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Article

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Chemical Resolution of *C*,*N*-Unprotected α-Substituted-β-Amino Acids Using Stable and Recyclable Proline-derived Chiral Ligands

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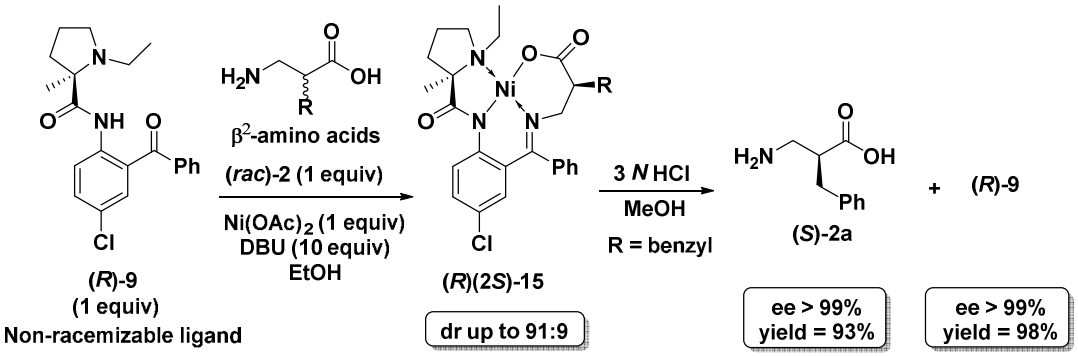


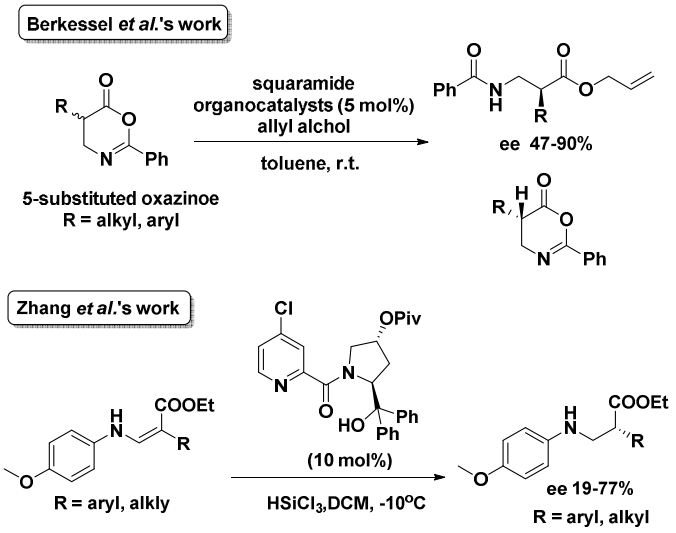
Abstract

We report the first purely chemical method for the resolution of *C*,*N*-unprotected racemic α-substituted-β-amino acids (β^2-AAs) using thermodynamically stable and recyclable chiral proline-derived ligands. The ligands and racemic β^2-AAs along with Ni(II) could form a pair of Ni(II) complex diastereoisomers with desirable diastereoselectivity (dr up to 91:9). Enantiomerically pure *C*,*N*-unprotected β^2-AAs could be obtained by simple hydrolysis of isolated favored-Ni(II) complex. The method featured unique versatility compared with enzymatic approaches, and characterized by its broad synthetic generality, good stereochemical outcome and mild reaction conditions, thus making it a powerful supplement in the field of chemical resolution of β^2-AAs.

Introduction

α-Substituted-β-amino acids (β^2-AAs) are being widely used increasingly in the pharmaceutical and healthcare industries,[1-8] and play as the vital building blocks in the pharmaceuticals and natural products.[9-11]Preparation of structurally varied β^2-AAs in enantiomerically pure forms has been a research focus in synthetic organic chemistry, leading to several ingenious asymmetric synthesis approaches.[12-13] However, current asymmetric synthesis methods to prepare enantiomerically pure β^2-AAs are relatively cumbersome, involving expensive, dangerous or toxic reagents, and requiring multiple steps to prepare substrates and elaborate reaction conditions.[14-16] By contrast, the resolution of racemic β^2-AAs is still used frequently in

practice, because there are a variety of methods to prepare racemic β^2-AAs.[17-18] However, the enzymatic resolution of racemic β^2-AA derivatives is limited to only a few examples.[19-25] For example, Berkessel *et al.* reported the enzymatic dynamic kinetic resolution of oxazinones[19] or β-lactams[24] to obtain optically pure β^2-AAs. These enzymatic approaches require high throughput screening for selective enzymes and multi-step preparation for special substrates. Similarly, the exploration of purely chemical methods for the resolution of racemic β^2-AAs is almost omitted with limited literatures. Berkessel *et al.* reported the kinetic resolution of 5-substituted oxazinone substrates with chiral squaramide organocatalysts to afford *N*-protected β^2-amino esters *via* alcoholytic ring opening.[26] Zhang *et al.* reported chiral Lewis base organocatalyzed asymmetric hydrosilylation of α-substituted β-enamino ester to afford enantioenriched β^2-amino esters *via* dynamic kinetic resolution.[27] Both methods require preparation of special β^2-AAs derivatives and resulted products are *C*,*N*-protected or substituted β^2-AAs, thus unfriendly to following applications (Scheme 1). Therefore, a purely chemical resolution of *C*,*N*-unprotected β^2-AAs, starting from simple and cheap starting materials, to obtain enantiomerically pure *C*,*N*-unprotected β^2-AAs, remains an important challenge for synthetic organic chemists.



Scheme 1. Reported chemical resolution methods to obtain chiral β^2-AAs or their derivatives.

Various enantiomerically pure non-natural amino acids, including α-AAs and β^3-AAs, could be obtained by dynamic resolution of racemic AAs *via* forming Ni(II) complexes with chiral ligands (Figure 1).[28] On the other hand, we have previously synthesized a series of racemic

α-aryl-/alkyl-substituted β-amino acids using Ni(II) complexed with the achiral PBP ligand.[18, 29-30] Encouraged by these works, we proposed to explore the possibility of chemical resolution of *C*,*N*-unprotected racemic β^2-AAs *via* a chiral ligand by forming Ni(II) complex to obtain the enantiomerically pure forms (Scheme 2). Unlike α-amino acids (α-AAs),[31-33] the kinetic rate of chelation reaction of β^2-AAs with the chiral ligand and Ni(II) is comparatively lower, since the resulted flexible six-membered ring goes against the Ni(II)-centered quadrilateral plane.

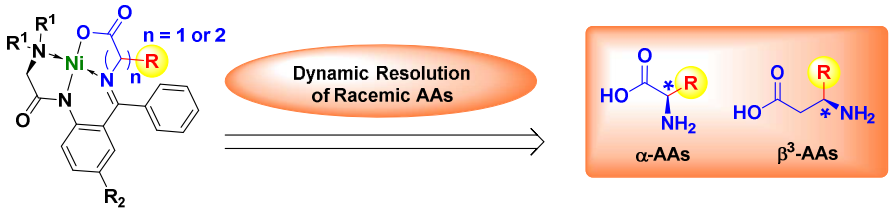
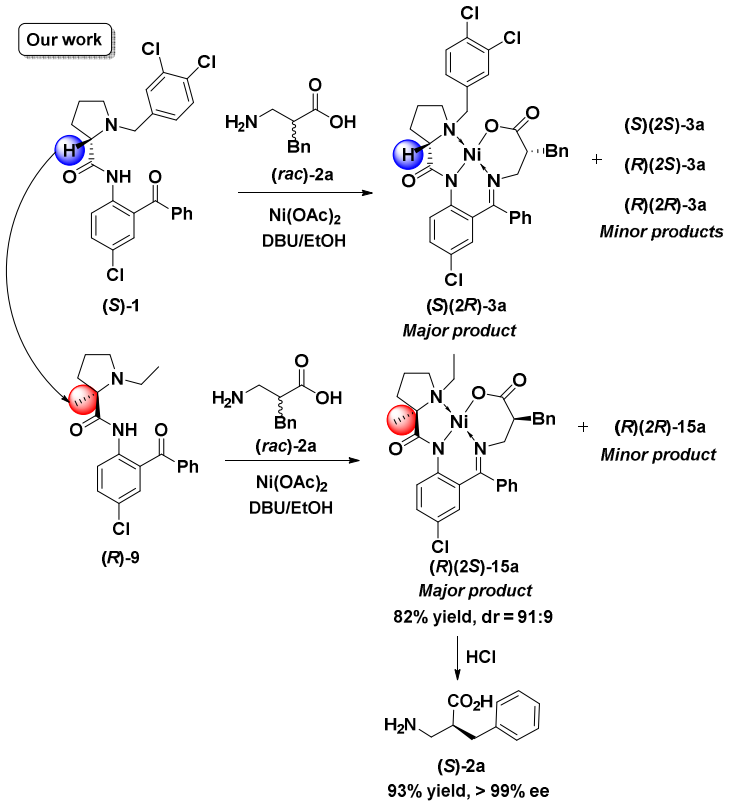


Figure 1. Dynamic resolution of racemic amino acids using Ni(II) complex



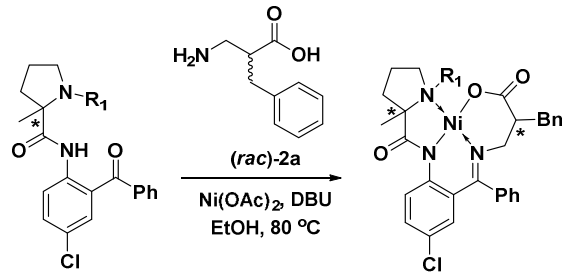
Scheme 2. Chemical resolution of *C*,*N*-unprotected racemic β^2-AAs by Ni(II) complexes.

Results and Discussion

In initial stage of the attempts, we selected the chiral proline-derived ligand **1** for the dynamic resolution of *C*,*N*-unprotected β^2-AAs, which has been successfully applied in the chemical resolution of α-AAs and β-substituted-β-amino acids (β^3-AAs).[32, 34] Interestingly, the reaction of racemic α-benzyl-β-alanine (*rac*)-**2a** (1 equiv) with (*S*)-**1** (1 equiv) generated two expected Ni(II) complex products, (*S*)(2*R*)-**3a** and (*S*)(2*S*)-**3a**, and two unexpected products, (*R*)(2*S*)-**3a** and (*R*)(2*R*)-**3a** (Scheme 1, Figures S1 and S2). Theoretically, racemization was able to occur at the α-position of both proline and β^2-AA moieties in the structure of the Ni(II) complex **3a** under base-catalyzed epimerization. According to above results, we could reasonably assume that the pK_a of α-H of the proline moiety is comparable with that of the β^2-AA moiety in the structure of the Ni(II) complex **3a**, which suggested that ligand (*S*)-**1** is inappropriate as a chiral auxiliary for the thermodynamic resolution of racemic β^2-AAs. To solve the thermodynamic instability of ligand **1**, we then designed a ligand, (*S*)-**4**, with a quaternary carbon stereogenic center by introducing a methyl at the α-position of the proline moiety in the structure of ligand **1**.

To confirm our ideas, we then reacted (*S*)-**4** with (*rac*)-**2a** under the standard reaction conditions: heating an ethanol solution of the ligand (*S*)-**4**, (*rac*)-**2a**, anhydrous $Ni(OAc)_2$ and DBU. In this case, as expected, we did not observe (*R*)(2*R*)-**10a** and (*R*)(2*S*)-**10a** (Figures S3 and S4), and the target nickel(II) complexes, (*S*)(2*R*)-**10a** and (*S*)(2*S*)-**10a**, were obtained at a yield of 76% and in a ratio of 81:19 (Table 1, entry 1). These results were encouraging, as they established that the direct chemical resolution of unprotected β^2-AAs by a simple reaction with (*S*)-**6** was feasible. Fortunately, we could easily got the diastereoisomers (*S*)(2*R*)-**10a** and (*S*)(2*S*)-**10a** by column chromatography on silica gel (v/v, dichloromethane/methanol = 20/1). After the determination of dr value of the diastereoisomers by ^{1}H NMR, the enantiomerically pure (*S*)(2*R*)-**10a** could be obtained by column chromatography on silica gel once again (v/v, dichloromethane/acetone = 5/1, R_f ((*S*)(2*R*)-**10a**) = 0.4, R_f((*S*)(2*S*)-**10a**) = 0.25). The definite and absolute configurations of Ni(II) complexes (*S*)(2*R*)-**10a** and (*S*)(2*S*)-**10a** were determined by X-ray analysis (Figure S5).[35]

Table 1. Optimization of chiral ligands for chemical resolution of unprotected racemic α-benzyl-β-alanine **2a**.[a]



(*S*)-4 R_1 = 3,4-dichlorobenzyl
(*S*)-5 R_1 = benzyl
(*S*)-6 R_1 = 3,4-dibromobenzyl
(*S*)-7 R_1 = 3,4-dimethoxybenzyl
(*S*)-8 R_1 = phenylpropyl
(*R*)-9 R_1 = ethyl

(*S*)(2*R*)-10a
(*S*)(2*R*)-11a
(*S*)(2*R*)-12a
(*S*)(2*R*)-13a
(*S*)(2*R*)-14a
(*R*)(2*S*)-15a

Entry	Ligand	Ni(II)-complex	yield (%)[b]	dr[c]
1	(*S*)-**4**	(*S*)(2*R*)-**10a**	76	81/19
2	(*S*)-**5**	(*S*)(2*R*)-**11a**	74	83/17
3	(*S*)-**6**	(*S*)(2*R*)-**12a**	89	68/32
4	(*S*)-**7**	(*S*)(2*R*)-**13a**	83	69/31
5	(*S*)-**8**	(*S*)(2*R*)-**14a**	69	82/18
6	(*R*)-**9**	(*R*)(2*S*)-**15a**	82	91/9

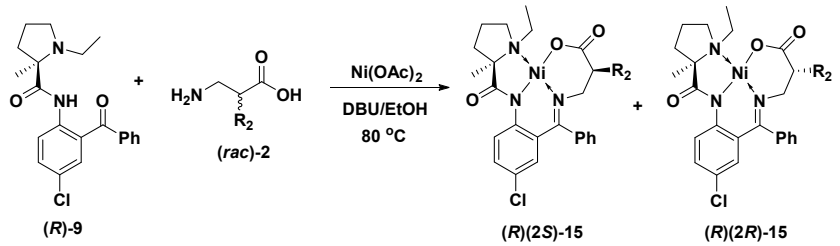
[a] Reaction condition: Ligand (0.1 mmol), (*rac*)-**2a** (0.1 mmol), anhydrous $Ni(OAc)_2$ (0.1 mmol) and DBU (1 mmol) were refluxed in ethanol (2 mL) at 80 °C for 96 h. [b] Combined yield of isolated products **10a**-**15a**. [c] dr was determined by ^1H NMR analysis of isolated products **10a**-**15a**.

To further improve the stereochemical outcome, various attempts at modifying of ligand **4** were conducted (Table 1, entries 2-6). The synthesis method of the proline-derived ligands **4**-**9** was extremely similar with the previous reported method, and ligands **4**-**5** and **8**-**9** have been well characterized.[36] When we substituted 3,4-dicholorobenzyl with a benzyl moiety on proline, it gave a comparable yield and diastereoselectivity (Table 1, entry 2). An apparent increase in yield and decrease in diastereoselectivity were observed when introducing electron-donating groups on the benzyl moiety (Table 1, entries 3-4). Prolonging benzyl to phenylpropyl gave a comparative diastereoselectivity but an undesired decrease in yield (Table 1, entry 5). Finally, it was found that ligand (*R*)-**9** with an ethyl substitution on proline showed a relatively good yield (82%) and diastereoselectivity (dr = 91:9) of the Ni(II) complex (Table 1, entry 6), which has been also selected as the best proline-derived ligand in the resolution of racemic β^3-AAs.[36] Further

investigation on the reaction time of ligand (*R*)-**9** with (*rac*)-**2a** revealed that the final thermodynamic control stopped at 96 h was the best choice. And with the longer reaction time, diastereoisomer (*R*)(2*R*)-**15a** could surely be interconverted to the thermodynamically more stable diastereoisomer (*R*)(2*S*)-**15a** while accompanied with the decomposition of Ni(II) complex **15a** (Table S1).

Furthermore, we investigated the generality of (*R*)-**9** in the resolution of β^2-AAs (Table 2). First, the α-benzyl-substituted β^2-AAs were applied successfully with satisfactory yields (≥ 70%) and good diastereoselectivity (dr ≥ 84:16) (Table 2, entries 1-5). Importantly, for these benzyl-substituted β^2-AAs, the electronic property of the substituents on the benzyl group did not show any apparent effects on the stereochemical outcome of the reactions. In addition, β^2-AAs bearing aliphatic substituents, such as methyl, *i*-butyl, *i*-propyl, and cyclohexyl also exhibited good yield (≥ 80%) and a slight decrease in diastereoselectivity compared with the benzyl-substituted β^2-AAs (Table 2, entries 6-9). For the sterically hindered *t*-butyl-substituted β^2-AA, the Ni(II) complexes **15j** were isolated with a moderate yield and diastereochemistry (dr = 62:38) (Table 2, entry 10). Unfortunately, the α-aryl-substituted β-AAs (*rac*)-**2k-2n** (Table 2, entries 11-14), bearing electron-withdrawing as well as electron-donating groups, and the sterically hindered 2-naphthyl, all resulted in products with poor diastereoselectivities (dr ≤ 62 : 38).

Table 2. Chemical resolution of various *C*,*N*-unprotected β^2-AAs (*rac*)-**2** using ligand (*R*)-**9**.[a]



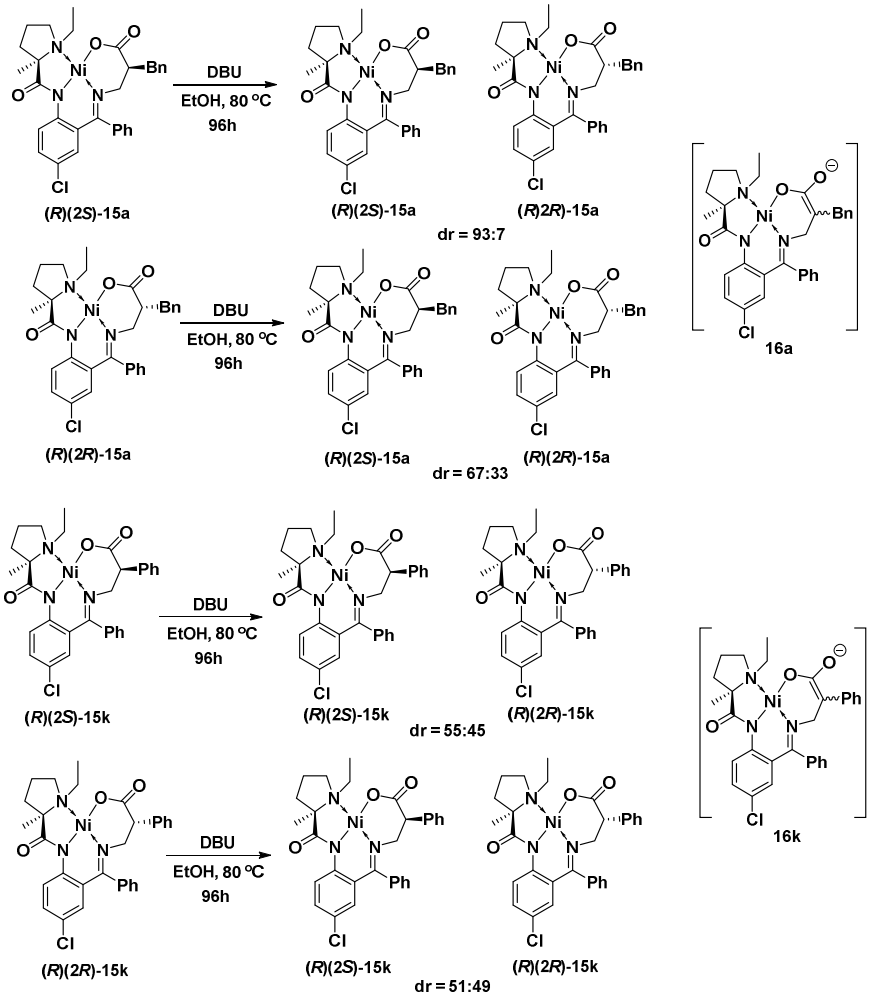
Entry	R_2	Ni(II)-complex	Yield (%) [b]	dr [c]
1	benzyl	(*R*)(2*S*)-**15a**	82	91/9
2	4-OMe-benzyl	(*R*)(2*S*)-**15b**	83	88/12
3	4-Me-benzyl	(*R*)(2*S*)-**15c**	70	84/16
4	4-F-benzyl	(*R*)(2*S*)-**15d**	76	89/11

5	4-CF_3-benzyl	(*R*)(2*S*)-**15e**	72	89/11
6	methyl	(*R*)(2*S*)-**15f**	83	73/27
7	*i*-butyl	(*R*)(2*S*)-**15g**	80	83/17
8	*i*-propyl	(*R*)(2*S*)-**15h**	81	76/24
9	cyclohexyl	(*R*)(2*S*)-**15i**	84	83/17
10	*t*-butyl	(*R*)(2*S*)-**15j**	69	62/38
11	phenyl	(*R*)(2*S*)-**15k**	73	51/49
12	4-MeO-phenyl	(*R*)(2*S*)-**15l**	65	54/46
13	4-Cl-phenyl	(*R*)(2*S*)-**15m**	69	62/38
14	2-naphthyl	(*R*)(2*S*)-**15n**	76	56/44

[a] Reaction condition: (*R*)-**9** (0.1 mmol), (*rac*)-**2** (0.1 mmol), anhydrous $Ni(OAc)_2$ (0.1 mmol) and DBU (1 mmol) were refluxed in ethanol (2 mL) at 80 °C for 96 h. [b] Combined yield of (*R*)(2*S*)-**15** and (*R*)(2*R*)-**15**. [c] dr was determined by ^{1}H NMR analysis of the mixtures of (*R*)(2*S*)-**15** and (*R*)(2*R*)-**15**.

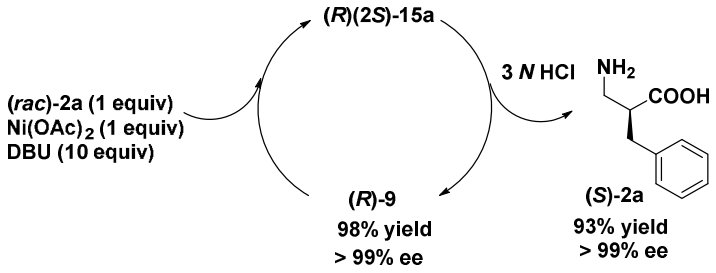
As we can see in Table 2, the yield of (*R*)(2*S*)-**15a** was 75%, exceeding more than 50%, convictively indicating that the resolution of racemic β^2-AAs was a dynamic process. To further understand this process, we isolated enantiomerically pure (*R*)(2*S*)-**15a** and (*R*)(2*R*)-**15a**, respectively, and treated with DBU (10 equiv) in EtOH. After heating for 96 h, 7% of pure (*R*)(2*S*)-**15a** was converted to (*R*)(2*R*)-**15a**, and in contrast, 67% of pure (*R*)(2*R*)-**15a** was transformed to (*R*)(2*S*)-**15a**, fully illustrating the two diastereisomers could be interconverted *via* keto-enol tautomerism (enol **16a** as the possible intermediate), and (*R*)(2*S*)-**15a** was undoubtedly identified as the thermodynamically favored diastereisomer (Scheme 3). When it came to Ni(II) complex **15k**, whether (*R*)(2*S*)-**15k** or (*R*)(2*R*)-**15k** as the starting diastereisomer, the ratio of (*R*)(2*S*)-**15k** and (*R*)(2*R*)-**15k** were both nearly 50:50 after the thermodynamic equilibrium transformation (Scheme 2), which consistented with the resolution result (Table 2, entry 11). One may agreed that the (*R*)(2*S*)-**15k** and (*R*)(2*R*)-**15k** featured with comparable intrinsic thermodynamical stability, thus exhibiting low diastereoselectivity in the resolution process. According to the previous report, the phenyl ring of the benzyl group could shield the Nickel atom

to form extra metal-phenyl attraction, which possibly illustrated the better diastereoselectivity for resolution of **2a** than **2k**.[37]



Scheme 3. Thermodynamic equilibrium transformation of **15a** and **15k**.

To achieve the final goal of this study, we selected **2a** as an example of resolution of β^2-AAs to obtain the enantiomerically pure forms. After simple purification by column chromatography, diastereoselectively pure (*R*)(2*S*)-**15a** was subjected to the disassembly procedure presented in Scheme 4. The disassembly procedure was also conducted under simple reaction conditions, thus producing the target α-benzyl-β-amino acid (*S*)-**2a** with an excellent chemical yield (93%) and enantioselectivity (ee > 99%). Furthermore, (*R*)-**9** could be recycled easily in almost quantitative yield (98%) with high enantiomeric purity (ee > 99%). Thus, the recovered (*R*)-**9** could be reused for repetitive thermodynamic resolution of other racemic β^2-AAs.



Scheme 4. Disassembly of Nickel(II) complex (*R*)(2*S*)-**15a** to afford (*S*)-**2a**.

Conclusion

In conclusion, we have developed the first purely chemical method for the resolution of *C*,*N*-unprotected racemic β^2-AAs using stable, and recyclable proline-derived ligands with a quaternary carbon stereogenic center. This new approach is more versatile compared with biocatalytic methods, especially without requiring multi-step preparation for resolution substrates. The method showed a broad synthetic generality for various α-alkyl-substituted *C*,*N*-unprotected β-AAs with good to moderate diastereoselectivities, featuring with simple operation and mild reaction conditions.

Experimental Section

General Information

The commercially available chemicals were used without further purification. Anhydrous nickel acetate was prepared by heating reagent grade tetrahydrate for 2 h at 110°C in vacuum. ^{1}H and ^{13}C NMR spectra was recorded on a 400 MHz or 500 MHz Bruker AV400 instrument. 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), multiplet (m), and broad (br). High-resolution mass spectra (HRMS) was measured on Micromass Ultra Q-TOF spectrometer. The determination of dr was performed *via* ^{1}H NMR or LC/MS analysis using Agilent 6120 spectrometer. Optical rotations were measured using a 1 mL cell with a 1 dm path length on an Autopol VI automatic polarimeter and are reported as follows: $[\alpha]^{20}_{D}$ (c: g/100 mL, in solvent).

General Procedures

Nickel(II)-(*S*)-*N*-(2-benzoyl-4-chlorophenyl)-1-(3,4-dichlorobenzyl)-2-methylpyrrolidine-2-carboxamide/(*R*)-3-amino-2-benzylpropanoic acid Schiff Base Complex ((*S*)(2*R*)-10a)

(*S*)-**4** (50.20 mg, 0.10 mmol), 3-amino-2-benzylpropanoic acid **2a** (17.93 mg, 0.10 mmol), $Ni(OAc)_2$ (17.68 mg, 0.10 mmol), were dissolved in EtOH (2 mL) followed by DBU (149.31 μL, 1.00 mmol) being added. After being refluxed for 96 h, the reaction was terminated by ice water of 5% acetic acid (10 mL). The mixture was extracted with dichloromethane (10 mL × 3). The combined organic layers were dried with Na_2SO_4, and then concentrated and purified by column chromatography on silica gel (v/v, dichloromethane/methanol = 20/1) to give the crude products **10a** (55.1 mg, yield 76%) for analysis (dr = 81/19). The crude product **10a** was purified again by column chromatography on silica gel (v/v, dichloromethane/acetone = 5/1, R_f((*S*)(2*R*)-**10a**) = 0.4, R_f((*S*)(2*S*)-**10a**) = 0.25) to give the major pure diastereomer (*S*)(2*R*)-**10a** as a brown solid. mp 128-130°C. $[\alpha]^{20}_D$ = +2426.5 (c = 0.034, $CHCl_3$).^{1}H NMR (400 MHz, Methanol-d_4) δ 8.91 (d, *J* = 2.1 Hz, 1H), 8.32 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.74 (d, *J* = 9.2 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.39 – 7.25 (m, 2H), 7.23 – 7.12 (m, 4H), 7.06 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.03 – 6.95 (m, 3H), 6.64 (dt, *J* = 7.6, 1.6 Hz, 1H), 6.42 (d, *J* = 2.6 Hz, 1H), 3.98 – 3.83 (m, 2H), 3.77 (d, *J* = 13.3 Hz, 1H), 3.58 – 3.48 (m, 1H), 3.40 (d, *J* = 13.3 Hz, 1H), 3.27 – 3.18 (m, 1H), 3.14 – 3.02 (m, 2H), 2.68 – 2.62 (m, 1H), 2.51 – 2.10 (m, 4H), 1.43 (s, 3H).^{13}C NMR (125 MHz, Methanol-d_4) δ 182.5, 180.4, 173.1, 141.3, 139.8, 138.2, 134.9, 134.6, 133.9, 133.5, 133.1, 132.7, 132.4, 132.2, 131.2, 131.0, 130.3, 130.2, 129.9, 129.6, 128.1, 127.7, 127.6, 126.8, 125.9, 74.9, 56.7, 56.3, 55.3, 49.3, 42.8, 37.2, 22.2, 18.6. LRMS (ESI+APCI) *m/z*: 718.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{36}H_{33}Cl_3N_3NiO_3$ 718.0935; Found 718.0940.

(*S*)-*N*-(2-benzoyl-4-chlorophenyl)-1-(3,4-dibromobenzyl)-2-methylpyrrolidine-2-carboxamide ((*S*)-6)

Yellow oil (3.7 g, yield 90%). $[\alpha]^{20}_D$ = -26.2 (c = 0.118, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.72 (s, 1H), 8.63 (d, *J* = 8.7 Hz, 1H), 7.83 (d, *J* = 1.9 Hz, 1H), 7.76 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.65 – 7.62 (m, 1H), 7.55 – 7.47 (m, 4H), 7.31 (d, *J* = 8.2 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 3.77 (d, *J* = 13.5 Hz, 1H), 3.38 (d, *J* = 13.5 Hz, 1H), 3.16 (t, *J* = 8.1 Hz, 1H), 2.40 (q, *J* = 8.1 Hz, 1H), 2.23 – 2.13 (m, 1H), 1.91 – 1.75 (m, 3H), 1.39 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.0, 176.5, 140.0, 138.4, 137.9, 133.8, 133.4, 133.3, 133.0, 132.2, 130.1, 128.8, 128.5, 127.2, 125.9,

124.7, 122.9, 122.8, 68.8, 53.4, 51.3, 40.1, 22.6, 16.4. LRMS (ESI+APCI) *m/z*: 590.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{24}Br_2ClN_2O_2$ 588.9888; Found 588.9877.

(*S*)-*N*-(2-benzoyl-4-chlorophenyl)-1-(3,4-dimethoxybenzyl)-2-methylpyrrolidine-2-carboxamide ((*S*)-7)

Yellow oil (3.5 g, yield 92%). $[\alpha]^{20}_D$ = -34.3 (c = 0.103, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.64 (s, 1H), 8.56 (d, *J* = 9.0 Hz, 1H), 7.73 – 7.69 (m, 2H), 7.64 – 7.59 (m, 1H), 7.52 – 7.48 (m, 3H), 7.45 (d, *J* = 2.5 Hz, 1H), 7.08 (d, *J* = 2.0 Hz, 1H), 6.83 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.58 (d, *J* = 8.2 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.37 (d, *J* = 13.0 Hz, 1H), 3.14 (td, *J* = 8.1, 7.6, 4.1 Hz, 1H), 2.43 – 2.36 (m, 1H), 2.18 – 2.08 (m, 1H), 1.85 – 1.69 (m, 4H), 1.39 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.8, 176.9, 148.9, 147.9, 138.2, 137.9, 133.2, 132.9, 131.8, 131.5, 130.0, 128.5, 127.3, 126.6, 123.2, 120.6, 111.8, 110.7, 68.5, 55.8, 54.0, 51.1, 40.2, 22.6, 16.2. LRMS (ESI+APCI) *m/z*: 493.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{30}ClN_2O_4$ 493.1889; Found 493.1875.

Nickel(II)-(*S*)-*N*-(2-benzoyl-4-chlorophenyl)-1-benzyl-2-methylpyrrolidine-2-carboxamide/(*R*)-3-amino-2-benzylpropanoic acid Schiff Base Complex ((*S*)(2*R*)-11a)

Brown solid (48.1 mg, yield 74%). mp 128-130 °C. $[\alpha]^{20}_D$ = +2739.1(c = 0.046, $CHCl_3$). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.58 – 8.50 (m, 2H), 7.59 (d, *J* = 9.1 Hz, 1H), 7.40 – 7.26 (m, 4H), 7.20 – 7.11 (m, 5H), 7.01 – 6.96 (m, 4H), 6.66 (dt, *J* = 7.3, 1.7 Hz, 1H), 6.40 (d, *J* = 2.6 Hz, 1H), 3.97 – 3.81 (m, 2H), 3.76 (d, *J* = 13.1 Hz, 1H), 3.65 – 3.53 (m, 1H), 3.40 (d, *J* = 13.1 Hz, 1H), 3.30 – 3.21 (m, 1H), 3.12 – 3.04 (m, 2H), 2.65 – 2.59 (m, 1H), 2.47 – 2.11 (m, 4H), 1.46 (s, 3H). ^{13}C NMR (125 MHz, Methanol-d_4) δ 182.8, 180.5, 172.9, 141.6, 139.9, 137.1, 135.0, 132.8, 132.6, 132.3, 131.2, 131.1, 130.2, 130.1, 130.1, 130.0, 129.6, 129.5, 128.1, 127.7, 127.6, 126.8, 126.5, 75.1, 57.9, 56.8, 55.3, 49.1, 42.9, 37.2, 22.6, 18.6. LRMS (ESI+APCI) *m/z*: 650.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{36}H_{35}ClN_3NiO_3$ 650.1715; Found 650.1721.

Nickel(II)-(*S*)-*N*-(2-benzoyl-4-chlorophenyl)-1-(3,4-dibromobenzyl)-2-methylpyrrolidine-2-carboxamide/(*R*)-3-amino-2-benzylpropanoic acid Schiff Base Complex ((*S*)(2*R*)-12a)

Brown solid (57.2 mg, yield 89%). mp 132-134 °C. $[\alpha]^{20}_{D}$ = +2723.3 (c = 0.048, $CHCl_3$). ^{1}H NMR (500 MHz, Methanol-d_4) δ 9.34 (d, *J* = 2.1 Hz, 1H), 8.08 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.77 (d, *J* = 9.2 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.23 – 7.15 (m, 4H), 7.09 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.03 (d, *J* = 7.9 Hz, 1H), 7.00 (dd, *J* = 6.5, 2.9 Hz, 2H), 6.67 (d, *J* = 7.6 Hz, 1H), 6.45 (d, *J* = 2.5 Hz, 1H), 3.93 (td, *J* = 12.6, 5.0 Hz, 1H), 3.86 (t, *J* = 12.4 Hz, 1H), 3.78 (d, *J* = 13.3 Hz, 1H), 3.60 – 3.48 (m, 1H), 3.40 (d, *J* = 13.3 Hz, 1H), 3.29 – 3.23 (m, 1H), 3.14 (dd, *J* = 13.8, 3.7 Hz, 1H), 3.05 (dd, *J* = 12.8, 3.8 Hz, 1H), 2.66 (dd, *J* = 13.8, 9.8 Hz, 1H), 2.49 – 2.36 (m, 2H), 2.33 – 2.24 (m, 1H), 2.22 – 2.13 (m, 1H), 1.45 (s, 3H). ^{13}C NMR (125 MHz, Methanol-d_4) δ 181.1, 179.1, 171.8, 139.8, 138.5, 137.6, 136.7, 134.3, 133.6, 131.9, 131.5, 131.2, 129.8, 129.5, 128.9, 128.8, 128.6, 128.2, 126.7, 126.3, 126.2, 125.5, 125.0, 124.5, 124.3, 78.1, 73.5, 55.3, 54.8, 53.9, 41.4, 35.8, 20.9, 17.3. LRMS (ESI+APCI) *m/z*: 809.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{36}H_{33}Br_2ClN_3NiO_3$ 805.9925; Found 805.9912.

Nickel(II)-(*S*)-*N*-(2-benzoyl-4-chlorophenyl)-1-(3,4-dimethoxybenzyl)-2-methylpyrrolidine-2-carboxamide/(*R*)-3-amino-2-benzylpropanoic acid Schiff Base Complex ((*S*)(2*R*)-13a)

Brown solid (53.8 mg, yield 83%). mp 130-132 °C. $[\alpha]^{20}_{D}$ = +2690.6 (c = 0.050, $CHCl_3$). ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.37 (d, *J* = 2.1 Hz, 1H), 7.88 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.70 (d, *J* = 9.2 Hz, 1H), 7.39 (tt, *J* = 7.5, 1.3 Hz, 1H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.24 – 7.17 (m, 4H), 7.04 – 6.97 (m, 4H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.68 (d, *J* = 7.6 Hz, 1H), 6.41 (d, *J* = 2.5 Hz, 1H), 3.96 (t, *J* = 12.5 Hz, 1H), 3.93 – 3.90 (m, 1H), 3.89 (s, 3H), 3.76 (d, *J* = 13.3 Hz, 1H), 3.71 (s, 3H), 3.65 – 3.56 (m, 1H), 3.23 (ddd, *J* = 11.2, 8.2, 1.5 Hz, 1H), 3.11 (dd, *J* = 13.8, 3.8 Hz, 1H), 3.08 (dd, *J* = 12.9, 3.9 Hz, 1H), 2.70 (dd, *J* = 13.8, 9.7 Hz, 1H), 2.50 – 2.36 (m, 3H), 2.34 – 2.25 (m, 1H), 2.18 (td, *J* = 10.9, 8.3 Hz, 1H), 1.48 (s, 3H). ^{13}C NMR (125 MHz, Methanol-d_4) δ 181.8, 179.2, 171.5, 149.3, 149.0, 140.4, 138.4, 133.6, 131.2, 130.9, 129.8, 129.8, 128.8, 128.8, 128.8, 128.6, 128.2, 126.8, 126.2, 125.1, 125.0, 123.7, 114.6, 111.7, 78.1, 73.3, 55.7, 55.4, 55.0, 54.7, 54.1, 41.8, 35.9, 21.0, 17.2. LRMS (ESI+APCI) *m/z*: 710.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{38}H_{39}ClN_3NiO_5$ 710.1926; Found 710.1926.

Nickel(II)-(*S*)-*N*-(2-benzoyl-4-chlorophenyl)-2-methyl-1-(3-phenylpropyl)pyrrolidine-2-carboxamide/(*R*)-3-amino-2-benzylpropanoic acid Schiff Base Complex ((*S*)(2*R*)-14a)

Brown solid (46.8 mg, yield 69%). mp 103-105 °C. $[\alpha]^{20}_{D}$ = +2756.3 (c = 0.048, $CHCl_3$). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.99 (d, *J* = 9.1 Hz, 1H), 7.38 – 7.29 (m, 2H), 7.25 – 7.10 (m, 10H), 7.02 – 6.93 (m, 3H), 6.73 – 6.68 (m, 1H), 6.52 (d, *J* = 2.6 Hz, 1H), 3.95 – 3.82 (m, 2H), 3.69 – 3.56 (m, 1H), 3.20 – 3.04 (m, 5H), 2.85 – 2.78 (m, 1H), 2.67 – 2.43 (m, 4H), 2.36 – 2.19 (m, 3H), 1.88 – 1.81 (m, 1H), 1.14 (s, 3H). ^{13}C NMR (125 MHz, Methanol-d_4) δ 183.3, 180.6, 173.1, 142.1, 141.8, 140.0, 135.0, 133.5, 133.1, 131.7, 131.1, 130.2, 130.1, 129.9, 129.6, 129.4, 129.4, 128.1, 127.8, 127.6, 127.1, 126.9, 126.5, 75.5, 57.0, 54.7, 54.3, 49.0, 41.7, 37.2, 34.7, 31.9, 23.4, 18.1. LRMS (ESI+APCI) *m/z*: 678.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{38}H_{39}ClN_3NiO_3$ 678.2028; Found 678.2035.

Nickel(II)-(*R*)-*N*-(2-benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*S*)-3-amino-2-benzylpropanoic acid Schiff Base Complex ((*R*)(2*S*)-15a)

Brown solid (48.2 mg, yield 82%). mp 120-122 °C. $[\alpha]^{20}_{D}$ = -2726.5 (c = 0.034, $CHCl_3$). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.14 (d, *J* = 9.2 Hz, 1H), 7.38 – 7.34 (m, 2H), 7.26 (dd, *J* = 9.1, 2.6 Hz, 1H), 7.17 – 7.11 (m, 4H), 7.04 – 6.92 (m, 3H), 6.81 – 6.70 (m, 1H), 6.53 (d, *J* = 2.6 Hz, 1H), 3.95 (t, *J* = 12.4 Hz, 1H), 3.86 – 3.61 (m, 2H), 3.23 – 3.07 (m, 3H), 2.66 – 2.41 (m, 3H), 2.39 – 2.24 (m, 3H), 1.93 – 1.86 (m, 4H), 1.24 (s, 3H). ^{13}C NMR (100 MHz, Methanol-d_4) δ 183.7, 180.6, 173.0, 141.9, 140.0, 135.0, 133.5, 133.0, 131.7, 131.1, 130.2, 130.1, 129.9, 129.6, 128.1, 127.9, 127.6, 126.9, 126.5, 74.9, 57.0, 54.6, 49.7, 48.9, 41.9, 37.2, 23.4, 18.1, 15.5. LRMS (ESI+APCI) *m/z*: 588.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{31}H_{33}ClN_3NiO_3$ 588.1558; Found 588.1564.

Nickel(II)-(*R*)-*N*-(2-benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*S*)-3-amino-2-(4-methoxybenzyl)propanoic acid Schiff Base Complex ((*R*)(2*S*)-15b)

Brown solid (51.3 mg, yield 83%). mp 127-129 °C. $[\alpha]^{20}_{D}$ = -3618.8 (c = 0.032, $CHCl_3$). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.14 (d, *J* = 9.1 Hz, 1H), 7.41 – 7.32 (m, 2H), 7.26 (d, *J* = 9.1 Hz, 1H), 7.15 (t, *J* = 8.5 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.91 – 6.84 (m, 2H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.72 – 6.66 (m, 2H), 6.53 (d, *J* = 2.6 Hz, 1H), 3.94 (t, *J* = 12.4 Hz, 1H), 3.79 (s, 3H), 3.78 – 3.71 (m, 1H), 3.20 – 3.02 (m, 3H), 2.64 – 2.49 (m, 2H), 2.45 – 2.26 (m, 4H), 1.91 (t, *J* = 7.4 Hz, 3H), 1.24 (s, 3H). ^{13}C NMR (125 MHz, Methanol-d_4) δ 183.7, 180.7, 173.0, 159.8, 142.0, 135.1, 133.5, 133.0, 131.9, 131.7, 131.0, 131.0, 130.2, 130.2, 128.1, 127.9, 126.9, 126.6, 115.0, 75.0, 57.0, 55.7,

54.58, 49.7, 49.3, 42.0, 36.3, 23.4, 18.1, 15.5. LRMS (ESI+APCI) *m/z*: 618.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{32}H_{35}ClN_3NiO_4$ 618.1664; Found 618.1667.

Nickel(II)-(*R*)-*N*-(2-benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*S*)-3-amino-2-(4-methylbenzyl)propanoic acid Schiff Base Complex ((*R*)(2*S*)-15c)

Brown solid (42.1 mg, yield 70%). mp 124-126 °C. $[\alpha]^{20}_D$ = -3277.3 (c = 0.034, $CHCl_3$). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.13 (d, *J* = 9.1 Hz, 1H), 7.40 – 7.32 (m, 2H), 7.28 – 7.21 (m, 1H), 7.15 – 7.09 (m, 1H), 6.99 – 6.93 (m, 3H), 6.85 (d, *J* = 8.0 Hz, 2H), 6.77 (d, *J* = 7.2 Hz, 1H), 6.53 (d, *J* = 2.6 Hz, 1H), 3.93 (t, *J* = 12.4 Hz, 1H), 3.84 – 3.68 (m, 2H), 3.20 – 3.06 (m, 3H), 2.62 – 2.53 (m, 2H), 2.44 – 2.39 (m, 1H), 2.39 – 2.34 (m, 1H), 2.32 (s, 3H), 2.31 – 2.22 (m, 2H), 1.92 – 1.87 (m, 4H), 1.24 (s, 3H). ^{13}C NMR (125 MHz, Methanol-d_4) δ 183.7, 180.6, 173.0, 142.0, 137.1, 136.9, 135.1, 133.5, 133.0, 131.7, 130.8, 130.3, 130.1, 129.9, 128.1, 127.9, 126.9, 126.6, 75.0, 57.0, 54.7, 49.69, 42.0, 36.8, 23.4, 21.1, 18.1, 15.5. LRMS (ESI+APCI) *m/z*: 601.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{32}H_{35}ClN_3NiO_3$ 602.1715; Found 602.1705.

Nickel(II)-(*R*)-*N*-(2-benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*S*)-3-amino-2-(4-fluorobenzyl)propanoic acid Schiff Base Complex ((*R*)(2*S*)-15d)

Brown solid (46.1 mg, yield 76%). mp 123-124 °C. $[\alpha]^{20}_D$ = -3310.5 (c = 0.038, $CHCl_3$). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.15 (d, *J* = 9.1 Hz, 1H), 7.41 – 7.33 (m, 2H), 7.26 (dd, *J* = 9.1, 2.6 Hz, 1H), 7.21 – 7.13 (m, 1H), 7.03 – 6.94 (m, 3H), 6.90 – 6.82 (m, 2H), 6.78 (dt, *J* = 6.6, 1.9 Hz, 1H), 6.53 (d, *J* = 2.6 Hz, 1H), 3.96 (t, *J* = 12.3 Hz, 1H), 3.86 – 3.73 (m, 2H), 3.22 – 3.06 (m, 3H), 2.62 – 2.29 (m, 6H), 1.94 – 1.86 (m, 4H), 1.24 (s, 3H). ^{13}C NMR (125 MHz, Methanol-d_4) δ 183.7, 180.3, 173.0, 163.9, 162.0, 141.9, 136.1, 136.1, 135.1, 133.4, 133.0, 131.7, 131.6, 131.6, 130.9, 130.2, 130.2, 128.1, 127.8, 126.9, 126.6, 116.3, 116.1, 75.0, 56.9, 54.5, 49.7, 49.1, 41.9, 36.3, 23.4, 18.1, 15.5. LRMS (ESI+APCI) *m/z*: 606.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{31}H_{32}ClFN_3NiO_3$ 606.1464; Found 606.1476.

Nickel(II)-(*R*)-*N*-(2-benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*S*)-3-amino-2-(4-(trifluoromethyl)benzyl)propanoic acid Schiff Base Complex ((*R*)(2*S*)-15e)

Brown solid (47.2 mg, yield 72%). mp 137-139 °C. $[\alpha]^{20}_{D}$ = -3950.5 (c = 0.046, $CHCl_3$). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.14 (d, *J* = 9.1 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.35 – 7.25 (m, 3H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.05 – 6.95 (m, 2H), 6.78 (d, *J* = 7.6 Hz, 1H), 6.52 (d, *J* = 2.5 Hz, 1H), 4.00 (t, *J* = 12.3 Hz, 1H), 3.88 – 3.78 (m, 2H), 3.30 – 3.26 (m, 1H), 3.21 (dd, *J* = 11.1, 7.4 Hz, 1H), 3.07 (dd, *J* = 12.7, 3.4 Hz, 1H), 2.61 – 2.44 (m, 3H), 2.39 – 2.30 (m, 3H), 1.94 – 1.87 (m, 4H), 1.25 (s, 3H). ^{13}C NMR (125 MHz, Methanol-d_4) δ 183.7, 179.9, 173.1, 145.1, 142.0, 135.1, 133.4, 133.1, 131.4, 131.0, 130.6, 130.1, 130.0, 129.8, 129.5, 128.0, 127.7, 126.9, 126.6, 126.5, 126.5, 75.0, 56.8, 54.5, 49.7, 42.0, 36.9, 23.4, 18.1, 15.5. LRMS (ESI+APCI) *m/z*: 655.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{32}H_{32}ClF_3N_3NiO_3$ 656.1432; Found 656.1431.

Nickel(II)-(*R*)-*N*-(2-benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*S*)-3-amino-2-methylpropanoic acid Schiff Base Complex ((*R*)(2*S*)-15f)

Brown solid (42.5 mg, yield 83%). mp 257-259 °C. $[\alpha]^{20}_{D}$ = -4854.5 (c = 0.044, $CHCl_3$). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.17 (d, *J* = 9.1 Hz, 1H), 7.66 – 7.49 (m, 3H), 7.45 – 7.35 (m, 1H), 7.29 (dd, *J* = 9.1, 2.5 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.65 (d, *J* = 2.6 Hz, 1H), 4.26 – 3.53 (m, 3H), 3.29 – 3.18 (m, 1H), 3.12 – 2.90 (m, 1H), 2.64 – 2.18 (m, 5H), 2.06 – 1.76 (m, 4H), 1.26 (s, 3H), 0.98 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, Methanol-d_4) δ 183.7, 182.0, 172.7, 142.0, 135.8, 133.6, 133.1, 131.5, 130.6, 130.1, 128.7, 128.3, 126.9, 126.6, 75.1, 59.8, 54.4, 49.8, 42.1, 41.9, 23.4, 18.1, 15.5, 15.2. LRMS (ESI+APCI) *m/z*: 512.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{29}ClN_3NiO_3$ 512.1245; Found 512.1259.

Nickel(II)-(*R*)-*N*-(2-benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*S*)-2-(aminomethyl)-4-methylpentanoic acid Schiff Base Complex ((*R*)(2*S*)-15g)

Brown solid (44.3 mg, yield 80%). mp 120-122 °C. $[\alpha]^{20}_{D}$ = -4383.3 (c = 0.048, $CHCl_3$). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.19 (d, *J* = 9.1 Hz, 1H), 7.60 – 7.52 (m, 3H), 7.44 – 7.42 (m, 1H), 7.29 (dd, *J* = 9.1, 2.6 Hz, 1H), 6.99 (dd, *J* = 7.7, 1.7 Hz, 1H), 6.67 (d, *J* = 2.6 Hz, 1H), 3.95 – 3.73 (m, 3H), 3.25 – 3.14 (m, 2H), 2.62 – 2.53 (m, 1H), 2.41 – 2.32 (m, 3H), 2.24 – 2.17 (m, 1H), 1.94 – 1.86 (m, 4H), 1.74 – 1.67 (m, 1H), 1.26 (s, 3H), 1.25 – 1.05 (m, 2H), 0.78 (dd, *J* = 6.5, 3.8 Hz, 6H). ^{13}C NMR (125 MHz, Methanol-d_4) δ 183.6, 181.9, 172.9, 142.0, 135.9, 133.5, 133.1, 131.4, 131.3, 130.7, 130.2, 128.5, 128.4, 126.9, 126.6, 75.1, 58.0, 54.3, 49.8, 45.2, 41.9, 40.8, 26.8, 23.6,

23.4, 22.2, 18.1, 15.5.LRMS (ESI+APCI) *m/z*: 554.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{35}ClN_3NiO_3$ 554.1715; Found 554.1720.

Nickel(II)-(*R*)-*N*-(2-benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*S*)-2-(aminomethyl)-3-methylbutanoic acid Schiff Base Complex ((*R*)(2*S*)-15h)

Brown solid (43.7 mg, yield 81%). mp 130-132 °C. $[\alpha]^{20}_D$ = -3241.0 (c = 0.034, $CHCl_3$). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.18 (d, *J* = 9.1 Hz, 1H), 7.61 – 7.53 (m, 3H), 7.46 – 7.39 (m, 1H), 7.29 (dd, *J* = 9.1, 2.6 Hz, 1H), 7.00 (d, *J* = 7.5 Hz, 1H), 6.66 (d, *J* = 2.6 Hz, 1H), 4.03 – 3.87 (m, 2H), 3.85 – 3.74 (m, 1H), 3.24 – 3.16 (m, 2H), 2.60 – 2.46 (m, 2H), 2.41 – 2.32 (m, 3H), 2.14 – 2.08 (m, 1H), 1.95 – 1.87 (m, 4H), 1.26 (s, 3H), 0.72 (d, *J* = 6.9 Hz, 3H), 0.65 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, Methanol-d_4) δ 183.6, 181.0, 173.1, 142.1, 135.7, 133.4, 133.1, 131.5, 130.6, 130.2, 128.6, 128.5, 126.9, 126.6, 75.1, 54.3, 54.0, 53.1, 49.8, 42.0, 29.7, 23.4, 20.9, 18.1, 17.9, 15.5. LRMS (ESI+APCI) *m/z*: 539.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{33}ClN_3NiO_3$ 540.1558; Found 540.1566.

Nickel(II)-(*R*)-*N*-(2-benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*S*)-3-amino-2-cyclohexylpropanoic acid Schiff Base Complex ((*R*)(2*S*)-15i)

Brown solid (48.7 mg, yield 84%). mp 145-147 °C. $[\alpha]^{20}_D$ = -3161.8 (c = 0.034, $CHCl_3$). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.18 (d, *J* = 9.1 Hz, 1H), 7.66 – 7.51 (m, 3H), 7.42 – 7.37 (m, 1H), 7.28 (dd, *J* = 9.1, 2.6 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.65 (d, *J* = 2.6 Hz, 1H), 4.02 – 3.69 (m, 2H), 3.26 – 3.03 (m, 2H), 2.65 – 2.50 (m, 1H), 2.41 – 2.32 (m, 2H), 2.27 – 2.19 (m, 1H), 2.14 – 2.05 (m, 1H), 1.96 – 1.54 (m, 8H), 1.46 – 0.54 (m, 11H). ^{13}C NMR (125 MHz, Methanol-d_4) δ 183.6, 180.9, 173.0, 142.0, 135.7, 133.5, 133.0, 131.5, 131.4, 130.6, 130.2, 128.6, 128.4, 126.9, 126.6, 75.1, 54.8, 54.3, 52.9, 49.9, 41.9, 40.2, 32.5, 29.3, 27.8, 27.6, 27.2, 23.3, 18.0, 15.5. LRMS (ESI+APCI) *m/z*: 580.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{30}H_{37}ClN_3NiO_3$ 580.1871; Found 580.1876.

Nickel(II)-(*R*)-*N*-(2-benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*S*)-2-(aminomethyl)-3,3-dimethylbutanoic acid Schiff Base Complex ((*R*)(2*S*)-15j)

Brown solid (38.2 mg, yield 69%). mp = 136-137 °C. $[\alpha]^{20}_D$ = -3670.0 (c = 0.048, $CHCl_3$). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.21 (d, *J* = 9.1 Hz, 1H), 7.63 – 7.58 (m, 2H), 7.56 – 7.52 (m, 1H), 7.42 – 7.37 (m, 1H), 7.29 (dd, *J* = 9.1, 2.6 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.67 (d, *J* = 2.6

Hz, 1H), 4.27 (t, *J* = 12.5 Hz, 1H), 4.07 – 3.97 (m, 1H), 3.93 – 3.84 (m, 1H), 3.33 (d, *J* = 4.7 Hz, 1H), 3.13 (dd, *J* = 10.9, 7.8 Hz, 1H), 2.66 (dq, *J* = 15.0, 7.5 Hz, 1H), 2.44 – 2.34 (m, 2H), 2.28 (dq, *J* = 14.1, 7.1 Hz, 1H), 2.07 (dd, *J* = 12.5, 4.7 Hz, 1H), 2.03 – 1.95 (m, 1H), 1.89 (t, *J* = 7.3 Hz, 3H), 1.24 (s, 3H), 0.84 (s, 9H). ^{13}C NMR (125 MHz, Methanol-d_4) δ 183.8, 181.5, 173.1, 142.3, 135.6, 133.5, 133.2, 131.7, 131.7, 130.6, 130.1, 128.8, 128.6, 126.9, 126.5, 74.9, 57.8, 56.4, 55.0, 49.5, 42.2, 33.9, 28.5, 23.7, 18.1, 15.5. LRMS (ESI+APCI) *m/z*: 655.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{35}ClN_3NiO_3$ 554.1715; Found 554.1728.

Nickel(II)-(*R*)-*N*-(2-benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*S*)-3-amino-2-phenylpropanoic acid Schiff Base Complex ((*R*)(2*S*)-15k)

Brown solid (41.9 mg, yield 73%). mp 150-151 °C. $[\alpha]^{20}_D$ = -3648.0 (c = 0.05, $CHCl_3$). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.20 (d, *J* = 9.1 Hz, 1H), 7.66 – 7.52 (m, 3H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.31 (dd, *J* = 9.1, 2.6 Hz, 1H), 7.28 – 7.16 (m, 3H), 7.10 – 7.03 (m, 2H), 6.91 (d, *J* = 7.7 Hz, 1H), 6.69 (d, *J* = 2.6 Hz, 1H), 4.34 (t, *J* = 13.0 Hz, 1H), 3.89 – 3.86 (m, 2H), 3.53 (dd, *J* = 11.8, 3.5 Hz, 1H), 3.29 – 3.97 (m, 1H), 3.15 (dd, *J* = 13.0, 3.6 Hz, 1H), 2.65 – 2.56 (m, 1H), 2.46 – 2.29 (m, 3H), 1.99 – 1.90 (m, 4H), 1.27 (s, 3H). ^{13}C NMR (125 MHz, Methanol-d_4) δ 183.7, 180.1, 173.3, 142.2, 139.1, 135.8, 133.7, 133.2, 131.6, 131.4, 130.6, 130.1, 129.8, 129.1, 128.5, 128.4, 128.4, 126.9, 126.7, 75.2, 60.1, 54.5, 54.3, 49.9, 41.9, 23.5, 18.1, 15.5. LRMS (ESI+APCI) *m/z*: 574.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{30}H_{31}ClN_3NiO_3$ 574.1402; Found 574.1405.

Nickel(II)-(*R*)-*N*-(2-benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*S*)-3-amino-2-(4-methoxyphenyl)propanoic acid Schiff Base Complex ((*R*)(2*S*)-15l)

Brown solid (39.3 mg, yield 65%). mp = 146-148 °C. $[\alpha]^{20}_D$ = -3052.4 (c = 0.042, $CHCl_3$). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.19 (d, *J* = 9.1 Hz, 1H), 7.68 – 7.52 (m, 3H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.31 (dd, *J* = 9.1, 2.6 Hz, 1H), 7.01 – 6.95 (m, 2H), 6.93 (d, *J* = 7.7 Hz, 1H), 6.84 – 6.77 (m, 2H), 6.69 (d, *J* = 2.6 Hz, 1H), 4.29 (t, *J* = 12.9 Hz, 1H), 3.91 – 3.78 (m, 2H), 3.73 (s, 3H), 3.48 (dd, *J* = 11.7, 3.6 Hz, 1H), 3.29 – 3.23 (m, 1H), 3.12 (dd, *J* = 13.0, 3.6 Hz, 1H), 2.64 – 2.56 (m, 1H), 2.44 – 2.34 (m, 3H), 1.95 (q, *J* = 10.3, 8.7 Hz, 4H), 1.27 (s, 3H). ^{13}C NMR (125 MHz, Methanol-d_4) δ 183.7, 180.6, 173.3, 160.4, 142.2, 135.8, 133.7, 133.2, 131.6, 131.4, 131.0, 130.6, 130.1, 128.5, 128.5, 126.9, 126.6, 115.2, 75.2, 60.2, 55.7, 54.4, 53.5, 49.9, 41.9, 23.5, 18.1, 15.5. LRMS (ESI+APCI) *m/z*: 604.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{31}H_{33}ClN_3NiO_4$ 604.1508; Found 604.1518.

Nickel(II)-(*R*)-*N*-(2-benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*S*)-3-amino-2-(4-chlorophenyl)propanoic acid Schiff Base Complex ((*R*)(2*S*)-15m)

Brown solid (42.0 mg, yield 69%). mp = 130-132 °C. $[\alpha]^{20}_{D}$ = -3312.5 (c = 0.048, $CHCl_3$). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.20 (d, *J* = 9.1 Hz, 1H), 7.65 – 7.44 (m, 4H), 7.31 (dd, *J* = 9.1, 2.6 Hz, 1H), 7.28 – 7.23 (m, 2H), 7.08 – 7.01 (m, 2H), 6.93 (d, *J* = 7.7 Hz, 1H), 6.69 (d, *J* = 2.6 Hz, 1H), 4.35 (t, *J* = 12.5 Hz, 1H), 3.97 – 3.81 (m, 2H), 3.54 (dd, *J* = 12.0, 3.4 Hz, 1H), 3.29 – 3.27 (m, 1H), 3.12 (dd, *J* = 12.9, 3.5 Hz, 1H), 2.63 – 2.50 (m, 1H), 2.46 – 2.31 (m, 3H), 1.98 – 1.90 (m, 4H), 1.27 (s, 3H). ^{13}C NMR (125 MHz, Methanol-d_4) δ 183.7, 179.6, 173.4, 142.2, 137.8, 135.7, 134.2, 133.7, 133.3, 131.6, 131.4, 130.8, 130.7, 130.1, 129.8, 128.6, 128.4, 127.0, 126.7, 75.2, 59.8, 54.4, 49.5, 41.9, 23.5, 18.1, 15.5. LRMS (ESI+APCI) *m/z*: 608.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{30}H_{30}Cl_2N_3NiO_3$ 608.1012; Found 608.1027.

Nickel(II)-(*R*)-*N*-(2-benzoyl-4-chlorophenyl)-1-ethyl-2-methylpyrrolidine-2-carboxamide/(*S*)-3-amino-2-(naphthalen-1-yl)propanoic acid Schiff Base Complex ((*R*)(2*S*)-15n)

Brown solid (47.4 mg, yield 76%). mp = 146-147 °C. $[\alpha]^{20}_{D}$ = -3440.0 (c = 0.046, $CHCl_3$). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.21 (d, *J* = 9.1 Hz, 1H), 7.80 – 7.72 (m, 3H), 7.65 (d, *J* = 4.6 Hz, 2H), 7.58 – 7.37 (m, 5H), 7.32 (dd, *J* = 9.1, 2.6 Hz, 1H), 7.18 (dd, *J* = 8.5, 1.8 Hz, 1H), 6.89 (dd, *J* = 7.8, 1.4 Hz, 1H), 6.70 (d, *J* = 2.6 Hz, 1H), 4.45 (t, *J* = 12.9, 11.8 Hz, 1H), 3.92 – 3.79 (m, 2H), 3.71 (dd, *J* = 11.7, 3.5 Hz, 1H), 3.38 – 3.32 (m, 1H), 3.22 (dd, *J* = 13.0, 3.5 Hz, 1H), 2.69 – 2.53 (m, 1H), 2.48 – 2.27 (m, 3H), 2.02 – 1.87 (m, 4H), 1.26 (s, 3H). ^{13}C NMR (125 MHz, Methanol-d_4) δ 183.7, 180.1, 173.4, 142.2, 136.4, 135.8, 134.9, 134.0, 133.7, 133.3, 131.6, 131.4, 130.6, 130.1, 129.5, 128.7, 128.6, 128.5, 128.5, 128.2, 127.3, 127.0, 127.0, 126.9, 126.7, 75.2, 60.0, 54.4, 54.4, 49.9, 41.9, 23.5, 18.1, 15.5.LRMS(ESI+APCI) *m/z*: 624.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{34}H_{33}ClN_3NiO_3$ 624.1558; Found 624.1576.

(*S*)-3-Amino-2-benzylpropanoic acid ((*S*)-2a)

A solution of (*R*)(2*S*)-**15a** (1.50 g, 2.55 mmol) in MeOH (20 mL) was added to a stirring solution of 3*N* HCl in MeOH (1/1, v/v) 40 mL at 50 °C. The mixture was gently heated under reflux for 30 min, the solution was 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 evaporated under vacuum to afford the free chiral ligand (*R*)-**9** (930 mg, yield 98%). The aqueous phase was evaporated under vacuum and dissolved in a

minimum amount of H_2O and loaded on a Dowex 50×2 100 ion-exchange column, which was washed with H_2O until neutral. The column was then washed with 10% aq NH_4OH. The first fraction (400 mL) was collected and evaporated under vacuum to afford the corresponding amino acid (*S*)-**2a** as a white solid (425 mg, yield 93%). mp = 208-210 ^oC. $[\alpha]^{20}_D$ = - 16.5 (c = 1, 1 *M* HCl). [ref.[38] $[\alpha]^{25}_D$ = - 16.0 (c = 1, 1 *M* HCl)]. ^1H NMR (400 MHz, D_2O) δ 7.39 – 7.16 (m, 5H), 3.08 – 2.69 (m, 5H). ^{13}C NMR (100 MHz, D_2O) δ 181.5, 140.4, 130.8, 130.5, 128.6, 49.0, 42.5, 38.0. LRMS (ESI+APCI) *m/z*: 180.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{14}NO_2$ 180.1019; Found 180.1014.

Supporting Information

X-ray crystal structures of (*S*)(2*R*)-**10a** and (*S*)(2*S*)-**10a**.

^1H NMR spectra for dr value determination of **10a-15a** and **15b-15n**.

HPLC spectra for ee value determination of (*S*)-**2a** and (*R*)-**9**.

^1H and ^{13}C NMR spectra for all compounds.

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