

# Palladium Supported on Silk Fibroin as Efficient Catalyst for Sonogashira Coupling and Sonogashira-Cacchi Type Annulation

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A palladium catalyst supported on silk fibroin (Pd/SF) has been tested in the Sonogashira coupling reactions of a wide range of aryl iodides and terminal alkynes. The best catalytic performance was obtained at 90 °C using only 0.25 mol% metal loading under copper-free conditions, in the presence of a H<sub>2</sub>O/EtOH (3:2 v/v) solvent mixture and triethylamine as the base, affording the coupling products in good yields. The Pd/SF-based protocol was then successfully extended to the synthesis

of benzofurans through Sonogashira-Cacchi type annulation of 2-iodophenol with terminal alkynes. Preliminary investigations on the recyclability and the heterogeneous behaviour of the catalyst were performed: hot filtration test and leaching test evidenced the presence of a small amount of soluble active palladium species into the reaction mixture. Nevertheless, Pd/SF could be reused in recharging test and it can be recycled in four consecutive runs with no significant deactivation.

## Introduction

Palladium-catalyzed chemistry is one of the most important tools for the synthesis of fine chemicals and biologically active compounds.<sup>[1]</sup> Among different protocols, the reaction between aryl/vinyl halides and terminal alkynes, known as Sonogashira coupling, is widely used for the synthesis of internal acetylenic compounds through the formation of a new C<sub>sp2</sub>-C<sub>sp</sub> bond.<sup>[2]</sup> Its carbonylative version, performed under CO atmosphere or in the presence of a suitable CO surrogate,<sup>[3]</sup> as well as its acyl version, involving the use of aroyl chlorides instead of aryl halides,<sup>[4]</sup> are used for the generation of aryl alkynes.

Almost any palladium complex can be used as homogeneous catalyst for Sonogashira reactions, but most of these compounds cannot be easily recovered, and their use often involves tedious procedures to isolate the cross-coupling product. On the contrary, supported metal catalysts can be easily separated and reused. Palladium species deposited on several kinds of matrices, such as activated carbon,<sup>[5]</sup> graphene

oxide,<sup>[6]</sup> magnetite,<sup>[7]</sup> metal organic frameworks,<sup>[8]</sup> mesoporous silica<sup>[9]</sup> and organic polymers,<sup>[10]</sup> have been successfully used as catalysts for Sonogashira reactions. In particular, among organic polymers, Uozumi and co-workers have developed a polystyrenepoly(ethylene glycol) (named PS-PEG) resin-supported palladium-phosphine complex, which was successfully used as catalyst for Sonogashira reactions of aryl halides and alkynes using water as solvent.<sup>[11]</sup> More recently, special attention has been paid to unexpensive natural polysaccharides as supports for palladium catalysts, including cellulose,<sup>[12]</sup> starch,<sup>[13]</sup> pectin,<sup>[14]</sup> chitosan<sup>[15]</sup> and agarose.<sup>[16]</sup> On the contrary, to the best of our knowledge only one example of Sonogashira couplings involving the use of protein-supported Pd catalyst has been described, that is, a tetrasulphophtalocyanine palladium complex grafted to keratin-modified graphene oxide; cross-coupling products were obtained in good yields, but a relevant palladium loading (1 mol%) and the need of copper iodide (4 mol%) as a co-catalyst were required.<sup>[17]</sup>

The lack of examples of application to Sonogashira reactions of palladium catalysts supported on polypeptides is quite surprising, considering that the electron-rich functional groups of amino acids can strongly bind metal species. Among protein biopolymers, a very promising material is silk fibroin (SF), that is, an amphiphilic fibrous protein available from cocoons of “*Bombyx mori*” silkworm, belonging to the moth family. Its unique structure, consisting of hydrophobic crystalline  $\beta$ -sheet regions alternated to hydrophilic disordered zones,<sup>[18]</sup> offers to SF mechanical stiffness and strength,<sup>[19]</sup> possibility of chemical modification<sup>[20]</sup> and good biocompatibility.<sup>[21]</sup> SF used as a support for Pd catalyst is obtained from natural silk with a process called “degumming”, which consists in removing sericin film which covers the native fibroin filament, and it is typically performed by basic hydrolysis. The obtained degummed SF is a biopolymer constituted by glycine (46%), alanine (30%), serine (12%) and other amino acids in smaller percentages.<sup>[22]</sup> Such

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amino acids of SF are able of coordinating Pd(0) or Pd(II), mainly thanks to the presence of oxygen and nitrogen atoms of the amide groups of peptide bridges, that already demonstrated their ability to bind metal ions through highly coordinated structures.<sup>[23]</sup>

The preparation of Pd/SF was described for the first time by Izumi in 1959<sup>[24]</sup>: the treatment of SF with PdCl<sub>2</sub> and the subsequent reduction of the Pd(II) with hydrogen afforded the final supported catalyst, which was eventually employed in the chemoselective hydrogenation of olefins, nitro compounds, nitriles, azides and carbonyl compounds.<sup>[25]</sup> A different Pd/SF was fabricated by Eshghi *et al.*, who absorbed Pd(OAc)<sub>2</sub> on degummed SF and then reduced it with NaBH<sub>4</sub> at room temperature to generate the final supported catalyst, used in the Mizoroki-Heck cross coupling of iodoarenes and alkenes.<sup>[26]</sup> Recently, we have proposed a new procedure for the synthesis of Pd/SF: degummed SF was soaked for 15 minutes in a boiling 6 mM aqueous solution of PdCl<sub>2</sub> to give Pd(II)-impregnated fibers, which were then treated in sequence with sodium ascorbate (twice, 10 equiv. + 10 equiv.) and sodium borohydride (10 equiv.) as reducing agents to give the final catalyst.<sup>[27]</sup> This new air stable Pd/SF was successfully used in the Suzuki-Miyaura reactions of aryl iodides using very low metal loading (0.38 mol%),<sup>[27]</sup> as well as in the Suzuki-Miyaura and Ullmann coupling of less reactive aryl chlorides.<sup>[28]</sup> In particular, the hypothesis of catalytic pockets where monoatomic palladium forms stable complexes with suitable coordination sites on the polypeptide chains of SF was supported by a series of control experiments and theoretical calculations, mimicking an enzyme-like selectivity.

Starting from the consideration of the lack of examples on the application of palladium catalysts supported on protein biopolymers to Sonogashira reactions and in continuation with our previous works,<sup>[27,28]</sup> we report here interesting results on the use of our Pd/SF catalytic system in the Sonogashira coupling of aryl iodides with terminal alkynes, performed with only 0.25 mol% metal loading and under copper-free conditions. The Pd/SF-based protocol is also extended to the synthesis of benzofurans through Sonogashira-Cacchi type annulation of 2-iodophenol with terminal alkynes.

## Results and Discussion

Pd/SF was prepared according to the procedure optimized in our previous works<sup>[27,28]</sup> (see Supporting Information for experimental details). The final material, obtained in the form of black fibers, was then subjected to an Energy Dispersive X-ray (EDX) analysis to determine the amount of palladium deposited on the SF: we found a Pd loading of 0.67 wt%. Further structural characterizations on the catalyst has been already reported in our previous works: in particular, Wide-Angle X-ray Scattering (WAXS) analysis highlighted the presence of monoatomic palladium species complexed to suitable coordination sites in the hydrophilic disordered regions of SF.<sup>[28]</sup>

Encouraged by the excellent results in terms of catalytic activity under environmentally benign conditions previously

observed in the Suzuki-Miyaura and Ullmann coupling,<sup>[27,28]</sup> here we report a study of its ability to promote "copper-free" Sonogashira reactions, performed in air and in sustainable reaction media. The optimization of reaction conditions was performed using phenylacetylene (**1a**) and iodobenzene (**2a**) as the model compounds, as summarised in Table 1. The first catalytic tests were carried out between equimolar amounts of **1a** and **2a**, with 0.1 mol% of palladium loading and Et<sub>3</sub>N as the base, at 75 °C for 24 h in different solvents (Table 1, entries 1–6). The obtained data disclosed a crucial role of H<sub>2</sub>O as a solvent to achieve good reagents conversion into product **3aa**. In fact, if the use of Et<sub>3</sub>N or EtOH as the solvent resulted in low conversion (Table 1, entries 1 and 2), in the presence of H<sub>2</sub>O the conversion into **3aa** increased up to of 57% (Table 1, entry 3). Similar values (60–67%) were observed using H<sub>2</sub>O:THF, H<sub>2</sub>O:1,4-dioxane or H<sub>2</sub>O:EtOH (3:2 v/v) mixtures (Table 1, entries 4–6). By keeping the last solvent mixture (H<sub>2</sub>O:EtOH, 3:2 v/v) but increasing the metal amount to 0.25 mol% (Table 1, entry 7), a conversion of 76% was achieved. On the contrary, a detrimental effect was observed when Et<sub>3</sub>N was changed with an inorganic base: with K<sub>2</sub>CO<sub>3</sub> (Table 1, entry 8) a 32% conversion was found, while with CsOH (Table 1, entry 9) a 59% conversion. Working with a small excess of **1a** (**1a/2a** molar ratio = 1.4:1), the Sonogashira coupling reached a 92% conversion (Table 1, entry 10), while the reaction finally took place with a quantitative conversion when carried out under the same conditions but at 90 °C (Table 1, entry 11). To establish the optimal duration of the process, we gradually reduced the reaction time from 24 h to 30 min (Table 1, entries 11–18): a 100% conversion was reached in 18 h (Table 1, entry 12), although after only 3 h it was already at 86% (Table 1, entry 15).

The optimized conditions (Pd loading 0.25 mol%, **1a/2a** molar ratio 1.4:1, Et<sub>3</sub>N, H<sub>2</sub>O/EtOH 3:2 v/v, 90 °C, 18 h, Table 1, entry 12) were then applied to the Sonogashira coupling of phenylacetylene (**1a**) with a wide range of aryl iodides (Table 2), affording the corresponding internal alkyne products in good to excellent yields (61–95%) regardless of the stereo-electronic features of the substrate. The reaction of **1a** with iodobenzene (**2a**) afforded the corresponding product **3aa** in 65% yield after column chromatography purification (Table 2, entry 1). Regarding electron-rich iodides, the reactivity was strictly related to the steric hindrance: if *p*-iodotoluene (**2b**) gave product **3ab** in 61% yield (Table 2, entry 2), in the case of *o*-methyl and *o*-methoxy-substituted iodides **2c** and **2d** a larger excess of **1a** (2 equiv.) and longer reaction time (48 h) were required to obtain alkynes **3ac–ad** in good yields (63–76%), Table 2, entries 3 and 4). Pd/SF exhibited better performance with electron-poor iodides **2e–i**: the presence of electron-withdrawing functional groups (–Cl, –CN, –NO<sub>2</sub>, –Br) on different positions of the benzene ring determined a general increase of products yields (78–87%) compared to electron-rich iodides (Table 2, entries 5–9). Moreover, 2-iodothiophene (**2j**) afforded the corresponding alkyne **3aj** in almost quantitative yield (95%, Table 2, entry 10), while sterically hindered substrates such as 4-iodobiphenyl (**2k**) and 1-iodonaphthalene (**2l**) required 48 h and an alkyne/iodide molar ratio of 2:1 to achieve the

**Table 1.** Pd/SF-catalyzed Sonogashira coupling of aryl iodides with terminal alkynes: optimization of the reaction conditions.<sup>[a]</sup>

Entry	Pd loading (mol%)	T (°C)	T (h)	1a/2a ratio	Base	Solvent	Conversion (%) <sup>[b]</sup>
1	0.1	75	24	1:1	Et <sub>3</sub> N	Et <sub>3</sub> N	16
2	0.1	75	24	1:1	Et <sub>3</sub> N	EtOH	10
3	0.1	75	24	1:1	Et <sub>3</sub> N	H <sub>2</sub> O	57
4	0.1	75	24	1:1	Et <sub>3</sub> N	H <sub>2</sub> O/THF (3:2 v/v)	60
5	0.1	75	24	1:1	Et <sub>3</sub> N	H <sub>2</sub> O/dioxane (3:2 v/v)	64
6	0.1	75	24	1:1	Et <sub>3</sub> N	H <sub>2</sub> O/EtOH (3:2 v/v)	67
7	0.25	75	24	1:1	Et <sub>3</sub> N	H <sub>2</sub> O/EtOH (3:2 v/v)	76
8	0.25	75	24	1:1	K <sub>2</sub> CO <sub>3</sub>	H <sub>2</sub> O/EtOH (3:2 v/v)	32
9	0.25	75	24	1:1	CsOH	H <sub>2</sub> O/EtOH (3:2 v/v)	59
10	0.25	75	24	1.4:1	Et <sub>3</sub> N	H <sub>2</sub> O/EtOH (3:2 v/v)	92
11	0.25	90	24	1.4:1	Et <sub>3</sub> N	H <sub>2</sub> O/EtOH (3:2 v/v)	100
12	0.25	90	18	1.4:1	Et <sub>3</sub> N	H <sub>2</sub> O/EtOH (3:2 v/v)	100
13	0.25	90	15	1.4:1	Et <sub>3</sub> N	H <sub>2</sub> O/EtOH (3:2 v/v)	98
14	0.25	90	8	1.4:1	Et <sub>3</sub> N	H <sub>2</sub> O/EtOH (3:2 v/v)	91
15	0.25	90	6	1.4:1	Et <sub>3</sub> N	H <sub>2</sub> O/EtOH (3:2 v/v)	88
16	0.25	90	3	1.4:1	Et <sub>3</sub> N	H <sub>2</sub> O/EtOH (3:2 v/v)	86
17	0.25	90	1	1.4:1	Et <sub>3</sub> N	H <sub>2</sub> O/EtOH (3:2 v/v)	71
18	0.25	90	0.5	1.4:1	Et <sub>3</sub> N	H <sub>2</sub> O/EtOH (3:2 v/v)	46

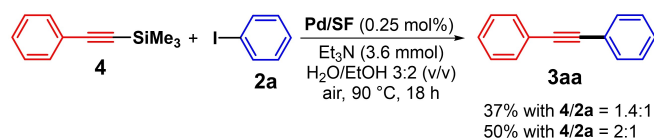
<sup>[a]</sup> All reactions were carried with 1.0–1.4 mmol of phenylacetylene (**1a**), 1.0 mmol of iodobenzene (**2a**), 3.6 mmol of base, 5.0 mL of solvent, under atmospheric conditions. <sup>[b]</sup> Conversion was estimated by <sup>1</sup>H-NMR analysis.

corresponding products **3 ak-al** in good yields (69–80%, Table 2, entries 11 and 12).

After that, we explored the performance of Pd/SF in the reaction of iodobenzene (**2a**) with different terminal alkynes (Table 3). Interestingly, aryl alkynes containing both electron-donating (*p*-Bu<sup>t</sup>, *p*-OMe and *m*-Me, Table 3, entries 2, 4, 6) and electron-withdrawing groups (*p*-F, *o*-CF<sub>3</sub>, *p*-Br, Table 3, entries 3, 5, 7) afforded cross-coupling products in good to excellent yields (respectively, 65–72% and 65–84%) with only a slight effect of the position of the functional groups on the aromatic ring. It is noteworthy that when 4-ethynyl-1,1'-biphenyl (**1h**) was used as a substrate (Table 3, entry 8), product **3ak** was generated in 92% yield, while in the case of 2-ethynylpyridine (**1i**) only a moderate yield of the pure product (31%) was isolated, probably because of a poisoning effect of pyridine ring on Pd/SF catalyst (Table 3, entry 9). Finally, a few Pd/SF-catalyzed Sonogashira reactions involving aliphatic alkynes were tested. When 1-hexyne (**1j**) was treated with **2a** under the optimized conditions (at 90 °C for 18 h), a complex mixture of products was detected in the <sup>1</sup>H-NMR spectrum, together with the disappearance of C≡CH signal (Table 3, entry 10). To minimize possible side reactions of the alkyne, the same coupling was repeated at lower temperature (50 and 25 °C) and in the presence of a larger excess of **1j**, but no improvement was observed. When trimethylsilylacetylene (**1k**) was reacted with iodobenzene (**2a**), a complete consumption of the alkyne and total recovery of iodobenzene were observed (Table 3,

entry 11). This result could suggest a possible desilylation of the alkyne under the reaction conditions. With the aim to verify this hypothesis, trimethyl(phenylethynyl)silane (**4**) and iodobenzene (**2a**) were treated under the optimized conditions of the Pd/SF-catalyzed Sonogashira coupling: to our delight, the reaction afforded diphenylacetylene **3aa** as a pure product in 37% yields (Scheme 1). Probably, in this case a so-called “sila-Sonogashira” reaction took place<sup>[29]</sup>: water or ethanol likely promote desilylation of the alkyne forming in situ phenylacetylene (**1a**), which is then coupled to iodobenzene affording product **3aa**. Moreover, when the reaction was repeated with a larger excess of alkyne (4/2a molar ratio = 2:1), an increase in the yield of **3aa** to 50% was observed.

From the data collected in Table 2 another very interesting point is evident: under the optimized experimental conditions, Pd/SF-catalyzed Sonogashira coupling of phenylacetylene (**1a**) occurs selectively on aryl iodides, leaving unchanged not only aryl chlorides (see Table 2, entry 5) but even aryl bromides (see



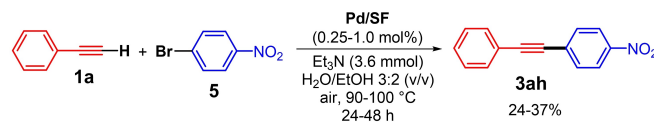
**Scheme 1.** Sila-Sonogashira reaction of trimethyl(phenylethynyl)silane (**4**) with iodobenzene (**2a**) catalyzed by Pd/SF.

**Table 2.** Pd/SF-catalyzed Sonogashira coupling of aryl iodides with terminal alkynes: substrate scope of aryl iodides.<sup>[a]</sup>

Entry	2	Ar	3	Sonogashira product	Yield (%) <sup>[b]</sup>
1	a	Ph	aa		65
2	b	<i>p</i> -Me-C <sub>6</sub> H <sub>4</sub>	ab		61
3 <sup>[c]</sup>	c	<i>o</i> -Me-C <sub>6</sub> H <sub>4</sub>	ac		63
4 <sup>[c]</sup>	d	<i>o</i> -MeO-C <sub>6</sub> H <sub>4</sub>	ad		76
5	e	<i>p</i> -Cl-C <sub>6</sub> H <sub>4</sub>	ae		78
6	f	<i>p</i> -CN-C <sub>6</sub> H <sub>4</sub>	af		83
7	g	<i>o</i> -CN-C <sub>6</sub> H <sub>4</sub>	ag		80
8	h	<i>p</i> -NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	ah		83
9	i	<i>o</i> -Br-C <sub>6</sub> H <sub>4</sub>	ai		87
10	j	2-Thienyl	aj		95
11 <sup>[c]</sup>	k	<i>p</i> -Ph-C <sub>6</sub> H <sub>4</sub>	ak		69
12 <sup>[c]</sup>	l	1-Naph	al		80

<sup>[a]</sup> Reactions were carried with 1.0 mmol of aryl iodide **2**, 1.4 mmol of phenylacetylene (**1a**), 0.25 mol% of Pd/SF, 3.6 mmol of Et<sub>3</sub>N, 5 mL of H<sub>2</sub>O/EtOH (3:2 v/v), at 90 °C for 18 h under atmospheric conditions. <sup>[b]</sup> Yields of pure products after column chromatography purification. <sup>[c]</sup> Reactions carried out with 2 mmol of phenylacetylene (**1a**) for 48 h.

Table 2, entry 9). Such selectivity is very helpful especially on aryl bromides, considering that typically such substrates are strongly sensitive to Sonogashira coupling reactions catalyzed by homogeneous palladium species. At the same time, this is not very surprising, as aryl bromides are less reactive than the corresponding iodo-derivatives. However, we explored the possibility of extending our Pd/SF-catalyzed protocol to the coupling of terminal alkynes with aryl bromides, with a preliminary study of the reaction between phenylacetylene (**1a**) and *p*-nitrophenyl iodide (**5**) (Scheme 2). The first reaction was performed under the conditions optimized for aryl iodides: **1a**/**5** molar ratio = 1.4:1, Pd/SF (Pd loading 0.25 mol%), Et<sub>3</sub>N as the base, H<sub>2</sub>O/EtOH (3:2 v/v) as the solvent, at 90 °C under air. After 24 h, only a moderate reagent conversion into coupling product

**Scheme 2.** Preliminary investigation of the Pd/SF-catalyzed Sonogashira reaction of phenylacetylene (**1a**) with *p*-nitrophenyl iodide (**5**).

**3ah** was observed (24%), which remained almost the same after longer reaction time (28% after 48 h) or with a 0.50 mol% Pd loading (31%). No significant improvement was obtained also with a larger excess of alkyne (**1a**/**5** molar ratio = 2:1) and a higher palladium loading (1 mol%): after 48 h, a conversion of only 37% was observed. Differently from what observed in our

**Table 3.** Pd/SF-catalyzed Sonogashira coupling of aryl iodides with terminal alkynes: substrate scope of terminal alkynes.<sup>[a]</sup>

Entry	1	R	3	Sonogashira product	Yield (%) <sup>[b]</sup>
1	a	Ph	aa		65
2	b	<i>p</i> -Bu <sup>t</sup> -C <sub>6</sub> H <sub>4</sub>	ba		68
3	c	<i>p</i> -F-C <sub>6</sub> H <sub>4</sub>	ca		65
4 <sup>[c]</sup>	d	<i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub>	da		65
5 <sup>[c]</sup>	e	<i>o</i> -CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	ea		84
6	f	<i>m</i> -Me-C <sub>6</sub> H <sub>4</sub>	fa		72
7	g	<i>p</i> -Br-C <sub>6</sub> H <sub>4</sub>	ga		70
8	h	<i>p</i> -Ph-C <sub>6</sub> H <sub>4</sub>	ak		92
9	i	2-Pyridyl	ia		31
10	j	Bu <sup>n</sup>	ja		//
11	k	Me <sub>3</sub> Si	ka		//

<sup>[a]</sup> Reactions were carried with 1.0 mmol of iodobenzene (**2a**), 1.4 mmol of terminal alkyne **1**, 0.25 mol% of Pd/SF, 3.6 mmol of Et<sub>3</sub>N, 5 mL of H<sub>2</sub>O/EtOH (3:2 v/v), at 90 °C for 18 h under atmospheric conditions. <sup>[b]</sup> Yields of pure products after column chromatography purification. <sup>[c]</sup> Reactions carried out with 2 mmol of terminal alkyne **1** for 48 h.

previous works for the Suzuki-Miyaura coupling,<sup>[27,28]</sup> where Pd/SF was able of efficiently activating both Ar-I and Ar-Cl bonds, all these results clearly indicate here high chemoselectivity of the Pd/SF catalyst towards aryl iodides rather than bromides, which can be then used for further transformations.

With the aim to further expand the synthetic applications of Pd/SF in the context of cross-coupling reactions, we also explored its possible use as a catalyst in the Sonogashira-Cacchi type annulation. This process represents a very useful organic transformation, typically used to generate 1*H*-indoles and benzofurans starting from the reaction of terminal alkynes with, respectively, *o*-amino and *o*-hydroxy iodoarenes.<sup>[30]</sup> In particular, we investigated the Sonogashira-Cacchi type annulation of 2-iodophenol (**2m**) with terminal alkynes (Table 4). A first test was performed between **2m** and phenylacetylene (**1a**) using PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> as a reference homogeneous catalyst: working with a **1a/2m** molar ratio of 1.4:1 in the presence of 2 mol% of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> and 4 mol% of CuI as the co-catalyst, in Et<sub>3</sub>N at 90 °C for 6 h, both 2-phenylethynyl phenol **3am** (30% yield)

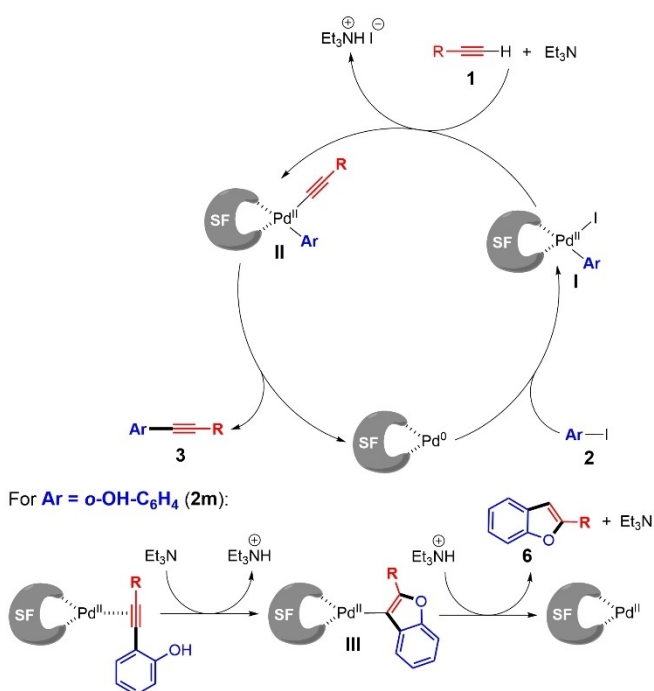
and 2-phenylbenzofuran **6a** (65% yield) were isolated as pure products (Table 4, entry 1). When the reaction between **2m** and **1a** was repeated with Pd/SF catalyst under the previously optimized conditions (**1a/2m** molar ratio=1.4:1; Pd loading 0.25 mol%, Et<sub>3</sub>N as the base, H<sub>2</sub>O/EtOH 3:2 v/v as the solvent, 90 °C, 18 h), benzofuran **6a** was isolated as the only product (23% yield, Table 4, entry 2). Moreover, by doubling the amount of Pd/SF (0.5 mol% palladium loading), yield of **6a** increased to 60% (Table 4, entry 3). Prompted by these results, such tandem process was applied to aryl alkynes possessing electron-donating (*p*-Bu<sup>t</sup>: **1b**) and electron-withdrawing (*p*-F: **1c**; *p*-Cl: **1l**) groups: in all cases, benzofurans were obtained in moderate to good yields (40–62%), which is very promising if we consider the small amount of catalyst employed (Table 4, entries 4–6).

We also proposed a plausible mechanism for the Pd/SF-promoted Sonogashira coupling and Sonogashira-Cacchi-type annulation reactions (Scheme 3). In our previous work on Suzuki-Miyaura and Ullmann reactions of aryl chlorides, we reported that metal catalysis presumably occurred into catalytic

**Table 4.** Pd/SF-catalyzed Sonogashira-Cacchi type annulation for the synthesis of 2-arylbenzofurans.<sup>[a]</sup>

Entry	1	R	Catalyst (Pd loading)	3	Yield of 3 (%) <sup>[b]</sup>	6	Yield of 6 (%) <sup>[b]</sup>
1 <sup>[c]</sup>	a	Ph	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> (2 mol %)	am	30	a	65
2	a	Ph	Pd/SF (0.25 mol %)	am	//	a	23
3 <sup>[d]</sup>	a	Ph	Pd/SF (0.5 mol %)	am	//	a	60
4 <sup>[d]</sup>	b	<i>p</i> -Bu <sup>t</sup> -C <sub>6</sub> H <sub>4</sub>	Pd/SF (0.5 mol %)	bm	//	b	45
5 <sup>[d]</sup>	c	<i>p</i> -F-C <sub>6</sub> H <sub>4</sub>	Pd/SF (0.5 mol %)	cm	//	c	62
6 <sup>[d]</sup>	l	<i>p</i> -Cl-C <sub>6</sub> H <sub>4</sub>	Pd/SF (0.5 mol %)	lm	//	l	40

<sup>[a]</sup> Reactions were carried with 1.0 mmol of 2-iodophenol (**2m**), 1.4 mmol of terminal alkyne **1**, Pd catalyst, 3.6 mmol of Et<sub>3</sub>N, 5 mL of H<sub>2</sub>O/EtOH (3:2 v/v), at 90 °C for 18 h under atmospheric conditions. <sup>[b]</sup> Yields of pure products after column chromatography purification. <sup>[c]</sup> Reaction carried out in the presence of 4 mol % of CuI as the co-catalyst, in 5.5 mL of Et<sub>3</sub>N as the solvent, at 90 °C for 6 h. <sup>[d]</sup> Reactions carried out with 2 mmol of terminal alkyne **1**.



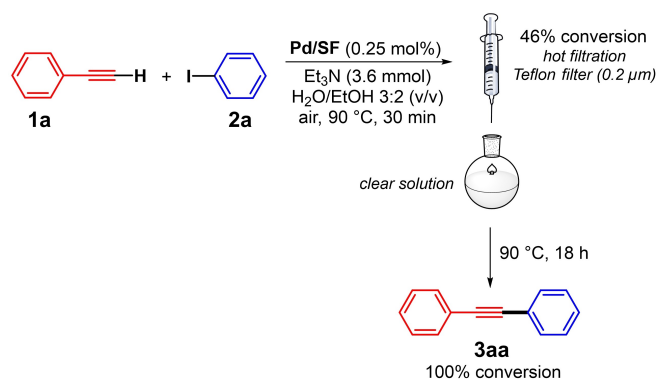
**Scheme 3.** Hypothetical mechanism for the Pd/SF-promoted Sonogashira coupling and Sonogashira-Cacchi-type annulation reactions, proposed according to the literature.<sup>[31,32]</sup>

pockets of SF, where monoatomic palladium forms stable complexes with suitable coordination sites on the polypeptide chains.<sup>[28]</sup> It is quite reasonable to assume that, even in this case, the formation of new carbon-carbon bonds can occur within such confined environment, where both partners must enter. In particular, the Sonogashira coupling can occur through a typical Pd(0)-Pd(II) mechanism<sup>[31]</sup>: after the starting oxidative addition of the aryl iodide **2** on the Pd(0) species to give the corresponding arylpalladium(II)/SF complex **I**, a triethylamine-promoted transmetalation of the alkyne **1** afforded the arylalkynyl-palladium(II)/SF intermediate **II**; finally, reductive elimination allowed the formation of the final product **3** and the

regeneration of starting Pd(0) species. However, when 2-iodophenol (**2m**) is used as the aryl iodide, the 2-(arylethynyl)phenol product can be subjected to a further transformation within the catalytic pockets: according to literature on Sonogashira-Cacchi-type annulation,<sup>[32]</sup> a Pd(II)-SF species (which can be present in the reaction environment) could give a sort of *trans* oxy-palladation to generate alkenyl-palladium(II)/SF intermediate **III**, then hydrolyzed to give the final benzofuran **6** and the starting Pd(II)-SF complex. Although some authors also claim that the cyclization step did not require the catalysis of transition metals,<sup>[33]</sup> the presence of palladium significantly accelerates the annulation rate.

After demonstrating the efficiency of Pd/SF in promoting Sonogashira coupling and Sonogashira-Cacchi type annulation, we have performed some heterogeneity tests to gain insight into the properties of the catalyst. Following Pagliaro's approach,<sup>[34]</sup> hot filtration test was carried out to look for the presence of active palladium species leached into the solution. A Sonogashira reaction between model substrates **1a** and **2a** was performed under the optimized conditions (0.25 mol % Pd/SF, H<sub>2</sub>O/EtOH 3:2 v/v, Et<sub>3</sub>N, 90 °C) and it was stopped after only 30 minutes, corresponding to 46% conversion (see Table 1, entry 18). The hot reaction mixture was filtered through a Teflon filter (0.2 μm), then the clear solution obtained was heated at 90 °C for further 18 h. After work-up, the <sup>1</sup>H-NMR analysis of the crude product evidenced a 100% conversion into alkyne **3aa** (Scheme 4). This result clearly indicated the presence of catalytically active palladium species solubilized into the reaction mixture.

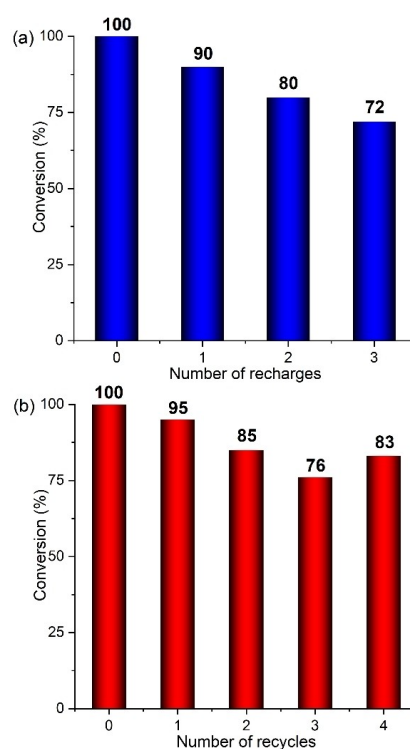
To calculate the amount of palladium leached into solution during the Pd/SF-catalyzed Sonogashira coupling, a leaching test was performed. Two parallel reactions between **1a** and **2a** were carried out under the usual optimized conditions: one was stopped after only 30 minutes (46% conversion, Table 1, entry 18), the other after 18 h (100% conversion, Table 1, entry 12). Both mixtures were filtered through a Teflon filter (0.2 μm) and the obtained clear solutions were mineralized with aqua regia. The palladium content into the solutions was



**Scheme 4.** Hot filtration test of the Pd/SF-catalyzed Sonogashira coupling reaction of phenylacetylene (1a) with iodobenzene (2a).

determined by ICP analysis and it was found to be 2.7 ppm (5% w/w) at the beginning of the reaction (after 30 minutes) and 3.7 ppm (7% w/w) after 18 h. These low values, together with the results of the hot filtration test, can reasonably suggest that a small amount of palladium is released from the SF fibers during the Sonogashira reaction and that it contributes to the catalytic activity. Since, in the case of our previous work on Suzuki-Miyaura reactions of aryl iodides, we have excluded any release of palladium into solution,<sup>[27]</sup> here we can hypothesize that Et<sub>3</sub>N (which is not used in the Suzuki-Miyaura protocol) can promote the dissolution of small amount of monoatomic Pd species by complexation. In fact, it has been previously reported, for other types of supported palladium catalysts, that Et<sub>3</sub>N can be responsible for a significant leaching of metal species into solution, especially in the context of Mizoroki-Heck reactions.<sup>[35]</sup>

Despite the occurrence of a small metal leaching from the SF fibers, Pd/SF catalyst can be here efficiently reused without remarkable loss of activity. For this purpose, we have carried out both recharging and recycling tests on the Pd/SF-catalyzed Sonogashira coupling between the model substrates 1a and 2a (Figure 1). In the recharging test, at the end of the reaction (after 24 h) the same batch of Pd/SF was recharged with fresh reagents without isolating it, *i.e.*, introducing in the reaction mixture a new amount of 1a, 2a and Et<sub>3</sub>N. The same operation was repeated three consecutive times. Interestingly, the Sonogashira reactions proceeded with still good conversion but with a small progressive reduction which reaches 72% at the third addition. This progressive reduction is likely due to the increased viscosity of the mixture (Figure 1a). In the recycling test, Pd/SF catalyst was isolated at the end of each reaction by simple filtration, washed with water and CH<sub>2</sub>Cl<sub>2</sub>, dried and then re-used for a further Sonogashira coupling between 1a and 2a under the optimized conditions. Considering the unavoidable loss of small amounts of Pd/SF during filtration operations after each run, responsible for a gradual reduction of the amount of the recovered catalyst (1<sup>st</sup> run: 40 mg; 2<sup>nd</sup> run: 35 mg, 3<sup>rd</sup> run: 33 mg; 4<sup>th</sup> run: 32 mg; 5<sup>th</sup> run: 31 mg), fresh reagents were adjusted with respect to the recovered Pd/SF, in order to keep the correct ratio between reagents and catalyst. However, the catalyst could be efficiently recycled four times with a quite



**Figure 1.** Recharging test (a) and recycling test (b) of the Pd/SF-catalyzed Sonogashira coupling, performed under the optimized conditions (1.0 mmol of aryl iodide 1a, 1.4 mmol of terminal alkyne 2a, 0.25 mol% of Pd/SF, 3.6 mmol di Et<sub>3</sub>N, 5 mL of H<sub>2</sub>O/EtOH 3:2 v/v, 90 °C for 24 h under atmospheric conditions). Conversion was estimated by <sup>1</sup>H-NMR analysis.

limited loss of activity (Figure 1b). More in detail, after the 1<sup>st</sup> and the 2<sup>nd</sup> runs with a reagent conversion of, respectively, 100% and 95%, Pd/SF seems to reach a plateau of its activity: a conversion of 85%, 76% and 83% was found for the subsequent three runs. This is not surprising: a decrease of efficiency in the second run was already observed for other SF supported palladium catalysts,<sup>[25a]</sup> including our Pd/SF catalyst in the previous work of Suzuki-Miyaura cross-coupling reactions of aryl iodides,<sup>[27]</sup> and it was attributed to a conformational rearrangement of SF in the reaction medium during the first cycles, making deposited palladium less accessible. However, in the case of Suzuki-Miyaura reactions, the gradual relaxation of SF fibers in the following cycles makes palladium more available again, resulting in a complete recovery of the catalytic activity of Pd/SF (used up to 25 times). In this case, a similar recovery was not found, although the experimental conditions (in particular, temperature and solvent mixture) adopted here for Sonogashira coupling were roughly similar. We believe that the presence of triethylamine as the base could play a crucial role during the conformational rearrangement of SF in the first two runs, strongly coordinating palladium and thus making it less accessible, or alternatively preventing the gradual relaxation of SF fibers.

## Conclusions

In conclusion, we have demonstrated that Pd/SF is an efficient catalyst for Sonogashira coupling reactions of aryl iodides with terminal alkynes and Sonogashira-Cacchi type annulation of 2-iodophenol with terminal alkynes to give benzofurans. All the reactions, performed in air, required a very small amount of catalyst (between 0.25 and 0.5 mol% of palladium loading) and did not need the presence of copper(I) species as co-catalyst. Preliminary investigations on the catalyst behavior have been performed. Hot filtration and leaching tests indicate the release of a small amount (3.7 ppm) of palladium into solution, which remains active till the end of the process. We hypothesized that Et<sub>3</sub>N molecules, small enough to easily enter the catalytic pockets of Pd/SF, could complex the monatomic Pd species present therein eventually solubilizing them into the reaction mixture. Nevertheless, recharging and recycling tests demonstrated that Pd/SF can be easily reused at least four times without significant loss in catalytic activity.

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## Conflict of Interests

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Keywords:** Palladium catalysis · Silk fibroin · Sonogashira coupling · Sonogashira-Cacchi annulations · Supported catalyst

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