RESEARCH PAPER

Highly efficient Suzuki cross-coupling reaction within an open channel plastic microreactor immobilized with palladium complexes

Hongling Li · Xiaotong Gao · Hui Ding · Min Yang · Qiaosheng Pu

Abstract A practical open channel microfluidic reactor with immobilized palladium complex was built on a cyclic olefin copolymer (COC) chip that was fabricated with a very simple hot-embossing technique. Palladium complex was immobilized on a photochemically grafted layer of polymerized N-[3-(dimethylamino)propyl]methacrylamide. Surface modification and catalyst immobilization onto COC were systematically characterized with streaming potential, surface contact angle, attenuated total reflection Fourier transform infrared spectrometry, scanning electron microscopy, atomic force microscopy and X-ray photoelectron spectroscopy. The reactor was comprised of a single 15 cm long serpentine channel of 120 μm (i.d.) and exhibited high efficiency for the Suzuki cross-coupling reaction of aryl iodides and bromides with arylboronic acids, affording good to excellent yields of the corresponding products. The reactions could be carried out smoothly with reduced reaction time and lower reactant consumption in the microreactor thermostated at 50°C. The proposed system may have great potential for high-throughput screening of catalysts and reaction conditions.

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Abbreviations

COC	Cyclic olefin copolymer
DMAPMA	N-[3-(dimethylamino)propyl] methacrylamide
ATR-FTIR	Attenuated total reflectance Fourier transform infrared spectrometer
SEM	Scanning electron microscope
AFM	Atomic force microscope
XPS	X-ray photoelectron spectroscopy

1 Introduction

With the raw materials becoming more limited, it is essential that we strive to make synthetic organic chemistry more efficient and sustainable. Among new strategies developed, microchip-based microreactor technology has received a great deal of attention in recent years, due to its unique advantages (deMello 2006; Watts and Wiles 2007; Jones et al. 2009; Yamada et al. 2009; Bernhard et al. 2010; Chan and Dong-Pyo 2010). Their small size prevents hot spots typically generated in batch reactors (Mason et al. 2007), offering better selectivity and yield for many organic reactions. High surface-area-to-volume ratio allow reactions that cannot be easily realized in traditional glassware (Jähnisch et al. 2004; Kawanami et al. 2007; Kobayashi et al. 2004), providing opportunities to run reactions efficiently with minimal waste. More importantly, microfluidic systems have the advantages such as high integration and easy combination with other techniques which make them possible to become useful tools in screening both catalysts

and reaction conditions (Lee et al. 2005; Li et al. 2008; Miller et al. 2007; Hartman et al. 2010; Uozumi et al. 2006). Safety can also be improved and production enhanced by avoiding large reactors.

A group of materials have been used to fabricate the microchips, but in most of the previously reported work, glass substrate was mainly chosen for organic synthesis. Although glassware is dominant in chemistry laboratories, the glass microreactors are normally expensive due to their tedious fabrication process, which limited their extensive use in synthetic organic chemistry. Therefore, developing new microreactors that are inexpensive, simple to build, and easy to modify is still of great significance. As an alternative, microchips made of plastic are becoming popular, particularly in analytical arena. Cyclic olefin copolymer (COC) has recently emerged as a highly attractive substrate material for microfluidic devices, due to its promising properties such as exceptionally good resistance to commonly used polar solvents, high optical transparency in the near UV range and ease of fabrication, etc. Since it is highly transparent at shorter wavelengths, the surface of COC can be easily modified by photografting method, which makes further immobilization of metal catalysts or other functional groups easy.

Transition metal-catalyzed Suzuki 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 good selectivity and versatile nature. However, homogeneous catalysis with soluble palladium catalyst experienced difficulty in their recovery of catalysts and purification of products. Development of more efficient heterogeneous catalytic system is a very hot topic. Various effective methods have been developed in recent years (Molnár 2011; Suzuki 2005; Doucet 2008; Singh et al. 2008; Carey et al. 2006). Traditional carriers of heterogeneous catalysts are porous materials, but more and more evidences indicated that mesoporous materials which with uniform pore structure might provide better catalytic efficiency. Microfluidic channels, which are small in size and highly uniform in shape, may be used both as the reaction containers and catalyst carriers. With this type of flow system, the collection and isolation of products can also be greatly simplified. The potential of high integration of microchannels might make it possible to screen the reaction condition and catalyst composition in high-throughput with very little consumption of reagents and less waste produced. Suzuki cross-coupling, which was catalyzed by palladium complex, is therefore a very good model reaction to check the efficacy of microfluidic devices as a platform of heterogeneous catalysis. Attempts to perform Suzuki reaction in microfluidic format have been reported previously. For example, He and co-workers (2004) have developed microwave-assisted Suzuki coupling reactions in glass microreactors using a syringe pump-driven flow and Pd/Al$_2$O$_3$ catalyst. Gömann and coworkers (2009) have successfully introduced organic monolith supports into narrow bore fused silica capillary microreactors for the formation of carbon–carbon bonds. Although solution could easily flow through an open channel in a typical laminar flow pattern (Jönsson et al. 2004), and it facilitates reactants reaching and products leaving from the active sites of catalysts that immobilized on the channel surface, Suzuki cross-coupling reaction within open channels of microchips has not been reported yet. In this work, we attempt to conduct Suzuki reaction in open channels of disposable COC chips, which were fabricated through an easy process and exhibited excellent efficiency for the Suzuki cross-coupling of aryl halides (X = I, Br) with aryl boronic acids. The reactions were carried out with reduced time and lower reactant consumption at 50°C achieved with a pre-heated thermostat.

2 Materials and methods

Pd(OAc)$_2$ (99%) was obtained from Strem; 4-iodoanisole (98%), 1-chloro-4-iodobenzene (98%), 1-bromo-4-nitro-benzene (99%), 4′-bromoacetophenone (98%), phenylbo-ronic acid (98%) and 4-formylphenylboronic acid (97%) were obtained from Acros; 4-methoxyphenylboronic acid (98%) were purchased from Lancaster; 4-chlorobenzenebo-ronic acid (98%) and 4-methylbenzeneboronic acid (98%) were purchased from Alfa Aesar; N-[3-(dimethylamino)propyl]methacrylamide (DMAPMA, 99%) was purchased from Sigma-Aldrich; Iodobenzene (CP) and biphenyl (CP) were obtained from Sinopharm Chemical Reagent Co., Ltd; Benzophenone (CP) and K$_2$CO$_3$ (99%) was purchased from Shanghai Chemical Reagent Company of Chinese Medical Group; DMF, triethylamine, acetone and absolute ethanol were analytical grade. All above reagents were used as received without further purification.

The infrared spectra were obtained with a Nicolet Nexus 870 Fourier transform infrared spectrometer. SEM data were recorded using a JEOL JSM-5601LV scanning electron microscope. All XPS measurements were made by a Thermon Scientific K-Alpha-surface Analyzer, with a mono-chromatization X-ray source. AFM image was obtained by a Nanoscope IIIa multimode atomic force microscope (AFM, Veeco) in tapping mode. The contact angles were measured on images of water drops on the surfaces. The conversion of the reaction was determined by a gas chromatograph (GC7890II, Techcomp) equipped with a SE-54 column (30 m × 0.32 mm × 0.50 μm film thickness) and a flame ionization detector using biphenyl as an internal standard.

3 Experiments

3.1 Fabrication of the COC plates and the microchips

Typically, a copper wire (about 120 μm in diameter, 20 cm in length) was placed on a COC plate (about 1.5 cm × 6.5 cm) in a predefined shape with its two ends extruded out the COC plate, then the plate together with the wire were sandwiched between two glass micro slides using four small binder clips. The assembly was put in an oven at 150°C for 20 min and allowed to cool down to room temperature. Then the plastic plate with copper wire was put into concentrated nitric acid for about 20 min to etch the copper wire away thoroughly and thus get the empty channel. The resulting channel plate and another blank COC plate with two holes previously drilled were sonicated in ethanol for 10 min. After drying, the two plates were assembled together with holes aligned along the channel and were sandwiched between two glass micro slides clamped by binder clips. The assembly was put in an oven at 122°C for 10 min to seal the chip and form enclosed microchannel. The channel open to the edge of the microchip was glued with dissolved COC in toluene after the reservoirs were glued at the holes. The effective channel length, which defined by the position of inlet and outlet access holes drilled on the channel was 15 cm unless mentioned otherwise (Fig. 1).

3.2 Surface modification of microfluidic channels and COC plates

Typically, the microchannel or COC plate was treated with concentrated H_2SO_4/H_2O_2 (V/V = 3:1) for 5 min and dried in a drying oven for further use. Modification solutions were prepared by dissolving 10% (V/V) of DMAPMA monomer in deionized water. Benzophenone (0.1%, as the photoinitiator) was added in the form of acetone solution of 100 mg/mL. For COC plates, the modification solution was applied on the surface and was covered with a plain quartz plate. The microchip or COC plate was subjected to UV irradiation (UV power was 3.5 mW/cm^2) for 5 min using a 500 W high-pressure
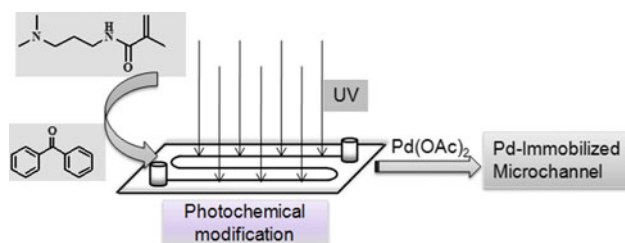

Fig. 1 Schematic illustration of COC-based microfluidic reactor and its surface modification processes

mercury lamp. The microchannel or COC plate was rinsed with ethanol to remove any non-attached polymer chains and was ready for further derivatization or film characterization. Finally, 0.05 M Pd(OAc)$_2$ acetone solution was introduced into the microchannel or COC plate at room temperature for 1 h to immobilize palladium catalysts to the surface. The microchannel or COC plate was rinsed with acetone to remove any free Pd(OAc)$_2$ and was ready for further film characterization or performance detection.

3.3 General procedure for the Suzuki cross-coupling reactions in microreactors

Typically, a solution of 1-iodo-4-methoxybenzene (0.067 M), phenylboronic acid (0.10 M), biphenyl (0.04 M), DMF/H$_2$O (2/1, 1 mL) and Et$_3$N (0.20 M) was prepared and then 200 μl of reactant mixture was introduced into the sample pool and flowed spontaneously in the channel from one side to the other at the desired reaction temperature by placing the microreactor on a pre-heated thermostat. The time that the reactant mixture flows inside the channel was taken as the reaction time which was approximately 1 min for channels 15 cm long. After 30 min, the reaction products were collected and analyzed off-line by GC.

4 Results and discussion

Palladium complexes were immobilized inside the channel and the efficiency of the reactor was examined using Suzuki cross-coupling as a model reaction. The COC plates and the microchips were fabricated through easily operational and inexpensive hot-embossing technique reported previously (Tsao and DeVoe 2009; Steigert et al. 2007; Pu et al. 2007). The inner surface of microchannel was modified by photographting (Mair et al. 2006; Bedair and Oleschuk 2006; Rohr et al. 2003; Samuel et al. 2010). The benzophenone-mediated photografting process generates a very thin layer of branched and cross-linked DMAPMA polymer architecture that is rich of dimethylamino groups on the substrate surface, which is ideal for anchoring palladium complex and providing proper microenvironment for Suzuki reaction.

The surface modification was evaluated by streaming potential measurement in the presence of 1 mmol/L PB buffer solution (pH = 7.20, conductivity = 219 μS/cm) at a pressure of 0.05 MPa. Typically, the streaming potential changed from −0.091 to 0.031 V after modification by DMAPMA, while after being functionalized with Pd(OAc)$_2$, the streaming potential changed to −0.070 V. These data suggest that the modification was successful.

To facilitate the characterization, surface contact angle, ATR-FTIR, SEM, AFM and XPS were performed on COC
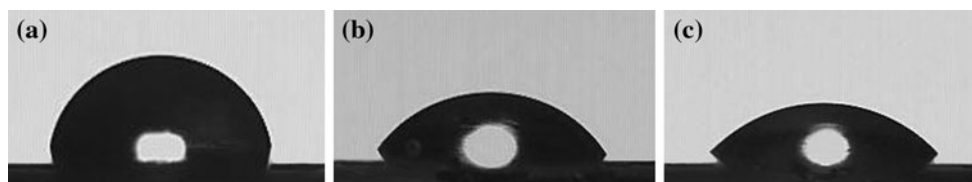
Fig. 2 Optical micrographs of the static contact angle of deionized water on the surface of **a** COC, **b** DMAPMA-modified COC and **c** COC modified by DMAPMA and Pd(OAc)$_2$ at room temperature of 27°C

plates that subjected to the same modification procedure as for micro channels. The hydrophobic COC chip, DMAPMA-modified COC chip, as well as COC chip further modified by Pd(OAc)$_2$ was investigated by means of the static contact angle measurement (Fig. 2). The largest static contact angle among three materials was observed on the surface of COC (78° for deionized water) due to its intrinsic high hydrophobicity. The contact angle decreased to 55° after being modified by DMAPMA, indicating the surface of COC chip has been successfully functionalized by DMAPMA. In addition, the contact angle decreased by another 10° after introduction of Pd(OAc)$_2$. It is reported that the lower the contact angle, the higher the driving force (Chung et al. 2009) for the flow inside a microchannel. Low contact angles of modified COC materials might be favorable for long-term self-driving of aqueous solution inside the channel. As shown in ATR-FTIR spectra (Fig. 3), for unmodified COC, the observed IR bands in the range of 2,945 and 2,868 cm^{-1} were attributed to C–H stretches and the peak around 1,457 cm^{-1} was for the C–H bend, which were in good agreement with that reported previously (Pu et al. 2007). After being modified with DMAPMA, the bands around 1,641 and 1,539 cm^{-1} could be attributed to amide groups. After being further modified by Pd(OAc)$_2$, the amide bands were still visible.

SEM analysis showed that the unmodified COC plate surface was relatively smooth (Fig. 4a). After being modified by DMAPMA, some microspots (most of which were around 1 μm) were found on the surface (Fig. 4b). But it did not imply that attached polymer was scattered over the plate, after being further modified with Pd(OAc)$_2$, Pd

particles were uniformly distributed over the surface (Fig. 4c). SEM-EDS spectrum indicated the presence of 3 wt% Pd (Fig. 5). The modification did result in larger roughness, the RMS roughness investigated by AFM for the DMAPMA photografted surface was 7.4 nm and that further modified by Pd(OAc)$_2$ was 21.5 nm (Fig. 6).

The valence state of elements and composition information of the COC surface before and after modification were also confirmed by XPS. As shown in Fig. 7a, no peak
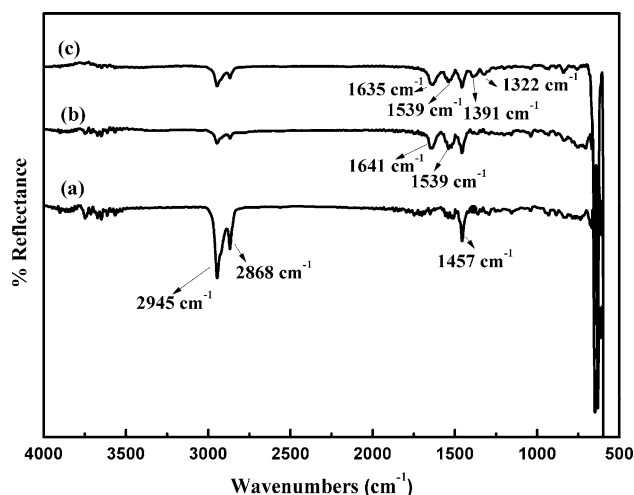

Fig. 3 ATR-FTIR spectra for **a** COC and COC modified with **b** DMAPMA, **c** DMAPMA and Pd(OAc)$_2$. Photochemical reaction solutions contain 10% (V/V) of monomers and 0.1% (w/v) benzophenone as photoinitiator. UV irradiation time is 5 min. UV power is 3.5 mW/cm^2
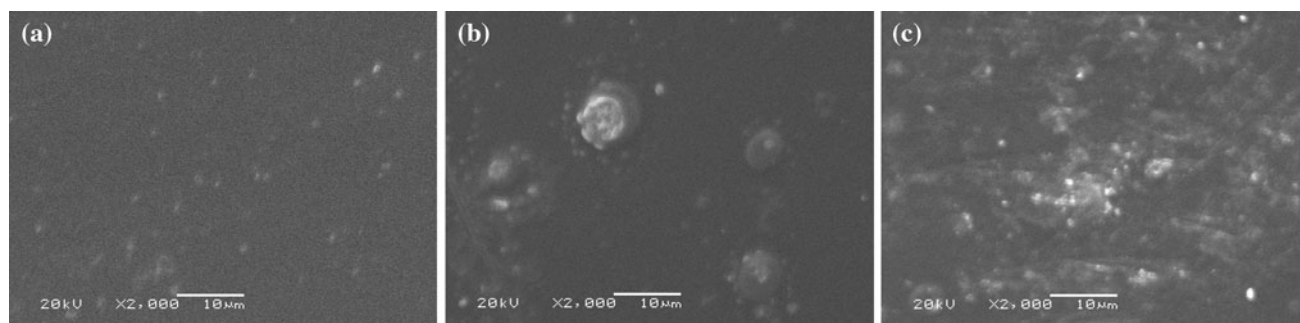

Fig. 4 SEM images of **a** COC and **b** COC modified with DMAPMA, **c** COC modified with DMAPMA and Pd(OAc)$_2$ sequentially

Fig. 5 SEM-EDS spectrum of the COC plate surface modified by DMAPMA and Pd(OAc)$_2$ sequentially
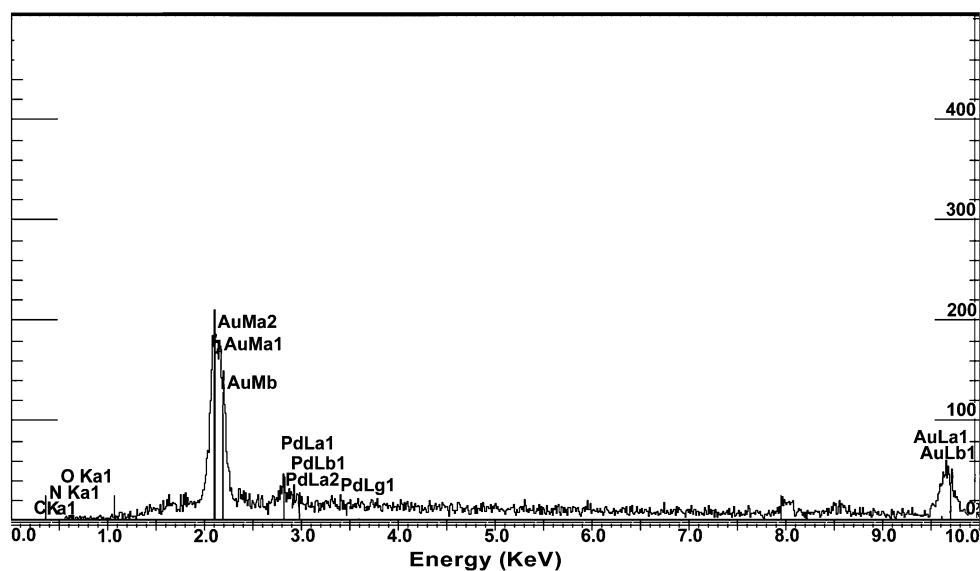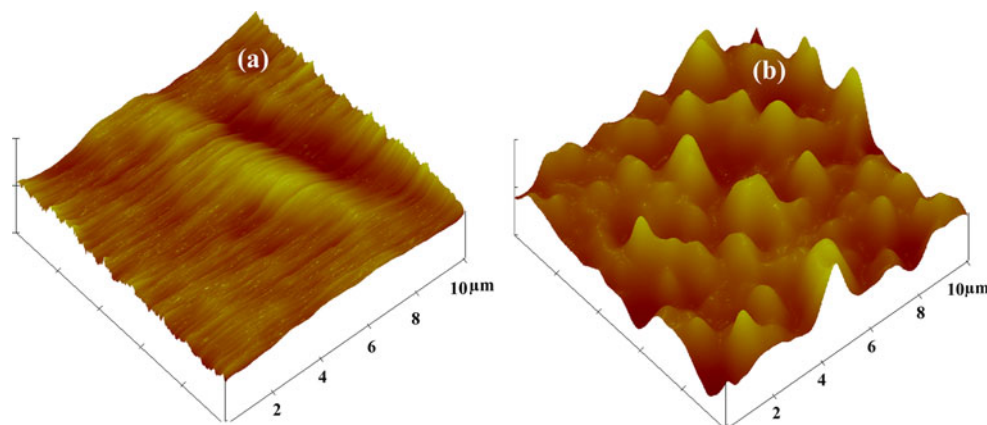

Fig. 6 Three-dimensional AFM images of **a** a photografted DMAPMA on COC, **b** Pd(OAc)$_2$ on COC

of other elements except C and O were observed in the XPS spectrum, indicating the main element of the unmodified COC plate surface was C. After being modified with DMAPMA, a strong peak at 398.82 eV could be attributed to N 1s which suggested that the DMAPMA was successfully introduced to the surface (Fig. 7b). Palladium-modified COC surface consists mainly of Pd(II) complex as evident from the measured binding energies of the Pd $3d_{5/2}$ and $3d_{3/2}$ electrons at 337.32 and 343.03 eV, respectively, corresponding to Pd(II) (Fig. 7d). However, during the modification process, in situ reduction of Pd(II) to Pd(0) occurred most likely by the solvent (Hegedus 2002; Li et al. 2010). According to the proposed mechanism of Suzuki cross-coupling reaction, Pd(0) plays an important role (Stang 1998). The in situ reduction of Pd(II) is confirmed by the measured binding energies of the Pd $3d_{5/2}$ and $3d_{3/2}$ electrons at 335.37 and 341.03 eV, respectively, after the modification, which corresponding to a mixture of Pd(II) and Pd(0).

To demonstrate the performance of the microfluidic reactor, Suzuki cross-coupling of 1-iodo-4-methoxybenzene with phenylboronic acid was chosen as the model reaction. The reactant mixture (200 μl) was introduced into the sample pool and flowed spontaneously in the channel from one side to the other. The reaction products were collected and analyzed off-line by GC with biphenyl as an internal standard. Several parameters including solvents, bases, channel lengths and temperature were screened to optimize the reaction conditions. DMF/H$_2$O was chosen as solvent in many reported catalytic systems because it provides high efficiency. A ratio of DMF and H$_2$O in 2:1 was chosen as the solvent to ensure the best activity of the catalyst. As shown in Table 1, K$_2$CO$_3$ as the base would provide the best yield, whereas the micro-channel was blocked very easily within a short period of time, due to its poor solubility in DMF/H$_2$O solvent (entry 3). Therefore, the organic compound, Et$_3$N, was chosen as the base. The effect of channel length on the cross-coupling reaction of 1-iodo-4-methoxybenzene with

Fig. 7 XPS spectra of **a** COC and COC modified with **b** DMAPMA, **c** DMAPMA and Pd(OAc)$_2$, **d** Pd 3*d* electrons' binding energies
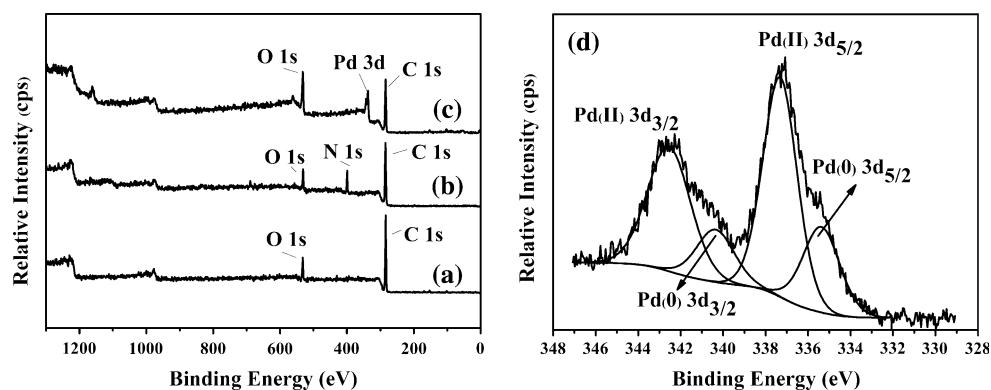

Table 1 Performance study of microfluidic reactor

Entry	Solvent (V/V)	Base (eq.)	GC yield (%)
1	DMF/H$_2$O (3:1)	Et$_3$N (2 eq.)	39
2	DMF/H$_2$O (3:1)	Et$_3$N (3 eq.)	42
3	DMF/H$_2$O (2:1)	K$_2$CO$_3$ (3 eq.)	93
4	DMF/H$_2$O (2:1)	Et$_3$N (3 eq.)	88

Reaction conditions: 1-iodo-4-methoxybenzene (0.067 M), phenylboronic acid (0.10 M), biphenyl (0.04 M), DMF/H$_2$O, base, 50°C

phenylboronic acid was then tested. As shown in Fig. 8, the yield increased with the increase of channel length until it reached 15 cm. Further increase in the channel length resulted with no obvious change in the yield. The effect of temperature was also examined (Fig. 9). The yield of the desired product increased with temperature, and 50°C was found to be optimal as further increase in reaction temperature resulted in lower product yield.

Under the optimized reaction conditions, various substrates could be carried out smoothly in the Pd-immobilized microchannels (Table 2). The microfluidic reactor exhibited high efficiency and good functional group compatibility. Substituents such as chloro, nitro, acetyl and methoxy groups on the aryl halides and methoxy, methyl, chloro and formyl groups on arylboronic acids were all tolerated. The coupling reactions worked well for aryl
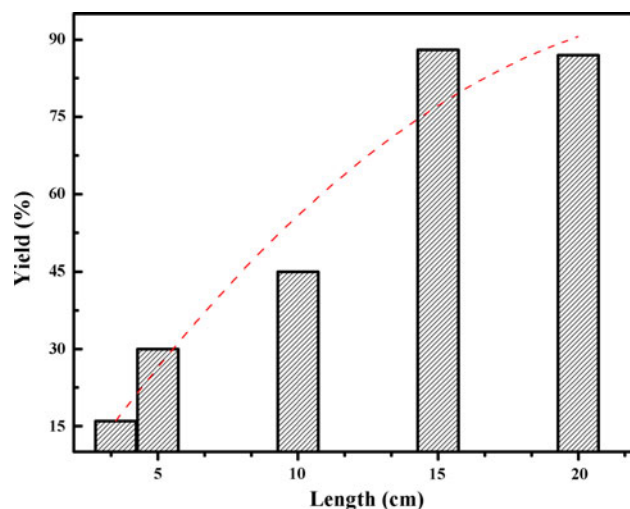

Fig. 8 Effect of channel length on the cross-coupling reaction of 1-iodo-4-methoxybenzene with phenylboronic acid. Reaction conditions: 1-iodo-4-methoxybenzene (0.067 M), phenylboronic acid (0.10 M), biphenyl (0.04 M), DMF/H$_2$O (2/1), Et$_3$N (3 eq.), 50°C
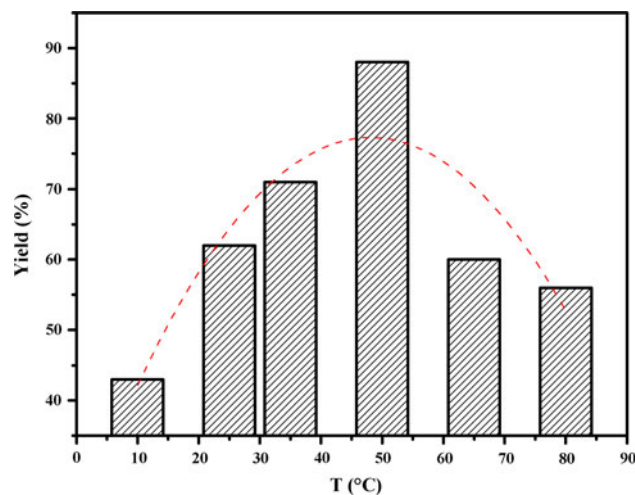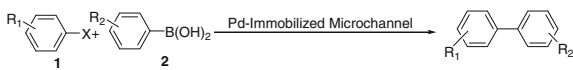

Fig. 9 Effect of temperature on the cross-coupling reaction of 1-iodo-4-methoxybenzene with phenylboronic acid. Reaction conditions: 1-iodo-4-methoxybenzene (0.067 M), phenylboronic acid (0.10 M), biphenyl (0.04 M), DMF/H$_2$O (2/1), Et$_3$N (3 eq.), channel length: 15 cm

Table 2 Suzuki cross-coupling of aryl halides with aryl boronic acids

$$R_1\text{–}C_6H_4\text{–}X + R_2\text{–}C_6H_4\text{–}B(OH)_2 \xrightarrow{\text{Pd-Immobilized Microchannel}} R_1\text{–}C_6H_4\text{–}C_6H_4\text{–}R_2$$
(**1**) (**2**)

Entry	X	R_1	R_2	GC yield (%)
1	I	H	4-MeO	96
2	I	H	4-Me	94
3	I	H	4-CHO	87
4	I	H	4-Cl	97
5	I	4-MeO	4-Me	97
6	I	4-Cl	H	91
7	Br	4-MeCO	H	100
8	Br	4-NO_2	H	98

Reaction conditions: **1** (0.067 M), **2** (0.10 M), biphenyl (0.04 M), DMF/H_2O (V/V = 2:1), Et_3N (0.20 M), 50°C

iodides and bromides of different electronic effects, affording good to excellent yields of the corresponding products (entries 1–8). Electron-donating groups like methoxy and methyl on the arylboronic acids gave high yields of the corresponding products (Table 2, entries 1 and 2). It could also work well for arylboronic acid with an electron-withdrawing formyl group (Table 2, entry 3). As proposed by Miyaura and Suzuki (1995), oxidative addition is often the rate-determining step in a catalytic cycle. Therefore, aryl halides activated by electron-withdrawing groups including acetyl and nitro are more reactive to the oxidative addition than those electron-donating groups, thus excellent yields could be obtained (Table 2, entries 7 and 8). For example, in the cross-coupling reaction of iodobenzene with 4-tolyl-boronic acid (Table 2, entry 2; the solution-catalyst contact time was less than 1 min and product collected over a 30-min period), comparative yield was obtained with the reported reference method which was carried out in organic monolith supports-based microreactor (Gömann et al. 2009; the solution-catalyst contact time was ca. 45 min and product collected over a period of 48 h). In addition, for the coupling reaction of 4-bromobenzonitrile with phenyl boronic acid (Table 2, entry 8), similar yield was obtained with that of reported method which was performed in microreactors using syringe pump-driven flow and a Pd/Al_2O_3 catalyst (He et al. 2004). However, in the later system, the reaction was carried out at a measured temperature of 90–98°C achieved with microwave enhancement (50 W).

In general, the heterogeneous catalysts with larger surface-area-to-volume ratios were often adopted to improve the catalytic performance in the conventional synthesis due to better molecular diffusion and heat transport they provided. Similar strategies have also been used in microfluidic devices (Jones et al. 2009). Although the surface-to-volume ratio of the microchannel we used is not as large as that of porous materials, good overall performance was still achieved in our open channel microreactor. This could be attributed to the advantages that offered by microfluidic channels, in which the smaller axial distances and laminar flow pattern might facilitate the substance exchange (reactant reaching and product leaving the active sites). In conventional flow-based heterogeneous systems, because quite lots of active sites of the catalysts locate deep inside of micropores, substance exchange between the main flow stream and the active sites might be retarded. In stirring systems, the catalyst particle might move together with the solution layer that enwrapped the particle, which could not effectively improve the substance exchange inside deep pores. In an open micro-channel, the active sites at the surface of the channel are uniformly exposed to the solution, as long as the channel is thin enough, the flow in the channel can effectively bring the reactants to the surface and take the products away, which is critical for better catalytic performance. The maximum channel size that can take advantage of this benefit was also related to the linear flow velocity and reaction rate happened on the channel surface. For the cases in which the flow velocity is around several millimeters per second, channels thinner than 200 μm in diameter should be applicable for catalytic reaction.

5 Conclusion

The Suzuki cross-coupling reaction of aryl halides (X = I, Br) with aryl boronic acid was successfully carried out in COC-based open channel microreactors with reduced time and lower reactant consumption, which showed great potential for high-throughput screening of catalysts or reaction conditions. The good performance might be a result of the unique flow pattern and diffusion behavior of molecules in microfluidic channels. Because the channel size is in micrometer range, diffusion of the molecules

between the main stream and the channel surface takes only several seconds or less. Therefore, continuous supply of reactants and effective removal of products through the laminar flow could be beneficial to heterogeneous catalysis in which catalysts are immobilized on the surface of the microchannel. We anticipate that, with similar experimental protocols, it should be possible to immobilize other catalysts such as gold, nickel or copper onto the inner surface of COC microchannels. Also, it is believed that, polymeric layer, such as DMAPMA, may provide a superior reaction environment for some transition metal-based heterogeneous catalytic reactions. Further study in this direction is currently in progress.

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