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Enantioselective three-component synthesis of 4-arylated dehydroprolines: [3+2] annulation of allenylstannane and α-imino ester

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Abstract—An enantioselective [3+2] annulation reaction of allenylstannane and α-imino ester was developed. Stille coupling of the resulting 4-stannyl dehydroproline gave optically active 4-arylated dehydroprolines in good yields.

1. Introduction

Proline is a ubiquitous component of proteins and peptides, and at the same time, a versatile reagent in synthetic organic chemistry. For instance, chiral diamines and amino alcohols (prolinols) prepared from (*S*)-proline are good ligands for asymmetric aldol reactions,[1a] alkylation of aldehydes,[1b] and Michael addition reactions.[1c] Chiral oxazaborolidines readily prepared from the prolinols are efficient catalysts both for asymmetric reduction of ketones[1d] and for asymmetric Diels–Alder reactions.[1e–h] Parent proline and its substituted form have recently attracted much attention due to their potentiality as organocatalysts.[2] Development of synthetic method of proline and its derivatives is thus a significant issue so as to supply these materials.[3]

In this communication, we describe a three-component synthesis of optically active 4-arylated dehydroprolines, which utilizes novel [3+2] annulation of allenylstannane and α-imino ester.

2. Results and discussion

Previously, we reported copper(I)-catalyzed enantioselective propargylation of α-imino ester with allenylstannanes.[4] As shown in Scheme 1, we could obtain homopropargylamine **3** of *S* isomer by a reaction of **1** and **2** in the presence of $[Cu(MeCN)_4]ClO_4$ and (*R*)-TolBINAP (1 mol % each)[5] at −30 °C (96% yield, 86% ee). In contrast, we recently found that reaction course changed dramatically when we attempted the propargylation under more harsh conditions: **1** and **2** reacted in the presence of 10 mol % of the catalyst at higher temperature to give [3+2] annulation product, dehydroproline **4** in 66% yield, 56% ee.[6,7]

In order to obtain dehydroproline **4** efficiently, we optimized the reaction conditions (Table 1). When the reaction was carried out in refluxing toluene, **4**, and stannyldehydroproline **5**[8] were obtained in 78% (71% ee) and 8% yield, respectively (entry 1).[6] The ee value of **4** increased up to 91% by carrying out the reaction in an oil bath of 80 °C (entry 5).[9] Interestingly, short reaction time led to improvement of the enantioselectivities (entries 1–2 and 3–6), but **3** was formed again when the reactions were quenched in 5 or 30 min (entries 2 and 6).

We initially surmised that this reaction proceeded by a migratory cyclization mechanism similar to cyclopentene annulation of silicon analogues (Scheme 2, left):[10] nucleophilic addition of **2** to **1** gives β-carbocation intermediate **6**. Compound **6** undergoes 1,2-migration and simultaneous cyclization gives the stannyl dehydroproline **5**, which affords **4** by protonolysis. But this mechanism was considerably suspicious because we obtained **3** when the reaction was carried out under mild conditions (e.g., in Scheme 1).

Keywords: Allenylstannane; Annulation; Asymmetric synthesis; α-Imino ester; Proline; Stille coupling.
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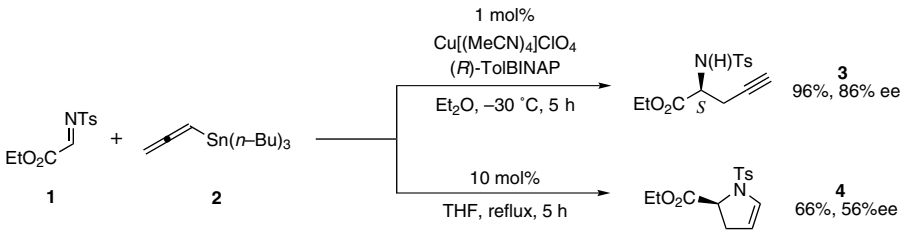
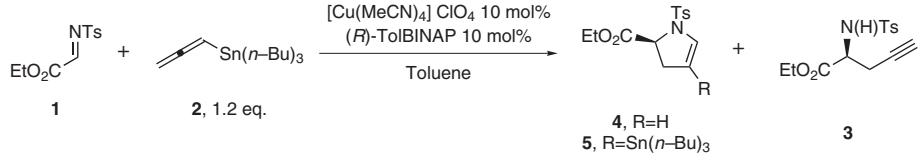


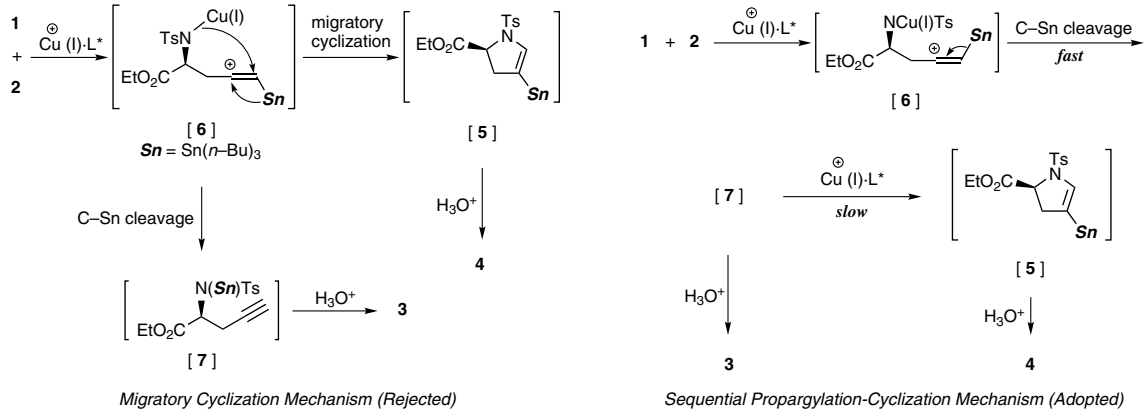
Scheme 1. Formation of dehydroproline **4**.

Table 1. Optimization of reaction temperature and time



Entry	Temperature	Time (h)	**4** (%)	ee of **4**[a] (%)	**5**[b] (%)	**3**[b] (%)
1	Reflux	1	78	71	8	—
2		5 min	25	89	20	39
3	80 °C	5	57	77	30	—
4		3	52	82	30	—
5		1	36	91	29	—
6		0.5	21	94	4	61

[a] ee values were determined by chiral HPLC analysis.
[b] ee values were not determined.



Scheme 2. Proposed reaction mechanisms.

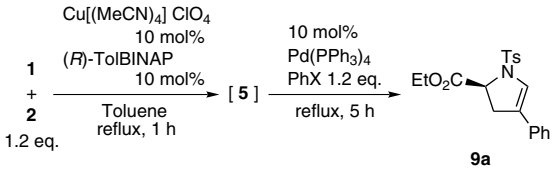
We thus rejected the migratory cyclization mechanism and adopted a sequential propargylation–cyclization mechanism (Scheme 2, right): **6**, generated from **1** and **2**, undergoes rapid C–Sn bond cleavage to give homopropargylamide **7**. Subsequent copper(I)-catalyzed cyclization of **7** gives stannyl dehydroproline **5** probably via Sn–Cu exchange and insertion to alkyne π bond.[11] The latter process is relatively slow and homopropargylamine **3** is obtained by hydrolysis of **7** when the reaction was quenched in a short period of time. Compound **7** (and/or **5**) presumably racemize(s) readily under the reaction conditions and short reaction time improved the optical purity of **4**.[12]

It is of great interest that cyclization mechanism of allenylstannane is quite different from that of silicon analogue. Weaker C–Sn bond might be responsible for the fast C–Sn bond cleavage of the intermediate **6**.

Three-component coupling was accomplished by application of Stille coupling reaction to **5** (Table 2). Stannyl dehydroproline **5**, 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 5 h reflux, 4-phenylated dehydroproline **9a** was obtained in good yields (entries 1 and 2) although chlorobenzene, phenyl trifluoromethanesulfonate, $[Cu(MeCN)_4]BF_4$, and $[Cu(MeCN)_4]PF_6$ gave disappointing results (entries 3–6).

We could synthesize optically active 4-arylated dehydroprolines **9** by means of the three-component coupling

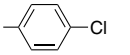
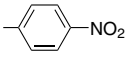
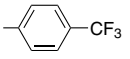
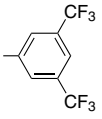
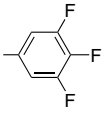
Table 2. Stille phenylation of **5**



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

[a] $Cu[(MeCN)_4]BF_4$ was employed.
[b] $Cu[(MeCN)_4]PF_6$ was employed.

Table 3. Three-component synthesis of 4-arylated dehydroprolines[a]

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

[a] **1**:**2**:[$Cu(MeCN)_4ClO_4$]–(*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] ee values were determined by chiral HPLC analysis.
[c] 24% yield of **4** was obtained (92% ee).

reaction (Table 3). Aryl bromides bearing electron-withdrawing group particularly gave good results.

In summary, we could develop a three-component synthesis of 4-arylated dehydroprolines, utilizing enantioselective [3+2] annulation reaction of allenylstannane with α-imino ester.

3. Experimental

3.1. Preparation of 4 and 5 (Table 1, entry 5)

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 **4** (21.4 mg, 36% yield, 91% ee) and **5** (33.8 mg, 29% yield) were collected (hexane/AcOEt = 8/1). The ee value of **4** was determined by chiral HPLC analysis (Daicel Chiralpak, AD-H, hexane/EtOH = 5/1). (*S*)-*1-Tosyl-4,5-dehydroproline ethyl ester* (**4**): ^1H NMR (400 MHz): $\delta = 1.31$ (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 (75 MHz): $\delta = 14.04$, 21.56, 35.23, 60.20, 61.71, 109.55, 127.70, 129.74, 130.35, 133.38, 144.15, 170.94; IR $\tilde{\nu} = 1016$, 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). (*S*)-*1-Tosyl-4-tributylstannyl-4,5-dehydroproline ethyl ester* (**5**): ^1H NMR (400 MHz): $\delta = 0.85$–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 (75 MHz): $\delta = 9.53$, 13.59, 14.06, 21.52, 27.12, 28.92, 41.88, 60.54, 61.53, 119.42, 127.68, 129.58, 133.45, 134.78, 143.88, 171.54; IR $\tilde{\nu} = 1167$, 1205, 1225, 1356, 1734, 1749, 3017, 3022 cm^{-1}; MS $m/z =$ 528 ($M^+ - C_4H_9$, $C_{22}H_{34}NO_4SSn$).

3.2. Preparation of 9a (Table 3, entry 1)

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 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 **4** (11.7 mg, 20%, 91% ee). The ee values of **9a** and **4** were determined by chiral HPLC analysis (Daicel Chiralcel, OD-H, hexane/*i*-PrOH = 5/1 for **9a**). (*S*)-*4-Phenyl-1-tosyl-4,5-dehydroproline ethyl ester* (**9a**):

^{1}H NMR (400 MHz): $\delta = 1.32$ (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, dd, $J = 1.8$, 1.8 Hz), 7.21 (1H, dd, $J = 6.4$, 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 (75 MHz): $\delta = 14.08$, 21.57, 35.82, 60.60, 61.90, 122.68, 124.67, 124.83, 127.34, 127.63, 128.62, 129.91, 132.92, 133.43, 144.31, 170.76; IR $\tilde{\nu} = 1167$, 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).

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8. Compound **4** was not detected just after concentration of the reaction mixture (^{1}H NMR analysis). Partial protonolysis of **5** took place on silica gel during purification.
9. Ee value was not improved further by carrying out the reaction in an oil bath of 60 °C (93% ee) and the yield of **4** decreased to 13%.
10. (a) Danheiser, R. L.; Carini, D. J.; Fink, D. M.; Basak, A. *Tetrahedron* **1983**, *39*, 935; (b) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293; See also: (c) Knölker, H.-J. *J. Prakt. Chem.* **1997**, *339*, 304; (d) Panek, J. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, p 579.
11. Compound **3** (69% ee) underwent cyclization in the presence of the copper(I) catalyst (10 mol %, toluene, 80 °C, 5 h) to give 18% yield of **4** (83% ee) and 82% recovery of **3** (62% ee). See also: Wolf, L. B.; Tjen, K. C. M. F.; ten Brink, H. T.; Blaauw, R. H.; Hiemstra, H.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2002**, *344*, 70.
12. It was confirmed that dehydroproline **4** did not racemize under the reaction conditions (10 mol % of $[Cu(MeCN)_4]ClO_4$, 10 mol % of (*R*)-TolBINAP, toluene, 80 °C). Compound **4** of 83% ee afforded 91% recovery of **4** with 83% ee even after 5 h stirring.