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One-Pot Synthesis of Furo- or Thienoquinolines through Sequential Imination and Intramolecular Palladium-Catalyzed Direct Arylation

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Keywords: Synthetic methods / Heterocycles / Fused-ring systems / Homogeneous catalysis / Palladium / P ligands / C–H functionalization

The sequential imination and intramolecular palladium-catalyzed direct arylation of thiophene-3-carbaldehyde or furan-3-carbaldehyde with 2-haloanilines provided a one-pot access to furo- or thienoquinolines in high yields with H_2O and HBr as the major waste. Both electron-withdrawing and -donating substituents on the 2-haloaniline derivatives were tolerated. These furo- or thienoquinoline derivatives can be employed in the direct arylation at C-5 of the furyl or thienyl moiety, and a variety of corresponding arylation products were obtained in high yields.

Introduction

Because of their biological activities, the preparation of fused heterocyclic compounds is of considerable interest in organic synthesis. For example, thieno-, furo-, or pyrrolo[3,2-*c*]quinolines are reported to present important pharmacological properties (see Figure 1).[1]

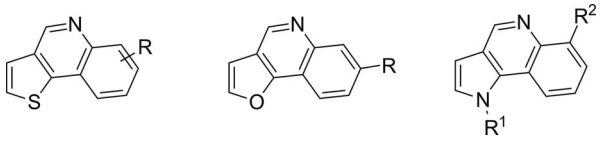

Figure 1. General structure of thieno-, furo-, and pyrrolo[3,2-*c*]-quinolines.

Related compounds have been prepared for antileukemic evaluations[1b] and antibacterial activity studies.[1c] Some thienoquinolines can also act as inhibitors for the protein kinases in cancer cells (see Figure 2).[1d]

For the past two decades, thieno[3,2-*c*]quinoline derivatives have received considerable attention in medicinal and material chemistry. Therefore, significant efforts are directed towards the discovery of more effective synthetic methods for the preparation of molecules containing this motif.[2] For example, Pierre and co-workers described the syntheses of aminothienoquinoline derivatives using a multistep procedure. First, thienolactam intermediates were prepared by the cross-coupling reaction of 2-bromothiophene-3-carboxylate with the corresponding aniline boronic acid. The reaction with phosphorus oxychloride ($POCl_3$) afforded the corresponding chlorothienoquinoline derivatives.[1d] In 1989, Yang and co-workers described the synthesis of a thienoquinoline derivative through the condensation/coupling reaction of (3-carboxaldehydethiophene-2-yl) boronic acid with *N*-acetyl-2-bromoaniline. Low yields were obtained for these reactions, and the protection of the 2-bromoaniline was crucial for the reaction to take place.[2a] In 2007, Lemaire and co-workers described a new approach to aryl-substituted benzothienoquinolines. After the preparation of the aniline-substituted benzothiophene, the addition of substituted benzaldehydes followed by refluxing triflic acid resulted in the corresponding arylated benzothienoquinolines through a Pictet–Spengler cyclization.[2d]

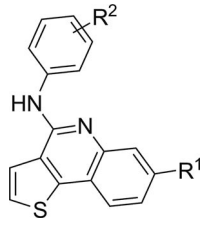

Figure 2. Structure of aniline-substituted thienoquinolines used as pharmaceutical precursors.

Although a number of useful synthetic protocols are available for the preparation of furo- and thienoquinolines, there remain many limitations such as the need of multistep reactions and the limited scope of substrates. Therefore, developing simpler, more general, and convenient processes using readily accessible building blocks for the synthesis of such motifs is highly desirable (see Scheme 1).

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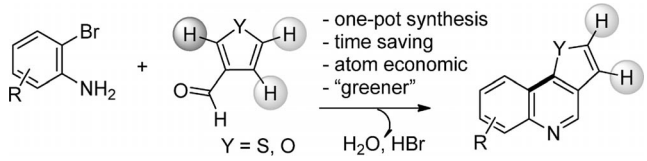
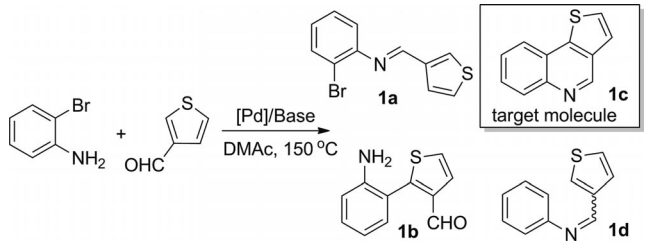


Scheme 1. Green and atom-economic synthetic method for furo- or thienoquinoline derivatives.

We now report a one-pot synthesis of such quinoline derivatives starting from 2-haloanilines and furan- or thiophene-3-carbaldehyde through the successive formation of the corresponding imine followed by a palladium-catalyzed intramolecular C–H bond functionalization.[3–8]

Results and Discussion

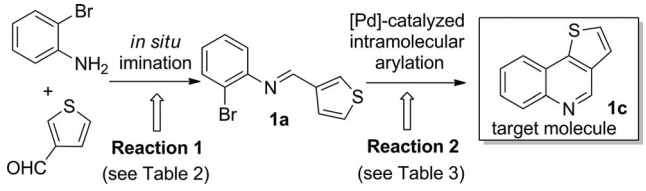
First, we examined the influence of different conditions previously applied to a direct arylation reaction.[7] We tried to achieve a one-pot concerted imination/arylation reaction of thiophene-3-carbaldehyde and 2-bromoaniline to prepare thienoquinoline **1c** (see Scheme 2 and Table 1).



Scheme 2. Direct condensation/arylation of thiophene-3-carbaldehyde with 2-bromoaniline.

In the presence of 2 mol-% $Pd(OAc)_2$ as the catalyst, KOAc as the base, and DMAc (*N*,*N*-dimethylacetamide) as the solvent at 150 °C, imination product **1a** was obtained in moderate yield, and no target **1c** was detected. The major byproduct was **1d** with 32% selectivity (see Table 1, Entry 1). No changes were detected when K_2CO_3 was used as the base. Higher loadings of the base or the aldehyde had no impact on the formation of desired product. On the other hand, the addition of the phosphane ligand dppb [1,4-bis(diphenylphosphanyl)butane] to the reaction mixture was found to give the desired thienoquinoline **1c** with 5% selectivity (see Table 1, Entry 7). Then, we explored the activity of $PdCl(C_3H_5)$(dppb), as we recently demonstrated it was one of the best catalysts for the direct arylation of some furans, thiophenes, or thiazoles.[7b] Using 4 mol-% of this catalyst precursor, the desired intramolecular arylation product **1c** was obtained with 20% selectivity (see Table 1, Entry 9).

To avoid the deleterious influence of a free amino group in the reaction mixture of the catalytic intramolecular arylation, an alternative synthetic route was applied (see Scheme 3). This method consisted of the complete in situ preparation of *N*-(2-bromophenyl)thiophene imine **1a** (see Table 2, Reaction 1) followed by the Pd-catalyzed intramolecular arylation to obtain quinoline derivative **1c** (see Table 3, Reaction 2).



Scheme 3. One-pot sequential imination and intramolecular arylation of thiophene-3-carbaldehyde with 2-bromoaniline.

Even though xylene and toluene are typical solvents for an imination reaction, we studied the influence of using DMAc, which is generally employed in Pd-catalyzed arylations (see Table 2). Using 4 equiv. of thiophene-3-carboxaldehyde in DMAc afforded **1a** in 98% yield. However, a smaller excess amount of thiophene-3-carbaldehyde and a more concentrated solution afforded **1a** in 84–95% yield (see Table 2, Entries 1–4). Use of toluene in the presence of molecular sieves (4 Å) at 130 °C afforded **1a** in 99% yield, whereas xylene with molecular sieves afforded **1a** in 98% yield (see Table 2, Entries 7 and 11). Finally, we observed that 1.2 equiv. of thiophene-3-carbaldehyde afforded full conversion to **1a** (see Table 2, Entry 9). Compound **1a** certainly has the *E* configuration, however, these compounds can isomerize to the reactive *Z* isomers.[9]

Then, *N*-(2-bromophenyl)thiophene imine **1a** prepared in situ from the addition of 2-bromoaniline to thiophene-3-carbaldehyde (see Scheme 3, Reaction 1) in toluene or xy-

Table 1. Influence of the reaction conditions on palladium-catalyzed coupling of thiophene-3-carbaldehyde with 2-bromoaniline (see Scheme 2).[a]

Entry	Pd catalyst [mol-%]	RCHO/R′NH_2	Base	**1a/1b/1c/1d**	Conv. [%]
1	$Pd(OAc)_2$ (2)	2:1	KOAc	68:0:0:32	65
2	$Pd(OAc)_2$ (2)	2:1	K_2CO_3	70:0:0:30	60
3	$Pd(OAc)_2$ (2)	4:1	KOAc	73:0;0:27	70
4[b]	$Pd(OAc)_2$ (2)	4:1	KOAc	77:0:0:23	83
5	$Pd(OAc)_2$ (2)	4:1	K_2CO_3	71:0:0:29	72
6[b]	$Pd(OAc)_2$ (2)	4:1	K_2CO_3	76:0:0:24	80
7[b]	$Pd(OAc)_2$/dppb (2)	4:1	KOAc	75:0:5:20	71
8[b]	$PdCl(C_3H_5)$(dppb) (2)	4:1	KOAc	68:0:9:23	75
9[b]	$PdCl(C_3H_5)$(dppb) (4)	1.2:1	KOAc	55:0:20:25	78

[a] Reagents and conditions: 2-bromoaniline (0.5 mmol), thiophene-3-carbaldehyde (0.6–2 mmol), Pd catalyst (2–4 mol-%), base (1 mmol), DMAc, 150 °C, 24 h, under argon, conversion of 2-bromoaniline. [b] Base (2 mmol).

Table 2. In situ preparation of *N*-(2-bromophenyl)thiophene imine **1a** (see Scheme 3, Reaction 1).[a]

Entry	Solvent [mL]	RCHO/R′NH$_2$	% Yield **1a**
1	DMAc (1)	2:1	70
2	DMAc (1)	4:1	98
3	DMAc (0.5)	1.2:1	95
4	DMAc (0.5)	1.05:1	84
5	CPME[b] (0.5)	4:1	95[c]
6	toluene (0.5)	4:1	52
7	toluene (1)	1.2:1	99[c,d]
8	xylene (0.5)	2:1	99
9	xylene (0.5)	1.2:1	99[c]
10	xylene (0.5)	1.05:1	92
11	xylene (1)	1.2:1	98[c,d]
12	xylene (0.5)	1.05:1	60[e]
13	neat	4:1	87

[a] Reagents and conditions: 2-bromoaniline (0.5 mmol), thiophene-3-carbaldehyde (0.525–2 mmol), 150 °C, 24 h, under argon, GC yields. [b] CPME = cyclopentyl methyl ether. [c] 130 °C. [d] Molecular sieves (MS, 4 Å, 200 mg). [e] Room temperature.

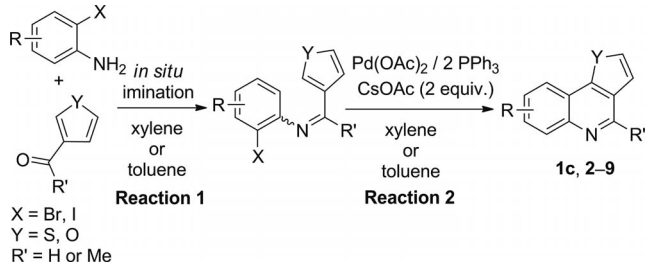
Table 3. Palladium-catalyzed in situ intramolecular arylation of *N*-(2-bromophenyl)thiophene imine **1a** (see Scheme 3, Reaction 2).[a]

Entry	Palladium catalyst/L [mol-%]	Base	Solvent [mL]	*T* [°C]	Time [h]	Yield of **1c** [%]
1	PdCl(C_3H_5)(dppb) (2)	K_2CO_3	DMAc (1)	150	48	14
2	PdCl(C_3H_5)(dppb) (2)	KOAc	DMAc (1)	150	48	15
3	PdCl(C_3H_5)(dppb) (2)	KOAc	CPME (1)	130	48	30
4	PdCl(C_3H_5)(dppb) (2)	KOAc	xylene (1)	150	18	47
5	PdCl(C_3H_5)(dppb) (2)	KF	xylene (1)	150	18	2
6	PdCl(C_3H_5)(dppb) (2)	NaOAc	xylene (1)	150	18	2
7	PdCl(C_3H_5)(dppb) (5)	KOPiv	xylene (1)	150	18	50[b]
8	PdCl(C_3H_5)(dppb) (2)	CsOAc	xylene (2)	150	18	81
9	Pd(OAc)$_2$/2 PPh_3 (5)	KOAc	xylene (1)	130	18	50
10	Pd(OAc)$_2$/2 PPh_3 (5)	Cs_2CO_3	xylene (1)	130	18	85
11	Pd(OAc)$_2$/2 PPh_3 (2)	CsOAc	xylene (2)	130	22	65
12	Pd(OAc)$_2$/2 PPh_3 (2)	CsOAc	xylene (2)	150	18	71
13	Pd(OAc)$_2$/2 PPh_3 (2)	CsOAc	xylene (2)	130	18	90[b] (80)
14	Pd(OAc)$_2$/dppb (2)	CsOAc	xylene (2)	130	22	61
15	Pd(OAc)$_2$/2 PPh_3 (2)	CsOAc	toluene (2)	130	24	95[b,c] (85)
16	Pd(OAc)$_2$/2 PCy_3 (2)	CsOAc	toluene (2)	130	24	91[b,c]
17	Pd(OAc)$_2$/2 PCy_3 (2)	Cs_2CO_3	toluene (2)	130	20	78[b,c]
18	Pd(OAc)$_2$ (2)	CsOAc	xylene (2)	130	18	0

[a] Reagents and conditions of Reaction 1: 2-bromoaniline (0.5 mmol), thiophene-3-carbaldehyde (0.6 mmol), xylene (0.5 mL), 130 °C, 24 h, under argon. [b] MS (4 Å, 200 mg) were added. [c] Followed by Reaction 2 in toluene, reagents and conditions: addition of palladium catalyst/L, base (2 equiv.), solvent (1 or 2 mL). Isolated yields are in parentheses.

lene was subjected to a palladium-catalyzed intramolecular direct arylation reaction (see Scheme 3 and Table 3). After an initial screening of various solvents and employing 1 or 2 mol-% of PdCl(C_3H_5)(dppb), we found that using xylene in Reactions 1 and 2 gave a better result than using DMAc, forming the desired thienoquinoline **1c** in 47% yield (see Table 3, Entries 1–4). Similar to the experiments presented in the Table 1, different bases were employed in combination with PdCl(C_3H_5)(dppb) and xylene to optimize the other reaction conditions. It was found that CsOAc led to a better yield of **1c** in 81% (see Table 3, Entries 5–8). It is known that palladium-catalyzed C–H activation/C–C bond-forming reactions using aryl halides as substrates are very sensitive to the structure of the catalyst and its ligand.[4] Therefore, we investigated the effect on the reaction of using Pd(OAc)$_2$ with various ligands (see Table 3, Entries 9–17). PPh_3 or PCy_3 (Cy = cyclohexyl) formed a suitable combination with Pd(OAc)$_2$ in this coupling reaction, and the best yields of **1c** were obtained in 90% yield using xylene (see Table 3, Entry 13) and in 95 and 91% yield using toluene (see Table 3, Entries 15 and 16, respectively). The use of a ligand-free palladium catalyst Pd(OAc)$_2$ did not result in the formation of the desired intramolecular arylation product **1c** (see Table 3, Entry 18).

The scope of the one-pot sequential imination and cyclization reactions of thiophene-3-carbaldehyde or furan-3-carbaldehyde with various 2-haloanilines was then investigated using Pd(OAc)$_2$ as the catalyst, PPh_3 as the ligand, CsOAc as the base, and either xylene or toluene as the solvents (see Scheme 4 and Table 4).

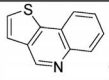
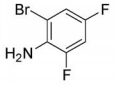
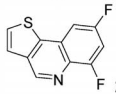
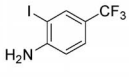
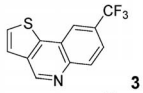
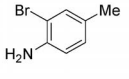
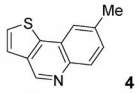
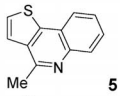
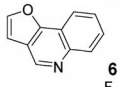
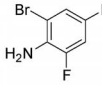
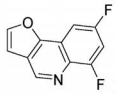
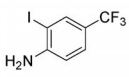
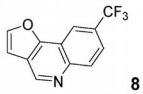
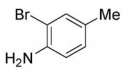
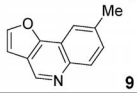


Scheme 4. Syntheses of furo and thienoquinoline derivatives.

First, we studied the reactivity of thiophene-3-carbaldehyde with different substituted 2-haloanilines. In the presence of electron-deficient 2-bromo-4,6-difluoroaniline, product **2** was obtained in 78% yield, when using xylene as the solvent (see Table 4, Entry 3) and in 90% yield when using toluene (see Table 4, Entry 4). Similar yields of product **3** were obtained in the presence of the 2-iodo-4-trifluoromethylaniline in either xylene or toluene (see Table 4, Entries 5 and 6). Lower yields of product **4** were obtained in 82% and 70% with 2-bromo-4-methylaniline (see Table 4, Entries 7 and 8, respectively). A lower reactivity with 3-acetylthiophene with 2-bromoaniline was observed, probably because of a more difficult imination reaction. In the best case, product **5** was obtained in 55% yield (see Table 4, Entry 9).

Then, we investigated the reactivity of furan-3-carbaldehyde with 2-bromoanilines.[10] The use of 2-bromoaniline in xylene afforded product **6** in 70% yield (see Table 4, En-

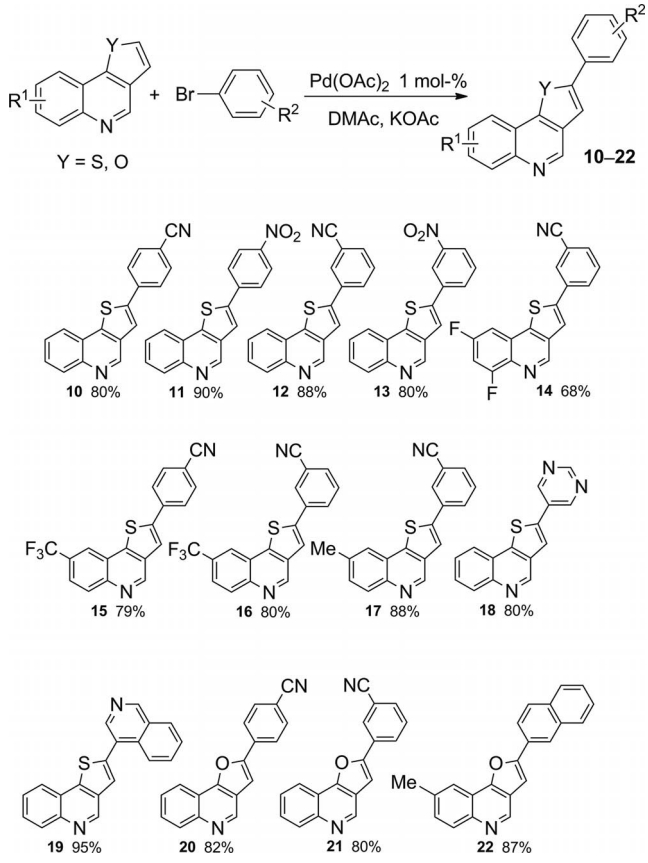
Table 4. Preparation of furo- and thienoquinoline derivatives through a one-pot sequential imination and intramolecular arylation (see Scheme 4).[a]

Entry	Furan or thiophene	Aryl halide	Product	Time for react. 2 (h)	Yield (%)
1			 **1c**	18	80
2				24	85[b]
3			 **2**	40	78
4				24	90[b]
5			 **3**	40	93[c]
6				24	90[b]
7			 **4**	40	82[c]
8				36	70[b]
9			 **5**	48	55
10			 **6**	40	70[c]
11				24	44[b]
12			 **7**	24	89
13			 **8**	40	70[c]
14				24	42[b]
15			 **9**	40	72
16				24	38[b]

[a] Reagents and conditions of Reaction 1: 2-haloaniline (0.5 mmol), thiophene-3-carboxaldehyde (0.6 mmol), MS (4 Å. 200 mg), 130 °C, 24 h, under argon, xylene (1 mL). Followed by Reaction 2, reagents and conditions: addition of $Pd(OAc)_2$/2 PPh_3 (2 mol-%), CsOAc (1 mmol), xylene (1 mL), 130 °C. [b] Toluene instead of xylene (1 mL). [c] $Pd(OAc)_2$/2 PPh_3 (4 mol-%).

try 10); whereas, the use of 2-bromo-4,6-difluoroaniline afforded product **7** in 89% yield (see Table 4, Entry 12). Similar results were obtained when using 4-trifluoromethyl-2-iodoaniline and 2-bromo-4-methylaniline to afford products **8** (see Table 4, Entries 13 and 14) and **9** (see Table 4, Entries 15 and 16), respectively.

We then studied the reactivity of some of the prepared thieno- and furoquinoline derivatives in an intermolecular palladium-catalyzed direct arylation at C-5 of the thienyl or furyl moiety. For this, we employed the conditions described in our previous work for the direct arylation of furans and thiophenes with different aryl bromides.[10b] We observed that by using 1 mol-% $Pd(OAc)_2$ as the catalyst, the 5-arylated thieno- or furoquinolines **10**–**22** were obtained with high to very high isolated yields (see Scheme 5). Similar reactivities were observed for the thieno- and furoquinolines with a minor influence from the presence of methyl, fluoro, and trifluoromethyl substituents on the quinoline derivative.



Scheme 5. Palladium-catalyzed direct arylation of thieno- or furoquinoline derivatives.

Conclusions

In summary, we demonstrated that when the appropriate reaction conditions were employed, the palladium-catalyzed intramolecular direct arylation of in situ prepared *N*-(2-haloaryl)thiophene imine or *N*-(2-haloaryl)furan imine derivatives proceeded regioselectively, starting from a variety of 2-haloaniline derivatives and thiophene-3-carbaldehyde or furan-3-carbaldehyde. This method provided a variety of furo- and thienoquinoline derivatives with the formation of water and HBr as the main byproducts. These furo- and thienoquinoline derivatives were then employed in the direct arylation at C-5 of the thienyl or furyl moiety, and a variety of corresponding arylation products were obtained in high yields.

Experimental Section

General Methods: All reactions were performed under argon in Schlenk tubes. Distilled toluene was used, and analytical grade xylene was not distilled prior to use. Cesium acetate (99+% purity) was used, and commercially available bromoanilines, thiophene-3-carbaldehyde, furan-3-carbaldehyde, and aryl bromides were used without purification. ^1H (500 MHz, 25 °C) and ^{13}C (125 MHz, 25 °C) NMR spectroscopic data were recorded using $CDCl_3$ solutions. Chemical shifts are reported in ppm relative to $CDCl_3$ (^1H NMR, 7.29; ^{13}C NMR, 77.0). Flash chromatography was per-

formed with silica gel (230–400 mesh), using pentane/ethyl ether or ethyl ether/methanol.

General Procedure for the Preparation of Thienoquinolines and Furoquinolines 1c and 2–9: As a typical experiment, 2-bromoaniline (0.086 g, 0.5 mmol) and thiophene-3-carbaldehyde (0.067 g, 0.6 mmol) were stirred in a Schlenk tube containing activated molecular sieves (4 Å, 200 mg). Toluene or xylene (1 mL) was added, and the reaction mixture was stirred under argon at room temperature or 130 °C until the full conversion to the aldimine was achieved. The addition of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), PPh_3 (5.2 mg, 0.02 mmol), CsOAc (0.191 g, 1 mmol), and toluene or xylene (1 mL) at 130 °C over 18–48 h under argon followed by evaporation of the toluene and filtration of the residue through silica gel (pentane/ether) afforded the corresponding thienoquinoline or furoquinoline products **1c** and **2**–**9**.

Thieno[3,2-*c*]quinoline (1c):[2a] The reaction of 2-bromoaniline (0.086 g, 0.5 mmol) with thiophene-3-carbaldehyde (0.067 g, 0.6 mmol) over activated molecular sieves (4 Å, 0.2 g) in xylene (1 mL) afforded **1c** (80%, 0.074 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.30 (s, 1 H), 8.24 (d, J = 8.2 Hz, 1 H), 8.14 (d, J = 8.2 Hz, 1 H), 7.73 (t, J = 8.2 Hz, 1 H), 7.66 (t, J = 8.2 Hz, 1 H), 7.60 (d, J = 5.3 Hz, 1 H), 7.58 (d, J = 5.3 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.6, 145.0, 143.8, 133.7, 130.3, 128.4, 127.1, 126.3, 124.3, 124.0, 123.4 ppm.

6,8-Difluorothieno[3,2-*c*]quinoline (2): The reaction of 2-bromo-4,6-difluoroaniline (0.104 g, 0.5 mmol) with thiophene-3-carbaldehyde (0.067 g, 0.6 mmol) over activated molecular sieves (4 Å, 0.2 g) in toluene (1 mL) afforded **2** (90%, 0.099 g) as a yellow solid; m.p. 214 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.27 (s, 1 H), 7.67 (d, J = 5.3 Hz, 1 H), 7.63 (d, J = 5.3 Hz, 1 H), 7.54 (d, J = 8.5 Hz, 1 H), 7.23 (t, J = 8.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.1 (dd, J = 250.0 and 12.1 Hz), 160.5 (dd, J = 260.0 and 13.5 Hz), 145.9, 143.9 (m), 134.8, 131.0 (dd, J = 11.3 and 2.0 Hz), 127.9, 125.9 (dd, J = 11.8 and 3.4 Hz), 124.3, 104.0 (dd, J = 28.7 and 23.3 Hz), 103.3 (dd, J = 22.9 and 4.8 Hz) ppm. $C_{11}H_5F_2NS$ (221.23): calcd. C 59.72, H 2.28; found C 59.71, H 2.33.

8-(Trifluoromethyl)thieno[3,2-*c*]quinoline (3): The reaction of 2-iodo-4-(trifluoromethyl)aniline (0.144 g, 0.5 mmol) with thiophene-3-carbaldehyde (0.067 g, 0.6 mmol) over activated molecular sieves (4 Å, 0.2 g) in xylene (1 mL) afforded **3** (93%, 0.118 g) as a brown solid; m.p. 130 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.39 (s, 1 H), 8.43 (s, 1 H), 8.35 (d, J = 8.7 Hz, 1 H), 7.91 (d, J = 8.7 Hz, 1 H), 7.69 (d, J = 5.3 Hz, 1 H), 7.66 (d, J = 5.3 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.5, 145.3, 145.0, 134.5, 131.4, 129.0 (q, J = 32.8 Hz), 127.5, 125.3 (q, J = 272.5 Hz), 124.2 (q, J = 3.2 Hz), 124.1, 123.7, 121.2 (q, J = 4.3 Hz) ppm. $C_{13}H_6F_3NS$ (253.24): calcd. C 56.91, H 2.39; found C 56.99, H 2.20.

8-Methylthieno[3,2-*c*]quinoline (4): The reaction of 2-bromo-4-methylaniline (0.093 g, 0.5 mmol) with thiophene-3-carbaldehyde (0.067 g, 0.6 mmol) over activated molecular sieves (4 Å, 0.2 g) in xylene (1 mL) afforded **4** (82%, 0.081 g) as a yellow solid; m.p. 96 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.18 (s, 1 H), 8.09 (d, J = 8.5 Hz, 1 H), 7.80 (s, 1 H), 7.51–7.45 (m, 3 H), 2.54 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.5, 144.3, 142.1, 137.0, 133.6, 130.3, 129.8, 126.0, 124.1, 123.8, 122.4, 21.5 ppm. $C_{12}H_9NS$ (199.27): calcd. C 72.33, H 4.55; found C 72.25, H 4.64.

4-Methylthieno[3,2-*c*]quinoline (5): The reaction of 2-bromoaniline (0.086 g, 0.5 mmol) with 3-acetylthiophene (0.076 g, 0.6 mmol) over activated molecular sieves (4 Å, 0.2 g) in xylene (1 mL) afforded **5** (55%, 0.055 g) as a brown solid; m.p. 128 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.16 (d, J = 8.5 Hz, 1 H), 8.09 (d, J = 8.5 Hz, 1 H), 7.70 (t, J = 8.5 Hz, 1 H), 7.63 (d, J = 5.4 Hz, 1 H), 7.61–7.54 (m, 2 H), 3.00 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.7, 145.0, 143.8, 133.3, 129.4, 128.4, 126.2, 125.8, 123.7, 123.5, 123.3, 23.6 ppm. $C_{12}H_9NS$ (199.27): calcd. C 72.33, H 4.55; found C 72.47, H 4.41.

Furo[3,2-*c*]quinoline (6): The reaction of 2-bromoaniline (0.086 g, 0.5 mmol) with furan-3-carbaldehyde (0.058 g, 0.6 mmol) over activated molecular sieves (4 Å, 0.2 g) in xylene (1 mL) afforded **6** (70%, 0.060 g) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.02 (s, 1 H), 8.12 (d, J = 8.4 Hz, 1 H), 8.08 (d, J = 8.4 Hz, 1 H), 7.58–7.53 (m, 2 H), 7.45 (t, J = 7.5 Hz, 1 H), 6.75 (d, J = 2.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.3, 145.6, 145.4, 144.7, 129.6, 128.0, 126.7, 119.9, 119.8, 117.1, 105.9 ppm. $C_{11}H_7NO$ (169.18): calcd. C 78.09, H 4.17; found C 78.19, H 4.37.

6,8-Difluorofuro[3,2-*c*]quinoline (7): The reaction of 2-bromo-4,6-difluoroaniline (0.104 g, 0.5 mmol) with furan-3-carbaldehyde (0.058 g, 0.6 mmol) over activated molecular sieves (4 Å, 0.2 g) in xylene (1 mL) afforded **7** (89%, 0.091 g) as a light brown solid; m.p. 148 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.12 (s, 1 H), 7.81 (d, J = 2.1 Hz, 1 H), 7.61 (d, J = 8.4 Hz, 1 H), 7.18 (t, J = 8.8 Hz, 1 H), 7.0 (d, J = 2.1 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.9 (dd, J = 249.0 and 11.8 Hz), 160.1 (dd, J = 261.0 and 13.3 Hz), 154.7, (t, J = 5.4 Hz), 145.9, 144.8, 132.8 (dd, J = 11.6 and 2.0 Hz), 121.5, 118.6 (dd, J = 12.1 and 3.7 Hz), 106.3, 103.9 (dd, J = 29.0 and 23.1 Hz), 100.0 (dd, J = 23.5 and 4.9 Hz) ppm. $C_{11}H_5F_2NO$ (205.16): calcd. C 64.40, H 2.46; found C 64.51, H 2.28.

8-Trifluoromethylfuro[3,2-*c*]quinoline (8): The reaction of 2-iodo-4-(trifluoromethyl)aniline (0.144 g, 0.5 mmol) with furan-3-carbaldehyde (0.058 g, 0.6 mmol) over activated molecular sieves (4 Å, 0.2 g) in xylene (1 mL) afforded **8** (70%, 0.083 g) as a brown solid; m.p. 100 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.23 (s, 1 H), 8.54 (s, 1 H), 8.27 (d, J = 8.8 Hz, 1 H), 7.85 (d, J = 8.8 Hz, 1 H), 7.82 (d, J = 2.0 Hz, 1 H), 7.01 (d, J = 2.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.5, 147.6, 146.4, 145.7, 130.8, 128.5 (q, J = 32.8 Hz), 125.1 (q, J = 272.3 Hz), 123.9 (q, J = 3.7 Hz), 121.0, 118.1 (q, J = 4.4 Hz), 116.4, 106.3 ppm. $C_{12}H_6F_3NO$ (237.18): calcd. C 60.77, H 2.55; found C 60.84, H 2.67.

8-Methylfuro[3,2-*c*]quinoline (9): The reaction of 2-bromo-4-methylaniline (0.093 g, 0.5 mmol) with furan-3-carboxaldehyde (0.058 g, 0.6 mmol) over activated molecular sieves (4 Å, 0.2 g) in xylene (1 mL) afforded **9** (72%, 0.066 g) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.13 (s, 1 H), 8.12 (d, J = 8.6 Hz, 1 H), 8.07 (s, 1 H), 7.79 (d, J = 2.1 Hz, 1 H), 7.55 (d, J = 8.6 Hz, 1 H), 6.99 (d, J = 2.1 Hz, 1 H), 2.62 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.3, 144.8, 144.6, 144.3, 137.0, 130.4, 129.4, 120.1, 118.9, 117.2, 106.1, 21.8 ppm. $C_{12}H_9NO$ (183.21): calcd. C 78.67, H 4.95; found C 78.79, H 4.99.

General Procedure for the Arylation of Furoquinolines and Thienoquinolines: As a typical experiment, the reaction mixture of the aryl bromide (0.5 mmol), the furo- or thienoquinoline derivative (1 mmol), and KOAc (0.098 g, 1 mmol) in DMAc (2 mL) in the presence of $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) was heated at 130 °C over 15–20 h under argon. Extraction with dichloromethane, evaporation of the solvent, and filtration of the residue through silica gel (pentane/diethyl ether or diethyl ether/methanol) afforded the corresponding arylation products **10**–**22**.

(4-Thieno[3,2-*c*]quinolin-2-yl)benzonitrile (10): The reaction of 4-bromobenzonitrile (0.091 g, 0.5 mmol) and **1c** (0.185 g, 1 mmol) over 18 h afforded **10** (80%, 0.114 g) as a yellow solid; m.p. 228 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.27 (s, 1 H), 8.24 (d, J = 8.3 Hz,

1 H), 8.11 (d, *J* = 8.3 Hz, 1 H), 7.87–7.83 (m, 3 H), 7.78–7.73 (m, 3 H), 7.76 (t, *J* = 8 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.5, 145.2, 144.0, 142.4, 137.8, 134.5, 132.9, 130.5, 129.1, 127.6, 126.8, 123.8, 123.3, 121.4, 118.5, 112.0 ppm. $C_{18}H_{10}N_2S$ (286.35): calcd. C 75.50, H 3.52; found C 75.32, H 3.35.

2-(4-Nitrophenyl)thieno[3,2-*c*]quinoline (11): The reaction of 4-bromonitrobenzene (0.101 g, 0.5 mmol) and **1c** (0.185 g, 1 mmol) over 15 h afforded **11** (90%, 0.138 g) as a bright yellow solid; m.p. 215 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.27 (s, 1 H), 8.32 (d, *J* = 8.3 Hz, 2 H), 8.23 (d, *J* = 7.8 Hz, 1 H), 8.10 (d, *J* = 7.8 Hz, 1 H), 7.91–7.86 (m, 3 H), 7.76 (t, *J* = 7.8 Hz, 1 H), 7.66 (t, *J* = 7.8 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.5, 146.6, 145.4, 144.1, 141.8, 139.6, 134.5, 130.5, 129.2, 127.6, 126.9, 124.6, 123.8, 123.3, 122.0 ppm. $C_{17}H_{10}N_2O_2S$ (306.34): calcd. C 66.65, H 3.29; found C 66.48, H 3.38.

(3-Thieno[3,2-*c*]quinolin-2-yl)benzonitrile (12): The reaction of 3-bromobenzonitrile (0.091 g, 0.5 mmol) and **1c** (0.185 g, 1 mmol) over 20 h afforded **12** (88%, 0.126 g) as a yellow solid; m.p. 220 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.24 (s, 1 H), 8.22 (d, *J* = 8.0 Hz, 1 H), 8.07 (d, *J* = 8.0 Hz, 1 H), 8.00 (s, 1 H), 7.94 (d, *J* = 7.2 Hz, 1 H), 7.77–7.71 (m, 2 H), 7.68–7.62 (m, 2 H), 7.58 (t, *J* = 7.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.5, 144.8, 144.0, 141.9, 134.8, 133.5, 131.7, 130.5, 130.4, 130.0, 129.8, 128.9, 127.5, 123.8, 123.3, 120.7, 118.2, 113.6 ppm. $C_{18}H_{10}N_2S$ (286.35): calcd. C 75.50, H 3.52; found C 75.67, H 3.59.

2-(3-Nitrophenyl)thieno[3,2-*c*]quinoline (13): The reaction of 3-bromonitrobenzene (0.101 g, 0.5 mmol) and **1c** (0.185 g, 1 mmol) over 20 h afforded **13** (80%, 0.122 g) as a dark bright yellow solid; m.p. 195 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.23 (s, 1 H), 8.54 (t, *J* = 1.9 Hz, 1 H), 8.20 (d, *J* = 8.3 Hz, 2 H), 8.05 (d, *J* = 8.1 Hz, 1 H), 8.00 (d, *J* = 8.1 Hz, 1 H), 7.81 (s, 1 H), 7.72 (t, *J* = 8.1 Hz, 1 H), 7.65–7.60 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.8, 146.5, 144.8, 144.0, 141.7, 135.1, 134.4, 131.9, 130.4, 130.2, 128.9, 127.5, 123.7, 123.2, 123.0, 121.1, 120.0 ppm. $C_{17}H_{10}N_2O_2S$ (306.34): calcd. C 66.65, H 3.29; found C 66.49, H 3.17.

3-(6,8-Difluorothieno[3,2-*c*]quinolin-2-yl)benzonitrile (14): The reaction of 3-bromobenzonitrile (0.091 g, 0.5 mmol) and **2** (0.110 g, 0.5 mmol) over 20 h afforded **14** (68%, 0.110 g) as a bright yellow solid; m.p. 249 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.28 (s, 1 H), 8.06 (s, 1 H), 8.00 (d, *J* = 8.1 Hz, 1 H), 7.86 (s, 1 H), 7.73 (d, *J* = 7.7 Hz, 1 H), 7.65 (t, *J* = 7.7 Hz, 1 H), 7.55 (d, *J* = 8.4 Hz, 1 H), 7.26 (t, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.4 (dd, *J* = 251.0 and 11.2 Hz), 160.5 (dd, *J* = 260.0 and 13.1 Hz), 145.9, 143.6, 136.6, 134.4, 132.3, 131.3 (q, *J* = 10.6 Hz), 130.7, 130.3, 130.0, 125.4 (q, *J* = 4.1 Hz), 120.9, 118.1, 113.8, 104.5 (dd, *J* = 28.7 and 23.5 Hz), 103.3 (dd, *J* = 23.0 and 4.5 Hz) ppm. $C_{18}H_8F_2N_2S$ (322.33): calcd. C 67.07, H 2.50; found C 66.87, H 2.69.

4-[8-(Trifluoromethyl)thieno[3,2-*c*]quinolin-2-yl]benzonitrile (15): The reaction of 4-bromobenzonitrile (0.091 g, 0.5 mmol) and **3** (0.253 g, 1 mmol) over 20 h afforded **15** (79%, 0.139 g) as a brown solid; m.p. 247 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.36 (s, 1 H), 8.49 (s, 1 H), 8.34 (d, *J* = 8.7 Hz, 1 H), 7.92 (d, *J* = 8.7 Hz, 1 H), 7.91 (s, 1 H), 7.87 (d, *J* = 8.3 Hz, 2 H), 7.79 (d, *J* = 8.3 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.5, 145.4, 145.2, 143.6, 137.3, 135.2, 133.1, 131.7, 129.1 (q, *J* = 33 Hz), 127.0, 124.7 (q, *J* = 3.0 Hz), 123.2, 122.8 (q, *J* = 272.5 Hz), 121.3, 121.1 (q, *J* = 4.2 Hz), 118.3, 112.4 ppm. $C_{19}H_9F_3N_2S$ (354.35): calcd. C 64.40, H 2.56; found C 64.51, H 2.70.

3-[8-(Trifluoromethyl)thieno[3,2-*c*]quinolin-2-yl]benzonitrile (16): The reaction of 3-bromobenzonitrile (0.091 g, 0.5 mmol) and **3** (0.253 g, 1 mmol) over 20 h afforded **16** (80%, 0.142 g) as a brown solid; m.p. 218 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.33 (s, 1 H), 8.36 (s, 1 H), 8.31 (d, *J* = 8.7 Hz, 1 H), 8.03 (s, 1 H), 7.96 (d, *J* = 7.8 Hz, 1 H), 7.90 (d, *J* = 8.7 Hz, 1 H), 7.82 (s, 1 H), 7.71 (d, *J* = 7.8 Hz, 1 H), 7.63 (t, *J* = 7.8 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.4, 145.2, 145.0, 143.2, 135.2, 134.4, 132.1, 131.6, 130.6, 130.2, 129.8, 129.2 (q, *J* = 32.7 Hz), 124.6 (q, *J* = 3.2 Hz), 123.1, 122.8 (q, *J* = 272.5 Hz), 121.0 (q, *J* = 4.4 Hz), 120.6, 118.1, 113.8 ppm. $C_{19}H_9F_3N_2S$ (354.35): calcd. C 64.40, H 2.56; found C 64.62, H 2.74.

3-(8-Methylthieno[3,2-*c*]quinolin-2-yl)benzonitrile (17): The reaction of 3-bromobenzonitrile (0.091 g, 0.5 mmol) and **4** (0.199 g, 1 mmol) over 20 h afforded **17** (88%, 0.132 g) as a brown solid; m.p. 192 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.16 (s, 1 H), 8.09 (d, *J* = 8.5 Hz, 1 H), 7.98 (s, 1 H), 7.93 (d, *J* = 7.8 Hz, 1 H), 7.82 (s, 1 H), 7.73 (s, 1 H), 7.65 (d, *J* = 7.8 Hz, 1 H), 7.58 (t, *J* = 7.8 Hz, 1 H), 7.55 (d, *J* = 8.5 Hz, 1 H), 2.61 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.6, 144.2, 142.4, 141.7, 137.7, 134.9, 134.5, 131.6, 131.0, 130.4, 130.1, 130.0, 129.7, 123.7, 122.4, 120.7, 118.2, 113.5, 21.5 ppm. $C_{19}H_{12}N_2S$ (300.38): calcd. C 75.97, H 4.03; found C 76.14, H 3.79.

2-(Pyrimidin-5-yl)thieno[3,2-*c*]quinoline (18): The reaction of 5-bromopyrimidine (0.080 g, 0.5 mmol) and **1c** (0.185 g, 1 mmol) over 20 h afforded **18** (80%, 0.105 g) as a light brown solid; m.p. 162 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.31 (s, 1 H), 9.26 (s, 1 H), 9.14 (s, 2 H), 8.25 (d, *J* = 8.3 Hz, 1 H), 8.14 (d, *J* = 7.9 Hz, 1 H), 7.90 (s, 1 H), 7.78 (t, *J* = 8.3 Hz, 1 H), 7.69 (t, *J* = 7.9 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.2, 154.1, 146.5, 145.4, 144.1, 136.7, 134.4, 130.5, 129.2, 128.1, 127.7, 123.8, 123.4, 121.7 ppm. $C_{15}H_9N_3S$ (263.32): calcd. C 68.42, H 3.45; found C 68.54, H 3.31.

2-(Isoquinolin-4-yl)thieno[3,2-*c*]quinoline (19): The reaction of 4-bromoisoquinoline (0.104 g, 0.5 mmol) and **1c** (0.185 g, 1 mmol) over 20 h afforded **19** (95%, 0.148 g) as a light brown solid; m.p. 167 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.34 (s, 1 H), 9.33 (s, 1 H), 8.76 (s, 1 H), 8.31 (d, *J* = 8.5 Hz, 1 H), 8.28 (d, *J* = 8.1 Hz, 1 H), 8.15 (d, *J* = 8.5 Hz, 1 H), 8.13 (d, *J* = 8.1 Hz, 1 H), 7.81 (t, *J* = 8.1 Hz, 1 H), 7.78–7.73 (m, 2 H), 7.71 (t, *J* = 7.8 Hz, 1 H), 7.66 (t, *J* = 7.8 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.4, 146.5, 145.6, 144.1, 143.8, 138.9, 134.2, 134.1, 131.5, 130.4, 128.7, 128.4, 128.2, 127.8, 127.4, 125.4, 124.6, 124.2, 123.9, 123.4 ppm. $C_{20}H_{12}N_2S$ (312.39): calcd. C 76.90, H 3.87; found C 68.68, H 3.69.

4-(Furo[3,2-*c*]quinolin-2-yl)benzonitrile (20): The reaction of 4-bromobenzonitrile (0.091 g, 0.5 mmol) and **6** (0.169 g, 1 mmol) over 18 h afforded **20** (82%, 0.110 g) as a light orange solid; m.p. 220 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.17 (s, 1 H), 8.32 (d, *J* = 8.2 Hz, 1 H), 8.22 (d, *J* = 8.2 Hz, 1 H), 7.98 (d, *J* = 8.5 Hz, 2 H), 7.75 (d, *J* = 8.5 Hz, 2 H), 7.73 (t, *J* = 8.2 Hz, 1 H), 7.67 (t, *J* = 8.2 Hz, 1 H), 7.30 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.7, 153.9, 146.1, 145.4, 133.6, 132.7, 129.9, 128.8, 127.2, 125.0, 121.4, 119.9, 118.5, 116.8, 112.0, 103.4 ppm. $C_{18}H_{10}N_2O$ (270.28): calcd. C 79.99, H 3.73; found C 79.84, H 3.61.

3-(Furo[3,2-*c*]quinolin-2-yl)benzonitrile (21): The reaction of 3-bromobenzonitrile (0.091 g, 0.5 mmol) and **6** (0.169 g, 1 mmol) over 18 h afforded **21** (80%, 0.108 g) as a yellow solid; m.p. 202 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.15 (s, 1 H), 8.31 (d, *J* = 7.8 Hz, 1 H), 8.20 (d, *J* = 8.2 Hz, 1 H), 8.15 (s, 1 H), 8.07 (d, *J* = 7.8 Hz, 1 H), 7.72 (t, *J* = 8.2 Hz, 1 H), 7.69–7.63 (m, 2 H), 7.58 (t, *J* = 7.8 Hz, 1 H), 7.22 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.4, 153.6, 146.0, 145.3, 131.8, 130.9, 129.9, 129.8, 128.7, 128.6, 128.1, 127.2, 121.3, 119.9, 118.2, 116.8, 113.4, 102.3 ppm. $C_{18}H_{10}N_2O$ (270.28): calcd. C 79.99, H 3.73; found C 79.78, H 3.89.

8-Methyl-2-(naphthalen-2-yl)furo[3,2-*c*]quinoline (22): The reaction of 2-bromonaphthalene (0.103 g, 0.5 mmol) and **9** (0.183 g, 1 mmol) over 15 h afforded **22** (87%, 0.135 g) as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.15 (s, 1 H), 8.47 (s, 1 H), 8.22 (s, 1 H), 8.14 (d, J = 8.5 Hz, 1 H), 8.01–7.94 (m, 3 H), 7.89 (d, J = 7.7 Hz, 1 H), 7.60–7.54 (m, 3 H), 7.30 (s, 1 H), 2.67 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.3, 155.1, 144.4, 144.3, 137.1, 133.4, 130.4, 129.6, 128.8, 128.4, 127.9, 127.2, 126.9, 126.8, 125.5, 124.0, 122.6, 122.0, 119.0, 117.0, 101.0, 21.9 ppm. $C_{22}H_{15}NO$ (306.36): calcd. C 85.41, H 4.89; found C 85.51, H 4.67.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H and ^{13}C NMR spectra of new compounds.

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[1] a) S. K. Kang, S. S. Park, S. S. Kim, J. K. Choi, E. K. Yum, *Tetrahedron Lett.* **1999**, *40*, 4379; b) J.-K. Luo, M. J. Musmar, R. N. Castle, *J. Heterocycl. Chem.* **1991**, *28*, 1309; c) E. A.-G. Bakhite, *Collect. Czech. Chem. Commun.* **1992**, *57*, 2359; d) F. Pierre, P. C. Chua, E. O'Brien, A. Siddiqui-Jain, P. Bourbon, M. Haddach, J. Michaux, J. Nagasawa, M. K. Schwaebe, E. Stefan, A. Vialettes, J. P. Whitten, T. K. Chen, L. Darjania, R. Stansfield, K. Anderes, J. Bliesath, D. Drygin, C. Ho, M. Omori, C. Proffitt, N. Streiner, K. Trent, W. G. Rice, D. M. Ryckman, *J. Med. Chem.* **2011**, *54*, 635.

[2] a) Y. Yang, A.-B. Hörnfeldt, S. Gronowitz, *J. Heterocycl. Chem.* **1989**, *26*, 865; b) B. S. Lee, J. H. Lee, D. Y. Chi, *J. Org. Chem.* **2002**, *67*, 7884; c) J. Liu, Z. Diwu, W.-Y. Leung, Y. Lu, B. Patch, R. P. Haugland, *Tetrahedron Lett.* **2003**, *44*, 4355; d) E. David, S. Pellet-Rostaing, M. Lemaire, *Tetrahedron* **2007**, *63*, 8999; e) S. K. Ock, S. W. Youn, *Bull. Korean Chem. Soc.* **2010**, *31*, 704.

[3] For a review on heterocycle formation through intramolecular palladium-catalyzed C–H bond functionalization, see: T.-S. Mei, L. Kou, S. Ma, K. M. Engle, J.-Q. Yu, *Synthesis* **2012**, *44*, 1778.

[4] For reviews on palladium-catalyzed C–H bond functionalizations, see: a) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174; b) T. Satoh, M. Miura, *Chem. Lett.* **2007**, *36*, 200; c) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173; d) B.-J. Li, S.-D. Yang, Z.-J. Shi, *Synlett* **2008**, 949; e) F. Bellina, R. Rossi, *Tetrahedron* **2009**, *65*, 10269; f) L. Ackermann, R. Vincente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792; g) C. Fischmeister, H. Doucet, *Green Chem.* **2011**, *13*, 741.

[5] A. Ohta, Y. Akita, T. Ohkuwa, M. Chiba, R. Fukunaga, A. Miyafuji, T. Nakata, N. Tani, Y. Aoyagi, *Heterocycles* **1990**, *31*, 1951.

[6] For selected examples of palladium-catalyzed intramolecular cyclizations with heteroarenes, see: a) E. M. Beccalli, G. Broggini, M. Martinelli, G. Paladino, C. Zoni, *Eur. J. Org. Chem.* **2005**, 2091; b) L.-C. Campeau, M. Parisien, A. Jean, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 581; c) A. Putey, L. Joucla, L. Picot, T. Besson, B. Joseph, *Tetrahedron* **2006**, *63*, 867; d) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Synthesis* **2008**, 136; e) A. Mori, N. Arai, T. Hatta, D. Monguchi, *Heterocycles* **2010**, *80*, 103.

[7] For a selection of recent contributions on direct arylations of heteroaromatics from our laboratory, see: a) J. Roger, H. Doucet, *Adv. Synth. Catal.* **2009**, *351*, 1977; b) F. Derridj, J. Roger, S. Djebbar, H. Doucet, *Org. Lett.* **2010**, *12*, 4320; c) J. Roger, F. Požgan, H. Doucet, *Adv. Synth. Catal.* **2010**, *352*, 696; d) L. Chen, J. Roger, C. Bruneau, P. H. Dixneuf, H. Doucet, *Chem. Commun.* **2011**, *47*, 1872; e) H. Y. Fu, H. Doucet, *Eur. J. Org. Chem.* **2011**, 7163; f) K. Beydoun, M. Zaarour, J. A. G. Williams, H. Doucet, V. Guerchais, *Chem. Commun.* **2012**, *48*, 1260.

[8] For selected examples of palladium-catalyzed direct arylations of thiophenes, see: a) T. Okazawa, T. Satoh, M. Miura, M. Nomura, *J. Am. Chem. Soc.* **2002**, *124*, 5286; b) K. Kobayashi, A. Sugie, M. Takahashi, K. Masui, A. Mori, *Org. Lett.* **2005**, *7*, 5083; c) H. A. Chiong, O. Daugulis, *Org. Lett.* **2007**, *9*, 1449; d) M. Nakano, H. Tsurugi, T. Satoh, M. Miura, *Org. Lett.* **2008**, *10*, 1851; e) B. Liégault, D. Lapointe, L. Caron, A. Vlassova, K. Fagnou, *J. Org. Chem.* **2009**, *74*, 1826; f) J. J. Dong, J. Roger, H. Doucet, *Tetrahedron Lett.* **2009**, *50*, 2778; g) K. Ueda, S. Yanagisawa, J. Yamaguchi, K. Itami, *Angew. Chem.* **2010**, *122*, 9130; *Angew. Chem. Int. Ed.* **2010**, *49*, 8946.

[9] J. E. Johnson, N. M. Morales, A. M. Gorczyca, D. Dolliver, M. A. McAllister, *J. Org. Chem.* **2001**, *66*, 7979.

[10] For selected examples of palladium-catalyzed direct arylations of furans, see: a) M. Parisien, D. Valette, K. Fagnou, *J. Org. Chem.* **2005**, *70*, 7578; b) T. A. Dwight, N. R. Rue, D. Charyk, R. Josselyn, B. DeBoef, *Org. Lett.* **2007**, *9*, 3137; c) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Synthesis* **2008**, 136; d) J. J. Dong, J. Roger, F. Pozgan, H. Doucet, *Green Chem.* **2009**, *11*, 1832; e) B. Liégaut, D. Lapointe, L. Caron, A. Vlassova, K. Fagnou, *J. Org. Chem.* **2009**, *74*, 1826; f) B. Liegault, I. Petrov, S. I. Gorelsky, K. Fagnou, *J. Org. Chem.* **2010**, *75*, 1047; g) M. Ionita, J. Roger, H. Doucet, *ChemSusChem* **2010**, *3*, 367; h) K. Si Larbi, H. Y. Fu, N. Laidaoui, K. Beydoun, M. Miloudi, D. El Abed, S. Djebbar, H. Doucet, *ChemCatChem* **2012**, *4*, 815.

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