An E-Factor Minimized Protocol for a Sustainable and Efficient Heck Reaction in Flow

Chiara Petrucci,[†] Giacomo Strappaveccia,[†] Francesco Giacalone,[‡] Michelangelo Gruttadauria,[‡] Ferdinando Pizzo,[†] and Luigi Vaccaro*,[†]

[†]CEMIN - Dipartimento di Chimica, Biologia e Biotecnologie, Università di Perugia, Via Elce di Sotto, 8, Perugia, Italia

[‡]Dipartimento di Scienze e Tecnologie Biologiche, Chimiche e Farmaceutiche (STEBICEF) Sez. di Chimica, Università di Palermo, Viale delle Scienze s/n, Ed. 17, 90128 Palermo, Italy

S *Supporting Information*

ABSTRACT: A highly sustainable and waste-minimized protocol for Heck coupling has been defined. Optimal conditions have been defined by exploiting a heterogeneous catalyst based on supported ionic liquid-like phases featuring high Pd loading (10 wt %) and by optimizing its efficiency in a recoverable green reaction medium (acetonitrile/water azeotrope). Pure products **4a−l** and **6a−h** 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 flow technology, the selected heterogeneous base and Pd catalyst have been fully recovered and reused, and minimum palladium leaching allowed for isolation of the final products with low residual palladium content (<5 ppm) without any purification step.

Heck reaction
Recyclable medium
Recyclable catalyst
E-factor minimized
Pd-content < 5 ppm

KEYWORDS: *Azeotrope media, Heck−Mizoroki reaction, Heterogeneous catalysis, Waste minimization, Flow chemistry*
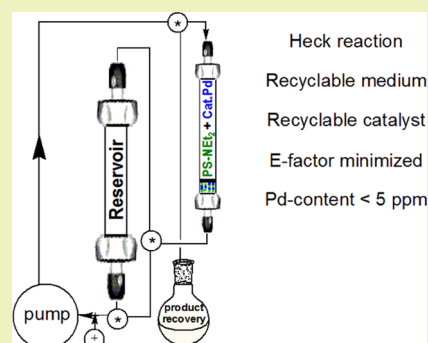
■ INTRODUCTION

The palladium-catalyzed vinylic hydrogen substitution reaction by an aryl, alkenyl, or benzyl halide was discovered independently by Heck and Mizoroki in the early 1970s.[1] Today, the Heck cross-coupling reaction is a very important synthetic tool that enables 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, research is focused on the definition of protocols featuring the use of efficient, recyclable, and reusable catalytic systems and 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 oxides,[6] and on functionalized silica.[7,8] Palladium nanoparticles (PdNPs) stabilized by renewable cellulose and sugars also have been recently reported.[9,10]

The design of recyclable catalysts for the Heck reaction is not trivial because 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 composition of 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′*-dimethylformamide (DMF) and *N*-methylpyrrolidinone (NMP),[13,14] whereas a great attention should be paid to the alternative safer media.[15] In addition, the Heck reaction may proceed through a "release and catch" mechanism[5,16−22] and therefore, much attention must be paid to the amount of palladium leached into the product. It should be also noted 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

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]

An effective strategy to minimize waste is based on the direct alkenylation of simple arenes catalyzed by homogeneous Pd or Rh catalysts.[33] This synthetic approach is highly attractive but also very challenging, and available protocols require the use of a large excess of arene, long reaction times, and often feature poor selectivity.

Recently, we have contributed to the development of sustainable approaches to cross-coupling reactions by using green reaction media and flow conditions and by preparing novel immobilized palladium nanoparticles based on imidazolium salts supported on silica gel (Figure 1).[34−36] The resulting

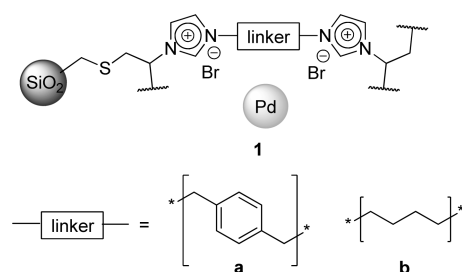Figure 1. Structures of the SILLP Pd catalysts 1.

material belongs to the category of Supported Ionic Liquid-Like Phases (SILLPs), features high Pd loading (10 wt %), and is proved to be highly efficient, but also recoverable and reusable, in the Suzuki−Miyaura reaction both under batch[34,35] and flow conditions.[36] Flow technique allowed a very high environmental efficiency to be reached by using our SILLP Pd catalyst in ethanol/water azeotrope as the medium.[36]

Although the reaction was carried out by using two separate columns containing the base and the catalyst, respectively, we observed a high catalytic efficiency. This can be ascribed to the known "release and catch" mechanism,[16−22] in which the supported palladium catalyst serves as a reservoir for active Pd species that are dissolved from the solid catalyst.[37−39] The active Pd species can move through the apparatus and then are effectively scavenged by the ionic liquid-like support.[40] As a result, the catalyst is still active and recyclable.[34−36]

Quaternary ammonium salts are responsible for the stabilization of the metal nanoparticles,[41−43] which may result in a low degree of leaching. Then, acting also as scavenger of the soluble metal species, they make the "release and catch" mechanism possible.

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]

In this contribution, we have developed a novel and highly sustainable protocol for 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, to reach this goal, 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 workup and/or column chromatography purifications.

Optimization of the reaction conditions therefore has been performed in recoverable and sustainable azeotropic mixtures avoiding the use of undesirable toxic dipolar aprotic solvents.[13,14] In combination, our strategy has focused on the use of an immobilized base with the intention of simplifing the workup procedures and allowing the isolation of the final product without additional purification steps. Initially, catalysts 1 (Figure 1) were used in the representative Heck reaction of iodobenzene (2a) and methyl acrylate (3a), and 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. GLC analyses were performed by using a Hewlett-Packard HP 5890A equipped with a capillary column DB-35MS (30 m, 0.53 mm), FID detector, and hydrogen as the 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 (^{1}H 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, Omnifit Glass Column as reservoir, and Supelco HPLC column blank as the 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 equiv) in toluene at 100 °C for 24 h. 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 Heck Reaction in CH$_3$CN/H$_2$O Azeotrope under Batch Conditions. To a solution of aryl iodide 2a−e (1 mmol) and alkene 3a−b or 5a−b (1.2−1.0 mmol) in CH$_3$CN/H$_2$O 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 product (4a−h or 6a−h) is isolated by distillation of the azeotrope.

Heck Reaction to Methyl Cinnamate (4a) under Flow Conditions at 130 °C. A premixed mixture of iodobenzene (2a) (50 mmol, 5.60 mL) and methyl acrylate (3a) (60 mmol, 5.40 mL) in CH$_3$CN/H$_2$O az. (50 mL) was charged into a glass column functioning as a reservoir. Diethylaminomethyl−polystyrene (∼4 mmol/g, 75 mmol, 18.75 g) and catalyst 1 (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 (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, CH$_3$CN/H$_2$O azeotrope (3 mL × 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

2814

dx.doi.org/10.1021/sc500584y | ACS Sustainable Chem. Eng. 2014, 2, 2813−2819

cyclically pumped through the base/catalyst column in two portions to remove residual TEA.

E-Factor Calculation for Batch Reaction in CH₃CN/Water 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 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 Batch Reaction in DMF/Water (4:1). Reference for the procedure: Pavia, C.; Giacalone, F.; Bivona, L. A.; Salvo, A. M.; Petrucci, C.; Strappaveccia, G.; Vaccaro, L.; Aprile, C.; Gruttadauria, M. *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 Information.
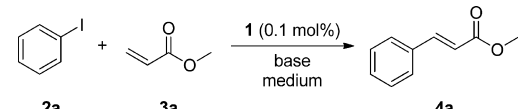
■ RESULTS AND DISCUSSION

We tested the activity of catalysts **1** (bis-imidazolium salt having a *p*-xylyl (**1a**) or linear C₄ (**1b**) linker[34]) 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.

According to our plan and in order to simplify the workup procedure toward 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 the 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 it 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 alternatives 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 the DMF/water mixture, but it needed slightly longer reaction times to reach complete conversion of **2a** (Table 1, entry 10).

Table 1. Screening of Optimal Reaction Conditions in Heck Coupling of Iodobenzene (2a) and Methyl Acrylate (3a)[a]

entry	medium (2a molarity)	cat.	base (eq)	T (°C)	time (h)	conv (%)[b]
1	DMF/H₂O (4:1) (0.2 M)	1a	TEA (2.0)	90	21	100
2	DMF/H₂O (4:1) (0.2 M)	1b	TEA (2.0)	90	21	100
3	DMF/H₂O (4:1) (0.2 M)	1a	PS-TEA (2.0)	90	30	95
4	DMF/H₂O (4:1) (0.2 M)	1b	PS-TEA (2.0)	90	30	100
5	DMF/H₂O (4:1) (1 M)	1b	PS-TEA (2.0)	90	30	100
6	Toluene (1 M)	1b	PS-TEA (2.0)	90	30	-
7	*i*-PrOAc (1 M)	1b	PS-TEA (2.0)	90	30	-
8	H₂O (1 M)	1b	PS-TEA (2.0)	90	30	78
9	EtOH az. (1 M)	1b	PS-TEA (2.0)	70	30	11
10	CH₃CN (1 M)	1b	PS-TEA (2.0)	70	30	90
11	CH₃CN/H₂O az. (1 M)	1b	PS-TEA (2.0)	70	36	100
12	CH₃CN/H₂O az. (1 M)[c]	1b	PS-TEA (1.5)	70	36	100
13	CH₃CN/H₂O az. (1 M)[c]	1b	PS-TEA (1.0)	70	36	94
14	CH₃CN/H₂O az. (1 M)[c]	1b	PS-TEA (1.5)	130	2	100

[a]**2a** (1.0 mmol), **3a** (1.5 mmol). [b]Conversion of **2a** to **4a** is measured by GLC analyses; the remaining material is unreacted **2a**. [c]**2a** (1.0 mmol), **3a** (1.2 mmol).

The use of sole water (Table 1, entry 8) as medium gave poorer results, confirming the need of combined organic/aqueous media to reach the 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 this 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 the medium (Table 1, entries 11−14). In fact, quantitative conversion of **2a** to **4a** was obtained in 36 h at 70 °C (Table 1, entry 12). The aqueous acetonitrile azeotrope is a promising alternative to DMF because it can be removed by distillation at about 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]

Afterward, 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 product **4a** isolated from

the reaction in batch at 70 °C (Table 1, entry 12), the 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 h (Table 1, entry 14), gave 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

Table 2. Heck Reaction between Aryl Iodides 2a–e and Alkyl Acrylates 3a–b[a]

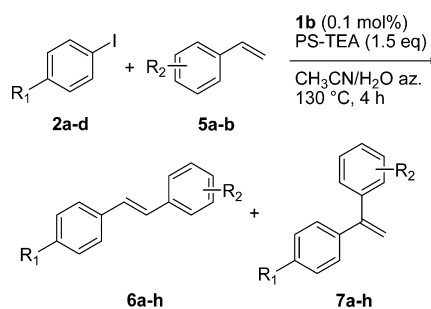| entry	product	Ar	R	yield (%)[b]
1	**4a**	Ph	CH_3	74
2	**4b**	4-OCH$_3$- C$_6$H$_4$	CH_3	99
3	**4c**	4′-COCH$_3$- C$_6$H$_4$	CH_3	96
4	**4d**	4-CH$_3$- C$_6$H$_4$	CH_3	98
5	**4e**[c]	Ph	n-Bu	99
6	**4f**[c]	4-OCH$_3$- C$_6$H$_4$	n-Bu	87
7	**4g**[c]	4′-COCH$_3$- C$_6$H$_4$	n-Bu	97
8	**4h**[c]	4-CH$_3$- C$_6$H$_4$	n-Bu	92
9	**4i**[d]	2-iodothiophene	CH_3	85
10	**4j**[c,d]	2-iodothiophene	n-Bu	80

[a]Reaction conditions: aryl iodide **2a–e** (1.0 mmol), alkyl acrylate **3a–b** (1.2 equiv), PS-TEA (1.5 equiv), CH$_3$CN/H$_2$O az. (1 mL), 130 °C, and 2 h. [b]Isolated yield of the pure product after filtration of the reaction mixture and without any further purification step. [c]1 equiv of butyl acrylate **3b** was used. [d]Reaction was carried out for 16 h to achieve complete conversion.

batch conditions and obtaining after 2 h from high to quantitative yields (Tables 2 and 3). The substrates reacted are represented in Figure 2. In the case of 2-iodothiophene (**2e**), longer reaction times were needed, but excellent results could be obtained (Table 2, entries 9 and 10).

When styrenes **5a–b** were employed, longer reaction times were needed to achieve quantitative conversions. Because the stylbene 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′-iodoaceto-phenone (**2c**) and 4-chlorostyrene (**5b**) (Table 3, entry 7), and therefore, in this case, product **6g** was purified by column chromatography.

In batch, the recovery of the catalyst is impossible because 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

Table 3. Heck Reaction between Aryl Iodides 2a–d and Styrenes 5a–b.[a]

entry	product	R$_1$	R$_2$	yield (%)[b]	6/7[c]
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

[a]Reaction conditions: aryl iodide **2** (1.0 mmol), styrene **5** (1.0 equiv), PS-TEA (1.5 equiv), CH$_3$CN/H$_2$O az. (1.5 mL) 130 °C, 4 h. [b]Isolated yield of the clean mixture of products 6/7 obtained after filtration and without any further purification step. [c]Determined by GLC or ¹HNMR analyses. [d]After column chromatography purification.

2a R$_1$ = H
2b R$_1$ = OCH$_3$
2c R$_1$ = COCH$_3$
2d R$_1$ = CH$_3$

2e

3a R$_2$ = CH$_3$
3b R$_2$ = C$_4$H$_9$

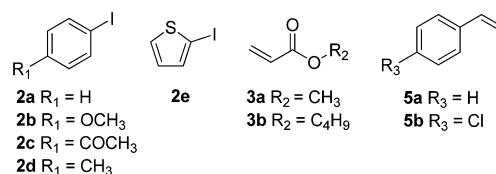**5a** R$_3$ = H
5b R$_3$ = Cl

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

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 for preserving 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).

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

Scheme 1. Schematic Flow Reactor for Representative Preparation of 4a, 4c, 6a, 6c
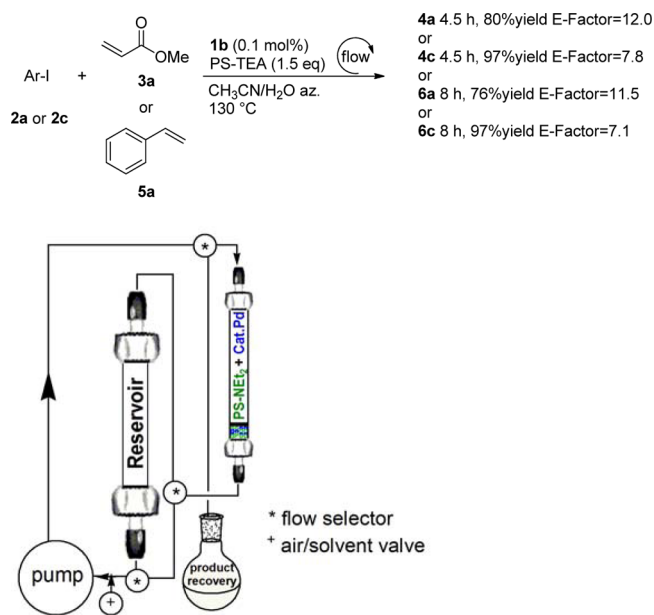
pumped through the columns at a 2.0 mL/min flow rate for the time required to obtain quantitative conversion.

As shown in Table 4, in the first run, 4.5 h were required to achieve reaction completion. The column containing the PS-

Table 4. Reusability of Catalyst in Flow Reactor for Representative Reaction to Methyl Cinnamate (4a)[a]
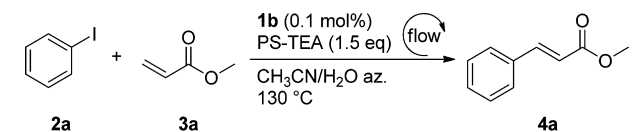
entry	cycle	time (h)	yield (%)[b]	Pd content in 4a (ppm)[c]
1	1	4.5	80	4.5
2	2	3	90	4.3
3	3	3	88	4.2
4	4	3	89	4.3
5[d]	1	30	75	14.2
6[d]	2	20	80	14.8

[a]Iodobenzene 2a (50 mmol), methyl acrylate 3a (60 mmol), PS-TEA (1.5 equiv), medium (50 mL). [b]Isolated yield of the pure product after filtration of the reaction mixture and without any other purification step. [c]Pd-content into product 4a measured by ICP analyses. [d]70 °C.

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 hydroiodic 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 h.

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 Photo-electron Spectroscopy).[36] In this case, it was not possible to determine the Pd(0) content of the catalyst after use because 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 by XPS analyses due to the very low Pd content of the overall mixture. The reuse of the catalyst was repeated for four representative runs (Table 4, entries 1−4), achieving a TON of about 4000 and a TOF of about 0.08 s^{-1}, and further recycles may clearly lead to higher values.

The CH$_3$CN 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 four 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 about 4 ppm was found in all of them (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 h 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 h 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 a palladium content of about 14 ppm observed in the corresponding batch protocol (Table 1, entry 12). The flow procedure at 130 °C was extended to other representative cases (Scheme 1) always obtaining comparable results in terms of yield and Pd content into the products (<5 ppm).

To evaluate the sustainability of our protocol, we calculated the E-Factor[31] values of both the batch and flow protocols in acetonitrile azeotrope. It should be pointed out that these processes cannot be properly compared because in batch conditions the heterogeneous base/catalyst mixture cannot be actually recovered and recycled and therefore must be accounted for as waste (see Supporting Information 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.

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

For comparative purpose, we calculated the E-factor for the batch protocol in a 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, that is, 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 the Heck

2817

dx.doi.org/10.1021/sc500584y | ACS Sustainable Chem. Eng. 2014, 2, 2813–2819

cross-coupling reaction, with a greener medium, that is, acetonitrile/water azeotrope. We consider that azeotropes are promising reaction media because they are recoverable and reusable allowing for reduction of the waste production.

The possibility of avoiding wasteful workup procedures was given by the use of a supported base, which could be regenerated at the end of the reaction. The use of flow conditions allowed us 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 for 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

Full characterization of compounds and copies of the ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Fax: +39 075 5855560. Tel: +39 075 5855541. E-mail: luigi. vaccaro@unipg.it.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) Heck, R. F.; Nolley, J. P., Jr. Palladium-catalyzed vinylic hydrogen substitution reactions with aryl, benzyl, and styryl halides. *J. Org. Chem.* **1972**, *37*, 2320−2322.

(2) Toborg, C.; Beller, M. Recent applications of palladium-catalyzed coupling reactions in the pharmaceutical, agrochemical, and fine chemical industries. *Adv. Synth. Catal.* **2009**, *351*, 3027−3043.

(3) Negishi, E., Ed.; *Handbook of Organopalladium Chemistry for Organic Synthesis*, Vol. 1; John Wiley & Sons: New York, 2002.

(4) Kohler, K.; Heidenreich, R. G.; Krauter, J. G. E.; Pietsch, J. Highly active palladium/activated carbon catalysts for heck reactions: Correlation of activity, catalyst properties, and Pd leaching. *Chem.— Eur. J.* **2002**, *8*, 622−631.

(5) Zhao, F.; Bhanage, B. M.; Shirai, M.; Arai, M. Heck reactions of iodobenzene and methyl acrylate with conventional supported palladium catalysts in the presence of organic and/or inorganic bases without ligands. *Chem.—Eur. J.* **2000**, *6*, 843−848.

(6) Prockl, S. S.; Kleist, W.; Gruber, M. A.; Kohler, K. In situ generation of highly active dissolved palladium species from solid catalysts—A concept for the activation of aryl chlorides in the Heck reaction. *Angew. Chem., Int. Ed.* **2004**, *43*, 1881−1882.

(7) Molnar, A.; Papp, A.; Miklos, K.; Forgo, P. Organically modified Pd−silica catalysts applied in Heck coupling. *Chem. Commun.* **2003**, 2626−2627.

(8) Khalafi-Nezhad, A.; Panahi, F. Size-controlled synthesis of palladium nanoparticles on a silica−cyclodextrin substrate: A novel palladium catalyst system for the Heck reaction in water. *ACS Sustainable Chem. Eng.* **2014**, *2*, 1177−1186.

(9) Camp, J. E.; Dunsford, J. J.; Cannons, E. P.; Restorick, W. J.; Gadzhieva, A.; Fay, M. W.; Smith, R. J. Glucose-derived palladium(0) nanoparticles as in situ-formed catalysts for Suzuki−Miyaura cross-coupling reactions in isopropanol. *ACS Sustainable Chem. Eng.* **2014**, *2*, 500−505.

(10) Rezayat, M.; Blundell, R. K.; Camp, J. E.; Walsh, D. A.; Thielemans, W. Green one-step synthesis of catalytically active palladium nanoparticles supported on cellulose nanocrystals. *ACS Sustainable Chem. Eng.* **2014**, *2*, 1241−1250.

(11) Yin, L.; Liebscher, J. Carbon−carbon coupling reactions catalyzed by heterogeneous palladium catalysts. *Chem. Rev.* **2007**, *107*, 133−173.

(12) Beletskaya, P.; Cheprakov, A. V. The Heck reaction as a sharpening stone of palladium catalysis. *Chem. Rev.* **2000**, *100*, 3009−3066.

(13) Henderson, R. K.; Jiménez-González, C.; Constable, D. J. C.; Alston, S. R.; Inglis, G. G. A.; Fisher, G.; Sherwood, J.; Binks, S. P.; Curzons, A. D. Expanding GSK's solvent selection guide − Embedding sustainability into solvent selection starting at medicinal chemistry. *Green Chem.* **2011**, *13*, 854−862.

(14) Alfonsi, K.; Colberg, J.; Dunn, P. J.; Fevig, T.; Jennings, S.; Johnson, T. A.; Kleine, H. P.; Knight, C.; Nagy, M. A.; Perry, D. A.; Stefaniak, M. Green chemistry tools to influence a medicinal chemistry and research chemistry based organisation. *Green Chem.* **2008**, *10*, 31−36.

(15) Parker, H. L.; Sherwood, J.; Hunt, A. J.; Clark, J. H. Cyclic carbonates as green alternative solvents for the Heck reaction. *ACS Sustainable Chem. Eng.* **2014**, *2*, 1739−1742.

(16) Gruttadauria, M.; Giacalone, F.; Noto, R. "Release and catch" catalytic systems. *Green Chem.* **2013**, *15*, 2608−2618.

(17) Köhler, K.; Kleist, W.; Pröckl, S. S. Genesis of coordinatively unsaturated palladium complexes dissolved from solid precursors during Heck coupling reactions and their role as catalytically active species. *Inorg. Chem.* **2007**, *46*, 1876−1883.

(18) Phan, N. T. S.; van der Sluys, M.; Jones, C. W. On the nature of the active species in palladium catalyzed Mizoroki−Heck and Suzuki−Miyaura couplings − Homogeneous or heterogeneous catalysis, a critical review. *Adv. Synth. Catal.* **2006**, *348*, 609−679.

(19) Webb, J. D.; MacQuarrie, S.; McEleney, K.; Crudden, C. M. Mesoporous silica-supported Pd catalysts: An investigation into structure, activity, leaching and heterogeneity. *J. Catal.* **2007**, *252*, 97−109.

(20) MacQuarrie, S.; Horton, J. H.; Barnes, J.; McEleney, K.; Loock, H. P.; Crudden, C. M. Visual observation of redistribution and dissolution of palladium during the Suzuki−Miyaura reaction. *Angew. Chem., Int. Ed.* **2008**, *47*, 3279−3282.

(21) Richardson, J. M.; Jones, C. W. Strong evidence of solution-phase catalysis associated with palladium leaching from immobilized thiols during Heck and Suzuki coupling of aryl iodides, bromides, and chlorides. *J. Catal.* **2007**, *251*, 80−93.

(22) Burguete, M. I.; Garcia-Verdugo, E.; Garcia-Villar, I.; Gelat, F.; Licence, P.; Luis, S. V.; Sans, V. Pd catalysts immobilized onto gel-supported ionic liquid-like phases (g-SILLPs): A remarkable effect of the nature of the support. *J. Catal.* **2010**, *269*, 150−160.

(23) Horniakova, J.; Raja, T.; Kubota, Y.; Sugi, Y. Pyridine-derived palladium complexes immobilized on ordered mesoporous silica as catalysts for Heck-type reactions. *J. Mol. Catal. A: Chem.* **2004**, *217*, 73−80.

(24) Zhaoa, F.; Shirai, M.; Ikushima, Y.; Arai, M. The leaching and re-deposition of metal species from and onto conventional supported

palladium catalysts in the Heck reaction of iodobenzene and methyl acrylate in *N*-methylpyrrolidone. *J. Mol. Catal. A: Chem.* **2002**, *180*, 211−219.

(25) Dams, M.; Drijkoningen, L.; Pauwels, B.; Van Tendeloo, G.; De Vos, D. E.; Jacobs, P. A. Pd−zeolites as heterogeneous catalysts in Heck chemistry. *J. Catal.* **2002**, *209*, 225−236.

(26) The amount of Pd allowed is 5 ppm: *Note for Guidance on Specification Limits for Residues of Metal Catalysts*; European Agency for the Evaluation of Medicinal Products: London, December 17, 2002.

(27) Barbaras, D.; Brozio, J.; Johannsen, I.; Allmendinger, T. Removal of heavy metals from organic reaction mixtures: preparation and application of functionalized resins. *Org. Process Res. Dev.* **2009**, *13*, 1068−1079.

(28) Girgis, M. J.; Kuczynski, L. E.; Berberena, S. M.; Boyd, C. A.; Kubinski, P. L.; Scherholz, M. L.; Drinkwater, D. E.; Shen, X.; Babiak, S.; Lefebvre, B. Removal of soluble palladium complexes from reaction mixtures by fixed-bed adsorption. *Org. Process Res. Dev.* **2008**, *12*, 1209−1217.

(29) Chemistry- Developing Solutions in a Changing World. EuCheMS, 2011. http://www.euchems.eu/publications/policy-positions/roadmap-chemistry-developing-solutions-in-a-changing-world.html (accessed October 2014).

(30) Cabri, W.; Candiani, I. Recent developments and new perspectives in the Heck reaction. *Acc. Chem. Res.* **1995**, *28*, 2−7.

(31) Sheldon, R. A. Catalysis and pollution prevention. *Chem. Ind. (London)* **1997**, 12−15.

(32) Sheldon, R. A. The E factor: Fifteen years on. *Green Chem.* **2007**, *9*, 1273−1283.

(33) Dams, M.; De Vos, D. E.; Celen, S.; Jacobs, P. A. Toward waste-free production of Heck products with a catalytic palladium system under oxygen. *Angew. Chem., Int. Ed.* **2003**, *42*, 3512−3515.

(34) Gruttadauria, M.; Liotta, L. F.; Salvo, A. M. P.; Giacalone, F.; La Parola, V.; Aprile, C.; Noto, R. Multi-layered, covalently supported ionic liquid phase (mlc-SILP) as highly cross-linked support for recyclable palladium catalysts for the Suzuki reaction in aqueous medium. *Adv. Synth. Catal.* **2011**, *353*, 2119−2130.

(35) Pavia, C.; Giacalone, F.; Bivona, L. A.; Salvo, A. M.; Petrucci, C.; Strappaveccia, G.; Vaccaro, L.; Aprile, C.; Gruttadauria, M. Evidences of release and catch mechanism in the Heck reaction catalyzed by palladium immobilized on highly cross-linked-supported imidazolium salts. *J. Mol. Catal. A: Chem.* **2014**, *387*, 57−62.

(36) Pavia, C.; Ballerini, E.; Bivona, L. A.; Giacalone, F.; Aprile, C.; Vaccaro, L.; Gruttadauria, M. Palladium supported on cross-linked imidazolium network on silica as highly sustainable catalysts for the Suzuki reaction under flow conditions. *Adv. Synth. Catal.* **2013**, *355*, 2007−2018.

(37) Prechtl, M. H. G.; Scholten, J. D.; Dupont, J. Carbon−carbon cross coupling reactions in ionic liquids catalysed by palladium metal nanoparticles. *Molecules* **2010**, *15*, 3441−3461.

(38) Cassol, C. C.; Umpierre, A. P.; Machado, G.; Wolke, S. I.; Dupont, J. The role of Pd nanoparticles in ionic liquid in the Heck reaction. *J. Am. Chem. Soc.* **2005**, *127*, 3298−3299.

(39) Gaikwad, A. V.; Holuigue, A.; Thathagar, M. B.; ten Elshof, J. E.; Rothenberg, G. Ion- and atom-leaching mechanisms from palladium nanoparticles in cross-coupling reactions. *Chem.—Eur. J.* **2007**, *13*, 6908−6913.

(40) Buscemi, R.; Giacalone, F.; Orecchio, S.; Gruttadauria, M. Cross-linked imidazolium salts as scavengers for palladium. *ChemPlusChem.* **2014**, *79*, 421−426.

(41) Reetz, M. T.; Helbig, W.; Quaiser, S. A.; Stimming, U.; Breuer, N.; Vogel, R. Visualization of surfactants on nanostructured palladium clusters by a combination of STM and high-resolution TEM. *Science* **1995**, *267*, 367−368.

(42) Reetz, M. T.; Breinbauer, R.; Wanninger, K. Suzuki and Heck reactions catalyzed by preformed palladium clusters and palladium-nickel bimetallic clusters. *Tetrahedron Lett.* **1996**, *37*, 4499−4502.

(43) Calò, V.; Nacci, A.; Monopoli, A. Effects of ionic liquids on Pd-catalysed carbon−carbon bond formation. *Eur. J. Org. Chem.* **2006**, 3791−3802.

(44) Vaccaro, L.; Marrocchi, A.; Lanari, D.; Strappaveccia, G. Flow approaches towards sustainability. *Green Chem.* **2014**, *16*, 3680−3704.

(45) For examples of Pd(0) nanoparticles supported on immobilized quaternary ammonium salts as catalysts for the Heck reaction under flow conditions see (a) Mennecke, K.; Kirschning, A. Polyionic polymers − Heterogeneous media for metal nanoparticles as catalyst in Suzuki−Miyaura and Heck−Mizoroki reactions under flow conditions. *Beilstein J. Org. Chem.* **2009**, *5*, No. 21. (b) Nikbin, N.; Ladlow, M.; Ley, S. V. Continuous flow ligand-free Heck reactions using monolithic Pd [0] nanoparticles. *Org. Process Res. Dev.* **2007**, *11*, 458−462.