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Enantioselective, copper(I)-catalyzed three-component reaction for the synthesis of β,γ-alkynyl α-amino acid derivatives

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ABSTRACT

The first catalytic asymmetric three-component reaction of ethyl glyoxylate, *para*-anisidine, and aliphatic, aromatic alkynes catalyzed by CuOTf·0.5C_6H_6/pybox **7** has been developed. The protocol provided the corresponding chiral β,γ-alkynyl α-amino acid derivatives in good yields and 66–74% ee.

1. Introduction

The transition metal-catalyzed multicomponent reaction (MCR) is a powerful synthetic tool for accessing complex structures from simple precursors via a one-pot procedure.[1] The discovery and development of MCRs are important research areas in combinatorial chemistry.[2] In this context, the development of novel catalytic asymmetric MCRs, which allow the stereoselective formation of several bonds in a one-pot procedure, is more desirable as asymmetric catalysis has become a mainstay of modern organic chemistry.[3]

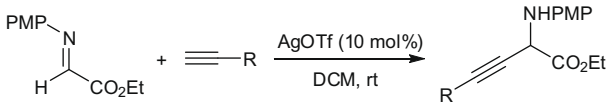
Chiral β,γ-alkynyl α-amino acids represent an important class of optically active nonproteinogenic α-amino acids.[4] It is recognized that α-ethynyl substituents can change the biological properties of certain natural amino acids, converting them from enzyme substrates to irreversible inhibitors with potential therapeutic utility.[5] However, the synthesis of enantiomerically enriched β,γ-alkynyl α-amino acid derivatives is a challenging undertaking.[6]

The metal-catalyzed enantioselective addition of terminal alkynes to imines is one of the most convenient methods for accessing propargylamines.[7] Recently, we extended this reaction to α-imino esters, and developed a novel synthesis of β,γ-alkynyl α-amino acid derivatives using the silver(I)-catalyzed addition of terminal alkynes to an α-imino ester (Scheme 1).[8] Based on this method, we demonstrated the first catalytic asymmetric synthesis of aliphatic alkynyl α-amino acid derivatives by employing chiral copper(I) complexes with 48–91% ee.[9a] To extend the scope of substrates, we also developed the first catalytic enantioselective addition of arylacetylenes to α-imino ester with 67–74% ee.[9b,7k] However, these strategies relied on the use of an α-imino ester that needs to be prepared and isolated beforehand. In addition, these substrates are highly moisture-sensitive and inconvenient to handle. For practical purposes, it is highly desirable to develop a more efficient and general method for the preparation of chiral β,γ-alkynyl α-amino acid derivatives.

To overcome these limitations and to facilitate wider applications, we initiated a study concerning the possibility of using α-imino esters generated in situ as well as developing a general, enantioselective procedure for both aliphatic and aromatic alkynes. Herein, we report the first enantioselective three-component reaction for the synthesis of chiral aliphatic and aromatic β,γ-alkynyl α-amino acid derivatives.[10] To the best of our knowledge, this represents the first asymmetric alkynylation of α-imino ester involving both aliphatic and aromatic alkynes.[9a,b,7k]

2. Results and discussion

A study using the model reaction of ethyl glyoxylate, *para*-anisidine, and 4-phenyl-1-butyne **1a** in the presence of CuOTf·0.5C_6H_6/pybox **7** (Fig. 1) was initially conducted to investigate the feasibility of catalytic asymmetric three-component synthesis of chiral β,γ-alkynyl α-amino acid derivatives. The desired product **2a** was obtained in 80% yield and 70% ee after 72 h. Encouraged by this result, we screened several chiral ligands (Fig. 1) for their utility in this transformation. The results are summarized in Table 1.



Scheme 1. Ag(I)-catalyzed alkynylation of α-imino ester.

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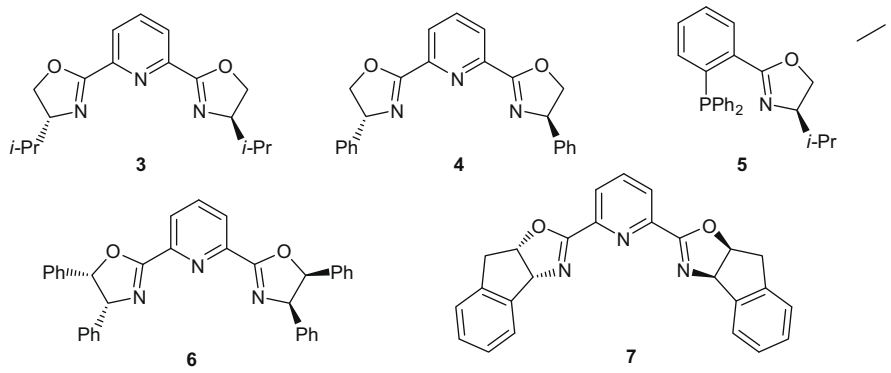
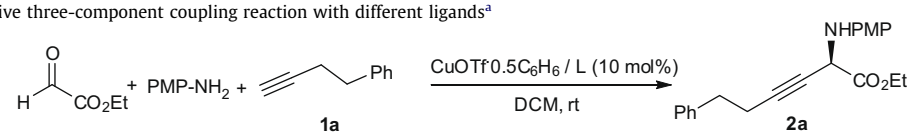


Figure 1. Chiral ligands screened in asymmetric three-component coupling reaction.

Table 1
Cu(I)-catalyzed enantioselective three-component coupling reaction with different ligands[a]



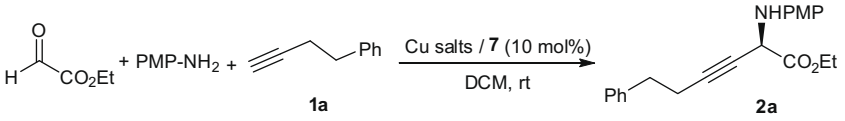
Entry	Ligand	Yield[b] (%)	ee[c] (%)
1	**3**	70	16
2	**4**	79	64
3	**5**	0	—
4	**6**	54	9
5	**7**	80	70
6[d]	**7**	10	72
7[e]	**7**	51	37

[a] All reactions were performed with ethyl glyoxylate (0.26 mmol), *para*-anisidine (0.25 mmol), 4-phenyl-1-butyne **1a** (0.5 mmol), CuOTf·0.5C_6H_6 (0.025 mmol, 10 mol %), and chiral ligand (0.025 mmol, 10 mol %) in dry CH_2Cl_2 (1.5 mL) at room temperature.
[b] Isolated yield after column chromatography.
[c] Determined by chiral HPLC using a Chiralpak AD column.
[d] 24 h; 4 Å MS were added.
[e] 4-Phenyl-1-butyne was added as the last reagent to the catalyst, ethyl glyoxylate, and *para*-anisidine mixture.

Among the chiral ligands that we have investigated, chiral ligand **7** provided the best result (80% yield, 70% ee) (entry 5). It is interesting to note that *i*-Pr-pybox **3**, which gave moderate enantioselectivity (59% ee) in a two-component reaction, led to only 16% enantiomeric excess (entry 1) in this reaction. In addition, *cis*-diphenyl-pybox **6** led to lower enantiomeric excess (entry 4). The use of chiral ligand **5** did not promote this three-component reaction (entry 3). On the other hand, a three-component reaction with molecular sieves as an additive became slower (entry 6). The order of the addition of the reagents was also investigated. Product **2a** was obtained in lower yield (51%) and enantioselectivity (37% ee) by adding 4-phenyl-1-butyne as the last reagent (entry 7).

The effect of copper salts on this reaction was also examined by using pybox ligand **7**, and the results were summarized in Table 2. Although Cu(I) hexafluorophosphate acetonitrile complex gave good yield and enantiomeric excess in the two-component reaction, it provided a lower yield (34%) and enantioselectivity (24% ee) in this three-component coupling reaction (entry 2). On the

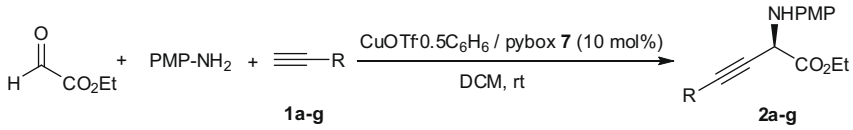
Table 2
Asymmetric three-component coupling reaction with different Cu salts[a]



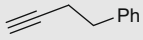
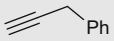
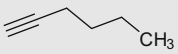
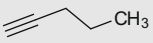
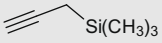
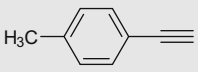
Entry	Cu salt	Yield[b] (%)	ee[c] (%)
1	CuOTf·0.5C_6H_6	80	70
2	$CuPF_6$·4MeCN	34	24
3	$Cu(OTf)_2$	72	58
4	CuBr	0	—
5	CuCl	0	—

[a] All reactions were performed with ethyl glyoxylate (0.26 mmol), *para*-anisidine (0.25 mmol), 4-phenyl-1-butyne **1a** (0.5 mmol), pybox **7** (0.025 mmol, 10 mol %), and Cu salt (0.025 mmol, 10 mol %) in dry CH_2Cl_2 (1.5 mL) at room temperature.
[b] Isolated yield.
[c] Determined by chiral HPLC using a Chiralpak AD column.

Table 3
Copper(I)-catalyzed enantioselective three-component coupling of ethyl glyoxylate, *para*-anisidine, and various terminal alkynes[a]



1a-g 2a-g

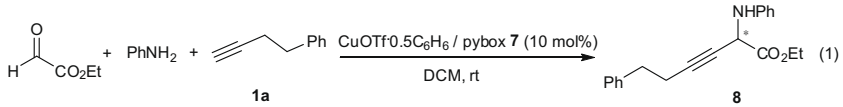
Entry	Alkyne	Product	Yield[b] (%)	ee[c] (%)
1		**2a**	80	70
2		**2b**	77	70
3		**2c**	74	74
4		**2d**	72	74
5		**2e**	61	66
6[d]		**2f**	79	67
7[e]		**2g**	78	71

[a] All reactions were performed with ethyl glyoxylate (0.26 mmol), *para*-anisidine (0.25 mmol), terminal alkyne (0.5 mmol), CuOTf·0.5C_6H_6 (0.025 mmol, 10 mol %), and pybox **7** (0.025 mmol, 10 mol %) in dry CH_2Cl_2 (1.5 mL) at room temperature.
[b] Isolated yield after column chromatography.
[c] Determined by chiral HPLC using a Chiralpak AD column except entries 6 and 7.
[d] Detemined by chiral HPLC using a Chiralpak AD-H column.
[e] Detemined by chiral HPLC using a Diacel Chiralcel OD-H column.

other hand, the Cu(II) triflate benzene complex produced a relatively lower yield (72%) and lower enantioselectivity (58% ee) (entry 3). CuBr and CuCl did not show any catalytic activity (entries 4 and 5). Therefore, the combination of Cu(I) triflate benzene complex and ligand **7** was chosen for further study of the asymmetric three-component reaction.

Under the optimized conditions, the general utility of this new asymmetric multicomponent reaction was investigated with various terminal alkynes. The results are shown in Table 3. The aliphatic terminal alkynes of 4-phenyl-1-butyne (entry 1), 3-phenyl 1-propyne (entry 2), 1-hexyne (entry 3), and 1-pentyne (entry 4) gave the desired alkynylation products in good yields and enantioselectivities, whereas the alkyne with a bulky trimethylsilyl group led to relatively lower yield and enantioselectivity (entry 5). The arylacetylenes such as phenylacetylene (entry 6) and 4-CH_3-phenylacetylene (entry 7) under these reaction conditions offered comparable yields and enantioselectivities.[9b]

Other primary amines were also investigated under the present catalytic system. The three-component reaction with aniline provided the corresponding product **8** in 71% yield and 61% ee (Eq. 1). On the other hand, the three-component reaction with *ortho*-anisidine proceeded very slowly. The lower reactivity might be due to the coordination of the neighboring methoxy group, causing a decrease in electrophilicity of the α-imino ester generated in situ. However, further investigations are needed to elucidate the reaction mechanism.



1a 8 (1)

(1)

3. Conclusion

In conclusion, we have developed the first catalytic asymmetric three-component synthesis of chiral β,γ-alkynyl α-amino acid derivatives in good yields and 66–74% ee by using CuOTf·0.5C_6H_6/pybox **7** as the catalyst. The protocol is applicable to both aliphatic and aromatic alkynes. The characteristic feature of this work is its operational simplicity, mild reaction conditions, good atom economy, readily available reagents, and broad scope of substrates as well as the potential of the structural diversity of the products.

4. Experimental

4.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance DPX 400 (400 and 100 MHz, respectively) NMR spectrometer at room temperature. Chemical shifts (δ) are expressed in ppm, and J values are given in Hertz. 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. All reactions were conducted under a nitrogen atmosphere. The enantiomeric excess was determined by Chiralpak AD, AD-H, or Chiralcel OD-H column using *n*-hexane and iso-propanol as eluents at 25 °C. All chemicals were used as received without further purification unless otherwise stated. CH_2Cl_2 was distilled from CaH_2. Flash column chromatography was performed on silica gel (230–400 mesh).

4.2. Typical procedure for the enantioselective three-component reaction of terminal alkynes with ethyl glyoxylate and *para*-anisidine

To a 1.0-mL CH_2Cl_2 solution of in-pybox **7** (9.8 mg, 0.025 mmol), at room temperature, under a nitrogen atmosphere, CuOTf·0.5C_6H_6 (6.3 mg, 0.025 mmol) was added. After stirring at room temperature for 1 h, the terminal alkyne (0.5 mmol) was added, followed by the addition of ethyl glyoxylate (0.26 mmol) and *para*-anisidine (0.25 mmol) in CH_2Cl_2 (0.5 mL). The resulting solution was stirred at room temperature until TLC monitored the completion of the reaction. The mixture was then passed through a short plug of silica gel and purified by flash silica gel column chromatography. The enantiomeric excess of the product was determined by chiral HPLC analysis.

4.3. Characterization of the products

4.3.1. Ethyl 2-(4-methoxyphenylamino)-6-phenylhex-3-ynoate 2a

Yield: 80%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.21 (m, 5H), 6.86–6.83 (m, 2H), 6.72–6.69 (m, 2H), 4.74 (br s, 1H), 4.31 (q, 2H, J = 7.0 Hz), 4.22 (br s, 1H), 3.81 (s, 3H), 2.85 (t, 2H, J = 7.4 Hz), 2.56–2.51 (m, 2H), 1.35 (t, 3H, J = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.3, 153.2, 140.4, 139.6, 128.4, 128.3, 126.2, 115.9, 114.7, 84.4, 75.9, 62.1, 55.6, 50.1, 34.7, 20.9, 14.0; The enantiomeric excess was determined by HPLC with a AD column (*n*-hexane/*i*-PrOH = 90:10, λ = 254 nm), 1.0 mL/min, t_R (major) = 16.10 min, t_R (minor) = 21.23 min.

4.3.2. Ethyl 2-(4-methoxyphenylamino)-5-phenylpent-3-ynoate 2b

Yield: 77%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.22 (m, 5H), 6.82–6.80 (m, 2H), 6.73–6.71 (m, 2H), 4.81 (m, 1H), 4.29 (q, 2H, J = 7.4 Hz), 3.76 (s, 3H), 3.62 (br s, 2H), 1.32 (t, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.2, 153.3, 139.5, 136.1, 128.4, 127.8, 126.6, 116.1, 114.5, 82.6, 77.6, 62.2, 55.6, 50.2, 25.0, 14.1; The enantiomeric excess was determined by HPLC with a AD column (*n*-hexane/*i*-PrOH = 90:10, λ = 254 nm), 1.0 mL/min, t_R (minor) = 25.61 min, t_R (major) = 42.25 min.

4.3.3. Ethyl 2-(4-methoxyphenylamino)oct-3-ynoate 2c

Yield: 74%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.81–6.74 (m, 2H), 6.72–6.62 (m, 2H), 4.71–4.69 (m, 1H), 4.26 (q, 2H, J = 7.0 Hz), 4.18–3.16 (m, 1H), 3.70 (s, 3H), 2.20–2.16 (m, 2H), 1.47–1.26 (m, 7H), 0.87 (t, 3H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.5, 153.2, 139.7, 115.9, 114.7, 85.3, 75.1, 62.1, 55.6, 50.2, 30.4, 21.8, 18.3, 14.0, 13.5; HRMS (ESI): calcd for $C_{17}H_{24}NO_3$ $[M+1]^+$, 290.1756; found, 290.1768. The enantiomeric excess was determined by HPLC with a OD-H column (*n*-hexane/*i*-PrOH = 90:10, λ = 254 nm), 1.0 mL/min), t_R (major) = 9.84 min, t_R (minor) = 14.89 min.

4.3.4. Ethyl 2-(4-methoxyphenylamino)hept-3-ynoate 2d

Yield: 72%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.85–6.82 (m, 2H), 6.74–6.71 (m, 2H), 4.76 (br s, 1H), 4.33 (q, 2H, J = 7.2 Hz), 4.24 (br s, 1H), 3.80 (s, 3H), 2.23–2.19 (m, 2H), 1.55 (q, 2H, J = 7.2 Hz), 1.35 (t, 3H, J = 7.2 Hz, 0.98 (t, 3H, J = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.5, 153.2, 139.7, 115.9, 114.7, 85.2, 75.2, 62.1, 55.6, 50.1, 21.8, 20.6, 14.0, 13.3; HRMS (ESI): calcd for $C_{16}H_{22}NO_3$ $[M+1]^+$, 276.1600; found, 276.1597. The enantiomeric excess was determined by HPLC with a AD column (*n*-hexane/*i*-PrOH = 90:10, λ = 254 nm), 1.0 mL/min, t_R (major) = 10.67 min, t_R (minor) = 16.37 min.

4.3.5. Ethyl 2-(4-methoxyphenylamino)-5-(trimethylsilyl)pent-3-ynoate 2e

Yield: 61%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.71–6.68 (m, 2H), 6.60–6.58 (m, 2H), 4.63 (br s, 1H), 4.18 (q, 2H, J = 7.0 Hz), 4.09 (br s, 1H), 3.66 (s, 3H), 1.37 (d, 2H, J = 2.7 Hz), 1.22 (t, 3H, J = 7.2 Hz), 0.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7, 153.1, 139.7, 115.9, 114.7, 83.2, 73.9, 62.0, 55.7, 50.2, 14.1, 7.1, −2.2. The enantiomeric excess was determined by HPLC with a AD column (*n*-hexane/*i*-PrOH = 90:10, λ = 254 nm), 1.0 mL/min, t_R (major) = 9.08 min, t_R (minor) = 15.73 min.

4.3.6. Ethyl 2-(4-methoxyphenylamino)-4-phenylbut-3-ynoate 2f

Yield: 79%; ^{1}H NMR (400 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 169.1, 153.4, 139.5, 132.0, 128.8, 128.3, 122.2, 116.1, 114.9, 84.4, 84.2, 62.5, 55.7, 50.7, 14.2. The enantiomeric excess was determined by HPLC with a AD-H column (*n*-hexane/*i*-PrOH = 90:10, λ = 254 nm), 1.0 mL/min, t_R (major) = 18.80 min, t_R (minor) = 23.40 min.

4.3.7. Ethyl 2-(4-methoxyphenylamino)-4-*p*-tolylbut-3-ynoate 2g

Yield: 78%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.35 (m, 2H), 7.16–7.14 (m, 2H), 6.88–6.86 (m, 2H), 6.81–6.79 (m, 2H), 5.00 (s, 1H), 4.36 (q, 2H, J = 7.1 Hz), 3.81 (s, 3H), 2.4 (s, 3H), 1.38 (t, 3H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.1, 153.3, 139.5, 138.8, 131.8, 129.0, 119.1, 116.0, 114.8, 84.5, 83.4, 62.3, 55.6,55.3, 50.7, 21.5, 14.1. The enantiomeric excess was determined by HPLC with a OD-H column (*n*-hexane/*i*-PrOH = 90:10, λ = 254 nm), 1.0 mL/min), t_R (major) = 11.40 min, t_R (minor) = 16.61 min.

Acknowledgments

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