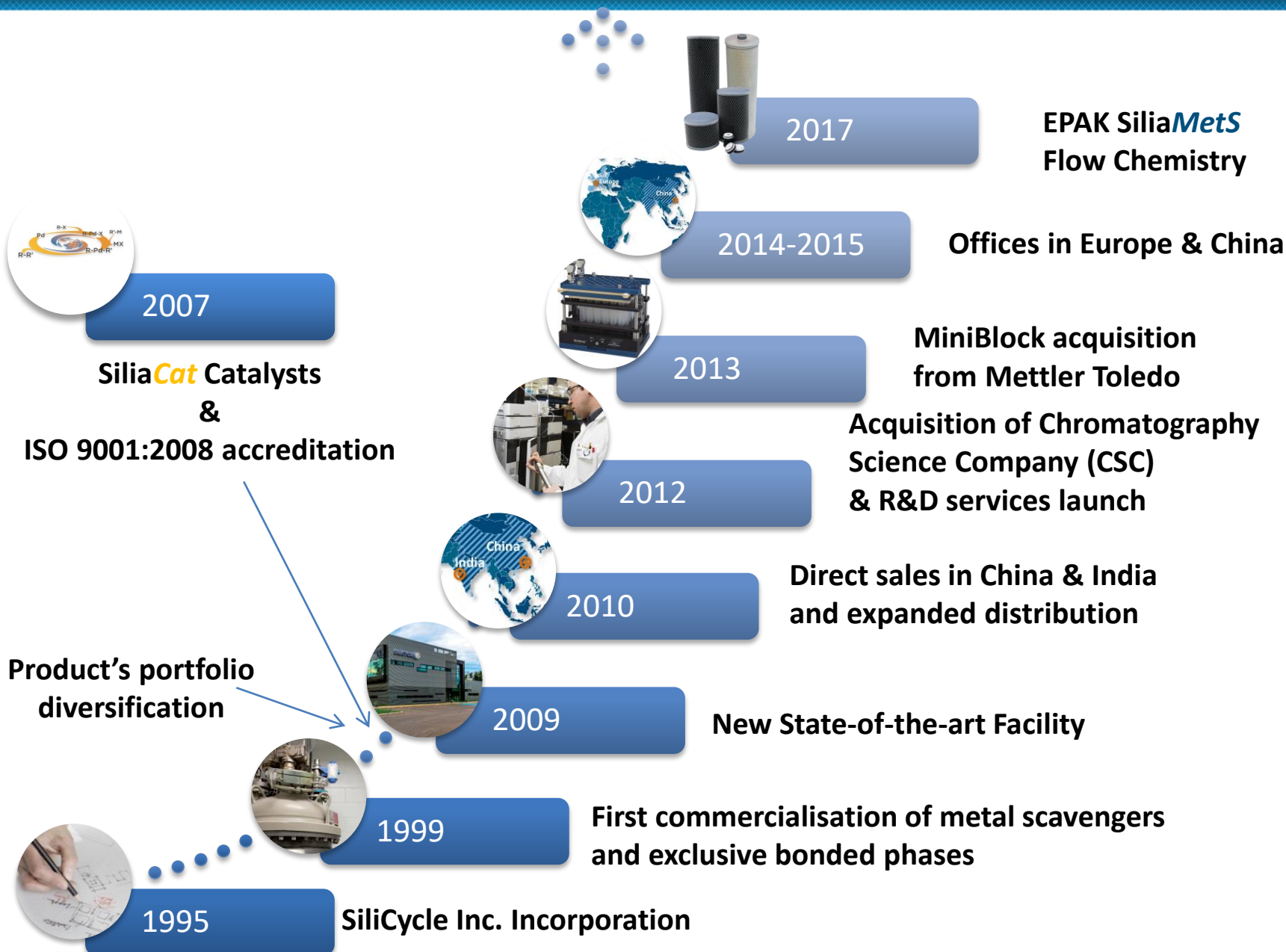




Eric Beausoleil, PhD
Director Business Development Europe
SiliCycle

**Functionalized Silicas Enabling
Flow Chemistry Applications for the
Development of
Fine and Speciality Chemicals**



Industries require more than ever **better performance** products, **quicker** and **safer**.

We at SiliCycle can provide help to our customers to reach their goals with our top-class capabilities in **silica-based chemistry & purification**.

Our solutions promote **safety**, process **economics** and **sustainability**

SiliCycle develops **solutions** based on innovative **silica products**.

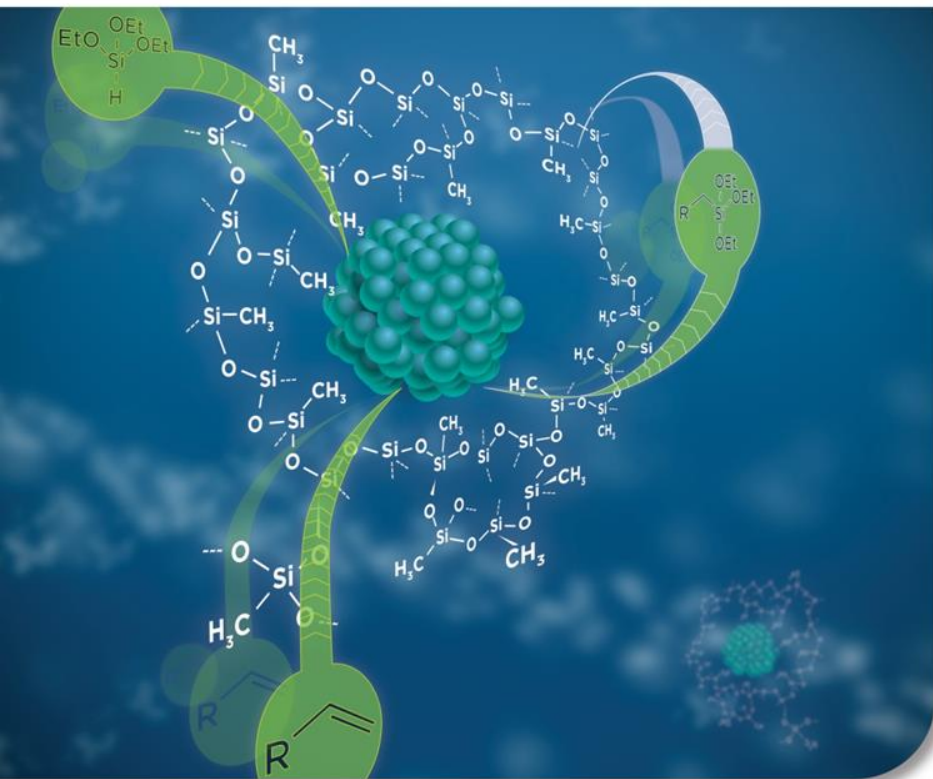
We design and manufacture **unique grafted adsorbents**.

We **set-up and optimize chemical reactions** with supported catalysts, oxidants and reagents.

We develop and **scale-up purification steps**.

We address our offer to **analytical laboratories**, to **development & scale-up facilities** and **commercial production**.

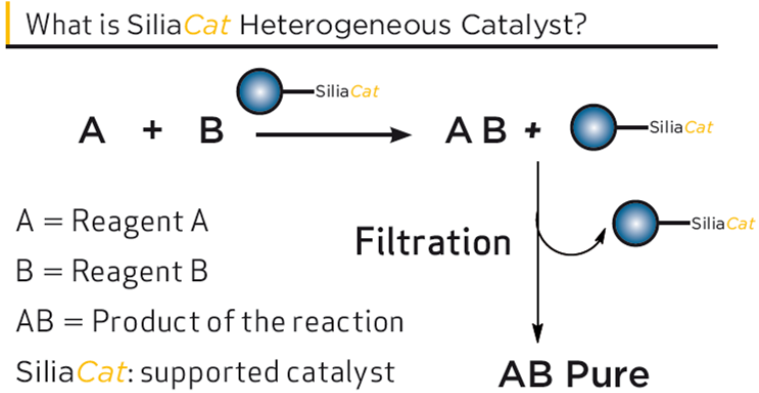
SiliCycle products and services will help our customer to **solve their challenges**, reach the highest product quality upon needs, produce cheaper molecules under a cleaner way, and shorten time-to-market.



SiliaCat

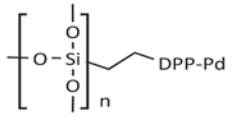

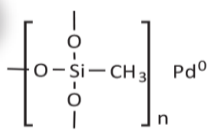

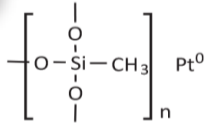
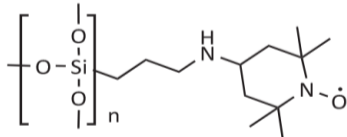
Heterogeneous Catalysts

- Usually, heterogeneous catalysts supported on a silica present a high degree of leaching (post-modification)
- With Silia*Cat*, the ligand is directly cross-linked in an organic-inorganic framework resulting in a high degree of stability of the catalysts
- Compared to homogeneous catalysts, Silia*Cat* exhibits:
 - a good reactivity and selectivity
 - a major advantage: the catalyst is eliminated from the reaction mixture by a simple filtration



- Ease of handling and purification
 - Free flowing, no static charge
 - Easily removed by simple filtration
- High turnover number (TON)
 - Catalytic amount (< 1 mol %)
 - High conversion and yield
- Reusability
 - Multi-uses possible
- No metal leaching or usually below the acceptable limits
 - No further purification required
 - Reduce metal removal costs associated with homogeneous catalysts

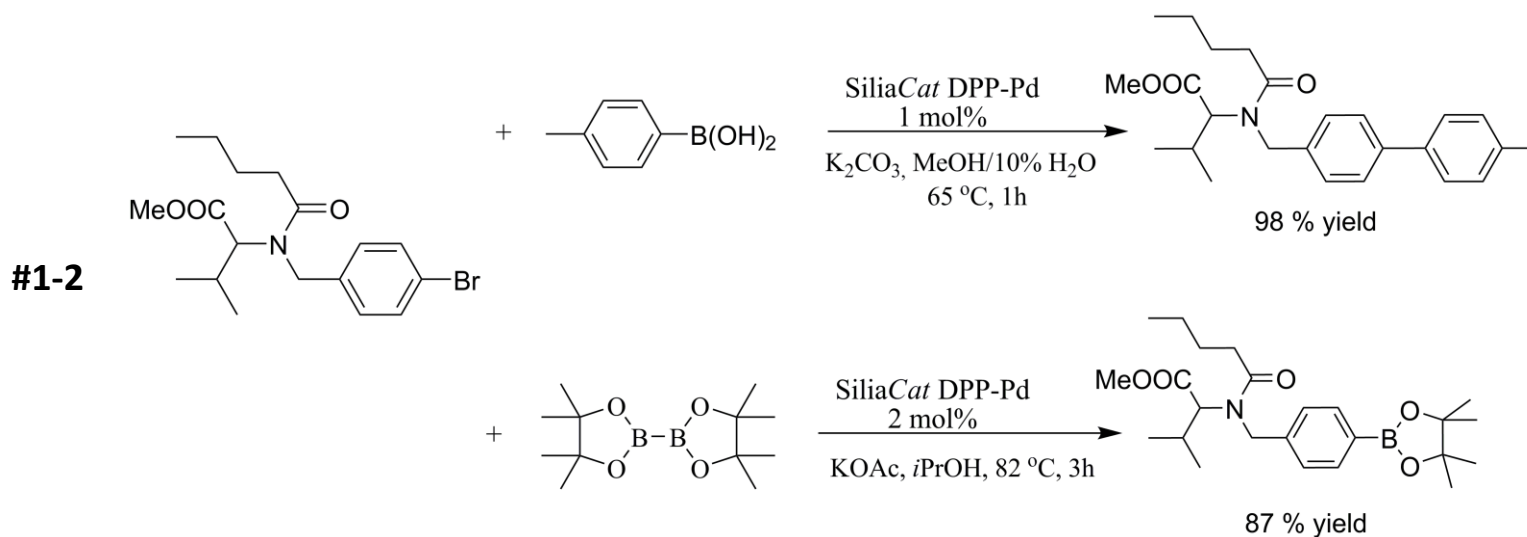
SiliaCat Heterogeneous Catalysts Portfolio*

SiliaCat	Structure	Brief Description	Typical Application	Molecular Loading	Typical Characteristics
SiliaCat DPP-Pd PN: R390-100		SiliaCat DPP-Pd is a unique diphenylphosphine palladium (<i>II</i>) heterogeneous catalyst made from a leach-resistant organoceramic matrix.	Suzuki, Heck Sonogashira, Kumada, Stille	≥ 0.2 mmol/g	Color: Yellow Endcapping: Yes Loading: ≥ 0.2 mmol/g Density: 415 g/L Solvent Compatibility: 1 Prolonged Storage: 1
 SiliaCat Pd ⁰ PN: R815-100		SiliaCat Pd ⁰ is a new series of patent-protected sol-gel-entrapped Pd nanocatalysts. It is made from highly dispersed Pd nanoparticles encapsulated within an organosilica matrix. <i>Patented</i>	Suzuki, Heck Sonogashira, Kumada, Stille, Selective debenzylation, Selective hydrogenation	Contact us	Color: Dark brown - Black Endcapping: Yes Solvent Compatibility: 1 Prolonged Storage: 2
 SiliaCat Pt ⁰ PN: R820-100		SiliaCat Pt ⁰ is made from a proprietary class of organosilica physically doped with nanostructured platinum (0), and is both stable and efficient. This catalyst was successfully prepared by a novel and simple sol-gel route. In the new procedure, Pt nanoparticles are encapsulated via an alcohol-free sol-gel process typical of enzyme sol-gel encapsulation. <i>Patented</i>	Selective reduction of nitroarenes, Hydrosilylation	Contact us	Color: Dark brown - Black Endcapping: Yes Solvent Compatibility: 1 Prolonged Storage: 3
SiliaCat TEMPO PN: R723-100		SiliaCat TEMPO is a new oxidizing catalyst made from a proprietary class of organosilica-entrapped radicals. The leach-resistant organoceramic matrix makes SiliaCat TEMPO highly efficient and selective compared to homogeneous polymer-supported TEMPO aldehyde vs acid oxidation is possible. <i>Patented</i>	Oxidation of alcohols or aldehydes	≥ 0.70 mmol/g	Color: Orange Endcapping: Yes Loading: ≥ 0.7 mmol/g Density: 639 g/L Solvent Compatibility: 1 Prolonged Storage: 1

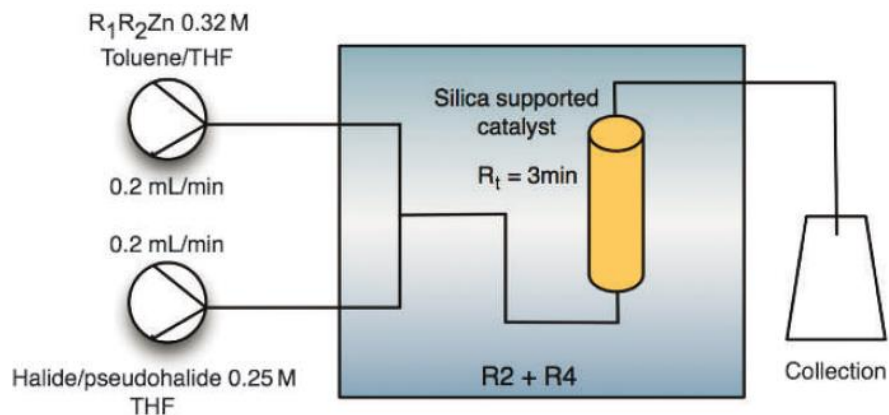
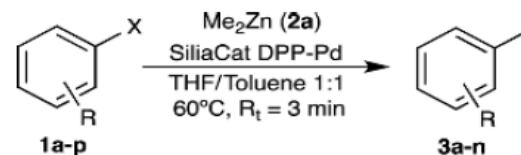
Solvent Compatibility: ¹ All solvents, aqueous and organic; ² All organic solvents.

Prolonged Storage: ¹ Keep dry; ² Keep cool (< 8°C) under argon; ³ Keep dry under argon.

- We studied the scale-up of the heterogeneous Suzuki-Miyaura coupling reaction in batch conditions for a key step in Valsartan synthesis
- The method developed can be effectively applied to the high yield synthesis of several coupling products, opening the route to efficient continuous coupling syntheses



- After screening various catalysts & conditions in batch, the SiliaCat DPP-Pd was identified as the most suitable catalyst
- Good to excellent conversions were achieved in most cases



Experimental setup of the Vapourtec flow system

Entry	Substrate	Product	Yield ^a
1	4-NO ₂ -C ₆ H ₄ -Br (1a)	3a	97
2	2,4,6-triMeC ₆ H ₂ -Br (1b)	3b	83
3	3-MeO-2-Br-pyridine (1c)	3c	83
4	4-MeO-C ₆ H ₄ -Br (1d)	3d	66 ^b
5	4-Et-C ₆ H ₄ -Br (1e)	3e	87
6	4-Ac-C ₆ H ₄ -Br (1f)	3f	82
7	4-CHO-C ₆ H ₄ -Br (1g)	3g	81
8	2-CN-C ₆ H ₄ -I (1h)	3h	73
9	4- <i>t</i> Bu-C ₆ H ₄ -I (1i)	3i	71 ^b
10	4-MeO-C ₆ H ₄ -I (1j)	3d	81 ^b
11	4-CO ₂ Et-C ₆ H ₄ -Cl (1k)	3j	73 ^c
12	6-MeO-2-Cl-pyridine (1l)	3k	35 ^c
13	3-MeO-2-Cl-pyridine (1m)	3l	43 ^c
14	6-Me-2-Cl-pyridine (1n)	3m	87 ^c
15	4-NO ₂ -C ₆ H ₄ -ONf (1o)	3a	—
16	4-Cl-C ₆ H ₄ -Br (1p)	3n	75 ^d

^a Isolated yield (%).

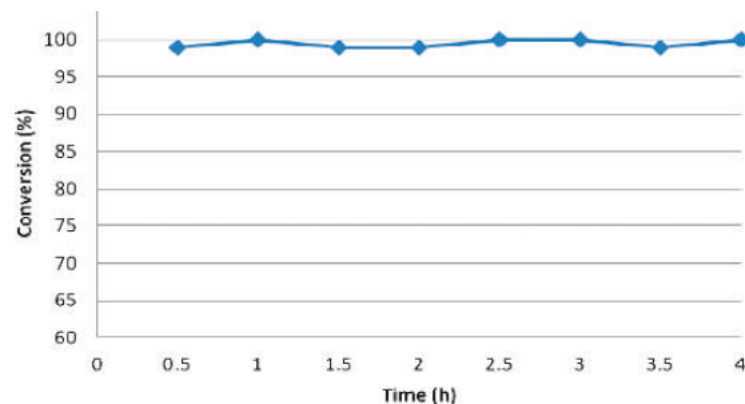
^b 0.1 M ArX, < 10 % homocoupling detected.

^c Reaction at 80 °C.

^d 5% dimethylated product.

Exploration of aryl halides

- The conversion remained constant even after 4 hours proving the stability of the catalyst for long runs (*coupling between 1f and Me₂Zn*)
- Various organometallic species were tried to prove the versatility of the procedure and to validate its utility



Entry	Ar–Br	R ₁ R ₂ Zn	Product	Yield ^a
1	1a	Et ₂ Zn (2b)	3o	85
2	1a	2-PyridylZnBr (2c)	3p	50 ^b
3	1a	cyPrZnBr (2d)	3q	62 ^b
4	1e	cyPrZnBr (2d)	3r	94 ^c
5	1e	2-PyridylZnBr (2c)	3s	90 ^c
6	1e	C ₆ H ₅ CH ₂ ZnBr (2e)	3t	74 ^c
7	1e	NC(CH ₂) ₄ ZnBr (2f)	3u	55 ^c
8	1e	(CH ₂ O) ₂ CH(CH ₂) ₂ ZnBr (2g)	3v	68 ^c
9	1e	EtO ₂ C(CH ₂) ₂ ZnBr (2h)	3w	51 ^c

Standard conditions: 0.25 M, THF/Toluene 1:1, 60 °C, 3-min residence time.

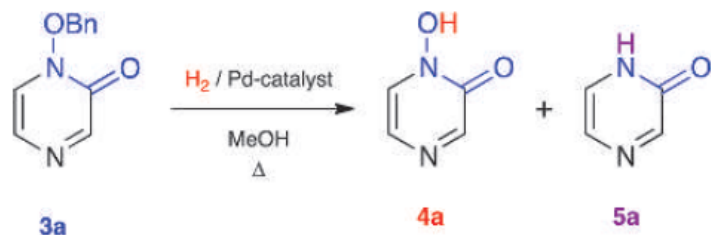
^a Isolated yield (%).

^b THF as solvent, 80 °C, 5-min residence time.

^c 2 equiv. organozinc reagent, THF as solvent, 2.5-min residence time.

Scope of organozinc reagents

Table 1. Batch debenzilation of 1-benzyloxypyrazin-2(1*H*)-one (3a)



Entry	Catalyst	Condition	Selectivity (%) ^a	
			4a	5a
1	5 % Pd-C	2 bar/rt/5 min	0	100
2	5 % Pd-C	1 bar/rt/10 min	25	75
3	5 % Pd-C	1 bar/rt/30 min	20	80
4	5 % Pd-C	1 bar/reflux/5 min	60	40
5	5 % Pd-BaSO ₄ ^b	1 bar/reflux/5 min	80	20
6	5 % Pd-BaSO ₄ ^c	1 bar/reflux/5 min	95	5

Reagents and conditions: 3a (0.1 mmol, 0.1 M), H₂ (in a Parr apparatus or with a balloon), palladium catalyst (5 %wt).

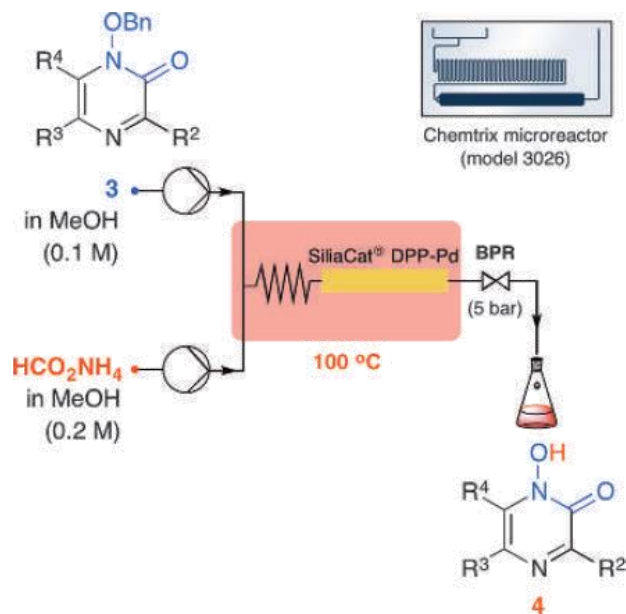
^a Quantitative conversion (quantification at 350 nm via RP HPLC-UV-MS).

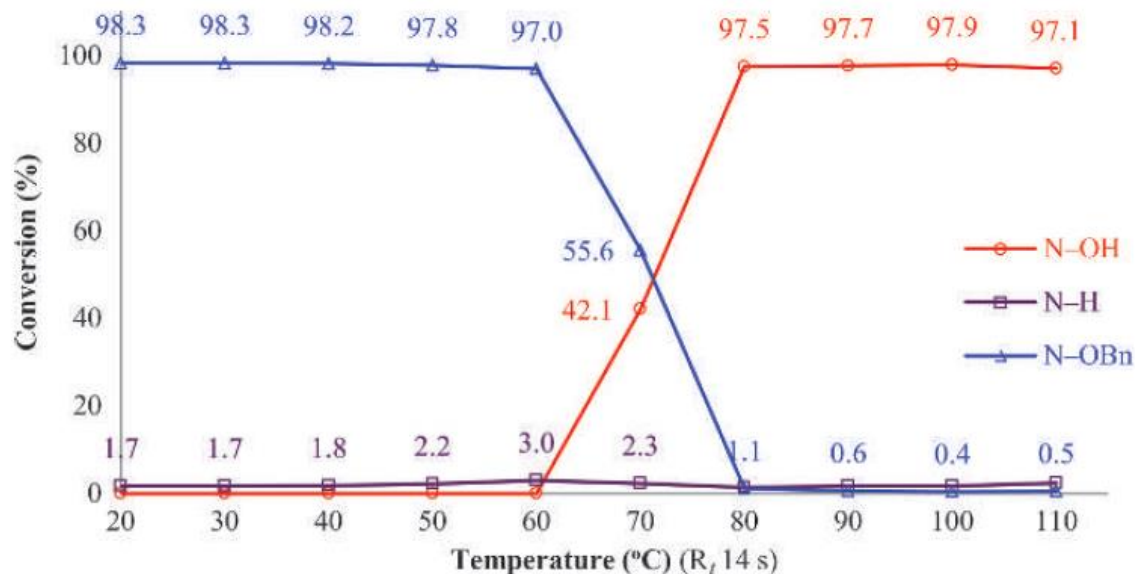
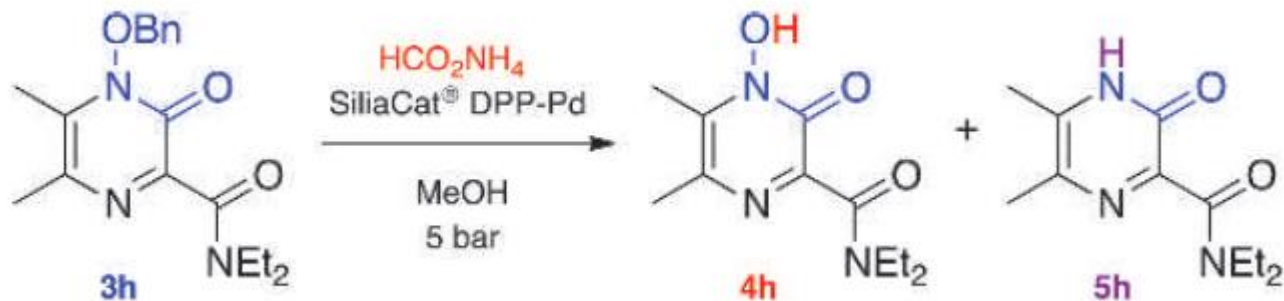
^b Pd-BaSO₄ reduced form.

^c Pd-BaSO₄ unreduced form.

- Flow technology allows for fine control over residence time

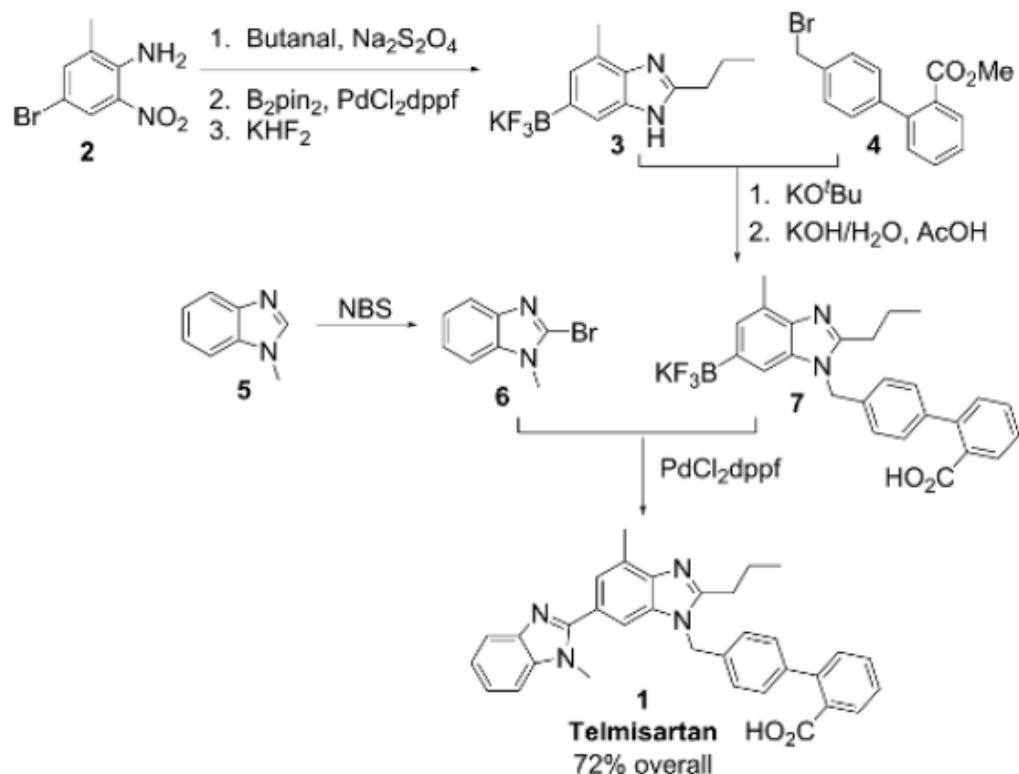
- Batch process gave poor *O*-debenzylation vs over-reduction selectivity and reproducibility
- Control of the contact time between reagent, product and catalyst was deemed to be key



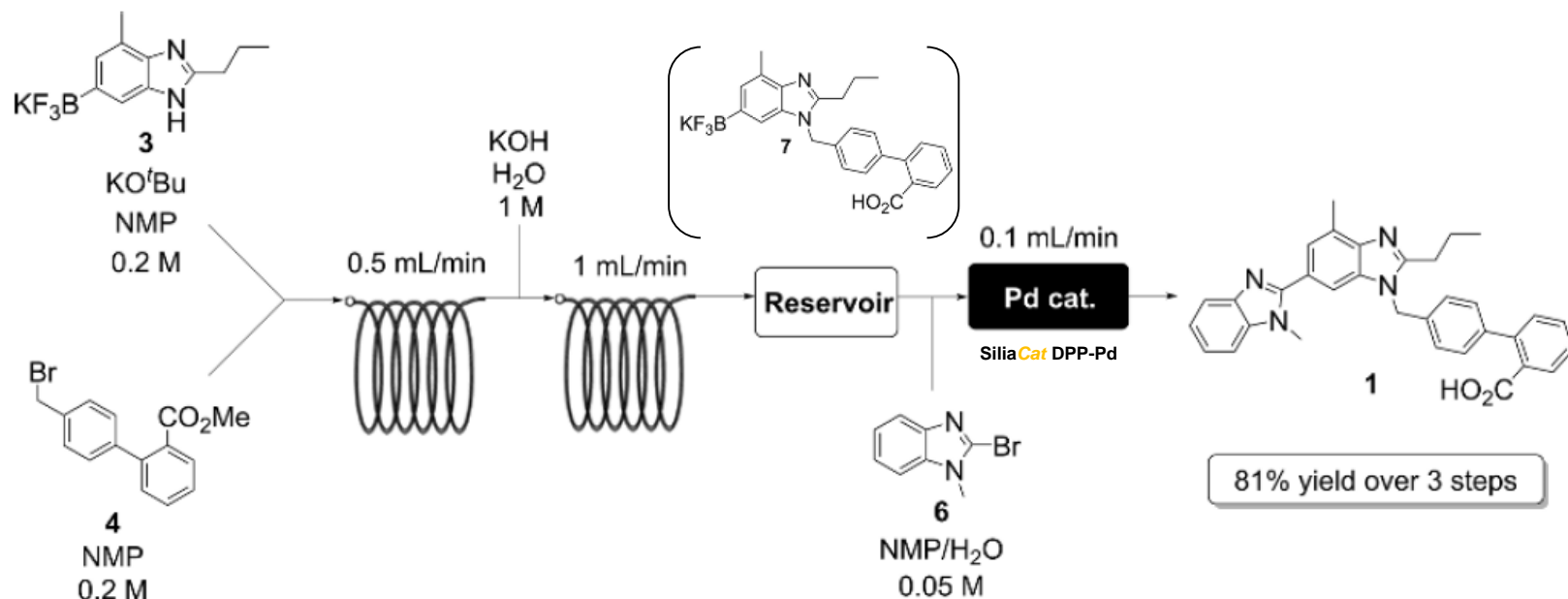


- This methodology allowed the efficient, safe and reproducible synthesis of a library of 28 *N*-hydroxypyrazin-2-(1*H*)-one analogues.

- Patent protection has expired on antihypertensive drug Telmisartan (*Micardis*)
- Batch process involves sequential *N*-alkylation followed by Suzuki coupling



- Last 3 steps involve basic conditions and compatible solvents



- Alkylation, saponification and Suzuki couplings were telescoped without isolation of intermediates or solvent exchange
- High yielding and clean process: 97% Purity (HPLC) obtained after simple aqueous workup



Batch mode
(scavengers in reactors)

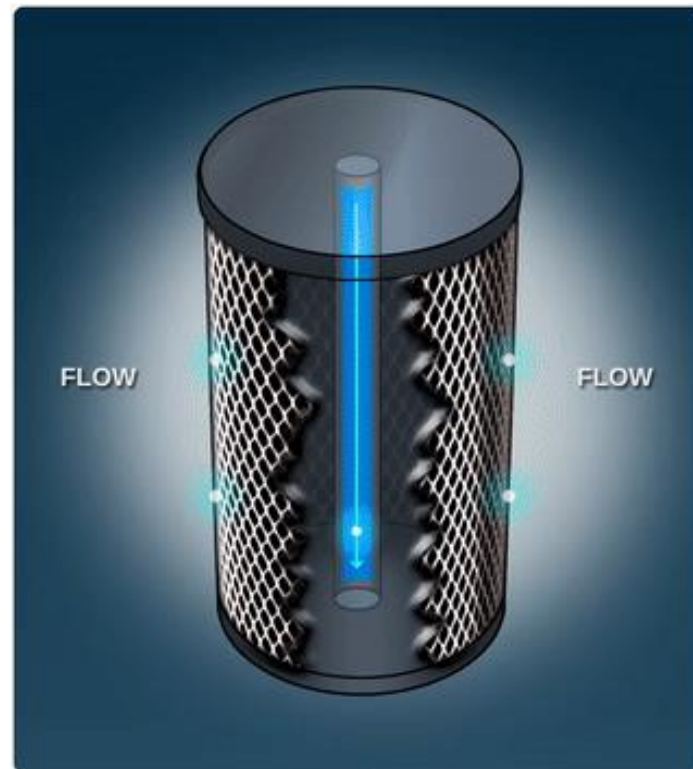


Flow or
continuous processing

- **Simple and reliable processing**

- Radial flow
- Low pressure drop
- Fixed bed (*no silica inside reactor*)
- No dust
- Compatible with organic solvents
- Fast kinetics
- Manufactured without glue to minimize extractables and facilitate use in non-polar solvents

- **Compatible with stacked disk housing systems on the market**



- Available with **SiliaMetS Thiol & DMT**
and 4 types of activated carbon
with different selectivity

5 x 1 cm

SiliaMetS: 8 g
Activated Carbon: 5 g
Max flow rate: 100 mL/min



5 x 10 cm

SiliaMetS: 75 g
Activated Carbon: 50 g
Max flow rate: 500 mL/min



5 x 25 cm

SiliaMetS: 200 g
Activated Carbon: 125 g
Max flow rate: 1 L/min



Note: These are maximum flow rates for < 75 psi back-pressure

- Various housing length available
- Operated with standard pump
- Typical pressure rating for housing 150 psi



- Pilot scale cartridges for purification of kilo quantities

16.5 x 12.5 cm

SiliaMetS: 1.25 kg
Activated Carbon: 850 g
Max flow rate: 2.5 L/min



16.5 x 25 cm

SiliaMetS: 2.5 kg
Activated Carbon: 1.7 kg
Max flow rate: 5 L/min



Note: These are maximum flow rates for < 75 psi back-pressure

- Can be operated in parallel to process batch sizes of $\geq 10,000$ L

16.5 x 50 cm

SiliaMetS: 5 kg

Activated Carbon: 3.4 kg

Max flow rate: 10 L/min



16.5 x 100 cm

SiliaMetS: 10 kg

Activated Carbon: 6.8 kg

Max flow rate: 20 L/min



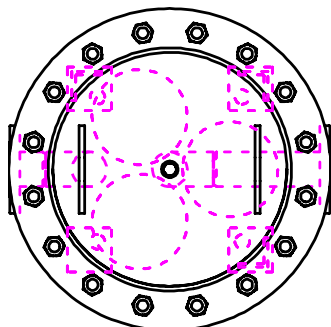
Note: These are maximum flow rates for < 75 psi back-pressure

- Houses the pilot/commercial scale cartridges up to 100 cm
- Available in stainless steel or Hastelloy
- 1, 3, 7, 12-round versions
- Code stamped ASME or CE
- Pressure rating: 150 psi

Single housing for
both 50 and 100 cm length cartridges

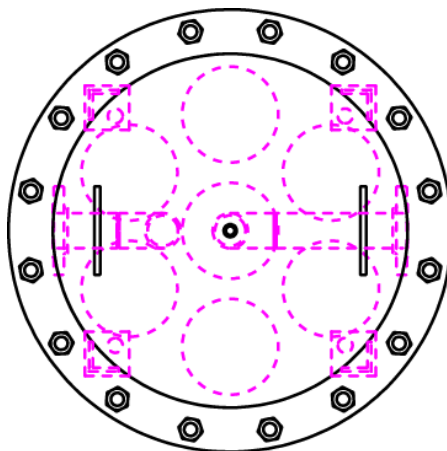


3-round



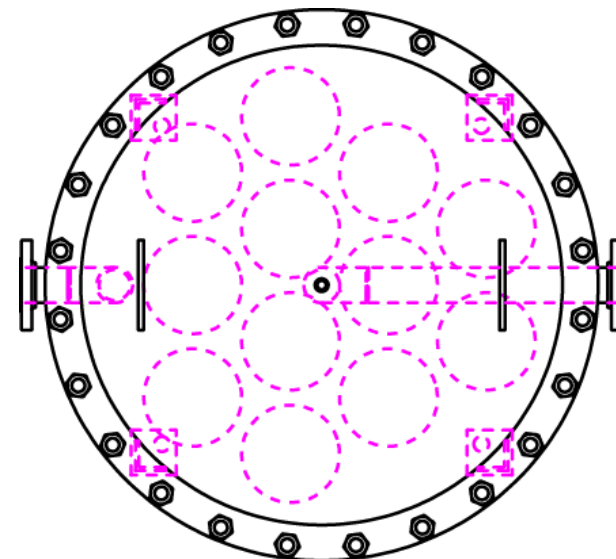
O. Diameter: 22"
Total length: 61"

7-round



O. Diameter: 30"
Total length: 65"

12-round



O. Diameter: 37"
Total length: 69"

Weight of sorbent

SiliaMetS: **30 kg** (3 x 10 kg)

Carbon: **20.4 kg** (3 x 6.8 kg)

Weight of sorbent

SiliaMetS: **70 kg** (7 x 10 kg)

Carbon: **47.6 kg** (7 x 6.8 kg)

Weight of sorbent

SiliaMetS: **120 kg** (12 x 10 kg)

Carbon: **81.6 kg** (12 x 6.8 kg)

Multiple housings can be connected in series if required

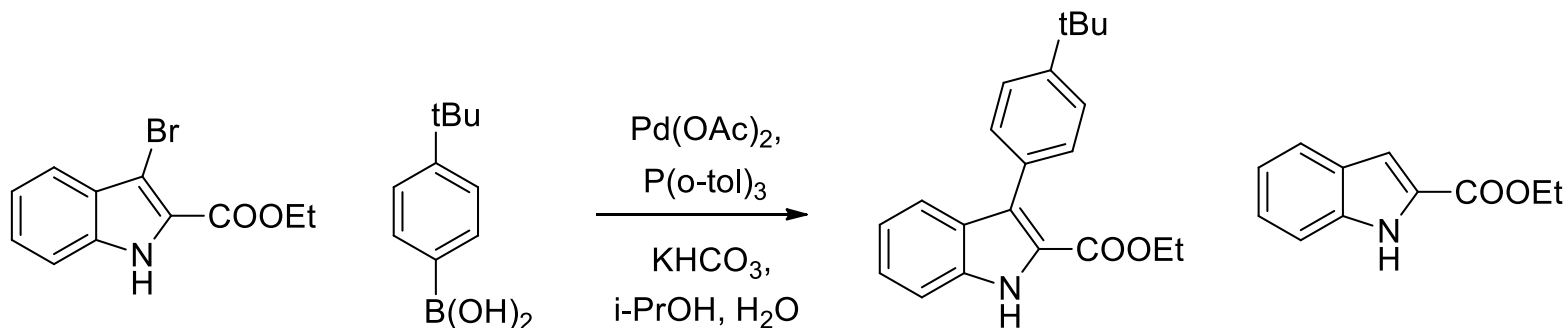
Experimental conditions

- SiliaMetS DMT E-PAK, 5 x 1 cm
- Solution recirculated overnight at 22°C using 400 mL of solvent



Flow rate (mL/min)	THF	AcOEt	DCM	Toluene	MeOH
50	0	0	0	0	0
75	1	0	0	0	0
100	12	9	5	8	9
125	25	17	16	20	19
150	29	30	29	30	29
175	36	39	44	42	43
200	51	50	58	56	58
225	66	65	74	70	77
250	80	82	91	92	90

A typical Suzuki-Miyaura reaction was performed:



Experimental conditions

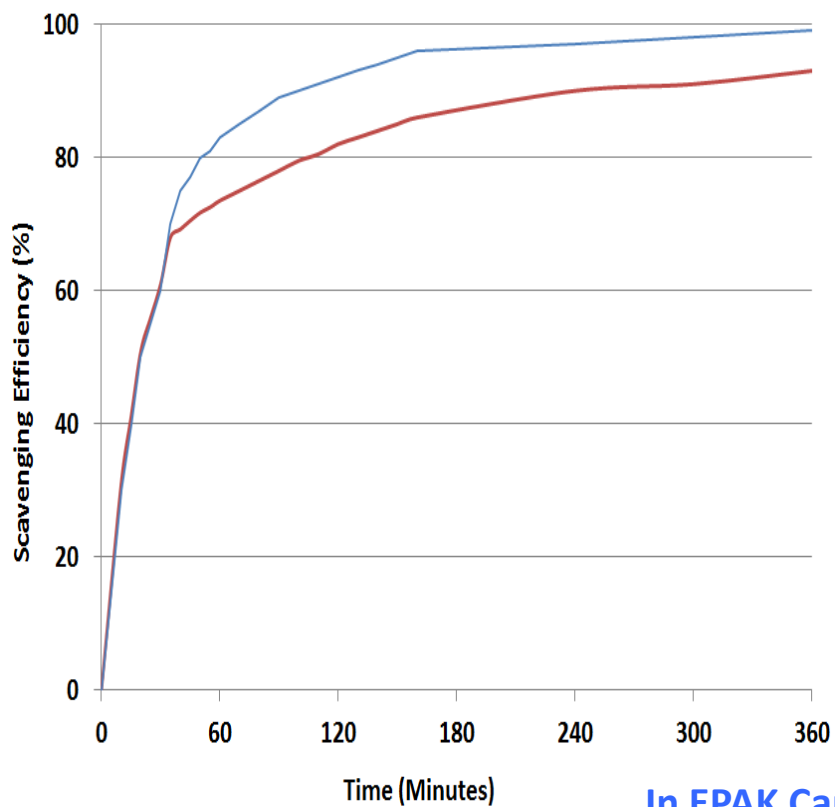
- SiliaMetS Thiol & DMT E-PAK, 5 x 1 cm (8 g, ~8 equiv.)
- Solution recirculated at 50 mL/min during 6h
- Initial Pd concentration: 303 ppm



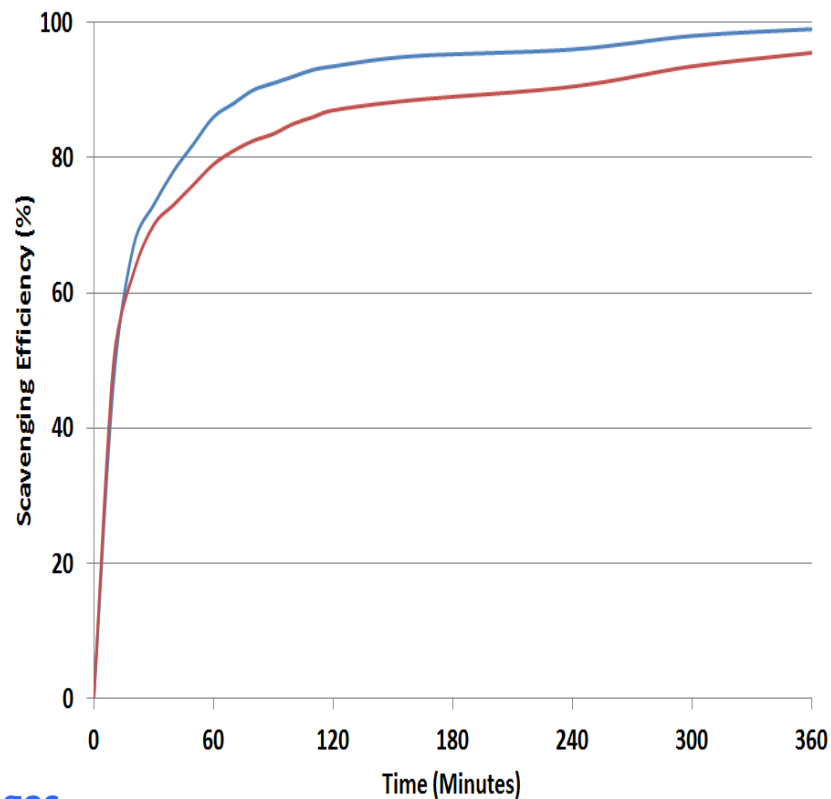
Observations

- No back-pressure observed
- No performance loss vs bulk mode, Pd scavenging was over 99 %

SiliaMetS Thiol



SiliaMetS DMT

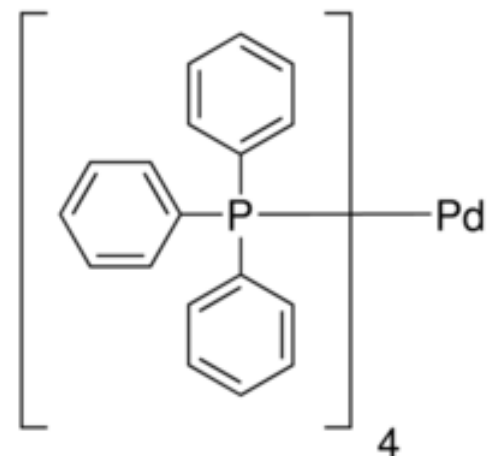


In EPAK Cartridges
In Bulk



Experimental conditions

- SiliaMetS Thiol & DMT E-PAK, 5 x 1 cm
- SiliaMetS weight: 8 g, ~8 equiv.
- Solution recirculated at 50 mL/min during 6h
- Initial Pd concentration: 375 ppm



Experimental conditions

- Lab scale formats of Silia*MetS* Thiol E-PAK
- Silia*MetS* molar equivalent: ~8 equiv.
- Residence time: 1 min 15 sec for each format
- Initial Pd concentration: 325 ppm in EtOAc



Run	1 cm (10 mL/min)		10 cm (100 mL/min)		25 cm (250 mL/min)	
	Pd (ppm)	Yield (%)	Pd (ppm)	Yield (%)	Pd (ppm)	Yield (%)
1	10.1 ppm	96.89 %	10.0 ppm	96.92 %	10.0 ppm	96.92 %
...	
5	8.5 ppm	97.38 %	8.5 ppm	97.38 %	8.4 ppm	97.41 %
...	
15	5.0 ppm	98.46 %	4.9 ppm	98.49 %	5.0 ppm	98.46 %
...	
20	3.8 ppm	98.83 %	3.9 ppm	98.80 %	3.8 ppm	98.83 %

Back-pressure:

0 psi

0 psi

71 psi

- SiliCycle has developed several silica-based technologies to expedite synthesis and purification
- +20 years of experience in dealing with the pharma industry
- Our expertise is available through our contract research division



Acknowledgment

- Steeves Potvin
- Valerica Pandarus
- Geneviève Gingras
- Raif Kadri
- François Béland
- Jérôme Théobald

