SiliaCat: A Versatile Catalyst Series for Synthetic Organic Chemistry

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ABSTRACT: Reviewing selected applications of the recently developed SiliaCat catalyst series to synthetic organic chemistry, we show the large applicative scope of these multipurpose sol−gel entrapped catalysts, which are increasingly adopted for manufacturing useful products such as active pharmaceutical ingredients, cis-only hydrogenated fats, silanes, anilines, fragrances, and emollients.

INTRODUCTION

The development of new solid catalysts for heterogeneously catalyzed synthetic processes for the fine chemical and pharmaceutical industries is one of the main objectives of contemporary chemical research.[1] Manufactured by the global fine chemical industry,[2] fine chemicals are polyfunctional molecules with specific valued properties sold to customers in four key markets (pharmaceutical, agrochemical, animal health, and life science industries).

Active pharmaceutical ingredients (API), for example, are traditionally synthesized within batch reactors, via multistep atom inefficient processes carried out in organic solvent, resulting in >200 kg of waste for every kilogram of API manufactured.[3]

In the last two decades, plenty of research efforts have been devoted to innovate some of the above syntheses, and a number of cleaner industrial processes are now run in industry using highly selective solid catalysts or biotechnology (enzymes and whole cells).[4]

Effective solid catalysts can not only be easily separated, recovered, and recycled, but also effectively applied to continuous chemical syntheses carried out under flow, opening the route to clean and much more efficient chemical synthesis.

In a recent account on flow chemistry for the manufacturing of APIs,[5] Kappe and co-workers emphasized that the reasons explaining why continuous, cost-effective, and atom efficient flow processes form the basis of the petrochemical and bulk chemicals industries, which are subject to (i) strong competition, (ii) stringent environmental and safety regulations, and (iii) low profit margins.

Besides the large difference in product volumes between the two industries, this situation is increasingly becoming the experience of many API manufacturing companies.[6] Accordingly, cost reduction by leaning and greening production processes via economically viable clean technologies has become an urgent priority at many fine chemical suppliers. This industry, for example, has replaced with heterogeneously catalyzed methods many former stoichiometric processes used for the synthesis of vitamins, carotenoids, flavoring, and fragrance compounds.[7] Furthermore, a growing number of fine chemicals and pharmaceutical companies are starting to employ heterogeneously catalyzed under continuous flow.[5]

Accordingly, several new catalysts have been commercialized in the past decade. Selected examples include NanoSelect (BASF), Fibrecat (Johnson Matthey), Noblyst (Evonik), EnCats (Reaxa; today's S. Amit), and Pd Tetrakis (polymer-bound) (Biotage). Along with the latter new catalysts, the SiliaCat (a trademark of SiliCycle) sol−gel nanostructured hybrid silicas immobilizing and stabilizing organocatalytic species and unstable metal nanoparticles have emerged as a versatile nanochemistry technology, applicable to a large variety of reactions of direct relevance to the manufacture of fine chemicals and APIs, including alcohol selective oxidation,[8] hydrogenation of nitroarenes,[9] fully stereoselective hydrogenation of vegetable oils,[10] carbon−carbon bond formation,[11] ultraselective hydrosilylation,[12] and hydrogenation of olefins.[13]

We have explained elsewhere[14,15] how their successful application derives from the deliberate chemical design of the right hybrid nanostructures. Their porous, yet highly stable, glassy structure makes them ideally suited for flow chemistry resulting in reactions which are much faster and cleaner than the analogous reactions in batch,[16] opening the route to the commercial manufacturing of valued molecules in high-throughput continuous processes.

Rather than reviewing all reactions possible with the available SiliaCat catalysts, in the following we refer to selected reactions of central relevance in today's specialty chemicals and pharmaceutical industries, aiming to show a unified picture of the advantages (and limitations) offered by these catalysts employed in atom efficient and process intensified synthetic processes.

FEATURES AND BENEFITS OF THE SILIACAT CATALYST SERIES

The synthesis of the organosilica-based SiliaCat catalyst family is an alternate general method whereby organometallic species,

organocatalysts and noble metal nanoparticles are encapsulated within porous organosilica in a simple one-pot synthesis.[15] This nanochemistry route leads to the production of new mesoporous *catalyst*@organosilica materials, with the catalytic functionality incorporated homogeneously into the accessible structure of the hybrid material.[14,15]

Table 1 summarizes the main benefits originating from the use of the mesoporous organosilica Silia*Cat* catalysts. Opposite to

Table 1. Features and Benefits of the Silia*Cat* Catalyst Series

feature	benefit
chemical inertness	high chemical stability in different media/reaction conditions
reagents concentrated at the material's inner surface	high conversion rate
huge, stable inner mesoporosity	ease of application under flow
ceramic matrix nature	no swelling; solvent independent and air-stable; no inert conditions required
leach-proof organoceramic matrix	no contamination of APIs
high turnover number (TON)	low catalytic amount required (<1%)
reusability	multiple uses possible
free-flowing, no static charge	ease of handling and removal by simple filtration
ease of scalability	scalable from mg up to multiton scale
flexible formats	in powder form or available in packaged cartridges
high (>0.2 mmol/g) and accurate loading	less catalyst required, and reliable, reproducible synthesis
physical robustness	high thermal and mechanical stability

traditional polymer-supported catalysts, the rigid and highly porous glassy structure chemically and physically protects the encapsulated catalyst, reducing the leaching of the active phase; the glassy organosilica material is compatible with a wide range of solvents (no swelling); it offers an excellent resistance to high temperatures and pressure, while minimal static charge ensures ease of handling of a free-flowing powder. The sol−gel synthesis, furthermore, allows reproducible accurate loading, while the huge (several hundreds m^2/g) accessible surface area leads to high turn over number (TON).

PALLADIUM-MEDIATED CROSS-COUPLING REACTIONS

Carbon−carbon bond forming reactions catalyzed by palladium complexes are perhaps the single most important chemical transformations in today's synthetic organic chemistry.[17] As of 2007, for example, some 25% of the global drugs synthetic manufacturing processes used one (or more) of these reactions.[18] However, the affinity of palladium for the substrates results in palladium being brought through into the product, requiring extensive purification of the product with loss of the valued homogeneous Pd catalyst and posing further environmental burden.[19]

Immobilized Pd catalysts, combining the wide range of reactivity and selectivity of Pd-mediated cross-coupling chemistry, with the process and environmental benefits of heterogeneous catalysis, may solve the problem. Indeed, several Pd-based catalysts were lately commercialized, even though few leach-proof catalysts actually exist.[20]

The Silia*Cat* palladium catalyst line, comprising the Silia*Cat* DPP-Pd (Figure 1) and Silia*Cat* Pd[0], is one example.
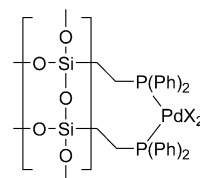

Figure 1. Silia*Cat* DPP-Pd palladium catalyst comprises a substituted diphenylphosphine (DPP) ligand covalently bound to the organosilica matrix.

Sol−gel entrapped diphenylphosphine-based palladium(II) Silia*Cat* DPP-Pd, for instance, is suitable for the fast conversion of a wide range of substrates in Suzuki, Sonogashira, and Heck coupling reactions.[21]

In 2013, the effective synthesis and successful scale-up of a key step in the valsartan synthesis via Suzuki−Miyaura coupling over Silia*Cat* DPP-Pd was reported.[22]

Marketed as the free acid under the Diovan or Angiotan trade names, valsartan (Figure 2) is one of the top 10 selling drugs in
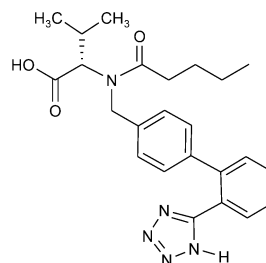

Figure 2. Chemical structure of valsartan: (*S*)-*N*-(1-carboxy-2-methyl-prop-1-yl)-*N*-pentanoyl-*N*-[2′-(1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine.

the US and in Europe, being indicated for treatment of high blood pressure, congestive heart failure, or postmyocardial infarction, as well as to reduce the incidence and progression of Alzheimer's disease and dementia.[23] The molecule dilates blood vessels and reduces blood pressure by blocking the action of angiotensin.[24]

In detail, 2-chlorobenzonitrile and 4-tolylboronic acid were heterogeneously cross-coupled over Silia*Cat* DPP-Pd in ethanol under reflux to produce 4′-methyl-2-biphenylcarbonitrile (the crucial step in valsartan synthesis). Covalent bonding of the encapsulated Pd(II) catalyst prevents metal leaching into the reaction mixture, eliminating the need for removal and disposal of undesired Pd contaminants.

Patents for making valsartan expired in September 2012,[25] opening the way to the production under current good manufacturing practices (cGMP) of the lower-cost generic antihypertensive drug of great relevance. However, companies willing to produce the molecule in Asia were denied permission by regulatory authorities, with the result that the price of the drug in the US reached historic high price.[27]

In another approach, ultrasmall Pd[0] nanoparticles are physically encapsulated within the organoceramic matrix affording the Silia*Cat* Pd[0] catalyst, which turns out to be an highly selective, stable, and reusable mediator for the conversion of a large number of substrates in Suzuki, Sonogashira, and Heck coupling reactions.[11]

For example, a 0.1−0.5 mol % catalyst amount is capable to mediate the Suzuki−Miyaura coupling reaction of iodide and

Table 2. Suzuki Coupling Reactions of Different Bromide Substrates over Silia*Cat* Pd(0)[a] [Reprinted in Part with Permission from Ref 11, Copyright 2011 Royal Society of Chemistry]

entry	substrate	Silia*Cat* Pd[0] (mol %)	PhB(OH)$_2$ (equiv)	solvent (M)	conversion (yield)[c] (%)
1[b]	4-iodonitrobenzene	0.1	1.1	MeOH (0.08 M)	100 (99.4)
2[b]	4-bromonitrobenzene	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. The molar concentration is with respect to the substrate. Substrate (0.8 mmol, 1 equiv), phenylboronic acid (0.96 mmol, 1.2 equiv), K$_2$CO$_3$ (1.6 mmol, 2 equiv), reaction times t = 2 h. [b]Reaction times = 1 h. [c]Conversion of the substrate in coupling product determined by GC/MS analysis (isolated yield).

bromide substrates with phenylboronic acid in EtOH or MeOH at reflux affording excellent yields of coupled products, for substrates with either electron-withdrawing or electron-donating groups, and also bearing different heteroatoms such as pyridine and quinolone (Table 2).

In each case, a modest 20% excess of phenylboronic acid is enough to observe reaction proceeding at completion with 100% selectivity, by suppressing nucleophilic aromatic substitution. Reusing the catalyst in seven consecutive cycles did not result in any loss in catalytic activity, with complete substrate conversion and 99.5% selectivity obtained even in the seventh cycle, with minimal (<0.2 ppm) leaching of valued Pd.

The Silia*Cat* palladium catalysts include also Silia*Cat* S-Pd, namely, an organosilica matrix encapsulating covalently bound thiol palladium(II) complex. Advantageously tested in a parallel synthesizer (MiniBlock) in all the main cross-coupling reactions mentioned above,[26] all of the Silia*Cat* palladium catalysts afforded high yields and selectivities of numerous aryl substrates. The only substrate that could not be fully converted was 2-iodoaniline, due to coordination of the aniline nitrogen.

Leaching of palladium from Silia*Cat* DPP-Pd, Silia*Cat* S-Pd, and Silia*Cat* Pd(0) employed in Suzuki−Miyaura and in Sonogashira coupling reactions was minimal (<10 ppm) and rather constant upon reuse, with the lowest values being obtained for Silia*Cat* Pd(0) affording in each case less than 2 ppm of leaching (only substrates with thiol and amino groups could coordinate and extract 5 and 14 ppm, respectively).

In 2013, we could already describe the excellent performance of Silia*Cat* Pd(II) catalysts under flow in a series of C−C Suzuki Miyaura coupling reactions using different aryl halide substrates which were optimized on a commercial flow reaction system (Syrris Asia 220).[16] By using flow chemistry, a 1 h batch process was successfully achieved in under a minute with 100% conversion and selectivity.

Shortly afterward, similar excellent results under flow conditions were confirmed at a pharmaceutical company in Spain by Alcázar and co-workers who used Silia*Cat* DPP-Pd for the Suzuki-Miyaura cross-coupling of more than 30 different aryl halides (0.125−0.30 M in THF) combined with an aqueous solution of boronic acid and KOH as base using the Vaportec R2+R4 system,[27] namely, with standard laboratory equipment and not with an expensive commercial flow system.

High yields and selectivities were rapidly obtained (TON values >100), with leaching of palladium in each case less than 10 ppb in the organic phase and 20 ppb in the aqueous phase. Accordingly, the same cartridge loaded with 1 g of catalyst could

be employed for more than 30 consecutive reactions without a decrease in activity.

In the long run (8 h) neither the yield nor the selectivity in the cross-coupling reaction of (4-methoxyphenyl)boronic acid and 1-bromo-2-methylbenzene changed with time. Different halides/pseudohalides and organoboron compounds (boronic esters, boranes, and borates) can be used without modifying the standard procedure.

Related excellent results were recently obtained by Alcázar's team in co-operation with McQuade who showed excellent constant yield in the continuous synthesis of organozinc halides coupled to Negishi reactions in a two column system. The first column uses an activated packed-bed of metallic zinc to form the organozinc precursor, and the second is filled with Silia*Cat* DPP-Pd to immediately cross-couple the organozinc molecule with aryl halides.[28]

A 3.3 mmol h^{-1} production rate of Negishi coupled product was achieved with an overall TON for the complete process of 175. The isolated yield of the reaction was 94% and the reaction was stable over the whole monitoring time (13 h, Figure 3)
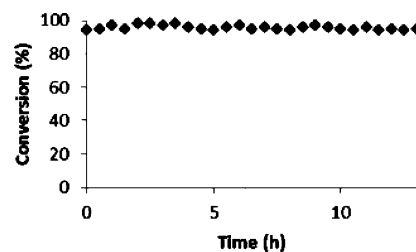

Figure 3. Catalytic flow system using two consecutive columns for the Negishi cross-coupling mediated by Silia*Cat* DPP-Pd of the as-formed organozinc precursor and different aryl halides bearing numerous functional groups. [Reproduced with permission from ref 28, Copyright 2014 John Wiley and Sons.]

leading the joint team to conclude that the reaction could be scaled to manufacturing volumes.

Most recently, a novel alkyl−aryl Negishi coupling was further developed by Alcázar's research group using Silia*Cat* DPP-PD in flow under very mild conditions.[29] Excellent conversions (up to 97%) and excellent functional group compatibility were reported for 26 substrates, including difunctionalized compounds, demonstrating the versatility of the method for the effective and clean coupling of aryl compounds (chloride, bromide, and iodide derivatives) with functionalized alkyl groups.

The scalability was assessed and confirmed, achieving a throughput of 7.5 mmol/h of processed substrate. A major advantage of the method is that all crude products were free from catalyst residue or phosphine derivative. As such, the products can be used directly in the subsequent reaction step.

Recently, thus, Kappe and co-workers conducted a comparative study of the activity, stability, and metal leaching of Pd Tetrakis (polymer-bound), FiberCat 1001, EnCat TPP30, and Silia*Cat* DPP-Pd, in continuous flow Mizoroki−Heck and Suzuki−Miyaura cross-coupling reactions.[30] The researchers evaluated the materials, as the most common immobilized diarylphosphine- and triarylphosphine-based palladium catalysts used in C−C coupling reactions, using two model reactions (the Heck reaction of 4-iodobenzonitrile with butyl acrylate, and the Suzuki reaction of the same halide with phenylboronic acid) performed in a commercial flow reactor (X-Cube, Figure 4).
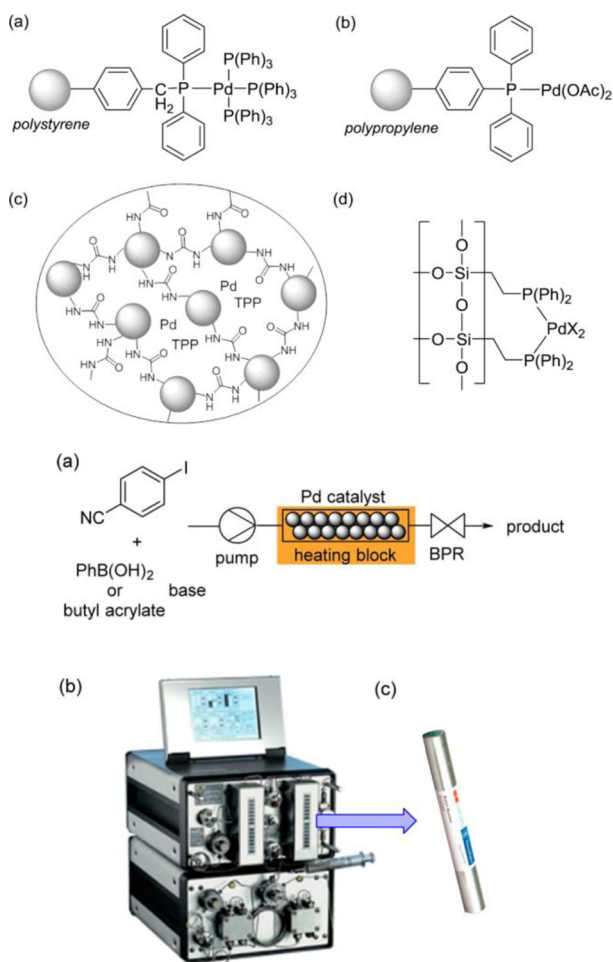

Figure 4. Structures of the (a) polymer-bound Pd Tetrakis, (b) FiberCat 1001, (c) EnCat TPP30, and (d) SiliaCat immobilized catalysts used in the continuous Mizoroki−Heck and Suzuki−Miyaura cross-coupling reactions carried out under flow in a ThalesNano X-Cube reactor. [Reproduced from ref 1, with kind permission. Copyright 2015 American Chemical Society.]

Notably, the Silia*Cat* DPP-Pd catalyst showed superior leaching resistance and stability with respect to the other three catalysts (Table 3). Confirming previous results, the combined utilization of THF/EtOH/H_2O as solvent and K_2CO_3 as base gave the best results regarding catalyst efficiency and leaching resistance (entries 11, 12 and 15, 16 in Table 3).

Furthermore, except for Silia*Cat* DPP-Pd, the Suzuki−Miyaura cross coupling produced a much higher amount of metal leaching and catalyst degradation than the Mizoroki−Heck reaction.

Kappe concluded that further development of this or other silica-based immobilized catalysts might lead to more leaching-resistant supports for preparative purposes. This is indeed what has been achieved with Silia*Cat* DPP-Pd for which the conditions for process intensification of the Suzuki−Miyaura reaction under flow in another modular flow microreactor (Syrris Asia 220) were lately developed with the aim of practical applications (substrate concentration of 0.5−1.0 M and flow rate up to 1.0 mL/min).[31]

Increased throughput requires the use of catalyst microparticles with sizes larger than 200 μm so as to avoid pressure drop throughout the solid catalyst packed in the microreactor. Results in Table 4 indicate that complete coupling conversion of several different aryl halides under process intensified flow conditions is obtained in less than 3 min (whereas the analogous conversion under batch requires up to 6 h); with very low values of Pd being leached in the APIs (<5 mg/kg), except for 3-bromopyridine which coordinates and extracts Pd(II).

Another remarkable result using the Silia*Cat* under microwave irradiation rather than under reflux was lately reported by Welch and co-workers who described the exceptional performance of Silia*Cat* DPP-Pd in the synthesis of the molecular semiconductor 5,5′(2,2′-bithiophene-5,5′-diyl)bis(2-hexylphthalimide) (SM-1, Scheme 1).[32]

These organic semiconductors yield high electron mobilities in thin-film transistors (of up to 0.2 cm^2 V^{-1} s^{-1}) and are ideally suited for organic electronics,[33] provided that cost-effective routes are developed for their synthesis from solution at low temperatures, with little scalable purification, or even better with no required product purification.

To amplify, the sol−gel entrapped catalyst outperformed well-known homogeneous catalysts $Pd(PPh_3)_4$ and $Pd(PPh_3)_2Cl_2$ in the Stille coupling reaction in terms of performance and catalyst loading, with catalyst loadings down to 0.1 mol %, exhibiting tolerance to ambient reaction conditions and 2-fold recyclability.

The material was then used to optimize direct heteroarylation under microwave irradiation in place of conventionally employed $Pd(OAc)_2$. Direct heteroarylation is more desirable, when compared to cross-coupling reactions, as it does not require toxic organotin or costly organoboron reagents, with considerable improvement in atom economy. The use of 0.1 mol % Silia*Cat* DPP-Pd afforded the desired product SM-1 in 87% yield with minimal formation of homocoupled aryl bromides, an undesirable side reaction generally occurring in the direct heteroarylation mediated by homogeneous Pd catalysts.

The catalyst turned out to be highly active and reusable twice. Leaching in the reaction product obtained from the Stille reaction carried out at 5 mol % afforded 0.08 mg/L Pd content. For comparison, the purified product obtained via homogeneous catalysis using $Pd(PPh_3)_4$ gave 26.25 mg/L Pd content.

These results, according to the researchers, open the route to both routine and selected synthesis of organic semiconductors relevant to the field of organic electronics.
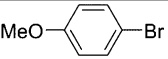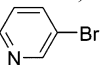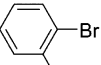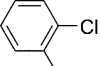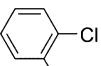
Indeed, the team subsequently used the Silia*Cat* DPP-Pd-mediated direct heteroarylation to synthesize an isoindigo derivative functionalized with electron deficient thiophene end-capping units bearing bulky aliphatic sides chains for organic photovoltaics applications, where it replaces costly fullerene derivatives.[34] The reaction was rapidly carried out at 80 °C under

Table 3. Total Pd Content in the Crude Continuous Flow Reaction Mixtures Collected from the Reactor Output, Determined by ICP-MS [Copyright 2015 American Chemical Society]

entry	catalyst	reaction	base[a]	substrate conc. [M]	solvent	T (°C)	Pd content (mg)	% Pd leached
1	Pd Tetrakis	Heck	TEA	0.5	MeCN	100	2.552	9
2	Pd Tetrakis	Suzuki	TEA	0.5	MeCN	100	4.614	15
3	FibreCat 1001	Heck	DIPEA	0.5	MeCN	120	2.578	16
4	FibreCat 1001	Suzuki	DIPEA	0.5	MeCN	120	2.433	15
5	Pd EnCat TPP30	Heck	TBAOAc	0.25	EtOH	120	1.029	5
6	Pd EnCat TPP30	Heck	TEA	0.5	MeCN	120	6.248	28
7	Pd EnCat TPP30	Suzuki	TBAOAc	0.25	EtOH	120	4.275	19
8	Pd EnCat TPP30	Suzuki	TEA	0.5	MeCN	120	2.71	12
9	SiliaCat DPP-Pd	Heck	TEA	0.5	MeCN	120	0.807	17
10	SiliaCat DPP-Pd	Suzuki	TEA	0.5	MeCN	120	1.251	27
11	SiliaCat DPP-Pd	Heck	K_2CO_3	0.25	THF/EtOH/H_2O	80	0.332	7
12	SiliaCat DPP-Pd	Suzuki	K_2CO_3	0.25	THF/EtOH/H_2O	80	0.039	1
13	SiliaCat DPP-Pd	Heck	KOH	0.25	THF/EtOH/H_2O	80	0.406	9
14	SiliaCat DPP-Pd	Suzuki	K_2CO_3	0.25	THF/H_2O	60	0.121	3
15	SiliaCat DPP-Pd	Heck	K_2CO_3	0.05	MeOH/H_2O	70	0.015	0.3
16	SiliaCat DPP-Pd	Suzuki	K_2CO_3	0.05	MeOH/H_2O	70	0.005	0.1

[a]TEA: trieethylamine; DIPEA: diisopropyltriethylamine; TBAOAc: tetrabutylammonium acetate.

Table 4. Suzuki−Miyaura Coupling of Different Substrates with Phenylboronic Acid over SiliaCat DPP-Pd under Intensified Flow Conditions[a] [Copyright 2014 American Chemical Society]

| Entry	Substrate (scale-up)	Catalyst (mol%)	t (h)	Flow conditions[e] Flow (mL/min)	RT (min)	Conv.[f] (%)	Select.[f] (%)	Leaching (mg/kg)[g] Pd	Si
1[b]	MeO—⟨benzene⟩—Br (330 mmol, 1320 mL solution)	0.13	30	0.75	2.85	98	99	3.36	42.69
2[c]	N-pyridine-Br (275 mmol, 1100 mL solution)	0.16	40	0.50	4.27	90	97	184.3	56.56
3[d]	⟨benzene⟩—Br (55 mmol, 220 mL solution)	0.8	5	0.75	2.85	92	99	0.67	5.79
4	+ (55 mmol, 220 mL solution)	0.4	5	0.75	2.85	90	97	4.95	38.63
5[d]	⟨benzene⟩—Cl / CN (55 mmol, 220 mL solution)	0.8	5	0.75	2.85	93	98	3.11	44.38
6[c,d]	⟨benzene⟩—Cl / CN (275 mmol, 1100 mL solution)	0.16	3 / 5 / 8 / 25	0.75	2.85	98 / 92 / 89 / 45	92	-	-

[a]Flow conditions: Two solutions were prepared. Solution 1: substrate (55 mmol, 1 equiv) in 70 mL THF; Solution 2: phenylboronic acid (68.75 mmol, 1.25 equiv), K_2CO_3 (82.5 mmol, 1.5 equiv) in 70 mL EtOH + 80 mL H_2O. SiliaCat DPP-Pd (1.76 g, 0.25 mmol/g Pd loading) was charged in the column reactor with an adjustable end (0.785 cm ID x 6.5 cm), at 70 °C. [b]Scale-up (×6) of conditions in note a. [c]Scale-up (×5) of conditions in note a. [d]4-Methyl-phenylboronic is used in place of phenylboronic acid. [e]Flow rate: 0.5 mL/min (0.16 mL/min solution 1 and 0.34 mL/min solution 2). [f]Conversion/selectivity determined by GC/MS. [g]Leaching of Pd and Si in the isolated crude product (by ICP-OES).

microwave irradiation and showed conversion of starting material to product in >70% yield with no need of organic extraction (the product readily precipitates from a 1:1 mixture of methanol and water to give a black solid, subsequently purified by flash column chromatography).

ROUTE TO VIABLE MANUFACTURING OF *CIS* FATS ONLY

Natural fats (both solid fats and liquid oils) are always found in the *cis* configuration. To increase their shelf life and enable more stable flavor making the fat less prone to rancidity (in which

Scheme 1. Synthesis of Target Molecular Semiconductor, SM-1, via Silia*Cat* DPP-Pd Catalyzed: (a) Cross Coupling Stille Reaction under Optimized Microwave Irradiation Conditions; (b) Direct Heteroarylation Reaction under Optimized Microwave Irradiation Conditions [Reproduced with Permission from Ref 32, Copyright 2015 Royal Society of Chemistry]
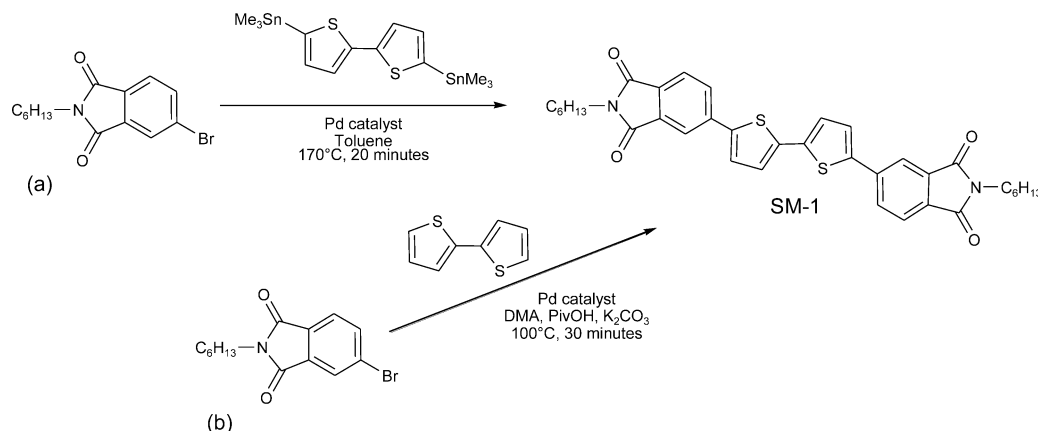
O_2 and oxygen-related radical species attack the double bond), vegetable oils are subjected to partial hydrogenation, a reaction of oils with hydrogen over traditional Ni catalysts discovered in 1901 in Germany by Normann.[35]

The reaction converts inexpensive liquid vegetable oils (primarily composed of linoleic acid and oleic acid triesters of glycerol, precursors of molecules with many critical biological functions in the human body) into shortenings and margarines but, unfortunately, the catalyst is not selective and fats are converted into a mixture of *cis* and *trans* monounsaturated fats (isomerization) creating *trans* fats as an undesired byproduct (Figure 5). For example, the *trans* bond in elaidic acid (the
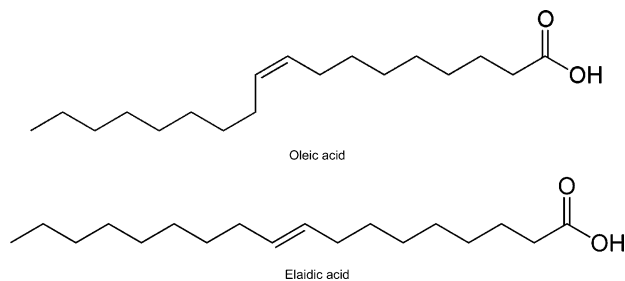

Figure 5. Oleic acid and elaidic acid are 18-carbon fatty acids with a single double bond. However, oleic acid (top) has a cis double bond, which causes a bend in the fatty acid chain, whereas elaidic acid (bottom) has a trans double bond, which straightens the fatty acid chain and profoundly alters its physiological effects.

principal *trans* unsaturated fatty acid in partially hydrogenated vegetable oils) imparts a structure similar to that of saturated fats, altering the physiological properties of the fatty acid.

Prolonged epidemiology studies, mostly carried out since the early 1980s by Willett in the US and Katan in Europe, respectively demonstrated that *trans* fats are linked to coronary heart disease,[36] and to increased levels of LDL cholesterol, reducing at the same time HDL cholesterol levels.[37] The *trans* fat content of vegetable oils and spreadable margarines, for example, should not exceed 2% of the total fat content.

Trans fats are abundant in fast food, snack food, and fried food. In the US, where in 2003 approximately 95% of prepared cookies, 100% of crackers, and 80% of frozen breakfast products contained *trans* fats,[38] since late 2013 partially hydrogenated fats are no longer "generally regarded as safe" (GRAS). Once the

ruling will become permanent, it will virtually eliminate industrially produced *trans* fat in the US, "saving thousands of lives each year".[39]

In brief, replacement of Ni-based catalysts in the hydrogenation of vegetable oils with more selective methods is of the utmost urgency in the food industry, and also for other fat/oil applications. A 2007 study[40] commissioned by Canada's Parliament urged the chemical industry to develop new hydrogenation catalysts to reduce or eliminate altogether the amount of *trans* fats in industrial foods.

Compared with nickel, catalysts based on noble metals such as Pd and Pt are generally more selective, albeit much less active. An economically viable Pd catalyst replacing Ni has been sought, without success, since the 1960s.

Reviewing the state of the art of the fat hydrogenation reaction in 2013, Jacobs and co-workers were concluding that the design "of such a smart catalyst will not be an obvious thing to do" because a hydrogenation process that combines low *cis/trans* isomerization with excellent hydrogenation selectivities requires heterogeneous catalysts with the right properties such as catalyst porosity, dispersion of the hydrogenating metal, and accessibility of the active metal centers to the bulky triglyceride molecules.[35]

It is therefore remarkable that the hydrogenation reaction of several vegetable oils (diluted in THF/MeOH) can be carried out at room temperature over 0.1 mol % Silia*Cat* Pd^0 affording quantitative yield of healthy *cis* monoinsaturated fats, with no *cis—trans* isomerization.[10]

Results in Table 5 show that in general complete substrate conversion of the vegetable oil to saturated product with no *cis—trans* isomerization is readily obtained after 3 h, with negligible leaching of valued palladium.[11] The product is easily separated from the solvent mixture which is recovered along with the catalyst and reused.

For example, used in linolenic acid (C18:3) hydrogenation in five consecutive cycles the Silia*Cat* Pd(0) catalyst fully retained its selective catalytic activity, with minimal leaching of Pd (<0.5 ppm in each case). In detail, complete substrate conversion in saturated product (C18:0) with 96% selectivity was obtained even after the fifth reaction cycle.

For comparison, the process is run at full efficiency at atmospheric pressure and room temperature, rather than under the harsh conditions (20 bar H_2 and T = 200 °C) of the traditional process using nonselective Ni catalysts.

Table 5. Full Hydrogenation of Vegetable Oils with Silia*Cat* Pd⁰ under Mild Conditions^a [Copyright 2012 American Chemical Society]

						leaching^c (ppm)	
entry	substrate	catalyst (mol %)	solvent (M)	time (h)	conv.^{b} (%)	Pd	Si
1	sunflower oil[41] (linoleic acid 64.5%, oleic acid 25.5%, and other 10%)	0.1	THF/MeOH (0.5 M)	3	99	0.3 (8.9)	0.2 (5.7)
2	sunflower oil (linoleic acid 64.5%, oleic acid 25.5%, and other 10%)	0.1	THF/MeOH (0.5 M)	2	99^d	0.1 (1.7)	0.19 (3.8)
3	corn oil (linoleic acid 54%, oleic acid 27%, and other 19%)	0.1	THF/MeOH (0.5 M)	3	98	0.2 (3.3)	0.2 (3.8)
4	soybean oil (linoleic acid 50%, oleic acid 27%, linolenic acid 9%, and other 14%)	0.1	THF/MeOH (0.5 M)	3	99	0.5 (10)	0.4 (8)
5	canola oil (linoleic acid 22%, oleic acid 58%, linolenic acid 9%, and other 11%)	0.1	THF/MeOH (0.5 M)	3	99	0.4 (7)	0.17 (3.3)
6	olive oil (linoleic acid 8%, oleic acid 72%, and other 20%)	0.1	THF/MeOH (0.5 M)	2	99	0.3 (6.3)	0.19 (3.7)

^{a}Experimental conditions: 14.5 mmol substrate in 30 mL of HPLC grade THF/MeOH 0.5 M with respect to the substrate (5:1 by volume ratio) over 0.1 mol % Silia*Cat* Pd(0) catalyst under hydrogen balloon room temperature conditions. ^{b}Conversion evaluated by TLC analysis (hexane–ethyl acetate = 5:1) using potassium permanganate stain and by ^{1}H RMN spectra in isolated crude product. ^{c}Leaching in Pd and Si determined by ICP-OES analysis in tetrachloroethane solution (50 mg/mL) and in solid crude product. ^{d}Reaction temperature 40 °C.

Subsequent detailed structural investigation[14] of the Silia*Cat* matrix suggests a reaction mechanism similar to that observed with enzymes, in which the exquisite selectivity of hydrogenation over Silia*Cat* Pd(0) is ascribed to the preferential entrance of the hydrophobic tails of the triglyceride molecule into the methylsilica sol–gel cage where the Pd nanoclusters are encapsulated.

The Pd nanoparticles (NPs) are encapsulated individually within open cylindrical mesopores between spheroidal particles of fairly uniform array. Quantitative DRIFT analysis shows that the ORMOSIL (organically modified silica) structure of the Silia*Cat* contains 80% of six-member siloxane rings (Figure 6A)
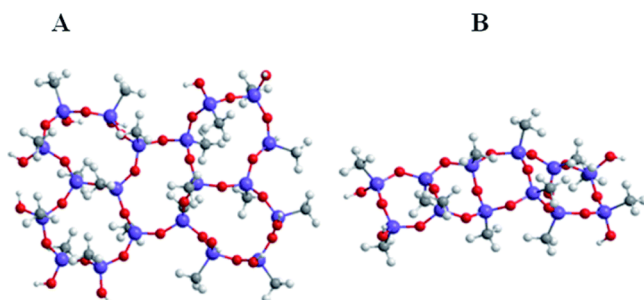

Figure 6. Schematic representation of a silica cluster containing five cyclic siloxane units: A, six-member [(SiO)₆]; B, four member [(SiO)₄]. [Reproduced with permission from ref 14, Copyright 2014 Royal Society of Chemistry.]

and 20% of four-member siloxane rings (Figure 6B), yielding an unique three-dimensional network of lipophilic sol–gel cages that allow the accommodation of larger loads of NPs, while promoting preferential adsorption of lipophilic functional groups in substrates adsorbed at the surface of the encapsulated nanoparticle. Finally, the sol–gel encapsulation prevents the mobility of the NPs on the supporting material's surface and thus prevents sintering observed with many conventional supported metal catalysts.

■ CATALYTIC HYDROGENATION OF OLEFINS

The heterogeneously catalyzed hydrogenation of alkenes is an essential industrial reaction for the synthesis of vitamins, complex natural products, pharmaceuticals, and fine chemicals.[42] Palladium on activated carbon (Pd/C) is widely used as catalyst of choice at industrial scale because of its high catalytic activity and higher selectivity when compared to Ni-based catalysts. However, the poor chemoselectivity exhibited by Pd/C prevents

its utilization when other reducible functionalities are present in the substrate.[43]

Bonrath has recently detailed[7] how, starting in the early 2000s, the fine chemical industry in Europe has developed a number of lead-free palladium catalysts for selective catalytic hydrogenations. These include Pd NPs supported on metal alloy carrier (the carrier material comprising Cr, Mo, or Fe, Ni, Co, Mo in various amounts)[44] and Cu-doped Pd on SiO₂.[45]

In 2012, we reported the Silia*Cat* Pd⁰-mediated heterogeneous selective hydrogenation of a wide variety of olefins functionalized with other reducible groups such as amine, halide, carbonyl, carboxyl, and esters, under hydrogen balloon conditions using a modest 0.1 mol % catalyst amount at room temperature (Table 6).[13]

Furthermore, different alkynes such as 1-heptyne, 1-octadecyne, and phenyl acetylene (entries 9–11) were respectively converted into into heptanes, octadecane, and ethylbenzene.

The values of palladium leached into the product were negligible (Table 7). Furthermore, the catalyst was recyclable at length, thus providing a suitable replacement for less selective and unstable Pd/C or palladium onto organic polymers[46] and inorganic oxides,[47] for which rapid reduction in the catalytic activity of Pd is generally observed.

In the hydrogenation of cinnamic acid, for example, Silia*Cat* Pd⁰ gave considerably higher yield in hydrocinnamic acid than a 5% Pd/C commercial catalyst.
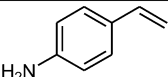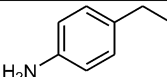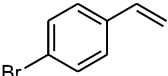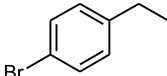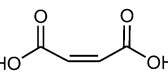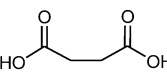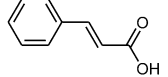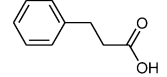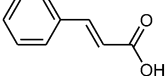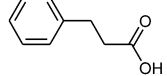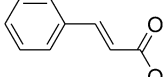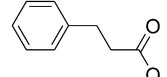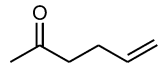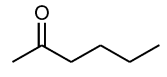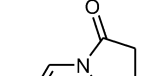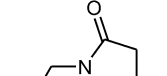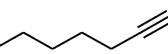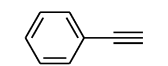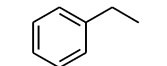
Expanding the scope of application, most recently the catalyst was successfully employed for the full chemoselective hydrogenation of highly unsaturated all-*trans* linear squalene into valuable fully saturated squalane, the best emollient known so far in cosmetics and in medicine.[48]

Once again, whereas the state-of-the-art industrial hydrogenation process makes use of nickel-Kieselguhr catalyst under 4 bar of H₂ at 200 °C, the new process over Silia*Cat* Pd⁰ is carried out in GRAS approved ethanol (0.50 M with respect to the squalene) over 0.5 mol % catalyst under 1 atm H₂ at 50 °C. Catalysis is truly heterogeneous, and the catalyst is stable and recyclable, which opens the route to an easier and less expensive hydrogenation of squalene.

■ CATALYTIC HYDROGENATION OF NITROARENES

Functionalized anilines are among the most important intermediates for pharmaceuticals, polymers, dyes, urethanes, and other industrially important chemical products. These molecules are generally obtained by catalytic hydrogenation of nitroarenes with various heterogeneous metal catalysts (supported nickel, copper, cobalt) including Pd/C.[49]

Table 6. Catalytic Hydrogenation of Functionalized Alkenes over Silia*Cat* Pd⁰ under Mild Conditions[a] [Copyright 2012 American Chemical Society]

Entry	Substrate	Catalyst (mol%)	Solvent (M)	Time (h)	Product	Conv(Yield)[b] (%)	Select[b] (%)
1		0.1	MeOH (0.25 M)	0.5 1		92 100 (99.1)	100
2		0.1	MeOH (0.25 M)	1 3		22 35	
3		0.1	THF (0.25 M)	1		100(99.4)	100
4[c]		0.1	EtOH (0.25 M)	1 4		90 100	100 75
5[c]		0.1	THF (0.25 M)	2 4		100 100 (99.6)	100 100
6		0.1	MeOH (0.25 M)	0.5		100(99.5)	100
7		0.1	EtOH (0.25 M)	0.5 2		72 100	100
8		0.1	MeOH (0.25 M)	0.5		100(99.5)	100
9		0.1	MeOH (0.25 M)	2	heptane	100	99
10[d]	1-Octadecyne	0.1	MeOH (0.25 M)	2 3	1-octadecane	100 100(97.3)	65 98
11[e]		0.1	MeOH (0.25 M)	1 2		100 100	20 100

[a]Experimental conditions: 6 mmol of substrate in 24 mL of solvent (HPLC grade) and 0.1 mol % Silia*Cat* Pd⁰ catalyst, under hydrogen balloon room temperature conditions. [b]Evaluated by GC/MS analysis. Isolated yield. [c]After more than 1 h the formation of methyl 3-phenylpropanoate was observed in methanol or ethyl 3-phenylpropanoate in ethanol. 100% selectivity was obtained in THF. [d]After 2 h complete conversion of 1-octadecyne in 1-octadecene (35%) and octadecane (65%); after 3 h complete conversion in octadecane. [e]After 1 h 100% conversion but 20% ethylbenzene and 80% styrene; after 2 h 100% ethylbenzene.

Table 7. Reusability of the Silia*Cat* Pd(0) in the Selective Catalytic Hydrogenation of *trans*-Cinnamic Acid under Mild Conditions [Copyright 2012 American Chemical Society]

run	time (h)	conversion (yield)[a] (%)	selectivity (%)	leaching[b] (ppm) Pd	leaching[b] (ppm) Si
1	2	100 (99.4)	100	0.09 (1.8)	0.06 (1.2)
2	2	100 (99.8)	100	0.09 (1.8)	0.03 (0.6)
3	2	100 (99.3)	100	0.12 (2.3)	0.02 (0.4)
4	2	100	99	0.09 (1.6)	0.03 (0.5)
5	2	100	99	0.08 (1.5)	0.02 (0.3)

[a]Conversion in final product determined by GC/MS analysis. Isolated yield of the crude product. [b]Leaching in Pd and Si determined by ICP-OES analysis in solution (DMF solvent 50 mg/mL, with respect to the crude product) and in the solid crude product.

However, the selective reduction of a nitro group over the above-mentioned catalysts, when other reducible groups are present in the substrate nitroarene molecule, is generally not feasible.[50] The use of supported Pd(0) nanoparticles for the hydrogenation of the nitro group in the presence of moderately reducible functional groups has been demonstrated, for example, using palladium NPs supported over carbon nanofibers,[51] in aluminum oxy-hydroxide[52] and over magnesium oxide.[53] However, the latter catalysts cannot be employed with more challenging substrates containing sensitive functionalities (such as double and triple bonds, carbonyls, etc.).[54]

The first highly selective nitroarene hydrogenation routes under mild conditions over a very low amount (0.5 mol %) of either Silia*Cat* palladium(0)[9] or Silia*Cat* platinum(0)[55] were reported in 2011. Carried out in methanol under hydrogen balloon conditions at room temperature, the reaction with both catalysts in general proceeds with high yield and most often goes

Table 8. Selective Catalytic Hydrogenation with Silia*Cat* Pt(0) under Mild Conditions of Different Nitro Compounds and of Different Nitro Compounds Containing Different Functionalities[a] [Reprinted in Part with Permission from Ref 55, Copyright 2011 John Wiley and Sons]

Entry	Substrates	Catalyst[b] (mol%)	Solvent[c] (M)	Time [h]	Product	Conv. (Yield)[d] [%]	Select.[d] [%]
1		0.5	MeOH (0.1 M)	1		100	100
2		0.5	MeOH (0.05M)	1		100	98[e]
3		1	MeOH (0.05M)	4		100	85[f]
4		0.5	MeOH (0.05M)	1		100 (99.3)	100
5		0.5	MeOH (0.05M)	1		98	100
6		0.5	MeOH (0.1 M)	1		100	100
7		0.5	MeOH (0.1 M)	1		100	95
8		1	MeOH (0.1 M)	0.5		92	13
9		0.5	MeOH (0.07 M)	2		100	80
10		0.5	MeOH (0.1 M)	0.5		100 (99.7)	100
11		1	MeOH (0.1 M)	1		100	100
12		0.5	MeOH (0.1 M)	2		100 (99.5)	100
13		0.5	MeOH (0.07 M)	0.5		100	95[g]
14		0.5	MeOH (0.07 M)	1		100 (99)	100[g]

[a]Experimental conditions: the substrate, 0.5−1 mol % Pt with respect to the substrate and the MeOH solvent (0.1 M, molar concentration with respect to the substrate) was stirred under hydrogen balloon room temperature conditions. [b]Catalyst identified in Table 1. [c]Molar concentartion of the solvent with respect to the substrate. [d]Conversion/selectivity with respect to desired product were evaluated by GC/MS analysis. Isolated yield in crude product. [e]5% pyrene. [f]15% antracene. [g]After 0.5 h one nitro group was reduced, and 1,2 diamino-4-nitrobenzene was 5%. After 1 h both nitro groups were reduced.

to completion. Table 8, for example, shows how the highly selective catalytic hydrogenation of different nitro compounds with different functionalities dissolved in MeOH is smoothly achieved over 0.5−1 mol % Silia*Cat* Pt⁰ at room temperature under hydrogen balloon conditions with complete substrate conversion generally obtained after 0.5−4 h.

Widely different nitroarenes could be selectively converted into nitroanilines in quantitative yield under ultramild conditions (Entries 1−5), whereas the nitro group of nitroarenes bearing other reducible groups such as carbonyl, amide, and esters was

selectively reduced under the same mild conditions are present (Entries 6−14).

It is also remarkable, from a practical process viewpoint, that the hydrogenation reaction takes place in two consecutive steps. Hence, the regioselective hydrogenation of a specific nitro group in a polynitroarene becomes possible by simply controlling the reaction time.

Finally, the leach-proof nature of the catalyst ensures its smooth reutilization in many consecutive reaction cycles, with no loss in catalytic activity and with minimal leaching of Pt and Si

Table 9. Reusability of the Silia*Cat* Pt^0 in the Selective Catalytic Hydrogenation of 4-Chloronitrobenzene [Reproduced with Permission from Ref 55, Copyright 2011 John Wiley and Sons]
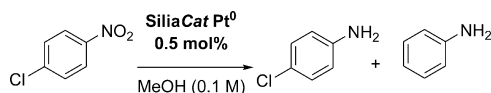
entry	time (h)	conversion (yield)[a] (%)		Leaching[b] (ppm)	
		4-chloroaniline	aniline	Pt	Si
Run 1	0.5	84	12	0.2 (0.69)	1.2 (4.2)
Run 2	0.5	89	11	0.04 (0.15)	0.4 (1.2)
Run 3	0.5	90	10	0.02 (0.4)	0.08 (0.4)
Run 4	0.5	92	8	0.17 (1.05)	0.1 (0.5)
Run 5	0.5	98	2	0.01 (0.1)	0.1 (0.5)
Run 6	0.5	99 (98.2)	1	0.01 (0.1)	0.12 (0.6)
Run 7	0.5	99 (98.5)	1	0.01 (0.1)	0.08 (0.4)

[a]Conversion in final product determined by GS/MS analysis. Isolated yield of the crude product. [b]Leaching in Pt and Si determined by ICP analysis in solution (DMF solvent 0.7 M, with respect to the crude product) and in the solid crude product.

(Table 9). Complete substrate conversion, for example, was obtained even after the seventh cycle, with 99% selectivity.

Silia*Cat* Pt^0 outperformed several state-of-the-art catalysts encapsulating Pt(0) nanoparticles (Table 10). For instance, in comparison to Pt/C, Pt/SiO$_2$, PtEnCat40, the sol–gel entrapped catalyst proved to be much more reactive affording complete conversion after 0.5 h with 0.5 mol % amount only, with only 4% aniline formed as byproduct and no other secondary products observed in solution.

Similar levels of selectivity for the chemoselective hydrogenation of nitroarenes were previously observed with platelet-type carbon nanofiber-supported Pt nanoparticles, but under 10 atm H$_2$ and temperature between 25 and 100 °C.[51]

Only recently, with the introduction of palladium NPs supported over nitrogen-functionalized active carbon obtained via heat treatment of the resultant mixture of active carbon and melamine through wet impregnation, the hydrogenation of nitroarenes at room temperature under H$_2$ ambient pressure was reported.[56]

HYDROSILYLATION OF OLEFINS

Hiydrosilylation is the most important chemical conversion employed by industry for the preparation of organosilicon compounds, namely, of silicones. The conventional process used by industry is homogeneously catalyzed by platinum-based Speier's catalyst.

Most heterogeneous catalysts quickly become inactive due to rapid nanoparticle sintering. For example, the heterogeneous hydrosilylation of alkynes in the presence of Pt/C, SiO$_2$/Pt or unsupported PtO, generally affords good yields and selectivities in the first run, but the catalysts cannot be reused.[57]

In 2013, our groups reported that a modest 0.5−1 mol % amount of Silia*Cat* Pt(0) selectively mediates the hydrosilylation of different olefins using a 30% molar excess of triethoxysilane in toluene under Ar atmosphere at 65 °C, depending on the substrate (Scheme 2).[12]

Different substrates were therefore subjected to hydrosilylation under the optimized reaction conditions. With the exception of linear olefins, reactions proceeded quickly with good yield and selectivity (Table 11).

Scale-up of the heterogeneous reaction is easily achieved. This was shown by carrying out the hydrosilylation of 1-octene using 50 and 100 mmol (rather than 5 mmol) of olefin substrate, keeping the catalyst amount at 0.5 mol % (Table 12).

The process scaled up 50 times retains both the high selectivity and conversion degree observed under the 2 mmol scale, affording pure octadecyltriethoxysilane in 53% yield (product loss occurred due to the nonoptimized isolation method, i.e. vacuum fractional distillation; real industrial process will use state-of-the art isolation techniques).

ALCOHOL SELECTIVE OXIDATION

Aldehydes and ketones obtained through alcohol selective oxidation are among the most valued fine chemicals. Fragrant aldehydes with a linear aliphatic carbon chain, for example, are widely used in the production of perfumes and essences. These aldehydes are found in many essential oils and fruits of plants, but the growing market demand requires their synthetic production from the corresponding long chain alcohols via selective oxidation.

Similarly, numerous synthons and APIs are actually manufactured in industry by selectively oxidizing alcohols, especially

Table 10. Catalytic Reactivity of Different Other Pt Heterogeneous Catalysts such as Pt/C, Pt/SiO$_2$, and Pt(0)EnCat40 in Selective Reduction of 4-Chloronitrobenzene[a] [Reproduced with Permission from Ref 55, Copyright 2011 John Wiley and Sons]

entry	catalyst	catalyst (mol %)	time (h)	conversion[b] (%)			
				total conv.	4-chloroaniline	aniline	other
1	Pt/C	5	1	98	82	14	2
2	Pt/C	1	1	94	65	4	25
3	Pt/C	0.5	1	79	43	0	36
4	Pt/SiO$_2$	5	1	100	84	13	3
5	Pt/SiO$_2$	1	2	100	88	10	2
6	Pt/SiO$_2$	0.5	2	60	48	2	9
7	Pt(0)EnCat40 wet	5	1	100	75	18	7
8	Pt(0)EnCat40 wet	1	2	100	78	14	8
9	Pt(0)EnCatTM40 wet	0.5	2	95	72	12	11
10	Pt(0)EnCat40 dry	5	0.5	100	87	13	0
11	Pt(0)EnCat40 dry	1	2	100	90	10	0
12	Pt(0)EnCat40 dry	0.5	2	100	86	13	1

[a]Experimental conditions: 2 mol of substrate in 20 mL of MeOH solvent (HPLC grade), under hydrogen balloon room temperature conditions. 1% Pt/C; 5% Pt/SiO$_2$, granules; Reaxa Pt(0)EnCat40, 0.112 mmol/g Pt, 40% humidity, were bought from Aldrich. [b]Conversion evaluated by GC/MS analysis.

Scheme 2. Hydrosilylation over Silia*Cat* Pt⁰ Closes the Organosilicon Cycle, Because the Silia*Cat* Silane Precursor Is Obtained from an Hydrosilylation Reaction [Copyright 2013 American Chemical Society]
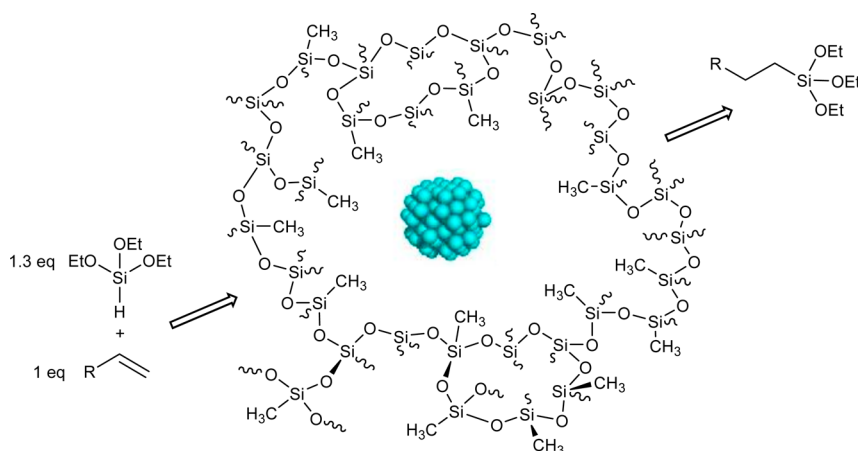

Table 11. Catalytic Hydrosilylation of Functionalized Alkenes with Triethoxysilane over Silia*Cat* Pt(0) under Different Reaction Conditions[a] [Copyright 2013 American Chemical Society]

Entry	Substrate	Catalyst (mol%)	Solvent (M)	T (°C)	Time (h)	Conv. (%)	Select. (%)	Pt leaching (mg/kg)[b]
1	$C_{15}H_{31}$ allyl	1	Toluene (0.5)	22	1 2 3	12 26 35	>95%	-
				40	1 2	88 100	ca. 65	-
				65	1	100	ca. 65	6
		0.5	Toluene (0.5)	65	1	100	ca. 50	5
				90	1 3 5	100	ca. 50	6
		1	Toluene (2.0)	40	1 3 5	85 97 99	ca. 80	-
2	OEt / OEt	1	Toluene (0.5)	65	1	100	100	25
		0.5		65	1 3	86 100	100 100	9
3	(ketone)	0.5	Toluene (0.5)	65	3	100#	100	-
		1	DCM (0.5)	22	1 3 5 23	30 36 33 100	100 100 100 100	-
4	(styrene)	0.5	Toluene (0.5)	65	1 3 5	60 80 86	100 100 100	16
5	C_8H_{17}	1	Toluene (0.5)	22	1 3 5 24	41 45 52 84	81 85 88 75	-
		0.5		60	1	100	68	12

[a]Experimental conditions: 2 mmol substrate, 30% molar excess of triethoxysilane in toluene solvent (HPLC grade, 0.5 M in substrate) under Ar, Silia*Cat* Pt(0) amount as shown in Table, T = 65 °C. [b]For the leaching test after reaction completion the reaction mixture was filtered, and the solvent evaporated. The crude product was directly analyzed by ICP-MS to determine the leaching of Pt (1 g crude product in 10 mL of DMF, 100 mg/mL concentration).

Table 12. Catalytic Hydrosilylation of 1-Octene with Triethoxysilane over Silia*Cat* Pt(0) at a Different Reaction Scale[a] [Copyright 2013 American Chemical Society]

entry	substrate	solvent	time (h)	conv. (%)	selectivity (%)	yield S (%)	isolated yield crude/purity
1	1-octene 5 mmol	toluene 0.5 M	1	82	84	69	
			3	93	82	76	
			5	95	80	76	
2	1-octene 50 mmol	toluene 0.5 M	1	93	77	72	7.4 g/90%); yield: 53%
			3	99	81	80	
3	1-octene 100 mmol	toluene 0.5 M	1	82	77	62	14.7 /(95%); yield: 53%
			3	97	81	68	

[a]Experimental conditions: mmol substrate as shown in Table, 30% molar excess of triethoxysilane in toluene solvent (HPLC grade, 0.5 M in substrate) under Ar, Silia*Cat* Pt(0) 0.5 mol %, T = 65 °C.

Scheme 3. Organosilica Sol−Gel Encapsulating the TEMPO Moiety in SiliaCat TEMPO Plays a Crucial Role in Ensuring Both Selective Activity and Prolonged Stability in the Anelli-Montanari Alcohol Oxidative Conversion [Copyright 2007 American Chemical Society]
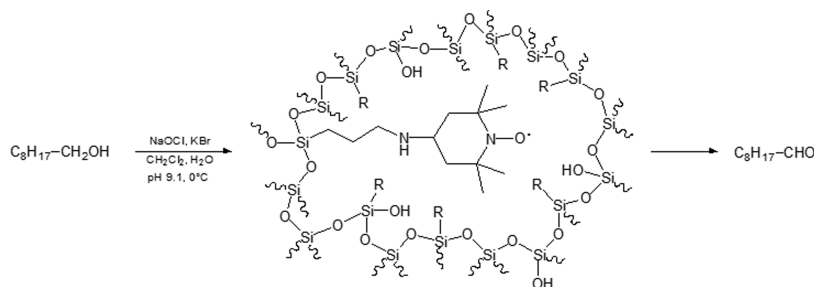

using the TEMPO radical coupled to bleach at low temperature (the Anelli−Montanari protocol) in replacement of obsolete stoichiometric processes using large amounts of highly toxic Cr(VI) or pyridine·SO_3.[58]

The sol−gel entrapped catalyst Silia*Cat* TEMPO[8] for the selective oxidation of delicate substrates into valued carbonyl derivatives (Scheme 3) was the first example of an ORMOSIL-entrapped catalyst commercialized after the organosilica-entrapped lipases developed by Reetz and co-workers in the mid 1990s.[59] The heterogeneous reaction allows easy product isolation from the catalyst, while the broad scope of the catalyst applicable to the conversion of several structurally different alcohols in different reaction media makes it ideally suited for practical application. A number of valued (benzyl, allylic, aliphatic) aldehydes[60] or α-hydroxy-[61] and even aminohydroxy[62] acids can be easily synthesized over Silia*Cat* TEMPO with greater yields and selectivity, compared to those resulting from classical reaction with homogeneous TEMPO.

Further expanding the catalytic technology and willing to replace hypochlorite as primary oxidant (which may afford formation of unwanted chlorinated byproducts)[63] with aqueous H_2O_2 (shown by Cao and co-workers to be far better in alcohol oxidation over Au/TiO_2 when compared to O_2),[64] Silia*Cat* Au, a new sol−gel-entrapped catalyst entrapping gold nanoparticles, recently showed excellent selective activity under base-free conditions.[65]

Following ideal performance in the model oxidation of 1-phenylethanol in water at 90 °C with 5% H_2O_2 added dropwise, the catalyst has further demonstrated the expected broad scope of application (Scheme 4),[67] with conversion in good to excellent yields of various structurally different primary and secondary alcohols, including nonactivated aliphatic alcohols, being oxidized to the corresponding carboxylic acids and ketones.

Once again, indeed, the mesoporous structure of organically modified silica matrices allows excellent diffusion of the reactants and reaction products to and from the encapsulated Au NPs.

Scheme 4. Carrying out the Base-Free Cao's Oxidation of Alcohols with Aqueous H_2O_2 over Silia*Cat* Au Eliminates All Waste at the Source, Affording High Yields of Valued Carbonyl or Carboxyl Compounds [Reprinted in Part with Permission from Ref 66, Copyright 2009 Royal Society of Chemistry]
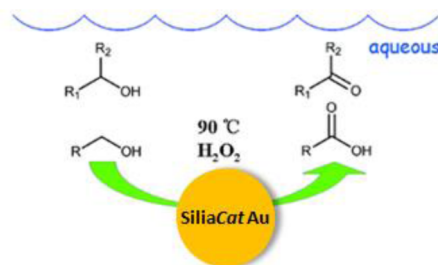
This process is particularly suitable for application in the pharmaceutical and fine-chemical industries because it does not require the use of oxygen gas in the presence of flammable organic solvents (a significant safety hazard).[68] This feature, coupled to excellent selective activity, broad synthetic scope and unique stability of the leach-proof catalyst, opens the route to ton-scale clean synthesis of carbonyl compounds and aliphatic acids using gold catalysis under organic solvent-free conditions.

■ **PERSPECTIVES AND CONCLUSIONS**

In a recent insight on today's chemical science and its connections with industry and government, Whitesides suggests that the old model of chemistry will not work in the years ahead in this century.[69] New generations, according to this viewpoint, will have to reinvent chemistry to integrate it with other disciplines such as biology, engineering, and nanoscience, to solve complex problems of large societal impact such as to develop renewable energy technologies and new, cleaner chemical manufacturing.

The development of heterogeneously catalyzed processes that eliminate waste at its source, we argue herein, is one notable example of this change currently taking place in chemistry. Catalyst development, to paraphrase Lee and co-workers, is no longer looked upon simply in terms of optimizing atom efficiency, but as a clean technology where all aspects of the overall process design (choice of solvent, methods of catalyst separation, waste disposal, batch or continuous process, etc.) are taken into account.[70]

Sol−gel encapsulated catalysts such as the SiliaCat materials partly reviewed in this account are one effective and versatile technology to streamline and greatly reduce the environmental impact of synthetic organic chemistry applied to specialty chemicals and drugs synthesis. These materials can directly replace homogeneous catalysts in stirred batch reactors and be recovered simply by filtration. Yet, the physically robust and highly accessible mesoporous silica framework of the SiliaCat matrix renders these catalysts ideally suited for continuous applications.

The technology has been used to synthesize numerous APIs, such as that required for valsartan manufacturing, as well as anilines, cis-only hydrogenated fatty acids, silanes, aldehydes, ketones, and carboxylic acids of high practical relevance, showing in each case exceptional results in increasing activity and selectivity against polyfunctionalized substrates.

One might wonder if the cost of these materials might constitute a barrier. Quite to the contrary, the use of these recyclable, long-life materials allows to compensate for the continuously rising price of noble metals such as Pt or Pd.[71] As put it by Alcázar referring to SiliaCat DPP-Pd, "the catalyst costs less than other commonly used palladium sources, such as palladium acetate or Pearlman's catalyst".[28]

It is also relevant here to notice that when the first supported homogeneous catalysts and the first scalable processes for fine chemistry became available, roughly one decade ago, industry readily showed its interest. However, as remarked by an industry's practitioners at a large pharmaceutical company,[72] the regulatory authorities have been a barrier for continuous processes within the pharmaceuticals industry. Only recently, authorities have become scientifically convinced that the quality of APIs obtained (at lower cost and far reduced environmental impact) via continuous processes is intact, and within the defined and validated range in terms of purity.

Contrary to mainstream belief, indeed, Chinese regulatory standards for APIs and drugs production are actually more restrictive than those in the US or Europe, specifying even what type of equipment manufacturers need to use.[73] Changing manufacturing processes, and switching to heterogeneous catalysts, preferably under flow, requires a great deal of effort well beyond the purely technical aspects. Now, however, this is gradually changing as it has become possible to argue for efficient and continuous processes due to the fact, to quote again the above industry practitioner at a major pharmaceutical company, "it is in the authorities' own interests, for cost and environmental reasons".[73]

The present summary including the multipurpose applications of the SiliaCat catalysts may assist in the practical green evolution of this central segment of the global chemical industry.

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