

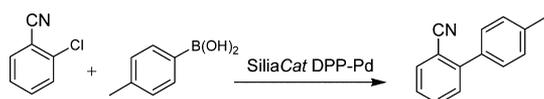
Greening the Valsartan Synthesis: Scale-up of Key Suzuki–Miyaura Coupling over SiliaCat DPP-Pd

Valerica Pandarus,[†] Delphine Desplandier-Giscard,[†] Geneviève Gingras, François Béland,^{†,*} Rosaria Ciriminna,[‡] and Mario Pagliaro^{‡,*}[†]SiliCycle Inc., 2500 Parc-Technologique Blvd, Quebec City, Quebec, Canada G1P 4S6[‡]Istituto per lo Studio dei Materiali Nanostrutturati, CNR, via U. La Malfa 153, 90146 Palermo, Italy

ABSTRACT: The study of the scale-up 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 allows to identify the optimal reaction conditions. The catalyst, regardless of limited Pd leaching, is not reusable, and the method can be effectively applied to the high yield synthesis of several coupling products, opening the route to efficient continuous coupling syntheses.

1. INTRODUCTION

Angiotensin receptor blockers such as *valsartan* (*Angiotan* or *Diovan*, 1) belong to a relevant therapeutic class called sartans, widely employed since the late 1980s to treat high blood pressure and congestive heart failure.¹ The treatment of hypertension is a



major global burden in both developed and developing countries, where nearly 26% of the world's adult population are affected by hypertension: 333 million people in industrialized countries and 639 million in developing countries.² The *Valsartan* patent expired in 2012, opening the route to the introduction of generic alternatives. Making medicines available for the world, especially in developing countries, is, of course, important and often requires significant reduction in manufacturing costs.³ The multistep *Valsartan*/hydrochlorothiazide production process originally published,⁴ for example, was redesigned ten years later first reducing the steps to four (using decarboxylative coupling)⁵ and then, with the redesign of three chemical steps of the original synthesis, increasing the throughput of the process and eliminating the use of halogenated solvents.⁶

The biphenyl unit is a common structural element in all sartans, and the synthetic pathway to valsartan originally published by industry practitioners includes the homogeneous synthesis of 4'-methyl-2-biphenylcarbonitrile by the Suzuki–Miyaura coupling reaction between the electrophilic reagent 2-chlorobenzonitrile and 4-tolylboronic acid.

In one approach, Negishi coupling of oxazoline moieties is used in place of more expensive coupling involving organoboronic acid.⁷ In another approach, a heterogeneous leach-proof catalyst that can be applied in a low amount (low loadings) to large-scale production is preferred, eventually avoiding contamination of the product with expensive and toxic metallic residues harmful to health. In general, the heterogeneous reaction over a solid-bound catalyst is greener because no

catalyst-product separation step is required at the end of the reaction, beyond simple filtration, while in many homogeneous syntheses of drugs the pharmaceutical industry produces between 25 and 200 kg or more of waste for every kilogram of active pharmaceutical ingredient (API) manufactured,⁸ with 75–80% of the waste produced being solvent (liquid) and 20–25% hazardous solid under strict regulation in most industrially advanced countries.⁹

On laboratory scale, one such catalyst applicable to numerous cross-coupling reactions is the sol–gel entrapped SiliaCat DPP-Pd,¹⁰ namely an organosilica matrix functionalized with diphenylphosphine ligands bound to Pd(II). In the following, we report the results of the scale-up of the Suzuki–Miyaura heterogeneous coupling reaction between 2-chlorobenzonitrile and 4-tolylboronic acid in batch mode over the sol–gel entrapped SiliaCat DPP-Pd (eq 1). A detailed study of the influence



of the aryl halide molar concentration, solvent, base, and amount of boronic acid and catalyst needed to achieve complete conversion for both small- and large-scale under batch conditions is reported. The results point to a number of general findings that will be useful in practical application of the optimal method identified.

2. EXPERIMENTAL SECTION

2.1. Typical Synthetic Procedure. Reactions were generally conducted under reflux (77 °C) in HPLC grade ethanol. Anhydrous solvents or inert conditions are not required. A three-necked round-bottom flask was equipped with a condenser and a stirring bar for reactions conducted under magnetic

Received: May 6, 2013

Published: June 17, 2013

Table 1. Scale-up from 6 to 36 mmol of 2-Chlorobenzonitrile^a

entry	aryl halide	catalyst (mol %)	boronic acid (equiv)	solvent (M) ^b	t (h)	conv ^c (%)	select ^c (%)	leaching ^d (mg/kg)	
								Pd	Si
1	6 mmol	1	1.25	EtOH/H ₂ O (10%) magnetic stirring (850 rpm)	0.5	100	96	40	189
2	6 mmol	1	1.1	EtOH/H ₂ O (10%) magnetic stirring (850 rpm)	0.5	100	97	47	235
3	36 mmol	1	1.1	EtOH/H ₂ O (10%) mechanical stirring (700 rpm)	0.5	85	98	155	365
					1.0	100			
4	36 mmol	0.5	1.1	EtOH/H ₂ O (10%) mechanical stirring (700 rpm)	0.5	65	98	188	76
					1.0	69			

^aExperimental conditions: 2-chlorobenzonitrile (6 or 36 mmol, 1 equiv), 4-tolylboronic acid (1.25 equiv or 1.1 equiv), K₂CO₃ (2 equiv), SiliaCat DPP-Pd (0.25 mmol/g Pd, from 0.5 to 1 mol % Pd). ^bMolar concentration with respect to the aryl halide. ^cConversion/selectivity determined by GC-MS analysis. ^dLeaching of Pd and Si determined by ICP-OES analysis in isolated crude product (mg/kg).

Table 2. Solvent Concentration Effect in Suzuki Coupling Reaction between 2-Chlorobenzonitrile and 4-Tolylboronic Acid over 1 mol % SiliaCat DPP-Pd^a

entry	base (equiv)	solvent (M) ^b	t (h)	conv ^c (%) ^b	select. ^c (%)	leaching ^d (mg/kg)	
						Pd	Si
1	K ₂ CO ₃ (2)	EtOH (0.12 M)	0.5	100	98.5	31.85	2.14
2	K ₂ CO ₃ (1.5)	EtOH (0.12 M)	0.5	100	98	2.6	3.05
3	K ₂ CO ₃ (1.5)	EtOH (0.25 M)	0.5	100	98	2.2	4.1
4	K ₂ CO ₃ (1.5)	EtOH (0.5 M)	0.5	100	98	1.4	4.5
5	K ₂ CO ₃ (1.5)	EtOH (1 M)	0.5	100	99	1.3	4.1
6	K ₂ CO ₃ (1.5)	EtOH (1.5 M)	0.5	81	99	1.2	4.5
			1.0	92			
7	KHCO ₃ (1.5)	EtOH (0.5 M)	0.5	100	99	1.75	3.79
8	KHCO ₃ (1.5)	EtOH (1 M)	0.5	71	99	0.74	3.80
			1.0	85			

^aExperimental conditions: 2-chlorobenzonitrile (6 mmol, 1 equiv), 4-tolylboronic acid (1.1 equiv), K₂CO₃ (1.5 equiv), SiliaCat DPP-Pd (1 mol %, 0.25 mmol/g Pd). ^bMolar concentration with respect to the aryl halide. ^cConversion/selectivity determined by GCMS analysis. ^dLeaching of Pd and Si determined by ICP-OES analysis in isolated crude product.

or mechanical stirring. The aryl halide, the boronic acid, and the base were mixed in HPLC solvent. The mixture was heated to reflux (77 °C), after which the catalyst was added. GC-MS was used to assess conversion and selectivity. The yields were also measured by isolating the reaction products, showing full agreement with the yield values obtained by GC-MS.

In a typical procedure, once the reaction was complete, the catalyst was recovered by filtration, washed with EtOAc, EtOH/H₂O (v/v, 1/1), and EtOH, dried at room temperature by simply letting the solvents evaporate in normal conditions, and stored in an open vessel prior to reuse. The filtrate (added with the catalyst rinses) was concentrated, and the coupling product was first extracted with EtOAc and then washed (three times) with brine. The organic layer was dried over magnesium sulfate. After filtration, the solvent was removed to obtain a crude product, purified by flash chromatography when needed. The leaching in Pd and Si was assessed by ICP-OES analysis of the isolated crude product in DMF solvent (100 mg/mL concentration). Leaching values are given in mg/kg API (active pharmaceutical product).

2.2. Scaled-up Preparation of 4'-Methyl-2-biphenyl-carbonitrile. A 2 L three-necked round-bottom flask was equipped with a condenser and a mechanical stirring system. The aryl halide (100 g, 727.2 mmol, 1 equiv), 4-tolylboronic acid (99.94 g, 734.5 mmol, 1.01 equiv), and K₂CO₃ (110.55 g, 799.9 mmol, 1.1 equiv) were mixed in 1.454 mL of EtOH (0.5 M molar concentration with respect to the aryl halide). The mixture was heated to reflux (77 °C), after which the SiliaCat DPP-Pd catalyst (0.7 mol %, 0.25 mmol/g Pd loading) was added. The mixture

was vigorously stirred under mechanical stirring at 700 rpm for 1 h. After that, the mixture was cooled to room temperature, and the catalyst was recovered by filtration through a glass filter connected to a water vacuum pump, washed with EtOAc, EtOH/H₂O (v/v, 1/1), and EtOH, dried, and stored in normal conditions prior to reuse. The filtrate was concentrated under reduced pressure (rotovapor). The neat oil thereby obtained containing the coupling product was further extracted with EtOAc (500 mL) and washed with brine (3 × 500 mL). The organic layer was dried over magnesium sulfate. After filtration, the solvent was removed to obtain the crude product in 98% yield (97% purity).

3. RESULTS AND DISCUSSION

This study started using the standard conditions developed for aryl chloride over SiliaCat DPP-Pd (Table 1),¹¹ namely Ar-Cl (1 equiv), boronic acid (1.25 equiv or 1.1 equiv), and K₂CO₃ (2 equiv), under reflux in ethanol/water (10%, v/v). The reaction was tested for 6 mmol of aryl halide under magnetic stirring (entries 1 and 2 in Table 1, wherein selectivity refers to selectivity for Suzuki product) and for 36 mmol of aryl halide under mechanical stirring (entries 3 and 4).

Magnetic stirring using 1.25 equiv or 1.1 equiv of boronic acid over 1 mol % of SiliaCat DPP gave complete conversion after 30 min. Under mechanical stirring (36 mmol of aryl halide), complete conversion was obtained over 1 mol % of SiliaCat DPP-Pd after 1 h (entry 3 in Table 1). When 0.5 mol % of catalyst was used (entry 4), only 69% of conversion was obtained after 1 h of reaction. The leaching values of the Pd and the Si were

Table 3. Base Effect in Suzuki Coupling Reaction between 2-Chlorobenzonitrile and 4-Tolylboronic Acid^a

entry	catalyst (mol %)	base (equiv)	solvent (M)	<i>t</i> (h)	conv ^b (%)	select. ^b (%)
1	1	K ₂ CO ₃ (1.5)	EtOH (0.5 M)	0.5	100	98
2	1	Na ₂ CO ₃ (1.5)	EtOH (0.5 M)	0.5	53.5	99
				1.0	78	
3	1	NaOAc·3H ₂ O (1.5)	EtOH (0.5 M)	0.5	44	99
				1.0	47	
4	1	KOAc (1.5)	EtOH (0.5 M)	0.5	41	95
				1.0	48	
5	1	NaOH (1.25)	EtOH (0.5 M)	0.5	87	95
				1.0	93	
6	1	NaOH (1.5)	EtOH (0.5 M)	0.5	73	95
				1.0	75	
7	1	KOH (1.25)	EtOH (0.5 M)	0.5	87	95
				1.0	87	
8	1	KOH (1.5)	EtOH (0.5 M)	0.5	70	92
				1.0	72	
9	1	KHCO ₃ (1.5)	EtOH (0.5 M)	0.5	100	99
10	1	KF (1.5)	EtOH (0.5 M)	1.0	70	90
11	1	K ₂ HPO ₄ (1.5)	EtOH (0.5 M)	1.0	55	87

^aExperimental conditions: 2-chlorobenzonitrile (6 mmol, 1 equiv), 4-tolylboronic acid (1.1 equiv), base (1.25 equiv or 1.5 equiv), SiliaCat DPP-Pd (1 mol %, 0.25 mmol/g Pd) in ethanol HPLC grade (0.5 M molar concentration with respect to the aryl halide). ^bConversion/selectivity determined by GC-MS analysis.

Table 4. Boronic Acid Effect in Suzuki Coupling Reaction between 2-Chlorobenzonitrile and 4-Tolylboronic Acid^a

entry	boronic acid (equiv)	<i>t</i> (h)	conv ^b (%)	select. ^b (%)
1	1.25	0.5	100	98
2	1.10	0.5	100	98
3	1.05	0.5	100	99
4	1.01	0.5	100	99
5	1.00	0.5	98	100
		2.0		

^aExperimental conditions: 2-chlorobenzonitrile (6 mmol, 1 equiv), 4-tolylboronic acid (from 1.25 equiv to 1 equiv), SiliaCat DPP-Pd (1 mol %), K₂CO₃ (1.5 equiv), SiliaCat DPP-Pd (1 mol %, 0.25 mmol/g Pd). Solvent is EtOH 0.5 M with respect to the aryl halide. ^bConversion/selectivity determined by GCMS analysis.

determined in the isolated crude product, and the values obtained are more than 100 mg/kg for Pd and Si, pointing to high leaching of both Pd and Si from the entrapping support, under said reaction conditions.

3.1. Solvent Concentration 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 (Table 2).

Complete conversion was obtained after 30 min only either in more diluted (0.12 M, entry 1 in Table 2) solution or in more concentrated solution (1 M, entry 5). Raising the concentration to 1.5 M resulted in 92% aryl halide conversion after 1 h, which is in agreement with the increased viscosity of the reaction mixture and consequent slow-down of aryl halide diffusion to (and from) the entrapped Pd nanoparticles.

Replacement of the solvent mixture (ethanol/water) with ethanol only, lower amounts (1.5 equiv) of K₂CO₃, and the use of KHCO₃ as base were then investigated with the aim to decrease the leaching of palladium and silicon from the catalyst matrix. With KHCO₃ (1.5 equiv), complete conversion and full selectivity were observed after 30 min using a 0.5 M aryl halide concentration (entry 7 in Table 2). Again, doubling the concentration to 1 M resulted in lower and slower conversion

Table 5. Potassium Carbonate Effect in Suzuki Coupling Reaction between 2-Chlorobenzonitrile and 4-Tolylboronic Acid^a

entry	boronic acid (equiv)	base (equiv)	conv ^{b,c} (%)	select. ^c (%)
1	1.01	K ₂ CO ₃ (1.5)	100	99
2	1.01	K ₂ CO ₃ (1.25)	100	100
3	1.01	K ₂ CO ₃ (1.1)	100	100
4	1.01	K ₂ CO ₃ (1)	100	100

^aExperimental conditions: 2-chlorobenzonitrile (6 mmol, 1 equiv), 4-tolylboronic acid (1.01 equiv), catalyst 1 mol % K₂CO₃ (from 1.5 equiv to 1 equiv), SiliaCat DPP-Pd (1 mol %, 0.25 mmol/g Pd). ^bMolar concentration with respect to the aryl halide. ^cConversion/selectivity determined by GC-MS analysis. Solvent is EtOH 0.5 M with respect to the aryl halide. Reaction time (*t*) = 0.5 h.

(71% conversion after 30 min and 85% after 1 h, entry 8). The leaching values of both Pd and the Si in the isolated crude product for each reaction tested clearly show that, using only 1.5 equiv of base, the values obtained are <5 mg/kg (ppm) for both metals.

3.2. Determination of the Optimal the Base. Different bases were therefore tested (Table 3). Potassium carbonates are by far the best reaction base, with complete conversions obtained with both K₂CO₃ and KHCO₃ after 30 min only.

Sodium carbonate (entry 2), however, is a poor base for the reaction, and even extending the reaction time to 1 h, the conversion does not exceed 78%. Potassium bicarbonate (entry 9), on the other hand, is an excellent base. The trend is reversed in the case of KOH and NaOH. Both afford lower yields compared to potassium carbonate, yet by diminishing from 1.5 to 1.25 equiv the amount of strong base, the conversion increases up to 93% after 1 h in the case of NaOH (entry 5 in Table 3). From a conversion viewpoint, the poorest base is sodium acetate hydrate (entry 3), which is not capable of affording aryl halide conversion higher than 47%. Coordinating species such as potassium fluoride (entry 10) and phosphite (entry 11) give both poor conversion and selectivity.

Table 6. SiliaCat DPP-Pd Catalyst Effect in Suzuki Coupling Reaction between 2-Chlorobenzonitrile and 4-Tolylboronic Acid^a

entry	catalyst (mol %)	boronic acid (equiv)	base (equiv)	solvent (M) ^b	t (h)	conv ^c (%)	select. ^d (%)
1	1	1.01	K ₂ CO ₃ (1)	EtOH (0.5 M)	0.5	100	98.5
2	0.5	1.01	K ₂ CO ₃ (1)	EtOH (0.5 M)	0.5	78	94
					1.0	79	
					4.0	84	
3	0.5	1.1	K ₂ CO ₃ (1)	EtOH (0.5 M)	1.0	85	100
4^d	0.5	1.25	K₂CO₃ (1)	EtOH (0.5 M)	0.5	100	100
5	0.5	1.1	K ₂ CO ₃ (1.25)	EtOH (0.5 M)	1.0	78	100
6	0.5	1.1	K ₂ CO ₃ (1.5)	EtOH (0.5 M)	1.0	96	100

^aExperimental conditions: 2-chlorobenzonitrile (6 mmol, 1 equiv), 4-tolylboronic acid (from 1.01 to 1.25 equiv), K₂CO₃ (from 1 equiv to 1.5 equiv), SiliaCat DPP-Pd (0.5 mol % and 1 mol % Pd, 0.25 mmol/g Pd). ^bMolar concentration with respect to the aryl halide. ^cConversion/selectivity determined by GC-MS analysis. ^dThe reaction was repeated three times to confirm the result.

Table 7. Scale-Up from 1 to 100 g of 2-Chlorobenzonitrile^a

entry	aryl halide	boronic acid (equiv)	catalyst (mol %)	base (equiv)	solvent (M) ^c	t (h)	conv ^d (%)	yield ^e (%)	leaching ^f (mg/kg)	
									Pd	Si
1	6 mmol 0.8 g	1.01	1	K ₂ CO ₃ (1.1)	EtOH (0.5 M) magnetic stirring (850 rpm)	0.5	100	98	0.7	1.1
2	72 mmol 10 g	1.01	1	K ₂ CO ₃ (1.1)	EtOH (0.5 M) magnetic stirring (850 rpm)	0.5	100	97.5	2	4.2
3	72 mmol 10 g	1.01	1	K ₂ CO ₃ (1.1)	EtOH (0.5 M) mechanical stirring (700 rpm)	0.5	100	98.6	0.6	8.5
4	360 mmol 50 g	1.01	1	K ₂ CO ₃ (1.1)	EtOH (0.5 M) mechanical stirring (700 rpm)	0.5	100	97	1.02	6.25
5	720 mmol 100 g	1.01	0.7	K ₂ CO ₃ (1.1)	EtOH (0.5 M) mechanical stirring (700 rpm)	0.5	90	98	2.32	3.81
						1	100			
6 ^b	6 mmol 0.8 g	1.25	0.5	K ₂ CO ₃ (1)	EtOH (0.5 M) magnetic stirring (850 rpm)	0.5	100	98.5	0.8	0.9
7 ^b	72 mmol 10 g	1.25	0.5	K ₂ CO ₃ (1)	EtOH (0.5 M) mechanical stirring (700 rpm)	0.5	82	96	3.07	3.12
						1	88			
						2	100			

^aExperimental conditions: 2-chlorobenzonitrile (from 6 to 720 mmol, 1 equiv), 4-tolylboronic acid (1.01 equiv), K₂CO₃ (1.1 equiv), SiliaCat DPP-Pd (1 mol % Pd, 0.25 mmol/g Pd). ^b2-Chlorobenzonitrile (from 6 to 72 mmol, 1 equiv), 4-tolylboronic acid (1.25 equiv), K₂CO₃ (1 equiv), SiliaCat DPP-Pd (0.5 mol % Pd, 0.25 mmol/g Pd). ^cMolar concentration with respect to the aryl halide. ^dConversion determined by GC-MS analysis. ^eIsolated yield. ^fLeaching of Pd and Si determined by ICP-OES analysis in isolated crude product.

3.3. Optimal Amount of Organoboronic Acid. Different amounts of valued boronic acid were used in Suzuki coupling, ranging from 1.25 to 1.0 equiv with respect to the aryl halide (Table 4). An increase in selectivity (from 98 to 99%) was observed by lowering the boronic acid relative amount to less than the 1.10 equiv threshold (entries 3–5).

Total aryl halide conversion was obtained even using 1.01 equiv (entry 4). This is important because aryl boronic acids are the most expensive reagents employed in Suzuki couplings, even if alternative routes¹² to the traditional bis(pinacolato)diboron synthesis are being developed. When 1 equiv only of boronic acid was used, the maximum conversion reached was 98%.

3.4. Effect of the Concentration of K₂CO₃. Different amounts of K₂CO₃ were used in Suzuki coupling from 1.5 to 1.0 equiv with respect to the aryl halide (Table 5).

Complete conversion was obtained even when 1 equiv of K₂CO₃ (2.2 equiv of total base) was used in the reaction (entry 4). In general, the conditions from Table 5, entry 3 were chosen for scaling-up the process.

3.5. Catalyst Concentration Effect. Investigation of the catalyst amount on the reaction shows (entry 1 in Table 6) that, after 30 min, complete conversion was obtained over 1 mol % of catalyst in EtOH 0.5 M with 1 equiv of K₂CO₃. When the amount of catalyst was decreased to 0.5 mol %, the conversion did not proceed at completion. Hence, after 4 h only 84% conversion was obtained (entry 2). To increase conversion with 0.5 mol % catalyst, the amount of boronic acid and base were thus increased.

Entry 4 in Table 6 shows that, now with 1.25 equiv of boronic acid and 1 equiv of base, complete conversion and 100% selectivity were obtained after 30 min. When the amount of base was further increased and the amount of valued boronic acid lowered to 1.1 equiv (entries 3, 5, and 6 in Table 6), the conversion did not reach completion.

3.6. Reaction Scale-Up. The conditions summarized in entry 3 in Table 5 (or in entry 4 in Table 6; both in bold) were therefore used to increase the amount of the aryl halide from 6 to 720 mmol. When 72 mmol (10 g) of starting material was used, complete conversion was obtained after 30 min under magnetic stirring at 850 rpm (entry 2 in Table 7) or under mechanical stirring at 700 rpm (entry 3).

The amount of the aryl halide was then increased to 360 mmol (50 g) under the same reaction conditions. Complete conversion was again obtained after 30 min (entry 4).

When the amount of the aryl halide was further increased to 720 mmol (100 g), the amount of catalyst was decreased to 0.7 mol %. Now, almost complete conversion was obtained after 1 h (98% yield and 97% purity; entry 5 in Table 7). To further decrease the catalyst load to 0.5 mol % palladium, the conditions developed in Table 6, entry 4, were applied. In the presence of 1.25 equiv of boronic acid and 1 equiv of base with mechanical stirring at 700 rpm, complete aryl halide conversion was obtained after 2 h (entry 7).

Table 7 shows that the values of palladium leached in isolated crude product are <5 mg/kg, and the values of leached silicon are <10 mg/kg.

Table 8. Reusability Test over 1 mol % SiliaCat DPP-Pd in Suzuki Coupling between 2-Chlorobenzonitrile and 4-Tolylboronic Acid^a

entry	solvent (M) ^b	t (h)	conv ^b (%)	select. ^c (%)	leaching (ppm) ^d	
					Pd	Si
run 1	EtOH (0.5 M) mechanical stirring (700 rpm)	0.5	100	100	1.02	6.25
run 2	EtOH (0.5 M) mechanical stirring (700 rpm)	0.5	88	100	5.79	11.26
		2.0	100			
run 3	EtOH (0.5 M) mechanical stirring (850 rpm)	0.5	57	98	5.70	6.83
		2.0	69			
		5.0	78			
run 4	EtOH (0.5 M) mechanical stirring (850 rpm)	0.5	30	98	42	188
		2.0	44			
		5.0	46			
		24.0	60			

^aExperimental conditions: aryl halide (1 equiv), 4-tolylboronic acid (1.01 equiv), K₂CO₃ (1.1 equiv), SiliaCat DPP-Pd (1 mol % Pd, 0.25 mmol/g Pd) in ethanol HPLC grade (0.5 M). ^bMolar concentration with respect to the aryl halide. ^cConversion/selectivity determined by GC-MS analysis. ^dLeaching of Pd and Si determined by ICP-OES analysis in isolated crude product.

3.7. Reusability Study. For the reusability study of the catalyst, we used 72 mmol of aryl halide in Run 1. After completion of the reaction, the catalyst was separated by filtration; washed two times with EtOAc, then three times with EtOH/H₂O (v/v, 1/1), and finally two times with EtOH; dried; and stored prior to reuse.

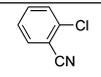
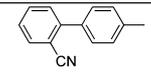
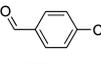
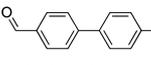
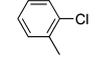
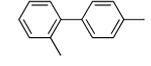
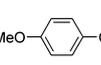
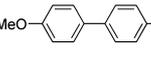
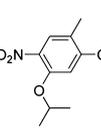
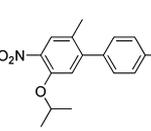
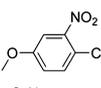
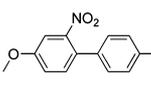
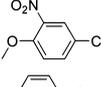
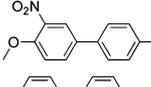
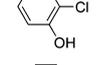
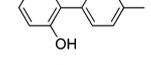
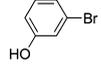
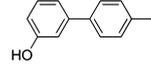
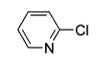
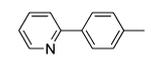
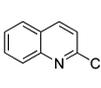
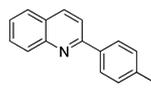
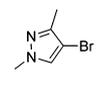
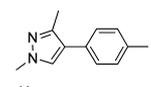
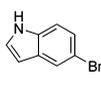
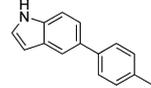
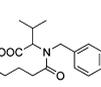
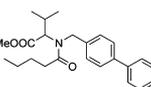
The results in Table 8 clearly show that the catalytic activity of the catalyst decreases already after the first run (entry 2), with considerable loss in activity after two runs (entry 3).

3.8. Scope of the Reaction. Finally, to investigate the scope of the method (1 equiv of Ar-X, 1.1 equiv of 4-tolylboronic acid, SiliaCat DPP, 1.5 equiv of K₂CO₃ in 0.5 M EtOH under reflux), the protocol was applied to several aryl halides with electron-withdrawing (nitrile and carbonyl) or electron-donating (methoxy, methyl, phenol, and amine) groups. Furthermore, we tested various heterocycle aryl halides such as pyrazole, pyridine, indole, and quinoline.

The results in Table 9 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. For 4-chloro-3-nitroanisole with a nitro group in the *ortho* position (entry 6 in Table 9), complete conversion was obtained after 2 h over 1 mol % catalyst, whereas 4-chloro-2-nitroanisole with the nitro group in the *meta* position (entry 7) gave only 53% yield after 2 h. For this aryl halide, the amount of the biphenyl product generated from boronic acid coupling 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 such as that for aryl halides in entries 5 and 14 does not affect conversion, with, again, almost complete conversions obtained after 0.5–2 h over 1 mol % of SiliaCat DPP.

Crude products were isolated after 2 h of reaction for all products tested in Table 9 and analyzed by ICP-OES to determine the palladium and silicon leaching. The leaching values obtained show clearly that the leaching in Pd and in Si depends of the aryl halide and on the amount of the catalyst used in the reaction. For 2-chloropyridine (entry 10), 4-bromo-1,3-dimethyl-1H-pyrazole

Table 9. Different Aryl Chloride Aryl Halides in Suzuki Coupling Reaction over 1 mol % SiliaCat DPP-Pd^a

Entry	Aryl halides	t (h)	Product	Yield ^c (%)	Leaching ^d (mg/kg)	
					Pd	Si
1		0.5		100	2	4.51
2		2.0		92	1.87	7.78
3		2.0		100	0.58	1.61
4		2.0		95	<0.5	2.53
5		0.5		99	<0.5	2.61
6		2.0		97	10.91	7.49
7		2.0		53 81 ^f	11.56	3.81
8		2.0		77 88 ^e	3.86 6.93	9.71 7.61
9		0.5		100	7.7	4.79
10		2.0		95	14.46	7.31
11		2.0		100	2.8	6.3
12		2.0		82 90 ^f	50.5 70.4	8.8 16.3
13		2.0		91	19.6	4.89
14		1.0		99 ^e	3.5	8.65

^aExperimental conditions: aryl halide (6 mmol, 1 equiv), 4-tolylboronic acid (1.1 equiv), K₂CO₃ (1.5 equiv), 1 mol % SiliaCat DPP-Pd (0.25 mmol/g Pd) in EtOH HPLC grade (0.5 M). ^bMolar concentration with respect to the aryl halide. ^cYield determined by GC-MS analysis. ^dLeaching of Pd and Si determined by ICP-OES analysis in isolated crude product. ^e2 mol % of SiliaCat DPP-Pd was used in the reaction. ^f2 equiv of 4-tolylboronic acid. ^g1.25 equiv of 4-tolylboronic acid in MeOH/10% H₂O (0.1 M).

(entry 12), and 5-bromoindole (entry 13), the enhanced leaching values are due to coordination of these aryl halides with the organosilica-tethered palladium species. As expected for a heterogeneous reaction, when higher loadings (2 mol % Pd) were used to increase yields, the leaching in Pd and in Si increased (entries 10 and 12 in Table 9).

In 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 points to a number of

interesting findings. First, to decrease the leaching of palladium and silicon, the optimal solvent is ethanol, showing the relevance of anhydrous conditions (the switch from EtOH/H₂O to EtOH only) to ensure limited hydrolytic decomposition of the organosilica matrix, likely induced by hydrolyzed base. Second, the optimal aryl halide and boronic acid amounts are, respectively, 1 M concentration and 1.01 equiv with respect to the aryl halide. Third, the optimal base is potassium carbonate in 1.1 M concentration. Finally, the optimal catalyst amount under scaled-up conditions is 0.7 mol %. The catalyst is barely reusable with considerable loss in catalytic activity after the first reaction run.

We have also shown that the method is general, as it enables the heterogeneous conversion of an ample variety of different aryl aryl halides, with yields in coupled product ranging from 70% to 100%. With certain substrates, the use of the immobilized SiliaCat DPP-Pd catalyst prevents the contamination of the product with palladium, reducing the Pd-level to <0.5 ppm. This is relevant from an applicative viewpoint, as one reason justifying the use of a heterogeneous catalyst is to avoid palladium contamination in the product to a content of less than 1 ppm metal (required for most applications in the pharmaceutical industry).

To further reduce leaching, which is also due to fast stirring (700 rpm) of the reaction mixtures and mechanical rupture of the silica microparticles, the reaction will usefully be carried out under continuous conditions. We have recently shown elsewhere¹³ that the mesoporous organosilica catalysts of the SiliaCat series, being nonswelling and highly accessible to reactants, are ideally suited for reactions in continuous mode. The results of this study will be useful in guiding further progress.

AUTHOR INFORMATION

Corresponding Author

*E-mail: FrançoisBeland@silicycle.com (F.B.); mario.pagliaro@cnr.it (M.P.).

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Mr. Pierre-Gilles Vaillancourt and Mr. Simon Bédard from the Quality Control Department of SiliCycle Inc. for their valuable contribution.

DEDICATION

This article is dedicated with love to the mother of one of us (V.P.).

REFERENCES

- (1) Wexler, R. R.; Greenlee, W. J.; Irvin, J. D.; Goldberg, M. R.; Prendergast, K.; Smith, R. D.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1996**, *39*, 625–656.
- (2) Kearney, P. M.; Whelton, M.; Reynolds, K.; Muntner, P.; Whelton, P. K.; He, J. *Lancet* **2005**, *365*, 217–223.
- (3) (a) Longstreet, A. R.; McQuade, D. T. *Acc. Chem. Res.* **2012**, *46*, 327–338. (b) McQuade, D. T. A Flow Chemistry Approach To Catalysis. FineCat 2013—Symposium on heterogeneous catalysis for fine chemicals, Palermo, Italy, 10–11 April 2013.
- (4) Bühlmayer, P.; Furet, P.; Criscione, L.; de Gasparo, M.; Whitebread, S.; Schmidlin, T.; Lattmann, R.; Wood, J. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 29–34.
- (5) Goossen, L. J.; Melzer, B. *J. Org. Chem.* **2007**, *72*, 7473–7476.
- (6) Beutler, U.; Boehm, M.; Fuenfschilling, P. C.; Heinz, T.; Mutz, J.-P.; Onken, U.; Mueller, M.; Zaugg, W. *Org. Process Res. Dev.* **2007**, *11*, 892–898.

(7) Ghosh, S.; Kumar, A. S.; Mehta, G. N. *Beilstein J. Org. Chem.* **2010**, *6*, No. 27.

(8) As stated by Dunn, the range of 25–100 kg of waste per kilogram of API proposed by Sheldon in 1992 at the end of the “racemic era” is probably now more realistically 25–200 in the “chiral era: Dunn, P. J. *Chem. Soc. Rev.* **2012**, *41*, 1452–1461.

(9) EPA Office of the Inspector General. EPA Inaction in Identifying Hazardous Waste Pharmaceuticals May Result in Unsafe Disposal, Report No. 12-P-0508; Washington, May 25, 2012.

(10) Lemay, M.; Pandarus, V.; Simard, M.; Marion, O.; Tremblay, L.; Béland, F. *Top. Catal.* **2010**, *53*, 1059–1062.

(11) Pandarus, V.; Gingras, G.; Béland, F.; Ciriminna, R.; Pagliaro, M. *Org. Process Res. Dev.* **2012**, *16*, 117–122.

(12) Molander, G. A.; Trice, S. L. J.; Dreher, S. D. *J. Am. Chem. Soc.* **2010**, *132*, 17701–17703.

(13) Pandarus, V.; Ciriminna, R.; Gingras, G.; Béland, F.; Drobod, M.; Jina, O.; Pagliaro, M. *Tetrahedron Lett.* **2013**, *54*, 1129–1132.