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# Strategy for synthesizing *O*-protected (*S*)- $\alpha$ -substituted serine analogs *via* sequential Ni(II)-complex-mediated cross-coupling and cycloaddition reactions†

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A strategy for the synthesis of enantiomerically enriched *O*-protected  $\alpha$ -substituted (*S*)-serine analogs involving a sequence of several named reactions in the coordination sphere of a square-planar Ni(II) Schiff base complex of dehydroalanine and the chiral auxiliary (*S*)-BPB was developed. The Michael addition of the methylate to the double bond of the dehydroalanine moiety yielded the *O*-methylserine complex, serving as an *O*-protected precursor of serine for subsequent transformations. The synthesis of  $\alpha$ -substituted serines—(*S*)- $\alpha$ -benzylserine, (*S*)- $\alpha$ -allylserine, and (*S*)- $\alpha$ -propargylserine—was then achieved *via* electrophilic  $C_{\alpha}$ -alkylation of the *O*-methylserine moiety using alkyl halides. The amino acid side chain was further modified. Thus, the terminal alkyne group of the  $\alpha$ -propargylserine complex was subjected to Glaser and Sonogashira cross-coupling reactions and [3+2] cycloaddition, while the terminal alkene group of the  $\alpha$ -allylserine was modified by Heck reaction. All target  $\alpha$ -substituted analogs of *O*-methyl-(*S*)-serine were obtained with high enantiomeric purity (ee >98%) and can serve as ready-made *O*-protected components for peptide synthesis. This strategy paves the way for the synthesis of novel enantiomerically pure  $\alpha$ -substituted  $\beta$ -hydroxy- $\alpha$ -amino acids with structurally diverse side chains and various *O*-protecting groups (Bn, *i*Pr, *t*Bu, *etc.*).

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## Introduction

Serine and its derivatives play a key role both in natural processes and in medical chemistry in the practice of synthesis of various antibacterial, antiviral, antitumor peptides and other pharmacologically active drugs.<sup>1–3</sup> For example, phenylisoserine is the main component of the anticancer drug *Taxol*,<sup>4</sup> *azaserine* is an active component of antibacterial drugs of antitumor activity<sup>5,6</sup> *etc.* In a series of serine analogs, its  $\alpha$ -substituted derivatives found in such natural products as *Myrocyn* and *Sphingofungin E* (antibiotic, immunosuppressant), *conagenin* (antitumor agent), *altemicidin* (antitumor), *omuralide*

and *lactacystin* (proteasome inhibitor), *etc.* occupy a special place.

Serine derivatives are also successfully used in the synthesis of synthetic peptides and other pharmaceuticals,<sup>7</sup> which dictates the relevance of their direct production in the form of *O*-protected analogs.<sup>8</sup>

In recent decades, significant efforts have been made to synthesize  $\alpha$ -substituted serine derivatives, and methods for their synthesis have been developed. Thus, an approach to the synthesis of enantiopure derivatives of  $\alpha$ -methylserine through the addition of Grignard reagents to the chiral nitron derivative of *L*-erythrose<sup>9</sup> was reported. Further, the synthesis of enantiomerically pure derivatives of (*R*)- $\alpha$ -methylserine and (*R*)- $\alpha$ -benzylserine was accomplished by the Strecker reaction.<sup>10,11</sup> Hegedus<sup>12</sup> reported a sequence involving the  $\alpha$ -alkylation of photochemically synthesized chiral bicyclic  $\beta$ -lactams, which were converted to a series of amino acids, including (*R*)- $\alpha$ -methylserine. Additionally, phase-transfer catalysis (PTC) protocols for alkylation of 2-phenyl-2-oxazoline-4-carbonylcamphorsultam<sup>13</sup> and  $\alpha$ -alkylation of  $\alpha$ -brommalonates<sup>14</sup> were disclosed.

However, the previously reported methods have several practical drawbacks, specifically, they involve complex multistep

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sequences, require costly reagents, and generally give low yields of final products, often accompanied by difficult-to-separate byproducts. Furthermore, these methods are unsuitable for scaling up since the key chiral auxiliaries are not regenerated.

In another published approach to the asymmetric synthesis of (*S*)- $\alpha$ -MeSer, Belokon<sup>15</sup> used planar-square Ni(II) Schiff base complexes of amino acids and the chiral auxiliary reagent (*S*)-BPB (Scheme 1A). The aldol condensation of formaldehyde with the alanine complex produced a mixture of diastereomeric complexes (*S*)- and (*R*)- $\alpha$ -MeSer in a 2 : 1 ratio, which was further subjected to *O*-acetylation, resulting in a diastereomeric mixture of  $\alpha$ -Me-*O*(Ac)Ser complexes. The (*S,S*)-diastereomer crystallized from the resulting mixture (63%), was then subjected to acid hydrolysis, giving enantiomerically pure (*S*)- $\alpha$ -MeSer with an overall yield of around 25%. After treatment of the mother

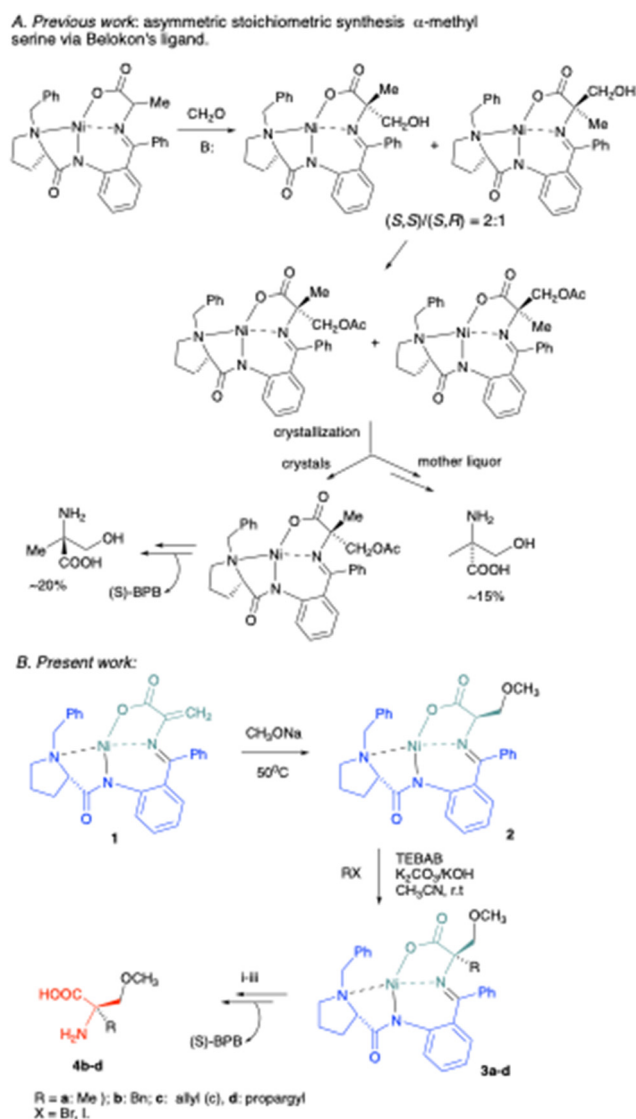
liquor with MeONa and acid hydrolysis, the other enantiomer, (*R*)- $\alpha$ -MeSer, was obtained. The main disadvantage of this approach is the low stereoselectivity in the aldol condensation step – (*S,S*)/(*S,R*) = 2/1 (de 32%), resulting in the low chemical yield of the target product. Additionally, this method is limited to the synthesis of only  $\alpha$ -MeSer. However, a notable advantage included a quantitative regeneration of the chiral auxiliary (*S*)-BPB, with complete retention of the initial chirality, allowing its repeated use in the asymmetric synthesis of amino acids. Consequently, the use of chiral auxiliary reagents in asymmetric synthesis proves to be both highly efficient and effective.<sup>16–19</sup>

The present work introduces an alternative strategy for the enantioselective synthesis of quaternary serine analogs with a wider scope of potential targets (Scheme 1B). It takes advantage of Belokon's planar-square Ni(II) complexes, however, instead of the aldol addition to the alanine moiety, it employs  $C_\alpha$ -alkylation of the serine fragment of the complexes. The high stereoselectivity of the reaction (de > 90%) enables the isolation of enantiomerically pure target amino acid directly from the reaction mixture with a yield of 50% and ee 99%. The method appears to be universal and enables the introduction of various alkyl groups (Bn, allyl, propargyl, etc.) at the  $\alpha$ -position of the serine moiety, maintaining the high stereo-differentiating ability of the complexes. Furthermore, the developed approach creates an opportunity for the synthesis of more complex  $\alpha$ -substituted serine analogs with various side chains through the use of cross-coupling reactions (Sonogashira, Heck, Glaser, [3+2] CuAAC, etc.) of the terminal alkene and alkyne moiety.

## Results and discussion

In the present work, the square-planar Ni(II) complex of the Schiff base of *O*-methyl serine and the chiral auxiliary BPB (2) was used as an *O*-protected serine precursor. It is prepared by the literature method through the Michael addition of the methoxide anion to the C=C double bond of dehydroalanine complex (1)<sup>20,21</sup> (Scheme 1B). The nucleophilic addition is thermodynamically controlled and provides the main (*S,S*)-diastereomer of 2 with conversion > 95% and de > 90%. The structure and configuration of 2 were established by NMR and polarimetry ([ $\alpha$ ]<sub>D</sub>). The minor diastereoisomer was not separated at this point, and after neutralization and extraction, the mixture was subjected to  $C_\alpha$ -alkylation.

$C_\alpha$ -Alkylation of the amino acid moiety of complex 2 was carried out employing methyl iodide, benzyl bromide, allyl bromide and propargyl bromide as alkylating agents. The alkylation process was monitored by TLC. This is a kinetically controlled process that ensures the formation of the main (*S,S*)-diastereomer of the product with a high de (see Table 1). Due to the low degree of conversion in the case of iodomethane (a) (up to 15%), product 3a was not characterized. The diastereomeric mixtures of products 3b–d were extracted from the reaction medium with chloroform, concentrated, and converted to the target amino acids. The structure and absolute configuration of the main (*S,S*)-diastereomers of the alkylated products 3b–d



**Scheme 1** (A) Asymmetric stoichiometric synthesis of (*S*)- $\alpha$ -MeSer via Belokon's ligand. (B) Alternative strategy realized in the current work for the enantioselective synthesis of quaternary serine analogs. (i) 2N HCl, 50 °C; (ii) Dowex 50-8; (iii) EtOH/H<sub>2</sub>O.



**Table 1** Results of  $C_\alpha$ -alkylation of complex **2** with alkyl halides

Entry	Alkylated complex	( <i>S,S</i> )/( <i>S,R</i> ) <sup>ab</sup> (ee, %)	Yield <sup>c</sup> , %
1	<b>3a</b>	na	10 <sup>c</sup>
2	<b>3b</b>	94.5/5.5 (90)	80
3	<b>3c</b>	96/4 (90)	82
4	<b>3d</b>	95/5 (90)	82
	$\alpha$ -Amino acid	ee <sup>d</sup> , %	Yield <sup>e</sup> , %
5	<b>4a</b>	na	na
6	<b>4b</b>	98	50
7	<b>4c</b>	99	58
8	<b>4d</b>	99	53

<sup>a</sup> Product ratio determined by NMR of a mixture of diastereomeric complexes. <sup>b</sup> Determined by chiral HPLC of the amino acid isolated from a mixture of diastereomeric complexes (before chromatography). <sup>c</sup> Conversion at the alkylation stage determined by NMR. <sup>d</sup> Enantiomeric purity of the isolated target amino acids determined by chiral HPLC. <sup>e</sup> Chemical yield of the isolated pure amino acids.

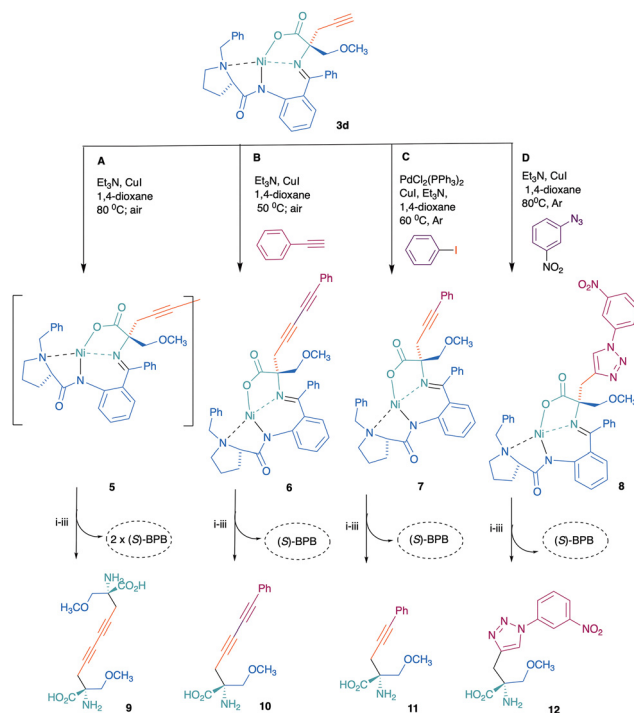
purified by chromatography were established by physicochemical methods.

The (*S*)-absolute configuration of the  $\alpha$ -carbon atom of the amino acid moiety of complexes **3** was assigned based on the positive sign of their optical rotation at 589 nm, in analogy with the data for similar Ni(II) complexes of other amino acids.<sup>22</sup> The assignment was additionally confirmed by the circular dichroism (CD) spectra: the positive Cotton effects for the main diastereomeric complexes **3b–d** in the 480–600 nm region indicate their (*S,S*)-absolute configuration. This agreed with the CD spectra of the (*S,S*)- and (*S,R*)-diastereomers of the previously reported similar alanine complexes, for which the absolute configuration was established by the X-ray crystallography.

The ratios of the (*S,S*)- and (*S,R*)-diastereomers of complexes **3b–d** were determined from their <sup>1</sup>H NMR spectra by integrating the methylene proton signals of the *N*-benzyl group. The ratios were further confirmed by chiral HPLC analysis of amino acids **4b–d**, isolated after acid hydrolysis of the mixture of diastereomeric complexes (before chromatography) and ion-exchange demineralization. The (*S,S*)-diastereoisomers of complexes **3b–d** were formed with a high diastereomeric excess. The results are given in Table 1.

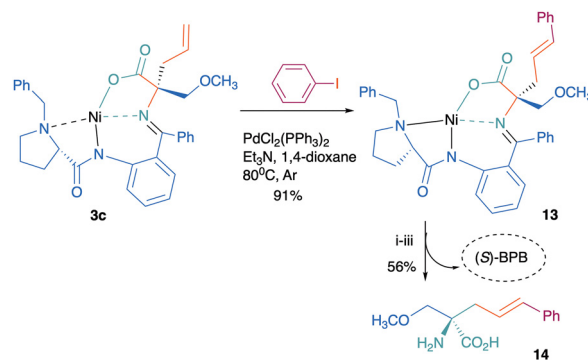
The isolation of target amino acids **4b–d** from the diastereomeric mixture of complexes **3b–d** was carried out according to the standard procedure involving acid hydrolysis, ion-exchange demineralization, and crystallization from aqueous ethanol. The enantiomeric purity of the isolated amino acids was around 99% (see Table 1, entries 6–8). The overall chemical yield of the target amino acids **4b–d**, based on the initial amount of complex **1**, exceeded 45% (note the yield of over 90% in the formation of complex **2**).

Importantly, including alkyne and alkene groups into the side chain of the amino acid fragments creates opportunities for further modification using cross-coupling reactions. In this context, complexes **3c** and **3d** were employed to explore various modifications of the  $\alpha$ -amino acid moiety. Complex **3d** with a terminal acetylene group was used in the Glaser (routes A, B)

**Scheme 2** Application of complex **3d** in the Glaser (A, B), Sonogashira (C), and [3+2]-cycloaddition reactions (D). (i) 2N HCl, 50 °C; (ii) Dowex 50-8; (iii) EtOH/H<sub>2</sub>O.

and Sonogashira (route C) cross-coupling reactions, as well as in [3+2]-cycloaddition (route D) (Scheme 2), whereas complex **3c** featuring a terminal double bond was subjected to the Heck reaction (Scheme 3).

In the cross-coupling reactions, enantiopure (*S,S*)-diastereoisomers of complexes **3c** and **3d** were used. It is worth noting that the  $C_\alpha$ -chiral atom of the amino acid moiety in **3** does not directly participate in the formation of a new carbon–carbon bond in the cross-coupling reactions. However, considering that the reactions were carried out in a weakly alkaline medium, a partial racemization of the  $C_\alpha$  atom of amino acid might be taking place. Therefore, the diastereomeric purity of complexes **5–8** and **13** was determined from the NMR spectra (before chromatography), whereas the enantiomeric purity of

**Scheme 3** Application of complex **3c** in the Heck coupling reaction. (i) 2N HCl, 50 °C; (ii) Dowex 50-8; (iii) EtOH/H<sub>2</sub>O.

**Table 2** Data from the cross-coupling and [3+2] cycloaddition reactions of complexes **3c** and **3d**<sup>a</sup>

Entry	Complex	Yield <sup>b</sup> , %
1	<b>5</b>	71
2	<b>6</b>	82
3	<b>7</b>	87
4	<b>8</b>	93
5	<b>13</b>	91
$\alpha$ -Amino acid		Yield <sup>c</sup> , %
6	<b>9</b>	49
7	<b>10</b>	54
8	<b>11</b>	67
9	<b>12</b>	72
10	<b>14</b>	57

<sup>a</sup> Diastereomeric excess (de) of complexes **5–8** and **13** (according to NMR data) and the enantiomeric purity (ee) of isolated amino acids **9–12** and **14** (according to chiral HPLC data) exceed 98%. <sup>b</sup> Yield of isolated pure product.

isolated amino acids **9–12** and **14** was established by chiral HPLC (before crystallization). The analysis revealed that the reactions in the side chain did not affect the stereogenic center. The main diastereoisomers of complexes **5–8** and **13** were purified by chromatography on silica, and their (*S,S*)-absolute configuration was confirmed by the polarimetric methods ( $[\alpha]_D$  and CD spectra).

The isolation of target amino acids **9–12** and **14** from complexes **5–8** and **13** was carried out according to the standard procedure.<sup>18</sup> All amino acids were recrystallized, and their structure and enantiomeric purity were established by spectral methods (ee > 98%). The results are presented in Table 2.

In all the reactions studied, the original chiral auxiliary (*S*)-BPB was regenerated with a nearly quantitative yield (>97%) and without loss of the enantiopurity, which allows for multiple reuses in the asymmetric synthesis of amino acids.

## Experimental

### Methods and materials

All reagents were obtained from commercial sources and used without further purification. TLC analyses were performed on glass plates coated with silica gel 60 F<sub>254</sub>. Column chromatography was performed on silica gel (60 × 120 mesh) on a glass column. Melting points (mp) were determined by "Electrothermal". <sup>1</sup>H and <sup>13</sup>C NMR spectra ("Mercury-300 Varian" 300 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 Nautilus-E column, 5  $\mu$ m, 4.6 mm × 250 mm (BioChemMak ST, Moscow, Russia), and a mixture of 20% MeOH and 80% 88 mM aqueous solution KH<sub>2</sub>PO<sub>4</sub> was used as the eluent. The optical rotation was measured on a PerkinElmer-341 polarimeter. The CD analyses were performed on Chirascan™ V100. The original **1** and **2** complexes were prepared following literature protocols.<sup>16,17</sup>

### General procedure for the synthesis of compounds **3a–d**: *C $\alpha$* -alkylation

Alkyl bromide (10.8 mmol) in 20 mL of acetonitrile was added dropwise to a stirred mixture containing KOH (0.62 g, 10.8 mmol), K<sub>2</sub>CO<sub>3</sub> (1.480 g, 10.8 mmol), and Bu<sub>4</sub>NBr (1.8 g, 5.4 mmol) in 40 mL of acetonitrile at room temperature. Subsequently, complex **2** (2 g, 3.6 mmol) was added to the reaction mixture, and stirring was continued at room temperature for 4–8 hours. The alkylation process was monitored by TLC (SiO<sub>2</sub>, CHCl<sub>3</sub>/CH<sub>3</sub>COCH<sub>3</sub> = 3 : 1) by the disappearance of traces of initial complex **2** and the appearance of diastereomeric complexes of *C $\alpha$* -alkylating products. After completion of the reaction, the mixture was neutralized with AcOH, filtered, and the solid residue was washed with CHCl<sub>3</sub> (20 mL).

The alkylation products were extracted from the combined filtrate with chloroform (200 mL), concentrated under vacuum, and used for the isolation of target amino acids. The main diastereomers of the alkylated complexes **3b–c** were chromatographed (SiO<sub>2</sub>, CHCl<sub>3</sub>/CH<sub>3</sub>COCH<sub>3</sub>/hexane = 3 : 1 : 1) and used for determining the structure and absolute configuration, as well as for their application in subsequent cross-coupling reactions.

### General procedure for the synthesis of compound **5**: Glaser homo-coupling

Complex **3d** (500 mg, 0.86 mmol, 1 equiv.) was slowly added to a stirred mixture of copper(I) iodide (160 mg, 0.8 mmol, 1 equiv.) and triethylamine (5 mL) in 15 mL of 1,4-dioxane under an oxygen atmosphere. The reaction mixture was maintained at 80 °C with continuous stirring for 8 hours. The reaction was monitored by TLC (SiO<sub>2</sub>, CHCl<sub>3</sub>/CH<sub>3</sub>COCH<sub>3</sub> = 3 : 1) by the disappearance of traces of initial complex **3d**. After completion of the reaction, the mixture was neutralized with AcOH and extracted with chloroform (3 × 20 mL). The chloroform extract of complex **5** was concentrated under vacuum and used for the isolation of the target dimeric amino acid **9**. For structural analysis of the dimeric complex **5**, the mixture was further purified on SiO<sub>2</sub> (CHCl<sub>3</sub>/CH<sub>3</sub>COCH<sub>3</sub> = 3 : 1).

### General procedure for synthesis of compound **6**: Glaser hetero-coupling

A clean and dry reaction flask was charged with 1.0 equivalent of CuI (160 mg, 0.8 mmol) dissolved in 10 mL of 1,4-dioxane, followed by the addition of 5 mL of triethylamine. After stirring for 20 minutes, 1.0 equivalent of complex **3d** (500 mg, 0.86 mmol) and 2.0 equivalents of phenylacetylene (0.19 mL, 1.7 mmol) were slowly added to the reaction mixture. The reaction was stirred at 50 °C for 10 hours under an air atmosphere. The progress of the reaction was monitored by TLC (SiO<sub>2</sub>, CHCl<sub>3</sub>/CH<sub>3</sub>COOC<sub>2</sub>H<sub>5</sub> = 3 : 1). After completion, 20 mL of water was added to the reaction mixture and the product was extracted with CHCl<sub>3</sub> (3 × 20 mL). The chloroform extract was concentrated under vacuum and used for the isolation of the target amino acid **10**. A small portion of complex **6** was purified on SiO<sub>2</sub> (CHCl<sub>3</sub>/CH<sub>3</sub>COOC<sub>2</sub>H<sub>5</sub> = 3 : 1) for structural analysis.





### General procedure for the synthesis of compound 7: Sonogashira coupling

To a clean, dry reaction flask, 2 equivalents of iodobenzene (0.19 mL, 1.7 mmol) were dissolved in 15 mL of triethylamine. The reaction mixture was then degassed by purging with an inert gas (argon or nitrogen) for 20 minutes. Next, 5 mol% of  $\text{PdCl}_2(\text{PPh}_3)_2$  (30 mg, 0.04 mmol) and 10 mol% of CuI (16 mg, 0.08 mmol) were added to the reaction flask. The reaction mixture was stirred for a few minutes. Subsequently, terminal alkyne complex **3d** (500 mg, 0.86 mmol), dissolved in 1,4-dioxane, was added dropwise to the reaction mixture over an extended period while maintaining an inert atmosphere. The reaction was stirred at 60 °C for 5 hours. The coupling process was monitored by TLC ( $\text{SiO}_2$ ,  $\text{CHCl}_3/\text{CH}_3\text{COOC}_2\text{H}_5 = 3:1$ ) by the disappearance of traces of initial complex **3d**. Upon completion of the reaction, 20 mL of water was added to the reaction mixture, and the product was extracted with ethyl acetate ( $3 \times 20$  mL). The organic layers were combined, concentrated under a vacuum, and used for the isolation of the target amino acid **11**. The structure of complex **7** was studied after its further purification ( $\text{SiO}_2$ ,  $\text{CHCl}_3/\text{CH}_3\text{COOC}_2\text{H}_5 = 3/1$ ).

### General procedure for synthesis of compound 8: [3+2]-cycloaddition

In a clean, dry reaction flask, 10 mol% of CuI (16 mg, 0.08 mmol), 5 mL of triethylamine, and 2 equiv. of 1-azido-3-nitrobenzene (280 mg, 1.7 mmol) were dissolved in 15 mL of 1,4-dioxane. The reaction mixture was degassed by purging with an inert gas (argon or nitrogen) for 20 minutes, then 1 equivalent of complex **3d** (500 mg, 0.86 mmol) was added to the reaction mixture. The reaction mixture was then stirred at room temperature for 40 minutes. After this, the mixture was heated to 80 °C and stirred for 1 hour. The cycloaddition process was monitored by TLC ( $\text{SiO}_2$ ,  $\text{CHCl}_3/\text{CH}_3\text{COOC}_2\text{H}_5 = 3:1$ ). Upon completion of the reaction, 20 mL of water was added to the reaction mixture and the product-complex was extracted with  $\text{CH}_3\text{COOC}_2\text{H}_5$  ( $3 \times 20$  mL). The organic layers were combined, concentrated under vacuum, and used for the isolation of the target amino acid **12**. For spectral characterization of complex **8**, the mixture was further chromatographed on  $\text{SiO}_2$  ( $\text{CHCl}_3/\text{CH}_3\text{COCH}_3 = 3:1$ ).

### General procedure for synthesis of compound 13: Heck coupling

In a clean, dry reaction flask 4 mL of trimethylamine was dissolved in 5 mL of 1,4-dioxane. The reaction mixture was degassed under an inert atmosphere (argon or nitrogen) for 10 minutes. To the degassed solution, 10 mol% of  $\text{PdCl}_2(\text{PPh}_3)_2$  (60 mg, 0.08 mmol) and 2 equivalents of iodobenzene (0.19 mL, 1.7 mmol) were added. The reaction mixture was stirred for a few minutes under the inert atmosphere, and then the terminal alkene complex **3c** (500 mg, 0.84 mmol) dissolved in 1,4-dioxane was added slowly over an extended period, ensuring the inert atmosphere was maintained. The reaction was stirred at 80 °C for 8 hours. The coupling process was monitored by

TLC ( $\text{SiO}_2$ ,  $\text{CHCl}_3/\text{CH}_3\text{COOC}_2\text{H}_5 = 5:1$ ). Upon completion of the reaction, 20 mL of water was added to the reaction mixture and the product was extracted with  $\text{CH}_3\text{COOC}_2\text{H}_5$  ( $3 \times 20$  mL). The organic layers were combined and concentrated under vacuum. The target amino acid **14** was isolated from the resulting mixture using the standard procedure.<sup>18</sup> For spectral characterization, complex **13** was further purified on  $\text{SiO}_2$  ( $\text{CHCl}_3/\text{CH}_3\text{COOC}_2\text{H}_5 = 3:1$ ).

### General procedure of isolation of the $\alpha$ -amino acids 4(b–d), 9–12 and 14

Isolation of  $\alpha$ -amino acids from the complexes was carried out according to the previously developed standard procedure.<sup>18</sup> For this, the obtained mixture of alkylation products **3b–d**, **5–8**, and **13** was dissolved in MeOH and then slowly added to 2 M HCl solution, and the mixture was heated at 50 °C. After the disappearance of the red color of the product complex, the solution was concentrated in a vacuum, then water was added, and the precipitated (*S*)-BPB  $\times$  HCl was filtered. To extract the residues of the chiral reagent, the filtrate was extracted with chloroform (50 mL). The target amino acids were isolated from the water layer by ion-exchange chromatography using Ku-2  $\times$  8  $\text{H}^+$  cation exchange resin and an aq. solution of  $\text{NH}_4\text{OH}$  (5%) as eluent. The eluate was concentrated in a vacuum, and the target  $\alpha$ -amino acids **4b–d**, **9–12**, and **14** were crystallized from aqueous ethanol.

## Conclusions

In conclusion, an efficient asymmetric synthesis of a series of  $\alpha$ -substituted *O*-methyl-(*S*)-serine analogs has been developed through a sequence of amino acid transformations performed on the ligand sphere of a square-planar Ni(II) Schiff base complex derived from dehydroalanine and the chiral auxiliary (*S*)-BPB. Nucleophilic addition of methanol to the  $\text{C}=\text{C}$  bond of the dehydroalanine moiety led to the formation of an *O*-methyl serine complex, which served as an *O*-protected precursor for subsequent electrophilic  $\alpha$ -alkylation reactions with alkyl halides. This approach enabled the asymmetric synthesis of (*S*)- $\alpha$ -benzyl-*O*-methylserine, (*S*)- $\alpha$ -allyl-*O*-methylserine, and (*S*)- $\alpha$ -propargyl-*O*-methylserine.

Further functionalization of the alkyne and alkene groups was achieved using Glaser and Sonogashira cross-coupling reactions, [3+2] cycloaddition, and the Heck reaction, expanding the synthetic routes toward novel  $\alpha$ -substituted *O*-methyl-(*S*)-serine derivatives. All target amino acids were obtained with high enantiomeric purity ( $\text{ee} > 98\%$ ) and can serve as *O*-protected building blocks in peptide synthesis, facilitating the incorporation of  $\alpha$ -substituted (*S*)-serines into peptide frameworks.

The developed synthetic strategy offers a versatile platform for the preparation of structurally diverse  $\alpha$ -substituted (*S*)-serine analogs with a broad range of branched side chains and various *O*-protecting groups (*e.g.*, Bn, *i*-Pr, *t*-Bu). This work opens new avenues for the design and synthesis of advanced



amino acid derivatives with potential applications in medicinal chemistry, peptide science, and the development of bioactive compounds.

## Author contributions

Anna S. Tovmasyan (AST): data curation, investigation, methodology, formal analysis; Anna F. Mkrtchyan (AFM): conceptualization, formal analysis, writing – original draft, writing – review & editing, resources, supervision; Avetis H. Tsaturyan (AHT): data curation, validation, visualization, Peter Langer (PL): methodology, writing – review & editing; Andrey Malkov (AM): formal analysis; methodology, visualization, writing – original draft, writing – review & editing; Ashot S. Saghyhan (ASS): funding acquisition, methodology, project administration, supervision, writing – original draft, writing – review & editing

## Conflicts of interest

There are no conflicts to declare.

## Data availability

The data supporting this article have been included as part of the ESI.† Additional datasets generated during the current study are available from the corresponding authors upon reasonable request.

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