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Research Article

A greener approach to Buchwald-Hartwig coupling. A sustainable Pd/C-catalyzed Csp^2–N bond formation under microwave irradiation and bio-based solvent

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ABSTRACT

The Buchwald-Hartwig coupling enables the grafting of nitrogen-containing functionalities onto molecules, facilitating the synthesis of a wide variety of molecular structures. However, several challenges impact the sustainability of this coupling. In our pursuit of a more sustainable Buchwald-Hartwig process, we report an optimized protocol that enhances energy efficiency and minimizes waste. Utilizing recoverable Pd/C as a catalyst, we performed the process in the bio-based solvent 2-MeTHF. To further boost energy efficiency, we employed microwave heating technology, resulting in improved overall process efficiency and reduced reaction times. This optimized approach allowed for the synthesis of a wide array of 17 variously functionalized aryl-amines. Thanks to the optimized workup procedure that facilitated the recovery and reuse of the catalyst, ligand, and 2-MeTHF, we achieved a reduced E-Factor ranging from 5.8 to 14.9, further contributing to the sustainability of the process.

1. Introduction

Designing synthetic processes with a reduced environmental footprint is crucial for the sustainable development of the current chemical production value chain. Although this goal is central to both the scientific community and the industrial sector, achieving it is complex and requires a holistic approach. Key considerations in green synthesis include the use of catalysts, choice of solvents, energy consumption, chemical feedstocks, safety of raw materials, overall process safety, and the recovery and reusability of materials. All these aspects should be comprehensively implemented in green synthesis [1–3].

C–N bond formation enables the assembly of complex molecules and grafts nitrogen-containing functionalities onto molecules, making it a versatile and powerful tool in the synthesis of natural products (NPs), sensors, ligands, polymers, and active pharmaceutical ingredients (APIs) [4]. The Pd-catalyzed Buchwald-Hartwig coupling has emerged as a general technology for the formation of Csp^2–N bonds, enabling the preparation of aromatic amines from aryl-halides and variously functionalized amines. Compared to traditional synthetic strategies [5–8], it offers the advantages of being a one-step reaction and showing greater tolerance towards functional groups. This coupling is widely applied in the large-scale synthesis of APIs, such as ZM54986F 5-HT receptor antagonist [9], LY2784544 JAK2 Inhibitor [10], PF-06815345 [11], EGFR T790 M Inhibitor [12], Abemaciclib [13], GDC-0022 RORc Inhibitors [14], Ziritaxestat, BIIB068 Hemi-Adipate Co-Crystal [15].

Given its wide applicability, Buchwald-Hartwig has seen three decades of intense research efforts to optimize and enhance its effectiveness, defining novel homogeneous catalysts and their ligands [16–19]. However, several challenges affect the sustainability of this coupling, including the high costs of homogeneous palladium catalysts and phosphine-based ligands, the large ecological footprint due to the required multi-step synthesis, difficulties in catalyst and ligand

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separation, recycling, and contamination of the final product. Reports about improving the sustainability of Buchwald-Hartwig coupling need to be included in the literature, making considerable room for improvement.

The first step is the adoption of heterogeneous catalysts [17,20,21]. Additionally, there is an ongoing commitment to improving energy efficiency and eco-compatibility, which has sparked interest in microwave-assisted reactions [22,23]. The latter has proven effective for heating chemical reactions and offers a cost-effective alternative to traditional methods, proving its powerfulness for a wide range of coupling reactions [24]. Solvents play a crucial role in the environmental impact of production processes, so avoiding the use of toxic and harmful solvents is essential [25–30]. Replacing solvents derived from fossil raw materials with safer, bio-based alternatives is highly desirable [31–36]. Looking for an eco-friendly and biomass-derived solvent, 2-methyltetrahydrofuran (2-MeTHF) presents a promising alternative to the ether solvents typically employed in this coupling [37]. This solvent boasts a promising environmental footprint, as it is derived from renewable feedstocks such as furfural and levulinic acid. Moreover, it undergoes abiotic degradation when exposed to sunlight and air [38–40].

Within our continued interest in the development of waste-minimized coupling reactions [41–44], herein, we report our efforts to minimize the environmental footprint of the Buchwald-Hartwig coupling method by combining the bio-based solvent 2-MeTHF with the readily available and widely applicable heterogeneous catalyst, commercial Pd/C. To enhance energy efficiency, we employed microwave heating, resulting in improved process efficiency and reduced reaction times. This approach facilitates the efficient synthesis of various functionalized arylamines, starting from primary and secondary aliphatic and aromatic amines (Fig. 1). Our methodology demonstrates superior sustainability compared to traditional Buchwald-Hartwig coupling, particularly through optimized workup procedures that eliminate the need for chromatographic columns.

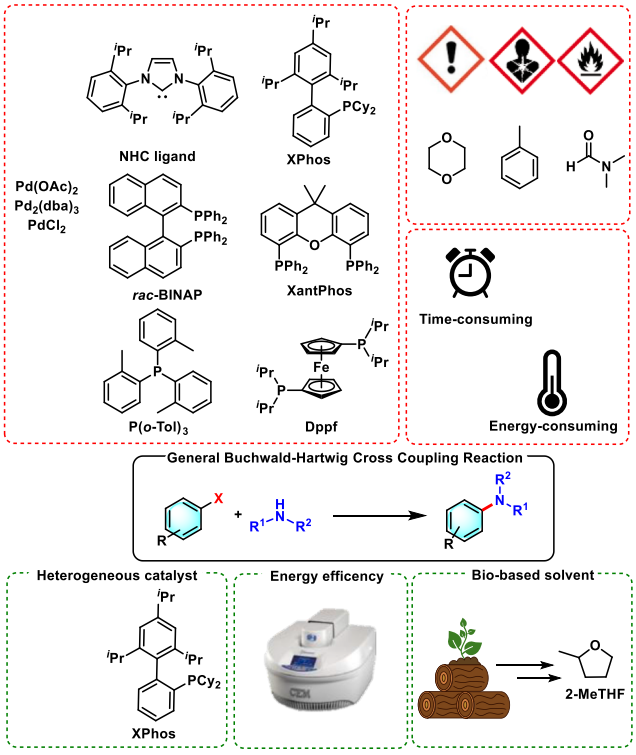
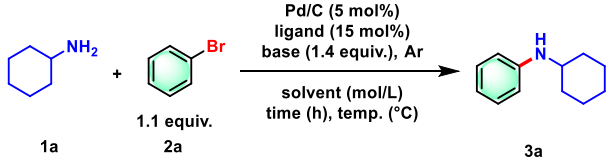


Fig. 1. Green features of the herein-reported Buchwald-Hartwig cross-coupling.

2. Results and discussion

Initial investigations were conducted by optimizing the reaction using model substrates cyclohexylamine (**1a**) and bromobenzene (**2a**) under conventional thermal heating. The reaction was first performed with Pd/C (10 wt%) as a heterogeneous catalyst, KO^{t}Bu (1.4 equiv.) as the base, and XPhos as the ligand, selected for its proven effectiveness with both aryl bromides and aryl chlorides [45]. Recognizing the solvent's crucial role in solubilizing the base and halide salts (KBr, NaBr), we evaluated the performance of the heterogeneous Pd catalyst in tetrahydrofuran (THF), mesitylene, toluene, and 1,4-dioxane. These experiments resulted in moderate conversion to compound **3a** (entries 1–4, Table 1). Notably, aromatic solvents such as toluene and mesitylene facilitated improved conversion rates compared to THF and 1,4-dioxane; however, complete conversion was not achieved. Aiming to minimize the environmental footprint, we tested various bio-based greener solvents: γ-valerolactone (GVL), cyclopentyl methyl ether (CPME), tert-amyl methyl ether (TAME), and 2-MeTHF (entries 5–8). The more polar GVL resulted in no conversion to the product **3a** (entry 5), whereas the lower polar TAME provided results comparable with 1,4-dioxane (entry 6). Conversely, CPME exhibited performance comparable to that of aromatic solvents, while the moderately polar solvent 2-MeTHF achieved enhanced conversion rates (entries 7 and 8). In addition to its optimal polarity range, which facilitates effective solubilization of bases while limiting the solubility of inorganic salts, thereby contributing to catalyst stability, 2-MeTHF enhances energy efficiency by accelerating the reaction rate compared to CPME. This improvement enables the reaction to proceed efficiently at 90 °C, achieving superior outcomes in just 6 h instead of 12 (entries 9 and 10). Among the tested inorganic bases, NaO^{t}Bu showed lower results compared to KO^{t}Bu (entry 11). Tricyclohexyl phosphine and triphenylphosphine ligands (entries 14

Table 1
Reaction condition optimization for the Pd/C-catalyzed Buchwald-Hartwig coupling under thermal heating[a].



Entry	Solvent	Base	Ligand	C (%)[b]
1	THF	KO^{t}Bu	XPhos	61
2	Mesitylene	KO^{t}Bu	XPhos	76
3	Toluene	KO^{t}Bu	XPhos	77
4	1,4 Dioxane	KO^{t}Bu	XPhos	50
5	GVL	KO^{t}Bu	XPhos	0
6	TAME	KO^{t}Bu	XPhos	49
7	CPME	KO^{t}Bu	XPhos	79
8[c]	2-MeTHF	KO^{t}Bu	XPhos	>99 (80)
9[d]	2-MeTHF	KO^{t}Bu	XPhos	86
10[c,d]	2-MeTHF	KO^{t}Bu	XPhos	87 (78)
11	2-MeTHF	NaO^{t}Bu	XPhos	69
12	2-MeTHF	CH_3CO_2Na	XPhos	<5
13	2-MeTHF	$CsCO_3$	XPhos	<5
14	2-MeTHF	KO^{t}Bu	Cy_3P	<5
15	2-MeTHF	KO^{t}Bu	Ph_3P	19
16	2-MeTHF	KO^{t}Bu	SPhos	73
17	2-MeTHF	KO^{t}Bu	QPhos	57
18	2-MeTHF	KO^{t}Bu	/	<5

[a] Reaction condition: 0.5 mmol (**1a**), 1.1 equiv. (**2a**), Pd/C (5 mol%), XPhos (15 mol%), base (1.4 equiv.), solvent (1.4 mol/L), 110 °C, 12 h, under Ar.
[b] Conversion determined by glc analysis, the remaining materials are unreacted **1a** and **2a**, unless otherwise stated.
[c] 90 °C.
[d] 6 h. The isolated yield is reported in parentheses.

and 15) resulted in low conversion rates. In contrast, bulkier and more rigid phosphine ligands effectively activated the catalyst, but none outperformed XPhos (entries 16 and 17). No reaction occurred without ligands (entry 18), emphasizing the essential role of the ligand in the mechanism (Table S1 in Supporting information for details).

To maximize energy efficiency and yield, we shifted from conventional thermal heating to microwave irradiation under our optimal conditions (entry 8, Table 1). The uniform heating across the sample accelerated the process and enhanced heating efficiency, avoiding the formation of unwanted side products. Despite the advantages of MW-based technology, it is worth mentioning that hot spot formation remains the main safety issue, especially when carbon-supported solid catalysts are used [46–49].

The optimization was performed under dynamic MW irradiation mode by maintaining a constant temperature with the power fixed at 150 W. Overpressure was carefully regulated at 10 bar to prevent the reaction components from evaporation. Kinetic experiments were carried out at different concentrations and temperatures to determine the optimal reaction time required for complete conversion. At 90 °C for 1.5 h, a lower conversion was observed compared to 110 °C. Increasing the temperature to 155 °C positively influenced conversion; however, it also resulted in the formation of hot spots. Complete conversion was achieved in just 2 h at 110 °C (Table S2 in Supporting information for details), reducing the reaction time by sixfold. A dilution of 0.7 mol/L ensures efficient mass transfer and prevents the formation of hot spots, favoring homogeneous irradiation. In contrast, higher dilution led to a decrease in reactivity (Fig. 2).

At this stage, we optimized the workup and purification process. Recognizing that the Br atom is released into the reaction mixture as KBr, thereby increasing the environmental footprint, we aimed to remove the inorganic salt without adding water by using recoverable solvents through distillation and avoiding chromatographic columns. At the end of the reaction, Pd/C was centrifuged and washed with 2-MeTHF. The bio-based solvent was efficiently recovered by distillation (b.p. 87 °C) with a yield of 95 %. The purity of the recovered solvent was confirmed by NMR analysis, allowing it to be reused multiple times in the same reactions. The inorganic salt (KBr) and excess base were removed by filtration from heptane, which was then distilled, recovering 90 %. Cold methanol was added to precipitate the XPhos, which was then recovered by filtration (91 % yield), dried under vacuum, and reused without any significant change in selectivity or conversion. NMR confirmed the purity of the XPhos. The pure product was recovered by distilling the methanol, recovering 95 %. This approach enabled the recovery and reuse of all reaction components except for the base and its byproducts (KBr and ^{t}BuOH).

The optimized reaction conditions for both thermal and microwave irradiations, along with a waste-minimizing workup, were applied in the synthesis of a wide range of various functionalized arylamines. This was achieved by varying both the amine (**1a-l**) and aryl halide (**2a-f**). Representatively, chlorobenzene (**2b**) was applied in the synthesis of products **3a**, **3k**, and **3l**, yielding comparable results to those obtained using bromobenzene (**2a**). In this context, it should be noted that the choice of aryl halides has already been quantified in terms of its impact on the cross-coupling reaction [50]. Cyclohexylamine (**1a**) was tested with variously functionalized aryl bromide (**2a**, **2c**, **2d**, and **2e**), obtaining products **3a**, **3b**, and **3c** in good yields. The reactivity was found to be strictly related to the aromaticity of the aryl halide. As expected, the use of 3-bromopyridine (**2e**) led to a moderate yield of **3d**, which can be attributed to the increased nucleophilic character of the pyridine ring. This electronic effect reduces the electrophilicity of the aryl halide, thereby lowering its reactivity in the coupling reaction. Linear aliphatic primary (**1b**) and secondary (**1c**) enable the obtainment of, respectively, **3e** and **3f** in good yields. Benzylamine (**1d**) was also efficiently utilized, yielding **3g** with good results. Cyclic secondary amines were also applied, obtaining products **3h**, **3i**, and **3j** with good yields.

Anilines, *N*-methyl aniline, and diphenylamine were successfully applied as well, producing **3k**, **3l**, **3m**, **3n**, **3o**, **3p,** and **3q** in good yields under both microwave and thermal irradiation conditions. Overall, the yield was improved under MW irradiation, reducing the reaction time compared to thermal heating. All the reported yields are isolated yields (Scheme 1).

The E-Factor was calculated for all the products, obtaining values

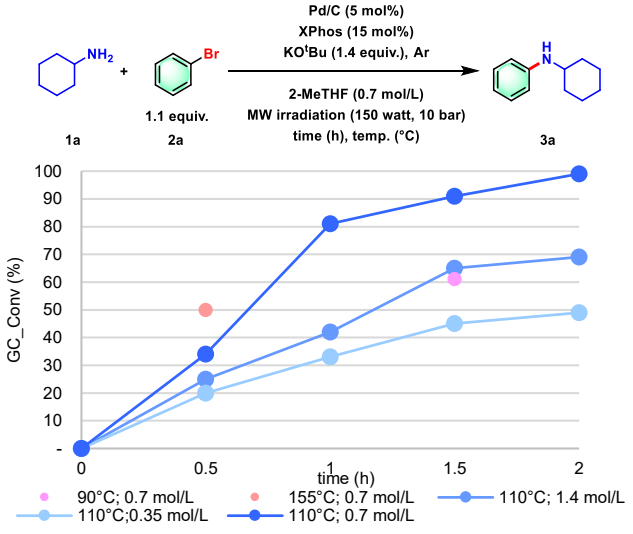
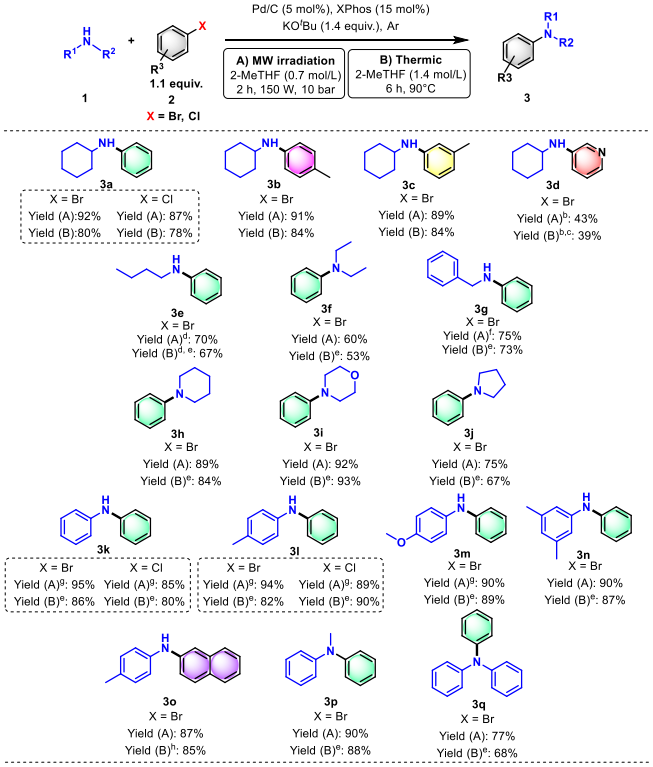


Fig. 2. Kinetic test under microwave irradiation at different concentrations. Reaction condition: 0.5 mmol (**1a**), 1.1 equiv. (**2a**), Pd/C (5 mol%), XPhos (15 mol%), KO^{t}Bu (1.4 equiv.), 2-MeTHF, pressure 10 bar, power 150 W.



[a]Reaction Condition: **Method A - 1a** (0.5 mmol), **2** (1.1 equiv.), Pd/C (5 mol%), XPhos (15 mol%), KO^{t}Bu (1.4 equiv.), 2-MeTHF (0.7 mol/L), 150 W, 10 bar, 2 h; **Method B - 1a** (0.5 mmol), **2** (1.1 equiv.), Pd/C (5 mol%), XPhos (15 mol%), KO^{t}Bu (1.4 equiv.), 2-MeTHF (1.4 mol/L), 90°C, 12 h; [b]Cromatographic column is required for the purification; [c]16 h, 90°C; [d]**1b** (2 equiv.), **2** (0.5 mmol); [e]6 h, 90°C; [f]1 h e 45 min; [g]1 h e 30 min; [h] 6 h, 110°C, 1 mol/L.

Scheme 1. The substrate scope of Pd/C catalyzed Buchwald-Hartwig coupling with 2-MeTHF under both microwave (**Method A**) and thermal (**Method B**) irradiation.

ranging from 5.8 to 14.9, excluding products in which a chromatographic column is required (Table S4, E-Factor calculation in Supporting information for details).

To enhance the applicability of the developed protocol, the reaction was scaled-up to a 10 mmol scale, resulting in the synthesis of compounds **3a** and **3i** with isolated yields of 96 % and 95 %, respectively. At this stage, we conducted a comprehensive evaluation of the metrics AE (Atom Economy), RME (Reaction Mass Efficency), MRP (Material Recovery Parameter), and E-Factor for product **3i**, comparing our results with established protocols in the literature. We selected a homogeneous Pd-catalyzed protocol reported by Buchwald *et al.* [45] and three heterogeneous Pd-catalyzed protocols: one using Pd/Al_2O_3-NHC reported by Glorius *et al.* [17], Pd/C-dppf reported by H. Sajiki *et al.* [51], and Pd-nanoparticles reported by M. Arisawa *et al.* [23]. The release of halo-atoms negatively impacted the atom economy of the process (Fig. 3). However, through optimized workup and purification, we were able to reduce the E-Factor to 2.2 (at 10 mmol scale) from over 100. Additionally, the recovery of XPhos and the solvent used allowed for an increase in the values of MRP and RME, ensuring a higher VMR, as visualized and quantified by the comparison of the radial polygons in Fig. 3. [52]. (Table S4 in Supporting information for details).

The synthetic utility of the heterogeneous catalyst is demonstrated by its easy recovery and reuse after reaction completion. Recycling experiments were conducted to evaluate the catalytic performance and stability of Pd/C. To stress the heterogeneous catalyst, its stability was examined under our optimized conditions for substrates **1a** and **2a** using microwave irradiation for 1.5 h, at which point the conversion was not yet complete. The catalyst was recovered and reused for five consecutive

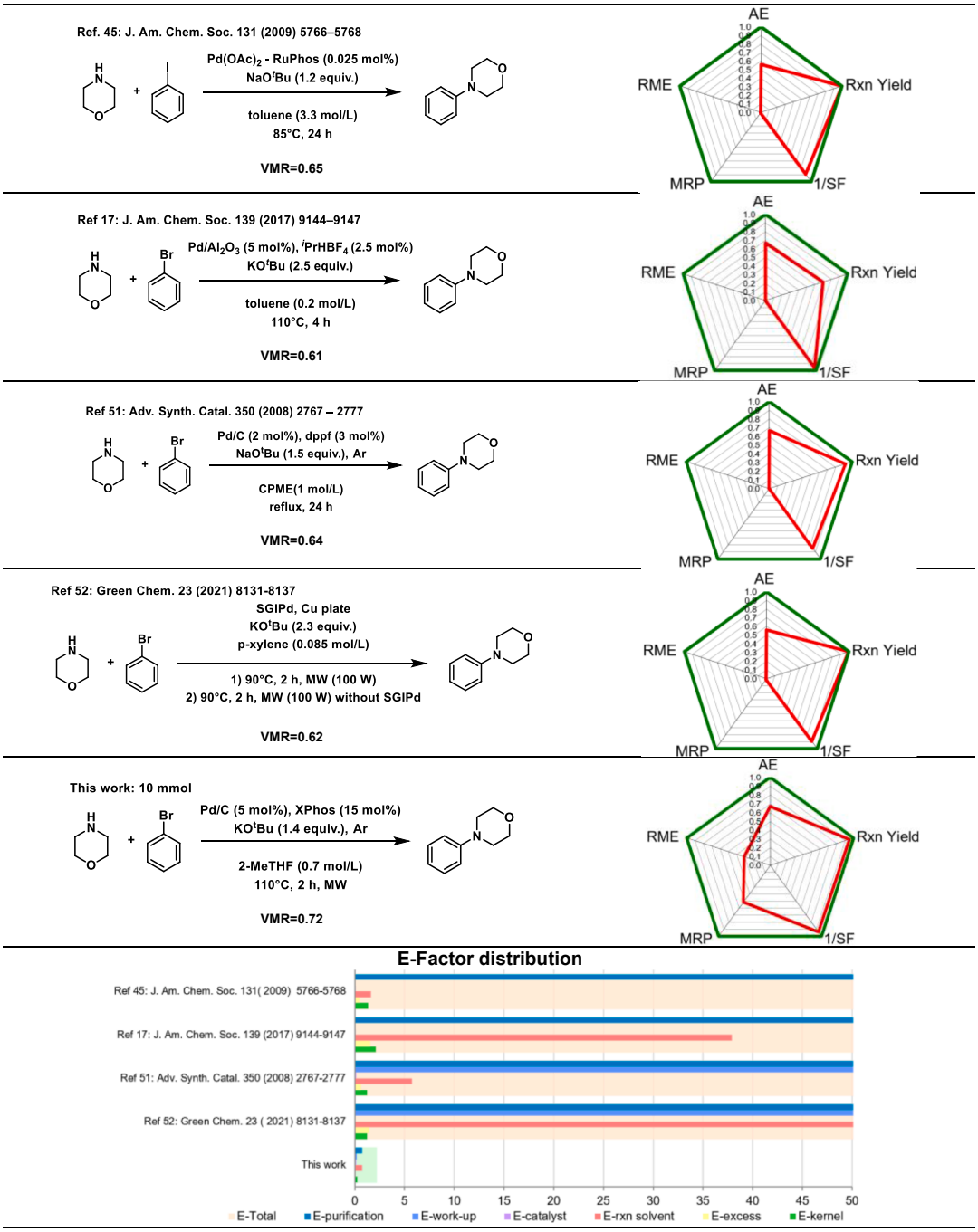


Fig. 3. Comparison of green metrics in Buchwald-Hartwig coupling and E-Factor distribution.

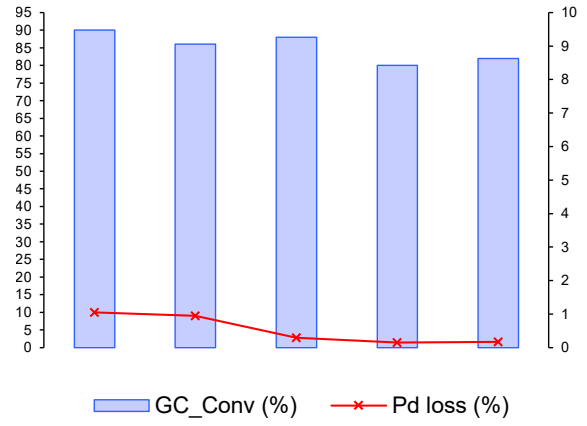


Fig. 4. Recycling of Pd/C under microwave irradiation. Reaction condition: 0.5 mmol (**1a**), 1.1 equiv. (**2a**), Pd/C (5 mol%), XPhos (15 mol%), KO^{t}Bu (1.4 equiv.), 2-MeTHF (0.7 mol/L), pressure 10 bar, power 150 W, time 1.5 h.

runs with negligible loss in efficiency. MP-AES analysis revealed a reduced percentage of Pd loss in solution with each run, ranging from 0.15 % to 1.05 % of the total amount of Pd used (Fig. 4). (Supplementary Materials, Table S3 in Supporting information for details).

The morphology of fresh and reused Pd/C catalysts, tested over five consecutive cycles under optimized MW irradiation conditions, was examined using HR-TEM and XPS analysis. Initial HR-TEM results showed that Pd nanoparticles in the fresh commercial sample were well-dispersed across the carbon support, with diameters of 2,7 nm ± 0.6. As expected, HR-TEM images at 100 μm after five cycles revealed significant morphological changes. Dynamic effects led to increased aggregation of Pd particles, resulting in a less uniform distribution across the support, though nanometric particle dimensions were preserved (Fig. 5, Fig. S1 in Supporting information for details). The XRD patterns of the fresh and spent Pd/C catalysts display two characteristic peaks for Pd nanoparticles at 40° and 46°, reflecting the crystalline structure of Pd on the carbon support. However, the XRD pattern of the spent Pd/C also shows prominent peaks at 27° and 38°, attributed to residual KBr, an inorganic contaminant produced during the process (Fig. 6; Fig. S2 in Supporting information for details). HR-TEM and XRD analyses confirm that, despite some degree of Pd particle aggregation and minor KBr contamination, the catalyst retained its nanometric particle size over five consecutive runs and maintained good catalytic activity, observing just a slight decrease in the conversion of less than 10 % within these cycles, as shown in Fig. 4. A more pronounced decline in activity occurred beyond the fifth cycle, likely due to progressive deactivation processes. KBr contamination is a key factor contributing to catalyst deactivation, but its removal is not straightforward. Thermal treatment at 130 °C under vacuum helped preserve a favorable distribution of Pd nanoparticles, which supported sustained catalytic performance (Fig. S3). Nevertheless, to mitigate long-term deactivation, future efforts should focus on developing strategies such as catalyst pre-treatment or regeneration.

Additional experiments have been done to hypothesize whether the catalytic mechanism can be considered heterogeneous. A hot-filtration test at 30 min showed no further conversion after filtration of the Pd-catalyst (34 % of GC_Conv), indicating the absence of active species in solutions. The related MP-AES revealed a negligible amount of Pd in the solution (0.01 %), confirming the previous observation. For safety reasons, the Hg test was performed under thermal conditions. After the

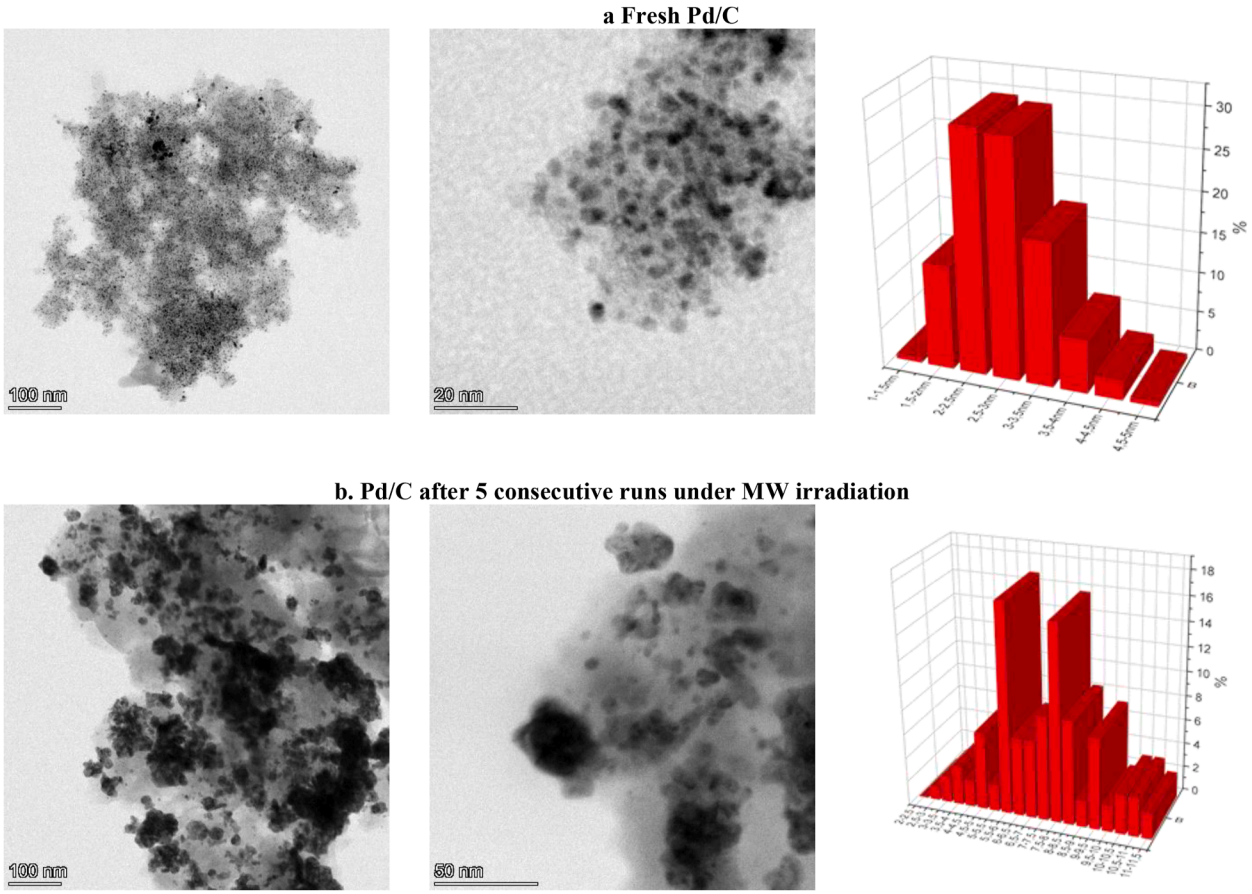


Fig. 5. TEM images of Pd/C: **a.** Fresh Pd/C; **b.** Spent Pd/C after 5 consecutive runs under microwave irradiation.

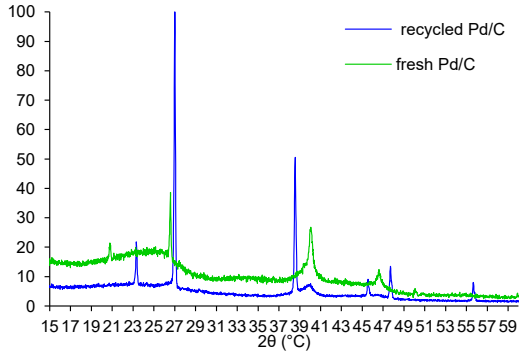


Fig. 6. The XRD pattern of the fresh and the spent Pd/C.

addition of Hg, the reaction experienced a significant slowdown, obtaining a conversion of just 24 % after the reaction time, suggesting the involvement of surface-bound Pd species. To further investigate the catalytically active species, a mixture of Pd/C (5 mol%) and XPhos (15 mol%), along with KO^{t}Bu (1.4 equiv.) in 2-MeTHF (0.7 mol/L), was placed under microwave irradiation at our optimized reaction conditions. After 2 h, the heterogeneous catalyst was filtered out, and the reactants **1a** and **2a** were added to the homogeneous solution under an inert atmosphere. This solution was then placed under microwave irradiation under the same optimized conditions. However, no conversion was observed, indicating that no leaching of Pd-XPhos, as confirmed by MP-AES analysis. Based on these experimental data, we propose a heterogeneous catalytic mechanism, contrasting with the findings of Sajiki et al., who identified a Pd–dppf complex as the active species, suggesting a homogeneous pathway when employing Pd/C as a catalyst. This divergence can be attributed to the use of a different ligand, XPhos, instead of dppf, along with the enhanced energy efficiency provided by microwave irradiation, which accelerates reaction kinetics. Additionally, the use of 2-MeTHF contributes to catalyst stabilization and mitigates palladium leaching, as evidenced by the absence of Pd–XPhos complex formation.

3. Conclusion

In conclusion, we report a general Buchwald-Hartwig process with a reduced environmental footprint that enhances energy efficiency and minimizes waste. The widely available commercial Pd/C was effectively utilized as a heterogeneous catalyst. The process was optimized using the bio-based solvent 2-MeTHF. To further improve energy efficiency, microwave heating technology was efficiently applied, reducing reaction times by sixfold. The catalyst was successfully recycled over five consecutive runs. HR-TEM and XRD analysis of the recovered material confirmed its nanometric dimensions.

The optimized conditions under both thermal and microwave irradiation enabled the synthesis of 17 variously functionalized arylamines with a reduced E-Factor ranging from 5.8 to 14.9.

Overall, the yield was improved under microwave irradiation, reducing reaction time compared to thermal heating. The workup procedure was optimized to enable the recovery and reuse of all reaction components—the Pd/C, XPhos ligand, and 2-MeTHF—except for the base and its by-products (KBr and ^{t}BuOH), further contributing to the process's sustainability.

4. Experimental

4.1. General procedure for buchwald-hartwig coupling under microwave irradiation (method A)

In a 10 mL microwave vial equipped with a magnetic stirrer, cyclohexylamine (**1a**) (0.5 mmol), KO^{t}Bu (0.7 mmol, 1.4 equiv.), Pd/C 10 wt % (5 mol%, 0.025 mmol), XPhos (15 mol%, 0.075 mmol), bromobenzene (**2a**) (1.1 equiv., 0.55 mmol), and 2-MeTHF (0.7 mL) were consecutively added under an argon atmosphere. The reaction was kept under dynamic microwave irradiation (T = 110 °C, μλ: 150 W, pressure: 10 bar) for 2 h. After the reaction time, the Pd/C was centrifuged and washed with 0.5 mL of 2-MeTHF. The 95 % of 2-MeTHF was distilled and recovered. The inorganic salts were filtered out by washing with 1.5 mL of heptane, and 90 % was recovered by distillation. Adding 5 mL of cold MeOH, product **3a** was purified from XPhos, which was recovered for 91 % by filtration. The pure product **3a** was obtained with a yield of 92 %

4.2. General procedure for buchwald-hartwig coupling under thermal heating (method B)

In a 4 mL vial equipped with a magnetic stirrer, cyclohexylamine (**1a**) (0.5 mmol), KO^{t}Bu (0.7 mmol, 1.4 equiv.), Pd/C 10 wt% (5 mol%, 0.025 mmol), XPhos (15 mol%, 0.075 mmol), bromobenzene (**2a**) (1.1 equiv., 0.55 mmol) and 2-MeTHF (0.35 mL) were consecutively added under an argon atmosphere. The reaction was kept under stirring at 90 °C for 12 h. After the reaction time, the Pd/C was centrifugated and washed with 0.5 mL of 2-MeTHF. The 95 % of 2-MeTHF was distilled and recovered. The inorganic component was filtered out by washing with 1.5 mL of heptane, and 90 % was recovered by distillation. Adding 5 mL of could MeOH product **3a** was purified from XPhos, which was recovered for 91 % by filtration. The pure product (**3a**) was obtained with a yield of 80 %

CRediT authorship contribution statement

Giulia Brufani: Writing – original draft, Methodology, Investigation. **Marta Ciani:** Writing – original draft, Methodology, Investigation. **Massimo Calamante:** Writing – original draft, Methodology, Formal analysis. **Francesco Mauriello:** Writing – original draft, Methodology, Funding acquisition. **Luigi Vaccaro:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gresc.2025.06.011.

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