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An E-factor minimized protocol for a sustainable and efficient Heck reaction in flow

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KEYWORDS azeotrope media; Heck-Mizoroki reaction; heterogeneous catalysis; waste minimization, flow chemistry.

ABSTRACT

A highly sustainable and waste-minimized protocol for the Heck coupling has been defined. Optimal conditions have been defined by exploiting a heterogeneous catalyst based on Supported Ionic Liquid-Like Phases featuring a high Pd loading (10 wt%) and by optimizing its efficiency in a recoverable green reaction medium (acetonitrile/water azeotrope). Pure products **4a-l** have been isolated chromatography-free in high yields (74-99%) and with extremely low

Environmental factor (E-factor) values (2.3-5.0). With the application of the flow technology the selected heterogeneous base and Pd-catalyst have been fully recovered and reused and the palladium leaching minimized allowing to isolate the final products with low residual palladium content (< 5 ppm) without any purification step.

INTRODUCTION

The palladium-catalyzed vinylic hydrogen substitution reactions by an aryl, alkenyl or benzyl halide was discovered independently by Heck and Mizoroki in the early 1970s.¹

Today Heck cross-coupling reaction is a very important synthetic tool that enables the access to molecular moieties often found in the preparation of pharmaceutical targets and organic semiconductors.^{2, 3}

Due to the industrial relevance of the Heck reaction, the research is focused on the definition of protocols featuring the use of efficient, recyclable and reusable catalytic systems, simple isolation of the final products and minimal waste production. Several heterogeneous systems have been proposed such as Pd on activated carbon,^{4,5} on metal oxides⁶ and on functionalized silica.^{7,8} Palladium nanoparticles (PdNPs) stabilized by renewable cellulose and sugars have also been recently reported.^{9,10}

The design of recyclable catalysts for the Heck reaction is not trivial, since the whole catalytic cycle is liable to changes in response to the chemical environment. It must be kept in mind that this reaction needs many different species (reagents, base, ligands) and breeds others (product, salts, etc.). As a result, the reaction mixture varies continually through all the process.^{11,12}

Heck reaction is usually carried out in highly undesirable aprotic polar solvents, such as *N,N'*-dimethyl formamide (DMF) and *N*-methylpyrrolidinone (NMP),^{13,14} whereas a great attention should be paid to the alternative safer media.¹⁵

In addition, Heck reaction may proceed through a “release and catch” mechanism,^{5,16-22} therefore much attention must be paid to the amount of palladium leached into the product. It should be also noticed that common dipolar aprotic media such as DMF or NMP strongly bind to soluble palladium species, facilitating their dissolution with a consequent significant leaching into the product.²³⁻²⁵

In some cases, such as for APIs (Active Pharmaceutical Ingredients), specification limits for residues of metals are very strict.²⁶ Purification methods for the removal of palladium from target materials already exist,^{27,28} but they are time and solvent consuming. Accordingly, to fulfill the current need for the definition of more environmentally-friendly procedures for transformations catalyzed by precious metals,²⁹ a waste-minimized and efficient protocol for the Heck reaction is highly desirable. Most importantly, this protocol should be able to limit the leaching of palladium in the products and minimize or avoid the need for purification steps.

Besides, the base selected has a fundamental role in the mechanism of the Heck reaction, as it acts in the last step of the catalytic cycle to regenerate the active Pd species.³⁰ A homogeneous tertiary amine is generally used with the consequent formation of the corresponding ammonium salt. As a result, the recovery of the pure product is achieved after several purification steps such as extraction and/or column chromatography, with a consequent large consumption of materials and production of waste. Therefore in addition to the palladium leaching, the amount of waste produced and the resulting E-factor values (kg of waste / kg of isolated desired product) are generally very high.^{31,32}

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6 An effective strategy to minimize waste is based on the direct alkenylation of simple arenes
7 catalyzed by homogeneous Pd or Rh catalysts.³³ This synthetic approach is highly attractive but
8 also very challenging and available protocols require the use of large excess of arene, long
9 reaction times and often feature poor selectivity.
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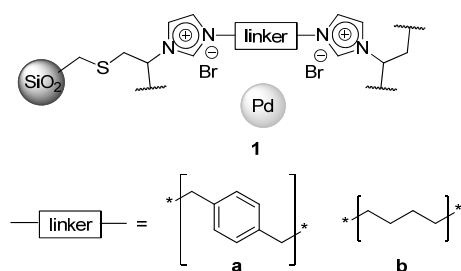
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15 Recently, we have contributed to the developing of sustainable approaches to cross-coupling
16 reactions by using green reaction media, flow conditions and by preparing novel immobilized
17 palladium nanoparticles based on imidazolium salts supported on silica gel (Figure 1).³⁴⁻³⁶ The
18 resulting material belongs to the category of Supported Ionic Liquid-Like Phases (SILLPs),
19 features a high Pd loading (10 wt%) and proved to be highly efficient, but also recoverable and
20 reusable, in the Suzuki-Miyaura reaction both under batch^{34,35} and flow conditions.³⁶ Flow
21 technique allowed to reach a very high environmental efficiency by using our SILLP Pd-catalyst
22 in ethanol/water azeotrope as medium.³⁶
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34 Although the reaction was carried out by using two separate columns containing the base and
35 the catalyst respectively, we observed a high catalytic efficiency. This can be ascribed to the
36 known "release and catch" mechanism,¹⁶⁻²² in which the supported palladium catalyst serves as a
37 reservoir for active Pd species that are dissolved from the solid catalyst.³⁷⁻³⁹ The active Pd
38 species can move through the apparatus, then are effectively scavenged by the ionic liquid-like
39 support,⁴⁰ as a result the catalyst is still active and recyclable.³⁴⁻³⁶
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47 Quaternary ammonium salts are responsible for the stabilization of the metal nanoparticles⁴¹⁻⁴³
48 which may results in low degree of leaching. Then, acting also as scavenger of the soluble metal
49 species, they make the "release and catch" mechanism possible.
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Indeed, the results obtained in the Suzuki-Miyaura reaction proved that our flow approach applied to cross coupling reactions can be a very powerful tool to reduce waste, optimize catalyst recovery and reuse, and simplify product isolation and solvent recovery.^{36,40,44}

Figure 1. Structures of the SILLP Pd-catalysts **1**.



In this contribution we have developed a novel and highly sustainable protocol for the Heck coupling using our SILLP Pd catalysts in flow and featuring a very low waste production.⁴⁵

Considering that solvents are responsible for the large majority of waste produced, therefore to reach this goal, along with the use of heterogeneous Pd-catalysts, to minimize waste, we have directed much efforts to the use of a recoverable reaction medium and to the definition of reactions conditions that would allow the isolation of products without any further work-up and/or column chromatography purifications.

Optimization of the reaction conditions has been therefore performed in recoverable and sustainable azeotropic mixtures avoiding the use of undesirable toxic dipolar aprotic solvents.^{13,14} In combination, our strategy has been focused on the use of an immobilized base with the intention of simplify the work up procedures and allow the isolation of the final product without additional purification steps.

Initially the catalysts **1** (Figure 1) were used in the representative Heck reaction of iodobenzene (**2a**) and methyl acrylate (**3a**), then the protocol was extended to several aryl iodides **2b-e**, acrylates **3b** and styrenes **5a-b**.

EXPERIMENTAL SECTION

Unless otherwise stated, all solvents and reagents were used as obtained from commercial sources without further purification. GC analyses were performed by using Hewlett-Packard HP 5890A equipped with a capillary column DB-35MS (30 m, 0.53 mm), a FID detector and hydrogen as gas carrier. GC-EIMS analyses were carried out by using a Hewlett-Packard HP 6890N Network GC system/5975 Mass Selective Detector equipped with an electron impact ionizer at 70 eV. NMR spectra were recorded on a Bruker DRX-ADVANCE 400 MHz (^1H at 400 MHz and ^{13}C at 100.6 MHz) in CDCl_3 using TMS as the internal standard. Elemental Analyses (EA) were conducted on a Fisons EA1108CHN. Melting points were measured on a Büchi 510. ICP-OES 710 Agilent Technology. Flow procedures were performed using a Jasco PU-2080 pump, a Omnifit Glass Column as reservoir and Supelco HPLC Column Blank as base/catalyst column.

Diethylaminomethyl-polystyrene was prepared by reacting Merrifield resin (200-400 mesh, 4.4 mmol/g Cl loading, 2% cross-linked with divinylbenzene) with diethylamine (2.5 eq) in toluene at 100 °C for 24 hours. The resin was washed with a 0.5 M solution of diethylamine in toluene, then toluene, dichloromethane, water, and acetone to remove the excess amine and finally dried under vacuum. The amine loading was determined by EA.

Typical procedure for the Heck reaction in CH₃CN/H₂O azeotrope under batch conditions

To a solution of the aryl iodide **2a-e** (1 mmol) and the alkene **3a-b** or **5a-b** (1.2-1.0 mmol) in CH₃CN/H₂O az. (1 M, 1 mL), diethylaminomethyl-polystyrene (~4 mmol/g, 1.5 equiv, 0.375 g) and catalyst **1** (0.1 mol%, 1 mg) were added. The reaction mixture was stirred at the desired temperature for the time necessary to complete conversion of the aryl iodide **2a-e**, monitored by GLC. The heterogeneous base and catalyst were separated by filtration and the product **4a-h** or **6a-h** isolated by distillation of the azeotrope.

Heck reaction to methyl cinnamate (4a) under flow conditions at 130° C

A pre-mixed mixture of iodobenzene (**2a**) (50 mmol, 5.60 mL) and methyl acrylate (**3a**) (60 mmol, 5.40 mL) in CH₃CN/H₂O az. (50 mL) was charged into a glass column functioning as a reservoir. Diethylaminomethyl-polystyrene (~4 mmol/g, 75 mmol, 18.75 g) and the catalyst (10 wt%, 0.1 mol%, 50 mg) were mixed and dispersed in 1 mm diameter solid glass beads and charged in a stainless steel HPLC column; the equipment was connected, by using the appropriate tubes and valves, to the pump and installed into a thermostated box. The reaction mixture was cyclically pumped (flow rate 2.0 mL/min) through the base - catalyst column at 130 °C until complete conversion of the reactants to methyl cinnamate (**4a**) was achieved (the reaction was monitored by GLC). At this stage, the pump was left to run in order to recover the reaction mixture into the reservoir. To completely recover the product and clean the reactor, CH₃CN/H₂O azeotrope (3 x 25 mL at a 2 mL/min) was cyclically pumped through the base - catalyst column for 15 min (each fraction) and then collected into the reservoir to isolate the product in 80 % yield, after removal and recovery of the azeotrope (95% of which was

recovered) via distillation. A solution of TEA (15 mL in 30 mL of aqueous acetonitrile azeotrope) was cyclically pumped through the base/catalyst column (2 mL/min, 30 min) to regenerate the diethylaminomethyl-polystyrene. Finally azeotrope (40 mL) was cyclically pumped through the base/catalyst column in two portions to remove residual TEA.

E-Factor Calculation for the batch reaction in CH₃CN azeotrope at 130 °C (1 mmol)

E-factor for Heck reaction of iodobenzene (**2a**) (1.0 mmol) and methyl acrylate (**3a**) (1.2 mmol) (75% isolated yield): E-factor = [0.204 g (iodobenzene (**2a**)) + 0.103 g (methyl acrylate (**3a**)) + 0.818 g (medium) + 0.375 g (PS-TEA) + 0.001 (catalyst) – 0.120 g (methyl cinnamate (**4a**))]/0.120 g (methyl cinnamate (**4a**)) = **11.5**

E-Factor Calculation for the reaction in flow at 130 °C (50 mmol)

E-factor for Heck reaction of iodobenzene (**2a**) (50 mmol) and methyl acrylate (**3a**) (60 mmol) (80% isolated yield): E-factor = [10.20 g (iodobenzene (**2a**)) + 5.40 g (methyl acrylate (**3a**)) + 102.25 g (medium) + 10.90 g (TEA) + 53.15g (TEA wash) – 6.50 g (methyl cinnamate (**4a**)) – 97.15 g (95% recovered medium)]/6.50 g (methyl cinnamate (**4a**)) = **12.0** (PS-TEA and catalyst **1b** were not considered due to their complete recovery).

E-Factor Calculation for the batch reaction in DMF/water (4:1)

Reference for the procedure: C. Pavia, F. Giacalone, L. A. Bivona, A. M. Salvo, C. Petrucci, G. Strappaveccia, L. Vaccaro, C. Aprile, M. Gruttadauria, *J. Mol. Catal. A: Chem.* **2014**, 387, 57-62.

E-factor for Heck reaction of iodobenzene (**2a**) (1 mmol) and methyl acrylate (**3a**) (74% isolated yield): E-factor = [0.204 g (iodobenzene (**2a**)) + 0.129 g (methyl acrylate (**3a**)) + 0.202 g (TEA) + 4.78 g (DMF/H₂O 4:1) + 101.2 g (water) + 332.5 g (CH₂Cl₂) – 0.10 g (methyl cinnamate (**4a**))]/0.10 g (methyl cinnamate (**2a**)) = **3657** (silica gel for purification has not been considered).

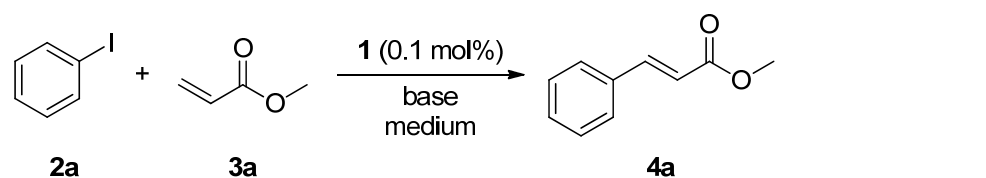
More details on E-factor calculations are in the Supporting Info.

RESULTS AND DISCUSSION

We tested the activity of the catalysts **1** (a bis-imidazolium salt having a *p*-xylyl (**1a**) or linear C₄ (**1b**) linker³⁴) in the Heck coupling under conventional conditions. The representative Heck reaction between iodobenzene (**2a**) and an excess of methyl acrylate (**3a**) was therefore carried out in DMF/H₂O (4:1) (0.2 M with respect to **2a**) with triethylamine (TEA) as the base (Table 1, entries 1 and 2).

Under these conditions, the catalysts could be recycled successfully for two cycles with no loss of their catalytic efficiency.

Table 1. Screening of the optimal reaction conditions in the Heck coupling of iodobenzene (**2a**) and methyl acrylate (**3a**).^a

						
2a	3a			4a		
Entry	Medium	Cat.	Base (eq.)	T (°C)	t (h)	Conv (%) ^b

(**2a** molarity)

1	DMF/H ₂ O (4:1)	1a	TEA	90	21	100
	(0.2 M)		(2.0)			
2	DMF/H ₂ O (4:1)	1b	TEA	90	21	100
	(0.2 M)		(2.0)			
3	DMF/H ₂ O (4:1)	1a	PS-TEA	90	30	95
	(0.2 M)		(2.0)			
4	DMF/H ₂ O (4:1)	1b	PS-TEA	90	30	100
	(0.2 M)		(2.0)			
5	DMF/H ₂ O (4:1)	1b	PS-TEA	90	30	100
	(1 M)		(2.0)			
6	Toluene (1 M)	1b	PS-TEA	90	30	-
			(2.0)			
7	<i>i</i> -PrOAc (1 M)	1b	PS-TEA	90	30	-
			(2.0)			
8	H ₂ O (1 M)	1b	PS-TEA	90	30	78
			(2.0)			
9	EtOH az.(1 M)	1b	PS-TEA	70	30	11
			(2.0)			
10	CH ₃ CN (1 M)	1b	PS-TEA	70	30	90
			(2.0)			
11	CH ₃ CN/H ₂ O az. (1 M)	1b	PS-TEA	70	36	100
			(2.0)			
12	CH ₃ CN/H ₂ O az. (1 M) ^c	1b	PS-TEA	70	36	100
			(1.5)			
13	CH ₃ CN/H ₂ O az. (1 M) ^c	1b	PS-TEA	70	36	94
			(1.0)			

14	CH ₃ CN/H ₂ O az. 1b	PS-TEA	130	2	100
	(1 M) ^c	(1.5)			

^a**2a** (1.0 mmol), **3a** (1.5 mmol). ^bConversion of **2a** to **4a** is measured by GLC analyses, the remaining material is unreacted **2a**. ^c**2a** (1.0 mmol), **3a** (1.2 mmol).

According to our plan and in order to simplify the work-up procedure towards a more efficient isolation of the product, we investigated the use a heterogeneous base, namely diethylaminomethyl-polystyrene (PS-TEA), which can trap the hydriodic acid and can be removed by simple filtration, therefore making possible the isolation of the final product without any purification process. The use of PS-TEA in 4:1 DMF/water mixture gave encouraging results (Table 1, entries 3 and 4) and complete conversion could be achieved also at higher concentration of the reactants (Table 1, entry 5 vs 4). This is an interesting outcome in view of our plan to define a waste-minimized protocol. Indeed, this experiment proved that is possible to use the easily removable solid base and a smaller amount of medium reaching satisfactory results.

Considering their comparable efficiency, investigation was continued using only catalyst **1b**, which showed a slightly higher activity (Table 1, entries 4 vs 3).

At this point we proceeded to the screening of safer media^{13,14} to be used as alternative to DMF. Toluene and *i*-PrOAc gave no reaction, proving that aqueous media are necessary for the efficiency of the process (Table 1, entries 6 and 7).

Acetonitrile gave comparable results with respect to DMF/water mixture, but needed slightly longer reaction times to reach complete conversion of **2a** (Table 1, entry 10).

The use of sole water (Table 1, entry 8) as medium gave poorer results confirming the need of combined organic/aqueous media to reach highest efficiency. Therefore, we focused our

attention to potentially recoverable media such as aqueous ethanol or acetonitrile azeotropes (96% and 84%, respectively). In particular, the use of aqueous azeotropes is truly interesting because, while they combine the properties of organic and aqueous media, they also have the potential of being recovered at the end of the reaction and reused without increasing the amount of waste.

In the Heck coupling we obtained poor results when EtOH/water azeotrope was used (Table 1, entry 9). Despite the lower reaction temperature, encouraging results were obtained with acetonitrile/water azeotrope as medium (Table 1, entries 11-14). In fact, quantitative conversion of **2a** to **4a** was obtained in 36 h at 70 °C. The aqueous acetonitrile azeotrope is a promising alternative to DMF, since it can be removed by distillation at ca. 75 °C and be efficiently reused. Moreover, according to solvent selection guide, CH₃CN is an acceptable solvent and its use as DMF replacement is recommended.^{13,14}

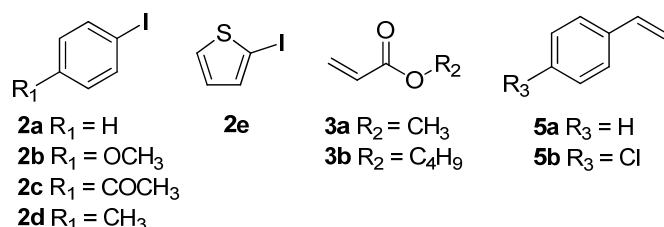
Afterwards, we screened different reaction conditions, using various amounts of PS-TEA and acrylate **3a**, in order to reduce the reagents excess. In addition, we have also measured the Pd content into isolated product **4a** by ICP (Inductively Coupled Plasma) analyses. We found that in the product **4a** isolated from the reaction in batch at 70 °C (Table 1 entry 12) palladium content was 14 ppm. This value is acceptable but it does not meet the specification limits fixed for APIs at 5 ppm.²⁶

At this stage we also considered that the ability of the solid supports to quantitatively scavenge soluble palladium species strongly depends on the temperature and medium used.^{4,22} Indeed, the same reaction carried out at 130°C, which was complete in 2 hours (Table 1, entry 14), gave the product **4a** with only 4 ppm of palladium content (ICP analyses) which meets the specification limit of 5 ppm.

The reaction conditions shown in Table 1, entry 14 using 1.5 equiv. of the supported base, 1.2 equiv. of methyl acrylate (**3a**) and 130 °C of reaction temperature were adopted as the optimal conditions for the subsequent experiments.

Several aryl iodides **2a-e** were reacted with acrylates **3a-b** (Table 2) and styrenes **5a-b** (Table 3) using the optimized batch conditions and obtaining from high to quantitative yields (Table 2 and 3). The substrates reacted are represented in Figure 2.

Figure 2. Substrates screened in the Heck reaction under optimized conditions.



In the case of 2-iodothiophene (**2e**) longer reaction times were needed but excellent results could be anyway obtained (Table 2, entries 9 and 10).

When styrenes **5a-b** were employed longer reaction times were needed to achieve quantitative conversions. Since the styrene products **6a-h** were less soluble in the acetonitrile azeotrope, with respect to the cinnamates **4a-l**, more diluted conditions were adopted (1.5 mL vs 1.0 mL of medium), in order to allow an easier recovery of the products. In some cases, a small amount of the *gem*-product **7a-h** was detected. Eventually we observed a small amount (below 2 %) of homocoupling product in the reaction between 4'-iodoacetophenone (**2c**) and 4-chlorostyrene (**5b**) (Table 3, entry 7) and therefore in this case the product **6g** was purified by column chromatography.

Table 2. Heck reaction between aryl iodides **2a-e** and alkyl acrylates **3a-b**.^a

Entry	Product	Ar	R	Yield (%) ^b
1	4a	Ph	CH ₃	74
2	4b	4-OCH ₃ - C ₆ H ₄	CH ₃	99
3	4c	4'-COCH ₃ - C ₆ H ₄	CH ₃	96
4	4d	4-CH ₃ - C ₆ H ₄	CH ₃	98
5	4e^c	Ph	<i>n</i> -Bu	99
6	4f^c	4-OCH ₃ - C ₆ H ₄	<i>n</i> -Bu	87
7	4g^c	4'-COCH ₃ - C ₆ H ₄	<i>n</i> -Bu	97
8	4h^c	4-CH ₃ -Ph	<i>n</i> -Bu	92
9	4i^d	2-iodothiophene	CH ₃	85
10	4j^{c d}	2-iodothiophene	<i>n</i> -Bu	80

^aReaction conditions: aryl iodide **2a-e** (1.0 mmol), alkyl acrylate **3a-b** (1.2 eq), PS-TEA (1.5 eq), CH₃CN/H₂O az. (1 mL), 130 °C, 2 h. ^bIsolated yield of the pure product after filtration of the reaction mixture and without any further purification step. ^c1 eq of butyl acrylate **3b** was used.

^dThe reaction was carried out for 16 hours to achieve complete conversion.

Table 3. Heck reaction between aryl iodides **2a-d** and styrenes **5a-b**.^a

Entry	Prod.	R ₁	R ₂	Yield (%) ^b	6/7^c
1	6a	Ph	Ph	95	6a
2	6b	4-OCH ₃ -C ₆ H ₄	Ph	98	6b
3	6c	4'-COCH ₃ -C ₆ H ₄	Ph	96	6c
4	6d	4-CH ₃ -C ₆ H ₄	Ph	98	6d
5	6e	Ph	4-CH ₃ -Ph	92	6e
6	6f	Ph	4-OCH ₃ -C ₆ H ₄	87	6f
7	6g	Ph	4'-COCH ₃ -C ₆ H ₄	97	6g
8	6h	Ph	2-iodothiophene	85	6h
9	7a	Ph	Ph	95	7a
10	7b	4-OCH ₃ -C ₆ H ₄	Ph	98	7b
11	7c	4'-COCH ₃ -C ₆ H ₄	Ph	96	7c
12	7d	4-CH ₃ -C ₆ H ₄	Ph	98	7d
13	7e	Ph	4-CH ₃ -Ph	92	7e
14	7f	Ph	4-OCH ₃ -C ₆ H ₄	87	7f
15	7g	Ph	4'-COCH ₃ -C ₆ H ₄	97	7g
16	7h	Ph	2-iodothiophene	85	7h

1	6a	H	H	72	95:5
2	6b	4-OCH ₃	H	72	97:3
3	6c	4'-COCH ₃	H	95	92:8
4	6d	4-CH ₃	H	79	95:5
5	6e	H	4-Cl	91	92:8
6	6f	4-OCH ₃	4-Cl	98	90:10
7	6g	4'-COCH ₃	4-Cl	83 ^d	97:3
8	6h	4-CH ₃	4-Cl	96	89:11

^aReaction conditions: aryl iodide **2** (1.0 mmol), styrene **5** (1.0 eq), PS-TEA (1.5 eq), CH₃CN/H₂O az. (1.5 mL). ^b Isolated yield of the clean mixture of products **6/7** obtained after filtration and without any further purification step. ^cDetermined by GLC or ¹HNMR analyses. ^dAfter column chromatography purification.

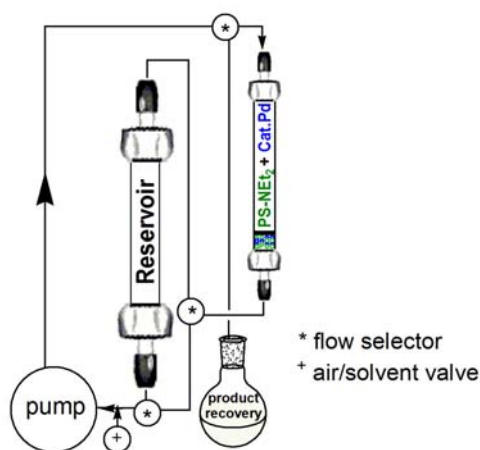
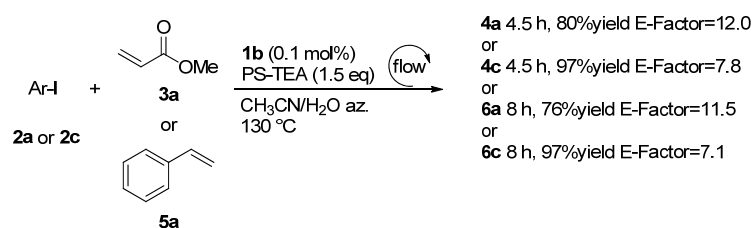
In batch, the recovery of the catalyst is impossible since it cannot be separated from the supported base after filtration. Therefore, to recover the catalyst it is also necessary to recover and regenerate the solid base and verify that this treatment does not affect the catalyst chemical integrity and efficiency.

These aspects could not be properly investigated under batch conditions due to several and obvious practical issues that hamper the quantitative recovery of the solid mixture of catalyst **1b** and PS-TEA base. It should be noticed that mechanical stirring causes the crunching of the solid making its recovery tedious and not reproducible at smaller and mostly at a larger scale.

We have recently focused the attention on the use of flow technology as an alternative efficient stirring method able to preserve the efficiency of a heterogeneous catalytic system and minimize waste.⁴⁰ In this context, to recover the mixture of catalyst and solid base we decided to apply the flow approach which may allow to preserve the physical integrity of the solid materials during all the stages of the process and simplify their recovery and reuse.

We have defined a flow protocol by charging a mixture of the catalyst **1b** and the supported base PS-TEA (1.5 equiv) in a stainless-steel HPLC column, while the reactants solution was charged in another glass column, acting as the reservoir (Scheme 1).

Scheme 1. Schematic flow reactor for the representative preparation of **4a**, **4c**, **6a**, **6c**.



All the equipment was connected, by using the appropriate tubes and valves, to a pump and installed into a thermostated box (not shown in Scheme 1 for clarity). After setting the temperature at 130 °C, the reaction mixture was cyclically pumped through the columns at a 2.0 mL/min flow rate for the time required to obtain quantitative conversion.

As shown in Table 4, in the first run 4.5 hours were required to achieve reaction completion. The column containing the PS-TEA and catalyst was then cyclically washed with a solution of TEA in acetonitrile/water azeotrope (1.5 equiv of TEA with respect to the supported base, 2

mL/min, 30 min) to remove the hydriodic acid formed during the reaction and regenerate the amine. The column was then cyclically washed with some azeotrope (2 mL/min, 30 min) to remove residual TEA.

After this treatment a second batch of reactants was charged in the reservoir and quantitative conversion to product **4a** was achieved again (Table 4, entry 2) in only 3 hours.

The shortening of the reaction time required to achieve complete conversion of the aryl iodide in the second run had already been observed before and was attributed to an increase in Pd(0) content in the catalytic material, likely due to an in situ reduction, which was confirmed by XPS (X-ray Photoelectron Spectroscopy).³⁶ Anyway, in this case it was not possible to determine the Pd(0) content of the catalyst after use, since it is dispersed into the large amount of solid base and cannot be separated from it. In these conditions Pd(0) species cannot be detected at XPS analyses due to the very low Pd content of the overall mixture.

The reuse of the catalyst was repeated for 4 representative runs (Table 4, entries 1-4), achieving a TON of ca. 4000 and a TOF of ca. 0.08 and further recycles may clearly lead to higher values.

The CH₃CN aqueous azeotrope used in the reaction was distilled off and recovered with a high purity (GLC analysis), totally comparable to the starting azeotropic mixture, thus being reusable without affecting the reaction yield.

After performing 4 consecutive runs, no apparent activity loss was observed and the products obtained after each cycle of the flow protocol were subjected to ICP analyses. A Pd content of ca. 4 ppm was found in all of them (see Table 4).

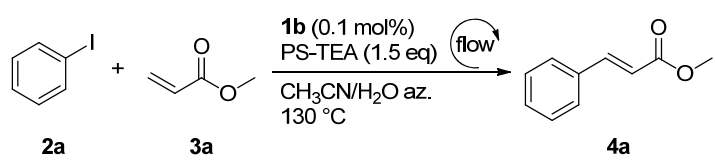
To confirm the results obtained in terms of residual palladium into the product from the reaction at 70 °C, we realized another flow protocol, carrying out the reaction at 70 °C (Table 4, entries 5 and 6).

We achieved complete conversion of iodobenzene **2a** after 30 hours of reaction time (Table 4 entry 5). The solid base was regenerated through the same procedure described above, in order to perform a second cycle. The recycling was successful and product **4a** was obtained after 20 hours of reaction (Table 4, entry 6), showing again the phenomenon of the reduction of reaction time.

Both the products from the reaction under flow conditions at 70 °C were isolated and subjected to ICP analyses, confirming the palladium content of ca. 14 ppm observed in the corresponding batch protocol (Table 1, entry 12).

The flow procedure at 130 °C was extended to other representative cases (see Scheme 1) always obtaining comparable results in terms of yield and Pd content into the products (< 5 ppm).

Table 4. Reusability of the catalyst in flow reactor for the representative reaction to methyl cinnamate (**4a**).^a

				
Entry	Cycle	Time (h)	Yield (%) ^b	Pd content in 4a (ppm) ^c
1	1	4.5	80	4.5
2	2	3	90	4.3

3	3	3	88	4.2
4	4	3	89	4.3
5 ^d	1	30	75	14.2
6 ^d	2	20	80	14.8

^aIodobenzene **2a** (50 mmol), methyl acrylate **3a** (60 mmol), PS-TEA (1.5 equiv), medium (50 mL). ^bIsolated yield of the pure product after filtration of the reaction mixture and without any other purification step. ^cPd-content into product **4a** measured by ICP analyses. ^d70°C.

To evaluate the sustainability of our protocol, we calculated the E-Factor³¹ values of both the batch and flow protocols in acetonitrile azeotrope. It should be pointed out that these processes cannot be properly compared, since in batch conditions the heterogeneous base/catalyst mixture cannot be actually recovered and recycled and therefore must be accounted as waste (see SI for E-factor calculation of PS-TEA). Therefore, in the case of the preparation of methyl cinnamate (**4a**), for the batch protocol a value of 11.5 was obtained without considering the waste for PS-TEA preparation and raises up to 151.2 when waste related to PS-TEA is accounted.

For the corresponding flow protocol the E-Factor value is 12.0, which includes the recovery and reuse of heterogeneous PS-TEA and catalysts after reactivation of the base with fresh TEA. This is an important feature proving the effectiveness of the flow approach, since it allowed us to preserve a high-value material (the PS-TEA/catalyst mixture) maintaining a low amount of waste.

For comparative purpose, we calculated the E-Factor for the batch protocol in DMF/water mixture finding a much higher value (> 3600) with respect to our batch and flow protocols. This value is mainly affected by the need of purification steps, i.e. extraction and column chromatography and by the use of an unrecoverable reaction medium.

In conclusion, in this contribution we have reported our protocol based on the use of a SILLP-based Pd catalyst (10 wt%) in the Heck reaction. We substituted a highly toxic dipolar aprotic solvent, such as DMF, commonly used in Heck cross-coupling reaction, with a greener medium, i.e. the acetonitrile/water azeotrope. We consider that azeotropes are promising reaction media, since they are recoverable and reusable allowing the reduction of the waste production.

The possibility of avoiding wasteful work up procedures was given by the use of a supported base, which could be regenerated at the end of the reaction.

The use of the flow conditions allowed to define a protocol with minimal production of waste. The flow approach proved to be an efficient technological solution to preserve the physical integrity of the catalyst and also to allow its easy recovery and recycle. In addition, with this technique it is possible to optimize the use of the solvent required in the process and minimize waste.

The combination of the flow technique and sustainable reaction conditions leads to a substantial reduction of the waste production, as proved by the low E-factor value of 12.

Finally, by adjusting the reaction conditions we were able to limit the amount of leached palladium in the final product, thus matching the specification limits of 5 ppm for API.

ASSOCIATED CONTENT

Supporting Information. For full characterization of compounds and copies of the ^1H and ^{13}C NMR spectra see Electronic Supporting Information (ESI). This information is available free of charge via the Internet at <http://pubs.acs.org/>.

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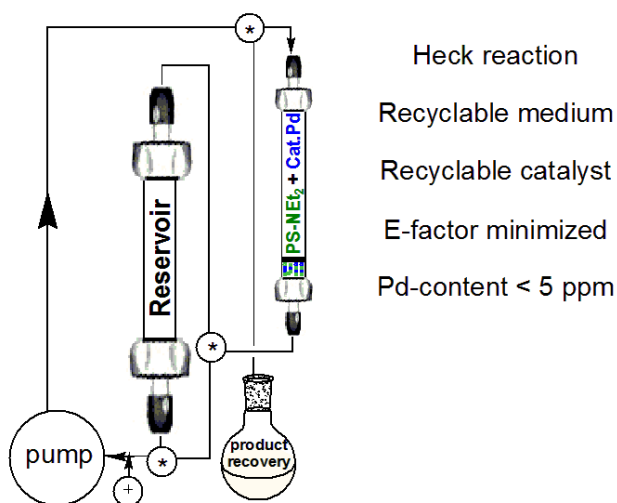
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TOC graphic

An E-factor minimized protocol for a sustainable and efficient Heck reaction in flow

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A highly sustainable protocol for Heck coupling featuring extremely low E-factor values. The flow technology allowed the recycle of solvent and catalyst with minimum palladium leaching.