Highly Diastereoselective Conjugate Addition–Elimination of Chiral Nickel(II) Glycinate with Activated Allylic Acetates for Asymmetric Synthesis of Glutamic Acid Derivatives

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Abstract: A practically feasible, diastereoselective conjugate addition–elimination reaction of a chiral nickel(II) complex of glycine **1** with allylic acetates **2** is described. The reaction pathway was successfully controlled, and the desired formation of a carbon–carbon bond was exclusively obtained with high diastereoselectivity. This reaction is an attractive route for the asymmetric synthesis of previously unavailable chainlike glutamic acid derivatives.

Key words: nickel(II) complex, asymmetric synthesis, glutamic acid, amino acids

Glutamic acid is the most abundant excitatory neurotransmitter in the mammalian nervous system. Its derivatives are used as fundamental building blocks for the synthesis of molecules that are important for the pharmaceutical and agrochemical industries, such as peptides, proteins, and other natural products.[1] In particular, glutamic acid derivatives are structural components of ligands for various types of glutamate receptors, which are potential therapeutic agents.[2] Asymmetric synthesis of glutamic acid derivatives is a difficult and challenging task. A number of potential methods have been developed for the synthesis of these compounds.[3] One of the most efficient methods of preparation of 3-substituted pyroglutamic acid derivatives is 1,4-addition of glycine derivatives to α,β-unsaturated esters or amides.[4] Recently, Kobayashi et al. reported an effective method for the asymmetric 1,4-addition synthesis of 3-substituted glutamic acids derivatives in good enantiomeric excess.[5] O'Donnell et al. described the enantioselective synthesis of 4-substituted glutamic acid derivatives efficiently catalyzed by a chiral phase-transfer catalyst;[6] however, it requires long reaction times (30–48 h) and an expensive phase-transfer catalysts, etc. However, no examples of the preparation of chainlike, 4-substituted glutamic acid derivatives by the asymmetric synthesis reaction have been reported. Various methodological and structural shortcomings of the literature approaches render these methods of limited synthetic application, in particular for the preparation of chainlike glutamic acid derivatives on a relatively large scale. Clearly, the development of improved procedures in which operational convenience and wide applications are used has remained an elusive goal.[7]

The use of the nickel(II) complex of the chiral Schiff base of glycine for the atom- and step-economical synthesis of functional and enantiopure α-amino acids has attracted considerable interest both in academia and industry. The numerous environmental and economic advantages of this method make it highly attractive for chemical syntheses. The notable merits of synthetic methods of employing the nickel(II) complex are high efficiency, low cost, and minimal environmental impact. Belokon and Soloshonok et al. developed efficient, large-scale synthesis of the nickel(II) complex, which has made the starting materials readily available and inexpensive.[8] These methods can generate various functionalized amino acids and are expected to have many applications in synthesis. Nickel(II) complexes are widely used for aldol condensations,[9] Michael additions,[10] and C-alkylation reactions.[11] Recently, efforts have been made toward the development of asymmetric Mannich reactions for the synthesis of *syn*-α,β-diamino acids.[12] However, to the best of our knowledge, nickel(II) complexes have not yet been used in conjugate addition–elimination reactions. In this paper, we describe a practically feasible, diastereoselective conjugate addition–elimination of a chiral nickel(II) complex of glycine **1** with activated allylic acetates **2**, which can progress to the asymmetric synthesis of enantiopure glutamic acid derivatives (Scheme 1).

As a model reaction, the addition–elimination reaction of the chiral (*S*)-nickel(II) complex of glycine with (*S*)-2-[(*N*-benzylprolyl)amino]benzophenone [(*S*)-BPB], (*S*)-**1**, and ethyl 2-[acetoxy(4-nitrophenyl)methyl]acrylate (**2a**) was investigated and the reaction conditions were optimized. The results are summarized in Table 1. First, cesium hydroxide monohydrate was selected as the base with dichloromethane as the solvent. This reaction afforded the conjugate addition–elimination adduct (*S*,2*R*)-**3a** in high yield (92%) but with poor diastereomeric excess (10%) (entry 1). Subsequently, a variety of alternative bases were investigated for this reaction. High diastereoselectivities (entries 2–4) were observed when sodium hydride, 1,8-diazabicyclo[5.4.0]undec-7-ene, and potassium hydroxide were used as the base. In particular, potassium hydroxide turned out to be an effective and a highly diastereoselective base. Following this, a variety of solvents were investigated for this conjugate addition–elimi-

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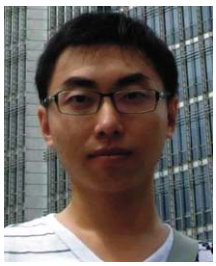

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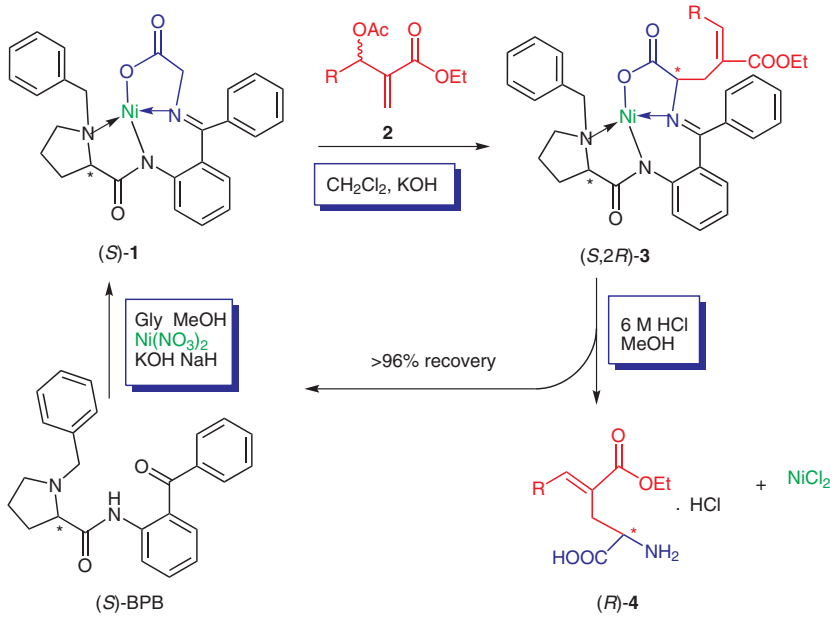
Prof. Hong Liu received her M.S. and Ph.D. in medicinal chemistry from the China Pharmaceutical University, under the supervision of Professor Weiyi Hua. After a postdoctoral stay with Professor Ruyun Ji and Professor Kaixian Chen at Shanghai Institute of Materia Medica, she joined the Shanghai Institute of Materia Medica and is now a Group Leader. As a visiting Scientist, she stayed with Professor James Halpert at the University of Texas Medical Branch at Galveston. Her research interests include medicinal chemistry, organic chemistry, computer modeling, and pharmacologically active molecules, especially those targeting tumors and diabetes.



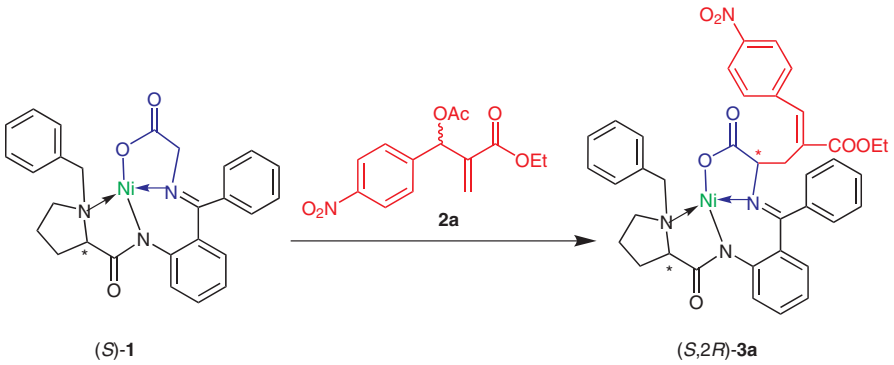
Scheme 1 Stereoselective synthesis of enantioenriched glutamic acid derivatives via a chiral nickel(II) complex with allylic acetates

nation reaction with potassium hydroxide as the base and an arbitrary reaction time of two hours. Solvent screening (entries 4–8) revealed that while acetonitrile and acetone afforded good results, the best combination of yield and diastereoselectivity could be realized when using dichloromethane (entry 4). The representative results in entries 1–8 suggest that the diastereoselectivity depends to a significant extent on the reaction conditions, while the thermodynamically controlled stereochemical outcome is only slightly influenced by the nature of the base and the solvent used. Further optimization studies showed that reactions carried out with potassium hydroxide as the base and dichloromethane as the solvent, and in which the temperatures ranged 50 to –60 °C (entries 9–13) afforded good product yields and high diastereoselectivities were achieved. The reaction rate was improved when the reaction was performed at a slightly elevated temperature (50 °C), presumably because of an increase in the solubility of the potassium hydroxide. On the other hand, the de values decreased when the reaction was carried out at low temperature. After optimizing the base, solvent, and temperature, the reaction was performed by using the following protocol: (*S*)-**1** was treated with ethyl 2-[acetoxy(4-nitrophenyl)methyl]acrylate (**2a**, 1.05 equiv) in the presence of potassium hydroxide (10.0 equiv) at ambient temperature in dichloromethane for two hours to afford the conjugate addition–elimination adduct (*S*,2*R*)-**3a** in high yield and with high diastereoselectivity.

After the reaction conditions had been optimized, we investigated the substrate scope of the conjugate addition–elimination reaction. The results are summarized in Table 2. The reaction was found to have a broad substrate scope and afforded products with high yields and high diastereoselectivities with a number of 4-aryl-substituted allylic acetates **2**. Phenyl rings with different substituents and other aromatic groups could be used in this reaction. The results suggest that this reaction can be regarded as a model reaction to 4-aryl-substituted alkylidene glutamic acids. This reaction was inert to steric effects. All the three regioisomeric methylphenyl-substituted allylic acetates **2** employed in the conjugate addition–elimination reactions afforded the desired products in high yields, and high selectivities (entries 3–5). In general, functionalized aryl allylic acetates were found to be excellent substrates for this reaction, regardless of the electronic effect. Aromatic systems bearing electron-donating and electron-withdrawing groups could also be tolerated (entries 1–10); moreover, this reaction could be extended to heterocyclic compounds as well (entries 11–13). It is worth mentioning that neither the position nor the electronic properties of the substituent on the aromatic ring had a significant impact on the diastereoselectivity of the reaction. The (*R*)-diastereomer was obtained as the product, as indicated by single crystal X-ray structural analysis (Figure 1).

To demonstrate the isolation of the target amino acid (*R*)-**4** from the nickel(II) complexes (*S*,2*R*)-**3**, (*S*,2*R*)-**3a** was decomposed under standard conditions to yield the previous unavailable amino acid (*R*)-**4a**. The products are a novel type of chainlike, 4-substituted, 5-esterified glutamic acid derivative. Several distinguished features of the product deserved to be mentioned: (i) it is the first synthesis of chainlike, 5-esterified glutamic acid derivatives; (ii) the geometry of all these target amino acids include an *E*-double bond; and (iii) broad substrate scope: both aromatic and heterocyclic substituted amino acids can be obtained. The chiral ligand (S)-BPB (Scheme 2) could be easily recovered in quantitative yields by a simple procedure and then reused. Decomposition of the (*S*,2*R*)-**3a** complex and isolation of amino acid (*R*)-**4a** was performed under standard conditions by heating a suspension of (*S*,2*R*)-**3a** in methanol–6 M hydrochloric acid to afford the target amino acid, metal ions, and (S)-BPB. The (*S*)-

Table 1 Optimization of the Reaction Conditions[a]

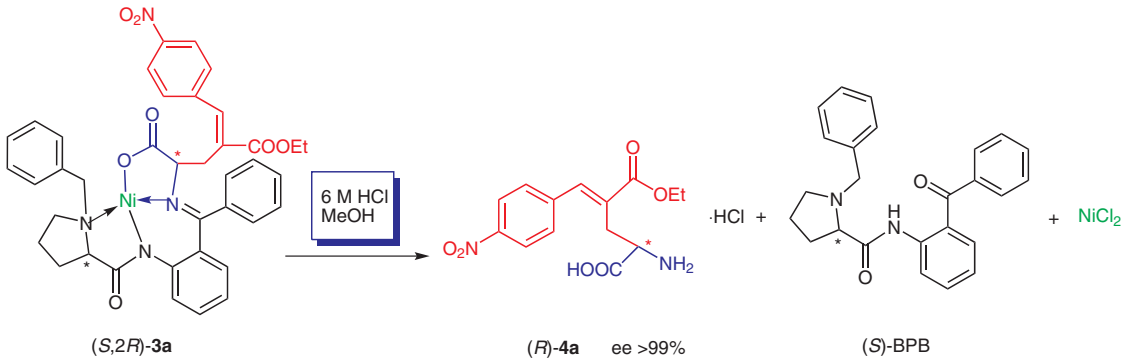


Entry	Base	Solvent	Temp (°C)	Yield (%)	de[b] (%)
1	CsOH	CH_2Cl_2	23	92	10
2	NaH	CH_2Cl_2	23	86	90
3	DBU	CH_2Cl_2	23	84	85
4	KOH	CH_2Cl_2	23	95	>99
5	KOH	MeCN	23	93	94
6	KOH	acetone	23	93	97
7	KOH	THF	23	92	82
8	KOH	DMF	23	85	80
9	KOH	CH_2Cl_2	50	93	98
10	KOH	CH_2Cl_2	0	86	97
11	KOH	CH_2Cl_2	–20	82	84
12	KOH	CH_2Cl_2	–40	77	80
13	KOH	CH_2Cl_2	–60	75	78

[a] Conditions: (*S*)-**1** (0.20 mmol), **2a** (0.24 mmol), base (2.0 mmol), solvent (10 mL), 2 h.
[b] Determined by chiral HPLC analysis.

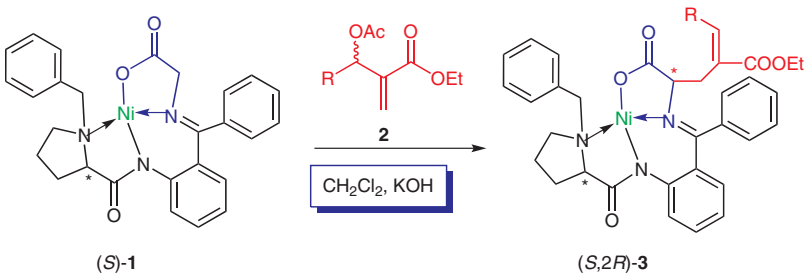
BPB could be recovered by extraction into dichloromethane and reused to form the nickel(II) complex of glycine in near quantitative yield, thereby eliminating any concern regarding the poor atom economy of this method.

In summary, we have developed a highly diastereoselective and practically feasible route to a novel type of chain-like, 4-substituted, 5-esterified glutamic acid derivatives via a conjugate addition–elimination reaction. A broad range of aryl- and heteroaryl-derived allylic acetates could be employed in this reaction under operationally convenient conditions, without the need for an inert atmosphere, dried solvents, and very low temperatures. Thus, the experimental procedure is simple and cost-effective.



Scheme 2 Decomposition of nickel(II) complex (*S*,2*R*)-**3a** to release amino acid (*R*)-**4a** and recovery of the ligand (*S*)-BPB

Table 2 Conjugate Addition–Elimination Reactions of (*S*)-Nickel(II) Complex **1** with Allylic Acetates **2**[a]



Entry	Product	R	Yield (%)	de[b] (%)
1	(*S*,2*R*)-**3a**	4-$O_2NC_6H_4$	95	>99
2	(*S*,2*R*)-**3b**	Ph	93	98
3	(*S*,2*R*)-**3c**	2-MeC_6H_4	92	98
4	(*S*,2*R*)-**3d**	3-MeC_6H_4	93	98
5	(*S*,2*R*)-**3e**	4-MeC_6H_4	91	98
6	(*S*,2*R*)-**3f**	4-$MeOC_6H_4$	90	98
7	(*S*,2*R*)-**3g**	4-FC_6H_4	94	98
8	(*S*,2*R*)-**3h**	4-ClC_6H_4	93	98
9	(*S*,2*R*)-**3i**	4-BrC_6H_4	94	98
10	(*S*,2*R*)-**3j**	2,6-$F_2C_6H_3$	92	97
11	(*S*,2*R*)-**3k**	2-furyl	91	>99
12	(*S*,2*R*)-**3l**	3-thienyl	92	98
13	(*S*,2*R*)-**3m**	2-naphthyl	90	98

[a] Conditions: (*S*)-**1** (0.20 mmol), **2** (0.24 mmol), KOH (2.0 mmol), CH_2Cl_2 (10 mL), r.t., 2 h.
[b] Determined by chiral HPLC analysis (see Supporting Information for details).

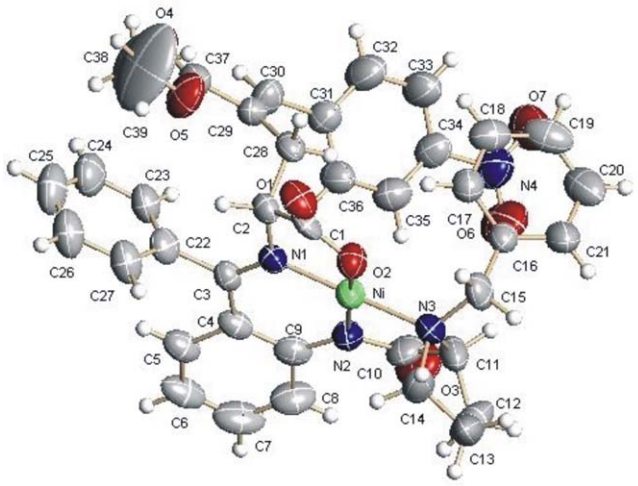


Figure 1 The crystal structure of (*S*,2*R*)-**3a** by X-ray crystal structure analysis

The absolute configuration of one of the products was determined. Owing to the high chemical yields of the products of the conjugate addition–elimination reaction and the simplicity of the experimental procedure, this reaction can be employed for the multigram-scale preparation of glutamic acid derivatives. Additional investigations into the reaction mechanism and synthetic applications of this reaction are in progress; the results thereof will be reported in the future.

The reagents (chemicals) were purchased from commercial sources and used without further purification. Petroleum ether = PE. Analytical TLC used HSGF 254 (0.15–0.20 mm thickness). All products were characterized by their NMR and MS spectra. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a 300 MHz instrument downfield from TMS. LR- and HRMS were measured on a Finnigan MAT-95, LCQ-DECA spectrometer. Optical rotations were reported as follows: $[\alpha]_D^{22}$ (*c* g/100 mL, solvent).

Analytical HPLC was carried out using the Dionex ASI-100 automated sampler, Chiralpak IA column; loading loop: 5 μL; eluent: isocratic mixture *n*-hexane–*i*-PrOH (60:40); flow rate: 1 mL/min, λ = 220 nm, unless otherwise stated.

Synthesis of (*S*,2*R*)-3; General Procedure

The Ni(II) complex of glycine **1** (100 mg, 0.201 mmol) was dissolved in CH_2Cl_2 (10 mL). The allylic acetate **2** (0.241 mmol) and KOH (113 mg, 2.01 mmol) were added at r.t. The mixture was then stirred at r.t. for 2 h. The crude mixture was concentrated, and then washed with H_2O (3 ×) and brine (3 ×); the combined aqueous phases were extracted with CH_2Cl_2 (3 ×). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by flash column chromatography (PE–EtOAc) to give (*S*,2*R*)-**3** as a red solid.

Ni(II)–(*S*)-BPB/5-Ethyl (2*R*,*E*)-4-(4-Nitrobenzylidene)-L-glutamate Schiff Base Complex 3a

Following the general procedure using **2a** and separation by flash column chromatography (PE–EtOAc, 2:3) gave **3a** as a red solid; yield: 95%; mp 119–120 °C; HPLC: t_R = 32.75 min (major); >99% de.

$[\alpha]_D^{22}$ +3311.8 (*c* 0.44, $CHCl_3$).

IR (KBr): 706, 756, 1165, 1256, 1346, 1439, 1519, 1591, 1641, 1675 (C=N), 1713 (C=O), 2929, 2958, 3434 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.58 (d, *J* = 9.6 Hz, 1 H), 7.97 (d, *J* = 9.0 Hz, 2 H), 7.91 (s, 1 H), 7.62–7.59 (m, 2 H), 7.51–7.28 (m, 9 H), 7.26–7.20 (m, 1 H), 7.11 (d, *J* = 7.2 Hz, 1 H), 6.71 (d, *J* = 4.2 Hz, 2 H), 4.70 (d, *J* = 13.2 Hz, 1 H), 4.19 (t, *J* = 12.6 Hz, 1 H), 4.08–3.94 (m, 3 H), 3.68 (d, *J* = 13.2 Hz, 1 H), 3.62–3.58 (m, 1 H), 3.30–3.26 (m, 2 H), 2.67–2.63 (m, 1 H), 2.41–2.28 (m, 1 H), 2.06–2.03 (m, 1 H), 1.79–1.63 (m, 2 H), 1.18 (t, *J* = 14.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.4, 177.8, 171.5, 166.7, 147.3, 142.5, 141.8, 139.6, 133.5, 132.5, 131.5, 129.7, 129.5, 128.9, 128.2, 127.4, 125.9, 123.8, 123.2, 120.5, 70.3, 69.4, 63.4, 61.5, 57.4, 32.4, 30.4, 23.7, 14.1.

MS (EI): *m*/*z* = 730 $[M]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{39}H_{36}N_4NiO_7$: 730.1937; found: 730.1937.

Ni(II)–(*S*)-BPB/5-Ethyl (2*R*,*E*)-4-Benzylidene-L-glutamate Schiff Base Complex 3b

Following the general procedure using **2b** and separation by flash column chromatography (PE–EtOAc, 2:3) gave **3b** as a red solid; yield: 93%; mp 107–108 °C; HPLC: t_R = 8.97 min (minor), 20.435 min (major); 98% de.

$[\alpha]_D^{22}$ +1551.3 (*c* 0.61, $CHCl_3$).

IR (KBr): 704, 754, 1099, 1165, 1256, 1334, 1441, 1543, 1591, 1638, 1678 (C=N), 1707 (C=O), 2931, 2976, 3442 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 9.0 Hz, 1 H), 8.04 (d, *J* = 6.9 Hz, 2 H), 7.86 (s, 1 H), 7.47–7.28 (m, 8 H), 7.25–7.09 (m, 5 H), 6.97 (d, *J* = 8.1 Hz, 1 H), 6.66–6.56 (m, 2 H), 4.34 (d, *J* = 12.6 Hz, 1 H), 4.26 (t, *J* = 7.2 Hz, 1 H), 4.01–3.92 (m, 2 H), 3.45–3.38 (m, 4 H), 3.29–3.23 (m, 2 H), 2.69–2.67 (m, 1 H), 2.44–2.40 (m, 1 H), 2.05–2.01 (m, 2 H), 1.14 (t, *J* = 14.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.3, 178.2, 171.2, 167.4, 142.5, 135.1, 133.6, 132.3, 131.4, 129.5, 128.9, 128.5, 127.5, 126.1, 123.2, 120.4, 70.4, 69.8, 63.2, 61.0, 57.3, 33.2, 30.5, 23.6, 14.1.

MS (EI): *m*/*z* = 685 $[M]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{39}H_{37}N_3NiO_5$: 685.2087; found: 685.2094.

Ni(II)–(*S*)-BPB/5-Ethyl (2*R*,*E*)-4-(2-Methylbenzylidene)-L-glutamate Schiff Base Complex 3c

Following the general procedure using **2c** and separation by flash column chromatography (PE–EtOAc, 2:3) gave 3c as a red solid; yield: 92%; mp 184–186 °C; HPLC: t_R = 8.154 (minor), 22.657 min (major); 98% de.

$[\alpha]_D^{22}$ +1910.7 (*c* 0.30, $CHCl_3$).

IR (KBr): 708, 756, 1163, 1257, 1333, 1439, 1519, 1591, 1633, 1668 (C=N), 1718 (C=O), 2868, 2924, 3059, 3435 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 8.7 Hz, 1 H), 8.03 (d, *J* = 7.5 Hz, 2 H), 7.84 (s, 1 H), 7.48–7.29 (m, 5 H), 7.23–7.02 (m, 7 H), 6.87 (d, *J* = 7.5 Hz, 1 H), 6.64–6.52 (m, 2 H), 4.32 (d, *J* = 12.3 Hz, 1 H), 4.21 (t, *J* = 14.1 Hz, 1 H), 3.98–3.92 (m, 1 H), 3.43–3.32 (m, 4 H), 3.04–2.99 (m, 2 H), 2.51–2.46 (m, 1 H), 2.32–2.28 (m, 1 H), 2.16 (s, 3 H), 1.97–1.95 (m, 1 H), 1.82–1.79 (m, 2 H), 1.13 (t, *J* = 14.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.5, 177.9, 170.9, 166.9, 142.4, 136.8, 134.7, 133.6, 132.2, 131.4, 130.0, 129.5, 128.8, 128.4, 127.5, 126.1, 123.2, 120.4, 70.2, 63.1, 60.8, 57.4, 33.6, 30.5, 29.7, 23.8, 19.9, 14.1.

MS (EI): *m*/*z* = 699 $[M]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{40}H_{39}N_3NiO_5$: 699.2243; found: 699.2245.

Ni(II)–(*S*)-BPB/5-Ethyl (2*R*,*E*)-4-(3-Methylbenzylidene)-L-glutamate Schiff Base Complex 3d

Following the general procedure using **2d**, and separation by flash column chromatography (PE–EtOAc, 2:3) gave **3d** as a red solid; yield: 93%; mp 119–121 °C; HPLC: t_R = 8.353 (minor), 16.327 min (major); 98% de.

$[\alpha]_D^{22}$ +2103.2 (*c* 0.54, $CHCl_3$).

IR (KBr): 706, 754, 1165, 1257, 1333, 1439, 1545, 1591, 1632, 1670 (C=N), 1718 (C=O), 2935, 2978, 3026, 3446 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 8.7 Hz, 1 H), 8.03 (d, *J* = 7.5 Hz, 2 H), 7.87 (s, 1 H), 7.50–7.44 (m, 2 H), 7.31–7.28 (m, 2 H), 7.23–7.10 (m, 8 H), 7.00–6.92 (m, 1 H), 6.62–6.55 (m, 2 H), 4.32 (d, *J* = 12.3 Hz, 1 H), 4.20 (t, *J* = 13.2 Hz, 1 H), 4.00–3.93 (m, 1 H), 3.48–3.20 (m, 6 H), 2.74–2.71 (m, 1 H), 2.36–2.32 (m, 1 H), 2.27 (s, 3 H), 2.12–1.85 (m, 3 H), 1.13 (t, *J* = 14.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.4, 178.1, 171.1, 167.4, 142.8, 142.4, 138.2, 135.1, 133.6, 132.2, 131.4, 129.6, 129.1, 128.7, 127.4, 125.9, 125.6, 123.1, 120.3, 70.4, 63.1, 60.9, 57.2, 32.8, 30.5, 23.4, 21.2, 14.0.

MS (EI): *m*/*z* = 699 $[M]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{40}H_{39}N_3NiO_5$: 699.2243; found: 699.2248.

Ni(II)–(*S*)-BPB/5-Ethyl (2*R*,*E*)-4-(4-Methylbenzylidene)-L-glutamate Schiff Base Complex 3e

Following the general procedure using **2e** and separation by flash column chromatography (PE–EtOAc, 2:3) gave **3e** as a red solid; yield: 91%; mp 121–123 °C; HPLC: t_R = 8.351 (minor), 19.368 min (major); 98% de.

$[\alpha]_D^{22}$ +1484.2 (*c* 0.37, $CHCl_3$).

IR (KBr): 704, 754, 1175, 1256, 1335, 1441, 1545, 1589, 1639, 1678 (C=N), 1701 (C=O), 2927, 2958, 3061, 3446 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 9.6 Hz, 1 H), 8.03 (d, *J* = 8.1 Hz, 2 H), 7.83 (s, 1 H), 7.48–7.30 (m, 5 H), 7.25–7.24 (m, 1 H), 7.22–7.11 (m, 6 H), 7.02 (d, *J* = 7.5 Hz, 1 H), 6.65–6.58 (m, 2 H), 4.33 (d, *J* = 12.6 Hz, 1 H), 4.24 (t, *J* = 13.8 Hz, 1 H), 3.99–3.92 (m, 1 H), 3.50–3.27 (m, 6 H), 2.73–2.69 (m, 1 H), 2.45–2.41 (m, 1 H), 2.34 (s, 3 H), 2.04–1.98 (m, 3 H), 1.13 (t, *J* = 13.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.3, 178.4, 171.2, 167.8, 159.9, 142.5, 142.4, 133.7, 133.5, 132.3, 131.4, 130.8, 129.5, 128.9, 128.6, 127.5, 127.3, 126.3, 126.1, 123.1, 120.4, 114.1, 70.5, 69.9, 63.2, 60.9, 57.2, 55.3, 33.2, 30.5, 23.5, 14.1.

MS (EI): *m*/*z* = 699 $[M]^+$.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{40}H_{39}N_3NiO_5$: 699.2243; found: 699.2235.

Ni(II)–(*S*)-BPB/5-Ethyl (2*R*,*E*)-4-(4-Methoxybenzylidene)-L-glutamate Schiff Base Complex 3f

Following the general procedure using **2f** and separation by flash column chromatography (PE–EtOAc, 2:3) gave **3f** as a red solid; yield: 90%; mp 125–127 °C; HPLC: t_R = 9.442 (minor), 21.007 min (major); 98% de.

$[\alpha]_D^{22}$ +1563.8 (*c* 0.59, $CHCl_3$).

IR (KBr): 704, 754, 1165, 1256, 1335, 1439, 1589, 1639, 1678 (C=N), 1705 (C=O), 2924, 2976, 3435 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 8.1 Hz, 1 H), 8.03 (d, *J* = 7.5 Hz, 2 H), 7.80 (s, 1 H), 7.47–7.30 (m, 5 H), 7.26–7.25 (m, 3 H), 7.22–7.03 (m, 3 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 6.61–6.60 (m, 2 H), 4.35 (d, *J* = 12.3 Hz, 1 H), 4.26 (t, *J* = 13.2 Hz, 1 H), 3.99–3.92 (m, 1 H), 3.80 (s, 3 H), 3.51–3.38 (m, 6 H), 2.78–2.74 (m, 1 H), 2.47–2.37 (m, 1 H), 2.05–1.92 (m, 3 H), 1.13 (t, *J* = 14.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.2, 178.2, 171.2, 167.6, 142.6, 138.5, 133.6, 132.2, 131.4, 129.5, 128.7, 127.6, 126.1, 123.1, 120.4, 70.4, 69.9, 63.1, 60.9, 57.2, 33.1, 30.4, 23.5, 21.3, 14.1.

MS (EI): *m/z* = 715 $[M]^+$.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{40}H_{39}N_3NiO_6$: 715.2192; found: 715.2189.

Ni(II)–(*S*)-BPB/5-Ethyl (2*R*,*E*)-4-(4-Fluorobenzylidene)-L-glutamate Schiff Base Complex 3g

Following the general procedure using **2g**, and separation by flash column chromatography (PE–EtOAc, 2:3) gave **3g** as a red solid; yield: 94%; mp 100–102 °C; HPLC: t_R = 8.536 (minor), 19.031 min (major); 98% de.

$[\alpha]_D^{22}$ +1316.4 (*c* 0.32, $CHCl_3$).

IR (KBr): 704, 754, 1165, 1256, 1335, 1441, 1589, 1639, 1678 (C=N), 1709 (C=O), 2931, 2958, 3442 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 8.7 Hz, 1 H), 8.03 (d, *J* = 7.5 Hz, 2 H), 7.80 (s, 1 H), 7.49–7.46 (m, 2 H), 7.37–7.30 (m, 4 H), 7.26–7.10 (m, 5 H), 7.03–7.01 (m, 2 H), 6.65–6.55 (m, 2 H), 4.33 (d, *J* = 12.3 Hz, 1 H), 4.23–4.17 (m, 1 H), 4.00–3.93 (m, 1 H), 3.49–3.33 (m, 5 H), 3.18–3.12 (m, 1 H), 2.74–2.65 (m, 1 H), 2.48–2.40 (m, 1 H), 2.07–1.91 (m, 3 H), 1.14 (t, *J* = 14.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.3, 178.1, 171.3, 167.4, 163.8, 161.3, 142.5, 141.3, 133.5, 132.3, 131.1, 130.8, 129.6, 128.5, 127.4, 126.0, 123.2, 120.5, 115.8, 115.6, 70.4, 69.7, 63.2, 61.1, 57.3, 38.9, 34.0, 32.8, 30.5, 22.9, 20.1, 19.1, 14.4, 11.4.

MS (EI): *m/z* = 703 $[M]^+$.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{39}H_{36}FN_3NiO_5$: 703.1992; found: 703.2002.

Ni(II)–(*S*)-BPB/5-Ethyl (2*R*,*E*)-4-(4-Chlorobenzylidene)-L-glutamate Schiff Base Complex 3h

Following the general procedure using **2h** and separation by flash column chromatography (PE–EtOAc, 2:3) gave **3h** as a red solid; yield: 93%; mp 105–107 °C; HPLC: t_R = 8.994 (minor), 19.395 min (major); 98% de.

$[\alpha]_D^{22}$ +1832.9 (*c* 0.69, $CHCl_3$).

IR (KBr): 704, 754, 1092, 1256, 1335, 1439, 1589, 1639, 1678 (C=N), 1709 (C=O), 2870, 2956, 3446 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 8.7 Hz, 1 H), 8.03 (d, *J* = 7.2 Hz, 2 H), 7.79 (s, 1 H), 7.50–7.28 (m, 7 H), 7.23–7.11 (m, 5 H), 7.01 (d, *J* = 7.5 Hz, 1 H), 6.66–6.55 (m, 2 H), 4.33 (d, *J* = 12.3 Hz, 1 H), 4.19 (t, *J* = 14.4 Hz, 1 H), 4.02–3.95 (m, 1 H), 3.49–3.26 (m, 5 H), 3.13–3.06 (m, 1 H), 2.74–2.65 (m, 1 H), 2.50–2.38 (m, 1 H), 2.06–1.89 (m, 3 H), 1.14 (t, *J* = 14.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.4, 178.0, 171.2, 167.1, 142.4, 141.0, 134.3, 133.6, 132.3, 131.4, 130.1, 129.6, 129.2, 128.9, 128.4, 127.4, 126.0, 123.2, 120.5, 70.4, 69.6, 63.2, 61.2, 57.3, 32.9, 30.5, 23.6, 14.1.

MS (EI): *m/z* = 719 $[M]^+$.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{39}H_{36}ClN_3NiO_5$: 719.1697; found: 719.1706.

Ni(II)–(*S*)-BPB/5-Ethyl (2*R*,*E*)-4-(4-Bromobenzylidene)-L-glutamate Schiff Base Complex 3i

Following the general procedure using **2i** and separation by flash column chromatography (PE–EtOAc, 2:3) gave **3i** as a red solid; yield: 94%; mp 106–108 °C; HPLC: t_R = 9.677 (minor), 20.750 min (major); 98% de.

$[\alpha]_D^{22}$ +1709.4 (*c* 0.55, $CHCl_3$).

IR (KBr): 704, 754, 1165, 1256, 1335, 1439, 1587, 1639, 1678 (C=N), 1709 (C=O), 2929, 2956, 3435 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 7.8 Hz, 1 H), 8.03 (d, *J* = 6.9 Hz, 2 H), 7.76 (s, 1 H), 7.50–7.28 (m, 7 H), 7.24–7.07 (m, 5 H), 7.01 (d, *J* = 7.2 Hz, 1 H), 6.66–6.54 (m, 2 H), 4.33 (d, *J* = 12.6 Hz, 1 H), 4.19 (t, *J* = 7.8 Hz, 1 H), 3.99–3.95 (m, 1 H), 3.49–3.23 (m, 4 H), 3.10–3.04 (m, 2 H), 2.73–2.67 (m, 1 H), 2.48–2.40 (m, 1 H), 2.06–1.95 (m, 3 H), 1.14 (t, *J* = 14.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.3, 177.9, 171.2, 167.1, 142.4, 140.9, 134.1, 133.4, 132.3, 131.8, 131.4, 130.4, 129.6, 129.2, 128.8, 128.4, 127.4, 126.1, 123.3, 122.6, 120.5, 70.3, 69.5, 63.2, 61.1, 57.3, 32.9, 30.5, 23.6, 22.6, 14.1.

MS (EI): *m/z* = 763 $[M]^+$.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{39}H_{36}BrN_3NiO_5$: 763.1192; found: 763.1156.

Ni(II)–(*S*)-BPB/5-Ethyl (2*R*,*E*)-4-(2,6-Difluorobenzylidene)-L-glutamate Schiff Base Complex 3j

Following the general procedure using **2j** and separation by flash column chromatography (PE–EtOAc, 2:3) gave **3j** as a red solid; yield: 92%; mp 111–113 °C; HPLC: t_R = 10.865 (minor), 21.884 min (major); 97% de.

$[\alpha]_D^{22}$ +1653.3 (*c* 0.34, $CHCl_3$).

IR (KBr): 704, 754, 1165, 1254, 1336, 1439, 1587, 1639, 1678 (C=N), 1713 (C=O), 2872, 2926, 3433 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 9.3 Hz, 1 H), 8.01 (d, *J* = 7.2 Hz, 2 H), 7.68 (s, 1 H), 7.50–7.39 (m, 3 H), 7.31–7.27 (m, 2 H), 7.24–7.09 (m, 5 H), 6.90–6.85 (m, 2 H), 6.65–6.55 (m, 2 H), 4.33 (d, *J* = 12.9 Hz, 1 H), 4.13–4.08 (m, 1 H), 4.04–3.87 (m, 1 H), 3.44–3.39 (m, 4 H), 3.12–2.94 (m, 2 H), 2.53–2.48 (m, 1 H), 2.40–2.34 (m, 1 H), 2.07–1.97 (m, 3 H), 1.13 (t, *J* = 14.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.5, 177.9, 171.8, 166.2, 160.9, 158.4, 142.5, 133.7, 132.2, 131.3, 130.3, 129.8, 129.4, 128.7, 127.3, 125.8, 122.8, 120.3, 112.5, 111.7, 111.4, 70.1, 63.2, 61.4, 57.4, 33.8, 30.5, 29.6, 23.6, 20.9, 14.1.

MS (EI): *m/z* = 721 $[M]^+$.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{39}H_{35}F_2N_3NiO_5$: 721.1898; found: 721.1903.

Ni(II)–(*S*)-BPB/5-Ethyl (2*R*,*E*)-4-(2-Furylmethylene)-L-glutamate Schiff Base Complex 3k

Following the general procedure using **2k** and separation by flash column chromatography (PE–EtOAc, 2:3) gave **3k** as a red solid; yield: 91%; mp 110–112 °C; HPLC: t_R = 8.91 (minor), 15.723 min (major); >99% de.

$[\alpha]_D^{22}$ +1605.6 (*c* 0.44, $CHCl_3$).

IR (KBr): 706, 754, 1209, 1256, 1335, 1439, 1589, 1637, 1676 (C=N), 1701 (C=O), 2931, 2976, 3442 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 8.7 Hz, 1 H), 8.04 (d, *J* = 7.5 Hz, 2 H), 7.55 (s, 1 H), 7.43–7.27 (m, 6 H), 7.22–7.07 (m, 5 H), 6.62–6.59 (m, 3 H), 4.35 (d, *J* = 12.9 Hz, 1 H), 4.27 (t, *J* = 13.2 Hz, 1 H), 4.04–3.96 (m, 1 H), 3.67–3.30 (m, 6 H), 2.97–2.92 (m, 1 H), 2.53–2.47 (m, 1 H), 2.11–2.02 (m, 3 H), 1.11 (t, *J* = 14.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.2, 178.5, 171.1, 167.9, 150.5, 144.7, 142.6, 133.6, 132.1, 131.4, 129.4, 129.1, 128.7, 127.5, 126.1, 123.2, 123.0, 120.3, 116.2, 112.2, 70.6, 69.8, 63.2, 60.4, 57.2, 33.1, 30.5, 23.6, 14.1.

MS (EI): *m*/*z* = 675 $[M]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{37}H_{35}N_3NiO_6$: 675.1879; found: 675.1882.

Ni(II)–(*S*)-BPB/5-Ethyl (2*R*,*E*)-4-(3-Thienylmethylene)-L-glutamate Schiff Base Complex 3l

Following the general procedure using **2l** and separation by flash column chromatography (PE–EtOAc, 2:3) gave **3l** as a red solid; yield: 92%; mp 112–114 °C; HPLC: t_R = 9.956 (minor), 21.054 min (major); 98% de.

$[\alpha]_D^{22}$ +1332.7 (*c* 0.22, $CHCl_3$).

IR (KBr): 704, 754, 1165, 1257, 1335, 1439, 1589, 1637, 1674 (C=N), 1701 (C=O), 2870, 2928, 3442 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 8.4 Hz, 1 H), 8.06 (d, *J* = 7.8 Hz, 2 H), 7.79 (s, 1 H), 7.48–7.28 (m, 7 H), 7.24–7.11 (m, 5 H), 6.66–6.57 (m, 2 H), 4.35 (d, *J* = 12.9 Hz, 1 H), 4.27 (t, *J* = 13.2 Hz, 1 H), 4.02–3.95 (m, 1 H), 3.70–3.41 (m, 6 H), 2.94–2.82 (m, 1 H), 2.53–2.44 (m, 1 H), 2.11–2.00 (m, 3 H), 1.14 (t, *J* = 14.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.3, 178.5, 171.3, 168.1, 142.5, 136.0, 135.8, 133.6, 132.3, 131.4, 129.6, 128.7, 127.4, 126.0, 123.1, 120.4, 70.5, 69.6, 63.3, 61.2, 57.4, 32.9, 30.5, 23.6, 14.1.

MS (EI): *m*/*z* = 691 $[M]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{37}H_{35}N_3NiO_5S$: 691.1651; found: 691.1636.

Ni(II)–(*S*)-BPB/5-Ethyl (2*R*,*E*)-4-(2-Naphthylmethylene)-L-glutamate Schiff Base Complex 3m

Following the general procedure using **2m** and separation by flash column chromatography (PE–EtOAc, 2:3) gave **3m** as a red solid; yield: 90%; mp 103–105 °C; HPLC: t_R = 7.895 (minor), 23.465 min (major); 98% de.

$[\alpha]_D^{22}$ +1438.5 (*c* 0.38, $CHCl_3$).

IR (KBr): 704, 752, 1165, 1256, 1335, 1439, 1589, 1639, 1676 (C=N), 1707 (C=O), 2926, 3057, 3433 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.4 Hz, 1 H), 8.01–7.97 (m, 3 H), 7.83–7.76 (m, 4 H), 7.49–7.28 (m, 7 H), 7.23–7.20 (m, 2 H), 7.15–7.08 (m, 2 H), 6.94 (d, *J* = 6.9 Hz, 1 H), 6.64–6.53 (m, 2 H), 4.30–4.21 (m, 2 H), 4.04–3.97 (m, 2 H), 3.60–3.17 (m, 6 H), 2.43–2.36 (m, 1 H), 2.21–2.04 (m, 2 H), 1.86–1.80 (m, 1 H), 1.16 (t, *J* = 14.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.3, 178.1, 171.0, 167.2, 165.7, 162.3, 162.2, 159.8, 142.4, 142.2, 140.1, 133.4, 133.1, 132.9, 132.6, 132.1, 131.3, 129.5, 128.6, 128.3, 127.5, 127.3, 126.6, 126.3, 126.0, 125.4, 123.2, 120.4, 117.3, 111.7, 70.3, 69.6, 64.1, 62.9, 60.9, 57.1, 32.9, 30.2, 22.9, 14.0.

MS (EI): *m*/*z* = 735 $[M]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{43}H_{39}N_3NiO_5$: 735.2243; found: 735.2266.

Synthesis of (*R*)-4a·HCl; Typical Procedure

The crystallized complex (*S*,2*R*)-**3a** (1 g, 1.37 mmol) was decomposed by refluxing a suspension in a mixture of aq 6 M HCl (1 mL) and MeOH (15 mL) for 30 min, until the red color of the soln had disappeared, as described previously. The reaction was cooled to r.t. and then evaporated to dryness. H_2O (20 mL) was added to the residue to form a clear soln, and this soln was then separated by column chromatography [C_{18}-reversed phase (230–400 mesh) silica gel]. Pure H_2O was employed as eluent to remove the green $NiCl_2$ and excess HCl; MeOH–H_2O (1:1) was then used to obtain enantiomerically pure product (*R*)-**4a**·HCl (363 mg, 96%).

$[\alpha]_D^{22}$ +11.1 (*c* 0.53, 6 M HCl).

The ligand BPB that decomposed from (*S*,2*R*)-**3a** was recovered by using MeOH as eluent (505 mg, 96%), and the chromatography column was washed with MeOH (100 mL) for further use.

5-Ethyl (2*R*,*E*)-4-(4-Nitrobenzylidene)-L-glutamate (4a)·HCl

Following the typical procedure using **3a** and separation by flash column chromatography (MeOH–H_2O, 1:1) gave **4a** as a white solid; yield: 96%; mp 148–150 °C; HPLC (flow rate 1.0 mL/min, λ = 254 nm): t_R = 40.492 min (major); >99% ee.

$[\alpha]_D^{22}$ +11.1 (*c* 0.53, 6 M HCl).

IR (KBr): 852, 1257, 1346, 1519, 1598, 1624, 1703 (C=O), 2985, 3427 cm^{-1}.

^1H NMR (300 MHz, D_2O): δ = 8.36 (d, *J* = 9.3 Hz, 2 H), 8.02 (s, 1 H), 7.66 (d, *J* = 11.1 Hz, 2 H), 4.40 (q, *J* = 21.3 Hz, 2 H), 3.95 (t, *J* = 15.0 Hz, 1 H), 3.18–3.00 (m, 2 H), 1.42 (t, *J* = 14.4 Hz, 3 H).

^{13}C NMR (100 MHz, D_2O): δ = 170.7, 168.4, 147.3, 142.1, 141.1, 129.7, 128.8, 123.8, 62.6, 51.7, 27.5, 13.4.

MS (ESI): *m*/*z* = 309 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{16}N_2O_6$: 331.0906; found: 331.0922.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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