Development of a Continuous-Flow System for Catalysis with Palladium(0) Particles

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Heterogeneous catalysis for organic synthesis under continuous-flow conditions becomes possible by a new reactor-based approach. Continuous-flow reactors with a monolithic glass/polymer composite interior are loaded with palladium particles by ion exchange followed by reduction. When incorporated into a continuous-flow setup (PASSflow) this reactor allows the transfer-hydrogenation of alkenes, alkynes, nitro-substituted aromatic compounds and benzyl ethers in the flow-through mode. In addition, the activity of the catalysts is well suited to achieve Suzuki, Sonogashira and Heck cross-coupling reactions in the absence of phosphanes or any other ligands, resulting in a greatly simplified purification. As an extension to this concept a bifunctional support was prepared inside the reactor consisting of Pd particles and an ion-exchange group (hydroxide form). In the Suzuki–Miyaura reaction the reactor serves as a base for immobilisation and activation of the boronic acid as boronate and as a catalyst for promoting the C–C coupling reaction under continuous-flow conditions.

Introduction

Solid supports functionalized with reactive species that are employed in solution-phase transformations have received a great deal of interest lately.[1] The intrinsic advantage of this hybrid solid/solution-phase technique lies in the simple purification and the possibility to use immobilised reagents in excess to drive reactions in solution to completion. Among functionalized supports, immobilised catalysts will play a major role in future applications because the realm of newly developed homogeneous transition-metal catalysts, including those with chiral ligand systems for asymmetric transformations, can be used under heterogeneous conditions.[2] Indeed, the supported catalyst can easily be separated from a reaction mixture by filtration and washing and be reused after regeneration. In some cases it has been shown that immobilised catalysts show chemical differences to their soluble counterparts, such as prolonged activity or altered selectivity. In addition, compared to stoichiometrically employed immobilised reagents, the degree of loading is often of minor interest. Finally, the opportunity to employ this technique in conjunction with continuous-flow processes is a particularly important feature as this setup creates an ideal, almost workup-free technique for automated solution-phase synthesis.[3] Recently, we reported on the polymer-assisted solution-phase synthesis in the follow-through mode (PASSflow) technique[4] which relies on a reactor system containing a monolithic block based on a chemically functionalized and highly porous polymer/glass composite material. The monolithic composite was designed in such a way that the polymer particles inside the pore volume can swell and shrink (but to a lesser extent than conventional resins), whereas the outer dimensions of the rod stay stable. This composite material was embedded in a solvent-resistant tube, followed by encapsulation within a pressure-resistant, fibre-reinforced epoxy resin casing with two standard HPLC fittings.[5] Thus, the technical problems such as bypassing or the high pressure-drop observed in sole polymer packings are avoided. A vinylbenzyl chloride based polymer was transformed into a quaternary ammonium ion which can be used for the loading of various anions that can react as immobilised stoichiometric agents in continuous-flow processes.[4] In the current study we disclose continuous-flow applications of catalysts by using the ionic exchange functionality for specifically positioning a palladium-based catalyst inside the reactor. The resulting catalytic system allows us to per-

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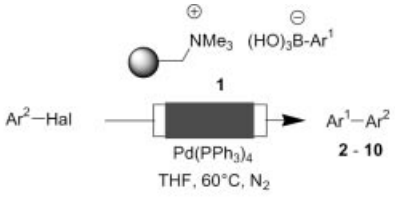
form transfer hydrogenations as well as C−C cross-coupling reactions in a continuous-flow environment without the need for additional ligands.[6]

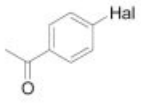
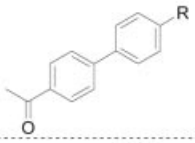
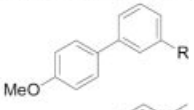
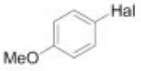
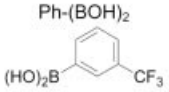
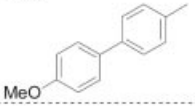
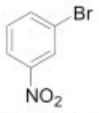
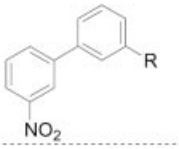
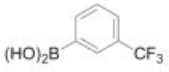
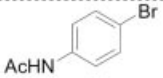
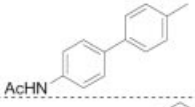
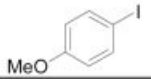
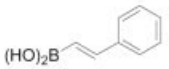
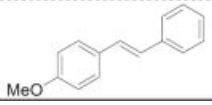
Results and Discussion

In initial studies we first tested a simple application of the Suzuki−Miyaura cross-coupling reaction under continuous-flow conditions. The Suzuki−Miyaura cross-coupling reaction is typically initiated by base-promoted activation of boronic acid under heterogeneous conditions, commonly with inorganic salts. This procedure can result in the formation of the tetrahedral $ArB(OH)_3^-$ anion, which is more reactive in electrophilic reactions than the neutral boronic acid itself.[7] However, in order to promote Suzuki−Miyaura cross-coupling reactions in our continuous-flow device containing irregular microchannels we had to choose homogeneous conditions that prevent blocking. According to Vaultier and co-workers[8] anionic exchange resins (hydroxide form) are ideally suited to activate boronic acids as tetrahedral arylboronate anions, which indeed is the case when pumping boronic acid (2−4 mmol) through a PASSflow reactor (hydroxide form; about 1 mmol capacity). The arylboronic acid or vinylboronic acid is loaded onto the reactor (about 0.7 mmol effective loading). After washing, the remaining aryl halide (0.15−0.3 mmol) and the catalyst [tetrakis(triphenylphosphane)palladium(0), 2−5 mol %] dissolved in tetrahydrofuran are circulated at 60 °C (oven temperature) through the reactor to finally yield the cross-coupling products **2**−**10** in good yields (Table 1; method A).

As expected, aryl iodides showed greater reactivity than aryl bromides. Aryl bromides with electron-withdrawing substituents (Table 1; Entries 1, 3, 9 and 10) turned out to be more reactive than those with electron-donating groups (Table 1; Entry 6), as oxidative addition of Pd^0 has been

Table 1. Suzuki−Miyaura cross-coupling reaction under continuous-flow conditions (method A)[a]

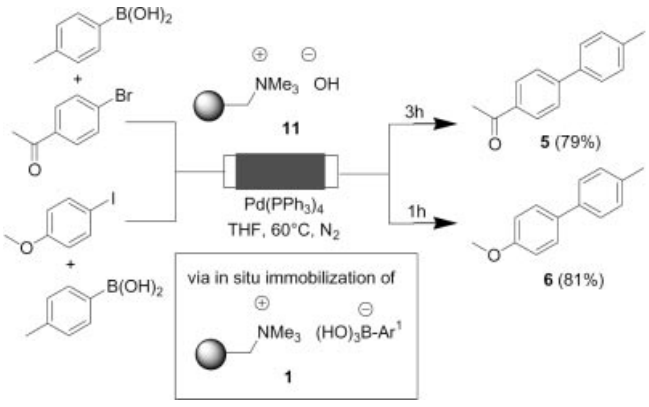


Entry	Ar^2-Hal	Ar^1-B(OH)$_2$	Conditions[b]	C-C coupling product (yield in %)[c]		
1	 Hal = Br	Ph-B(OH)$_2$	10h		**2** R = H	84
2	Hal = I	Ph-B(OH)$_2$	2.5h		**2** R = H	91
3	Hal = Br	Tol-B(OH)$_2$	4.5h		**3** R = Me	85
4	Hal = I	Tol-B(OH)$_2$	5h		**3** R = Me	84
5	Hal = I	Ph-(BOH)$_2$	2h		**4** R = H	89
6	Hal = Br		48h		**5** R = CF_3	62
7	 Hal = I		2h		**5** R = CF_3	93
8	Hal = I	Tol-B(OH)$_2$	1.5h		**6**	86
9		Ph-(BOH)$_2$	19h		**7** R = H	81
10			5.5h		**8** R = CF_3	67
11		Tol-B(OH)$_2$	18h		**9**	85
12			10h		**10**	76

[a] After washing of the reactor with 2 M HCl, 1 N NaOH, and water (pH = 7) it was reused more than 20 times. [b] All reaction temperatures in this report refer to oven temperatures. As the reaction mixture is pumped as a convective flow through the reactor it never reaches the oven temperature. We determined that the reaction mixture leaves the reactor at about 40−45 °C. [c] Isolated yields after flash column chromatography.

demonstrated to be the rate-determining step for aryl bromides.[7] The vinylboronic acid (Table 1; Entry 12) showed only moderate reactivity in comparison to arylboronic acids. In some cases, formation of minor amounts of arylboronic acid derived symmetrical biaryl compounds was observed.[9] This side reaction has no influence on the product yields because the boronic acids were typically employed in excess. In this context it is noteworthy that the excess of boronic acid as well as the boron-based by-products are not released into solution but stay immobilised in the reactor by ion exchange.

Interestingly, the Suzuki−Miyaura cross-coupling reaction in the PASSflow mode can also be carried out without preliminary immobilisation of the boronic acids on the anion-exchange resin. In a modified procedure (method B), a solution of the arylboronic acid (1.5 equiv.), aryl halide (1.0 equiv.), and palladium catalyst (2 mol %) in THF was passed through the reactor **11** (hydroxide form), which led to immediate trapping of the boronic acid (as **1**) while both the aryl halide and the catalyst were circulated through the system until the reaction was complete (Scheme 1).



Scheme 1. Suzuki−Miyaura cross-coupling reaction without preliminary immobilisation of the boronic acids (method B); isolated yields after flash column chromatography; for the regeneration procedure see Table 1

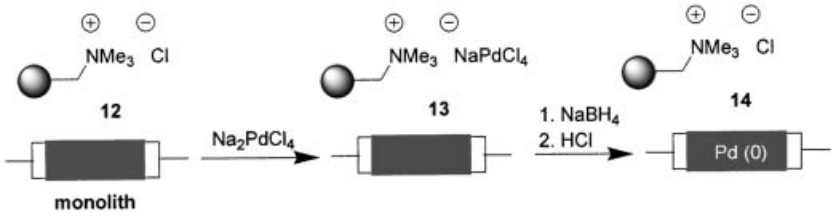
Yields for biaryl compounds **3** and **6**, reaction times and conditions are comparable with those found with pre-immobilisation of the boronic acid (see Table 1). However, simplification of the continuous-flow process is substantial in terms of handling, time and amount of boronic acid needed.

Nevertheless, the use of a soluble Pd^0 catalyst is still a major drawback of this process, particularly when scaling-up is envisaged. In the context of ligand-free catalysis transition-metal nanoparticles[10] have attracted a great deal of attention in the last decade.[11] Nanoparticles are defined as having a diameter of 1−50 nm. In this size range metals show size-dependent properties: the smaller the cluster of atoms the higher the percentage of atoms on the surface, rendering particles with diverse catalytic properties.[6] Indeed, transition-metal nanoparticles are highly active heterogeneous catalysts partly as a result of their high surface/volume ratio. Colloidal nanoclusters based on Pd/Cu which are stabilised by tetraoctylammonium bromide show enhanced activity due to synergistic effects.[12] In this context, Zecca and co-workers have investigated the activity enhancement in relation to various acidic cation-exchange resins of different properties bearing immobilised palladium(0).[13] Additionally, palladium(0) particles can be generated after reduction of tetrachloropalladate anions deposited on anion-exchange resins. Taking advantage of ionic stabilisation, as demonstrated by Reetz et al.,[14,15] we anticipated long life-cycles of our reactors and easy regeneration of the palladium(0) catalyst.

We continued the project by uniformly immobilising palladium on the surface of the polymeric composite material inside the PASSflow reactor. This was achieved by treatment of the anion-exchange resin **12** (chloride form) with an aqueous solution of sodium tetrachloropalladate (Na_2PdCl_4; Scheme 2).

Each palladate anion was then exchanged onto the quaternary trimethylammonium groups **13** and its reduction with hydrazine or a borohydride solution led to palladium(0) particles **14**. These are stable inside the reactor and hence easily storable. At this stage, we can only speculate about the size of the metal particles generated by this method. From the high reactivity of the palladium(0) species reported here, we assume that nanoparticles of so far unknown size are the active species.[6]

Scanning electron microscopy with a microprobe [electron probe microanalysis (EPMA), energy dispersive X-ray microanalysis (EDX)] revealed that two kinds of palladium particles are present. Larger palladium clusters are found on the surface of the polymer (bright white spots in Figures 1 and 2), whereas much smaller particles are often located inside the polymeric beads (size close to the detection limit of the equipment). From the mass balance calculated after the loading step it can be concluded that most of the palladium is located inside the polymer particles as nanoparticles. It seems that the reduction with $NaBH_4$ leads to



Scheme 2. Immobilisation of palladium(0) particles onto the monolithic phase inside the microreactor

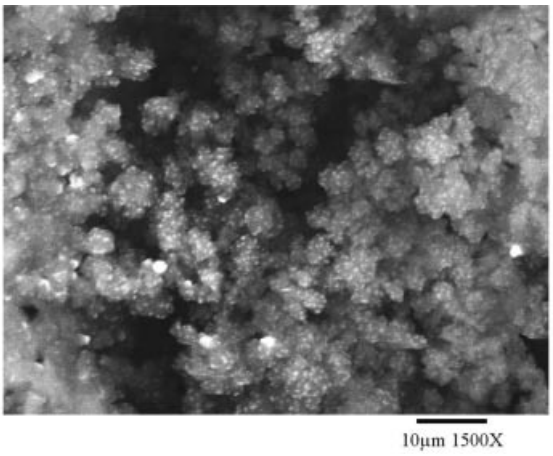


Figure 1. Palladium particles on/inside polymer phase of the microreactors after reduction with $NaBH_4$ (the light areas reveal the locations of the palladium particles but not the polymeric spheres)

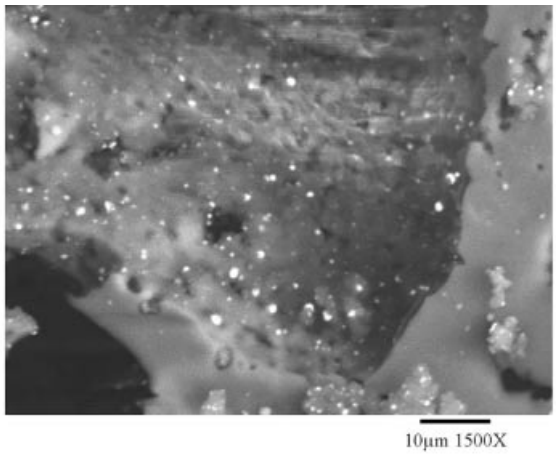
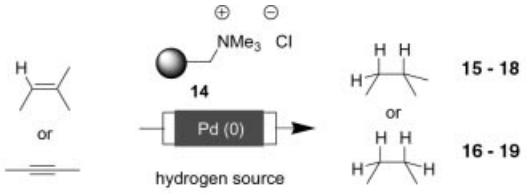
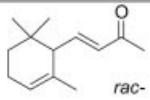
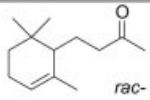
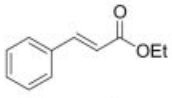
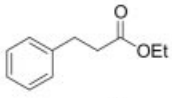
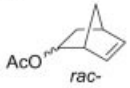
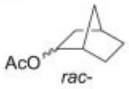
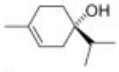
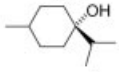
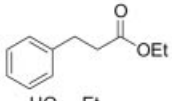
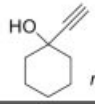
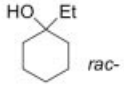


Figure 2. Palladium particles on/inside polymer phase of the microreactors after reduction with hydrazine

Table 2. Transfer hydrogenation of alkenes and alkynes in the continuous-flow mode using palladium(0) particles (yields refer to purified products)[a]



Entry	Alkene / alkyne	Conditions	Hydrogenation product	Yield in %[b]
1		HCO_2Li, EtOH, 120°C, 3h		**15** 84
2	rac-	HCO_2NHEt_3, EtOH, 100°C, 70h	rac-	**15** 99
3		1,4-cyclohexadiene, THF or EtOH, 60-70°C, 48h		**16** 99
4		H_2NNH_2, MeOH, 40°C, 12h		**16** 97
5	 rac-	HCO_2Li, EtOH, 100°C, 1h	 rac-	**17** 64
6		1,4-cyclohexadiene, THF or EtOH, 60-70°C, 16h		**18** 64
7		cyclohexene, 70°C, 4h		**16** 98
8	 rac-	1,4-cyclohexadiene, THF or EtOH, 60-70°C, 24h	 rac-	**19** 49

[a] After washing of the reactor with ethanol, water, 1 N NaOH, water, 1 M HCl and finally water, it was reused in further experiments. [b] Isolated yields after flash column chromatography.

smaller numbers of larger sized particles on the polymer surface. However, in the catalytic reduction of nitrobenzene to aniline no rate differences were found.

Since catalytic hydrogenation is a key step in various industrial processes,[16] we first tested the supported palladium(0) species **14** under transfer-hydrogenation and continuous-flow conditions. During the last few years the development of versatile heterogeneous catalysts has received much attention in light of their selectivity, their removal from the reaction mixture and their reuse for further reac-

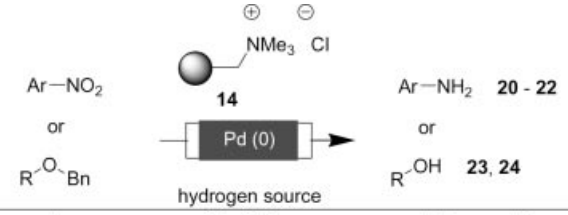
tions, thereby reducing process costs. Thus, triethylammonium formate was used as a hydrogen source in the reduction of α-ionone (Table 2; Entries 1 and 2) which selectively yielded a single reduction product within 70 h in 99% yield and high purity (> 95%). The reaction time can be decreased to 3 h by using lithium formate as the hydrogen source. Other alkenes (Table 2; Entries 3 and 5) react similarly, even when 1,4-cyclohexadiene or hydrazine are used as transfer reagents. Trisubstituted double bonds, such as those present in menthenol (Table 2; Entry 6), are hydrogenated after prolonged reaction times under these conditions. Other functional groups include triple bonds in alkynes (Table 2; Entries 7 and 8), which are reduced to the corresponding alkanes; in these cases, the less-reactive cyclohexene can also serve as a hydrogen source.[17] With this transfer reagent, which at the same time serves as solvent, workup is highly simplified by direct concentration of the reaction mixture in vacuo, leading to almost pure compounds.

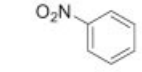
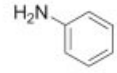
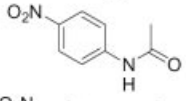
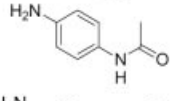
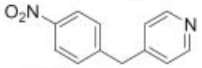
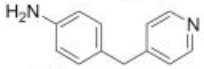
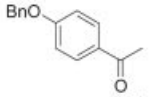
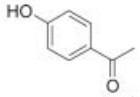
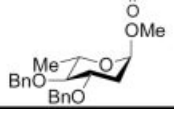
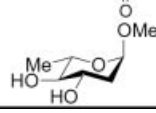
Depending on the extent of palladium leaching, the reactor could be reused up to 20 times after simple washing. From ICP-MS analysis, we found that leaching is influenced by the polarity of the solvents used: more leaching was observed when reactions were performed in polar solvents or in strongly acidic media. Higher temperatures also seem to result in greater leaching. In contrast, in transfer hydrogenations using cyclohexene as solvent, leaching did not exceed 6 ppm. The amount of immobilised catalyst inside the reactor could not be determined directly, although as a conclusion from experiments with identical glass/polymer composite materials shaped as Raschig rings a loading of 0.24 mmol of palladium was determined by elemental analysis. The PASSflow reactor could conveniently by regenerated after the palladium particles had lost their activity by reloading of the anion-exchange resin with chloride ions and their exchange with palladate anions, followed by reduction (see Scheme 2).

Reduction of nitro-substituted aromatic compounds (Table 3; Entries 1−3) to primary amines is achieved without the common formation of by-products like hydroxylamines,[18] as was carefully checked by GC-MS analysis. Hydrogenolysis of *p*-benzyloxyacetophenone (Table 3; Entry 4) afforded the free hydroxy group at 55 °C after only 1.5 h and without the need for molecular hydrogen. Again, workup was highly simplified as only removal of the solvent in vacuo was necessary to isolate the pure product. A methyl glycoside which contains two benzyl ether protecting groups (Table 3; Entry 5) could also be deblocked under transfer-hydrogenation conditions.[19]

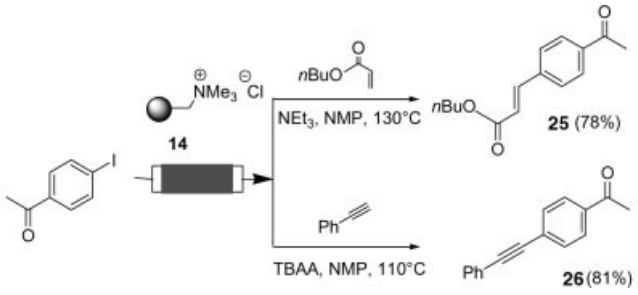
In the next stage of the project we studied the use of the Pd^0 particles dispersed inside the composite material for C−C-coupling reactions. The Heck reaction is a versatile tool for palladium-catalysed vinylation of aryl halides.[21] Using the palladium(0) particles, iodoacetophenone smoothly underwent coupling with *n*-butyl acrylate (Scheme 3).[22] The coupling product **25** was obtained in 78% yield [only (*E*) isomer] and free of homocoupled by-products after aqueous workup. At this point we evaluated the activity of the palladium particles in the Heck reaction of 4-iodoanisole and isobutyl acrylate. Using 0.5 mol % of Pd^0 loaded on the glass/polymer composite material (chloride form), DMF as solvent and triethylamine as base, com-

Table 3. Transfer hydrogenation of nitro-substituted aromatic compounds and benzyl ethers (yields refer to purified products)[20]



Entry	Nitroarene / benzylether	Conditions	Hydrogenation product	Yield in %[a,b]
1		cyclohexene, EtOH, 100°C, 16h		**20** 95
2		HCO_2Li, EtOH, 100°C, 1.5h		**21** 81
3		HCO_2NHEt_3, EtOH, 100°C, 48h		**22** 99
4		1,4-cyclohexadiene, THF or EtOH, 55°C, 1.5h		**23** 99
5		HCO_2Li, EtOH, 70°C, 72h		**24** 44

[a] For the regeneration procedure see Table 2. [b] Isolated yields after flash column chromatography.



Scheme 3. Ligand-free palladium-catalysed Heck and Sonogashira reactions in the PASSflow reactor (yields refer to purified products; TBAA = tetrabutylammonium acetate; NMP = *N*-methylpyrrolidinone)

plete transformation was achieved at 110 °C within 30 min affording isobutyl ester **27** (see Exp. Sect.). The material was reused directly several times for the same transformation after washing of the material with DMF after each run. After 3 h, the amount of transformation was determined as: 92% (2nd run), 90% (3rd run), 90% (4th run), 88% (5th run), 84% (6th run) and 71% (7th run), irrespective of whether the material was reloaded with chloride ions in between each run.

The Sonogashira reaction offers a convenient access to substituted alkynes.[23] The reactions are usually conducted in polar solvents like NMP or DMF employing a palladium catalyst and copper iodide as co-catalyst. This co-catalyst is insoluble under these conditions and may block the irregular microchannels within the reactor. Therefore, we chose to adapt Nájera's homogeneous copper-free conditions,[24] which are based on a palladacarbacycle as catalyst, tetrabutylammonium acetate (TBAA) as base and NMP as solvent. Using the palladium(0) particles, the Sonogashira reaction of phenylacetylene and 4-iodoacetophenone led to complete consumption of the starting material and formation of alkyne **26** with only negligible traces (< 9%) of homo-coupling product, as judged by GC-MS analysis (Scheme 3).[25]

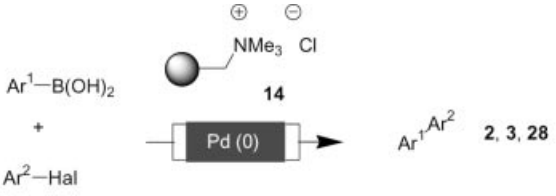
Finally, we studied the Suzuki−Miyaura reaction, which has become one of the most versatile and important reactions for the construction of C−C bonds.[26] Again, the Pd^0-doped reactor proved to be well suited for the coupling of 4-iodoacetophenone (Table 4; Entries 2 and 4) and other aryl halides (Table 4; Entries 1, 3 and 5) with arylboronic acids to yield the corresponding biaryl compounds **2**, **3** and **28** within 3 h without formation of homocoupling by-products. After collecting the reaction solution, aqueous workup is necessary in order to remove the base and residual boronate. However, soluble palladium(0) catalysts like $Pd(PPh_3)_4$ often require complex chromatographic purification due to the phosphane ligands present in the reaction mixture (vide supra).

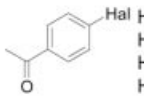
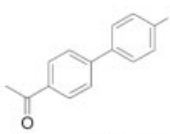
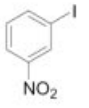
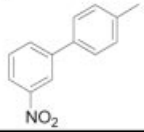
Therefore, we have combined the concept of immobilisation of boronic acid as boronate (see Scheme 1) with the catalytic activity of specifically located Pd nanoparticles (see Scheme 2) by exchanging the chloride anions in resin **14** by hydroxide anions (Table 5). The resulting bifunctionalised monolith **29**, which is located inside the reactor, shows good activity in the Suzuki−Miyaura reaction. The crude products contained traces of starting materials (Entries 1 and 2) or small amounts of homocoupled dimers (Entry 6).

Conclusions

In summary, we have developed a new palladium(0)-loaded microreactor that can be used in continuous-flow mode, providing a range of advantages. Since the catalyst is present in high concentration while the substrates passes

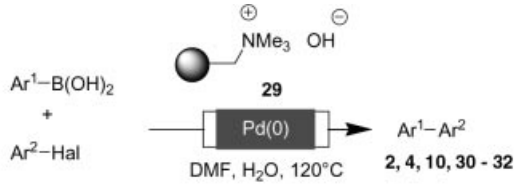
Table 4. Ligand-free palladium-catalysed Suzuki−Miyaura reactions in the PASSflow reactor

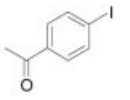
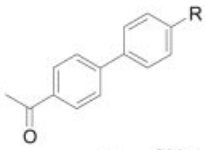
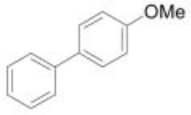
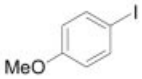
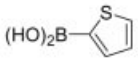
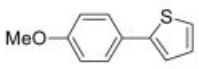
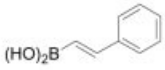
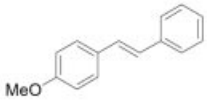
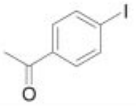
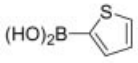
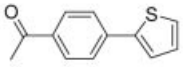


Entry	Ar^2-Hal	Ar^1-$B(OH)_2$	Conditions[a]	C-C coupling product (yield in %)[b,c]
1	 Hal = Br	Ph-$B(OH)_2$	24h	 **2** R = H 72 (98)
2	Hal = I	Ph-$B(OH)_2$	3h	**2** R = H 77 (99)
3	Hal = Br	Tol-$B(OH)_2$	7.5h	**3** R = Me 77 (98)
4	Hal = I	Tol-$B(OH)_2$	7.5h	**3** R = Me 74 (98)
5		Tol-$(BOH)_2$	4.5h	 **28** 76 (98)

[a] KOH, H_2O, DMF, 100 °C. [b] Isolated yields after flash column chromatography (yield of transformation in parentheses). [c] For the regeneration procedure see Table 2.

Table 5. Suzuki−Miyaura cross-coupling reaction under continuous-flow conditions (method A)[a,b]



Entry	Ar^2-Hal	Ar^1-$B(OH)_2$	Conditions	C-C coupling product (yield in %)			
1		$Ph-B(OH)_2$	2h		**2**	R= H	99
2		4-MeO-Ph-B(OH)_2	3h		**30**	R= OMe	87
3		4-MeO-Ph-(BOH)_2	4h		**4**		78
4			3.5h		**31**		69
5			5h		**10**		88
6			5h		**32**		67

[a] Isolated yields after flash column chromatography. [b] The reactor was regenerated by washing with ethanol, water, 1 N NaOH and water.

through the microreactor, the reactions can rapidly be forced to completion. The catalyst facilitates its separation from the reaction mixture, is reusable more than 20 times after simple washing, and it is easy to store. We have demonstrated its application in transfer-hydrogenation reactions using various transfer reagents, thereby circumventing the need for molecular hydrogen. The palladium(0)-doped microreactor also revealed high performance in three types of C−C cross-coupling reactions. This is one of very few examples which allows recovery and reuse of the catalytically active dispersed palladium without substantial loss of activity. It is important to note that this continuous-flow approach offers great potential for industrial applications, especially with respect to rapid scaleup from laboratory scale to the process plant without the need for substantial optimisation. Indeed, the transfer hydrogenation could be scaled-up to 2 mol [reduction of nitrobenzene using the transfer reagent cyclohexene; Pd^0 (5 mmol)] without altering the conditions found for the millimol-scale hydrogenation. For this purpose, a continuous-flow apparatus typical in process engineering was constructed at the Institut für Chemische Verfahrenstechnik (Technische Universität Clausthal).[27]

Experimental Section

General: NMR spectra were recorded with a Bruker DPX-400 spectrometer at 400 MHz (^{1}H NMR) and at 100 MHz (^{13}C NMR) using $CDCl_3$ and $[D_6]$DMSO both as solvents and internal standards (δ = 7.26 ppm and 2.50 ppm, respectively, for ^{1}H NMR and δ = 77.16 ppm and 39.52 ppm, respectively, for ^{13}C NMR). Mass spectra (EI) were obtained at 70 eV with a type VG autospec apparatus (Micromass). GC analyses were conducted using an HPGC series 6890 Series Hewlett Packard equipped with an SE-54 capillar column (25 m, Macherey−Nagel) and an FID detector 19231 D/E. IR spectra were recorded with a Bruker FT-IR Vector 22 apparatus. Melting points were determined in open glass capillaries with a Gallenkamp apparatus and are uncorrected. Analytical thin-layer chromatography was performed using precoated silica gel 60 F_{254} plates (Merck, Darmstadt), and the spots were visualised with UV light at 254 nm. Merck silica gel 60 (230−400 mesh) was used for flash column chromatography. Tetrahydrofuran was distilled from sodium/benzophenone ketyl. Commercially available reagents and dry solvents (toluene, dimethylformamide) were used as received. The reported compounds 4-acetyl-1,1′-biphenyl (**2**),[28] 4-acetyl-4′-methyl-1,1′-biphenyl (**3**),[29] 4-methoxy-1,1′-biphenyl (**4**),[29] 4-methoxy-3′-(trifluoromethyl)-1,1′-biphenyl (**5**),[29] 4-methoxy-4′-methyl-1,1′-biphenyl (**6**),[30] 3-nitro-1,1′-biphenyl (**7**),[31] 3-nitro-3′-(trifluoromethyl)-1,1′-biphenyl (**8**),[29] 4-acetamido-4′-methyl-1,1′-

biphenyl (**9**),[29] (*E*)-1-(4-methoxyphenyl)-2-phenylethene (**10**),[32] 4′-methyl-3-nitro-1,1′-biphenyl (**28**),[33] 4-acetyl-4′-methoxy-1,1′-biphenyl (**30**),[34] *p*-(2-thienyl)anisole (**31**),[35] *p*-(2-thienyl)acetophenone (**32**)[36] (see Scheme 1 and Tables 1, 4, and 5), 4-(2,6,6-trimethylcyclohex-2-enyl)-butan-2-one (**15**),[37] ethyl 3-phenylpropionate (**16**),[38] 2-acetoxybicyclo[2.2.1]heptane (**17**),[39] *p*-menthan-4-ol (**18**),[40] 1-ethylcyclohexanol (**19**),[41] 4-(4-aminobenzyl)pyridine (**22**),[42] *N*-(4-aminophenyl)acetamide (**21**),[43] methyl 2-deoxy-α-L-rhamnopyranoside (**24**),[44] commercially available aniline and *p*-hydroxyacetophenone (see Tables 2 and 3), n-butyl *trans*-4-acetylcinnamate (**25**),[45] 1-(4-acetylphenyl)-2-phenylethyne (**26**)[46] (see Scheme 3) isobutyl 4-methoxycinnamate (**27**)[47] have been described previously and were identified by comparison of their physical and spectroscopic data (^{1}H and ^{13}C NMR, IR, MS) with those in the cited references; their purities were confirmed by GC analyses. All reactions were carried out in a continuous-flow apparatus from Chelona GmbH, Potsdam. All reaction temperatures in this report refer to oven temperatures. As the reaction mixture is pumped as a convective flow through the reactor it never reaches the oven temperature. When the reaction mixture leaves the column it is about 10 to 15 °C below the oven temperature.

General Procedure for the Suzuki−Miyaura Cross-Coupling Reaction using Pre-Immobilised Boronic Acid (Method A; Table 1): The PASSflow reactor (anion exchange; chloride form) was washed successively with NaOH (1 N, 60 mL), water (until the eluate reached pH = 7), methanol (15 mL), and anhydrous THF (15 mL). Then, a solution of 4-methylbenzeneboronic acid (544 mg, 4 mmol) in anhydrous THF (20 mL) was pumped through the reactor followed by anhydrous THF (30 mL). After this procedure, a degassed solution of 4-bromoacetophenone (25.8 mg, 0.129 mmol) and tetrakis(triphenylphosphane)palladium(0) (7.0 mg, 6 μmol) in anhydrous THF (3 mL) was allowed to circulate through the reactor (2.5 mL/min) at 60 °C (external thermostat) under nitrogen. After completion of the reaction (4.5 h, GC monitoring), the reactor system was rinsed with anhydrous THF (10 mL) and methanol (10 mL). The combined organic extracts were concentrated in vacuo to yield a white solid. Flash chromatography on silica gel (cyclohexane/ethyl acetate, 95:5) afforded pure 4-acetyl-4′-methyl-1,1′-biphenyl (**3**; 23 mg, 0.109 mmol; 85%) as a white solid; m.p. 118−119 °C (ref.[29] 118−120 °C).

General Procedure for the Suzuki−Miyaura Cross-Coupling Reaction without Preliminary Immobilisation of the Boronic Acid in the Reactor (Method B; Scheme 1): The PASSflow reactor (hydroxide form) was washed successively with methanol (15 mL) and anhydrous THF (30 mL). Then, a degassed solution of 4-methylbenzeneboronic acid (26.3 mg, 0.193 mmol), 4-iodoanisole (30.2 mg, 0.129 mmol), and tetrakis(triphenylphosphane)palladium(0) (2.9 mg, 2.5 μmol) in anhydrous THF (3 mL) was pumped through the reactor (2.5 mL/min) in a cycle mode under nitrogen, the reactor being heated at 60 °C. After complete conversion of the aryl iodide (1 h, GC monitoring), the reactor was rinsed with anhydrous THF (10 mL) and methanol (10 mL). The combined organic mixtures were concentrated in vacuo to yield a white solid. Flash chromatography on silica gel (cyclohexane/ethyl acetate, 98.5:1.5) afforded pure 4-methoxy-4′-methyl-1,1′-biphenyl (**6**; 22 mg, 0.111 mmol; 86%) as a white solid; m.p. 107−108 °C (ref.[30] 108 °C).

Preparation of the Palladium-Loaded Microreactor 14: Sodium tetrachloropalladate (348 mg, 1 mmol) in water (100 mL) was pumped (0.5 mL/min flow rate) through the reactor (chloride form, maximum capacity 0.4 mmol). This step was repeated once again with the recycled solution. After rinsing the column with water (30 mL; 3 mL/min flow rate), an aqueous solution of $NaBH_4$ (0.2 M, 50 mL) was pumped through the reactor (1 mL/min), followed by water (30 mL; 3 mL/min flow rate), HCl (1 M, 10 mL; 3 mL/min flow rate), water (30 mL; 3 mL/min) and finally EtOH (20 mL) which regenerated the chloride form on the resin. A total loading of 0.24 mmol of palladium was determined. This standardised reactor was used in all the following transformations.

General Procedure for the Transfer Hydrogenation of Alkenes Using Microreactor 14

1. 1,4-Cyclohexadiene as Transfer Agent: Just before starting the reaction, the column **14** (prepared as described above) was rinsed with THF (15 mL). A solution of the starting material (1 mmol) and 1,4-cyclohexadiene (190 μL, 160 mg, 2 mmol) in THF (7 mL) was circulated (2 mL/min) through the microreactor at 60 °C for 48 h. The microreactor was washed with THF (20 mL) and the combined organic solutions were concentrated under vacuum to yield the pure products. For regenerating the reactor into the chloride form, it was washed with ethanol (20 mL), water (20 mL), aq. NaOH (15 mL), water (20 mL), HCl (1 M, 25 mL) and finally water (40 mL).

2. Lithium Formate as Transfer Agent: The starting material (1 mmol) in ethanol (10 mL) was added to lithium formate monohydrate (210 mg, 3 mmol), dissolved in water (3 mL). The resulting solution was circulated through the column **14** (chloride form, previously rinsed with ethanol) at 120 °C for 3 h. For product isolation, the column was washed with ethanol (10 mL) and the combined solutions were concentrated almost to dryness. The product was dissolved in hexane, sodium sulfate was added to remove residual water, and the solution was filtered. Evaporation of the solvents yielded the pure products.

3. Cyclohexene as Transfer Agent: Just before the reaction was initiated, the reactor column **14** (chloride form, previously rinsed with ethanol) was rinsed with cyclohexene (10 mL). A solution of the starting material (1 mmol) in cyclohexene (10 mL) was circulated (3 mL/min) at 70 °C for 24 h. For product isolation, the microreactor was washed with EtOH (20 mL) and the combined organic solutions were concentrated under vacuum to yield the products.

4. Triethylammonium Formate as Transfer Agent: The starting material (1 mmol) was dissolved in formic acid (5 mL) and ethanol (5 mL). Triethylamine (10 mL) was slowly added, and the mixture was circulated through the reactor column **14** (chloride form, previously rinsed with ethanol) at 100 °C. The reactor column was rinsed with ethanol (20 mL). The combined organic solutions were subjected to aqueous workup and evaporation of the solvent yielded the pure product.

5. Hydrazine as Transfer Agent: The starting material (1 mmol) was dissolved in methanol (10 mL). Hydrazine (3 mmol) was added, and the solution was passed through the reactor column **14** (chloride form, previously rinsed with methanol) at 40 °C (oven temp.). Evaporation of the solvent gave the pure products.

General Procedure for the Heck Reaction in the PASSflow Mode Using Microreactor 14: The microreactor (chloride form) was washed with THF (20 mL) and NMP (10 mL). A solution of 4-iodoacetophenone (246 mg, 1 mmol), *n*-butyl acrylate (192 mg, 1.5 mmol) and NEt_3 (0.2 mL, 1.4 mmol) in NMP (10 mL) was pumped through the microreactor **14** at 130 °C (oven temperature). After completion of the reaction (2.5 h), the microreactor was rinsed with NMP (10 mL) and dichloromethane (10 mL). The com-

bined organic mixtures were diluted with hexane, washed with water, dried with Na_2SO_4 and concentrated in vacuo to yield the pure product **25** (192 mg, 0.78 mmol; 78%). For regeneration, the microreactor was washed with ethanol (20 mL). In case of deactivation of the catalyst, the microreactor can be washed with ethanol (20 mL), water (20 mL), NaOH aq. (15 mL), water (20 mL), HCl (1 M, 20 mL) and finally water (20 mL). The reactor is then ready to be reloaded with palladate as described above.

General Procedure for the Sonogashira Reaction in the PASSflow Mode Using Microreactor 14: The microreactor **14** (chloride form) was washed with methanol (20 mL) and NMP (20 mL). A solution of 4-iodoacetophenone (492 mg, 2 mmol), tetrabutylammonium acetate (1.2 g, 4 mmol) and phenylacetylene (308 mg, 3 mmol) in NMP (14 mL) was circulated through the microreactor **14** (3 mL/min) at 110 °C (oven temperature). After completion of the reaction, the microreactor was rinsed with NMP (10 mL) and dichloromethane (10 mL). The combined organic mixtures were diluted with hexane, washed with water, dried with Na_2SO_4 and concentrated in vacuo to yield the pure product **26** (356 mg, 1.62 mmol; 81%). Regeneration was conducted as described above.

General Procedure for the Suzuki−Miyaura Reaction in the PASSflow Mode Using Microreactor 14: 4-Iodoacetophenone (246 mg, 1 mmol), phenylboronic acid (151 mg, 1.2 mmol) and aqueous potassium hydroxide (0.5 N, 1 mL) were dissolved in DMF (10 mL). The resulting homogeneous solution was circulated through the reactor column **14** (3 mL/min) at 100 °C (oven temp.) for 3 h. Aqueous workup and column chromatography afforded the pure product **2** (151 mg, 0.77 mmol; 77%).

General Procedure for the Suzuki−Miyaura Reaction Using Bifunctionalised Solid Phase 29: The microreactor loaded with palladium particles (**14**; chloride form) was transformed into the hydroxide form as described above (Suzuki−Miyaura reaction; Table 1, method A). The microreactor **29** obtained was washed with DMF (20 mL). Then, a solution of organoboronic acid (0.24 mmol) and aryl iodide (0.2 mmol) in a mixture of DMF and water (10:1; 11 mL) was circulated through the microreactor at 120 °C (oven temperature). The microreactor was washed with DMF (20 mL), the combined organic phases were diluted with water (40 mL) and extracted with cyclohexane (3 × 20 mL). The combined organic phases were washed with an aqueous solution of saturated NaCl, dried (Na_2SO_4) and concentrated in vacuo. The microreactor was regenerated by the washing procedure ethanol (20 mL), water (20 mL), aqueous NaOH (1 N, 50 mL) and water (30 mL).

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