



Greening heterogeneous catalysis for fine chemicals

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ABSTRACT

Simple flow chemistry technology coupled to newly developed solid organosilica catalysts can be successfully applied to enhance the efficiency and selectivity of two representative homogeneous syntheses widely employed by chemical companies. The method is general and can be extended to many other reactions using similar solid catalysts to afford reactions that are faster and cleaner than conventional homogeneous and heterogeneous conversions.

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Flow chemistry in micro reactors is now a well established technique in the pharmaceutical industry due to numerous advantages including higher selectivity and yields due to efficient mixing, inherent safety in handling hazardous reagents and excellent heat transfer.¹ A number of successful applications of flow chemistry in industry on a variety of scales have been reported.²

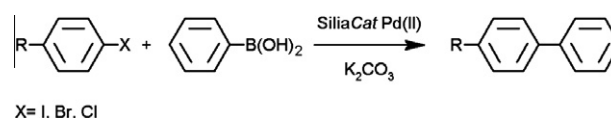
The process can be accomplished on scales from milligrams, to grams, to kilograms, all on the same instrument. The same compound can then be produced on a commercial scale by transferring the flow chemistry process with minor modifications to a continuous manufacturing plant. Traditional batch reactions may need some adaptation in order to work in flow, but the results are often worth the time spent as flow chemistry brings extra advantages to existing transformations. For example, a multiple-step, multiple-day, difficult batch synthesis can be performed in one flow process in a matter of minutes.³

Today, the examples of commercial syntheses run on large scale with remarkable process intensification that include asymmetric hydrogenation⁴ and many syntheses of active pharmaceutical ingredients.⁵ In each case, as put it by Jamison,^{1b} the development of new solid-supported catalysts for multiple steps in flow systems

is integral to the future of synthesis under flow conditions. Leach-proof solid catalysts of large surface area are highly desirable in flow chemistry because work-up is eliminated while the small volume of reactants flowing in the small reactor (from μL to mL) leads to enhanced catalyst/reagent ratios and thus to conversion rates higher than in batch. However, traditional resins-supported catalysts are often not suitable for flow chemistry applications, due to poor chemical and mechanical stability.⁶

Using selected SiliaCat silica-based catalysts⁷ we show here how flow chemistry can be successfully used to enhance heterogeneous catalytic reactions typically employed in the synthesis of fine chemicals, namely C–C coupling and selective alcohol oxidation.

We first attempted the Suzuki–Miyaura coupling reaction (Scheme 1) using different aryl halide substrates under flow in a modular flow reaction microreactor (ASIA, Fig. 1) that allows a fast and reproducible mixing⁸ using SiliaCat DPP–Pd and SiliaCat S–Pd (Fig. 2). The latter catalysts are recyclable C–C coupling heterogeneous catalysts made, respectively, from a leach-resistant



Scheme 1. Heterogeneous Suzuki–Miyaura coupling of haloarenes over SiliaCat Pd(II) entrapped catalysts.

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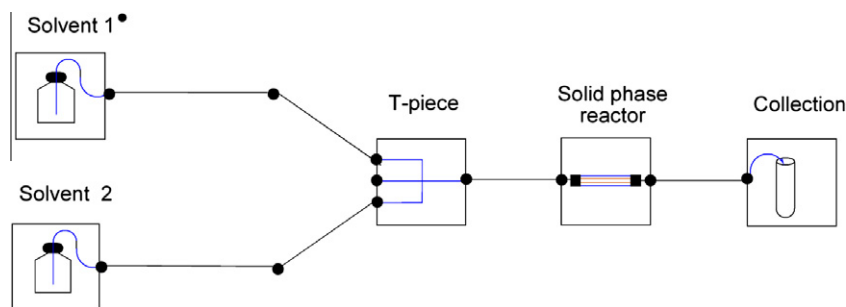


Figure 1. Fluidic set-up for the heterogeneous Suzuki–Miyaura coupling of different substrates in flow over SiliaCat DPP-Pd and SiliaCat S-Pd.

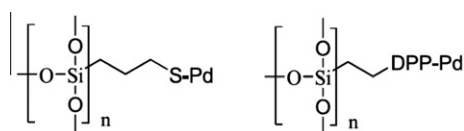


Figure 2. Chemical structures of SiliaCat S-Pd (left) and SiliaCat DPP-Pd (right). These sol–gel catalysts typically have 0.2–0.6 mmol/g loading and a large (300–650 m²/g) surface area.

organoceramic matrix bearing diphenylphosphine and thiol based ligands bound to palladium(II).⁹

A first attempt with 4-iodonitrobenzene as the substrate yielded disappointing results, with no conversion at room temperature and only 50% conversion (albeit with 100% selectivity) at 70 °C. The mixing efficiency was then increased by pre-mixing both reagent solutions. The resulting solution was processed using the both pump (but a single pump could also be used) channels

Table 1
Suzuki coupling reactions of different aryl halides over SiliaCat Pd(II) catalyst under flow conditions

#	Substrate	Solvent	T (°C)	SiliaCat DPP-Pd				SiliaCat S-Pd			
				Flow (μL/min)	Volume reactor (mL)	Residence time ^e (min)	Conv/select ^d (%)	Flow (μL/min)	Volume reactor (mL)	Residence time ^e (min)	Conv/select ^d (%)
1 ^a		MeOH/H ₂ O	20	250	0.7	1	100/100	250	2.4	3.4	100/100
2 ^b		MeOH/H ₂ O	70	500	0.7	0.5	100/100	250	2.4	3.4	100/100
3 ^b		MeOH/H ₂ O	70	250	0.7	1	74/91	250	2.4	3.4	65/65
4 ^c		EtOH/H ₂ O	80	50	0.7	5.2	78/91	50	2.4	17.2	29/23

^a Experimental conditions: 1 equiv 4-iodonitrobenzene, 1.1 equiv phenylboronic acid, 1.5 equiv K₂CO₃ in MeOH/H₂O (80:20) volume ratio), 0.02 M with respect to the substrate.

^b Experimental conditions: 1 equiv aryl bromide, 1.1 equiv phenylboronic acid, 1.5 equiv K₂CO₃ in MeOH/H₂O (80:20) volume ratio), 0.05 M with respect to the substrate.

^c Experimental conditions: 1 equiv aryl chloride, 1.1 equiv phenylboronic acid, 1.5 equiv K₂CO₃ in MeOH/H₂O (80:20) volume ratio), 0.05 M with respect to the substrate.

^d Experimental conditions: conversion/selectivity determined by GC–MS analysis.

^e Experimental conditions: the residence time was calculated in function of the catalyst density and the pore volume. The actual reactor volume needs to take the volume of SiliaCat into account: 0.7 and 2.4 mL are the volumes of empty columns. The real reactor volume will be lower.

Table 2
Suzuki coupling reactions of different aryl halides over SiliaCat Pd(II) catalyst under batch conditions

#	Substrate	Solvent	T (°C)	SiliaCat DPP-Pd			SiliaCat S-Pd		
				Catalyst (mol %)	Time (min)	Conv/select (%)	Catalyst (mol %)	Time (min)	Conv/select (%)
1 ^a		MeOH/H ₂ O	20	1	60	100/100	2	120	100/100
2 ^b		MeOH	65	0.1	15	100/100	0.1	15	100/100
3 ^b		MeOH	65	0.5	15	100/100	0.5	15	100/100
4 ^c		EtOH	77	1	120	98/96	2	360	0

^a Experimental conditions: 1 equiv 4-iodonitrobenzene, 1.1 equiv phenylboronic acid, 1.5 equiv K₂CO₃ in MeOH/H₂O (80:20) volume ratio), 0.02 M with respect to the substrate.

^b Experimental conditions: 1 equiv aryl bromide, 1.1 equiv phenylboronic acid, 1.5 equiv K₂CO₃ in MeOH 0.10 M with respect to the substrate.

^c Experimental conditions: 1 equiv aryl chloride, 1.1 equiv phenylboronic acid, 1.5 equiv K₂CO₃ in EtOH, 0.15 M with respect to the substrate.

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