chemistry proceedings

MDPI

Proceedings

Direct Arylation-Based Synthesis of Carbazoles Using an Efficient Palladium Nanocatalyst under Microwave Irradiation †

H. Sebastián Steingruber [1], Pamela Mendioroz [1], María A. Volpe [2] and Darío C. Gerbino [1,*]

[1] Instituto de Química del Sur INQUISUR (CONICET-UNS), Departamento de Química, Universidad Nacional del Sur, Avenida Alem 1253, Bahía Blanca 8000, Argentina; sebastian.steingruber@uns.edu.ar (H.S.S.); pamelamendioroz@gmail.com (P.M.)

[2] Planta Piloto de Ingeniería Química, PLAPIQUI (CONICET-UNS), Camino La Carrindanga Km 7, Bahía Blanca 8000, Argentina; mvolpe@plapiqui.edu.ar

* Correspondence: dgerbino@uns.edu.ar; Tel./Fax: +54-291-459-5187

† Presented at the 24th International Electronic Conference on Synthetic Organic Chemistry, 15 November–15 December 2020; Available online: https://ecsoc-24.sciforum.net/.

Abstract: Herein, an eco-friendly palladium-catalyzed tandem reaction for the one-pot synthesis of carbazoles under microwave irradiation is reported. This approach involves an amination and a direct arylation from available and inexpensive anilines and 1,2-dihaloarenes. For the development of this purpose, a novel recoverable palladium nanocatalyst supported on a green biochar under ligand-free conditions is used. Compared with other existing palladium-based protocols, the present synthetic methodology shows a drastic reduction in reaction times and excellent compatibility with different functional groups, allowing to obtain a small library of carbazoles with high yields and regioselectivity. The novel heterogeneous palladium nanocatalyst can be recycled and reused up to five times without significant loss activity.

Keywords: carbazoles; tandem reaction; microwave-assisted synthesis; palladium nanoparticles; green biochar

Citation: Steingruber, H.S.; Mendioroz, P.; Volpe, M.A.; Gerbino, D.C. Direct Arylation-Based Synthesis of Carbazoles Using an Efficient Palladium Nanocatalyst under Microwave Irradiation *Chem. Proc.* **2021**, *3*, 70. https://doi.org/10.3390/ecsoc-24-08314

Published: 14 November 2020

1. Introduction

9H-carbazole constitutes a predominant nitrogen-containing heterocyclic compound present in both synthetic and naturally occurring alkaloids. Their planar structure is broadly distributed in natural bioactive products with significant biological properties including antibiotic, antimicrobial, anti-inflammatory, antioxidant, neuroprotector, and antitumoral [1,2]. In addition, carbazole scaffolds are useful π-extending building blocks for organic materials, such as polymeric light-emitting diodes (PLEDs) and organic light-emitting devices (OLEDs) (Figure 1) [3].

Owing to the relevance of the carbazole framework, it has emerged as an important molecular target in certain areas such as medicinal chemistry, science of materials, and industry. An extensive amount of research has been dedicated to introducing structural modifications to natural occurring carbazoles, as well as the synthesis of brand-new derivatives and finding new and efficient ways to obtain them from readily available, low-cost materials. In this context, direct-arylation of arenes is an outstanding strategy from an economic and environmental point of view in cross-coupling reactions, using stoichiometric quantities of organometallic reactants. Among the aryl halides, the most interesting would be the chlorides, owing to their low costs and wide diversity [4].

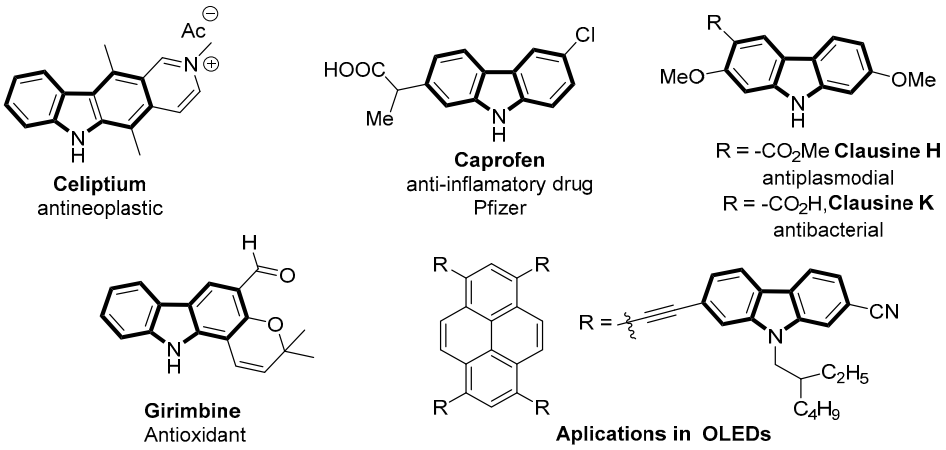


Figure 1. Relevance of carbazole motif in active alkaloids and organic materials. OLED, organic light-emitting device.

Manifold synthetic approaches for the construction of the central pyrrole ring have been extensively reported in the last decade. This aim has been achieved by transition-metal catalyzed intramolecular C-H amination of substituted biaryls and intramolecular coupling of *N,N*-diarylamines through C–C bond formation (Figure 2) [5].

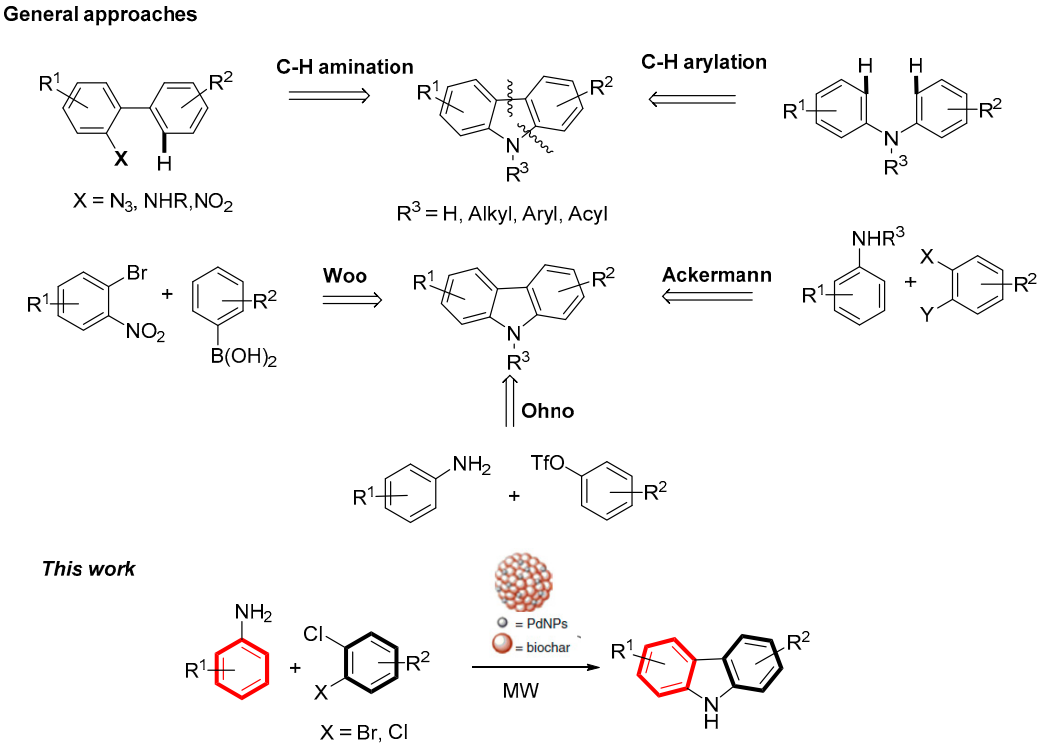


Figure 2. Approaches towards the synthesis of carbazole derivatives.

On the other hand, direct synthesis of carbazoles through sequential palladium catalysed cross-coupling C-N/C-C bond formation has emerged as an attractive synthetic approach in the last decade.

In 2009, Ohno and co-workers reported an interesting *N*-arylation and oxidative biaryl coupling for the carbazole synthesis from anilines and aryl triflates under homogenous palladium (II) acetate as catalyst [6].

In 2016, Woo and co-workers reported the one-pot synthesis of carbazoles via Suzuki cross-coupling and consecutive reductive Cadogan cyclization employing *ortho*-halonitroarenes and arylboronic acids as starting materials [7]. Despite these considerable advances, they require complex precursors, drastic reaction conditions, expensive non-recoverable catalysts, and the presence of phosphine ligands and/or additives.

These drawbacks could be addressed by heterogeneous nanocatalysis based on transition metals, which represent enormous progress in both industry and academic areas, owing to their advantages related to atomic economy, low toxicity, atomic efficiency, and eco-friendliness [8].

In this context, microwave-assisted organic synthesis (MAOS) denotes a mighty and useful tool in heterocyclic chemistry that allows to reduce reaction time and the generation of by-products, leading to an improvement in the overall yields. Therefore, the combination of MAOS and heterogeneous catalysis represents an attractive eco-friendly approach for the synthesis of functionalized carbazoles [9].

Ackerman and co-workers reported an elegant palladium-catalyzed *N*-arylation and C-H activation, leading to the synthesis of carbazoles from easily attainable anilines and 1,2-dihaloarenes [10]. The cited protocol is limited because of the need for activated anilines, long reaction times, the presence of phosphine as a ligand, and unrecoverable palladium catalysts.

Inspired by these results, we herein propose an alternative, efficient, and straightforward palladium-catalyzed intermolecular C-N bond formation and intramolecular C-H arylation between anilines and 1,2-dihaloarenes, which allows access to carbazole derivatives through a *one-pot* process. For this purpose, a novel palladium heterogeneous catalyst and microwave irradiation were employed. The nanoparticles of palladium are supported on biochar (henceforth referred to as PdNPs/BC)—the solid residue of the pyrolysis of sunflower seed hulls, a plentiful and regional agricultural waste.

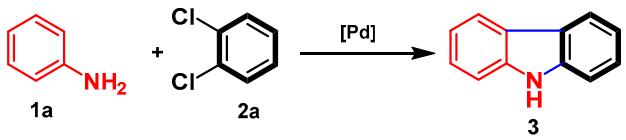
Moreover, through the application of microwave irradiation, the severe reaction conditions used by other known protocols have been improved and reaction times have been shortened from up to 18 h to barely 25 min.

2. Results and Discussion

We began our investigations using aniline 1a and 1,2-dichlorobenzene 2a as starting materials in the presence of a set of palladium-based catalysts, both homogeneous and heterogeneous (Table 1). For this purpose, the reaction conditions proposed by Ackermann were used as a starting point {[Pd] (5 mol%), *N*,*N*-dimethylpyrrolidine (NMP), K_3PO_4, 130 °C, 18 h} (Table 1). During control experiments, the tested homogeneous catalysts showed low activity and efficiency in the generation of our desired product. To improve these results, we made use of a powerful and versatile tool to decrease reaction times and limit the generation of by-products; that is, microwave-assisted organic synthesis. No reaction progress was detected when the reaction was performed without catalyst (entry 1). To our satisfaction, the corresponding carbazole **3** was obtained in 19% yield when our novel PdNPs/BC was used under microwave irradiation (entry 7). In contrast, the thermal conditions at both 130 °C and 180 °C for 18 h led to carbazole in low yields (entries 7 and 10). An improvement of the yield (43%) was accomplished when the reaction was subjected at 200 W and 180 °C for 25 min. Among the commercial homogeneous catalysts tested, $PdCl_2(PPh_3)_2$ and $PdCl_2(MeCN)_2$ led to **3** in low yields (entry 2 and 3), whereas $Pd(PPh3)_4$ and $Pd_2(dba)_3$ showed less or no activity (entry 2 and 4). By increasing the temperature using the homogeneous $PdCl_2(MeCN)_2$, no reaction progress was detected (entry 6). Additionally, other nanopalladium heterogeneous catalysts were tested. PdNPs/Al_2O_3 led to **3** in low yields in both thermal and microwave conditions at 130 °C and 180 °C, whereas PdNPs/PbO were inactive in the same reaction conditions (entries 8 and 9).

The low reactivity of both PdNPs supported on Al_2O_3 and PbO, respectively, by comparison with PdNPs/BC strongly suggests that BC is not an innocent support for the reaction. The reason for BC promoting Pd catalytic features would be related the peculiar surface chemistry of BC, which is a highly functionalized material. Unveiling the exact nature of BC surface and its role in reaction is beyond the scope of the present study, and will be discussed in future studies of our group.

Table 1. Preliminary screening of Pd catalyst.

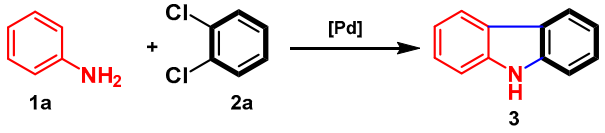


Entry	[Pd]	Temperature (°C)	Yield (%) Thermal [a,c]	Yield (%) MW [b,c]
1	---	130	---	---
2	$PdCl_2(PPh_3)_2$	130	6	trace
3	$Pd_2(dba)_3$	130	---	trace
4	$PdCl_2(MeCN)_2$	130	8	--
5	$Pd(PPh_3)_4$	130	---	---
6	$PdCl_2(MeCN)_2$	160	---	---
7	PdNPs/BC	130	11	19
8	PdNPs/PbO	130	--	trace
9	$PdNPs/Al_2O_3$	130	trace	9
10	PdNPs/BC	180	18	43
11	$PdNPs/Al_2O_3$	180	10	12

Standard reaction conditions: [a] Aniline (**1a**) 1.2 mmol, 1,2-dichlorobenzene (**2a**) (1 mmol), K_3PO_4 (3 mmol.). Palladium catalyst supported on biochar (PdNPs/BC) (5 mol%), *N*,*N*-dimethylpyrrolidine (NMP) (10.0 mL), 18 h. [b] Reaction was conducted at 200 W for 25 min. Time reaction monitored by TLC and GC-MS. [c] Isolated yield.

Subsequently, various reaction conditions such as solvents, bases, and PdNPs/BC loading were evaluated (Table 2). Upon decreasing the catalyst load to 2.5 mol%, a low yield of 3 (16%) was obtained (entry 1). Surprisingly, when the reaction was carried out using 15 mol% of the PdNPs/BC, the carbazole was obtained in 76% yield (entry 3). A moderate yield (57%) of carbazole was obtained when an intermediate load of catalyst (10 mol%) was used (entry 2). Next, several polar solvents with elevated boiling points were evaluated. Among the solvents tested, dimethyl sulfoxide (DMSO) at 180 °C demonstrated the best efficiency (entry 6), whereas *N*,*N*-dimethylformamide (DMF) and *N*,*N*-dimethylacetamide (DMAc) showed no significant changes in comparison with *N*-Methyl-2-pyrrolidone (NMP) (entries 4 and 5). Finally, different bases were examined. The inorganic base KOAc showed the best performance (entry 9), whereas different carbonates and organic bases such as NaO*t*-Bu did not improve yields (entries 8–11).

Table 2. Optimization of the reaction conditions for the one-pot synthesis of 9*H*-carbazole. [a].



Entry	PdNPs/BC (mol%)	Solvent	Base	Yield (%) [b]
1	2.5	NMP	K_3PO_4	16

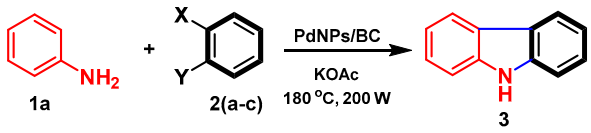
2	10	NMP	K_3PO_4	57
3	15	NMP	K_3PO_4	76
4	15	DMF	K_3PO_4	71
5	15	DMAc	K_3PO_4	73
6	15	DMSO	K_3PO_4	85
7	15	DMSO	KOAc	88
8	15	DMSO	K_2CO_3	84
9	15	DMSO	Cs_2CO_3	82
10	15	DMSO	Na_2CO_3	81
11	15	DMSO	NaO*t*-Bu	61

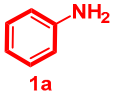
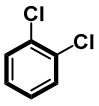
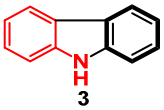
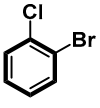
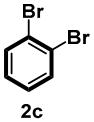
Reaction conditions: [a] Aniline (**1a**) 1.2 mmol, 1,2-dichlorobenzene (1 mmol), (**2a**) (2.1 mmol), base (3 mmol.). PdNPs/BC (mol%), solvent (5 mL) at 180 °C under microwave irradiation at 200 W for 25 min. Time reaction monitored by TLC and GC-MS. [b] Isolated yield. DMSO; DMF,; DMAc,.

Additionally, the effect sof irradiation time and power were also evaluated. When the reaction was subjected to 200 W for 25 min, a complete conversion of starting materials was observed, whereas prolonged times led to an increase in the formation of by-products. Performing the reaction at 100 W led to no reaction progress both at reaction times of 25 and 60 min. Irradiation power at 300 W for more than 25 min led to the carbazole in a lower yield. Therefore, the use of irradiation power at 200 W for 25 min was determined as the optimal condition.

Under the optimized reaction conditions (Table 2, entry 9), we carried out the scope and limitations to our methodology by employing different 1,2-dihaloarenes and aniline (**1a**) (Table 3). When the reaction was carried out using 1,2-dibromobenzene (**2c**), carbazole **3** was obtained in an excellent yield (90%). Besides, using 1-bromo-2-chlorobenzene (**2c**) as substrate, the desired product **3** was obtained in 81% yield. As shown in Table 3, the formation of carbazole was not limited while resorting to 1,2-dihaloarenes bearing good leaving groups, such as bromine. In this context, it is important to note that the present methodology enables to obtain carbazole using inexpensive aryl chlorides as electrophilic reagent. In addition, neither formation of homocoupling by-products nor significant differences in term of yields were observed using aryl chlorides instead of aryl bromides.

Table 3. Substrate scope for the synthesis of *9H*-carbazole. [a].

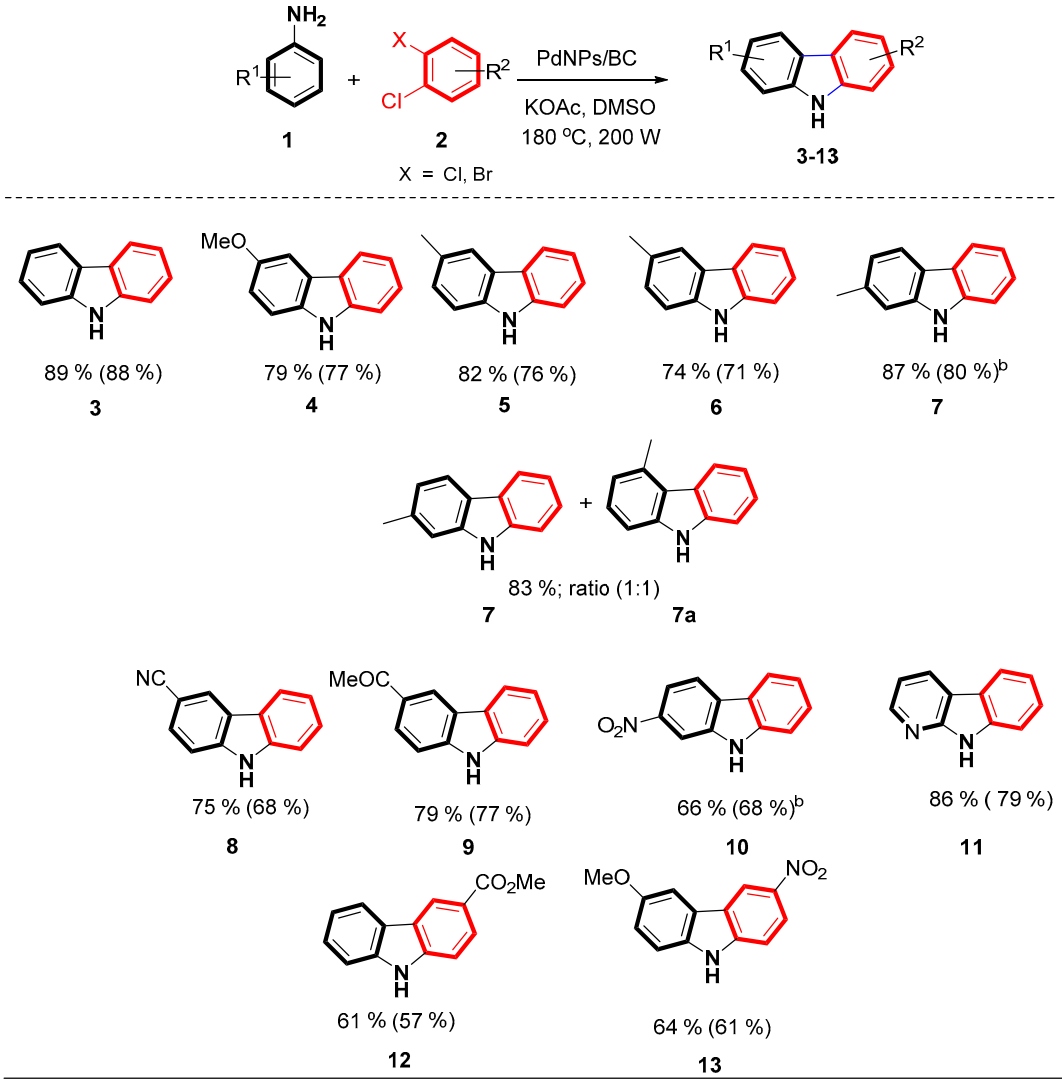


Entry	Aniline	1,2-Dihalobenzene	9*H*-Carbazole	Yield (%) [b]
1				88
2	**1a**		**3**	81
3	**1a**		**3**	90 [c]

[a] **Reaction conditions**: Aniline (1.2 mmol), *ortho*-dihalobenzene (1 mmol), PdNPs/BC (15 mol%), KOAc (3 mmol) in DMSO (5 mL) at 180 °C under MW (200 W) for 25 min. [b] Isolated yield. [c] Homocoupling products were detected (<5%).

Having established the reaction conditions, we studied the scope of the reaction using several anilines and 1,2-dihaloarenes bearing electron-donating and electron-withdrawing groups. As shown in Table 4, the present protocol is compatible with a variety of functional groups, including fluorine, nitro, methoxy, alkyl, and methyl ketones. The presence of moderate or stronger electron-donating groups in position 4, such as methyl or methoxy in aniline, afforded products **4** and **6** in excellent yields. In addition, the scope with anilines bearing electron-withdrawing groups, such as fluorine, nitrile, or methyl ketone groups, led to products **5**, **8**, and **9** in excellent yields (68–75%).

Table 4. Substrate scope for the direct synthesis of functionalized 9*H*-carbazoles [a].



Reagent and conditions: [a] Aniline (**1**) 1.2 mmol, *ortho*-dihalobenzene (**2**) (1 mmol), PdNPs/BC (15 mol%), KOAc (3 mmol), DMSO (5 mL), at 180 °C under microwave irradiation (200 W) for 25 min. Isolated yield after purification (in parentheses). [b] The reaction was conducted using 1-bromo-2-chlorobenzene.

Moreover, the chemo- and regioselectivity of the process was evaluated using asymmetrical anilines. When the reaction was carried out using 3-methylaniline and 1,2-dichlorobenzene, products **7** and **7a** were detected in the isomeric ratio of 1:1 by ^{1}H NMR, which denotes a low control of the regioselectivity. However, an excellent regioselectivity of

product **7** was observed using 1-bromo-2-chlorobenzene (**2c**) as *ortho*-dihalobenzene. Considering the regioselectivity observed, we studied the scope using anilines bearing strong electron-withdrawing groups such as 3-nitroaniline. To our satisfaction, using 3-nitroaniline and **2c**, product **10** was obtained in good yield (61%). The 1,2-dichlorobenzenes bearing moderate or strong electron-withdrawing groups in position 4 led to products **12** and **13** with an excellent yield and regioselectivity. Additionally, this protocol enabled access to the α-carboline **11** in excellent yields from 2-aminopyridine and 1-bromo-2-chlorobenzene (**2c**) as starting materials.

Finally, the recyclability of the PdNPs/BC catalyst was studied using the direct synthesis of carbazole **3** as the reaction model. After completion of the reaction (monitored by TLC), the nanocatalyst was easily separated from the reaction mixture by filtration and washed several times with EtOAc, and then dried under vacuum to be used directly for further catalytic reactions. As shown in Figure 3, no significant loss of catalytic efficiency was observed up to five cycles.

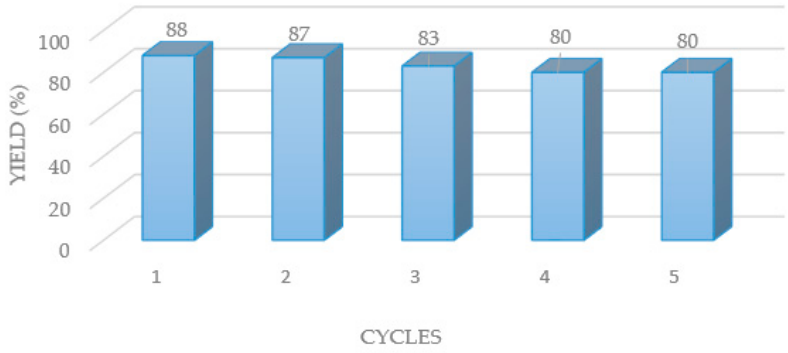


Figure 3. Recyclability of the PdNPs/BC catalyst in the direct synthesis of carbazole **3**.

3. Conclusions

In conclusion, we have developed a practical, eco-friendly, and selective methodology for the synthesis of carbazoles promoted by a catalytic system based on PdNPs supported on green biochar. The novel catalyst could be recycled up to at least five times without significant loss activity. Additionally, the present methodology enabled us to access a variety of carbazoles using inexpensive aryl chlorides as electrophiles and anilines as starting materials. Moreover, the prolonged reaction times were drastically reduced to minutes using microwave irradiation. Furthermore, the present protocol is compatible with different functional groups and does not require the presence of ligands or additives as the traditional methods reported up to date.

4. Materials and Methods

4.1. General Information

Unless otherwise noted, reagents were obtained commercially and used without further purification. Solvents were dried and distilled in accordance with standard procedure (ref). Reactions were monitored by thin-layer chromatography on silica gel plates (60F-254) visualized under UV light and/or using 5% phosphomolybdic acid in ethanol. All ^{1}H and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ or DMSO-d_6 on a Bruker Avance ARX-300 spectrophotometer. Chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane (TMS) using the residual solvent resonance ($CDCl_3$: 7.26 ppm for ^{1}H NMR, 77.16 ppm for ^{13}C NMR. Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; brs = broad signal). IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer in the ATR mode at

room temp. Melting points were determined using a Büchi 510 apparatus and are not corrected. Mass spectra (EI) were obtained at 70 eV on a Hewlett Packard HP-5890 GC-MS instrument equipped with a HP-5972 selective mass detector. The purity of volatile compounds and the chromatographic analyses (GC) was determined with a GC Shimadzu (GC-14B) with a flame ionization detector equipped with a HP-5MS column (30 m × 0.25 mm × 0.25 μm) using nitrogen as carrier gas. High resolution mass spectra were recorded on Thermo Fisher LTQ Orbitrap XL (for EI) and a Finnigen MAT 95 (for ESI). Flash column chromatography was performed using Macherey Nagel MN silica gel 60M (0.040–0.063 mm/230–240 mesh ASTM). Microwave reactions were performed using microwave oven CEM Discover in sealed reaction vessels. The palladium loading of the catalyst was determined by atomic absorption spectrometry (AAS) using Perkin Elmer AAnalyst 700 equipment. Powder X-ray diffraction (XRD) patterns were recorded on a Philips PW1710 BASED Diffractometer, operating at 45 kV and 30 mA, fitted with a graphite monochromator getting Cu Ka 1 radiation (ʎ ¼ 0.15406 nm). The samples were characterized by transmission electron microscopy (TEM), employing Joel 100 CX2 (Tokyo, Japan) apparatus. Approximately one hundred palladium particles were measured to perform the particle size distribution in order to obtain the mean particle size (d) [11]. Nitrogen adsorption/desorption isotherm at 77 K was obtained with a Nova 1200e Quantachrome Instrument. The specific surface areas were measured following the Brunauer–Emmett–Teller (BET) method.

4.2. Microwave Reactions

All microwave reactions were carried out following the same procedure. Anilines (1.2 mmol), 1,2-dihaloarenes (1 mmol), KOAc (3 mmol), PdNPs/BC (15 mol%), and dry DMSO (5 mL) were added to a vessel tube with a magnetic stirring bar. The resulting mixture was heated at 180 °C under microwave irradiation (200 W) for 25 min. The progress of the reaction was monitored by TLC and GC-MS. The crude product was treated with EtOAc. The catalyst was recovered by filtration and washed several times with the same solvent. The filtrate was washed twice with a brine and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the desired carbazole was purified by column chromatography using silica gel 60 as adsorbent.

9*H*-Carbazole (3). The title compound was prepared from aniline and 1,2-dicholorobenzene to give a white solid (0.14 g, 0.88 mmol, 88% yield), m.p. 245–246 °C. SiO_2 (hexane/EtOAc = 7:3). The spectral data were in accordance with those reported in the literature [12].

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.13 (t, *J* = 7.6 2 H), 7.35 (t, *J* = 7.6, 2H) 7.48 (d, *J* = 8.1 Hz, 2 H), 8.11 (d, *J* = 8 Hz, 2 H), δ 11.26 (s, 1 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 110.9, 118.5, 120.1, 122.4, 125.5, 139.7. IR (KBr) ν [cm-1] = 3392, 3049, 1625, 1449, 1327, 1240. HRMS (EI) for $C_{12}H_9N$: calcd. 167.0735; found: 167.0738.

3-methoxy-9*H*-carbazole (4). The title compound was prepared from 4-methoxyaniline and 1,2-dichlorobenzene to give a white solid (0.15 g, 0.77 mmol, 77% yield), m.p. 139–140 °C. SiO_2 (petroleum ether/EtOAc = 10:1). The spectral data were in accordance with those reported in the literature [13].

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.93 (s, 3H), 7.05 (dd, *J* = 8.8, 2.4, 1H), 7.19–7.23 (m, 1H), 7.34 (d, *J* = 8.8, 1H), 7.41 (d, *J* = 3.6, 2H), 7.56 (d, *J* = 2.4, 1H), 7.91 (brs, 1H), 8.04 (d, *J* = 8.0, 1H), ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.2, 103.2, 110.8, 111.4, 115.1, 119.1, 120.3, 123.4, 123.8, 125.9, 134.4, 140.3, 153.9. IR (KBr) ν [cm^{-1}] = 3404, 2925, 1612, 1460, 1310, 1255, 1041. HRMS (EI) for $C_{13}H_{11}NO$ calcd. 197.0738; found 197.0736.

3-fluoro-9*H*-carbazole (5). The title compound was prepared from 4-fluoroaniline and 1,2-dichlorobenzene to give a white solid (0.14 g, 0.76 mmol, 76% yield), m.p. 208–209 °C. SiO_2 (petroleum ether/EtOAc = 9:1). The spectral data were in accordance with those reported in the literature [13].

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16 (td, *J* = 9.2, 2.4, 1H), 7.21–7.28 (m, 1H), 7.34 (dd, *J* = 8.8, 4.2, 1H), 7.40–7.48 (m, 2H), 7.73 (dd, *J* = 9.2, 2.4, 1H), 8.01–8.03 (m, 2H). ^{13}C NMR (75

MHz, $CDCl_3$): δ 106.1 (d, J_{CF} = 23.6), 110.9, 111.22 (d, J_{CF} = 9.2), 113.7 (d, J_{CF} = 25.6), 119.5, 120.6, 123.2 (d, J_{CF} = 4.0), 123.9 (d, J_{CF} = 9.6), 126.5, 135.8, 140.6, 157.6 (d, J_{CF} = 235.6). ^{19}F NMR (75 MHz, $CDCl_3$) δ -124.4. IR (KBr) ν [cm^{-1}] = 3411, 3043, 1362, 1238, 807. HRMS (EI) for $C_{12}H_8FN$: calcd.184.0568; found 184.0562.

3-methyl-9*H*-carbazole (6). The title compound was prepared from 4-methylaniline and 1,2-dichlorobenzene to give a white solid (0.13 g, 0.71 mmol, 71% yield), m.p. 169–171 °C. SiO_2 (petroleum ether/EtOAc = 9:1). The spectral data were in accordance with those reported in the literature [14].

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.54 (s, 3H), 7.17–7.28 (m, 2H), 7.32 (d, *J* = 8.0, 1H), 7.40 (d, *J* = 3.6, 2H), 7.89 (s, 1H), 7.94 (brs, 1H), 8.05 (d, *J* = 7.6, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6, 110.4, 110.7, 119.3, 120.4, 120.3, 123.3, 123.6, 125.7, 127.3, 128.8, 137.8, 139.9. IR (KBr) ν [cm^{-1}] = 3404, 2921, 1459, 1333, 1217. HRMS (EI) for $C_{13}H_{11}N$: calcd. 181.0814; found 181.0819.

2-Methyl-9*H*-carbazole (7). The title compound was prepared from 3-methyaniline and 1-bromo-2-chlorobenzene to give a colorless solid (0.14 g, 0.80 mmol, 80% yield), m.p. 245–246 °C. SiO_2 (petroleum ether/EtOAc = 8:2). The spectral data were in accordance with those reported in the literature [15].

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.53 (s, 3H), 7.07 (d, *J* = 8.0 Hz, 1H), 7.18–7.24 (m, 2H), 7.35–7.42 (m, 2H), 7.95 (d, *J* = 7.9 Hz, 2H), 8.03 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.2, 110.6, 110.8, 119.5, 120.1, 120.1, 121.1, 121.2, 123.6, 125.4, 136.1, 139.6, 140.1. IR (KBr) ν [cm^{-1}] = 3397, 3051, 2921, 1652, 1510, 1365, 1244. HRMS (EI) for $C_{13}H_{11}N$ calcd. 181.0891; found 181.0894.

3-carbonitrile-9*H*-carbazole (8). The title compound was prepared from 4-aminobenzonitrile and 1,2-dicholorobenzene to give a colorless solid (0.13 g, 0.68 mmol, 68% yield), m.p. 188–189 °C. SiO_2 (petroleum ether/EtOAc = 6:4). The spectral data were in accordance with those reported in the literature [14].

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.25 (t, *J* = 7.6, 1H), 7.48 (t, *J* = 7.6, 1H), 7.57 (d, *J* = 8.0, 1H), 7.63 (d, *J* = 8.4, 1H), 7.75 (d, *J* = 8.4, 1H), 8.24 (d, *J* = 8.0, 1H), 8.71 (s, 1H), 11.81 (brs, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 100.2, 111.6, 112.1, 119.9, 120.7, 121.0, 121.6, 122.7, 125.6, 127.06, 128.6, 140.3, 141.7. IR (KBr) ν [cm^{-1}] 3293, 3097, 2220, 1620, 1465, 1326, 1242, 1127. HRMS (EI) for $C_{13}H_9N_2$: calcd. 192. 0585; found: 192.0588.

1-(9*H*-carbazol-3-yl)ethan-1-one (9). The title compound was prepared from 1-(4-aminophenyl)ethan-1-one and 1,2-dichlorobenzene to give a yellow solid 177–178 °C (0.16 g, 0.77 mmol, 77% yield). SiO_2 (petroleum ether/EtOAc = 7:3). The spectral data were in accordance with those reported in the literature [16].

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.73 (s, 3H), 7.28–7.33 (m, 1H), 7.42–7.47 (m, 3H), 8.03–8.10 (m, 2H), 8.50 (brs, 1H), 8.74 (d, *J* = 1.5, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.8, 110.4, 111.2, 120.51, 120.6, 122.0, 123.2, 123.5, 126.7, 126.8, 129.4, 140.1, 142.5, 198.1. IR (neat) ν [cm^{-1}] 3294, 2924, 1660, 1329, 1246, 1015. HRMS (EI) for $C_{14}H_{11}NO$: calcd. 197.0841; found: 197.0839.

2-Nitro-9*H*-carbazole (10). The title compound was prepared from 3-nitroaniline and 2-bromo-1-chlorobenzene to give a white solid (0.14 g, 0.68 mmol, 68% yield), m.p. 202–203 °C. SiO_2 (petroleum ether/EtOAc = 10:1). The spectral data were in accordance with those reported in the literature [17].

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–7.36 (m, 1*H*), 7.49–7.59 (m, 2*H*), 8.13–8.17 (m, 3*H*), 8.36–8.39 (m, 1*H*), 8.41 (brs, 1*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 106.8, 111.3, 115.0, 120.3, 120.8, 121.5, 122.0, 128.3, 128.5, 138.3, 141.6, 145.9. IR (KBr) ν [cm^{-1}] = 3372, 3047, 1632, 1569, 1470, 1384, 1343, 1276, 804. HRMS (EI) for $C_{12}H_8N_2O_2$: calcd. 212.0658; found 212.0653.

9*H*-pyrido[2,3-b]indole (11). The title compound was prepared from 2-amino-piryd-ine and 2-bromo1-chlorobenzene to give a white solid (0.13 g, 0.79 mmol, 79% yield), m.p. 214–215 °C. SiO_2 (petroleum ether/EtOAc = 40:1). The spectral data were in accordance with those reported in the literature [18].

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.17–7.25 (m, 2H), 7.42–7.48 (m, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 8.41 (d, *J* = 4.8, 1.6 Hz, 1H), 8.49 (dd, *J* = 7.7, 1.6 Hz, 1H),

11.80 (s, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 111.3, 115.0, 115.2, 119.4, 120.4, 121.2, 126.6, 128.4, 138.8, 146.1, 151.9. IR (KBr) ν [cm^{-1}] = 3400, 3048, 1615, 1403, 1328, 1275. HRMS (EI) for calcd. $C_{11}H_9N_2$: 168.0766; found 168.0769.

Methyl 9*H*-carbazole-3-carboxylate (12). The title compound was prepared from aniline and 4-bromo-3-chlorobenzoate to give a white solid (0.13 g, 0.57 mmol, 57% yield), m.p. 170–172 °C. SiO_2 (petroleum ether/EtOAc = 6:4). The spectral data were in accordance with those reported in the literature [19].

^{1}H NMR (acetone-d_6 300 MHz): δ 3.92 (s, 3H), 7.25–7.29 (m, 1H), 7.44–7.48 (m, 1H), 7.58 (d, *J* = 8.3, 3.5 Hz, 2H), 8.09 (d, *J* = 8.6, 1.6 Hz, 1H), 8.26 (d, *J* = 7.8 Hz, 1H), 8.82 (s, 1H), 10.9 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): 51.9, 110.1, 110.9, 120.3, 120.6, 121.4, 122.9, 123.1, 123.3, 126.5, 127.4, 139.9, 142.3, 167.9. IR (KBr) ν [cm-^{1}] = 3344, 2947, 1710, 1590, 1497, 1327, 1244, 1286, 1119. HRMS (EI) for $C_{14}H_{11}NO_2$: calcd. 225.0863; found: 225.0865.

3-Nitro-6-methoxy-9*H*-carbazole (13). The title compound was prepared from 3-methoxyaniline and 1,2-dichloro-4-nitrobenzene to give a yellow solid (0,15 g, 0.61 mmol, 61% yield). SiO_2 (petroleum ether/EtOAc = 7:3). The spectral data were in accordance with those reported in the literature [19].

^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.93 (s, 3 H), 7.14 (dd, *J* = 8.5, 2.5 Hz, 1 H), 7.39 (d, *J* = 9.0 Hz, 1 H), 7.41 (d, *J* = 9.0 Hz, 1 H), 7.58 (d, *J* = 2.5 Hz, 1 H), 8.31 (dd, *J* = 9.0, 2.0 Hz, 1 H), 8.96 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 56.2, 103.5, 110.5, 112.3, 117.37, 117.6, 121.8, 123.2, 123.9, 135.3, 141.1, 143.4, 155.2. IR (neat) ν [cm^{-1}] = 3420, 2825, 1636, 1483, 1325, 1295, 1171, 1032. HRMS (EI) for $C_{13}H_{10}N_2O_3$: calcd. 241.0613; found: 241.0617.

4.3. Synthesis and Characterization of the Catalyst

Palladium catalyst supported on biochar (PdNPs/BC) was prepared following the precipitation-reduction method, employing $PdCl_2$ as the metal precursor and biochar (BC) as the support. BC was obtained as a product of the pyrolysis of lignocellulosic biomass [20,21].

Firstly, the BC was put in contact with a 10% nitric acid solution at room temperature for 2 h under stirring. The solid was extensively washed with deionized water. Afterwards, approximately 1 g of the sample was put in contact with a HCl aqueous solution of palladium chloride at 80 °C under stirring. A 37% formaldehyde solution and a 30% NaOH solution up to basic pH were added to attain palladium precipitation on support. Afterwards, the resulting solid was filtered and washed exhaustively with deionized water in order to remove the chloride. Finally, the catalyst was dried at 100 °C for 2 h and, just before the reaction, it was calcined in air at 350 °C over 2 h.

A TEM study was carried out in order to determine the palladium particle size. Highly dispersed spherical nanoparticles on BC, with an average particle size of 2.0 nm, were observed.

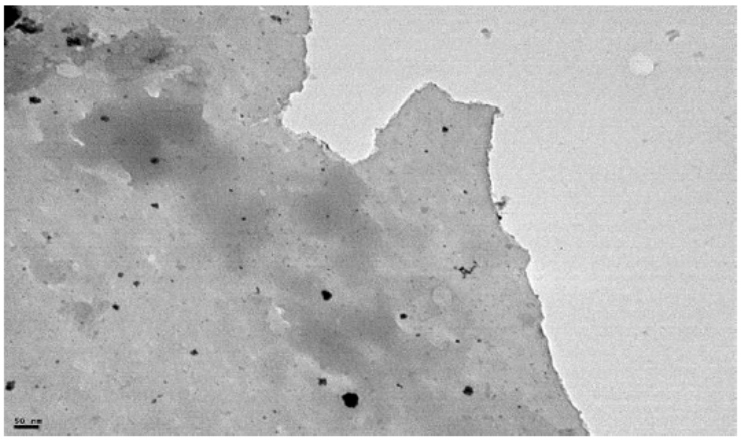


Figure 4. Transmission electron microscopy (TEM) micrograph of PdNPs/BC.

The XRD pattern showed peaks associated with char as well as the ones corresponding to palladium species.

The specific surface area of the PdNPs/BC, as measured by BET methodology, was 65m^2/g.

Funding: This research was funded by the National Council of Scientific and Technical Research (Consejo Nacional de Investigaciones Científicas y Técnicas; CONICET), the National Agency for Scientific and Technological Promotion (Agencia Nacional de Promoción Científica y Tecnológica; ANPCyT), and the Universidad Nacional del Sur (Secretaría General de Ciencia y Tecnología, Universidad Nacional del Sur; SGCyT-UNS), Argentina.

Acknowledgments: H.S.S. and P.M. thank CONICET and ANPCyT for a doctoral fellowship.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Głuszynska, A. Biological potential of carbazole derivatives. *Eur. J. Med. Chem.* **2015**, *94*, 405–426.
2. Oishi, S.; Watanabe, T.; Sawada, J.-I.; Asai, A.; Ohno, H.; Fujii, N. Kinesin Spindle Protein (KSP) Inhibitors with 2,3-Fused Indole Scaffolds. *J. Med. Chem.* **2010**, *53*, 5054–5058.
3. Ledwon, P. Recent advances of donor-acceptor type carbazole-based molecules for light emitting applications. *Org. Electron.* **2019**, *5*, 1–15.
4. Campeau, C.L.; Fagnou, K. Palladium-catalyzed direct arylation of simple arenes in synthesis of biaryl molecules. *Chem. Commun.* **2006**, 1253–1264.
5. Georgiades, S.N.; Nicolau, P.J. Recent advances in carbazole Syntheses. *Adv. Heterocycl. Chem*. **2019**, *129*, 1–88.
6. Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. Palladium-Catalyzed Direct Synthesis of Carbazoles via One-PotN-Arylation and Oxidative Biaryl Coupling: Synthesis and Mechanistic Study. *J. Org. Chem.* **2009**, *74*, 4720–4726.
7. Goo, D.-Y.; Woo, S.K. One-pot synthesis of carbazoles via tandem C–C cross-coupling and reductive amination. *Org. Biomol. Chem.* **2016**, *14*, 122–130.
8. Mpungose, P.P.; Vundla, Z.P.; Glenn, E.M.; Maguire, G.E.M.; Holger, B.; Friedrich, H.B. The Current Status of Heterogeneous Palladium Catalyzed Heck and Suzuki Cross-Coupling Reactions. *Molecules* **2018**, *23*, 1676–2000.
9. Kokel, A.; Schäfer, C.; Béla Török, B. Application of microwave-assisted heterogeneous catalysis in sustainable synthesis design. *Green Chem.* **2017**, *19*, 3729–3751.
10. Ackermann, L.; Althammer, A. Domino N-H/C-H bond activation: Palladium-catalyzed synthesis of annulated heterocycles using dichloro(hetero)arenes. *Angew. Chem*. **2007**, *46*, 1627.
11. Schölten, J.F.; Pijpers, A.P.; Hustings, M.L. Surface Characterization of Supported and Non-supported Hydrogenation Catalysts. *Cold Reg. Sci. Eng*. **1985**, *27*, 151–276.
12. Takamatsu, K.; Hirano, K.; Satoh, T.; Miura, M. Synthesis of Carbazoles by Copper-Catalyzed Intramolecular C–H/N–H Coupling. *Org. Lett*. **2014**, *16*, 2892–2895.
13. Jiang, Q.; Mu, D.; Zhong, W.; Chen, H.; Yan, H. Amino-Directed Rh (III)-Catalyzed C-H Activation Leading to One-Pot Synthesis of N-H Carbazoles. *Eur. J*. **2013**, *19*, 1903–1907.
14. Guerra, W.A.; Rossi, R.A.; Pierini, A.B.; Barolo, S.M. Transition-Metal-Free Synthesis of Carbazoles by Photostimulated Reactions of 2′-Halo[1 ,1′-biphenyl]-2-amines. *J. Org. Chem*. **2015**, *80*, 928–941.
15. Alcaide, P.; Almendros, J.M.; Alonso, M.T.; Quirós, G.P. Gold- or palladium-catalyzed allene carbocyclization/functionalization: Simple and efficient synthesis of carbazoles. *Adv. Synth. Catal.* **2011**, *353*, 1871–1876.
16. Stokes, B.J.; Jovanović, B.; Dong, H.; Richert, K.J.; Riell, R.D.; Driver, T.G. Rh_2(II)-Catalyzed Synthesis of Carbazoles from Biaryl Azides. *J. Org. Chem.* **2009**, *74*, 3225–3228.
17. Laha, J.K.; Petrou, P.; Cuny, G.D. One-Pot Synthesis of α-Carbolines via Sequential Palladium-Catalyzed Aryl Amination and Intramolecular Arylation. *J. Org. Chem.* **2009**, *74*, 3152–3155.
18. Rasheed, S.; Rao, D.N.; Reddy, K.R.; Aravinda, S.; Vishwakarma, R.A.; Das, P. C–N bond formation via Cu-catalyzed cross-coupling with boronic acids leading to methyl carbazole-3-carboxylate: Synthesis of carbazole alkaloids. *RSC Adv.* **2014**, *4*, 4960–4969.
19. Khan, A.; Karim, R.; Dhimane, H.; Alam, S. Mild and Efficient Synthesis of Functionalized Carbazoles via a DBU-Assisted Sequence Involving Cu- and Pd-Catalyzed Coupling Reactions. *Chem. Sel.* **2019**, *4*, 6598–6605.
20. Mozingo, R. Palladium Catalysts. *Org. Synth.* **1955**, *3*, 685–686.
21. Casoni, A.I.; Hoch, P.; Volpe, M.; Gutierrez, V.J. Catalytic conversion of furfural from pyrolysis of sunflower seed hulls for producing bio-based furfuryl alcohol. *J. Clean. Prod*. **2018**, *178*, 237–246.