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François Béland, Mario Pagliaro *et al.*
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Fine chemical syntheses under flow using SiliaCat catalysts

Rosaria Ciriminna,^a Valerica Pandarus,^b François Béland*^b and Mario Pagliaro*^a

After reviewing selected recent applications from diverse laboratories, we show how mesoporous organosilica-entrapped catalysts of the SiliaCat series have been successfully used for clean manufacturing of APIs in a number of different reactions carried out under laminar flow in microreactors. The advantages and disadvantages linked to these catalysts in terms of technical and economical sustainability are highlighted. Insight into the scale-up of this technique and related catalytic technologies from the lab scale to industrial production concludes the study.

Introduction

Roughly >70% of all organic reactions may be carried out under flow in microreactors with significant economic, environmental and technical advantages.¹ Yet, “the price for this is a demanding and laborious reinvention of chemistry beyond the green chemistry needs”.¹ Obviously, one would need to minimize such reinvention efforts. One way to do so in the synthesis of fine chemicals and active pharmaceutical ingredients (APIs), as we argue in this study, is to employ solid catalysts, including organosilica-entrapped sol-gel catalysts of the SiliaCat series.²

For example, a truly heterogeneous Pd catalyst active under flow enables cross-coupling reactions to be carried out in intensified processes,³ in which the small volume of reactants flowing under laminar conditions in the microreactor (from μL to mL) establishes a uniform reaction environment leading to enhanced catalyst/reagent ratios, and thus to conversion rates much higher than that in batch.⁴

A striking demonstration of the synthetic potential of heterogeneous catalysis under flow has been reported lately by Kobayashi and co-workers with the 8-step synthesis of (*R*)-rolipram (an anti-inflammatory drug) under flow using *only* heterogeneous catalysts, without the isolation of any intermediates and without the separation of any catalysts, co-products, by-products, and excess reagents.⁵

Yet, aiming to explain why industry is still reluctant to use immobilized homogeneous catalysts, de Vries and Farina recently concluded that this would be due to the poor stability of solid catalysts, with immobilized palladium catalysts used

for C–C bond-forming reactions being “invariably converted to nanoparticles after the first run”.⁶

With the purpose to provide a critical evaluation of the advantages and disadvantages linked to SiliaCat catalysts under flow, in this study we refer to selected recent examples applied to the synthesis of fine chemicals and APIs showing their technical, economical and environmental sustainability in the scale-up from the lab scale to industrial production.

SiliaCat peculiar characteristics

SiliaCat catalysts are generally composed of methylsilica matrices with catalytic centers 3-D entrapped within the huge inner surface area (several hundreds of $\text{m}^2 \text{g}^{-1}$), and not 2-D adsorbed at the outer surface as it observed with previous generation heterogeneous catalysts.⁷ The versatile sol-gel encapsulation process through which SiliaCat catalysts are obtained allows high catalytic loading (0.3 mmol g^{-1}) to be accessed, whereas the very same process enables true nanochemistry tailoring of the material textural properties, micro-particle shape, hydrophilic-lipophilic balance (HLB) and material morphology (powder, disk, rod, monolith, *etc.*).

Contrary to many resins and polymers, functionalized silicas do not swell in any solvent and share uniquely high thermal, mechanical and chemical stability. The overall outcome is often enhanced reactivity and selective activity even compared to a homogeneous catalyst in solution.⁸ This has been shown for many reactions and for different entrapped catalysts since the mid 1990s when Avnir, Blum and co-workers in Israel started the field by investigating sol-gel entrapped transition metal catalysts,⁹ up to recent findings of Welch's team in Canada who reported lately that SiliaCat-DPP-Pd is an excellent catalyst in the synthesis of molecular organic semiconductors *via* the Stille, Suzuki–Miyaura and direct heteroarylation reactions, while the homogenous catalyst gave only poor yields.¹⁰

^a Istituto per lo Studio dei Materiali Nanostrutturati, CNR, via U. La Malfa 153, 90146 Palermo, Italy. E-mail: mario.pagliaro@cnr.it

^b SiliCycle, 2500, Parc-Technologique Blvd, Québec, Québec, G1P 4S6 Canada. E-mail: FrancoisBeland@silicycle.com

Finally, contrary to closed polymer beads not accessible to reactants in which fluid flows around beads,¹¹ mesoporous SiliaCat catalysts are open with huge inner pores accessible to reactants towards which sol-gel silicas actually act as chemical sponges, adsorbing and concentrating reactants at the outer surface of the sol-gel cages.¹²

Commercial SiliaCat catalysts are by no means the only functionalized silicas that have shown excellent performance in catalyzing diverse reactions under flow-through conditions. It is sufficient here to mention the oxidation of thioethers to sulfoxides and sulphones over silica functionalized with peroxometalate,¹³ the direct synthesis of amides *via* condensation reaction over SBA mesoporous silicas,¹⁴ or the leach-proof Pd-entrapped silica monolith for Suzuki-Miyaura coupling reaction.¹⁵ Furthermore, the use of “quick and easy to employ” functionalized silicas for heterogeneous reactions under flow was recommended as early as of 2009.¹⁶

Numerous other immobilized Pd catalysts have been developed and commercialized in the last decade, including polymer-bound Pd Tetrakis, FiberCat, and Pd EnCat. A detailed comparative investigation of the SiliaCat catalyst with respect to state-of-the-art flow-chemistry catalysts was lately reported by Kappe and co-workers.¹⁷ In the following sections, we comment on these findings and review the outcomes of several other independent research reports. This study is concluded by pointing out the challenges that, in our view, need to be addressed *en route* to broad adoption of this versatile green chemistry technology for preparative purposes in both research laboratories and industrial manufacturing.

Cross-coupling reactions

Homogeneous palladium-catalyzed C–C cross-coupling reactions are widely employed by industry to prepare biaryls and heterobiaryls which are ubiquitous chemical moieties in fine chemicals, pharmaceuticals, natural products, dyes, organic semiconductors and many other functional products.¹⁸ Aiming to reuse the expensive catalyst, prevent product contamination with Pd, and cut waste treatment costs, plenty of research efforts have been dedicated to efficient heterogenization of Pd catalytic species.¹⁹

One such catalysts is SiliaCat DPP-Pd composed of an amorphous sol-gel derived organosilica matrix functionalized with a diphenylphosphine ligand bound to Pd²⁺, which is an excellent mediator in numerous cross-coupling batch reactions,²⁰ such as Suzuki-Miyaura, Heck-Mizoroki, Sonogashira, Kumada, Stille and Buchwald reactions.

This glassy material has typically 0.2–0.3 mmol g⁻¹ palladium loading, high surface area (>600 m² g⁻¹) and large accessible mesopores, ideally suited for reactions under flow.²¹ In 2013, along with Jina and Drobot, we described its successful utilization in the Suzuki-Miyaura coupling reaction of different aryl halides with phenylboronic acid under flow,²² using dilute reagent mixtures (0.02–0.05 M) under flow in the 50–250 μL min⁻¹ rate range.

Using a mesoporous catalyst of such textural properties allows the scale-up of the flow-through reaction by simply increasing the throughput. Hence, in 2014 we reported the same Suzuki reaction in flow over 0.1–0.8 mol% catalytic amount of SiliaCat DPP-Pd using substrate solutions of notably higher concentration (0.5–1.0 M) under a flow rate up to 1.0 mL min⁻¹, which is considered a practically relevant threshold.²³

Using a modular, fully automated flow reaction system (Asia 220, Syrris), whose reactor was charged with the solid catalyst, complete conversion of several aryl halides was rapidly achieved (Scheme 1).

The catalyst is stable and could be used up to 30 h without showing any decrease in activity, while the method does not require the use of inert conditions common when Pd complexes are used in cross-coupling reactions. This method is general, as it enables the heterogeneous conversion of an ample variety of different aryl halides, with yields of coupled products ranging from 70% to 100%, and reduced levels of Pd leaching (<0.5 ppm in the reaction products), which is obviously relevant from an applicative viewpoint, as less than 1 ppm palladium contamination in the product is required in the pharmaceutical industry.

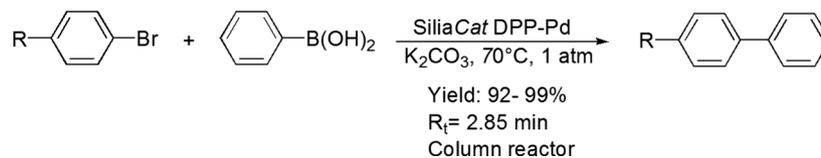
Aryl chlorides are also easily cross-coupled, but the catalyst in this case rapidly loses its original high activity leading to its deactivation due to the formation of sintered Pd nanoparticles.

In the industrially relevant cross-coupling of 2-chlorobenzonitrile and 4-methyl phenylboronic in the presence of K₂CO₃, it was enough to use a 70% (v/v) aqueous ethanol solution starting from a single 144 mL solution containing 72 mmol of substrates within the column reactor, kept at 77 °C and charged with 0.345 g of SiliaCat DPP-Pd (0.06 mol% catalytic amount) using a flow rate of 1 mL min⁻¹, to afford 79% isolated yield.

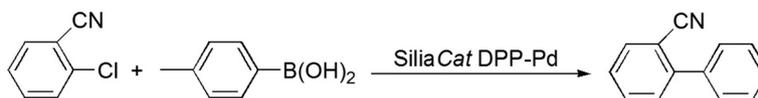
In 2013, we had described the optimal conditions and preliminary scale-up of the coupling reaction between 2-chlorobenzonitrile and 4-methyl-phenylboronic acid (from 1 to 100 g of aryl halide, Scheme 2), an important step reaction in valsartan synthesis which can be successfully carried out under similar conditions in batch.²⁴

Valsartan and telmisartan are the active ingredients of the most widely employed antihypertensive drugs. In 2015, Gupton and co-workers reported an elegant three-step convergent continuous-flow process for the synthesis of telmisartan, the active ingredient in the antihypertensive drug *Micardis*.²⁵ The key step is the Suzuki-Miyaura cross-coupling reaction between two functionalized benzimidazoles catalyzed by SiliaCat DPP-Pd (Scheme 3).

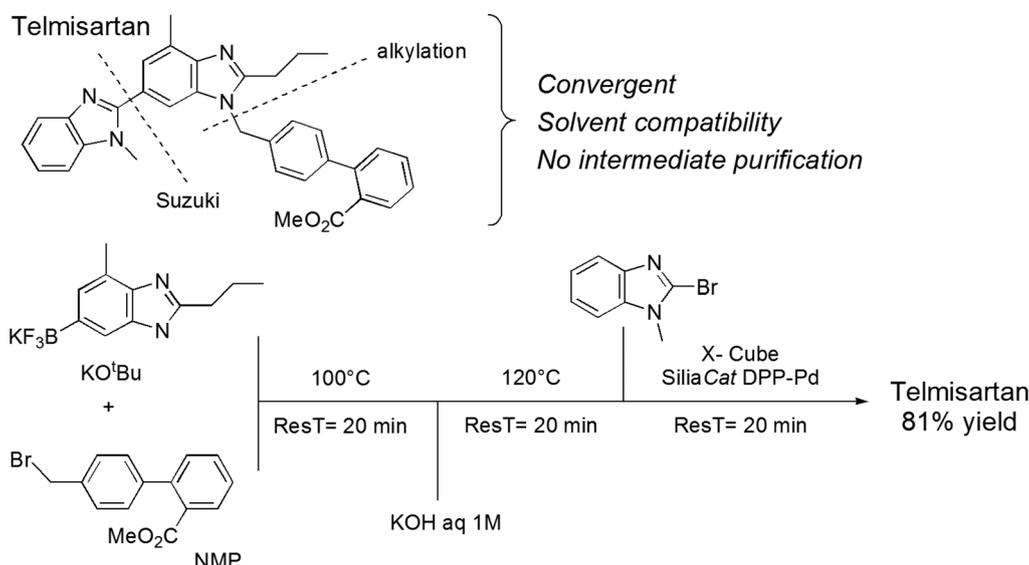
In detail, a commercial flow system (E-Series, Vapourtec) fitted with two 10 mL reactor coils in series was used for the alkylation and de-esterification reaction steps. The outlet solution is collected prior to the introduction of aqueous KOH for the de-esterification reaction, after which the alkylated benzimidazole (from the reservoir) and bromobenzimidazole are introduced at a flow rate of 0.1 mL min⁻¹ (at 40 bar) *via*



Scheme 1 Heterogeneously catalyzed Suzuki-Miyaura coupling of diverse substrates in flow over SiliaCat DPP-Pd [adapted from ref. 23, with kind permission].



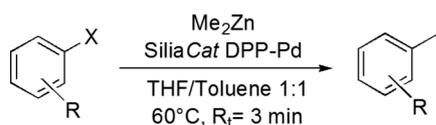
Scheme 2 Heterogeneous Suzuki-Miyaura coupling of 2-chlorobenzonitrile over SiliaCat DPP-Pd [adapted from ref. 24, with kind permission].



Scheme 3 The three-step telmisartan synthesis under flow-through conditions developed by Gupton and co-workers [adapted from jflowchemistryblog.wordpress.com, with kind permission].

two separate inlet streams into the packed bed cartridge charged with SiliaCat DPP-Pd held in another commercial flow system (X-Cube, ThalesNano) kept at 180 °C. A residence time of 5 min is enough to give telmisartan with an overall isolated yield of 81%.

Following McQuade's introduction of the continuous synthesis of organozinc halides coupled to Negishi reactions mediated by SiliaCat DPP-Pd,²⁶ in 2014 Alcázar and co-workers at a pharmaceutical company in Spain reported the first example of an alkyl-aryl Negishi coupling over SiliaCat DPP-Pd in flow under very mild conditions (Scheme 4) using di-



Scheme 4 Heterogeneously catalyzed alkyl-aryl Negishi coupling of diverse aryl halides with dimethylzinc over SiliaCat DPP-Pd [reproduced from ref. 19, with kind permission]. [Adapted from ref. 27, with kind permission].

methylzinc and diverse aryl halides dissolved in a THF/toluene mixture.²⁷

Due to the versatility of the method, good to excellent conversions and good functional group compatibility were achieved in most cases with a short (3 min) residence time, and products were isolated directly after aqueous work-up or with minimal purification, improving yields and extending the scope of other previously reported procedures in batch.

In detail, aryl bromides, iodides, and activated chlorides gave excellent conversions, while the process has very good functional group compatibility (including reactive groups such as esters, ketones and aldehydes), being applicable to heterocyclic substrates and compounds bearing *ortho* substituents, too. All crude products were free from phosphine derivatives and ready for use in subsequent reaction steps.

The stability of the catalyst is clearly shown by the stable conversion, checked every 30 min, in the prolonged (and a larger scale) Negishi coupling of substrates bearing carbonyl functional groups, continuously feeding the reagents into the reactor for a longer period of time (Fig. 1).

The same catalyst cartridge could be employed for more than 20 consecutive reactions without a decrease in activity. The scalability was assessed, too, and a throughput of 7.5 mmol of processed substrate per hour was achieved, always with very good isolated yields.

Finally, when a functionalized organozinc compound was used in place of simple $\text{Zn}(\text{Me})_2$, difunctionalized molecules of great synthetic potential were rapidly obtained, such as in the case of the aryl aldehyde further functionalized with the dioxolanylethyl fragment isolated in 81% yield (Scheme 5).

For comparison, the same compound was obtained for the first time in 2009 in 50% yield in batch under homogeneous conditions using organotrifluoroborate and an expensive palladium diphosphine complex in 5 mol% catalytic amount.²⁸

Debenzylation and direct borylation

Most recently, De Borggraeve and co-workers described the selective and reproducible debenylation of benzyloxy pyrazinones (*O*-benzyl protected cyclic hydroxamates) over SiliaCat DPP-Pd to yield *N*-hydroxypyrazinones (Scheme 6) in a commercial flow microreactor (Chemtrix, model 3026).²⁹

The conversion is constant and complete in a wide range of temperatures (80–110 °C; above 60 °C ammonium formate efficiently decomposes in the presence of Pd) at a residence time of 14 s without losing selectivity for the formation of the desired product (*N*-OH form, 97–98%) with only 1–2% of the over-reduced pyrazin-2 product (*N*-H form).

Once again, the process is easily scalable. Hence, an experiment was performed with 1-benzyloxy pyrazin-2(1*H*)-one 3-carboxamide in a Milliflow system (X-Cube, Thales Nano) equipped with a catalyst cartridge containing SiliaCat DPP-Pd (188 mg) kept at 110 °C, using 30 bar backpressure. Excellent conversion and selectivity (98%) were obtained at a flow rate of 3.0 mL min⁻¹, with 2.2 g of substrate converted into 1.4 g of the corresponding 1-hydroxypyrazin-2(1*H*)-one 3-carboxamide after 4 h (90 % isolated yield).

In 2014, we demonstrated fast and clean borylation of aryl halides under flow over SiliaCat DPP-Pd,³⁰ through which boronic acid pinacol esters are selectively obtained starting from aryl halides and bis(pinacolato)diboron (Fig. 2), with dramatic enhancement in reaction rate and catalyst stability, compared to reaction under batch conditions.³¹

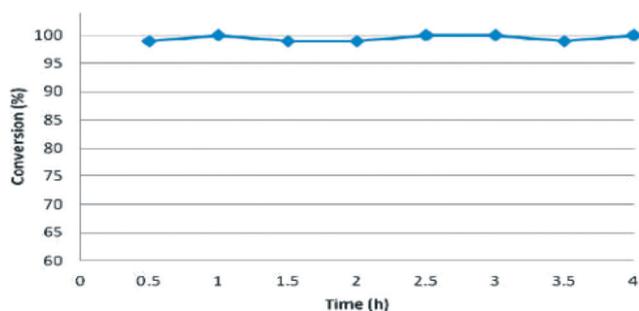


Fig. 1 Conversion after 30 min observed in 4 h of reaction under flow in the Negishi coupling between 4-Ac-C₆H₄-Br and $\text{Zn}(\text{Me})_2$ mediated by SiliaCat DPP-Pd [reproduced from ref. 27, with kind permission].



Scheme 5 Heterogeneously catalyzed synthesis of a difunctionalized compound under flow over SiliaCat DPP-Pd [adapted from ref. 27, with kind permission].

In detail, only one solution is prepared by mixing the substrate, bis(pinacolato)diboron (Bi_2Pin_2) and base (KOAc) in *i*-PrOH as solvent. The column reactor is packed with 0.8 g of SiliaCat DPP-Pd, and the flow system is initialized for 20 min at room temperature. After 20 min, the reactor was heated at 82 °C, and the solution containing 5–10 mmol of substrate kept at room temperature was processed directly through the solid-phase reactor *via* a T-piece at 0.50 mL min⁻¹ or at 0.25 mL min⁻¹.

For comparison, while the borylation of 4-bromobenzonitrile under batch requires 1 hour for complete conversion, under flow-through conditions at 0.50 mL min⁻¹ flow rate the quantitative conversion to the corresponding arylboronate requires a residence time of 2.05 min only. Again, to investigate the stability of the encapsulated catalyst the reaction (using 2-bromotoluene as the substrate) was carried out by feeding the reagents continuously into the reactor for a much longer period of time (7 h) and checking the conversion every hour.

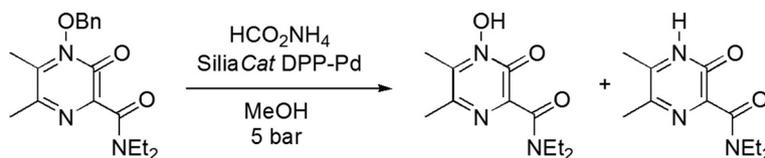
Fig. 3 shows that the outcome of the reaction does not change with time, thus proving also in this case the required long-term stability of the solid catalyst needed for practical synthetic applications.

Technical and economic sustainability

The technical advantages of using leach-proof catalytic mesoporous silicas under flow are numerous and significant.^{7,16}

- Prolonged use of the catalyst.
- High catalyst:substrate ratio in the packed reactor increases the reaction rate.
- Robust and air-stable (easy manipulation).
- Highly active (short residence time and mild conditions).
- No catalyst separation required.
- Incorporation into multistep processes (subsequent reactions can follow on immediately).
 - Reaction time and temperature profiles are precisely controlled.
 - Proven reactions can be rapidly scaled up.
 - Silicas do not swell with any solvent, and pores are not clogged.
 - Diffusion limitations minimized.

It is enough to place the catalyst, generally supplied as a mesoporous powder, inside the solid-phase reactor included in commercial flow systems and run the reaction. In general, functionalized silicas do not leach from the tightly entrapped



Scheme 6 Debenzylation of the representative precursor 1-benzyloxy-pyrazin-2(1H)-one 3-carboxamide in flow with HCO_2NH_4 /SiliaCat DPP-Pd in methanol. 80 °C and a residence time of 14 s are enough for complete debenzylation [adapted from ref. 29, with kind permission].

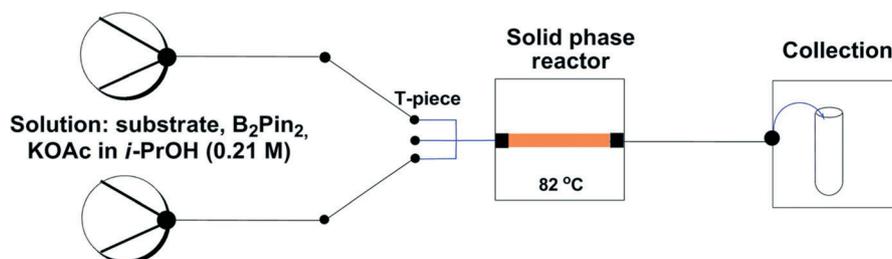


Fig. 2 Setup of the off-the-shelf system (Asia 220, Syrris) to carry out the borylation reaction under flow over SiliaCat DPP-Pd [reproduced from ref. 30, with kind permission].

catalyst, and do not swell with any solvent mixture. Mesopores do not clog, and diffusion limitations are minimized.

Metal leaching in general is absent or minimal. As another example, Alcázar and co-workers in 2012 reported that SiliaCat DPP-Pd can be used in the Suzuki–Miyaura cross-coupling of more than 30 different halides/pseudo-halides and organoboron compounds under flow (1 g of catalyst using the R2+ R4 Vapourtec system), for more than 8 h of continuous processing without a decrease in activity due to low leaching (less than 10 ppb Pd in the organic phase and 20 ppb in the aqueous phase).³²

Most recently, Kappe and co-workers in Austria conducted a comparative study of the activity, stability, and metal leaching of the most common immobilized diarylphosphine- and triarylphosphine-based palladium catalysts used in C–C coupling reactions, namely polymer-bound Pd Tetrakis, FiberCat 1001, EnCat TPP30, and SiliaCat DPP-Pd, by carrying

out two model reactions (the Heck reaction of 4-iodobenzonitrile with butyl acrylate and the Suzuki–Miyaura reaction of the same halide with phenylboronic acid) in an X-Cube (Thales Nano) flow reactor.¹⁷

As previously reported,²⁴ the combination of a protic solvent and an inorganic base (THF/EtOH/H₂O and K₂CO₃) results in very good conversions and selectivities also in continuous flow.

In general, the team found that the SiliaCat DPP-Pd catalyst showed far superior leaching resistance and stability with respect to the other three catalysts, with very low levels of leached Pd (332 µg for the Mizoroki–Heck reaction and 39 µg for the Suzuki–Miyaura reaction).

In both cases, after the flow system dead time, the reactions rapidly stabilized, and a constant profile was achieved (Fig. 4). No drop of conversion was observed during the flow experiment and the amount of metal contaminating the reaction mixture was very low. Further inspection of the catalyst cartridge placed out of the reactor after reaction showed the formation of Pd(0), with higher degradation observed at the first part of the material placed in the first part of the catalyst cartridge.

The team concluded that “it is likely that when larger reaction mixtures are processed all of the catalyst material will be degraded”.¹⁷ Yet, as put by Alcázar and co-workers, the SiliaCat DPP-Pd catalyst “costs less than other commonly used palladium sources, such as palladium acetate or Pearlman’s catalyst”,³² whereas the continuous reaction under flow does not require catalyst separation from the product, drastically reducing solvent utilization, while providing increased yields of valued cross-coupled products at a much faster rate than any homogeneously catalyzed process in a batch reactor. This directly translates into reduced operational expenditure (dramatically reduced solvent usage, yield improvement, radical cut in waste treatment costs).

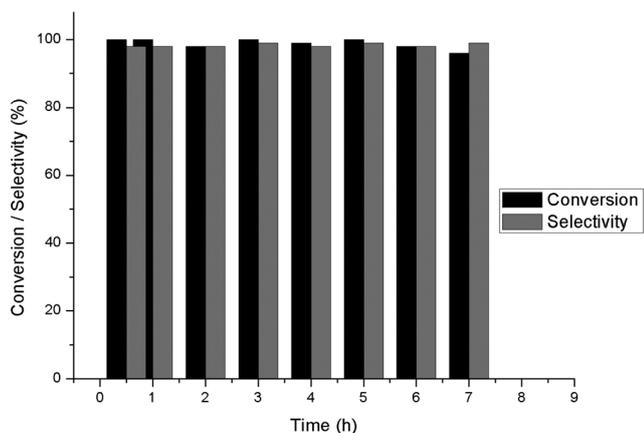


Fig. 3 Stability of the SiliaCat DPP-Pd supported catalyst in borylation reaction under flow [reproduced from ref. 30, with kind permission].

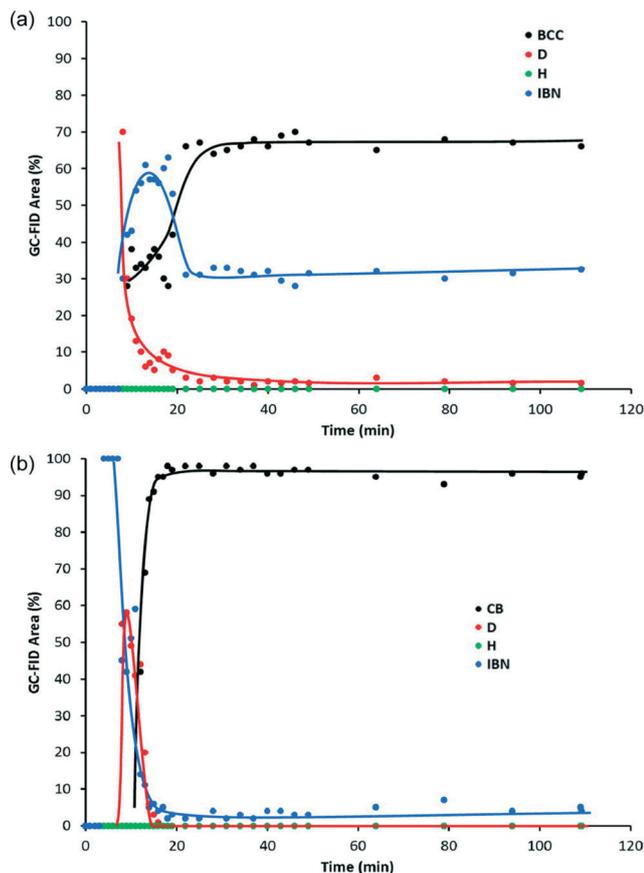


Fig. 4 Conversion profiles obtained for the continuous-flow Mizoroki-Heck (a) and Suzuki-Miyaura (b) reactions catalyzed by SiliaCat DPP-Pd. Conditions: 0.25 M substrate in THF/EtOH/H₂O, 1.5 equiv. of K₂CO₃, 1.25 equiv. of PhB(OH)₂ or *n*-butyl acrylate, 80 °C, 0.2 mL min⁻¹ [reproduced from ref. 17, with kind permission].

Concerning capital expenditure, a unique and particularly attractive feature for the production of fine chemicals and pharmaceuticals under flow lies in the possibility of rapidly scaling-out, rather than scaling-up, the reaction under laboratory-optimised conditions, by simply putting in parallel an increased number of flow chemistry tubular reactors.³³ This in practice translates into transferring the reaction conditions generated in micro channels to production reactors in parallel using ‘meso’ scale reactors (which contain mm-sized channels).

Suppliers of flow chemistry systems, such as Chemtrix in the Netherlands or AM Technology in the UK, already offer industrial flow reactors for industrial production that can be adapted to multiphase processes. These relatively small reactors (for example the 400 L h⁻¹ Plantrix reactor of Chemtrix) can be used to scale-out production by using multiple reactors in parallel, thereby meeting changes in customer demand by simply increasing or decreasing the number of devices employed.

This avoids scale-up costs and pilot plant investment, so that the return of investment following purchase of industrial flow reactors is quicker.

Outlook and conclusions

Within the next two decades, the pharmaceutical and fine chemicals industries will rely on heterogeneously catalyzed processes using molecular, metal and enzymatic catalysts with little or no waste generation, and minimal energy and resource utilization.³⁴ Reactions will be carried out in flow reactors located in industrial plants 20 or 30 times smaller than today's batch plants of similar output.³⁵

We have argued elsewhere³⁴ that industry will accept to undertake this transition to green chemistry when the *economic* advantages of the new and cleaner processes – affordable capital investment, reduced operational costs, quick payback time, better product quality – will be clearly demonstrated and communicated.

The numerous advantages of heterogeneous catalysis under flow face significant challenges *en route* to broad industrial adoption. First, rather than investing in new continuous reactors, companies will continue to use existing equipment (batch reactors) until its natural degradation, so that new continuous processing systems will be purchased on a case-by-case basis.³⁶ Another major issue lately identified among fine chemicals and API manufacturers evaluating synthetic processes under flow is the aversion to investment in new technology at its early stages.³⁷

Furthermore, better academic involvement and new educational investments are required to fill the educational gap (training of students lagging behind demand) identified by Jamison,³⁸ Baxendale,³⁹ and Pagliaro⁴⁰ amongst the main barriers to green innovation *via* flow chemistry and nanocatalysis in the chemical industry.

Eventually, however, the rapidly increasing offer of continuous reactors of ever lower cost, as well as of new generation heterogeneous catalysts joined to expanded marketing will result in the adoption of heterogeneously catalyzed continuous synthetic processes.

Most synthetic organic chemistry requirements, including high reproducibility and enhanced ease of scale-up, are already met by using heterogeneous catalysis under flow. Along with other catalysts of similar stability and good selective activity, functionalized silicas such as the hybrid SiliaCat catalytic materials will be used in new flow chemistry reactors for lean manufacturing of fine chemicals and APIs.⁴¹

The large applicative potential of the SiliaCat catalyst series under flow, in conclusion, goes much beyond the few examples discussed in this succinct study and includes the use of SiliaCat TEMPO in the selective oxidation of alcohols,²² hydrogenation of nitroarenes,⁴² stereoselective hydrogenation of vegetable oils,⁴³ hydrosilylation,⁴⁴ and hydrogenation of olefins.⁴⁵ Furthermore, SiliaCat Pd⁰ composed of ultrasmall Pd nanoparticles affording ultralow values of palladium leaching (<0.1 ppm) in several Sonogashira and Suzuki-Miyaura quantitative cross-coupling reactions⁴⁶ will find widespread adoption under flow in continuous processes, such as in the selective hydrogenation of nitroarenes under very mild conditions.⁷ Just referring to the flow-based Negishi

reaction mediated by SiliaCat DPP-Pd developed by Alcázar's team,²⁷ one may notice that the method provides a general selective alternative to dibenzimidazoles, *i.e.* an important class of pharmacophores. As mentioned in the introduction, Welch has used SiliaCat DPP-Pd for the green synthesis of diverse organic semiconductors.⁴⁷ A logical next step will thus be to combine organic semiconductor synthesis and continuous flow cross-coupling reactions with a SiliaCat palladium catalyst, leading to green organic electronics based on green materials synthesis.⁴⁸ These and several other examples will shortly be reported.

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References

- 1 *Novel Process Windows*, ed. V. Hessel, D. Kralisch and N. Kockmann, Weinheim, Wiley-VCH, 2015.
- 2 R. Ciriminna, V. Pandarus, A. Fidalgo, L. M. Ilharco, F. Béland and M. Pagliaro, *Org. Process Res. Dev.*, 2015, **19**, 755–768.
- 3 W. R. Reynolds and C. G. Frost, *Coupling Reactions in Continuous-Flow Systems In Palladium-Catalyzed Coupling Reactions: Practical Aspects and Future Developments*, ed. A. Molnár, Weinheim, Wiley-VCH, 2013, pp. 409–443.
- 4 K. D. Nagy, B. Shen, T. F. Jamison and K. F. Jensen, *Org. Process Res. Dev.*, 2012, **16**, 976–981.
- 5 T. Tsubogo, H. Oyamada and S. Kobayashi, *Nature*, 2015, **520**, 329–332.
- 6 S. Hübner, J. G. de Vries and V. Farina, *Adv. Synth. Catal.*, 2016, **358**, 3–25.
- 7 R. Ciriminna, L. M. Ilharco, V. Pandarus, A. Fidalgo, F. Béland and M. Pagliaro, *Nanoscale*, 2014, **6**, 6293–6300.
- 8 R. Ciriminna, P. Demma Carà, M. Sciortino and M. Pagliaro, *Adv. Synth. Catal.*, 2011, **353**, 677–687.
- 9 J. Blum, D. Avnir and H. Schumann, *CHEMTECH*, 1999, **29**, 32–38.
- 10 S. M. McAfee, J. S. J. McCahill, C. M. Macaulay, A. D. Hendsbee and G. C. Welch, *RSC Adv.*, 2015, **5**, 26097–26106.
- 11 D. T. McQuade and P. H. Seeberger, *J. Organomet. Chem.*, 2013, **78**, 6384–6389.
- 12 D. Avnir, *Acc. Chem. Res.*, 1995, **28**, 328–334.
- 13 S. Doherty, J. G. Knight, M. A. Carroll, J. R. Ellison, S. J. Hobson, S. Stevens, C. Hardacre and P. Goodrich, *Green Chem.*, 2015, **17**, 1559–1571.
- 14 J. W. Comerford, T. J. Farmer, D. J. Macquarrie, S. W. Breeden and J. H. Clark, *ARKIVOC*, 2012, **7**, 282–293.
- 15 P. He, S. J. Haswell, P. D. I. Fletcher, S. M. Kelly and A. Mansfield, *Beilstein J. Org. Chem.*, 2011, **7**, 1150–1157.
- 16 D. Guthrie, *Follow the pharma flow*, Speciality Chemicals Magazine, 2009, pp. 28–29.
- 17 R. Greco, W. Goessler, D. Cantillo and C. O. Kappe, *ACS Catal.*, 2015, **5**, 1303–1312.
- 18 A. Dumrath, C. Lübbe and M. Beller, *Palladium-Catalyzed Cross-Coupling Reactions-Industrial Applications In Palladium-Catalyzed Coupling Reactions: Practical Aspects and Future Developments*, Weinheim, Wiley-VCH, 2013, pp. 445–489.
- 19 M. Pagliaro, V. Pandarus, R. Ciriminna, F. Béland and P. Demma Carà, *ChemCatChem*, 2012, **4**, 432–445.
- 20 M. Lemay, V. Pandarus, M. Simard, O. Marion, L. Tremblay and F. Béland, *Top. Catal.*, 2010, **53**, 1059–1062.
- 21 See at the URL: <http://www.silicycle.com/products/siliacat-heterogeneous-catalysts/r390-100> (last time accessed, 29 February 2016).
- 22 V. Pandarus, R. Ciriminna, F. Béland, G. Gingras, M. Drobot, O. Jina and M. Pagliaro, *Tetrahedron Lett.*, 2013, **54**, 1129–1132.
- 23 V. Pandarus, G. Gingras, F. Béland, R. Ciriminna and M. Pagliaro, *Org. Process Res. Dev.*, 2014, **18**, 1550–1555.
- 24 V. Pandarus, D. Desplantier-Giscard, G. Gingras, F. Béland, R. Ciriminna and M. Pagliaro, *Org. Process Res. Dev.*, 2013, **17**, 1492–1497.
- 25 A. D. Martin, A. R. Siamaki, K. Belecki and B. F. Gupton, *J. Flow Chem.*, 2015, **5**, 145–147.
- 26 N. Alonso, L. Zane Miller, J. De M. Muñoz, J. Alcázar and D. T. McQuade, *Adv. Synth. Catal.*, 2014, **356**, 3737–3741.
- 27 B. Egle, J. De M. Muñoz, N. Alonso, W. M. De Borggraeve, A. de la Hoz, A. Díaz-Ortiz and J. Alcázar, *J. Flow Chem.*, 2014, **4**, 22–25.
- 28 N. Fleury-Brégeot, D. Oehrich, F. Rombouts and G. A. Molander, *Org. Lett.*, 2013, **15**, 1536–1539.
- 29 A. H. Mai and W. M. De Borggraeve, *J. Flow Chem.*, 2015, **5**, 6–10.
- 30 V. Pandarus, G. Gingras, F. Béland, R. Ciriminna and M. Pagliaro, *Org. Process Res. Dev.*, 2014, **18**, 1556–1559.
- 31 V. Pandarus, G. Gingras, F. Béland, R. Ciriminna and M. Pagliaro, *Beilstein J. Org. Chem.*, 2014, **10**, 897–901.
- 32 J. De M. Muñoz, J. Alcázar, A. de la Hoz and A. Díaz-Ortiz, *Adv. Synth. Catal.*, 2012, **354**, 3456–3460.
- 33 P. Watts, Scale out of chemical synthesis in flow reactors, White paper, Chemtrix, Geleen: 2015. Available at the URL: <http://microreactortechnology.org/system/files/attachments/Paul%20Watts.pdf> (last time accessed, 29 February 2016).
- 34 R. Ciriminna and M. Pagliaro, *Org. Process Res. Dev.*, 2013, **17**, 1479–1484.
- 35 (a) S. Ley, *Chem. Rec.*, 2012, **12**, 378–390; (b) B. Guttman, D. Cantillo and C. O. Kappe, *Angew. Chem., Int. Ed.*, 2015, **54**, 6688–6728.
- 36 G. Tiene, Reaping the benefits of a continuous process, Manufacturingchemist.com, 3 September 2015, www.manufacturingchemist.com/news/article_page/Reaping_the_benefits_of_a_continuous_process/111592 (last time accessed 1 March 2016).

- 37 C. A. Challener, Potential Benefits Drive Interest in Continuous Manufacturing, *Pharm. Tech*, May 1, 2014, www.harmtech.com/bioprocessing-and-sterile-manufacturing.
- 38 T. Jamison, Interview to D. Stanton, Lack of talent will hamper continuous manufacturing adoption, Says MIT Prof, *In-Pharmatechnologist.com*, 13 May 2015.
- 39 M. Baumann and I. R. Baxendale, *Beilstein J. Org. Chem.*, 2015, **11**, 1194–1219.
- 40 M. Pagliaro, *Chem. – Eur. J.*, 2015, **21**, 11931–11936.
- 41 B. Trout, *Continuous manufacturing: the ultra lean way of manufacturing*, Biochemical Engineering XVI, Burlington (VT), July 2009.
- 42 V. Pandarus, R. Ciriminna, F. Béland and M. Pagliaro, *Catal. Sci. Technol.*, 2011, **1**, 1616–1623.
- 43 V. Pandarus, G. Gingras, F. Béland, R. Ciriminna and M. Pagliaro, *Org. Process Res. Dev.*, 2012, **16**, 1307–1311.
- 44 R. Ciriminna, V. Pandarus, G. Gingras, F. Béland and M. Pagliaro, *ACS Sustainable Chem. Eng.*, 2013, **1**, 249–253.
- 45 V. Pandarus, G. Gingras, F. Béland, R. Ciriminna and M. Pagliaro, *Org. Process Res. Dev.*, 2012, **16**, 1230–1234.
- 46 M. Pagliaro, V. Pandarus, F. Béland, R. Ciriminna, G. Palmisano and P. Demma Carà, *Catal. Sci. Technol.*, 2011, **1**, 736–739.
- 47 (a) S. M. McAfee, J. M. Topple, A. J. Payne, J. P. Sun, I. G. Hill and G. C. Welch, *ChemPhysChem*, 2015, **16**, 1190–1202; (b) A. D. Hendsbee, S. M. McAfee, J. P. Sun, T. M. McCormick, I. G. Hill and G. C. Welch, *J. Mater. Chem. C*, 2015, **3**, 8904–8915.
- 48 As shown for instance by Leclerc and co-workers in Quebec who have successfully used continuous flow catalysis to synthesize conjugated polymers for organic solar cells: F. Grenier, B. Reda Aïch, Y. Y. Lai, M. Guerette, A. B. Holmes, Y. Tao, W. W. H. Wong and M. Leclerc, *Chem. Mater.*, 2015, **27**, 2137–2143.