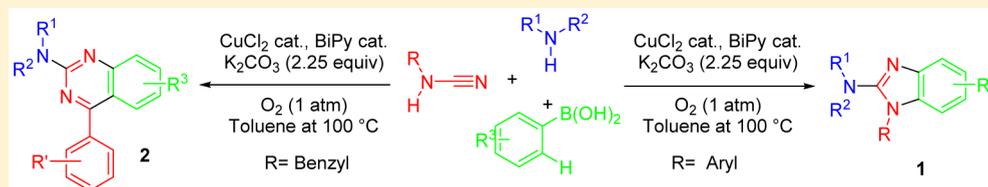


Copper-Catalyzed Domino Three-Component Approach for the Assembly of 2-Aminated Benzimidazoles and Quinazolines

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S Supporting Information



ABSTRACT: A copper-promoted three-component synthesis of 2-aminobenzimidazoles (1) or of 2-aminoquinazolines (2) involving cyanamides, arylboronic acids, and amines has been developed. The operationally simple oxidative process, performed in the presence of K₂CO₃, a catalytic amount of CuCl₂·2H₂O, 2,2'-bipyridine, and an O₂ atmosphere (1 atm), allows the rapid assembly of either benzimidazoles or quinazolines starting from aryl- or benzyl-substituted cyanamides, respectively. In this process, the copper promotes the formation of three bonds, two C–N bonds, and an additional bond resulting from C–H functionalization event.

INTRODUCTION

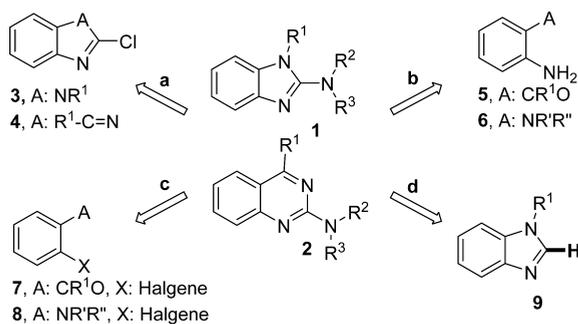
Nitrogen-containing heterocycles are fundamental targets in the pharmaceutical industry as well as in materials science.¹ Among these, benzimidazoles² and quinazolines³ have been successfully explored as drug-like scaffolds, and some of their 2-aminated counterparts have, for example, led to the commercialization of compounds such as astemizole⁴ or prazosin.⁵

Several strategies can be adopted to build such heterocycles. Performing a nucleophilic aromatic substitution (S_NAr) between 2-halogenated azoles and amines constitute one approach to build 2-aminated targets (Scheme 1a).⁶ Alternatively, condensations of 1,2-disubstituted aromatic units such as 1,2-diaminated arenes or ortho-carbonylated anilines, with carbodiimides, thioisocyanates, or amino-ureas followed by dehydrative cyclization, have also been reported (Scheme 1b).⁷ While valuable, these methods suffer from the poor availability

of the precursors. Limitations have been reduced through the development of strategies relying on metal-catalyzed C–N bond-forming reactions,⁸ allowing more accessible ortho-functionalized aryl halides (Scheme 1c) to be used.⁹ Additionally, ingenious domino processes combining the in situ formation of a properly functionalized precursor followed by cyclization have also been studied for the synthesis of benzimidazoles, rendering the overall process easier.¹⁰ Direct functionalization of the C–H bond is an attractive strategy that is gaining in popularity, featuring an easy access to precursors.¹¹ In this context, copper-catalyzed C–H functionalization has recently been used in a number of strategies toward heterocycle assembly.¹² Following Buchwald's work,^{13a} various oxidative processes dealing with the synthesis of benzimidazoles or quinazolines have been reported, including intermolecular C–H amination of 1*H*-benzo[*d*]imidazole (Scheme 1d) and metal-free promoted reaction.^{13–15} Notwithstanding the efficiency of these reaction sequences, alternative simple and modulable protocols, which would allow working from simple precursors, are still in demand.

We have been involved in exploring metal-catalyzed transformation for the synthesis of heterocyclic structures¹⁶ including strategies based on C–H bond functionalization and C–N bond formation.¹⁷ Focusing on copper-catalyzed aerobic transformations¹⁸ we reported a direct synthesis of benzimidazoles in which a single catalytic system promoted a Chan–Lam–Evans N-arylation¹⁹ and a C–H activation/C–N bond-forming process in a tandem way and developed an oxidative

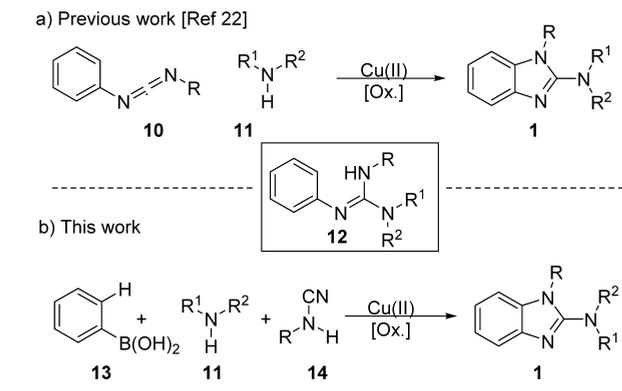
Scheme 1. Major Disconnections for the Synthesis of 2-Aminated Benzimidazoles and Quinazolines



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copper promoted three-component synthesis of N,N',N'' trisubstituted guanidines.²⁰ With this multicomponent reaction in hand, we became interested in performing a cyclizative postfunctionalization²¹ to build 2-aminated benzimidazoles. On the basis of Bao's elegant one-pot synthesis of benzimidazoles using carbodiimides as precursor and involving a discrete guanidine (**12**) as intermediate (Scheme 2a),²² we anticipated

Scheme 2. Copper-Catalyzed Three-Component Synthesis of 2-Aminobenzimidazoles



that copper should be a suitable promotor for the postfunctionalization and decided to explore whether 2-aminated benzimidazoles could be directly obtained from cyanamides in a multicomponent cascades reaction using a single catalyst (Scheme 2b).

From this study, we now report conditions allowing the construction of 2-aminated benzimidazoles or quinazolines, depending on the substitution of the cyanamide, through an aerobic copper-promoted three-component reaction involving amines, arylboronic acids, and cyanamides.²³

RESULTS AND DISCUSSION

We began to evaluate the reaction by reacting *p*-tolyl boronic acid (**13a**), piperidine (**11a**), and *p*-tolylcyanamide (**14a**) under the conditions previously established for the three-component synthesis of *N*-arylated guanidines [Table 1, entry 1]. Delightfully, the expected benzimidazole could be isolated in 63% yield upon extending the reaction time from 0.5 h to 24 h. Further evaluation led to the following conclusion (Table 1): K_2CO_3 proved to be clearly superior to stronger bases such as CS_2CO_3 or *t*-BuOK and its stoichiometry was best established as 2.25 equiv even if reducing its amount to 1.5 equiv only marginally affected the yield. Several additives/ligands have been evaluated: (1,10-phenanthroline (Phen), 2,2'-bipyridine (BiPy), triphenylphosphine oxide, *N,N'*-dimethylethylenediamine, *N*-methylimidazole), and we found that BiPy was the most effective. Reactions performed under air instead of an O_2 atmosphere (entry 11) or with 2 equiv of copper under anaerobic conditions (N_2 atmosphere, entry 16) resulted in low yields. We also noticed that a temperature of 100 °C was necessary to induce the cyclization step. Indeed, at 50 °C, the reaction stalled at the guanidine stage and degradation was observed over extended time. Using $Cu(OAc)_2$ in place of $CuCl_2 \cdot H_2O$ (entry 17) or lowering the amount of $CuCl_2 \cdot H_2O$ to 7.5 mol % (entry 15) reduced the outcome of the reaction. Finally, as in many multicomponent reactions, the ratio between the reacting partners had an influence and 1.5/1.0/1.5 (**13a**/**11a**/**14a**) was found to be optimal for the reaction.

Table 1. Copper-Catalyzed Three-Component Domino Process: Survey of Reaction Conditions

entry	13a (equiv)	11a (equiv)	ligand	base	yield (%) ^b
1	1.5	1.5	BiPy	K_2CO_3	63
2 ^c	1.5	1.5	BiPy	K_2CO_3	60
3	1.5	1.5	BiPy	–	30
4	1.5	1.5	BiPy	CS_2CO_3	10
5	1.5	1.5	BiPy	<i>t</i> -BuOK	5
6	1.5	1.5	–	–	20
7 ^c	1.0	1.0	Phen	K_2CO_3	56
8 ^c	1.0	1.0	$O=PPh_3$	K_2CO_3	30
9 ^c	1.5	1.5	<i>N,N'</i> -dimethylethylenediamine	K_2CO	36
10	1.5	1.5	<i>N</i> -methylimidazole	K_2CO_3	59
11 ^d	1.5	1.5	BiPy	K_2CO_3	42
12 ^e	1.0	1.0	BiPy	K_2CO_3	63
13 ^e	1.0	1.5	BiPy	K_2CO_3	48
14 ^e	1.5	1.0	BiPy	K_2CO_3	82
15 ^{ef}	1.5	1.0	BiPy	K_2CO_3	37
16 ^{eg}	1.5	1.0	BiPy	K_2CO_3	14
17 ^{eh}	1.5	1.0	BiPy	K_2CO_3	72

^aGeneral conditions: $CuCl_2 \cdot H_2O$ (0.2 equiv), ligand (0.2 equiv), base (2.25 equiv), O_2 (1 atm), cyanamide **14a** (1.0 equiv), *p*-tolylboronic acid **13a**, piperidine **11a**, toluene, 100 °C, 24 h. ^bIsolated yield. ^cBase (1.5 equiv). ^dUnder air instead of O_2 at 50 °C for 24 h, then at 100 °C for 24 h. ^e1.5 equiv of cyanamide **14a**. ^fReaction performed with 0.075 equiv of $CuCl_2 \cdot H_2O$ and ligand. ^gReaction performed with 2.0 equiv of $CuCl_2 \cdot H_2O$ and ligand under N_2 . ^h $Cu(OAc)_2$ was used instead of $CuCl_2 \cdot H_2O$.

With suitable conditions in hand [Table 1 entry 14], the scope was investigated (Figure 1).

Various *N*-arylated 2-amino benzimidazoles were prepared from aryl cyanamides as illustrated in Figure 1. The presence of an electron-donating or -withdrawing group at the para-position of arylcyanamides (OMe for **14b** or CF_3 for **14c**) was tolerated in the sequence, but *N*-(4-(trifluoromethyl)phenyl)cyanamide (**14c**) furnished a reduced yield of benzimidazole **1j**. In the latter case, while the intermediate amidine was formed uneventfully, the cyclization step was more sluggish. Using two different aryl groups in the cyanamide and the boronic acid residue resulted in the formation of an isomeric mixture as found with the synthesis of compound **1k** and **1k'**. It should be noted that cyclization on the most electronically enriched arene did predominate. Steric hindrance was clearly detrimental in the reaction, as observed using *o*-tolyl cyanamide (**14d**) and *o*-tolylboronic acid (**13c**) to assemble benzimidazole **1l**, isolated in 36% yield. Increasing the reaction temperature to 130 °C (in xylene) and applying prolonged reaction (48 h) was however necessary to reach this yield. A competitive pathway accounted for the modest yield observed in such case. Indeed, we were able to isolate from the reaction a side product resulting from a Csp^3 -H activation/cyclization process,²⁴ namely 2-amino-1-phenylquinazolin-4(1*H*)-one **15**, albeit in a low 15% yield.

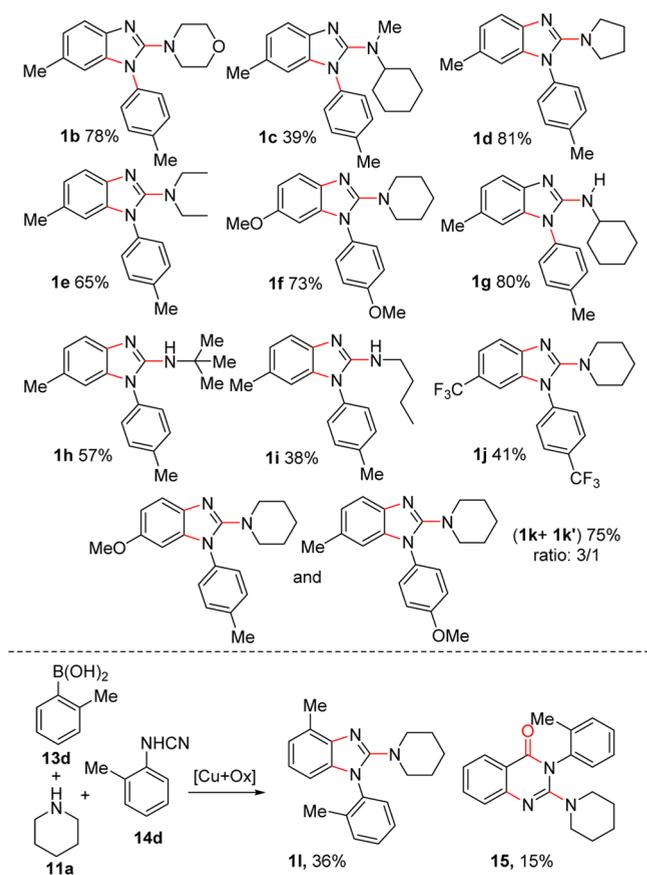
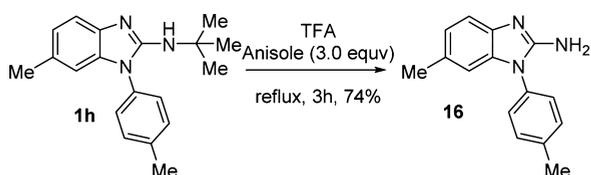


Figure 1. Scope of the Cu-catalyzed synthesis of 2-aminated N_1 -arylbenzimidazoles.

Secondary amines, whether cyclic or acyclic, produced the corresponding 2-amino-benzimidazoles **1b**, **1d**, and **1e** in good yields. A significant but reduced yield of 39% of compound **1c** was obtained when performing the reaction with the relatively crowded N -methylcyclohexylamine. Primary amines can also be engaged in the reaction but proved to be less efficient probably due to the competitive N -dealkylation under oxidative conditions.²⁵ Biologically relevant NH_2 N^1 -aryl-2-aminobenzimidazoles²⁶ could not be directly obtained using aqueous ammonia in the three-component process.²⁷ However, as illustrated in Scheme 3, deprotection of N^2 -*tert*-butyl amino-benzimidazole **1h** was easily achieved by refluxing in trifluoroacetic acid in the presence of anisole, which acts as a butyl cation scavenger.

N -Alkylcyanamides (*n*-propyl, isopropyl, and *tert*-butyl) were not suitable reacting partners for the sequence leading to degradation, even if the intermediate guanidines were properly formed. When benzylcyanamide (**17a**) was used in the sequence, a different outcome occurred, and the anticipated^{15,22}

Scheme 3. Synthesis of 6-Methyl-1-(*p*-tolyl)-1*H*-benzo[*d*]imidazol-2-amine (16**)**



2-aminoquinazoline **2a** was isolated in 36% yield (Figure 2). The yield could not be improved by performing the reaction in

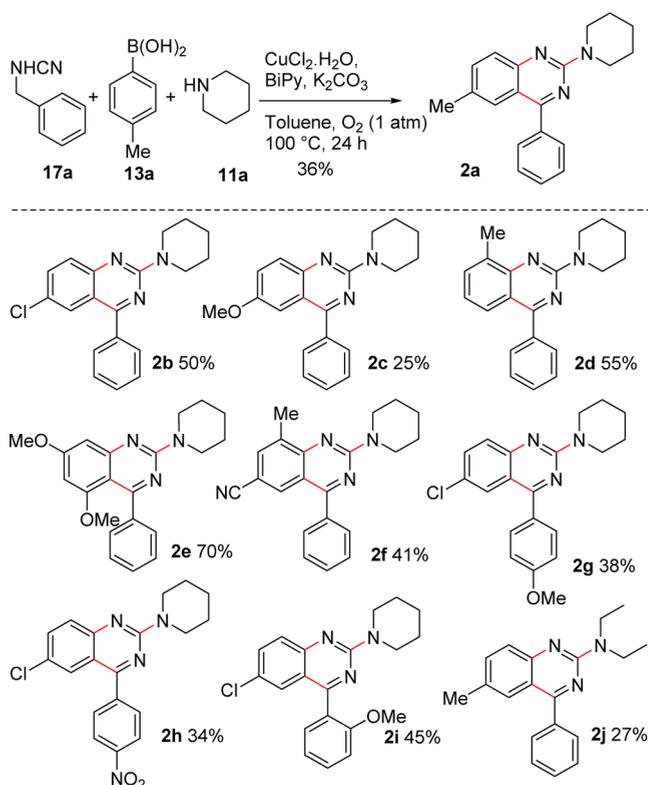


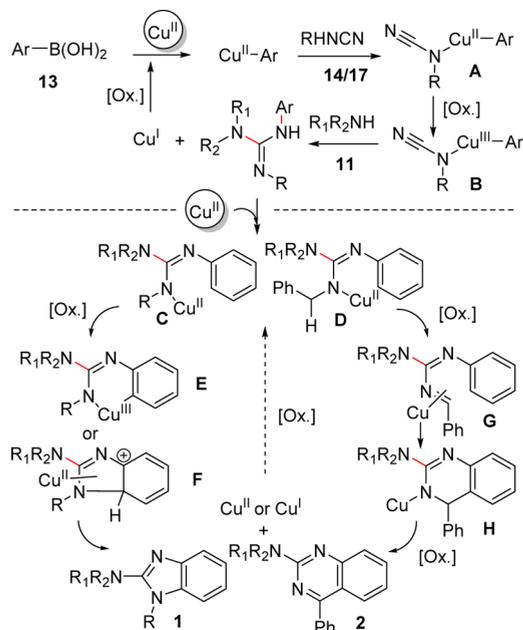
Figure 2. Scope of the Cu-catalyzed synthesis of 4-arylquinazolin-2-amines.

DMF, with or without base, but interestingly when the reaction was run under air, the yield only slightly decreased (32%). Nevertheless, considering that three bonds were formed during the process, such a result represents an average of 70% yield per bond, making the process still valuable.

On the basis of this sequence, other 2-aminoquinazolines could be prepared as shown in Figure 2. The electronic nature and the position of the substituent on the arylboronic acid significantly influence the outcome of the reaction. The presence of an electron-withdrawing group at the para position was beneficial, as can be seen when comparing the results obtained for compounds **2b** and **2c**, isolated in 50% and 25% yields, respectively. Compound **2d** was isolated in 55% yield, demonstrating that ortho-substituted arylboronic acids were not only tolerated but apparently beneficial in the process when compared to the para position. Nevertheless, the electronic/steric picture is not clear, as the highest isolated yield was observed using (3,5-dimethoxyphenyl)boronic acid as reacting species. Interestingly, the presence of an additional cyano group did not interfere in the reaction leading to compound **2f** isolated in a decent yield of 41%. Variation of the amine constituent was possible even if the yield remained rather low (**2j**, 27%). In addition, the reaction was not limited to the sole benzylcyanamide **17a**, as nitro- or methoxy-substituted benzyl cyanamides could also be successfully transformed into their corresponding quinazolines. It should be noted that in all reactions we observed variable amounts of benzaldehyde, accounting for the modest yield obtained.

Mechanism. The mechanism of the overall transformation is not clear, but several facts have been established based on current knowledge²⁸ (Scheme 4): (1) *N*-arylguanidine is clearly

Scheme 4. Possible Reaction Pathway of the Domino Three-Component/C–H Functionalization Process



one intermediate in the reaction, as it can be isolated at the beginning of the reaction or at lower temperature. Such a compound does not result from a sequence of nucleophilic addition of amine to cyanamide followed by a Cu-catalyzed Chan–Lam–Evans type *N*-arylation with boronic acid as established previously.^{20b} (2) Intramolecular cyclization occurs in a distinct subsequent step. In that event, the reaction could be initiated by the formation of a copper complex **C** or **D** through coordination and deprotonation of the guanidine. Activation of the C–H bond and subsequent reductive elimination via intermediate **E** or nucleophilic attack of the arene on the activated copper-bound nitrogen via intermediate **F** followed by aromatization could be invoked for the benzimidazole formation. Oxidation of the copper from state II to state III either by oxygen or by copper itself by disproportionation is probably involved before the intramolecular C–N formation.^{13a} For the quinazoline formation, oxidation of the benzylic position of complex **D** would first furnish imine **G**. Such an oxidation might proceed through a hydrogen atom transfer or a single electron transfer achieved with a copper peroxo species, generated from O₂ and copper.²⁹ A Pictet–Spengler type cyclization, probably assisted by copper, would next lead to 3,4-dihydroquinazoline **H**, which upon oxidative aromatization should deliver the quinazoline and liberate the copper that can re-enter the cycle.

CONCLUSIONS

We have disclosed a novel Cu-catalyzed three-component reaction of arylboronic acids, arylcyanamides, and amines leading to the direct synthesis of 2-aminated benzimidazoles. The analogous reaction performed with benzyl-substituted cyanamides delivered 2-amino quinazolines. The yields of the present transformations ranged from poor to good, but the ease

of the procedure (single step), the inexpensive and relatively ecofriendly catalytic system (O₂ as terminal oxidant), and the readily available precursors should make it attractive, allowing a rapid introduction of three points of diversity.³¹

EXPERIMENTAL SECTION

General Information. Melting points (mp) were obtained in open capillary tubes using a micro melting point apparatus and are uncorrected. Infrared spectra were measured using FT-IR spectrometer and reported in cm⁻¹. High resolution mass spectra were obtained through electrospray ionization using a time-of-flight (TOF) analyzer in a positive-ion or negative-ion detection mode (ES⁺ or ES⁻). NMR spectra are reported relative to residual proton signals in CDCl₃ (δ = 7.26, 77.16) using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, sex. = sextet, m = multiplet, and br = broad resonance. Reagents were obtained from commercial suppliers and solvent routinely dried and/or distilled prior to use. CuCl₂·H₂O > 99.0% was purchased from Sigma-Aldrich. Spectral properties of known products are consistent with literature values.

Synthesis of Cyanamides. Cyanamides were commonly prepared by reacting the corresponding amine with cyanogen bromide (BrCN) either in toluene or in a 1/1 mixture of *tert*-butyl methyl ether/tetrahydrofuran with or without base (NaHCO₃).³⁰

General Procedure for the Preparation 1-Aryl-1*H*-benzo[d]imidazol-2-amines **1 and 4-Arylquinazolin-2-amines **2**.** To a round-bottom flask were added successively cyanamide **14** or **17** (1.5 equiv), CuCl₂·H₂O (0.2 equiv), 2,2'-bipyridine (0.2 equiv), K₂CO₃ (2.25 equiv), and boronic acid **13** (1.5 equiv). The reaction was sealed with a rubber stopper, evacuated, and backfilled with oxygen (balloon). Toluene and amine **11** (1.0 equiv) were added, and the reaction was heated to 100 °C and stirred for 24 h. The reaction mixture was cooled to room temperature, filtered through a glass funnel, and washed with EtOAc. The filtrate was concentrated under reduced pressure to give a residue, which was purified by preparative TLC (SiO₂), using a mixture of 4/1:hept/EtOAc or 20/1/1/1:heptane/EtOAc/MeOH/Et₃N as eluent.

Reactions were performed using 0.2 mmol of amines **11** as limiting reagent in 1 mL of toluene for the synthesis of benzimidazoles and for the synthesis of **2j**. Reactions were performed using 0.25 mmol of amines **11** in 1.5 mL of toluene for the synthesis of quinazolines.

6-Methyl-2-(piperidin-1-yl)-1-(*p*-tolyl)-1*H*-benzo[d]imidazole (1a**).**²² Following the general procedure, the title compound was obtained as a light yellow solid (50 mg, 82%). mp 100–102 °C (lit.: 94–96 °C). ¹H NMR (300 MHz, CDCl₃): δ 7.46 (d, *J* = 8.0 Hz, 1H), 7.32–7.39 (m, 4H), 6.98 (dd, *J* = 8.0, 0.6 Hz, 1H), 6.87 (broad s, 1H), 3.17 (t, *J* = 5.0 Hz, 4H), 2.44 (s, 3H), 2.36 (s, 3H), 1.52 (br s, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 157.15, 139.4, 137.6, 136.1, 134.9, 130.5, 130.3, 125.7, 123.0, 116.7, 108.9, 50.0, 25.3, 24.2, 21.6, 21.2. IR (neat, cm⁻¹): ν 2930, 2835, 1514, 1529, 1396, 1279, 1254, 827, 804.

4-(6-Methyl-1-(*p*-tolyl)-1*H*-benzo[d]imidazol-2-yl)morpholine (1b**).**²² Following the general procedure, the title compound was obtained as light yellow solid (48 mg, 78%). mp 127–129 °C (lit.: 123 °C). ¹H NMR (300 MHz, CDCl₃): δ 7.48 (d, *J* = 7.9 Hz, 1H), 7.33–7.38 (m, 4H), 7.0 (d, *J* = 7.9 Hz, 1H), 6.87 (s, 1H), 3.65 (t, *J* = 4.5 Hz, 4H), 3.21 (t, *J* = 4.5 Hz, 4H), 2.45 (s, 3H), 2.37 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 155.9, 139.1, 138.0, 136.1, 134.3, 131.0, 130.2, 125.8, 123.2, 117.0, 109.0, 66.3, 49.1, 21.6, 21.2. IR (neat, cm⁻¹): ν 2917, 2856, 1610, 1528, 1514, 1402, 1274, 1120, 929, 828, 806.

***N*-Cyclohexyl-*N*,6-dimethyl-1-(*p*-tolyl)-1*H*-benzo[d]imidazol-2-amine (**1c**).** Following the general procedure, the title compound was obtained as a yellow oil (26 mg, 39%). ¹H NMR (300 MHz, CDCl₃): δ 7.44 (d, *J* = 7.9 Hz, 1H), 7.28–7.35 (m, 4H), 6.96 (dd, *J* = 7.9, 1.0 Hz, 1H), 6.78 (s, 1H), 3.32 (tt, *J* = 11.6, 3.5 Hz, 1H), 2.81 (s, 3H), 2.45 (s, 3H), 2.35 (s, 3H), 1.35–1.67 (m, 7 H), 0.93–1.01 (m, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 157.5, 139.6, 137.8, 136.7, 135.4, 130.3, 130.0, 126.4, 122.8, 116.3, 108.8, 59.5, 31.9, 29.5, 25.8, 25.6, 21.5, 21.2. IR (neat, cm⁻¹): ν 2926, 2855, 1595, 1532, 1514, 1400,

1270, 805, 728. HRMS (m/z , ESI⁺) calcd for C₂₂H₂₈N₃ ([M + H]⁺) 334.2283, found 334.2278.

6-Methyl-2-(pyrrolidin-1-yl)-1-(*p*-tolyl)-1*H*-benzo[d]imidazole (1d).^{10c} Following the general procedure, the title compound was obtained as a light yellow solid (47 mg, 81%). mp 139–141 °C (lit.: 135–137 °C). ¹H NMR (300 MHz, CDCl₃): δ 7.38 (d, *J* = 8.2 Hz, 1H), 7.26–7.33 (m, 4H), 6.93 (dd, *J* = 8.1, 0.9 Hz, 1H), 6.66 (s, 1H), 3.28 (qu, *J* = 3.5 Hz, 4H), 2.45 (s, 3H), 2.33 (s, 3H), 1.82 (qu, *J* = 3.5 Hz, 4H). ¹³C NMR (75 MHz, CDCl₃): δ 155.3, 140.08, 138.1, 137.1, 134.7, 130.1, 129.2, 127.5, 122.7, 115.5, 108.6, 49.7, 25.5, 21.5, 21.2. IR (neat, cm⁻¹): ν 2968, 2870, 1597, 1542, 1514, 1408, 1268, 804, 727.

***N,N*-Diethyl-6-methyl-1-(*p*-tolyl)-1*H*-benzo[d]imidazol-2-amine (1e).**²² Following the general procedure, the title compound was obtained as a light yellow oil (38 mg, 65%). ¹H NMR (300 MHz, CDCl₃): δ 7.46 (d, *J* = 8.1 Hz, 1H), 7.29–7.36 (m, 4H), 6.98 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.79 (s, 1H), 3.20 (q, *J* = 7.1 Hz, 4H), 2.45 (s, 3H), 2.36 (s, 3H), 1.04 (t, *J* = 7.1 Hz, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 156.5, 139.7, 137.8, 136.6, 134.9, 130.3, 130.18, 126.4, 122.9, 116.4, 108.8, 44.7, 21.5, 21.2, 12.7. IR (neat, cm⁻¹): ν 3031, 2931, 2862, 1602, 1535, 1514.48, 1404, 1279, 805.

6-Methoxy-1-(4-methoxyphenyl)-2-(piperidin-1-yl)-1*H*-benzo[d]imidazole (1f).²² Following the general procedure, the title compound was obtained as a yellow solid (49 mg, 73%). mp 97–98 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.37–7.47 (m, 3H), 7.05 (br s, 2H), 6.77 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.58 (d, *J* = 2.5 Hz, 1H), 3.88 (s, 3H), 3.74 (s, 3H), 3.13 (t, *J* = 4.7 Hz, 4H), 1.50 (br s, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 158.8, 157.2, 155.3, 136.6, 135.6, 130.0, 127.1, 117.5, 114.9, 109.2, 94.1, 55.9, 55.5, 50.1, 25.3, 24.1. IR (neat, cm⁻¹): ν 2932, 2823, 1617, 1533, 1509, 1401, 1254, 1244, 1031, 924, 814. HRMS (m/z , ESI⁺) calcd for C₁₉H₂₄N₃ ([M + H]⁺) 294.1970, found 294.1963.

***N*-Cyclohexyl-6-methyl-1-(*p*-tolyl)-1*H*-benzo[d]imidazol-2-amine (1g).** Following the general procedure, the title compound was obtained as a yellow solid (51 mg, 80%). mp 71–73 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.37–7.40 (m, 3H), 7.26–7.30 (m, 2H), 6.92 (dd, *J* = 7.9, 0.9 Hz, 1H), 6.70 (s, 1H), 3.89–4.01 (m, 2H: 1 CH and NH), 2.47 (s, 3H), 2.34 (s, 3H), 2.08–2.13 (m, 2 H), 1.58–1.72 (m, 3H), 1.37–1.50 (m, 2H), 1.07–1.19 (m, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 152.8, 140.5, 138.7, 135.4, 132.2, 131.0, 129.2, 126.8, 122.5, 115.6, 108.1, 51.5, 33.7, 25.6, 24.8, 21.2, 21.2. IR (neat, cm⁻¹): ν 2927, 2854, 1600, 1555, 1516, 1261, 805. HRMS (m/z , ESI⁺) calcd for C₂₁H₂₆N₃ ([M + H]⁺) 320.2127, found 320.2136.

***N*-(*tert*-Butyl)-6-methyl-1-(*p*-tolyl)-1*H*-benzo[d]imidazol-2-amine (1h).**²² Following the general procedure, the title compound was obtained as a yellow waxy solid (33 mg, 57%). ¹H NMR (300 MHz, CDCl₃): δ 7.37–7.44 (m, 3H), 7.27 (d, *J* = 8.1 Hz, 2H), 6.93 (dd, *J* = 7.3, 0.6 Hz, 1H), 6.69 (s, 1H), 4.04 (s, NH), 2.47 (s, 3H), 2.35 (s, 3H), 1.48 (s, 9H). ¹³C NMR (75 MHz, CDCl₃): δ 151.9, 140.9, 138.7, 134.9, 132.5, 131.0, 129.2, 127.1, 122.3, 116.0, 108.05, 51.96, 29.38, 21.44, 21.21. IR (neat, cm⁻¹): ν 3417, 2964, 2921, 1599, 1551, 1515, 1366, 1204, 805, 730.

***N*-Butyl-6-methyl-1-(*p*-tolyl)-1*H*-benzo[d]imidazol-2-amine (1i).** Following the general procedure, the title compound was obtained as a purple waxy solid (22 mg, 38%). ¹H NMR (300 MHz, CDCl₃): δ 7.37–7.40 (m, 3H), 7.29 (d, *J* = 8.3 Hz, 2H), 6.93 (d, *J* = 7.9 Hz, 1H), 6.71 (s, 1H), 4.09 (s, NH), 3.50 (q, *J* = 7.0 Hz, 2H), 2.46 (s, 3H), 2.35 (s, 3H), 1.60 (qu, *J* = 7.3 Hz, 2H), 1.36 (sex., *J* = 7.3 Hz, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 153.5, 140.4, 138.8, 135.5, 132.2, 131.0, 129.4, 126.8, 122.5, 115.8, 108.2, 43.0, 31.9, 21.5, 21.2, 20.0, 13.8. IR (neat, cm⁻¹): ν 2957, 2925, 2963, 1601, 1559, 1516, 1482, 1278, 1258, 804. HRMS (m/z , ESI⁺) calcd for C₁₉H₂₄N₃ ([M + H]⁺) 294.1970, found 294.1957.

2-(Piperidin-1-yl)-6-(trifluoromethyl)-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazole (1j). Following the general procedure, the title compound was obtained as a white solid (34 mg, 41%). mp 142–143 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.86 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.26 (s, 1H), 3.21 (m, 4H), 1.55 (m, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 158.4, 144.3, 140.1, 135.1, 130.5 (q, *J* =

34.5 Hz, C_{CF₃}), 127.7, 126.3, 125.1 (q, *J* = 269.2 Hz, C_{Ar-CF₃}), 123.7 (q, *J* = 272.5 Hz, C_{Ar-CF₃}), 123.4 (q, *J* = 32.3 Hz, C_{CF₃}), 120.1, 117.5, 105.9, 50.2, 25.2, 23.9. IR (neat, cm⁻¹): ν 2962, 2855, 1616, 1541, 1454, 1324, 1259, 1058, 1008, 793, 737. HRMS (m/z , ESI⁺) calcd for C₂₀H₁₇F₆N₃ ([M + H]⁺) 414.1414, found 414.1394.

1-(4-Methoxyphenyl)-6-methyl-2-(piperidin-1-yl)-1*H*-benzo[d]imidazole and 6-Methoxy-2-(piperidin-1-yl)-1-(*p*-tolyl)-1*H*-benzo[d]imidazole (1k/1k'). Following the general procedure, a mixture of the title compounds was obtained as a white waxy solid (48 mg, 75%). ¹H NMR (300 MHz, CDCl₃): δ 7.44–7.48 (m, 0.8H), 7.31–7.40 (m, 3.2H), 7.02–7.07 (m, 0.8 H), 6.97 (dd, *J* = 8.1, 1.0 Hz, 0.2H), 6.83 (s, 0.2H), 6.78 (dd, *J* = 8.7, 2.4 Hz, 0.8 H), 6.62 (d, *J* = 2.4 Hz, 0.8 H), 3.88 (s, 0.8H), 3.75 (s, 2.2H), 3.14–3.18 (m, 4H), 2.44 (s, 2.2H), 2.36 (s, 0.8H), 1.51 (br, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 158.8, 157.25, 157.1, 155.3, 139.3, 137.6, 136.4, 136.3, 135.8, 134.7, 130.5, 130.3, 130.2, 127.2, 125.6, 122.9, 117.5, 116.7, 114.8, 109.3, 108.8, 94.3, 55.9, 55.5, 50.1, 50.0, 25.3, 25.3, 24.1, 21.6, 21.2. IR (neat, cm⁻¹): ν 2935, 2831, 1618, 1597, 1534, 1513, 1482, 1399, 1273, 1255, 1212, 1160, 1032, 924, 817, 728. HRMS (m/z , ESI⁺) calcd for C₂₀H₂₄N₃O ([M + H]⁺) 322.1919, found 322.1918.

4-Methyl-2-(piperidin-1-yl)-1-(*o*-tolyl)-1*H*-benzo[d]imidazole (1l).²² Following the general procedure (using xylene as solvent and reaction temperature of 130 °C), the title compound was obtained as a light yellow waxy solid (22 mg, 36%). ¹H NMR (300 MHz, CDCl₃): δ 7.26–7.41 (m, 4H), 6.89–6.99 (m, 2H), 6.60 (d, *J* = 7.7 Hz, 1H), 3.15–3.33 (m, 4H), 2.65 (s, 3H), 2.11 (s, 3H), 1.43–1.51 (m, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 156.94, 140.8, 136.5, 135.9, 135.6, 131.5, 128.6, 128.1, 127.2, 126.9, 122.4, 120.4, 106.4, 49.7, 25.47, 24.2, 17.8, 16.7. IR (neat, cm⁻¹): ν 2934, 2852, 1605, 1531, 1452, 1399, 1291, 919, 745.

2-(Piperidin-1-yl)-3-(*o*-tolyl)quinazolin-4(3*H*)-one (15). Following the general procedure, the title compound was obtained as a white solid (9.5 mg, 15%). mp 142–143 °C. ¹H NMR (300 MHz, CDCl₃): δ 8.18 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.67 (dt, *J* = 7.9, 1.6 Hz, 1H), 7.53 (d, *J* = 7.9, 1H), 7.35–7.25 (m, 5H), 3.16 (m, 2H), 3.06 (m, 2H), 2.11 (s, 3H), 1.40 (m, 2H), 1.24 (m, 4H). ¹³C NMR (75 MHz, CDCl₃): δ 164.1, 155.3, 148.4, 137.2, 135.7, 134.6, 131.3, 129.8, 128.5, 127.5, 126.5, 126.0, 124.6, 119.4, 50.6, 25.3, 24.3, 18.1. IR (neat, cm⁻¹): ν 2934, 2851, 1682, 1609, 1578, 1560, 1464, 1552, 1370, 1305, 1256, 1240, 1105, 1000, 906, 882, 767, 728. HRMS (m/z , ESI⁻) calcd for C₂₀H₂₁N₃O ([M - H]⁻) 318.1612, found 318.1652.

6-Methyl-1-(*p*-tolyl)-1*H*-benzo[d]imidazole-2-amine (16).^{9d} To a round-bottom flask were added benzimidazole 1h (59 mg, 0.20 mmol), TFA (3 mL), and anisole (70 μL, 0.6 mmol, 3.0 equiv), and the mixture was heated at reflux for 3 h. After cooling to room temperature, the reaction was diluted with dichloromethane, concentrated under vacuum, and purified by flash column chromatography (SiO₂, AcOEt) to deliver the title compound as a light brown solid (35 mg, 74%). mp 116–118 °C (lit.: 108–109 °C). ¹H NMR (300 MHz, CDCl₃): δ 7.39 (d, *J* = 7.1 Hz, 2H), 7.31–7.29 (m, 2H), 6.98 (d, *J* = 7.1 Hz, 1H), 6.75 (s, 1H), 2.45 (s, 3H), 2.34 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 152.8, 139.3, 132.1, 131.7, 131.2, 130.4, 126.8, 123.4, 122.9, 115.7, 109.1, 21.7, 21.4. IR (neat, cm⁻¹): ν 2924, 1670, 1517, 1452, 1263, 1037, 806, 732.

6-Methyl-4-phenyl-2-(piperidin-1-yl)quinazoline (2a).²² Following the general procedure, the title compound was obtained as a yellow solid (27 mg, 36%). mp 109–110 °C (lit.: 108–109 °C). ¹H NMR (300 MHz, CDCl₃): δ 7.73–7.76 (m, 2H), 7.52–7.57 (m, 5H), 7.46 (dd, *J* = 8.7, 1.7 Hz, 1H), 3.96 (t, *J* = 5.7 Hz, 4H), 2.37 (s, 3H), 1.63–1.68 (m, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 168.2, 158.6, 152.2, 138.3, 135.4, 131.2, 129.8, 129.3, 128.2, 125.9, 125.9, 117.3, 45.0, 25.9, 25.0, 21.3. IR (neat, cm⁻¹): ν 2930, 2851, 1543, 1474, 1441, 1250, 1228, 1127, 961, 827, 730, 699.

6-Chloro-4-phenyl-2-(piperidin-1-yl)quinazoline (2b).²² Following the general procedure, the title compound was obtained as a yellow solid (40 mg, 50%). mp 125–126 °C (lit.: 116–117 °C). ¹H NMR (300 MHz, CDCl₃): δ 7.74–7.73 (m, 1H), 7.71–7.67 (m, 2H), 7.56–7.50 (m, 5H), 3.96–3.95 (m, 4H), 1.66–1.22 (m, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 168.5, 158.9, 152.6, 138.6, 137.7, 134.2,

130.0, 129.9, 128.6, 127.9, 126.2, 117.9, 45.2, 26.2, 25.1. IR (neat, cm^{-1}): ν 2934, 1562, 1542, 1459–1444, 1250, 1024, 960, 834, 733, 700.

6-Methoxy-4-phenyl-2-(piperidin-1-yl)quinazoline (2c).²²

Following the general procedure, the title compound was obtained as a yellow solid (20 mg, 25%). mp 75–77 °C. ¹H NMR (300 MHz, CDCl_3): δ 7.76–7.73 (m, 2H), 7.58–7.50 (m, 4H), 7.31 (dd, J = 8.9, 2.8 Hz, 1H), 7.14 (d, J = 2.8 Hz, 1H), 3.93–3.91 (m, 4H), 3.74 (s, 3H), 1.65–1.62 (m, 6H). ¹³C NMR (75 MHz, CDCl_3): δ 167.6, 158.5, 154.6, 150.0, 138.6, 129.8, 129.6, 128, 127.9, 125.7, 117.6, 105.5, 55.7, 45.2, 26.1, 25.2. IR (neat, cm^{-1}): ν 2929–2853, 1580–1546, 1477–1411, 1253–1216, 1030, 792–661. HRMS (m/z , ESI^+) calcd for $\text{C}_{20}\text{H}_{22}\text{N}_3\text{O}$ ($[\text{M} + \text{H}]^+$) 320.1763, found 320.1751.

8-Methyl-4-phenyl-2-(piperidin-1-yl)quinazoline (2d). Following the general procedure, the title compound was obtained as a yellow solid (42 mg, 55%). mp 118–120 °C. ¹H NMR (300 MHz, CDCl_3): δ 7.73–7.72 (m, 2H), 7.65–7.62 (m, 1H), 7.50–7.46 (m, 4H), 6.98 (dd, J = 7.4 Hz, 1H), 3.98 (m, 4H), 2.6 (s, 3H), 1.68 (m, 6H). ¹³C NMR (75 MHz, CDCl_3): δ 169.4, 158.4, 152.9, 138.7, 134.3, 133.1, 130.1, 129.5, 128.4, 125.1, 121.3, 117.2, 45.2, 26.1, 25.3, 17.7. IR (neat, cm^{-1}): ν 3002–2850, 1609–1551, 1258, 1023, 853–698. HRMS (m/z , ESI^+) calcd for $\text{C}_{20}\text{H}_{21}\text{N}_3$ ($[\text{M} + \text{H}]^+$) 304.1774, found 304.1780.

5,7-Dimethoxy-4-phenyl-2-(piperidin-1-yl)quinazoline (2e).

Following the general procedure, the title compound was obtained as a yellow solid (61 mg, 70%). mp 120–122 °C. ¹H NMR (300 MHz, CDCl_3): δ 7.50–7.47 (m, 2H), 7.39–7.36 (m, 3H), 6.61 (s, 1H), 6.08 (s, 1H), 3.93–3.90 (m, 4H), 3.89 (s, 3H), 3.47 (s, 3H), 1.64–1.60 (m, 6H). ¹³C NMR (75 MHz, CDCl_3): δ 167.0, 164.6, 158.8, 158.3, 157.5, 142.6, 128.8, 128.2, 127.1, 105.9, 97.7, 95.1, 55.7, 55.1, 44.9, 26.1, 25.1. IR (neat, cm^{-1}): ν 2928–2851, 1614, 1571–1541, 1392, 1274–1206, 828, 697. HRMS (m/z , ESI^+) calcd for $\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_2$ ($[\text{M} + \text{H}]^+$) 350.1842, found 350.1830.

8-Methyl-4-phenyl-2-(piperidin-1-yl)quinazoline-6-carbonitrile (2f). Following the general procedure, the title compound was obtained as a yellow solid (34 mg, 41%). mp 138–140 °C. ¹H NMR (300 MHz, CDCl_3): δ 8.02 (s, 1H), 7.70–7.69 (m, 2H), 7.6–7.57 (m, 3H), 4.06–4.04 (m, 4H), 2.62 (s, 3H), 1.76–1.70 (m, 6H). ¹³C NMR (75 MHz, CDCl_3): δ 170.2, 158.9, 154.9, 137.3, 136.0, 133.3, 132.0, 130.4, 129.9, 128.8, 119.9, 116.3, 103.5, 45.2, 26.2, 25.1, 17.6. IR (neat, cm^{-1}): ν 2961–2853, 2223, 1551, 1258, 1082–1013, 791. HRMS (m/z , ESI^+) calcd for $\text{C}_{21}\text{H}_{20}\text{N}_4$ ($[\text{M} + \text{H}]^+$) 329.1766, found 329.1770.

6-Chloro-4-(4-methoxyphenyl)-2-(piperidin-1-yl)quinazoline (2g). Following the general procedure, the title compound was obtained as a yellow solid (33 mg, 38%). mp 158–160 °C. ¹H NMR (300 MHz, CDCl_3): δ 7.79 (s, 1H), 7.70 (d, J = 8.7 Hz, 2H), 7.51 (m, 2H), 7.04 (d, J = 8.7 Hz, 1H), 3.95–3.93 (m, 4H), 3.88 (s, 3H), 1.66–1.63 (m, 6H). ¹³C NMR (75 MHz, CDCl_3): δ 167.9, 161.3, 158.9, 152.6, 134.1, 131.6, 130.2, 127.9, 126.7, 126.2, 118.0, 114.1, 55.7, 45.1, 26.2, 25.2. IR (neat, cm^{-1}): ν 3003–2851, 1608–1539, 1458, 1247, 1028, 829. HRMS (m/z , ESI^+) calcd for $\text{C}_{20}\text{H}_{20}\text{ClN}_3\text{O}$ ($[\text{M} + \text{H}]^+$) 354.1373, found 354.1375. calcd for $\text{C}_{20}\text{H}_{20}\text{ClN}_3\text{O}$ ($[\text{M} + \text{H}]^+$) 356.1350, found 356.1347.

6-Chloro-4-(4-nitrophenyl)-2-(piperidin-1-yl)quinazoline (2h). Following the general procedure, the title compound was obtained as a yellow solid (31 mg, 34%). mp 139–140 °C. ¹H NMR (300 MHz, CDCl_3): δ 8.34 (d, J = 8.7 Hz, 2H), 7.81 (d, J = 8.7 Hz, 2H), 7.54–7.47 (m, 3H), 3.89–3.86 (m, 4H), 1.67–1.55 (m, 6H). ¹³C NMR (75 MHz, CDCl_3): δ 166.1, 158.6, 152.7, 148.8, 143.7, 134.8, 130.8, 128.3, 127.5, 125.1, 123.9, 117.4, 45.2, 26.12, 25.0. IR (neat, cm^{-1}): ν 2923, 2852, 1566, 1542, 1459, 1348, 1250, 1015, 775. HRMS (m/z , ESI^+) calcd for $\text{C}_{19}\text{H}_{17}\text{ClN}_3\text{O}_2$ ($[\text{M} + \text{H}]^+$) 369.1118, found 369.1117. calcd for $\text{C}_{19}\text{H}_{17}\text{ClN}_3\text{O}_2$ ($[\text{M} + \text{H}]^+$) 371.1122, found 371.1115.

6-Chloro-4-(2-methoxyphenyl)-2-(piperidin-1-yl)quinazoline (2i). Following the general procedure, the title compound was obtained as a yellow solid (40 mg, 45%). mp 123–125 °C. ¹H NMR (300 MHz, CDCl_3): δ 7.50–7.47 (m, 3H), 7.37–7.30 (m, 2H), 7.12–7.02 (m, 2H), 3.93–3.89 (m, 4H), 3.73 (s, 3H), 1.64–1.60 (m, 6H). ¹³C NMR (75 MHz, CDCl_3): δ 167.7, 159.2, 157.1, 151.5, 134.0,

131.0, 127.6, 127.1, 126.6, 126.5, 121.1, 119.2, 111.6, 55.7, 45.2, 26.1, 25.1. IR (neat, cm^{-1}): ν 2927–2852, 1568–1541, 1444, 1250, 1020, 794, 750. HRMS (m/z , ESI^+) calcd for $\text{C}_{20}\text{H}_{20}\text{ClN}_3\text{O}$ ($[\text{M} + \text{H}]^+$) 354.1355, found 354.1364. calcd for $\text{C}_{20}\text{H}_{20}\text{ClN}_3\text{O}$ ($[\text{M} + \text{H}]^+$) 356.1377, found 356.1371.

6-Methyl-N,N-diethyl-4-phenylquinazolin-2-amine (2j).²²

Following the general procedure, the title compound was obtained as a yellow solid (16 mg, 27%). mp 80–82 °C (lit.: 83–84 °C). ¹H NMR (300 MHz, CDCl_3): δ 7.74–7.71 (m, 2H), 7.54–7.41 (m, 6H), 3.77 (q, J = 6.8 Hz, 4H), 2.34 (s, 3H), 1.26–1.21 (t, J = 7.1 Hz, 6H). ¹³C NMR (75 MHz, CDCl_3): δ 168.2, 158.2, 152.7, 138.6, 135.4, 130.9, 130.0, 129.4, 128.4, 127.0, 126.1, 126.0, 117.3, 41.8, 21.5, 13.2. IR (neat, cm^{-1}): ν 2934, 1562, 1542, 1459–1444, 1250, 831, 700.

ASSOCIATED CONTENT

Supporting Information

Copies of ¹H and ¹³C NMR spectra of each benzimidazole and quinazoline. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00614.

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Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930.
- (2) For a monograph, see: (a) Alamgir, M.; Black, D. St. C.; Kumar, N. *Synthesis, Reactivity and Biological Activity of Benzimidazoles. In Topics In Heterocyclic Chemistry*; Springer: Berlin, Germany, 2007; Vol. 9, pp 87–118. (b) Carvalho, L. C. R.; Fernandes, E.; Marques, M. M. B. *Chem.—Eur. J.* **2011**, *17*, 12544–12555. (c) Bansal, Y.; Silakari, O. *Bioorg. Med. Chem.* **2012**, *20*, 6208–6236.
- (3) Khan, I.; Ibrar, A.; Ahmed, W.; Saeed, A. *Eur. J. Med. Chem.* **2015**, *90*, 124–169.
- (4) Cooper, D. G.; Young, R. C.; Durant, G. J.; Gamelline, C. R. In *Comprehensive Medicinal Chemistry*; Hansch, C., Sammes, P. G., Taylor, J. B., Eds.; Pergamon Press: Oxford, UK, 1990; Vol. 3, p 323.
- (5) Campbell, S. F.; Davey, M. J.; Hardstone, J. D.; Lewis, B. N.; Palmer, M. J. *J. Med. Chem.* **1987**, *30*, 49–57.
- (6) For a monograph, see: (a) *Modern Nucleophilic Aromatic Substitution*; Terrier, F., Ed.; Wiley-VCH: Weinheim, 2013. (b) Barrett, I. C.; Kerr, M. A. *Tetrahedron Lett.* **1999**, *40*, 2439–2442. (c) Kawasaki, I.; Taguchi, N.; Yoneda, Y.; Yamashita, M.; Ohta, S. *Heterocycles* **1996**, *43*, 1375–1379. (d) Martínez-Vituro, C. M.; Domínguez, D. J. *Heterocycl. Chem.* **2007**, *44*, 1035–1043.
- (7) For a recent example, see: Deasy, R. E.; Slattery, C. N.; Maguire, A. R. *J. Org. Chem.* **2014**, *79*, 3688–3695.
- (8) For reviews involving copper, see: (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449. (b) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954–6971. (c) Liu, T.; Fu, H. *Synthesis* **2012**, *44*, 2805–2824. For reviews involving palladium, see: (d) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534–1544. (e) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27–50.
- (9) Selected examples. For benzimidazoles, see: (a) Rivas, F. M.; Giessert, A. J.; Diver, S. T. *J. Org. Chem.* **2002**, *67*, 1708–1711. (b) Evidar, G.; Batey, R. A. *Org. Lett.* **2003**, *5*, 133–136. (c) Wang

- F.; Cai, S.; Liao, Q.; Xi, C. *J. Org. Chem.* **2011**, *76*, 3174–3180.
- (d) Ramana, T.; Punniyamurthy, T. *Chem.—Eur. J.* **2012**, *18*, 13279–13283. (e) Vlaar, T.; Cioc, R. C.; Mampuy, P.; Maes, B. U. W.; Orru, R. V. A.; Ruijter, E. *Angew. Chem., Int. Ed.* **2012**, *51*, 13058–13061. For quinazolines, see: (f) Huang, X.; Yang, Y.; Qiao, R.; Zhao, Y. *Synthesis* **2009**, 2679–2688. (g) Liu, Q.; Zhao, Y.; Fu, H.; Cheng, C. *Synlett.* **2013**, *24*, 2089–2094.
- (10) (a) Yang, D. S.; Fu, H.; Hu, L. M.; Jiang, Y. Y.; Zhao, Y. F. *J. Org. Chem.* **2008**, *73*, 7841–7844. (b) Deng, X. H.; McAllister, H.; Mani, N. S. *J. Org. Chem.* **2009**, *74*, 5742–5745. (c) Lv, X.; Bao, W. *J. Org. Chem.* **2009**, *74*, 5618–5621. (d) Deng, X. H.; Mani, N. S. *Eur. J. Org. Chem.* **2010**, 680–686. (e) Jin, H.; Xu, X.; Gao, J.; Zhong, J.; Wang, Y. *Adv. Synth. Catal.* **2010**, *352*, 347–350. (f) Shen, G.; Bao, W. *Adv. Synth. Catal.* **2010**, *352*, 981–986. (g) Wang, F.; Cai, S.; Liao, Q.; Xi, C. *J. Org. Chem.* **2011**, *76*, 3174–3180.
- (11) For a monograph, see: (a) C–H Activation. In *Topics in Current Chemistry*; Yu, J.-Q., Shi, Z., Eds.; Springer: New York, 2010; Vol. 292, pp 1–380. (b) For selected reviews, see: Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740–4761. (c) Cho, S.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068–5083. (d) Stokes, B. J.; Driver, T. G. *Eur. J. Org. Chem.* **2011**, 4071–4088. (e) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960–9009. (f) Hickman, A.; Sanford, M. S. *Nature* **2012**, *484*, 177–185. (g) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236–10254. (h) For metal-free C–H functionalization processes, see: Samanta, R.; Matcha, K.; Antonchick, A. P. *Eur. J. Org. Chem.* **2013**, 5769–5804.
- (12) Guo, X.-X.; Gu, D.-W.; Wu, Z.; Zhang, W. *Chem. Rev.* **2015**, *115*, 1622–1651.
- (13) (a) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932–1934. (b) Masters, K.-S.; Rauws, T. R. M.; Yadav, A. K.; Herrebout, W. A.; van der Veken, B.; Maes, B. U. W. *Chem.—Eur. J.* **2011**, *17*, 6315–6320. (c) Lv, Y.; Li, Y.; Xiong, T.; Pu, W.; Zhang, H.; Sun, K.; Liu, Q.; Zhang, Q. *Chem. Commun.* **2013**, 49, 6439–6441.
- (14) (a) Wang, Q.; Schreiber, S. L. *Org. Lett.* **2009**, *11*, 5178–5180. (b) Yang, D.; An, B.; Wei, W.; Tian, L.; Huang, B.; Wang, H. *ACS Comb. Sci.* **2015**, *17*, 113–119. For a related process involving copper nanoparticles, see: (c) Satish, G.; Harsha Vardhan Reddy, K.; Anil, B. S. P.; Shankar, J.; Uday Kumar, R.; Nageswar, Y. V. D. *Tetrahedron Lett.* **2014**, *55*, 5533–5538.
- (15) Selected metal-free C–H functionalization processes: (a) Xue, D.; Long, Y.-Q. *J. Org. Chem.* **2014**, *79*, 4727–4734. (b) Lin, J.-P.; Zhang, F.-H.; Long, Y.-Q. *Org. Lett.* **2014**, *16*, 2822–2825. (c) Yan, Y. Z.; Zhang, Y. H.; Feng, C. T.; Zha, Z. G.; Wang, Z. Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 8077–8081. (d) Yan, Y. Z.; Wang, Z. Y. *Chem. Commun.* **2011**, *47*, 9513–9515.
- (16) (a) Pinto, A.; Jia, Y.; Neuville, L.; Zhu, J. *Chem.—Eur. J.* **2007**, *13*, 961–967. (b) Salcedo, A.; Neuville, L.; Rondot, C.; Retailleau, P.; Zhu, J. *Org. Lett.* **2008**, *10*, 857–860.
- (17) (a) Pinto, A.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 3291–3295. (b) Gerfaud, T.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 572–577. (c) Jaegli, S.; Dufour, J.; Wei, H.-L.; Piou, T.; Duan, X.-H.; Vors, J.-P.; Neuville, L.; Zhu, J. *Org. Lett.* **2010**, *12*, 4498–4501. (d) Piou, T.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 11561–11565.
- (18) For reviews, see: (a) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062–11087. (b) Campbell, A. N.; Stahl, S. S. *Acc. Chem. Res.* **2012**, *45*, 851–863. (c) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381–3429.
- (19) For reviews, see: (a) Qiao, J. X.; Lam, P. Y. S. *Synthesis* **2011**, 829–856. (b) Rao, K. S.; Wu, T.-S. *Tetrahedron* **2012**, *68*, 7735–7754. Selected recent examples: (c) Racine, E.; Monnier, F.; Vors, J.-P.; Taillefer, M. *Chem. Commun.* **2013**, 49, 7412–7414. (d) Huang, F.; Quach, T. D.; Batey, R. A. *Org. Lett.* **2013**, *15*, 3058–3061. (e) Moon, S.-Y.; Nam, J.; Rathwell, K.; Kim, W.-S. *Org. Lett.* **2014**, *16*, 338–341. (f) El Khatib, M.; Molander, G. A. *Org. Lett.* **2014**, *16*, 4944–4947.
- (20) (a) Li, J.; Bénard, S.; Neuville, L.; Zhu, J. *Org. Lett.* **2012**, *14*, 5980–5983. For related sequences, see: (b) Li, J.; Neuville, L. *Org. Lett.* **2013**, *15*, 1752–1755. (c) Li, J.; Neuville, L. *Org. Lett.* **2013**, *15*, 6124–6127.
- (21) (a) Marcaccini, S.; Torroba, T. In *Multicomponent Reaction*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005; pp 33–75. (b) Akritopoulou-Zanze, I.; Djuric, S. W. *Heterocycles* **2007**, *73*, 125–147.
- (22) He, H.-F.; Wang, Z.-J.; Bao, W. *Adv. Synth. Catal.* **2010**, *352*, 2905–2912.
- (23) Larraufie, M.-H.; Maestri, G.; Malacria, M.; Ollivier, C.; Fensterbank, L.; Lacôte, E. *Synthesis* **2012**, *44*, 1279–1292.
- (24) (a) Li, Y.; Li, Z.; Xiong, T.; Zhang, Q.; Zhang, X. *Org. Lett.* **2012**, *14*, 3522–3525. (b) Zhang, M.; Zhang, A.-Q.; Peng, Y. *J. Organomet. Chem.* **2013**, *723*, 224–232.
- (25) (a) Mahapatra, S.; Halfen, J. A.; Wilkinson, E. C.; Pan, G.; Wang, X.; Young, V. G.; Cramer, C. J.; Que, L.; Tolman, W. B. *J. Am. Chem. Soc.* **1996**, *118*, 11555–11574. (b) Mahapatra, S.; Halfen, J. A.; Tolman, W. B. *J. Am. Chem. Soc.* **1996**, *118*, 11575–11586.
- (26) Ding, K.; Wang, A.; Boerneke, M. A.; Dibrov, S. M.; Hermann, T. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3113–3117.
- (27) Alternative preparation of N¹-arylated 2-aminobenzimidazoles, see: (a) Ueda, S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 10364–10367. (b) Rao, N.; Rasheed, S.; Vishwakarma, R. A.; Das, P. *Chem. Commun.* **2014**, *50*, 12911–12914.
- (28) (a) See ref 18a and references cited therein, as well as refs 15 and 22 for relevant mechanistic pathways. (b) CuCl₂·H₂O and Cu(OAc)₂ were both suitable metals salts (Table 1) in promoting the reaction; however, as pointed out by one referee, we cannot exclude that metal contaminants other than copper could be responsible for the present sequence. For the importance of metal impurities, see: Buchwald, S. L.; Bolm, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5586–5587.
- (29) Kim, S.; Ginsbach, J. W.; Lee, J. Y.; Peterson, R. L.; Liu, J. J.; Siegler, M. A.; Sarjeant, A. A.; Solomon, E. I.; Karlin, K. D. *J. Am. Chem. Soc.* **2015**, *137*, 2867–2874.
- (30) (a) Cockerill, A. F.; Deacon, A.; Harrison, R. G.; Osborne, D. J.; Prime, D. M.; Ross, W. J.; Todd, A.; Verge, J. P. *Synthesis* **1976**, 591–593. (b) Kumar, V.; Kaushik, M. P.; Mazumdar, A. *Eur. J. Org. Chem.* **2008**, 1910–1916.
- (31) For a discussion defining diversity, see: O’Connell, K. M. G.; Galloway, W. R. J. D.; Spring, D. R. in *Diversity-Oriented Synthesis: Basics and Applications in Organic Synthesis, Drug Discovery, and Chemical Biology*; Trabocchi, A., Ed.; John Wiley & Sons, Inc., Hoboken, NJ, 2013; pp 5–8.