Research Article

Biomass Waste-Derived Pd−PiNe Catalyst for the Continuous-Flow Copper-Free Sonogashira Reaction in a CPME−Water Azeotropic Mixture

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ABSTRACT: Herein, we report on the development of a waste minimization/valorization methodology applied to the representative benchmark Sonogashira cross-coupling reaction performed in a continuous-flow reactor, featuring a continuous-flow downstream membrane organic/aqueous separator to recover medium and products with minimal waste. The protocol is based on the use of a biomass waste-derived heterogeneous Pd-based catalyst, which is obtained from the valorization of urban-waste pine needles (PiNe). In a circular economy approach, the PiNe biomass has been proven to be capable of producing an effective active carbon support for Pd nanoparticle immobilization. In addition, the catalyst has been utilized in an azeotropic mixture formed by industrial waste-derived cyclopentyl methyl ether (CPME) and water. Thanks to this combination and with the adoption of flow conditions, high yields of final target products could be accessed with high stability and durability of the catalyst. Final isolation of the products has been realized by setting an in-line liquid−liquid separator in flow, which has also allowed CPME recovery with a significant reduction of the waste generated. The protocol has been applied to the representative preparation of eniluracil, a GSK API.

KEYWORDS: waste valorization, waste minimization, waste-derived heterogeneous catalyst, circular economy, copper-free Sonogashira, continuous flow, CPME/water azeotrope
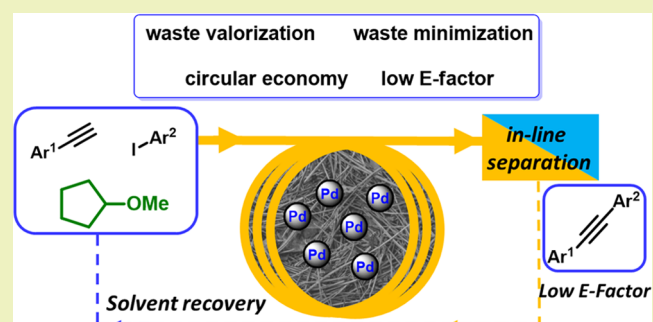
INTRODUCTION

Sonogashira cross-coupling is a widely useful synthetic tool allowing the introduction of an acetylenic moiety in a variety of molecular structures.[1−4] Since the seminal work by Sonogashira and Hagihara,[5] the protocol has been largely studied and improved by exploiting the use of inorganic or organic bases under homogeneous or heterogeneous conditions and in the presence of a wide range of reaction media.[6−15]

Among the metal catalysts, palladium is arguably the preferred choice for the promotion of Sonogashira cross-coupling reactions. In all cases, the need for its complete removal from products must be considered, and therefore, especially when homogeneous palladium catalytic systems are used, additional wasteful purification steps are necessary.

In recent decades, several heterogeneous palladium catalytic systems have been developed and proposed with the intention of not only simplifying the separation of the catalyst from the reaction mixtures but also realizing its effective reuse to minimize the loss of extremely precious palladium. Among the heterogeneous Pd-based catalysts used in the Sonogashira cross-coupling, Pd/C is an effective and preferred choice due to its thermal stability, low cost, and large availability.[16,17]

Our research program aims at developing efficient metal heterogeneous catalytic systems,[18−21] while we are also contributing to a circular economy approach working on biomass valorization.[22−25] Recently, we dedicated our attention to the valorization of urban waste and exploited biochar derived from local biomass as a viable alternative to carbonaceous supports for the preparation of Pd-based heterogeneous catalysts.

Biochar is abundant and can be a valuable means to dispose and add value to waste biomass. Biochar is a porous, high-carbon material produced from the conversion of renewable biomass. Importantly, its physical and chemical properties can be tuned depending on the conditions used for its preparation. As a result, a very wide range of functional carbon materials can be produced for different applications such as soil
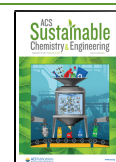
conditioning or adsorption/degradation of pollutants in water.[26,27] Despite its good advantages, biochar has arguably received scarce attention in the field of heterogeneous catalysis. Only very recently has sulfonated biochar been used for the production of biodiesel from waste oils, highlighting its potential as a catalyst.[28] It has also been proven that it may be effectively used as a surrogate for commercial activated carbon to stabilize metal nanoparticles.[29−31]

On the coast of central Italy and also in several other Mediterranean areas, pine needles represent a large portion of annoying urban waste that occupies large volumes and needs to be appropriately collected and burned for being disposed. New ways to transform this waste into a valuable product are desirable and may pave the route to a change in the local micro- or small-manufacturing opportunities.[32]

While aiming at the development of novel heterogeneous catalytic systems, it is always necessary to consider how its efficiency can be strongly affected by the solvent used as a medium during the catalytic tests. Accordingly, solvent selection represents a critical aspect also in the Sonogashira reaction, influencing not only the chemical efficiency but also and directly the waste produced. Harmful dipolar aprotic solvents such as dimethylformamide (DMF) and *N*-methyl-2-pyrrolidone (NMP) have been generally used as a medium for this process with only very few exceptions.[33−35] Also, when safe/green water is used as the medium, the necessary work-up procedure requires the utilization of organic solvents, and also, in these cases, large amounts of waste can be generated.[36−39] Mixtures of organic solvents and water are also often used as they offer the advantage of solubilizing organic and inorganic reagents giving effective chemical results. Specifically, in the Sonogashira cross-coupling, a mixture of an organic solvent and water is used as it allows the solubilization of the halide salts stoichiometrically produced in the process. However, these mixtures cannot be easily recovered leading to additional complicated issues arising from the disposal of hazardous waste.[40−50]

In this context, we have been interested in the use of aqueous azeotropic mixtures that are constituted by a precise combination of water and an organic solvent. They can allow the opportunity of exploiting both types of media still acting as a single recoverable substance. In this view, they can constitute an effective tool for minimizing waste while allowing a high chemical efficiency.[51−56] To this aim, we have been attracted by the peculiar properties of cyclopentyl methyl ether (CPME). This solvent forms a heterogeneous aqueous azeotrope, which boils at 83 °C.[57,58] In addition, CPME is also very interesting as it is produced from petrochemical waste with a 100% atom economy process, and it features very good toxicity and safety profiles.[58] Production of CPME starting from biomasses is also under evaluation.[57,58]

In this work, we report our results on the exploration of a local biomass urban waste material (pine needle) to design and develop an effective palladium catalytic system and combine its use with the safe solvent CPME derived from industrial waste aiming at implementing the "circular economy" approach into the definition of sustainable synthetic tools (Scheme 1). Therefore, we have applied our strategy to the widely representative copper-free Sonogashira (also known as Cassar−Heck,[59,60] named after the first researchers who defined a protocol where a copper cocatalyst was not employed) cross-coupling to define an effective waste-minimized protocol. It should be mentioned that generally

Scheme 1. Features of the Pd/PiNe-Catalyzed Continuous-Flow Sonogashira Reaction
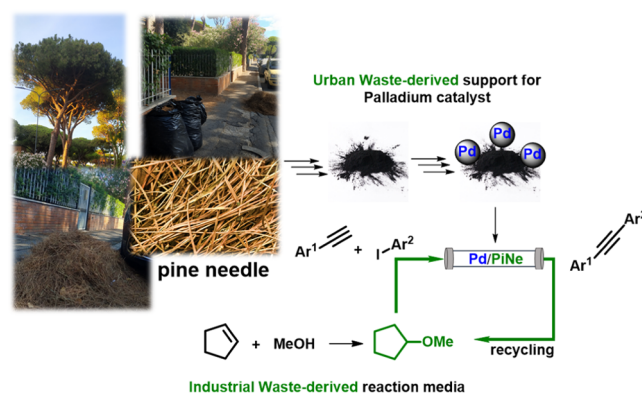
the Sonogashira cross-coupling is performed on aryl iodides and rarely on bromides, while aryl chlorides represent a challenge for both academia and industry; the latter are anyway more toxic and arguably less sustainable (see the Supporting Information (SI) for data). Considering that the Sonogashira reaction is a mature synthetic tool and aiming at optimizing the sustainability of this reaction under the umbrella of a circular economy, waste minimization approach, and sustainability approaches, we preferred to focus on iodides and the production of a very cheap and efficient catalyst system utilizing an effective and recoverable medium. To this aim, we have set a continuous-flow reactor protocol allowing a multigram-scale production not only to optimize the recovery and reuse of both the catalytic system and reaction medium but also to minimize the waste produced.[61−65]

RESULTS AND DISCUSSION

We began our investigation with the preparation of the waste-derived pine needle biochar (PiNe). After pretreatment[66] of the collected common urban waste, the subsequent formation of PiNe was achieved in agreement with protocols reported in the literature (see the Supporting Information for further details).[67] Subsequently, palladium nanoparticles were deposited onto PiNe and efficiently immobilized following a modified polyol method to afford the corresponding Pd/PiNe catalyst (see the Supporting Information for further details).[68] Transmission electron microscopy (TEM) images of the samples show the formation of Pd nanoparticles with an average particle size of 4.5 ± 1.8 nm (Figures 1 and S1). The Pd loading was measured using microwave plasma atomic emission spectrometers (MP-AES) analysis and resulted to be 9.9% w/w. We consider these features quite interesting as they make our Pd/PiNe comparable and competitive in terms of metal contents with the most widely commercially available Pd/C heterogeneous catalysts.

At this stage, we have tested the Pd/PiNe catalyst under batch conditions in the representative copper-free Sonogashira cross-coupling between aryl iodide **1a** and phenylacetylene **2a** using the mentioned CPME/water azeotropic mixture (Table 1).

By conducting the reaction at 60 °C in the presence of potassium carbonate, no conversion into the expected product **3a** was observed (Table 1, entry 1); similar results were obtained using polystyrene-supported dimethylamine (Table 1, entry 3) as the base. Homogeneous organic bases gave slightly better results (Table 1, entries 2 and 4). Based on these results,
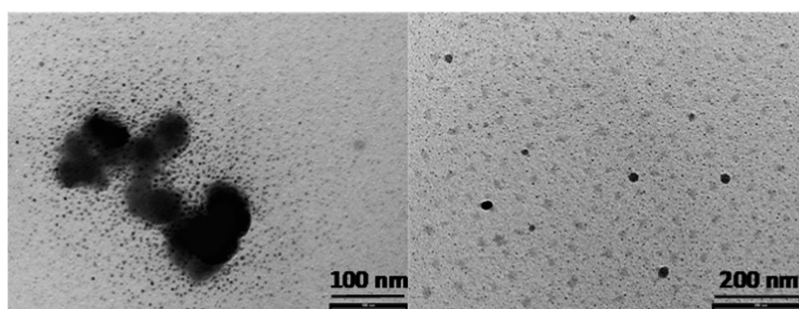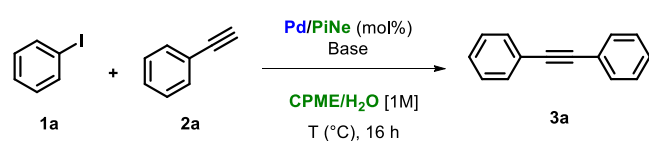
Figure 1. TEM images of the Pd/PiNe heterogeneous catalyst.

Table 1. Optimization of Sonogashira Cross-Coupling of 1a[a]

entry	base	CPME/H$_2$O (wt %)	Pd/PiNe (mol %)	T (°C)	C (%)[b]
1	K$_2$CO$_3$	84/16 (azeotrope)	0.5	60	0
2	Et$_3$N	84/16 (azeotrope)	0.5	60	20
3	PS−N(Me)$_2$	84/16 (azeotrope)	0.5	60	0
4	DABCO	84/16 (azeotrope)	0.5	60	45
5	DABCO	84/16 (azeotrope)	0.5	85	65
6	DABCO	84/16 (azeotrope)	0.5	110	70
7	DABCO	84/16 (azeotrope)	1	85	80
8	DABCO	84/16 (azeotrope)	5	85	99
9	DABCO	84/16 (azeotrope)	1	85	85[c]
10	DABCO	16/84	5	85	45
11	DABCO	50/50	5	85	50

[a]Reaction conditions: **1a** (1 mmol), **2a** (1.5 mmol), Pd/PiNe, base (1.2 equiv), reaction medium (1 mL, 1 M), 16 h. [b]GLC conversion has been determined using samples of pure compounds as reference standards; the remaining materials are **1a** and **2a**. [c]Reaction performed using commercially available Pd/C (10% w/w loading).

we selected 1,4-diazabicyclo[2.2.2]octane (DABCO) for further optimization at different reaction temperatures. We identified as optimal conditions the use of DABCO and 5 mol % Pd/PiNe in CPME/water azeotrope at 85 °C, where complete conversion to **3a** could be achieved (Table 1, entry 8).

In addition, the comparative experiments using commercially available Pd/C (10% w/w loading) showed negligible differences with our Pd/PiNe catalytic system (Table 1, entry 9).

Although we aimed at the use of the azeotropic mixture, we also evaluated whether a different ratio between CPME and water would influence the process as reported in Table 1. Under the optimized reaction conditions, only CPME/water azeotrope gave satisfactory results (Table 1, entry 8), while moving to 16/84 or 50/50 ratios dramatically impacts the conversion observed (Table 1, entries 10−11).

The reusability of the catalyst has also been checked by recovering the system and reusing it for different consecutive runs (Table 2) without loss in efficiency.

Next, we screened the substrate scope of the process and applied the optimized conditions to differently substituted acetylenic compounds and aryl halides (Scheme 2). Gratifyingly, we observed that high yields could be achieved in the

Table 2. Recycle and Reuse of the Pd/PiNe Catalyst in Batch[a]
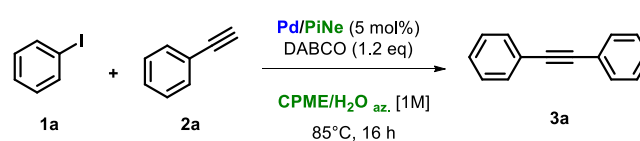
run	C (%)[b]
1	>99
2	>99
3	>99
4	98
5	99

[a]Reaction conditions: **1a** (1 mmol), **2a** (1.5 mmol), Pd/PiNe (5 mol %), DABCO (1.2 mmol), CPME/water azeotrope (1 mL). [b]Gas−liquid chromatography (GLC) conversion has been determined using samples of pure compounds as reference standards; the remaining materials are **1a** and **2a**.

presence of both electron-donating and electron-withdrawing groups in the aryl iodide, as well as when electron-withdrawing groups are incorporated in the acetylenic compounds. However, the yields slightly decrease in the presence of an electron-donating group on the acetylenic moiety.

Interestingly, the reaction conditions were also found to be compatible with alkyl-substituted acetylenic compounds (**5ca** and **5da**) leading to high isolated yields.

To further test the efficiency of our Pd/PiNe catalyst, we checked the feasibility of the reaction conditions on generally more challenging aryl bromides (Scheme 3). As expected, with a highly activated aryl bromide such as the 4-nitro derivative, a high yield was obtained. However, in the presence of fewer electron-withdrawing substituents under the same reaction conditions, the efficiency slightly decreased.

We then started to investigate the process under flow conditions. Aiming at a system able to run the process on a larger scale, we have used a 6 mm internal diameter poly(tetrafluoroethylene) (PTFE) tube filled with our Pd/PiNe. Initially, we tested various lengths of the reactor together with different flow parameters to achieve the optimal balance in terms of reactivity/time for the copper-free Sonogashira reaction (Table 3). When a 0.2 m coil length and a 75 psi back-pressure regulator (BPR) were used, only a 10% conversion to the desired product could be achieved (Table 3, entry 1) due to a low residence time. By increasing the catalyst amount from 0.6 to 2 g and the reactor length, the conversion slightly increased (Table 3, entry 2). Satisfactory results were only obtained with a reactor length of 4 m and a BPR of 250 psi (Table 3, entry 4).

Scheme 2. Scope of Sonogashira in Batch Using the Pd/PiNe Catalyst
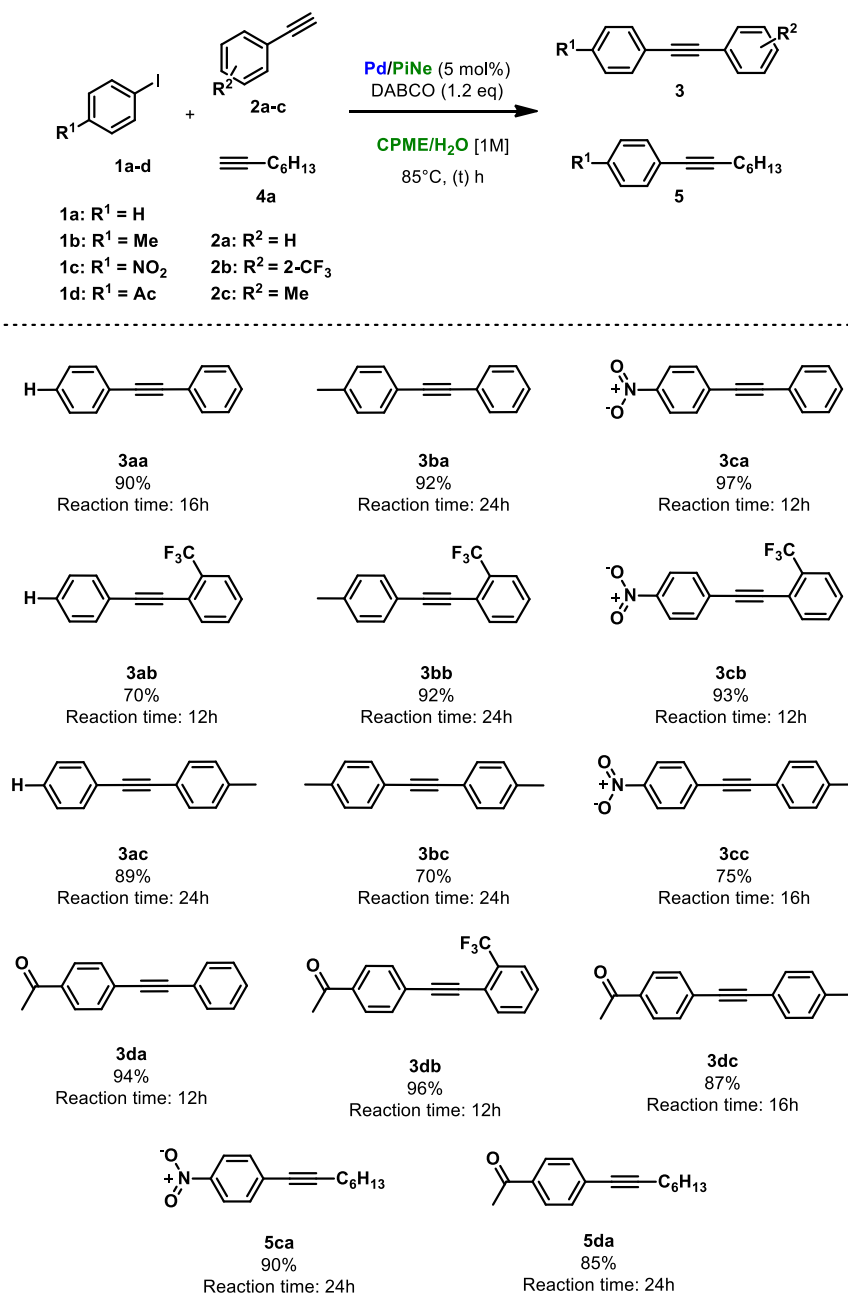
During these experiments, we noted that the initial CPME/water emulsion pumped through the reactor was subjected to a partial separation. To control this phenomenon, we further conducted the optimization by adding sodium dodecyl sulfate (SDS) as an emulsifier (Table 4). We observed that using 0.1 M SDS in water with a 4 h residence time the reaction gave better results, leading to 87% conversion (Table 4, entry 1). By decreasing the SDS concentration to 1×10^{-4} M, good conversion was maintained (Table 4, entry 2). Finally, under these conditions and with a longer residence time (8 h), we achieved almost a full conversion to the desired product (Table 4, entry 3).

The optimized flow conditions were then applied to the representative synthesis of various substrates (Table 5) on a multigram scale. The reactor (Figure 2) remained operative for 15 consecutive days, and the leaching of metal in solution was monitored over time (Scheme 4). To our delight, Pd/PiNe showed very high stability with a very low palladium loss on applying flow conditions. As reported in the literature, by experimental and/or in operando analysis, this effect is due to the increased stability and preservation against mechanical friction.[69−74]

In addition, an in-line continuous liquid−liquid membrane separator (Zaiput Inc) was connected to the Pd/PiNe flow reactor. This operation allowed us to easily recover the CPME with its consequent reuse. The water in which salt DABCO-I is solubilized therefore represents the only (also inevitable) major waste associated with the reaction.

To quantify the environmental efficiency of our continuous flow protocol, we compared the E-factor with other Sonogashira processes. For comparison, both flow and batch protocols were selected, featuring low E-factor values[53] and

Scheme 3. Scope of Sonogashira in Batch Using the Pd/PiNe Catalyst with Aryl Bromides

1e-h

1e: R = NO$_2$
1f: R = CHO
1g: R = Ac
1f: R = CO$_2$Me

3ea
90%

3fa
76%

3ga
71%

3ha
27%
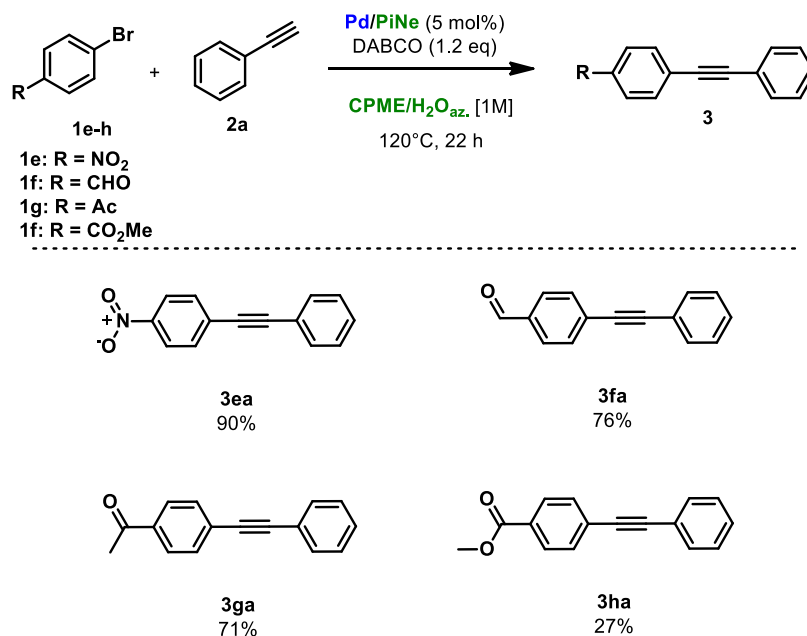
Table 3. Optimization of Flow Parameters^a
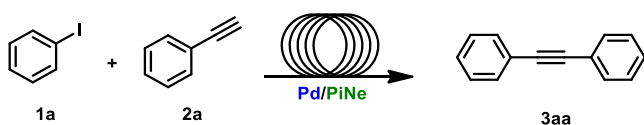
entry	coil length (m)	catalyst (g)	Pd (mol %)	BPR gauge (psi)	residence time (h)	C (%)^b
1	0.2	0.6	30	75	0.5	10
2	2	2	37	100	2	35
3	4	2	19^c	100	4	68
4	4	2	19^c	250	8	88

^{a}Optimization of flow parameters conducted at a constant flow rate of 0.01 mL min^{-1}. ^{b}GLC conversion has been determined using samples of pure compounds as reference standards; the remaining materials are **1a** and **2a**. ^{c}For these experiments, the same reactor was used.

Table 4. Optimization of Flow Parameters with the Addition of SDS to Water
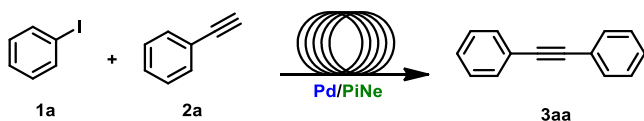

entry	coil length (m)^a	residence time (h)	BPR gauge (psi)	[SDS] in water^b	C (%)^c
1	4	4	100	0.1	87
2	4	4	100	1×10^{-4}	90
3	4	8	250	1×10^{-4}	99

^{a}The coil was filled with 2 g of Pd/PiNe (12 mol %). ^{b}Expressed as molar concentration in water. ^{c}GLC conversion has been determined using samples of pure compounds as reference standards; the remaining materials are **1a** and **2a**.

different solvent recovery strategies[50] (Table 6). Due to the in-line separation and reuse of CPME and the high throughput of the flow system, the *E*-factor value associated with our protocol is very low (2.8).

As additional demonstration of the synthetic utility and applicability of our flow protocol based on the urban waste-

Table 5. Substrate Scope for the Sonogashira Reaction in Flow^a
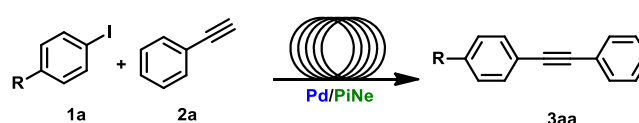
entry	R-	flow rate (μL min^{-1})	mmol of 1a	C (%)^b
1	H (3aa)	14	50	>99% (96)
2	Ac (3da)	24	20	>99% (96)
3	NO$_2$ (3ca)	24	20	>99% (98)
4	OMe (3ia)	10	20	45 (42)

^{a}Reaction conditions: **1** (1 equiv), **2a** (1.5 equiv), CPME/water azeotrope [1 M], SDS (1×10^{-4} in water), the reactor, filled with 2 g of Pd/PiNe (1.7 mol %), was installed into a thermostated box at 85 °C, 250 psi BPR. ^{b}GLC conversion has been determined using samples of pure compounds as reference standards; the remaining materials are **1a** and **2a**. Isolated yields are given in parenthesis.
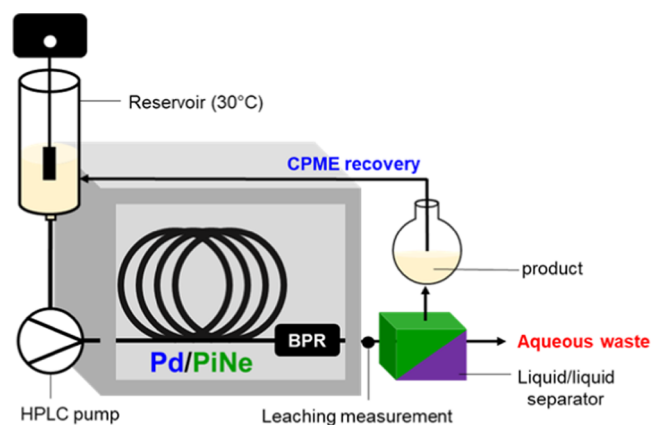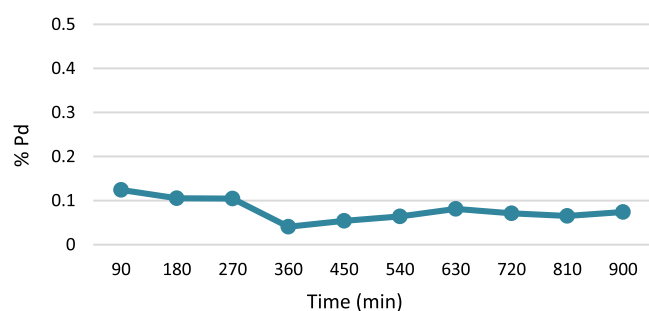

Figure 2. Schematic representation of flow setup.

derived Pd/PiNe catalyst, we attempted the telescoped flow synthesis of an active pharmaceutical ingredient: eniluracil. The above-mentioned flow system has therefore been

Scheme 4. Leaching Measurement during the Flow Procedure

Table 6. E-factor Evaluation and Comparison

| ref	yield (%)[a]	E-factor
64 (flow)	74	1491
65 (flow)	81	111
53 (batch)	77	17
50 (batch)	92	211
this work (batch)	90	40[a]
this work (flow)	95	2.8

[a]Calculated without considering CPME recovery. A value of 8.6 was obtained if the CPME recovery was considered.

implemented to achieve the initial Sonogashira coupling between 5-iodouracil and trimethylsilylacetylene with a residence time of 8 h and telescoped with an in-line desilylation reaction using 1 M NaOH (Scheme 5).

After a 30 min loop in which the desilylation reaction occurs, further liquid–liquid separation of the CPME fraction and evaporation led to eniluracil in 92% yield. It is noteworthy to highlight that with this flow methodology an E-factor value of 25 has been obtained for the synthesis of eniluracil, which is a consistent reduction compared with the value (E-factor = 104) of the optimized process reported by GlaxoSmithKline.[75] The low solubility of **1j** forces us to use more diluted conditions (0.2 M) hindering the possibility of further reducing the E-factor value.

Finally, the catalyst was recovered from the reactor and analyzed. TEM images (Figure S2 in the Supporting Information) show a slight particle increase (8.8 ± 4.8 nm) mainly due to the presence of particle aggregates. This result was expected and it strongly suggests the presence of a "release and catch mechanism".[76–78] The noncovalent immobilization of Pd nanoparticles on the PiNe support may allow the release of the palladium active species in solution at the beginning stage of the catalytic cycle. Only at the end of the process was the metal in solution re-deposited on the support as confirmed by both low leaching and a slight increase of Pd nanoparticles.
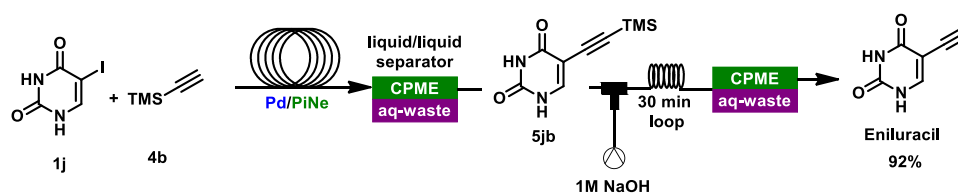
CONCLUSIONS

In conclusion, we have reported that a Pd/PiNe catalyst derived from urban pine needle waste is an effective catalytic system and it can be effectively used in combination with an industrial waste-derived CPME/water azeotropic mixture allowing the definition of a sustainable circular economy inspired protocol for the Sonogashira cross-coupling. We have set a continuous flow protocol exploiting the efficient recoverability and stability of Pd/PiNe and also the recoverability of CPME from water via continuous liquid–liquid separation. Our flow reactor was left to operate continuously for 15 days, showing constant efficiency and a minimal metal leaching with an average throughput of 0.95 mmol h^{-1}. Low E-factor values have been calculated thanks to the optimal stability of the catalyst and the easy continuous separation of CPME from water. Indeed, the possibility of separating in-line the reaction medium and reusing it continuously allowed for an additional waste minimization for the representative copper-free Sonogashira reaction reported here. Additionally, the flow system reported has been successfully applied to the synthesis of eniluracil with good yield and a low E-factor.

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acssuschemeng.1c03634.

Experimental procedures; compound characterizations; and copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra (PDF)

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Scheme 5. Telescoped Flow Synthesis of Eniluracil

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Author Contributions

F.F. and F.V. contributed equally to this work. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS

CPME   cyclopentyl methyl ether
DMF   *N,N*-dimethylformamide
NMP   *N*-methyl-2-pyrrolidone
DABCO   1,4-diazabicyclo[2.2.2]octane
SDS   sodium dodecyl sulfate
BPR   back-pressure regulator

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