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Palladium-Catalyzed Carbonylation of β-Arylethylamide Directed by Oxalyl Amide in the Presence of Carbon Monoxide

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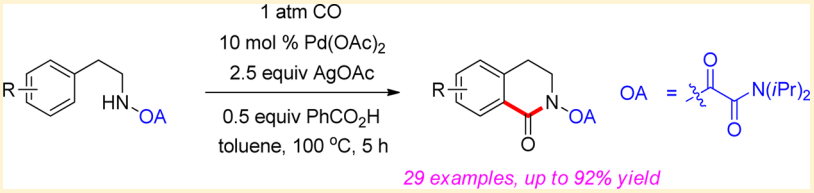
Supporting Information



ABSTRACT: Pd-catalyzed regioselective coupling of β-C(sp^2)−H bonds in aromatic amines protected by oxalyl amide with carbon monoxide is reported. The reaction could tolerate various functional groups and could afford good to excellent yields of the corresponding 3,4-dihydroisoquinolinone derivatives. Remarkably, it could also tolerate β-arylethylamino acid and thiopheneethylamine derivatives, thus showing their potential for producing several important units for bioactive compound synthesis.

Over the past decades, transition-metal-catalyzed direct C−H functionalization has become a powerful approach for forming carbon−carbon and carbon−heteroatom bonds. It provides an alternative route for the synthesis of bioactive compounds, natural products, and pharmaceutical agents.[1−3] Meanwhile, development in the carbonylation of C−H bonds using CO as the carbon source has also seen significant progress.[4−11] The first carbonylation of the arene C−H bond was reported by the Fujiwara group in 1980. Carbonylation of some arenes is carried out in an autoclave utilizing CO (15 atm) and palladium catalyst, which afforded poor to moderate yields of the corresponding carboxylic acids.[12] The lack of regioselectivity with substituted arenes hindered application of the method. Some research groups have addressed this problem by using a directing-group strategy or special substrates.[13] For example, a $Pd(OAc)_2$-catalyzed selective ethoxycarbonylation reaction of arene C−H bonds employing diethyl azodicarboxylate together with Oxone or $K_2S_2O_8$ was disclosed by Yu and co-workers in 2008.[13a] Palladium-catalyzed oxidative carbonylation of *N*-sulfonyl-2-aminobiaryls via C−H bond activation has been reported by Chung and co-workers.[13b] Yu and co-workers reported a protocol for the carboxylation of anilides that yielded *N*-acetylaniline acids.[14] The Daugulis group developed carbonylation of aminoquinoline benzamides using cobalt as the catalyst.[15] The Orito group reported a procedure for benzolactam synthesis via direct carbonylation of *N*-alkyl-ω-arylalkylamines using a $Pd(OAc)_2/Cu(OAc)_2$/air system.[16] Similarly, the Granell group described free NH_2-assisted carbonylation for preparing benzolactams.[17] However, their substrates were limited to quaternary α-amino α-alkyl esters. A concurrent study by Gaunt and co-workers reported carbonylation directed by a secondary amine for benzolactam synthesis using a palladium catalyst.[18] In recent years, the oxidative carbonylation of Csp^3−H bonds has also been achieved. For example, the Yu group reported the γ-C−H carbonylation of aliphatic acids by using a combination of a quinoline-based ligand and a weakly coordinating amide directing group.[13c] The groups of Wang[13d] and Zhao,[13e] respectively, developed the oxidative γ-C(sp3)−H carbonylation reaction to afford the pyrrolidones via the directing group strategy.

3,4-Dihydroisoquinolinones are key synthetic units in many natural products and in biologically active moieties of pharmaceuticals (Figure 1).[19,20] Examples of such pharmaceuticals include palonosetron **A**, which is a potent, highly selective antagonist of the serotonin 5-HT(3) receptor that has been studied for its use in the prevention of chemotherapy-induced nausea and vomiting; compound **C**, an inhibitor of glycogen synthase kinase-3 compound; and **D**, which is a potent inhibitor used in treating thromboembolic disorders. Herein, we report a palladium-catalyzed C−H carbonylation assisted by oxalyl amide for 3,4-dihydroisoquinolinone synthesis.

At the outset of our study, we treated β-phenylethylamine protected by oxalyl amide **1a** with CO (1 atm) in toluene at 100 °C for 5 h, using $Pd(OAc)_2$ as catalyst and AgOAc as oxidant. The desired 3,4-dihydroisoquinolinone **2a** was obtained in 72% yield. We then used various oxidants, including $Cu(OAc)_2$, 1,4-benzoquinone, Ag_2O, AgOAc, O_2, and $PhI(OAc)_2$ (Table 1, entries 1−6). The results reveal that AgOAc is indispensable for the carbonylation. It might be the appropriate oxidant to oxidize the palladium(0) to palladium(II) in the catalytic cycle. We subsequently tested different

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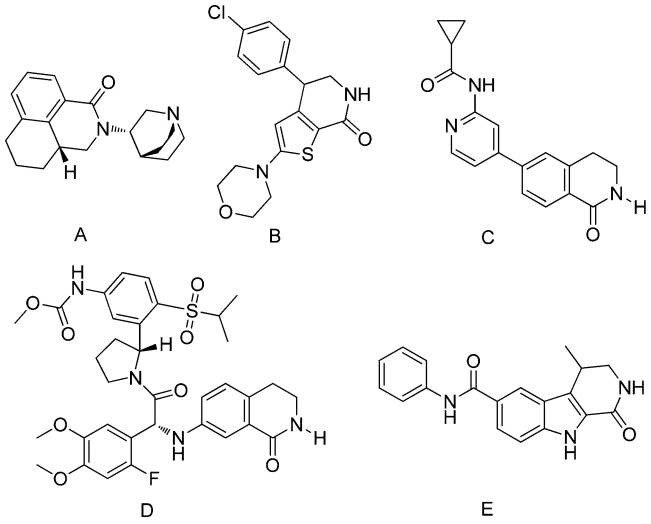
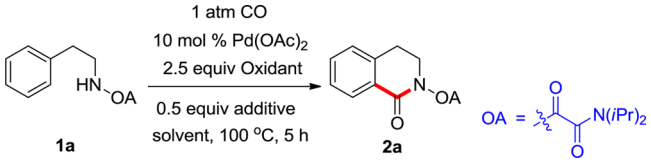


Figure 1. Representative drugs from 3,4-dihydroisoquinolinones.

Table 1. Optimization of the Reaction Conditions[a]



entry	oxidant	additive	solvent	yield[b] (%)
1	$Cu(OAc)_2$	none	toluene	<5
2	BQ	none	toluene	<5
3	Ag_2O	none	toluene	39
4	AgOAc	none	toluene	72
5	O_2	none	toluene	<5
6	$PhI(OAc)_2$	none	toluene	6
7	AgOAc	PivOH	toluene	54
8	AgOAc	Na_2CO_3	toluene	62
9	AgOAc	HOAc	toluene	31
10	AgOAc	Ac-Gly-OH	toluene	43
11	AgOAc	$(BnO)_2PO_2H$	toluene	58
12	AgOAc	$MesCO_2H$	toluene	72
13	AgOAc	$C_2H_5CO_2H$	toluene	55
14	AgOAc	m-CF_3CO_2H	toluene	76
15	AgOAc	9-Anthroic	toluene	70
16	AgOAc	$PhCO_2H$	toluene	87 (84)[c]
17	AgOAc	$PhCO_2H$	DCE	68
18	AgOAc	$PhCO_2H$	1,4-dioxane	53
19	AgOAc	$PhCO_2H$	HFIP	32
20	AgOAc	$PhCO_2H$	$PhCF_3$	70
21[d]	AgOAc	$PhCO_2H$	toluene	0

[a]Reaction conditions: **1a** (0.2 mmol), CO (1 atm), $Pd(OAc)_2$ (10 mol %), oxidant (2.5 equiv), additive (0.5 equiv), solvent (1 mL), 100 °C, 5 h. [b]GC yield of **2a** determined using tridecane as internal standard. [c]Isolated yield. [d]No catalyst.

additives to optimize the yield of **2a**. Well-known additives such as PivOH, AcOH, Ac-Gly-OH, $(BnO)_2PO_2H$, $MesCO_2H$, and Na_2CO_3, afforded **2a** in low yields.[21] We found that among the tested additives, benzoic acid gave the best result. Although the role of benzoic acid remains unclear, it probably takes part in proton transfer and in stabilization of palladium(0) during the catalytic cycle. During optimization studies, the reaction proceeded cleanly; only **2a** and starting material **1a** were observed by GC. The control reaction revealed that no reaction proceeded without the palladium catalyst, indicating the indispensable role of $Pd(OAc)_2$ in the carbonylation.

With the optimized conditions, various β-arylethylamines protected by oxalyl amide were examined (Table 2). In general, carbonylation proceeded smoothly with substrates bearing electron-rich (methyl, methoxy, and methylenedioxy) or electron-withdrawing (fluoride, chlorides, bromides, and trifluoromethyl) functional groups, affording the corresponding products in moderate to high yield. The multiple substituted β-arylethylamines also have good yields of carbonylation products. It is worth noting that the functional group bromide, which could be easily transformed to other functional groups, was well tolerated (**2q**, **2x**, **2v**). Stronger electron-withdrawing substituents afforded lower yield under standard reaction conditions (**2s**). Notably, the carbonylation was selective, occurring only at less sterically hindered positions, leading to single products.

To further expand the substrate scope, amino esters protected by oxalyl amide were also subjected to standard conditions. To our satisfaction, the carbonylation products were obtained in good yields (Table 3). For example, β-arylethylamino ester could be carbonylated well in this transformation (**2y**, **2z**). It is worth mentioning that several thiopheneethylamine derivatives could produce good yields of the corresponding carbonylated products (**2aa**, **2ab**, **2ac**).

The gram-scale reaction was achieved in 82% yield using 5 mol % of $Pd(OAc)_2$, CO (1 atm), and toluene at 120 °C for 16 h. Subsequent removal of oxalylamide under basic conditions afforded **3** in quantitative yield (Scheme 1).

A plausible mechanism for carbonylation assisted by oxalyl amide is proposed on the basis of our previous studies and pioneering reports (Scheme 2). In the path A, the palladium complex **II** could be generated through a concerted metalation−deprotonation pathway. The combination of one molecule of CO with the Pd(II) center is followed by 1,1 migratory insertion of CO into the Pd−C bond, which then forms the key palladium intermediate **IV**. The catalytic cycle might be undergo a pathway where the palladium complex **I** combined with one molecular of CO and then with the insertion of CO to generate the palladium complex III (path B), followed by C−H activation, affording the key intermediate **IV**.This seven-membered palladacycle IV then undergoes reductive elimination to the desired product.

CONCLUSION

In summary, we have developed a practical approach for the synthesis of 3,4-dihydroisoquinolinone derivatives from β-arylethylamines protected by oxalyl amide using palladium as catalyst under 1 atm CO. The reaction could tolerate various functional groups and could afford good to excellent yields of the corresponding 3,4-dihydroisoquinolinone derivatives. Remarkably, it could also tolerate β-arylethylamino acid and thiopheneethylamine derivatives, thus showing their potential for producing several important units for bioactive compound synthesis.

EXPERIMENTAL SECTION

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. HRMS analyses were carried out using TOF-MS instrument with ESI source. Multiplicities are recorded as s = singlet, d = doublet, t = triplet, dd = doublet of

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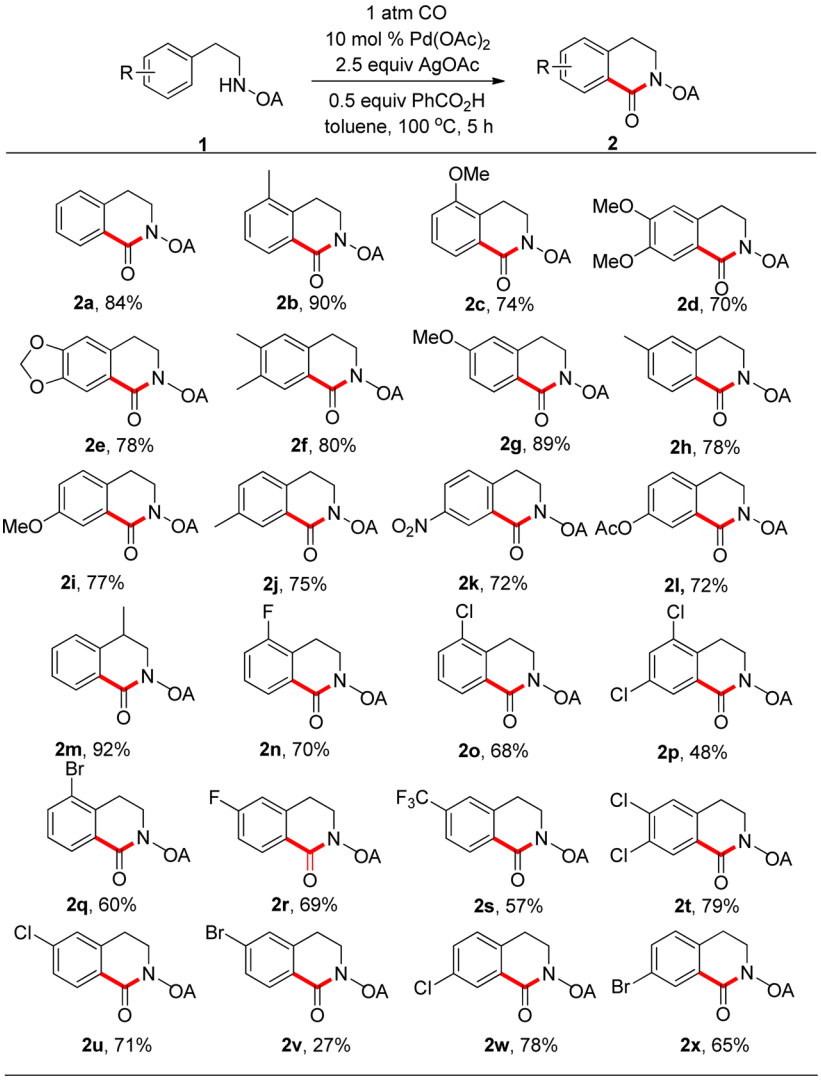
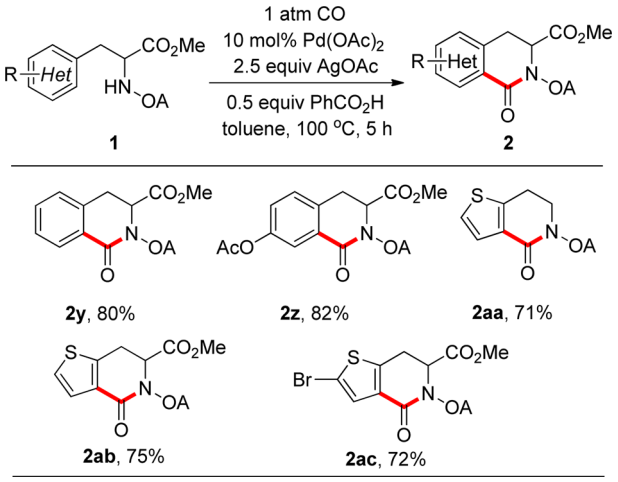
Table 2. Substrate Scope of *β*-Arylethylamide[a]



[a]Reaction conditions: **1a** (0.2 mmol), CO (1 atm), $Pd(OAc)_2$ (10 mol %), AgOAc (2.5 equiv), $PhCO_2H$ (0.5 equiv), toluene (1 mL), 100 °C, 5 h.

Table 3. Substrate Scope of *β*-Arylethylamino Ester[a]



[a]Reaction conditions: **1a** (0.2 mmol), CO (1 atm), $Pd(OAc)_2$ (10 mol %), AgOAc (2.5 equiv), $PhCO_2H$ (0.5 equiv), toluene (1 mL), 100 °C, 5 h.

doublets, m = multiplet. General procedures for the synthesis of products are represented as follows:

General Procedure for Palladium-Catalyzed Carbonylation of *γ*-C(sp^2)–H Bonds (Tables 2 and 3) (2a–z, 2aa–ac). A mixture of oxalamide (0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (4.5 mg, 0.1 equiv), AgOAc (83.4 mg, 2.5 equiv), $PhCO_2H$ (12.2 mg, 0.5 equiv), and toluene (0.5 mL) in a 20 mL glass vial was purged with CO (3×) and sealed with a Teflon septum. The vial was heated at 100 °C in an oil bath for 5 h, and then the reaction mixture was cooled to rt and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to give the product **2**.

***N,N*-Diisopropyl-2-oxo-2-(1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)acetamide (2a).** Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (6/1) as an eluent: yield 84% (50.8 mg); pale yellow soild; mp 118–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (t, J = 6.7 Hz, 1H), 7.57–7.47 (m, 1H), 7.36 (m, 1H), 7.26 (d, J = 7.5 Hz, 1H), 4.35 (s, 1H), 3.82 (s, 1H), 3.69–3.58 (m, 1H), 3.57–3.44 (m, 1H), 3.16 (s, 1H), 3.00 (s, 1H), 1.52 (s, 6H), 1.25 (s, 6H); ^{13}C NMR (101 MHz,$CDCl_3$) δ 167.1, 164.6, 163.8, 140.1, 134.0, 129.7, 127.8, 127.6, 127.5, 51.1, 45.7, 41.1, 27.8, 20.2, 19.9; HRMS calcd for $C_{17}H_{22}N_2O_3Na$ [M + Na^+] 325.1528, found 325.1535.

***N,N*-Diisopropyl-2-(5-methyl-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoacetamide (2b).** Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (8/1) as an

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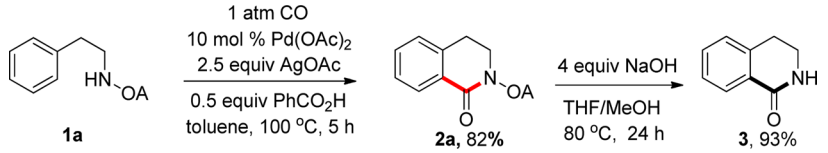
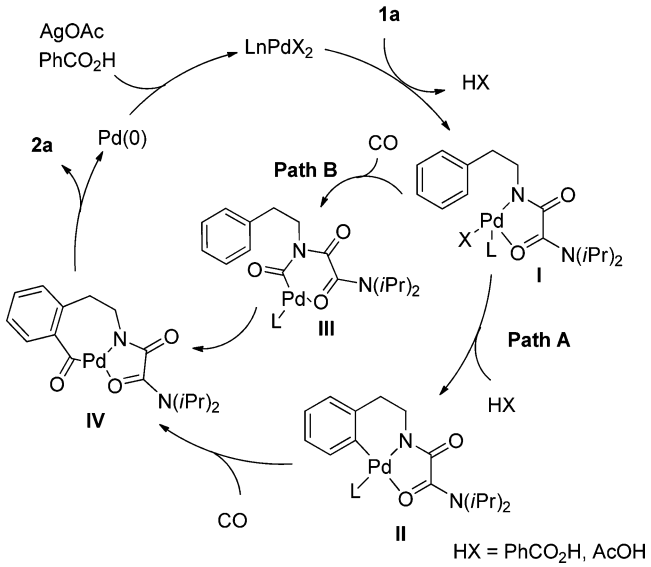
Scheme 1. Large-Scale Synthesis and Removal of Directing Group



Scheme 2. Proposed Catalytic Cycle



eluent: yield 90% (56.9 mg); pale yellow solid; mp 159−161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 7.4 Hz, 1H), 7.27 (t, J = 7.7 Hz, 1H), 4.36 (s, 1H), 3.79 (s, 1H), 3.68−3.61 (m, 1H), 3.56−3.49 (m, 1H), 3.00 (d, J = 5.2 Hz, 2H), 2.33 (s, 3H), 1.53 (s, 6H), 1.26 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 164.8, 163.8, 138.6, 135.4, 135.3, 127.9, 127.6, 126.9, 51.1, 45.7, 40.4, 24.7, 20.2, 19.9, 19.1; HRMS calcd for $C_{18}H_{24}N_2O_3Na$ [M + Na^+] 339.1685, found 339.1684.

***N,N*-Diisopropyl-2-(5-methoxy-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoacetamide) (2c).** Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (7/1) as an eluent: yield 74% (49.2 mg); pale yellow solid; mp 142−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.7 Hz, 1H), 7.32 (t, J = 8.0 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 4.33 (s, 1H), 3.87 (s, 3H), 3.78 (s, 1H), 3.66−3.60 (m, 1H), 3.55−3.48 (m, 1H), 3.08 (s, 1H), 3.01 (s, 1H), 1.53 (s, 6H), 1.25 (d, J = 3.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 164.6, 163.8, 155.8, 129.0, 127.8, 121.3, 115.10, 55.9, 51.1, 45.7, 40.7, 21.2; HRMS calcd for $C_{18}H_{24}N_2O_4Na$ [M + Na^+] 355.1634, found 355.1641.

2-(6,7-Dimethoxy-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N,N*-diisopropyl-2-oxoacetamide (2d). Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (4/1) as an eluent: yield 70% (50.68 mg); pale yellow solid; mp 179−182 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 6.66 (s, 1H), 4.35 (s, 1H), 3.91 (d, J = 9.8 Hz, 6H), 3.75 (d, J = 9.1 Hz, 1H), 3.61−3,61 (m, 1H), 3.55−3.48 (m, 1H), 3.11 (s, 1H), 2.89 (s, 1H), 1.54 (s, 3H), 1.51 (s, 3H),1.24 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 164.2, 163.9, 153.8, 148.4, 134.8, 120.0, 111.2, 109.5, 56.3, 51.1, 45.7, 41.3, 27.5, 20.5, 20.3, 19.9, 19.7; HRMS calcd for $C_{19}H_{26}N_2O_5Na$ [M + Na^+] 385.1739, found 385.1730.

***N,N*-Diisopropyl-2-oxo-2-(5-oxo-7,8-dihydro[1,3]dioxolo-[4,5-*g*]isoquinolin-6(5*H*)-yl)acetamide (2e).** Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (5/1) as an eluent: yield 78% (53.9 mg); pale yellow solid; mp 168−169 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 6.67 (s, 1H), 6.03 (s, 2H), 4.34 (s, 1H), 3.75 (s, 1H), 3.66−3.59 (m, 1H), 3.54−3.57 (m, 1H), 3.08 (s, 1H), 2.99−2.80 (m, 1H), 1.52 (s, 6H), 1.24 (d, J = 14.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 163.9, 152.6, 147.5, 136.9, 121.7, 108.9, 107.3, 102.1, 51.1, 45.7, 41.1, 28.0, 20.3, 20.1, 19.8, 19.6, 20.1; HRMS calcd for $C_{18}H_{22}N_2O_5Na$ [M + Na^+] 369.1429, found 369.1453.

2-(6,7-Dimethyl-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N,N*-diisopropyl-2-oxoacetamide (2f). Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (8/1) as an eluent: yield 80% (52.8 mg); pale yellow solid; mp 174−175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.01 (s, 1H), 4.32 (s, 1H), 3.77 (s, 1H), 3.66−3.59 (m, 1H), 3.54−3.47 (m, 1H), 3.08 (s, 1H), 2.90 (s, 1H), 2.29 (s, 3H), 2.26 (s, 3H), 1.53 (s, 6H), 1.24 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 164.8, 163.9, 143.9, 137.8, 136.2, 130.4, 128.8, 125.3, 51.1, 45.7, 41.3, 27.4, 20.2, 19.4; HRMS calcd for $C_{19}H_{26}N_2O_3Na$ [M + Na^+] 353.1841, found 353.1852.

***N,N*-Diisopropyl-2-(6-methoxy-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoacetamide (2g).** Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (5/1) as an eluent: yield 89% (59.1 mg); pale yellow solid; mp 163−164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.7 Hz, 1H), 6.86 (d, J = 8.8, 2.0 Hz, 1H), 6.71 (d, J = 2.0 Hz, 1H), 4.37 (s, 1H), 3.86 (s, 3H), 3.76 (s, 1H), 3.66−3.60 (m, 1H), 3.54−3.47 (m, 1H), 3.15 (s, 1H), 2.94 (s, 1H), 1.52 (d, J = 15.0 Hz, 6H), 1.25 (s, 6H); ^{13}C NMR (101 MHz,$CDCl_3$) δ 167.1, 164.3, 163.9, 142.6, 132.2, 120.5, 113.6, 112.2, 55.7, 51.1, 45.7, 41.1, 28.3; HRMS calcd for $C_{18}H_{24}N_2O_4Na$ [M + Na^+] 355.1634, found 355.1622.

***N,N*-Diisopropyl-2-(6-methyl-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoacetamide (2h).** Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (8/1) as an eluent: yield 78% (49.3 mg); pale yellow solid; mp 162−164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.0 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.06 (s, 1H), 4.34 (s, 1H), 3.79 (s, 1H), 3.66−3.60 (m, 1H), 3.55−3.48 (m, 1H), 3.12 (s, 1H), 2.94 (s, 1H), 2.39 (s, 3H), 1.53 (s, 6H), 1.25 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 164.6, 163.9, 145.1, 140.2, 129.9, 128.5, 128.2, 125.3, 51.1, 45.8, 41.2, 27.9, 21.9; HRMS Calcd for $C_{18}H_{24}N_2O_3Na$ [M + Na^+] 339.1689, found 339.1694.

***N,N*-Diisopropyl-2-(7-methoxy-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoacetamide (2i).** Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (6/1) as an eluent: yield 78% (51.1 mg); pale yellow solid; mp 145−148 °C; ^{1}H NMR (400 MHz, CDC_{l3}) δ 7.61 (d, J = 2.7 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.08 (dd, J = 8.4, 2.7 Hz, 1H), 4.31 (s, 1H), 3.84 (s, 4H), 3.67−3.60 (m, 1H), 3.55−3.49 (m, 1H), 3.03 (s, 1H), 2.99−2.84 (m, 1H), 1.53 (s, 6H), 1.26 (s, 6H); ^{13}C NMR (101 MHz, CDC_{l3}) δ 167.1, 164.6, 163.8, 159.0, 132.6, 128.8, 121.9, 112.4, 55.8, 51.1, 45.8, 41.4, 27.0; HRMS calcd for $C_{18}H_{24}N_2O_4Na$ [M + Na^+] 355.1634, found 355.1646.

***N,N*-Diisopropyl-2-(7-methyl-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoacetamide (2j).** Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (9/1) as an eluent: yield 75% (47.4 mg); pale yellow solid; mp 127−129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 2.7 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.08 (dd, J = 8.4, 2.7 Hz, 1H), 4.31 (s, 1H), 3.84 (s, 4H), 3.67−3.60 (m, 1H), 3.55−3.48 (m, 1H), 3.11 (s, 1H), 2.95 (s, 1H), 2.37 (s, 3H), 1.53 (s, 6H), 1.26 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 164.6, 163.8, 159.0, 132.6, 128.8, 121.9, 112.6, 55.8, 51.1, 45.7, 41.4, 27.0; HRMS calcd for $C_{18}H_{24}N_2O_3Na$ [M + Na^+] 339.1685, found 339.1692.

***N,N*-Diisopropyl-2-(7-nitro-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoacetamide (2k).** Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (3/1) as an eluent: yield 72% (49.9 mg); pale yellow solid; mp 209−210 °C; ^{1}H

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NMR (400 MHz, $CDCl_3$) δ 8.98 (d, J = 2.4 Hz, 1H), 8.37 (dd, J = 8.4, 2.4 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 4.43 (s, 1H), 3.82 (s, 1H), 3.69−3.61 (m, 1H), 3.58−3.49 (m, 1H), 3.21 (s, 2H), 1.52 (d, J = 5.9 Hz, 6H), 1.28 (d, J = 5.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 163.2, 162.8, 147.7, 146.6, 129.3, 128.1, 125.0, 51.3, 45.9, 40.5, 28.0; HRMS calcd for $C_{17}H_{21}N_3O_5Na$ [M + Na^+] 370.1379, found 370.1392.

2-(2-(Diisopropylamino)-2-oxoacetyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl Acetate (2l). Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (6/1) as an eluent: yield 72% (51.8 mg); pale yellow solid; mp 148−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 2.2 Hz, 1H), 7.30−7.23 (m, 2H), 4.37 (s, 1H), 3.78 (s, 1H), 3.63−3.57 (m, 1H), 3.54−3.47 (m, 1H), 3.13 (s, 1H), 3.00 (s, 1H), 2.29 (s, 3H), 1.51 (s, 6H), 1.24 (d, J = 5.3 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 167.0, 163.8, 163.6, 150.0, 137.6, 129.0, 127.5, 122.7, 51.1, 45.8, 41.1, 27.3, 21.0; HRMS calcd for $C_{19}H_{24}N_2O_5Na$ [M + Na^+] 383.1583, found 383.1589.

***N*,*N*-Diisopropyl-2-(4-methyl-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoacetamide (2m).** Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (7/1) as an eluent: yield 92% (58.1 mg); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, J = 7.8, 0.9 Hz, 1H), 7.56 (t, J = 7.4 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.30 (s, 1H), 4.22 (s, 1H), 3.83 (s, 1H), 3.66 (s, 1H), 3.55−3.49 (m, 1H), 3.20 (s, 1H), 1.53 (s, 6H), 1.38 (d, J = 7.0 Hz, 3H), 1.25 (d, J = 6.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 163.6, 133.9, 129.6, 127.1, 50.9, 45.5, 19.5; HRMS calcd for $C_{18}H_{24}N_2O_3Na$ [M + Na^+] 339.1685, found 339.1689.

2-(5-Fluoro-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*,*N*-diisopropyl-2-oxoacetamide (2n). Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (8/1) as an eluent: yield 70% (44.8 mg); pale yellow solid; mp 162−165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 7.7 Hz, 1H), 7.37 (dd, J = 13.3, 7.9 Hz, 1H), 7.33−7.28 (m, 1H), 4.41 (s, 1H), 3.82 (s, 1H), 3.68−3.62 (m, 1H), 3.57−3.50 (m, 1H), 3.12 (s, 2H), 1.54 (d, J = 4.7 Hz, 6H), 1.28 (d, J = 6.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 163.8, 163.5, 159.0 (d, J_{C-F} = 240.0 Hz), 129.8 (d, J_{C-F} = 4.0 Hz), 128.4 (d, J_{C-F} = 8.0 Hz), 127.3 (d, J_{C-F} = 190.0 Hz), 125.4 (d, J_{C-F} = 3.0 Hz), 120.7 (d, J_{C-F} = 8.0 Hz), 120.5, 51.2, 45.8, 40.5, 20.7; HRMS calcd for $C_{17}H_{21}FN_2O_3Na$ [M + Na^+] 343.1434, found 343.1444.

2-(5-Chloro-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*,*N*-diisopropyl-2-oxoacetamide (2o). Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (9/1) as an eluent: yield 68% (45.7 mg); pale yellow solid; mp 172−173 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, J = 7.8, 0.9 Hz, 1H), 7.60 (dd, J = 8.0, 1.2 Hz, 1H), 7.33 (t, J = 7.9 Hz, 1H), 4.36 (s, 1H), 3.83 (s, 1H), 3.66−3.60 (m, 1H), 3.55−3.49 (m, 1H), 3.18 (s, 2H), 1.52 (d, J = 5.8 Hz, 6H), 1.26 (d, J = 6.3 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 163.2, 162.9, 137.4, 133.9, 132.5, 129.2, 127.7, 50.6, 45.2, 39.6, 24.6; HRMS calcd for $C_{17}H_{21}ClN_2O_3Na$ [M + Na^+] 359.1138, found 359.1147.

2-(5,7-Dichloro-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*,*N*-diisopropyl-2-oxoacetamide (2p). Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (10/1) as an eluent: yield 48% (35.5 mg); pale yellow solid; mp 208−210 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 2.1 Hz, 1H), 7.60 (d, J = 2.2 Hz, 1H), 4.39 (s, 1H), 3.78 (s, 1H), 3.65−3.58 (m, 1H), 3.56−3.49 (m, 1H), 3.15 (s, 2H), 1.51 (d, J = 5.9 Hz, 6H), 1.26 (d, J = 6.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 163.3, 162.9, 136.5, 134.1, 130.7, 128.3, 127.1, 51.2, 45.9, 40.2, 24.9; HRMS Calcd for $C_{17}H_{20}Cl_2N_2O_3Na$ [M + Na^+] 393.0749, found 393.0762.

2-(5-Bromo-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*,*N*-diisopropyl-2-oxoacetamide (2q). Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (10/1) as an eluent: yield 60% (45.6 mg); pale yellow solid; mp 175−177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (m, 1H), 7.77 (m, 1H), 7.26 (d, J = 15.8 Hz, 1H), 4.36 (s, 1H), 3.82 (s, 1H), 3.68−3.58 (m, 1H), 3.57−3.47 (m, 1H), 3.18 (s, 2H), 1.52 (s, 6H), 1.26 (d, J = 6.3 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 163.8, 163.5, 139.8, 137.8, 129.9, 129.1, 128.6, 123.4, 51.2, 45.9, 40.3, 28.1, 20.1, 20.0; HRMS calcd for $C_{17}H_{21}BrN_2O_3Na$ [M + Na^+] 403.0633, found 403.0642.

2-(6-Fluoro-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*,*N*-diisopropyl-2-oxoacetamide (2r). Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (6/1) as an eluent: yield 69% (44.2 mg); pale yellow solid; mp 168−171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 7.7 Hz, 1H), 7.37 (dd, J = 13.3, 7.9 Hz, 1H), 7.33−7.28 (m, 1H), 4.41 (s, 1H), 3.82 (s, 1H), 3.68−3.62 (m, 1H), 3.57−3.50 (m, 1H), 3.12 (s, 2H), 1.54 (d, J = 4.7 Hz, 6H), 1.28 (d, J = 6.0 Hz, 6H);^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 166.6, 164.4, 163.3 (d, J_{C-F} = 2 Hz), 142.9 (d, J_{C-F} = 10 Hz), 132.5 (d, J_{C-F} = 10 Hz), 123.9 (d, J_{C-F} = 3 Hz), 114.8 (d, J_{C-F} = 22 Hz), 114.1 (d, J_{C-F} = 22 Hz), 50.8, 45.4, 40.6, 27.6; HRMS calcd for $C_{17}H_{21}FN_2O_3Na$ [M + Na^+] 343.1434, found 343.1441.

***N*,*N*-Diisopropyl-2-oxo-2-(1-oxo-6-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)acetamide (2s).** Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (8/1) as an eluent: yield 57% (42.2 mg); pale yellow solid; mp 116−119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 8.2 Hz, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.55 (s, 1H), 4.36 (s, 1H), 3.88 (s, 1H), 3.64 (m, 1H), 3.53 (m, 1H), 3.17 (s, 2H), 1.53 (d, J = 6.1 Hz, 6H), 1.27 (d, J = 6.3 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 162.9, 162.8, 140.2, 134.7 (d, J_{C-F} = 33 Hz), 130.4, 129.8, 124.2 (d, J_{C-F} = 4 Hz), 123.8 (d, J_{C-F} = 4 Hz), 122.9 (d, J_{C-F} = 271 Hz), 50.6, 45.3, 40.3, 27.2; HRMS calcd for $C_{18}H_{21}F_3N_2O_3Na$ [M + Na^+] 393.1402, found 393.1397.

2-(6,7-Dichloro-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*,*N*-diisopropyl-2-oxoacetamide (2t). Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (7/1) as an eluent: yield 79% (58.5 mg); pale yellow solid; mp 196−197 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.39 (s, 1H), 4.37 (s, 1H), 3.78 (s, 1H), 3.65−3.58 (m, 1H), 3.55−3.48 (m, 1H), 3.05 (d, J = 40.3 Hz, 2H), 1.51 (d, J = 5.5 Hz, 6H), 1.26 (d, J = 6.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 163.4, 163.0, 139.5, 138.5, 132.4, 131.5, 129.7, 127.6, 51.2, 45.9, 40.9, 27.2; HRMS calcd for $C_{17}H_{20}Cl_2N_2O_3Na$ [M + Na^+] 393.0749, found 393.0759.

2-(6-Chloro-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*,*N*-diisopropyl-2-oxoacetamide (2u). Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (8/1) as an eluent: yield 71% (47.7 mg); pale yellow solid; mp 135−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.4 Hz, 1H), 7.32 (m, 1H), 7.25 (s, 1H), 4.35 (s, 1H), 3.78 (s, 1H), 3.60 (m, 1H), 3.51 (m, 1H), 3.13 (s, 1H), 2.99 (s, 1H), 1.51 (s, 6H), 1.24 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 163.8, 163.6, 141.8, 140.4, 131.3, 128.0, 127.7, 126.3, 51.2, 45.8, 40.9, 27.7, 20.0; HRMS calcd for $C_{17}H_{21}ClN_2O_3Na$ [M + Na^+]: 359.1138, found 359.1146.

2-(6-Bromo-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*,*N*-diisopropyl-2-oxoacetamide (2v). Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (8/1) as an eluent: yield 27% (20.5 mg); pale yellow solid; mp 183−184 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.4 Hz, 1H), 7.51 (m 1H), 7.44 (s, 1H), 4.36 (s, 1H), 3.80 (s, 1H), 3.62 (m, 1H), 3.51 (m, 1H), 3.16 (s, 1H), 2.98 (s, 1H), 1.52 (s, 6H), 1.25 (d, J = 3.4 Hz, 6H); ^{13}C NMR (101 MHz,$CDCl_3$) δ 166.9, 164.0, 163.6, 141.9, 131.4, 131.1, 130.8, 129.2, 126.8, 51.2, 45.8, 40.9, 27.6, 20.3, 20.0; HRMS calcd for $C_{17}H_{21}BrN_2O_3Na$ [M + Na^+] 403.0633, found 403.0645.

2-(7-Chloro-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*,*N*-diisopropyl-2-oxoacetamide (2w). Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (6/1) as an eluent: yield 78% (52.4 mg); pale yellow solid; mp 168−170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 2.2 Hz, 1H), 7.48 (dd, J = 8.1, 2.2 Hz, 1H), 7.22 (d, J = 8.1 Hz, 1H), 4.36 (s, 1H), 3.78 (s, 1H), 3.65−3.58 (m, 1H), 3.55−3.48 (m, 1H), 3.10 (s, 1H), 3.00 (s, 1H), 1.52 (s, 6H), 1.25 (d, J = 5.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 163.6, 138.4 (s), 133.9, 133.7, 129.6, 129.0, 51.2, 45.8, 41.02, 27.3; HRMS calcd for $C_{17}H_{21}ClN_2O_3Na$ [M + Na^+] 359.1138, found 359.1148.

2-(7-Bromo-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*,*N*-diisopropyl-2-oxoacetamide (2x). Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (5/1) as an

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eluent: yield 65% (49.4 mg); pale yellow solid; mp 169−171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 2.1 Hz, 1H), 7.64 (dd, J = 8.1, 2.1 Hz, 1H), 7.16 (d, J = 8.1 Hz, 1H), 4.37 (s, 1H), 3.79 (s, 1H), 3.67−3.59 (m, 1H), 3.56−3.49 (m, 1H), 3.09 (s, 1H), 2.98 (s, 1H), 1.53 (s, 6H), 1.26 (d, J = 5.3 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 162.9, 138.3, 136.2, 131.9, 129.0, 128.8, 120.8, 50.6, 45.2, 40.4, 30.5, 26.8; HRMS calcd for $C_{17}H_{21}BrN_2O_3Na$ [M + Na^+] 403.0633, found 403.0645.

Methyl 2-(2-(Diisopropylamino)-2-oxoacetyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (2y). Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (6/1) as an eluent: yield 80% (57.6 mg); pale yellow solid; mp 137−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 7.8 Hz, 1H), 7.52 (m, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 5.46 (d, J = 4.7 Hz, 1H), 3.81 (d, J = 3.9 Hz, 1H), 3.64 (s, 3H), 3.58−3.39 (m, 3H), 1.59 (d, J = 6.8 Hz, 3H), 1.51 (d, J = 6.7 Hz, 3H), 1.32 (d, J = 6.5 Hz, 3H), 1.22 (d, J = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 166.9, 163.5, 163.4, 136.6, 134.4, 129.8, 128.1, 127.9, 127.3, 53.2, 50.9, 45.8, 30.1, 20.6, 20.4, 19.8, 19.6; HRMS calcd for $C_{19}H_{24}N_2O_5Na$ [M + Na^+] 383.1583, found 383.1589.

Methyl 7-Acetoxy-2-(2-(diisopropylamino)-2-oxoacetyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (2z). Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (3/1) as an eluent: yield 82% (68.6 mg); pale yellow solid; mp 152−153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.28 (d, J = 2.3 Hz, 2H), 5.46 (s, 1H), 3.80 (s, 1H), 3.66 (s, 3H), 3.57−3.50 (m, 1H), 3.48 (d, J = 3.5 Hz, 2H), 2.29 (s, 3H), 1.58 (d, J = 6.8 Hz, 3H), 1.50 (d, J = 6.7 Hz, 3H), 1.31 (d, J = 6.5 Hz, 3H), 1.22 (d, J = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.7, 133.4, 128.5, 127.29, 122.0, 52.7, 52.5, 50.3, 45.2, 28.9, 20.5, 19.9, 19.6, 19.5, 19.1; HRMS calcd for $C_{21}H_{26}N_2O_7Na$ [M + Na^+] 441.1638, found 441.1643.

***N,N*-Diisopropyl-2-oxo-2-(4-oxo-6,7-dihydrothieno[3,2-*c*]-pyridin-5(4*H*)-yl)acetamide (2aa).** Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (4/1) as an eluent: yield 71% (43.7 mg); pale yellow solid; mp 114−117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 5.3 Hz, 1H), 7.14 (d, J = 5.3 Hz, 1H), 4.56 (s, 1H), 3.85 (s, 1H), 3.70−3.58 (m, 1H), 3.56−3.44 (m, 1H), 3.20 (s, 1H), 3.14 (s, 1H), 1.51 (s, 6H), 1.25 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 163.7, 160.7, 150.5, 131.2, 126.7, 124, 51.1, 45.7, 42.2, 24.3, 20.5, 19.8; HRMS calcd for $C_{15}H_{20}N_2O_3SNa$ [M + Na^+] 331.1092, found 331.1101

Methyl 5-(2-(Diisopropylamino)-2-oxoacetyl)-4-oxo-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine-6-carboxylate (2ab). Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (6/1) as an eluent: yield 75% (54.9 mg); pale yellow solid; mp 157−158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 5.1 Hz, 1H), 7.16 (d, J = 5.3 Hz, 1H), 5.59 (d, J = 5.4 Hz, 1H), 3.89−3.78 (m, 1H), 3.74−3.65 (m, 4H), 3.55−3.47 (m, 2H), 1.57 (d, J = 6.7 Hz, 3H), 1.49 (d, J = 6.3 Hz, 3H), 1.32 (d, J = 6.1 Hz, 3H), 1.22 (d, J = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 162.8, 158.8, 146.5, 130.4, 126.2, 124.5, 53.6, 52.8, 50.3, 45.2, 25.9, 20.0, 19.9, 19.2, 19.0; HRMS calcd for $C_{17}H_{22}N_2O_5SNa$ [M + Na^+] 389.1147, found 389.1149.

Methyl 2-Bromo-5-(2-(diisopropylamino)-2-oxoacetyl)-4-oxo-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine-6-carboxylate (2ac). Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (5/1) as an eluent: yield 72% (63.9 mg); pale yellow solid; mp 172−174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 5.55 (d, J = 5.5 Hz, 1H), 3.83−3.75 (m, 1H), 3.72 (s, 3H), 3.60 (d, J = 17.2 Hz, 1H), 3.51 (dd, J = 13.7, 6.8 Hz, 1H), 3.42 (dd, J = 17.3, 6.3 Hz, 1H), 1.54 (d, J = 6.8 Hz, 3H), 1.48 (d, J = 6.8 Hz, 3H), 1.30 (d, J = 6.5 Hz, 3H), 1.21 (d, J = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 166.0, 162.6, 157.5, 147.5, 131.0, 128.4, 111.7, 53.3, 52.9, 50.3, 45.2, 26.0, 20.0, 19.7, 19.0; HRMS calcd for $C_{17}H_{21}BrN_2O_5SNa$ [M + Na^+] 467.0252, found 467.0266.

Gram-Scale Preparation of 2a (Scheme 1). A mixture of oxalamide (1.0 g, 3.6 mmol, 1.0 equiv), $Pd(OAc)_2$ (40.8 mg, 0.05 equiv), AgOAc (1.5 g, 2.5 equiv), $PhCO_2H$ (221 mg, 0.5 equiv), and toluene (20 mL) in a 100 mL glass vial was purged with CO (3×) and CO balloon and sealed with a Teflon septum. The vial was heated at 120 °C in an oil bath for 16 h, and then the reaction mixture was cooled to rt and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to give the product **2a** as a pale yellow solid (1.09 g) in 82% yield.

Gram-Scale Preparation of 3 (Scheme 1). Compound **2a** (0.15 g, 0.5 mmol, 1.0 equiv) was dissolved in a mixture of THF/MeOH (0.4/0.1 mL). NaOH (80 mg, 2.0 mmol, 4.0 equiv) was added later. The mixture was heated at 80 °C for 24 h and then diluted with water (10 mL) and extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give the desired product **3** (68.4 mg) as a pale yellow oil in 93% yield.

3,4-Dihydroisoquinolin-1(2*H*)-one (3). Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (2/1) as an eluent: yield 93% (68.4 mg); pale white solid; mp 61−63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07−8.05 (m, 1H), 7.46−7.42 m, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 6.74 (s, 1H), 3.69−3.55 (m, 2H), 2.99 (t, J = 6.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 139.0, 132.3, 129.1, 128.1, 127.3, 40.3, 28.0; HRMS calcd for C_9H_9NONa [M + Na^+] 170.0582, found 170.0585.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00932.

^{1}H and ^{13}C NMR spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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