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Nickel-Catalyzed Multicomponent Coupling Reaction of Alkyl Halides, Isocyanides and H_2O: An Expedient Way to Access Alkyl Amides

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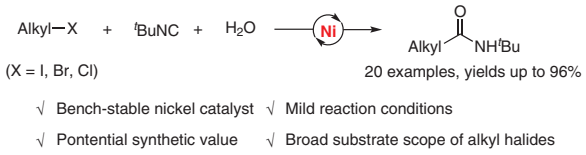

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Abstract We herein describe a Ni-catalyzed multicomponent coupling reaction of alkyl halides, isocyanides, and H_2O to access alkyl amides. Bench-stable $NiCl_2$(dppp) is competent to initiate this transformation under mild reaction conditions, thus allowing easy operation and adding practical value. Substrate scope studies revealed a broad functional group tolerance and generality of primary and secondary alkyl halides in this protocol. A plausible catalytic cycle via a SET process is proposed based on preliminary experiments and previous literature.

Key words nickel catalysis, isocyanide, alkyl halides, multicomponent coupling reaction, amide

The widespread use of alkyl amides in biology, pharmaceutics, and material sciences has stimulated huge interest in amide synthesis over the past decades.[1] Among them, the condensation of carboxylic acid derivatives and amines represents the most common way to access amides via C–N bond formation.[2] Alternatively, a catalytic version of transition-metal-catalyzed aminocarbonylation of alkyl (pseudo)halides, CO, and amines in which an amide bond is constructed via a consecutive C–C/C–N coupling reaction has received considerable attention.[3] However, although the starting materials are easily available, high-energy irradiation, toxic organotin reagents or high-pressure CO gas are usually required in these strategies. In addition, isocyanate is also a useful building block to construct alkyl amides. For example, the Martin group described a nickel-catalyzed reductive amidation of unactivated alkyl bromides with isocyanides.[4] Primary, secondly, and tertiary alkyl bromides are all tolerated under mild reaction conditions. Later, the Molander group disclosed a nickel/photoredox catalyzed amidation of alkyl silicate with isocyanates in which $Ru(bpy)_3(PF_6)_2$ was used as the photocatalyst and blue LEDs as the light source.[5] More recently, the Komeyama group reported a Ni/Co co-catalyzed reductive amidation of alkyl tosylates with isocyanates.[6] Interestingly, the $NiCl_2$(6,6'-Me_2bpy)/VB_{12} catalytic system shows unique regioselectivity when the alkyl ditosylate have two tosyloxy groups at the different positions. A less-bulk alkyl tosylate moiety could be selectively transformed into amides. Isocyanide has emerged as a promising surrogate to replace CO in aminocarbonylaton reactions due to its easy application as either a liquid or a solid, relatively benign toxicity compared with CO, and diverse reactivity.[7] Notably, Pd-catalyzed multicomponent coupling reaction of aromatic halide, isocyanide, and H_2O was well known,[7a] whereas the corresponding reaction involving alkyl halides remains underdeveloped. In 2017, the Zhu[8] and Yang[9] groups independently reported Pd-catalyzed amidations of activated alkyl halides with isocyanides and H_2O in which a key ketenimine intermediate was proposed to be generated from the oxidative addition of palladium to the C–X bond and subsequent β-H elimination. A similar research work was also disclosed by the Barriault group[10] using a dimeric gold(I) photoredox catalyst. In this case, only one example of bromocyclohexane was shown in 30% yield (Scheme 1a). In this regard, the exploration of transition-metal-catalyzed amidation of unactivated alkyl halide with isocyanide and H_2O is highly desirable.

Nickel catalysts can undergo a single electron transfer (SET) processes in cross-coupling reactions, thus allowing the use of alkyl (pseudo)halides as electrophiles;[11] however, the reaction is still challenging for palladium catalysts.[12] Furthermore, nickel-catalyzed isocyanide insertion reactions have received considerable attention.[13] Based on these considerations, we envisioned that alkyl amides would be readily prepared from Ni-catalyzed multicomponent coupling reaction of alkyl halides, isocyanides, and H_2O. Indeed, the Chen and Qu group[13d] elegantly described such reaction during our final data collection and manuscript

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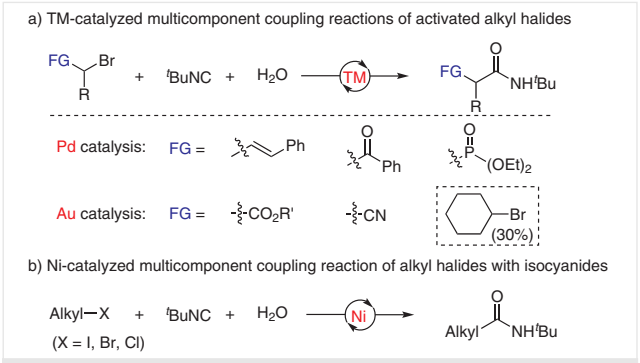
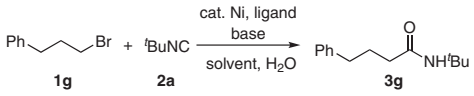
preparation. Although an array of primary and secondary alkyl iodides with various functional groups are reasonably well tolerated in this reaction, air-sensitive $Ni(COD)_2$ was utilized as a catalyst. Herein, we wish to report a bench-stable $NiCl_2$(dppp)-catalyzed multicomponent coupling reaction of alkyl halides, isocyanides, and H_2O under mild reaction conditions (Scheme 1b). Note that alkyl iodines, bromides, and chlorides are successfully employed as viable electrophiles in our protocol.

Initially, we conducted the reaction of (3-bromopropyl)benzene (**1g**), *tert*-butyl isocyanide (**2a**), and H_2O in toluene at 150 °C for 22 h. The desired product **3g** was detected in 6% GC yield when $NiCl_2$ was used as catalyst, 1,2-bis(diphenylphosphino)ethane (dppe) as ligand, and ^{t}BuONa as base, whereas the use of 4,4′-di-*tert*-butyl-2,2′-

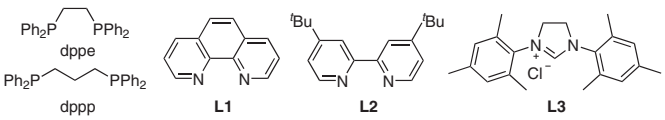


Scheme 1 Amide formation from alkyl halides and isocyanides

Table 1 Reaction Parameter Screening[a]



Entry	Ni cat.	Ligand	Base	Temp (°C)	Yield (%)[b]
1	$NiCl_2$	dppe	^{t}BuONa	150	6
2	$NiCl_2$	L1	^{t}BuONa	150	ND
3	$NiCl_2$	L2	^{t}BuONa	150	ND
4	$NiCl_2$	L3	^{t}BuONa	150	ND
5	$NiCl_2$(dppe)	–[c]	^{t}BuONa	150	67
6	$Ni(acac)_2$	–[c]	^{t}BuONa	150	ND
7	$Ni(cod)_2$	–[c]	^{t}BuONa	150	75
8	$NiCl_2$(dme)	–[c]	^{t}BuONa	150	53
9	$NiCl_2$(dppp)	–[c]	^{t}BuONa	150	90
10	$NiCl_2$(dppp)	–[c]	NaOH	150	85
11	$NiCl_2$(dppp)	–[c]	Na_2CO_3	150	65
12	$NiCl_2$(dppp)	–[c]	NaOEt	150	26
13	$NiCl_2$(dppp)	–[c]	NaH	150	23
14	$NiCl_2$(dppp)	–[c]	^{t}BuOLi	150	31
15	$NiCl_2$(dppp)	–[c]	$CsCO_3$	150	78
16[d]	$NiCl_2$(dppp)	–[c]	^{t}BuONa	150	97
17[d]	$NiCl_2$(dppp)	–[c]	^{t}BuONa	80	90
18[d]	$NiCl_2$(dppp)	–[c]	^{t}BuONa	60	90
19[d]	$NiCl_2$(dppp)	–[c]	^{t}BuONa	40	92
20[d]	$NiCl_2$(dppp)	–[c]	^{t}BuONa	25	88

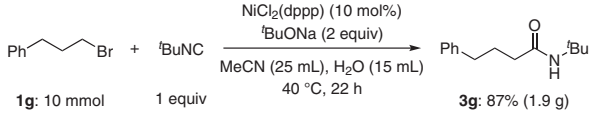


[a] Reaction conditions: **1g** (0.1 mmol), **2a** (0.1 mmol), $NiCl_2$(dppp) (10 mol%), ^{t}BuONa (2 equiv), toluene (0.3 mL), H_2O (0.2 mL), 22 h.
[b] Yield was estimated by GC analysis using dodecane as internal standard; ND = not detected.
[c] No ligand was added.
[d] MeCN was used as solvent.

bipyridine, 1,10-phenanthroline, or NHC salt did not promote the reaction at all (Table 1, entry 1). To our delight, the yield of **3g** was greatly improved by using $NiCl_2$(dppe) as a catalyst (entry 5). Other nickel salts were then screened in which $NiCl_2$(dppp) gave the product in 90% yield (entry 9). Next, we examined a series of bases, but ^{t}BuONa remained optimal (entries 10–15). Solvent screening revealed that the use of acetonitrile improved the yield slightly compared with toluene (entry 16; see the Supporting Information for details). Finally, we performed the reaction at different reaction temperatures and found that the model reaction proceeded most efficiently at 40 °C (entries 17–20).

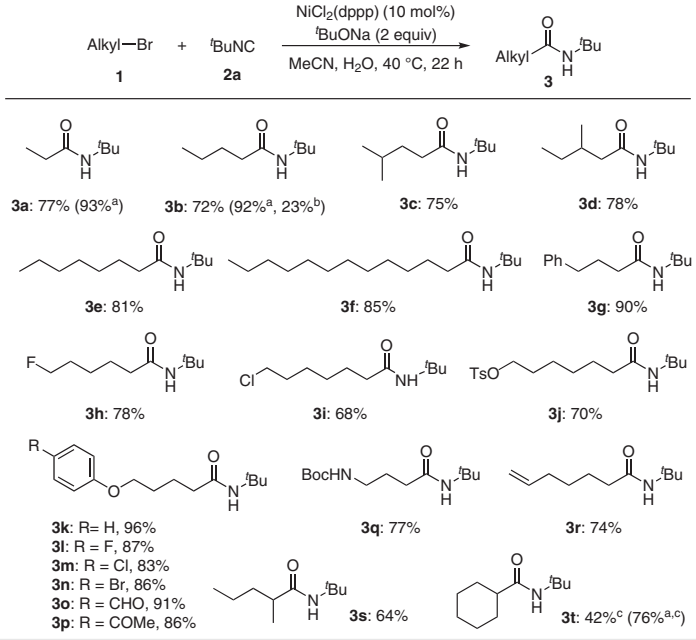
With the optimized reaction conditions in hand, we started to evaluate the substrate scope of alkyl halides. First, alkyl halides with a range of carbon chains reacted with *tert*-butyl isocyanide and H_2O efficiently to provide alkyl amides in good yields (Scheme 2, 3a–f). As expected, the reactivity of alkyl halides decreased in order from iodide to bromide and to chloride (Scheme 2, 3b). Fluorine and chlorine substituted alkyl bromides underwent reaction selectively at the C–Br bond (Scheme 2, 3h–i). We then screened alkyl bromides with various phenoxy groups at the terminal carbon position. Aromatic C–F, C–Cl, and C–Br bonds at the phenyl ring were left intact after reaction (Scheme 2, 3l–n), and sensitive formyl and acetyl group were also compatible with reaction conditions (Scheme 2, 3o–p). In addition, N-Boc protected amino group did not suppress the reactivity of alkyl bromide, affording the product in 77% yield (Scheme 2, 3q). Notably, a remote alkenyl group was tolerated under the standard conditions without formation of the cyclized product (Scheme 2, 3r). Secondary alkyl halides were then examined, and the results confirmed that 2-bromopentane and bromocyclohexane also reacted to give moderate yields (Scheme 2, 3s,t). Again, alkyl iodines such as iodocyclohexane showed higher reactivity.

We next conducted a gram-scale reaction (Scheme 3). To our delight, the model reaction of (3-bromopropyl)benzene (**1g**), *tert*-butyl isocyanide (**2a**), and H_2O under the optimal reaction conditions gave the desired product **3g** in 87% yield. The approach thus provides a practical strategy for the synthesis of alkyl amides.

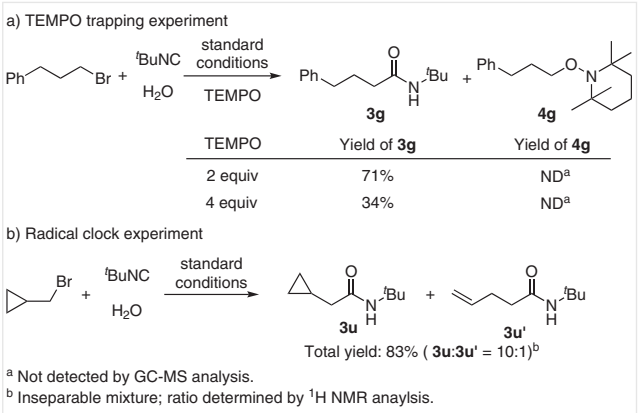


Scheme 3 Gram-scale reaction

To understand the possible reaction mechanism, we first carried out a 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) trapping experiment. The addition of two or four equivalents of TEMPO to the model reaction resulted in a sharp decrease in the yields when the amount of TEMPO was doubled (Scheme 4a). A radical clock experiment was also conducted under the standard reaction conditions (Scheme 4b). Expectedly, ring-opening product **3u′** was detected by ^{1}H NMR analysis. This result indicated that an alkyl radical might be involved in this reaction.

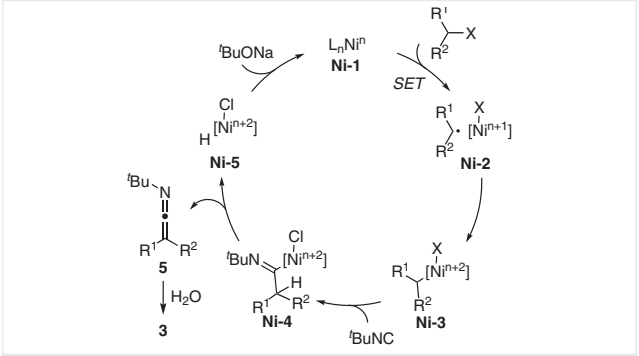


Scheme 2 Substrate scope of the reaction with alkyl halides. *Reagents and conditions*: **1** (0.2 mmol), **2a** (0.2 mmol), $NiCl_2$(dppp) (10 mol%), ^{t}BuONa (2 equiv), MeCN (0.5 mL), H_2O (0.3 mL), 22 h. [a] Alkyl iodine used. [b] Alkyl chloride used. [c] At 100 °C.



Scheme 4 Mechanistic experiments

Although some mechanistic experiments were carried out, details of the mechanism remain elusive. According to previous research by Qu and Chen,[13d] we herein propose a similar reaction mechanism as shown in Scheme 5. First, active nickel catalyst **Ni-1** reacts with alkyl halide via a single-electron transfer (SET) process to give intermediate **Ni-2**. An isocyanide insertion of the C–Ni bond of **Ni-3** takes place, resulting in the formation of imidoyl nickel species **Ni-4**, which further undergoes a β-H elimination to produce intermediate **Ni-5** and ketenimines **5**. Finally, the **Ni-1** is regenerated from intermediate **Ni-5** in the presence of ^{t}BuONa. Hydrolysis of ketenime **5** gives the amide **3**.



Scheme 5 Proposed mechanism

In conclusion, we have developed a Ni-catalyzed multicomponent coupling reaction of alkyl halides, isocyanides, and H_2O under mild conditions. Bench-stable $NiCl_2$(dppp) could be used as a powerful catalyst instead of expensive and unstable $Ni(COD)_2$. Additionally, this protocol features a broad substrate scope of alkyl halides and high functional group tolerance. A range of alkyl amides including primary and secondary amides were successfully obtained. The further exploration of isocyanide insertion in Ni-catalyzed coupling reactions of alkyl halides is underway in our laboratory.

Unless otherwise noted, all reactions were conducted in 25 mL flame-dried Schlenk tubes under positive nitrogen atmosphere. ^{1}H NMR spectra were recorded with a 500 MHz Bruce NMR spectrometer. Chemical shifts (δ) are reported as parts per million (ppm) downfield from tetramethylsilane. High-resolution mass spectra were recorded with a Thermo Q Exactive Plus. Melting points were measured with an X4 melting-point apparatus and are uncorrected. Flash column chromatography was performed on silica gel (200–300 mesh) with the indicated solvent mixtures.

Synthesis of Alkyl Amides; Typical Procedure

To a 25 mL flame-dried Schlenk tube, alkyl halide (0.2 mmol), *tert*-butyl isocyanide (0.2 mmol), $NiCl_2$(dppp) (10 mol%, 0.02 mmol), ^{t}BuONa (2 equiv, 0.4 mmol), acetonitrile (0.5 mL), and H_2O (0.3 mL) were added sequentially under nitrogen. The tube was sealed and stirred at 40 °C for 22 h. The combined organic phase was concentrated and purified by silica gel column chromatography (petroleum ether–EtOAc, 20:1 to 5:1) to provide the product **3**.

N-(*tert*-Butyl)propionamide (3a)

Yield: 77% (19.9 mg); white solid; mp 81–83 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.37 (s, 1 H), 2.10 (q, *J* = 7.6 Hz, 2 H), 1.32 (s, 9 H), 1.09 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.12, 50.89, 30.48, 28.78, 9.80.

The spectroscopic data matched those reported.[14]

N-(*tert*-Butyl)pentanamide (3b)

Yield: 72% (22.6 mg); white solid; mp 45–47 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.47 (s, 1 H), 2.08–2.02 (m, 2 H), 1.56–1.50 (m, 2 H), 1.31–1.24 (m, 11 H), 0.86 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.52, 50.83, 37.27, 28.70, 27.82, 22.22, 13.72.

The spectroscopic data matched those reported.[15]

N-(*tert*-Butyl)-4-methylpentanamide (3c)

Yield: 75% (25.7 mg); white solid; mp 65–67 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.33 (s, 1 H), 2.05–1.98 (m, 2 H), 1.54–1.46 (m, 1 H), 1.46–1.39 (m, 2 H), 1.27 (s, 9 H), 0.82 (d, *J* = 6.5 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.68, 50.93, 35.65, 34.61, 28.79, 27.76, 22.30.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{22}NO^+$: 172.16959; found: 172.16904.

N-(*tert*-Butyl)-3-methylpentanamide (3d)

Yield: 78% (26.7 mg); white solid; mp 70–71 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.49 (s, 1 H), 2.15–2.07 (m, 1 H), 1.95–1.79 (m, 2 H), 1.42–1.30 (m, 10 H), 1.24–1.11 (m, 1 H), 0.96–0.85 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.05, 50.95, 45.01, 32.31, 29.31, 28.75, 18.99, 11.26.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{22}NO^+$: 172.16959; found: 172.16907.

N-(*tert*-Butyl)octanamide (3e)

Yield: 81% (32.3 mg); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.56 (s, 1 H), 2.06–1.97 (m, 2 H), 1.57–1.45 (m, 2 H), 1.27 (s, 9 H), 1.24–1.16 (m, 8 H), 0.81 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.51, 50.74, 37.46, 31.54, 29.02, 28.89, 28.64, 25.68, 22.42, 13.87.

The spectroscopic data matched those reported.[13d]

***N*-(*tert*-Butyl)tridecanamide (3f)**

Yield: 85% (45.8 mg); white solid; mp 48–50 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.38 (s, 1 H), 2.09–2.02 (m, 2 H), 1.62–1.52 (m, 2 H), 1.32 (s, 9 H), 1.29–1.20 (m, 18 H), 0.86 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.53, 50.90, 37.65, 31.85, 29.59, 29.57, 29.55, 29.45, 29.33, 29.28, 29.17, 28.77, 25.76, 22.62, 14.04.

The spectroscopic data matched those reported.[6]

***N*-(*tert*-Butyl)-4-phenylbutanamide (3g)**

Yield: 90% (39.5 mg); white solid; mp 65–67 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.27 (m, 2 H), 7.23–7.16 (m, 3 H), 5.29 (s, 1 H), 2.65 (t, *J* = 7.5 Hz, 2 H), 2.10 (t, *J* = 7.5 Hz, 2 H), 1.99–1.91 (m, 2 H), 1.35 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.95, 141.57, 128.40, 128.25, 125.80, 50.94, 36.63, 35.03, 28.73, 27.08.

The spectroscopic data matched those reported.[6]

***N*-(*tert*-Butyl)-6-fluorohexanamide (3h)**

Yield: 78% (29.5 mg); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.48 (s, 1 H), 4.40 (dt, *J* = 47.3, 6.1 Hz, 2 H), 2.07 (t, *J* = 7.5 Hz, 2 H), 1.72–1.57 (m, 4 H), 1.43–1.34 (m, 2 H), 1.30 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.08, 83.78 (d, $^1J_{C-F}$ = 164.2 Hz), 50.90, 37.21, 30.04 (d, $^2J_{C-F}$ = 19.6 Hz), 28.67, 25.18, 24.70 (d, $^3J_{C-F}$ = 5.4 Hz).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{21}FNO^+$: 190.16017; found: 190.15942.

***N*-(*tert*-Butyl)-7-chloroheptanamide (3i)**

Yield: 68% (29.9 mg); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.36 (s, 1 H), 3.53 (t, *J* = 6.7 Hz, 2 H), 2.09 (t, *J* = 7.5 Hz, 2 H), 1.81–1.73 (m, 2 H), 1.66–1.58 (m, 2 H), 1.49–1.42 (m, 2 H), 1.36–1.31 (m, 11 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.21, 51.02, 44.97, 37.39, 32.34, 28.80, 28.33, 26.52, 25.45.

The spectroscopic data matched those reported.[6]

7-(*tert*-Butylamino)-7-oxoheptyl 4-Methylbenzenesulfonate (3j)

Yield: 70% (49.8 mg); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.3 Hz, 2 H), 7.35 (d, *J* = 8.2 Hz, 2 H), 5.29 (s, 1 H), 4.01 (t, *J* = 6.4 Hz, 2 H), 2.45 (s, 3 H), 2.05 (t, *J* = 7.5 Hz, 2 H), 1.66–1.61 (m, 2 H), 1.58–1.52 (m, 2 H), 1.34–1.33 (m, 9 H), 1.30–1.20 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.19, 144.69, 133.18, 129.82, 127.84, 70.55, 51.06, 37.34, 28.82, 28.63, 28.43, 25.36, 25.09, 21.61.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{30}NO_4S^+$: 356.18901; found: 356.18823.

***N*-(*tert*-Butyl)-5-phenoxypentanamide (3k)**

Yield: 96% (47.9 mg); white solid; mp 91–93 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30–7.24 (m, 2 H), 6.96–6.91 (m, 1 H), 6.90–6.86 (m, 2 H), 5.52 (s, 1 H), 3.96 (t, *J* = 5.9 Hz, 2 H), 2.20–2.13 (m, 2 H), 1.83–1.76 (m, 4 H), 1.34 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.97, 158.84, 129.32, 120.50, 114.38, 67.41, 50.96, 37.01, 28.73, 28.58, 22.42.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{24}NO_2^+$: 250.18015; found: 250.17957.

***N*-(*tert*-Butyl)-5-(4-fluorophenoxy)pentanamide (3l)**

Yield: 87% (46.5 mg); white solid; mp 93–94 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.95–6.88 (m, 2 H), 6.81–6.76 (m, 2 H), 5.53 (s, 1 H), 3.89 (s, 2 H), 2.14 (t, *J* = 6.7 Hz, 2 H), 1.79–1.72 (m, 4 H), 1.32 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.89, 157.02 (d, $^1J_{C-F}$ = 237.9 Hz), 155.00 (d, $^4J_{C-F}$ = 2.0 Hz), 115.60 (d, $^2J_{C-F}$ = 23.0 Hz), 115.31 (d, $^3J_{C-F}$ = 8.0 Hz), 68.14, 50.95, 36.95, 28.70, 28.60, 22.31.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{22}FNNaO_2^+$: 290.15268; found: 290.15159.

***N*-(*tert*-Butyl)-5-(4-chlorophenoxy)pentanamide (3m)**

Yield: 83% (52.8 mg); white solid; mp 104–106 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21–7.15 (m, 2 H), 6.81–6.74 (m, 2 H), 5.53 (s, 1 H), 3.89 (t, *J* = 5.7 Hz, 2 H), 2.14 (t, *J* = 6.9 Hz, 2 H), 1.79–1.70 (m, 4 H), 1.31 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.85, 157.46, 129.11, 125.21, 115.63, 67.80, 50.94, 36.89, 28.69, 28.48, 22.24.

The spectroscopic data matched those reported.[6]

5-(4-Bromophenoxy)-*N*-(*tert*-butyl)pentanamide (3n)

Yield: 86% (56.5 mg); white solid; mp 103–105 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.30 (m, 2 H), 6.77–6.71 (m, 2 H), 5.44 (s, 1 H), 3.91 (t, *J* = 5.9 Hz, 2 H), 2.17–2.12 (m, 2 H), 1.80–1.74 (m, 4 H), 1.33 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.82, 157.99, 132.11, 116.21, 112.58, 67.79, 51.02, 36.96, 28.75, 28.52, 22.27.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{22}BrNNaO_2^+$: 350.07261; found: 350.07150.

***N*-(*tert*-Butyl)-5-(4-formylphenoxy)pentanamide (3o)**

Yield: 91% (50.5 mg); white solid; mp 92–93 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.82 (s, 1 H), 7.85–7.73 (m, 2 H), 6.99–6.91 (m, 2 H), 5.49 (s, 1 H), 4.03 (t, *J* = 5.5 Hz, 2 H), 2.17 (t, *J* = 6.8 Hz, 2 H), 1.80 (dt, *J* = 11.8, 4.8 Hz, 4 H), 1.33 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.76, 171.81, 164.02, 131.92, 129.73, 114.68, 67.97, 51.07, 36.88, 28.75, 28.43, 22.17.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{24}NO_3^+$: 278.17507; found: 278.17468.

5-(4-Acetylphenoxy)-*N*-(*tert*-butyl)pentanamide (3p)

Yield: 86% (50.1 mg); white solid; mp 87–89 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.9 Hz, 2 H), 6.88 (d, *J* = 8.9 Hz, 2 H), 5.50 (s, 1 H), 4.01 (t, *J* = 5.5 Hz, 2 H), 2.52 (s, 3 H), 2.16 (t, *J* = 6.9 Hz, 2 H), 1.84–1.75 (m, 4 H), 1.33 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.76, 171.85, 162.88, 130.50, 130.11, 114.06, 67.81, 51.06, 36.91, 28.75, 28.47, 26.23, 22.22.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{26}NO_3^+$: 292.19072; found: 292.19014.

tert-Butyl (4-(tert-Butylamino)-4-oxobutyl)carbamate (3q)

Yield: 77% (39.8 mg); white solid; mp 77–79 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.06 (s, 1 H), 5.07 (s, 1 H), 3.19–3.12 (m, 2 H), 2.14 (t, *J* = 7.0 Hz, 2 H), 1.81–1.76 (m, 2 H), 1.43 (s, 9 H), 1.35 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.01, 156.34, 78.92, 50.96, 39.70, 34.56, 28.65, 28.30, 26.19.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{24}NO_3^+$: 259.20162; found: 259.20105.

N-(tert-Butyl)hept-6-enamide (3r)

Yield: 74% (27.1 mg); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.82–5.70 (m, 1 H), 5.43 (s, 1 H), 4.97 (ddt, *J* = 17.1, 1.8, 1.7 Hz, 1 H), 4.93–4.89 (m, 1 H), 2.08–2.00 (m, 4 H), 1.62–1.55 (m, 2 H), 1.42–1.32 (m, 2 H), 1.31 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.28, 138.42, 114.43, 50.86, 37.30, 33.37, 28.70, 28.33, 25.15.

The spectroscopic data matched those reported.[13d]

N-(tert-Butyl)-2-methylpentanamide (3s)

Yield: 64% (21.9 mg); white solid; mp 79–81 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.30 (s, 1 H), 2.10–1.99 (m, 1 H), 1.39–1.24 (m, 13 H), 1.09 (dd, *J* = 6.8, 0.7 Hz, 3 H), 0.90 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.00, 50.89, 42.11, 36.68, 28.85, 20.63, 17.95, 14.08.

The spectroscopic data matched those reported.[4]

N-(tert-Butyl)cyclohexanecarboxamide (3t)

Yield: 42% (14.4 mg); white solid; mp 153–155 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.29 (s, 1 H), 1.98–1.88 (m, 1 H), 1.83–1.72 (m, 4 H), 1.66–1.59 (m, 1 H), 1.45–1.35 (m, 2 H), 1.33–1.29 (m, 9 H), 1.25–1.16 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.56, 50.71, 46.27, 29.75, 28.83, 25.74.

The spectroscopic data matched those reported.[4]

N-(tert-Butyl)-2-cyclopropylacetamide (3u) and N-(tert-Butyl)pent-4-enamide (3u′)

Inseparable mixture; total yield: 83% (25.8 mg) (**3u**/**3u′** = 10:1); white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.75 (s, 1 H, overlap), 2.02 (d, *J* = 7.1 Hz, 2 H), 1.32 (s, 9 H), 0.94–0.85 (m, 1 H), 0.54 (q, *J* = 5.1 Hz, 2 H), 0.13 (q, *J* = 5.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.75, 50.88, 42.36, 28.77, 7.32, 4.40.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.85–5.71 (m, 1 H, overlap), 5.50 (s, 1 H), 5.01 (dd, J_1 = 17.1 Hz, J_2 = 0.9 Hz, 1 H), 4.95 (d, *J* = 10.2 Hz, 1 H), 2.35–2.29 (m, 2 H), 2.15 (t, *J* = 7.5 Hz, 2 H), 1.35 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.57, 137.21, 115.23, 51.02, 36.61, 29.66, 28.74.

The spectroscopic data matched those reported.[13d]

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Supporting Information

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