Synthesis T. Sakai et al. Paper

Benzyl Acetylcarbamate Potassium Salt (BENAC-K): A Simple Nucleophilic *N*-Acetamide Equivalent

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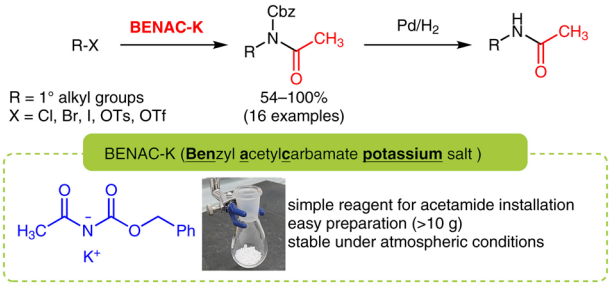

Received: 27.05.2019
Accepted after revision: 29.05.2019
Published online: 19.06.2019
DOI: 10.1055/s-0039-1690097; Art ID: ss-2019-f0289-op

Abstract Benzyl acetylcarbamate potassium salt (BENAC-K) has been developed as a simple nucleophilic acetamide equivalent. A broad variety of alkyl halides were converted into benzyloxycarbonyl-protected *N*-alkylacetamides in high yields by simple treatment with an almost equimolar (1.1 equiv) amount of BENAC-K in a polar solvent.

Key words alkylation, acetamide, S_N2 reaction, nitrogen nucleophile, BENAC-K

The *N*-alkylacetamide moiety is an important structural motif present in a wide range of pharmaceutical and natural products. For example, members of the *N*-alkylacetamide family, such as the antibiotic linezolid[1] and the antidepressant agomelatine,[2] are widely used in clinical practice. Brevisamide[3] and the tamulamides[4] are examples of acetamide-containing marine polyketide alkaloids (Figure 1).

Alkyl halides and alkyl sulfonates are important precursors to *N*-alkylacetamides. Direct nucleophilic substitution with acetamide is the most straightforward approach to access the *N*-alkylacetamides from alkyl halides or alkyl sulfonates (Scheme 1a).[5] However, this strategy has several limitations, such as the necessity for a large excess of acetamide to avoid the formation of the undesired dialkylated product, and a narrow scope for the direct acetamide installation, along with low yields reported in several studies.[5e,g,6] Due to such challenges, the acetamide moiety is typically introduced instead by the acetylation of a primary amine, prepared by the azidation–reduction protocol (Scheme 1b). This traditional method is highly reliable but requires a multistep sequence involving the synthesis of a potentially explosive organic azide.[7] The Gabriel amine synthesis can be used alternatively, but unavoidably involves the use of the toxic hydrazine for demasking the phthalimide protection. Thus, the development of an easy and safe procedure for installation of the acetamide moiety is an important objective to enable efficient syntheses of *N*-alkylacetamide-containing pharmaceuticals and natural products.

N-Acylcarbamates are useful nitrogen nucleophiles.[8] We recently reported a convenient method for the synthesis of an *N*-alkylacetamide using benzyl *N*-acetylcarbamate (**1**) during the total synthesis of brevisamide (Scheme 2),[6] where **1** was deprotonated with potassium hexamethyldisilazide (KHMDS), and the benzyl acetylcarbamate potassium salt (BENAC-K) (**2**) generated in situ was reacted with alkyl triflate **3** to afford the *N*-benzyloxycarbonyl-protected acetamide derivative **4**. The simultaneous deprotection of the benzyloxycarbonyl and benzyl protecting groups in **4** by hydrogenation afforded amido alcohol **5**. While this method serves as an effective two-step protocol for the introduction

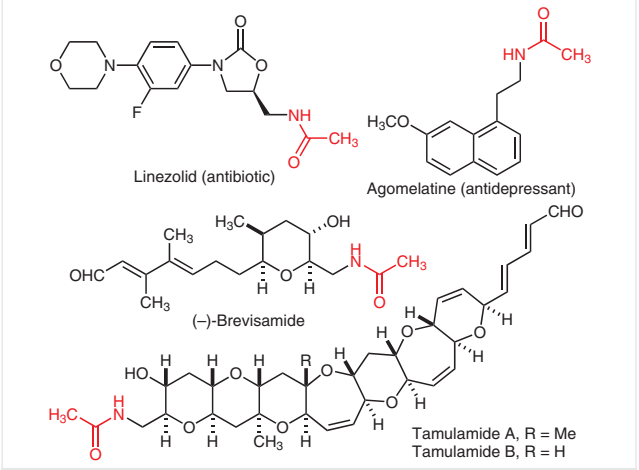

Figure 1 Medicinal and natural products bearing an acetamide moiety

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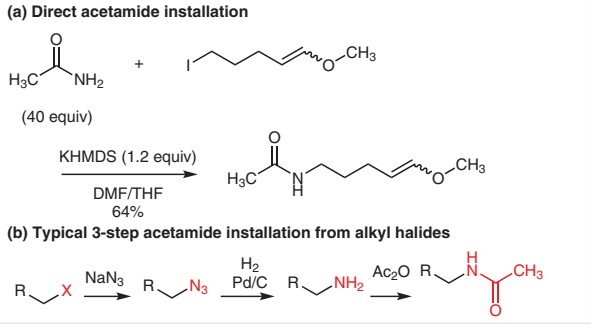
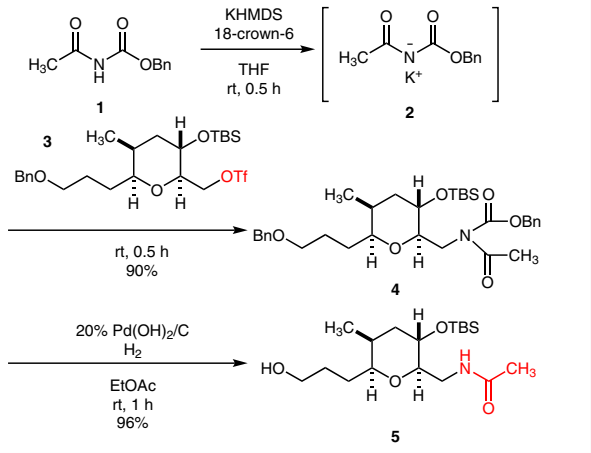


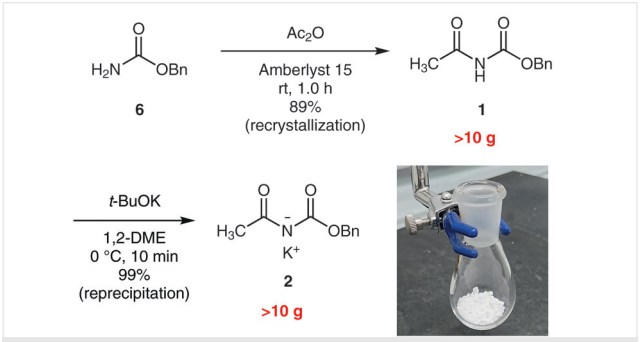
Scheme 1 (a) An example of direct acetamide installation from an alkyl iodide, reported by Lévesque and Bélanger.[5f] (b) A typical three-step procedure for acetamide installation from alkyl halides.

of the acetamide moiety via *N*-alkylacetamide synthesis and debenzylation, the need for BENAC-K (**2**) formation in situ under anhydrous conditions is a disadvantage. To circumvent this challenge, we isolated BENAC-K (**2**) and developed it as a straightforward reagent for *N*-acetamide installation.



Scheme 2 Acetamide installation using in situ generated BENAC-K (**2**) during the total synthesis of brevisamide

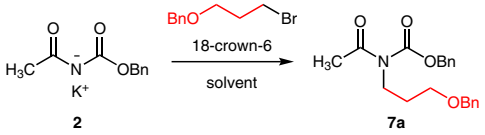
BENAC-K (**2**) was prepared on a 10-gram scale by a simple two-step sequence, without column chromatographic purification (Scheme 3). The commercially available benzyl carbamate (**6**) was acetylated with acetic anhydride under Amberlyst 15 catalysis to afford benzyl *N*-acetylcarbamate (**1**) in 89% yield as a highly crystalline solid after a single recrystallization. Treatment of **1** with an equimolar amount of potassium *tert*-butoxide in 1,2-dimethoxyethane (1,2-DME)[8i] afforded a white precipitate, which upon filtration furnished BENAC-K (**2**) as a fine, non-hygroscopic powder, which is stable at ambient temperature in the presence of air for 24 hours and can be stored in a refrigerator for more than a year without change of physical properties. We confirmed a good reproducibility for the alkylation reaction with **2** that was stored for 18 months at –14 °C (Table 1, footnote b).[9]



Scheme 3 Synthesis and isolation of BENAC-K (**2**)

Having prepared BENAC-K (**2**), we screened the substitution reaction of 3-(benzyloxy)propyl bromide with 2 equivalents of **2** in various solvents in the presence of 18-crown-6 (Table 1). The reaction rate was faster as the polarity of the solvents increased, a trend indicative of the conventional S_N2 reaction (entries 1–6). Notably, an almost equimolar (1.1 equiv) amount of BENAC-K (**2**) was sufficient for the substitution reaction in CH_3CN or DMF (entries 7 and 8) which highlights the highly efficient alkylation with **2** in comparison with acetamide alkylation, which requires a large excess of the reagent. Further, at 60 °C in DMF, 18-crown-6 was not necessary for reaction completion (entry 9).

Table 1 Solvent Screening



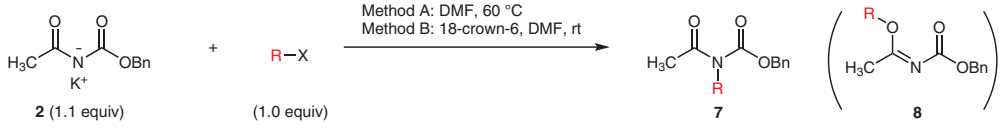
Entry	Solvent	**2** (equiv)	18-crown-6 (equiv)	Temp	Time (h)	Yield (%)
1	toluene	2.0	2.0	50 °C	26	77
2	CPME[a]	2.0	2.0	rt	52	10
3	EtOAc	2.0	2.0	rt	120	85
4	THF	2.0	2.0	rt	29	88
5	CH_3CN	2.0	2.0	rt	4.5	88
6	DMF	2.0	2.0	rt	2.0	85
7	CH_3CN	1.1	1.0	rt	26	84
8	DMF	1.1	1.0	rt	1.5	85
9	DMF	1.1	0	60 °C	3.0	91[b]

[a] Cyclopentyl methyl ether.
[b] Product **7a** was obtained in 87% yield when using an aged BENAC-K that was stored for 18 months at –14 °C.

The scope and limitations of alkyl halides and sulfonates were investigated using 1.1 equivalents of BENAC-K (**2**) in DMF under two reaction conditions for each alkylating reagent. Method A involved heating at 60 °C, and method B involved stirring at room temperature in the presence of 1.0 equivalent of 18-crown-6 (Table 2). Both alkyl iodide and alkyl tosylate showed comparable reactivity with the corresponding alkyl bromide to afford **7a** (entries 1–4). Alkylation with alkyl chloride afforded the product **7b** in good yield, albeit at a low reaction rate (entries 5 and 6). The reaction with alkyl triflate could not be carried out in DMF due to its reactivity with DMF. In CH_3CN, both the N-alkylated product **7c** and O-alkylated byproduct **8c** were obtained in 71% and 19% yield, respectively (entry 7). The yield of **7c** improved to 90% whereas that of **8c** decreased to 7% when the reaction was performed in toluene in the presence of 18-crown-6 (entry 8). The *tert*-butyldimethylsilyl ether and acetyl ester functionalities were tolerated under the reaction conditions, and furnished **7d** and **7e**, respectively (entries 9–12). The reaction of 3-bromo-1-propanol with **2** afforded acetyl-migrated product **9** (entry 13). Prednisolone 21-mesylate was transformed to oxetane **10** via a deprotonation of the tertiary alcohol (entry 14). These reactions indicate the necessity of hydroxy group protection.

The highly lipophilic dodecyl bromide required a slightly extended reaction time (24 h) and delivered the acetamide **7f** (entries 15 and 16). Highly reactive alkyl bromides including allyl bromide, propargyl bromide, benzyl bromide, and ethyl bromoacetate furnished the desired products **7g–j** in excellent yields over short reaction times (entries 17–24). The products **7k** and **7l** were obtained in moderate yields starting from phenethyl bromide and 1-bromo-2-chloroethane due to the propensity of the substrates for elimination and double substitution (entries 25–28). The reactivity was markedly decreased with the use of bulky primary alkyl halides such as isobutyl bromide and cyclohexylmethyl bromide (entries 29–32). Particularly, neopentyl bromide gave only 9% of the N-alkylated product **7o** even after heating at 80 °C for 36 hours with 18-crown-6 (entry 33). Secondary alkyl halides and nosylates also afforded the corresponding N-alkylated products **7p–r**, although the yields were lower compared to the use of primary alkyl halides due to the formation of O-alkylated byproducts **8p–r** (entries 34–38). A possible explanation for the partial O-alkylation is that the rate of the N-alkylation was decreased kinetically due to steric repulsion between the secondary alkyl group and the two substituents on the nitrogen atom of **2**.

Table 2 Scope and Limitations



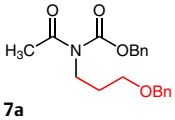
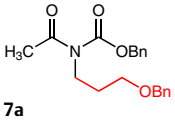
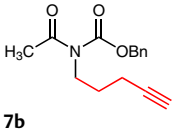
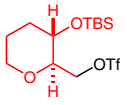
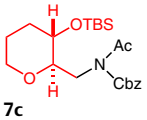
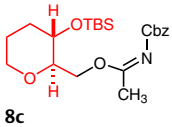
Entry[a]	R-X	Method	Time (h)	Product **7**	Yield (%)	Byproduct	Yield (%)
1		A	2.0	 **7a**	91		
2		B	1.0		98		
3		A	2.3	 **7a**	89		
4		B	21.0		90		
5		A (100 °C)[b]	18.0	 **7b**	77		
6		B	42.0		81		
7		A (CH_3CN)[c]	4.0	 **7c**	71	 **8c**	19
8		B (toluene)[d]	0.5		90		7

Table 2 (continued)

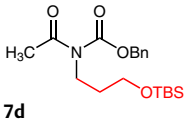
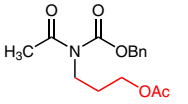
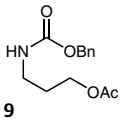
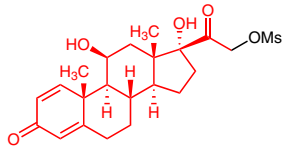
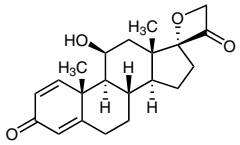
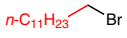
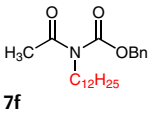
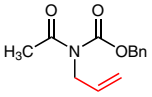
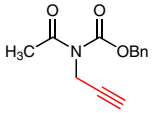
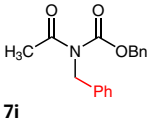
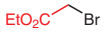
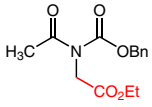
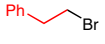
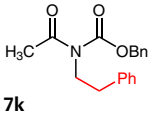
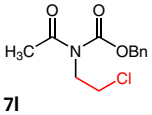
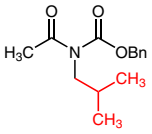
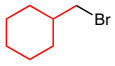
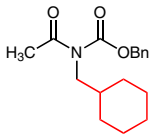
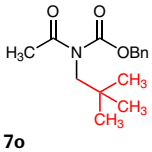
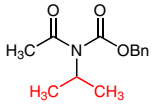
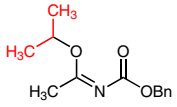
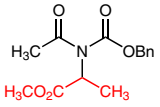
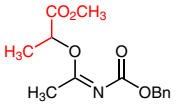
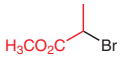
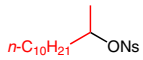
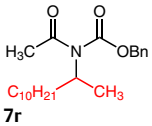
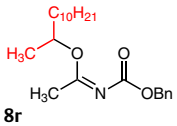
Entry[a]	R-X	Method	Time (h)	Product **7**	Yield (%)	Byproduct	Yield (%)
9		A	2.0	 **7d**	85		
10		B	0.5		83		
11		A	0.3	 **7e**	60		
12		B	1.0		73		
13		B (CH_3CN)[c]	4.0		0	 **9**	50
14		B (CH_3CN)[c]	4.0		0	 **10**	66
15		A	24.0	 **7f**	90		
16		B	24.0		100		
17		A	0.2	 **7g**	95		
18		B	2.0		90		
19		A	1.0	 **7h**	92		
20		B	0.5		100		
21		A	1.0	 **7i**	100		
22		B	1.0		100		
23		A	0.2	 **7j**	96		
24		B	0.2		97		
25		A	2.5	 **7k**	54		
26		B	1.0		54		
27		A	3.0	 **7l**	70		
28		B	20.0		54		

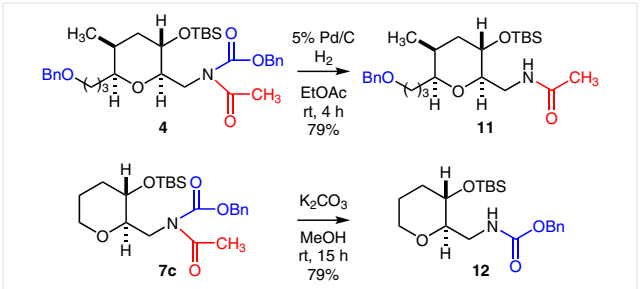
Table 2 (continued)

Entry[a]	R-X	Method	Time (h)	Product **7**	Yield (%)	Byproduct	Yield (%)
29		A	23.0	 **7m**	79		
30		B	24.0		70		
31		A	42.0	 **7n**	89		
32		B	42.0		91		
33		B (80 °C)[e]	36.0	 **7o**	9		
34		A[f]	4.0	 **7p**	24	 **8p**	8
35		B[f]	18.5		47		9
36		A	3.0	 **7q**	68	 **8q**	22
37		B	19.5		80		19
38		B (CH_3CN)[c,g]	7.0	 **7r**	55	 **8r**	15

[a] All reactions were carried out in a 0.2–1.0 M concentration range. Product yields were not influenced by the concentration.
[b] Reaction was carried out at 100 °C in entry 5.
[c] Reactions were carried out in CH_3CN instead of DMF in entries 7, 13, 14, and 38.
[d] Reaction was carried out in toluene instead of DMF in entry 8.
[e] Reaction was carried out at 80 °C, and an excess amount of neopentyl bromide (1.5 equiv) was used relative to 1.0 equivalent of BENAC-K (**2**) in entry 33.
[f] A slight excess amount of isopropyl iodide (1.1 equiv) was used relative to 1.0 equivalent of BENAC-K (**2**) in entries 34 and 35.
[g] BENAC-K (1.3 equiv) was used in entry 38.

Finally, deprotection of the formed products was examined (Scheme 4). We previously reported the deprotection of both the benzyl and benzyloxycarbonyl groups of **4** by hydrogenation with 20% $Pd(OH)_2$ (Scheme 2).[6] The benzyloxycarbonyl group was selectively hydrogenated using the milder 5% Pd/C instead of 20% $Pd(OH)_2$, and the selective removal of the acetyl group from **7c** was also achieved, by methanolysis[8h] under basic conditions.

In conclusion, benzyl acetylcarbamate potassium salt (BENAC-K) (**2**) has been developed as a new reagent for efficient installation of the *N*-benzyloxycarbonyl-protected acetamide group.[10] BENAC-K afforded N-alkylated products in good yields with a wide range of alkyl halides and alkyl sul-



Scheme 4 Selective deprotection of a benzyloxycarbonyl group and an acetyl group

fonates and will serve as a simple and powerful tool for the synthesis of alkaloids and bioactive compounds containing the *N*-alkylacetamide structure. Further study of the BENAC-K applications is ongoing in our laboratory.

N-Alkylation reactions were carried out in a closed vessel using commercially available, anhydrous solvents. The term 'dried' refers to the drying of an organic solution over $MgSO_4$. Flash chromatography was carried out with silica gel (spherical, neutral, particle size 40–50 μm). IR spectra were recorded on a JASCO FT/IR-410 spectrophotometer. NMR spectra were recorded on ACANCE III HD (600 MHz) or JNM-ECA (500 MHz) spectrometers. Chemical shifts are reported in ppm relative to internal TMS (δ 0.00 ppm) or to the solvent signal δ 2.50 ppm (DMSO-d_6) for ^{1}H NMR spectra, and to the solvent signals δ 77.0 ppm ($CDCl_3$) or δ 39.5 ppm (DMSO-d_6) for ^{13}C NMR spectra. Data are reported as follows: chemical shift, multiplicity (standard abbreviations), coupling constant(s), integration. High-resolution mass spectra were recorded on a JMS-HX110 magnetic sector FAB mass spectrometer, a JMS-700 magnetic sector EI mass spectrometer, or an Exactive Plus Orbitrap DART mass spectrometer.

Benzyl Acetylcarbamate Potassium Salt (BENAC-K, 2) (Scheme 3)

Benzyl *N*-acetylcarbamate (**1**) was prepared according to the literature method,[6] on a larger reaction scale. A solution of benzyl carbamate (**6**) (10.0 g, 66.2 mmol) in acetic anhydride (100 mL) was added to Amberlyst 15 Dry (1.0 g), and the mixture was stirred at rt for 1 h. The Amberlyst 15 Dry was removed by filtration and the filtrate was concentrated under reduced pressure. The resulting white solid was purified by recrystallization (toluene/hexane, 1:1; ca. 100 mL), which afforded **1** (11.4 g, 89%) as colorless needles.

A solution of **1** (11.4 g, 59.1 mmol) in 1,2-DME (60 mL) at 0 °C was added to *t*-BuOK (6.63 g, 59.1 mmol), and the mixture was stirred at 0 °C for 10 min. The resulting precipitate was collected by suction filtration and washed with Et_2O. The obtained white powder was dried under reduced pressure (25 °C, 2 mmHg) overnight to afford BENAC-K (**2**) (13.5 g, 99%) as a colorless powder. Alkylation reactions were carried out using the powder of BENAC-K without further purification.

Mp 270–280 °C (dec).

IR (KBr): 3069, 3030, 2990, 2968, 1676, 1622, 1398, 1231 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.33–7.30 (m, 4 H), 7.24 (m, 1 H), 4.85 (s, 2 H), 1.80 (s, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 178.5, 161.7, 139.3, 128.0, 127.2, 126.9, 64.3, 26.6.

HRDARTMS: *m*/*z* $[M - K]^-$ calcd for $C_{10}H_{10}NO_3$: 192.0666; found: 192.0668.

Benzyl Acetyl(3-(benzyloxy)propyl)carbamate (7a)

Method A (Table 1, Entry 9)

A solution of BENAC-K (**2**) (83 mg, 0.36 mmol, 1.1 equiv) and benzyl 3-bromopropyl ether (74 mg, 0.32 mmol, 1.0 equiv) in DMF (1.7 mL) was stirred at 60 °C for 3.0 h. After cooling to rt, the reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (15% EtOAc in *n*-hexane) afforded N-alkylated product **7a** (99 mg, 91%) as a colorless oil.

Method B (Table 1, Entry 8)

A solution of BENAC-K (**2**) (76 mg, 0.33 mmol, 1.1 equiv), 18-crown-6 (79 mg, 0.30 mmol, 1.0 equiv), and benzyl 3-bromopropyl ether (67 mg, 0.30 mmol, 1.0 equiv) in DMF (0.3 mL) was stirred at rt for 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (15% EtOAc in *n*-hexane) afforded N-alkylated product **7a** (87 mg, 85%) as a colorless oil.

IR (film): 3032, 2955, 2859, 1738, 1702, 1353, 1197 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 10 H), 5.22 (s, 2 H), 4.43 (s, 2 H), 3.88 (AA′XX′, $J_{AA'}$ = 13.0 Hz, $J_{XX'}$ = 13.0 Hz, J_{AX} = 8.4 Hz, $J_{AX'}$ = 6.0 Hz, 2 H), 3.48 (t, *J* = 6.2 Hz, 2 H), 2.49 (s, 3 H), 1.86 (m, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.9, 154.5, 138.4, 135.1, 128.7, 128.5, 128.3, 128.2, 127.53, 127.47, 72.7, 68.4, 68.0, 41.9, 28.8, 26.8.

HRFABMS: *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{23}NO_4Na$: 364.1525; found: 364.1530.

Benzyl Acetyl(pent-4-yn-1-yl)carbamate (7b)

Method A (Table 2, Entry 5)

A solution of BENAC-K (**2**) (254 mg, 1.10 mmol, 1.1 equiv) and 5-chloro-1-pentyne (103 mg, 1.00 mmol, 1.0 equiv) in DMF (1.0 mL) was stirred at 100 °C for 18 h. After cooling to rt, the reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (20% EtOAc in *n*-hexane) afforded N-alkylated product **7b** (199 mg, 77%) as a colorless oil.

Method B (Table 2, Entry 6)

A solution of BENAC-K (**2**) (254 mg, 1.10 mmol, 1.1 equiv), 18-crown-6 (264 mg, 1.00 mmol, 1.0 equiv), and 5-chloro-1-pentyne (103 mg, 1.00 mmol, 1.0 equiv) in DMF (1.0 mL) was stirred at rt for 42 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (20% EtOAc in *n*-hexane) afforded N-alkylated product **7b** (210 mg, 81%) as a colorless oil.

IR (film): 3291, 1736, 1698, 1176 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.40–7.34 (m, 5 H), 5.24 (s, 2 H), 3.85 (AA′XX′, $J_{AA'}$ = 13.4 Hz, $J_{XX'}$ = 13.4 Hz, J_{AX} = 8.8 Hz, $J_{AX'}$ = 6.1 Hz, 2 H), 2.50 (s, 3 H), 2.19 (td, *J* = 7.0, 2.7 Hz, 2 H), 1.90 (t, *J* = 2.7 Hz, 1 H), 1.76 (m, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.9, 154.4, 135.0, 128.7, 128.6, 128.3, 83.3, 68.6, 68.5, 43.3, 27.3, 26.8, 16.1.

HRDARTMS: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{18}NO_3$: 260.1281; found: 260.1283.

Benzyl Acetyl(((2*R*,3*S*)-3-((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-yl)methyl)carbamate (7c)

Method A (Table 2, Entry 7)

A solution of BENAC-K (**2**) (76 mg, 0.33 mmol, 1.1 equiv) and ((2*R*,3*S*)-3-((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-yl)methyltrifluoromethanesulfonate[11] (113 mg, 0.30 mmol, 1.0 equiv) in CH_3CN (0.3 mL) was stirred at 60 °C for 4 h. After cooling to rt, the reaction was quenched with saturated aqueous NH_4Cl solution, and the result-

ing mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (20% EtOAc in *n*-hexane) afforded N-alkylated product **7c** (89 mg, 71%) and O-alkylated product **8c** (24 mg, 19%).

Method B (Table 2, Entry 8)

A solution of BENAC-K (**2**) (76 mg, 0.33 mmol, 1.1 equiv), 18-crown-6 (79 mg, 0.30 mmol, 1.0 equiv), and ((2*R*,3*S*)-3-((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-yl)methyl trifluoromethanesulfonate (113 mg, 0.30 mmol, 1.0 equiv) in toluene (0.3 mL) was stirred at rt for 0.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (20% EtOAc in *n*-hexane) afforded N-alkylated product **7c** (114 mg, 90%) and O-alkylated product **8c** (9 mg, 7%). Spectroscopic data for **7c** and **8c** were identical with our previous report.[6]

Benzyl Acetyl(3-((*tert*-butyldimethylsilyl)oxy)propyl)carbamate (7d)

Method A (Table 2, Entry 9)

A solution of BENAC-K (**2**) (270 mg, 1.17 mmol, 1.1 equiv) and (3-bromopropoxy)(*tert*-butyl)dimethylsilane (271 mg, 1.07 mmol, 1.0 equiv) in DMF (1 mL) was stirred at 60 °C for 2 h. After cooling to rt, the reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (10% EtOAc in *n*-hexane) afforded N-alkylated product **7d** (334 mg, 85%) as a colorless oil.

Method B (Table 2, Entry 10)

A solution of BENAC-K (**2**) (255 mg, 1.10 mmol, 1.1 equiv), 18-crown-6 (264 mg, 1.00 mmol, 1.0 equiv), and (3-bromopropoxy)(*tert*-butyl)dimethylsilane (253 mg, 1.00 mmol, 1.0 equiv) in DMF (1 mL) was stirred at rt for 0.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (5% EtOAc in *n*-hexane) afforded N-alkylated product **7d** (304 mg, 83%) as a colorless oil.

IR (film): 2954, 2929, 2857, 1741, 1705, 1197 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.39–7.35 (m, 5 H), 5.24 (s, 2 H), 3.81 (AA′XX′, $J_{AA'}$ = 13.5 Hz, $J_{XX'}$ = 13.5 Hz, J_{AX} = 9.4 Hz, $J_{AX'}$ = 5.6 Hz, 2 H), 3.63 (t, *J* = 6.2 Hz, 2 H), 2.50 (s, 3 H), 1.75 (m, 2 H), 0.88 (s, 9 H), 0.03 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.8, 154.6, 135.2, 128.7, 128.5, 128.2, 68.3, 61.0, 41.9, 31.8, 26.8, 25.8, 18.2, –5.4.

HRDARTMS: *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{32}NO_4Si$: 366.2095; found: 366.2094.

3-(*N*-((Benzyloxy)carbonyl)acetamido)propyl Acetate (7e)

Method A (Table 2, Entry 11)

A solution of BENAC-K (**2**) (255 mg, 1.1 mmol, 1.1 equiv) and 3-bromopropyl acetate (181 mg, 1.0 mmol, 1.0 equiv) in DMF (1 mL) was stirred at 60 °C for 0.3 h. After cooling to rt, the reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (30% EtOAc in *n*-hexane) afforded N-alkylated product **7e** (175 mg, 60%) as a colorless oil.

Method B (Table 2, Entry 12)

A solution of BENAC-K (**2**) (255 mg, 1.10 mmol, 1.1 equiv), 18-crown-6 (264 mg, 1.00 mmol, 1.0 equiv), and 3-bromopropyl acetate (181 mg, 1.0 mmol, 1.0 equiv) in DMF (1 mL) was stirred at rt for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (30% EtOAc in *n*-hexane) afforded N-alkylated product **7e** (213 mg, 73%) as a colorless oil.

IR (film): 2965, 2899, 1739, 1702, 1236, 1201 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.41–7.35 (m, 5 H), 5.23 (s, 2 H), 4.05 (t, *J* = 6.2 Hz, 2 H), 3.85 (t, *J* = 7.2 Hz, 2 H), 2.51 (s, 3 H), 1.97 (s, 3 H), 1.87 (tt, *J* = 7.2, 6.2 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.8, 170.9, 154.3, 134.9, 128.73, 128.68, 128.3, 68.6, 62.1, 41.4, 27.8, 26.8, 20.8.

HRDARTMS: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{20}NO_5$: 294.1336; found: 294.1339.

3-(((Benzyloxy)carbonyl)amino)propyl Acetate (9)

Method B (Table 2, Entry 13)

A solution of BENAC-K (**2**) (262 mg, 1.13 mmol, 1.1 equiv), 18-crown-6 (267 mg, 1.01 mmol, 1.0 equiv), and 3-bromopropanol (140 mg, 1.01 mmol, 1.0 equiv) in CH_3CN (1 mL) was stirred at rt for 4 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (30% EtOAc in *n*-hexane) afforded **9** (126 mg, 50%) as a colorless oil.

IR (film): 3293, 3089, 2963, 1748, 1659, 1652, 1556, 1274 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.39–7.33 (m, 5 H), 5.85 (br s, 1 H), 5.16 (s, 2 H), 4.22 (t, *J* = 6.1 Hz, 2 H), 3.32 (q, *J* = 6.4 Hz, 2 H), 1.95 (s, 3 H), 1.88 (quint, *J* = 6.4 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.2, 155.2, 135.1, 128.6 (2 ×), 128.3, 69.7, 65.7, 36.3, 28.6, 23.2.

HRDARTMS: *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{18}NO_4$: 252.1230; found: 252.1227.

17,21-Anhydroprednisolone (10)

Method B (Table 2, Entry 14)

A solution of BENAC-K (**2**) (30.0 mg, 0.130 mmol, 1.1 equiv), 18-crown-6 (31.5 mg, 0.117 mmol, 1.0 equiv), and prednisolone 21-mesylate[12] (51.3 mg, 0.117 mmol, 1.0 equiv) in CH_3CN (1 mL) was stirred at rt for 4 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (30% acetone in *n*-hexane) afforded **10** (26.4 mg, 66%) as a colorless solid.

Mp 202–205 °C; $[\alpha]_D^{25}$ +167.5 (*c* 0.50, $CHCl_3$). Both the melting point and specific optical rotation are slightly lower than the literature data[13] (mp 243–244 °C, $[\alpha]_D^{23}$ +182 ($CHCl_3$)), possibly due to trace impurities in our sample.

IR (film): 3448, 2934, 1809, 1656, 1615, 753 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 10.1 Hz, 1 H), 6.28 (dd, *J* = 10.1, 1.8 Hz, 1 H), 6.02 (t, *J* = 1.5 Hz, 1 H), 5.03 and 4.88 (d, *J* = 14.8 Hz, each 1 H), 4.54 (m, 1 H), 2.57 (tdd, *J* = 13.5, 5.5, 1.4 Hz, 1 H), 2.42 (ddd, *J* = 15.6, 10.5, 2.6 Hz, 1 H), 2.34 (ddd, *J* = 13.5, 4.8, 2.0 Hz, 1 H), 2.15 (dd, *J* = 14.0, 3.3 Hz, 1 H), 2.14–2.10 (m, 2 H), 2.08 (ddd, *J* = 15.6, 9.1, 6.6 Hz, 1 H), 1.86 (dddd, *J* = 11.6, 9.1, 6.6, 2.6 Hz, 1 H), 1.71 (dd, *J* = 14.0, 2.7 Hz, 1 H), 1.47 (s, 3 H), 1.39 (dddd, *J* = 12.3, 11.6, 10.5, 6.6 Hz, 1 H), 1.33 (ddd, *J* = 12.3, 10.6, 6.6 Hz, 1 H), 1.32 (br s, 1 H), 1.15 (m, 1 H), 1.14 (s, 3 H), 1.11 (dd, *J* = 11.2, 3.3 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 205.7, 186.5, 169.9, 156.1, 127.8, 122.4, 118.0, 85.6, 69.9, 55.1, 51.1, 47.9, 44.0, 39.9, 33.8, 33.1, 31.9, 30.8, 24.6, 21.1, 16.2.

HRDARTMS: *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{27}O_4$: 343.1904; found: 343.1905.

Benzyl Acetyl(1-dodecyl)carbamate (7f)

Method A (Table 2, Entry 15)

A solution of BENAC-K (**2**) (255 mg, 1.10 mmol, 1.1 equiv) and 1-bromododecane (249 mg, 1.00 mmol, 1.0 equiv) in DMF (1 mL) was stirred at 60 °C for 24 h. After cooling to rt, the reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (5% EtOAc in *n*-hexane) afforded N-alkylated product **7f** (325 mg, 90%) as a colorless oil.

Method B (Table 2, Entry 16)

A solution of BENAC-K (**2**) (255 mg, 1.10 mmol, 1.1 equiv), 18-crown-6 (264 mg, 1.00 mmol, 1.0 equiv), and 1-bromododecane (249 mg, 1.00 mmol, 1.0 equiv) in DMF (1 mL) was stirred at rt for 24 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (5% EtOAc in *n*-hexane) afforded N-alkylated product **7f** (361 mg, 100%) as a colorless oil.

IR (film): 2925, 2854, 1738, 1704, 1148 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.41–7.35 (m, 5 H), 5.23 (s, 2 H), 3.71 (AA′XX′, $J_{AA'}$ = 12.4 Hz, $J_{XX'}$ = 12.4 Hz, J_{AX} = 8.8 Hz, $J_{AX'}$ = 6.4 Hz, 2 H), 2.49 (s, 3 H), 1.50 (m, 2 H), 1.30–1.23 (m, 18 H), 0.88 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.9, 154.7, 135.2, 128.7, 128.6, 128.2, 68.4, 44.2, 31.9, 29.63 (2 ×), 29.57, 29.5, 29.35, 29.25, 28.7, 26.9, 26.8, 22.7, 14.1.

HRFABMS: *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{35}NO_3Na$: 384.2515; found: 384.2504.

Benzyl Acetyl(allyl)carbamate (7g)

Method A (Table 2, Entry 17)

A solution of BENAC-K (**2**) (255 mg, 1.10 mmol, 1.1 equiv) and allyl bromide (87 μL, 121 mg, 1.00 mmol, 1.0 equiv) in DMF (3 mL) was stirred at 60 °C for 0.2 h. After cooling to rt, the reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (15% EtOAc in *n*-hexane) afforded N-alkylated product **7g** (223 mg, 95%) as a colorless oil.

Method B (Table 2, Entry 18)

A solution of BENAC-K (**2**) (255 mg, 1.10 mmol, 1.1 equiv), 18-crown-6 (264 mg, 1.00 mmol, 1.0 equiv), and allyl bromide (87 μL, 121 mg, 1.00 mmol, 1.0 equiv) in DMF (1 mL) was stirred at rt for 2.0 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (15% EtOAc in *n*-hexane) afforded N-alkylated product **7g** (210 mg, 90%) as a colorless oil.

IR (film): 3033, 2958, 1737, 1704, 1216 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.33 (m, 5 H), 5.80 (ddt, *J* = 17.4, 10.1, 5.7 Hz, 1 H), 5.22 (s, 2 H), 5.102 (dq, *J* = 17.4, 1.4 Hz, 1 H), 5.101 (dq, *J* = 10.1, 1.4 Hz, 1 H), 4.35 (dt, *J* = 5.7, 1.4 Hz, 2 H), 2.52 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.5, 154.3, 135.0, 132.9, 128.6, 128.5, 128.2, 116.8, 68.5, 46.0, 26.6.

HRFABMS: *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{15}NO_3Na$: 256.0950; found: 256.0956.

Benzyl Acetyl(prop-2-yn-1-yl)carbamate (7h)

Method A (Table 2, Entry 19)

A solution of BENAC-K (**2**) (255 mg, 1.10 mmol, 1.1 equiv) and propargyl bromide (9.2 M in toluene; 0.109 mL, 1.0 mmol, 1.0 equiv) in DMF (3 mL) was stirred at 60 °C for 1 h. After cooling to rt, the reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (15% EtOAc in *n*-hexane) afforded N-alkylated product **7h** (210 mg, 92%) as a colorless oil.

Method B (Table 2, Entry 20)

A solution of BENAC-K (**2**) (255 mg, 1.10 mmol, 1.1 equiv), 18-crown-6 (264 mg, 1.00 mmol, 1.0 equiv), and propargyl bromide (9.2 M in toluene; 0.109 mL, 1.0 mmol, 1.0 equiv) in DMF (3 mL) was stirred at rt for 0.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (15% EtOAc in *n*-hexane) afforded N-alkylated product **7h** (231 mg, 100%) as a colorless oil.

IR (film): 3288, 3034, 2961, 1743, 1709, 1214 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.43–7.34 (m, 5 H), 5.28 (s, 2 H), 4.52 (d, *J* = 2.5 Hz, 2 H), 2.53 (s, 3 H), 2.16 (t, *J* = 2.5 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.9, 153.5, 134.8, 128.64, 128.62, 128.2, 79.1, 70.7, 68.8, 33.3, 26.4.

HRDARTMS: *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{14}NO_3$: 232.0968; found: 232.0969.

Benzyl Acetyl(benzyl)carbamate (7i)

Method A (Table 2, Entry 21)

A solution of BENAC-K (**2**) (198 mg, 0.84 mmol, 1.1 equiv) and benzyl bromide (130 mg, 0.76 mmol, 1.0 equiv) in DMF (0.8 mL) was stirred at 60 °C for 1 h. After cooling to rt, the reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (10% EtOAc in *n*-hexane) afforded N-alkylated product **7i** (216 mg, 100%) as a colorless oil.

Method B (Table 2, Entry 22)

A solution of BENAC-K (**2**) (255 mg, 1.10 mmol, 1.1 equiv), 18-crown-6 (264 mg, 1.00 mmol, 1.0 equiv), and benzyl bromide (171 mg, 1.00 mmol, 1.0 equiv) in DMF (1 mL) was stirred at rt for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (10% EtOAc in *n*-hexane) afforded N-alkylated product **7i** (283 mg, 100%) as a colorless oil.

IR (film): 3032, 2961, 1739, 1702, 1203 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.37–7.35 (m, 3 H), 7.30–7.22 (m, 7 H), 5.21 (s, 2 H), 4.98 (s, 2 H), 2.60 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 173.0, 154.4, 137.6, 134.8, 128.62, 128.59, 128.4, 128.3, 127.8, 127.3, 68.7, 47.0, 26.8.

HRFABMS: *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{17}NO_3Na$: 306.1106; found: 306.1112.

Ethyl *N*-Acetyl-*N*-((benzyloxy)carbonyl)glycinate (7j)

Method A (Table 2, Entry 23)

A solution of BENAC-K (**2**) (255 mg, 1.10 mmol, 1.1 equiv) and ethyl bromoacetate (167 mg, 1.00 mmol, 1.0 equiv) in DMF (1 mL) was stirred at 60 °C for 0.2 h. After cooling to rt, the reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (20% EtOAc in *n*-hexane) afforded N-alkylated product **7j** (267 mg, 96%) as a colorless oil.

Method B (Table 2, Entry 24)

A solution of BENAC-K (**2**) (255 mg, 1.10 mmol, 1.1 equiv), 18-crown-6 (264 mg, 1.00 mmol, 1.0 equiv), and ethyl bromoacetate (167 mg, 1.00 mmol, 1.0 equiv) in DMF (1 mL) was stirred at rt for 0.2 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (20% EtOAc in *n*-hexane) afforded N-alkylated product **7j** (271 mg, 97%) as a colorless oil.

IR (film): 2920, 2851, 1715, 1682, 1671, 1192 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.33 (m, 5 H), 5.23 (s, 2 H), 4.50 (s, 2 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 2.58 (s, 3 H), 1.20 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.6, 168.7, 153.7, 134.9, 128.8 (2 ×), 128.3, 69.0, 61.5, 45.1, 26.3, 14.1.

HRFABMS: *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{17}NO_5Na$: 302.1004; found: 302.1016.

Benzyl Acetyl(phenethyl)carbamate (7k)

Method A (Table 2, Entry 25)

A solution of BENAC-K (**2**) (76 mg, 0.33 mmol, 1.1 equiv) and phenethyl bromide (56 mg, 0.30 mmol, 1.0 equiv) in DMF (1.7 mL) was stirred at 60 °C for 2.5 h. After cooling to rt, the reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (15% EtOAc in *n*-hexane) afforded N-alkylated product **7k** (47 mg, 54%) as a colorless oil.

Method B (Table 2, Entry 26)

A solution of BENAC-K (**2**) (255 mg, 1.10 mmol, 1.1 equiv), 18-crown-6 (264 mg, 1.00 mmol, 1.0 equiv), and phenethyl bromide (185 mg, 1.00 mmol, 1.0 equiv) in DMF (1 mL) was stirred at rt for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (15% EtOAc in *n*-hexane) afforded N-alkylated product **7k** (161 mg, 54%) as a colorless oil.

IR (film): 3029, 2968, 1736, 1698, 1174 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.41–7.36 (m, 5 H), 7.26–7.24 (m, 2 H), 7.19 (m, 1 H), 7.13–7.12 (m, 2 H), 5.15 (s, 2 H), 3.95 (AA′XX′, $J_{AA'}$ = 13.2 Hz, $J_{XX'}$ = 13.2 Hz, J_{AX} = 9.8 Hz, $J_{AX'}$ = 6.0 Hz, 2 H), 2.80 (AA′XX′, $J_{AA'}$ = 13.2 Hz, $J_{XX'}$ = 13.2 Hz, J_{AX} = 9.8 Hz, $J_{AX'}$ = 6.0 Hz, 2 H), 2.51 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.7, 154.4, 138.6, 135.0, 128.9, 128.70, 128.66, 128.4, 128.3, 126.4, 68.5, 45.6, 34.9, 26.8.

HRDARTMS: *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{20}NO_3$: 298.1438; found: 298.1440.

Benzyl Acetyl(2-chloroethyl)carbamate (7l)

Method A (Table 2, Entry 27)

A solution of BENAC-K (**2**) (79 mg, 0.34 mmol, 1.1 equiv) and 1-bromo-2-chloroethane (45 mg, 0.31 mmol, 1.0 equiv) in DMF (1.7 mL) was stirred at 60 °C for 3 h. After cooling to rt, the reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (20% EtOAc in *n*-hexane) afforded N-alkylated product **7l** (55 mg, 70%) as a colorless oil.

Method B (Table 2, Entry 28)

A solution of BENAC-K (**2**) (255 mg, 1.10 mmol, 1.1 equiv), 18-crown-6 (264 mg, 1.00 mmol, 1.0 equiv), and 1-bromo-2-chloroethane (143 mg, 1.00 mmol, 1.0 equiv) in DMF (1 mL) was stirred at rt for 20 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (20% EtOAc in *n*-hexane) afforded N-alkylated product **7l** (137 mg, 54%) as a colorless oil.

IR (film): 2964, 1738, 1702, 1171 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.41–7.36 (m, 5 H), 5.25 (s, 2 H), 4.10 (t, *J* = 6.8 Hz, 2 H), 3.59 (t, *J* = 6.8 Hz, 2 H), 2.52 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.8, 154.0, 134.7, 128.80, 128.77, 128.4, 68.9, 45.1, 41.1, 26.6.

HRFABMS: *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{14}ClNO_3Na$: 278.0560; found: 278.0565.

Benzyl Acetyl(isobutyl)carbamate (7m)

Method A (Table 2, Entry 29)

A solution of BENAC-K (**2**) (255 mg, 1.10 mmol, 1.1 equiv) and isobutyl bromide (137 mg, 1.00 mmol, 1.0 equiv) in DMF (3 mL) was stirred at 60 °C for 23 h. After cooling to rt, the reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (10% EtOAc in *n*-hexane) afforded N-alkylated product **7m** (195 mg, 79%) as a colorless oil.

Method B (Table 2, Entry 30)

A solution of BENAC-K (**2**) (255 mg, 1.10 mmol, 1.1 equiv), 18-crown-6 (264 mg, 1.00 mmol, 1.0 equiv), and isobutyl bromide (137 mg, 1.00 mmol, 1.0 equiv) in DMF (1 mL) was stirred at rt for 24 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (10% EtOAc in *n*-hexane) afforded N-alkylated product **7m** (173 mg, 70%) as a colorless oil.

IR (film): 2961, 1736, 1703, 1686, 1233, 1159 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.42–7.34 (m, 5 H), 5.22 (s, 2 H), 3.60 (d, *J* = 7.5 Hz, 2 H), 2.51 (s, 3 H), 1.93 (t-spt, *J* = 7.5, 6.8 Hz, 1 H), 0.84 (d, *J* = 6.8 Hz, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 173.1, 155.0, 135.1, 128.7, 128.6, 128.3, 68.4, 50.7, 27.8, 26.9, 19.9.

HRDARTMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{20}NO_3$: 250.1438; found: 250.1439.

Benzyl Acetyl(cyclohexylmethyl)carbamate (7n)

Method A (Table 2, Entry 31)

A solution of BENAC-K (**2**) (255 mg, 1.10 mmol, 1.1 equiv) and (bromomethyl)cyclohexane (177 mg, 1.00 mmol, 1.0 equiv) in DMF (1 mL) was stirred at 60 °C for 42 h. After cooling to rt, the reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (10% EtOAc in *n*-hexane) afforded N-alkylated product **7n** (258 mg, 89%) as a colorless oil.

Method B (Table 2, Entry 32)

A solution of BENAC-K (**2**) (255 mg, 1.10 mmol, 1.1 equiv), 18-crown-6 (264 mg, 1.00 mmol, 1.0 equiv), and (bromomethyl)cyclohexane (177 mg, 1.00 mmol, 1.0 equiv) in DMF (1 mL) was stirred at rt for 42 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (10% EtOAc in *n*-hexane) afforded N-alkylated product **7n** (263 mg, 91%) as a colorless oil.

IR (film): 2925, 2851, 1735, 1703, 1203, 1149 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.40–7.34 (m, 5 H), 5.22 (s, 2 H), 3.61 (d, *J* = 6.8 Hz, 2 H), 2.49 (s, 3 H), 1.68–1.65 (m, 2 H), 1.63–1.50 (m, 4 H), 1.18–1.06 (m, 3 H), 0.96–0.84 (m, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 173.1, 155.0, 135.1, 128.64, 128.57, 128.3, 68.4, 49.7, 37.2, 30.6, 26.8, 26.3, 25.8.

HRDARTMS: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{24}NO_3$: 290.1751; found: 290.1750.

Benzyl Acetyl(neopentyl)carbamate (7o)

Method B (Table 2, Entry 33)

A solution of BENAC-K (**2**) (231 mg, 1.00 mmol, 1.0 equiv), 18-crown-6 (264 mg, 1.00 mmol, 1.0 equiv), and neopentyl bromide (189 μL, 1.50 mmol, 1.5 equiv) in DMF (1 mL) was stirred at 80 °C for 36 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (2% EtOAc in benzene) afforded N-alkylated product **7o** (25 mg, 9%) as a colorless oil.

IR (film): 2963, 2870, 1737, 1707, 1196 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.39–7.36 (m, 5 H), 5.20 (s, 2 H), 3.70 (s, 2 H), 2.49 (s, 3 H), 0.84 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 173.1, 155.5, 134.8, 128.7 (2 ×), 128.6, 68.6, 53.1, 33.5, 28.1, 26.7.

HRDARTMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{22}NO_3$: 264.1594; found: 264.1594.

Benzyl Acetyl(isopropyl)carbamate (7p)

Method A (Table 2, Entry 34)

A solution of BENAC-K (**2**) (231 mg, 1.00 mmol, 1.0 equiv) and isopropyl iodide (110 μL, 1.10 mmol, 1.1 equiv) in DMF (1 mL) was stirred at 60 °C for 4 h. After cooling to rt, the reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (10% EtOAc in *n*-hexane) afforded N-alkylated product **7p** (57 mg, 24%) and O-alkylated product **8p** (18 mg, 8%).

Method B (Table 2, Entry 35)

A solution of BENAC-K (**2**) (231 mg, 1.00 mmol, 1.0 equiv), 18-crown-6 (264 mg, 1.00 mmol, 1.0 equiv), and isopropyl iodide (110 μL, 1.10 mmol, 1.1 equiv) in DMF (1 mL) was stirred at rt for 18.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (5% EtOAc in benzene) afforded N-alkylated product **7p** (110 mg, 47%) and O-alkylated product **8p** (21 mg, 9%).

N-Alkylated Product 7p

Colorless oil.

IR (film): 2972, 2938, 1732, 1697, 1261, 1149 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.40–7.36 (m, 5 H), 5.24 (s, 2 H), 4.87 (spt, *J* = 6.8 Hz, 1 H), 2.40 (s, 3 H), 1.28 (d, *J* = 6.8 Hz, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.9, 155.1, 134.9, 128.72, 128.67, 128.6, 68.5, 46.9, 27.1, 20.4.

HRFABMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{17}NO_3Na$: 258.1106; found: 258.1111.

O-Alkylated Product 8p

Colorless oil.

IR (film): 2980, 2936, 1720, 1669, 1244 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.42–7.40 (m, 2 H), 7.38–7.35 (m, 2 H), 7.33 (m, 1 H), 5.19 (s, 2 H), 5.07 (spt, *J* = 6.2 Hz, 1 H), 2.03 (s, 3 H), 1.25 (d, *J* = 6.2 Hz, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 167.2, 161.7, 136.0, 128.54, 128.45, 128.3, 70.3, 68.1, 21.5, 18.9.

HREIMS: *m*/*z* [M^+] calcd for $C_{13}H_{17}NO_3$: 235.1208; found: 235.1217.

Methyl *N*-Acetyl-*N*-((benzyloxy)carbonyl)alaninate (7q)

Method A (Table 2, Entry 36)

A solution of BENAC-K (**2**) (255 mg, 1.10 mmol, 1.1 equiv) and methyl 2-bromopropionate (167 mg, 1.00 mmol, 1.0 equiv) in DMF (1 mL) was stirred at 60 °C for 3 h. After cooling to rt, the reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (20% EtOAc in *n*-hexane) afforded N-alkylated product **7q** (187 mg, 68%) and O-alkylated product **8q** (60 mg, 22%).

Method B (Table 2, Entry 37)

A solution of BENAC-K (**2**) (255 mg, 1.10 mmol, 1.1 equiv), 18-crown-6 (264 mg, 1.00 mmol, 1.0 equiv), and methyl 2-bromopropionate (110 µL, 1.00 mmol, 1.0 equiv) in DMF (1 mL) was stirred at rt for 19.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (20% EtOAc in benzene) afforded N-alkylated product **7q** (223 mg, 80%) and O-alkylated product **8q** (53 mg, 19%).

N-Alkylated Product 7q

Colorless oil.

IR (film): 2998, 2951, 1757, 1703, 1390, 1263, 1175, 1119, 1085 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.43–7.38 (m, 5 H), 5.34 (q, *J* = 7.0 Hz, 1 H), 5.29 and 5.21 (d, *J* = 11.9 Hz, each 1 H), 3.55 (s, 3 H), 2.56 (s, 3 H), 1.49 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.2, 171.1, 153.5, 134.5, 128.8, 128.7, 128.6, 68.9, 52.1, 51.7, 26.5, 15.4.

HRFABMS: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{17}NO_5Na$: 302.1004; found: 302.1013.

O-Alkylated Product 8q

Colorless oil.

IR (film): 2993, 2953, 1745, 1723, 1676, 1232 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.39–7.32 (m, 5 H), 5.171 and 5.169 (d, *J* = 12.3 Hz, each 1 H), 5.17 (q, *J* = 7.0 Hz, 1 H), 3.74 (s, 3 H), 2.11 (s, 3 H), 1.50 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.1, 166.7, 160.7, 135.7, 128.5, 128.4, 128.3, 70.7, 68.2, 52.3, 18.1, 17.0.

HRFABMS: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{17}NO_5Na$: 302.1004; found: 302.1013.

2-Dodecyl 2-Nitrobenzenesulfonate

To a solution of 2-dodecanol (670 µL, 2.99 mmol) in THF (7 mL) at –78 °C was added *n*-BuLi (1.63 M in *n*-hexane; 2.20 mL, 3.59 mmol) under argon, and the mixture was stirred for 10 min at –78 °C. A solution of 2-nitrobenzenesulfonyl chloride (730 mg, 3.29 mmol) in THF (3 mL) was added, and the mixture was warmed to rt. After 1 h, the reaction was quenched with water, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, filtered, and concentrated. A byproduct, 2-chlorododecane, was removed by flash chromatography on silica gel (0 → 20% EtOAc in *n*-hexane) to afford a mixture of 2-dodecyl 2-nitrobenzenesulfonate and 2-dodecanol, that was separated by flash chromatography (0 → 2% EtOAc in CH_2Cl_2). 2-Dodecyl 2-nitrobenzenesulfonate (465 mg, 42%) was obtained as a pale yellow oil.

IR (film): 2926, 2854, 1549, 1372, 1188, 909 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.14 (m, 1 H), 7.80–7.72 (m, 3 H), 4.94 (sxt, *J* = 6.3 Hz, 1 H), 1.74 (m, 1 H), 1.60 (m, 1 H), 1.39 (d, *J* = 6.3 Hz, 3 H), 1.34–1.18 (m, 16 H), 0.88 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 148.3, 134.4, 132.0, 130.93, 130.88, 124.6, 83.8, 36.5, 31.9, 29.54, 29.47, 29.4, 29.3, 29.2, 24.8, 22.7, 20.8, 14.1.

HRDARTMS: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{30}NO_5S$: 372.1839; found: 372.1840.

Benzyl Acetyl(dodecan-2-yl)carbamate (7r)

Method B (Table 2, Entry 38)

To a solution of 2-dodecyl 2-nitrobenzenesulfonate (200 mg, 0.539 mmol, 1.0 equiv) and 18-crown-6 (142 mg, 0.539 mmol, 1.0 equiv) in CH_3CN (1 mL) was added BENAC-K (**2**) (160 mg, 0.693 mmol, 1.3 equiv), and the mixture was stirred at rt for 7 h. The reaction was quenched with saturated aqueous NH_4Cl solution and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, and concentrated. Flash chromatography on silica gel (benzene) afforded N-alkylated product **7r** (107 mg, 55%) and O-alkylated product **8r** (30 mg, 15%).

N-Alkylated Product 7r

Colorless oil.

IR (film): 2925, 2854, 1732, 1702, 1685, 1247 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.40–7.35 (m, 5 H), 5.24 and 5.22 (d, *J* = 12.1 Hz, each 1 H), 4.69 (sxt, *J* = 7.0 Hz, 1 H), 2.41 (s, 3 H), 1.75 (m, 1 H), 1.52 (m, 1 H), 1.31–1.10 (m, 19 H), 0.88 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 173.2, 155.3, 135.0, 128.69, 128.66, 128.6, 68.4, 51.4, 34.3, 31.9, 29.58, 29.56, 29.5, 29.4, 29.3, 27.1, 26.8, 22.7, 19.0, 14.1.

HRDARTMS: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{36}NO_3$: 362.2690; found: 362.2690.

O-Alkylated Product 8r

Colorless oil.

IR (film): 2927, 2854, 1725, 1669, 1240, 1027 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.42–7.40 (m, 2 H), 7.38–7.35 (m, 2 H), 7.32 (m, 1 H), 5.19 (s, 2 H), 4.95 (sxt, *J* = 6.3 Hz, 1 H), 2.03 (s, 3 H), 1.61 (m, 1 H), 1.47 (m, 1 H), 1.31–1.25 (m, 16 H), 1.22 (d, *J* = 6.2 Hz, 3 H), 0.88 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 167.5, 161.8, 136.0, 128.5, 128.4, 128.3, 73.8, 68.0, 35.7, 31.9, 29.59, 29.55, 29.51, 29.49, 29.3, 25.3, 22.7, 19.3, 18.8, 14.1.

HRDARTMS: *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{36}NO_3$: 362.2690; found: 362.2692.

Acetamide 11 (Scheme 4)

A solution of **4**[6] (57.0 mg, 0.0978 mmol) and 5% Pd/C (6 mg) in EtOAc (1 mL) was stirred under H_2 atmosphere at rt for 4 h. The reaction mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. Flash chromatography (70 → 80% EtOAc in *n*-hexane) afforded acetamide **11** (34.5 mg, 79%) as a colorless oil.

$[\alpha]_D^{26}$ +24.6 (*c* 1.11, $CHCl_3$).

IR (film): 3302, 3031, 2953, 2856, 1651, 1104 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.36–7.32 (m, 4 H), 7.28 (m, 1 H), 5.84 (br s, 1 H), 4.51 (s, 2 H), 3.76 (m, 1 H), 3.50 (dt, *J* = 9.2, 6.4 Hz, 1 H), 3.48 (dt, *J* = 9.2, 6.4 Hz, 1 H), 3.53 (ddd, *J* = 11.0, 8.6, 4.6 Hz, 1 H), 3.40 (ddd, *J* = 7.9, 5.3, 2.2 Hz, 1 H), 3.13–3.07 (m, 2 H), 1.95 (s, 3 H), 1.87 (ddd, *J* = 12.7, 4.8, 2.6 Hz, 1 H), 1.83 (qddd, *J* = 7.0, 4.6, 2.6, 2.2 Hz, 1 H), 1.71 (m, 1 H), 1.65–1.54 (m, 3 H), 1.42 (m, 1 H), 0.94 (d, *J* = 7.0 Hz, 3 H), 0.88 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.7, 138.4, 128.3, 127.61, 127.55, 81.2, 79.5, 72.9, 70.1, 65.7, 41.4, 40.8, 32.5, 29.3, 26.5, 25.7, 23.3, 17.9, 12.6, –4.2, –4.8.

HRFABMS: *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{44}NO_4Si$: 450.3040; found: 450.3022.

Benzyl Carbamate 12 (Scheme 4)

To a solution of **7c** (27.7 mg, 0.0658 mmol) in MeOH (1 mL) was added K_2CO_3 (1.6 mg, 0.012 mmol, 0.18 equiv), and the reaction mixture was stirred at rt. After 15 h, the mixture was concentrated under reduced pressure. Flash chromatography on silica gel (6 → 20% EtOAc in *n*-hexane) afforded benzyl carbamate **12** (19.7 mg, 79%) as a colorless oil.

$[\alpha]_D^{24}$ +47.7 (*c* 1.64, $CHCl_3$).

IR (film): 3344, 2929, 2856, 1728, 1098 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.38–7.33 (m, 4 H), 7.30 (m, 1 H), 5.14 (br s, 1 H), 5.11 and 5.09 (d, *J* = 12.3 Hz, each 1 H), 3.86 (ddt, *J* = 11.9, 3.4, 1.7 Hz, 1 H), 3.71 (m, 1 H), 3.35 (ddd, *J* = 10.2, 8.3, 5.1 Hz, 1 H), 3.30 (m, 1 H), 3.14–3.09 (m, 2 H), 2.01 (m, 1 H), 1.65–1.60 (m, 2 H), 1.43 (m, 1 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 156.3, 136.7, 128.5, 128.1, 128.0, 81.1, 69.0, 67.6, 66.5, 42.8, 33.2, 25.8, 25.4, 17.9, –4.1, –4.9.

HRFABMS: *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{34}NO_4Si$: 380.2257; found: 380.2241.

Funding Information

This research was partially supported by Grants-in-Aid for Scientific Research (C) (16K08182 and 16K08183) from the Japan Society for the Promotion of Science (JSPS) and the Research Foundation for Pharmaceutical Sciences.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690097.

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