Reports of NAS RA
ՀՀ ԳԱԱ Զեկույցներ
NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF ARMENIA
ՀԱՅԱՍՏԱՆԻ ՀԱՆՐԱՊԵՏՈՒԹՅԱՆ ԳԻՏՈՒԹՅՈՒՆՆԵՐԻ ԱԶԳԱՅԻՆ ԱԿԱԴԵՄԻԱ

2026 **Volume 126** **Issue 2** **Article No. 6**

Category: Chemistry
Type of Paper: Original Research Article
Received: March 31, 2026, **Revised:** June 3, 2026, **Accepted:** June 30, 2026
Published: September 10, 2026

DOI: 10.54503/0321-1339-2026.126.2-6

Ni(II)-Mediated Asymmetric Synthesis of a Conjugated Diyne-Containing Non-Proteinogenic Amino Acid via Glaser Heterocoupling

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Abstract

Non-proteinogenic amino acids bearing acetylenic motifs are valuable building blocks in medicinal chemistry and chemical biology due to their structural rigidity, synthetic versatility, and biological relevance. Herein, we report an asymmetric synthesis of (S)-2-amino-8-(3,4-dihydroisoquinolin-2(1H)-yl)octa-4,6-diynoic acid using a Belokon Ni(II) square-planar complex as a chiral scaffold. The synthetic route involves the preparation of a propargylglycine-derived Ni(II) complex followed by a Glaser heterocoupling reaction with 2-(prop-2-yn-1-yl)-1,2,3,4-tetrahydroisoquinoline, enabling the stereocontrolled construction of a conjugated diyne side chain. Subsequent acidic hydrolysis of the Ni(II) complex, ion-exchange demineralization, and recrystallization from aqueous ethanol afforded the target non-proteinogenic amino acid in high purity with retention of the (*S*)-configuration. This work demonstrates the compatibility of oxidative alkyne coupling reactions with Ni(II)-mediated asymmetric amino acid synthesis and expands the synthetic toolbox for accessing structurally complex, acetylenic amino acid derivatives.

Keywords: asymmetric synthesis, non-proteinogenic amino acids, Glaser heterocoupling reaction

1. Introduction

Non-proteinogenic (non-canonical) amino acids (NPAAs) substantially expand the structural and functional diversity accessible to peptide and peptidomimetic design. Incorporation of NPAAs can improve proteolytic stability, potency, permeability, and overall bioavailability of peptide-based therapeutics, while also enabling fine-tuning of conformational preferences and target selectivity.[1,2] More broadly, unnatural amino acids are now widely used as modular building blocks in medicinal chemistry and chemical biology, supporting both discovery and optimization of bioactive molecules.[3]

Within this space, alkyne- and diyne-containing amino acids are especially attractive because the C≡C unit combines (i) a rigid, linear geometry that can influence peptide conformation, and (ii) high synthetic versatility, enabling late-stage diversification and conjugation. Terminal-alkyne amino acids, in particular, provide a handle for bioorthogonal transformations such as Cu(I)-catalyzed azide-alkyne cycloaddition (“click” chemistry), and are widely used in chemical-biology workflows, including metabolic labeling strategies (e.g., BONCAT), where alkyne-containing methionine surrogates are incorporated into proteins and then selectively tagged.[4–6] In parallel, terminal-alkyne amino acids have been discovered in biosynthetic contexts, highlighting their relevance as functional motifs rather than purely synthetic curiosities.[7]

Acetylenic amino acids are also associated with distinct biological effects. A well-known example is propargylglycine, an acetylenic amino acid reported as a mechanism-based (suicide) inactivator of pyridoxal phosphate-dependent enzymes such as γ-cystathionase (cystathionine γ-lyase).[8] Such observations support the broader view that introducing acetylenic functionality into amino acid scaffolds can yield compounds with meaningful biological activity profiles, motivating continued development of stereocontrolled synthetic access to these motifs.

From a synthetic standpoint, efficient asymmetric routes to α-amino acids bearing extended acetylenic/diyne side chains remain valuable. Among established asymmetric strategies, Ni(II) square-planar complexes derived from Belokon-type chiral ligands have long served as powerful "masked glycine" equivalents. These complexes enable stereocontrolled C–C bond formation at the α-position under operationally practical conditions and have evolved into a broadly adopted platform for preparing tailor-made amino acids[9]. The methodology continues to be refined and summarized in modern reviews emphasizing practicality, scalability, and ligand design.[10]

Conjugated 1,3-diynes, meanwhile, are efficiently assembled via oxidative coupling of terminal alkynes, with the Glaser reaction and its variants (e.g., Glaser–Hay conditions) forming a core set of methods in diyne synthesis.[11] A comprehensive review highlights the development of improved and greener Glaser-type protocols and documents the broad utility of 1,3-diynes in complex-molecule synthesis, materials, and biologically active structures.[11] Despite this maturity, the use of Glaser heterocoupling in the context of stereodefined amino acid synthesis—particularly when the stereochemical information is embedded in a chiral metal complex—remains comparatively underexplored.

Related investigations have previously been carried out in Armenia, including by our scientific group. In particular, chiral Ni(II) Schiff base complexes have been successfully used for the asymmetric synthesis of enantiomerically enriched non-proteinogenic amino acids containing acetylenic fragments. The application of Ni(II)–BPB complexes of propargylglycine in Glaser and Glaser-type coupling reactions has also been reported for the preparation of amino acids bearing conjugated diyne units.[12–14] Thus, the present work continues this research direction and expands it toward the synthesis of a new tetrahydroisoquinoline-containing diyne amino acid, namely (S)-2-amino-8-(3,4-dihydroisoquinolin-2(1H)-yl)octa-4,6-diynoic acid.

In this work, we integrate these concepts by using a Belokon Ni(II) square-planar complex to access an acetylenic amino acid framework and employing a Glaser heterocoupling reaction as the key C–C bond-forming step. Specifically, we report the synthesis of (S)-2-amino-8-(3,4-dihydroisoquinolin-2(1H)-yl)octa-4,6-diynoic acid via oxidative coupling of a propargylglycine-derived Ni(II) complex with 2-(prop-2-yn-1-yl)-1,2,3,4-tetrahydroisoquinoline, followed by acidic decomplexation and purification to furnish the target NPAA with retention of stereochemical integrity.

2. Materials and Methods

Detailed experimental procedures are provided in Supplementary Materials.

All initial reagents were obtained from commercial sources and used without further purification. TLC analyses were performed on glass plates coated with silica gel 60 F254. Column chromatography was performed on silica gel (60×120 mesh) on a glass column. Melting points (mp) were determined by Electrothermal. ^{1}H and ^{13}C NMR spectra (Mercury-300 Varian 300 MHz and 75 MHz, respectively) were recorded using TMS as an internal standard (0 ppm). Elemental analyses were done by elemental analyzer EURO EA 3000. The enantiomeric purity of the amino acids was determined by HPLC (Waters Alliance 2695 HPLC System) on the chiral phase Diaspher-110- Chirasel-E-PA 6.0 μm 4.0×250 mm, and a mixture of 20% MeOH and 80% 0.1 M aqueous solution $NaH_2PO_4 \cdot 2H_2O$ was used as the eluent. The optical rotation was measured on a Perkin Elmer-341 polarimeter. LCMS analysis was done by Shimadzu LCMS 2020 with prominence-I LC-2030C 3D. The CD analyses were carried out by Chirascan™ V100.

Procedures

Synthesis of Complex 3

Copper iodide (0.71 g, 3.73 mmol) and 2-(prop-2-yn-1-yl)-1,2,3,4-tetrahydroisoquinoline 1.27 g (7.4 mmol) were added to a mixture of1,4-dioxane (5 mL) and triethylamine (5 mL). After 15 minutes 2 g (3.73 mmol) complex 1 was added and stirred at 70°C. The progress of the reaction was monitored by TLC on silica using a 3:1 $CH_3COOC_2H_5$/ $CHCl_3$ mixture as a mobile phase. After the reaction was complete, the mixture was extracted with chloroform and distilled water. The organic phase was dried with anhydrous $MgSO_4$ to remove residual moisture, filtered, and concentrated. Complex 3 was purified using silica gel column chromatography (SiO_2, $CH_3COOC_2H_5$/ $CHCl_3$ = 3/1). The reaction duration was 24 h.

Copper iodide (0.71 g, 3.73 mmol) and 2-(prop-2-yn-1-yl)-1,2,3,4-tetrahydroisoquinoline (1.27 g, 7.4 mmol) were added to a mixture of 1,4-dioxane (5 mL) and triethylamine (5 mL).

Complex 3

Yield 72% (1.87 g), Mp +149°C, $[\alpha]_D^{20}$ +1845 (c=0.15, CH_3OH). ESI-MS (m/z): 705.05 (found), 705.24 (calculated for $[C_{42}H_{38}N_4NiO_3 + H]^+$).

^{1}H NMR: (300 MHz, $CDCl_3$) δ=2.0–2.16 (2H, m, α, β- H_a Pro); 2.18 (1H, s); 2.33 (1H, dd, J=17.17); 2.41–2.55 (1H, m); 2.77 (1H, dd, J=17.7); 2.85 (2H, dd, J=6.3); 2.90–3.01 (3H, m); 3.44 (1H, dd, J=10.4); 3.65 (5H, d, J=15.4); 3.78 (2H, s); 4.01 (1H, dd, J=6.6); 4.45 (1H, d, J=12.6); 6.61–6.69 (2H, m); 7.00–7.06 (2H, m); 7.09–7.27 (8H, m); 7.36 (2H, t, J=7.6); 7.45–7.55 (3H, m); 8.04 (2H, dd, J=7.1); 8.26 (1H, d, J=8.7).

^{13}C NMR: (75 MHz, $CDCl_3$) δ=23.55 (CH_2); 24.361 (β-CH_2 Pro); 29.311; 30.945 (γ -CH_2 Pro); 47.535 (CH_2); 49.905 (NCH_2); 54.516 (NCH_2); 57.323 (CH_2N); 63.381 (δ-CH_2 Pro); 67.660 (≡C); 70.127 (C≡); 70.572; 73.541; 73.897(≡C); 77.670 (C≡); 120.707 (Ar); 123.878 (Ar); 125.787 (Ar); 126.288 (Ar); 126.652 (Ar); 126.733 (Ar); 127.760 (Ar); 128.731 (Ar); 128.941 (Ar); 129.006 (Ar); 129.200 (Ar); 129.232 (Ar); 130.074 (Ar); 131.740 (Ar); 132.646 (Ar); 133.253 (Ar); 133.536 (Ar); 133.697 (Ar); 134.150 (Ar); 134.150 (Ar); 134.353 (Ar); 143.161 (Ar); 172.176 (C=O); 178.429 (Ar); 180.572 (C=O).

Procedure for isolation of amino acid

A suspension of the complex in CH_3OH was slowly added to a vigorously stirred 2 M aqueous HCl solution at 50°C. After the complexes were decomposed (10–20 min), the free amino acids were purified using a cation-exchange column (Dowex-8 (H+ form)).

2-amino-8-(3,4-dihydroisoquinolin-2(1H)-yl)octa-4,6-diynoic acid (4)

Yield 43.8% (0.46 g), Mp +212°C, $[\alpha]_D^{20}$ -10° (c=0.2, 6 N HCl). ESI-MS (m/z): 282.95 (found), 283.14 (calculated for $[C_{17}H_{18}N_2O_2 + H]^+$).

^{1}H NMR: (300 MHz, DMSO/CCl_4/CF_3COOD) δ= 3.54 (2H, t, *J* = 6.3; CH_2); 4.10 (1H, t, *J* = 5.5); 4.40 (4H, d, *J* = 13.6, Ar); 7.21 (4H, m; Ar).

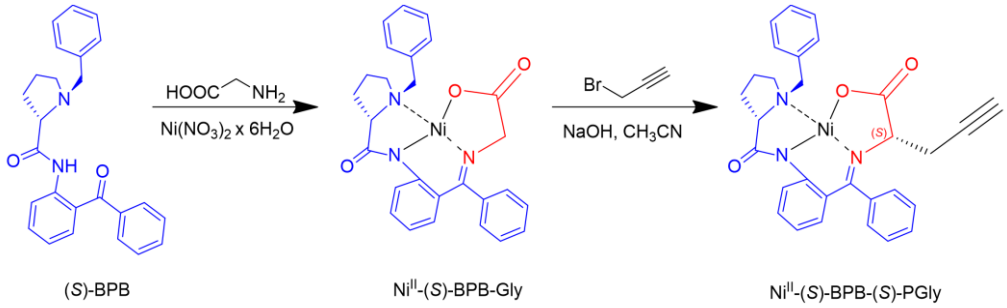
^{13}C NMR: (75 MHz, DMSO/CCl_4/CF_3COOD) δ=20.686 (CH_2); 25.215 (CH_2); 38.667; 40.333; 44.855; 48.349; 50.193; 51.496; 66.913; 67.188 (CH_2N); 73.327 (≡C); 75.600 (C≡); 126.414 (Ar); 126.454 (Ar); 127.457 (Ar); 128.096 (Ar); 130.846 (Ar); 158.777 (Ar); 168.694 (C=O).

3. Results and Discussion

The synthesis commenced with the preparation of the Ni(II)–(S)-BPB–Gly complex from the corresponding Belokon ligand according to established procedures.[9] The resulting square-planar complex was obtained as a stable solid and served as a versatile precursor for subsequent α-functionalization.

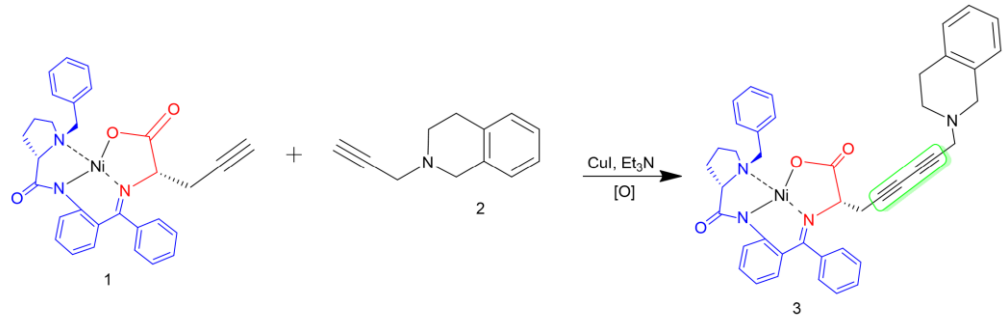
Alkylation of the Ni(II)–(*S*)-BPB–Gly complex with propargyl bromide afforded the corresponding Ni(II)–(S)-BPB–PGly(propargylglycine) complex (Scheme 1). The transformation proceeded smoothly, providing the alkyne-functionalized amino acid complex in good yield while preserving the stereochemical integrity imposed by the chiral BPB ligand. The resulting alkyne-

functionalized complex was sufficiently stable to be isolated and handled under standard laboratory conditions and served as a key intermediate for subsequent oxidative coupling.



Scheme 1. Synthesis of Ni(II)–(S)-BPB–PGly complex.

With the propargylglycine-derived Ni(II) complex in hand, its reactivity in a Glaser heterocoupling reaction was investigated. Treatment of Ni(II)–(*S*)-BPB–PGly with 2-(prop-2-yn-1-yl)-1,2,3,4-tetrahydroisoquinoline under oxidative coupling conditions resulted in the formation of the desired diyne-containing Ni(II) complex (Scheme 2).



Scheme 2. Glaser heterocoupling reaction.

Reaction conditions were optimized by varying the solvent, temperature, and reagent ratios (Table 1).

Table 1. Results of reaction optimization.

Entry	Base	Solvent	Ratio (**1**:**2**:base)	Temperature (°C)	Yield (%)*	Stereoselectivity (*S,S*; *S,R*)
1	DIPA	CH_3CN	1:2:3	65	-	-
2	DIPA	DMSO	1:2:3	65	-	-
3	DIPA	1,4-dioxane	1:2:5	80	-	-
4	DIPA	1,4-dioxane	1:3:5	80	-	-
5	Et_3N	DMSO	1:2:5	70	37	80/20
6	Et_3N	DMSO	1:2:10	70	49	80/20
7	Et_3N	1,4-dioxane	1:2:5	70	58	98/2
8	Et_3N	1,4-dioxane	1:2:10	70	72	98/2

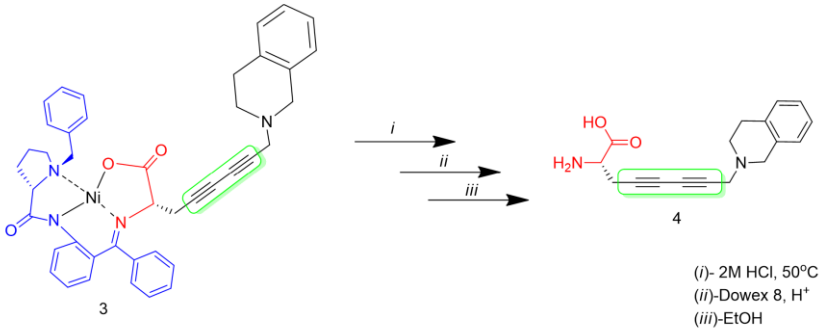
*Isolated yields

The successful formation of the heterocoupled product demonstrates that the terminal alkyne functionality remains accessible within the sterically defined Ni(II) square-planar framework and that the Belokon complex tolerates oxidative conditions required for Glaser coupling. Importantly, no significant side reactions, such as homocoupling or decomposition of the metal complex, were observed under the applied conditions. The reaction mixture was monitored by TLC. No additional

spot other than that corresponding to the desired heterocoupled product was observed. Furthermore, comparison with independently available standards of the possible homocoupling products confirmed that the isolated product was not the homocoupling product. Thus, no detectable formation of the homocoupling product was observed under the applied reaction conditions. The (*S*)-absolute configuration of the α-carbon atom of the amino acid moiety of the complex was assigned using the positive sign of $[\alpha]_D$ in analogy with previously reported similar Ni(II) complexes of other amino acids. Additional verification was obtained by the circular dichroism (CD) spectra: positive Cotton effects of the diastereomeric complex in the 500–580 nm region indicated (*S*)-absolute configuration of the α-carbon atom of the amino acid moiety (see ESI). For comparison, the CD spectra of (*S*,*S*)- and (*S*,*R*)-diastereomers of the similar alanine complexes with known absolute configuration unambiguously established by X-ray crystallography, are also given. These results highlight the compatibility of Glaser-type oxidative alkyne coupling with chiral Ni(II)-mediated amino acid synthesis.

Following successful heterocoupling, the resulting Ni(II) complex was subjected to acidic hydrolysis, leading to cleavage of the metal–ligand framework and release of the free amino acid. Subsequent ion-exchange demineralization efficiently removed residual nickel ions and inorganic byproducts, affording the amino acid in its protonated form.

Final purification by recrystallization from aqueous ethanol yielded the target non-proteinogenic amino acid, (S)-2-amino-8-(3,4-dihydroisoquinolin-2(1H)-yl)octa-4,6-diynoic acid, as a pure solid (Scheme 3).



Scheme 3. Isolation of target amino acid.

The structure and purity of the isolated compound were confirmed by spectroscopic analysis (see ESI). The preservation of the (*S*)-configuration after decomplexation confirms that no racemization occurred during either the oxidative coupling or hydrolytic steps.

The presented synthetic strategy demonstrates that Glaser heterocoupling reactions can be effectively integrated into Ni(II)-mediated asymmetric amino acid synthesis. The use of a propargylglycine-derived Ni(II)–BPB complex enables modular extension of the amino acid side chain through oxidative alkyne coupling, providing access to conjugated diyne-containing structures that are otherwise challenging to obtain in a stereocontrolled manner.

Notably, the tolerance of the Ni(II) square-planar complex toward oxidative conditions expands the scope of transformations compatible with Belokon-type chemistry. The ability to introduce complex, biologically relevant heterocyclic fragments—such as the tetrahydroisoquinoline moiety—further enhances the utility of this approach for the synthesis of structurally diverse non-proteinogenic amino acids.

Conclusions

In summary, we have developed an efficient asymmetric approach to the synthesis of (S)-2-amino-8-(3,4-dihydroisoquinolin-2(1H)-yl)octa-4,6-diynoic acid based on the use of a Belokon Ni(II) square-planar complex as a chiral scaffold. The key transformation involves a Glaser heterocoupling reaction

between a propargylglycine-derived Ni(II) complex and a terminal alkyne-functionalized tetrahydroisoquinoline, enabling stereocontrolled construction of a conjugated diyne side chain.

Subsequent acidic decomplexation, ion-exchange demineralization, and recrystallization furnished the target non-proteinogenic amino acid in high purity with retention of the (*S*)-configuration. The successful compatibility of oxidative alkyne coupling conditions with the Ni(II)–BPB framework expands the scope of transformations accessible within Ni(II)-mediated asymmetric amino acid synthesis.

This methodology provides a modular and versatile route to structurally complex, acetylenic amino acids and may find further application in the preparation of non-proteinogenic amino acid derivatives for peptide science, medicinal chemistry, and chemical biology.

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Supplementary Materials: Supplementary Information is provided with this article as a separate file and includes detailed experimental procedures, analytical and spectroscopic characterization, NMR and mass spectra, HPLC data, optical rotation data, and circular dichroism spectra.

Funding: The research was supported by the Higher Education and Science Committee of MESCS RA in the frame of research project SCS 23AA-1D021.

Acknowledgments: The author gratefully acknowledges the late Dr. Henrik Panosyan for assistance with NMR measurements. The author also thanks the Scientific and Educational Center for Control and Monitoring of the Quality of Medicines of the Institute of Pharmacy, YSU, for assistance with LCMS and HPLC measurements. The author is grateful to Dr. Anna Mkrtchyan for helpful scientific discussions.

Conflicts of Interest: The author declares no conflict of interest.

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ԱՄՓՈՓԱԳԻՐ

Գլազերի հետերոհամակցման միջոցով կոնյուգացված դիին պարունակող ոչ սպիտակուցային ամինաթթվի Ni(II)-ով միջնորդավորված ասիմետրիկ սինթեզ

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Ացետիլենային խմբեր պարունակող ոչ սպիտակուցային ամինաթթուները կարևոր կառուցվածքային բլոկներ են հանդիսանում ժամանակակից բժշկական քիմիայում, կենսաբանությունում՝ շնորհիվ իրենց կառուցվածքային կայունության, սինթետիկ ունիվերսալության և կենսաբանական նշանակության: Այս աշխատանքում ներկայացվում է (*S*)-2-ամինո-8-(3,4-դիհիդրոիզոքինոլին-2(1H)-իլ)օկտա-4,6-դիինաթթվի ասիմետրիկ սինթեզը՝ օգտագործելով Ni(II) հարթ քառակուսային կոմպլեքսները, որպես քիրալային կմախք: Սինթեզի ուղին իր մեջ ներառում է նախկինում մշակված մեթոդով պրոպարգիլգլիցինային կոմպլեքսի ստացումը, 2-(պրոպ-2-ին-1-իլ)-1,2,3,4-տետրահիդրոիզոքինոլինի հետ հաջորդող Գլազերի հետերոհամակցման ռեակցիան, ինչը հնարավորություն է տվել կառուցել դիինային կոնյուգացված կողմնային շղթա: Հաջորդող թթվային հիդրոլիզը, իոնափոխանակային դեմիներալիզացիան և վերաբյուրեղացումը հնարավորություն են տվել ստանալ բարձր էնանտիոմերային մաքրությամբ նպատակային ոչ սպիտակուցային ամինաթթուն՝ (*S*)-կոնֆիգուրացիայի պահպանմամբ: Այս աշխատանքը ցուցադրում է ալկինային օքսիդատիվ միացման ռեակցիաների համատեղելիությունը ոչ սպիտակուցային ամինաթթուների ասիմետրիկ սինթեզի հետ և ընդլայնում է կառուցվածքային բարդ՝ ացետիլենային խմբեր պարունակող ամինաթթուների նոր ածանցյալների սինթետիկ գործիքակազմը:

Բանալի բառեր՝ ասիմետրիկ սինթեզ, ոչ սպիտակուցային ամինաթթուներ, Գլազերի հետերոհամակցման ռեակցիա