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# Chan-Lam Cross-Coupling Reaction Based on the $Cu_2S$/TMEDA System

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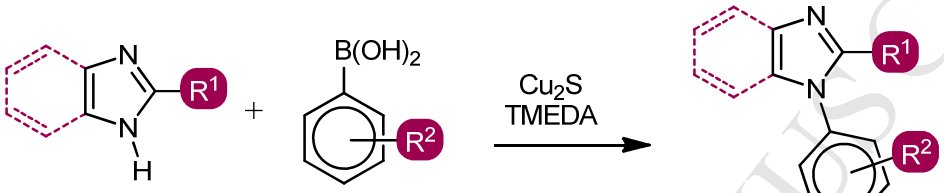



♣ imidazole, benzimidazole, benzimidazolone

♦ atropisomerism observed, when **$R^1$ = OH** and **$R^2$ = 2-Me**

♣ an example of the one-pot Chan-Lam/Suzuki-Miyaura coupling

**Abstract**

A catalyst based on the readily available $Cu_2S$/TMEDA system using a stable copper(I) source was developed for the Chan-Lam cross-coupling reaction. The capability of the catalyst was demonstrated with 1*H*-benzo[*d*]imidazol-2(3*H*)-one, 1*H*-benzo[*d*]imidazole, and 1*H*-imidazole together with electron-deficient, electron-rich, and sterically demanding boronic acids at room temperature in the presence of atmospheric oxygen to give the cross-coupling products in moderate to excellent yields. In addition, the coupling reaction of 1*H*-benzo[*d*]imidazole with several pinacol or neopentylglycol boronates indicated further potential of the catalyst. The reaction conditions tolerate the hydroxyl and bromo functional groups. The catalytic system also enables to synthesize the mono-*N*-substituted anilines from primary aliphatic amines. However, the two model compounds for the secondary and aromatic amines, piperidine and aniline, do not react. Two sterically demanding products with the restricted C-N bond rotation, synthesized by the *N*-arylation of 1*H*-benzo[*d*]imidazol-2(3*H*)-one with *o*-tolylboronic acid, enabled to confirm the atropisomers prepared by the Chan-Lam cross-coupling reaction. Furthermore, an example of one-pot Chan-Lam and Suzuki-Miyaura reaction has been reported.

## Introduction

The *N*-arylazole structural motif is common in numerous biologically active compounds.[1] Therefore, procedures allowing simple and efficient construction of such patterns would represent a significant contribution to the field of medicinal chemistry.[2] Apart from less universal and time consuming *de novo* synthetic methods,[3] there are several reactions enabling direct arylation of heterocycles. Presumably, the oldest method is classical nucleophilic aromatic substitution utilizing aryl halides,[4] which, however, suffers from the poor substrate scope, as only electron deficient aryl halides offer reasonable reactivity.[5] The activation of C-halogen bonds *via* oxidative addition by transitional metals significantly improved the reactivity, and also extended the substrate scope. Nevertheless, the requirement of high reaction temperature and/or strong base limits such C-N couplings, typically referred as Ullman-Goldberg[6] or Buchwald-Hartwig reactions.[7]

Copper mediated coupling of arylboronic acids with various types of nucleophiles, known as the Chan-Lam reaction, represents an experimentally simple procedure that forms C($sp^2$)-heteroatom bond under mild reaction conditions, thus allowing incorporation of otherwise sensitive substrates.[8] Moreover, the reaction tolerates various functionalities including halogens; therefore it offers compatibility with subsequent transformations of C-halogen bonds, such as Suzuki-Miyaura reaction.[9]

Synthetically relevant *N*-arylations (or alkenylations) of heterocycles via Chan-Lam reaction have been reported with various copper salts or complexes, ligands or bases, and solvents.[10] Despite significant progress being made with copper catalysts since seminal reports by Chan, Lam, and Evans (1999), there still remains space for the development. The goal would be stable, inexpensive, and easily available copper catalyst, which enables arylation of *N*-heterocycles at room temperature, especially with electron-poor or sterically demanding boronic acids. Ideally, the reaction should be performed under ambient atmosphere without a need for additional oxidant or oxygen atmosphere.[11]

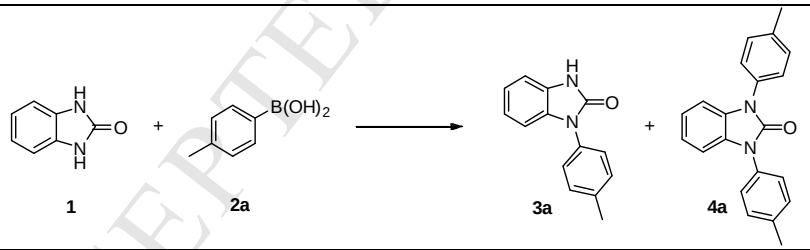
Herein, we present a novel $Cu_2S$/TMEDA system as a readily available catalyst for the Chan-Lam reaction using just 5 mol% of $Cu_2S$ (10 mol% of [Cu]) at room temperature and under ambient atmosphere. The $Cu_2S$/TMEDA system originally came out from the optimization of *N*-arylation involving benzimidazolone **1** as a model substrate. The fact that benzimidazolone **1** possess two reactive sites brought a question, if this compound can be substituted selectively to form monoaryl derivatives, or diarylated compounds will be unavoidable (side)products of the reaction. Furthermore, this method was extended to the *N*-arylation of 1*H*-benzo[*d*]imidazole, 1*H*-imidazole, and primary aliphatic amines.

## Results and Discussion

Our experiments started with a mixture of benzimidazolone **1**, *p*-tolylboronic acid **2a** (2 equiv.), copper acetate (0.5 equiv.), and TMEDA (1 equiv.) in $CH_2Cl_2$ under ambient atmosphere (Table 1, entry 1). The reaction produced only 13% of mono-arylated compound **3a** together with 6% of di-arylated compound **4a** after 24 hours, while 77% of starting material **1** remained unchanged. From $CH_2Cl_2$, MeOH, MeCN, and DMF tested in the combination with $Cu(OAc)_2$/TMEDA (entries 1-4), DMF performed best, yet it led to compound **3a** in only 27% after 24 hours.

Substitution of $Cu(OAc)_2$ with CuCl significantly improved the rate of the Chan-Lam reaction (entry 5), thus 45% of mono-arylated product **3a** was formed after 3 hours, together with 5% of di-arylated derivative **4a**. Prolonging the reaction time to 24 hours revealed 47 % of **3a**, 15 % of **4a**, and 36% of starting material **1**. Slightly lower reactivity was observed with CuI and $Cu_2O$ (entries 6 and 7), while 25 mol% of $Cu_2S$ (entry 8) displayed the most promising catalytic activity from all tested copper compounds, giving 50% of mono-arylated derivative **3a**, 8% of di-arylated derivative **4a**, and 39% of starting material **1** after 3 hours. Increasing TMEDA to two equivalents did not have any significant effect on the reaction (entry 9). Examination of pyridine and $Et_3N$ as plausible ligands for $Cu_2S$ brought inferior yields in comparison to the $Cu_2S$/TMEDA system (entries 10 and 11). The Chan-Lam coupling reaction using $Cu_2S$ without any ligand was very sluggish (entry 12).

**Table 1.** Optimization of the Chan-Lam reaction




| Entry | [Cu] | Ligand | Solvent | Time [h] | **1** (%) [a] | **3a** (%) [a] | **4a** (%) [a] |
|---|---|---|---|---|---|---|---|
| 1 | $Cu(OAc)_2$ | TMEDA | $CH_2Cl_2$ | 24 | 77 | 13 | 6 |
| 2 | $Cu(OAc)_2$ | TMEDA | MeOH | 24 | 73 | 19 | 3 |
| 3 | $Cu(OAc)_2$ | TMEDA | MeCN | 24 | 78 | 17 | 3 |
| 4 | $Cu(OAc)_2$ | TMEDA | DMF | 24 | 60 | 27 | 5 |
| 5 | CuCl | TMEDA | DMF | 3 (24) | 46 (36) | 45 (47) | 5 (15) |
| 6 | CuI | TMEDA | DMF | 3 (24) | 58 (44) | 32 (43) | 3 (9) |
| 7 | $Cu_2O$ | TMEDA | DMF | 3 (24) | 53 (5) | 34 (26) | 3 (49) |
| 8 | $Cu_2S$ | TMEDA | DMF | 3 (24) | 39 (7) | 50 (33) | 8 (55) |
| 9 | $Cu_2S$ | TMEDA[b] | DMF | 3 (24) | 35 (4) | 49 (31) | 11 (56) |
| 10 | $Cu_2S$ | Pyridine | DMF | 3 (24) | 44 (25) | 37 (43) | 4 (16) |
| 11 | $Cu_2S$ | $Et_3N$ | DMF | 3 (24) | 58 (42) | 30 (40) | 2 (9) |
| 12 | $Cu_2S$ | none | DMF | 3 (24) | 95 (94) | 2 (2) | < 1 (< 1) |

General conditions: Benzimidazolone **1** (0.5 mmol), boronic acid **2a** (1.0 mmol), ligand (0.5 mmol), copper salt (0.25 mmol for $Cu(OAc)_2$, CuCl and CuI; or 0.125 mmol for $Cu_2O$ and $Cu_2S$), solvent (2 mL), rt, air. [a] HPLC yield determined from LCMS after 3 or 24 hours using *N*-Fmoc-L-alanine as an internal standard. [b] 1.0 mmol (2 equiv.) of TMEDA were used.

HPLC analyses after 3 and 24 hours demonstrated that mono-aryl derivative **3a** was a major product after 3 hours and its concentration decreased after 24 hours as a consequence of formation of di-arylated derivative **4a** (Table 1, entry 8). This observation prompted us to explore the reaction progress with the $Cu_2S$/TMEDA using various amounts (25%, 10%, 5% and 2.5%) of $Cu_2S$, one equivalent of TMEDA, and two equivalents of boronic acid **2a** in DMF (Figures 1A-D). Use of $Cu_2S$ at 25% molar ratio (50% of [Cu]) showed that the amount of product **3a** was increasing up to 3 hours, when it reached its maximum at 49% (Figure 1A). Then it began to decrease, while the percentage of **4a** was constantly increasing. After approximately 5 hours, the amount of both arylated products **3a**

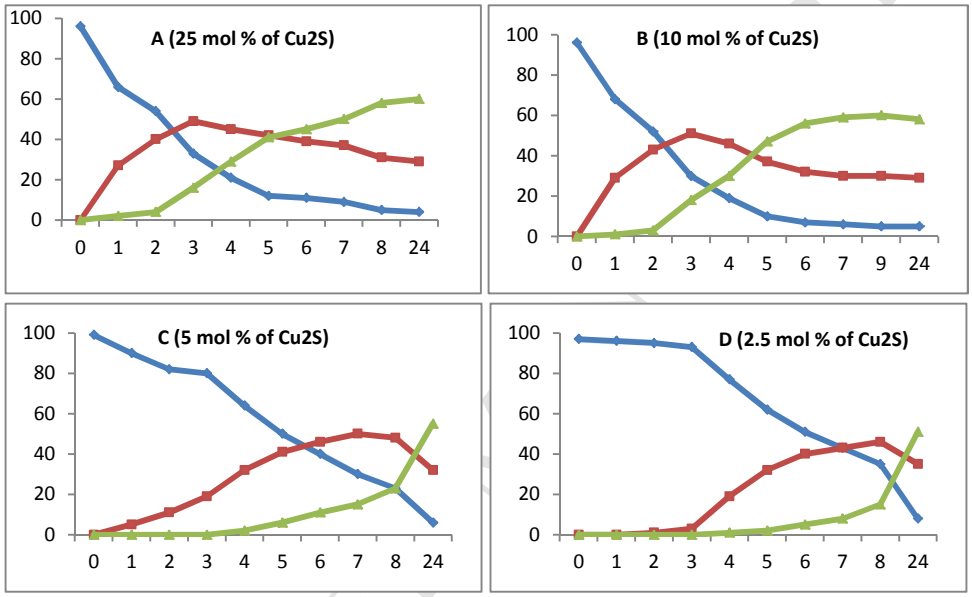


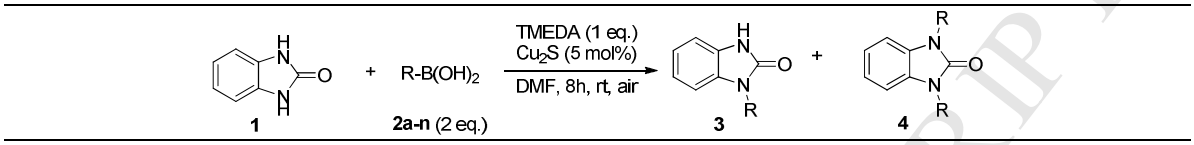

**Figure 1.** Reaction progress was monitored with HPLC using *N*-Fmoc-L-alanine as an internal standard after 1 – 8 and 24 hours. Starting material **1** is depicted as a blue line, mono-arylated compound **3a** as a red line, and di-arylated compound **4a** as a green line.

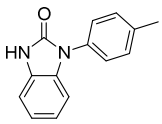
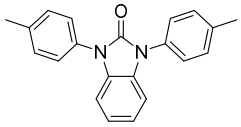
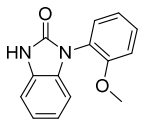
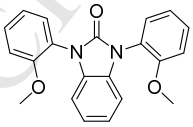
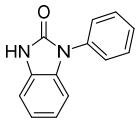
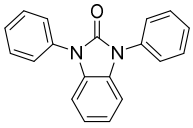
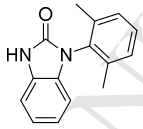
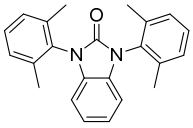
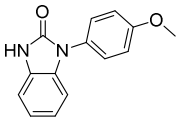
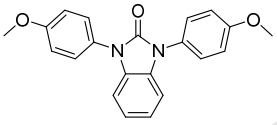
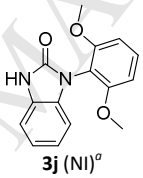
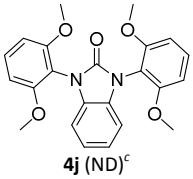
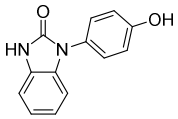
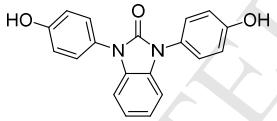
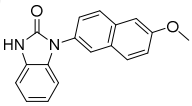
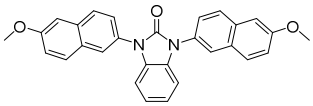
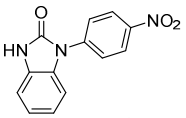
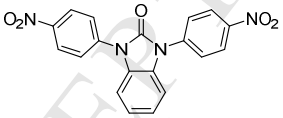
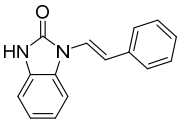
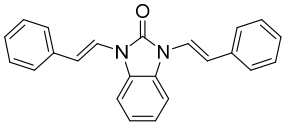
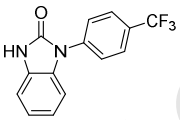
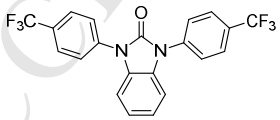
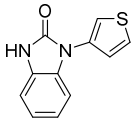
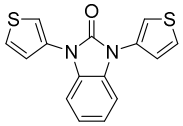
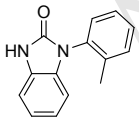
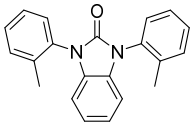
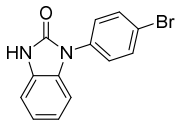
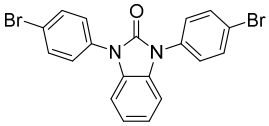
and **4a** was equal. Around 6 hours **4a** became the major compound in the reaction mixture and after 24 hours it reached 60%, while **3a** was formed in 29% and 4% of staring material **1** remained.

Almost identical results were obtained with 10% of $Cu_2S$ (Figure 1B). The same trend, but lower reaction rate was observed with molar ratio at 5% and 2.5% of $Cu_2S$ (Figure 1C and 1D). It seems that the reaction has an induction period at the 2.5% catalyst loading (Figure 1D), which was not observed at the higher loadings. Then, it was obvious from all diagrams that both benzimidazolones **1a** and **3a** underwent *N*-arylation at similar rate. While the amount of **3a** increased in time, it became more available for subsequent *N*-arylation to yield **4a**. Therefore no more than approximately 50% of **3a** can be obtained from this reaction. However, the limit 50% can be potentially exceeded in case of a significantly slower rate of second *N*-arylation caused by stereo-electronic effects (*vide infra*). Reducing the ratio of benzimidazolone **1**/boronic acid **2a** to 1:1 did not avoid the formation of **4a**, only led to a higher content of unreacted starting material **1**.

Despite 10% of $Cu_2S$ was optimal for the model Chan-Lam reaction in study, molar ratio at 5% also offered acceptable reaction rate and product conversion; therefore 5% of $Cu_2S$ (10% of [Cu]), 1 equivalent of TMEDA, and two equivalents of boronic acid **2a-n** were used in subsequent experiments. Boronic acids **2a-n** with various stereo-electronic substitution patterns were employed in the Chan-Lam reaction using benzimidazolone **1** as a substrate (Table 2).

**Table 2.** Scope of the Chan-Lam reaction with benzimidazolone **1**




| Compound **3** | Compound **4** | Compound **3** | Compound **4** |
|---|---|---|---|
|  **3a** (40%) |  **4a** (17%) |  **3h** (34%) |  **4h** (NI)[a] |
|  **3b** (40%) |  **4b** (6%) |  **3i** (60%) |  **4i** (ND)[c] |
|  **3c** (41%) |  **4c** (39%) |  **3j** (NI)[a] |  **4j** (ND)[c] |
|  **3d** (NI)[a] |  **4d** (NI)[a] |  **3k** (44%) |  **4k** (22%) |
|  **3e** (48%)[b] |  **4e** (ND)[b,c] |  **3l** (40%) |  **4l** (NI)[c] |
|  **3f** (41%)[b] |  **4f** (ND)[b,c] |  **3m** (37%) |  **4m** (14%) |
|  **3g** (42%) |  **4g** (20%) |  **3n** (42%) |  **4n** (39%) |

[a] Compounds were formed, but not isolated in acceptable purity. [b] Reaction time 24 hours. [c] Not detected.

When the Chan-Lam reaction between benzimidazolone **1** and *p*-tolylboronic acid **2a** was quenched after 8 hours, mono-arylated product **3a** was isolated in 40% yield and di-arylated product **4a** in 17% yield. In general, the separation of **1**, **3**, and **4** by column chromatography was facile due to distinct

polarity of most compounds. Using unsubstituted phenylboronic acid **2b**, phenyl derivative **3b** was obtained together with di-substituted derivative **4b** in 40% and 6% yield, respectively. Electron-donating *p*-methoxy group possessed positive effect on the reactivity, which resulted in the isolation of compounds **3c** and **4c** in 41% and 39% yield, respectively. Hydroxyphenylboronic acid **2d** also displayed favorable reactivity in the *N*-arylation of **1**, while the competitive *O*-arylation of phenolic hydroxyl was negligible. The respective products **3d** and **4d** were formed in approximately 1:1 ratio after 8 hours as major compounds together with small amount of residual starting material **1**. However, we failed to separate **3d** from **4d**, which were obtained as a 1:1 mixture after column chromatography.

The reactivity of phenylboronic acids **2e** (*p*-$NO_2$) and **2f** (*p*-$CF_3$) was lower in the Chan-Lam arylation, therefore the reaction time was prolonged to 24 hours in order to obtain mono-arylated compounds **3e** and **3f** in 48% and 41% yield, respectively. Di-arylated compounds **4e** and **4f** were not formed during the reaction of benzimidazolone **1** with boronic acids bearing electron-withdrawing substituents.

Next, sterically hindered boronic acids **2g-j** were employed in the Chan-Lam reaction. One methyl substituent in the *ortho* position of boronic acid **2g** was compatible with the reaction, leading to benzimidazoles **3g** and **4g** in 42% and 20% yield, respectively. 2-Methoxyphenylboronic acid **2h** partially decomposed under the reaction conditions, therefore mono-aryl product **3h** was obtained in only 34% yield. Di-arylated derivative **4h** was detected in the crude mixture in approximately 5% and all attempts to isolate **4h** in acceptable purity failed. To our delight, mono-arylated derivative **3i**, bearing two *ortho* methyl substituents, was isolated in 60% yield. Two *ortho* methyl substituents precluded the formation of di-arylated compound **4i**, which was not detected in the crude reaction mixture. 2,6-Dimethoxyphenylboronic acid **2j** possessed, similarly to 2-methoxyphenylboronic acid **2h**, lower stability under the reaction conditions, therefore mono-aryl product **3j** was detected in less than 5% in the crude mixture and its isolation failed. Di-aryl product **4j** was not detected.

Compounds **3k** and **4k**, bearing large naphthyl substituent, were obtained in the reaction with boronic acid **2k** in 44% and 22% yield, respectively. Alkenyl substituent was introduced into the benzimidazole core via styrylboronic acid **2l**, yielding compound **3l** in 40% yield. Small amount of di-substituted derivative **4l** was detected in the crude mixture; however, its isolation failed. Thienylboronic acid **2m** showed moderate reactivity, providing mono-aryl product **3m** and di-aryl product **4m** in 37 and 14% yield, respectively. As expected, bromo-substituent in the structures **3n** and **4n** was preserved during the Chan-Lam reaction.

Both $^{1}H$ and $^{13}C$ NMR spectra of di-arylated benzimidazolone **4g** showed two sets of peaks at the ratio of 3:2. The ratio was independent on the solvent ($CDCl_3$ or DMSO-$d_6$) and temperature (20 – 120 °C in DMSO-$d_6$), suggesting the occurrence of stable isomers. Further analysis using chiral HPLC revealed three peaks at the ratio of 1:3:1. Chiral detector revealed that two minor peaks belong to the optically active compounds, while the major compound was inactive. These data clearly indicated the presence of atropisomers **4g$_x$**, **4g$_y$**, and optically inactive mesoform **4g$_z$** (Figure 2). To the best of our knowledge, this is the first example of atropisomers being formed by the Chan-Lam reaction, although not in the stereoselective fashion.[12] Moreover, chiral HPLC allowed observation of atropisomers in mono-aryl derivative **3g** (*ortho*-Me), while no isomers were separated in compound **3h** bearing *ortho* methoxy group.

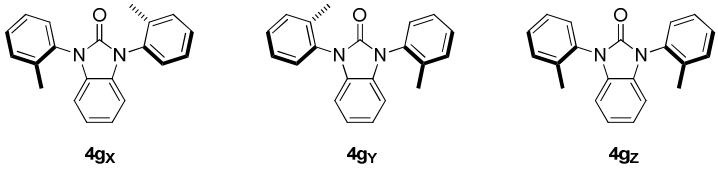



**Figure 2.** Atropisomers

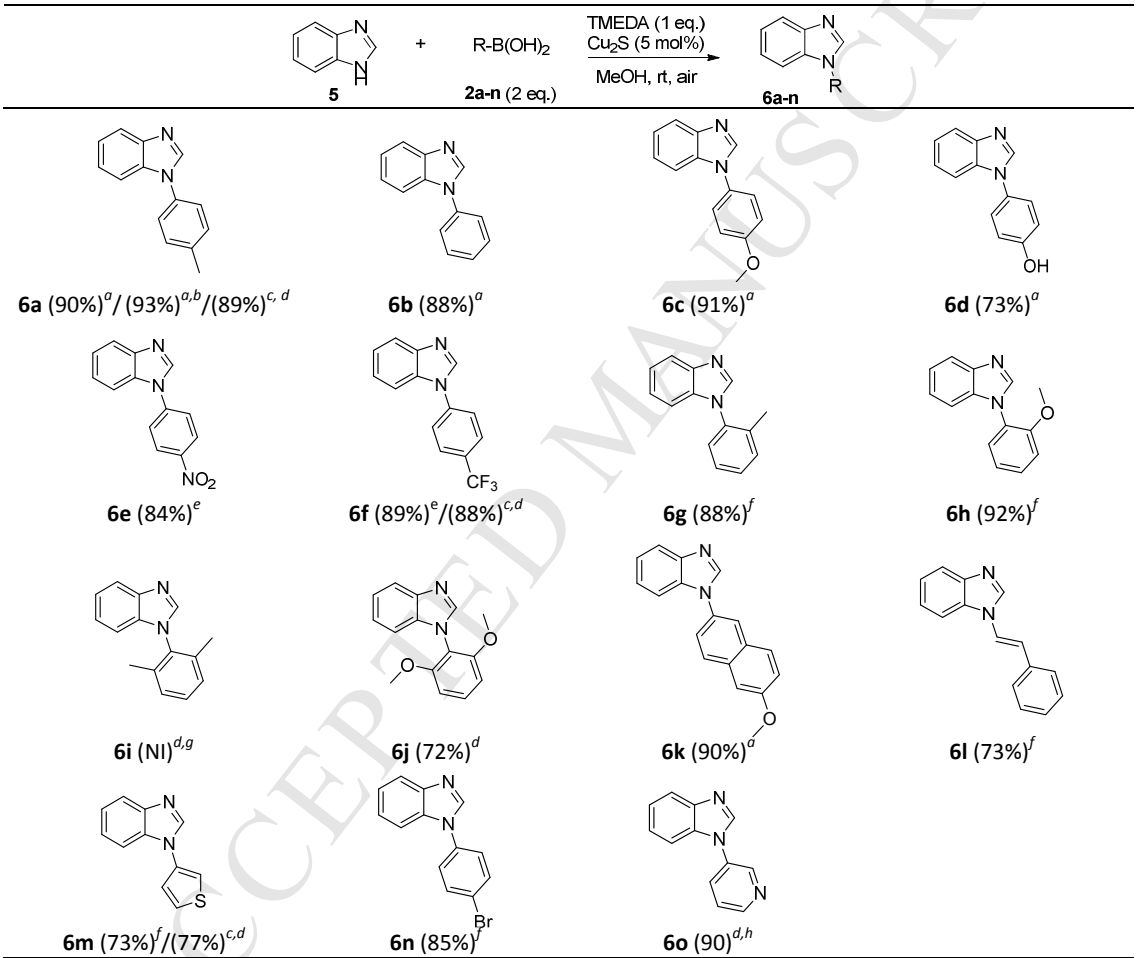
The scope of the Chan-Lam reaction using 5 mol% of $Cu_2S$ and one equivalent of TMEDA as a ligand was further explored on the *N*-arylation of benzimidazole **5**. The reaction of *p*-tolylboronic acid **2a** with benzimidazole **5** took 24 hours to consume all starting material. Inspired by the work of Sreedhar,[10c] we switched to MeOH as a solvent, which resulted in the complete conversion of benzimidazole **5** in 8 hours and respective product **6a** was isolated in 90% yield. Therefore, we employed MeOH instead of DMF for the *N*-arylation of benzimidazole **5** (Table 3) using boronic acids **2a-n**.

Unsubstituted **2b**, electron-rich **2c** and **2d**, and bulky boronic acid **2k** completely arylated benzimidazole **5** within 8 hours, providing desired products **6b**, **6c**, and **6k** in high yields (88 – 91%), except for **6d**, which was obtained in 73% yield, as a result of losses during purification. The reaction with electron-poor boronic acids **2e** and **2f** proceeded slowly (48 hours), but still provided high yield of desired products **6e** (84%) and **6f** (89%). Methyl or methoxy substituent in *ortho* position did not decrease the yield, albeit the reaction required longer time (24 hours) for compounds **6g** and **6h**. Methyl groups in both *ortho* positions retarded the formation of product **6i**, which was found in a trace amount in the crude reaction mixture after 72 hours together with unreacted benzimidazole **5** and boronic acid **2i**. Compound **2j** bearing two *ortho* methoxy groups proved to be a suitable coupling partner, giving product **6j** in 70% yield after 72 hours. *N*-Styryl and *N*-thienyl derivatives **6l**

and **6m** were obtained in good yields (both 73%). Boronic acid **2n** containing bromo-substituent gave desired product **6n** in 85% yield, preserving bromo-substituent for further possible transformations.

*N*-arylated benzimidazoles **6a**, **6f**, and **6m** were also obtained in the high yields with the respective pinacol esters, although it was necessary to increase the reaction time to 72 hours. Neopentylglycol ester of 3-pyridylboronic acid gave benzimidazole **6o** in 90% under the same conditions. Furthermore, the reaction of benzimidazole **5** and boronic acid **2a** was performed at a gram scale (20 mmol of benzimidazole **5**) yielding 93% of product **6a** in 8 hours**.**

**Table 3.** Scope of the Chan-Lam reaction with benzimidazole **5**



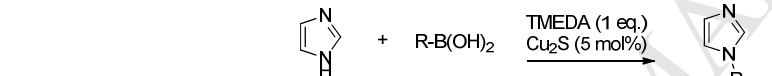

[a] Reaction time 8 hours. [b] 20 mmol scale of benzimidazole **5**. [c] Pinacol ester of the respective boronic acid was used. [d] Reaction time 72 hours. [e] Reaction time 48 hours. [f] Reaction time 24 hours. [g] Not isolated. [h] Neopentylglycol ester of 3-pyridineboronic acid was used.

As in the case of benzimidazole **5**, the *N*-arylation of imidazole **7** with *p*-tolylboronic acid **2a** was sluggish in DMF, leaving unreacted starting material **7** after 24 hours. As previously shown, switching solvent to MeOH allowed full conversion in a shorter time. In general, the *N*-arylation of imidazole **7** was slower compared to benzimidazole **5**. For instance, full consumption of the imidazole **7** was achieved after 24 hours (versus 8 hours for benzimidazole **5**) on the reaction with *p*-tolylboronic acid

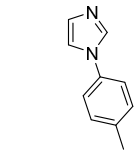
**2a** in MeOH, providing product **8a** in 89% yield. Results summarizing C-N coupling of imidazole **7** and boronic acids **2a-n** are depicted in Table 4.

The *N*-arylation proceeded smoothly and in high isolated yields with phenylboronic acid **2b**, electron-rich **2c**, naphtyl **2k**, and sterically hindered boronic acids **2g** and **2h**. Unprotected phenolic OH was compatible with the reaction. Compound **8d** was isolated in 60% yield, while the side product resulting from the competitive *O*-arylation was formed in a negligible amount (approximately 5% according to LCMS). More sterically demanding boronic acid **2i** gave only a trace amount of the product **8i**, which precluded its isolation, while 2,6-dimethoxyphenyl boronic acid **2j** gave the desired product in 79% yield after 48 hours. Styryl derivative **8l** was obtained in 74% yield on the prolonged reaction time, 48 hours, as well as thiophene substituted derivative **8m** (60% yield), which required one additional equivalent of boronic acid **2m**. Imidazoles bearing electron-withdrawing substituents (**8e** and **8f**) were obtained in the high yields, although they required 48 hours and one additional equivalent of boronic acid. Furthermore, brominated derivative **8n** was obtained in high yield of 90%.

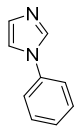
**Table 4.** Scope of the Chan-Lam reaction with imidazole **7**



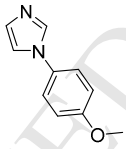

**7** **2a-n** (2 eq.) **8a-n**



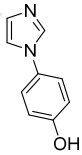
**8a** (87%)



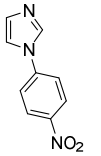
**8b** (85%)



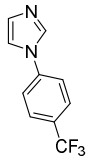
**8c** (90%)



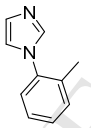
**8d** (60%)



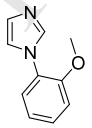
**8e** (76%)[a,b]



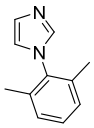
**8f** (79%)[a,b]



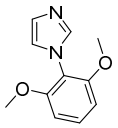
**8g** (85%)



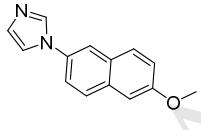
**8h** (86%)



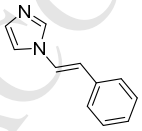
**8i** (NI)



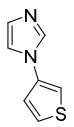
**8j** (79%)[a]



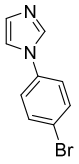
**8k** (88%)



**8l** (74%)[a]



**8m** (60%)[a,b]



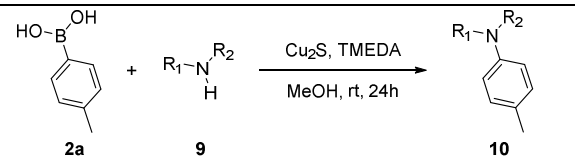
**8n** (90%)[a]

[a] Reaction time 48 hours. [b] Additional one equivalent of boronic acid was added after 24h.

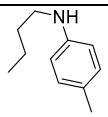
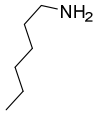
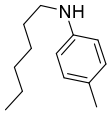
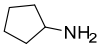
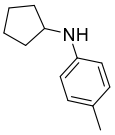
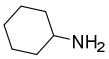
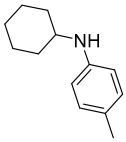
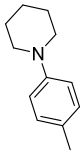
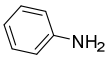
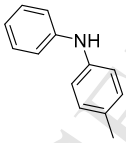
The $Cu_2S$/TMEDA proved to be efficient catalyst system for the *N*-arylation of primary aliphatic amines **9a-d** (Table 5), although it was necessary to adjust amine/boronic acid ratio to 1.5:1. The respective mono-substituted anilines **10a-d** were obtained in 78 – 85% yields. The formation of di-

substituted anilines from primary amines was not observed. Unfortunately, secondary amine **9e** and aromatic amine **9f** were formed in trace amount under the standard reaction conditions.

**Table 5.** *N*-arylation of amines




**2a** **9** **10**

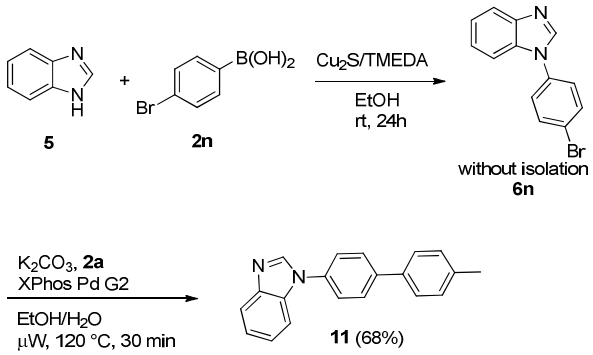
| Amine | Product Yield |
|---|---|
| **9a**  |  **10a** (81%) |
| **9b**  |  **10b** (85%) |
| **9c**  |  **10c** (79%) |
| **9d**  |  **10d** (78%) |
| **9e**  |  **10e** (NI)[a] |
| **9f**  |  **10f** (NI)[a] |

General conditions: amine (1.5 mmol), boronic acid **2a** (1.0 mmol), $Cu_2S$ (0.05 mmol), TMEDA (1.0 mmol), MeOH (4 mL), rt, air, 24h. [a] Not isolated.

Finally, we explored whether two seemingly incompatible reactions, the Chan-Lam and Suzuki-Miyaura coupling, can be performed in a one-pot fashion (Scheme 1). Benzimidazole **5** reacted with a slight excess of (4-bromophenyl)boronic acid **2n** under our Chan-Lam conditions providing intermediate **6n** in 24 hours. Then, the mixture was flushed with nitrogen, diluted with water, and treated with boronic acid **2a**, $K_2CO_3$ (3 equivalents), and XPhos Pd G2 (1 mol%) at 70 °C (external temperature). After 24 hours, the HPLC/MS showed approximately 1:1 ratio of the desired product **11** and intermediate **6n**. We envisioned that the higher reaction temperature in the second step can

improve the rate of C-C coupling; therefore we switched a solvent from MeOH to EtOH. Performing the Chan-Lam arylation in EtOH with **5** and **2n** gave almost exclusively brominated intermediate **6n**, which upon heating with boronic acid **2a** and XPhos Pd G2 in EtOH/$H_2O$ gave almost exclusively desired product **11**.[13] Practically the same results were obtained when the Suzuki-Miyaura reaction was performed in an oil bath (80 °C, 24 hours), or in a microwave reactor (120 °C, 30 minutes). Column chromatography over silica gel gave compound **11** in 93% yield, which was contaminated with 2% of **6n** and two unknown impurities (both approximately 1%). Subsequent crystallization from MeOH provided analytically pure **11** in 68% yield.

**Scheme 1.** One-pot Chan-Lam and Suzuki-Miyaura reaction




## Conclusion

In Summary, we developed the $Cu_2S$/TMEDA system for the Chan-Lam C-N coupling of several imidazole-based heterocycles with boronic acids. Two reactive sites of benzimidazolone **1** underwent the first and second *N*-arylation at similar rates, leading to mono- and di-arylated benzimidazolones **3** and **4**. Benzimidazole and imidazole gave the high yields of the *N*-aryl products **6** and **8** with a range of diversely substituted arylboronic acids or esters. It was demonstrated, that the Chan-Lam coupling with $Cu_2S$/TMEDA can be reliably reproduced at the 20 mmol scale and performed in a one-pot fashion with the Suzuki-Miyaura coupling, when the brominated boronic acid **2n** was used. Furthermore, the $Cu_2S$/TMEDA catalyst enabled the preparation of mono-*N*-substituted anilines **10** from boronic acid **2a** and primary aliphatic amines in the high yields. Benzimidazolones **3g** and **4g** with the restricted C-N bond rotation allowed to confirm the atropisomers synthesized by the Chan-Lam coupling.

## Experimental Section

**General procedure for compounds 3 and 4 (Table 2):** A 10 mL round bottom flask was charged with a magnetic stirring bar, benzimidazolone **1** (67 mg, 0.5 mmol), boronic acid **2** (1.0 mmol), $Cu_2S$ (4 mg, 0.025 mmol), and DMF (2 mL), then followed by the addition of TMEDA (0.075 mL, 0.5 mmol). The

flask was sealed with a septum, through which was inserted 18-gauche needle. This setup allowed access of air and avoided contamination. The reaction mixture was stirred from 400 to 600 rpm for 8 hours and extracted with EtOAc (2x 15 mL). Combined organic layers were washed with a saturated aqueous solution of ethylenediaminetetraacetic acid disodium salt (15 mL), then with water (2x 15 mL), and dried over anhydrous $Na_2SO_4$. Volatiles were removed under reduced pressure and the residue was purified by column chromatography (silica gel, hexanes – EtOAc) to yield the title product, which was characterized by $^1$H NMR, $^{13}$C NMR, HRMS, and melting point (if solid).

**1-(*p*-Tolyl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (3a):**[14] Prepared according to general procedure using boronic acid **2a**. Title product was obtained as a white solid (45 mg, 40%), mp 221 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ = 11.09 (s, 1 H), 7.39 (d, $J$ = 8.6 Hz, 2 H), 7.35 (d, $J$ = 8.6 Hz, 2 H), 7.08 - 7.02 (m, 2 H), 7.01 – 6.96 (m, 1 H), 6.95 - 6.91 (m, 1 H), 2.38 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ = 153.3, 136.8, 132.0, 130.2, 129.8, 128.4, 125.8, 121.7, 120.8, 109.1, 108.0, 20.7 ppm. HRMS (ESI-Orbitrap): calcd for $C_{14}H_{12}N_2O$ $[M + H]^+$ 225.1022; found 225.1023.

**1-Phenyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (3b):**[15] Prepared according to general procedure using boronic acid **2b**. Title product was obtained as a white solid (42 mg, 40%), mp 201-202 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ = 11.13 (s, 1 H), 7.58 – 7.51 (m, 4 H), 7.45 – 7.40 (m, 1 H), 7.09 – 7.03 (m, 2 H), 7.02 – 6.97 (m, 2 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ = 153.2, 134.6, 130.0, 129.4, 128.4, 127.3, 125.9, 121.8, 120.9, 109.2, 108.1 ppm. HRMS (ESI-Orbitrap): calcd for $C_{13}H_{10}N_2O$ $[M + H]^+$ 211.0866; found 211.0870.

**1-(4-Methoxyphenyl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (3c):**[14] Prepared according to general procedure using boronic acid **2c**. Title product was obtained as a pale yellow solid (49 mg, 41%), mp 238-240 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ = 11.05 (s, 1 H), 7.41 (ddd, $J$ = 8.9, 3.4, 2.2 Hz, 2 H), 7.10 (ddd, $J$ = 8.9, 3.4, 2.2 Hz, 2 H), 7.07 – 7.01 (m, 2 H), 7.00 – 6.96 (m, 1 H), 6.89 – 6.86 (m, 1 H), 3.82 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ = 158.3, 153.5, 130.6, 128.3, 127.5, 127.1, 121.5, 120.8, 114.6, 109.0, 107.8, 55.4 ppm. HRMS (ESI-Orbitrap): calcd for $C_{14}H_{12}N_2O$ $[M + H]^+$ 241.0972; found 241.0971.

**1-(4-Nitrophenyl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (3e):**[16] Prepared according to general procedure (reaction time 24 hours) using boronic acid **2e**. Title product was obtained as a yellow solid (61 mg, 48%), mp 306-308 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 11.39 (s, 1 H), 8.40 (d, $J$ = 9.1 Hz, 2 H), 7.91 (d, $J$ = 9.1 Hz, 2 H), 7.22 (d, $J$ = 7.8 Hz, 1 H), 7.16 – 7.09 (m, 2 H), 7.06 (ddd, $J$ = 8.0, 6.4, 2.5 Hz, 1 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$ ): δ = 152.7, 145.2, 140.7, 128.7, 128.7, 125.7, 124.8, 122.7, 121.2, 109.6, 108.8 ppm. HRMS (ESI-Orbitrap): calcd for $C_{13}H_9N_3O_3$ $[M - H]^-$ 254.0571; found 254.0564.

**1-(4-(Trifluoromethyl)phenyl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (3f):**[14] Prepared according to general procedure (reaction time 24 hours) using boronic acid **2f**. Title product was obtained as a white solid (57 mg, 41%), mp 260-261 °C. $^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$ = 11.29 (s, 1 H), 7.93 (d, *J* = 8.8 Hz, 2 H), 7.83 (d, *J* = 8.8 Hz, 2 H), 7.17 - 7.13 (m, 1 H), 7.12 - 7.08 (m, 2 H), 7.04 (qd, *J* = 8.0, 4.3 Hz, 1 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ = 152.9, 138.4, 129.1, 128.6, 127.1 (q, *J* = 32 Hz), 126.5 (q, *J* = 4 Hz), 126.0, 122.4, 121.1, 124.1 (q, *J* = 272 Hz), 109.4, 108.5 ppm. HRMS (ESI-Orbitrap): calcd for $C_{14}H_9F_3N_2O$ [M - H]$^-$ 277.0594; found 277.0586.

**1-(*o*-Tolyl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (3g):** Prepared according to general procedure using boronic acid **2g**. Title product was obtained as a white solid (47 mg), mp 170-173 °C. $^{1}$H NMR (400 MHz, DMSO-$d_6$): δ = 11.07 (s, 1 H), 7.47 – 7.43 (m, 1 H), 7.41 (td, *J* = 7.4, 1.7 Hz, 1 H), 7.37 (td, *J* = 7.4, 2.0 Hz, 1 H), 7.32 (dd, *J* = 7.6, 1.5 Hz, 1 H), 7.08 (dd, *J* = 7.7, 1.1 Hz, 1 H), 7.04 (td, *J* = 7.5, 1.1 Hz, 1 H), 6.95 (td, *J* = 7.5, 1.5 Hz, 1 H), 6.55 (d, *J* = 7.7 Hz, 1 H), 2.07 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 153.2, 136.3, 133.1, 131.2, 130.8, 128.8, 128.6, 128.5, 127.1, 121.5, 120.8, 109.1, 107.8, 17.3 ppm. HRMS (ESI-Orbitrap): calcd for $C_{14}H_{12}N_2O$ [M + H]$^+$ 225.1022; found 225.1023.

**1-(2-Methoxyphenyl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (3h):**[14] Prepared according to general procedure using boronic acid **2h**. Title product was obtained as a pale yellow solid (41 mg, 34%), mp 173-176 °C. $^{1}$H NMR (400 MHz, DMSO-$d_6$): δ = 10.98 (s, 1 H), 7.52 – 7.45 (m, 1 H), 7.37 (dd, *J* = 7.7, 1.7 Hz, 1 H), 7.25 (dd, *J* = 8.4, 1.0 Hz, 1 H), 7.10 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.04 (dd, *J* = 7.8, 1.6 Hz, 1 H), 7.00 (td, *J* = 7.6, 1.0 Hz, 1 H), 6.93 (td, *J* = 7.4, 1.6 Hz, 1 H), 6.54 (d, *J* = 7.7 Hz, 1 H), 3.73 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 155.3, 153.4, 131.0, 130.1, 129.9, 128.5, 122.5, 121.2, 120.8, 120.6, 112.7, 108.8, 108.2, 55.6 ppm. HRMS (ESI-Orbitrap): calcd for $C_{14}H_{12}N_2O_2$ [M + H]$^+$ 241.0972; found 241.0973.

**1-(2,6-Dimethylphenyl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (3i):** Prepared according to general procedure using boronic acid **2i**. Title product was obtained as a white solid (71 mg, 60%), 246-249 °C. $^{1}$H NMR (400 MHz, DMSO-$d_6$): δ = 11.10 (s, 1 H), 7.33 (dd, *J* = 8.5, 6.5 Hz, 1 H), 7.29 – 7.23 (m, 2 H), 7.09 (d, *J* = 7.7 Hz, 1 H), 7.04 (td, *J* = 7.6, 1.0 Hz, 1 H), 6.95 (td, *J* = 7.6, 1.2 Hz, 1 H), 6.42 (d, *J* = 7.7 Hz, 1 H), 1.98 (s, 6 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 152.9, 136.9, 131.9, 129.9, 128.9, 128.7, 128.5, 121.5, 121.0, 109.2, 107.5, 17.4 ppm. HRMS (ESI-Orbitrap): calcd for $C_{15}H_{14}N_2O$ [M + H]$^+$ 239.1179; found 239.1180.

**1-(6-Methoxynaphthalen-2-yl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (3k):** Prepared according to general procedure using boronic acid **2k**. Title product was obtained as a white solid (64 mg, 44%), mp 256-258 °C. $^{1}$H NMR (400 MHz, DMSO-$d_6$): δ = 11.16 (s, 1 H), 8.01 (d, *J* = 1.7 Hz, 1 H), 7.98 (d, *J* = 8.8 Hz, 1 H), 7.92 (d, *J* = 9.0 Hz, 1 H), 7.60 (dd, *J* = 8.7, 2.1 Hz, 1 H), 7.43 (d, *J* = 2.4 Hz, 1 H), 7.24 (dd, *J*

= 9.0, 2.5 Hz, 1 H), 7.12 – 7.07 (m, 2 H), 7.04 – 7.00 (m, 2 H), 3.91 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 157.7, 153.5, 133.2, 130.3, 129.9, 129.4, 128.5, 128.5, 127.8, 124.7, 124.2, 121.7, 120.9, 119.3, 109.1, 108.2, 106.0, 55.3 ppm. HRMS (ESI-Orbitrap): calcd for $C_{18}H_{14}N_2O_2$ $[M + H]^+$ 291.1128; found 291.1125.

**(*E*)-1-Styryl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (3l):** Prepared according to general procedure using boronic acid **2l**. Title product was obtained as a white solid (47 mg, 40%), mp 188-190 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 11.25 (s, 1 H), 7.70 – 7.65 (m, 1 H), 7.61 – 7.55 (m, 3 H), 7.40 – 7.33 (m, 2 H), 7.28 (d, *J* = 14.8 Hz, 1 H), 7.26 – 7.22 (m, 1 H), 7.13 – 7.04 (m, 3 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 152.9, 136.2, 128.7, 128.3, 128.1, 126.9, 125.8, 122.3, 121.3, 121.1, 116.2, 109.7, 109.2 ppm. HRMS (ESI-Orbitrap): calcd for $C_{15}H_{12}N_2O$ $[M + H]^+$ 237.1022; found 237.1023.

**1-(Thiophen-3-yl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (3m):**[17] Prepared according to general procedure using boronic acid **2m**. Title product was obtained as a white solid (40 mg, 37%), mp 181-184 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 11.15 (s, 1 H), 7.74 (dd, *J* = 3.1, 1.5 Hz, 1 H), 7.71 (d, *J* = 5.1, 3.2 Hz, 1 H), 7.40 (dd, *J* = 5.1, 1.5 Hz, 1 H), 7.12 (dt, *J* = 7.2, 1.2 Hz, 1 H), 7.08 – 7.00 (m, 3 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 152.9, 132.5, 129.7, 128.3, 126.2, 124.3, 121.9, 121.0, 118.2, 109.1, 108.5 ppm. HRMS (ESI-Orbitrap): calcd for $C_{11}H_8N_2OS$ $[M + H]^+$ 217.0430; found 217.0431.

**1-(4-Bromophenyl)- 1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (3n):**[18] Prepared according to general procedure using boronic acid **2n**. Title product was obtained as a white solid (66 mg, 42%), mp 241-242 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 11.18 (s, 1 H), 7.76 – 7.72 (m, 2 H), 7.54 – 7.50 (m, 2 H), 7.09 – 7.04 (m, 2 H), 7.04 – 6.99 (m, 2 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 153.0, 133.9, 132.3, 129.6, 128.5, 127.9, 122.0, 121.0, 119.8, 109.3, 108.2 ppm. HRMS (ESI-Orbitrap): calcd for $C_{13}H_9BrN_2O$ $[M + H]^+$ 288.9971 and 290.9951; found 288.9974 and 290.9947.

**1,3-Di-*p*-tolyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (4a):** Prepared according to general procedure using boronic acid **2a**. Title product was obtained as a white solid (27 mg, 17%), mp 157 - 160 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 7.48 (d, *J* = 8.3 Hz, 4 H), 7.39 (d, *J* = 8.3 Hz, 4 H), 7.13 – 7.08 (m, 2 H), 7.06 – 7.02 (m, 2 H), 2.40 (s, 6 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 151.8, 137.3, 131.7, 130.0, 129.3, 126.2, 122.0, 108.5, 20.8 ppm. HRMS (ESI-Orbitrap): calcd for $C_{21}H_{18}N_2O$ $[M + H]^+$ 315.1492; found 315.1491.

**1,3-Diphenyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (4b):**[19] Prepared according to general procedure using boronic acid **2b**. Title product was obtained as a pale yellow solid (9 mg, 6%), mp 99-101 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 7.66 – 7.57 (m, 8 H), 7.52 – 7.45 (m, 2 H), 7.16 – 7.06 (m, 4

H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 151.6, 134.2, 129.6, 129.1, 127.8, 126.3, 122.2, 108.6 ppm. HRMS (ESI-Orbitrap): calcd for $C_{19}H_{14}N_2O$ $[M + H]^+$ 287.1179; found 287.1180.

**1,3-Bis(4-methoxyphenyl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (4c):**[6c] Prepared according to general procedure using boronic acid **2c**. Title product was obtained as a white solid (68 mg, 39%), mp 178-179 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 8.9 Hz, 4 H), 7.13 – 7.06 (m, 8 H), 3.90 (s, 6 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 159.1, 153.0, 130.1, 127.8, 127.3, 122.0, 114.9, 108.8, 55.7 ppm. HRMS (ESI-Orbitrap): calcd for $C_{21}H_{18}N_2O_3$ $[M + H]^+$ 347.1390; found 347.1390.

**1,3-Di-*o*-tolyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (4g):** Prepared according to general procedure using boronic acid **2g**. Title product was obtained as a white solid (32 mg, 20%), mp 187-189 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.46 – 7.33 (m, 8 H), 7.09 – 7.05 (m, 2 H), 6.81 – 6.75 (m, 2 H), 2.27 and 2.26 (s, 6 H, 2:3 ratio) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 152.2, 152.1, 137.1, 137.0, 133.2, 133.1, 131.7, 131.6, 130.6, 130.50, 129.3, 129.2, 128.8, 128.7, 127.3, 127.2, 122.0, 108.9, 108.8, 18.1, 18.0 ppm. HRMS (ESI-Orbitrap): calcd for $C_{21}H_{18}N_2O$ $[M + H]^+$ 315.1492; found 315.1490.

**1,3-Bis(6-methoxynaphthalen-2-yl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (4k):** Prepared according to general procedure using boronic acid **2k**. Title product was obtained as a yellow solid (49 mg, 22%), mp 247-249 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 2.0 Hz, 2 H), 7.92 (d, *J* = 8.7 Hz, 2 H), 7.81 (dd, *J* = 6.2, 3.4 Hz, 2 H), 7.70 (dd, *J* = 8.7, 2.1 Hz, 2 H), 7.25 – 7.17 (m, 6 H), 7.16 – 7.11 (m, 2 H), 3.97 (s, 6 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 158.4, 153.1, 134.0, 130.1, 129.6, 129.2, 128.4, 125.0, 124.8, 122.3, 119.8, 109.1, 106.0, 105.9, 55.5 ppm. HRMS (ESI-Orbitrap): calcd for $C_{29}H_{22}N_2O_3$ $[M + H]^+$ 447.1703; found 447.1703.

**1,3-Di(thiophen-3-yl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (4m):** Prepared according to general procedure using boronic acid **2m**. Title product was obtained as a white solid (21 mg, 14%), mp 106-107 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 7.86 – 7.83 (m, 2 H), 7.78 – 7.75 (m, 2 H), 7.44 (ddd, *J* = 5.2, 1.3, 0.8 Hz, 2 H), 7.23 – 7.14 (m, 4 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 151.1, 131.9, 128.7, 126.6, 124.5, 122.4, 119.6, 108.9 ppm. HRMS (ESI-Orbitrap): calcd for $C_{15}H_{10}N_2OS_2$ $[M + H]^+$ 299.0307; found 299.0306.

**1,3-Bis(4-bromophenyl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (4n):**[20] Prepared according to general procedure using boronic acid **2n**. Title product was obtained as a white solid (85 mg, 39%), mp 219-220 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.70 – 7.67 (m, 4 H), 7.51 – 7.48 (m, 4 H), 7.16 – 7.10 (m, 4 H) ppm. $^{13}$C NMR (400 MHz, $CDCl_3$): δ = 152.1, 133.6, 132.9, 129.3, 127.8, 122.7, 121.6, 109.1 ppm. HRMS (ESI-Orbitrap): calcd for $C_{19}H_{12}Br_2N_2O$ $[M + H]^+$ 442.9377, 444.9369 and 446.9348; found 442.9389, 444.9371 and 446.9346.

**General procedure for compounds 6a-o (Table 3):** A 10 mL round bottom flask was charged with a magnetic stirring bar, benzimidazole **1** (59 mg, 0.5 mmol), boronic acid **2** (1.0 mmol), $Cu_2S$ (4 mg, 0.025 mmol), and MeOH (2 mL), followed with the addition of TMEDA (0.075 mL, 0.5 mmol). The flask was sealed with a septum, through which was inserted 18-gauche needle. This setup allowed air to go into the reaction and avoid contamination of a mixture. The reaction mixture was stirred from 400 to 600 rpm for appropriate time and extracted with EtOAc (2x 15 mL).. Combined organic layers were washed with saturated aqueous solution of ethylenediaminetetraacetic acid disodium salt (15 mL), and then dried over anhydrous $Na_2SO_4$. Volatiles were removed under reduced pressure and the residue was purified by column chromatography (silica gel, hexanes – EtOAc) to yield the title product, which was characterized by $^1$H NMR, $^{13}$C NMR, HRMS, and melting point (if solid).

**1-(*p*-Tolyl)-1*H*-benzo[*d*]imidazole (6a):**[11a] Prepared from boronic acid **2a** (reaction time 8 hours or 72 hours with the pinacol ester). Title product was obtained as a white solid (94 mg, 90%; 92 mg, 89% with the pinacol ester; 3.87 g, 93% at the 20 mmol scale), mp 50-52 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.51 (s, 1 H), 7.81 – 7.72 (m, 1 H), 7.59 – 7.52 (m, 3 H), 7.43 (d, *J* = 8.1 Hz, 2 H), 7.35 – 7.26 (m, 2 H), 2.41 (s, *J* = 9.7 Hz, 3 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 143.8, 143.3, 137.3, 133.5, 133.2, 130.4, 123.6, 123.4, 122.3, 119.9, 110.6, 20.6 ppm. HRMS (ESI-Orbitrap): calcd for $C_{14}H_{12}N_2$ $[M + H]^+$ 209.1073; found 209.1074.

**1-Phenyl-1*H*-benzo[*d*]imidazole (6b):**[21] Prepared from boronic acid **2b** (reaction time 8 hours). Title product was obtained as a pale yellow oil (86 mg, 88%). $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.56 (s, 1 H), 7.80 – 7.76 (m, 1 H), 7.71 – 7.60 (m, 5 H), 7.53 – 7.47 (m, 1 H), 7.36 – 7.29 (m, 2 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 144.4, 143.8, 136.5, 133.6, 130.6, 128.3, 124.2, 124.0, 123.0, 120.5, 111.2 ppm. HRMS (ESI-Orbitrap): calcd for $C_{13}H_{10}N_2$ $[M + H]^+$ 195.0917; found 195.0917.

**1-(4-Methoxyphenyl)-1*H*-benzo[*d*]imidazole (6c):**[22] Prepared from boronic acid **2c** (reaction time 8 hours). Title product was obtained as a white solid (102 mg, 91%), mp 89-92 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.47 (s, 1 H), 7.80 – 7.71 (m, 1 H), 7.58 (d, *J* = 8.9 Hz, 2 H), 7.53 – 7.48 (m, 1 H), 7.34 – 7.26 (m, 2 H), 7.17 (d, *J* = 8.9 Hz, 2 H), 3.85 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 158.7, 143.4, 143.4, 133.6, 128.8, 125.4, 123.3, 122.2, 119.8, 115.1, 110.4, 55.5 ppm. HRMS (ESI-Orbitrap): calcd for $C_{14}H_{12}N_2O$ $[M + H]^+$ 225.1022; found 225.1023.

**4-(1*H*-Benzo[*d*]imidazol-1-yl)phenol (6d):**[23] Prepared from boronic acid **2d** (reaction time 8 hours). Title product was obtained as an orange solid (77 mg, 73%), mp 188-190 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 9.87 (s, 1 H), 8.41 (s, 1 H), 7.78 – 7.71 (m, 1 H), 7.51 – 7.46 (m, 1 H), 7.44 (d, *J* = 8.8 Hz, 2 H), 7.32 – 7.24 (m, 2 H), 6.98 (d, *J* = 8.8 Hz, 2 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 157.1,

143.5, 143.5, 133.7, 127.3, 125.6, 123.2, 122.1, 119.8, 116.3, 110.5 ppm. HRMS (ESI-Orbitrap): calcd for $C_{13}H_{10}N_2O$ $[M + H]^+$ 211.0866; found 211.0867.

**1-(4-Nitrophenyl)-1*H*-benzo[*d*]imidazole (6e):**[24] Prepared from boronic acid **2e** (reaction time 48 hours). Title product was obtained as a yellow solid (101 mg, 88%), mp 180-182 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.74 (s, 1 H), 8.46 (d, *J* = 9.1 Hz, 2 H), 8.03 (d, *J* = 9.0 Hz, 2 H), 7.84 – 7.74 (m, 2 H), 7.43 – 7.33 (m, 2 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 145.7, 144.1, 143.3, 141.4, 132.3, 125.6, 124.1, 123.78, 123.2, 120.3, 111.0 ppm. HRMS (ESI-Orbitrap): calcd for $C_{13}H_9N_3O_2$ $[M + H]^+$ 240.0768; found 240.0768.

**1-(4-(Trifluoromethyl)phenyl)-1*H*-benzo[*d*]imidazole (6f):**[25] Prepared from boronic acid **2f** (reaction time 48 hours or 72 hours with the pinacol ester). Title product was obtained as a white solid (117 mg, 89%; 115 mg, 88% with the pinacol ester), mp 149-151 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.68 (s, 1 H), 8.00 (d, *J* = 8.7 Hz, 2 H), 7.96 (d, *J* = 8.6 Hz, 2 H), 7.81 (ddd, *J* = 7.8, 3.8, 3.1 Hz, 1 H), 7.75 – 7.69 (m, 1 H), 7.40 – 7.30 (m, 2 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 144.0, 143.3, 139.3, 132.6, 127.7 (q, *J* = 32 Hz), 127.2 (q, *J* = 4 Hz), 124.0 (q, *J* = 272 Hz), 123.8, 122.9, 120.1, 125.6, 110.8 ppm. HRMS (ESI-Orbitrap): calcd for $C_{14}H_9F_3N_2$ $[M + H]^+$ 263.0791; found 263.0793.

**1-(o-Tolyl)-*1H*-benzo[*d*]imidazole (6g):**[10b] Prepared from boronic acid **2g** (reaction time 24 hours). Title product was obtained as a pale yellow oil (92 mg, 88%). $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.38 (s, 1 H), 7.81 – 7.73 (m, 1 H), 7.55 – 7.47 (m, 2 H), 7.46 – 7.39 (m, 2 H), 7.31 – 7.24 (m, 2 H), 7.16 – 7.09 (m, 1 H), 2.04 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 144.6, 143.6, 135.2, 135.1, 134.9, 132.0, 129.7, 128.1, 127.8, 123.8, 122.6, 120.3, 110.9, 17.7 ppm. HRMS (ESI-Orbitrap): calcd for $C_{14}H_{12}N_2$ $[M + H]^+$ 209.1073; found 209.1074.

**1-(2-Methoxyphenyl)-1*H*-benzo[*d*]imidazole (6h):**[10b] Prepared from boronic acid **2h** (reaction time 24 hours). Title product was obtained as a colorless oil (103 mg, 92%). $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.33 (s, 1 H), 7.77 – 7.71 (m, 1 H), 7.56 – 7.48 (m, 2 H), 7.34 (dd, *J* = 8.3, 1.0 Hz, 1 H), 7.29 – 7.20 (m, 3 H), 7.16 (td, *J* = 7.5, 0.9 Hz, 1 H), 3.78 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 154.3, 144.9, 143.6, 134.8, 130.6, 128.1, 124.6, 123.6, 122.5, 121.5, 120.1, 113.5, 111.4, 56.3 ppm. HRMS (ESI-Orbitrap): calcd for $C_{14}H_{12}N_2O$ $[M + H]^+$ 225.1022; found 225.1023.

**1-(2,6-Dimethoxyphenyl)-1*H*-benzo[*d*]imidazole (6j):** Prepared from boronic acid **2j** (reaction time 72 hours). Title product was obtained as a pale yellow oil (91 mg, 72%). $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.17 (s, 1 H), 7.76 – 7.66 (m, 1 H), 7.50 (t, *J* = 8.5 Hz, 1H), 7.27 – 7.16 (m, 2 H), 7.07 – 6.99 (m, 1 H), 6.92 (d, *J* = 8.5 Hz, 2 H), 3.71 (s, 6 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$):δ = 155.8, 145.2,

142.9, 134.5, 130.6, 122.7, 121.6, 119.4, 112.3, 110.7, 104.9, 56.0.ppm. HTMS (ESI-Orbitrap): calcd for $C_{15}H_{14}N_2O_2$ $[M + H]^+$ 255.1128; found 255.1127.

**1-(6-Methoxynaphthalen-2-yl)-1*H*-benzo[*d*]imidazole (6k):** Prepared from boronic acid **2k** (reaction time 8 hours). Title product was obtained as a white solid (123 mg, 90%), mp 144-146 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.63 (s, 1 H), 8.16 (d, *J* = 2.1 Hz, 1 H), 8.07 (d, *J* = 8.8 Hz, 1 H), 7.97 (d, *J* = 9.0 Hz, 1 H), 7.83 – 7.79 (m, 1 H), 7.76 (dd, *J* = 8.7, 2.2 Hz, 1 H), 7.70 – 7.65 (m, 1 H), 7.47 (d, *J* = 2.5 Hz, 1 H), 7.37 – 7.31 (m, 2 H), 7.29 (dd, *J* = 9.0, 2.6 Hz, 1 H), 3.92 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 158.3, 144.3, 144.1, 133.9, 133.9, 132.0, 130.0, 129.2, 129.2, 124.0, 123.3, 122.9, 122.2, 120.5, 120.4, 111.3, 106.6, 55.9 ppm. HRMS (ESI-Orbitrap): calcd for $C_{18}H_{14}N_2O$ $[M + H]^+$ 275.1179; found 275.1181.

**(*E*)-1-Styryl-1*H*-benzo[*d*]imidazole (6l)**:[26] Prepared from boronic acid **2l** (reaction time 24 hours). Title product was obtained as a pale yellow solid (80 mg, 73%), mp 88-91 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.76 (s, 1 H), 8.07 (d, *J* = 14.8 Hz, 1 H), 8.02 (d, *J* = 8.0 Hz, 1 H), 7.74 (d, *J* = 8.0 Hz, 1 H), 7.69 – 7.63 (m, 2 H), 7.44 – 7.35 (m, 3 H), 7.33 – 7.28 (m, 2 H), 7.26 (d, *J* = 14.7 Hz, 1 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 143.6, 141.7, 135.3, 132.4, 128.7, 127.5, 126.2, 123.5, 122.7, 122.2, 119.8, 117.7, 111.4 ppm. HRMS (ESI-Orbitrap): calcd for $C_{15}H_{12}N_2$ $[M + H]^+$ 221.1073; found 221.1073.

**1-(Thiophen-3-yl)-1*H*-benzo[*d*]imidazole (6m):**[10d] Prepared from boronic acid **2m** (reaction time 24 hours or 72 hours with the pinacol ester). Title product was obtained as pale yellow oil (73 mg, 73%; 77 mg, 77% with the pinacol ester). $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.59 (s, 1 H), 7.93 (dd, *J* = 3.1, 1.5 Hz, 1 H), 7.84 (dd, *J* = 5.2, 3.1 Hz, 1 H), 7.78 – 7.75 (m, 1 H), 7.70 (ddd, *J* = 8.0, 1.4, 0.7 Hz, 1 H), 7.58 (dd, *J* = 5.2, 1.5 Hz, 1 H), 7.38 – 7.33 (m, 1 H), 7.33 – 7.28 (m, 1 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 143.5, 143.3, 134.3, 132.9, 127.8, 123.6, 123.0, 122.5, 119.9, 116.0, 111.0 ppm. HRMS (ESI-Orbitrap): calcd for $C_{11}H_8N_2S$ $[M + H]^+$ 201.0481; found 201.0481.

**1-(4-Bromophenyl)-1*H*-benzo[*d*]imidazole (6n):**[5] Prepared from boronic acid **2n** (reaction time 24 hours). Title product was obtained as a white solid (116 mg, 85%), mp 109-112 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.08 (s, 1 H), 7.90 – 7.86 (m, 1 H), 7.72 – 7.69 (m, 2 H), 7.52 – 7.47 (m, 1 H), 7.42 – 7.39 (m, 2 H), 7.37 – 7.32 (m, 2 H) ppm. $^{13}$C NMR (400 MHz, $CDCl_3$): δ = 144.2, 142.1, 135.5, 133.6, 133.4, 125.7, 124.1, 123.2, 121.8, 120.9, 110.3 ppm. HRMS (ESI-Orbitrap): calcd for $C_{13}H_9BrN_2$ $[M + H]^+$ 273.0022 and 275.0001; found 273.0027 and 274.9999.

**1-(Pyridin-3-yl)-1*H*-benzo[d]imidazole (6o):**[27] Prepared from pyridin-3-ylboronic acid neopentylglycol ester **2o** (reaction time 72 hours). Title product was obtained as a white solid (88 mg, 90%), mp 88-90 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.86 (s, 1 H), 8.73 (d, *J* = 4.0 Hz, 1 H), 8.16 (s, 1 H), 7.91 – 7.86 (m, 2

H), 7.56 – 7.49 (m, 2 H), 7.38 – 7.36 (m, 2 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 149.4, 145.4, 144.0, 141.9, 133.5, 133.2, 131.5, 124.6, 124.4, 123.5, 120.9, 110.1 ppm. HRMS (ESI-Orbitrap): calcd for $C_{12}H_9N_3$ $[M + H]^+$ 196.0869; found 196.0871.

**General method for compounds 8-n (Table 4):** The same procedure as for compounds **6a-n** was employed, except imidazole **7** (34 mg, 0.5 mmol) was used as a starting material.

**1-(*p*-Tolyl)-1*H*-imidazole (8a):**[11a] Prepared from boronic acid **2a** (reaction time 24 hours). Title product was obtained as a white solid (69 mg, 87%), mp 39-41 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.20 – 8.18 (m, 1 H), 7.69 (t, *J* = 1.3 Hz, 1 H), 7.52 (d, *J* = 8.5 Hz, 2 H), 7.33 – 7.28 (m, 2 H), 7.09 – 7.08 (m, 1 H), 2.34 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 136.2, 135.4, 134.6, 130.2, 129.7, 120.2, 118.0, 20.4 ppm. HRMS (ESI-Orbitrap): calcd for $C_{10}H_{10}N_2$ $[M + H]^+$ 159.0917; found 159.0917.

**1-Phenyl-1*H*-imidazole (8b):**[10c] Prepared from boronic acid **2b** (reaction time 24 hours). Title product was obtained as pale yellow oil (61 mg, 85%). $^1$H NMR (400 MHz, DMSO-$d_6$): *δ* = 8.26 (s, 1 H), 7.75 (s, 1 H), 7.65 (dd, *J* = 7.3, 1.6 Hz, 2 H), 7.52 (t, *J* = 8.0 Hz, 2 H), 7.36 (t, *J* = 7.3 Hz, 1 H), 7.11 (s, 1 H) ppm. $^{13}$C NMR (101 MHz, DMSO-*d6*): *δ* = 136.9, 135.5, 129.9, 129.8, 126.8, 120.3, 118.0 ppm. HRMS (ESI-Orbitrap): calcd for $C_9H_8N_2$ $[M + H]^+$ 145.0760; found 145.0761.

**1-(4-Methoxyphenyl)-1*H*-imidazole (8c):**[11a] Prepared from boronic acid **2c** (reaction time 24 hours). Title product was obtained as a white solid (78 mg, 90%), mp 60-62 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.12 (t, *J* = 1.3 Hz, 1 H), 7.63 (t, *J* = 1.3 Hz, 1 H), 7.54 (d, *J* = 9.0 Hz, 2 H), 7.07 (t, *J* = 1.3 Hz, 1 H), 7.06 (d, *J* = 9.0 Hz, 2 H), 3.80 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 158.0, 135.5, 130.3, 129.5, 122.0, 118.3, 114.9, 55.5 ppm. HRMS (ESI-Orbitrap): calcd for $C_{10}H_{10}N_2O$ $[M + H]^+$ 175.0866; found 175.0867.

**4-(1*H*-Imidazol-1-yl)phenol (8d):**[28] Prepared from boronic acid **2d** (reaction time 24 hours). Title product was obtained as a reddish solid (48 mg, 60%), mp 189-190 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 9.75 (s, 1 H), 8.09 (br. s, 1 H), 7.61 (br. s, 1 H), 7.40 (d, *J* = 8.4 Hz, 2 H), 7.10 (br. s, 1 H), 6.87 (d, *J* = 8.4 Hz, 2 H) ppm. $^{13}$C NMR (101 MHz, DMSO-*d6*): *δ* = 156.4, 129.7, 129.1, 122.3, 119.3, 116.1 ppm. HRMS (ESI-Orbitrap): calcd for $C_9H_8N_2O$ $[M + H]^+$ 161.0709; found 161.0710.

**1-(4-Nitrophenyl)-1*H*-imidazole (8e):**[29] Prepared from boronic acid **2e** (additional 0.5 mmol of boronic acid **2e** was added after 24 hours, total reaction time 48 hours). Title product was obtained as a yellow solid (72 mg, 76%), mp 196-198 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.51 – 8.47 (m, 1 H), 8.36 (d, *J* = 9.0 Hz, 2 H), 8.00 – 7.96 (m, 2 H), 7.95 – 7.94 (m, 1 H), 7.19 – 7.17 (m, 1 H) ppm. $^{13}$C NMR

(100 MHz, DMSO-$d_6$): δ = 145.3, 141.7, 136.0, 130.8, 125.5, 120.4, 117.9 ppm. HRMS (ESI-Orbitrap): calcd for $C_9H_7N_3O_2$ $[M + H]^+$ 190.0611; found 190.0611.

**1-(4-(Trifluoromethyl)phenyl)-1*H*-imidazole (8f):**[30] Prepared from boronic acid **2f** (additional 0.5 mmol of boronic acid **2f** was added after 24 hours, total reaction time 48 hours). Title product was obtained as a white solid (84 mg, 79%), mp 65-67 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.42 (br.s, 1 H), 7.92 (d, *J* = 8.9 Hz, 2 H), 7.90 – 7.85 (m, 3 H), 7.16 (br.s, 1 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): *δ* = 139.9, 135.8, 130.4, 127.1 (q, *J* = 4 Hz), 126.6 (q, *J* = 32 Hz), 120.6, 124.0 (q, *J* = 272 Hz), 117.9 ppm. HRMS (ESI-Orbitrap): calcd for $C_{10}H_7F_3N_3$ $[M + H]^+$ 213.0634; found 213.0634.

**1-(*o*-Tolyl)-1*H*-imidazole (8g):**[11a] Prepared from boronic acid **2g** (reaction time 24 hours). Title product was obtained as pale yellow oil (67 mg, 85%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.57 (br. s, 1 H), 7.36 – 7.32 (m, 2 H), 7.30 – 7.25 (m, 1 H), 7.21 – 7.19 (m, 2 H), 7.05 (br. s, 1 H), 2.17 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): *δ* = 137.6, 136.7, 134.0, 131.4, 129.4, 128.9, 127.0, 126.6, 120.6, 17.7 ppm. HRMS (ESI-Orbitrap): calcd for $C_{10}H_{10}N_2$ $[M + H]^+$ 159.0917; found 159.0916.

**1-(2-Methoxyphenyl)-1*H*-imidazole (8h):**[11a] Prepared from boronic acid **2h** (reaction time 24 hours). Title product was obtained as a white solid (75 mg, 86%), mp 53-54 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 7.88 (s, 1 H), 7.47 – 7.34 (m, 3 H), 7.25 (d, *J* = 8.2 Hz, 1 H), 7.12 – 6.99 (m, 2 H), 3.82 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 152.1, 137.6, 128.9, 128.3, 126.0, 125.5, 120.9, 120.5, 112.9, 55.9 ppm. HRMS (ESI-Orbitrap): calcd for $C_{10}H_{10}N_2O$ $[M + H]^+$ 175.0866; found 175.0868.

**1-(2,6-Dimethoxyphenyl)-1*H*-benzo[*d*]imidazole (8j):**[31] Prepared from boronic acid **2j** (reaction time 48 hours). Title product was obtained as a white solid (81 mg, 79%), mp 145-147 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 7.56 (s, 1 H), 7.39 (t, *J* = 8.5 Hz, 1 H), 7.11 (d, *J* = 0.9 Hz, 1 H), 6.99 (d, *J* = 0.9 Hz, 1 H), 6.83 (d, *J* = 8.5 Hz, 2 H), 3.73 (s, 6 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 155.0, 138.6, 129.8, 127.5, 121.5, 114.8, 104.8, 56.1 ppm. HRMS (ESI-Orbitrap): calcd for $C_{11}H_{12}N_2O_2$ $[M + H]^+$ 205.0972; found 205.0974.

**1-(6-Methoxynaphthalen-2-yl)-1*H*-imidazole (8k):**[32] Prepared from boronic acid **2k** (reaction time 24 hours). Title product was obtained as pale yellow solid (99 mg, 88%), mp 76-78 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.34 (br.s, 1 H), 8.11 (d, *J* = 2.3 Hz, 1 H), 7.97 (d, *J* = 8.8 Hz, 1 H), 7.87 (d, *J* = 9.0 Hz, 1 H), 7.83 (t, *J* = 1.3 Hz, 1 H), 7.78 (dd, *J* = 8.8, 2.3 Hz, 1 H), 7.40 (d, *J* = 2.5 Hz, 1 H), 7.25 (dd, *J* = 9.0, 2.6 Hz, 1 H), 7.15 (br.s, 1 H), 3.89 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 157.5, 135.7, 132.9, 132.6, 129.9, 129.3, 128.5, 128.5, 120.1, 119.9, 118.2, 117.7, 106.0, 55.3 ppm. HRMS (ESI-Orbitrap): calcd for $C_{14}H_{12}N_2O$ $[M + H]^+$ 225.1022; found 225.1023.

**(*E*)-1-Styryl-1*H*-imidazole (8l):**[26] Prepared from boronic acid **2l** (reaction time 48 hours). Title product was obtained as pale yellow solid (63 mg, 74%), mp 78-79 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.02 (br.s, 1 H), 7.85 (d, *J* = 14.8 Hz, 1 H), 7.71 (br.s, 1 H), 7.50 (d, *J* = 7.3 Hz, 2 H), 7.38 (t, *J* = 7.6 Hz, 2 H), 7.26 (t, *J* = 7.3 Hz, 1 H), 7.06 (br.s, 1 H), 7.03 (d, *J* = 14.8 Hz, 1 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 137.0, 135.1, 129.8, 128.8, 127.4, 126.0, 123.8, 116.9, 116.6 ppm. HRMS (ESI-Orbitrap): calcd for $C_{11}H_{10}N_2$ $[M + H]^+$ 171.0917; found 171.0918.

**1-(Thiophen-3-yl)-1*H*-imidazole (8m):**[10d] Prepared from boronic acid **2m** (additional 0.5 mmol of boronic acid **2m** was added after 24 hours, total reaction time 48 hours). Title product was obtained as a white solid (45 mg, 60%), mp 82-83 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.25 – 8.20 (m, 1 H), 7.75 (dd, *J* = 3.2, 1.6 Hz, 1 H), 7.73 – 7.69 (m, 2 H), 7.53 (dd, *J* = 5.1, 1.6 Hz, 1 H), 7.07 – 7.05 (m, 1 H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 136.0, 135.8, 129.4, 127.8, 121.0, 118.3, 111.9 ppm. HRMS (ESI-Orbitrap): calcd for $C_7H_6N_2S$ $[M + H]^+$ 151.0324; found 151.0326.

**1-(4-Bromophenyl)-1*H*-imidazole (8n):**[10c] Prepared from boronic acid **2n** (reaction time 24 hours). Title product was obtained as a white solid (100 mg, 90%), mp 109-111 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.82 (s, 1 H), 7.62 – 7.58 (m, 2 H), 7.28 – 7.25 (m, 2 H), 7.24 (s, 1 H), 7.21 (s, 1 H). $^1$H NMR (400 MHz, $CDCl_3$): δ = 136.5, 135.6, 133.2, 130.9, 123.1, 121.1, 118.3 ppm. HRMS calcd for $C_9H_7BrN_2$ $[M + H]^+$ 222.9873 and 224.9845; found 222.9865 and 224.9845.

**General procedure for compounds 10 (Table 5):** A 25 mL round bottom flask was charged with a magnetic stirring bar, amine **9** (1.5 mmol), *p*-tolylboronic acid **2a** (1.0 mmol), $Cu_2S$ (8 mg, 0.05 mmol), and MeOH (4 mL), followed with the addition of TMEDA (0.15 mL, 1.0 mmol). The flask was sealed with a septum, through which was inserted 18-gauche needle. This setup allowed air to go into the reaction and avoid contamination of a mixture. The reaction mixture was stirred from 400 to 600 rpm for 24 hours, and then extracted with dichloromethane (2x 15 mL). Combined organic layers were washed with saturated aqueous solution of ethylenediaminetetraacetic acid disodium salt (15 mL), and then dried over anhydrous $Na_2SO_4$. Volatiles were removed under reduced pressure and the residue was purified by column chromatography (silica gel, hexanes – EtOAc) to yield the title product, which was characterized by $^1$H NMR, $^{13}$C NMR, HRMS, and melting point (if solid).

***N*-butyl-4-methylaniline (10a):**[33] Title product was prepared from butylamine **9a** and obtained as a pale yellow oil (116 mg, 81%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.03 – 6.99 (m, 2 H), 6.58 – 6.55 (m, 2 H), 3.11 (t, *J* = 7.2 Hz, 2 H), 2.26 (s, 3 H), 1.65 – 1.58 (m, 2 H), 1.45 (sextet, *J* = 7.2 Hz, 2 H), 0.98 (t, *J* = 7.2 Hz, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 146.4, 129.8, 126.5, 113.1, 44.2, 31.8, 20.5, 20.4, 14.1 ppm. HRMS (ESI-Orbitrap): calcd for $C_{11}H_{17}N$ $[M + H]^+$ 164.1434; found 164.1435.

***N*-hexyl-4-methylaniline (10b):**[34] Title product was prepared from hexylamine **9b** and obtained as a white solid (162 mg, 85%), mp 35-36 °C. $^{1}$H NMR (400 MHz, $CDCl_3$): δ = 7.01 – 6.98 (m, 2 H), 6.58 – 6.54 (m, 2 H), 3.09 (t, *J* = 7.3 Hz, 2 H), 2.25 (s, 3 H), 1.62 (quintet, *J* = 7.3 Hz, 2 H), 1.44 – 1.28 (m, 6 H), 0.9  0.89 (m, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 146.3, 129.8, 126.6, 113.2, 44.6, 31.8, 29.7, 27.0, 22.8, 20.5, 14.2 ppm. HRMS (ESI-Orbitrap): calcd for $C_{13}H_{21}N$ $[M + H]^+$ 192.1747; found 192.1745.

***N*-cyclopentyl-4-methylaniline (10c):**[35] Title product was prepared from cyclopentyl **9c** and obtained as a colorless oil (138 mg, 79%). $^{1}$H NMR (400 MHz, $CDCl_3$): δ = 7.01 – 6.98 (m, 2 H), 6.58 – 6.55 (m, 2 H), 3.81 – 3.75 (m, 1 H), 2.25 (s, 3 H), 2.05 – 1.98 (m, 2 H), 1.75 – 1.68 (m, 2 H), 1.65 – 1.59 (m, 2 H), 1.51 – 1.43 (m, 2 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 145.8, 129.8, 126.4, 113.6, 55.2, 33.5, 24.2, 20.5 ppm. HRMS (ESI-Orbitrap): calcd for $C_{12}H_{17}N$ $[M + H]^+$ 176.1434; found 176.1434.

***N*-cyclohexyl-4-methylaniline (10d):**[36] Title product was prepared from cyclohexylamine **9d** and obtained as a white solid (147 mg, 78%), mp 39-41 °C. $^{1}$H NMR (400 MHz, $CDCl_3$): δ = 6.99 (d, *J* = 7.9 Hz, 2 H), 6.57 – 6.54 (m, 2 H), 3.27 – 3.20 (m, 1 H), 2.25 (s, 3 H), 2.10 – 2.05 (m, 2 H), 1.80 – 1.75 (m, 2 H), 1.69 – 1.64 (m, 1 H), 1.43 – 1.33 (m, 2 H), 1.30 – 1.10 (m, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 145.1, 129.9, 126.3, 113.7, 52.2, 33.6, 26.1, 25.2, 20.5 ppm. HRMS (ESI-Orbitrap): calcd for $C_{13}H_{19}N$ $[M + H]^+$ 190.1590; found 190.1591.

**One-pot Suzuki-Miyaura and Chan-Lam reaction**

**1-(4'-Methyl-[1,1'-biphenyl]-4-yl)-1*H*-benzo[*d*]imidazole (11)**: A microwave vial was charged with a magnetic stirring bar, benzimidazole **5** (118 mg, 1.0 mmol), boronic acid **2n** (220 mg, 1.1 mmol), $Cu_2S$ (8 mg, 0.05 mmol), and EtOH (4 mL), then followed with the addition of TMEDA (0.15 mL, 1.0 mmol). The flask was sealed with a septum, through which was inserted 18-gauche needle. This setup allowed access of air and avoided contamination. The reaction mixture was stirred from 400 to 600 rpm for 24 hours. Then the mixture was flushed with nitrogen. To the flask was subsequently added water (1.0 mL), $K_2CO_3$ (417 mg, 3.0 mmol), boronic acid (272 mg, 2.0 mmol), and XPhos Pd G2 (8 mg, 0.01 mmol). The vial was sealed and inserted into a microwave reactor, where it was irradiated at variable power, so the temperature was maintained at 120 °C for 30 minutes. Then the mixture was partitioned between dichloromethane (20 mL) and water (20 mL). The organic layer was separated and aqueous layer extracted twice with dichloromethane (2x 20 mL). Combined organic layers were dried over anhydrous $Na_2SO_4$. Volatiles were removed under reduced pressure and the residue was purified by column chromatography (silica gel, hexanes – EtOAc) to yield the title compound **11** as a white solid (264 mg, 93% yield, 96% HPLC purity). This material contained 2% of compound **6n**, and two unknown impurities (both 1% HPLC area). Crystallization from boiling MeOH (4 mL) gave

compound **11** as a white crystalline solid (193 mg, 68%), mp 154 – 156 °C. $^{1}$H NMR (500 MHz, $CDCl_3$): δ = 8.16 (s, 1 H), 7.92 – 7.89 (m, 1 H), 7.77 (d, *J* = 8.6 Hz, 2 H), 7.61 – 7.59 (m, 1 H), 7.58 (d, *J* = 8.6 Hz, 2 H), 7.55 (d, *J* = 8.2 Hz, 2 H), 7.38 – 7.34 (m, 2 H), 7.31 (d, *J* = 8.2 Hz, 2 H), 2.43 (s, 3 H) ppm. $^{13}$C NMR (500 MHz, $CDCl_3$): δ = 142.4, 141.2, 138.0, 137.0, 135.3, 129.9, 128.6, 127.1, 124.4, 123.9, 122.9, 120.8, 110.7, 21.3 ppm. HRMS calcd for $C_{20}H_{16}N_2$ $[M + H]^+$ 285.1386, found 285.1395.

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## Supporting Information

Copies of $^{1}$H NMR and $^{13}$C NMR spectra for all prepared compounds, HPLC for one-pot Chan-Lam/Suzuki-Miyaura reactions, chiral HPLC for compounds **3g** and **4g** are included.

## References and Notes

(1) Examples of *N*-arylazoles with biological activities: (a) Cozzi, P.; Carganico, G.; Fusar, D.; Grossoni, M.; Menichincheri, M.; Pinciroli, V.; Tonani, R.; Vaghi, F.; Salvati, P. *J. Med. Chem.* **1993**, *36*, 2964-2972. (b) Lange, J. H. M.; van Stuivenberg, H. H.; Coolen, H. K. A. C.; Adolfs, T. J. P.; McCreary, A. C.; Keizer, H. G.; Wals, H. C.; Veerman, W.; Borst, A. J. M.; de Looff, W.; Verveer, P. C.; Kruse, C. G. *J. Med. Chem.* **2005**, *48*, 1823-1838. (c) Quan, M.L.; Lam, P. Y. S.; Han, Q.; Pinto, D. J. P.; He, M. Y.; Li, R.; Ellis, C. D.; Clark, C. G.; Teleha, C. A.; Sun, J.-H.; Alexander, R. S.; Bai, S.; Luettgen, J. M.; Knabb, R. M.; Wong, P. C.; Wexler, R. R. *J. Med. Chem*. **2005**, *48*, 1729-1744.

(2) Gaba, M.; Mohan, C. *Med. Chem. Res.* **2016**, *25*, 173-210.

(3) Methods involving construction of heterocycle ring: (a) Pooi, B.; Lee, J.; Choi, K.; Hirao, H.; Hong, S. H. *J. Org. Chem.* **2014**, *79*, 9231-9545. (b) Tang, D.; Wu, P.; Liu, X.; Chen, Y.-X.; Guo, S.-B.; Chen, W.-L.; Li, J.-G.; Chen, B.-H. *J. Org. Chem.* **2013**, *78*, 2746-2750. (c) Caron, S.; Jones, B. P.; Wei, L. *Synthesis*, **2012**, *44*, 3049-3054.

(4) Gungor, T.; Fouquet, A.; Teulon, J. M.; Prevost, D.; Cazes, M.; Cloarec, A. *J. Med. Chem.* **1992**, *35*, 4455-4463.

(5) Catalyst-free *N*-arylation using unactivated fluorobenzenes was reported, but it requires harsh reaction conditions: Diness, F.; Fairlie, D. P. *Angew. Chem. Int. Ed.* **2012**, *51*, 8012-8016.

(6) Ullman-type *N*-arylation of heterocycles: (a) Chen, H.; Wang, D.; Wang, X.; Huang, W.; Cai, Q.; Ding, K. *Synthesis* **2010**, 1505-1511. (b) Altman, R. A.; Buchwald, S. L. *Org. Let.* **2006**, *8*, 2779-2782. (c) Lee, Ch.-Ch.; Wang, P.-S.; Viswanath, M. B.; Leung, M. *Synthesis* **2008**, *9*, 1359 – 1366.

(7) Buchwald-Hartwig *N*-arylation of heterocycles: (a) Boyd, E. M.; Sperry, J. *Org. Lett.* **2014**, *16*, 5056-5059. (b) Ueda, S.; Su, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012**, *134*, 700-706. (c) Sandtorv, A. H.; Leitch, C.; Bedringaas, S. L.; Gjertsen, B. T.; Bjørsvik, H.-R. *Chem. Med. Chem.* **2015**, *10*, 1522-1527.

(8) Recent reports on the Chan-Lam reaction: (a) Roy, S.; Sarma, M. J.; Kashyap, B.; Phukan, P. *Chem. Commun.* **2016**, *52*, 1170-1173. (b) Vantourout, J. C.; Miras, H. N.; Isidro-Llobet, A.; Sproules, S.; Watson, A. J. B. *J. Am. Chem. Soc.* **2017**, *139*, 4769-4779. (c) Yoo, W.J.; Tsukamoto, T.; Kobayashi, S. *Angew, Chem. Int. Ed.* **2015**, *54*, 6587-6590.

(9) Application of the Chan-Lam and Suzuki-Miyaura coupling in one reaction sequence, but not in a one-pot manner: (a) Chen, T.; Luo, Y.; Hu, Y.; Yang, B.; Lu, W. *Eur. J. Med. Chem.* **2013**, *64*, 613-620. (b) Namani, V.; Goud, B. B. K.; Kumari, Y. B.; Kumbham, R. *Heterocycl. Lett.* **2015**, *5*, 673-677.

(10) Selected examples of the Chan-Lam arylation of heterocycles: (a) Nishiura, K.; Urawa, Y.; Soda, S. *Adv. Synth. Catal.* **2004**, *346*, 1679-1684. (b) Wentzel, M. T. ; Hewgley, J. B.; Kamble, R. M.; Wall, P. D; Kozlowski, . M. C.; *Adv. Synth. Catal.* **2009**, *351*, 931-937. (c) Sreedhar, B.; Venkanna, G. T.; Kumar, K. B. S.; Balasubrahmanyam, V. *Synthesis* **2008**, 795-799. (d) Begouin, A.; Queiroz, M.-J. R. P. *Helv. Chim. Acta* **2013**, *96*, 853-863.

(11) Efficient Chan-Lam reaction protocols requiring stoichiometric oxidant or oxygen atmosphere: (a) Collman, J. P.; Zhong, M. *Org. Lett.* **2000**, *2*, 1233-1236. (b) Xue, J.Y.; Li, J.-C.; Li, H.-X.; Li, H.-Y.; Lang, J.-P. *Tetrahedron* **2016**, *72*, 7014-7020. (c) Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K. *Tetrahedron Lett.* **2001**, *42*, 3415-3418.

(12) Qiao, J. X.; Lam, P. Y. S. *Synthesis* **2011**, 829-856.

(13) HPLC/MS analysis of the crude reaction mixture is shown in the supporting information.

(14) Liu, H.; Tang, J.; Jiang, L.; Zheng, T.; Wang, X.; Lv, X. *Org. Lett.* **2008**, *10*, 3263-3266.

(15) Barbero, N.; Carril, M.; SanMartin, R.; Domínguez, E. *Tetrahedron* **2008**, *64*, 7283-7288.

(16) Tipparaju, S. K.; Muench, S. P.; Mui, E. J.; Ruzheinikov, S. N.; Lu, J. Z.; Hutson, S. L.; Kirisits, M. J.; Prigge, S. T.; Roberts, C. W.; Henriquez, F. L.; Kozikowski, A. P.; Rice, D. W.; McLeod, R. L. *J. Med. Chem.* **2010**, *53*, 6287-6300.

(17) Hromatka, O.; Binder, D.; Eichinger, K. *Monatsh. Chem.* **1975**, *106*, 555-558.

(18) Li, Z.; Sun, H.; Jiang, H.; Liu, H. *Org. Lett.* **2008**, *10*, 363-3266.

(19) Yu, J.; Gao, Ch.; Song, Z.; Yang, H.; Fu, H. *Eur. J. Org. Chem.* **2015**, 5869-5875.

(20) Ward, R. E.; Meyer, T. Y. *Macromolecules* **2003**, *36*, 4368-4373.

(21) Winternheimer, D. J.; Merlic, C. A. *Org. Lett.* **2010**, *12*, 2508-2510.

(22) Zhu, X.; Su, L.; Huang, L.; Chen, G.; Wang, J.; Song, H.; Wan, Y. *Eur. J. Org. Chem.* **2009**, 635-642.

(23) Tashiro, M.; Itoh, T.; Fukata, G. *Synthesis* **1982**, 217-219.

(24) Yang, K.; Qiu, Y.; Li, Z.; Wang, Z.; Jiang, S. *J. Org. Chem.* **2011**, *76,* 3151-3159.

(25) Liu, B.; Liu, B.; Zhou, Y.; Chen, W. *Organometallics* **2010**, *29*, 1457-1464.

(26) Reddy, V. P. ; Kumar, A. V. ; Rao, K. R. *Tetrahedron Lett*. **2010**, *51*, 3181-3185.

(27) Zhang, Z.; Mao, J.; Zhu, D.; Wu, F.; Chen, H.; Wan, B. *Tetrahedron* **2006**, *62*, 4435-4443.

(28) Zhu, L.; Cheng, L.; Zhang, Y.; Xie, R.; You, J. *J. Org. Chem.* **2007**, *72*, 2737-2743.

(29) Das, S.; Maity, T.; Koner**,** S. *Appl. Catal. A-Gen.* **2016**, *513*, 53-66.

(30) Cristau, H.-J. ; Cellier, P. P.; Spindler, J.-F. ; Taillefer, M. *Chem. Eur. J.* **2004**, *10*, 5607-5622.

(31) Majumder, A.; Gupta, R.; Mandal, M.; Babu, M.; Chakraborty, D. *J. Organomet. Chem*. **2015**, *781*, 23-34.

(32) Lv, X.; Wang, Z.; Bao, W. *Tetrahedron* **2006**, *62*, 4756-4761.

(33) Dai, Q.; Gao, W.; Liu, D.; Kapes, L. M.; Zhang, X. *J. Org. Chem.* **2006**, *71*, 3928-3934.

(34) Cawley, M. J.; Cloke, F. G. N.; Fitzmaurice, R. J.; Pearson, S. E.; Scott, J. S.; Caddick, S. *Org. Biomol. Chem.* **2008**, *6*, 2820-2825.

(35) Kattamuri, P. V.; Yin, J.; Siriwongsup, S.; Kwon, D.-H.; Ess, D. H.; Li, Q.; Li, G.; Yousufuddin, M.; Richardson, P. F.; Sutton, S. C.; Kürti, L. *J. Am. Chem. Soc.* **2017**, *139*, 11184-11196.

(36) Wu, Z.; Zhou, L.; Jiang, Z.; Wu, D.; Li, Z.; Zhou, X. *Eur. J. Org. Chem.* **2010**, 4971-4975.