



Enhanced heterogeneously catalyzed Suzuki–Miyaura reaction over SiliaCat Pd(0)



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ABSTRACT

The SiliaCat Pd(0) solid catalyst can be efficiently employed in the Suzuki–Miyaura cross-coupling of an ample variety of haloarenes, including economically viable chloroarenes. The catalyst can be extensively recycled without loss of activity and with low leaching of valued palladium, opening the route to widespread utilization of the method to afford high yields of biaryls devoid of contaminating by-products.

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The palladium catalyzed Suzuki–Miyaura cross-coupling of arylboronic acids with aryl halides is one of the most powerful tools for carbon–carbon bond formation in modern organic synthesis.¹ The reaction tolerates a broad range of functional groups in the coupling partners and is usually performed in solution, at room temperature in many cases, and often using simple palladium salts such as PdCl₂, with low amounts of catalyst.²

The original paper³ described cross-coupling of two functionalized alkenes, but subsequent work mostly addressed the synthesis of biaryls, whose structure is found in various biologically active compounds, in organic light emitting diodes, and in conducting polymers. The two main problems adding cost to the products of traditional Suzuki–Miyaura reaction, lie in the Pd impurities left in the reaction product (for e.g., the EMEA approved upper limit for Pd in final pharmaceuticals is in the 5–10 ppm range);⁴ and to the fact that low cost chloroarenes cannot be employed due to the stability of the C–Cl bond. A large body of research has therefore been devoted in the last decade to identify recyclable and truly heterogeneous Pd catalysts of broad scope.⁵

In this context, we have recently reported that the heterogeneous Suzuki–Miyaura cross-coupling of iodo and bromoarenes in environmentally benign alcohol over the sol–gel entrapped Silia-

Cat Pd(0)⁶ catalyst selectively affords high yields of coupled products.⁷ Now, we show how to broaden the scope of the method to convert also readily available aryl chlorides and access high reaction rates for both aryl chlorides and bromides using microwave irradiation.

The two catalyst samples used throughout this work are those now commercially available following optimization in light of manufacturing requirements.⁸ The catalysts were first tested at 60 °C and at room temperature (22 °C) in the conversion of aryl iodides under optimized conditions in MeOH, EtOH, or *n*-PrOH/MeOH (v/v, 1/1) mixture as protic solvents which are generally required for optimal reaction, while K₂CO₃ was the base normally employed. No inert atmosphere was required.

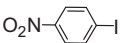
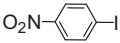
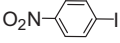
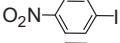
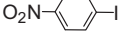
Results in Table 1 show that using 0.5 mol % SiliaCat Pd(0) the Suzuki–Miyaura can also be carried out at room temperature, with complete conversion of the substrate after 6.5 h (entry 4 in Table 1). The reaction time can be lowered to 2 h upon by simply doubling the catalyst amount to 1 mol % (entry 5). The previous conditions, using a slight excess (1.2 equiv) of boronic acid, were thus tested in the cross-coupling of other aryl iodide substrates with different boronic acid pinacol esters (Table 2).

Complete conversion was obtained for 2-iodothiophene after 1 h using phenylboronic acid pinacol ester (entry 1 in Table 2) or 4-chlorophenylboronic acid pinacol ester (entry 2). For 4-iodo-1-methyl-1H-pyrazole more than 90% yield was obtained after 4 h over 0.5 mol % catalyst (entry 3) or after 1 h when using 1 mol % SiliaCat Pd(0).

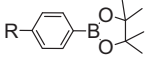





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Table 1Suzuki–Miyaura conversion of 4-iodonitrobenzene over SiliaCat Pd(0) under different conditions^a

Entry	Substrate	Catalyst ^b mol %	Solvent/M ^c	T (°C)	Time	Yield ^d %	TON	TOF/h
1		Si-Pd-1 0.5	MeOH 0.08	60	5 min	100	200	2500
2		Si-Pd-2 0.5	MeOH 0.08	60	5 min	100	200	2500
3		Si-Pd-1 0.1	MeOH 0.08	60	30 min	100	1000	2000
4 ^e		Si-Pd-2 0.5	MeOH/H ₂ O 0.02	22	6.5 h	100	200	31
5 ^e		Si-Pd-2 1	MeOH/H ₂ O 0.02	22	2 h	100	100	50

^a Experimental conditions: Reactions performed in methanol HPLC grade. Substrate (0.8 mmol, 1 equiv), phenylboronic acid (0.88 mmol, 1.1 equiv), K₂CO₃ (1.2 mmol, 1.5 equiv), catalyst, from 0.5 to 1 mol % Pd.^b Catalyst identified in Ref. 8.^c Molar concentration with respect to the substrate.^d Yield evaluated by GC–MS analysis.^e MeOH/H₂O (v/v, 9/1).**Table 2**Suzuki–Miyaura coupling of different aryl iodides with different boronic acid pinacol esters over SiliaCat Pd(0)^a

Entry	Substrate		Catalyst ^b mol %	Solvent/M ^c	T (°C)	t (h)	Conv/Yield ^d %
1		R: H	Si-Pd-1 0.5	MeOH 0.1	60	1	100/99.8
2		R: Cl	Si-Pd-1 0.5	MeOH 0.1	60	1	100/99
3		R: H	Si-Pd-1 0.5	MeOH 0.1	60	4	98/93
4		R: Cl	Si-Pd-1 0.5	MeOH 0.1	60	4	95/90
5		R: Cl	Si-Pd-1 1	MeOH 0.1	60	1	97/93

^a Experimental conditions: Reactions were performed in methanol HPLC grade. Substrate (1 equiv), phenylboronic acid pinacol ester (1.2 equiv), K₂CO₃ (1.5 equiv), from 0.5 to 1 mol % SiliaCat Pd(0).^b Catalyst identified in Ref. 8.^c Molar concentration with respect to the substrate.^d Conversion evaluated by GC–MS analysis, isolated yield.

A wide variety of aryl bromide substrates bearing both electron withdrawing and electron donating groups could be coupled with phenylboronic acid using only 0.1 mol % of SiliaCat Pd(0) catalyst with excellent yields in both ethanol or *n*-propanol/methanol (v/v, 1/1) at 60 °C (Table 3). Reaction times of 0.5–2 h are common, depending on the substrate.

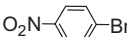

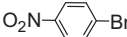


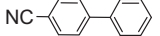
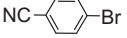
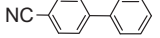

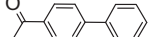
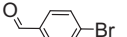
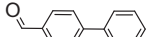
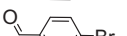
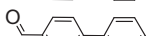
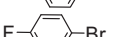
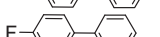
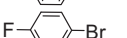
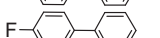
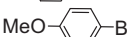
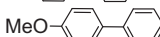
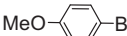

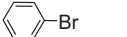
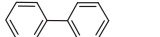
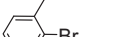
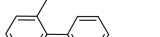


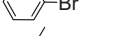
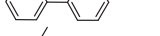
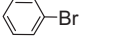
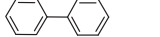
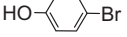
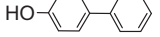
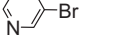
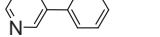
Under the conditions above, chloroarenes are generally not converted. Hence, entries 4 and 5 in Table 4 show that 4-chloronitrobenzene does not react with phenylboronic acid, with a modest 35% conversion into coupled product being observed (entry 6) only in the presence of a phosphine ligand, under inert conditions.

We therefore attempted the conversion of aryl chlorides over SiliaCat Pd(0) under microwave irradiation, which is an effective heating alternative to obtain cross-coupling of various halide substrates.⁹

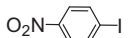
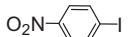
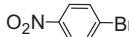
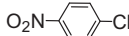
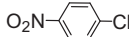
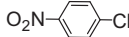
Results in Table 5 show that now most substrates tested can be cross-coupled with phenylboronic acid in short time, ranging from 5 through 15 min. Only the unactivated isomers of chlorophenol (entries 6–8) did not react, while chlorobenzene, *p*-chloroacetophenone, *p*-chloroanisole, and *p*-chlorotoluene (entries 1, 4, 5, and 9) afforded the coupled product in 100%, 56%, 64%, and 53% yield, respectively.

As expected, cross-coupling of aryl bromides under microwave irradiation proceeded faster than under conventional heating. Now, very high TOF values of 12,500 h^{−1} are reached, with a substrate such as *p*-bromophenol being entirely converted after 5 min only (entry 3 in Table 6), while under conventional heating at 60 °C after 2 h only 53% yield was reached (entry 16 in Table 3). Furthermore, showing the versatility of the method, heterocycles such as 3-bromoquinoline (entry 9 in Table 6) and 3-bromopyridine (entry 10) are also smoothly converted into coupled product.

Table 3Suzuki–Miyaura conversion of different aryl bromides over 0.1 mol % SiliaCat Pd(0) catalyst^a


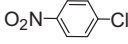
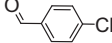
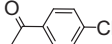
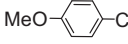
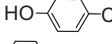



Entry	Substrate	Solvent ^b	Coupling product	<i>t</i> (h)	Yield ^c %
1		EtOH		0.5	100
2		<i>n</i> -PrOH/MeOH		0.5	100
3		EtOH		0.5	100
4		<i>n</i> -PrOH/MeOH		0.5	100
5		<i>n</i> -PrOH/MeOH		0.5	100
6		EtOH		0.5	65
7		<i>n</i> -PrOH/MeOH		2	67
8		EtOH		2	91
9		<i>n</i> -PrOH/MeOH		2	95
10		EtOH		2	81
11		<i>n</i> -PrOH/MeOH		2	58
12		<i>n</i> -PrOH/MeOH		2	94
13		EtOH		2	86
14		<i>n</i> -PrOH/MeOH		2	90
15 ^d		DMF/MeOH		2	88
16		EtOH		2	53
17		EtOH		2	78
18		<i>n</i> -PrOH/MeOH		2	85

^a Experimental conditions: Reactions in ethanol or *n*-propanol/methanol (v/v, 1/1) HPLC grade, at 60 °C. Substrate (1 equiv), phenylboronic acid (1.2 equiv), K₂CO₃ (1.5 equiv), over 0.1 mol % of Si-Pd-1, catalyst identified in Ref. 8.^b 0.2 M molar concentration with respect to the substrate.^c Yield evaluated by GC–MS analysis.^d Na₂CO₃ was used as base in DMF/MeOH (v/v, 1/1).**Table 4**Suzuki–Miyaura conversion of different aryl halides over SiliaCat Pd(0)^a

Entry	Substrate	Catalyst ^d mol %	Solvent/M ^e	T (°C)	<i>t</i> (h)	Yield ^d %	TON	TOF (h)
1		Si-Pd-2 0.5	MeOH/ 0.08	60	5 min	100	200	2500
2		Si-Pd-1 0.1	MeOH/ 0.08	60	0.5	100	1000	2000
3		Si-Pd-1 0.1	EtOH/ 0.2	60	0.5	100	1000	2000
4		Si-Pd-1 0.1	EtOH/ 0.2	60	24	0	—	—
5 ^b		Si-Pd-2 0.1	EtOH/H ₂ O/0.125	75	24	—	—	—
6 ^c		Si-Pd-2 1 P(t-Bu) ₃	PrOH/H ₂ O/0.125	95	22	35	—	—

^a Experimental conditions: Reactions in methanol or ethanol HPLC grade. Substrate (1 equiv), phenylboronic acid (1.2 equiv), K₂CO₃ (1.5 equiv), over SiliaCat Pd(0) catalyst identified Ref. 8.^b Reaction in ethanol/H₂O (v/v, 9/1) HPLC grade, substrate (1 equiv), phenylboronic acid (1.2 equiv), K₂CO₃ (2 equiv) over SiliaCat Pd(0) catalyst.^c Reaction in *n*-propanol/H₂O (v/v, 9/1) HPLC grade, substrate (1 equiv), phenylboronic acid (1.2 equiv), K₂CO₃ (2 equiv), over 1 mol % SiliaCat Pd(0) catalyst and 3 mol % P(t-Bu)₃, under inert conditions.^d Yield evaluated by GC–MS analysis.^e Molar concentration with respect to the substrate.

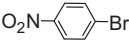
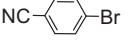
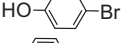



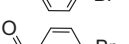
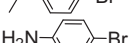
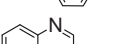

Table 5Suzuki–Miyaura conversion of different aryl chlorides over SiliaCat Pd(0) under microwave irradiation^a

Entry	Substrate	Catalyst mol %	Microwave conditions				Yield ^b %
			Power/ W	PSI	T (°C)	t (min)	
1		Si-Pd-1 0.5	200	200	100	5	100
2		Si-Pd-1 0.5	200	200	100	5	100
3		Si-Pd-1 0.5	200	200	100	10	100
4		Si-Pd-1 1	200	200	120	10	56
5		Si-Pd-1 0.5	200	200	100	10	64
6		Si-Pd-1 0.5	200	200	100	15	0
7		Si-Pd-1 0.5	200	200	100	15	0
8		Si-Pd-1 0.5	200	200	100	15	0
9		Si-Pd-1 0.5	200	200	100	15	53

^a Experimental conditions: Reactions in methanol HPLC grade, 0.2 M concentration with respect to the substrate, substrate (1 equiv), phenylboronic acid (1.2 equiv), K₂CO₃ (1.5 equiv), over SiliaCat Pd(0) catalyst identified in Ref. 8.

^b Yield evaluated by GC–MS analysis.

Table 6Suzuki–Miyaura conversion of different aryl bromides over SiliaCat Pd(0) under microwave irradiation^a

Entry	Substrate	Catalyst/mol %	Solvent/M	Microwave conditions				Yield ^b %	TON	TOF (h)
				Power/W	PSI	T (°C)	t (min)			
1		Si-Pd-1 0.1	MeOH 0.1	200	200	100	5	100	1000	12,500
2		Si-Pd-1 0.1	MeOH 0.1	150	150	75	5	100	1000	12,500
3		Si-Pd-1 0.1	MeOH 0.1	150	150	75	5	100	1000	12,500
4		Si-Pd-1 0.1	MeOH 0.2	200	200	100	5	100	1000	12,500
5		Si-Pd-1 0.1	MeOH 0.1	150	150	75	5	100	1000	12,500
6		Si-Pd-1 0.1	MeOH 0.1	150	150	75	5	100	1000	12,500
7		Si-Pd-1 0.1	MeOH 0.2	150	150	75	5	100	1000	12,500
8		Si-Pd-1 0.1	MeOH 0.1	200	200	75	5	100	1000	12,500
9		Si-Pd-1 0.1	EtOH/H ₂ O 0.23	200	200	125	20	88	—	—
10		Si-Pd-1 0.1	EtOH/H ₂ O 0.23	200	200	125	15	73	—	—

^a Experimental conditions: Reactions in methanol HPLC grade from 0.1 to 0.23 M concentration with respect to the substrate, substrate (1 equiv), phenylboronic acid (1.2 equiv), K₂CO₃ (1.5 equiv), over SiliaCat Pd(0) catalyst identified in Ref. 8.

^b Yield by GC–MS analysis.

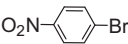
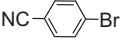
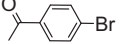
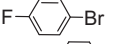
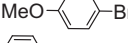
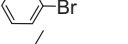
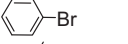
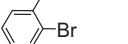
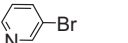
Pd and Si leaching values from the catalyst were analyzed by ICP–OES in an isolated solid crude product for different substrates (Table 7). Minimal Pd leaching values (below 7 ppm) were observed, except for 3-bromopyridine most likely due to palladium coordination of the electron pair of the nitrogen atom (entry 9).

Reutilization of the catalyst was possible, with full retention of the activity of the catalyst in all 7 consecutive reaction runs in which the catalyst was reused using 4-iodonitrobenzene as the

representative substrate.⁶ No further reaction of the hot filtrate at 50% conversion was observed.¹⁰

In conclusion, the Suzuki–Miyaura reaction can be smoothly carried out over a 0.1–1 mol % catalytic amount of SiliaCat Pd(0), opening the route to widespread utilization of this simple green methodology for the synthesis of fine chemicals, with recovery and reuse of valued catalyst, while avoiding time-consuming catalyst separation and product purification steps which impact cost and worsen the environmental footprint of the reaction. Low levels

Table 7Suzuki–Miyaura conversion of different aryl bromides over 0.1 mol % SiliCat Pd(0) catalyst^a

Entry	Substrate	Solvent	Yield ^b %	Leaching (mg/kg) ^c	
				Pd	Si
1		<i>n</i> -PrOH/MeOH	100	2.5	7.2
2		<i>n</i> -PrOH/MeOH	100	6.9	9.8
3		<i>n</i> -PrOH/MeOH	100	2	4
4		<i>n</i> -PrOH/MeOH	95	2.5	6.1
5		<i>n</i> -PrOH/MeOH	58	1.9	10.8
6		<i>n</i> -PrOH/MeOH	94	5.6	19.6
7		<i>n</i> -PrOH/MeOH	90	2	11.1
8 ^d		DMF/MeOH	88	1.8	5.9
9		<i>n</i> -PrOH/MeOH	85	40.6	11.2

^a Experimental conditions: Reactions in *n*-propanol/methanol (v/v, 1/1) HPLC grade, 0.2 M molar concentration with respect to the substrate at 60 °C for 2 h. Substrate (1 equiv), phenylboronic acid (1.2 equiv), K₂CO₃ (1.5 equiv), over 0.1 mol % Si-Pd-1, catalyst identified in Ref. 8.

^b Yield evaluated by GC–MS analysis.

^c Leaching of Pd and Si evaluated by ICP–OES analysis of isolated crude product in DMF (50 mg/ml concentration).

^d Na₂CO₃ was used as the base in DMF/MeOH (v/v, 1/1).

of leached Pd are observed and catalysis is truly heterogeneous. Conversion of readily available chloroarenes requires microwave irradiation. Under 200 W power irradiation, activated aryl chlorides are coupled to arylboronic acid affording good yields of coupled products, while under irradiation aryl bromides are converted

in extremely short reaction times with TOF values up to 12,500 h^{−1}. Conversion of aryl iodides can be carried out even at room temperature.

Acknowledgements

This letter is dedicated to Mr. Hugo St-Laurent and to all the staff of SiliCycle, Inc., on the occasion of the 15th anniversary of the company. We thank Mr. Pierre-Gilles Vaillancourt and Mr. Simon Bédard from the Quality Control Department of SiliCycle Inc. for their valuable contribution.

References and notes

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