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Ruthenium-Catalyzed Carbonylation of Oxalyl Amide-Protected Benzylamines with Isocyanate as the Carbonyl Source

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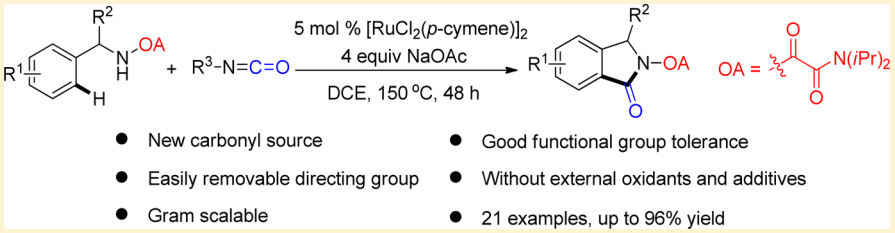
Supporting Information



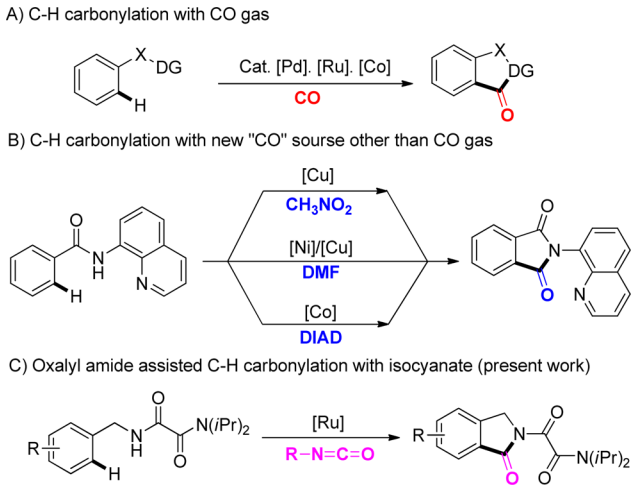
ABSTRACT: An efficient synthesis of isoindolin-1-ones from oxalyl amide-protected benzylamines, through ruthenium-catalyzed intramolecular C(sp^2)-H carbonylation, has been developed. Variously substituted benzylamines could be well tolerated in this new protocol, affording the corresponding products in moderate to excellent yields. This approach constitutes the first example of Ru(II)-catalyzed C(sp^2)-H carbonylation with isocyanate as a novel commercially available carbonyl source.

INTRODUCTION

Transition-metal-catalyzed direct C−H functionlization has become a powerful and efficient tool for the synthesis of hererocycles from relatively simple starting compounds, and substantial achievements have been made during the past decades.[1] Among these strategies, transition-metal-catalyzed carbonylation of C(sp^2)-H with carbon monoxide (CO) as a C1 source is widely applicated in the synthesis of natural products, pharmaceuticals, argrochemicals, and functional materials.[2] In 1980, Fujiwara group first reported carbonylation of some aromatic compounds with CO (15 atm), giving the corresponding carboxylic acids in poor to moderate yields.[3] However, the lack of regioselecetivity with substituted arenes hampered further application of this method. To solve this problem, several groups employed a directing group to direct carbonylation with various transition-metal-catalyst.[4−6] For example, Pd, Ru, and Co-catalyzed processes have been well established on C(sp^2)-H and C(sp^3)-H activation (Scheme 1A).

Despite CO is the most widely used and direct carbonyl source, its application associated with several drawbacks, such as high toxicity. Furthermore, such reactions require high pressure and high temperature limiting the application of strategy. Thus, finding a new carbonyl source is desirable. Recently, Ge group developed a highly regioselecetive copper-promoted carbonylation of unactivated C(sp^3)-H and aromatic C(sp^2)-H bonds of amides using nitromethane as a novel carbon source.[7] Simultaneously, the same group described a chelation-assisted site-selective carbonylation of amides through nickel/copper synergistic catalysis with *N*,*N*-dimethylforamide (DMF) as a new carbon source under atmospheric O_2.[8] Subsequently, Zhang group reported commercially available and easily handling azodicarboxylate as a nontoxic carbonyl source for the same carbonylation reaction under the cobalt catalysis.[9]

Scheme 1. Transition-Metal-Catalyzed Carbonylation of C(sp^2)-H Bonds with Various Carbonyl Source



Isocyanates are versatile intermediates in organic synthesis which readily undergo nucleophilic addition, due to their high reactivity toward a wide variety of reagents. Very recently, Rh^{III} and Ru^{II}-catalyzed amidation of aryl and vinyl C−H bonds with isocyanates has been developed.[10] When the method is applied to achieve the amination of benzylamine substrates with

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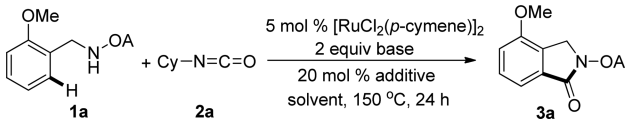
isocyanate, carbonylated product is obtained unexpectedly. Isoindolin-1-one is an important class of building blocks because they are a key synthetic unit of many biologically active and natural products.[11] Herein, we report a Ru-catalyzed carbonylation of oxalyl amide-protected benzylamines with isocyanate as a new carbonyl source.

RESULTS AND DISCUSSION

At the beginning of our study, we treated oxalyl-amide protected benzylamine **1a** with isocyanatocyclohexane **2a** by employing $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) as catalyst, NaOAc (2 equiv) as base in 1,2-dichloroethane (DCE) at 150 °C for 24 h in a sealed vial. Unfortunately, only 38% yield of isoindolin-1-one **3a** was detected by GC at the first run (Table 1, entry1).

Table 1. Optimization of the Reaction Conditions[a]



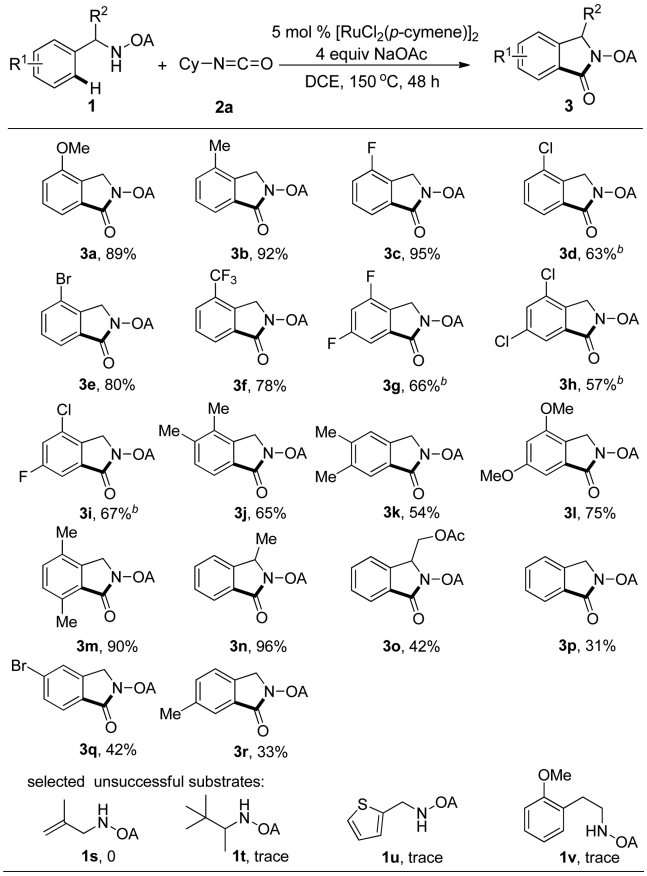
entry	base	additive	solvent	yield (%)[b]
1	NaOAc	none	DCE	38
2	NaOAc	none	toluene	11
3	NaOAc	none	$PhCF_3$	17
4	NaOAc	none	1,4-dioxane	0
5	NaOAc	none	*t*-amyl−OH	0
6	CsOAc	none	DCE	<5
7	KOAc	none	DCE	12
8	$Cu(OAc)_2$	none	DCE	<5
9	Na_2CO_3	none	DCE	9
10	NaOAc	$AgSbF_6$	DCE	30
11	NaOAc	$AgNTf_2$	DCE	7
12	NaOAc	$MesCO_2H$	DCE	<5
13	NaOAc	HOAc	DCE	<5
14[c]	NaOAc	none	DCE	54
15[d]	NaOAc	none	DCE	66
16[e]	NaOAc	none	DCE	95(89)[f]
17[g]	NaOAc	none	DCE	0

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), base (0.2 mmol), additive (20 mol%), solvent (0.5 mL), 150 °C, 24 h. [b]GC yield of **3a** determined using tridecane as internal standard. [c]NaOAc (0.3 mmol). [d]NaOAc (0.4 mmol). [e]**2a** (0.6 mmol), NaOAc (0.4 mmol), 48 h. [f]Isolated yield. [g]No catalyst.

Screening other solvents, including toluene, benzotrifluoride, 1,4-dioxane, and *t*-amyl−OH, led to the identification of DCE as the optimal solvent (Table 1, entries 2−5). We subsequently tested other bases, such as CsOAc, KOAc, $Cu(OAc)_2$, and Na_2CO_3. However, none of them gave better results. Additives, such as $AgSbF_6$, $AgNTf_2$, $MesCO_2H$, and HOAc, were also investigated, displaying no positive effect on the product yield and even inhibiting the reaction (Table 1, entries 10−13). It was notable that the yield of **3a** was improved greatly to 66% with the increase of the amount of NaOAc (Table 1, entries 14−15). Further optimazation showed this reaction could be significantly improved to 95% yield by increasing the amount of isocyanatocyclohexane to 6 equiv and prolonging the reaction time to 48 h (Table 1, entry 16). We have also noticed that the reaction could not proceed without a ruthenium catalyst, indicating the irreplaceable role of Ru catalyst for this process.

With the optimized conditions in hand, the scope of oxalyl-amide protected benzylamine was examined. As illustrated in Table 2, a broad range of benzylamine substrates were tolerated and carbonylated products were obtained in moderate to

Table 2. Substrate Scope of Benzylamide[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (1.2 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), NaOAc (0.8 mmol), DCE (1 mL), 150 °C, 48 h. Isolated yields. [b]160 °C.

excellent yields. With either electron-donating groups (MeO, Me) or electron-withdrawing (halide, CF_3), benzylamine was readily converted to the corresponding products (**3a−f**). Lower yields were observed in the cases of disubstituted substrates, for example, 66% for **3g**, 65% for **3j**. It was worth it to mention that the 2,5-dimethyl substitued benzylamine showed good compatibility with the protocol under the standard conditions, affording the desired product in 90% yield (**3m**). For substitution on α position, such as Me and CH_2OAc, it was found that both of them could be carbonylated with isocyanatocyclohexane in moderate to excellent yields (**3n−o**). Unfortuantely, when the *meta*- and *para*-substitued substrates were applied to the method, the reaction did not proceed cleanly and unreacted starting materials recovered, and the corresponding products were obtained in low yields. Notably, *ortho*-substitution effect is obvious, we speculate that the *ortho* functional group causes the alkyl chain hard to spin easily, which is beneficial for the sequent cyclization. A series of other oxalyl amide protected amines (**1s−v**) were also tested, all failing to give any carbonylated products.

Meanwhile, other commercially available isocyanatates were examined in this protocol (Table 3). We were pleased to observe that they were also suitable as the carbonyl source, and desired product **3a** was obtained in low to moderate yields.

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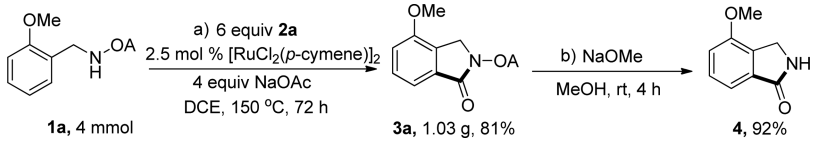
Scheme 2. Scaling Up and Removal of Directing Group



Scheme 3. Preliminary Mechanistic Studies

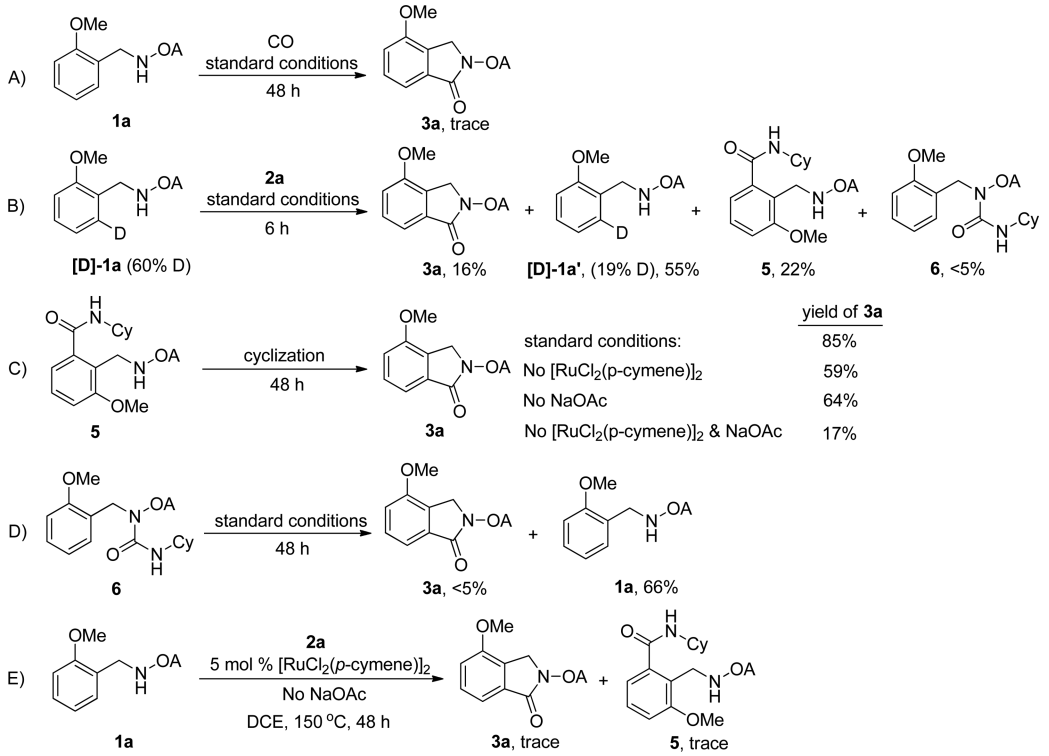
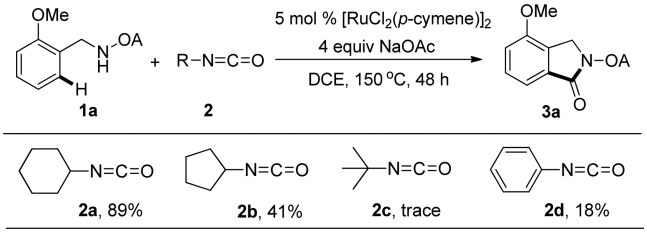


Table 3. Substrate Scope of Isocyanate[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2** (1.2 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), NaOAc (0.8 mmol), DCE (1 mL), 150 °C, 48 h. Isolated yields.

Besides, the gram-scale reaction was successfully achieved with 2.5 mol% $[RuCl_2(p\text{-cymene})]_2$ in 81% yield, which highlighted the power of this approach. And the oxalyl amide directing group could be removed readily under mild conditions in excellent yield (Scheme 2).

To gain insight into the mechanism of this C−H carbonylation process, some additional experiments were performed. First, we attempted to carbonylate the substrate **1a** with CO gas. This did not lead to the formation of the desired product **2a**, thus only starting material **1a** was recovered after 48 h. It indicated that the reaction did not involve CO insertion (Scheme 3A). A deuterium-labeling experiment was then conducted to further probe the mechanism. As shown in Scheme 3B, an apparent H/D exchange of the substrate was observed when [**D**]-**1a** was subjected to the standard conditions for 6 h, suggesting that C−H bond cleavage was a reversible step. Meanwhile, the amidated product **5** was obtained in 22% yield and the urea derivative **6** was detected in <5% yield by HRMS (Scheme 3B). The amidated product **5** could be converted to the carbonylated product **3a** in 85% yield under standard conditions (Scheme 3C). However, the urea derivative **6** prepared could only be converted to the desired product **5** in <5% yield under the standard conditions, along with the starting material **1a** recovered (Scheme 3D). We speculated that the amidated product **5** was most likely the key intermediate in this protocol. A series of control experiments were carried out to investigate the transformation of **5** to **3a**. It was found that the catalyst $[RuCl_2(p\text{-cymene})]_2$, the base NaOAc, and the high temperature all promoted the cyclization reaction. However, neither the product **3a** nor the key intermediate **5** was obtained under standard conditions without NaOAc, indicating the base played an important role in this process (Scheme 3E).

Based on the previous report of transition-metal-catalyzed C−H bond activation[12−14] and above mechanistic studies, a possible mechanism to account for the present catalytic reaction is proposed (Scheme 4). The catalytic cycle is likely initiated by the dissociation of the $[RuCl_2(p\text{-cymene})]_2$ dimer into the coordinatively unsaturated monomer and the exchange of acetate with the coordinated chloro ligand to form an acetate-ligated species.[10] Then the subsequent acetate-mediated

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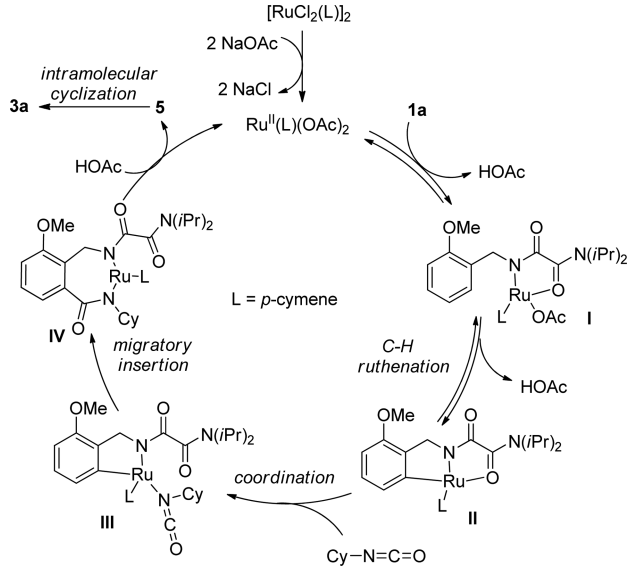
Scheme 4. Proposed Reaction Catalytic Cycle



deprotonation leads to ruthenacycle **I**, which undergo reversible cyclometalation to give the complex **II**. Coordination of the isocyanate **2a**, followed by migratory insertion, forms the C−C bond and produces key intermediate **III**. Protonation of **IV** by acetic acid affords the amidated product **5** and regenerates the active Ru(II) species for the next cycle. The key intermediate **5** subsequently goes through an intramolecular N-nucleophilic cyclization to afford isoindolin-1-one product **3a**.

CONCLUSION

In summary, we have developed a novel ruthenium-catalyzed carbonylation of oxalyl amide-protected benzylamines with isocyanate for the synthesis of isoindolin-1-one. Variously substituted benzylamines could be well tolerated in this new protocol, affording the corresponding products in moderate to excellent yields. The mechanism of this C−H carbonylation process is investigated in detail and the amidated product is recognized as the key intermediate in this protocol. To the best of our knowledge, this is the first example where Ru(II)-catalyzed direct C(sp^2)-H functionalization of amide using isocyanate as a commercially available and novel carbonyl source.

EXPERIMENTAL SECTION

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. HRMS analysis was carried out using TOF-MS instrument with ESI source. Multiplicities are recorded as s = singlet, d = doublet, t = triplet, dd = doublet of doublets, br s = broad singlet, m = multiplet. General procedures for the synthesis of products are represented as follows:

Preparation of S1. A solution of diisopropylamine (7.01 mL, 50 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) was added dropwise to a solution of oxalyl chloride (6.44 mL, 75 mmol, 1.5 equiv) in CH_2Cl_2 (100 mL) at 0 °C. After 5 min of stirring, triethylamine (7.30 mL, 52.5 mmol, 1.05 equiv) was added dropwise. The solution was warmed to room temperature and stirred for 6 h. Excess oxalyl chloride and solvent were removed under reduced pressure, and CH_2Cl_2 (30 mL) was added and evaporated. This operation was performed twice to give **S1** as a pale yellow solid. The crude product was used in the next step without any purification.

*N,N-Diisopropyloxamoyl Chloride **S1***. Yield 95% (8.4 g); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (m, 1H), 3.51 (m, 1H), 1.41 (d, J = 6.9 Hz, 6H), 1.24 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 158.8, 51.0, 46.5, 20.3, 19.8; HRMS calcd for $C_8H_{14}ClNNaO_2$ [M+Na$^+$] 214.0611, found: 214.0609.

General Procedures for Preparation of Oxalyl Amide Protected Amines (1a−1v). A solution of amine (20 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL) was added dropwise to a solution of *N,N*−diisopropyloxamoyl chloride **S1** (25 mmol, 1.25 equiv) in CH_2Cl_2 (50 mL) at 0 °C. After 5 min of stirring, triethylamine (2.92 mL, 21 mmol, 1.05 equiv) was added dropwise, and then the mixture was stirred for 6 h at room temperature before being quenched by water (50 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (20 mL × 3). The combined organic phase was washed with brine (30 mL) and dried over anhydrous Na_2SO_4. Evaporation and column chromatography on silica gel afforded corresponding amide substrates as white solid >70% yield.

*N^1,N^1-Diisopropyl-N^2-(2-methoxybenzyl)oxalamide (**1a**)*. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (7/1) as an eluent; yield 86% (5.03 g); white solid; mp = 113−114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (br s, 1H), 7.28−7.25 (m, 2H), 6.93−6.86 (m, 2H), 4.77−4.73 (m, 1H), 4.46 (d, J = 5.8 Hz, 2H), 3.85 (s, 3H), 3.51−3.48 (m, 1H), 1.41 (d, J = 6.6 Hz, 6H), 1.21 (d, J = 6.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 162.9, 157.6, 129.7, 129.1, 125.5, 120.6, 110.3, 55.4, 49.6, 46.5, 39.1, 20.9, 20.1; HRMS Calcd for $C_{16}H_{24}N_2NaO_3$ [M+Na$^+$]: 315.1685; Found: 315.1678.

*N^1,N^1-Diisopropyl-N^2-(2-methylbenzyl)oxalamide (**1b**)*. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (8/1) as an eluent; yield 88% (4.86 g); white solid; mp = 124−125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.21 (m, 1H), 7.20−7.14 (m, 3H), 7.11 (br s, 1H), 4.81−4.74 (m, 1H), 4.45 (d, J = 5.7 Hz, 2H), 3.54−3.48 (m, 1H), 2.33 (s, 3H), 1.41 (d, J = 6.8 Hz, 6H), 1.24 (d, J = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0, 162.9, 136.5, 135.2, 130.6, 128.6, 128.0, 126.4, 49.8, 46.7, 41.6, 21.0, 20.2, 19.1; HRMS Calcd for $C_{16}H_{24}N_2NaO_2$ [M+Na$^+$]: 299.1735; Found: 299.1729.

*N^1-(2-Fluorobenzyl)-N^2,N^2-diisopropyloxalamide (**1c**)*. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (10/1) as an eluent; yield 79% (4.42 g); white solid; mp = 111−113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.32 (m, 1H), 7.30−7.24 (m, 2H), 7.23 (br s, 1H), 7.13−7.09 (m, 1H), 7.17−7.02 (m, 1H), 4.83−4.76 (m, 1H), 4.52 (d, J = 6.2 Hz, 2H), 3.55−3.48 (m, 1H), 1.42 (d, J = 6.8 Hz, 6H), 1.23 (d, J = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 162.7, 135.9, 131.4 (d, J_{C-F} = 222.0 Hz), 128.4 (d, J_{C-F} = 30.0 Hz), 127.9, 126.2 (d, J_{C-F} = 6.0 Hz), 126.0 (d, J_{C-F} = 29.0 Hz), 49.8, 46.8, 39.9, 21.0, 20.1; HRMS Calcd for $C_{15}H_{21}FN_2NaO_2$ [M+Na$^+$]: 303.1485; Found: 303.1485.

*N^1-(2-Chlorobenzyl)-N^2,N^2-diisopropyloxalamide (**1d**)*. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (10/1) as an eluent; yield 83% (4.91 g); white solid; mp = 147−149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (br s, 1H), 7.38−7.33 (m, 2H), 7.22−7.20 (m, 2H), 4.71−4.64 (m, 1H), 4.54 (d, J = 6.2 Hz, 2H), 3.52−3.45 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 1.20 (d, J = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 162.9. 134.9, 133.7, 129.9, 129.6, 129.0, 127.1, 49.7, 46.6, 41.2, 20.9, 20.1; HRMS Calcd for $C_{15}H_{21}ClN_2NaO_2$ [M+Na$^+$]: 319.1189; Found: 319.1188.

*N^1-(2-Bromobenzyl)-N^2,N^2-diisopropyloxalamide (**1e**)*. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (10/1) as an eluent; yield 82% (5.58 g); white solid; mp = 155−157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, J = 7.9, 1.0 Hz, 1H), 7.39 (dd, J = 7.6, 1.5 Hz, 1H), 7.35 (br s, 1H), 7.30−7.27 (m, 1H), 7.17−7.13 (m, 1H), 4.79−4.73 (m, 1H), 4.54 (d, J = 6.3 Hz, 2H), 3.55−3.48 (m, 1H), 1.41 (d, J = 6.8 Hz, 6H), 1.22 (d, J = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 162.8, 136.6, 133.0, 130.1, 129.4, 127.9, 123.8, 49.7, 46.7, 43.7, 21.0, 20.2; HRMS Calcd for $C_{15}H_{21}BrN_2NaO_2$ [M+Na$^+$]: 363.0684; Found: 363.0677.

*N^1,N^1-Diisopropyl-N^2-(2-(trifluoromethyl)benzyl)oxalamide (**1f**)*. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (9/1) as an eluent; yield 73% (4.82 g); white solid; mp = 121−123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 7.9 Hz, 1H), 7.57−7.51 (m, 2H), 7.41−7.38 (m, 1H), 7.20 (br s, 1H),

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4.82−4.75 (m, 1H), 4.66 (d, J = 6.3 Hz, 2H), 3.56−3.49 (m, 1H), 1.42 (d, J = 6.8 Hz, 6H), 1.24 (d, J = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 162.8, 161.1 (d, J_{C-F} = 245.0 Hz), 130.2 (d, J_{C-F} = 5.0 Hz), 129.6 (d, J_{C-F} = 8.1 Hz), 124.6 (d, J_{C-F} = 15.0, Hz), 124.4 (d, J_{C-F} = 4.0 Hz), 115.6 (d, J_{C-F} = 21.0 Hz), 49.7, 46.7, 37.4 (d, J_{C-F} = 4.0 Hz), 21.0, 20.2; HRMS Calcd for $C_{16}H_{21}F_3N_2NaO_2$ [M+Na$^+$]: 353.1453; Found: 353.1459.

*N^1-(2,4-Difluorobenzyl)-N^2,N^2-diisopropyloxalamide (**1g**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (12/1) as an eluent; Yield 90% (5.36 g); white solid; mp = 105−106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (br s, 1H), 7.31 (dd, J = 14.9, 8.3 Hz, 1H), 6.83−6.75 (m, 2H), 4.71−4.65 (m, 1H), 4.44 (d, J = 6.1 Hz, 2H), 3.52−3.45 (m, 1H), 1.37 (d, J = 6.8 Hz, 6H), 1.20 (d, J = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 163.1 (dd, J_{C-F} = 154.0 Hz, 12.0 Hz), 163.0, 160.6 (dd, J_{C-F} = 154.0 Hz, 12.0 Hz), 131.1 (dd, J_{C-F} = 10.0 Hz, 6.0 Hz), 120.7 (dd, J_{C-F} = 15.0 Hz, 4.0 Hz), 111.5 (dd, J_{C-F} = 22.0 Hz, 4.0 Hz), 104.0 (t, J_{C-F} = 26.0 Hz), 49.8, 46.7, 36.8, 36.7, 20.9, 20.1; HRMS Calcd for $C_{15}H_{20}F_2N_2NaO_2$ [M+Na$^+$]: 321.1391, Found: 321.1394.

*N^1-(2,4-Dichlorobenzyl)-N^2,N^2-diisopropyloxalamide (**1h**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (10/1) as an eluent; yield 78% (5.15 g); white solid; mp = 114−115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (br s, 1H), 7.38 (d, J = 2.1 Hz, 1H), 7.33 (d, J = 8.3 Hz, 1H), 7.21 (dd, J = 8.3, 2.1 Hz, 1H), 4.76−4.69 (m, 1H), 4.50 (d, J = 6.3 Hz, 2H), 3.54−3.48 (m, 1H), 1.40 (d, J = 6.8 Hz, 6H), 1.22 (d, J = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4, 163.0, 134.3, 134.0 133.8, 130.7, 129.4, 127.4, 49.8, 46.6, 40.6, 20.9, 20.1; HRMS Calcd for $C_{15}H_{20}Cl_2N_2NaO_2$ [M+Na$^+$]: 353.0800, Found: 353.0776.

*N^1-(2-Chloro-4-fluorobenzyl)-N^2,N^2-diisopropyloxalamide (**1i**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (12/1) as an eluent; yield 83% (5.21 g); white solid; mp = 98−100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (br s, 1H), 7.35 (dd, J = 8.5, 6.0 Hz, 1H), 7.09 (dd, J = 8.4, 2.6 Hz, 1H), 6.94−6.90 (m, 1H), 4.67−4.60 (m, 1H), 4.48 (d, J = 6.2 Hz, 2H), 3.51−3.44 (m, 1H), 1.36 (d, J = 6.8 Hz, 6H), 1.19 (d, J = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 163.0, 162.0 (d, J_{C-F} = 248.0 Hz), 134.3 (d, J_{C-F} = 5.0 Hz), 131.14, 131.10, 131.05, 117.0 (d, J_{C-F} = 25.0 Hz), 114.3 (d, J_{C-F} = 21.0 Hz), 49.8, 46.6, 40.6, 20.9, 20.1; HRMS Calcd for $C_{15}H_{20}ClFN_2NaO_2$ [M+Na$^+$]: 337.1095, Found 337.1091.

*N^1-(2,3-Dimethylbenzyl)-N^2,N^2-diisopropyloxalamide (**1j**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (10/1) as an eluent; yield 91% (5.28 g); white solid; mp = 93−95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12−7.07 (m, 3H), 6.96 (br s, 1H), 4.82−4.75 (m, 1H), 4.47 (d, J = 5.6 Hz, 2H), 3.54−3.48 (m, 1H), 2.29 (s, 3H), 2.22 (s, 3H), 1.41 (d, J = 6.8 Hz, 6H), 1.24 (d, J = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0, 162.9, 137.5, 135.2, 135.0, 129.8, 126.8, 125.8, 49.8, 46.6, 42.3, 21.0, 20.5, 20.1, 14.9; HRMS Calcd for $C_{17}H_{26}N_2NaO_2$ [M+Na$^+$]: 313.1892; Found: 313.1887.

*N^1-(3,4-Dimethylbenzyl)-N^2,N^2-diisopropyloxalamide (**1k**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (12/1) as an eluent; yield 92% (5.33 g); white solid; mp = 113−115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (br s, 1H), 7.09−7.01 (m, 3H), 4.80−4.74 (m, 1H), 4.37 (d, J = 5.7 Hz, 2H), 3.53−3.47 (m, 1H), 2.23 (s, 6H), 1.40 (d, J = 6.8 Hz, 6H), 1.23 (d, J = 6.6 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.0, 137.0, 136.0, 134.8, 130.0, 129.26, 125.3, 49.7, 46.6, 43.2, 20.9, 20.1, 19.8, 19.5; HRMS Calcd for $C_{17}H_{26}N_2NaO_2$ [M+Na$^+$]: 313.1892; Found: 313.1877.

*N^1-(2,4-Dimethoxybenzyl)-N^2,N^2-diisopropyloxalamide (**1l**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (8/1) as an eluent; yield 76% (4.89 g); white solid; mp = 137−139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19−7.17 (m, 2H), 6.44−6.40 (m, 2H), 4.80−4.73 (m, 1H), 4.38 (d, J = 6.0 Hz, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.52−3.45 (m, 1H), 1.40 (d, J = 6.8 Hz, 6H), 1.21 (d, J = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 162.8, 160.7, 158.7, 130.5, 118.1, 103.9, 98.6, 55.44, 55.42, 49.6, 46.5, 38.8, 20.9, 20.1; HRMS Calcd for $C_{17}H_{26}N_2NaO_4$ [M+Na$^+$]: 345.1790; Found: 345.1783.

*N^1-(2,5-Dimethylbenzyl)-N^2,N^2-diisopropyloxalamide (**1m**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (9/1) as an eluent; yield 88% (5.10 g); white solid; mp = 95−97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (br s, 1H), 7.06−7.04 (m, 2H), 7.01−6.99 (m, 1H), 4.75−4.67 (m, 1H), 4.40 (d, J = 5.7 Hz, 2H), 3.53−3.46 (m, 1H), 2.29−2.28 (m, 6H), 1.39 (d, J = 6.8 Hz, 6H), 1.23 (d, J = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2. 163.0, 135.7, 134.9, 133.2, 130.4, 129.3, 128.5, 49.7, 46.5, 41.4, 21.0, 20.9, 20.1, 18.6; HRMS Calcd for $C_{17}H_{26}N_2NaO_2$ [M+Na$^+$]: 313.1892; Found: 313.1894.

*N^1,N^1-Diisopropyl-N^2-(1-phenylethyl)oxalamide (**1n**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (10/1) as an eluent; yield 86% (4.75 g); white solid; mp = 142−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (br s, 1H), 7.35−7.28 (m, 4H), 7.25−7.20 (m, 1H), 5.07−5.00 (m, 1H), 4.65−4.61 (m, 1H), 3.51−3.44 (m, 1H), 1.48 (d, J = 7.0 Hz, 3H), 1.40 (dd, J = 9.7, 6.8 Hz, 6H), 1.18 (dd, J = 9.9, 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 162.4, 143.0, 128.7, 127.3, 126.1, 49.7, 49.1, 46.5, 22.0, 20.8, 20.1; HRMS Calcd for $C_{16}H_{24}N_2NaO_2$ [M+Na$^+$]: 299.1735; Found: 299.1734.

*2-(2-(Diisopropylamino)-2-oxoacetamido)-2-phenylethyl Acetate (**1o**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (7/1) as an eluent; yield 82% (5.48 g); white solid; mp = 114−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.2 Hz, 1H), 7.33−7.27 (m, 5H), 5.26−5.21 (m, 1H), 4.74−4.67 (m, 1H), 4.35 (d, J = 5.8 Hz, 2H), 3.55−3.48 (m, 1H), 2.03 (s, 3H), 1.42 (dd, J = 9.7, 6.8 Hz, 6H), 1.21 (dd, J = 6.6, 4.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 162.8, 137.8, 128.9, 128.1, 126.8, 66.2, 52.4, 49.7, 46.7, 20.9, 20.8, 20.2, 20.1; HRMS Calcd for $C_{18}H_{26}N_2NaO_4$ [M+Na$^+$]: 357.1790; Found: 357.1791.

*N^1-Benzyl-N^2,N^2-diisopropyloxalamide (**1p**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (6/1) as an eluent; yield 91% (4.77 g); white solid; mp = 102−103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.27 (m, 5H), 7.20 (br s, 1H), 4.87−4.80 (m, 1H), 4.46 (d, J = 6.0 Hz, 2H), 3.56−3.49 (m, 1H), 1.42 (d, J = 6.8 Hz, 6H), 1.24 (d, J = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 163.0, 137.5, 128.8, 127.9, 127.7, 49.7, 46.7, 43.4, 21.0, 20.1; HRMS Calcd for $C_{15}H_{22}N_2NaO_2$ [M+Na$^+$]: 285.1579; Found: 285.1579.

*N^1-(3-Bromobenzyl)-N^2,N^2-diisopropyloxalamide (**1q**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (9/1) as an eluent; yield 84% (5.71 g); white solid; mp = 103−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (br s, 1H), 7.41−7.39 (m, 2H), 7.24−7.18 (m, 2H), 4.82−4.75 (m, 1H), 4.42 (d, J = 6.1 Hz, 2H), 3.56−3.49 (m, 1H), 1.41 (d, J = 6.8 Hz, 6H), 1.24 (d, J = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 163.0, 140.0, 130.8, 130.7, 130.3, 126.4, 122.8, 49.8, 46.7, 42.7, 20.9, 20.1; HRMS Calcd for $C_{15}H_{21}BrN_2NaO_2$ [M+Na$^+$]: 363.0684; Found: 363.0677.

*N^1,N^1-Diisopropyl-N^2-(4-methylbenzyl)oxalamide (**1r**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (12/1) as an eluent; yield 80% (4.42 g); white solid; mp = 112−113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (br s, 1H), 7.19−7.12 (m, 4H), 4.83−4.77 (m, 1H), 4.40 (d, J = 5.9 Hz, 2H), 3.54−3.47 (m, 1H), 2.32 (s, 3H), 1.40 (d, J = 6.8 Hz, 6H), 1.23 (d, J = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1, 136.4, 133.5, 128.5, 126.9, 48.7, 45.7, 42.2, 20.2, 20.0, 19.2; HRMS Calcd for $C_{16}H_{24}N_2NaO_2$ [M+Na$^+$]: 299.1735; Found: 299.1734.

*N^1,N^1-Diisopropyl-N^2-(2-methylallyl)oxalamide (**1s**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (8/1) as an eluent; yield 82% (3.71 g); white solid; mp = 60−61 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (br s, 1H), 4.86 (d, J = 10.1 Hz, 2H), 4.74−4.67 (m, 1H), 3.81 (d, J = 6.2 Hz, 2H), 3.53−3.47 (m, 1H), 1.74 (s, 3H), 1.41 (dd, J = 6.8, 2.2 Hz, 6H), 1.22−1.21 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4, 163.3, 141.2, 111.4, 49.8, 46.6, 44.8, 20.9, 20.4, 20.1; HRMS Calcd for $C_{12}H_{22}N_2NaO_2$ [M+Na$^+$]: 249.1579; Found: 249.1573.

*N^1-(3,3-Dimethylbutan-2-yl)-N^2,N^2-diisopropyloxalamide (**1t**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (9/1) as an eluent; yield 82% (3.71 g); white solid; mp = 111−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (br s, 1H),

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4.64−4.60 (m, 1H), 3.85−3.78 (m, 1H), 3.49−3.46 (m, 1H), 1.40−1.38 (m, 6H), 1.20−1.19 (m, 6H), 1.07 (dd, J = 6.8, 1.7 Hz, 3H), 0.89 (d, J = 1.9 Hz, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 162.8, 53.0, 49.8, 46.5, 34.4, 26.2, 21.0, 20.9, 20.8, 20.3, 20.2, 20.1, 15.8; HRMS Calcd for $C_{14}H_{28}N_2NaO_2$ [M+Na$^+$]: 279.2048; Found: 279.2043.

*N^1,N^1-Diisopropyl-N^2-(thiophen-2-ylmethyl)oxalamide (**1u**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (8/1) as an eluent; yield 77% (4.13 g); white solid; mp = 127−129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (br s, 1H), 7.21 (d, J = 5.1 Hz, 1H), 6.98 (d, J = 3.0 Hz, 1H), 6.94−6.92 (m, 1H), 4.74−4.68 (m, 1H), 4.60 (d, J = 5.9 Hz, 2H), 3.53−3.46 (m, 1H), 1.39 (d, J = 6.8 Hz, 6H), 1.22 (d, J = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0, 140.1, 127.0, 126.4, 125.4, 49.8, 46.7, 38.0, 21.0, 20.1; HRMS Calcd for $C_{13}H_{20}N_2NaO_2S$ [M+Na$^+$]: 291.1143; Found: 291.1136.

*N^1,N^1-Diisopropyl-N^2-(2-methoxyphenethyl)oxalamide (**1v**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (10/1) as an eluent; yield 92% (5.63 g); white solid; mp = 80−81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22−7.18 (m, 1H), 7.14−7.12 (m, 2H), 6.90−6.83 (m, 2H), 4.64−4.57 (m, 1H), 3.82 (s, 3H), 3.53−3.43 (m, 3H), 2.86 (t, J = 6.9 Hz, 2H), 1.39 (d, J = 6.8 Hz, 6H), 1.18 (d, J = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 156.6, 129.6, 126.9, 126.1, 119.6, 109.3, 54.3, 48.6, 45.4, 38.6, 29.1, 19.9, 19.1; HRMS Calcd for $C_{17}H_{25}N_2O_3$ [M−H$^+$]: 305.1865; Found: 305.1865.

General Procedure for Ruthenium-Catalyzed Carbonylation of Benzylamine with Isocyanatocyclohexane (Table 2) (3a−3c, 3e−3f, 3j−3r). A mixture of oxalyl amide-protected benzylamine **1** (0.2 mmol, 1 equiv), isocyanatocyclohexane **2a** (1.2 mmol, 6 equiv), $[RuCl_2(p\text{-cymene})_2]_2$ (6.1 mg, 5 mol %), NaOAc (65.6 mg, 4 equiv), and DCE (1 mL) in a 15 mL glass vial [sealed with poly(tetrafluoroethylene) (PTFE) cap] was heated at 150 °C with vigorous stirring for 48 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through Celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel to give the corresponding product.

*N,N-Diisopropyl-2-(4-methoxy-1-oxoisoindolin-2-yl)-2-oxoacetamide (**3a**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (4/1) as an eluent; yield 89% (56.6 mg); white solid; mp = 176−178 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.44 (m, 2H), 7.12 (dd, J = 6.4, 2.5 Hz, 1H), 4.76 (s, 2H), 3.92 (s, 3H), 3.69−3.62 (m, 1H), 3.59−3.52 (m, 1H), 1.57 (s, 6H), 1.24 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 164.1, 162.9, 155.1, 131.6, 130.7, 130.5, 117.0, 115.4, 55.8, 51.1, 46.0, 45.0, 34.0, 25.7, 25.1, 20.3; HRMS Calcd for $C_{17}H_{22}N_2NaO_4$ [M+Na$^+$]: 341.1477; Found: 341.1466.

*N,N-Diisopropyl-2-(4-methyl-1-oxoisoindolin-2-yl)-2-oxoacetamide (**3b**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (5/1) as an eluent; yield 92% (55.6 mg); white solid; mp = 193−194 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 7.4 Hz, 1H), 7.49−7.41 (m, 2H), 4.77 (s, 2H), 3.70−3.63 (m, 1H), 3.60−3.53 (m, 1H), 2.39 (s, 3H), 1.57 (s, 6H), 1.24 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 164.3, 162.9, 140.9, 135.4, 133.7, 130.0, 129.3, 123.0, 51.1, 46.3, 46.1, 20.5, 17.6; HRMS Calcd for $C_{17}H_{22}N_2NaO_3$ [M+Na$^+$]: 325.1528; Found: 325.1527.

*2-(4-Fluoro-1-oxoisoindolin-2-yl)-N,N-diisopropyl-2-oxoacetamide (**3c**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (7/1) as an eluent; yield 95% (58.1 mg); pale yellow solid; mp = 143−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 7.6 Hz, 1H), 7.55−7.50 (m, 1H), 7.38 (t, J = 8.4 Hz, 1H), 4.89 (s, 2H), 3.69−3.63 (m, 1H), 3.60−3.53 (m, 1H), 1.56 (d, J = 4.8 Hz, 6H), 1.25 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 164.0, 162.5, 157.9 (d, J_{C-F} = 251.0 Hz), 133.1 (d, J_{C-F} = 4.0 Hz), 131.3 (d, J_{C-F} = 7.0 Hz), 128.3 (d, J_{C-F} = 19.0 Hz), 121.5 (d, J_{C-F} = 4.0 Hz), 121.2 (d, J_{C-F} = 19.0 Hz), 51.2, 46.1, 44.1, 20.6, 19.9; HRMS Calcd for $C_{16}H_{19}FN_2NaO_3$ [M+Na$^+$]: 329.1277; Found: 329.1281.

*2-(4-Bromo-1-oxoisoindolin-2-yl)-N,N-diisopropyl-2-oxoacetamide (**3e**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (7/1) as an eluent; yield 80% (58.6 mg); brown solid; mp = 222−223 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 7.6 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 4.78 (s, 2H), 3.70−3.63 (m, 1H), 3.60−3.54 (m, 1H), 1.57 (d, J = 4.0 Hz, 6H), 1.25 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 164.0, 162.6, 142.5, 137.5, 132.3, 130.9, 124.4, 118.7, 51.2, 47.9, 46.1, 20.6, 20.0; HRMS Calcd for $C_{16}H_{19}BrN_2NaO_3$ [M+Na$^+$]: 389.0477; Found: 389.0461.

*N,N-Diisopropyl-2-oxo-2-(1-oxo-4-(trifluoromethyl)isoindolin-2-yl)acetamide (**3f**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (6/1) as an eluent; yield 78% (55.6 mg); brown solid; mp = 130−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 7.7 Hz, 1H), 7.93 (d, J = 7.7 Hz, 1H), 7.69−7.66 (m, 1H), 5.01 (s, 2H), 3.69−3.62 (m, 1H), 3.59−3.53 (m, 1H), 1.55 (s, 6H), 1.23 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 163.8, 162.4, 139.2 (q, J_{C-F} = 2.0 Hz), 132.0, 131.3 (q, J_{C-F} = 4.0 Hz), 129.8, 129.0, 126.7 (q, J_{C-F} = 34.0 Hz), 123.4 (q, J_{C-F} = 271.0 Hz), 51.2, 46.5, 46.4, 46.1, 20.6, 19.9; HRMS Calcd for $C_{17}H_{19}F_3N_2NaO_3$ [M+Na$^+$]: 379.1245; Found: 379.1238.

*2-(4,5-Dimethyl-1-oxoisoindolin-2-yl)-N,N-diisopropyl-2-oxoacetamide (**3j**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (7/1) as an eluent; yield 65% (41.1 mg); pale yellow solid; mp = 195−196 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 7.8 Hz, 1H), 4.76 (s, 2H), 3.70−3.63 (m, 1H), 3.59−3.52 (m, 1H), 2.40 (s, 3H), 2.27 (s, 3H), 1.58 (s, 6H), 1.24 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 164.4, 163.0, 144.3, 141.2, 132.0, 131.1, 127.7, 122.9, 51.1, 46.4, 46.0, 20.3, 14.8; HRMS Calcd for $C_{18}H_{24}N_2NaO_3$ [M+Na$^+$]: 339.1685; Found: 339.1678.

*2-(5,6-Dimethyl-1-oxoisoindolin-2-yl)-N,N-diisopropyl-2-oxoacetamide (**3k**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (8/1) as an eluent; yield 54% (34.1 mg); pale yellow solid; mp = 189−191 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.29 (s, 1H), 4.77 (s, 2H), 3.70−3.63 (m, 1H), 3.59−3.52 (m, 1H), 2.39 (s, 3H), 2.34 (s, 3H), 1.60 (s, 6H), 1.24 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 164.3, 163.1, 145.0, 140.0, 138.2, 128.0, 125.9, 124.6, 51.1, 46.7, 46.0, 20.9, 20.1; HRMS Calcd for $C_{18}H_{24}N_2NaO_3$ [M+Na$^+$]: 339.1685; Found: 339.1677.

*2-(4,6-Dimethoxy-1-oxoisoindolin-2-yl)-N,N-diisopropyl-2-oxoacetamide (**3l**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (5/1) as an eluent; yield 75% (52.2 mg); white solid; mp = 194−196 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.68 (d, J = 1.9 Hz, 1H), 4.67 (d, J = 7.2 Hz, 2H), 3.86 (s, 3H), 3.81 (s, 3H), 3.68−3.62 (m, 1H), 3.57−3.51 (m, 1H), 1.55 (s, 6H), 1.22 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 164.1, 162.9, 162.3, 155.8, 132.0, 123.9, 105.3, 98.3, 60.0, 55.8, 51.1, 46.0, 44.7, 20.9, 20.2, 19.6; HRMS Calcd for $C_{18}H_{24}N_2NaO_5$ [M+Na$^+$]: 371.1583; Found: 371.1573.

*2-(4,7-Dimethyl-1-oxoisoindolin-2-yl)-N,N-diisopropyl-2-oxoacetamide (**3m**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (6/1) as an eluent; yield 90% (56.9 mg); white solid; mp = 208−209 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 7.6 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 4.69 (s, 2H), 3.69−3.62 (m, 1H), 3.60−3.53 (m, 1H), 2.64 (s, 3H), 2.32 (s, 3H), 1.58 (s, 6H), 1.24 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 164.4, 163.2, 141.3, 137.5, 134.9, 131.0, 130.6, 127.2, 51.1, 46.0, 45.6, 20.4, 17.6, 17.2; HRMS Calcd for $C_{18}H_{24}N_2NaO_3$ [M+Na$^+$]: 339.1685; Found: 339.1675.

*N,N-Diisopropyl-2-(1-methyl-3-oxoisoindolin-2-yl)-2-oxoacetamide (**3n**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (7/1) as an eluent; yield 96% (58.0 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 7.7 Hz, 1H), 7.72−7.68 (m, 1H), 7.53−7.48 (m, 2H), 5.22 (dd, J = 12.3, 6.0 Hz, 1H), 3.70−3.64 (m, 1H), 3.59−3.52 (m, 1H), 1.67 (s, 3H), 1.60 (s, 3H), 1.54 (s, 6H), 1.25 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 163.7, 162.4, 147.8, 134.2, 128.5, 128.4, 124.9, 122.3, 50.5, 45.4, 20.2, 19.7, 19.0, 18.4; HRMS Calcd for $C_{17}H_{22}N_2NaO_3$ [M+Na$^+$]: 325.1528; Found: 325.1531.

*(2-(2-(Diisopropylamino)-2-oxoacetyl)-3-oxoisoindolin-1-yl)-methyl Acetate (**3o**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (5/1) as an eluent; yield 42% (30.3

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mg); brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 7.6 Hz, 1H), 7.70 (t, J = 7.3 Hz, 1H), 7.54 (t, J = 7.8 Hz, 2H), 5.39 (s, 1H), 4.82−4.56 (m, 2H), 3.71 (s, 1H), 3.59−3.54 (m, 1H), 1.83 (s, 3H), 1.59 (s, 3H), 1.52 (s, 3H), 1.24 (d, J = 6.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 164.2, 162.6, 143.4, 134.9, 129.8, 129.7, 125.5, 123.5, 62.4, 57.9, 51.0, 46.0, 20.8, 20.4, 20.2, 19.6; HRMS Calcd for $C_{19}H_{24}N_2NaO_5$ [M+Na$^+$]: 383.1583; Found: 383.1585.

*N,N-Diisopropyl-2-oxo-2-(1-oxoisoindolin-2-yl)acetamide (**3p**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (4/1) as an eluent; yield 31% (24.1 mg); white solid; mp = 194−195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 7.7 Hz, 1H), 7.72−7.68 (m, 1H), 7.55−7.51 (m, 2H), 4.86 (s, 2H), 3.71−3.64 (m, 1H), 3.60−3.54 (m, 1H), 1.58 (s, 6H), 1.25 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 161.9, 141.0, 133.7, 129.3, 128.1, 124.6, 122.9, 50.2, 46.0, 45.1, 33.1, 24.8, 24.1; HRMS Calcd for $C_{16}H_{20}N_2NaO_3$ [M+Na$^+$]: 311.1372; Found: 311.1362.

*2-(5-Bromo-1-oxoisoindolin-2-yl)-N,N-diisopropyl-2-oxoacetamide (**3q**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (6/1) as an eluent; yield 42% (30.7 mg); white solid; mp = 192−194 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.2 Hz, 1H), 7.72 (s, 1H), 7.67 (d, J = 8.2 Hz, 1H), 4.83 (s, 2H), 3.69−3.63 (m, 1H), 3.60−3.53 (m, 1H), 1.56 (d, J = 3.9 Hz, 6H), 1.25 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 164.0, 162.6, 143.5, 132.8, 129.9, 129.2, 127.3, 126.9, 51.2, 46.6, 46.1; HRMS Calcd for $C_{16}H_{19}BrN_2NaO_3$ [M+Na$^+$]: 389.0477; Found: 389.0475.

*N,N-Diisopropyl-2-(6-methyl-1-oxoisoindolin-2-yl)-2-oxoacetamide (**3r**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (8/1) as an eluent; yield 33% (19.9 mg); white solid; mp = 185−187 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.42 (d, J = 7.8 Hz, 1H), 4.80 (s, 2H), 3.70−3.63 (m, 1H), 3.60−3.53 (m, 1H), 2.44 (s, 3H), 1.57 (s, 6H), 1.24 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 164.3, 163.0, 139.3, 135.9, 130.4, 125.6, 123.6, 51.1, 46.9, 46.1, 21.4; HRMS Calcd for $C_{17}H_{22}N_2NaO_3$ [M+Na$^+$]: 325.1528; Found: 325.1519.

General Procedure for Ruthenium-Catalyzed Carbonylation of Benzylamine with Isocyanatocyclohexane (Table 2) (3d, 3g−3i). A mixture of oxalyl amide-protected benzylamine **1** (0.2 mmol, 1 equiv), isocyanatocyclohexane **2a** (1.2 mmol, 6 equiv), $[RuCl_2(p\text{-cymene})_2]_2$ (6.1 mg, 5 mol%), NaOAc (65.6 mg, 4 equiv), and DCE (1 mL) in a 15 mL glass vial [sealed with poly(tetrafluoroethylene) (PTFE) cap] was heated at 160 °C with vigorous stirring for 48 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through Celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel to give the corresponding product.

*2-(4-Chloro-1-oxoisoindolin-2-yl)-N,N-diisopropyl-2-oxoacetamide (**3d**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (7/1) as an eluent; yield 63% (45.1 mg); yellow solid; mp = 171−173 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 7.6 Hz, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.50 (t, J = 7.7 Hz, 1H), 4.84 (s, 2H), 3.70−3.63 (m, 1H), 3.61−3.54 (m, 1H), 1.57 (d, J = 4.9 Hz, 6H), 1.25 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 164.0, 162.6, 140.2, 134.5, 132.3, 130.7, 130.4, 123.9, 51.2, 46.4, 46.1, 20.6, 20.0; HRMS Calcd for $C_{16}H_{19}ClN_2NaO_3$ [M+Na$^+$]: 345.0982; Found: 345.0976.

*2-(4,6-Difluoro-1-oxoisoindolin-2-yl)-N,N-diisopropyl-2-oxoacetamide (**3g**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (8/1) as an eluent; yield 66% (42.8 mg); yellow solid; mp = 157−158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 6.6 Hz, 1H), 7.16−7.12 (m, 1H), 4.85 (s, 2H), 3.67−3.60 (m, 1H), 3.59−3.52 (m, 1H), 1.54 (d, J = 5.9 Hz, 6H), 1.23 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 165.11, 165.07, 165.04, 163.8, 163.7 (dd, J_{C-F} = 251.0 Hz, 9.0 Hz), 162.4, 158.0 (dd, J_{C-F} = 254.0 Hz, 11.0 Hz), 139.9, 135.9, 134.0 (dd, J_{C-F} = 10.0 Hz, 6.0 Hz), 133.3, 129.2, 128.7, 124.2 (dd, J_{C-F} = 19.0 Hz, 3.0 Hz), 110.1 (dd, J_{C-F} = 27.0 Hz, 23.0 Hz), 108.4 (dd, J_{C-F} = 23.0 Hz, 4.0 Hz), 51.3, 46.2, 44.0, 21.2, 20.6, 20.3, 20.1; HRMS Calcd for $C_{16}H_{18}F_2N_2NaO_3$ [M+Na$^+$]: 347.1183; Found: 347.1181.

*2-(4,6-Dichloro-1-oxoisoindolin-2-yl)-N,N-diisopropyl-2-oxoacetamide (**3h**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (7/1) as an eluent; yield 57% (40.6 mg); yellow solid; mp = 187−189 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 1.5 Hz, 1H), 7.66 (d, J = 1.6 Hz, 1H), 4.81 (s, 2H), 3.67−3.61 (m, 1H), 3.60−3.53 (m, 1H), 1.55 (d, J = 6.4 Hz, 6H), 1.24 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0, 163.8, 162.3, 138.5, 136.4, 134.3, 133.4, 131.2, 124.0, 51.3, 46.2, 46.2, 20.6, 19.9; HRMS Calcd for $C_{16}H_{18}Cl_2N_2NaO_3$ [M+Na$^+$]: 379.0592; Found: 379.0580.

*2-(4-Chloro-6-fluoro-1-oxoisoindolin-2-yl)-N,N-diisopropyl-2-oxoacetamide (**3i**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (8/1) as an eluent; yield 67% (40.6 mg); pale yellow solid; mp = 147−149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, J = 6.8, 2.2 Hz, 1H), 7.43 (dd, J = 8.4, 2.2 Hz, 1H), 4.81 (s, 2H), 3.68−3.61 (m, 1H), 3.60−3.53 (m, 1H), 1.56 (d, J = 6.4 Hz, 6H), 1.24 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3 (d, J_{C-F} = 4.0 Hz), 164.5, 163.8, 162.3, 162.0, 135.9 (d, J_{C-F} = 2.0 Hz), 133.5 (d, J_{C-F} = 9.0 Hz), 131.3 (d, J_{C-F} = 11.0 Hz), 122.6 (d, J_{C-F} = 26.0 Hz), 110.8 (d, J_{C-F} = 24.0 Hz), 51.2, 46.2, 46.0, 20.6, 20.0; HRMS Calcd for $C_{16}H_{18}ClFN_2NaO_3$ [M+Na$^+$]: 363.0888; Found: 363.0888.

General Procedure for Ruthenium-Catalyzed Carbonylation of 1a with Different Isocyanates (Table 2) (2a−2d). A mixture of oxalyl amide-protected benzylamine **1a** (0.2 mmol, 1 equiv), isocyanate **2** (1.2 mmol, 6 equiv), $[RuCl_2(p\text{-cymene})_2]_2$ (6.1 mg, 5 mol%), NaOAc (65.6 mg, 4 equiv), and DCE (1 mL) in a 15 mL glass vial [sealed with poly(tetrafluoroethylene) (PTFE) cap] was heated at 150 °C with vigorous stirring for 48 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through Celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel to give the corresponding product **3a** in <5% to 89% yield.

Scaling Up and Removal of Directing Group (Scheme 2). A mixture of oxalyl amide-protected benzylamine **1a** (4 mmol, 1 equiv), isocyanatocyclohexane **2a** (24 mmol, 6 equiv), $[RuCl_2(p\text{-cymene})_2]_2$ (61.2 mg, 2.5 mol%), NaOAc (1.31g, 4 equiv), and DCE (10 mL) in a 50 mL glass vial [sealed with poly(tetrafluoroethylene) (PTFE) cap] was heated at 150 °C with vigorous stirring for 72 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through Celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel to give the desired product **3a** in 1.03 g, 81% yield.

The compound **3a** (63.6 mg, 0.2 mmol) was dissolved in a mixture of MeOH (1 mL), NaOMe (21.6 mg, 0.4 mmol) was then added. The mixture stirred at room temperature for 4 h. Water was added and the mixture was extracted with EtOAc. The combined organic layers was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ester/ethyl acetate = 1:1) to give the desired product **4** as white solid in 30.0 mg, 92% yield.

*4-Methoxyisoindolin-1-one (**4**).* White solid; mp = 183−185 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.48−7.41 (m, 2H), 7.02 (dd, J = 7.3, 1.4 Hz, 1H), 4.39 (s, 2H), 3.90 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 154.9, 133.9, 132.0, 129.8, 115.8, 113.0, 55.5, 43.7; HRMS Calcd for $C_9H_9NNaO_2$ [M+Na$^+$]: 186.0531; Found: 186.0520.

Preliminary Mechanistic Studies (Scheme 3A). A mixture of oxalyl amide-protected benzylamine **1a** (0.2 mmol, 1 equiv), $[RuCl_2(p\text{-cymene})_2]_2$ (6.1 mg, 5 mol%), NaOAc (65.6 mg, 4 equiv), and DCE (1 mL) in a 15 mL glass vial was purged with CO (3-times) [sealed with poly(tetrafluoroethylene) (PTFE) cap]. The vial was heated at 150 °C with vigorous stirring for 48 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through Celite.

Preliminary Mechanistic Studies (Scheme 3B). A mixture of oxalyl amide-protected benzylamine [**D**]-**1a** (0.2 mmol, 1 equiv), isocyanatocyclohexane **2a** (1.2 mmol, 6 equiv), $[RuCl_2(p\text{-cymene})_2]_2$ (6.1 mg, 5 mol%), NaOAc (65.6 mg, 4 equiv), and DCE (1 mL) in a 15 mL glass vial [sealed with poly(tetrafluoroethylene) (PTFE) cap] was heated at 150 °C with vigorous stirring for 6 h. The reaction

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mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through Celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel to give the products and starting material.

*N^1-(2-(Cyclohexylcarbamoyl)-6-methoxybenzyl)-N^2,N^2-diisopropyloxalamide (**5**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (1/1) as an eluent; yield 22% (18.4 mg); pale yellow solid; mp = 178−180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 8.4 Hz, 2H), 7.27 (t, J = 8.0 Hz, 1H), 7.07 (dd, J = 7.7, 0.7 Hz, 1H), 6.90 (d, J = 8.1 Hz, 1H), 4.52−4.45 (m, 3H), 4.00−3.93 (m, 1H), 3.86 (s, 3H), 3.49−3.42 (m, 1H), 2.03−2.00 (m, 2H), 1.76−1.72 (m, 2H), 1.62 (d, J = 13.4 Hz, 1H), 1.39 (d, J = 12.8 Hz, 2H), 1.35 (d, J = 6.8 Hz, 6H), 1.32−1.24 (m, 3H), 1.18 (d, J = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 163.5, 158.1, 139.0, 129.2, 122.6, 120.4, 111.9, 56.0, 49.8, 49.1 46.4, 36.8, 32.9, 25.7, 25.1, 20.9, 20.1; HRMS Calcd for $C_{23}H_{35}N_3NaO_4$ [M+Na$^+$]: 440.2525; Found: 440.2521.

Preliminary Mechanistic Studies (Scheme 3C). A mixture of **5** (0.2 mmol, 1 equiv), $[RuCl_2(p\text{-cymene})_2]_2$ (6.1 mg, 5 mol%), NaOAc (65.6 mg, 4 equiv), and DCE (1 mL) in a 15 mL glass vial [sealed with poly(tetrafluoroethylene) (PTFE) cap] was heated at 150 °C with vigorous stirring for 48 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through Celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel to give the desired product **3a** in 85% yield. The reaction was then repeated in the absence of (1) $[RuCl_2(p\text{-cymene})_2]_2$, (2) NaOAc, or (3) $[RuCl_2(p\text{-cymene})_2]_2$ and NaOAc both, affording products **3a** in 59, 64, or 17% yields, respectively.

Preliminary Mechanistic Studies (Scheme 3D). A mixture of **1a** (0.5 mmol, 1 equiv) in tetrahydrofuran (THF, 4 mL) was stirred for 5 min at −10 °C, NaH (60%) (2.5 mmol, 5 equiv) was slowly added, and then the mixture was stirred for another 1 h. Isocyanatocyclohexane **2a** (1.5 mmol, 3 equiv) was added slowly for 30 min. The mixture was stirred for 2 h, quenched with water (20 mL), and extracted with CH_2Cl_2 (10 mL × 2). The combined organic phase was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Evaporation and column chromatography on silica gel with petroleum ester/ethyl acetate (10/1) as an eluent afforded **6** (175.3 mg) as a pale yellow oil in 84% yield. A mixture of **6** (0.2 mmol, 1 equiv), $[RuCl_2(p\text{-cymene})_2]_2$ (6.1 mg, 5 mol %), NaOAc (65.6 mg, 4 equiv), and DCE (1 mL) in a 15 mL glass vial [sealed with poly(tetrafluoroethylene) (PTFE) cap] was heated at 150 °C with vigorous stirring for 48 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through Celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel to give the product and starting material.

*N^1-(Cyclohexylcarbamoyl)-N^2,N^2-diisopropyl-N^1-(2-methoxybenzyl)oxalamide (**6**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (br s, 1H), 7.18 (s, 1H), 6.99−6.82 (m, 3H), 5.07 (s, 2H), 3.79 (s, 4H), 3.34 (d, J = 40.9 Hz, 2H), 1.98 (s, 2H), 1.71 (s, 2H), 1.58 (d, J = 10.0 Hz, 2H), 1.42−1.21 (m, 16H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 162.3, 156.4, 153.2, 128.1, 126.2, 120.9, 110.0, 55.3, 51.3, 49.6, 46.0, 42.7, 33.0, 25.7, 24.8, 20.2, 19.9; HRMS Calcd for $C_{23}H_{35}N_3NaO_4$ [M+Na$^+$]: 440.2525; Found: 440.2526.

Preliminary Mechanistic Studies (Scheme 3E). A mixture of oxalyl amide-protected benzylamine **1a** (0.2 mmol, 1 equiv), isocyanatocyclohexane **2a** (1.2 mmol, 6 equiv), $[RuCl_2(p\text{-cymene})_2]_2$ (6.1 mg, 5 mol%), and DCE (1 mL) in a 15 mL glass vial [sealed with poly(tetrafluoroethylene) (PTFE) cap] was heated at 150 °C with vigorous stirring for 48 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through Celite.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00975.

^{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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