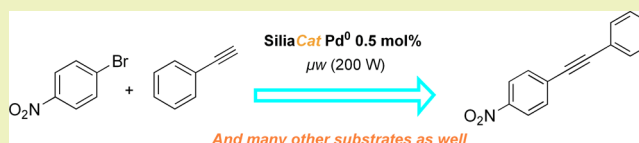


Heterogeneous Sonogashira Coupling over Nanostructured SiliaCat Pd(0)

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ABSTRACT: Sol–gel entrapped catalyst SiliaCat Pd(0) heterogeneously mediates the Sonogashira coupling of different aryl halides and phenylacetylene either under thermal conditions or, much more efficiently, under microwave irradiation, affording good conversions of coupled products. Leaching of valued Pd is limited, and the catalyst can be reused.

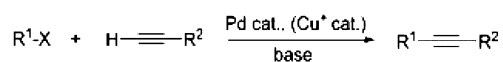
KEYWORDS: Sonogashira coupling, Heterogeneous, Sol–gel, Pd catalysis, SiliaCat



INTRODUCTION

The palladium-catalyzed coupling reaction of aryl halides and terminal acetylenes (Scheme 1) is a versatile organic chemistry

Scheme 1. Sonogashira Coupling ($R^1 = \text{Aryl, Vinyl}$; $X = \text{I, Br, Cl, OTf}$; $R^2 = \text{Aryl, Alkenyl, Alkyl}$)



synthetic methodology allowing the single-step formation of a new C–C bond affording arylalkynes and conjugated enynes, which are precursors for natural products, pharmaceuticals, and molecular organic materials that are useful in different applications.¹ Named after Sonogashira since the discovery that addition of a catalytic amount of copper(I) iodide greatly accelerates the alkylation reaction,² the process traditionally involves the use of a palladium–phosphane complex as catalyst (5–10 mol %) in the presence of a catalytic amount of copper(I) and an amine in large excess (often as a solvent), and is generally carried out under homogeneous conditions at high temperature (60–100 °C, Scheme 1).

Aiming to improve the environmental and economical sustainability of the reaction, intense research efforts have been devoted to find suitable heterogeneous Pd catalysts of broad scope, capable of allowing the elimination of both copper and amine solvent as well as affording recovery and reuse of valued palladium while avoiding costly catalyst separation and product purification steps, which impact cost and worsen the environmental footprint of the reaction.³ A notable example of true green conditions for the Sonogashira reaction, for instance, was reported in 2004,⁴ whereas a catalytic method based on Pd/C enabling conversion of aryl chlorides was reported in 2006.⁵

Indeed, a significant problem, especially for the pharmaceutical industry, associated to widespread utilization of palladium

homogeneous catalysis lies in the Pd impurities left in the desired compound because the allowed limit for Pd impurities is very low (typically 5 ppm). Removing residual palladium in a pharmaceutical substance to reduce its content to the maximum acceptable concentration limit requires a slow and costly purification process that often makes use of silica-based scavengers.⁶

In this context, we have recently reported that the sol–gel entrapped catalyst SiliaCat Pd(0) heterogeneously mediates the Sonogashira coupling of phenylacetylene and 4-iodonitrobenzene in ethanol, with only K_2CO_3 as base, affording excellent conversions of coupled product over an extremely low amount (0.1 mol %) of solid palladium catalyst.⁷ This reusable catalyst is made of ultrasmall Pd(0) nanoparticles dispersed in the inner porosity of an organosilica matrix. Sol–gel encapsulation within the organosilica cages, in its turn, ensures high chemical and physical stabilization of the entrapped nanoparticles.⁸

Another advantageous feature of this new catalyst is that it does not require the typical deaerated conditions typical of Sonogashira coupling reactions using palladium(0) complexes, which are unstable in the air. We now show how to broaden the scope of the method under thermal conditions to couple different iodo- and bromoarenes with phenylacetylene, accessing enhanced reaction rates and conversions via microwave irradiation. Aryl chlorides are not converted using this ligand-free and Cu-free protocol.

RESULTS AND DISCUSSION

We have described elsewhere⁵ the preparation of a typical SiliaCat Pd(0) catalyst. The samples used throughout this work are those commercially available following optimization in light of manufacturing requirements (Table 1).

Received: June 28, 2012

Published: September 24, 2012

Table 1. Textural Properties and Loading of SiliaCat Pd(0) Samples

name	Pd loading (mmol/g)	surface (m ² /g)	pore size (Å)
Si-Pd-1	0.03	720	38
Si-Pd-1a	0.04	732	38
Si-Pd-1b	0.06	754	40
Si-Pd-2	0.11	774	45

Catalysts in Table 1 were thus first tested in the Sonogashira coupling of different aryl iodides with phenylacetylene under reflux in EtOH and in MeOH under different conditions. Results in Table 2 show that catalyst Si-Pd-2 with higher palladium loading (0.11 mmol/g) was completely inactive in methanol (entry 1 in Table 2). The same catalyst in ethanol (entry 2) affords complete conversion into coupling product after 3 h.

In general, as expected, the best SiliaCat Pd(0) catalyst has the lowest Pd loading (entry 5 in Table 2) whereas the best solvent system for reaction is MeOH with a 0.05 M substrate concentration. This catalyst, indeed, encapsulates the smallest (3 nm) Pd nanocrystallites, known to display the highest catalytic activity.⁶

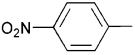
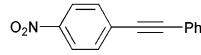
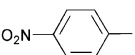
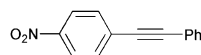
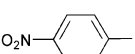
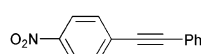
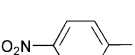
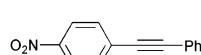
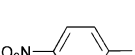
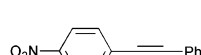
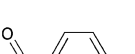
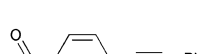
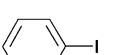
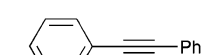
Using this catalyst, also 4-iodoacetophenone (entry 6 in Table 2) and 2-iodotoluene (entry 7) are converted with good to excellent conversions over 0.1 mol % despite requiring longer reaction times. These results were somehow expected, as similar good results in the Sonogashira coupling of these aryl iodides with phenylacetylene under thermal conditions were observed with different palladium catalysts of the SiliaCat series in a parallel synthesizer.⁹

However, not all silica-entrapped palladium nanoparticles are able to afford similar good conversions. For example, Pd(0) nanoparticles sol-gel encapsulated in a SiO₂ matrix by heating a mixture of Pd(PPh₃)₄, tetra(ethylene glycol), and TMOS (tetramethylorthosilicate) were recyclable and active as catalysts in the coupling of methyl 4-iodobenzoate and phenylacetylene but required copper cocatalysis, a reaction temperature of 110 °C, and the use of triethylamine as cosolvent in dimethylformamide (DMF).¹⁰

The SiliaCat Pd(0) catalyst Si-Pd-1 was thus tested in the Sonogashira coupling of different aryl bromides with phenylacetylene under reflux using different solvent and base. Results in Table 3 show that conversions under said thermal conditions were low to null, except in the case of 4-bromonitrobenzene (entry 2), whose complete conversion after 5 h required an equivalent mixture of DMF/H₂O as solvent, Et₃N as base, and a 10-fold increase in catalyst amount from 0.1 to 1 mol %. Potassium carbonate as base could be used in water only, also requiring the use of phase-transfer agent tetra-*n*-butylammonium bromide (TBAB). In this case, conversion of 4-bromonitrobenzene (entry 3) attained 37% after 1 h, whereas coupling of 4-bromoacetophenone (entry 5) did not exceed 28% after 4 h.

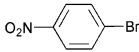
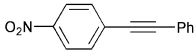
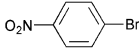
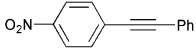
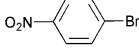
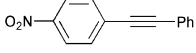
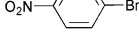
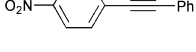
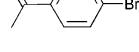
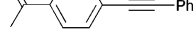
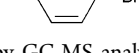
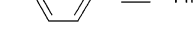
Bromoarenes, especially nonactivated aryl bromides, are notoriously less reactive due to the stability of the C-Br bond (relative reactivities of Ar-X are correlated to their respective bond dissociation energies: Ph-Cl, 96 kcal/mol; Ph-Br, 81 kcal/mol; Ph-I, 65 kcal/mol). Microwaves, in their turn, are an effective alternative means to heat the reaction mixture and obtain Sonogashira coupling of various substrates in the homogeneous phase.¹¹

Table 2. Sonogashira Coupling of Different Iodoarenes with Phenylacetylene over SiliaCat Pd(0) (Si-Pd-1 and Si-Pd-2) under Reflux^a

Entry	Substrate	Catalyst mol%	Ph-C≡CH (eq)	Base (eq)	Solvent (M)	Temp./Time	Coupling product	Yield ^b %	TON	TOF
1		Si-Pd-2 0,1	1.05	K ₂ CO ₃ 1.5	MeOH (0.05 M)	Reflux 1h		0	-	-
2		Si-Pd-2 0,1	1.05	K ₂ CO ₃ 1.5	EtOH (0.1 M)	Reflux 3h		100	1000	333
3		Si-Pd-1-b 0,1	1.05	K ₂ CO ₃ 1.5	EtOH (0.1 M)	Reflux 2h		100	1000	500
4		Si-Pd-1-a 0,1	1.05	K ₂ CO ₃ 1.5	MeOH (0.05 M)	Reflux 1h		100	1000	1000
5		Si-Pd-1 0,1	1.05	K ₂ CO ₃ 1.5	MeOH (0.05 M)	Reflux 30 min		100	1000	5000
6		Si-Pd-1 0,1	1.1	K ₂ CO ₃ 1.5	MeOH (0.1 M)	Reflux 2h		100	1000	500
7		Si-Pd-1 0,1	1.1	K ₂ CO ₃ 1.5	MeOH (0.1 M)	Reflux 2h		77	-	-

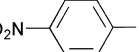
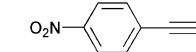
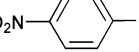
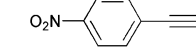
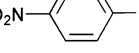
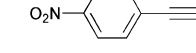
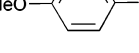
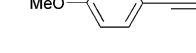

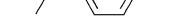
^aExperimental conditions: reactions performed in methanol high-performance liquid chromatography (HPLC) grade, from 0.05 to 0.1 M molar concentration in respect to the substrate, at reflux. Substrate (1 equiv), phenylacetylene (1.05 equiv), K₂CO₃ (1.5 equiv), over 0.1 mol % SiliaCat Pd⁰; catalyst identified in Table 1. ^bYield evaluated by GC-MS analysis.

Table 3. Sonogashira Coupling of Different Bromoarenes with Phenylacetylene over SiliaCat Pd(0) (Si-Pd-1) under Reflux

Entry	Substrate	Catalyst mol%	Ph-C≡CH (eq)	Base (eq)	Solvent (M)	Temp./Time	Coupling product	Yield. ^a %
1		Si-Pd-1 2	1,1	Cs ₂ CO ₃ 2	Acetonitrile /H ₂ O (0.2 M)	Reflux 2h		4
2		Si-Pd-1 1	1,1	Et ₃ N 1,5	DMF/H ₂ O (0.1 M)	Reflux 1h 3h 5h		54 82 100
3		Si-Pd-1 0,5	1,1	K ₂ CO ₃ 2	H ₂ O+TBAB (0.4 M)	Reflux 1h		37
4		Si-Pd-1 0,5	1,1	Piperidine 2	H ₂ O+TBAB (0.1 M)	Reflux 1h		51
5		Si-Pd-1 0,5	1,1	K ₂ CO ₃ 2	H ₂ O+TBAB (0.4 M)	Reflux 1h 2h 4h		7 26 28
6		Si-Pd-1 0,5	1,1	K ₂ CO ₃ 2	H ₂ O+TBAB (0.4 M)	Reflux 30 min		0

^aYield determined by GC-MS analysis.

Table 4. Sonogashira Coupling of Different Bromoarenes with Phenylacetylene over SiliaCat Pd⁰ (Si-Pd-1) under Microwave

Entry	Substrate	Catalyst mol%	Solvent (M)	Microwave Conditions				Coupling product	Yield. ^a %
				W	PSI	T (°C)	t (min)		
1		Si-Pd-1 0,5	MeOH (0.2 M)	200	200	100	5 10		24 46
2		Si-Pd-1 0,5	MeOH/H ₂ O (0.2 M)	200	200	100	15		60
3		Si-Pd-1 0,5	DMF (K ₂ CO ₃) (0.1 M)	200	200	125	15		100
4		Si-Pd-1 0,5	EtOH/H ₂ O (0.2 M)	200	200	120	5 15		18 25
5		Si-Pd-1 0,5	H ₂ O/Toluene + TBAB (0.333 M)	200	200	150	15		49

^aYield determined by GC-MS analysis.

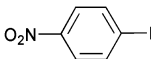
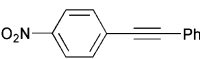
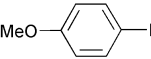
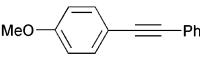

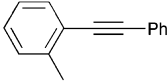

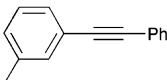
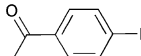
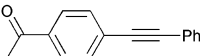
We thus conducted the conversion of aryl bromides over Si-Pd-1 under 200 W microwave irradiation power, using different substrates, solvent, concentration of reactants, mol % of catalyst, and base. Results in Table 4 show significant improvement in conversions and reaction times. Entry 1 in Table 4 shows that 4-bromonitrobenzene is now rapidly coupled to afford 46% conversion after 10 min. The use of aqueous MeOH as reaction solvent affords a further increase to 60% in the conversion of the same substrate (entry 2). Finally, complete conversion of 4-bromonitrobenzene is obtained using DMF and K₂CO₃ as base (entry 3). Conversion of 4-methoxyiodobenzene did not exceed 25% (entry 4), whereas

4-bromoacetophenone could now be coupled with phenylacetylene, affording 49% conversion after 15 min (entry 5).

Under the same microwave irradiation, iodoarene substrates (Table 5) are coupled with phenylacetylene in MeOH to afford conversion in quantitative conversion over a small 0.1 mol % catalytic amount, in 5 min only (1000 turnover number (TON)).

Only 4-methoxyiodobenzene substrate (entry 2 in Table 5) afford a 88% conversion, which is likely due to the affinity of the methoxy group for the methyl-modified surface of the SiliaCat Pd catalyst and possible partial retention of the substrate in the catalyst matrix.

Table 5. Sonogashira Coupling of Different Iodoarenes with Phenylacetylene over Siliacat Pd(0) (Si-Pd-1) under Microwave

Entry	Substrate	Catalyst mol%	Solvent (M)	Microwave Conditions				Coupling product	Yield. ^a %	TON	TOF
				W	PSI	T (°C)	t (min)				
1		Si-Pd-1 0,1	MeOH (0.1 M)	150	150	75	5		100	1000	12500
2		Si-Pd-1 0,1	MeOH (0.1 M)	150	150	75	5		88	-	-
3		Si-Pd-1 0,1	MeOH (0.2 M)	150	150	100	5		100	1000	12500
4		Si-Pd-1 0,1	MeOH (0.2 M)	150	150	100	5		100	1000	12500
5		Si-Pd-1 0,1	MeOH (0.2 M)	150	150	100	5		100	1000	12500

^aYield determined by GC-MS analysis.

The reaction under microwave irradiation catalysis remains heterogeneous. Indeed, the hot filtration test of the reaction mixtures under reflux with 4-iodonitrobenzene in methanol over Siliacat Pd(0) catalyst Si-Pd-1 showed that no further reaction takes place in the filtrate. Furthermore, recycle of the catalyst was possible, with full retention of the catalyst activity in all 5 consecutive reaction runs in which the catalyst was reused using 4-iodonitrobenzene as representative substrate.

This shows that the small amount of leached Pd species is catalytically inactive. Indeed, limited leaching of Pd was experimentally observed with levels of Pd leached in crude product being at a maximum 8 ppm (in the case of 4-bromoacetophenone (entry 5 in Table 3) and generally <6 ppm for all other substrates. Indeed, for analogous coupling reactions mediated by Pd/C in aqueous solvent, it has been recently shown that Pd-leaching (mainly due to the oxidative addition of arylbromides to Pd) is independent of the reaction solvent and of temperature and that only the Pd(0) nanoparticles that are leached in solution (and not Pd²⁺ ions) are catalytically active.¹²

In conclusion, the important Sonogashira reaction can be smoothly carried out over an ultrasmall amount (0.5–1 mol %) of nanostructured palladium(0) organosilica catalyst under ligand-free and copper-free conditions. The scope of the method does not include aryl chlorides. Yet, conversion of aryl iodides can be carried out at completion under thermal conditions or, much more efficiently, using microwave heating when, under the same 200 W μ w power irradiation, also arylbromides, which under reflux afford poor conversion, are rapidly coupled to phenylacetylene, affording moderate to good conversion extent into coupled products. Low levels of leached Pd are observed. In each case, no inert atmosphere is required to carry out the reaction, offering a simple methodology for carrying out the Sonogashira reaction.

EXPERIMENTAL SECTION

For reactions conducted under reflux, a two-neck, round-bottom flask was equipped with a condenser and a rubber stopper. The substrate and the base were mixed in HPLC solvent. The phenylacetylene was thus added, heating the resulting mixture under reflux for 10 min (or until complete homogenization was achieved). Then the solid catalyst was added, and the substrate conversion in coupling product was determined by thin-layer chromatography (TLC) and GC-MS.

For reactions under microwave irradiation, the substrate, phenylacetylene, and base were mixed in HPLC solvent into a microwave tube. The tube was placed in a sonicator for 5 min to ensure complete homogenization, after which the catalyst was added. The tube was inserted into the sample holder of the Discover system (CEM, Matthews, U.S.A.). Following the setting of the reaction parameters (power, pressure, and temperature), the reaction was started. Conversion of the substrate in coupling product was determined by TLC and GC-MS. Conversions were also measured by isolating the reaction products, showing full agreement with the conversion values obtained by GC-MS. In a typical procedure, the reaction mixture was washed with EtOAc and water three times. The organic layer was each time separated via gravity and stirred with magnesium sulfate to remove water. The mixture was then filtered to remove MgSO₄. After extraction with EtOAc filtration, the solvent was removed by a rotovapor to obtain a solid that was weighed and analyzed by GC-MS analysis to identify reaction products. Leaching was assessed by inductively coupled plasma (ICP) analysis of the isolated crude.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This article is dedicated to Prof. Carsten Bolm, eminent chemist and dear friend, in memory of the nice 2002 stay of one us (M.P.) at his Aacheñs RWTH Laboratories. We thank Mr. Pierre-Gilles Vaillancourt and Mr Simon Bédard from the Quality Control Department of SiliCycle Inc. for their valuable contribution.

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■ NOTE ADDED AFTER ASAP PUBLICATION

There were errors in the author affiliations in the version published ASAP on October 2, 2012. The corrected version was published ASAP on October 19, 2012.