

Article

Aqueous Synthesis of 1-*H*-2-Substituted Benzimidazoles via Transition-Metal-Free Intramolecular Amination of Aryl Iodides

Chunxia Chen ^{1,2}, Chen Chen ¹, Bin Li ^{1,2,*}, Jingwei Tao ¹ and Jinsong Peng ^{1,*}

¹ Department of Chemistry and Chemical Engineering, College of Science, Northeast Forestry University, Harbin 150040, China

² Post-Doctoral Mobile Research Station of Forestry Engineering, Northeast Forestry University, Harbin 150040, China

* Authors to whom correspondence should be addressed; E-Mails: libinzh62@163.com (B.L.); jspeng1998@163.com (J.P.); Tel.: +86-451-8219-0679 (B.L.); Fax: +86-451-8219-2699 (B.L.).

Received: 25 September 2012; in revised form: 17 October 2012 / Accepted: 21 October 2012 /

Published: 24 October 2012

Abstract: A straightforward method has been developed for the synthesis of the benzimidazole ring system through a carbon-nitrogen cross-coupling reaction. In the presence of 2.0 equiv. of K₂CO₃ in water at 100 °C for 30 h, the intramolecular cyclization of *N*-(2-iodoaryl)benzamidines provides benzimidazole derivatives in moderate to high yields. Remarkably, the procedure occurs exclusively in water and doesn't require the use of any additional reagent/catalyst, rendering the methodology highly valuable from both environmental and economical points of view.

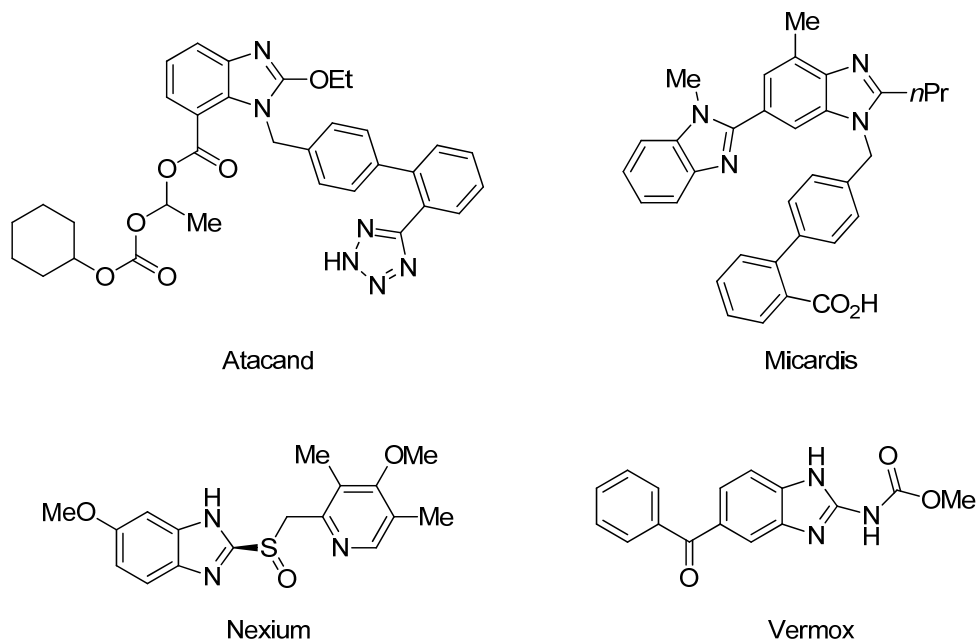
Keywords: benzimidazoles; aqueous synthesis; *N*-arylation; transition-metal-free conditions; aryl iodides

1. Introduction

Benzimidazoles are an important class of heterocycles that are frequently used in drug and agrochemical discovery programs. For examples, the benzimidazole core structure is found in a variety of commercial drugs such as Atacand, Nexium, Micardis, Protonix, and Vermox (Figure 1). Recent medicinal chemistry applications of benzimidazole analogs include antibacterial and antifungal agents [1–3], anthelmintic agents [4], HIV-1-induced cytopathic inhibitor [5], anti-inflammatory and antiulcer agents [6], cytotoxic and antitumor agents [7,8], DNA binding agents [9], enzyme and

receptor agonists or antagonists [10]. Other applications of benzimidazoles include their use as organic ligands [11,12], fluorescent whitening agent dyes [13] and functional materials [14,15]. Therefore, the construction of these heterocycles has always been of great interest to organic and medicinal chemists and has consequently received much attention [16].

Figure 1. Structures of some pharmacologically important benzimidazoles.

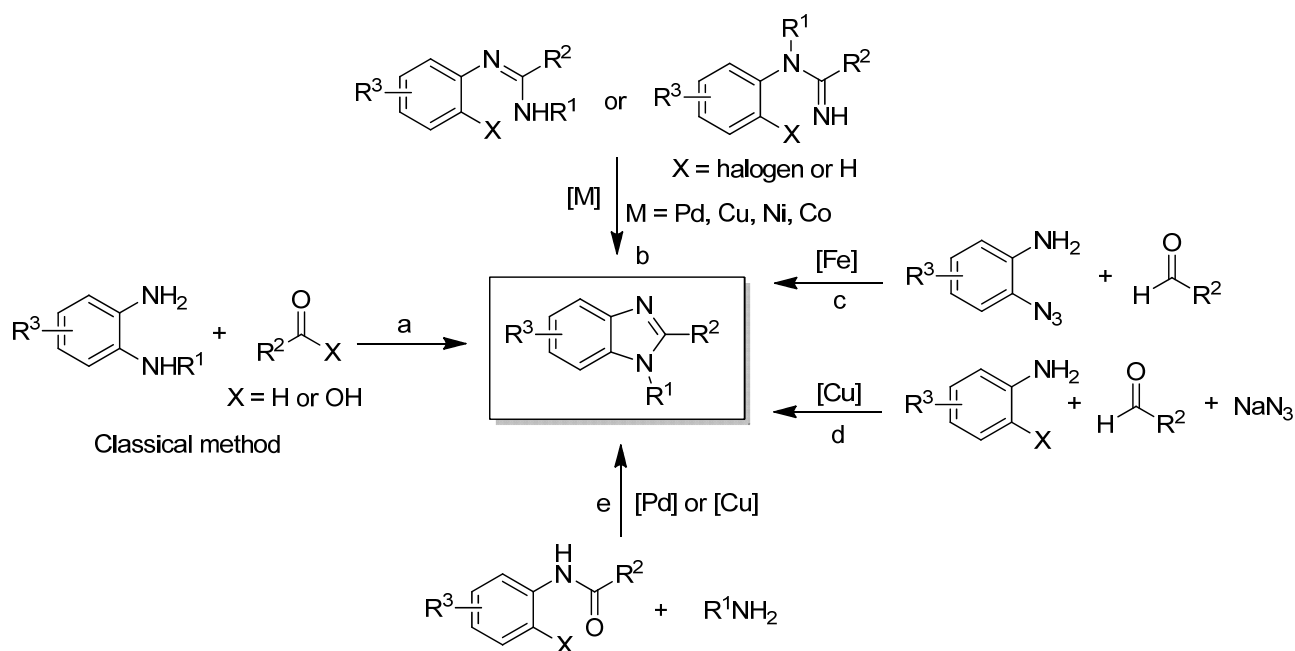


The classical and most common methods to assemble benzimidazoles involve the condensation of benzene-1,2-diamines with aldehydes, carboxylic acids, or their derivatives (Scheme 1, route a) under strong acid/high temperature conditions or using a stoichiometric oxidant [17–20]. Although these transformations are widely used owing to their inherent simplicity, this method is restricted to the available starting materials and involves harsh reaction conditions [17–20]. Furthermore, this methodology is not suitable for the regioselective synthesis of *N*-substituted benzimidazoles, as both syntheses result in regioisomers and disubstituted products from the 1,2-diaminoarene. To circumvent these restrictions, the transition-metal-catalyzed amination approach is a viable strategy to construct the benzimidazole ring regioselectively. Among the different catalysts, palladium- [21–25], copper- [26–33], nickel- [34], iron- [35], and cobalt-based [36] complexes are generally employed for this coupling reaction (Scheme 1, routes b–e). Despite these recent advances, transition-metal-catalyzed methods are often expensive and require especially designed ligands. Another disadvantage is the need to find ways to remove metal-related impurities from products, an important issue in the synthesis of pharmaceutical compounds.

Transition-metal-free *N*-arylation reactions [37–44] are also known to occur either by nucleophilic aromatic substitutions [45] or aryne-type intermediates [46–50] in the presence of a base. The former usually requires dipolar aprotic solvents (such as DMF, NMP and DMSO) and sometimes high reaction temperatures; the latter method requires strongly basic reaction conditions (generally potassium amide in liquid ammonia or *n*-BuLi in hexane). Both synthetic procedures have some drawbacks: harsh reaction conditions, inconvenient handling and workup, or a relatively narrow scope

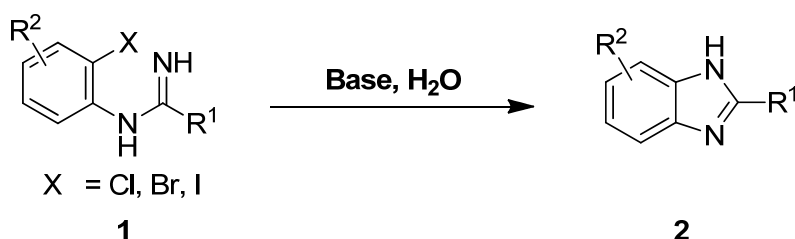
of substrates. Green reaction conditions in synthetic processes have been advocated, and extensive efforts have been devoted to finding sustainable reaction media. Notably the use of water as solvent has attracted much attention in recent years [51–54]. In parallel with our efforts to develop metal-free synthetic protocols for the production of pharmaceutical and agrochemical heterocyclic compounds [55,56], we envisaged the application of more sustainable protocol to the aqueous synthesis of the benzimidazole framework under transition metal-free conditions.

Scheme 1. Available methods to assemble benzimidazole derivatives.



As shown in Scheme 2, we propose the synthesis of benzimidazole derivatives **2** through a direct base-mediated intramolecular *N*-arylation reaction in water, starting from the corresponding *N*-(2-haloaryl) amidine **1**.

Scheme 2. Proposed approach to the synthesis of benzimidazoles **2**.



N-(2-Halophenyl) benzamidines **1a–a''** were selected as model substrates for this *N*-arylation reaction. In fact, our recently reported copper-catalyzed amination [28] showed that 2-iodoarylbenzamidines **1a** (with a concentration of 0.67 mol/L on a 1 mmol scale) can be transformed into the corresponding product in 19% yield with K₂CO₃ in water at 100 °C for 30 h. The use of Cu₂O/DMEDA as the catalyst could efficiently promote this transformation giving 98% yield. Based on the above observations, we wondered whether this copper-free chemical reaction can be improved by changing heterogeneity, oil-water interface, and modes of aggregation “on” the surface of water or in water [57,58].

Further investigations showed that using a relatively low concentration (about 0.1 mol/L on a 0.25 mmol scale), benzimidazole can be obtained in moderate to high yields with vigorous stirring in water.

2. Results and Discussion

Optimization of other reaction conditions such as base, temperature and time is shown in Table 1. At first, the control experiment of **1a** was examined in the absence of a base (entry 1, Table 1), and the desired product was not observed. The intramolecular carbon-nitrogen cross-coupling reaction of *N*-(2-iodophenyl)benzamidine (**1a**) using potassium carbonate (K_2CO_3 , 2.0 equiv.) as the base in water at 100 °C for 30 h was then examined. To our delight, benzimidazole **2a** was smoothly obtained in 80% yield (entry 2, Table 1).

Table 1. Optimization of base-mediated intramolecular C–N cross-coupling of benzamidine **1a–c** in water ^[a].

1a: X = I; 1a': X = Br; 1a'': X = Cl

Entry	Substrate	Base	Temperature (°C)	Time (h)	Yield (%) ^[b]
1	1a	—	100	30	0
2	1a	K_2CO_3	100	30	80
3	1a	KOH	100	30	63
4	1a	K_3PO_4	100	30	trace
5	1a	NaOH	100	30	0
6	1a	$NaHCO_3$	100	30	0
7	1a	Na_2CO_3	100	30	0
8	1a	Cs_2CO_3	100	30	84
9	1a	Et_3N	100	30	0
10	1a	Pyridine	100	30	0
11 ^[c]	1a	K_2CO_3	80	30	trace
12	1a	K_2CO_3	90	30	60
13	1a	K_2CO_3	100	20	50
14	1a	K_2CO_3	100	48	74
15 ^[d]	1a	K_2CO_3	120	30	78
16 ^[d]	1a	K_2CO_3	150	30	66
17	1a'	K_2CO_3	100	30	0
18	1a''	K_2CO_3	100	30	0

^[a] The reaction was carried out with *N*-(2-halophenyl)benzamidine (0.25 mmol) and base (0.5 mmol) in water (2.0 mL) with vigorous stirring at 80–150 °C for 20–48 h; ^[b] Isolated yield after column chromatography;

^[c] Complete recovery of starting material; ^[d] Decomposition product *o*-bromoaniline was also obtained under the given reaction conditions.

Recent research has revealed that metal impurities in commercially available reagents might potentially affect their reactions [59–62]. To eliminate this possibility, different sources of K_2CO_3 and

purified K_2CO_3 with high purities (99.9%) were used with new glassware, and metal reagents were avoided in synthetic steps wherever possible, and almost the same yields were obtained. Furthermore, based on the data from entries 2 to 10 in Table 1, we concluded that the presence of trace metal impurities weren't involved in this carbon-nitrogen bond formation reaction [63]. The nature of base was very important to the reaction outcome. KOH and Cs_2CO_3 were also effective in promoting this C–N bond formation in water, and the following yields were obtained: 63% (KOH) and 84% (Cs_2CO_3). Surprisingly, other bases such as NaOH, $NaHCO_3$, K_3PO_4 , Na_2CO_3 , Et_3N and pyridine gave no product. The reactions performed at 100 °C gave the best result, because at lower temperature the conversions remained incomplete (entries 11 and 12, Table 1), at higher temperature the undesired decomposition of substrate to *o*-iodoaniline happened (entries 15 and 16, Table 1). The *ortho*-substituted halogen on the aniline moiety was very important to this intramolecular carbon-nitrogen cross-coupling reaction. Aryl chloride and aryl bromide, which were expected to be more reactive than their iodo analogues in a substitution reaction proceeding by the S_NAr mechanism [64,65], gave no product. Obviously an aromatic nucleophilic substitution process is inconsistent with our experimental results (entries 17 and 18, Table 1), so this reaction presumably occurred by an aryne-type intermediate in the presence of a base.

With the optimized reaction conditions in hand, the generality of the aniline moiety in the amination process was explored first. As shown in Table 2, (*o*-iodoaryl)benzamidines can smoothly be converted to the desired products in moderate to high yields, however, the use of aryl bromides to effect such transformations afforded none of the desired products (entries 3 and 9, Table 2). For aryl iodides, a variety of substituents such as F, Cl, Br, Me and MeO can be used. It is worth noting that reaction conditions compatible with C–Br or C–Cl combinations are particularly appealing, since these substituents offer great opportunity for further synthetic manipulations (entries 4 and 21, Table 2). 3-Iodo-2-aminopyridine substrate **1g** can be transformed into the corresponding benzimidazole in 44% yield (entry 8, Table 2), however, 2-iodo-3-aminopyridine substrate **1h** gave no product (entry 10, Table 2) that probably attributed to failure to generate an aryne intermediate by *ortho*-deprotonations followed by iodide elimination. These results as well as the order of reactivity of aryl halides (entries 2, 17 and 18, Table 1) further pointed to the involvement of aryne-type intermediates.

The scope and limitation of the nitrile moiety were next studied (Table 3). Obviously, the electronic nature of the benzonitrile motifs had a great effect on the yields. Substrates bearing various electron-donating substituents such as Me–, MeO– and Me₂N– can be converted smoothly into the desired products in moderate to high yields (entries 1–6, Table 3). Furthermore, the steric hindrance of *ortho* substituents on the benzonitrile moiety seemed not to hamper *N*-arylation reaction, the benzimidazoles could be obtained in similar yields (entries 1–4, Table 2). However, the presence of relatively electron-withdrawing or stronger electron-withdrawing functional groups completely held back intramolecular amination process. Other electron-rich aromatic and heteroaromatic substrates such as **1q**, **1r** and **1s** could be efficiently transformed into the corresponding benzimidazoles in satisfactory yields (entries 9–11, Table 3). In addition, *N'*-phenylated alkylamidine substrate **1u** could also be converted to the desired product **2u** under these conditions (entry 13, Table 3). In contrast to electron-rich aromatic substituents, *N*-(2-iodophenyl)amidine with an aliphatic functional group (Me–) provided a trace amount of the product (entry 12, Table 3), the most of the starting materials were unchanged and recovered from the reaction mixture.

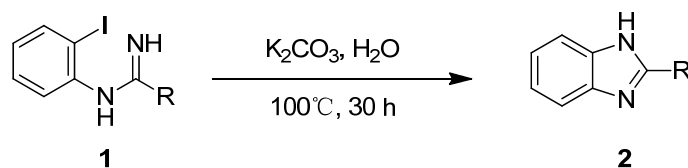
Table 2. Direct weak base-mediated synthesis of 2-phenylbenzimidazole derivatives in water ^[a].

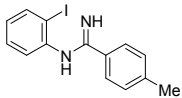
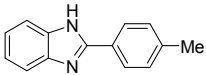
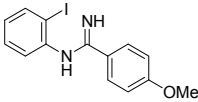
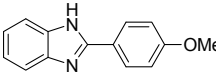
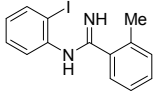
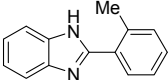
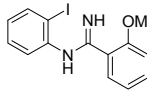
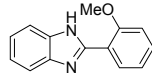
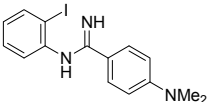
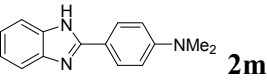
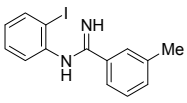
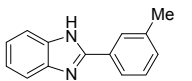
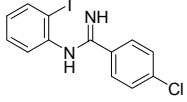
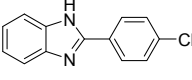
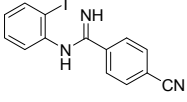
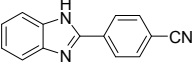
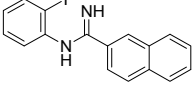
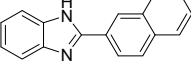
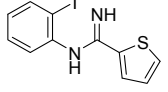
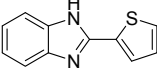
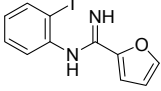
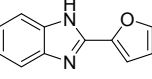
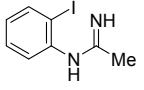
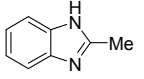
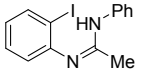
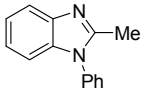
$\text{X} = \text{Br}, \text{I} \quad \mathbf{1} \xrightarrow[100^\circ\text{C}, 30 \text{ h}]{\text{K}_2\text{CO}_3, \text{H}_2\text{O}} \mathbf{2}$

Entry	Substrate	Product	Yield (%) ^[b]
1	1a	2a	80
2	1b	2b	77
3 ^c	1b'	2b	0
4	1c	2c	66
5	1d	2d	54
6	1e	2e	67
7	1f	2f	67
8	1g	2g	44
9 ^[c]	1g'	2g	0
10 ^[c]	1h	2h	0

^[a] Reaction conditions: 1.0 equiv. of *N*-(2-haloaryl)benzamidines (0.25 mmol) and 2.0 equiv. of K_2CO_3 in water (2.0 mL) at 100 °C with vigorous stirring for 30 h; ^[b] Isolated yield after column chromatography;

^[c] Complete recovery of starting material.

Table 3. Synthesis of 2-arylbenzimidazole derivatives in water ^[a].

Entry	Substrate	Product	Yield (%) ^[b]
1	 1i	 2i	60
2	 1j	 2j	63
3	 1k	 2k	58
4	 1l	 2l	64
5	 1m	 2m	70
6	 1n	 2n	50
7 ^[c]	 1o	 2o	0
8 ^[c]	 1p	 2p	0
9	 1q	 2q	48
10	 1r	 2r	60
11	 1s	 2s	48
12 ^[c]	 1t	 2t	0
13	 1u	 2u	33

^[a] Reaction conditions: 1.0 equiv. of *N*-(2-iodophenyl)amidine (0.25 mmol) and 2.0 equiv. of K₂CO₃ in water (2.0 mL) at 100 °C with vigorous stirring for 30 h; ^[b] Isolated yield after column chromatography;

^[c] Complete recovery of starting material.

3. Experimental

3.1. General

Chemicals and solvents were all purchased from commercial supplies and used without further purification. Amidines were prepared through the addition of an aniline to a nitrile according to known procedures [20–24]. Silica gel (100 mesh) was used for chromatographic separation. Silica gel G was used for TLC. Petroleum ether refers to the fraction boiling between 60 °C and 80 °C. All reactions were carried out in dried glassware. ¹H-NMR spectra were recorded on a Bruker-400 MHz spectrometer and ¹³C-NMR spectra were recorded at 100 MHz using tetramethylsilane (TMS) as the internal standard in DMSO-*d*₆. Chemical shifts (δ) are given in parts per million (ppm) downfield relative to TMS (¹H-NMR: TMS at 0.00 ppm, DMSO at 2.50 ppm; ¹³C-NMR: DMSO at 40.0 ppm). Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ¹H-NMR. Melting points were determined by use of a Buchi melting point apparatus and not corrected. High-resolution mass spectra were recorded on a Bruker BIO TOF Q mass spectrometer.

3.2. Chemistry

3.2.1. General Procedure for the Preparation of Benzimidazoles **2a–u**

A 10 mL Schlenk tube equipped with a magnetic stirring bar was charged with the (*o*-iodoaryl)-benzamidine substrate (0.25 mmol, 1.0 equiv.) and K₂CO₃ (69 mg, 0.5 mmol, 2.0 equiv.), then H₂O (2.0 mL) was added via syringe at room temperature. The tube was sealed and put into a pre-heated oil bath at 100 °C for 30 h. The reaction mixture was cooled to room temperature, quenched with water (3 mL), and diluted with ethyl acetate (5 mL). The layers were separated and the aqueous layer was extracted with (2 × 5 mL) ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel (H), eluting with 5–10% ethyl acetate/petroleum ether.

2-Phenyl-1H-benzo[d]imidazole (2a). White solid; m.p. 293–295 °C; yield: 80%. ¹H-NMR: δ 12.92 (br s, 0.19H), 8.21–8.19 (d, 2H, *J* = 7.6 Hz), 7.69–7.67 (d, 1H, *J* = 6.8 Hz), 7.58–7.48 (m, 4H), 7.24–7.22 (d, 2H, *J* = 6.8 Hz). ¹³C-NMR: δ 151.55, 144.23, 135.30, 130.57, 130.32, 129.42, 126.89, 123.02, 122.15, 119.34, 111.75. HRMS-ESI (*m/z*): [M+Na]⁺ calcd. for C₁₃H₁₀N₂Na 217.0742; found 217.0745.

5-Fluoro-2-phenyl-1H-benzo[d]imidazole (2b). White solid; m.p. 243–244 °C; yield: 77%. ¹H-NMR: δ 13.06 (br s, 0.14H), 8.18–8.16 (d, 2H, *J* = 8.0 Hz), 7.69–7.31 (m, 5H), 7.12–7.04 (m, 1H). ¹³C-NMR: δ 160.15, 153.33, 140.91, 130.60, 130.28, 126.95, 120.19, 111.19, 110.44, 104.90, 98.28. HRMS-ESI (*m/z*): [M+Na]⁺ calcd. for C₁₃H₉FN₂Na 235.0647; found 235.0649.

5-Chloro-2-phenyl-1H-benzo[d]imidazole (2c). White solid; m.p. 209–211 °C; yield: 66%. ¹H-NMR: δ 13.13 (br s, 0.18H), 8.20–8.18 (d, 2H, *J* = 7.2 Hz), 7.74–7.51 (m, 5H), 7.26–7.24 (d, 1H, *J* = 8.0 Hz). ¹³C-NMR: δ 152.55, 144.63 (142.48), 135.52 (133.60), 130.15, 129.56, 128.94, 126.50, 122.53 (122.08), 120.02, 118.18, 112.53 (110.92). HRMS-ESI (*m/z*): [M+Na]⁺ calcd. for C₁₃H₉ClN₂Na 251.0352; found 251.0356.

5-Bromo-2-phenyl-1H-benzo[d]imidazole (2d). White solid; m.p. 202–203 °C; yield: 54%. $^1\text{H-NMR}$: δ 13.09 (br s, 0.26H), 8.18–8.16 (d, 2H, $J = 8.0$ Hz), 7.87–7.50 (m, 5H), 7.37–7.33 (m, 1H). $^{13}\text{C-NMR}$: δ 145.20, 142.82, 130.27, 129.54, 129.01, 126.57, 125.21, 124.70, 114.71, 113.87, 113.07. HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{13}\text{H}_9\text{BrN}_2\text{Na}$ 294.9847; found 294.9849.

5-Methyl-2-phenyl-1H-benzo[d]imidazole (2e). White solid; m.p. 242–243 °C; yield: 67%. $^1\text{H-NMR}$: δ 12.80 (br s, 0.22H), 8.20 (m, 2H), 7.55 (m, 5H), 7.05 (m, 1H), 2.45 (s, 3H). $^{13}\text{C-NMR}$: δ 150.80, 141.94, 135.08, 131.53, 130.24, 129.59, 128.84, 128.01, 126.26, 123.51, 118.29, 110.86, 21.27. HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{Na}$ 231.0898; found 231.0896.

5-Methoxy-2-phenyl-1H-benzo[d]imidazole (2f). White solid; m.p. 148–150 °C; yield: 67%. $^1\text{H-NMR}$: δ 13.07 (br s, 0.13H), 8.29–8.13 (m, 2H), 7.58–7.48 (m, 4H), 7.25–7.08 (m, 1H), 7.02–7.01 (m, 1H), 3.83–3.82 (s, 3H). $^{13}\text{C-NMR}$: δ 156.8, 151.4, 137.4, 136.2, 130.4 (130.1), 129.4 (129.2), 127.5, 126.8, 114.2, 112.4, 94.99 (94.94), 56.4. HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{NaO}$ 247.0847; found 247.0849.

2-Phenyl-3H-imidazo[4,5-b]pyridine (2g). White solid; m.p. 283–284 °C; yield: 44%. $^1\text{H-NMR}$ δ 13.48 (br s, 1H), 8.34 (dd, $J = 4.8, 1.5$ Hz, 1H), 8.25–8.21 (m, 2H), 8.02 (d, $J = 7.5$ Hz, 1H), 7.61–7.51 (m, 3H), 7.25 (dd, $J = 8.1, 4.8$ Hz, 1H). $^{13}\text{C-NMR}$: δ 152.32, 143.75, 135.57, 130.52, 129.57, 129.00, 126.70, 126.27, 119.16, 118.09. HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{12}\text{H}_9\text{N}_3\text{Na}$ 218.0694; found 218.0697.

2-p-Tolyl-1H-benzo[d]imidazole (2i). White solid; m.p. 276–278 °C; yield: 60%. $^1\text{H-NMR}$: δ 12.83 (br s, 0.15H), 8.09–8.07 (d, 2H, $J = 7.6$ Hz), 7.65–7.53 (m, 2H), 7.37–7.35 (d, 2H, $J = 8.0$ Hz), 7.20 (m, 2H), 2.39 (s, 3H). $^{13}\text{C-NMR}$: δ 151.17, 143.71, 139.49, 134.74, 129.42, 127.31, 126.30, 122.23, 121.50, 118.62, 111.04, 20.87. HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{Na}$ 231.0898; found 231.0895.

2-(4-Methoxyphenyl)-1H-benzo[d]imidazole (2j). White solid; m.p. 221–223 °C; yield: 63%. $^1\text{H-NMR}$: δ 12.76 (br s, 0.11H), 8.14–8.12 (d, 2H, $J = 8.8$ Hz), 7.57 (m, 2H), 7.20–7.17 (m, 2H), 7.13–7.11 (d, 2H, $J = 8.8$ Hz), 3.85 (s, 3H). $^{13}\text{C-NMR}$: δ 160.59, 151.25, 143.73, 134.97, 127.98, 122.61, 122.07, 121.74, 118.43, 114.34, 111.05, 55.29. HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{NaO}$ 247.0847; found 247.0851.

2-o-Tolyl-1H-benzo[d]imidazole (2k). White solid; m.p. 206–208 °C; yield: 58%. $^1\text{H-NMR}$ δ 12.64 (br s, 0.11H), 7.76–7.74 (d, 1H, $J = 6.8$ Hz), 7.62 (m, 2H), 7.39–7.37 (m, 3H), 7.23–7.21 (m, 2H), 2.62 (s, 3H). $^{13}\text{C-NMR}$ δ 151.73, 136.91, 131.15, 129.94, 129.33, 129.22, 125.85, 121.78, 20.90. HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{Na}$ 231.0898; found 231.0901.

2-(2-Methoxyphenyl)-1H-benzo[d]imidazole (2l). White solid; m.p. 181–182 °C; yield: 64%. $^1\text{H-NMR}$ δ 12.13 (br s, 0.22H), 8.35–8.32 (dd, 1H, $J = 7.6, 1.6$ Hz), 7.66–7.62 (m, 2H), 7.52–7.47 (m, 1H), 7.27–7.25 (d, 1H, $J = 8.0$ Hz), 7.21–7.19 (m, 2H), 7.15–7.11 (m, 1H), 4.04 (s, 3H). $^{13}\text{C-NMR}$ δ 156.74, 152.87, 141.72, 141.68, 131.25, 129.70, 122.02, 129.33, 121.50, 120.85, 118.45, 117.93, 112.07, 55.74. HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{NaO}$ 247.0847; found 247.0849.

4-(1*H*-Benzo[d]imidazol-2-yl)-*N,N*-dimethylaniline (**2m**). White solid; m.p. 272–274 °C; yield: 70%. ¹H-NMR: δ 12.57 (br s, 0.29H), 8.01 (d, 2H, *J* = 8.0 Hz), 7.57–7.46 (m, 2H), 7.15–7.13 (dd, 2H, *J* = 6.0, 2.8 Hz), 6.85–6.83 (d, 2H, *J* = 8.0 Hz), 3.00 (s, 6H). ¹³C-NMR: δ 152.12, 151.22, 144.01, 134.78, 127.52, 121.48, 121.16, 117.99, 117.31, 111.81, 110.60, 41.07. HRMS-ESI (*m/z*): [M+Na]⁺ calcd. for C₁₅H₁₅N₃Na 260.1164; found 260.1168.

2-(*m*-Tolyl)-1*H*-benzo[d]imidazole (**2n**). White solid; m.p. 213–215 °C; yield: 50%. ¹H-NMR: δ 12.88 (br s, 0.21H), 8.03 (s, 1H), 7.98–7.96 (d, 1H, *J* = 8.0 Hz), 7.65–7.54 (m, 2H), 7.47–7.43 (t, 1H, *J* = 8.0 Hz), 7.33–7.31 (d, 1H, *J* = 8.0 Hz), 7.22–7.21 (m, 2H), 2.43 (s, 3H). ¹³C-NMR: δ 151.13, 143.26, 138.15, 130.47, 129.92, 129.86, 128.83, 126.96, 123.55, 122.46, 121.64, 118.78, 111.22, 21.02. HRMS-ESI (*m/z*): [M+Na]⁺ calcd. for C₁₄H₁₂N₂Na 231.0898; found 231.0899.

2-(Naphthalen-2-yl)-1*H*-benzo[d]imidazole (**2q**). White solid; m.p. 206–207 °C; yield: 48%. ¹H-NMR: δ 13.11 (br s, 0.29H), 8.76 (s, 1H), 8.34 (d, 1H, *J* = 8.0 Hz), 8.11–8.05 (m, 2H), 8.01–7.99 (m, 1H), 7.73–7.71 (m, 1H), 7.64–7.59 (m, 3H), 7.25 (m, 2H). ¹³C-NMR: δ 151.23, 143.87, 134.96, 133.45, 132.79, 128.54, 128.42, 127.77, 127.53, 127.10, 126.91, 125.79, 123.91, 122.67, 121.76, 118.88, 111.31. HRMS-ESI (*m/z*): [M+Na]⁺ calcd. for C₁₇H₁₂N₂Na 267.0898; found 267.0899.

2-(Thiophen-2-yl)-1*H*-benzo[d]imidazole (**2r**). White solid; m.p. 341–343 °C; yield: 60%. ¹H-NMR: δ 12.94 (br s, 0.24H), 7.83 (dd, *J* = 3.6, 0.8 Hz, 1H), 7.72 (dd, *J* = 4.8, 0.8 Hz, 1H), 7.62–7.60 (m, 1H), 7.50 (dd, *J* = 6.9, 2.1 Hz, 1H), 7.25–7.16 (m, 3H). ¹³C-NMR: δ 146.86, 143.54, 134.49, 133.59, 128.73, 128.25, 126.67, 122.61, 121.74, 118.51, 111.02. HRMS-ESI (*m/z*): [M+Na]⁺ calcd. for C₁₁H₈N₂NaS 223.0306; found 223.0304.

2-(Furan-2-yl)-1*H*-benzo[d]imidazole (**2s**). White solid; m.p. 285–286 °C; yield: 48%. ¹H-NMR: δ 12.92 (br s, 0.26H), 7.95 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.55 (br s, 2H), 7.24–7.20 (m, 3H), 6.73 (dd, *J* = 3.3, 1.8 Hz, 1H). ¹³C-NMR: δ 145.5, 144.6, 143.5, 134.3, 122.3, 121.6, 118.7, 112.3, 111.4, 110.5. HRMS-ESI (*m/z*): [M+Na]⁺ calcd. for C₁₁H₈N₂NaO 207.0534; found 207.0536.

2-Methyl-1-phenyl-1*H*-benzo[d]imidazole (**2u**). White solid; m.p. 127–129 °C; yield: 33%. ¹H-NMR: δ 7.67–7.63 (m, 3H), 7.59–7.53 (m, 3H), 7.24–7.12 (m, 3H), 2.43 (s, 3H). ¹³C-NMR δ 143.2, 136.1, 134.3, 130.4, 129.2, 127.3, 124.5, 122.8, 122.4, 118.9, 110.3, 14.6. HRMS-ESI (*m/z*): [M+Na]⁺ calcd. for C₁₄H₁₂N₂Na 231.0898; found 231.0896.

4. Conclusions

In summary, a straightforward weak base-mediated protocol had been developed for the intramolecular C–N bond formation to provide benzimidazole derivatives in moderate to high yields. Particularly interesting, the use of water as a benign and accessible solvent should render the methodology described herein economical and environmentally attractive, providing an alternative synthetic protocol for potential industrial applications without the addition of any exogenous transition metal catalysts.

Acknowledgments

We are grateful for the funding support from the Fundamental Research Funds for the Central Universities (DL12DB03), China Postdoctoral Science Foundation (20110491013, 2012T50319) and Heilongjiang Postdoctoral Grant (LBH-Z11251).

References and Notes

1. Desai, K.G.; Desai, K.R. Green route for the heterocyclization of 2-mercaptobenzimidazole into β -lactum segment derivatives containing –CONH– bridge with benzimidazole: Screening *in vitro* antimicrobial activity with various microorganisms. *Bioorg. Med. Chem.* **2006**, *14*, 8271–8279.
2. Güven, Ö.Ö.; Erdoğan, T.; Göker, H.; Ylidiz, S. Synthesis and antimicrobial activity of some novel phenyl and benzimidazole substituted benzyl ethers. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2233–2236.
3. Igual-Adell, R.; Oltra-Alcaraz, C.; Soler-Company, E.; Sánchez-Sánchez, P.; Matogo-Oyany, J.; Rodríguez-Dalabuig, D. Efficacy and safety of ivermectin and thiabendazole in the treatment of strongyloidiasis. *Expert Opin. Pharmacother.* **2004**, *5*, 2615–2619.
4. Mavrova, A.T.; Anichina, K.K.; Vuchev, D.I.; Tsenov, J.A.; Denkova, P.S.; Kondeva, M.S.; Micheva, M.K. Antihelminthic activity of some newly synthesized 5(6)-(un)substituted-1*H*-benzimidazol-2-ylthioacetyl piperazine derivatives. *Eur. J. Med. Chem.* **2006**, *41*, 1412–1420.
5. Barreca, M.L.; Chimirri, A.; de Clercq, E.; de Luca, L.; Monforte, A.-M.; Monforte, P.; Rao, A.; Zappala, M. Anti-HIV agents: Design and discovery of new potent RT inhibitors. *Il Farmaco* **2003**, *58*, 259–263.
6. Leonard, J.T.; Rajesh, O.S.; Jeyaseeli, L.; Muruges, K.; Sivakumar, R.; Gunasekaran, V. Synthesis, Antiinflammatory and Antibacterial Activities of Substituted Phenyl Benzimidazoles. *Asian J. Chem.* **2007**, *19*, 116–120.
7. Baraldi, P.G.; Bovero, A.; Fruttarolo, F.; Preti, D.; Tabrizi, M.A.; Pavani, M.G.; Romagnoli, R. DNA minor groove binders as potential antitumor and antimicrobial agents. *Med. Res. Rev.* **2004**, *24*, 475–528.
8. Singh, A.K.; Lown, J.W. Design, synthesis and antitumor cytotoxicity of novel bis-benzimidazoles. *Anticancer Drug Des.* **2000**, *15*, 265–275.
9. Chaudhuri, P.; Ganguly, B.; Bhattacharya, S. An Experimental and Computational Analysis on the Differential Role of the Positional Isomers of Symmetric Bis-2-(pyridyl)-1*H*-benzimidazoles as DNA Binding Agents. *J. Org. Chem.* **2007**, *72*, 1912–1923.
10. Alamgir, M.; Black, D.St.C.; Kumar, N. Synthesis, Reactivity and Biological Activity of Benzimidazoles. In *Topics in Heterocyclic Chemistry*; Khan, M.T.H., Ed.; Springer: Berlin, Germany, 2007; Volume 9, pp. 87–118.
11. Pal, S.; Hwang, W.-S.; Lin, I.J.B.; Lee, C.-S. Benzene benzimidazole containing Pd(II) metallacycle: Synthesis, X-ray crystallographic characterization and its use as an efficient Suzuki coupling catalyst. *J. Mol. Catal. A: Chem.* **2007**, *269*, 197–203.

12. Hao, P.; Zhang, S.; Sun, W.-H.; Shi, Q.; Adewuyi, S.; Lu, X.; Li, P. Synthesis, Characterization and Ethylene Oligomerization Studies of Nickel Complexes Bearing 2-Benzimidazolylpyridine Derivatives. *Organometallics* **2007**, *26*, 2439–2446.
13. Rajadhyaksha, D.D.; Rangnekar, D.W. Synthesis of pyrazolo[4',3':5,6]pyrido[1,2-a]benzimidazole derivatives and study of their fluorescence properties. *J. Chem. Technol. Biotechnol.* **1986**, *36*, 300–304.
14. Asensio, J.A.; Gomez-Romero, P. Recent Developments on Proton Conducting Poly(2,5-benzimidazole) (ABPBI) Membranes for High Temperature Polymer Electrolyte Membrane Fuel Cells. *Fuel Cells* **2005**, *5*, 336–343.
15. Schwartz, G.; Fehse, K.; Pfeiffer, M.; Walzer, K.; Leo, K. Highly efficient white organic light emitting diodes comprising an interlayer to separate fluorescent and phosphorescent regions. *Appl. Phys. Lett.* **2006**, *89*, doi:10.1063/1.2338588.
16. Carvalho, L.C.R.; Fernandes, E.; Marques, M.M.B. Developments Towards Regioselective Synthesis of 1,2-Disubstituted Benzimidazoles. *Chem. Eur. J.* **2011**, *17*, 12544–12555.
17. Grimmett, M.R. Ring Syntheses Involving Formation of Two Bonds: [4+1] Fragments. In *Imidazole and Benzimidazole Synthesis*; Meth-Cohn, O., Ed.; Academic: London, UK, 1997; pp. 63–102.
18. Yang, D.; Fokas, D.; Li, J.; Yu, L.; Baldino, C.M. A Versatile Method for the Synthesis of Benzimidazoles from *o*-Nitroanilines and Aldehydes in One Step via a Reductive Cyclization. *Synthesis* **2005**, 47–56.
19. Bahrami, K.; Khodaei, M.M.; Naali, F. Mild and Highly Efficient Method for the Synthesis of 2-Arylbenezimidazoles and 2-Arylbenzothiazoles. *J. Org. Chem.* **2008**, *73*, 6835–6837.
20. Goossen, L.J.; Knauber, T. Concise Synthesis of Telmisartan via Decarboxylative Cross-Coupling. *J. Org. Chem.* **2008**, *73*, 8631–8634.
21. Brain, C.T.; Brunton, S.A. An intramolecular palladium-catalysed aryl amination reaction to produce benzimidazoles. *Tetrahedron Lett.* **2002**, *43*, 1893–1895.
22. Brain, C.T.; Brunton, S.A. An Improved Procedure for the Synthesis of Benzimidazoles, Using Palladium-Catalyzed Aryl-Amination Chemistry. *J. Org. Chem.* **2003**, *68*, 6814–6816.
23. Zhao, D.; Hu, J.; Wu, N.; Huang, X.; Qin, X.; Lan, J.; You, J. Regiospecific Synthesis of 1,2-Disubstituted (Hetero)aryl Fused Imidazoles with Tunable Fluorescent Emission. *Org. Lett.* **2011**, *13*, 6516–6519.
24. Xiao, Q.; Wang, W.-H.; Liu, G.; Meng, F.-K.; Chen, J.-H.; Yang, Z.; Shi, Z.-J. Direct Imidation to Construct 1*H*-Benzo[*d*]imidazole through Pd^{II}-Catalyzed C-H Activation Promoted by Thiourea. *Chem. Eur. J.* **2009**, *15*, 7292–7296.
25. Zheng, N.; Anderson, K.W.; Huang, X.H.; Nguyen, H.N.; Buchwald, S.L. A Palladium-Catalyzed Regiospecific Synthesis of *N*-Aryl Benzimidazoles. *Angew. Chem.* **2007**, *119*, 7653–7656; *Angew. Chem. Int. Ed. Engl.* **2007**, *46*, 7509–7512.
26. Evindar, G.; Batey, R.A. Copper- and Palladium-Catalyzed Intramolecular Aryl Guanidinylation: An Efficient Method for the Synthesis of 2-Aminobenzimidazoles. *Org. Lett.* **2003**, *5*, 133–136.
27. Szczepankiewicz, B.G.; Rohde, J.J.; Kurukulasuriy, R. Synthesis of Purines and Other Fused Imidazoles from Acyclic Amidines and Guanidines. *Org. Lett.* **2005**, *7*, 1833–1835.

28. Peng, J.; Ye, M.; Zong, C.; Hu, F.; Feng, L.; Wang, X.; Wang, Y.; Chen, C. Copper-Catalyzed Intramolecular C–N Bond Formation: A Straightforward Synthesis of Benzimidazole Derivatives in Water. *J. Org. Chem.* **2011**, *76*, 716–719.
29. Brasche, G.; Buchwald, S.L. C–H Functionalization/C–N Bond Formation: Copper-Catalyzed Synthesis of Benzimidazoles from Amidines. *Angew. Chem.* **2008**, *120*, 1958–1960; *Angew. Chem. Int. Ed. Engl.* **2008**, *47*, 1932–1934.
30. Zou, B.L.; Yuan, Q.L.; Ma, D.-W. Synthesis of 1,2-Disubstituted Benzimidazoles by a Cu-Catalyzed Cascade Aryl Amination/Condensation Process. *Angew. Chem.* **2007**, *119*, 2652–2655; *Angew. Chem. Int. Ed. Engl.* **2007**, *46*, 2598–2601.
31. Kim, Y.; Kumar, M.R.; Park, N.; Heo, Y.; Lee, S. Copper-Catalyzed, One-Pot, Three-Component Synthesis of Benzimidazoles by Condensation and C–N Bond Formation. *J. Org. Chem.* **2011**, *76*, 9577–9583.
32. Deng, X.; Mani, N.S. Reactivity-Controlled Regioselectivity: A Regiospecific Synthesis of 1,2-Disubstituted Benzimidazoles. *Eur. J. Org. Chem.* **2010**, 680–686.
33. Deng, X.; McAllister, H.; Mani, N.S. CuI-Catalyzed Amination of Arylhalides with Guanidines or Amidines: A Facile Synthesis of 1-*H*-2-Substituted Benzimidazoles. *J. Org. Chem.* **2009**, *74*, 5742–5745.
34. Amrani, R.O.; Thomas, A.; Brenner, E.; Schneider, R.; Fort, Y. Efficient Nickel-Mediated Intramolecular Amination of Aryl Chlorides. *Org. Lett.* **2003**, *5*, 2311–2314.
35. Shen, M.; Driver, T.G. Iron(II) Bromide-Catalyzed Synthesis of Benzimidazoles from Aryl Azides. *Org. Lett.* **2008**, *10*, 3367–3370.
36. Saha, P.; Ali, M.A.; Ghosh, P.; Punniyamurthy, T. Cobalt-catalyzed intramolecular C–N and C–O cross-coupling reactions: Synthesis of benzimidazoles and benzoxazoles. *Org. Biomol. Chem.* **2010**, *8*, 5692–5699.
37. Roberts, J.D.; Semenow, D.A.; Simmons, H.E., Jr.; Carlsmith, L.A. The Mechanism of Aminations of Halobenzenes. *J. Am. Chem. Soc.* **1956**, *78*, 601–611.
38. Ross, S.D. Nucleophilic Displacement Reactions in Aromatic Systems. IV. Rates of Reaction of 1-Halo-2,4-dinitrobenzene with *n*-Butylamine in Chloroform and with *n*-Butylamine and *t*-Butylamine in Dimethylformamide. *J. Am. Chem. Soc.* **1959**, *81*, 2113–2115.
39. Beller, M.; Breindl, C.; Riermeier, R.H.; Tillack, A. Synthesis of 2,3-Dihydroindoles, Indoles, and Anilines by Transition Metal-Free Amination of Aryl Chlorides. *J. Org. Chem.* **2001**, *66*, 1403–1412.
40. Shi, L.; Wang, M.; Fan, C.-A.; Zhang, F.-M.; Tu, Y.-Q. Rapid and Efficient Microwave-Assisted Amination of Electron-Rich Aryl Halides without a Transition-Metal Catalyst. *Org. Lett.* **2003**, *5*, 3515–3517.
41. Varala, R.; Ramu, E.; Alam, M.M.; Adapa, S.R. Scope and Utility of CsOH·H₂O in Amination Reactions via Direct Coupling of Aryl Halides and *sec*-Alicyclic Amines. *Synlett* **2004**, 1747–1750.
42. Bolliger, J.L.; Frech, C.M. Transition metal-free amination of aryl halides—A simple and reliable method for the efficient and high-yielding synthesis of *N*-arylated amines. *Tetrahedron* **2009**, *65*, 1180–1187.
43. Poirier, M.; Goudreau, S.; Poulin, J.; Savole, J.; Beaulieu, P.L. Metal-Free Coupling of Azoles with 2- and 3-Haloindoles Providing Access to Novel 2- or 3-(Azol-1-yl)indole Derivatives. *Org. Lett.* **2010**, *12*, 2334–2337.

44. Yuan, Y.; Thomé, I.; Kim, S.H.; Chen, D.; Beyer, A.; Bonnamour, J.; Zuidema, E.; Chang, S.; Bolm, C. Dimethyl Sulfoxide/Potassium Hydroxide: A Superbase for the Transition Metal-Free Preparation of Cross-Coupling Products. *Adv. Synth. Catal.* **2010**, *352*, 2892–2898.
45. March, J. Aromatic Nucleophilic Substitution. In *Advanced Organic Chemistry, Reactions, Mechanisms and Structure*, 4th ed.; John Wiley & Sons: New York, NY, USA, 1992; p. 641.
46. Huisgen, R.; König, H. Erweitertes Makromolekulares Kolloquium, Freiburg. *Angew. Chem.* **1957**, *69*, 268–272.
47. Huisgen, R.; Sauer, J. Nucleophile aromatische Substitutionen über Arine. *Angew. Chem.* **1960**, *72*, 91–108.
48. Hrutford, B.F.; Bunnett, J.F. A General Principle for the Synthesis of Heterocyclic and Homocyclic Compounds. *J. Am. Chem. Soc.* **1958**, *80*, 2021–2022.
49. Bunnett, J.F.; Hrutford, B.F. Ring Closure via Aryne Intermediates: A General Principle of Synthesis. *J. Am. Chem. Soc.* **1961**, *83*, 1691–1697.
50. Sielecki, T.M.; Meyers, A.I. Formamidines in synthesis. An efficient one-pot synthesis of 7-substituted indolines via intramolecular cyclization of (2-phenethyl)formamidines. An asymmetric route to benzopyrrocoline alkaloids. *J. Org. Chem.* **1992**, *57*, 3673–3676.
51. Grieca, P.A., Ed. *Organic Synthesis in Water*; Blackie A & P: London, UK, 1998.
52. Chanda, A.; Fokin, V.V. Organic Synthesis “On Water”. *Chem. Rev.* **2009**, *109*, 725–748.
53. Butler, R.N.; Coyne, A.G. Water: Nature’s Reaction Enforcer—Comparative Effects for Organic Synthesis “In-Water” and “On-Water”. *Chem. Rev.* **2010**, *110*, 6302–6337.
54. Simon, M.-O.; Li, C.-J. Green chemistry oriented organic synthesis in water. *Chem. Soc. Rev.* **2012**, *41*, 1415–1427.
55. Peng, J.; Zong, C.; Ye, M.; Chen, T.; Gao, D.; Wang, Y.; Chen, C. Direct transition-metal-free intramolecular C–O bond formation: Synthesis of benzoxazole derivatives. *Org. Biomol. Chem.* **2011**, *9*, 1225–1230.
56. Wang, Y.; Song, Z.; Chen, C.; Peng, J. Pictet-Spengler condensation reactions catalyzed by a recyclable H⁺-montmorillonite as a heterogeneous Brønsted acid. *Sci. Chin. Chem.* **2010**, *53*, 562–568.
57. Pirrung, M.C. Acceleration of Organic Reactions through Aqueous Solvent Effects. *Chem. Eur. J.* **2006**, *12*, 1312–1317.
58. Jung, Y.; Marcus, R.A. On the Theory of Organic Catalysis “On Water”. *J. Am. Chem. Soc.* **2007**, *129*, 5492–5502.
59. Buchwald, S.L.; Bolm, C. On the Role of Metal Contaminants in Catalyses with FeCl₃. *Angew. Chem.* **2009**, *121*, 5694–5695; *Angew. Chem. Int. Ed. Engl.* **2009**, *48*, 5586–5587.
60. Larsson, P.-F.; Correa, A.; Carril, M.; Norrby, P.-O.; Bolm, C. Copper-Catalyzed Cross-Couplings with Part-per-Million Catalyst Loadings. *Angew. Chem.* **2009**, *121*, 5801–5803; *Angew. Chem. Int. Ed. Engl.* **2009**, *48*, 5691–5693.
61. Thomé, I.; Nijs, A.; Bolm, C. Trace metal impurities in catalysis. *Chem. Soc. Rev.* **2012**, *41*, 979–987.
62. Leadbeater, N.E. When is free really free? *Nat. Chem.* **2010**, *2*, 1007–1009.

63. Trace metal amounts in the commercially available bases were analyzed by inductively coupled plasma atomic emission spectroscopy (ICP-AES): for K_2CO_3 2 ppm of Pd, <1 ppm of Cu, 2 ppm of Ni, 3 ppm of Fe; for KOH 5 ppm of Pd, <1 ppm of Cu, 2 ppm of Ni, 3 ppm of Fe; for NaOH 4 ppm of Pd, <1 ppm of Cu, 4 ppm of Ni, 3 ppm of Fe; for K_3PO_4 6 ppm of Pd, <1 ppm of Cu, <1 ppm of Ni, 3 ppm of Fe; for $NaHCO_3$ 8 ppm of Pd, <1 ppm of Cu, 1 ppm of Ni, 5 ppm of Fe; for Na_2CO_3 10 ppm of Pd, <1 ppm of Cu, 3 ppm of Ni, 4 ppm of Fe; for Cs_2CO_3 6 ppm of Pd, <1 ppm of Cu, 2 ppm of Ni, 5 ppm of Fe.
64. Briner, G.P.; Miller, J.; Liveris, M.; Lutz, P.G. The S_N mechanism in aromatic compounds. Part VII. *J. Chem. Soc.* **1954**, 1265–1266.
65. Bartoli, G.; Todesco, P.E. Nucleophilic substitution. Linear free energy relations between reactivity and physical properties of leaving groups and substrates. *Acc. Chem. Res.* **1977**, *10*, 125–132.

Sample Availability: Samples of the compounds are available from the authors.

© 2012 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (<http://creativecommons.org/licenses/by/3.0/>).