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 hydrogenation[4] 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 Silia*Cat* silica-based catalysts[7] 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 mixing[8] using Silia*Cat* DPP-Pd and Silia*Cat* S-Pd (Fig. 2). The latter catalysts are recyclable C–C coupling heterogeneous catalysts made, respectively, from a leach-resistant
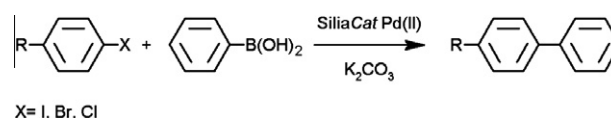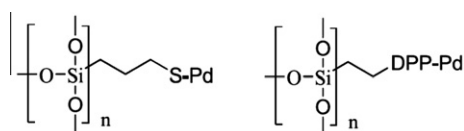
Scheme 1. Heterogeneous Suzuki–Miyaura coupling of haloarenes over Silia*Cat* Pd(II) entrapped catalysts.

X= I, Br, Cl
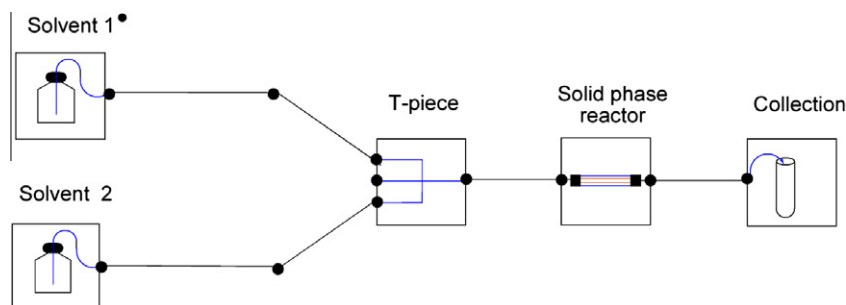
Figure 1. Fluidic set-up for the heterogenous Suzuki–Miyaura coupling of different substrates in flow over SiliaCat DPP-Pd and SiliaCat S-Pd.

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]	O_2N—⬡—I	MeOH/H₂O	20	250	0.7	1	100/100	250	2.4	3.4	100/100
2[b]	O_2N—⬡—Br	MeOH/H₂O	70	500	0.7	0.5	100/100	250	2.4	3.4	100/100
3[b]	MeO—⬡—Br	MeOH/H₂O	70	250	0.7	1	74/91	250	2.4	3.4	65/65
4[c]	MeO—⬡—Cl	EtOH/H₂O	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 K_2CO_3 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 K_2CO_3 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 K_2CO_3 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]	O_2N—⬡—I	MeOH/H₂O	20	1	60	100/100	2	120	100/100
2[b]	O_2N—⬡—Br	MeOH	65	0.1	15	100/100	0.1	15	100/100
3[b]	MeO—⬡—Br	MeOH	65	0.5	15	100/100	0.5	15	100/100
4[c]	MeO—⬡—Cl	EtOH	77	1	120	98/96	2	360	0

[a] Experimental conditions: 1 equiv 4-iodonitrobenzene, 1.1 equiv phenylboronic acid, 1.5 equiv K_2CO_3 in MeOH/H₂O (80:20) volume ration), 0.02 M with respect to the substrate.
[b] Experimental conditions: 1 equiv aryl bromide, 1.1 equiv phenylboronic acid, 1.5 equiv K_2CO_3 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 K_2CO_3 in EtOH, 0.15 M with respect to the substrate.
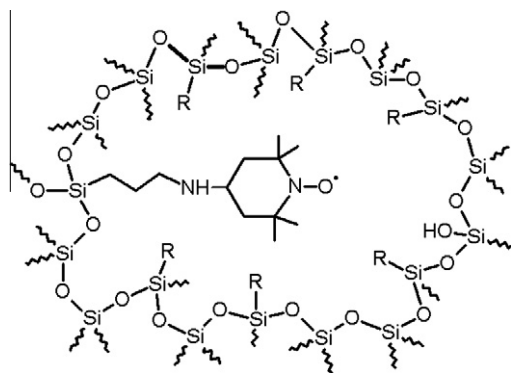
Figure 3. Chemical structure of SiliaCat TEMPO. This sol–gel catalyst typically has 0 8 mmol/g loading and a large (600 m^2/g) surface area.
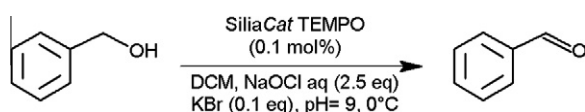
Scheme 2. Heterogeneous oxidation of benzyl alcohol over SiliaCat TEMPO under batch conditions.

directly through the solid phase reactor at room temperature via a T-piece, a tube reactor adaptor enabling up to three flows of reagents to be combined at the input of the reactor charged with the solid phase (Fig. 1). Now 100% conversion and 100% selectivity was achieved even at room temperature.

Under these optimised conditions, substrates displayed in Table 1 were rapidly converted into coupled products in good to excellent yields for iodo and bromoarenes, while showing the known low reactivity of chloroarene substrates.

Reacting the same substrates at the same reaction temperature under batch conditions (Table 2) shows that conversions were much slower. Eventually, after 15 min 4-Bromoanisole (entry 3 in 2) was entirely converted under batch conditions into the

corresponding coupled product, likely due to better solubility in MeOH solvent compared to the MeOH/H$_2$O mixture employed under flow conditions.

Overall, results in Table 1 show that Suzuki–Miyaura conversion can be effectively carried out in flow over SiliaCat palladium catalysts, especially well over SiliaCat DPP-Pd, rapidly affording good yields of coupled products, while avoiding the use of microwave irradiation. Microwave reactions indeed are often used for activation in Suzuki reactions. However they are severely limited in scale, so that a flow chemistry process allowing continuous Suzuki–Miyaura coupling is desirable.

We thus investigated the oxidation of benzyl alcohol in flow using metal-free catalyst SiliaCat TEMPO (Fig. 3). TEMPO is the 2,2,6,6-tetramethylpiperidine-1-oxyl nitroxyl radical widely employed as the selective oxidation catalyst under the mild conditions of the Anelli–Montanari reaction with bleach as the primary oxidant.[10] The batch reaction under optimised conditions using SiliaCat TEMPO (Scheme 2) yields benzaldehyde in 97% yield after 1 h.[11]

Again, an excellent mixing was crucial. When the reaction was carried out without the glass microchip, the conversion did not exceed 20%. We then increased the flow rate from 50 to 500 µL/min to reduce the residence time down to 0.3 min, leading again to full conversion to pure benzaldehyde. Under batch conditions, it took 1 h to achieve maximum 97% conversion (entry 3 in Table 3). Moreover, the reaction under flow (Fig. 4) can be performed at room temperature, and does not require the use of KBr, a known corroding agent, as the co-catalyst. For comparison, the same oxidative reaction over resin-immobilized TEMPO under flow still required cooling at 0 °C and the use of co-catalyst KBr for optimal yields and selectivity.[12]

In conclusion, we have shown how simple flow chemistry techniques coupled to newly developed solid organosilica catalysts can be successfully applied to enhance the efficiency and selectivity of two representative homogeneous syntheses in the liquid phase widely employed by chemical companies to manufacture highly valued fine chemicals, namely Suzuki coupling and TEMPO-mediated oxidation.[13] Conditions similar to those required by industry to access enhanced process yields (more concentrated solutions

Table 3
Applications in flow chemistry for benzyl alcohol oxidation over SiliaCat TEMPO

Entry	Catalyst (mol %)	T (°C)	Flow (µL/min)	Volume reactor (mL)	Residence time[a] (min)	Conv/select[b] (%)
1	SiliaCat TEMPO	20	50	0.7	3.2	100/100
2			100		1.6	
	SiliaCat TEMPO	20	250	0.7	0.6	100/100
			500		0.3	
3	SiliaCat TEMPO (0.1)	0	Batch		60	97/100

[a] The residence time was calculated in function of the catalyst density and the pore volume.
[b] Conversion/selectivity determined by GC–MS analysis.
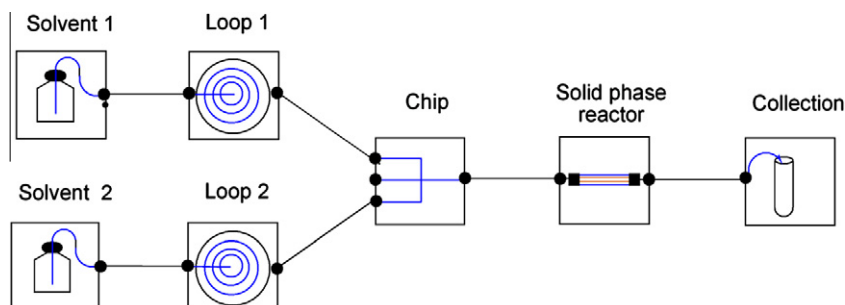
Figure 4. Fluidic set-up for the heterogenous oxidation of benzyl alcohol in flow over SiliaCat TEMPO.

at higher flow rates) can easily be accessed and will be reported in further reports. What is relevant here is that the method is general and can be extended to many other reactions using similar organosilica, stable catalysts to afford reactions that are faster and cleaner than conventional heterogeneous conversions.

Acknowledgements

References and notes

1. (a) Malet-Sanz, L.; Susanne, F. *J. Med. Chem.* **2012**, *55*, 4062–4098; (b) Webb, D.; Jamison, T. F. *Chem. Sci.* **2010**, *1*, 675–680.
2. For an updated review on many of the continuous processes used to intensify industrial processes, see: Anderson, N. G. *Org. Process Res. Dev.* **2012**, *16*, 852–869.
3. Herath, A.; Cosford, N. D. P. *Org. Lett.* **2010**, *12*, 5182–5185.
4. Johnson, M. D.; May, S. A.; Calvin, J. R.; Remacle, J.; Stout, J. R.; Diseroad, W. D.; Zaborenko, N.; Haeberle, B. D.; Sun, W.-M.; Miller, M. T.; Brennan, J. *Org. Process Res. Dev.* **2012**, *16*, 1017–1038.
5. For a thorough review on micro reactors and flow chemistry for industrial applications, see: Baraldi, P. T.; Hessel, V. *Green Process Synth.* **2012**, *1*, 149–167.
6. M. Benaglia (Ed.), In *Recoverable Organic Catalysts*, John Wiley & Sons, Ltd: Chichester, UK, 2009 (Chapter 11).
7. For detailed information on these catalysts, see at the URL: www.silicycle.com/applications/catalysis.
8. The Asia 220 flow chemistry system: a fully automated device combining smooth flow and a wide range of temperatures and pressures and flow rates. For detailed information, see at the URL: http://syrris.com/flow-products/asia-flow-chemistry.
9. Lemay, M.; Pandarus, V.; Simard, M.; Marion, O.; Tremblay, L.; Béland, F. *Top. Catal.* **2010**, *53*, 1059–1062.
10. Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559–2562.
11. Michaud, A.; Gingras, G.; Morin, M.; Béland, F.; Ciriminna, R.; Avnir, D.; Pagliaro, M. *Org. Process Res. Dev.* **2007**, *11*, 766–768.
12. Bogdan, A. R.; McQuade, D. T. *Beilstein J. Org. Chem.* **2009**, *5*, 17.
13. *Experimental details:* The SiliaCat DPP-Pd catalyst (0.36 g, 0.25 mmol/g Pd loading) was packed in a 0.7 mL solid phase reactor while the SiliaCat S-Pd[7] (1.24 g, 0.5 mmol/g Pd loading) was packed in a 2.4 mL solid phase reactor. Both were encased on a heater module to allow accurate temperature control. Reagent mixtures 'solvent 1' (0.020 M solution of benzyl halide in 20 vol % methanol/water) and 'solvent 2' (0.022/0.030 M solution of phenyl boronic acid/potassium carbonate in 20 vol % methanol/water) were pressurised at 1 bar and processed through the solid phase reactor at room temperature via a flow microreactor (Asia) that allows a fast and reproducible mixing, while varying residence times and temperatures for a better optimisation of the conversion. Conversion and selectivity were measured by GC–MS.
For the oxidation reaction, a 0,7 mL solid phase reactor was packed with 0.44 g SiliCat TEMPO[7] (0.82 mmol/g) connected to the microchip output and to a product collector. Two 5 mL PTFE loops were connected to a 250 μL glass microreactor (chip) in a fluidic pathway (Fig. 4). The reactant mixtures, a 0.2 M solution of benzyl alcohol in DCM (solvent 1) and a 0.5 M aq NaOCl buffered at pH 9 (solvent 2), were then premixed in the glass chip at room temperature prior to injection in the solid phase reactor. In detail, solvent 1 and 2 were pressurised to 1 bar and pumped at a flow rate ranging from 50 to 500 μL/min to achieve the desired residence time (from 3.2 to 0.3 min) in the solid phase reactor. At 50 μL/min flow rate (entry 1 in Table 3) pure benzaldehyde was the only product obtained with full conversion of the alcohol substrate.