Organic Process Research & Development **2008,** *12,* 468–474

Reviews

Transition Metal-Catalyzed Carbon−Carbon Bond Formation Suzuki, Heck, and Sonogashira Reactions Using Microwave and Microtechnology

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Abstract:

The fast growing field of microwave and microreactor technology has a significant impact on scaling up when combined with microwave irradiation for a wide variety of transition metal-catalyzed reactions. The combination of reactor design with immobilisation techniques is very important for the flow process, allowing maximal interaction between reagents and a catalyst with no clogging problem. In this review, we have presented the scale-up possibilities for a variety of transition metal-catalyzed C−C bond-forming reactions applying microwave heating and microtechnology.

Introduction

In the past decade, metal-catalyzed cross-coupling reactions have emerged as a tremendously powerful synthetic tool and have reached a level of sophistication that allows a wide range of coupling partners to be combined efficiently. Homogeneous transition metal-catalyzed reactions represent one of the most important and best-studied reaction types in microwave-assisted organic synthesis (MAOS). Transition metal-catalyzed carbon−carbon and carbon−heteroatom bond-forming reactions typically need hours or days to reach completion with traditional heating and often require an inert atmosphere. The use of metal catalysts in conjunction with microwaves (MW) may have significant advantages over traditional heating methods, since the inverted temperature gradients under microwave conditions may lead to an increased lifetime of the catalyst through elimination of wall effects. So far, most of the chemistry performed in dedicated microwave instruments has been performed on a small (up to 1 g) scale, whereas industrial companies need reactors allowing the formation of kilograms of product with a minimal reoptimization of the synthetic protocol. Scale-up of microwave-promoted reactions has been an issue of considerable interest over the past few years. Although chemists have demonstrated that microwave chemistry has the advantage of greatly reducing reaction times and even improving product yields when reactions are run on a small scale, translation of methodologies to a larger scale can be problematic.

Two different approaches have been followed leading to the creation of batch and continuous-flow reactors (mono- and multimode). The major drawback of batch reactors appeared to be a restricted penetration depth of the microwaves, in the order of a few centimeters, depending on the dielectrical properties of the medium and the dimensions of the cavity. Therefore, scale-up of batch-mode reactions beyond 1 L seemed not to be feasible.[1] This problem was partially solved by the introduction of multivessel rotors which allow the irradiation of a selectively large total volume in one run without a penetration depth issue.[2]

On the other hand, the first continuous-flow reactor was introduced by Strauss in 1994, combining two “enabling technologies”, microwave heating and flow processing.[3] The modern continuous-flow reactors allow reactions to be carried out on a multigram scale using commercially available MW equipment.[2] However, clogging is often a problem in case of heterogeneous reaction mixtures. As a consequence, the stop-flow technique (automated batch processing) was developed which combines benefits of the batch method and some features of flow processing. The reaction mixture is pumped into the reaction vessel, irradiated, and consecutively pumped into a receiver, evacuating the vial for the next reaction to be launched. In recent years, new systems were introduced which have certain advantages over commercially available equipment making the large-scale preparations more efficient.

In order to improve the efficiency of microwave-assisted flow reactors, a flow cell was designed using a monomode MW synthesizer with the temperature control by a built-in IR sensor. This flow cell presented a standard glass tube, and thus, no additional and expensive equipment is required, other than a

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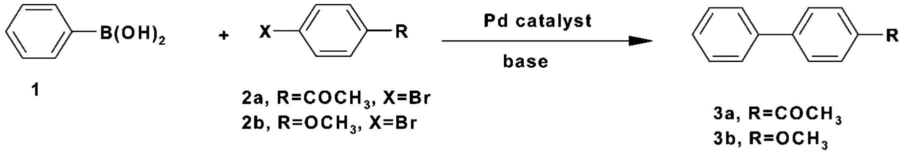
Scheme 1. **Palladium-catalyzed Suzuki cross-coupling reaction applying a flow-injection packed-bed microreactor**



short HPLC pump. Heterogeneous reactions can be carried out simply by immobilizing a catalyst on the support of the glass tube.[4]

Microreactor technology has also received great attention for scale-up of organic reactions.[2,5,6] Microreactors are inherently less wasteful than traditional reactors and allow unprecedented reaction control. Microreactors consist of a series of small (10−100 μm) connected channels that allow for manipulation of small amounts of fluids where diffusion is responsible for efficient mixing. Because of this and the rapid heat transfer, reactions can be carried out significantly faster that those in batches, often resulting in an increase in both yield and selectivity. For scale-up purpose, multiple reactors can be coupled in parallel, avoiding the need for additional optimization once moved to production scale.[5] A novel plastic microcapillary flow disk reactor (MFD) made from a thermosetting plastic film, shows good potential for scale-up due to the presence of a large number of microchannels per device and the simplicity for arranging several of these devices in parallel. The high surface-to-volume ratio is beneficial in terms of higher boiling points, greater solubility, and higher diffusion rates. It is also ideal for the immobilization of reagents, catalysts and scavengers.[7]

In this review we will focus on the scale-up of transition metal-catalyzed carbon−carbon bond-forming reactions applying microwave and microreactor technology.

Transition-Metal Catalyzed Reactions. The Suzuki−Miyaura cross-coupling reaction is one of the most commonly used methods for carbon−carbon bond formation in the chemical and pharmaceutical industry due to its selectivity and mild and versatile nature. The Suzuki coupling reaction of on aryl halide or its synthetic equivalent such as an aryl triflate with an organoboron compound requires a palladium catalyst, most frequently tetrakis(triphenylphosphine)palladium(0) in solvents such as dimethoxyethane (DME), benzene, or tetrahydrofuran (THF).[8–10] However, the degradation of the homogeneous catalyst system can result in undesirable byproducts in the final product, as for example, triphenylphosphine oxide and palladium metal. To circumvent this, Beller et al.[11] have performed a Suzuki coupling reaction of phenylboronic acid (**1**) and the aryl halide **2**, reporting a yield of 83% using palladacycles as efficient catalysts (using a mere 0.02 mol % of the catalyst) at 130 °C.

Haswell and co-workers have studied microwave-assisted Suzuki coupling reactions (Scheme 1) in a flow-injection packed-bed (1.8% Pd/SiO_2) microreactor using an electroosmotic flow.[12] The authors have demonstrated that the formation of triphenylphosphine oxide and colloidal palladium, which are difficult to isolate, can be prevented by using a supported immobilized palladium catalyst. The use of this reactor setup also prevents the diffusion of the catalyst into solution, allowing long-term activity and avoiding the removal of catalyst impurities afterwards. This flow-injection microreactor has been used for a large number of reactions (operation over 35 h) with no apparent loss of catalytic activity.

In their further studies, the authors developed a more general method for running Suzuki reactions in microreactors using a syringe-pump-driven flow.[13] In this case, Pd on alumina served as the catalyst. For efficient energy transfer, the authors used microwave irradiation and implanted a thin gold patch directly over the packed channel (Figure 1).[12] In this case, the gold served to absorb the MW radiation and heat the interior of the channel to approximately 100 °C. Although the gold patch showed degradation after extended MW exposure, reactions achieved 58−99% conversion with irradiation time of a mere 60 s. The authors also developed a more general method for running Suzuki reactions in microreactors, using a syringe-pump-driven flow.[13] In this case, 4% Pd anchored on polystyrene beads was effective, giving similar conversions and providing a more cost-effective solution, when compared to the gold patch (Figure 2).[13]

New enabling techniques have emerged in the past decades that have influenced the way in which organic synthesis is performed on a laboratory scale.[14] These techniques combine reactor design with optimized monolithic solid phase as well as reversible immobilization techniques. They have been applied in laboratory-scale synthesis using heterogeneous catalyst under continuous-flow conditions (Scheme 2).[14] Ley and co-workers investigated the use of a polyurea-encapsulated palladium(II) acetate [PdEnCat] precatalyst in conjunction with tetrabutylammonium acetate in ethanol for Suzuki cross-coupling, using microwaves under continuous-flow conditions (Figure 3).[15] They have found that this catalyst system when used in conjunction with microwave heating shows high reactivity and prolonged lifetime. They have also observed improved yield and product purities, employing simultaneous cooling. They have used this pulsing or power cycling regime for a number of Suzuki cross-coupling reactions and found dramatic decrease in side reaction products, and thermal decomposition of product and catalyst.[15]

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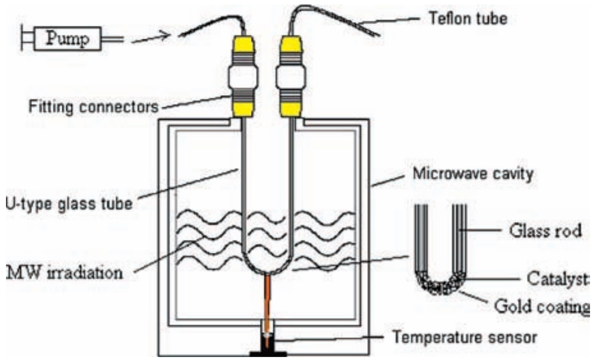


Figure 1. **Setup for microwave-assisted coupling reactions using solid Pd-supported catalyst located within a continuous-flow capillary reactor.**

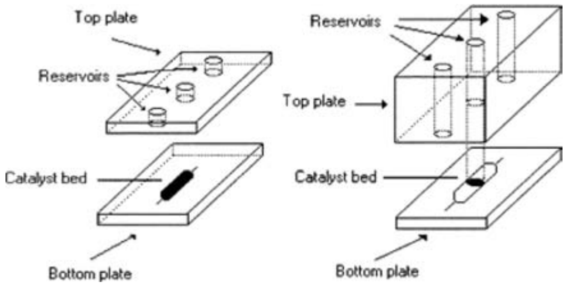
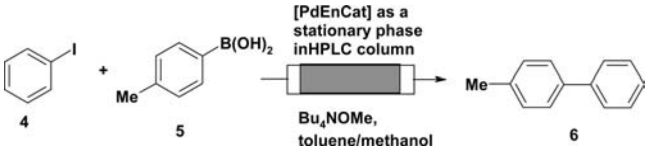


Figure 2. **Linear channel microreactor design and catalyst packing strategies used to perform Suzuki-based reactions.**

Scheme 2. **Transition metal-catalyzed Suzuki cross-coupling reactions under continuous-flow conditions**



At 55 °C, low to moderate yields were obtained in the presence of Bu_4NOAc and Bu_4NF as bases. Better results were obtained with Bu_4NOH and Bu_4NOMe, affording 70 and 85% yields, respectively, after three passes through the column. The best result was attained with Bu_4NOMe at 70 °C after a single pass through the [PdEnCat] column. Noteworthy, Bu_4NOMe was the only base employed that did not result in phase separation of the reaction mixture. Obviously, the stable homogeneous state of the reaction mixture during the whole run of the reaction period is very important for the continuous-flow process allowing maximum interaction between reagents and catalyst.[14]

The previously discussed methods, where the outside surface of the reaction chamber was coated with a gold film, provides heat transfer by convection.[12] An alternative method was demonstrated by Organ, where the capillaries were internally coated with a film of Pd metal. This provided a tremendous acceleration in rate for Suzuki reactions and enhanced conversion.[16] It was found that the percent conversion in capillary-irradiation-based reactions was influenced by the flow rate, capillary internal diameter, power setting, metal coating in the capillary, and molarity and choice of the solvent.[17] Reactions that contained solids showed no problems with blocked channels, which is very important for continuous-flow preparations.

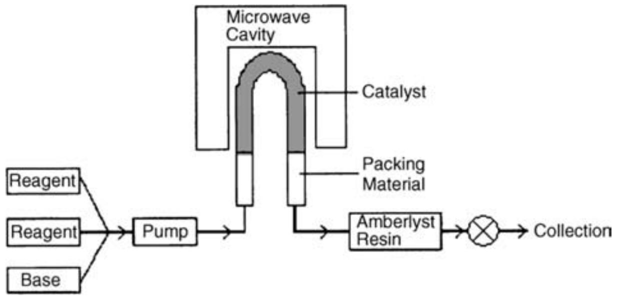


Figure 3. **Flow reactor.**

More recently, the same group has described the highly porous Pd films composed of nanometer-sized grains containing 94.0 wt % Pd and 5.5 wt % carbon (Figure 4).[17] These grains served as excellent catalyst for Suzuki−Miyaura reactions given the very short time (of less than 1 min) the reaction mixture actually spends in the capillary. Scale-up can be achieved by simply flowing for longer times, so no reoptimization for the different batch sizes was needed. The authors have prepared gram quantities of the coupled product by flowing the reaction mixture through the single capillary for about 90 min.[18]

Leadbeater has reported the microwave-assisted ligand-free palladium-catalyzed Suzuki couplings of aryl halides with boronic acids using water as solvent.[19] Palladium acetate loadings as low as 0.4 mol % proved to be sufficient, and with addition of 1 equiv of the phase-transfer catalyst, tetrabutylammonium bromide (TBAB), aryl bromides and iodides could be coupled successfully in high yields and short reaction times. For reactions with aryl chlorides, the temperature had to be raised to 175 °C, although lower yields were obtained. By applying the same protocol, a 10-fold scale-up was possible under microwave-assisted open-vessel reflux conditions for 10 min at 110 °C, achieving nearly identical yields to the closed-vessel runs.[20] They have clearly demonstrated that under these condition Suzuki cross-coupling can be performed equally well using microwave and conventional heating without nonthermal microwave effect. As oil baths are more readily available in laboratories than focused microwave reactors, the conventional thermal heating method is perhaps of more synthetic use and offers an easy and fast method for making gram quantities of biaryls. In their further investigations, the authors discovered a “transition metal-free Suzuki-type coupling” where, without the addition of any palladium source, high yields of biaryl compounds were achieved.[21] Later they found that ultralow levels of palladium, as low as 50 ppb, included in the sodium carbonate base, were responsible for the successful Suzuki couplings.[22] For a further scale-up, the authors switched to an open-vessel microwave protocol again using low levels of Pd

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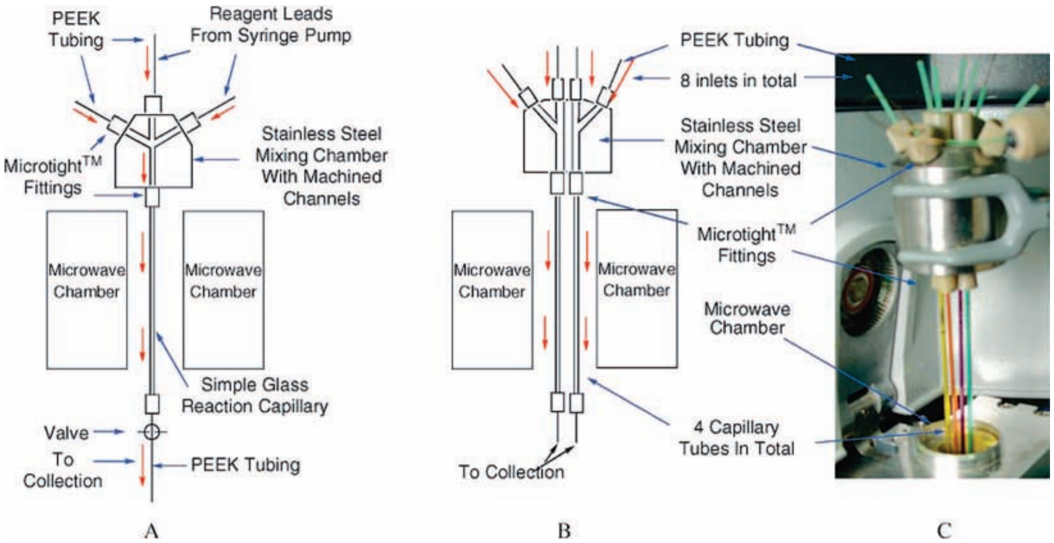
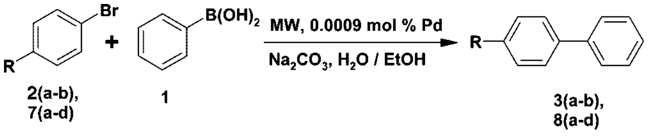


Figure 4. **Continuous-flow, capillary MW microreactors. (A) Single capillary reactor system. (B) Parallel, capillary multireactor system. (C) Photograph of the parallel, capillary multireactor system.**

Table 1. **Open-vessel microwave-assisted Suzuki reactions in water on the 1 mol scale**[a]



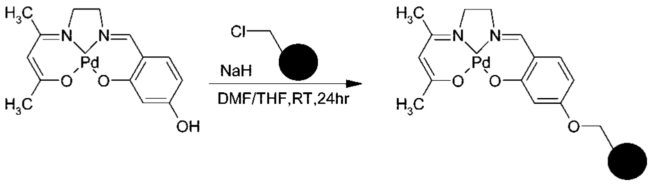
entry	aryl bromide (R =)	product conversion (%)
2a	$COCH_3$	99 (99)[b]
2b	OMe	99 (96)[b]
7a	NO_2	94
7b	Me	87
7c	COOH	94 (93)[b]
7d	NH_2	50 (99)[c]

[a] Reactions were performed using 1 mol aryl halide, 1.2 mol phenylboronic acid, and 0.0009 mol % Pd as catalyst. Reaction mixtures were heated from room temperature to reflux (80−83 °C) using an initial microwave power of 600 W and held at this temperature for 20 min. [b] Isolated product yield. [c] Using 0.0045 mol % Pd as catalyst.

catalyst (as low as 0.0009 mol %).[23] The TBAB/water combination was changed for a water/ethanol (1:1) mixture due to purification problems and economy reasons when going from small to a larger scale. Different para-substituted aryl bromides **2**(**a**,**b**), **7**(**a**,**d**) could be coupled with phenylboronic acid (**1**) in good to excellent yields under reflux microwave conditions (20 min at 80−83 °C) with a Pd loading of 1−5 ppm. The reaction can be scaled up from 5 mmol employing a single-mode instrument in a 100 mL round-bottom flask up to 1 mol using a 3 L reaction vessel in a multimode reactor (Table 1).[24]

In another attempt to scale up Suzuki coupling reactions, Leadbeater used a MW setup which combines the advantages of a batch reactor with continuous-flow equipment.[25] As in the previous experiments, in order to increase the solubility of the organic reagents an ethanol/water (1:1) mixture was used as the solvent. However, this led to solubility problems caused by the inorganic base, resulting in line clogging problems. Several amine bases were scanned, and the best results were obtained applying 1 equiv of DBU (1,8- diazabicyclo[5.4.0]undec-7-ene) in combination with 0.4 mol % of $Pd(OAc)_2$ in a mixture of water/ethanol (1:1) at 150 °C for 10 min on a 1 mmol scale. Appling the same methodology, the reactions could be scaled up to 20 mmol per batch using a hybrid stop-flow apparatus to afford biaryl components in similar yields as in the small-scale experiment.[25]

Scheme 3. **Immobilisation of the salen-type palladium(II) complex**



Styring et al. have performed continuous-flow Suzuki−Miyaura reactions in a pressure-driven miniflow reactor packed with Merrifield resin supported on salen-type palladium(II) complex (Scheme 3).[26] Reasonable conversions providing yields of 37−91% could be achieved, a 20-fold increase in the rate of the model reaction between 4-bromoanisole (**2b**) and phenylboronic acid (**1**) (Scheme 4) was obtained compared with that of the classical stirred batch reaction. This was explained by the increased reagent−catalyst contact in the continuous-flow process. Moreover, the immobilized catalyst could be used over several cycles for the Suzuki−Miyaura couplings without a significant drop of activity.

The palladium-catalyzed C−C coupling reaction between unsaturated halides or triflates and activated alkenes in the presence of a base is referred to as the Heck reaction, or sometimes as the Mizoroki−Heck reaction.[27] Recent developments in the catalysts and reaction conditions have resulted in

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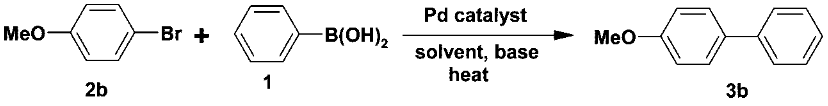
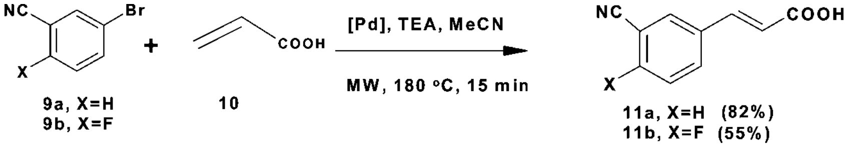
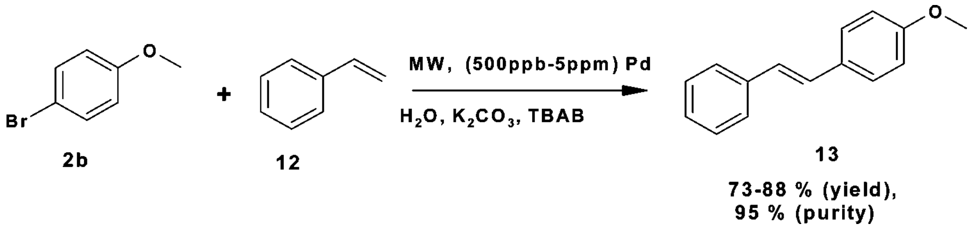
Scheme 4. **Suzuki−Miyaura reaction of 4-bromoanisole and phenylboronic acid on immobilized salen-type palladium(II) complex**



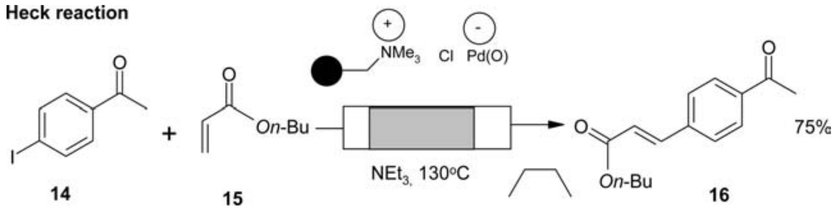
Scheme 5. **Heck reaction using multimode microwave batch reactor**



Scheme 6. **Optimization of conditions for the scale-up of microwave-promoted Heck coupling reaction in water using an automated batch stop-flow reactor**



Scheme 7. **Heck transformations applying a continuous-flow reactor containing a mega-porous glass carrier material**



a much broader range of coupling partners being amenable to this chemistry.

In 2003, Kappe described the scale-up of a Heck reaction using a prototype laboratory-scale multimode MW batch reactor.[28] In their study they initially used a homogeneous $Pd(OAc)_2$/tri(*o*-tolyl)phosphine catalyst system and then changed to a heterogeneous catalyst (5% Pd/C, <0.1 mol %). They have shown that the yields for the coupling of aryl bromide **9**(**a**,**b**) with acrylic acid (**10**) (Scheme 5) are similar using either homogeneous or heterogeneous Pd catalyst under small-scale (2 mmol) single-mode condition.[28] For scale-up, they used the same protocol of homogeneous catalyst on a 4 × 20 mmol scale in a multimode batch reactor and found consistency in yields with the small-scale microwave experiments. In their further studies, they found that the homogeneous catalyst system $Pd(OAc)_2$/tri(*o*-tolyl)phosphine and heterogeneous catalyst system Pd/C provided identical isolated yields for these couplings.

Leadbeater et al. have described the application of an automated batch stop-flow microwave apparatus for scaling up of a Heck coupling reaction in water using ultralow catalyst concentration.[29] Using 4-bromoanisole (**2b**) and styrene (**12**) (Scheme 6) as test substrates, they have optimized the amount of base, phase transfer catalyst TBAB, solvent system, and the catalyst. By running 10 cycles of a 10 mmol reaction, the authors obtained the desired alkene (14.9 g) in a yield of 85%.

Kunz et al. have described Heck cross-coupling reactions using a continuous-flow reactor based on the megaporous glass carrier material with suitable polymer functionalization (Scheme 7) introduced into the pore volume of this support.[30] For this purpose, a basic ion-exchange resin-loaded monolith was used in order to create the close neighborhood of ionic sites and Pd(0) sites. Pure products were collected without the necessity of extensive purification steps. The combination of composite-based flow-through reactors with microwave irradiation may lead to new and effective methods to scale up organic reactions.

Recently, Organ has prepared highly porous Pd films composed of nanometer-size grains.[16] These Pd films served as an excellent catalyst for Heck reactions under continuous-flow microwave conditions. The authors have shown that 10 mg of product can be obtained from this reactor system within 1 min. Gram quantities of the products have been obtained by flowing reaction mixtures through a single capillary for about 90 min.

Very recently, Ley has developed an automated reactor for performing ligand-free Heck reactions in continuous-flow mode.[31] The reactor utilizes a monolithic reactor cartridge derivatized with Pd(0) nanoparticles in-line with a scavenging

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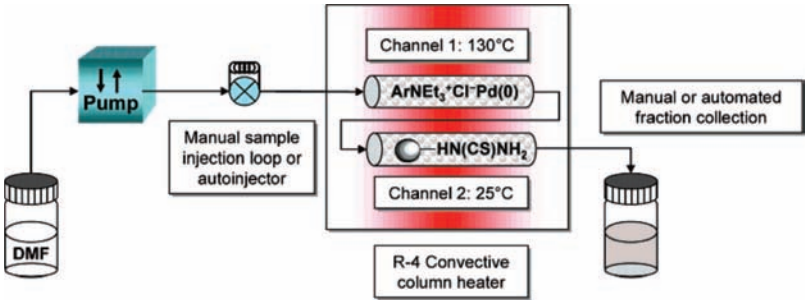
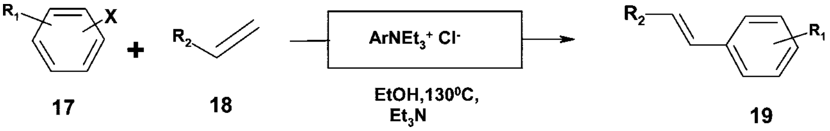
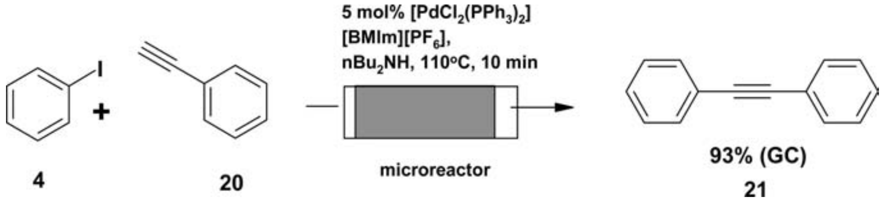


Figure 5. **Flow-through reactor setup.**

Scheme 8. **Heck cross-coupling reaction in superheated ethanol**



Scheme 9. **Sonogashira cross-coupling in microreactor using ionic liquid**



cartridge containing Quadrapure-TU (Figure 5) to efficiently capture palladium residues, affording Heck reaction products in high purity.[31] The authors have examined initially the effectiveness of this monolithic reactor to promote Heck cross-coupling using a variety of aryl halides **17** and alkenes **18** in DMF as solvent, taking benefit of its high boiling point. Later on, because of toxicity and difficulty in removing DMF from the reaction mixture, DMF was replaced by ethanol, operating under superheating conditions at elevated pressure to prevent boiling. The reaction mixtures were safely heated at 130 °C under continuous-flow conditions (Scheme 8), and it was noted that the reactions proceeded just as efficiently as when DMF was used as the solvent system.

The palladium- and copper-cocatalyzed coupling of terminal alkynes with aryl halides, the Sonogashira reaction, is one of the most widely used tools for C−C bond formation. The Sonogashira reaction has a broad scope and tolerates several functional groups. Since its discovery, a variety of modifications were reported, including microwave-assisted conditions, as well as Pd-free and copper-free versions.[32]

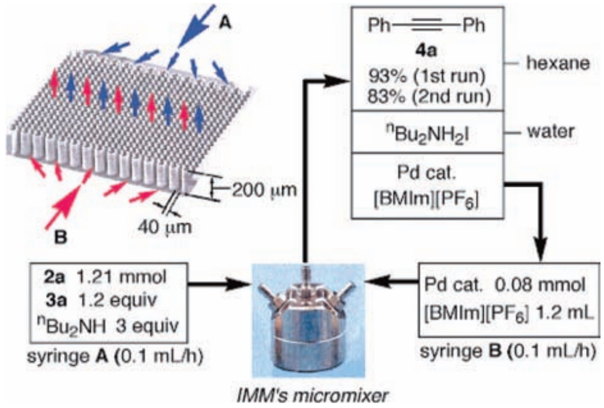


Figure 6. **Sonogashira reaction in a microflow system.**

Ryu described the first successful example of a Sonogashira cross-coupling reaction in a microflow reaction device (Figure 6).[33] This example is one of the first homogeneous metal-catalyzed reactions performed in a microreactor. A mixture of iodobenzene (**4**), phenylacetylene (**20**) and *n*-dibutylamine was introduced at one inlet of a micromixer. The catalyst [PdCl$_2$(PPh$_3$)$_2$] in the ionic liquid [BMIm][PF$_6$] (*N*-butyl-*N*′-methyl-imidazolium hexafluorophosphate) was introduced at 110 °C through a second inlet by means of syringe pumps at flow rates of 0.1 mL/h (Scheme 9). After homogenizing the reagents in the micromixer, the reaction mixture was collected from the outlet after 10 min. The product could be easily separated by extraction with hexane/water, leaving the catalyst in the ionic liquid allowing efficient recycling and reuse. They have also observed that when this reaction was performed without the microreactor the yield was almost same with longer reaction time of 2 h.

Haswell has developed a salen-type nickel(II) complex immobilized on Merrifield resin which was used to perform Kumada−Corriu coupling reactions of aromatic halides with Grignard reagents in continuous-flow mode (Scheme 10).[34] A microreactor was constructed by placing a plug of catalyst into the polypropylene tube. Standard HPLC connectors and a syringe pump were applied to drive a premixed solution of equivalent quantities of the 4-bromoanisole (**2b**) and Grignard reagent **22** through the reactor. An enhanced rate (3300) of the

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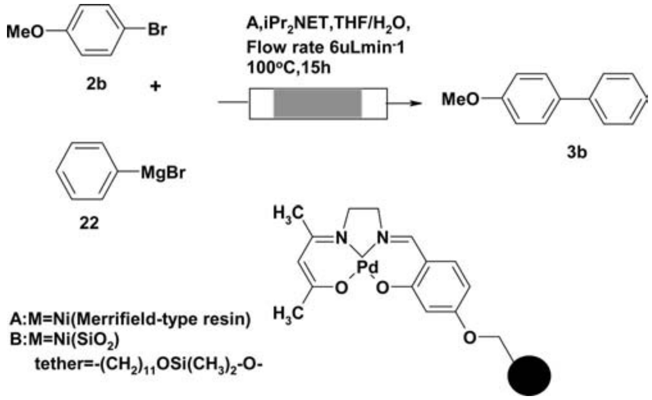
(32) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874–922.
(33) Fukuyama, T.; Shinmen, M.; Nishitani, S.; Sato, M.; Ryu, I. *Org. Lett.* **2002**, *4*, 1691–1694.
(34) Haswell, S. J.; O'Sullivan, B.; Styring, P. *Lab Chip* **2001**, *1*, 164–166.

Scheme 10. **Kumada−Corriu coupling reactions in continuous flow**



4-methoxybiphenyl (**3b**) formation was observed in the microreactor as compared with that of the batch method.

The same nickel(II) complex was immobilized onto functionalized silica gel using a convenient tethering method.[35] The Kumada−Corriu coupling reaction was carried out at room temperature in a pressure-driven microflow reactor (length 25 mm, inner diameter 3 mm) containing functionalized silica (ca. 0.15 mmol Ni/g silica gel loading) to yield the coupling product within 5 h. The authors claimed negligible leaching of the metal into solution and noted that the major advantage of these functionalized inorganic materials are their nonswelling properties which is a common problem associated with polymeric supports.

Conclusion

Transition metal-catalyzed carbon−carbon bond formation is an undoubtedly fast-growing research field with enormous academic and industrial interest. Microwave heating seems to be particularly competitive with the transition metal-catalyzed process, not only bringing long reaction times down to minutes but also minimizing the levels of undesired side products as well as preventing the catalytic system from collapse. The introduction of dedicated microwave ovens has solved many of safety and reproducibility issues, allowing the formation of several hundred milligrams of the product per run. Nevertheless, microwave synthesis is not easily scalable to multikilogram and especially to the semiplant scale.[1]

For scale-up purposes, historically two different approaches, batch and continuous-flow, have been followed. The fast-growing field of microreactor technology can have a significant impact on scaling up when combined with microwave irradiation. The increased control over reactions and the potential for catalyst recycling may offer a better solution for optimizing transition metal-catalyzed chemistry on both laboratory and industrial scale.

In this review, we have summarized the scale-up possibilities for a variety of transition metal-catalyzed C−C bond-forming reactions applying microwave heating and flow conditions. The combination of reactor design with immobilisation techniques is very important for the flow process, allowing maximal interaction between reagents and catalysts with no clogging problem. Moreover, the immobilized catalysts could be used over several cycles without a significant drop of activity.

Received for review March 3, 2008.

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(35) Phan, N. T. S.; Brown, D. H.; Styring, P. *Green Chem.* **2004**, *6*, 526–532.