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Reactivity-Controlled Regioselectivity: A Regiospecific Synthesis of 1,2-Disubstituted Benzimidazoles

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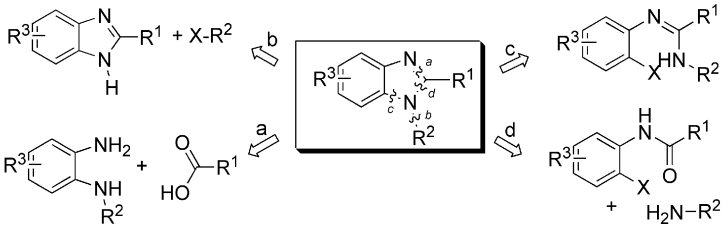
We demonstrate exceptional levels of regioselectivity in the tandem amination reactions between 1,2-differentiated dihaloarenes and *N*-substituted amidines. The regiochemical outcome of this CuI-catalyzed reaction is achieved through a combination of N^1/N^2 chemoselectivity on the amidine and reactivity-controlled X^1/X^2 chemoselectivity on the 1,2-dihaloarene. This reaction proves to be fairly general for the regiospecific synthesis of 1,2-substituted benzimidazoles.

Introduction

The benzimidazole scaffold is a "privileged" structural motif[1] for the development of bioactive compounds in the pharmaceutical industry. Benzimidazole derivatives are widely found in commercial drugs such as Prilosec, Nexium, Protonix, (proton pump inhibitors) Atacand (hypertension), Famvir (antiviral), and Vermox (broad spectrum anthelmintic) as well as numerous experimental drug candidates.[2] Therefore, it is not surprising that the efficient synthesis of benzimidazoles has always been a topic of interest for organic and medicinal chemists.[3] The classic synthesis of benzimidazoles involves the condensation of carboxylic acids (or their variants) with 1,2-diaminoarenes (Scheme 1, path a).[4] However, this method is usually not suitable for the regioselective synthesis of *N*-substituted benzimidazoles. Because of the difficulty of differentiating the two nitrogen atoms, a mixture of two regioisomers is often obtained.[5] *N*-Substitution reactions of 1*H*-benzimidazoles are usually not regiospecific either (path b). Furthermore, *N*-substitution reactions typically favor substitution onto the sterically less hindered nitrogen.[6] This makes the sterically more hindered products extremely difficult to obtain.[7] Therefore, a regiospecific benzimidazole synthesis remains a significant challenge for synthetic chemists.[8]

The recent development of the metal-catalyzed Buchwald–Hartwig amination reaction[9] makes the alternative C–N bond disconnection a viable strategy to construct the benzimidazole ring regiospecifically via an intramolecular amination cyclization (path c).[10] However, it usually takes a multi-step synthesis to prepare the requisite *o*-halo-phenylamidine precursor. Very recently, Ma[11] and Buchwald[12] and co-workers independently developed an elegant regioselective benzimidazole synthesis based on a cascade arylamination/condensation process (path d). Despite these progresses, a facile, regiospecific benzimidazole synthesis is still in high demand. Herein, we report a modular, regiospecific synthesis of 1,2-substituted benzimidazoles with a distinctive bond disconnection, starting from 1,2-dihaloarenes and 1,2-disubstituted amidines. Taking advantage of the reactivity difference of the two differentiated halides (I–Br, I–Cl, or Br–Cl), exclusive regioselectivity is achieved, regardless of the steric and electronic characters of the substrates. Both starting materials are readily available and the reaction scope is quite broad. We believe that this methodology is a valuable contribution to the benzimidazole synthesis toolkit.



Scheme 1. Literature syntheses of *N*-substituted benzimidazoles.

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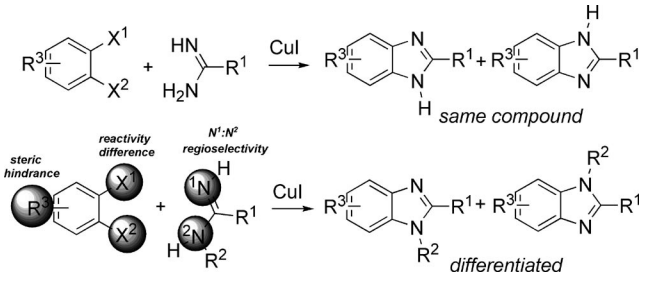
Results and Discussion

In recent years, Cu-mediated amination reaction has been extensively studied because of the cheaper metal price and the complementary reactivity in many cases, compared to the Pd-catalyzed reactions.[13] We recently reported a CuI-catalyzed tandem amination reaction of 1,2-dihaloarenes with guanidines and amidines, which provided a facile, one-step synthesis of 1-*H*-2-substituted benzimidazoles.[14] In that study, one particularly important aspect of this reaction, i.e. regioselectivity, was left out because of the equivalence of the two nitrogen atoms of the 1-*H*-benzimidazole product (Scheme 2). In contrast, with *N*-substituted amidine starting material ($R^2 \neq H$), the two nitrogen atoms are differentiated, which potentially would afford two distinct regioisomeric 1,2-disubstituted benzimidazole products. Although it has been shown that regioselectivity could be achieved through the sequential C–N and C–O bond formation in the analogous benzoxazole synthesis,[15] to the best of our knowledge, the regioselectivity on substrates with two closely associated nitrogen atoms such as amidines has not been reported. To control the regiochemical outcome of this tandem amination reaction, we recognized that three factors would play critical roles (Scheme 2): a) the N^1:N^2 chemoselectivity on the first amination step; b) the steric and electronic effect of the R^3 substituent on the arene ring; and c) the reactivity difference of the two differentiated halides. Which of these three controlling factors is the determining factor and if/how they interfere with each other were the main questions we tried to answer.

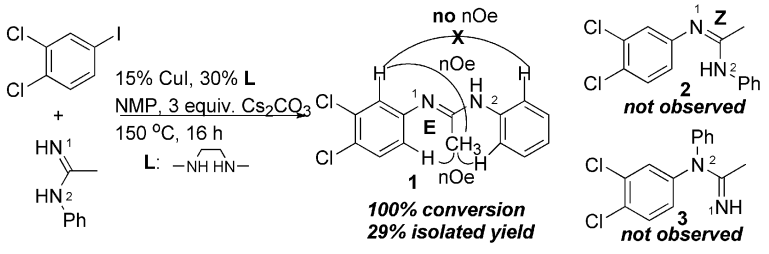


Scheme 2. Tandem amination of 1,2-dihaloarenes with amidines.

To determine the N^1:N^2 chemoselectivity of the first amination step, we chose to study the mono-amination reaction of 3,4-dichloro-1-iodobenzene with *N*-phenylacetamidine. Under the same amination conditions used in our previous paper with *N*-unsubstituted amidines,[14a] single regioisomer **1** was isolated in 29% yield (Scheme 3). The low yield of **1** was probably partially due to the instability of the compound during the purification process at room temperature.[16] Careful nOe studies revealed that the amination reaction took place exclusively at the N^1 position. No N^2 amination product **3** was observed whatsoever. This exclusive N^1 chemoselectivity is particularly interesting because this is the first time that the high level of chemoselectivity in the metal-catalyzed C–N bond formation reactions was achieved on substrates with two closely associated nitrogen atoms such as amidines. In the literature, sporadic examples were found for the chemoselective C–N bond formation on substrates with two reactive nitrogen atoms. However, the process appears to be extremely complex, with the outcome highly dependent on the substrates,[17] metals,[18] ligands,[19] and bases.[20] Recent mechanistic studies showed that two interdependent events, i.e., coordination of the NH to the metal atom and the subsequent deprotonation of the metal–NH complex,[21] played crucial roles in the chemoselectivity. However, the exact origin of this exclusive N^1 chemoselectivity requires further exploration.

Another important observation was that the C–N double bond of compound **1** took exclusively the *E* conformation presumably because of the thermodynamical stability. Apparently, in the case of the benzimidazole synthesis through the tandem double aminations of 1,2-dihaloarenes, the *Z*/*E* isomerization would have to take place first to align the N^2 atom to the requisite *Z* conformation for the second amination to occur.

The second controlling factor we examined was the steric effect of the substituents on the aromatic ring (Table 1, Entries 1–3). The same standard reaction conditions were purposely used without individual optimization for the direct comparison reason. Because of the low reactivity of 1,2-dibromides, low conversions and yields were observed on Entries 1 and 2. Nevertheless, useful amount of materials were obtained for the studies of the regioselectivity of the reaction. Assuming that electronically the reactivity of the two halides is similar, any observed regioselectivity should be dictated by the steric effect of the substituents. With 3,4-dibromotoluene, the steric effect was rather small, affording two stable, chromatographically inseparable regioisomers in a 1:1.1 ratio (Entry 1). Compound **4b** was slightly favored presumably to avoid the interaction between the methyl group and the *N*-phenyl group. Increasing the size of the substituent to a bulkier *tert*-butyl group only slightly increased the regioselectivity to a 1:1.4 ratio (Entry 2). In con-



Scheme 3. The N^1:N^2 chemoselectivity.

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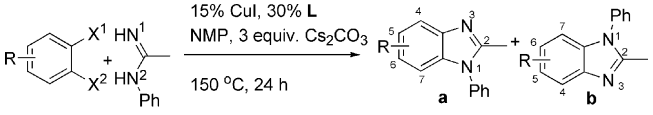
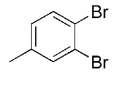
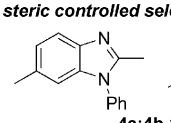
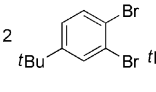
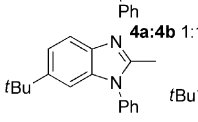
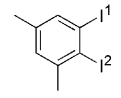
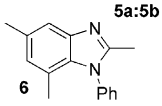
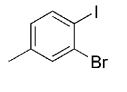
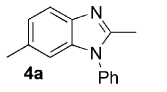
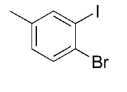
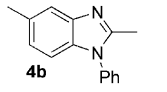
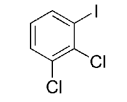
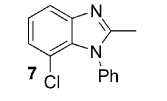
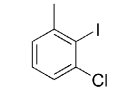
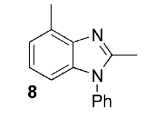
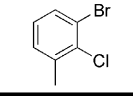
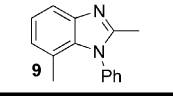
trast, 1,2-diiodo-3,5-dimethylbenzene, with a methyl substituent close to the halides, gave rise to exclusive regioisomer **6** (Entry 3).[22] This regiospecificity likely stemmed from the steric hindrance of the methyl substituent adjacent to the I^2 atom forcing the first amination reaction take place at the I^1 atom, far away from the methyl group.

Table 1. Steric and reactivity control of regioselectivity.



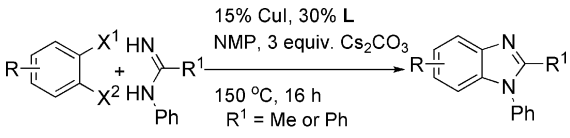
Entry	Dihaloarene	Product	Yield[a]
	steric controlled selectivity		
1			11%[b] (50% conversion)
2		**4a:4b** 1:1.1 	14%[b] (40% conversion)
3		**5a:5b** 1:1.4  **6**	**b** *not observed* 51%
	reactivity controlled selectivity		
4		 **4a**	**4b** *not observed* 53%
5		 **4b**	**4a** *not observed* 57%
6		 **7**	**b** *not observed* 24%
7		 **8**	**b** *not observed* 38%
8		 **9**	**b** *not observed* 10% (35% conversion)

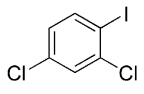
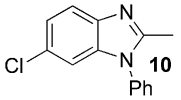
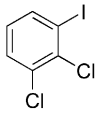
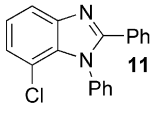
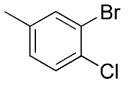
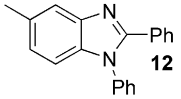
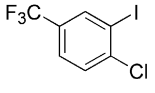
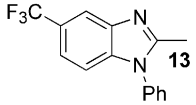
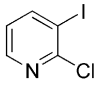
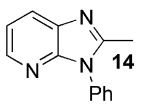
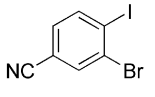
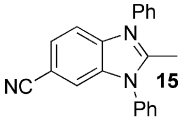
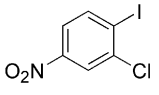
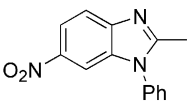
[a] Isolated yield. [b] Two regioisomers combined. The ratio was determined on the basis of ^{1}H NMR integration of the purified product.

The reactivity control of differentiated halides on the regioselectivity was next studied (Table 1, Entries 4–8). In our previous paper,[14a] we found that the first amination step was the rate-determining step, with the reaction rate of I > Br >> Cl (unreactive). The second intramolecular amination step appeared to be rather fast for I, Br and Cl and did not affect the overall reaction rate. Thus, when the two halides are differentiated, there are two possible scenarios, match and mismatch of the steric control and the reactivity control. When the steric effect was minimum, single regioisomers were obtained exclusively (Entries 4 and 5). Apparently, the first amination reaction occurred preferentially on the more reactive iodide (also N^1-selective) and the tandem intramolecular amination (at the N^2 position) on the bromide afforded the benzimidazole product regiospecifically. Not surprisingly, when the steric control and the reactivity control were matched, a single product **7** was isolated (Entry 6). Interestingly, in the case that steric control and reactivity control were mismatched, the reactivity difference of the two halides was the dominant factor to afford a single regioisomer **8** exclusively (Entry 7). In addition to the I–Br and I–Cl 1,2-dihalide combinations, the Br–Cl combination also provided the same degree of regioselectivity although the reaction was usually sluggish (Entry 8).

With the knowledge that the N^1 chemoselectivity and the reactivity control were the dominant factors, we further explored a number of 1,2-differentiated dihaloarenes bearing various functional groups (Table 2). In all cases, single regioisomers were isolated, suggesting that reactivity control overruled the electronic and steric effects of the substituents on the arene ring. A heteroaromatic pyridine ring was compatible with the reaction conditions (Entry 5). It is worth noting that in the presence of electron-withdrawing cyano

Table 2. Reaction scope: 1,2-dihaloarenes.



Entry	1,2-dihaloarene	Product	Yield[a]
1		 **10**	41%
2		 **11**	29%
3		 **12**	20%[b]
4		 **13**	24%
5		 **14**	39%[c]
6		 **15**	31%[d]
7			0[e]

[a] Isolated yield. [b] 3-Bromo-4-chlorotoluene (≈ 40%) remained unreacted. [c] The solvent was DMA. [d] The reaction temperature was at 130 °C. [e] Decomposition of the dihalide was observed even at 100 °C with DMA as the solvent.

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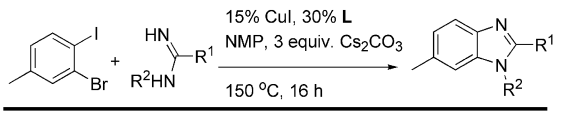
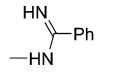
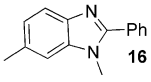
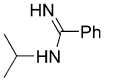
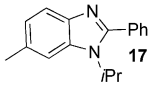
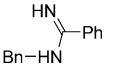
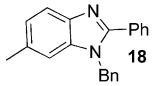
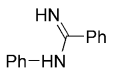
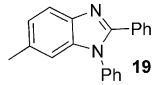
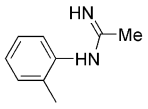
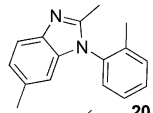
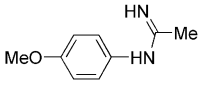
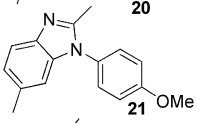
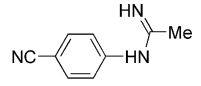
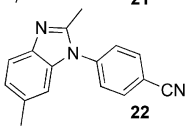
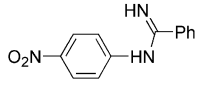
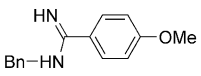
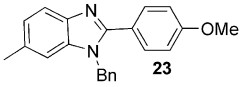
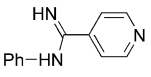
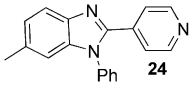
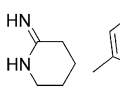
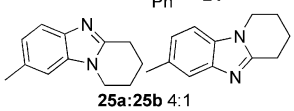
group, the reaction took place at lower temperature (Entry 6). Unfortunately, the nitro group appeared to be incompatible with the reaction conditions (Entry 7). Even at 100 °C, complete decomposition of the 3-chloro-4-iodo-1-nitrobenzene was observed within 3 h.

We next investigated the scope of the reaction with respect to different amidines that were readily prepared from corresponding amines and nitriles. All the reactions were performed under the standard conditions without individual optimization. At the R^2 position, the steric bulkiness of various alkyl groups (Table 3, Entries 1–3) did not affect the regioselectivity of this reaction. Amidines with various aromatic groups at the R^2 position (Entries 4–7) also afforded the desired benzimidazole products regiospecifically. Electron-donating substituents on the phenyl ring such as methyl (Entry 5) and methoxy (Entry 6) were also well tolerated in the reaction. In contrast, substrates with electron-withdrawing substitutents on the R^2 arene ring proved problematic. With *N*-(4-cyanophenyl)acetamidine, decomposition of the amidine to 4-cyanoaniline was the major side reaction (Entry 7). Nevertheless, by lowering the reaction temperature to 100 °C, the desired benzimidazole **22** was isolated in a moderate yield. Unfortunately, the dissociation of *N*-(4-nitrophenyl)benzamidine to 4-nitroaniline and benzonitrile was facile even at 100 °C and no amination product was observed (Entry 8). At the R^1 position, either alkyl (Entry 5–7, 11) or aromatic (including heteroaromatic) groups (Entries 1–4, 9–10) were tolerated, again affording the benzimidazole products regioselectively. The only exception was with 2-iminopiperidine where the minor regioisomer **25b** was observed in a 1:4 (**25b**/**25a**) ratio (Entry 11). We believe that the regioselectivity drop was the result of the poor N^1:N^2 selectivity at the first amination step.

Table 3. Reaction scope: amidines.



Entry	Amidine	Product	Yield[a]
1		 **16**	48%
2		 **17**	24%
3		 **18**	11%
4		 **19**	56%
5		 **20**	49%
6		 **21**	48%
7		 **22**	41%[b]
8		–	0%[c]
9		 **23**	16%
10		 **24**	56%[d]
11		 **25a**:**25b** 4:1	29%[e]

[a] Isolated yield. [b] 100 °C in DMA for 16 h. 3-Bromo-4-iodotoluene (≈ 25%) remained unreacted. 4-Cyanoaniline was the major side product. [c] Complete decomposition of the amidine to benzonitrile and 4-nitroaniline took place at 100 °C for 1 h in DMA. [d] DMA was the solvent. [e] Two isomers combined. Ratio was determined on the basis of ^{1}H NMR integration of the purified product.

Conclusions

In summary, the regioselectivity of the reaction of 1,2-dihaloarenes with *N*-substituted amidines was carefully studied. The first amination step is exclusively N^1-selective on the amidines, and the chemoselectivity on the 1,2-dihaloarenes is predominantly controlled by the halide reactivity differences. On the basis on these findings, a highly regiospecific benzimidazole synthesis was developed. Both starting materials are readily available, and the reaction scope is quite broad. One drawback of this methodology is the low yield on some substrates, which might result from the instability of the substrates and products under the high-temperature conditions. The search for more active catalyst systems is ongoing and will be reported in due course.

Experimental Section

General Experimental Methods: ^{1}H and ^{13}C NMR spectra were recorded at a 600-MHz or a 500-MHz NMR spectrometers. The nOe and NOSEY experiments were performed using the literature method[25] with a mixing time of 0.8 s. Flash column chromatography was performed using Merck silica gel 60. HRMS (ESI) was performed on a μTof apparatus.

The reaction flasks were flame-dried prior to use. DMA and NMP was purchased from commercial sources and used as it was. CuI was purchased from Aldrich with at least 99.99% purity. All the halides were purchased from commercial sources and used without further purification. Amidines were either purchased from commercial sources or prepared from the corresponding nitriles and amines by the literature procedures.[26] The detailed ^{1}H NMR chemical shift assignments could be found in the Supporting Information section.

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Typical Procedure for the Regioselective Benzimidazole Synthesis

2,6-Dimethyl-1-phenyl-1*H*-benzimidazole (4a): A Schlenk tube equipped with a strong magnetic stirring bar was charged with CuI (43 mg, 0.22 mmol, 0.15 equiv.), *N*-phenylacetamidine (282 mg, 2.1 mmol, 1.4 equiv.), and Cs_2CO_3 (1.5 g, 4.5 mmol, 3 equiv.). The Schlenk tube was evacuated and backfilled with N_2 three times. Under N_2, DMA or NMP (4 mL), 2-bromo-1-iodo-4-methylbenzene (445 mg, 1.5 mmol, 1.0 equiv.) and *N*,*N*′-dimethylethylenediamine (39 mg, 0.45 mmol, 0.3 equiv.) were added sequentially via syringe. The reaction mixture was stirred under N_2 at the indicated temperature (150 °C) for 24 h and then cooled to room temperature. The inorganic salt was filtered off and washed with EtOAc. The filtered EtOAc solution was washed with brine, dried with $MgSO_4$, and concentrated. The crude product was purified on silica gel with EtOAc/hexanes as the eluents to afford the pure title compound (176 mg, 0.79 mmol, 53%).

***N*-(3,4-Dichlorophenyl)-*N*′-phenylacetamidine (1):** Following the general procedure, the title compound was obtained in 29% yield (121 mg). R_f = 0.1 (1:4 EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 13.78 (br. s, 1 H), 7.52 (d, J = 8.5 Hz, 1 H), 7.48–7.43 (m, 2 H), 7.41 (d, J = 2.4 Hz, 1 H), 7.42–7.38 (m, 1 H), 7.25 (d, J = 7.5 Hz, 2 H), 7.15 (dd, J = 8.5, 2.4 Hz, 1 H), 2.16 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.9, 135.1, 134.9, 133.9, 132.9, 131.5, 130.0, 128.8, 127.7, 125.7, 125.2, 16.0 ppm. HRMS-ESI (*m*/*z*): [M + H]$^+$ calcd. for $C_{14}H_{12}Cl_2N_2$ 279.0450; found 279.0445.

Mixture of 2,6-Dimethyl-1-phenyl-1*H*-benzimidazole (4a) and 2,5-Dimethyl-1-phenyl-1*H*-benzimidazole (4b): (Table 1, Entry 1) Following the general procedure, the title compounds (an inseparable mixture of **4a** and **4b** in a 1:1.1 ratio according to ^{1}H NMR integration of the purified product) were obtained in 11% combined yield (36 mg).[23] R_f = 0.12 (1:1 EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$, **4a**): δ = 7.61 (d, J = 8.2 Hz, 1 H), 7.56–7.52 (m, 2 H), 7.50–7.47 (m, 1 H), 7.38–7.33 (m, 2 H), 7.08 (dd, J = 8.2, 1.0 Hz, 1 H), 6.91 (s, 1 H), 2.48 (s, 3 H), 2.41 (s, 3 H) ppm. **4:** ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.56–7.52 (m, 3 H), 7.50–7.48 (m, 1 H), 7.38–7.33 (m, 2 H), 7.01 (s, 2 H), 2.49 (s, 3 H), 2.48 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, **4a+4b**, 1:1.1): δ = 151.4, 151.0, 143.0, 140.7, 136.7, 136.3, 136.3, 134.6, 132.5, 132.0, 129.9, 129.8, 128.7, 128.6, 127.1, 127.0, 123.9, 123.8, 118.8, 118.5, 109.9, 109.4, 21.7, 21.5, 14.4, 14.4 ppm. HRMS-ESI (*m*/*z*): [M + H]$^+$ calcd. for $C_{15}H_{14}N_2$ 223.1230; found 223.1227.

Mixture of 6-*tert*-Butyl-2-methyl-1-phenyl-1*H*-benzimidazole (5a) and Methyl-1-phenyl-1*H*-benzimidazole (5b): (Table 1, Entry 2) Following the general procedure, the title compounds (an inseparable mixture of **5a 5b** in a 1:1.4 ratio according to ^{1}H NMR integration of the purified product) were obtained in 14% combined yield (55 mg).[24] R_f = 0.3 (1:1 EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) **5a** δ = 7.86 (d, J = 8.7 Hz, 1 H), 7.77–7.69 (m, 3 H), 7.62 (dd, J = 8.6, 1.4 Hz, 1 H), 7.49–7.40 (m, 2 H), 7.16 (d, J = 1.5 Hz, 1 H), 2.78 (s, 3 H), 1.32 (s, 9 H) ppm. ^{1}H NMR (600 MHz, $CDCl_3$, **5b**): δ = 7.90 (s, 1 H), 7.77–7.69 (m, 3 H), 7.54 (dd, J = 8.8, 0.9 Hz, 1 H), 7.49–7.41 (m, 2 H), 7.19 (d, J = 8.8 Hz, 1 H), 2.81 (s, 3 H), 1.39 (s, 9 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, **5a + 5b**): δ = 151.0, 150.8, 150.3, 150.3, 133.3, 132.4, 132.3, 131.3, 131.2, 131.2, 130.95, 130.87, 129.0, 126.8, 126.7, 125.0, 124.6, 115.0, 111.7, 111.2, 107.6, 35.3, 31.5, 31.4, 12.0, 12.0 ppm. HRMS-ESI (*m*/*z*): [M + H]$^+$ calcd. for $C_{18}H_{20}N_2$ 265.1699; found 265.1693.

2,5,7-Trimethyl-1-phenyl-1*H*-benzimidazole (6): Following the general procedure, the title compound was obtained in 51% yield (181 mg). R_f = 0.16 (1:1 EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.54–7.47 (m, 3 H), 7.38 (s, 1 H), 7.32 (dd, J = 6.7, 2.9 Hz, 2 H), 6.75 (s, 1 H), 2.42 (s, 3 H), 2.33 (s, 3 H), 1.86 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 152.1, 143.2, 137.9, 133.0, 131.6, 129.3, 129.2, 128.7, 126.3, 120.6, 116.7, 21.3, 17.6, 14.3 ppm. HRMS-ESI (*m*/*z*): [M + H]$^+$ calcd. for $C_{16}H_{16}N_2$ 237.1386; found 237.1386.

2,6-Dimethyl-1-phenyl-1*H*-benzimidazole (4a): Following the general procedure, the title compound was obtained in 53% yield (176 mg). R_f = 0.13 (1:1 EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.61 (d, J = 8.2 Hz, 1 H), 7.56–7.52 (m, 2 H), 7.50–7.47 (m, 1 H), 7.33 (dd, J = 8.3, 1.2 Hz, 2 H), 7.06 (dd, J = 8.2, 1.0 Hz, 1 H), 6.90 (s, 1 H), 2.47 (s, 3 H), 2.39 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 150.9, 140.7, 136.7, 136.2, 132.5, 129.8, 128.6, 127.0, 123.8, 118.5, 109.8, 21.6, 14.4 ppm. HRMS-ESI (*m*/*z*): [M + H]$^+$ calcd. for $C_{15}H_{14}N_2$ 223.1230; found 223.1224.

2,5-Dimethyl-1-phenyl-1*H*-benzimidazole (4b): Following the general procedure, the title compound was obtained in 57% yield (190 mg). R_f = 0.13 (1:1 EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.57–7.52 (m, 3 H), 7.49 (t, J = 7.5 Hz, 1 H), 7.36–7.31 (m, 2 H), 7.00 (s, 2 H), 2.48 (s, 3 H), 2.47 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 151.4, 143.0, 136.3, 134.6, 132.0, 129.8, 128.6, 127.0, 123.9, 118.8, 109.4, 21.5, 14.4 ppm. HRMS-ESI (*m*/*z*): [M + H]$^+$ calcd. for $C_{15}H_{14}N_2$ 223.1230; found 223.1223.

7-Chloro-2-methyl-1-phenyl-1*H*-benzimidazole (7): Following the general procedure, the title compound was obtained in 24% yield (87 mg). R_f = 0.23 (1:1 EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.65 (d, J = 7.7 Hz, 1 H), 7.56–7.47 (m, 3 H), 7.37–7.30 (m, 2 H), 7.19–7.10 (m, 2 H), 2.37 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 153.4, 144.5, 136.4, 132.2, 129.3, 129.1, 128.8, 123.9, 122.7, 117.9, 116.1, 14.3 ppm. HRMS-ESI (*m*/*z*): [M + H]$^+$ calcd. for $C_{14}H_{11}ClN_2$ 243.0684; found 243.0673.

2,4-Dimethyl-1-phenyl-1*H*-benzimidazole (8): Following the general procedure, the title compound was obtained in 38% yield (127 mg). R_f = 0.21 (1:1 EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.53 (ddd, J = 7.9, 4.6, 1.2 Hz, 2 H), 7.50–7.45 (m, 1 H), 7.35–7.30 (m, 2 H), 7.11–7.02 (m, 2 H), 6.97–6.91 (m, 1 H), 2.71 (s, 3 H), 2.51 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 150.6, 141.8, 136.3, 136.1, 129.8, 128.8, 128.6, 127.0, 122.8, 122.4, 107.5, 16.7, 14.4 ppm. HRMS-ESI (*m*/*z*): [M + H]$^+$ calcd. for $C_{15}H_{14}N_2$ 223.1230; found 223.1225.

2,7-Dimethyl-1-phenyl-1*H*-benzimidazole (9): Following the general procedure, the title compound was obtained in 10% yield (33 mg). About 65% starting material 3-bromo-2-chlorotoluene remained unreacted. R_f = 0.18 (1:1 EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.78 (d, J = 8.3 Hz, 1 H), 7.75–7.71 (m, 1 H), 7.70–7.65 (m, 2 H), 7.47–7.43 (m, 2 H), 7.42–7.36 (m, 1 H), 7.18 (d, J = 7.4 Hz, 1 H), 2.66 (s, 3 H), 1.93 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 150.9, 134.1, 131.5, 131.4, 130.4, 129.5, 128.5, 128.0, 126.3, 123.5, 113.5, 17.4, 11.9 ppm. HRMS-ESI (*m*/*z*): [M + H]$^+$ calcd. for $C_{15}H_{14}N_2$ 223.1230; found 223.1225.

6-Chloro-2-methyl-1-phenyl-1*H*-benzimidazole (10): Following the general procedure, the title compound was obtained in 41% yield (149 mg). R_f = 0.25 (1:1 EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.64 (d, J = 8.5 Hz, 1 H), 7.62–7.58 (m, 2 H), 7.56–7.52 (m, 1 H), 7.38–7.33 (m, 2 H), 7.23 (dd, J = 8.5, 2.0 Hz, 1 H), 7.11–7.09 (m, 1 H), 2.50 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 152.5, 141.2, 137.0, 135.5, 130.1, 129.2, 128.4, 127.0, 123.0, 119.8, 110.1, 14.4 ppm. HRMS-ESI (*m*/*z*): [M + H]$^+$ calcd. for $C_{14}H_{11}ClN_2$ 243.0684; found 243.0674.

7-Chloro-1,2-diphenyl-1*H*-benzimidazole (11): Following the general procedure, the title compound was obtained in 29% yield (132 mg). R_f = 0.14 (1:4 EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.80 (dd, J = 7.5, 1.5 Hz, 1 H), 7.53–7.49 (m, 2 H), 7.48–7.44 (m,

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1 H), 7.42–7.38 (m, 2 H), 7.38–7.33 (m, 2 H), 7.33–7.28 (m, 1 H), 7.28–7.18 (m, 4 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 154.0, 144.8, 137.0, 132.8, 129.7, 129.7, 129.6 (2 C), 129.3, 128.8, 128.2, 124.9, 123.2, 118.7, 116.7 ppm. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd. for $C_{19}H_{13}ClN_2$ 305.0840; found 305.0834.

5-Methyl-1,2-diphenyl-1*H*-benzimidazole (12): Following the general procedure, the title compound was obtained in 20% yield (85 mg). About 40% starting material 3-bromo-4-chlorotoluene remained unreacted. R_f = 0.14 (1:4 EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.67 (s, 1 H), 7.58–7.51 (m, 2 H), 7.47–7.38 (m, 3 H), 7.33–7.23 (m, 5 H), 7.10 (d, *J* = 8.2 Hz, 1 H), 7.06 (d, *J* = 1.0 Hz, 1 H), 2.49 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 152.3, 143.4, 137.2, 135.4, 132.7, 130.1, 129.8, 129.4, 129.3, 128.4, 128.3, 127.3, 124.8, 119.6, 110.0, 21.6 ppm. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd. for $C_{20}H_{16}N_2$ 285.1386; found 285.1377.

2-Methyl-1-phenyl-5-trifluoromethyl-1*H*-benzimidazole (13): Following the general procedure, the title compound was obtained in 24% yield (99 mg). R_f = 0.42 (1:1 EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 0.7 Hz, 1 H), 7.64–7.58 (m, 2 H), 7.57–7.55 (m, 1 H), 7.44 (dd, *J* = 8.5, 1.2 Hz, 1 H), 7.39–7.34 (m, 2 H), 7.19 (d, *J* = 8.4 Hz, 1 H), 2.53 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 153.8, 142.2, 138.4, 135.4, 130.2, 129.4, 127.0, 124.9 (q, *J* = 272 Hz, 1 C), 124.9 (q, *J* = 32 Hz, 1 C), 119.6 (q, *J* = 3.7 Hz, 1 C), 116.7 (q, *J* = 3.7 Hz, 1 C), 110.3, 77.3, 77.1, 76.9, 14.5 ppm. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd. for $C_{15}H_{11}F_3N_2$ 277.0947; found 277.0941.

2-Methyl-3-phenyl-3*H*-imidazo[4,5-*b*]pyridine (14): Following the general procedure, the title compound was obtained in 39% yield (122 mg). R_f = 0.11 (1:1 EtOAc/hexanes). ^{1}H NMR (600 MHz, MeOD): δ = 8.47 (dd, *J* = 4.8, 1.3 Hz, 1 H), 8.25 (dd, *J* = 8.2, 1.3 Hz, 1 H), 7.74–7.64 (m, 3 H), 7.63–7.59 (m, 2 H), 7.57 (dd, *J* = 8.2, 4.8 Hz, 1 H), 2.73 (s, 3 H) ppm. ^{13}C NMR (151 MHz, MeOD): δ = 155.3, 147.5, 133.7, 131.7, 131.2, 129.8, 128.8, 128.4, 125.6, 122.5, 13.5 ppm. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd. for $C_{13}H_{11}N_3$ 210.1026; found 210.1021.

2-Methyl-3-phenyl-3*H*-benzimidazole-5-carbonitrile (15): Following the general procedure, the title compound was obtained in 31% yield (108 mg). R_f = 0.28 (1:1 EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.3 Hz, 1 H), 7.68–7.62 (m, 2 H), 7.62–7.57 (m, 1 H), 7.53 (dd, *J* = 8.3, 1.5 Hz, 1 H), 7.45 (d, *J* = 0.9 Hz, 1 H), 7.39–7.35 (m, 2 H), 2.56 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 155.3, 145.6, 136.2, 134.9, 130.3, 129.7, 126.9, 126.1, 119.9, 119.8, 114.8, 105.5, 14.5 ppm. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd. for $C_{15}H_{11}N_3$ 234.1026; found 234.1016.

1,6-Dimethyl-2-phenyl-1*H*-benzimidazole (16): Following the general procedure, the title compound was obtained in 48% yield (160 mg). R_f = 0.39 (1:1 EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.75–7.71 (m, 2 H), 7.69 (d, *J* = 8.2 Hz, 1 H), 7.52–7.43 (m, 3 H), 7.15 (d, *J* = 0.7 Hz, 1 H), 7.14–7.09 (m, 1 H), 3.78 (d, *J* = 3.9 Hz, 3 H), 2.51 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 153.3, 141.0, 136.8, 132.7, 130.3, 129.5, 129.3, 128.6, 124.0, 119.3, 109.6, 31.5, 21.9 ppm. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd. for $C_{15}H_{14}N_2$ 223.1230; found 223.1228.

1-Isopropyl-6-methyl-2-phenyl-1*H*-benzimidazole (17): Following the general procedure, the title compound was obtained in 24% yield (90 mg). R_f = 0.41 (1:1 EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.2 Hz, 1 H), 7.65–7.59 (m, 2 H), 7.51–7.45 (m, 3 H), 7.41 (d, *J* = 0.7 Hz, 1 H), 7.10 (dd, *J* = 8.2, 0.7 Hz, 1 H), 4.78 (hepta, *J* = 7.0 Hz, 1 H), 2.52 (s, 3 H), 1.62 (d, *J* = 7.0 Hz, 6 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 153.1, 141.9, 133.8, 132.0, 131.2, 129.5, 129.4, 128.6, 123.6, 119.7, 112.2, 48.6, 22.0, 21.4 ppm. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd. for $C_{17}H_{18}N_2$ 251.1543; found 251.1535.

1-Benzyl-6-methyl-2-phenyl-1*H*-benzimidazole (18): Following the general procedure, the title compound was obtained in 11% yield (49 mg). R_f = 0.07 (1:4 EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 8.2 Hz, 1 H), 7.70–7.62 (m, 2 H), 7.48–7.38 (m, 3 H), 7.38–7.27 (m, 3 H), 7.15–7.12 (m, 1 H), 7.12–7.08 (m, 2 H), 7.00 (s, 1 H), 5.41 (s, 2 H), 2.43 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 153.7, 141.3, 136.6, 136.4, 133.1, 130.2, 129.7, 129.2, 129.0, 128.7, 127.7, 125.9, 124.3, 119.5, 110.3, 48.2, 21.8 ppm. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd. for $C_{21}H_{18}N_2$ 299.1543; found 299.1530.

6-Methyl-1,2-diphenyl-1*H*-benzimidazole (19): Following the general procedure, the title compound was obtained in 56% yield (239 mg). R_f = 0.55 (1:1 EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.2 Hz, 1 H), 7.57–7.52 (m, 2 H), 7.49–7.39 (m, 3 H), 7.33–7.22 (m, 5 H), 7.17–7.12 (m, 1 H), 7.03–6.99 (m, 1 H), 2.42 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 151.9, 141.1, 137.4, 137.1, 133.4, 130.1, 129.8, 129.3, 129.2, 128.4, 128.2, 127.4, 124.5, 119.3, 110.2, 21.8 ppm. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd. for $C_{20}H_{16}N_2$ 285.1386; found 285.1376.

2,6-Dimethyl-1-*o*-tolyl-1*H*-benzimidazole (20): Following the general procedure, the title compound was obtained in 49% yield (174 mg). R_f = 0.20 (1:1 EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 8.2 Hz, 1 H), 7.47–7.39 (m, 2 H), 7.38–7.33 (m, 1 H), 7.20 (d, *J* = 7.6 Hz, 1 H), 7.07 (dd, *J* = 8.2, 1.1 Hz, 1 H), 6.69 (s, 1 H), 2.38 (s, 3 H), 2.36 (s, 3 H), 1.97 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 151.1, 140.8, 136.5, 136.4, 134.9, 132.4, 131.4, 129.5 128.4, 127.3, 123.6, 118.5, 109.8, 21.6, 17.3, 13.9 ppm. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd. for $C_{16}H_{16}N_2$ 237.1386; found 237.1382.

1-(4-Methoxyphenyl)-2,6-dimethyl-1*H*-benzimidazole (21): Following the general procedure, the title compound was obtained in 48% yield (182 mg). R_f = 0.14 (1:1 EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 6.3 Hz, 1 H), 7.27–7.21 (m, 2 H), 7.10–7.03 (m, 3 H), 6.89 (s, 1 H), 3.88 (s, 3 H), 2.44 (s, 3 H), 2.39 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 159.7, 151.4, 140.7, 137.1, 132.3, 128.8, 128.3, 123.6, 118.4, 115.0, 109.9, 55.6, 21.6, 14.3 ppm. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd. for $C_{16}H_{16}N_2O$ 253.1335; found 253.1330.

4-(2,6-Dimethylbenzimidazol-1-yl)benzonitrile (22): Following the general procedure, the title compound was obtained in 41% yield (152 mg). In addition to ca. 25% unreacted starting material 3-bromo-4-iodotoluene, decomposition product of the amidine, 4-aminobenzonitrile was also isolated. R_f = 0.19 (1:1 EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.97–7.84 (m, 2 H), 7.62 (d, *J* = 8.2 Hz, 1 H), 7.58–7.50 (m, 2 H), 7.17–7.06 (m, 1 H), 6.93 (s, 1 H), 2.52 (s, 3 H), 2.43 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 150.2, 140.8, 140.2, 135.8, 133.9, 133.3, 127.7, 124.5, 118.9, 117.8, 112.5, 109.5, 21.7, 14.6 ppm. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd. for $C_{16}H_{13}N_3$ 248.1182; found 248.1174.

1-Benzyl-2-(4-methoxyphenyl)-6-methyl-1*H*-benzimidazole (23): Following the general procedure, the title compound was obtained in 16% yield (78 mg). R_f = 0.33 (1:1 EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.2 Hz, 1 H), 7.61–7.55 (m, 2 H), 7.37–7.26 (m, 3 H), 7.13–7.08 (m, 3 H), 6.97 (s, 1 H), 6.95–6.90 (m, 2 H), 5.38 (s, 2 H), 3.81 (s, 4 H), 2.42 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 160.8, 153.7, 141.3, 136.7, 136.4, 132.8, 130.6, 129.0, 127.6, 125.9, 124.1, 122.5, 119.2, 114.1, 110.2, 55.3, 48.2, 21.8 ppm. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd. for $C_{22}H_{20}N_2O$ 329.1648; found 329.1645.

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6-Methyl-1-phenyl-2-(pyridin-4-yl)-1*H*-benzimidazole (24): Following the general procedure, the title compound was obtained in 56% yield (240 mg). R_f = 0.12 (1:1 EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.54 (dd, J = 4.6, 1.6 Hz, 2 H), 7.78 (d, J = 8.3 Hz, 1 H), 7.60–7.51 (m, 3 H), 7.43 (dd, J = 4.5, 1.7 Hz, 2 H), 7.35–7.30 (m, 2 H), 7.18 (d, J = 8.3 Hz, 1 H), 7.02 (s, 1 H), 2.45 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 149.9, 148.8, 140.9, 137.7, 137.6, 136.5, 134.6, 130.2, 129.1, 127.4, 125.2, 123.0, 119.8, 110.4, 21.9 ppm. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd. for $C_{19}H_{15}N_3$ 286.1339; found 286.1328.

Mixture of 8-Methyl-1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazole (25a) and 7-Methyl-1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazole (25b): (Table 3, Entry 11) Following the general procedure, the title compounds (an inseparable mixture of **25a/25b** in a 4:1 ratio determined by ^{1}H NMR integration of the purified product) were obtained in 29% combined yield (81 mg). R_f = 0.20 (5% MeOH in EtOAc). Two sets of peaks (4:1, **25a/25b**): ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.69 (d, J = 8.4 Hz, 1 H), 7.62 (s, 0.25 H), 7.41 (d, J = 8.4 Hz, 0.25 H), 7.32 (s, 1 H), 7.28 (d, J = 8.4 Hz, 1.25 H), 4.24 (t, J = 6.1 Hz, 2.5 H), 3.34 (t, J = 6.2 Hz, 2.5 H), 2.52 (s, 3 H), 2.48 (s, 0.75 H), 2.27–2.23 (m, 2.5 H), 2.12–2.08 (m, 2.5 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 149.9, 149.9, 136.9, 136.1, 131.6, 131.5, 129.5, 129.3, 127.8, 127.0, 114.9, 114.7, 110.6, 110.4, 43.0, 42.9, 22.3, 22.3, 21.6, 21.5, 21.3, 21.3, 18.3, 18.3 ppm. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd. for $C_{12}H_{14}N_2$ 187.1230; found 187.1237.

Supporting Information (see also the footnote on the first page of this article): NMR spectra (^{1}H, ^{13}C, COSY, nOe, NOSEY) of compounds **1**, **4**–**25**.

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