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Copper-Catalyzed Intramolecular Dehydrogenative Amidation of Unactivated C(sp^3)−H Bonds Using O_2 as the Sole Oxidant

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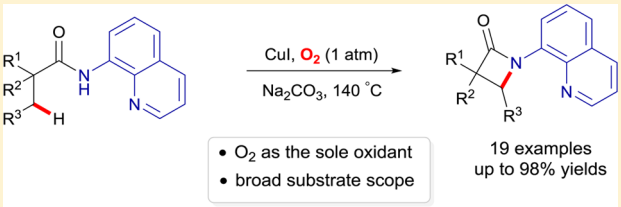
Supporting Information

ABSTRACT: In this work, an aerobic copper-catalyzed intramolecular C(sp^3)−H amidation has been disclosed, which presents a rare example of copper-catalyzed functionalization of an unactivated C(sp^3)−H bond with O_2 as the sole oxidant. In addition, a new protocol for the preparation of a removable 5-methoxyquinolyl moiety has been documented.



Recently, transition-metal-catalyzed C−H bond activation has emerged as a highly efficient strategy for selective functionalization of targeted molecules and construction of synthetically enabling structures.[1] Notably, transition-metal-catalyzed C−H/X−H (X = C, N, O) dehydrogenative cross-coupling reaction with O_2 as the sole oxidant is regarded as an ideal approach to facilely assemble carbon−carbon bonds and carbon−heteroatom bonds due to its high atom-economy, efficiency, and environmental friendliness.[2] Although significant progress has been achieved in transition-metal-catalyzed aerobic oxidative functionalization of C(sp^2)−H bonds over the past decade,[2b−h] the analogous transformations of unactivated C(sp^3)−H bonds with air or O_2 as the oxidant are still scarce. To our knowledge, only aerobic palladium-catalyzed olefination[3a] and oxygenation[3b] of inert C(sp^3)−H bonds have been achieved with the assistance of a redox cocatalyst by Sanford and co-workers.

Lactams are important structural features that exist in a range of pharmaceuticals, agrochemicals, and natural products. Recently, tremendous efforts have been devoted to the synthesis of these compounds via transition-metal-catalyzed intramolecular amidation of inert C(sp^3)−H bonds and/or C(sp^2)−H bonds.[4,5] Although these approaches are concise and efficient, they generally require the use of excess amounts of oxidants such as Ag_2CO_3, BQ, $PhI(OAc)_2$, and TEMPO, which render these processes less appealing due to the increased cost and formation of stoichiometric undesired byproducts. Considering that the different oxidation states of copper (Cu(I), Cu(II), and Cu(III)) could be mutually converted with the assistance of O_2,[6,7] we reasoned that copper would enable aerobic catalytic C(sp^3)−H amidation reaction. In this work, we disclose a Cu-catalyzed intramolecular dehydrogenative amidation of unactivated C(sp^3)−H bonds with O_2 as the sole oxidant (Scheme 1). It should be noted that transition-metal-catalyzed functionalization of inert C(sp^3)−H bonds using O_2 as the sole oxidant is still underrepresented.

We commenced our study with *N*-(quinolin-8-yl)pivalamide as the model substrate (Table 1). Gratifyingly, *β*-lactam **2a** was obtained in 11% isolated yield in the presence of CuI (20 mol %) and Na_2CO_3 (2.0 equiv) at 140 °C under 1 atm of O_2 (entry 1). Encouraged by this result, we next investigated the bases. However, other bases, such as K_2CO_3, Cs_2CO_3, K_3PO_4, CsF, and Li^{t}Bu, were proved to be ineffective for this reaction (entries 2−6). Interestingly, although most solvents failed to give the desired product in our tests (entries 7−11), benzonitrile was identified as a superior solvent (entry 12). Further investigation of the copper catalyst precursors revealed that the reaction was highly influenced by the nature of the copper source, and the highest yield was achieved with CuI (entries 12−17). Finally, 92% yield of **2a** could be afforded when the reaction was performed in a mixture of benzonitrile and *o*-xylene (3/2) at 140 °C under 1 atm of O_2 for 34 h (entry 21). In addition, the yield of **2a** was dramatically decreased to 36% when the reaction was carried out under an air atmosphere (entry 22). No product **2a** was detected when other directing groups were employed under the optimized condition (**II**−**IV**). It should be mentioned that only trace amounts of **2a** were obtained when amide **1a** was subjected to the modified conditions of Ge, Kuninobu, and Kanai,[5c,d] in which O_2 was used as the sole oxidant instead.

With the optimized condition in hand, we next investigated the substrate scope of this reaction (Table 2). As expected, a variety of aliphatic amides were converted into the corresponding *β*-lactams in good to excellent yields. A preference for amidation of C(sp^3)−H bonds of the *β*-methyl groups over *γ*- and *δ*-methyl groups was observed (**2b**−**d**), indicating that the formation of five-membered ring intermediates is more favorable in the cyclometalation step. In addition, this reaction showed a site-selectivity on the *β*-methyl groups over the methylene groups even in the existence of a *β*-benzylic site (**2b** and **2d**−**n**). This result is distinctly different from the previous reports on copper-catalyzed C(sp^3)−H amidation, in which a preference for the *β*-benzylic C−H was observed.[5c,d] However, when amides bearing

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Scheme 1. Transition-Metal-Catalyzed Dehydrogenative Intramolecular Amidation of Unactivated C(sp^3)−H Bonds

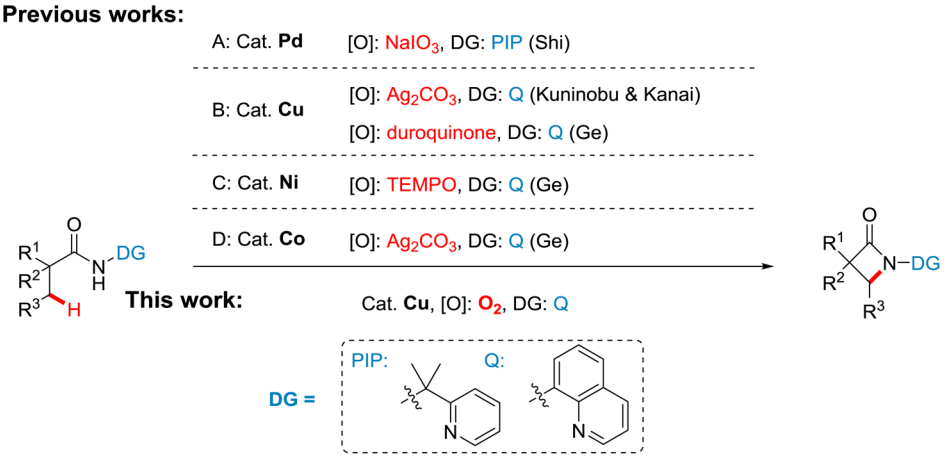
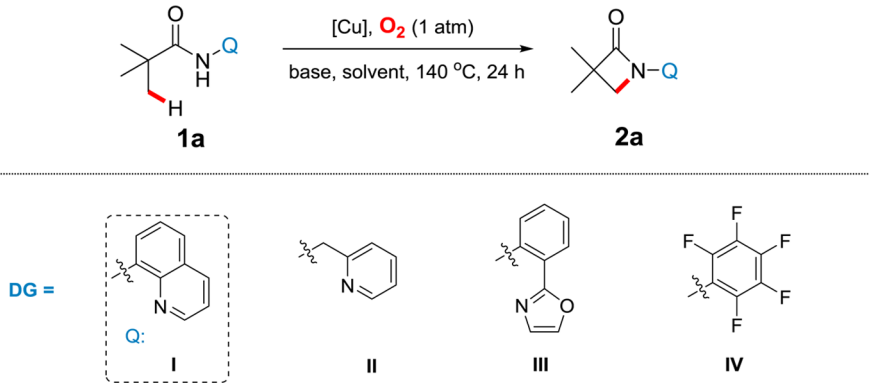


Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	base	solvent	yield[b] (%)
1	CuI	Na_2CO_3	*o*-xylene	11
2	CuI	K_2CO_3	*o*-xylene	trace
3	CuI	Cs_2CO_3	*o*-xylene	n. d.
4	CuI	K_3PO_4	*o*-xylene	n. d.
5	CuI	CsF	*o*-xylene	n. d.
6	CuI	Li^{t}OBu	*o*-xylene	trace
7	CuI	Na_2CO_3	DCE	trace
8	CuI	Na_2CO_3	DMF	n. d.
9	CuI	Na_2CO_3	NMP	n. d.
10	CuI	Na_2CO_3	1,2-dioxane	trace
11	CuI	Na_2CO_3	CH_3CN	trace
12	CuI	Na_2CO_3	PhCN	41
13	CuCl	Na_2CO_3	PhCN	11
14	CuBr	Na_2CO_3	PhCN	17
15	Cu_2O	Na_2CO_3	PhCN	trace
16	$Cu(acac)_2$	Na_2CO_3	PhCN	trace
17	$Cu(OAc)_2$	Na_2CO_3	PhCN	trace
18	CuI	Na_2CO_3	PhCN/*o*-xylene (2/3)	52
19	CuI	Na_2CO_3	PhCN/*o*-xylene (3/2)	72
20	CuI	Na_2CO_3	PhCN/*o*-xylene (4/1)	66
21[c]	**CuI**	**Na_2CO_3**	**PhCN/*o*-xylene (3/2)**	**92**
22[d]	CuI	Na_2CO_3	PhCN/*o*-xylene (3/2)	36

[a]General conditions: **1a** (0.25 mmol), catalyst (20 mol %), and base (2.0 equiv) were stirred in solvent (0.5 mL) at 140 °C for 24 h under an atmosphere of O_2. [b]Isolated yields. [c]Stirred at 140 °C for 34 h. [d]Air instead of O_2. n. d. = not detected.

cyclic chains were used as substrates, both the *β*-methyl and the methylene amidated products were obtained, with a slight preference for the spiro-products (**2o−q**). Furthermore, 2-phenyl-substituted propanamide was also suitable for the reaction condition and exclusively gave the methyl C(sp^3)−H amidated product in good yield (**2r**).

To further understand the mechanism, 2,6-di-*tert*-butyl-*p*-cresol (BHT), which is known as a radical inhibitor, was added. It

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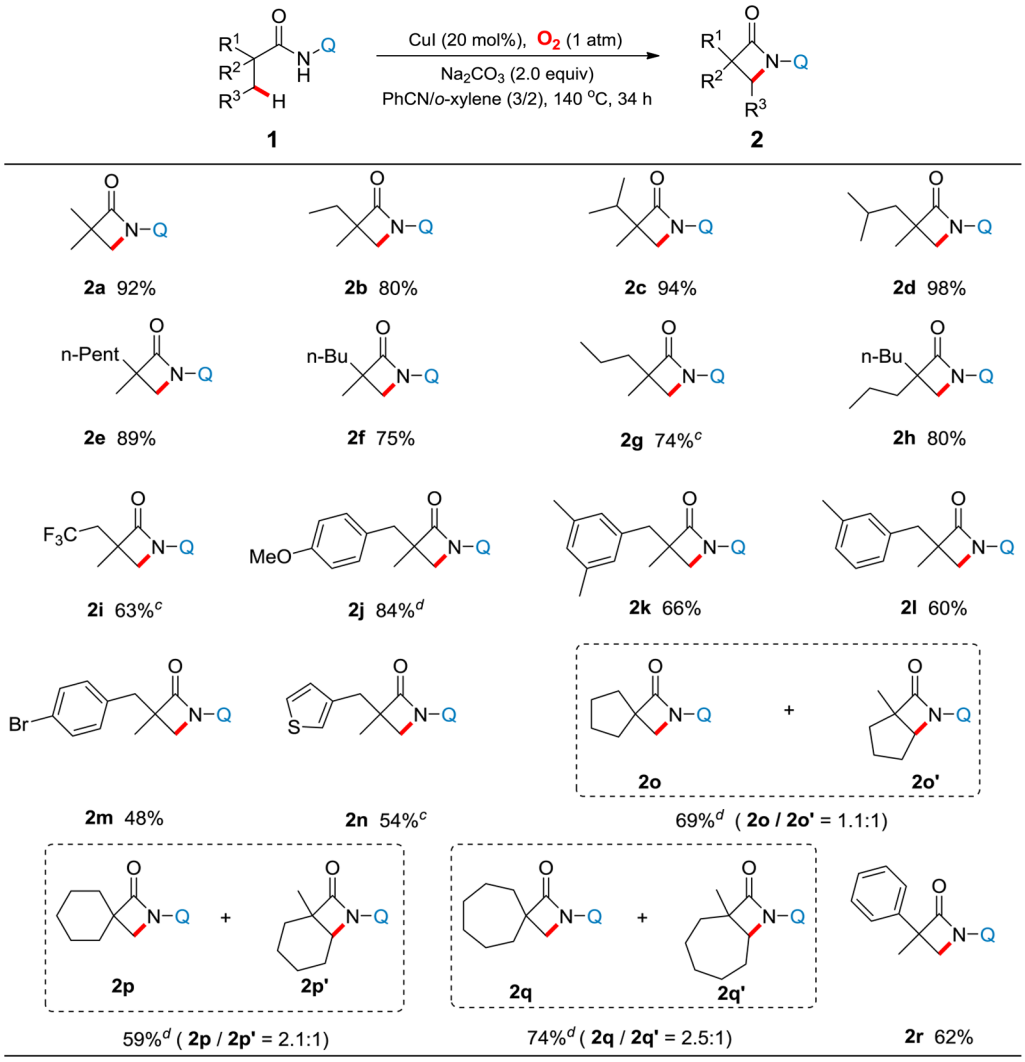
Table 2. Investigation of Substrate Scope[a,b]



[a]Reaction conditions: **1** (0.25 mmol), CuI (20 mol %), and Na_2CO_3 (2.0 equiv) were stirred in PhCN/*o*-xylene (0.3 mL/0.2 mL) at 140 °C for 34 h under an O_2 atmosphere. [b]Isolated yields. [c]Stirred at 170 °C for 34 h. [d]CuCl instead of CuI was used, 34 h, 170 °C.

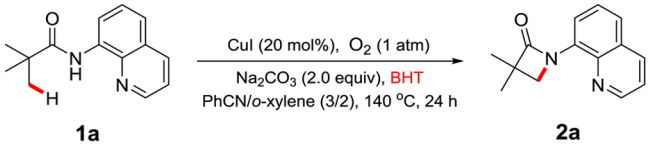
was observed that BHT could significantly suppress this reaction, and no product **2a** was detected in the presence of 2.0 equiv of BHT (Scheme 2), thus indicating that a radical process may be involved in this transformation.

On the basis of the above observations as well as previous reports,[5d,6,7] a plausible mechanism is shown in Scheme 3. Initially, Cu(I) reacts with O_2 to afford a Cu(II)-superoxide radical, which undergoes electron transfer oxidation and H-abstraction to produce a Cu(II)-hydroperoxo species.[6a] Next, the resulting Cu(II) species coordinates with amide **1** to form the *N*,*N*-chelated copper complex **A**. Next, the C(sp^3)−H cupration delivers the cyclometallic intermediate **B**, followed by a disproportionation process to generate Cu(III) complex **C**. It should be mentioned that the possibility of direct oxidation of Cu(II) complex **B** to Cu(III) species **C** by O_2 could not be ruled out at this stage.[2d,7a] Finally, reductive elimination of the complex **C** releases the *β*-lactam **2** and Cu(I) species to accomplish the catalytic cycle.

Removal of the quinolyl moiety is a key step to give free *β*-lactams. However, the current methods generally need the use of the 5-methoxy analogue, which requires a multiple synthetic procedure to access.[5a] Inspired by the transition-metal-catalyzed C(sp^2)−H methoxylation,[8] we found that free *β*-lactams could be feasibly afforded by sequential nickel-catalyzed methoxylation, copper-catalyzed amidation, and oxidative cleavage, which significantly shortened the synthetic route (Scheme 4).

To conclude, a copper-catalyzed intramolecular amidation of an unactivated C(sp^3)−H bond of aliphatic acid derivatives using O_2 as the sole oxidant has been reported. Compared with previously reported transition-metal-catalyzed amidation reactions, the aerobic oxidative functionalization of C(sp^3)−H bonds

Scheme 2. Radical Trapping Experiments



BHT (equiv)	0.2	0.5	1.0	2.0
yield (%)	50	43	17	n. d.

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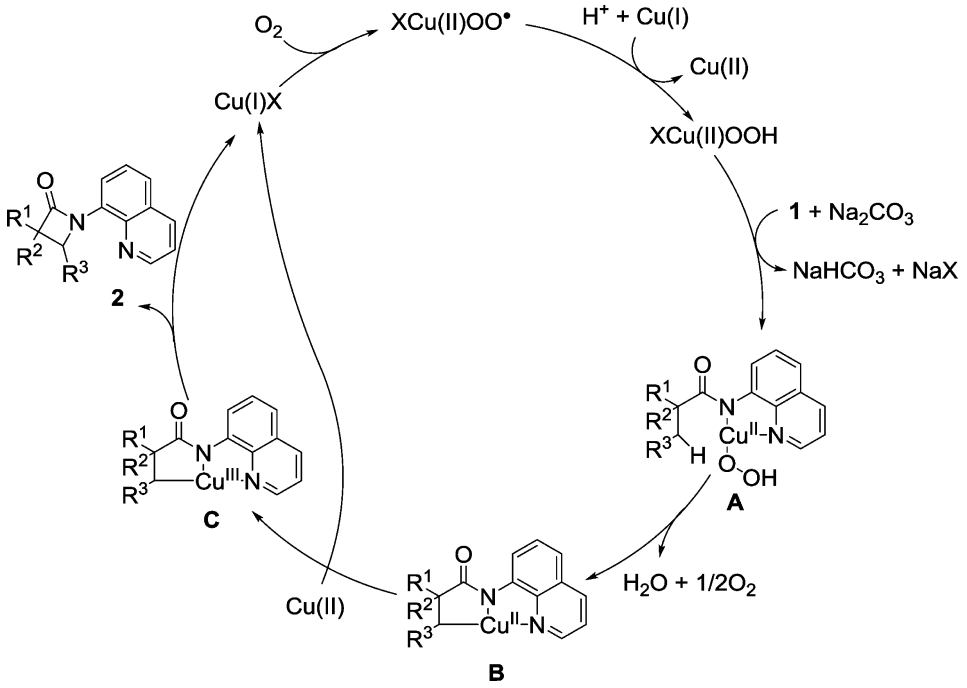
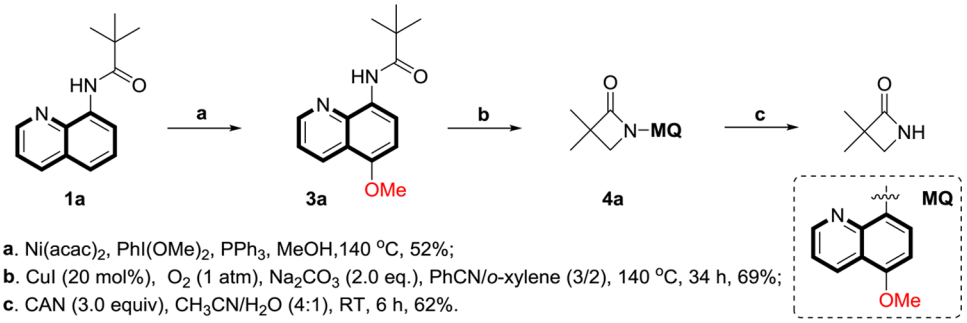
Scheme 3. Proposed Mechanism



Scheme 4. Synthesis of Free *β*-Lactams



a. $Ni(acac)_2$, $PhI(OMe)_2$, PPh_3, MeOH,140 °C, 52%;
b. CuI (20 mol%), O_2 (1 atm), Na_2CO_3 (2.0 eq.), PhCN/*o*-xylene (3/2), 140 °C, 34 h, 69%;
c. CAN (3.0 equiv), CH_3CN/H_2O (4:1), RT, 6 h, 62%.

developed herein provides a more economical and practical approach to diverse *β*-lactams.

EXPERIMENTAL SECTION

General Information. The ^1H NMR (400 MHz) chemical shifts were measured using $CDCl_3$ or TMS as the internal reference ($CDCl_3$: δ = 7.26 ppm, TMS: δ = 0.00 ppm). The ^{13}C NMR (100 MHz) chemical shifts are given using $CDCl_3$ as the internal standard ($CDCl_3$: δ = 77.16 ppm). High-resolution mass spectra (HR-MS) were obtained with a Q-TOF (ESI). Compounds **1a**−**1r** were prepared according to the literature procedure.[5]

2,2,4-Trimethyl-*N*-(quinolin-8-yl)pentanamide (1d). Compound **1d**, pale yellow oil (5.41 g, 67%), was prepared from methyl isobutyrate (3.06 g, 30 mmol) and 1-iodo-2-methylpropane (8.28 g, 45 mmol). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (d, J = 6.8 Hz, 6H), 1.41 (s, 6H), 1.69 (d, J = 6.4 Hz, 2H), 1.73−1.81 (m, 1H), 7.43 (dd, J = 8.4 Hz, 4.4 Hz, 1H), 7.45−7.54 (m, 2H), 8.13 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 8.79−8.82 (m, 2H), 10.28 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.1, 25.4, 26.5, 43.6, 50.4, 116.2, 121.2, 121.6, 127.5, 128.0, 134.7, 136.4, 138.8, 148.3, 177.0 ppm. HRMS (ESI^+): calcd for $C_{17}H_{23}N_2O$ [M + H]$^+$ 271.1810, found 271.1810.

2,2-Dimethyl-*N*-(quinolin-8-yl)hexanamide (1f). Compound **1f**, pale yellow oil (3.89 g, 48%), was prepared from methyl isobutyrate (3.06 g, 30 mmol) and 1-iodobutane (8.28 g, 45 mmol). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.8 Hz, 3H), 1.31−1.34 (m, 4H), 1.40 (s, 6H), 1.69−1.73 (m, 2H), 7.43 (dd, J = 8.0 Hz, 4.0 Hz, 1H), 7.46−7.54 (m, 2H), 8.13 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 8.80 (d, J = 1.6 Hz, 1H), 8.82 (dd, J = 3.2 Hz, 1.6 Hz, 1H), 10.25 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 23.4, 25.8, 27.2, 41.5, 43.9, 116.3, 121.3, 121.6, 127.5, 128.0, 134.8, 136.4, 138.9, 148.3, 176.9 ppm. HRMS (ESI^+): calcd for $C_{17}H_{23}N_2O$ [M + H]$^+$ 271.1810, found 271.1812.

2,2-Dimethyl-*N*-(quinolin-8-yl)pentanamide (1g). Compound **1g**, pale yellow oil (2.48 g, 32%), was prepared from methyl isobutyrate (3.06 g, 30 mmol) and 1-iodopropane (7.65 g, 45 mmol). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, J = 7.2 Hz, 3H), 1.32−1.41 (m, 8H), 1.66−1.70 (m, 2H), 7.40 (dd, J = 8.0 Hz, 4.0 Hz, 1H), 7.43−7.53 (m, 2H), 8.10 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 8.79−8.82 (m, 2H), 10.25 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7, 18.3, 25.7, 43.9, 44.0, 116.2, 121.2, 121.6, 127.5, 127.9, 134.7, 136.3, 138.8, 148.3, 176.8 ppm. HRMS (ESI^+): calcd for $C_{16}H_{21}N_2O$ [M + H]$^+$ 257.1654, found 257.1653.

2-Methyl-2-propyl-*N*-(quinolin-8-yl)hexanamide (1h). Compound **1h**, pale yellow oil (0.85 g, 29%), was prepared from 2-methylpentanoic acid (1.16 g, 10 mmol) and 1-iodobutane (2.76 g, 15 mmol). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.8 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H), 1.24−1.37 (m, 5H), 1.38 (s, 3H), 1.40−1.46 (m, 1H), 1.52−1.62 (m, 2H), 1.77−1.87 (m, 2H), 7.45 (dd, J = 8.4 Hz, 4.4 Hz, 1H), 7.47−7.55 (m, 2H), 8.15 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 8.80−8.83 (m, 2H), 10.23 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 14.8, 18.0, 21.4, 23.5, 26.9, 40.4, 43.0, 47.5, 116.3, 121.2, 121.6, 127.6, 128.1, 134.8, 136.4, 139.0, 148.3, 176.4 ppm. HRMS (ESI^+): calcd for $C_{19}H_{27}N_2O$ [M + H]$^+$ 299.2123, found 299.2125.

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2,2-Dimethyl-3-trifluoromethyl-*N*-(quinolin-8-yl)propanamide (1i). Compound **1i**, yellow oil (0.92 g, 31%), was prepared from methyl isobutyrate (1.02 g, 10 mmol) and 2-iodo-1,1,1-trifluoroethane (4.20 g, 20 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.58 (d, J = 0.8 Hz, 6H), 2.65 (q, J = 11.2 Hz, 2H), 7.47 (dd, J = 8.0 Hz, 4.0 Hz, 1H), 7.51−7.57 (m, 2H), 8.17 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 8.78 (dd, J = 6.4 Hz, 2.4 Hz, 1H), 8.82(dd, J = 4.4 Hz, 1.6 Hz, 1H), 10.38 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 25.8, 41.30−41.33 (m), 43.0 (q, J = 28 Hz), 116.5, 121.8, 121.9, 126.5 (q, J = 276 Hz), 127.5, 128.1, 134.4, 136.5, 138.9, 148.5, 174.2 ppm. HRMS (ESI$^+$): calcd for $C_{15}H_{16}F_3N_2O$ $[M + H]^+$ 297.1215, found 297.1217.

2,2-Dimethyl-*N*-(quinolin-8-yl)-3-(3-thienyl)propanamide (1n). Compound **1n**, yellow solid (7.24 g, 78%), was prepared from methyl isobutyrate (3.06 g, 30 mmol) and 3-bromomethylthiophene (7.97 g, 45 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 6H), 3.07 (s, 2H), 6.92 (dd, J = 4.8 Hz, 1.2 Hz, 1H), 7.01 (d, J = 1.6 Hz, 1H), 7.13 (dd, J = 4.8 Hz, 3.2 Hz, 1H), 7.44 (dd, J = 8.4 Hz, 4.4 Hz, 1H), 7.49−7.57 (m, 2H), 8.15 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 8.77 (dd, J = 4.4 Hz, 1.6 Hz, 1H), 8.83 (dd, J = 7.6 Hz, 1.6 Hz, 1H), 10.19 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.6, 41.5, 44.9, 116.4, 121.5, 121.7, 123.0, 125.0, 127.6, 128.1, 129.7, 134.7, 136.4, 138.4, 138.9, 148.3, 176.2 ppm. HRMS (ESI$^+$): calcd for $C_{18}H_{19}N_2OS$ $[M + H]^+$ 311.1218, found 311.1218.

General Procedure for Copper-Catalyzed C(sp^3)−H Amidation. Amide **1** (0.25 mmol), CuI (9.5 mg, 0.05 mmol), Na_2CO_3 (53.0 mg, 0.5 mmol), and PhCN/*o*-xylene (0.5 mL, 3/2) were added into an oven-dried 35 mL Schlenk tube with a magnetic stir bar under an O_2 atmosphere. Then, the vial was sealed and stirred rigorously at 140 °C for 34 h. After removal of the solvent, the residue was purified by chromatography on silica gel (petroleum ether/EtOAc, 10/1) to give the desired product **2**.

3,3-Dimethyl-1-(quinolin-8-yl)azetidin-2-one (2a).[5d] Purified by column chromatography (petroleum ether/EtOAc, 10/1) as a colorless oil (52.0 mg, 92%).

3-Ethyl-3-methyl-1-(quinolin-8-yl)azetidin-2-one (2b).[5d] Purified by column chromatography (petroleum ether/EtOAc, 10/1) as a pale yellow oil (48.1 mg, 80%).

3-Isopropyl-3-methyl-1-(quinolin-8-yl)azetidin-2-one (2c). Purified by column chromatography (petroleum ether/EtOAc, 10/1) as a pale yellow oil (59.8 mg, 94%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (d, J = 6.8 Hz, 3H), 1.08 (d, J = 6.8 Hz, 3H), 1.41 (s, 3H), 2.03−2.10 (m, 1H), 4.17 (d, J = 7.2 Hz, 1H), 4.39 (d, J = 7.2 Hz, 1H), 7.36 (dd, J = 8.4 Hz, 4.0 Hz, 1H), 7.45−7.50 (m, 2H), 8.08 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 8.49 (dd, J = 5.6 Hz, 3.2 Hz, 1H), 8.80 (dd, J = 4.4 Hz, 2.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.6, 17.8, 18.4, 31.9, 57.0, 59.3, 119.4, 121.2, 122.8, 126.8, 129.1, 135.1, 136.0, 140.5, 148.5, 173.5 ppm; HRMS (ESI$^+$): calcd for $C_{16}H_{18}N_2ONa$ $[M + Na]^+$ 277.1317, found 277.1317.

3-Isobutyl-3-methyl-1-(quinolin-8-yl)azetidin-2-one (2d). Purified by column chromatography (petroleum ether/EtOAc, 10/1) as a pale yellow oil (65.7 mg, 98%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (d, J = 6.4 Hz, 3H), 1.00 (d, J = 6.4 Hz, 3H), 1.44 (s, 3H), 1.55−1.61 (m, 1H), 1.81−1.91 (m, 2H), 4.31 (d, J = 7.6 Hz, 1H), 4.45 (d, J = 7.6 Hz, 1H), 7.37 (dd, J = 8.4 Hz, 4.0 Hz, 1H), 7.46−7.51 (m, 2H), 8.09 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 8.50 (dd, J = 6.4 Hz, 3.2 Hz, 1H), 8.80 (dd, J = 4.4 Hz, 2.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.3, 22.7, 24.4, 25.2, 43.1, 54.9, 60.1, 119.5, 121.3, 122.8, 126.9, 129.1, 135.3, 136.0, 140.5, 148.6, 174.0 ppm; HRMS (ESI$^+$): calcd for $C_{17}H_{20}N_2ONa$ $[M + Na]^+$ 291.1473, found 291.1469.

3-Methyl-3-pentyl-1-(quinolin-8-yl)azetidin-2-one (2e).[5d] Purified by column chromatography (petroleum ether/EtOAc, 10/1) as a pale yellow oil (62.8 mg, 89%).

3-Butyl-3-methyl-1-(quinolin-8-yl)azetidin-2-one (2f). Purified by column chromatography (petroleum ether/EtOAc, 10/1) as a pale yellow oil (50.3 mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, J = 7.2 Hz, 3H), 1.34−1.41 (m, 3H), 1.44 (s, 3H), 1.48−1.60 (m, 1H), 1.73−1.77 (m, 2H), 4.25 (d, J = 7.2 Hz, 1H), 4.40 (d, J = 7.6 Hz, 1H), 7.37 (dd, J = 8.4 Hz, 4.0 Hz, 1H), 7.48−7.49 (m, 2H), 8.09 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 8.50 (dd, J = 5.6 Hz, 3.2 Hz, 1H), 8.80 (dd, J = 4.4 Hz, 2.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 19.7, 23.2, 27.1, 34.8, 55.4, 58.8, 119.5, 121.3, 122.8, 126.9, 129.1, 135.2, 136.0, 140.5, 148.5, 173.6 ppm; HRMS (ESI$^+$): calcd for $C_{17}H_{20}N_2ONa$ $[M + Na]^+$ 291.1473, found 291.1477.

3-Methyl-3-propyl-1-(quinolin-8-yl)azetidin-2-one (2g). Purified by column chromatography (petroleum ether/EtOAc, 10/1) as a pale yellow oil (47.1 mg, 74%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, J = 7.2 Hz, 3H), 1.39−1.48 (m, 4H), 1.54−1.63 (m, 1H), 1.71−1.75 (m, 2H), 4.25 (d, J = 7.2 Hz, 1H), 4.41 (d, J = 7.2 Hz, 1H), 7.37 (dd, J = 8.4 Hz, 4.4 Hz, 1H), 7.46−7.51 (m, 2H), 8.09 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 8.49 (dd, J = 6.0 Hz, 3.2 Hz, 1H), 8.80 (dd, J = 4.0 Hz, 1.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6, 18.3, 19.7, 37.3, 55.5, 58.8, 119.5, 121.3, 122.8, 126.9, 129.1, 135.2, 136.0, 140.5, 148.5, 173.6 ppm; HRMS (ESI$^+$): calcd for $C_{16}H_{18}N_2ONa$ $[M + Na]^+$ 277.1317, found 277.1315.

3-Butyl-3-propyl-1-(quinolin-8-yl)azetidin-2-one (2h). Purified by column chromatography (petroleum ether/EtOAc, 10/1) as a pale yellow oil (59.3 mg, 80%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, J = 6.8 Hz, 3H), 0.97 (t, J = 7.2 Hz, 3H), 1.32−1.61 (m, 6H), 1.71−1.78 (m, 4H), 4.30−4.35 (m, 2H), 7.38 (dd, J = 8.4 Hz, 4.4 Hz, 1H), 7.46−7.51 (m, 2H), 8.10 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 8.50 (dd, J = 6.0 Hz, 3.2 Hz, 1H), 8.81 (dd, J = 4.0 Hz, 1.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 14.7, 18.1, 23.4, 26.9, 33.2, 35.7, 56.5, 59.5, 119.4, 121.3, 122.7, 126.9, 129.1, 135.1, 136.0, 140.5, 148.6, 173.2 ppm; HRMS (ESI$^+$): calcd for $C_{19}H_{25}N_2O$ $[M + H]^+$ 297.1967, found 297.1975.

3-Methyl-1-(quinolin-8-yl)-3-(2,2,2-trifluoroethyl)azetidin-2-one (2i). Purified by column chromatography (petroleum ether/EtOAc, 10/1) as a pale yellow oil (46.3 mg, 63%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.59 (s, 3H), 2.59−2.67 (m, 2H), 4.42 (d, J = 8.0 Hz, 1H), 4.65 (d, J = 8.0 Hz, 1H), 7.39 (dd, J = 8.0 Hz, 4.0 Hz, 1H), 7.47−7.56 (m, 2H), 8.11 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 8.44 (dd, J = 7.6 Hz, 1.6 Hz, 1H), 8.82 (dd, J = 4.0 Hz, 1.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1, 38.1 (q, J = 28 Hz), 51.17−51.19 (m), 58.7, 119.9, 121.5, 123.5, 126.6 (q, J = 277 Hz), 126.8, 129.0, 134.7, 136.1, 140.5, 148.9, 170.3 ppm; HRMS (ESI$^+$): calcd for $C_{15}H_{13}F_3N_2ONa$ $[M + Na]^+$ 317.0878, found 317.0873.

3-(4-Methoxybenzyl)-3-methyl-1-(quinolin-8-yl)azetidin-2-one (2j).[5c] Purified by column chromatography (petroleum ether/EtOAc, 10/1) as a pale yellow oil (69.8 mg, 84%).

3-(3,5-Dimethylbenzyl)-3-methyl-1-(quinolin-8-yl)azetidin-2-one (2k). Purified by column chromatography (petroleum ether/EtOAc, 10/1) as a pale yellow oil (54.5 mg, 66%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 3H), 2.29 (s, 6H), 2.89 (d, J = 14.0 Hz, 1H), 3.14 (d, J = 14.0 Hz, 1H), 4.32 (d, J = 7.2 Hz, 1H), 4.41 (d, J = 7.6 Hz, 1H), 6.85 (s, 1H), 6.92 (s, 2H), 7.36 (dd, J = 8.4 Hz, 4.4 Hz, 1H), 7.48−7.51 (m, 2H), 8.08 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 8.44 (dd, J = 6.4 Hz, 2.8 Hz, 1H), 8.79 (dd, J = 4.4 Hz, 2.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.0, 21.4, 40.7, 56.0, 58.1, 119.8, 121.3, 123.0, 126.8, 127.9, 128.3, 129.0, 135.0, 136.0, 137.3, 137.8, 140.6, 148.6, 173.3 ppm; HRMS (ESI$^+$): calcd for $C_{22}H_{22}N_2ONa$ $[M + Na]^+$ 353.1630, found 353.1633.

3-Methyl-3-(3-methylbenzyl)-1-(quinolin-8-yl)azetidin-2-one (2l). Purified by column chromatography (petroleum ether/EtOAc, 10/1) as a pale yellow oil (47.5 mg, 60%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 3H), 2.33 (s, 3H), 2.92 (d, J = 13.6 Hz, 1H), 3.16 (d, J = 14.0 Hz, 1H), 4.31 (d, J = 7.6 Hz, 1H), 4.42 (d, J = 7.2 Hz, 1H), 7.02 (d, J = 7.2 Hz, 1H), 7.09−7.11 (m, 2H), 7.18 (t, J = 7.6 Hz, 1H), 7.36 (dd, J = 8.0 Hz, 4.0 Hz, 1H), 7.45−7.51 (m, 2H), 8.08 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 8.42 (dd, J = 6.4 Hz, 2.4 Hz, 1H), 8.78 (dd, J = 4.0 Hz, 2.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.0, 21.6, 40.8, 56.0, 58.1, 119.8, 121.3, 123.0, 126.8, 127.1, 127.5, 128.3, 129.1, 130.9, 135.0, 136.0, 137.4, 138.0, 140.6, 148.6, 173.1 ppm; HRMS (ESI$^+$): calcd for $C_{21}H_{20}N_2ONa$ $[M + Na]^+$ 339.1473, found 339.1480.

3-(4-Bromobenzyl)-3-methyl-1-(quinolin-8-yl)azetidin-2-one (2m).[5c] Purified by column chromatography (petroleum ether/EtOAc, 10/1) as a pale yellow oil (45.8 mg, 48%).

3-Methyl-1-(quinolin-8-yl)-3-(thiophen-3-ylmethyl)azetidin-2-one (2n). Purified by column chromatography (petroleum ether/EtOAc, 10/1) as a pale yellow oil (41.6 mg, 54%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 (s, 3H), 3.03 (d, J = 14.4 Hz, 1H), 3.18 (d, J = 14.4 Hz, 1H), 4.32 (d, J = 7.2 Hz, 1H), 4.39 (d, J = 7.2 Hz, 1H), 7.07 (dd, J = 4.8

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Hz, 1.2 Hz, 1H), 7.12 (d, J = 2.0 Hz, 1H), 7.24 (dd, J = 4.8 Hz, 2.8 Hz, 1H), 7.36 (dd, J = 8.4 Hz, 4.0 Hz, 1H), 7.45−7.52 (m, 2H), 8.08 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 8.42 (dd, J = 6.8 Hz, 2.4 Hz, 1H), 8.78 (dd, J = 4.0 Hz, 1.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.9, 35.4, 55.8, 58.1, 119.7, 121.3, 122.9, 123.1, 125.5, 126.8, 129.0, 129.3, 134.9, 136.0, 137.6, 140.5, 148.6, 172.9 ppm; HRMS (ESI$^+$): calcd for $C_{18}H_{16}N_2OSNa$ $[M + Na]^+$ 331.0881, found 331.0883.

2-(Quinolin-8-yl)-2-azaspiro[3.4]octan-1-one (2o).[5d] Purified by column chromatography (petroleum ether/EtOAc, 10/1) as a pale yellow oil (22.1 mg, 35%).

1-Methyl-6-(quinolin-8-yl)-6-azabicyclo[3.2.0]heptan-7-one (2o′).[5d] Purified by column chromatography (petroleum ether/EtOAc, 10/1) as a pale yellow oil (21.4 mg, 34%).

2-(Quinolin-8-yl)-2-azaspiro[3.5]nonan-1-one (2p).[5d] Purified by column chromatography (petroleum ether/EtOAc, 10/1) as a pale yellow oil (26.6 mg, 40%).

1-Methyl-7-(quinolin-8-yl)-7-azabicyclo[4.2.0]octan-8-one (2p′). Purified by column chromatography (petroleum ether/EtOAc, 10/1) as a pale yellow oil (12.7 mg, 19%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36−1.43 (m, 2H), 1.45 (s, 3H), 1.50−1.57 (m, 1H), 1.61−1.73 (m, 2H), 1.82−1.98 (m, 3H), 4.99 (t, J = 3.6 Hz, 1H), 7.39 (dd, J = 8.4 Hz, 4.4 Hz, 1H), 7.49−7.57 (m, 2H), 8.11 (dd, J = 8.0 Hz, J = 1.6 Hz, 1H), 8.39 (dd, J = 7.2 Hz, J = 1.6 Hz, 1H), 8.84 (dd, J = 4.0 Hz, J = 1.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0, 18.4, 21.3, 23.6, 27.9, 53.3, 64.0, 121.3, 123.7, 127.0, 129.2, 134.4, 136.1, 140.7, 148.9, 173.6 ppm; HRMS (ESI$^+$): calcd for $C_{17}H_{18}N_2ONa$ $[M + Na]^+$ 289.1317, found 289.1320.

2-(Quinolin-8-yl)-2-azaspiro[3.6]decan-1-one (2q).[5d] Purified by column chromatography (petroleum ether/EtOAc, 10/1) as a pale yellow oil (37.1 mg, 53%).

1-Methyl-8-(quinolin-8-yl)-8-azabicyclo[5.2.0]nonan-9-one (2q′).[5d] Purified by column chromatography (petroleum ether/EtOAc, 10/1) as a pale yellow oil (14.7 mg, 21%).

3-Methyl-3-phenyl-1-(quinolin-8-yl)azetidin-2-one (2r).[5d] Purified by column chromatography (petroleum ether/EtOAc, 10/1) as a pale yellow oil (44.7 mg, 62%).

1-(5-Methoxyquinolin-8-yl)-3,3-dimethylazetidin-2-one (4a).[5d] Purified by column chromatography (petroleum ether/EtOAc, 8/1) as a pale yellow oil (44.2 mg, 69%).

Synthesis of Compound 3a. Amide **1a** (0.25 mmol), $Ni(acac)_2$ (6.4 mg, 0.05 mmol), $PhI(OMe)_2$ (133.0 mg, 0.5 mmol), PPh_3 (13.1 mg, 0.05 mmol), and MeOH (2 mL) were added into an oven-dried 50 mL Schlenk tube with a magnetic stir bar under an air atmosphere. Then, the vial was sealed and stirred rigorously at 140 °C for 24 h. After removal of the solvent, the residue was purified by chromatography on silica gel (2% EtOAc in petroleum ether, v/v) to afford the desired product **3a** in 52% (33.6 mg) yield as a slightly yellow solid.[5d]

Effect of Radical Scavenger BHT on Copper-Catalyzed C(sp^3)−H Amidation. Amide **1** (0.25 mmol), CuI (9.5 mg, 0.05 mmol), Na_2CO_3 (53.0 mg, 0.5 mmol), BHT (110.2 mg, 0.5 mmol), and PhCN/*o*-xylene (0.5 mL, 3/2) were added into an oven-dried 35 mL Schlenk tube with a magnetic stir bar under an O_2 atmosphere. Then, the vial was sealed and stirred rigorously at 140 °C for 24 h. Upon completion, no desired product was detected.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01302.

Copies of ^{1}H NMR and ^{13}C NMR spectra of the products (PDF)

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Notes

The authors declare no competing financial interest.

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