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Palladium(II)-Catalyzed Regioselective Arylation of Naphthylamides with Aryl Iodides Utilizing a Quinolinamide Bidentate System

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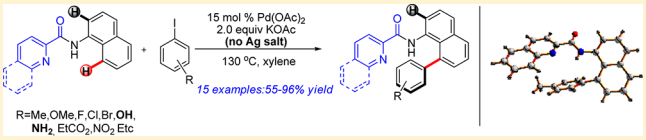
Supporting Information

ABSTRACT: A palladium(II)-catalyzed quinolinamide-directed 8-arylation of 1-naphthylamides with aryl iodides is reported. The bidentate directing group (quinolinamide) proved to be crucial for a highly regioselective transformation. In addition, the amide directing group can be easily hydrolyzed under basic conditions to offer a range of 8-aryl-1-naphthylamine derivatives. The theoretical calculations suggest that the C−H arylation reaction proceeds through a sequential C−H activation/oxidative addition pathway.



INTRODUCTION

8-Aryl-1-naphthylamine scaffolds as an important structural unit widely exist in functional molecules,[1] such as potential chiral ligands,[1a,b] organic semiconductors,[1e,f] and electroluminescent materials.[1f−h] This key scaffold can be accessed by representative cross-coupling reactions between an arylmetal and an aryl halide.[1a,b] In recent years, emerging strategies for making C−C biaryl linkages based on C−H arylation of arenes have been developed.[2] The newer transformations do not require preparation of arylmetals and/or aryl halides in advance as coupling partners. Hence, these transformations provide rapid and environmentally benign access to biaryls. However, the desired regioselectivity of C−H arylation remains a major concern.[3] Monodentate group-assisted transformation has emerged as a powerful alternative method for *ortho*-C−H arylation to control the regiochemistry.[4] For example, Daugulis and co-worker reported a palladium(II)-catalyzed *ortho*-arylation of anilides with aryl iodides; the only *C*-2 arylated product was formed when naphthylpivalamide was used as a substrate (Scheme 1).[5]

In view of the value of 8-aryl-1-naphthylamine scaffolds, our goal was to seek strategies for the efficient and regioselective *C*-8 arylation of 1-naphthylamine. A bidentate system that has been used for the successful arylation of C−H bonds drew our attention.[6] A pioneering work by Daugulis and co-workers describes the method by employing bidentate system for the direct arylation of unactivated sp^3 C−H bonds.[7] This methodology by Corey et al. has been used in β-C−H arylation of α-amino acid derivatives.[8] Chen and co-workers have applied their strategy of arylation to total synthesis of natural product celogentin and (+)-obafluorin.[9] The method by Zhang et al. has also been utilized for arylation/oxidation of benzylic C−H bonds in sequential process.[10] Very recently, Chatani et al. have reported on the ruthenium-catalyzed *ortho*-arylation of aromatic amides with aryl bromides assisted by a bidentate directing group.[11] Based on the previous work, we expected that the bidentate system would bind tightly to catalysts, thereby bringing the catalyst into close proximity to the 8-C−H bond of 1-naphthylamides to form intermediate **A** (Scheme 1). Herein we report on the palladium(II)-catalyzed quinolinamide-directed regioselective *C*-8 arylation of 1-naphthylamides with a range of aryl iodides without the use of silver salt.

RESULTS AND DISCUSSION

To evaluate the feasibility of this methodology, naphthylquinoline-2-carboxamide **1a** was chosen as a test substrate reacted with iodobenzene under various palladium-catalyzed conditions. The initial trial using $Pd(OAc)_2$ as the catalyst and AgOAc as the additive in xylene provided only trace amounts of product **3a** (Table 1, entry 1). Replacing AgOAc with $Cu(OAc)_2$ as the additive gave a slight improvement (Table 1, entry 2). Addition of HOAc only moderately improved the yield, and CF_3COOH completely suppressed product **3a** formation (Table 1, entries 3 and 4). Variation in inorganic base additives was then investigated (Table 1, entries 5−10). Most of the examined inorganic base additives displayed low efficiencies except for $K_3PO_4{\cdot}3H_2O$ and KOAc. Addition of $K_3PO_4{\cdot}3H_2O$ increased the yield of **3a** to 75% (Table 1, entry 9). To our delight, the optimal reaction was achieved with 2 equiv of KOAc as the additive in xylene at 130 °C for 12 h (Table 1, entry 10). A control experiment without the use of additive resulted in a decreased yield (Table 1, entry 11). The result demonstrated that inorganic base additives play a critical role on the transformation. Other palladium catalysts such as $PdCl_2$, $Pd_2(dba)_3$, and $Pd(CH_3CN)_2Cl_2$ also worked in this transformation but delivered slightly lower yields (Table 1,

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Scheme 1. Pd(II)-Catalyzed Regioselective C−H Arylation of 1-Naphthylamides with Aryl Iodides

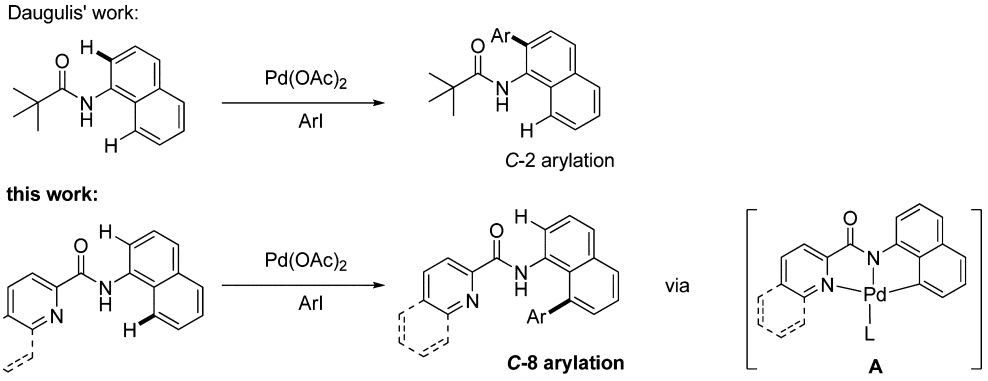
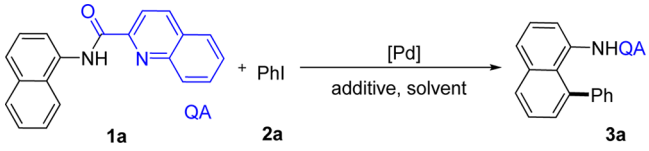


Table 1. Optimization of Reaction Conditions[a]



entry	catalyst (mol %)	additive	solvent	yield (%)
1	$Pd(OAc)_2$	AgOAc	xylene	5
2	$Pd(OAc)_2$	$Cu(OAc)_2$	xylene	23
3	$Pd(OAc)_2$	HOAc	xylene	34
4	$Pd(OAc)_2$	CF_3COOH	xylene	trace
5	$Pd(OAc)_2$	NaOAc	xylene	22
6	$Pd(OAc)_2$	NaOTf	xylene	28
7	$Pd(OAc)_2$	Na_2CO_3	xylene	34
8	$Pd(OAc)_2$	Cs_2CO_3	xylene	32
9	$Pd(OAc)_2$	$K_3PO_4·3H_2O$	xylene	75
10	**$Pd(OAc)_2$**	**KOAc**	**xylene**	**96**
11	$Pd(OAc)_2$		xylene	40
12	$PdCl_2$	KOAc	xylene	72
13	$Pd_2(dba)_3$	KOAc	xylene	88
14	$Pd(CH_3CN)_2Cl_2$	KOAc	xylene	90
15	$Pd(OAc)_2$	KOAc	toluene	82
16	$Pd(OAc)_2$	KOAc	DMF	N.D
17	$Pd(OAc)_2$	KOAc	$ClCH_2CH_2Cl$	32
18	$Pd(OAc)_2$	KOAc	*t*-BuOH	5

[a]Reaction conditions: **1a** (0.5 mmol), Pd catalyst (0.075 mmol), PhI (2.0 mmol, 408 mg), additive (1.0 mmol), solvent (5 mL), 130 °C, 12 h.

entries 12−14). Screening of the solvents indicated that xylene gave the best yield (Table 1, entries 10, 15−18).

Under the optimal reaction conditions, the substrate scope of aryl iodides was examined as shown in Table 2. Aryl iodides with both electron-withdrawing and electron-donating groups presented excellent compatibility (Table 2, entries 1−13). Even the sensitive free-hydroxyl and amine group substituted aryl iodides were not affected in the reaction (Table 2, entries 6 and 7) and efficiently participated in the reaction giving the corresponding arylated products **3f** and **3g** in 80% and 82% yields, respectively. Notably, introducing functional groups such as Cl, Br, COOEt, OH, and NH_2 added flexibility to further elaborate the arylated products (Table 2, entries 6−9, 12). As for the substitution pattern, *meta*-substituted aryl iodides also worked well in the reaction to give the desired product (Table 2, entries 3 and 11). However, an attempt to employ the *ortho*-substituted aryl iodides failed to yield the expected product in the reaction, showing that steric factors clearly reduced the reaction efficiency (Table 2, entry 4). Furthermore, the structure of **3b** was confirmed by X-ray crystallography (see the Supporting Information).

Various 1-naphthylamides were then evaluated as shown in Scheme 2. When the analogue *N*-(naphthalen-1-yl)-picolinamides were used in place of **1a** as the substrates, the aryl iodides with both electron-withdrawing (COOEt) and electron-donating substituents (OMe) underwent this transformation to form the corresponding products in moderate to good yields (Scheme 2, **3n−p**). But no arylated products (**3q,r**) were obtained when the corresponding benzamide or acetamide was used in place of **1a** as the substrate, indicating that the coordination in a bidentate N,N fashion is a key step for the reaction to proceed.

Since the 8-aryl-1-naphthylamine scaffolds widely exist in functional molecules, especially electroluminescent materials, we applied this protocol to test on polycyclic aromatic amines. To our disappointment, no reaction occurred when 1- or 9-anthracenamide (**1c,d**) was used in place of **1a** as the substrate presumably due to the steric factor or rigid structure (Scheme 3). Furthermore, no desired product was achieved when 1-hexahydronaphthalenamide **1e** was employed as the substrate.

Some preliminary mechanistic studies have been carried out to probe the details of this C−H arylation reaction. The H/D exchange in **1a** was examined by heating the substrate with a catalytic amount of $Pd(OAc)_2$ in a D_2O (40 equiv)/xylene mixture (Scheme 4). After 12 h at 130 °C, 91% deuterium incorporation was observed at the 8-position of 1-naphthylamide **3s**. No deuterated product was observed in the absence of $Pd(OAc)_2$ (Scheme 4). These experiments indicated that the palladation process was reversible and C−H activation could take place under the reaction conditions without the involvement of the ArI substrate and KOAc. However, our efforts to obtain the putative palladacycle intermediate have been unsuccessful.

Based on the previous studies[12] and our experimental results, two plausible reaction paths were proposed as shown in Scheme 5. First, intermediate **B** was formed by the coordination of $Pd(OAc)_2$ with substrate **1a**.[13] In path a, intermediate **B** underwent a sequential C−H activation[14]/oxidative addition with aryl iodides to produce the Pd(IV) intermediate **D**,[15] which was followed by a reductive elimination to result in the arylation product **3a** and regenerated the catalyst. Through a different order than path a, the intermediate **B** underwent a sequential oxidative addition/C−H activation with aryl iodides to produce the Pd(IV) intermediate **D** in path b. To determine the order of

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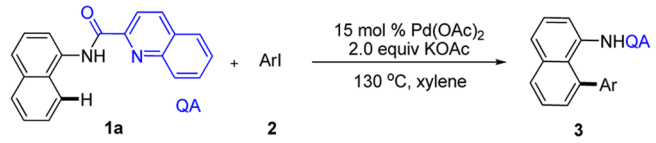
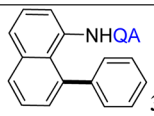
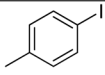
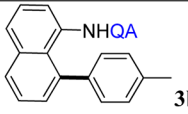
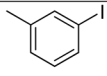
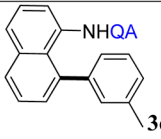
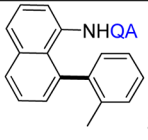
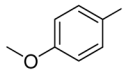
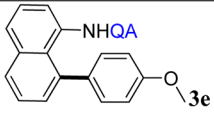
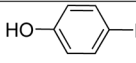
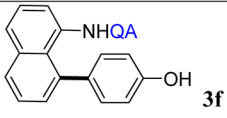
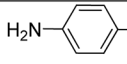
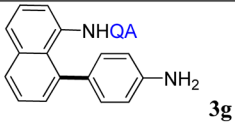
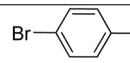
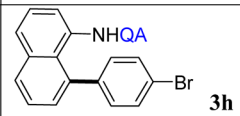
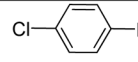
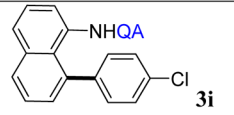
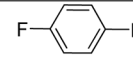
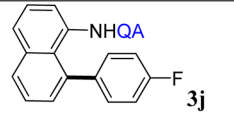
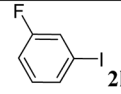
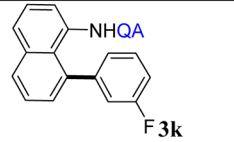
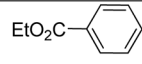
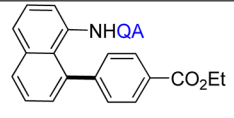
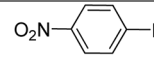
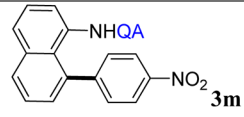
Table 2. Scope of the Aryl Iodides[a]



entry	ArI	product	Yield
1	 **2a**	 **3a**	96(92[b])
2	 **2b**	 **3b**	85
3	 **2c**	 **3c**	82
4	 **2d**	 **3d**	N.D
5	 **2e**	 **3e**	92
6	 **2f**	 **3f**	80
7	 **2g**	 **3g**	82
8	 **2h**	 **3h**	74
9	 **2i**	 **3i**	89
10	 **2j**	 **3j**	89
11	 **2k**	 **3k**	89
12	 **2l**	 **3l**	84
13	 **2m**	 **3m**	82

[a]Reaction conditions: **1a** (0.5 mmol, 149 mg), $Pd(OAc)_2$ (0.075 mmol, 16 mg), ArI (2.0 mmol), KOAc (1.0 mmol, 98 mg), xylene (5 mL), 130 °C, 12 h. [b]Isolated yield on a 5.0 mmol scale, 66 h.

C−H activation process versus the oxidative addition of ArI to Pd(II), we performed theoretical calculations on the two pathways (Figure 1).[16] The optimized structures of selected transition states were shown in Figure 2. As can be seen in Figure 1, the energy barrier of path a was 25.3 kcal/mol, and the oxidative addition step via transition state $TS_{C'\text{-}D}$ was the rate-determining step. On the other hand, the oxidative addition step in path b required higher activation energy of 28.8 kcal/mol. Although not conclusive, our calculations favored a sequential C−H activation/oxidative addition pathway for this C−H arylation reaction.

Futhermore, the amide directing group could be simply hydrolyzed (Scheme 6). The arylated substrates **3a** and **3n** were heated with NaOH in ethanol to afford 92% and 85% yields of 8-phenyl-1-naphthylamine **3t**, respectively.

CONCLUSIONS

In conclusion, we have demonstrated a powerful methodology for the Pd-catalyzed regioselective arylation of the 1-naphthylamides by employing a bidentate system. This transformation tolerates a broad range of aryl iodides, even including the sensitive free-hydroxyl and amine group

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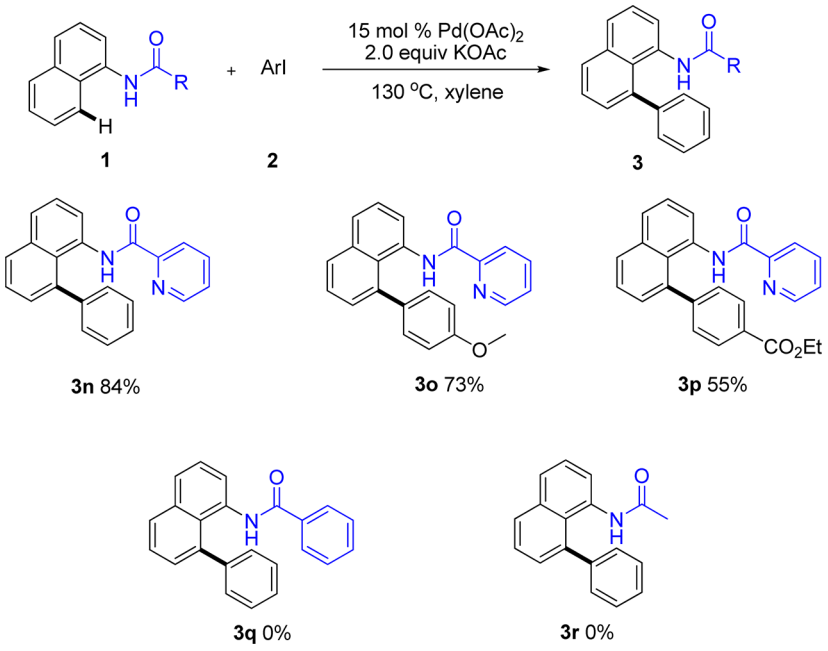
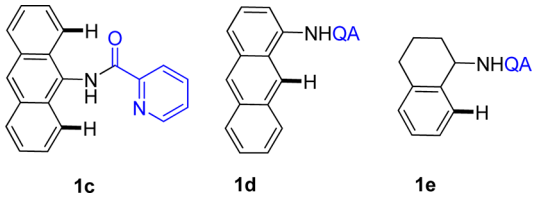
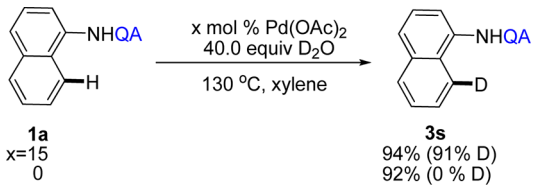
Scheme 2. Screening of 1-Naphthylamides Auxiliaries



Scheme 3. Unreactive Substrates



Scheme 4. Preliminary Mechanistic Studies



substituted. The amide auxiliary is effectively detached under mild conditions to provide a synthetic method for 8-phenyl-1-naphthylamine. Furthermore, the comparison of two plausible reaction paths is conducted by theoretical calculations. The result indicates that a sequential C−H activation/oxidative addition pathway is favorable for the C−H arylation reaction.

EXPERIMENTAL SECTION

General Methods. Unless otherwise stated, all reactions were carried out in an oven-dried flask in air. ^{1}H NMR spectra were recorded at 400 MHz, and the chemical shifts were reported in parts per million (δ) relative to internal standard TMS (0 ppm) for $CDCl_3$ or DMSO-d_6. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublet. The coupling constants, J, are reported in hertz (Hz). ^{13}C NMR spectra were recorded at 100 MHz and referenced to the internal solvent signals (center peak is 77.00 ppm in $CDCl_3$ or 39.90 ppm in DMSO-d_6). High-resolution mass spectra (HRMS-ESI) were obtained on a FT-ICR spectrometer. Amide derivatives **1a−e**[10] were synthesized according to the literature procedure. *N*-(Naphthalen-1-yl)benzamide and *N*-(naphthalen-1-yl)acetamide[17] were prepared by known method. Other materials were purchased from common commercial sources and used without additional purification.

Preparation of Amide Compounds 1a−e.[10] Amine (20 mmol), picolinic acid, or quinoline-2-carboxylic acid (20 mmol), and Et_3N (40 mmol, 5.6 mL) were dissolved in CH_2Cl_2 (40 mL) followed by dropwise addition of $POCl_3$ (3.76 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 0.5 h and warmed to room temperature for 2 h. Then the reaction mixture was cooled to 0 °C. Ice−water was added slowly to quench the reaction. The organic layer was collected, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was washed by saturated $NaHCO_3$ (2 × 40 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was crystallized from CH_2Cl_2/petroleum ether to give the desired product.

***N*-(Naphthalen-1-yl)quinoline-2-carboxamide (1a, CAS no. 298193-67-6):** 4.29 g, 72% yield; pink solid; mp = 146−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.95 (s, 1 H), 8.43 (d, J = 8.4 Hz, 2 H), 8.36 (d, J = 8.0 Hz, 1 H), 8.25 (d, J = 8.4 Hz, 1 H), 8.16 (d, J = 8.4 Hz, 1 H), 7.91 (d, J = 8.0 Hz, 2 H), 7.81 (t, J = 7.2 Hz, 1 H), 7.71 (d, J = 8.4 Hz, 1 H), 7.59 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 149.9, 146.3, 138.0, 134.2, 132.5, 130.4, 129.9, 129.5, 128.9, 128.2, 127.9, 126.5, 126.3, 126.1, 126.0, 125.1, 120.5, 118.8, 118.7. HRMS (ESI) calcd for $C_{20}H_{14}N_2O$ $[M + H]^+$ 299.1179, found 299.1182.

***N*-(Naphthalen-1-yl)picolinamide (1b, CAS no. 75358-95-1):**[14] 2.98 g, 60% yield; pink solid; mp = 128−129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.75 (s, 1 H), 8.70 (d, J = 5.2 Hz, 1 H), 8.41 (d, J = 7.2 Hz, 1 H), 8.36 (d, J = 7.6 Hz, 1 H), 8.09 (d, J = 8.4 Hz, 1 H), 7.91 (m, 2 H), 7.70 (d, J = 8.4 Hz, 1 H), 7.55 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 150.1, 148.2, 137.8, 134.1, 132.4, 128.8, 126.5, 126.4, 126.3, 126.0, 125.9, 125.0,122.5, 120.5, 118.6. HRMS (ESI) calcd for $C_{16}H_{12}N_2O$ $[M + H]^+$ 249.1022, found 249.1020.

***N*-(Anthracen-9-yl)picolinamide (1c):** 1.49 g, 25% yield; light yellow solid; mp =197−198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.27 (s, 1 H), 8.72 (s, 1 H), 8.45 (s, 1 H), 8.37 (d, J = 8.0 Hz, 1 H), 8.12 (d, J = 8.4 Hz, 2 H), 8.02 (d, J = 8.4 Hz, 2 H), 7.94 (m, 1 H), 7.49 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 149.7, 148.4, 137.7, 131.8, 128.7, 128.4, 127.9, 127.0, 126.8, 126.4, 125.4, 123.5, 122.9; HRMS (ESI) calcd for $C_{20}H_{14}N_2O$ $[M + H]^+$ 299.1179, found 299.1181.

***N*-(Anthracen-1-yl)quinoline-2-carboxamide (1d):** 4.66 g, 67% yield; dark green solid; mp = 196−197 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.06 (s, 1 H), 8.58 (s, 1 H), 8.41 (m, 3 H), 8.34 (d, J = 8.0 Hz, 1 H), 8.26 (d, J = 8.0 Hz, 1 H), 8.05 (d, J = 6.8 Hz, 1 H), 7.95 (d, J = 6.8 Hz, 1 H), 7.88 (d, J = 7.6 Hz, 1 H), 7.81 (d, J = 8.0 Hz, 2 H),

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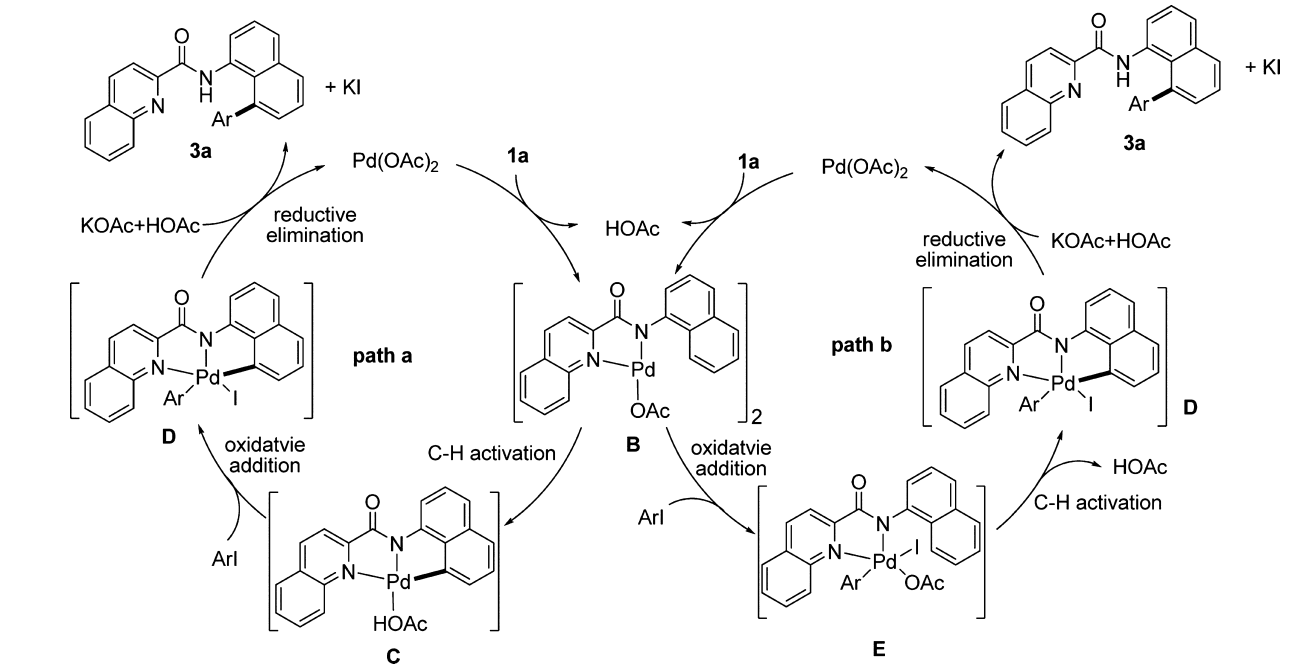
Scheme 5. Plausible Mechanism



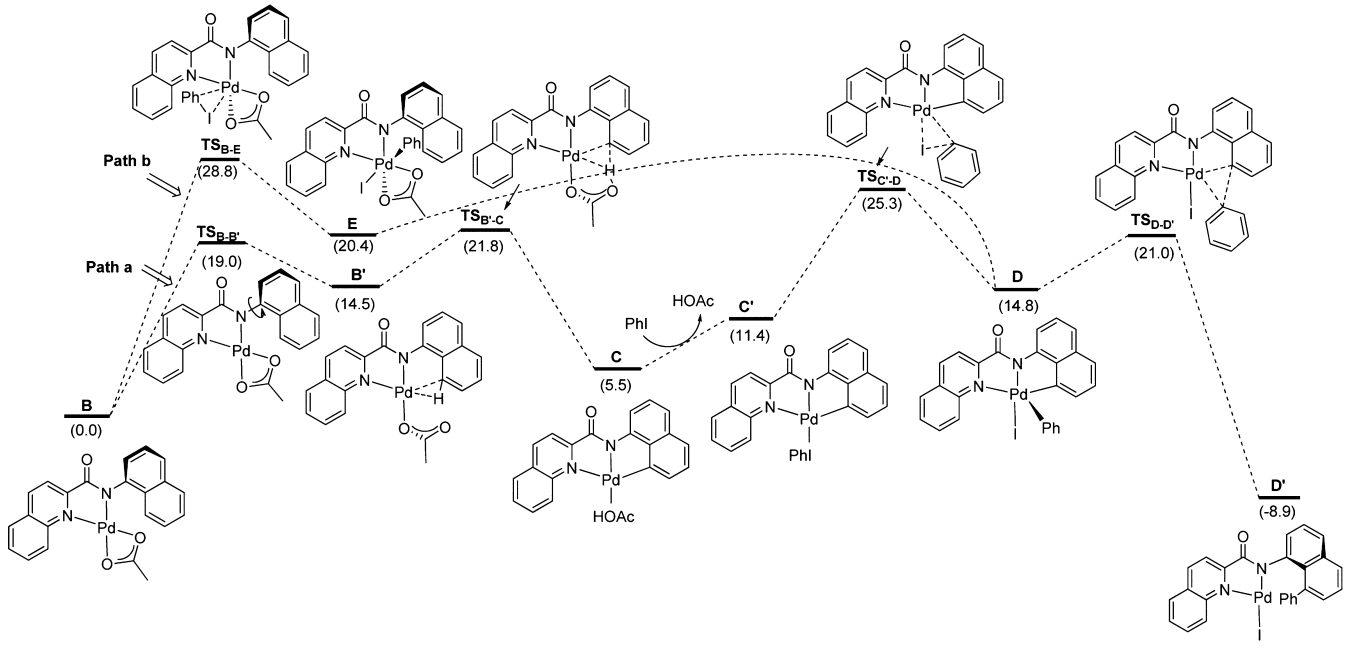


Figure 1. Potential energy surfaces of path a (sequential C−H activation/oxidative addition) and path b (sequential oxidative addition/C−H activation).

7.63 (t, J = 8.0 Hz, 1 H), 7.49 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 149.9, 146.3, 138.0, 132.2, 132.1, 131.6, 131.5, 130.4, 129.9, 129.5, 128.5, 128.2, 128.0, 127.9, 127.2, 125.8, 125.5, 125.4, 125.2, 119.1, 118.8, 117.3; HRMS (ESI) calcd for $C_{24}H_{16}N_2O$ $[M + H]^+$ 349.1335, found 349.1338.

***N*-(1,2,3,4-Tetrahydronaphthalen-1-yl)quinoline-2-carboxamide (1e, CAS no. 781628-15-7):** 3.02 g, 50% yield; white solid; mp = 133−134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 9.2 Hz, 1 H), 8.37 (d, J = 8.4 Hz, 1 H), 8.26 (d, J = 8.8 Hz, 1 H), 8.02 (d, J = 8.8 Hz, 1 H), 7.81 (d, J = 8.0 Hz, 1 H), 7.67 (t, J = 8.0 Hz, 1 H), 7.54 (t, J = 8.0 Hz, 1 H), 7.38 (d, J = 8.0 Hz, 1 H), 7.16 (m, 3 H), 5.47 (m, 1 H), 2.83 (m, 2 H), 2.20 (m, 1 H), 1.94 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 149.9, 146.5, 137.7, 137.5, 136.8, 130.1, 129.7, 129.3, 129.2, 128.8, 127.9, 127.8, 127.3, 126.4, 119.0, 47.8, 30.5, 29.4, 20.5.

Typical Procedure for Arylation Products 3a−r. A mixture of naphthylamide (0.5 mmol, 1.0 equiv), aryl iodides (2.0 mmol, 4.0 equiv), $Pd(OAc)_2$ (0.075 mmol, 15 mol %), anhydrous KOAc (1.0 mmol, 2.0 equiv), and xylene (5 mL) was placed in a 35 mL Schlenk tube with a rubber plug under air. The tube was heated at 130 °C for 12 h. The reaction mixture was cooled to rt, diluted with ethyl acetate, filtered through Celite, and concentrated in vacuo. The residue was purified by silica gel column chromatography with ethyl acetate/petroleum ether to afford the desired product.

***N*-(8-Phenylnaphthalen-1-yl)quinoline-2-carboxamide (3a):** 183 mg, 96% yield; light yellow solid after purification by column

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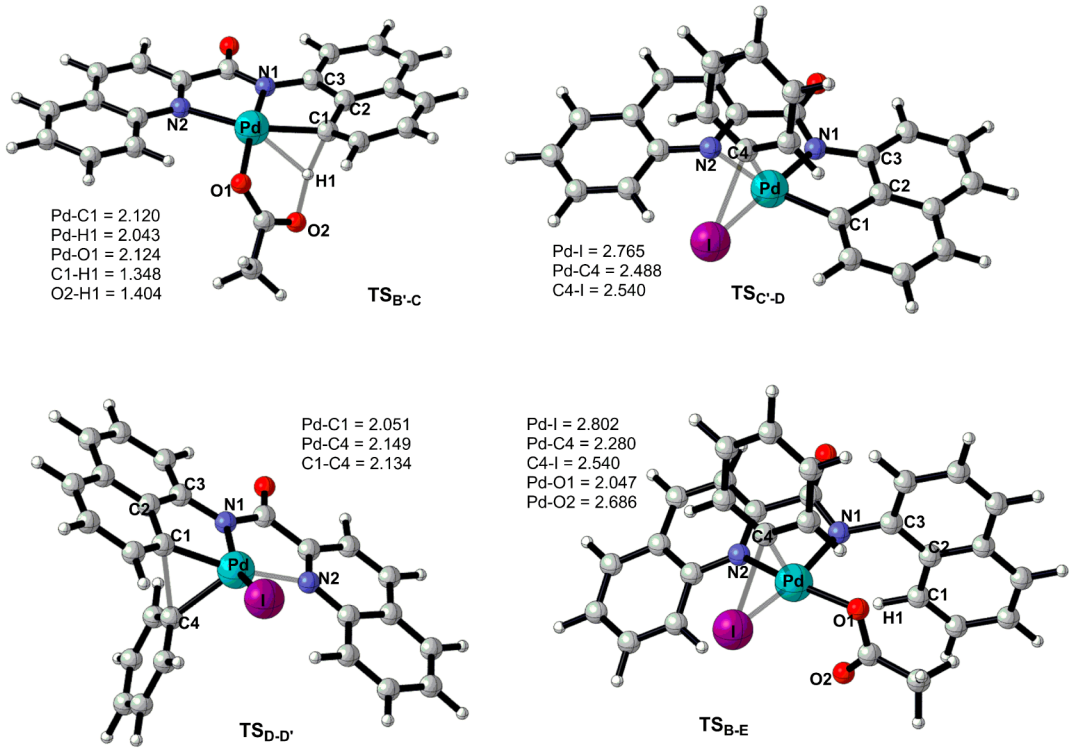
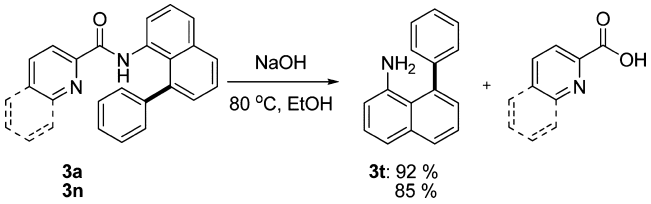


Figure 2. Optimized structures of selected transition states in paths a and b. Bond lengths in angstroms.

Scheme 6. Hydrolysis of Amide 3



chromatography (eluent, ethyl acetate/petroleum ether = 1/10, v/v); mp = 134−135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1 H), 8.20 (m, 2 H), 8.10 (d, J = 7.6 Hz, 1 H), 7.89 (d, J = 7.6 Hz, 1 H), 7.84 (m, 3 H), 7.74 (t, J = 7.2 Hz, 1 H), 7.59 (m, 2 H), 7.49 (t, J = 7.2 Hz, 1 H), 7.38 (d, J = 8.0 Hz, 2 H), 7.33 (d, J = 7.2 Hz, 1 H), 6.93 (t, J = 7.6 Hz, 2 H), 6.39 (t, J = 7.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 149.6, 145.7, 142.8, 137.9, 137.1, 135.6, 132.7, 130.4, 130.3, 129.6, 129.2, 128.8, 128.7, 127.9, 127.7, 127.6, 126.8, 126.3, 125.9, 125.7, 125.0, 123.7, 118.4; HRMS (ESI) calcd for $C_{26}H_{18}N_2O$ [M + H]$^+$ 375.1492, found 375.1497.

***N*-(8-Tolylnaphthalen-1-yl)quinoline-2-carboxamide (3b):** 165 mg, 85% yield; light yellow solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1/10, v/v); mp =145−146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1 H), 8.25 (d, J = 8.4, 1 H), 8.22 (t, J = 8.4 Hz, 1 H), 8.08 (d, J = 7.2 Hz, 1 H), 7.87 (m, 4 H), 7.78 (t, J = 8.4 Hz,1 H), 7.62 (t, J = 8.4 Hz, 1 H), 7.60 (t, J = 8.0 Hz, 1 H), 7.49 (t, J = 7.2 Hz, 1 H), 7.33 (d, J = 7.2 Hz, 1 H), 7.26 (d, J = 8.0 Hz, 2 H), 6.69 (d, J = 7.2 Hz, 2 H), 1.25 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 149.7, 145.7, 139.7, 137.9, 137.1, 136.2, 135.5, 132.6, 130.3, 130.2, 129.7, 129.2, 128.7, 128.6, 128.5, 127.7, 127.6, 126.8, 125.9, 125.7, 125.0, 123.8, 118.4, 20.0. HRMS (ESI) calcd for $C_{27}H_{20}N_2O$ [M + H]$^+$ 389.1648, found 389.1651.

***N*-(8-*m*-Tolylnaphthalen-1-yl)quinoline-2-carboxamide (3c):** 159 mg, 82% yield; light yellow solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1/10, v/v); mp = 128−129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (s, 1 H), 8.07 (s, 2 H), 7.91 (d, J = 7.6 Hz, 1 H), 7.71 (m, 4 H), 7.59 (t, J = 7.2 Hz, 1 H), 7.46 (t, J = 7.6 Hz, 1 H), 7.43 (t, J = 6.8 Hz, 1 H), 7.33 (t, J = 7.6 Hz, 1 H), 7.19 (d, J = 7.2 Hz, 1 H), 7.05 (d, J = 7.2 Hz, 1 H), 7.02 (s, 1 H), 6.67 (t, J = 7.6 Hz, 1 H), 6.01 (d, J = 7.6 Hz, 1 H), 1.77 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 149.5, 145.9, 142.6, 138.0, 137.2, 137.0, 135.6, 132.7, 130.3, 129.8, 129.6, 129.2, 128.6, 127.8, 127.8, 127.6, 127.2, 127.0, 125.9, 125.8, 125.1, 124.2, 118.4, 21.1. HRMS (ESI) calcd for $C_{27}H_{20}N_2O$ [M + H]$^+$ 389.1648, found 389.1651.

***N*-(8-(4-Methoxyphenyl)naphthalen-1-yl)quinoline-2-carboxamide (3e).** 186 mg, 92% yield; light yellow solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether =1/6, v/v); mp =168−169 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1 H), 8.26 (t, J = 8.4, 1 H), 8.24 (t, J = 8.4 Hz, 1 H), 8.10 (d, J = 7.6 Hz, 1 H), 7.87 (m, 4 H), 7.78 (t, J = 7.6 Hz, 1 H), 7.62 (t, J = 8.0, 1 H), 7.60 (t, J = 8.4 Hz, 1 H), 7.50 (t, J = 8.0 Hz, 1 H), 7.34 (d, J = 6.8 Hz, 1 H), 7.30 (t, J = 8.4 Hz, 2 H), 6.44 (d, J = 8.4 Hz, 2 H), 2.90 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 158.2, 149.8, 145.7, 137.5, 137.2, 135.6, 135.0, 132.7, 130.4, 130.2, 129.9, 129.7, 129.3, 128.4, 127.7, 127.6, 126.7, 125.9, 125.7, 125.0, 123.6, 118.5, 113.2, 54.1. HRMS (ESI) calcd for $C_{27}H_{20}N_2O_2$: [M + H]$^+$ 405.1598; Found, 405.1595.

***N*-(8-(4-hydroxyphenyl)naphthalen-1-yl)quinoline-2-carboxamide (3f):** 156 mg, 80% yield; light yellow solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1/3, v/v); mp = 256−257 °C; ^{1}H NMR (400 MHz, C_2D_6SO) δ 9.85 (s, 1 H), 8.81 (s, 1 H), 8.51 (d, J = 8.8, 1 H), 8.13 (d, J = 7.6 Hz, 1 H), 8.08 (d, J = 8.4 Hz, 1 H), 8.04 (d, J = 8.4 Hz, 1 H), 7.98 (d, J = 7.6 Hz, 2 H), 7.92 (d, J = 8.0 Hz, 1 H), 7.87 (t, J = 7.6 Hz, 1 H), 7.72 (t, J = 7.6 Hz, 1 H), 7.63 (t, J = 7.6 Hz, 1 H), 7.56 (t, J = 7.2 Hz, 1 H), 7.31 (d, J = 6.8 Hz, 1 H), 7.19 (d, J = 8.4 Hz, 2 H), 6.49 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, C_2D_6SO) δ 161.9, 157.0, 149.5, 145.8, 138.2, 138.1, 135.7, 133.4, 132.8, 131.0, 130.7, 130.3, 130.1, 129.3, 128.4, 128.2, 126.7, 126.1, 125.7, 125.2, 122.7, 118.4, 115.3; HRMS (ESI) calcd for $C_{26}H_{18}N_2O_2$ [M + H]$^+$ 391.1441, found 391.1437.

***N*-(8-(4-Aminophenyl)naphthalen-1-yl)quinoline-2-carboxamide (3g):** 160 mg, 82% yield; light yellow solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1/2, v/v); mp = 154−155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1 H), 8.24 (s, 2 H), 8.18 (d, J = 7.6, 1 H), 7.96 (d, J = 8.4 Hz, 1 H), 7.80 (m, 4 H), 7.59 (t, J = 8.0 Hz, 1 H), 7.57 (t, J = 7.6 Hz, 1 H), 7.46 (t, J

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= 8.0 Hz, 1 H), 7.32 (d, *J* = 7.2 Hz, 1 H), 7.16 (d, *J* = 8.4 Hz, 2 H), 6.23 (d, *J* = 8.8 Hz, 2 H), 2.56 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 150.1, 145.9, 145.2, 138.0, 137.1, 135.6, 132.9, 132.7, 130.4, 129.8, 129.5, 129.2, 128.2, 127.7, 127.6, 126.5, 125.8, 125.4, 125.1, 122.8, 118.6, 114.6; HRMS (ESI) calcd for $C_{26}H_{19}N_3O$ $[M + H]^+$ 390.1601, found 390.1597.

***N*-(8-(4-Bromophenyl)naphthalen-1-yl)quinoline-2-carboxamide (3h):** 168 mg, 74% yield; light yellow solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1/10, v/v); mp = 162−163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1 H), 8.30 (d, *J* = 8.4, 1 H), 8.23 (d, *J* = 8.4 Hz, 1 H), 8.03 (d, *J* = 7.8 Hz, 1 H), 7.92 (d, *J* = 7.6 Hz, 1 H), 7.87 (t, *J* = 8.4 Hz, 3 H), 7.79 (t, *J* = 8.0 Hz, 1 H), 7.64 (t, *J* = 8.4 Hz, 1 H), 7.61 (t, *J* = 8.4 Hz, 1 H), 7.50 (t, *J* = 8.0 Hz, 1 H), 7.31 (d, *J* = 7.2 Hz, 1 H), 7.24 (d, *J* = 7.6 Hz, 2 H), 7.01 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 149.2, 145.8, 141.7, 137.5, 136.6, 135.5, 132.3, 130.8, 130.4, 130.2, 130.1, 130.0, 129.6, 129.1, 127.9, 127.8, 127.1, 126.1, 125.8, 125.0, 124.6, 120.7, 118.2; HRMS (ESI) calcd for $C_{26}H_{17}BrN_2O$ $[M + H]^+$ 453.0597, found 453.0591.

***N*-(8-(4-Chlorophenyl)naphthalen-1-yl)quinoline-2-carboxamide (3i):** 182 mg, 89% yield; light yellow solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1/10, v/v); mp = 158−159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1 H), 8.28 (d, *J* = 8.4, 1 H), 8.21 (d, *J* = 8.4 Hz, 1 H), 8.03 (d, *J* = 7.6 Hz, 1 H), 7.91 (d, *J* = 8.0 Hz, 1 H), 7.86 (m, 3 H), 7.78 (t, *J* = 8.0 Hz, 1 H), 7.61 (m, 2 H), 7.49 (t, *J* = 8.0 Hz, 1 H), 7.29 (d, *J* = 8.4 Hz, 3 H), 6.86 (d, *J* = 8.4, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 149.3, 145.8, 141.2, 137.5, 136.6, 135.5, 132.7, 132.3, 130.3, 130.1, 130.0, 129.9, 129.5, 129.1, 127.9, 127.8, 127.1, 126.1, 125.8, 125.0, 124.5, 118.2; HRMS (ESI) calcd for $C_{26}H_{17}ClN_2O$ $[M + H]^+$ 409.1102, found 409.1107.

***N*-(8-(4-Fluorophenyl)naphthalen-1-yl)quinoline-2-carboxamide (3j):** 174 mg, 89% yield; light yellow solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1/10, v/v); mp = 172−173 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1 H), 8.25 (t, *J* = 8.4, 1 H), 8.23 (t, *J* = 8.4 Hz, 1 H), 8.08 (d, *J* = 7.2 Hz, 1 H), 7.86 (m, 4 H), 7.77 (t, *J* = 7.6 Hz, 1 H), 7.62 (m, 2 H), 7.48 (t, *J* = 7.6 Hz, 1 H), 7.30 (m, 3 H), 6.62 (t, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 161.9, 160.4, 149.4, 145.7, 138.8, 138.7, 137.5, 136.7, 135.6, 132.5, 130.5, 130.4, 130.3, 129.9, 129.8, 129.3, 128.9, 127.9, 127.7, 126.9, 126.0, 125.8, 125.0, 124.1, 118.4, 114.8, 114.6; HRMS (ESI) calcd for $C_{26}H_{17}FN_2O$ $[M + H]^+$ 393.1398, found 393.1393.

***N*-(8-(3-Fluorophenyl)naphthalen-1-yl)quinoline-2-carboxamide (3k):** 174 mg, 89% yield; light yellow solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1/10, v/v); mp = 125−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (s, 1 H), 8.24 (t, *J* = 8.4, 1 H), 8.22 (t, *J* = 8.4 Hz, 1 H), 8.06 (d, *J* = 7.6 Hz, 1 H), 7.91 (t, *J* = 8.8 Hz, 2 H), 7.85 (d, *J* = 8.0 Hz, 2 H), 7.77 (t, *J* = 6.8 Hz, 1 H), 7.61 (m, 2 H), 7.49 (t, *J* = 7.2 Hz, 1 H), 7.31 (d, *J* = 6.0 Hz, 1 H), 7.19 (d, *J* = 8.4 Hz, 1 H), 7.08 (d, *J* = 7.6 Hz, 1 H), 6.80 (td, *J* = 8.0, 7.6 Hz, 1 H), 6.07 (t, *J* = 8.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 162.1, 161.0, 149.3, 145.8, 145.1, 145.0, 137.3, 136.5, 136.4, 135.5, 132.4, 130.3, 130.1, 129.8, 129.3, 129.2, 129.1, 127.9, 127.6, 127.0, 126.1, 125.8, 125.0, 124.9, 124.4, 118.4, 116.0, 115.8, 113.3, 113.1; HRMS (ESI) calcd for $C_{26}H_{17}FN_2O$ $[M + H]^+$ 393.1398, found 393.1403.

Ethyl 4-(8-quinoline-2-carboxamido)naphthalen-1-yl)-benzoate (3l): 187 mg, 84% yield; light yellow solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1/6, v/v); mp = 127−128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1 H), 8.21 (t, *J* = 8.4, 1 H), 8.20 (t, *J* = 8.8 Hz, 1 H), 7.98 (d, *J* = 7.6 Hz, 1 H), 7.94 (d, *J* = 8.4 Hz, 1 H), 7.88 (d, *J* = 8.4 Hz, 1 H), 7.81 (d, *J* = 9.2 Hz, 2 H), 7.75 (t, *J* = 6.8 Hz, 1 H), 7.62 (m, 2 H), 7.56 (d, *J* = 8.4 Hz, 2 H), 7.51 (t, *J* = 8.0 Hz, 1 H), 7.43 (d, *J* = 8.0 Hz, 2 H), 7.33 (d, *J* = 7.2 Hz, 1 H), 3.81 (q, *J* = 7.2 Hz, 2 H), 1.09 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 162.1, 149.2, 147.5, 145.5, 137.3, 136.9, 135.5, 132.2, 130.1, 130.0, 129.9, 129.3, 129.0, 128.8, 128.2, 127.7, 127.5, 127.3, 126.1, 126.0, 125.0, 118.3, 60.3, 14.0; HRMS (ESI) calcd for $C_{29}H_{22}N_2O_3$ $[M + H]^+$ 447.1703, found 447.1709.

***N*-(8-(4-Nitrophenyl)naphthalen-1-yl)quinoline-2-carboxamide (3m):** 171 mg, 82% yield; light yellow solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1/6, v/v); mp = 211−212 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (s, 1 H), 8.23 (d, *J* = 8.4, 1 H), 8.17 (d, *J* = 8.4 Hz, 1 H), 7.96 (t, *J* = 8.6 Hz, 2 H), 7.90 (d, *J* = 8.0 Hz, 1 H), 7.82 (d, *J* = 8.0 Hz, 1 H), 7.76 (d, *J* = 3.2 Hz, 2 H), 7.70 (d, *J* = 8.4 Hz, 2 H), 7.62 (m, 2 H), 7.51 (m, 3 H), 7.31 (d, *J* = 7.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 150.1, 148.9, 145.9, 145.2, 137.7, 135.6, 135.5, 131.9, 130.5, 130.2, 130.0, 129.6, 129.3, 129.2, 128.3, 127.9, 127.6, 126.4, 126.1, 125.7, 125.0, 122.9, 118.2. HRMS (ESI) calcd for $C_{26}H_{17}N_3O_3$ $[M + H]^+$ 420.1343, found 420.1349.

***N*-(8-Phenylnaphthalen-1-yl)picolinamide (3n):** 136 mg, 84% yield; light yellow solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1/10, v/v); mp = 125−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (s, 1 H), 8.26 (d, *J* = 7.6 Hz, 1 H), 8.14 (d, *J* = 4.8 Hz, 1 H), 8.07 (d, *J* = 7.6 Hz, 1 H), 7.87 (d, *J* = 8.0 Hz, 1 H), 7.79 (d, *J* = 8.0 Hz, 1 H), 7.72 (t, *J* = 7.6 Hz, 1 H), 7.57 (t, *J* = 8.0 Hz, 1 H), 7.46 (t, *J* = 8.0 Hz, 1 H), 7.38 (d, *J* = 7.2 Hz, 2 H), 7.33 (m, 2 H), 7.16 (t, *J* = 7.6 Hz, 2 H), 6.98 (t, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 149.8, 147.4, 142.8, 137.7, 137.0, 135.5, 132.9, 130.5, 129.2, 128.8, 128.1, 126.8, 126.4, 125.9, 125.7, 125.0, 124.9, 122.5, 121.8; HRMS (ESI) calcd for $C_{22}H_{16}N_2O$ $[M + H]^+$ 325.1335, found 325.1331.

***N*-(8-(4-Methoxyphenyl)naphthalen-1-yl)picolinamide (3o):** 129 mg, 73% yield; light yellow solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1/6, v/v); mp = 154−155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1 H), 8.29 (d, *J* = 7.6, 1 H), 8.19 (d, *J* = 4.4 Hz, 1 H), 8.11 (d, *J* = 8.0 Hz, 1 H), 7.86 (d, *J* = 7.6, 1 H), 7.78 (t, *J* = 7.6 Hz, 2 H), 7.57 (t, *J* = 7.6, 1 H), 7.47 (t, *J* = 8.4 Hz, 1 H), 7.32 (m, 4 H), 6.72 (d, *J* = 8.4 Hz, 2 H), 3.59 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 158.9, 150.0, 147.4, 137.3, 136.9, 135.5, 135.1, 133.0, 130.5, 130.3, 128.5, 126.3, 125.9, 125.7, 125.0, 124.9, 122.2, 121.9, 113.6, 55.0; HRMS (ESI) calcd for $C_{23}H_{18}N_2O_2$ $[M + H]^+$ 355.1441, found 355.1440.

Ethyl 4-(8-(picolinamido)naphthalen-1-yl)benzoate (3p): 109 mg, 55% yield; light yellow solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1/6, v/v); mp = 109−110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1 H), 8.12 (m, 2 H), 8.07 (t, *J* = 7.6 Hz, 1 H), 7.92 (d, *J* = 8.0 Hz, 1 H), 7.83 (m, 3 H), 7.73 (t, *J* = 7.6 Hz, 1 H), 7.59 (t, *J* = 8.0 Hz, 1 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 7.44 (d, *J* = 8.4 Hz, 2 H), 7.31 (d, *J* = 7.2 Hz, 1 H), 7.24 (dd, *J* = 7.6, 4.8 Hz, 1 H), 4.30 (q, *J* = 7.2 Hz, 2 H), 1.36 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 161.9, 149.5, 147.6, 147.4, 137.0, 136.7, 135.5, 132.4, 130.1, 129.3, 129.2, 129.1, 128.8, 126.8, 126.1, 125.8, 125.3, 124.9, 123.7, 121.9, 60.7, 14.4; HRMS (ESI) calcd for $C_{25}H_{20}N_2O_3$ $[M + H]^+$ 397.1547, found 397.1543.

Procedure for Deuteration of Naphthylquinoline-2-carboxamide 1a. A mixture of naphthylquinoline-2-carboxamide **1a** (0.5 mmol, 149 mg), $Pd(OAc)_2$ (0.075 mmol, 16 mg), D_2O (20.0 mmol, 400 mg), and xylene (5 mL) was placed in a 35 mL Schlenk tube with rubber plug under air. The tube was heated at 130 °C for 12 h. The reaction mixture was cooled to rt, diluted with ethyl acetate, filtered through Celite, and concentrated in vacuo. The residue was purified by silica gel column chromatography with ethyl acetate/petroleum ether to afford the desired product.

D-*N*-(Naphthalen-1-yl)quinoline-2-carboxamide (3s): 140 mg, 94% yield (91% D); light yellow solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1/10, v/v); mp = 146−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.86 (s, 1 H), 8.43 (d, *J* = 7.2 Hz, 1 H), 8.35 (d, *J* = 8.4 Hz, 1 H), 8.23 (d, *J* = 8.4 Hz, 1 H), 8.16 (d, *J* = 8.4 Hz, 1 H), 8.08 (d, *J* = 8.4 Hz, 0.09 H), 7.83 (d, *J* = 8.4 Hz, 1 H), 7.78 (d, *J* = 7.6 Hz, 1 H), 7.72 (d, *J* = 8.0 Hz, 1 H), 7.64 (d, *J* = 8.4 Hz, 1 H), 7.51 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 149.8, 146.2, 137.9, 134.2, 132.5, 130.4, 129.8, 129.4, 128.9, 128.2, 127.8, 126.4, 126.2, 126.1, 126.0, 125.9, 125.0, 118.8, 118.5; HRMS (ESI) calcd for $C_{20}H_{13}DN_2O$ $[M + H]^+$ 300.1242, found 300.1246.

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Procedure for Hydrolysis of Amides 3a and 3n. Quinoline-2-carboxamide **3a** or picolinamide **3n** (0.25 mmol) and NaOH (240 mg, 6 mmol) were heated in ethanol (3 mL) for 12 h at 80 °C. After completion, the mixture was diluted with ethyl acetate, filtered through Celite, and concentrated in vacuo. The residue was purified by silica gel column chromatography with ethyl acetate/petroleum ether to afford the desired product.

8-Phenylnaphthalen-1-amine (3t, CAS no. 1254293-67-8):[1b] 50 mg, 92% yield; brown oil after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1/20, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.4 Hz, 1 H), 7.35 (m, 7 H), 7.23 (d, J = 8.0 Hz, 1 H), 7.11 (d, J = 7.2 Hz, 1 H), 6.55 (d, J = 7.2 Hz, 1 H), 3.57 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 149.7, 148.3, 137.7, 131.8, 128.7, 128.4, 127.8, 127.0, 126.7, 126.4, 125.4, 123.5, 122.9.

COMPUTATIONAL METHODS

All the calculations were performed using Gaussian 09 programs.[18] Geometry optimization was conducted using B3LYP method[19] with the combined basis set, i.e., LANL2DZ for Pd, I atoms and 6-31+G(d) for the other elements. Frequency analysis was conducted at the same level of theory to confirm the stationary points to be minima or saddle points. For all of the saddle points, intrinsic reaction coordinate analysis (IRC)[20] was performed to verify that them connect the right reactants and products on the potential energy surface. Single-point energy calculations in solution phase were calculated using the M06-L method[21] with a larger basis set, i.e., LANL2DZ with an added f-polarization shell for Pd, I and 6-311++g(2df,2p) for the other elements. Solvent effect was accounted for using the polarizable continuum model (PCM) with the radii and nonelectrostatic terms for the Truhlar and co-workers' universal solvation model (SMD).[22] Xylene was used as the solvent. Single-point energy corrected by the Gibbs free energy correction from frequency calculation was used as Gibbs free energy to describe the reaction energetics.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full spectroscopic data for all new compounds, crystallographic data of compound **3b**, energy properties, and Cartesian coordinates of reactants, intermediates, and transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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