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PEG_{3400}–Cu_2O–Cs_2CO_3: an efficient and recyclable microwave-enhanced catalytic system for ligand-free Ullmann arylation of indole and benzimidazole

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ABSTRACT

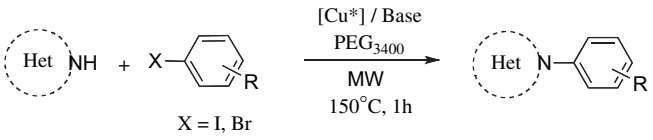
A mild, simple and efficient microwave-enhanced copper-catalyzed protocol for N-arylation using high molecular weight poly(ethylene glycol) (PEG_{3400}) as a solvent is reported. Indole and benzimidazole have been *N*-arylated in the presence of cuprous oxide, cesium carbonate, and PEG_{3400}, under microwave activation, with no supplementary ligands. Simple treatment by precipitation in Et_2O and filtration provided the expected product after evaporation and recovery of the catalytic system as a precipitate. The recovery and one successful re-use of the catalytic system is also described. The formation of copper-based nanoparticles was demonstrated by TEM analysis.

1. Introduction

Poly(ethylene glycol)s (PEGs) is a family of solvents, which can substitute volatile organic solvents. They are commercially available at low cost, being formed from ethylene oxide by simple ring epoxide opening. PEGs with low molecular weight (less than 800 Da) are liquid at room temperature. High molecular weight PEGs (more than 800 Da) are solids at room temperature but they melt at a moderate temperature (45–55 °C) and can therefore be used as a suitable liquid medium at a temperature higher than the melting point.[1–8] PEG is a hydrophilic polymer, easily soluble in water and several organic solvents including toluene, dichloromethane, alcohol, and acetone, but is not soluble in less polar solvents such as hexane, cyclohexane or diethyl ether.[1] As an ongoing project related to the use of higher molecular weight poly(ethylene glycol)s as polymeric support[1,7,9–11] and organic solvent[1–5,8] we describe in this study a very simple and convenient experimental procedure, including a practical precipitation/filtration work-up, for the copper-catalyzed Ullmann-type N-arylation of nitrogen heterocycles[12–20] under microwave activation, with solid PEG_{3400} as reaction matrix.

2. Results and discussion

In our experiments, indole **1** or benzimidazole **10** was selected as substrate for the arylation reaction. In a typical experiment, the heterocycle and one or two equivalents of the aryl halide, depending on its nature, were heated in the presence of 2 equiv of Cs_2CO_3 and a catalytic amount (0.1 equiv) of copper source, in the microwave synthesizer for 1 h, in PEG_{3400} (Scheme 1). Then the mixture was cooled to room temperature, dissolved in a small amount of CH_2Cl_2, and precipitated by pouring into diethyl ether, a solvent in which the polymer becomes insoluble. The solid catalytic system PEG/Cu/base was recovered as a precipitate,[2,3] while the expected product was recovered in the filtrate, isolated by simple evaporation of the diethyl ether, and analyzed by ^1H NMR using CH_2Br_2 as an internal standard. All the reactions were performed under no special conditions. In general, and aiming to avoid purification steps, we chose to run the experiments by using stoichiometric quantity of substrate and arylating agent. Unfortunately, in most of the cases, it was necessary to increase the quantity of arylhalide to two equivalents to overcome problems related to its instability (e.g., nitro group) or to its intrinsic physical-chemical properties (e.g., boiling point or sublimation) at the operating condition.



Scheme 1. General method for N-arylation of heterocycles (indole and benzimidazole). N-Arylation of indole with aryl halides.

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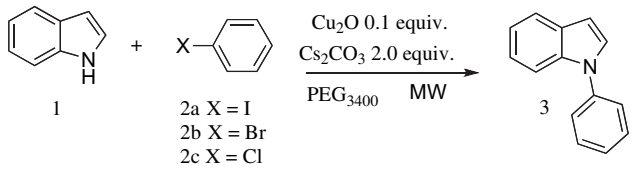
Indole was chosen as substrate to perform the arylation reaction, since *N*-arylindoles are central structural elements in many pharmacologically important and bioactive compounds.[21–23] It was shown that cuprous oxide (Cu_2O) was much more efficient than cupric oxide (CuO), or copper iodide (CuI) to perform the coupling reaction. Cu_2O was particularly interesting as a copper source owing to its low cost and insensitivity to light and air.

The Cu_2O-catalyzed coupling reaction of indole **1** with iodobenzene (**2a**, X=I), mixed together with PEG_{3400} and cesium carbonate, became the model for testing the reaction conditions under microwave irradiation. In all cases and independently on the nature of the phenylhalide, 2 equiv of arylating agent were used. Since the reactions were performed in a sealed tube at 150 °C, it is possible that the aryl halide would vaporize and, probably, less than an equimolar amount could be effectively present in the reaction mixture. Table 1 shows the most significant results.

Table 1
Screening of the conditions for the N-arylation of indole **1** with aryl halides **2a**, **2b**, and **2c**



Entry	X	*T* [°C]	*t* [h]	Additive[a]	Yield[b,c] [%]
1	I	80	1	—	Traces
2	I	100	1	—	23
3	I	120	1	—	71
4	I	150	1	—	88
5	I	150	1	—	98[d]
6	I	150	2	—	89
7	I	150	1	—	14[e]
8	Br	150	1	—	46
9	Br	150	2	—	48
10	Br	150	1	NaI	20
11	Br	150	1	KI	32
12	Br	150	1	CsI	15
13	Cl	150	1	—	Traces
14	Cl	150	1	KI	0
15	Cl	150	1	CsI	0

[a] MI (M=Na, K, Cs) 4.0 equiv.
[b] Yields were calculated by ^1H NMR using CH_2Br_2 as an internal standard.
[c] Ph–X (X=I, Br, Cl) 2.0 equiv was used.
[d] Yield is given for a second cycle.
[e] The reaction vessel was heated up under classical conditions using an oil bath.

The reaction mixture was heated in a range of temperature between 80 °C and 150 °C (entries 1–4) for 1 h. The results showed that the Ullmann-type condensation was efficiently performed at 150 °C (entry 4) and no improvements were observed on doubling the reaction time (entry 6). Without microwave irradiation, the above-described cross-coupling reaction did not proceed, indicating that there is a pivotal heating effect supplied by the PEG_{3400}, cesium carbonate, and metal particles, able to convert efficiently microwave energy into heat. In fact, when we performed the experiment using an oil bath to heat up the sample (entry 7) *N*-phenylindole **3** was obtained in a very poor yield (14%).

The poly(ethylene glycol) is an excellent reaction medium for the microwave irradiation because of its permanent dipole and high boiling point.[24] Together with Cs_2CO_3 and the metallic catalyst, the absorbance level of the medium is important, favorizing good absorption of microwave energy, and consequently efficient heating.

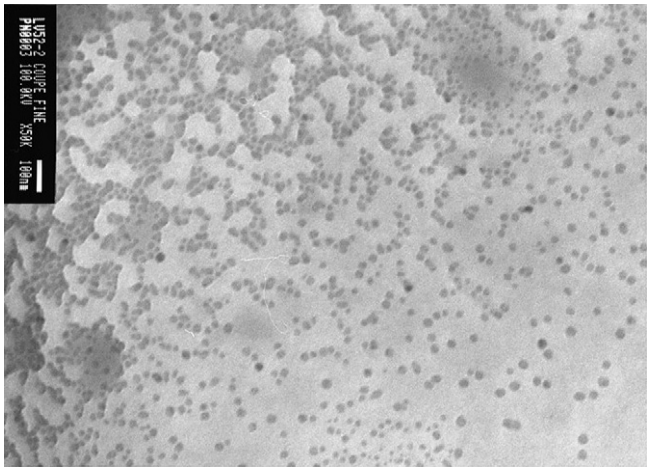


Figure 1. TEM images of ethanol-dispersed Cu-based nanoparticles prepared in situ by microwave irradiation of Cu_2O–PEG_{3400}–Cs_2CO_3.

The absorption of microwave irradiation can be accentuated by the presence of irregularities in the sample, leading to the creation of 'hot-spots'.[25] Moreover, PEG_{3400} acts as protective polymer to stabilize copper-based nanoparticles from agglomeration, as demonstrated by transmission electron microscopy (TEM) micrographs (Fig. 1).

One of the objective of using solid PEG as a support/solvent was to study the recyclability of the system. The reaction was repeated for a second cycle (entry 5) under the same experimental conditions: the precipitate obtained from the first experiment was fed again with indole **1**, iodobenzene **2a**, and cesium carbonate, and after microwave irradiation/precipitation/filtration steps, excellent yield of the corresponding *N*-arylated indole was reached (entry 5), showing that the catalytic system needed some induction period to be fully effective.[3,26] Despite this excellent result, it was not possible to run a third run, because only a small quantity of precipitate was recovered, maybe due to PEG depolymerization (degradation) in our conditions. Encouraged by these promising results, the scope of the process with respect to aryl halide structure was investigated, and the N-arylation was performed in the presence of bromobenzene **2b** as source of arylating agent, under our standard conditions. The reaction with bromobenzene **2b** relative to iodobenzene **2a** was slower with a low conversion of starting materials (entry 8), even after extending the reaction time (entry 9).

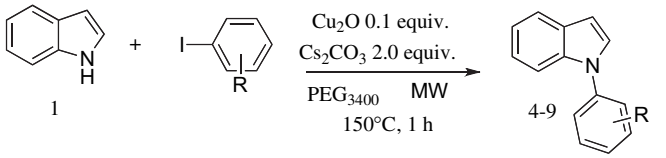
We tried to overcome this problem by performing the reaction via the more reactive iodide that was generated in situ, by Cu-catalyzed halide exchange[27] followed by the reaction with indole **1**, in a two-step/one-pot sequence (entries 10–12), but *N*-phenylindole **3** was always obtained in low yield.

Coupling reaction of indole **1** with chlorobenzene **2c** was also tested, and the chloride showed lower reactivity compared with bromide and iodide (entries 13–15). Independently on the aryl halide used (**2a**–**2c**) the reactions were never accompanied by the formation of biaryl homocoupling byproducts.

The scope of the process with respect to aryl iodide structure and its tolerance of functional groups were also investigated and the results are summarized in Table 2.

Both electron-withdrawing (entries 1–3) and electron-donating (entries 4–6) group-substituted aryl iodides reacted with indole **1** to give the corresponding *N*-arylated indoles **4**–**9** with moderate to good yields. This weak sensitivity to electronic effects is very interesting with regard to electron-rich substrates, since transition-metal catalyzed reaction involving these arylating agents are traditionally less straightforward, particularly when metal is palladium.[28,29]

Table 2
N-Arylation of indole **1** with aryl iodides



Entry	R	Coupling product	Yield[a,b] [%]
1	4-CN	**4**	80
2	4-NO_2	**5**	47 (57)[c]
3	2-NO_2	**6**	61
4	4-OMe	**7**	76
5	2-OMe	**8**	83
6	4-Me	**9**	57 (57)[d]

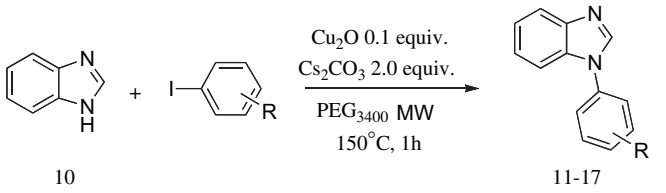
[a] Yields were calculated by ^{1}H NMR using CH_2Br_2 as an internal standard.
[b] Aryl iodide (1.0 equiv) was always used, except if differently stated.
[c] Aryl iodide (2.0 equiv) was used.
[d] Yield is given for 2 h reaction.

N-Arylations are known to be very sensitive to steric hindrance. In our case, the substitution at the *ortho* position (entries 3 and 5) did not affect the reaction. Surprisingly, and in contrast to which is normally reported for aryl halides bearing electron withrawing substituents,[20] in the presence of 3-fluoro-iodobenzene the cross-coupling product was obtained in low yield (9%), due to a scarce reactivity of the arylating agent, which was recovered in the crude, together with indole.

In the coupling of *p*-nitroiodobenzene (entry 2) and *o*-nitro-iodobenzene (entry 3) traces of product with the nitro group reduced into amino were detected, together with the corresponding *N*-arylated products **5** and **6** and other unidentified byproducts due to nitro group instability/degradation in our conditions. In all cases, the results were not improved when the reaction time was extended to 2 h, or by increasing the amounts of arylating agent. Byproducts resulting from biaryl coupling or arising from C-3 arylation of indole were never observed.

Such last side reaction has been observed in literature with palladium catalysis[30] with aryl halides or with copper catalysis[30] and with triarylbismuthanes as arylating agents. It is worth noting that we report here a general method for the N-arylation of a monoazole like indole, known to be a poor substrate for copper-catalyzed methods with organometal or organometalloid reagents (arylbismuthanes, arylplumbanes, aryl boronic acids, etc.).[31–34]

Table 3
N-Arylation of benzimidazole **10** with different aryliodides



Entry	R	Coupling product	Yield[a] [%]
1	H	**11**	77[b]
2	4-CN	**12**	44
3	4-NO_2	**13**	39[b]
4	2-NO_2	**14**	69[b]
5	4-OMe	**15**	53[b]
6	2-OMe	**16**	46
7	4-Me	**17**	35

[a] Yields were calculated by ^{1}H NMR using CH_2Br_2 as an internal standard.
[b] Aryl iodide (2.0 equiv) was used.

In the hope of broadening the scope of our protocol, we decided to check the efficiency of our catalytic system for the N-arylation of other classes of nitrogen heterocycles such as benzimidazole **10**. The same reaction conditions were suitable to perform N-arylation reaction in the presence of a variety of functionalized aryl iodides, to afford the corresponding *N*-arylated products **11**–**17**. Results are summarized in Table 3.

Coupling in the presence of iodobenzene (entry 1) resulted in the formation of *N*-phenyl-benzimidazole **11** with a good yield. It is evident from the results in Table 3 that independently from the substitution pattern with electron-withdrawing (entries 2 and 3) or electron-donating groups (entries 5 and 7), in *para* position with respect to the iodine atom on the aryl iodide, the yields remain moderate. For an *ortho*-nitro substitution, the cross-coupling product 1-(2-nitrophenyl)-1*H*-benzimidazole **14** (entry 4) was obtained in good yield, only if 2 equiv of 2-nitro-iodobenzene was used, maybe because of the instability of the nitro group in our conditions. Interestingly, 4-iodoanisole sublimates during the reaction with benzimidazole, demonstrated by ^{1}H NMR characterization of the white needles formed on the top of the sealed tube at the end of the reaction. Two equivalents were necessary to reach satisfying yields of product **15** (entry 5, Table 3). In all cases, yields were not improved by extending reaction times. Yields are also affected by the presence of two main side reactions involving: (i) the formation of traces of an unidentified product deriving from the ring opening of the benzimidazole (entries 2–4 and 7) and (ii) the formation of bisarylated benzimidazole, on the nitrogen and on the C-2 carbon atom (entries 4 and 5).

3. Conclusions

In conclusion, we have demonstrated the utility of the combination of PEG_{3400}–Cs_2CO_3–Copper pre-catalyst under microwave activation and in the absence of any supplementary ligand, to perform the N-arylation of indole and benzimidazole with different aryl iodides.

The recyclability of the catalytic system has been explored,[2,3] and to our knowledge, this is the first example of reuse of a solid[35] PEG-based catalytic system[36] in the Ullmann-type coupling for the N-arylation of heterocycles. The catalyst system has the advantage of using available and inexpensive reagents that are easily removable (by simple precipitation/filtration step), it is safe and environmentally benign. The reaction we have set up is operationally simple and cross-coupling product can be obtained in good yields. The pivotal role of PEG_{3400} for this catalytic system based on in situ generated stable copper-based nanoparticles has been demonstrated, as a green and safe matrix for organometallic reactions, with no homocoupling product detected in the crude. Since the recovery of the PEG-based catalytic system is achieved on a precipitation step, this system is a very practical alternative to the other catalytic system for the N-arylation reaction of heterocycles. Further studies are needed to generalize this type of heterocyclic arylation, to allow the cross-coupling with more hindered substrates combinations.

4. Experimental section

4.1. Instrumentation, analysis and starting materials

All reagents were purchased from Aldrich Chemical Co. and used without further purification. ^{1}H and ^{13}C NMR analyses were performed with Bruker Avance DPX 200 MHz, Bruker Avance AM 300 MHz or Bruker AC-400 MHz and are reported in parts per million and calibrated using residual undeuterated solvents as an internal reference. Data are reported as: br=broad, s=singlet,

d=doublet, t=triplet, q=quartet, m=multiplet; coupling constant(s) in hertz, integration. Mass spectra (electrospray ionization mode, ESI-MS) were recorded on a Micromass (Manchester, UK) Q-TOF quadrupole mass spectrometer fitted with an electrospray interface. The mass spectrometer was calibrated in the positive- and negative-ion ESI mode. The samples were dissolved in a mixture H_2O/CH_3CN (50/50 v/v). Microwave-assisted reactions were performed in sealed vessels with a Biotage Initiator 60 EXP® instrument. The temperature was measured with an IR sensor on the outer surface of the reaction vial. Transmission Electron Microscopy (TEM) experiments were performed on a JEOL 1200EX2 (Made in Tokyo, Japan—1990) at 100 kV. Samples for TEM analysis have been prepared by freezing and cut in the frozen state (cryocut) by ultramicrotome LEICA ULTRACUT EMFCS, with a diamond blade DIATOME. The samples (100 nm thick) were recovered on copper–parlodion–charcoal grids. Analytical high performance liquid chromatography (HPLC) was performed on a Waters Millenium 717 equipped with Autosampler, with a variable wavelength diode detector using a CHROMOLITH RP18 column (50×4,6 mm), flow 5 mL/min, linear gradient CH_3CN in water 0–100% (+0.1% TFA) in 4.5 min. In some cases, the arylated heterocycle was recovered after a purification by ISOLERA Flash Purification system (Biotage).

4.2. General experimental procedure for the N-arylation of heterocycles indole 1 and benzimidazole 10

In a typical experiment, to a mixture of copper catalyst (0.023 mmol, 0.1 equiv), finely powdered Cs_2CO_3 (150 mg, 0.46 mmol, 2.0 equiv), and PEG_{3400}–OH (250 mg) were added the suitable heterocycle (0.23 mmol, 1.0 equiv) and aryl iodide (1.0 or 2.0 equiv depending on the substrate). The resulting mixture was heated by microwave irradiation at 150 °C (initial power 400 W) for 1 h. After cooling, the reaction mixture was solubilized in CH_2Cl_2, and precipitated in Et_2O. Filtration and evaporation afforded the title compounds **3**–**9** (Tables 1 and 2) and **11**–**17** (Table 3). Yields were measured by ^1H NMR using CH_2Br_2 as an internal standard. For a second catalytic cycle, the precipitate was reused in a similar reaction with finely powdered Cs_2CO_3 (0.150 g, 0.46 mmol, 2.0 equiv), indole (27 mg, 0.23 mmol, 1.0 equiv), and aryl iodide (1.0 or 2.0 equiv depending on the substrate), to afford the title compound **3** in 98% yield (Table 1, entry 5).

*4.2.1. 1-Phenyl-1H-indole (**3**)*[37]. Following the general procedure (150 °C, 1 h), indole **1** (27 mg, 0.23 mmol) was coupled with iodobenzene (51.3 μL, 0.46 mmol), by using Cu_2O (3.3 mg, 0.023 mmol), PEG_{3400}–OH (250 mg), and Cs_2CO_3 (150 mg, 0.46 mmol), to afford the title compound **3** as a pale yellow oil in 88% yield. Following the procedure described for a second catalytic cycle, the precipitate was charged again, with finely powdered Cs_2CO_3 (150 mg, 0.46 mmol), indole **1** (27 mg, 0.23 mmol), and iodobenzene (51.3 μL, 0.46 mmol) to afford the title compound **3** as a pale yellow oil in 98% yield. ^1H NMR ($CDCl_3$): δ=7.75–7.80 (m, 1H), 7.60 (m, 1H), 7.50–7.58 (m, 4H), 7.34–7.47 (m, 1H), 7.40 (m, 1H), 7.20–7.33 (m, 2H), 6.63 (dd, J=3.2 and 0.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ=139.9, 135.9, 129.7, 129.4, 128.0, 126.5, 124.4, 122.4, 121.2, 120.4, 110.6, 103.7; ESI-MS: m/z 194.1 $[M+H]^+$.

*4.2.2. 1-(4-Cyanophenyl)-1H-indole (**4**)*[38]. Following the general procedure (150 °C, 1 h), indole **1** (27 mg, 0.23 mmol) was coupled with 4-iodobenzonitrile (52.7 mg, 0.23 mmol), by using Cu_2O (3.3 mg, 0.023 mmol), PEG_{3400}–OH (250 mg) and Cs_2CO_3 (150 mg, 0.46 mmol), to afford the title compound **4** in 80% yield. An analytical sample was purified by silica gel column chromatography: AcOEt/cyclohexane (2/98 to 10/90 v/v) as developing solvents. ^1H NMR ($CDCl_3$): δ=7.82–7.75 (m, 2H), 7.72 (m, 1H), 7.58–7.68 (m, 3H), 7.37–7.18 (m, 3H), 6.76 (dd, J=3.4 and 0.5 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ=143.5, 135.8, 135.2, 129.9, 127.11, 123.5, 123.2, 121.61, 121.4, 118.5, 111.2, 109.3, 105.8; Q-TOF MS ES(+): m/z 219.1 $[M+H]^+$.

*4.2.3. 1-(4-Nitrophenyl)-1H-indole (**5**)*[39]. Following the general procedure (150 °C, 1 h), indole **1** (27 mg, 0.23 mmol) was coupled with 1-iodo-4-nitrobenzene (57.3 mg, 0.23 mmol), by using Cu_2O (3.3 mg, 0.023 mmol), PEG_{3400}–OH (250 mg), and Cs_2CO_3 (150 mg, 0.46 mmol), to afford the title compound **5** in 47% yield. An analytical sample was purified by silica gel column chromatography: AcOEt/cyclohexane (2/98 to 50/50 v/v) as developing solvents. ^1H NMR ($CDCl_3$): δ=8.30 (d, J=7.3 Hz, 2H), 7.79 (d, J=7.8 Hz, 1H), 7.67–7.60 (m, 3H), 7.30 (d, J=3.4 Hz, 1H), 7.21 (td, J=7.9z and 1.1 Hz, 1H), 7.13 (td, J=7.9 and 1.1 Hz, 1H), 6.69 (dd, J=3.4 and 0.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ=145.1, 144.9, 135.2, 130.1, 127.12, 125.5, 123.4, 123.3, 121.7, 121.6, 110.5, 106.2; Q-TOF MS ES(+): m/z 239.1 $[M+H]^+$.

*4.2.4. 1-(2-Nitrophenyl)-1H-indole (**6**)*[40,41]. Following the general procedure (150 °C, 1 h), indole **1** (27 mg, 0.23 mmol) was coupled with 1-iodo-2-nitrobenzene (52.7 mg, 0.23 mmol), by using Cu_2O (3.3 mg, 0.023 mmol), PEG_{3400}–OH (250 mg), and Cs_2CO_3 (150 mg, 0.46 mmol), to afford the title compound **6** in 61% yield. An analytical sample was purified by silica gel column chromatography: AcOEt/cyclohexane (2/98 to 5/95 v/v) as developing solvents. ^1H NMR ($CDCl_3$): δ=7.96 (dd, J=7.9 and 1.3 Hz, 1H), 7.68–7.57 (m, 2H), 7.15–7.04 (m, 6H), 6.66 (d, J=3.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ=145.2, 145.0, 135.2, 134.6, 130.1, 127.8, 127.1, 125.5, 123.5, 123.4, 123.3, 121.7, 110.5, 106.2; Q-TOF MS ES(+): m/z 239.1 $[M+H]^+$.

*4.2.5. 1-(4-Methoxyphenyl)-1H-indole (**7**)*[42]. Following the general procedure (150 °C, 1 h), indole **1** (27 mg, 0.23 mmol) was coupled with 4-iodoanisole (53.8 mg, 0.23 mmol), by using Cu_2O (3.3 mg, 0.023 mmol), PEG_{3400}–OH (250 mg), and Cs_2CO_3 (150 mg, 0.46 mmol), to afford the title compound **7** in 76% yield. An analytical sample was purified by silica gel column chromatography: AcOEt/cyclohexane (2/98 to 6/94 v/v) as developing solvents. ^1H NMR ($CDCl_3$): δ=7.58 (dd, J=7.0 and 1.7 Hz, 1H), 7.47 (d, J=6.8 Hz, 1H), 7.39 (d, J=8.0 Hz, 1H), 7.29 (d, J=3.2 Hz, 2H), 7.18 (d, J=4.4 Hz, 1H), 7.17–7.05 (m, 2H), 6.92 (d, J=3.3 Hz, 1H), 6.59 (d, J=2.1 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$): δ=158.2, 136.3, 132.9, 128.9, 128.3, 126.0, 122.2, 121.1, 120.1, 114.8, 110.4, 102.9, 55.6; ESI-MS: m/z 224.1 $[M+H]^+$.

*4.2.6. 1-(2-Methoxyphenyl)-1H-indole (**8**)*[43]. Following the general procedure (150 °C, 1 h), indole **1** (27 mg, 0.23 mmol) was coupled with 2-iodoanisole (60 μL, 0.46 mmol), by using Cu_2O (3.3 mg, 0.023 mmol), PEG_{3400}–OH (250 mg), and Cs_2CO_3 (150 mg, 0.46 mmol), to afford the title compound **8** in 83% yield. An analytical sample was purified by silica gel column chromatography: AcOEt/cyclohexane (1/99 to 7/93 v/v) as developing solvents. ^1H NMR ($CDCl_3$): δ=7.7 (dd, J=7.8 and 1.6 Hz, 1H), 7.31–6.92 (m, 8H), 6.71 (d, J=2.1 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$): δ=158.1, 154.5, 129.6,128.5, 128.0, 124.2, 122.9, 122.6, 121.9, 120.7, 119.4, 113.9, 111.1, 102.6, 55.8; Q-TOF ES(+): m/z 224.1 $[M+H]^+$.

*4.2.7. 1-(4-Methylphenyl)-1H-indole (**9**)*[43]. Following the general procedure (150 °C, 1 h), indole **1** (27 mg, 0.23 mmol) was coupled with 4-iodotoluene (50.1 mg, 0.23 mmol), by using Cu_2O (3.3 mg, 0.023 mmol), PEG_{3400}–OH (250 mg), and Cs_2CO_3 (150 mg, 0.46 mmol), to afford the title compound **9** in 57% yield. An analytical sample was purified by silica gel column chromatography: AcOEt/cyclohexane (2/98 to 3/97 v/v) as developing solvents. ^1H NMR ($CDCl_3$): δ=7.65 (d, J=6.9 Hz, 1H), 7.48 (t, J=8.1 Hz, 1H), 7.31 (d, J=3.2 Hz, 1H), 7.23–7.01 (m, 6H), 6.61 (d, J=3.2 Hz, 1H), 2.4 (s, 3H); ^{13}C NMR ($CDCl_3$): δ=137.3, 136.4, 136.0, 130.2, 129.2, 128.1, 124.4,

122.2, 121.1, 120.2, 110.5, 103.8, 21.7; Q-TOF MS ES(+): *m*/*z* 208.2 $[M+H]^+$.

*4.2.8. 1-Phenyl-1H-benzimidazole (**11**)*[44]. Following the general procedure (150 °C, 1 h), benzimidazole **10** (27.2 mg, 0.23 mmol) was coupled with iodobenzene (51.3 μL, 0.46 mmol), by using Cu_2O (3.3 mg, 0.023 mmol), PEG_{3400}–OH (250 mg), and Cs_2CO_3 (150 mg, 0.46 mmol), to afford the title compound **11** in 77% yield. An analytical sample was purified by silica gel column chromatography: AcOEt/cyclohexane (2/98 to 4/96) as developing solvents. ^1H NMR ($CDCl_3$): δ=8.2 (s, 1H), 7.93–7.78 (m, 1H), 7.77–7.50 (m, 6H), 7.45–7.35 (m, 2H); ^{13}C NMR ($CDCl_3$): δ=144.0, 142.3, 136.4, 133.7, 128.1, 124.1, 123.7, 122.8, 120.6, 110.5; ESI-MS: *m*/*z* 195.0 $[M+H]^+$.

*4.2.9. 1-(4-Cyanophenyl)-1H-benzimidazole (**12**)*[45–47]. Following the general procedure (150 °C, 1 h), benzimidazole **10** (27.2 mg, 0.23 mmol) was coupled with 4-iodobenzonitrile (52.7 mg, 0.23 mmol), by using Cu_2O (3.3 mg, 0.023 mmol), PEG_{3400}–OH (250 mg), and Cs_2CO_3 (150 mg, 0.46 mmol), to afford the title compound **12** in 44% yield. An analytical sample was purified by silica gel column chromatography: AcOEt/cyclohexane (10/90 to 20/80 v/v) as developing solvents. ^1H NMR [$(CD_3)_2SO$] δ=8.70 (s, 1H), 8.13 (d, *J*=8.9 Hz, 2H), 7.97 (d, *J*=8.9 Hz, 2H), 7.81 (d, *J*=6.7 Hz, 1H), 7.74 (d, *J*=6.7 Hz, 1H), 7.46–7.18 (m, 2H); ^1H NMR ($CDCl_3$) δ=8.22 (s, 1H), 7.90 (d, *J*=8.5 Hz, 3H), 7.69 (d, *J*=8.5 Hz, 2H), 7.39 (m, 3H); ^{13}C NMR [$(CD_3)_2SO$]: δ=144.0, 143.2, 139.8, 134.3, 133.55, 123.9, 123.8, 123.9, 120.1, 118.4, 110.8, 109.8; ESI-MS: *m*/*z* 220.1 $[M+H]^+$.

*4.2.10. 1-(4-Nitrophenyl)-1H-benzimidazole (**13**)*[47]. Following the general procedure (150 °C, 1 h), benzimidazole **10** (27.2 mg, 0.23 mmol) was coupled with 1-iodo-4-nitrobenzene (114.6 mg, 0.46 mmol), by using Cu_2O (3.3 mg, 0.023 mmol), PEG_{3400}–OH (250 mg), and Cs_2CO_3 (150 mg, 0.46 mmol), to afford the title compound **13** in 39% yield. An analytical sample was purified by silica gel column chromatography: AcOEt/cyclohexane (1/99 to 8/92 v/v) as developing solvents. ^1H NMR [$(CD_3)_2SO$]: δ=8.76 (s, 1H), 8.47 (d, *J*=9.0 Hz, 2H), 8.04 (d, *J*=9.0 Hz, 2H), 7.80 (m, 2H), 7.48–7.32 (m, 2H); ^1H NMR ($CDCl_3$): δ=8.47 (d, *J*=8.9 Hz, 2H), 8.22 (s, 1H), 7.89 (m, 1H), 7.73 (d, *J*=8.9 Hz, 1H), 7.61 (m, 2H), 7.41–7.35 (m, 2H); ^{13}C NMR [$(CD_3)_2SO$]: δ=145.7, 144.2, 143.7, 141.3, 135.2, 125.8, 125.5, 123.7, 120.2 110.9; ESI-MS: *m*/*z* 240.0 $[M+H]^+$.

*4.2.11. 1-(2-Nitrophenyl)-1H-benzimidazole (**14**)*[45,46]. Following the general procedure (150 °C, 1 h), benzimidazole **10** (27.2 mg, 0.23 mmol) was coupled with 1-iodo-2-nitrobenzene (114.6 mg, 0.46 mmol), by using Cu_2O (3.3 mg, 0.023 mmol), PEG_{3400}–OH (250 mg), and Cs_2CO_3 (150 mg, 0.46 mmol), to afford the title compound **14** in 69% yield. An analytical sample was purified by silica gel column chromatography: AcOEt/cyclohexane (2/98 to 10/90 v/v) as developing solvents. ^1H NMR [$(CD_3)_2SO$]: δ=8.50 (s, 1H), 8.32 (dd, *J*=8.2 and 1.4 Hz, 1H), 8.00 (ddd, *J*=16.5, 6.5, and 1.4 Hz, 1H), 7.90–7.80 (m, 2H), 7.78 (d, *J*=6.7 Hz, 1H), 7.35–7.25 (m, 2H), 7.25–7.15 (m, 1H); ^1H NMR ($CDCl_3$): δ=8.17 (dd, *J*=8.11 and 1.44 Hz, 1H), 8.03 (s, 1H), 7.87 (d, *J*=6.1 Hz, 1H), 7.83 (t, *J*=7,7 Hz, 1H), 7.72 (t, *J*=9.0 Hz, 1H), 7.58 (dd, *J*=8.11 and 1.44 Hz, 1H), 7.32 (m, 2H), 7.14 (dd, *J*=7.9 and 1.4 Hz, 1H); ^{13}C NMR [$(CD_3)_2SO$]: δ=147.7, 145.1, 141.1, 135.1, 130.4, 130.1, 129.8, 125.9, 123.7, 123.2, 122.6, 109.7; ESI-MS: *m*/*z* 240.0 $[M+H]^+$.

*4.2.12. 1-(4-Methoxyphenyl)-1H-benzimidazole (**15**)*[48]. Following the general procedure (150 °C, 1 h), benzimidazole **10** (27.2 mg, 0.23 mmol) was coupled with 4-iodoanisole (107.7 mg, 0.46 mmol), by using Cu_2O (3.3 mg, 0.023 mmol), PEG_{3400}–OH (250 mg), and Cs_2CO_3 (150 mg, 0.46 mmol), to afford the title compound **15** in 53% yield. An analytical sample was purified by silica gel column chromatography: AcOEt/cyclohexane (10/90 to 80/20 v/v) as developing solvents. ^1H NMR ($CDCl_3$): δ=8.05 (s, 1H), 7.90–7.84 (m, 1H), 7.50–7.35 (m, 3H), 7.35–7.27 (m, 2H), 7.10–7.05 (m, 2H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$): δ=159.4, 138.1, 129.1, 125.2, 123.5, 122.6, 120.4, 115.1, 110.5, 55.6; ESI-MS: *m*/*z* 224.9 $[M+H]^+$.

*4.2.13. 1-(2-Methoxyphenyl)-1H-benzimidazole (**16**)*[45,49,46,47]. Following the general procedure (150 °C, 1 h), benzimidazole **10** (27.2 mg, 0.23 mmol) was coupled with 2-iodoanisole (30 μL, 0.23 mmol), by using Cu_2O (3.3 mg, 0.023 mmol), PEG_{3400}–OH (250 mg), and Cs_2CO_3 (150 mg, 0.46 mmol), to afford the title compound **16** in 46% yield. An analytical sample was purified by silica gel column chromatography: AcOEt/cyclohexane (2/98 to 12/88 v/v) as developing solvents. ^1H NMR ($CDCl_3$): δ=8.12 (br s, 1H), 7.88 (d, *J*=6.5 Hz, 1H), 7.50–7.43 (m, 3H), 7.36–7.28 (m, 2H), 7.14 (d, *J*=7.9 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$): δ=153.9, 129.8, 127.3, 123.3, 122.9, 122.5, 120.2, 120.1, 115.7, 112.5, 110.8, 56.7; ESI-MS: *m*/*z* 225.1 $[M+H]^+$.

*4.2.14. 1-(4-Methylphenyl)-1H-benzimidazole (**17**)*[34]. Following the general procedure (150 °C, 1 h), benzimidazole **10** (27.2 mg, 0.23 mmol) was coupled with 4-iodotoluene (50.1 mg, 0.23 mmol), by using Cu_2O (3.3 mg, 0.023 mmol), PEG_{3400}–OH (250 mg), and Cs_2CO_3 (150 mg, 0.46 mmol), to afford the title compound **17** in 35% yield. An analytical sample was purified by silica gel column chromatography: AcOEt/cyclohexane (10/90 to 60/40 v/v) as developing solvents. ^1H NMR [$(CD_3)_2SO$]: δ=8.6 (s, 1H), 7.8 (m, 1H), 7.41–7.31 (m, 2H), 7.62–7.51 (m, 3H), 7.38–7.28 (m, 2H), 2.5 (s, 3H); ^1H NMR $CDCl_3$: δ=8.07 (s, 1H), 7.87 (m, 1H), 7.53 (m, 1H), 7.43–7.28 (m, 6H), 2.5 (s, 3H); ^{13}C NMR [$(CD_3)_2SO$]: δ=137.2, 136.8, 133.4, 131.4, 130.4, 123.5, 123.3, 122.2, 121.6, 119.9, 110.6, 22.9; ESI-MS: *m*/*z* 209.2 $[M+H]^+$.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.03.065.

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