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Copper-Catalyzed Amine–Alkyne–Alkyne Addition Reaction: An Efficient Method For the Synthesis of γ,δ-Alkynyl-β-amino Acid Derivatives

Lei Zhou,[a, b] Qi Shuai,[a] Huan-feng Jiang,*[b] and Chao-Jun Li*[a]

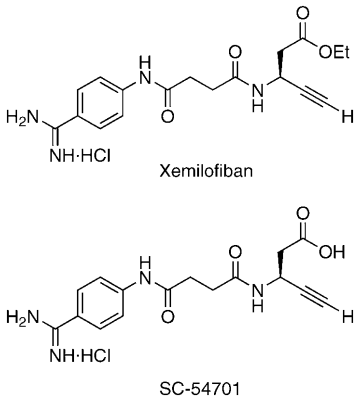
Abstract: A simple and efficient method for the synthesis of γ,δ-alkynyl-β-amino acid derivatives by a copper-catalyzed three-component amine–alkyne–alkyne addition reaction was developed. Various γ,δ-alkynyl-β-amino acid derivatives were synthesized in moderate to good yields in one step. With chiral prolinol derivatives employed as the amine component, excellent diastereoselectivities (up to >99:1 diastereomeric ratio (dr)) were obtained. The scope of the reaction and further transformations of the resulting amino acid derivatives, such as deprotection and cyclization are also described.

Keywords: alkynes · amines · amino esters · copper · multicomponent reactions

Introduction

Multicomponent reactions are among the most efficient synthetic methods for the construction of organic molecules.[1] The ability to form two or more C–C and/or C–heteroatom bonds with high levels of stereocontrol and in a single operation is highly desirable in synthetic chemistry. Such reactions provide the potential methods for the construction of complex molecular architectures from simple precursors with high atom economy[2] and without the need for isolation of intermediates.

β-Amino acid derivatives are important building blocks for the preparation of natural products,[3] pharmaceutical agents,[4] and polypeptides with unique structural properties. Free β-amino acids show interesting biological and pharmacological properties, such as antiketogenic,[5] antihelminthic,[6] and antitumor properties.[7] Among the various β-amino acids, γ,δ-alkynyl-β-amino acid derivatives are a special class of nonproteinogenic amino acids. It is now recognized that β-ethynyl-substituted amino acids can not only greatly change the biological properties of some natural amino acids, but are also the key intermediates of certain designed drugs, such as Xemilofiban and SC-54701, which are platelet aggregation inhibitors that can prevent ischemia, heart attacks, and other major adverse cardiac events, (Scheme 1).[8]



Scheme 1. Structure of Xemilofiban and SC-54701.

Recently, we discovered a new copper-catalyzed amine–alkyne–alkyne addition reaction, which proceeds via an enamine intermediate.[9] In addition, we also reported the diastereoselective synthesis of α-oxyamines through gold-, silver-, and copper-catalyzed three-component couplings of α-oxyaldehydes, alkynes, and amines in water.[10] With our continued interest in synthesizing β-amino acids and propargylamines,[11] we wish to disclose herein our detailed studies on the different parameters influencing the outcome of this

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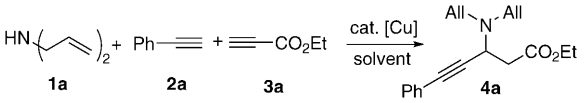
reaction. The broad scope and synthetic utility of this reaction were also demonstrated. Furthermore, excellent diastereoselectivity (up to >99:1) was observed when chiral prolinol derivatives were employed as the amine component.

Results and Discussion

In our previous investigations, we discovered that heating a mixture of diallylamine (**1a**), phenylacetylene (**2a**), and ethyl propiolate (**3a**) with CuBr (5 mol%) as the catalyst at 60°C for 24 h generated **4a** in a 26% yield (Table 1, entry 1). Increasing the reaction temperature increased the yield; carrying out the reaction at 80 and 100°C gave the product in 47 and 81% yield, respectively (Table 1, entries 2 and 3). Adding a ligand, such as bipyridine or phenanthroline did not favor the reaction (Table 1, entries 4 and 5). Among the various copper catalysts examined, aside from CuBr (Table 1, entries 6–11), $CuBr_2$ gave better results than other copper salts. The use of different solvents also affected the reaction. Toluene is the best choice for the reaction; the use of which resulted in high conversions to the desired product. The use of polar solvents, such as DMF, *N*-methylpyrrolidinone (NMP), and ethanol, gave lower yields of the product than the less polar 1,4-dioxane and xylene (Table 1, entries 12–16). The use of pure water as a solvent also resulted in 21% yield, whereas no product was obtained when tetrabutylammonium bromide (TBAB) was added as a phase transfer reagent (Table 1, entries 17 and 18).

Table 1. The addition reaction of **1a**, **2a**, and **3a** catalyzed by copper.[a]



1a 2a 3a 4a

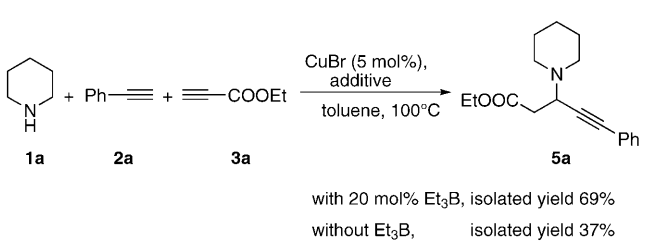
	Catalyst[b]	T [°C]	Solvent	Yield [%][c]
1	CuBr	60	toluene	26
2	CuBr	80	toluene	47
3	CuBr	100	toluene	81
4	CuBr/bipyridine	100	toluene	trace
5	CuBr/phenanthroline	100	toluene	<10
6	CuCN	100	toluene	<10
7	CuI	100	toluene	40
8	Cu(IMes)Cl	100	toluene	0
9	$CuBr_2$	100	toluene	84
10	$Cu(CF_3CO_2)_2$	100	toluene	77
11	$Cu(OTf)_2$	100	toluene	27
12	$CuBr_2$	100	DMF	23
13	$CuBr_2$	100	NMP	15
14	$CuBr_2$	100	EtOH	11
15	$CuBr_2$	100	1,4-dioxane	75
16	$CuBr_2$	100	xylene	69
17	$CuBr_2$	100	water	21
18	$CuBr_2$	100	water/TBAB	0

[a] All reactions were carried out by using **1a** (0.5 mmol), **3a** (0.5 mmol), **2a** (0.75 mmol), and 5% mol of the copper catalysts in solvent (2 mL) for 24 h. [b] IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazole, OTf = trifluoromethanesulfonate. [c] Measured by ^{1}H NMR spectroscopy.

We then explored the scope of the reaction under the optimized conditions (Table 2). Treatment of **1a** and **3a** with different terminal alkynes **2a**–**2h** furnished the corresponding γ,δ-alkynyl-β-amino esters **4a**–**4h** in moderate to good yields (Table 2, entries 1–8). The reaction can tolerate various functional groups present in alkyne **2**, including halogen, alkyne, and protected alcohols. In the reaction of **1a**, **3a**, and 1,4-diethynylbenzene (**2h**), a monoaddition adduct was isolated as the sole product (Table 2, entry 8) in 60% yield. For these reactions, we chose amines with readily removable protecting groups as substrates. In fact, only bisalkylated amines (R^1, R^2 = alkyl) yielded the β-amino acid derivatives **4**, whereas the replacement of alkyl groups by acetyl or tosyl groups did not give any of the desired product **4**. By increasing the steric hindrance of the protecting groups, the yields of the reaction decreased ($(All)_2$ > (All)Bn > Bn_2; All = allyl). Treatment of **3a** and **2a** with allylbenzylamine (**1b**) or dibenzylamine (**1c**) gave the corresponding γ,δ-alkynyl-β-amino ester derivatives **4k** and **4m** in 72 and 70% yields, respectively (Table 2, entries 11 and 13). It is noteworthy that the yield of this addition reaction is substantially affected by the substituents on the alkyne component **3**. For example, 2-butynoate gave a lower yield than **3a** (Table 2, entries 9 and 16) and with the use of diethyl acetylenedicarboxylate in place of **3a**, the desired product was not detected (Table 2, entry 10).

Next, we turned our attention to the Cu-catalyzed amine–alkyne–alkyne addition reaction with cyclic amines as the substrates. However, compared with **1a** or **1c**, the addition reaction of piperidine (**1d**) with **3a** and **2a** gave a lower yield of the desired product. Recently, Rueping and coworkers reported the addition of terminal alkynes to α-amino esters by using a Brønsted acid and silver in dual catalysis.[12] Enlightened by this report, we examined various Brønsted and Lewis acids, such as HOAc, HCl, $ScCl_3$, and $Sc(OTf)_3$. However, these additives did not affect the reaction favorably. Further studies to optimize the reaction conditions revealed that the yield of the desired product could be increased to 69% with the addition of 20 mol% of Et_3B (Scheme 2).

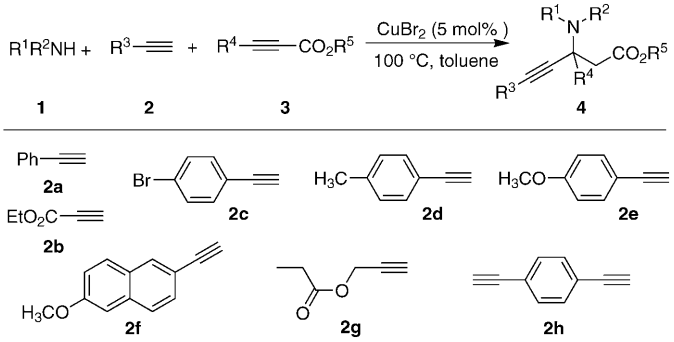
With these results obtained, we then examined the reaction with various amines and alkynes (Table 3). The addition reaction of **1d**, **3a**, and 1-ethynyl-3-fluorobenzene led to the formation of β-amino ester **5b** in 75% yield (Table 3, entry 2). A high yield (77%) was also observed for the addition reaction of the phenyl-substituted piperidine **1e**

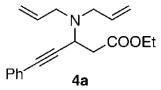
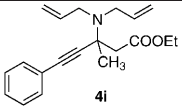
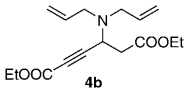
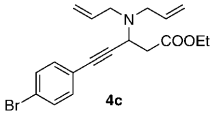
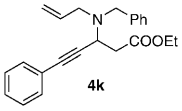
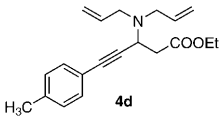
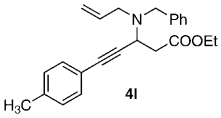
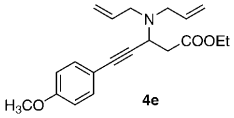
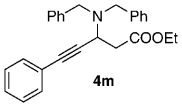
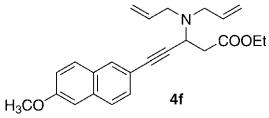
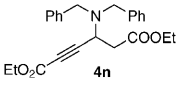
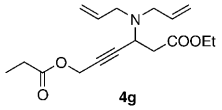
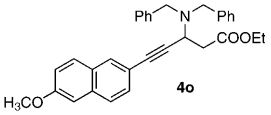
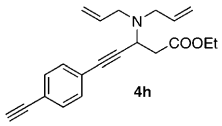
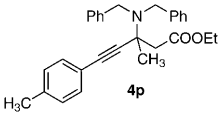


1a 2a 3a 5a

Scheme 2. Copper-catalyzed three-component addition reaction of **2a**, **3a**, and **1d**.

Table 2. Copper-catalyzed amine–alkyne–alkyne addition reaction in toluene.[a]

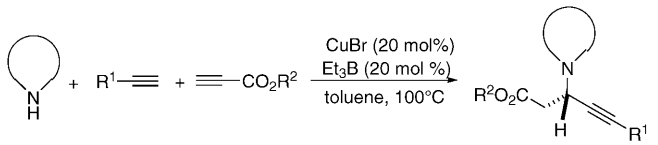


	1	2	R^4	Product	Yield [%][b]		1	2	R^4	Product	Yield [%][b]
1	**1a**	**2a**	H	 **4a**	77	9	**1a**	**2a**	CH_3	 **4i**	51
2	**1a**	**2b**	H	 **4b**	82	10	**1a**	**2a**	CO_2Et	n.d.[c]	0
3	**1a**	**2c**	H	 **4c**	75	11	**1b**	**2a**	H	 **4k**	72
4	**1a**	**2d**	H	 **4d**	66	12	**1b**	**2d**	H	 **4l**	61
5	**1a**	**2e**	H	 **4e**	57	13	**1c**	**2a**	H	 **4m**	70
6	**1a**	**2f**	H	 **4f**	62	14	**1c**	**2b**	H	 **4n**	74
7	**1a**	**2g**	H	 **4g**	71	15	**1c**	**2f**	H	 **4o**	48
8	**1a**	**2h**	H	 **4h**	60	16	**1c**	**2d**	CH_3	 **4p**	46

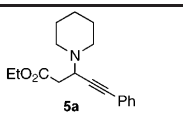
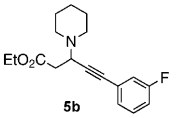
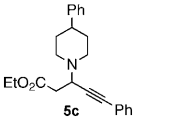
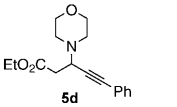
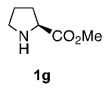
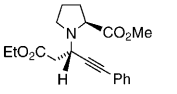
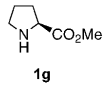
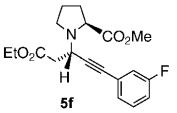
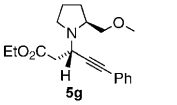
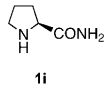
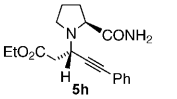
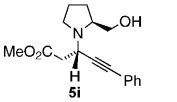
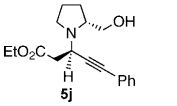
[a] All the reactions were carried out by using amine (0.5 mmol), alkyne (0.5 mmol), and terminal alkyne (0.75 mmol) with $CuBr_2$ (5 mol%) as the catalyst in toluene (2 mL) at 100°C for 24 h. [b] Yield of the isolated product. [c] n.d. = not detected, only the hydroamination product of **3** was obtained.

(Table 3, entry 3). Morpholine (**1f**) appeared to be slightly less reactive and a 51% yield of the desired product was obtained upon treatment with **3a** and **2a** (Table 3, entry 4). When optically pure methyl prolinoate (**1g**) was used as the amine component, compound **5e** was obtained in 82% yield as a mixture of diastereomers (81:19 diastereomeric ratio (dr)) (Table 3, entry 5). Replacement of **2a** with 1-ethynyl-3-fluorobenzene, gave amino ester **5f** in 80% yield with a 68:32 dr (Table 3, entry 6). With prolinol methyl ether (**1h**), compound **5g** was obtained with an improved diastereoselectivity (95:5 dr), but in a slightly lower yield of 64% (Table 3, entry 7). Of special interest is the reaction of prolinamide (**1i**), which resulted in the introduction of an amide moiety directly into the β-amino ester without the need for functional group protection and deprotection (Table 3, entry 8). An excellent diastereoselectivity (>99:1 dr) was obtained in the reaction of (*S*)-prolinol (**1j**) with methyl propiolate to give **5i** in 75% yield (Table 3, entry 9). To further demonstrate the effects of **1j** on the diastereoselectivity of the reaction, (*R*)-prolinol (**1k**) was employed in a reac-

Table 3. Three-component addition reaction catalyzed by CuBr.[a]



1 2 3 5

	Amine	R^1	R^2	Product	Yield [%][b]	dr[c]
1	 1d	Ph	Et	 5a	69	–
2	 1d	*m*-FC_6H_4	Et	 5b	75	–
3	 1e	Ph	Et	 5c	77	–
4	 1f	Ph	Et	 5d	51	–
5	 1g	Ph	Et	 5e	82	81:19
6	 1g	*m*-FC_6H_4	Et	 5f	80	68:32
7	 1h	Ph	Et	 5g	64	95:5
8	 1i	Ph	Et	 5h	55	97:3
9	 1j	Ph	Me	 5i	75	>99:1
10	 1k	Ph	Et	 5j	55	98:2

[a] All of the reactions were carried out by using amine (0.2 mmol), propiolate (0.2 mmol), and terminal alkyne (0.5 mmol) with CuBr (20 mol%) as the catalyst in toluene (1 mL) at 100°C for 30 h. [b] Yield of the isolated product. [c] The dr was determined by LC–MS and/or ^1H NMR spectroscopy.

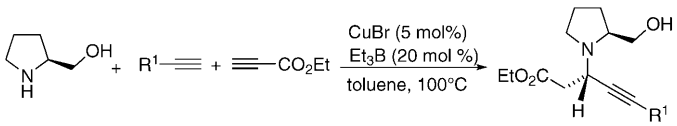
tion with **3a** and **2a**, which gave the desired product **5j** in 55% yield with a 98:2 dr (Table 3, entry 10). These results indicated that the chiral carbon atom and α substituents on the prolinol substrates play key roles in the diastereoselectivity of the reaction.

Encouraged by these results, we then examined the scope of the reaction with **1j**, **3a**, and various terminal alkynes (Table 4). It was shown that the reactions of aromatic alkynes with different substituents, such as alkyl, phenyl, fluoro, and naphthyl, all proceeded smoothly with **1j** and **3a** to afford the desired three-component addition products in good yields and with excellent diastereoselectivities (Table 4, entries 1–6). With the use of diyne **2h** as a substrate, a monoaddition adduct **5q** was obtained as the major product (Table 4, entry 7). The absolute configuration was assigned by analogy to the literature.[13]

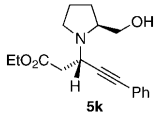
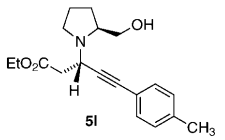
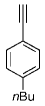
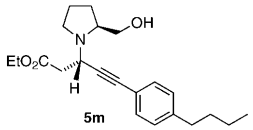
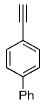
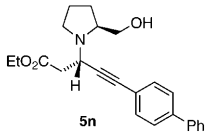
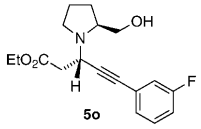
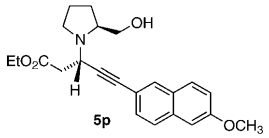
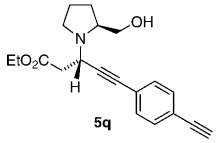
Free β-amino esters can be obtained selectively by the removal of the diallyl or dibenzyl groups according to known methods.[14,15] Treatment of the γ,δ-alkynyl-β-amino acid derivative **4a** with thiosalicylic acid (**6**) in the presence of the palladium(0) catalyst [$Pd(dba)_2$] (dba = dibenzylideneacetone; 5 mol%) and 1,4-bis(diphenylphosphino)butane (DPPB; 10 mol%) at room temperature for 1 h led to the formation of the monoallylated β-amino ester **7** in 85% yield (Scheme 3a). The free β-amino ester **8** can be obtained in 68% yield by increasing the temperature and the loading of **6** (Scheme 3a). Primary amines can also be obtained by hydrogenation of the γ,δ-alkynyl-β-amino acid derivatives **4**. For example, hydrogenation of **4m** in the presence of Pd/C in methanol under a hydrogen atmosphere (1 bar) gave β-amino ester **9** in 55% yield (Scheme 3b). To demonstrate further the synthetic applications of this methodology, allyl-protected amino ester **4a** was employed in a cyclization reaction to produce the α-chloromethylene pyrrolidine derivative, **10**. In the presence of [$PdCl_2(PhCN)_2$], $CuCl_2$, and LiCl, the cyclic compound **10** was obtained as the sole product in 92% yield (Scheme 3c).[16]

Recently, we reported a method for site-specific carbon functionalization of peptides and glycine derivatives by direct C–H bond functionalization.[17] Using this method, we introduced a phenylethynyl group into a simple peptide, **11**,

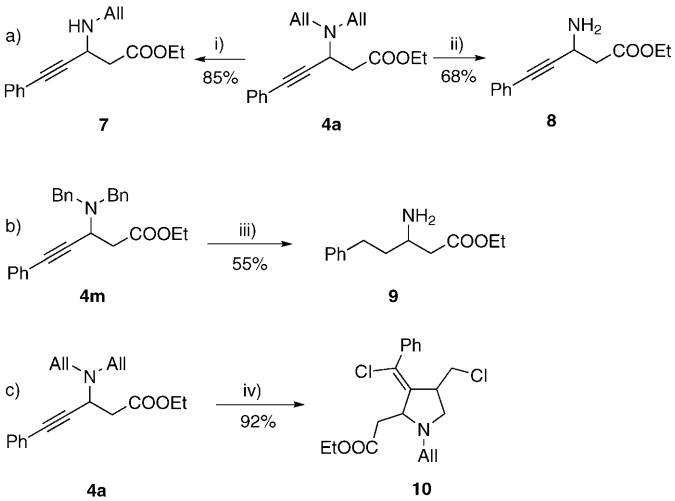
Table 4. Highly diastereoselective addition of **1j** and **3a** with various terminal alkynes.[a]



1j **2** **3a** **5k–5q**

	2	Product	Yield [%][b]	dr[c]
1	**2a**	 **5k**	70	95:5
2	**2d**	 **5l**	68	93:7
3		 **5m**	77	97:3
4		 **5n**	65	>99:1
5		 **5o**	51	98:2
6	**2f**	 **5p**	60	>99:1
7	**2h**	 **5q**	62	>99:1

[a] All the reactions were carried out by using **1j** (0.2 mmol), **3a** (0.2 mmol), and terminal alkyne (0.5 mmol) with CuBr (20 mol%) as the catalyst in toluene (1 mL) at 100°C for 30 h. [b] Yield of the isolated product. [c] The dr was determined by LC–MS and ^{1}H NMR spectroscopy.



Scheme 3. Selective transformations of γ,δ-alkynyl-β-amino acid derivatives: i) [Pd(dba)$_2$] (5 mol%), DPPB (10 mol%), thiosalicylic acid (**6**, 1.2 equiv), THF, RT, 1 h; ii) [Pd(dba)$_2$] (5 mol%), DPPB (10 mol%), **6**, (4 equiv), THF, 60°C, 24 h; iii) Pd/C (10%), H_2 (1 atm), MeOH, RT, 24 h; iv) [$PdCl_2(PhCN)_2$] (5 mol%), $CuCl_2$ (5 equiv), LiCl (2 equiv), CH_3CN, RT, 48 h.

by an oxidative C–H/C–H coupling (Scheme 4a). Complementary to the earlier report, γ,δ-alkynyl peptide **13** could easily be formed by the present copper-catalyzed three-component addition of **2a**, **1a**, and ynamide **12**. The addition reaction proceeded at 100°C in toluene for 24 h, affording the addition product **13** in 82% yield (Scheme 4b).

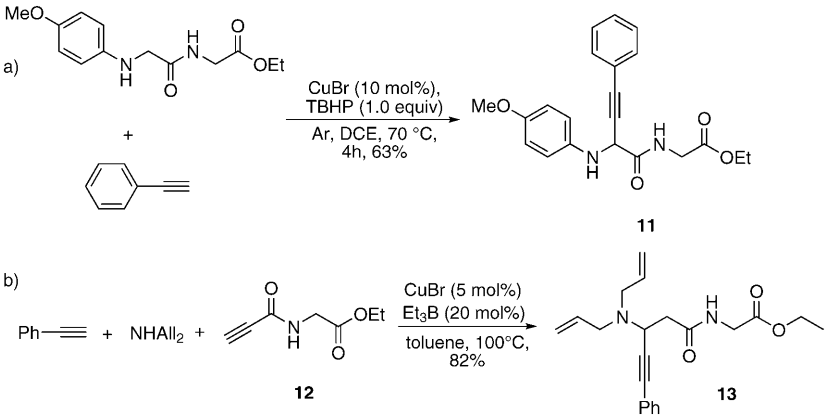
A plausible mechanism for the copper-catalyzed three-component amine–alkyne–alkyne addition reaction is shown in Scheme 5. A copper-catalyzed hydroamination[18] of the electron-deficient propiolate **3** by amine **1** generates intermediate **A**. Reaction of **A** with alkyne **2** results in the formation of intermediate **B**, which is protonated to give an iminium intermediate **C**.[19] Subsequently, an intramolecular transfer of the alkyne moiety to the iminium ion produces the γ,δ-alkynyl-β-amino ester **4** and regenerates the copper catalyst.

Conclusion

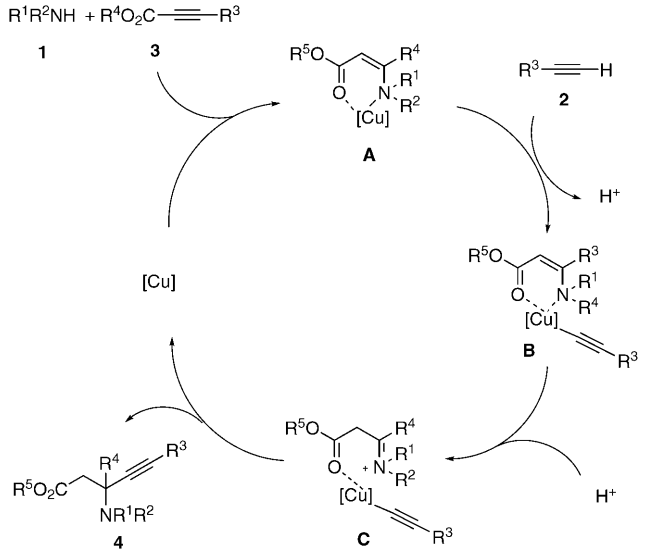
We have developed a simple and efficient method for synthesizing γ,δ-alkynyl-β-amino acid derivatives by a new copper-catalyzed amine–alkyne–alkyne addition reaction. Various γ,δ-alkynyl-β-amino acid derivatives were obtained in moderate to good yields in one step. With chiral prolinol derivatives as the amine component, excellent diastereoselectivities (up to >99:1) have been observed. The resulting amino ester derivatives can undergo further transformations readily, such as deprotection and cyclization. This copper-catalyzed three-component addition reaction also provides a new approach for synthesizing γ,δ-alkynyl peptide derivatives.

Experimental Section

General: Propynoylaminoacetic acid ethyl ester[20] (**12**) and allylbenzylamine[21] (**1b**) were prepared according to published procedures. Other chemicals were purchased from Aldrich Chemicals and Acros Chemicals, and were used without further purification. All experiments were carried out under an atmosphere of nitrogen. Flash column chromatography was performed over SORBENT silica gel 30–60 μm. ^{1}H and ^{13}C NMR spectra were acquired with Varian 400 and 100 MHz, or 300 and 75 MHz spectrometers, respectively. Some of the anisidic protons could not be observed in ^{1}H NMR spectra with $CDCl_3$ as the solvent. MS data were obtained by using an Agilent 6890N Network GC System/Agilent 5973 Mass Selective Detector. HRMS (ESI) measurements were performed at McGill University.



Scheme 4. Copper-catalyzed oxidative C–H/C–H coupling and three-component addition reaction. TBHP = *tert*-butylhydroperoxide, DCE = 1,2-dichloroethane.



Scheme 5. Tentative mechanism for the copper-catalyzed amine–alkyne–alkyne addition reaction.

Representative experimental procedure: synthesis of 4a: $CuBr_2$ (6 mg, 0.025 mmol, 5 mol%) was suspended in toluene (2 mL) in a 10 mL Schlenk tube under nitrogen. Then **1a** (49 mg, 0.5 mmol), **3a** (49 mg, 0.5 mmol), and **2a** (76.5 mg, 0.75 mmol) were added. The resulting solution was stirred at 100 °C for 24 h. After cooling to room temperature, the resulting mixture was filtered through a short path of silica gel in a pipette, eluting with ethyl acetate. The volatile compounds were removed in vacuo and the residue was purified by column chromatography (SiO_2, hexane/ethyl acetate 10:1) to give **4a** as a pale yellow oil (114 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.40 (m, 2H), 7.31–7.29 (m, 3H), 5.86–5.77 (m, 2H), 5.23 (d, J = 17.2 Hz, 2H), 5.14 (d, J = 10.0 Hz, 2H), 4.31 (t, J = 8.4 Hz, 1H), 4.17 (q, J = 7.6 Hz, 2H), 3.33 (dt, J = 14.0, 2.4 Hz, 2H), 2.98 (dd, J = 14.0, 8.0 Hz, 2H); 2.74–2.68 (m, 2H), 1.26 ppm (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.8, 136.5, 132.0, 128.5, 128.3, 123.2, 117.5, 86.2, 85.8, 60.7, 54.2, 50.0, 39.9, 14.4 ppm; MS (70 eV): m/z (%): 296 [M^+], 256, 210 (100); HRMS (EI): m/z calcd for $C_{19}H_{23}NO_2$: 296.1651 [M^+]; found: 296.1643.

The experiments in Table 2 were carried out analogously. All products were purified by column chromatography and characterized by NMR spectroscopy and standard/high-resolution mass spectrometry.

Generation of the free γ,δ-alkynyl-β-amino ester: A mixture of [Pd(dba)$_2$] (5 mol%) and DPPB (10 mol%) in THF (0.5 mL) was stirred at room temperature under nitrogen for 15 min. The preformed catalyst and thiosalicylic acid (1.2 or 4 equiv) were added to a solution of **4a** in THF and the reaction mixture was stirred under argon at 20 or 60 °C. After completion of the reaction (the reaction was monitored by TLC and GC–MS), the mixture was treated with a 10% aqueous solution of HCl and the byproduct and the catalyst were extracted into the organic layer with AcOEt. The aqueous layer containing the protonated amine was basified with 1 M NaOH and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and concentrated in vacuo, affording clean crude products. Further purification was performed by flash chromatography on silica gel with hexane/AcOEt (3:1) as the eluent.

Representative experimental procedure: synthesis of 5k: A mixture of CuBr (20 mol%), **1j** (20.2 mg, 0.2 mmol), and **3a** (19.8 mg, 0.2 mmol) in toluene (1 mL) was stirred at 60 °C (the temperature fluctuated slightly during the reaction) for 2 h under an atmosphere of nitrogen. Then triethylborane (1 M solution in THF, 40 μl, 20 mol%) and **2a** (51 mg, 0.5 mmol) were added and the resulting solution was stirred at 100 °C for 30 h. After cooling to room temperature, the resulting mixture was filtered through a short path of silica gel in a pipette, eluting with ethyl acetate. The volatile compounds were removed in vacuo and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 3:1 to 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.42–7.39 (m, 2H), 7.32–7.26 (m, 3H), 4.38 (t, J = 8.0 Hz, 1H), 4.24–4.14 (m, 2H), 3.71 (dd, J = 10.8, 3.2 Hz, 1H), 3.38 (dd, J = 10.8, 3.6 Hz, 1H), 3.05–2.95 (m, 2H), 2.89–2.83 (m, 1H), 2.76–2.72 (m, 2H), 1.88–1.72 (m, 4H), 1.27 ppm (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.4, 132.0, 128.6, 128.5, 122.9, 86.0, 85.9, 62.8, 62.5, 61.1, 49.5, 47.4, 40.2, 27.7, 24.0, 14.4 ppm; MS (70 eV): m/z (%): 301 [M^+], 216, 188 (100), 173, 145, 128, 115; HRMS (EI): m/z calcd for $C_{18}H_{23}NO_3$ [M^+]: 301.1678, found: 301.1672.

The experiments in Tables 3 and 4 were carried out analogously. All products were purified by column chromatography and characterized by NMR spectroscopy and standard/high-resolution mass spectrometry.

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