Catalytic asymmetric alkynylation of α-imino ester: A versatile approach to optically active unnatural α-amino acid derivatives

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The catalytic asymmetric introduction of alkynyl functionality to α-amino acid derivatives was realized by the direct addition of terminal alkynes to α-imino ester in the presence of chiral Cu(I) complex under mild reaction conditions. Owing to the rich chemistry to which alkyne can be subjected, the present system provides a remarkably versatile tool for the construction of optically active α-amino acid derivatives. Good yields and enantiomeric excess values were achieved with an array of terminal alkynes and challenging, biologically active, unnatural α-amino acid derivatives could be conveniently obtained.

asymmetric catalysis

Optically active nonproteinogenic α-amino acids are of exceptional and rapidly increasing popularity as important tools in protein engineering and peptide-based drug discovery due mainly to their implementation into nonscissile peptide mimics and peptide isosteres (1–7). Hence, intense research has been focused on the preparation of enantiomerically enriched unnatural α-amino acids, and, so far, several approaches, such as bioresolution routes (8–10) and the rhodium- or ruthenium-catalyzed asymmetric hydrogenation of dehydroamino acids derivatives (11–13), have shown much promise. Nevertheless, there is still a great demand for more efficient and, especially, technically feasible methods for convenient construction of various types of rational designed unnatural amino acid derivatives. In this regard, enantioselective nucleophilic addition to α-imino esters represents one of the most direct strategies (14), because a new chiral center and a new C—C bond can be built in a single operation and an appropriately designed side chain can be introduced in the meantime. Previous work in this field mainly focused on the catalytic asymmetric alkylation of α-imino esters, in which enol silane (15–18), allyl-metal compounds (19, 20), trimethylsilyl nitronate (21), ketone (22), and nitroalkane (23) have been used as nucleophiles.

Recently, we reported the successful alkynylation of α-imino ester by demonstrating the feasibility of direct addition of terminal alkynes to α-imino ester **1** in the presence of Ag(I) salts under mild reaction conditions (Scheme 1) (24). In this process, a new bond between an sp^3 carbon and an sp carbon is formed.

Capitalizing on this method, we envisioned an attractive route to optically active α-amino acid derivatives via the direct asymmetric alkynylation of α-imino ester. The following considerations are particularly noteworthy:

1. The HC≡C moiety is an excellent two-carbon medium for the delivery of biologically interesting units into the γ-position of α-amino acids, because it could be easily hydrogenated to saturated status after completing the nucleophile role. In contrast, owing to the rich chemistry to which alkyne can be subjected, the presence of a C≡C bond in the desired targets offers a unique and highly valuable opportunity for further synthetic elaboration on the β,γ-positions of α-amino acids. For example, semireduction of the products could
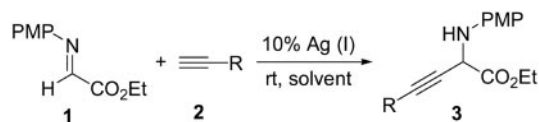
Scheme 1. Ag(I)-catalyzed alkynylation of α-imino ester.

directly afford vinyl glycine derivatives, which are of increasing potential in therapeutic utility although their catalytic synthesis remains a challenge (25–28).

2. This reaction is really atom economical as the nucleophile is generated directly. In previous study, the similar alkynylglycine skeleton was formed via coupling of α-haloglycinates with excessive reactive metal alkynilides (29, 30), which were prepared by deprotonation of terminal alkynes with stoichiometric BuLi or EtMgBr in a separate procedure.

3. A number of terminal alkynes are commercially available, and furthermore, there have been several routine procedures providing general and convenient accesses to a wide range of terminal alkynes with comprehensive substituents.

In this paper, we report the first catalytic asymmetric alkynylation of α-imino ester. Good to high yields and enantiomeric excess (ee) values were obtained when employing CuPF$_6$·4MeCN/bis(oxazolidine)-pyridine (pybox) **9** (31) and CuOTf·0.5C$_6$H$_6$/pybox **9** as catalysts. As a simple illustration of the application of this methodology, one of the alkynylation products was conveniently transformed to synthetically challenging, biologically active, unnatural α-amino acid derivatives.

Experimental Procedures

General Information. ^{1}H NMR and ^{13}C NMR spectra were recorded in CDCl$_3$ on a Varian AS 500 (500 and 125 MHz, respectively) NMR spectrometer at room temperature. Chemical shifts (δ) are expressed in ppm, and J values are given in Hz. High-resolution mass spectrometry (HRMS) was carried out by using the electrospray ionization (ESI) method on a Fisons VG platform or a MAT-95 spectrometer (Finnigan–MAT, San Jose, CA). HPLC analyses were performed by using a Waters 600 analytical liquid chromatography system with a Waters 486 UV detector. Optical rotations were measured on a PerkinElmer 341 polarimeter in a 10-cm cell. All reactions were conducted under a nitrogen atmosphere. All chemicals and solvents were used as received without further purification unless otherwise stated. CH$_2$Cl$_2$ was distilled from CaH$_2$. Compound **1** (14) and pybox **9** (31) were synthesized according to established methods. Flash

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column chromatography was performed on silica gel (230–400 mesh).

General Procedure for Catalytic Asymmetric Alkynylation of α-Imino Ester. Pybox **9** (9.7 mg, 0.025 mmol) and CuOTf·0.5C$_6$H$_6$ (6.3 mg, 0.025 mmol) were added to a dried 10-ml round-bottom flask containing a magnetic stirring bar. CH$_2$Cl$_2$ (1.0 ml) was added, and the mixture was stirred at room temperature for 1 h. The solution was cooled to −10°C, and then α-imino ester **1** (52.3 mg, 0.25 mmol) in CH$_2$Cl$_2$ (400 μl), alkyne (0.5 mmol), and *p*-methoxyphenyl (PMP)-NH$_2$ (3.2 mg, 0.025 mmol) in CH$_2$Cl$_2$ (100 μl) were sequentially added under vigorous stirring. The resulting solution was stirred at −10°C, and the reaction was monitored by TLC. Upon completion of the reaction (36–48 h), the mixture was then passed through a short plug of silica gel that was subsequently washed with EtOAc (10 ml). The combined solution was poured into a separatory funnel and diluted with EtOAc (25 ml) and H$_2$O (5 ml). After mixing, the aqueous layer was discarded and the organic layer was washed with saturated aqueous brine (5 ml), dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated *in vacuo*. The purification of the residue by flash silica gel column chromatography (9:1 hexane/EtOAc as eluents) yielded the desired alkynylation product as a light yellow oil.

Ethyl-2-(*p*-methoyphenylamino)-6-phenyl-3-hexynoate. Compound **3a** was obtained in 90% yield according to the general procedure. The ee value (85%) was determined by chiral HPLC analysis with a 25-cm × 4.6-mm Diacel Chemical Industries (Tokyo) CHIRALPAK AD column (eluent, 90:10 hexane:*i*-PrOH; flow rate, 1.0 ml/min; detection, 254-nm light): t_R (major) = 11.48 min, t_R (minus) = 16.75 min. $[\alpha]_D^{20}$ −64.7° (*c* 0.5, CHCl$_3$). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.28–7.25 (m, 2H), 7.20–7.16 (m, 3H), 6.80–6.78 (m, 2H), 6.67–6.65 (m, 2H), 4.69 (t, 1H, *J* = 2.3 Hz), 4.27–4.24 (q, 2H, *J* = 7.5 Hz), 3.76 (s, 3H), 2.80–2.77 (t, 2H, *J* = 7.3 Hz), 2.49–2.46 (dt, 2H, *J* = 7.3, 2.0 Hz), 1.31–1.28 (t, 3H, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, CDCl$_3$): δ 169.5, 153.7, 140.6, 137.6, 128.7, 128.6, 126.6, 116.5, 114.9, 84.8, 75.4, 62.5, 55.9, 50.5, 34.9, 21.1, 14.3. HRMS (ESI): calculated for C$_{21}$H$_{24}$NO$_3$ [M + 1]$^+$, 338.1756; found, 338.1782.

Ethyl-2-(*p*-methoyphenylamino)-5-phenyl-3-pentynoate. Compound **3b** was obtained in 92% yield according to the general procedure. The ee value (83%) was determined by chiral HPLC analysis with a 25-cm × 4.6-mm Daicel Chemical Industries CHIRALPAK AD column (eluent, 90:10 hexane:*i*-PrOH; flow rate, 1.0 ml/min; detection, 254-nm light): t_R (minor) = 21.49 min, t_R (major) = 35.00 min. $[\alpha]_D^{20}$ −38.1° (*c* 0.4, CHCl$_3$). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.31–7.24 (m, 5H), 6.83–6.81 (m, 2H), 6.74–6.72 (m, 2H), 4.83 (t, 1H, *J* = 2.2 Hz), 4.32–4.28 (q, 2H, *J* = 7.2 Hz), 3.76 (s, 3H), 3.62 (d, 1H, *J* = 2.0Hz), 1.27 (t, 3H, *J* = 7.3 Hz). ^{13}C NMR (125 MHz, CDCl$_3$): δ 169.5, 153.6, 139.7, 136.3, 128.7, 128.1, 126.9, 116.4, 115.0, 82.9, 72.8, 62.5, 55.8, 50.5, 25.2, 14.3. HRMS (ESI): calculated for C$_{20}$H$_{22}$NO$_3$ [M + 1]$^+$, 324.1600; found, 324.1596.

Ethyl-2-(*p*-methoyphenylamino)-3-decynoate. Compound **3c** was obtained in 89% yield according to the general procedure. The ee value (91%) was determined by chiral HPLC analysis with a 25-cm × 4.6-mm Daicel Chemical Industries CHIRALPAK AD column (eluent, 90:10 hexane:*i*-PrOH; flow rate, 1.0 ml/min; detection, 254-nm light): t_R (major) = 9.96 min, t_R (minus) = 12.63 min. $[\alpha]_D^{20}$ −62.3° (*c* 0.4, CHCl$_3$). ^{1}H NMR (500 MHz, CDCl$_3$): δ 6.79–6.77 (m, 2H), 6.70–6.68 (m, 2H), 4.70 (t, 1H, *J* = 2.3 Hz), 4.29–4.24 (q, 2H, *J* = 7.3 Hz), 3.75 (s, 3H), 2.19–2.15 (dt, 2H, *J* = 7.0, 2.3 Hz), 1.47–1.44 (m, 2H), 1.34–1.20 (m, 9H), 0.89–0.86 (t, 3H, *J* = 7.0 Hz). ^{13}C NMR (125 MHz, CDCl$_3$): δ = 169.6, 153.7, 139.3, 116.6, 114.9, 86.0, 75.0, 62.4, 55.8, 50.6, 31.5,

28.6, 28.5, 22.8, 18.9, 14.3, 14.2. HRMS (ESI): calculated for C$_{19}$H$_{28}$NO$_3$ [M + 1]$^+$, 318.2069; found, 318.2091.

Ethyl-2-(*p*-methoyphenylamino)-4-cyclopropyl-3-butynoate. Compound **3d** was obtained in 92% yield according to the general procedure. The ee value (79%) was determined by chiral HPLC analysis with a 25-cm × 4.6-mm Daicel Chemical Industries CHIRALPAK AD column (eluent, 90:10 hexane:*i*-PrOH; flow rate, 1.0 ml/min; detection, 254-nm light): t_R (major) = 11.08 min, t_R (minus) = 19.46 min. $[\alpha]_D^{20}$ −47.4° (*c* 0.7, CHCl$_3$). ^{1}H NMR (500 MHz, CDCl$_3$): δ 6.78–6.74 (m, 2H), 6.66–6.62 (m, 2H), 4.64 (d, 1H, *J* = 2.3 Hz), 4.26–4.21 (q, 2H, *J* = 7.0), 3.17 (s, 3H), 1.26 (t, 3H, *J* = 7.0 Hz), 1.12–1.08 (m, 1H), 0.67–0.64 (m, 2H), 0.63–0.60 (m, 2H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 169.9, 153.7, 140.1, 116.4, 115.2, 88.8, 70.6, 62.6, 56.1, 50.7, 14.5, 8.8, 8.7. HRMS (ESI): calculated for C$_{16}$H$_{20}$NO$_3$ [M + 1]$^+$, 274.1443; found, 274.1453.
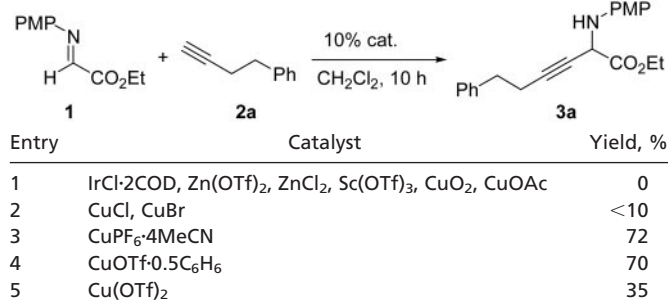
Ethyl-2-(*p*-methoyphenylamino)-5-(trimethylsilyl)-3-pentynoate. Compound **3e** was obtained in 63% yield according to the general procedure. The ee value (77%) was determined by chiral HPLC analysis with a 25-cm × 4.6-mm Daicel Chemical Industries CHIRALPAK AD column (eluent, 90:10 hexane:*i*-PrOH; flow rate, 1.0 ml/min; detection, 254-nm light): t_R (major) = 18.03 min, t_R (minus) = 27.63 min. $[\alpha]_D^{20}$ −36.3° (*c* 0.5, CHCl$_3$). ^{1}H NMR (500 MHz, CDCl$_3$): δ 6.79–6.72 (m, 2H), 6.68–6.66 (m, 2H), 4.71 (t, 1H, *J* = 2.5Hz), 4.28–4.24 (q, 2H, *J* = 7.2 Hz), 3.74 (s, 3H), 1.46–1.45 (d, 2H, *J* = 3.0 Hz), 1.32–1.29 (t, 3H, *J* = 7.3 Hz), 0.04 (s, 9H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 169.8, 153.5, 139.6, 116.3, 114.9, 83.7, 73.9, 62.2, 55.9, 50.5, 14.3, 7.3, −1.9. HRMS (ESI): calculated for C$_{17}$H$_{26}$NO$_3$Si [M + 1]$^+$, 320.1682; found, 320.1711.

Ethyl-2-(*p*-methoyphenylamino)-4-(trimethylsilyl)-3-butynoate. Compound **3f** was obtained in 55% yield according to the general procedure. The ee value (48%) was determined by chiral HPLC analysis with a 25-cm × 4.6-mm Daicel Chemical Industries CHIRALPAK AD column (eluent, 90:10 hexane:*i*-PrOH; flow rate, 1.0 ml/min; detection, 254-nm light): t_R (major) = 6.97 min, t_R (minus) = 9.15 min. $[\alpha]_D^{20}$ −98.5° (*c* 0.3, CHCl$_3$). ^{1}H NMR (500 MHz, CDCl$_3$): δ 6.65–6.63 (m, 2H), 6.55–6.53 (m, 2H), 4.58 (s, 1H), 4.15–4.11 (q, 2H, *J* = 7.0), 3.60 (s, 3H), 1.15 (t, 3H, *J* = 7.0 Hz), 0.04 (s, 9H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 169.0, 153.6, 139.5, 116.4, 114.9, 100.1, 90.0, 62.5, 55.8, 51.2, 14.2, −0.1. HRMS (ESI): calculated for C$_{16}$H$_{24}$NO$_3$Si [M + 1]$^+$, 306.1525; found, 306.1529.

Ethyl-2-(*p*-methoyphenylamino)-5-phenylpentanoate. A solution of compound **3b** (37.6 mg, 0.12 mmol) in EtOAc (3 ml) was hydrogenated with 10% Pd/C (11 mg) at room temperature for 3 h. After filtering-off the solid catalyst, the solution was evaporated under reduced pressure. The residue was purified by a short silica gel column (hexane/EtOAc at 3:1) to afford compound **10** in quantitative yield (38.1 mg). $[\alpha]_D^{20}$ +15.2° (*c* 0.5, CHCl$_3$). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.21–7.07 (m, 5H), 6.69–6.66 (m, 2H), 6.53–6.51 (m, 2H), 4.08–4.04 (q, 2H, *J* = 7.0 Hz), 3.89 (t, 1H, *J* = 6.5 Hz), 3.64 (s, 3H), 2.58–2.55 (m, 2H), 1.78–1.66 (m, 4H), 1.14 (t, 3H, *J* = 7.0 Hz). ^{13}C NMR (125 MHz, CDCl$_3$): δ 173.2, 151.7, 140.7, 139.8, 127.4, 127.3, 124.8, 114.2, 113.8, 59.9, 56.8, 54.6, 34.4, 31.6, 26.3, 13.2. HRMS (ESI): calculated for C$_{20}$H$_{26}$NO$_3$ [M + 1]$^+$, 328.1913; found, 328.1903.

Ethyl-2-(*p*-methoyphenylamino)-5-phenyl-3-pentenoate. A solution of compound **3b** (20.4 mg, 0.06 mmol) in EtOAc (3 ml) was hydrogenated in the presence of 5% Pd/BaSO$_4$ (9 mg) at room temperature for 1 h. After filtering-off the solid catalyst, the solution was evaporated under reduced pressure. The residue was purified by a short silica gel column (hexane/EtOAc at 4:1)

CHEMISTRY

Table 1. 4-Phenyl-1-butyne addition to α-imino ester catalyzed by different metal salts

Entry	Catalyst	Yield, %
1	IrCl·2COD, Zn(OTf)$_2$, ZnCl$_2$, Sc(OTf)$_3$, CuO$_2$, CuOAc	0
2	CuCl, CuBr	<10
3	CuPF$_6$·4MeCN	72
4	CuOTf·0.5C$_6$H$_6$	70
5	Cu(OTf)$_2$	35

Condition: Compounds **1** (0.25 mmol) and **2a** (0.5 mmol) in CH$_2$Cl$_2$ (1.5 ml). Yield refers to isolated yields.

Fig. 1. Chiral ligands for screen.

to afford compound **11** (19.5 mg, 95% yield). $[\alpha]_D^{20}$ $-36.9°$ (c 0.3, CHCl$_3$). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.35–7.22 (m, 5H), 6.81–6.77 (m, 2H), 6.63–6.59(m, 2H), 5.91(dt, 1H, J = 10.5 Hz, 7.5 Hz), 5.45(dd, 1H, J = 10.5 Hz, 9.0 Hz), 4.91 (d, 1H, J = 9.0 Hz), 4.27–4.18 (q, 2H, J = 7.2 Hz), 3.75 (s, 3H), 3.66 (d, 2H, 7.5Hz), 1.25 (t, 3H, J = 7.2 Hz). ^{13}C NMR (125 MHz, CDCl$_3$): δ 172.7, 153.2, 140.7, 140.0, 134.3, 129.0, 128.9, 127.6, 126.6, 115.7, 115.2, 61.9, 56.2, 56.1, 34.7, 14.5. HRMS (ESI): calculated for C$_{20}$H$_{24}$NO$_3$ [M + 1]$^+$, 326.1756; found, 326.1759.

Ethyl-2-amino-5-phenylpentanoate. Ammonium cerium nitrate (0.22 g, 0.41 mmol) dissolved in H$_2$O (1.5 ml) was added to a solution of compound **10** (35.4 mg, 0.11 mmol) in acetonitrile (3 ml) at 0°C under a nitrogen atmosphere. The reaction mixture was stirred for 30 min and then neutralized with 0.5 M NaOH aqueous and extracted with CH$_2$Cl$_2$ (3 × 4 ml). The organic layers were collected and concentrated *in vacuo*. The crude residue was purified by flash chromatography (hexane/EtOAc at 2:3) to give compound (R)-**12** (18.2 mg, 76% yield). Alternatively, a modified procedure was performed under the same condition except by using crude compound **10** as starting material, which was concentrated from the filtered solution of the hydrogenation of compound **3b** (37.1 mg, 0.11 mmol), to give compound (R)-**12** (18.0 mg, 74% yield). $[\alpha]_D^{20}$ $-11.7°$ (c 0.4, CHCl$_3$) for sample that is 83% ee [literature value: $[\alpha]_D^{20}$ $+14.5°$ (c 0.4, CHCl$_3$) for optically pure compound (S)-**12** (32)]. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.45–7.12 (m, 5H), 4.17 (q, 1H, J = 7.0 Hz), 3.43 (dd, 1H, J = 7.3, 5.1 Hz), 2.64–2.58 (m, 2H), 1.75–1.56 (m, 4H), 1.26 (t, 3H, J = 7.0 Hz). ^{13}C NMR (125 MHz, CDCl$_3$): δ 176.6, 142.6, 129.2, 129.1, 126.6, 61.4, 55.1, 36.3, 35.2, 28.2, 14.9. HRMS (ESI): calculated for C$_{13}$H$_{19}$NO$_2$ [M + 1]$^+$, 222.1494; found, 222.1497.

Results and Discussion

In the initial study, with our Ag(I)-catalyzed racemic process in hand, we envisioned that the corresponding asymmetric version could be realized by using an appropriate chiral ligand. The asymmetric addition of 4-phenyl-1-butyne to α-imino ester **1** was explored in the presence of AgOTf or AgNO$_3$ and an additional ligand, respectively. However, it turned out unsuccessful when a series of chiral ligands, including aminophosphanes, diphosphanes, and pybox were subjected to this Ag(I)-catalyzed reaction. All of the reactions resulted in extremely low conversions, and no enantioselectivity was observed.

We then switched our efforts to other transition metals, such as Zn(II), Cu(I)/(II), Ir(I), and Sc(III) (Table 1), some of which have been reported to lead the formation of metal alkynilides (33–41). In the investigation of 4-phenyl-1-butyne **2a** addition to α-imino ester **1**, none of the target was essentially detected in the
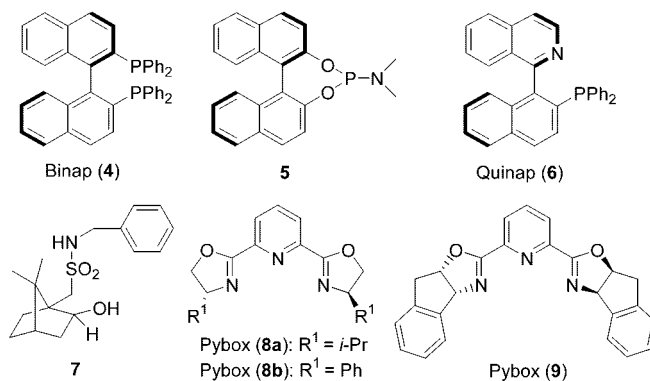
presence of IrCl·2COD, Zn(OTf)$_2$, ZnCl$_2$, and Sc(OTf)$_3$ (entry 1). The desired product **3a** was obtained in good yields when using CuPF$_6$·4MeCN (entry 3) and CuOTf·0.5C$_6$H$_6$ (entry 4) as catalysts, whereas the other Cu complexes, including Cu(OTf)$_2$ (entry 5), CuCl, CuBr (entry 2), CuO$_2$, and CuOAc (entry 1), showed much lower or undetectable catalytic activity.

These interesting results led us to examine the effect of a variety of chiral ligands (Fig. 1, compounds **4–8a**) in CuPF$_6$·4MeCN-catalyzed asymmetric addition of 4-phenyl-1-butyne to α-imino ester **1** (Table 2). Encouragingly, although the reaction rates suffered noticeably with the use of 2,2′-bis(diphenyllphosphino)-1,1′-binaphthyl; Pybox, bis(oxazolidine)-pyridine (entry 1) and 1-(2-diphenylphosphino-1-naphthyl)isoquinoli (entry 3) as chiral ligands, different degrees of ligand acceleration were observed when employing compounds **5** and **7** and pybox (**8a**) as ligands (entries 2, 4, and 5), and the addition reaction in the presence of CuPF$_6$·4MeCN/**8a** furnished target **3a** with promising enantioselectivity (59% ee) and chemical yield (73% yield, entry 5).
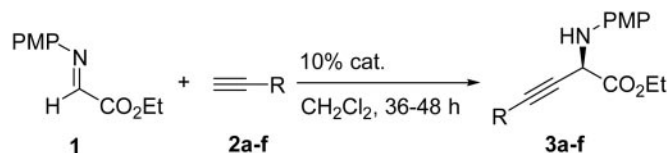
Table 2. Asymmetric addition of 4-phenyl-1-butyne to α-imino ester

Entry	Catalyst	Additive	Yield, %	ee, %
1	CuPF$_6$·4MeCN/**4**	—	Trace	nd
2	CuPF$_6$·4MeCN/**5**	—	92	<5
3	CuPF$_6$·4MeCN/**6**	—	Trace	nd
4	CuPF$_6$·4MeCN/**7**	—	75	<5
5	CuPF$_6$·4MeCN/**8a**	—	73	59
6	CuPF$_6$·4MeCN/**8a**	A	Trace	nd
7	CuPF$_6$·4MeCN/**8a**	B	Trace	nd
8	CuPF$_6$·4MeCN/**8a**	C	86	57
9	CuPF$_6$·4MeCN/**8a**	D	90	57
10	CuPF$_6$·4MeCN/**8b**	D	93	69
11	CuPF$_6$·4MeCN/**9**	D	91	77
12	CuOTf·0.5C$_6$H$_6$/**9**	D	91	82
13*	CuOTf·0.5C$_6$H$_6$/**9**	D	90	85
14	Cu(OTf)$_2$/**9**	D	78	56

Condition: Compounds **1** (0.25 mmol) and **2a** (0.5 mmol) in CH$_2$Cl$_2$ (1.5 ml) at 0°C. Yield refers to isolated yields. A, 0.5 equivalent of Et$_3$N; B, 0.5 equivalent of i-Pr$_2$NH; C, 0.5 equivalent of PMP-NH$_2$; D, 0.1 equivalent of PMP-NH$_2$; nd, not determined.
*Reaction was conducted at $-10°$C.

Table 3. Alkynylation of α-imino ester catalyzed by CuOTf·0.5C₆H₆/9

| Entry	Alkyne	Product	Yield, %	ee, %
1	⟋⟋ Ph (4-phenyl-1-butyne)	**3a**	90	85
2	⟋⟋ Ph (3-phenyl propyne)	**3b**	92	83
3	⟋⟋ (1-octyne)	**3c**	89	91
4	⟋⟋ ◁ (cyclopropylacetylene)	**3d**	92	79
5	⟋⟋ Si	**3e**	63	77
6	⟋⟋ Si	**3f**	55	48

Yield refers to isolated yields.

Further investigation involved the addition of amine bases and the use of other Cu sources and structurally different pybox ligands (Table 2). It is known that metal alkynilides, which were used in a couple of C—C bond formation reactions, were generated in the presence of a base, such as Et₃N (34, 35). Interestingly, in our alkynylation system, the reaction was markedly retarded by adding 0.5 equivalent of Et₃N (entry 6) or i-Pr₂NH (entry 7). In contrast, the utilization of 0.5 or 0.1 equivalent of PMP-NH₂ as additives facilitated an enhancement in yields of compound **3a** from 73% to 86% and 90%, respectively, with no diminution of enantioselectivities (entries 8 and 9 vs. entry 5). Subsequent optimization led to the preferred conditions, using CuOTf·0.5C₆H₆ as a metal source and confirmationally more restricted pybox (**9**) as a chiral ligand at −10°C, which afforded the desired product **3a** in 90% yield and 85% ee (entry 13).

To establish the general utility of this methodology, the direct alkynylation of α-imino ester **1** with a spectrum of terminal alkynes were performed under the optimized conditions, and the representative results are summarized in Table 3. To our delight, in a like manner for the addition of 4-phenyl-1-butyne (entry 1), the addition reactions of 3-phenyl propyne (entry 2), 1-octyne (entry 3), and cyclopropylacetylene (entry 4) provided the

corresponding alkynylation products in good yields and ee values, whereas alkynes with a bulky substituted group, such as trimethylsilyl group (entry 6), next to the triple bond led to a lower reaction rate and enantioselectivity. Noticeably, the present cyclopropylacetylene addition to α-imino ester **1** (entry 4) represents a direct and convenient access to α-amino acid derivatives containing conformationally constrained cyclopropane rings, which have recently attracted much attention because of their important biological activities (2, 42–46).

A useful application of this catalytic methodology is illustrated by the modification of product **3b**, which yielded bishomophenylalanine derivative (*R*)-**12** (Scheme 2). Compound (*R*)-**12** is a key intermediate of peptide-type growth hormone secretagogue, which can be used to promote the growth of food animals and to treat some human diseases, such as congestive heart failure and short stature in growth hormone-deficient children (47–50). Previous studies on the synthesis of compound **12** was focused on the bioresolution approach using D-aminoacylase as a resolution enzyme (47–50) and chiral auxiliaries-induced stoichiometric asymmetric synthesis (32). In this study, chemical catalytic synthesis of compound (*R*)-**12** was achieved. The alkynylation product **3b** was hydrogenated to compound **10** in quantitative yield. Subsequent treatment of compound **10** with cerium ammonium nitrate afforded the target molecule (*R*)-**12** in 76% yield. The absolute configuration of compound **3b** was thus determined to be *R* by inference [[α]$_D^{20}$ −11.7° (*c* 0.4, CHCl₃) for (*R*)-**12** (32), [α]$_D^{20}$ +14.5° (*c* 0.4, CHCl₃) for its *S* enantiomer]. Furthermore, the semireduction of compound **3b** in the presence of Lindlar catalyst (Pd/BaSO₄) conveniently yielded (*Z*)-vinyl amino acid derivative **11**. The construction of β,γ-vinyl amino acid derivatives has attracted considerable attention recently because of their significant mechanism-based enzyme inhibitory properties (51, 52), and, so far, several relatively long routes using chiral starting materials or auxiliaries have been developed for this aim (53–57). The present catalytic asymmetric alkynylation of α-imino ester **1**, combined with semireduction, provides a catalytic introduction of the vinyl group to amino acid derivatives. Additionally, the hydrogenation of compound **11** using Pd/C also furnished intermediate **10** in quantitative yield.

It has been suggested that the mechanism of the formation of "soft" metal alkynilides involves the deprotonation of the corresponding metal-alkyne π complex with a mild base (36, 58). Accordingly, a speculated mechanism of the catalytic alkynylation of α-imino ester is outlined in Scheme 3. The successive complexation of substrate **1** and alkyne **2** to the metal center produced the intermediate (**13**), in which substrate **1** acted as the base in the formation of active Cu(I) alkynilide and as a electrophile, through the activation by the Cu(I) ion and the terminal hydrogen of alkyne. Complex **13** underwent intramolecular proton and alkyne transfer to afford complex **14**. Subsequent decomplexation of complex **14** delivered the free prod-
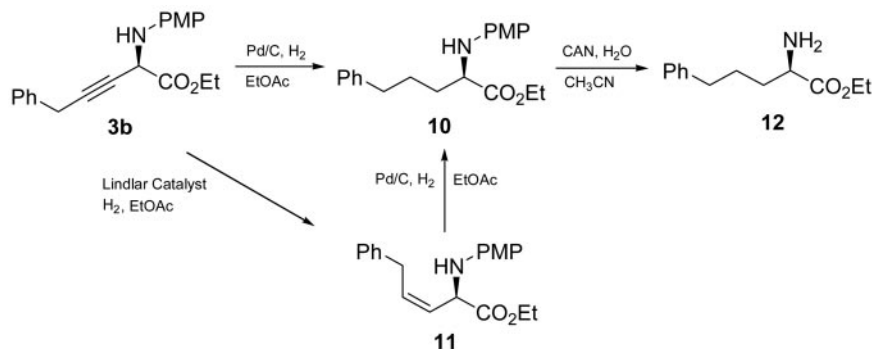
Scheme 2. Modification of compound **3b**.

CHEMISTRY
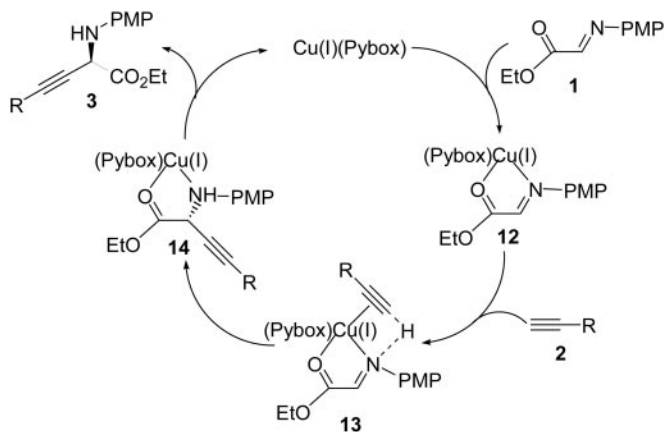
Scheme 3. Proposed mechanism for the alkynylation of α-imino ester.

uct **3** and concomitantly regenerated the catalyst. In this system, the reaction was retarded significantly by adding a tertiary amine [for Et₃N, entry 6 (Table 2); an additional experiment using ^{i}Pr₂EtN gave the same result]. This finding was in contrast to those of previous studies that showed that tertiary amines were essential to produce Cu(I) alkynilides by deprotonation in some

related C—C formation processes (34, 35). These results could be explained as follows: The tertiary amine competed for the terminal proton of alkyne under the catalytic conditions (34, 35) and deprived the proton source, which was necessary for the activation of **1**, resulting in the inhibition of the desired addition.

Conclusion

In conclusion, catalytic synthesis of enantiomerically enriched β,γ-alkynyl α-amino acid derivatives has been developed by realizing the direct asymmetric alkynylation of α-imino ester. The rich chemistry of alkynyl functionality makes the present method a powerful and versatile approach to a wide range of optically active α-amino acid derivatives. Taking into account the combination of desirable features, such as high potential to generate structural variety, truly atom-economic and readily available starting materials, simple experimental procedures, and mild reaction conditions, this catalytic system is expected to provide an excellent opportunity for applications in increasingly important protein engineering and peptide-based pharmaceutical research. Further work is necessary to elucidate the precise reaction mechanism and the utility of this reaction in the construction of complex unnatural amino acid derivatives.

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