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Polymer-supported palladium catalysed Suzuki–Miyaura reactions in batch and a mini-continuous flow reactor system

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Abstract—A polymer-supported palladium(II) salen-type complex exhibited catalytic activity in the cross-coupling reaction of various aryl bromides and heteroaryl bromides with phenylboronic acid in a mini-continuous flow reactor system at elevated temperatures in a phosphine-free system. The reaction was also performed in batch using a number of different solvent systems in order to optimise conditions. The catalytic mini-reactor can be used repeatedly over several cycles in the Suzuki–Miyaura cross-coupling reaction. While the diameter of the flow channel is 3 mm, the macroporous resin supported catalyst is solvent expanded to completely fill the channel. Consequently, the liquid path is through the micro channels of the macroporous resin structure. Intensification of the process over the stirred batch reaction is through increased reagent-catalyst contact and results in a 20-fold increase in the rate of reaction. The residence/space time on the reactor is 10.5 min, compared to 24 h in batch, which means that a diversity of starting materials can be screened over a short period of time. To demonstrate the utility of the system, a diversity of aryl and heteroaryl bromides have been studied.

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1. Introduction

Metal-catalysed cross-coupling reactions have gained popularity over the past 30 years, in particular as convenient techniques for the formation of carbon–carbon bonds.[1] Numerous reactions have been developed to achieve cross-coupling, of which the Suzuki–Miyaura reaction is one of the most efficient methods for the synthesis of biaryl and heterobiaryl derivatives.[2,3] The tolerance of various functional groups in the coupling process, the diversity of organoboron compounds that are environmentally safer than other organometallic reagents, and the ease of handling and removal of boron-containing by-products offer the Suzuki–Miyaura reaction advantages over other related techniques.[4] Catalysts used in the standard processes are generally based on either homogeneous nickel or palladium phosphine complexes, which are rarely recoverable without elaborate and wasteful procedures, and, therefore, commercially undesirable.[2,5] Moreover, phosphine ligands are expensive, toxic, and in large-scale applications the phosphines may be a more serious economical burden than even the metal itself.[6] In recent years there has been an increasing interest in developing greener processes. In this context, heterogeneous catalysis is emerging as an alternative to homogeneous processes so that catalysts can be recovered and reused several times before they deactivate completely.[7] At the same time, the catalyst recovery also decreases contamination of the desired products with hazardous or harmful compounds, and also environmental pollution caused by residual of toxic metals and organic and inorganic waste can be reduced.[8] So far, palladium metal immobilised on cross-linked polystyrene resins and silica gels have been used in Suzuki–Miyaura reactions.[9,10] However, they normally suffer from limited mass transfer, low specificity and selectivity and leaching of the catalytic species from the surface of the support.[9] Recently new catalysts have been described that go some way to achieving greener heterogeneous processing, in particular the now commercially available EnCat™ polymer encapsulated palladium complexes[11] of Ley et al. and the Chitosan-supported materials[12] reported by Hardy et al. Kwong and co-workers have also described reactions using chloroaromatics at low catalyst loading that give excellent turnover numbers and yields[13] but which is at present confined to homogeneous catalysts with semi-labile phosphine ligands.

Reactor miniaturisation, for example micro reactors in which microlitre quantities of reagents are manipulated, has been shown to confer many advantages over conventional laboratory scale chemical apparatus.[14] Micro reactor technology clearly offers considerable advantages in performing safer and more efficient chemical reactions. In particular, the number of compounds that can be prepared and screened can be considerably increased thereby

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Keywords: Suzuki–Miyaura; Palladium; Cross-coupling; Continuous flow.

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enhancing the discovery phase.[15,16] Furthermore, the capability of producing a parallel network of micro reactors, the so-called 'scaling out' of the process, offers a clear route to generating product volume on demand, at the point of use, so reducing the need to store and transport hazardous or highly reactive chemicals.[17,18] To date the scope of liquid phase synthesis in micro reactors has, in the majority, been limited to non metal-catalysed reactions, with the exception of a few examples of heterogeneous catalysis.[19,20] There are only a couple of reports of heterogeneously catalysed Suzuki–Miyaura reactions in miniaturised continuous-flow reactors. Greenway et al., have reported the Suzuki–Miyaura reaction within a micro reactor operating under electro osmotic flow, using palladium on silica as catalyst to produce 4-cyanobiphenyl in 67% yield at room temperature.[21] However, the electric field played a major role in this catalytic process as no reaction was observed in an identical reactor system where EOF was replaced by pressure driven flow. He et al., recently investigated the microwave-assisted heterogeneous Suzuki–Miyaura reaction in a micro reactor, with 99% yield of 4-cyanobiphenyl being achieved at 100 °C.[22]

Recently we reported the synthesis and characterisation of an unsymmetrical salen-type palladium(II) complex and its immobilisation onto a polystyrene–divinylbenezene cross-linked Merrifield resin.[23] The supported catalyst was air- and moisture-stable, and could be reused several times without a significant degradation in catalytic activity in the Suzuki–Miyaura reaction of 4-bromoanisole and phenylboronic acid at 90 °C. Importantly, the reaction was carried out successfully without the need for intrinsic or added phosphine ligands. Leaching of the palladium into solution from the supported catalyst proved almost negligible.[24] In this paper we report for the first time, to the best of our knowledge, the cross-coupling reactions of various aryl bromides and heteroaryl bromides with phenylboronic acid in a mini-continuous flow reactor system using the heterogeneously polymer-supported homogeneous palladium catalyst. The use of the polymer-supported catalyst in the continuous flow system enabled product streams to be palladium free as leaching was minimised, removing the requirement for downstream catalyst separation. Reasonable conversions could be achieved in a matter of minutes, compared to conversions obtained after 24 h in a batch reaction, albeit on a much smaller scale. This allows small quantities of products to be prepared and screened quickly, allowing diversity studies and high throughput synthesis to be carried out. The compact design of the reactors also offer the opportunity of scale-out through reactor parallelisation although this will not be discussed in this paper.

2. Results and discussion

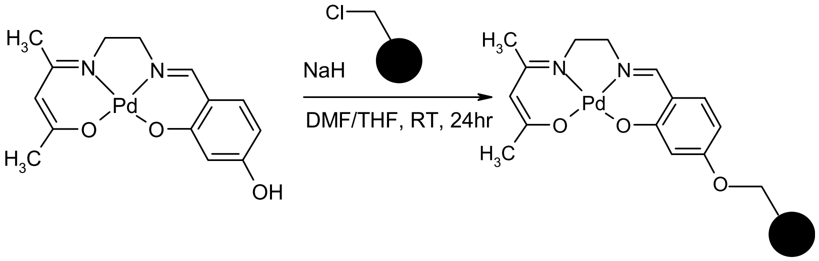
2.1. Catalyst preparation

The Merrifield resin-supported salen-type palladium(II) complex was prepared according to previously reported procedures (Scheme 1).[23]

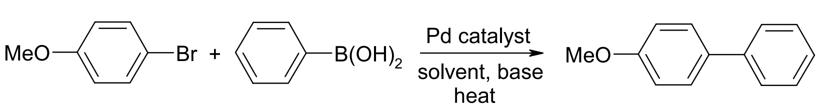
Inductively coupled plasma-atomic emission spectroscopy (ICP-AES) analysis indicated there to be ca. 2% (wt/wt) palladium on the Merrifield beads, corresponding to a catalyst loading of 0.2 mmol palladium/g of resin. Initial studies focused on the coupling reaction of 4-bromoanisole and phenylboronic acid (Scheme 2) in stirred batch reactors in order to obtain comparative data.

2.2. Solvent studies in batch

The combination of K_3PO_4 suspended in DMF and the palladium resin catalyst has been shown to produce the desired coupling product, that is, 4-methoxybiphenyl, in satisfactory yields.[24] However, in order to transfer the reaction to a continuous flow reactor, a totally homogeneous mixture was necessary as any solid in the flowing liquid would potentially cause blockages in the reactor. It was, therefore, decided to investigate a number of solvent-base combinations in order to optimise the process. Reactions were carried out in a Radley's Carousel Parallel Synthesiser fitted with a fuzzy logic temperature controller, using DME/water 1:1, ethanol/water 1:1 and PEG-300/water 1:1 and 4:1 with sodium carbonate as base and also DMF/H_2O 1:1 with *N*,*N*-diisopropyl ethyl amine as the base. In each case the reaction time was set to 24 h and the temperature thermostated at 100 °C. Yields were determined by GC against standard calibrations for each of the expected products. These data were used to determine the turnover frequencies (TOFs) before transferring the optimised



Scheme 1. The immobilisation of the salen-type palladium(II) complex.



Scheme 2. The Suzuki–Miyaura reaction of 4-bromoanisole and phenylboronic acid.

conditions to the continuous flow system. All reactions were carried out under a nitrogen atmosphere to prevent oxidation of the boronic acid to the phenol, which leads to the formation of the homocoupled product, unsubstituted biphenyl.

Reactions in PEG-300/water 1:1 and ethanol/water 1:1 failed to yield any product while DME/water 1:1 gave only 5% yield, although the homocoupled product was detected. It was, therefore, decided to use a procedure modified from a method that originally involved microwave heating of the reaction solution.[25] The original procedure used palladium(II) chloride in a mixture of PEG-400/water. Reactions were attempted using PEG-300/water in the ratio 4:1 using the palladium resin catalyst as well as homogeneous $PdCl_2$. The reactions were studied over a 24 h period and the kinetics studied as well as determining the TOFs. For the homogeneous catalyst a pseudo-first order overall rate constant of $1.4\times10^{-5}\ s^{-1}$ was determined at 100 °C using sodium carbonate as the base. The heterogeneous resin supported catalyst showed an enhanced rate with a pseudo-first order overall rate constant of $3\times10^{-5}\ s^{-1}$ under the same conditions. TOF studies also revealed some interesting characteristics of the heterogeneous catalyst relative to $PdCl_2$. All reactions were performed using 1.0 mmol of 4-bromoanisole and 1.1 mmol benzene boronic acid with an accurately weighed quantity of catalyst. A higher mole fraction of the homogeneous salt was required (28 mol%) giving a typical TOF of $0.18\ h^{-1}$. For the resin-supported palladium catalyst TOFs of 0.40 and $0.38\ h^{-1}$ were determined at 5 and 18 mol%, respectively. Further reactions were studied using 18 mol% of the resin-supported catalyst with increasing amounts of starting materials, maintaining a 10% excess of the boronic acid. At 2.0 and 5.0 mmol 4-bromoanisole respective TOFs of 0.74 and 1.84 were determined. However, after due consideration it was decided to use DMF/H_2O 1:1 and *N*,*N*-diisopropyl ethyl amine as the solvent/base system in the flow reactor. Although this organic amine has been shown to be less effective than Na_3CO_3 or K_3PO_4[21] in the Suzuki–Miyaura reaction in batch, it is totally soluble under the reaction conditions used in the continuous flow reactor and showed satisfactory results in our batch studies. Using a mole fraction of only 0.5 mol%, a TOF of 6.4 was determined.[24] The results from the TOF studies are summarised in Table 1.

2.3. Mini flow reactor studies

The continuous Suzuki–Miyaura reaction was carried out in a pressure driven mini flow reactor (bed size = 25 mm × 3 mm) constructed from Omnifit glassware with back-pressure being supplied by a syringe pump (RAZAL A-99).

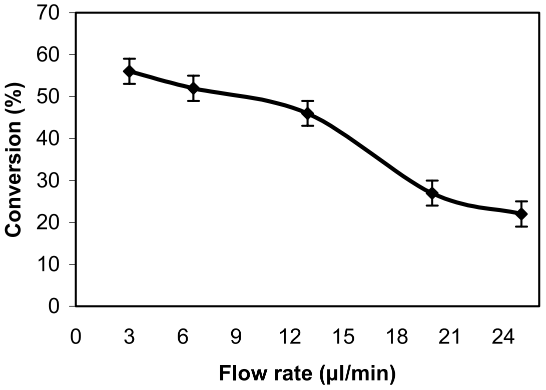


Figure 1. Study of the conversion dependence on flow rates in the continuous Suzuki–Miyaura reaction between 4-bromoanisole and phenylboronic acid at 100 °C.

The Omnifit reactor is a low pressure liquid chromatography column, which is packed with the catalyst particles; these are held in place by 25 µm pore size stainless steel frits integrated in to the screw caps that connect the column to the fluidic system, at the reactor entrance and exit. The catalyst particles swell in the solvent to tightly pack into the reactor body. Solvent removal allows the particles to de-swell. The design of the reactor system makes catalyst filling and removal an extremely easy and quick process. The reactor was heated by immersing it in a water bath at 100 °C. Reactants from a syringe at room temperature were then pumped through 0.8 mm internal diameter PTFE tubing at 100 °C and then through the palladium resin catalyst in the flow reactor at known flow rates for 5 h.

The reaction was carried out in the continuous flow reactor at different flow rates to investigate the effect of the residence time of the reagents within the catalyst bed on the coupling process. The results of conversion dependence on flow rates are shown in Figure 1. It was found that 4-methoxybiphenyl was formed in a yield of only 46% at a flow rate of 13 µl/min. This indicates that the residence time at this flow rate was too fast for the continuous Suzuki–Miyaura reaction, reducing reagent contact with the catalyst bed. Increasing the flow rate to more than 13 µl/min resulted in a significant drop in reaction conversion, with only 27 and 22% of 4-methoxybiphenyl being produced at flow rates of 20 and 25 µl/min, respectively. As expected, decreasing the flow rate to less than 13 µl/min increased the conversion to 52% at a 6 µl/min flow rate and up to 56% conversion for 3 µl/min. Since the reaction conditions such as concentration, ratio of phenylboronic acid to 4-bromoanisole, base, solvent and temperature remained unchanged in all cases, the observed increase in conversion with decreasing flow rate was obviously due to an effective increase in residence

Table 1. Turnover frequencies (TOF) in the Suzuki–Miyaura reaction of 4-bromoanisole with 1.1 equiv $PhB(OH)_2$ at 100 °C with different palladium catalysts, base and solvent under stirred batch conditions (based on GC–S data)

Substrate concn (mol)	Catalyst (mol%)	Solvent system	Base	TOF (h^{-1})
1.0	$PdCl_2$ (28)	$PEG300/H_2O$ (4:1)	Na_2CO_3	0.18
1.0	Pd resin (5)	$PEG300/H_2O$ (4:1)	Na_2CO_3	0.40
1.0	Pd resin (18)	$PEG300/H_2O$ (4:1)	Na_2CO_3	0.38
2.0	Pd resin (18)	$PEG300/H_2O$ (4:1)	Na_2CO_3	0.74
5.0	Pd resin (18)	$PEG300/H_2O$ (4:1)	Na_2CO_3	1.84
1.0	Pd resin (0.5)	DMF/H_2O (1:1)	$^iPr_2NEt$	6.40

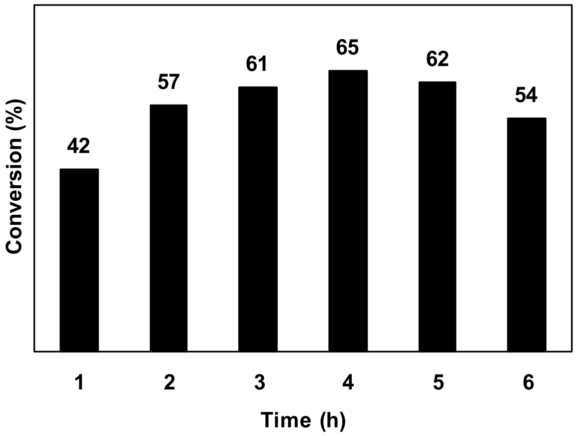


Figure 2. Study of the conversion against reactor run time in the continuous Suzuki–Miyaura reaction at the flow rate of 3 μl/min over 6 h. The actual residence time was 21 min.

time within the continuous reactor and hence an increase in the reaction time. It should be noted that because of the solvent induced swelling of the catalyst particles, the catalyst tightly packs the body of the reactor causing fluid and reagent flow through the internal macroporous structure of the resin as well as, to some extent, around the particles.

The conversion data presented in Figure 1 were achieved using a total 5 h reaction time (i.e., the average conversion over this period). However, it became clear that the reaction conversion changed during the period. The continuous reactor using the supported palladium catalyst was run continuously for 6 h at the flow rate of 3 μl/min with product samples being collected every hour. The results of this study are shown in Figure 2. It was found that 4-methoxybiphenyl was produced in a yield of approximately 40% over the first hour while an average conversion of approximately 60% was achieved over the subsequent 4 h. The lower conversion achieved in the first hour is most likely due to an induction period that corresponds to the delay required for the reduction of the catalyst precursor Pd(II) to the catalytically active Pd(0) oxidation state, although a complete reaction pathway for the Suzuki–Miyaura reaction using the polymer-supported salen-type palladium(II) catalyst is on-going and still remains to be elucidated. As the palladium catalyst could be reused in the batch reaction without a significant degradation in activity, we decided to test the activity of the recycled catalyst after this 6 h period of reaction in the continuous flow reactor. The palladium catalyst was washed several times with DMF, water and THF to remove any excess or surface deposited reagents, and dried under vacuum prior to re-use. A similar trend in activity was observed for the recycled catalyst.

2.4. Kinetics studies

Many chemical reactions have been demonstrated to show improved reactivity, product yield and selectivity when performed in micro reactors, compared with those generated using conventional laboratory practices.[14–17] We, therefore, decided to investigate if there was an enhancement of the observed rate constant for the continuous flow reaction of 4-bromoanisole and phenylboronic acid, when compared with that of the batch reaction under the same reaction conditions. For the batch reaction, aliquots were withdrawn at different time intervals to measure the corresponding conversion. The data were then analysed using the first order reaction design equation (Eq. 1), where x is the mole fraction of 4-methoxybiphenyl produced and t is the corresponding reaction time (Fig. 3). The reaction was shown to be pseudo first order overall with respect to the bromide, giving an observed overall rate constant of $5\times10^{-5}\ \mathrm{s}^{-1}$ ($0.18\ \mathrm{h}^{-1}$). It should be noted that in a continuous flow reactor, the mean residence time is also the reaction time and that the residence time in the mini flow reactor is much shorter than in the batch process. The continuous reaction was also assumed to be pseudo first order because the mechanism in batch and flow modes should be the same, so comparisons were made using this assumption. The residence time of the solution within the catalyst bed was measured according to a standard literature procedure[26], giving a value of 10.5 min at the flow rate of 6 μl/min. This means that the observed rate constant of the coupling reaction was considerably faster, with $k_{\mathrm{obs}}=1\times10^{-3}\ \mathrm{s}^{-1}$ ($3.6\ \mathrm{h}^{-1}$) using the continuous mini flow reactor. This represents an enhancement of the reaction rate of 20 times as compared to the batch reaction. This enhancement of the rate can be reconciled with the fact that the actual relative catalyst concentration within the element of the continuous flow reactor, relative to the reactants, is much higher than in the stirred batch reactor system. This means that there is much more efficient contacting of the reactants with the catalyst surface, and interior, as the reaction solution if

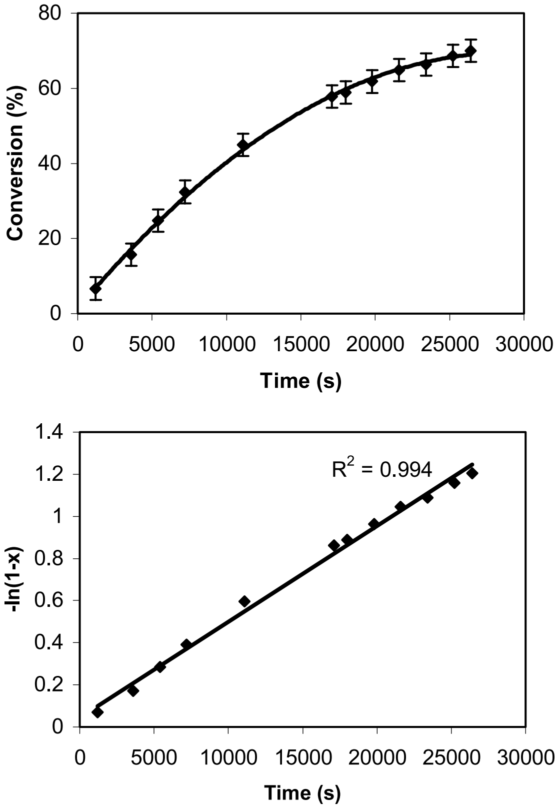


Figure 3. Kinetic data of the Suzuki–Miyaura reaction in a stirred batch reactor using the palladium resin catalyst over 7 h at 100 °C, showing an observed pseudo first order rate constant of $5\times10^{-5}\ \mathrm{s}^{-1}$.

pumped through the fixed bed when compared to the batch system, which is dependent on mass transport phenomena between the liquid and solid phases.

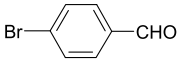
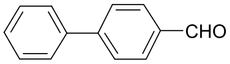
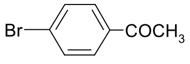
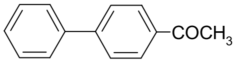
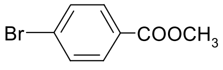
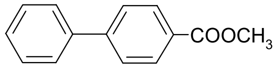
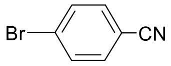
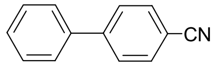
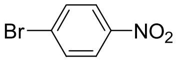
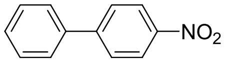
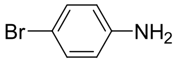
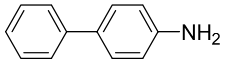
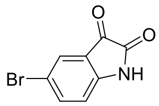
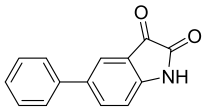
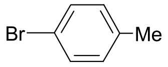
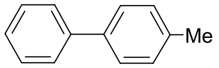
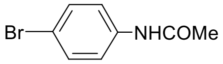
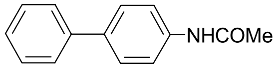
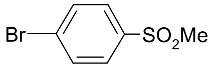
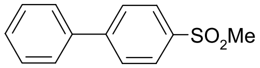
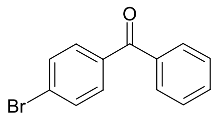
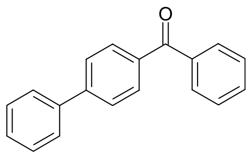
$$k_{\mathrm{obs}} = -[\ln(1-x)] \times \frac{1}{t} \tag{1}$$

2.5. Substrate diversity studies

The study was then extended to several substituted bromobenzenes containing both electron-withdrawing and electron-donating groups using the palladium resin catalyst, in order to test the tolerance of functional groups as well as their effects on the conversion. The reactions in the continuous flow reactor were run for 5 h at the flow rate of 6 μl/min at 100 °C. The results are shown in Table 2. As with the batch reactions,[24] it was found that electron-deficient substrates such as 4-bromobenzaldehyde (entry 1), 4-bromoacetophenone (entry 2) and 4-bromobenzonitrile (entry 4) were more reactive than 4-bromoanisole, giving higher yields of 74, 67 and 77%, respectively. The ester function (entry 3) survived the reaction, giving the ester-substituted coupled product in a yield of 65% with no detectable traces of the corresponding carboxylic acid. A favourable effect of electron-withdrawing substituents is normally observed in palladium-catalysed coupling reactions.[27] However, the continuous Suzuki–Miyaura reaction of 4-bromonitrobenzene failed with the coupling product being detected only in trace amount (entry 5), despite the fact that the nitro group is strongly electron-withdrawing. All attempts to carry out the reaction of 4-bromoaniline (entry 6) were also unsuccessful. Similarly, 5-bromoisatin, which possesses a secondary amine function and two carbonyl groups (entry 7), was also completely unreactive. This unexpected behaviour with this catalytic system still remains to be clarified but further studies are on-going. 4-Bromotoluene, which is electron-rich, still afforded the coupling product in a good conversion of 68% (entry 8). This is in accordance with the results of Ikegami et al., where 4-bromotoluene was found to be more reactive than 4-bromoanisole in the Suzuki–Miyaura reaction.[28] However, conversely Leadbeater et al. have also reported that the reaction of 4-bromoanisole and phenylboronic acid gave a better yield.[29,30]

Because of the synthetic importance of heterobiaryl derivatives, we also wished to carry out the Suzuki–Miyaura reactions of bromopyridines, bromothiophenes

Table 2. The Suzuki–Miyaura reaction of aryl bromides in the continuous flow reactor using the palladium resin catalyst, 1.5 equiv $PhB(OH)_2$, 3 equiv *N*,*N*-diisopropyl ethyl amine in DMF/water 1:1 at 100 °C, at the flow rate of 6 μl/min

Entry	Substrate	Product	Conversion (%)
1			74
2			65
3			65
4			77
5			Trace
6			0
7			0
8			68
10			37
11			71
12			76[a]

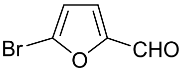
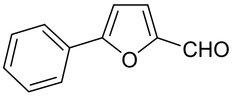
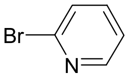
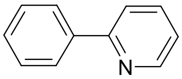
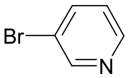
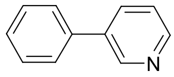
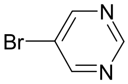
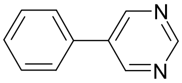
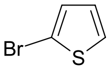
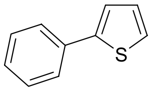
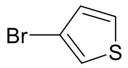
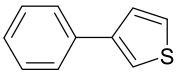
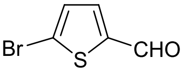
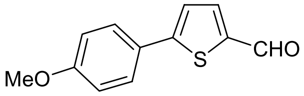
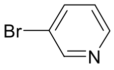
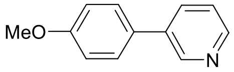
The data represent conversions of the bromides to cross-coupling products (based on GC–S data).

[a] DMF/water 3:1 was used instead of DMF/water 1:1.

and bromofurans with phenylboronic acid in the continuous flow reactor using the palladium resin catalyst (Table 3). Palladium was previously found to possess strong thiophilicity, which was reflected in the poisoning effect of the sulphur atom on some palladium-catalysed reactions. This poisoning effect was also observed in the presence of nitrogen atoms.[31] For this reason, the position of the bromide on a heteroaromatic ring should have an important effect on the coupling reaction. Due to the electronegativity of the nitrogen atom, it was reasoned that 2-bromopyridine should be more reactive towards the oxidative addition, which is normally the rate-limiting step of the reaction, than 3-bromopyridine.[32] In fact, a conversion of 70% was achieved for the reaction of 3-bromopyridine with phenylboronic acid (entry 15), while 2-bromopyridine remained almost unreacted under the same reaction conditions (entry 14). The same trend in the reactivity between substitution in the 2- and 3-postitions has also been observed by others, although the difference in reactivity between the two isomers of bromopyridines was much less significant.[31–34] It was previously presumed that the capacity for 2-bromopyridine to complex to the palladium catalyst prevented the coupling reaction.[34] The reaction of 5-bromopyrimidine, although it is an electron-poor heteroaryl bromide, proceeded with low yield (entry 16). The Suzuki–Miyaura reaction of 5-bromo-2-furaldehyde proceeded with very good conversion being achieved (entry 13), in accordance with results of Feuerstein et al.[31,32] It was found that the reaction of 2-bromothiophene led to a high yield of over 80% (entry 17), while a conversion of only 39% was afforded in the reaction of 3-bromothiphene (entry 18). This is in accordance with results previously reported by Molander and Biolatto.[34] However, over 10% of both 2- and 3-bromothiophene ended up in the corresponding homo-coupling product, which was not observed in the Suzuki–Miyaura reaction of any other organobromide used in this study. It is possible there is a substrate–metal interaction in one of the possible catalytic transition states that is affecting the outcome. However, a complete reaction pathway still remains to be elucidated. It is interesting that in general no homocoupled product was observed, even though the continuous flow reactions were not carried out in a nitrogen atmosphere. Therefore, the reaction in the mini-reactor is more selective than the reaction in batch.

Wiles et al. have recently reported a Michael addition reaction in a micro reactor under EOF conditions, in which enhancements in conversions through the application of the stopped flow technique were achieved.[35] This procedure involved the mobilisation of reagents through the glass micro reactor device for a designated period of time using an applied electric field, and the flow was subsequently paused by the removal of the applied field, prior to re-applying the field. The authors proposed that the observed increase in conversion, when using the technique of stopped flow, was due to an effective increase in residence time within the reactor. We, therefore, decided to apply the stopped-flow technique to the Suzuki–Miyaura reaction of 4-bromobenzaldehyde with phenylboronic acid using the palladium resin catalyst in the continuous flow reactor. In fact, this technique is an alternative route to decreasing the flow rate to increase the space time of reagents within the catalyst bed. The results are shown in Figure 4. As the residence time was found to be 10.5 min at a flow rate of

Table 3. The Suzuki–Miyaura reaction of heteroaryl bromides in the continuous flow reactor using the palladium resin catalyst, 1.5 equiv $PhB(OH)_2$, 3 equiv *N*,*N*-diisopropyl ethyl amine in DMF/water 1:1 at 100 °C, at the flow rate of 6 μl/min

Entry	Substrate	Product	Conversion (%)
13			91
14			1
15			70
16			42
17			82
18			39
19			88[a]
20			55[a]

The data represent conversions of the bromides to cross-coupling products (based on GC–S data).

[a] 4-Methoxybenzeneboronic acid was used instead of benzeneboronic acid.

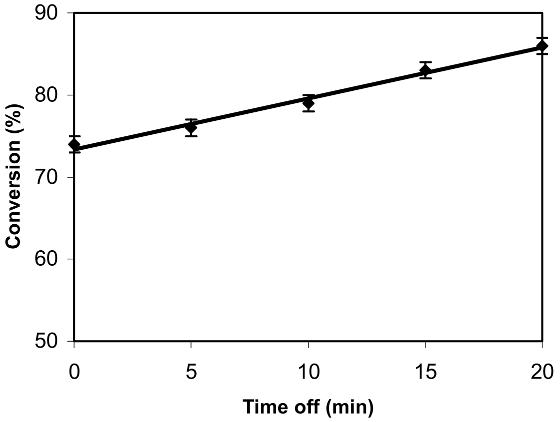


Figure 4. Study of stopped flow technique in the Suzuki–Miyaura reaction of 4-bromobenzaldehyde using the continuous flow reactor at the low rate of 6 μl/min, with the regime of 10 min on and between 0 and 20 min off.

6 μl/min, reactants were pumped through the reactor for 10 min and the flow was subsequently paused for a designated period of time, prior to re-injecting the solution. The syringe pump was controlled using an automated cyclic timer unit, which was designed and constructed in-house. Using the regime of 10 min on and 5 min off, the conversions were slightly improved to 76%. Lengthening the stopped flow period to 10 min resulted in a further increase to around 80% conversion. The conversion could be improved to 83 and 86% by stopping the flow for 15 and 20 min, respectively. No by-products were observed, the mass balance being completed by unreacted starting material.

3. Conclusions

The polymer-supported palladium(II) complex exhibited catalytic activity in the cross-coupling reactions of various aryl bromides and heteroaryl bromides with phenylboronic acid in a mini-continuous flow reactor system without the need for phosphine ligands. Using the mini-flow reactor system, reasonable conversions can be achieved in a matter of minutes. Although simple in design and concept, with easily replaceable catalyst beds and interchangeable reagents premixes, as there is no reaction in the absence of the catalyst, the mini-flow reactor system provides a powerful tool in catalyst screening and a route to high throughput synthesis. Therefore, the mini flow system is ideal for the rapid production of small inventories of reagents. Products can be generated on demand, at the point of use, so reducing the need to store and transport hazardous chemicals. Furthermore, we have demonstrated that the use of stopped-flow techniques are applicable to the Suzuki–Miyaura reaction, leading to increased residence time in the reactor and an increase in product yield.

4. Experimental

4.1. General

Chemicals were obtained from Aldrich and Fisher and were used as received. The unsymmetrical salen-type palladium(II) complex was synthesised according to previously published methods.[20] Mass Spectra were recorded by Jane Stanbra and Simon Thorpe, ICP-ES analyses were performed on a Spectro Ciros^{CDD} instrument (Spectro Analytical, UK) by Ian Staton from the Department of Chemistry, The University of Sheffield. GC–MS analyses were performed using a Perkin Elmer GC–MS with a 30 m×0.25 mm×0.25 μm Phenomenex-2B5 column. The temperature program was 60–260 °C at 10 °C min^{-1} with a final temperature isothermal hold for 10 min. The MS mass limit was set between 50 and 450 Da.

4.2. Catalyst preparation

A yellow solution of palladium complex (0.20 g, 0.54 mmol) in dry DMF (40 ml) and THF (20 ml) was added dropwise at room temperature to a dispersion of excess 60% sodium hydride in mineral oil (0.06 g, 1.5 mmol) and the resulting mixture stirred for 10 min. A suspension of Merrifield resin (2 g, 200–400 mesh, 1.7 mmol-Cl/g, 3.4 mmol) that had been pre-swelled in DMF (40 ml) for 30 min was then added and the mixture stirred gently at room temperature for 24 h. The initially white Merrifield resin beads became yellow and the solution turned pale yellow. The beads were filtered off, washed several times with water (3×50 ml), triturated several times for a total of 24 h with DMF (5×50 ml), THF (3×50 ml), diethyl ether (3×50 ml) to remove physically adsorbed palladium complex and air-dried to yield yellow beads (2.0 g). Inductively coupled plasma-atomic emission spectroscopy (ICP-AES) measurements showed there to be ca. 2% (wt/wt) palladium on the Merrifield beads, corresponding to a catalyst loading of 0.2 mmol palladium/g of resin.

4.3. ICP analysis of the supported catalysts

Calibration against palladium standards and a blank was linear, using 2% nitric acid solutions containing 0, 1, 5 and 10 ppm palladium made from a 1000 ppm stock solution (Aristar). Weighed samples (20.0 mg) of immobilised palladium catalysts were placed in glass tubes and digested at 180 °C in a mixture of concentrated nitric acid (5 cm^3, Aristar) and concentrated perchloric acid (0.5 cm^3, Aristar). Three parallel samples were digested in 2, 4 and 6 h, respectively. The yellow palladium catalyst became a white residue after digestion. The digest was then diluted to 50 cm^3 with water. Analysis showed that all the palladium was removed from the support within 2 h as increasing the digestion time to 4 and 6 h achieved no increase in the amount of the palladium in the digest.

4.4. Catalysis studies

4.4.1. Batch reactions. Unless otherwise stated, a solution of 4-bromoanisole (0.0561 g, 0.3 mmol) in DMF (0.75 ml) was added to a Radley's Carousel reaction tube constaining the palladium resin catalyst (7.5 mg, 0.0015 mmol). A solution of *N*,*N*-diisopropyl ethyl amine (0.116 g, 0.9 mmol) in water (1.5 ml) and a solution of phenylboronic acid (0.054 g, 0.45 mmol) in DMF (0.75 ml) were then added and the tube was heated at 100 °C for 24 h with magnetic stirring under a nitrogen atmosphere. To work-up, the mixture was allowed to cool to room temperature and saturated aqueous NaCl solution (3 ml) was added. The organic components were extracted into diethyl ether (3× 3 ml), which was dried over anhydrous $MgSO_4$ and the resulting solution analysed by GC and GC–MS with reference to standard solutions of 4-methoxybiphenyl.

4.4.2. Micro flow reactions. Unless otherwise stated, the Suzuki–Miyaura coupling reaction of 4-bromoanisole with phenylboronic acid was carried out in a pressure driven micro flow reactor (length = 25 mm; I.D. = 3 mm) build up from Omnifit glassware containing the Merrifield resin-supported palladium catalyst (110 mg). Standard HPLC connectors allowed one end of the reactor to be connected to a disposable solvent-resistant syringe, while the other end was attached to a syringe needle leading to a quenching vessel containing diethyl ether and saturated aqueous Na_2CO_3. The reactor was heated by immersing it in a water bath at 100 °C. Reactant mixtures consisting of 4-bromoanisole (0.1 M), phenylboronic acid (0.15 M) and *N*,*N*-diisopropyl ethyl amine (0.3 M) in DMF/water 1:1 at room temperature were then pumped continuously through the palladium resin catalyst bed at known flow rates for 5 h, using a syringe pump (RAZAL, A-99). The organic components were extracted into diethyl ether and analysed by GC and GC–S as described above.

4.5. Residence time distribution measurement

The mean residence/space time of the reaction solution within the catalyst bed was measured using a standard experimental method, the step experiment.[22] A solution of $CoCl_2$ in DMF/water 1:1 was pumped through the Omnifit flow reactor containing the palladium resin catalyst (110 mg) at the flow rate of 6 μl/min. The outlet absorbance distribution, and hence the outlet concentration distribution, versus time was measured online using a fibre optic spectrometer (USB 2000-UV–vis, Ocean Optics Inc.) at different wavelength ranging from 450 to 560 nm. The absorbance distribution at the wavelengths of 520 nm versus time is shown in Figure 5. Taking into account the residence time of the solution in the HPLC standard connectors based on their volumes and the known flow rate, the mean space time within the catalyst bed was found to be 10.5 min at the flow rate of 6 μl/min.

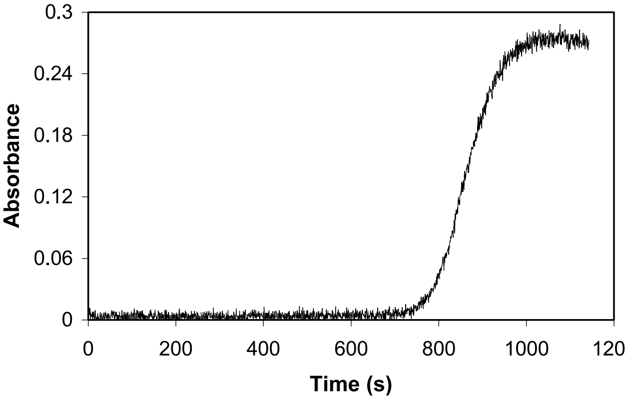


Figure 5. The outlet absorbance distribution versus time at the wavelength of 520 nm and the flow rate of 6 μl/min using $CoCl_2$ in DMF/H_2O.

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