STEREOSELECTIVE SYNTHESIS OF 2,5-DI- AND 2,2,5-TRISUBSTITUTED PYRROLIDINES BY ALLYLATION REACTON OF ACYLIMINIUM ION
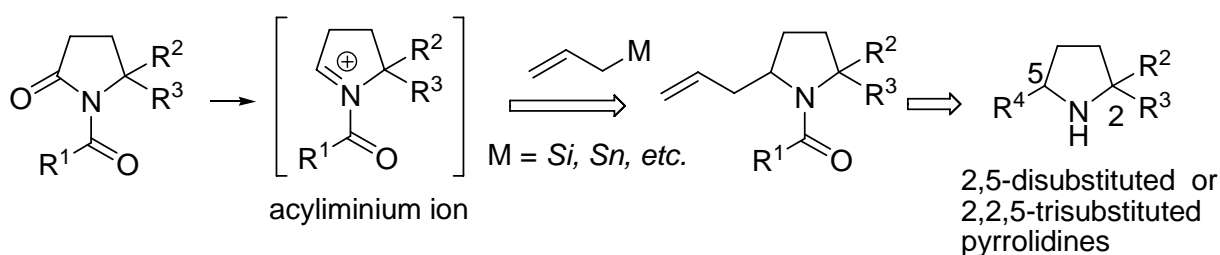
Tetsuro Shinada,* Makoto Hamada, Masanori Kawasaki, and Yasufumi Ohfune*

Graduate School of Science, Osaka City University, Sumiyoshi, Sugimoto, Osaka 558-8585, Japan. ohfune@sci.osaka-cu.ac.jp, shinada@sci.osaka-cu.ac.jp

Abstract – Allylation reactions of allytrimethylsilane and an allylcopper reagent to acyliminium ions derived from several 2-monosubstituted and 2,2-disubstituted pyrrolidinones were examined. These reactions proceeded in a stereoselective manner to give the corresponding allylated adducts. The stereochemical outcomes of these reactions were dependent upon the allylating reagents or the structures of the acyliminium ions.

INTRODUCTION

2,5-Disubstitued pyrrolidine is a basic heterocyclic framework of a wide range of natural products and pharmaceutically interesting molecules.[1] Recently, biologically active pyrrolidine derivatives having a 2,2,5-trisubstituted pyrrolidine skeleton, *e.g.*, kaitocephalin[2] and cylindricines,[3] have been isolated. To date, many synthetic efforts have been made for the stereoselective construction of 2,5- and 2,2,5-substituted pyrrolidines. Among them, an allylation reaction to an acyliminium intermediate derived from a pyroglutamate derivative is a useful approach to this end (Scheme 1).[1,4,5]
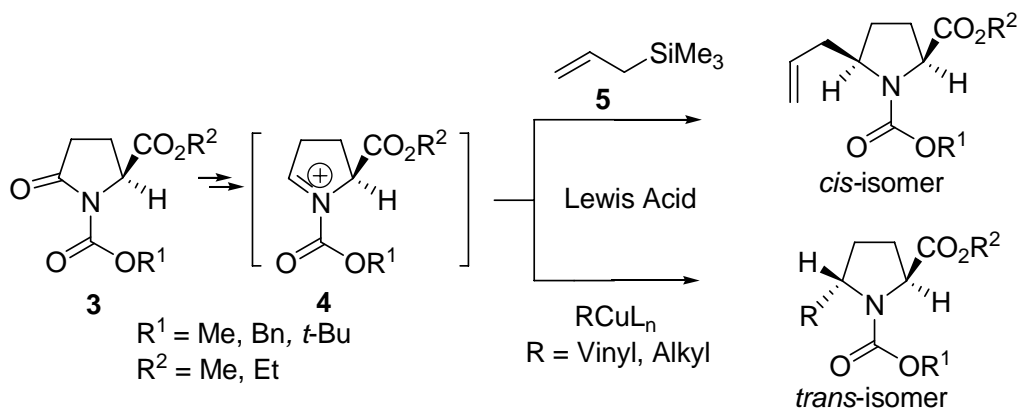

Scheme 1

This paper is dedicated to the memory of the Emeritus Professor Kenji Koga of Tokyo University.

Recently, we have reported the total synthesis of kaitocephalin by an allylation reaction of an acyliminium ion as a key step (Scheme 2).[6] During the course of this study, we found that the stereoselectivity of the key allylation reaction was dependent upon the allylic metal reagents. When an allylcopper reagent was employed for the allylation reaction of **1**, *cis*-isomer (**2a**) was obtained as a major product (**2a**:**2b** = 2:1). In contrast, the use of allyltrimethylsilane (**5**) gave *trans*-isomer (**2b**), exclusively. It is worthwhile to note that the stereoselectivity observed in the above allylation reactions was opposite to the case of pyroglutamate (**3**) (Scheme 3). It has been reported that Lewis acid-mediated addition reactions of allyltrimethylsilane or allyltributyltin to **4** proceeded in a stereoselective manner to give *cis*-isomers.[5g-k] Although addition reactions of alkyl and vinylcopper reagents gave *trans*-isomers as major products [7] the allylation reaction of **4** with an allylcopper reagent has not been examined. These results led us to investigate the origin of the reagent- and substrate-dependent allylation reactions. In this study, we report stereoselective allylation reactions of several 2-monosubstituted and 2,2-disubstitued pyrrolidinones (**9a-d**) using allyltrimethylsilane and an allylcopper reagent.
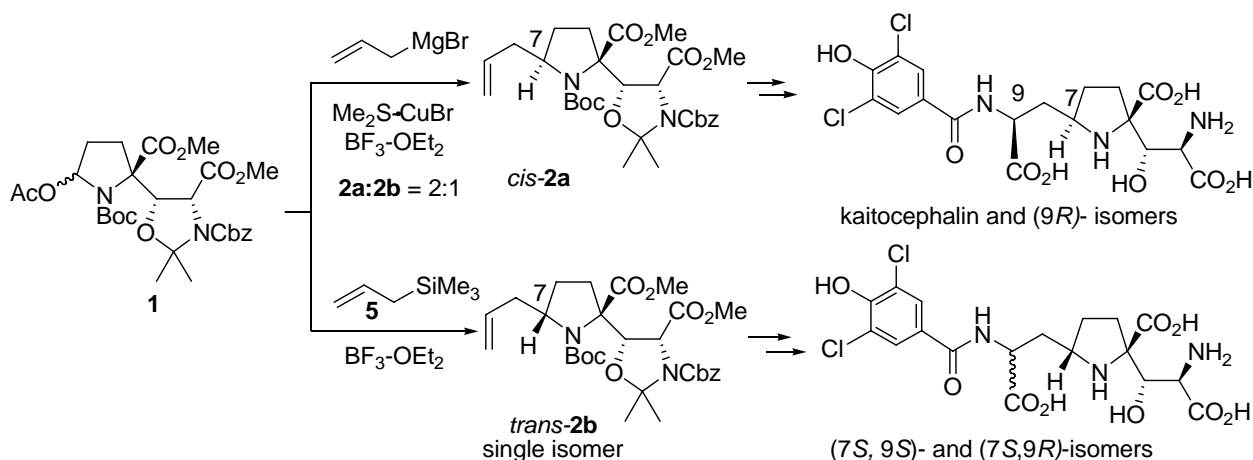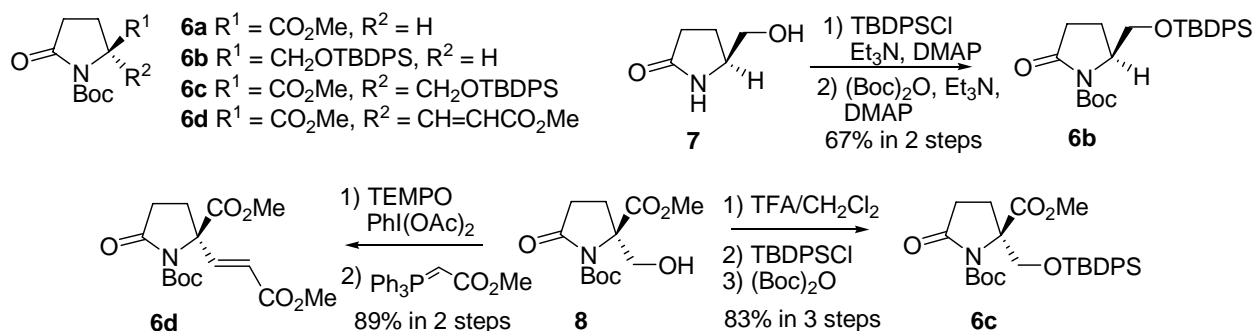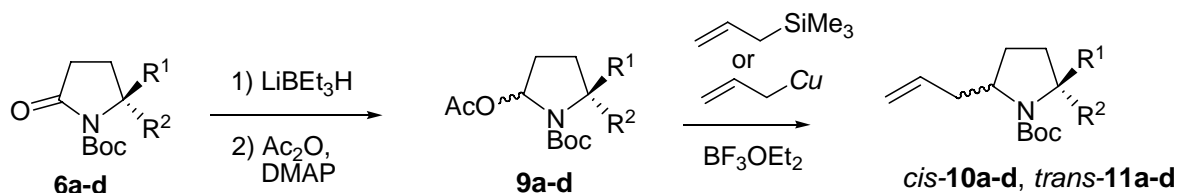

Scheme 2

Scheme 3

RESULTS AND DISCUSSION

Four substrates (**6a-d**) bearing substituents at C2 were employed for the addition reactions (Scheme 4). The silyloxy derivative (**6b**) was synthesized in 2 steps from **7**. The 2,2-disubstituted compound (**6c**) was prepared by silylation of alcohol (**8**).[6] The *E*-α,β-unsaturated ester (**6d**)[6] was synthesized by oxidation of **8** to an aldehyde followed by Wittig olefination.

Scheme 4

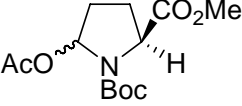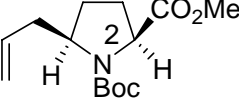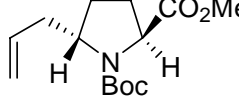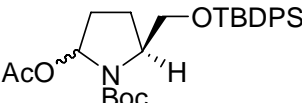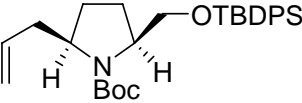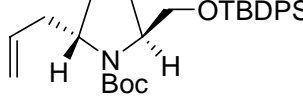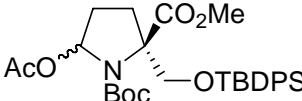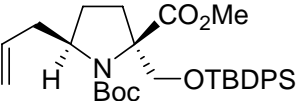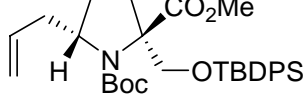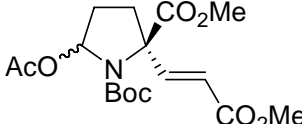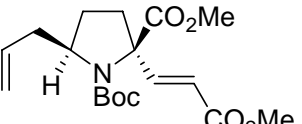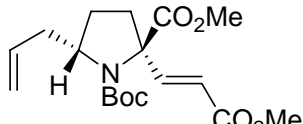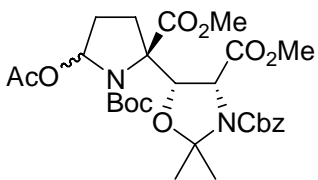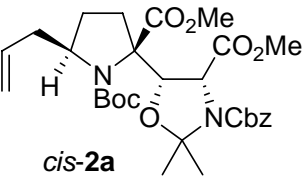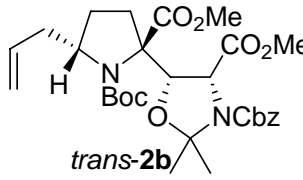*N*-Boc-lactams (**6a-d**) were converted to acyliminium ion precursors (**9a-d**) by a chemoselective reduction with LiBEt$_3$H followed by treatment with Ac$_2$O (Scheme 5). Since **9a-d** were labile for purification on silica gel, the crude acetates (**9a-d**) were used for the allylation reaction without purification. Addition reaction with allyltrimethylsilane (5 equiv.) was performed in the presence of BF$_3$-OEt$_2$ (1.2 equiv.) in CH$_2$Cl$_2$ at -78 $^{\circ}$C for 15 min. The addition reaction of an allyl copper reagent to an acyliminium ion has been unprecedented except for the case of **1**.[6] After numerous attempts, we established the following reproducible procedure: i) allylmagnesium bromide was added to Me$_2$S-CuBr in THF at -40 $^{\circ}$C and stirred for 0.5 h, ii) the mixture was cooled to -78 $^{\circ}$C, iii) to the mixture was added BF$_3$-OEt$_2$ at -78 $^{\circ}$C, iv) **9** was added dropwise to the mixture, and v) the reaction mixture was gradually warmed to 0 $^{\circ}$C. These results are listed in Table 1.

Scheme 5

The ratios and structures of the adducts (**10**) and (**11**) were determined by ^{1}H-NMR spectral data and NOE spectral experiments of the corresponding pyrrolidine derivatives (Figure 1). Boc derivatives (**10**) and (**11**) showed complex and broad signals due to the formation of a mixture of the rotamers in CDCl$_3$ in their ^{1}H-NMR spectra. To obtain simple NMR spectral patterns, these compounds were converted to the corresponding amines (**12a-d**) by the removal of the Boc groups. The NOESY spectral experiments

Table 1. Allylation Reactions of **9a-d** and **1**.

Entry	Substrate	Products[a,b]

9a

cis-**10a**   *trans*-**11a**

Si [c] 84:16 (56%)
Cu [d] 31:69 (48%)

9b

cis-**10b**   *trans*-**11b**

Si 28:72 (37%)[e]
Cu 28:72 (74%)

9c

cis-**10c**   *Si* 75:25 (51%)[f]   *trans*-**11c**
Cu 68:32 (60%)

9d

cis-**10d**   *trans*-**11d**

Si >98:2 (57%)
Cu 80:20 (20%)[g]

1

cis-**2a**   *trans*-**2b**

Si 2:>98 (80%)
Cu 66:34 (60%)

[a] *Cis* is the term meaning where the allyl group is placed in the same face as the upper substituents
at C2 in **2a** and **10a-d**. *Trans* is the term meaning in the opposite sense to *cis*.

[b] Product ratios were determined by ^{1}H-NMR spectrum of the corresponding amines.

[c] *Si* : addition of **5**.

[d] *Cu*: addition of an allycopper reagent.

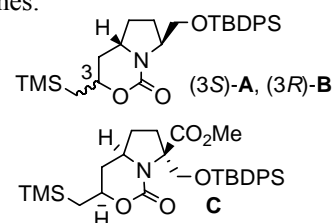[e] Cyclic carbamates (**A**) and (**B**) were obtained as a minor product.
The yeild of **A** and **B** were counted in the trans product.

[f] Cyclic carbamates (**C**) was obtained as a minor product.
The yield of **C** was counted in the *cis* product.

[g] A complex mixture was obtained. One of the major products was a Michael adduct.

(3*S*)-**A**, (3*R*)-**B**

C

of **12a-d** confirmed the *cis*-relationship between R^1 and the allyl group (Figure 1). The structures of **2a** and **2b** were determined by its conversion to kaitocephalin and its C7-epimer, respectively. Based on these results, the structures of *trans*-**11a-d** and **2b** were unambiguously established.
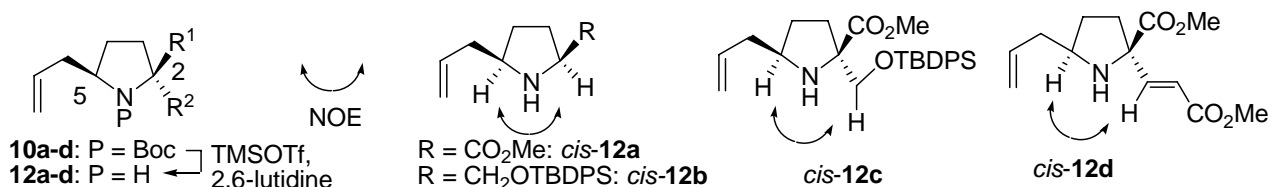
Figure 1. Structure determination of the allylated adducts by NOE experiments.

Stereoselectivity of the allylation reactions using **9a** and **1** were dependent on the metal species on the allylic carbanion (Entries 1 and 5). In contrast, the allylation reactions using **9b** and **9c** were not affected by the allylating reagents to give *trans*-**11b** and *cis*-**10c** as a major product, respectively (Entries 2 and 3). The addition reaction of **9d** with **5** gave *cis*-**10d**, exclusively (Entry 4). The use of the allylcopper reagent to **9d** also gave *cis*-**10d** as a major product in low yield due to a competition with a conjugate addition reaction (Entry 4). The allylation reaction of **9b** and **9c** with **5** afforded cyclic carbamates (**A**, **B**, and **C**) as a minor product (Entries 2 and 3).[9] These side reactions were suppressed when the allylcopper reagent was used.

Two transition state models (**TS-A)** and (**TS-B**) were proposed for explanation of the *cis*-selective allylation reaction of **9a** using allytrimethylsilane (**5**).[5g-k,8] **TS-A** involves a considerable steric repulsion between the methoxy carbonyl and the Boc groups. Accordingly, the *t*-Bu group occupies the α-face (Figure 2).[5g] The addition reaction of **5** to **TS-A** preferentially occurs from the sterically less hindered β-face to give *cis*-**10a**. Recently, Tomoda et al. have reported that an electrostatic or an orbital interaction between the carbonyl and silyl groups attributes to the *cis*-selectivite deuteration of **9a** with R_3SiD (**TS-B**, X = D).[8] Similar attractive interaction would also account for the *cis*-selective allylation of **5** as shown in **TS-B** (X = allyl).

Figure 2. Proposed **TS** for stereoselective addition reactions of **5** to **1** and **9a**.

The addition reaction of **5** to **1** gave *trans*-**2b**, exclusively (Table 1, Entry 5). The stereochemical outcome was opposite to the case of **9a**. We assumed that the acyliminium ion intermediate derived from **1** would

form **TS-C**. The sterically bulky acetonide moiety in **TS-C** would compel the *t*-Bu group into the β-position. Thus, the addition reaction of **5** took place selectively from the α-face to avoid the sterically bulky Boc group. Alternative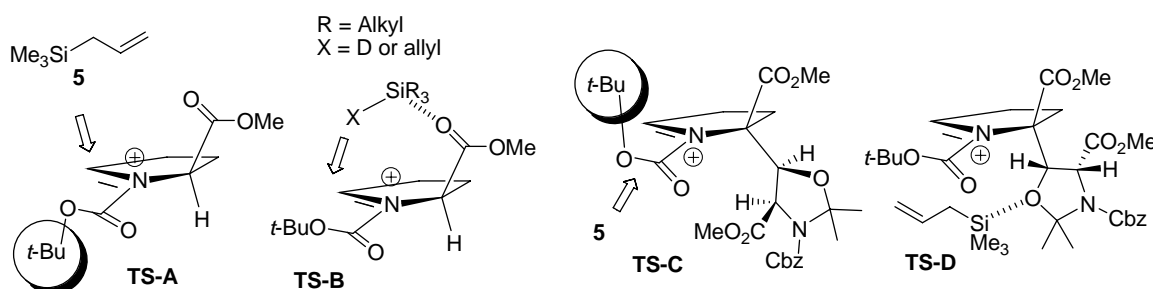ly, the electron-donating acetonide group would attract **5** to form **TS-D**, leading the selective allylation reaction from the bottom face.

The addition reaction of the allylcopper reagent prepared by the optimized protocol to **9a** gave *trans*-**11a** with moderate stereoselectivity (Table 1, Entry 1). The stereochemical outcome was relevant to those of vinyl and alkylcopper reagents.[7] In this context, a similar TS model (**TS-E**) proposed by Wistrand *et al.* would account for the *trans*-selective allylation reaction observed in this experiment.[7g] They suggested formation of a copper complex between the methoxycarbonyl group and a copper species (**TS-E**, alkyl and vinyl *Cu*). The copper reagents preferentially attack from the opposite side to the copper complex, giving *trans*-products. The same reaction pathway would be involved in the allylation reaction of the allylcopper reagents to **9a** (**TS-E**, allyl *Cu*). In contrast, the allylation reaction of **1** occurred from the same side of the methoxycarbonyl group. The reverse stereoselectivity (β-face attack) would be attributed to the stronger Lewis basic character of the alkoxy group than that of the carbonyl group, that induces the formation of copper complex in the α-face (**TS-F**).
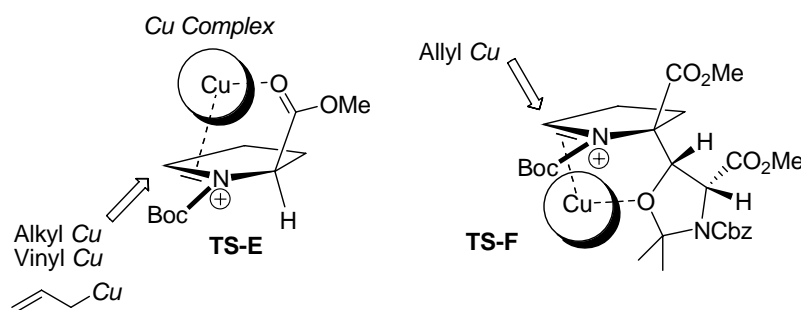
Figure 3. Proposed **TS** for stereoselective allylation reactions of **1** and **9a** with allylcopper reagent.

Allylation reactions of **9b** and **9c** with allyltrimethylsilane gave *trans*-**11b** (28:72) and *cis*-**10c** (68:32), respectively (Table 1, Entries 2 and 3). The addition reactions of the allylcopper reagents resulted in a same manner. These results indicated that the silyloxymethyl group exerts the large influence on the stereoselectivity. The effects of the alkoxy- and hydroxymethyl groups in the allylation reactions has been discussed by Shono *et al.*[5i] and Langlois *et al.*[10] They proposed **TS-G** which includes neighboring group paticipation of the hydroxy and acetyloxy groups to the acyliminium ion (Figure 4). It is assumed that the allylation reactions of **9b** and **9c** using the allylcopper reagent proceeded *via* similar intermediates (**TS-G** and **TS-H**). Recently, the effect of the silyloxymethyl group upon reduction of an acyliminium ion such as **9b** using R_3SiD has been evaluated by the exterior frontier orbital extension model by Tomoda *et al.*[8] They suggested that the steric congestion of the silyloxymethyl group of **9b** is a crucial factor for the

stereochemical outcome rather than the neighboring group participation (**TS-I**). This possibility could not be ruled out in our cases (**TS-I** and **TS-J**).
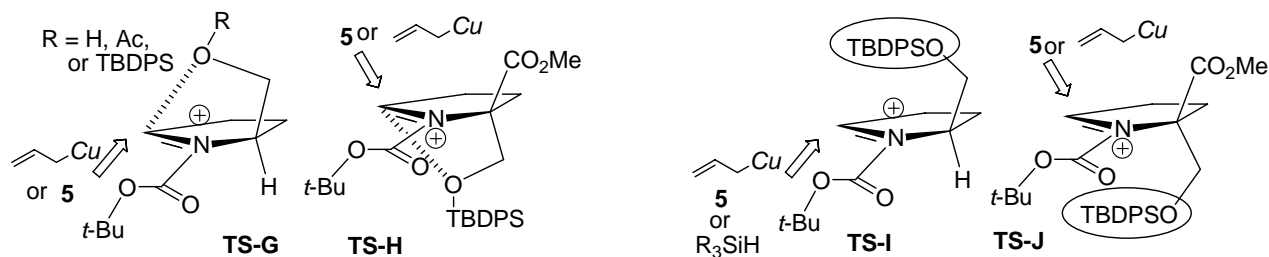
Figure 4. Effects of the silyloxymethyl group of **9b** and **9c** for the stereoselective allylation reactions.

In summary, we have demonstrated allylation reactions of allyltrimethylsilane and the allylcopper reagent to various acyliminium intermediates. These results would provide valuable information for the stereoselective synthesis of 2,5-disubstituted and 2,2,5-trisubstituted pyrrolidines.

EXPERIMENTAL

All reagents and solvents were purchased from either Aldrich Chemical Company, Inc., Nacalai Tesque Company, Ltd., Tokyo Kasei Kogyo Co., Ltd., or Wako Pure Chemical Industries, Ltd., and used without further purification unless otherwise indicated. Dichloromethane (CH_2Cl_2) was distilled from phosphoric pentaoxide (P_2O_5). Optical rotations were taken on JASCO P-1030 polarimeter with a sodium lamp (D line). FTIR spectra were measured on a JASCO FT/IR-420 infrared spectrophotometer. ^{1}H NMR spectra were recorded on either JEOL JNM-LA 300 (300 MHz), JEOL JNM-LA 400 (400 MHz), or Bruker AVANCE 600 (600 MHz) spectrometer. Chemical shifts of ^{1}H NMR spectrum were reported in parts per million (ppm, δ) relative to CHCl$_3$ (δ = 7.26) in CDCl$_3$. ^{13}C NMR spectra were recorded on an either JEOL JNM-LA 300 (75 MHz) or JEOL JNM-LA 400 (100 MHz) spectrometer. Chemical shifts of ^{13}C NMR spectrum were reported in ppm (δ) relative to CHCl$_3$ (δ = 77.0) in CDCl$_3$. Low resolution mass (LRMS) and high resolution mass (HRMS) spectra were obtained on a JEOL JMS-AX500 for fast atom bombardment ionization (FAB), chemical ionization (CI), or electron ionization (EI). All reactions were monitored by thin layer chromatography (TLC), which was performed with precoated plates (silica gel 60 F-254, 0.25 mm thickness, manufactured by Merck). TLC visualization was carried out by using UV lamp (254 nm) or a charring solution (ethanoic *p*-anisaldehyde, ethanoic phosphomolybdic acid, aqueous potassium permanganate, and butanoic ninhydrin). Daisogel IR-60 1002W (40/63 μm) was used for flash column chromatography on silica gel. Compounds (**6d**) and (**8**) were prepared according to the literature method.[6] Structures of **10a** and **11a** were determined by comparisons of their spectral data with those of the authentic data.[5a] Structures of **2a**, **2b**, and **10d** were determined by comparisons of their NMR spectral

data with those of the authentic samples.[6]

(*S*)-*tert*-Butyl 2-*tert*-butyldiphenylsilyloxymethyl-5-oxopyrrolidine-1-carboxylate (6b)

To a solution of **7** (497 mg, 4.32 mmol) in CH_2Cl_2 (21.6 mL) were added TBDPSCl (1.68 mL, 6.47 mmol), Et_3N (0.902 mL, 6.47 mmol), and DMAP (52.8 mg, 0.432 mmol) at 0 °C. The mixture was stirred for 18 h at rt, quenched with sat. NH_4Cl (20 mL), and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (60 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. To a solution of the residue in THF (21.6 mL) were added Boc_2O (1.49 mL, 6.47 mmol), Et_3N (0.902 mL, 6.47 mmol), and DMAP (52.8 mg, 0.432 mmol) at 0 °C. The mixture was stirred for 19 h at rt, quenched with sat. NH_4Cl (20 mL), and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (60 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 10/1-5/1) to give **6b** (1.31 g, 67%) as colorless amorphous powder.

$[\alpha]^{21.3}_D$ -38.0° (*c* 0.75, $CHCl_3$); IR (neat) 2985, 2931, 2858, 1789, 1750, 1712, 1473, 1428, 1367, 1312, 1153, 1112, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.57 (m, 4 H), 7.45-7.30 (m, 6 H), 4.21-4.16 (m, 1 H), 3.87 (dd, *J* = 10.5, 4.16 Hz, 1 H), 3.68 (dd, *J* = 10.5, 2.4 Hz, 1 H), 2.76 (dt, *J* = 17.3, 10.5 Hz, 1 H), 2.45-2.37 (m, 1 H), 2.14-2.10 (m, 2 H), 1.41 (s, 9 H), 1.02 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 149.7, 135.5, 133.0, 132.6, 120.9, 129.8, 127.8, 82.6, 77.3, 65.0, 58.8, 32.3, 28.0, 26.8, 21.1, 19.1; HRMS (FAB) *m/z* (M+H)$^+$ calcd for $[C_{26}H_{35}NO_4Si+H]^+$ 454.2413, found 454.2415.

(*R*)-1-*tert*-Butyl 2-methyl 2-*tert*-butyldiphenylsilyloxymethyl-5-oxopyrrolidine-1,2-dicarboxylate (6c)

To a solution of **8** (194 mg, 0.501 mmol) in CH_2Cl_2 (2.5 mL) was added TFA (2.5 mL) at 0 °C. The mixture was stirred at rt for 1 h and concentrated under reduced pressure. To a solution of the residue in CH_2Cl_2 were added TBDPSCl (0.20 mL, 0.752 mmol), Et_3N (105 μL, 0.752 mmol), and DMAP (6.1 mg, 0.05 mmol) at 0 °C. The mixture was stirred at rt under argon for 19 h, quenched with sat. NH_4Cl (2 mL), and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (60 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. To a solution of the residue in THF (2.5 mL) were added Boc_2O (173 μL, 0.752 mmol), Et_3N (105 μL, 0.752 mmol), and DMAP (6.1 mg, 0.05 mmol) at 0 °C. The mixture was stirred at rt under argon for 18 h, quenched with sat. NH_4Cl (2 mL), and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (6 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 8/1-6/1) to give **6c** (218 mg, 85%) as a colorless oil.

$[\alpha]^{25}_D$ +10.9 ° (*c* 4.76, CHCl$_3$); IR (neat) 2955, 2858, 1792, 1748, 1715, 1429, 1369, 1309, 1257, 1157, 1113, 1074 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.64-7.53 (m, 4 H), 7.43-7.31 (m, 6 H), 4.27 (d, *J* = 10.7 Hz, 1 H), 3.99 (d, *J* = 10.7 Hz, 1 H), 3.66 (s, 3 H), 2.80 (ddd, *J* = 17.5, 10.3, 8.4 Hz, 1 H), 2.56 (ddd, *J* = 17.5, 10.7, 4.4 Hz, 1 H), 2.31 (ddd, *J* = 12.9, 10.3, 4.4 Hz, 1 H), 2.09 (ddd, *J* = 12.9, 10.7, 8.4 Hz, 1 H), 1.36 (s, 9 H), 1.02 (s, 9 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 174.4, 171.8, 149.1, 135.7, 135.5, 132.9, 132.4, 130.0, 127.9, 83.6, 69.0, 65.5, 52.4, 31.6, 27.9, 26.8, 19.2; HRMS (FAB) *m/z* (M+H)$^+$ calcd for $[C_{28}H_{37}NO_6Si+H]^+$ 512.2468, found 512.2460.

General procedure for allylation with allyltrimethylsilane.

To a solution of **6a-d** (0.100 mmol) in THF (0.5 mL) was added LiBEt$_3$H (1 M solution in THF, 150 μL, 0.150 mmol) at -78 °C. The mixture was stirred at -78 °C under argon for 10 min, quenched with sat. NaHCO$_3$/30% H$_2$O$_2$ (1:1, 5 mL), stirred at rt for 3 h, and extracted with Et$_2$O (5 mL x 3). The combined organic layers were washed with brine (15 mL), dried over anhydrous MgSO$_4$, filtered, and concentrated under reduced pressure. To a solution of the residue in CH$_2$Cl$_2$ (0.5 mL) were added Ac$_2$O (18.9 μL, 0.200 mmol) and DMAP (24.4 mg, 0.200 mmol) at 0 °C. The mixture was stirred for 18 h at rt, quenched with sat. NH$_4$Cl (0.5 mL), and extracted with Et$_2$O (1 mL x 3). The combined organic layers were washed with brine (1.5 mL), dried over anhydrous MgSO$_4$, filtered, and concentrated under reduced pressure. To a solution of the residue in CH$_2$Cl$_2$ (1.00 mL) were added allyltrimethylsilane (79.5 μL, 0.500 mmol) and BF$_3$-OEt$_2$ (33.7μl, 0.125 mmol) at -78 °C. The mixture was stirred for 10 min under argon at -78 °C, quenched with sat. NaHCO$_3$ (1 mL), and extracted with Et$_2$O (1 mL x 3). The combined organic layers were washed with brine (3 mL), dried over anhydrous MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hexane/AcOEt (20:1 to 1:3))to give a mixture of **10** and **11**. The products ratios and yields are depicted in Table 1.

Allylation of 9a with 5.

10a and **11a** were obtained as an inseparable mixture. These NMR spectral data were identical with those of the authentic samples.[5a]

Allylation of 9b with 5.

An inseparable mixture of **10b** and **11b**, **A**, and **B** was obtained in 37 %, 15%, and 14% yields, respectively. The structures of **A** and **B** were determined by their NOE spectral experiments. The *cis:trans* ratio was calculated by the following equation: **10b**:(**11b**+**A**+**B**) = 28:72.

10b and **11b**.

Colorless oil; IR (neat) 3072, 2962, 2858, 1694, 1474, 1427, 1390, 1365, 1256, 1174, 1112, 997 cm^{-1}; ^{1}H

NMR (300 MHz, CDCl$_3$) δ 7.68-7.60 (m, 4 H), 7.46-7.24 (m, 6 H), 5.81-5.61 (m, 1 H), 5.07-4.93 (m, 2 H), 3.95-3.70 (m, 7/2 H), 3.47-3.41 (m, 1/2 H), 2.63-2.47 (m, 1 H), 2.12-1.75 (m, 4 H), 1.71-1.62 (m, 1 H), 1.60 (s, 5/2 H), 1.35 (br, 2 H), 1.29 (s, 9/2 H), 1.05 (s, 4 H), 1.04 (s, 5 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 154.8, 153.7, 135.7, 135.5, 133.8, 133.7, 133.6, 129.72, 129.68, 129.6, 127.7, 117.0, 116.98, 116.7, 79.21, 79.18, 79.1, 64.0, 63.7, 59.8, 58.8, 58.3, 57.8, 57.6, 38.7, 37.2, 28.64, 28.58, 28.47, 27.9, 27.0, 26.9, 26.3, 26.0, 25.8; HRMS (FAB) m/z (M+H)$^+$ calcd for [C$_{29}$H$_{41}$NO$_3$Si+H]$^+$ 480.2934, found 480.2939.

(3S,4aS,7S)-Hexahydro-7-*tert*-butyldiphenylsilyloxymethyl-3-(trimethylsiliylmethyl)pyrrolo[1,2-*c*][1,3]oxazin-1-one (A) .

Colorless oil; [α]$^{23}_D$ -8.1^o (*c* 0.88, CHCl$_3$); IR (neat) 2956, 2854, 1698, 1427, 1312, 1250, 1113 cm^{-1};
^{1}H NMR (600 MHz, CDCl$_3$) δ 7.64-7.60 (m, 4 H), 7.41 (t, J = 7.4 Hz, 2 H), 7.37 (t, J = 7.3 Hz, 4 H), 4.29-4.25 (m, 1 H), 4.14-4.11 (m, 1 H), 4.02 (dd, J = 10.3, 4.4 Hz, 1 H), 3.79 (dd, J = 10.3, 2.3 Hz, 1 H), 3.59 (tt, J = 11.0, 4.9 Hz, 1 H), 2.15-2.10 (m, 2 H), 2.09-2.04 (m, 2 H), 1.42-1.30 (m, 2 H), 1.17 (dd, J = 14.5, 6.8 Hz, 1 H), 1.06 (s, 9 H), 0.92 (dd, J = 14.5, 7.7 Hz, 1 H), 0.088 (s, 9 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 153.3, 135.7, 133.9, 133.7, 129.8, 127.8, 75.6, 64.3, 59.4, 57.7, 36.8, 32.9, 26.8, 25.5, 24.1, 19.2, -1.05; HRMS (FAB) m/z (M+H)$^+$ calcd for [C$_{28}$H$_{41}$NO$_3$Si$_2$+H]$^+$ 496.2703, found 496.2708.

(3R,4aS,7S)-Hexahydro-7-*tert*-butyldiphenylsilyloxymethyl-3-(trimethylsiliylmethyl)pyrrolo[1,2-*c*][1,3]oxazin-1-one (B) .

Colorless oil; [α]$^{23}_D$ -47.4^o (*c* 0.65, CHCl$_3$); IR (neat) 2954, 2854, 1694, 1427, 1291, 1250, 1111 cm^{-1};
^{1}H NMR (600 MHz, CDCl$_3$) δ 7.65 (d, J = 7.3 Hz, 2 H), 7.62 (d, J = 7.2 Hz, 2 H), 7.43-7.36 (m, 6 H), 4.62 (dd, J = 11.9, 6.9 Hz, 1 H), 4.18 (dd, J = 10.3, 3.3 Hz, 1 H), 4.14 (m, 1 H), 3.81 (tt, J = 11.0, 4.6 Hz, 1 H), 3.64 (d, J = 10.3 Hz, 1 H), 2.18-2.07 (m, 2 H), 2.04-1.98 (m, 2 H), 1.72 (dd, J = 13.2, 4.6 Hz, 1 H), 1.43 (tt, J = 11.4, 10.8 Hz, 1 H), 1.28 (dd, J = 14.5, 10.3 Hz, 1 H), 1.06 (s, 9 H), 0.95 (dd, J = 14.5, 7.4 Hz, 1 H), 0.058 (s, 9 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 152.5, 135.74, 135.70, 133.6, 133.4, 129.84, 129.81, 127.9, 127.8, 74.6, 63.8, 59.6, 53.6, 33.6, 33.1, 26.8, 24.9, 22.2, 19.1, -1.38; HRMS (FAB) m/z (M+H)$^+$ calcd for [C$_{28}$H$_{41}$NO$_3$Si$_2$+H]$^+$ 496.2703, found 496.2708.

Allylation reaction of 9c with 5.

10c, **11c** and **C** were obtained in 36%, 15% and 9% yields, respectively. The structure of **C** was determined by NOE spectral experiment. The *cis*:*trans* ratio was calculated by the following equation:
(**10c+C**):**11c** = 75:25.

(2*R*,5*R*)-1-*tert*-Butyl   2-methyl   5-allyl-2-*tert*-butyldiphenylsilyloxymethylpyrrolidine-1,2-dicarboxylate (10c).

Colorless oil; $[\alpha]^{21.3}_D$ +16.6° (*c* 1.72, CHCl$_3$); IR (neat) 3072, 2955, 2858, 1741, 1697, 1473, 1429, 1391, 1367, 1256, 1173, 1149, 1112, 1042 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.64 (m, 4 H), 7.38 (m, 6 H), 5.81 (m, 1 H), 5.07 (d, *J* = 16.8 Hz, 1 H), 5.03 (d, *J* = 9.0 Hz, 1 H), 4.40 (d, *J* = 14.6 Hz, 1/3 H), 4.10-3.92 (m, 8/3H), 3.64 (s, 3 H), 2.80 (m, 3/5 H), 2.63 (m, 2/5 H), 2.15-2.38 (m, 4 H), 1.72 (m, 1 H), 1.47 (s, 37/10 H), 1.22 (s, 53/10 H), 1.04 (s, 6 H), 1.03 (s, 3 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 174.1, 173.9, 153.3, 152.6, 136.1, 136.0, 135.8, 135.7, 135.62, 135.57, 133.8, 133.5, 133.2, 133.1, 129.80, 129.78, 129.70, 127.84, 127.78, 127.73, 116.9, 80.1, 79.7, 69.7, 69.2, 65.9, 64.9, 59.9, 59.7, 52.1, 51.0, 38.7, 37.2, 34.7, 34.2, 28.5, 28.3, 27.1, 26.9, 19.3; HRMS (FAB) *m/z* (M+H)$^+$ calcd for [C$_{31}$H$_{43}$NO$_5$Si+H]$^+$ 538.2989, found 538.2986.

(2*R*,5*S*)-1-*tert*-Butyl   2-methyl   5-allyl-2-*tert*-butyldiphenylsilyloxymethylpyrrolidine-1,2-dicarboxylate (11c).

Colorless oil; $[\alpha]^{24.6}_D$ +5.63° (*c* 2.01, CHCl$_3$); IR (neat) 3072, 2955, 2858, 1742, 1698, 1429, 1390, 1366, 1156, 1112, 1042 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.73-7.57 (m, 4 H), 7.38 (m, 6 H), 5.76 (m, 1 H), 5.01 (d, *J* = 18.6 Hz, 1 H), 4.99 (d, *J* = 10.2 Hz, 1 H), 4.43 (d, *J* = 14.9 Hz, 1/3 H), 4.20-3.89 (m, 8/3 H), 3.62 (s, 3 H), 2.70-2.57 (m, 2 H), 2.24-2.20 (m, 1 H), 2.08-1.98 (m, 1 H), 1.93-1.80 (m, 1 H), 1.75-1.65 (m, 1 H), 1.51 (s, 3 H), 1.26 (s, 6 H), 1.07 (s, 6 H), 1.05 (s, 3 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.9, 173.6, 154.2, 153.8, 136.0, 135.9, 135.78, 135.75, 135.72, 133.35, 133.32, 129.80, 129.77, 129.7, 129.6, 127.8, 127.7, 116.8, 116.7, 80.1, 79.7, 70.5, 70.0, 63.9, 62.5, 59.9, 59.8, 52.02, 51.96, 39.8, 39.2, 32.5, 31.1, 28.6, 28.5, 28.3, 28.2, 27.0, 26.9, 26.5, 26.1, 19.43, 19.38; HRMS (FAB) *m/z* (M+H)$^+$ calcd for [C$_{31}$H$_{43}$NO$_5$Si+H]$^+$ 538.2989, found 538.2991.

(3*R*,4a*R*,7*R*)-Methyl   hexahydro-7-*tert*-butyldiphenylsilyloxymethyl-3-(trimethylsilylmethyl)-1-oxo-1*H*-pyrrolo[1,2-*c*][1,3]oxazine-7-carboxylate (C).

Colorless oil; $[\alpha]^{28.5}_D$ + 9.0° (*c* 0.35, CHCl$_3$); IR (neat) 2952, 2890, 2857, 1742, 1697, 1472, 1427, 1369, 1314, 1249, 1208, 1155, 1112, 1091 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.64 (d, *J* = 6.8 Hz, 1 H), 7.62 (d, *J* = 6.6 Hz, 1 H), 7.42 (t, *J* = 7.1 Hz, 2 H), 7.37 (t, *J* = 7.1 Hz, 4 H), 4.50 (d, *J* = 10.5 Hz, 1 H), 4.37-4.33 (m, 1 H), 3.97 (d, *J* = 10.5 Hz, 1 H), 3.76 (tt, *J* = 11.3, 4.3 Hz, 1 H), 3.65 (s, 3 H), 2.52 (td, *J* = 13.0, 6.7 Hz, 1 H), 2.16 (m, 1 H), 2.08 (m, 1 H), 1.93 (dd, *J* = 13.0, 7.2 Hz, 1 H), 1.79 (dtd, *J* = 12.7, 11.6, 7.3 Hz, 1 H), 1.55 (td, *J* = 13.1, 11.5 Hz, 1 H), 1.22 (dd, *J* = 14.5, 6.7 Hz, 1 H), 1.06 (s, 9 H), 1.00 (dd, *J* = 14.5, 7.7 Hz, 1 H), 0.10 (s, 9 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 172.7, 151.8, 135.6, 135.5, 133.6, 133.0, 129.74, 129.69, 127.74, 127.70, 76.8, 69.7, 63.0, 58.9, 52.2, 36.8, 31.4, 31.2, 26.9, 24.3, 19.4, -0.82;

HRMS (FAB) *m/z* (M+H)$^+$ calcd for [C$_{30}$H$_{43}$NO$_5$Si$_2$+H]$^+$ 554.2758, found 554.2759.

Allylation reaction of 9d with 5.

10d was obtained as a sole product. The NMR spectral data was identical with those of the authentic data.[6]

Addition of allylcopper reagent to 9a-d.

To a suspension of CuBr-SMe$_2$ (822 mg, 4 mmol) in THF (5 mL) was added dropwise   allylmagnesium bromide (1 M solution in Et$_2$O, 4 mL, 4 mmol) at -40 $^{\circ}$C. The mixture was stirred for 45 min at -40 $^{\circ}$C under argon, cooled to -78 $^{\circ}$C, and stirred for 15 min. To the mixture was added dropwise BF$_3$-Et$_2$O (1.08 mL, 4 mmol) at -78 $^{\circ}$C. The mixture was stirred for 15 min at -78 $^{\circ}$C. To the mixture was added dropwise a solution of **9a-d** (1 mmol) in THF (5 mL), stirred for 15 min, and gradually warmed to 0 $^{\circ}$C for 3 h. The reaction mixture was quenched with sat. NH$_4$Cl and concd NH$_3$ (1:1, 20 mL), stirred for 1 h at rt, and extracted with Et$_2$O (3 x 20 mL). The combined organic layers were washed with brine (60 mL), dried over anhydrous MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/AcOEt (20:1 to 3:1))on silica gel. The products ratios and yields are depicted in Table 1.

Allylation of 9a with the allylcopper reagent.

10a and **11a** were obtained as an inseparable mixture. These NMR spectral data were identical with those of the authentic sample.[5a]

Allylation of 9b with the allylcopper reagent.

10b and **11b** were obtained as an inseparable mixture. The NMR spectral data was identical with those of **10b** and **11b** obtained *via* the allylation reaction of **9b** with **5**.

Allylation of 9c with the allylcopper reagent.

10c and **11c** were obtained. These spectral data were identical with those of **10c** and **11c** obtained *via* the allylation reaction of **9c** with **5**.

Allylation of 9d with the allylcopper reagent.

10d and **11d** were obtained as an inseparable mixture.

10d and **11d** (8:2): IR (neat) 2977, 2953, 1746, 1732, 1700, 1655, 1457, 1436, 1379, 1252, 1171, 1042 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.44-7.37 (m, 1/5 H), 7.37-7.28 (m, 4/5 H), 5.92-5.61 (m, 2 H), 5.06-4.92 (m, 2 H), 4.15-3.87 (m, 1 H), 3.73-3.63 (m, 6 H), 2.78-2.49 (m, 1 H), 2.35-1.62 (m, 5 H),

1.41-1.27 (m, 9 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 172.8, 172.57, 172.56, 172.51, 172.4, 172.3, 166.9, 166.59, 166.58, 166.56, 152.9, 152.4, 148.4, 147.5, 147.1, 146.1, 135.5, 135.3, 135.2, 134.9, 119.3, 119.0, 118.8, 117.5, 117.35, 117.31, 80.6, 80.5, 70.1, 69.72, 69.70, 59.6, 59.5, 59.01, 58.96, 52.8, 52.6, 51.8, 51.74, 51.71, 39.0, 38.3, 38.0, 36.9, 36.1, 35.0, 28.4, 28.2, 28.0, 26.9, 25.1; HRMS (FAB) *m/z* (M+H)$^+$ calcd for[C$_{18}$H$_{27}$NO$_6$+H]$^+$ 354.1916, found 354.1917.

Removal of the Boc group from 10 and 11

To a solution of an inseparable mixture of **10b** and **11b** in CH$_2$Cl$_2$ (0.1 M) were added TMSOTf (2 equiv) and 2,6-lutidine (3 equiv) at 0 ^{o}C. The mixture was stirred at rt, quenched with sat. NaHCO$_3$, and extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine, dried over anhydrous MgSO$_4$, filtered, and concentrated under reduced pressure to give crude amines quantitatively. The residue was purified by preparative TLC (hexane/AcOEt (4:1)) to give **12b** and its isomers. A mixture of **10c** and **11c** were transformed to **12c** and its isomer in the same manner.

(2*S*,5*S*)-2-Allyl-5-(*tert*-butyldiphenylsilyloxymethyl)pyrrolidine (12b).

Pale yellow oil; IR (neat) 2956, 2930, 2858, 1641, 1428, 1112 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.66 (d, *J* = 6.8 Hz, 4 H), 7.43 (t, *J* = 7.1 Hz, 2 H), 7.38 (t, *J* = 7.3 Hz, 4 H), 5.77 (ddt, *J* = 17.1, 9.3, 7.0 Hz, 1 H), 5.08 (dd, *J* = 17.1, 0.8 Hz, 1 H), 5.04 (dd, *J* = 9.3, 0.8 Hz, 1 H), 3.56 (dd, *J* = 10.2, 5.5 Hz, 1 H), 3.54 (dd, *J* = 10.2, 6.4 Hz, 1 H), 3.43 (quint, *J* = 6.2 Hz, 1 H), 3.15 (quint, *J* = 6.5 Hz, 1 H), 2.19 (t, *J* = 6.6 Hz, 2 H), 1.98 (br, 1 H), 1.91-1.86 (m, 2 H), 1.48-1.35 (m, 2 H), 1.06 (s, 9 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 136.3, 135.6, 129.8, 127.8, 116.6, 66.6, 58.8, 56.8, 40.7, 31.0, 27.1, 26.8, 19.2;

(2*R*)-Isomer of 12b.

^{1}H NMR (600 MHz, CDCl$_3$) δ 7.67 (d, *J* = 6.0 Hz, 4 H), 7.43 (t, *J* = 7.1 Hz, 2 H), 7.38 (t, *J* = 7.3 Hz, 4 H), 5.83 (ddt, *J* = 17.1, 9.5, 7.0 Hz, 1 H), 5.11 (dd, *J* = 17.1, 0.8 Hz, 1 H), 5.05 (dd, *J* = 9.5, 0.8 Hz, 1 H), 3.73 (dd, *J* = 10.2, 4.6 Hz, 1 H), 3.62 (dd, *J* = 10.2, 5.1 Hz, 1 H), 3.28 (quint, *J* = 6.7 Hz, 1 H), 3.18 (quint, *J* = 6.6 Hz, 1 H), 2.45 (br, 1 H), 2.26 (t, *J* = 6.7 Hz, 2 H), 1.92-1.84 (m, 1 H), 1.78 (dq, *J* = 12.6, 7.8 Hz, 1 H), 1.65-1.58 (m, 1 H), 1.48-1.35 (m, 1 H), 1.06 (s, 9 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 135.9, 135.7, 129.8, 127.8, 116.9, 66.4, 60.1, 58.7, 40.3, 27.3, 26.8, 19.1; HRMS (FAB) *m/z* (M+H)$^+$ calcd for [C$_{24}$H$_{33}$NOSi+H]$^+$ 380.2409, found 380.2416.

(2*R*,5*R*)-Methyl 5-allyl-2-*tert*-butyldiphenylsilyloxymethylpyrrolidine-2-carboxylate (12c).

Pale yellow oil; [α]$^{24.2}_D$ -4.1^o (*c* 3.57, CHCl$_3$); IR (neat) 2931, 2858, 1738, 1429, 1234, 1113, 998 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.68 (d, *J* = 6.7 Hz, 2 H), 7.65 (d, *J* = 6.7 Hz, 2 H), 7.43 (t, *J* = 6.8 Hz, 2 H), 7.38 (t, *J* = 6.9 Hz, 4 H), 5.80 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1 H), 5.10 (d, *J* = 17.1 Hz, 1 H), 5.04 (d, *J*

= 10.1 Hz, 1 H), 3.82 (d, J = 9.5 Hz, 1 H), 3.72 (s, 3 H), 3.64 (d, J = 9.5 Hz, 1 H), 3.11 (dt, J = 14.8, 6.6 Hz, 1 H), 2.37 (br, 1 H), 2.27 (quint, J = 6.9 Hz, 1 H), 2.21-2.15 (m, 2 H), 1.84-1.79 (m, 1 H), 1.66 (dt, J = 13.2, 9.2 Hz, 1 H), 1.36 (ddt, J = 12.2, 9.0, 8.8 Hz, 1 H), 1.04 (s, 9 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 176.2, 136.0, 135.7, 135.6, 129.6, 127.6, 116.4, 70.4, 68.9, 57.7, 52.1, 40.6, 31.8, 30.8, 26.7, 19.3; HRMS (FAB) m/z (M+H)$^+$ calcd for [C$_{26}$H$_{35}$NO$_3$Si+H]$^+$ 438.2464, found 438.2464.

(2*S*)-Isomer of 12c.

Pale yellow oil; [α]$^{24.4}_{D}$ -7.2^o (*c* 1.44, CHCl$_3$); IR (neat) 2931, 2858, 1738, 1473, 1429, 1229, 1113 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.70 (d, J = 6.7 Hz, 1 H), 7.65 (d, J = 6.7 Hz, 1 H), 7.42 (t, J = 7.2 Hz, 2 H), 7.38 (t, J = 7.2 Hz, 4 H), 5.83 (ddt, J = 17.2, 10.1, 7.0 Hz, 1 H), 5.08 (d, J = 17.2 Hz, 1 H), 5.02 (d, J = 10.1 Hz, 1 H), 3.91 (d, J = 9.3 Hz, 1 H), 3.72 (s, 3 H), 3.66 (d, J = 9.3 Hz, 1 H), 3.28 (dt, J = 14.7, 6.5 Hz, 1 H), 2.23 (quint, J = 6.8 Hz, 1 H), 2.17 (quint, J = 6.5 Hz, 1 H), 2.06 (dt, J = 13.1, 8.0 Hz, 1 H), 1.84-1.80 (m, 1 H), 1.74 (ddd, J = 13.7, 9.5, 4.8 Hz, 1 H), 1.36 (ddt, J = 11.9, 8.7, 8.6 Hz, 1 H), 1.02 (s, 9 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 177.0, 136.3, 135.9, 135.8, 133.6, 133.5, 129.76, 129.74, 127.8, 127.7, 116.4, 70.8, 70.5, 57.8, 52.0, 40.9, 31.1, 30.1, 26.5, 19.1; HRMS (FAB) m/z (M+H)$^+$ calcd for [C$_{26}$H$_{35}$NO$_3$Si+H]$^+$ 438.2464, found 438.2456.

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