ChemPubSoc Europe

DOI: 10.1002/ejoc.201800120

EurJOC European Journal of Organic Chemistry

Full Paper

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# Configurationally Stable (*S*)- and (*R*)-α-Methylproline-Derived Ligands for the Direct Chemical Resolution of Free Unprotected β³-Amino Acids

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**Abstract:** Reported herein is a chemical method for the direct resolution of unprotected racemic β-substituted-β-amino acids (β³-AAs) that uses specially designed, stable, and recyclable α-methylproline-derived chiral ligands. The versatility of this methodology is unmatched by biocatalytic approaches. The method shows a broad synthetic generality for various aryl- or alkyl-substituted β³-AAs, and the new nonracemizable ligands can be accessed readily. Furthermore, the presented method produces an excellent stereochemical outcome and has a fully recyclable source of chirality, and the reaction conditions are operationally simple and convenient. The procedure has also been successfully applied to the scalable synthesis of the anti-HIV drug maraviroc.

## Introduction

Tailor-made amino acids (AAs)[1] are in extremely high demand in nearly every sector of the healthcare industry.[2] In particular, unnatural β³-AAs and their analogs[3] are becoming an increasingly common structural feature in newly developed pharmaceuticals.[4] In this regard, the availability of structurally varied β³-AAs has become a critically important rate-determining factor in the exploration of the rich biochemistry and applications of β³-AAs. For practicality, biocatalyst-based approaches[5] are usually more commercially viable than purely chemical methods.[3,6] Furthermore, the resolution of racemic β³-AAs might be the most economically feasible approach, as we can readily obtain the corresponding racemates through the Rodionov reaction.[7] However, previously developed chemical[8] or chemoenzymatic[9] methods do not work for free β³-AAs that require chemical protection steps.

Owing to our interest in the synthetic methodology for α-[10] and β-AAs,[11] we initiated a research project on the resolution of unprotected AAs through the application of $Ni^{II}$ complexes.[12] As detailed in Scheme 1, free racemic α-AAs **2** react readily under rather mild conditions with the tridentate ligand (*R*)- or (*S*)-**1** to form the tetracoordinate $Ni^{II}$ complex (*R*,2*R*)-**3**.[13] This transformation is a multistep process that results in the in situ formation of the ester/Schiff base to protect the free α-AA-**2**.[12] The absolute configuration of the α-AA residue in (*R*,2*R*)-**3** is thermodynamically controlled,[14] and the ratio usually exceeds 98:2. The disassembly of purified complexes (*R*,2*R*)-**3** is performed under acidic conditions[12] to afford the target α-AAs (*R*)-**2**, along with a nearly quantitative recovery of the stereochemically intact ligand **1**. This process represents a true chemical resolution that allows the transformation of all of the starting racemate into the target enantiomer. In sharp contrast, the reactions of racemic β³-AAs **4** with ligand (*R*)-**1** require relatively harsh conditions, most likely because of the unfavorable seven-membered chelated ring of the β³-AA in the $Ni^{II}$ complex (*R*,2*S*)-**5**. Nevertheless, if strong bases such as NaH, KO*t*Bu, or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) are used, ligand **1** reacts preferentially with one of the enantiomers of β³-AAs **4** to enable the resolution process. For example, (*R*)-**1** reacts relatively enantioselectively with (*S*)-**4** (R = aryl) to afford complexes (*R*,2*S*)-**5** in yields of up to 95 % and diastereomeric ratios of more than 90:10.[13a] Through further work on these reactions, we found that the stereochemical integrity of ligands **1** has an innate limit. Thus, when the reactions were conducted under slightly more forceful conditions, for example, at increased temperatures or for longer reaction times, we detected a noticeable degree of racemization at the proline stereogenic center. For instance, in these cases, the routine control of the enantiomeric purity of the recovered ligand **1** showed between 2–13 % racemization (Supporting Information, Table S1, Figures S1–S6). Hence, it became clear that the structure of ligand **1** is rather incompatible with the harsh conditions required for

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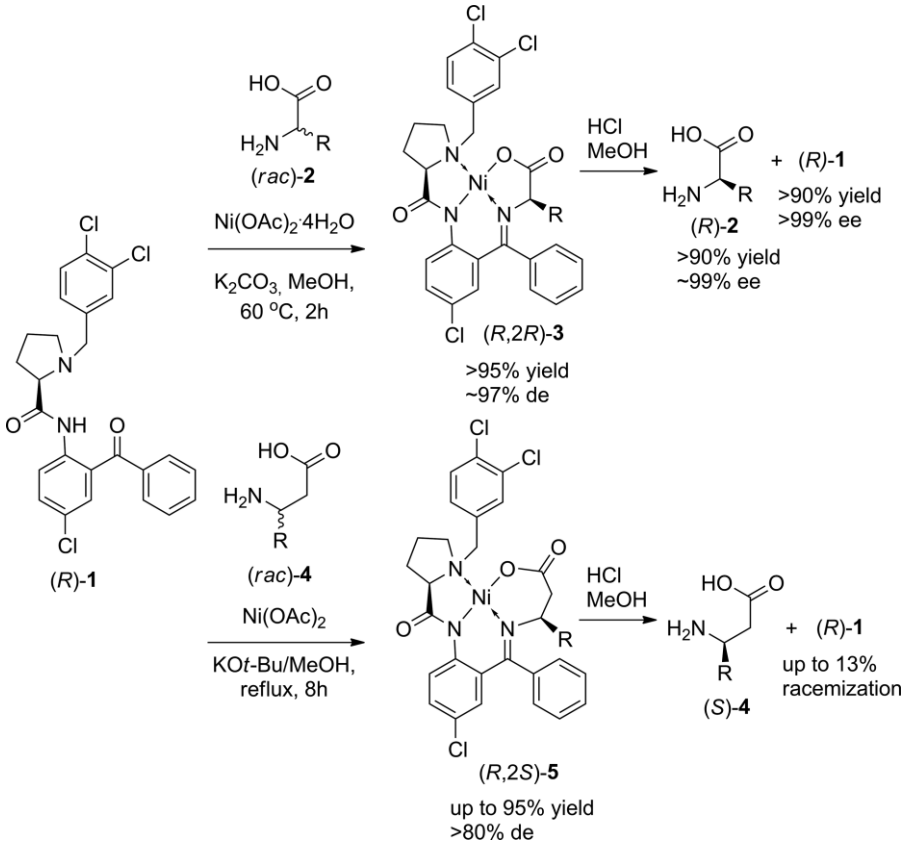
*Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201800120.*




Scheme 1. Application of proline-derived ligands (*R*)- or (*S*)-**1** for the chemical resolution of free, unprotected α-AAs and the kinetic resolution of $\beta^3$-AAs.

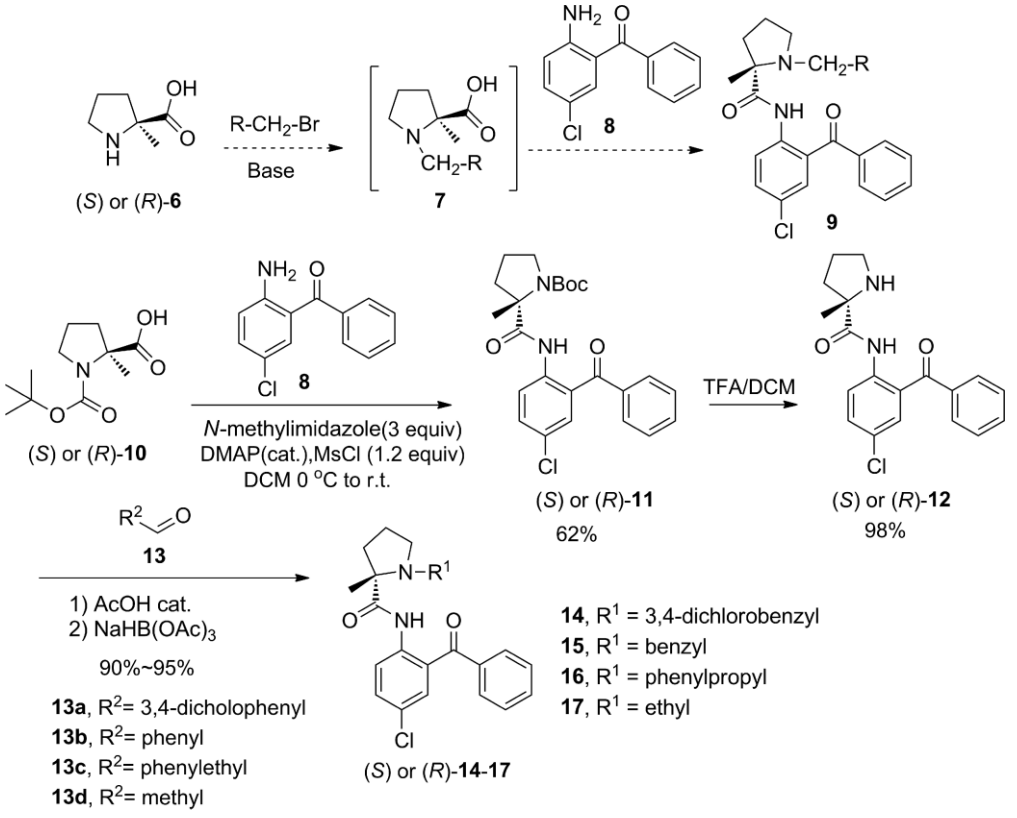
the reactions with β-AAs. In this work, we present a solution to this problem through the design of a new family of ligands based on the nonracemizable α-methylproline. We disclose a new synthetic approach that allows structural diversity in the designed ligands, the evaluation of their stereochemical performances, and their application for the chemical resolution of β-substituted-β-amino acids. We also demonstrate the practical use of the developed procedure for the preparation of maraviroc, an antiretroviral drug for the treatment of HIV.[15]

## Results and Discussion

The established synthetic procedure for the large-scale preparation of proline ligands (*S*)- and (*R*)-**1** includes the *N*-benzylation of free proline, followed by a reaction with an *o*-aminobenzophenone derivative.[16] Quite surprisingly, attempts to reproduce this process with α-methylproline (**6**, Scheme 2) failed. Thus, the reaction of **7** with benzyl or 3,4-dichlorobenzyl bromide did not produce the expected *N*-benzylated product **9**. This problem was largely unanticipated but can be reasonably rationalized by the presence of the quaternary, *tert*-butyl-like substituent, which renders the corresponding $S_N2$ substitution virtually impossible.[17]

Thus, facing the need for the development of an entirely new synthetic approach to α-methylproline-derived ligands, we explored a series of options and focused on the cost, structure, and potential process scalability. Ultimately, as shown in Scheme 2, we implemented a procedure based on *N*-Boc-α-methylproline (**10**, Boc = *tert*-butyloxycarbonyl), which is commercially available in both the (*S*) and the (*R*) enantiomeric forms. As the amino group in **10** is Boc-protected, we formed the amide bond by the mixed-anhydrate method. Although the consumption of both starting materials **8** and **10** was almost complete, the target product **11** was isolated in a somewhat low yield of 62 %, most probably because of the vulnerability of the Boc protecting group to the slightly acidic reaction medium. However, we found this reaction quite reliable, reproducible, and operationally convenient for scaling up and, therefore, satisfactory. On the other hand, the advantage of Boc-protection is that the deprotection of **11** is almost quantitative and affords **12** in an average 98 % yield without the need for additional purification. The final stage of this process is a reductive amination, which is a convenient and well-researched reaction that shows tolerance to the steric bulk of the α-methylproline moiety. It was rather stimulating to realize that the necessity to develop a new procedure can result in an exciting synthetic bonus. Thus, the reductive amination reaction with **12** and aldehydes **13** showed some exceptional generality and allowed the preparation of various *N*-substituted derivatives under the same standard reaction conditions. Taking advantage of this methodological opportunity, we synthesized a series of new ligands **14**–**17** bearing alkyl and benzyl substituents.

As we had reliable access to the α-methylproline-derived ligands **14**–**17**, we decided to briefly explore their reactivity and

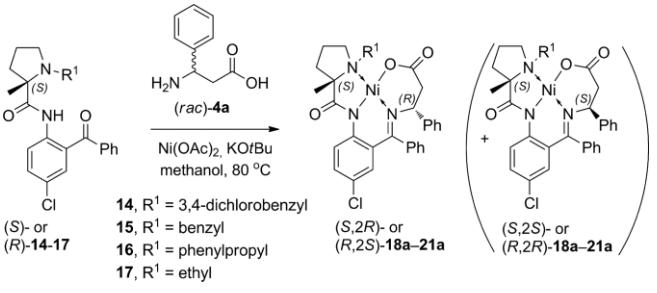



Scheme 2. Synthetic approach to the family of α-methylproline-derived ligands (*S*)- and (*R*)-**14**–**17**.

stereocontrolling properties, as the known data relevant to the reactions with $\beta^3$-AAs are limited solely to the reactions of *N*-3,4-dichlorobenzyl ligands such as **1**. To this end, we conducted a series of reactions between racemic $\beta^3$-AA **4a** and ligands **14**–**17**, and selected data are collected in Table 1.

It follows from the data presented in Table 1, Entries 1–4 that the nature of the substituent on the proline nitrogen atom does not have a substantial effect on the stereochemical outcome of the reaction. Thus, the chemical yields of the isolated nickel complexes were in the range 54 (Table 1, Entry 2) to 83 % (Table 1, Entry 4), and the diastereomeric ratios were even closer and varied between 95:5 (Table 1, Entry 1) and 88:12 (Table 1, Entry 3). The observed subtle differences can be attributed to the steric effects of the substituent on the stabilities of the major and minor products under strongly basic conditions that promote the hydrolysis and oxidation of the $Ni^{II}$ complexes.[18] Consequently, drawing from our experience, we selected the *N*-ethyl ligand **17** for a more detailed study. Our choice was based not only on the optimal yield and diastereoselectivity obtained with **17** (Table 1, Entry 4) but also on its lowest cost and molecular weight and as well as its attractive physicochemical properties such as its solubility and the crystallinity of the target products **21**. The options for the solvent and base for these reactions are rather limited (Table S2), and we conducted a brief study to optimize the stoichiometry. A comparable yield was obtained in the reaction when stoichiometric amounts of ligand **17** and $Ni(OAc)_2$ were used (Table 1, Entry 4 vs. 5). On the other hand, the reduction of the amount of **4a** from 3 equiv. to only 1 equiv. resulted in a gradual decrease in the chemical yield (Table 1, Entry 5 vs. 6 and 7). The absolute configuration of the major diastereoisomer (*R*,2*S*)-**21a** was de-

Table 1. Chemical resolution of β-phenyl-β-alanine **4a** with new chiral ligands **14**–**17**.



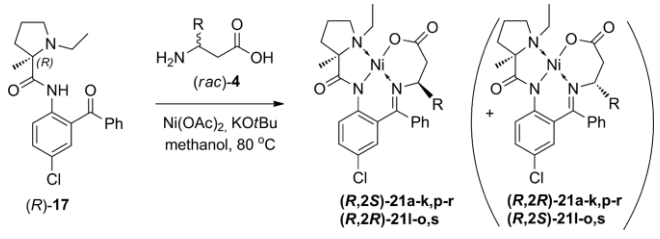

| Entry | Ligand | $Ni^{II}$ complex | Yield [%][b] | *dr*[c] |
|---|---|---|---|---|
| 1[a] | (*S*)-**14** | (*S*)(2*R*)-**18a** | 65 | 95:5 |
| 2[a] | (*S*)-**15** | (*S*)(2*R*)-**19a** | 54 | 93:7 |
| 3[a] | (*S*)-**16** | (*S*)(2*R*)-**20a** | 77 | 88:12 |
| 4[a] | (*R*)-**17** | (*R*)(2*S*)-**21a** | 83 | 93:7 |
| 5[d] | (*R*)-**17** | (*R*)(2*S*)-**21a** | 87 | 93:7 |
| 6[e] | (*R*)-**17** | (*R*)(2*S*)-**21a** | 66 | 93:7 |
| 7[f] | (*R*)-**17** | (*R*)(2*S*)-**21a** | 34 | 93:7 |

[a] Ligand (0.1 mmol), (*rac*)-**4a** (0.3 mmol), anhydrous $Ni(OAc)_2$ (0.2 mmol), and KO*t*Bu (1 mmol) in methanol (2 mL) were heated under reflux at 80 °C for 8 h. [b] The combined yield of the isolated major and minor nickel complexes. [c] The *dr* values were determined by HPLC analysis of the crude reaction mixtures. [d] The same conditions as [a], except $Ni(OAc)_2$ (0.1 mmol) was used. [e] The same conditions as [a], except (*rac*)-**4a** (0.2 mmol) was used. [f] The same conditions as [a], except (*rac*)-**4a** (0.1 mmol) was used.

termined by its disassembly and the isolation of enantiomerically pure β-AA (*S*)-**4a**.[19]

The optimized reaction conditions (Table S2) presented in Table 1, Entry 5 were used to study the substrate generality of this method for the preparation of various enantiomerically pure $\beta^3$-AAs through the reactions of ligand **17** with the corresponding racemic $\beta^3$-AAs **4**. The main results are collected in Table 2.

Table 2. Substrate generality study of the reaction of ligand **17** with racemic $\beta^3$-AAs **4**.[a]




| Entry | $Ni^{II}$ complex | R | Yield [%][b] | *dr*[c] |
|---|---|---|---|---|
| 1[d] | (*R*)(2*S*)-**21a** | phenyl | 87 | 93:7 |
| 2 | (*R*)(2*S*)-**21b** | 2-F-phenyl | 92 | 89:11 |
| 3 | (*R*)(2*S*)-**21c** | 4-Cl-phenyl | 93 | 92:8 |
| 4 | (*R*)(2*S*)-**21d** | 3,4-diOMe-phenyl | 93 | 93:7 |
| 5 | (*R*)(2*S*)-**21e** | 4-isopropylphenyl | 92 | 93:7 |
| 6 | (*R*)(2*S*)-**21f** | 4-OMe-phenyl | 93 | 88:12 |
| 7 | (*R*)(2*S*)-**21g** | 3-OMe-phenyl | 90 | 90:10 |
| 8 | (*R*)(2*S*)-**21h** | 3-$CF_3$-phenyl | 50 | 96:4 |
| 9 | (*R*)(2*S*)-**21i** | 3-pyridyl | 80 | 98:2 |
| 10 | (*R*)(2*S*)-**21j** | 2-thienyl | 95 | 98:2 |
| 11 | (*R*)(2*S*)-**21k** | 2-naphthyl | 91 | 92:8 |
| 12 | (*R*)(2*R*)-**21l** | methyl | 87 | 90:10 |
| 13 | (*R*)(2*R*)-**21m** | ethyl | 94 | 96:4 |
| 14 | (*R*)(2*R*)-**21n** | *n*-butyl | 97 | 94:6 |
| 15 | (*R*)(2*R*)-**21o** | isobutyl | 91 | 92:8 |
| 16 | (*R*)(2*S*)-**21p** | isopropyl | 76 | 95:5 |
| 17 | (*R*)(2*S*)-**21q** | cyclopropyl | 93 | 98:2 |
| 18 | (*R*)(2*S*)-**21r** | cyclohexyl | 85 | 94:6 |
| 19 | (*R*)(2*R*)-**21s** | 2,4,5-trifluorobenzyl | 87 | 95:5 |

[a] Reaction conditions: (*R*)-**17** (0.1 mmol), (*rac*)-**4** (0.3 mmol), anhydrous $Ni(OAc)_2$ (0.1 mmol), and KO*t*Bu (1 mmol) in methanol (2 mL) were heated under reflux at 80 °C for 8 h. [b] The combined yield of the isolated products (*R*)(2*S*)-**21** and (*R*)(2*R*)-**21**. [c] The *dr* values were determined by HPLC analysis of the crude reaction mixtures. [d] Large-scale synthesis with (*R*)-**17** (13.48 mmol).

For the series of β-phenyl-substituted racemates **4a**–**4h**, the corresponding diastereomers **21a**–**21h** were obtained with average chemical yields of ca. 90 % and strong diastereomeric preferences of more than 90:10 on average (Table 2, Entries 1–8). The presence of halogen atoms (Table 2, Entries 2 and 3) or alkyl (Table 2, Entry 5), methoxy (Table 2, Entries 4, 6, and 7), and trifluoromethyl (Table 2, Entry 8) groups did not show any noticeable influence on the stereochemical outcomes of these reactions. Racemic $\beta^3$-AAs **4i**–**4k** containing heterocyclic moieties, such as pyridyl (Table 2, Entry 9), thienyl (Table 2, Entry 10), or naphthyl (Table 2, Entry 11) groups, reacted with ligand **17** without any complications to furnish products **21i**–**21k** with excellent yields and diastereomeric ratios. In the aliphatic series, we first studied racemates **4l**–**4n** bearing straight chains such as methyl (Table 2, Entry 12), ethyl (Table 2, Entry 13), and *n*-butyl (Table 2, Entry 14) groups, all of which reacted readily with ligand **17** to afford diastereomers **21l**–**21n** with excellent stereochemical outcomes. Importantly, $\beta^3$-AA side chains with increased steric bulk (Table 2, Entries 15–18) were perfectly compatible with the formation of the corresponding $Ni^{II}$ complexes, and derivatives **21o**–**21r** (Table 2, Entries 15–18) were prepared with the excellent yields and diastereomeric preferences generally observed in these reactions. Finally, we prepared compound **21s**, which features a pharmacophoric 2,4,5-trifluorobenzyl group, in an isolated yield of 87 % and a diastereomeric ratio (*dr*) of 95:5 (Table 2, Entry 19). One might agree that these examples convincingly underscore the rather wide generality of this approach for the preparation of various enantiomerically pure β-substituted-β-amino acids from unprotected racemic $\beta^3$-AA **4**.

To gain a more detailed view of the process, we conducted analysis (HPLC) of the progress and diastereoselectivity of the reaction of (*R*)-**17** with (*rac*)-**4a** over time (Figure 1, Table S3).

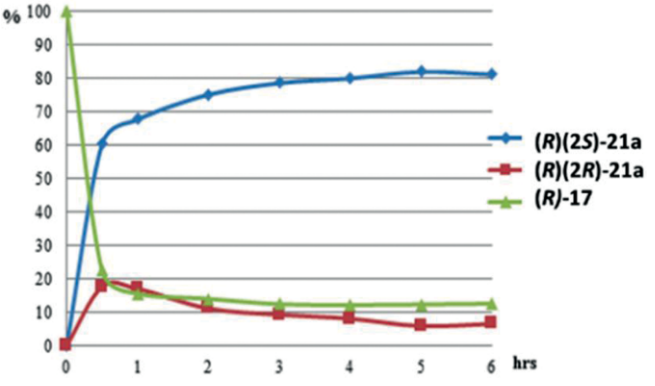
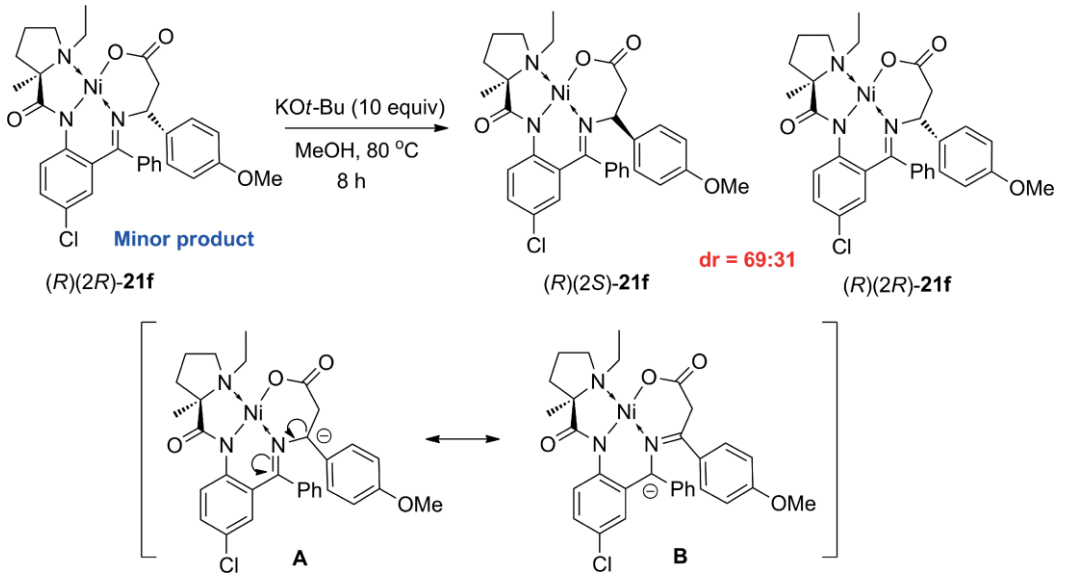



Figure 1. Progress and diastereoselectivity of the reaction of (*R*)-**17** with (*rac*)-**4a** over time.

As shown in Figure 1, (*R*)-**17** reacts preferentially with the (*S*)-enantiomer of AA **4a** to afford diastereomers (*R*)(2*S*)-**21a**/(*R*)(2*R*)-**21a** in ca. 60:20 ratio at the point of 80 % consumption. The following observations are quite interesting and important for understanding the process under study. First, the proportion of the minor diastereomer (*R*)(2*R*)-**21a** reaches ca. 20 % in the early stages of the reaction and then gradually decreases to less than 10 %. Second, the amount of the major product (*R*)(2*S*)-**21a** progressively increases to over 80 %. Third, the minor diastereomer (*R*)(2*R*)-**21a** is probably thermodynamically unstable and undergoes gradual epimerization into the major product (*R*)(2*S*)-**21a**. To validate this assumption, we conducted a special epimerization experiment, as presented in Scheme 3.

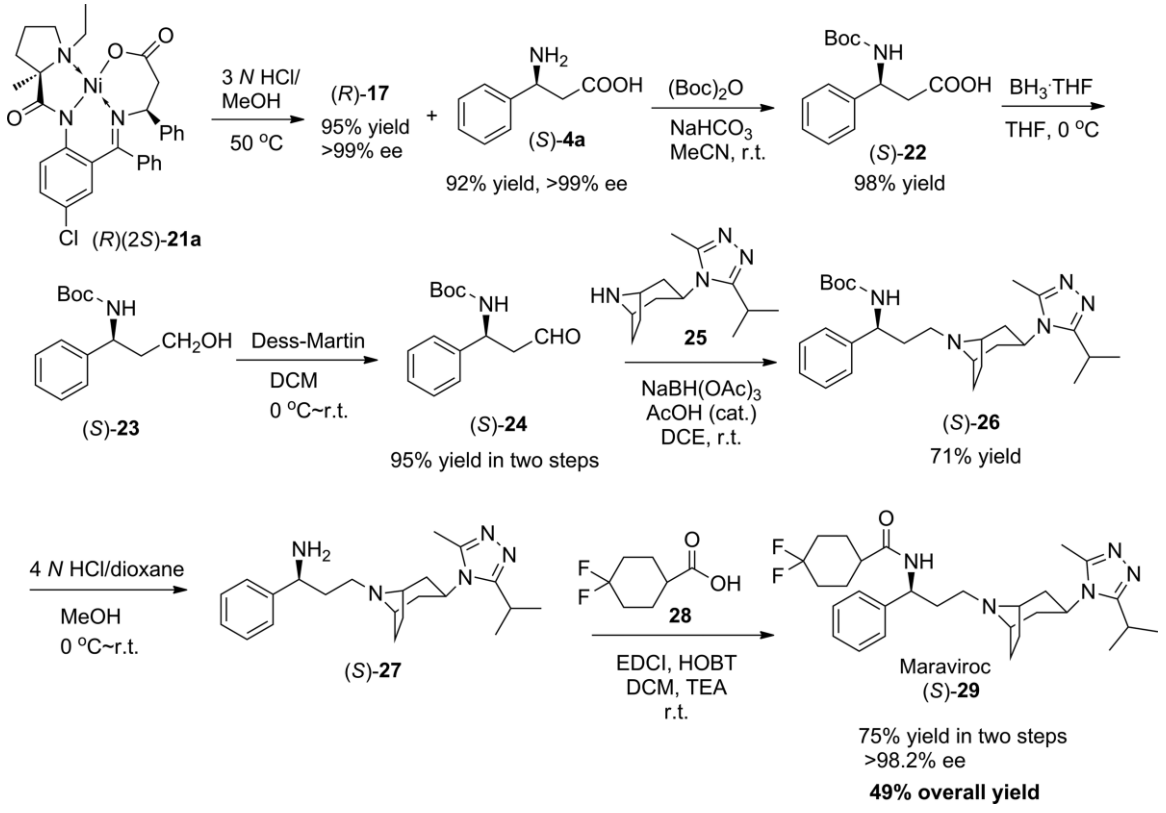
Thus, the minor product (*R*)(2*R*)-**21f** was obtained in diastereomerically pure form by column chromatography and exposed to the standard reaction conditions. As is evident form this epimerization experiment, minor diastereomer (*R*)(2*R*)-**21f** is indeed thermodynamically unstable and undergoes gradual transformation into the major product (*R*)(2*S*)-**21f**. It is quite reasonable to assume that the deprotonated β-carbanion **A** can be efficiently stabilized through the formation of the dibenzylic anion **B**, which might be further stabilized by the delocalization of the negative charge onto two phenyl rings. This mode of β-




Scheme 3. Epimerization of the thermodynamically unstable minor diastereomer (*R*)(2*R*)-**21f** to the major diastereomer (*R*)(2*S*)-**21f**.

anion stabilization can explain the relatively high C–H acidity of the β-carbon atom and the concomitant epimerization. One may agree that all of these data point to the possibility of the dynamic resolution that we observe in this process.

In the final part of this work, we disassembled the major diastereomer (*R*)(2*S*)-**21a** and used the isolated enantiomerically pure $\beta^3$-AA **4a** for the synthesis of the antiretroviral drug maraviroc.[20] To this end, the synthesis of the major diastereomer (*R*)(2*S*)-**21a** was repeated on a large scale (13.48 mmol), and it was purified to a diastereomerically pure state by column chromatography. As shown in Scheme 4, the disassembly of $Ni^{II}$ complex (*R*)(2*S*)-**21a** was conducted under the usual acidic conditions to afford the target AA (*S*)-**4a**. After the Boc-protection of (*S*)-**4a** in quantitative yield, acid (*S*)-**22** was subjected to a reduction reaction with $BH_3$·THF (THF = tetrahydrofuran), followed by Dess–Martin oxidation to obtain aldehyde (*S*)-**24** in




Scheme 4. Disassembly of major diastereomer (*R*)(2*S*)-**21a**, isolation of free enantiomerically pure $\beta^3$-AA **4a**, and the synthesis of maraviroc (*S*)-**29**.

an overall yield of 95 %. Then, the reductive amination reaction between (*S*)-**24** and amine **25** was conducted to afford (*S*)-**26** in 71 % yield. Finally, after Boc-deprotection, the condensation between amine (*S*)-**27** and acid **28** in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) and hydroxybenzotriazole (HOBT) was performed to successfully afford maraviroc (*S*)-**29** in 75 % yield with high enantiomeric purity (>98.2 % *ee*).

## Conclusions

We have developed a purely chemical method for the resolution of unprotected racemic $\beta^3$-AAs that uses specially designed, stable, and recyclable ligands. The new ligands have better thermodynamic stabilities than those we used previously. The methods showed a broad synthetic generality for various substituted $\beta^3$-AAs. Furthermore, the presented method has an excellent stereochemical outcome, a fully recyclable source of chirality, and involves operationally simple and convenient reaction conditions that allow its scalability. Furthermore, we successfully applied the method to obtain the essential intermediate $\beta^3$-AA in the synthesis of the anti-HIV drug maraviroc in an overall yield of 49 %, which possibly makes it of great interest to industry.

## Experimental Section

**General Information:** The commercially available chemicals were used without further purification. Anhydrous nickel acetate was prepared by heating reagent-grade nickel acetate tetrahydrate for 2 h at 110 °C under vacuum. The $^1$H and $^{13}$C NMR spectra were recorded at 400 MHz or 500 MHz with a Bruker AV400 instrument. The chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. The proton coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). The high-resolution mass spectroscopy (HRMS) was performed with a Micromass Ultra Q-TOF spectrometer. The determination of the *dr* values was performed by HPLC or LC–MS analysis with an Agilent 1260 Infinity spectrometer. The optical rotations were measured with a 1 mL cell with a 1 dm path length with an Autopol VI automatic polarimeter, and the $[\alpha]_{20}^{D}$ values are reported as follows (*c* [g/100 mL], solvent).

### General Procedure

***tert*-Butyl (*S*)-2-[(2-Benzoyl-4-chlorophenyl)carbamoyl]-2-methylpyrrolidine-1-carboxylate [(*S*)-11]:** (*S*)-1-(*tert*-Butoxycarbonyl)-2-methylpyrrolidine-2-carboxylic acid (**10**, 10 g, 43.62 mmol), 1-methyl-1*H*-imidazole (10.33 mL, 130.85 mmol), and 4-dimethylaminopyridine (DMAP, cat.) were dissolved in anhydrous dichloromethane (DCM, 200 mL), and the mixture was cooled to 0 °C under $N_2$ protection. Methanesulfonyl chloride (MsCl, 4.05 mL, 52.34 mmol) was added with a syringe. After 15 min, a solution of (2-amino-5-chlorophenyl)(phenyl)methanone (**8**, 11.12 g, 47.98 mmol) in DCM (40 mL) was added with a syringe. The reaction mixture was stirred at 5 °C overnight. Once the condensation was complete, as determined by TLC (petroleum ether/ethyl ester 8:1), saturated $NH_4Cl$(aq) was added to the reaction mixture, which was extracted three times with $CH_2Cl_2$. The combined organic layers were dried with $Na_2SO_4$ and then concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, EtOAc/hexane 1:20) to give product (*S*)-**11** (12 g, 62 % yield). $^1$H NMR {500 MHz, [$D_6$]dimethyl sulfoxide ([$D_6$]DMSO)}: $\delta$ = 10.39 (s, 1 H), 8.02 (d, *J* = 8.9 Hz, 1 H), 7.76–7.71 (m, 1 H), 7.70–7.63 (m, 3 H), 7.54 (t, *J* = 7.7 Hz, 2 H), 7.46 (d, *J* = 2.6 Hz, 1 H), 3.64–3.50 (m, 1 H), 3.42–3.38 (m, 1 H), 1.79–1.62 (m, 4 H), 1.39 (s, 3 H), 1.26 (s, 9 H) ppm.

**(*S*)-*N*-(2-Benzoyl-4-chlorophenyl)-2-methylpyrrolidine-2-carboxamide [(*S*)-12]:** (*S*)-**11** (8.5 g, 19.19 mmol) was dissolved in DCM (20 mL), and then trifluoroacetic acid (TFA, 20 mL) was added. The reaction mixture was stirred for 4 h and distilled in vacuo to give (*S*)-*N*-(2-benzoyl-4-chlorophenyl)-2-methylpyrrolidine-2-carboxamide [(*S*)-**12**] as a light yellow solid (6.5 g, yield 98 %). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 11.95 (s, 1 H), 8.63 (d, *J* = 8.9 Hz, 1 H), 7.78–7.72 (m, 2 H), 7.66–7.56 (m, 1 H), 7.54–7.44 (m, 4 H), 3.16 (dt, *J* = 10.6, 6.4 Hz, 1 H), 3.00–2.91 (m, 1 H), 2.35–2.24 (m, 1 H), 1.82–1.63 (m, 4 H), 1.46 (s, 3 H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 196.9, 177.4, 137.9, 137.9, 133.2, 132.9, 131.8, 130.1, 128.5, 127.3, 126.7, 122.8, 67.4, 47.2, 38.1, 26.5, 25.8 ppm.

**(*S*)-*N*-(2-Benzoyl-4-chlorophenyl)-1-(3,4-dichlorobenzyl)-2-methylpyrrolidine-2-carboxamide [(*S*)-14]:** (*S*)-**12** (5 g, 14.58 mmol), 3,4-dichlorobenzaldehyde (**13a**, 2.81 g, 16.04 mmol) were dissolved in 1,2-dichloroethane (DCE, 15 mL), and AcOH (cat. amount) was added. The resulting mixture was stirred at room temperature for 0.5 h. Sodium triacetoxyborohydride (4.64 g, 21.88 mmol) was added, and the solution was stirred overnight. The reaction was terminated with $NaHCO_3$ (20 mL). The mixture was extracted with dichloromethane (10 mL × 3). The combined organic layers were dried with $Na_2SO_4$, concentrated, and purified by silica gel column chromatography (petroleum ether/ethyl acetate 4:1) to give the product (*S*)-**14** as a white solid (7 g, yield 95 %). M.p. 110–111 °C. $[\alpha]_D^{20}$ = –22.54 (*c* = 0.1, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 11.76 (s, 1 H), 8.65 (d, *J* = 8.7 Hz, 1 H), 7.86–7.40 (m, 8 H), 7.22–7.13 (m, 2 H), 3.79 (d, *J* = 13.5 Hz, 1 H), 3.39 (d, *J* = 13.6 Hz, 1 H), 3.15 (t, *J* = 7.4 Hz, 1 H), 2.39 (dd, *J* = 15.9, 7.9 Hz, 1 H), 2.23–2.14 (m, 1 H), 1.95–1.75 (m, 3 H), 1.39 (s, 3 H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 197.1, 176.5, 139.2, 138.4, 137.9, 133.4, 132.9, 132.3, 132.2, 130.8, 130.6, 130.1, 130.1, 128.5, 127.9, 127.2, 125.9, 122.8, 68.8, 53.5, 51.3, 40.1, 22.7, 16.4 ppm. MS (ESI+, APCI): *m/z* = 501.1. HRMS (ESI): calcd. for $C_{26}H_{23}Cl_3N_2O_2^+$ $[M + H]^+$ 501.0898; found 501.0900.

**(*S*)-*N*-(2-Benzoyl-4-chlorophenyl)-1-benzyl-2-methylpyrrolidine-2-carboxamide [(*S*)-15]:** White solid (3 g, yield 96 %). M.p. 72–73 °C. $[\alpha]_D^{20}$ = –127.1 (*c* = 0.118, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 11.52 (s, 1 H), 8.58 (d, *J* = 8.9 Hz, 1 H), 7.78–7.73 (m, 2 H), 7.66–7.60 (m, 1 H), 7.53–7.43 (m, 4 H), 7.35–7.28 (m, 2 H), 7.15–7.03 (m, 3 H), 3.79 (d, *J* = 13.0 Hz, 1 H), 3.40 (d, *J* = 13.1 Hz, 1 H), 3.18–3.04 (m, 1 H), 2.45–2.35 (m, 1 H), 2.20–2.10 (m, 1 H), 1.86–1.70 (m, 3 H), 1.39 (s, 3 H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 196.7, 176.9, 138.9, 138.0, 137.9, 133.1, 133.1, 131.6, 130.2, 128.7, 128.3, 127.4, 127.0, 127.0, 123.0, 68.7, 54.4, 51.3, 40.4, 22.9, 16.5 ppm. MS (ESI+, APCI): *m/z* = 433.1. HRMS (ESI): calcd. for $C_{26}H_{25}ClN_2O_2^+$ $[M + H]^+$ 433.1677; found 433.1682.

**(*S*)-*N*-(2-Benzoyl-4-chlorophenyl)-2-methyl-1-(3-phenylpropyl)pyrrolidine-2-carboxamide [(*S*)-16]:** Yellow oil (4 g, yield 92 %). $[\alpha]_D^{20}$ = –95.0 (*c* = 0.1, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 11.60 (s, 1 H), 8.57 (d, *J* = 9.0 Hz, 1 H), 7.73 (d, *J* = 7.6 Hz, 2 H), 7.60 (t, *J* = 7.4 Hz, 1 H), 7.52–7.40 (m, 4 H), 7.17–7.05 (m, 3 H), 6.96 (d, *J* = 6.7 Hz, 2 H), 3.41–3.31 (m, 1 H), 2.55–2.33 (m, 5 H), 2.14–2.06 (m, 1 H), 1.93 (s, 1 H), 1.86–1.69 (m, 4 H), 1.24 (s, 3 H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 196.6, 177.4, 142.1, 138.0, 137.9, 133.1, 131.6, 130.2, 128.6, 128.3, 128.3, 127.3, 127.0, 125.7, 123.1, 68.6, 51.5, 49.9, 40.4, 33.9, 30.9, 22.9, 16.3 ppm. MS (ESI+, APCI): *m/z* = 461.1. HRMS (ESI): calcd. for $C_{28}H_{29}ClN_2O_2^+$ $[M + H]^+$ 461.1990; found 461.1989.

**(*R*)-*N*-(2-Benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide [(*R*)-17]:** Yellow solid (10 g, yield 95 %). M.p. 87–88 °C. $[\alpha]_D^{20}$ = +143.5 (*c* = 0.108, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 11.62 (s, 1 H), 8.60 (d, *J* = 9.0 Hz, 1 H), 7.75 (d, *J* = 7.2 Hz, 2 H), 7.61 (t, *J* = 7.4 Hz, 1 H), 7.49 (t, *J* = 7.6 Hz, 3 H), 7.42 (d, *J* = 2.5 Hz, 1 H), 3.39–3.32 (m, 1 H), 2.57–2.45 (m, 1 H), 2.43–2.32 (m, 2 H), 2.14–2.03 (m, 1 H), 1.78–1.67 (m, 3 H), 1.25 (s, 3 H), 1.10 (t, *J* = 7.2 Hz, 3 H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 196.5, 177.5, 137.9, 137.9, 133.1, 133.0, 131.5, 130.1, 128.6, 127.2, 127.1, 122.9, 68.4, 51.0, 43.9, 40.5, 22.8, 16.2, 14.5 ppm. MS (ESI+, APCI): 371.1. HRMS (ESI): calcd. for $C_{21}H_{23}ClN_2O_2^+$ [M + H]$^+$ 371.1521; found 371.1527.

**Nickel(II) (*S*)-(2-Benzoyl-4-chlorophenyl)-1-(3,4-dichlorobenzyl)-2-methylpyrrolidine-2-carboxamide/(*R*)-3-amino-3-phenylpropanoic Acid Schiff Base Complex [(*S*)(2*R*)-18a]:** (*S*)-14 (50.20 mg, 0.10 mmol), 3-amino-3-phenylpropanoic acid (**4a**, 49.57 mg, 0.30 mmol), and $Ni(OAc)_2$ (35.37 mg, 0.20 mmol) were dissolved in MeOH (2 mL), and KO*t*Bu (112.25 mg, 1.00 mmol) was added. The resulting mixture was heated under reflux at 80 °C for 8 h. The reaction was terminated by the addition of ice water with 5 % acetic acid (10 mL). The mixture was extracted with DCM (10 mL × 3). The combined organic layers were dried with $Na_2SO_4$, concentrated for analysis (*dr* = 95:5), and purified to give the crude products **18a** (46 mg, yield 65 %). The crude product was purified by silica gel column chromatography (dichloromethane/methanol 40:1) to give the major pure diastereomer (*S*)(2*R*)-**18a** as a brown solid (45.8 mg, yield 65 %). M.p. 160–162 °C. $[\alpha]_D^{20}$ = +1892.1 (*c* = 0.038, $CHCl_3$). $^1H$ NMR (500 MHz, [$D_4$]methanol): $\delta$ = 8.89 (d, *J* = 2.1 Hz, 1 H), 8.34 (dd, *J* = 8.2, 2.1 Hz, 1 H), 7.83 (d, *J* = 9.2 Hz, 1 H), 7.69–7.42 (m, 10 H), 7.10 (dd, *J* = 9.2, 2.6 Hz, 1 H), 7.06 (d, *J* = 7.7 Hz, 1 H), 6.60 (d, *J* = 2.6 Hz, 1 H), 4.51 (t, *J* = 3.5 Hz, 1 H), 3.59 (d, *J* = 13.3 Hz, 1 H), 3.29–3.21 (m, 2 H), 2.97 (dd, *J* = 17.9, 2.8 Hz, 1 H), 2.92–2.85 (m, 1 H), 2.63 (dd, *J* = 17.9, 4.2 Hz, 1 H), 2.05–1.95 (m, 1 H), 1.86–1.78 (m, 1 H), 1.74–1.55 (m, 2 H), 1.30 (s, 3 H) ppm. $^{13}C$ NMR (125 MHz, [$D_4$]methanol): $\delta$ = 182.6, 176.7, 173.4, 141.9, 140.9, 138.3, 136.1, 134.5, 134.0, 133.7, 133.4, 133.1, 132.5, 132.2, 131.6, 130.8, 130.6, 130.4, 129.7, 128.4, 128.2, 127.8, 126.9, 126.0, 74.8, 63.8, 56.5, 54.6, 42.2, 38.6, 20.5, 18.4 ppm. MS (ESI+, APCI): *m/z* = 704.0. HRMS (ESI): calcd. for $C_{35}H_{30}Cl_3N_3NiO_3^+$ [M + H]$^+$ 704.0779; found 704.0783.

**Nickel(II) (*S*)-*N*-(2-Benzoyl-4-chlorophenyl)-1-benzyl-2-methylpyrrolidine-2-carboxamide/(*R*)-3-amino-3-phenylpropanoic Acid Schiff Base Complex [(*S*)(2*R*)-19a]:** Brown solid (34.3 mg, yield 54 %). M.p. 160–161 °C. $[\alpha]_D^{20}$ = +2822.7 (*c* = 0.044, $CHCl_3$). $^1H$ NMR (500 MHz, [$D_4$]methanol): $\delta$ = 8.52 (d, *J* = 7.6 Hz, 2 H), 7.83–6.98 (m, 15 H), 6.59 (d, *J* = 2.6 Hz, 1 H), 4.52 (t, *J* = 3.6 Hz, 1 H), 3.56 (d, *J* = 13.1 Hz, 1 H), 3.42–3.27 (m, 2 H), 2.97–2.81 (m, 2 H), 2.60 (dd, *J* = 17.8, 4.2 Hz, 1 H), 2.07–1.95 (m, 1 H), 1.85–1.55 (m, 3 H), 1.33 (s, 3 H) ppm. $^{13}C$ NMR (125 MHz, [$D_4$]methanol): $\delta$ = 182.9, 176.8, 173.3, 142.2, 140.9, 137.2, 136.2, 133.4, 132.8, 132.5, 131.5, 130.8, 130.8, 130.6, 130.3, 130.2, 129.6, 129.5, 128.4, 128.3, 127.7, 126.9, 126.5, 75.1, 63.8, 58.3, 54.4, 42.2, 38.5, 20.7, 18.3 ppm. MS (ESI+, APCI): *m/z* = 636.2. HRMS (ESI): calcd. for $C_{35}H_{32}ClN_3NiO_3^+$ [M + H]$^+$ 636.1558; found 636.1573.

**Nickel(II) (*S*)-*N*-(2-Benzoyl-4-chlorophenyl)-2-methyl-1-(3-phenylpropyl)pyrrolidine-2-carboxamide/(*R*)-3-amino-3-phenylpropanoic Acid Schiff Base Complex [(*S*)(2*R*)-20a]:** Brown solid (51.1 mg, yield 77 %). M.p. 135–137 °C. $[\alpha]_D^{20}$ = +2582.6 (*c* = 0.046, $CHCl_3$). $^1H$ NMR (500 MHz, [$D_4$]methanol): $\delta$ = 8.02 (d, *J* = 9.0 Hz, 1 H), 7.73–7.41 (m, 9 H), 7.32–7.05 (m, 7 H), 6.71 (d, *J* = 2.6 Hz, 1 H), 4.58 (t, *J* = 3.4 Hz, 1 H), 3.24 (td, *J* = 12.3, 5.3 Hz, 1 H), 3.12–2.98 (m, 2 H), 2.92 (dd, *J* = 17.8, 2.8 Hz, 1 H), 2.84–2.73 (m, 2 H), 2.69 (dd, *J* = 17.8, 4.2 Hz, 1 H), 2.60–2.46 (m, 1 H), 2.31 (td, *J* = 12.4, 5.0 Hz, 1 H), 2.15 (td, *J* = 12.3, 11.8, 4.3 Hz, 1 H), 1.96–1.84 (m, 1 H), 1.78–1.66 (m, 1 H), 1.61–1.54 (m, 1 H), 1.53–1.43 (m, 1 H), 1.02 (s, 3 H) ppm. $^{13}C$ NMR (125 MHz, [$D_4$]methanol): $\delta$ = 183.3, 177.0, 173.5, 142.5, 142.3, 140.9, 136.1, 134.0, 133.5, 131.6, 131.4, 130.8, 130.6, 130.4, 129.6, 129.4, 129.4, 128.5, 128.4, 127.8, 127.1, 126.9, 126.4, 75.5, 64.0, 55.1, 53.5, 40.9, 38.3, 34.7, 32.0, 21.5, 17.7 ppm. MS (ESI+, APCI): *m/z* = 664.2. HRMS (ESI): calcd. for $C_{37}H_{36}ClN_3NiO_3^+$ [M + H]$^+$ 644.1871; found 664.1884.

**Nickel(II) (*R*)-*N*-(2-benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*S*)-3-amino-3-phenylpropanoic Acid Schiff Base Complex [(*R*)(2*S*)-21a]:** (*R*)-**17** (5 g, 13.48 mmol), 3-amino-3-phenylpropanoic acid (**4a**, 6.68 g, 40.44 mmol), and $Ni(OAc)_2$ (4.77 g, 26.96 mmol), were dissolved in MeOH (200 mL), and KO*t*Bu (15.13 g, 134.82 mmol) was added. The mixture was heated under reflux at 80 °C for 8 h, and then the reaction was terminated by the addition of ice water/5 % acetic acid (200 mL). The mixture was extracted with dichloromethane (100 mL × 3). The combined organic layers were dried with $Na_2SO_4$, concentrated for analysis (*dr* = 93:7), and purified to give the crude products **21a** (6.8 g, yield 87 %). The crude product was further purified by silica gel column chromatography (dichloromethane/methanol 40:1) to give the major pure diastereomer (*R*)(2*S*)-**21a** as a brown solid. M.p. 174–176 °C. $[\alpha]_D^{20}$ = –2531.8 (*c* = 0.044, $CHCl_3$). $^1H$ NMR (400 MHz, [$D_4$]methanol): $\delta$ = 8.18 (d, *J* = 9.1 Hz, 1 H), 7.71–7.46 (m, 9 H), 7.31 (dd, *J* = 9.1, 2.6 Hz, 1 H), 7.20 (d, *J* = 7.6 Hz, 1 H), 6.72 (d, *J* = 2.6 Hz, 1 H), 4.60 (d, *J* = 3.7 Hz, 1 H), 3.23 (td, *J* = 12.3, 11.3, 7.1 Hz, 1 H), 2.93 (dd, *J* = 17.8, 2.8 Hz, 1 H), 2.80 (t, *J* = 9.2 Hz, 1 H), 2.69 (dd, *J* = 17.8, 4.1 Hz, 1 H), 2.40 (dq, *J* = 14.5, 7.3 Hz, 1 H), 2.23 (dq, *J* = 13.8, 6.9 Hz, 1 H), 2.02–1.91 (m, 1 H), 1.87 (t, *J* = 7.3 Hz, 3 H), 1.80–1.45 (m, 3 H), 1.10 (s, 3 H) ppm. $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ = 182.1, 172.8, 171.3, 142.0, 139.8, 134.9, 133.0, 132.9, 130.5, 130.0, 129.9, 129.5, 129.4, 128.5, 127.3, 126.9, 126.6, 125.6, 125.3, 73.3, 63.1, 53.5, 49.1, 40.5, 38.2, 20.3, 17.3, 15.3 ppm. MS (ESI+, APCI): *m/z* = 574.1. HRMS (ESI): calcd. for $C_{30}H_{30}ClN_3NiO_3^+$ [M + H]$^+$ 574.1402; found 574.1405.

**Nickel(II) (*R*)-*N*-(2-Benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*S*)-3-amino-3-(2-fluorophenyl)-propanoic Acid Schiff Base Complex [(*R*)(2*S*)-21b]:** Brown solid (54.5 mg, yield 92 %, *dr* 89:11). M.p. 180–181 °C. $[\alpha]_D^{20}$ = –3281.3 (*c* = 0.048, $CHCl_3$). $^1H$ NMR (400 MHz, [$D_4$]methanol): $\delta$ = 8.21 (d, *J* = 9.1 Hz, 1 H), 7.69–7.50 (m, 5 H), 7.45–7.35 (m, 3 H), 7.30 (dd, *J* = 9.1, 2.6 Hz, 1 H), 7.12–7.05 (m, 1 H), 6.65 (d, *J* = 2.6 Hz, 1 H), 4.71 (t, *J* = 3.3 Hz, 1 H), 3.26–3.14 (m, 1 H), 2.93–2.82 (m, 2 H), 2.73 (dd, *J* = 18.0, 4.4 Hz, 1 H), 2.44–2.33 (m, 1 H), 2.30–2.18 (m, 1 H), 2.04–1.92 (m, 1 H), 1.90–1.78 (m, 4 H), 1.75–1.55 (m, 2 H), 1.09 (s, 3 H) ppm. $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ = 181.5, 171.7, 162.0, 142.1, 135.1, 133.1, 132.9, 131.0, 130.5, 130.2, 129.6, 128.8, 128.7, 128.6, 127.3, 127.3, 126.5, 125.4, 125.1, 124.8, 116.7, 116.5, 73.7, 60.0, 53.2, 49.2, 40.6, 38.9, 20.7, 16.7, 15.2 ppm. MS (ESI+, APCI): *m/z* = 592.2. HRMS (ESI): calcd. for $C_{30}H_{29}ClFN_3NiO_3^+$ [M + H]$^+$ 592.1308; found 592.1311.

**Nickel(II) (*R*)-*N*-(2-Benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*S*)-3-amino-3-(4-chlorophenyl)-propanoic Acid Schiff Base Complex [(*R*)(2*S*)-21c]:** Brown solid (56.5 mg, yield 93 %, *dr* 92:8). M.p. 180–182 °C. $[\alpha]_D^{20}$ = –3512.5 (*c* = 0.04, $CHCl_3$). $^1H$ NMR (500 MHz, [$D_4$]methanol): $\delta$ = 8.19 (d, *J* = 9.1 Hz, 1 H), 7.68–7.47 (m, 8 H), 7.31 (dd, *J* = 9.1, 2.6 Hz, 1 H), 7.21 (dt, *J* = 7.6, 1.5 Hz, 1 H), 6.71 (d, *J* = 2.6 Hz, 1 H), 4.57 (t, *J* = 3.3 Hz, 1 H), 3.30–3.21 (m, 1 H), 2.90 (dd, *J* = 17.9, 2.8 Hz, 1 H), 2.86–2.79 (m, 1 H), 2.70 (dd, *J* = 17.9, 4.1 Hz, 1 H), 2.46–2.37 (m, 1 H), 2.28–2.19 (m, 1 H), 2.07–1.99 (m, 1 H), 1.88 (t, *J* = 7.3 Hz, 3 H), 1.85–1.77 (m, 1 H), 1.75–1.63 (m, 1 H), 1.61–1.52 (m, 1 H), 1.12 (s, 3 H) ppm.

$^{13}$C NMR (125 MHz, [D$_4$]Methanol): $\delta$ = 183.6, 176.7, 173.8, 142.6, 139.8, 136.1, 135.6, 134.1, 133.5, 131.6, 131.2, 130.8, 130.6, 130.4, 129.6, 128.4, 128.3, 126.9, 126.6, 75.0, 63.5, 53.7, 50.2, 41.3, 38.3, 21.4, 17.7, 15.5 ppm. MS (ESI+, APCI): *m/z* = 608.1. HRMS (ESI): calcd. for $C_{30}H_{29}Cl_2N_3NiO_3^+$ [M + H]$^+$ 608.1012; found 608.1027.

**Nickel(II) (*R*)-*N*-(2-Benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*S*)-3-amino-3-(3,4-dimethoxyphenyl)propanoic Acid Schiff Base Complex [(*R*)(2*S*)-21d]:** Brown solid (59.0 mg, yield 93 %, *dr* 93:7). M.p. 160–162 °C. $[\alpha]_D^{20}$ = –2768.3 (*c* = 0.06, $CHCl_3$). $^1$H NMR (400 MHz, [D$_4$]methanol): $\delta$ = 8.16 (d, *J* = 9.1 Hz, 1 H), 7.67–7.50 (m, 4 H), 7.32 (dd, *J* = 9.1, 2.6 Hz, 1 H), 7.24 (d, *J* = 8.4 Hz, 1 H), 7.20–7.13 (m, 1 H), 7.09–7.03 (m, 1 H), 6.89 (d, *J* = 2.2 Hz, 1 H), 6.71 (d, *J* = 2.6 Hz, 1 H), 4.56 (t, *J* = 3.4 Hz, 1 H), 3.93 (s, 3 H), 3.82 (s, 3 H), 3.27–3.16 (m, 1 H), 2.94–2.79 (m, 2 H), 2.67 (dd, *J* = 17.8, 4.1 Hz, 1 H), 2.46–2.35 (m, 1 H), 2.31–2.21 (m, 1 H), 2.04–1.81 (m, 5 H), 1.72–1.50 (m, 2 H), 1.12 (s, 3 H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 182.0, 172.9, 171.0, 149.7, 149.4, 142.0, 135.0, 133.0, 132.9, 132.5, 130.5, 130.0, 129.9, 129.4, 127.2, 126.7, 125.7, 125.3, 119.6, 112.0, 110.0, 73.4, 62.9, 56.4, 56.3, 53.4, 49.1, 40.4, 38.4, 20.5, 17.3, 15.3 ppm. MS (ESI+, APCI): *m/z* = 634.2. HRMS (ESI): calcd. for $C_{32}H_{34}ClN_3NiO_5^+$ [M + H]$^+$ 634.1613; found 634.1627.

**Nickel(II) (*R*)-*N*-(2-Benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*S*)-3-amino-3-(4-isopropylphenyl)propanoic Acid Schiff Base Complex [(*R*)(2*S*)-21e]:** Brown solid (56.7 mg, yield 92 %, *dr* 93:7). M.p. 120–122 °C. $[\alpha]_D^{20}$ = –2287.5 (*c* = 0.048, $CHCl_3$). $^1$H NMR (400 MHz, [D$_4$]methanol): $\delta$ = 8.17 (d, *J* = 9.2 Hz, 1 H), 7.66–7.47 (m, 6 H), 7.39 (d, *J* = 8.0 Hz, 2 H), 7.31 (dd, *J* = 9.1, 2.6 Hz, 1 H), 7.22–7.16 (m, 1 H), 6.72 (d, *J* = 2.6 Hz, 1 H), 4.56 (d, *J* = 3.5 Hz, 1 H), 3.27–3.17 (m, 1 H), 3.10–2.98 (m, 1 H), 2.90 (dd, *J* = 17.8, 2.8 Hz, 1 H), 2.79 (t, *J* = 9.1 Hz, 1 H), 2.67 (dd, *J* = 17.8, 4.2 Hz, 1 H), 2.45–2.34 (m, 1 H), 2.28–2.17 (m, 1 H), 1.97–1.82 (m, 4 H), 1.77–1.45 (m, 3 H), 1.34 (d, *J* = 6.9 Hz, 6 H), 1.10 (s, 3 H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 182.0, 172.9, 171.1, 149.6, 142.0, 137.3, 135.0, 133.0, 132.9, 130.5, 130.0, 130.0, 129.4, 127.6, 127.4, 127.0, 126.7, 125.6, 125.3, 73.4, 62.9, 53.3, 49.1, 40.3, 38.1, 34.1, 24.3, 24.2, 20.4, 17.2, 15.3 ppm. MS (ESI+, APCI): *m/z* = 616.2. HRMS (ESI): calcd. for $C_{33}H_{36}ClN_3NiO_3^+$ [M + H]$^+$ 616.1871; found 616.1886.

**Nickel(II) (*R*)-*N*-(2-Benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*S*)-3-amino-3-(4-methoxyphenyl)propanoic Acid Schiff Base Complex [(*R*)(2*S*)-21f]:** Brown solid (56.2 mg, yield 93 %, *dr* 88:12). M.p. 172–173 °C. $[\alpha]_D^{20}$ = –3139.6 (*c* = 0.048, $CHCl_3$). $^1$H NMR (500 MHz, [D$_4$]methanol): $\delta$ = 8.18 (d, *J* = 9.1 Hz, 1 H), 7.65–7.49 (m, 4 H), 7.40–7.36 (m, 2 H), 7.30 (dd, *J* = 9.1, 2.6 Hz, 1 H), 7.23–7.16 (m, 3 H), 6.70 (d, *J* = 2.6 Hz, 1 H), 4.53 (t, *J* = 3.5 Hz, 2 H), 3.89 (s, 3 H), 3.30–3.19 (m, 1 H), 2.90–2.79 (m, 2 H), 2.65 (dd, *J* = 17.8, 4.2 Hz, 1 H), 2.47–2.35 (m, 1 H), 2.27–2.16 (m, 1 H), 2.01–1.82 (m, 5 H), 1.69–1.50 (m, 2 H), 1.11 (s, 3 H) ppm. $^{13}$C NMR (125 MHz, [D$_4$]Methanol): $\delta$ = 183.6, 177.0, 173.0, 161.6, 142.6, 136.2, 134.0, 133.4, 132.9, 131.6, 131.5, 130.8, 130.3, 129.1, 128.5, 128.4, 126.9, 126.5, 115.9, 75.0, 63.6, 56.1, 53.8, 50.1, 41.3, 38.4, 21.3, 17.6, 15.5 ppm. MS (ESI+, APCI): *m/z* = 604.1. HRMS (ESI): calcd. for $C_{31}H_{32}ClN_3NiO_4^+$ [M + H]$^+$ 604.1508; found 604.1518.

**Nickel(II) (*R*)-*N*-(2-Benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*S*)-3-amino-3-(3-methoxyphenyl)propanoic Acid Schiff Base Complex [(*R*)(2*S*)-21g]:** Brown solid (54.4 mg, yield 90 %, *dr* 90:10). M.p. 165–167 °C. $[\alpha]_D^{20}$ = –2850.0 (*c* = 0.048, $CHCl_3$). $^1$H NMR (500 MHz, [D$_4$]methanol): $\delta$ = 8.17 (d, *J* = 9.1 Hz, 1 H), 7.70–7.47 (m, 5 H), 7.31 (dd, *J* = 9.1, 2.6 Hz, 1 H), 7.20–6.95 (m, 4 H), 6.71 (d, *J* = 2.6 Hz, 1 H), 4.56 (t, *J* = 3.4 Hz, 1 H), 3.85 (s, 3 H), 3.31–3.25 (m, 1 H), 2.97–2.77 (m, 2 H), 2.67 (dd, *J* = 17.8, 4.1 Hz, 1 H), 2.47–2.34 (m, 1 H), 2.30–2.21 (m, 1 H), 2.03–1.76 (m, 5 H), 1.68–1.47 (m, 2 H), 1.12 (s, 3 H) ppm. $^{13}$C NMR (125 MHz, [D$_4$]methanol): $\delta$ = 183.6, 177.0, 173.4, 162.1, 142.6, 142.4, 136.1, 134.1, 133.5, 131.9, 131.6, 131.4, 130.8, 130.4, 128.4, 128.4, 126.9, 126.6, 119.9, 114.4, 114.1, 75.1, 64.0, 55.9, 53.6, 50.2, 41.0, 38.4, 21.4, 17.7, 15.5 ppm. MS (ESI+, APCI): *m/z* = 604.1. HRMS (ESI): calcd. for $C_{31}H_{32}ClN_3NiO_4^+$ [M + H]$^+$ 604.1508; found 604.1518.

**Nickel(II) (*R*)-*N*-(2-Benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*S*)-3-amino-3-(3-(trifluoromethyl)phenyl)propanoic Acid Schiff Base Complex [(*R*)(2*S*)-21h]:** Brown solid (32.1 mg, yield 50 %, *dr* 96:4). M.p. 158–160 °C. $[\alpha]_D^{20}$ = –3280.6 (*c* = 0.036, $CHCl_3$). $^1$H NMR (500 MHz, [D$_4$]methanol): $\delta$ = 8.19 (d, *J* = 9.2 Hz, 1 H), 7.86 (dd, *J* = 28.1, 4.2 Hz, 3 H), 7.69–7.50 (m, 5 H), 7.33 (dd, *J* = 9.1, 2.7 Hz, 1 H), 7.18 (d, *J* = 7.7 Hz, 1 H), 6.73 (d, *J* = 2.6 Hz, 1 H), 4.68 (t, *J* = 3.3 Hz, 1 H), 3.24–3.12 (m, 1 H), 2.98 (dd, *J* = 18.0, 2.9 Hz, 1 H), 2.87–2.73 (m, 2 H), 2.45–2.19 (m, 2 H), 2.06–1.94 (m, 1 H), 1.88 (t, *J* = 7.3 Hz, 3 H), 1.72–1.48 (m, 3 H), 1.12 (s, 3 H) ppm. $^{13}$C NMR (125 MHz, [D$_4$]methanol): $\delta$ = 183.6, 176.6, 174.2, 142.7, 142.4, 136.0, 134.2, 133.7, 132.8, 132.6, 132.2, 131.7, 131.7, 131.2, 130.9, 130.5, 128.4, 128.2, 127.0, 126.6, 126.5, 123.9, 75.0, 63.6, 53.5, 50.2, 41.1, 38.3, 21.4, 17.7, 15.5 ppm. MS (ESI+, APCI): *m/z* = 642.1. HRMS (ESI): calcd. for $C_{31}H_{29}ClF_3N_3NiO_3^+$ [M + H]$^+$ 642.1276; found 642.1268.

**Nickel(II) (*R*)-*N*-(2-Benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*S*)-3-amino-3-(pyridin-3-yl)propanoic Acid Schiff Base Complex [(*R*)(2*S*)-21i]:** Brown solid (46.0 mg, yield 80 %, *dr* 98:2). M.p. 138–140 °C. $[\alpha]_D^{20}$ = –2835.4 (*c* = 0.048, $CHCl_3$). $^1$H NMR (400 MHz, [D$_4$]methanol): $\delta$ = 8.78 (d, *J* = 2.5 Hz, 1 H), 8.76 (dd, *J* = 4.6, 1.4 Hz, 1 H), 8.19 (d, *J* = 9.2 Hz, 1 H), 8.00–7.92 (m, 1 H), 7.75–7.51 (m, 5 H), 7.33 (dd, *J* = 9.2, 2.6 Hz, 1 H), 7.24 (d, *J* = 7.7 Hz, 1 H), 6.72 (d, *J* = 2.6 Hz, 1 H), 4.70 (t, *J* = 3.6 Hz, 1 H), 3.29–3.18 (m, 1 H), 2.99 (dd, *J* = 17.9, 2.9 Hz, 1 H), 2.87–2.73 (m, 2 H), 2.44–2.25 (m, 2 H), 2.09–1.98 (m, 1 H), 1.88 (t, *J* = 7.3 Hz, 3 H), 1.74–1.50 (m, 3 H), 1.13 (s, 3 H) ppm. $^{13}$C NMR (125 MHz, [D$_4$]methanol): $\delta$ = 183.4, 176.4, 174.4, 150.1, 148.6, 142.7, 137.7, 136.5, 136.0, 134.1, 133.7, 131.7, 131.1, 130.9, 130.5, 128.3, 128.3, 126.9, 126.6, 125.9, 75.1, 62.4, 53.4, 50.3, 41.1, 38.1, 21.4, 17.7, 15.5 ppm. MS (ESI+, APCI): *m/z* = 575.1. HRMS (ESI): calcd. for $C_{29}H_{29}ClN_4NiO_3^+$ [M + H]$^+$ 575.1354; found 575.1347.

**Nickel(II) (*R*)-*N*-(2-Benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*S*)-3-amino-3-(thiophen-2-yl)propanoic Acid Schiff Base Complex [(*R*)(2*S*)-21j]:** Brown solid (55.1 mg, yield 95 %, *dr* 98:2). M.p. 145–146 °C. $[\alpha]_D^{20}$ = –2775.0 (*c* = 0.048, $CHCl_3$). $^1$H NMR (500 MHz, [D$_4$]methanol): $\delta$ = 8.16 (d, *J* = 9.1 Hz, 1 H), 7.72 (d, *J* = 5.1 Hz, 1 H), 7.68–7.48 (m, 4 H), 7.35–7.25 (m, 2 H), 7.19–7.11 (m, 2 H), 6.70 (d, *J* = 2.6 Hz, 1 H), 4.72 (t, *J* = 4.1 Hz, 1 H), 3.39 (ddd, *J* = 13.2, 11.5, 5.4 Hz, 1 H), 2.97–2.91 (m, 1 H), 2.86–2.68 (m, 2 H), 2.50–2.40 (m, 1 H), 2.33–2.23 (m, 1 H), 2.22–2.12 (m, 1 H), 2.08–2.00 (m, 1 H), 1.92 (t, *J* = 7.3 Hz, 3 H), 1.83–1.71 (m, 1 H), 1.64–1.55 (m, 1 H), 1.15 (s, 3 H) ppm. $^{13}$C NMR (125 MHz, [D$_4$]methanol): $\delta$ = 183.6, 176.3, 173.3, 145.2, 142.7, 135.8, 134.1, 133.6, 131.7, 131.2, 130.7, 130.4, 129.2, 128.4, 128.4, 127.9, 126.9, 126.7, 126.4, 75.1, 61.9, 53.8, 50.3, 41.3, 39.4, 21.8, 17.8, 15.6 ppm. MS (ESI+, APCI): *m/z* = 580.1. HRMS (ESI): calcd. for $C_{28}H_{28}ClN_3NiO_3S^+$ [M + H]$^+$ 580.0966; found 580.0976.

**Nickel(II) (*R*)-*N*-(2-Benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*S*)-3-amino-3-(naphthalen-1-yl)propanoic Acid Schiff Base Complex [(*R*)(2*S*)-21k]:** Brown solid (56.8 mg, yield 91 %, *dr* 92:8). M.p. 145–147 °C. $[\alpha]_D^{20}$ = –2292.0 (*c* = 0.05, $CHCl_3$). $^1$H NMR (400 MHz, [D$_4$]methanol): $\delta$ = 8.19 (d, *J* = 9.2 Hz, 1 H), 8.14 (d, *J* = 8.6 Hz, 1 H), 8.02–7.94 (m, 3 H), 7.68–7.51 (m, 7 H), 7.33 (dd, *J* = 9.1, 2.6 Hz, 1 H), 7.31–7.26 (m, 1 H), 6.75 (d, *J* = 2.5 Hz, 1 H), 4.75 (t, *J* = 3.5 Hz, 1 H), 3.10–3.03 (m, 1 H), 3.03–2.93 (m, 1 H), 2.78 (dd, *J* = 17.9, 4.1 Hz, 1 H), 2.72–2.64 (m, 1 H),

2.43–2.30 (m, 1 H), 2.22–2.11 (m, 1 H), 1.86 (t, *J* = 7.3 Hz, 3 H), 1.71–1.59 (m, 1 H), 1.39 (q, *J* = 9.9 Hz, 1 H), 1.22–1.05 (m, 2 H), 1.01 (s, 3 H) ppm. $^{13}$C NMR (150 MHz, [D$_4$]methanol): $\delta$ = 182.1, 172.8, 171.3, 142.1, 137.0, 135.0, 133.6, 133.1, 133.0, 130.6, 130.1, 130.0, 129.5, 129.3, 128.5, 127.8, 127.3, 127.1, 127.0, 126.7, 125.7, 125.5, 125.3, 124.9, 63.3, 53.5, 49.0, 40.2, 38.4, 19.9, 17.1, 15.3 ppm. MS (ESI+, APCI): *m*/*z* = 624.2. HRMS (ESI): calcd. for $C_{34}H_{32}ClN_3NiO_3^+$ [M + H]$^+$ 624.1558; found 624.1576.

**Nickel(II) (*R*)-*N*-(2-Benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*R*)-3-aminobutanoic Acid Schiff Base Complex [(*R*)(2*R*)-21l]:** Brown solid (44.5 mg, yield 87 %, *dr* 90:10). M.p. 240–242 °C. $[\alpha]_D^{20}$ = –4309.5 (*c* = 0.042, CHCl$_3$). $^1$H NMR (500 MHz, [D$_4$]methanol): $\delta$ = 8.14 (d, *J* = 9.1 Hz, 1 H), 7.64–7.43 (m, 4 H), 7.27 (dd, *J* = 9.1, 2.6 Hz, 1 H), 6.98 (d, *J* = 7.6 Hz, 1 H), 6.65 (d, *J* = 2.6 Hz, 1 H), 4.34–4.23 (m, 1 H), 3.62–3.52 (m, 1 H), 3.44–3.35 (m, 1 H), 3.29–3.16 (m, 1 H), 2.50–2.28 (m, 5 H), 2.21 (d, *J* = 6.6 Hz, 3 H), 2.11 (dd, *J* = 17.5, 2.5 Hz, 1 H), 1.94 (t, *J* = 7.3 Hz, 3 H), 1.87–1.78 (m, 1 H), 1.27 (s, 3 H) ppm. $^{13}$C NMR (125 MHz, [D$_4$]methanol): $\delta$ = 183.1, 176.7, 172.1, 141.9, 136.7, 133.8, 133.1, 131.5, 131.3, 130.8, 130.3, 127.9, 127.9, 126.9, 126.5, 75.9, 58.9, 53.2, 50.7, 41.7, 41.0, 22.4, 22.2, 17.1, 15.5 ppm. MS (ESI+, APCI): *m*/*z* = 512.1. HRMS (ESI): calcd. for $C_{25}H_{28}ClN_3NiO_3^+$ [M + H]$^+$ 512.1245; found 512.1259.

**Nickel(II) (*R*)-*N*-(2-Benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*R*)-3-aminopentanoic Acid Schiff Base Complex [(*R*)(2*R*)-21m]:** Brown solid (49.4 mg, yield 94 %, *dr* 96:4). M.p. 248–250 °C. $[\alpha]_D^{20}$ = –4370.5 (*c* = 0.044, CHCl$_3$). $^1$H NMR (600 MHz, [D$_4$]methanol): $\delta$ = 8.18 (d, *J* = 9.1 Hz, 1 H), 7.59 (tdd, *J* = 9.0, 5.2, 1.6 Hz, 2 H), 7.55–7.50 (m, 1 H), 7.46 (dt, *J* = 7.0, 1.9 Hz, 1 H), 7.28 (dd, *J* = 9.1, 2.6 Hz, 1 H), 6.92 (dd, *J* = 7.6, 1.5 Hz, 1 H), 6.62 (d, *J* = 2.5 Hz, 1 H), 4.22–4.10 (m, 1 H), 3.61–3.52 (m, 1 H), 3.37–3.32 (m, 2 H), 3.26–3.12 (m, 1 H), 2.52–2.14 (m, 7 H), 1.93 (t, *J* = 7.3 Hz, 3 H), 1.87–1.77 (m, 1 H), 1.27 (s, 3 H), 1.19 (t, *J* = 7.4 Hz, 3 H) ppm. $^{13}$C NMR (150 MHz, [D$_4$]methanol): $\delta$ = 183.2, 176.8, 173.1, 142.2, 136.9, 134.0, 133.2, 131.7, 131.3, 130.6, 130.3, 128.8, 128.1, 126.8, 126.3, 75.8, 64.9, 53.3, 50.6, 41.6, 40.2, 30.6, 22.2, 17.2, 15.5, 11.9 ppm. MS (ESI+, APCI): *m*/*z* = 526.1. HRMS (ESI): calcd. for $C_{26}H_{30}ClN_3NiO_3^+$ [M + H]$^+$ 526.1402; found 526.1408.

**Nickel(II) (*R*)-*N*-(2-Benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*R*)-3-aminoheptanoic Acid Schiff Base Complex [(*R*)(2*R*)-21n]:** Brown solid (53.7 mg, yield 97 %, *dr* 94:6). M.p. 110–112 °C. $[\alpha]_D^{20}$ = –3400.0 (*c* = 0.046, CHCl$_3$). $^1$H NMR (400 MHz, [D$_4$]methanol): $\delta$ = 8.17 (d, *J* = 9.1 Hz, 1 H), 7.65–7.42 (m, 4 H), 7.29 (dd, *J* = 9.1, 2.6 Hz, 1 H), 6.96–6.86 (m, 1 H), 6.61 (d, *J* = 2.5 Hz, 1 H), 4.18 (td, *J* = 12.3, 6.7 Hz, 1 H), 3.60–3.33 (m, 3 H), 3.26–3.10 (m, 1 H), 2.51–2.11 (m, 7 H), 1.93 (t, *J* = 7.3 Hz, 3 H), 1.88–1.74 (m, 2 H), 1.60–1.36 (m, 2 H), 1.27 (s, 3 H), 1.24–1.12 (m, 1 H), 0.98 (t, *J* = 7.4 Hz, 3 H) ppm. $^{13}$C NMR (125 MHz, [D$_4$]methanol): $\delta$ = 181.5, 172.7, 170.7, 141.4, 135.6, 132.9, 132.6, 130.2, 129.7, 129.2, 127.6, 126.3, 125.5, 125.0, 74.1, 62.7, 52.9, 49.5, 40.8, 40.4, 36.8, 29.1, 22.9, 21.5, 16.8, 15.3, 14.1 ppm. MS (ESI+, APCI): *m*/*z* = 554.2. HRMS (ESI): calcd. for $C_{28}H_{34}ClN_3NiO_3^+$ [M + H]$^+$ 554.1715; found 554.1720.

**Nickel(II) (*R*)-*N*-(2-Benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*R*)-3-amino-5-methylhexanoic Acid Schiff Base Complex [(*R*)(2*R*)-21o]:** Brown solid (50.4 mg, yield 91 %, *dr* 92:8). M.p. 248–251 °C. $[\alpha]_D^{20}$ = –3029.5 (*c* = 0.044, CHCl$_3$). $^1$H NMR (400 MHz, [D$_4$]methanol): $\delta$ = 8.16 (d, *J* = 9.1 Hz, 1 H), 7.66–7.46 (m, 4 H), 7.28 (dd, *J* = 9.1, 2.6 Hz, 1 H), 6.96 (dt, *J* = 8.3, 1.4 Hz, 1 H), 6.62 (d, *J* = 2.6 Hz, 1 H), 4.32–4.18 (m, 1 H), 3.58–3.49 (m, 1 H), 3.41–3.33 (m, 2 H), 3.26–3.10 (m, 1 H), 2.56–2.27 (m, 6 H), 2.17 (dd, *J* = 17.5, 2.5 Hz, 1 H), 1.92 (t, *J* = 7.3 Hz, 3 H), 1.86–1.68 (m, 2 H), 1.27 (s, 3 H), 0.96 (d, *J* = 6.6 Hz, 3 H), 0.73 (d, *J* = 6.5 Hz, 3 H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 181.5, 172.7, 170.5, 141.4, 135.5, 133.0, 132.6, 130.3, 130.2, 129.6, 129.2, 127.8, 126.4, 125.5, 125.0, 74.1, 60.6, 52.8, 49.6, 46.4, 40.8, 40.3, 25.1, 22.8, 22.8, 21.4, 16.8, 15.3 ppm. MS (ESI+, APCI): *m*/*z* = 554.2. HRMS (ESI): calcd. for $C_{28}H_{34}ClN_3NiO_3^+$ [M + H]$^+$ 554.1715; found 554.1728.

**Nickel(II) (*R*)-*N*-(2-Benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*S*)-3-amino-4-methylpentanoic Acid Schiff Base Complex [(*R*)(2*S*)-21p]:** Brown solid (41.0 mg, yield 76 %, *dr* 95:5). M.p. 150–152 °C. $[\alpha]_D^{20}$ = –3242.9 (*c* = 0.042, CHCl$_3$). $^1$H NMR (400 MHz, [D$_4$]methanol): $\delta$ = 8.18 (d, *J* = 9.1 Hz, 1 H), 7.66–7.42 (m, 4 H), 7.29 (dd, *J* = 9.1, 2.6 Hz, 1 H), 6.90 (dt, *J* = 7.6, 1.0 Hz, 1 H), 6.60 (d, *J* = 2.6 Hz, 1 H), 4.27–4.03 (m, 2 H), 3.37–3.32 (m, 1 H), 3.23–3.09 (m, 1 H), 2.99 (dt, *J* = 10.3, 3.3 Hz, 1 H), 2.51–2.24 (m, 6 H), 1.93 (t, *J* = 7.3 Hz, 3 H), 1.88–1.76 (m, 1 H), 1.35 (d, *J* = 6.7 Hz, 3 H), 1.27 (s, 3 H), 0.91 (d, *J* = 6.6 Hz, 3 H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 181.5, 173.0, 170.7, 141.5, 135.8, 133.0, 132.6, 130.2, 129.6, 129.3, 127.8, 126.3, 125.6, 125.0, 74.0, 69.3, 53.1, 49.5, 40.6, 38.4, 34.0, 21.6, 21.3, 19.9, 17.0, 15.3 ppm. MS (ESI+, APCI): *m*/*z* = 540.1. HRMS (ESI): calcd. for $C_{27}H_{32}ClN_3NiO_3^+$ [M + H]$^+$ 540.1558; found 540.1556.

**Nickel(II) (*R*)-*N*-(2-Benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*S*)-3-amino-3-cyclopropylpropanoic Acid Schiff Base Complex [(*R*)(2*S*)-21q]:** Brown solid (50.0 mg, yield 93 %, *dr* 98:2). M.p. 150–151 °C. $[\alpha]_D^{20}$ = –3892.1 (*c* = 0.038, CHCl$_3$). $^1$H NMR (600 MHz, [D$_4$]methanol): $\delta$ = 8.18 (dd, *J* = 9.3, 2.9 Hz, 1 H), 7.61–7.24 (m, 5 H), 6.92 (d, *J* = 7.7 Hz, 1 H), 6.58 (d, *J* = 2.6 Hz, 1 H), 4.42–4.29 (m, 1 H), 4.18–4.02 (m, 1 H), 3.42–3.33 (m, 1 H), 3.18–3.06 (m, 1 H), 2.97–2.85 (m, 1 H), 2.56–2.25 (m, 6 H), 2.02–1.82 (m, 4 H), 1.26 (s, 3 H), 1.20–1.12 (m, 1 H), 0.85–0.73 (m, 1 H), 0.24–0.14 (m, 1 H), 0.08–0.03 (m, 1 H) ppm. $^{13}$C NMR (150 MHz, [D$_4$]methanol): $\delta$ = 183.2, 177.1, 171.8, 142.1, 136.5, 133.9, 133.2, 131.7, 131.4, 130.6, 130.3, 128.8, 128.1, 126.9, 126.4, 75.9, 69.0, 53.4, 50.6, 41.9, 40.3, 22.2, 18.2, 16.9, 15.5, 6.2, 5.4 ppm. MS (ESI+, APCI): *m*/*z* = 538.1. HRMS (ESI): calcd. for $C_{27}H_{30}ClN_3NiO_3^+$ [M + H]$^+$ 538.1402; found 538.1413.

**Nickel(II) (*R*)-*N*-(2-Benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*S*)-3-amino-3-cyclohexylpropanoic Acid Schiff Base Complex [(*R*)(2*S*)-21r]:** Brown solid (49.3 mg, yield 85 %, *dr* 94:6). M.p. 155–157 °C. $[\alpha]_D^{20}$ = –2770.0 (*c* = 0.04, CHCl$_3$). $^1$H NMR (400 MHz, [D$_4$]methanol): $\delta$ = 8.17 (d, *J* = 9.1 Hz, 1 H), 7.63–7.42 (m, 4 H), 7.28 (dd, *J* = 9.1, 2.6 Hz, 1 H), 6.95–6.86 (m, 1 H), 6.58 (d, *J* = 2.6 Hz, 1 H), 4.27–4.13 (m, 1 H), 4.04–3.88 (m, 1 H), 3.39–3.33 (m, 1 H), 3.24–3.13 (m, 1 H), 3.09–3.00 (m, 1 H), 2.64–2.25 (m, 7 H), 1.99 (d, *J* = 13.1 Hz, 1 H), 1.91 (t, *J* = 7.3 Hz, 3 H), 1.86–1.70 (m, 5 H), 1.52–1.38 (m, 1 H), 1.27 (s, 3 H), 1.17–1.09 (m, 1 H), 0.81–0.59 (m, 2 H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 181.4, 173.3, 170.7, 141.5, 135.7, 133.0, 132.6, 130.3, 130.2, 129.6, 129.2, 128.0, 126.3, 125.6, 124.9, 74.2, 68.1, 52.8, 49.6, 43.1, 40.6, 37.7, 31.3, 29.8, 26.4, 26.3, 26.0, 21.5, 16.7, 15.3 ppm. MS (ESI+, APCI): *m*/*z* = 580.2. HRMS (ESI): calcd. for $C_{30}H_{36}ClN_3NiO_3^+$ [M + H]$^+$ 580.1871; found 580.1876.

**Nickel(II) (*R*)-*N*-(2-Benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*R*)-3-amino-4-(2,4,5-trifluorophenyl)butanoic Acid Schiff Base Complex [(*R*)(2*R*)-21s]:** Brown solid (55.86 mg, yield 87 %, *dr* 95:5). M.p. 140–141 °C. $[\alpha]_D^{20}$ = –2814.0 (*c* = 0.05, CHCl$_3$). $^1$H NMR (500 MHz, [D$_4$]methanol): $\delta$ = 8.15 (d, *J* = 9.1 Hz, 1 H), 7.62–7.48 (m, 2 H), 7.46–7.34 (m, 2 H), 7.28 (dd, *J* = 9.1, 2.5 Hz, 1 H), 7.12 (td, *J* = 9.9, 6.6 Hz, 1 H), 7.03 (ddd, *J* = 10.7, 8.7, 6.7 Hz, 1 H), 6.59 (d, *J* = 2.6 Hz, 1 H), 6.49–6.38 (m, 1 H), 4.38 (dd, *J* = 13.8, 6.9 Hz, 1 H), 4.20 (ddd, *J* = 13.4, 11.4, 5.7 Hz, 1 H), 4.01–3.91 (m, 1 H), 3.62 (tdd, *J* = 6.9, 4.3, 2.5 Hz, 1 H), 3.51–3.33 (m, 2 H), 2.58–2.28 (m, 5 H), 2.09 (dd, *J* = 17.6, 2.6 Hz, 1 H), 2.01 (t, *J* = 7.3 Hz, 3 H), 1.89–1.78 (m, 1 H), 1.31 (s, 3 H) ppm. $^{13}$C

NMR (125 MHz, [D$_4$]methanol): $\delta$ = 183.4, 176.4, 173.6, 157.6 (ddd, $J$ = 245.1, 9.5, 2.2 Hz), 150.6 (dt, $J$ = 250.2, 13.8 Hz), 148.07 (ddd, $J$ = 244.1, 12.5, 3.1 Hz), 142.2, 136.5, 134.0, 133.4, 131.3, 131.0, 130.4, 130.2, 128.0, 127.8, 126.8, 126.6, 122.1 (dt, $J$ = 18.6, 5.0 Hz), 120.0 (dd, $J$ = 19.3, 5.9 Hz), 106.9 (dd, $J$ = 28.9, 21.2 Hz), 75.7, 64.0, 53.2, 50.9, 41.4, 39.2, 35.9, 22.6, 18.0, 15.6 ppm. MS (ESI+, APCI): $m/z$ = 642.1. HRMS (ESI): calcd. for $C_{31}H_{29}ClF_3N_3NiO_3^+$ [M + H]$^+$ 642.1276; found 642.1287.

**(*S*)-3-Amino-3-phenylpropanoic Acid [(*S*)-4a]:** A solution of (*R*)(2*S*)-**21a** (3.0 g, 5.22 mmol) in MeOH (40 mL) was added to a stirring solution of 3 N HCl in MeOH (1:1 v/v, 80 mL) at 50 °C. The mixture was gently heated under reflux for 30 min and then evaporated to dryness. Water (50 mL) was added, and the resultant mixture was treated with an excess of concentrated $NH_4OH$ and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ extracts were dried ($Na_2SO_4$), and the solvents were evaporated under vacuum to afford the free chiral ligand (*R*)-**17** (1.85 g, yield 95 %). The aqueous phase was evaporated under vacuum and dissolved in a minimum amount of $H_2O$, and the solution was loaded on a Dowex 50X2-100 ion-exchange column, which was washed with $H_2O$ until neutral. The column was then washed with 10 % aqueous $NH_4OH$. The first fraction (500 mL) was collected, and the solvents were evaporated under vacuum to afford the corresponding amino acid (*S*)-**4a** as a white solid (800 mg, yield 92 %). M.p. 223–224 °C. $[\alpha]_D^{20}$ = –12 ($c$ = 0.1, $H_2O$). $[\alpha]_D^{20}$ = –7.7 ($c$ = 0.1, $H_2O$). $^1$H NMR (500 MHz, $D_2O$): $\delta$ = 7.58–7.41 (m, 5 H), 4.70 (t, $J$ = 7.3 Hz, 1 H), 3.11–2.86 (m, 2 H) ppm. $^{13}$C NMR (125 MHz, $D_2O$): $\delta$ = 175.93, 135.66, 129.38, 129.27, 126.91, 52.29, 39.48 ppm. MS (ESI+, APCI): $m/z$ = 166.1. HRMS (ESI): calcd. for $C_9H_{11}NO_2^+$ [M + H]$^+$ 166.0863; found 166.0858.

**(*S*)-3-*tert*-Butoxycarbonylamino-3-phenylpropionic Acid [(*S*)-22]:** To a solution of (*S*)-**4a** (0.33 g, 2 mmol) in $NaHCO_3$ (50 % sat. aq., 3 mL) were added di-*tert*-butyl dicarbonate (0.52 g, 2.2 mmol) and acetonitrile (10 mL). The reaction mixture was stirred at room temperature for 24 h. The solution was concentrated under reduced pressure and diluted with $H_2O$ (30 mL), and the aqueous layer was acidified with 1 N HCl and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($Na_2SO_4$), and filtered, and the solvents were evaporated to dryness under vacuum to afford the crude product, which was loaded on a silica gel column, and immediate chromatography (petroleum ether/EtOAc 1:2) furnished the pure product as a white solid (yield: 0.52 g, 98 %). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.34–7.24 (m, 5 H), 5.48 (br s, 1 H), 5.11–4.93 (m, 1 H), 2.84 (s, 2 H), 1.41 (br s, 9 H) ppm. MS (ESI+, APCI): $m/z$ = 264.0 [M – H]$^-$.

***tert*-Butyl (*S*)-3-Hydroxy-1-phenylpropylcarbamate [(*S*)-23]:** A mixture of (*S*)-**22** (0.40 g, 1.5 mmol) was slurried in THF (5 mL) under an atmosphere of nitrogen and cooled to 0 °C. $BH_3$·THF (1 M solution in THF, 3 mL) was added slowly to the reaction mixture, which was then stirred for a further 5 h. The excess $BH_3$·THF was quenched by the addition of acetone. The THF was removed by concentration under reduced pressure, and the residue was dissolved in $H_2O$ (40 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($Na_2SO_4$), filtered, and evaporated to dryness under vacuum to afford the crude product (0.39 g, 104 %). MS (ESI+, APCI): $m/z$ = 252.1 [M + H]$^+$.

***tert*-Butyl (*S*)-3-Oxo-1-phenylpropylcarbamate [(*S*)-24]:** A solution of (*S*)-**23** (0.39 g, 1.5 mmol) in dichloromethane (10 mL) was cooled to 0 °C. Dess–Martin periodinane (0.76 g, 1.8 mmol) was added slowly to the reaction mixture, which was then stirred at room temperature for 1 h. $NaHCO_3$ (sat. aq., 30 mL) was added, and the reaction mixture was extracted with dichloromethane (3 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($Na_2SO_4$), filtered, and evaporated to dryness under vacuum to afford the crude product, which was loaded on a silica gel column and immediately chromatographed (petroleum ether/EtOAc 3:1) to furnish the pure product as a white solid (yield 0.34 g, 92 %). MS (ESI+, APCI): $m/z$ = 250.1 [M + H]$^+$.

***tert*-Butyl (1*S*)-3-[3-(3-Isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-*exo*-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropylcarbamate [(*S*)-26]:** Amine **25** (0.28 g, 1.2 mmol) was slurried in 1,2-dichloroethane (10 mL) and treated with a solution of (*S*)-**24** (0.25 g, 1 mmol) as a 1,2-dichloroethane concentrate, and then acetic acid (12 µL, 0.2 mmol) was added. To the resultant solution was added sodium triacetoxyborohydride (0.32 g, 1.5 mmol) portionwise with the temperature maintained below 30 °C. The resultant slurry was stirred at ambient temperature for 24 h and then diluted with $H_2O$ (30 mL) and dichloromethane (30 mL). The aqueous layer was adjusted to pH 11–12 by the addition of a 2 M sodium hydroxide solution. The layers were separated, and the aqueous phase was extracted with dichloromethane (2 × 30 mL). The organic extracts were combined, washed with brine (100 mL), dried ($Na_2SO_4$), filtered, and evaporated to dryness under vacuum to afford the crude product, which was loaded on a silica gel column and immediately chromatographed (dichloromethane/ methanol 15:1) to furnish the pure product as a white solid (yield: 0.33 g, 71 %). MS (ESI+, APCI): $m/z$ = 468.3 [M + H]$^+$.

**4,4-Difluoro-*N*-{(1*S*)-3-[*exo*-3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-cyclohexanecarboxamide [(*S*)-29]:** A solution of (*S*)-**26** (93.4 mg, 0.2 mmol) in methanol (5 mL) was cooled to 0 °C. A 4 N HCl/dioxane solution (5 mL) was added slowly to the reaction mixture, which was then stirred at room temperature for 3 h. The resultant solution was concentrated under reduced pressure to afford the crude intermediate product (*S*)-**27**. Amine (*S*)-**27** was slurried in dichloromethane (5 mL) and treated with triethylamine (138.7 µL, 1 mmol), followed by 4,4-difluorocyclohexanecarboxylic acid (**28**, 39.4 mg, 0.24 mmol), EDCI (46.0 mg, 0.24 mmol), and HOBT (32.4 mg, 0.24 mmol). The reaction mixture was stirred at room temperature for a further 12 h, and diluted with $H_2O$ (30 mL) and dichloromethane (30 mL). The aqueous layer was adjusted to pH 11–12 by the addition of a 2 M sodium hydroxide solution. The layers were separated, and the aqueous phase was extracted with dichloromethane (2 × 30 mL). The organic extracts were combined, washed with brine (100 mL), dried ($Na_2SO_4$), filtered, and evaporated to dryness under vacuum to the afford crude product, which was loaded on a silica gel column and immediately chromatographed (dichloromethane/methanol 10:1) to furnish the pure product as a white solid (yield: 76.9 mg, 75 %, >98.2 % *ee*). $[\alpha]_D^{25}$ = –28.4 ($c$ = 0.5, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.35–7.31 (m, 2 H), 7.28–7.26 (m, 3 H), 6.82–6.66 (br m, 1 H), 5.12–5.07 (m, 1 H), 4.32–4.26 (m, 1 H), 3.40 (br d, 2 H), 3.01–2.94 (m, 1 H), 2.48 (s, 3 H), 2.44 (t, $J$ = 8 Hz, 2 H), 2.28–1.64 (m, 19 H), 1.37 (d, $J$ = 4 Hz, 6 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 173.71, 159.23, 150.70, 141.97, 128.77, 127.49, 126.49, 58.99, 58.37, 51.94, 47.99, 47.30, 42.74, 35.40, 35.28, 34.66, 32.95 ($J_{^{13}C,^{19}F}$ = 6 Hz), 32.82, 32.79, 32.63 ($J_{^{13}C,^{19}F}$ = 4.5 Hz), 26.66, 26.62, 25.98 ($J_{^{13}C,^{19}F}$ = 9 Hz), 25.89 ($J_{^{13}C,^{19}F}$ = 9 Hz), 25.80, 21.63, 13.07 ppm. MS (ESI+, APCI): $m/z$ = 514.3 [M + H]$^+$. HRMS (ESI): calcd. for $C_{29}H_{42}F_2N_5O^+$ [M + H]$^+$ 514.3552; found 514.3551.

## Acknowledgments

We gratefully acknowledge financial support from the National Natural Science Foundation of China (81620108027

and 21632008) and the Major Project of Chinese National Programs for Fundamental Research and Development (2015CB910304).

**Keywords:** Amino acids · Chemical resolution · Nickel · Nonracemizable ligands · Antiviral agents

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Received: January 23, 2018

 