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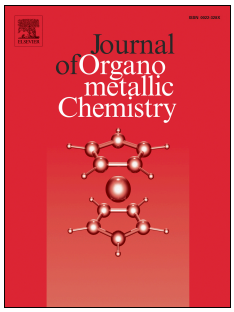

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PII: S0022-328X(19)30406-1

DOI: https://doi.org/10.1016/j.jorganchem.2019.120963

Reference: JOM 120963

To appear in: *Journal of Organometallic Chemistry*

Received Date: 16 July 2019

Revised Date: 17 September 2019

Accepted Date: 28 September 2019

Please cite this article as: K. Ramesh, G. Satyanarayana, Microwave-assisted intramolecular reductive Heck in aqueous medium: Synthesis of 3,3′-Disubstituted heterocyclic compounds, *Journal of Organometallic Chemistry* (2019), doi: https://doi.org/10.1016/j.jorganchem.2019.120963.

Microwave-Assisted Intramolecular Reductive Heck in Aqueous Medium: Synthesis of 3,3'-Disubstituted Heterocyclic Compounds

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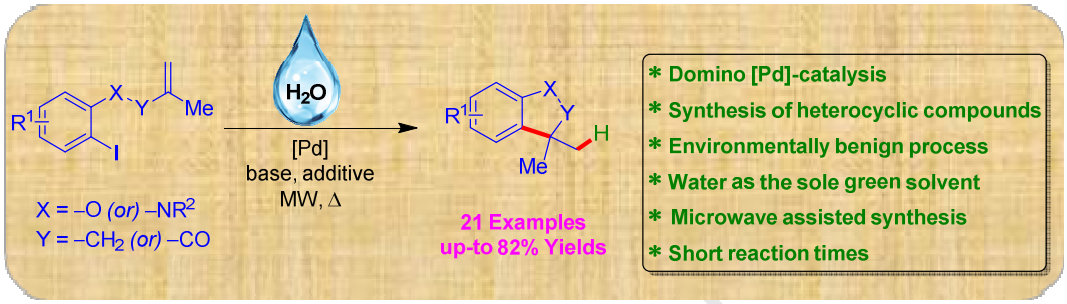


Abstract: Heterocyclic products have been accomplished using microwave-assisted [Pd]-catalyzed intramolecular reductive Heck coupling. The protocol found suitable in delivering indolines, oxindoles, and dihydrobenzofurans. Notably, the process was successful in sole aqueous medium and furnished the products bearing a quaternary carbon center.

Keywords: [Pd]-Catalysis; Reductive Heck; Microwave; Water.

Introduction:

The synthesis of heterocyclic structures using ring-closing strategies is indispensable in organic synthesis.[1] Whereas, the transition metal catalysis has proved to be a prominent and powerful synthetic tool for obtaining the key cyclic compounds of natural as well as unnatural products of biological significance.[2] Among transition metals, palladium is the most widely used metal that facilitates a variety of chemical reactions.[3] Specifically, palladium-catalyzed intramolecular reductive Heck coupling (or hydroarylation) of haloarene moiety with a suitably substituted internal alkene is an important chemical process, for the accomplishment of carbo-/hetero-cyclic compounds efficiently.[4]

The 3,3'-disubstituted dihydrobenzofurans[5], indolines[6,] and oxindoles[7] belongs to ubiquitous structural cores of many heterocyclic natural products and also compounds with interesting biological features.[8] As a result, apart from classical synthetic routes,[9] a notable number of transition metal-catalyzed synthetic approaches have also been presented in the literature for the construction of heterocyclic compounds.[10] Particularly, 2,3-

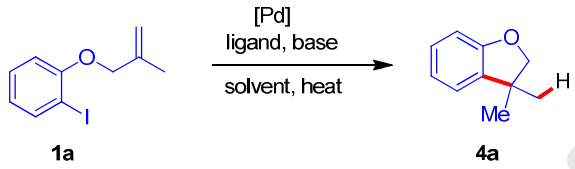
dihydrobenzofurans have been achieved in their chiral[11] or racemic[12] forms using intramolecular reductive Heck reactions. In addition, these products have also been synthesized *via* radical-mediated conditions.[13] Based on our interest in developing domino transition metal-catalyzed strategies,[14] Recently, our group presented a one-pot approach to alkyne bearing 3,3'-disubstituted dihydrobenzofurans under microwave irradiation *via* palladium catalysis.[15] Later, this concept has been further elaborated to generate other heterocyclic products possessing alkyne functionality, particularly, by making use of water as the solvent, under microwave irradiation conditions.[16] Herein, we report the preparation of indolines, oxindoles and dihydrobenzofurans containing a quaternary center at 3-position, catalyzed by palladium, under microwave assisting conditions in aqueous medium. Also, it was observed that quaternary ammonium salt as an additive is necessary for this reductive Heck coupling.[17]

Result and Discussions

The optimization study was initiated by taking *ortho*-iodophenyl allyl ether **1a**, as stating material. Our main intention was to perform the reactions, under microwave irradiation conditions. Thus, initially, *ortho*-iodophenyl allyl ether **1a** was treated using $Pd(OAc)_2$ (5 mol%), ligand BINAP (10 mol%), base K_2CO_3 (4 equiv), additive tetrabutylammonium bromide (TBAB, 1 equiv) and solvent H_2O (0.5 mL) for 10 min, at 100 °C, under microwave irradiation (Table 1, entry 1). However, there was no progress, and the starting material was recovered back. Almost similar results were noted when the reaction was conducted using different ligands (Table 1, entries 2 to 4). Even at elevated temperature (120 °C), no betterment was noticed (Table 1, entry 5). Similar results were observed with the catalyst $Pd_2(dba)_3$ for 10 min, at 100 °C, under microwave irradiation (Table 1, entry 6). The expected product **4a** was formed in trace amounts when the temperature was relatively high, i.e. 110 °C (Table 1, entry 7). With these observations of temperature effect, **1a** was treated at 120 °C for 10 min, under microwave irradiation (Table 1, entry 8). Delightfully, resulted the formation of **4a** in 40% yield. Interestingly, when the irradiation time was prolonged to 20 min, at 120 °C, the product **4a** yield was raised to 80% (Table 1, entry 9). The yield of **4a** was dropped to 65% when the irradiation time was reduced to 15 min (Table 1, entry 10). While the product **4a** yield was slightly decreased when tetrabutylammonium iodide (TBAI) and benzyl triethylammonium chloride (BTEAC), were used as additives

(Table 1, entry 11 &12). In solvent DMF instead of H_2O, **4a** was obtained, in very good yields (Table 1, entry 13). Nevertheless, our intension was to perform the reaction by using non-toxic and environmentally benign H_2O solvent; hence we decided to proceed further to examine the generality of the process by employing optimal conditions of entry 9 of Table 1.

Table 1. Screening study to generate **4a**.[a],[b],[c]



1a **4a**

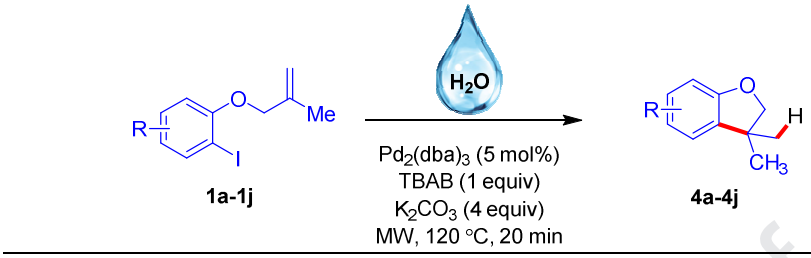
entry	ligand (10 mol%)	catalyst (5 mol%)	additive (1 equiv)	solvent (0.5 mL)	temp (°C)	time (min)	yield **4a**[b] (%)
1	BINAP	$Pd(OAc)_2$	TBAB	H_2O	100	10 min (μw)	-[c]
2	Xantphos	$Pd(OAc)_2$	TBAB	H_2O	100	10 min (μw)	-[c]
3	$P(Cy)_3$	$Pd(OAc)_2$	TBAB	H_2O	100	10 min (μw)	-[c]
4	PPh_3	$Pd(OAc)_2$	TBAB	H_2O	100	10 min (μw)	-[c]
5	PPh_3	$Pd(OAc)_2$	TBAB	H_2O	120	120 min (μw)	-[c]
6	-	$Pd_2(dba)_3$	TBAB	H_2O	100	10 min (μw)	-[c]
7	-	$Pd_2(dba)_3$	TBAB	H_2O	110	10 min (μw)	trace
8	-	$Pd_2(dba)_3$	TBAB	H_2O	120	10 min (μw)	(40%)
9	-	**$Pd_2(dba)_3$**	**TBAB**	H_2O	**120**	**20 min (μw)**	**(80%)**
10	-	$Pd_2(dba)_3$	TBAB	H_2O	120	15 min (μw)	(62%)
11	-	$Pd_2(dba)_3$	TBAI	H_2O	120	20 min (μw)	(72%)
12	-	$Pd_2(dba)_3$	BTEAC	H_2O	120	20 min (μw)	(68%)
13	-	$Pd_2(dba)_3$	-	DMF	120	20 min (μw)	(81%)

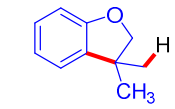
[a]Reaction conditions: 1-iodo-2-((2-methylallyl)oxy)benzene **1a (**68.5 mg, 0.25 mmol), K_2CO_3 (138.6 mg, 1 mmol, 4 equiv), [Pd]-catalyst (5 mol%), ligand (10 mol%), additive (0.25 mmol, 1 equiv) and solvent (0.5 mL), microwave irradiation (150 W, closed vessel). [b]Yields isolated of product **4a**. [c] Starting material was recovered.

Thus, based on the standardized reaction conditions [i.e. catalyst (11.6 mg, 5 mol%), K_2CO_3 (138.6 mg, 4 equiv), TBAB (80. 5 mg, 1 equiv), microwave irradiation for 20 min, at 120 °C (Table 1, entry 9)], next, to study the feasibility of the protocol, other *ortho*-iodophenyl allyl ethers were examined. Significantly, the dihydrobenzofurans **4a-4i** were isolated in the range of 50 to 82% yields (Table 2). Particularly, the method was feasible on *ortho*-iodophenyl allyl ethers **1b-1d** wherein the aromatic ring has alkyl substituent (**4b-4d**, Table 2). The method was also found suitable with phenyl substituent on the iodoaryl allyl ether **1e** and gave the product **4e**. Gratifyingly, this method was tolerable with aromatic ring connected to electron deactivating F, Cl, and Br functional groups (**4f-4h**, Table 2). Since in the product **4h**, the bromo moiety was intact, further transition metal-catalyzed cross-coupling reactions would be feasible. Quite remarkably, this reductive Heck coupling was

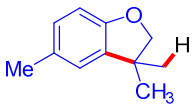
also tolerable with electron-withdrawing aldehyde group on the aromatic ring of iodoarene **1i** (**4i**, Table 2). However, the hetero-iodoarene **1j** was decomposed, under standard optimized conditions.

Table 2: Scope of formation of dihydrobenzofurans **4a-4j** from *ortho*-iodophenyl allyl ethers **1a-1j**.[a],[b]

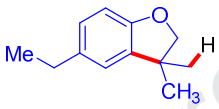




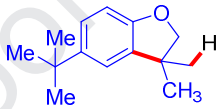
4a (80%)



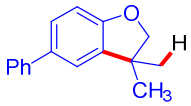
4b (75%)



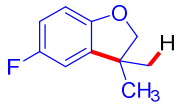
4c (78%)



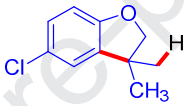
4d (76%)



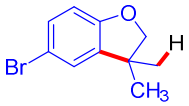
4e (82%)



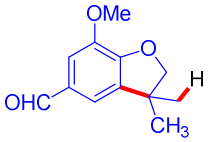
4f (72%)



4g (70%)



4h (68%)



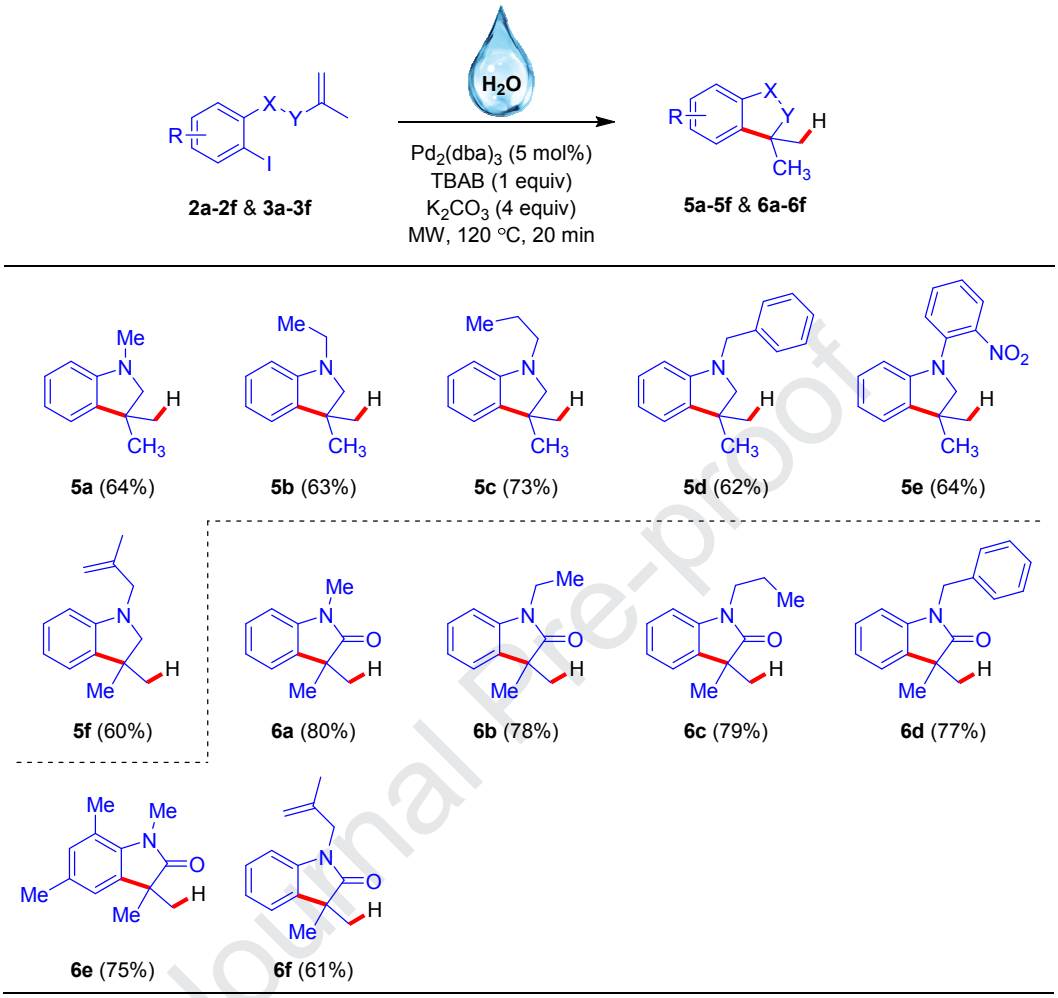
4i (50%)

4j (0%)

[a]Reaction conditions: *ortho*-iodophenyl allyl ethers **1a-1j** (0.25 mmol), $Pd_2(dba)_3$ (5 mol%), TBAB (1 equiv), K_2CO_3 (4 equiv) and solvent H_2O (0.5 mL), 120 C, 20 minutes, microwave irradiation (150 W, closed vessel). [b]Yields are isolated yields of products **4a-4i**.

After achieving the preparation of dihydrobenzofruans **4a-4i** (Table 2), to emphasize the utility of this protocol, the strategy was targeted to perform the reaction with nitrogen analogues. Thus, various *ortho*-iodophenyl alkylallyl amines **2a-2f** were subjected to reaction using standard microwave irradiation conditions (i.e., Table 1, entry 9). Notably, the methodology was smooth enough and afforded indolines **5a-5f**, in good yields (Table 3). Moreover, to signify generality of the method, it was also tested with *ortho*-iodophenyl enamides **3a-3f**. Remarkably the reaction was quite amenable and furnished oxindoles **6a-6f**, in the range of 50 to 82% yields (Table 3). Particularly, the allyl enamide **3f** may pose a chemoselective issue, as both olefins may compete in the initial intramolecular Heck step. However, the reaction was found to be highly chemoselective, in which enamide double bond has selectively underwent the Heck coupling and furnished oxindole **6f**.

Table 3: Scope to give indolines **5a-5f** and oxindoles **6a-6f**.[a],[b]

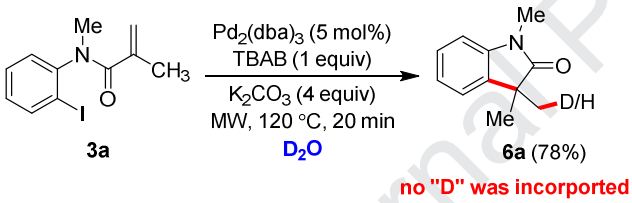


[a]Reaction conditions: 2-iodo-*N*-alkyl-(2-methylallyl)aniline **2a-2f** (0.25 mmol), *N*-(2-iodophenyl)-N-alkylmethacrylamide **3a-3f** (0.25 mmol), $Pd_2(dba)_3$ (5 mol%), TBAB (1 equiv), K_2CO_3 (4 equiv) and solvent H_2O (0.5 mL), 120 C, 20 minutes, microwave irradiation (150 W, closed vessel). [b]Yields are isolated yields of products **5a-5f**/**6a-6f**.

In order to probe the role of water and additive TBAB, we have carried out the reactions by changing the reaction conditions with respect to solvent and additive. When the reaction was performed on **1a** under neat conditions (i.e. without solvent water), the reaction was found to be very slow and the conversion of the desired product was only 15% (rest was the starting material **1a**). Whereas the reaction of **1a** without additive (TBAB), there was, no progress in the reaction except the starting material. This implies the importance TBAB as an additive to drive the reaction. Moreover, according to the literature precedence, it was noted that TBAB can acts as palladium nanoparticle stabilizer.[18] Based on this and from our observation, i.e. the reaction did not progress without the additive TBAB, it may be presumed that TBAB can act as palladium nanoparticles stabilizer. To further understand whether or not

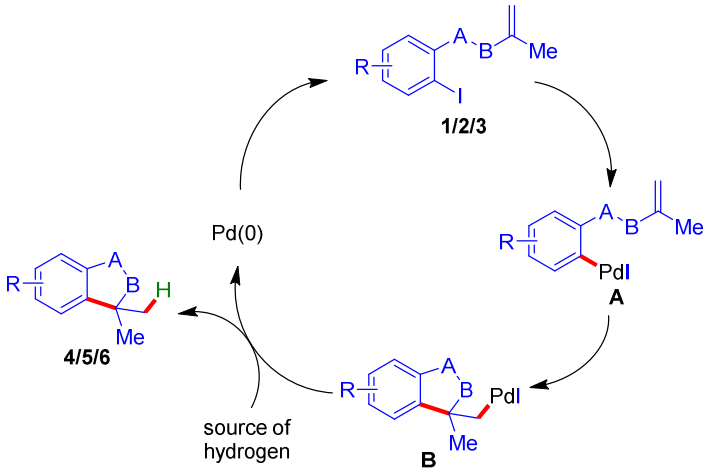
the palladium nanoparticles were present in the reaction mixture, the crude reaction was subjected to Transmission Electron Microscopy (TEM) analysis. From the analysis of TEM images and lattice fringes, it was realized the formation of palladium nanoparticles in the chemical reaction (for details, see: supporting information).

The source of hydrogen required for this reductive Heck coupling is not clear yet. It was hypothesized that the hydrogen might come from the H_2O solvent. Thus, to further understand the source of hydrogen, the reaction was conducted on enamide **3a** by using D_2O in place of H_2O, under established conditions (Scheme 1). However, $^{1}H/^{13}C\{^{1}H\}$ NMR spectra revealed that no deuterium was incorporated in the product **6a**. Indeed, this observation was in good agreement with established reports.[12c,19] In addition, there are other established reports, wherein *tert*-amines have been utilized as hydrogen sources instead of hydride based reagents.[20] Hydrogen source might be due to sacrificial agent that might be oxidized or from the ligand species.



Scheme 1: Reductive Heck coupling in D_2O solvent.

Though the exact reaction mechanism is not very much clear yet, a plausible path in furnishing **4/5/6** is shown in Scheme 2. Initially, the organopalladium(II) species **A** could be generated through the catalyst insertion across carbon-iodo bond of **1**/**2**/**3**. Intramolecular Heck cyclization of **A**, would furnish the bicyclic alkyl-Pd(II) intermediate **B**. Ultimately, regeneration of the catalyst *via* reductive elimination of **B** and in the presence of hydrogen source, gives the desired heterocyclic products **4**/**5**/**6**.



Scheme 2: Plausible mechanism to generate the products **4**/**5**/**6**.

Conclusions

In summary, a facile method affording heterocyclic products, is described. Palladium-catalyzed intramolecular reductive Heck was employed as the key transformation of the strategy. Moreover, unlike previous reports on reductive Heck reaction, the present process was feasible in sole aqueous medium and accelerated by microwave irradiation conditions. Indolines, oxindoles, and dihydrobenzofurans containing a quaternary center have been accomplished. Moreover, TEM studies revealed the formation of palladium nanoparticles and could serve as an active catalyst.

Experimental

General: IR spectra were recorded on a Bruker Tensor 37 (FTIR) spectrophotometer. ^{1}H NMR spectra were recorded on Bruker Avance 400 (400 MHz) spectrometer at 295 K in $CDCl_3$; chemical shifts (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either internal standard tetramethylsilane (TMS) (δ_H = 0.00 ppm) or $CDCl_3$ (δ_H = 7.25 ppm). ^{13}C{^{1}H} NMR spectra were recorded on Bruker Avance 400 (100 MHz) spectrometer at RT in $CDCl_3$; chemical shifts (δ ppm) are reported relative to $CDCl_3$ [δ_C = 77.00 ppm (central line of the triplet)]. In the ^{13}C{^{1}H} NMR, the nature of carbons (C, CH, CH_2 and CH_3) was determined by recording the DEPT-135 spectra, and is given in parentheses and noted as s = singlet (for C), d = doublet (for CH), t = triplet (for CH_2) and q = quartet (for CH_3). In the ^{1}H-NMR, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui =quintet, sept = septet, dd = doublet of doublet, m = multiplet and br. s = broad singlet. The assignment of signals was confirmed by

^{1}H, $^{13}C\{^{1}H\}$ CPD, and DEPT spectra. High-resolution mass spectra (HR-MS) were recorded on an Agilent 6538 UHD Q-TOF electron spray ionization (ESI) mode and atmospheric pressure chemical ionization (APCI) modes. The microwave irradiation experiments were carried out in a dedicated CEM-Discover monomode microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W. The reactions were carried out in 10 mL glass tubes, sealed with Teflon septum and placed in the microwave cavity. The reactions were irradiated at the required set temperature for the stipulated time and then cooled to ambient temperature with air-jet cooling. Reactions were monitored by TLC on silica gel using a combination of hexane and ethyl acetate as eluents. Solvents were distilled prior to use; petroleum ether with a boiling range of 60 to 80 °C was used. $Pd_2(dba)_3$, TBAB (tetrabutylammonium bromide) and K_2CO_3 were purchased from Sigma-Aldrich and used as received. Methacryloyl bromide and phenols were purchased from local sources and used as received. *ortho*-Iodoaniline and 3-chloro-2-methylpropene were purchased from TCI and used as received. Acme's silica gel (60–120 mesh) was used for column chromatography (approximately 20 g per one gram of crude material). It is worth noting that these sort of experimental procedures have already been published elsewhere.[14b & 14c, 15, 16]

GP (General Procedure for the Synthesis of 3,3'-Disubstituted Heterocyclic Compounds 4/5/6): To an oven dried 10 mL glass tube sealed with teflon septum was equipped with a magnetic stir bar, were added *ortho*-iodoaryl allyl ether **1**/*ortho*-iodophenyl allylic amines **2**/*ortho*-iodophenyl enamide **3** (68 to 88 mg, 0.25 mmol), followed by $Pd_2(dba)_3$ (11.4 mg, 5 mol%), K_2CO_3 (138.6 mg, 1 mmol), TBAB (80.5 mg, 0.25 mmol) and solvent water (0.5 mL) at room temperature. The resultant reaction mixture was subjected to microwave irradiation at 120 °C for 20 min, 150 W, closed vessel. The progress of the reaction was monitored by TLC till the reaction is completed. The reaction mixture was cooled to room temperature, quenched with an aqueous $NaHCO_3$ solution and extracted with ethyl acetate (3 × 10 mL). The organic layers were washed with saturated NaCl solution, dried (Na_2SO_4) and filtered. Evaporation of the solvent(s) under reduced pressure and purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate), furnished the 3,3'-disubstituted heterocyclic compounds **4/5/6** (50 to 82%) as oil/solid.

5-ethyl-3,3-dimethyl-2,3-dihydro-1-benzofuran (**4c**)**: GP** was carried out with 4-ethyl-2-iodo-1-[(2-methylprop-2-enyl)oxy]benzene **1c** (75 mg, 0.25 mmol), $Pd_2(dba)_3$ (11.4 mg, 5 mol%), TBAB (80.5 mg, 0.25 mmol), K_2CO_3 (138.6 mg, 1 mmol) and water (0.5 mL). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 99:1) furnished the benzofuran **4c** (33.5 mg, 78%) as light yellow liquid, [TLC control (petroleum ether/ethyl acetate 100:0), R_f(**1c**)=0.9, R_f(**4c**)=0.8, UV detection]. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3031, 2960, 2875, 1607, 1473, 1247, 1193, 983, 759, 697, 642 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ=6.95 (dd, 1H, J = 8.3 and 2.0 Hz, A–H), 6.92 (s, 1H, Ar–H), 6.70 (d, 1H, J = 8.3 Hz, Ar–H), 4.20 (s, 2H, Ar–O–CH_2), 2.59 (q, 2H, J = 7.3 Hz, A–H), 1.33 (s, 6H, 2 × CH_3), 1.21 (t, 3H, J = 7.3 Hz, A–H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ=157.2 (s, Ar–C), 136.5 (s, 2 × Ar–C), 127.1 (d, Ar–CH), 121.6 (d, Ar–CH), 109.2 (d, Ar–CH), 84.5 (t, CH_2), 41.9 (s, C), 28.4 (t, CH_2), 27.5 (q, 2 × CH_3), 16.0 (q, CH_3) ppm. HR-MS m/z calculated for $[C_{12}H_{20}NO]^+$=$[M+NH_4]^+$: 194.1539; found 194.1533.

5-*tert*-butyl-3,3-dimethyl-2,3-dihydro-1-benzofuran (**4d**)**: GP** was carried out with 4-*tert*-butyl-2-iodo-1-[(2-methylprop-2-enyl)oxy]benzene **1d** (82 mg, 0.25 mmol), $Pd_2(dba)_3$ (11.4 mg, 5 mol%), TBAB (80.5 mg, 0.25 mmol), K_2CO_3 (138.6 mg, 1 mmol) and water (0.5 mL). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 99:1) furnished the benzofuran **4d** (38.4 mg, 76%) as light yellow liquid, [TLC control (petroleum ether/ethyl acetate 100:0), R_f(**1d**)=0.9, R_f(**4d**)=0.8, UV detection]. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2959, 2875, 1605, 1487, 1365, 1223, 1127, 980, 818, 750, 691 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ=7.14 (dd, 1H, J = 8.3 and 2.1 Hz A–H), 7.11 (d, 1H, J = 2.1 Hz, Ar–H), 6.71 (d, 1H, Ar–H, J = 8.3 Hz), 4.21 (s, 2H, Ar–O–CH_2), 1.34 (s, 6H, 2 × CH_3), 1.34 (s, 9H, 3 × CH_3) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ=156.9 (s, Ar–C), 143.6 (s, Ar–C), 136.0 (s, Ar–C), 124.7 (d, Ar–CH), 119.0 (d, Ar–CH), 108.7 (d, Ar–CH), 84.6 (t, CH_2), 42.0 (s, C), 34.4 (s, C), 31.8 (q, 3 × CH_3), 27.5 (q, 2 × CH_3) ppm. HR-MS m/z calculated for $[C_{14}H_{20}O]^+$=M^+: 204.1509; found 204.1575.

3,3-dimethyl-5-phenyl-2,3-dihydro-1-benzofuran (**4e**)**: GP** was carried out with 3-iodo-1,1'-biphenyl-4-yl 2-methylprop-2-enyl ether **1e** (87.5 mg, 0.25 mmol), $Pd_2(dba)_3$ (11.4 mg, 5 mol%), TBAB (80.5 mg, 0.25 mmol), K_2CO_3 (138.6 mg, 1 mmol) and water (0.5 mL). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 99:1) furnished the benzofuran **4e** (45.5 mg, 82%) as light yellow liquid,

[TLC control (petroleum ether/ethyl acetate 100:0), R_f(**1e**)=0.8, R_f(**4e**)=0.7, UV detection]. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3032, 2960, 2875, 1607, 1472, 1249, 1192, 981, 819, 757, 696 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ=7.60–7.50 (m, 2H, Ar–H), 7.50–7.35 (m, 2H, Ar–H), 7.37 (dd, 1H, J = 8.2 and 2.0 Hz, Ar–H), 7.35–7.25 (m, 1H, Ar–H), 7.33 (d, 1H, J = 2.0 Hz, Ar–H), 6.87 (d, 1H, J = 8.2 Hz, Ar–H), 4.29 (s, 2H, Ar–O–CH_2), 1.39 (s, 6H, 2 × CH_3) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ=158.8 (s, Ar–C), 141.4 (s, Ar–C), 137.2 (s, Ar–C), 134.2 (s, Ar–C), 128.7 (d, 2 × Ar–CH), 127.0 (d, Ar–CH), 126.8 (d, 2 × Ar–CH), 126.5 (d, Ar–CH), 121.2 (d, Ar–CH), 109.8 (d, Ar–CH), 84.8 (t, CH_2), 41.9 (s, C), 27.5 (q, 2 × CH_3) ppm. HR-MS m/z calculated for $[C_{16}H_{17}O]^+$=$[M+H]^+$: 225.1274; found 225.1269.

5-fluoro-3,3-dimethyl-2,3-dihydro-1-benzofuran (**4f**)**: GP** was carried out with 4-fluoro-2-iodo-1-[(2-methylprop-2-enyl)oxy]benzene **1f** (73 mg, 0.25 mmol), $Pd_2(dba)_3$ (11.4 mg, 5 mol%), TBAB (80.5 mg, 0.25 mmol), K_2CO_3 (138.6 mg, 1 mmol) and water (0.5 mL). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 99:1) furnished the benzofuran **4f** (29.8 mg, 72%) as light yellow liquid, [TLC control (petroleum ether/ethyl acetate 100:0), R_f(**1f**)=0.9, R_f(**4f**)=0.8, UV detection]. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2957, 2868, 1612, 1488, 1363, 1263, 1195, 1109, 1028, 887, 817 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ=6.83–6.73 (m, 2H, Ar–H), 6.68 (dd, 1H, J = 9.3 and 3.9 Hz, Ar–H), 4.23 (s, 2H, Ar–O–CH_2), 1.32 (s, 6H, 2 × CH_3) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ=158.9 (s, Ar–C), 155.5 (d, $J_{c\text{-}f}$ = 161.0 Hz, Ar–C–F), 138.1 (d, $J_{c\text{-}f}$ = 7.0 Hz, Ar–C), 114.0 (d, $J_{c\text{-}f}$ = 24.0 Hz, Ar–CH), 109.7 (d, J = 8.0 Hz, Ar–CH), 109.4 (d, J = 24.0 Hz, Ar–CH), 84.8 (t, CH_2), 42.3 (s, C), 27.2 (q, 2 × CH_3) ppm. HR-MS m/z calculated for $[C_{10}H_{12}FO]^+$=$[M+H]^+$: 166.0867; found 166.0859.

5-bromo-3,3-dimethyl-2,3-dihydro-1-benzofuran (**4h**)**: GP** was carried out with 4-bromo-2-iodo-1-[(2-methylprop-2-enyl)oxy]benzene **1h** (88.2 mg, 0.25 mmol), $Pd_2(dba)_3$ (11.4 mg, 5 mol%), TBAB (80.5 mg, 0.25 mmol), K_2CO_3 (138.6 mg, 1 mmol) and water (0.5 mL). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 99:1) furnished the benzofuran **4h** (38.5 mg, 68%) as colorless liquid, [TLC control (petroleum ether/ethyl acetate 100:0), R_f(**1h**)=0.9, R_f(**4h**)=0.8, UV detection]. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2923, 2859, 1602, 1458, 1374, 1230, 1032, 980, 755 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ=7.20 (dd, J = 8.8 and 2.4 Hz 1H, Ar–H), 7.17 (d, 1H, J = 2.0 Hz, Ar–H), 6.65 (d, 1H, J = 8.3 Hz, Ar–H), 4.22 (s, 2H, Ar–O–CH_2), 1.32 (s, 6H, 2 × CH_3)

ppm. $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ=158.3 (s, Ar–C), 139.1 (s, Ar–C), 130.6 (d, Ar–CH), 125.5 (d, Ar–CH), 112.3 (s, Ar–C), 111.3 (d, Ar–CH), 84.8 (t, CH_2), 42.2 (s, C), 27.4 (q, 2 × CH_3) ppm. HR-MS m/z calculated for $[C_{10}H_{11}BrO]^+=M^+$: 225.9988; found 225.9853.

7-methoxy-3,3-dimethyl-2,3-dihydro-1-benzofuran-5-carbaldehyde (**4i**)**: GP** was carried out with 3-iodo-5-methoxy-4-[(2-methylprop-2-enyl)oxy]benzaldehyde **1i** (82.7 mg, 0.25 mmol), $Pd_2(dba)_3$ (11.4 mg, 5 mol%), TBAB (80.5 mg, 0.25 mmol), K_2CO_3 (138.6 mg, 1 mmol) and water (0.5 mL). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 99:1) furnished the benzofuran **4i** (25.0 mg, 50%) as colorless liquid, [TLC control (petroleum ether/ethyl acetate 60:40), R_f(**1i**)=0.7, R_f(**4i**)=0.6, UV detection]. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2959, 2750, 1682, 1590, 1459, 1314, 1220, 1129, 1056, 949, 854, 755, 709 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=9.82 (s, 1H, Ar–CHO), 7.31 (d, 1H, J = 1.5 Hz, Ar–H), 7.30 (d, 1H, J = 1.5 Hz, Ar–H), 4.42 (s, 2H, Ar–O–CH_2), 3.93 (s, 3H, Ar–OCH_3), 1.38 (s, 6H, 2 × CH_3) ppm. $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ=190.6 (s, Ar–CO), 153.3 (s, Ar–C), 145.1 (s, Ar–C), 138.2 (s, Ar–C), 131.5 (s, Ar–C), 118.8 (d, Ar–CH), 111.4 (d, Ar–CH), 86.2 (t, CH_2), 56.1 (q, OCH_3), 42.1 (s, C), 27.6 (q, 2 × CH_3) ppm. HR-MS m/z calculated for $[C_{12}H_{15}O_3]^+=[M+H]^+$: 207.1016; found 207.1110.

1-ethyl-3,3-dimethylindoline (**5b**)**: GP** was carried out with 2-iodo-*N*-ethyl-2-iodo-*N*-(2-methylallyl)aniline **2b** (75.2 mg, 0.25 mmol) $Pd_2(dba)_3$ (11.4 mg, 5 mol%), TBAB (80.5 mg, 0.25 mmol), K_2CO_3 (138.6 mg, 1 mmol) and water (0.5 mL). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 98:2) furnished the indoline **5b** (27.4 mg, 63%) as light yellow liquid, [TLC control (petroleum ether/ethyl acetate 100:0), R_f(**2b**)=0.9, R_f(**5b**)=0.8, UV detection]. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3051, 2957, 2809, 1718, 1605, 1489, 1376, 1299, 1248, 749 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.06 (ddd, 1H, J = 7.8, 7.8 and 1.0 Hz, Ar–H), 7.00 (dd, 1H, J = 7.3 and 1.0 Hz, Ar–H), 6.67 (ddd, 1H, J = 7.3, 7.3 and 1.4 Hz, Ar–H), 6.45 (d, 1H, J = 7.8 Hz, Ar–H), 3.14 (q, 2H, J = 7.3 Hz, CH_2), 3.09 (s, 2H, CH_2), 1.29 (s, 6H, 2 × CH_3), 1.16 (t, 3H, J = 7.3 Hz, CH_3) ppm. $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ=150.9 (s, Ar–C), 139.2 (s, Ar–C), 127.3 (d, Ar–CH), 121.6 (d, Ar–CH), 117.4 (d, Ar–CH), 107.1 (d, Ar–CH), 66.5 (t, CH_2), 42.6 (t, CH_2), 40.0 (s, C), 27.6 (q, 2 × CH_3), 11.8 (q, CH_3) ppm. HR-MS m/z calculated for $[C_{12}H_{17}N]^+=M^+$: 175.1361; found 175.1251.

3,3-dimethyl-1-propylindoline (**5c**)**: GP** was carried out with 2-iodo-*N*-(2-methylallyl)-*N*-propylaniline **2c** (78.7mg, 0.25 mmol), $Pd_2(dba)_3$ (11.4 mg, 5 mol%), TBAB (80.5 mg, 0.25 mmol), K_2CO_3 (138.6 mg, 1 mmol) and water (0.5 mL). Purification of the crude material by silica gel column chromatography petroleum ether/ethyl acetate, 100:0 to 96:4) furnished the indoline **5c** (34.1 mg, 73%) as light yellow liquid, [TLC control (petroleum ether/ethyl acetate 100:0), R_f(**2c**)=0.9, R_f(**5c**)=0.8, UV detection]. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2959, 2925, 1670, 1601, 1484, 1371, 1262, 1093, 1034, 804, 752 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ=7.06 (ddd, *J* = 7.3, 7.3 and 1.0 Hz, 1H, Ar–H), 7.00–6.98 (dd, 1H, *J* = 7.3 and 1.0 Hz, Ar–H), 6.63 (ddd, 1H, *J* = 7.3, 7.3 and 1.0 Hz, Ar–H), 6.45 (d, 1H, *J* = 7.8 Hz, Ar–H), 3.09 (s, 2H, CH_2), 3.00 (t, 2H, *J* = 7.3 Hz, CH_2), 1.60 (m, 2H,), 1.28 (s, 6H, 2 × CH_3), 0.96 (t, 3H, *J* = 7.3 Hz, CH_3) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ=151.3 (s, Ar–C), 138.8 (s, Ar–C), 127.4 (d, Ar–CH), 121.6 (d, Ar–CH), 117.1 (d, Ar–CH), 106.7 (d, Ar–CH), 67.3 (t, CH_2), 50.4 (t, CH_2), 40.1 (s, C), 27.6 (q, 2 × CH_3), 20.6 (t, CH_2), 11.7 (q, CH_3) ppm. HR-MS m/z calculated for $[C_{13}H_{19}N]^+=M^+$: 189.1512; found 189.1656.

3,3-dimethyl-1-(2-nitrophenyl)indoline (**5e**)**: GP** was carried out with *N*-(2-iodophenyl)-*N*-(2-methylprop-2-enyl)-*N*-(2-nitrophenyl)amine **2e** (76 mg, 0.25 mmol), $Pd_2(dba)_3$ (11.4 mg, 5 mol%), TBAB (80.5 mg, 0.25 mmol), K_2CO_3 (138.6 mg, 1 mmol) and water (0.5 mL). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 92:8) furnished the indoline **5e** (42.6 mg, 64%) as liquid, [TLC control (petroleum ether/ethyl acetate 100:0), R_f(**2e**)=0.9, R_f(**5e**)=0.8, UV detection]. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2959, 2861, 1595, 1517, 1484, 1339, 1284, 1030, 801, 740 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ=7.93 (dd, 1H, *J* = 7.8 and 1.0 Hz, Ar–H), 7.54–7.50 (m, 2H, Ar–H), 7.15–7.04 (m, 3H, Ar–H), 6.87 (ddd, 1H, *J* = 7.3, 7.3 and 1.0 Hz, Ar–H), 6.62 (d, 1H, *J* = 7.8 Hz, Ar–H), 3.61 (s, 2H, CH_2), 1.37 (s, 6H, 2 × CH_3) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ=144.9 (s, Ar–C), 142.1 (s, Ar–C), 140.5 (s, Ar–C), 138.8 (s, Ar–C), 133.7 (d, Ar–CH), 127.1 (d, Ar–CH), 126.3 (d, Ar–CH), 122.5 (d, Ar–CH), 122.4 (d, Ar–CH), 122.3 (s, Ar–C), 120.9 (s, Ar–C), 109.4 (d, Ar–CH), 67.8 (t, CH_2), 41.2 (s, C), 27.3 (q, 2 × CH_3) ppm. HR-MS m/z calculated for $[C_{16}H_{16}N_2NaO_2]^+=[M+Na]^+$: 291.1104; found 291.1096.

3,3-dimethyl-1-(2-methylprop-2-enyl)indoline (**5f**)**: GP** was carried out with *N*-(2-iodophenyl)-*N*,*N*-bis(2-methylprop-2-enyl)amine **2f** (81.7 mg, 0.25 mmol), $Pd_2(dba)_3$ (11.4 mg, 5 mol%), TBAB (80.5 mg, 0.25 mmol), K_2CO_3 (138.6 mg, 1 mmol) and water (0.5 mL).

Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 98:2) furnished the indoline **5f** (29.8 mg, 60%) as liquid, [TLC control (petroleum ether/ethyl acetate 100:0), R_f(**2f**)=0.9, R_f(**5f**)=0.8, UV detection]. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2956, 2860, 2808, 1604, 1489, 1454, 1376, 1156, 1068, 749 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ=7.05 (ddd, 1H, J = 7.3, 7.3 and 1.0 Hz, Ar–H), 7.00 (dd, 1H, J = 7.3 and 1.0 Hz, Ar–H), 6.66 (ddd, 1H, J = 7.3, 7.3 and 1.0 Hz, Ar–H), 6.46 (d, 1H, J = 7.8 Hz, Ar–H), 4.94 (s, 1H, CH_aH$_b$=C), 4.87 (s, 1H, CH$_a$$H_b$=C), 3.56 (s, 2H, CH_2), 3.07 (s, 2H, CH_2), 1.76 (s, 2H,), 1.29 (s, 6H, 2 × CH_3) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ=151.1 (s, Ar–C), 142.4 (s, Ar–C), 138.8 (s, Ar–C), 127.3 (d, Ar–CH), 121.6 (d, Ar–CH), 117.3 (d, Ar–CH), 111.9 (t, CH_2), 106.6 (d, Ar–CH), 67.8 (t, CH_2), 55.3 (t, CH_2), 40.0 (s, C), 27.6 (q, 2 × CH_3), 20.3 (q, CH_3) ppm. HR-MS m/z calculated for $[C_{14}H_{20}N]^+$=$[M+H]^+$: 202.1590; found 202.1512.

3,3-dimethyl-1-propyl-1,3-dihydro-2*H*-indol-2-one (**6c**)**: GP** was carried out with *N*-(2-iodophenyl)-2-methyl-*N*-propylacrylamide **3c** (82.2 mg, 0.25 mmol), $Pd_2(dba)_3$ (11.4 mg, 5 mol%), TBAB (80.5 mg, 0.25 mmol), K_2CO_3 (138.6 mg, 1 mmol) and water (0.5 mL). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 90:10) furnished the oxindole **6c** (39.8 mg, 79%) as liquid, [TLC control (petroleum ether/ethyl acetate 100:0), R_f(**3c**)=0.8\4, R_f(**6c**)=0.5, UV detection]. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2969, 2929, 2869, 1707, 1611, 1487, 1460, 1361, 1215, 1129, 750 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ=7.25–7.18 (m, 2H, Ar–H), 7.03 (ddd, 1H, J = 7.3, 7.3 and 1.0 Hz, Ar–H), 6.84 (d, 1H, J = 7.8 Hz, Ar–H), 3.67 (t, 2H, J = 7.3 Hz, CH_2), 1.70 (m, 2H), 1.36 (s, 6H, 2 × CH_3), 0.94 (t, 3H, J = 7.3 Hz, CH_3) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ=181.4 (s, Ar–CO), 142.1 (s, Ar–C), 136.0 (s, Ar–C), 127.5 (d, Ar–CH), 122.4 (d, Ar–CH), 122.2 (d, Ar–CH), 108.3 (d, Ar–CH), 44.1 (s, C), 41.3 (t, CH_2), 24.5 (q, 2 × CH_3), 20.7 (t, CH_2), 11.3 (q, CH_3) ppm. HR-MS m/z calculated for $[C_{13}H_{18}NO]^+$=$[M+H]^+$: 204.1383; found 204.1370.

3,3-dimethyl-1-(2-methylprop-2-enyl)-1,3-dihydro-2*H*-indol-2-one (**6f**)**: GP** was carried out with *N*-(2-iodophenyl)-2-methyl-*N*-(2-methylprop-2-enyl)acrylamide **3f** (85.2 mg, 0.25 mmol), $Pd_2(dba)_3$ (11.4 mg, 5 mol%), TBAB (80.5 mg, 0.25 mmol), K_2CO_3 (138.6 mg, 1 mmol) and water (0.5 mL). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the oxindole **6f**

(32.6 mg, 61%) as liquid, [TLC control (petroleum ether/ethyl acetate 100:0), R_f(**3f**)=0.6, R_f(**6f**)=0.7, UV detection]. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2963, 2927, 2868, 1711, 1611, 1462, 1368, 1202, 1133, 802 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.25–7.16 (m, 2H, Ar–H), 7.04 (ddd, 1H, J = 7.3, 7.3 and 1.0 Hz, Ar–H), 6.82 (dd, 1H, J = 7.3 and 1.0 Hz, Ar–CH), 4.91 (s, 1H, CH_aH$_b$=C), 4.82 (s, 1H, CH$_a$$H_b$=C), 4.26 (s, 2H, CH_2), 1.71 (s, 3H, CH_3), 1.39 (s, 6H, 2 × CH_3) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ=181.2 (s, Ar–CO), 141.9 (s, Ar–C), 139.2 (s, Ar–C), 135.7 (s, Ar–C), 127.5 (d, Ar–CH), 122.4 (d, Ar–CH), 122.2 (d, Ar–CH), 112.2 (t, CH_2), 109.1 (d, Ar–CH), 45.5 (t, CH_2), 44.1 (s, C), 24.5 (q, 2 × CH_3), 19.8 (q, CH_3) ppm. HR-MS m/z calculated for $[C_{14}H_{18}NO]^+$=$[M+H]^+$: 216.1383; found 216.1366.

Acknowledgement

We are grateful to the Department of Science and Technology-Science and Engineering Research Board (DST-SERB) [NO.:EMR/2017/005312], New Delhi, for financial support. K.R. thanks MHRD, New Delhi, for the award of a research fellowship.

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- Reductive Heck Coupling
- [Pd]-catalysis
- Synthesis of heterocyclic compounds
- Environmentally benign process
- Water as the sole green solvent
- Microwave-assisted synthesis
- Short reaction times