DOI: 10.1002/adsc.201200678

Cross-Coupling in Flow using Supported Catalysts: Mild, Clean, Efficient and Sustainable Suzuki–Miyaura Coupling in a Single Pass

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Received: July 31, 2012; Published online: November 28, 2012

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200678.

Abstract: A mild, clean, practical, sustainable and high yielding procedure for Suzuki–Miyaura cross-coupling in a single pass using a silica-supported palladium catalyst is described. The catalyst can be used in more than 30 reactions and for more than 8 h of continuous processing without a decrease in reactivity due to the low leaching observed. Different halides/pseudo-halides and organoboron compounds can be used without modifying the standard procedure.

Keywords: C−C bond formation; cross-coupling; flow chemistry; solid-supported catalyst; Suzuki–Miyaura reaction

The ability to conduct complex and routine chemical transformations in a clean, sustainable and easily scalable way without recourse to costly reagents, catalysts, lab equipment or purification processes is highly desirable. The design of efficient and practical procedures is an important goal in chemistry and especially in process chemistry. In recent years flow chemistry has been developed to improve the performance of chemical synthesis.[1] Among other advantages, this technology allows very efficient heat transfer, good control of reaction temperature and enhanced mass transfer, thus avoiding the problems associated with highly exothermic reactions and dangerous or air- and moisture-sensitive compounds. This approach permits the integration of several steps into one single streamlined process, thus shortening the time from research to development and production.[2]

Coupling these methodologies with heterogeneous catalysis produces a synergistic effect, since in most cases, they complement each other. Catalyst immobilization is of significance for flow chemistry due to the simple recovery and reuse.[3] In addition, typical packed-bed reactors provide a high ratio of catalyst *vs.* substrate during the course of the reaction, an advantage that significantly increases the rate of reaction and simplifies the purification of the final products. However, leaching of Pd species, swelling of polymer supports, deposition of products/by-products and poor catalyst cartridge life cycles complicate their use in continuous flow systems.[4]

Metal-catalyzed cross-coupling chemistry[5] has had a great impact on the pharmaceutical and other industries, as well as on the synthesis of natural products and other biologically active compounds.[6] The Suzuki–Miyaura cross-coupling reaction (SMC) is one of the most important methods for the construction of carbon-carbon bonds.[7] Several studies have been focused on the development of flow methods to perform this reaction using either homogeneous[8] or heterogeneous catalysts. Within the field of heterogeneous catalysts a broad range of solid supports has been developed and these include monolithic supports,[9] polymer beads[10] and PdEnCat™.[11] However, swelling and degradation of the polymer supports,[12] gradual leaching of the catalytically active palladium,[13] the need to perform several passes through the catalyst to achieve full conversion,[11] the replacement of the cartridge after performing a limited number of reactions and the need to synthesize the supported catalyst in the cartridge[9] limit their practical use in organic and medicinal chemistry and decrease the sustainability of the processes.

Silica-supported catalysts offer better chemical and thermal stability as well as a rigid but porous structure devoid of swelling properties, a characteristic that makes them compatible with a wide range of solvents. The use of these catalysts for Suzuki–Miyaura cross-coupling (SMC) has been described in two articles. The first paper concerned the combined use of electroosmotic flow with the microporous silicate structure in palladium-catalyzed organic synthesis.[14] This coupling reaction illustrated the use of the flow injection microreactor but the reaction itself was not optimized. The second article concerned silica-supported nanoparticles, which can be heated by magnetic induction.[15] However, due to leaching of palladium, the catalyst could be reused only three times. Additionally the use of a third silica-supported catalyst has been described in an application note.[15c] Even though good conversions and acceptable catalyst capacity are reported, measurements of palladium leaching and number of cycles that can be used without a drop in activity are not provided. Moreover, a relationship between metal leaching and the high temperatures employed to complete the reaction (from 130 °C to 150 °C) was found.

Recently, a new commercially available silica-supported catalyst (SiliaCat®) has been described.[16] It is claimed that this novel catalyst presents several advantages, such as high turnover number (TON) and low leaching. The catalyst costs less than other commonly used palladium sources, such as palladium acetate or Pearlman's catalyst. Herein, an efficient, clean and high yielding procedure for Suzuki–Miyaura cross-coupling using this silica-supported palladium catalyst is reported.

We started our investigation by examining the reaction of bromobenzene **2a** and (4-methoxyphenyl)boronic acid **1a** using SiliaCat® DPP-Pd[16] as the supported catalyst. A solution of the aryl halide in THF was combined with a solution of the boronic acid and the base in water using the Vapourtec R2+R4 system.[17] The biphasic solvent system was used to ensure complete dissolution of any solid, thus avoiding any subsequent clogging. The mixture was then passed through a 6.6 mm (i.d.) Omnifit column containing 1 g of supported catalyst (Figure 1). The residence time was calculated based on flow and confirmed using violet crystal as tracer (see the Supporting Information). The outcome was collected and analyzed. On using KOH as a base, bromobenzene **2a** successfully coupled with boronic acid **1a** at 60 °C with a residence time of 10 min (Table 1, entry 1). A clean crude product was obtained in this first experiment (Figure 2). The residence time can be shortened to 5 min without a reduction in conversion (Table 1, entry 2), but the conversion falls dramatically when the residence time was decreased below 2 min, even on increasing the temperature (Table 1, entries 3–5). The use of K_2CO_3 as base also provided excellent conversion and this represents an interesting alternative to KOH. However, the use of $NaHCO_3$ resulted in incomplete conversion (Table 1, entries 6 and 7). The concentration of reagents is important as the use of higher concentrations did not lead to full conversion (Table 1, entry 8). Finally, a different silica-supported catalyst was tested under the best conditions found, but this catalyst proved to be less efficient (Table 1, entry 9).

The mild flow conditions shown in Table 1 entry 2 were chosen to explore the scope of the SMC reaction to different halides/pseudo-halides with boronic acid **1a** (Table 2, entries 1–4). Bromobenzene **2a**, iodobenzene **2b**, chlorobenzene **2c** and phenyl triflate **2d** provided excellent yields on using the same reaction conditions. Despite the fact that chloro- and bromobenzene gave similar results, it is possible to couple selectively the bromo substituent in the chloro-bromo de-

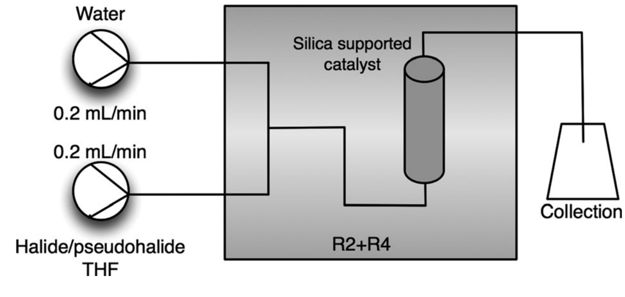
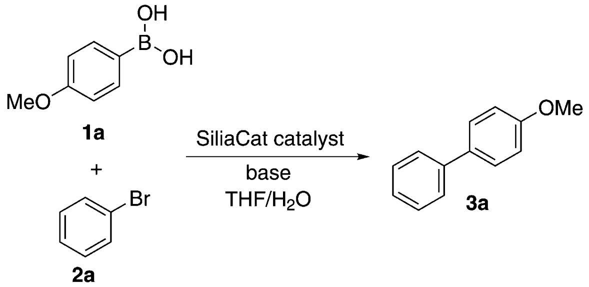


Figure 1. Experimental set-up of the flow system.

Table 1. Optimization of the SMC reaction of bromobenzene **2a** and (4-methoxyphenyl)boronic acid **1a**.



Entry[a]	Base	Temp. [°C]	Time [min]	Conv.[b] [%]	Sel.[b] [%]
1	KOH	60	10	100	100
2	KOH	60	5	100	100
3	KOH	60	1	56	100
4	KOH	80	1	59	100
5	KOH	60	2	72	100
6	K_2CO_3	60	5	94	100
7	$NaHCO_3$	60	5	70	98
8[c]	KOH	60	5	85	100
9[d]	KOH	60	5	76	100

[a] 1-mmol scale, SiliaCat DPP-Pd as catalyst, 0.15 M boronic acid, 0.125 M halide.
[b] Conversions (based on halide consumption) and selectivities (product *vs.* hydrodeboronation or hydrodehalogenation) were determined by GC/MS.
[c] 1-mmol scale, SiliaCat DPP-Pd as catalyst, 0.3 M boronic acid, 0.25 M halide.
[d] SiliaCat S-Pd as catalyst.

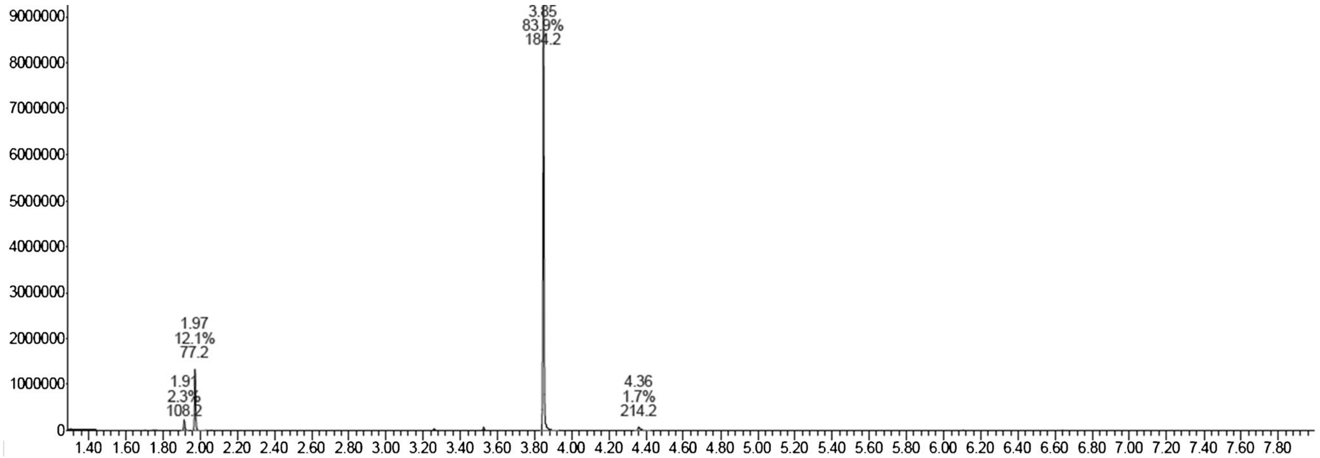
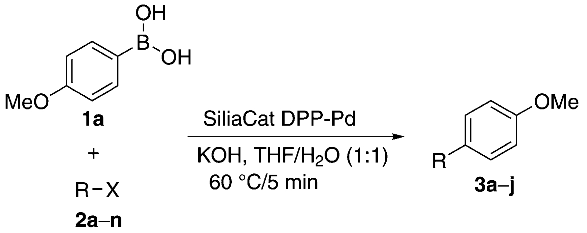


Figure 2. GC-mass spectra of the crude reaction mixture of bromobenzene **2a** and (4-methoxyphenyl)boronic acid **1a**.

Table 2. Scope of the reaction with different aryl bromides (**2**) and **1a**.



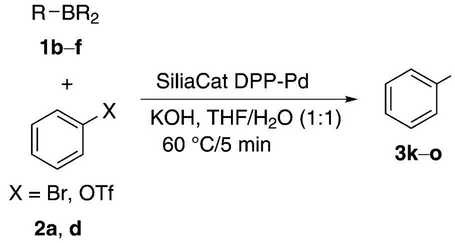
Entry[a]	R-X	Compound [%][b]
1	C_6H_5-Br (**2a**)	**3a** (98)
2	C_6H_5-I (**2b**)	**3a** (99)
3	C_6H_5-Cl (**2c**)	**3a** (98)
4	C_6H_5-OTf (**2d**)	**3a** (93)
5	4-Cl-C_6H_4-Br (**2e**)	**3b** (90)
6	4-NO_2-C_6H_4-Br (**2f**)	**3c** (96)
7	4-Cl- C_6H_4CHO (**2g**)	**3d** (90)
8	o-MeC_6H_4-Br (**2h**)	**3e** (95)
9	o-MeOC_6H_4-Br (**2i**)	**3f** (88)
10	2,4-diMeOC_6H_3-Br (**2j**)	**3g** (50)
11	3-Br-pyridine (**2k**)	**3h** (72)
12	2-Br-pyridine (**2l**)	**3i** (81)
13	2-Cl-pyridine (**2m**)	**3i** (77)
14	4-Br-$C_6H_4CO_2$Me (**4n**)	**3j** (86)

[a] 1-mmol scale, SiliaCat DPP-Pd as catalyst, 0.15 M boronic acid, 0.125 M halide.

[b] Isolated yield in brackets.

rivative **2e** (entry 5). The reaction conditions also allowed the presence of other functional groups, including an aromatic ring bearing several electron-donor groups (**2j**), although the yield decreased to 50% (entry 10). Chloro- and bromopyridines also provided good yields without further optimization (entries 11–13). Ester functions were also tolerated despite the use of the strong base (entry 14).

Table 3. Use of different organoboron derivatives (**1b–g**).[a]



Entry	R-BR$_2$	R-X	Comp. [%][b]
1	4-CF_3-C_6H_4-B$(OH)_2$ (**1b**)	**2a**	**3k** (97)
2	4-NO_2-C_6H_4-B$(OH)_2$ (**1c**)	**2a**	**3l** (87)
3	2-furyl-B$(OH)_2$ (**1d**)	**2a**	**3m** (87)
4	3,5-diMeO-C_6H_3bpin (**1e**)	**2a**	**3n**(99)
5	3-pyridine-B$(Et)_2$ (**1f**)	**2d**	**3o** (89)
6	4-MeO-C_6H_4-B(O-*i*-Pr)$_3$Li (**1g**)	**2a**	**3a** (96)

[a] 1-mmol scale, SiliaCat DPP-Pd as catalyst, 0.15 M boronic acid, 0.125 M halide.

[b] Isolated yield in brackets.

In order to explore further the scope of the reaction, other boronic acids and organoboranes were tested with bromobenzene **2a** or phenyl triflate **2d** (Table 3). Boronic acids **1b** and **1c** were selected due to their low solubility in water (entries 1 and 2). Although cloudy solutions in water were observed for both compounds, they coupled in good yields using the injection loops provided in the R2 + R4 instrument. The reaction mixture clarified after passing through the catalyst and this avoided clogging at the back pressure regulator. It is worth noting that the reaction allows the use of different boron derivatives, boronic esters **1e**, boranes **1f** and borates **1g**, freshly prepared from the corresponding bromo derivative by metalation[8a,b] (entries 4–6). The excellent yields ob-

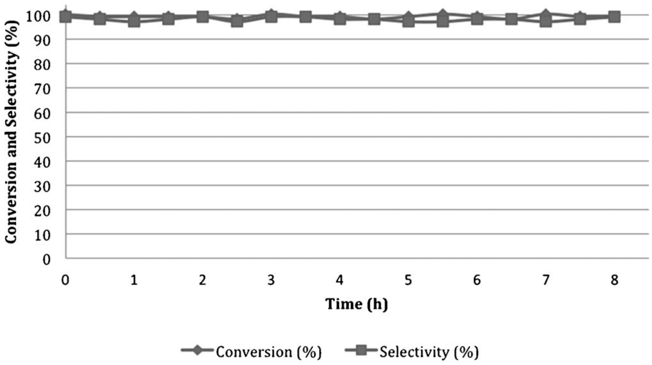


Figure 3. SMC between (4-methoxyphenyl)boronic acid **1a** and 1-bromo-2-methylbenzene **2h** for 8 h.

tained in all the cases increase the versatility of the process.

The procedure is highly robust and reproducible and similar results were obtained using an empty Xterra column (4.6×50 mm) refilled with 400 mg of catalyst, heated with a column heater (Lab Alliance), both of which are generally used for HPLC purifications, and pumping the reagents with a dual syringe pump (Harvard Apparatus). In consequence, an expensive commercial flow system is not a requirement and the reaction can be performed with standard laboratory equipment. Furthermore, purification of products was a matter of separation and evaporation of the organic phase. Crude products are clean and free of phosphine ligand, thus avoiding the need for chromatographic purification.

Finally, we studied the stability of the supported catalyst. It was found that the same cartridge could be employed for more than 30 consecutive reactions without a decrease in activity. The calculated TON was higher than 100. In order to check the behaviour of the catalyst, a long run (8 h) of the SMC between (4-methoxyphenyl)boronic acid **1a** and 1-bromo-2-methylbenzene **2h** was performed, using the optimized conditions with 1 g of new catalyst. The results are represented in Figure 3 and it can be seen that the outcome of the reaction did not change with time, thus proving the efficiency of the catalyst for long runs. The use of this flow procedure allowed up to 1.71 mmol/h of product to be produced without a decrease in the activity of the catalyst. Moreover, this system could be used later for other reactions. Leaching of palladium was determined for the coupling reaction both in the organic and aqueous layers. In the organic phase less than 10 ppb of Pd were determined. In the aqueous phase only 20 ppb were detected. These results demonstrate the low level of leaching of metal catalyst from the support, compared with other reported silica-supported catalyst where leaching in the ppm range is described.[15]

In summary, a clean, mild, reproducible, scalable and high yielding continuous flow process for Suzuki–Miyaura cross-coupling using a silica-supported catalyst has been developed. A wide scope of different functional groups, that is, halides/pseudo-halides and organoboron compounds, can be used with excellent results. The low leaching of palladium, the consistent outcome and the high yields of the reaction after 8 h of continuous processing, the stability of the catalyst after more than 30 reactions and the robustness of the protocol, all of which can be reproduced in a custom made instrument, are worth noting. This low leaching together with the clean crude products, which are devoid of ligand residues, as well as the affordable price of the supported catalyst make this procedure an efficient and practical alternative to perform Suzuki–Miyaura cross-couplings. Further applications of this methodology to the preparation of compounds with pharmaceutical interest will be the topic of future publications.

Experimental Section

General Flow Procedure

Two solution, boronic acid (1.2 equiv., 0.15 M) and KOH (2 equiv., 0.25 M) in water and halide (1 equiv., 0.125 M) in THF were pumped at 0.2 mL min^{-1} (each one) using the R2+R4 system. The mixed solution was driven to a column containing the catalyst supported (1 g), giving a residence time of 5 min. The outlet solution was diluted with water and extracted with ethyl acetate. The organic layer was separated, dried ($MgSO_4$), filtered and the solvents evaporated under vacuum.

Acknowledgements

The authors acknowledge Dr. L. Iturrino, Dr. L. M. Font and Dr. F. Béland for their collaboration in the preparation of this manuscript. Dr. C. J. Sánchez is thanked for leaching measurements. Financial support from the Spanish Ministerio de Ciencia e Innovación (project CTQ2011-22410) and the Junta de Comunidades de Castilla-La Mancha (projects HITO 2010-54 and PII2I09-0100).

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