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Brønsted acid catalyzed proto-functionalization of enecarbamates and enamides: A convenient route to *N,O*-acetals

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ABSTRACT

N,O-acetals are important structures found in many bioactive natural products, and this unique organic functional group can serve as a useful synthetic precursor to the unstable *N*-acylimines. In this paper, a convenient route to synthesize *N*-carbamoyl-*N,O*-acetals and *N*-acyl-*N,O*-acetals from enecarbamates and enamides in the presence of alcohols as the solvents and nucleophile sources under Brønsted acid conditions was reported. This strategy could be used to prepare various *N,O*-acetals from a range of enecarbamates and enamides with light alcohols, and the products are obtained in good yields (52–98%).

1. Introduction

N,O-acetals are of great importance due to their role in the bioactivity of medicinally-relevant molecules and potential application as a synthetic building block for the construction of various nitrogen-containing compounds. There are numerous bioactive natural products with an *N,O*-acetal moiety [1] including cytotoxic agents psymberin (**1**) [2] and pederin (**2**) [3] (Fig. 1), and structure-activity studies demonstrated that the *N,O*-acetal moiety of **1** and **2** was necessary for potent bioactivity [4]. Additionally, such acetals have attracted attention as synthetic equivalents to unstable reactive *N*-acylimines and useful intermediates in organic synthesis [5].

To date, several synthetic routes to *N,O*-acetals have been developed. The unique structures can be constructed through condensation of aldehydes with amides in the presence of titanium ethoxide [6], methylmagnesium chloride [7], diphenyl phosphate [8], benzotriazole [9] or sodium benzenesulfinate [10], as well as addition of alcohols or phenols to unstable *N*-benzoylimines [11] and insertion of aldehydes into *N*-acyl phthalimides and *N*-acyl azoles [12]. Another approach is based on the hydrozirconization of nitriles followed by acylation and trapping of the acylimine with alcohols [13]. Recently, electrochemical decarboxylative methoxylation of *N*-acetyl-α-amino acids and electrochemical α-methoxylation of *N*-alkylamides were used to generate *N*-(α-methoxyalkyl) amides [14].

Enamide derivatives are stable enamine surrogates with high reactivity[15], and functionalization of enamides in the presence of XtalFluor-E® with alcohols as nucleophilic source yielding *N,O*-acetals was reported by Borhan [16]. We also took advantage of enamide derivatives, and synthesized *N,O*-acetals using enecarbamates and enamides with alcohols catalyzed by Brønsted acid. It is noteworthy that Toste and coworkers have developed an enantioselective oxyfluorination of enamides using chiral phosphoric acid and Selectfluor[17] (Scheme 1).

2. Results and discussion

We initiated our studies by running the reactions under 5 mol% of various Brønsted acid conditions with enecarbamate **1** in the presence of ethanol as the solvent and nucleophile source. As

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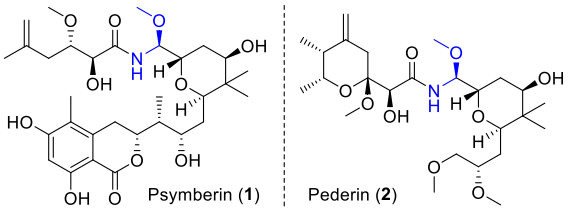
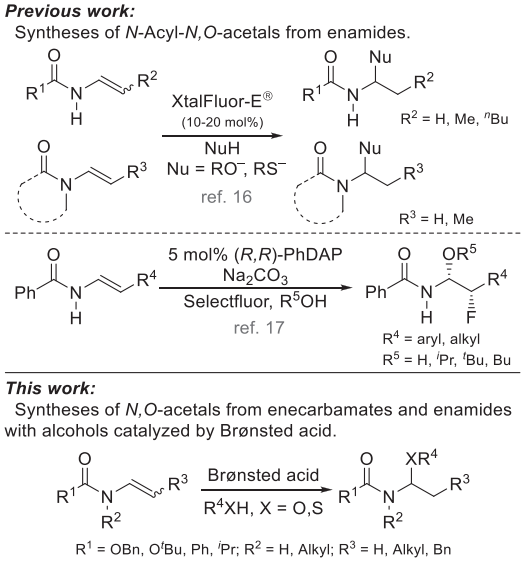


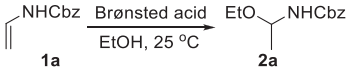
Fig. 1. Natural compounds containing the *N*-acyl-*N,O*-acetal motif.



Scheme 1. Synthesis of *N,O*-acetals from enamide derivatives, previous and current strategies.

tabulated in Table 1, acetic acid as a weak-acidic catalyst could not promote the title reaction, while *p*-toluenesulfonic acid monohydrate, trifluoroacetic acid and 1,1′-binaphthyl-2,2′-diylhydrogenphosphate (BNDHP) provided moderate to good isolated yields of benzyl (1-ethoxyethyl)carbamate **2**. Surprisingly, relatively low yields were obtained when catalyzed by camphor sulfonic acid (CSA) and 2M hydrochloric acid, which is probably due to their enhanced acidity. With considering further research on enantioselectivity, our best catalyst was determined to be BNDHP which provided **2** in 81% yield. Then the impact of catalyst dosage was examined, it was found that optimum yield was obtained with

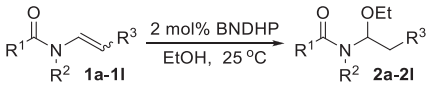
Table 1
Catalyst optimization for synthesis of benzyl (1-ethoxyethyl)carbamate 2[a].



Entry	Catalyst	Time (h)	Yield[b] (%)
1	CH_3COOH	24	NR
2	$TsOH•H_2O$	1	73
3	CF_3COOH	3	92
4	BNDHP	1	81
5	CSA	0.5	30
6	2M HCl	0.5	40

[a] Performed with **1a** (0.2 mmol) and the catalyst (0.005 mmol) in EtOH (2.0 mL) at 25 °C, reactions were stopped after complete conversion of starting enecarbamate **1a**.
[b] Isolated yield. NR = no reaction.

Table 2
Reaction of enamide derivatives in EtOH to give *N,O*-acetals[a].



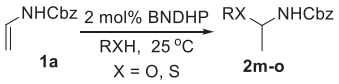
Entry	Enecarbamate/Enamide [19]	*N,O*-acetal	Yield[b] (%)
1	NHCbz **1a**	EtO NHCbz **2a**	90
2	NHBoc **1b**	EtO NHBoc **2b**	95
3	NHBz **1c**	EtO NHBz **2c**	85
4	H N O **1d**	EtO H N O **2d**	98
5	NHBoc **1e**, *cis*	EtO NHBoc **2e**	91
6	NHBoc **1e'**, *trans*	EtO NHBoc **2e**	63
7	NHBoc **1f**, *cis/trans*	EtO NHBoc **2f**	84
8	NHBoc ⁿBu **1g**, *cis/trans*	EtO NHBoc ⁿBu **2g**	87
9	NHBoc Bn **1h**, *cis*	EtO NHBoc Bn **2h**	98
10[c]	N Cbz **1i**	EtO N Cbz **2i** (rotamers 1:0.7)	76
11[c]	N Boc Bn **1j**, *cis*	EtO NBoc Bn **2j** (rotamers 1:1)	70
12[c]	Boc N **1k**	Boc EtO N **2k** (rotamers 1:1)	52
13[c]	Boc N **1l**	Boc EtO N **2l** (rotamers 1:0.8)	79

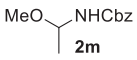
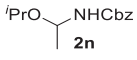
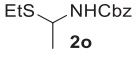
[a] Performed with enamide derivative (0.2 mmol) and BNDHP (1.4 mg, 0.002 mmol) in ethanol (2.0 mL) at 25 °C, reactions were stopped after complete conversion of starting enamide derivatives.
[b] Isolated yield.
[c] The ratio of two rotamers was determined by ^1H NMR.

2 mol% of BNDHP after 2 h [18] (see Tables 2 and 3).

In order to demonstrate the generality of the reaction, a series of enamide derivatives were synthesized and subjected to the reaction conditions. Enamide derivatives with different acyl groups (R^1 = OBn, O^{t}Bu, Ph, ^{i}Pr, $R^2 = R^3$ = H) were first investigated, and gratifyingly, the reactions resulted in the corresponding *N*-carbamoyl-*N,O*-acetals (**2a**, **2b**) and *N*-acyl-*N,O*-acetals (**2c**, **2d**) with

Table 3
Reactions with different alcohols[a].



Entry	NuH	Product	Yield (%)[b]
1	MeOH	 **2m**	56
2	^{i}PrOH	 **2n**	64
3	EtSH	 **2o**	77

[a] Performed with **1a** (35.6 mg, 0.2 mmol) and BNDHP (1.4 mg, 0.002 mmol) in alcohol (2.0 mL) at 25 °C, reactions were stopped after complete conversion of starting enecarbamate **1a**.
[b] Isolated yield.

good yields. Besides, enecarbamates **1e**–**1h** (R^1 = O^{t}Bu, R^2 = H, R^3 = Me, Bn, ^{n}Bu, Bu) bearing different substituents on the terminal carbon of the CC double bond were also examined, affording products **2e**–**2h** in 63%–98% yields. Particularly noteworthy is that the reaction efficiency of *cis*-enecarbamate **1e** is higher than that of its isomer *trans*-enecarbamate **1e′**, mostly due to the steric effect. The reaction is not limited to secondary enecarbamates, as methylated enecarbamates **1i**, **1j** and cyclic-tertiary enecarbamates **1k**, **1l** could also result in products with moderate yields, which were shown to exist as a mixture of amide rotamers by NMR spectroscopy.

With regard to the nature of the protic nucleophile, other light alcohols like methanol, 2-propanol and ethanethiol were used to successfully give the corresponding *N,O*-acetal and *N,S*-acetal products. Noteworthily, the reaction was also applicable to *tert* butyl alcohol and benzyl alcohol judging from TLC and the mass spectrum, however, the products were difficult to separate, which impelled us to search for new methodology to solve this problem.

3. Conclusion

In conclusion, we have developed a convenient method to synthesize *N,O*-acetals. Reaction of enecarbamates and enamides under the Brønsted acid conditions leads to the proto-functionalization of olefins, yielding *N,O*-acetals when alcohols are used as the solvent and nucleophile proton source. The reaction is efficient with multiple types of enamide derivatives, while the scope of alcohols is restricted. Efforts toward efficient construction of *N,O*-acetals with various alcohols are in progress and will be reported in due course.

4. Experimental section

4.1. General information

All reactions were monitored by thin-layer chromatography (TLC) on silica gel F254 plates using UV light as visualizing agent (if applicable), and a solution of phosphomolybdic acid (50 g/L) in EtOH followed by heating as developing agents. The products were purified by flash column chromatography on silica gel (200–300 meshes from the Anhui Liangchen Silicon Material Company in China).

^{1}H NMR and ^{13}C NMR spectra were recorded in acetone-d_6 solution on a Bruker AM 400 MHz instrument. Chemical shifts were denoted in ppm (δ), and calibrated by using residual undeuterated solvent acetone-d_6 (2.05 ppm) for ^{1}H NMR and acetone-d_6 (206.26 ppm) for ^{13}C NMR. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, br = broad, brs = broad singlet, dt = double triplet, m = multiplet. The high-resolution mass spectral analysis (HRMS) data were measured on Thermo Fisher Orbitrap Elite Mass Spectrometer by means of the ESI technique. IR spectra of the compound were recorded in the range of 400–4000 cm^{-1} with a PerkinElmer Frontier FTIR/NIR spectrometer using KBr pellets.

4.2. Syntheses of enamide derivatives

The enamide derivatives **1a** [20], **1b** [20], **1c** [16], **1d** [16], **1f** [21], **1g** [22], **1h** [23], **1i** [20], **1k** [24]and **1l** [24] were prepared according to the reported literature procedures.

4.2.1. tert-butyl (Z)-but-1-en-1-ylcarbamate 1e and tert-butyl (E)-but-1-en-1-ylcarbamate 1e′

In a 50 mL flask, formic acid (2.4 mL, 64 mmol) was added to a solution of *n*-butylaldehyde (1.4 mL, 10.8 mmol), sodium benzenesulfinate (1.64 g, 10.0 mmol) and *tert*-butyl carbamate (10.0 mmol) in H_2O (10 mL) and THF (4 mL). The reaction mixture was stirred for 24 h at 25 °C. The precipitate formed during the reaction was filtered and washed with water and diethyl ether. *tert*-Butyl (1-(phenylsulfonyl)butyl)carbamate was obtained as solid and used in the next step without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.92 (d, J = 7.6 Hz, 2H), 7.64–7.52 (m, 3H), 0.93 (brs, 1H), 4.86 (td, J = 3.2, 10.8 Hz, 1H), 2.28–2.15 (m, 1H), 1.80–1.65 (m, 1H), 1.64–1.52 (m,1H), 1.47–1.42 (m, 1H), 1.21 (s, 9H), 0.97 ppm (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 153.8, 1367.0, 133.7, 129.2, 129.0, 80.7, 70.5, 28.2, 27.9, 18.7, 13.4 ppm.

tert-Butyl (1-(phenylsulfonyl)butyl)carbamate (3.13 g, 10.0 mmol), dried K_2CO_3 (5.13 g, 37.2 mmol) and Na_2SO_4 (6.16 g, 43.4 mmol) in tetrahydrofuran (80 mL) were refluxed for 12 h. The suspension was cooled to room temprature, the suspension was filtered through a pad of celite and the filtrate was concentrated. The reaction mixture was directly purified by silica gel column chromatography (Hexane/EtOAc = 50:1–20:1 as eluent) to give a colorless liquid of **1e** (479 mg, 28% for two steps) and **1e'** (462 mg, 27% for two steps).

1e: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.38 (t, J = 10 Hz, 1H), 6.13 (brs, 1H), 4.57 (q, J = 7.2 Hz, 1H), 2.00–1.92 (m, 2H), 1.48 (s, 9H), 1.01 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.8, 121.5, 109.9, 80.3, 28.3, 18.8, 14.0 ppm.

1e': ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.43 (t, J = 12 Hz, 1H), 6.12 (brs, 1H), 5.04–4.92 (m, 2H), 2.04–1.97 (m, 2H), 1.46 (s, 9H), 0.98 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.9, 122.9, 111.6, 80.1, 28.3, 22.8, 14.4 ppm.

4.2.2. tert-butyl (Z)-methyl(3-phenylprop-1-en-1-yl)carbamate 1j

Sodium hydride (120 mg, 1.5 mmol, 60 wt% in oil) was added to the magnetically stirred benzyl vinylcarbamate **1h** (466 mg, 2.0 mmol) in anhydrous THF (10 mL) and then iodomethane (0.25 ml, 4.0 mmol) was added dropwise to the mixture at 0 °C. After the addition was complete, the mixture was kept at 0 °C for 30 min and stirred at room temperature. The reaction was monitored by TLC. After the reaction was completed, the reaction mixture was partitioned between saturated aqueous NH_4Cl and ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with water, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography with petroleum ether/EtOAc (20:1) to give corresponding product **1j** as white solid (356 mg, 72%). **^{1}H NMR** (400 MHz, $CDCl_3$):

δ = 7.32–7.17 (m, 5H), 6.30 (brs, 1H), 5.10 (q, J = 7.6 Hz, 1H), 3.45 (d, J = 7.2 Hz, 2H), 3.08 (s, 3H), 1.49 ppm (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 154.6, 140.3, 129.3, 128.4, 128.2, 126.0, 118.6, 80.4, 36.0, 33.1, 28.3 ppm.

4.4. General experimental procedure for BNDHP catalyzed proto-functionalization of enamide derivatives

To a solution of enecarbamate **1a**, **1d-1l** or enamide **1b**, **1c** (0.2 mmol) in alcohol (2.0 mL) was added the BNDHP (1.4 mg, 0.002 mmol), and the reaction mixture was stirred at 25 °C. When the starting materials disappeared as judged by TLC, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether/EtOAc to afford the product **2a-2o**.

4.4.1. Benzyl (1-ethoxyethyl)carbamate 2a

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.46–7.24 (m, 5H), 6.74 (brs, 1H), 5.14–5.06 (m, 1H), 5.08 (s, 2H), 3.63–3.52 (m, 1H), 3.49–3.38 (m, 1H), 1.30 (d, J = 6.0 Hz, 3H), 1.10 ppm (t, J = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, acetone-d_6): δ = 156.8, 138.2, 129.2, 128.6 {One carbon signal for CH overlapped}, 79.2, 66.5, 63.1, 21.9, 15.6 ppm; **IR**: $\bar{\upsilon}$ = 3324, 3035, 1706, 1530, 1452, 1333, 1242, 1090 cm^{-1}; **HRMS** (ESI): *m/z* calcd for $C_{12}H_{17}NO_3Na$: 246.1101; found: 246.1096 [M+Na]$^+$.

4.4.2. tert-butyl (1-ethoxyethyl)carbamate 2b

^{1}H NMR (400 MHz, acetone-d_6): δ = 6.31 (brs, 1H), 5.07–4.94 (m, 1H), 3.61–3.50 (m, 1H), 3.46–3.36 (m, 1H), 1.41 (s, 9H), 1.25 (d, J = 6 Hz, 3H), 1.10 ppm (t, J = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, acetone-d_6): δ = 156.2, 78.9, 78.6, 63.0, 28.6, 21.9, 15.7 ppm; **IR**: $\bar{\upsilon}$ = 3341, 2979, 2932, 1703, 1520, 1367, 1156, 1091 cm^{-1}; **HRMS** (ESI): *m/z* calcd for $C_9H_{19}NO_3Na$: 212.1257; found: 212.1255 [M+Na]$^+$.

4.4.3. N-(1-ethoxyethyl)benzamide 2c

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.94 (d, J = 7.2 Hz, 3H), 7.49 (dt, J = 30.8, 7.6 Hz, 2H), 7.45 (brs, 1H), 5.60–5.52 (m, 1H), 3.66–3.57 (m, 1H), 3.54–3.45 (m, 1H), 1.38 (d, J = 6.0 Hz, 3H), 1.12 ppm (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, acetone-d_6): δ = 167.34, 135.5, 132.2, 129.2, 128.2, 77.3, 63.5, 21.9, 15.6 ppm; **IR**: $\bar{\upsilon}$ = 3308, 2980, 1645, 1530, 1488, 1282, 1095, 698 cm^{-1}; **HRMS** (ESI): *m/z* calcd for $C_{11}H_{15}NO_2Na$: 216.0995; found: 216.0992 [M+Na]$^+$.

4.4.4. N-(1-ethoxyethyl)isobutyramide 2d

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.35 (brs, 1H), 5.35–5.23 (m, 1H), 3.57–3.46 (m, 1H), 3.44–3.33 (m, 1H), 2.50–2.37 (m, 1H), 1.23 (d, J = 6.0 Hz, 3H), 1.11–1.04 ppm (m, 9H); **^{13}C NMR** (100 MHz, acetone-d_6): δ = 177.4, 76.1, 63.0, 35.6, 21.8, 20.1, 19.7, 15.5 ppm; **IR**: $\bar{\upsilon}$ = 3437, 3289.74, 2976, 1650, 1542, 1444, 1380, 1098 cm^{-1}; **HRMS** (ESI): *m/z* calcd for $C_8H_{17}NO_2Na$: 182.1151; found: 182.1149 [M+Na]$^+$.

4.4.5. tert-butyl (1-ethoxybutyl)carbamate 2e

^{1}H NMR (400 MHz, acetone-d_6): δ = 6.21 (brs, 1H), 4.86 (dd, J = 15.6, 6.4 Hz, 1H), 3.64–3.54 (m, 1H), 3.46–3.36 (m, 1H), 1.67–1.55 (m, 1H), 1.54–1.31 (m, 3H), 1.41 (s, 9H), 1.10 (t, J = 6.8 Hz, 3H), 0.90 ppm (t, J = 7.6, 3H); **^{13}C NMR** (100 MHz, acetone-d_6): δ = 156.6, 82.0, 78.9, 63.2, 38.3, 28.7, 19.2, 15.7, 14.1 ppm; **IR**: $\bar{\upsilon}$ = 2968, 2934, 1704, 1518, 1368, 1252, 1174, 1084 cm^{-1}; **HRMS** (ESI): *m/z* calcd for $C_{11}H_{23}NO_3Na$: 240.1570; found: 240.1568 [M+Na]$^+$.

4.4.6. tert-butyl (1-ethoxypropyl)carbamate 2f

^{1}H NMR (400 MHz, acetone-d_6): δ = 6.21 (brs, 1H), 4.81–4.73 (m, 1H), 3.66–3.54 (m, 1H), 3.47–3.36 (m, 1H), 1.68–1.58 (m, 1H), 1.48–1.48 (m, 1H), 1.41 (s, 9H), 1.11 (t, J = 6.8 Hz, 3H), 0.89 ppm (t, J = 7.6 Hz, 3H); **^{13}C NMR** (100 MHz, acetone-d_6): δ = 156.7, 83.6, 79.0, 68.2, 63.2, 28.7, 15.7, 10.0 ppm; **IR**: $\bar{\upsilon}$ = 3340, 2975, 2923, 1704, 1518, 1367, 1175, 1082 cm^{-1}; **HRMS** (ESI): *m/z* calcd for $C_{10}H_{21}NO_3Na$: 226.1414; found: 226.1411 [M+Na]$^+$.

4.4.7. tert-butyl (1-ethoxyhexyl)carbamate 2g

^{1}H NMR (400 MHz, acetone-d_6): δ = 6.21 (d, J = 6.8 Hz, 1H), 4.91–4.77 (m, 1H), 3.66–3.53 (m, 1H), 3.48–3.34 (m, 1H), 1.68–1.58 (m, 1H), 1.57–1.48 (m, 1H), 1.41 (m, 9H), 1.38–1.26 (m, 6H), 1.10 (t, J = 7.2 Hz, 3H), 0.88 ppm (t, J = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, acetone-d_6): δ = 156.6, 82.3, 79.0, 63.2, 36.3, 32.4, 28.8, 25.8, 23.5, 15.8, 14.5 ppm, **IR**: $\bar{\upsilon}$ = 2931, 2866, 1702, 1518, 1368, 1248, 1174, 1085 cm^{-1}; **HRMS** (ESI): *m/z* calcd for $C_{13}H_{27}NO_3Na$: 268.1883; found: 268.1880 [M+Na]$^+$.

4.4.8. tert-butyl (1-ethoxy-3-phenylpropyl)carbamate 2h

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.35–7.11 (m, 5H), 6.35 (d, J = 8.8 Hz, 1H), 4.96–4.80 (m, 1H), 3.68–3.56 (m, 1H), 3.49–3.56 (m, 1H), 2.69 (t, J = 7.6 Hz, 2H), 2.01–1.81 (m, 2H), 1.43 (s, 9H), 1.14 ppm (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, acetone-d_6): δ = 156.6, 142.8, 129.4, 129.3, 126.7, 81.7, 79.1, 63.3, 38.1, 32.4, 28.7, 15.8 ppm; **IR**: $\bar{\upsilon}$ = 2976, 2931, 1702, 1499, 1368, 1248, 1170, 1086 cm^{-1}; **HRMS** (ESI): *m/z* calcd for $C_{16}H_{25}NO_3Na$: 302.1727; found: 302.1721 [M+Na]$^+$.

4.4.9. Benzyl (1-ethoxyethyl)(methyl)carbamate 2i

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.53–7.20 (m, 5H + 5H × 0.7), 5.58–5.51 (m, 1H), 5.51–5.43 (m, 1H × 0.7), 5.21–5.09 (m, 2H + 2H × 0.7), 3.43–3.24 (m, 2H + 2H × 0.7), 2.76 (s, 3H), 2.74 (s, 3H × 0.7), 1.24 (s, 3H), 1.22 (s, 3H × 0.7), 1.14–1.07 ppm (m, 3H + 3H × 0.7); **^{13}C NMR** (100 MHz, acetone-d_6): δ = 156.9, 156.3, 138.4, 138.3, 129.4, 128.9, 128.8, 128.7 {Two carbon signals for CH overlapped}, 82.3 {One carbon signal for CH overlapped}, 67.6, 67.4, 63.3, 63.2, 26.5, 26.4, 19.8, 19.44, 15.5 {One carbon signal for CH_3 overlapped} ppm, **IR**: $\bar{\upsilon}$ = 2980, 1706, 1449, 1404, 1328, 1139, 1107, 1083 cm^{-1}; **HRMS** (ESI): *m/z* calcd for $C_{13}H_{19}NO_3Na$: 260.1257; found: 260.1255 [M+Na]$^+$.

4.4.10. tert-butyl (1-ethoxy-3-phenylpropyl)(methyl)carbamate 2j

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.40–7.06 (m, 5H + 5H), 5.37 (t, J = 6.4 Hz, 1H), 5.20 (t, J = 6.4 Hz, 1H), 3.48–3.38 (m, 2H), 3.37–3.26 (m, 2H), 2.68 (s, 6H), 2.66–2.50 (m, 4H), 2.02–1.89 (m, 2H), 1.88–1.73 (m, 2H), 1.47 (s, 9H), 1.40 (s, 9H), 1.19–1.11 ppm (m, 6H); **^{13}C NMR** (100 MHz, acetone-d_6): δ = 156.7, 155.9, 142.8, 142.6, 129.5, 129.4, 126.9 {Three carbon signals for CH overlapped}, 85.1, 84.6, 80.1, 79.9, 63.3, 63.1, 35.7, 35.5, 32.3, 32.1, 28.8 {One carbon signal for CH_3 overlapped}, 27.1, 26.2, 15.59, 15.55 ppm; **IR**: $\bar{\upsilon}$ = 2975, 1698, 1452, 1396, 1342, 1258, 1145, 1084 cm^{-1}; **HRMS** (ESI): *m/z* calcd for $C_{17}H_{27}NO_3Na$: 316.1883; found: 316.1890 [M+Na]$^+$.

4.4.11. tert-butyl 2-ethoxypyrrolidine-1-carboxylate 1k

^{1}H NMR (400 MHz, acetone-d_6): δ = 5.07 (s, 1H), 5.01 (s, 1H), 3.50–3.31 (m, 4H), 3.22–3.10 (m, 4H), 1.90–1.78 (m, 2H), 1.75–1.59 (m, 6H), 1.32 (s, 18H), 1.02–0.93 ppm (m, 6H); **^{13}C NMR** (100 MHz, acetone-d_6): δ = 155.6, 154.7, 88.1, 87.9, 79.8, 79.6, 64.0, 63.8, 46.7, 46.2, 33.8, 33.2, 28.7 {One carbon signal for CH_3 overlapped}, 23.6, 22.6, 16.0 {One carbon signal for CH_3 overlapped} ppm; **IR**: $\bar{\upsilon}$ = 3438, 2975, 1702, 1454, 1388, 1253, 1169, 1094 cm^{-1}; **HRMS** (ESI): *m/z* calcd for $C_{11}H_{21}NO_3Na$: 238.1414; found: 238.1420 [M+Na]$^+$.

4.4.12. tert-butyl 2-ethoxyazepane-1-carboxylate 1l

^{1}H NMR (400 MHz, acetone-d_6): δ = 5.41 (t, J = 8.0 Hz, 1H), 5.30 (t, J = 8.0 Hz, 1H × 0.8), 3.65–3.31 (m, 3H + 3H × 0.8), 2.96–2.86 (m, 1H + 1H × 0.8), 2.21–2.13 (m, 1H + 1H × 0.8), 1.77 (d, J = 12.8, 1H + 1H × 0.8), 1.63–1.44 (m, 4H + 4H × 0.8); 1.46 (s, 9H + 9H × 0.8), 1.35–1.28 (m, 1H + 1H × 0.8), 1.17–1.04 ppm (m, 4H + 4H × 0.8); **^{13}C NMR** (100 MHz, acetone-d_6): δ = 156.8, 155.6, 85.2, 84.3, 80.0, 79.6, 62.9, 62.8, 41.4, 40.9, 36.0, 35.7, 30.84, 30.77, 29.1, 28.71, 28.67, 28.5, 23.6, 23.5, 15.71, 15.69 ppm; **IR**: $\bar{\upsilon}$ = 2975, 2930, 1698, 1472, 1414, 1366, 1162, 1081 cm^{-1}; **HRMS** (ESI): *m/z* calcd for $C_{13}H_{25}NO_3Na$: 266.1727; found: 266.1725 $[M+Na]^+$.

4.4.13. Benzyl (1-methoxyethyl)carbamate 2m

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.45–7.26 (m, 5H), 6.76 (brs, 1H), 5.09 (s, 2H), 5.02–4.93 (m, 1H), 3.24 (s, 3H), 1.29 ppm (t, J = 6.0 Hz, 3H); **^{13}C NMR** (100 MHz, acetone-d_6): δ = 156.9, 138.2, 129.2, 128.7 {One carbon signal for CH overlapped}, 80.8, 66.6, 55.0, 21.5 ppm; **IR**: $\bar{\upsilon}$ = 3330, 2939, 1709, 1528, 1454, 1337, 1246, 1080 cm^{-1}; **HRMS** (ESI): *m/z* calcd for $C_{11}H_{15}NO_3Na$: 232.0944; found: 232.0944 $[M+Na]^+$.

4.4.14. Benzyl (1-isopropoxyethyl)carbamate 2n

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.51–7.19 (m, 5H), 6.72 (s, 1H), 5.25–5.14 (m, 1H), 5.08 (s, 2H), 3.90–3.75 (m, 1H), 1.27 (d, J = 5.6 Hz, 3H), 1.09 ppm (dd, J = 20.8, 5.2 Hz, 6H); **^{13}C NMR** (100 MHz, acetone-d_6): δ = 156.8, 138.3, 129.3, 128.7 {One carbon signal for CH overlapped}, 77.1, 68.3, 66.6, 23.9, 22.6, 22.0 ppm; **IR**: $\bar{\upsilon}$ = 3342, 2976, 1710, 1526, 1330, 1241, 1084, 986 cm^{-1}; **HRMS** (ESI): *m/z* calcd for $C_{13}H_{19}NO_3Na$: 260.1257; found: 260.1259 $[M+Na]^+$.

4.4.15. Benzyl (1-(ethylthio)ethyl)carbamate 2°

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.52–7.19 (m, 5H), 6.72 (d, J = 6.4 Hz, 1H), 5.13–5.14 (m, 3H), 2.70–2.59 (m, 1H), 2.56–2.46 (m, 1H), 1.44 (d, J = 6.8 Hz, 3H), 1.21 ppm (t, J = 7.6 Hz, 3H); **^{13}C NMR** (100 MHz, acetone-d_6): δ = 156.4, 138.2, 129.2, 128.7 {One carbon signal for CH overlapped}, 66.7, 52.4, 24.8, 22.6, 15.5 ppm; **IR**: $\bar{\upsilon}$ = 3320, 1700, 1524, 1452, 1326, 1226, 1066, 1029 cm^{-1}; **HRMS** (ESI): *m/z* calcd for $C_{12}H_{17}NO_2SNa$: 262.0872; found: 262.0873 $[M+Na]^+$.

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Appendix A. Supplementary data

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