Heterogeneous Catalysis

SiliaCat® Silica-Supported Catalysts

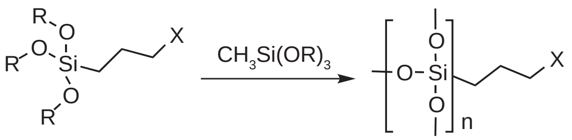
Catalytic Reactions with Silia*Cat*®

Advantages of using Silia*Cat* heterogeneous catalysts over traditional methods include:

- High stability and accurate loading
- Rigid & porous structure
- Compatibility with a wide range of solvents
- Ease of use: no swelling or static charge
- Minimal leaching
- Fast kinetics

The Silia*Cat* Matrix

Inspired by the ORganically MOdified SILica (*ORMOSIL*) technology, the Silia*Cat* family is composed of new and innovative catalysts. Resulting from the co-condensation of two organosilane monomers by the sol-gel process, the hybrid organic-inorganic materials present the highest stability and reactivity available with heterogeneous catalysts. Furthermore, the highly cross-linked framework presents a better resistance compared to post-functionalization process.

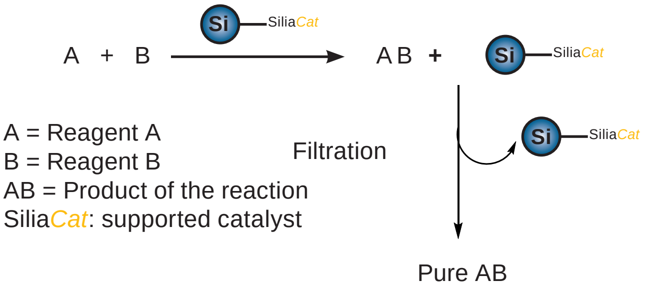


X = DPP, TEMPO

What is Silia*Cat* Heterogeneous Catalyst?

Usually, heterogeneous catalysts supported on a silica matrix are immobilized by post-modification of the inorganic support. These supports, however, present a high degree of leaching due to the poor stability of the immobilized phase. For example, with Silia*Cat* the ligand is directly cross-linked in an organic-inorganic framework. This results in a high degree of stability of the catalysts. Compared to homogeneous catalysts, Silia*Cat* exhibits a good reactivity and selectivity with one of the major advantages being that the catalyst is eliminated from the reaction mixture by a simple filtration. Forget your purification problems with our Silia*Cat* catalysts family.

What is Silia*Cat* Heterogeneous Catalyst?



A = Reagent A
B = Reagent B
AB = Product of the reaction
Silia*Cat*: supported catalyst

Features and Benefits of Silia*Cat* Catalysts

Features & Benefits of Silia*Cat*

Features	Benefits
Reagent concentrated at the surface of the material	Reproducible synthesis with high conversion and yield
Robustness	High thermal and mechanical stability
Rigid and porous structure	No swelling, solvent independent and air stable (*no inert conditions required*)
Minimal leaching of organoceramic matrix	Easier purification
High and accurate catalyst loading	Less catalyst required over competitive products
High turnover number (*TON*)	Low catalytic amount required (< *1 mol %*)
Reusability	Multi-uses possible
Ease of handling and purification	Free flowing, no static charge Easily removed by simple filtration
Ease of scalability	Scalable from mg up to multi-ton scale
Available in bulk quantities	Can be delivered in large quantities and always in stock

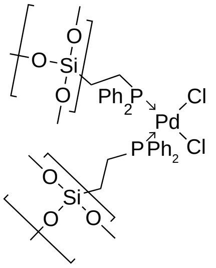
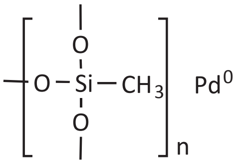
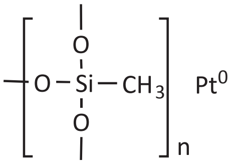
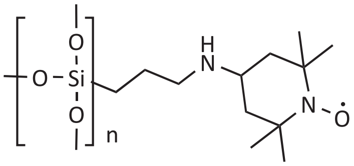
Silia*Cat*: A Versatile Catalyst Series for Organic Chemistry

Silia*Cat* catalysts can be used in a wide range of applications, and to manufacture products such as active pharmaceutical ingredients (*API*), *cis*-only hydrogenated fats, silanes, anilines, fragrances and emollients.

Silia*Cat*
a Versatile Catalyst Series
for Synthetic Organic Chemistry

- Multiple C-C cross coupling reactions (*Suzuki-Miyaura, Mizoroki-Heck, Sonogashira, etc.*)
- Selective oxidation of alcohols to carbonyls or carboxylic acids
- Highly efficient continuous flow C-C for cross coupling and oxidation reactions
- Full hydrogenation of terpenes
- Chemoselective hydrogenation of nitroarenes
- Isomerization-free hydrogenation of vegetable oils

SiliaCat Heterogeneous Catalysts Product Range

SiliaCat Heterogeneous Catalysts Portfolio			
SiliaCat Name	**Product Number**	**Structure**	**Brief Description**
SiliaCat DPP-Pd	R390-100		SiliaCat DPP-Pd is a unique diphenylphosphine palladium (II) heterogeneous catalyst made from a leach-resistant organoceramic matrix.
SiliaCat Pd⁰	R815-100		SiliaCat Pd⁰ is a new series of patent-protected sol-gel-entrapped Pd nanocatalysts. It is made from highly dispersed Pd nanoparticles (*uniformly in the range 2.0 - 6.0 nm*) encapsulated within an organosilica matrix. It is a safer alternative for hydrogenation over Pd/C.
SiliaCat Pt⁰	R820-100		SiliaCat Pt⁰ is made of organosilica physically doped with nanostructured platinum (0), and is both stable and efficient. Pt nanoparticles (*uniformly in the range 1.5 - 6 nm*) are encapsulated via an alcohol-free sol-gel process typical of enzyme sol-gel encapsulation.
SiliaCat TEMPO	R723-100		SiliaCat TEMPO is an oxidizing catalyst made from a proprietary class of organosilica-entrapped radicals. This encapsulation process confers enhanced reactivity and properties. The leach-resistant organoceramic matrix makes SiliaCat TEMPO highly efficient and selective compared to homogeneous TEMPO. It also has a superior performance compared to polymer-supported TEMPO in terms of both selectivity and stability. With SiliaCat TEMPO, no activation is required prior to use and selective aldehyde vs acid oxidation is possible.

All catalysts are available in the following format sizes:
5 g, 10 g, 25 g, 50 g, 100 g, 250 g, 500 g, 1 kg, 5 kg, 10 kg, 25 kg, etc.

Silia*Cat* Heterogeneous Catalysts Portfolio

Typical Applications	Silia*Cat* Typical Characteristics						Silia*Cat* Name
	Color	Endcapping	Loading / Metal	Typical Tap Density	Solvent Compatibility	Prolonged Storage	
Suzuki, Heck, Negishi, Borylation, Sonogashira, Kumada, Stille	Orange	Yes	0.2 - 0.3 mmol/g (*2.1 - 3.2 % Pd*)	0.300 - 0. 400 g/mL	All solvents, aqueous and organic	Keep Cool (< *8°C*) and dry	Silia*Cat* DPP-Pd
Selective debenzylation, Selective hydrogenation, Suzuki, Heck Sonogashira, Kumada, Stille	Black	Yes	0.2 - 0.3 mmol/g (*2.1 - 3.2 % Pd*)	0.300 - 0. 400 g/mL	All solvents, aqueous and organic	Keep Cool (< *8°C*), dry and under argon	Silia*Cat* Pd^0
Selective reduction of nitroarenes, Hydrosilylation	Black	Yes	0.15 - 0.25 mmol/g (*2.9 - 4.9 % Pt*)	0.300 - 0. 400 g/mL	All solvents, aqueous and organic	Keep Cool (< *8°C*), dry and under argon	Silia*Cat* Pt^0
Oxidation of alcohols or aldehydes	Orange	Yes	≥ 0.70 mmol/g	0.550 - 0.650 g/mL	All solvents, aqueous and organic	Keep Cool (< *8°C*) and dry	Silia*Cat* TEMPO

Available Kits

Because all reactions are unique, and that small differences can influence the catalysis efficiency, doing a screening is often recommended, especially if you are new to this technology. This is why we created a special kit containg our four catalysts.

This kit is available in 5 g, 10 g, 25 g, 50 g and 100 g formats (*custom formats are also available, contact us for more details*).

Silia*Cat* Heterogeneous Catalysts Kit

Kit Name	Kit PN	Composition
Silia*Cat* Heterogeneous Catalysts Kit	K305-100	DPP-Pd, Pd^0, Pt^0 & TEMPO

Catalyst Services

CONFIDENTIALITY GUARANTEED

You can take advantage of SiliCycle's expertise in catalysis and our R&D team can assist you in your catalysis challenges. Our Catalyst Services provide a turnkey solution with an easy technology transfer.

Working with the substrates you identify, our chemists can quickly develop the most efficient catalysis process or optimize an existing one, test the feasibility of a new one, understand metal-catalyzed reaction, etc.

As a catalyst designer & manufacturer, our skilled and competent catalysis group can investigate any reaction parameter (*catalyst nature and loading, solvent, ligand, base / additive nature, concentration, temperature, time, etc.*) to maximize yields and purities as well as to reduce waste and cost.

Our most popular catalysis services include the following:

- Catalyst evaluation, testing and screening services
- Catalytic process optimization
- Scale-up of catalytic reactions
- Tailor-made catalyst development to fit your requirements
- Scavenging of residual metal catalyst

Contact us to discuss how we can help you reach your goals.

Silia*Cat* - Regulatory Information

Silia*Cat* are more and more used in GMP pharmaceutical, biotechnology and fine chemical industries as well as contract research and manufacturing organizations. Many have run their own analysis proving Silia*Cat* can safely be used without compromising the purity of their compounds.

SiliCycle is committed to high quality standards and strives to provide default-free products. All products are manufactured in an ISO 9001:2008 compliant facility and submitted to stringent quality control. Every lot must meet the quality specifications to be released and a sample from every batch is stored as reference for subsequent analysis. All products are shipped with the following information:

- Certificate of Analysis
    - Purity (*leachables and extractables*)
    - Molecular loading of active metal
    - Surface coverage
    - Volatile content
- Material Safety Data Sheets (*MSDS*)
- Relevant technical information

Note: BSE / TSE Declaration (*no animal origin*) available under request.

Need specific data for your regulatory files?
SiliCycle can work with you to fulfill your requirements.
We can provide custom regulatory documentations that include specific analytical tests in line with your needs.

Beyond the Basics

This section is a step-by-step guide for the most common technical questions that you might have when using our Silia*Cat* catalysts in your synthesis.

Every catalyst is different and the way you use it has an influence on the performance. It is highly recommended to use our typical experimental procedure presented at the end of each reaction as a starting point from which you can optimize conditions for optimum yields & purity in your own experimental conditions.

If you want we can determine for you the best conditions for your reaction in our labs with our catalyst services.

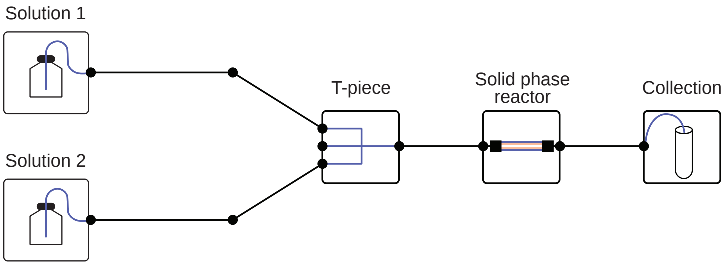
If you need a custom supported-catalyst to run your synthesis, we can also develop it for you.

Compatibility with Different Technologies

Silia*Cat* Catalysts in Flow Chemistry

Silia*Cat* works wonders in flow chemistry as it is non-leaching, very stable & will last for many runs. Simply place the heterogeneous catalyst inside the solid-phase reactor provided with your flow system (*e.g.: in a Syrris Asia® Solid Phase Chemistry Reactors*) and letting the catalytic reaction run. Multiple reactors can be placed in serie and can be heated to obtain optimum conversions and yields.

Please refer to the applications presented in the following section identified with this logo for various examples. Detailed experimental procedure are described inside each publication.



Silia*Cat* Catalysts in Microwave-Assisted Chemistry

Reactions catalyzed with Silia*Cat* can also be done under microwave irradiation to provide excellent yields in just minutes. Add all products listed for each procedure (*see following pages*) to a microwave tube equipped with a magnetic stirrer and set microwave conditions to:

- Power: 150 W
- Pressure: 150 psi
- Temperature: 75 - 150°C
- Reaction Time: 5 - 15 min

Some optimization can be required but these settings are a good starting point. Use the same work-up conditions provided for each procedure.

Applications developed in microwave are identified by this logo (*refer to related publications for details*).

Typical Apparatus

Under Magnetic Stirring
for Screening or Small-scale Synthesis

Advantages	Disadvantages
• Very small scale • Screening tests	• Possible catalyst attrition due to grinding • Possible metal leaching

Typical apparatus:
100 mL three-neck round-bottom flask equipped with a condenser, a magnetic stir bar and a digital temperature controller.

Under Mechanical Stirring
for Reusability or Large-scale Synthesis

Advantages	Disadvantages
• Superior catalyst reusability • Catalyst morphology is not altered, easily removed by filtration	• Higher quantity of reagents needed (*half of the flask needs to be filled with solvent*)

Typical apparatus #1:
100 mL three-neck round-bottom flask equipped with a condenser, a mechanical stirrer and a digital temperature controller.

Typical apparatus #2:
High pressure reactor (*bomb reactor*) for **hydrogenation** reactions.

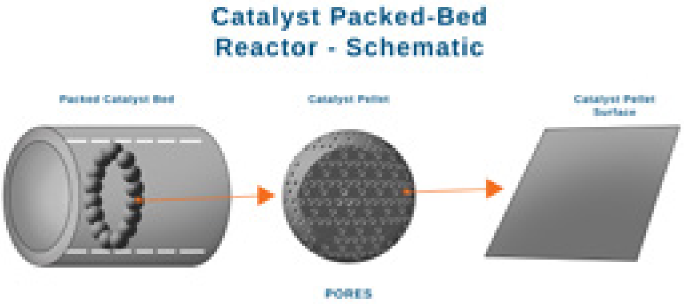
Heterogeneous Catalytic Reactions Basics

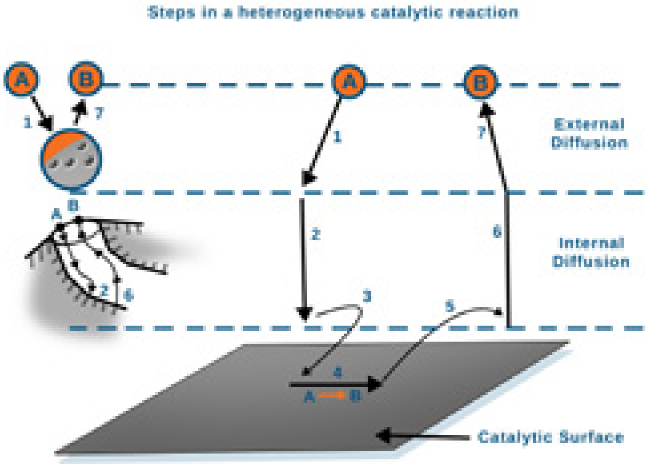
To maximize reaction rate on a porous catalyst, it is essential to maximize accessibility of all reactants to the active catalytic sites, which are dispersed through the internal pore structure of the catalyst.

Imagine a reactant **A** flowing through a bulk liquid and a bed of a heterogeneous catalyst and reacting on the catalytic surface to form a species **B**.

Schemes at right present the physical and chemical steps that must occur to **A** to convert to **B**:

1. Mass transfer (*diffusion*) of the reactant(*s*) (*e.g. species A*) from the bulk liquid and a separate liquid film surrounding each suspended catalyst particle to the external surface of the catalyst particle.
2. Diffusion of the reactant from the pore mouth through the catalyst pores to the immediate vicinity of the internal catalytic surface.
3. Adsorption of reactant A onto the catalyst surface.
4. Reaction on the surface of the catalyst (*e.g.* $A \rightarrow B$).
5. Desorption of the products (*e.g. B*) from the surface.
6. Diffusion of the products from the interior of the pellet to the pore mouth at the external surface.
7. Mass transfer of the products from the external pellet surface to the bulk fluid.





Application Notes and Case Studies

We have selected a few applications to help you understand how our catalysts can be introduced in your daily synthesis routine.

Application Notes

You can read through our “Application Notes” section to learn more about different SiliCycle applications that were developed in our labs.

In the following section, applications notes are identified by this logo:

Case Studies

Don’t take our word for granted. Discover and learn what some of our customers are doing with our heterogeneous catalysts in the “Case Studies” section. Visit regularly our website to get the entire publication portfolio available.

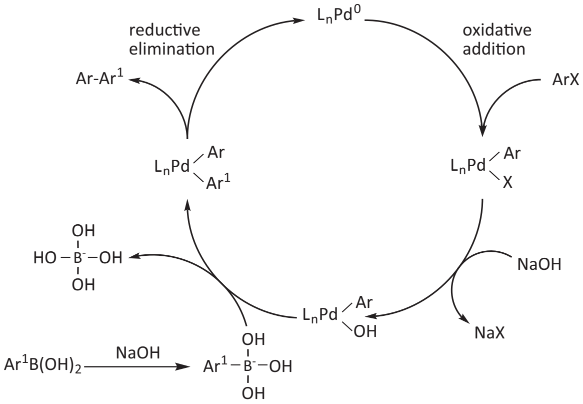
In the following section, customers’ case studies are identified by this logo:

Nothing speaks more than lab examples!

Suzuki Coupling Using Pd-based Silia*Cat*

The Suzuki coupling (*also called Suzuki-Miyaura reaction*) is the reaction between a boronic acid and a halide, catalyzed by a palladium (0) catalyst. At first, only aryl and vinyl substrates could undergo Suzuki coupling. Now, catalysts are becoming so powerful that the substrate scope has broadened to include: alkyl-, alkenyl- & alkynyl-halides, triflates and organoboranes, trifluoroborates or borate esters.

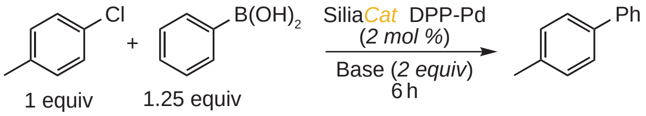
Note: detailed experimental procedure can be found at page 36.



Solvent and Base Effects

The choice of solvent and base play an important part in the Suzuki reaction. Different solvents and bases were tested to find the most suitable combination. Total conversion was obtained in both ethanol and propanol. With THF, dioxane, toluene and DMF, the kinetics were lower.

As for the base, potassium carbonate (K_2CO_3) is the best. However, in some cases, sodium carbonate (Na_2CO_3) and sodium acetate (*NaOAc*) can also be used.



Solvent and Base Effects

Solvent	Temp. (°C)	Conversion / Selectivity (%)					
		K_2CO_3	Na_2CO_3	KOAc	NaOAc	K_2HPO_4	Et_3N
MeOH	64	74 / 95	69 / 99	63 / 98	63 / 98	73 / 100	72 / 93
EtOH	77	100 / 98	100 / 97	82 / 99	85 / 100	79 / 100	77 / 93
EtOH / H_2O (*15 %*)	77	100 / 100	82 / 100	78 / 100	88 / 100	86 / 98	89 / 95
1-PrOH	90	100 / 95	70 / 97	90 / 99	91 / 99	15 / 100	20 / 95
2-PrOH	77	100 / 100	43 / 93	90 / 99	72 / 100	50 / 100	20 / 100
THF	64	30 / 93	15 / -	45 / 89	35 / 94	37 / 95	5 / -
MeTHF	77	40 / 95	33 / 100	39 / 100	56 / 100	30 / 97	4 / -
Dioxane	90	50 / 90	30 / 93	56 / 93	35 / 94	20 / 90	No reaction
Toluene	90	47 / 98	23 / 87	49 / 96	10 / 90	65 / 95	No reaction
DMF	90	50 / 100	30 / 100	15 / 100	17 / 100	7 / 100	No reaction

Catalyst Concentration Effect

Decreasing the mol % of the Pd catalyst lowers the kinetics of the reaction, but the total conversion can still be achieved by increasing reaction time.

In this example, the addition of water significantly improves catalyst activity even if the catalyst amount is reduced significantly.

(*Conditions: PhB(OH)$_2$ (1.1 equiv), K_2CO_3 (1.5 equiv) RT*).

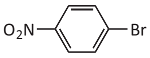
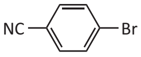
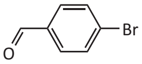
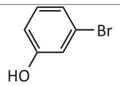
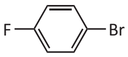
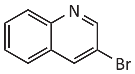
Silia*Cat* DPP-Pd Concentration Effect

mol % Pd	Molar Concentration (*M*)	Time (*h*)	Conv. (*%*)
0.2	EtOH (*0.05*)	0.5	100
0.1	EtOH (*0.05*)	1	100
0.01	EtOH / H_2O (*0.08*)	2	100
0.002	EtOH / H_2O (*0.08*)	16	100

Pd-Based SiliaCat Catalytic Performance Comparison and Reusability

The table below presents the best conditions for bromo-substrates. It can be seen that even with half the catalyst amount, Silia*Cat* Pd⁰ is the most active catalyst. For substrates with electron-withdrawing groups, Silia*Cat* can be reused more than 5 times with a minimal leaching and loss of activity. For substrates containing an electron-donating group, Silia*Cat* can be used up to 3 times with only a small effect on activity. The reaction can also be done using boronic acid pinacol esters.

Pd-Based Silia*Cat* Catalytic Performance Comparison and Reusability

	Substrate (*R*)	Silia*Cat* Performance Comparison [*Conversion / Selectivity (%)*]		Reusability [*Conversion / Selectivity (%)*] Pd & Si Leaching (*ppm*)[1]			
		DPP-Pd (*1 mol %*)[a-b]	Pd⁰ (*0.5 mol %*)[c]	Run 2	Run 3	Run 4	Run 5
Electron-Withdrawing		100 / 100 Pd: 0.1, Si: 2	100 / 99	100 / 100 Pd: 0.05, Si: 1	100 / 100 Pd: 0.08, Si: 1.5	100 / 100 Pd: 0.1, Si: 3	99 / 98 Pd: 0.1, Si: 3.5
		100 / 97 Pd: 0.1, Si: 3	99 / 97	98 / 99 Pd: 0.1, Si: 8	98 / 99 Pd: 0.07, Si: 5	100 / 99 Pd: 0.1, Si: 6	99 / 98 Pd: 0.1, Si: 5
		100 / 97 Pd: 0.1, Si: 6	95 / 98	99 / 90 Pd: 0.2, Si: 7	97 / 92 Pd: 0.2, Si: 8	99 / 98 Pd: 0.1, Si: 4	98 / 97 Pd: 0.1, Si: 5
Electron-Donating		100 / 99 Pd: 0.9, Si: 5	83 / 100	100 / 100 Pd: 0.6, Si: 9	100 / 98 Pd: 0.4, Si: 7	60 / 97 Pd: 0.05, Si: 6	-
		100 / 80 Pd: 0.07, Si: 3	98 / 99	99 / 99 Pd: 0.04, Si: 1.5	98 / 98 Pd: 0.1, Si: 2	81 / 94 Pd: 0.06, Si: 2	73 / 95 Pd: 0.03, Si: 7
		100 / 99 Pd: 2.1, Si: 10	97 / 95	88 / 90 Pd: 0.3, Si: 7	75 / 95 Pd: 4, Si: 9	87 / 99 Pd: 0.6, Si: 10	68 / 96 Pd: 04, Si: 11

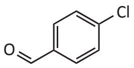
[a] Corresponds to "Run 1" in the reusability study.
General exp. cond.: 1 equiv substrate, 1.2 equiv $PhB(OH)_2$, 2 equiv K_2CO_3;
[b] MeOH (*0.1 M*), 2 h, 65°C;
[c] EtOH (*0.12 M*) 2 h, 77°C.

[1] Using Silia*Cat* DPP-Pd as catalyst under the same conditions previously described. Run #1 is the result presented in the performance comparison section of the table.

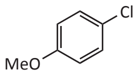
Suzuki Coupling in Microwave and Flow Chemistry

The performance of Silia*Cat* DPP-Pd for Suzuki coupling was also compared in microwave assisted experiments for brominated and chlorinated substrates. After only 5 minutes, 100 % of the product is obtained in most experiments with excellent selectivities.

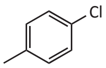
The Silia*Cat* DPP-Pd can also be used for Suzuki coupling with chlorinated substrates in both conventional and microwave conditions. Conversion and yield (*in %*) results are presented below.



Conv.: 98 %
Yield: 93 %

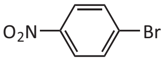
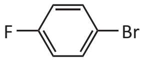
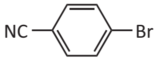
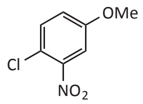
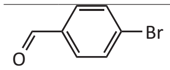


Conv.: 98 %
Yield: 96 %



Conv.: 99 %
Yield: -

Catalytic Performance in Microwave (*MW*)

Substrate	Conversion / Yield (%)	Substrate	Conversion / Yield (%)
	100 / 99.5		98 / 97.3
	100 / 99.4		Batch: 100 / 98
	100 / 88		MW: 100 / 95

General exp. cond.: 0.5 mol % of Silia*Cat* DPP-Pd, 1 equiv substrate, 1.1 equiv $PhB(OH)_2$, 1.5 equiv K_2CO_3; [a] MeOH (*0.2 M*), 5 min, 75°C, 150 W, 150 psi; [b] MeOH (*0.2 M*), 5 min, 75°C, 200 W, 200 psi

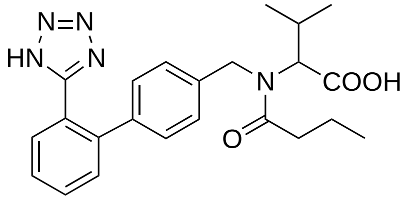
Suzuki Coupling in Flow Chemistry

The Suzuki coupling in flow chemistry was also investigated on various substrates using the Silia*Cat* DPP-Pd with diluted and more concentrated solutions. Usually, complete conversion is obtained in less than 3 min, whereas the analogous conversion under batch requires up to 6 h.

Reactions were scaled-up from 6 mmol up to 275 mmol with high conversions and selectivities. For all results and substrate scope, please consult the following publication: *Org. Proc. Res. Dev.*, **2014**, *18,* 1550-1555

Greening the Valsartan Synthesis Using SiliaCat DPP-Pd

Angiotensin receptor blockers such as valsartan (*also called Diovan*) belong to a relevant therapeutic class called sartans, widely employed since the late 1980s to treat high blood pressure and congestive heart failure.

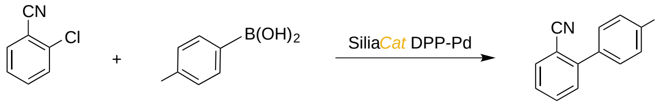


Valsartan

The Valsartan patent expired in 2012, opening the route to the introduction of generic alternatives. This section presents the study of the heterogeneous Suzuki-Miyaura coupling reaction in batch conditions between 2-chlorobenzonitrile and 4-tolylboronic acid, a key step in valsartan synthesis, to produce 4′-methyl-2-biphenylcarbonitrile over the SiliaCat DPP-Pd catalyst in ethanol under reflux.
See *Tet. Letters*, **2013**, *54*, 4712-4716 for all details.

Solvent Concentration and Base Effects

Different concentrations of aryl halide were tested over 1 mol % of SiliaCat DPP-Pd, with the aim to identify the optimal molar concentration required for the scale-up.



Complete conversion was obtained after 30 min for concentration from 0.12 M to 1 M. Raising the concentration to 1.5 M resulted in 92 % aryl halide conversion after 1 h (*increase in the viscosity of the reaction which results in diffusion problem*).

Different bases (*K_2CO_3, Na_2CO_3, $NaOAc.3H_2O$, KOAc, NaOH, KOH, $KHCO_3$*) were tested and potassium carbonates were by far the most suitable ones.

Conditions: 2-chlorobenzonitrile (1 equiv), 4-tolylboronic acid (1.1 equiv), Base (1.5 equiv), SiliaCat DPP-Pd (1 mol %)

Solvent Concentration and Base Effects

Base (*1.5 equiv*)	Conc. (*M*)	Time (*h*)	Conv. / Yield (*%*)
K_2CO_3	0.12 / 0.25 / 0.5	0.5	100 / 98
	1.0	0.5	100 / 99
	1.5	0.5	81 / 99
		1.0	92 / -
$KHCO_3$	0.5	0.5	100 / 99
	1.0	1.0	85 / 99

Reaction Scale-Up

Using the established optimized conditions, the reaction was scaled up from 6 to 720 mmol of aryl halide. Even if the amount of aryl halide was increased to 720 mmol, complete conversion was obtained. At that scale, the quantity of catalyst can also be decreased for cost consideration.

Conditions: 2-chlorobenzonitrile (1 equiv), 4-tolylboronic acid (1.01 equiv), K_2CO_3 (1.1 equiv), SiliaCat DPP-Pd, EtOH (0.5 M)

Reaction Scale-Up Results

Aryl Halide scale	Catalyst (*mol %*)	Time (*h*)	Conv. / Yield (*%*)
6 mmol (*0.8 g*)	1	0.5	100 / 98.0
72 mmol (*10 g*)	1	0.5	100 / 97.5
360 mmol (*50 g*)	1	0.5	100 / 97
720 mmol (*100 g*)	0.7	1	100 / 98

Reaction Scope

To investigate the scope of the method, reactions were done using the following protocol: 1 equiv of aryl halide, 1.1 equiv of 4-tolylboronic acid, 1 mol % SiliaCat DPP-Pd, 1.5 equiv of K_2CO_3 in EtOH (*0.5 M*) under reflux. Several aryl halides with electron with drawing (*nitrile and carbonyl*) or electron-donating (*methoxy, methyl, phenol and amine*) groups along with various heterocycle aryl halides (*such as pyrazole, pyridine, indole and quinoline*) were tested.

The results show that usually more than 90 % yields were obtained after 0.5 - 2 h, except for the aryl halides in entries 8 and 12, which required 2 mol % catalyst to achieve more than 80 % yield.

We also found that the position of the functional group had an influence on the reactivity. For example, with a nitro in ortho position (*entry 6, 4-chloro-3-nitroanisole*), complete conversion was obtained after 2 h over 1 mol % catalyst, whereas in meta position (*entry 7, 4-chloro-2-nitroanisole*) gave only 53 % yield after 2 h (*the amount of the biphenyl product generated was significant*). To increase the conversion in the desired product, 2 equiv of 4-tolylboronic acid was needed to achieve 81 % yield after 2 h.

Steric hindrance of aryl halides (*entries 5 and 14*) does not affect conversion, with almost complete conversions obtained after 0.5 - 2 h over 1 mol % of SiliaCat DPP-Pd.

Conclusion

The study of the scale-up (*from 1 to 100 g of aryl halide*) of the heterogeneous Suzuki-Miyaura coupling reaction in batch between 2-chlorobenzonitrile and 4-tolylboronic acid over SiliaCat DPP-Pd catalyst at 77°C was succesfully achieved. We have also shown that the method is general, as it enables the heterogeneous conversion of an ample variety of different aryl halides.

Related Publications for Suzuki Coupling

Top. Catal., **2010**, *53*, 1059-1062

Catal. Sci. Technol., **2011**, *1*, 736-739

Org. Proc. Res. Dev., **2012**, *16*, 117-122

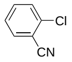
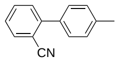
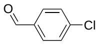
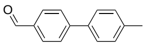
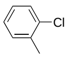
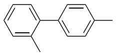
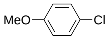
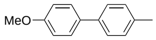
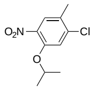
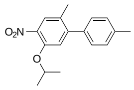
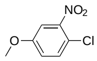
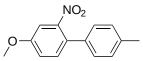
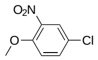
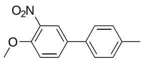
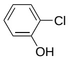
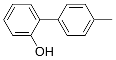
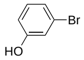
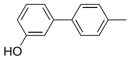
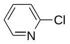
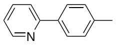
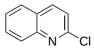
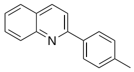
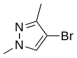
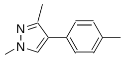
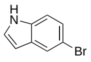
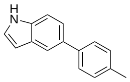
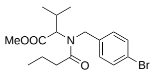
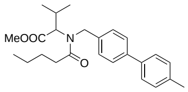
RSC Adv., **2012**, *2*, 10798-10804

Tet. Letters, **2013**, *54*, 1129-1132

Tet. Letters, **2013**, *54*, 4712-4716

Org. Proc. Res. Dev., **2013**, *17*, 1492-1497

Reaction Scope

Entry	Aryl halides	t (*h*)	Product	Yield (%)
1		0.5		100
2		2.0		92
3		2.0		100
4		2.0		95
5		0.5		99
6		2.0		97
7		2.0		81
8		2.0		88
9		0.5		100
10		2.0		95
11		2.0		100
12		2.0		90
13		2.0		91
14		1.0		99

Conditions: 1 equiv of Ar-X, 1.1 equiv of 4-tolylboronic acid, 1 mol % SiliaCat DPP-Pd, 1.5 equiv of K_2CO_3 in 0.5 M EtOH under reflux.

Comparison of Various Heterogeneous Pd-Catalysts

The effectiveness of Silia*Cat* DPP-Pd for the Suzuki coupling were investigated and compared with other catalysts (*heterogeneous and homogeneous*) available on the market. **It is very important to note that for all reactions, all catalysts were used in the manufacturer's optimized conditions and not just SiliCycle's** in order to be able to make relevant conclusions.

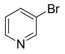
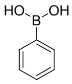
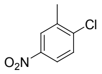
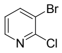
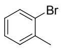
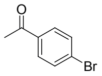
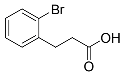
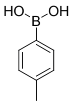
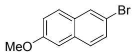
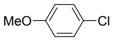
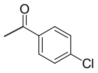
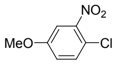
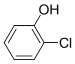
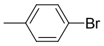
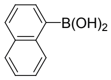
Note: results using EnCat40 are not presented here due to extremely low conversion obtained (< *10 %*).

Conclusion

In conclusion, for brominated compounds, Silia*Cat* DPP-Pd presents excellent results and compared favorably with a homogeneous catalyst. The PhosphonicS' catalyst was also effective, but showed heavy Pd leaching compared to Silia*Cat*.

For chlorinated compounds, Silia*Cat* was by far superior to all competing products.

Suzuki Coupling Conversion Comparison (*in %*)

Aryl Halide	Boronic Acid	Silia*Cat* DPP-Pd	FibreCat	PhosphonicS	$Pd(PPh_3)_4$
		**100**	0	**100**	87
		**98**	0	49	3
		**100**	0	81	**100**
		**100**	83	**100**	**100**
		**100**	**100**	**100**	96
		**100**	0	**100**	-
		**100**	5	51	68
		**95**	0	1	0
		**92**	0	14	1
		**97**	0	0	0
		77	0	1	0
		**93**	82	84	87

Experimental conditions

- Protocol with Silia*Cat* DPP-Pd was drawn from *Org. Proc. Res. Dev.*, **2013**, *17*, 1492-1497 [*1 mol % SiliaCat DPP-Pd; K_2CO_3; EtOH; 77°C; 30 min*]
- Protocol with PhosphonicS was drawn from *Journal of Molecular Catalysis A: Chemical*, **2008**, *293*, 25-28 [*0.1 - 0.2 mol % Si-ethylphosphatrioxaadamantane; EtOH:H_2O:DME (1:2:4); 130°C; 30 min*]
- Protocol for Johnson-Matthey FibreCat 1001 was drawn from *Topics in Catalysis*, **2008**, *48*, 91-98 [*1 mol % FibreCat 1001; K_2CO_3 / Toluene; 81°C, 2 h*]
- Typical protocol with the homogeneous catalyst: 1 mol % $Pd(PPh_3)_4$; K_2CO_3; EtOH / H_2O; 80°C; 30 min

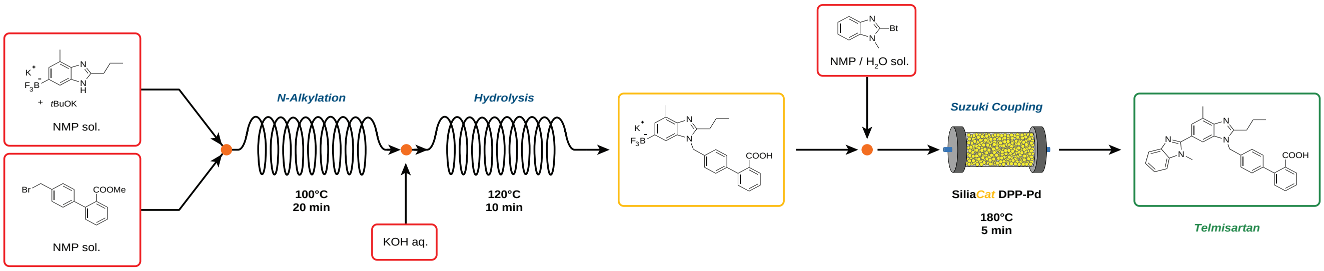
Case Study: Suzuki Cross-Coupling Using SiliaCat DPP-Pd in the Synthesis of Telmisartan

Authors: Gupton (*Virginia Commonwealth University*) *et al.*
Publication: *Org. Proc. Res. Dev.*, **2016**, *20*, 2-25

Overview

Telmisartan is the API present in the antihypertensive drug Micardis. It is an angiotensin receptor antagonist and, compared to other similar drugs, has several advantageous: longer half-life, higher protein binding affinity and lower daily dosage.

Gupton and co-workers developed a continuous flow convergent multistep synthesis of telmisartan which did not require any intermediate purification nor switch of solvent. Suzuki cross-coupling took place using SiliaCat as the metal catalyst, with a residence time of 5 min only. Upon acid-base workup, telmisartan was isolated in an overall yield of 81 % (*97 % HPLC purity*).



Conclusion

This fully automated process represents a significant improvement over traditional batch procedure since it reduces waste and unit operations.

Case Study: SiliaCat DPP-Pd in Suzuki Coupling for the Synthesis of Anti-Stroke Therapies Products

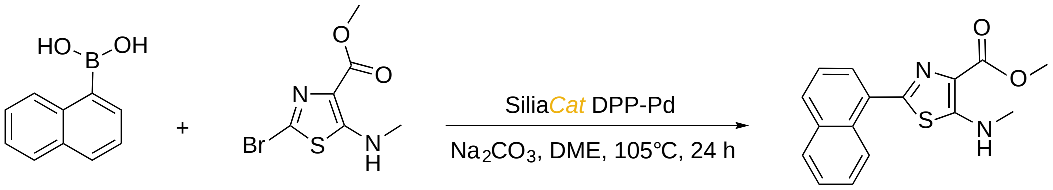
Authors: Leyen (*Massachusetts General Hospital*), Maloney (*NIH*), Holman (*University of California*) and coworkers
Publication: *Journal of Medicinal Chemistry,* **2014***, 57,* 4035-4048

Overview

Because of the broad implications of 12/15-Lipoxygenase (*12/15-LOX*) in stroke regulation, Leyen, Maloney, Holman and coworkers highlighted the need for small molecule inhibitors that could effectively cross the blood brain barrier.

Their 2014 publication represents the first report of a selective inhibitor of human 12/15-LOX with demonstrated in vivo activity in proof-of-concept mouse models of stroke.

In the synthesis of various analogues, one intermediate was prepared from 1-naphthyl boronic acid using a classical Suzuki reactions, which yield limited success. Yet, this same Suzuki coupling reaction much more successful using SiliaCat DPP-Pd under reflux conditions over 24 h.



Case Study: Suzuki-Miyaura Coupling Using Silia*Cat* DPP-Pd

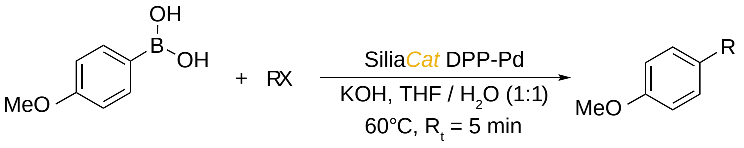
Authors: Alcázar (*Janssen Research and Development*) *et al.*
Publication: *Advanced Synthesis and Catalysis,* **2012**, *354*, 3456-3460

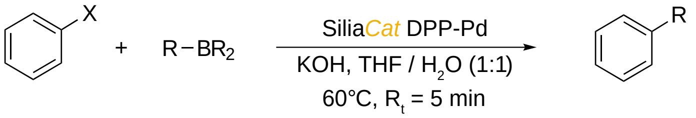
Overview

Alcázar's research group at Janssen Research and Development used Silia*Cat* DPP-Pd as a silica-supported catalyst to develop a mild, clean and high yielding procedure for Suzuki-Miyaura cross-coupling in a single pass. Silia*Cat* DPP-Pd could be used in more than 30 reactions and for more than 8 hours of continuous flow without any observed decrease in activity. This was possible due to the non-leaching nature of Silia*Cat* DPP-Pd. The lab team describes a reliable method, easily scalable, with commercially available instrumentation for mild and clean Suzuki-Miyaura coupling in single pass.

As stated in their publication: *"Within the field ot heterogeneous catalyst a broad range of solid supports were developed such as monolithic supports, polymer beads and PdEnCat™.* ***However swelling and denaturalization of the polymer supports, gradual leaching of the catalytic active palladium, the need to perform several passes through the catalyst to get full conversion, and the replacement of the cartridge after performing a limited number of reactions as well as the need to synthesize the supported catalyst in the cartridge limit their general use in organic and medicinal chemistry****"*.

The scope of the reaction was studied both between different aryl bromides and boronic acid, and between other boronic acids & organoboranes and boromobenzene or phenyltriflate.





Conclusion

In conclusion, the authors obtained good to excellent yields using Silia*Cat* DPP-Pd. Extremely low level of leaching were detected (*10 - 20 ppb in reaction*). They also reported that *"**silica-supported catalyst offer better chemical and thermal stability as well as rigid but porous structure devoid of swelling properties that makes it compatible with a range of solvents**."*

Case Study: Silia*Cat* DPP-Pd in the Synthesis of Organic Photovoltaics, using Suzuki Coupling

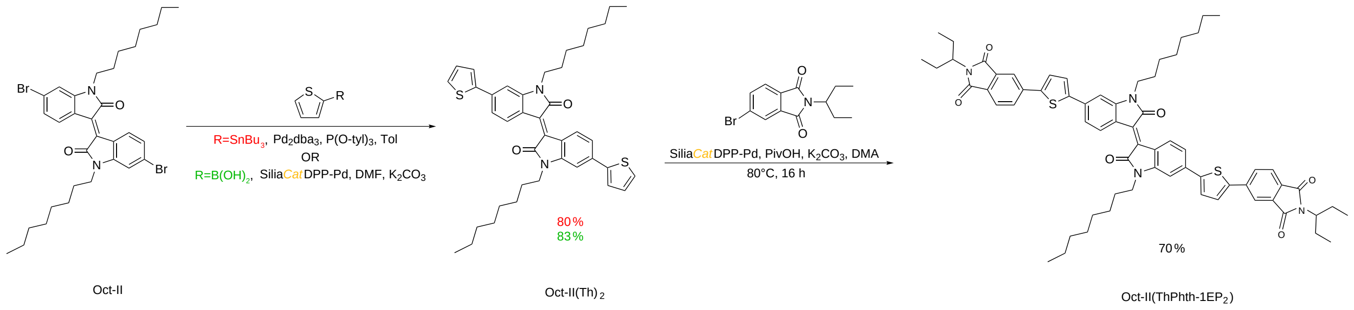
Authors: Welch (*Dalhousie University*) *et al.*
Publication: *ChemPhysChem*, **2015**, *16*, 1190-1202

Overview

More and more, soluble organic small molecules seem to represent a highly advantageous & promising alternatives vs more traditional polymer-fullerenes in the field of organic photovoltaics (*OPVs*). Silia*Cat* DPP-Pd was chosen as a heterogeneous catalyst for the synthesis of Oct-II(Th)$_2$, a small molecule with unique morphologies, as a fullerene alternative in OPVs. In this context:

- For the coupling between the brominated alkylisoindigo core and a 2-tributystannyl thiophene, both a Stille coupling catalyzed by Pd_2dba_3 and a Suzuki coupling catalyzed by Silia*Cat* DPP-Pd were considered as synthetic strategies.
- For the last step, a direct heteroarylation was chosen in order to obtain the target molecule.

Case Study: SiliaCat DPP-Pd in the Synthesis of Organic Photovoltaics, using Suzuki Coupling (*con't*)



Conclusion

In the synthetic step for Oct-II(Th)^2, both Stille and Suzuki couplings gave similar good yields. Yet, two points favour the Suzuki coupling using SiliaCat DPP-Pd as a catalyst:

1. Despite the two couplings giving similar yields, the two purification needs were very different, For the Stille reaction, in order to remove the toxic organotin residue, a flash chromatography was needed. For the Suzuki coupling, an aqueous work up could get rid of most impurities.
2. Moreover, Suzuki couplings involve environmentally benign boronic acids, whereas Stille couplings involve toxic organotin reagents.

Direct heteroarylation somehow represent the apex of atom economy for C-C bond forming reactions, since they do not require tin or boron extra organic material as Stille or Suzuki couplings do. This last step did not require any air sensitive manipulation.

Case Study: Comparative Investigation Between Most Common Immobilized Pd catalysts

Authors: Kappe (*University of Graz, Austria*) et al.
Publication: *ACS Catalysis,* **2015**, *5*, 1303-1312

Overview

When choosing a heterogeneous Pd catalyst for cross-coupling reactions, for all the benefits they bring in comparison with homogeneous catalysts, the key parameters of concern are the overall efficiency, the leaching resistance and the recyclability character of the catalyst. In this report, a comparative investigation of some of the most common and popular immobilized phosphine based Pd catalysts, namely SiliaCat DPP-Pd, Pd Tetrakis (*polymerbound*), FiberCat 1001 and EnCat TPP30, was performed.

Comparative results & Conclusions

- *"**Except for SiliaCat DPP-Pd**, the Suzuki-Miyaura cross-coupling produced a much higher amount of metal leaching and catalyst degradation than the Mizoroki-Heck reaction"*.
- *"In the case of the Pd EnCat TPP30, a constant drop in conversion was observed when EtOH as solvent in combination with TBAOAc as base were utilized for the Mizoroki-Heck reaction"*.
- *"**SiliaCat DPP-Pd** combined with THF / EtOH / H_2O as solvent and K_2CO_3 as base **gave the best results** regarding catalyst efficiency and leaching resistance"*.
- *"Notably, the **SiliaCat DPP-Pd** system described herein has shown superior leaching resistance and stability with respect to the other three cases studied"*.

Typical Experimental Procedure: Suzuki Couplings over Silia*Cat* DPP-Pd

Note: Please refer to the table presented below for specific conditions (*recommended solvents, scale of the reaction, reaction time, temperature, etc.*). Anhydrous solvents or inert conditions are not required. We suggest to work one or two degrees below the boiling point of the solvent.

Reaction in batch mode

- Using the appropriate apparatus recommended for the screening or for the reusability reactions, the aryl halide substrate and the reagents are added to the reaction solvent.
- The mixture is then warmed to the desired temperature after which Silia*Cat* DPP-Pd is added.
- The reaction mixture is then vigorously stirred (*700 RPM*) until maximum conversion is observed (*as determined by TLC or GC/MS analysis*).

Reaction in flow

- Solution Preparation:
  - Solution 1: aryl halide (*1 equiv*) in THF (*0.8 M*)
  - Solution 2: boronic acid (*1.25 equiv*) and base *(1.5 equiv*) in EtOH / H_2O
- Both solutions are pumped using the flow system and mixed in a T-piece device, are driven through a preheated glass column reactor with an adjustable end (*0.785 cm ID × 6.5 cm length*) packed manually with the Silia*Cat* DPP-Pd.

Work-up

Catalyst recovery

- Once the reaction is deemed complete as determined by TLC or by GC/MS analysis, the catalyst is recovered by filtration at room temperature through a Büchner funnel using a glass fiber filter (*grade 691*).
- The catalyst (*between 0.25 - 1.00 g*) is washed with EtOAc (*2 x 15 mL*), EtOH / H_2O (*v/v, 1/1, 3 x 15 mL*) and THF (*2 x 15 mL*).
- The catalyst is then dried under air at room temperature and can be stored in a closed vessel prior to reuse.
  For prolonged storage, keep under argon at 8°C.

Isolation of the coupling product

- The filtrate is concentrated in vacuo and the residue is dissolved in EtOAc or Et_2O.
- The organic layer is then washed twice with water.
- The organic layer is dried using anhydrous magnesium sulfate and then concentrated in vacuo, yielding a high purity crude product that typically does not require extensive purification. If needed, a flash chromatography can be done.

Suzuki Coupling Reactions over Silia*Cat* DPP-Pd

Substrates	Aryl-Iodide (*1 equiv*)	Aryl-Bromide (*1 equiv*)	Aryl-Chloride (*1 equiv*)
Boronic Acid	1.2 equiv		
Base [K_2CO_3]	1.5 equiv [*alternate bases:* Na_2CO_3, $KHCO_3$, $NaHCO_3$, *NaOH, KOH, NaOAc, KOAc*]		
Silia*Cat* Loading	≤ 0.5 mol % Pd		≤ 1.0 mol % Pd
Best Solvents & Temperature	MeOH or EtOH	EtOH	
	[*alternate solvents: n-PrOH, i-PrOH, 2-BuOH, THF /* H_2O *(20 %), Toluene /* H_2O *(20 %)*] ; 1 - 2°C *under boiling point*		
Reaction Time	0.5 - 2.0 h		
Typical Scale	• Under Magnetic Stirring for Screening: 6 mmol scale of aryl halide in 12 mL solvent. • Under Mechanical Stirring for Reusability: 25 mmol scale of aryl halide in 50 mL solvent.		

Suzuki Coupling Reactions in Flow over Silia*Cat* DPP-Pd

Substrates	*Solution 1*: Aryl-Halide 0.79 M in THF (*HPLC grade*)
Boronic acid	*Solution 2*: Boronic acid (*1.25 equiv*) and base K_2CO_3 (*1.5 equiv*) in EtOH / H_2O (*1:1.15, v/v, 0.45 M in regards to boronic acid*)
Silia*Cat* Catalyst	Preheated glass column reactor with an adjustable end (*0.785 cm ID* × *6.5 cm length*) charged with Silia*Cat* DPP-Pd.
Temperature	70°C
Residence Time	2.85 min
Flow Rate	For 0.75 mL/min: *solution 1:* 0.25 mL/min & *solution 2:* 0.50 mL/min

Optimization Steps

If the reaction fails or if the conversion of the aryl halide is not complete, optimization steps can be undertaken. The example below (written for Suzuki coupling using SiliaCat DPP-Pd) presents the pathway (order) you need to follow to optimize your reaction.

Always using 1.0 mol % Silia*Cat* DPP-Pd:

Step 1: Solvent Screening
Different solvents may be tried, such as: MeOH, EtOH, *n*-PrOH, *i*-PrOH, 2-BuOH, THF / H_2O (*20 %*) or Toluene / H_2O (*20 %*).

Step 2: Solvent Concentration Optimization
Once the best solvent has been determined, different concentrations (*from 0.25 M to 1.0 M*) should be explored.

Step 3: Base Concentration Screening
Using the best solvent and concentration, different amounts of K_2CO_3 (*from 1.25 equiv to 2 equiv*) should be tried.

Step 4: Amount of Boronic Acid
Then, the number of molar equivalents of boronic acid (*from 1.1 equiv to 1.5 equiv*) should be varied.

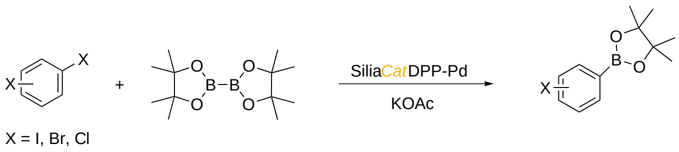
Step 5: Silia*Cat* Palladium Loading (*mol %*)
Finally, the loading of Silia*Cat* DPP-Pd should be optimized.

If the reaction **is not complete**,
the amount of catalyst should be increased up to 1.0 mol % of Silia*Cat* DPP-Pd.

If the reaction **is complete**,
the catalyst loading can be decreased from as low as 0.1 mol % Pd (*or less in some cases*).

Borylation of Aryl Halides Using Silia*Cat* DPP-Pd

The borylation reaction is a fast and clean synthesis of boronic acid pinacol esters starting from aryl halides and bis-(pinacolato)diboron (*B_2Pin_2*) or bis(catecholato)diborane (*B_2Cat_2*). Silia*Cat* DPP-Pd can be used to heterogeneously catalyze this reaction with largely enhanced reaction rate and catalyst stability. The borylation can either be done under standard condition or flow chemistry. A few examples of the scope of this reaction are presented here but all results can be found in the related publications.



Base and Solvent Nature Effects

The reaction conditions were optimized by using 4-bromobenzonitrile as a substrate. Stronger bases, such as K_3PO_4 or K_2CO_3, promoted further reactions of the arylboronic esters thus formed with the haloarenes resulting in contamination by a substantial amount of dimer (*36 - 60 % yield*). Milder KOAc base was unexpectedly the best basic species. Best results in terms of conversion and selectivity were obtained by performing the reaction in alcohol (*i-PrOH, n-BuOH, 2-BuOH*) and alcohol mixtures such as *n*-PrOH / MeOH. The use of anhydrous solvent generally increases the selectivity. Results presented in this table were obtained using 1 mol % of catalyst for the coupling of B_2Pin_2 and 4-bromobenzonitrile.

Base and Solvent Nature Effect

Entry	Solvent	t [*h*]	Conv. (*Select.*)* [%]
1*	anhydrous EtOH	1	100 (82)
2	*n*-PrOH HPLC	1	97 (63)
3	anhydrous *n*-PrOH	1	99 (90)
4	*i*-PrOH HPLC	1	100 (80)
5	anhydrous *i*-PrOH	1	100 (99)
6	*n*-BuOH HPLC	1	96 (62)
7	anhydrous 2-BuOH	1	100 (85)
8	anhydrous DMF	1	94
		2	100 (85)
9	anhydrous DMF / *i*-PrOH	1	100 (84)
10	anhydrous DMSO	1	69
		2	71 (84)

Experimental conditions: Substrate (*5 mmol, 1 equiv*), KOAc (*2 equiv*), solvent (*20 mL; 0.5 M, molar concentration with respect to the reagents or substrate*), Silia*Cat* DPP-Pd (*0.2 g, Pd loading 0.25 mmol/g*), 1 h at 82°C.
* Conversion / selectivity evaluated by GC-MS.

Scale-up Study

A scale-up reaction from 10 mmol to 200 mmol substrate was studied for the borylation reaction of 4-bromoanisole over 2 mol % Silia*Cat* DPP-Pd.

The study reveals that there is no induction period. More than 70 % of 4-bromoanisole was converted to the borylation product within the first 30 min of reaction and nearly all (*98 - 99 %*) substrate was converted in 90 min, except for the reaction with 10 mmol substrate in which the complete conversion required approximately 3 h.

Scale-up Study

Substrate [*mmol*] / [*equiv*]	t [*h*]	Conv. (*Select.*) [%]	Yield [%]
10 / 1	0.5	77	95
	2	92	
	3	100 (97)	
20 / 1	0.5	77	97
	1.5	98	
	2	100 (98)	
40 / 1	0.5	77	97.2
	1.5	99	
	2	100 (98)	
40 / 1	0.5	78	97.5
	1.5	98	
	2	100 (98)	
200 / 1	0.5	79	97
	1.5	99	
	2	100 (98)	

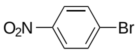
Reaction Method Variation

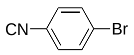
During our investigation, we found out that the substrate's nature has a direct influence on the performance of the borylation. Two methods were developed, one for substrates bearing electron-withdrawing groups and another for substrates containing electron-donating groups and heteroatoms.

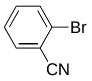
Substrate Scope

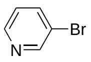
To explore the scope of the borylation using Silia*Cat* DPP-Pd, we extended its application to various aryl chlorides, bromides and iodides carrying electron-withdrawing or electron-donating groups, and to heteroatom substrates such as pyridine, indole and quinoline. In general, borylation proceeded in good to excellent yields, achieving the desired boronic ester in 3 h. Few examples of conversion and selectivity evaluated by GC-MS are presented below (*refer to the related publication for all results*).

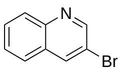
Substrate Scope Conversion and Selectivity Results of Coupling Reaction with of B_2Pin_2 (*conversion / selectivity in %*)

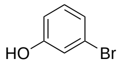

100 / 97

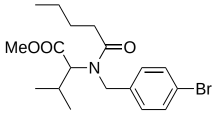

100 / 99

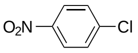

99 / 87

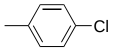

100 / 98

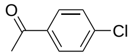

100 / 88

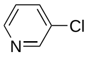

100 / 98

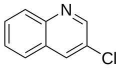

100 / 97

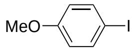

100 / 75

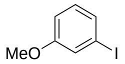

100 / 97


100 / 98


98 / 96


100 / 70


82 / 98

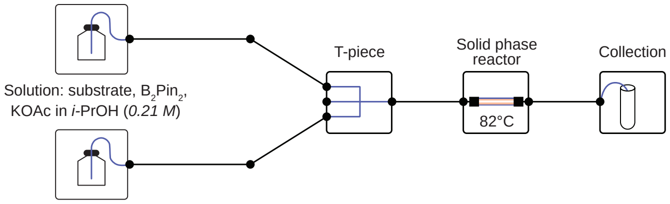

100 / 98

Borylation in Flow Chemistry Scope

The borylation coupling can also be done in flow chemistry. The figure to the right presents the setup used to allow fast and reproducible mixing of liquid reactants in the presence of the solid catalyst. Only one solution was prepared mixing the substrate, bis(pinacolato)diboron and base (*KOAc*) in *i*-PrOH solvent. The solid-phase reactor (*2.4 or 5.1 mL*) was thus charged with respectively 0.80 g and 1.76 g of Silia*Cat* DPP-Pd.

The optimal reaction conditions developed in the batch reaction over Silia*Cat* DPP-Pd for the borylation reaction of 4-bromobenzonitrile, 4-bromoanisole and 2-bromotoluene were tested under flow in the modular Asia 220 flow chemistry system commercialized by Syrris using a more diluted solution to ensure a homogeneous reaction mixture.

For all experiments, faster kinetics were observed in flow with excellents conversion and selectivities.



Borylation in Flow Chemistry using Silia*Cat* DPP-Pd

Substrate	Silia*Cat* DPP-Pd	*i*-PrOH (*M*)*	Conditions Flow (*mL/min*)	Conditions RT (*min*)	Conv. (*%*)	Select. (*%*)
4-bromo-benzonitrile	1 mol %	0.50	Batch	60	100	99
	0.8 g (*R_1*)	0.25	0.50	2.05	100	95
4-bromo-anisole	2 mol %	0.75	Batch	180	100	99
	1.76 g (*R_2*)	0.21	0.25	8.67	92	95
2-bromo-toluene	2 mol %	0.75	Batch	120	100	98
	1.76 g (*R_2*)	0.21	0.25	8.67	97	98

* Molar concentration with respect to the substrate

Conclusion for the Borylation Reaction

The heterogeneously catalyzed direct synthesis of boronic esters can now be performed with a wide range of aryl chlorides, bromides and iodides, and bis(pinacolato)diboron as the borylating agent over Silia*Cat* DPP-Pd. The use of anhydrous non-toxic *i*-PrOH as a reaction solvent avoids homocoupling and increases the selectivity.

Excellent yields and selectivities were achieved with very low leaching of Pd during catalysis. All the reagents utilized are stable in air and can be easily scaled up. Hence, the process does not require the use of a glovebox or inert conditions, with relevant practical advantages over existing methods that often require the exclusion of air and humidity from the reaction system.

Related Publications for Borylation Reactions

Chem. Cat. Chem., **2014**, *6*, 1340-1348
Org. Proc. Res. Dev., **2014**, *18*, 1556-1559
J. Org. Chem., **2014**, *10*, 897-901

Typical Experimental Procedure: Borylation over SiliaCat DPP-Pd

Note: Please refer to the table presented below for specific conditions (*recommended solvents, scale of the reaction, reaction time, temperature, etc.*). Anhydrous solvents or inert conditions are not required. We suggest to work one or two degrees below the boiling point of the solvent.

Reaction in batch mode

- Using the appropriate apparatus recommended for the screening or for the reusability reactions, bis(pinacolato)diboron and the base are added to the reaction solvent.
- After 5 minutes stirring, the aryl halide is added to the resulting mixture.
- The mixture is then warmed to the desired temperature after which Silia*Cat* DPP-Pd is added.
- The reaction mixture is then vigorously stirred (*700 RPM*) until maximum conversion is observed (*as determined by TLC or GC/MS analysis*).

Work-up

Catalyst recovery

- Once the reaction is deemed complete as determined by TLC or by GC/MS analysis, the catalyst is recovered by filtration at room temperature through a Büchner funnel using a glass fiber filter (*grade 691*).
- The catalyst (*between 0.25 - 1.00 g*) is washed with EtOAc (*2 x 15 mL*), EtOH / H_2O (*v/v, 1/1, 3 x 15 mL*) and THF (*2 x 15 mL*).
- The catalyst is then dried under air at room temperature and can be stored in a closed vessel prior to reuse.
  For prolonged storage, keep under argon at 8°C.

Isolation of the coupling product

- The filtrate is concentrated in vacuo and the residue is dissolved in EtOAc or Et_2O.
- The organic layer is then washed twice with water.
- The organic layer is dried using anhydrous magnesium sulfate and then concentrated in vacuo, yielding a high purity crude product that typically does not require extensive purification. If needed, a flash chromatography can be done.

Optimization Steps

Please see "*Optimization Steps*" presented at page 37.

Miyaura Borylation Reactions over Silia*Cat* DPP-Pd

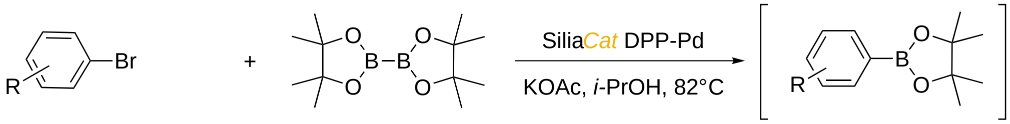
Substrates	Aryl-Iodide (*1 equiv*)	Aryl-Bromide (*1 equiv*)	Aryl-Chloride (*1 equiv*)
Bis(pinacolato)diboron	1.2 equiv		1.5 equiv
Base KOAc	2.2 equiv		3.0 equiv
Silia*Cat* Loading	≤ 2.0 mol % Pd		
Best Solvents (*anhydrous*)	*i*-PrOH (*0.75 M*)*		*i*-PrOH (*1.25 M*)*
	[*alternate solvents: 2-BuOH, DMF, EtOH (anhydrous solvents)*]		
Temperature	80 - 82°C		
Reaction Time	0.5 - 3.0 h		3.0 - 20 h
Typical Scale	• Under Magnetic Stirring for Screening: 10 mmol scale of aryl halide in 30 mL solvent (*for Ar-Br and Ar-Cl*) or in 20 mL solvent (*for Ar-I*) • Under Mechanical Stirring for Reusability: 20 mmol scale of aryl halide in 60 mL solvent (*for Ar-Br and Ar-Cl*) or in 40 mL solvent (*for Ar-I*).		

* Molar concentration in rapport to the substrate

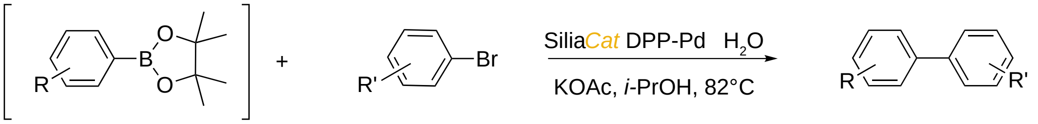
One-Pot Borylation and Suzuki-Miyaura Coupling Reactions of Aryl Halide

Unsymmetrically coupled biaryls are synthesized in high yield starting from different aryl bromides and bis(pinacolato) diboron by carrying out the Miyaura borylation reaction followed by Suzuki-Miyaura reaction in the same reaction pot over 1 - 2 mol % Silia*Cat* DPP-Pd. This catalyst is air-stable and the method does not require the use of inert conditions. The use of non-toxic isopropanol or 2-butanol as reaction solvent further adds to the environmental benefits of this new green synthetic methodology. We present here a brief overview of all results presented in the related publication.

The Silia*Cat* DPP-Pd catalyst mediates the borylation and the subsequent Suzuki-Miyaura reaction in an elegant one-pot sequential synthesis. Hence, an aryl bromide is first converted into the corresponding boronic acid pinacol ester (*step 1*). A different aryl bromide is then added along with aqueous base (*step 2*).



step 1

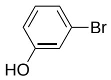
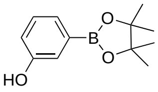
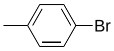
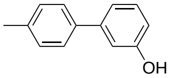
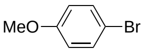
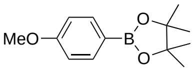
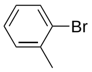
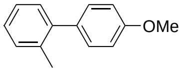
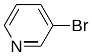
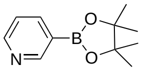
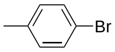
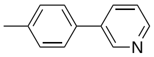


step 2

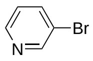
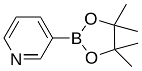
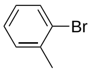
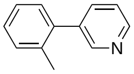
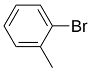
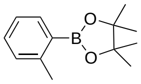
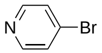
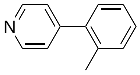
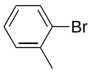
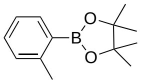
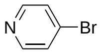
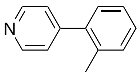
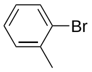
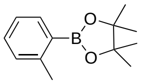
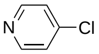
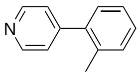
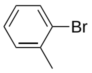
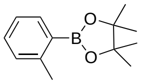
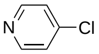
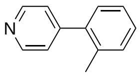
One-Pot Reaction Scope

Some experiments were tried to demonstrate the versatility of the method. The reaction is carried out in *i*-PrOH or in 2-BuOH. No work-up is performed after the borylation in the first step, nor is any catalyst added prior to conducting the second step of the sequence, the Suzuki-Miyaura reaction. Results shows that different unsymmetrically coupled compounds were obtained in good to excellent yields by coupling numerous different aryl bromides with different aryl halides, including heteroatom-containing aryls.

One-Pot Silia*Cat* DPP-Pd-catalysed Borylation and Suzuki-Miyaura Coupling Reactions

Entry	Substrate	Catalyst (*mol %*)	Base (*equiv*)	Solvent (*M*)	Product	t (*h*)	Conv / Selec (*Yield*) (%)
1		Silia*Cat* DPP-Pd 2	KOAc 2.2	*i*-PrOH (*0.75*)		2	100 / 99
		-	K_2CO_3 2.3	+ 8 mL H_2O		2 3	85
2		Silia*Cat* DPP-Pd 2	KOAc 2.2	*i*-PrOH (*0.75*)		3	99 / 98
		-	K_2CO_3 2.3	+ 8 mL H_2O		2 3	92 / 97 (88)
3		Silia*Cat* DPP-Pd 2	KOAc 2.2	*i*-PrOH (*0.75*)		2 3	89 100 / 98
		-	K_2CO_3 2.3	+ 8 mL H_2O		2 3	83

One-Pot SiliaCat DPP-Pd-catalysed Borylation[a] and Suzuki-Miyaura Coupling[b] Reactions (con't)

Entry	Substrate	SiliaCat DPP-Pd (mol %)	Base (equiv)	Solvent (M)[c]	Product	t (h)	Conv / Selec (Yield)[d] (%)
4		2	KOAc 2.2	i-PrOH (0.75)		3	100 / 98
		-	K_2CO_3 2.3	+ 8 mL H_2O		2 3	82
5		2	KOAc 2.2	i-PrOH (0.75)		1 2	90 100 / 99
	 HCl	-	K_2CO_3 2.3	+ 8 mL H_2O		1 3	99 / 95 (89)
6[e]		1	KOAc 2.2	2-BuOH (1.00)		1 2	98 100 / 99
	 HCl	-	K_2CO_3 2.3	+ 8 mL H_2O		1 3	100 / 98 (94)
7[e]		1	KOAc 2.2	2-BuOH (1.00)		1 2	98 100 / 99
	 HCl	-	K_2CO_3 2.3	+ 8 mL H_2O		3 17	86
8[e]		1	KOAc 2.2	2-BuOH (1.00)		1 2	98 100 / 99
	 HCl	1	K_2CO_3 2.3	+ 8 mL H_2O		1 3	95

Experimental conditions. [a]Step 1: Substrate 1 (*10 mmol, 1 equiv*), B_2Pin_2 (*11 mmol, 1.1 equiv*), KOAc (*22 mmol, 2.2 equiv*), 28 mL anhydrous *i*-PrOH, 2 mol % Silia*Cat* DPP-Pd (*0.25 mmol/g palladium loading*), at 82°C. [b]Step 2: Substrate 2 (*12 mmol, 1.2 equiv relative to substrate 1*), K_2CO_3 (*23 mmol, 2.3 equiv relative to substrate 1*), 8 mL distilled H_2O (*i-PrOH / H_2O, 3.5:1, v/v*). [c]Molar concentration with respect to the substrate and to B_2Pin_2. [d]Conversion / selectivity in cross-coupling product evaluated by GC-MS. Yield of the isolated product is given in parentheses. [e]The borylation reaction is carried out at 98°C in 21 mL anhydrous 2-BuOH (*1.0 M molar concentration with respect to the reagents.*)

Conclusion for One-Pot Borylation and Suzuki Coupling

Unsymmetrically coupled biaryls can be synthesized in high yields starting from different aryl bromides and bis(pinacolato) diboron by carrying out the Miyaura borylation reaction followed by the Suzuki-Miyaura reaction over 1 - 2 mol % catalytic amount of Silia*Cat* DPP-Pd in the same reaction pot. There is no need to isolate the intermediate boronic ester, while the air stable sol-gel entrapped palladium catalyst does not require the use of inert conditions.

Finally, the use of isopropanol or 2-butanol as reaction solvents further points out the environmental benefits of the method. As the fine chemicals and pharmaceutical industries are eventually adopting green chemistry synthetic methodologies, this method provides both industries with a clean route to valued compounds that are widely used in many industrial sectors.

Related Publication for Borylation Reactions

Beilstein J. Org. Chem., **2014**, *10*, 897-901

Typical Experimental Procedure: One-Pot Miyaura Borylation / Suzuki Coupling

Note: Please refer to the table presented below for specific conditions (*recommended solvents, scale of the reaction, reaction time, temperature, etc.*). Anhydrous solvents or inert conditions are not required.

Step1: Miyaura Borylation Reaction

- Using the appropriate apparatus recommended for the screening or the reusability reactions, the bis(pinacolato)diboron and the base are added to the reaction solvent.
- After 5 minutes stirring, the aryl halide (*substrate 1*) is added to the resulting mixture and is then warmed up to the desired temperature after which Silia*Cat* is added.
- The reaction mixture is then vigorously stirred (*700 RPM*) until maximum conversion is observed (*as determined by TLC or GC/MS analysis*). No work-up is performed after the borylation in the first step.

Step 2. Suzuki-Miyaura Coupling Reaction

- After maximum conversion of substrate 1 (*as determined by TLC or GC/MS analysis*), substrate 2 (*aryl bromide or aryl chloride*) and an aqueous K_2CO_3 solutions are added to the reaction mixture.
- The reaction mixture is then vigorously stirred (*700 RPM*) until maximum conversion of boronic acid obtained in step 1 is reached (*as determined by TLC or GC/MS analysis*).

Work-up

Catalyst recovery

- Once the reaction is deemed complete as determined by TLC or by GC/MS analysis, the catalyst is recovered by filtration at room temperature through a Büchner funnel using a glass fiber filter (*grade 691*).
- Silia*Cat* (*between 0.25 - 1.00 g*) is washed with EtOAc (*2 x 15 mL*), EtOH / H_2O (*v/v, 1/1, 3 x 15 mL*) and THF (*2 x 15 mL*).
- Silia*Cat* is dried under air at room temperature and can be stored in a closed vessel prior to reuse in these conditions.

Isolation of the coupling product

- The filtrate is concentrated in vacuo and the residue is dissolved in ethyl acetate (*EtOAc*) or diethyl ether (Et_2O).
- The organic layer is then washed twice with water.
- The organic layer is dried using anhydrous magnesium sulfate and then concentrated in vacuo, yielding a high purity crude product that typically does not require extensive purification. If needed, a flash chromatography can be done.

Optimization Steps

Please see "*Optimization Steps*" presented at page 37.

Step 1: Miyaura Borylation Reaction using Silia*Cat* DPP-Pd

Substrates 1	Aryl-Bromide (*1 equiv*)	Aryl-Chloride (*1 equiv*)
Bis(pinacolato)diboron	1.1 equiv	
Base: KOAc	2.2 equiv	
Silia*Cat* Loading	≤ 2.0 mol % Pd	
Best Solvents (*anhydrous*)	*i*-PrOH (*0.75 M*)	*i*-PrOH (*0.75 M*) or 2-BuOH (*1.00 M*)
	Molar concentration with respect to the substrate and the bis(pinacolato)diboron	
Temperature	80 - 82°C	
Reaction Time	0.5 - 3 h	3 - 20 h

Step 2: Suzuki-Miyaura Coupling using Silia*Cat* DPP-Pd

Substrates 2	Aryl Bromide (*1.2 equiv*)	Aryl Chloride (*1.2 equiv*)
Base K_2CO_3	2.3 equiv	
Co-solvent	H_2O (*i-PrOH / H_2O, 3.5:1, v/v*)	H_2O (*2-BuOH / H_2O, 2.6:1, v/v*)
Temperature	80 - 80°C	96 - 98°C
Reaction Time	2 - 4 h	2 - 17 h
Typical Scale	• Under Magnetic Stirring for Screening: 10 mmol scale of aryl halide in 30 mL of *i*-PrOH or in 20 mL of 2-BuOH. • Under Mechanical Stirring for Reusability: 20 mmol scale of aryl halide in 60 mL of *i*-PrOH or in 40 mL of 2-BuOH.	

Negishi Coupling Reaction Using Silia*Cat* DPP-Pd

The Negishi C-C coupling is a widely used reaction that couples organic halides, triflates or acetyloxy groups with organozinc using either a palladium or a nickel catalyst. This coupling is gaining in popularity and is often used to synthesize acyclic terpenoid systems. However the reaction needs to be performed under inert and anhydrous conditions due to the sensitivity of the organozincs.

$$R{-}X \quad + \quad R_1{-}ZnX' \xrightarrow{PdL_n \text{ or } NiL_n} R{-}R_1$$

This section presents results in flow chemistry using Silia*Cat* DPP-Pd as catalyst for the Negishi coupling.

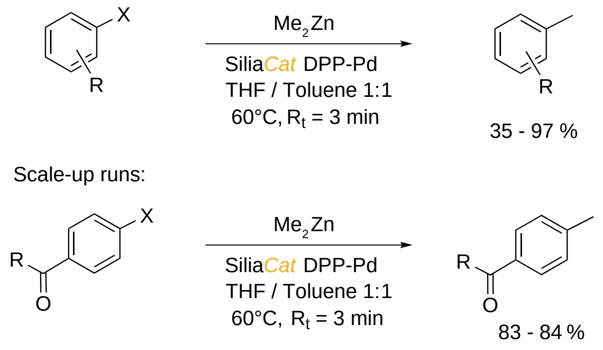
Case Study: Silia*Cat* DPP-Pd in a Mild Alkyl-Aryl Negishi Cross-Coupling in Flow Chemistry

Authors: Alcázar (*Janssen Research and Development*) *et al.*
Publication: *Journal of Flow Chemistry*, **2014**, *4*, 22-25

Overview

After obtaining excellent results for a mild Suzuki-Miyaura coupling catalyzed by Silia*Cat* DPP-Pd (*p. 34*), Alcázar *et al*. later reported using the same catalyst for a novel alkyl-aryl Negishi cross-coupling in flow, in very mild and clean conditions.

The group reports that *“after screening a wide variety of reaction conditions in batch using microwave irradiation,* Silia*Cat* *DPP-Pd was identified as the most suitable catalyst for the coupling of a model system consisting of 1-bromo-4-nitrobenzene and dimethylzinc”*.



Conclusion

The reaction was achieved in very mild conditions and quickly. Good to excellent yields were obtained in most cases: esters, ketones, aldehydes, heterocyclic substrates and compounds bearing ortho substituents were compatible in the process, as well as aryl bromides, iodides and activated chlorides. Triflates and nonaflates, on the other hand, could not be coupled efficiently.

The same catalyst cartridge could be re-used for more than 20 consecutive reactions without any decrease in activity and minimal leaching, even on scale-up runs (*27 ppb of Pd*).

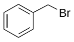
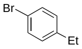
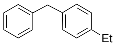
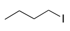
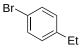
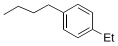
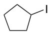
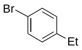
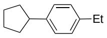
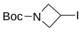
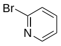
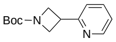
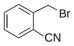
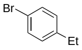
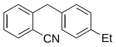
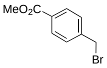
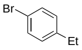
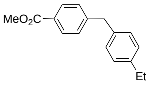
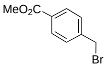
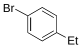
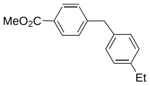
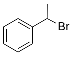
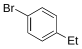
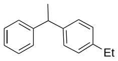
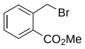
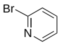
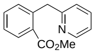
Case Study: Silia*Cat* DPP-Pd in the Synthesis of Organozinc Halides Coupled to Negishi Reactions

Authors: Alcázar (*Janssen Research and Development*) *et al.*
Publication: *Advanced Synthesis & Catalysis,* **2014**, *356,* 3737-3741

Overview

Negishi coupling is one of the very useful carbon-carbon bond forming coupling reaction, but a little less known than other types of coupling due to the less available organozinc species. Alcázar (*Janssen-Cilag*), McQuade (*Florida State University*) and coworkers reported an effective and reproducible synthesis of organozinc halides with excellent yields, using an activated packed-bed of metallic zinc. Such organozinc species could further be used downstream in subsequent Negishi couplings, catalysed with Silia*Cat* DPP-Pd.

Negishi Coupling

Entry	R-X	Aryl-X	Product	Yield *(%)*
1[a]				81
2[b]				74
3[c]				83
4[d]				71
5[a]				81
6[a]				79
7[b]				82
8[b]				84
9[a]				86

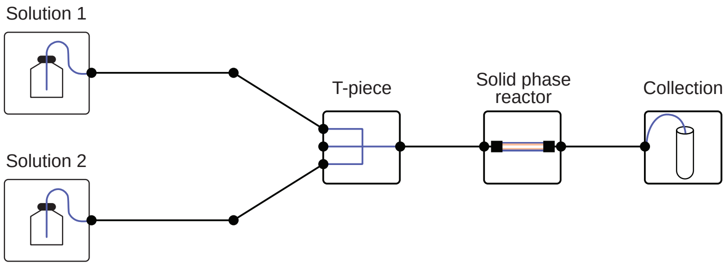
[a] Zn column, r.t.; Silia*Cat* DPP-Pd column 60°C., [b] Zn column, 60°C; Silia*Cat* DPP-Pd 60°C.
[c] Zn column, 60°C and LiCl (*1 equiv*) as additive; Silia*Cat* DPP-Pd column, 80°C.
[d] Zn column, 110°C and LiCl (*1 equiv*) as additive; Silia*Cat* DPP-Pd column, 60°C. [e] Zn column, r.t.; Silia*Cat* DPP-Pd column, 80°C.

Conclusion

It was demonstrated that a large library of organozinc halides could be produced from shelf-stable halides and used *in situ* in a continuous packed-bed approach. Moreover the team reports that "*the two stage zinc insertion / Negishi reaction functions at the high end laboratory scale with ease suggesting that the approach is stable and robust enough to support much larger scale chemistry*".

Typical Experimental Procedure: Negishi Couplings in Flow Using Silia*Cat* DPP-Pd

- Typical coupling reactions are performed in an appropriate solvent (*HPLC grade*) at the recommended temperature (*see table below*). Anhydrous solvents and inert conditions are required.



- Typical Flow Setup:
- Solution Preparation:
    - *Solution 1*: aryl halide (*1 equiv*) in dry THF (*0.20 M*)
    - *Solution 2*: organozinc reagent (*1.3 equiv*) in dry toluene (*0.30 M*)
- The two solutions are pumped using the flow system.
- The solutions, mixed in a T-piece device, are driven through a preheated glass column reactor with an adjustable end (*0.785 cm ID × 6.5 cm length*) packed manually with Silia*Cat* DPP-Pd (*1 g*).
- The conversion of the aryl halide is monitored at the reactor outlet using GC-MS.

Work-up

Isolation of the coupling product

- The outlet solution is concentrated in vacuo and the residue is redissolved in ethyl acetate (*EtOAc*) or diethyl ether (Et_2O)
- The organic layer is then washed twice with water and once with brine.
- The organic layer is separated, dried using anhydrous magnesium sulfate, filtered and then concentrated in vacuo, yielding a high purity crude product that typically does not require extensive purification. If needed, a flash chromatography can be done.

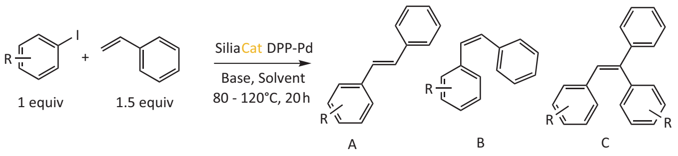
Negishi Coupling in Flow using Silia*Cat* DPP-Pd	
Substrates	***Solution 1*: Halide & Pseudohalide solution, 0.25 M in anhydrous THF (*1 equiv*)**
R_1R_2Zn	*Solution 2*: Organozinc solution, 0.30 M in anhydrous toluene (*1.3 equiv*)
Silia*Cat* Catalyst (*column reactor*)	Preheated glass column reactor with an adjustable end (*0.785 cm ID x 6.5 cm length*) charged with 1 g supported catalyst.
Temperature	60°C
Residence Time	3 min
Flow Rate	*Solution 1*: 0.20 mL/min *Solution 2*: 0.30 mL/min

Heck Coupling Using Silia*Cat* DPP-Pd

The Heck reaction, also known as the Mizoroki-Heck reaction, is the coupling of a halide with an alkene in the presence of a base and a palladium catalyst. This coupling allows a substitution reaction on alkenes and is of great importance in pharmaceutical research. We determined that the best catalyst for this reaction is Silia*Cat* DPP-Pd. It showed good reactivity for aryl iodides, bromides and chlorides.

Base and Solvent Effects

The Heck coupling between iodobenzene and styrene was used to evaluate the influence of solvent and base. The best combinations are KOAc / DMF, Et_3N / MeCN and nPropyl / neat. Using these systems, high yields and great selectivity in favor of product A were obtained.



Base and Solvent Effects (*SiliaCat DPP-Pd*)

Silia*Cat* (*mol %*)	Base	Solvent (*0.4 M*)*	Time (*h*)	Conversion A / B / C (%)
0.5	KOAc	DMF	24	100 (90 / 9.5 / 0.5)
	Na_2CO_3		24	67 (62 / 47 / 0)
0.1	Et_3N	MeCN	24	93 (77 / 6 / 11)
		H_2O	24	75 (70 / 5 / 0)
	nPropyl	(*neat*)	20	100 (95 / 5 / 0)

* Solvent substrate concentration

Catalytic Performance and Comparison vs Homogeneous Catalyst

Silia*Cat* DPP-Pd is a very efficient catalyst for the Heck coupling and allows greater selectivity over a homogeneous Pd catalyst (*TPP is required*). In addition to affording a higher yield of the desired product, the catalyst left minimal residual Pd, TPP or TPPO in solution that would have otherwise required the use of a metal scavenger, chromatography or trituration to remove.

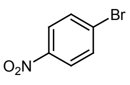
Catalytic Performance and Comparaison vs Homogeneous

Substrate		Silia*Cat* DPP-Pd (*mol %*)	Base	Solvent (*0.4 M*)*	Conversion A / B / C (%)	Phosphine Leaching (*ppm*)
R	X					
4-CN	Br	0.25	NaOAc	DMF	100 (95 / 5 / -)	-
$4-NO_2$					99 (97 / 2 / -)	-
$2-CH_3$			Et_3N	MeCN	71 (67 / 5 / -)	-
4-OMe	I				75 (60 / 15 / -)	-
H	I	0.1			100 (98 / 2 / -)	0
H	I	1.0 $Pd(OAc)_2$ PPh_3	Et_3N	MeCN	100 (70 / 22 / 8)	6,030

* Solvent substrate concentration

Substrate Scope and Microwave Compatibility

Silia*Cat* DPP-Pd is an efficient catalyst in the Heck coupling with different substrates. In all cases, conversion and selectivity were excellent. Microwave technology allows faster kinetics with good yields.



Substrate #1

Substrate #2

Substrate Scope and Microwave Compatibility

Substrate	Mode	mol %	Time	Temp. (°C)	Conv. / Sel. (%)
#1	Batch	0.5	24 h	120	100 / 97
	Microwave	0.2	10 m	125	93 / 85
#2	Batch	0.2	24 h	135	100 / 98
	Microwave	0.2 0.5[1]	10 m 30 m[1]	125 150[1]	92 / 81 99 / 93[1]

[1] Et_3N in water

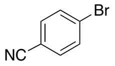
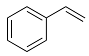
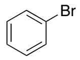
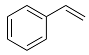
Comparison of Various Heterogeneous Pd-Catalysts

The effectiveness of Silia*Cat* DPP-Pd for the Heck coupling were investigated and compared with other catalysts (*heterogeneous and homogeneous*) available on the market often used for this coupling.
It is very important to note that for all reactions, all catalysts were used in the manufacturer's optimized reactions and not just SiliCycle's in order to be able to make relevant conclusions. Experiments were performed with two different aryl halides and alkenes.

Experimental conditions

- Protocol with Silia*Cat* DPP-Pd was drawn from *Topics in Catalysis*, **2010**, *53*, 1059-1062
  [*0.1 mol % Silia*Cat* DPP-Pd; Et$_3$N; H$_2$0; 100°C; 24 h*]
- Protocol with PhosphonicS was drawn from *Journal of Molecular Catalysis A: Chemical*, **2007**, *273*, 298-302
  [*5 mol % Si-Palladium acetate ethylthioglycolate; K$_2$CO$_3$; NMP; 110°C; 24 h*]
- Protocol for Johnson-Matthey Pd-Smopex-111 was drawn from *Org. Proc. Res. Dev.*, **2007**, *11*, 769-772
  [*2.5 weight % Pd-Smopex-111; NMP; 118°C; 20 - 24 h*]. Synthetized from Smopex-111 and Pd(OAc)$_2$.
- Typical protocol with the homogeneous catalyst: 1 mol % Pd(OAc)$_2$, PPh$_3$; TMEDA, 125°C; 24 h.

Heck Coupling Conversion Comparison (*in %*)

Aryl Halide	Vinyl	Silia*Cat* DPP-Pd	Pd Smopex-111	Phosphonics SCRPd	Pd(OAc)$_2$
		**98**	23	63	0
		**76**	0	0	0

Conclusion

Experiments showed that Silia*Cat* DPP-Pd was the most effective catalyst. PhosphonicS' catalyst showed good results, but 10 times more w/w, 20 times more mol % Pd were required.

Conclusion for Heck Coupling

Various aryl iodides and aryl bromides were tested in the Heck coupling using the Silia*Cat* DPP-Pd in batch mode and under microwave irradiation. Obtained results show good conversions for aryl iodide and bromide substrates with different electron-withdrawing groups and electron-donating groups. The use of Silia*Cat* DPP-Pd for the Heck coupling allows clean final product with minimal purification and no contamination with palladium, TPP or TPPO.

Related Publication for Heck Coupling

Org. Proc. Res. Dev., **2012**, *16*, 117-122

Typical Experimental Procedure: Heck Couplings over Silia*Cat* DPP-Pd

Note: Please refer to the table presented below for specific conditions (*recommended solvents, scale of the reaction, reaction time, temperature, etc.*). Anhydrous solvents or inert conditions are not required. We suggest to work one or two degrees below the boiling point of the solvent.

Reaction in batch mode

- Using the appropriate apparatus recommended for the screening or for the reusability reactions, the aryl halide substrate and the reagents are added to the reaction solvent.
- The mixture is then warmed to the desired temperature after which Silia*Cat* DPP-Pd is added.
- The reaction mixture is then vigorously stirred (*700 RPM*) until maximum conversion is observed (*as determined by TLC or GC/MS analysis*).

Work-up

Catalyst recovery

- Once the reaction is deemed complete as determined by TLC or by GC/MS analysis, the catalyst is recovered by filtration at room temperature through a Büchner funnel using a glass fiber filter (*grade 691*).
- The catalyst (*between 0.25 - 1.00 g*) is washed with EtOAc (*2 x 15 mL*), EtOH / H_2O (*v/v, 1/1, 3 x 15 mL*) and THF (*2 x 15 mL*).
- The catalyst is then dried under air at room temperature and can be stored in a closed vessel prior to reuse. For prolonged storage, keep under argon at 8°C.

Isolation of the coupling product

- The filtrate is concentrated in vacuo and the residue is dissolved in EtOAc or Et_2O.
- The organic layer is then washed twice with water.
- The organic layer is dried using anhydrous magnesium sulfate and then concentrated in vacuo, yielding a high purity crude product that typically does not require extensive purification. If needed, a flash chromatography can be done.

Optimization Steps

Please see "*Optimization Steps*" presented at page 37.

Heck Coupling Reactions over Silia*Cat* DPP-Pd

Substrates	**Aryl-Iodide (*1 equiv*)**	**Aryl-Bromide (*1 equiv*)**
Olefin	1.5 equiv	
Base	1.5 equiv [Et_3N or NaOAc]	1.5 equiv [NaOAc]
Silia*Cat* Loading	≤ 0.5 mol % Pd	
Best Solvents & Temperature	MeCN (*80°C*) or DMF (*120°C*)	DMF (*120°C*)
Reaction Time	20 - 24 h	
Typical Scale	• Under Magnetic Stirring for Screening: 20 mmol scale of aryl halide in 15 mL MeCN or in 20 mL DMF. • Under Mechanical Stirring for Reusability: 40 mmol scale of aryl halide in 30 mL MeCN or in 40 mL DMF.	

Sonogashira Coupling Using Silia*Cat* DPP-Pd & Pd^0

The Sonogashira coupling reaction of aryl halides and terminal acetylenes is an effective method for the formation of substituted acetylenes. This reaction is frequently utilized as a key step in natural product chemistry and for the synthesis of acetylene compounds, which have several applications.

Catalyst Concentration and Solvent Effects

Sonogashira coupling between iodonitrobenzene and phenylacetylene was achieved easily and without the need for co-catalysts to activate the alkyne, making the use of Silia*Cat* an efficient method for the formation of substituted acetylenes. All catalysts screened presented excellent efficiency, even in low amounts.

Catalyst Concentration and Solvent Effects

Silia*Cat* DPP-Pd

mol (%)	Solvent (*M*)*	Time	Conv. (%)
0.5	EtOH / H_2O (*0.07*)	30 min	100
	MeOH / H_2O (*0.07*)	5 min	100
0.1	EtOH / H_2O (*0.07*)	1 h	100
	MeOH / H_2O (*0.07*)	15 min	100
0.01	EtOH / H_2O (*0.13*)	3 h	100
0.002	EtOH / H_2O (*0.13*)	8 h	100

Catalyst Concentration and Solvent Effects

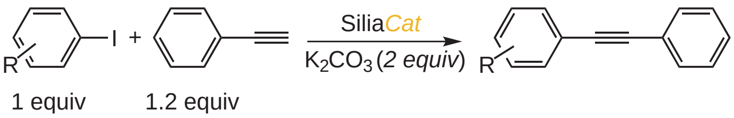
Silia*Cat* Pd^0

mol (%)	Solvent (*M*)*	Time	Conv. (%)
0.1	EtOH (*0.1*)	2 h	100
	EtOH (*0.05*)	30 min	100

* Solvent substrate concentration

Iodo-Substrate Scope and Microwave Compatibility

Couplings with iodoaryls and phenylacetylene were also investigated. The table below shows that Silia*Cat* is an efficient tool for the formation of substituted acetylenes.



Iodo-Substrate Scope and Microwave Compatibility

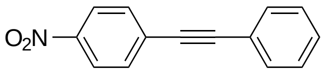
R	Mode	Silia*Cat* DPP-Pd			Silia*Cat* Pd^0		
		mol (%)	Conditions	Conv. / Sel. (%)	mol (%)	Conditions	Conv. / Sel. (%)
4-NO_2	Batch	1	EtOH (*0.08 M*) 77°C, 4 h	100 / 100	1	EtOH (*0.08 M*) 77°C, 4 h	100 / 100
	MW	0.6	MeOH / H_2O (*0.2 M*) 100°C, 2 min	100 / -	0.1	MeOH (*0.1 M*) 75°C, 5 min	100 / -
4-OMe	Batch	1	EtOH (*0.08 M*) 77°C, 4 h	99 / 98	1	EtOH (*0.08 M*) 77°C, 4 h	99 / 98
4-CH_3	Batch	1	EtOH (*0.08 M*) 77°C, 4 h	100 / 100	1	EtOH (*0.08 M*) 77°C, 4 h	100 / 100
	MW	0.5	MeOH / H_2O (*0.2 M*) 100°C, 2 min	90 / -	0.1	MeOH (*0.2 M*) 75°C, 5 min	100 / -

Bromo-Substrate Scope and Microwave Compatibility

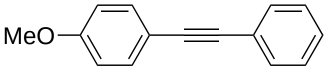
Silia*Cat* DPP-Pd and Pd^0 are also efficient catalysts for use with bromo substrates. A few examples of the Sonogashira coupling between various bromoaryls substrates (*1 equiv*) and phenylacetylene (*1.25 equiv*) using K_2CO_3 (*2 equiv*) in MeOH (*0.2 M*) are shown below.

Conversions obtained with 1 mol % of Silia*Cat* DPP-Pd and / or Pd^0 under microwave irradiation are presented below. Classical heating is also possible, but kinetics are significantly lower (*a few hours compared to 15 minutes*).

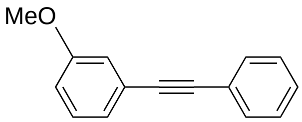
From Aryl Iodide Substrate Scope Conversion Results



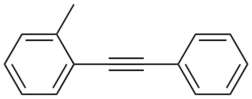
DPP-Pd: 99 %
Pd^0: 99 %



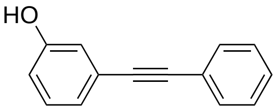
DPP-Pd: 98 %
Pd^0: 98 %



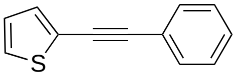
DPP-Pd: 99 %
Pd^0: 97 %



DPP-Pd: 98 %
Pd^0: 90 %

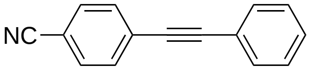


DPP-Pd: 89 %
Pd^0: 80 %

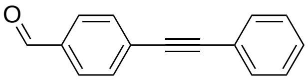


DPP-Pd: 82 %
Pd^0: 74 %

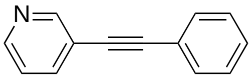
From Aryl Bromide Substrate Scope Conversion Results



DPP-Pd: 98 %
Pd^0: 98 %



DPP-Pd: 98 %
Pd^0: 98 %



DPP-Pd: 86 %
Pd^0: 82 %

Conclusion for Sonogashira Coupling

Sonogashira cross couplings can be smoothly carried out over a small amount (*0.5 - 1 mol %*) of Silia*Cat* DPP-Pd or Pd^0 catalyst under ligand-free and copper-free conditions. The scope of the method does not include aryl chlorides yet.

Related Publications for Sonogashira Coupling

Catal. Sci. Technol., **2011**, *1*, 736-739
Org. Proc. Res. Dev., **2012**, *16*, 117-122
ACS Sustainable Chem. Eng., **2013**, *1*, 57-61

Typical Experimental Procedure: Sonogashira Couplings over Silia*Cat*

Note: Please refer to the table presented below for specific conditions (*recommended solvents, scale of the reaction, reaction time, temperature, etc.*). Anhydrous solvents or inert conditions are not required. We suggest to work one or two degrees below the boiling point of the solvent.

Reaction in batch mode

- Using the appropriate apparatus recommended for the screening or for the reusability reactions, the aryl halide substrate and the reagents are added to the reaction solvent.
- The mixture is then warmed to the desired temperature after which Silia*Cat* DPP-Pd or Pd^0 is added.
- The reaction mixture is then vigorously stirred (*700 RPM*) until maximum conversion is observed (*as determined by TLC or GC/MS analysis*).

Work-up

Catalyst recovery

- Once the reaction is deemed complete as determined by TLC or by GC/MS analysis, the catalyst is recovered by filtration at room temperature through a Büchner funnel using a glass fiber filter (*grade 691*).
- The catalyst (*between 0.25 - 1.00 g*) is washed with EtOAc (*2 x 15 mL*), EtOH / H_2O (*v/v, 1/1, 3 x 15 mL*) and THF (*2 x 15 mL*).
- The catalyst is then dried under air at room temperature and can be stored in a closed vessel prior to reuse.
  For prolonged storage, keep under argon at 8°C.

Isolation of the coupling product

- The filtrate is concentrated in vacuo and the residue is dissolved in EtOAc or Et_2O.
- The organic layer is then washed twice with water.
- The organic layer is dried using anhydrous magnesium sulfate and then concentrated in vacuo, yielding a high purity crude product that typically does not require extensive purification. If needed, a flash chromatography can be done.

Optimization Steps

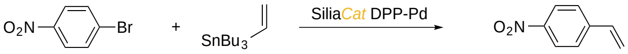
Please see "*Optimization Steps*" presented at page 37.

Sonogashira Coupling Reactions over Silia*Cat* Catalysts

Products	Aryl Iodide	Aryl Bromide
Alkyne	1.2 equiv	1.3 equiv
Base	K_2CO_3 2.0 equiv	KOAc 2.0 equiv
Silia*Cat* Catalyst	Silia*Cat* DPP-Pd or Pd^0 (*CuI free*)	
Silia*Cat* Loading	≤ 1.0 mol % (*DPP-Pd*) ≤ 0.5 mol % (*Pd^0*)	≤ 2.0 mol %
Best Solvent (*HPLC Grade*) & Temperature	MeOH (*63°C*) or EtOH (*77°C*)	DMF or DMAc (*80°C*)
Reaction Time	0.5 - 4.0 h	2.0 - 4.0 h
Typical Scale	• Under Magnetic Stirring for Screening: 6 mmol scale of aryl iodide in 60 mL MeOH or EtOH. • Under Mechanical Stirring for Resusability: 20 mmol scale of aryl bromide in 40 mL solvent.	

Stille Coupling Using Silia*Cat* DPP-Pd

The Stille coupling is a versatile reaction for C-C bond formation. It is a coupling between a halide and an organotin compound. This reaction is widely used in synthesis, but a major drawback is the toxicity of the tin compounds involved. In Stille couplings, a Pd^0 or Pd^{II} catalyst is required and it must be compatible with a wide variety of functional groups (*very few limitation on the R-group*). SiliCycle has developed catalysts that are highly efficient for Stille couplings, as shown below.



Catalyst Concentration and Solvent Effects

In this work we report the heterogeneous Silia*Cat* DPP-Pd Stille coupling reaction of 4-bromonitrobenzene with tributylvinyltin in dioxane or in toluene.

The results presented in the table show the importance of the solvent. Al low catalyst concentration (*0.25 mol % of SiliaCat DPP-Pd in toluene*) the reaction was complete in 17 h.

However, under the same conditions but in dioxane as solvent, only 50 % conversion was obtained in 17 h and 74 % in 22 h. To improve the conversion in dioxane the amount of catalyst was increased from 0.25 mol % to 2 mol % of Silia*Cat* DPP-Pd with complete conversion in 17 h.

As a general rule, if the solvent and concentration of the substrate are kept constant, increasing the amount of catalyst, thus increasing the number of catalytic sites, will speed up the kinetics of the reaction.

Catalyst Concentration and Solvent Effects

Silia*Cat* DPP-Pd (*mol %*)	Solvent (*M*)*	Time (*h*)	Conversion (*%*)
0.25	Toluene (*0.1 M*)	17	99
	Dioxane (*0.1 M*)	17	50
		22	74
0.5		17	80
		22	100
2.0		17	99

Silia*Cat* DPP-Pd Reusability and Leaching

The evaluation of reusability and leaching was done using Stille coupling reaction of 4-bromonitrobenzene with tributylvinyltin in dioxane (*0.1 M*) over 2 mol % Pd, for 17 h. The minimal leaching and the robustness of the organoceramic matrix are important factors that allow Silia*Cat* DPP-Pd to be reused several times. After four runs, 100 % conversion is still achieved.

Scope Substrates and Additive CsF Influence

Reactions were performed at reflux until the GC/MS analysis showed maximum conversion. Anhydrous conditions are not required.

Catalytic Performance and Additive CsF Influence

Substrate		Silia*Cat* DPP-Pd (*mol %*)	Additive (*equiv*)	Solvent (*0.1 M*)	Time (*h*)	Conversion (*%*)
(*R*)	(*X*)					
4-CN	Br	2	-	Dioxane	18	87
4-F		10	-		24	99
			CsF (*2*)	Toluene		100
H			-			100
4-CH$_3$			CsF (*2*)	Dioxane		100
4-OCH$_3$						100
H	I			Toluene		100
4-NO$_2$		2	-	Dioxane	18	88

Note: R'SnBu$_3$ was vinyl (*1.1 equiv*)

Silia*Cat* DPP-Pd vs Competitive Catalysts

Always using the same reaction as for the reusability and leaching, comparative analysis with other Pd catalysts available on the market demonstrates Silia*Cat* DPP-Pd to be comparable or better in standard Stille conditions.

Silia*Cat* DPP-Pd vs Competitive Catalysts (*results in %*)					
Silia*Cat* DPP-Pd	**Escat 1351**	**EnCat 30**	**Royer Catalyst**	**$Pd(PPh_3)_4$**	**$Pd(OAc)_2$**
99	44	95	90	72	20

Case Study: Stille Reaction using the Silia*Cat* DPP-Pd in the Synthesis of a Thiophene-Phthalimide-Based Molecular Semiconductor under Microwave-Irradiation Conditions

Authors: Welch (*Dalhousie University*) *et al*.
Publication: *RSC Adv.*, **2015**, *5*, 26097-26106

Welch's group from Dalhousie University have studied the utility of a heterogeneous Pd catalyst for the synthesis of a molecular semiconductor, via various cross-coupling reactions (*Stille, Suzuki and direct heteroarylation*).

Stille Reaction

The target molecule, SM1 (*5,50(2,20-bithiophene-5,50 -diyl)- bis(2-hexylphthalimide)*), was synthetized under microwave irradiation via Stille reaction.

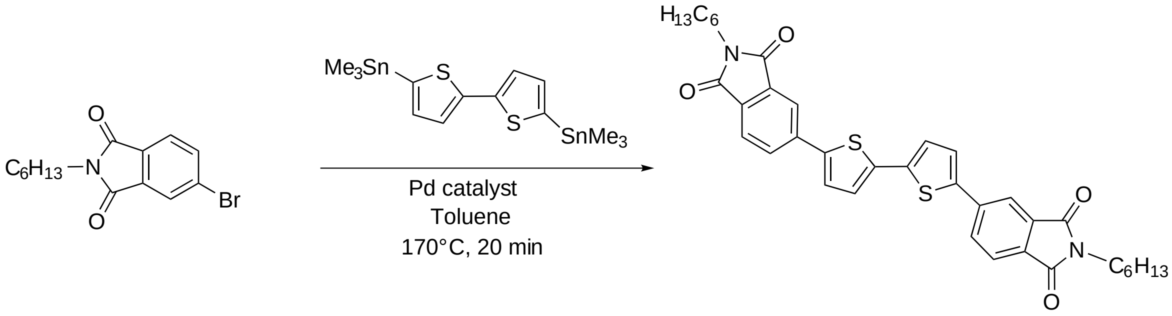
Three Pd-based catalysts were used for their initial screening:

1) $Pd(PPh_3)_4$
2) $Pd(PPh_3)_2Cl_2$
3) Silia*Cat* DPP-Pd

Welch and coworkers report that, while starting reagents were converted to SM1 with all three catalysts, Silia*Cat* DPP-Pd gave high yields, and SM1 was the major product albeit small baseline impurities (*H^1 NMR analysis*).

Conclusions

- *"Stille reaction protocols have highlighted the excellent performance of Silia*Cat* DPP-Pd in comparison to homogeneous catalyst alternatives and demonstrated effective conversion of starting material to product with catalyst loadings down to 0.1 mol %. Silia*Cat* DPP-Pd proved to be tolerant to both lab grade reagents and the capacity for two-fold recyclability without any significant impact on the material product and the respective yield"*.
- *"The robust and efficient performance of Silia*Cat* DPP-Pd coupled with its capacity to be used and stored under ambient conditions should be extremely useful for both routine and selected synthesis of organic semiconductors relevant to the field of organic electronics, in particular photovoltaics and thin-film transistors"*.

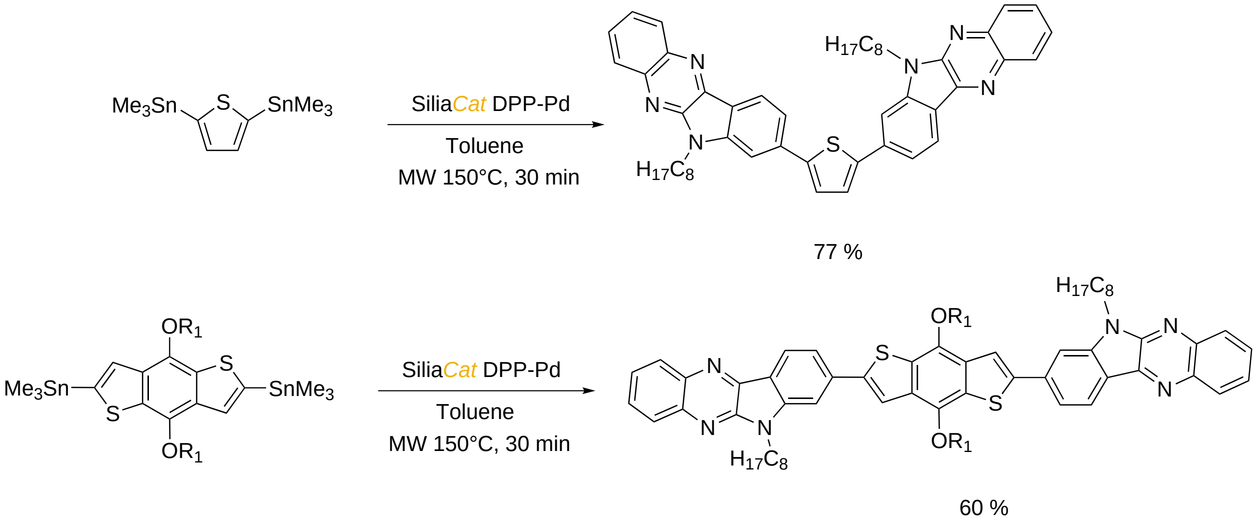


Case Study: Stille Coupling Using the SiliaCat DPP-Pd for the Synthesis of Indoloquinoxaline for Organic Electronics

Authors: Welch (*Dalhousie University*) *et al.*
Publication: *Dyes and Pigments*, **2015**, *123,* 139-146

Welch's group from Dalhousie University studied the utility of SiliaCat DPP-Pd in the synthesis of Indoloquinoxaline, a terminal building block for the construction of π-conjugated small molecules relevant to organic electronics. Indeed, indoloquinoxaline is a π-conjugated system that combines both electron withdrawing and donating nitrogen atoms.

Carbon-carbon bond forming reactions were done via a Stille coupling under microwave, using SiliaCat DPP-Pd.



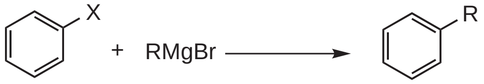
Conclusion for Stille Coupling

The SiliaCat DPP-Pd is a great alternative to homogenous catalysts for the Stille coupling. It can be used in various type of applications such as the synthesis of active intermediates and also in electronics. The catalyst is reusable and yields coupling products with minimal leaching.

Note: Typical experimental procedure for the Stille Coupling can be found at page 57.

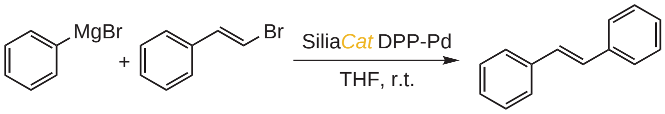
Kumada Coupling Using Silia*Cat* DPP-Pd

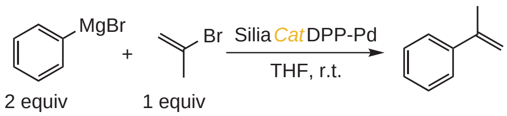
The Kumada coupling is the direct cross-coupling between an alkyl or an aryl Grignard and a halocarbon. It can be catalyzed by a Pd or a Ni catalyst.



Catalyst Concentration Effect

At a constant concentration of substrate, an increase of the amount of Silia*Cat* DPP-Pd from 0.1 (*or 0.2*) to 1.0 will increase the kinetics (*completed in only 15 minutes*). By increasing the concentration of the catalyst, thus thereby increasing the number of active sites, conversion of the substrate will be favored.





Catalyst Concentration Effect			
Silia*Cat* DPP-Pd (*mol %*)	**Solvent (*M*)**	**Time (*min*)**	**Conversion (*%*)**
1.0	THF (*0.07 M*)	15	96
0.5	THF (*0.07 M*)	15	95
0.2	THF (*0.08 M*)	120	94

Catalyst Concentration Effect			
Silia*Cat* DPP-Pd (*mol %*)	**Solvent (*M*)**	**Time (*min*)**	**Conversion (*%*)**
1.0	THF (*0.08 M*)	15	98
0.5		90	96
0.2		240	98

Catalyst Reusability and Leaching

Minimal leaching and robustness of the organoceramic matrix are important factors that allow it to be reused.

Silia*Cat* Reusability and Leaching			
Reusability	**Conversion (*%*)**	**Leaching (*ppm*)**	
		Pd	**Si**
1st	98	0.20	1.5
2nd	95	0.20	2.3
3rd	94	0.50	1.7

Catalytic Activity

Silia*Cat* DPP-Pd showed good reactivity for aryl iodides and bromides. Inert conditions are required for Kumada couplings due to the presence of Grignard reagent. Reactions were done in THF (*0.05 - 0.08 M*).

Catalytic Activity							
Substrate (*R*) / Halide (*X*)	**R-MgBr (*2 equiv*)**	**Time (*h*)**	**Conversion (*%*)**	**Substrate (*R*) / Halide (*X*)**	**R-MgBr (*2 equiv*)**	**Time (*h*)**	**Conversion (*%*)**
4-OCH_3 / Br	Ph-MgBr	18	98	4-F / Br	Ph-MgBr	24	94
	i-Bu-MgBr		95	H / I			99
4-CH_3 / Br	Ph-MgBr		96	4-OCH_3 / I			94
	i-Bu-MgBr		98	4-CH_3 / I			95

Conclusion of the Kumada Coupling

Silia*Cat* DPP-Pd can be succesfully used for the Kumada coupling for various substrates and shows good reactivity.

Typical Experimental Procedure: Stille & Kumada Couplings over Silia*Cat* DPP-Pd

Note: Please refer to the table presented below for specific conditions (*recommended solvents, scale of the reaction, reaction time, temperature, etc.*).
Anhydrous solvents or inert conditions are not required. We suggest to work one or two degrees below the boiling point of the solvent.

Reaction in batch mode

- Using the appropriate apparatus recommended for the screening or for the reusability reactions, the aryl halide substrate and the reagents are added to the reaction solvent.
- The mixture is then warmed to the desired temperature after which Silia*Cat* DPP-Pd is added.
- The reaction mixture is then vigorously stirred (*700 RPM*) until maximum conversion is observed (*as determined by TLC or GC/MS analysis*).

Work-up

Catalyst recovery

- Once the reaction is deemed complete as determined by TLC or by GC/MS analysis, the catalyst is recovered by filtration at room temperature through a Büchner funnel using a glass fiber filter (*grade 691*).
- The catalyst (*between 0.25 - 1.00 g*) is washed with EtOAc (*2 x 15 mL*), EtOH / H_2O (*v/v, 1/1, 3 x 15 mL*) and THF (*2 x 15 mL*).
- The catalyst is then dried under air at room temperature and can be stored in a closed vessel prior to reuse.
For prolonged storage, keep under argon at 8°C.

Isolation of the coupling product

- The filtrate is concentrated in vacuo and the residue is dissolved in EtOAc or Et_2O.
- The organic layer is then washed twice with water.
- The organic layer is dried using anhydrous magnesium sulfate and then concentrated in vacuo, yielding a high purity crude product that typically does not require extensive purification. If needed, a flash chromatography can be done.

Optimization Steps

Please see "*Optimization Steps*" presented at page 37.

Stille Coupling Reactions over Silia*Cat* DPP-Pd

Substrates	Aryl-Iodide (*1 equiv*)	Aryl-Bromide (*1 equiv*)
$R'SnBu_3$	1.1 equiv	
Additive (*CsF*)	2.0 equiv (*if needed for higher conversion*)	
Silia*Cat* Loading	≤ 2.0 mol % Pd	≤ 10 mol % Pd
Best Solvent & Temperature	Dioxane (*100°C*) or Toluene (*100°C*)	
Reaction Time	18 - 24 h	
Typical Scale	• Under Magnetic Stirring for Screening: 3 mmol scale of aryl halide in 30 mL solvent. • Under Mechanical Stirring for Reusability: 5 mmol scale of aryl halide in 50 mL solvent.	

Kumada Coupling Reactions over Silia*Cat* DPP-Pd

Substrates	Aryl-Iodide (*1 equiv*)	Aryl-Bromide (*1 equiv*)
R'MgBr	2.0 equiv Ph MgBr, *i*-BuMgBr, *i*-PrMgBr	
Silia*Cat* Loading	≤ 2.0 mol %	≤ 10 mol %
Best Solvent & Temperature	THF (*60°C*)	
Reaction Time	18 - 24 h	
Typical Scale	• Under Magnetic Stirring for Screening: 3 mmol scale of aryl halide in 35 - 60 mL anhydrous solvent under inert conditions. • Under Mechanical Stirring for Reusability: 3 mmol scale of aryl halide in 35 - 60 mL anhydrous solvent under inert conditions.	

Hydrogenation of Nitroarenes Using Silia*Cat* Pd^0 & Pt^0

Functionalized anilines are important intermediates in various industries such as pharmaceuticals, polymers and dyes. Simple aromatic amines are generally obtained by catalytic hydrogenation of nitroarene compounds with various heterogeneous commercial catalysts (*supported nickel, copper, cobalt*) including Pd/C and Pt/C. Yet, the selective reduction of a nitro group with H_2 when other reducible groups are present in the same molecule is generally not feasible with these catalytic materials and requires the use of advanced heterogeneous catalysts. Silia*Cat* Pd^0 and Pt^0 exhibit chemoselective catalytic activity for the hydrogenation reaction of a series of substituted nitro compounds under remarkably mild conditions, namely at room temperature in methanol under a H_2 filled balloon (*1 atm*), using 0.5 mol % catalyst amount.

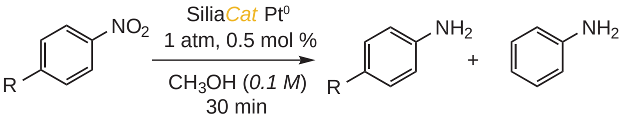
Silia*Cat* Pd^0 is an excellent catalyst choice for the hydrogenation of nitroarene in presence of “moderately” reducible functional groups. However, when more challenging substrates containing sensitive functionalities (*such as double or triple bonds, carbonyls*) or with halo-nitroarenes, the use of Silia*Cat* Pt^0 is recommended.

Note: detailed experimental procedure can be found at page 66.

Silia*Cat* Reusability

The reusability tests of Silia*Cat* Pd^0 & Pt^0 were studied using 4-chloronitrobenzene as substrate. Reusing both catalysts in 7 consecutive cycles did not result in any loss of catalytic activity. Complete substrate conversion was obtained even after the seventh cycle, with 99 % selectivity.

For the Silia*Cat* Pt^0, the selectivity of the reaction even improves with each subsequent cycle going from 84 % in the first run up to 99 % in run 7. The positive-feedback phenomenon of effective selectivity in consecutive reaction cycles is probably attributed to the silica matrix alkylation.



Silia*Cat* Reusability in (%)

Reusability	Silia*Cat* Pd^0 Conv. (*Selectivity*)	Silia*Cat* Pt^0 Conv. (*Selectivity*)
1	100 (99.7)	100 (84.1)
2	100 (99.6)	100 (89.7)
3	100 (99.6)	100 (90.5)
4	100 (99.2)	100 (92.6)
5	100 (99.7)	100 (98.8)
6	100 (99.6)	100 (99.5)
7	100 (99.3)	100 (99.3)

Silia*Cat* Pt^0 vs Competitive Catalysts

Other commercially available Pt heterogeneous catalysts [*Pt/C, Pt/*SiO_2 *and Reaxa Pt(0)EnCat40*] were tested in the selective reduction of 4-chloro-nitrobenzene. In comparison to other Pt(0) heterogeneous catalysts, the Silia*Cat* Pt^0 catalyst proved to be much more reactive, with complete conversion after 0.5 h with just 0.5 mol %. Furthermore, selectivity was significantly higher with only 4 % aniline formed as by-product. No secondary product was observed in solution.

Silia*Cat* Pt^0 vs Competitive Catalysts

Catalyst	Silia*Cat* Pt^0			Pt/C			Pt/SiO_2			Reaxa Pt(0)EnCat40 dry		
Mol (%)	5	1	0.5	5	1	0.5	5	1	0.5	5	1	0.5
Time (*h*)	0.5	0.5	0.5	1	1	1	1	2	2	0.5	2	2
Product (%)	96	92	88	82	65	43	84	88	48	87	90	86
Aniline (%)	4	8	12	14	4	0	13	10	2	13	10	13

Exp. conditions: 2 mmol substrate in 20 mL MeOH under hydrogen balloon at room temperature.

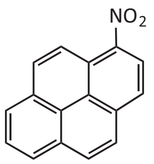
Substrate Scope and Selectivity

The hydrogenation of different nitro compounds containing various functionalities, was attempted to demonstrate the selectivity of Silia*Cat* catalysts in a wide range of reactions. The reaction was tested under hydrogen balloon, at room temperature conditions in methanol (*0.05 - 0.1 M*) using 0.5 - 1 mol % Silia*Cat* catalysts. Conversion and selectivity are presented below for various substrates. Please see the related publication for all details as well as other examples.

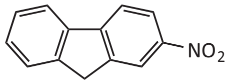
Substrate Scope and Selectivity Results

Substrate #	Silia*Cat* Pd⁰			Silia*Cat* Pt⁰		
	Time (*h*)	Conversion (%)	Selectivity (%)	Time (*h*)	Conversion (%)	Selectivity (%)
1	1	100	100	1	100	98
2		100	100		98	100
3		100	98		100	100
4		100	100	2	100	98
5		100	92	1	100	100
6		100	100		100	100
7		100	100		100	100
8		100	100		100	100
9	2	100	65	0.5	100	93
10	1	100	97	1	100	91
11		100	10		100	80
12	4	100	0		100	80

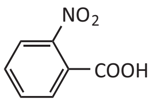
Substrate Structures



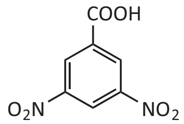
1



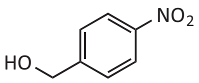
2



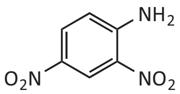
3



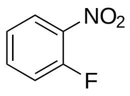
4



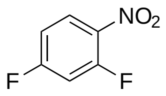
5



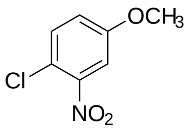
6



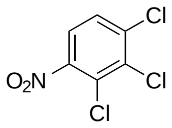
7



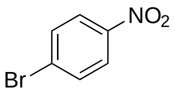
8



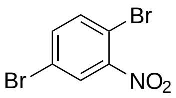
9



10



11

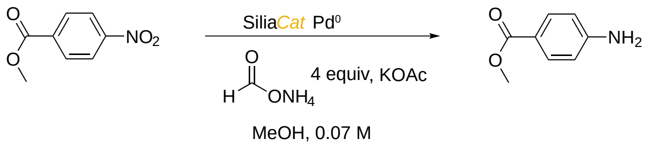


12

Selective Hydrogenation in Flow using Ammonium Formate

The use of ammonium formate as a hydrogen source was investigated in flow chemistry and compared with batch mode using Silia*Cat* Pd⁰. Compared to the same process performed under batch conditions, the operation under continuous flow affords fully selective conversion in only 14 minutes, versus 60 minutes required for maximum 95 % selectivity in batch reactions.

Note: reactions were done at room temperature.



Hydrogenation using Ammonium Formate

Mode	Time (*min*)	Conversion (%)	Selectivity (%)
Batch	60	95	100
Flow	14	100	100

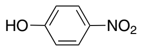
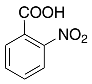
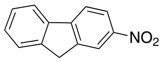
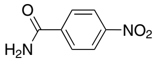
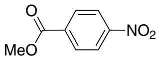
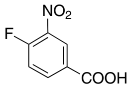
Comparison of Various Heterogeneous Pd-Catalysts

The effectiveness of Silia*Cat* Pd^0 for the hydrogenation of nitroarenes was investigated and compared with other heterogeneous catalysts available on the market. **It is very important to note that for all reaction conditions, all catalysts were used in the manufacturer's optimized reaction conditions and not just SiliCycle's** in order to be able to make relevant conclusions. Reactivity of Silia*Cat* Pd^0 was compared with Reaxa EnCat Pt^0 catalyst as well as with palladium on carbon Pd/C (*conventional hydrogenation method*) for six different compounds.

Experimental conditions

- For Silia*Cat* Pd^0: 1 mol % Silia*Cat* Pd^0; MeOH; H_2 (*1 atm*); 30 min
- For Reaxa EnCat Pt^0: 5 mol % Pt^0 EnCat; MeOH; H_2 (*1 atm*); 30 min
- For Pd/C: 1 mol % Pd/C; MeOH; H_2 (*1 atm*); 30 min

Hydrogenation Conversion Comparison (*in %*)

Nitroaryl	Silia*Cat* Pd^0	Reaxa EnCat Pt^0	Pd/C (*5 %*)
	**100**	15	**99**
	**98**	0	**100**
	**100**	45	**100**
	**100**	12	**100**
	**100**	22	**100**
	**100**	46	**100**

Conclusion

In all cases, Silia*Cat* Pd^0 and Pd/C were comparable, but handling is simpler with Silia*Cat*, making this catalyst a **safer** replacement for Pd/C. For all reactions, the EnCat results were significantly lower compared to the other catalysts.

Conclusion of Selective Hydrogenation of Nitroarenes

The selective hydrogenation of different nitro compounds in the presence of various functionalities, including reducible carbonyl, amide, ester, amine and halide groups was achieved with Silia*Cat* Pd^0 or Pt^0 catalyst in methanol at room temperature and under 1 atm H_2 pressure.

Related Publications for Hydrogenation of Nitroarenes

Adv. Synth. Catal., **2011**, *353*, 1306-1316
Catal. Sci. Technol., **2011**, *1*, 1616-1623
Nanoscale, **2014**, *6*, 6293-6300

Hydrogenation of Alkenes and Alkynes Using Silia*Cat* Pd^0

Catalytic hydrogenation of unsaturated C-C bonds can be achieved using either homogeneous or heterogeneous catalysts. However, with many catalysts, purification of the desired alkene is really hard due to lack of selectivity. Silia*Cat* Pd^0 can be used to mediate at room temperature the selective hydrogenation of a wide variety of alkenes under 1 atm of H_2 using 0.1 mol % of catalyst amount. Various solvents can be used (*methanol, ethanol, THF or MeOH / THF*) at 0.25 M concentration in respect to the substrate. The catalyst is reusable with negligeable leaching of palladium, providing the chemical industry with a suitable replacement for less selective metal-based catalysts.

Silia*Cat* Pd^0 Reusability and Leaching

The reusability of Silia*Cat* Pd^0 was explored in the hydrogenation of *trans*-cinnamic acid. Reusing the catalyst in five consecutive cycles did not show any loss in catalytic activity with minimal leaching of Pd and Si (*assessed by ICP-OES*). Complete substrate conversion was obtained even after the fifth cycle, with 99 % selectivity.

Silia*Cat* Pd^0 Reusability and Leaching

Run	Conversion (%)	Selectivity (%)	Leaching (*ppm*)	
			Pd	Si
1	100	100	0.09	0.06
2	100	100	0.09	0.03
3	100	100	0.12	0.02
4	100	99	0.09	0.03
5	100	99	0.08	0.02

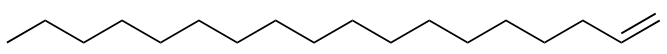
Substrate Scope and Selectivity

The hydrogenation of various alkenes was done to demonstrate the versatility of this catalyst. The material was tested under 1 atm of H_2, at room temperature conditions in different solvents at 0.25 M using 0.1 mol % Silia*Cat* Pd^0. Conversion and selectivity are presented below for various substrates. Please see the related publication for all details as well as other examples.

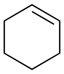
Substrate Scope and Selectivity Results

Substrate	Time (*h*)	Conversion (%)	Selectivity (%)	Substrate	Time (*h*)	Conversion (%)	Selectivity (%)
1	0.5	100	99	5	0.5	100	97
2	1	100	99	6	2	100	100
3	1	100	99.5	7	0.5	100	100
4	2	100	100	8*	2	100	99

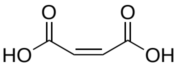
Substrate Structures



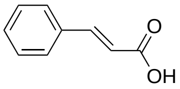
1



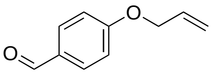
2



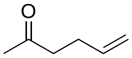
3



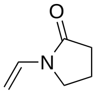
4



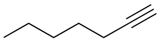
5



6



7



8*

* The hydrogenation is not selective and forms the corresponding alkane.

Related Publication for Hydrogenation of Alkenes & Alkynes

Org. Proc. Res. Dev., **2012**, *16*, 1230-1234

Selective Hydrogenation of Vegetable Oils over Silia*Cat* Pd^0

Silia*Cat* Pd^0 is an efficient heterogeneous catalyst for the hydrogenation of a wide variety of vegetable oils under 1 atm of H_2 in methanol over 0.1 mol % of catalyst. A low concentration of catalyst is enough to promote full hydrogenation of fatty acids, fatty acid methyl esters and vegetable oils with no isomerisation and negligible leaching of palladium. The catalyst is fully reusable, opening the route to replacement of Ni-based catalyst in the oleochemicals industry.

Silia*Cat* Pd^0 Reusability and Leaching

Silia*Cat* Pd^0 can be reused several time without any loss in the reactivity and minimal leaching of Pd and Si. Complete data is provided inside the related publication.

Substrate Scope

To further investigate the catalyst selectivity, hydrogenation of different fatty acids containing different numbers of double bonds were attempted to form the corresponding saturated product. Reactions were conducted in methanol 0.25 M over 0.1 - 0.2 mol % Silia*Cat* Pd^0.

Substrate Scope and Leaching Results

Substrate	Catalyst *(mol %)*	Time *(h)*	Conversion *(%)*	Yield *(%)*	Leaching *(ppm)*	
					Pd	Si
Oleic acid (*cis C18:1*)	0.1	3	100	99.5	0.25	0.10
Linoleic acid (*cis C18:2*)		4	100	97.5	0.25	0.19
α-linolenic acid (*cis C18:3*)		5	100	99.4	0.29	0.07
Eicosapentaenoic acid ethyl esther (*cis C20:5*)	0.2	3	100	N/A	0.13	0.18
Erucic acid (*cis C22:1*)			100	N/A	-	-

To explore the scope of the method, different vegetable oils were then hydrogenated in THF / MeOH (*0.5 M*) over 0.1 mol % Silia*Cat* Pd^0. In general, complete substrate conversion of the vegetable oil to saturated product was obtained after 3 h.

Substrate Scope and Leaching Results of Vegetable Oils

Substrate	Time *(h)*	Conversion *(%)*	Leaching *(ppm)*	
			Pd	Si
Sunflower oil (*linoleic acid 64.5 %, oleic acid 25.5 % and other 10 %*)	3	99	0.3	0.19
	2	99	0.08	0.19
Corn oil (*linoleic acid 54 %, oleic acid 27 % and other 19 %*)	3	98	0.17	0.19
Soybean oil (*linoleic acid 50 %, oleic acid 27 %, linolenic acid 9 % and other 14 %*)		99	0.52	0.42
Canola oil (*linoleic acid 22 %, oleic acid 58 %, linolenic acid 9 % and other 11 %*)		99	0.36	0.16
Olive oil (*linoleic acid 8 %, oleic acid 72 % and other 20 %*)	2	99	0.32	0.19

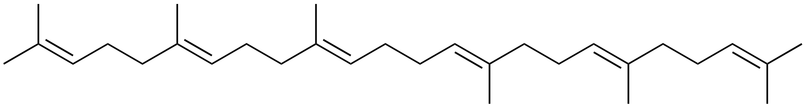
Conclusion of Hydrogenation of Vegetable Oils

In conclusion, only 0.1 mol % of Silia*Cat* Pd^0 selectively mediates the full conversion to saturated vegetable oils at room temperature under 1 atm of H_2. The catalyst is also reusable, offers minimal leaching and provides pure product (*no purification usually required*).

Related Publication for Hydrogenation of Vegetable Oils

Org. Proc. Res. Dev., **2012**, 16, 1307-1311

Hydrogenation of Squalene to Squalane Using SiliaCat Pd^0



Squalene

The complete hydrogenation of highly unsaturated all-trans linear squalene into valuable fully saturated squalane is achieved smoothly under mild conditions over the sol-gel entrapped Pd catalyst SiliaCat Pd^0. The catalysis is truly heterogeneous, and the catalyst is stable and reusable, which opens the route to an easier and less expensive hydrogenation of squalene. A brief overview of our results are presented here. Please refer to the related publication for all the details.

Solvent Effect

We first performed a series of experiments using a commercial squalene sample (*98 wt % purity*) aimed to identify the best solvent for the catalytic hydrogenation of squalene over the SiliaCat Pd^0 catalyst under 1 atm of H_2 at temperatures between 22 and 50°C.

The best conditions identified were, 0.5 mol % SiliaCat Pd^0 in ethanol 0.50 M with respect to squalene under 1 atm H_2 at 50°C.

Solvent Effect

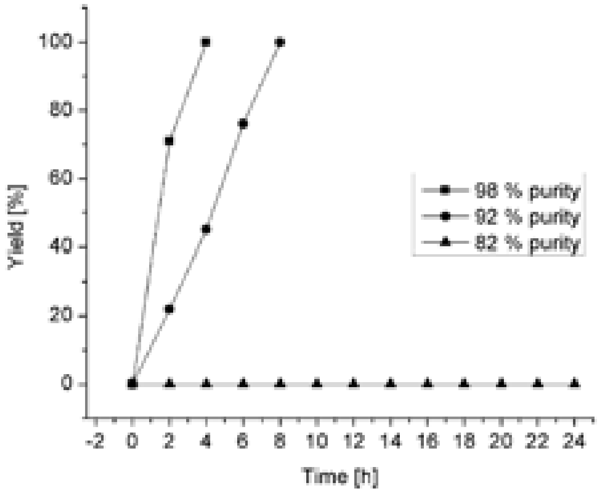
Solvent (*Conc. [M]*)	Tempature (°C)	Time (*h*)	Conversion (*isolated yield %*)
EtOH (*0.25*)	22	6	100 (-)
	30	6	100 (98.4)
	50	5	100 (99.2)
EtOH (*0.33*)	30	6	100 (99.2)
	50	4	100 (99.5)
EtOH (*0.50*)	50	4	100 (99*)
MeTHF / EtOH 1:1 (*0.50*)	50	4	100 (75*)
	50	6	100 (98*)

* Yield evaluated by GC-MS analysis.

Squalene Purity Effect

The purity of the squalene used has a direct influence on the success of the hydrogenation. Using the optimal condition determined in the previous section, three grades of squalene were evaluated. The higher the purity, the easier is the hydrogenation reaction.

Using squalene with purity above 90 % allows complete conversion in a very short period of time. However, less pure squalene (*82 wt % purity*) did not provide any reaction using these conditions. Another set of conditions were developed for this grade of squalene without solvent using 0.3 mol % SiliaCat Pd^0 under 3 atm H_2 at 100°C for 24 hours (*100 % conversion, 85 % yield*).



Conclusion for Hydrogenation of Squalene to Squalane

This reaction is still under development but SiliaCat Pd^0 can be succesfully used for the hydrogenation of squalene and can be reused several time without loss in the reactivity. Reaction can also be done without any solvent and on various purity grades of squalene. Please refer to our website for all the datas.

Related Publication for Hydrogenation of Squalene

Chem. Cat. Chem., **2015**, *7*, 2071-2076

Selective Debenzylation Using Silia*Cat* Pd^0

The selective debenzylation of aryl benzyl ethers, benzyl esters and benzyl amines, while leaving other sensitive groups intact, can be carried out in high yield under mild conditions (*namely at room temperature under 1 atm H_2, using 0.5 mol % SiliaCat Pd^0*).

Selective and smooth deprotection is critical. The commonly used method makes use of catalytic hydrogenolysis to cleave benzylic groups with H_2 under pressure and in the presence of a heterogeneous catalyst such as Pd/C or Raney Ni. However, very often the deprotection reaction conditions are not compatible with other functional groups, such as nitro, unsaturated bonds and halogen groups. Silia*Cat* catalysts offer a number of additional advantages over traditional Pd/C. They are non pyrophoric and have a higher density and lower catalytic consumption (< *1 mol % vs 5 - 10 % for Pd/C*) due to fast kinetics and high turnover.

Solvent & Catalyst Concentration Effects

Solvent choice is critical for any debenzylation reaction. Therefore, in order to optimize the reaction conditions, 1-(benzyloxy)-4-methoxybenzene was used as our substrate of choice. A series of commonly employed solvents were screened under 1 atm of H_2 at room temperature using 2 mol % of catalyst at different solvent concentrations. The best results were achieved with methanol and ethanol.

The molar concentration of the solvent is crucial for this reaction. The best results were achieved by using a methanol concentration of 0.07 M and 0.5 - 1 mol % Silia*Cat* Pd^0, with complete conversion obtained after 1 - 2 hours.
(*refer to related publication for all the details*).

Solvent Effect

Solvent	Substrate Conc. (*M*)	Time (*h*)	Conversion (*%*)
EtOH	0.1 / 0.07	16 / 4	17 / 100
MeOH		16 / 0.5	15 / 100
THF	0.07	20	15
EtOAc			20
Hexane			21

Silia*Cat* Pd^0 Reusability and Leaching

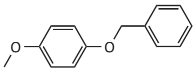
Catalyst stability and reusability are crucial features of any catalyst seeking commercial applications. Silia*Cat* Pd^0 was thus reused six consecutive times in the O-debenzylation reaction of 1-(benzyloxy)-4-methoxybenzene under the standard mild conditions developed in our laboratory. The activity remained approximately constant, and expanding the reaction time by 50 % was sufficient to keep conversion constant.

Silia*Cat* Pd^0 Reusability and Leaching

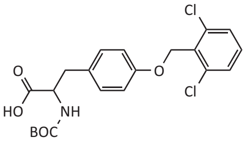
Reusability	Time (*h*)	Conversion (*%*)	Leaching (*ppm*)	
			Pd	Si
1st	1	100	0.7	2.5
2nd		100	0.3	1.3
3rd	1.5	100	0.3	2.3
4th		100	0.2	1.4
5th		99	0.2	0.8
6th		100	0.1	0.5

Substrate Scope and Selectivity

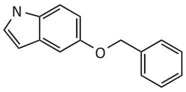
Silia*Cat* Pd^0 is an efficient catalyst for the selective debenzylation of different aryl benzyl ethers, benzyl amino-acids and benzylprotected sugars leaving other sensitive groups intact. Refer to our publication in *ChemCatChem,* **2011**, *3*, 1-5 for more examples. Conversion and yields (*in %*) of some key examples using 1 mol % of catalyst are presented here.



100 / 99.7
(*1 h*)



100 / 98.6
(*1 h*)



100 / 98.0
(*20 h*)

Silia*Cat* Pd^0 vs a Competitive Catalyst

Using the same reaction as the one used to demonstrate the reusability of Silia*Cat* Pd^0 in the O-debenzylation reaction, we also tested the commercial catalyst Pd^0 EnCat, a polyurea-entrapped catalyst.

Silia*Cat* shows better performance over the EnCat catalyst.

Silia*Cat* Pd^0 vs a Competitive Catalyst

Catalyst (*mol %*)	Time (*h*)	Conversion (%)	Selectivity (%)
Silia*Cat* Pd^0 (*0.5*)	1 / 2	95 / 100	- / 100
Silia*Cat* Pd^0 (*1.0*)	0.5 / 1	75 / 100	- / 100
Pd^0 EnCat (*10*)	16	100	100

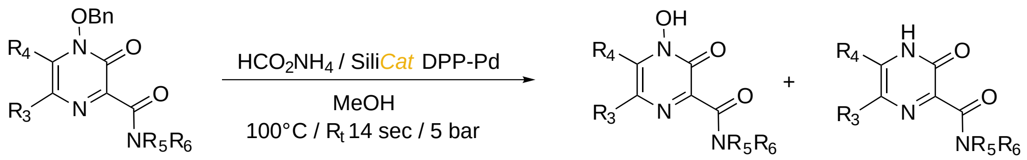
Case Study: Selective *O*-Debenzylation Using Silia*Cat* DPP-Pd in Flow Chemistry

Authors: De Borggraeve (*University of Leuven*) *et al*.
Publication: *Journal of Flow Chemistry*, **2015**, *5*, 6-10

De Borggraeve's research group has developed a new synthesis of *N*-hydroxypyrazin-2(*1H*)-ones via the selective O-debenzylation of 1-benzyloxypyrazin-2(*1H*)-ones using flow chemistry. An appropriate catalyst was needed for the debenzylation and Silia*Cat* DPP-Pd showed excellent results.

The optimization reaction was done using the model system 1-benzyloxy-*N,N*-diethyl-5,6-dimenthylpyrazin-2(1*H*)-one-3-carboxamide. The reaction showed acceptable conversion at 60 °C and was complete at 80 - 100°C at a residence time of 14 sec without losing selectivity for the formation of the desired prodcut (*N-OH form : N-H form = 97 - 98 % : 1 - 2 %)*

Based on these promising results, a large library of aspergillic acid-like hydroxamic acids was produced under the experimental conditions for debenzylation that were considered to be optimal. The obtained yields were good to very good, and the selectivities good to excellent.



1 **2** **3**

Yield: 72 - 96 %

Conclusion of Selective Debenzylation

Silia*Cat* Pd^0 is suitable for the selective debenzylation of numerous substrates under mild conditions with only 1 - 2 mol % catalyst amount. Benzyl-protected sugars, amino acids, ethers and esters are smoothly debenzylated under 1 atm of H_2 at room temperature.

Related Publication for Selective Debenzylation

Chem. Cat. Chem., **2011**, *3*, 1146-1150

Typical Experimental Procedure: Hydrogenation Using SiliaCat Pd^0 & Pt^0

Note: For each hydrogenation reaction, please refer to the related table presented next page for specific conditions (*recommended solvents, scale of the reaction, reaction time, temperature, etc.*). The hydrogenation reaction being an exothermic reaction, an exotherm may be observed as the reaction progresses.Reusability tests are done using a high pressure reactor.

Palladium on carbon (*Pd/C*) frequently ignites when it first comes in contact with methanol (*and to a lesser extent, any flammable organic solvent*) and as such represents a significant safety risk. Even if SiliaCat is a safer alternative, these procedures are recommended whenever this catalyst is used in conjunction with hydrogen gas.

Hydrogenation using a balloon

1. Weigh out SiliaCat and transfer into a round bottom flask equipped with a condenser and a stirring bar.
   ***Note**: we suggest using a two-neck flask*.
2. Add solvent and the reaction substrate.
3. Attach a balloon of hydrogen to the condenser with an adapter that allows the balloon to be closed off from the reaction flask.
4. While stirring, the reaction mixture is purged by cycling an inert gas (*nitrogen or argon*) and vacuo twice.
5. The reaction mixture is degassed twice with hydrogen for one minute by opening the balloon adapter.
6. The reactor is now ready for the hydrogenation reaction.

Hydrogenation using a high pressure reactor (*bomb reactor*)

1. Weigh out SiliaCat and transfer into the appropriate bomb reactor.
2. Add solvent and the reaction substrate and seal the reactor.
3. While stirring, the reaction mixture is purged by cycling an inert gas (*nitrogen or argon*) and vacuo twice.
4. Fill the reactor with hydrogen up to the desired pressure using the gauge.
5. Seal the reactor by closing off the hydrogen source and disconnect the reactor from the regulator.
6. You can now run your hydrogenation reaction.

Work-up Procedures: When the hydrogenation is finished, please use the following procedure for the work-up.

Destructive work-up (*if you do not want to use SiliaCat for another reaction*)

1. Remove the hydrogen balloon from the flask (*for balloon reactions*) or slowly allow the reactor to return to atmospheric pressure.
2. Purge reaction vessel twice with an inert gas (*nitrogen or argon*).
3. The reaction mixture can also be purged through bubbling of nitrogen or argon for 10 - 15 minutes for added safety.
4. Under a moderate vacuum, filter the reaction mixture through a Büchner funnel using a glass fiber filter (*grade 691*).
5. Rinse the flask with your preferred solvent (*we suggest using an aprotic solvent like ethyl acetate (EtOAc) or tetrahydrofuran (THF) for safety reasons*).
6. Using the same solvent as step 5, wash SiliaCat on the Buchner to make sure any product of interest is not adsorbed on the catalyst.
7. Disconnect the Büchner funnel from the receiving flask and then add several mL of water to the filter.
8. Discard the wet SiliaCat and filtering aid in a dedicated waste jar that contains water.

Nondestructive work-up (*if you want to reuse SiliaCat for another reaction)*

***Note**: reusability study for large scale in progress.*

1. Follow steps 1 - 4 from the procedure above (*"Destructive work-up"*).
2. Under vacuum, rinse the SiliaCat on the Buchner with an aprotic solvent (*EtOAc or THF*) using 4-fold the amount of catalyst used. **DO NOT DRY COMPLETELY THE CATALYST.**
3. Transfer the humid SiliaCat in a round flask and dry the solid under argon during several hours (*overnight*).
4. Store the catalyst under normal conditions, in a closed vessel prior to reuse. For prolonged storage, keep under argon at 8°C.

Caution! The catalyst can be isolated by filtration under vacuum but it should not be dried under vacuum in presence of air / methanol.

If for any reason the catalyst is dried completely under vacuo, the adsorbed hydrogen can slowly react (*after a few minutes of drying*) with oxygen to create an exothermic reaction (> *320°C*). If the catalyst is dried completely, close the vacuum and wash with water.

Functionalized Nitroarene Hydrogenation Reactions using Silia*Cat* Catalysts

Substrate	Nitroarenes & Nitro-functionalized Aryl Halides	
Silia*Cat* Catalyst	Silia*Cat* Pd^0	Silia*Cat* Pt^0
Silia*Cat* Loading	≤ 1.0 mol % Pd or Pt	
Best Solvents	MeOH, THF, MeTHF, EtOH	MeOH, THF, MeTHF, EtOAc, EtOH, hexane
Temperature	20 - 22°C	
H$_2$ Pressure	1 atm	
Reaction Time	0.5 - 4 h	
Typical Scale	• Under Magnetic Stirring for Screening: 2 mmol scale of functionalized nitroarene in 20 mL solvent (*HPLC grade*). • Under Mechanical Stirring for Reusability: 20 mmol scale of functionalized nitroarene in 200 mL solvent (*HPLC grade*).	

Alkene Hydrogenation Reactions Using Silia*Cat* Pd^0

Substrate	Non-functionnalized and functionnalized Alkenes
Silia*Cat* Loading	≤ 0.5 mol % Pd
Best Solvents	MeOH or EtOH [THF, MeTHF, MeOH / THF(*1:1, v/v*)]
Temperature	20 - 22°C
H$_2$ Pressure	1 atm
Reaction Time	0.5 - 4 h
Typical Scale	• Under Magnetic Stirring for Screening: 6 mmol scale of alkene in 25 mL solvent (*HPLC grade*). • Under Mechanical Stirring for Reusability: 50 mmol scale of alkene in 200 mL solvent (*HPLC grade*).

Vegetable Oil Hydrogenation Reactions Using Silia*Cat* Pd^0

Substrate	Vegetable Oils
Silia*Cat* Loading	≤ 0.5 mol % Pd
Best Solvents	MeOH (*0.25 M or 0.5 M*) THF, MeTHF, EtOAc, EtOH, THF / MeOH (*5:1, v/v*)
Temperature	20 - 40°C
H$_2$ Pressure	1 atm
Reaction Time	0.5 - 6 h
Typical Scale	• Under Magnetic Stirring for Screening: 15 mmol scale of fatty acid (*or vegetable oil*) in 60 mL solvent (*HPLC grade*). • Under Mechanical Stirring for Reusability: 50 mmol scale of fatty acid (*or vegetable oil*) in 200 mL solvent (*HPLC grade*).

Squalene Hydrogenation Using Silia*Cat* Pd^0

Substrate	Squalene	
Silia*Cat* Loading	≤ 1.0 mol % Pd	
Best Solvents	EtOH	EtOH or neat
Temperature	50°C	50 - 70°C
H$_2$ Pressure	1 atm	1 - 3 atm
Reaction Time	4 - 8 h	2 - 24 h
Typical Scale	• Under Magnetic Stirring for Screening: 10 mmol scale of squalene in 30 mL solvent (*HPLC grade*). • Under Mechanical Stirring for Reusability: 50 mmol scale of ene in 150 mL solvent (*HPLC grade*).	

Debenzylation Reactions Using Silia*Cat* Pd^0

Substrate	Benzyl Protected Group
Silia*Cat* Loading	≤ 2.0 mol % Pd
Best Solvents	EtOH [MeOH, THF, MeTHF, EtOAc, Hexane]
Temperature	20 - 22°C
H$_2$ Pressure	1 atm
Reaction Time	0.5 - 24 h
Typical Scale	• Under Magnetic Stirring for Screening: 4 mmol scale of benzyl protected group in 40 mL solvent (*HPLC grade*). • Under Mechanical Stirring for Reusability: 20 mmol scale of benzyl protected group in 200 mL solvent (*HPLC grade*).

Optimization Steps

If the reaction fails or if the conversion is incomplete, optimization steps can be undertaken. The alkene hydrogenation example presents the pathway (*order*) you need to follow for each type of hydrogenation.

Step 1: Handling

- Ensure that the degassing step by vacuum-inert gas cycling followed by H_2 purge is performed adequately.
- Ensure that the internal reaction temperature is at least 20°C. The hydrogenation reaction is an exothermic reaction.

Always using 0.1 mol % Silia*Cat* Pd^0:

Step 2: Solvent Screening

Different solvents may be tried such as MeOH, EtOH, EtOAc, THF, MeTHF, hexane.
For substrates poorly soluble in MeOH, the preferred solvent system is MeOH-THF (*1:1, v/v*).

Step 3: Solvent Concentration Optimization

Once the best solvent has been determined, different alkene solvent concentrations (*from 0.25 M to 1.0 M*) should be explored.

Step 4: Silia*Cat* Loading (*mol %*)

Finally, the loading of Silia*Cat* Pd^0 should be optimized.

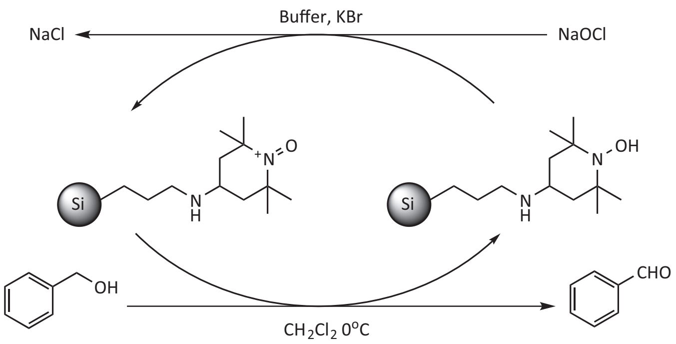
If the reaction **is not complete**,
the amount of catalyst should be increased from 0.1 mol % to 0.5 or 1.0 mol % Pd.

If the reaction **is complete**,
the catalyst loading can be decreased from 0.1 mol % to 0.05 or 0.01 mol % Pd.

Oxidation Using Silia*Cat* TEMPO

Aldehydes and ketones, either as starting materials, synthetic intermediates, or final products, are of great interest in synthetic chemistry. Such carbonyl-containing products can lead to carbon-carbon (*i.e. Wittig, Aldol, alkylation*) or carbon-nitrogen bond formation. Over the years, chemists have discovered various oxidizing agents such as pyridinium chlorochromate (*PCC*), MnO_2, Dess-Martin periodinane or Swern oxidation conditions. Although all of these methods lead to the aldehyde (*limited oxidation of the aldehyde to the carboxylic acid*), they have drawbacks such as the hazards and toxicity associated with residual metal contamination.

The development of environmentally friendly methods for the selective catalytic oxidation of alcohols to aldehydes and ketones can have significant impact on modern methods of chemical synthesis. Silia*Cat* TEMPO is the oxidation solution of choice.



Catalytic Performance and Leaching

Silia*Cat* TEMPO was investigated under the Montanari-Anelli conditions. The catalytic cycle involves regeneration of the oxidative species with NaOCl in presence of KBr as co-catalyst to form the anion OBr^-.

Silia*Cat* TEMPO can be used in quantity as low as 0.01 mol % to provide the desired aldehyde in short reaction times. ICP analysis confirms that the catalyst is leach-resistant (*[Si] ≤ 3 ppm*).

Catalytic Performance and Leaching

Silia*Cat* *(mol %)*	Time *(h)*	Conversion *(%)*	Si Leaching *(ppm)*
0.1	1	95	-
0.01	2	83	3
	3	95	1.6
	4	97	1.5
0.02	2	96	-
	3	100	2

Silia*Cat* TEMPO Reusability

The minimal leaching profile and the robustness of Silia*Cat* TEMPO's organoceramic matrix allow it to be reused several times. Silia*Cat* TEMPO is recycled by post-reaction filtration, DCM washes and air drying.

Silia*Cat* TEMPO Reusability

Reusability	Time *(min)*	Conversion *(%)*	Reusability	Time *(min)*	Conversion *(%)*	Reusability	Time *(min)*	Conversion *(%)*
1st	30	100	Results for run 3 to 7 were similar to 1 - 2			9th	30 / 60	97 / 100
2nd	30	100	8th	30 / 60	95 / 100	10th	30 / 60	90 / 100

Influence of Co-Catalyst and Temperature

SiliCycle investigated wether it was necessary to use a co-catalyst (*KBr*) for the reaction to proceed effectively. As shown in the table, although KBr is not required for the reaction, it does have a significant impact on kinetics. The reaction can still proceed to completion without KBr but requires longer time and / or more Silia*Cat* TEMPO. It was also demonstrated that the reaction can be carried out at room temperature without KBr.

Influence of KBr and Temperature

Silia*Cat* *(mol %)*	KBr *(equiv)*	Temp. *(°C)*	Time *(min)*	Conversion *(%)*
0.1	0.1	0	60	95
	0		60	80
			210	100
0.2			105	96
		22	60	76
			90	87

Influence of Solvents, pH and NaOCl

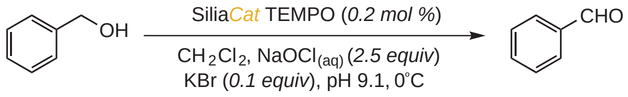
As shown on the right, the reaction can be carried out at pH 9.0 or at pH 7.5 with high conversions. The catalytic conditions are selective towards the aldehyde, rather than the carboxylic acid, even with 10 equiv of NaOCl.
***Note**: the reaction can also be pursued in water or with other organic solvents.*

Influence of Solvent, pH and $NaOCl_{(aq)}$

Silia*Cat* (*mol %*)	$NaOCl_{(aq)}$ (*equiv*)	Solvent	pH	Time (*min*)	Conversion (*%*)
0.2	2.50	DCM	9.0	60	98
	10.00			90	98
	1.25		7.5	60 / 90	83 / 86
	2.50				94 / 98

Silia*Cat* TEMPO vs Homogeneous TEMPOs

Comparative analysis versus homogeneous TEMPOs demonstrates the Silia*Cat* TEMPO to be comparable or better at neutral pH and significantly superior in basic conditions.



Silia*Cat* TEMPO vs Homogeneous TEMPOs

pH	Silia*Cat* TEMPO	4-MeO-TEMPO	4-Oxo-TEMPO
7.5	91	99	45
9.0	98	55 (40)[1]	73

[1] In parenthesis = conversion to carboxylic acid.

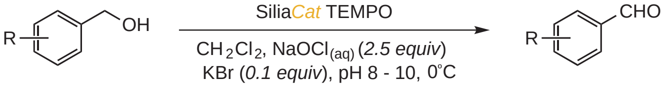
Substrate Scope with Silia*Cat* TEMPO

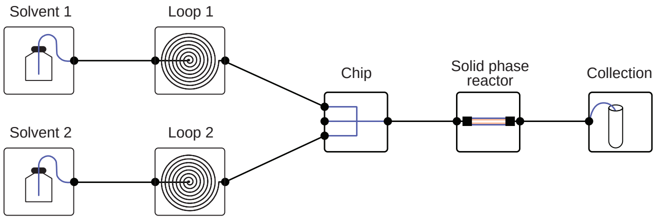
Silia*Cat* TEMPO is efficient with different substrates under standard condition as presented in the table at right.

It is also suitable for continuous synthesis under flow chemistry using the pathway presented below. Silia*Cat* TEMPO was placed at 20°C using a 0.7 mL reactor packed with the catalyst and different flow rates (*from 50 to 500 µL/min*). In all experiments, complete conversion was obtained with 100 % selectivity.

Substrate Scope with Silia*Cat* TEMPO

Substrate (*R*)	Catalyst (*mol %*)	Time (*min*)	Conversion (*%*)
3-NO_2	0.4	90	100
4-NO_2			98
4-Cl			95
3-phenyl-1-propanol		60	97
1-phenyl-3-propanol		180	95[1]





Conclusion of Oxidation of alcohols

Silia*Cat* TEMPO is an effective oxidizing catalyst presenting unique advantages such as high activity, robustness, leach-proof properties and selectivity toward the oxidation of alcohols into aldehydes and ketones, both very valuable functional groups in organic chemistry.

Related Publications for Oxidation

Nanoscale, **2014**, *6*, 6293-6300
Topics in Catalysis, **2010**, *53*, 1110-1113
Org. Proc. Res. Dev., **2010**, *14*, 245-251
Chemistry Today, **2009**, *27*, 13-16
Org. Proc. Res. Dev., **2007**, *11*, 766-768

Typical Experimental Procedure: Alcohol Oxidation Using Silia*Cat* TEMPO

Note: Please refer to the table presented below for specific conditions (*recommended solvents, scale of the reaction, reaction time, temperature, etc.*). Anhydrous solvents or inert conditions are not required.

- Typical reactions are conducted using a 500 mL three-necked round-bottom flask equipped with a mechanical stirring system and a digital temperature controller in dichloromethane (*HPLC grade*) at 0°C (*ethyl acetate can also be used*).
- The primary alcohol and *n*-decane (*used as internal standard calibration curve*) are dissolved in dichloromethane (*60 mL*).
- The alcohol-decane solution is then mixed with aqueous KBr solution (*2.55 mL*) and maintained at 0°C in an ice bath.
- The resulting mixture is then treated with Silia*Cat* TEMPO , then by aqueous NaOCl (*60 mL*) buffered at pH 9.0 using $NaHCO_3$.
  Note*: The reaction is exothermic and aqueous NaOCl is added slowly over a 10 min period.*
- The reaction mixture is then vigorously stirred (*1,000 RPM*) at 0°C until maximum conversion is reached (*as determined by GC/FID analysis with n-decane as internal standard*).

Work-up

Catalyst recovery

- Once the reaction is deemed complete as determined by GC/FID analysis, the catalyst is recovered by filtration at room temperature through a Büchner funnel using a glass fiber filter (*grade 691*).
- The catalyst (*between 0.03 - 1.00 g*) is washed with deionized water (*3 x 10 mL*) and DCM (*3 x 10 mL*).
- The catalyst is then dried under air at room temperature and can be stored in a closed vessel prior to reuse.

Isolation of the oxidation product

- The organic layer is washed 3 times with deionized water (*3 x 100 mL*).
- The organic layer is dried using anhydrous magnesium sulfate and then concentrated in vacuo, yielding a high purity crude product that typically does not require extensive purification. If needed, a flash chromatography can be done.

Optimization Steps

If the reaction fails or if the conversion of the primary alcohol is not complete, optimization steps can be undertaken.

- **Step 1: Handling**
  - Check if the reaction temperature is 0°C.
  - Check if the reaction mixture, which must be a two phase system, is vigorously stirred at 1,000 RPM.

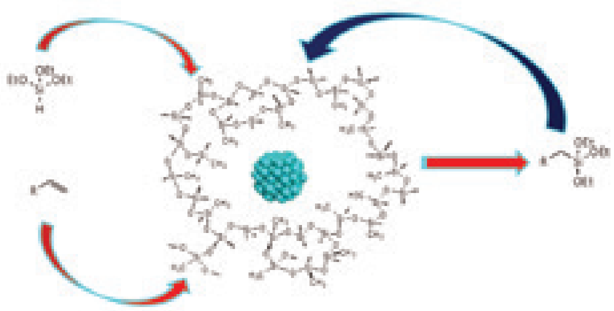
Always using 0.5 mol % Silia*Cat* TEMPO:

- **Step 2: Solvent Screening**
  Different solvents may be tried such as as DCM or EtOAc.
- **Step 3: Solvent Concentration Optimization**
  Once the best solvent has been determined, different solvent concentrations (*from 0.2 M to 1.0 M*) should be explored.

	Primary Alcohol Oxidation over Silia*Cat* TEMPO
Substrates	**60 mL primary alcohol in dichloromethane solution (*0.2 M, 12 mmol alcohol, 1 equiv*)**
n-Decane	0.3 equiv
Additive (*KBr*)	2.55 mL of KBr aqueous solution (*0.5 M, 0.1 equiv*)
NaOCl	60 mL of NaOCl aqueous solution (*2.5 equiv*) (*buffered at pH 9.0 using* $NaHCO_3$)
Silia*Cat* Loading	≤ 1.0 mol %
Best Solvents	Dichloromethane or Ethyl Acetate (*ETOAc*)
Temperature	0°C
Reaction Time	0.5 - 24 h
Typical Scale	Under Mechanical Stirring (*1,000 RPM*) for Reusability: 12 mmol scale of primary alcohols in dichloromethane.

Hydrosilylation Using Silia*Cat* Pt^0

Hydrosilylation reactions are a widely used method to prepare organosilicon products. The reaction consists of the addition of *Si*-H bonds on unsaturated bonds like alkenes, alkynes or ketones, where catalysts are often required (*usually* H_2PtCl_6). Silia*Cat* Pt^0 can be used for hydrosilylation reactions.

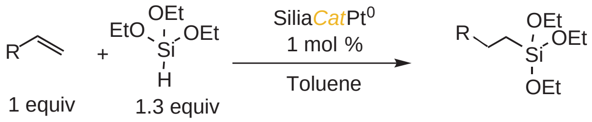


Closing the Organosilicon Synthetic Cycle:
Hydrosilylation of Alkenes over Silia*Cat* Pt^0

Substrate Scope and Selectivity

A number of representative alkenes reacted with triethoxysilane over the solid catalyst under the conditions shown in the table below were tested. Non-functionalized alkenes such as 1-octene or 1-decene are smoothly converted into the corresponding organo-alkoxysilanes at room temperature or faster at 60°C. Usually, raising the reaction temperature slightly enhances the conversion of longer chain alkenes and dramatically improves the selectivity.

The hydrosilylation of linear olefins involves a certain degree of isomerization, namely, either shift of the double bond or even skeletal modification of the starting molecules. Hence, in order to slow down isomerization and obtain a higher reaction rate, reaction is best carried out at 60°C over 1 mol % catalyst amount.



Substrate Scope and Selectivity Results						
Substrate	**Catalyst (*mol %*)**	**Substr. Solvent Conc. (*M*)**	**Temp. (°C)**	**Time (*h*)**	**Conversion (%)**	**Selectivity (%)**
1-octene	1.0	Toluene (*0.5*)	22 / 60	5	88 / 99	98 / 99
1-decene					100 / 100	97 / 98
1-octadecene					95 / 98	56 / 83
3,3-diethoxyprop-1-ene					94 / 100	93 / 81
4-vinyl-benzamine			60	5 / 24	47 / 80	96 / 96
Styrene	0.5			1	100	68
Acrolein diethyl acetal	0.5 / 1.0			1 / 3	100 / 100	100 / 100
5-hexen-2-one	1.0	DCM (*0.5*)	22	23	100	100

Conclusion of Hydrosilylation

We have discovered that 0.5 - 1 mol % of Silia*Cat* Pt^0 selectively mediates the hydrosilylation of different olefins under inert atmosphere at room temperature or at 60°C, depending on the substrate. Ultra-low leaching of Pt ensures very low levels of metal contamination in crude product.

Related Publications for Hydrosilylation

ACS Sustainable Chem. Eng., **2013**, *1*, 249-253
Eur. J. Org. Chem., **2013**, 6227-6235

Typical Experimental Procedure: Hydrosilylation Reactions Using Silia*Cat* Pt^0

Note: Please refer to the table below for specific conditions (*recommended solvents, scale of the reaction, reaction time, temperature, etc.*).
The reaction is performed in anhydrous toluene under inert conditions.

- Using a dry vessel and a mechanical stirrer, the desired amount of Silia*Cat* Pt^0 is added and degassed three times by applying vacuum and then purging with an inert gas (*nitrogen or argon*).
- The olefin and triethoxysilane (*previously degassed for 15 minutes with an inert gas*) are dissolved in anhydrous solvent.
- Under mechanical stirring, the mixture is warmed up to the desired temperature.
- The reaction mixture is then vigorously stirred (*700 RPM*) until maximum conversion is observed (*as determined by TLC or GC/MS analysis*).

Work-up

Catalyst recovery

- Once the reaction is deemed complete as determined by TLC or by GC/MS analysis, the catalyst is recovered by filtration at room temperature through a Büchner funnel using a glass fiber filter (*grade 691*).
- The catalyst (*between 0.25 - 1.00 g*) is washed with toluene (*3 x 15 mL*) and THF (*3 x 15 mL*).
- Silia*Cat* is dried under air at room temperature and can be stored in a closed vessel prior to reuse in these conditions.

Isolation of the coupling product

- The filtrate is concentrated under vacuum yielding a high purity crude product that typically does not require extensive purification. If needed, the crude product can be purified using flash chromatography or distillation.

Optimization Steps

If the reaction fails or if the conversion of the primary alcohol is not complete, optimization steps can be undertaken.

- **Step 1: Handling**
  - Check if the reaction temperature is adequate.
  - Check if the reaction mixture, which must be a two phase system, is vigorously stirred at 700 RPM.

Always using 2.0 mol % Silia*Cat* Pt^0:

- **Step 2: Solvent Concentration Optimization**
  Always using anhydrous toluene as solvent, different alkene solvent concentrations (*from 0.25 M to 1.0 M*) should be explored.

- **Step 3: Silia*Cat* Loading (*mol %*)**
  Finally, the loading of Silia*Cat* Pt^0 should be optimized
  a. If the reaction is not complete, the amount of catalyst should be increased from 2.0 mol % to 2.5 mol % Pt.
  b. If the reaction is complete, the catalyst loading can be decreased from 2.0 mol % to 1 mol % or to 0.05 mol % Pt.

	Hydrosilylation Reactions Using Silia*Cat* Pt^0
Substrates	**Olefine (*0.5 M in anhydrous toluene*) 1 equiv**
$HSi(OEt)_3$	1.3 equiv
Silia*Cat* Catalyst	Silia*Cat* Pt^0 (*0.2 mmol/g Pt loading*)
Silia*Cat* Loading	≤ 2.0 mol % Pt
Best Solvent	Anhydrous Toluene
Temperature	65 - 90°C
Reaction Time	1 - 24 h
Typical Scale	• Under Mechanical Stirring for Reusability: 20 mmol scale of olefine in 40 mL anhydrous solvent under inert conditions.