Received: 23 October 2020 | Revised: 24 November 2020 | Accepted: 3 December 2020

DOI: 10.1002/chir.23291

REGULAR ARTICLE

Chirality WILEY

Asymmetric synthesis of (*S*)-3-methyleneglutamic acid and its *N*-Fmoc derivative via Michael addition–elimination reaction of chiral glycine Ni (II) complex with enol tosylates

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Abstract

The use of chiral Ni (II)-complexes of glycine Schiff bases has recently emerged as a leading methodology for asymmetric synthesis of structurally diverse Tailor-Made Amino Acids™, playing a key role in the design of modern pharmaceuticals. Here, we report first example of enantioselective preparation of (*S*)-3-methyleneglutamic acid and its *N*-Fmoc derivative via a new type of Michael addition–elimination reaction between chiral nucleophilic glycine equivalent and enol tosylates. This reaction was found to proceed with excellent yield (91%) and diastereoselectivity (>99/1 de) allowing straightforward asymmetric synthesis of (*S*)-3-methyleneglutamic acid derivatives and analogues. The observed results bode well for general application of this Ni (II) complex approach for preparation and biological studies of this previously unknown type of Tailor-Made Amino Acids™

KEYWORDS

asymmetric synthesis, chiral tridentate ligands, enol tosylates, Michael addition–elimination reactions, Schiff bases, square-planar Ni (II)-complexes, Tailor-Made Amino Acids™

1 | INTRODUCTION

Tailor-Made Amino Acids™[1,2] are important building blocks in the modern medicinal chemistry and drug design. Structural features of amino acids (AAs), including chemically orthogonal amino and carboxyl groups, as well as the stereogenic center and, practically, any type of side chains, furnishes a three-dimensional architecture possessing an extraordinary degree of biological functionality. These properties make AAs perfectly suited for design of complex biologically relevant molecules used in the development of modern pharmaceuticals.[3–6] It should be pointed out that over 30% of small-molecule marketed drugs are derived from Tailor-Made Amino Acids™, and this number is continuing to grow.[3–8] One might also mention the increasing acceptance and market-share of fully AAs-based classes of pharmaceuticals, such as peptidomimetics and peptides.[9–14] Consequently, the need for convenient and scalable synthetic approaches allowing preparation of enantiomerically pure Tailor-Made Amino Acids™ is at an all-time high.[15–24] Over the last 10 years, the chemistry of chiral

Abbreviations: DIPEA, diisopropylethylamine; EDTA, ethylenediaminetetraacetic acid; Fmoc, Fluorenylmethyloxycarbonyl; NMI, N-methylimidazole; TMEDA, tetramethylethyldiamine.

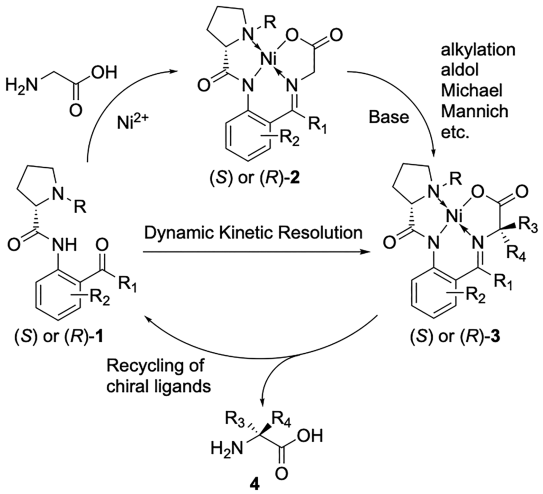
Ni (II)-complexes of Schiff bases derived from tridentate ligands and glycine or higher AAs has emerge as a leading methodology for asymmetric synthesis of Tailor-Made Amino Acids™.[25–30] Generally, chiral ligands (*S*)-**1**[31,32] are being used for synthesis of nucleophilic glycine equivalents (*S*)-**2**, which are then applied as the starting compounds for transformation into the desired higher AAs. Alkyl halide alkylation's,[33,34] aldol,[35] Mannich,[36] and Michael[37–39] additions are the most commonly used types of the reactions to install the desired side chain. Additionally, multistep reaction sequences are also frequently used for preparation of some types of cyclic AAs[40,41] as well α-hydroxy-β-amino acids.[42] Another type of methodology includes the direct reactions of ligands **1** with unprotected higher AAs to afford Ni-complexes **3**. This process was demonstrated to be efficient to accomplish dynamic kinetic resolution (DKR) as well as related processes such as, deracemization or (*S*) to (*R*) interconversion of unprotected α-[43–45] and β-AAs[46] (Scheme 1).

Building on our long-standing interest in chemistry of fluorine-,[22,47,48] phosphorus-containing,[49,50] and sterically constrained AAs,[12,51] in this work, we examine the application of chiral Schiff base Ni (II)-complex methodology for asymmetric synthesis of (*S*)-3-methyleneglutamic acid (*S*)-**5** and its *N*-Fmoc derivative (Figure 1).

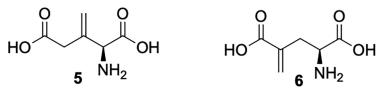
2 | MATERIALS AND METHODS

2.1 | General information

All solvents were reagent grade. All commercial reagents were of the highest purity available. Optical rotations were determined with a JASCO DIP-371 polarimeter at the sodium D line. IR spectra of sample were obtained as films



SCHEME 1 Asymmetric synthesis of Tailor-Made Amino Acids™ via chiral Schiff base Ni (II)-complex methodology



(*S*)-3-methleneglutamic acid (**5**) (*S*)-4-methleneglutamic acid (**6**)

FIGURE 1 (*S*)-3-methyleneglutamic acid (*S*)-**5** and (*S*)-4-methyleneglutamic acid (*S*)-**6**

with a JASCO FT-IR 460 spectrometer. ^{1}H (500 MHz),^{13}C (125 MHz), and ^{19}F NMR (466 MHz) were determined on JNM-ECX500. Chemical shifts are reported in ppm with reference to tetramethylsilane (^{1}H NMR: $CDCl_3$ (0.00)), or solvent signals (^{1}H NMR: $CDCl_3$ (7.26), ^{13}C NMR: $CDCl_3$ (77.16)). High-resolution mass spectra were recorded on a JEOL AccuTOF JMS-T100LC (ESI-MS). Analytical thin layer chromatography (TLC) was performed on Merck Silica gel $60F_{254}$. Crude products were purified by column chromatography on silica gel 60 N (Kanto, particle size, spherical, neutral) 63–210 μm. Enantiomeric excesses were determined by chiral high-performance liquid chromatography (HPLC) analysis on DAICEL CHIRALPAK IH with UV detector at 254 nm.

2.2 | Experiment procedure

2.2.1 | (*E*)-Ethyl 3-(*p*-toluenesulfonyloxy) butenoate (*E*-9)

A solution of ethyl acetoacetate (3.94 g, 30 mmol) in MeCN (20 ml) was added NMI (4.77 ml, 60 mmol) and Et_3N (8.35 ml, 60 mmol) and the mixture was stirred at −15°C for 10 min. *p*-TsCl (11.4 g, 60 mmol) in MeCN (50 ml) was added, and the mixture was stirred at same temperature for 1 h and at ambient temperature for 12 h. The reaction mixture was added to AcOEt and H_2O. Separated aqueous layer was extracted twice with AcOEt. Combined organic layer was washed with 1 N HCl, H_2O, brine, dried over $MgSO_4$, and evaporated in *vacuo*. The residue was purified by column chromatography Hexane : AcOEt (8:1) to give the (*E*)-ethyl 3-(*p*-toluenesulfonyloxy)butenoate (*E*-**9**) (8.24 g, 28.9 mmol, 96%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.81 (d, J = 7.5 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 5.71 (s, 1H), 4.14 (q, J = 7.5, 2H), 2.46 (s, 3H), 2.27 (s, 3H), 1.19 (t, J = 7.5, 3H). This compound has been previously reported.[52]

2.2.2 | (*Z*)-Ethyl 3-(*p*-toluenesulfonyloxy) butenoate (*Z*-9)

A solution of ethyl acetoacetate (9.76 g, 75 mmol) in AcOEt (75 mL) was added LiCl (3.81 g, 90 mmol) TMEDA

(13.4 ml, 90 mmol) and *p*-TsCl (17.1 g, 90 mmol) at −5°C, and the mixture was stirred for 1 h. The reaction mixture was added H_2O and extracted twice with AcOEt. The organic layer was washed with 1 M HCl, brine, dried over $MgSO_4$, and evaporated in *vacuo*. The residue was purified by column chromatography Hexane : AcOEt (8:1) to give the (*Z*)-ethyl 3-(*p*-toluenesulfonyloxy)butenoate (*Z*-**9**) (15.0 g, 53.0 mmol, 71%) as a colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 7.91 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 5.50 (s, 1H), 4.05 (q, *J* = 7.0 Hz, 2H), 2.45 (s, 3H), 2.11 (s, 3H), 1.20 (t, *J* = 7.0 Hz, 3H). This compound has been previously reported.[52]

2.2.3 | Ni (II)-glycine compound (*S*)(2*S*)-11

A solution of (*E*)-ethyl 3-(*p*-toluenesulfonyloxy) butenoate (*E*-**9**) (53.5 mg, 0.19 mmol) in *i*-PrOH (30 ml) was added (*S*)-**7** (75.5 mg, 0.13 mmol) and K_2CO_3 (172 mg, 1.23 mmol), and the reaction mixture was stirred at 50°C for 18 h under N_2 atmosphere. The reaction mixture was added to 5% AcOH, and aqueous layer was extracted twice with CH_2Cl_2. The organic layer was washed with H_2O, brine, dried over $MgSO_4$, and evaporated in *vacuo*. The residue was purified by column chromatography $CHCl_3$: MeOH (99:1) to give the Ni (II)-glycine compound (*S*)(2*S*)-**11** (81.0 mg, 0.11 mmol, 91%) as a red solid. $[\alpha]_D^{25}$ = +2,348 (*c* = 0.1 in $CHCl_3$). IR (KBr, νmax cm^{-1}): 3,448, 3,051, 2,981, 2,963, 2,922, 2,871, 2,363, 2,236, 1,731, 1,680, 1,644, 1,535, 1,463, 1,396, 1,355, 1,318, 1,251, 1,029, 824, 723, 588, 443. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.89 (d, *J* = 2.5 Hz, 1H), 8.11 (d, *J* = 9.5 Hz, 1H), 7.78 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.48–7.56 (m, 2H), 7.38 (d, *J* = 8.5 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.13 (dd, *J* = 9.5, 2.5 Hz, 1H), 6.82 (d, *J* = 7.5 Hz, 1H), 6.62 (d, *J* = 2.5 Hz, 1H), 5.74 (s, 1H), 5.35 (s, 1H), 4.35 (s, 1H), 4.30 (d, *J* = 12.5 Hz, 1H), 3.94 (m, 2H), 3.62–3.66 (m, 1H), 3.51 (dd, *J* = 6.0, 4.0 Hz, 1H), 3.46 (d, *J* = 16.0 Hz, 1H) 3.37 (q, *J* = 5.5 Hz, 1H), 3.22 (d, *J* = 12.5 Hz, 1H), 3.12 (d, *J* = 16.0 Hz, 1H), 2.65–2.74 (m, 1H), 2.56–2.65 (m, 1H), 2.17–2.23 (m, 1H), 2.01–2.07 (m, 1H), 1.15 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 180.3, 176.1, 171.9, 170.0, 141.0, 139.3, 134.9, 133.7, 133.7, 133.5, 132.7, 132.5, 131.2, 130.1, 130.1, 129.0, 127.5, 127.3, 126.7, 125.9, 124.3, 117.0, 75.5, 71.5, 63.1, 61.0, 58.7, 38.9, 30.9, 23.9, 14.2. HRMS (ESI, *m/z*): $[M + Na]^+$ calcd. for $C_{33}H_{30}Cl_3N_3NaNiO_5$, 734.0502; found 734.0494. (*R*)(2*R*)-**11**: $[\alpha]_D^{25}$ = −2,145 (*c* = 0.1 in $CHCl_3$).

2.2.4 | Fmoc-3-methylene-Gln (OEt)-OH (17)

A solution of (*S*)(2*S*)-**11** (37.5 mg, 52.5 μmol) in (4 ml) was added 4 M HCl and stirred at ambient temperature for 2 h. AcOEt was added and extracted twice with H_2O. The aqueous layer was freeze dried. The residue was added sat. $NaHCO_3$ (5 ml) and EDTA (30.7 mg, 0.15 mmol), and the mixture was added Fmoc-OSu (53.1 mg 0.15 mmol) in 1,4-dioxane (2.5 ml) and stirred at ambient temperature for 10 h. H_2O was added, extracted twice with Et_2O. Aqueous layer was added 2 M of HCl and extracted with AcOEt three times. The combined organic layer was washed with H_2O, dried over $MgSO_4$, and evaporated in *vacuo*. The residue was purified by column chromatography $CHCl_3$: MeOH (90:10) to give Fmoc-3-methylene-Glu (OEt)-OH (*S*)-**17** (10.6 mg, 25.8 μmol, 49%) as a colorless oil. $[\alpha]_D^{25}$ = +11.2 (*c* = 0.25 in MeOH). IR (NaCl, νmax cm^{-1}): 3,352, 2,924, 2,853, 1,726, 1,516, 1,450, 1,256, 1,049, 918, 760, 740, 439. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.74 (d, *J* = 7.5 Hz, 2H), 7.57 (d, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 6.27 (brs, 1H), 5.39 (s, 1H), 5.25 (s, 1H), 4.78 (d, *J* = 6.0 Hz, 1H), 4.34 (d, *J* = 7.0 Hz, 2H), 4.20 (d, *J* = 6.0 Hz, 3H), 3.55 (d, *J* = 18.0 Hz, 1H), 3.30 (d, *J* = 18.0 Hz, 1H), 1.26 (t, *J* = 6.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 173.7, 155.9, 143.9, 143.8, 141.4, 138.2, 127.8, 127.2, 125.2, 120.2, 120.1, 67.3, 62.1, 58.1, 47.2, 40.5, 14.1. HRMS (ESI, *m/z*): $[M + Na]^+$ calcd. for $C_{23}H_{23}NNaO_6$, 432.1423; found 432.1446. The enantiomeric excess was determined to be 97.7% ee by HPLC using a DAICEL CHIRALPAK-IH column (0.46 × 25 cm): elution with 80% MeOH in H_2O (0.1% TFA), t_R = 16.1 min for (*S*)-isomer, t_R = 17.5 min for (*R*)-isomer. (*R*)-**17**: $[\alpha]_D^{25}$ = −10.4 (*c* = 0.25 in MeOH), 97.8% ee.

2.2.5 | (*E*)-Ethyl 4,4,4-trifluoro-3-(*p*-toluenesulfonyloxy)butanoate (15)

A solution of ethyl 4,4,4-trifluoroacetoacetate (261 mg, 1.42 mmol) in MeCN (5 mL) was added NMI (0.169 ml, 2.12 mmol), Et_3N (0.297 ml, 2.12 mmol), and *p*-TsCl (406 mg, 2.12 mmol) and stirred at ambient temperature for 1 h. The reaction mixture was evaporated in *vacuo*, and the residue was purified by column chromatography Hexane : AcOEt (8:1) to give (*E*)-ethyl 4,4,4-trifluoro-3-(*p*-toluenesulfonyloxy)butanoate (**15**) (406 mg, 1.20 mmol, 85%) as a colorless oil. IR (NaCl, νmax cm^{-1}): 3,583, 3,089, 2,986, 1,737, 1,596, 1,396, 1,294, 1,202, 1,059,

904, 814, 672, 558. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.85 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 8.5 Hz, 2H), 6.37 (s, 1H), 4.31 (q, J = 7.5 Hz, 2H), 2.46 (s, 3H), 1.35 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 161.7, 146.4, 141.8 (q, J = 38.3 Hz), 132.9, 123.0, 128.3, 117.7 (q, J = 277.6 Hz), 117.2 (d, J = 3.5 Hz), 62.0, 21.7, 13.9. ^{19}F NMR (466 MHz, $CDCl_3$, δ): −70.89 (s). HRMS (ESI, *m/z*): $[M + Na]^+$ calcd. for $C_{13}H_{13}F_3NaO_5S$, 361.0327; found 361.0351.

2.2.6 | Ni (II)-glycine compound (*S*)(2*S*)-16

A solution of (*E*)-ethyl 4,4,4-trifluoro-3-(*p*-toluenesulfonyloxy)butanoate (162 mg, 0.48 mmol) in *i*-PrOH (5 ml) was added (*S*)-**7** (96 mg, 0.16 mmol) and K_2CO_3 (110 mg, 0.80 mmol), and the reaction mixture was stirred at ambient temperature for 7 h under N_2 atmosphere. The reaction mixture was added to 5% AcOH, and aqueous layer was extracted twice with $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in *vacuo*. The residue was purified by column chromatography CH_2Cl_2 : acetone (3:1) to give the Ni (II)-glycine compound (*S*)(2*S*)-**16** (79 mg, 0.11 mmol, 64%) as a red solid. $[\alpha]_D^{25}$ = +1,696 (c = 0.25 in $CHCl_3$). IR (NaCl, νmax cm^{-1}): 2,983, 2,929, 1,726, 1,687, 1,640, 1,530, 1,462, 1,395, 1,356, 1,311, 1,280, 1,251, 1,202, 1,181, 1,133, 1,029, 902, 838, 755, 705, 666. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.92 (d, J = 2.0 Hz, 1H), 8.18 (d, J = 9.0 Hz, 1H), 7.77 (dd, J = 7.5, 2.0 Hz, 1H), 7.48 (t, J = 7.5 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.37 (d, J = 8.5 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.28 (d, J = 7.5 Hz, 1H), 7.12 (dd, J = 7.0, 2.5 Hz, 1H), 6.71 (d, J = 7.5 Hz, 1H), 6.58 (s, 1H), 6.48 (d, J = 3.0 Hz, 1H), 6.06 (s, 1H), 4.28 (d, J = 12.5 Hz, 1H), 3.90–4.04 (m, 2H), 3.60 (dd, J = 7.0, 3.5 Hz, 1H), 3.30–3.40 (m, 2H), 3.24 (d, J = 12.5 Hz, 1H), 2.70–2.80 (m, 1H), 2.52–2.63 (m, 1H), 1.99–2.15 (m, 2H), 1.20 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 180.6, 174.2, 174.2, 162.6, 141.4, 135.2, 133.8, 133.6, 133.6, 133.4, 133.0, 132.6, 131.2, 130.1, 129.8, 129.6, 128.6, 127.6, 127.3, 127.0, 126.0, 125.9, 125.9, 125.8, 124.4, 71.6, 65.5, 63.5, 61.3, 58.7, 31.1, 22.8, 13.9. The resonance of the CF_3 carbon is obscured due to its low intensity. ^{19}F NMR (466 MHz, $CDCl_3$, δ): −61.19 (s). HRMS (ESI, *m/z*): $[M + H]^+$ calcd. for $C_{33}H_{28}Cl_3F_3N_3NiO_5$, 766.0400; found 766.0395.

3 | RESULTS AND DISCUSSION

It is interesting to note that while the corresponding (*S*)-4-methyleneglutamic acid **6** is a naturally occurring compound[53,54] and was prepared in enantiomerically pure form,[55–57] our target (*S*)-3-methyleneglutamic acid **5** was reported only as a racemic compound and tested as potential suicide inhibitors of pig heart glutamate–aspartate transaminase.[58,59] For the present work, we chose to use recently developed ligand **7** and the corresponding glycine complex **8**. Nucleophilic glycine equivalent **8** was shown to possess excellent stereochemical properties due to a rationally designed parallel displaced type of aromatic interactions between the strategically chlorinated *o*-amino-benzophenone and *N*-benzyl rings.[60] Ligand **7**[30] and glycine-Ni (II) complex **8**[61] are readily available on a multikilogram scale in both (*S*)- and (*R*)-enantiomeric forms. Recently, we reported Michael addition reactions of glycine complex (*S*)-**8** with crotonates[62,63] as a general method for preparation of 3-substituted glutamic acid derivatives. Thus, the original idea of this project was an attempt to extend this approach for preparation of 3-substituted as well as 3,4-unsaturated glutamic acid derivatives for our ongoing research into analogs of natural peptides containing tailor-made AAs.[40] We envisioned that this synthetic goal can be achieved via tandem Michael addition–elimination between nucleophilic glycine equivalent (*S*)-**8** and enol tosylates **9**.[52,64] As presented in Table 1, the first attempt to perform the addition between glycine equivalent (*S*)-**8** and enol tosylate *E*-**9** at ambient (entry 1) or elevated (50°C) (entry 2), temperature, using Na_2CO_3 as a base and *i*-PrOH as a solvent, did not give any products. Using diisopropylethylamine (DIPEA)[65] as a base (entry 3), provided an advantage of fully homogeneous reaction conditions, however, the desired addition reaction did not proceed. In sharp contrast, application of K_2CO_3 (entry 4) as a base, resulted in a fast and clean reaction furnishing virtually individual product with quantitative yield. Interestingly, the combination of enol tosylate **9**, K_2CO_3, and *i*-PrOH was effective to proceed this reaction (Scheme 2).

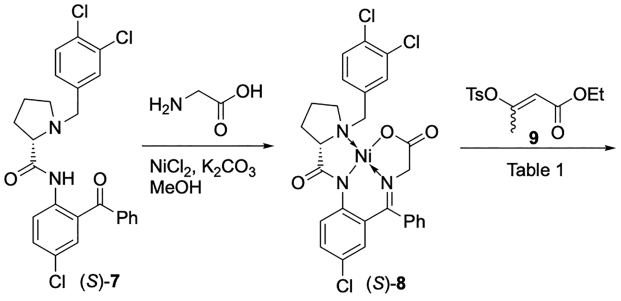
Our initial attempts to confirm the structure of the isolated product by NMR analysis gave rather inconclusive results as we could not match the observed spectral data with the structure of expected product **10**. Therefore, we performed single-crystal X-ray analysis that gave us totally unexpected result. As it follows from the crystallographic data, the product obtained in this Michael addition reaction was complex (*S*)(2*S*)-**11** containing a residue of 3-methyleneglutamic acid. From the scientific standpoint, preparation of previously unknown in enantiomerically pure form 3-methyleneglutamic acid was considered as much more synthetically valuable outcome then originally envisioned synthesis of isomeric product **10** (Figure 2 and see supporting information).

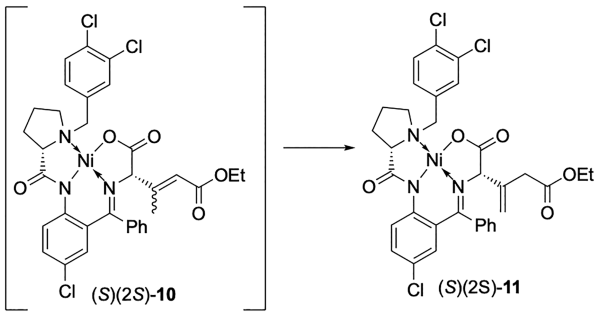
Being excited by this finding, we continued to optimize the reaction conditions in terms of most economical

TABLE 1 Optimization of the reaction conditions for Michael additions-elimination reaction between nucleophilic glycine equivalent (*S*)-**8** and enol tosylates **9**

Entry[a]	Acceptor (eq.)	Base (eq.)	Time (h)	Product 11 (%)
1	*E*-**9** (1.5)	Na_2CO_3 (10)	18	N/A
2[b]	*E*-**9** (3.0)	Na_2CO_3 (10)	6	N/A
3[b]	*E*-**9** (3.0)	DIPEA (5)	6	N/A
4	*E*-**9** (3.0)	K_2CO_3 (48)	5	>98
5	*E*-**9** (1.5)	K_2CO_3 (10)	6	24
6	*E*-**9** (1.5)	K_2CO_3 (20)	6	41
7	*E*-**9** (1.5)	K_2CO_3 (10)	12	71
8	*E*-**9** (1.5)	K_2CO_3 (10)	18	91
9	*Z*-**9** (1.5)	K_2CO_3 (10)	18	50
10[c]	*E*-**9** (3.0)	K_2CO_3 (10)	12	55

[a]Reactions were carried out at 50°C under N_2 atmosphere in *i*-PrOH.
[b]Reactions were carried out at 60°C under N_2 atmosphere.
[c]Gram-scale synthesis {9.18 g (3.0 eq.) of *E*-**9**} was carried out to give **11** with 3.55 g (4.97 mmol).





SCHEME 2 Michael addition reactions of glycine complex (*S*)-**8** and enol tosylates **9**

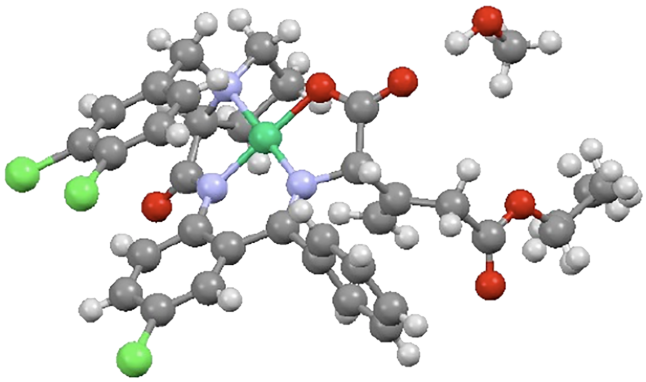
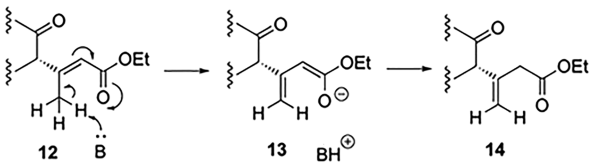
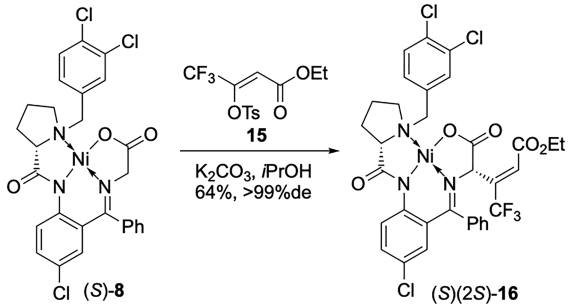


FIGURE 2 Crystal structure of (*S*)(2*S*)-**11**

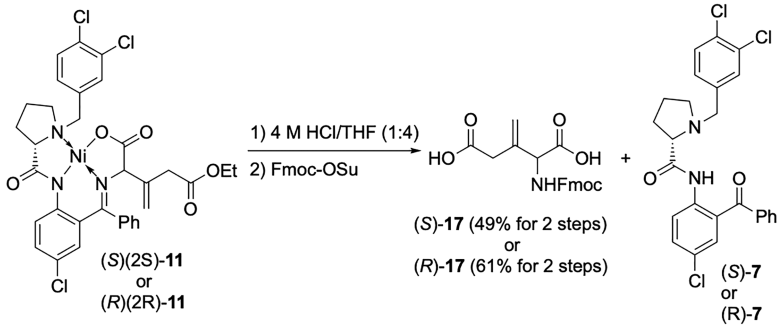


SCHEME 3 Isomerization of the side chain in the addition product **12** to afford **14**



SCHEME 4 Michael addition reaction of glycine complex (*S*)-**8** with CF_3-containing enol tosylate **15**

stoichiometry of all starting compounds and reagents (entries 5–8). Consequently, we believe that the conditions presented in entry 8 might be called optimized despite incomplete chemical yield of the addition product **11** (91%). Importantly, under these conditions, there are no any detectable amounts of the second diastereomer or byproducts complicating the isolation and purification of complex **11**. Using these conditions, we conducted the addition reaction using enol tosylate **9** of (*Z*)-geometric configuration (entry 9). Interestingly, the reaction product was the same diastereomer **11**, albeit obtained with a lower isolated yield. Also, the reaction was somewhat slower, which can be probably explained by different stereochemical requirements of (*Z*)- and (*E*)-isomers **9**.



SCHEME 5 Disassembly of diastereomerically pure (*S*)(2*S*)- and (*R*)(2*R*)-**11**: Preparation of *N*-Fmoc amino acid (*S*)- and (*R*)-**17** and recovery of chiral ligand (*S*)- and (*R*)-**7**

Finally, we performed gram-scale synthesis (entry 10) to demonstrate a preparative value of this method (Table 1).

It should be noted that chemistry of enol tosylate **9** is poorly studies and their reactivity, besides the cross-coupling reactions is virtually unknown. In particular they never been previously used as Michael acceptors, which stimulate our interest in these compounds[52,64] Nevertheless, we believe they do react as regular Michael acceptors and undergo the elimination step to furnish the expected products **10**. However, one may consider a possibility of a base-catalyzed isomerization **12** to **14** as presented in Scheme 3. In general, the isomerization **12**–**14** is rather similar to the biomimetic transamination (azomethine–azomethine isomerization)[65–67] which is driven by a greater thermodynamic stability of a more acidic isomer (**12** vs. **14**) under basic reaction conditions (Scheme 3).

To validate this hypothesis, we prepared trifluoromethyl analogue enol tosylate **15** and performed its reaction with nucleophilic glycine equivalent (*S*)-**8**. Because the trifluoromethyl group cannot participate in the isomerization, we expected the formation of the corresponding unisomerized α,β-unsaturated product. The reaction was conducted under the standard conditions using K_2CO_3 as a base and *i*PrOH as a solvent at ambient temperature. It should be noted that the addition proceeded at greater rate, due to the electron-withdrawing effect of the CF_3 and, most importantly, affording expected product (*S*)(2*S*)-**16** as a single diastereomer with 64% yield. These results suggest that enol tosylates **9** and **15** have high potential for Michael addition/elimination reaction and moreover application for the synthesis of various unsaturated analogues of glutamic acid and related compounds are expected (Scheme 4).

As the final stage of this project, we demonstrated disassembly of Ni (II)-complexes and isolation of the target AAs. It should be noted that we reproduced the reactions discussed in Scheme 2 using (*R*)-configured ligand **7** and glycine complex **8** to obtain both (*S*)- and (*R*)-enantiomers of 3-methyleneglutamic acid **5**. As presented in Scheme 5, a suspension of orange-red complex (*S*)(2*S*)- and (*R*)(2*R*)-**11** was treated with 4 M HCl/THF (1:4) at ambient temperature until the formation (~2 h) of green-colored homogeneous solution, which was freeze-dried and treated with Fmoc-OSu under standard reaction condition to furnish *N*-Fmoc protected derivatives (*S*)-**17** and (*R*)-**17**, respectively. According to chiral HPLC, enantiomeric purity of thus prepared compounds was >97.5% ee (see supporting information). As always, along with isolation of AA products, chiral ligands (*S*)- and (*R*)-**7** were recovered and reused[68] (Scheme 5).

4 | CONCLUSION

In summary, we demonstrated that the Ni (II)-complexes methodology can be quite successfully used for asymmetric synthesis of *N*-Fmoc protected derivative of (*S*)-3-methyleneglutamic acid. In particular, we found that the Michael addition reaction between chiral nucleophilic glycine equivalent and enol tosylates occurs with excellent yield affording virtually a single diastereomeric product. Novelty of the application of enol tosylates as Michael acceptors and the addition–elimination sequence for construction of glutamic acid skeleton should be emphasized. Furthermore, this method is the first account describing asymmetric synthesis of 3-methyleneglutamic acid derivatives and their isolation in enantiomerically pure form (>97% ee). Biological properties of these derivatives and their incorporation into peptides are currently under investigation.

ACKNOWLEDGMENTS

This work was supported in part by YU-COE (C) program of Yamagata University.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supporting information of this article.

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How to cite this article: Shigeno Y, Han J, Soloshonok VA, Moriwaki H, Fujiwara W, Konno H. Asymmetric synthesis of (*S*)-3-methyleneglutamic acid and its *N*-Fmoc derivative via Michael addition–elimination reaction of chiral glycine Ni (II) complex with enol tosylates. *Chirality*. 2021;33:115–123. https://doi.org/10.1002/chir.23291