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Base mediated intramolecular decarboxylative synthesis of alkylamines from alkanoyloxycarbamates

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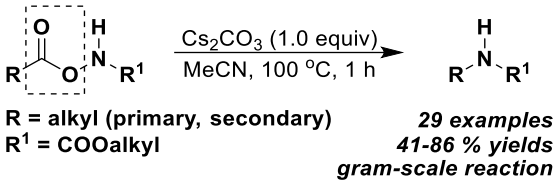
Supporting Information Placeholder

ABSTRACT: A general and effective method for the synthesis of alkylamine via intramolecular decarboxylation of alkanoyloxycarbamates is described. The alkanoyloxycarbamates are readily prepared with alkyl carboxylic acids and hydroxylamine. The reaction shows broad range of substrates (primary, secondary alkyl) with functional tolerance and the corresponding products were obtained in good yield under mild conditions.



INTRODUCTION

Direct decarboxylation coupling of alkylated carbon-carbon and carbon-heteroatom bonds with available carboxylic acids as useful alkylating agents has received widespread attention in recent years.[1] The value of these transformations lies in the stability and abundant biomass feedstock aliphatic carboxylic acid as alkylating resources instead of organometallic reagents.[2] Employing transition metal catalyzed decarboxylation coupling methodologies, a variety of elegant works has been established to build carbon−carbon bonds.[3] In particular, Pd, Cu, Ni catalyzed redox neutral cross-coupling and oxidative decarboxylation coupling reactions become a highly efficient and selective fashion.[4] Because of highly site-selective and well atom-efficient alternatives to traditional cross-coupling, this new protocol has been reported to construct carbon−nitrogen bond (alkylamine).[5] Alkylamine derivatives are important intermediates in organic synthesis as they are widespread structural motifs in natural products, pharmaceutical, agrochemical, and materials industry.[6] Consequently, numerous significant methods have been developed to form alkylamine, such as the alkylation by alkyl halides,[7] reductive amination,[8] coupling of amines with aryl halides,[9] hydroamination,[10] and direct coupling of amines with alcohols.[11] In such experiments, using an excess of amines, noble metal catalyst, and overalkylations need be improved. Unlike these methods, decarboxylation coupling is an attractive, sustainable approach to afford the desired alkylated amines neither using alkyl halide nor borohydride. In this regard, an increasing number of metal-catalyzed decarboxylation carbon−nitrogen formation (aryl or alkyl carboxylic acids as starting materials) have been established.[5,12,13] Initially, research into Cu-mediated carbon−nitrogen bond construction has undergone a breakthrough via decarboxylation coupling reaction.[5] For example, Tang[5b] and Fu[5c] groups developed Cu-catalyzed decarboxylation coupling of aliphatic carboxylic acids to synthesize alkylamine derivatives (Scheme 1a, 1b). Despite the significance of these methods, there are no reported examples of base mediated intramolecular decarboxylation carbon−nitrogen coupling reaction. Additionally, the use of specific carboxylic acid and amine precursors as substrates is still existing. Therefore, it's desirable to develop a general and practical strategies for the synthesis of alkylamine. In our initial study[13a], we found that aroyloxycarbamates can be converted to arylamines in the presence of $PdCl_2(PPh_3)_2$ (5 mol%) and Cs_2CO_3 (2 equiv) in chlorobenzene at 85 °C (Scheme 1c). Unfortunately, we did not obtain alkylamines from alkanoyloxycarbamates under this reaction condition. An alternative approach is necessary and many experiments have been carried out on this purpose. Until now, we have found that alkylamines could be afforded in the presence of Cs_2CO_3 in acetonitrile at 100 °C (Scheme 1d). And the base takes a major

Scheme 1. Decarboxylation synthesis of alkylamines

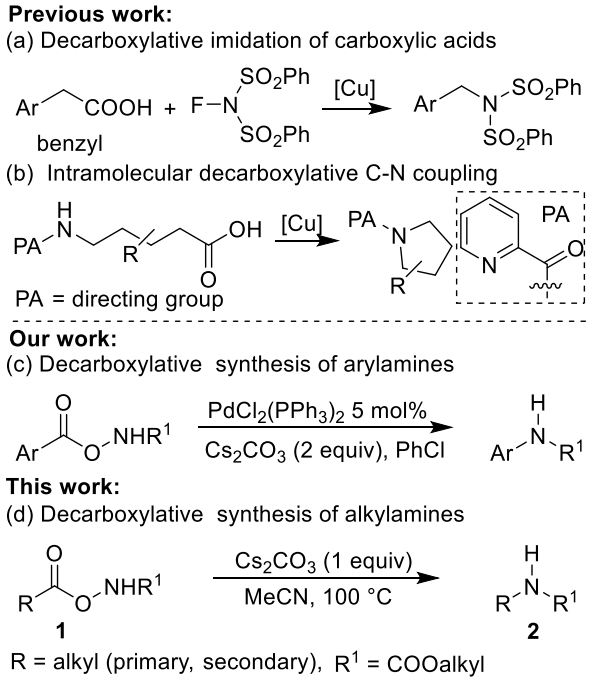
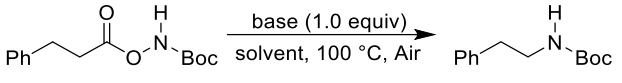


Table 1. Optimization of reaction conditions[a]



entry	base (equiv)	solvent	T (°C)	yield[b] (%)
1	Cs_2CO_3	toluene	100	57
2	-	toluene	100	0
3	K_2CO_3	toluene	100	53
4	Ag_2CO_3	toluene	100	0
5	^{t}BuONa	toluene	100	52
6	Et_3N	toluene	100	0
7	DBU	toluene	100	46
8	Cs_2CO_3	benzene	100	78
9	Cs_2CO_3	PhCl	100	71
10	Cs_2CO_3	MeCN	100	85 (81)[c]
11	Cs_2CO_3	$CHCl_3$	100	53
12	Cs_2CO_3 (0.5)	MeCN	100	45
13	Cs_2CO_3 (1.5)	MeCN	100	79
14	Cs_2CO_3	MeCN	80	76
15	Cs_2CO_3	MeCN	120	85

[a]Reaction conditions: **1f** (0.20 mmol), base (1.0 equiv) in solvent (2.0 mL) for 1.0 h under air atmosphere. [b]The yields were determined by GC analysis using biphenyl as internal standard. [c]Isolated yield for parenthesis. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, PhCl = chlorobenzene.

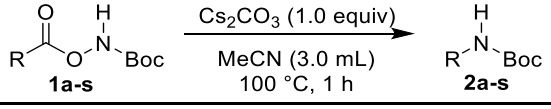
role in this reaction. This transformation is similar to the Curtius rearrangement which is a very general reaction for the synthesis of amine derivatives from carboxylic acids. Herein, we communicate the details of this study.

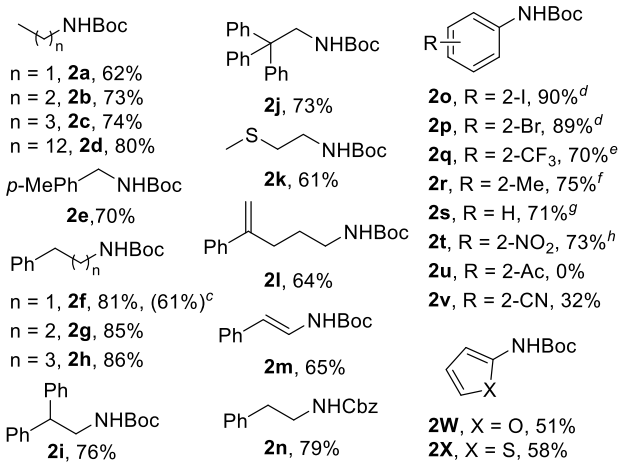
RESULTS AND DISCUSSION

Initially, *tert*-butyl ((3-phenylpropanoyl)oxy)carbamate (**1f**) was chosen as the model substrate to test decarboxylation amination reaction (Table 1). As expected, the desired product **2f** was obtained in 57% yield in the presence of Cs_2CO_3 (1.0 equiv) at 100 °C in toluene for 1.0 h (Table 1, entry 1). After screening kinds of base (Cs_2CO_3, K_2CO_3, Ag_2CO_3, ^{t}BuONa, Et_3N, DBU), we found that cesium carbonate was the best base (Table 1, entries 1-7). Solvent variation indicated that CH_3CN was the optimal solvent in 85 % yield (Table 1, entries 8-11). To improve the efficiency of reaction, we examined the different amount of Cs_2CO_3 and 1.0 equiv Cs_2CO_3 was the best condition (Table 1, entries 12-13). Further investigations on the temperatures showed that the best yield was obtained at 100 °C. Finally, the optimal conditions are as follows: 1.0 equivalent of Cs_2CO_3 in 2 mL of acetonitrile at 100 °C under air.

With the optimal conditions in hand, we investigated the substrate scope of this decarboxylation carbon−nitrogen coupling reaction. As shown in Table 2, a variety of *N*-Boc-protected primary aliphatic carboxylic acids bearing alkyl chains were proceeded smoothly in moderate to good yields. The reaction

Table 2. Substrate scope[a]



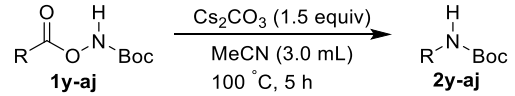


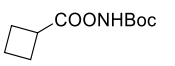
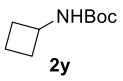
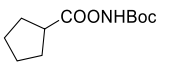
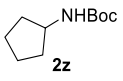
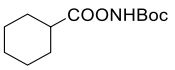
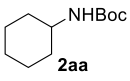
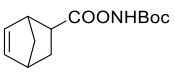
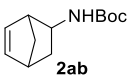
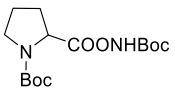
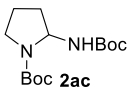
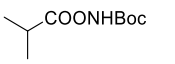
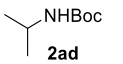
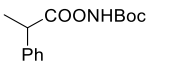
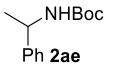
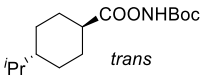
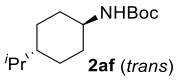
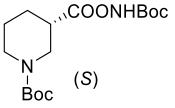
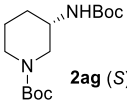
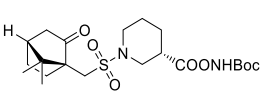
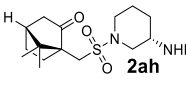
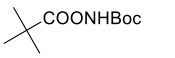
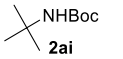
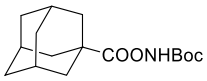
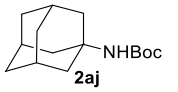
[a]Reaction conditions: **1** (0.30 mmol), Cs_2CO_3 (1.0 equiv), MeCN (3.0 mL), 100 ^{0}C, 1 h. [b]Isolated yield. [c]In situ yield (using the **1f** without purification (in situ)). [d]r.t., 8 h. [e]r.t., 5 h. [f]80 ^{0}C, 1 h. [g]80 ^{0}C, 2 h, [h]r.t., 6 h,

readily occurred with short alkyl chain acids (**2a**, **2b**) in 62% and 73% yields, respectively. In contrast, long-chain aliphatic carboxylic acids, such as myristic acid delivered the corresponding product **2d** in higher yield (80% yield). Compared with Cu-catalyzed decarboxylation carbon−nitrogen coupling to synthesize benzyl (Bn) amine in 54% yield,[5b] we obtained the desired product **2e** in 70% yield. Gratifyingly, the decarboxylation reaction yields were up to 80% for phenyl substituted alkyl chain acids (**2f-h**). Sterically more hindered substituted alkyl chain acids transformed into the desired products in good yields (**2i-j**). Substrate with alkyl sulfide could also undergo decarboxylation in 61% yield (**2k**). Interestingly, alkenyl substituted alkyl chains were well-tolerated to obtain **2l**, **2m** in 64% and 65% yields, respectively. The *N*-protected (Cbz) substrate well transformed to the corresponding product **2n** in 79% yield. The aroyloxycarbamates could also deliver to the desired products in moderate to good yields under this mild condition (**2o-t**, **2v-x**).

To further investigate the property of decarboxylation amination reaction, we evaluated the secondary aliphatic carboxylic acids. As shown in Table 3, all the reactions were proceeded smoothly and converted to the corresponding product in moderate to good yields (Table 3). Cyclic secondary alkyl acids, such as cyclobutanecarboxylic acid, cyclopentanecarboxylic acid, and cyclohexanecarboxylic acid were well-tolerated, and the desired products **2y**, **2z**, **2aa** were obtained in 51%, 62%, and 71% yields, respectively. Cyclic secondary alkyl acids with different group, such as **1ab** and **1ac** could be well transformed to the corresponding products. Acyclic secondary alkyl acids, including isobutyric acid, and 2-phenylpropanoic acid were also tested and afforded the products *tert*-butyl isopropylcarbamate **2ad**, and *tert*-butyl (1-phenylethyl)carbamate **2ae** in 41% and 62% yields, respectively. It is worth noting that **1af** (*trans*), **1ag** (*S*) and **1ah** converted to *trans*-product **2af**, (*S*)-product **2ag** and **2ah**,

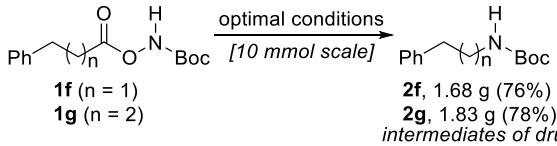
Table 3. Substrate scope[a]



entry	substrate	product	yield (%)[b]
1		 **2y**	51
2		 **2z**	62
3		 **2aa**	71
4		 **2ab**	43
5		 **2ac**	51
6		 **2ad**	41
7		 **2ae**	62
8[c]	 *trans*	 **2af** (*trans*)	68
9[c]	 (*S*)	 **2ag** (*S*)	61
10[c]		 **2ah**	50
11		 **2ai**	0
12		 **2aj**	0

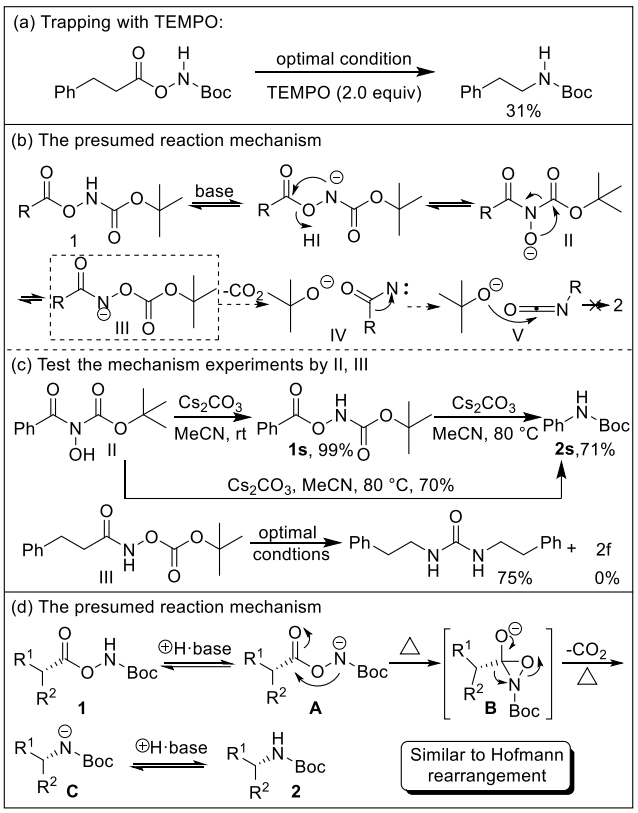
[a]Reaction conditions: **1** (0.30 mmol), Cs_2CO_3 (1.5 equiv), MeCN (3.0 mL), 100 ^{0}C, 5 h. [b]Isolated yield. [c]The **2aa**, **2ac** *trans/cis* ratio was detected by crude H NMR >99/1.

Scheme 2. Large-scale synthesis of 2f, **2g**.



respectively. The results indicated that the native structures of **1af** (*trans*), **1ag** (*S*) and **1ah** were maintained (see supporting information S35-39).These results illustrated that the mechanism of this reaction may be a rearrangement process.

Scheme 3. Mechanistic studies



To demonstrate the practical utility of this new method, the reactions of **1f**, **1g** were performed on a scale of 10 mmol. The desired **2f**, **2g** (intermediates of drug)[14] were formed in 76%, 78% yields, respectively (Scheme 2). These results are identical to Table, 2 (Table, 2, entries 6-7).

To understand the present reaction mechanism, we conducted several control experiments. Under optimal reaction conditions, the trapping experiment was explored by TEMPO (Scheme 3a). The result indicates that the reaction mechanism may not be free radicals under this optimal condition. The alkenyl substituted alkyl chain **1l** was also confirmed above the result. It is revealed that radical or carbonium ion intermediate is not involved as a result of the lack of cyclization/isomerization product (Table 2, **1l**). The above information suggests that a mechanism of carbon anion migration may be occurred in the reaction. So, a possible mechanism is shown in Scheme 3b (based on Hoffman rearrangement or Curtius rearrangement mechanism). Unfortunately, the intermediate **II** was transformed to the **1s** instead of **III** in 99% yield under room temperature or 80 °C (5 min) (Scheme 3c). And the desired product **2f** was not obtained in the presence of the intermediate **III** under optimal conditions (Scheme 3c). Based on the **1af**, **1ag**, **1ah** results and the mechanism study, a plausible pathway is proposed. As shown in Scheme 3d, in the first step of the catalytic cycle, **1** is transformed to the complex **A** through deprotonation with the assistance of the base. Then **A** undergoes a S_N2 reaction via nitrogen as a nucleophilic. The complex **C** was formed by an intermedate **B** through a concerted rearrangement. This process is similar to Hofmann rearrangement.

CONCLUSION

In summary, we have developed the base mediated intramolecular decarboxylative synthesis of protected alkylamines. This practical protocol exhibits an efficient method for the formation of primary, secondary alkylamines and arylamines with a wide range of substrates. In contrast to traditional metal-catalyzed decarboxylation carbon−nitrogen coupling, this method relies on the use of base mediated system to provide the desired amines efficiently. Regardless, we have unequivocally demonstrated that the air stable, environment-friendly, abundant starting materials aliphatic carboxylic acid and gram-scale reaction is tractable in this transformation. The futher study of mechanism underway in cooperated other group.

EXPERIMENTAL SECTION

General Remarks

All commercially available reagents were used without further purification. Unless stated otherwise, all reactions were carried out in Schlenk Tube under a dry argon or nitrogen atmosphere. All solvents were purified and dried according to standard methods prior to use. Column chromatography was performed on silica gel (200-400 mesh). GC-MS data were performed on Agilent 7890A. GC analyses were performed on a Shimadzu GC-2014 equipped with a capillary column (HP-5 30 m × 0.25 μm) using a flame ionization detector. Melting points were determined using an X-4 apparatus and are uncorrected. The FTIR spectra were recorded from KBr pellets in the range 4000–400 cm^{-1} on Nicolet 170 SXFT/IR spectrometer. NMR spectra were taken with a Bruker 400 spectrometer at 400 MHz (^1H) and 101 MHz (^{13}C) using $CDCl_3$ as the solvent with TMS as internal standard. Chemical shifts were reported in ppm referenced to the center of a triplet at 77.0 ppm of chloroform-*d*. HRMS was performed on TOF LC-MS in ESI mode.

Representative procedure for the synthesis of alkanoyloxycarbamates :

General procedure for the preparation of *N*-hydroxyl carbamate (BocNHOH): *N*-hydroxyl *tert*-butyl carbamate was prepared from hydroxylamine hydrochloride with $(Boc)_2O$, according to a known procedure. A suspension of $NH_2OH{\cdot}HCl$ (9.6 g, 0.14 mol, 1.5 equiv) and K_2CO_3 (7.2 g, 0.07 mol, 1.5 equiv) in Et_2O (60 mL) and H_2O (2 mL) was stirred for about 1 h at room temperature with evolution of CO_2 gas. A solution of Boc_2O (20.0 g, 92 mmol) in Et_2O (40 mL) was then added dropwise at 0 °C and the suspension was stirred at room temperature for 12 h. The organic phase was decanted and the solid was washed with Et_2O (30 mL × 2) and the organic layers were combined and concentrated. Recrystallization with a cyclohexane/toluene mixture afforded the desired product (80% yield).[15]

General procedure for the preparation of *N*-hydroxyl carbamate (ROCONHOH, Bn): *N*-hydroxyl carbamates were prepared from hydroxylamine with the corresponding chloroformates according to a known procedure. Hydroxylamine hydrochloride (13.9 g, 200 mmol) was added to aqueous solution of NaOH (1.5 M, 160 mL, 240 mmol). The solution was cooled to 0 °C and chloroformate (38 mmol) was added dropwise. Upon the completion of addition, the mixture was warmed up to room temperature and stirred for additional 2 h. The reaction was then acidified with aqueous HCl (6 M) till pH is around 4.5. Then the mixture was extracted with Et_2O (200 mL × 3) and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, the *N*-hydroxyl carbamate was used directly without further purification.[15]

General procedure for the preparation of alkanoyloxycarbamates (1f): To a 250 mL flame-dried round bottom flask equipped with a stir bar, an *N*-hydroxyl carbamate (20 mmol, 1.0 equiv), 3-phenylpropionic acid (3.15 g, 21 mmol) and anhydrous CH_2Cl_2 (80 mL) were added. The flask was cooled to -15 °C. DCC (4.53 g, 22 mmol, dissolved in 20 mL of anhydrous CH_2Cl_2) solution was then added dropwise. The reaction mixture was stirred at the same temperature for additional 30 min until the *N*-hydroxyl carbamate was fully consumed (monitored by TLC). The white precipitate (N, N'-dicyclohexylurea) was removed by filtration and the filtrate was concentrated in vacuo and dissolved again in Et_2O (30 mL). The solution was cooled to -20 °C for 2 h and filtered again to remove additional precipitate. The organic layer was then concentrated in vacuo and purified by silica gel chromatography using a mixture of hexanes and EtOAc (hexane:EtOAc = 10:1) to provide the desired **1f** in 92% yield as a colorless oil.[15]

tert-butyl ((3-phenylpropanoyl)oxy)carbamate (**1f**): oil (4.88 g, 92% yield); R_f = 0.55 (hexane:EtOAc = 10:1); ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (brs, 1H), 7.30 (t, J = 7.2 Hz, 2H), 7.22 (t, J = 7.2 Hz, 3H), 3.02 (t, J = 7.6 Hz, 2H), 2.78 (t, J = 7.6 Hz, 2H), 1.49 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.1, 155.4, 139.6, 128.6, 128.3, 126.5, 83.3, 33.4, 30.5, 27.9; HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ Calcd for $C_{14}H_{23}N_2O_4$ 283.1653; found 283.1656.

General procedure for the synthesis of alkylamines (2a-aj)

To a solution of **1f** (79.6 mg, 0.3 mmol) and Cs_2CO_3 (0.3 mmol, 1.0 equiv) in MeCN (3.0 mL) in a pressure tube (10 mL) with a sealing cap under air atmosphere, the reaction mixture was vigorously stirred at 100 °C for 1 h, quenched by ethyl acetate, and purified by silica gel chromatography using a mixture of hexanes and EtOAc (hexane:EtOAc = 20:1) to provide the desired **2f** (oil, 54 mg, 81% yield).

*tert-butyl ethylcarbamate (**2a**, Table 2, entry 1)*.[16] Oil (27 mg, 62% yield); R_f = 0.57 (hexane:EtOAc = 20:1); ^1H NMR (400 MHz, $CDCl_3$): δ 4.48 (brs, 1H), 3.16 (t, J = 6.4 Hz, 2H), 1.45 (s, 9H), 1.11 (t, J = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.8, 79.0, 35.4, 28.4, 15.3.

*tert-butyl propylcarbamate (**2b**, Table 2, entry 2)*.[17] Oil (35 mg, 73% yield); R_f = 0.55 (hexane:EtOAc = 20:1); ^1H NMR (400 MHz, $CDCl_3$): δ 4.57 (brs, 1H), 3.08-3.03 (m, 2H), 1.49-1.44 (m, 2H), 1.42 (s, 9H), 0.88 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.0, 78.9, 42.3, 28.4, 23.2, 11.2.

tert-butyl butylcarbamate *(**2c**, Table 2, entry 3)*.[18] Oil (38 mg, 74% yield); R_f = 0.55 (hexane:EtOAc = 20:1); ^1H NMR (400 MHz, $CDCl_3$): δ 4.49 (brs, 1H), 3.11 (d, J = 6.4 Hz, 2H), 1.48-1.44 (m, 11H), 1.38-1.28 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.0, 79.0, 40.3, 32.1, 28.4, 19.9, 13.7.

*tert-butyl tridecylcarbamate (**2d**, Table 2, entry 4)*.[19] White solid (72 mg, 80% yield); mp: 39-40 °C; R_f = 0.52 (hexane:EtOAc = 20:1); ^1H NMR (400 MHz, $CDCl_3$): δ 4.51 (s, 1H), 3.11-3.06 (m, 2H), 1.43 (s, 9H), 1.24 (s, 22H), 0.86 (t, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.9, 78.9, 40.6, 31.9, 30.0, 29.7, 29.6, 29.5, 29.5, 29.3, 29.2, 28.4, 26.8, 22.7, 14.1.

*tert-butyl (4-methylbenzyl)carbamate (**2e**, Table 2, entry 5)*.[20] White solid (46 mg, 70% yield); mp: 75-77 °C; R_f = 0.39 (hexane:EtOAc = 20:1); ^1H NMR (400 MHz, $CDCl_3$): δ 7.18-7.12 (m, 4H), 4.79 (s, 1H), 4.27 (d, J = 5.6 Hz, 2H), 2.33 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.8, 137.0, 135.9, 129.2, 127.5, 79.4, 44.4, 28.4, 21.1.

*tert-butyl phenethylcarbamate (**2f**, Table 2, entry 6)*.[21] Oil (54 mg, 81% yield); R_f = 0.42 (hexane:EtOAc = 20:1); ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.31 (t, J = 7.7 Hz, 2H), 7.22 (t, J = 7.0 Hz, 1H), 7.20 (d, J = 7.7 Hz, 2H), 4.56 (s, 1H), 3.39 (d, J = 6.3 Hz, 2H), 2.80 (t, J = 7.0 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR (175 MHz, $CDCl_3$): δ 155.8, 139.0, 128.8, 128.5, 126.4, 79.2, 41.7, 36.2, 28.4.

*tert-butyl (3-phenylpropyl)carbamate (**2g**, Table 2, entry 7)*.[22] White solid (60 mg, 85% yield); mp: 36-37 °C; R_f = 0.42 (hexane:EtOAc = 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.26 (m, 2H), 7.20-7.16 (m, 3H), 4.54 (s, 1H), 3.15 (d, J = 6.4 Hz, 2H), 2.64 (t, J = 7.6 Hz, 2H), 1.85-1.77 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.0, 141.6, 128.4, 128.4, 125.9, 79.1, 40.2, 33.1, 31.8, 28.4.

*tert-butyl (4-phenylbutyl)carbamate (**2h**, Table 2, entry 8)*.[23] Oil (64 mg, 86% yield); R_f= 0.43 (hexane:EtOAc = 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (t, J = 8.0 Hz, 2H), 7.17 (t, J = 6.8 Hz, 3H), 4.52 (s, 1H), 3.13 (d, J = 6.4 Hz, 2H), 2.62 (t, J = 7.6 Hz, 2H), 1.66-1.60 (m, 2H), 1.54-1.44 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.9, 142.1, 128.3, 128.2, 125.7, 79.0, 40.4, 35.4, 28.6, 28.5, 28.4.

*tert-butyl (2,2-diphenylethyl)carbamate (**2i**, Table 2, entry 9)*. White solid (68 mg, 76% yield); mp: 87-88 °C; R_f = 0.36 (hexane:EtOAc = 20:1); IR (film) 3358, 2969, 1712, 1503, 1247, 1168, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.18 (m, 10H), 4.52 (brs, 1H), 4.16 (t, J = 7.6 Hz, 1H), 3.76 (t, J = 6.4 Hz, 2H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.7, 141.9, 128.6, 128.0, 126.7, 79.2, 51.0, 44.9, 28.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{24}NO_2$ 298.1802; found 298.1805.

*tert-butyl (2,2,2-triphenylethyl)carbamate (**2j**, Table 2, entry 10)*. White solid (82 mg, 73% yield); mp: 57-59 °C; R_f= 0.34 (hexane:EtOAc = 20:1); IR (film) 2972, 1760, 1244, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.22 (m, 15H), 4.34 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.6, 145.2, 129.1, 128.2, 126.5, 79.4, 56.9, 48.9, 28.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{28}NO_2$ 374.2120; found 374.2124.

*tert-butyl (2-(methylthio)ethyl)carbamate (**2k**, Table 2, entry 11)*.[24] Oil (35 mg, 61% yield); R_f= 0.49 (hexane:EtOAc = 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.92 (s, 1H), 3.32 (d, J = 6.0 Hz, 2H), 2.61 (t, J = 6.4 Hz, 2H), 2.10 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.8, 79.4, 39.0, 34.2, 28.4, 15.0.

*tert-butyl (4-phenylpent-4-en-1-yl)carbamate (**2l**, Table 2, entry 12)*.[25] Oil (50 mg, 64% yield); R_f= 0.39 (hexane:EtOAc = 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J = 7.2 Hz, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.28-7.24 (m, 1H), 5.28 (s, 1H), 5.08 (s, 1H), 4.51 (brs, 1H), 3.14 (d, J = 6.0 Hz, 2H), 2.54 (t, J = 7.6 Hz, 2H), 1.67-1.60 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.9, 147.6, 140.9, 128.3, 127.4, 126.1, 112.7, 79.0, 40.2, 32.5, 28.5, 28.4.

*tert-butyl-styrylcarbamate (**2m**, Table 2, entry 13)*.[26] White solid (43 mg, 65% yield); mp: 117-119 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.18 (m, 5H), 7.16-7.11 (m, 1H), 6.46 (d, J = 7.2 Hz, 1H), 5.89 (d, J = 14.4 Hz, 1H), 1.49 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.7, 136.5, 128.5, 125.9, 125.1, 124.3, 109.6, 80.7, 28.2.

benzyl phenethylcarbamate *(**2n**, Table 2, entry 14)*.[27] White solid (60 mg, 79% yield); mp: 61-63°C; R_f = 0.29 (hexane:EtOAc = 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.09 (m, 10H), 5.01 (s, 2H), 4.77 (s, 1H), 3.40-3.35 (m, 2H), 2.73 (t, J = 7.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.2, 138.6, 136.5, 128.7, 128.5, 128.4, 128.0, 126.4, 66.5, 42.1, 36.0.

*tert-butyl (2-iodophenyl)carbamate (**2o**, Table 2, entry 15)*.[28] Orange oil (86 mg, 90% yield); R_f = 0.49 (hexane:EtOAc = 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (dd, J = 8.3, 1.0 Hz, 1H), 7.74 (dd, J = 7.9, 1.4 Hz, 1H), 7.36-7.27 (m, 1H), 6.83 (s, 1H), 6.78-6.71 (m, 1H), 1.54 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.5, 138.8, 129.1, 124.6, 120.1, 88.7, 81.0, 28.3.

*tert-butyl (2-bromophenyl)carbamate (**2p**, Table 2, entry 16)*.[29] Colorless oil (73 mg, 89% yield); R_f = 0.48 (hexane:EtOAc = 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (dd, J = 8.3, 1.1 Hz, 1H), 7.51 (dd, J = 8.0, 1.5 Hz, 1H), 7.33-7.23 (m, 1H), 7.03 (s, 1H), 6.93-6.89 (m, 1H), 1.56 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.3, 136.3, 132.2, 128.2, 123.8, 120.0, 112.3, 81.0, 28.2.

*tert-butyl (2-(trifluoromethyl)phenyl)carbamate (**2q**, Table 2, entry 17)*.[30] Colorless oil (55 mg, 70% yield); R_f = 0.51 (hexane:EtOAc = 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 7.9 Hz, 1H), 7.52 (t, J = 7.9 Hz, 1H), 7.13 (t, J = 7.7 Hz, 1H), 6.80 (s, 1H), 1.53 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$); δ 152.5, 136.2, 132.8, 125.9 (q, J = 5.4), 124.1 (q, J = 273.8), 123.0, 122.3, 118.9 (q, J = 29.7), 81.3, 28.2.

*tert-butyl o-tolylcarbamate (**2r**, Table 2, entry 18)*.[31] White solid (55 mg, 70% yield); mp: 83-84 °C; R_f = 0.55 (hexane:EtOAc = 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J = 7.8 Hz, 1H), 7.23-7.08 (m, 2H), 6.98 (t, J = 7.2 Hz, 1H), 6.30 (brs, 1H), 2.25 (s, 3H), 1.54 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.0, 136.3, 130.2, 127.3, 126.7, 123.6, 120.9, 80.3, 28.3, 17.6.

*tert-butyl phenylcarbamate (**2s**, Table 2, entry 19)*.[32] White solid (41 mg, 71% yield); mp: 135-136 °C; R_f = 0.57 (hexane:EtOAc = 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, J = 7.9 Hz, 2H), 7.32-7.26 (m, 2H), 7.08-6.96 (m, 1H), 6.60 (s, 1H), 1.53 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.8, 138.3, 128.9, 122.9, 118.5, 80.4, 28.3.

*tert-butyl (2-nitrophenyl)carbamate (**2t**, Table 2, entry 20)*.[33] Yellow solid (52 mg, 73% yield); mp: 89-90 °C; R_f = 0.48 (hexane:EtOAc = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.64 (s, 1H), 8.55 (dd, J = 8.6, 1.0 Hz, 1H), 8.17 (dd, J = 8.5, 1.5 Hz, 1H), 7.65-7.52 (m, 1H), 7.07 (ddd, J = 8.4, 7.4, 1.2 Hz, 1H), 1.54 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.1, 135.9, 135.7, 125.8, 121.8, 120.6, 81.8, 28.2.

*tert-butyl (2-cyanophenyl)carbamate (**2v**, Table 2, entry 22)*.[34] Oil (20 mg, 32% yield); R_f = 0.51 (hexane:EtOAc = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.4 Hz, 1H), 7.55 (t, J = 8.6 Hz, 2H), 7.08 (t, J = 7.6 Hz, 1H), 7.02 (s, 1H), 1.53 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.8, 141.4, 134.1, 132.2, 122.7, 119.1, 116.5, 100.6, 81.9, 28.2.

*tert-butyl furan-2-ylcarbamate (**2w**, Table 2, entry 23)*.[35] White solid (28 mg, 51% yield); mp: 90-92°C; R_f = 0.41 (hexane:EtOAc = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (s, 1H), 6.57 (s, 1H), 6.34 (s, 1H), 6.03 (s, 1H), 1.50 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.8, 145.3, 136.1, 111.3, 95.2, 81.3, 28.2.

*tert-butyl thiophen-2-ylcarbamate (**2x**, Table 2, entry 24)*.[36] White solid (35 mg, 58% yield); mp: 155-156 °C; R_f= 0.36 (hexane:EtOAc = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (brs, 1H), 6.83-6.79 (m, 2H), 6.53-6.52 (m, 1H), 1.52 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 139.9, 124.2, 116.8, 111.1, 84.5, 28.0.

*tert-butyl cyclobutylcarbamate (**2y**, Table 3, entry 1)*.[37] White solid (26 mg, 51% yield); mp: 72-73 °C; R_f = 0.39 (hexane:EtOAc = 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.70 (s, 1H), 4.10-4.08 (m, 1H), 2.29-2.27 (m, 2H), 1.84-1.74 (m, 2H),

1.68-1.57 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.8, 79.0, 45.7, 31.5, 28.4, 14.7.

*tert-butyl cyclopentylcarbamate (**2z**, Table 3, entry 2)*.[38] White solid (34 mg, 62% yield); mp: 74-75 °C; R_f = 0.42 (hexane:EtOAc = 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.47 (s, 1H), 3.91 (s, 1H), 1.95-1.90 (m, 2H), 1.67-1.53 (m, 4H), 1.43 (s, 9H), 1.39-1.33 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.5, 79.0, 52.3, 33.3, 28.4, 23.5.

*tert-butyl cyclohexylcarbamate (**2aa**, Table 3, entry 3)*.[21] White solid (42 mg, 71% yield); mp: 77-78 °C; R_f = 0.45 (hexane:EtOAc = 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.41 (s, 1H), 3.40 (s, 1H), 1.93-1.89 (m, 2H), 1.71-1.65 (m, 2H), 1.60-1.55 (m, 1H), 1.43 (s, 9H), 1.35-1.26 (m, 2H), 1.18-1.03 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.2, 78.9, 49.4, 33.5, 28.4, 25.5, 24.9.

*tert-butyl bicyclo[2.2.1]hept-5-en-2-ylcarbamate (**2ab**, Table 3, entry 4)*. White solid (27 mg, 43% yield); mp: 57-59 °C; R_f = 0.46 (hexane:EtOAc = 20:1); IR (film) 2981, 1763, 1368, 1239, 1047 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.34-6.32 (m, 1H), 6.02-6.00 (m, 1H), 4.21 (s, 2H), 3.00 (s, 1H), 2.81 (s, 1H), 2.23-2.12 (m, 1H), 1.45-1.43 (m, 10H), 1.30 (d, J = 8.4 Hz, 1H), 0.66 (d, J = 12.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.6, 139.9, 131.6, 79.0, 50.4, 48.6, 46.2, 42.6, 35.8, 28.4; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{20}NO_2$ 210.1494; found 210.1494.

*tert-butyl 2-((tert-butoxycarbonyl)amino)pyrrolidine-1-carboxylate (**2ac**, Table 3, entry 5)*. White solid (43 mg, 51% yield); mp:125-126 °C; R_f = 0.29 (hexane:EtOAc = 20:1); IR (film) 3311, 1671, 1530, 1359, 1144 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.38 (s, 1H), 4.72 (s, 1H), 3.45-3.42 (m, 1H), 3.27-3.21 (m, 1H), 2.03-1.86 (m, 4H), 1.45 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.3, 154.1, 80.0, 79.4, 65.2, 45.8, 34.4, 28.4, 28.4, 22.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{27}N_2O_4$ 287.1965; found 287.1962.

*tert-butyl isopropylcarbamate (**2ad**, Table 3, entry 6)*.[39] Oil (19 mg, 41% yield); R_f = 0.53 (hexane:EtOAc = 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.34 (s, 1H), 3.74 (s, 1H), 1.44 (s, 9H), 1.12 (d, J = 6.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.2, 78.9, 42.5, 28.4, 23.1.

*tert-butyl (1-phenylethyl)carbamate (**2ae**, Table 3, entry 7)*.[40] White solid (41 mg, 62% yield); mp: 77-79 °C; R_f = 0.33 (hexane:EtOAc = 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.22 (m, 5H), 4.80 (s, 2H), 1.45-1.42 (m, 12H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.1, 143.9, 128.5, 127.1, 125.8, 79.4, 50.1, 28.3, 22.6.

*tert-butyl (4-isopropylcyclohexyl)carbamate (**2af**, Table 3, entry 8)*. (trans/cis ratio >99/1); White solid (49 mg, 68% yield); mp: 106-107 °C; R_f = 0.46 (hexane:EtOAc = 20:1); IR (film) 3352, 2928, 1677, 1518, 582 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.36 (s, 1H), 4.32 (s, 1H), 2.03-2.00 (m, 2H), 1.72-1.68 (m, 2H), 1.43-1.36 (m, 10H), 1.05-0.96 (m, 5H), 0.84 (d, J = 6.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.2, 78.9, 50.0, 43.2, 33.7, 32.5, 28.5, 28.4, 19.9; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{28}NO_2$ 242.2115; found 242.2117.

*tert-butyl (S)-3-((tert-butoxycarbonyl)amino)piperidine-1-carboxylate (**2ag**, Table 3, entry 9)*.[41] White solid (55 mg, 61% yield); mp: 64-66 °C; R_f = 0.31 (hexane:EtOAc = 3:1); $[\alpha]_D$ = -2.1 (*c* 1.0, $CHCl_3$), 80% ee (from **1ag** 80 % ee)[Chiralcel AD-H column (0.46 cmI.D. × 25 cmL, n-hexane/i-PrOH = 95/5, 0.6mL/min, 210 nm; t_{minor} = 16.4 min, t_{major} = 19.5 min)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.85 (s, 1H), 3.56-3.15 (m, 5H), 1.81-1.39 (m, 22H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.0, 154.9, 79.6, 79.2, 48.7, 46.1, 43.5, 30.1, 28.3, 28.2, 22.4.

*tert-butyl ((S)-1-((((1S,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methyl)sulfonyl)p-iperidin-3-yl)carbamate (**2ah**, Table 3, entry 10)*. (trans/cis ratio >99/1); Oil (62 mg, 50% yield); R_f = 0.25 (hexane:EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (s, 1H), 3.82 (s, 1H), 3.50-3.19 (m, 4H), 3.08 (s, 1H), 2.71 (d, J = 14.5 Hz, 1H), 2.51 (t, J = 12.5 Hz, 1H), 2.36 (d, J = 18.6 Hz, 1H), 2.16-1.99 (m, 2H), 1.93 (d, J = 18.5 Hz, 1H), 1.79 (s, 1H), 1.74 – 1.54 (m, 4H), 1.43 (s, 10H), 1.11 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.5, 154.9, 79.5, 58.3, 50.4, 48.1, 46.2, 45.4, 45.2, 42.8, 42.6, 29.1, 28.4, 26.9, 25.2, 21.9, 19.9, 19.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{35}N_2O_5S$ 415.2261; found 415.2255.

General procedure for the synthesis of alkylamines (2f-2g) (gram scale): To a solution of **1f** (2.65 g, 10.0 mmol) and Cs_2CO_3 (10.0 mmol, 1.0 equiv) in MeCN (30 mL) in a round bottom flask equipped with a stir bar, the reaction mixture was vigorously stirred at 100 °C for 1 h, quenched by ethyl acetate, and purified by silica gel chromatography using a mixture of hexanes and EtOAc (hexane:EtOAc = 20:1) to provide the desired **2f** (oil, 1.68 g, 76% yield).

General procedure for the synthesis of alkylamines (2f) (in situ): To a 50 mL flame-dried round bottom flask equipped with a stir bar, an *N*-hydroxyl carbamate (5 mmol, 0.665 g, 1.0 equiv), 3-phenylpropionic acid (0.787 g, 5.25 mmol) and anhydrous MeCN (20 mL) were added. The flask was cooled to -15 °C. DCC (1.13 g, 5.5 mmol, dissolved in 10 mL of anhydrous MeCN) solution was then added dropwise. The reaction mixture was stirred at the same temperature for additional 30 min until the *N*-hydroxyl carbamate was fully consumed (monitored by TLC). Then the mixture was warmed up to room temperature and add Cs_2CO_3 (0.3 mmol, 1.0 equiv), then the reaction mixture was vigorously stirred at 100 °C with reflow equipment (monitored by TLC). After reaction completed, quenched by ethyl acetate, and purified by silica gel chromatography using a mixture of hexanes and EtOAc (hexane:EtOAc = 20:1) to provide the desired **2f** (oil, 0.674 g, 61% yield).

Mechanistic studies

General Procedure for the Trapping with TEMPO

To a solution of **1f** (79.6 mg, 0.3 mmol) Cs_2CO_3 (0.3 mmol), and TEMPO (93.8 mg, 0.6 mmol) in MeCN (3.0 mL) in a pressure tube (10 mL) with a sealing cap under air atmosphere, the reaction mixture was vigorously stirred at 100 °C for 1 h, quenched by ethyl acetate, and purified by silica gel chromatography using a mixture of hexanes and EtOAc (hexane:EtOAc = 20:1) to provide the desired **2f** (oil, 23.9 mg, 31% yield).

Test the mechanism experiments by II

***tert*-butyl (*tert*-butyldimethylsilyl)oxycarbamate:** A 250 mL round-bottom flask charged with *tert*-butyl hydroxycarbamate (2.66 g, 20 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) and triethylamine (2.22 g, 22 mmol, 1.1 equiv) was cooled to 0 °C, and TBSCl (3.0 g, 20 mmol, 1.00 equiv) in CH_2Cl_2 (30 mL) was added. The reaction was allowed to warm to ambient temperature and stirred for 12 h. Upon completion, the reaction was diluted with H_2O, the organic layer washed with H_2O, brine, dried over $MgSO_4$ and concentrated in vacuo to afford 1 (4.94 g, 20 mmol, quant) as a low melting solid that was used in the next step without further purification.[42]

***tert*-butyl benzoyl((*tert*-butyldimethylsilyl)oxy)carbamate:** To a well stirred solution of *tert*-butyl ((*tert*-butyldimethylsilyl)oxy)carbamate *tert*-butyl (*tert*-

butyldimethylsilyl)oxycarbamate (10 mmol) and triethylamine (11 mmol) in dry methylene chloride (50 mL) at 0 °C, a solution of benzoyl chloride (10 mmol) in dry methylene chloride (30 mL) was added. The reaction mixture was warmed to room temperature and allowed to stir for 2 h. It was diluted with water (100 mL), and the organic layer was washed with 1 N HCl (2 × 20 mL) and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was then purified by flash chromatography using a mixture of hexanes and EtOAc (hexane:EtOAc = 20:1) to provide the desired *tert*-butyl benzoyl((*tert*-butyldimethylsilyl)oxy)carbamate (oil, 90% yield).[43]

***tert*-butyl benzoyl(hydroxy)carbamate (II)**: A 100 mL round-bottom flask charged with *tert*-butyl benzoyl((*tert*-butyldimethylsilyl)oxy)carbamate (1.75 g, 5 mmol, 1.0 equiv) in a solution of HF:CH_3CN = 5:95 (50 mL) at 0 °C. The reaction mixture was warmed to room temperature and allowed to stir for 2 h. Upon completion, it was diluted with water (20 mL), and the mixture was extracted with CH_2Cl_2 (10 mL × 3) and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Then removal of the solvent in vacuo, and purified by silica gel chromatography using a mixture of hexanes and EtOAc (hexane:EtOAc = 5:1) to provide the desired **II** (90% yield). *tert*-butyl benzoyl(hydroxy)carbamate (**II**): colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.0 Hz, 2H), 7.50 (t, J = 7.5 Hz, 1H), 7.39 (t, J = 7.7 Hz, 2H), 7.10 (s, 1H), 1.27 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 150.1, 134.5, 131.5, 128.1, 127.9, 85.1, 27.4; HRMS (APCl-TOF) *m/z*: $[M + NH_4]^+$ Calcd for $C_{12}H_{19}N_2O_4$ 255.1345; found 255.1337.

To a solution of **II** (119, 0.5 mmol) and Cs_2CO_3 (0.5 mmol, 1.0 equiv) in MeCN (3.0 mL) in a pressure tube (10 mL) with a sealing cap under air atmosphere. The reaction mixture was stirred at room temperature, The mixture was monitored by TLC, 5 min later, quenched by ethyl acetate, and purified by silica gel chromatography using a mixture of hexanes and EtOAc (hexane:EtOAc = 20:1) to provide the **1s** (118 mg, 99% yield).

To a solution of **II** (119, 0.5 mmol) and Cs_2CO_3 (0.5 mmol, 1.0 equiv) in MeCN (3.0 mL) in a pressure tube (10 mL) with a sealing cap under air atmosphere, the reaction mixture was stirred at 80 °C. The mixture was monitored by TLC, 5 min later, **II** transform to **1s** completely. Continue stirred at 80 °C for 2 h, quenched by ethyl acetate, and purified by silica gel chromatography using a mixture of hexanes and EtOAc (hexane:EtOAc = 20:1) to provide the **2s** (68 mg, 70% yield).

Test the mechanism experiments by III

General Procedure for the Synthesis of *N*-hydroxy-3-phenylpropanamide: CDI (4.5 mmol, 1.5 eq) was added to a solution of carboxylic acid (3.0 mmol) in dry tetrahydrofuran (THF) (5 ml). The reaction mixture was stirred for 1 h. Powdered hydroxylamine hydrochloride (417 mg, 6 mmol) was added. The resulting mixture was stirred overnight. The mixture was diluted with 5% aq. $KHSO_4$ (30 ml) and extracted with EtOAc (2×30 ml). The combined organic phase was washed with brine (30 ml) and dried over Na_2SO_4. The extract was filtered and concentrated in vacuo to give the product *N*-hydroxy-3-phenylpropanamide (90% yield).[44]

General Procedure for the Synthesis of III: Boc_2O (480 mg, 1.1 equiv.) was added to a suspension of *N*-hydroxy-3-phenylpropanamide (2 mmol, 330 mg, 1 equiv.) in CH_2Cl_2 (15 mL). As seen by TLC, the conversion was low after 2h stirring at room temperature. NaO^{t}Bu (0.1 mmol, 9.6 mg, 0.05 equiv.) was added and the reaction mixture was allowed to stir for 16 hours at room temperature. More CH_2Cl_2 was added and the reaction mixture was washed twice with sat. $NaHCO_3$ after which the organic phase was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The purification was made by flash column chromatography using 10-30% EtOAc in pet. ether as eluent to provide the **III** (85% yield).[45] *N*-((*tert*-butoxycarbonyl)oxy)-3-phenylpropanamide (**III**): White solid; mp: 62-64 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.27 (m, 2H), 7.22-7.19 (m, 3H), 2.99 (t, J = 8.0 Hz, 2H), 2.54 (brs, 2H), 1.51 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.5, 152.5, 140.2, 128.6, 128.3, 126.4, 85.9, 34.6, 30.9, 27.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{20}NO_4$ 266.1387; found 266.1389.

To a solution of **III** (79.6 mg, 0.3 mmol) and Cs_2CO_3 (0.3 mmol, 1.0 equiv) in MeCN (3.0 mL) in a pressure tube (10 mL) with a sealing cap under air atmosphere, the reaction mixture was vigorously stirred at 100 °C for 1 h, quenched by ethyl acetate, and purified by silica gel chromatography using a mixture of hexanes and EtOAc (hexane:EtOAc = 3:1) to provide 1,3-diphenethylurea (White solid, 30 mg, 75% yield) and no desired product **2f**. 1,3-diphenethylurea: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (t, J = 7.6 Hz, 4H), 7.21 (t, J = 6.8 Hz, 2H), 7.17 (d, J = 7.6 Hz, 4H), 4.40 (brs, 2H), 3.39 (q, J = 6.8 Hz, 4H), 2.77 (t, J = 6.8 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.9, 139.1, 128.8, 128.5, 126.4, 41.6, 36.4.[46]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

^{1}H and ^{13}C NMR spectra of all the compounds **2a-2aj**, **1f**, **II**, **III** and 1,3-diphenethylurea 1,3-diphenethylurea

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Notes

The authors declare no competing financial interests.

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