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Palladium-Catalyzed Direct Arylation of Heteroaromatic Compounds: Improved Conditions Utilizing Controlled Microwave Heating

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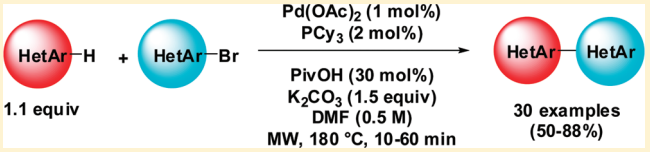
Supporting Information

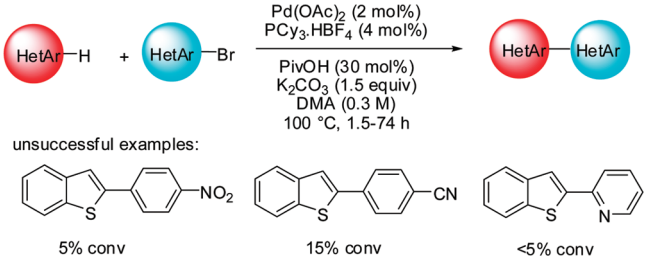
ABSTRACT: A versatile and rapid microwave-assisted procedure for the palladium-catalyzed direct arylation of heterocycles by aryl bromides and heteroaryl bromides is described. This novel protocol features short coupling times (10−60 min) and low catalyst loadings (1 mol %) and allows the successful arylation of previously unreactive heterocyclic substrates.



The formation of carbon−carbon bonds via palladium-catalyzed direct arylation to form biaryl or aryl−heteroaryl products is an attractive alternative to the more traditional cross-coupling chemistry involving organometallic species, since the organometallic coupling partner can be replaced by a simple arene.[1] In recent years direct arylation reactions received a considerable amount of attention for the synthesis of heteroatom-containing biaryls, which are common motifs in natural products[2] and pharmaceutically relevant compounds.[3] Since the pioneering investigations on direct arylation in the early 1980s,[4] many research groups have been involved in the development of new methods based on direct arylation chemistry for the preparation of heteroatom-containing biaryl structures.[1,5] In 2006, the Fagnou group pioneered a robust synthetic protocol for the direct arylation of benzene,[6] which subsequently—after some modification—was also applied for the arylation of a wide range of electron-rich heterocycles (Scheme 1).[7] It was suggested that palladium catalyzes the arylation through a concerted metalation−deprotonation (CMD) pathway.[8] In the reported catalytic system, a key factor was the use substoichiometric amounts of pivalic acid, which was proposed to function as a proton shuttle during the aryl C−H cleavage step.[6−10]

Despite these impressive recent improvements in reaction scope, the Fagnou direct arylation protocol still suffers from some disadvantages, such as long reaction times (1.5−74 h, for most published examples more than 12 h) and low reactivity for several important substrate classes, resulting in low yields or even no conversion (Scheme 1).[7] Furthermore, under the reported conditions, attempts for direct arylation with heteroatom-containing aryl bromides such as 2-bromopyridine proved to be unsuccessful (Scheme 1).[7] Herein we report an improved microwave-assisted procedure for the direct arylation of heteroatom-containing aromatic compounds. Exploiting controlled sealed-vessel microwave heating,[11] the C−H arylation of a wide range of heterocycles with different types of (hetero)aryl bromides takes place within a short period of time (10−60 min). The corresponding coupling products were obtained in good to excellent yields, despite utilizing lower catalyst and ligand loadings. Most importantly, the reactivity of electron-poor aryl bromides in this palladium-catalyzed direct arylation protocol improved significantly compared to that in the original Fagnou protocol.

Scheme 1. Fagnou Protocol for Direct Arylation of Aromatic Heterocycles[7]



Following the original Fagnou protocol (Scheme 1), the conditions were reoptimized applying controlled microwave heating with accurate internal temperature monitoring.[12,13] After an extensive screening of different reaction parameters (see the Supporting Information), we arrived at conditions that involved the use of palladium acetate (1 mol %) as a catalyst, tricyclohexylphosphine (PCy_3) (2 mol %) as a ligand, pivalic acid (30 mol %) as an additive, and potassium carbonate (K_2CO_3) as a base (1.5 equiv) in *N*,*N*-dimethylformamide (DMA; 0.5 M) as a solvent. Using these conditions, even cases that were originally reported as unsuccessful (Scheme 1)[2] could be arylated efficiently,

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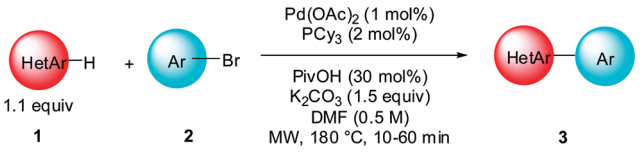
providing high isolated product yields within 10 min at 180 °C (Table 2, entry 1). Control experiments using conductive heating at the same temperature have demonstrated that the observed enhancements are due to a purely thermal effect (see the Supporting Information).[13]

Encouraged by the results obtained in the optimization experiments, the direct arylation of heterocycles **1** with different types of aryl bromides **2** was investigated using the microwave protocol (Table 1). Para-, meta-, and ortho-substituted aryl bromides all coupled with heterocyclic compounds in moderate to excellent yields. Notably, the presence of aldehyde (entries 15−18) and nitrile (entries 2 and 11) groups was well tolerated under the reaction conditions. It was found that in most cases aryl bromides with electron-withdrawing groups on the aryl ring undergo the direct arylation with lower amounts of palladium catalyst within a shorter period of time (entries 1 and 4). Variation of the substituents at the aryl ring of aryl bromides **2** was unproblematic, and both electron-rich and electron-deficient aryl bromides coupled with heterocycles **1** to generate heteroatom-containing biaryls **3a**−**r** in moderate to high yields. The results of our investigation revealed that the protocol is applicable for direct C−H arylation of a wide range of heterocyclic compounds (Table 1). In particular, the reactivity of the imidazole ring for C−H arylation increased significantly under these high-temperature conditions compared to that in previous reports (entries 6−8).[7,14] Other types of heterocyclic structures such as thiophene (entries 11−13 and 16), furan (entry 17), thiazole (entry 14 and 15), and benzothiazole worked nicely under the optimized microwave conditions. Notably, some of the products prepared in good yields (**2a**, **2b**) using microwave heating at 180 °C had been reported as unsuccessful coupling reactions employing conventional heating at 100 °C.[7] All of these results are in agreement with the proposed relative reactivities of the different C−H bonds of the heterocyclic substrates in a CMD pathway.[9a]

Similar to biaryl structures, the biheteroaryl motif is prevalent in polymers, advanced materials, liquid crystals, ligands, molecules of medicinal interest, and natural products.[15] Therefore, the successful arylation of heterocycles by aryl bromides **2** encouraged us to extend our studies also to heteroaryl bromides of type **4**. The results are summarized in Table 2 and demonstrate that the reactivity follows the same general trend observed for the aryl bromides **2**. Particularly notable in this regard is the use of 2-bromopyridine (**4a**) in the reaction with benzothiophene (**1a**) (entry 1), since no conversion to the desired product was obtained at 100 °C by Fagnou and co-workers.[7] Bromopyrazoles underwent direct arylation reaction with different types of heterocycles (entries 4, 7, and 11), and it should be mentioned that to the best of our knowledge this is the first report on utilizing these substrates in direct arylation reactions. 5-Bromo-2-chloropyridine (**4e**) was selectively arylated with 2-methylthiophene (**1d**) at the C5 position of the pyridine ring. The resulting product **5j** would therefore be able to undergo further arylation at the C2 position of the pyridine ring through a Suzuki coupling.

In conclusion, a facile and versatile microwave-assisted procedure was developed for the direct arylation of heterocyclic C−H bonds by aryl bromides and heteroaryl bromides. Compared to the originally published method by Fagnou,[7] this modified protocol features coupling times of only 10−60 min and in most examples allows a reduction in catalyst loading while retaining high coupling efficiency. Most importantly, by executing the arylation processes at high temperatures under microwave irradiation, it was possible to increase the reactivity of some substrates dramatically and therefore prepare arylation products which were not accessible using the previously published method.

Table 1. Direct Arylation of Heterocycles 1 with Aryl Bromides 2[a]



Entry	1	3	Time (min)	Yield (%)[b]
1	1a	3a	10	75
2	1a	3b	10	80
3	1a	3c	30	80
4[d]	1a	3d	60	55
5	1a	3e	10	55
6[c]	1b	3f	10	75
7[c,d]	1b	3g	30	68
8[c]	1b	3h	10	88
9	1c	3i	10	79
10[d]	1c	3j	30	85
11	1d	3k	10	85
12	1d	3l	30	60
13	1d	3m	10	85
14[c,d]	1e	3n	60	55
15	1e	3o	10	80
16[c]	1f	3p	10	84
17	1g	3q	10	85
18	1h	3r	30	65

[a] Reaction conditions: sealed vessel single-mode microwave heating (Monowave 300) with internal fiber-optic temperature control and magnetic stirring; 1.1 mmol of **1**, 1 mmol of **2**, 0.01 mmol of $Pd(OAc)_2$, 0.02 mmol of PCy_3, 0.3 mmol of PivOH, and 1.5 mmol of K_2CO_3 in 2 mL of DMF; 180 °C. [b] Isolated yield. [c] 1.5 equiv of **1**. [d] 2 mol % $Pd(OAc)_2$, 4 mol % PCy_3.

EXPERIMENTAL SECTION

General Experimental Details. ^1H NMR and ^{13}C NMR spectra were recorded on a 300 MHz instrument at 300 and 75 MHz, respectively. Chemical shifts (δ) are expressed in parts per million

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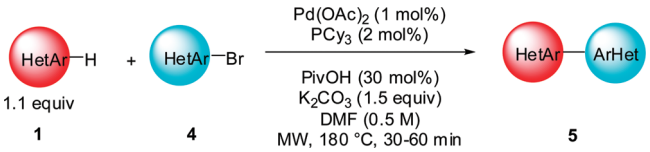
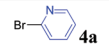
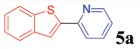
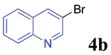
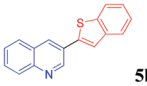
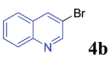
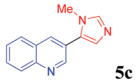
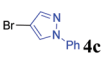
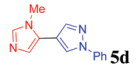
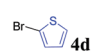
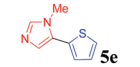
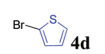
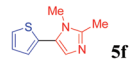
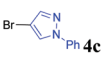
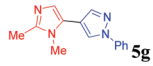
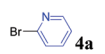
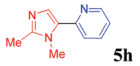
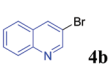
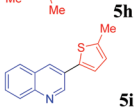
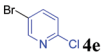
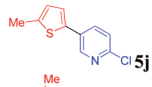
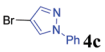
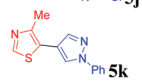
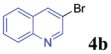
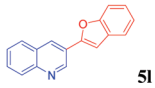
Table 2. Direct Arylation of Heterocycles 1 with Heteroaryl Bromides 4[a]



Entry	1	4	5	Time (min)	Yield (%)[b]
1[c,d]	 1a	 4a	 5a	60	55
2	 1a	 4b	 5b	30	65
3[c]	 1b	 4b	 5c	30	80
4[c]	 1b	 4c	 5d	30	75
5[c]	 1b	 4d	 5e	30	60
6	 1c	 4d	 5f	30	60
7	 1c	 4c	 5g	30	62
8[c,d]	 1c	 4a	 5h	60	55
9	 1d	 4b	 5i	30	58
10[d]	 1d	 4e	 5j	60	64
11	 1e	 4c	 5k	30	70
12	 1i	 4b	 5l	60	50

[a] Reaction conditions: sealed vessel single-mode microwave heating (Monowave 300) with internal fiber-optic temperature control and magnetic stirring; 1.1 mmol of **1**, 1 mmol of **4**, 0.01 mmol of $Pd(OAc)_2$, 0.02 mmol of PCy_3, 0.3 mmol of PivOH, and 1.5 mmol of K_2CO_3 in 2 mL of DMF; 180 °C. [b] Isolated yield. [c] 1.5 equiv of **1**. [d] 2 mol % $Pd(OAc)_2$, 4 mol % PCy_3.

downfield from TMS as the internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet. High-resolution mass spectrometry (HRMS) was performed in the EI mode (70 eV). GC–MS conditions were as follows: splitless injection, injection temperature 250 °C, HP-5 MS column (30 m × 0.25 mm i.d., 0.25 μm film), carrier gas helium 5.0, flow 1 mL/min, temperature gradient programmed from 60 to 300 at 20 °C/min after an initial time of 6 min. The MS conditions were as follows: positive EI ionization, ionization energy 70 eV, ionization source temperature 280 °C, emission current 100 μA. Melting points were obtained on a standard melting point apparatus in open capillary tubes. The synthesized compounds were purified via flash chromatography on silica gel or an automated flash chromatography system using cartridges packed with KP-SIL, 60 Å (32–63 μm particle size). TLC analyses were performed on precoated (silica gel 60 HF254) plates. 3-Bromo-1-phenylpyrazole (**4c**) was synthesized according to a known procedure;[16] characterization data (^1H and ^{13}C NMR, MS) are in agreement with literature values. The purity of all synthesized products (>98%) was determined by HPLC-UV (215 nm) chromatography and ^1H NMR spectroscopy. All anhydrous solvents (stored over molecular sieves) and chemicals were obtained from standard commercial vendors and were used without any further purification except where stated otherwise.

Microwave Irradiation Experiments. Microwave irradiation experiments were performed using a Monowave 300 single-mode microwave reactor.[12,13] The reaction temperature is monitored by an internal fiber-optic (FO) temperature probe (ruby thermometer) protected by a borosilicate immersion well inserted directly into the reaction mixture. Reaction times refer to the hold time at the desired set temperature and not to the total irradiation time. Pressure sensing is achieved by a hydraulic sensor integrated in the swiveling cover of the instrument. The reusable 10 mL Pyrex vial is sealed with PEEK snap caps and standard PTFE-coated silicone septa. Reaction cooling is performed by compressed air automatically after the heating period has elapsed. The required force of 6–8 bar is also used to pneumatically seal the vials tightly at the beginning to withstand 30 bar and to ensure smooth release of potentially remaining pressure before the cover is opened.

General Procedure for Direct C–H Arylation Reactions. K_2CO_3 (1.5 equiv, 1.5 mmol, 206 mg), $Pd(OAc)_2$ (1 mol %, 0.01 mmol, 2.2 mg), PCy_3 (2 mol %, 0.02 mmol, 5.6 mg), and PivOH (30 mol %, 0.3 mmol, 30 mg) were weighed in air and placed in a 5 mL microwave vial equipped with a magnetic stir bar. The appropriate heterocycles **1** (1.1 equiv, 1.1 mmol) and aromatic bromides **2** and **4** (1 equiv, 1 mmol) were added at this point if solids. The vial was purged with argon, and DMF (2 mL) was added. The heterocycle (1.1 equiv, 1.1 mmol) and the aromatic bromides (1 equiv, 1 mmol) were added at this point if liquids. The sealed reaction vial was then placed in the microwave reactor and stirred at 180 °C over the indicated time (see Tables 1 and 2). The solution was then cooled to rt, diluted with EtOAc, washed with H_2O (3 times), dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding product.

2-(4-Nitrophenyl)benzo[*b*]thiophene (3a).[17] Yellow solid. Mp: 201–202 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.39–7.44 (m, 2H), 7.73 (s, 1H), 7.84–7.90 (m, 4H), 8.30 (d, J = 9.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.2, 141.2, 140.6, 140.3, 131.3, 130.3, 126.8, 125.6, 125.1, 124.4, 124.3, 122.4.

4-(Benzo[*b*]thiophene-2-yl)benzonitrile (3b).[5i] White solid. Mp: 190–191 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.44 (m, 2H), 7.63 (s, 1H), 7.66 (d, J = 8.7 Hz, 2H), 7.75 (d, J = 8.7 Hz, 2H), 7.79–7.86 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.6, 140.3, 139.9, 138.5, 132.7, 126.7, 125.4, 125.0, 124.2, 122.4, 121.8, 118.7, 111.3.

2-(4-Methylphenyl)benzo[*b*]thiophene (3c).[7] Off-white solid. Mp: 160–162 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 2.46 (s, 3H), 7.29 (d, J = 8.1 Hz, 2H), 7.34–7.44 (m, 2H), 7.56 (s, 1H), 7.68 (d, J = 8.1 Hz, 2H), 7.82 (dd, J = 6.9, 1.5 Hz, 1H), 7.88 (dd, J = 6.9, 1.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.5, 140.9, 139.4, 138.3, 131.6, 129.7, 126.4, 124.5, 124.2, 123.5, 122.3, 118.9, 21.3.

2-(4-Methoxyphenyl)benzo[*b*]thiophene (3d).[7] Off-white solid. Mp:188–189 °C. ^1H NMR δ 3.78 (s, 3H), 6.89 (d, J = 8.7 Hz, 2H), 7.18–7.29 (m, 2H), 7.33 (s, 1H), 7.57 (d, J = 8.7 Hz, 2H), 7.67 (d, J = 7.5, 1H), 7.72 (d, J = 8.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.5, 140.9, 139.4, 138.3, 131.6, 129.7, 126.4, 124.5, 124.2, 123.5, 122.3, 118.9, 21.3.

2-(Naphthalen-1-yl)benzo[*b*]thiophene (3e).[18] White solid. Mp: 104–106 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.42–7.60 (m, 6H), 7.70–7.75 (m, 1H), 7.89–7.96 (m, 4H), 8.37 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.2, 140.4, 140.3, 133.9, 132.5, 131.9, 128.9, 128.5, 128.4, 126.7, 126.2, 125.8, 125.3, 124.5, 124.3, 124.1, 123.6, 122.1.

1-Methyl-5-(4-nitrophenyl)-1*H*-imidazole (3f).[19] Yellow solid. Mp: 166–167 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 3.75 (s, 3H),

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7.23 (s, 1H), 7.54−7.57 (m, 3H), 8.24 (d, J = 8.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.8, 140.9, 136.3, 131.3, 130.3, 128.2, 124.1, 33.0.

5-(4-Methoxyphenyl)-1-methyl-1*H*-imidazole (3g).[14b] Pale yellow solid. Mp: 106−108 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.64 (s, 3H), 3.86 (s, 3H), 6.98 (d, J = 9 Hz, 2H), 7.05 (s, 1H), 7.33 (d, J = 9 Hz, 2H), 7.52 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5, 138.5, 133.2, 130.0, 127.4, 122.1, 114.2, 55.3, 32.4.

5-(6-Methoxynaphthalen-2-yl)-1-methyl-1*H*-imidazole (3h).[14b] White solid. Mp: 157−159 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.72 (s, 3H), 3.95 (s, 3H), 7.17−7.24 (m, 3H), 7.47 (dd, J = 8.4, 1.5 Hz, 1H), 7.56 (s, 1H), 7.75−7.81 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.1, 139.0, 133.9, 133.6, 129.5, 128.8, 128.1, 127.2, 126.9, 124.9, 119.5, 105.7, 55.4, 32.6.

1,2-Dimethyl-5-(4-nitrophenyl)-1*H*-imidazole (3i).[20] Yellow solid. Mp: 150−151 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.48 (s, 3H), 3.68 (s, 3H), 7.12 (s, 1H), 7.53 (d, J = 8.7 Hz, 2H), 8.28 (d, J = 9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.1, 146.6, 137.0, 131.6, 128.4, 128.2, 124.2, 31.9, 13.9.

5-(4-Methoxyphenyl)-1,2-dimethyl-1*H*-imidazole (3j).[20] Pale yellow solid. Mp: 112−113 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 3H), 3.41 (s, 3H), 3.76 (s, 3H), 6.90 (d, J = 9 Hz, 2H), 7.21 (d, J = 9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 145.4, 133.2, 130.0, 125.3, 122.9, 114.0, 55.3, 31.1, 13.7.

2-(5-Methylthiophene-2-yl)benzonitrile (3k).[21] Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.54 (d, J = 0.9 Hz, 3H), 6.81 (dd, J = 3.6, 0.9 Hz, 1H), 7.30−7.36 (m, 1H), 7.47 (d, J = 3.6 Hz, 1H), 7.55−7.57 (m, 2H), 7.70 (d, J = 7.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.3, 137.8, 137.0, 134.3, 132.9, 129.2, 127.7, 127.0, 126.6, 119.1, 109.4, 15.4.

2-Methyl-5-(3-methylphenyl)thiophene (3l).[22] Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.46 (s, 3H), 2.58 (s, 3H), 6.79−6.80 (m, 1H), 7.13−7.18 (m, 2H), 7.32 (t, J = 7.5 Hz, 1H), 7.44−7.46 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.2, 139.3, 138.4, 134.7, 128.8, 127.9, 126.3, 126.2, 122.9, 122.7, 21.5, 15.5.

2-Methyl-5-(4-nitrophenyl)thiophene (3m).[22] Yellow solid. Mp: 130−131 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.55 (d, J = 0.9 Hz, 3H), 6.81 (dd, J = 3.6, 1.2 Hz, 1H), 7.29 (d, J = 3.6 Hz, 1H), 7.65 (d, J = 9 Hz, 2H), 8.20 (d, J = 9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.2, 143.0, 140.8, 139.1, 127.0, 125.8, 125.3, 124.4, 15.6.

5-(4-Methoxyphenyl)-4-methylthiazole (3n).[7] Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.51 (s, 3H), 3.83 (s, 3H), 6.95 (d, J = 8.7 Hz, 2H), 7.36 (d, J = 8.7 Hz, 1H), 8.63 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.4, 149.7, 147.9, 131.7, 130.5, 124.2, 114.2, 55.3, 16.0.

4-(4-Methylthiazol-5-yl)benzaldehyde (3o). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.52 (s, 3H), 7.56 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 8.1 Hz, 2H), 8.70 (s, 1H), 7.63 (d, J = 8.4 Hz, 2H), 9.98 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.4, 151.4, 149.8, 138.1, 135.3, 130.0, 129.6, 126.7, 16.4. HRMS (EI$^+$): m/z calcd for $C_{12}H_{10}O_2$ M^+ 186.0681, found 186.0672.

4-(Thiophene-2-yl)benzaldehyde (3p).[23] White solid. Mp: 73−74 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.02 (dd, J = 5.1, 3.9 Hz, 1H), 7.28 (dd, J = 5.1, 1.2 Hz, 1H), 7.34 (dd, J = 3.6, 1.2 Hz, 1H), 7.63 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.4 Hz, 2H), 9.88 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.4, 142.7, 140.1, 135.1, 130.5, 128.5, 126.9, 126.0, 125.1.

3-(5-Methylfuran-2-yl)benzaldehyde (3q). Brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 3H), 5.97−5.98 (m, 1H), 6.52 (d, J = 3.3 Hz, 1H), 7.39 (t, J = 4.8 Hz, 1H), 7.59 (dt, J = 7.5, 1.5 Hz, 1H), 7.74 (dt, J = 7.8, 1.8 Hz, 1H), 7.99 (t, J = 1.5 Hz, 1H), 9.91 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.3, 152.8, 150.8, 136.8, 132.1, 129.3, 128.8, 127.7, 124.2, 108.0, 107.3, 13.7.

4-(Benzo[*d*]thiazol-2-yl)benzaldehyde (3r).[24] Yellow solid. Mp: 132−133 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35−7.39 (m, 2H), 7.56−7.59 (m, 1H), 7.76−7.79 (m, 1H), 7.97 (d, J = 8.7 Hz, 2H), 8.36 (d, J = 8.4 Hz, 2H), 10.05 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.3, 161.5, 150.8, 141.9, 137.9, 132.1, 130.0, 128.0, 125.9, 124.9, 120.4, 110.8.

2-(Benzo[*b*]thiophene-2-yl)pyridine (5a).[25] White solid. Mp: 126 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18−7.22 (m, 1H), 7.35−7.40 (m, 2H), 7.71 (td, J = 7.5, 1.5 Hz, 1H), 7.78−7.90 (m, 4H), 8.65 (d, J = 4.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.5, 149.7, 144.8, 140.7, 140.5, 136.6, 125.1, 124.5, 124.1, 122.6, 121.1, 119.6.

3-(Benzo[*b*]thiophene-2-yl)quinoline (5b). Pale yellow solid. Mp: 173−174 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35−7.43 (m, 2H), 7.56−7.61 (m, 1H), 7.70−7.75 (m, 2H), 7.82−7.89 (m, 3H), 8.14 (d, J = 8.4 Hz, 1H), 8.34 (s, 1H), 9.31 (d, J = 1.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.5, 147.6, 140.6, 140.5, 139.7, 132.4, 129.7, 129.3, 128.0, 127.8, 127.5, 127.4, 124.9, 124.9, 123.9, 122.3, 120.9. HRMS (EI$^+$): m/z calcd for $C_{17}H_{11}NS$ M^+ 261.0612, found 261.0616.

3-(1-Methyl-1*H*-imidazol-5-yl)quinoline (5c). Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.74 (s, 3H), 7.26 (d, J = 0.9 Hz, 1H), 7.56−7.61 (m, 2H), 7.71−7.77 (m, 1H), 7.84 (dd, J = 5.1, 1.2 Hz, 1H), 8.11−8.14 (m, 2H), 8.96 (d, J = 2.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.0, 147.3, 139.9, 134.4, 130.2, 129.9, 129.4, 129.3, 127.8, 127.6, 127.4, 123.1, 32.7. HRMS (EI$^+$): m/z calcd for $C_{13}H_{11}N_3$ M^+ 209.0953, found 209.0951.

4-(1-Methyl-1*H*-imidazol-5-yl)-1-phenyl-1*H*-pyrazole (5d). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.58 (s, 3H), 7.30 (d, J = 0.9 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.34−7.39 (m, 3H), 7.61 (d, J = 7.5 Hz, 2H), 7.69 (s, 1H), 7.90 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.1, 153.1, 147.6, 147.5, 130.7, 129.8, 129.4, 128.9, 128.2, 127.7, 127.3, 125.0, 123.7, 123.3, 121.2, 111.3, 103.0. HRMS (EI$^+$): m/z calcd for $C_{13}H_{12}N_4$ M^+ 224.1062, found 224.1068.

1-Methyl-5-(thiophene-2-yl)-1*H*-imidazole (5e). Brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.71 (s, 3H), 7.08−7.12 (m, 2H), 7.18 (d, J = 1.2 Hz, 1H), 7.36 (dd, J = 4.8, 1.5 Hz, 1H), 7.51 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.2, 130.6, 129.2, 127.9, 127.6, 126.2, 125.9, 32.6. HRMS (EI$^+$): m/z calcd for $C_8H_8N_2S$ M^+ 164.0408, found 164.0401.

1,2-Dimethyl-5-(thiophene-2-yl)-1*H*-imidazole (5f).[26] Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H), 3.48 (s, 3H), 6.94−6.95 (m, 2H), 6.99−7.02 (m, 1H), 7.25 (dd, J = 8.1, 1.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.3, 131.5, 127.5, 127.3, 126.4, 126.3, 125.8, 31.2, 13.7.

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-1-phenyl-1*H*-pyrazole (5g). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.34 (s, 3H), 3.46 (s, 3H), 6.89 (s, 1H), 7.35−7.41 (m, 3H), 7.61−7.64 (m, 2H), 7.67 (s, 1H), 7.88 (s, 1H), 8.14 (d, J = 8.4 Hz, 1H), 8.34 (s, 1H), 9.31 (d, J = 1.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.7, 140.1, 139.8, 129.5, 126.8, 126.0, 125.9, 124.9, 119.1, 113.4, 31.1, 13.7. HRMS (EI$^+$): m/z calcd for $C_{14}H_{14}N_4$ M^+ 238.1218, found 238.1228.

2-(1,2-Dimethyl-1*H*-imidazol-5-yl)pyridine (5h).[27] Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.47 (s, 3H), 3.91 (s, 3H), 7.15 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H), 7.31 (s, 1H), 7.52 (dt, J = 8.1, 0.9 Hz, 1H), 7.69 (td, J = 7.8, 1.8, 1H), 8.58−8.61 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.6, 148.9, 147.8, 136.6, 131.8, 127.9, 121.8, 121.3, 31.9, 13.4.

3-(5-Methylthiophene-2-yl)quinoline (5i).[28] Pale yellow solid. Mp: 124−125 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.46 (d, J = 0.9 Hz, 3H), 6.71 (dd, J = 3.6, 1.2 Hz, 1H), 7.20 (d, J = 3.6 Hz, 1H), 7.44 (td, J = 6.9, 1.2 Hz, 1H), 7.57−7.63 (m, 1H), 7.67−7.70 (m, 1H), 8.05−8.07 (m, 2H), 9.11 (d, J = 2.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.3, 147.0, 140.9, 138.2, 130.4, 129.2, 128.9, 128.0, 127.8, 127.7, 127.1, 126.6, 124.3, 15.5. HRMS (EI$^+$): m/z calcd for $C_{10}H_8ClNS$ M^+ 209.0066, found 209.0072.

2-Chloro-5-(5-methylthiophene-2-yl)pyridine (5j). Pale yellow solid. Mp: 94−95 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.50 (d, J = 0.9 Hz, 3H), 6.74 (dd, J = 3.6, 0.9 Hz, 1H), 7.11 (d, J = 3.6 Hz, 1H), 7.26 (dd, J = 8.4, 0.6 Hz, 1H), 7.71 (dd, J = 8.4, 2.7 Hz, 1H), 8.53 (d, J =

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2.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.3, 146.0, 141.4, 136.4, 135.1, 129.7, 126.6, 124.6, 124.2, 15.5.

4-Methyl-5-(1-phenyl-1*H*-pyrazol-4-yl)thiazole (5k). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.59 (s, 3H), 7.33 (t, J = 7.5 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 7.73 (dd, J = 8.7, 1.2, 2H), 7.85 (s, 1H), 8.04 (s, 1H), 8.64 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.4, 148.7, 140.3, 139.7, 129.6, 127.0, 125.1, 122.4, 119.2, 115.0, 16.3. HRMS (EI^+): m/z calcd for $C_{13}H_{11}N_3S$ M^+ 241.0674, found 241.0683.

3-(Benzofuran-2-yl)quinoline (5l).[17] Colorless solid. Mp: 134−136 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (s, 1H), 7.27−7.37 (m, 2H), 7.67−7.73 (m, 1H), 7.85 (d, J = 8.1 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.52 (s, 1H), 9.33 (d, J = 2.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.1, 153.1, 147.6, 147.5, 130.7, 129.8, 129.4, 128.9, 128.2, 127.7, 127.3, 125.0, 123.7, 123.3, 121.2, 111.3, 103.0.

■ ASSOCIATED CONTENT

Supporting Information. Optimization studies and copies of ^{1}H NMR spectra for all compounds and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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