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Purely Chemical Approach for Preparation of D-α-Amino Acids via (*S*)-to-(*R*)-Interconversion of Unprotected Tailor-Made α-Amino Acids

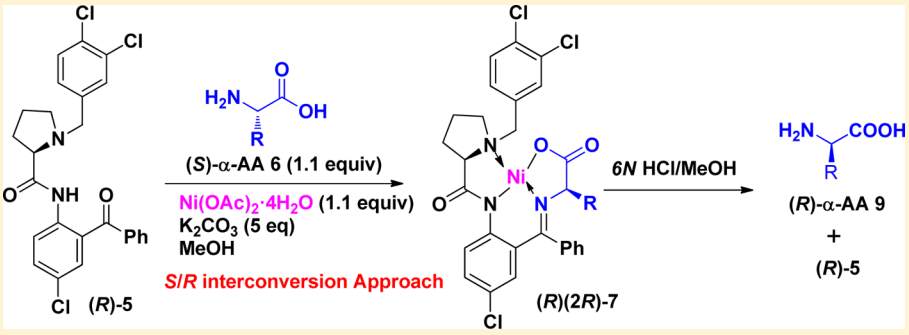
Yong Nian,[†] Jiang Wang,[†] Shengbin Zhou,[†] Wenhao Dai,[†] Shuni Wang,[†] Hiroki Moriwaki,[‡] Aki Kawashima,[‡] Vadim A. Soloshonok,*[,§] and Hong Liu*[,†]

[†]CAS Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai 201203, China

[‡]Hamari Chemicals Ltd., 1-4-29 Kunijima, Higashi-Yodogawa-ku, Osaka 533-0024, Japan

[§]Department of Organic Chemistry I, Faculty of Chemistry, University of the Basque Country UPV/EHU and IKERBASQUE, Basque Foundation for Science, Alameda Urquijo 36-5, Plaza Bizkaia, 48011 Bilbao, Spain

Supporting Information



ABSTRACT: Unnatural (*R*)-α-amino acids (α-AAs) are in growing demand in the biomedical research and pharmaceutical industries. In this work, we present development of a purely chemical approach for preparation of (*R*)-α-AAs via (*S*)-to-(*R*)-interconversion of natural and tailor-made (*S*)-α-AAs. The method can be used on free, unprotected α-AAs and features a remarkable structural generality including substrates bearing tertiary alkyl chains and reactive functional groups. These attractive characteristics, combined with simplicity of reaction conditions and virtually complete stereochemical outcome, constitute a true methodological advance in this area, rivaling previously reported chemical and biocatalytic approaches.

INTRODUCTION

Naturally occurring D-α-amino acids (D-α-AAs) have been identified in peptides of numerous bacteria as well as multicellular organisms including snails, spiders, clams, lobsters, and frogs.[1] In most cases, a single D-α-AA residue is located near the peptide N-terminus, providing for its protease stability. Furthermore, the presence of an D-α-AA residue allows for the formation of specific tertiary structures that cannot be generated from all-L-α-AA peptides.[2] These and other advantages rendered by the presence of D-α-AAs in peptides are being increasingly used in medicinal chemistry and drug design.[2,3]

Currently, preparation of enantiomerically pure α-AAs in general,[4] and D-α-AAs, in particular,[5] is virtually entirely dominated by biocatalytic approaches, which enjoy operational simplicity but have certain substrate restrictions. Purely chemical, synthetic approaches, despite their potential substrate generality and efficiency, are disproportionally less developed[6,7] and prohibitively expensive.[8] One of the least studied areas of α-AA chemistry is the L-to-D interconversion. Nevertheless, a thoughtful consideration of the synthetic structure of this process and the fact that L-amino acids are readily available from inexpensive and renewable natural sources suggest that the development of chemical methods for conversion of L-α-amino acids to the corresponding D-enantiomers appears to be of great synthetic prospective. However, this potential was somehow overlooked as there is only a handful of reports dealing with the L-to-D interconversion. In particular, Solladié-Cavallo,[9] Chin,[10] and our groups[11,12] have reported ligands **1**−**4** (Figure 1) as suitable for direct conversion of L- to D-α-AAs.

From a mechanistic standpoint, ligands **1**−**4** work similarly to the pyridoxal-5′-phosphate-dependent enzymes,[13] producing the corresponding α-AA Schiff bases followed by base-catalyzed epimerization to thermodynamically controlled diastereomer. In spite of the obvious methodological progress, ligands **1**−**4** still cannot rival the exceptional efficiency of the enzymatic approaches. For instance, compounds **1**−**3** have a limited substrate generality and provide for incomplete stereoselectivity (90/10−95/5 dr), necessitating laborious purification. The best, so far, performing ligand **4**[12] cannot be used for α-AAs containing tertiary groups and it is rather expensive. Recently,

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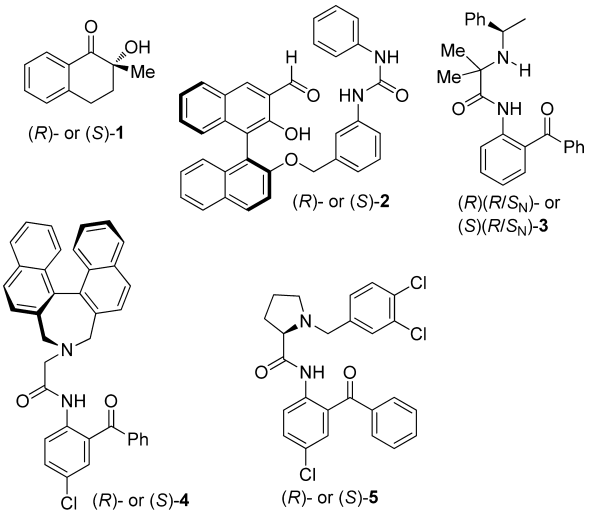

Figure 1. Compounds **1**−**4** as reported in the literature and synthetically advantageous proline-derived ligands **5** used in the present work.

we found that ligands **5** can be employed for substantially advancing the purely chemical dynamic thermodynamic resolution (DTR) of unprotected racemic tailor-made[14] α-amino acids (TM-α-AAs), enabling the first DTR of TM-α-AAs bearing tertiary alkyl chains as well as multiple unprotected functional groups, which can rival convenience, generality, and overall economic efficiency of the biocatalytic approaches.[15] Inspired by the exciting results obtained for the DTR of tailor-made *rac*-α-AAs, we decided to explore an additional methodological opportunity, *S*/*R*-interconversion of α-AAs, which was one of the least studied areas of α-AAs chemistry as we described above. Compared to the DTR of *rac*-α-AAs, conversion of (*S*)-α-AAs to (*R*) enantiomers and vice versa is obviously of much lesser general use for production of enantiomerically pure α-AAs. However, in some cases, such as utilization of undesired enantiomers, availability of the *S*/*R*-interconversion method can be of critical practical importance. Furthermore, a synthetic concept allowing the use of the same chiral ligands, reagents, and even conditions to pursue simply by choice of either DTR or *S*/*R* interconversion would be also interesting to realize. Thus, the obvious novelty of this idea was an additional motivation to conduct the present study. Consistent with our interest in the general asymmetric synthesis of α-AAs,[16] herein, we report an advanced method for preparation of D-α-AAs via (*S*)-to-(*R*)-interconversion of unprotected tailor-made α-AAs using ligands **5**. The major advantage of compounds **5** over literature analogues **1**−**4** is that the former possess ultimately wide substrate generality, showing excellent stereochemical outcome in all studied cases, in particular, the most challenging sterically constrained α-AAs bearing tertiary groups. Last but not least, ligands **5** are very inexpensive readily available in both enantiomeric forms and can be fully recycled and reused. One may agree that these features position the present method well to rival any catalytic approaches including biotransformations.

RESULTS AND DISCUSSION

Reaction conditions of ligands (*S*)- or (*R*)-**5** with (*S*)- or (*R*)-α-AAs-**6** were carefully studied, gauging the stereochemical outcome as a function of the following parameters: stoichiometry of reactants, solvent, base, source of Ni(II) ions, temperature, and time. We found that the reactions readily proceed in MeOH using K_2CO_3 as a base. In most cases, a 10% excess of α-AA-**6** vs ligand **5** was sufficient to ensure a complete consumption of the latter. Some representative experimental data demonstrating the generality of ligands **5** are presented in Table 1. A full collection of the examples consisting of 39 entries can be found in the Supporting Information (Table S1).

For this study, we selected proteinogenic as well as tailor-made (*S*)-α-AAs differing in steric and electronic characteristics bearing various unprotected functional groups. As an example of (*S*)-to-(*R*) transformation of α-AA containing straight alkyl chains, we studied the reaction of (*R*)-**5** with α-(amino)-hexanoic mode acid **6a** (entries 1 and 2). The process conducted under two temperature modes, ambient temperature and heating at 60 °C, gave similarly excellent stereochemical outcomes, indicating that product **7** is chemically stable and the reaction is not complicated by decomposition and byproduct formation. The (*S*)-to-(*R*)-conversions of phenylalanine-type α-AAs **6b**−**f** are presented in entries 3−7. Notably, virtually complete chemical yields and stereoselectivity were generally observed in these cases. Of particular interest are the reactions of (*S*)-tyrosine **6f** and benzophenone-containing (*S*)-**6f** bearing unprotected hydroxy and keto functional groups. Heterocyclic-type amino acids containing, for instance, a free indolic NH group, are exemplified by the conversion of (*S*)-**6g** (entry 8), which proceeded with excellent stereochemical outcome. Other pharmaceutically important types of tailor-made α-AAs containing unsaturated moieties are presented in entries 9 and 10. Thus, allyl- and cinnamylglycines (*S*)-**6h**, **i** were easily converted to (*R*)-configured products **7** with complete yields and stereocontrol.

With this quite impressive performance of ligand (*R*)-**5**, we were in a position to take on more difficult types of tailor-made α-AAs bearing sterically bulky and functionalized residues. The (*S*)-to-(*R*) conversion of isopropyl-containing valine (*S*)-**6j** proceeded flawlessly, affording (*R*)-**7j** with near-perfect stereochemical outcome (entry 11). As expected, the treatment of (*S*)-**6k**, featuring a *tert*-butyl group, was rather challenging. At ambient temperature, the process was very sluggish in terms of both Schiff base **7** formation and thermodynamic control (entry 12). Gratifyingly, at elevated temperature (entry 13), the latter was fully complete (> 99/1), allowing isolation of the diastereomerically pure α-(*R*)-**7k**. Additionally, when we performed this reaction at 80 °C in *n*-butanol for 24 h, only a trace amount of product appeared. Although one may agree that even the isolated yield of 48% still needs improvement, this reaction presents the first successful case of fully stereochemically controlled alteration of the α-configuration of α-AA-containing α-quaternary carbon.

Another conventionally challenging type of α-AA is that which contains reactive functional groups, which traditionally should be protected to perform any chemoselective transformation. Examples of this kind, including (*S*)-methionine **6l**, (*S*)-glutamine **6m**, and (*S*)-glutamic acid **6n**, are presented in entries **14**−**16**. One may agree that (*S*)-to-(*R*) conversion of these difficult cases was quite exceptional, highlighting synthetic generality and superior performance of ligand (*R*)-**3**.

Considering a situation where the opposite, (*R*)-to-(*S*), transformation may be needed in some special cases, we provide an example of (*R*)-2-aminopent-4-ynoic acid **6o** and benzophenone-containing (*R*)-**6f** reactions with ligand (*S*)-**5** to form α-(*S*)-configured products **7**, which proceeded with excellent stereochemical outcome (entries 17 and 18). Last

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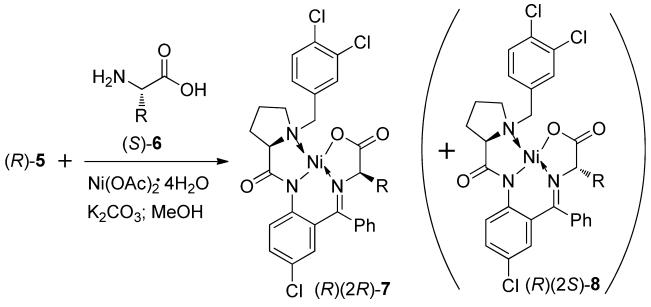
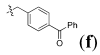
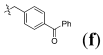
Table 1. (*S*)-to-(*R*)-Interconversion of Unprotected Tailor-Made *α*-Amino Acids 6 Using Ligand (*R*)-5[a]



Entry	5	R	T(°C)	t (h)	Yield (%)[b]	dr[c]
1	(*R*)	*n*-butyl (**a**)	60	2.5	98	98:2
2	(*R*)	*n*-butyl (**a**)	r.t.	72	93	99:1
3	(*R*)	benzyl (**b**)	60	2.5	99	99:1
4	(*R*)	4-Me-benzyl (**c**)	r.t.	72	96	> 99:1
5	(*R*)	4-Cl-benzyl (**d**)	60	2.5	97	99:1
6	(*R*)	4-OH-benzyl (**e**)	60	72	97	99:1
7	(*R*)	 (**f**)	60	72	83	99:1
8	(*R*)	 (**g**)	60	3.5	98	> 99:1
9	(*R*)	 (**h**)	r.t.	72	98	99:1
10	(*R*)	 (**i**)	60	1.5	99	99:1
11	(*R*)	*i*-propyl (**j**)	60	3	98	99:1
12	(*R*)	*t*-butyl (**k**)	r.t.	72	8	80:20
13	(*R*)	*t*-butyl (**k**)	60	72	48	> 99:1
14	(*R*)	 (**l**)	60	4	98	98:2
15	(*R*)	 (**m**)	60	3	98	98:2
16	(*R*)	 (**n**)	60	11	97	99:1
17	(*S*)	 (**o**)	60	72	86	97:3
18	(*S*)	 (**f**)	60	72	91	99:1
19[d]	(*R*)	benzyl (**b**)	60	3.5	98	99:1
20[d]	(*R*)	4-Me-benzyl (**c**)	60	5	97	99:1
21[d]	(*R*)		60	5	98	99:1

[a]Reaction conditions: (*R*)-**5** or (*S*)-**5** (0.20 mmol), (*S*)- or (*R*)-*α*-amino acids **6** (0.22 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (0.22 mmol), and K_2CO_3 (1 mmol) in methanol (4 mL). [b]Combined yield of isolated crude products **7**. [c]Determined by LC/MS analysis of the crude products. [d](*R*)- or (*S*)-**5** (20 mmol), (*S*)- or (*R*)-*α*-amino acids **6** (22 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (22 mmol), K_2CO_3 (100 mmol) in methanol (300 mL).

but not least, we included three large-scale experiments to fully illustrate the utility of the process (entries 19−21). To validate the configurational stability of the proline-derived stereogenic center in the Ni(II) complex, we conducted the reaction of (*R*)(2*R*)-**7g** with *t*-BuOK refluxing in methanol for 24 h. The results suggested that no epimerization of Ni(II) complex was observed (ee 99%; for details, see the Supporting Information). For further validation, when reaction of (*R*)(2*R*)-**7g** with *t*-BuOK was conducted at higher temperature (80 °C) in *n*-butanol for 24 h, slight epimerization of the Ni(II) complex was observed (ee 97%; for details, see the Supporting Information).

To better understand the stereochemical preferences in these transformations, we conducted a series of experiments by carefully monitoring the reaction composition over time using HPLC analysis. In particular, with an aim observing the formation of both diastereomers, we conducted the reaction of ligand (*S*)-**5** with racemic alanine **6r**. The results are presented in Figure 2.

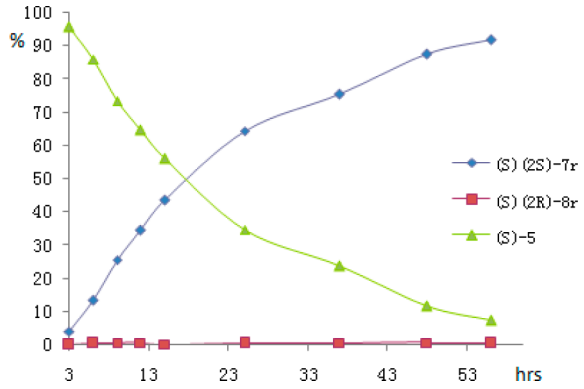


Figure 2. Reaction of (*S*)-**5** (0.2 mmol), *rac*-alanine **6r** (0.22 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (0.22 mmol), K_2CO_3 (1 mmol) in methanol (4 mL) at 15 °C.

As one can see from Figure 2, the amount of major diastereomer (*S*)(2*S*)-**7r** was rapidly increasing while the quantity of minor stereoisomer (*S*)(2*R*)-**8r** was, at all times, barely above the detection level. Interestingly the rate of consumption of ligand (*S*)-**5** and formation for the major diastereomer were quite similar mirroring each other at the 50% point. After 56 h of the reaction time, major product (*S*)(2*S*)-**7r** was isolated in diastereomerically pure form (dr > 99%) with excellent 90% yield. It can be reasonably assumed that under the reaction conditions minor diastereomer (*S*)(2*R*)-**8r** undergoes very fast base-catalyzed *α*-epimerization, via the corresponding intermediate enolate, to form the thermodynamically preferred product (*S*)(2*S*)-**7r** (see Table S2, Supporting Information).

Additionally, we conducted the reaction of (*S*)(2*R*)-**8r** with K_2CO_3 in methanol at 35 °C. The results are presented in Figure 3. As expected, quite rapid interconversion of the relative amounts of (*S*)(2*R*)-**8r** gradually decreased, while diastereomer (*S*)(2*S*)-**7r** became a major product after about 1 h of reaction time. Ultimately, after 82 h under full thermodynamic control, kinetic product (*S*)(2*R*)-**8r** completely transformed to (*S*)(2*S*)-**7r** with a final ratio of 96.5:3.5 (see Table S3, Supporting Information). This experiment clearly illustrated that the method is indeed a thermodynamic process.

As a final goal of this study, we demonstrated the isolation of free enantiomerically pure *α*-AAs (*S*)-**9o** and (*R*)-**9g** from

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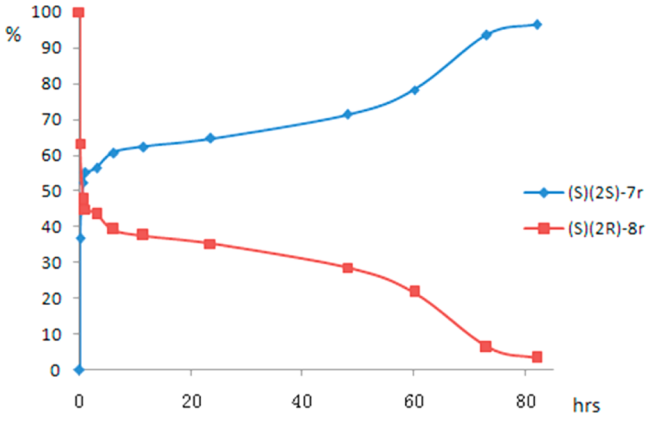
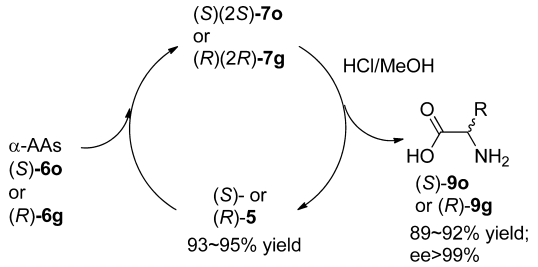


Figure 3. Reaction of (*S*)(2*R*)-**8r** (0.2 mmol) and K_2CO_3 (1 mmol) in methanol (4 mL) at 35 °C.

Schiff complexes **7**. Diastereomerically pure (*S*)(2*S*)-**7o** and (*R*)(2*R*)-**7g** were disassembled using standard HCl/MeOH conditions[14,17] (Scheme 1) affording free target α-AAs (*S*)-**9o**, and (*R*)-**9g** and allowing recovery and full recycling of chiral ligands (*S*)- and (*R*)-**5**. The latter, (*S*)- and (*R*)-**5**, as demonstrated in Scheme 1, can be readily reused for another cycle of (*S*)-to-(*R*) or the opposite stereochemical transformation.

Scheme 1. Reactions (*S*)- or (*R*)-α-AAs 6 with Chiral Ligands (*S*)- or (*R*)-5, Formation of Diastereomers (*S*)(2*S*)-7o and (*R*)(2*R*)-7g, and Their Disassembly To Release Free α-AAs (*S*)-9o and (*R*)-9g, along with Recycling and Reuse of (*S*)- and (*R*)-5



CONCLUSIONS

To summarize, we report here a successful development of a purely chemical approach for preparation of unnatural (*R*)-α-AAs via (*S*)-to-(*R*)-interconversion of natural and tailor-made (*S*)-α-AAs. The method can be used on free, unprotected α-AAs and features a remarkable structural generality including substrates bearing tertiary alkyl chains and reactive functional groups. These attractive characteristics, combined with simple reaction conditions and virtually complete stereochemical outcome, constitute a true methodological advance in this area, rivaling previous chemical and biocatalytic approaches. The operational convenience and practical efficiency of this method bode well with its widespread application for synthesis of various tailor-made (*R*)-α-AA derivatives of high pharmaceutical value.

EXPERIMENTAL SECTION

General Information. The chemicals were purchased from commercial sources and used without further purification. Analytical thin-layer chromatography (TLC) was performed on 0.15−0.2 mm thickness silica gel plates. All products were characterized by NMR and MS spectra. ^1H and ^{13}C NMR spectra were recorded in deuteriochloroform ($CDCl_3$), dimethyl sulfoxide-d_6 (DMSO-d_6), methanol-d_4 (CD_3OD), or deuterium oxide (D_2O) on 400 or 500 MHz instruments. Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton-coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (p), doublet of triplets (dt), and multiplet (m). High-resolution mass spectra (HRMS) were measured on a Q-TOF spectrometer. The determination of dr was performed via LC/MS analysis. The determination of ee was performed via HPLC analysis. Optical rotations were measured using a 1 mL cell with a 10 mm path length on a polarimeter and were reported as follows: $[\alpha]^{25}_D$ (*c*: g/100 mL, in solvent). Melting points were measured on a melting point apparatus. All physicochemical data reported for the Ni(II) complexes are due to the single diastereomers after purification by chromatography or crystallization.

General Procedure. *General Procedure for the Synthesis of (R)(2R)-**7a**.* (*R*)-**5** (97.6 mg, 0.20 mmol), (*S*)-2-aminohexanoic acid **6a** (28.9 mg, 0.22 mmol), and $Ni(OAc)_2{\cdot}4H_2O$ (54.7 mg, 0.22 mmol) were dissolved in MeOH (4 mL) followed by addition of K_2CO_3 (138 mg, 1 mmol). The resulting mixture was refluxed for 2.5 h. After the ligand (*R*)-**5** was consumed as indicated by TLC, the reaction was terminated by ice−water of 5% acetic acid (20 mL). The mixture was extracted with dichloromethane (10 mL × 3). The combined organic layers were dried with Na_2SO_4 and then concentrated to give the crude products (*R*)(2*R*)-**7a**/(*R*)(2*S*)-**8a** (128 mg, yield 98%) for analysis (dr = 98:2). The crude product was purified by column chromatography on silica gel (dichloromethane/methanol = 40/1) to give the major pure diastereomer (*R*)(2*R*)-**7a** as a brown solid.

*Disassembly of Ni(II) Complexes (S)(2S)-**7o** and (R)(2R)-**7g**. Synthesis of (S)-**9o**·HCl.* To a stirring solution of (*S*)(2*S*)-**7o** (640 mg, 1 mmol) in MeOH (20 mL) was added 6 N HCl (5.6 mL) at 70 °C for 0.5 h, and the reaction mixture was concentrated in vacuo.The resultant mixture was adjusted to pH 9 with concentrated ammonium hydroxide and extracted with CH_2Cl_2. The methylene chloride extracts were dried over Na_2SO_4, evaporated in vacuo, and recrystallized with EtOH to afford the ligand (*S*)-**5** (0.454 g, yield 93%). The aqueous solution was evaporated in vacuo, dissolved in a minimum amount of water, and purified by reversed-phase preparative chromatography (MeOH/water, 5/95) resulting in optically pure product (*S*)-**9o**·HCl as a white solid (133 mg, 89%).

*Synthesis of (R)-**9g**·HCl.* To a stirring solution of (*R*)(2*R*)-**7g** (731 mg, 1 mmol) in MeOH (20 mL) was added 6 N HCl (5.6 mL) at 70 °C for 50 min, and the reaction mixture was concentrated in vacuo. The resultant mixture was adjusted to pH 9 with concentrated ammonium hydroxide and extracted with CH_2Cl_2. The methylene chloride extracts were dried over Na_2SO_4 and evaporated in vacuo and recrystallized with EtOH to afford the ligand (*R*)-**5** (0.464 g, yield 95%). The aqueous solution was evaporated in vacuo, dissolved in a minimum amount of water, and purified by reversed-phase preparative chromatography (MeOH/water, 15/85) resulting in optically pure product (*R*)-**9g**·HCl as a white solid (221 mg, 92%).

*Analytical Characterization Data of Products. Ni(II)−(R)-N-(2-benzoyl-4-chlorophenyl)-1-(3,4-dichlorobenzyl)pyrrolidine-2-carboxamide/(R)-2-aminohexanoic acid Schiff base complex **7a**:* brown solid (128 mg, yield 98%); mp 237−238 °C; $[\alpha]^{25}_D$ = −2376 (*c* 0.040, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, *J* = 2.0 Hz, 1H), 8.06 (d, *J* = 9.3 Hz, 1H), 7.77 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.58−7.51 (m, 2H), 7.49−7.44 (m, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.30−7.26 (m, 1H), 7.11 (dd, *J* = 9.3, 2.6 Hz, 1H), 6.86 (d, *J* = 7.5 Hz, 1H), 6.58 (d, *J* = 2.6 Hz, 1H), 4.33 (d, *J* = 12.6 Hz, 1H), 3.91 (dd, *J* = 7.8, 3.4 Hz, 1H), 3.66−3.52 (m, 2H), 3.37 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.21 (d, *J* = 12.5 Hz, 1H), 2.72 (ddd, *J* = 9.0, 8.5, 4.2 Hz, 1H), 2.61 (tt, *J* = 13.6, 8.9 Hz, 1H), 2.27−2.13 (m, 2H), 2.12−2.03 (m, 1H), 1.94−1.83 (m, 1H), 1.68−1.64 (m, 1H), 1.60 (dd, *J* = 9.1, 4.5 Hz, 1H), 1.29−1.14 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.1, 179.3, 170.0, 140.6, 135.0, 133.8, 133.6, 133.5, 133.0, 132.4, 132.2, 131.2, 130.3, 130.1, 129.4, 129.3, 127.7, 127.4, 127.4, 125.9, 124.2, 71.5, 70.8, 63.2, 58.4, 35.1, 31.0, 27.7, 23.7, 22.6, 15.0,

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14.0; HRMS (ESI) m/z calcd for $C_{31}H_{31}Cl_3N_3NiO_3^+$ $[M + H]^+$ 656.0784, found 656.0768. The dr was determined by HPLC with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (H_2O/MeOH = 25/75, λ = 254 nm, 1.0 mL/min): t_R (major diastereomer) = 15.733 min, t_R (minor diastereomer) = 31.642 min, 98:2 dr.

Ni(II)−(R)-N-(2-benzoyl-4-chlorophenyl)-1-(3,4-dichlorobenzyl)-pyrrolidine-2-carboxamide/(R)-2-amino-3-phenylpropanoic acid Schiff base complex ***7b:*** brown solid (137 mg, yield 99%); mp 237−238 °C; $[\alpha]^{25}_D$ = −2325 (c 0.048, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, J = 2.0 Hz, 1H), 8.15 (d, J = 9.3 Hz, 1H), 7.58 (dddd, J = 8.8, 7.7, 5.4, 1.7 Hz, 3H), 7.46−7.37 (m, 4H), 7.31 (dd, J = 10.1, 4.9 Hz, 2H), 7.19−7.13 (m, 2H), 7.10 (dd, J = 9.3, 2.6 Hz, 1H), 6.76 (d, J = 7.7 Hz, 1H), 6.60 (d, J = 2.5 Hz, 1H), 4.28 (t, J = 5.0 Hz, 1H), 4.17 (d, J = 12.5 Hz, 1H), 3.22−3.04 (m, 4H), 2.80 (dd, J = 13.8, 5.4 Hz, 1H), 2.43−2.24 (m, 3H), 1.91 (td, J = 10.0, 6.3 Hz, 1H), 1.76−1.71 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.0, 178.3, 170.9, 141.1, 135.7, 135.0, 133.8, 133.4, 133.3, 132.6, 132.5, 131.0, 130.7, 130.3, 129.8, 129.5, 129.3, 129.0, 127.7, 127.3, 127.2, 125.7, 123.9, 71.8, 71.5, 63.4, 58.6, 39.8, 31.0, 23.1; HRMS (ESI) m/z calcd for $C_{34}H_{29}Cl_3N_3NiO_3^+$ $[M + H]^+$ 690.0628, found 690.0620. The dr was determined by HPLC with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (H_2O/MeOH = 15/85, λ = 254 nm, 1.0 mL/min): t_R (major diastereomer) = 9.126 min, t_R (minor diastereomer) = 16.097 min, 99:1 dr.

Ni(II)−(R)-N-(2-benzoyl-4-chlorophenyl)-1-(3,4-dichlorobenzyl)-pyrrolidine-2-carboxamide/(R)-2-amino-3-(p-tolyl)propanoic acid Schiff base complex ***7c:*** brown solid (135 mg, yield 96%); mp 146−147 °C; $[\alpha]^{25}_D$ = −2421 (c 0.048, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (d, J = 2.0 Hz, 1H), 8.15 (d, J = 9.3 Hz, 1H), 7.65−7.52 (m, 3H), 7.44 (td, J = 7.4, 1.4 Hz, 1H), 7.31 (dd, J = 11.3, 4.9 Hz, 2H), 7.22 (d, J = 7.8 Hz, 2H), 7.10 (dd, J = 9.3, 2.6 Hz, 1H), 7.05 (d, J = 7.9 Hz, 2H), 6.82 (d, J = 7.6 Hz, 1H), 6.60 (d, J = 2.6 Hz, 1H), 4.25 (t, J = 4.9 Hz, 1H), 4.17 (d, J = 12.5 Hz, 1H), 3.15 (ddd, J = 10.2, 8.3, 4.9 Hz, 2H), 3.09−2.98 (m, 2H), 2.74 (dd, J = 13.9, 5.6 Hz, 1H), 2.44−2.32 (m, 4H), 2.30−2.20 (m, 2H), 1.92 (td, J = 10.1, 6.5 Hz, 1H), 1.75−1.70 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.9, 178.4, 170.8, 141.1, 137.3, 135.0, 133.8, 133.4, 133.4, 133.3, 132.5, 132.4, 131.0, 130.6, 130.3, 129.8, 129.7, 129.5, 129.3, 127.7, 127.3, 127.2, 125.7, 123.9, 71.9, 71.6, 63.4, 58.6, 39.2, 30.8, 22.8, 21.3; HRMS (ESI) m/z calcd for $C_{35}H_{31}Cl_3N_3NiO_3^+$ $[M + H]^+$ 704.0784, found 704.0765. The dr was determined by HPLC with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (H_2O/MeOH = 15/85, λ = 254 nm, 1.0 mL/min): t_R (major diastereomer) = 11.683 min, t_R (minor enantiomer) = not found, > 99:1 dr.

Ni(II)−(R)-N-(2-benzoyl-4-chlorophenyl)-1-(3,4-dichlorobenzyl)-pyrrolidine-2-carboxamide/(R)-2-amino-3-(4-chlorophenyl)-propanoic acid Schiff base complex ***7d:*** brown solid (141 mg, yield 97%); mp 287−288 °C; $[\alpha]^{25}_D$ = −2246 (c 0.044, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (d, J = 1.8 Hz, 1H), 8.15 (d, J = 9.3 Hz, 1H), 7.64−7.55 (m, 3H), 7.48 (dd, J = 10.9, 4.8 Hz, 1H), 7.40 (d, J = 8.2 Hz, 2H), 7.32 (dd, J = 12.5, 7.5 Hz, 2H), 7.13−7.07 (m, 3H), 6.86 (d, J = 7.7 Hz, 1H), 6.61 (d, J = 2.5 Hz, 1H), 4.27 (t, J = 4.8 Hz, 1H), 4.17 (d, J = 12.5 Hz, 1H), 3.21 (dd, J = 10.1, 6.3 Hz, 1H), 3.16−3.05 (m, 2H), 3.01 (dd, J = 13.9, 4.2 Hz, 1H), 2.73 (dd, J = 13.8, 5.4 Hz, 1H), 2.48−2.39 (m, 1H), 2.37−2.24 (m, 2H), 1.95 (td, J = 9.9, 6.7 Hz, 1H), 1.82 (ddd, J = 14.5, 7.4, 4.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.1, 178.1, 171.1, 141.2, 135.0, 134.2, 134.0, 133.8, 133.5, 133.4, 133.3, 132.8, 132.5, 132.1, 131.1, 130.5, 129.8, 129.7, 129.4, 129.2, 127.6, 127.3, 127.1, 125.9, 124.0, 71.5, 71.5, 63.5, 58.7, 38.9, 31.0, 23.0; HRMS (ESI) m/z calcd for $C_{34}H_{28}Cl_4N_3NiO_3^+$ $[M + H]^+$ 724.0238, found 724.0218. The dr was determined by HPLC with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (H_2O/MeOH = 25/75, λ = 254 nm, 1.0 mL/min): t_R (major diastereomer) = 18.422 min, t_R (minor diastereomer) = 41.635 min, 99:1 dr.

Ni(II)−(R)-N-(2-benzoyl-4-chlorophenyl)-1-(3,4-dichlorobenzyl)-pyrrolidine-2-carboxamide/(R)-2-amino-3-(4-hydroxyphenyl)-propanoic acid Schiff base complex ***7e:*** brown solid (137 mg, yield 97%); mp 273−274 °C; $[\alpha]^{25}_D$ = −2173 (c 0.048, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (d, J = 1.9 Hz, 1H), 8.09 (d, J = 9.3 Hz, 2H), 7.58 (ddd, J = 14.3, 10.5, 4.6 Hz, 3H), 7.49−7.43 (m, 1H), 7.31 (dd, J = 9.7, 4.9 Hz, 2H), 7.10 (dd, J = 9.3, 2.6 Hz, 1H), 6.99 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 7.6 Hz, 1H), 6.60 (d, J = 2.6 Hz, 1H), 4.25 (t, J = 4.8 Hz, 1H), 4.15 (d, J = 12.5 Hz, 1H), 3.24 (dd, J = 9.5, 7.0 Hz, 1H), 3.18−3.10 (m, 1H), 3.06 (d, J = 12.6 Hz, 1H), 2.98 (dd, J = 14.0, 3.9 Hz, 1H), 2.69 (dd, J = 14.1, 5.6 Hz, 1H), 2.46−2.28 (m, 3H), 1.92 (td, J = 9.4, 6.4 Hz, 1H), 1.78−1.68 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.3, 179.0, 170.9, 157.0, 140.5, 135.1, 133.8, 133.5, 133.4, 133.2, 132.6, 132.6, 131.7, 131.1, 130.5, 129.8, 129.7, 129.4, 127.6, 127.5, 127.3, 126.3, 126.2, 124.0, 116.0, 72.1, 71.7, 63.5, 58.8, 38.7, 31.1, 23.0; HRMS (ESI) m/z calcd for $C_{34}H_{29}Cl_3N_3NiO_4^+$ $[M + H]^+$ 706.0577, found 706.0558. The dr was determined by HPLC with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (H_2O/MeOH = 15/85, λ = 254 nm, 1.0 mL/min): t_R (major diastereomer) = 6.224 min, t_R (minor diastereomer) = 7.911 min, 99:1 dr.

Ni(II)−(R)-N-(2-benzoyl-4-chlorophenyl)-1-(3,4-dichlorobenzyl)-pyrrolidine-2-carboxamide/(R)-2-amino-3-(4-benzoylphenyl)-propanoic acid Schiff base complex ***7f:*** brown solid (132 mg, yield 83%); mp 147−148 °C; $[\alpha]^{25}_D$ = −1805 (c 0.046, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (d, J = 2.0 Hz, 1H), 8.13 (d, J = 9.3 Hz, 1H), 7.86 (d, J = 8.2 Hz, 2H), 7.79 (dd, J = 7.9, 0.9 Hz, 2H), 7.65−7.55 (m, 4H), 7.48 (dd, J = 10.5, 4.7 Hz, 3H), 7.38−7.29 (m, 2H), 7.27 (s, 1H), 7.25 (s, 1H), 7.11 (dd, J = 9.3, 2.6 Hz, 1H), 6.86 (d, J = 7.6 Hz, 1H), 6.61 (d, J = 2.5 Hz, 1H), 4.33 (dd, J = 5.7, 4.6 Hz, 1H), 4.18 (d, J = 12.5 Hz, 1H), 3.24−3.05 (m, 4H), 2.91 (dd, J = 13.6, 5.9 Hz, 1H), 2.46−2.31 (m, 2H), 2.29−2.19 (m, 1H), 1.93 (td, J = 10.2, 6.5 Hz, 1H), 1.79 (dq, J = 15.0, 7.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.0, 180.0, 177.8, 171.0, 141.1, 140.4, 137.3, 137.0, 135.0, 133.7, 133.3, 133.2, 133.2, 132.6, 132.3, 131.0, 130.6, 130.4, 129.9, 129.8, 129.6, 129.3, 128.4, 127.5, 127.3, 127.0, 125.7, 123.9, 71.3, 63.3, 58.6, 39.7, 30.9, 23.1; HRMS (ESI) m/z calcd for $C_{41}H_{33}Cl_3N_3NiO_4^+$ $[M + H]^+$ 794.0885, found 794.0908. The dr was determined by HPLC with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (H_2O/MeOH = 15/85, λ = 254 nm, 1.0 mL/min): t_R (major diastereomer) = 6.574 min, t_R (minor diastereomer) = 9.788 min, 99:1 dr.

Ni(II)−(R)-N-(2-benzoyl-4-chlorophenyl)-1-(3,4-dichlorobenzyl)-pyrrolidine-2-carboxamide/(R)-2-amino-3-(1H-indol-3-yl)propanoic acid Schiff base complex ***7g:*** brown solid (143 mg, yield 98%); mp 298−299 °C; $[\alpha]^{25}_D$ = −2211 (c 0.042, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, J = 2.0 Hz, 1H), 8.48 (s, 1H), 8.17 (d, J = 9.3 Hz, 1H), 7.60−7.49 (m, 3H), 7.44 (d, J = 8.2 Hz, 1H), 7.40−7.26 (m, 4H), 7.22−7.17 (m, 1H), 7.11 (dd, J = 9.3, 2.6 Hz, 1H), 7.03 (d, J = 2.1 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H), 6.63 (d, J = 2.6 Hz, 1H), 4.31 (t, J = 4.7 Hz, 1H), 4.08 (d, J = 12.5 Hz, 1H), 3.31 (dd, J = 14.8, 4.5 Hz, 1H), 3.06−2.95 (m, 3H), 2.88−2.82 (m, 1H), 2.18−2.07 (m, 1H), 1.87−1.70 (m, 2H), 1.58 (ddd, J = 20.5, 8.4, 4.4 Hz, 1H), 1.50−1.41 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.6, 179.3, 170.5, 140.9, 136.7, 135.0, 133.7, 133.2, 133.1, 132.4, 130.9, 130.2, 129.8, 129.5, 129.1, 128.3, 127.7, 127.3, 127.2, 125.6, 124.6, 123.9, 122.4, 119.9, 119.5, 111.4, 109.3, 72.0, 71.4, 63.1, 58.3, 30.6, 30.4, 22.5; HRMS (ESI) m/z calcd for $C_{36}H_{30}Cl_3N_4NiO_3^+$ $[M + H]^+$ 729.0737, found 729.0725. The dr was determined by HPLC with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (H_2O/MeOH = 25/75, λ = 254 nm, 1.0 mL/min): t_R (major diastereomer) = 12.712 min, t_R (minor enantiomer) = not found, > 99:1 dr.

Ni(II)−(R)-N-(2-benzoyl-4-chlorophenyl)-1-(3,4-dichlorobenzyl)-pyrrolidine-2-carboxamide/(R)-2-aminopent-4-enoic acid Schiff base complex ***7h:*** brown solid (126 mg, yield 98%); mp 232−233 °C; $[\alpha]^{25}_D$ = −2693 (c 0.040, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, J = 2.0 Hz, 1H), 8.08 (d, J = 9.3 Hz, 1H), 7.75 (dd, J = 8.2, 2.1 Hz, 1H), 7.59−7.51 (m, 2H), 7.48 (ddd, J = 7.3, 4.5, 1.9 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.31−7.27 (m, 1H), 7.11 (dd, J = 9.3, 2.6 Hz, 1H), 6.91−6.87 (m, 1H), 6.58 (d, J = 2.5 Hz, 1H), 6.42 (ddt, J = 17.3, 10.0, 7.4 Hz, 1H), 5.42 (d, J = 10.1 Hz, 1H), 5.19 (dd, J = 17.0, 1.3 Hz, 1H), 4.31 (d, J = 12.5 Hz, 1H), 4.02 (dd, J = 6.5, 3.9 Hz, 1H), 3.66−3.50 (m, 2H), 3.34 (dd, J = 10.9, 6.1 Hz, 1H), 3.21 (d, J = 12.6 Hz, 1H), 2.79−2.68 (m, 1H), 2.60 (dq, J = 13.4, 8.8 Hz, 1H), 2.51−2.41 (m, 1H), 2.34 (dt, J = 14.2, 7.2 Hz, 1H), 2.25−2.13 (m, 1H), 2.11−1.99 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.0, 178.5, 170.5, 140.7, 135.0, 133.7, 133.5, 133.4, 133.1, 132.4, 132.2, 132.0, 131.1, 130.4,

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130.0, 129.5, 129.3, 127.5, 127.5, 127.2, 125.8, 124.1, 120.3, 71.5, 70.6, 63.2, 58.4, 38.6, 31.0, 23.4; HRMS (ESI) m/z calcd for $C_{30}H_{26}Cl_3N_3NiO_3Na^+$ $[M + Na]^+$ 662.0285, found 662.0299. The dr was determined by HPLC with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (H_2O/MeOH = 15/85, λ = 254 nm, 1.0 mL/min): t_R (major diastereomer) = 4.215 min, t_R (minor diastereomer) = 5.720 min, 99:1 dr.

Ni(II)−(R)-N-(2-benzoyl-4-chlorophenyl)-1-(3,4-dichlorobenzyl)-pyrrolidine-2-carboxamide/(R)-(E)-2-amino-5-phenylpent-4-enoic acid Schiff base complex ***7i:*** brown solid (142 mg, yield 99%); mp 158−159 °C; $[\alpha]^{25}_D$ = −2361 (c 0.036, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO) δ 8.70 (d, J = 1.9 Hz, 1H), 8.47 (dd, J = 8.2, 1.8 Hz, 1H), 7.99 (d, J = 9.3 Hz, 1H), 7.69−7.49 (m, 7H), 7.36 (t, J = 7.5 Hz, 2H), 7.28 (dd, J = 12.7, 6.7 Hz, 2H), 7.14 (dd, J = 9.3, 2.6 Hz, 1H), 6.76 (dt, J = 15.4, 7.6 Hz, 1H), 6.50 (d, J = 15.8 Hz, 1H), 6.43 (d, J = 2.6 Hz, 1H), 4.04 (d, J = 12.3 Hz, 1H), 3.81 (dd, J = 6.1, 3.7 Hz, 1H), 3.51 (dd, J = 10.7, 6.4 Hz, 1H), 3.37 (d, J = 12.4 Hz, 1H), 3.15−3.07 (m, 1H), 2.84 (qd, J = 16.1, 9.3 Hz, 1H), 2.46−2.30 (m, 2H), 2.21−2.09 (m, 1H), 2.01 (td, J = 10.7, 6.3 Hz, 1H), 1.92−1.83 (m, 1H), 1.71−1.61 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.0, 178.7, 170.7, 140.9, 137.0, 135.2, 135.0, 133.7, 133.4, 133.3, 133.2, 132.5, 132.3, 131.1, 130.4, 129.9, 129.5, 129.3, 128.7, 128.0, 127.7, 127.4, 127.2, 126.7, 125.7, 124.0, 123.2, 71.5, 70.9, 63.3, 58.6, 37.7, 30.9, 23.3; HRMS (ESI) m/z calcd for $C_{36}H_{31}Cl_3N_3NiO_3^+$ $[M + H]^+$ 716.0779, found 716.0777. The dr was determined by HPLC with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (H_2O/MeOH = 15/85, λ = 254 nm, 1.0 mL/min): t_R (major diastereomer) = 6.175 min, t_R (minor diastereomer) = 10.007 min, 99:1 dr.

Ni(II)−(R)-N-(2-benzoyl-4-chlorophenyl)-1-(3,4-dichlorobenzyl)-pyrrolidine-2-carboxamide/(R)-2-amino-3-methylbutanoic acid Schiff base complex ***7j:*** brown solid (126 mg, yield 98%); mp 143−144 °C; $[\alpha]^{25}_D$ = −1950 (c 0.044, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO) δ 8.75 (d, J = 2.0 Hz, 1H), 8.45 (dd, J = 8.2, 1.9 Hz, 1H), 8.05 (d, J = 9.3 Hz, 1H), 7.67 (t, J = 7.4 Hz, 1H), 7.56 (qd, J = 14.8, 7.5 Hz, 4H), 7.19−7.10 (m, 2H), 6.42 (d, J = 2.6 Hz, 1H), 4.09 (d, J = 12.3 Hz, 1H), 3.69 (dd, J = 10.7, 6.3 Hz, 1H), 3.50 (d, J = 3.1 Hz, 1H), 3.44 (d, J = 12.3 Hz, 1H), 3.27−3.17 (m, 2H), 2.58−2.51 (m, 1H), 2.48−2.41 (m, 1H), 2.20−2.10 (m, 2H), 1.82 (d, J = 6.5 Hz, 3H), 1.73 (tt, J = 13.6, 5.0 Hz, 1H), 0.58 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.0, 177.6, 170.5, 140.7, 135.2, 133.9, 133.5, 133.4, 133.2, 132.4, 131.1, 130.2, 129.9, 129.5, 129.2, 127.8, 127.5, 127.4, 125.8, 123.9, 75.7, 71.7, 63.5, 58.3, 34.4, 31.0, 23.2, 19.8, 18.3; HRMS (ESI) m/z calcd for $C_{30}H_{29}Cl_3N_3NiO_3^+$ $[M + H]^+$ 642.0628, found 642.0620. The dr was determined by HPLC with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (H_2O/MeOH = 25/75, λ = 254 nm, 1.0 mL/min): t_R (major diastereomer) = 11.537 min, t_R (minor diastereomer) = 21.747 min, 99:1 dr.

Ni(II)−(R)-N-(2-benzoyl-4-chlorophenyl)-1-(3,4-dichlorobenzyl)-pyrrolidine-2-carboxamide/(R)-2-amino-3,3-dimethylbutanoic acid Schiff base complex ***7k:*** brown solid (11 mg, yield 8%); mp 289−290 °C; $[\alpha]^{25}_D$ = +2709 (c 0.028, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.31 (d, J = 9.2 Hz, 1H), 7.62 (d, J = 7.9 Hz, 1H), 7.57−7.49 (m, 2H), 7.45−7.35 (m, 2H), 7.22 (d, J = 8.0 Hz, 1H), 7.04 (d, J = 9.3 Hz, 1H), 6.86 (d, J = 7.5 Hz, 1H), 6.66 (d, J = 1.9 Hz, 1H), 4.25 (d, J = 12.5 Hz, 1H), 3.84 (s, 1H), 3.53 (t, J = 8.2 Hz, 1H), 3.38 (dd, J = 9.6, 7.2 Hz, 1H), 3.25−3.12 (m, 1H), 3.06 (d, J = 12.4 Hz, 1H), 2.88 (tt, J = 14.1, 7.2 Hz, 1H), 2.70−2.59 (m, 1H), 2.12 (tt, J = 14.0, 7.1 Hz, 2H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.6, 177.0, 171.8, 141.1, 135.4, 133.7, 133.5, 133.5, 133.4, 133.1, 132.8, 131.1, 130.8, 130.5, 129.4, 129.3, 128.7, 128.5, 127.5, 125.7, 122.5, 79.7, 72.4, 64.0, 58.5, 36.7, 31.2, 28.4, 22.8; HRMS (ESI) m/z calcd for $C_{31}H_{31}Cl_3N_3NiO_3^+$ $[M + H]^+$ 656.0784, found 656.0778. The dr was determined by HPLC with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (H_2O/MeOH = 25/75, λ = 254 nm, 1.0 mL/min): t_R (major diastereomer) = 19.868 min, t_R (minor diastereomer) = 40.411 min, 80:20 dr.

Ni(II)−(R)-N-(2-benzoyl-4-chlorophenyl)-1-(3,4-dichlorobenzyl)-pyrrolidine-2-carboxamide/(R)-2-amino-4-(methylthio)butanoic acid Schiff base complex ***7l:*** brown solid (132 mg, yield 98%); mp 224−225 °C; $[\alpha]^{25}_D$ = −2561 (c 0.044, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, J = 2.0 Hz, 1H), 8.05 (d, J = 9.3 Hz, 1H), 7.76 (dd, J = 8.2, 2.1 Hz, 1H), 7.60−7.51 (m, 2H), 7.50−7.45 (m, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.31−7.27 (m, 1H), 7.11 (dd, J = 9.3, 2.6 Hz, 1H), 6.89 (d, J = 7.5 Hz, 1H), 6.57 (d, J = 2.5 Hz, 1H), 4.32 (d, J = 12.5 Hz, 1H), 3.98 (dd, J = 8.8, 3.8 Hz, 1H), 3.65−3.51 (m, 2H), 3.37 (dd, J = 11.1, 5.8 Hz, 1H), 3.22 (d, J = 12.6 Hz, 1H), 3.04 (ddd, J = 13.0, 9.9, 4.9 Hz, 1H), 2.71 (dt, J = 12.5, 6.6 Hz, 1H), 2.65−2.48 (m, 2H), 2.35−2.20 (m, 2H), 2.12−2.03 (m, 1H), 1.98 (s, 3H), 1.94−1.84 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.0, 178.5, 170.4, 140.7, 135.0, 133.7, 133.6, 133.5, 132.9, 132.5, 132.2, 131.1, 130.4, 130.0, 129.6, 129.4, 127.5, 127.4, 125.9, 124.3, 71.4, 69.8, 63.2, 58.5, 35.3, 30.9, 30.0, 29.8, 24.0, 15.8; HRMS (ESI) m/z calcd for $C_{30}H_{28}Cl_3N_3NiO_3SNa^+$ $[M + Na]^+$ 696.0168, found 696.0151. The dr was determined by HPLC with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (H_2O/MeOH = 15/85, λ = 254 nm, 1.0 mL/min): t_R (major diastereomer) = 7.897 min, t_R (minor diastereomer) = 11.876 min, 98:2 dr.

Ni(II)−(R)-N-(2-benzoyl-4-chlorophenyl)-1-(3,4-dichlorobenzyl)-pyrrolidine-2-carboxamide/(R)-2,5-diamino-5-oxopentanoic acid Schiff base complex ***7m:*** brown solid (132 mg, yield 98%); mp 191−192 °C; $[\alpha]^{25}_D$ = −2360 (c 0.046, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, J = 1.9 Hz, 1H), 8.05 (d, J = 9.3 Hz, 1H), 7.75 (dd, J = 8.2, 2.0 Hz, 1H), 7.57−7.48 (m, 3H), 7.36 (d, J = 8.1 Hz, 1H), 7.26−7.22 (m, 1H), 7.11 (dd, J = 9.3, 2.6 Hz, 1H), 6.94 (d, J = 7.3 Hz, 1H), 6.59 (d, J = 2.5 Hz, 1H), 6.02 (s, 1H), 5.24 (s, 1H), 4.30 (d, J = 12.6 Hz, 1H), 3.82 (dd, J = 10.9, 4.3 Hz, 1H), 3.74−3.61 (m, 1H), 3.51 (dd, J = 10.3, 6.1 Hz, 1H), 3.38 (dd, J = 11.2, 5.6 Hz, 1H), 3.22 (d, J = 12.6 Hz, 1H), 2.76−2.54 (m, 3H), 2.46 (ddd, J = 12.7, 7.7, 5.0 Hz, 1H), 2.31−2.19 (m, 2H), 2.07 (td, J = 11.3, 5.9 Hz, 1H), 1.98−1.89 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.0, 178.8, 173.4, 170.6, 140.6, 134.9, 133.7, 133.7, 133.5, 132.6, 132.4, 132.3, 131.2, 130.4, 130.0, 129.7, 129.3, 127.3, 127.0, 125.9, 124.3, 71.4, 69.7, 63.1, 58.5, 31.8, 30.9, 24.2; HRMS (ESI) m/z calcd for $C_{30}H_{27}Cl_3N_4NiO_4^+$ $[M + H]^+$ 671.0524, found 671.0518. The dr was determined by HPLC with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (H_2O/MeOH = 20/80, λ = 254 nm, 1.0 mL/min): t_R (major diastereomer) = 4.340 min, t_R (minor diastereomer) = 6.024 min, 98:2 dr.

Ni(II)−(R)-N-(2-benzoyl-4-chlorophenyl)-1-(3,4-dichlorobenzyl)-pyrrolidine-2-carboxamide/(R)-2-aminopentanedioic acid Schiff base complex ***7n:*** brown solid (131 mg, yield 97%); mp 221−222 °C; $[\alpha]^{25}_D$ = −2356 (c 0.042, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, J = 1.9 Hz, 1H), 8.02 (d, J = 9.3 Hz, 1H), 7.74 (dd, J = 8.2, 1.9 Hz, 1H), 7.58−7.50 (m, 2H), 7.49−7.44 (m, 1H), 7.32 (d, J = 8.1 Hz, 1H), 7.25 (d, J = 1.8 Hz, 1H), 7.09 (dd, J = 9.3, 2.6 Hz, 1H), 7.03 (d, J = 7.4 Hz, 1H), 6.57 (d, J = 2.5 Hz, 1H), 4.27 (d, J = 12.4 Hz, 1H), 3.93 (dd, J = 8.5, 3.9 Hz, 1H), 3.63 (ddd, J = 24.2, 15.2, 9.3 Hz, 1H), 3.55−3.46 (m, 1H), 3.40 (dd, J = 11.3, 5.6 Hz, 1H), 3.20 (d, J = 12.6 Hz, 1H), 3.05 (dt, J = 16.7, 6.9 Hz, 1H), 2.72−2.60 (m, 1H), 2.57−2.42 (m, 2H), 2.36 (td, J = 14.7, 7.1 Hz, 1H), 2.21−2.13 (m, 1H), 2.04 (td, J = 11.0, 6.0 Hz, 1H), 1.85 (dtd, J = 11.7, 7.3, 4.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.4, 179.0, 175.8, 171.4, 140.4, 135.2, 133.7, 133.5, 133.4, 132.8, 132.5, 132.4, 131.2, 130.4, 130.0, 129.4, 127.6, 127.5, 127.1, 126.0, 124.1, 71.4, 69.8, 63.3, 58.6, 30.6, 29.9, 29.2, 23.8; HRMS (ESI) m/z calcd for $C_{30}H_{27}Cl_3N_3NiO_5^+$ $[M + H]^+$ 672.0370, found 672.0351. The dr was determined by HPLC with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (H_2O/MeOH = 30/70, λ = 254 nm, 1.0 mL/min): t_R (major diastereomer) = 3.697 min, t_R (minor diastereomer) = 13.200 min, 99:1 dr.

Ni(II)−(S)-N-(2-benzoyl-4-chlorophenyl)-1-(3,4-dichlorobenzyl)-pyrrolidine-2-carboxamide/(S)-2-aminopent-4-ynoic acid Schiff base complex ***7o:*** brown solid (108 mg, yield 86%); mp 246−247 °C; $[\alpha]^{25}_D$ = +2182 (c 0.036, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, J = 2.0 Hz, 1H), 8.12 (d, J = 9.3 Hz, 1H), 7.74 (dd, J = 8.2, 2.1 Hz, 1H), 7.59−7.53 (m, 2H), 7.52−7.47 (m, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.28 (dd, J = 4.3, 2.2 Hz, 1H), 7.13 (dd, J = 9.3, 2.6 Hz, 1H), 6.95 (dd, J = 7.4, 0.7 Hz, 1H), 6.58 (d, J = 2.5 Hz, 1H), 4.33 (d, J = 12.6 Hz, 1H), 4.01 (dd, J = 6.7, 2.8 Hz, 1H), 3.76−3.57 (m, 2H), 3.35 (dd, J = 10.7, 6.4 Hz, 1H), 3.25 (d, J = 12.6 Hz, 1H), 2.79−2.68 (m, 1H), 2.67−2.53 (m, 3H), 2.23 (ddd, J = 17.2, 6.7, 2.8 Hz, 1H), 2.08 (ddd, J = 17.2, 10.2, 6.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.1,

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178.3, 171.6, 141.1, 135.0, 133.8, 133.6, 133.4, 133.1, 132.7, 132.3, 131.1, 130.5, 130.1, 129.6, 129.5, 127.4, 127.3, 126.8, 125.8, 124.3, 78.9, 74.1, 71.6, 67.9, 63.4, 58.5, 31.0, 23.4, 23.2; HRMS (ESI) m/z calcd for $C_{30}H_{25}Cl_3N_3NiO_3^+$ $[M + H]^+$ 638.0309, found 638.0311. The dr was determined by HPLC with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (H_2O/MeOH = 25/75, λ = 254 nm, 1.0 mL/min): t_R (major diastereomer) = 10.167 min, t_R (minor diastereomer) = 14.743 min, 97:3 dr.

Ni(II)−(S)-N-(2-benzoyl-4-chlorophenyl)-1-(3,4-dichlorobenzyl)-pyrrolidine-2-carboxamide/(S)-2-amino-3-(4-benzoylphenyl)-propanoic acid Schiff base complex ***7f:*** brown solid (145 mg, yield 91%); mp 144−145 °C; $[\alpha]^{25}_D$ = +1757 (c 0.038, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (d, J = 2.0 Hz, 1H), 8.13 (d, J = 9.3 Hz, 1H), 7.86 (d, J = 8.2 Hz, 2H), 7.80 (dd, J = 8.0, 1.0 Hz, 2H), 7.66−7.55 (m, 4H), 7.52−7.46 (m, 3H), 7.38−7.33 (m, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.27 (s, 1H), 7.25 (d, J = 1.0 Hz, 1H), 7.11 (dd, J = 9.3, 2.6 Hz, 1H), 6.86 (d, J = 7.7 Hz, 1H), 6.61 (d, J = 2.6 Hz, 1H), 4.33 (dd, J = 5.8, 4.5 Hz, 1H), 4.18 (d, J = 12.5 Hz, 1H), 3.23−3.05 (m, 4H), 2.91 (dd, J = 13.6, 5.9 Hz, 1H), 2.45−2.31 (m, 2H), 2.30−2.20 (m, 1H), 1.93 (td, J = 10.3, 6.5 Hz, 1H), 1.83−1.75 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.0, 180.0, 177.9, 171.1, 141.1, 140.4, 137.3, 137.1, 135.0, 133.7, 133.4, 133.3, 133.2, 132.7, 132.4, 131.0, 130.6, 130.5, 130.0, 129.8, 129.7, 129.4, 128.5, 127.5, 127.3, 127.0, 125.8, 123.9, 71.4, 63.3, 58.6, 39.7, 31.0, 23.1; HRMS (ESI) m/z calcd for $C_{41}H_{33}Cl_3N_3NiO_4^+$ $[M + H]^+$ 794.0885, found 794.0898. The dr was determined by HPLC with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (H_2O/MeOH = 15/85, λ = 254 nm, 1.0 mL/min): t_R (major diastereomer) = 6.466 min, t_R (minor diastereomer) = 9.616 min, 99:1 dr.

Ni(II)−(R)-N-(2-benzoyl-4-chlorophenyl)-1-(3,4-dichlorobenzyl)-pyrrolidine-2-carboxamide/(R)-2-amino-2-phenylacetic acid Schiff base complex ***7p:*** brown solid (123 mg, yield 91%); mp 228−229 °C; $[\alpha]^{25}_D$ = −2083 (c 0.046, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.90 (d, J = 2.0 Hz, 1H), 8.10 (d, J = 9.3 Hz, 1H), 7.83 (dd, J = 8.2, 2.1 Hz, 1H), 7.73 (dd, J = 7.4, 1.8 Hz, 2H), 7.52 (t, J = 7.6 Hz, 1H), 7.47−7.35 (m, 2H), 7.34−7.26 (m, 4H), 7.15 (dd, J = 9.3, 2.6 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 6.64 (d, J = 2.5 Hz, 1H), 6.07 (d, J = 7.8 Hz, 1H), 4.79 (s, 1H), 4.38 (d, J = 12.6 Hz, 1H), 3.60−3.45 (m, 2H), 3.41 (dd, J = 11.1, 5.7 Hz, 1H), 3.27 (d, J = 12.6 Hz, 1H), 2.84−2.74 (m, 1H), 2.64 (tt, J = 13.4, 9.3 Hz, 1H), 2.21−2.12 (m, 1H), 2.08−2.00 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.4, 177.7, 172.0, 140.9, 137.8, 135.0, 133.8, 133.7, 133.5, 133.0, 132.6, 132.2, 131.2, 130.2, 129.9, 129.0, 128.8, 128.8, 128.4, 127.3, 126.9, 126.5, 126.3, 126.0, 124.6, 74.9, 71.4, 63.1, 58.5, 31.1, 23.82; HRMS (ESI) m/z calcd for $C_{33}H_{26}C_{l3}N_3NiO_3^+$ $[M + H]^+$ 676.0471, found 676.0456. The dr was determined by HPLC with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (H_2O/MeOH = 15/85, λ = 254 nm, 1.0 mL/min): t_R (major diastereomer) = 8.885 min, t_R (minor diastereomer) = 14.762 min, 95:5 dr.

Ni(II)−(R)-N-(2-benzoyl-4-chlorophenyl)-1-(3,4-dichlorobenzyl)-pyrrolidine-2-carboxamide/(R)-2-amino-2-(4-fluorophenyl)acetic acid Schiff base complex ***7q:*** brown solid (129 mg, yield 93%); mp 244−245 °C; $[\alpha]^{25}_D$ = −2005 (c 0.046, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, J = 1.6 Hz, 1H), 8.10 (d, J = 9.2 Hz, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.67 (dd, J = 8.3, 5.3 Hz, 2H), 7.54 (t, J = 7.6 Hz, 1H), 7.41 (t, J = 8.2 Hz, 2H), 7.29 (s, 1H), 7.16 (dd, J = 9.3, 2.3 Hz, 1H), 7.04 (dt, J = 17.2, 8.1 Hz, 3H), 6.63 (d, J = 2.2 Hz, 1H), 6.08 (d, J = 7.8 Hz, 1H), 4.79 (s, 1H), 4.38 (d, J= 12.6 Hz, 1H), 3.55−3.46 (m, 2H), 3.42 (dd, J = 11.1, 5.7 Hz, 1H), 3.28 (d, J = 12.7 Hz, 1H), 2.82−2.72 (m, 1H), 2.64 (dt, J = 14.3, 9.2 Hz, 1H), 2.19 (s, 1H), 2.05 (dd, J = 17.4, 11.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.5, 177.6, 172.3, 163.6, 161.6, 141.0, 134.9, 133.8, 133.7, 133.6, 133.0, 132.8, 132.3, 131.2, 130.2, 130.1, 129.1, 128.9, 128.0, 128.0, 127.2, 126.8, 126.5, 126.1, 124.6, 115.9, 115.7, 74.0, 71.4, 63.2, 58.6, 31.1, 23.9; HRMS (ESI) m/z calcd for $C_{33}H_{25}C_{l3}FN_3NiO_3^+$ $[M + H]^+$ 694.0377, found 694.0357. The dr was determined by HPLC with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (H_2O/MeOH = 25/75, λ = 254 nm, 1.0 mL/min). t_R (major diastereomer) = 13.077 min, t_R (minor diastereomer) = 23.758 min, 94:6 dr.

Ni(II)−(S)-N-(2-benzoyl-4-chlorophenyl)-1-(3,4-dichlorobenzyl)-pyrrolidine-2-carboxamide/(S)-2-aminopropanoic acid Schiff base complex ***7r:*** brown solid; mp 271−272 °C; $[\alpha]^{25}_D$ = +2599 (c 0.042, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, J = 2.0 Hz, 1H), 8.02 (d, J = 9.3 Hz, 1H), 7.80 (dd, J = 8.2, 2.1 Hz, 1H), 7.58−7.50 (m, 2H), 7.47 (ddd, J = 7.5, 4.4, 1.6 Hz, 1H), 7.38 (d, J = 8.1 Hz, 1H), 7.28 (dd, J = 3.6, 1.9 Hz, 1H), 7.11 (dd, J = 9.3, 2.6 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 6.57 (d, J = 2.5 Hz, 1H), 4.31 (d, J = 12.5 Hz, 1H), 3.90 (q, J = 7.0 Hz, 1H), 3.79−3.65 (m, 1H), 3.57 (dd, J = 10.1, 6.3 Hz, 1H), 3.38 (dd, J = 11.2, 5.6 Hz, 1H), 3.22 (d, J = 12.5 Hz, 1H), 2.74−2.54 (m, 2H), 2.32−2.22 (m, 1H), 2.11−2.02 (m, 1H), 1.58 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.2, 180.1, 170.0, 140.4, 135.0, 133.7, 133.7, 133.5, 132.7, 132.4, 132.1, 131.2, 130.3, 130.1, 129.5, 129.3, 127.6, 127.3, 127.3, 125.9, 124.4, 71.4, 67.0, 63.0, 58.6, 31.0, 24.2, 22.0; HRMS (ESI) m/z calcd for $C_{28}H_{25}Cl_3N_3NiO_3^+$ $[M + H]^+$ 614.0315, found 614.0309. The dr was determined by HPLC with an Extend XDB-C18 column (5 μm, 4.6 × 150 mm) (H_2O/MeOH = 15/85, λ = 254 nm, 1.0 mL/min): t_R (major diastereomer) = 3.923 min, t_R (minor diastereomer) = 5.250 min, 98:2 dr.

Ni(II)−(S)-N-(2-benzoyl-4-chlorophenyl)-1-(3,4-dichlorobenzyl)-pyrrolidine-2-carboxamide/(R)-2-aminopropanoic acid Schiff base complex ***8r:*** brown solid; mp 241−242 °C; $[\alpha]^{25}_D$ = −2029 (c 0.026, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, J = 9.4 Hz, 1H), 8.41 (s, 1H), 7.82 (d, J = 8.3 Hz, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.52 (s, 3H), 7.21−7.12 (m, 2H), 7.03 (d, J = 5.5 Hz, 1H), 6.67 (d, J = 1.6 Hz, 1H), 4.32−4.20 (m, 2H), 3.90 (q, J = 6.9 Hz, 1H), 3.56 (t, J = 6.7 Hz, 81H), 3.23 (d, J = 12.9 Hz, 1H), 2.72−2.51 (m, 2H), 2.27 (dd, J = 13.8, 6.4 Hz, 2H), 2.07−1.95 (m, 1H), 1.42 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.7, 180.8, 170.9, 141.3, 134.3, 134.1, 133.8, 133.5, 133.3, 132.5, 132.5, 131.2, 130.8, 130.2, 129.5, 129.0, 128.1, 126.9, 126.7, 125.7, 125.1, 69.3, 66.9, 60.7, 60.0, 30.4, 23.3, 21.4; HRMS (ESI) m/z calcd for $C_{28}H_{24}Cl_3N_3NiO_3Na^+$ $[M + Na]^+$ 636.0153, found 636.0134. The dr was determined by HPLC with an Extend XDB-C18 column (5 μm, 4.6 × 150 mm) (H_2O/MeOH = 15/85, λ = 254 nm, 1.0 mL/min): t_R (major diastereomer) = 3.812 min, t_R (minor diastereomer) = 5.059 min, 51:49 dr.

(R)-2-Amino-3-(1H-indol-3-yl)propanoic acid·HCl: white solid (221 mg, yield 92%); mp 231−232 °C; $[\alpha]^{25}_D$ = −3.778 (c 1.050, MeOH); ^{1}H NMR (400 MHz, D_2O) δ 7.46 (d, J = 7.9 Hz, 1H), 7.32 (d, J = 8.2 Hz, 1H), 7.12 (s, 1H), 7.07 (t, J = 7.4 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 4.18 (t, J = 6.2 Hz, 1H), 3.26 (qd, J = 15.4, 6.3 Hz, 2H); ^{13}C NMR (101 MHz, D_2O) δ 171.6, 136.2, 126.4, 125.3, 122.1, 119.4, 118.1, 111.9, 106.0, 53.0, 25.6; HRMS (ESI) m/z calcd for $C_{11}H_{13}N_2O_2^+$ $[M + H]^+$ 205.0972, found 205.0975. The ee was determined by HPLC with an Astec CHIROBIOTIC T chiral HPLC column (4.6 mm × 25 cm, 5 μm) (MeOH/H_2O = 90/10, λ = 214 nm, 0.5 mL/min): t_R (major enantiomer) = 21.932 min, t_R (minor enantiomer) = not found, ee > 99%.

(S)-2-Aminopent-4-ynoic acid·HCl: white solid (133 mg, yield 89%); mp 265−266 °C; $[\alpha]^{25}_D$ = +6.700 (c 1.214, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 4.12 (t, J = 5.4 Hz, 1H), 2.90 (ddd, J = 5.2, 2.7, 1.4 Hz, 2H), 2.51 (t, J = 2.7 Hz, 1H); ^{13}C NMR (101 MHz, CD_3OD) δ 170.1, 77.0, 75.1, 52.5, 21.2; HRMS (ESI) m/z calcd for $C_5H_8NO_2^+$ $[M + H]^+$ 114.0550, found 114.0547. The ee was determined by HPLC with an Astec CHIROBIOTIC T chiral HPLC column (4.6 mm × 25 cm, 5 μm) (MeOH/H_2O = 90/10, λ = 214 nm, 0.5 mL/min): t_R (major enantiomer) = 15.848 min, t_R (minor enantiomer) = not found, ee > 99%.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02707.

LC/MS and HPLC experimental data; ^{1}H and ^{13}C NMR spectra (PDF)

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AUTHOR INFORMATION

Corresponding Authors

*E-mail: vadym.soloshonok@ehu.es.
*E-mail: hliu@simm.ac.cn.

Notes

The authors declare no competing financial interest.

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