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Graphical Abstract





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ABSTRACT



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Green and scalable procedure for extremely fast ligandless Suzuki-Miyaura cross-coupling reactions in aqueous IPA using solidsupported Pd in continuous flow

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Undoubtedly, for the pharmaceutical and fine chemical industry, the Suzuki-Miyaura cross-coupling reaction¹ represents probably the most widely used carbon-carbon bond forming process, with application mainly in the construction of (hetero)biaryls that are common scaffolds in natural products and bioactive compounds.² Such reactions are usually catalyzed by Pd(II) /Pd(0) complexes in the presence of phosphines or other ligands. However, these additives are expensive and often require difficult purification steps to remove ligand and Pd from the desired product. Moreover, in many cases, ligands are air and moisture sensitive, which makes reaction setup too complex for straightforward scale-up and makes ligand-free palladium applications the alternative of choice from a green chemistry perspective.³

Among the supported catalytic systems available,⁴ palladium on carbon (Pd/C) is probably the most frequently used agent for industrial processes due to its low price, high catalytic activity and easy removal after completion of the reaction. Moreover, the possible use of aqueous media in combination with this catalyst, with concomitant reduction in use of organic solvents, makes this approach highly desirable in terms of environmental protection.⁵ Some recent studies suggest, however, that the active species in the cross-coupling process is homogeneous, resulting from a leaching process from the support matrix, and is, after the reductive elimination, adsorbed again, giving rise to low free Pd levels in the crude reaction mixtures.⁶ Palladium on charcoal is a highly pyrophoric material and when used in batch on large scale the filtration operations are especially hazardous, where ignition can occur if not cautiously performed. Because of this, operations are typically carried out under inert atmospheres, thus adding further complexity.⁷

To overcome many of these issues, we envisioned a continuous flow procedure using a packed bed reactor with a ligand-free Palladium source for the Suzuki-Miyaura cross-coupling reaction of arylorganoboron species and aryl halides.⁸ It is well known that flow chemistry offers advantages over batch processes in two main areas, improvement of mass transfer and heat transfer, and that such features can make scale-up campaigns both higher yielding and more reproducible, having a desired impact on sustainability.⁹ In this case, the combined use of a packed bed reactor, reported to increase interfacial contact between organic and aqueous layers¹⁰ and the use of high temperatures to create a new processing window¹¹ both enhance the efficiency of the process, dramatically reducing the reaction time to seconds.

Our flow chemistry setup consisted of a ThalesNano H-Cube MIDI @, a commercial packed bed flow hydrogenator, in our case used only to work at high pressures and temperatures, without H₂ generation. The reactants were injected using integrated HPLC-type pump, and flowed into a MIDI Cart catalyst packed bed reactor at the desired temperature, controlled accurately by the system.¹² (Figures 1 and 2). We used that system for convenience but any setup consisting in a pump, the cartridge (commercially available) a way to heat the cartridge (e.g. oven, oil bath etc) and back pressure regulator could be used as well.





Continuous-Flow setup for Suzuki cross-coupling





H-Cube Midi modified setup for cross-coupling reactions.

As the starting point for our continuous flow investigation we used 3-bromophenol (1 equiv) or 3-iodophenol (1 equiv) and phenylboronic acid (1 equiv) as model reagents for the Suzuki-Miyaura cross-coupling, a 10% Pd/C packed-bed cartridge as the flow reactor,¹³ and screened several bases described for the transformation (Na₃PO₄, K₃PO₄, Li₂CO₃, Na₂CO₃, K₂CO₃; 3 equiv) in aqueous media. As our initial aim was to have the greenest possible protocol, we used water as solvent in the first place,⁵ nevertheless, upon mixing these reagents, a slurry was formed, precluding a continuous flow process. In order to have a clear solution we added small portions of methanol while applying ultrasonic irradiation until a complete solution was formed, choosing finally K₂CO₃ (due to solubility and cost efficiency) in a 3:2 mixture of H₂O/MeOH as the best option. With this result in hand, we determined that the maximum viable concentration to maintain solubility was 0.15M for the aryl halide, so we used this value from in all subsequent experiments. Subsequently, we performed the reaction by pumping the reactant mixture through the cartridge at the minimum flow rate available (3 ml/min),¹⁴ heated at different T controlled by the H-Cube MIDI system with no H₂ gas generation. The results of this optimization showed that conversion to the desired product increased with T, reaching a plateau at around 140°C-150°C with the iodide derivative much more reactive, having a conversion

of 88% to the desired heteroaryl coupling product (Error! Reference source not found.). The pinacol boronic ester derivative was also tested, producing this time a slightly lower conversion of 62% to the desired product. Finally, the influence of the alcohol solvent was studied, whereupon isopropanol was identified as the most efficient in terms of desired product generation.



Table 1

Optimization of the reaction conditions for the Pd/C catalyzed Suzuki cross-coupling in flow

	Entry	X	R	T (C)	Solvent	Conversion ^a	
	1	Br	ОН	80°C	МеОН	0% ^b	
	2	Br	ОН	110°C	MeOH	3% ^b	
	3	Ι	ОН	80 °C	MeOH	50% ^c	
	4	Ι	ОН	100 °C	MeOH	55% °	
	5	Ι	ОН	120 °C	MeOH	60%°	
	6	Ι	ОН	140°C	MeOH	70% [°]	
G	7	Ι	ОН	150°C	MeOH	73% ^c	
6	8	Ι	ОН	150°C	EtOH	80%°	
	9	Ι	ОН	150°C	iPrOH	88% ^c	
	10	Ι	-pinacol-	150°C	iPrOH	70% °	

^aHPLC peak integration.

^bMixtures of SM, aryl halide homocoupling and dehalogenated species were formed.

^cNon-product HPLC peaks corresponded to unreacted SM and aryl halide homo-coupling.

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With this set of variables optimized, we turned our attention to the influence of the residence time in the conversion values observed. Thus, we designed a new equipment setup with control over smaller flow rates so residence times could be increased.¹⁵ The results showed that residence time had little influence over the Suzuki cross-coupling reactivity, using the same reaction partners and catalyst, with similar values across the range. (Figure 3).





Figure 3 Influence of flow rate over conversion.

A further important parameter that was investigated was the palladium support.¹² As shown in figure 4, the use of Pd/C 10% or Pd over alumina 5% provided highest conversion, being largely comparable. When using Pd/C Powder type¹⁶ or Pd black, conversion figures were more modest. For the case of Pd on silica, inconsistent results were obtained, along with some overpressure issues and so this support was disregarded. Interestingly, when a Pd black cartridge was employed the impurity profile of the crude samples changed dramatically, showing only unreacted SM and product with no detected aryl halide homocoupling byproducts.



Figure 4

Influence of the palladium support upon conversion for the reaction between 3-iodophenol and phenylboronic acid.

With these optimization results in hand, we designed a more extensive study of the scope of this transformation based on the electronic nature of both aryl halide and boronic acid (Table 2). Thus, various *ortho-*, *metha-* and *para-* substituted aryl iodides and bromides were cross-coupled with boronic acids. As demonstrated previously, bromide derivatives proved less efficient than the corresponding iodide derivatives (compare entries 5 and 6, and entries 10 and 12). Interestingly, the reactivity of simple iodobenzene (entry 1) was moderate compared with more substituted aromatics, regardless of electronic factors. Notably, the transformation was successful with electron-donating (entries 2, 3, 4) and electron-withdrawing substituents (entries 5-15) as well as heteroaromatic substitution (entry 16). With regard to the boronic acid, the methoxyphenyl derivative gave excellent results compared with phenyl boronic acid (entries 2-3, 7-9 and 10-14) whereas (E)-styryl boronic acid provided only moderate conversion to the desired cross-coupling product (entry 13).

The reusability of the supported catalyst¹⁷ is a very important factor for the reproducibility of scale-up preparations under a continuous flow regime, and is also desirable for economic and environmental reasons.¹⁸ With the aim of assessing the stability of the supported catalyst over time and also to verify the data obtained by HPLC peak integration, we performed several experiments at multigram scale, isolating the final compounds. To our delight, we found that catalyst activity was not diminished over time¹⁹ and we were able to scale-up some examples up to 10 g (entries 7-8) and 100 g (entries 10-11), obtaining excellent yields after isolation.²⁰

The residual palladium content was also investigated for some selected examples, to evaluate the extent of metal leaching from the solid support. The results showed Pd levels in the crude reaction solutions to be in the low double-digit ppm range using either Pd/C or Pd/Al₂O₃ (entries 7-8 and 10-11). Interestingly, the experiments run at larger scale (entries 7-8, and 10-11) gave a similar outcome, showing the robustness and reliability of the procedure.

Entry	Aryl Halide	Boronic acid	Product (scale) ^a	Cartridge	Purity ^b (%)	Pd content (ppm) ^c
1		но в об		Pd/C 10%	51	_e _
2	ОН	PhB(OH)2	HO	Pd/C 10%	70	_e
3	ОН	но но		Pd/C 10%	68	_e
4	ОН	PhB(OH)2	OH (1 g)	Pd/C 10%	88	40

Table 2 Suzuki cross-coupling reactions with supported Pd catalysis under continuous flow conditions





^aProduct obtained using a 0.15M solution of aryl halide and boronic acid, 150°C, 3 mL/min, 0.5 g scale unless otherwise noted. ^bHPLC peak integration at 214 nm.

^cPd content values obtained by Inductively Coupled Plasma Mass Spectrocopy (ICP-MS).

^dIsolated yield.

^eNot determined

In conclusion, we have developed an easy and scalable procedure for the Suzuki-Miyaura cross-coupling reaction of aryl halides and arylboronic acids using supported Pd catalysis in continuous flow. The packed-bed reactors used are commercially available and, with the reaction conditions described herein, provided great stability over time and reproducible results. The methodology was demonstrated to be viable for large-scale preparations of organic compounds presenting low levels of residual Pd in the crude reaction products. Moreover, the use of benign isopropanol/water solution mixtures, very short residence times and reduced catalyst amounts without the need of expensive ligands offers a sustainable, safe and cost-effective synthetic approach to the synthesis of biaryls. Additionally, the simple nature of the flow chemistry method potentially allows for multistep automation. Work is being undertaken in our laboratories in this regard and will be reported in due course.

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References and notes

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¹² ThalesNano Nanotechnology Inc., Graphisoft Park, H-1031 Budapest, Zahony u.7., Hungary. <u>http://www.ThalesNano.com</u>. Palladium packed bed cartridges are available on various supports: none (Pd black), charcoal (standard and powder type), alumina and silica.

¹³ The void volume for an H-Cube MIDI cartridge is around 1-1.2 mL (measured experimentally).

¹⁴ Estimated residence time is 20 seconds based on calculated cartridge void volume.

¹⁵ The equipment setup consisted of a new external syringe pump that injected the reactant solution into the cartridge, placed in the H-Cube MIDI for temperature control. The output of the cartridge was connected to a 100 psi back pressure regulator (to prevent gas bubble formation and ensure accurate residence times).

¹⁶ The difference between the powder type and the 10% Pd/C are in the particle size; the powder type is sieved to be higher than 32 micron, and so has a larger active surface area compared to the 10% Pd/C, which is of 20-40 mesh.

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¹⁹ The same catalyst cartridge was under continuous operation for 18 h.

²⁰ **Representative large-scale continuous-flow procedure**: A solution of 2-iodo-benzonitrile (100 g, 1,00 equiv; 436,64 mmoles) and phenylboronic acid (1 equiv, 436,64 mmoles; 53,24 g) in 2-propanol (1800 mL) was combined with a solution of

potassium carbonate (3 equiv, 1,31 moles; 181,04 g in water (1200 mL). The resulting mixture was sonicated until a clear biphasic solution was obtained. The solution was added to a round bottomed flask and was pumped, while stirring, through a Pd/C 10% H-Cube midi cartridge at 150°C at a rate of 3 ml/min (approx. 20 seconds residence time) and without H₂ generation, using an H-Cube MIDI apparatus. After all the solution had passed through the cartridge, it was washed with 2-propanol/water (3:2 ratio. 200 mL) and the product solution was combined with the wash run. 2-Propanol was removed on the rotavap and the aqueous residue was extracted with ethyl acetate (2x100 ml). The combined organic phases were washed with brine (50 mL), dried over sodium sulfate and concentrated to afford a crude product (tan solid) that was purified via SiO₂ pad filtration (MTBE/hexane mixtures as eluent) to afford 2-phenylbenzonitrile (76.5 g, 98% yield). ¹H-NMR data was consistent with reported values.

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Highlights

- Large-Scale Suzuki-Miyaura cross-coupling in continuous flow.
- Simple and sustainable flow chemistry procedure.

Acceleration