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Microwave assisted batch and continuous flow Suzuki–Miyaura reactions in GVL using a Pd/PiNe biowaste-derived heterogeneous catalyst†

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Aiming at the development of alternative and low-impact synthetic pathways, we herein report the exploitation and the simultaneous employment of different tools to improve the overall sustainability of the Suzuki–Miyaura (SM) cross-coupling process with a circular economy approach. For the first time, in this study, we have combined the use of our biowaste-derived heterogeneous catalyst Pd/PiNe with the biomass-derived reaction medium γ -valerolactone (GVL) proving that an optimised protocol can be obtained for the SM process with a significant substrate scope. The microwave irradiation technology highly enhanced the energy efficiency, allowing the synthesis of different biphenyls and reducing the reaction time. In addition, the good efficiency and selectivity of the SM reaction led to further optimisation of the work-up procedure, minimising the waste generation and the *E*-factor values associated with the process (3.2–9.4). The optimised conditions tolerated the free carboxylic acid group well, realizing the step-economical preparation of the non-steroidal anti-inflammatory analgesic Fenbufen in quantitative yield. Finally, the scale-up of the MW-assisted process was performed in synergy with the optimisation of the continuous flow protocol and the waste minimised synthesis of Fenbufen was achieved.

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Introduction

One of the main challenges of modern social, economic and scientific development is the development of more sustainable methods aimed at achieving the main objectives defined by the United Nations plan called “Transforming our world: the 2030 Agenda for Sustainable Development”.¹ In this context, the principles of the circular economy (CE) model represent promising guidelines for achieving these objectives.² In fact, the redesign of products and procedures, aimed at saving resources and minimizing waste, not only contributes to creating new jobs but also reduces the environmental impact of industrial processes and waste management which contribute approximately 9 and 3%, respectively, to the total EU greenhouse gas emission.³

In this context, sustainable design plays a crucial role in both chemistry and engineering. However, the optimization and consolidation of alternative and low-impact synthetic pathways are not trivial. Several aspects should be considered, such as the toxicity, safety and environmental profile of raw materials, catalysts, additives and solvents as well as the efficiency and large-scale implementation of the synthetic route designed.⁴

It is well known that solvents contribute to the major percentage (around 80–90%)⁵ of wastes produced as they are exploited in different steps (*i.e.* as a reaction medium, in work-up and purification procedures) and also play a crucial role in the synthetic process.⁶ For this reason, great efforts have been made in the last decade to replace harmful solvents in all the steps with a particular focus on the use of bio-renewable alternatives.⁷

Due to the crucial role of cross-coupling reactions in diverse fields, such as pharmaceuticals, optoelectronics, polymer science and many other fields,⁸ green alternatives have been developed for these processes⁹ also driven by the definition of strict regulations prohibiting the use of critical solvents.¹⁰

Among the C–C coupling processes awarded with the Nobel Prize in 2010,¹¹ the Suzuki–Miyaura (SM) reaction has emerged as a particularly attractive strategy to gain ever-increasing interest.¹² Indeed, the SM reaction easily allows the

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formation of biaryls under mild conditions and with the use of non-toxic boronic acids. For these reasons, the SM cross-coupling represents a key step in several transformations for the total synthesis of highly relevant and valuable products.¹³

Sherwood *et al.* have recently studied the influence of green solvents on the SM reaction, concluding the difficulty in unambiguously defining the role of a reaction medium to achieve the best results.¹⁴ Anyway, the popularity and the value of the SM reaction in the synthesis of target materials are still related to an intense research activity aimed at the development of green approaches, including solvent selection,¹⁵ to improve the sustainability of this widely useful cross-coupling reaction.¹⁶

The imperative need to shift towards a more sustainable chemical production can also be summarised by the valuable suggestion given by Varma and Sedghi in a recent review article.^{15d} Anyway, to the best of our knowledge, SM protocols realizing the optimization of reaction conditions for the use of biomass-derived γ -valerolactone (GVL) have not been defined and reported in the literature. GVL has been intriguingly considered to form blending solvent systems by Sherwood under homogeneous catalytic conditions¹⁴ but with no relevant success. GVL has recently found use in reducing the viscosity of dihydrolevoglucosenone (CyreneTM).¹⁷

As mentioned above, the reaction medium is a crucial parameter, promoting the dissolution of both organic and inorganic reagents. In this context, GVL has already been well demonstrated to be a valid alternative to reprotoxic classic solvents such as DMF and NMP.¹⁸

The choice of a renewable reaction medium is additionally crucial when it is also combined with the use of a recoverable and reusable heterogeneous catalytic system. Indeed, the possibility to easily separate the metal from the reaction mixture can reduce the waste at the purification stage, especially in the pharmaceutical and optoelectronics fields where strict regulations limit metal contamination.¹⁹ Moreover, the recycling of precious exhaustive metals is of utmost importance.

In the area of heterogeneous metal-based catalysts, porous supports are among the most employed, thanks to their tolerance to different reaction conditions, stability in various solvents and ability to stabilize Pd nanoparticles.²⁰ Although highly engineered and efficient catalysts are available in the literature,²¹ the employment of renewable waste-derived supports and/or catalysts is crucial in the context of circular economy.²²

Moreover, the combination of both renewable and low-impact reaction media and catalyst supports may highly enhance the overall sustainability of the process.^{15d} In this context, we herein demonstrate the efficiency of our waste-derived heterogeneous catalyst in SM cross-coupling in a biomass-derived GVL reaction medium.

The Pd/PiNe catalyst,²³ obtained by the careful design of a low-cost heterogeneous support *via* local urban-waste upcycling, showed comparable catalytic performances to commercially available Pd/C while reducing the metal leaching in solution. It is worth mentioning that this approach well meet the CE requirements, not only proposing an alternative strategy to

pine needle urban-waste incineration but also inspiring small-town administrations towards sustainable waste disposal.²

In addition, in this study we considered the use of microwave irradiation-based technology (MW) to improve the process efficiency and reduce the reaction time compared to conventional heating.²⁴ The use of MW in SM reactions has gained increasing interest both under batch²⁵ and flow conditions.²⁶

However, despite the advantages of the MW-based technology, it is worth mentioning that hot spot formation is still one of the main safety issues related to MW irradiation, especially when easily accessible carbon-supported solid catalysts are used.²⁷ Nevertheless, GVL has proven its ability to avoid hot spot formation,²⁸ demonstrating also good efficiency with different catalysts in diverse processes.^{28,29}

Therefore, in this study, we have developed a sustainable and safe protocol to access different biphenyls under the CE and green chemistry guidelines. We have identified the optimal conditions to perform the SM reaction in GVL as the reaction medium under MW irradiation. In addition, we have prepared and employed the biomass-waste derived Pd/PiNe catalyst and optimized the reaction conditions to access active pharmaceutical ingredients (APIs) in high yield. Representatively, Fenbufen, a non-steroidal anti-inflammatory analgesic, can be obtained *via* different synthetic pathways,³⁰ exploiting SM coupling as the key step. Although in some areas, including the EU, Fenbufen was withdrawn from the market, it is still commercialized in other countries, and strategies for possible repurposing should not be overlooked.³¹ For the aim of this contribution, including Fenbufen in the substrate scope of the process is of interest. In fact, in its structure different functional groups are present, furnishing a particularly intriguing case study for the versatility and functional group tolerance of the protocol.

Moreover, to consider the limitations related to the scale-up of the MW-based process,^{26a} a continuous flow protocol was efficiently optimized in combination with MW irradiation. In this context, it is worth mentioning that the careful selection of the reaction medium benefited the continuous process of solubilizing both organic and inorganic compounds, thus avoiding the need for reactor regeneration by washing.

Results and discussion

The collected dry pine needle urban waste was initially extracted in a Soxhlet apparatus using a toluene-methanol azeotropic mixture, 95% recovered by distillation. This simple chemical pre-treatment gives the support preparation procedure an added value by enabling the valorisation of the sole lignocellulosic residue, usually underutilized, without wasting the extractive components. Indeed, the importance of the use of essential oils from pine-needles in cosmetics, as flavour additives and in the polymer field is well documented.³²

Once the pine needle lignocellulosic component was isolated, the PiNe support was prepared following a chemical car-



bonization method under mild conditions.³³ The as-prepared biochar was used without any further modification to immobilize Pd nanoparticles using a polyol method.²³ After the addition of H₂PdCl₄ precursor to the diethylene glycol suspension of PiNe, the reduction step was performed at 130 °C under an Ar atmosphere, affording the final Pd/PiNe heterogeneous catalyst. The described procedure led to small Pd nanoparticles with a size distribution centred at 4.5 nm.²³

The metal loading on the biowaste-derived PiNe was measured by MP-AES (microwave plasma atomic emission spectroscopy) analysis (8 wt%).

With the freshly prepared Pd/PiNe catalyst, we started to optimize the SM coupling by selecting 4-bromobenzaldehyde (**1a**) and phenylboronic acid (**2a**) as model substrates, employing only 0.5 mol% of our Pd-based catalyst (Table 1). By performing the reaction under conventional heating and using K₂CO₃ as the base, a conversion of 76% into product **3a** was obtained after 16 h in pure GVL as the reaction medium (entry 1, Table 1). Upon addition of different amounts of water to GVL (entries 2–4, Table 1), the conversion of **1a** gradually increased to 92% when a mixture of GVL : H₂O (1 : 4) was used (entry 3, Table 1).

In contrast, by replacing the conventional heating with MW irradiation at a defined temperature, high conversion into **3a** was obtained in only 30 minutes using GVL as the sole reaction medium (entry 5, Table 1), also with an energetic efficiency advantage. However, the insolubility of K₂CO₃ in GVL is an evident limit for a process in flow, and this aspect led us to investigate the use of other organic bases, but only poor results could be obtained (entries 6–8, Table 1).

Still with the goal of defining a continuous flow procedure, we further explored the possibility to reach the homogeneity of the reaction mixture. For this reason, the solubility of different

bases in various ratios of the GVL : H₂O mixture was investigated. Particular attention was paid to reducing the water excess in order to prevent product precipitation during the process. Indeed, because biphenyls have low solubility in water, their precipitation may complicate the heterogeneous catalyst recovery and the flow scale-up.

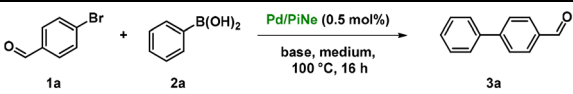
Despite K₂CO₃ and NaOAc being completely soluble in a mixture of GVL : H₂O (1 : 1), under these conditions, phase separation was also observed. Tetrabutylammonium acetate (TBAAC) in GVL and KOPIV in GVL : H₂O (5 : 1) were initially individuated as promising candidates due to their capability of forming clear and homogeneous mixtures in the presence of **1a** and **2a**.

The latter were tested in the SM coupling as model substrates under MW irradiation (entries 9 and 10, Table 1). Although the use of TBAAC allowed the use of pure GVL and quantitative conversion of **1a**, 30% of simple biphenyl was also formed due to the concomitant decarbonylation reaction of **3a**. For this reason, KOPIV in a GVL : H₂O reaction medium was selected for further optimization, and under these conditions, pure **3a** could be obtained. The removal of the base was detrimental, affording mainly triphenylboroxine as a byproduct (entry 11, Table 1).

Keeping in mind the use of fixed MW-irradiation power mode during the flow scale-up, we optimized the reaction conditions in batch using cyclic MW irradiation at a fixed power in the temperature range of 90–120 °C (Table 2).

By decreasing the MW irradiation from 150 to 100 W, an increment in **1a** conversion was observed after the same 10 cycles (entries 1 and 2, Table 2). The increase in cycles from 10 to 15 (entry 3, Table 2) led to a quantitative formation of the desired product **3a**. However, after checking the reusability of the recovered Pd/PiNe under these conditions, a reduced cata-

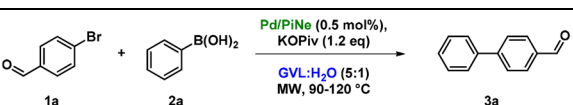
Table 1 Catalytic tests of Pd/PiNe in SM coupling between **1a** and **2a**^a



Entry	Reaction medium	Conc. (M)	Base	Conv ^b (%)
1	GVL	1	K ₂ CO ₃	76 (71)
2	GVL : H ₂ O (4 : 1)	1	K ₂ CO ₃	82 (78)
3	GVL : H ₂ O (1 : 4)	1	K ₂ CO ₃	92 (88)
4	GVL : H ₂ O (1 : 4)	0.5	K ₂ CO ₃	74 (70)
5 ^c	GVL	1	K ₂ CO ₃	90 (86)
6	GVL	1	DABCO	35
7	GVL	1	DBU	Traces
8	GVL	1	TEA	Traces
9 ^c	GVL	0.7	TBAAC	>99 ^d (64)
10 ^c	GVL : H ₂ O (5 : 1)	0.5	KOPIV	91 (86)
11 ^c	GVL	0.5	—	Traces

^a Reaction conditions: **1a** (0.5 mmol), **2a** (1.1 eq.), Pd/PiNe (0.5 mol%), base (1.2 eq.), reaction medium, 100 °C, 16 h. ^b Determined by GLC analysis; the remaining materials are unreacted **1a** and **2a**. The yield of **3a** is reported in parentheses. ^c Performed under MW irradiation (MW dynamic mode) in 30 min. ^d 30% of biphenyl was detected as a byproduct.

Table 2 Optimization of SM coupling between **1a** and **2a** under MW irradiation^a



Entry	MW power	No. of cycles	Conv ^b (%)
1	150	10	96 (91)
2	100	10	99 (94)
3	100	15	>99 (95)
4 ^c	100	15	70 (64)
5	50	20	87 (82)
6	50	30	93 (88)
7	50	40	>99 (95)
8 ^d	50	40	>99 (95)
9 ^e	50	40	>99 (95)

^a Reaction conditions: **1a** (0.5 mmol), **2a** (1.1 eq.), Pd/PiNe (0.5 mol%), KOPIV (1.2 eq.), GVL : H₂O (1 M), 90–120 °C, MW fixed power ($t_{MW} = 2$ min; $t_{cool} = 1$ min). ^b Determined by GLC analysis; the remaining materials are unreacted **1a** and **2a**. The yield of **3a** is reported in parentheses. ^c Performed using Pd/PiNe recovered from entry 3. ^d Commercially available Pd/C (10 wt%) was used. ^e GVL : H₂O (9 : 1).



lytic efficiency during the second run was observed (entry 4, Table 2).

In order to succeed in the conservation of the Pd/PiNe catalytic efficiency as well, the MW irradiation was further reduced to 50 W (entries 5–7, Table 2), affording good results after 40 cycles (entry 7, Table 2). These conditions were also employed with commercially available Pd/C, as a representative of cheap and available palladium systems. In fact, optimum results in terms of efficiency were obtained (entry 8, Table 2). Additionally, the optimization was further assessed by evaluating the metal leaching in solution in both the processes, and with the use of Pd/C, higher Pd leaching was observed compared to Pd/PiNe (77 vs. 14 ppm, respectively). These final performance data of our biowaste-derived Pd-based catalyst are of great interest as they demonstrate the chemical efficiency and sustainability of the newly defined catalyst and conditions.

Ultimately, a further reduction of the water amount in the GVL:H₂O mixture (9:1 ratio) led to a quantitative conversion into product **3a** (entry 9, Table 2). Under such conditions, the Pd/PiNe catalyst was recovered and reused (see the ESI file for further information[†]), showing no loss in efficiency (Fig. 1).

Moreover, to demonstrate the stability of our heterogeneous catalyst, we decided to stress the recycle test by performing the recovery and reuse of Pd/PiNe after 30 MW cycles instead of at full conversion (see Figure ESI-1 in the ESI file[†]). Also, upon reducing the reaction time, Pd/PiNe showed good recyclability.

Given the good catalytic performance of our Pd/PiNe, further efforts were devoted to minimizing the waste generated during the work-up step. At the end of the process, the catalyst was separated from the reaction mixture and washed with pure GVL. Water was removed under vacuum and GVL was recovered by distillation. The solid residue was then washed with water to remove excess **2a** and residual KOPiv, affording the pure product **3a** in a high isolated yield (95%). The environmental factor (*E*-factor) associated with this procedure was 14.6 (see the ESI file for further details[†]). When water is also recovered by distillation (90%), the *E*-factor was reduced to 70%, leading to a calculated value of 4.3. The *E*-factor profile³⁴ is shown in Fig. 2 (see the ESI file for further information[†]).

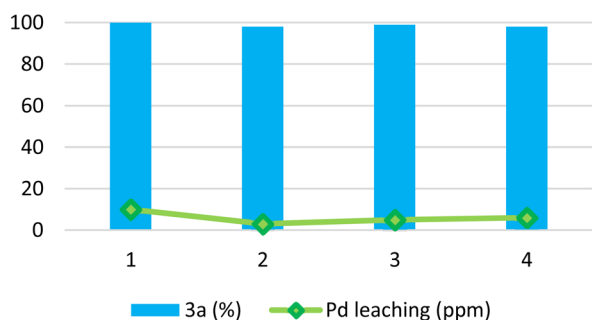


Fig. 1 Pd/PiNe recycling and Pd leaching under batch conditions and MW irradiation. Reaction conditions: **1a** (0.5 mmol), **2a** (1.1 eq.), Pd/PiNe (0.5 mol%), KOPiv (1.2 eq.), 0.5 mL GVL:H₂O (9:1), 90–120 °C, 50 W, MW fixed power (t_{MW} = 2 min; t_{cool} = 1 min), and 40 cycles.

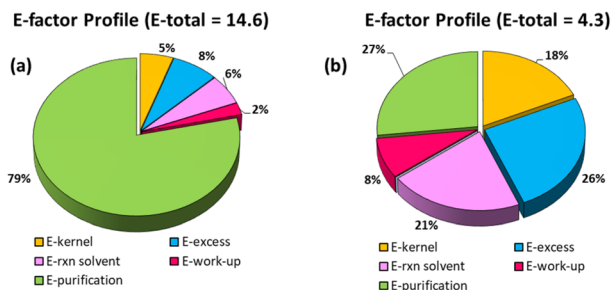
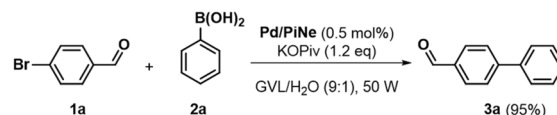
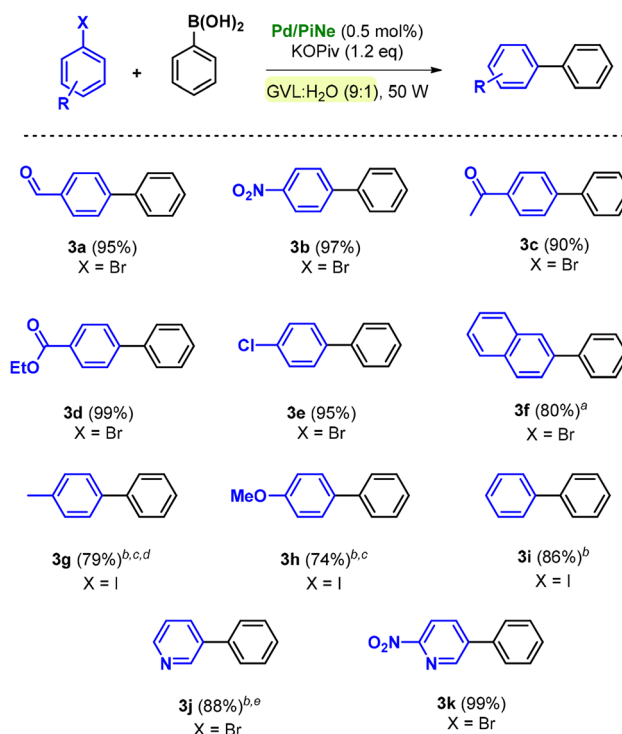


Fig. 2 *E*-Factor profile for the model SM reaction between **1a** and **2a** before (a) and after (b) the recovery of H₂O used in product purification.

The optimized reaction conditions and the low-impact purification step were then extended to the SM coupling of different aryl halides (**1a–i**) with phenylboronic acid **2a** (Scheme 1).

By using bromoarenes substituted with electron withdrawing groups **1a–e**, good to excellent isolated yields (90–99%) were obtained under the optimal reaction conditions.



Scheme 1 SM coupling between aryl halides and **2a** using Pd/PiNe. Reaction conditions: **1** (0.5 mmol), **2a** (1.1 eq.), Pd/PiNe (0.5 mol%), KOPiv (1.2 eq.), 0.5 mL GVL:H₂O (9:1), 90–120 °C, 50 W, MW fixed power (t_{MW} = 2 min; t_{cool} = 1 min), and 40 cycles. ^a60 cycles. ^b100–150 °C. ^c100 W, 80 cycles. ^d1 mL GVL:H₂O (9:1). ^e45 cycles.



Representatively, when **1c** and **1d** were replaced with the corresponding aryl chlorides, only traces of the desired products **3c** and **3d** could be detected.

Product **3f**, obtained by the coupling of 2-bromonaphthalene (**1f**) with **2a**, was isolated in 80% yield after increasing the number of cycles to 60.

In contrast, bromoarenes substituted with electron donating groups or unsubstituted bromobenzene poorly reacted under the optimized conditions. The corresponding iodoarenes led to good isolated yields in the range of 74–86% (Scheme 1). In this context, it should be noted that this choice was balanced on both the intrinsic and extrinsic impacts of the haloarene as already quantified and proven.^{9a}

Indeed, the simple replacement of bromides with iodides allowed us to avoid the employment of ligands or extra additives still keeping high the process efficiency.^{9a} Moreover, the synthesis of bromobenzene, compared to iodobenzene as well as the substituted *para*-methoxy and *para*-methyl counterparts, exhibits a higher ecological footprint; generally higher yields are associated with lower environmental impact.^{9a}

The efficiency of the Pd/PiNe catalyst under MW irradiation afforded good results also in the SM coupling of N-containing heterocyclic bromides, allowing high isolated yields of arylated pyridines **3j** and **3k** (Scheme 1). It should be mentioned that for the product **3j**, the work-up protocol was modified due to the low melting point of the synthesized compound. The extraction work-up used to isolate the product **3j** led to an increase in the *E*-factor value up to 34 (see the ESI file† for further information and *E*-factor calculation). However, this value can be reduced by almost four times (7.9) by recovering both the aqueous phase and the heptane used for the extraction.

The conditions were further extended to different substituents such as phenylboronic acids (**2b–f**), leading always to satisfactory isolated yields (Scheme 2).

It should be mentioned that the number of cycles and MW irradiation were adjusted based on the substitution of halo-benzene rather than phenylboronic acid.

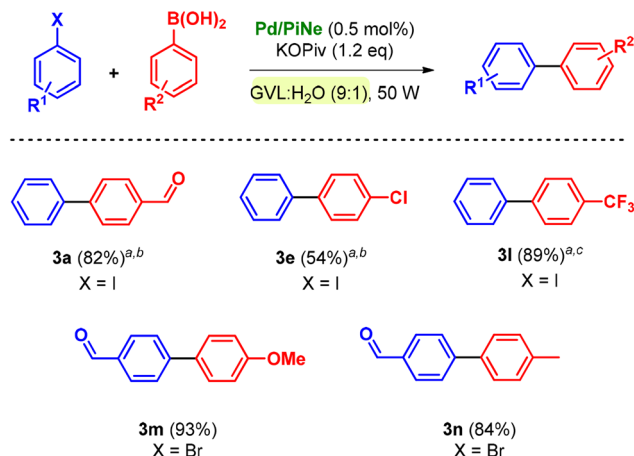
All the products were efficiently isolated following the optimized work-up procedure, achieving high yields and low environmental impact (see the ESI file† for *E*-factor calculation).

Due to the presence of different functional groups, the access to Fenbufen is of synthetic relevance, and different sustainable alternative technologies have been recently proposed for its production, including the use of mechanochemistry,¹³ⁱ flow-chemistry^{13a} and heterogeneous catalysis.^{13c}

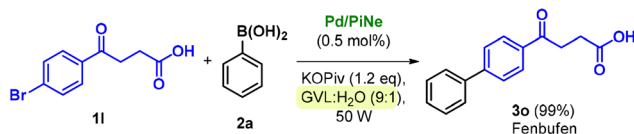
Our newly defined protocol proved to be highly efficient in the synthesis of Fenbufen, achieving almost quantitative yield (Scheme 3) with an associated low waste-generation (see the ESI file for further information†).

This result is even more important since it is generally not trivial to work directly in the presence of free carboxylic acid groups. However, the high yield obtained well highlights the versatility of the optimized conditions.

Given the impressive results obtained with our waste-derived heterogeneous catalyst, we decided to overcome the



Scheme 2 SM coupling under batch conditions using Pd/PiNe. Reaction conditions: **1** (0.5 mmol), **2** (1.1 eq.), Pd/PiNe (0.5 mol%), KOPIv (1.2 eq.), 0.5 mL GVL : H₂O (9 : 1), 90–120 °C, 50 W, MW fixed power (t_{MW} = 2 min; t_{cool} = 1 min), and 40 cycles. ^a100–150 °C, 100 W. ^b60 cycles. ^c80 cycles.



Scheme 3 Pd/PiNe catalyses the synthesis of the Fenbufen API in the GVL : H₂O reaction medium under MW irradiation. Reaction conditions: **1** (0.5 mmol), **2a** (1.1 eq.), Pd/PiNe (0.5 mol%), KOPIv (1.2 eq.), 0.5 mL GVL : H₂O (9 : 1), 90–120 °C, 50 W, MW fixed power (t_{MW} = 2 min; t_{cool} = 1 min), and 40 cycles.

scale-up limitations by combining the MW irradiation with the continuous flow protocol.

A 50 cm PTFE tube was packed with 100 mg of Pd/PiNe blended in 2 g of quartz powder (see the ESI file for further details†) and a mixture of **1a**, **2a** and KOPIv in GVL : H₂O was fluxed through the reactor under MW irradiation (Table 3).

Different flow parameters were screened and varied before defining the optimal conditions for the continuous flow protocol. Despite the homogeneity of the selected mixture, a high concentration led to poor conversion into the desired product **3a** (entries 1–3, Table 3). At the same time, a high dilution had a detrimental effect on the flow performances (see entries 4 and 5, Table 3).

When the MW irradiation power was increased from 50 to 75 and 100 W (entries 7 and 8, Table 3), boroxine was detected as the byproduct due to the dehydration side reaction of **2a**, confirming the irradiation at 50 W as the optimal parameter (entry 10, Table 3). Under these conditions, a quantitative conversion was observed with a flow rate of 0.1 mL min⁻¹.

To further highlight the efficiency and selectivity of our bio-waste-derived Pd/PiNe, a commercially available Pd/C catalyst was compared under the optimized flow conditions, leading to



Table 3 Optimization of SM coupling between **1a** and **2a** under MW irradiation and continuous flow conditions^a

Entry	Conc. [M]	KOPIv (eq)	GVL : H ₂ O	MW	Flow ^b (mL min ⁻¹)	Conv ^c (%)
1	1.00	1.2	9 : 1	50	0.1	33
2	0.75	1.2	9 : 1	50	0.1	38
3	0.75	1.2	9 : 1	50	0.05	58
4	0.50	1.2	9 : 1	50	0.2	40
5	0.25	1.2	9 : 1	50	0.2	21
6	0.33	1.2	9 : 1	50	0.1	56
7	0.33	1.2	9 : 1	100	0.1	39 ^d
8	0.50	1.2	9 : 1	75	0.1	54 ^d
9	0.50	1.2	9 : 1	60	0.1	63
10	0.50	1.2	9 : 1	50	0.1	99
11	0.50	1.2	9 : 1	40	0.1	43
12	0.50	1.0	9 : 1	50	0.1	61
13 ^e	0.50	1.2	9 : 1	50	0.1	99
14	0.50	1.2	5 : 1	50	0.1	91
15	0.50	1.2	5 : 2	50	0.1	65
16	0.50	1.2	95 : 5	50	0.1	70

^a Reaction conditions: **1a** (1 mmol), **2a** (1.1 eq.), Pd/PiNe (100 mg), KOPIv, GVL : H₂O, MW fixed power. ^b Measured at the flow outlet. ^c Determined by GLC analysis; the remaining materials are unreacted **1a** and **2a**. ^d Boroxine was detected as a dehydration product. ^e Reactor packed with commercially available Pd/C; biphenyl was detected as the main product.

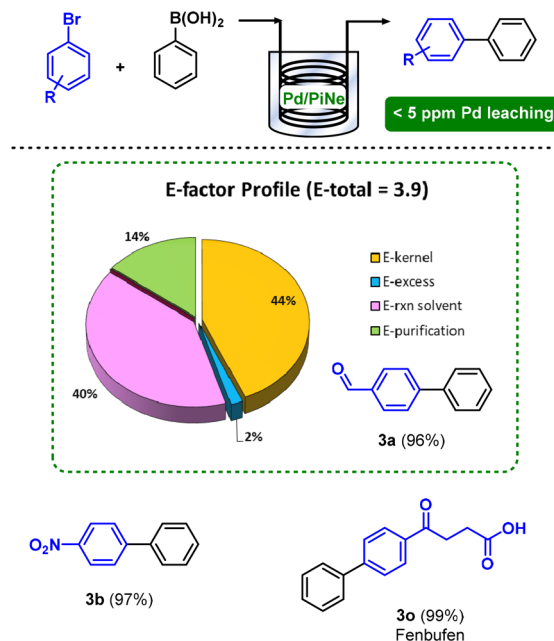
the formation of a decarbonylated byproduct as the main product (entry 13, Table 3).

The exploitation of flow technology not only allowed an easy scale-up of the process, being efficient for the continuous conversion of representative 50 mmol of **1a**, but also contributed to an increment of the overall sustainability by lowering the *E*-factor to 3.9. Indeed, the work-up contribution to the *E*-factor was suppressed, as well as the auxiliary decreased, enhancing the *E*-kernel from 18%, in the batch process, to 44% (Fig. 3).

The Pd leaching in solution was continuously monitored during the time, showing very good values constantly below 5 ppm.

To confirm the versatility of the flow protocol, representative substrates were selected and fluxed through the same reactor. When **1b** was tested, a higher dilution (0.33 M) was employed due to its low solubility. However, product **3b** was obtained in a high yield (97%). Finally, Fenbufen API was continuously synthesized, exploiting the possibility of a step-economical access to the API through the synergy between MW irradiation and the flow technology.

To highlight the synergic role of different strategies to improve the overall sustainability of the process, we compared the *E*-factor values of our protocol with those of selected recent

**Fig. 3** Continuous flow SM coupling between **1** and **2a** and the *E*-factor profile for the synthesis of the product **3a**.

reports employing MW irradiation, whether in batches^{16h,25} or under flow conditions.²⁶ Attention was directed to those reports specifically dedicated to the design of a sustainable protocol for the SM reaction (see the ESI file for further details[†]).¹⁶ Besides the waste minimisation obtained by our newly reported protocol, it should be noted that many processes combining the continuous flow protocol and MW reported the use of toxic DMF as a reaction medium under highly diluted conditions.

Conclusions

The biowaste-derived Pd/PiNe catalyst and the biomass-derived GVL reaction medium were simultaneously employed to define a sustainable Suzuki–Miyaura cross-coupling process with a circular economy approach. To the best of our knowledge, this represents the first study dedicated to the Suzuki–Miyaura reaction using a heterogeneous catalyst in bioderived GVL as the reaction medium, also reporting a general substrate scope. To further improve the overall sustainability of the process, MW irradiation was exploited to improve the energy efficiency, drastically decreasing the reaction time. With the aim to overcome the scale-up limitations and thus to move towards a continuous flow protocol, the conditions were optimized, balancing the efficiency with the mixture homogeneity using a minimum water content. This was crucial to avoid the precipitation of biphenyl products in the final mixture, thus allowing both an easy separation of the heterogeneous catalyst and a continuous flow protocol without additional regeneration and/or washing steps.



The optimized conditions were efficient in the coupling of different substituents; both aryl halides and phenylboronic acids achieved good to excellent isolated yields (54–99%). It should be mentioned that the optimized protocol led also to the definition of a step-economical synthesis of Fenbufen, well tolerating the presence of a free carboxylic acid group and thus affording the desired product in quantitative yield.

Thanks to the good performances of Pd/PiNe, further efforts were devoted to the optimization of the work-up to minimize the waste generation and access low *E*-factor values (3.2–9.4). The choice of the reaction medium promoted the continuous flow synthesis of biphenyls and further decreased the waste generation associated with the process, enhancing the *E*-kernel contribution to the total *E*-factor.

Author contributions

The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript. F. V.: investigation, methodology, data analysis, and manuscript preparation – review; B. D. E., M. C., and S. C.: investigation and manuscript editing; Y. G.: project administration and manuscript preparation – review and editing; L. V.: conceptualization, project administration, and manuscript preparation – review and editing.

Conflicts of interest

There are no conflicts to declare.

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