JOC The Journal of Organic Chemistry

ACS AUTHORCHOICE

pubs.acs.org/joc Article

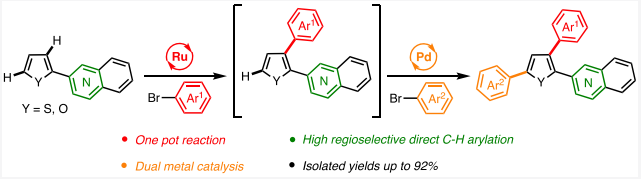
Regioselective Ru(II)/Pd(0) Dual Catalysis: One-Pot C−H Diarylation of Five-Membered Heterocyclic Derivatives

Hamad H. Al Mamari, Uroš Grošelj, Franc Požgan, and Helena Brodnik*

Cite This: J. Org. Chem. 2021, 86, 3138−3151 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Herein, we report a one-pot site-selective dual metal catalyzed C−H diarylation reaction for the synthesis of multiarylated thiophene and furan derivatives in yields up to 92%. The regioselectivity of the developed methodology was achieved with the sequential use of two metal catalysts within a single vessel, starting with a Ru(II)-catalyzed C3 arylation assisted by an azine directing group, followed by a Pd(0)-catalyzed C−H functionalization on the C5-position of the five-membered heterocycle. Furthermore, the kinetic studies support that the position of the nitrogen atom within the azine moiety exhibits an evident effect on the efficiency of the ruthenium-catalyzed arylation step.



INTRODUCTION

The development of synthetic methods to perform a successful multiple bond formation within a single vessel without the isolation or purification of intermediates continues to be a goal for synthetic chemists.[1−9] The importance of such step-economical processes also lies in the reduction of cost, waste, and time, which are the essential aspects of green and sustainable chemistry.[10] The immense progress of transition metal (TM) catalysis over the last five decades has allowed the development of efficient novel one-pot transformations in which all newly formed bonds are based on TM catalysis.[11] In order to access a large number of reactions within a single vessel, one-pot processes catalyzed by only one transition-metal complex often limits access to chemical space diversity. Therefore, the rise of dual catalysis,[12−15] where two different catalysts activate a specific site in the molecule, makes multitransformation reactions highly regioselective.

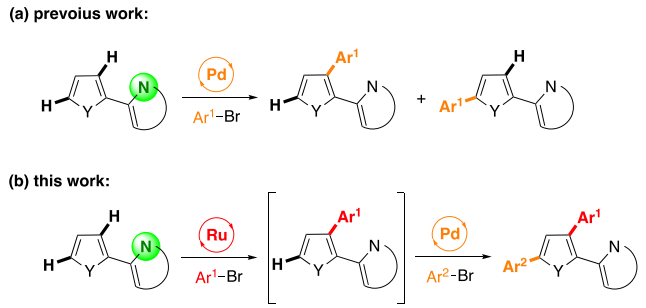
Focused on one-pot C−H functionalization reactions based on ruthenium and palladium catalysis, an early report by Trost and Machacek describes a one-pot procedure for the formation of diastereoselective heterocycles combining a Pd-catalyzed asymmetric allylic alkylation with a Ru-catalyzed ene-yne coupling.[16] Soon after, in 2005, Chang and co-workers reported a novel application of cooperative catalysis to the coupling of an aldehyde with iodoarenes or organostannanes, in which Ru and Pd collaborate, presumably through catalytic transmetalation pathways for the preparation of ketones from aldehydes.[17] An important contribution was also made by Ackermann and Althammer as they reported a one-pot synthesis of 2-aryl- and 2-vinylindoles, which relies on a regioselective $Ru_3(CO)_{12}$-catalyzed hydroamination followed by a palladium-catalyzed intramolecular Heck reaction.[18] Anderson and co-workers described the first example of palladium-catalyzed enynamide cycloisomerization, together with a ruthenium-catalyzed process resulting in high stereo- and regioselectivity, affording a wide diversity of interesting azacyclic scaffolds.[19] A report on direct arylation of imidazo-[1,5-*a*]azines through ruthenium and palladium catalysis in the same flask was published by Charette and co-workers, where the protocol included a two-step sequential C−H arylation reaction allowing rapid synthesis of highly conjugated compounds.[20] In 2016, Sutherland and co-workers developed a procedure for the formation of diversely functionalized aminobicyclo[4.3.0]nonanes as a one-pot three-step tandem process that involved a palladium-catalyzed Overman rearrangement with a ruthenium-catalyzed ring closing enyne metathesis and hydrogen bond directed Diels−Alder reaction.[21] In 2016, Lautens and co-workers reported a dual-metal-catalyzed enantioselective one-pot synthesis that combines a ruthenium-catalyzed C−H functionalization and a palladium-catalyzed asymmetric allylic alkylation reaction for the formation of chiral 3-allyl-3-aryl oxindoles.[22] A highly interesting multicomponent tandem reaction was developed by Prestat and co-workers, as they performed a one-pot Pd/Pd/Ru/Pd-catalyzed procedure allowing the formation of four C−C bonds through four consecutive catalytic cycles.[23]

Recently, we have reported a paper that focuses on the reactivity of C2-quinoline-substituted five-membered heterocycles in a Pd-catalyzed direct C−H functionalization reaction (Scheme 1a).[24] Unfortunately, the presence of only one TM catalyst rendered the protocol to be nonregioselective, as direct arylation proceeded on both the C3 (nitrogen-directed

Received: August 17, 2020
Published: January 29, 2021

https://dx.doi.org/10.1021/acs.joc.0c01983
J. Org. Chem. 2021, 86, 3138−3151

Scheme 1. Transition-Metal Catalyzed C−H Arylation of Five-Membered Heterocycles

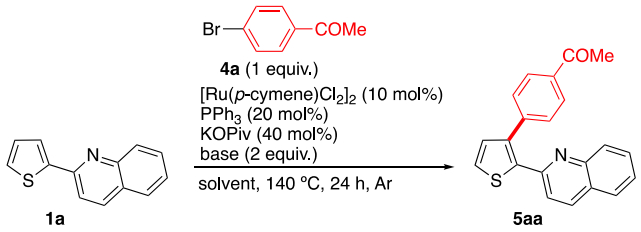


reaction) and the C5 (reaction at more reactive position) position of the five-membered heterocycle; however, the synthesized compounds[25] were exemplified as promising inhibitors toward human cysteine protease Cathepsin B in tumor progression.[26] Driven to develop a methodology that would allow highly regioselective C−H arylation of five-membered heterocyclic derivatives, we turned our attention to the combination of palladium and ruthenium catalysis, as the latter functions solely through the directing group coordination. Herein, we report a two-step sequential one-pot direct C−H arylation catalyzed by ruthenium and palladium for the rapid synthesis of highly conjugated heteroaromatic compounds (Scheme 1b).

RESULTS AND DISCUSSION

On the basis of our previous study,[24] we chose 2-(thiophene-2-yl)quinoline (**1a**) as the model substrate for the optimization of the Ru-catalyzed C−H functionalization step. We anticipated that the reaction would proceed exclusively on the C3 position of the thiophene ring through the formation of a more stable five-membered ruthenacycle, whereas using palladium already in the first C−H functionalization step would afford C3 as well as C5 arylated products, as reported by us[24] and Doucet and co-workers.[27,28] We initiated our investigation with the reaction of **1a** with 4-bromoacetophenone (**4a**) in the presence of [Ru(*p*-cymene)Cl_2]$_2$ as the selected (pre)catalyst. The reactions were run at 140 °C for 24 h. The use of solely [Ru(*p*-cymene)Cl_2]$_2$ (10 mol %) gave only a 10% conversion to the desired product **5aa** (Table 1, entry 1), whereas the combination of PPh_3 and KOPiv allowed the exclusive formation of the monoarylated product **5aa** in quantitative yield (Table 1, entry 4). The use of either PPh_3 or KOPiv as a sole ligand gave lower conversion (Table 1, entries 2 and 3). KOPiv as a carboxylate ligand is presumed to coordinate to the metal center and facilitate the C−H bond cleavage to significantly enhance the direct functionalization process.[29] The combination of both, a phosphine and carboxylate ligand, also proved beneficial in our previous report on the Ru-catalyzed C−H bond functionalization of quinazolines.[30−32] Next, we turned our attention to solvent screening. Among the tested solvents, 1,4-dioxane, toluene, and NMP (*N*-methyl-2-pyrrolidone) all proved to be efficient (Table 1, entries 4−6). However, 1,4-dioxane was chosen as the leading solvent, as toluene and NMP did not perform well in the second, Pd-catalyzed arylation step. Furthermore, the screening of different bases showed full conversion to the desired product **5aa** in the presence of K_2CO_3, Na_2CO_3, and K_3PO_4 (Table 1, entries 4, 9, and 10), whereas acetate bases

Table 1. Optimization of the Ru-Catalyzed Direct C−H Arylation of 2-(Thiophene-2-yl)quinoline (1a) with 4a[a]



entry	base	solvent	conversion (%)[e]
1[b]	K_2CO_3	1,4-dioxane	10
2[c]	K_2CO_3	1,4-dioxane	71
3[d]	K_2CO_3	1,4-dioxane	63
4	**K_2CO_3**	**1,4-dioxane**	**100**
5	K_2CO_3	toluene	100
6	K_2CO_3	NMP	100
7	K_2CO_3	THF	80
8	K_2CO_3	MeCN	11
9	Na_2CO_3	1,4-dioxane	100
10	K_3PO_4	1,4-dioxane	100
11	NaOAc	1,4-dioxane	31
12	KOAc	1,4-dioxane	26

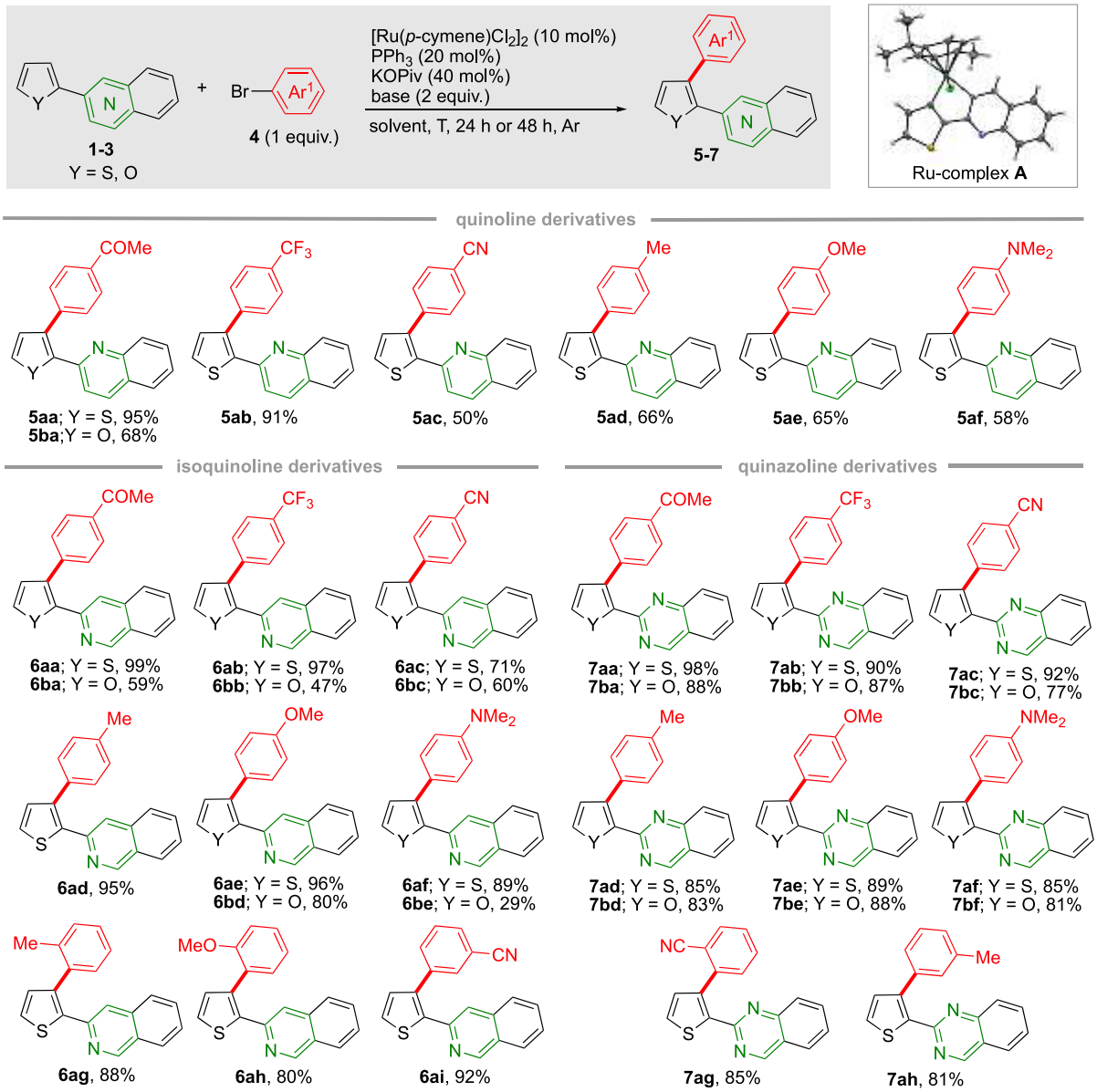
[a]Standard reaction conditions: **1a** (0.5 mmol), **4a** (0.5 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (10 mol %), PPh_3 (20 mol %), KOPiv (40 mol %), base (2 equiv), solvent (2 mL), 140 °C, 24 h, argon. [b]Reaction carried out without PPh_3 and KOPiv. [c]Reaction carried out without PPh_3. [d]Reaction carried out without KOPiv. [e]Conversion determined on the basis of ^{1}H NMR analysis of the crude reaction mixture.

performed poorly (Table 1, entries 11 and 12). Additionally, a series of phosphine and nitrogen-based ligands as well as carboxylate ligands were also examined (for results, see the Supporting Information), but the combination of PPh_3 and KOPiv surpassed them all (Table 1, entry 4). Finally, lowering the reaction temperature resulted in an incomplete conversion to **5aa** after 24 h (for results, see the Supporting Information).

With the optimized reaction conditions ([Ru(*p*-cymene)Cl_2]$_2$ (10 mol %), PPh_3 (20 mol %), KOPiv (40 mol %), K_2CO_3 (2 equiv), 1,4-dioxane, 140 °C, 24 h) in hand, we explored the versatility of quinoline-assisted direct C−H arylation on the C3 position of the thiophene ring (Scheme 2). A series of *para*-substituted aryl bromides were tested, showing high tolerance toward electronic effects of the coupling partner and affording products in moderate to excellent yields (**5aa−f**, 50−95%). Since the Ru-catalyzed direct arylation step is exclusively controlled by a present directing group, we were curious to see if the position of the nitrogen atom in the site directing the azine moiety affects the reactivity of the *in situ* formed Ru species. Satisfyingly, both azine derivatives, 3-(thiophen-2-yl)isoquinoline (**2a**) and 2-(thiophen-2-yl)quinazoline (**3a**), produced noticeably higher conversions compared to our model substrate **1a**, yielding the final products in good to excellent yields (**6aa−f**, 71−99%; **7aa−f**, 85−98%). Moreover, *ortho*- and *meta*-substituted aryl bromides were also exemplified as suitable coupling partners (**6ag−i**, 80−92%; **7ag**, 85%; **7ah**, 81%), proving the method's versatile aspect. Comparing the quinoline, isoquinoline, and quinazoline moieties, we assume that the difference of the efficiency of the Ru-catalyzed arylation may originate in the formation of a stable ruthenacycle complex. Thus, we managed to isolate and determine the structure of Ru-quinazoline-

https://dx.doi.org/10.1021/acs.joc.0c01983
J. Org. Chem. 2021, 86, 3138−3151

Scheme 2. Scope of Ru-Catalyzed Direct C3 Arylation of Compounds 1−3 with Aryl Bromides 4[a]



[a]The yields given refer to the isolated pure products **5**−**7**.

complex **A** using X-ray analysis (Scheme 2), which proved that the metal center favors coordination to the N3-nitrogen rather than to the N1-nitrogen atom of quinazoline; a similar finding also made by Gandhi and co-workers.[33] Furthermore, we also determined that the reaction in the case of quinazoline **3a** proceeded to complete conversion to **7aa** at 120 °C after 24 h, whereas in the case of isoquinoline **2a** to **6aa**, it occurred at an even lower temperature, 100 °C.

To assess the broadness of the method even further, we managed to prepare a set of arylated furan derivatives (Scheme 2), which were more challenging compared to their thiophene analogues. To achieve satisfying conversions, the reaction time needed to be prolonged to 48 h. Therefore, reacting **1b** with **4a** yielded C3-arylated product **5ba** in a good 68% isolated yield. Pleasingly, the Ru-catalyzed arylation of furan derivatives **2b** and **3b** with **4** also showed high reactivity and good substituent tolerance with various aryl bromides, as electron-donating and electron-withdrawing groups showed no influence on the yield of the formed products; C3-arylated furans were isolated in moderate to good yields (**6ba**−**e**, 29−80%; **7ba**−**f**, 77−88%).

To gain a better understanding in the difference of the reactivity of the studied azine derivatives, a set of control experiments were conducted. First, we were interested in the kinetics of the Ru-catalyzed arylation (Figure 1). The progress of the reaction of quinoline **1a**, isoquinoline **2a**, and quinazoline **3a** with **4a**, respectively, under the standard reaction conditions was followed over the period of 6 h. The crude reaction mixture was analyzed by ^{1}H NMR to determine the conversion of the starting material to the monoarylated product. The data show (Figure 1) superior reactivity of the isoquinoline substrate **2a**.

To support our assumption on this matter, three separate competition experiments were carried out. A 1:1 mixture of two substrates (**1a** and **2a**; **2a** and **3a**; **2b** and **3b**) was reacted with an overall 1 equiv of 4-bromoacetophenone (**4a**) under the standard reaction conditions (Scheme 3). The results of

https://dx.doi.org/10.1021/acs.joc.0c01983
J. Org. Chem. 2021, 86, 3138−3151

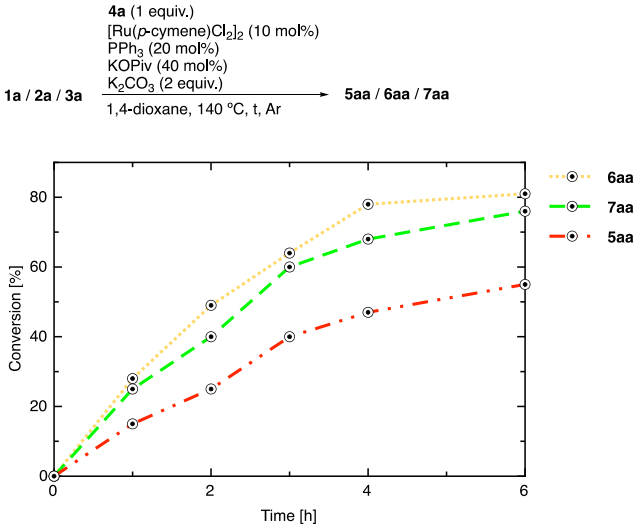
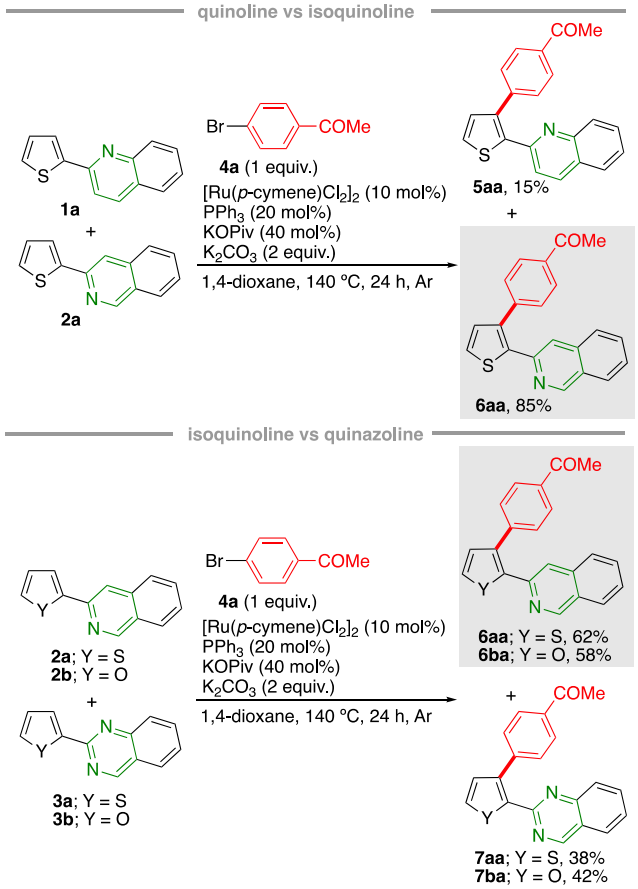


Figure 1. Progress of the reaction over time of Ru-catalyzed C−H arylation of substrates **1a**/**2a**/**3a** under standard reaction conditions. Conversion determined on the basis of ^{1}H NMR analysis of the crude reaction mixture.

Scheme 3. Competition Experiments[a]

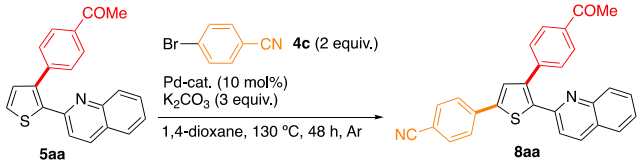


[a]Competition experiments between quinoline derivative **1a** and isoquinoline derivative **2a** (top); isoquinoline derivative **2a** and quinazoline derivative **3a** (bottom); isoquinoline derivative **2b** and quinazoline derivative **3b** (bottom). The ratio between the monoarylated products was determined on the basis of ^{1}H NMR analysis of the crude reaction mixture.

the competition experiments are in line with the observed difference in the initial reactivity (Figure 1) of the three nitrogen-based substrates **1**−**3**, revealing the isoquinoline derivative **2a** to be the most reactive, followed by the quinazoline **3a** and the quinoline **1a** as the least reactive substrate. The observed results suggest that the position of the nitrogen atom in the azine moiety does have a noticeable effect on the efficiency of the Ru-catalyzed reaction. Therefore, one can conclude that, in the Ru-catalyzed arylation step, the isoquinoline moiety exhibits the strongest directing potential for the C3 arylation of the five-membered heterocycle.

After completion of the Ru-catalyzed functionalization step, we continued our investigation on the second, Pd-catalyzed arylation. The reaction would proceed on the C5 position of the five-membered heterocycle, which represents the more reactive position in the ring opposed to C4.[34] For optimization of the Pd-catalyzed arylation, compound **5aa** was chosen as the model substrate and 4-bromobenzonitrile (**4c**), as the selected aryl bromide. A set of different palladium catalysts (Table 2)

Table 2. Optimization of the Pd-Catalyzed Direct C−H Arylation of Compound 5aa with 4-Bromobenzonitrile (4c)[a]



entry	Pd-cat.	conversion (%)[c]
1	**PdCl(C_3H_5)(dppe)**	**80**
2	PdCl(C_3H_5)(dppb)	66
3[b]	Pd($OAc)_2$	62
4	Pd($PPh_3)_4$	56
5	Pd($dba)_4$	6

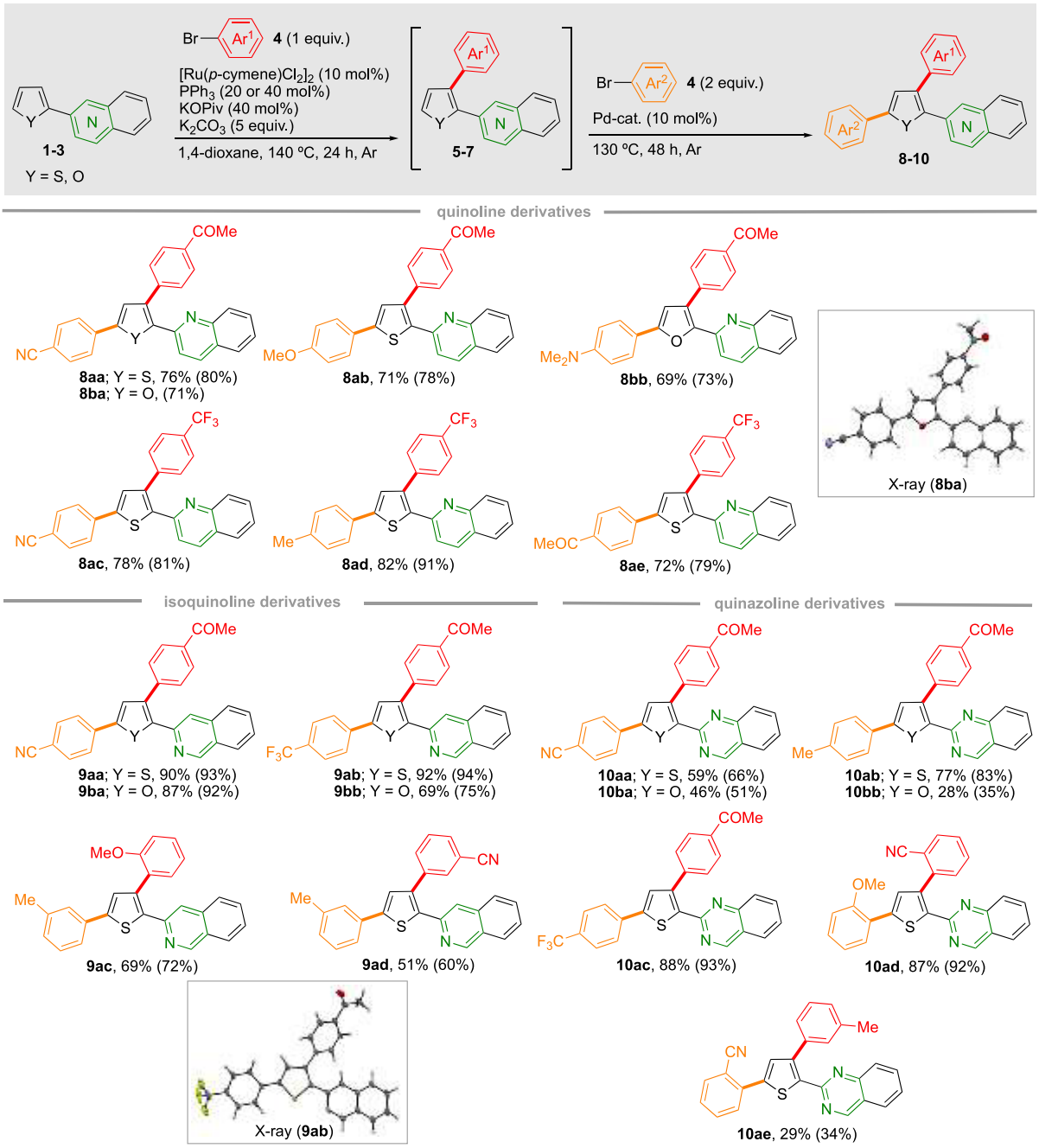
[a]Standard reaction conditions: **5aa** (0.5 mmol), **4c** (1.0 mmol), Pd-cat. (10 mol %), K_2CO_3 (3 equiv), 1,4-dioxane (2 mL), 130 °C, 48 h, argon. [b]PPh_3 (20 mol %) was added to the reaction mixture. [c]Conversion determined on the basis of ^{1}H NMR analysis of the crude reaction mixture.

were tested, out of which PdCl(C_3H_5)(dppe), prepared according to Jutand and co-workers,[35] gave the best result (Table 2, entry 1). It should be noted that in the case of isoquinoline **6aa** the combination of Pd($OAc)_2$ (10 mol %) with PPh_3 (20 mol %) resulted in a 95% conversion to the final product **9aa**, whereas PdCl(C_3H_5)(dppe) gave a 66% conversion. For achieving high conversions to the desired diarylated products **8**−**10**, the reactions were run for 48 h at 130 °C.

Finally, we wanted to combine both metal-catalyzed arylation steps in a single flask to explore the possibility of developing a sequential one-pot procedure (Scheme 4). The initial azine derivatives **1**−**3**, in the presence of [Ru(*p*-cymene)$Cl_2]_2$ (10 mol %), PPh_3 (20 or 40 mol %), KOPiv (40 mol %), and K_2CO_3 (5 equiv) in 1,4-dioxane, were reacted with 1 equiv of aryl bromide **4** at 140 °C for 24 h. After completion of the Ru-catalyzed arylation step, PdCl(C_3H_5)-(dppe) (10 mol %) or Pd($OAc)_2$ (10 mol %) and the corresponding aryl bromide **4** (2 equiv) were added to the reaction flask, and the mixture was stirred for an additional 48 h at 130 °C. Pleasingly, the transformations carried out as a

https://dx.doi.org/10.1021/acs.joc.0c01983
J. Org. Chem. 2021, 86, 3138−3151

Scheme 4. Scope of One-Pot Sequential Ru/Pd-Catalyzed Regioselective Direct Arylation of Five-Membered Heterocycles 1−3[a]



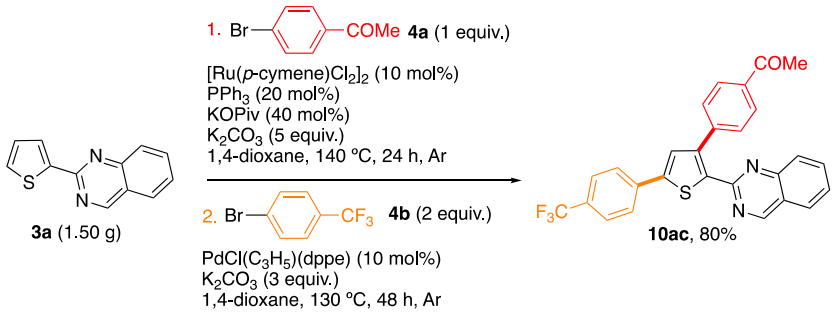
[a]The yields given refer to the isolated pure products **8**−**10** obtained in the one-pot procedure. The yields in brackets were obtained in the Pd-catalyzed arylation step starting from isolated intermediate **5**−**7**. In the case of quinolines **5** and quinazolines **7**, $PdCl(C_3H_5)(dppe)$ was chosen as the catalyst, whereas $Pd(OAc)_2$ was chosen in the case of isoquinoline **6**; therefore, 40 mol % of PPh_3 was added in the first C−H arylation step.

one-pot reaction proceeded equally well in comparison to arylations performed stepwise (with purification of intermediates **5**−**7**). Even the use of *ortho*- and *meta*-substituted aryl bromides yielded the final diarylated products in good yields with the exception of **10ae** (29%). Moreover, products **9ba** (92%) and **9bb** (75%) were isolated in significantly higher yields in the one-pot synthesis, proving the efficiency, simplicity, and economical aspect of the developed methodology for the formation of highly conjugated heterocyclic systems. Additionally, an X-ray analysis of two final diarylated products **8ba** and **9ab** undoubtedly confirmed the established arylation sequence of the developed protocol (Scheme 4).

The developed dual metal one-pot diarylation sequence was also tested on a gram scale where 1.50 g of the starting quinazoline derivative **3a** was reacted with 1 equiv of 4-bromoacetophenone (**4a**) under Ru-catalyzed reaction conditions (Scheme 5). After completion of the first C3 arylation step, 2 equiv of **4b** along with 10 mol % of $PdCl(C_3H_5)(dppe)$ were added to the reaction mixture for the second arylation to proceed on the C5-position of the thiophene ring. Hence, the

https://dx.doi.org/10.1021/acs.joc.0c01983
J. Org. Chem. 2021, 86, 3138−3151

Scheme 5. Scale-up Synthesis of 10ac



final diarylated product **10ac** was isolated in a good 80% overall yield.

CONCLUSIONS

In conclusion, we have developed a regioselective dual metal Ru(II)/Pd(0) catalyzed one-pot C−H diarylation reaction of five-membered heterocycles allowing access to a variety of polyconjugated molecular architectures. The methodology demonstrates its simplicity and regioselectivity by implementing two consecutive arylation steps within a single flask with the use of a nitrogen-based directing group to carry out the Ru-catalyzed reaction at the C3 site, followed by a Pd-catalyzed C5 arylation. Furthermore, competition studies between the azine and diazine derivatives in the Ru-catalyzed arylation step indicate that, among the quinoline, quinazoline, and isoquinoline moieties, the latter possesses the strongest directing efficiency for the direct C3 arylation of the five-membered heterocyclic derivatives, even overpowering the quinazoline structural motif (bearing two nitrogen atoms; both capable of directing the site of arylation).

EXPERIMENTAL SECTION

General Information. The reagents and solvents were used as received from commercial suppliers. A heating mantle was used as the heat source for all the described transformations. 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. Infrared spectra were recorded on a FT-IR spectrometer and are reported in reciprocal centimeters (cm^{-1}). Routine nuclear magnetic resonance spectra were recorded on a Bruker 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), and ddd (doublet doublet of doublets), number of equivalent nuclei (by integration), and 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 = 77.160 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. Single-crystal X-ray diffraction data was collected on the Agilent Technologies SuperNova Dual diffractometer with an Atlas detector using monochromated Mo Kα radiation (λ = 0.71073 Å) and Cu Kα radiation (λ = 1.54184 Å) at 150 K. The data was processed using CrysAlis PRO.[36] Using Olex2.1.2.,[37] the structures were solved by direct methods implemented in SHELXS[38] or SHELXT[39] and refined by a full-matrix least-squares procedure based on F^2 with SHELXT-2014/7.[40] All nonhydrogen atoms were refined anisotropically. Hydrogen atoms were placed in geometrically calculated positions and were refined using a riding model. The drawings and the analysis of bond lengths, angles, and intermolecular interactions were carried out using Mercury[41] and Platon.[42]

Synthesis of Quinoline Derivatives 1 and Isoquinoline Derivatives 2.[25] 2-Bromoquinoline or 3-bromoisoquinoline (5.00 mmol, 1.04 g), 2-thienylboronic acid or 2-furanylboronic acid (7.50 mmol), $Pd(OAc)_2$ (56 mg, 0.25 mmol), PPh_3 (131 mg, 0.50 mmol), and K_2CO_3 (1.38 g, 10 mmol) were dissolved in a mixture of 1,4-dioxane (12 mL) and water (3 mL). The reaction mixture was stirred in a sealed glass tube at 100 °C for 24 h under an inert atmosphere. The mixture was allowed to cool to room temperature; water was added (10 mL), and the product was extracted into EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography.

*2-(Thiophen-2-yl)quinoline (**1a**).* Column chromatography on silica gel (eluting with petroleum ether/EtOAc, 50/1). White solid (1.00 g, 95%). Melting point = 129−131 °C. FT-IR (ATR, neat): 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{^{1}H} 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-(Furan-2-yl)quinoline (**1b**).* Column chromatography on silica gel (eluting with petroleum ether/EtOAc, 50/1). White solid (737 mg, 76%). Melting point = 87−89 °C. FT-IR (ATR, neat): 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{^{1}H} 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.

*3-(Thiophen-2-yl)isoquinoline (**2a**).* Column chromatography on silica gel (eluting with petroleum ether/EtOAc, 10/1). Yellow solid (1.02 g, 97%). Melting point = 114−119 °C. FT-IR (ATR, neat): 3051, 2162, 1959, 1622, 1488, 1345, 1013, 939, 856, 699 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.22 (s, 1H), 7.98 (s, 1H), 7.95 (dd, J = 8.2, 1.0 Hz, 1H), 7.82 (dd, J = 8.3, 1.0 Hz, 1H), 7.70 (dd, J = 3.7, 1.2 Hz, 1H), 7.67 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.55 (ddd, J = 8.1, 6.9, 1.1 Hz, 1H), 7.40 (dd, J = 5.0, 1.1 Hz, 1H), 7.15 (dd, J = 5.0, 3.7 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 152.6 (2C), 146.7, 145.2, 136.6, 130.9, 128.3, 127.9, 127.9, 127.0, 126.8, 124.0, 114.5

https://dx.doi.org/10.1021/acs.joc.0c01983
J. Org. Chem. 2021, 86, 3138−3151

ppm. HRMS (ESI$^+$): m/z calcd. for $C_{13}H_{10}NS$ $(M + H)^+$, 212.0528; found, 212.0534.

*3-(Furan-2-yl)isoquinoline (**2b**).* Column chromatography on silica gel (eluting with petroleum ether/EtOAc, 10/1). Yellow solid (890 mg, 91%). Melting point = 71−75 °C. FT-IR (ATR, neat): 3113, 2982, 1725, 1620, 1484, 1317, 1155, 998, 864, 738 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.23 (s, 1H), 8.02 (s, 1H), 7.94 (dd, J = 8.2, 1.0 Hz, 1H), 7.84 (dd, J = 8.3, 1.0 Hz, 1H), 7.67 (ddd, J = 8.2, 6.8, 1.2 Hz, 1H), 7.57−7.53 (m, 2H), 7.13 (dd, J = 3.3, 0.8 Hz, 1H), 6.57 (dd, J = 3.4, 1.8 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 154.3, 152.7, 143.6, 143.1, 136.5, 130.9, 127.9, 127.9, 127.1, 127.0, 114.3, 112.3, 108.4 ppm. HRMS (ESI$^+$): m/z calcd. for $C_{13}H_{10}NO$ $(M + H)^+$, 196.0757; found, 196.0754.

Synthesis of Quinazoline Derivatives 3.[43] A solution of 2-aminobenzylamine (10 mmol, 1.22 g) and thiophene-2-carbaldehyde or 2-furaldehyde (10 mmol) in MeOH (35 mL) was stirred at room temperature for 20 h. The mixture was then cooled to 0 °C to which 10% NaOCl (55 mmol, 34 mL) was added dropwise over a period of 30 min and further stirred at room temperature for 5 h. The mixture was then washed with brine (40 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography.

*2-(Thiophen-2-yl)quinazoline (**3a**).* Column chromatography on silica gel (eluting with petroleum ether/EtOAc, 10/1). Light yellow solid (1.98 g, 93%). Melting point = 136−139 °C. FT-IR (ATR, neat): 3109, 3080, 3061, 1616, 1583, 1552, 1423, 1395, 1377, 1044, 800, 763, 708 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.36 (d, J = 0.8 Hz, 1H), 8.15 (dd, J = 3.7, 1.2 Hz, 1H), 8.03−7.99 (m, 1H), 7.90−7.85 (m, 2H), 7.57 (ddd, J = 8.1, 6.9, 1.1 Hz, 1H), 7.52 (dd, J = 5.0, 1.2 Hz, 1H), 7.20 (dd, J = 5.0, 3.7 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 160.7, 158.0, 150.8, 144.0, 134.5, 130.1, 129.4, 128.5, 128.3, 127.4, 127.1, 123.5 ppm. HRMS (ESI$^+$): m/z calcd. for $C_{12}H_9N_2S$ $(M + H)^+$, 213.0481; found, 213.0484.

*2-(Furan-2-yl)quinazoline (**3b**).* Column chromatography on silica gel (eluting with petroleum ether/EtOAc, 10/1). Light yellow solid (1.53 g, 78%). Melting point = 118−121 °C. FT-IR (ATR, neat): 3132, 3099, 3055, 1587, 1480, 1413, 1379, 1166, 1074, 1002, 765, 721 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.37 (d, J = 0.8 Hz, 1H), 8.11−8.06 (m, 1H), 7.92−7.85 (m, 2H), 7.68 (dd, J = 1.8, 0.9 Hz, 1H), 7.61−7.56 (m, 1H), 7.45 (dd, J = 3.4, 0.9 Hz, 1H), 6.61 (dd, J = 3.4, 1.7 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 160.9, 154.2, 152.6, 150.5, 145.5, 134.7, 128.5, 127.4, 127.4, 123.5, 114.2, 112.5 ppm. HRMS (ESI$^+$): m/z calcd. for $C_{12}H_9N_2O$ $(M + H)^+$, 197.0709; found, 197.0712.

General Method for Ruthenium-Catalyzed C−H Arylation. A mixture of the azine substrates **1**−**3** (0.50 mmol), aryl bromide **4** (0.50 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (0.05 mmol, 31 mg), PPh_3 (0.10 mmol, 26 mg), KOPiv (0.20 mmol, 28 mg), and K_2CO_3 (1.00 mmol, 138 mg) in 1,4-dioxane (2 mL) was stirred for 24 h at 140 °C under argon in a sealed tube. The mixture was then cooled to room temperature, and DCM (10 mL) was added, after which the inorganic salts were filtered off and washed with DCM (5 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by radial chromatography on silica gel to yield the monoarylated products **5**−**7**.

*1-(4-(2-(Quinolin-2-yl)thiophen-3-yl)phenyl)ethan-1-one (**5aa**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 10/1). Greenish-brown solid (156 mg, 95%). Melting point = 100−103 °C. FT-IR (ATR, neat): 3034, 1672, 1614, 1500, 1261, 1014, 823, 767, 721, 655 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, J = 8.4, 1.0 Hz, 1H), 7.95 (AA′BB′, J = 8.55 Hz, 2H), 7.88 (d, J = 8.7, 0.8 Hz, 1H), 7.77−7.68 (m, 2H), 7.55−7.46 (m, 4H), 7.18 (d, J = 5.2 Hz, 1H), 7.10 (d, J = 8.6 Hz, 1H), 2.63 (s, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 197.9, 152.9, 148.4, 141.7, 140.8, 139.4, 136.2, 136.1, 130.8, 130.0, 129.6, 129.5, 128.8, 127.8, 127.6, 127.1, 126.7, 121.1, 26.8 ppm. HRMS (ESI$^+$): m/z calcd for $C_{21}H_{16}NOS$ $(M + H)^+$, 330.0947; found, 330.0942.

*2-(3-(4-(Trifluoromethyl)phenyl)thiophen-2-yl)quinoline (**5ab**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 20/1). Yellow solid (161 mg, 91%). Melting point = 112−115 °C. FT-IR (ATR, neat): 3041, 1614, 1552, 1320, 1161, 1102, 947, 852, 783, 727 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, J = 8.4, 0.9 Hz, 1H), 7.91 (d, J = 8.6, 0.8 Hz, 1H), 7.76−7.70 (m, 2H), 7.62 (d, 2H), 7.56−7.48 (m, 4H), 7.17 (d, J = 5.2 Hz, 1H), 7.09 (d, J = 8.6 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 152.9, 148.4, 140.8, 140.5 (C−F, $^1J_{C-F}$ = 3.9 Hz), 139.0, 136.2, 130.8, 130.0, 129.7, 129.7, (C−F, $^3J_{C-F}$ = 32.5 Hz), 129.5, 127.8, 127.6, 127.1, 126.8, 125.7 (C−F, $^2J_{C-F}$ = 3.9 Hz), 124.4 (C−F, $^1J_{C-F}$ = 272.5 Hz), 120.9 ppm. ^{19}F NMR (471 MHz, $CDCl_3$): δ −62.5 ppm. HRMS (ESI$^+$): m/z calcd for $C_{20}H_{13}F_3NS$ $(M + H)^+$, 356.0715; found, 356.0713.

*4-(2-(Quinolin-2-yl)thiophen-3-yl)benzonitrile (**5ac**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 50/1). Yellow solid (78 mg, 50%). Melting point = 137−139 °C. FT-IR (ATR, neat): 3056, 2223, 1906, 1590, 1311, 1223, 992, 840, 822, 741 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (dd, J = 8.5, 0.9 Hz, 1H), 7.93 (dd, J = 8.6, 0.9 Hz, 1H), 7.76 (dd, J = 8.1, 1.4 Hz, 1H), 7.74−7.70 (m, 1H), 7.64 (AA′BB′, J = 8.56 Hz, 2H), 7.56−7.47 (m, 4H), 7.16 (d, J = 5.1 Hz, 1H), 7.09 (d, J = 8.6 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 152.5, 148.4, 141.6, 141.1, 138.5, 136.3, 132.5, 130.5, 130.1 (2C), 129.5, 128.0, 127.6, 127.1, 126.9, 121.0, 118.9, 111.3 ppm. HRMS (ESI$^+$): m/z calcd for $C_{20}H_{13}N_2S$ $(M + H)^+$, 313.0794; found, 313.0794.

*2-(3-(p-Tolyl)thiophen-2-yl)quinoline (**5ad**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 5/1). White solid (99 mg, 66%). Melting point = 123−125 °C. FT-IR (ATR, neat): 3100, 3076, 1592, 1497, 1422, 1228, 1075, 858, 816, 752 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (dd, J = 8.3, 0.9 Hz, 1H), 7.85 (dd, J = 8.7, 0.8 Hz, 1H), 7.76−7.65 (m, 2H), 7.52−7.43 (m, 2H), 7.29 (AA′BB′, J = 8.06 Hz, 2H), 7.20−7.12 (m, 4H), 2.40 (s, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 153.6, 148.3, 140.9, 139.4, 137.6, 135.8, 133.9, 131.3, 129.7, 129.5, 129.4, 129.3, 127.5, 127.4, 127.0, 126.4, 121.0, 21.4 ppm. HRMS (ESI$^+$): m/z calcd for $C_{20}H_{16}NS$ $(M + H)^+$, 302.0998; found, 302.0997.

*2-(3-(4-Methoxyphenyl)thiophen-2-yl)quinoline (**5ae**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 50/1). White solid (103 mg, 65%). Melting point = 125−127 °C. FT-IR (ATR, neat): 2999, 2842, 1573, 1458, 1302, 1123, 994, 828, 725, 688 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (dd, J = 8.5, 0.9 Hz, 1H), 7.86 (dd, J = 8.7, 0.8 Hz, 1H), 7.75−7.66 (m, 2H), 7.54−7.43 (m, 2H), 7.32 (AA′BB′, J = 8.75 Hz, 2H), 7.16 (d, J = 8.7 Hz, 1H), 7.13 (d, J = 5.1 Hz, 1H), 6.90 (AA′BB′, J = 8.81 Hz, 2H), 3.84 (s, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 159.3, 153.7, 148.3, 140.6, 139.0, 135.7, 131.2, 130.6, 129.7, 129.4, 129.2, 127.5, 127.4, 127.0, 126.4, 121.0, 114.2, 55.4 ppm. HRMS (ESI$^+$): m/z calcd for $C_{20}H_{16}NOS$ $(M + H)^+$, 318.0947; found, 318.0946.

*N,N-Dimethyl-4-(2-(quinolin-2-yl)thiophen-3-yl)aniline (**5af**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 50/1). Yellow solid (96 mg, 58%). Melting point = 158−160 °C. FT-IR (ATR, neat): 3104, 2883, 2802, 1542, 1500, 1343, 1194, 1067, 816, 741 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (dd, J = 8.5, 0.9 Hz, 1H), 7.86 (dd, J = 8.7, 0.8 Hz, 1H), 7.76−7.64 (m, 2H), 7.51−7.46 (m, 1H), 7.45 (d, J = 5.1 Hz, 1H), 7.30−7.26 (m, 3H), 7.14 (d, J = 5.2 Hz, 1H), 6.72 (AA′BB′, J = 8.89 Hz, 2H), 3.00 (s, 6H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 154.1, 150.0, 148.3, 141.3, 138.0, 135.5, 131.3, 130.2, 129.6, 129.4, 127.5, 127.2, 127.0, 126.2, 124.6, 121.2, 112.5, 40.6 ppm. HRMS (ESI$^+$): m/z calcd for $C_{21}H_{19}N_2S$ $(M + H)^+$, 331.1263; found, 331.1259.

*1-(4-(2-(Quinolin-2-yl)furan-3-yl)phenyl)ethan-1-one (**5ba**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 20/1). Light brown solid (106 mg, 68%). Melting point = 62−64 °C. FT-IR (ATR, neat): 3040, 1767, 1504, 1309, 1224, 1141, 1054, 951, 821, 736 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (dd, J = 8.7, 0.8 Hz, 1H), 8.02−7.97 (m, 3H), 7.77 (dd, J = 8.2, 1.4 Hz, 1H), 7.74 (AA′BB′, J = 8.42 Hz, 2H), 7.72−7.65 (m, 2H), 7.61 (d, J = 8.6 Hz, 1H), 7.55−7.47 (m, 1H), 6.71 (d, J = 1.8 Hz, 1H), 2.65 (s, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 197.9, 149.5, 148.6, 148.1, 143.5, 138.9, 136.4, 136.3, 130.0, 129.7, 129.7, 128.4, 127.6, 127.3, 126.8, 125.8, 119.5, 114.4, 26.8 ppm. HRMS (ESI$^+$): m/z calcd for $C_{21}H_{16}NO_2$ $(M + H)^+$, 314.1176; found, 314.1171.

https://dx.doi.org/10.1021/acs.joc.0c01983
J. Org. Chem. 2021, 86, 3138−3151

*1-(4-(2-(Isoquinolin-3-yl)thiophen-3-yl)phenyl)ethan-1-one (**6aa**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 7/1). Dark geen solid (163 mg, 99%). Melting point = 151−153 °C. FT-IR (ATR, neat): 3002, 1676, 1601, 1578, 1404, 1359, 1267, 1014, 960, 740 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.23 (s, 1H), 7.98−7.92 (m, 3H), 7.62−7.46 (m, 6H), 7.42 (s, 1H), 7.15 (d, J = 5.1 Hz, 1H), 2.63 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 197.9, 152.6, 146.2, 142.3, 140.6, 138.1, 136.0, 131.0, 130.8, 129.5, 128.9, 127.7, 127.6, 127.5, 127.0, 126.8, 118.5, 26.8 ppm. HRMS (ESI^+): m/z calcd for $C_{21}H_{16}NOS$ $(M + H)^+$, 330.0947; found, 330.0944.

*3-(3-(4-(Trifluoromethyl)phenyl)thiophen-2-yl)isoquinoline (**6ab**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 20/1). White solid (172 mg, 97%). Melting point = 119−122 °C. FT-IR (ATR, neat): 3066, 1624, 1457, 1326, 1159, 1102, 1060, 828, 729, 670 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.24 (s, 1H), 7.94 (dd, J = 8.2, 1.1 Hz, 1H), 7.65−7.60 (m, 4H), 7.58 (dd, J = 13.0, 1.3 Hz, 1H), 7.56−7.49 (m, 2H), 7.48 (d, J = 5.2 Hz, 1H), 7.39 (s, 1H), 7.14 (d, J = 5.2 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 152.6, 146.2, 141.0, 140.6, 137.8, 136.0, 130.9 (C−F, $^2J_{C-F}$ = 12.3 Hz), 129.7, 129.5 (C−F, $^3J_{C-F}$ = 33.0 Hz), 127.7, 127.6, 127.5, 127.0, 126.8, 125.8 (C−F, $^2J_{C-F}$ = 3.8 Hz), 124.4 (C−F, $^1J_{C-F}$ = 272.2 Hz), 118.4 ppm. ^{19}F NMR (471 MHz, $CDCl_3$): δ −62.4 ppm. HRMS (ESI^+): m/z calcd for $C_{20}H_{13}F_3NS$ $(M + H)^+$, 356.0715; found, 356.0715.

*4-(2-(Isoquinolin-3-yl)thiophen-3-yl)benzonitrile (**6ac**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 10/1). Orange solid (111 mg, 71%). Melting point = 120−124 °C. FT-IR (ATR, neat): 3110, 3027, 2223, 1692, 1622, 1602, 1490, 1273, 882, 743 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.23 (s, 1H), 7.95 (dd, J = 8.1, 1.1 Hz, 1H), 7.66−7.62 (m, 3H), 7.57 (ddd, J = 8.1, 6.9, 1.3 Hz, 1H), 7.55−7.51 (m, 3H), 7.49 (d, J = 5.2 Hz, 1H), 7.40 (s, 1H), 7.14 (d, J = 5.2 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 152.7, 145.9, 142.1, 141.0, 137.3, 136.0, 132.6, 131.0, 130.6, 130.0, 127.78, 127.7, 127.0, 126.9, 119.1, 118.7, 111.0 ppm. HRMS (ESI^+): m/z calcd for $C_{20}H_{13}N_2S$ $(M + H)^+$, 313.0794; found, 313.0794.

*3-(3-(p-Tolyl)thiophen-2-yl)isoquinoline (**6ad**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 10/1). Light brown solid (143 mg, 95%). Melting point = 85−88 °C. FT-IR (ATR, neat): 3026, 1621, 1542, 1504, 1332, 1023, 885, 815, 736, 694 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.23 (s, 1H), 7.92 (dd, J = 8.1, 1.1 Hz, 1H), 7.58−7.45 (m, 5H), 7.48 (AA′BB′, J = 8.2 Hz, 2H), 7.19 (AA′BB′, J = 8.1 Hz, 2H), 7.11 (d, J = 5.1 Hz, 1 H), 2.41 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 152.3, 146.8, 139.4, 139.3, 137.3, 136.0, 134.4, 131.6, 130.6, 129.6, 129.1, 127.7, 127.5, 127.1, 127.1, 126.2, 117.8, 21.4 ppm. HRMS (ESI^+): m/z calcd for $C_{20}H_{16}NS$ $(M + H)^+$, 302.0998; found, 302.0997.

*3-(3-(4-Methoxyphenyl)thiophen-2-yl)isoquinoline (**6ae**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 10/1). White solid (152 mg, 96%). Melting point = 110−113 °C. FT-IR (ATR, neat): 3050, 2992, 2841, 1748, 1606, 1500, 1374, 1241, 1030, 736 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.23 (s, 1H), 7.91 (dd, J = 8.0, 1.1 Hz, 1H), 7.59−7.47 (m, 3H), 7.45 (s, 1H), 7.42 (d, J = 5.2 Hz, 1H), 7.36 (AA′BB′, J = 8.0 Hz, 2H), 7.10 (d, J = 5.2 Hz, 1H), 6.92 (AA′BB′, J = 8.1 Hz, 2H), 3.86 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 159.1, 152.3, 146.8, 139.1, 136.1, 131.6, 130.6, 130.4, 129.69, 127.7, 127.5, 127.1, 126.2, 117.8, 114.3, 55.5 ppm. HRMS (ESI^+): m/z calcd for $C_{20}H_{16}NOS$ $(M + H)^+$, 318.0947; found, 318.0950.

*4-(2-(Isoquinolin-3-yl)thiophen-3-yl)-N,N-dimethylaniline (**6af**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 10/1). Yellow solid (148 mg, 89%). Melting point = 112−116 °C. FT-IR (ATR, neat): 3061, 2849, 2103, 1676, 1610, 1508, 1440, 1347, 884, 737 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.23 (s, 1H), 7.91 (dd, J = 8.0, 1.1 Hz, 1H), 7.58−7.47 (m, 4H), 7.40 (d, J = 5.1 Hz, 1H), 7.32 (AA′BB′, J = 8.8 Hz, 2H), 7.11 (d, J = 5.1 Hz, 1H), 6.75 (AA′BB′, J = 8.8 Hz, 2H), 3.00 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 152.2, 150.0, 147.1, 139.8, 138.2, 136.1, 131.8, 130.4, 130.1, 129.8, 127.7, 127.4, 127.1, 126.9, 126.0, 125.2, 117.6, 112.7, 40.7, 30.9 ppm. HRMS (ESI^+): m/z calcd for $C_{21}H_{19}N_2S$ $(M + H)^+$, 331.1263; found, 331.1261.

*3-(3-(o-Tolyl)thiophen-2-yl)isoquinoline (**6ag**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 20/1). Colorless oil (133 mg, 88%). FT-IR (ATR, neat): 3056, 2919, 1622, 1580, 1455, 1275, 939, 883, 824, 755, 733, 664, 630 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.19 (s, 1H), 7.88 (dd, J = 8.1, 1.2 Hz, 1H), 7.52 (ddd, J = 8.2, 6.8, 1.4 Hz, 1H), 7.49−7.47 (m, 1H), 7.45 (d, J = 5.1 Hz, 1H), 7.38−7.27 (m, 5H), 7.04 (s, 1H), 7.01 (d, J = 5.1 Hz, 1H), 2.11 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 152.1, 146.7, 140.3, 138.7, 137.6, 136.8, 136.2, 131.5, 130.6, 130.5, 129.8, 128.1, 127.6, 127.4, 127.2, 127.0, 126.5, 126.1, 115.7, 20.1 ppm. HRMS (ESI^+): m/z calcd for $C_{20}H_{16}NS$ $(M + H)^+$, 302.0998; found, 302.1000.

*3-(3-(2-Methoxyphenyl)thiophen-2-yl)isoquinoline (**6ah**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 5/1). Light yellow solid (127 mg, 80%). Melting point = 145−146 °C. FT-IR (ATR, neat): 3024, 2964, 2829, 1600, 1486, 1459, 1250, 1023, 890, 753, 728, 660 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.20 (s, 1H), 7.93−7.87 (m, 1H), 7.53 (ddd, J = 8.1, 6.8, 1.3 Hz, 1H), 7.48 (ddd, J = 8.1, 6.8, 1.3 Hz, 1H), 7.43 (d, J = 5.1 Hz, 1H), 7.42−7.37 (m, 2H), 7.33−7.29 (m, 2H), 7.11 (d, J = 5.2 Hz, 1H), 7.03−6.97 (m, 2H), 3.62 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 157.1, 151.9, 147.1, 140.7, 136.2, 135.3, 132.1, 131.5, 130.4, 129.3, 127.7, 127.4, 127.0, 126.9, 126.4, 125.7, 121.1, 116.4, 111.5, 55.6 ppm. HRMS (ESI^+): m/z calcd for $C_{20}H_{16}NOS$ $(M + H)^+$, 318.0947; found, 318.0945.

*3-(2-(Isoquinolin-3-yl)thiophen-3-yl)benzonitrile (**6ai**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 7/1). Yellow solid (144 mg, 92%). Melting point = 147−150 °C. FT-IR (ATR, neat): 3058, 3034, 2226, 1575, 1478, 1016, 875, 825, 727, 700, 655, 623, 611 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.22 (s, 1H), 7.95 (dd, J = 8.1, 1.1 Hz, 1H), 7.74 (m, 1H), 7.66−7.60 (m, 3H), 7.57 (ddd, J = 8.1, 6.9, 1.3 Hz, 1H), 7.53 (dd, J = 8.1, 1.1 Hz, 1H), 7.48 (d, J = 5.2 Hz, 1H), 7.47−7.43 (m, 1H), 7.38 (s, 1H), 7.12 (d, J = 5.1 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 152.7, 145.9, 140.8, 138.7, 136.7, 136.0, 133.9, 132.8, 131.0, 131.0, 130.7, 129.6, 127.8, 127.7, 127.6, 127.0, 126.9, 118.8, 118.4, 113.0 ppm. HRMS (ESI^+): m/z calcd for $C_{20}H_{13}N_2S$ $(M + H)^+$, 313.0794; found, 313.0789.

*1-(4-(2-(Isoquinolin-3-yl)furan-3-yl)phenyl)ethan-1-one (**6ba**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 5/1). Orange oil (92 mg, 59%). FT-IR (ATR, neat): 3056, 2965, 1951, 1761, 1676, 1602, 1488, 1356, 1266, 728 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.18 (s, 1H), 7.97−7.92 (m, 3H), 7.90 (s, 1H), 7.75−7.72 (m, 1H), 7.68−7.61 (m, 4H), 7.57 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 6.68 (d, J = 1.8 Hz, 1H), 2.62 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 197.9, 152.5, 148.9, 143.8, 142.8, 139.2, 136.2, 135.9, 130.8, 129.3, 128.5, 127.9, 127.8, 127.6, 127.1, 123.9, 117.7, 114.1, 26.7 ppm. HRMS (ESI^+): m/z calcd for $C_{21}H_{16}NO_2$ $(M + H)^+$, 314.1176; found, 314.1174.

*3-(3-(4-(Trifluoromethyl)phenyl)furan-2-yl)isoquinoline (**6bb**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 20/1). White solid (80 mg, 47%). Melting point = 73−77 °C. FT-IR (ATR, neat): 3057, 1618, 1575, 1433, 1320, 1160, 1117, 961, 885, 748 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.19 (s, 1H), 7.95 (dd, J = 8.2, 1.0 Hz, 1H), 7.91 (d, J = 1.0 Hz, 1H), 7.76 (dd, J = 8.3, 1.1 Hz, 1H), 7.69−7.65 (m, 3H), 7.65−7.56 (m, 4H), 6.67 (d, J = 1.8 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 152.5, 148.7, 143.7, 142.8, 137.9, 136.2, 130.9, 129.5, 129.3 (C−F, $^3J_{C-F}$ = 32.3 Hz), 128.0, 127.8, 127.6, 127.1, 125.3 (C−F, $^2J_{C-F}$ = 3.8 Hz), 124.6 (C−F, $^1J_{C-F}$ = 271.8 Hz), 123.6, 117.6, 114.3 ppm. ^{19}F NMR (471 MHz, $CDCl_3$): δ −62.4 ppm. HRMS (ESI^+): m/z calcd for $C_{20}H_{13}F_3NO$ $(M + H)^+$, 340.0944; found, 340.0936.

*4-(2-(Isoquinolin-3-yl)furan-3-yl)benzonitrile (**6bc**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 10/1). Light orange solid (89 mg, 60%). Melting point = 132−135 °C. FT-IR (ATR, neat): 3114, 2222, 1607, 1572, 1452, 1220, 1159, 1048, 836, 749 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.15 (d, J = 1.0 Hz, 1H), 7.97−7.93 (m, 2H), 7.79 (dd, J = 8.2, 1.1 Hz, 1H), 7.72−7.58

https://dx.doi.org/10.1021/acs.joc.0c01983
J. Org. Chem. 2021, 86, 3138−3151

(m, 7H), 6.66 (d, J = 1.8 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 152.4, 149.1, 143.6, 142.9, 139.1, 136.2, 132.0, 131.0, 129.9, 128.0, 127.8, 127.7, 127.1, 123.3, 119.3, 117.7, 114.0, 110.7 ppm. HRMS (ESI^+): m/z calcd for $C_{20}H_{13}N_2O$ $(M + H)^+$, 297.1022; found, 297.1016.

*3-(3-(4-Methoxyphenyl)furan-2-yl)isoquinoline (**6bd**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 10/1). Orange oil (120 mg, 80%). FT-IR (ATR, neat): 2998, 2834, 1945, 1755, 1658, 1623, 1515, 1244, 1159, 747 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.24 (s, 1H), 7.92 (dd, J = 8.1, 1.1 Hz, 1H), 7.83 (d, J = 1.0 Hz, 1H), 7.67 (dd, J = 8.3, 1.1 Hz, 1H), 7.64−7.58 (m, 2H), 7.53 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 7.46 (AA′BB′, J = 8.2 Hz, 2H), 6.92 (AA′BB′, J = 8.2 Hz, 2H), 6.61 (d, J = 1.8 Hz, 1H), 3.85 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 159.0, 152.5, 147.5, 144.1, 142.5, 136.2, 130.6, 130.2, 127.7, 127.6, 127.2, 127.0, 126.4, 124.6, 117.2, 114.5, 114.0, 55.4 ppm. HRMS (ESI^+): m/z calcd for $C_{20}H_{16}NO_2$ $(M + H)^+$, 302.1176; found, 302.1168.

*4-(2-(Isoquinolin-3-yl)furan-3-yl)-N,N-dimethylaniline (**6be**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 10/1). Orange oil (46 mg, 29%). FT-IR (ATR, neat): 2884, 2802, 1924, 1613, 1521, 1444, 1352, 1319, 1195, 746 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.26 (s, 1H), 7.93 (dd, J = 8.1, 1.1 Hz, 1H), 7.88 (d, J = 1.1 Hz, 1H), 7.70−7.66 (m, 1H), 7.64−7.56 (m, 2H), 7.53 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 7.42 (AA′BB′, J = 8.8 Hz, 2H), 6.76 (AA′BB′, J = 8.8 Hz, 2H), 6.61 (d, J = 1.8 Hz, 1H), 3.00 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 152.5, 150.0, 147.1, 144.4, 142.5, 136.2, 130.5, 129.7, 127.7, 127.6, 127.1, 127.1, 125.2, 121.9, 117.1, 114.5, 112.6, 40.7 ppm. HRMS (ESI^+): m/z calcd for $C_{21}H_{19}N_2O$ $(M + H)^+$, 315.1492; found, 315.1485.

*1-(4-(2-(Quinazolin-2-yl)thiophen-3-yl)phenyl)ethan-1-one (**7aa**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 7/1). Light yellow solid (162 mg, 98%). Melting point = 150−154 °C. FT-IR (ATR, neat): 3100, 3081, 3060, 3041, 1671, 1562, 1550, 1486, 1420, 1379, 1271, 892, 749, 729 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.23 (d, J = 0.8 Hz, 1H), 7.97 (AA′BB′, J = 8.4 Hz, 2H), 7.86−7.80 (m, 2H), 7.73 (dd, J = 8.4, 0.6 Hz, 1H), 7.59 (AA′BB′, J = 8.4 Hz, 2H), 7.56 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H), 7.53 (d, J = 5.1 Hz, 1H), 7.19 (d, J = 5.1 Hz, 1H), 2.66 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 198.2, 160.3, 158.0, 150.3, 142.5, 142.4, 138.5, 135.9, 134.4, 132.0, 130.0, 128.6, 128.6, 128.0, 127.5, 127.3, 123.3, 26.9 ppm. HRMS (ESI^+): m/z calcd for $C_{20}H_{15}N_2OS$ $(M + H)^+$, 331.0900; found, 331.0901.

*2-(3-(4-(Trifluoromethyl)phenyl)thiophen-2-yl)quinazoline (**7ab**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 7/1). White solid (160 mg, 90%). Melting point = 126−129 °C. FT-IR (ATR, neat): 3065, 3024, 1616, 1586, 1541, 1326, 1277, 1160, 1092, 1061, 830, 731, 666 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.24 (d, J = 0.8 Hz, 1H), 7.86−7.80 (m, 2H), 7.71 (dd, J = 8.4, 1.0 Hz, 1H), 7.66−7.59 (m, 4H), 7.56 (ddd, J = 8.1, 6.9, 1.1 Hz, 1H), 7.53 (d, J = 5.1 Hz, 1H), 7.17 (d, J = 5.1 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 160.3, 158.0, 150.3, 142.2, 141.2 (C−F, $^2J_{C-F}$ = 1.2 Hz), 138.5, 134.5, 132.0, 130.1, 129.3 (C−F, $^3J_{C-F}$ = 23.3 Hz), 128.6, 128.4, 127.5, 127.3, 124.7 (C−F, $^2J_{C-F}$ = 3.9 Hz), 124.6 (C−F, $^1J_{C-F}$ = 272.3 Hz), 123.3 ppm. ^{19}F NMR (471 MHz, $CDCl_3$): δ −62.3 ppm. HRMS (ESI^+): m/z calcd for $C_{19}H_{12}F_3N_2S$ $(M + H)^+$, 357.0668; found, 357.0671.

*4-(2-(Quinazolin-2-yl)thiophen-3-yl)benzonitrile (**7ac**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 5/1). Light brown solid (144 mg, 92%). Melting point = 163−166 °C. FT-IR (ATR, neat): 3096, 3055, 2217, 1926, 1671, 1618, 1456, 1423, 1396, 833, 800, 743, 722 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.24 (d, J = 0.8 Hz, 1H), 7.87−7.82 (m, 2H), 7.71−7.65 (m, 3H), 7.62−7.56 (m, 3H), 7.54 (d, J = 5.1 Hz, 1H), 7.15 (d, J = 5.1 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 160.3, 157.7, 150.2, 142.4, 141.6, 138.9, 134.6, 131.7, 131.6, 130.5, 128.9, 128.4, 127.6, 127.3, 123.3, 119.4, 110.8 ppm. HRMS (ESI^+): m/z calcd for $C_{19}H_{12}N_3S$ $(M + H)^+$, 314.0746; found, 314.0743.

*2-(3-(p-Tolyl)thiophen-2-yl)quinazoline (**7ad**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 10/1). Light brown solid (128 mg, 85%). Melting point = 87−90 °C. FT-IR (ATR, neat): 3097, 3071, 3019, 2913, 1616, 1585, 1564, 1539, 1420, 1376, 1026, 804, 718 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.24 (d, J = 0.6 Hz, 1H), 7.85−7.78 (m, 3H), 7.55 (ddd, J = 8.1, 6.1, 2.1 Hz, 1H), 7.48 (d, J = 5.1 Hz, 1H), 7.41 (AA′BB′, J = 8.1 Hz, 2H), 7.20−7.16 (m, 3H), 2.42 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 160.2, 158.6, 150.5, 143.8, 137.0, 137.0, 134.3, 134.2, 132.4, 129.6, 128.6, 128.5, 128.1, 127.2, 123.2, 21.5 ppm. HRMS (ESI^+): m/z calcd for $C_{19}H_{15}N_2S$ $(M + H)^+$, 303.0900; found, 303.0947.

*2-(3-(4-Methoxyphenyl)thiophen-2-yl)quinazoline (**7ae**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 10/1). Light yellow solid (141 mg, 89%). Melting point = 119−122 °C. FT-IR (ATR, neat): 3108, 3064, 3031, 2838, 1609, 1585, 1378, 1274, 1201, 1024, 821, 747 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.25 (s, 1H), 7.85−7.78 (m, 3H), 7.55 (ddd, J = 8.1, 6.2, 1.9 Hz, 1H), 7.48 (d, J = 5.1 Hz, 1H), 7.45 (AA′BB′, J = 8.8 Hz, 2H), 7.17 (d, J = 5.1 Hz, 1H), 6.92 (AA′BB′, J = 8.8 Hz, 2H), 3.87 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 160.2, 159.1, 158.6, 150.5, 143.4, 136.7, 134.2, 132.4, 130.9, 129.7, 128.5, 128.1, 127.2, 123.2, 113.2, 55.4 ppm. HRMS (ESI^+): m/z calcd for $C_{19}H_{15}N_2OS$ $(M + H)^+$, 319.0900; found, 319.0897.

*N,N-Dimethyl-4-(2-(quinazolin-2-yl)thiophen-3-yl)aniline (**7af**).* Radial chromatography on silica gel (eluting with petroleum ether/DCM; 1/2). Yellow solid (141 mg, 85%). Melting point = 98−101 °C. FT-IR (ATR, neat): 3062, 2881, 2798, 1608, 1547, 1507, 1417, 1395, 1223, 1194, 1166, 815, 802, 722 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.26 (d, J = 0.8 Hz, 1H), 7.87−7.78 (m, 3H), 7.54 (ddd, J = 8.1, 6.8, 1.4 Hz, 1H), 7.46 (d, J = 5.1 Hz, 1H), 7.43 (AA′BB′, J = 8.7 Hz, 2H), 7.18 (d, J = 5.1 Hz, 1H), 6.74 (AA′BB′, J = 8.7 Hz, 2H), 3.00 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 160.2, 159.0, 150.6, 150.0, 144.0, 135.6, 134.1, 132.4, 130.6, 128.5, 128.0, 127.2, 127.0, 125.2, 123.1, 111.9, 40.7 ppm. HRMS (ESI^+): m/z calcd for $C_{20}H_{18}N_3S$ $(M + H)^+$, 332.1216; found, 332.1214.

*2-(2-(Quinazolin-2-yl)thiophen-3-yl)benzonitrile (**7ag**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 5/1). Light yellow solid (133 mg, 85%). Melting point = 145−146 °C. FT-IR (ATR, neat): 3111, 3061, 2220, 1420, 1379, 1029, 973, 894, 766, 747, 731 689 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.21 (s 1H), 7.81 (ddd, J = 8.1, 1.5, 0.6 Hz, 1H), 7.79−7.73 (m, 2H), 7.65−7.61 (m, 1H), 7.57−7.55 (m, 2H), 7.54−7.50 (m, 2H), 7.50−7.47 (m, 1H), 7.17 (d, J = 5.1 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 160.2, 157.6, 150.2, 142.3, 140.1, 139.3, 134.3, 132.5, 132.1, 131.8, 130.7, 128.7, 128.4, 127.5, 127.4, 127.3, 123.2, 118.7, 113.7 ppm. HRMS (ESI^+): m/z calcd for $C_{19}H_{12}N_3S$ $(M + H)^+$, 314.0746; found, 314.0744.

*2-(3-(m-Tolyl)thiophen-2-yl)quinazoline (**7ah**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 10/1). Colorless oil (122 mg, 81%). FT-IR (ATR, neat): 3018, 2916, 1549, 1418, 1375, 935, 804, 736, 700, 661 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.23 (s, 1H), 7.82−7.75 (m, 3H), 7.52 (ddd, J = 8.1, 6.6, 1.4 Hz, 1H), 7.48 (d, J = 5.0 Hz, 1H), 7.36−7.35 (m, 1H), 7.29−7.23 (m, 2H), 7.19−7.16 (m, 2H), 2.37 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 160.1, 158.5, 150.4, 143.9, 137.3, 137.3, 137.1, 134.2, 132.4, 130.3, 128.4, 128.1, 128.0, 127.6, 127.2, 127.2, 126.9, 123.1, 21.6 ppm. HRMS (ESI^+): m/z calcd for $C_{19}H_{15}N_2S$ $(M + H)^+$, 303.0950; found, 303.0946.

*1-(4-(2-(Quinazolin-2-yl)furan-3-yl)phenyl)ethan-1-one (**7ba**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 5/3). Light brown solid (138 mg, 88%). Melting point = 152−156 °C. FT-IR (ATR, neat): 3089, 3058, 1732, 1671, 1583, 1483, 1381, 1270, 951, 833, 804, 760, 727 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.31 (s, 1H), 8.00 (AA′BB′, J = 8.3 Hz, 2H), 7.96 (d, J = 8.7 Hz, 1H), 7.91−7.86 (m, 2H), 7.76 (AA′BB′, J = 8.3 Hz, 2H), 7.73 (m, 1H), 7.60 (m, 1H), 6.72 (s, 1H), 2.66 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 198.0, 160.5, 154.7, 150.4, 147.0, 144.4, 138.9, 136.2, 134.6, 130.0, 129.0, 128.6, 128.0, 127.8, 127.3, 123.6, 115.0, 26.8 ppm. HRMS (ESI^+): m/z calcd for $C_{20}H_{15}N_2O_2$ $(M + H)^+$, 315.1128; found, 315.1125.

*2-(3-(4-(Trifluoromethyl)phenyl)furan-2-yl)quinazoline (**7bb**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 10/1). Light yellow solid (148 mg, 87%). Melting point =

https://dx.doi.org/10.1021/acs.joc.0c01983
J. Org. Chem. 2021, 86, 3138−3151

102−105 °C. FT-IR (ATR, neat): 3060,1618, 1565, 1552, 1320, 1170, 1127, 1106, 1018, 842, 755, 744, 615 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.31 (d, J = 0.8 Hz, 1H), 7.98−7.94 (m, 1H), 7.91−7.86 (m, 2H), 7.80−7.75 (m, 2H), 7.73 (d, J = 1.8 Hz, 1H), 7.66 (d, J = 8.2 Hz, 2H), 7.63−7.58 (m, 1H), 6.71 (d, J = 1.8 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 160.6, 154.7, 150.4, 147.0, 144.4, 137.6 (C−F, $^2J_{C-F}$ = 1.4 Hz), 134.7, 130.1, 129.6 (C−F, $^3J_{C-F}$ = 32.5 Hz), 128.8, 128.6, 227.8, 127.3, 124.8 (C−F, $^2J_{C-F}$ = 3.8 Hz), 124.5 (C−F, $^1J_{C-F}$ = 271.3 Hz), 123.6, 115.0 ppm. ^{19}F NMR (471 MHz, $CDCl_3$): δ −62.4 ppm. HRMS (ESI^+): m/z calcd for $C_{19}H_{12}F_3N_2O$ $(M + H)^+$, 341.0896; found, 341.0896.

*4-(2-(Quinazolin-2-yl)furan-3-yl)benzonitrile (**7bc**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 3/1). Light brown solid (114 mg, 77%). Melting point = 154−158 °C. FT-IR (ATR, neat): 3121, 3099, 3056, 2230, 1582, 1497, 1378, 1166, 892, 839, 804, 752, 650 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.32 (s, 1H), 7.96−7.92 (m, 1H), 7.92−7.88 (m, 2H), 7.77 (AA′BB′, J = 8.3 Hz, 2H), 7.74 (d, J = 1.8 Hz, 1H), 7.69 (AA′BB′, J = 8.3 Hz, 2H), 7.62 (ddd, J = 8.8, 5.6, 2.2 Hz, 1H), 6.70 (d, J = 1.8 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 160.6, 154.5, 150.4, 147.1, 144.6, 138.9, 134.8, 131.7, 130.6, 128.6, 128.3, 127.9, 127.4, 123.7, 119.3, 114.8, 111.2 ppm. HRMS (ESI^+): m/z calcd for $C_{19}H_{12}N_3O$ $(M + H)^+$, 298.0975; found, 298.0975.

*2-(3-(p-Tolyl)furan-2-yl)quinazoline (**7bd**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 5/1). Light brown solid (118 mg, 83%). Melting point = 69−74 °C. FT-IR (ATR, neat): 3064, 3015, 2960, 2917, 2222, 1617, 1563, 1515, 1415, 813, 804, 753, 721 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.29 (d, J = 0.6 Hz, 1H), 7.98 (dd, J = 8.4, 0.8 Hz, 1H), 7.87−7.81 (m, 2H), 7.68 (d, J = 1.8 Hz, 1H), 7.59−7.53 (m, 3H), 7.21 (d, J = 7.9 Hz, 2H), 6.68 (d, J = 1.8 Hz, 1H), 2.41 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 160.4, 155.1, 150.5, 146.1, 144.0, 137.4, 134.3, 130.7, 130.2, 129.6, 128.6, 128.5, 127.3, 127.2, 123.4, 115.3, 21.4 ppm. HRMS (ESI^+): m/z calcd for $C_{19}H_{15}N_2O$ $(M + H)^+$, 287.1179; found, 287.1178.

*2-(3-(4-Methoxyphenyl)furan-2-yl)quinazoline (**7be**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 5/1). Light brown solid (133 mg, 88%). Melting point = 133−136 °C. FT-IR (ATR, neat): 3135, 3112, 3020, 2930, 2836, 1613, 1583, 1514, 1485, 1253, 1026, 819, 764 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.32 (d, J = 0.7 Hz, 1H), 8.00−7.97 (m, 1H), 7.88−7.84 (m, 2H), 7.68 (d, J = 1.8 Hz, 1H), 7.63 (AA′BB′, J = 8.9 Hz, 2H), 7.60−7.56 (m, 1H), 6.95 (AA′BB′, J = 8.9 Hz, 2H), 6.68 (d, J = 1.8 Hz, 1H), 3.87 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 160.5, 159.3, 155.2, 150.6, 146.0, 144.1, 134.4, 131.0, 130.1, 128.6, 127.4, 127.3, 126.1, 123.5, 115.3, 113.4, 55.4 ppm. HRMS (ESI^+): m/z calcd for $C_{19}H_{15}N_2O_2$ $(M + H)^+$, 303.1128; found, 303.1126.

*N,N-Dimethyl-4-(2-(quinazolin-2-yl)furan-3-yl)aniline (**7bf**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 5/1). Light brown solid (128 mg, 81%). Melting point = 50−53 °C. FT-IR (ATR, neat): 3061, 2883, 2802, 2220, 1613, 1582, 1549, 1500, 1446, 1166, 1011, 890, 752, 720 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.32 (d, J = 0.5 Hz, 1H), 8.01 (d, J = 8.9 Hz, 1H), 7.88−7.83 (m, 2H), 7.67 (d, J = 1.8 Hz, 1H), 7.62 (AA′BB′, J = 8.9 Hz, 2H), 7.58−7.54 (m, 1H), 6.77 (AA′BB′, J = 8.9 Hz, 2H), 6.69 (d, J = 1.8 Hz, 1H), 3.01 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 160.4, 155.5, 150.6, 150.2, 145.5, 144.1, 134.3, 130.7, 130.6, 128.6, 127.2, 127.2, 123.4, 121.4, 115.2, 111.9, 40.7 ppm. HRMS (ESI^+): m/z calcd for $C_{20}H_{18}N_3O$ $(M + H)^+$, 316.1444; found, 316.1442.

General Method for Palladium-Catalyzed C−H Arylation. A mixture of the monoarylated substrates **5**−**7** (0.50 mmol), aryl bromide **4** (1.00 mmol), $PdCl(C_3H_5)(dppe)$ (0.05 mmol, 29 mg) or $Pd(OAc)_2$ (0.05 mmol, 11 mg)/PPh_3 (0.10 mmol, 26 mg), and K_2CO_3 (1.50 mmol, 207 mg) in 1,4-dioxane (2 mL) was stirred for 48 h at 130 °C under argon in a sealed tube. The mixture was then cooled to room temperature, and DCM (10 mL) was added, after which the inorganic salts were filtered off and washed with DCM (5 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by radial chromatography on silica gel to yield the diarylated products **8**−**10**.

*4-(4-(4-Acetylphenyl)-5-(quinolin-2-yl)thiophen-2-yl)benzonitrile (**8aa**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 10/1). Yellow solid (172 mg, 80%). Melting point = 98−101 °C. FT-IR (ATR, neat): 3045, 2221, 1675, 1591, 1467, 1354, 1264, 823, 758, 729 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.11 (d, 1H), 7.99 (AA′BB′, J = 8.49 Hz, 2H), 7.90 (d, J = 8.7, 0.9 Hz, 1H), 7.80 (AA′BB′, J = 8.52 Hz, 2H), 7.74 (d, 2H), 7.73−7.68 (m, 2H), 7.56−7.51 (m, 3H), 7.47 (s, 1H), 7.10 (d, J = 8.6 Hz, 1H), 2.65 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 197.7, 152.2, 148.4, 143.3, 142.2, 141.2, 140.5, 138.2, 136.7, 136.2, 133.0, 130.2, 129.6, 129.5, 129.0, 128.5, 127.7, 127.3, 127.0, 126.2, 120.5, 118.8, 111.4, 26.8 ppm. HRMS (ESI^+): m/z calcd for $C_{28}H_{19}N_2OS$ $(M + H)^+$, 431.1213; found, 431.1208.

*1-(4-(5-(4-Methoxyphenyl)-2-(quinolin-2-yl)thiophen-3-yl)-phenyl)ethan-1-one (**8ab**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 20/1). Yellow solid (170 mg, 78%). Melting point = 72−76 °C. FT-IR (ATR, neat): 2955, 2834, 1678, 1593, 1516, 1464, 1248, 1110, 820, 692 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, 1H), 7.97 (AA′BB′, J = 8.43 Hz, 2H), 7.85 (d, J = 8.7, 0.8 Hz, 1H), 7.74−7.68 (m, 2H), 7.65 (AA′BB′, J = 8.80 Hz, 2H), 7.54 (AA′BB′, J = 8.48 Hz, 2H), 7.51−7.45 (m, 1H), 7.26 (d, J = 3.0 Hz, 1H), 7.08 (d, J = 8.6 Hz, 1H), 6.96 (AA′BB′, J = 8.78 Hz, 2H), 3.85 (s, 3H), 2.64 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 197.9, 159.9, 152.9, 148.4, 146.2, 141.9, 140.3, 138.8, 136.3, 135.9, 130.0, 129.6, 129.4, 128.9, 127.6, 127.3, 127.0, 126.7, 126.6, 125.7, 120.7, 114.6, 55.6, 26.8 ppm. HRMS (ESI^+): m/z calcd for $C_{28}H_{22}NO_2S$ $(M + H)^+$, 436.1366; found, 436.1362.

*4-(5-(Quinolin-2-yl)-4-(4-(trifluoromethyl)phenyl)thiophen-2-yl)-benzonitrile (**8ac**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 50/1). Yellow solid (185 mg, 81%). Melting point = 67−71 °C. FT-IR (ATR, neat): 3055, 2224, 1592, 1426, 1321, 1119, 1064, 958, 824, 708 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.11 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 8.6 Hz, 1H), 7.80 (d, J = 8.1 Hz, 2H), 7.78−7.69 (m, 4H), 7.67 (d, J = 8.0 Hz, 2H), 7.60−7.51 (m, 3H), 7.45 (s, 1H), 7.09 (d, J = 8.6 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 152.0, 148.3, 143.4, 142.1, 140.1, 140.0 (C−F, $^2J_{C-F}$ = 1.3 Hz), 138.1, 136.3, 133.0, 130.3 (C−F, $^3J_{C-F}$ = 32.3 Hz), 130.3, 129.7, 129.4, 128.6, 127.7, 127.2, 127.0, 126.2, 125.9 (C−F, $^2J_{C-F}$ = 3.8 Hz), 124.2 (C−F, $^1J_{C-F}$ = 272.8 Hz), 120.4, 118.8, 111.4. ppm. ^{19}F NMR (471 MHz, $CDCl_3$): δ −62.5 ppm. HRMS (ESI^+): m/z calcd for $C_{27}H_{16}F_3N_2S$ $(M + H)^+$, 457.0981; found, 457.0975.

*2-(5-(p-Tolyl)-3-(4-(trifluoromethyl)phenyl)thiophen-2-yl)-quinoline (**8ad**).* Radial chromatography on silica gel (eluting with petroleum ether/DCM, 3/1). Yellow solid (202 mg, 91%). Melting point = 167−169 °C. FT-IR (ATR, neat): 2917, 1614, 1468, 1410, 1237, 1102, 932, 812, 750, 695 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.11 (d, J = 8.4, 1.0 Hz, 1H), 7.89 (d, J = 8.7, 0.8 Hz, 1H), 7.76−7.69 (m, 2H), 7.67−7.60 (m, 4H), 7.57 (d, 2H), 7.53−7.49 (m, 1H), 7.32 (s, 1H), 7.24 (d, 2H), 7.09 (d, J = 8.6 Hz, 1H), 2.40 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 152.8, 148.4, 146.4, 140.7 (C−F, $^2J_{C-F}$ = 1.4 Hz), 139.9, 139.2, 138.4, 136.0, 131.1, 130.0, 129.9, 129.9 (C−F, $^3J_{C-F}$ = 32.3 Hz), 129.7, 129.4, 127.6, 127.0, 126.7, 126.3, 125.9, 125.8 (C−F, $^2J_{C-F}$ = 3.8 Hz), 124.4 (C−F, $^1J_{C-F}$ = 272.7 Hz), 120.6, 21.4 ppm. ^{19}F NMR (471 MHz, $CDCl_3$): δ −62.4 ppm. HRMS (ESI^+): m/z calcd for $C_{27}H_{19}F_3NS$ $(M + H)^+$, 446.1185; found, 446.1182.

*1-(4-(5-(Quinolin-2-yl)-4-(4-(trifluoromethyl)phenyl)thiophen-2-yl)phenyl)ethan-1-one (**8ae**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 10/1). Yellow solid (187 mg, 79%). Melting point = 167−169 °C. FT-IR (ATR, neat): 3052, 1556, 1467, 1412, 1269, 1163, 884, 833, 768, 668 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.12 (d, J = 8.2, 1.0 Hz, 1H), 8.02 (AA′BB′, J = 8.53 Hz, 2H), 7.92 (d, J = 8.7, 0.8 Hz, 1H), 7.81 (AA′BB′, J = 8.65 Hz, 2H), 7.78−7.70 (m, 2H), 7.66 (d, J = 8.1 Hz, 2H), 7.57 (d, 2H), 7.56−7.50 (m, 1H), 7.47 (s, 1H), 7.09 (d, J = 8.6 Hz, 1H), 2.64 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 197.4, 152.3, 148.4, 144.4, 141.5, 140.3 (C−F, $^2J_{C-F}$ = 1.4 Hz), 140.1, 138.2, 136.4, 136.2, 130.2, 130.2 (C−F, $^3J_{C-F}$ = 33.0 Hz), 129.7, 129.5, 129.4, 128.2,

https://dx.doi.org/10.1021/acs.joc.0c01983
J. Org. Chem. 2021, 86, 3138−3151

127.7, 127.2, 126.9, 125.9, (C−F, $^2J_{C-F}$ = 3.7 Hz), 128.8, 124.3 (C−F, $^1J_{C-F}$ = 272.3 Hz), 120.5, 26.8 ppm. ^{19}F NMR (471 MHz, $CDCl_3$): δ −62.5 ppm. HRMS (ESI$^+$): m/z calcd for $C_{28}H_{19}F_3NOS$ (M + H)$^+$, 474.1134; found, 474.1130.

*4-(4-(4-Acetylphenyl)-5-(quinolin-2-yl)furan-2-yl)benzonitrile (**8ba**).* Radial chromatography on silica gel (eluting with petroleum ether/DCM, 1/1). Yellow solid (147 mg, 71%). Melting point = 237−242 °C. FT-IR (ATR, neat): 3108, 2221, 1677, 1594, 1416, 1307, 1143, 967, 823, 758 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (d, J = 8.7, 0.8 Hz, 1H), 8.02 (AA′BB′, J = 8.54 Hz, 2H), 7.97−7.89 (m, 3H), 7.86−7.78 (m, 4H), 7.74 (AA′BB′, J = 8.53 Hz, 2H), 7.72−7.67 (m, 1H), 7.57−7.48 (m, 1H), 7.12 (s, 1H), 2.67 (s, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 197.9, 152.1, 149.3, 149.0, 148.0, 138.1, 136.6, 136.5, 133.8, 132.9, 130.1, 129.8, 129.7, 128.3, 128.1, 127.7, 127.4, 127.1, 124.6, 119.4, 118.9, 112.5, 111.3, 26.9 ppm. HRMS (ESI$^+$): m/z calcd for $C_{28}H_{19}N_2O_2$ (M + H)$^+$, 415.1441; found, 415.1439.

*1-(4-(5-(4-(Dimethylamino)phenyl)-2-(quinolin-2-yl)furan-3-yl)-phenyl)ethan-1-one (**8bb**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 10/1). Orange solid (158 mg, 73%). Melting point = 210−214 °C. FT-IR (ATR, neat): 3124, 2893, 1676, 1592, 1484, 1258, 1126, 867, 834, 758 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, J = 8.8, 0.9 Hz, 1H), 8.01 (AA′BB′, J = 8.57 Hz, 2H), 7.91−7.86 (m, 3H), 7.83 (d, J = 8.7 Hz, 1H), 7.78−7.70 (m, 3H), 7.68−7.62 (m, 1H), 7.51−7.44 (m, 1H), 6.79 (AA′BB′, J = 8.96 Hz, 2H), 6.77 (s, 1H), 3.03 (s, 6H), 2.67 (s, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 198.1, 155.6, 150.5, 149.9, 148.0, 146.6, 139.3, 136.2, 136.1, 129.8, 129.7, 129.5, 128.3, 128.1, 127.5, 127.1, 126.3, 125.8, 119.3, 118.4, 112.3, 107.0, 40.5, 26.9 ppm. HRMS (ESI$^+$): m/z calcd for $C_{29}H_{25}N_2O_2$ (M + H)$^+$, 433.1911; found, 433.1908.

*4-(4-(4-Acetylphenyl)-5-(isoquinolin-3-yl)thiophen-2-yl)-benzonitrile (**9aa**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 5/1). Yellow solid (200 mg, 93%). Melting point = 239−241 °C. FT-IR (ATR, neat): 3051, 2291, 2220, 1764, 1672, 1621, 1598, 1269, 820 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.24 (s, 1H), 8.02 (AA′BB′, J = 8.3 Hz, 2H), 7.95 (dd, J = 8.2, 1.2 Hz, 1H), 7.79 (AA′BB′, J = 8.2 Hz, 2H), 7.70 (AA′BB′, J = 8.1 Hz, 2H), 7.64−7.54 (m, 4H), 7.48 (dd, J = 8.1, 1.2 Hz, 1H), 7.44 (s, 1H), 7.41 (s, 1H), 2.66 (s, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 197.8, 152.7, 145.4, 142.2, 142.2, 141.7, 139.2, 138.3, 136.5, 135.9, 133.0, 131.1, 129.5, 129.1, 128.9, 128.1, 127.8, 127.1, 125.9, 118.9, 118.3, 111.1, 26.9 ppm. HRMS (ESI$^+$): m/z calcd for $C_{28}H_{19}N_2OS$ (M + H)$^+$, 431.1213; found, 431.1209.

*1-(4-(2-(Isoquinolin-3-yl)-5-(4-(trifluoromethyl)phenyl)thiophen-3-yl)phenyl)ethan-1-one (**9ab**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 5/1). Yellow solid (222 mg, 94%). Melting point = 175−180 °C. FT-IR (ATR, neat): 3063, 1672, 1605, 1580, 1414, 1320, 1270, 1109, 1065, 832 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.25 (s, 1H), 8.01 (AA′BB′, J = 8.3 Hz, 2H), 7.95 (dd, J = 8.0, 1.2 Hz, 1H), 7.82−7.79 (m, 2H), 7.67 (AA′BB′, J = 8.2 Hz, 2H), 7.63−7.54 (m, 4H), 7.48 (dd, J = 8.1, 1.2 Hz, 1H), 7.42 (d, J = 2.5 Hz, 2H), 2.66 (s, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 197.8, 152.7, 145.6, 142.9, 141.9, 141.2, 139.1, 137.4, 136.4, 135.9, 132.6 (C−F, $^2J_{C-F}$ = 10.3 Hz), 131.0, 129.8 (C−F, $^3J_{C-F}$ = 32.8 Hz), 129.5, 129.1, 128.2, 127.8, 127.8, 127.7, 127.1, 126.2 (C−F, $^2J_{C-F}$ = 3.8 Hz), 125.8, 124.3 (C−F, $^1J_{C-F}$ = 272.2 Hz) 118.3, 26.9 ppm. ^{19}F NMR (471 MHz, $CDCl_3$): δ −62.6 ppm. HRMS (ESI$^+$): m/z calcd for $C_{28}H_{19}F_3NOS$ (M + H)$^+$, 474.1134; found, 474.1132.

*3-(3-(2-Methoxyphenyl)-5-(m-tolyl)thiophen-2-yl)isoquinoline (**9ac**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 10/1). Yellow solid (147 mg, 72%). Melting point = 156−157 °C. FT-IR (ATR, neat): 3008, 2834, 1733, 1459, 1274, 1025, 780, 753, 692, 674 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.21 (s, 1H), 7.90 (dd, J = 8.1, 1.1 Hz, 1H), 7.58−7.52 (m, 3H), 7.48 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 7.45−7.39 (m, 2H), 7.38 (dd, J = 7.4, 1.8 Hz, 1H), 7.33 (s, 1H), 7.31−7.27 (m, 2H), 7.13−7.10 (m, 1H), 7.06−7.01 (m, 2H), 3.65 (s, 3H), 2.40 (s, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 157.1, 151.9, 147.0, 143.8, 139.8, 138.6, 136.1, 136.1, 134.4, 131.4, 130.5, 129.5, 128.9, 128.5, 128.1, 127.7, 127.4, 127.0, 126.8, 126.6, 126.6, 122.9, 121.1, 116.2, 111.5, 55.7, 21.6 ppm. HRMS (ESI$^+$): m/z calcd for $C_{27}H_{22}NOS$ (M + H)$^+$, 408.1417; found, 408.1411.

*3-(2-(Isoquinolin-3-yl)-5-(m-tolyl)thiophen-3-yl)benzonitrile (**9ad**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 7/1). Yellow solid (121 mg, 60%). Melting point = 168−170 °C. FT-IR (ATR, neat): 3052, 2918, 2223, 1621, 1580, 1479, 1275, 801, 781, 687 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.23 (s, 1H), 7.95 (dd, J = 8.1, 1.1 Hz, 1H), 7.81−7.80 (m, 1H), 7.71−7.69 (m, 1H), 7.68−7.65 (m, 1H), 7.62 (ddd, J = 8.1, 6.9, 1.3 Hz, 1H), 7.56 (ddd, J = 8.1, 6.8, 1.3 Hz, 1H), 7.54−7.46 (m, 4H), 7.37 (s, 1H), 7.33−7.30 (m, 2H), 7.17−7.14 (m, 1H), 2.42 (s, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 152.7, 145.9, 145.4, 139.6, 138.9, 138.8, 137.4, 136.0, 133.9, 133.8, 132.8, 131.2, 131.0, 129.7, 129.1, 129.1, 127.8, 127.7, 127.6, 126.9, 126.6, 126.6, 123.0, 118.8, 118.0, 113.1, 21.6 ppm. HRMS (ESI$^+$): m/z calcd for $C_{27}H_{19}N_2S$ (M + H)$^+$, 403.1263; found, 403.1260.

*4-(4-(4-Acetylphenyl)-5-(isoquinolin-3-yl)furan-2-yl)benzonitrile (**9ba**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 3/1). Yellow solid (180 mg, 87%). Melting point = 186−190 °C. FT-IR (ATR, neat): 3049, 2227, 1925, 1672, 1601, 1560, 1352, 1275, 813, 748 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.18 (s, 1H), 8.04 (s, 1H), 8.01−7.95 (m, 4H), 7.94−7.90 (m, 2H), 7.85−7.81 (m, 1H), 7.74−7.67 (m, 4H), 7.62 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.09 (s, 1H), 2.65 (s, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 197.8, 152.6, 151.6, 149.7, 143.3, 138.5, 136.2, 136.1, 134.0, 132.8, 131.1, 129.4, 128.5, 128.1, 127.9, 127.9, 127.2, 126.5, 124.4, 119.0, 118.1, 112.4, 111.0, 26.8 ppm. HRMS (ESI$^+$): m/z calcd for $C_{28}H_{19}N_2O_2$ (M + H)$^+$, 415.1441; found, 415.1439.

*1-(4-(2-(Isoquinolin-3-yl)-5-(4-(trifluoromethyl)phenyl)furan-3-yl)phenyl)ethan-1-one (**9bb**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 3/1). Yellow solid (158 mg, 69%). Melting point = 193−195 °C. FT-IR (ATR, neat): 1674, 1616, 1404, 1329, 1269, 1165, 1107, 1050, 841, 756 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.18 (s, 1H), 8.05 (s, 2H), 8.01−7.91 (m, 4H), 7.83 (d, J = 8.3 Hz, 1H), 7.74−7.67 (m, 5H), 7.61 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H), 7.05 (s, 1H), 2.65 (s, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 197.9, 152.5, 152.2, 149.2, 143.5, 138.7, 136.2 (C−F, $^2J_{C-F}$ = 9.5 Hz), 133.3, 131.0, 129.7 (C−F, $^3J_{C-F}$ = 32.5 Hz), 129.4, 128.4, 128.1, 127.9, 127.8, 127.2, 126.3, 126.0 (C−F, $^2J_{C-F}$ = 3.9 Hz), 124.4 (C−F, $^1J_{C-F}$ = 271.7 Hz), 124.3, 117.9, 111.4, 26.8 ppm. ^{19}F NMR (471 MHz, $CDCl_3$): δ −62.5 ppm. HRMS (ESI$^+$): m/z calcd for $C_{28}H_{19}F_3NO_2$ (M + H)$^+$, 458.1362; found, 458.1358.

*4-(4-(4-Acetylphenyl)-5-(quinazolin-2-yl)thiophen-2-yl)-benzonitrile (**10aa**).* Radial chromatography on silica gel (eluting with petroleum ether/DCM, 1/5). Yellow solid (142 mg, 66%). Melting point = >250 °C. FT-IR (ATR, neat): 3069, 3051, 2224, 1670, 1600, 1584, 1466, 1274, 1178, 863, 819, 730, 717 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.25 (d, J = 0.8 Hz, 1H), 8.01 (AA′BB′, J = 8.3 Hz, 2H), 7.88−7.84 (m, 2H), 7.82 (AA′BB′, J = 8.5 Hz, 2H), 7.75 (d, J = 1.0 Hz, 1H), 7.72 (AA′BB′, J = 8.5 Hz, 2H), 7.64 (AA′BB′, J = 8.3 Hz, 2H), 7.59 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H), 7.49 (s, 1H), 2.68 (s, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 198.1, 160.3, 157.5, 150.3, 143.7, 143.6, 142.0, 139.6, 138.1, 136.2, 134.7, 133.0, 129.9, 129.7, 128.5, 128.0, 127.8, 127.4, 126.3, 123.4, 118.8, 111.6, 26.9 ppm. HRMS (ESI$^+$): m/z calcd for $C_{27}H_{18}N_3OS$ (M + H)$^+$, 432.1165; found, 432.1163.

*1-(4-(2-(Quinazolin-2-yl)-5-(p-tolyl)thiophen-3-yl)phenyl)ethan-1-one (**10ab**).* Radial chromatography on silica gel (eluting with petroleum ether/DCM, 1/5). Yellow solid (174 mg, 83%). Melting point = 157−160 °C. FT-IR (ATR, neat): 3075, 3055, 3010, 2914, 2854, 1737, 1672, 1584, 1465, 1352, 1239, 799, 752, 716 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.22 (d, J = 0.8 Hz, 1H), 8.00 (AA′BB′, J = 8.5 Hz, 2H), 7.85−7.79 (m, 2H), 7.74−7.70 (m, 1H), 7.67−7.62 (m, 4H), 7.55 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.36 (s, 1H), 7.26−7.22 (m, 2H), 2.67 (s, 3H), 2.40 (s, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 198.2, 160.2, 158.0, 150.4, 146.9, 143.4, 142.7, 138.6, 136.7, 135.9, 134.4, 131.0, 130.0, 129.9, 128.4, 127.9, 127.5, 127.3, 127.3, 125.9, 123.2, 26.9, 21.4 ppm. HRMS (ESI$^+$): m/z calcd for $C_{27}H_{21}N_2OS$ (M + H)$^+$, 421.1369; found, 421.1359.

https://dx.doi.org/10.1021/acs.joc.0c01983
J. Org. Chem. 2021, 86, 3138−3151

*1-(4-(2-(Quinazolin-2-yl)-5-(4-(trifluoromethyl)phenyl)thiophen-3-yl)phenyl)ethan-1-one (**10ac**).* Radial chromatography on silica gel (eluting with petroleum ether/DCM, 1/3). Yellow solid (220 mg, 93%). Melting point = 168−171 °C. FT-IR (ATR, neat): 3067, 3033, 2998, 2960, 1739, 1673, 1326, 1098, 1068, 820, 757, 717 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.24 (d, J = 0.8 Hz, 1H), 8.01 (AA′BB′, J = 8.3 Hz, 2H), 7.85−7.81 (m, 4H), 7.75−7.72 (m, 1H), 7.71−7.67 (m, 2H), 7.65 (AA′BB′, J = 8.3 Hz, 2H), 7.58 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.47 (s, 1H), 2.68 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 198.1, 160.3, 157.6, 150.3, 144.5, 143.5, 142.2, 138.8, 137.2 (C−F, $^2J_{C-F}$ = 1.4 Hz), 136.1, 134.6, 130.2 (C−F, $^3J_{C-F}$ = 32.9 Hz), 130.0, 129.1, 128.5, 128.0, 127.7, 127.3, 126.2 (C−F, $^2J_{C-F}$ = 4.0 Hz), 126.1,124.2 (C−F, $^1J_{C-F}$ = 272.3 Hz), 123.3, 26.9 ppm. ^{19}F NMR (471 MHz, $CDCl_3$): δ −62.6 ppm. HRMS (ESI^+): m/z calcd for $C_{27}H_{18}F_3N_2OS$ $(M + H)^+$, 475.1086; found, 475.1085.

*2-(5-(2-Methoxyphenyl)-2-(quinazolin-2-yl)thiophen-3-yl)-benzonitrile (**10ad**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 5/1). Yellow solid (193 mg, 92%). Melting point = 195−197 °C. FT-IR (ATR, neat): 2941, 2223, 1616, 1426, 1281, 1020, 863, 760, 746, 676 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.22 (s, 1H), 7.81−7.73 (m, 4H), 7.66−7.63 (m, 1H), 7.60−7.54 (m, 3H), 7.53−7.47 (m, 2H), 7.33 (ddd, J = 8.6, 7.4, 1.7 Hz, 1H), 7.06−7.01 (m, 2H), 4.01 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 160.1, 157.9, 156.2, 150.3, 142.7, 142.3, 139.2, 138.8, 134.2, 132.5, 132.1, 130.7, 129.9, 129.4, 128.4, 128.4, 127.4, 127.3, 127.1, 123.1, 122.6, 121.1, 118.8, 113.8, 111.8, 55.8 ppm. HRMS (ESI^+): m/z calcd for $C_{26}H_{18}N_3OS$ $(M + H)^+$, 420.1165; found, 420.1160.

*2-(5-(Quinazolin-2-yl)-4-(m-tolyl)thiophen-2-yl)benzonitrile (**10ae**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 5/1). White solid (69 mg, 34%). Melting point = 177−180 °C. FT-IR (ATR, neat): 2913, 2220, 1616, 1585, 1565, 1467, 1030, 756, 696, 670, 654 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.26 (s, 1H), 7.87−7.82 (m, 2H), 7.82−7.76 (m, 2H), 7.73 (s, 1H), 7.67−6.64 (m, 1H), 7.58 (ddd, J = 8.2, 6.8, 1.3 Hz, 1H), 7.46−7.42 (m, 2H), 7.36−7.32 (m, 1H), 7.29−7.25 (m, 2H), 7.19 (d, J = 7.6 Hz, 1H), 2.39 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 160.2, 158.1, 150.4, 144.8, 141.0, 138.87, 137.5, 137.3, 136.6, 134.6, 134.4, 133.2, 132.6, 130.3, 129.7, 128.6, 128.4, 128.2, 127.8, 127.5, 127.3, 127.0, 123.3, 118.8, 110.2, 21.7 ppm. HRMS (ESI^+): m/z calcd for $C_{26}H_{18}N_3S$ $(M + H)^+$, 404.1216; found, 404.1212.

*4-(4-(4-Acetylphenyl)-5-(quinazolin-2-yl)furan-2-yl)benzonitrile (**10ba**).* Radial chromatography on silica gel (eluting with petroleum ether/EtOAc, 5/1). Light yellow solid (106 mg, 51%). Melting point = 147−151 °C. FT-IR (ATR, neat): 3054, 2925, 2226, 1671, 1606, 1484, 1406, 1356, 1266, 825, 760, 724 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.36 (d, J = 0.7 Hz, 1H), 8.05−7.99 (m, 4H), 7.96−7.89 (m, 3H), 7.78 (AA′BB′, J = 8.5 Hz, 2H), 7.75 (AA′BB′, J = 8.5 Hz, 2H), 7.64 (ddd, J = 8.1, 6.6, 1.5 Hz, 1H), 7.12 (s, 1H), 2.68 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 198.0, 160.6, 154.4, 153.0, 150.5, 147.8, 138.4, 136.5, 134.7, 133.7, 132.8, 131.1, 129.9, 128.7, 128.1, 128.1, 127.4, 125.1, 123.7, 118.9, 112.8, 111.6, 26.9 ppm. HRMS (ESI^+): m/z calcd for $C_{27}H_{18}N_3O_2$ $(M + H)^+$, 416.1394; found, 416.1393.

*1-(4-(2-(Quinazolin-2-yl)-5-(p-tolyl)furan-3-yl)phenyl)ethan-1-one (**10bb**).* Radial chromatography on silica gel (eluting with petroleum ether/DCM, 1/3). Yellow solid (57 mg, 28%). Melting point = 70−75 °C. FT-IR (ATR, neat): 3058, 2959, 2921, 2856, 2246, 1677, 1606, 1484, 1293, 908, 807, 762, 725 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.33 (d, J = 0.8 Hz, 1H), 8.04−7.99 (m, 2H), 7.93−7.90 (m, 1H), 7.90−7.84 (m, 3H), 7.84−7.78 (m, 4H), 7.59 (ddd, J = 7.9, 6.8, 1.2 Hz, 1H), 7.28 (d, J = 0.8 Hz, 1H), 6.92 (s, 1H), 2.67 (s, 3H), 2.41 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 198.1, 160.5, 155.7, 154.8, 150.5, 146.0, 139.2, 138.8, 136.2, 134.5, 131.2, 130.0, 129.6, 129.6, 128.6, 128.0, 127.5, 127.3, 127.1, 124.9, 123.5, 26.9, 21.6 ppm. HRMS (ESI^+): m/z calcd for $C_{27}H_{21}N_2O_2$ $(M + H)^+$, 405.1598; found, 405.1592.

General Method for One-Pot Dual Metal Ruthenium/Palladium-Catalyzed C−H Arylation. A mixture of the azine substrates **1**−**3** (0.50 mmol), aryl bromide **4** (0.50 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (0.05 mmol, 31 mg), PPh_3 (0.10 mmol, 26 mg or 0.20 mmol, 52 mg), KOPiv (0.20 mmol, 28 mg), and K_2CO_3 (2.50 mmol, 345 mg) in 1,4-dioxane (2 mL) was stirred for 24 h at 140 °C under argon in a sealed tube. The mixture was then cooled to room temperature, and the corresponding aryl bromide **4** (1.00 mmol) and $PdCl(C_3H_5)(dppe)$ (0.05 mmol, 29 mg) or $Pd(OAc)_2$ (0.05 mmol, 11 mg) were added. The mixture was further stirred for 48 h at 130 °C under argon in a sealed tube. After completion of the second arylation, the mixture was cooled to room temperature and DCM (10 mL) was added, after which the inorganic salts were filtered off and washed with DCM (5 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by radial chromatography on silica gel to yield the diarylated products **8**−**10**.

Scale-up Synthesis of Compound 10ac According to the General Method for One-Pot Dual Metal Ruthenium/Palladium-Catalyzed C−H Arylation. A mixture of the substrate **3a** (7.07 mmol, 1.50 g), aryl bromide **4a** (7.07 mmol, 1.41 g), $[Ru(p\text{-cymene})Cl_2]_2$ (0.71 mmol, 433 mg), PPh_3 (1.41 mmol, 370 mg), KOPiv (2.83 mmol, 396 mg), and K_2CO_3 (35.35 mmol, 4.88 g) in 1,4-dioxane (15 mL) was stirred for 24 h at 140 °C under argon in a sealed tube. The mixture was then cooled to room temperature, and the corresponding aryl bromide **4b** (14.14 mmol, 1.98 mL, d = 1.61 g/mL) and $PdCl(C_3H_5)(dppe)$ (0.71 mmol, 413 mg) was added. The mixture was further stirred for 48 h at 130 °C under argon in a sealed tube. After completion of the second arylation, the mixture was cooled to room temperature and DCM (20 mL) was added, after which the inorganic salts were filtered off and washed with DCM (10 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel eluting with petroleum ether/DCM (1/3) to yield the diarylated product **10ac** as a yellow solid (2.68 g, 80%).

Synthesis of Ru-Complex A.[44] A solution of $[RuCl_2(p\text{-cymene})]_2$ (0.25 mmol, 153 mg), 2-(thiophen-2-yl)quinazoline (**3a**) (0.50 mmol, 106 mg), and KOAc (1.00 mmol, 98 mg) in MeOH (4 mL) was stirred at room temperature for 72 h, after which an orange solid began to precipitate. The solid was filtered off and washed with MeOH (3 × 3 mL) and dried at room temperature overnight. Orange solid (205 mg, 99%). Melting point = >250 °C. FT-IR (ATR, neat): 3039, 2963, 2869, 1614, 1585, 1477, 1416, 1371, 1031, 989, 862, 797, 783, 738 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.91 (d, J = 0.8 Hz, 1H), 7.92−7.88 (m, 1H), 7.85−7.77 (m, 2H), 7.64 (q, J = 4.7 Hz, 2H), 7.50 (ddd, J = 8.0, 6.8, 1.1 Hz, 1H), 5.71 (dd, J = 5.9, 1.2 Hz, 1H), 5.63 (dd, J = 5.9, 1.2 Hz, 1H), 5.28 (dd, J = 5.8, 1.2 Hz, 1H), 5.15 (dd, J = 5.8, 1.3 Hz, 1H), 2.55−2.45 (m, 1H), 2.07 (s, 3H), 1.04 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 181.9, 164.9, 164.0, 150.7, 136.6, 135.6, 134.8, 131.6, 127.8, 127.2, 126.5, 121.5, 101.7, 100.9, 89.2, 88.1, 83.5, 82.2, 31.1, 22.8, 21.9, 19.0 ppm. HRMS (ESI^+): m/z calcd for $C_{22}H_{22}ClN_2Ru^{96}S$ $(M + H)^+$, 477.0263; found, 477.0260.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01983.

Copies of ^1H, ^{13}C, and ^{19}F NMR spectra for the reported compounds; single crystal X-ray diffraction data for **8ba**, **9ab**, and Ru-complex **A**; optimization of Ru-catalyzed C−H arylation of **1a** with **4a**; competition experiments (PDF)

Accession Codes

CCDC 2010488, 2010491, and 2011442 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

https://dx.doi.org/10.1021/acs.joc.0c01983
J. Org. Chem. 2021, 86, 3138−3151

AUTHOR INFORMATION

Corresponding Author

Helena Brodnik − *Department of Organic Chemistry, Faculty of Chemistry and Chemical Technology, University of Ljubljana, 1000 Ljubljana, Slovenia;* orcid.org/0000-0002-0099-2236; Email: helena.brodnik@fkkt.uni-lj.si

Authors

Hamad H. Al Mamari − *Department of Chemistry, College of Science, Sultan Qaboos University, 123 Muscat, Oman*

Uroš Grošelj − *Department of Organic Chemistry, Faculty of Chemistry and Chemical Technology, University of Ljubljana, 1000 Ljubljana, Slovenia*

Franc Požgan − *Department of Organic Chemistry, Faculty of Chemistry and Chemical Technology, University of Ljubljana, 1000 Ljubljana, Slovenia;* orcid.org/0000-0001-6040-294X

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c01983

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Dedicated to Prof. Pierre H. Dixneuf for his outstanding contribution to organometallic chemistry and ruthenium catalysis. Special thanks go to Maša Kastner, Tina Pečarič Strnad, and Urša Rozman for laboratory support. We thank the Slovenian Research Agency for financial support through grant P1-0179. We also acknowledge the Centre of Excellence EN-FIST.

REFERENCES

(1) Lee, J. M.; Na, Y.; Han, H.; Chang, S. Cooperative multi-catalyst systems for one-pot organic transformations. *Chem. Soc. Rev.* **2004**, *33*, 302−312.

(2) Batey, R. A. Domino Reactions in Organic Synthesis. *J. Am. Chem. Soc.* **2007**, *129*, 7476−7476.

(3) Hall, N. Chemists Clean Up Synthesis With One-Pot Reactions. *Science* **1994**, *266*, 32−34.

(4) Bruggink, A.; Schoevaart, R.; Kieboom, T. Concepts of Nature in Organic Synthesis: Cascade Catalysis and Multistep Conversions in Concert. *Org. Process Res. Dev.* **2003**, *7*, 622−640.

(5) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. Concurrent Tandem Catalysis. *Chem. Rev.* **2005**, *105*, 1001−1020.

(6) Tietze, L. F.; Brasche, G.; Gericke, K. In *Domino Reactions in Organic Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinhiem, 2006.

(7) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. Cascade Reactions in Total Synthesis. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134−7186.

(8) Behr, A.; Vorholt, A. J.; Ostrowski, K. A.; Seidensticker, T. Towards resource efficient chemistry: tandem reactions with renewables. *Green Chem.* **2014**, *16*, 982−1006.

(9) Hayashi, Y. Pot economy and one-pot synthesis. *Chem. Sci.* **2016**, *7*, 866−880.

(10) Anastas, P. T.; Warner, J. C. In *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, U.K., 1998.

(11) Müller, T. J. J. In *Metal Catalyzed Cascade Reactions; Topics in Organometallic Chemistry*; Springer-Verlag: Berlin Heidelberg, 2006.

(12) Allen, A. E.; Macmillan, D. W. C. Synergistic catalysis: A powerful synthetic strategy for new reaction development. *Chem. Sci.* **2012**, *3*, 633−658.

(13) Du, Z.; Shao, Z. Combining transition metal catalysis and organocatalysis − an update. *Chem. Soc. Rev.* **2013**, *42*, 1337−1378.

(14) Afewerki, S.; Córdova, A. Combinations of Aminocatalysts and Metal Catalysts: A Powerful Cooperative Approach in Selective Organic Synthesis. *Chem. Rev.* **2016**, *116*, 13512−13570.

(15) Pye, D. R.; Mankad, N. P. Bimetallic catalysis for C−C and C−X coupling reactions. *Chem. Sci.* **2017**, *8*, 1705−1718.

(16) Trost, B. M.; Machacek, M. R. An efficient one-pot enantio- and diastereoselective synthesis of heterocycles. *Angew. Chem., Int. Ed.* **2002**, *41*, 4693−4697.

(17) Ko, S.; Kang, B.; Chang, S. Cooperative Catalysis by Ru and Pd for the Direct Coupling of a Chelating Aldehyde with Iodoarenes or Organostannanes. *Angew. Chem., Int. Ed.* **2005**, *44*, 455−457.

(18) Ackermann, L.; Althammer, A. One-Pot 2-Aryl/Vinylindole Synthesis Consisting of a Ruthenium-Catalyzed Hydroamination and a Palladium-Catalyzed Heck Reaction Using 2-Chloroaniline. *Synlett* **2006**, *2006*, 3125−3129.

(19) Walker, P. R.; Campbell, C. D.; Suleman, A.; Carr, G.; Anderson, E. A. Palladium- and Ruthenium-Catalyzed Cycloisomerization of Enynamides and Enynhydrazides: A Rapid Approach to Diverse Azacyclic Frameworks. *Angew. Chem., Int. Ed.* **2013**, *52*, 9139−9143.

(20) Sustac Roman, D.; Poiret, V.; Pelletier, G.; Charette, A. B. Direct Arylation of Imidazo[1,5-*a*]azines Through Ruthenium and Palladium Catalysis. *Eur. J. Org. Chem.* **2015**, *2015*, 67−71.

(21) Mostafa, M. A. B.; Grafton, M. W.; Wilson, C.; Sutherland, A. A one-pot, three-step process for the diastereoselective synthesis of aminobicyclo[4.3.0]nonanes using consecutive palladium(II)- and ruthenium(II)-catalysis. *Org. Biomol. Chem.* **2016**, *14*, 3284−3297.

(22) Yamamoto, K.; Qureshi, Z.; Tsoung, J.; Pisella, G.; Lautens, M. Combining Ru-Catalyzed C−H Functionalization with Pd-Catalyzed Asymmetric Allylic Alkylation: Synthesis of 3-Allyl-3-aryl Oxindole Derivatives from Aryl α-Diazoamides. *Org. Lett.* **2016**, *18*, 4954−4957.

(23) Manick, A.-D.; Berhal, F.; Prestat, G. Development of a One-Pot Four C−C Bond-Forming Sequence Based on Palladium/Ruthenium Tandem Catalysis. *Org. Lett.* **2018**, *20*, 194−197.

(24) Štefane, B.; Grošelj, U.; Svete, J.; Požgan, F.; Kočar, D.; Brodnik, H. The Influence of the Quinoline Moiety on Direct Pd-Catalyzed Arylation of Five-Membered Heterocycles. *Eur. J. Org. Chem.* **2019**, *2019*, 432−441.

(25) Brodnik, H.; Požgan, F.; Štefane, B. Synthesis of 8-heteroaryl nitroxoline analogues *via* one-pot sequential Pd-catalyzed coupling reactions. *Org. Biomol. Chem.* **2016**, *14*, 1969−1981.

(26) Sosič, I.; Mitrović, A.; Ćurić, H.; Knez, D.; Brodnik, H.; Štefane, B.; Kos, J.; Gobec, S. Cathepsin B inhibitors: Further exploration of the nitroxoline core. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 1239−1247.

(27) Laroche, J.; Beydoun, K.; Guerchais, V.; Doucet, H. Direct heteroarylation of 5-bromothiophen-2-ylpyridine and of 8-bromoquinoline*via*palladium-catalysed C−H bond activation: simpler access to heteroarylated nitrogen-based derivatives. *Catal. Sci. Technol.* **2013**, *3*, 2072−2080.

(28) Bheeter, C. B.; Chen, L.; Soulé, J.-F.; Doucet, H. Regioselectivity in palladium-catalysed direct arylation of 5-membered ring heteroaromatics. *Catal. Sci. Technol.* **2016**, *6*, 2005−2049.

(29) Ackermann, L. Carboxylate-Assisted Transition-Metal-Catalyzed C−H Bond Functionalizations: Mechanism and Scope. *Chem. Rev.* **2011**, *111*, 1315−1345.

(30) Štefane, B.; Brodnik, H.; Grošelj, U.; Kuzman, P.; Svete, J.; Požgan, F. Quinazoline-Directed C−H Bond Functionalization Catalyzed by Ruthenium(II) Carboxylate − Construction of Polyconjugated Aryl-Heteroaryl Systems. *Eur. J. Org. Chem.* **2017**, *2017*, 1855−1864.

(31) Drev, M.; Grošelj, U.; Ledinek, B.; Perdih, F.; Svete, J.; Štefane, B.; Požgan, F. Microwave-Promoted *ortho*-C−H Bond (Hetero)-arylation of Arylpyrimidines in Water Catalyzed by Ruthenium(II)−Carboxylate. *ChemCatChem* **2018**, *10*, 3824−3832.

(32) Drev, M.; Grošelj, U.; Ledinek, B.; Perdih, F.; Svete, J.; Štefane, B.; Požgan, F. Ruthenium(II)-Catalyzed Microwave-Promoted Multiple C-H Activation in Synthesis of Hexa(heteroaryl)benzenes in Water. *Org. Lett.* **2018**, *20*, 5268−5273.

(33) Rajkumar, S.; Karthik, S.; Gandhi, T. Ru(II)-Catalyzed β-Carboline Directed C−H Arylation and Isolation of Its Cycloruthenated Intermediates. *J. Org. Chem.* **2015**, *80*, 5532−5545.
(34) Rossi, R.; Bellina, F.; Lessi, M.; Manzini, C. Cross-Coupling of Heteroarenes by C−H Functionalization: Recent Progress towards Direct Arylation and Heteroarylation Reactions Involving Heteroarenes Containing One Heteroatom. *Adv. Synth. Catal.* **2014**, *356*, 17−117.
(35) Cantat, T.; Génin, E.; Giroud, C.; Meyer, G.; Jutand, A. Structural and kinetic effects of chloride ions in the palladium-catalyzed allylic substitutions. *J. Organomet. Chem.* **2003**, *687*, 365−376.
(36) *CrysAlis PRO*; Agilent Technologies UK Ltd.: Yarnton, Oxfordshire, England, 2011.
(37) Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. *OLEX2*: a complete structure solution, refinement and analysis program. *J. Appl. Crystallogr.* **2009**, *42*, 339−341.
(38) Sheldrick, G. M. A short history of *SHELX*. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **2008**, *64*, 112−122.
(39) Sheldrick, G. M. Crystal structure refinement with *SHELXL*. *Acta Crystallogr., Sect. A: Found. Adv.* **2015**, *71*, 3−8.
(40) Sheldrick, G. M. Crystal structure refinement with *SHELXL*. *Acta Crystallogr., Sect. C: Struct. Chem.* **2015**, *71*, 3−8.
(41) Macrae, C. F.; Edgington, P. R.; McCabe, P.; Pidcock, E.; Shields, G. P.; Taylor, R.; Towler, M.; van de Streek, J. Mercury: visualization and analysis of crystal structures. *J. Appl. Crystallogr.* **2006**, *39*, 453−457.
(42) Spek, A. L. Single-crystal structure validation with the program *PLATON*. *J. Appl. Crystallogr.* **2003**, *36*, 7−13.
(43) Maheswari, C. U.; Kumar, G. S.; Venkateshwar, M.; Kumar, R. A.; Kantam, M. L.; Reddy, K. R. Highly Efficient One-Pot Synthesis of 2-Substituted Quinazolines and 4*H*-Benzo[*d*][1,3]oxazines *via* Cross Dehydrogenative Coupling using Sodium Hypochlorite. *Adv. Synth. Catal.* **2010**, *352*, 341−346.
(44) Li, B.; Roisnel, T.; Darcel, C.; Dixneuf, P. H. Cyclometallation of arylimines and nitrogen-containing heterocycles *via* room-temperature C−H bond activation with arene ruthenium(II) acetate complexes. *Dalton Trans.* **2012**, *41*, 10934−10937.

https://dx.doi.org/10.1021/acs.joc.0c01983
J. Org. Chem. 2021, 86, 3138−3151