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One-pot synthesis of chiral dehydroproline esters: [3+2]-type cycloaddition reaction of allenylstannane and α-imino ester

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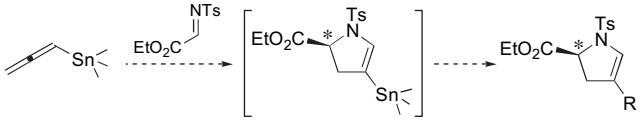
Abstract—An enantioselective [3+2]-type cycloaddition of allenylstannane and α-imino ester was developed. Synthetic utility of the 4-stannyldehydroproline ester intermediate was demonstrated: iodine oxidation and Stille coupling reaction of the intermediate afforded optically active 4-iodo- and 4-aryldehydroproline esters in good yields and in high ees, respectively.

1. Introduction

Development of the novel synthetic method of proline and its derivatives in optically pure form is an important objective because they play key roles as chiral sources in synthetic organic chemistry. For instance, chiral diamines and amino alcohols (prolinols), prepared from optically active proline are efficient ligands for asymmetric aldol reactions,[1a] alkylation of aldehydes,[1b] and Michael addition reactions.[1c] Chiral oxazaborolidine, prepared from optically active prolinols, are useful catalysts for asymmetric borane reduction of ketones[1d] and Diels–Alder reactions.[1e–h] Parent proline and its substituted form have lately emerged as an efficient chiral organocatalysts.[2] Prolines have, thus, found increasing synthetic utility as chiral catalysts in addition to chiral building blocks.

Previously, we reported [3+2]-type cycloaddition reactions of allenylsilanes with α-imino ester, and we could obtain 4-silylated dehydroproline esters in an enantioselective manner.[3] This result encouraged us to examine the [3+2]-type cycloaddition reactions of allenylstannane and α-imino ester (Scheme 1): in analogy to the chemistry of the allenylsilanes,[3,4] it is expected that allenylstannane also undergoes [3+2]-type cycloaddition with α-imino ester.[5] The resulting 4-stannylated dehydroproline ester would be a useful synthetic intermediate for the preparation of optically active 4-substituted dehydroproline esters because C–Sn bond is more reactive than the corresponding C–Si bond.[6]



Scheme 1. Our approach to optically active dehydroproline esters.

Based on the consideration, we studied (1) the cycloaddition reaction of allenylstannane and α-imino ester and (2) functionalization of the resulting [3+2]-type cycloadduct.[7]

2. Results and discussion

2.1. Cycloaddition reaction of allenylstannane and α-imino ester

At the outset, we studied the reaction of α-imino ester **1** and allenyl(tributyl)stannane **2** (Scheme 2). Compounds **1** and **2** were heated in the presence of $[Cu(MeCN)_4]ClO_4$ and (*R*)-TolBINAP (10 mol % each). After stirring for 5 h, we could obtain chiral dehydroproline ester **3** in 66% yield and 56% ee. Compound **3** is a protonolysis product of the expected stannyldehydroproline ester **4**.

This result is in clear contrast to our enantioselective propargylation reaction:[8,9] in the presence of 1 mol % of the catalyst at −30 °C, **1** reacted with **2** to give (*S*)-homopropargylamine **5** in 96% yield and 86% ee. It is found that propargylation product was obtained under mild conditions and that [3+2]-type cycloaddition product was obtained under more harsh conditions.

We found that the product distribution of the cycloadduct(s) and the propargylation product was also dependent on the

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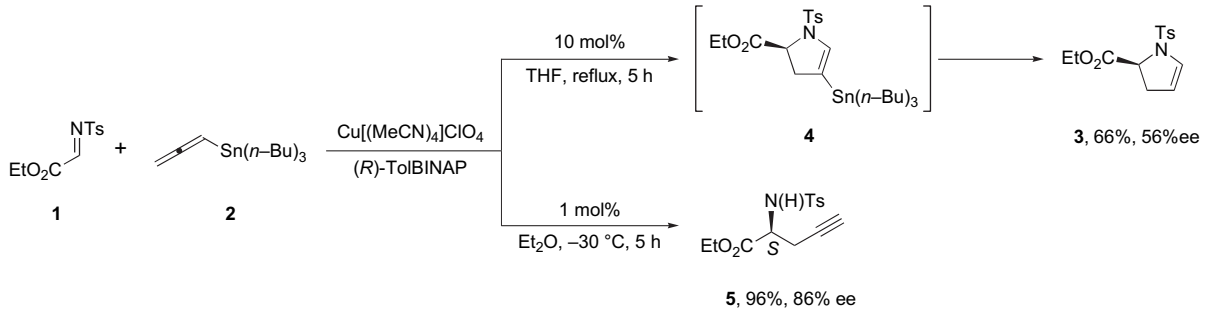
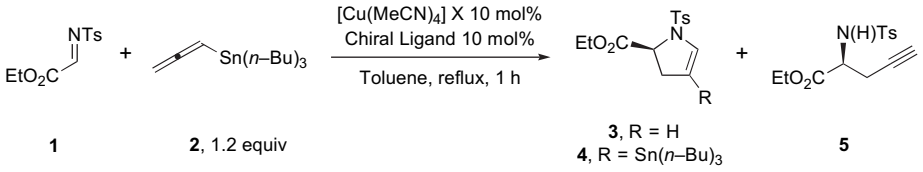


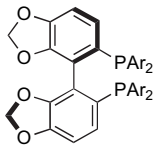
Scheme 2. [3+2]-Type cycloadditions of **1** and **2**.

Table 1. Ligand effect



Entry	Chiral ligand	X	**3**+**4** (%) (**3**/**4**), ee of **3** (%)[a]	**5** (%)[a,b]
1	(*R*)-TolBINAP	ClO_4	86 (91/9), 71	—
2	(*R*)-TolBINAP	BF_4	93 (63/37), 84	—
3	(*R*)-TolBINAP	PF_6	78 (87/13), 85	—
4	(*R*)-SEGPHOS	ClO_4	64 (66/34), 81	—
5	(*R*)-SEGPHOS	BF_4	9 (100/0), 70	55
6	(*R*)-SEGPHOS	PF_6	Trace (—), —	58, 63% ee
7	(*R*)-DM–SEGPHOS	ClO_4	26 (46/54), 72	56, 70% ee
8	(*R*)-DTBM–SEGPHOS	ClO_4	Trace (—), —	70

[a] The ee values of **3** and **5** were determined by chiral HPLC analysis.
[b] The ee values were not determined unless otherwise indicated.



Ar=Ph for (*R*)-SEGPHOS
Ar=(3,5-Me_2)C_6H_3 for (*R*)-DM-SEGPHOS
Ar=(3,5-*t*–Bu_2)(4-MeO)C_6H_2 for (*R*)-DTBM-SEGPHOS

nature of the phosphine ligand employed (Table 1). When **1** and **2** (1.2 equiv) were refluxed in toluene for 1 h in the presence of (*R*)-TolBINAP and cuprous salt ([Cu(MeCN)$_4$]ClO_4, –BF_4, –PF_6) (10 mol % each), cycloadducts (**3** and survived **4**) were obtained in good yields and propargylation product **5** was not obtained at all (Entries 1–3).[10] However, when (*R*)-SEGPHOS was used, **5** was produced by means of the BF_4 and PF_6 salts (Entries 5 and 6). When (*R*)-DM-SEGPHOS was used as a chiral ligand, **5** was formed preferentially even in the case of ClO_4 salt (Entry 7). Use of (*R*)-DTBM-SEGPHOS gave **5** as an essentially sole product (Entry 8). It seems that electron-donating ligand gives homopropargylamine **5** preferentially.

The structure of **4** was characterized spectroscopically. ^1H and ^{13}C NMR spectra were consistent with the structure of the expected 4-stannyldehydroproline ester. The isotope pattern of observed fragment ion ($M^+-C_4H_9$, $C_{22}H_{34}NO_4SSn$), in particular, was in complete agreement with its computer simulation (Fig. 1).

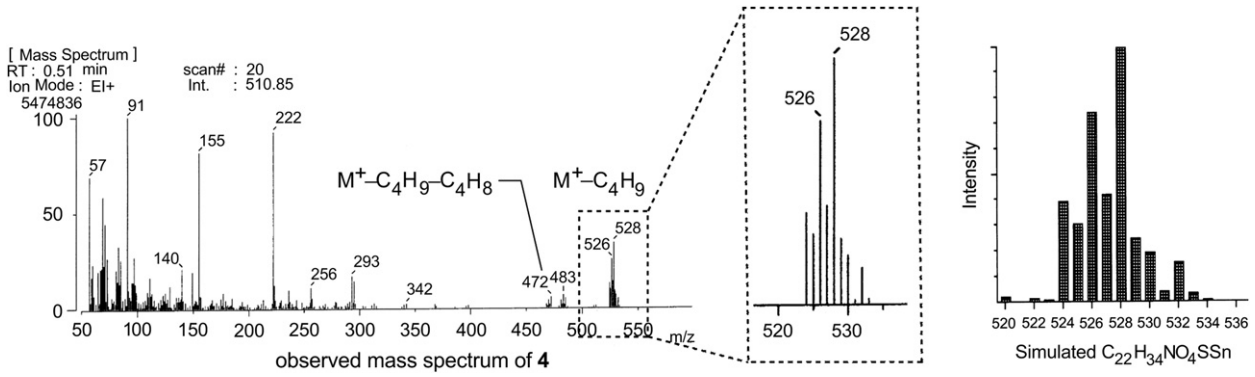


Figure 1. Mass spectrum of stannyldehydroproline **4**.

Table 2. Temperature and reaction time[a]

Entry	Temp	Time (h)	ee of **3** (%)[b]	**3**+**4** (%) (Ratio)	**5** (%)
1	Reflux	1	71	86 (91/9)	—
2	Reflux	5 min	89	45 (56/44)	39
3	80 °C	5	77	87 (66/34)	—
4	80 °C	3	82	82 (63/37)	—
5	80 °C	1	91	65 (55/45)	—
6	80 °C	0.5	94	25 (84/16)	61

[a] **1**/**2**/[Cu(MeCN)$_4$]ClO$_4$/(*R*)-TolBINAP=1/1.2/0.1/0.1, toluene.
[b] The ee values were determined by chiral HPLC analysis.

We optimized the reaction conditions by means of the [Cu(MeCN)$_4$]ClO$_4$/(*R*)-TolBINAP system. High ee values were achieved by carrying out the reaction at lower temperature and that prolonging the reaction time decreased the ee values (Table 2): the value of 71% ee (**3**) obtained by refluxing **1** and **2** for 1 h in toluene (Entry 1) increased up to 91% ee by carrying out the reaction in an oil bath of 80 °C (Entry 5).[11] When the reaction was allowed to proceed longer, the ee value decreased gradually (Entries 1, 2, and 3–6).

Besides, we could obtain considerable amount of **5** when the reaction was quenched in a short period of time (Entries 2 and 6). This propargylation product disappeared by prolonged time, and cycloaddition products were obtained.

In analogy to the silicon analogues,[4a–c] we initially surmised that this reaction proceeded by a migratory cyclization mechanism (left, in Scheme 3): allenylstannane **2** undergoes copper(I)-catalyzed nucleophilic addition with the α-imino ester **1**, giving a β-carbocation intermediate **6**. **6** undergoes C–Sn bond cleavage under mild conditions (e.g., in Scheme 2) to give stannylamide intermediate **7**, which is readily hydrolyzed to furnish homopropargylamine **5**. On the other hand, stannyl moiety of **6** undergoes 1,2-migration under more harsh conditions and simultaneous cyclization gives the stannyldehydroproline ester **4** and its protonolysis product **3**.

However, this mechanism is apparently inconsistent with the fact that we could obtain considerable amount of **5** in a short period of time, and after prolonging reaction time, we could obtain **3** and **4**, instead (Table 2)—regeneration of **6** from **7** is highly unlikely.

We thus rejected the migratory cyclization mechanism and adopted a sequential propargylation–cyclization mechanism (right, in Scheme 3): **6**, generated from **1** and **2**, undergoes rapid C–Sn bond cleavage to give **7**.[12] **7** is a resting intermediate and the subsequent copper(I)-catalyzed cyclization gives the stannyldehydroproline ester **4** probably via copper(I)-alkyne π complex.[13] On the other hand, when the reaction is carried out under mild conditions or quenched in a short period of time, the resting **7** is hydrolyzed during work-up to give **5**.[14] Use of electron-donating ligand retards the electrophilic cyclization process and also results in the formation of **5** (Table 1). Prolonged reaction time decreased enantioselectivity, indicating that **7** (and/or **4**) readily racemize(s) under the reaction conditions.[15]

We suppose that the absolute stereochemistry of the cycloadducts **3** and **4** is *S* because our enantioselective propargylation reaction afforded (*S*)-**5** (Scheme 1)[8] and enantioselective [3+2]-type cyclization of **1** and allenylsilanes afforded silyldehydroproline esters of *S* isomers.[3a] *Re* face of **1** might be shielded by pseudoequatorial tolyl group on copper(I)/(*R*)-TolBINAP/**1** complex (Fig. 2).

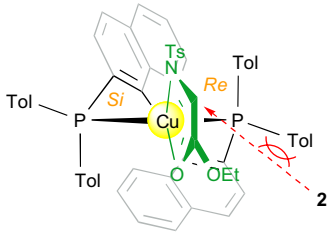
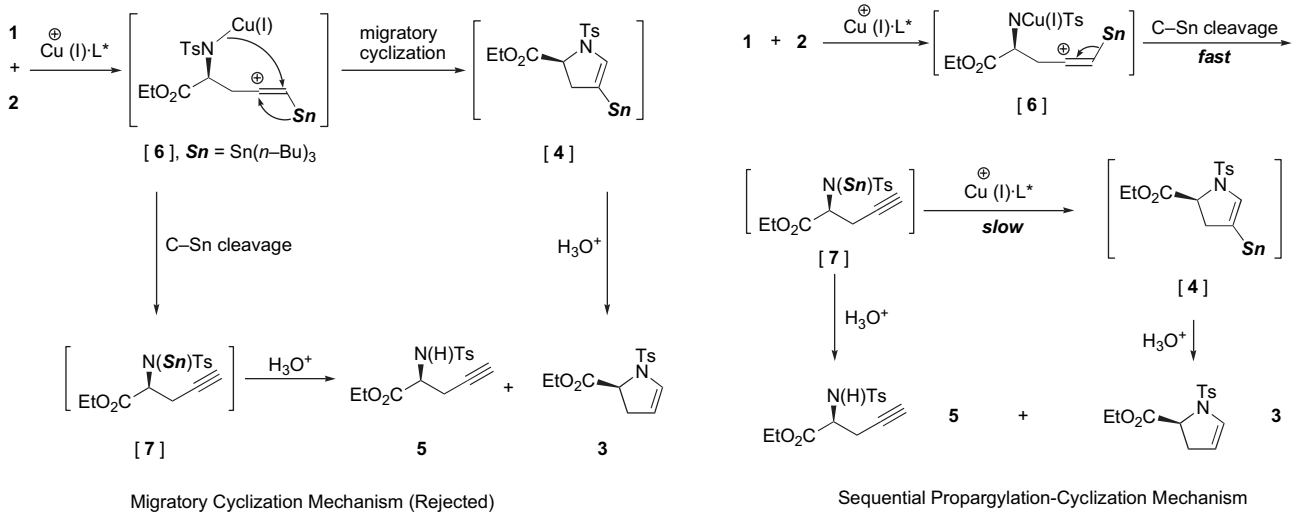


Figure 2. Working hypothesis of *Si*-face selective attack.

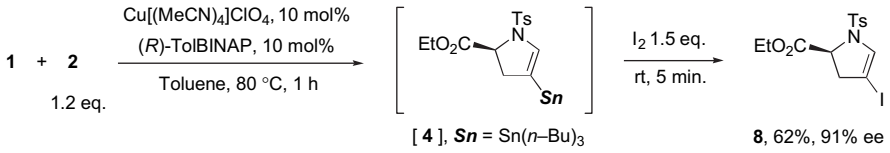
2.2. Functionalization of 4—iodine oxidation

The stannyldehydroproline ester **4** appeared to be an electron-rich, and thus reactive alkenylstannane. We expected

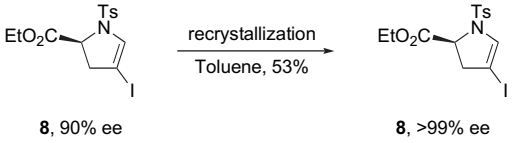


Scheme 3. Reaction mechanisms.

that **4** was a useful intermediate for synthesis of chiral dehydroproline ester derivatives: after **1** and **2** (1.2 equiv) were stirred for 1 h at 80 °C in the presence of $[Cu(MeCN)_4]ClO_4$ and (*R*)-TolBINAP (10 mol %, each), the resulting mixture containing **4** was treated with iodine (I_2, 1.5 equiv) at room temperature in the same flask. The iodine was consumed quite rapidly and reductive work-up with aqueous $Na_2S_2O_3$ gave 4-iododehydroproline ester **8** in 62% yield and 91% ee (Scheme 4). It should be noted that one recrystallization of **8** (90% ee) from toluene dramatically improved the ee value (Scheme 5). The minor enantiomer was not detected by chiral HPLC analysis and it is estimated that optical purity is >99% ee.



Scheme 4. Synthesis of chiral 4-iododehydroproline **8**.



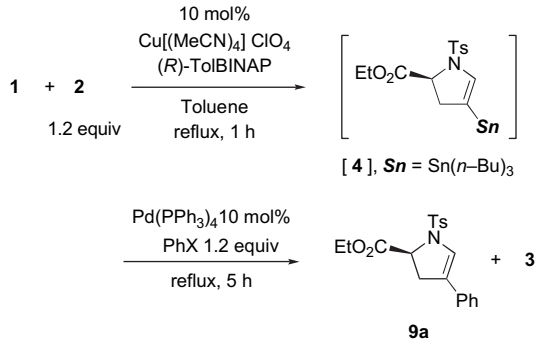
Scheme 5. Recrystallization of **8**.

2.3. Functionalization of 4—Stille coupling reaction

Three-component coupling was also accomplished by application of the Stille coupling reaction to **4** (Table 3). Stannyldehydroproline **4**, generated from **1** and **2** (toluene, reflux, 1 h), was subsequently treated with 1.2 equiv of iodo- or bromobenzene and 10 mol % of $Pd(PPh_3)_4$ in the same flask. After refluxing for 5 h, 4-phenylated dehydroproline ester **9a** was obtained in good yields (Entries 1 and 2). Chlorobenzene, phenyl trifluoromethanesulfonate, $[Cu(MeCN)_4]BF_4$, and $[Cu(MeCN)_4]PF_6$ gave disappointing results (Entries 3–6).

We could synthesize various 4-arylated dehydroproline esters in good yields and in high ees by the three-component coupling reaction, using aryl bromides particularly bearing electron-withdrawing group on their aromatic rings (Table 4).

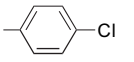
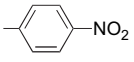
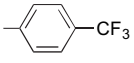
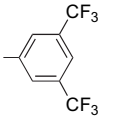
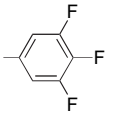
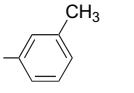
Table 3. Stille-type phenylation of **4**



Entry	PhX	**9a** (%), ee (%)[a]	**3** (%), ee (%)[a]
1	PhI	76, 78	20, 78
2	PhBr	81, 81	15, 85
3	PhCl	—	76, 75
4	PhOTf	—	80, 75
5[b]	PhI	4[d]	22, 72
6[c]	PhI	6[d]	41, 75

[a] The ee values were determined by chiral HPLC analysis.
[b] $Cu[(MeCN)_4]BF_4$ was employed.
[c] $Cu[(MeCN)_4]PF_6$ was employed.
[d] The ee values were not determined.

Table 4. Three-component synthesis of **9**[a]

Entry	Ar	**9** (%), ee (%)[b]	**3** (%), ee (%)[b]
1	Ph	62, 90 (**9a**)	20, 91
2		46, 93 (**9b**)	20, 93
3		80, 84 (**9c**)	13, 87
4		66, 90 (**9d**)	18, 92
5		43, 84 (**9e**)	20, 91
6		68, 87 (**9f**)	18, 72
7		34, 74 (**9g**)	24, 92

[a] **1/2**/$[Cu(MeCN)_4]ClO_4$/(*R*)-TolBINAP=1/1.2/0.1/0.1, toluene, 80 °C, 1 h; then ArBr (1.2 equiv), $Pd(PPh_3)_4$ (10 mol %), reflux, 5 h.
[b] The ee values were determined by chiral HPLC analysis.

3. Conclusion

We have developed a novel enantioselective [3+2]-type cycloaddition reactions of allenylstannane and α-imino ester. The reaction could be rationalized by a sequential propargylation–cyclization mechanism. Synthetic utility of the stannyldehydroproline ester intermediate was demonstrated; iodine oxidation and Stille coupling reaction afforded

optically active 4-iodo- and 4-aryldehydroproline esters in good yields and in high ees, respectively.

4. Experimental

4.1. General

NMR spectra were recorded on an Unity Inova-400 instrument (Varian Japan Ltd, 400 MHz for ^{1}H, 100 MHz for ^{13}C) and JNM-Al300 instrument (JEOL, 300 MHz for ^{1}H, 75 MHz for ^{13}C) using $CDCl_3$ as a solvent. Chemical shifts (δ) for ^{1}H were referenced to tetramethylsilane (δ=0.00 ppm) as an internal standard. Chemical shifts (δ) for ^{13}C were referenced to a solvent signal ($CDCl_3$, δ=77.00 ppm). IR spectra were recorded on FTIR-8600PC instrument (Shimadzu Co.) using $CHCl_3$ as a solvent. Elemental analysis (EA) was carried out on EA1110 instrument (Amco Inc.). Mass spectra (MS) were recorded on JMS-AX505HA instrument (JEOL). Specific rotation was recorded on SEPA-300 instrument (HORIBA, Ltd).

4.1.1. Preparation of the starting materials. α-Imino ester **1** was prepared according to the literature[16] $[Cu(MeCN)_4]PF_6$ was prepared according to the literature,[17] and its ClO_4 and BF_4 analogues were prepared by its modification. Allenyl(tributyl)stannane **2** was prepared by the following procedure: to a flask containing magnesium (0.44 g, 18 mmol), lead dibromide (0.33 g, 0.90 mmol), tetrahydrofuran (30 mL), and chloro(tributyl)stannane was added propargyl bromide (2.14 g, 18 mmol) over 5 min and the mixture was heated carefully. The mixture was stirred for 1 h at ambient temperature, quenched with saturated aqueous ammonium chloride, filtered through a pad of Celite®, and the residue was washed with ethyl acetate. Products were extracted with ethyl acetate and the combined organic layers were dried over anhydrous sodium sulfate. Solvents were evaporated under vacuum and purification by column chromatography (SiO_2, Hexane) gave allenyl(tributyl)stannane **2** (4.35 g, 88%).

4.1.2. Synthesis of 3 and 4 (Entry 5, Table 2). To a toluene solution (0.5 mL) containing $[Cu(MeCN)_4]ClO_4$ (6.5 mg, 0.020 mmol) and (*R*)-TolBINAP (14.9 mg, 0.022 mmol) were added **1** (51.1 mg, 0.20 mmol in 0.8 mL toluene) and **2** (79.0 mg, 0.24 mmol in 0.7 mL toluene) successively. The solution was stirred in an oil bath of 80 °C for 1 h. The resulting mixture was filtered through Celite® and the filtrate was concentrated under vacuum. The crude mixture was put on a silica gel (2 cm×30 cm) and a mixed eluent (Hexane/AcOEt=10/1, 150 mL) was passed through the SiO_2 column to remove non-polar stannane residue and then fractions containing **3** (21.4 mg, 36% yield, 91% ee) and **4** (33.8 mg, 29% yield) were collected (Hexane/AcOEt=8/1). The ee value of **3** was determined by chiral HPLC analysis (Daicel Chiralpak, AD-H, Hexane/EtOH=5/1).

4.1.3. Synthesis of 8 (Scheme 4). To a toluene solution (0.5 mL) containing $[Cu(MeCN)_4]ClO_4$ (4.7 mg, 0.014 mmol) and (*R*)-TolBINAP (11.2 mg, 0.016 mmol) were added **1** (38.3 mg, 0.15 mmol in 0.5 mL toluene) and **2** (59.2 mg, 0.18 mmol in 0.5 mL toluene) successively. The solution was stirred in an oil bath of 80 °C for 1 h. To the resulting mixture were added iodine (I_2, 57.1 mg, 0.23 mmol in 1.0 mL toluene) at room temperature, and after 5 min, saturated aqueous sodium thiosulfate was added. Products were extracted with ethyl acetate and combined organic layers were dried over anhydrous sodium sulfate. Purification by column chromatography (SiO_2, Hexane/AcOEt=8/1) gave **8** (101.9 mg, 62% yield, 91% ee). The ee value of **8** was determined by chiral HPLC analysis (Daicel Chiralpak, AS-H, Hexane/*i*-PrOH=5/1).

4.1.4. Synthesis of 9a (Entry 1, Table 4). To a toluene solution (0.5 mL) containing $[Cu(MeCN)_4]ClO_4$ (6.5 mg, 0.020 mmol) and (*R*)-TolBINAP (14.9 mg, 0.022 mmol) were added **1** (51.9 mg, 0.20 mmol in 0.8 mL toluene) and **2** (79.0 mg, 0.24 mmol in 0.7 mL toluene) successively. The solution was stirred in an oil bath of 80 °C for 1 h. To the resulting mixture were added $Pd(PPh_3)_4$ (23.3 mg, 0.020 mmol) and bromobenzene (37.7 mg, 0.24 mmol in 1 mL of toluene) at room temperature and the solution was refluxed for 5 h. The resulting mixture was filtered through Celite® and the filtrate was concentrated under vacuum. The crude mixture was put on a silica gel (2 cm×30 cm) and a mixed eluent (Hexane/AcOEt=10/1, 150 mL) was passed through the SiO_2 column to remove non-polar stannane residue. Fractions containing the products were collected (Hexane/AcOEt=5/1, 200 mL) and purification by preparative TLC (SiO_2, toluene/MeCN=5/1) gave **9a** (45.8 mg, 62% yield, 90% ee) and **3** (11.7 mg, 20%, 91% ee). The ee values of **9a** and **3** were determined by chiral HPLC analysis (Daicel Chiralcel, OD-H, Hexane/*i*-PrOH=5/1 for **9a**).

4.1.5. Compound data.

4.1.5.1. (*S*)-1-Tosyl-4,5-dehydroproline ethyl ester (3). ^{1}H NMR δ=1.31 (3H, t, *J*=7.2 Hz), 2.44 (3H, s), 2.65 (1H, ddt, *J*=16.4, 7.2, 2.4 Hz), 2.78 (1H, ddt, *J*=16.4, 11.2, 2.4 Hz), 4.23 (1H, dd, *J*=11.2, 7.2 Hz), 4.25 (2H, q, *J*=7.2 Hz), 5.07 (1H, dt, *J*=4.4, 2.4 Hz), 6.37 (1H, dt, *J*=4.4, 2.4 Hz), 7.33 (2H, d, *J*=8.2 Hz), 7.70 (2H, d, *J*=8.2 Hz); ^{13}C NMR δ=14.0, 21.6, 35.2, 60.2, 61.7, 109.6, 127.7, 129.7, 130.4, 133.4, 144.2, 170.9; IR $\overline{\nu}$=1016, 1169, 1362, 1734, 1749, 3022 cm^{-1}; EA Calcd for $C_{14}H_{17}NO_4S$: C 56.93, H 5.80, N 4.74, S 10.86%; Found: C 56.78, H 5.87, N 4.71, S 10.98%; $[\alpha]_D^{27}$ −443.10 (*c* 1.00, $CHCl_3$, 91% ee, Daicel Chiralpak AD-H, Hexane/EtOH=5/1, Flow rate 0.7 mL/min, UV=228 nm, t_R=16.91 min, t_S=21.43 min).

4.1.5.2. (*S*)-1-Tosyl-4-tributylstannyl-4,5-dehydroproline ethyl ester (4). ^{1}H NMR δ=0.85–0.91 (15H, m), 1.23–1.32 (9H, m), 1.38–1.44 (6H, m), 2.43 (3H, s), 2.68 (1H, ddd, *J*=16.2, 7.4, 2.0 Hz), 2.81 (1H, ddd, *J*=16.2, 10.8, 2.0 Hz), 4.11 (1H, dd, *J*=10.8, 7.4 Hz), 4.24 (2H, q, *J*=7.2 Hz), 6.18 (1H, t, *J*=2.0 Hz), 7.31 (2H, d, *J*=8.2 Hz), 7.68 (2H, d, *J*=8.2 Hz); ^{13}C NMR δ=9.5, 13.6, 14.1, 21.5, 27.1, 28.9, 41.9, 60.5, 61.5, 119.4, 127.7, 129.6, 133.5, 134.8, 143.9, 171.5; IR $\overline{\nu}$=1167, 1205, 1225, 1356, 1734, 1749, 3017, 3022 cm^{-1}; MS (DI) Isotope pattern of fragment ion ($M^+-C_4H_9$, $C_{22}H_{34}NO_4SSn$) was in complete agreement with its computer simulation (see text).

4.1.5.3. Ethyl (*S*)-2-tosylamino-4-pentynoate (5). ^{1}H NMR δ=1.17 (3H, t, *J*=7.2 Hz), 2.03 (1H, t, *J*=2.6 Hz), 2.42 (3H, s), 2.65 (1H, ddd, *J*=16.8, 5.2, 2.6 Hz), 2.72

(1H, ddd, J=16.8, 4.4, 2.6 Hz), 4.02–4.11 (3H, m), 5.43 (1H, d, J=8.4 Hz), 7.30 (2H, d, J=8.0 Hz), 7.75 (2H, d, J=8.0 Hz); ^{13}C NMR δ=13.9, 21.5, 24.1, 54.0, 62.2, 72.2, 127.2, 129.7, 136.9, 143.8, 169.5; IR $\overline{\nu}$=1018, 1094, 1163, 1229, 1371, 1740, 3013 cm^{-1}; EA Calcd for $C_{14}H_{17}NO_4S$: C 56.93, H 5.80, N 4.74, S 10.86%; Found: C 57.10, H 5.82, N 4.53, S 10.64%; $[\alpha]_D^{26}$ +15.20 (c 1.00, $CHCl_3$, 67% ee, Daicel Chiralpak AD-H, Hexane/EtOH=5/1, Flow rate 0.5 mL/min, UV=228 nm, t_R=42.46 min, t_S=36.14 min).

4.1.5.4. (*S*)-4-Iodo-1-tosyl-4,5-dehydroproline ethyl ester (8). ^{1}H NMR δ=1.30 (3H, t, J=7.2 Hz), 2.45 (3H, s), 2.82 (1H, ddd, J=16.2, 7.2, 2.0 Hz), 2.97 (1H, ddd, J=16.2, 11.2, 2.0 Hz), 4.25 (2H, q, J=7.2 Hz), 4.27 (1H, dd, J=11.2, 7.2 Hz), 6.53 (1H, t, J=2.0 Hz), 7.36 (2H, d, J=8.2 Hz), 7.70 (2H, d, J=8.2 Hz); ^{13}C NMR δ=14.1, 21.8, 44.4, 61.1, 62.1, 67.9, 127.6, 129.8, 132.9, 135.3, 144.5, 169.7; IR $\overline{\nu}$=1099, 1169, 1296, 1364, 1734, 3032 cm^{-1}; EA Calcd for $C_{14}H_{16}INO_4S$: C 39.92, H 3.83, N 3.33, S 7.61%; Found: C 39.98, H 3.74, N 3.31, S 7.58%; $[\alpha]_D^{27}$ −175.80 (c 1.00, $CHCl_3$, >99% ee, Daicel Chiralpak AS-H, Hexane/*i*-PrOH=5/1, Flow rate 0.7 mL/min, UV=228 nm, t_S=36.73 min).

4.1.5.5. (*S*)-4-Phenyl-1-tosyl-4,5-dehydroproline ethyl ester (9a). ^{1}H NMR δ=1.32 (3H, t, J=7.2 Hz), 2.42 (3H, s), 2.98 (1H, ddd, J=15.6, 7.2, 1.8 Hz), 3.15 (1H, ddd, J=15.6, 11.6, 1.8 Hz), 4.28 (2H, q, J=7.2 Hz), 4.37 (1H, dd, J=11.6, 7.2 Hz), 6.85 (1H, t, J=1.8 Hz), 7.21 (1H, t, J=6.4 Hz), 7.23 (2H, d, J=7.8 Hz), 7.26–7.35 (4H, m), 7.74 (2H, d, J=7.8 Hz); ^{13}C NMR δ=14.1, 21.6, 35.8, 60.6, 61.9, 122.7, 124.7, 124.8, 127.3, 127.6, 128.6, 129.9, 132.9, 133.4, 144.3, 170.8; IR $\overline{\nu}$=1167, 1205, 1227, 1362, 1734, 1749, 3024 cm^{-1}; EA Calcd for $C_{20}H_{21}NO_4S$: C 64.67, H 5.70, N 3.77, S 8.63%; Found: C 64.80, H 5.62, N 3.59, S 8.46%; $[\alpha]_D^{26}$ −41.30 (c 1.00, $CHCl_3$, 90% ee, Daicel Chiralcel OD-H, Hexane/*i*-PrOH=5/1, Flow rate 0.5 mL/min, UV=228 nm, t_R=21.96 min, t_S=34.47 min).

4.1.5.6. (*S*)-4-(4-Chlorophenyl)-1-tosyl-4,5-dehydroproline ethyl ester (9b). ^{1}H NMR δ=1.32 (3H, t, J=7.2 Hz), 2.43 (3H, s), 2.95 (1H, ddd, J=15.6, 7.2, 1.8 Hz), 3.14 (1H, ddd, J=15.6, 11.4, 1.8 Hz), 4.27 (2H, q, J=7.2 Hz), 4.39 (1H, dd, J=11.4, 7.2 Hz), 6.84 (1H, t, J=1.8 Hz), 7.14 (2H, d, J=8.4 Hz), 7.26 (2H, d, J=8.4 Hz), 7.33 (2H, d, J=8.4 Hz), 7.73 (2H, d, J=8.4 Hz); ^{13}C NMR δ=14.1, 21.6, 35.8, 60.6, 62.0, 121.4, 125.4, 125.8, 127.6, 128.8, 130.0, 131.5, 132.9, 133.4, 144.5, 170.6; IR $\overline{\nu}$=1096, 1167, 1211, 1362, 1495, 1636, 1734, 2359, 3017 cm^{-1}; EA Calcd for $C_{20}H_{20}ClNO_4S$: C 59.18, H 4.97, N 3.45, S 7.90%; Found: C 58.99, H 4.83, N 3.20, S 7.70%; $[\alpha]_D^{25}$ −17.37 (c 0.95, $CHCl_3$, 93% ee, Daicel Chiralpak AD-H, Hexane/*i*-PrOH=5/1, Flow rate 0.5 mL/min, UV=228 nm, t_R=51.82 min, t_S=56.96 min).

4.1.5.7. (*S*)-4-(4-Nitrophenyl)-1-tosyl-4,5-dehydroproline ethyl ester (9c). ^{1}H NMR δ=1.32 (3H, t, J=7.2 Hz), 2.44 (3H, s), 3.04 (1H, ddd, J=15.6, 7.2, 1.8 Hz), 3.26 (1H, ddd, J=15.6, 11.6, 1.8 Hz), 4.27 (2H, q, J=7.2 Hz), 4.49 (1H, dd, J=11.6, 7.2 Hz), 7.09 (1H, t, J=1.8 Hz), 7.33 (2H, d, J=8.6 Hz), 7.36 (2H, d, J=8.6 Hz), 7.76 (2H, d, J=8.6 Hz), 8.15 (2H, d, J=8.6 Hz); ^{13}C NMR δ=14.0, 21.6, 35.6, 60.7, 62.1, 119.8, 124.1, 124.8, 127.6, 129.1, 130.1, 133.6, 139.7, 144.8, 146.2, 170.2; IR $\overline{\nu}$=1169, 1205, 1225, 1344, 1518, 1734, 3024 cm^{-1}; EA Calcd for $C_{20}H_{20}N_2O_6S$: C 57.68, H 4.84, N 6.73, S 7.70%; Found: C 57.72, H 4.93, N 6.79, S 7.60%; $[\alpha]_D^{25}$ +42.35 (c 1.00, $CHCl_3$, 84% ee, Daicel Chiralcel OD-H, Hexane/EtOH=5/1, Flow rate 0.5 mL/min, UV=350 nm, t_R=63.20 min, t_S=53.82 min).

4.1.5.8. (*S*)-1-Tosyl-4-(4-trifluoromethylphenyl)-4,5-dehydroproline ethyl ester (9d). ^{1}H NMR δ=1.32 (3H, t, J=7.0 Hz), 2.43 (3H, s), 3.00 (1H, ddd, J=15.6, 7.2, 1.8 Hz), 3.20 (1H, ddd, J=15.6, 11.4, 2.0 Hz), 4.27 (2H, q, J=7.0 Hz), 4.43 (1H, dd, J=11.4, 7.2 Hz), 6.97 (1H, s), 7.30 (2H, d, J=8.6 Hz), 7.34 (2H, d, J=8.0 Hz), 7.53 (2H, d, J=8.6 Hz), 7.75 (2H, d, J=8.0 Hz); ^{13}C NMR δ=14.0, 21.6, 35.7, 60.6, 62.0, 120.9, 124.7, 125.6 (q, $^3J_{C-F}$=3.8 Hz), 127.1, 127.6, 127.9 (q, $^1J_{C-F}$=285 Hz), 129.0 (q, $^2J_{C-F}$=33 Hz), 123.0, 133.5, 136.5, 144.6, 170.5; IR $\overline{\nu}$=1130, 1169, 1209, 1325, 1616, 1749, 2359, 3018 cm^{-1}; EA Calcd for $C_{21}H_{20}NO_4S$: C 57.40, H 4.59, N 3.19, S 7.30%; Found: C 57.47, H 4.37, N 3.28, S 7.12%; $[\alpha]_D^{24}$ −26.90 (c 1.00, $CHCl_3$, 90% ee, Daicel Chiralpak AD-H, Hexane/EtOH=5/1, Flow rate 0.5 mL/min, UV=228 nm, t_R=65.07 min, t_S=56.22 min).

4.1.5.9. (*S*)-4-[3,5-Bis(trifluoromethyl)phenyl]-1-tosyl-4,5-dehydroproline ethyl ester (9e). ^{1}H NMR δ=1.33 (3H, t, J=7.2 Hz), 2.44 (3H, s), 3.03 (1H, ddd, J=15.6, 7.2, 1.8 Hz), 3.27 (1H, ddd, J=15.6, 11.6, 1.8 Hz), 4.27 (2H, q, J=7.2 Hz), 4.49 (1H, dd, J=11.6, 7.2 Hz), 7.06 (1H, s), 7.36 (2H, d, J=8.6 Hz), 7.59 (2H, s), 7.68 (1H, s), 7.77 (2H, d, J=8.6 Hz); ^{13}C NMR δ=14.0, 21.6, 35.6, 60.5, 62.2, 119.2, 120.1–120.5 (m), 124.2, 127.6, 128.3, 130.1, 132.0 (q, $^2J_{C-F}$=33 Hz), 133.6, 135.3, 144.8, 170.2; IR $\overline{\nu}$=1142, 1169, 1184, 1281, 1369, 1634, 1749, 3032 cm^{-1}; EA Calcd for $C_{22}H_{19}F_6NO_4S$: C 52.07, H 3.77, N 2.76, S 6.32%; Found: C 52.30, H 3.76, N 2.50, S 6.57%; $[\alpha]_D^{24}$ −42.90 (c 1.00, $CHCl_3$, 84% ee, Daicel Chiralpak AD-H, Hexane/EtOH=50/1, Flow rate 0.5 mL/min, UV=228 nm, t_R=30.72 min, t_S=23.26 min).

4.1.5.10. (*S*)-1-Tosyl-4-(3,4,5-trifluorophenyl)-4,5-dehydroproline ethyl ester (9f). ^{1}H NMR δ=1.32 (3H, t, J=7.0 Hz), 2.44 (3H, s), 2.91 (1H, ddd, J=15.6, 7.2, 1.6 Hz), 3.11 (1H, ddd, J=15.6, 11.6, 1.6 Hz), 4.26 (2H, q, J=7.0 Hz), 4.42 (1H, dd, J=11.6, 7.2 Hz), 6.80 (2H, dd, J=6.4, 8.4 Hz), 6.82 (1H, s), 7.35 (2H, d, J=8.4 Hz), 7.74 (2H, d, J=8.4 Hz); ^{13}C NMR δ=14.1, 21.6, 35.7, 60.5, 62.1, 108.6 (dd, $^2J_{C-F}$=15 Hz, $^3J_{C-F}$=6.8 Hz), 119.4–119.6 (m), 127.0, 127.6, 129.7, 130.0, 133.5, 138.8 (d, $^1J_{C-F}$=252 Hz), 144.7, 151.3 (d, $^1J_{C-F}$=236 Hz), 170.3; IR $\overline{\nu}$=1016, 1169, 1205, 1227, 1533, 1734, 1749, 3017, 3024 cm^{-1}; EA Calcd for $C_{20}H_{18}F_3NO_4S$: C 56.46, H 4.26, N 3.29, S 7.54%; Found: C 56.28, H 4.29, N 3.30, S 7.54%; $[\alpha]_D^{26}$ −64.05 (c 1.00, $CHCl_3$, 87% ee, Daicel Chiralpak AD-H, Hexane/EtOH=5/1, Flow rate 0.7 mL/min, UV=228 nm, t_R=25.56 min, t_S=18.11 min).

4.1.5.11. (*S*)-4-(3-Tolyl)-1-tosyl-4,5-dehydroproline ethyl ester (9g). ^{1}H NMR δ=1.32 (3H, t, J=7.0 Hz), 2.32 (3H, s), 2.42 (3H, s), 2.96 (1H, ddd, J=15.8, 7.1, 1.8 Hz), 3.14 (1H, ddd, J=15.8, 11.5, 1.8 Hz), 4.27 (2H, q,

J=7.0 Hz), 4.35 (1H, dd, J=11.5, 7.1 Hz), 6.84 (1H, t, J=1.8 Hz), 7.01–7.05 (2H, m), 7.16–7.24 (2H, m), 7.32 (2H, d, J=8.1 Hz), 7.73 (2H, d, J=8.1 Hz); ^{13}C NMR δ=14.1, 21.4, 21.6, 35.9, 60.6, 61.9, 121.8, 122.8, 124.7, 125.4, 127.6, 128.2, 128.5, 129.9, 132.8, 133.4, 138.2, 144.3, 170.8; IR $\bar{\nu}$=1092, 1167, 1362, 1734, 3018 cm^{-1}; EA Calcd for $C_{21}H_{23}NO_4S$: C 65.43, H 6.01, N 3.63, S 8.32%; Found: C 65.24, H 5.95, N 3.61, S 8.17%; $[\alpha]_D^{27}$ −19.04 (c 0.99, $CHCl_3$, 74% ee, Daicel Chiralpak AS-H, Hexane/EtOH=5/1, Flow rate 0.5 mL/min, UV=228 nm, t_R=23.22 min, t_S=18.28 min).

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10. Compound **3** was not observed just after concentration of the reaction mixture (^{1}H NMR analysis). Partial protonolysis of the cycloadduct **4** took place on silica gel during purification. Compounds **3** and **4** were isolated and total yields are indicated in Table 1 for clarity.
11. The ee value was not improved further by carrying out the reaction in an oil bath of 60 °C (93% ee) and the yield of **3** miserably decreased to 13%.
12. We suppose that weaker C–Sn bond is responsible for this fast process.
13. In the presence of the copper(I) catalyst, **5** (69% ee) underwent cyclization to give 18% yield of **3** (83% ee) and 82% recovery of **5** (62% ee) (10 mol % of $[Cu(MeCN)_4]ClO_4$, 10 mol % (*R*)-TolBINAP, toluene, 80 °C, 5 h). For Pd(0)-catalyzed cyclization of methyl ester corresponding to **5** see: Wolf, L. B.; Tjen, K. C. M. F.; Rutjes, F. P. J. T.; Hiemstra, H.; Schoemaker, H. E. *Tetrahedron Lett.* **1998**, *39*, 5081; We also treated **5** with *n*-BuLi/*n*-Bu_3SnCl in THF at –78 °C and then attempted Cu(I)-catalyzed cyclization. Indeed, **3** was obtained, but in 3% yield.
14. When the catalyst loading was lowered to 1 mol %, the cyclization did not take place to give homopropargylamine **5** exclusively in 75% yield, 64% ee (toluene, reflux, 1 h).
15. It was confirmed that dehydroproline ester **3** did not racemize under the reaction conditions. Compound **3** of 83% ee afforded 91% recovery of **3** with 83% ee even after 5 h stirring (10 mol % of $[Cu(MeCN)_4]ClO_4$, 10 mol % (*R*)-TolBINAP, toluene, and 80 °C).
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