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Palladium-Catalyzed Cs_2CO_3-Promoted Arylation of Unactivated C(sp^3)–H Bonds by (Diacetoxyiodo)arenes: Shifting the Reactivity of (Diacetoxyiodo)arenes from Acetoxylation to Arylation

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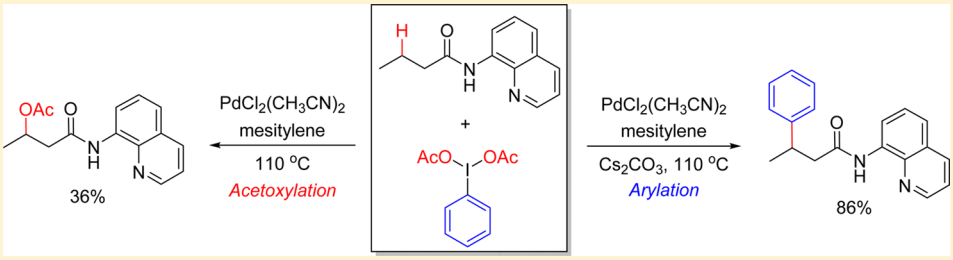
Supporting Information



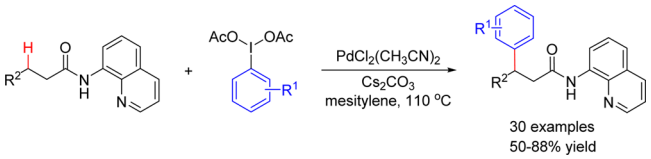
ABSTRACT: $PdCl_2(CH_3CN)_2$-catalyzed arylation of unactivated C(sp^3)–H bonds using (diacetoxyiodo)arenes as arylation reagents is reported. The reactivity of (diacetoxyiodo)arenes as arylation reagents is enabled in the presence of Cs_2CO_3 under the reaction conditions. This arylation method is highly efficient and occurs without the use of silver salt. The reaction tolerates a broad substrate scope that was not demonstrated by other silver salt-free C(sp^3)–H bond arylation conditions. The synthetic utility of the method is further illustrated in the synthesis of the psychotropic drug phenibut. A detailed mechanism study has been conducted to understand the reaction pathway.

INTRODUCTION

C(sp^3)–C(sp^2) bonds are present in a broad range of pharmaceuticals, agricultural chemicals, and synthetic intermediates. Direct construction of C(sp^3)–C(sp^2) bonds through C(sp^3)–H bond activation is an increasingly frequent strategy since it eliminates the need to prefunctionalize substrates and, therefore, shortens synthetic sequences.[1] Recent years have seen significant advances in transition-metal-catalyzed direct arylation of unactivated C(sp^3)–H bonds using an auxiliary-directing strategy[2,3] or a ligand-control strategy.[4] In these arylation methods, the catalyst is usually palladium,[2−4] iron,[5] or nickel,[6] and the arylation reagents are typically aryl halides. When aryl halides are used for this purpose, such reactions usually require a stoichiometric amount of expensive silver salts as halide scavengers.[2c−g,3] As a result, this generates a significant amount of toxic silver metal waste and increases the cost and difficulty of synthetic processes. To avoid these disadvantages, many laboratories have been working to develop silver salt-free conditions for arylation of C(sp^3)–H bonds, exemplified by recent excellent reports.[7] Nevertheless, new silver salt-free conditions to expand the scope and limitations of the current methods are highly desired.

(Diacetoxyiodo)arenes play important roles as reagents in many organic transformations with great stability, wide availability, and low toxicity.[8] It has already proven useful as acetoxylation reagents in palladium-catalyzed acetoxylation of C–H bonds.[9] To the best of our knowledge, no example of using (diacetoxyiodo)arenes as arylation reagents in arylating unactivated C(sp^3)–H bonds has been reported, despite recent examples of arylating C(sp^2)–H bonds.[10] Here, we describe the first use of (diacetoxyiodo)arenes to arylate unactivated β-C(sp^3)–H bonds of carboxylic acid derivatives (Scheme 1).

Scheme 1. Arylation of Unactivated C(sp^3)–H Bonds by (Diacetoxyiodo)arenes



The reaction relies on 8-aminoquinoline, a powerful bidentate directing group that was first reported by Daugulis and co-workers in β-arylation of carboxylic acid derivatives and was subsequently adapted to many other C–H activation reactions.[3]

RESULTS AND DISCUSSION

In a program directed to develop new C–C bond forming reactions,[11] we envisioned that, by optimizing reaction

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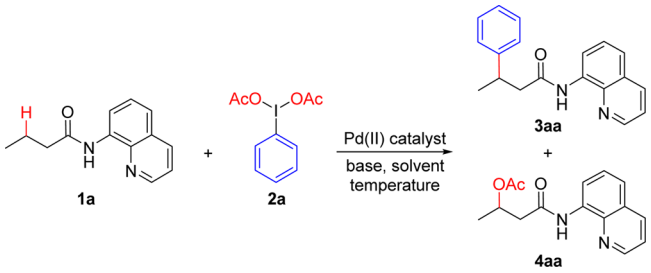
conditions, we might be able to shift (diacetoxyiodo)arenes away from their well-established acetoxylation activity to work instead as arylation reagents of C(sp^3)−H bonds.[9d,e] We chose the model reaction of *N*-(quinolin-8-yl)butyramide **1a** with $PhI(OAc)_2$ **2a** for optimizing conditions (Table 1). This

Table 1. Optimization of Reaction Conditions[a]



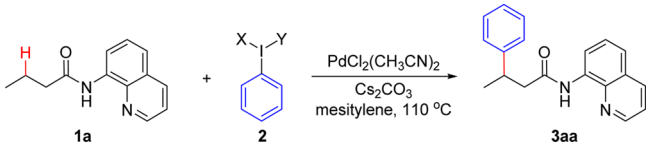
entry	Pd(II)	base	solvent	yield[b] 3aa	yield[b] 4aa
1	$Pd(OAc)_2$	Cs_2CO_3	CH_3CN	0	0
2	$Pd(OAc)_2$	Cs_2CO_3	dioxane	35	9
3	$Pd(OAc)_2$	Cs_2CO_3	*t*-$BuOCH_3$	27	0
4	$Pd(OAc)_2$	Cs_2CO_3	toluene	58	5
5	$Pd(OAc)_2$	Cs_2CO_3	*m*-xylene	55	0
6	$Pd(OAc)_2$	Cs_2CO_3	mesitylene	60	0
7	$Pd(TFA)_2$	Cs_2CO_3	mesitylene	9	0
8	$PdCl_2(COD)$	Cs_2CO_3	mesitylene	27	0
9	$PdCl_2(PPh_3)_2$	Cs_2CO_3	mesitylene	trace	0
10	$PdCl_2(dppf)$	Cs_2CO_3	mesitylene	32	0
11	**$PdCl_2(CH_3CN)_2$**	**Cs_2CO_3**	**mesitylene**	**86**	**0**
12	$PdCl_2(CH_3CN)_2$		mesitylene	0	36
13	$PdCl_2(CH_3CN)_2$	CsOAc	mesitylene	trace	15
14	$PdCl_2(CH_3CN)_2$	CsF	mesitylene	0	trace
15	$PdCl_2(CH_3CN)_2$	CsOPiv	mesitylene	trace	0
16	$PdCl_2(CH_3CN)_2$	Li_2CO_3	mesitylene	0	23
17	$PdCl_2(CH_3CN)_2$	Na_2CO_3	mesitylene	25	trace
18	$PdCl_2(CH_3CN)_2$	K_2CO_3	mesitylene	0	trace
19[c]	$PdCl_2(CH_3CN)_2$	Cs_2CO_3	mesitylene	trace	0

[a]General procedure: **1a** (0.20 mmol), **2a** (0.50 mmol), Pd(II) (10 mol %), and base (0.80 mmol) in solvent (1.0 mL) at 110 °C for 24−48 h with TLC control. [b]Determined by analysis of crude mixture with benzyl bromide as internal standard by 400 MHz ^{1}H NMR. [c]Reaction temperature: 90 °C.

reaction could, in principle, generate arylation product **3aa** or acetoxylation product **4aa**. Screening various solvents in the presence of $Pd(OAc)_2$ as catalyst and Cs_2CO_3 as base, we found that the solvent influenced the relative proportions of arylation and acetoxylation products (Table 1, entries 1−6). Mesitylene proved optimal for affording **3aa** exclusively (Table 1, entry 6). Of the various palladium catalysts screened (Table 1, entries 7−11), $PdCl_2(CH_3CN)_2$ improved the yield of **3aa** to 86% (Table 1, entry 11). We further investigated the effects of base on reaction efficiency. Omitting Cs_2CO_3 from the reaction gave acetoxylation product **4aa** exclusively in 36% yield (Table 1, entry 12). Bases composed of different cations or anions from Cs_2CO_3 gave low yields of **3aa** (Table 1, entries 13−18). Lowering the reaction temperature to 90 °C resulted in trace amounts of **3aa** (Table 1, entry 19). In the end, the optimal reaction conditions to obtain arylation product **3aa** were $PdCl_2(CH_3CN)_2$ (10 mol %), $PhI(OAc)_2$ (2.5 equiv), and Cs_2CO_3 (4.0 equiv) in mesitylene at 110 °C.

Subsequently, we studied how steric and electronic properties of various ligands attached to hypervalent iodine reagents PhIXY affected the arylation of **1a** (Table 2). $PhI(O_2CBu)_2$ and

Table 2. Examination of Ligand Effects of Hypervalent Iodine Reagents PhIXY[a]



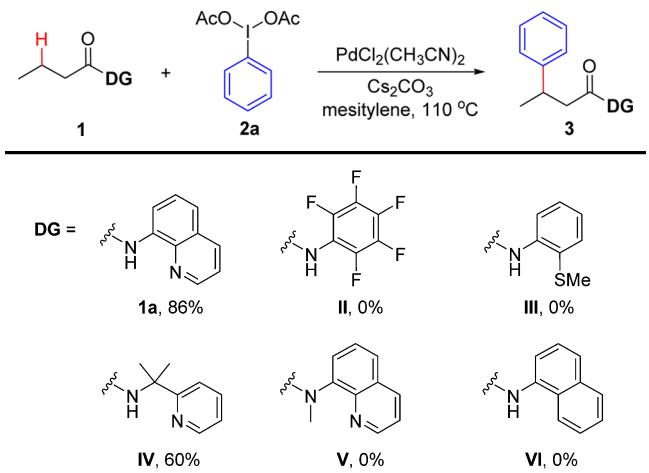
entry	PhIXY	yield[b]
1	X, Y = OAc	86
2	X, Y = O_2CBu	48
3	X, Y = OPiv	11
4	X, Y = O_2CPh	20
5	X, Y = O_2CCF_3	trace
6	X = OH, Y = OTs	0

[a]Optimal reaction conditions: **1a** (0.20 mmol), **2** (0.50 mmol), $PdCl_2(CH_3CN)_2$ (10 mol %), and Cs_2CO_3 (0.80 mmol) in mesitylene (1.0 mL) at 110 °C for 24−48 h with TLC control. [b]Determined by analysis of crude mixture with benzyl bromide as internal standard by 400 MHz ^{1}H NMR.

$PhI(OPiv)_2$, possessing ligands with increasing steric hindrance, showed lower reactivity than $PhI(OAc)_2$ (Table 2, entries 2−3). Reagents with more electron-deficient ligands, including $PhI(O_2CPh)_2$, $PhI(TFA)_2$, and PhI(OH)OTs, were also less effective than $PhI(OAc)_2$, affording little **3aa** (Table 2, entries 4−6).

Next, we evaluated the efficiency of other well-known directing groups besides 8-aminoquinoline in assisting the arylation of *β*-C(sp^3)−H bonds of carboxylic acid derivatives under the optimal reaction conditions (Table 3). These directing groups included the weakly coordinating perfluoroaniline (**II**),[2b] 2-methylthioaniline (**III**),[7a] and 2-(pyridine-2-yl)-

Table 3. Examination of Efficiency of Various Directing Groups[a,b]



[a]Optimal reaction conditions: **1** (0.20 mmol), **2a** (0.50 mmol), $PdCl_2(CH_3CN)_2$ (10 mol %), and Cs_2CO_3 (0.80 mmol) in mesitylene (1.0 mL) at 110 °C for 24−48 h with TLC control. [b]Determined by analysis of crude mixture with benzyl bromide as internal standard by 400 MHz ^{1}H NMR.

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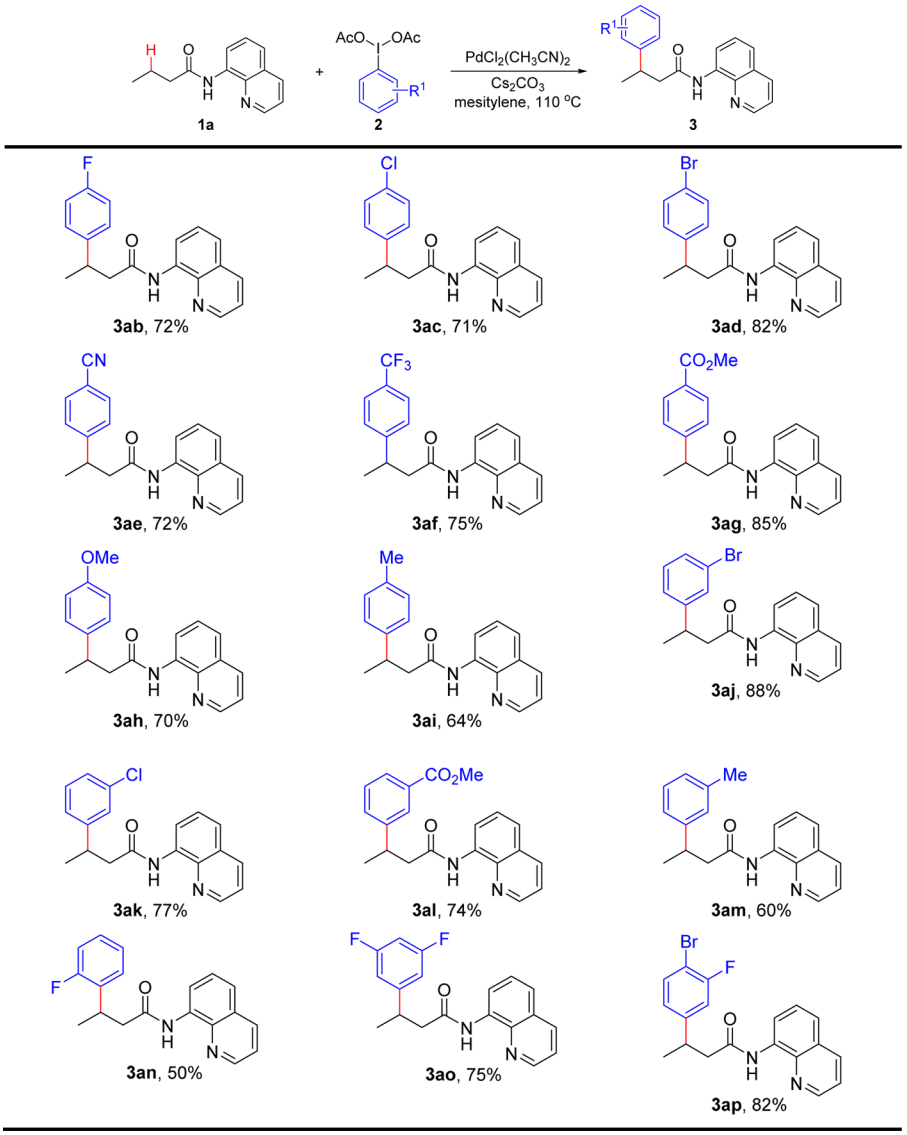
Table 4. Substrate Scope of (Diacetoxyiodo)arenes[a]



[a]Optimal reaction conditions: **1a** (0.20 mmol), **2** (0.50 mmol), $PdCl_2(CH_3CN)_2$ (10 mol %), and Cs_2CO_3 (0.80 mmol) in mesitylene (1.0 mL) at 110 °C for 24−48 h with TLC control.

isopropylamine (**IV**).[7c] It turned out that only **IV** afforded the desired arylation product in moderate 60% yield. None of the other directing groups gave any arylation product. The bidentate chelation nature of 8-aminoquinoline as directing group was confirmed by the fact that *N*-methyl-*N*-(quinolin-8-yl)butyramide (**V**) or *N*-(naphthalen-1-yl)butyramide (**VI**), which lack bidentate chelation ability, did not afford any arylation product. In this study, 8-aminoquinoline was superior to other directing groups in assisting arylation of the β-C(sp^3)−H bond of butyric acid derivatives by $PhI(OAc)_2$.

With the optimal reaction conditions in hand, we examined the scope of (diacetoxyiodo)arenes in the arylation of **1a** (Table 4). We were delighted to find that various *para*-, *meta*-, and *ortho*-substituted (diacetoxyiodo)arenes were well tolerated. All *para*-substituted (diacetoxyiodo)arenes with either electron-rich or electron-deficient groups afforded the desired arylation products in good yields (Table 4, **3ab**−**3ai**). *Meta*-substituted (diacetoxyiodo)arenes also worked smoothly to give the desired products in good yields (Table 4, **3aj**−**3am**). Notably, sterically hindered *ortho*-substituted (diacetoxyiodo)-arene also performed efficiently, though it gave the desired product in moderate yield (Table 4, **3an**). The substrate scope even included very electron-deficient dihalogen-substituted (diacetoxyiodo)arenes (Table 4, **3ao**−**3ap**). Various functional groups including F, Cl, Br, CN, and CO_2Me survived under the reaction conditions, and they could be utilized as useful handles for downstream transformations.

Additionally, we investigated the scope of carboxylic acid derivatives under the optimal reaction conditions (Table 5). Simple aliphatic carboxylic acid derivatives were well tolerated, affording the arylation products in excellent yields (Table 5, **3ba**−**3ca**). Phenyl and benzyl analogues also worked, though they gave the products in moderate yields presumably due to their unfavorable electronic or steric properties (Table 5, **3da**−**3ea**). In comparison, branched alkyl and cycloalkyl derivatives exhibited good reactivity (Table 5, **3fa**−**3ha**). In addition, substrates with functional groups including protected alcohols, protected amines, and ester also performed well to afford the arylation products in good yields (Table 5, **3ia**−**3ja**, **3ka**−**3ma**, **3na**). Moreover, the utility of the method was demonstrated in

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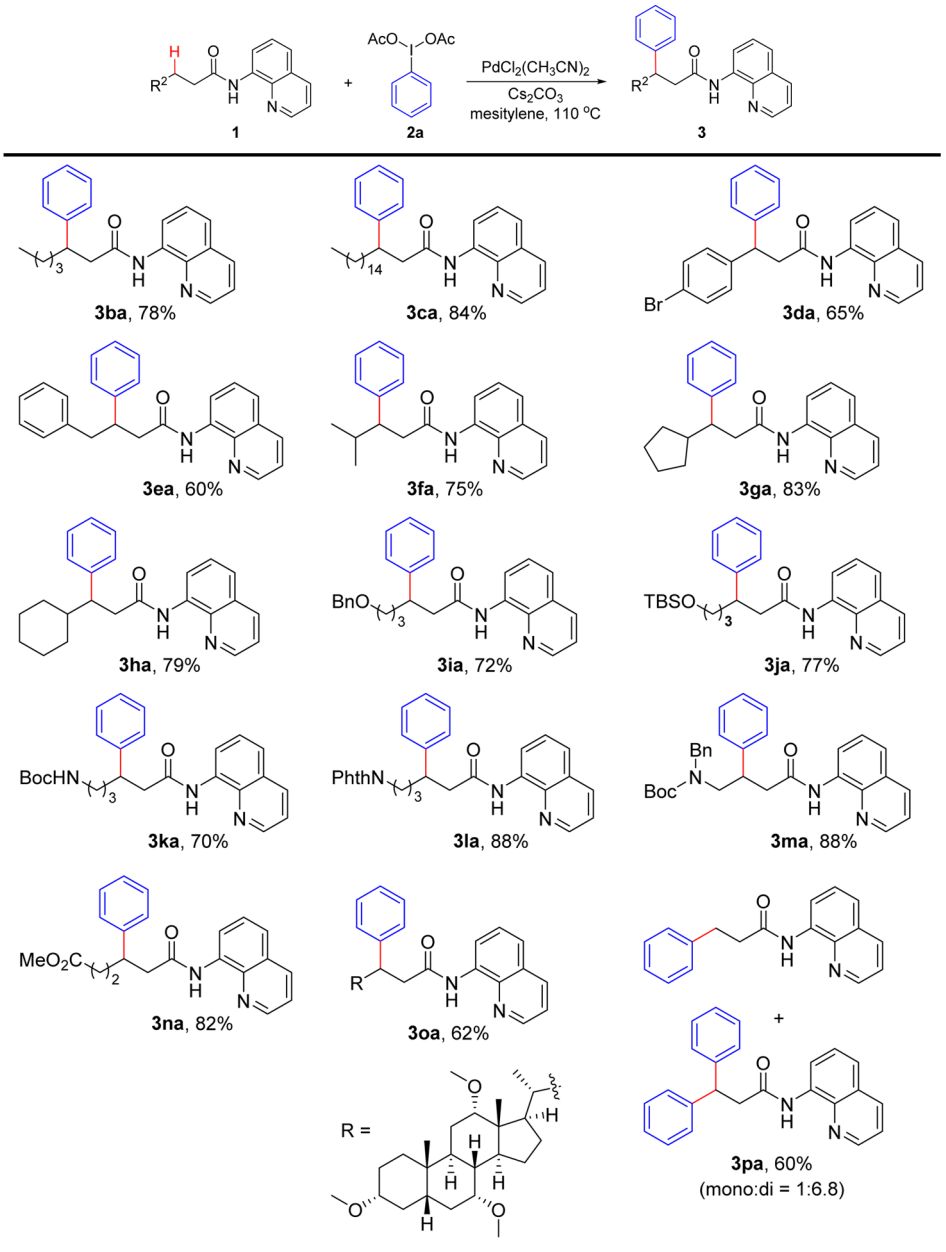
Table 5. Substrate Scope of Carboxylic Acid Derivatives[a]



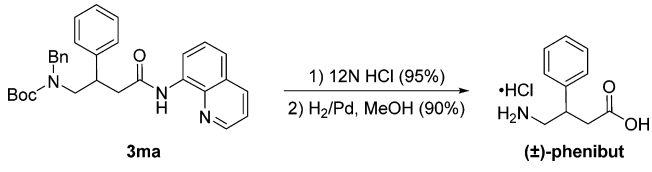
[a]Optimal reaction conditions: **1** (0.20 mmol), **2a** (0.50 mmol), $PdCl_2(CH_3CN)_2$ (10 mol %), and Cs_2CO_3 (0.80 mmol) in mesitylene (1.0 mL) at 110 °C for 24−48 h with TLC control.

the arylation of bile acid analogue to give **3oa** in high diastereoselectivity (dr > 20:1 determined by chiral HPLC; see the Supporting Information). Compounds like that were found to be FXR antagonists and could have potential applications in the treatment of dyslipidemia and other diseases.[12] It was remarkable that our arylation conditions tolerated a variety of useful functional groups that were not demonstrated in other silver salt-free C(sp^3)−H bond arylation approaches using aryl iodides as arylation reagents.[7] Arylation of a primary C(sp^3)−H bond gave a mixture of mono- and diarylation products in a 1:6.8 ratio (Table 5, **3pa**). Overall, a variety of functional carboxylic acid derivatives were arylated by $PhI(OAc)_2$ **2a** at the secondary β-C(sp^3)−H bonds in good to excellent yields.

As a further illustration of the synthetic utility of the method, we converted arylation product **3ma** into the psychotropic drug (±)-phenibut in 85% overall yield (Scheme 2).[13] This transformation was accomplished in two steps, including one-pot removal of the 8-aminoquinolinyl and Boc groups under acidic conditions, followed by a hydrogenative debenzylation.

To understand the reaction mechanism, we studied the kinetics of reaction. Consistent with Fairlamb's report,[10b] the

Scheme 2. Synthesis of (±)-Phenibut



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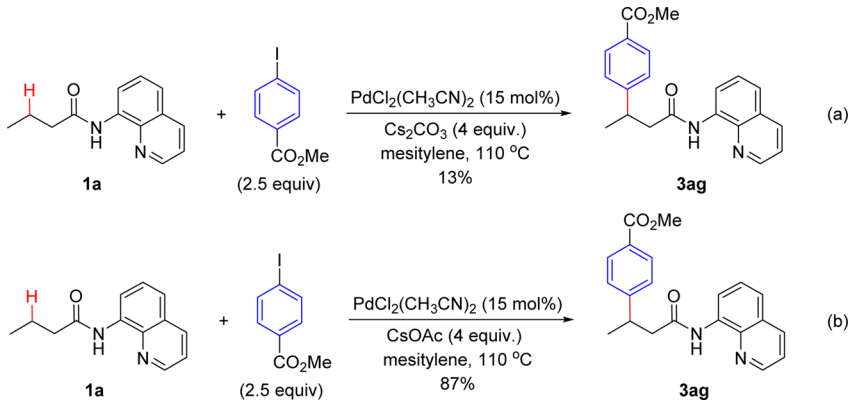
Scheme 3. Control Experiments



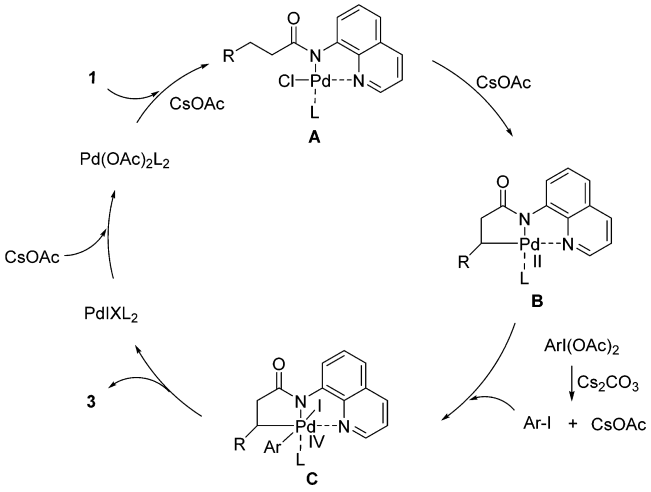
decomposition of (p-CO_2Me)PhI(OAc)$_2$ (**2g**) into (p-CO_2Me)PhI was done in 50 min (Cs_2CO_3, mesitylene, 110 °C). The product **3ag** did not start to form until the decomposition of **2g** into (p-CO_2Me)PhI was complete (after 50 min), and the reaction was finished in 40 h, during which (p-CO_2Me)PhI remained constantly as the major component of the reaction mixture (see the Supporting Information). The above results suggested that the actual arylation reagent of the reaction may be aryl iodides. However, simply replacing (p-CO_2Me)PhI(OAc)$_2$ (**2g**) with (p-CO_2Me)PhI without modifying other reaction parameters only afforded 13% **3ag**, which was consistent with one catalytic turnover of the palladium(II) catalyst (Scheme 3, a). This result promoted us to hypothesize the other role of (diacetoxyiodo)arenes in the reaction. We thought that the acetoxy anions, another byproduct generated from the decomposition of (diacetoxyiodo)arenes, could have acted as ligand to reactivate the palladium catalyst. Indeed, this hypothesis was confirmed in an additional control experiment (Scheme 3, b). In this experiment, the reaction afforded **3ag** in 87% yield by further replacing Cs_2CO_3 with CsOAc and using (p-CO_2Me)PhI as arylation reagent. Therefore, we concluded that the (diacetoxyiodo)arenes played dual roles not only as the arylation reagent but also as the promoter of the palladium catalysis in that it provided the source of acetoxy anions. The kinetic isotope experiments (parallel intermolecular KIE = 1.17, one-pot intermolecular KIE = 3.17, intramolecular KIE = 3.07; see the Supporting Information) suggested that the cleavage of the β-C(sp^3)−H bond of the substrate occurred as part of the reaction pathway, but not the rate-limiting step.[14] Overall, it was noteworthy that our method avoided the use of silver salts which were commonly utilized to assist the catalytic cycle in the C(sp^3)−H bond arylation conditions,[2,3] since the (diacetoxyiodo)arenes acted not only as the arylation reagent but also as the promoter of the palladium catalysis.

Based on the above scenario, a reaction mechanism was proposed in Scheme 4. The coordination of substrate **1** with palladium catalyst formed intermediate **A**, which further underwent activation of the β-C(sp^3)−H bond to give **B**. Subsequently, an oxidative addition of **B** into Ph-I took place to afford **C**, which eventually generated product **3** after reductive elimination. The catalytic cycle was restored after ligand exchange of $PdIXL_2$ with CsOAc.

CONCLUSION

We have disclosed $PdCl_2(CH_3CN)_2$-catalyzed arylation of β-C(sp^3)−H bonds of carboxylic acid derivatives using

Scheme 4. Proposed Reaction Mechanism



(diacetoxyiodo)arenes as arylation reagents with the assistance of an 8-aminoquinolinyl directing group. It has been shown that the Cs_2CO_3 unusually shifts the reactivity of (diacetoxyiodo)-arenes from acetoxylation to arylation of C(sp^3)−H bonds under the reaction conditions. This arylation method is highly efficient and avoids the use of a stoichiometric amount of silver salt. It tolerates a broader substrate scope than other silver salt-free C(sp^3)−H bond arylation approaches using aryl iodides as arylation reagents. The utility of the method is further demonstrated in the synthesis of the psychotropic drug phenibut. It has been shown that the dual roles of (diacetoxyiodo)arenes as both the arylation reagent and the promoter of the palladium catalysis are essential to the success of the reaction.

EXPERIMENTAL SECTION

General Information. NMR spectra were recorded on a 300 or 400 MHz spectrometer. High-resolution mass spectra (HRMS) were obtained by the ESI method from an LC/MSD TOF instrument. The infrared spectra (IR) were acquired on a FT-IR spectrometer. Palladium catalysts and other reagents were purchased from commercial vendors and used directly without further purification. Solvents were distilled with a proper drying reagent and stored in a molecular sieve.

Synthesis of Hypervalent Iodine(I^{3+}) Reagents. PhI($OPiv$)$_2$, PhI(O_2CPh)$_2$, PhI(O_2CBu)$_2$, and ArI(OAc)$_2$ were prepared according to the reported literature procedures.[15]

Synthesis of Starting Amides. Amides **1a**−**1i**, **1l**, **1n**, and **1p** were prepared by the reaction of corresponding acid chlorides with 8-

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aminoquinoline.[3b] Amide **1m** was synthesized by the condensation of 8-aminoquinoline with 4-(benzyl(*tert*-butoxycarbonylamino)-butanoic acid using EDCI and HOBt.[16a,b] Other amides were synthesized according to literature procedures.[16c]

***N*-(Quinolin-8-yl)butyramide (1a).** ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.80 (s, 1H), 9.00−8.59 (m, 2H), 8.16 (d, J = 1.6 Hz, 1H), 7.56−7.47 (m, 2H), 7.44 (dd, J = 8.3, 4.2 Hz, 1H), 2.54 (t, J = 7.5 Hz, 2H), 1.94−1.77 (m, 2H), 1.06 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ = 171.9, 148.2, 138.5, 136.5, 134.7, 128.1, 127.6, 121.7, 121.4, 116.5, 40.3, 19.3, 14.0. The spectral data of the compound (**1a**) were in accordance with those reported in the literature.[3b]

***N*-(Quinolin-8-yl)heptanamide (1b).** ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.80 (s, 1H), 8.95−8.64 (m, 2H), 8.14 (d, J = 8.3 Hz, 1H), 7.60−7.35 (m, 3H), 2.56 (t, J = 7.6 Hz, 2H), 1.88−1.71 (m, 2H), 1.38−1.32 (m, 6H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ = 172.1, 148.2, 138.5, 136.5, 134.7, 128.1, 127.6, 121.7, 121.4, 116.5, 77.5, 77.2, 76.8, 38.4, 31.7, 29.1, 25.8, 22.7, 14.2. The spectral data of the compound (**1b**) were in accordance with those reported in the literature.[3f]

***N*-(Quinolin-8-yl)stearamide (1c).** ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.81 (s, 1H), 8.93−8.68 (m, 2H), 8.16 (dd, J = 8.3, 1.4 Hz, 1H), 7.69−7.32 (m, 3H), 2.56 (t, J = 7.6 Hz, 2H), 1.87−1.73 (m, 2H), 1.48−1.18 (m, 28H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ = 172.1, 148.2, 138.5, 136.5, 134.8, 128.1, 127.6, 121.7, 121.4, 116.6, 38.5, 32.1, 29.8, 29.7, 29.6, 29.5, 29.5, 25.9, 22.8, 14.3; HRMS (ESI) m/z Calcd for $C_{27}H_{43}N_2O$ $(M + H)^+$: 411.3369, found: 411.3370; IR (neat, cm^{-1}) ν = 3289, 2920, 1675, 1530, 1474, 1326, 790.

3-(4-Bromophenyl)-*N*-(quinolin-8-yl)propanamide (1d). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.76 (s, 1H), 8.77 (d, J = 4.6 Hz, 2H), 8.14 (d, J = 8.3 Hz, 1H), 7.57−7.46 (m, 2H), 7.46−7.37 (m, 3H), 7.16 (d, J = 8.0 Hz, 2H), 3.09 (t, J = 7.6 Hz, 2H), 2.85 (t, J = 7.6 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ = 170.4, 148.2, 139.9, 138.4, 136.5, 134.4, 131.7, 130.3, 128.0, 127.5, 121.7, 121.7, 120.2, 116.6, 39.5, 30.9. The spectral data of the compound (**1d**) were in accordance with those reported in the literature.[16c]

4-Phenyl-*N*-(quinolin-8-yl)butanamide (1e). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.79 (s, 1H), 8.87−8.71 (m, 2H), 8.14 (d, J = 8.3 Hz, 1H), 7.60−7.37 (m, 3H), 7.36−7.12 (m, 5H), 2.77 (t, J = 7.5 Hz, 2H), 2.57 (t, J = 7.4 Hz, 2H), 2.22−2.07 (m, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ = 171.6, 148.2, 141.6, 138.4, 136.5, 134.6, 128.7, 128.5, 128.0, 127.5, 126.1, 121.7, 121.5, 116.6, 37.4, 35.3, 27.2. The spectral data of the compound (**1e**) were in accordance with those reported in the literature.[16c]

4-Methyl-*N*-(quinolin-8-yl)pentanamide (1f). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.81 (s, 1H), 8.90−8.73 (m, 2H), 8.15 (d, J = 8.2 Hz, 1H), 7.57−7.47 (m, 2H), 7.45 (dd, J = 8.2, 4.2 Hz, 1H), 2.78−2.33 (m, 2H), 1.85−1.49 (m, 3H), 0.98 (d, J = 5.9 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ = 172.2, 148.2, 138.5, 136.5, 134.7, 128.1, 127.6, 121.7, 121.4, 116.6, 36.4, 34.6, 28.0, 22.5. The spectral data of the compound (**1f**) were in accordance with those reported in the literature.[16b]

3-Cyclopentyl-*N*-(quinolin-8-yl)propanamide (1g). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.81 (s, 1H), 8.90−8.70 (m, 2H), 8.15 (d, J = 8.2 Hz, 1H), 7.58−7.47 (m, 2H), 7.44 (dd, J = 8.2, 4.2 Hz, 1H), 2.67−2.49 (m, 2H), 1.87 (m, 5H), 1.72−1.43 (m, 4H), 1.33−1.00 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ = 172.2, 148.2, 138.5, 136.5, 134.7, 128.1, 127.6, 121.7, 121.4, 116.6, 39.9, 37.7, 32.7, 32.0, 25.3. The spectral data of the compound (**1g**) were in accordance with those reported in the literature.[16d]

3-Cyclohexyl-*N*-(quinolin-8-yl)propanamide (1h). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.80 (s, 1H), 8.90−8.68 (m, 2H), 8.15 (dd, J = 8.3, 1.4 Hz, 1H), 7.51 (dt, J = 8.2, 7.5 Hz, 2H), 7.45 (dd, J = 8.3, 4.2 Hz, 1H), 2.64−2.51 (m, 2H), 1.87−1.58 (m, 7H), 1.42−1.31 (m, 1H), 1.31−1.11 (m, 3H), 1.04−0.89 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ = 172.3, 148.2, 138.5, 136.5, 134.8, 128.1, 127.6, 121.7, 121.4, 116.5, 37.5, 35.9, 33.3, 33.2, 26.7, 26.4. The spectral data of the compound (**1h**) were in accordance with those reported in the literature.[16c]

6-(Benzyloxy)-*N*-(quinolin-8-yl)hexanamide (1i). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.80 (s, 1H), 8.94−8.65 (m, 2H), 8.14 (dd, J = 8.3, 1.5 Hz, 1H), 7.56−7.46 (m, 2H), 7.43 (dd, J = 8.3, 4.2 Hz, 1H), 7.35−7.31 (m, 4H), 7.30−7.22 (m, 1H), 4.49 (s, 2H), 3.49 (t, J = 6.5 Hz, 2H), 2.57 (t, J = 7.6 Hz, 2H), 1.85 (dt, J = 15.3, 7.6 Hz, 2H), 1.71 (dt, J = 14.5, 6.7 Hz, 2H), 1.60−1.45 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ = 171.8, 148.2, 138.7, 138.4, 136.5, 134.7, 128.5, 128.1, 127.7, 127.6, 127.5, 121.7, 121.5, 116.5, 73.0, 70.3, 38.3, 29.7, 26.0, 25.6; HRMS (ESI) m/z Calcd for $C_{22}H_{25}N_2O_2$ $(M + H)^+$: 349.1910, found: 349.1910; IR (neat, cm^{-1}) ν = 3354, 2925, 1683, 1528, 1099, 796, 747.

6-((*tert*-Butyldimethylsilyl)oxy)-*N*-(quinolin-8-yl)hexanamide (1j). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 9.81 (s, 1H), 8.88−8.70 (m, 2H), 8.14 (dd, J = 8.1, 1.5 Hz, 1H), 7.58−7.42 (m, 3H), 3.63 (t, J = 6.3 Hz, 2H), 2.57 (t, J = 7.5 Hz, 2H), 1.90−1.75 (m, 2H), 1.66−1.56 (m, 2H), 1.53−1.42 (m, 2H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, ppm): δ = 171.9, 148.2, 138.5, 136.5, 134.7, 128.1, 127.6, 121.7, 121.4, 116.5, 63.1, 38.4, 32.7, 26.1, 25.7, 25.6, 18.5, −5.2; HRMS (ESI) m/z Calcd for $C_{21}H_{33}N_2O_2Si$ $(M + H)^+$: 373.2305, found: 373.2303; IR (neat, cm^{-1}) ν = 3440, 2925, 1634, 1520, 1475, 1258, 1095, 833, 780.

***tert*-Butyl (6-Oxo-6-(quinolin-8-ylamino)hexyl)carbamate (1k).** ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.79 (s, 1H), 8.78−8.66 (m, 2H), 8.14 (dd, J = 8.3, 1.5 Hz, 1H), 7.65−7.30 (m, 3H), 4.60 (br, 1H), 3.13 (d, J = 6.3 Hz, 2H), 2.55 (t, J = 7.5 Hz, 2H), 1.89−1.75 (m, 2H), 1.54 (dd, J = 14.4, 7.5 Hz, 2H), 1.48−1.35 (m, 11H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ = 171.7, 156.1, 148.2, 138.4, 136.5, 134.6, 128.1, 127.5, 121.7, 121.5, 116.5, 79.1, 40.5, 38.1, 30.0, 28.5, 26.6, 25.3; HRMS (ESI) m/z Calcd for $C_{20}H_{28}N_3O_3$ $(M + H)^+$: 358.2125, found: 358.2126; IR (neat, cm^{-1}) ν = 3353, 2933, 1697, 1533, 1378, 1325, 1256, 1169, 787.

6-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)hexanamide (1l). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.78 (s, 1H), 8.87−8.66 (m, 2H), 8.14 (d, J = 8.3 Hz, 1H), 7.81 (dt, J = 6.7, 3.4 Hz, 2H), 7.73−7.64 (m, 2H), 7.55−7.39 (m, 3H), 3.70 (t, J = 7.2 Hz, 2H), 2.56 (t, J = 7.5 Hz, 2H), 1.93−1.68 (m, 4H), 1.56−1.43 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ = 171.6, 168.5, 148.2, 138.4, 136.5, 134.6, 134.0, 132.3, 128.0, 127.5, 123.3, 121.7, 121.5, 116.5, 38.0, 38.0, 28.6, 26.7, 25.3. The spectral data of the compound (**1l**) were in accordance with those reported in the literature.[16d]

***tert*-Butyl Benzyl(4-oxo-4-(quinolin-8-ylamino)butyl)-carbamate (1m).** ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.79 (s, 1H), 8.98−8.61 (m, 2H), 8.14 (d, J = 8.0 Hz, 1H), 7.56−7.47 (m, 2H), 7.44 (dd, J = 8.2, 4.2 Hz, 1H), 7.35−7.15 (m, 5H), 4.48 (s, 2H), 3.45−3.20 (m, 2H), 2.65−2.40 (m, 2H), 2.15−1.90 (m, 2H), 1.44 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ = 171.2, 171.1, 156.1, 148.2, 138.5, 136.4, 134.6, 128.59, 128.1, 127.8, 127.5, 127.3, 121.7, 121.5, 116.6, 79.9, 50.5, 50.1, 46.0, 35.3, 28.5, 24.0. The spectral data of the compound (**1m**) were in accordance with those reported in the literature.[16b]

Methyl 6-Oxo-6-(quinolin-8-ylamino)hexanoate (1n). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.80 (s, 1H), 8.90−8.70(m, 5.7 Hz, 2H), 8.15 (d, J = 8.3 Hz, 1H), 7.57−7.41 (m, 3H), 3.66 (s, 3H), 2.58 (t, J = 7.2 Hz, 2H), 2.40 (t, J = 7.2 Hz, 2H), 1.92−1.71 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ = 174.0, 171.3, 148.3, 138.4, 136.5, 134.6, 128.1, 127.6, 121.7, 121.5, 116.6, 51.7, 37.8, 34.0, 25.2, 24.7. The spectral data of the compound (**1n**) were in accordance with those reported in the literature.[16b]

(*R*)-*N*-(Quinolin-8-yl)-4-((3*R*,5*S*,7*R*,8*R*,9*S*,10*S*,12*S*,13*R*,-14*S*,17*R*)-3,7,12-trimethoxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)pentanamide (1o). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.81 (s, 1H), 8.95−8.59 (m, 2H), 8.15 (dd, J = 8.2, 1.3 Hz, 1H), 7.64−7.34 (m, 3H), 3.38 (s, 1H), 3.33 (s, 3H), 3.27 (s, 3H), 3.21 (s, 3H), 3.14 (d, J = 2.5 Hz, 1H), 3.04−2.93 (m, 1H), 2.61 (dd, J = 10.3, 4.8 Hz, 1H), 2.47 (dd, J = 10.6, 4.2 Hz, 1H), 2.28−1.86 (m, 6H), 1.86−1.40 (m, 11H), 1.38−1.11 (m, 5H), 1.09−0.78 (m, 9H), 0.67 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ = 172.6, 148.2, 138.5, 136.5, 134.8, 128.1, 127.6, 121.7, 121.3, 116.5, 82.2, 80.9, 56.0, 55.8, 55.5, 46.5, 46.3, 42.8, 42.1, 39.8, 35.4, 35.3, 35.1, 35.0, 34.6, 31.7, 28.1, 27.9, 27.6, 26.9, 23.3, 23.0,

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22.1, 17.7, 12.7; HRMS (ESI) m/z Calcd for $C_{36}H_{53}N_2O_4$ $(M + H)^+$: 577.3999, found: 577.3997; IR (neat, cm^{-1}) ν = 3354, 2932, 1692, 1529, 1467, 1376, 1097, 912, 734.

***N*-(Quinolin-8-yl)propionamide (1p).** ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.82 (s, 1H), 8.79 (d, J = 7.3 Hz, 2H), 8.14 (d, J = 8.2 Hz, 1H), 7.58−7.41 (m, 3H), 2.60 (q, J = 7.6 Hz, 2H), 1.34 (t, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ = 172.6, 148.2, 138.5, 136.5, 134.7, 128.1, 127.6, 121.7, 121.4, 116.5, 31.4, 9.9. The spectral data of the compound (**1p**) were in accordance with those reported in the literature.[5]

***N*-(2-(Pyridin-2-yl)propan-2-yl)butyramide (II).** ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 8.49 (d, J = 4.9 Hz, 1H), 7.78−7.62 (m, 2H), 7.39 (d, J = 8.1 Hz, 1H), 7.21−7.08 (m, 1H), 2.22 (t, J = 7.5 Hz, 2H), 1.74 (s, 6H), 1.72−1.62 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ = 172.4, 164.8, 147.7, 137.2, 121.9, 119.6, 56.5, 39.8, 27.7, 19.3, 13.8. The spectral data of the compound (**II**) were in accordance with those reported in the literature.[16e]

***N*-(Perfluorophenyl)butyramide (III).** ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.61 (s, 1H), 2.39 (t, J = 7.2 Hz, 2H), 1.78−1.66 (m, 2H), 1.06−0.91 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ = 172.4, 144.4, 142.0, 141.5, 139.1, 139.0, 136.6, 112.0, 111.9, 38.1, 19.1, 13.5; HRMS (ESI) m/z Calcd for $C_{10}H_9NOF_5$ $(M + H)^+$: 254.0598, found: 254.0594; IR (neat, cm^{-1}) ν = 3259, 2976, 1689, 1495, 1205, 1009, 951, 680.

***N*-(2-(Methylthio)phenyl)butyramide (IV).** ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 8.35−8.25 (m, 2H), 7.46 (d, J = 7.7 Hz, 1H), 7.30−7.24 (m, 1H), 7.04 (t, J = 7.6 Hz, 1H), 2.40 (dd, J = 10.0, 4.8 Hz, 2H), 2.36 (s, 3H), 1.84−1.72 (m, 2H), 1.02 (t, J = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ = 171.4, 138.4, 132.9, 128.9, 125.2, 124.3, 120.7, 40.1, 19.2, 19.0, 13.8; HRMS (ESI) m/z Calcd for $C_{11}H_{16}NOS$ $(M + H)^+$: 210.0947, found: 210.0949; IR (neat, cm^{-1}) ν = 3289, 2962, 1679, 1516, 1434, 1295, 1184, 1080, 965, 751, 668.

***N*-Methyl-*N*-(quinolin-8-yl)butyramide (V).** ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 8.91 (d, J = 2.2 Hz, 1H), 8.17 (d, J = 8.2 Hz, 1H), 7.80 (d, J = 7.5 Hz, 1H), 7.57−7.45 (m, 2H), 7.41 (dd, J = 8.2, 4.1 Hz, 1H), 3.34 (s, 3H), 2.00−1.71 (m, 2H), 1.59−1.55(m, 2H), 0.67 (t, J = 6.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ = 174.0, 151.0, 144.4, 141.8, 136.3, 129.5, 128.7, 128.3, 126.5, 121.9, 37.3, 36.0, 18.8, 13.8; HRMS (ESI) m/z Calcd for $C_{14}H_{17}N_2O$ $(M + H)^+$: 229.1335, found: 229.1336; IR (neat, cm^{-1}) ν = 2946, 1654, 1478, 1385, 1259, 1133, 1072, 792, 637.

***N*-(Naphthalen-1-yl)butyramide (VI).** ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.89−7.80 (m, 3H), 7.68 (d, J = 8.0 Hz, 1H), 7.61 (s, 1H), 7.50−7.38 (m, 3H), 2.46 (t, J = 6.8 Hz, 2H), 1.86−1.79 (m, 2H), 1.06 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ = 172.0, 134.3, 132.5, 128.9, 127.4, 126.4, 126.1, 125.9, 121.3, 120.8, 39.7, 19.5, 14.0; HRMS (ESI) m/z Calcd for $C_{14}H_{16}NO$ $(M + H)^+$: 214.1226, found: 214.1224; IR (neat, cm^{-1}) ν = 2946, 1654, 1478, 1385, 1259, 1133, 1072, 792, 637.

3-Phenyl-*N*-(quinolin-8-yl)propanamide-D. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.79 (s, 1H), 8.78 (t, J = 6.0 Hz, 2H), 8.15 (d, J = 8.3 Hz, 1H), 7.59−7.47 (m, 2H), 7.44 (dd, J = 8.2, 4.2 Hz, 1H), 7.30 (d, J = 4.2 Hz, 4H), 7.20 (dd, J = 8.6, 4.3 Hz, 1H), 3.13 (t, J = 7.7 Hz, 1H), 2.88 (d, J = 7.9 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ = 170.9, 148.2, 140.9, 138.5, 136.5, 134.6, 128.7, 128.6, 128.1, 127.6, 126.4, 121.7, 121.6, 116.7, 39.8, 31.5, 31.3, 31.1; HRMS (ESI) m/z Calcd for $C_{18}H_{16}DN_2O$ $(M + H)^+$: 278.1413, found: 278.1410; IR (neat, cm^{-1}) ν = 3452, 2357, 1679, 1634, 1528, 1385, 747.

3-Phenyl-*N*-(quinolin-8-yl)propanamide-3,3-D2. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.80 (s, 1H), 8.85−8.71 (m, 2H), 8.15 (dd, J = 8.3, 1.5 Hz, 1H), 7.59−7.39 (m, 3H), 7.31 (m, 4H), 7.21 (m, 1H), 2.88 (s, 2H).; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ = 170.9, 148.2, 140.8, 138.4, 136.5, 134.6, 128.7, 128.5, 128.1, 127.6, 126.4, 121.7, 121.6, 116.6, 39.7; HRMS (ESI) m/z Calcd for $C_{18}H_{15}D_2N_2O$ $(M + H)^+$: 279.1491, found: 279.1491.

General Synthetic Procedure of Arylation. A 10 mL Teflon-capped vial was charged with **1** (0.2 mmol), $PdCl_2(CH_3CN)_2$ (10 mol %), **2** (0.5 mmol), $CsCO_3$ (0.8 mmol), and mesitylene (1.0 mL) under an air atmosphere. The vial was then tightly capped. The mixture was stirred at room temperature for 1 min for proper mixing of the reactants, and then heated at 110 °C with vigorous stirring. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a small pad of Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (EtOAc/petroleum ether) to afford the desired product **3**.

3-Phenyl-*N*-(quinolin-8-yl)butanamide (3aa). The title compound **3aa** was prepared according to the general procedure as a colorless oil (50.0 mg, 86%); R_f = 0.50 (EtOAc/petroleum ether 1:5); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.66 (s, 1H), 8.69 (m, 2H), 8.06 (dd, J = 8.3, 1.4 Hz, 1H), 7.40 (m, 3H), 7.29−7.19 (m, 4H), 7.11 (dd, J = 9.3, 4.4 Hz, 1H), 3.51−3.35 (m, 1H), 2.82 (dd, J = 14.5, 6.6 Hz, 1H), 2.69 (dd, J = 14.5, 8.3 Hz, 1H), 1.34 (d, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ = 170.5, 148.2, 146.1, 138.4, 136.4, 134.6, 128.7, 128.0, 127.5, 127.0, 126.5, 121.7, 121.5, 116.6, 47.0, 37.0, 21.9. The spectral data of the compound (**3aa**) were in accordance with those reported in the literature.[7e]

3-(4-Fluorophenyl)-*N*-(quinolin-8-yl)butanamide (3ab). The title compound **3ab** was prepared according to the general procedure as a colorless oil (44.4 mg, 72%); R_f = 0.62 (EtOAc/petroleum ether 1:5); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.69 (s, 1H), 8.74 (d, J = 7.9 Hz, 2H), 8.12 (d, J = 8.3 Hz, 1H), 7.54−7.35 (m, 3H), 7.27 (dd, J = 8.4, 5.7 Hz, 2H), 6.97 (t, J = 8.7 Hz, 2H), 3.48 (dd, J = 14.3, 7.1 Hz, 1H), 2.79 (qd, J = 14.5, 7.4 Hz, 2H), 1.39 (d, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ = 170.2, 161.6 (d, J = 242.4 Hz), 148.2, 141.6, 138.3, 136.4, 134.4, 128.4 (d, J = 7.7 Hz), 128.0, 127.5, 121.7, 121.6, 116.5, 115.4 (d, J = 21.0 Hz), 47.1, 36.3, 22.1. The spectral data of the compound (**3ab**) were in accordance with those reported in the literature.[7e]

3-(4-Chlorophenyl)-*N*-(quinolin-8-yl)butanamide (3ac). The title compound **3ac** was prepared according to the general procedure as a colorless oil (46.0 mg, 71%); R_f = 0.65 (EtOAc/petroleum ether 1:5); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.68 (s, 1H), 8.86−8.63 (m, 2H), 8.10 (dd, J = 8.2, 1.3 Hz, 1H), 7.58−7.36 (m, 3H), 7.25 (d, J = 8.3 Hz, 4H), 3.55−3.40 (m, 1H), 2.78 (qd, J = 14.6, 7.4 Hz, 2H), 1.37 (d, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ = 170.0, 148.2, 144.4, 138.3, 136.4, 134.4, 132.1, 128.8, 128.4, 128.0, 127.4, 121.7, 121.6, 116.5, 46.8, 36.4, 21.9. The spectral data of the compound (**3ac**) were in accordance with those reported in the literature.[7b]

3-(4-Bromophenyl)-*N*-(quinolin-8-yl)butanamide (3ad). The title compound **3ad** was prepared according to the general procedure as a colorless oil (60.4 mg, 82%); R_f = 0.63 (EtOAc/petroleum ether 1:5); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.69 (s, 1H), 8.82−8.65 (m, 2H), 8.13 (dd, J = 8.3, 1.3 Hz, 1H), 7.58−7.33 (m, 5H), 7.20 (d, J = 8.4 Hz, 2H), 3.46 (h, J = 7.1 Hz, 1H), 2.79 (qd, J = 14.6, 7.4 Hz, 2H), 1.38 (d, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ = 170.0, 148.2, 145.0, 138.3, 136.4, 134.4, 131.8, 128.8, 128.0, 127.5, 121.7, 121.6, 120.2, 116.6, 46.8, 36.5, 21.9. The spectral data of the compound (**3ad**) were in accordance with those reported in the literature.[7b]

3-(4-Cyanophenyl)-*N*-(quinolin-8-yl)butanamide (3ae). The title compound **3ae** was prepared according to the general procedure as a light yellow oil (45.4 mg, 72%); R_f = 0.42 (EtOAc/petroleum ether 1:5); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.69 (s, 1H), 8.83−8.65 (m, 2H), 8.13 (d, J = 8.3 Hz, 1H), 7.56 (d, J = 8.2 Hz, 2H), 7.53−7.46 (m, 2H), 7.43 (dd, J = 12.1, 6.2 Hz, 3H), 3.55 (dd, J = 14.2, 7.1 Hz, 1H), 2.91−2.74 (m, 2H), 1.40 (d, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ = 169.5, 151.5, 148.2, 138.3, 136.5, 134.2, 132.5, 128.0, 127.9, 127.4, 121.7, 121.8, 119.0, 116.6, 110.4, 46.2, 37.0, 21.6. The spectral data of the compound (**3ae**) were in accordance with those reported in the literature.[7e]

***N*-(Quinolin-8-yl)-3-(4-(trifluoromethyl)phenyl)butanamide (3af).** The title compound **3af** was prepared according to the general procedure as a colorless oil (53.7 mg, 75%); R_f = 0.51 (EtOAc/petroleum ether 1:5); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.60 (s, 1H), 8.72−8.56 (m, 2H), 8.03 (d, J = 8.2 Hz, 1H), 7.60−7.35 (m,

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7H), 3.70−3.50 (m, 1H), 2.74 (qd, J = 14.6, 7.4 Hz, 2H), 1.33 (d, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ = 169.8, 150.1, 148.2, 138.4, 136.5, 134.4, 128.8 (q, J = 32.0 Hz), 128.0, 127.5, 127.4, 125.7, 121.7, 116.6, 46.5, 36.8, 21.8. The spectral data of the compound (**3af**) were in accordance with those reported in the literature.[7e]

Methyl 4-(4-Oxo-4-(quinolin-8-ylamino)butan-2-yl)benzoate (3ag). The title compound **3ag** was prepared according to the general procedure as a colorless oil (59.2 mg, 85%); R_f = 0.32 (EtOAc/petroleum ether 1:5); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.71 (s, 1H), 8.79−8.68 (m, 2H), 8.13 (dd, J = 8.3, 1.5 Hz, 1H), 7.97 (d, J = 8.3 Hz, 2H), 7.54−7.37 (m, 5H), 3.88 (s, 3H), 3.56 (dd, J = 14.3, 7.1 Hz, 1H), 2.84 (ddd, J = 22.5, 14.6, 7.4 Hz, 2H), 1.42 (d, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ = 169.9, 167.1, 151.5, 148.2, 138.4, 136.5, 134.4, 130.1, 128.5, 128.0, 127.5, 127.1, 121.7, 121.7, 116.6, 52.1, 46.6, 37.0, 21.8. The spectral data of the compound (**3ag**) were in accordance with those reported in the literature.[7b]

3-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)butanamide (3ah). The title compound **3ah** was prepared according to the general procedure as a colorless oil (44.8 mg, 70%); R_f = 0.40 (EtOAc/petroleum ether 1:5); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.70 (s, 1H), 8.83−8.69 (m, 2H), 8.11 (d, J = 8.2 Hz, 1H), 7.56−7.36 (m, 3H), 7.24 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 3.74 (s, 3H), 3.45 (dd, J = 14.3, 7.1 Hz, 1H), 2.79 (ddd, J = 22.4, 14.4, 7.4 Hz, 2H), 1.38 (d, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ = 170.6, 158.2, 148.1, 138.4, 138.1, 136.4, 134.5, 128.0, 127.9, 127.5, 121.6, 121.5, 116.5, 114.1, 55.3, 47.3, 36.2, 22.1. The spectral data of the compound (**3ah**) were in accordance with those reported in the literature.[7e]

***N*-(Quinolin-8-yl)-3-(*p*-tolyl)butanamide (3ai).** The title compound **3ai** was prepared according to the general procedure as a yellow oil (38.9 mg, 64%); R_f = 0.60 (EtOAc/petroleum ether 1:5); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.75 (s, 1H), 8.78 (t, J = 6.3 Hz, 2H), 8.12 (d, J = 8.2 Hz, 1H), 7.58−7.36 (m, 3H), 7.29−7.19 (m, 2H), 7.13 (d, J = 7.8 Hz, 2H), 3.49 (dd, J = 14.4, 7.1 Hz, 1H), 2.83 (ddd, J = 22.7, 14.5, 7.5 Hz, 2H), 2.31 (s, 3H), 1.41 (d, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ = 170.5, 148.1, 143.0, 138.4, 136.4, 135.9, 134.5, 129.4, 128.0, 127.5, 126.8, 121.6, 121.5, 116.5, 47.1, 36.6, 22.0, 21.1. The spectral data of the compound (**3ai**) were in accordance with those reported in the literature.[7e]

3-(3-Bromophenyl)-*N*-(quinolin-8-yl)butanamide (3aj). The title compound **3aj** was prepared according to the general procedure as a colorless oil (64.8 mg, 88%); R_f = 0.50 (EtOAc/petroleum ether 1:5); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.72 (s, 1H), 8.76 (ddd, J = 8.6, 5.7, 1.4 Hz, 2H), 8.12 (dd, J = 8.3, 1.4 Hz, 1H), 7.55−7.39 (m, 4H), 7.35−7.21 (m, 2H), 7.14 (t, J = 7.8 Hz, 1H), 3.53−3.40 (m, 1H), 2.80 (ddd, J = 22.6, 14.6, 7.4 Hz, 2H), 1.39 (d, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ = 169.9, 148.4, 148.2, 138.4, 136.4, 134.4, 130.3, 130.0, 129.6, 128.0, 127.4, 125.9, 122.8, 121.7, 121.6, 116.6, 46.6, 36.7, 21.8; HRMS (ESI) m/z Calcd for $C_{19}H_{17}N_2ONaBr$ $(M + Na)^+$: 391.0416, found: 391.0416; IR (neat, cm^{-1}) ν = 3349, 2962, 1684, 1526, 1479, 1380, 1326, 1163, 789, 693.

3-(3-Chlorophenyl)-*N*-(quinolin-8-yl)butanamide (3ak). The title compound **3ak** was prepared according to the general procedure as a colorless oil (49.9 mg, 77%); R_f = 0.60 (EtOAc/petroleum ether 1:5); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.72 (s, 1H), 8.76 (dd, J = 9.4, 5.0 Hz, 2H), 8.11 (dd, J = 8.2, 1.1 Hz, 1H), 7.46 (m, 3H), 7.32 (s, 1H), 7.23−7.11 (m, 3H), 3.48 (dd, J = 14.4, 7.1 Hz, 1H), 2.80 (ddd, J = 22.6, 14.6, 7.4 Hz, 2H), 1.39 (d, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ = 169.9, 148.2, 148.1, 138.3, 136.4, 134.5, 134.4, 130.0, 128.0, 127.4, 127.1, 126.7, 125.4, 121.7, 121.6, 116.5, 46.6, 36.7, 21.8; HRMS (ESI) m/z Calcd for $C_{19}H_{17}N_2ONaCl$ $(M + Na)^+$: 347.0921, found: 347.0923; IR (neat, cm^{-1}) ν = 3348, 2963, 1684, 1526, 1479, 790, 693.

Methyl 3-(4-Oxo-4-(quinolin-8-ylamino)butan-2-yl)benzoate (3al). The title compound **3al** was prepared according to the general procedure as a light yellow oil (47.4 mg, 74%); R_f = 0.30 (EtOAc/petroleum ether 1:5); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.71 (s, 1H), 8.80−8.68 (m, 2H), 8.11 (d, J = 8.2 Hz, 1H), 8.02 (s, 1H), 7.86 (d, J = 7.7 Hz, 1H), 7.55−7.39 (m, 4H), 7.35 (t, J = 7.7 Hz, 1H), 3.89 (s, 3H), 3.56 (dd, J = 14.4, 7.1 Hz, 1H), 2.85 (ddd, J = 22.6, 14.6, 7.4 Hz, 2H), 1.43 (d, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ = 170.0, 167.3, 148.2, 146.4, 138.4, 136.4, 134.4, 132.0, 130.6, 128.8, 128.0, 127.9, 127.8, 127.4, 121.7, 121.6, 116.6, 52.2, 46.7, 36.8, 21.9; HRMS (ESI) m/z Calcd for $C_{21}H_{21}N_2O_3$ $(M + H)^+$: 349.1546, found: 349.1551; IR (neat, cm^{-1}) ν = 3349, 2958, 1715, 1679, 1529, 1283, 1198, 754, 695.

***N*-(Quinolin-8-yl)-3-(*m*-tolyl)butanamide (3am).** The title compound **3am** was prepared according to the general procedure as a colorless oil (36.5 mg, 60%); R_f = 0.58 (EtOAc/petroleum ether 1:5); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.74 (s, 1H), 8.77 (dd, J = 6.5, 4.0 Hz, 2H), 8.13 (dd, J = 8.3, 1.4 Hz, 1H), 7.58−7.37 (m, 3H), 7.25−7.08 (m, 3H), 7.01 (d, J = 7.3 Hz, 1H), 3.47 (m, 1H), 2.90 (dd, J = 14.5, 6.5 Hz, 1H), 2.76 (dd, J = 14.5, 8.4 Hz, 1H), 2.33 (s, 3H), 1.41 (d, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ = 170.6, 148.1, 146.0, 138.4, 138.2, 136.4, 134.6, 128.6, 128.0, 127.8, 127.5, 127.3, 123.9, 121.6, 121.5, 116.5, 47.0, 36.9, 22.0, 21.6. The spectral data of the compound (**3am**) were in accordance with those reported in the literature.[7b]

3-(2-Fluorophenyl)-*N*-(quinolin-8-yl)butanamide (3an). The title compound **3an** was prepared according to the general procedure as a colorless oil (30.8 mg, 50%); R_f = 0.59 (EtOAc/petroleum ether 1:5); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.78 (s, 1H), 8.77 (t, J = 6.0 Hz, 2H), 8.13 (d, J = 8.2 Hz, 1H), 7.54−7.39 (m, 3H), 7.32 (t, J = 7.5 Hz, 1H), 7.17 (dd, J = 13.7, 6.5 Hz, 1H), 7.11−6.98 (m, 2H), 3.84−3.71 (m, 1H), 2.90 (ddd, J = 23.1, 14.7, 7.4 Hz, 2H), 1.44 (d, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ = 170.2, 161.0 (d, J = 243.8 Hz), 148.2, 138.4, 136.4, 134.5, 132.6 (d, J = 14.0 Hz), 128.5, 128.5, 128.0, 127.9, 127.5, 124.4, 121.7, 121.5, 116.6, 115.8 (d, J = 22.3 Hz), 45.0, 31.3, 20.6. The spectral data of the compound (**3an**) were in accordance with those reported in the literature.[7b]

3-(3,5-Difluorophenyl)-*N*-(quinolin-8-yl)butanamide (3ao). The title compound **3ao** was prepared according to the general procedure as a colorless oil (48.9 mg, 75%); R_f = 0.58 (EtOAc/petroleum ether 1:5); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.72 (s, 1H), 8.79−8.89 (m, 2H), 8.12 (d, J = 8.2 Hz, 1H), 7.55−7.34 (m, 3H), 6.92−6.78 (m, 2H), 6.61 (tt, J = 8.9, 2.2 Hz, 1H), 3.59−3.40 (m, 1H), 2.79 (ddd, J = 37.3, 14.7, 7.4 Hz, 2H), 1.38 (d, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ = 169.6, 163.3 (dd, J = 246.4, 12.8 Hz), 150.1 (t, J = 8.3 Hz), 148.2, 138.3, 136.4, 134.3, 128.0, 127.4, 121.7, 116.6, 109.9 (d, J = 24.6 Hz), 101.9 (t, J = 25.2 Hz), 46.3, 36.7, 21.6; HRMS (ESI) m/z Calcd for $C_{19}H_{16}N_2OF_2Na$ $(M + Na)^+$: 349.1122, found: 349.1120; IR (neat, cm^{-1}) ν = 3348, 2954, 1685, 1528, 1478, 1323,1116, 988.

3-(4-Bromo-3-fluorophenyl)-*N*-(quinolin-8-yl)butanamide (3ap). The title compound **3ap** was prepared according to the general procedure as a colorless oil (63.3 mg, 82%); R_f = 0.45 (EtOAc/petroleum ether 1:5); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.68 (s, 1H), 8.74 (dd, J = 18.5, 5.4 Hz, 2H), 8.13 (d, J = 8.2 Hz, 1H), 7.58−7.36 (m, 4H), 7.10 (d, J = 9.8 Hz, 1H), 6.99 (d, J = 7.6 Hz, 1H), 3.56−3.40 (m, 1H), 2.79 (qd, J = 14.6, 7.4 Hz, 2H), 1.39 (d, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ = 169.7, 159.3 (d, J = 245.5 Hz), 148.3, 148.0 (d, J = 6.1 Hz), 138.4, 136.5, 134.3, 133.6, 128.0, 127.5, 124.1, 121.7, 116.6, 115.1 (d, J = 21.9 Hz), 106.6 (d, J = 20.8 Hz), 46.6, 36.5, 21.8; HRMS (ESI) m/z Calcd for $C_{19}H_{17}N_2OFBr$ $(M + H)^+$: 387.0502, found: 387.0500; IR (neat, cm^{-1}) ν = 3348, 2964, 1684, 1528, 1479, 1161, 753, 695.

3-Phenyl-*N*-(quinolin-8-yl)heptanamide (3ba). The title compound **3ba** was prepared according to the general procedure as a colorless oil (51.8 mg, 78%); R_f = 0.61 (EtOAc/petroleum ether 1:5); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.67 (s, 1H), 8.79−8.68 (m, 2H), 8.10 (d, J = 8.2 Hz, 1H), 7.55−7.36 (m, 3H), 7.32−7.25 (m, 4H), 7.21−7.09 (m, 1H), 3.29 (dq, J = 9.4, 7.4 Hz, 1H), 2.93−2.75 (m, 2H), 1.85−1.63 (m, 2H), 1.37−1.07 (m, 5H), 0.82 (t, J = 7.0 Hz, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ = 170.5, 148.1, 144.5, 138.4, 136.4, 134.5, 128.6, 127.8, 127.5, 126.5, 121.5, 116.5, 77.5, 77.2, 76.8, 46.0, 42.7, 36.1, 29.7, 22.8, 14.1; HRMS (ESI) m/z Calcd for $C_{22}H_{25}N_2O$ $(M + H)^+$: 333.1961, found: 333.1967; IR (neat, cm^{-1}) ν = 3351, 2928, 1678, 1526, 1481, 1325, 1136, 760.

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3-Phenyl-*N*-(quinolin-8-yl)octadecanamide (3ca). The title compound **3ca** was prepared according to the general procedure as a white solid (81.7 mg, 84%); R_f = 0.60 (EtOAc/petroleum ether 1:5); mp 53−55 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.68 (s, 1H), 8.75 (dd, J = 8.8, 4.5 Hz, 2H), 8.12 (d, J = 8.3 Hz, 1H), 7.54−7.44 (m, 2H), 7.45−7.39 (m, 1H), 7.29 (d, J = 4.5 Hz, 4H), 7.21−7.13 (m, 1H), 3.48−3.12 (m, 1H), 2.93−2.68 (m, 2H), 1.94−1.49 (m, 2H), 1.22 (d, J = 23.3 Hz, 28H), 0.88 (t, J = 6.7 Hz, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ = 170.5, 148.1, 144.6, 138.4, 136.4, 134.6, 128.6, 128.0, 127.7, 127.5, 126.5, 121.6, 121.4, 116.5, 46.0, 42.8, 36.4, 32.1, 29.8, 29.7, 29.6, 29.5, 27.6, 22.8, 14.3; HRMS (ESI) m/z Calcd for $C_{33}H_{47}N_2O$ $(M + H)^+$: 487.3682, found: 487.3682; IR (neat, cm^{-1}) ν = 3355, 2917, 1687, 1528, 1474, 756, 699.

3-(4-Bromophenyl)-3-phenyl-*N*-(quinolin-8-yl)propanamide (3da). The title compound **3da** was prepared according to the general procedure as a colorless oil (55.9 mg, 65%); R_f = 0.67 (EtOAc/petroleum ether 1:5); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.74 (s, 1H), 8.83−8.60 (m, 2H), 8.12 (d, J = 8.0 Hz, 1H), 7.51−7.36 (m, 5H), 7.33−7.26 (m, 4H), 7.21 (d, J = 8.3 Hz, 3H), 4.74 (t, J = 7.7 Hz, 1H), 3.29 (t, J = 7.9 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ = 169.3, 148.2, 143.3, 142.9, 138.3, 136.4, 134.3, 131.8, 129.7, 128.9, 128.0, 127.8, 127.5, 126.9, 121.7, 120.5, 116.7, 46.7, 44.3; HRMS (ESI) m/z Calcd for $C_{24}H_{19}N_2ONaBr$ $(M + Na)^+$: 453.0572, found: 453.0571; IR (neat, cm^{-1}) ν = 3301, 1662, 1523, 1332, 1140, 968, 690.

3,4-Diphenyl-*N*-(quinolin-8-yl)butanamide (3ea). The title compound **3ea** was prepared according to the general procedure as a colorless oil (43.9 mg, 60%); R_f = 0.55 (EtOAc/petroleum ether 1:5); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.67 (s, 1H), 8.87−8.61 (m, 2H), 8.09 (d, J = 8.2 Hz, 1H), 7.57−7.29 (m, 3H), 7.33−7.03 (m, 10H), 3.65 (p, J = 7.4 Hz, 1H), 3.15−2.79 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ = 170.2, 148.1, 143.6, 139.7, 138.3, 136.4, 134.4, 129.4, 128.5, 128.3, 127.9, 127.8, 127.4, 126.6, 126.2, 121.6, 121.5, 116.5, 44.2, 44.0, 43.0. The spectral data of the compound (**3ea**) were in accordance with those reported in the literature.[7b]

4-Methyl-3-phenyl-*N*-(quinolin-8-yl)pentanamide (3fa). The title compound **3fa** was prepared according to the general procedure as a light yellow oil (47.7 mg, 75%); R_f = 0.47 (EtOAc/petroleum ether 1:5); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.64 (s, 1H), 8.70 (dd, J = 32.0, 5.4 Hz, 2H), 8.10 (d, J = 8.2 Hz, 1H), 7.54−7.36 (m, 3H), 7.25 (dd, J = 8.4, 5.3 Hz, 5H), 7.13 (dd, J = 7.2, 4.9 Hz, 1H), 3.16−2.99 (m, 2H), 2.85 (dd, J = 14.6, 9.4 Hz, 1H), 1.99 (dq, J = 13.5, 6.7 Hz, 1H), 1.02 (d, J = 6.7 Hz, 3H), 0.83 (d, J = 6.7 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ = 170.9, 148.1, 143.0, 138.4, 136.4, 134.6, 128.5, 128.3, 128.0, 127.5, 126.4, 121.6, 121.4, 116.5, 49.2, 42.4, 33.3, 21.0, 20.3. The spectral data of the compound (**3fa**) were in accordance with those reported in the literature.[7b]

3-Cyclopentyl-3-phenyl-*N*-(quinolin-8-yl)propanamide (3ga). The title compound **3ga** was prepared according to the general procedure as a colorless oil (57.1 mg, 83%); R_f = 0.48 (EtOAc/petroleum ether 1:5); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.57 (s, 1H), 8.69 (dd, J = 23.7, 5.5 Hz, 2H), 8.08 (d, J = 8.2 Hz, 1H), 7.51−7.34 (m, 3H), 7.33−7.18 (m, 5H), 7.11 (t, J = 7.2 Hz, 1H), 3.19−2.98 (m, 2H), 2.83 (dd, J = 14.4, 9.7 Hz, 1H), 2.28−2.07 (m, 1H), 1.95 (dt, J = 14.6, 5.6 Hz, 1H), 1.74−1.62 (m, 1H), 1.57 (dt, J = 8.4, 5.3 Hz, 2H), 1.50−1.32 (m, 3H), 1.17−0.97 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ = 170.7, 148.0, 144.4, 138.3, 136.4, 134.6, 128.5, 128.1, 128.0, 127.5, 126.4, 121.6, 121.3, 116.5, 48.5, 46.5, 44.8, 31.6, 31.5, 25.5, 25.1. The spectral data of the compound (**3ga**) were in accordance with those reported in the literature.[7b]

3-Cyclohexyl-3-phenyl-*N*-(quinolin-8-yl)propanamide (3ha). The title compound **3ha** was prepared according to the general procedure as a white solid (56.6 mg, 79%); R_f = 0.50 (EtOAc/petroleum ether 1:5); mp 75−76 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.63 (s, 1H), 8.81−8.61 (m, 2H), 8.10 (d, J = 8.2 Hz, 1H), 7.50−7.37 (m, 3H), 7.25 (d, J = 4.4 Hz, 4H), 7.13 (dd, J = 8.6, 4.3 Hz, 1H), 3.10 (ddd, J = 26.8, 14.5, 5.7 Hz, 2H), 2.83 (dd, J = 14.6, 9.1 Hz, 1H), 1.92 (d, J = 12.5 Hz, 1H), 1.75 (d, J = 13.0 Hz, 1H), 1.68−1.50 (m,4H), 1.33−0.96 (m, 4H), 0.94−0.81 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ = 170.9, 148.0, 143.3, 138.4, 136.4, 134.6, 128.5, 128.3, 128.0, 127.5, 126.4, 121.6, 121.3, 116.5, 48.5, 43.2, 42.2, 31.3, 30.8, 26.7, 26.6, 26.6; HRMS (ESI) m/z Calcd for $C_{24}H_{27}N_2O$ $(M + H)^+$: 359.2117, found: 359.2115; IR (neat, cm^{-1}) ν = 335, 2924, 1684, 1527, 1383, 1157, 754, 699.

6-(Benzyloxy)-3-phenyl-*N*-(quinolin-8-yl)hexanamide (3ia). The title compound **3ia** was prepared according to the general procedure as a yellow oil (61.1 mg, 72%); R_f = 0.51 (EtOAc/petroleum ether 1:5); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.68 (s, 1H), 8.73 (dt, J = 7.9, 4.0 Hz, 2H), 8.10 (d, J = 8.2 Hz, 1H), 7.52−7.37 (m, 3H), 7.32−7.20 (m, 9H), 7.19−7.13 (m, 1H), 4.42 (s, 2H), 3.42 (t, J = 6.5 Hz, 2H), 3.37−3.26 (m, 1H), 2.86 (t, J = 8.3 Hz, 2H), 1.91 (m, 1H), 1.83−1.67 (m, 1H), 1.67−1.44 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ = 170.3, 148.1, 144.0, 138.7, 138.4, 136.4, 134.5, 128.7, 128.4, 128.0, 127.7, 127.5, 127.5, 126.6, 121.6, 121.5, 116.5, 72.9, 70.3, 45.9, 42.6, 32.8, 27.8; HRMS (ESI) m/z Calcd for $C_{28}H_{29}N_2O_2$ $(M + H)^+$: 425.2223, found: 425.2222; IR (neat, cm^{-1}) ν = 3353, 2933, 1685, 1528, 1482, 1102, 749, 699.

6-((*tert*-Butyldimethylsilyl)oxy)-3-phenyl-*N*-(quinolin-8-yl)-hexanamide (3ja). The title compound **3ja** was prepared according to the general procedure as a colorless oil (69.0 mg, 77%); R_f = 0.60 (EtOAc/petroleum ether 1:5); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.71 (s, 1H), 8.77 (ddd, J = 8.9, 5.7, 1.6 Hz, 2H), 8.15 (dd, J = 8.3, 1.6 Hz, 1H), 7.56−7.42 (m, 3H), 7.36−7.29 (m, 4H), 7.19 (ddd, J = 8.6, 5.6, 2.5 Hz, 1H), 3.62−3.54 (m, 2H), 3.33 (dtd, J = 9.9, 7.4, 5.1 Hz, 1H), 2.88 (d, J = 7.4 Hz, 2H), 1.96−1.84 (m, 1H), 1.83−1.70 (m, 1H), 1.57−1.36 (m, 2H), 0.86 (s, 9H), 0.01 (d, J = 4.4 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ = 170.4, 148.1, 144.2, 138.4, 136.4, 134.5, 128.7, 128.0, 127.7, 127.5, 126.6, 121.6, 121.5, 116.5, 63.1, 46.1, 42.6, 32.5, 30.8, 26.1, 18.4, −5.2; HRMS (ESI) m/z Calcd for $C_{27}H_{37}N_2O_2Si$ $(M + H)^+$: 449.2618, found: 449.2619; IR (neat, cm^{-1}) ν = 3358, 2942, 1683, 1528, 1479, 1381, 1246, 1091, 837, 776, 690.

***tert*-Butyl (6-Oxo-4-phenyl-6-(quinolin-8-ylamino)hexyl)-carbamate (3ka).** The title compound **3ka** was prepared according to the general procedure as a yellow oil (60.7 mg, 70%); R_f = 0.50 (EtOAc/petroleum ether 1:5); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.68 (s, 1H), 8.85−8.63 (m, 2H), 8.11 (dd, J = 8.2, 1.1 Hz, 1H), 7.55−7.35 (m, 3H), 7.27 (dd, J = 6.0, 3.0 Hz, 4H), 7.17 (td, J = 5.7, 3.2 Hz, 1H), 4.56 (s, 1H), 3.38−3.22 (m, 1H), 3.08 (s, 2H), 2.84 (d, J = 7.3 Hz, 2H), 1.93−1.64 (m, 4H), 1.39 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ = 170.2, 156.0, 148.2, 143.9, 138.4, 136.4, 134.5, 128.8, 128.0, 127.6, 127.4, 126.7, 121.6, 121.5, 116.6, 79.0, 45.8, 42.3, 40.4, 33.3, 29.8, 28.5; HRMS (ESI) m/z Calcd for $C_{26}H_{32}N_3O_3$ $(M + H)^+$: 434.2438, found: 434.2439; IR (neat, cm^{-1}) ν = 3432, 2925, 1683, 1523, 1160, 760, 694.

6-(1,3-Dioxoisoindolin-2-yl)-3-phenyl-*N*-(quinolin-8-yl)hexanamide (3la). The title compound **3la** was prepared according to the general procedure as a colorless oil (81.5 mg, 88%); R_f = 0.42 (EtOAc/petroleum ether 1:2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.66 (s, 1H), 8.80−8.70 (m, 1H), 8.67 (dd, J = 6.5, 2.3 Hz, 1H), 8.11 (d, J = 8.3 Hz, 1H), 7.76 (dd, J = 5.3, 3.1 Hz, 2H), 7.65 (dd, J = 5.3, 3.0 Hz, 2H), 7.51−7.36 (m, 3H), 7.30−7.20 (m, 4H), 7.15 (t, J = 6.3 Hz, 1H), 3.64 (t, J = 7.2 Hz, 2H), 3.43−3.25 (m, 1H), 2.85 (d, J = 7.3 Hz, 2H), 1.95−1.47 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ = 170.1, 168.4, 148.1, 143.6, 138.4, 136.4, 134.5, 133.9, 132.2, 128.8, 128.0, 127.6, 127.5, 126.8, 123.2, 121.6, 121.5, 116.5, 45.7, 42.4, 38.0, 33.5, 26.7; HRMS (ESI) m/z Calcd for $C_{29}H_{26}N_3O_3$ $(M + H)^+$: 464.1968, found: 464.1969; IR (neat, cm^{-1}) ν = 3351, 2931, 2355, 1708, 1526, 1391, 1033, 714.

***tert*-Butylbenzyl(4-oxo-2-phenyl-4-(quinolin-8-ylamino)-butyl)carbamate (3ma).** The title compound **3ma** was prepared according to the general procedure as a brown oil (81.2 mg, 88%); R_f = 0.55 (EtOAc/petroleum ether 1:5); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.53 (s, 1H), 8.52 (dd, J = 19.2, 4.8 Hz, 2H), 7.91 (d, J = 6.7 Hz, 1H), 7.37−7.17 (m, 3H), 7.15−6.93 (m, 10H), 4.33 (t, J = 16.7 Hz, 1H), 3.89 (dd, J = 38.9, 15.8 Hz, 1H), 3.73−2.99 (m, 3H), 2.90−2.50 (m, 2H), 1.16 (d, J = 57.4 Hz, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ = 170.0, 169.6, 156.2, 156.0, 148.1, 141.9, 138.4, 136.3, 134.6, 128.8, 128.6, 128.0, 127.4, 127.2, 127.0, 121.6, 121.5, 116.6, 80.0, 51.9, 51.5, 50.4, 50.0, 42.0, 41.6, 40.8, 28.4; HRMS

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(ESI) m/z Calcd for $C_{31}H_{34}N_3O_3$ $(M + H)^+$: 496.2594, found: 496.2592; IR (neat, cm^{-1}) ν = 3353, 2974, 1688, 1528, 1477, 1165, 750, 699.

Methyl 6-Oxo-4-phenyl-6-(quinolin-8-ylamino)hexanoate (3na). The title compound **3na** was prepared according to the general procedure as a yellow oil (59.4 mg, 82%); R_f = 0.51 (EtOAc/petroleum ether 1:5); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.69 (s, 1H), 8.73 (ddd, J = 8.7, 5.6, 1.5 Hz, 2H), 8.12 (dd, J = 8.3, 1.3 Hz, 1H), 7.52−7.37 (m, 3H), 7.32−7.26 (m, 4H), 7.19 (dd, J = 9.4, 4.5 Hz, 1H), 3.58 (s, 3H), 3.37−3.27 (m, 1H), 2.88 (d, J = 7.4 Hz, 2H), 2.30−2.12 (m, 3H), 2.09−1.96 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ = 173.8, 169.9, 148.1, 143.0, 138.3, 136.4, 134.4, 128.9, 128.0, 127.7, 127.5, 126.9, 121.7, 121.6, 116.6, 51.6, 45.6, 42.1, 32.3, 31.2; HRMS (ESI) m/z Calcd for $C_{22}H_{23}N_2O_3$ $(M + H)^+$: 363.1703, found: 363.1707; IR (neat, cm^{-1}) ν = 3350, 2941, 1733, 1684, 1436, 1159, 757, 699.

(4*R*)-3-Phenyl-*N*-(quinolin-8-yl)-4-((3*R*,5*S*,7*R*,8*R*,10*S*,12*S*,13*R*,14*S*,17*R*)-3,7,12-trimethoxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)pentanamide (3oa). The title compound **3oa** was prepared according to the general procedure as a white solid (80.9 mg, 62%); R_f = 0.45 (EtOAc/petroleum ether 1:3); mp 110−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.83 (s, 1H), 8.78 (dd, J = 4.2, 1.6 Hz, 1H), 8.65 (dd, J = 5.6, 3.4 Hz, 1H), 8.12 (dd, J = 8.3, 1.6 Hz, 1H), 7.49−7.39 (m, 3H), 7.34−7.24 (m, 5H), 7.14 (t, J = 7.2 Hz, 1H), 3.63 (d, J = 10.7 Hz, 1H), 3.35 (s, 1H), 3.34 (s, 3H), 3.29 (s, 3H), 3.22 (s, 3H), 3.17 (d, J = 2.6 Hz, 1H), 3.06−2.89 (m, 3H), 2.37−2.04 (m, 6H), 1.91−1.45 (m, 13H), 1.39−1.07 (m, 8H), 1.00−0.80 (m, 8H), 0.68 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ = 171.2, 148.1, 144.2, 138.4, 136.4, 134.7, 128.3, 128.2, 128.0, 127.5, 126.1, 121.6 121.2, 116.6, 82.0, 80.9, 56.0, 55.8, 55.6, 46.4, 44.9, 44.1, 43.1, 42.8, 42.1, 39.9, 35.4, 35.1, 34.6, 34.6, 28.2, 27.9, 26.9, 23.3, 23.0, 22.1, 12.6, 12.3; HRMS (ESI) m/z Calcd for $C_{42}H_{57}N_2O_4$ $(M + H)^+$: 653.4312, found: 653.4310; IR (neat, cm^{-1}) ν = 3353, 2929, 1686, 1526, 1378, 1096, 794, 752.

3,3-Diphenyl-*N*-(quinolin-8-yl)propanamide (3pa). The title compound **3pa** was prepared according to the general procedure as a white solid (42.3 mg, 60%); R_f = 0.59 (EtOAc/petroleum ether 1:5); mp 128−130 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 9.75 (s, 1H), 8.72 (dd, J = 18.1, 5.5 Hz, 2H), 8.10 (d, J = 8.2 Hz, 1H), 7.51−7.38 (m, 3H), 7.34 (d, J = 7.7 Hz, 4H), 7.27 (dd, J = 12.8, 5.1 Hz, 4H), 7.16 (t, J = 7.2 Hz, 2H), 4.79 (t, J = 7.7 Hz, 1H), 3.31 (d, J = 7.7 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ = 169.7, 148.1, 143.9, 138.4, 136.4, 134.4, 128.8, 127.9, 127.5, 126.6, 121.7, 121.6, 116.6, 47.3, 44.5. The spectral data of the compound (**3pa**) were in accordance with those reported in the literature.[7b]

Synthesis of Drug Molecule Phenibut. A mixture of **3ma** (1 g) and 12 N HCl (20 mL) was vigorously stirred at 130 °C. After this period, the mixture was made basic with 1 N aqueous NaOH solution, and extracted with DCM for 3 times. Afterward, the aqueous layer was acidified by conc. HCl and concentrated at reduced pressure. The resulting solid was taken up in MeOH and filtered. Finally, the filtrate was concentrated under reduced pressure to give the desired product **4ma** as a white solid (585 mg, 95%); R_f = 0.30 (CH_2Cl_2/MeOH 3:1); mp 95−96 °C; ^{1}H NMR (400 MHz, D_2O, ppm): δ = 7.60−7.18 (m, 10H), 4.18 (q, J = 13.2 Hz, 2H), 3.47−3.24 (m, 3H), 2.81−2.40 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, D_2O, ppm): δ = 178.9, 139.5, 130.3, 129.9, 129.7, 129.3, 129.3, 128.1, 127.7, 51.4, 51.1, 42.0, 39.9; HRMS (EI) m/z Calcd for $C_{17}H_{20}ClNO_2$ $(M)^+$: 305.1183, found: 305.1174; IR (neat, cm^{-1}) ν = 3384, 2923, 2852, 1684, 1432, 1248, 749, 698.

A mixture of **4ma** (100 mg) and Pd/C (10%, 20 mg) in MeOH (5 mL) was stirred under H_2 pressure (1 atm) at room temperature until the reaction was complete (TLC control). The mixture was then filtered via a small pad of Celite and washed with MeOH (10 mL). The combined filtrate was concentrated in vacuum to give (±)-phenibut (63 mg, 90%). ^{1}H NMR (400 MHz, D_2O, ppm): δ = 7.52−7.30 (m, 5H), 3.51−3.20 (m, 2H), 3.31−3.20 (m, 1H), 2.94−2.69 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, D_2O, ppm): δ = 176.1, 138.6, 129.4, 128.3, 128.0, 44.0, 40.1, 38.8.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for starting materials and products, deuterium-labeling experiments, and studies of the reaction kinetics. 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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