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One-Pot Synthesis of α-Amino Acids through Carboxylation of Ammonium Ylides with CO_2 Followed by Alkyl Migration

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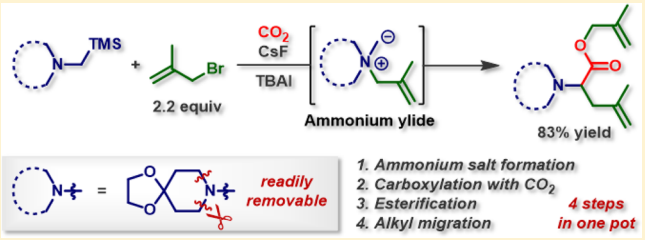
Supporting Information

ABSTRACT: A simple, yet powerful protocol for α-amino acid synthesis using carbon dioxide (CO_2) was developed. α-Amino silanes could undergo four successive reactions (formation of ammonium salt, carboxylation, esterification, and 2,3- or 1,2-Stevens rearrangement) in the presence of allylic or benzylic halides under a CO_2 atmosphere (1 atm). It is noteworthy that carboxylation at the position adjacent to a nitrogen atom proceeded via an ammonium ylide intermediate under mild conditions.



An α-amino carbanion is a synthetically useful intermediate for preparing α-substituted amino compounds such as amino acids, amino alcohols, and diamines. Since the α-hydrogen of amine derivatives is not acidic enough, the generation of an α-amino carbanion necessitated highly basic conditions in classical organic chemistry: (1) deprotonation of α-hydrogen of amine derivatives with a powerful base such as *n*-, *s*-, or *t*-BuLi;[1] (2) transmetalation of α-amino stannanes with organolithium (Sn−Li exchange);[1] and (3) reductive generation from imine equivalents with alkali metals or SmI_2.[2] In the former two cases, a chelating carbonyl group for a lithium cation (Boc, oxazolidinone, etc.) was introduced on the nitrogen atom to assist the event. In contrast, α-amino carbanions can also be accessed by treatment of α-amino silanes with a fluoride ion.[3] These desilylative methods require neither toxic stannane reagents nor strong reductants. Moreover, carbanion formation can proceed under almost neutral conditions. Therefore, the desilylative substitution would have great potential for the synthesis of a variety of amine compounds.

We have already developed desilylative carboxylation of α-amino silanes with CO_2,[4] an abundant, inexpensive, and relatively nontoxic C1 source,[5] to synthesize α-amino acids. Taking advantage of the accessibility of *N*-Boc-α-amino silanes from *N*-Boc-imines by silylation, we also developed a novel one-pot procedure for the synthesis of α-amino acids from imine precursors, α-amino sulfones. However, this carboxylation with CO_2 limitedly proceeded at the benzylic and allylic positions, so that only phenyl and alkenyl glycine derivatives were able to be prepared (Figure 1A). Thereby, we next turned our attention to how to prepare α-alkylated amino acids. In order to realize fast and quantitative generation of an α-carbanion without an α-substituent for delocalizing the resultant anion, we considered employing ammonium ylide derived from a silylmethyltrialkylammonium salt (Figure 1B). Desilylative formation of ammonium ylide and its applications have been widely studied by several research groups, and it was

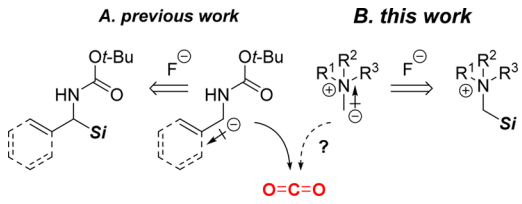


Figure 1. Our new strategy for carboxylation.

shown that ammonium ylide can be generated even without the assistance of the carbonyl group and charge delocalization by π-conjugation. In 1979, Vedejs and co-workers developed a method for the generation of ammonium ylides using tertiary amines with $TMSCH_2OTf$ followed by treatment of CsF.[6a] This method has advantages over the use of organolithium reagents[7] including (1) regioselective generation of ylides from the corresponding ammonium salts and (2) high functional group tolerability under mild conditions. There were several reports with regard to intramolecular rearrangements[6] and ring expansion reactions.[8] However, reactions of ammonium ylides generated in this manner with carbonyl compounds have been limited, and only the reaction with aldehydes was reported.[9] If this species can react with CO_2 selectively with suppression of rearrangement/ring expansion, the framework of an α-amino acid would be created.

Our synthetic plan for α-alkylated α-amino acids is shown in Scheme 1. α-Amino silane, which is prepared from an amine and $TMSCH_2Cl$, is alkylated with an allylic halide to form an ammonium salt. A fluoride ion such as CsF would then promote the formation of ammonium ylide followed by carboxylation with CO_2, affording ammonium carboxylate. It would undergo 2,3-allylic rearrangement (2,3-Stevens rearrangement[10,11]) in the presence of an appropriate base after

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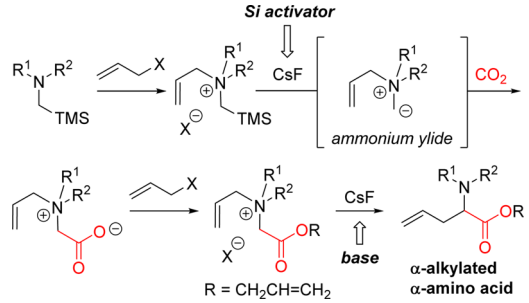
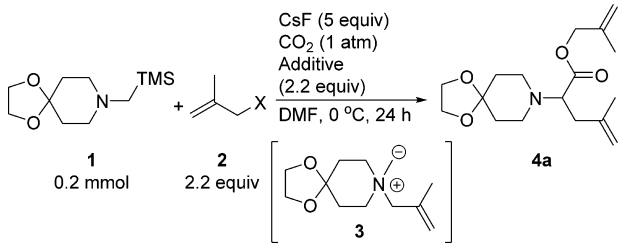
Scheme 1. Plan for the Synthesis of α-Alkylated α-Amino Acids



esterification with allylic halide. If the base-induced 2,3-allylic rearrangements of ammonium ester can be mediated by the fluoride as well, all steps would be carried out in a single flask as a one-pot operation.

To determine the feasibility of the planned one-pot α-amino acid synthesis, α-amino silane **1** was treated with β-methallyl iodide (2.2 equiv) and CsF (5 equiv) in DMF at 0 °C for 24 h under CO_2 (1 atm: balloon). The desired one-pot reaction actually proceeded to afford the corresponding α-amino ester **4a** in 60% yield (Table 1, entry 1). The use of β-methallyl bromide instead of the iodide decreased the yield to some extent (entry 2). We then attempted in situ generation of the reactive β-methallyl iodide by adding an iodide salt. Although the yields did not improve with alkali metal iodides (entries 3 and 4), tetrabutylammonium iodide (TBAI) greatly accelerated the reaction, affording the desired product in 73% yield (entry 5). A larger-scale synthesis (5 mmol) improved the yield to 83% (entry 6). To confirm the role of TBAI, several reaction conditions were investigated. The substrate **1** was completely consumed even without CsF, but intermediate **A** depicted in Scheme 3 was obtained quantitatively (entry 7). This result suggested that the iodide ion of TBAI was not involved in silane activation. The addition of a catalytic amount of TBAI or a stoichiometric amount of tetrabutylammonium bromide (TBAB) instead of TBAI was not effective (entries 8 and 9). According to these results, TBAI is thought to be a stoichiometric iodide source to form β-methallyl iodide in situ, rather than either a silane activator or a phase transfer catalyst. Furthermore, the combination with TBAI actually worked well for less reactive β-methallyl chloride and tosylate (entries 10 vs 11 and entries 12 vs 13).

Table 1. Condition Screening



entry	temp (°C)	X	additive	yield (%)[a]
1	0	I (**2aa**)	–	60
2	0	Br (**2ab**)	–	40
3	0	Br	NaI	0
4	0	Br	KI	34
5	0	Br	TBAI	73 (66)
6[b]	0	Br	TBAI	(83)
7[c]	0	Br	TBAI	0
8[d]	0	Br	TBAI	46
9	0	Br	TBAB	32
10	rt	Cl (**2ac**)	–	0
11	rt	Cl	TBAI	43
12	rt	OTs (**2ad**)	–	32
13	rt	OTs	TBAI	70

[a]Yields were determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. Isolated yields are given in parentheses. [b]Conducted in 5 mmol scale. [c]Without CsF. [d]20 mol % of TBAI was added.

With the optimal conditions in hand, we then investigated the substrate scope for allylic halides (Figure 2). The use of β-substituted and nonsubstituted allylic halides gave **4a–c** in good yields. The reaction with allyl bromide was readily scalable, and the product **4c** was obtained with 2.2 g (10 mmol). α-Amino acids **4d** and **4e** were obtained in high yields with 1:1 dr from γ-monosubstituted allylic chloride and bromide. γ-Disubstituted and fully substituted allylic bromides were also applicable, affording **4f–h** in good yields. The different substitution pattern between the ester moieties and the α-alkyl groups in **4d–h** indicated that α-alkylation should occur via 2,3-Stevens rearrangement. Moreover, benzylic halides were also active in this one-pot carboxylation. When benzyl bromide and benzyl chlorides with an electron-donating substituent at the *para*-position were employed, 1,2-Stevens rearrangement products **4i–k** were selectively obtained in moderate yields. In contrast, when *p*-bromobenzyl bromide was used, the migration pattern was changed to 2,3-allylic rearrangement (Sommelet–Hauser rearrangement[10,11]), affording **4l** as a major product.[11a] Furthermore, one-pot reactions with 1-naphthylmethyl chloride and 2-naphthylmethyl bromide also selectively promoted Sommelet–Hauser rearrangement to afford **4m** and **4n** in good yields. Sommelet–Hauser rearrangement is comprised of 2,3-allylic rearrangement and the following rearomatization. Depending on substrate structures, however, an isotoluene intermediate was sometimes obtained ahead of rearomatization as a stable product.[6c,12] Sato and coworkers demonstrated that rearomatization of the isotoluene intermediate was facilitated by DBU.[6e] According to their report, after completion of the reactions of *p*-bromobenzyl bromide and 2-naphthylmethyl bromide, the resulting mixtures were treated with 5 equiv of DBU to afford the products **4l** and **4n** in 52% and 57% yield, respectively.

To obtain information about the reaction course, we first conducted carboxylation in the absence of allylic halide (Scheme 2a). The substrate was completely recovered at room temperature. Even when the reaction was conducted at a high temperature (150 °C, in NMP), **5** was obtained only in 26% yield after esterification. This result clearly indicated that the formation of ammonium ylide was inevitable for carboxylation with CO_2. Next, potential intermediates (**A**, **B**, and **C**) in this one-pot reaction were prepared and subjected to the reaction conditions (Schemes 2b–d). In all cases, α-amino acid **4a** was obtained in yields comparable to that of the one-pot reaction (83% yield). Furthermore, 2,3-Stevens rearrangement of **B** did not proceed in the absence of allylic halide, suggesting that esterification is indispensable for the following base-induced alkyl migration (Scheme 2e).

Based on the above experimental data, we propose a reasonable reaction mechanism for the one-pot α-amino acid synthesis from α-amino silane and CO_2 (Scheme 3). The

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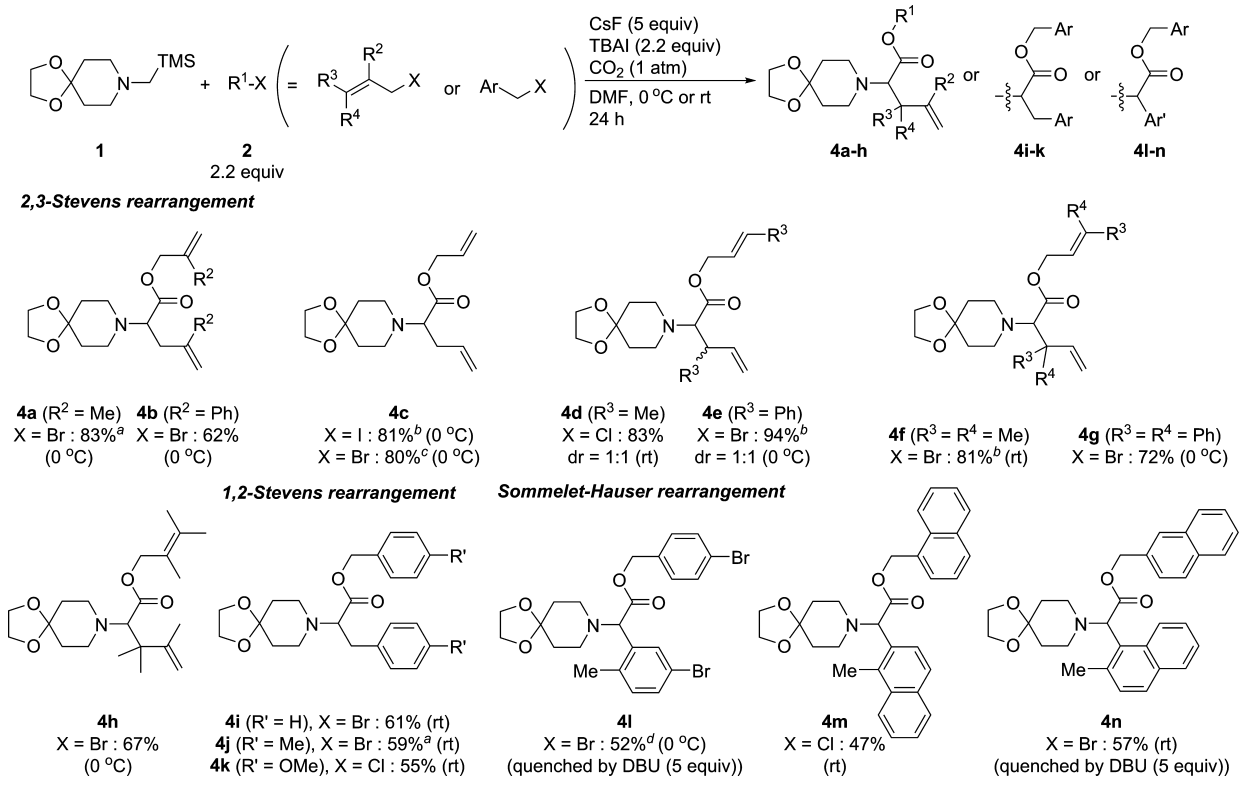
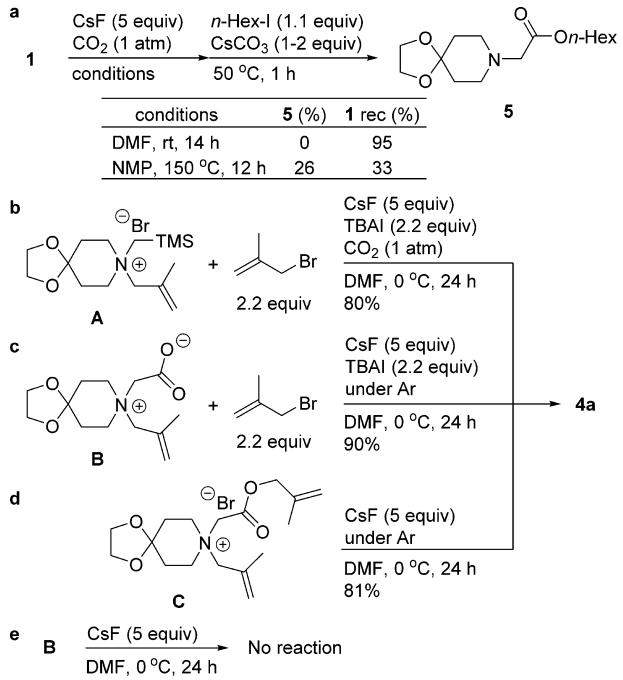
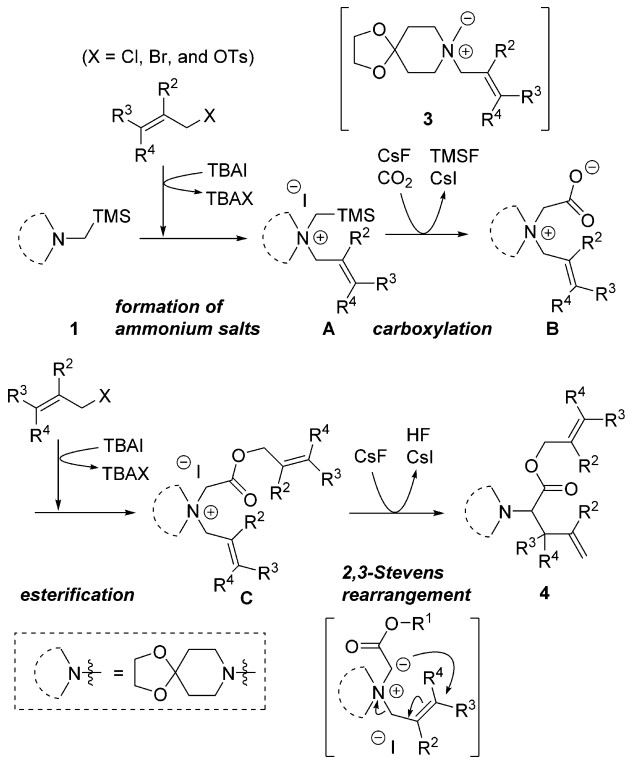


Figure 2. Substrate scope for α-amino acid synthesis (0.2 mmol scale). Isolated yields are shown unless otherwise noted. [a] Conducted in 5 mmol scale. [b] Without TBAI. [c] Conducted in 10 mmol scale for **4c**. [d] Determined by ^{1}H NMR. Isolated yield was 38%.

Scheme 2. Mechanistic Studies



Scheme 3. Proposed Reaction Pathway



reaction is initiated by the formation of ammonium salt **A** from α-amino silane **1** and allylic halide followed by fluoride-mediated silane activation to generate ammonium ylide **3**. Carboxylation then takes place to give zwitterionic ammonium carboxylate **B**, which is esterified by an excess amount of allylic halide to form ammonium ester **C**. Finally, base-promoted 2,3-Stevens rearrangement of **C** occurs to afford the target α-amino acid **4**. In this reaction sequence, CsF functions as both a silane activator and a base to promote the formation of ammonium ylides (the former: unstable ylide **3** to react with CO_2; the latter: stable ylide to undergo allylic rearrangement). TBAI

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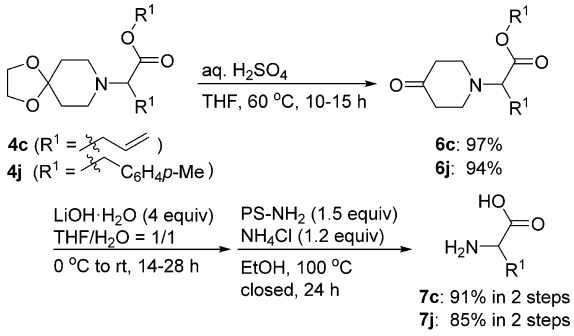
should accelerate both the formation of ammonium salt and esterification by halide exchange with less reactive allylic compounds (Cl, Br, and OTs). Notably, four successive reactions proceeded in a single flask as a one-pot operation.

Considering the synthetic utility of the products, the removal of the protecting group was demonstrated (Scheme 4). Carreira

Scheme 4. Removal of the Protecting Group



and co-workers reported the removal of 4-piperidone by using aminomethylated polystyrene resin to afford the corresponding primary amine.[13] According to their report, we then investigated deprotection of the piperidone acetal moiety of compounds **4c** (R^1 = allyl) and **4j** (R^1 = *p*-methylbenzyl). Acidic hydrolysis of acetal moieties gave **6c** and **6j** in nearly quantitative yields. Saponification of the ester was conducted followed by heating with the basic resin in the presence of NH_4Cl in EtOH. The transfer alkylation cleanly proceeded, and the unprotected α-amino acids **7c** and **7j** were obtained in 91% and 85% yields, respectively, in two steps after purification using acidic ion-exchange column chromatography (Dowex 50W-X2).

In summary, we have developed a simple but powerful method for α-amino acid synthesis with CO_2. The reaction cascade consists of four consecutive transformations (formation of ammonium salt, carboxylation, esterification, and alkyl migration). Various substituted allylic halides and benzylic halides can be used to afford α-alkylated α-amino acid derivatives.

EXPERIMENTAL SECTION

General. NMR spectra were recorded on 500 MHz (^{1}H) and 125 MHz (^{13}C) instruments. Chemical shifts were reported in the scale relative to $CHCl_3$ (7.26 ppm), C_6D_6 (7.16 ppm), acetone-d_6 (2.05 ppm), and D_2O (4.79 ppm) for ^{1}H NMR and to $CDCl_3$ (77.00 ppm), C_6D_6 (128.06 ppm), and acetone-d_6 (206.26 ppm) for ^{13}C NMR as internal references. For D_2O, chemical shifts were reported in the scale relative to CH_3OH (49.50 ppm) for ^{13}C NMR as an external standard. High-resolution mass spectra were obtained with EI-HRMS (TOF) and ESI-HRMS (orbitrap) instruments. Column chromatography was performed with neutral silica gel (40−50 μm). In general, all manipulations were performed under an argon atmosphere unless otherwise stated. Dry DMF was purified under argon using a solvent purification system.

Synthesis of α-Amino Silane 1. In a round-bottom flask, 1,4-dioxa-8-azaspiro[4.5]decane (1.3 mL, 10 mmol), chloromethyltrimethylsilane (1.7 mL, 11 mmol, 1.1 equiv), potassium carbonate (1.5 g, 11 mmol, 1.1 equiv), and potassium iodide (3.0 g, 18 mmol, 1.8 equiv) in DMF (10 mL, 1.0 M) were stirred for 5 h at 80 °C. Water was added to quench the reaction. The product was extracted with AcOEt three times, and the combined organic layer was washed with water followed by brine and then dried over Na_2SO_4. After the solvent was removed under reduced pressure, the crude product was purified by silica gel column chromatography (hexane/AcOEt, 5/1 to 2/1) to afford α-amino silane **1** (2.0 g, 8.7 mmol, 87% yield) as a colorless oil.

*8-((Trimethylsilyl)methyl)-1,4-dioxa-8-azaspiro[4.5]decane (**1**).* IR (neat): 2953, 2881, 2796, 1363, 1303, 1248, 1140, 1092, 1041, 850 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.91 (s, 4H), 2.52−2.36 (m, 4H), 1.91 (s, 2H), 1.74−1.63 (m, 4H), 0.03 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 106.9, 64.1, 55.2, 50.3, 35.0, −1.3 ppm; HRMS (EI) *m*/*z* calcd for $C_{11}H_{23}O_2NSi$ [M]$^+$: 229.1498. Found: 229.1491.

Supply of Allylic and Benzylic Halides. Allylic halides **2aa**,[14] **2b**,[15] **2g**,[16] and **2h**[17] were prepared according to the reported methods. Allylic tosylate **2ad** was prepared from 3-chloro-2-methylpropene using the reported method.[18] The NMR data for **2ad** were identical to those for the reported product.[19] Other allylic/benzylic halides are commercially available.

General Procedure of One-Pot Synthesis of α-Amino Acids. A test tube was charged with CsF (151.9 mg, 1.0 mmol, 5 equiv), which was dried with a heat gun for 2 min under vacuum (<5 mmHg at ca. 400 °C). After the displacement with CO_2 gas, TBAI (162.5 mg, 0.44 mmol, 2.2 equiv) was added followed by α-amino silane **1** (45.9 mg, 0.20 mmol) in DMF (1 mL, 0.2 M). After the reaction mixture was cooled to 0 °C, 3-bromo-2-methyl-1-propene **2ab** (45 μL, 0.44 mmol, 2.2 equiv) was added and the solution was stirred for 24 h at the same temperature. The reaction was quenched by the addition of water. The product was extracted with AcOEt three times, washed with water followed by brine and then dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The yield was determined by ^{1}H NMR at this stage using 1,3,5-trimethoxybenzene (δ = 6.1 ppm in $CDCl_3$, 3H) as an internal standard (73%). The crude product was purified by silica gel column chromatography (hexane/AcOEt, 5/1 to 2/1) to afford **4a** (40.8 mg, 131.9 mmol, 66% yield) as a colorless oil.

*2-Methylallyl 4-Methyl-2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-pent-4-enoate (**4a**).* Colorless oil (5 mmol scale in 0.4 M DMF, 1.29 g, 4.16 mmol, 83% yield); IR (neat): 3078, 2958, 2881, 1733, 1651, 1442, 1162, 1092, 1039, 910 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.00 (s, 1H), 4.93 (s, 1H), 4.77 (s, 1H), 4.73 (s, 1H), 4.51 (s, 2H), 3.93 (s, 4H), 3.48 (dd, *J* = 9.3, 5.9 Hz, 1H), 2.80−2.71 (m, 2H), 2.70−2.62 (m, 2H), 2.54 (dd, *J* = 14.2, 9.3 Hz, 1H), 2.35 (dd, *J* = 14.2, 5.9 Hz, 1H), 1.78−1.64 (m, 10H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 171.3, 141.9, 139.8, 113.3, 112.6, 107.2, 67.4, 65.9, 64.2, 47.5, 37.7, 35.4, 22.4, 19.6 ppm; HRMS (EI) *m*/*z* calcd for $C_{17}H_{27}O_4N$ [M]$^+$: 309.1940. Found: 309.1937.

*2-Phenylallyl 4-Phenyl-2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-pent-4-enoate (**4b**).* Colorless oil (0.2 mmol scale, 53.7 mg, 123.9 μmol, 62% yield); IR (neat): 3056, 2956, 1732, 1634, 1496, 1316, 1161, 1089, 909, 778 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.43−7.38 (m, 2H), 7.36−7.22 (m, 8H), 5.53 (s, 1H), 5.34 (s, 1H), 5.19 (s, 1H), 5.04 (s, 1H), 4.99 (d, *J* = 13.8 Hz, 1H), 4.93 (d, *J* = 13.8 Hz, 1H), 3.92 (s, 4H), 3.32 (dd, *J* = 9.1, 6.1 Hz, 1H), 2.92 (dd, *J* = 14.3, 9.1 Hz, 1H), 2.83 (dd, *J* = 14.3, 6.1 Hz, 1H), 2.72−2.62 (m, 2H), 2.61−2.48 (m, 2H), 1.70−1.50 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 171.2, 145.1, 142.5, 140.7, 138.0, 128.4, 127.9, 127.4, 126.3, 126.1, 115.6, 115.0, 107.1, 66.0, 65.4, 64.1, 47.4, 35.5, 35.2 ppm; HRMS (EI) *m*/*z* calcd for $C_{27}H_{31}O_4N$ [M]$^+$: 433.2253. Found: 433.2244.

*Allyl 2-(1,4-Dioxa-8-azaspiro[4.5]decan-8-yl)pent-4-enoate (**4c**).* Yellow oil (10 mmol of allyl bromide **2c** were used in 0.4 M DMF, 2.24 g, 8.0 mmol, 80% yield); IR (neat): 3079, 2956, 2833, 1732, 1643, 1364, 1166, 1088, 1039, 914 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.97−5.87 (m, 1H), 5.83−5.72 (m, 1H), 5.33 (d, *J* = 16.9 Hz, 1H), 5.23 (d, *J* = 10.3 Hz, 1H), 5.09 (d, *J* = 16.9 Hz, 1H), 5.04 (d, *J* = 10.3 Hz, 1H), 4.61 (d, *J* = 5.5 Hz, 1H), 3.93 (s, 4H), 3.31 (dd, *J* = 8.5, 6.5 Hz, 1H), 2.77−2.70 (m, 2H), 2.68−2.61 (m, 2H), 2.57−2.48 (m, 1H), 2.46−2.37 (m, 1H), 1.78−1.65 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 171.1, 134.3, 132.2, 118.3, 117.2, 107.1, 67.2, 64.8, 64.1, 47.6, 35.3, 33.9 ppm; HRMS (EI) *m*/*z* calcd for $C_{12}H_{18}O_4N$ [M-($CH_2CH{=}CH_2$)]$^+$: 240.1236. Found: 240.1236.

*(E)-But-2-en-1-yl 3-Methyl-2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)pent-4-enoate (**4d**).* Colorless oil (0.2 mmol scale, 51.3 mg, 165.8 μmol, 83% yield with 1:1 dr); IR (neat): 3078, 2959, 2880, 1729, 1456, 1340, 1224, 1146, 1088, 966 cm^{-1}; ^{1}H NMR (diastereomixture:

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500 MHz, $CDCl_3$) δ = 5.86−5.71 (m, 3H), 5.65−5.50 (m, 3H), 5.06−4.92 (m, 4H), 4.53 (d, J = 7.0 Hz, 2H), 4.48 (d, J = 7.0 Hz, 2H), 3.92 (s, 4H), 3.90 (s, 4H), 2.96 (d, J = 11.0 Hz, 1H), 2.90 (d, J = 11.0 Hz, 1H), 2.74−2.58 (m, 6H), 2.57−2.47 (m, 4H), 1.76−1.56 (m, 14H), 1.03 (d, J = 6.3 Hz, 3H), 0.94 (d, J = 6.3 Hz, 3H) ppm; ^{13}C NMR (diastereomixture: 125 MHz, $CDCl_3$) δ = 170.6, 170.5, 141.0, 140.3, 131.4, 131.1, 125.3, 125.2, 115.6, 113.7, 107.32, 107.30, 72.5, 72.1, 64.6, 64.4, 64.11, 64.09, 47.3, 37.2, 36.6, 35.4, 17.74, 17.71, 17.4, 16.7 ppm; HRMS (EI) m/z calcd for $C_{13}H_{20}O_4N$ [M-(CH_2CH=$CHCH_3$)]$^+$: 254.1392. Found: 254.1395.

*Cinnamyl 3-Phenyl-2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)pent-4-enoate (**4e**).* White solids (0.2 mmol scale, 81.4 mg, 187.8 μmol, 94% yield with 1:1 dr); mp 98−100 °C; IR (neat): 3027, 2955, 2835, 1727, 1494, 1341, 1220, 1156, 1087, 917 cm^{-1}; ^{1}H NMR (diastereomixture: 500 MHz, C_6D_6) δ = 7.25 (d, J = 7.0 Hz, 2H), 7.21 (d, J = 7.0 Hz, 2H), 7.14−6.97 (m, 16H), 6.44 (d, J = 15.8 Hz, 1H), 6.29−6.11 (m, 3H), 6.01−5.91 (m, 1H), 5.80 (dt, J = 15.8, 6.3 Hz, 1H), 5.20 (d, J = 17.0 Hz, 1H), 5.05 (d, J = 10.3 Hz, 1H), 5.01 (d, J = 10.3 Hz, 1H), 4.97 (d, J = 17.0 Hz, 1H), 4.73−4.63 (m, 2H), 4.37 (d, J = 6.0 Hz, 2H), 4.06−3.98 (m, 2H), 3.74 (d, J = 3.8 Hz, 1H), 3.72 (d, J = 3.8 Hz, 1H), 3.50 (s, 4H), 3.40 (s, 4H), 3.13−3.03 (m, 2H), 3.02−2.92 (m, 2H), 2.86−2.77 (m, 2H), 2.76−2.67 (m, 2H), 1.92−1.65 (m, 4H), 1.61−1.51 (m, 2H), 1.49−1.39 (m, 2H) ppm; ^{13}C NMR (diastereomixture: 125 MHz, C_6D_6) δ = 169.9, 169.2, 141.5, 141.2, 139.7, 139.4, 136.9, 134.3, 133.8, 129.1, 128.82, 128.79, 128.57, 128.49, 128.3, 128.01, 127.97, 127.1, 127.02, 126.6, 124.0, 123.9, 116.7, 115.7, 107.6, 107.4, 72.3, 71.3, 64.7, 64.4, 64.2, 64.1, 50.0, 49.4, 48.0, 36.1, 35.8 ppm; HRMS (EI) m/z calcd for $C_{18}H_{22}O_4N$ [M-(CH_2CH=CHC_6H_5)]$^+$: 316.1549. Found: 316.1547.

*3-Methylbut-2-en-1-yl 3,3-Dimethyl-2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)pent-4-enoate (**4f**).* Colorless oil (0.2 mmol scale, 54.8 mg, 162.4 μmol, 81% yield); IR (neat): 2957, 2877, 1732, 1442, 1363, 1214, 1138, 1084, 1040, 912 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.11 (dd, J = 17.1, 11.8 Hz, 1H), 5.40−5.34 (m, 1H), 5.00 (d, J = 17.7 Hz, 1H), 4.96 (d, J = 11.8 Hz, 1H), 4.63−4.54 (m, 2H), 3.92 (s, 4H), 2.98 (s, 1H), 2.96−2.88 (m, 2H), 2.51−2.42 (m, 2H), 1.75 (s, 3H), 1.73−1.62 (m, 7H), 1.13 (s, 3H), 1.06 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 170.3, 145.2, 138.9, 118.8, 111.9, 107.1, 75.5, 64.1, 60.4, 50.3, 40.4, 35.6, 25.6, 25.4, 23.6, 18.0 ppm; HRMS (EI) m/z calcd for $C_{14}H_{22}O_4N$ [M-(CH_2CH=$C(CH_3)_2$]$^+$: 268.1549. Found: 268.1551.

*3,3-Diphenylallyl 3,3-Diphenyl-2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)pent-4-enoate (**4g**).* Yellow amorphous solid (0.2 mmol scale, 84.5 mg, 144.3 μmol, 72% yield); IR (neat): 3021, 2955, 2830, 1734, 1495, 1444, 1219, 1149, 1079, 756 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ = 7.46−7.11 (m, 21H), 5.98 (t, J = 7.0 Hz, 1H), 5.33 (d, J = 10.8 Hz, 1H), 4.59 (d, J = 17.8 Hz, 1H), 4.52 (dd, J = 12.5, 7.0 Hz, 1H), 4.44 (dd, J = 12.5, 7.0 Hz, 1H), 3.89 (s, 4H), 2.98−2.88 (m, 2H), 2.64−2.47 (m, 2H), 1.71−1.56 (m, 4H) ppm; ^{13}C NMR (125 MHz, acetone-d_6) δ = 168.8, 146.9, 146.1, 145.9, 143.8, 142.5, 139.7, 130.9, 130.6, 130.2, 129.4, 129.2, 128.83, 128.80, 128.61, 128.57, 128.1, 127.4, 127.0, 123.7, 118.1, 107.4, 77.4, 64.9, 62.4, 58.3, 51.7, 36.6 ppm; MS (ESI) m/z calcd for $C_{39}H_{39}O_4NNa$ [M + Na]$^+$: 608.29. Found: 608.28; HRMS (EI) m/z calcd for $C_{39}H_{39}O_4N$ [M]$^+$: 585.2879. Found: 585.2869.

*2,3-Dimethylbut-2-en-1-yl 3,3,4-Trimethyl-2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)pent-4-enoate (**4h**).* White solids (0.2 mmol scale, 49.3 mg, 134.9 μmol, 67% yield); mp 52−54 °C; IR (neat): 2957, 2926, 2881, 1733, 1634, 1451, 1363, 1121, 1082, 912 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.78 (s, 1H), 4.77 (s, 1H), 4.57 (d, J = 11.8 Hz, 1H), 4.54 (d, J = 11.8 Hz, 1H), 3.91 (s, 4H), 3.26 (s, 1H), 2.98−2.87 (m, 2H), 2.58−2.45 (m, 2H), 1.79−1.60 (m, 16H), 1.17 (s, 3H), 1.15 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 170.8, 151.1, 131.8, 122.8, 110.8, 107.1, 73.5, 64.9, 64.1, 50.7, 43.0, 35.7, 25.4, 22.8, 20.9, 20.4, 20.3, 17.2 ppm; HRMS (EI) m/z calcd for $C_{15}H_{24}O_4N$ [M-($CH_2C(CH_3)$=$C(CH_3)_2$]$^+$: 282.1705. Found: 282.1706.

*Benzyl 3-Phenyl-2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-propanoate (**4i**).* Colorless oil (0.2 mmol scale, 46.3 mg, 121.4 μmol, 61% yield); IR (neat): 2957, 2882, 1731, 1604, 1455, 1215, 1144, 1038, 911, 734 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.32−7.14 (m, 10H), 5.08 (d, J = 12.0 Hz, 1H), 5.04 (d, J = 12.0 Hz, 1H), 3.95 (s, 4H), 3.55 (dd, J = 9.6, 5.7 Hz, 1H), 3.10 (dd, J = 13.4, 9.6 Hz, 1H), 2.97 (dd, J = 13.4, 5.7 Hz, 1H), 2.88−2.80 (m, 2H), 2.75−2.66 (m, 2H), 1.81−1.65 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 171.1, 138.0, 135.7, 129.2, 128.4, 128.3, 128.1, 126.3, 107.1, 69.4, 65.9, 64.2, 47.8, 35.8, 35.3 ppm; HRMS (EI) m/z calcd for $C_{16}H_{20}O_4N$ [M-($CH_2C_6H_5$)]$^+$: 290.1392. Found: 290.1391.

*4-Methylbenzyl 2-(1,4-Dioxa-8-azaspiro[4.5]decan-8-yl)-3-(p-tolyl)propanoate (**4j**).* Colorless oil (5 mmol scale in 0.4 M DMF, 1.21 g, 2.95 mmol, 59% yield); IR (neat): 2956, 2881, 1732, 1517, 1159, 1088, 1040, 912, 805, 734 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.13−7.01 (m, 8H), 5.03 (d, J = 12.0 Hz, 1H), 4.98 (d, J = 12.0 Hz, 1H), 3.95 (s, 4H), 3.50 (dd, J = 9.9, 5.8 Hz, 1H), 3.04 (dd, J = 13.2, 9.9 Hz, 1H), 2.92 (dd, J = 13.2, 5.8 Hz, 1H), 2.85−2.76 (m, 2H), 2.74−2.65 (m, 2H), 2.35 (s, 3H), 2.31 (s, 3H), 1.80−1.63 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 171.3, 137.8, 135.7, 134.9, 132.7, 129.04, 129.03, 128.9, 128.3, 107.1, 69.5, 65.8, 64.1, 47.8, 35.4, 35.3, 21.2, 21.0 ppm; HRMS (EI) m/z calcd for $C_{17}H_{22}O_4N$ [M-($CH_2C_6H_4CH_3$)]$^+$: 304.1549. Found: 304.1541.

*4-Methoxybenzyl 3-(4-Methoxyphenyl)-2-(1,4-dioxa-8-azaspiro-[4.5]decan-8-yl)propanoate (**4k**).* White solids (0.2 mmol scale, 48.6 mg, 110.1 μmol, 55% yield); mp 62−64 °C; IR (neat): 2957, 2836, 1730, 1613, 1515, 1249, 1145, 1088, 1037, 912 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ = 7.18 (d, J = 8.5 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 6.79 (d, J = 8.0 Hz, 2H), 5.03 (d, J = 13.0 Hz, 1H), 4.98 (d, J = 13.0 Hz, 1H), 3.89 (s, 4H), 3.79 (s, 3H), 3.76 (s, 3H), 3.54−3.39 (m, 1H), 2.98 (dd, J = 13.0, 9.5 Hz, 1H), 2.89−2.74 (m, 3H), 2.68−2.54 (m, 2H), 1.70−1.53 (m, 4H) ppm; ^{13}C NMR (125 MHz, acetone-d_6) δ = 171.7, 160.6, 159.3, 131.3, 131.2, 130.9, 129.3, 114.7, 114.5, 107.7, 70.3, 66.0, 64.8, 55.7, 55.5, 48.5, 36.4, 35.6 ppm; HRMS (EI) m/z calcd for $C_{17}H_{22}O_5N$ [M-($CH_2C_6H_4OCH_3$)]$^+$: 320.1498. Found: 320.1496.

*4-Bromobenzyl 2-(5-Bromo-2-methylphenyl)-2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)acetate (**4l**).* After 24 h, CO_2 was released and then DBU (149 μL, 1.0 mmol, 5 equiv) was added. The reaction mixture was stirred at 0 °C for 5 h. The yield of the product **4l** was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene (δ = 6.1 ppm in $CDCl_3$, 3H) as an internal standard (52%) after the extraction. The crude mixture was purified by GPC to afford **4l**. Colorless amorphous solid (0.2 mmol scale, 40.8 mg, 75.7 μmol, 38% yield); IR (neat): 2957, 2880, 2823, 1741, 1488, 1368, 1217, 1144, 1091, 754 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.64 (s, 1H), 7.42 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.3 Hz, 1H), 7.06 (d, J = 8.3 Hz, 2H), 7.01 (d, J = 8.3 Hz, 1H), 5.06 (s, 2H), 4.28 (s, 1H), 3.93 (s, 4H), 2.58−2.50 (m, 4H), 2.32 (s, 3H), 1.76−1.68 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 170.8, 136.7, 136.2, 134.5, 132.2, 131.6, 131.03, 130.99, 129.6, 122.3, 120.0, 107.0, 69.2, 64.2, 48.9, 34.8, 19.2 ppm; HRMS (EI) m/z calcd for $C_{16}H_{19}BrO_4N$ [M-($CH_2C_6H_4Br$)]$^+$: 368.0498. Found: 368.0499.

*Naphthalen-1-ylmethyl 2-(1-Methylnaphthalen-2-yl)-2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)acetate (**4m**).* White amorphous soild (0.2 mmol scale, 44.8 mg, 93.0 μmol, 47% yield); IR (neat): 2958, 2881, 1741, 1511, 1367, 1229, 1144, 1095, 947, 755 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ = 8.05 (d, J = 8.0 Hz, 1H), 7.88−7.81 (m, 3H), 7.77−7.68 (m, 3H), 7.56−7.49 (m, 2H), 7.44 (d, J = 7.0 Hz, 1H), 7.41 (dd, J = 8.0, 7.0 Hz, 1H), 7.35 (dd, J = 8.0, 7.0 Hz, 1H), 7.21 (dd, J = 8.0, 7.0 Hz, 1H), 5.56 (d, J = 12.8 Hz, 1H), 5.53 (d, J = 12.8 Hz, 1H), 4.68 (s, 1H), 3.86 (s, 4H), 2.66 (s, 3H), 2.64−2.50 (m, 4H), 1.68−1.55 (m, 4H) ppm; ^{13}C NMR (125 MHz, acetone-d_6) δ = 172.0, 134.7, 134.3, 134.2, 133.9, 133.2, 132.6, 132.5, 130.1, 129.4, 129.3, 128.2, 127.24, 127.20, 127.02, 127.00, 126.79, 126.75, 126.1, 125.4, 124.5, 107.6, 70.9, 65.5, 64.9, 49.7, 36.0, 14.6 ppm; HRMS (EI) m/z calcd for $C_{20}H_{22}O_4N$ [M-($CH_2C_{10}H_7$)]$^+$: 340.1549. Found: 340.1544.

*Naphthalen-2-ylmethyl 2-(2-Methylnaphthalen-1-yl)-2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)acetate (**4n**).* After 24 h, CO_2 was released and then DBU (149 μL, 1.0 mmol, 5 equiv) was added. The reaction mixture was stirred at rt for 5 h. White solids (0.2 mmol scale, 55.3 mg, 114.8 μmol, 55% yield); mp 125−127 °C; IR (neat): 3051, 2958, 2816, 1746, 1508, 1366, 1144, 1096, 815, 752 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ = 9.18 (d, J = 10.0 Hz, 1H), 7.87−7.77 (m,

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3H), 7.69 (d, J = 9.0 Hz, 1H), 7.61−7.54 (m, 1H), 7.48−7.37 (m, 5H), 7.33 (s, 1H), 7.11 (d, J = 8.5 Hz, 1H), 5.27 (d, J = 13.3 Hz, 1H), 5.12 (d, J = 13.3 Hz, 1H), 5.02 (s, 1H), 3.88 (s, 4H), 2.85−2.65 (m, 5H), 2.45−2.35 (m, 2H), 1.73−1.59 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 171.8, 137.2, 134.2, 134.1, 133.9, 133.6, 130.9, 130.6, 129.6, 129.0, 128.9, 128.8, 128.5, 127.4, 127.1, 127.0, 126.7, 126.6, 126.1, 125.8, 107.6, 69.6, 66.5, 64.9, 50.3, 36.1, 22.0 ppm; HRMS (EI) m/z calcd for $C_{20}H_{22}O_4N$ [M-($CH_2C_{10}H_7$)]$^+$: 340.1549. Found: 340.1540.

Carboxylation of α-Amino Silane 1. A test tube was charged with CsF (152 mg, 1.0 mmol, 5 equiv), which was dried with a heat gun for 2 min under vacuum (<5 mmHg at ca. 400 °C). After the displacement with CO_2 gas, α-amino silane **1** (45.9 mg, 0.20 mmol) in NMP (2 mL, 0.1 M) was added. After the reaction mixture was heated to 150 °C, the solution was stirred for 24 h at the same temperature. CO_2 was released, and then hexyl iodide (35 mL, 0.24 mmol, 1.2 equiv) was added followed by Cs_2CO_3 (65.2 mg, 0.20 mmol, 1.0 equiv); the reaction mixture was stirred for 1 h at 50 °C. The reaction was quenched by the addition of water. The product was extracted with AcOEt three times, and the combined organic layers were washed with water followed by brine and then dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The yield was determined by ^{1}H NMR at this stage using 1,3,5-trimethoxybenzene (δ = 6.1 ppm in $CDCl_3$, 3H) as an internal standard (26% of **5** and 33% of recovered substrate). The crude product was purified by silica gel column chromatography (hexane/AcOEt, 5/1 to 1/1) to afford **5** (15.5 mg, 54.3 μmol, 27% yield) as a colorless oil.

*Hexyl 2-(1,4-Dioxa-8-azaspiro[4.5]decan-8-yl)acetate (**5**).* IR (neat): 2957, 2931, 2251, 1744, 1468, 1187, 1098, 1040, 914, 732 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.10 (t, J = 6.8 Hz, 2H), 3.93 (s, 4H), 3.21 (s, 2H), 2.69−2.58 (m, 4H), 1.82−1.74 (m, 4H), 1.62 (tt, J = 7.0, 6.8 Hz, 2H), 1.37−1.22 (m, 6H), 0.87 (t, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 170.6, 106.7, 64.7, 64.2, 59.2, 51.4, 34.7, 31.4, 28.5, 25.5, 22.5, 13.9 ppm; HRMS (ESI) m/z calcd for $C_{15}H_{28}O_4N$ [M + H]$^+$: 286.2013. Found: 286.2010.

Removal of Protecting Groups. Ester **4c** (56.3 mg, 0.20 mmol) in 10% H_2SO_4 aq./THF (3/1, 2.4 mL, 0.08 M) was stirred at 60 °C. After 15 h, the reaction mixture was cooled to 0 °C and then neutralized by 3 M NaOH aq. The product was extracted with AcOEt three times, washed with brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford **6c** (46.2 mg, 194.7 μmol, 97% yield) as a colorless oil. The product was used for the next reaction without further purification.

*Allyl 2-(4-Oxopiperidin-1-yl)pent-4-enoate (**6c**).* IR (neat): 3079, 2962, 2823, 1717, 1645, 1417, 1345, 1173, 988, 919 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.95−5.75 (m, 2H), 5.32 (d, J = 17.0 Hz, 1H), 5.24 (d, J = 10.5 Hz, 1H), 5.12 (d, J = 17.0 Hz, 1H), 5.07 (d, J = 10.5 Hz, 1H), 4.64−4.55 (m, 2H), 3.46 (t, J = 7.8 Hz, 1H), 3.03−2.95 (m, 2H), 2.90−2.82 (m, 2H), 2.61−2.52 (m, 1H), 2.50−2.35 (m, 5H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 208.8, 170.9, 134.1, 131.9, 118.8, 117.4, 66.6, 65.1, 49.0, 41.9, 34.0 ppm; HRMS (EI) m/z calcd for $C_{10}H_{14}O_3N$ [M-($CH_2CH{=}CH_2$)]$^+$: 196.0974. Found: 196.0971.

Ester **4j** (409.6 mg, 1.0 mmol) in 10% H_2SO_4 aq./THF (3/1, 24.8 mL, 0.04 M) was stirred at 60 °C. After 10 h, the reaction mixture was cooled to 0 °C and then neutralized by 3 M NaOH aq. The product was extracted with AcOEt three times, washed with brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford **6j** (344.4 mg, 942.3 μmol, 94% yield) as white solids. The product was used for the next reaction without further purification.

*4-Methylbenzyl 2-(4-Oxopiperidin-1-yl)-3-(p-tolyl)propanoate (**6j**).* Mp 98−99 °C; IR (neat): 2959, 2823, 1733, 1518, 1441, 1218, 1160, 1059, 1000, 755 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.14−7.05 (m, 8H), 5.01 (s, 2H), 3.63 (dd, J = 8.8, 6.9 Hz, 1H), 3.08 (dd, J = 13.4, 8.8 Hz, 1H), 3.05−2.98 (m, 2H), 2.94 (dd, J = 13.4, 6.9 Hz, 1H), 2.89−2.81 (m, 2H), 2.46−2.33 (m, 7H), 2.32 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 208.8, 171.1, 138.2, 136.0, 134.6, 132.5, 129.2, 129.1, 129.0, 128.5, 68.9, 66.2, 49.3, 41.9, 35.6, 21.2, 21.0 ppm; HRMS (EI) m/z calcd for $C_{15}H_{18}O_3N$ [M-($CH_2C_6H_4CH_3$)]$^+$: 260.1287. Found: 260.1282.

Ester **6c** (108.4 mg, 0.46 mmol) was dissolved in THF/H_2O (1/1, 4.6 mL, 0.1 M) and treated by LiOH·H_2O (38.6 mg, 0.92 mmol, 2 equiv) at 0 °C. The reaction mixture was allowed to warm to room temperature. After stirring for 23 h, LiOH·H_2O (38.6 mg, 0.92 mmol, 2 equiv) was added. After stirring for an additional 5 h. The reaction mixture was acidified by 3 M HCl, and solvent was removed under reduced pressure.

The crude product was dissolved in EtOH (4.6 mL, 0.1 M) and transferred to a sealed tube. Aminomethylated polystyrene resin (PS-NH_2, 2.1 mmol/g) (328.6 mg, 0.69 mmol, 1.5 equiv) and NH_4Cl (29.5 mg, 0.55 mmol, 1.2 equiv) were added to the mixture. The test tube was sealed and then heated at 100 °C. After 24 h, the reaction mixture was filtered through a Celite pad and washed with EtOH and 3 M HCl. After neutralization to pH 7 using 3 M NaOH aq. followed by concentration under reduced pressure, the crude product was loaded on a cationic ion exchange column chromatography instrument (Dowex 50W-X2, 50−100 mesh, H^+ form). After the column was washed with water, ammonia solution (28% w/w) was introduced into the column. Ninhydrin-active fractions were collected, and the water was removed under high vacuum to afford free α-amino acid **7c** (48.4 mg, 420.4 μmol, 91% yield in two steps) as yellow solids.

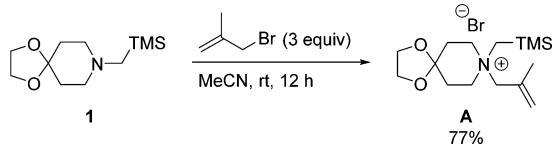
*2-Aminopent-4-enoic Acid (**7c**).* Mp 245−247 °C; IR (neat): 2932, 2856, 1588, 1455, 1404, 1333, 1164, 1106, 913, 706 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ = 5.82−5.71 (m, 1H), 5.27 (d, J = 17.0 Hz, 1H), 5.25 (d, J = 10.0 Hz, 1H), 3.80 (dd, J = 6.3, 5.3 Hz, 1H), 2.70−2.55 (m, 2H) ppm; ^{13}C NMR (125 MHz, D_2O) δ = 174.8, 132.0, 121.2, 54.7, 35.5 ppm; HRMS (ESI) m/z calcd for $C_5H_{10}O_2N$ [M + H]$^+$: 116.0706. Found: 116.0707.

Ester **6j** (146.2 mg, 0.40 mmol) was dissolved in THF/H_2O (1/1, 4.0 mL, 0.1 M) and treated by LiOH·H_2O (67.1 mg, 1.6 mmol, 4 equiv) at 0 °C. The reaction mixture was allowed to warm to room temperature. After stirring for 14 h, the reaction mixture was acidified by 3 M HCl, and solvent was removed under reduced pressure.

The crude product was dissolved in EtOH (4.0 mL, 0.1 M) and transferred to a sealed tube. Aminomethylated polystyrene resin (PS-NH_2, 2.1 mmol/g) (285.7 mg, 0.60 mmol, 1.5 equiv) and NH_4Cl (26.2 mg, 0.48 mmol, 1.2 equiv) were added to the mixture. The test tube was sealed and then heated at 100 °C. After 24 h, the reaction mixture was filtered through a Celite pad and washed with EtOH and 3 M HCl. After neutralization to pH 7 using 3 M NaOH aq. followed by concentration under reduced pressure, the crude product was loaded on a cationic ion exchange column chromatography instrument (Dowex 50W-X2, 50−100 mesh, H^+ form). After the column was washed with water, ammonia solution (28% w/w) was introduced into the column. Ninhydrin-active fractions were collected, and the water was removed under high vacuum to afford free α-amino acid **7j** (61.1 mg, 340.9 μmol, 85% yield) as yellow solids.

*2-Amino-3-(p-tolyl)propanoic Acid (**7j**).* Mp 227−229 °C; IR (neat): 1583, 1504, 1411, 1308, 1156, 1106, 856, 804, 761, 676 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ = 7.25 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 3.95 (dd, J = 7.9, 5.0 Hz, 1H), 3.23 (dd, J = 14.9, 5.0 Hz, 1H), 3.07 (dd, J = 14.9, 7.9 Hz, 1H), 2.32 (s, 3H) ppm; ^{13}C NMR (125 MHz, D_2O) δ = 174.7, 138.5, 132.6, 130.4, 130.0, 56.7, 36.6, 20.8 ppm; HRMS (EI) m/z calcd for $C_{10}H_{13}O_2N$ [M]$^+$: 179.0946. Found: 179.0944.

Synthesis of Ammonium Salt Intermediates. Intermediate **A** was prepared by the following procedure. α-Amino silane **1** (688.2 mg,



3 mmol) and 3-bromo-2-methyl-1-propene (914 μL, 9 mmol, 3.0 equiv) in MeCN (3 mL, 1.0 M) were stirred for 12 h at room temperature. After the solvent was removed under reduced pressure, the desired ammonium salt **A** was obtained (839.0 mg, 2.3 mmol, 77% yield) as a yellow amorphous solid.

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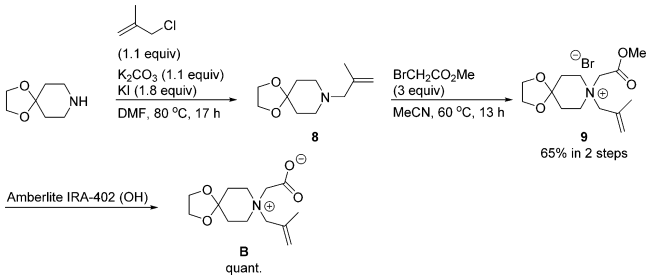
*8-(2-Methylallyl)-8-((trimethylsilyl)methyl)-1,4-dioxa-8-azaspiro-[4.5]decan-8-ium Bromide (**A**).* IR (neat): 3393, 2954, 2895, 1637, 1457, 1255, 1169, 1119, 1034, 856 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ = 5.61 (s, 1H), 5.37 (s, 1H), 4.10−4.04 (m, 4H), 4.02 (s, 2H), 3.66−3.57 (m, 2H), 3.50−3.42 (m, 2H), 3.19 (s, 2H), 2.22−2.09 (m, 4H), 2.00 (s, 3H), 0.30 (s, 9H) ppm; ^{13}C NMR (125 MHz, D_2O) δ = 133.9, 128.4, 104.5, 69.4, 65.32, 65.29, 60.0, 54.2, 30.0, 24.3, −0.8 ppm; HRMS (ESI) m/z calcd for $C_{15}H_{30}O_2NSi$ $[M\text{-}Br]^+$: 284.2040. Found: 284.2035.

Intermediate **B** was prepared by the following procedure. In a round-bottom flask, 1,4-dioxa-8-azaspiro[4.5]decane (1.9 mL, 15 mmol), 3-chloro-2-methyl-propene (1.6 mL, 16.5 mmol, 1.1 equiv), potassium carbonate (2.3 g, 16.5 mmol, 1.1 equiv), and potassium iodide (4.5 g, 27 mmol, 1.8 equiv) in DMF (15 mL, 1.0 M) were stirred for 17 h at 80 °C. Water was added to quench the reaction. The product was extracted with AcOEt three times, and the combined organic layer was washed with water followed by brine and then dried over Na_2SO_4. After evaporation of the solvent, the crude product **8** was used for the next reaction without further purification.

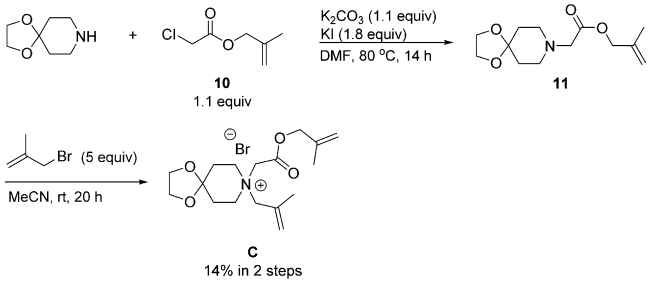


Amine **8** and methylbromoacetate (4.1 mL, 45 mmol, 3.0 equiv) in MeCN (15 mL, 1.0 M) were stirred for 13 h at 60 °C. The solids were washed with hexane to afford **9** (3.4 g, 9.7 mmol, 65% in two steps) as white solids.

Ammonium salt **9** (1.05 g, 3.0 mmol) dissolved in water was passed through an ion-exchange chromatography column (Amberlite IRA-402(OH)). The solvent was removed under reduced pressure to afford **B** (808.4 mg, quant.) as colorless solids.

*2-(8-(2-Methylallyl)-1,4-dioxa-8-azaspiro[4.5]decan-8-ium-8-yl)-acetate (**B**).* Mp 196−198 °C; IR (neat): 3445, 2974, 1635, 1456, 1384, 1217, 1169, 1118, 944, 751 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ = 5.43 (s, 1H), 5.29 (s, 1H), 4.32 (s, 2H), 3.93 (s, 4H), 3.90−3.80 (m, 2H), 3.55 (s, 2H), 3.48−3.38 (m, 2H), 2.02−1.85 (m, 7H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ = 163.9, 134.4, 126.2, 103.8, 64.2, 64.0, 63.3, 58.1, 56.5, 29.1, 23.6 ppm; HRMS (ESI) m/z calcd for $C_{13}H_{21}O_4NNa$ $[M + Na]^+$: 278.1363. Found: 278.1361.

Intermediate **C** was prepared by the following procedure. In a round-bottom flask, 1,4-dioxa-8-azaspiro[4.5]decane (1.3 mL, 10 mmol), α-chloroacetate **10**[20] (1.6 g, 1.1 equiv), potassium carbonate (1.5 g, 11 mmol, 1.1 equiv), and potassium iodide (3.0 g, 18 mmol, 1.8 equiv) in DMF (10 mL, 1.0 M) were stirred for 14 h at 80 °C. Water was added to quench the reaction. The product was extracted with AcOEt three times, and the combined organic layer was washed with water followed by brine and then dried over Na_2SO_4. After evaporation of the solvent, the crude product **11** was used for the next reaction without further purification.



Amine **11** and 3-bromo-2-methyl-propene (5 mL, 50 mmol, 5 equiv) in MeCN (10 mL, 1.0 M) were stirred for 20 h at room temperature. After evaporation, the crude product was dissolved in water and washed with AcOEt. The water layer was evaporated followed by trituration with hexane. The solids were filtered and washed with hexane and AcOEt to afford **C** (561.1 mg, 1.44 mmol, 14% yield in two steps) as yellow solids.

*8-(2-Methylallyl)-8-(2-((2-methylallyl)oxy)-2-oxoethyl)-1,4-dioxa-8-azaspiro[4.5]decan-8-ium Bromide (**C**).* Mp 169−171 °C; IR (neat): 3420, 2968, 1747, 1646, 1445, 1383, 1191, 1088, 945, 752 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ = 5.57 (s, 1H), 5.36 (s, 1H), 5.06 (s, 1H), 5.02 (s, 1H), 4.70 (s, 2H), 4.53 (s, 2H), 4.34 (s, 2H), 4.03 (s, 4H), 3.99−3.90 (m, 2H), 3.82−3.71 (m, 2H), 2.22−2.06 (m, 4H), 2.00 (s, 3H), 1.80 (s, 3H) ppm; ^{13}C NMR (125 MHz, CD_3OD) δ = 116.2, 140.4, 134.8, 128.8, 115.1, 104.5, 70.6, 67.4, 66.0, 65.9, 60.5, 56.3, 30.8, 23.8, 19.6 ppm; HRMS (ESI) m/z calcd for $C_{17}H_{28}O_4N$ $[M\text{-}Br]^+$: 310.2013. Found: 310.2011.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00837.

^1H and ^{13}C NMR spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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