

A new class of heterogeneous Pd catalysts for synthetic organic chemistry†

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A new series of leach-proof nanostructured Pd(0) catalysts able to catalyze a number of fundamental organic transformations including C–C bond formation has been developed. Reactions in general proceed with high yield and often at completion, while the catalysts can be reused in further reaction runs. This establishes a new class of relevant solid catalysts for synthetic organic chemistry trademarked SiliCat Pd⁰ Hydrogel.

Introduction

Palladium-catalyzed cross coupling reactions such as those named after Suzuki–Miyaura, Mizoroki–Heck, Negishi and Sonogashira are the most powerful and versatile methods for carbon–carbon bond formation impacting a broad spectrum of the chemical sciences from medicinal and materials chemistry to polymer and synthetic organic chemistry.¹ In general, a homogeneous palladium catalyst mediates the reaction between an electrophile and a nucleophile. In the Suzuki–Miyaura reaction coupling takes place between phenylboronic acid and vinyl- or aryl halides;² whereas in the Sonogashira reaction, carbon–carbon bond formation occurs on reacting terminal alkynes with aryl or vinyl halides.³ In both cases, the reaction is catalysed by Pd(0) formed *in situ* while a base is required to neutralize the hydrogen halide produced as a by-product. These reactions are powerful because, along with broad versatility, they generally tolerate the presence of functional groups in the coupling partners, and thus do not require protection and deprotection of functional groups in the reagents.

Homogeneous cross-coupling reactions, however, have several shortcomings such as limited reusability of the expensive catalyst, which impacts cost, and palladium contamination in the product.⁴ Removing residual palladium—for instance with silica-based scavengers⁵—provides a challenging task for

chemists in the pharmaceutical industry to reduce its content in a pharmaceutical substance to a maximum acceptable concentration limit meeting the demanding requirements required by drug regulators (Table 1).

Nonetheless, given their enormous synthetic relevance, the pharmaceutical industry widely employs these homogeneous reactions and today some 25% of the global drugs synthetic manufacturing processes make use of one or more of these reactions.⁶ The unfortunate side effect is that for every kg of the active pharmaceutical ingredient (API) manufactured, between 25 and 100 kg of waste are by-produced in the form of spent solvents and metal catalysts.⁷

Many methods have been lately introduced to address the palladium contamination issue and, to the best of our knowledge, three major commercial solid catalysts have reached the market. Johnson Matthey commercializes *Smopex-111*, a styryl thiol-grafted polyolefin fiber treated with Pd(OAc) to yield a leach-proof catalyst for Heck and Suzuki reactions;⁸ as well as the *Pd-FibreCat* series made of co-entrapped ligand and Pd for coupling reactions using sterically hindered and electron rich substrates.⁹ Finally, Reaxa manufactures a catalyst series made of Pd micro-encapsulated in a polyurea framework (*PdEnCat*)¹⁰ that actually acts as a heterogeneous source, or reservoir, for catalytically active soluble Pd species.¹¹ Now, we report a new sol–gel catalyst series made of nanostructured Pd(0) organosilica xerogels suitable for application to truly heterogeneous Sonogashira and Suzuki coupling reactions, as well as to a variety of relevant organic reactions that will be the subject of other communications.

Table 1 Specification limits for residues of metal catalysts in the EU

Metal	Concentration/ppm	
	Oral	Parenteral
Pt, Pd, Ir, Rh, Ru, Os	5	0.5
Mo, V, Ni, Cr	10	1.0
Cu, Mn	15	1.5
Zn, Fe	20	2.0

Source: European Medicines Agency (EMA)-Guidelines on the Specification Limits for Residues of Metal Catalysts and Metal Reagents, 2008.

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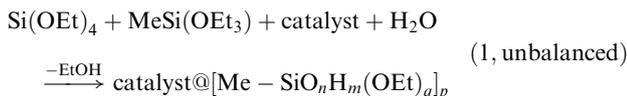
^b SiliCycle Inc., 2500, Parc-Technologique Blvd, Quebec City, Quebec, Canada G1P 4S6. E-mail: fbeland@silicycle.com; Fax: +1 418 874 0355

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c1cy00119a

Results and discussion

Preparation and characterization of the catalysts

The synthetic method is typical of biocompatible bottom-up routes for enzymes sol-gel encapsulation in biohybrid silica-based materials,¹² namely a mild entrapment process which starts with controlled distillation in a rotavapor of the alcohol released with ongoing hydrolysis and condensation of the MeSi(OEt)₃ and Si(OEt)₄ precursors (eqn (1)):



The resulting alcohol-free sol is doped with a Pd(II) salt and undergoes further basic or acid catalyzed polycondensation to yield a microporous hydrogel that is dried under mild conditions to afford a xerogel doped with Pd²⁺. The latter material undergoes hydrogenation under mild conditions to yield a nanostructured encapsulated catalyst such as *SiliaCat* Pd⁰.

In a typical preparation, a mixture of methyltriethoxysilane (27 g, 30 mL, 151.4 mmol) and 10 mL of 0.042 M HCl was stirred for 15 minutes. The resulting solution was concentrated with a rotavapor under reduced pressure at 30 °C until complete ethanol removal (about 15 minutes). The alcohol-free sol thereby obtained was added with K₂PdCl₄ (from 0.004 to 0.02 equivalent) dissolved in H₂O (from 5 to 10 mL) and 60 mL acetonitrile. This mixture was added with 1 M NaOH (from 0.023 to 0.053 equivalent) to favour gelation that indeed rapidly occurred. The resulting transparent gel was left to dry in air for 4 days after which the xerogel was reduced at room temperature under inert conditions with a solution of sodium triacetoxyborohydride (Pd : Na(AcO)₃BH = 1 : 6 molar ratio) in 80 mL THF, washed with THF and H₂O and dried in air to afford a *SiliaCat* Pd⁰ catalyst.

A whole series of different 75%-methyl modified ORMOSIL catalysts (a series of organically modified silicates in which 75% of the Si atoms are methylated) doped with Pd(0) were prepared according to the latter methodology by changing the synthetic conditions as listed in Table 2. The metal load in each catalyst was measured using the CAMECA SX100 instrument equipped with an EPMA analyzer, a fully qualitative and quantitative method of non-destructive elemental analysis of micron-sized volumes at the surface of materials, with sensitivity at the ppm level.

The SEM pictures of one such *SiliaCat* Pd⁰ catalyst reveal the typical matrix structure of organosilica particles (Fig. 1). The amorphous nature of the MeSiO_{1/2} material (the catalyst support) sol-gel prepared in our laboratory¹³ was confirmed by the characteristic wide diffractogram (Fig. S1a in ESI†). The dopant metallite particles, however, are made of nanostructured

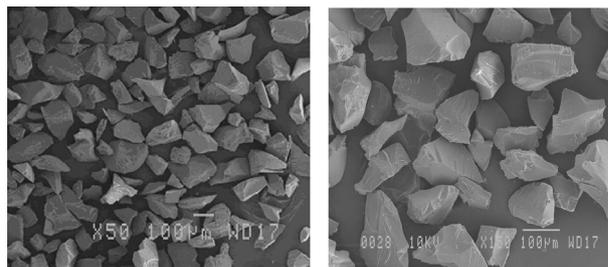


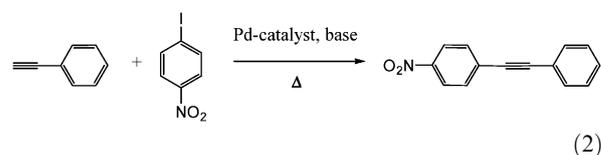
Fig. 1 *SiliaCat* Pd⁰-1—particle sizes: from 60 to 125 µm.

crystalline palladium(0). This was clearly shown by the XRD pattern of the powder in which the crystalline nature of the active nano-phase is evident from the succession of peaks (Table S1 and Fig. S1b in ESI†) characteristic of the face centered cubic structure of metallic Pd, for which a typical 5.7 nm (for *SiliaCat* Pd⁰-4) crystallite size was calculated using the Scherrer formula from the line broadening of (111) reflection.

In agreement with previous findings describing significant increase in selective activity in Heck coupling reactions with decreasing crystallite size for Pd on carbon,¹⁴ we also observe higher catalytic activity for our *SiliaCat* Pd⁰-1 catalyst with the smallest Pd crystallite size (3.2 nm). No significant changes in the XRD, ²⁹Si NMR and IR spectra were observed before and after the catalytic runs. However, other factors beyond metal dispersion (and its retention) influence the overall reactivity of these materials. A detailed structure-activity analysis will be the object of a forthcoming report.

Sonogashira reactions

All catalysts of the *SiliaCat* Pd⁰-Hydrogel series in Table 2 were first tested in Sonogashira catalysis using triethylamine and potassium carbonate as base (eqn (2)):



Results in Table 3 show that in DCM no reaction takes place, whereas in ethanol reaction proceeds with good yields over an extremely low amount (0.1 mol%) of the nanostructured solid catalyst in 0.5–2 h for *SiliaCat* Pd⁰-1 and in 24 h for *SiliaCat* Pd⁰-2, 3, and 4.

Reactions in Table 3 were *not* conducted under deaerated conditions. In other words, it is another remarkable feature of these new catalysts, that the sol-gel encapsulation of Pd in the organosilica matrix *prevents* the use of deaerated conditions typical of Sonogashira coupling reactions using palladium(0) complexes that are unstable in the air (oxygen promotes the formation of homocoupled acetylenes).

Table 2 Textural properties, load and preparation parameters of *SiliaCat* Pd⁰-Hydrogel catalysts

Sample	Pd loading/mmol g ⁻¹	Surface/m ² g ⁻¹	Pore size range/Å	MTES : K ₂ PdCl ₄ : H ₂ O : NaOH 1 M (equiv.)
<i>SiliaCat</i> Pd ⁰ -1	0.03	754	40.00	1 : 0.004 : 1.83 : 0.023
<i>SiliaCat</i> Pd ⁰ -2	0.112	774	45.00	1 : 0.009 : 2.20 : 0.033
<i>SiliaCat</i> Pd ⁰ -3	0.148	724	48.75	1 : 0.013 : 2.57 : 0.043
<i>SiliaCat</i> Pd ⁰ -4	0.163	721	52.50	1 : 0.018 : 2.93 : 0.053

Table 3 Sonogashira reactions mediated by *SiliaCat* Pd⁰ Hydrogel entrapped palladium^a

Entry	Catalyst ^b	Substrate	Acceptor	Solvent	Reaction time/h	Yield (%)
1 ^c	<i>SiliaCat</i> Pd ⁰ -1	Phenylacetylene	4-Iodo-nitrobenzene	DCM	24	0%
2	<i>SiliaCat</i> Pd ⁰ -1	Phenylacetylene	4-Iodo-nitrobenzene	EtOH	0.5	100 (99.5)
3	<i>SiliaCat</i> Pd ⁰ -2	Phenylacetylene	4-Iodo-nitrobenzene	EtOH	24	100 ^d
4	<i>SiliaCat</i> Pd ⁰ -3	Phenylacetylene	4-Iodo-nitrobenzene	EtOH	24	100 ^d
5	<i>SiliaCat</i> Pd ⁰ -4	Phenylacetylene	4-Iodo-nitrobenzene	EtOH	24	100 ^d
6	<i>SiliaCat</i> Pd ⁰ -1	Phenylacetylene	4-Iodo-acetophenone	EtOH	2	100 (99.6)
7	<i>SiliaCat</i> Pd ⁰ -1	Phenylacetylene	2-Iodo-toluene	EtOH	2	99 (98.3)

^a Experimental conditions: reactions performed in ethanol HPLC grade (40 ml) at reflux. Aryl iodide (4 mmol, 1 eq.), phenylacetylene (4.8 mmol, 1.2 eq.), K₂CO₃ (6 mmol, 1.5 eq.), and 0.1 mol% *SiliaCat* Pd⁰. The presence of a co-catalyst is not required. ^b Catalyst identified in Table 2.

^c The CH₂Cl₂ was used as solvent and Et₃N as base. ^d Conversion determined by GC/MS analysis.

Table 4 Suzuki coupling reactions of different bromide substrates and phenylboronic acid with *SiliaCat* Pd⁰ Hydrogel catalyst^a

Entry	Substrate	<i>SiliaCat</i> Pd ⁰ -1 ^c (mol%)	PhB(OH) ₂ (eq.)	Solvent (M)	Conversion (yield) ^d (%)
1 ^b	4-Iodo-nitrobenzene	0.1	1.1	MeOH (0.08 M)	100 (99.4)
2 ^b	4-Bromo-nitrobenzene	0.1	1.2	MeOH (0.1 M)	100 (99.4)
3	4-Bromoanisole	0.5	1.2	EtOH (0.12 M)	100
4	4-Bromophenol	0.5	1.2	EtOH (0.12 M)	100
5	4-Bromotoluene	0.5	1.2	EtOH (0.12 M)	95
6	4-Bromoaniline	0.5	1.2	EtOH (0.12 M)	100
7	2-Bromopyridine	0.5	1.2	EtOH (0.12 M)	100
8	3-Bromoquinoline	0.5	1.2	EtOH (0.12 M)	97

^a Experimental conditions: reactions performed in methanol or ethanol HPLC grade at reflux. Molar concentration is with respect to the substrate. Substrate (0.8 mmol, 1 eq.), phenylboronic acid (0.96 mmol, 1.2 eq.), K₂CO₃ (1.6 mmol, 2 eq.), reaction times *t* = 2 h. ^b Reaction times = 1 h.

^c Catalyst identified in Table 2. ^d Conversion of the substrate in the coupling product determined by GC/MS analysis (isolated yield).

Suzuki–Miyaura reactions

The *SiliaCat* Pd⁰-Hydrogel catalyst was thus used in the Suzuki–Miyaura coupling reaction of iodide and bromide substrates with phenylboronic acid (Table 4).

Results in Table 4 show that the reaction proceeds in excellent yield for the substrate with electron withdrawing groups such as –NO₂ (entries 1 and 2) and for substrates with different electron donating groups such as methoxy, methyl, amine (entries 3–6) and different heteroatoms such as pyridine and quinoline (entries 7 and 8). In each case, a modest 20% excess of phenylboronic acid reaction is enough to observe reaction proceeding at completion with 100% selectivity by suppressing nucleophilic aromatic substitution.

Catalyst leaching and reusability

Isolation and reuse of the catalyst, a crucial requirement for any practical application, involves simple filtration of the *SiliaCat* Pd⁰-Hydrogel catalyst. Reusability was thus studied using *SiliaCat* Pd⁰-1 with 4-iodo-nitrobenzene as substrate under the optimal reaction conditions identified in Table 4. Reusing the catalyst in 7 consecutive cycles (Table 5) did not result in any loss in catalytic activity with minimal (<0.2 ppm) leaching of Pd and Si (assessed by ICP-OES). Complete substrate conversion was obtained even after the seventh cycle, with 99.5% selectivity.

Finally, catalysis with *SiliaCat* Pd⁰-Hydrogel is truly heterogeneous. Indeed, hot filtration of the solid catalyst *SiliaCat* Pd⁰-1 employed in the same Suzuki coupling of 4-iodo-nitrobenzene and phenylboronic acid shortly after reaction start (after 10 min, achieving about 20% substrate conversion) gave an inert filtrate with no further conversion of

Table 5 Reusability of the *SiliaCat* Pd⁰-1 Hydrogel in Suzuki coupling reactions of 4-iodo-nitrobenzene and phenylboronic acid^a

Entry	Time/h	Conversion (yield) ^b (%)	Leaching ^c /ppm	
			Pd	Si
Run 1	1	100 (99.4)	0.18	1.0
Run 2	1	100 (99.2)	0.05	0.3
Run 3	1	100 (99.6)	0.04	0.09
Run 4	1	100 (99.4)	0.11	0.11
Run 5	1	100 (99.1)	0.02	0.09
Run 6	1	100 (99.3)	0.02	0.10
Run 7	1	100 (99.5)	0.01	0.09

^a Experimental conditions in Table 4. ^b The amount of final product determined by GC/MS analysis. Isolated yield of the crude product.

^c Leaching of Pd and Si determined by ICP analysis in solution.

the substrate left in solution. Reaction, however, re-started and went to completion following re-addition to the effluent mixture of the filtered catalyst. It is of relevance here to notice that this is not the case for each of the palladium catalysts obtained by reduction of Pd(OAc)₂ supported on amorphous silica, mercapto-functionalized silica and amine functionalized for which in a similar Heck reaction leached Pd was the active phase for all of the catalysts tested.¹⁵

SiliaCat Pd-Hydrogel differs from all previously developed heterogeneous technologies because nanostructured Pd(0) is the only active species (no ligand is employed) and in that the organosilica matrix ensures unprecedented stability and versatility of use. To date no efficient sol–gel entrapped Pd(0) catalysts for synthetic organic chemistry have been commercially available. Classical sol–gel encapsulation based on hydrolytic polycondensation of silicon alkoxides,¹⁶ in fact,

releases large amounts of alcohols (methanol, ethanol) that rapidly reduce the Pd(II) precursor to *bulk* Pd(0). The latter metal species is catalytically inactive, as only nanostructured Pd is able to mediate C–C coupling reactions.¹⁷

The closest silica-based technology makes use of phenyl-modified silica doped with 0.3 mol% adsorbed Pd (Pd-on-silica catalysts)¹⁸ that in Heck coupling showed performance identical to that of 10% Pd/C, the best commercial catalyst for heterogeneous Heck coupling available in 2003. The materials synthetic methodology, however, considerably differs from our homogeneous bottom-up procedure typical of nanochemistry. Indeed, the latter adsorbed catalysts were obtained by first treating silica with various chlorohydrosilanes to prepare the organically modified silica materials, and then reacting the modified silicas with a methanol solution saturated in PdCl₂.

Two related heterogeneous processes to dope silica with Pd make use of expensive and delicate periodic mesoporous organosilica (SBA-15 functionalized with mercaptopropyl)¹⁹ or MCM-41.²⁰ Again, the performance of the resulting catalysts in coupling reactions was good but the materials and their preparation processes considerably differ by the straightforward homogeneous encapsulation procedure described in our invention to obtain an entrapped and highly active nano-phase of crystalline Pd.

In conclusion, organosilica xerogels doped with nanostructured Pd(0) are highly active and stable catalysts suitable for mediating the Sonogashira and Suzuki coupling reactions to give coupled products in high yield and selectivity without the need to exclude air or moisture. The catalysts exhibit unprecedented stability among Pd heterogeneous catalysts and can be reused several times to achieve complete conversion without any additional activation treatment. Trademarked SiliaCat Pd⁰-Hydrogel, this new catalyst line is commercially available.

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References

- 1 For a recent account on cross coupling reactions, see the themed issue (Ed. S. Buchwald): *Acc. Chem. Res.*, 2008, **41**, 1439. Professors A. Suzuki, E. Negishi and R. F. Heck shared the 2010 Nobel Prize in Chemistry for developing Pd-catalyzed coupling methods for synthesizing complex molecules.
- 2 A. Suzuki, *J. Organomet. Chem.*, 1999, **576**, 147.
- 3 R. Chinchilla and C. Nájera, *Chem. Rev.*, 2007, **107**, 874.
- 4 A. M. Rouhi, *Chem. Eng. News*, 2004, **82**(36), 49.
- 5 C. E. Garrett and K. Prasad, *Adv. Synth. Catal.*, 2004, **346**, 889.
- 6 J. L. LaMattina, *Drug Truths: Dispelling the Myths About Pharma R&D*, Wiley, New York, 2008.
- 7 B. W. Cue Jr., *Chem. Eng. News*, 2005, **83**(39), 46.
- 8 X. Jiang, J. Sclafani, K. Prasad, O. Repi and T. J. Blacklock, *Org. Process Res. Dev.*, 2007, **11**, 769.
- 9 See at the URL: <http://www.jmccatalysts.com>.
- 10 See at the URL: <http://www.reaxa.com>.
- 11 S. J. Broadwater and D. T. McQuade, *J. Org. Chem.*, 2006, **71**, 2131.
- 12 M. L. Ferrer, F. dal Monte and D. Levy, *Chem. Mater.*, 2002, **14**, 3619.
- 13 According to the procedure described in patent WO/2010/015081.
- 14 K. Köhler, R. G. Heidenreich, J. G. E. Krauter and J. Pietsch, *Chem.–Eur. J.*, 2002, **8**, 622.
- 15 Y. Ji, S. Jain and R. J. Davis, *J. Phys. Chem. B*, 2005, **109**, 17232.
- 16 R. Ciriminna, L. M. Ilharco, A. Fidalgo, S. Campestrini and M. Pagliaro, *Soft Matter*, 2005, **1**, 231.
- 17 M. T. Reetz and J. G. de Vries, *Chem. Commun.*, 2004, 1559.
- 18 Á. Molnár, A. Papp, K. Miklós and P. Forgo, *Chem. Commun.*, 2003, 2626.
- 19 C. M. Crudden, M. Sateesh and R. Lewis, *J. Am. Chem. Soc.*, 2005, **127**, 10045.
- 20 A. Papp, G. Galbács and Á. Molnár, *Tetrahedron Lett.*, 2005, **46**, 7725.