A Newly Designed Carbohydrate-Derived Alkylamine Promotes Ullmann Type C–N Coupling Catalyzed by Copper in Water

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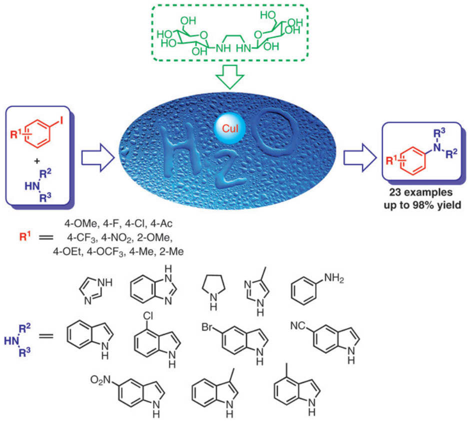

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Abstract A green and biodegradable carbohydrate-derived alkylamine was designed and employed as ligand for Ullmann type C–N coupling catalyzed by copper in water. The coupling of aryl iodide and N-nucleophiles were examined and moderate to excellent yields were obtained. In addition, the in-water coupling strategy was expanded successfully to the reaction of indoles with 4-iodoanisole. By measuring the solubility, it is speculated that carbohydrate-derived alkylamine plays the role of chelating copper and promoting the dissolution of 4-iodoanisole in water. Remarkably, this methodology was environmentally friendly and economical because of the use of aqueous media in place of organic solvents.

Key words glycosyl ligand, in water, copper, Ullmann reaction, green chemistry

N-Heterocycles are among the most important components in modern organic synthesis, and they play a major role in drug structure,[1] pesticides,[2] and N-heterocyclic carbene chemistry.[3] As an important strategy for C–N bond formation, copper-catalyzed Ullmann type coupling reaction has attracted increasing attention.[4] In the past few decades, a range of excellent co-catalysts have emerged including diamines,[5] amino acids,[6] phenanthrolines,[7] diketones,[8] oximes,[9] and others,[10] which could efficiently promote Ullmann coupling under milder conditions. However, most of these coupling reactions are carried out in toxic organic solvent, e.g., DMF, DMSO, dioxane or toluene, which do not meet the principles of green chemistry.

As a cheap, safe, non-toxic and green medium, water has attracted considerable interest for organic reactions given that it is abundant, easy to work with, and environmentally friendly. Recently, some metal-catalyzed reactions, e.g., Suzuki reactions,[11] Mizoroki–Heck reactions,[12] Olefin metathesis reactions[13] and arylation reactions,[14] were performed successfully in water. Moreover, the industrial process in water achieved a breakthrough by using membrane separation and phase separation to recover water solvent. Compared with common organic solvents,[15] water possesses some unique advantages; for example, it is environmental friendly, forms strong hydrogen bonds, and weak noncovalent bonds, and possesses a large dielectric constant. However, the solubility of organic compounds in water remains a challenge. To overcome this, great efforts have been made on the exploration of aqueous reactions, and important concepts including *in-water* reaction of homogeneous systems and *on-water* reaction of heterogeneous systems,[16] have been proposed. Especially for insoluble organic reactants, there remains a great reluctance to use water. However, the addition of a surfactant which acts as phase-transfer catalyst[17] or forms micelles[18] can enable the organic reactions to run readily in water. Even in the absence of surfactants, some effective ligands with metals can also catalyze the reactions efficiently in water,[19] which is attributed to the Breslow hydrophobic effect, hydrogen-bonding effect, and polarity effect.[16b] To date, various surfactants such as polyoxyethanyl α-tocopheryl sebacate (PTS),[20] polyoxyethanyl-α-tocopheryl succinate (TPGS-750-M),[21] and Triton X-100,[22] have been developed to efficiently promote metal-catalyzed coupling reactions. In addition, some N-O ligands such as pyridine *N*-oxide,[23] 6,7-dihydroquinolin-8(5*H*)-one oxime,[24] and N- or O-heteroatom-functionalized heterogeneous complexes,[25] were used in water to provide good results for the Ullmann reaction. Despite this great progress, some demerits still exit, such as toxicity and cost. Thus, it is always challenging and interesting to explore eco-friendly and more simple protocols in water.

As green and biodegradable natural compounds, carbohydrates are not only employed as organocatalysts,[26] but also widely used as ligands in metal-catalyzed coupling reactions.[27] In 2008, Cheng et al.[28] reported that D-glucosamine in DMSO efficiently promoting copper-catalyzed Ullmann C–N coupling. Several reports selected mixed water solvent replacement of DMSO to improve this reaction.[29] Although these approaches are operated efficiently, toxic organic solvent, e.g., DMF, DMSO, is required. Moreover, the contradiction of water-soluble catalyst and water-insoluble reactant remains unaddressed. Based on these studies, in this paper we report the development of a carbohydrate-derived alkylamine co-catalyst that could effectively promote Ullmann C–N coupling reaction in water and in the absence of co-solvent. This study surveys the various copper compounds, different bases, and reaction temperature to establish the optimal protocol and reaction conditions to promote the Ullmann C–N coupling reaction.

To design an environmentally friendly ligand that would effectively promote Ullmann C–N coupling reaction, this study chose the coupling reactions of 4-iodoanisole (1.0 equiv, **1a**) and imidazole (1.2 equiv, **2a**) as model reaction using water as solvent. Several commercially available amine ligands such as D-glucosamine (**L1**, used in Cheng's study[30]), ethylenediamine (**L3**), diethylenetriamine (**L4**) and two newly designed carbohydrate-derived alkylamines (**L5–L6**) (shown in Figure 1) were tested for the catalytic activity. For comparison with D-glucosamine (**L1**), glucose (**L2**) was also tested. For this baseline comparison among these six ligands (**L1–L6**), the initial reaction used CuI as catalyst, Cs_2CO_3 as base, and the reaction temperature was set at 100 °C. The results showed that no coupling products could be obtained in the presence of D-glucosamine (**L1**) and glucose (**L2**) (Table 1, entries 1 and 2). When ethylenediamine (**L3**) and diethylenetriamine (**L4**) were used as co-catalyst in water, the desired product **3a** was only obtained in 40% and 58% yields, respectively (entries 3 and 4). Considering the poor efficiency of these co-catalysts, it was necessary to fine-tune the structure of alkylamine by introducing the hydrophilic group in the head position of the primary amine. For example, glucose is easily soluble in water, which makes it a green and biodegradable natural carbohydrate. However, this solubility in water turns out to be against the Ullmann reaction. Thus, carbohydrate-derived alkylamines (**L5–L6**) were designed[31] in the hope it could promote the Ullmann coupling reactions in water as an effective co-catalyst. The anomeric configurations of these carbohydrate-derived alkylamines were confirmed as β-configuration by measuring $^1J[^{13}CH(1)]$ coupling constants.[29] As the excellent flexibility of ligand structure, **L5** and **L6** exhibited high catalytic activity with 92% and 88% yields, respectively (entries 5 and 6).

From the above baseline test results, one can see that the carbohydrate-derived alkylamines **L5** has the best yield in the batch. It was then necessary to optimize other reaction conditions such as copper source, base used, and temperature; the results are summarized in Table 1. Compared with Cs_2CO_3, several bases such as K_2CO_3, Na_2CO_3, NaOH, and KOH gave inferior results (entries 7–10). Furthermore, with **L5** as the ligand, optimization of other reaction conditions such as copper source and temperature was performed. Different copper sources, i.e., CuBr, CuCl, CuI, $CuSO_4$, $Cu(CF_3SO_3)_2$, and $Cu(CH_3COO)_2$, were screened (entries 5 and 11–15). Although all copper salts catalyze this coupling reaction, CuI was found to be the most effective catalyst, and 92% yield was obtained. With regard to the reaction temperature, the isolated yield decreased markedly correspondingly with the temperature drop (entries 16–20). Therefore, the use of CuI as catalyst, Cs_2CO_3 as the base, and 100 °C reaction temperature was established as the optimum conditions.

Subsequently, an extensive investigation was performed by varying the nucleophile and aryl halide of the above model reaction to investigate the generality of the protocol;

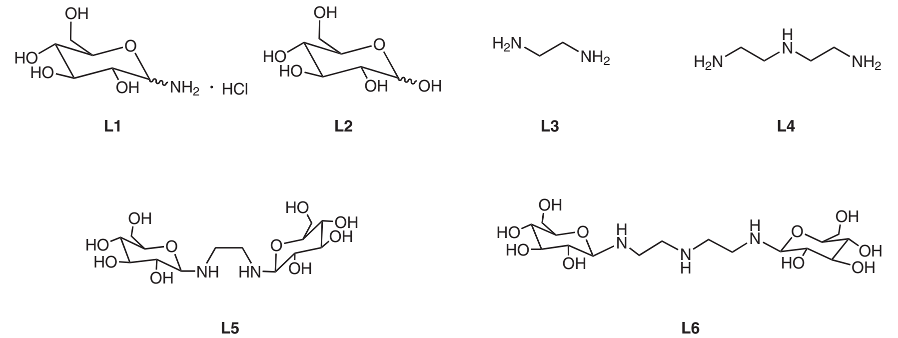
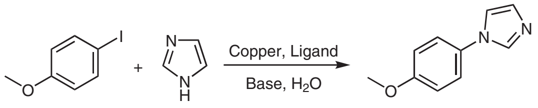


Figure 1 Structures of ligands screened herein

Table 1 Optimization of Reaction Conditions[a]



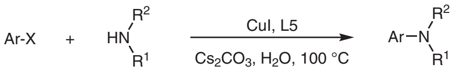
1a **2a** **3a**

Entry	Ligand	Copper salt	Base	Temp. (°C)	Yield (%)[b]
1	**L1**	CuI	Cs_2CO_3	100	0
2	**L2**	CuI	Cs_2CO_3	100	0
3	**L3**	CuI	Cs_2CO_3	100	40
4	**L4**	CuI	Cs_2CO_3	100	58
5	**L5**	CuI	Cs_2CO_3	100	92
6	**L6**	CuI	Cs_2CO_3	100	88
7	**L5**	CuI	K_2CO_3	100	70
8	**L5**	CuI	Na_2CO_3	100	85
9	**L5**	CuI	NaOH	100	60
10	**L5**	CuI	KOH	100	75
11	**L5**	CuBr	Cs_2CO_3	100	70
12	**L5**	CuCl	Cs_2CO_3	100	65
13	**L5**	$Cu(CF_3SO_3)_2$	Cs_2CO_3	100	40
14	**L5**	$Cu(CH_3COO)_2$	Cs_2CO_3	100	35
15	**L5**	$CuSO_4$	Cs_2CO_3	100	20
16	**L5**	CuI	Cs_2CO_3	90	60
17	**L5**	CuI	Cs_2CO_3	80	45
18	**L5**	CuI	Cs_2CO_3	70	20
19	**L5**	CuI	Cs_2CO_3	50	0
20	**L5**	CuI	Cs_2CO_3	25	0

[a] Reaction conditions: 4-iodoanisole **1a** (1.0 mmol), imidazole **2a** (1.2 mmol), copper salt (0.1 mmol), ligand (0.1 mmol), base (2.0 mmol), water (5 mL), 24 h.
[b] Isolated yield.

the results are summarized in Table 2. Electron-withdrawing and electron-donating effects of the group substituted on the aryl ring have significant influence on the coupling reaction with imidazole (entries 1–11). When electron-withdrawing groups, e.g., F, Cl, acetyl, and CF_3, were located in the aryl ring, the corresponding yields were low (entries 2–5). However, when an electron-withdrawing NO_2 group was present on the aryl ring, the yield was higher than that with an electron-donating Me group (entries 6 and 10). This result may be explained by the interaction of the electron cloud of the NO_2 group with the ligand leading to an increase in the solubility of the reactant. Aryl iodides with a methoxyl, ethoxyl, or trifluoromethoxy group in any position can couple excellently with imidazole, and the desired products were obtained in 92–98% yield (entries 1 and 7–9). To our surprise, substituted aryl halides bearing an electron-donating methyl group only gave inferior results (entries 10 and 11). In addition, for the bromobenzene, it was noted that its reactivity was much lower than iodobenzene and no desired product was obtained (entries 12 and 13). Finally, coupling with different nucleophiles, e.g., 1*H*-benzoimidazole, pyrrolidine, 4-methyl-1*H*-imidazole and aniline was performed, and the corresponding products were obtained in moderate to good yields (entries 14–17).

Table 2 CuI/L5-Catalyzed Coupling of Aryl Halides and Nitrogen Nucleophiles in Water[a]



1 2 3

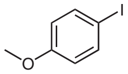
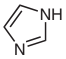
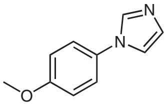
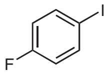
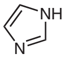
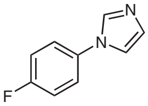
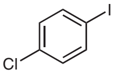
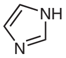
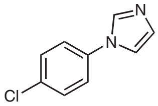
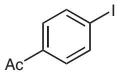
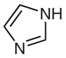
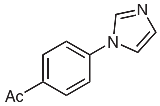
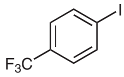
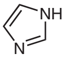
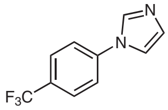
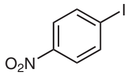
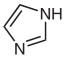
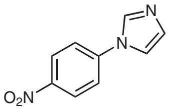
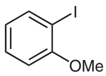
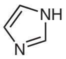
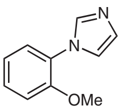
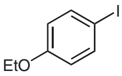
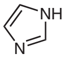
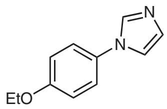
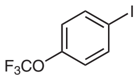
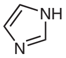
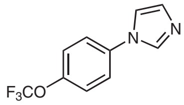
Entry	Aryl halides	Nitrogen compound	Product	Yield (%)[b]
1				92 (**3a**)
2				45 (**3b**)
3				25 (**3c**)
4				40 (**3d**)
5				50 (**3e**)
6				71 (**3f**)
7				97 (**3g**)
8				98 (**3h**)
9				89 (**3i**)

Table 2 (continued)

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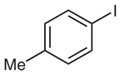
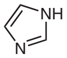
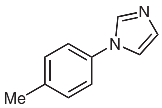
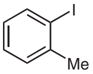
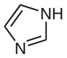
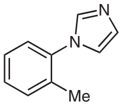
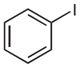
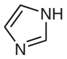
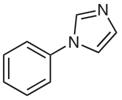
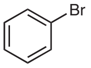
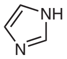
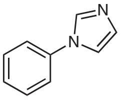
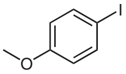
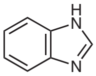
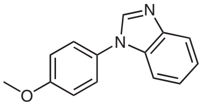
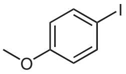
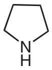
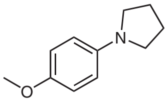
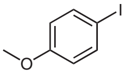
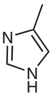
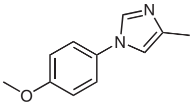
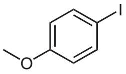
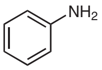
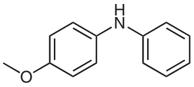
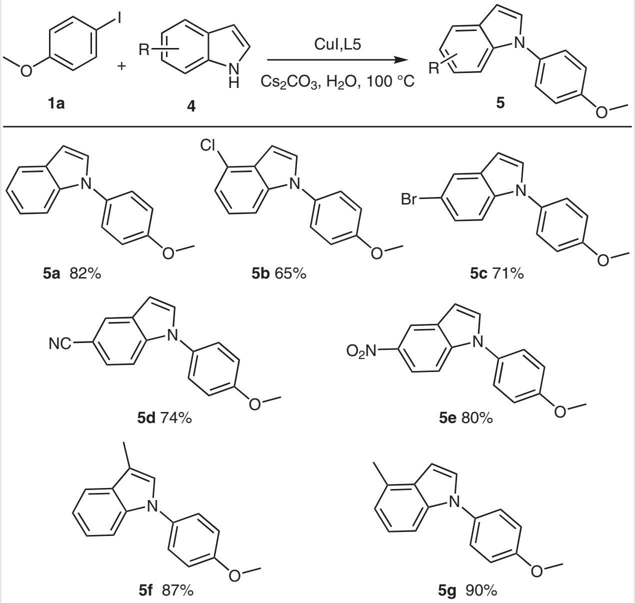
10				65 (**3j**)
11				50 (**3k**)
12				80 (**3l**)
13				trace
14				80 (**3m**)
15				75 (**3n**)
16				70 (**3o**)
17				60 (**3p**)

[a] Reaction conditions: aryl halide (1.0 mmol), nitrogen nucleophiles (1.2 mmol), CuI (0.1 mmol), **L5** (0.1 mmol), Cs_2CO_3 (2.0 mmol), water (5 mL), 100 °C, 24 h.
[b] Isolated yield.

To expand the scope of this procedure, this in-water catalytic system was applied to various indole derivatives; the results are summarized in Scheme 1. Interestingly, without a substituent on the indole ring, the reaction with unsubstituted indole produced 82% yield of product **5a**. However, when indoles bearing electron-withdrawing groups including Cl, Br, CN, and NO_2 were used, the yields were lower than that with unsubstituted indole. Notably, indoles with electron-donating substituents, even with a relatively weak electron-donating group such as 3-methylindole and 4-methylindole gave the coupling products in high yields. Regardless, these extensive experiments with indole derivatives suggest that the *in-water* coupling reaction is much more effective with indoles.



Scheme 1 Reaction of various indoles with 4-Iodoanisole. *Reaction conditions*: 4-Iodoanisole (1.0 mmol), indole (1.2 mmol), CuI (0.1 mmol), **L5** (0.1 mmol), Cs_2CO_3 (2.0 mmol), water (5 mL), 100 °C, 24 h.

To make a thorough inquiry on our catalytic system, we measured the solubilities of 4-iodoanisole in pure water and the aqueous solution of the designed ligand **L5**, respectively, using a set of experimental studies (Figure 2).[32] In these investigations, by using an electromagnetic agitator, 4-iodoanisole was dissolved in a 50 mL jacketed glass vessel at different temperatures kept by continuous circulating water from a thermostat, with the temperatures determined with a microthermometer. By using an electronic analytical balance, the mass of the solutes was measured. To prevent the evaporation of the solvent, we add a condenser pipe to the jacked vessel. We make use of a laser monitoring system which included a laser generator, a laser receiver, and a light signal display, to determine the dissolution's equilibrium point according to varying laser signal.

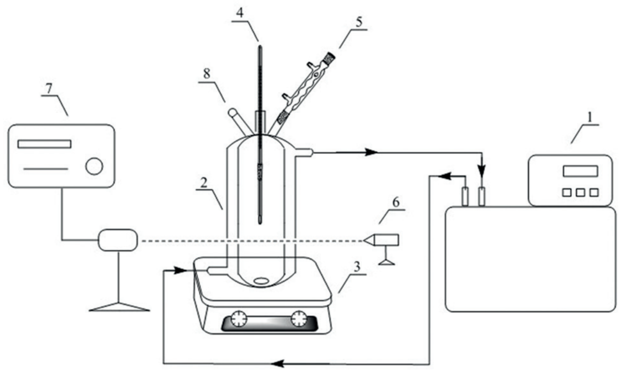


Figure 2 Experimental apparatus. 1: thermostatic bath; 2: jacked vessel; 3: electromagnetic agitator; 4: microthermometer; 5: condenser pipe; 6: laser generator; 7: laser receiver; 8: feed inlet.

As shown in Figure 3, there was not much difference between the solubilities of 4-iodoanisole in pure water and the aqueous solution of carbohydrate-derived alkylamine **L5** from 70 to 85 °C. Surprisingly, at 90 °C, the mass of 4-iodoanisole dissolved in the aqueous solution (a) increased dramatically over the pure water (b). Thus, it was speculated that **L5** could promote the solubility of 4-iodoanisole in water at 90 °C. This increased solubility also explained why the coupling of 4-iodoanisole gave better results at 90 °C than at 70 and 80 °C (Table 1, entries 16–18). Once 4-iodoanisole comes in contact with **L5**, it is distributed between bulk water and **L5** depending on its polarity or charge. Thus, in this in-water catalytic system, carbohydrate-derived alkylamine **L5** plays the role of chelating copper and promoting the dissolution of 4-iodoanisole in water.

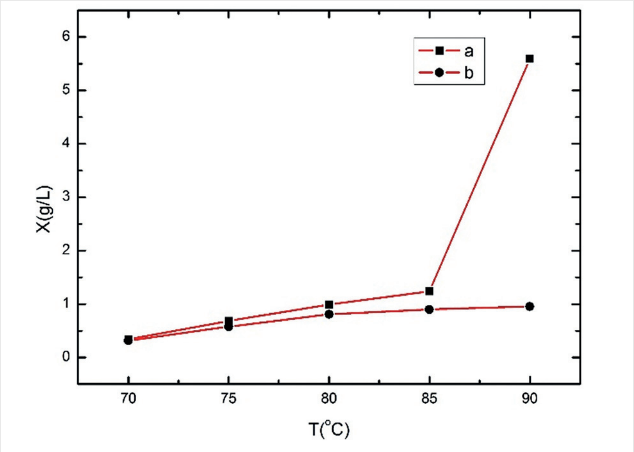


Figure 3 Solubility of 4-iodoanisole in two different solvents from 70 to 90 °C. (a) The aqueous solution of **L5**; (b) pure water.

In summary, we have described a green and degradable carbohydrate-derived alkylamine for copper-catalyzed Ullmann C–N coupling in water, without the presence of surfactant.[33,34] Extensive works were performed by employing various aryl iodides and N-nucleophiles as substrates. Moderate to excellent yields are achieved in this in-water catalytic system. Moreover, the in-water coupling strategy was expanded successfully to the reaction of indoles with 4-iodoanisole. By measuring the solubility, it is speculated that the carbohydrate-based ligand formed an intermolecular force together with water to increase the solubility of 4-iodoanisole in water. This would eventually make the Ullmann C–N coupling of aryl halides with N-nucleophiles more efficient in water.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611695.

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(33) **Preparation of *N*,*N′*-Di-β-D-glucopyansoyl Ethylenediamine L5**

A mixture of glucose (3.6 g, 20 mmol), ethylenediamine (0.6 g, 10 mmol) and acetic acid (0.1 g, 1.67 mmol) in CH_3OH was heated at reflux at 30 °C. After 8 h the solvent was removed under vacuum. The pure product **L5** was recrystallized in ethanol as a white solid. Mp 125.3–126.1 °C. $[\alpha]_D^{20}$ = –29.6 (*c* 1.00, H_2O). ^{1}H NMR (600 MHz, D_2O): δ = 3.92 (d, *J* = 8.0 Hz, 2 H), 3.80 (d, *J* = 11.8 Hz, 2 H), 3.69–3.55 (m, 2 H), 3.37 (d, *J* = 8.0 Hz, 2 H), 3.33–3.20 (m, 4 H), 3.11 (t, *J* = 8.2 Hz, 2 H), 2.89 (d, *J* = 6.4 Hz, 2 H), 2.74 (d, *J* = 6.8 Hz, 2 H). ^{13}C NMR (150 MHz, D_2O): δ = 89.73, 76.77, 76.68, 72.94, 69.84, 60.86, 44.89. $^1J[^{13}CH(1)]$=151.5. IR (KBr): 3290 and 3230 [ν(O-H)], 2877 [ν(C-H)], 1469 and 1361 [δ(C-H)], 1268 [ν(C-O-C)], 1076 and 1014 [ν(C-N)], 811 [δ(N-H)]. MS (EI): *m*/*z* = 384 $[M]^+$.

(34) **CuI/L5 Catalyzed Ullmann Type C–N Coupling of Aryl Halides and Nitrogen Nucleophiles in Water; General Procedure**

To a stirred solution of H_2O (5 mL) were added CuI (0.1 mmol, 19 mg), aryl halide (1.0 mmol), nitrogen nucleophile (1.2 mmol), Cs_2CO_3 (2 mmol, 651 mg) and **L5** (0.1 mmol), and the mixture was heated to 100 °C under air and stirred for 24 h. When the reaction was complete, the mixture was cooled and partitioned by adding ethyl acetate (20 mL) and water (20 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (2 × 20 mL). The combined organic phases were washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography through silica gel, eluting with ethyl acetate/petroleum ether solvent mixture, to give the pure product.

Data for 1-(4-Methoxyphenyl)-1*H*-imidazole 3a as Typical Example

Pale-yellow solid; mp 60–61 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (s, 1 H), 7.30 (d, *J* = 8.8 Hz, 2 H), 7.20 (d, *J* = 6.6 Hz, 2 H), 6.99 (d, *J* = 12.0 Hz, 2 H), 3.85 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 135.8, 130.7, 129.9, 123.3, 118.8, 114.9, 55.6. MS (EI): *m*/*z* = 174 $[M]^+$.