ChemPubSoc Europe

DOI: 10.1002/ejoc.201800842

EurJOC European Journal of Organic Chemistry

Full Paper

Palladium Catalysis

The Influence of the Quinoline Moiety on Direct Pd-Catalyzed Arylation of Five-Membered Heterocycles

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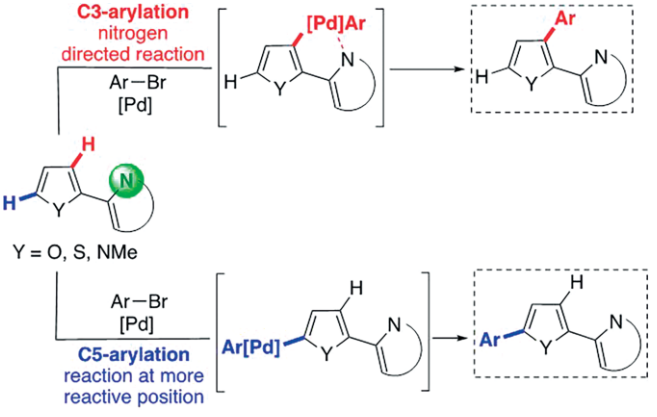
Dedicated to Professor Emertius Branko Stanovnik, University of Ljubljana, on the occasion of his 80th birthday.

Abstract: Herein we report a study on the reactivity of C2-quinoline-substituted furan, thiophene and pyrrole derivatives in palladium-catalyzed direct C–H arylation. The regioselectivity of the reaction was strongly influenced by site position of the attached five-membered heterocycle thus giving rise to C3- and/or C5-arylated products. Furthermore, the Hammett correlation performed on 5-substituted-8-(furan-2-yl)quinolines indicates that a marginally positive charge is building up in the rate determining transition state and thus pointing towards the electrophilic metalation-deprotonation reaction mechanism.

Introduction

Palladium-catalyzed direct arylation of five-membered heteroaromatics such as furan, thiophene and pyrrole generally proceeds at the C2- and/or C5-position due to their electronic effect.[1–4] However, the regioselectivity can be altered by introducing different substituents on the heterocycle, the nature of the coupling partner, and also by type of catalyst, base, solvent or additives used. N-containing directing groups have often been used to mediate the regioselectivity due to the coordinating ability of the nitrogen atom. However, when using heterocycles bearing such directing groups, the electronic nature of the heteroring can often surpass the coordination assistance of the directing group (Scheme 1).[5–7] For example, Wu and co-workers demonstrated a low catalyst loading direct arylation of 2-(thiophen-2-yl)pyridine which resulted in C5-arylated product excluding the pyridine ring acting as a directing group.[8] A similar behavior was observed by Nagarajan et al. in arylation of N-heterocycle embedded thiophenes and furans with aryl boronic acids under Pd-catalyzed oxidative reaction conditions which resulted in high C(5)–H arylation selectivity thus enabling an easy access to 2,5-disubstituted thiophenes.[9]

One of the first examples of exclusive palladium-catalyzed C3-arylation of thiophenes was reported by Miura and co-workers by using a 3-carbamoyl moiety as the directing group.[10] Furthermore, Doucet et al. observed that palladium-catalyzed direct arylation of furans and thiophenes containing a secondary carbamoyl group at the C2-position proceeded regioselectively either at C3- or C5-position strongly depending on the reaction conditions used. In the presence of potassium acetate,



Scheme 1. Arylation reaction of 2-substituted five-membered heterocycles.

direct arylation proceeded at the C5-position,[11,12] whereas the use of cesium acetate led to C3-arylated furans and thiophenes.[13] The same research group also showed the Pd-catalyzed coupling reaction between 2-(thiophen-2-yl)pyridine and aryl bromides to be highly non-regioselective. They assumed that the formation of the C5-arylated product is associated with a concerted metalation deprotonation (CMD) mechanism,[14] whereas the formation of the C3-arylated regioisomer arose from the coordination assisted mechanism of the pyridine nitrogen atom. Pd-catalyzed C–H arylation of 2-pyridyl-substituted thiophenes in the presence of TEMPO as the external oxidant has also been proven to undergo pyridyl-directed C–H arylation yielding C2,C3-disubstituted products in moderate yields.[15] Recently, Bach et al. demonstrated that a pyridin-2-yl group exerted a noticeable directing influence on the Pd-catalyzed C–H alkylation of five-membered heterocycles with alkylboronic acids thus leading exclusively to C3-functionalized products.[16]

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Results and Discussion

Recently we reported a focused set of compounds used to further explore[17–21] the chemical space and the structure-activity relationship of nitroxoline-based derivatives.[22] Consequently, we have also developed a one-pot sequential Pd-catalyzed coupling reaction for the direct arylation of 8-heteroarylquinolines with aryl bromides giving rise to a variety of polyconjugated quinoline compounds.[23] Accordingy, arylation of C2-quinolyl-substituted pyrroles led to formation of C3-arylated products suggesting a directing ability of the quinoline nitrogen atom in the C–H activation reaction. To gain more insight into the reactivity, regarding the directing influence of the quinoline moiety, we prepared a series of 2-, 3-, and 8-heteroarylquinoline substrates in C2-arylation of furan, thiophene and *N*-pyrrole with **1** by applying our previously reported protocol (Table 1).[23]

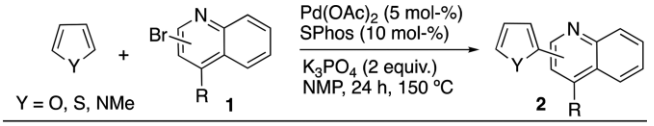
First, we examined the coupling reaction between 8-heteroarylquinolines **2a**–**c** and 4-bromobenzonitrile in the presence of a $Pd(OAc)_2/PPh_3$ catalytic system for 48 h at 120 °C in dioxane (Table 2). According to the literature,[1–7] the direct arylation of compounds **2a**–**j** should proceed on the C5- and/or C3-positions of the five-membered heteroring, whereas in the case of **2k**–**m** only C5-arylated products would be formed. To examine the influence of the quinoline directing group on C–H arylation of the five-membered heterocycle only a slight excess of 4-bromobenzonitrile (1.1 equiv.) was used. However, it must be noted that the yields of isolated products provided in Table 2 were achieved using 2 equivalents of the 4-bromobenzonitrile as the arylating agent.

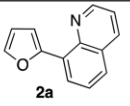
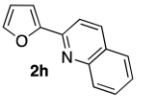
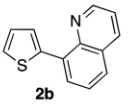
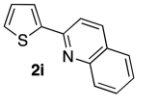
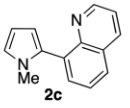
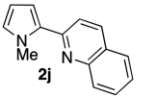
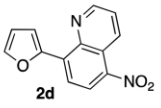
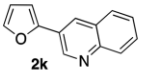
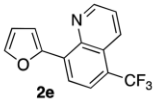
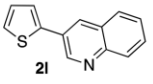
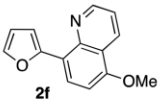
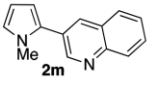
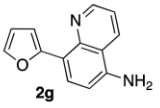
Detailed NMR analysis confirmed that arylation of 8-(furan-2-yl)quinoline (**2a**) and 8-(1-methyl-1*H*-pyrrol-2-yl)quinoline (**2c**) predominantly occurred at the C3 position to give **3a** and **3c** suggesting a six-membered palladacyclic transition state due to coordination assistance of the quinoline nitrogen atom. However, the isolation of the byproducts **5a** and **5c** implies that the second arylation at the C5-position took place only after the C3-position has been functionalized. In contrast with furan substrate **2a**, 8-(thiophene-2-yl)quinoline reacted with 4-bromobenzonitrile almost equally at the C5-position to give products **3b** and **4b** in a ratio of 1:1.3. The above-mentioned results suggest that in less reactive furan derivative **2a**[24,25] the quinoline-directed C3-arylation surpasses the reactivity of the most nucleophilic C5-site of the five-membered heteroarene, while in thiophene substrate **2b** its electronic nature equally contributes to the mixture of C3- and C5- arylated products.

We continued our study on direct arylation of 8-heteroarylquinolines **2d**–**g** bearing different substituents on the C5-position of the quinoline ring (Table 2, Entries 4–7). According to our previous findings[23] we speculated that by introducing different electron-donating and -withdrawing substituents on the quinoline moiety we could alter the reactivity of the furan ring to selectively achieve the C3- or C5-functionalization. While both quinolines bearing electron-withdrawing (**2d**,**e**) and electron-donating groups (**2f**,**g**) were preferentially arylated at the C3-position, the reactions with the latter proceeded with significantly higher conversion (Table 2, Entries 6 and 7).

Next, we turned our attention to 2-heteroarylquinolines **2h**–**j** as substrates in Pd^{II}-catalyzed arylation with 4-bromobenzonitrile at slightly elevated temperature (130 °C). Surprisingly, the C3-arylation selectivity was significantly reduced in comparison to 8-quinolyl analogues **2a**–**g** thus giving mixtures of **3** and **4** with predominant formation of C5-arylated products **4** (Table 2, Entries 8–10). These results suggest that the formation of six-membered palladacyclic intermediate resulting from 8-quinolyl coupling partners **2a**–**g** more efficiently promotes C3-arylation whereas in 2-quinolyl heteroarenes **2h**–**j** the enhanced C5-reactivity of the five-membered heterocycle predominates. To confirm the competition between C–H arylation reactivity of the five-membered heterocycle arising from chelation assistance of the quinoline nitrogen atom and that being a consequence of the electronic nature, compounds **2k**–**m** bearing a 3-quinolyl moiety were subjected to C–H arylation reaction conditions

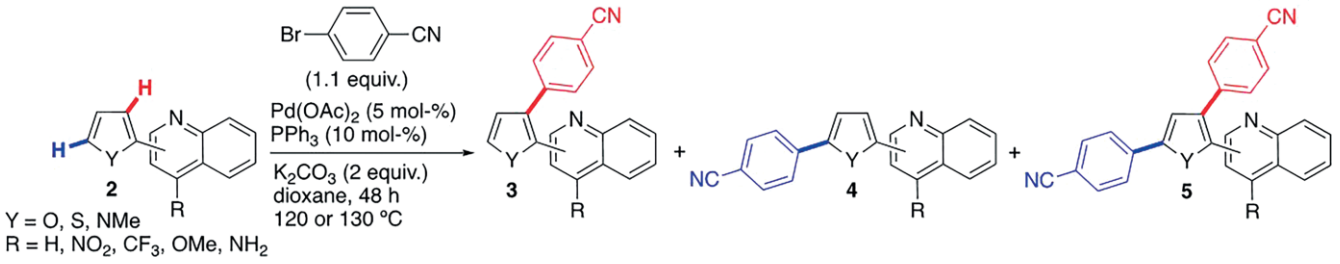
Table 1. Palladium-catalyzed direct heteroarylation of simple five-membered heterocycles.



Entry	Product **2**	Yield [%][b]	Entry	Product **2**	Yield [%][b]
1	 **2a**	62	8	 **2h**	68
2	 **2b**	56	9	 **2i**	63
3	 **2c**	61	10	 **2j**	48
4	 **2d**	44	11	 **2k**	71
5	 **2e**	63	12	 **2l**	51
6	 **2f**	83	13	 **2m**	54
7[c]	 **2g**	72			

[a] Reaction conditions: $Pd(OAc)_2$ (5 mol-%), SPhos (10 mol-%), K_3PO_4 (2 equiv.), quinoline **1** (0.5 mmol), heteroarene (1.0 mL), NMP (1 mL), under argon. [b] Isolated yields. [c] Product **2g** was synthesized by reduction of **2d** with 10 % of Pd/C (10 mol-%), H_2 (1 atm), methanol, 18 h. Given yield after reduction reaction.

Table 2. Palladium-catalyzed direct arylation of compounds **2** with 4-bromobenzonitrile.



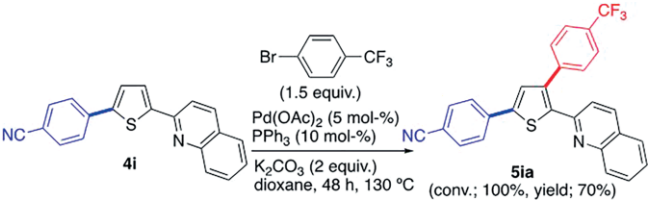
Entry	Compound **2**	Quinolyl	Y	R	Conversion [%][b]	Ratio (**3**/**4**/**5**)[b]	Yield (**3**, **4**, **5**) [%][c]
1	**2a**	8-quinolyl	O	H	89	1.7:0:1	40, /, 32
2	**2b**		S	H	71	1:1.3:0	22, 25, /
3	**2c**		NMe	H	85	10:0:1	45, /, 35
4	**2d**		O	NO_2	41	1:0:0	34, /, /
5	**2e**		O	CF_3	68	1.3:0:1	44, /, 39
6	**2f**		O	OMe	94	2.1:0:1	57, /, 28
7	**2g**		O	NH_2	81	1:0:0	54, /, /
8	**2h**	2-quinolyl	O	H	65	1:7.3:0	7, 41, /
9	**2i**		S	H	71	1:2:2	20, 61, 12
10	**2j**		NMe	H	62	1:3.3:0	22, 38, /
11	**2k**	3-quinolyl	O	H	86	0:1:0	/, 71, /
12	**2l**		S	H	69	0:1:0	/, 75, /
13	**2m**		NMe	H	75	0:1:0	/, 67, /

[a] Reaction conditions: Compound **2** (0.50 mmol), $Pd(OAc)_2$ (5 mol-%), PPh_3 (10 mol-%), K_2CO_3 (2 equiv.), 4-bromobenzonitrile (1.1 equiv.), 1,4-dioxane (2 mL), under argon. [b] Conversions and ratios were determined by ^1H NMR analysis of the crude reaction mixture; reaction carried out with 1.1 equiv. of 4-bromobenzonitrile. [c] Isolated yields using 2 equiv. of 4-bromobenzonitrile.

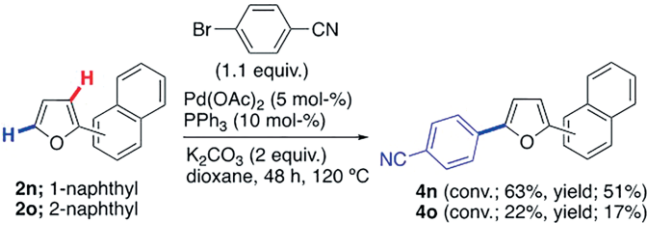
with 4-bromobenzonitrile. As expected, the arylation proceeded only at the C5-position as the quinoline moiety was unable to dictate the regioselectivity, resulting in the formation of C5-arylated products **4** in good yields (Table 2, Entries 11–13).

To further demonstrate the directing ability of the quinoline nitrogen atom, C2,C5-diarylated thiophene **4i** was subjected under direct C–H activation conditions given in Scheme 2 using 4-bromobenzotrifluoride as the proelectrophile. The arylation took place at the C3 position of the thiophene ring exclusively giving rise to a good 70 % yield of isolated product **5ia**, even though C4 arylation is not excluded. The experiment proved to be in line with the proposed directing ability of the quinoline nitrogen atom for the regioselective functionalization reaction of the five-membered heterocycle. 2-(Naphthalen-1-yl)furan (**2n**) and 2-(naphthalen-2-yl)furan (**2o**) were prepared following the procedure given in Table 1 in order to confirm the formation of the major regioisomer where the coordination nature of the quinoline moiety was completely excluded. The 2-furyl-substituted compounds **2n** and **2o** were subjected to palladium-catalyzed reaction giving rise to solely C5-arylated products **4n** and **4o** in low to moderate yields (Scheme 3). Other research groups reported similar yields for the preparation of such C2,C5-diarylated furans by using different synthetic methods.[26–28] The more sluggish reaction of C2-naphthyl furans **2n** and **2o** in comparison to 3-quinolyl analogues **2k**–**m** additionally confirmed the influence of the quinoline directing group on the regioselectivity of C–H arylation.

Concerning the structural determination of regioisomers, ^1H NMR analysis of products **4o**, **4h** and **3h** revealed a significant



Scheme 2. Nitrogen atom-directed palladium-catalyzed arylation of C2,C5-diarylated thiophene **4i** with 4-bromobenzotrifluoride.



Scheme 3. Palladium-catalyzed direct arylation of C2-naphthyl-substituted furans **2j** and **2k** with 4-bromobenzonitrile.

difference in the chemical shift of the protons in the furan ring.

Furthermore, examining compound **3h** (Figure 1), we noticed that proton H^c had a strong downfield chemical shift due to the adjacent oxygen atom, whereas in the case of **4o** and **4h**, protons H^a and H^b were positioned in a more homogeneous

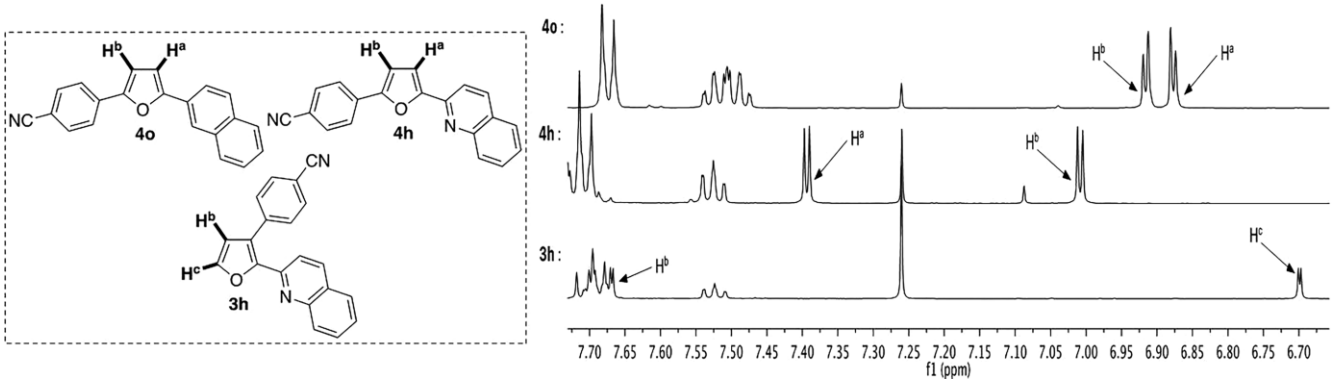


Figure 1. Comparison of chemical shifts in ^{1}H NMR spectra of products **4o**, **4h**, and **3h**.

electronic environment resulting in similar chemical shifts (Figure 1). Moreover, structures of **4b**, **4h** and **4m** were unambiguously confirmed by X-ray analysis (Figure 2).

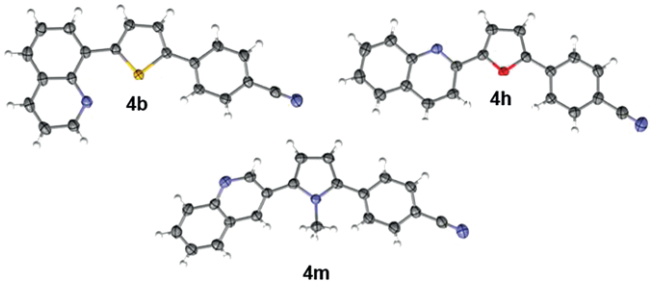
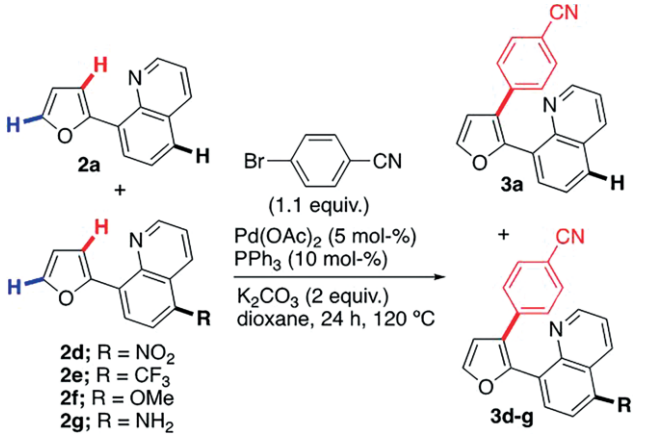


Figure 2. X-ray structures of compounds **4b**, **4h**, and **4m** (ellipsoids are shown in 60 % probability).

Finally, we carried out competition studies between electronically different 5-substituted-8-(furan-2-yl)quinolines (Scheme 4). Equimolar amounts of **2a** and substrates **2d**–**g** were treated with 1.1 equiv. of 4-bromobenzonitrile in the presence of the $Pd(OAc)_2/PPh_3$ catalytic system at 120 °C for 24 h. From the collected data we were able to construct a Hammett plot which showed a linear (R^2 = 0.93) relationship between σ and $\log(k_X/k_H)$. Although, the resulting ρ value of –0.70 is relatively small and must be interpreted with caution, the negative sign is indicative for minor, yet mechanistically significant, adjustments to the redistribution of the electron charge density during traversal of the rate determining transition state (Figure 3).[29] The observed relatively small negative ρ value can also be contributed to the extended conjugation of the reactive center in the mechanistic probe, thus indicating that marginally positive charge is building up in the rate determining transition state and suggesting the electrophilic metalation-deprotonation reaction mechanism.

Mechanistically, it is assumed that the transformation with 2-(heteroar-2-yl)quinolines **2h**–**j** and 8-substituted analogues **2a**–**g** follows the reaction pathway involving the coordination-assisted direct C(3)–H arylation of the five-membered heterocycle as outlined in Scheme 5 for the transformation of **2** into **3**. Oxidative addition into the aryl halide provides an arylated Pd^{II} species which upon coordination to the quinoline nitrogen atom and the five-membered heteroarene moiety (most likely



Scheme 4. Competition reaction between quinoline derivatives **2d**–**g** and 8-(furan-2-yl)quinoline (**2a**).

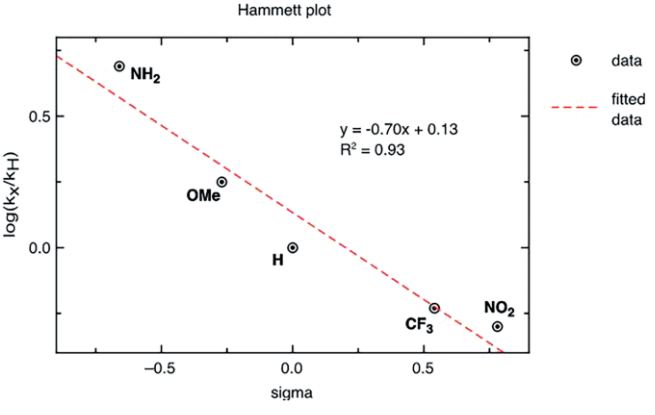
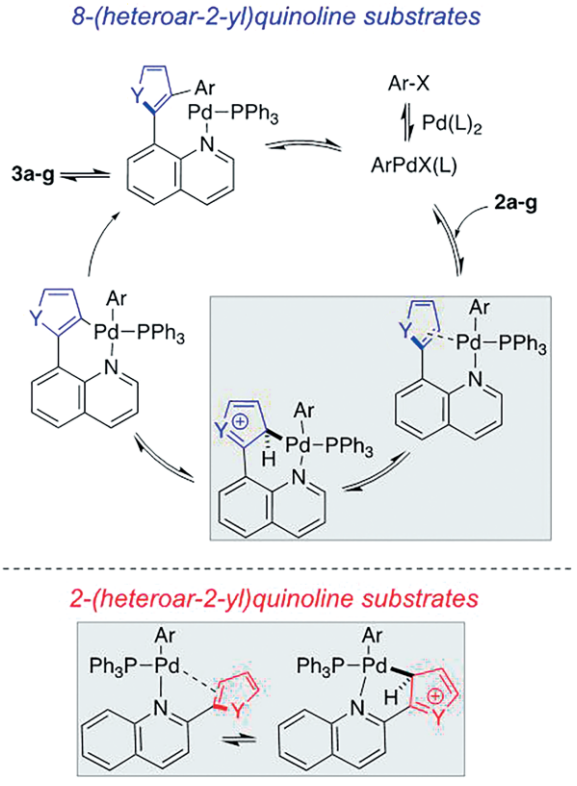


Figure 3. Hammett plot for competition experiments between **2d**–**g** and **2a**.

weakly η^2-heteroarene complexation) forms the corresponding cyclopalladated intermediate via electrophilic metalation-deprotonation step. Reductive elimination then gives the C3-arylated product and regenerates the catalytic Pd^0-species. Unlike in 8-(heteroar-2-yl)quinolines **2a**–**g**, the coordination assistance of the quinoline nitrogen atom in 2-(heteroar-2-yl)quinolines **2h**–**j** [being in line with 2-(heteroar-2-yl)pyridine analogues][16,30] is less pronounced and intrinsic positional reactivity of C–H activation at the C5 position noticeably participates.



Scheme 5. Mechanistic proposal for coordination-assisted Pd-catalyzed arylation of five-membered heterocycles **2a**–**g** and **2h**–**j**.

Conclusions

In summary, we have demonstrated that the quinolyl group exerts a notable directing influence on the palladium-catalyzed C–H arylation reaction of five-membered heterocycles with aryl bromides which is more pronounced in the 8-heteroaryl series than the 2-heteroarylquinolines. Even though direct functionalization of these heteroaromatics generally proceeds at the C2- and/or C5-position, we were able to influence the regioselecitvity of C–H arylation by introducing a nitrogen-directing group. Moreover, competition studies between quinoline derivatives **2a** and **2d**–**g** indicated that substrates with an electron-donating group at the C5-quinoline position react preferably, indicating there is a marginal localization of positive charge on the furan ring in the rate-determining step.

Experimental Section

General Methods: The reagents and solvents were used as received from commercial suppliers. Reactions were monitored by analytical thin-layer chromatography (TLC) and visualization of the developed TLC chromatogram was performed by UV absorbance. Column chromatography was performed on 230–400 mesh silica gel with the indicated solvent system. Merck silica gel 60 PF254 containing gypsum was used to prepare chromatotron plates. Radial chromatography was performed with a Harrison Research, model 7924 T chromatotron. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials. Melting points are uncorrected. Infra-red spectra were recorded on a FT-IR spectrometer and are reported in reciprocal centimetres (cm^{-1}). Routine nuclear magnetic resonance spectra were recorded either on a Bruker Avance DPX 300 or Avance 500 MHz spectrometer in $CDCl_3$. Chemical shifts for ^{1}H NMR spectra are recorded in parts per million (ppm) from tetramethylsilane as an internal standard. The multiplicities are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), ddd (doublet doublet of doublets), and br (broad), number of equivalent nuclei (by integration), coupling constants (*J*) quoted in Hertz (Hz). Chemical shifts for the ^{13}C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of the solvent resonance as an internal standard ($CDCl_3$ triplet at δ = 77.0 ppm). All spectra were obtained with complete proton decoupling. High-resolution mass spectra were recorded on an Agilent 6224 Accurate Mass TOF/MS instrument by electrospray ionization.

CCDC 1846799 (for **4b**), 1846800 (for **4m**), and 1846801 (for **4h**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

General Procedure for Pd-Catalyzed Direct (Hetero)arylation of Simple Five-Membered Heterocycles with Quinolines (1a–m) and Naphthalenes (1n–o): The corresponding quinoline (**1a**–**m**) or naphthalene (**1n**–**o**) (0.50 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), SPhos (20.5 mg, 0.050 mmol) and K_3PO_4 (212 mg, 1.00 mmol) were dissolved in NMP (1 mL) to which the furan, thiophene or pyrrole (1 mL) was added. The reaction mixture was stirred in a sealed glass tube at 150 °C for 24 h under inert atmosphere. The mixture was cooled to room temperature (room temp.) to which water was added (3 mL) and the product was extracted into ethyl acetate (2 × 3 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by radial chromatography to yield pure product **2**.

8-(Furan-2-yl)quinoline (2a):[23] Radial chromatography (petroleum ether/EtOAc, 20:1). Colorless oil (60 mg, 62 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.00 (dd, *J* = 4.0, 2.0 Hz, 1 H), 8.24 (dd, *J* = 7.5, 1.5 Hz, 1 H), 8.16 (dd, *J* = 8.5, 2.0 Hz, 1 H), 7.81 (d, *J* = 3.5 Hz, 1 H), 7.71 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.60–7.75 (m, 2 H), 7.43 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.61 (dd, *J* = 3.5, 2.0 Hz, 1 H) ppm.

8-(Thiophen-2-yl)quinoline (2b):[23] Radial chromatography (petroleum ether/EtOAc, 50:1). Colorless oil (59 mg, 56 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.01 (dd, *J* = 4.0, 2.0 Hz, 1 H), 8.16 (dd, *J* = 8.0, 2.0 Hz, 1 H), 8.06 (dd, *J* = 7.5, 1.5 Hz, 1 H), 7.79 (dd, *J* = 3.5, 1.0 Hz, 1 H), 7.73 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.55 (dd, *J* = 8.0, 7.5 Hz, 1 H), 7.48 (dd, *J* = 5.0, 1.0 Hz, 1 H), 7.43 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.17 (dd, *J* = 5.0, 3.5 Hz, 1 H) ppm.

8-(1-Methyl-1*H*-pyrrol-2-yl)quinoline (2c):[23] Radial chromatography (petroleum ether/EtOAc, 50:1). Colorless oil (63 mg, 61 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.95 (dd, *J* = 4.0, 2.0 Hz, 1 H), 8.18 (dd, *J* = 8.0, 2.0 Hz, 1 H), 7.83 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.73 (dd, *J* = 7.0, 1.5 Hz, 1 H), 7.58–7.55 (m, 1 H), 7.39 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.84–6.83 (m, 1 H), 6.32–6.29 (m, 1 H), 3.47 (s, 3 H) ppm.

8-(Furan-2-yl)-5-nitroquinoline (2d):[23] Radial chromatography (petroleum ether/EtOAc, 20:1). Yellow solid (53 mg, 44 %); m.p. 153–156 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.11 (dd, *J* = 9.0, 2.0 Hz, 1 H), 9.07 (dd, *J* = 4.0, 2.0 Hz, 1 H), 8.43 (d, *J* = 8.5 Hz, 1 H), 8.28 (d, *J* = 8.5 Hz, 1 H), 8.08 (d, *J* = 3.5 Hz, 1 H), 7.67–7.65 (m, 2 H), 6.66 (dd, *J* = 3.5, 2.0 Hz, 1 H) ppm.

8-(Furan-2-yl)-5-(trifluoromethyl)quinoline (2e): Radial chromatography (petroleum ether/EtOAc, 50:1). White solid (83 mg, 63 %); m.p. 55–57 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 3076, 1580, 1507, 1489, 1317, 1183, 1094, 1078, 1018, 931, 815, 789, 734 cm^{-1}. ^{1}H NMR (500 MHz,

$CDCl_3$): δ = 9.05 (dd, J = 4.1, 1.7 Hz, 1 H), 8.52–8.49 (m, 1 H), 8.24 (d, J = 7.9 Hz, 1 H), 7.95–7.92 (m, 2 H), 7.60 (d, J = 1.6 Hz, 1 H), 7.54 (dd, J = 8.7, 4.1 Hz, 1 H), 6.63 (dd, J = 3.4, 1.8 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 150.3, 150.1, 144.1, 142.9, 132.8, 132.7 (q, J = 2.4 Hz), 125.1 (q, J = 5.8 Hz), 124.8, 124.3 (q, J = 273.2 Hz), 124.2 (q, J = 30.7 Hz), 123.7, 115.5, 112.5 ppm. ^{19}F NMR (500 MHz, $CDCl_3$): δ = –58.8 ppm. HRMS (ESi+): m/z calcd. for $C_{14}H_9F_3NO$ [M + H]$^+$ 264.0631, found 264.0630.

8-(Furan-2-yl)-5-methoxyquinoline (2f): Compound **2f** was prepared from **1f** which was synthesized from readily available 5-methoxyquinolin-8-amine according to the following procedure: 5-Methoxyquinolin-8-amine (92 mg, 0.50 mmol, 95 %) was dissolved in water (2 mL) and HBr (2 mL, 48 %), cooled to °C to which $NaNO_2$ (38 mg, 0.55 mmol) in water (1.5 mL) was added. The mixture was stirred at 0 °C for 1 h after which it was slowly added to a cooled (0 °C) suspension of CuBr (143 mg, 1.00 mmol) in HBr (1.5 mL, 48 %). The reaction mixture was warmed to room temp. and stirred overnight. The mixture was again cooled to 0 °C to which aqueous ammonia was added (5 mL) and product **1f** was extracted in dichloromethane (2 × 5 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 10:1) to yield pure product **1f** as a yellow sold (98 mg, 82 %). Compound **1f** was further reacted with furan according to the given general procedure. Radial chromatography (petroleum ether/EtOAc, 50:1). Yellow oil (93 mg, 83 %). FT- IR (ATR, neat): $\tilde{\nu}$ = 2962, 2833, 1588, 1467, 1298, 1277, 1226, 1089, 809, 786, 730 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.00 (dd, J = 4.2, 1.9 Hz, 1 H), 8.61 (dd, J = 8.4 Hz, 1.9 1 H), 8.14 (d, J = 8.3 Hz, 1 H), 7.62 (dd, J = 3.3, 0.8 Hz, 1 H), 7.53 (dd, J = 1.8, 0.8 Hz, 1 H), 7.42 (dd, J = 8.5, 4.2 Hz, 1 H), 6.93 (d, J = 8.3 Hz, 1 H), 6.58 (dd, J = 3.3, 1.8 Hz, 1 H), 4.04 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.3, 151.6, 145.0, 141.0, 130.9, 126.4, 121.9, 120.8, 111.9, 110.6, 104.2, 55.7 ppm. HRMS (ESi+): m/z calcd. for $C_{14}H_{12}NO_2$ [M + H]$^+$ 226.0863, found 226.0862.

8-(Furan-2-yl)quinolin-5-amine (2g): Compound **2g** was prepared by reduction of **2d** according to the following procedure: Compound **2d** (120 mg, 0.50 mmol) was dissolved in methanol (10 mL) and 10 % of Pd/C (20 mg, 10 %) was added to which a flow of H_2 (1 atm) was passed. The reaction mixture was shaken at room temp. for 18 h after which it was filtered through a pad of Celite and washed with methanol (2 × 5 mL). The solvent was evaporated under reduced pressure. The crude product was purified by radial chromatography to yield pure product **2g**. Radial chromatography (petroleum ether/EtOAc, 5:1). Yellow solid (76 mg, 72 %); m.p. 88–90 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 3427, 3317, 1626, 1582, 1467, 1356, 1022, 952, 809, 785, 729 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.99 (dd, J = 4.1, 1.8 Hz, 1 H), 8.18 (dd, J = 8.5, 1.8 Hz, 1 H), 8.04 (d, J = 8.0 Hz, 1 H), 7.53 (dd, J = 3.3, 0.8 Hz, 1 H), 7.54–7.50 (m, 1 H), 7.39 (dd, J = 8.5, 4.1 Hz, 1 H), 6.87 (d, J = 8.0 Hz, 1 H), 6.57 (dd, J = 3.3, 1.8 Hz, 1 H), 4.24 (s, 2 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 152.0, 149.8, 145.1, 141.6, 140.7, 129.5, 127.2, 120.6, 119.5, 118.6, 111.8, 110.0, 109.9 ppm. HRMS (ESi+): m/z calcd. for $C_{13}H_{11}N_2O$ [M + H]$^+$ 211.0866, found 211.0875.

2-(Furan-2-yl)quinoline (2h): Radial chromatography (petroleum ether/EtOAc, 50:1). White solid (66 mg, 68 %); m.p. 87–89 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 3106, 3061, 1385, 1306, 1286, 1126, 1008, 912, 787, 741 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.17 (dd, J = 8.6, 0.8 Hz, 1 H), 8.13 (dd, J = 8.5, 1.0 Hz, 1 H), 7.83 (d, J = 8.6 Hz, 1 H), 7.79 (dd, J = 8.0, 1.4 Hz, 1 H), 7.71 (ddd, J = 8.4, 6.9, 1.5 Hz, 1 H), 7.63 (dd, J = 1.8, 0.8 Hz, 1 H), 7.50 (ddd, J = 8.0, 6.8, 1.1 Hz, 1 H), 7.22 (dd, J = 3.4, 0.8 Hz, 1 H), 6.60 (dd, J = 3.4, 1.8 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.7, 149.0, 148.1, 144.1, 136.6, 129.8, 129.4, 127.5, 127.1, 126.2, 117.4, 112.2, 110.1 ppm. HRMS (ESi+): m/z calcd. for $C_{13}H_{10}NO$ [M + H]$^+$ 196.0757, found 196.0751.

2-(Thiophen-2-yl)quinoline (2i): Radial chromatography (petroleum ether/EtOAc, 50:1). White solid (66 mg, 63 %); m.p. 129–131 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 3100, 3059, 1614, 1551, 1498, 1359, 1142, 1056, 933, 786, 708 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.13 (d, J = 8.6 Hz, 1 H), 8.08 (d, J = 8.5 Hz, 1 H), 7.80–7.76 (m, 2 H), 7.73 (dd, J = 3.7, 1.1 Hz, 1 H), 7.69 (ddd, J = 8.5, 6.9, 1.5 Hz, 1 H), 7.50–7.46 (m, 2 H), 7.16 (dd, J = 5.1, 3.6 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 152.3, 148.1, 145.4, 136.6, 129.8, 129.3, 128.5, 128.0, 127.5, 127.2, 126.1, 125.8, 117.6 ppm. HRMS (ESi+): m/z calcd. for $C_{13}H_{10}NS$ [M + H]$^+$ 212.0528, found 212.0522.

2-(1-Methyl-1*H*-pyrrol-2-yl)quinoline (2j): Radial chromatography (petroleum ether/EtOAc, 50:1). Pale yellow solid (50 mg, 48 %); m.p. 50–52 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 3054, 2966, 1599, 1486, 1366, 1249, 1123, 1015, 868, 719 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.04 (d, J = 8.7 Hz, 1 H), 8.01 (dd, J = 8.4, 1.0 Hz, 1 H), 7.73 (dd, J = 8.1, 1.4 Hz, 1 H), 7.69 (d, J = 8.7 Hz, 1 H), 7.65 (ddd, J = 8.5, 6.9, 1.4 Hz, 1 H), 7.44 (ddd, J = 8.1, 6.9, 1.1 Hz, 1 H), 6.80–6.79 (m, 1 H), 6.77 (dd, J = 3.8, 1.8 Hz, 1 H), 6.22 (dd, J = 3.8, 2.6 Hz, 1 H), 4.20 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 152.2, 147.6, 135.8, 132.2, 129.3, 129.0, 127.6, 127.4, 126.0, 125.4, 120.1, 112.3, 107.8, 37.7 ppm. HRMS (ESi+): m/z calcd. for $C_{14}H_{13}N_2$ [M + H]$^+$ 209.1073, found 209.1072.

3-(Furan-2-yl)quinoline (2k): Radial chromatography (petroleum ether/EtOAc, 20:1). White solid (69 mg, 71 %); m.p. 79–81 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 3850, 3109, 1492, 1336, 1292, 1048, 963, 903, 785, 741 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.22 (d, J = 2.2 Hz, 1 H), 8.36 (d, J = 2.2 Hz, 1 H), 8.09 (dd, J = 8.4, 1.1 Hz, 1 H), 7.84 (dd, J = 8.1, 1.3 Hz, 1 H), 7.68 (ddd, J = 8.4, 6.8, 1.4 Hz, 1 H), 7.57 (d, J = 1.7 Hz, 1 H), 7.55 (ddd, J = 8.1, 6.9, 1.2 Hz, 1 H), 6.88 (d, J = 3.4 Hz, 1 H), 6.56 (dd, J = 3.4, 1.8 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 151.4, 147.1, 147.0, 143.1, 129.3, 129.2, 129.1, 127.9, 127.8, 127.2, 124.0, 112.0, 106.7 ppm. HRMS (ESi+): m/z calcd. for $C_{13}H_{10}NO$ [M + H]$^+$ 196.0757, found 196.0754.

3-(Thiophen-2-yl)quinoline (2l): Radial chromatography (petroleum ether/EtOAc, 20:1). Pale yellow solid (54 mg, 51 %); m.p. 62–66 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 3065, 3034, 1568, 1490, 1429, 1346, 1122, 1023, 859, 781, 746, 688 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.21 (d, J = 2.3 Hz, 1 H), 8.29 (dd, J = 2.4, 0.8 Hz, 1 H), 8.10 (dd, J = 8.4, 1.0 Hz, 1 H), 7.86–7.84 (m, 1 H), 7.70 (ddd, J = 8.4, 6.9, 1.5 Hz, 1 H), 7.57 (ddd, J = 8.2, 6.9, 1.2 Hz, 1 H), 7.51 (dd, J = 3.6, 1.1 Hz, 1 H), 7.41 (dd, J = 5.1, 1.1 Hz, 1 H), 7.18 (dd, J = 5.1, 3.6 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 148.6, 147.3, 140.8, 131.4, 129.3, 128.4, 127.9, 127.8, 127.6, 1217.2, 126.1, 124.4 ppm. HRMS (ESi+): m/z calcd. for $C_{13}H_{10}NS$ [M + H]$^+$ 212.0528, found 212.0539.

3-(1-Methyl-1*H*-pyrrol-2-yl)quinoline (2m): Radial chromatography (petroleum ether/EtOAc, 10:1). Pale yellow oil (56 mg, 54 %). FT- IR (ATR, neat): $\tilde{\nu}$ = 3053, 1493, 1188, 1124, 1057, 1001, 908, 786, 780, 711 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.02 (d, J = 2.3 Hz, 1 H), 8.11 (dd, J = 8.4, 1.0 Hz, 1 H), 8.09 (dd, J = 2.3, 0.8 Hz, 1 H), 7.81 (dd, J = 8.1, 1.4 Hz, 1 H), 7.69 (ddd, J = 8.4, 6.9, 1.4 Hz, 1 H), 7.55 (ddd, J = 8.1, 6.9, 1.2 Hz, 1 H), 6.81 (dd, J = 2.7, 1.8 Hz, 1 H), 6.41 (dd, J = 3.7, 1.8 Hz, 1 H), 6.28 (dd, J = 3.6, 2.7 Hz, 1 H), 3.73 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 150.9, 146.6, 133.6, 130.9, 129.2, 129.1, 127.7, 127.6, 127.0, 126.4, 124.9, 124.9, 110.2, 108.3, 35.2 ppm. HRMS (ESi+): m/z calcd. for $C_{14}H_{13}N_2$ [M + H]$^+$ 209.1073, found 209.1076.

2-(Naphthalen-1-yl)furan (2n): Radial chromatography (petroleum ether). Colorless oil (82 mg, 85 %). FT- IR (ATR, neat): $\tilde{\nu}$ = 3049, 1509,

1391, 1014, 970, 796, 771, 731, 655 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.40 (dd, J = 8.8, 1.1 Hz, 1 H), 7.90–7.88 (m, 1 H), 7.84 (d, J = 8.3 Hz, 1 H), 7.73 (dd, J = 7.2, 1.3 Hz, 1 H), 7.62 (dd, J = 1.8, 0.8 Hz, 1 H), 7.55–7.79 (m, 3 H), 6.72 (dd, J = 3.3, 0.8 Hz, 1 H), 6.59 (dd, J = 3.3, 1.8 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.5, 142.4, 133.9, 130.4, 128.6, 128.5, 128.4, 126.5, 126.1, 125.9, 125.5, 125.3, 111.4, 109.2 ppm.

2-(Naphthalen-2-yl)furan (2o): Radial chromatography (petroleum ether). White solid (89 mg, 92 %); m.p. 63–64 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 3050, 1155, 1009, 862, 801, 749 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.14 (d, J = 1.6 Hz, 1 H), 7.86–7.75 (m, 4 H), 7.51 (d, J = 2.1 Hz, 1 H), 7.48–7.42 (m, 2 H), 6.76 (dd, J = 3.4, 0.7 Hz, 1 H), 6.51 (dd, J = 3.3, 1.8 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.0, 142.3, 133.5, 132.6, 128.3, 128.2, 128.1, 127.7, 126.4, 125.9, 122.3, 122.1, 111.8, 105.6 ppm.

General Procedure for Pd-Catalyzed Direct Arylation of Compounds 2 with 4-Bromobenzonitrile: Corresponding compound **2** (0.50 mmol), 4-bromobenzonitrile (183 mg, 1.00 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PPh_3 (13.1 mg, 0.050 mmol) and K_2CO_3 (207 mg, 1.50 mmol) were dissolved in 1,4-dioxane (2 mL). The reaction mixture was stirred in a sealed glass tube at 120 or 130 °C for 48 h under inert atmosphere. The mixture was cooled to room temperature (room temp.) to which water was added (3 mL) and the product was extracted into ethyl acetate (2 × 3 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The crude products were purified by radial chromatography to yield pure products **3**–**5**.

4-[2-(Quinolin-8-yl)furan-3-yl]benzonitrile (3a): Radial chromatography (petroleum ether/EtOAc, 5:1). Yellow solid (59 mg, 40 %); m.p. 82–84 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 2923, 2223, 1700, 1685, 1605, 1570, 1491, 830, 793, 726 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.77 (dd, J = 4.2, 1.8 Hz, 1 H), 8.21 (dd, J = 8.3, 1.8 Hz, 1 H), 7.92 (dd, J = 8.2, 1.5 Hz, 1 H), 7.78 (dd, J = 7.2, 1.5 Hz, 1 H), 7.71 (d, J = 1.9 Hz, 1 H), 7.58 (dd, J = 8.2, 7.1 Hz, 1 H), 7.42–7.40 (m, 3 H), 7.28–7.26 (m, 2 H), 6.83 (d, J = 2.0 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 150.7, 149.0, 146.1, 143.3, 139.1, 136.3, 132.0, 131.8, 130.0, 129.6, 128.8, 128.0, 126.2, 123.1, 121.5, 119.1, 111.5, 109.6 ppm. HRMS (ESi+): m/z calcd. for $C_{20}H_{13}N_2O$ $[M + H]^+$ 297.1022, found 297.1020.

4-[2-(Quinolin-8-yl)thiophen-3-yl]benzonitrile (3b): Radial chromatography (petroleum ether/EtOAc, 7:1). Yellow solid (34 mg, 22 %); m.p. 120–123. FT- IR (ATR, neat): $\tilde{\nu}$ = 2922, 2852, 2223, 1599, 1493, 1310, 1176, 835, 806, 787, 749 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 9.05 (dd, J = 4.1, 1.8 Hz, 1 H), 8.22 (dd, J = 8.3, 1.8 Hz, 1 H), 8.14 (dd, J = 7.4, 1.4 Hz, 1 H), 7.82–7.79 (m, 4 H), 7.68–7.66 (m, 2 H), 7.62–7.59 (m, 1 H), 7.51–7.48 (m, 2 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 149.5, 144.4, 144.1, 141.4, 139.2, 136.5, 132.9, 132.7, 128.8, 127.9, 127.7, 127.5 (2 C), 126.5, 125.8, 124.7, 121.4, 110.1 ppm. HRMS (ESi+): m/z calcd. for $C_{20}H_{13}N_2S$ $[M + H]^+$ 313.0794, found 313.0803.

4-[1-Methyl-2-(quinolin-8-yl)-1*H*-pyrrol-3-yl]benzonitrile (3c):[23] Radial chromatography (petroleum ether/diethyl ether, 2:1). Pale yellow solid (70 mg, 45 %). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.96 (dd, J = 4.2, 1.8 Hz, 1 H), 8.26 (dd, J = 8.3, 1.8 Hz, 1 H), 7.93 (dd, J = 7.5, 2.2 Hz, 1 H), 7.56–7.51 (m, 2 H), 7.46 (dd, J = 8.3, 4.2 Hz, 1 H), 7.29 (AA′BB′, J = 8.5 Hz, 2 H), 7.09 (AA′BB′, J = 8.5 Hz, 2 H), 6.88 (d, J = 2.9 Hz, 1 H), 6.55 (d, J = 2.9 Hz, 1 H), 3.35 (s, 3 H) ppm.

4-[2-(5-Nitroquinolin-8-yl)-furan-3-yl]benzonitrile (3d): Radial chromatography (petroleum ether/EtOAc, 5:1). Red solid (58 mg, 34 %); m.p. 127–130 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 2925, 2224, 1606, 1502, 1331, 1179, 844, 815, 804, 792, 753 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 9.01 (dd, J = 8.8, 1.7 Hz, 1 H), 8.69 (dd, J = 4.1, 1.7 Hz, 1 H), 8.40 (d, J = 8.1 Hz, 1 H), 7.95 (d, J = 8.1 Hz, 1 H), 7.77 (d, J = 1.9 Hz, 1 H), 7.59 (dd, J = 8.9, 4.1 Hz, 1 H), 7.45 (AA′BB′, J = 8.5 Hz, 2 H), 7.23 (AA′BB′, J = 8.5 Hz, 2 H), 6.84 (d, J = 1.9 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 151.0, 146.5, 145.4, 145.0, 144.4, 139.1, 136.5, 132.1, 132.0, 129.1, 128.3, 125.8, 124.2, 124.1, 121.7, 118.8, 112.6, 110.2 ppm. HRMS (ESi+): m/z calcd. for $C_{20}H_{12}N_3O_3$ $[M + H]^+$ 342.0873, found 342.0870.

4-{2-[5-(Trifluoromethyl)quinolin-8-yl]-furan-3-yl}benzonitrile (3e): Radial chromatography (petroleum ether/EtOAc, 5:1). Yellow oil (80 mg, 44 %). FT- IR (ATR, neat): $\tilde{\nu}$ = 2926, 2226, 1607, 1507, 1318, 1117, 957, 839, 729 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.75 (dd, J = 4.1, 1.7 Hz, 1 H), 8.55–8.52 (m, 1 H), 7.96 (d, J = 7.7 Hz, 1 H), 7.86 (d, J = 7.7 Hz, 1 H), 7.73 (d, J = 1.9 Hz, 1 H), 7.51 (dd, J = 8.7, 4.1 Hz, 1 H), 7.44 (AA′BB′, J = 8.5 Hz, 2 H), 7.25 (AA′BB′, J = 8.5 Hz, 2 H), 6.83 (d, J = 1.9 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 150.8, 147.4, 145.6, 143.9, 139.0, 134.5, 132.6 (q, J = 2.6 Hz), 132.0, 129.7, 128.1, 127.1 (q, J = 31.1 Hz), 124.9, 124.7 (q, J = 5.7 Hz), 124.5, 123.8 (q, J = 274.1 Hz), 122.6, 118.9, 112.1, 109.9 ppm. ^{19}F NMR (377 MHz, $CDCl_3$): δ = –59.1 ppm. HRMS (ESi+): m/z calcd. for $C_{21}H_{12}F_3N_2O$ $[M + H]^+$ 365.0896, found 365.0894.

4-[2-(5-Methoxyquinolin-8-yl)-furan-3-yl]benzonitrile (3f): Radial chromatography (petroleum ether/EtOAc, 5:1). Yellow solid (93 mg, 57 %); m.p. 175–177 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 2965, 2926, 2840, 2223, 1621, 1605, 1225, 1085, 839, 783, 748, 727, 631 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.79 (dd, J = 4.2, 1.8 Hz, 1 H), 8.63 (dd, J = 8.4, 1.8 Hz, 1 H), 7.67 (d, J = 1.9 Hz, 1 H), 7.65 (d, J = 8.0 Hz, 1 H), 7.42–7.37 (m, 3 H), 7.28 (AA′BB′, J = 8.5 Hz, 2 H), 6.88 (d, J = 8.1 Hz, 1 H), 6.81 (d, J = 1.9 Hz, 1 H), 4.06 (s, 3 H), ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.4, 151.0, 149.6, 147.0, 142.9, 139.2, 132.3, 131.9, 130.9, 127.8, 122.2, 122.1, 121.1, 120.6, 119.2, 111.2, 109.3, 104.0, 55.9 ppm. HRMS (ESi+): m/z calcd. for $C_{21}H_{15}N_2O_2$ $[M + H]^+$ 327.1128, found 327.1127.

4-[2-(5-Aminoquinolin-8-yl)-furan-3-yl]benzonitrile (3g): Radial chromatography (petroleum ether/EtOAc, 5:1). Yellow solid (84 mg, 54 %); m.p. 92–95 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 3460, 3372, 3212, 2222, 1605, 1582, 1509, 1467, 1324, 908, 833, 724 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.77 (dd, J = 4.2, 1.6 Hz, 1 H), 8.19 (dd, J = 8.5, 1.7 Hz, 1 H), 7.64 (d, J = 2.0 Hz, 1 H), 7.53 (d, J = 7.8 Hz, 1 H), 7.40 (AA′BB′, J = 8.5 Hz, 2 H), 7.35 (dd, J = 8.5, 4.2 Hz, 1 H), 7.29 (AA′BB′, J = 8.5 Hz, 2 H), 6.81 (d, J = 7.9 Hz, 1 H), 6.79 (d, J = 2.0 Hz, 1 H), 4.45 (s, 2 H), ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 150.6, 147.1, 144.0, 142.7, 139.4, 133.9, 132.9, 132.0, 131.9, 129.5, 128.0, 127.7, 121.7, 120.0, 115.8, 111.1, 109.3, 109.1 ppm. HRMS (ESi+): m/z calcd. for $C_{20}H_{14}N_3O$ $[M + H]^+$ 312.1131, found 312.1131.

4-[2-(Quinolin-2-yl)furan-3-yl]benzonitrile (3h): Radial chromatography (petroleum ether/diethyl ether, 5:1). Pale yellow solid (10 mg, 7 %); m.p. 83–86 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 3057, 2923, 2221, 1598, 1508, 1445, 905, 825, 740 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.14 (d, J = 8.6 Hz, 1 H), 7.90 (dd, J = 8.6, 1.1 Hz, 1 H), 7.81–7.78 (m, 3 H), 7.72–7.67 (m, 5 H), 7.52 (ddd, J = 8.1, 6.8, 1.2 Hz, 1 H), 6.70 (d, J = 1.8 Hz, 1 H), ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 149.2, 148.6, 147.7, 143.4, 138.7, 136.5, 131.8, 130.1, 129.9, 129.4, 127.5, 127.2, 126.8, 124.9, 119.1, 119.0, 114.1, 110.9 ppm. HRMS (ESi+): m/z calcd. for $C_{20}H_{13}N_2O$ $[M + H]^+$ 297.1022, found 297.1025.

4-[2-(Quinolin-2-yl)thiophen-3-yl]benzonitrile (3i): Radial chromatography (petroleum ether/diethyl ether, 5:1). Pale yellow solid (31 mg, 20 %); m.p. 136–138 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 3054, 2217, 1595, 1499, 1316, 861, 829, 817, 796, 741 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.16 (d, J = 8.5 Hz, 1 H), 8.09 (dd, J = 8.4, 1.0 Hz, 1 H), 7.81–7.76 (m, 5 H), 7.70 (d, J = 3.9 Hz, 1 H), 7.68 (AA′BB′, J = 8.5 Hz,

2 H), 7.51 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1 H), 7.46 (d, *J* = 3.9 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 151.6, 148.1, 146.8, 144.3, 143.5, 138.4, 136.7, 132.8, 132.7, 130.0, 129.2, 127.9, 127.5, 127.3, 126.7, 126.4, 126.0, 117.2 ppm. HRMS (ESi+): *m/z* calcd. for $C_{20}H_{13}N_2S$ $[M + H]^+$ 313.0794, found 313.0789.

4-[1-Methyl-2-(quinolin-2-yl)-1*H*-pyrrol-3-yl]benzonitrile (3j): Radial chromatography (petroleum ether/diethyl ether, 5:1). Yellow solid (34 mg, 22 %); m.p. 82–86 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 2923, 2222, 1596, 1509, 1498, 1427, 830, 742, 729, 717 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.14 (dd, *J* = 8.4, 1.0 Hz, 1 H), 7.99 (dd, *J* = 8.6, 0.9 Hz, 1 H), 7.81 (dd, *J* = 8.1, 1.4 Hz, 1 H), 7.76 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1 H), 7.57 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1 H), 7.47 (AA'BB', *J* = 8.5 Hz, 2 H), 7.30 (AA'BB', *J* = 8.5 Hz, 2 H), 7.16 (d, *J* = 8.5 Hz, 1 H), 6.84 (d, *J* = 2.8 Hz, 1 H), 6.39 (d, *J* = 2.8 Hz, 1 H), 3.85 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 151.8, 148.2, 141.6, 135.9, 132.1, 130.1, 129.8, 129.3, 128.8, 127.6, 126.7, 126.6, 125.4, 124.1, 124.0, 119.3, 108.9, 108.6, 35.9 ppm. HRMS (ESi+): *m/z* calcd. for $C_{21}H_{16}N_3$ $[M + H]^+$ 310.1339, found 310.1342.

4-[5-(Quinolin-8-yl)thiophen-2-yl]benzonitrile (4b): Radial chromatography (petroleum ether/EtOAc, 7:1). Yellow solid (34 mg, 22 %); m.p. 161–162 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 3054, 2922, 2223, 1603, 1493, 834, 824, 797, 749 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.83 (dd, *J* = 4.1, 1.8 Hz, 1 H), 8.18 (dd, *J* = 8.3, 1.8 Hz, 1 H), 7.83 (dd, *J* = 8.2, 1.5 Hz, 1 H), 7.58–7.55 (m, 2 H), 7.46 (dd, *J* = 8.2, 7.2 Hz, 1 H), 7.41–7.38 (m, 3 H), 7.30 (d, *J* = 5.3 Hz, 1 H), 7.26 (AA'BB', *J* = 8.5 Hz, 2 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 150.4, 146.3, 141.9, 138.5, 137.2, 136.2, 132.8, 132.5, 131.9, 129.1, 128.7, 128.6, 128.5, 126.7, 126.1, 121.4, 119.0, 109.8 ppm. HRMS (ESi+): *m/z* calcd. for $C_{20}H_{13}N_2S$ $[M + H]^+$ 313.0794, found 313.0800.

4-[5-(Quinolin-2-yl)furan-2-yl]benzonitrile (4h): Radial chromatography (petroleum ether/diethyl ether, 5:1). Yellow solid (61 mg, 41 %); m.p. 154–158 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 3060, 2226, 1605, 1594, 1496, 1018, 927, 808, 788, 755 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 8.5 Hz, 1 H), 8.11 (dd, *J* = 8.5, 1.0 Hz, 1 H), 7.94 (d, *J* = 8.6 Hz, 1 H), 7.89 (AA'BB', *J* = 8.5 Hz, 2 H), 7.81 (dd, *J* = 8.1, 1.3 Hz, 1 H), 7.75–7.70 (m, 3 H), 7.53 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1 H), 7.39 (d, *J* = 3.6 Hz, 1 H), 7.01 (d, *J* = 3.6 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.7, 152.9, 148.4, 148.2, 136.8, 134.1, 132.6, 130.0, 129.3, 127.6, 127.3, 126.5, 124.2, 118.9, 117.3, 112.3, 110.9, 110.7 ppm. HRMS (ESi+): *m/z* calcd. for $C_{20}H_{13}N_2O$ $[M + H]^+$ 297.1022, found 297.1019.

4-[5-(Quinolin-2-yl)thiophen-2-yl]benzonitrile (4i): Radial chromatography (petroleum ether/diethyl ether, 5:1). Pale yellow solid (96 mg, 61 %); m.p. 139–143 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 3058, 2224, 1591, 1501, 1456, 1427, 841, 823, 742, 727 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.07 (dd, *J* = 8.4, 1.0 Hz, 1 H), 7.93 (dd, *J* = 8.6, 0.8 Hz, 1 H), 7.75 (dd, *J* = 8.1, 1.4 Hz, 1 H), 7.72 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1 H), 7.63 (AA'BB', *J* = 8.5, Hz, 2 H), 7.54–7.48 (m, 4 H), 7.16 (d, *J* = 5.2 Hz, 1 H), 7.08 (d, *J* = 8.6 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 152.4, 148.2, 141.4, 141.0, 138.3, 136.1, 132.3, 130.3, 130.0 (2 C), 129.3, 127.8, 127.5, 126.9, 126.7, 120.8, 118.8, 111.1 ppm. HRMS (ESi+): *m/z* calcd. for $C_{20}H_{13}N_2S$ $[M + H]^+$ 313.0794, found 313.0794.

4-[1-Methyl-5-(quinolin-2-yl)-1*H*-pyrrol-2-yl]benzonitrile (4j): Radial chromatography (petroleum ether/diethyl ether, 5:1). Yellow solid (59 mg, 38 %); m.p. 140–145 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 2946, 2224, 1597, 1498, 1346, 1218, 1069, 841, 823, 762 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.13 (dd, *J* = 8.7, 0.8 Hz, 1 H), 8.06 (dd, *J* = 8.4, 0.9 Hz, 1 H), 7.79 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.74–7.69 (m, 4 H), 7.62 (AA'BB', *J* = 8.5, Hz, 2 H), 7.50 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1 H), 6.83 (d, *J* = 3.9 Hz, 1 H), 6.44 (d, *J* = 3.9 Hz, 1 H), 4.09 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 151.7, 147.7, 137.7, 137.5, 136.3, 136.2, 132.3, 129.6, 129.1, 129.0, 127.5, 126.3, 126.0, 120.7, 119.0, 112.8, 110.9, 110.3, 36.0 ppm. HRMS (ESi+): *m/z* calcd. for $C_{21}H_{16}N_3$ $[M + H]^+$ 310.1339, found 310.1338.

4-[5-(Quinolin-3-yl)furan-2-yl]benzonitrile (4k): Radial chromatography (petroleum ether/diethyl ether, 1:1). Yellow solid (105 mg, 71 %); m.p. 132–135 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 2923, 2224, 1605, 1489, 977, 953, 900, 840, 787, 746 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.26 (d, *J* = 2.2 Hz, 1 H), 8.45 (d, *J* = 2.1 Hz, 1 H), 8.11 (d, *J* = 8.5 Hz, 1 H), 7.89 (dd, *J* = 8.3, 1.4 Hz, 1 H), 7.86 (AA'BB', *J* = 8.5, Hz, 2 H), 7.74–7.71 (m, 3 H), 7.61–7.58 (m, 1 H), 7.01 (d, *J* = 3.6 Hz, 1 H), 6.97 (d, *J* = 3.6 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 152.4, 152.3, 147.4, 146.9, 134.0, 132.7, 129.7, 129.5, 129.4, 128.0, 127.7, 127.5, 124.0, 123.3, 118.9, 110.6, 110.5, 109.3 ppm. HRMS (ESi+): *m/z* calcd. for $C_{20}H_{13}N_2O$ $[M + H]^+$ 297.1022, found 297.1023.

4-[5-(Quinolin-3-yl)thiophen-2-yl]benzonitrile (4l): Radial chromatography (petroleum ether/diethyl ether, 1:1). Orange solid (117 mg, 75 %); m.p. 204–205 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 3053, 2225, 1600, 1537, 1496, 928, 903, 801, 784, 745 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.21 (d, *J* = 2.3 Hz, 1 H), 8.30 (d, *J* = 2.1 Hz, 1 H), 8.11 (dd, *J* = 8.4, 1.0 Hz, 1 H), 7.86 (dd, *J* = 8.1, 1.4 Hz, 1 H), 7.75–7.67 (m, 5 H), 7.59 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1 H), 7.52 (d, *J* = 3.9 Hz, 1 H), 7.47 (d, *J* = 3.9 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 148.1, 147.5, 142.3, 142.2, 138.1, 132.8, 131.4, 129.7, 129.4, 127.9, 127.8, 127.5, 126.9, 126.3, 125.9, 125.7, 118.7, 110.9 ppm. HRMS (ESi+): *m/z* calcd. for $C_{20}H_{13}N_2S$ $[M + H]^+$ 313.0794, found 313.0792.

4-[1-Methyl-5-(quinolin-3-yl)-1*H*-pyrrol-2-yl]benzonitrile (4m): Radial chromatography (petroleum ether/diethyl ether, 1:1). Pale yellow solid (104 mg, 67 %); m.p. 164–167 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 2917, 2220, 1603, 1514, 1458, 863, 833, 787, 765, 753 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.08 (d, *J* = 2.3 Hz, 1 H), 8.19 (d, *J* = 1.8 Hz, 1 H), 8.14 (dd, *J* = 8.4, 1.0 Hz, 1 H), 7.87 (dd, *J* = 8.1, 1.3 Hz, 1 H), 7.76–7.71 (m, 3 H), 7.62–7.59 (m, 3 H), 6.53 (d, *J* = 3.8 Hz, 1 H), 6.51 (d, *J* = 3.8 Hz, 1 H), 3.71 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 150.7, 146.9, 137.3, 136.1, 135.3, 134.3, 132.4, 129.6, 129.3, 128.5, 127.8, 127.7, 127.2, 126.0, 118.9, 111.2, 110.1, 34.7 ppm. HRMS (ESi+): *m/z* calcd. for $C_{20}H_{13}N_2S$ $[M + H]^+$ 313.0794, found 313.0792.

4-[5-(Naphthalen-1-yl)furan-2-yl]benzonitrile (4n): Radial chromatography (petroleum ether/EtOAc, 50:1). Yellow solid (63 mg, 43 %); m.p. 106–109 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 2954, 2220, 1606, 1527, 1412, 992, 840, 831, 789, 774 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.45 (dd, *J* = 8.5, 1.2 Hz, 1 H), 7.93–7.87 (m, 2 H), 7.84–7.80 (m, 3 H), 7.68 (AA'BB', *J* = 8.5 Hz, 2 H), 7.59–7.53 (m, 3 H), 7.00 (d, *J* = 3.5 Hz, 1 H), 6.86 (d, *J* = 3.5 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.7, 151.6, 134.5, 134.0, 132.6, 130.2, 129.2, 128.7, 127.8, 126.9, 126.4, 126.1, 125.3, 125.2, 123.8, 119.0, 111.8, 110.1 (2 C) ppm. HRMS (ESi+): *m/z* calcd. for $C_{21}H_{14}NO$ $[M + H]^+$ 296.1070, found 296.1071.

4-[5-(Naphthalen-2-yl)furan-2-yl]benzonitrile (4o): Radial chromatography (petroleum ether/EtOAc, 50:1). Yellow solid (71 mg, 48 %); m.p. 158–162 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 2855, 2218, 1602, 1177, 1025, 866, 827, 786, 753 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.18 (s, 1 H), 7.89–7.77 (m, 6 H), 7.66 (AA'BB', *J* = 8.5 Hz, 2 H), 7.52–7.46 (m, 2 H), 6.90 (d, *J* = 3.6 Hz, 1 H), 6.86 (d, *J* = 3.6 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.1, 151.4, 134.4, 133.4, 132.9, 132.6, 128.6, 128.2, 127.8, 127.3, 126.7, 126.3, 123.7, 122.6, 122.1, 119.0, 110.6, 110.0, 108.2 ppm. HRMS (ESi+): *m/z* calcd. for $C_{21}H_{14}NO$ $[M + H]^+$ 296.1070, found 296.1073.

4,4'-[5-(Quinolin-8-yl)furan-2,4-diyl]dibenzonitrile (5a): Radial chromatography (petroleum ether/EtOAc, 5:1). Yellow solid (64 mg, 32 %); m.p. 247–250 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 2922, 2220, 1602,

1493, 1176, 851, 798, 789, 762 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.69 (dd, J = 4.1, 1.8 Hz, 1 H), 8.22 (dd, J = 8.3, 1.8 Hz, 1 H), 7.97 (dd, J = 8.2, 1.5 Hz, 1 H), 7.92 (dd, J = 7.2, 1.5 Hz, 1 H), 7.85 (AA′BB′, J = 8.5 Hz, 2 H), 7.70 (AA′BB′, J = 8.5 Hz, 2 H), 7.65 (dd, J = 8.2, 7.2 Hz, 1 H), 7.44 (AA′BB′, J = 8.5 Hz, 2 H), 7.41 (dd, J = 8.3, 4.1 Hz, 1 H), 7.30 (AA′BB′, J = 8.5 Hz, 2 H), 7.23 (s, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 152.2, 150.7, 149.9, 145.7, 138.6, 136.3, 134.2, 132.7, 132.0, 131.7, 130.0, 129.5, 128.8, 127.9, 126.2, 125.7, 124.1, 121.7, 118.9, 118.8, 110.7, 110.1, 109.7 ppm. HRMS (ESi+): m/z calcd. for $C_{27}H_{16}N_3O$ $[M + H]^+$ 398.1288, found 398.1284.

4,4′-[1-Methyl-5-(quinolin-8-yl)-1*H*-pyrrol-2,4-diyl]dibenzonitrile (5c):[23] Radial chromatography (petroleum ether/diethyl ether, 2:1). Pale yellow solid (72 mg, 35 %). ^1H NMR (500 MHz, $CDCl_3$): δ = 9.01 (dd, J = 4.0, 2.0 Hz, 1 H), 8.30 (dd, J = 8.5, 2.0 Hz, 1 H), 7.97 (dd, J = 8.0, 2.0 Hz, 1 H), 7.74 (AA′BB′, J = 8.5 Hz, 2 H), 7.68 (AA′BB′, J = 8.5 Hz, 2 H), 7.61–7.54 (m, 2 H), 7.51 (dd, J = 8.5, 4.0 Hz, 1 H), 7.34 (AA′BB′, J = 8.5 Hz, 2 H), 7.13 (AA′BB′, J = 8.5 Hz, 2 H), 6.74 (s, 1 H), 3.37 (s, 3 H) ppm.

4,4′-{5-[5-(Trifluoromethyl)quinolin-8-yl]furan-2,4-diyl}dibenzonitrile (5e): Radial chromatography (petroleum ether/EtOAc, 5:1). Yellow solid (91 mg, 39 %); m.p. 228–232 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 3059, 2223, 1604, 1507, 1316, 1097, 964, 848, 798, 786, 732 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.70 (dd, J = 4.1, 1.7 Hz, 1 H), 8.56–8.54 (m, 1 H), 8.03–7.98 (m, 2 H), 7.86 (AA′BB′, J = 8.5 Hz, 2 H), 7.71 (AA′BB′, J = 8.5 Hz, 2 H), 7.52 (dd, J = 8.7, 4.1 Hz, 1 H), 7.48 (AA′BB′, J = 8.5 Hz, 2 H), 7.29 (AA′BB′, J = 8.5 Hz, 2 H), 7.24 (d, J = 1.9 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 152.8, 150.8, 148.2, 145.4, 138.4, 133.9, 133.8, 132.8, 132.6 (q, J = 2.4 Hz), 132.1, 129.7, 128.1, 127.5 (q, J = 31.0 Hz), 127.1, 125.0, 124.7 (q, J = 5.7 Hz), 124.2, 123.8 (q, J = 274.6 Hz), 122.7, 118.7 (2 C), 111.0, 110.4, 110.1 ppm. ^{19}F NMR (377 MHz, $CDCl_3$): δ = –59.2 ppm. HRMS (ESi+): m/z calcd. for $C_{28}H_{15}F_3N_3O$ $[M + H]^+$ 466.1162, found 466.1166.

4,4′-[5-(5-Methoxyquinolin-8-yl)furan-2,4-diyl]dibenzonitrile (5f): Radial chromatography (petroleum ether/EtOAc, 5:1). Yellow solid (60 mg, 28 %); m.p. 248–250 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 2925, 2223, 1603, 1588, 1465, 1405, 1266, 1222, 1086, 840, 812, 786 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.71 (dd, J = 4.1, 1.8 Hz, 1 H), 8.64 (dd, J = 8.5, 1.8 Hz, 1 H), 7.83 (AA′BB′, J = 8.5 Hz, 2 H), 7.80 (d, J = 8.1 Hz, 1 H), 7.68 (AA′BB′, J = 8.5 Hz, 2 H), 7.43 (AA′BB′, J = 8.5 Hz, 2 H), 7.39 (dd, J = 8.5, 4.2 Hz, 1 H), 7.31 (AA′BB′, J = 8.5 Hz, 2 H), 7.22 (s, 1 H), 6.95 (d, J = 8.1 Hz, 1 H), 4.09 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.7, 151.8, 151.0, 150.5, 146.7, 138.7, 134.3, 132.6, 132.2, 132.0, 131.0, 127.8, 124.8, 124.0, 121.6, 121.1, 120.7, 119.0, 118.9, 110.4, 109.8, 109.5, 104.1, 56.0 ppm. HRMS (ESi+): m/z calcd. for $C_{28}H_{18}N_3O_2$ $[M + H]^+$ 428.1394, found 428.1396.

4,4′-[5-(Quinolin-2-yl)thiophene-2,4-diyl]dibenzonitrile (5i): Radial chromatography (petroleum ether/diethyl ether, 5:1). Yellow solid (25 mg, 12 %); m.p. 196–199 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 3044, 2222, 1592, 1556, 1495, 1425, 826, 786, 751 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.09 (dd, J = 8.6, 1.1 Hz, 1 H), 7.95 (d, J = 8.6 Hz, 1 H), 7.81–7.68 (m, 8 H), 7.57–7.54 (m, 3 H), 7.45 (s, 1 H), 7.08 (d, J = 8.6 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 151.6, 148.2, 143.4, 142.3, 140.9, 139.4, 137.8, 136.3, 132.9, 132.6, 130.2, 129.9, 129.3, 128.0, 127.6, 127.1, 126.0, 120.2, 118.6, 118.5, 111.7, 111.4 ppm. HRMS (ESi+): m/z calcd. for $C_{27}H_{16}N_3S$ $[M + H]^+$ 414.1059, found 414.1056.

Nitrogen Atom-directed Pd-Catalyzed Arylation of Compound 4i with 4-Bromobenzotrifluoride: Compound **4i** (0.25 mmol), 4-bromobenzotrifluoride (53 µL, 0.375 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), PPh_3 (6.6 mg, 0.025 mmol) and K_2CO_3 (69 mg, 0.50 mmol) were dissolved in 1,4-dioxane (1 mL). The reaction mixture was stirred in a sealed glass tube at 130 °C for 48 h under inert atmosphere. The mixture was cooled to room temperature (room temp.) to which water was added (3 mL) and the product was extracted into ethyl acetate (2 × 3 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by radial chromatography to yield pure product **5ia**. Radial chromatography (petroleum ether/ethyl acetate, 10:1). Yellow solid (80 mg, 70 %); m.p. 199–202 °C. FT- IR (ATR, neat): $\tilde{\nu}$ = 3066, 2226, 1609, 1591, 1501, 1321, 1163, 1109, 1067, 1013, 825, 816, 748 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.10 (d, J = 8.4 Hz, 1 H), 7.94 (d, J = 8.6 Hz, 1 H), 7.82–7.80 (m, 2 H), 7.78–7.73 (m, 2 H), 7.69–7.68 (m, 4 H), 7.56–7.53 (m, 3 H), 7.42 (s, 1 H), 7.09 (d, J = 8.6 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 152.0, 148.4, 144.3, 141.6, 141.3, 139.4, 137.1, 136.4, 132.7, 130.5, 130.3, 130.1, 129.5, 127.7, 127.6, 127.2, 127.1, 126.2 (q, J = 3.7 Hz), 126.1, 124.3 (q, J = 271.9 Hz), 120.5, 118.8, 111.8 ppm. ^{19}F NMR (377 MHz, $CDCl_3$): δ = –62.6 ppm. HRMS (ESi+): m/z calcd. for $C_{27}H_{16}F_3N_2S$ $[M + H]^+$ 457.0981, found 457.0976.

Acknowledgments

We thank the Slovenian Research Agency for financial support through grant P1-0179. We also acknowledge the Centre of Excellence EN-FIST.

Keywords: Quinoline · C–H arylation · Nitrogen directed reaction · Palladium catalysis · Heterocycles

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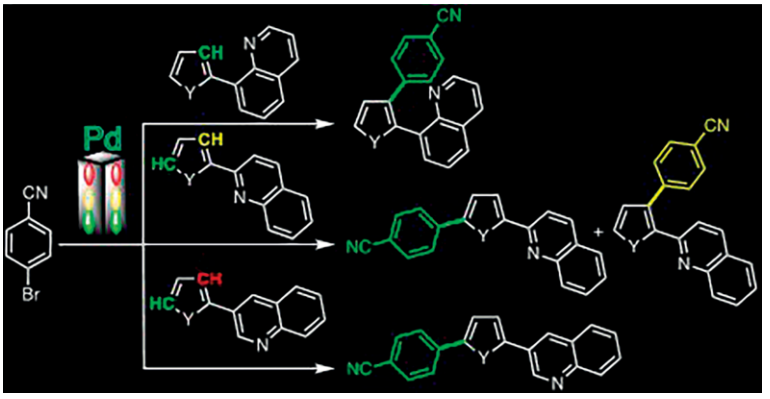
Received: June 1, 2018

Palladium Catalysis



The regioselectivity of the arylation reaction of five-membered heterocycles bearing a quinoline directing group was studied. The transformation was strongly influenced by site position of the attached five-membered heterocycle thus giving rise to C3- and/or C5-arylated products.

DOI: 10.1002/ejoc.201800842