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Microwave-Assisted Suzuki Coupling Reactions with an Encapsulated Palladium Catalyst for Batch and Continuous-Flow Transformations

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Abstract: This article describes the design, optimisation and development of a Suzuki cross-coupling protocol mediated by an efficient palladium-encapsulated catalyst (Pd EnCat™) under microwave irradiation. The methodology has been used in both batch mode for classical library preparation and in continuous-flow applications furnishing multigram quantities of material. Described is a method that uses direct focused microwave heating whilst applying an external cooling source. This enables a lower than normal bulk temperature to be maintained throughout the reaction period leading to significant improvements in the overall yield and purity of the reaction products. Additional aspects of this novel heating protocol are discussed in relation to the prolonged lifetime and enhanced reactivity of the immobilised catalyst system.

Keywords: C–C coupling · flow reactors · microwaves · supported catalysts · Suzuki reaction

Introduction

The development of focused microwaves has significantly enhanced the productivity and expanded the armoury of chemical transformations available to the modern day organic chemist. The impact and value of this enabling technology is evidenced by the exponential increase and diverse nature of the literature dedicated to the many synthetic preparations facilitated by this protocol.[1] It is proven that use of focused microwave heating generally leads to a marked reduction in overall reaction times as well as associated improvements in product purity and yield. One of the key areas that has benefited greatly from the advances in focused microwave reactor design is medicinal chemistry compound collections, especially those obtained from cross-coupling reactions.[2]

The Suzuki reaction is by far the most versatile synthetic method available for the generation of unsymmetrical biaryl compounds.[3] The reaction, unlike most other palladium-catalysed coupling processes, is tolerant of water and a wide range of functional groups, employs readily accessible starting materials and yields nontoxic by-products. However, the inherent expense and potential toxicity of the palladium catalysts employed is often problematic especially upon scale-up. Therefore methodology enabling immobilisation and thus permitting facile recycling is of strategic and economic importance. We have previously reported[5] on a polyurea microencapsulated palladium catalyst (Pd EnCat™;[4] Figure 1) that has been applied to a range of cross-coupling and reduction reactions in both conventional solvent systems and in supercritical carbon dioxide. It has been shown that the use of this Pd EnCat catalyst significantly facilitates these reactions, benefiting from a much simplified workup procedure: the heterogeneous catalyst is readily removed by filtration and has been successfully recycled multiple times with no detectable deterioration in reactivity. In addition, inductively coupled plasma (ICP) analysis of product mixtures following simple filtration has proven palladium levels to be less than 10 ppm, corresponding to less than 1% leaching of the original palladium content of the capsules; an important consideration regarding metal contamination in medicinal chemistry programs.

Within our laboratories, EnCat has been successfully utilised as a catalyst for the Suzuki reaction with a selection of boronic acids and aryl halides.[5a,c,d] The previously optimised conditions involved heating a toluene/water/ethanol (4:2:1) solvent system at reflux for several hours, giving excellent

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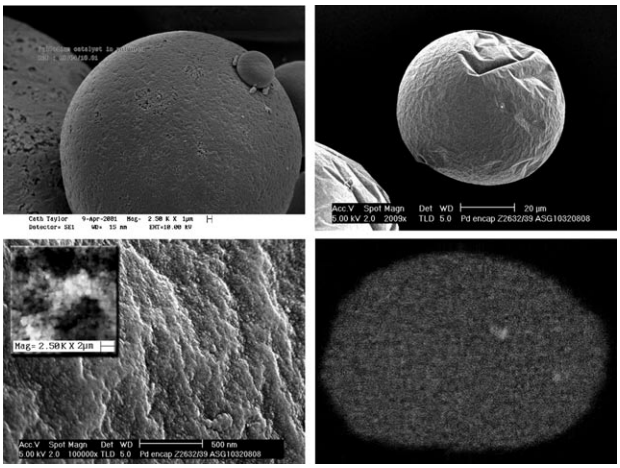
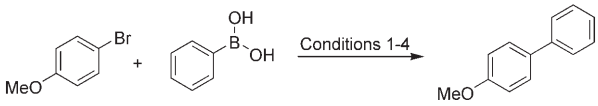


Figure 1. Pd EnCat catalyst. Top: Images of the Pd EnCat bead with magnification. Bottom Left: Magnified surface of Pd-EnCat (0.4 mmol g^{-1}) with inlayed higher magnification image of the particulate surface. Bottom right: EDX of sectioned Pd EnCat showing an even distribution of palladium.

overall yields. It was envisaged that microwave heating used in conjunction with the Pd EnCat would enhance the reactivity, thereby reducing reaction times and allowing the use of more diverse and sensitive substrates. We have previously shown that microwaves can vastly expedite the production of compound arrays,[6] as well as being amenable to the processing of reactions in flow mode, allowing the preparation of multigram quantities of products in a single, continuous operation.[7] Indeed, the design of specific flow reactors is of particular interest to an industry sensitive to process intensification issues. The tremendous benefits of adopting flow-type operations have already been demonstrated for a variety of microscale reactions.[8] It was our intention to pursue a systematic course of research that would ultimately result in the design of a microwave-activated, heterogeneously catalysed, continuous-flow reactor for conducting Suzuki cross-coupling reactions.

Results and Discussion

The optimised reaction conditions previously devised in our laboratories for the EnCat-catalysed Suzuki reaction required 5 mol% of the catalyst (0.4 mmol g^{-1} Pd) and three equivalents of potassium carbonate as the base. The solvent mixture used as previously described (toluene/water/ethanol 4:2:1) became monophasic at the elevated reaction temperatures (100 °C), but was principally biphasic at ambient temperature. As a comparative marker to evaluate the microwave-assisted reaction we used the simple coupling reaction between 4-bromoanisole and phenyl boronic acid (Scheme 1). By employing similar conditions as used for the thermal reaction in the microwave (albeit at a slightly higher temperature of 120 °C), the reaction time was shortened from 8 h to just 10 min corresponding to a 48-fold rate increase. To rationalise the effect of the raised temperature

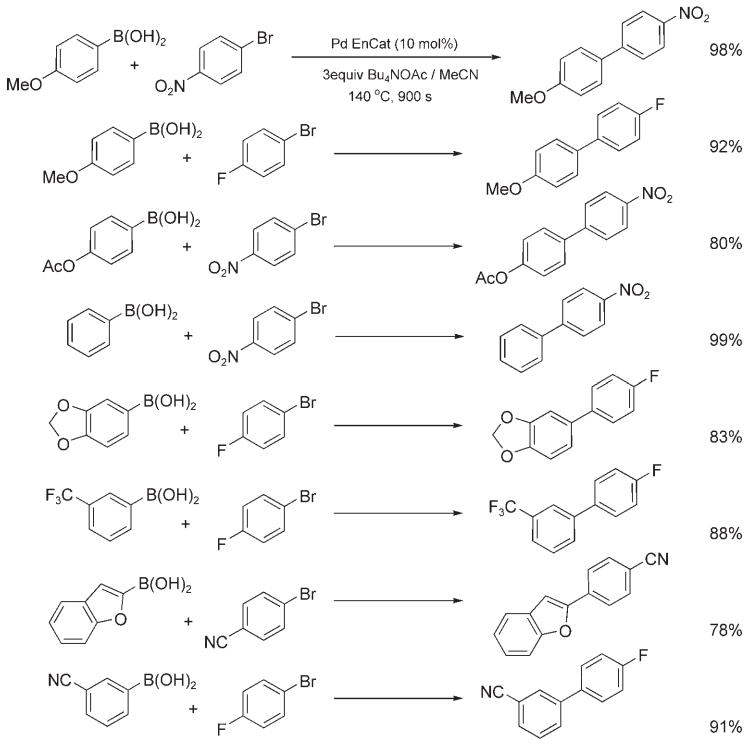


Scheme 1. Conditions developed for the microwave-assisted Suzuki coupling reaction. 1) 5 mol% EnCat, 3 equiv K_2CO_3, PhMe/H_2O/EtOH (4:2:1), 100 °C, 8 h, 97% conversion. 2) 5 mol% EnCat, 3 equiv K_2CO_3, PhMe/H_2O/EtOH (4:2:1), 120 °C, sealed tube, 3.5 h, >98% conversion. 3) 5 mol% EnCat, 3 equiv K_2CO_3, PhMe/H_2O/EtOH (4:2:1), microwave, 120 °C, 10 min, >98% conversion. 4) 5 mol% EnCat, 2 equiv Bu_4NOAc, EtOH, microwave, 120 °C, 10 min, >98% conversion.

and determine any potential acceleration of the reaction due to working in a sealed vessel, the corresponding analogous reaction involving classical heating of a sealed vial with an oil bath was conducted. Although this demonstrated an improvement in the required reaction time from 8 h to 3.5 h, it still only represented the expected Arrhenius step change. The hypothesis is therefore, that this enhanced catalytic activity is a direct consequence of the microwave heating. Indeed, the mechanism of molecular interactions leading to the heating phenomenon through the direct coupling of metallic species with microwave irradiation is well documented as being a very efficient process.[1,2] Furthermore, a number of studies have shown that metal-tethered or metal-impregnated catalysts demonstrate enhanced reactivity and prolonged lifetimes under microwave-heating conditions. These two features have been attributed to the selective absorption of the metal particles that can be heated directly without notably heating the support material as a result of the drastic difference in their dielectric constants.[9] It was therefore our aim to further harness this increased microwave-induced reactivity to broaden the scope of the Pd EnCat system.

In addition, to simplify any future compound library preparation by eliminating the time intensive aspects of the workup procedure, replacement of the reaction solvent was investigated; such a change also necessitated a re-evaluation of the accompanying base. Evident from this basic screening process was that two potential solvents afforded themselves to the reaction (EtOH and MeCN) and that with their use the inorganic base potassium carbonate could be successfully replaced with tetrabutylammonium acetate (Scheme 1, conditions 4). For the initial development work, MeCN was adopted as the solvent of choice, because it gave slightly enhanced yields. Applying the new conditions we processed a trial set of typical coupling partners to determine the generality and compatibility of the reaction conditions (Scheme 2).

To ensure complete conversion was achieved, reaction times of 15 min and a temperature of 140 °C were used. All reactions were conducted based on a 0.5 mmol scale of each coupling partner. The workup procedure consisted of only a simple filtration and elution through a fritted sulfonic acid functionalised silica cartridge to remove the excess base followed by evaporation of the solvent. The palladium catalyst could be easily recovered and recycled in subsequent reactions by decanting it from the top of the fritted tube. The reactions all showed excellent purity (>95%) and gave very



Scheme 2. Microwave-assisted Suzuki cross-coupling reactions. Percentage conversion quoted based on transformation of the aryl halide. Conditions: 1 equiv aryl halide, 1.05 equiv boronic acid. Pd EnCat (10 mol%), 3 equiv Bu_4NOAc in MeCN (5 mL), 140 °C for 15 minutes.

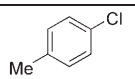
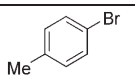
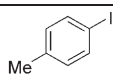
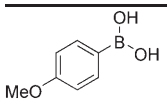
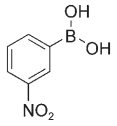
high isolated yields; however, it was observed that certain substrates and their derived products were not very soluble in the acetonitrile solvent system. Although this did not create significant problems in workup for this small test set, it was envisaged that for a more expansive compound collection precipitation and insolubility problems could complicate isolation. For this reason, the alternative solvent ethanol was applied throughout the remainder of the study. Interestingly, we determined that using this solvent permitted the equivalents of the tetrabutylammonium base to be reduced to two equivalents without diminishing the conversions or increasing reaction times.

This was demonstrated with three analogous aryl halides (Table 1). As expected, 4-chlorotoluene was significantly less reactive than the analogous bromide and iodide. However, heating to a higher temperature (140 °C) allowed even this chloride to react completely. At this elevated temperature, no homocoupling adducts or other decomposition products were observed.

Library synthesis: The preliminary decision-making processes for successful library generation are quite complex. Balancing the contrasting problems of extensive optimisation to create generic conditions against the desire to diversify the array components as widely as possible (in terms of structure and electronic characteristics) are often divergent operations. The compromise that is often reached will ultimately lead to the creation of a compound collection consisting of mixed purity products. Following such a strategy it was our aim to construct a small library prepared by using the Pd EnCat-catalysed Suzuki reaction. Our intention was twofold, initially in that selecting a challenging set of substrates we would compare the effectiveness of the immobilised catalyst against the accepted catalyst standards. Additionally, we would also have access to a realistic set of experimental data incorporating a selection of less effective coupling reactions that we could use as markers to elucidate additional advantages of other modified microwave-heating processes.

A total of 11 boronic acids and 31 aryl halides and triflates were selected, generating a potential array of 341 compounds (Figure 2). The coupling partners chosen contained a range of chemical structures, including some sensitive functionality such as a primary alcohol, aldehyde or phenol, in addition to a variety of heterocyclic and biaryl systems. The substituted benzene derivatives comprised both electron-rich and electron-poor substrates, as well as compounds containing sterically hindering *ortho* substituents.

Table 1. Comparison of reactivity for different aryl halides. (0.5 mmol halide, 0.5 mmol boronic acid, 1.0 mmol Bu_4NOAc, 5 mol% Pd EnCat, EtOH, microwave irradiation. In all cases conversion was >98% as determined by LC-MS and ^1H NMR spectroscopy.)

			
	140 °C 10 min	120 °C 10 min	120 °C 6 min
	140 °C 10 min	120 °C 10 min	120 °C 6 min

As in the previous study the workup procedure consisted of only a simple filtration and elution through a fritted sulfonic acid functionalised silica cartridge to remove the excess base, followed by evaporation of the solvent. In cases in which the product contained a basic heterocyclic system, the reaction mixture was evaporated to dryness before the

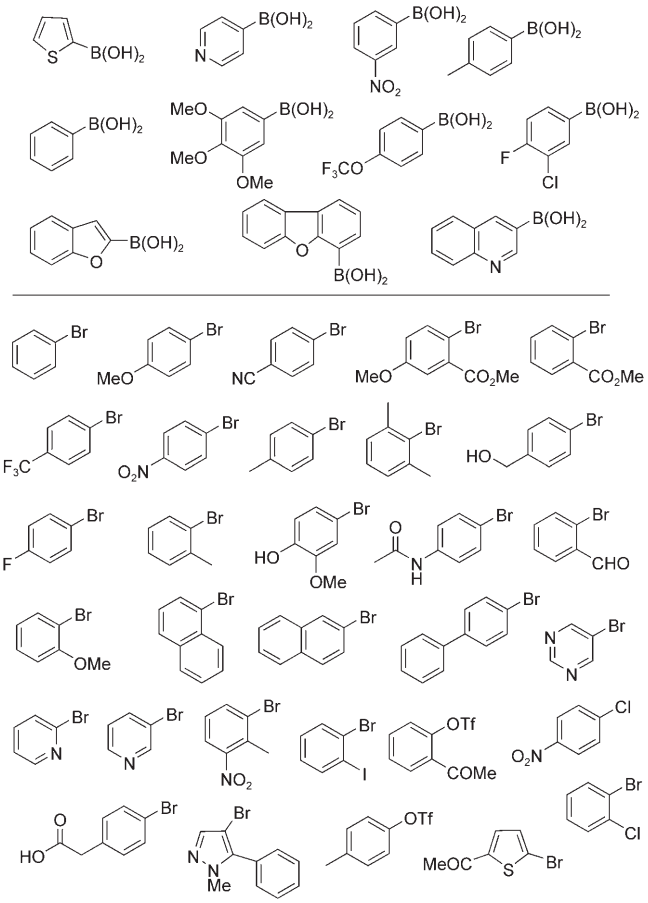


Figure 2. Coupling partners used in library preparation.

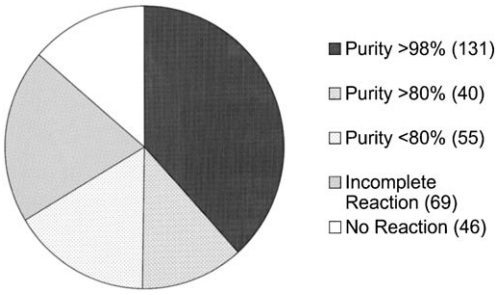


Figure 3. Results of the library synthesis.

residue was taken up in dichloromethane and filtered through a short plug of silica. No further purification was used in either case. All products were analysed by both LC-MS and ^{1}H NMR spectroscopy and the general library results are shown in Figure 3.

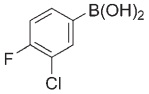
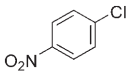
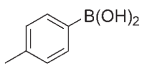
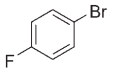
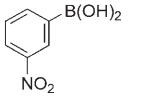
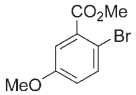
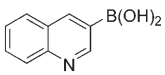
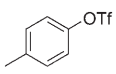
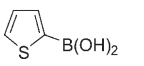
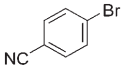
Of the 341 reactions undertaken, 131 (38%) generated products which were pure by both ^{1}H NMR spectrsocopy and LC-MS. A further 40 (12%) had purities well in excess of 80%. In all cases the isolated yields for these reactions were greater than 80%, with the majority being above 90%. An additional set of 69 combinations (20%) did not react fully during the ten minute heating period, their reaction mixtures comprising of only starting materials and product. Exposing some of these reactions to an extended heating time of 20 min was enough to drive the reactions to completion (Table 2). The only exception was the reaction with a thiophene-containing boronic acid, in which catalyst poisoning is probably the cause of the depleted conversion.

As expected, a proportion of the reactions (16%) gave products of low purity; these reactions would become the reactions of particular interest in our later experiments. Of the 55 failed reactions, only 4 represented substrates which have been cited in the literature previously as successful Suzuki coupling reactions, although these were largely with very specific catalyst and ligand combinations.[10] Indeed, most were known to be incompatible coupling partners.[10]

The Pd EnCat system benefits clearly benefits from low palladium leaching and the ease with which the catalyst may be removed and recycled. Further to this, the range of substrates used within the library array demonstrates a broad scope of reactions that proceed in high yield and with high levels of purity; there was no sign of common side reactions, such as dehalogenation or homocoupling. Additionally, no expensive, potentially difficult to remove or toxic ligands were required, as the reactions proceed well with Pd EnCat, a palladium(II) acetate immobilised catalyst.

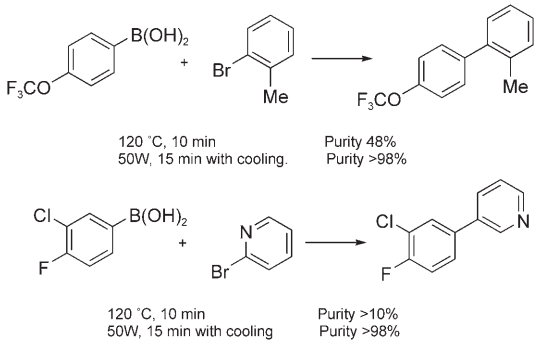
Cooled microwave heating: Microwave heating has been shown to dramatically improve the yields of reactions in

Table 2. Improvement in conversion from extended heating times. (0.5 mmol halide, 0.5 mmol boronic acid, 1.0 mmol Bu_4NOAc, 5 mol% Pd EnCat, EtOH, microwave irradiation at 120°C. [a]Conversion based on transformation of the boronic acid measured by LC-MS and ^{1}H NMR spectroscopy).

Entry	Boronic acid	Coupling partner	Conversion [%] after 10 min	Conversion [%] after 20 min
1			83	>98
2			77	>98
3			64	>98
4			50	94
5			26	32

which the starting materials suffer from thermal decomposition.[1] This is largely due to the reduced reaction times and the more even application of energy to the reaction media as opposed to any specific microwave effect. Therefore, in principle, cooling the reaction mixture whilst applying microwave energy should retard the thermal decomposition pathway still further. Indeed it has previously been shown that microwave irradiation used in heat/cool cycles or through pulsing the microwave power to limit the heating as well as applying external cooling can generate products of significantly higher purity.[11] The adoption of these types of heating procedures offer additional advantages when applied to metal-catalysed processes. Microwave energy couples best with molecules possessing a large dipole moment or with metals. Therefore metallic systems such as the encapsulated palladium catalyst and its associated reaction intermediates will be affected by the microwave radiation to a far greater degree than the starting materials or products. In our system, a large proportion of the microwave energy put into the reaction will be absorbed by the immobilised palladium catalyst, thereby enhancing the rate of reaction. However, simultaneously cooling the bulk reaction mixture will prevent many of the accompanying thermal decomposition pathways. In practice it is a simple procedure to heat a reaction in a focused microwave cavity, whilst cooling the vessel by blowing regulated compressed air over it.[12] It was envisaged that the two segments from the above library preparation representing the lower purity products would provide a suitable platform to facilitate an in-depth investigation into the potential for inhibiting side reactions by the use of simultaneous microwave heating with externally applied reaction cooling.

Initial results were extremely promising; two sets of substrates that had generated impure products under the standard library reaction conditions were heated with simultaneous cooling (Scheme 3). The reactions that were heated at 50 W attained global temperatures not exceeding 76 °C, significantly cooler than the 120 °C used in the standard reaction conditions, but employing a comparable amount of microwave energy. In both cases product purity improved dramatically (Figure 4), although slightly extended reaction times of 15 mins were required as opposed to the original 10 mins. Again, isolated product yields were also excellent



Scheme 3. Improvement in product purity when simultaneous cooling was applied with microwave heating. (0.5 mmol halide, 0.5 mmol boronic acid, 1.0 mmol Bu_4NOAc, 5 mmol% Pd EnCat, EtOH, microwave irradiation. Product purity was measured by LC-MS and ^1H NMR spectroscopy.)

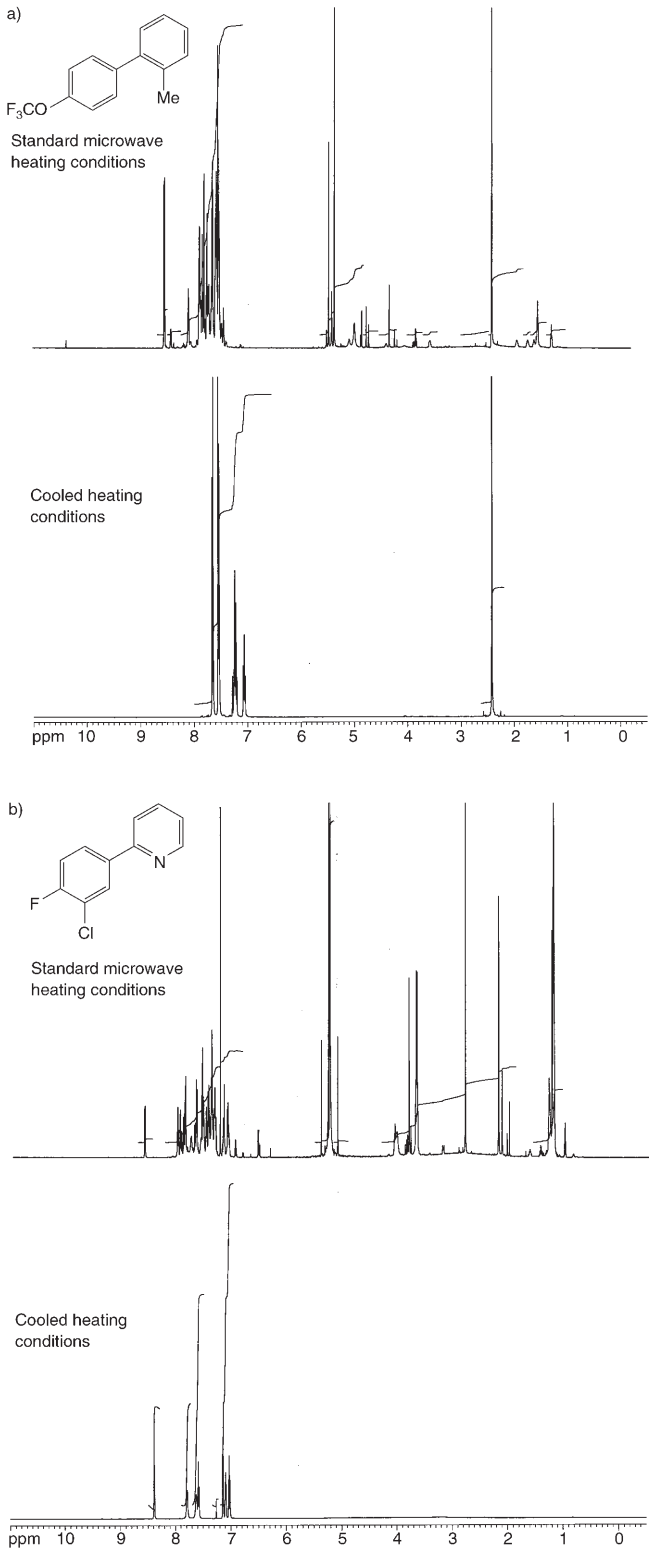
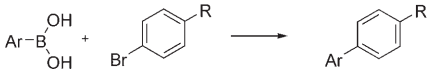


Figure 4. ^1H NMR spectra comparison of the effect of external cooling on the crude product purity.

(>90%) and no further purification was required as can be seen from the NMR spectra (Figure 4) and as confirmed by HPLC.[13] When the same reactions were performed at 76°C without the application of external cooling for the same 15 mins, the reactions were incomplete and a mixture of by-products was also generated.

Taking three particularly problematic substrates, namely, 4-bromobenzylic alcohol, 4-bromoacetanilide and 4-bromobiphenyl, which had all shown a high propensity for generating multiple by-products, we further investigated this cooled heating protocol with a wider selection of boronic acid coupling partners (Table 3). Again, the purity of the products was significantly enhanced and the overall isolated yields were excellent, all greater than 80% and most in excess of 90%.

Table 3. Coupling of problematic substrates under modified conditions. (0.5 mmol halide, 0.5 mmol boronic acid, 1.0 mmol Bu_4NOAc, 5 mmol% Pd EnCat, EtOH, microwave irradiation. NR = No reaction)

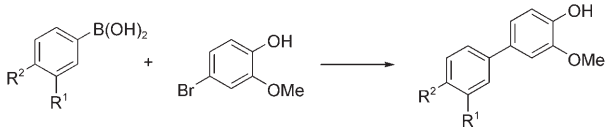


Entry	R	Ar	Purity [%][a] (normal heating)[b]	Purity [%][a] (cooled heating)[c]
1	CH_2OH	Ph	46	>98
2	CH_2OH	3,4,5-MeOPh	<10	90
3	CH_2OH	4-(F_3CO)Ph	32	88
4	CH_2OH	3-NO_2Ph	31	96
5	CH_2OH	2-benzofuran	41	97
6	CH_2OH	3-quinolene	<10	81
7	CH_2OH	2-thiophene	NR	NR
8	NHAc	Ph	>98	>98
9	NHAc	3,4,5-MeOPh	27	90
10	NHAc	4-(F_3CO)Ph	50	88
11	NHAc	3-NO_2Ph	32	96
12	NHAc	2-benzofuran	<10	97
13	NHAc	3-quinolene	<10	81
14	NHAc	2-thiophene	NR	NR
15	Ph	Ph	>98	>98
16	Ph	3,4,5-MeOPh	<10[d]	89
17	Ph	4-(F_3CO)Ph	NR	89
18	Ph	3-NO_2Ph	<10	93
19	Ph	2-benzofuran	<10	86
20	Ph	3-quinolene	<10	74
21	Ph	2-thiophene	NR	NR

[a] Purity measured by LC-MS and ^1H NMR spectroscopy. [b] Heating to 120°C for 10 min. [c] Heating at 50 W with compressed air cooling for 15 min. [d] The remaining material was unreacted starting material.

The use of the simultaneous cooling allows additional microwave energy to be input to a reaction mixture whilst maintaining a moderate temperature. Hence, reactions that were incomplete following 10 mins heating under the standard reaction conditions could be heated with higher energy, but cooled to maintain an acceptable temperature. Thus the reaction could be accelerated without having a deleterious effect on product purity or yield. For example, the reactions of 4-bromo-2-methoxyphenol with phenylboronic acid and 4-fluoro-3-chlorophenylboronic acid under the standard conditions developed for the library preparation were incomplete (Table 4). Heating the reactions for extended periods or to higher temperatures (≥140°C) generated impure product mixtures. However, the same reactions could be driven to completion in just 10 min by heating at a comparably higher power of 60 W using the simultaneous cooling. Although the reaction proceeded at a faster rate, the recorded temperature of the solution was actually lower—a maximum temperature of just 83°C was reached.

Table 4. Coupling of 4-bromo-2-methoxyphenol. (0.5 mmol halide, 0.5 mmol boronic acid, 1.0 mmol Bu_4NOAc, 5 mmol% Pd EnCat, EtOH, microwave irradiation. Conversion based on transformation of the boronic acid measured by ^1H NMR spectroscopy and LC-MS.)



R^1	R^2	Conversion [%][a]	Conversion [%][b]
H	H	23	>98
Cl	F	5	>98

[a] After 10 min reaction time at 120°C. [b] After 10 min reaction time at 60 W power setting with cooling.

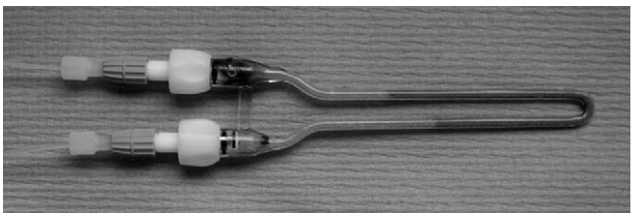


Figure 5. Flow reactor microwave insert.

Flow-based Suzuki reactions: To fully exploit the potential of the heterogeneous EnCat catalyst and to investigate the process intensification of its multisequential and scaled applications, we performed the same Suzuki reactions in a flow-type process. The reactor design is based upon a simple continuous glass U-tube that may be packed with the heterogeneous catalyst and inserted into the microwave cavity (Figure 5). Capillary-based flow systems have been previously reported for Suzuki coupling reactions under microwave heating conditions although only for microscale applications.[11]

Stock solutions of the boronic acid, aryl halide and tetrabutylammonium acetate base were prepared at concentrations of 0.07 M (0.14 M in terms of the base) and constantly fed through to the flow reactor which was heated in the microwave cavity (Figure 6). A flow rate of 0.1 mL min^{-1} was

employed corresponding to a total residence time of 225 s, although the solution was present in the microwave cavity only for 65 s of this time. As the reaction mixture left the reactor chamber, it progressed through a column of Amberlyst 15 sulfonic acid resin to remove any residual base and boronic acid salts. A back pressure regulator (40 bar) was also used in-line to maintain a constant flow profile. The solution could then be collected allowing direct evaporation and isolation of the product without the need for further purification. If additional product quality was required, then passage through a metal-scavenging material such as Quadrapure™ was especially effective.

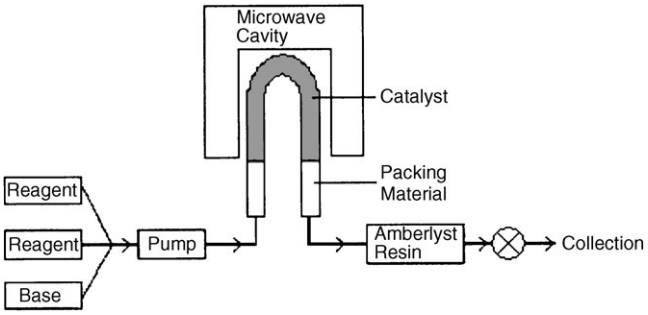
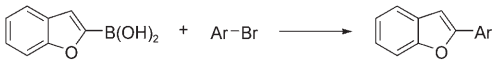
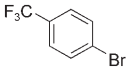
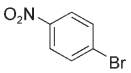
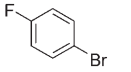
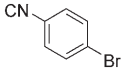
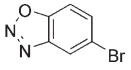


Figure 6. The flow reactor.

Initial investigations focused on reactions that had proved successful in batch mode (Table 5). In these reactions the reactor was heated at a constant power level of 50 W. However, prolonged continuous use of the reactor showed that constant heating at this power setting was detrimental; the palladium catalyst became exceptionally hot, causing the polymer matrix to collapse, melt and eventually block the tube. Therefore a modified heating protocol was established in which the microwave irradiation was pulsed. The application of microwave irradiation being cycled through a heating phase at 50 W for 30 s, followed by 18 s of cooling with no power application. All reactions were performed over a 40 min time period, equating to a 0.28 mmol scale. As before, all products were analysed by LC-MS and ^{1}H NMR spectroscopy. The yields and purities of the reaction products were comparable if not slightly improved relative to those achieved in the corresponding batch reactions.

Table 5. Flow-based microwave Suzuki reaction. (0.28 mmol halide, 0.28 mmol boronic acid, 0.56 mmol Bu_4NOAc in EtOH. Pd EnCat, EtOH, microwave irradiation.)



Entry	Bromide	Batch yield [%][a,c]	Flow yield [%][a,b,c]
1		92	87
2		89	92
3		78	91
4		89	90
5		72	81

[a] Isolated yield. [b] Flow rate 0.1 mL min^{-1}. [c] All purities were >98% as measured by LC-MS and ^{1}H NMR spctroscopy.

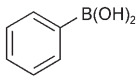
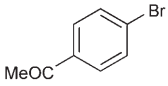
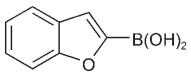
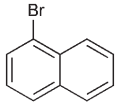
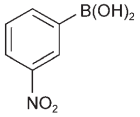
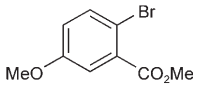
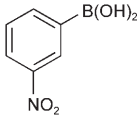
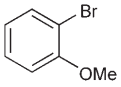
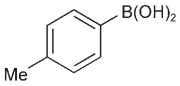
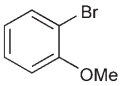
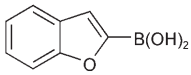
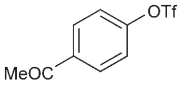
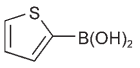
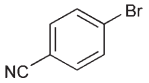
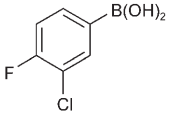
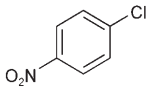
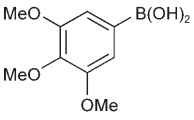
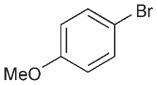
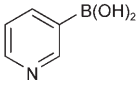
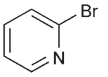
Additional studies were carried out investigating the performance of those coupling partners that had shown incomplete conversion under the conditions used in the batch reactions. Ten representative pairs of substrates were selected to cover a range of reactivities (Table 6). To ensure complete reaction, the concentrations of the substrates were reduced to 0.01 M (with respect to the halide and the boronic acid), although the flow rate was maintained at 0.1 mL min^{-1}. This resulted in an increased effective catalyst loading, enhancing conversion without affecting the specified substrate residence time.

All of the flow reactions attempted were successful, resulting in dramatic increases in both isolated yield and product purity. Even the synthesis of the bipyridyl compound (Entry 10; Table 6), which had been unsuccessful in batch, was achieved with a good yield of 82% under the flow conditions. Of particular note is that the complete set of reactions (Entries 1–10; Table 6) were performed in a sequential automated fashion using the same flow reactor without regeneration or replacement of the catalyst. Hence, a stream of the substrates were passed through the reactor for 40 min, followed by an equal volume of ethanol, before the next set of substrates were added. Such a processing procedure is clearly amenable to high-throughput automated synthesis of compound libraries. Especially considering that throughout the duration of these reactions no noticeable deterioration in the catalyst activity or any cross contamination of the reactions was observed. In addition, the products of the flow process were generally of a higher purity than those generated through the corresponding batch reactions. This is probably due to the fast reaction times; the substrates are only heated for approximately one minute, although during that period the effective catalyst concentration is extremely high. Thus the desired cross coupling is able to take place, but the short time frame does not allow for much decomposition or for many side reactions to occur.

As a consequence of our previous work involving the cooled heating methodology, we decided to re-evaluate this approach in an attempt to further enhance the flow-mode reactions. The utilisation of cooled heating had already been used to inhibit the formation of by-products in these coupling reactions, but performing the reaction in flow improved the reactions still further (Table 7). All products were obtained with very high levels of purity and could be isolated without the need for any additional purification following the inline acid scavenging process.

Additional advantages in terms of substrate selectivity could be derived from the extremely short reaction times

Table 6. Sequential processing of multiple substrates in flow. (1 equiv halide, 1 equiv boronic acid, 2 equiv Bu_4NOAc in EtOH. Pd EnCat, EtOH, microwave irradiation.)

Entry	Boronic acid	Halide	Batch[a] yield [%][c] (purity [%][d])	Flow[b] yield [%][c] (purity [%][d])
1			88 (>98)	90 (>98)
2			84 (82)	87 (>98)
3			94 (64)	94 (>98)
4			94 (54)	92 (92)
5			77 (40)	88 (94)
6			100 (30)	97 (91)
7			72 (26)	76 (>98)
8			82 (23)	89 (>98)
9			92 (16)	94 (91)
10			81 (<10)	95 (82)

[a] 120 °C, 10 min. [b] Flow rate 0.1 mL min^{-1}, 50 W with external cooling. [c] Isolated yield. [d] Purity measured by LC-MS and ^{1}H NMR spectroscopy.

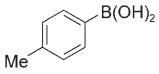
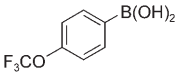
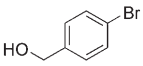
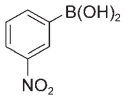
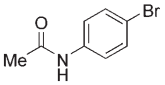
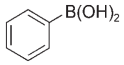
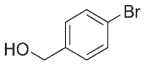
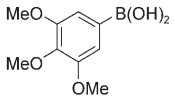
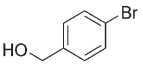
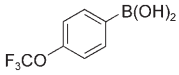
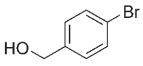
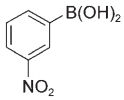
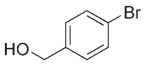
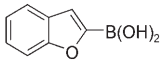
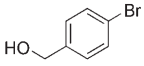
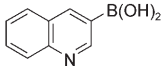
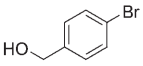
and mild reaction conditions. The reactive 2-iodobromobenzene was used as a substrate because in the corresponding batch reaction between this iodide and 2-benzofuran boronic acid, only the double addition product was detected (Scheme 4). However, when the same coupling was performed in flow, the boronic acid reacted only at the iodide, generating the single addition product. Hence, the flow reaction works in a complementary fashion to the batch process, giving enhanced levels of functional selectivity and acceptability.

Finally, to investigate the ultimate catalytic capacity of the loaded flow reactor, two separate coupling reactions were undertaken on a larger scale (Scheme 5). Solutions were prepared at 0.2 M concentration and fed into the reactor at a flow rate 0.2 mL min^{-1}. The reactor was heated at 50 W with simultaneous compressed air cooling and the outflow analysed for product conversion and purity. The reactions were seen to progress efficiently for many hours, before finally conversion dropped dramatically, allowing the biaryl products to be generated on a multigram scale. This corresponds to a relative catalyst loading of just 0.2 mol%, which is exceptionally low for this type of catalyst. The amount of product obtained in a single operation was an 80-fold increase on that produced in a single batch reaction.

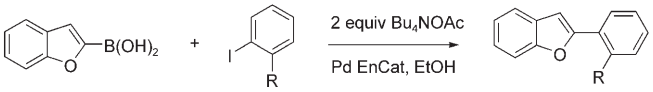
Conclusion

Microencapsulated palladium (Pd EnCat) used in conjunction with tetrabutylammonium acetate in ethanol is an excellent catalyst for the Suzuki reaction between aryl halides/triflates and boronic acids. The catalyst system is highly efficient when used in conjunction with microwave heating, showing enhanced reactivity and a prolonged lifetime. A small library of biaryl compounds has been generated in a relatively short space of time by using this approach. Furthermore, the yields and product purities may be dramatically improved if simultaneous cooling is employed as microwave energy is supplied to the reaction system. In such a way a controlled temperature profile can be maintained against a constant microwave power input. Alternatively, a pulsing or power cycling regime can be established permitting periods of higher power levels to be utilised for short durations of time, whilst limiting the eventual overall system temperature. Such heating processes and encapsulated catalysts lend themselves well to flow synthesis applications. A number of Suzuki cross-coupling reactions have been prepared in this way demonstrating a dramatic decrease in side reactions and thermal decomposition of products and catalyst. Consequently a single flow reactor may be used to generate multiple products in a sequential fashion or several grams of clean product when used in continuous operation without having to regenerate or replace the catalyst. The reactions described are highly reproducible from run to run. The equipment described is easily assembled and extremely reliable and, in principle, is readily adapted to be able to con-

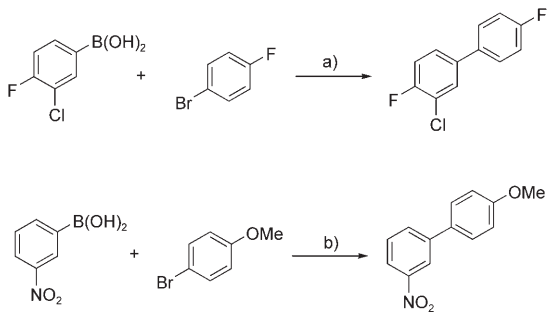
Table 7. Comparison of batch, cooled heating in batch and flow processing. (1 equiv halide, 1. equiv boronic acid, 2 equiv Bu_4NOAc in EtOH. Pd EnCat, microwave irradiation.)

Entry	Boronic acid	Halide	Purity % [a]		
			Batch[b]	Batch with cooling[c]	Flow[d]
1			42	86	>98
2			48	>98	>98
3			32	96	>98
4			46	>98	>98
5			<10	88	>98
6			32	86	92
7			31	94	>98
8			41	97	>98
9			<10	81	91

[a] Purity measured by LCMS and ^{1}H NMR spectroscopy. [b] 120 °C, 10 min. [c] 50 W with cooling, 20 min. [d] Flow rate 0.1 mL min^{-1}, 50 W, power setting with simultaneous cooling.



Scheme 4. Reaction of 2-benzofuranboronic acid with 2-iodobromobenzene. Batch conditions: 120 °C, 10 min, R = 2-benzofuran. Flow conditions: 50 W with cooling, 0.07 M, 0.1 mL min^{-1}, R = Br.



Scheme 5. Continuous production of biaryl compounds. (1 equiv halide, 1 equiv boronic acid, 2 equiv Bu_4NOAc, 0.2 M in EtOH. Pd EnCat, microwave irradiation. Flow rate 0.2 mL min^{-1}.) a) 172 mg catalyst, 28 h reaction, 7.53 g (33.6 mmol) product, 0.2 mol% catalyst. b) 182 mg catalyst, 34 h reaction, 9.34 g (40.8 mmol) product, 0.2 mol% catalyst.

duct multipath-flow microwave processes in single reaction cavities. The future results on these concepts will be reported at a later date.

Experimental Section

General: All reagents and solvents were used as supplied. ^{1}H NMR spectra were recorded on a Bruker DPX-400 or DRX-600 spectrometer with residual chloroform as the internal reference ($\delta = 7.26$ ppm). ^{13}C NMR spectra were recorded on a Bruker Avance 500 spectrometer with the central peak of chloroform as the internal reference ($\delta = 77.0$ ppm). LC-MS analysis was performed on a Hewlett–Packard HPLC 1100 chromatograph (Mercury hexylphenyl column) attached to a HP LC/MSD Platform LC APCI mass spectrometer. Microwave experiments were performed on an Emrys synthesiser available from Biotage AB (Uppsala, Sweden).

General procedure for the microwave-assisted Suzuki coupling in batch: The aryl halide (0.5 mmol) and boronic acid (0.5 mmol) were dissolved in ethanol (6 mL, 95%) in a microwave vial. Tetrabutylammonium acetate (1 mmol) was added in ethanol (1 mL) followed by Pd EnCat-30™ (63 mg, 5 mol%). The reaction was irradiated in a microwave apparatus at 120 °C for 10 min.[14] After cooling to ambient temperature in the microwave cavity the reaction mixture was purified on an SCXII cartridge using DCM (10 mL) as eluent and evaporated to dryness.

General procedure for the microwave-assisted Suzuki coupling in batch with compressed air cooling: The aryl halide (0.5 mmol) and boronic acid (0.5 mmol) were dissolved in ethanol (95%, 6 mL) in a microwave vial. Tetrabutylammonium acetate (1 mmol) was added in ethanol (1 mL) followed by Pd EnCat-30™ (63 mg, 5 mol%).[4] The reaction was irradiated in a microwave apparatus at 50 W for 15 min with compressed air cooling (4 bar, 22 °C temperature).[13] After cooling to ambient temperature in the microwave cavity the reaction mixture was purified on an SCX II cartridge using DCM (10 mL) as eluent and evaporated to dryness.

General procedure for the microwave-assisted Suzuki coupling in flow: The flow reactor was packed with Pd EnCat-30™ (170–190 mg, 0.06–0.07 mmol) and sand used as an inert packing material at the outer (non-microwaved) regions of the flow reactor. Ethanol was pumped through the cell at a flow rate of 0.1 mL min^{-1} for 10 min to purge the system by means of a Gilson 402 syringe pump. Stock solutions of the aryl halide (0.5 mmol), boronic acid (0.5 mmol) and tetrabutylammonium acetate (1.0 mmol) in ethanol (0.01, 0.07 or 0.2 M) were fed into the reactor at a flow rate of 0.1 mL min^{-1} for the required time (pumping controlled by Gilson 402 syringe pumps). During this period the flow reactor was irradiated in a microwave apparatus at 50 W with compressed air cooling (4 bar, 22 °C temperature).[13] The product was diverted through a scavenging column containing Amberlyst 15 resin (4 g) before collection and evaporated to dryness. Following the reaction ethanol was pumped into the reactor at a rate of 0.1 mL min^{-1} in order to flush the system before passing in the next components.

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