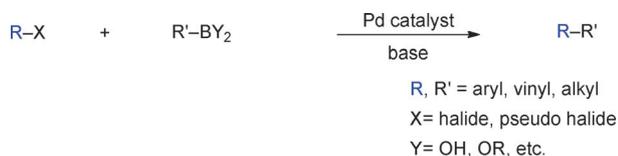
Due to the significance of cross-coupling reactions for the development of new drugs and materials, many methods have been developed to perform these reactions under continuous-flow conditions. It is the goal of this review to discuss the different continuous-flow methodologies that have been utilized in cross-coupling reactions and to illustrate the power of continuous processing compared to the traditional batch model.

2. C–C bond formation in flow

2.1 Suzuki–Miyaura cross-coupling reactions in flow

The Suzuki–Miyaura cross-coupling reaction (SMC) can be regarded as one of the most important methods for the construction of carbon–carbon bonds.^{29,86–88} The SMC protocol allows for the coupling of aryl, vinyl and alkyl halides/pseudo halides with organoboron compounds (Scheme 1). The latter are very convenient coupling partners due to their stability to heat, oxygen, and water, as well as their commercial availability.⁸⁹

Many studies have been focused on the development of heterogeneous catalysts for cross-coupling reactions.^{90–92} Catalyst immobilization is of significant importance for flow chemistry applications (see recent review by Frost and Mutton)⁵⁹ and holds

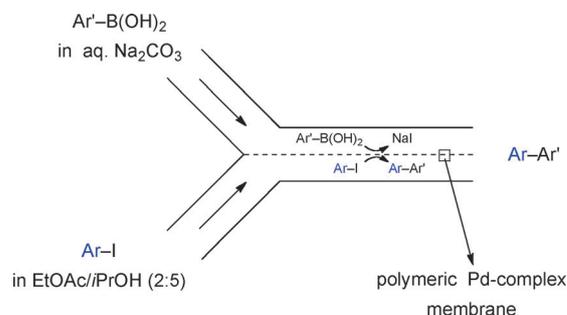


Scheme 1 Suzuki–Miyaura cross-coupling reaction.

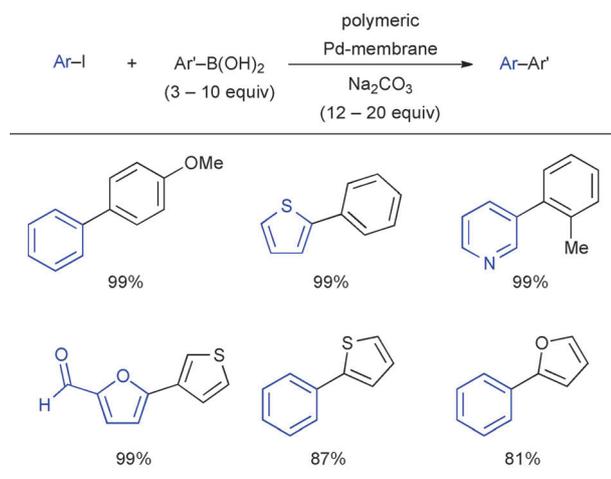
promise because of the simplicity of catalyst recovery and reuse.⁹³ In addition, typical packed bed reactors provide a large amount of catalyst, which can accelerate the rate of reaction significantly. Hence, a broad range of solid supports were developed and applied in SMC flow chemistry, such as, silica,⁹⁴ monolithic supports,^{95–104} polymer beads¹⁰⁵ and PdEnCat™.^{106,107} These packed bed reactors showed increased yield with less by-products compared to the corresponding batch reactions. However, strong evidence indicates that these solid supports function as ‘palladium reservoir’ and gradually leach the catalytically active Pd species into solution.^{108–115} Furthermore, swelling of the polymer supports, deposition of products/by-products and the necessity to periodically replace the cartridges can complicate their use in continuous-flow chemistry.

An effective example of catalyst immobilization was reported by Uozumi and coworkers.^{116–118} The catalyst was immobilized in a membrane, which was positioned at the center of a microchannel. A solution of aryl iodide in ethyl acetate/isopropanol (2:5) and a solution of aryl boronic acid in aqueous Na₂CO₃ were introduced into two channels separated by the catalytic membrane (Scheme 2). This reactor design offers the advantage to maximize the contact area between the organic/aqueous phase while the reaction takes place at the catalytic interfacial surface. This device allowed for the cross-coupling of various aryl iodides with a wide range of boronic acids in good to excellent yield (Scheme 3). Complete conversion was observed with residence times of only 4 to 5 s (240 μg h⁻¹). ICP-AES analysis revealed minimal, if any, leaching of the palladium catalyst (Pd < 0.044 ppm).

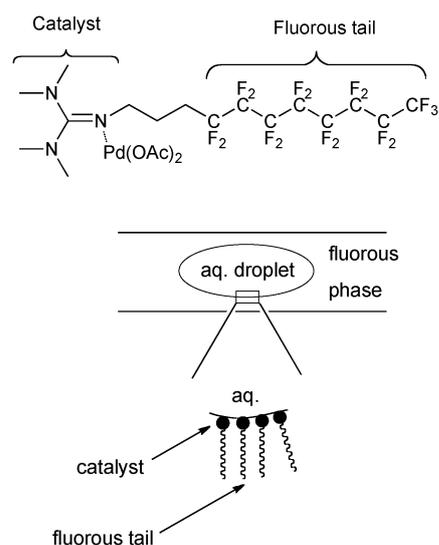
Another approach to catalyst recycling involved the use of a fluororous-tagged palladium complex.¹¹⁹ This fluororous tag ensured that the catalyst remained in the fluororous solvent while the reagents/products were in the aqueous phase. Aryl bromide, aryl boronic acid and base were dissolved in water and were brought in contact with the fluororous phase in a tee-mixer establishing a slug flow regime (segmented flow). This flow regime is characterized by a series of small aqueous slugs (droplets), which are separated by a fluororous continuous phase. At the interface, the polar catalyst was assembled, which could catalyze the reaction inside the droplet (Scheme 4). Several biaryls were obtained in good to excellent yield (63–99% yield) with residence times varying from 45 min to 8 h. Furthermore, to demonstrate the possibility of catalyst recycling in flow, the fluororous catalyst-containing phase was



Scheme 2 SMC reaction at the surface of a catalytic membrane, which was installed at the center of a microchannel (Uozumi *et al.*).¹¹⁶



Scheme 3 SMC reaction of aryl iodides and aryl boronic acids using a catalytic membrane-installed microchannel device (Uozumi *et al.*).¹¹⁶

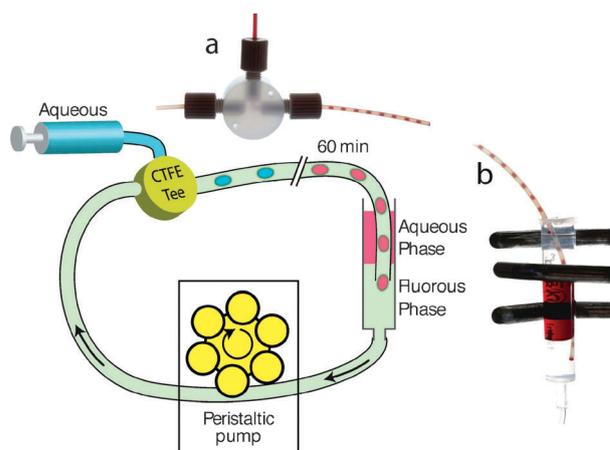


Scheme 4 A fluororous-tagged palladium catalyst, which forms a catalytically active interface.¹¹⁹

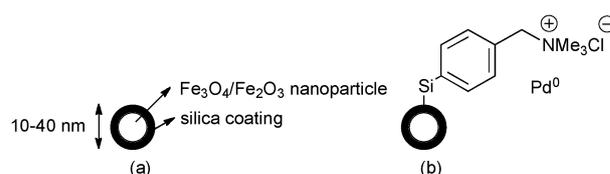
recycled approximately four times, after which the catalyst was still active (Scheme 5). ICP-MS analysis showed that less than 0.5 ppm palladium was leached into the aqueous phase, which represented less than 2% of the total amount of palladium.

The increased heat-transfer rate of microreactors compared to batch reactors is one of the major advantages of microfluidics. This can be attributed to the high surface-to-volume ratio of microchannels. Effective heat-transfer allows for efficient activation of the molecules and, therefore, enables fast reactions in microreactors (*vide infra*). Typically, these reactors are heated by means of conventional heat sources, such as, standard hot plates, oil baths, molten salt baths, GC ovens or cartridge heaters.¹²⁰

Kirschning and coworkers have developed silica-coated magnetic nanoparticles, which can be heated *via* magnetic induction (Scheme 6).^{121,122} A flowthrough mesoreactor was filled with these magnetic nanoparticles and allowed for remote heating of the flow reactor without electrical connections. Inductive heating



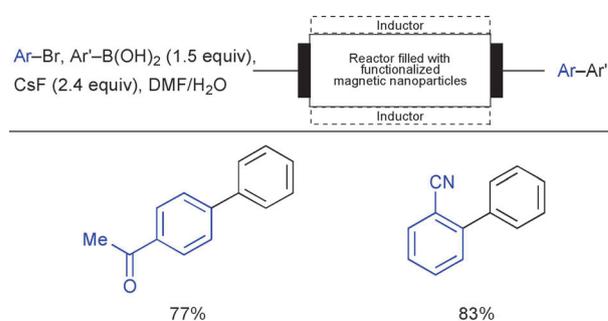
Scheme 5 Schematic representation of the microfluidic setup used for catalyst recycling in the presence of a fluororous-tagged palladium catalyst. Inset (a) shows the formation of the water droplets in a fluororous phase. Inset (b) depicts the phase separation. Reproduced by permission of the Royal Society of Chemistry.¹¹⁹



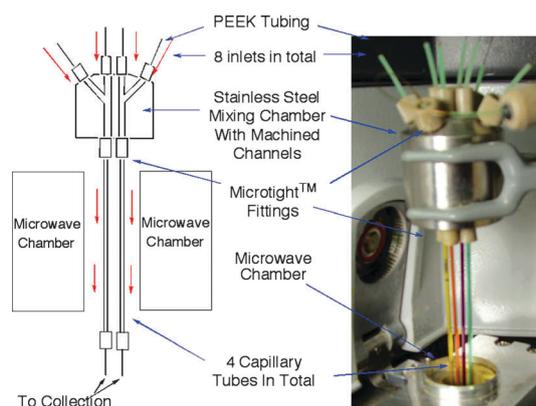
Scheme 6 Unfunctionalized (a) and functionalized (b) nanoparticles.¹²¹

offers the advantage of allowing heat to be generated inside the reactor directly where the reaction takes place. The silica coating could be further functionalized and, as a result, palladium particles were immobilized on the surface of these magnetic nanoparticles (Scheme 6, b).¹²³ These particles were employed for the SMC reaction of aryl bromides and phenyl boronic acid (Scheme 7). ICP-MS analysis indicated that 34 ppm of palladium was leached and the catalyst could be reused more than three times without a decrease in activity.

Alternatively, efficient heating can be achieved *via* microwave irradiation. Typically, microwave-assisted organic synthesis is difficult to scale-up due to the restricted dimensions of the standing wave cavity and the limited penetration depth of the irradiation. This issue has recently been circumvented by the



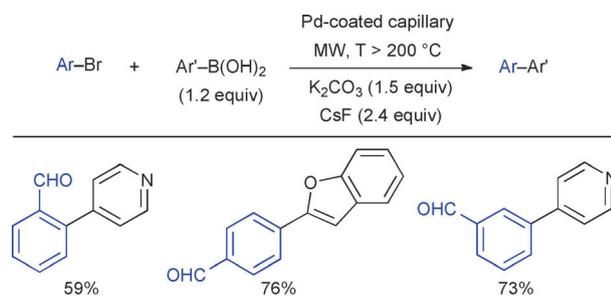
Scheme 7 SMC reaction of aryl bromides and phenyl boronic acid in a mesoflow reactor filled with functionalized magnetic nanoparticles (Kirschning *et al.*).¹²¹



Scheme 8 A microcapillary system for microwave-assisted continuous-flow organic synthesis (Organ *et al.*). (Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.¹²⁹)

emergence of continuous-flow methodologies.^{124,125} One of the first examples of microwave-assisted continuous-flow organic synthesis was described by Haswell and coworkers.^{126,127} This method involved coating of the reactor with a gold film, which led to a more efficient absorption of the microwaves and enabled the microwave power to be reduced to less than 100 W. The necessity to employ a gold-coated reactor indicates that the microwave irradiation heated the reactor and not directly the solvent. As a proof of concept, several aryl halides were coupled with phenyl boronic acid in the presence of a heterogeneous Pd/Al₂O₃ catalyst.

Organ developed a microwave-assisted capillary-based flow system and demonstrated its utility in SMC reactions (Scheme 8).^{128,129} The use of capillaries coated with a thin film of palladium and the utilization of microwave heating (up to 225 °C) allowed for the efficient coupling of aryl bromides with aryl boronic acids (Scheme 9). ICP-AES analysis of the crude cross-coupling product showed that some of the palladium had leached (19.2 ppm). When the reaction was repeated in an oil bath in the absence of microwave irradiation, a much lower conversion was observed. Recently, Organ, Li and coworkers discovered that, by using a high definition IR camera, much higher temperatures (700–950 °C) were obtained in thin-film coated capillaries than was originally reported. It was speculated that the reaction conditions are similar to the conditions obtained in flash vacuum thermolysis.¹³⁰

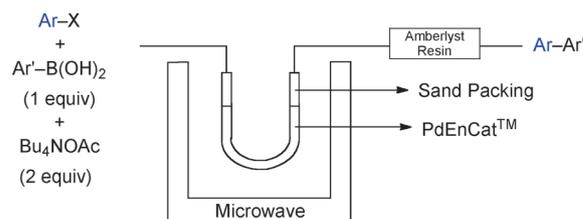


Scheme 9 SMC reaction of aryl bromides and heteroaryl boronic acids in a microwave-assisted continuous-flow setup (Organ *et al.*).¹²⁹

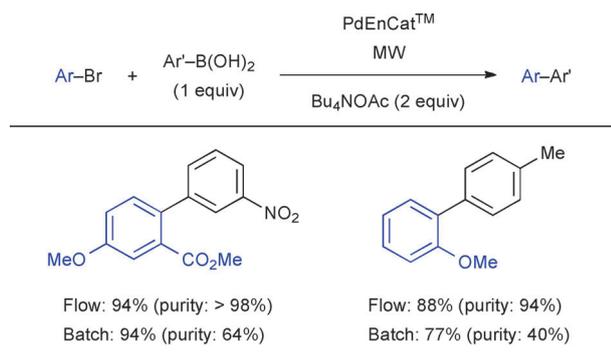
Organ extended this method to a continuous-flow, sequential and parallel synthesis of biaryls.¹³¹ The multireactor assembly consisted of a stainless steel holder with 8 inlets in total, divided in four pairs (Scheme 8). These four pairs, which contained either boronic acid or arylbromide, were combined in a Y-mixer and led to capillaries, which could be heated simultaneously in the microwave cavity. As a result, four different compounds could be synthesized at the same time (parallel synthesis). By switching the inlet streams for other boronic acids, different compounds, which were separated by time, could be obtained (sequential synthesis).

Ley and coworkers documented the use of a simple U-shaped glass tube, which could be filled with PdEnCatTM¹³² and inserted into a microwave cavity (Scheme 10).¹³³ Upon exiting the reactor, the reaction mixture was passed through a column of Amberlyst 15 sulfonic acid resin to remove residual base and boronic acid salts. In certain cases, an additional purification was required to remove residual palladium by passing the reaction mixture through a metal-scavenging QuadrapureTM TU (thiourea) column. No further purification by column chromatography was needed and pure biaryl product could be obtained by concentrating the reaction mixture *in vacuo*. It was demonstrated that prolonged heating of the reactor at a constant power level of 50 W was detrimental for the polymer support, causing it to collapse, melt and eventually clog the tube. This was bypassed by applying a modified heating protocol in which the microwave-heating phase (30 s, 50 W) was followed by a cooling phase (18 s, no power application). Biaryls could be obtained in a sequential automated fashion without the necessity to replace the catalyst (10 examples). Notably, yield and purity of the products were superior to those obtained in the corresponding batch reactions (Scheme 11). This was attributed to the fast reaction times, which could be achieved in flow. The products were only heated for a very short amount of time (1 min), preventing decomposition and side reactions from occurring.

As stated above, microwave-assisted continuous-flow organic synthesis typically allows for a straightforward scale-up of small-volume single-mode microwave reactors. Moreover, it eliminates tedious reactor parameter re-optimizations and circumvents the use of expensive multimode microwave reactors.¹³⁴ Workers at Boehringer Ingelheim Pharmaceuticals described the design of a flow cell that consisted of 22 borosilicate glass coils.¹³⁵ This flow cell could be placed in a commercially available single-mode microwave reactor. An SMC reaction could be efficiently scaled-up providing multi-gram quantities of the target compound.



Scheme 10 SMC reaction of aryl halides and heteroaryl boronic acids in a microwave-assisted continuous-flow setup (Ley *et al.*).¹³³

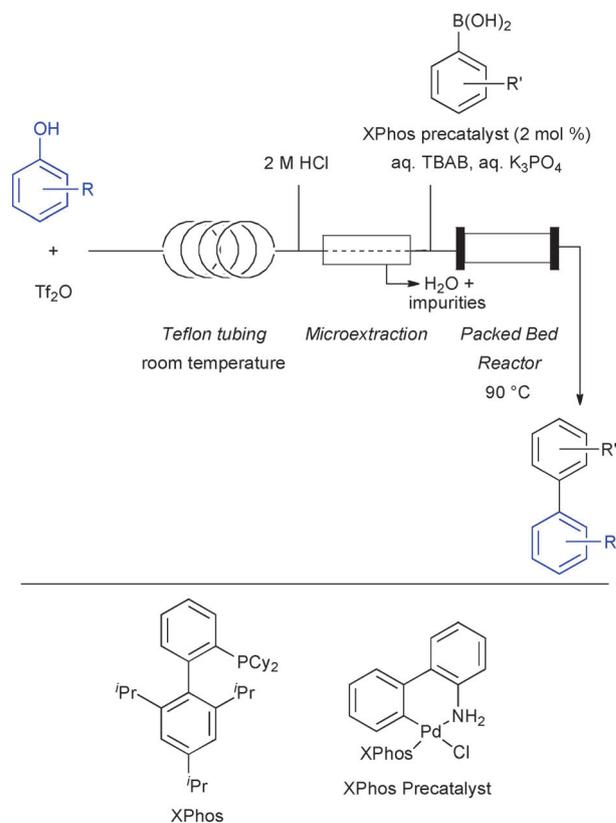


Scheme 11 Comparison of the results obtained under flow conditions and batch conditions for the SMC reaction of aryl bromides and aryl boronic acids (Ley *et al.*).¹³³

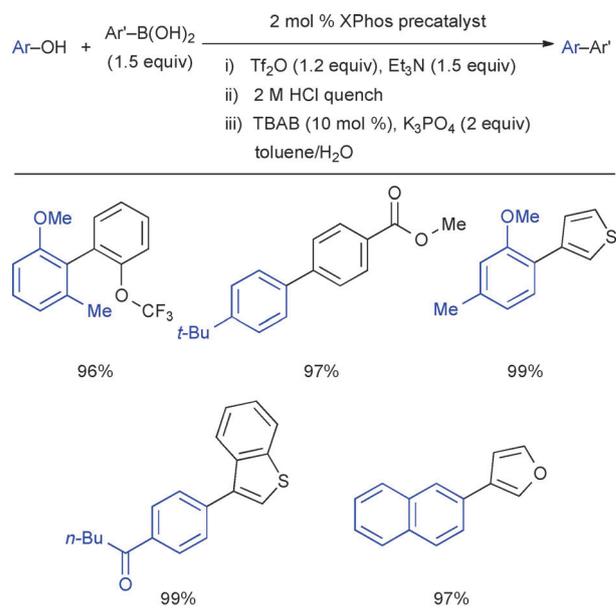
Researchers at GlaxoSmithKline demonstrated that the SMC reaction conditions could be optimized in 500 μL slugs using a design of experiments methodology (DoE).¹³⁶ These slugs were separated from each other with a fluoruous solvent as spacer that enabled the use of small reaction volumes and avoided carry-over from one reaction slug to another. As a result, these slugs can be regarded as small independent microreactors. The reaction conditions, optimized for smaller slugs, could be easily translated to larger slugs (scale-up).

The use of continuous-flow reactors for multistep syntheses allows for the integration of individual reaction steps in one single streamlined process without the need to isolate the intermediates.⁵⁶ However, continuous-flow multi-step organic syntheses are extremely challenging since excess reagents and impurities formed during the reaction must be effectively removed or must be compatible with the downstream reactions. To this end, several unit operations have been developed in order to achieve separations and purifications in a continuous fashion.⁶⁴ Buchwald, Jensen and coworkers have developed a two-step continuous-flow microfluidic system in which a continuous extraction device was employed (Scheme 12). The system allowed the transformation of phenols into aryl triflates, which were, subsequently, converted into biaryls through an SMC reaction.¹³⁷ It was shown that impurities, formed in the triflate synthesis, and excess of triflic anhydride were effectively removed *via* this continuous extraction. ^{138,139} Subsequently, the organic phase, containing the aryl triflate coupling partner, was merged with palladium-based XPhos precatalyst,^{140,141} boronic acid, aqueous K_3PO_4 and aqueous tetrabutylammonium bromide (TBAB). The resulting biphasic mixture was introduced into a packed bed reactor filled with stainless steel spheres (60–125 μm), which ensured adequate mixing between the two phases (*vide infra*).¹⁴² Several biaryls could be obtained (Scheme 13).

Glasnov and Kappe have described a two-step flow synthesis of 2-amino-4'-chlorobiphenyl, which is a key-intermediate in the industrial preparation of the fungicide Boscalid[®] (Scheme 14).¹⁴³ The first step involved a homogeneous SMC reaction with 0.25 mol% $\text{Pd}(\text{PPh}_3)_4$ and superheating of the solvent mixture in an X-Cube Flash[™] reactor, a commercially available flow reactor. Next, the homogeneous palladium catalyst was scavenged in a Quadrapure[™] TU (thiourea) column, which was installed in an X-Cube[™]. Without this

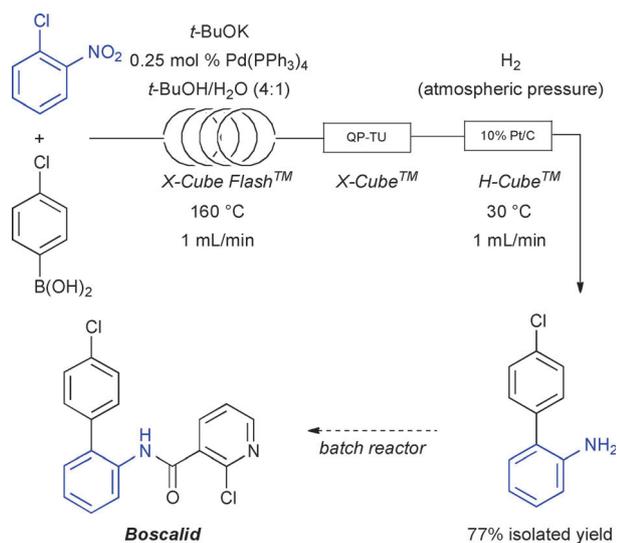


Scheme 12 Microreactor setup for the continuous-flow two-step synthesis of biaryls *via* palladium-catalyzed SMC reactions starting from substituted phenols (Buchwald, Jensen *et al.*).¹³⁷



Scheme 13 SMC reaction of phenols and aryl boronic acids in a continuous-flow two-step synthesis (Buchwald, Jensen *et al.*).¹³⁷

in-line scavenging step, a significant amount of overreduced product (~12%) was formed in the hydrogenation step. After exiting the QP-TU cartridge, the reaction mixture was introduced in an H-Cube[™] hydrogenation reactor using Pt/C as a



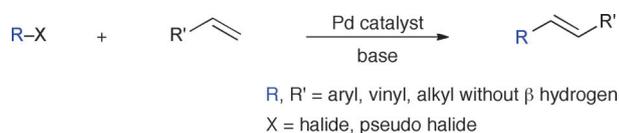
Scheme 14 Continuous-flow synthesis of a key-intermediate in the preparation of Boscalid[®] (Glasnov and Kappe).¹⁴³

catalyst and the key-intermediate of Boscalid[®] was formed in good overall yield (77%).

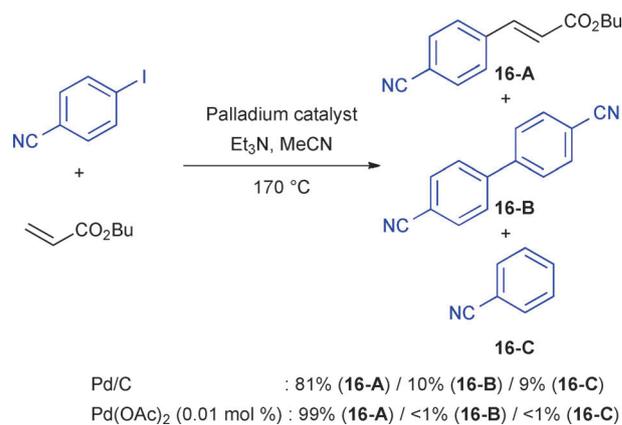
2.2 Mizoroki–Heck alkenylation reactions in flow

The Mizoroki–Heck alkenylation^{144–147} is a versatile transformation, which allows for the coupling of aryl and vinyl halides/pseudo halides with olefins (Scheme 15).^{148–150} Due to its excellent functional group tolerance, it has found widespread use in the synthesis of active pharmaceutical ingredients,¹⁵¹ fine chemicals,¹⁵² and natural products.^{153,154} However, because of the absence of a transmetallation step, the Mizoroki–Heck alkenylation cannot be categorized as a traditional cross-coupling reaction. Nevertheless, this transformation can arguably be considered as one of the most important palladium-catalyzed carbon–carbon bond forming processes. Therefore, a detailed discussion of its application in continuous-flow will be included.

Similar to the SMC reaction, significant effort has been devoted to the application of heterogeneous catalyst systems in the Mizoroki–Heck alkenylation, such as, monolithic supports,^{95,97,99,155–157} thin films of palladium nanoparticles¹²⁹ and Pd/C.^{158,159} Kappe and coworkers reported the use of Pd/C as a catalyst for the Mizoroki–Heck coupling (Scheme 16).¹⁶⁰ Not unexpectedly, it was found that significant leaching occurred and more by-products (homocoupling product **16-B** and dehalogenation product **16-C**) were observed than in the corresponding batch experiments. However, when Pd(OAc)₂ was used as a precatalyst for a homogeneous palladium catalyst, fewer side reactions were observed and the catalyst loading could be reduced to 0.01 mol%.

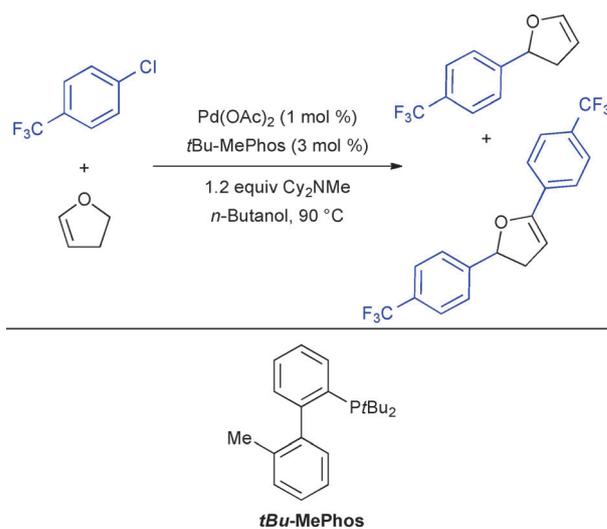


Scheme 15 Mizoroki–Heck alkenylation reaction.

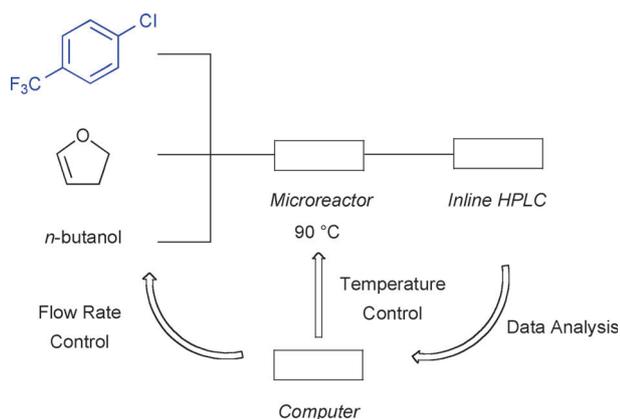


Scheme 16 Selectivities obtained in the Mizoroki–Heck coupling of 4-iodobenzonitrile with butylacrylate using Pd/C or Pd(OAc)₂ as a palladium source (Kappe *et al.*).¹⁶⁰

Improving and optimizing reaction conditions is a common goal in chemistry and can be very labor-intensive and time-consuming. This is due to the large numbers of possible variations, such as, temperature, reaction time, concentration of the reagents, *etc.*, that need to be investigated in order to obtain an optimal solution.¹⁶¹ Jensen, Buchwald and coworkers have developed an ‘intelligent’ and completely automated microfluidic system, which is capable of maximizing the yield of a Mizoroki–Heck reaction by adjusting several reaction parameters (Scheme 17).^{162–164} At certain time intervals, the yield and selectivity (monoarylated/diarylated) of the reaction were analyzed by inline HPLC (Scheme 18). This data was analyzed by using DoE software and immediate feed back regarding concentration and residence time resulted in an adjustment of the pump flow rates. As a result, the reaction of 4-chlorobenzotrifluoride with 2,3-dihydrofuran could be optimized after 19 automated experiments, requiring only a small amount of starting material (Scheme 17). The optimal reaction conditions required a residence time of 6 min and



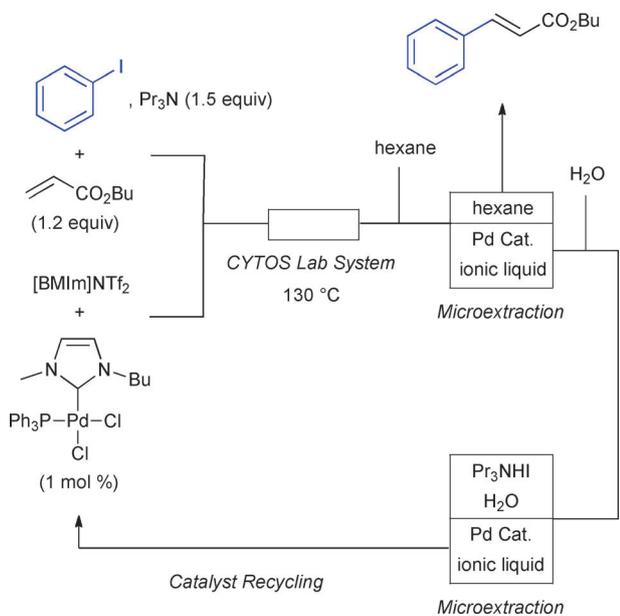
Scheme 17 Mizoroki–Heck coupling of 4-chlorobenzotrifluoride with 2,3-dihydrofuran as a model reaction for the development of a microfluidic system for self-optimization (Jensen, Buchwald *et al.*).¹⁶²



Scheme 18 An 'intelligent' and automated microfluidic system for self-optimization of a Mizoroki-Heck coupling (Jensen, Buchwald *et al.*).¹⁶²

5 equivalents of dihydrofuran leading to a 83% yield of the desired compound. Subsequently, the reaction conditions acquired on microscale were successfully translated to a meso-scale flow reactor. This result demonstrates that optimized reaction conditions can be scaled-up conveniently in flow.

Ionic liquids are typically considered as 'green' solvents due to their low vapor pressure.⁴⁴ Ryu and coworkers immobilized a palladium catalyst in a low viscosity ionic liquid,¹⁶⁵ which allowed for a continuous catalyst recycling in flow (Scheme 19).¹⁶⁶ The reagents were introduced into a CYTOS lab system (17 min residence time, 1.0 ml min⁻¹ flow rate), a commercially available microreactor system. Next, the Mizoroki-Heck coupled product was removed from the ionic liquid in a hexane wash. After removal of the ammonium salt in a H₂O wash, the catalyst could be recycled. The system was run for 11.5 h producing 115.3 g of *trans*-butyl cinnamate



Scheme 19 Microfluidic setup for catalyst recycling in the Mizoroki-Heck coupling using an ionic liquid and a palladium-carbene complex (Ryu *et al.*).¹⁶⁶

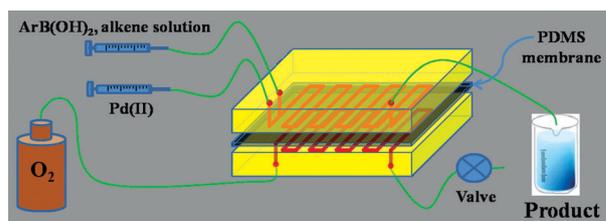
(80% yield, 10 g h⁻¹) in which the catalyst system was recycled a total of five times.

The transition metal-catalyzed coupling of organoboronic acids with olefins, an oxidative Heck coupling, requires the presence of an oxidant to reoxidize Pd(0) to Pd(II) after each catalytic cycle.¹⁶⁷⁻¹⁶⁹ Park and Kim developed a dual-channel microreactor, in which the microfluidic channels are separated by a thin porous poly(dimethylsiloxane) (PDMS) membrane (Scheme 20).¹⁷⁰ O₂ was introduced as an oxidant in one channel while the reagents dissolved in DMF flowed through the other microchannel. This reactor design allowed maximization of the contact area between the gas and the liquid phase resulting in better selectivities (**21-A/21-B**), yields and decreased reaction times compared to the corresponding batch reaction. Furthermore, the dual-channel microreactor was compared to a traditional mono-channel microreactor in which a segmented gas-liquid flow (slug flow) was established (Scheme 21). Because of the high viscosity of DMF, it was found that the slug formation in the mono-channel reactor was difficult to control. Similar to the dual channel reactor, better selectivities compared to batch reactors were obtained in the mono-channel reactor; however, due to the lower contact area between the two phases, a significantly lower conversion was observed.

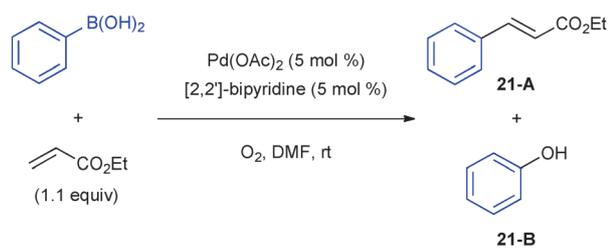
Oxidative Heck reactions in continuous-flow were also investigated by Lahred and coworkers.¹⁷¹ It was found that aryl boronic acids were efficiently coupled with *n*-butyl acrylate and *n*-butyl vinyl ether in the presence of *p*-benzoquinone as the oxidant (Scheme 22 and 23). The authors described also a two-step continuous-flow vinylation-arylation protocol yielding a disubstituted styrene (Scheme 24). The α/β regioisomer ratio could be adjusted by switching the order of addition of the two boronic acids.

Organ and coworkers employed a microwave-assisted capillary flow system (*vide supra*) for the continuous-flow synthesis of an intermediate of Aplysamine 6, which is an alkaloid inhibitor of ICMT (isoprenylcysteine carboxyl methyltransferase) (Scheme 25).¹⁷² The use of a microwave-assisted continuous-flow synthesis provided an excellent method to scale-up the synthesis without the need for process reoptimization. The Mizoroki-Heck coupled product could be obtained in good yield on a 5 mmol scale. Subsequent transformations towards the natural product were also performed in flow; however, intermediate purifications were carried out offline.

Distillation can be regarded as one of the most powerful unit operations in chemical synthesis because it allows for a solvent switch and a purification of reagents. The fabrication

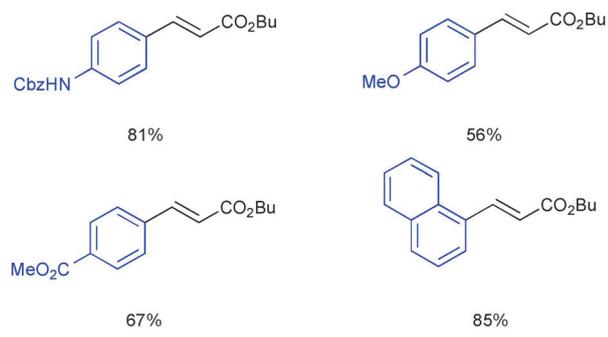


Scheme 20 Schematic representation of a dual-channel microreactor (Park and Kim). (Reprinted with permission from ref. 170. Copyright 2010 American Chemical Society.)

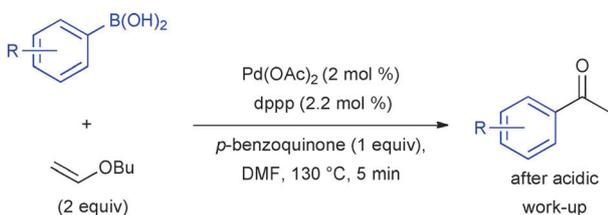


| Reactor Type | Residence Time | Yield (21-A : 21-B) |
|--------------|----------------|---------------------|
| Batch | 12 h | 69:24 |
| Mono-Channel | 30 min | 59:6 |
| Dual-Channel | 30 min | 82:8 |

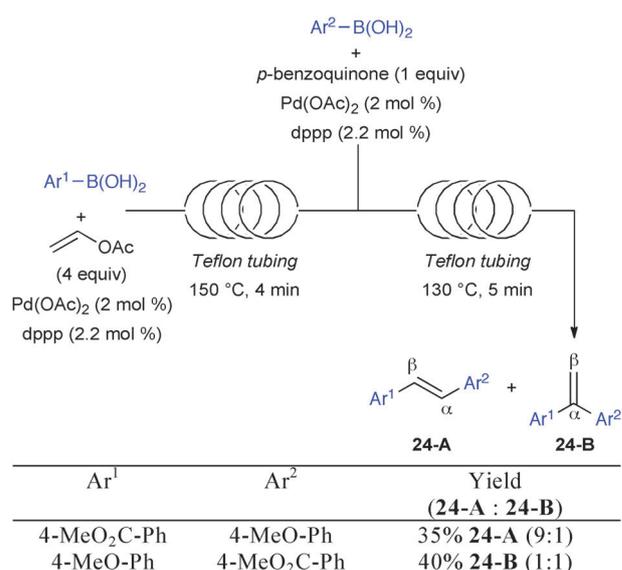
Scheme 21 Comparison of the oxidative Heck coupling in a batch reactor, mono-channel microreactor and dual-channel microreactor (Park and Kim).¹⁷⁰



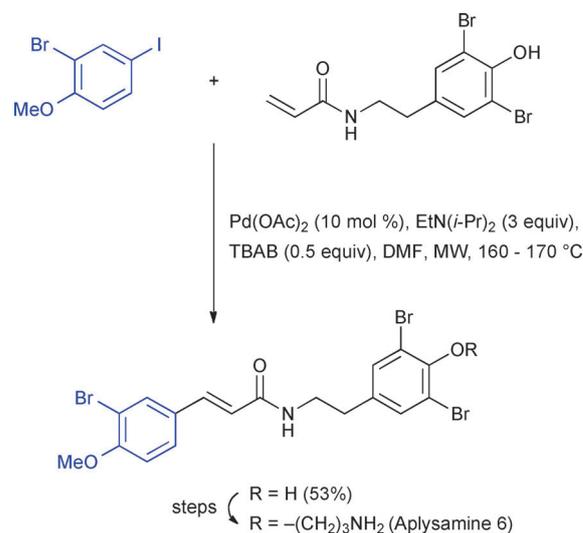
Scheme 22 Continuous-flow oxidative Heck coupling of aryl boronic acids with n-butyl acrylate (Lahred *et al.*).¹⁷¹



Scheme 23 Continuous-flow oxidative Heck coupling of aryl boronic acids with n-butyl vinyl ether (Lahred *et al.*).¹⁷¹

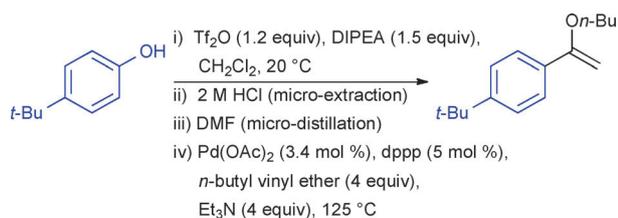


Scheme 24 Two-step continuous-flow vinylation-arylation protocol yielding a disubstituted styrene (Lahred *et al.*).¹⁷¹

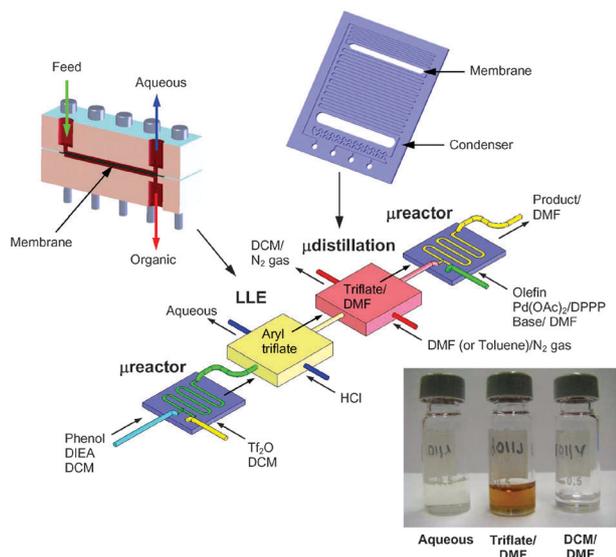


Scheme 25 Continuous-flow synthesis of an intermediate of Aplysamine 6 by Mizoroki–Heck coupling (Organ *et al.*).¹⁷²

of a silicon-based device, which enables a distillation on a microfluidic scale, was reported by Jensen.¹⁷³ As a proof of concept, Jensen, Buchwald and coworkers have integrated this device in a two-step continuous-flow sequence to prepare enol ethers from phenols and olefins (Scheme 26).¹⁷⁴ The first step involved the synthesis of an aryl triflate in dichloromethane, followed by a liquid–liquid extraction (LLE) with 2 M HCl facilitating the removal of triethylammonium salts (Scheme 27). The organic stream was further mixed with pure dimethylformamide (DMF) and the combined organic streams were delivered to the microfluidic distillation device. As a result, dichloromethane was exchanged with the higher boiling DMF, which was required for the Mizoroki–Heck coupling. The target product could be obtained in 79% overall yield (0.135 mmol h⁻¹).



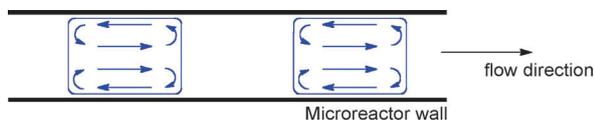
Scheme 26 Continuous-flow two-step synthesis of an n-butyl vinyl ether starting from *p*-*tert*-butylphenol.¹⁷⁴



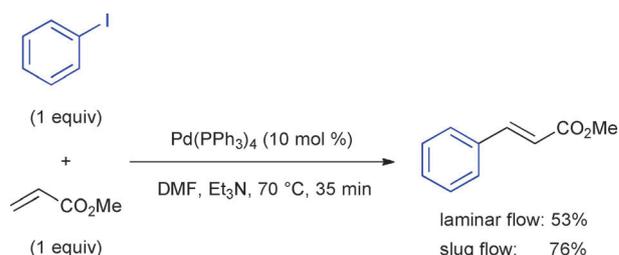
Scheme 27 Microfluidic setup for the synthesis of n-butyl vinyl ether in continuous-flow (Jensen, Buchwald *et al.*). (Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)¹⁷⁴

Wirth and coworkers have taken advantage of the excellent mixing capacity of segmented flow (liquid–liquid slug flow) to increase reaction rates in microfluidic flow.^{175–177} In such a slug, an internal circulation is established which arises from friction between the two phases and from the slip velocity (Scheme 28). The slip velocity can be defined as the difference in velocity between two phases. The internal circulation in a slug greatly increases the mixing as compared to what is achieved by molecular diffusion in laminar flow. Wirth *et al.* used perfluorodecalin as an inert and immiscible liquid spacer; significantly better results were obtained for the Mizoroki–Heck reaction in a slug flow regime (Scheme 29).

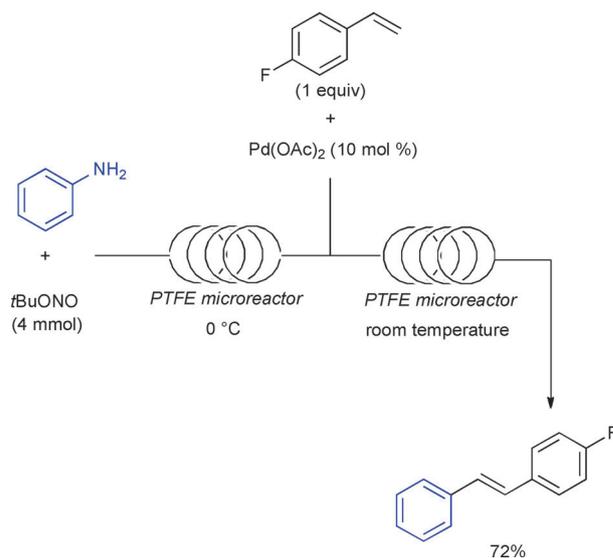
The same segmented flow method was applied to a Matsuda–Heck reaction.^{178,179} This two-step continuous-flow protocol started with the *in situ* generation of a diazonium species at 0 °C, which is immediately consumed in the next step to yield the Heck-coupled product (Scheme 30).¹⁷⁶ This example demonstrates another advantage of microfluidics, which is the ability to process explosive compounds (diazonium salt)



Scheme 28 Schematic representation of liquid–liquid slug flow with internal circulation of the fluid.



Scheme 29 Comparison between slug and laminar flow for the Mizoroki–Heck coupling of iodobenzene with methyl acrylate (Wirth *et al.*).¹⁷⁶

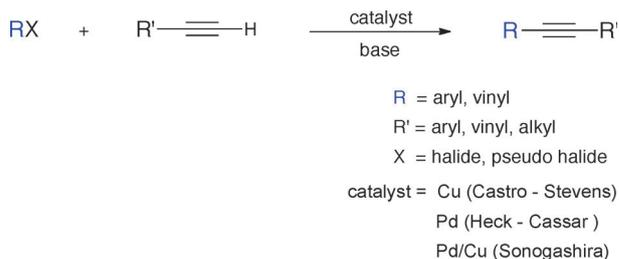


Scheme 30 Microreactor setup for the continuous-flow two-step Matsuda–Heck coupling (Wirth *et al.*).¹⁷⁶

in a safe and controlled manner. Only small quantities of the diazonium salt are generated, thus minimizing the risks associated with this compound and rendering a much safer protocol.

2.3 Alkyne coupling reactions in flow

The first cross-coupling of sp and sp^2 carbon atoms was developed by Castro and Stevens in the early 1960s (Scheme 31).^{180,181} This reaction involved the use of stoichiometric amounts of copper. A major improvement came in 1975, when three groups independently discovered that palladium could catalyze the formation of substituted alkynes (Scheme 31). Dieck & Heck and Cassar showed that a palladium-based system could catalyze the cross-coupling

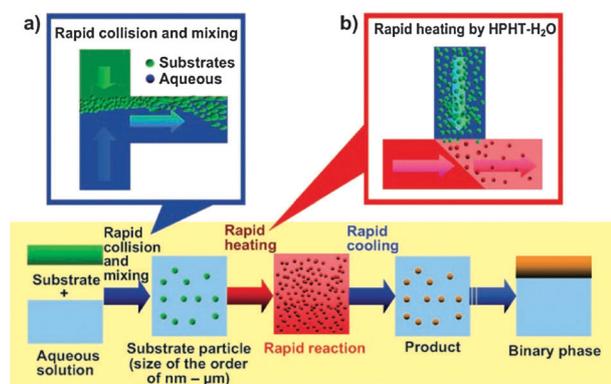


Scheme 31 Alkyne cross-coupling reactions.

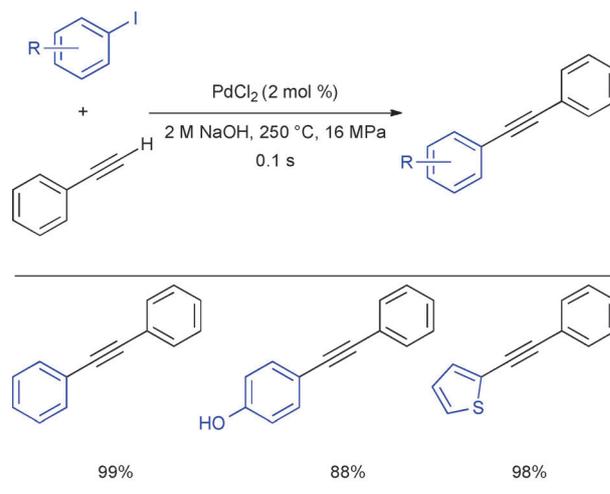
reaction of an aryl and vinyl halide with a terminal alkyne in the presence of a base.^{182,183} However, the mildest method was developed by Sonogashira and involved a palladium catalyst and a copper cocatalyst.^{184–187}

Kawanami and Ikushima have developed a high-pressure and high-temperature protocol using water as the solvent (HPHT-H₂O) to perform Heck–Cassar alkynylations in flow (Scheme 32).¹⁸⁸ In this system, the substrates (neat) are first interacted with an aqueous mixture containing PdCl₂ and NaOH at very high pressures (25 MPa) and ambient temperature in a micromixer. Next, the reaction mixture is merged with a high-speed flow of high-pressure and high-temperature H₂O. At this point, the reaction mixture is immediately heated to 250 °C. As a consequence of the high pressure and temperature, the organic reagents are completely dissolved in water and no organic solvents are required. Several diaryl substituted alkynes could be obtained in less than 1 s residence time (Scheme 33). Upon cooling and lowering the pressure, the product readily separated from the aqueous layer and palladium black precipitated out. The authors suggested that, at such high pressures and temperatures, a hydrogen bond between the terminal hydrogen atom of the alkyne and H₂O was formed, which lowered the activation energy for the reaction and, consequently, allowed fast alkyne cross-coupling reactions to occur. Unfortunately, the formation of palladium black could not be circumvented in some cases, leading to clogging of the microchannels. Suzuki, Kawanami and coworkers developed a tubular microreactor on which a thin layer of Pd–Cu alloy was deposited.¹⁸⁹ As a result, no additional homogeneous catalyst was required, thus, avoiding the formation of precipitation. The Sonogashira coupling of ethynylbenzene and iodobenzene could be performed in this tubing in 1.6 s and a conversion 84%.

Other Heck–Cassar alkynylations in flow involved the use of ionic liquids¹⁹⁰ or made use of immobilized palladium catalysts.^{96,103} Specifically, researchers from Novartis performed alkyne cross-coupling reactions in a copper tube flow reactor.¹⁹¹ Small amounts of copper were leached from the tubing into the reaction mixture, which could efficiently catalyze the reaction. To prevent clogging of the microchannels, dimethylformamide (DMF) as a solvent and



Scheme 32 Schematic representation of a high-pressure and high-temperature protocol using water as the solvent (HPHT-H₂O) (Kawanami, Ikushima *et al.*). (Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission).¹⁸⁸



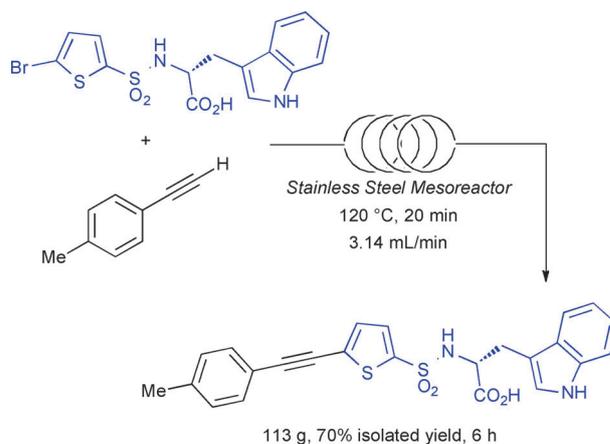
Scheme 33 Heck–Cassar alkynylation of aryl iodides with phenylacetylene in a HPHT-H₂O microfluidic system.¹⁸⁸

tetra-*n*-butylammonium acetate as a soluble base were used. Most reactions could be efficiently carried out; however, less reactive substrates required the use of a catalytic amount of palladium. The leached copper could be removed offline with Quadrapure TU resin.

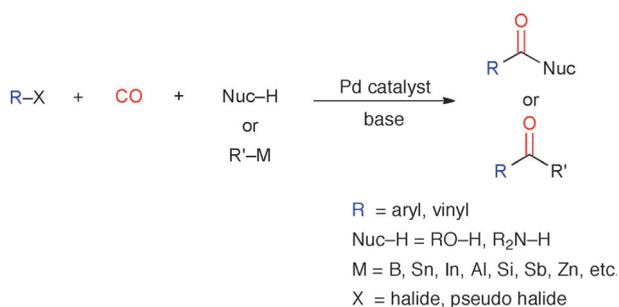
Fukuyama and coworkers developed an automated micro-reactor system, which could optimize the Sonogashira reaction of a bromothiophene derivative with *p*-tolylacetylene.¹⁹² The synthesis of the coupled product, a matrix metalloproteinase inhibitor, could be efficiently scaled-up in a mesoreactor (Scheme 34).

2.4 Palladium-catalyzed carbonylative cross-coupling reactions in flow

Palladium-catalyzed carbonylation reactions (Heck carbonylations)^{193–195} represent a versatile method for the regioselective synthesis of carbonyl containing compounds.^{196,197} They allow for the incorporation of a carbonyl into an aryl or vinyl halide/pseudohalide under a carbon monoxide (CO) atmosphere and in the presence of an appropriate nucleophile (Scheme 35).



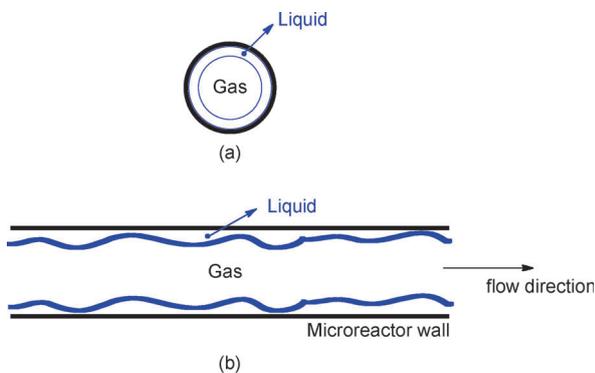
Scheme 34 Continuous-flow synthesis of a matrix metalloproteinase inhibitor (Fukuyama *et al.*).¹⁹²



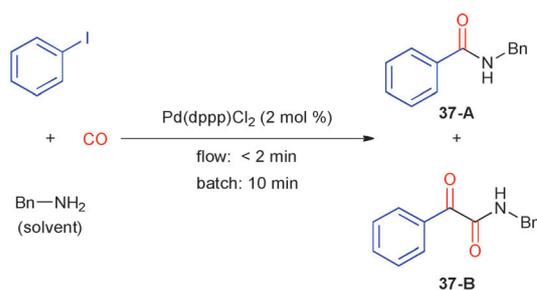
Scheme 35 Palladium carbonylative cross-coupling reactions.

Miller and coworkers developed a glass-fabricated microchip to perform gas-liquid aminocarbonylation reactions.¹⁹⁸ Liquid reagents were introduced into the chip, while the CO gas pressure was kept constant (3–4 bar). An annular flow was created whereby the gas phase flows at a higher velocity in the center of the microchannel, while the liquid phase wets the reactor walls (Scheme 36).¹⁹⁹ As a result, interfacial contact between gas and liquid is significantly enhanced resulting in an increased yield compared to that realized in batch reactions (Scheme 37). In addition, lower flow rates resulted in higher conversions, which can probably be attributed to a better defined distribution of the liquid reagents on the reactor walls and a longer residence time. Interestingly, α -ketoamide (**37-B**) formation was observed in flow arising from an excellent interfacial gas-liquid contact. This compound could not be detected in batch. Miller *et al.* also demonstrated that this chip could be employed to screen several catalysts in a time-efficient way using only a limited amount of product and catalyst.²⁰⁰

Given the fast reaction times typically obtained for carbonylations in flow, this method was also used to perform rapid carbon-11 ($t_{1/2} = 20.4$ min) radiolabeling.^{201,202} As a proof of principle, Miller developed a microfluidic system in which ¹¹CO was first trapped and pre-concentrated on molecular sieves at -196 °C in order to increase the efficiency of the carbonylation process (Scheme 38). Next, a plug of reagents and the concentrated ¹¹CO were simultaneously released into the microfluidic system. An annular flow regime was used to increase the interfacial area, which enhanced the reaction rate. The authors found that an annular flow regime was easier to control than a segmented gas-liquid flow. Remarkably, the

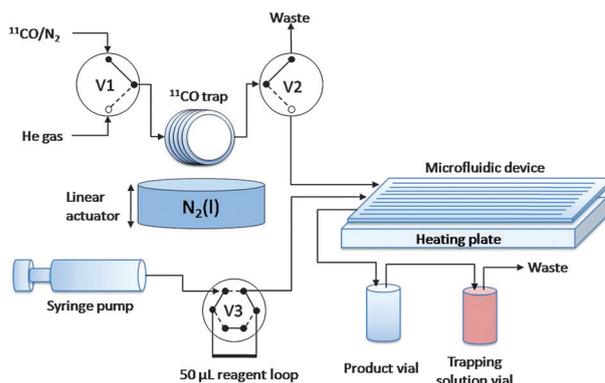


Scheme 36 Schematic representation of annular flow: Inset (a) depicts a radial cross-section of the microchannel, while inset (b) represents an axial cross-section of the microchannel.



| | Flow Rate ($\mu\text{L}/\text{min}$) | Yield 37-A (%) | Yield 37-B (%) |
|-------|---|--------------------------|--------------------------|
| Flow | 20 | 31 | 18 |
| Flow | 10 | 37 | 17 |
| Flow | 5 | 46 | 9 |
| Batch | - | 25 | - |

Scheme 37 Aminocarbonylation of iodobenzene with benzylamine utilizing Pd(dppp)Cl₂ as a catalyst system (Miller *et al.*).¹⁹⁸

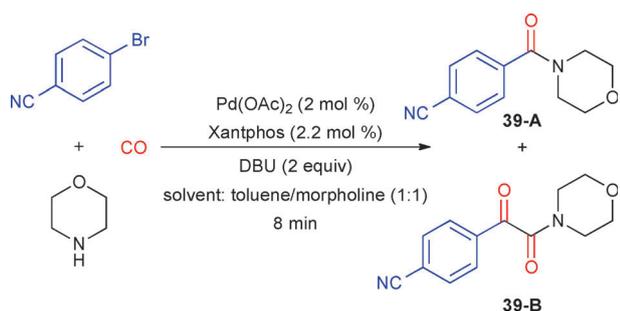


Scheme 38 Microfluidic setup for the aminocarbonylation with ¹¹CO (Miller *et al.*). (Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)²⁰²

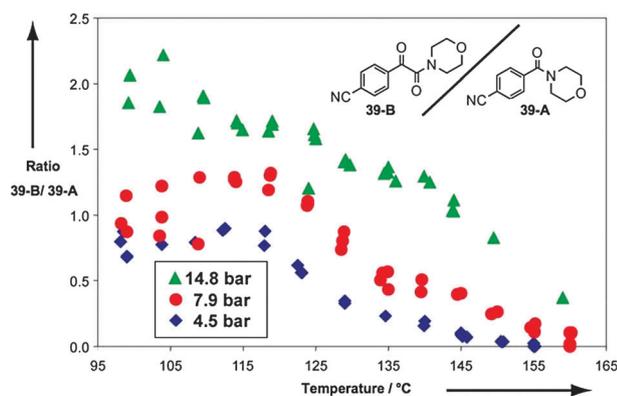
entire labeling process was finished within 15 min from generation of ¹¹CO to the collection of the aminocarbonylated product; fast reaction times are required for medical applications. Currently, relatively simple substrates have been functionalized in this manner.

Jensen, Buchwald and coworkers investigated the palladium-catalyzed aminocarbonylation of 4-bromobenzonitrile in the presence of morpholine as a nucleophile (Scheme 39).²⁰³ This reaction could be accelerated at elevated pressures and temperatures in a pressurized microreactor. The use of a microreactor allowed for a rapid optimization of the reaction parameters, such as, temperature, CO pressure and residence time (Scheme 40). This process would be a time-consuming undertaking using traditional batch reactions with an autoclave or Parr bomb. It was found that an increase in temperature favored the formation of the amide product (**39-A**), whereas higher CO pressures promoted the formation of α -ketoamide (**39-B**).

Researchers from ThalesNano Inc. have reported the use of an X-Cube™ microreactor for the aminocarbonylation of halogenated aryl carboxylic acids (Scheme 41).²⁰⁴ The best results were obtained with 30 bar of CO pressure, a polymer supported Pd(Ph₃)₄ catalyst and triethylamine as a base.

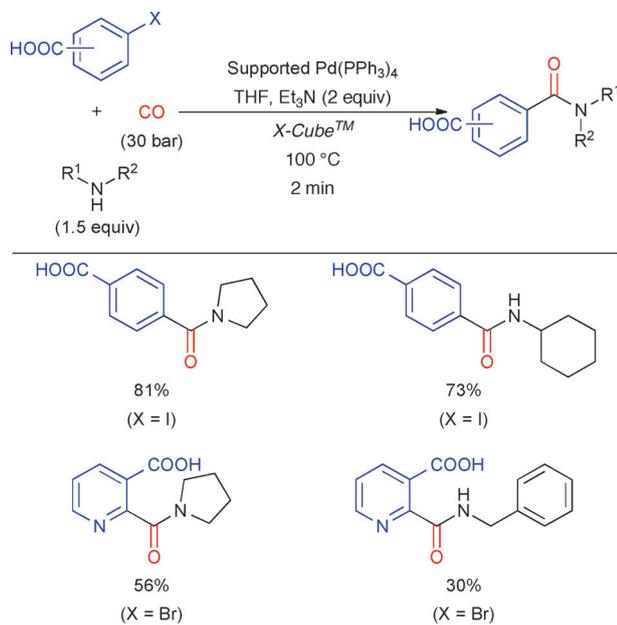


Scheme 39 Aminocarbonylation of 4-bromobenzonitrile with morpholine utilizing Pd(OAc)₂/Xantphos as a catalyst system.²⁰³



Scheme 40 Influence of temperature and pressure on the product ratio of α -ketoamide to amide for the aminocarbonylation in flow. (Reproduced by permission of the Royal Society of Chemistry)⁶⁴

Temperatures above 100 °C were not feasible due to decomposition of the polymer support. It was shown that flow chemistry provided higher reaction rates and a safer handling of hazardous CO than the corresponding batch reactions.



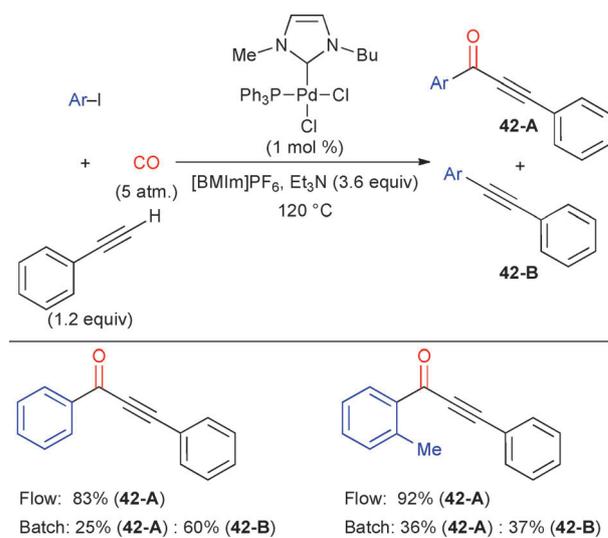
Scheme 41 Aminocarbonylation of halogenated aryl carboxylic acids in flow.²⁰⁴

Ryu, Fukuyama and coworkers have performed a carbonylative Heck–Cassar alkylation of iodoarenes in an ionic liquid ([BMIm]PF₆) in flow.²⁰⁵ Excellent selectivity for the α,β -acetylenic ketone (**42-A**) could be obtained under flow conditions whereas the Heck–Cassar coupled aryl alkyne (**42-B**) was the major product in batch (Scheme 42). The selectivity is mainly controlled by the diffusion of CO due to the very low solubility of CO in viscous ionic liquids. As a result, the superior performance of microfluidics can be attributed to the smaller length scale in segmented gas–liquid flow, which significantly reduces the diffusion time of CO into the ionic liquid.

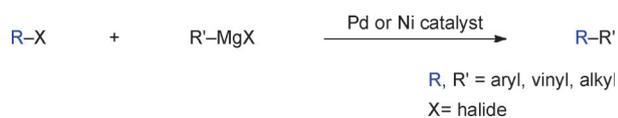
2.5 Kumada–Corriu cross-coupling reactions in flow

The Kumada–Corriu cross-coupling of Grignard reagents with aryl, vinyl, and alkyl halides/pseudo halides is of great importance as it set the stage for the development of many other cross-coupling reactions (Scheme 43).^{1,2} However, its utility is somewhat limited due to its rather poor functional group tolerance.^{206,207}

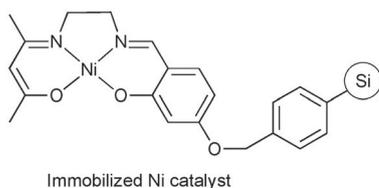
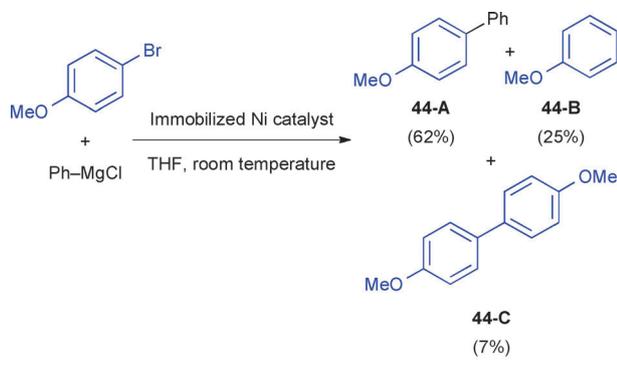
Styring, Haswell and coworkers have immobilized a salen-nickel complex onto Merrifield resin.²⁰⁸ This immobilized catalyst was successfully employed for Kumada–Corriu cross-coupling reactions in batch. Unfortunately, the resin exhibits significant swelling in pure THF and application in flow led to blockage of the microreactor. However, when a silicon-supported catalyst was used, no significant swelling was observed.^{209,210} In a flow reactor, filled with this immobilized catalyst, a Kumada–Corriu cross-coupling of 4-bromoanisole with phenylmagnesium chloride was performed (Scheme 44). The coupled product (**44-A**) was obtained in 62% yield together with a significant amount of reduced product (**44-B**, 25%) and homocoupling (**44-C**, 7%). In addition, after a few hours, the yield dropped due to deposition of magnesium salts on the surface of the immobilized catalyst. This problem can be overcome through incorporation of an intermediate washing step.



Scheme 42 Comparison of the results obtained under flow conditions and batch conditions for the carbonylative Heck–Cassar alkylation (Ryu, Fukuyama *et al.*).²⁰⁵



Scheme 43 Kumada–Corriu cross-coupling reaction.

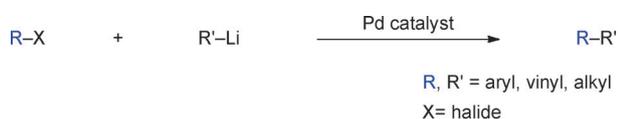


Scheme 44 Kumada–Corriu cross-coupling in flow utilizing an immobilized nickel catalyst (Styring *et al.*).²⁰⁹

2.6 Murahashi cross-coupling reactions in flow

The Murahashi cross-coupling is analogous to the Kumada–Corriu reaction but uses organolithium reagents as nucleophiles instead (Scheme 45).^{211–213} Likewise, it has found only limited use in cross-coupling chemistry due to the high reactivity of the organolithium species.²¹⁴

Due to its excellent heat- and mass-transfer characteristics, microfluidics is ideally suited to perform extremely fast reactions in a controlled fashion (flash chemistry).⁵⁰ Towards this end, Yoshida has pioneered the use of organolithium species in multistep continuous-flow syntheses.^{215,216} Typically, these compounds are difficult to handle in batch due to their instability and reactive nature, and require handling at very low temperatures. However, microfluidics allows for the generation and use of organolithium compounds at much higher temperatures, enabling reactions to be performed on a timescale of only seconds. Recently, Yoshida and coworkers developed a microfluidic setup for the integration of an aryl halogen–lithium exchange and subsequent Murahashi coupling (Scheme 46).²¹⁷ When the Murahashi coupling was too slow, the generated aryl lithium species reacted faster with *n*BuBr, which is generated in the lithium–halogen exchange step. In order to minimize this side reaction, PEPPSI-SIPr was selected as the catalyst to increase the



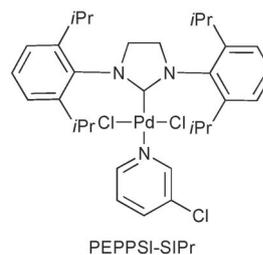
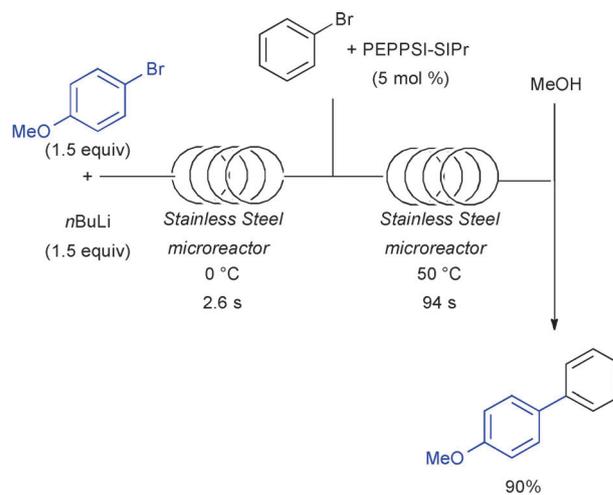
Scheme 45 Murahashi cross-coupling reaction.

reaction rate of the reaction. Next, the influence of reaction temperature and residence time on the Murahashi coupling was investigated in flow. As can be seen from Scheme 47, the yield of the cross-coupling was dependent on both parameters. The target product could be obtained in excellent yield when the reaction was performed at $> 50\text{ }^{\circ}\text{C}$ with a residence time of more than 16 s. This method was applicable to the cross-coupling of several other aryl bromides. Typically, reactions were complete within one minute total residence time.

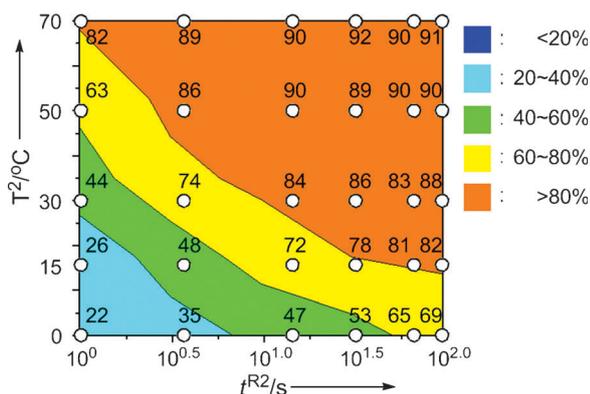
2.7 Decarboxylative cross-coupling reactions in flow

Recently, Gooßen and coworkers described a decarboxylative cross-coupling reaction as a new method to prepare biaryls (Scheme 48).^{218,219} The organometallic carbon nucleophile is generated *in situ* via a copper-catalyzed protodecarboxylation of aryl carboxylic acids.^{220,221}

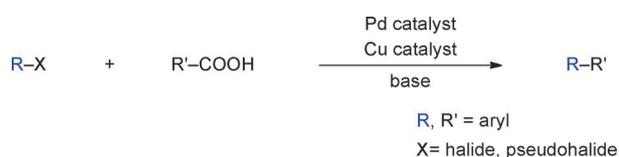
Underwood, Gooßen *et al.* have developed a microfluidic setup, which enables decarboxylative biaryl cross-coupling reactions to be performed in continuous-flow.²²² The reaction was performed in a stainless steel microreactor (10 mL) which was installed in a commercially available Vapourtec flow system. Special care was required in order to prevent clogging of the microreactor. It was found that the use of *N*-methyl-2-pyrrolidinone (NMP) as a solvent ensured a complete dissolution of all the reagents. However, when aryl halides were used, the precipitation of inorganic potassium halide by-products could not be circumvented. Therefore, aryl triflates were selected as coupling partners since potassium triflate is completely soluble. In some cases, it was found that potassium carboxylates precipitated during the reaction.



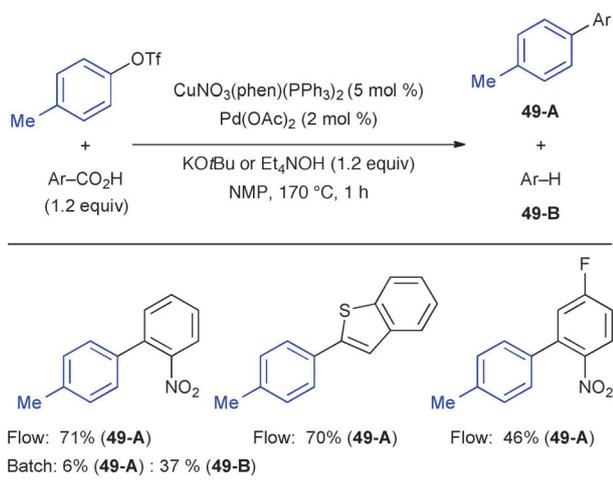
Scheme 46 Microreactor setup for the continuous-flow two-step lithiation/Murahashi coupling (Yoshida *et al.*).²¹⁷



Scheme 47 Influence of reaction temperature (T^2) and residence time (t^{R^2}) on the Murahashi coupling in flow. (Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)²¹⁷



Scheme 48 Decarboxylative cross-coupling protocol.



Scheme 49 Decarboxylative cross-coupling of aryl triflates and aryl carboxylic acids in continuous flow (Underwood, Gooßen *et al.*)²²²

In order to overcome this problem, potassium *tert*-butoxide (KOtBu) was replaced as the base by tetraethylammonium hydroxide (Et₄NOH). Several biaryls could be obtained in good yield (Scheme 49). Compared to batch, better yields, few side reactions (arising from protodecarboxylation and homocoupling) and shorter reaction times (1 h *versus* 16 h in batch) were typically observed in flow.

3. C–N bond formation in flow

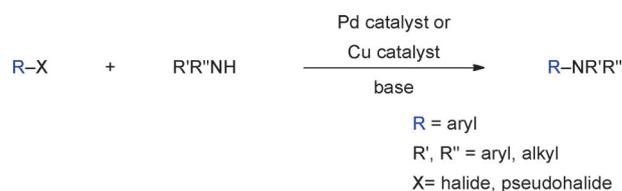
Palladium-catalyzed amination reactions constitute an important tool for the construction of C–N bonds in the synthesis of natural products, pharmaceuticals and material science (Scheme 50).^{26,28,30,223,224} This methodology allows for the

coupling of aryl electrophiles with a variety of nitrogen nucleophiles.

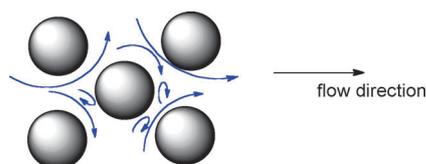
Performing palladium-catalyzed C–N cross-coupling reactions under flow conditions has proven to be challenging due to the formation of inorganic salts, which are insoluble in non-polar solvents typically used for these transformations. The formation of precipitates usually leads to irreversible clogging of the microchannels. Naber and Buchwald have described the use of a biphasic amination reaction in toluene and water, which could solubilize both the organic and inorganic salts.¹⁴² However, the use of immiscible liquid phases results in slug flow, which is characterized by a relatively small interfacial area. This could be overcome when packed bed reactors, filled with stainless steel spheres (60–125 μm), were used which improves the contact between the two phases (Scheme 51). In addition, it was found that the mixing efficiency was dependent on the flow rate; high flow rates provided the most efficient mixing, making the use of packed bed reactors more effective for fast reactions (Scheme 52).

Although biphasic conditions are an effective way to deal with solid precipitations,^{225–227} adding an additional solvent requires a reoptimization of the reaction conditions and can reduce the reaction efficiency. Therefore, in order to increase the efficiency of palladium-catalyzed C–N cross-coupling reactions in continuous-flow, Jensen, Buchwald and coworkers studied the mechanisms that lead to microchannel blockage.²²⁸ It was found that particle-to-particle interactions can lead to the formation of larger aggregates, which ultimately form a ‘bridge’ across the microchannel (Scheme 53, a). This clogging mechanism is called bridging and is enhanced due to the presence of particles with larger diameters (D_p). However, the authors found that applying ultrasonic irradiation could break these agglomerates apart and reduce the average particle size diameter (D_p), which eliminated clogging due to bridging.²²⁹ Upon closer inspection of the reactor, a second mechanism that leads to clogging was identified. Although the reactor was not yet irreversibly clogged, it was found that material was deposited on the surface of the reactor walls, which gives rise to a time-dependent decrease of the channel diameter (D_1 decreases to D_2 over time) (Scheme 53, b). This clogging mechanism is referred to as constriction and governs plugging over time. By increasing the fluid velocity, constriction could be avoided through abrasive interactions with the suspended particles.

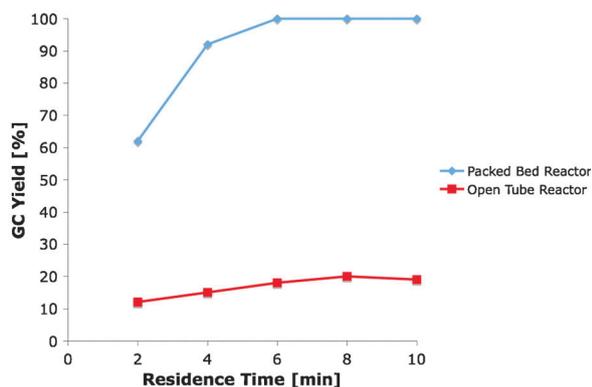
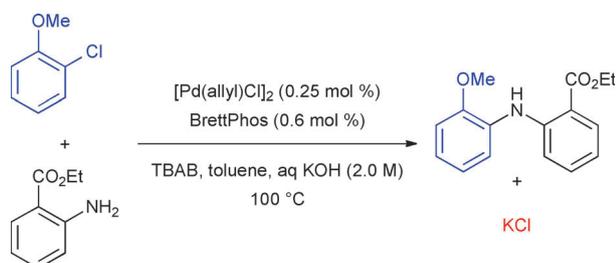
Based on these results, Buchwald, Jensen and coworkers developed an automated microfluidic system, immersed in an ultrasonication bath, that could handle the solid by-products formed in the palladium-catalyzed amination reaction (Scheme 54).²³⁰ Two situations that caused clogging were



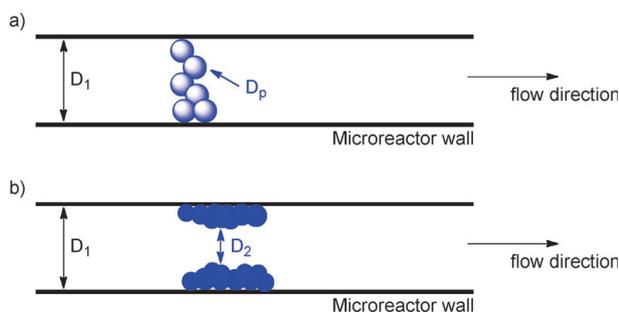
Scheme 50 C–N cross-coupling reaction.



Scheme 51 Mixing of fluid elements in a packed bed reactor.

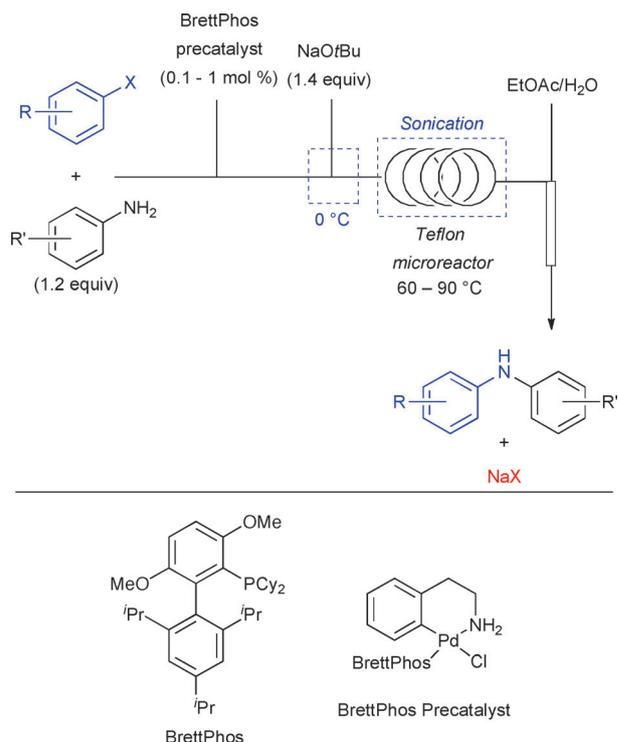


Scheme 52 Comparison of the yield obtained in a packed bed reactor and an open tube reactor for the coupling of *o*-chloroanisole and ethyl 2-aminobenzoate under biphasic conditions (Naber and Buchwald).¹⁴²



Scheme 53 Schematic representation of the clogging mechanisms observed in continuous-flow palladium-catalyzed aminations: Inset (a) shows bridging, while inset (b) depicts constriction.

identified. First, when using precatalysts based on dialkyl biarylmonophosphines,^{231–233} reactions were initiated and finished within seconds. However, these conditions caused clogging at the tee-mixer due to a fast generation of solids. Cooling prevented any significant reaction from taking place in the mixer and, as a result, clogging was prevented. Second, blockage at the end of the reactor was observed for slower reactions (reaction time ≥ 5 min). This could be circumvented when the reaction was quenched with water and ethyl acetate

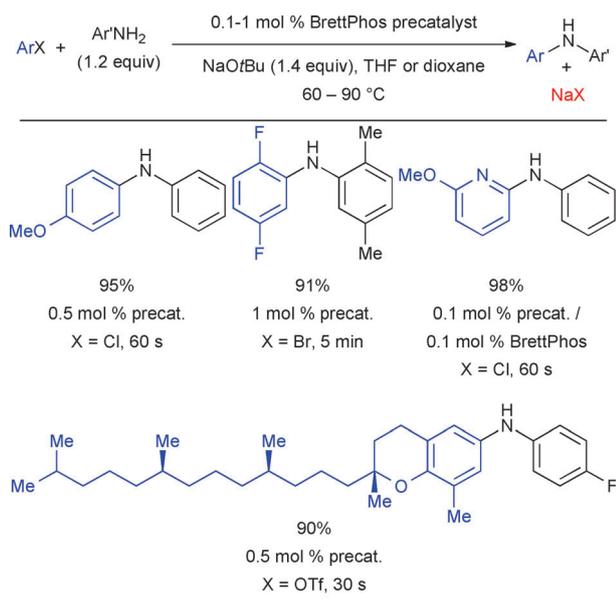


Scheme 54 Microreactor setup that can handle solids formed during the palladium-catalyzed C–N cross-coupling reactions (Buchwald, Jensen *et al.*).²³⁰

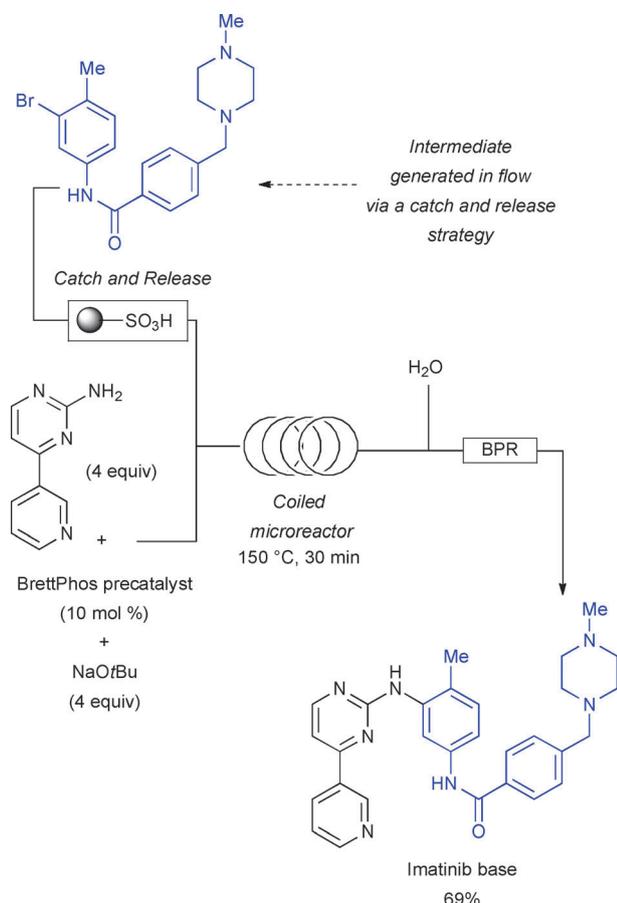
in a piece of larger diameter tubing, which provided enough time for the dissolution of the precipitates. Next, the optimized system was used in the palladium-catalyzed amination reaction of aryl chlorides, aryl bromides and aryl triflates (Scheme 55). It was shown that there was no loss in activity under continuous-flow conditions. Due to the increased mass- and heat-transfer in microfluidics, a higher activity was observed in flow compared to batch at very short residence times (*e.g.*, 20 s).

In certain cases, the formation of inorganic salts could be circumvented when soluble organic bases and polar solvents were employed.^{121,191} Researchers at Rhodia Recherches reported that slurries formed during the amination reaction could be handled without clogging when high flow rates (1 mL min^{-1}) and diluted conditions were used.²³⁴

Ley and coworkers have extensively detailed the use of immobilized reagents, catalysts and scavengers in flow.^{70,81,235–237} This strategy allows for the synthesis and purification of complex molecules without the use of conventional work-up procedures. More recently, Ley reported the synthesis of imatinib base (Gleevec[®]) in flow, a protein kinase inhibitor used in the treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors (Scheme 56).²³⁸ The final step involved a palladium-catalyzed C–N cross-coupling reaction. The intermediate for the C–N coupling was synthesized in flow using a ‘catch and release’ strategy, which allowed for purifications and solvent switches in an automated fashion. Next, this intermediate was loaded on a silica-supported sulfonic acid column and was, subsequently, released with DBU and 1,4-dioxane/*t*BuOH (2:1). This stream was merged

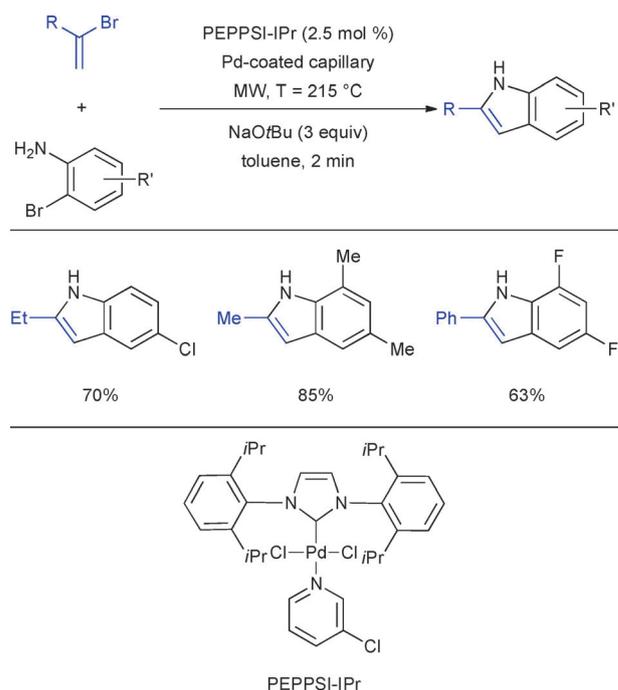


Scheme 55 Formation of diarylamines in a continuous-flow synthesis (Buchwald, Jensen *et al.*).²³⁰



Scheme 56 Flow synthesis of imatinib base (Ley *et al.*).²³⁸

with a solution of amine, BrettPhos precatalyst and NaOtBu in 1,4-dioxane/*t*BuOH (2 : 1), which was preloaded in a sample loop. The combined streams were then introduced into a



Scheme 57 Microwave-assisted continuous-flow synthesis of indoles involving a sequential aryl amination/Heck coupling (Organ *et al.*).²³⁹

coiled reactor heated to 150 °C. The authors found that the use of the BrettPhos precatalyst was required to eliminate the formation of palladium black. Clogging of the backpressure regulator (BPR) due to NaBr formation could be avoided by the addition of a water stream before the BPR. Imatinib base could be obtained in good yield for the final step (69%) on a 0.094 mmol scale.

Organ and coworkers used a microwave-assisted capillary-based flow system (*vide supra*) for the two-step synthesis of indoles.²³⁹ The synthesis involved a sequential amination/Heck coupling employing a PEPPSI-IPr catalyst (Scheme 57). It was shown that the combination of the PEPPSI-IPr catalyst and the use of a Pd-coated capillary was required to obtain complete conversions.

Conclusions and outlook

The primary motivation behind the development of continuous-flow synthesis methods is to eliminate waste within all aspects of the manufacturing process.^{240–244} Implementation of continuous-flow processes allows for reductions in building footprint, less handling of intermediates, and decreased throughput time from starting material to final product. However, despite these appealing advantages, the evolution from batch to continuous-flow methods is often not straightforward and has met with skepticism.²⁴⁵ In particular, the use of continuous-flow for multistep syntheses remains a challenging undertaking since the presence of excess reagents and impurities often complicate downstream reactions.

To address these issues, the development and implementation of new and more powerful microfluidic continuous unit operations will be necessary, such as multi-stage microfluidic distillations, crystallizations, and solid particle separators.

Moreover, in order to run the continuous manufacturing process at a steady state without any intermediate handling, advances in the development of robust process control systems are expected. Realization of these goals will require a multi-disciplinary approach in which chemists, engineers, software developers are involved.

A remarkable amount of progress has been reported during the last few years for the application of cross-coupling reactions in continuous-flow. Enhanced reactivities and selectivities compared to batch are typically observed. In continuous-flow, cross-coupling reactions can be performed under conditions that cannot be easily realized in traditional reaction flasks due to safety reasons (e.g., use of solvents at elevated temperatures and pressures). However, many opportunities still remain for improvement in these systems. Notably, the development of more efficient catalyst recycling systems would be interesting from an economical and ecological standpoint and would require the development of highly stable catalyst systems and innovative catalyst recycling units. Additionally, active pharmaceutical ingredients (API) are typically highly polar and insoluble in many solvents, rendering them difficult to handle in microfluidic systems.²⁴⁶ Thus, the development of devices that can introduce and handle slurries is of utmost importance.

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