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# Orthoester in Cyclodehydration of Carbamate-Protected Amino Alcohols under Acidic Conditions

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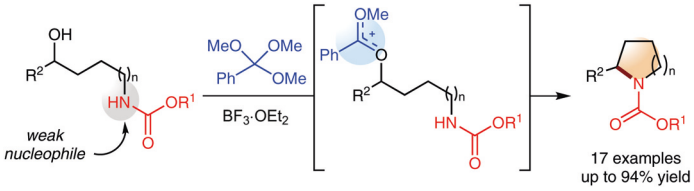


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**Abstract** The first acid-promoted reaction system to form azaheterocycles from *N*-carbamate-protected amino alcohols is described. The reaction involves the activation of the hydroxyl group via the use of orthoesters. Despite the reduced nucleophilicity of carbamate nitrogen, this reaction system provides several types of pyrrolidines and piperidines in good to high yields. Using this protocol, prolinol derivatives can also be synthesized from carbamate-protected amino diols with regio- and stereoselectivity.

**Key words** *N*-carbamate, cyclization, Lewis acids, azaheterocycles, orthoester, oxocarbenium

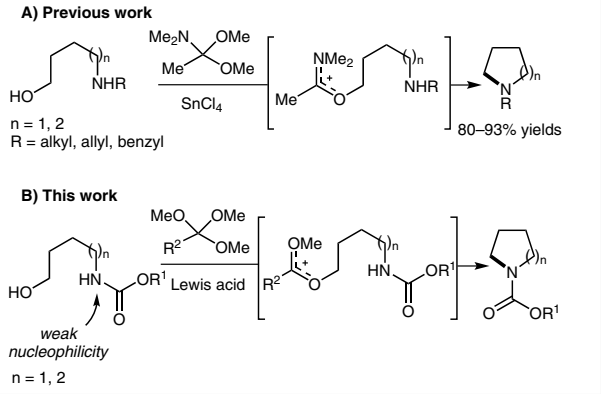
During the synthesis of amine-containing compounds, an amino group is generally protected because of its basic and nucleophilic properties.[1] Carbamates are among the most commonly used functional groups for this purpose.[2] Sometimes, electrophilic substitution of carbamate, particularly *N*-alkylation, is necessary during the synthetic sequence for efficient and concise synthesis. The *N*-alkylation of carbamates is normally achieved under harsh reaction conditions, such as the use of a strong base or excess of reagents, because of the attenuated nucleophilicity of carbamate groups.

The intramolecular version of the carbamate *N*-alkylation provides a convenient access to *N*-carbamate-protected azaheterocycles.[1b,3] In this type of transformation, an alkylating moiety is mostly derived from a hydroxyl group during the synthetic sequence.[4–6] A halide or sulfonate ester group is frequently used to activate the hydroxyl group.[4] In some cases, the hydroxyl group can be activated in situ.[5]

Although the formation of an *N*-carbamate-protected azaheterocycle from the corresponding linear amino alcohol substrate is generally achieved under basic conditions, it can also be realized under acidic conditions via the carbocation intermediate.[6] However, the previous examples are only limited to the substrates with a benzylic hydroxyl group. There are no examples for the substrates with aliphatic hydroxyl group. This is probably due to the generation of a simple alkyl carbocation or its equivalents that are reactive enough to react with a carbamate nitrogen-nucleophile is not easy to achieve under nonvigorous conditions. The development of the reaction system, which works in mild acidic conditions, is highly desirable because it will significantly expand the substrate scope.

We recently reported the mild and efficient acid-promoted cyclodehydration of amino alcohols, as shown in Scheme 1 A, which involves the use of *N*,*N*-dimethylacetamide dimethyl acetal (DMADA) as the in situ activating agent for the hydroxyl group.[7] The reaction was effective even for the acid salt of the amino alcohol whose amino group is largely deactivated by protonation. The reaction takes advantage of a thermodynamic equilibrium and proceeds via an aza-oxo-stabilized carbenium ion intermediate. Partially inspired by this previous work, we envisioned that the cyclodehydration of *N*-carbamate-protected amino alcohols would be achievable in a similar fashion if the thermodynamic factors were sufficiently favorable to compensate for the weak nucleophilicity of carbamate nitrogen (Scheme 1 B). Herein, we report our studies on the formation of azaheterocycles from *N*-carbamate-protected amino alcohols by the in situ activation of the hydroxyl group via the use of orthoester and Lewis acid.

*N*-Cbz-protected amino alcohol **1a** (Table 1) was selected as the model substrate to examine the feasibility of acid-promoted cyclodehydration of *N*-carbamate-protected amino alcohol. First, **1a** was treated with DMADA and $SnCl_4$ in $CH_2Cl_2$ at room temperature, which was our cyclodehydration conditions for an unprotected amino alcohol.[7] The reaction remained incomplete even after 18 hours. The de-



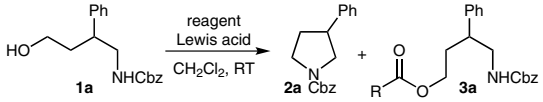

**Scheme 1** Acid-promoted synthesis of azaheterocycles

sired cyclized product **2a** was only obtained in very low yield (Table 1, entry 1). A substantial amount of the *O*-acyl derivative **3aa** was formed. Our trial on just raising the reaction temperature failed to complete the reaction and to prevent the formation of **3aa** (entry 2). The formation of *O*-acyl derivative **3aa** implied that the intermediate **A** (Scheme 2) was generated via transacetalization. However, the preferential formation of **3aa** suggests that the carbenium ion function in the postulated intermediate **A** did not react with the pendant carbamate nitrogen preferentially (*path a*) because of its low nucleophilicity, but instead the oxocarbenium function reacted readily with the adventitious water, at the position of the $sp^2$ oxocarbenium carbon (*path b*).

To change the chemicophysical properties of carbenium function, several other carbenium ion precursors were screened in the presence of a catalytic amount of $SnCl_4$ (0.1 equiv). The use of another amide acetal, *N*,*N*-dimethylformamide dimethyl acetal (DMFDA), did not yield the desired product (Table 1, entry 3). However, when orthoesters[8] were used, the reaction was completed probably due to the increased reactivity of the carbenium function in the postulated intermediate **A**. Trimethyl orthobenzoate (TMOB) was more efficient than trimethyl orthoformate (TMOF) and trimethyl orthoacetate (TMOA) (entries 4–6). A range of Lewis acids were examined to optimize the reaction with TMOB, and the typical results are shown in Table 1 (entries 6–9). $BF_3{\cdot}OEt_2$ was identified as the optimal choice. A catalytic amount (0.1 equiv) of $BF_3{\cdot}OEt_2$ provided the product **2a** after 2 hours at room temperature in 87% yield (entry 9). When the amount of $BF_3{\cdot}OEt_2$ was increased, the yield was slightly enhanced with minimal formation of the *O*-acylated by-product **3ac** (entries 10–12). Under strictly anhydrous condition, the formation of the main by-product **3a** decreased and the yield of product **2a** was increased even with a catalytic amount (0.1 equiv) of $BF_3{\cdot}OEt_2$ (entry 13).

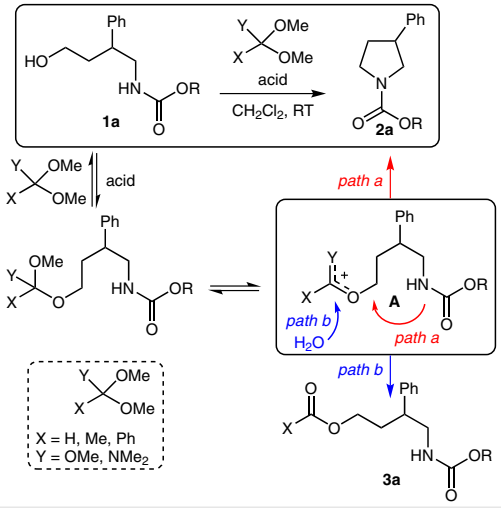
Under the optimized reaction conditions (1.5 equiv of TMOB, 0.1 equiv of $BF_3{\cdot}OEt_2$, $CH_2Cl_2$, r.t.), acid-labile *N*-Boc group and base-labile *N*-Fmoc group were well tolerated to

**Table 1** Optimization of Reaction Conditions for the Cyclization of Substrate **1a**[a]




| Entry | Reagent[b] (equiv) | Lewis acid (equiv) | Time (h) | **2a**/**3a**[c] | Yield of **2a** (%)[d] |
|---|---|---|---|---|---|
| 1 | DMADA (2) | $SnCl_4$ (0.1) | 18 | 1:10 | 2 (8)[e] |
| 2[f] | DMADA (2) | $SnCl_4$ (0.1) | 18 | 1:2 | 7 (32)[e] |
| 3 | DMFDA (2) | $SnCl_4$ (0.1) | 18 | –[g] | –[g] |
| 4 | TMOF (1.5) | $SnCl_4$ (0.1) | 18 | 1:2 | 32 |
| 5 | TMOA (1.5) | $SnCl_4$ (0.1) | 2 | 4:1 | 65 |
| 6 | TMOB (1.5) | $SnCl_4$ (0.1) | 2 | 6:1 | 73 |
| 7 | TMOB (1.5) | CuOTf (0.1) | 10 | 5:1 | 54 |
| 8 | TMOB (1.5) | $FeCl_3$ (0.1) | 10 | 6:1 | 75 |
| 9 | TMOB (1.5) | $BF_3{\cdot}OEt_2$ (0.1) | 2 | 9:1 | 87 |
| 10 | TMOB (1.5) | $BF_3{\cdot}OEt_2$ (0.5) | 2 | 10:1 | 88 |
| 11 | TMOB (1.5) | $BF_3{\cdot}OEt_2$ (1) | 1 | 12:1 | 89 |
| 12 | TMOB (1.5) | $BF_3{\cdot}OEt_2$ (3) | 1 | 18:1 | 91 |
| 13[h] | TMOB (1.5) | $BF_3{\cdot}OEt_2$ (0.1) | 2 | 18:1 | 91 |

[a] Reaction conditions: **1a** (0.50 mmol), reagent, Lewis acid, $CH_2Cl_2$ (10 mL) at r.t. under $N_2$.
[b] Reagent for carbenium ion precursor.
[c] Determined by $^1H$ NMR analysis using the crude product.
[d] Isolated yield of **2a**.
[e] The value in parentheses indicates the yield based on recovered starting material.
[f] The reaction was performed at reflux temperature.
[g] Desired product **2a** was not detected.
[h] Anhydrous condition.



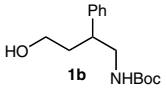
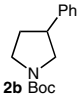
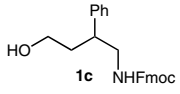
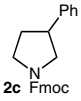
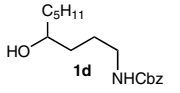
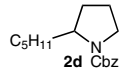
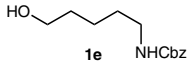
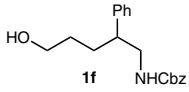
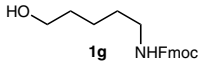
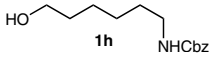
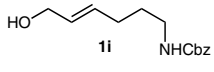
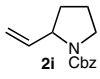
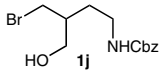
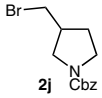
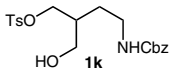
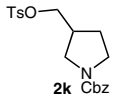

**Scheme 2** Plausible reaction mechanism for the formation of **2a** and **3a**

afford the corresponding cyclized products in high yields (Table 2, entries 1 and 2). The substrate with a secondary hydroxyl group was also well suited for the reaction, although the reaction required heating and longer reaction times for completion (entry 3). The addition of an excess of $BF_3{\cdot}OEt_2$ increased the rate of this reaction and yield (entry 4). The six-membered piperidine ring formation was also achieved (entries 5–7) under the reaction conditions of entry 5. The yield was lower than the pyrrolidine system because of the increased production of the *O*-acylated byproduct.[9] The formation of a seven-membered azepane ring was not detected even after with exposure to prolonged high temperature (entry 8). The substrate with the allylic hydroxyl group underwent an intramolecular $S_N2'$-type reaction under the optimized conditions to produce 2-vinyl-substituted pyrrolidine **2i** (entry 9). The reaction was completely chemoselective for the hydroxyl group over the halide and sulfonate leaving groups and produced **2j** and **2k** only as a cyclized product (entries 10 and 11). These results demonstrate the marked distinction of this acid-promoted azaheterocycle formation reaction compared to the base-induced reactions.

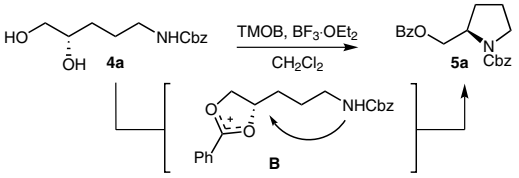
To further explore the reaction scope, we investigated the cyclization of vicinal diols **4a–e** and 1,3-diol **4f** (Table 3). Prolinol derivatives **5a–e** were produced from *N*-carbamate-protected amino vicinal diols **4a–e** in good yields without the formation of the six-membered piperidine ring (Table 3, entries 1–5). The cyclization of the enantiomerically pure (ee >99%) substrate **4a** led to the formation of prolinol benzoate **5a** (ee >99%) without complete inversion of configuration at the chiral center (entry 1).[10] This result suggests that the reaction proceeds via an $S_N2$-like mechanism. The incorporation of the benzoate group into the product suggests that the reaction proceeds via a cyclic oxocarbenium intermediate **B** (Scheme 3) formed on the diol moiety.[11] Comparable results were obtained for *syn*- and *anti*-vicinal diols **4b** and **4c**, which produced the corresponding $S_N2$-type products in high yields (entries 2 and 3). Both *N*-Boc and *N*-Fmoc groups were well tolerated with the conditions that were used (entries 4 and 5). The 1,3-diol **4f** also successfully cyclized to form the benzoate incorporated product **5f** (entry 6).

In summary, we have developed a new method in which carbamate-protected amines undergo intramolecular alkylation with the hydroxyl group to form azaheterocycles. Our method is unique compared to previous methods in that the cyclization proceeds via reactive oxocarbenium to activate the hydroxyl group under mild acidic conditions. Despite the reduced nucleophilicity of carbamate-nitrogen, several types of pyrrolidines and piperidines were successfully prepared in good to high yields from the carbamate-protected amino alcohols. Moreover, we found that the vicinal and 1,3-diols with carbamate-protected amine could

**Table 2** Results of Cyclization of *N*-Carbamate-Protected Amino Alcohols **1**[a]

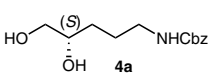
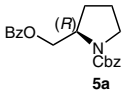
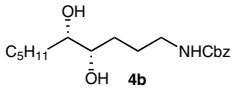
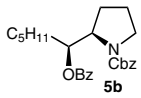
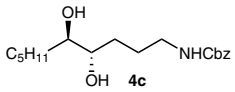
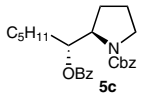
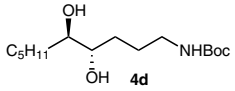
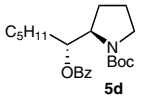
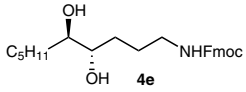
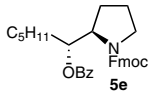
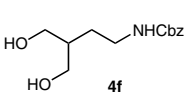
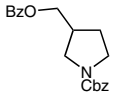
| Entry | Substrate **1** | Time (h) | Product **2** | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  **1b** | 2 |  **2b** | 85 |
| 2 |  **1c** | 2 |  **2c** | 87 |
| 3[c] |  **1d** | 20 |  **2d** | 79 |
| 4[c,d] | | 2 | | 85 |
| 5[c,d] |  **1e** | 5 |  **2e** | 68 |
| 6[c,d] |  **1f** | 5 |  **2f** | 68 |
| 7[c,d] |  **1g** | 7 |  **2g** | 62 |
| 8[c,d] |  **1h** | 20 | –[e] | –[e] |
| 9 |  **1i** | 2 |  **2i** | 83 |
| 10 |  **1j** | 2 |  **2j** | 83 |
| 11 |  **1k** | 2 |  **2k** | 87 |

[a] Reaction conditions: **1** (0.50 mmol), TMOB (0.75 mmol), $BF_3{\cdot}OEt_2$ (0.050 mmol), $CH_2Cl_2$ (10 mL) at r.t. under $N_2$.
[b] Isolated yield of **2**.
[c] The reaction was performed at reflux temperature.
[d] Three equiv of $BF_3{\cdot}OEt_2$ was used.
[e] Desired product **2h** was not detected and only 58% of *O*-benzoyl by-product was obtained.




**Scheme 3** Plausible reaction mechanism for the formation of **5a** via cyclic oxocarbenium intermediate

**Table 3** Results of Cyclization of *N*-Carbamate-Protected Amino Vicinal Diols **4a–e** and 1,3-Diol **4f**[a]

| Entry | Substrate **4** | Product **5** | Yield (%)[b] |
|---|---|---|---|
| 1 |  **4a** |  **5a** | 94 |
| 2[c] |  **4b** |  **5b** | 91 |
| 3[c] |  **4c** |  **5c** | 87 |
| 4[c] |  **4d** |  **5d** | 89 |
| 5[c] |  **4e** |  **5e** | 91 |
| 6[d] |  **4f** |  **5f** | 93 |

[a] Reaction conditions: **4** (0.50 mmol), TMOB (0.75 mmol), $BF_3{\cdot}OEt_2$ (0.050 mmol), $CH_2Cl_2$ (10 mL) at reflux temperature under $N_2$.
[b] Isolated yield of **5**.
[c] Relative configuration.
[d] The reaction was performed at r.t.

undergo the facile reaction under slightly higher temperatures. These results broaden the synthetic routes to azaheterocycles, which are important synthetic motifs in organic synthesis.

All chemicals were of reagent grade and used as received. All reactions were performed under dry $N_2$ using distilled, anhyd solvents. The reactions were monitored by TLC (Merck silica gel 60 F254). Flash column chromatography was performed on silica gel (230–400 mesh). $^1H$ (300, 400, or 500 MHz) and $^{13}C$ NMR (75, 100, or 125 MHz) spectra were recorded. Chemical shifts (δ) are reported in ppm relative to the nondeuterated solvent as the internal reference; the coupling constants (*J*) are given in Hz. The multiplicities are denoted using standard abbreviations. The $^1H$ NMR spectra are presented as follows: chemical shift (multiplicity, coupling constant, integration). The IR spectra were recorded on a Fourier transform IR spectrophotometer. High-resolution mass spectra (HRMS) were obtained by fast-atom bombardment (FAB). Previously reported compounds were confirmed by comparing their $^1H$ NMR data with those given in the references.

Detailed procedures for the preparation of the starting materials **1a–k** and **4a–f** are provided in the Supporting Information.

### $BF_3{\cdot}OEt_2$-Mediated Cyclization of *N*-Carbamate-Protected Amino Alcohols 1; General Procedure

To a stirred solution of the respective *N*-carbamate protected amino alcohol **1** (0.50 mmol, 1 equiv) in $CH_2Cl_2$ (10 mL, 0.05 M) were added $BF_3{\cdot}OEt_2$ (50 µL, 0.050 mmol, 0.1 equiv or 150 µL, 0.15 mmol, 3 equiv, 1.0 M solution in $CH_2Cl_2$) and trimethyl orthobenzoate (0.13 mL, 0.75 mmol, 1.5 equiv) at r.t. The resulting mixture was stirred at r.t. under $N_2$ until TLC showed complete conversion of the substrate. The reaction was quenched with sat. aq $NaHCO_3$ and extracted with EtOAc (2 ×). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane/EtOAc) to give the desired product **2**.

### Benzyl 3-Phenylpyrrolidine-1-carboxylate (2a)[12]

Yield: 123 mg (87%); colorless oil.

$^1H$ NMR ($CDCl_3$, 400 MHz): δ = 7.42–7.28 (m, 7 H), 7.28–7.20 (m, 3 H), 5.16 (s, 2 H), 3.98–3.82 (m, 1H), 3.77–3.62 (m, 1 H), 3.52–3.43 (m, 1 H), 3.42–3.32 (m, 2 H), 2.27 (br s, 1 H), 2.00 (q, *J* = 10.1 Hz, 1 H).

### *tert*-Butyl 3-Phenylpyrrolidine-1-carboxylate (2b)[13]

Yield: 105 mg (85%); colorless oil.

$^1H$ NMR ($CDCl_3$, 400 MHz): δ = 7.32–7.28 (m, 2 H), 7.24–7.21 (m, 3 H), 3.80 (t, *J* = 7.6 Hz, 1 H), 3.59 (t, *J* = 8.8 Hz, 1 H), 3.41–3.26 (m, 3 H), 2.28–2.20 (m, 1 H), 2.00 (q, *J* = 10.1 Hz, 1 H), 1.46 (s, 9 H).

### (9*H*-Fluoren-9-yl)methyl 3-Phenylpyrrolidine-1-carboxylate (2c)

Yield: 160 mg (87%); colorless oil.

IR (neat): 3031, 2949, 2879, 1696, 1416, 1354, 1115, 908, 729 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 300 MHz): δ = 7.76 (t, *J* = 6.6 Hz, 2 H), 7.62 (t, *J* = 8.1 Hz, 2 H), 7.44–7.21 (m, 9 H), 4.43 (d, *J* = 12.5 Hz, 2 H), 4.26 (q, *J* = 6.8 Hz, 1 H), 3.96–3.85 (m, 1 H), 3.75–3.62 (m, 1 H), 3.55–3.31 (m, 3 H), 2.39–2.24 (m, 1 H), 2.11–1.95 (m, 1 H).

$^{13}C$ NMR ($CDCl_3$, 75 MHz): δ = 154.8, 144.1 (2 C), 141.3, 141.2, 141.1, 128.7, 128.6, 127.6 (2 C), 127.0 (3 C), 126.9, 126.8, 125.1 (2 C), 119.9 (2 C), 67.2 (0.5 C), 67.1 (0.5 C), 52.3 (0.5 C), 52.2 (0.5 C), 47.4, 46.1 (0.5 C), 45.7 (0.5 C), 44.2 (0.5 C), 43.2 (0.5 C), 33.3 (0.5 C), 32.5 (0.5 C).

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{24}NO_2$: 370.1807; found: 370.1812.

### Benzyl 2-Pentylpyrrolidine-1-carboxylate (2d)

Yield: 117 mg (85%); colorless oil.

IR (neat): 3033, 2952, 2882, 1695, 1416, 1357, 1116, 907, 727 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 400 MHz): δ = 7.36–7.25 (m, 5 H), 5.12–5.07 (m, 2 H), 3.81 (br s, 1 H), 3.50–3.33 (m, 2 H), 2.02–1.73 (m, 3 H), 1.64 (br s, 1 H) 1.27 (br s, 8 H), 0.88–0.85 (m, 3 H).

$^{13}C$ NMR ($CDCl_3$, 100 MHz): δ = 154.8, 137.2, 128.4 (0.5 C), 128.3 (2 C), 128.0 (0.5 C), 127.7 (2 C), 66.5 (0.5 C), 66.3 (0.5 C), 58.0 (0.5 C), 57.3 (0.5 C), 46.6 (0.5 C), 46.2 (0.5 C), 34.5 (0.5 C), 33.8 (0.5 C), 31.8, 30.5 (0.5 C), 29.7 (0.5 C), 25.8, 23.8 (0.5 C), 23.0 (0.5 C), 22.5, 14.0.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{26}NO_2$: 276.1964; found: 276.1965.

### Benzyl Piperidine-1-carboxylate (2e)[14]

Yield: 75 mg (68%); colorless oil.

$^1H$ NMR ($CDCl_3$, 300 MHz): δ = 7.35–7.26 (m, 5H ), 5.10 (s, 2 H), 3.42 (t, *J* = 5.4 Hz, 4 H), 1.55–1.51 (m, 6 H).

**Benzyl 3-Phenylpiperidine-1-carboxylate (2f)**

Yield: 100 mg (68%); colorless oil.

IR (neat): 2934, 1738, 1698, 1427, 1233, 1044, 698 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 500 MHz): δ = 7.34 (br s, 4 H), 7.30 (t, *J* = 7.5 Hz, 3 H), 7.21 (t, *J* = 7.3 Hz, 3 H), 5.14 (s, 2 H), 4.23 (br s, 2 H), 2.80 (br s, 2 H), 2.69 (br s, 1 H), 2.02 (d, *J* = 10.5 Hz, 1 H), 1.80–1.73 (m, 1 H), 1.69–1.55 (m, 2 H), 1.64 (br s, 1 H) 1.27 (br s, 8 H), 0.88–0.85 (m, 3 H).

$^{13}C$ NMR ($CDCl_3$, 125 MHz): δ = 155.3, 143.2, 136.9, 128.52 (2 C), 128.46 (2 C), 127.9, 127.8 (2 C), 127.1 (2 C), 126.7, 67.0, 50.6, 44.4, 42.6, 31.7, 25.4.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}NO_2$: 296.1651; found: 296.1658.

**(9*H*-Fluoren-9-yl)methyl Piperidine-1-carboxylate (2g)**[14]

Yield: 95.2 mg (62%); colorless oil.

$^1H$ NMR ($CDCl_3$, 300 MHz): δ = 7.75 (d, *J* = 7.5 Hz, 2 H), 7.57 (d, *J* = 7.3 Hz, 2 H), 7.38 (t, *J* = 7.3 Hz, 2 H), 7.30 (t, *J* = 7.3 Hz, 2 H), 4.38 (d, *J* = 6.8 Hz, 2 H), 4.24 (t, *J* = 6.9 Hz, 1 H), 3.43 (t, *J* = 5.3 Hz, 4 H) 1.59–1.53 (m, 6 H).

**Benzyl 2-Vinylpyrrolidine-1-carboxylate (2i)**[15]

Yield: 95.9 mg (83%); yellow oil.

$^1H$ NMR ($CDCl_3$, 400 MHz): δ = 7.39–7.25 (m, 5 H), 5.74 (br s, 1 H), 5.20–5.01 (m, 4 H), 4.38 (br s, 1 H), 3.46 (br s, 2 H), 2.08–1.94 (m, 1 H), 1.93–1.79 (m, 2 H), 1.76–1.68 (m, 1 H).

**Benzyl 3-(Bromomethyl)pyrrolidine-1-carboxylate (2j)**

Yield: 123 mg (83%); colorless oil.

IR (neat): 2953, 2879, 1695, 1414, 1357, 1113, 736, 696 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 400 MHz): δ = 7.37–7.27 (m, 5 H), 5.11 (s, 2 H), 3.65 (br s, 1 H), 3.56 (br s, 1 H), 3.43–3.31 (m, 3 H), 3.17 (t, *J* = 9.0 Hz, 1 H), 2.60 (t, *J* = 7.1 Hz, 1 H), 2.10–2.03 (m, 1 H), 1.73 (br s, 1 H).

$^{13}C$ NMR ($CDCl_3$, 75 MHz): δ = 154.6, 136.7, 128.4 (2 C), 127.9 (2 C), 127.8, 66.7, 50.6 (0.5 C), 50.3 (0.5 C), 45.7 (0.5 C), 45.2 (0.5 C), 41.3 (0.5 C), 40.4 (0.5 C), 34.3, 30.6 (0.5 C), 29.9 (0.5 C).

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{17}BrNO_2$: 298.0443; found: 298.0435.

**Benzyl 3-[(Tosyloxy)methyl]pyrrolidine-1-carboxylate (2k)**

Yield: 169 mg (87%); colorless oil.

IR (neat): 2954, 2885, 1697, 1417, 1356, 1174, 1096, 950, 813, 767, 664 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 400 MHz): δ = 7.76 (d, *J* = 8.1 Hz, 2 H), 7.35–7.28 (m, 7 H), 5.09 (s, 2 H), 4.00–3.91 (m, 2 H), 3.53 (dd, *J* = 7.7, 10.9 Hz, 1 H), 3.44 (br s, 1 H), 3.39–3.32 (m, 1 H), 3.07 (dd, *J* = 7.0, 11.1 Hz, 1 H), 2.58–2.51 (m, 1 H), 2.42 (s, 3 H), 2.02–1.92 (m, 1 H), 1.71–1.58 (m, 1 H).

$^{13}C$ NMR ($CDCl_3$, 75 MHz): δ = 154.6, 145.0, 136.7, 132.5, 129.9 (3 C), 128.4 (2 C), 127.9, 127.8 (3 C), 70.7, 66.8, 48.3 (0.5 C), 48.0 (0.5 C), 45.2 (0.5 C), 44.8 (0.5 C), 38.1 (0.5 C), 37.2 (0.5 C), 28.0 (0.5 C), 27.1 (0.5 C), 21.7.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{24}NO_5S$: 390.1375; found: 390.1367.

**$BF_3$·$OEt_2$-Mediated Cyclization of *N*-Carbamate-Protected Amino Vicinal Diol 4; General Procedure**

To a stirred solution of the respective N-carbamate-protected amino vicinal diol **4** (0.50 mmol, 1 equiv) in $CH_2Cl_2$ (10 mL, 0.05 M) were added $BF_3$·$OEt_2$ (50 µL, 0.050 mmol, 0.1 equiv, 1.0 M solution in $CH_2Cl_2$) and trimethyl orthobenzoate (0.13 mL, 0.75 mmol, 1.5 equiv) at r.t. The resulting mixture was refluxed or stirred at r.t. under $N_2$ until TLC showed complete conversion of the substrate. The reaction was quenched with sat. aq $NaHCO_3$ and extracted with EtOAc (2 ×). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane/EtOAc) to give the desired product **5**.

**Benzyl (*R*)-2-[(Benzoyloxy)methyl]pyrrolidine-1-carboxylate (5a)**

Yield: 159 mg (94%); colorless oil; $[\alpha]_D^{20}$ +61.9 (*c* 1.0, $CHCl_3$).

IR (neat): 2960, 2885, 2252, 1695, 1412, 1271, 1098, 906, 727 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 500 MHz): δ = 8.00 (t, *J* = 8.9 Hz, 2 H), 7.52 (t, *J* = 7.4 Hz, 1 H), 7.40 (t, *J* = 7.6 Hz, 2 H), 7.34 (t, *J* = 6.9 Hz, 2 H), 7.31 (t, *J* = 7.3 Hz, 2 H), 7.27 (d, *J* = 6.4 Hz, 1 H), 5.18 (d, *J* = 13.0 Hz, 0.5 H), 5.14 (s, 1 H), 5.07 (d, *J* = 12.4 Hz, 0.5 H), 4.42 (br s, 1 H), 4.34 (br s, 1 H), 4.27 (br s, 0.5 H), 4.22 (br s, 0.5 H), 3.59–3.41 (m, 2 H), 2.08–1.81 (m, 4 H).

$^{13}C$ NMR ($CDCl_3$, 125 MHz): δ = 166.1, 154.7, 136.7 (0.5 C), 136.5 (0.5 C), 132.9 (0.5 C), 132.8 (0.5 C), 129.9 (0.5 C), 129.8 (0.5 C), 129.4 (2 C), 128.3 (2 C), 128.2 (2 C), 127.7 (2 C), 127.6, 66.8 (0.5 C), 66.5 (0.5 C), 65.1 (0.5 C), 64.6 (0.5 C), 56.1 (0.5 C), 55.5 (0.5 C), 46.9 (0.5 C), 46.5 (0.5 C), 28.6 (0.5 C), 27.8 (0.5 C), 23.7 (0.5 C), 22.9 (0.5 C).

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{22}NO_4$: 340.1549; found: 340.1543.

**Benzyl (*R**)-2-[(*S**)-1-(Benzoyloxy)hexyl]pyrrolidine-1-carboxylate (5b)**

Yield: 187 mg (91%); colorless oil.

IR (neat): 2933, 2874, 2251, 1698, 1409, 1268, 1107, 909, 709 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 500 MHz): δ (two rotamers, 1:1) = 8.02 (s, 2 H), 7.52 (t, *J* = 7.4 Hz, 1 H), 7.42–7.40 (m, 3 H), 7.38–7.25 (m, 4 H), 5.71 (br s, 0.5 H), 5.62 (br s, 0.5 H), 5.16 (d, *J* = 12.6 Hz, 2 H), 4.10 (br s, 0.5 H), 4.02 (br s, 0.5 H), 3.55 (q, *J* = 7.4 Hz, 0.5 H), 3.44 (q, *J* = 8.4 Hz, 0.5 H), 3.22 (d, *J* = 7.5 Hz, 1 H), 2.15–2.09 (m, 1 H), 2.00–1.92 (br s, 2 H), 1.81–1.59 (m, 2 H), 1.45–1.19 (m, 7 H), 0.85–0.82 (m, 3 H).

$^{13}C$ NMR ($CDCl_3$, 125 MHz): δ (two rotamers, 1:1) = 165.7 (0.5 C), 165.6 (0.5 C), 154.8 (0.5 C), 154.7 (0.5 C), 136.9 (0.5 C), 136.5 (0.5 C), 132.7 (0.5 C), 132.6 (0.5 C), 130.4 (0.5 C), 130.2 (0.5 C), 129.3 (2 C), 128.2 (3 C), 127.9, 127.7, 127.54, 127.47, 74.2 (0.5 C), 74.0 (0.5 C), 67.0 (0.5 C), 66.4 (0.5 C), 60.2 (0.5 C), 59.4 (0.5 C), 46.9 (0.5 C), 46.4 (0.5 C), 31.7, (0.5 C), 31.51 (0.5 C), 31.46 (0.5 C), 31.2 (0.5 C), 25.9 (0.5 C), 25.1 (1.5 C), 24.3 (0.5 C), 23.6 (0.5 C), 22.2, 13.7.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{32}NO_4$: 410.2331; found: 410.2335.

**Benzyl (*R**)-2-[(*R**)-1-(Benzoyloxy)hexyl]pyrrolidine-1-carboxylate (5c)**

Yield: 185 mg (87%); colorless oil.

IR (neat): 2957, 1715, 1409, 1271, 1108, 712 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 500 MHz): δ (two rotamers, 1:1) = 8.05 (br s, 1 H), 8.00 (br s, 1 H), 7.52 (t, *J* = 7.4 Hz, 1 H), 7.42–7.17 (m, 7 H), 5.29 (br s, 0.5 H), 5.21 (br s, 0.5 H), 5.12 (d, *J* = 12.2 Hz, 0.5 H), 5.05 (d, *J* = 12.8 Hz,

0.5 H), 5.00 (d, *J* = 12.6 Hz, 0.5 H), 4.92 (d, *J* = 12.0 Hz, 0.5 H), 4.24 (br s, 1 H), 3.62 (br s, 0.5 H), 3.47 (br s, 0.5 H), 3.39 (br s, 1 H), 2.00–1.62 (m, 5 H), 1.40–1.19 (m, 7 H), 0.83 (br s, 3 H).

$^{13}$C NMR ($CDCl_3$, 125 MHz): δ (two rotamers, 1:1) = 166.2 (0.5 C), 166.0 (0.5 C), 155.5 (0.5 C), 155.2 (0.5 C), 136.8 (0.5 C), 136.7 (0.5 C), 132.8, 130.3 (0.5 C), 130.2 (0.5 C), 129.8, 129.6, 128.3 (3 C), 127.95, 127.89, 127.7 (2 C), 75.7 (0.5 C), 75.3 (0.5 C), 67.0 (0.5 C), 66.6 (0.5 C), 59.6 (0.5 C), 58.8 (0.5 C), 47.1 (0.5 C), 46.5 (0.5 C), 31.6, 31.5 (0.5 C), 30.5 (0.5 C), 28.0 (0.5 C), 27.7 (0.5 C), 25.3, 23.9 (0.5 C), 23.3 (0.5 C), 22.4, 13.9.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{32}NO_4$: 410.2331; found: 410.2342.

**_tert_-Butyl (*R**)-2-[(*R**)-1-(Benzoyloxy)hexyl]pyrrolidine-1-carboxylate (5d)**

Yield: 167 mg (89%); colorless oil.

IR (neat): 2961, 2874, 1719, 1696, 1389, 1271, 1170, 1110, 711 cm$^{-1}$.

$^1$H NMR ($CDCl_3$, 500 MHz): δ (two rotamers, 1:1) = 8.04–7.98 (m, 2 H), 7.53–7.47 (m, 1 H), 7.42–7.37 (m, 2 H), 5.42 (br s, 0.5 H), 5.10 (br s, 0.5 H), 4.13 (br s, 0.5 H), 4.06 (br s, 0.5 H), 3.55 (br s, 0.5 H), 3.31 (br s, 1.5 H), 1.93–1.60 (m, 6 H), 1.50–1.32 (m, 2 H), 1.45 (s, 4 H), 1.23 (s, 9 H), 0.85–0.82 (m, 3 H).

$^{13}$C NMR ($CDCl_3$, 125 MHz): δ (two rotamers, 1:1) = 166.3 (0.5 C), 165.9 (0.5 C), 154.9 (0.5 C), 154.8 (0.5 C), 132.8 (0.5 C), 132.6 (0.5 C), 130.4, 129.8, 129.6, 128.3, 128.1, 79.7 (0.5 C), 78.9 (0.5 C), 75.4 (0.5 C), 75.1 (0.5 C), 58.9 (0.5 C), 58.6 (0.5 C), 46.8 (0.5 C), 46.5 (0.5 C), 31.6 (1.5 C), 29.6 (0.5 C), 28.4, 28.3, 28.2, 27.7 (0.5 C), 27.5 (0.5 C), 25.5 (0.5 C), 25.1 (0.5 C), 23.9 (0.5 C), 23.4 (0.5 C), 22.4, 13.9.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{34}NO_4$: 376.2488; found: 376.2491.

**(9*H*-Fluoren-9-yl)methyl (*R**)-2-[(*R**)-1-(Benzoyloxy)hexyl]pyrrolidine-1-carboxylate (5e)**

Yield: 182 mg (91%); colorless oil.

IR (neat): 2958, 2874, 2253, 1711, 1415, 1272, 1111, 905, 725 cm$^{-1}$.

$^1$H NMR ($CDCl_3$, 500 MHz): δ (two rotamers, 1:1) = 8.07 (d, *J* = 7.1 Hz, 1.2 H), 7.96 (br s, 0.8 H), 7.76–7.62 (m, 2.4 H), 7.49 (br s, 1.6 H), 7.42–7.25 (m, 7 H), 5.23 (br s, 1 H), 4.53 (br s, 0.4 H), 4.33–4.15 (m, 2 H), 4.10 (t, *J* = 9.6 Hz, 1 H), 3.93 (br s, 0.6 H), 3.58 (br s, 0.4 H), 3.52–3.43 (m, 1.2 H), 3.39 (br s, 0.4 H), 2.08–1.61 (m, 5 H), 1.45–1.24 (m, 7 H), 0.87 (br s, 3 H).

$^{13}$C NMR ($CDCl_3$, 125 MHz): δ (two rotamers, 0.6:0.4) = 165.2 (0.6 C), 165.9 (0.4 C), 155.3, 144.3 (0.6 C), 144.2 (0.4 C), 143.9 (0.4 C), 143.7 (0.6 C), 141.2 (1.2 C), 141.0 (0.8 C), 132.7, 130.1, 129.7 (1.2 C), 129.5 (0.8 C), 128.1 (2 C), 127.4, (2 C), 126.8 (2 C), 125.1, 125.0 (0.4 C), 124.8 (0.6 C), 119.7 (2 C) 75.5 (0.6 C), 74.8 (0.4 C), 67.1 (0.4 C), 66.9 (0.6 C), 59.6 (0.6 C), 59.2 (0.4 C), 47.3 (0.4 C), 47.1 (0.6 C), 46.8 (0.4 C), 46.4 (0.6 C), 31.6, 31.5 (0.6 C), 30.8 (0.4 C), 28.1 (0.4 C), 27.7 (0.6 C), 25.2, 23.9 (0.6 C), 23.0 (0.4 C), 22.4, 13.9.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{32}H_{36}NO$: 498.2644; found: 498.2650.

**Benzyl 3-[(Benzoyloxy)methyl]pyrrolidine-1-carboxylate (5f)**

Yield: 158 mg (93%); colorless oil.

IR (neat): 2951, 2880, 1696, 1416, 1267, 1096, 1069, 1025, 709 cm$^{-1}$.

$^1$H NMR ($CDCl_3$, 500 MHz): δ = 8.01 (d, *J* = 8.0 Hz, 2 H), 7.54 (t, *J* = 7.3 Hz, 1 H), 7.42 (t, *J* = 7.2 Hz, 2 H), 7.37–7.31 (m, 4 H), 7.31–7.27 (m, 1 H), 5.13 (s, 2 H), 4.38–4.30 (m, 1 H), 4.25–4.21 (m, 1 H), 3.71–3.62 (m, 1 H), 3.62–3.53 (m, 1 H), 3.47–3.39 (m, 1 H), 3.31 (t, *J* = 8.9 Hz, 0.5 H), 3.25 (t, *J* = 9.0 Hz, 0.5 H), 2.71–2.66 (m, 1 H), 2.10–2.05 (m, 1 H), 1.81–1.74 (m, 1 H).

$^{13}$C NMR ($CDCl_3$, 125 MHz): δ = 166.3, 154.7, 136.8, 133.0, 129.8, 129.5 (2 C), 128.4 (2 C), 128.3 (2 C), 127.9 (2 C), 127.8, 66.7, 65.7, 49.0 (0.5 C), 48.5 (0.5 C), 45.5 (0.5 C), 45.1 (0.5 C), 38.2 (0.5 C), 37.2 (0.5 C), 28.4 (0.5 C), 27.6 (0.5 C).

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{22}NO_4$: 340.1549; found: 340.1543.

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## Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588750.

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