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Heck, Sonogashira, and Hiyama Reactions Catalyzed by Palladium Nanoparticles Stabilized by Tris-Imidazolium Salt

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Palladium nanoparticles, prepared by the hydrogenation of $Pd(dba)_2$ in the presence of a tris-imidazolium iodide as stabilizer, act as an efficient catalyst for Heck and copper-free Sonogashira reactions with a range of aryl iodides and bromides at 0.2 mol-% Pd loading. Moreover, we describe a convenient protocol for the fluoride-free Hiyama coupling of vinylsilanes with aryl iodides that involves the use of sodium hydroxide as promoter in a methanol/water mixture. Under the developed conditions, one-pot, double Heck and Hiyama–Heck reactions are successfully achieved.

Introduction

Palladium-catalyzed carbon–carbon bond-forming processes[1] such as the Mizoroki–Heck,[2] Sonogashira,[3] Suzuki–Miyaura,[4] and Hiyama[5] reactions are widely used both in academia and in industry. Such reactions are key steps in the total synthesis[6] of a large number of natural products, biologically active compounds, and a great variety of organic building blocks with applications in many fields, such as in the pharmaceutical, agrochemical, and fine-chemical industries,[7] as well as in polymer and materials science.[8] The award in 2010 of the Nobel Prize in Chemistry to Professors Heck, Negishi, and Suzuki, key figures in the development of this cross-coupling methodology, highlights the paramount importance of these processes.[1] Despite the many years of important advances, the search continues for new catalytic systems (metal precursors and ligands) that might provide better performance. In this context, the use of preformed metal nanoparticles (NPs) as catalyst precursors has attracted a great deal of attention[9] because these tend to be more reactive (in comparison with the bulk metal) as a result of increased surface area with decreased particle size. However, a protecting shield is necessary to prevent the aggregation of nanoparticles in solution towards the thermodynamically favored bulk metal.[10] The stabilization of NPs can be achieved by electrostatic and/or steric protection (electrosteric stabilization). A variety of capping agents have been developed such as polymers, dendrimers, β-cyclodextrins, and surfactants, in addition to nitrogen-, phosphorus- and sulfur-based ligands and several ionic compounds. The nature of the stabilizing agent determines, to a great extent, not only the solubility of the nanocatalyst but also its activity and selectivity. Over the last decade, some of us have been interested in the preparation of Pd NPs with fluorinated[11] and PEG-based[12] stabilizers for use in C–C bond-forming reactions in fluorous and aqueous media, respectively.

Recently, we became interested in studying the properties of palladium nanoparticles stabilized by polyimidazolium species.[13] This interest stemmed from several previous reports on the use of palladium salts as precatalysts in imidazolium ionic liquids, often leading to formation of nanoparticles in situ. Based on this premise, we went on to prepare and fully characterize a series of Pd NPs stabilized by tris-imidazolium salts, and the solid-state ^{13}C NMR spectroscopic analysis of these species revealed a possible Pd–carbene interaction, which is likely to contribute to the catalytic activity.[13a] Indeed, the catalyst **1**-Pd, obtained by using the tris-imidazolium iodide **1**, was found to be efficient in the Suzuki cross-coupling of aryl bromides with several aryl and heteroarylboronic acids (Figure 1, left). Interestingly, simply by changing the counterion to tetrafluoroborate gave a new catalyst **1′**-Pd that, although being less suitable for the Suzuki coupling, was highly effective in the hydrosilylation of a wide range of internal alkynes (Figure 1, right).[13b]

As an extension of this work, we went on to explore the potential of the **1**-Pd nanoparticulate system as a catalyst for other C–C bond-forming processes, particularly the Heck and the Sonogashira cross-coupling reactions. In ad-

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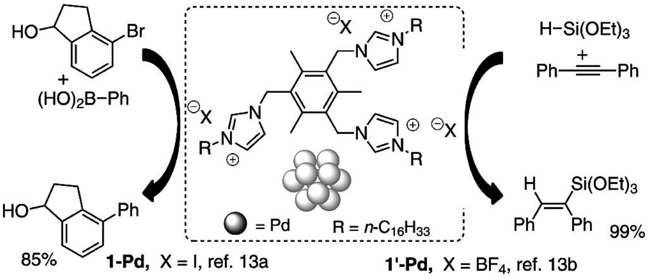


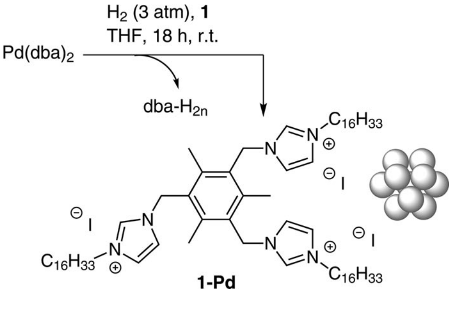
Figure 1. Previous applications of tris-imidazolium-stabilized palladium nanoparticles in catalysis.

dition, our previous experience in the preparation of vinylsilanes, which are stable and easy to handle, led us to investigate the use of **1**-Pd in the Hiyama coupling,[5] a process that is gaining importance in cross couplings and for which only a few nanoparticle catalysts have been reported so far.[14] The results of this work are described herein.

Results and Discussion

Tris-Imidazolium Iodide-Stabilized Palladium Nanoparticles, 1-Pd

Palladium nanoparticles **1**-Pd[13a] were prepared by following the organometallic approach developed by Chaudret and co-workers,[15] which involved, in this case, hydrogenative (3 atm) displacement of the olefinic dibenzylidene acetone ligand from the zero-valent $Pd(dba)_2$[16] precursor in the presence of tris-imidazolium iodide **1**[17] (Scheme 1). As previously reported, the isolated nanoparticles **1**-Pd were fully characterized by high-resolution electron microscopy, electron diffraction, dynamic light scattering, inductively-coupled plasma, and ^1H NMR spectroscopic analysis in solution and ^{13}C CP MAS NMR spectroscopy in the solid state.[13a]

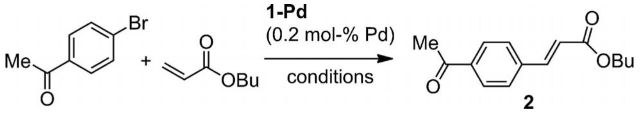


Scheme 1. Preparation of nanocatalyst **1**-Pd by the hydrogenation of $Pd(dba)_2$ in the presence of **1**.

The Heck Reaction Catalyzed by 1-Pd

The activity of **1**-Pd (0.2 mol-% Pd catalyst loading) was probed in a model Heck reaction between *p*-bromoacetophenone and *n*-butyl acrylate. The tests were conducted at 130 °C for 16 h, and initially three commonly used solvents, toluene/water (4:1), acetonitrile (CH_3CN), and *N*,*N*-dimethylformamide (DMF), and three common bases, Et_3N, NaOAc, and K_2CO_3 (3 × 3 combinations, Table 1) were employed. Of the three solvents, only DMF was found to favor catalytic activity. Combination of this solvent with K_2CO_3 led to complete consumption of the ArBr and a 75% yield of the desired (*E*)-butyl 3-(4-acetylphenyl)acrylate (**2**).

Table 1. Initial screening (3 × 3 parameters) of conditions in a model Heck coupling reaction catalyzed by **1**-Pd.[a,b,c]



Base	Solvent Toluene/H₂O (4:1)	CH₃CN	DMF
Et_3N	<5%	<5%	71
NaOAc	<5%	<5%	17
K_2CO_3	<5%	<5%	100 (75)

[a] Reaction conditions: ArBr (1.25 mmol), *n*-butyl acrylate (1.88 mmol, 1.5 equiv.), base (1.88 mmol, 1.5 equiv.), solvent (1.25 mL), closed reactor. [b] Reaction performed at 130 °C (temp. of external heating element) for 16 h. [c] Conversions determined by GC analysis by using $n\text{-}C_{11}H_{24}$ as internal standard (isolated yield in parentheses).

With these conditions as a starting point, the effect of admixed water was investigated (Figure 2, bottom trend), with the best result achieved by using a mixture of DMF and H_2O (95:5). For the same solvent, raising the temperature to 140 °C (top trend) allowed the reaction to reach completion in just 3 h to give acrylate **2** in 79% yield.

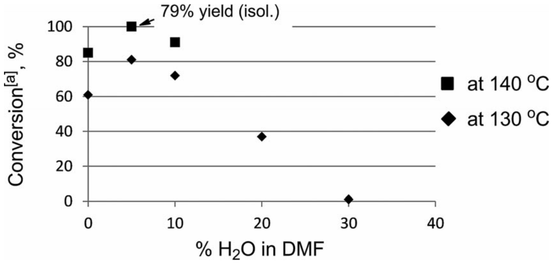
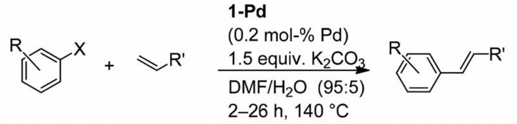


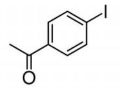
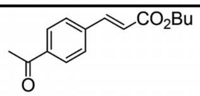
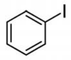
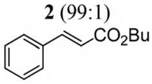
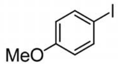
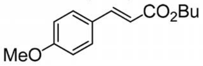
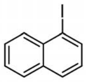
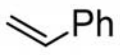
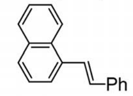
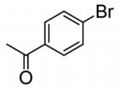
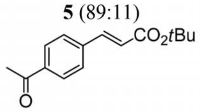
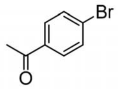
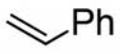
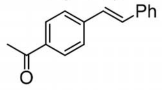
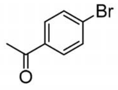
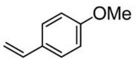
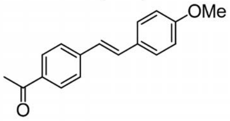
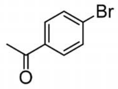
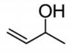
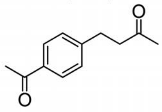
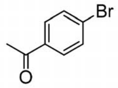
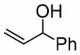
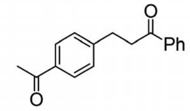
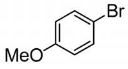
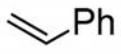
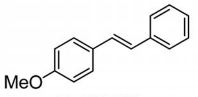
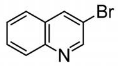
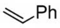
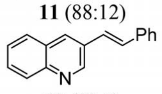
Figure 2. Solvent optimization in the model Heck process performed at the indicated temperature for 3 h (other conditions as detailed in Table 1).

The optimized protocol {0.2 mol-% Pd, [ArX] = 1 M, 1.5 equiv. alkene, 1.5 equiv. K_2CO_3, DMF/H_2O (95:5), 140 °C} was extended to the Heck coupling reaction of a range of aryl iodides and bromides with several alkenes (Table 2).

Activated and deactivated aryl iodides were successfully coupled with *n*-butyl acrylate or styrene, with exclusive (or predominant) formation of the corresponding *trans*-1,2-disubstituted olefins (Table 2, entries 1–4). *p*-Bromoacetophenone was also found to be a suitable substrate, affording good yields in the coupling with *tert*-butyl acrylate, styrene, *p*-methoxystyrene, as well as with the two allylic alcohols tested, 3-buten-2-ol and 1-phenyl-2-propen-1-ol (Table 2, entries 5–9). In the latter two cases, ketones **9** and **10** were isolated as the result of concomitant migration of the

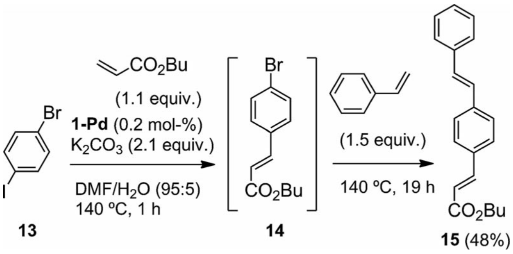
Table 2. Heck reaction between aryl iodides and bromides with different alkenes catalyzed by **1**-Pd.[a]



Entry	ArX	Alkene	Product (E/Z)[b]	Yield [%][c]
1			 **2** (99:1)	79
2			 **3** (99:1)	80
3			 **4** (99:1)	81
4			 **5** (89:11)	85
5			 **6** (72:28)	71
6			 **7** (94:6)	78
7			 **8** (93:7)	96
8			 **9**	73
9			 **10**	64
10			 **11** (88:12)	60
11			 **12** (93:7)	81

[a] Reaction conditions: ArX (1.25 mmol), alkene (1.5 equiv.), K_2CO_3 (1.5 equiv.), DMF/H_2O (95:5, 1.25 mL), 140 °C, closed vessel; see the Supporting Information for the reaction time. [b] The E/Z ratio was determined by GC analysis. [c] Isolated yield.

double bond.[18] The coupling of styrene with a deactivated and a heterocyclic aryl bromide (Table 2, entries 10 and 11, respectively) was also found to proceed efficiently, once again, with complete β-regioselectivity and high E stereoselectivities. A one-pot preparation of the double Heck reaction product **15** was achieved in 48% overall isolated yield through sequential selective reaction of 4-bromoiodobenzene **13** with n-butyl acrylate (1.1 equiv.) to give **14**, followed by the addition of styrene (Scheme 2).

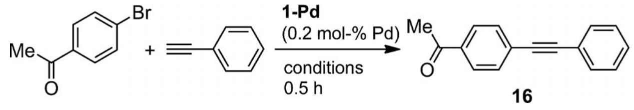


Scheme 2. One-pot sequential double Heck reaction.

The Sonogashira Reaction Catalyzed by 1-Pd

We then turned our attention to the copper-free[3e,19] and phosphine-free Sonogashira process. The activity of **1**-Pd was first assayed in the reaction between p-bromoacetophenone and phenylacetylene, to give unsymmetrical diarylalkyne **16**. During the initial screening, the substrates were exposed to a 0.2 mol-% loading of palladium in the presence of several bases (1.5 equiv.) and solvents (for selected examples, see Table 3). The most efficient coupling was observed for the reaction conducted in DMF at 130 °C and using piperidine as base. Under these conditions (entry 4), the reaction was complete in 30 min and afforded a 76% yield of **16**. This optimized protocol was then extended to the Sonogashira reaction of phenylacetylene with a variety of iodo- and bromoarenes (Table 4).

Table 3. Screening of reaction conditions in a model Sonogashira reaction catalyzed by nanoparticles **1**-Pd.[a]

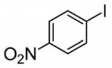
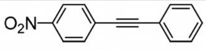
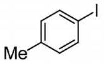
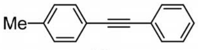
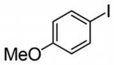
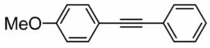
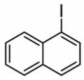
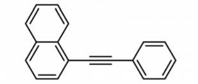
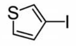
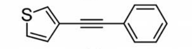
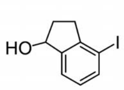
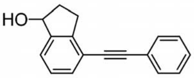
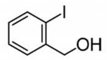
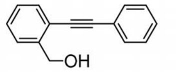
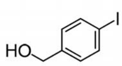
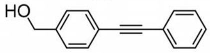
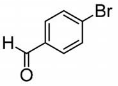
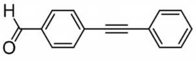
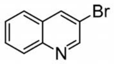
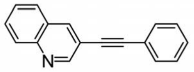


Entry	Base	Solvent	T [°C]	Conv. [%][b]
1	iPrNH$_2$	DMF	130	43
2	iPrNH$_2$	toluene/H_2O (9:1)	130	6
3	piperidine	toluene/H_2O (9:1)	130	7 (79)[c]
4	piperidine	DMF	130	100 (76)[d]
5	piperidine	DMF	90	42[c]
6	Bu_4NOAc	DMF	130	4
7	Bu_4NOAc	toluene/H_2O (9:1)	130	85
8	Bu_4NOAc	CH_3CN	130	<1
9	Bu_4NOAc	toluene/H_2O (95:5)	90	<1

[a] Reaction conditions: ArBr (1.25 mmol), phenylacetylene (1.88 mmol, 1.5 equiv.), base (1.88 mmol, 1.5 equiv.), solvent (1.25 mL), closed vessel. [b] Conversion determined by GC analysis with n-$C_{11}H_{24}$ as internal standard. [c] Conversion after 18 h. [d] Isolated yield in parentheses.

The reaction with activated and deactivated iodoarenes, including the 3-iodothiophene, gave the corresponding internal alkynes in moderate-to-good isolated yields (Table 4, entries 1–5). The coupling process also took place in the

Table 4. Sonogashira reaction of phenylacetylene with aryl iodides and bromides catalyzed by **1**-Pd.[a]

Entry	ArX	Product	Yield [%][b]
1		 **17**	84
2		 **18**	60
3		 **19**	46
4		 **20**	68
5		 **21**	62
6		 **22**	65
7		 **23**	95
8		 **24**	50
9		 **25**	67
10		 **26**	82

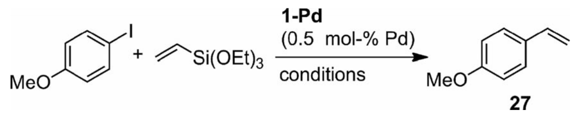
[a] Reaction conditions: ArX (1.25 mmol), phenylacetylene (1.88 mmol, 1.5 equiv.), piperidine (1.88 mmol, 1.5 equiv.), DMF (1.25 mL), 130 °C, 0.5–6 h, closed vessel. [b] Isolated yield.

presence of aliphatic hydroxy groups (Table 4, entries 6–8), including the *ortho*-substituted iodoindanol and 2-iodobenzyl alcohol. Finally, whereas good results were achieved with activated aryl bromides (i.e., a *para* carbonyl substituent or a quinolone moiety, see scheme in Table 3 and entries 9 and 10 in Table 4), the reactions with nonactivated aryl bromides proved sluggish.

The Hiyama Reaction Catalyzed by 1-Pd

Palladium-catalyzed cross-coupling between aryl halides and organosilanes,[5] first reported by Hiyama and Hanataka,[20] is classically performed in the presence of a fluoride source, which is needed to generate the pentacoordinate silicon species that is nucleophilic enough to undergo the transmetallation process. However, the same authors have also suggested that the same effect could be achieved by the use of a nucleophilic base, such as hydroxide anion.[21] The Hiyama reaction catalyzed by Pd NPs has been mainly reported for aryl–aryl coupling,[14a–14c,14f,14h] whereas the analogous vinyl–aryl coupling has been less studied.[14d,14g,14i] We chose the model reaction between *p*-iodoanisole and triethoxy(vinyl)silane to give *p*-methoxystyrene (**27**) to find suitable conditions for the nanocatalyst **1**-Pd. It should be mentioned that whereas tetrabutylammonium fluoride (TBAF) alone was able to promote the Hiyama coupling using **1**-Pd in either toluene or tetrahydrofuran (THF), the use of this promoter in more environmentally benign water or water/methanol mixtures failed. To overcome this lack of activity, several inorganic bases and three different solvent systems [water, methanol/water (1:1), and methanol] were then tested, both with and without added fluoride (TBAF; Table 5).

Table 5. Screening of reaction conditions in a model Hiyama reaction catalyzed by nanoparticles **1**-Pd.[a]



27

Entry	Base [equiv.]	Solvent[b]	F⁻[c]	T [°C]/ t [h]	Conv. [%][d]
1	KOH (4)	H_2O	TBAF	70/24	–
2	LiOH (4)	H_2O	TBAF	70/24	20
3	NaOH (4)	H_2O	TBAF	70/24	29
4	K_2CO_3 (4)	H_2O	TBAF	70/24	5
5	NaOAc (4)	H_2O	TBAF	70/24	–
6	NaOH (4)	MeOH/H_2O	TBAF	70/24	100
7	KOH (4)	MeOH/H_2O	TBAF	70/24	5
8	LiOH (4)	MeOH/H_2O	TBAF	70/24	100
9	K_2CO_3 (4)	MeOH/H_2O	TBAF	70/24	–
10	NaOAc (4)	MeOH/H_2O	TBAF	70/24	–
11	NaOH (4)	MeOH	TBAF	70/24	17
12	LiOH (4)	MeOH	TBAF	70/24	4
13	NaOH (4)	MeOH/H_2O	–	70/24	100
14	LiOH (4)	MeOH/H_2O	–	70/24	84
15	NaOH (3)	MeOH/H_2O	–	70/24	100
16	NaOH (2)	MeOH/H_2O	–	70/24	34
17	NaOH (4)	MeOH/H_2O	–	25/24	–
18	NaOH (3)	MeOH/H_2O	–	100/5	100
19	NaOH (3)	MeOH/H_2O	–	100/5	100[e]
20	NaOH (3)	MeOH/H_2O	–	70/24	89[f]

[a] Reaction conditions: *p*-iodoanisole (0.25 mmol), triethoxy(vinyl)silane (0.50 mmol, 2.0 equiv.), base, solvent (2 mL), closed vessel. [b] A mixture of MeOH/H_2O (1:1). [c] TBAF (0.38 mmol, 1.5 equiv.). [d] Conversions were determined by GC analysis using n-$C_{11}H_{24}$ as internal standard. [e] At 0.25 mol-% Pd loading. [f] At 0.13 mol-% Pd loading.

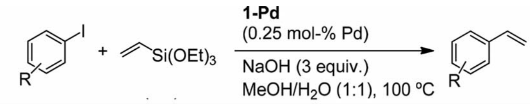
Initial attempts to perform the reaction by using the different bases in the presence of TBAF in water at 70 °C gave poor results (Table 5, entries 1–5), the best results came from the use of LiOH and NaOH, and the conversions were improved with these nucleophilic bases when the reaction medium was changed to a methanol/water (1:1) mixture (Table 5, entries 6–10). The presence of water seems to be beneficial because the reactions in pure methanol, in the presence of these two bases under analogous conditions, gave low conversions (Table 5, entries 11–12). We then found that the addition of a fluoride source was unnecessary (Table 5, entries 13 and 14), although sodium hydroxide gave better conversion than lithium hydroxide under these fluoride-free conditions. A decrease in the amount of

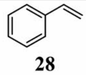
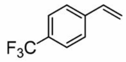
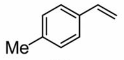
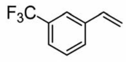
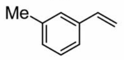
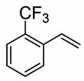
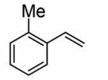
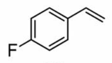
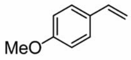
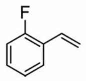
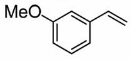
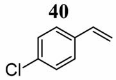
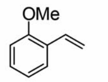
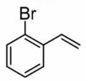
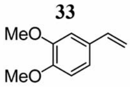
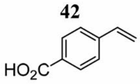
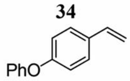
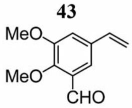
NaOH from 4 to 3 equiv. had no deleterious effect, but further reduction to 2 equiv. base led to low conversion (Table 5, compare entries 13, 15 and 16). The effect of temperature on the reaction was then examined. The reaction did not proceed at room temperature (Table 5, entry 17), whereas only 5 h were required to achieve full conversion at 100 °C (Table 5, compare entries 15 and 18). We were pleased to find that full conversion was also achieved even at 0.25 mol-% Pd (Table 5, entry 19).

With these optimized conditions in hand [3 equiv. NaOH, MeOH/H_2O (1:1), 100 °C], the reaction of triethoxy(vinyl)silane with other aryl iodides was assayed using 2 equiv. silane and 0.25 mol-% palladium (Table 6). Iodobenzene and aryl iodides bearing electron-neutral, electron-donating, and electron-withdrawing substituents in different positions gave moderate-to-excellent isolated yields of the corresponding styrenes, with the *ortho*-substituted substrates requiring relatively longer reaction times (Table 6, entries 4, 7, 12 and 16). As expected, the selective mono-vinylation of substrates possessing two different halogen atoms was attained by taking advantage of the higher reactivity of the carbon–iodine bond (Table 6, entries 13–16). Moreover, the catalytic system was compatible with the presence of the potentially reactive carboxy and formyl groups (Table 6, entries 17 and 18). It is noteworthy that, under the conditions and stoichiometry detailed in Table 6, further Heck coupling of the resulting styrenes was only detected in a few examples.

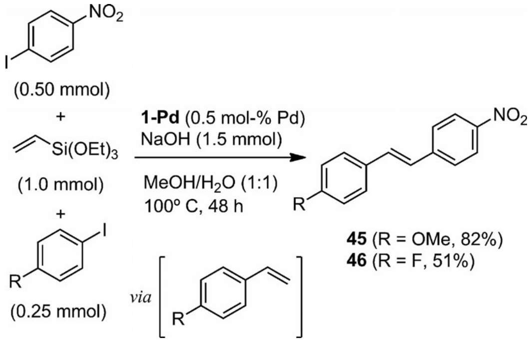
Finally, we were pleased to achieve a three-component synthesis of unsymmetrical stilbenes from triethoxy(vinyl)silane and two different aryl iodides (Scheme 3). This one-pot transformation was feasible under the optimized Hiyama coupling conditions by using either the *p*-OMe- or the *p*-F-substituted iodobenzene as the limiting reagents in the presence of 4 equiv. vinylsilane and 2 equiv. 1-iodo-4-nitrobenzene. Control experiments demonstrated that the Hiyama reaction with 1-iodo-4-methoxybenzene or 1-iodo-4-fluorobenzene takes place first, followed by Heck reaction of 1-iodo-4-nitrobenzene with the resulting *p*-substituted styrene.

Table 6. Hiyama reaction of triethoxy(vinyl)silane with aryl iodides catalyzed by **1**-Pd.[a]



Entry	Product	Time [h]	Yield [%][b]	Entry	Product	Time [h]	Yield [%][b]
1	 **28**	5	90	10	 **36**	5	93
2	 **29**	5	81	11	 **37**	5	92
3	 **30**	5	83	12	 **38**	24	63
4	 **31**	24	82	13	 **39**	5	81
5	 **27**	5	97	14	 **40**	5	66
6	 **32**	5	97	15	 **41**	10	86
7	 **33**	20	92	16	 **42**	18	88
8	 **34**	8	78	17	 **43**	18	59
9	 **35**	10	83	18	 **44**	24	60

[a] Reaction conditions: ArI (0.5 mmol), triethoxy(vinyl)silane (1.0 mmol, 2 equiv.), NaOH (1.5 mmol, 3 equiv.), MeOH/H_2O (1:1, 4 mL), 100 °C, closed vessel. [b] Isolated yield.



Scheme 3. One-pot Hiyama–Heck reactions.

Conclusions

Palladium nanoparticles **1**-Pd, prepared by the hydrogenation of $Pd(dba)_2$ in the presence of a tris-imidazolium iodide as stabilizer, have been used as an efficient catalyst in several C–C bond-formation reactions. Effective conditions have been found for Heck and copper-free Sonogashira reactions with aryl iodides and bromides at 0.2 mol-% Pd loading. The nanocatalyst proved to be tolerant to a range of functional groups, with the expected products being obtained in moderate-to-good yields. A one-pot, double Heck reaction was carried out by selective reactions of 4-bromoiodobenzene with two different alkenes. Moreover, a convenient protocol has been developed for the fluoride-free Hiyama coupling of a vinylsilane with aryl iodides involving the use of sodium hydroxide as promoter in aqueous medium (methanol/water, 1:1), furnishing the corresponding styrenes in moderate-to-excellent yields. Few precedents exist for the use of preformed palladium nanoparticles for this type of C–C coupling process involving organosilane precursors. The three-component synthesis of unsymmetrically-substituted stilbenes has been achieved through a one-pot domino Hiyama–Heck reaction between *p*-iodonitrobenzene, triethoxy(vinyl)silane, and other aryl iodides.

Experimental Section

General Remarks: Milli-Q or distilled water were used for the preparation and purification of compounds. Catalytic runs with magnetic stirring were carried out in a Radleys Discovery System equipped with 12 sealed 40 mL glass vessels. All starting materials were commercially available (Aldrich, Acros, Alfa Aesar), and the best grade materials were purchased and used without further purification. All NMR measurements were carried out at the Servei de Ressonància Magnètica Nuclear of the Universitat Autònoma de Barcelona and the Serveis Tècnics d'Investigació de la Universitat d'Alacant. Spectra were recorded with Bruker AC250 (250 MHz for ^1H) or Avance 300, 360, and 400 (300, 360, and 400 MHz for ^1H, respectively) spectrometers. Infrared spectra were recorded with Bruker Tensor 27 or Jasco 4100LE instruments equipped with an ATR Golden Gate cell and a diamond window. Gas chromatographic analysis was accomplished with an Agilent Technologies 7890A GC and a Hewlett Packard HP-6890 system equipped with an Agilent HP-5 column (30 m × 0.320 mm × 0.25 µm). MS analyses of the products were carried out with Agilent 5973 and 6850 GC systems equipped with EI Mass Detectors. Melting points were determined with a Reichert brand melting-point apparatus and are uncorrected. Alugram SIL G/UV_{254} sheets (Macherey–Nagel) were used for thin-layer chromatography. Column chromatography was carried out using SDS brand silica gel with a grain size of 35–70 or 40–60 µm and a pore size of 60 Å. The preparation of **1**-Pd has been reported previously.[13a]

Heck Reaction Catalyzed by 1-Pd Nanoparticles (Table 2); General Procedure: A screw-top sealable tube was charged with a magnetic stir bar, aryl halide (1.25 mmol), alkene (1.88 mmol, 1.5 equiv.), K_2CO_3 (1.5 equiv.), and **1**-Pd NPs (0.2 mol-% Pd). A mixture of DMF/water (95:5, 1.25 mL) was added and the tube was sealed and heated to 140 °C for the time indicated in the Supporting Information (the consumption of aryl halide was monitored by GC analysis). The tube was then cooled to room temperature and the solvent was removed under vacuum. The residue was purified by column chromatography (SiO_2; hexane/ethyl acetate mixtures). See the Supporting Information for details and characterization of compounds.

Sonogashira Reaction Catalyzed by 1-Pd Nanoparticles (Table 4); General Procedure: A screw-top sealable tube was charged with a magnetic stir bar, aryl halide (1.25 mmol), phenylacetylene (1.88 mmol, 1.5 equiv.), piperidine (1.88 mmol, 1.5 equiv.), and **1**-Pd NPs (0.2 mol-% Pd). DMF (1.25 mL) was added and the tube was sealed and heated to 130 °C for the time indicated in the Supporting Information (the consumption of aryl halide was monitored by GC analysis). The tube was then cooled to room temperature and the solvent was removed under vacuum. The residue was purified by column chromatography (SiO_2; hexane/ethyl acetate mixtures). See the Supporting Information for details and characterization of compounds.

Hiyama Reaction Catalyzed by 1-Pd Nanoparticles (Table 6); General Procedure: A screw-top sealable tube was charged with a magnetic stir bar, aryl iodide (0.5 mmol), triethoxy(vinyl)silane (1.0 mmol, 2 equiv.), NaOH (1.5 mmol, 3 equiv.), and **1**-Pd NPs (0.25 mol-% Pd). A mixture of methanol/water (1:1, 4 mL) was added and the tube was sealed and heated to 100 °C for the time indicated in Table 6 (the consumption of aryl halide was monitored by TLC and GC analysis). The tube was then cooled to room temperature, the reaction mixture was passed through a pad of Celite, and the solvent was removed under vacuum. In some cases, purification of the crude reaction mixture by column chromatography was required (SiO_2; hexane). See the Supporting Information for details and characterization of compounds.

One-Pot, Double Heck Reaction Catalyzed by 1-Pd Nanoparticles (Scheme 2): A screw-top sealable tube was charged with a magnetic stir bar, 4-bromoiodobenzene (354 mg, 1.25 mmol), *n*-butyl acrylate (195 µL, 1.38 mmol, 1.1 equiv.), K_2CO_3 (363 mg, 2.62 mmol), and **1**-Pd NPs (0.2 mol-% Pd). A mixture of DMF/water (95:5, 1.25 mL) was added and the tube was sealed and heated to 140 °C for 1 h (the consumption of aryl halide was monitored by GC analysis). Styrene (250 µL, 1.875 mmol, 1.5 equiv.) was added and the mixture was stirred at 140 °C overnight (the consumption of the intermediate cinnamate was monitored by GC analysis). The tube was then cooled to room temperature, water (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with water (3 × 30 mL), dried with anhydrous Na_2SO_4, and the solvent was removed under vacuum. The residue was purified by column chromatography (SiO_2; hexane/ethyl acetate, 10:1) to afford **15**[22] (184 mg, 48 %).

One-Pot Hiyama–Heck Reaction Catalyzed by 1-Pd Nanoparticles (Scheme 3): A screw-top sealable tube was charged with a magnetic stir bar, 1-iodo-4-nitrobenzene (124.5 mg, 0.5 mmol), the corresponding aryl iodide (0.25 mmol), triethoxy(vinyl)silane (210 µL, 1.0 mmol, 2 equiv.), NaOH (60 mg, 1.5 mmol), and **1**-Pd NPs (0.25 mol-% Pd). A mixture of methanol/water (1:1, 4 mL) was added and the tube was sealed and heated to 100 °C for 48 h (TLC and GC monitoring). The tube was then cooled to room temperature, the solvent was removed under vacuum and the residue was purified by column chromatography (SiO_2; hexane) to afford stilbene derivatives **45**[23] (55 mg, 82 %) and **46**[24] (31 mg, 51 %).

Supporting Information (see footnote on the first page of this article): Details of catalytic runs and characterization data of the corresponding products.

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[1] a) X.-F. Wu, P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2010**, *49*, 9047–9050; *Angew. Chem.* **2010**, *122*, 9231–9234; b) C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062–5085; *Angew. Chem.* **2012**, *124*, 5150–5174.

[2] For some reviews dealing with the Heck reaction and its applications, see: a) I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009–3066; b) N. J. Whitcombe, K. K. Hii, S. E. Gibson, *Tetrahedron* **2001**, *57*, 7449–7476; c) F. Alonso, I. P. Beletskaya, M. Yus, *Tetrahedron* **2005**, *61*, 11771–11835; d) A. F. Schmidt, A. Al Halaiqa, V. V. Smirnov, *Synlett* **2006**, 2861–2878; e) J. P. Knowles, A. Whiting, *Org. Biomol. Chem.* **2007**, *5*, 31–44; f) A. M. Trzeciak, J. J. Ziółkowski, *Coord. Chem. Rev.* **2007**, *251*, 1281–1293; g) D. McCartney, P. J. Guiry, *Chem. Soc. Rev.* **2011**, *40*, 5122–5150.

[3] For selected reviews dealing with the Sonogashira reaction and its applications, see: a) K. Sonogashira, *Sonogashira Alkyne Synthesis* in: *Handbook of Organopalladium Chemistry for Organic Synthesis* (Eds.: E. Negishi, A. de Meijere), Wiley-Interscience, New York, **2002**, vol. I, chapter III.2.8.1, p. 493–529; b) E. Negishi, L. Anastasia, *Chem. Rev.* **2003**, *103*, 1979–2017; c) R. Chinchilla, C. Nájera, *Chem. Rev.* **2007**, *107*, 874–922; d) H. Doucet, J.-C. Hierso, *Angew. Chem. Int. Ed.* **2007**, *46*, 834–871; *Angew. Chem.* **2007**, *119*, 850–888; e) R. Chinchilla, C. Nájera, *Chem. Soc. Rev.* **2011**, *40*, 5084–5121.

[4] For selected reviews dealing with the Suzuki coupling and its applications, see: a) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147–168; b) S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2001**, *40*, 4544–4568; *Angew. Chem.* **2001**, *113*, 4676; c) S. Kotha, K. Lahiri, D. Kashinath, *Tetrahedron* **2002**, *58*, 9633–9695; d) F. Bellina, A. Carpita, R. Rossi, *Synthesis* **2004**, 2419–2440; e) F. Alonso, I. P. Beletskaya, M. Yus, *Tetrahedron* **2008**, *64*, 3047–3101; f) G. A. Molander, B. Canturk, *Angew. Chem. Int. Ed.* **2009**, *48*, 9240–9261; *Angew. Chem.* **2009**, *121*, 9404–9425; g) M. M. Heravi, E. Hashemi, *Tetrahedron* **2012**, *68*, 9145–9178.

[5] For selected recent reviews on the palladium-catalyzed cross-coupling of organosilicon reagents, see: a) Y. Nakao, T. Hiyama, *Chem. Soc. Rev.* **2011**, *40*, 4893–4901; b) H. F. Sore, W. R. J. D. Galloway, D. R. Spring, *Chem. Soc. Rev.* **2012**, *41*, 1845–1866.

[6] K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489; *Angew. Chem.* **2005**, *117*, 4516–4563.

[7] a) H.-U. Blaser, A. Indolese, F. Naud, U. Nettekoven, A. Schnyder, *Adv. Synth. Catal.* **2004**, *346*, 1583–1598; b) J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651–2710; c) C. Toborg, M. Beller, *Adv. Synth. Catal.* **2009**, *351*, 3027–3043; d) C. A. Busacca, D. R. Fandrick, J. J. Song, C. H. Senanayake, *Adv. Synth. Catal.* **2011**, *353*, 1825–1864.

[8] a) A. D. Schlüter, Z. Bo, *Synthesis of Conjugated Polymers for Materials Science*, in: *Handbook of Organopalladium Chemistry for Organic Synthesis* (Eds.: E. Negishi, A. de Meijere), Wiley-Interscience, New York, **2002**, vol. I, chapter III.2.17.2, p. 825–861; b) M. Hoyos, M. L. Turner, O. Navarro, *Curr. Org. Chem.* **2011**, *15*, 3263–3290.

[9] For catalytic applications of metal nanoparticles, see: a) *Nanoparticles and Catalysis* (Ed.: D. Astruc), Wiley-VCH, Weinheim, Germany, **2008**; b) A. Roucoux, J. Schulz, H. Patin, *Chem. Rev.* **2002**, *102*, 3757–3778; c) M. Moreno-Mañas, R. Pleixats, *Acc. Chem. Res.* **2003**, *36*, 638–643; d) J. A. Widegren, R. G. Finke, *J. Mol. Catal. A* **2003**, *191*, 187–207; e) D. Astruc, F. Lu, J. Ruiz Aranzaes, *Angew. Chem. Int. Ed.* **2005**, *44*, 7852–7872; *Angew. Chem.* **2005**, *117*, 8062–8083; f) J. G. De Vries, *Dalton Trans.* **2006**, 421–429; g) D. Astruc, *Inorg. Chem.* **2007**, *46*, 1884–1894; h) A. Roucoux, K. Philippot, in: *Handbook of Homogeneous Hydrogenations* (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH, Weinheim, Germany, **2007**, vol. 9, p. 217–256; i) A. Corma, H. García, *Chem. Soc. Rev.* **2008**, *37*, 2096–2126; j) S. Roy, M. A. Pericàs, *Org. Biomol. Chem.* **2009**, *7*, 2669–2677; k) F. Alonso, P. Riente, M. Yus, *Acc. Chem. Res.* **2011**, *44*, 379–391; For a recent review on the use of Pd NPs for C–C coupling reactions, see: l) A. Balanta, C. Godard, C. Claver, *Chem. Soc. Rev.* **2011**, *40*, 4973–4985.

[10] L. Starkey Ott, R. G. Finke, *Coord. Chem. Rev.* **2007**, *251*, 1075–1100.

[11] a) M. Moreno-Mañas, R. Pleixats, S. Villarroya, *Organometallics* **2001**, *20*, 4524–4528; b) M. Moreno-Mañas, R. Pleixats, S. Villarroya, *Chem. Commun.* **2002**, 60–61.

[12] a) A. Serra-Muns, R. Soler, E. Badetti, P. de Mendoza, M. Moreno-Mañas, R. Pleixats, R. M. Sebastián, A. Vallribera, *New J. Chem.* **2006**, *30*, 1584–1594; b) N. Mejías, A. Serra-Muns, R. Pleixats, A. Shafir, M. Tristany, *Dalton Trans.* **2009**, 7748–7755; c) N. Mejías, R. Pleixats, A. Shafir, M. Medio-Simón, G. Asensio, *Eur. J. Org. Chem.* **2010**, 5090–5099.

[13] a) M. Planellas, R. Pleixats, A. Shafir, *Adv. Synth. Catal.* **2012**, *354*, 651–662; b) M. Planellas, W. Guo, F. Alonso, M. Yus, A. Shafir, R. Pleixats, T. Parella, *Adv. Synth. Catal.* **2014**, *356*, 179–188.

[14] Few precedents exist on the use of preformed Pd NPs in the Hiyama reaction, see: a) L. Durán Pachón, M. B. Thathagar, F. Hartl, G. Rothenberg, *Phys. Chem. Chem. Phys.* **2006**, *8*, 151–157; b) D. Srimani, S. Sawoo, A. Sarkar, *Org. Lett.* **2007**, *9*, 3639–3642; c) D. Shah, H. Kaur, *J. Mol. Catal. A: Chem.* **2012**, *359*, 69–73; d) A. Grirrane, H. García, A. Corma, *J. Catal.* **2013**, *302*, 49–57. For other examples involving Pd NP generated in situ, see: e) R. Dey, K. Chattopadhyay, B. C. Ranu, *J. Org. Chem.* **2008**, *73*, 9461–9464; f) B. C. Ranu, R. Dey, K. Chattopadhyay, *Tetrahedron Lett.* **2008**, *49*, 3430–3432; g) E. Alacid, C. Nájera, *J. Org. Chem.* **2008**, *73*, 2315–2322; h) P. S. Bäuerlein, I. J. S. Fairlamb, A. G. Jarvis, A. F. Lee, C. Müller, J. M. Slattery, R. J. Thatcher, D. Vogt, A. C. Whitwood, *Chem. Commun.* **2009**, 5734–5736; i) T. Chatterjee, R. Dey, B. C. Ranu, *New J. Chem.* **2011**, *35*, 1103–1110; j) D. Srimani, A. Bej, A. Sarkar, *J. Org. Chem.* **2010**, *75*, 4296–4299.

[15] K. Philippot, B. Chaudret, *Organometallic Derived Metals, Colloids and Nanoparticles*, in: *Comprehensive Organometallic Chemistry III* (Eds.: R. H. Crabtree, M. P. Mingos), Elsevier **2007**, vol. 12, chapter 12–03, p. 71–99.

[16] M. F. Rettig, P. M. Maitlis, *Inorg. Synth.* **1990**, *28*, 110–113.

[17] M. Trilla, R. Pleixats, T. Parella, C. Blanc, P. Dieudonné, Y. Guari, M. Wong Chi Man, *Langmuir* **2008**, *24*, 259–265.

[18] Palladium-catalyzed reactions of aromatic halides with allylic alcohols leading to the formation of β-aromatic carbonyl compounds have been previously reported, see: M. Larhed, A. Hallberg, *Scope, Mechanism, and Other Fundamental Aspects of the Intermolecular Heck Reaction*, in: *Handbook of Organopalladium Chemistry for Organic Synthesis* (Eds.: E. Negishi, A. de Meijere), Wiley-Interscience, New York, **2002**, vol. I, chapter IV.2.1.1, p. 1145–1146. The formation of β-aromatic α,β-unsaturated alcohols in the Heck reactions of aryl halides with allylic alcohols has been achieved by the use of a silver salt (silver acetate as the base), see: T. Jeffery, *Tetrahedron Lett.* **1991**, *32*, 2121–2124.

[19] M. García-Melchor, M. C. Pacheco, C. Nájera, A. Lledós, G. Ujaque, *ACS Catal.* **2012**, *2*, 135–144.

[20] Y. Hanataka, T. Hiyama, *J. Org. Chem.* **1989**, *54*, 268–270.

[21] E. Hagiwara, K. Gouda, Y. Hatanaka, T. Hiyama, *Tetrahedron Lett.* **1997**, *38*, 439–442.

[22] X. Zhang, A. Liu, W. Chen, *Org. Lett.* **2008**, *10*, 3849–3852.

[23] P. Colbon, J. H. Barnard, M. Purdie, K. Mulholland, I. Kozhevnikov, J. Xiao, *Adv. Synth. Catal.* **2012**, *354*, 1395–1400.

[24] S. Wu, H. Ma, X. Jia, Y. Zhong, Z. Lei, *Tetrahedron* **2011**, *67*, 250–256.

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