

Synthetic Approaches to Sterically Hindered *N*-Arylimidazoles through Copper-Catalyzed Coupling Reactions

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Optimization studies allowed the efficient synthesis of a simple structural motif based on *meta*-bis(1-imidazolyl)benzenes **1** through copper-catalyzed coupling of 1,3-diiodobenzene and imidazole under mild reaction conditions. This protocol was then used to prepare a representative sterically hindered *N*-arylimidazole **2a**, the most common structural motif among *N*-heterocyclic carbenes (NHC). Having optimized the main variables governing Cu^I-catalyzed imidazole *N*-arylation, the

first Ullmann-type synthesis of *N*-mesitylimidazole (**2a**) is reported. Moreover, the coupling between boronic acids as the aryl donor partners and either imidazole or benzimidazole was examined; in all cases the reactions proceeded in very low yield.

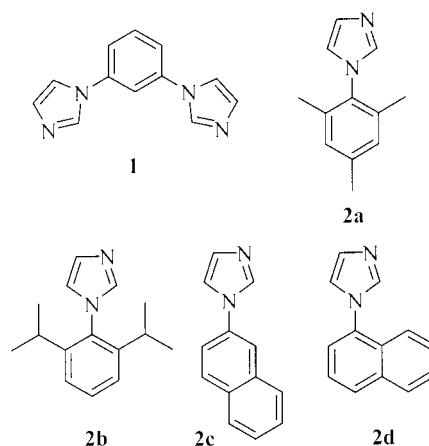
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Introduction

A variety of coupling protocols for copper-mediated C(aryl)–N bond formation, especially the application of Ullmann-type condensations to the *N*-arylation of nitrogen heterocycles, have led to practical synthesis of sterically unhindered *N*-arylimidazoles together with other azoles and indoles. Among the synthetic routes available, the common “aryl donor” partners of imidazole are either aryl halides or arylboronic acids, and the aryl groups are sterically unhindered moieties.^[1] To the best of our knowledge, only two reports include several *ortho*-substituted Ar–I(Br)^[2a] or arylboronic acids,^[3] while no report deals with di-*ortho*-substituted aryl derivatives, such as 2-iodo-1,3,5-trimethylbenzene or 2,4,6-trimethylphenylboronic acid. Buchwald et al. have made advances in the development of Ullmann-type methodology, and *N*-arylation of *NH*-heteroaromatic compounds yields unhindered *N*-arylazoles,^[2b] e.g. *N*-arylimidazoles, and more or less hindered *N*-arylindoles,^[2a] together with *N*-arylpyrroles and *N*-arylpyrazoles.^[2c] Moreover, Cristau et al. have examined the copper-catalyzed *N*-arylation of azoles.^[2d,2e] As for the coupling of arylboronic acids with imidazoles,^[1] the latest development is a catalytic reaction in dry MeOH in the presence of a simple copper salt, such as CuCl or CuI.^[3]

In parallel, *N*-arylimidazoles are found in a broad array of imidazolium quaternary salts used as key precursors to

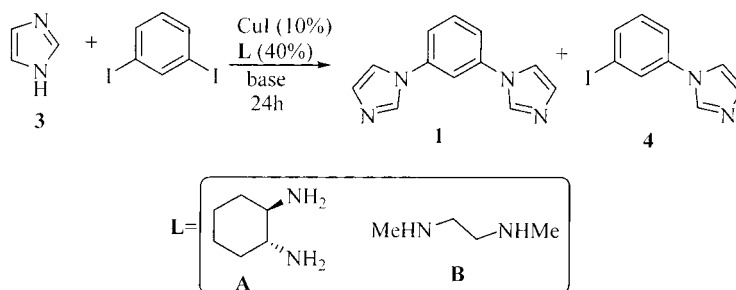
imidazolylienes, the largest class of *N*-heterocyclic carbenes (NHCs).^[4] As part of our ongoing research on imidazolium quaternary salts as the main structural motifs within dicationic imidazoliophanes,^[5a] and especially dicationic open-chain systems,^[5b] we pursued the synthesis of more or less sterically hindered *N*-arylimidazoles: bis(imidazole) **1** and *N*-arylimidazoles **2a–d**.



We examined the use of these protocols in the synthesis of simple targeted *N*-arylimidazole subunits, and we now report a mild protocol for an Ullmann-type condensation that allows the synthesis of bis(imidazole) **1**, the simple structural motif based on *meta*-bis(1-imidazolyl)benzenes, in excellent yield.^[6] More importantly, having optimized the relevant variables governing Cu-catalyzed *N*-arylation of imidazole, the first Ullmann-type synthesis of the sterically hindered 1-mesitylimidazole (**2a**) was accomplished in 50% isolated yield after chromatographic purification.

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Scheme 1.

Results and Discussion

Cu-catalyzed *N*-arylation of imidazole (**3**) was first addressed, in order to prepare 1,3-bis-(1-imidazolyl)benzene (**1**). We examined the coupling of imidazole (**3**) and 1,3-diiodobenzene under standard Buchwald *N*-arylation conditions:^[2b,7] 5 mol-% of air-stable CuI in combination with 20% of ligand, 1 M in 1,4-dioxane (Scheme 1). Since the aryl halide is disubstituted, the mol-% of CuI and the ligand were doubled; the selected ligands were the racemic *trans*-1,2-cyclohexanediamine (**A**)^[2b] together with *N,N'*-dimethylethylenediamine (**B**), which have been used in the *N*-arylation of indoles.^[2a]

Initially, K₂CO₃ was used as the base, but only monosubstituted derivative **4** was isolated (Table 1, entry 1). When the base was changed to Cs₂CO₃, the yield was improved to 80% for bis(imidazole) **1**. When coupling was carried out in a sealed tube at 95 °C, the yield was improved to 95% (entry 4), whereas in the presence of ligand **B** practically no reaction was observed. This approach works well for scale-up purposes because no chromatographic separations were required to obtain good yields (entry 6).

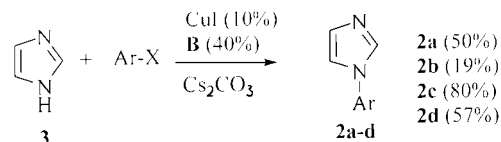
Table 1. Reactions of imidazole (**3**) with 1,3-diiodobenzene.^[a]

Entry	L	Base	<i>T</i> [°C]	Yield [%] ^[b] 1	4
1	A	K ₂ CO ₃	110	5 ^[c]	34
2	A	Cs ₂ CO ₃	110	80	15
3	A	Cs ₂ CO ₃	110 ^[d]	79	15
4	A	Cs ₂ CO ₃	95 ^[e]	95	5
5	B	Cs ₂ CO ₃	95 ^[e]	—	10 ^[e]
6 ^[f]	A	Cs ₂ CO ₃	95 ^[e]	89 ^[g]	8

[a] All reactions 0.5 M in 1,4-dioxane with respect to 1,3-diiodobenzene unless otherwise noted. [b] Isolated yield after chromatographic purification. [c] Calculated by ¹H NMR from treated reaction mixture. [d] 48 h. [e] Sealed tube. [f] Scale up to 5 mmol. [g] 76% yield from first crystallization of reaction mixture in hexane/Me₂CO.

We next examined the utility of this modified Cu-catalyzed *N*-arylation procedure for the preparation of sterically hindered *N*-arylimidazoles (Scheme 2).

For *N*-mesitylimidazole (**2a**), only three experimental procedures are described in the literature, excluding patents. The classical multicomponent imidazole synthesis has been applied starting from mesitylammonium salt^[8] or from mesitylamine;^[4c,9] yields range from 17% to 43%.^[10]



Scheme 2.

As a starting point, we assayed conditions similar to those used to prepare the *meta*-bis(*N*-imidazolyl)benzene (**1**), but no reaction was observed since the C-aryl donor is 2-iodo-1,3,5-trimethylbenzene. Other conditions were then examined by raising the reaction temperature and by changing the catalyst, solvent (1,4-dioxane, toluene, DME, DMF) and ligand (see Supporting Information). At 170 °C, in DMF with 10 mol-% of CuI and 40 mol-% of ligand **B**, the reaction progressed to afford the *N*-mesitylimidazole (**2a**) in 26% yield (see Table 2, entry 1). With a reaction time of 48 h, the yield reached 50% after chromatographic purification (entry 2), and this isolated yield was maintained when the reaction was scaled up to 10 mmol.

Table 2. Selected results in the preparation of 1-mesitylimidazole (**2a**), in the presence of Cs₂CO₃ as a base.^[a]

Entry	L	Solvent	<i>T</i> [°C]	Time [h]	Yield [%] ^[b]
1	B	DMF	170	24	26
2	B	DMF	170	48	50
3 ^[c]	B	DMF	170	48	47
4	A	DMF	170	48	37
5 ^[d]	B	DMF	170	48	38
6 ^[e]	B	DMF	170	48	54

[a] All reactions 1 M with respect to 2-iodo-1,3,5-trimethylbenzene unless otherwise noted. [b] Isolated yield after chromatographic purification. [c] With 5 mol-% CuI and 20 mol-% L. [d] 0.5 M. [e] 2 M.

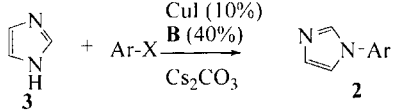
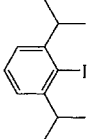
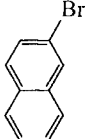
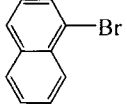
Similar results were observed when the standard percentages,^[7] 5 mol-% of CuI and 20 mol-% of ligand, were used (entry 3), whereas the use of ligand **A** reduced the yield (entry 4). Although the optimal initial concentration of the starting materials with respect to 2-iodo-1,3,5-trimethylbenzene showed that the coupling was most efficient at 2 M (en-

try 6), when the reaction was scaled up to 10 mmol, the yield was decreased by 25%, and the formation of mesitylene was observed.

As for the base,^[1] a mild Ullmann-type condensation procedure has recently been applied to the synthesis of secondary arylamines through the use of CuI and CsOAc in the absence of ligand.^[11] Thus, Cs₂CO₃ was replaced by CsOAc, and the results are compiled in Table S2 (see Supporting Information). The first run gave *N*-mesitylimidazole (**2a**) in 33% yield and the workup was very simple. In addition, the coupling was subjected to the same conditions as reported,^[11] and the yield was decreased to 12% (see Supporting Information).

The best reaction conditions for the preparation of **2a** were then applied to other *N*-arylimidazoles such as **2b–d** (Scheme 2, Table 3 and Supporting Information). Coupling of imidazole (**3**) with the sterically congested 2-iodo-1,3-diisopropylbenzene was clearly less efficient, and when we scaled up the reaction to 10 mmol, the yield was maintained; curiously, at higher temperatures, the yield decreased. The best way to prepare **2b** is by the two-step modified classical imidazole synthesis starting from 2,6-diisopropylaniline.^[9]

Table 3. Selected results for reactions of aryl halides with imidazole (**3**).^[a]

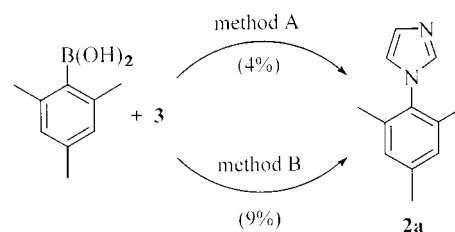
					
Compd.	Ar-X	Conc.	<i>T</i> [°C]	Time [h]	Yield [%] ^[b]
2b		1M	170	48	19
		2M	170	48	16
2c		0.5M ^[c,d]	95	24	n.r.
		1M	170	48	80
2d		1M	170	48	57

[a] All reactions were carried out in DMF unless otherwise noted.
[b] Isolated yield. [c] With 5 mol-% CuI and 20 mol-% ligand **A**.
[d] In 1,4-dioxane.

On the other hand, the Ullmann-type condensation should work very well with unhindered aryl halides under standard coupling conditions;^[1,2] by using this one-step route, 1-(2-naphthyl)-1*H*-imidazole (**2c**) has recently been prepared in 54% isolated yield from 2-bromonaphtha-

lene.^[4c] By exploiting the modified protocol applied to 1,3-iodobenzene (see Table 1, entry 4), no reaction was observed, whereas by forcing the conditions, 1-(2-naphthyl)-1*H*-imidazole (**2c**) was obtained in good yield (Table 3); following our protocol, the yield was 26% higher than that previously reported.^[4c] In contrast, 1-(1-naphthyl)-1*H*-imidazole (**2d**) was obtained in 57% isolated yield, whereas yields of 85% have been reported.^[4c]

An alternative protocol for C–N bond formation involves the reactions of arylboronic acids with *NH*-azoles using stoichiometric or catalytic amounts of a copper source; the Chan–Evans–Lam modified Ullmann condensation appears to be an efficient *N*-arylation method for azoles including imidazole (**3**).^[1] For reasons of brevity, unproductive experiments related with the application of the Chan–Evans–Lam modified Ullmann condensation, both stoichiometric and catalytic Cu^{II} protocols,^[12] are omitted (see Supporting Information). Coupling with the sterically hindered 2,4,6-trimethylphenylboronic acid was then examined under a variety of reaction conditions, and the best experiment gave *N*-mesitylimidazole (**2a**) in very low yield as shown in Scheme 3 (method A). Other arylboronic acids were also used, including simple phenylboronic and 1-naphthylboronic acids (see Supporting Information).

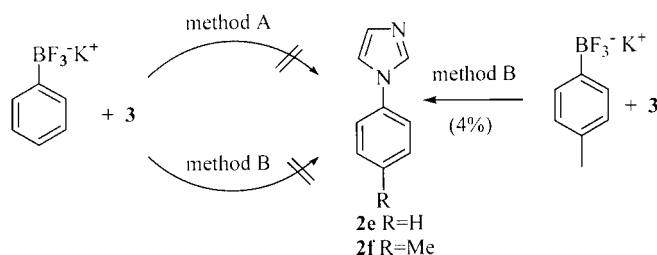


Scheme 3. Reagents and conditions: Method A = Ar-B(OH)₂ (2 mmol), Cu(OAc)₂ (1.1 mmol), Py (2.2 mmol), **3** (1 mmol), dry CH₂Cl₂, air, 25 °C, 48 h; Method B = Ar-B(OH)₂ (1 mmol), CuI (0.05 mmol), **3** (1.2 mmol), dry MeOH, air, reflux, 6 h.

Concurrently with our work, Yu et al.^[3] reported that a simple copper salt catalyzed the coupling of imidazole with arylboronic acids in MeOH, but this recent coupling protocol has not yet been extended to the preparation of 1-mesitylimidazole (**2a**), even though 2,4,6-trimethylphenylboronic acid is currently commercially available. We attempted to apply this new protocol to the coupling between 2,4,6-trimethylphenylboronic acid and imidazole (**3**) (Scheme 3, method B).

By following the same experimental procedure,^[3] and with CuCl (5 mol-%), the coupling reaction afforded an 8% yield of the desired 1-mesitylimidazole (**2a**, entry 1, Table 4), whereas with CuI (5 mol-%) the average yield was 9% (entries 2 and 3, Table 4). Other variables such as solvent and mol-% of the catalyst were examined, and neither product formation nor any trace of **2a** were observed (see Supporting Information). For **2d** and **2e**, the coupling yields were lower than those reported.^[3] Consequently, these protocols were not further investigated.

Since potassium aryltrifluoroborate salts are another source of arylboron,^[1,13,14] the reaction of imidazole (**3**)



Scheme 4. Reagents and conditions: Method A = Ph-BF₃[−]K⁺ (2 mmol), Cu(OAc)₂ (1.1 mmol), Py (2.2 mmol), **3** (1 mmol), dry CH₂Cl₂, air, 25 °C, 48 h; Method B = Ar-BF₃[−]K⁺ (1 mmol), CuI (0.05 mmol), **3** (1.2 mmol), dry MeOH, air, reflux, 3 h.

Table 4. Selected results in the reactions of arylboronic acids and imidazole (**3**).

Compd.	Ar-X	Conc.	T [°C]	Time [h]	Yield [%] ^[b]
2b		1M	170	48	19
		2M	170	48	16
2c		0.5M ^[c,d]	95	24	n.r
		1M	170	48	80
2d		1M	170	48	57

[a] Isolated yield.

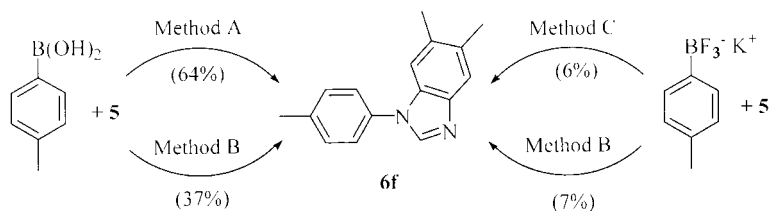
with unhindered potassium aryltrifluoroborate salts was then examined (Scheme 4). Potassium phenyltrifluoroborate gave no trace of **2e**, whereas potassium 4-methylphenyltrifluoroborate generated the unhindered *N*-arylimidazole **2f** in very low yield (4%). This is the first example of *N*-arylation of azoles by ArBF₃[−]K⁺ salts.

N-Arylation of Benzimidazole

Given the results for 1*H*-imidazole (**3**), *N*-arylation of 5,6-dimethyl-1*H*-benzimidazole (**5**)^[15a] was examined. To date, coupling protocols for copper-mediated C(aryl)–N bond formation when benzimidazoles are the nucleophilic reaction partner have received little attention.^[1] For aryl halides as the aryl donor, Buchwald et al. have introduced a general Ullmann-type synthesis of unhindered *N*-arylazoles^[1,2b] and unhindered 1-(3,5-dimethylphenyl)-1*H*-benzimidazole, for example, has been obtained in 91% yield.^[15b] Accordingly, several experiments involving the Cu-catalyzed coupling between 2-iodo-1,3,5-trimethylbenzene and 5,6-dimethyl-1*H*-benzimidazole (**5**) were carried out, under the best reaction conditions found for preparation of **2a**, with changes in the concentration or the reaction temperature (see Table S5 in Supporting Information). Surprisingly, none of these experiments generated *N*-mesityl-5,6-dimethylbenzimidazole (**6a**), thus necessitating other experimental conditions beyond the scope of the present study. It is clear that the general conditions should be adapted for each substrate type.

When ArB(OH)₂ is the aryl donor,^[1] this copper-catalyzed C(aryl)–N bond formation has many drawbacks, which, in particular cases, have been resolved.^[3,12] To the best of our knowledge, there are two protocols for the synthesis of *N*-arylated benzimidazoles^[12] and imidazoles^[3] that merit attention due to their efficiency; unhindered *N*-arylazoles have been obtained in respectable yields.

Accordingly, coupling of unhindered ArB reagents^[1,13] and 5,6-dimethyl-1*H*-benzimidazole (**5**) was examined by using the stoichiometric Cu^{II} method^[12a] and the catalytic Cu^I method^[3] (Scheme 5). When ArB(OH)₂ was the aryl donor, method A^[12a] gave the unhindered *N*-arylbenzimidazole **6f** in 64% yield, whereas by using method B,^[3] the yield



Scheme 5. Reagents and conditions: Method A = Ar-B(OH)₂ (2 mmol), Cu(OAc)₂ (1.1 mmol), Py (2.2 mmol), **5** (1 mmol), dry CH₂Cl₂, air, room temperature, 48 h; Method B = Ar-BX_n (1 mmol), CuI (0.05 mmol), **5** (1.2 mmol), dry methanol, air, reflux, 3 h; Method C = Ar-BF₃[−]K⁺ (1.1 mmol), Cu(OAc)₂ (1.1 mmol), Py (2.2 mmol), **5** (1 mmol), dry 1,4-dioxane, air, room temperature, 24 h.

was reduced to 37%. Alternatively, the coupling of the corresponding $\text{ArBF}_3\text{--K}^+$ salt and benzimidazole **5** (method C) produced **6f**, albeit in low yields.^[14]

Conclusions

The Ullmann-type condensation between 1,3-diiodobenzene and imidazole (**3**) under mild reaction conditions afforded simple *meta*-bis(1-imidazolyl)benzene (**1**) in excellent yield, and application of this Cu-catalyzed *N*-arylation protocol to the synthesis of basic sterically hindered *N*-arylimidazoles was examined. We identified the optimal conditions for the coupling of 2-iodo-1,3,5-trimethylbenzene and imidazole (**3**), and the best experiment gave *N*-mesitylimidazole (**2a**) in 50% yield, although the reaction temperature is high. As an alternative route, the coupling of 2,4,6-trimethylphenylboronic acid with imidazole (**3**) was also examined, and after a trial of a variety of conditions, the best experiment gave **2a** in very low yield, confirming the capricious nature of the reaction with arylboronic acids as aryl donor partners. From these optimization studies for the synthesis of topical and useful imidazole units **1**, **2a**, **2c** and **2d** we conclude that the method of choice is Ullmann-type condensation with aryl halides as aryl donors and CuI as the catalyst, whereas the best option to prepare 1-(2,6-diisopropylphenyl)-imidazole (**2b**) is a recently reported two-step modified classical imidazole synthesis. Efforts are currently being directed toward the use of these imidazole building blocks for the construction of molecular scaffolds ranging from dicationic and polycationic systems to their metal complexes.

Experimental Section

General Remarks: All reactions were carried out in glassware that had been oven-dried and cooled under a stream of argon. Commercially available reagents were used without further purification. 1-Iodo-2,6-diisopropylbenzene was synthesized according to literature procedure.^[11] All materials were weighed in air. All yields reported in Tables 1–6 refer to isolated yields (average of two runs) of compounds estimated to be pure as determined by ¹H NMR and TLC. The new compounds **4** and **6f** were further characterized by elemental analysis. Compounds described in the literature were characterized by comparison of their ¹H NMR spectra to previously reported data.

1,3-Bis(1-imidazolyl)benzene (1): An oven-dried resealable tube was back-filled with argon and charged with imidazole **3** (0.163 g, 2.4 mmol), CuI (0.019 g, 0.1 mmol), Cs_2CO_3 (1.368 g, 4.2 mmol), 1,3-diiodobenzene (0.330 g, 1 mmol), racemic *trans*-1,2-cyclohexanediamine (0.048 mL, 0.4 mmol) and 2 mL of dry 1,4-dioxane under a stream of argon. The reaction tube was quickly sealed and the contents were stirred at 95 °C for 24 h. The cooled reaction mixture was diluted with EtOAc, filtered through a plug of silica gel and eluted with additional EtOAc saturated with NH_3 . The filtrate was concentrated, and the resulting residue was purified by column chromatography [hexane/EtOAc (1:1); EtOAc/ NH_3 ; EtOAc/MeOH (9:1)] to provide 1-(3-iodophenyl)-1*H*-imidazole (**4**, 0.014 g, 5% yield) and bis(1-imidazolyl)benzene (**1**, 0.200 g, 95% yield).

1,3-Bis(1-imidazolyl)benzene (1): ¹H NMR (300 MHz, CDCl_3): δ = 7.91 (br.s, 2 H), 7.61 (t, 1 H, J = 8 z), 7.42 (s, 1 H), 7.41 (d, 2 H, J = 8 z), 7.33 (br.s, 2 H), 7.24 (br.s, 2 H) ppm. ¹³C NMR (75.4 MHz, CDCl_3): δ = 138.6, 135.4, 131.4, 131.0, 120.1, 118.0, 114.5 ppm. EI-MS: m/z (%): 210 (100) [M^+]. M.p. 136–137 °C. The NMR spectroscopic data are in accordance with those reported.^[6]

1-(3-Iodophenyl)-1*H*-imidazole (4): Colorless foam. ¹H NMR (300 MHz, CDCl_3): δ = 7.84 (br.s, 1 H), 7.75 (br.s, 1 H), 7.70 (d, 1 H), 7.36 (d, 1 H), 7.26 (br.s, 1 H), 7.23–7.17 (m, 2 H) ppm. ¹³C NMR (50.3 MHz, CDCl_3): δ = 138.1, 136.3, 135.3, 131.1, 130.6, 130.2, 120.5, 117.9, 94.6 ppm. EI-MS: m/z (%): 270 (100) [M^+]. $\text{C}_9\text{H}_7\text{IN}_2\cdot 0.5\text{Me}_2\text{CO}$ (299.11): calcd. C 42.16, H 3.37, N 9.37; found C 42.43, H 3.16, N 9.08.

Typical Procedure for *N*-Arylation of Imidazole: An oven-dried resealable tube was back-filled with argon and charged with aryl halide (1 mmol), imidazole **3** (0.082 g, 1.2 mmol), CuI (0.019 g, 0.1 mmol), dry DMF (1 mL), *N,N'*-dimethylethylenediamine (0.041 mL, 0.4 mmol) and Cs_2CO_3 (0.684 g, 2.1 mmol) under a stream of argon. The tube was sealed with a Teflon valve and the reaction mixture was stirred magnetically at 170 °C for 48 h. The resulting suspension was cooled to room temperature, and Cl_2CH_2 (20 mL) and NH_4OH (20 mL) were added. The separate layers were washed, combined organic layers were dried, and solvent was removed. The residue was purified by flash chromatography (EtOAc) to afford pure product.

1-(2,4,6-Trimethylphenyl)-1*H*-imidazole (2a): The product was obtained as a colorless crystalline solid (0.095 g, 50% yield). ¹H NMR (200 MHz, CDCl_3): δ = 7.44 (s, 1 H), 7.24 (s, 1 H), 6.97 (s, 2 H), 6.90 (s, 1 H), 2.34 (s, 3 H), 1.99 (s, 6 H) ppm. M.p. 116–117 °C. The NMR spectroscopic data are in accordance with those reported.^[4c]

1-(2,6-Diisopropylphenyl)-1*H*-imidazole (2b): The product was obtained as colorless needles (0.044 g, 19% yield). ¹H NMR (200 MHz, CDCl_3): δ = 7.51 (br.s, 1 H), 7.45 (t, 1 H), 7.27 (d, 2 H), 7.24 (s, 1 H), 6.95 (br.s, 1 H), 2.39 (m, 1 H), 1.13 (d, 6 H) ppm. M.p. 122–123 °C. The NMR^[4c] data and m.p.^[9] are in accordance with those reported.

1-(2-Naphthyl)-1*H*-imidazole (2c): The product was obtained as a white solid (0.156 g, 80% yield). ¹H NMR (200 MHz, CDCl_3): δ = 8.00–7.83 (m, 5 H), 7.78 (s, 1 H), 7.59–7.51 (m, 3 H), 7.42 (br.s, 1 H), 7.27 (s, 1 H) ppm. M.p. 122–123 °C. The NMR spectroscopic data and m.p. are in accordance with those reported.^[4c]

1-(1-Naphthyl)-1*H*-imidazole (2d): The product was obtained as a white solid (0.112 g, 57% yield). ¹H NMR (200 MHz, CDCl_3): δ = 7.98–7.94 (m, 2 H), 7.78 (s, 1 H), 7.61–7.44 (m, 5 H), 7.31–7.27 (m, 2 H) ppm. M.p. 72 °C. The NMR spectroscopic data are in accordance with those reported.^[4c]

Preparation of 1-(2,4,6-Trimethylphenyl)imidazole (2a) from 2,4,6-Trimethylphenylboronic Acid. Method A: An oven-dried two-necked round-bottomed 50 mL flask containing a magnetic stirrer bar was charged with 2,4,6-trimethylphenylboronic acid (0.695 g, 4.24 mmol), anhydrous $\text{Cu}(\text{OAc})_2$ (0.423 g, 2.33 mmol), pyridine (0.375 mL, 4.66 mmol) and CH_2Cl_2 (10 mL). After five minutes, imidazole (0.144 g, 2.12 mmol) was added and the reaction mixture was stirred under air at room temperature for 48 h. MeOH/ NH_3 (6 mL) was added, the solution was evaporated, and the residue was filtered through a 1 × 1 cm pad of silica gel and eluted with EtOAc. Purification by flash chromatography on alumina (3 × 15 cm; CH_2Cl_2) provided *N*-(2,4,6-trimethylphenyl)imidazole (**2a**, 0.016 g, 4% yield).

Method B: An oven-dried round-bottomed 50 mL flask containing a magnetic stirrer bar was charged with 2,4,6-trimethylphenylbo-

ronic acid (0.164 g, 1 mmol), CuI (0.009 g, 0.05 mmol), and dry MeOH (5 mL). After five minutes, imidazole (0.082 g, 1.2 mmol) was added and the reaction mixture was stirred under air at reflux for 6 h. The solvent was evaporated, and NH_4OH solution (10%, 5 mL) and EtOAc (5 mL) were added. The organic layer was washed with water and dried, and the solvent was removed. Purification by flash chromatography on silica (1 \times 15 cm; EtOAc) provided *N*-(2,4,6-trimethylphenyl)imidazole (**2a**, 0.017 g, 9% yield).

5,6-Dimethyl-1-(4-methylphenyl)-1*H*-benzimidazole (6f). **Method A:** An oven-dried two-necked round-bottomed 50 mL flask containing a magnetic stirrer bar was charged with 4-methylphenylboronic acid (0.272 g, 2 mmol), anhydrous $\text{Cu}(\text{OAc})_2$ (0.200 g, 1.1 mmol), pyridine (0.18 mL, 2.2 mmol) and CH_2Cl_2 (4 mL). After five minutes, 5,6-dimethylbenzimidazole (**5**, 0.146 g, 1 mmol) was added and the reaction mixture was stirred under air at room temperature for 48 h. MeOH/ NH_3 (3 mL) was added, the solution was evaporated, and the residue was filtered through a 1 \times 1 cm pad of silica gel and eluted with EtOAc. Purification by flash chromatography on silica gel (2 \times 15 cm; EtOAc) provided 5,6-dimethyl-1-(4-methylphenyl)benzimidazole (**6f**, 0.151 g, 64% yield).

Method B: An oven-dried round-bottomed 50 mL flask containing a magnetic stirrer bar was charged with 4-methylphenylboronic acid (0.136 g, 1 mmol) or potassium 4-methylphenyltrifluoroborate (0.198 g, 1 mmol), CuI (0.009 g, 0.05 mmol) and dry MeOH (4 mL). After five minutes, 5,6-dimethylbenzimidazole (**5**, 0.175 g, 1.2 mmol) was added and the reaction mixture was stirred under air at reflux for 3 h. The solvent was evaporated, and NH_4OH solution (10%, 5 mL) and EtOAc (5 mL) were added. The organic layer was washed with water and dried, and the solvent was removed. Purification by flash chromatography on silica (1 \times 15 cm; EtOAc) provided 5,6-dimethyl-1-(4-methylphenyl)benzimidazole (**6f**; see Scheme 5).

Method C: An oven-dried two-necked round-bottomed 50 mL flask containing a magnetic stirrer bar was charged with potassium 4-methylphenyltrifluoroborate (0.217 g, 1.1 mmol), anhydrous $\text{Cu}(\text{OAc})_2$ (0.200 g, 1.1 mmol), pyridine (0.18 mL, 2.2 mmol) and dry 1,4-dioxane (4 mL). After five minutes, 5,6-dimethylbenzimidazole (**5**, 0.146 g, 1 mmol) was added and the reaction mixture was stirred under air at room temperature for 24 h. MeOH/ NH_3 (6 mL) was added, the solution was evaporated, and the residue was filtered through a 1 \times 1 cm pad of silica gel and eluted with EtOAc. Purification by preparative chromatography on a silica gel plate with EtOAc/ CHCl_3 (75:25) as the eluent provided 5,6-dimethyl-1-(4-methylphenyl)benzimidazole (**6f**, 0.013 g, 6% yield).

5,6-Dimethyl-1-(4-methylphenyl)-1*H*-benzimidazole (6f): ^1H NMR (400 MHz, CDCl_3): δ = 8.00 (s, 1 H), 7.65 (s, 1 H), 7.39–7.34 (AA'BB' syst., 4 H), 7.27 (s, 1 H), 2.45 (s, 3 H), 2.39 (s, 3 H), 2.35 (s, 3 H) ppm. ^{13}C NMR (100.6 MHz, CDCl_3): δ = 142.3, 141.7, 138.2, 134.0, 133.2, 132.6, 132.0, 130.7, 124.1, 120.6, 110.8, 21.3, 20.8, 20.5 ppm. M.p. 96–97 °C. EI-MS: *m/z* (%): 236 (100) [M^+]. $\text{C}_{16}\text{H}_{16}\text{N}_2$ (236.31): calcd. C 81.32, H 6.82, N 11.85; found C 81.16, H 6.98, N 11.67.

Supporting Information Available (see also footnote on the first page of this article): Tables S2 and S5. Complete Tables 2, 3 and 4. Experimental procedures not detailed in the printed manuscript and attempted preparation of *N*-arylazoles from arylboronic acids (Schemes 6 and 7).

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[15] a) For ¹H NMR spectral simplification, 5,6-dimethyl-1*H*-benzimidazole (**5**) was used instead of 1*H*-benzimidazole. b) Cu-catalyzed coupling of 5-iodo-1,3-dimethylbenzene with 1*H*-benzimidazole was reported to proceed in 91% yield.^[2b,c]

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