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Asymmetric synthesis of (*S*)-α-(octyl)glycine via alkylation of Ni(II) complex of chiral glycine Schiff base

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Abstract

Over last decade, the use of Ni(II) complexes, derived from of glycine Schiff bases with chiral tridentate ligands, has emerge as a leading methodology for preparation of structurally diverse Tailor-Made Amino Acids, the key structural units in modern medicinal chemistry, and drug design. Here, we report asymmetric synthesis of derivatives of (*S*)-α-(octyl)glycine ((*S*)-2-aminodecanoic acid) and its *N*-Fmoc derivative via alkylation of chiral nucleophilic glycine equivalent with *n*-octyl bromide. Under the optimized conditions, the alkylation proceeds with excellent yield (98.1%) and diastereoselectivity (98.8% de). The observed stereochemical outcome and convenient reaction conditions bode well for application of this method for large-scale asymmetric synthesis of (*S*)-2-aminodecanoic acid and its derivatives.

KEYWORDS

amino acids, asymmetric synthesis, chiral tridentate ligands, Schiff bases, square-planar Ni(II) complexes, Tailor-Made Amino Acids™

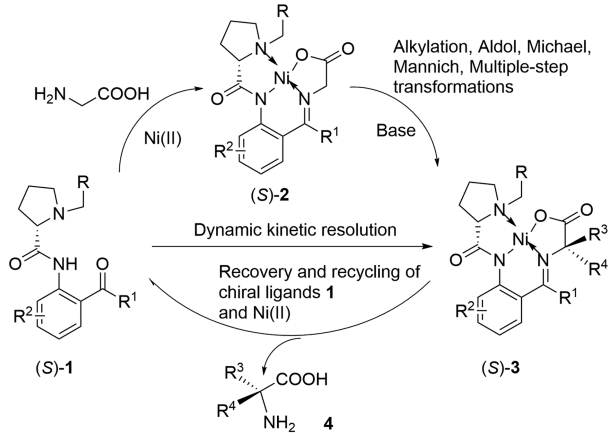
1 | INTRODUCTION

Tailor-Made Amino Acids™ (Tailor-Made Amino Acids™ is a trade-mark registered by Hamari Chemicals; for definition of Tailor-Made Amino Acids, see Soloshonok et al.[1]) are important structural motifs in modern medicinal chemistry and drug design. The presence of the chemically orthogonal amino and carboxyl groups, combined with the stereogenic carbon and side chains, provides a three-dimensional structural scaffold with an extraordinary degree of chemical/biological functionality. These properties render amino acids (AAs) ideally suited for design of complex molecules used as the basic components in modern pharmaceutical industry.[2–5] Notably, over 30% of small-molecule drugs contain residues of Tailor-Made Amino Acids™.[2–7] One should also mention the growing acceptance and importance of AAs-based classes of drugs, such as peptidomimetics and peptides.[8–13] Subsequently, the current need for synthetic approaches affording enantiomerically pure Tailor-Made

Amino Acids™ is at an all-time high.[14–21] Over the last decade, transformations of chiral Ni(II) complexes of Schiff bases derived from tridentate ligands and AAs (Scheme 1) have emerge as a leading methodology for asymmetric synthesis of tailor-made AAs.[22–27]

Typically, tridentate ligands (*S*)-**1**[28,29] are used for preparation of nucleophilic glycine equivalents (*S*)-**2** that serve as the starting templates for incorporation of the desired side-chain(s). Most generally used types of the reactions include alkyl halide alkylations[30,31] aldol,[32] Mannich,[33] and Michael[34–36] addition reactions. Furthermore, multiple step reaction sequences allow for preparation of several types of cyclic AAs[37,38] as well α-hydroxy-β-amino acids.[39] Ligands **1** can also be used for direct reactions with unprotected AAs to afford Ni complexes **3**. This process was shown to be quite efficient to perform deracemization, dynamic thermodynamic resolution, or (*S*) to (*R*) interconversion of unprotected α-[40–42] and β-AAs.[43] In this work, we examine the application of this methodology for asymmetric synthesis of (*S*)-α-(octyl)glycine,[44–49] a characteristic representative of naturally occurring class of lipidic α-AAs serving as key structural units in the design of lipophilic analogs of various biologically active peptides, such as enzymes, hormones, and therapeutic drugs.[50–55]

For this work, we selected tri-dentate ligand **5** (Scheme 2) and the corresponding glycine complex **6**, which show enhanced stereocontrolling properties due to a parallel displaced type of aromatic interactions between the selectively chlorinated *o*-amino-benzophenone and Pro *N*-benzyl rings.[56] Ligand **5**[29] and glycine-Ni (II) complex **6**[57] are available on over a kilogram scale in both enantiomeric forms.



SCHEME 1 General asymmetric synthesis of Tailor-Made Amino Acids™ via Ni(II) complex methodology

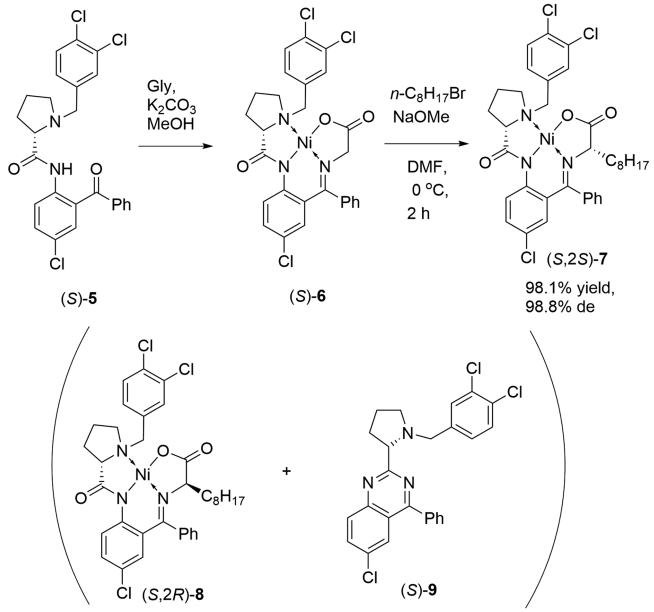
2 | MATERIALS AND METHODS

2.1 | General information

All reagents and solvents were used as received. Flash chromatography was performed with the indicated solvents on silica gel (particle size 0.064–0.210 mm). HPLC was performed on a SHIMADZU LC-2010CHT chromatograph with a CLASS-VP™ analysis data system using the Inertsil™ ODS-3 column (particle size 3 μm, 150 × 4.6 mm i.d.) operated at 1.0 ml/min, 30°C and monitored at wavelength of 254 nm with a linear gradient of 10-mM aqueous ammonium formate containing 0.1% formic acid (eluent A) and acetonitrile (eluent B). ^{1}H- and ^{13}C-NMR spectra were recorded on Brüker AVANCE III-600 spectrometer. Optical rotations were recorded on a DIP-370 polarimeter (Jasco, Inc.). Melting points were recorded on a Mettler Toledo MP70 Melting Point System and are not corrected.

2.1.1 | Alkylation of Ni complex (*S*)-6 with BrC_8H_{17}

To a 20-mL four-necked flask was added complex (*S*)-**6** (10.0 g, 1.0 equiv) together with *N*,*N*-dimethyl-formamide (DMF) (100 mL) under nitrogen atmosphere at 0°C. Then, 1-bromooctane (3.44 mL, 1.2 equiv) and NaOMe (3.59 g, 4.0 equiv) were added to the flask. The mixture was stirred at 0 °C under a nitrogen atmosphere for 2 h.



SCHEME 2 Preparation of chiral glycine-Ni(II) complex **6** and its alkylation with *n*-octyl bromide

After that, the reaction mixture was added to 5% AcOH aq. (525 mL, 52.5 v) and stirred for 1 h at 0°C. Precipitate was formed gradually. Then, the precipitate was filtered and washed with H_2O (150 mL). The obtained solid was dried by air then was dried under vacuum at 50°C to give the product (*S*)(2*S*)-**7** (11.6 g, 98.1% yield, 98.8% de).

*(S)(2S)-**7** (major isomer)*

Red solid, mp = 114–116°C, $[\alpha]_D^{25}$ = +2233.7 (c = 0.63, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.90 (s, 1H), 8.09 (d, *J* = 9.24 Hz, 1H), 7.81 (d, *J* = 8.22 Hz, 1H), 7.59–747 (m, 3H), 7.38 (d, *J* = 8.16 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 9.24 Hz, 1H), 6.89 (d, *J* = 7.62 Hz, 1H), 6.60 (s, 1H), 4.36–4.33 (m, 1H), 3.93 (d, *J* = 7.62 Hz, 1H), 3.62–3.57 (m, 2H), 3.40–3.37 (m, 1H), 3.24–3.22 (m, 1H), 2.77–2.61 (m, 2H), 2.26–2.06 (m, 4H), 1.95–1.89 (m, 1H), 1.68–1.62 (m, 3H), 1.31–1.20 (m, 9H), 0.91 (t, *J* = 6.96 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 179.9, 179.1, 169.8, 140.5, 134.9, 133.6, 133.5, 133.4, 132.9, 132.2, 132.1, 131.0, 130.1, 129.9, 129.3, 129.2, 127.5, 127.3, 127.2, 125.7, 124.1, 71.4, 70.7, 63.1, 58.3, 35.4, 31.8, 31.6, 30.9, 29.4, 29.3, 29.2, 25.4, 23.6, 22.6, 14.1. MS (ESI): calculated for $C_{36}H_{39}Cl_3N_2NaNiO_3^+$ $[M + Na]^+$ 733.1, found 733.5.

*(S)(2R)-**8** (minor isomer)*

Red solid, mp = 103–105°C, $[\alpha]_D^{25}$ = −643.3 (c = 0.57, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.90 (d, *J* = 2.04 Hz, 1H), 8.09 (d, *J* = 9.24 Hz, 1H), 7.81–7.79 (m, 1H), 7.59–7.54 (m, 2H), 7.50–7.47 (m, 1H), 7.39 (d, *J* = 8.22 Hz, 1H), 7.31 (d, *J* = 7.2 Hz, 1H), 7.14–7.12 (m, 1H), 6.90–6.88 (m, 1H), 6.60 (d, *J* = 2.58 Hz, 1H), 4.36 (d, *J* = 12.6 Hz, 1H), 3.94–3.92 (m, 1H), 3.63–3.57 (m, 2H), 3.41–3.38 (m, 1H), 3.25 (d, *J* = 12.6 Hz, 1H), 2.78–2.72 (m, 1H), 2.67–2.60 (m, 1H), 2.27–2.02 (m, 4H), 1.95–1.89 (m, 1H), 1.64 (s, 3H), 1.31–1.25 (m, 9H), 0.91 (t, *J* = 7.17 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 178.3, 176.6, 169.7, 139.8, 137.8, 133.9, 133.8, 133.4, 133.3, 131.1, 130.3, 129.9, 129.1, 129.0, 128.4, 128.3, 127.2, 126.6, 126.2, 71.4, 65.1, 61.8, 58.7, 31.7, 30.1, 29.9, 29.8, 29.3, 29.2, 29.0, 27.2, 24.1, 22.6, 14.1.

2.1.2 | Disassembly of (*S*)(2*S*)-7 and preparation of (*S*)-10

To a 100-mL four-necked flask was added methanol (40 mL, 10 v), Ni complex (*S*,2*S*)-**7** (4.0 g, 1.0 equiv) and HCl (3 N, 9.34 mL, 5.0 equiv). The mixture was heated to 60°C and stirred at this temperature for 4 h. After that, the solution was changed from red suspension to yellow solution. The mixture was cooled to room temperature and stirred for another 1 h. The precipitate was filtered and washed with methanol to give the ligand (*S*)-**5**. The filtrate was evaporated and the residue was added DCM (40 mL) and H_2O (40 mL). The insoluble solid was washed with DCM (20 mL × 3) and then washed with H_2O and dried under vacuum at 50°C to give a solution of (*S*)-**10** (0.82 g, 78.1% yield).

2.1.3 | (*S*)-10

White solid, mp = 221–223°C, $[\alpha]_D^{25}$ = −230 (c = 0.02, DMSO). ^{1}H NMR (400 MHz, DMSO): δ = 8.39 (s, 2H), 3.86 (t, *J* = 6.1 Hz, 1H), 1.80–1.75 (m, 2H), 1.43–1.26 (m, 12H), 0.88 (t, *J* = 6.46 Hz, 3H). ^{13}C NMR (100 MHz, DMSO): δ = 171.5, 52.4, 31.7, 31.5, 30.4, 29.1, 29.0, 24.6, 22.6, 14.4.

2.1.4 | Fmoc-protection of octylglycine (*S*)-10

To a 300-mL four-necked flask was added (*S*)-octylglycine (0.60 g, 1.0 equiv), H_2O (60 mL, 100 v), acetone (60 mL, 100 v), Na_2CO_3 (1.01 g, 3.0 equiv). With stirring, Fmoc-OSu (1.1 equiv, 1.19 g) was added. The resulted mixture was stirred at room temperature for 3 h. The reaction mixture was acidified to pH 3 with 1 N HCl aq (25 mL) and then evaporated to remove acetone under vacuum. EtOAc (30 mL) was added and separated. The combined organic layer was washed with saturated $NaHCO_3$ (30 mL × 3), and then the filtrate was concentrated. The resulted solution was added heptane (30 mL). Precipitate formed, which was filtered and washed with heptane. The precipitate was dried in vacuo at 50°C to afford (*S*)-**11** (1.3 g, 99.4% yield, >99% ee, a white powder).

2.1.5 | (*S*)-11

White solid, mp = 140–142°C, $[\alpha]_D^{25}$ = −75 (c = 0.04, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66–7.61 (m, 2H), 7.45–7.41 (m, 2H), 7.26–7.22 (m, 2H), 7.14–7.09 (m, 2H), 5.91 (s, 1H), 4.35 (s, 1H), 4.16–3.97 (m, 3H), 1.29–1.10 (m, 14H), 0.83 (t, *J* = 7.02 Hz, 3H).

3 | RESULTS AND DISCUSSION

Methodical optimization of the reaction conditions included the following standard parameters: stoichiometry, nature of a base, solvent, temperature, and the reaction time. Some key experimental data are presented in Table 1 (Data S1). In particular, we found that

application of 1.2 equivalents of the alkylating reagent was optimal for a near-complete conversion of the starting Ni(II) complex to the target alkylated product. The reactions conducted in DMSO (entries 1–3) occurred with high rates, but resulted in noticeable amounts of some by-products leading to unsatisfactory chemical yields of product **7**. By contrast, the reactions conducted in methanol (entries 4 and 5) were relatively slow, though producing much less of the by-products.

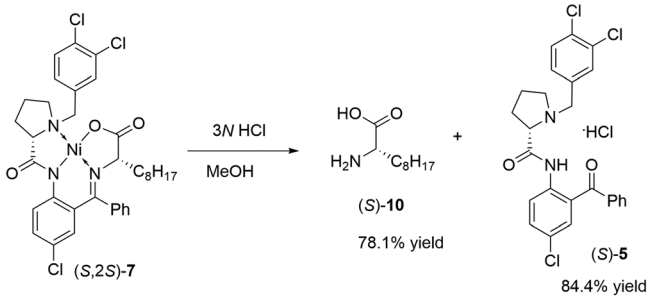
Finally, DMF was found to be an optimal solvent (entries 6–10) allowing for excellent stereochemical outcome of the alkylation. The best results of 98% yield and >98% de were obtained in the reactions conducted at 0°C (entries 9 and 10). These results were successfully reproduced on the 10-g scale of starting glycine complex **6** (entry 10).

It should be noted that the excellent diastereoselectivity in this reaction is rather robust as it was not noticeably influenced by the reaction conditions. The absolute configuration of major product (*S*,2*S*) was assigned on the basis of spectral and chiroptical properties of **7**.[22–27] Despite the formation of minor diastereomer (*S*,2*R*)-**8** in minute amounts, we were able to isolate it in diastereomerically pure form by column chromatography. As expected, major diastereomer (*S*,2*S*)-**7** showed positive optical rotation $\{[\alpha]_D^{25} = +2233.7$ (c = 0.63, MeOH)}, while minor product (*S*,2*R*)-**8** exhibited negative sign $\{[\alpha]_D^{25} = -643.3$ (c = 0.57, MeOH)}. Besides minor diastereomer (*S*,2*R*)-**8**, we detected negligible amounts (<0.5%) of previously described heterocyclic compound (*S*)-**9**.[58] Formation of by-product (*S*)-**9** is a result of oxidative degradation of starting glycine complex (*S*)-**6**[59,60] and can be prevented by using inert atmosphere and deoxygenated DMF. The stereochemical outcome in this alkylation reaction is thermodynamically controlled involving equilibration between major (*S*,2*S*)-**7** and minor (*S*,2*R*)-**8** diastereomers.[22] The same principle of the thermodynamic control is operating in the application of this methodology for chemical dynamic kinetic resolution and (S)/(R)-interconversion of unprotected α-amino acids.[41–43]

TABLE 1 Reaction conditions for alkylation of glycine complex 6 to product 7[a]

Entry	Time (min)	Solvent	Yield (%, 7)	% de
1	10	DMSO	73	98.5
2	30	DMSO	80	97.5
3	60	DMSO	75	99.0
4	60	MeOH	62	99.0
5	120	MeOH	70	98.2
6	10	DMF	88	98.7
7	30	DMF	92	99.0
8	60	DMF	96	98.4
9	120	DMF[b]	98	98.5
10	120	DMF[b,c]	98	98.8

[a]Reactions were conducted at room temperature using ~1 g of starting Ni(II) complex 6.
[b]The reaction was conducted at 0°C.
[c]The reaction was conducted using ~10 g of glycine complex 6.



SCHEME 3 Disassembly of (*S*,2*S*)-**7**: Preparation of amino acid (*S*)-**10** and recovery of chiral ligand (*S*)-**5**

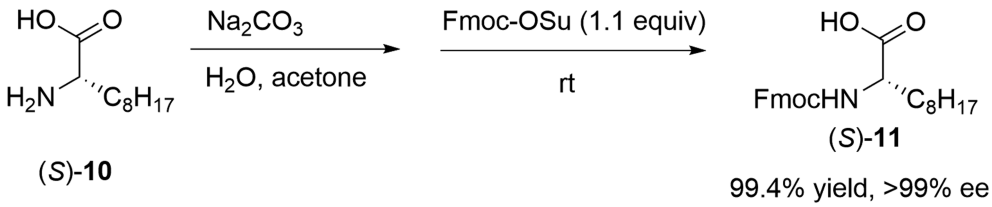
Diastereomerically pure major complex (*S*,2*S*)-**7** was disassembled under acidic conditions to furnish (*S*)-α-(octyl)glycine **10**, along with recovery of chiral ligand (*S*)-**5** (Scheme 3).

As presented in Scheme 3, and described in the Experimental Procedure, complex (*S*,2*S*)-**7** was disassembled to afford chiral ligand (*S*)-**5** and zwitterionic (*S*)-**10**, which was isolated with 78.1%. Taking into account the overall simplicity of this isolation procedure, merely washing with water and organic solvent, we considered the yield of ~78% as perfectly satisfactory. Hence, it was interesting to find that due to the apparent enhanced lipophilic profile of amino acid (*S*)-**10**, its zwitterionic form is virtually insoluble in both aqueous and organic medium, facilitating its isolation and purification.

Nevertheless, zwitterionic (*S*)-**10** can be dissolved in aqueous acidic or basic solutions. As shown in Scheme 4, treatment of (*S*)-**10** with aqueous Na_2CO_3 was used as the first step in the preparation of the corresponding *N*-Fmoc protected derivative (*S*)-**11** with excellent chemical yield.

4 | CONCLUSION

In summary, we demonstrated that the Ni(II) complexes methodology can be quite successfully used for



SCHEME 4 Fmoc-protection of octyl-glycine (*S*)-**10**

asymmetric synthesis of (*S*)-α-(octyl)glycine and its *N*-Fmoc protected derivative. In particular, we found that the alkylation of chiral nucleophilic glycine equivalent with *n*-octyl bromide occurs with excellent stereochemical outcome (∼98% yield and ∼98% de). Interestingly, due to very high lipophilic profile of α-(octyl)glycine, its zwitterionic form is virtually insoluble in both aqueous and organic medium facilitating its isolation and purification. The excellent stereochemical outcome and experimentally convenient conditions reported in this work bode well for application of this method for large-scale asymmetric synthesis of (*S*)-2-aminodecanoic acid and its derivatives.

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DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

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