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A Convenient Method for the Asymmetric Synthesis of Fluorinated α-Amino Acids from Alcohols

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Due to their numerous applications, fluorinated amino acids have recently attracted significant attention. The preparation of fluorine-containing phenylalanines, heteroaryl alanines and aliphatic fluorinated amino acids using Mitsunobu–Tsunoda alkylation of a chiral nucleophilic glycine equivalent with readily available alcohol substrates is described. The reaction proceeds in high yields and with excellent diastereoselectivity. This method provides an efficient synthetic route to fluorinated amino acids for which asymmetric approaches are scarce.

Introduction

Fluorine-containing compounds have emerged as a major target for new synthetic methods. Indeed, due to the interesting physical, chemical and biological properties conferred by the presence of fluorine, introduction of this atom is becoming a key strategy in agrochemical and pharmaceutical discovery as well as in materials science.[1] In particular, fluorinated amino acids are remarkable building blocks for peptide and protein design as they demonstrate enhanced chemical and thermal stability compared to their non-fluorinated counterparts resulting in novel chemical and biological properties.[2] Interesting effects have also been observed on the structure and overall assemblies of protein materials containing fluorinated amino acids.[2a,3] Consequently, synthetic studies focusing on fluorinated amino acids have attracted much attention.[4]

The high demand for fluorinated amino acids, has prompted several research groups to focus their effort on the development of asymmetric syntheses for the preparation of side-chain fluorinated α-amino acids.[4a,4e] A common approach for construction of compounds relies on the stereoselective alkylation of an enantiopure auxiliary.[5] Previous work by Soloshonok describing the use of the Ni^{II} chiral complex developed by Belokon,[6] is of particular interest.[5a,5b] However such methods suffer from drawbacks associated with the use of expensive alkyl halides. Although organohalides can be readily synthesized from alcohol precursors, they often have limited shelf-lives and are best used immediately after their preparation, thus restricting their application in high throughput synthesis. Owing to the limited range of commercially available alkyl halides, studies into the scope of the reaction are often limited to only a few examples. A general method allowing access to a wide range of side-chain fluorinated enantiopure α-amino acids is therefore of great interest.

We recently reported an efficient preparation of chiral amino acids by Mitsunobu–Tsunoda alkylation of a nickel(II) complex of the glycine Schiff base (**1**) with various alcohols using (cyanomethylene)tributylphosphorane (CMBP) **2**.[7] This new route to non-proteinogenic α-amino acids by C–C bond formation offers many advantages over currently used approaches. Firstly, it is well-suited for the synthesis of libraries of compounds since a vast pool of structurally diverse commercially available alcohols can be used as pro-electrophiles. Secondly, it consistently proceeds with high stereoselectivity and does not require harsh reaction conditions. Finally, chiral auxiliary **1** is easily prepared in excellent yields from inexpensive starting materials in only three steps.[8] To the best of our knowledge, alkylation of the Belokon complex by fluorinated alcohols has not been studied. Herein, we report the synthesis of aromatic and aliphatic fluorinated amino acids by Mitsunobu–Tsunoda alkylation chemistry.

Results and Discussion

We initially studied alkylation of the nickel complex **1** with 4,4,4-trifluorobutanol **3l** in the presence of CMBP (**2**) (Table 1). According to Tsunoda, better results can be obtained when the Mistunobu-type reaction is performed at high temperature.[9] In addition, the high diastereoselectivities observed in our previous report,[7] despite the elevated

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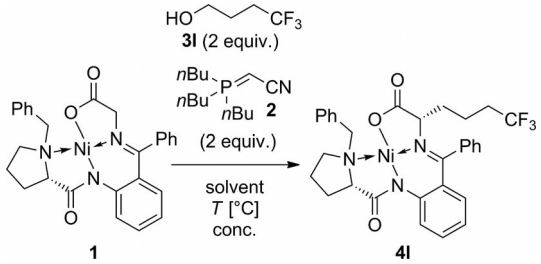
temperature employed, suggest that alkylation of the Belokon complex under Mitsunobu–Tsunoda conditions takes place under thermodynamic control. Consequently, it was envisaged that carrying out the reaction in high boiling point solvents might lead to substantially higher yields and diastereoselectivities. When the reaction was performed at 120 °C in toluene, expected product **4l** was obtained in 71% yield with a diastereoisomeric ratio of 84:16 in favour of the (*S*,*S*)-diastereoisomer (Table 1, Entry 1).

Table 1. Optimization of reaction conditions.[a]



Entry	Solvent	*T* [°C]	Conc. [M]	Yield[d] [%]	*dr*[e]
1	toluene	120	1	71	84:16
2	dichloroethane	90	1	0	–
3	*tert*-butyl acetate	105	1	25	88:12
4	di-*n*-butyl ether	120	1	79	89:11
5	butyronitrile	120	1	76	85:15
6	DMF	120	1	83	86:14
7	dioxane	105	1	71	85:15
8	xylene	120	1	84	88:12
9	trifluorotoluene	105	1	84	91:9
10[b]	trifluorotoluene	105	1	84	92:8
11[c]	trifluorotoluene	105	1	82	91:9
12	trifluorotoluene	105	0.5	90	91:9
13	trifluorotoluene	105	0.3	79	91:9

[a] Reaction conditions: a mixture of **1**/crude **2**/**3l** (1:2:2) dissolved in solvent was heated in a sealed tube for 20 h. [b] Using distilled CMBP **2**. [c] Using commercial CMBP **2**. [d] Yields refer to chromatographically pure mixture of diastereoisomers **4**. [e] *dr* (*S*,*S*)/(*S*,*R*) determined by ^{1}H NMR analysis of the isolated isomeric mixture.

Although no reaction was found to occur when using dichloroethane as the reaction solvent (Table 1, Entry 2), most solvents examined enabled formation of alkylated Ni^{II} complex **4l** with good diastereoselectivity. Use of *tert*-butyl acetate as solvent led to the desired compound in only 25% yield (Table 1, Entry 3). However, it was interesting to observe that yields up to 70% were attainable when the reaction was performed in di-*n*-butyl ether, butyronitrile, DMF, dioxane or xylene (Table 1, Entries 4–8). Finally, we postulated that use of a fluorinated solvent might improve both the yield and stereoselectivity of the reaction. The reaction was thus performed in trifluorotoluene (Table 1, Entry 9), resulting in an improved diastereoisomeric ratio of 91:9 and an 84% yield.

The quality of cyanophosphorane reagent **2** was also examined. Tsunoda previously reported that higher yields were obtained using freshly distilled CMBP **2** for the Mitsunobu reaction on *p*-toluenesulfonamide.[10] In the present work the reaction was performed using both distilled and commercial CMPB (Table 1, Entries 10, 11). Notably, **4l** was generated in both cases with yields and stereoselectivities that were comparable regardless of CMBP purity levels; the use of distilled **2** afforded only very slightly improved yields and stereoselectivity relative to crude **2**. The concentration of the reaction was also investigated (Table 1, Entries 12, 13). Although no difference in stereochemical outcomes was observed, an improved yield of 90% (versus 79%) was achieved using a concentration of 0.5 versus 1.0 M.

With optimized reaction conditions in hand, we proceeded to investigate the scope of the reaction using various commercially available fluorinated alcohols (Table 2). The ^{1}H NMR spectra of crude reaction mixtures were used to determine the diastereoisomeric ratios of (*S*,*S*)- and (*S*,*R*)-Ni^{II} complexes **4**.

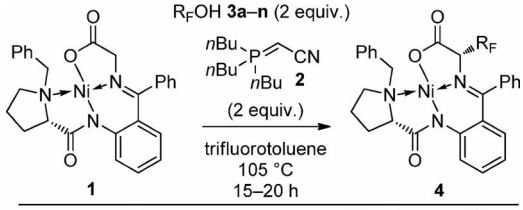
Initially, fluorinated benzyl alcohols were studied. Such fluorinated phenylalanine derivatives are of particular interest for structure and interaction studies of proteins and peptides.[2a,11] The reaction proceeded smoothly in high yields and with good selectivities when the aromatic ring was mono-, di- or tri-fluorinated (Table 2, Entries 1–4). Pure (*S*,*S*)-Ni^{II} complexes **4a**–**d** were isolated in yields ranging from 90–94%. However, the use of pentafluorobenzyl alcohol (Table 2, Entry 5) failed to afford desired alkylated product **4e**. Moreover, Mitsunobu–Tsunoda reaction of **3e** resulted only in full consumption of the CMBP and alcohol whereas Ni^{II} complex **1** was completely recovered.

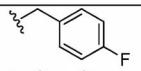
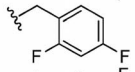
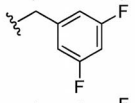
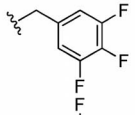
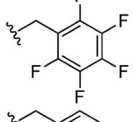
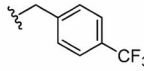
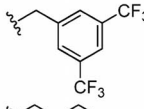
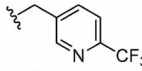
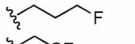
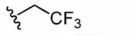
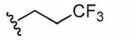
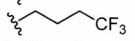
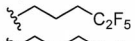
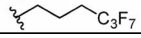
We next investigated the use of trifluoromethyl-substituted aromatic and heteroaromatic derivatives in this reaction to generate mono or bis(trifluoromethyl)benzyl-substituted glycine derivatives **4f** and **4g** (Table 2, Entries 6, 7) as well as (trifluoromethyl)pyridinyl derivative **4h** (Table 2, Entry 8) in high diastereoisomeric purity. Interestingly, the reaction was found to also proceed well when using various aliphatic linear fluorinated alcohols. Although lower yields and selectivities were observed relative to trials employing benzylic alcohols, the production of different linear fluorinated amino acids with this method represents a significant advance in this field. Indeed, with the exception of Soloshonok's report on the synthesis of linear trifluoromethylated amino acids,[5a] to the best of our knowledge, no general synthetic method for generating α-amino acids bearing a fluorinated linear chain has been described to date. Use of this Mitsunobu–Tsunoda glycine alkylation reaction resulted in isolation of major (*S*,*S*)-Ni^{II} complexes **4i** (Table 2, Entry 9) and **4l**–**n** (Table 2, Entries 12–14) in 50–80% yield.

Interestingly, attempts to carry out Mitsunobu–Tsunoda alkylation using 2,2,2-trifluoroethanol **3j** (Table 2, Entry 10) did not result in the formation of anticipated **4j**. In this case the cyanomethyl-substituted nickel(II) complex **5j** was isolated as a single diastereoisomer in i) 25% yield after heating with 2 equiv. of trifluoroethanol for 64 h, or ii) 65% yield using 4 equiv. of trifluoroethanol (Scheme 1).

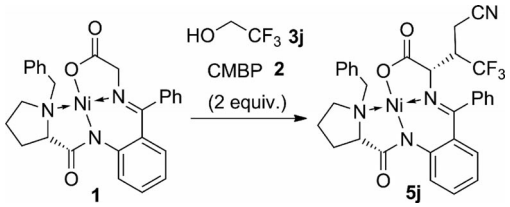
The structure of this adduct was confirmed by both NMR and MS analyses. The MS data revealed an excess mass of 39 g/mol relative to that anticipated for expected product **4j** consistent with the presence of a cyanomethyl

Table 2. Synthesis of fluorinated amino acid derivatives by Mitsunobu–Tsunoda alkylation of the Belokon complex.[a]



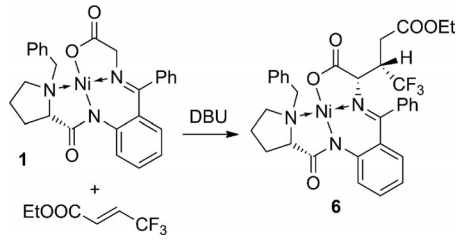
Entry	R_F		Yield[b] [%] (*S*,*S*)-**4**	*dr*[c] (*S*,*S*)/(*S*,*R*)
1		**a**	94	95/5
2		**b**	90	92/8
3		**c**	90	91/9
4		**d**	92	94/6
5		**e**	0	–
6		**f**	93	95/5
7		**g**	86	91/9
8		**h**	90	92/8
9		**i**	76	85/15
10		**j**	0	–
11		**k**	0	–
12		**l**	80	91/9
13		**m**	50	87/13
14		**n**	63	88/12

[a] Reaction conditions: A mixture of **1**/crude **2**/**3** (1:2:2) dissolved in trifluorotoluene was heated at 105 °C in a sealed tube until completion (15 to 20 h). [b] Yields were determined after isolation of the major (*S*,*S*)-**4** isomer by flash chromatography. [c] *dr* were determined by ^{1}H NMR analysis of the crude isomeric mixture **4**.



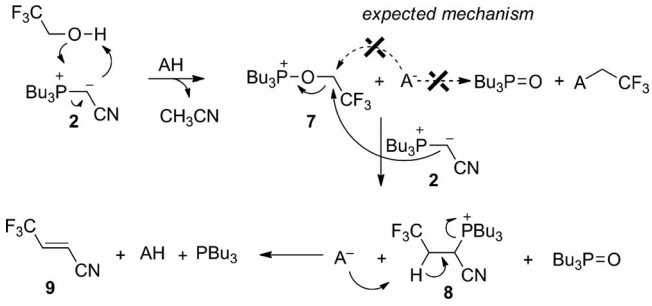
Scheme 1. Formation of cyanomethylated adduct **5j**.

group. The presence of this extra appendage was confirmed by analysis of the C–F coupling constant in the ^{13}C NMR of **5j** (see Supporting Information). One possible explanation for formation of **5j** entails the addition of trifluorobut-2-enenitrile to nickel(II) complex **1**. Indeed, a similar addition has been reported by Soloshonok et al. who reported that Michael reaction between (*E*)-ethyl trifluorobut-2-enoate and Ni^{II} complex **1** resulted in stereoselective formation of (*S*,*S*,*S*)-diastereoisomer **6** (Scheme 2).[12]



Scheme 2. Previously reported Michael reaction between **1** and (*E*)-ethyl trifluorobut-2-enoate.[12]

In the present work, trifluorobut-2-enenitrile could potentially be formed by formation of phosphonium salt **8** (Scheme 3).

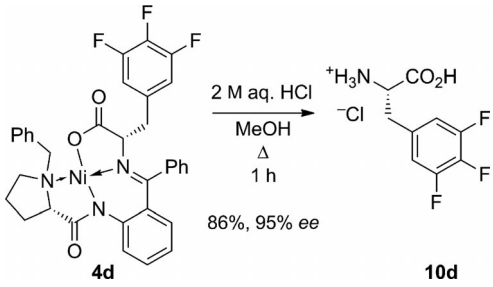


Scheme 3. Postulated mechanism for formation of trifluorobut-2-enenitrile (**9**).

In the expected reaction mechanism, stabilized methylene phosphoranes **2** are in equilibrium with their ylide forms. The ylide first deprotonates the alcohol, the resulting alkoxide then attacks the phosphonium part of ylide **2** to form oxyphosphonium ion **7** and acetonitrile anion. The latter deprotonates the pronucleophile, thus liberating acetonitrile and forming a nucleophilic species (A$^-$), which in turn forms desired alkylated product together with phosphine oxide by S_N2 reaction with oxyphosphonium intermediate **7**. However, instead of reacting with deprotonated Ni^{II} complex (A$^-$), oxyphosphonium salt **7** is attacked by a second equivalent of the ylide form of CMPB, forming phosphonium salt **8**. The deprotonated Ni^{II} complex then facilitates elimination of *n*-tributylphosphine to afford trifluorobut-2-enenitrile (**9**).

Finally, when 3,3,3-trifluoropropan-1-ol **3k** was employed as the pro-electrophile, no formation of desired product **4k** was observed. Again, the Ni^{II} complex **1** was recovered whereas CMBP **2** and alcohol **3k** were both consumed. It appears that when the strongly electron-withdrawing fluorinated group is too close to the alcohol functionality the reaction cannot proceed. Interestingly, in this case, the formation of the cyanomethyl-substituted product, which was previously isolated using trifluoroethanol, was not observed.

The chiral auxiliary can ultimately be cleaved in mildly acidic conditions according to our previously established protocol,[7] affording the amino acids in good yields and with little to no racemization. For instance, after heating compound **4d** at reflux for 1 h with 2 M aqueous HCl in methanol, the reaction was concentrated and filtered to render the precipitated BPB ligand. Reverse-phase column chromatography then afforded the pure HCl salt of fluorinated amino acid **10d** in 86% yield and with 95% *ee*, as determined by chiral HPLC (Scheme 4).



Scheme 4. Cleavage of Ni complex **4d** under mild conditions.

Conclusions

In summary, we have developed an efficient and rapid synthesis of enantiopure α-amino acids bearing fluorinated side-chains. Using the readily synthesized chiral Ni^{II} Belokon complex of glycine, the Mitsunobu–Tsunoda reaction has been demonstrated to proceed with high diastereoselectivity thus providing an efficient method for the asymmetric synthesis of a variety of aliphatic, benzylic or pyridinyl-substituted fluorinated α-amino acids. The commercial availability of both a wide range of fluorinated alcohols as well as the CMBP Tsunoda reagent make this synthetic process highly convenient for the preparation of α-amino acids containing fluorinated side-chains to enable systematic study of their biological and materials science applications.

Experimental Section

General: All reactions were carried out under an argon atmosphere in dried glassware with magnetic stirring. Solvents were dried with activated molecular sieves (4 Å). Reagents were purchased from commercial suppliers and used without further purification unless otherwise noted.

Analytical thin layer chromatography (TLC) was performed on 0.2 mm aluminium plates of silica gel 60 F_{254} (Merck) and compounds were visualized by ultraviolet fluorescence or by staining with a ninhydrin solution. Flash chromatography was carried out using Kieselgel S 63–100 μm (Riedel-de Haën) silica gel. Reversed-phase chromatography was performed using Davisil® chromatographic C18 bonded silica (633NC18E 60 Å 35–70 micron) (Grace GmbH & Co. KG) with indicated solvents. Infrared spectra were obtained with a Perkin–Elmer Spectrum One Fourier Transform infrared spectrometer with a universal ATR sampling accessory using neat samples and absorption maxima are expressed in wavenumbers (cm^{-1}). Proton NMR (^1H) spectra were recorded at 400 MHz, carbon NMR (^{13}C) spectra were recorded at 100 MHz and phosphorus NMR (^{31}P) spectra were recorded at 202 MHz. NMR experiments were carried out in $CDCl_3$ or D_2O. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent as an internal reference (^1H: 7.26, ^{13}C: 77.0 ppm for $CHCl_3$ and ^1H: 4.79 for DMSO). Data are reported as follows: chemical shift, multiplicity (s singlet, d doublet, t triplet, q quartet, m multiplet), coupling constants (Hz) and integration. Infrared spectra were recorded using neat samples, with a 100 FT-IR spectrometer and the characteristic IR absorption frequencies are reported in cm^{-1}. Optical rotations were performed with a polarimeter (589 nm) using a 700-μL cell with a path length of 1 dm. Enantiomeric excesses were determined using chiral HPLC with a Dionex Ultimate 3000 system using a Chirobiotic T 250 × 4.6 mm 5 μm column. The samples were injected at a volume of 5 μL and a concentration of 1 mg/mL. Mass spectra were obtained from with an AEI MS-9 using electron spray ionization (ESI). The HRMS spectra were measured using a MALDI-TOF instrument.

General Procedure for the Synthesis of (*S*,*S*)-4: Ni^{II} complex of glycine **1** (125 mg, 0.25 mmol), (cyanomethylene)tributylphosphorane **2** (130 μL, 0.50 mmol), and fluorinated alcohol **3** (0.50 mmol) were combined in trifluorotoluene (0.5 mL). The red mixture was heated in a sealed tube at 105 °C for 15 to 20 h. The red solution was cooled to room temperature and then purified by flash chromatography on silica gel using CH_2Cl_2/acetone (8:2) or EtOAc/toluene (8:2) as eluent.

General Procedure for the Synthesis of (*S*)-10: Substituted nickel complex (*S*,*S*)-**4** was dissolved in MeOH and 2 M HCl (2:1) to generate a solution of **4** (0.016 M). The bright red solution was heated at reflux (80 °C) for 30 min, until the red colour of the solution disappeared. The resulting yellow to green solution was cooled to room temperature and the solvents evaporated to dryness. Water was added to the residue which was then separated by column chromatography on C18 reverse phase silica gel. Pure water was employed as an eluent to remove the green $NiCl_2$ and excess HCl. A water/MeOH gradient elution was then used to obtain optically pure product **10** which was lyophilized. Released BPB ligand was recovered by elution with MeOH.

Ni^{II}-(*S*)-BPB/(*S*)-2-Amino-3-(4-fluorophenyl)propanoic Acid Schiff Base Complex (4a): Yield 95%, red crystal (m.p. 246–248 °C). $[\alpha]_D^{25}$ = +2052 (*c* = 0.1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3025, 2964, 2932, 2860, 1737, 1639, 1679, 1585, 1540, 1508, 1439, 1365, 1338, 1259, 1224, 1165, 751, 709, 624 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 8.7 Hz, 1 H), 8.05–7.95 (m, 2 H), 7.59–7.48 (m, 2 H), 7.47–7.41 (m, 1 H), 7.33–7.27 (m, 3 H), 7.19–7.04 (m, 6 H), 6.91–6.83 (m, 1 H), 6.70–6.62 (m, 2 H), 4.29 (d, *J* = 12.7 Hz, 1 H), 4.24 (dd, J_1 = 5.8, J_2 = 4.4 Hz, 1 H), 3.46 (d, *J* = 12.7 Hz, 1 H), 3.32 (dd, J_1 = 8.9, J_2 = 7.8 Hz, 1 H), 3.17–3.08 (m, 1 H), 3.04 (dd, J_1 = 13.8, J_2 = 4.4 Hz, 1 H), 2.83 (dd, J_1 = 13.8, J_2 = 5.8 Hz, 1 H), 2.51–2.30 (m, 3 H), 2.03–1.91 (m, 1 H), 1.82–1.70 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.2, 178.2, 171.1, 162.3 (d, *J* = 246 Hz), 142.7, 134.0, 133.3, 133.1, 132.3, 131.8 (d, *J* = 8 Hz, 2 C), 131.4 (d, *J* = 3 Hz), 131.3 (2 C), 129.7, 129.0, 128.8, 128.7, 128.6 (2 C), 127.6, 127.0, 125.9, 123.2, 120.5, 115.5 (d, *J* = 21 Hz, 2 C), 71.2, 70.2, 63.2, 57.1, 38.8, 30.6, 23.0 ppm. HRMS (ESI) *m*/*z* calculated for $C_{34}H_{30}FN_3NaNiO_3$ $[M + Na]^+$ 628.1517, found 628.1522.

Ni^{II}-(*S*)-BPB/(*S*)-2-Amino-3-(2,4-difluorophenyl)propanoic Acid Schiff Base Complex (4b): Yield 90%, red crystal (m.p. 119–121 °C). $[\alpha]_D^{21}$ = +2060 (*c* = 0.1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3025, 2969, 2945, 1742, 1676, 1644, 1439, 1370, 1219, 1232 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.30–8.24 (m, 1 H), 8.02–7.96 (m, 2 H),

7.57–7.49 (m, 2 H), 7.48–7.42 (m, 1 H), 7.35–7.27 (m, 3 H), 7.22–7.10 (m, 3 H), 7.02–6.97 (m, 1 H), 6.95–6.86 (m, 2 H), 6.69–6.62 (m, 2 H), 4.30 (d, J = 12.7 Hz, 1 H), 4.24 (dd, J_1 = 6.0, J_2 = 4.5 Hz, 1 H), 3.51 (d, J = 12.7 Hz, 1 H), 3.34 (dd, J_1 = 8.9, J_2 = 8.3 Hz, 1 H), 3.20–3.10 (m, 2 H), 2.90 (dd, J_1 = 14.0, 4.5 Hz, 1 H), 2.57–2.45 (m, 1 H), 2.43–2.34 (m, 2 H), 2.02–1.93 (m, 1 H), 1.85–1.74 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.2, 178.2, 172.0, 162.6 (dd, J_1 = 249, J_2 = 12 Hz), 161.8 (dd, J_1 = 249, J_2 = 12 Hz), 142.8, 134.0, 133.5, 133.3 (dd, J_1 = 10, J_2 = 6 Hz), 133.1, 132.4, 131.5 (2 C), 129.7, 129.0, 128.9, 128.8, 128.7 (2 C), 128.0 (d, J = 3 Hz), 127.1, 126.1, 123.3, 120.5, 118.9 (dd, J_1 = 16, J_2 = 4 Hz), 111.8 (dd, J_1 = 21, J_2 = 3 Hz), 103.9 (dd, J_1 = J_2 = 26 Hz), 70.6, 70.3, 63.3, 57.0, 32.8, 30.8, 23.1 ppm. HRMS (ESI) m/z calculated for $C_{34}H_{29}F_2N_3NaNiO_3$ [M + Na]$^+$ 646.1423, found 646.1424.

Ni^{II}-(*S*)-BPB/(*S*)-2-Amino-3-(3,5-difluorophenyl)propanoic Acid Schiff Base Complex (4c): Yield 90%, red crystal (m.p. 114–116 °C). $[\alpha]_D^{24}$ = +2063 (c = 0.1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2960, 2926, 2864, 1727, 1677, 1636, 1593, 1540, 1462, 1437, 1338, 1167, 1120, 1079, 1033, 809, 753 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28–8.17 (m, 1 H), 8.08–7.93 (m, 2 H), 7.62–7.50 (m, 2 H), 7.50–7.42 (m, 1 H), 7.36–7.26 (m, 3 H), 7.19–7.08 (m, 2 H), 6.97–6.86 (m, 1 H), 6.77 (tt, J_1 = 8.8, J_2 = 2.4 Hz, 1 H), 6.70–6.62 (m, 2 H), 6.62–6.54 (m, 2 H), 4.30 (d, J = 12.6 Hz, 1 H), 4.21 (dd, J_1 = 6.3, J_2 = 4.3 Hz, 1 H), 3.49 (d, J = 12.6 Hz, 1 H), 3.34 (dd, J_1 = 10.2, J_2 = 7.0 Hz, 1 H), 3.28–3.18 (m, 1 H), 2.98 (dd, J_1 = 13.8, J_2 = 4.3 Hz, 1 H), 2.89 (dd, J_1 = 13.8, 6.3 Hz, 1 H), 2.78–2.62 (m, 1 H), 2.53–2.33 (m, 2 H), 2.04–1.94 (m, 1 H), 1.93–1.81 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.2, 177.8, 171.3, 162.9 (dd, J_1 = 249, J_2 = 13 Hz, 2 C), 142.8, 139.5 (dd, J_1 = J_2 = 9 Hz), 133.8, 133.3, 133.1, 132.5, 131.4 (2 C), 129.9, 129.2, 128.9, 128.7, 128.6 (2 C), 127.5, 127.0, 125.8, 123.4, 120.5, 113.0 (dd, J_1 = 18, J_2 = 7 Hz, 2 C), 102.7 (dd, J_1 = J_2 = 25 Hz), 70.6, 70.2, 63.2, 57.1, 39.7, 30.6, 23.2 ppm. HRMS (ESI) m/z calculated for $C_{34}H_{29}F_2N_3NaNiO_3$ [M + Na]$^+$ 646.1423, found 646.1446.

Ni^{II}-(*S*)-BPB/(*S*)-2-Amino-3-(3,4,5-trifluorophenyl)propanoic Acid Schiff Base Complex (4d): Yield 92%, red crystal (m.p. 115–117 °C). $[\alpha]_D^{24}$ = +2012 (c = 0.1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2958, 2927, 2855, 1726, 1676, 1639, 1586, 1530, 1469, 1441, 1357, 1335, 1258, 1165, 1075, 1047, 1016, 799, 752, 705 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, J = 8.7 Hz, 1 H), 8.07–7.97 (m, 2 H), 7.61–7.53 (m, 2 H), 7.53–7.45 (m, 1 H), 7.36–7.27 (m, 3 H), 7.20–7.11 (m, 2 H), 6.97–6.91 (m, 1 H), 6.71–6.64 (m, 2 H), 6.64–6.56 (m, 2 H), 4.32 (d, J = 12.7 Hz, 1 H), 4.17 (t, J = 5.5 Hz, 1 H), 3.50 (d, J = 12.7 Hz, 1 H), 3.58 (d, J_1 = 10.1, J_2 = 6.8 Hz, 1 H), 3.33–3.23 (m, 1 H), 2.99–2.89 (m, 2 H), 2.89–2.75 (m, 1 H), 2.54–2.39 (m, 2 H), 2.08–1.92 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.3, 171.4, 152.3, 151.0 (ddd, J_1 = 251, J_2 = 9, J_3 = 4 Hz, 2 C), 142.8, 139.2 (ddd, J_1 = 251, J_2 = J_3 = 15 Hz), 133.8, 133.4, 133.1, 132.6, 132.0 (ddd, J_1 = J_2 = 8, J_3 = 5 Hz), 131.4 (2 C), 130.0, 129.3, 129.0, 128.8, 128.7 (2 C), 127.5, 127.1, 125.9, 123.6, 120.7, 114.0 (dd, J_1 = 15, J_2 = 6 Hz, 2 C), 70.6, 70.2, 63.3, 57.2, 39.7, 30.6, 23.3 ppm. HRMS (ESI) m/z calculated for $C_{34}H_{28}F_3N_3NaNiO_3$ [M + Na]$^+$ 664.1328, found 664.1323.

Ni^{II}-(*S*)-BPB/(*S*)-2-Amino-3-[4-(trifluoromethyl)phenyl]propanoic Acid Schiff Base Complex (4f): Yield 93%, red crystal (m.p. 130–132 °C). $[\alpha]_D^{25}$ = +2020 (c = 0.1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3027, 2959, 2927, 2871, 1736, 1675, 1641, 1585, 1546, 1442, 1368, 1325, 1259, 1165, 1126, 1067, 754, 706 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, J = 8.5 Hz, 1 H), 7.99 (d, J = 7.5 Hz, 2 H), 7.67 (d, J = 8.0 Hz, 2 H), 7.61–7.51 (m, 2 H), 7.50–7.42 (m, 1 H), 7.34–7.26 (m, 5 H), 7.20–7.11 (m, 2 H), 6.92 (d, J = 7.5 Hz, 1 H), 6.73–6.61 (m, 2 H), 4.35–4.30 (m, 1 H), 4.28 (d, J = 12.8 Hz, 1 H), 3.46 (d, J = 12.8 Hz, 1 H), 3.29 (dd, J_1 = 10, J_2 = 6.5 Hz, 1 H), 3.13–3.01 (m, 2 H), 2.87 (dd, J_1 = 13.8, J_2 = 5.7 Hz, 1 H), 2.38–2.15 (m, 3 H), 1.96–1.83 (m, 1 H), 1.75–1.60 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.3, 178.0, 171.5, 142.8, 139.9, 134.0, 133.5, 133.2, 132.5, 131.3 (2 C), 130.8 (2 C), 129.9, 129.7 (q, J = 32 Hz), 129.2, 128.9, 128.7 (2 C), 127.6, 127.0, 125.9, 125.6 (q, J = 2 Hz, 2 C), 124.1 (q, J = 271 Hz, 2 C), 123.3, 120.6, 70.8, 70.2, 63.3, 57.0, 39.2, 30.6, 22.9 ppm. HRMS (ESI) m/z calculated for $C_{35}H_{30}F_3N_3NaNiO_3$ [M + Na]$^+$ 678.1485, found 678.1475.

Ni^{II}-(*S*)-BPB/(*S*)-2-Amino-3-[3,5-bis(trifluoromethyl)phenyl]propanoic Acid Schiff Base Complex (4g): Yield 90%, red crystal (m.p. 129–131 °C). $[\alpha]_D^{22}$ = +2024 (c = 0.1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3028, 2972, 2927, 2873, 1739, 1676, 1644, 1437, 1375, 1370, 1277, 1229, 1219, 1168, 1137, 900, 754, 703 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, J = 8.8 Hz, 1 H), 8.07–8.00 (m, 2 H), 7.78 (s, 1 H), 7.63–7.56 (m, 2 H), 7.55–7.48 (m, 1 H), 7.38–7.30 (m, 3 H), 7.25–7.21 (m, 2 H), 7.21–7.13 (m, 2 H), 6.99–6.93 (m, 1 H), 6.73–6.65 (m, 2 H), 4.36 (d, J = 12.6 Hz, 1 H), 4.16 (dd, J_1 = 8.2, J_2 = 3.7 Hz, 1 H), 3.53 (d, J = 12.6 Hz, 1 H), 3.41 (dd, J_1 = 10.5, J_2 = 6.2 Hz, 1 H), 3.39–3.32 (m, 1 H), 3.28 (dd, J_1 = 13.7, J_2 = 8.3 Hz, 1 H), 3.10 (dd, J_1 = 13.7, J_2 = 3.7 Hz, 1 H), 3.06–2.92 (m, 1 H), 2.54–2.36 (m, 2 H), 2.07–1.96 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.4, 177.5, 171.5, 142.8, 138.4, 133.7, 133.3, 133.2, 132.7, 131.6 (q, J = 33 Hz, 2 C), 131.4 (2 C), 130.2, 129.8 (q, J = 3 Hz, 2 C), 129.4, 129.1, 128.9, 128.8 (2 C), 127.4, 127.3, 125.8, 123.7, 123.0 (q, J = 271 Hz, 2 C), 121.2 (qq, J_1 = J_2 = 3 Hz), 120.7, 70.5, 70.1, 63.2, 57.3, 40.8, 30.5, 23.7 ppm. HRMS (ESI) m/z calculated for $C_{36}H_{29}F_6N_3NaNiO_3$ [M + Na]$^+$ 746.1359, found 746.1350.

Ni^{II}-(*S*)-BPB/(*S*)-2-Amino-3-[6-(trifluoromethyl)pyridin-3-yl]propanoic Acid Schiff Base Complex (4h): Yield 90%, red crystal (m.p. 201–203 °C). $[\alpha]_D^{21}$ = +2403 (c = 0.1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3022, 2972, 2951, 1739, 1676, 1644, 1442, 1365, 1341, 1230, 1219, 1134, 1089, 754, 706 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (d, J = 1.8 Hz, 1 H), 8.26 (d, J = 8.6 Hz, 1 H), 8.03–7.95 (m, 2 H), 7.88 (d, J = 8.0 Hz, 1 H), 7.62–7.55 (m, 3 H), 7.52–7.46 (m, 1 H), 7.35–7.29 (m, 3 H), 7.21–7.14 (m, 2 H), 6.98–6.93 (m, 1 H), 6.72–6.66 (m, 2 H), 4.31 (d, J = 12.7 Hz, 1 H), 4.28 (dd, J_1 = 6.6, J_2 = 4.2 Hz, 1 H), 3.51 (d, J = 12.7 Hz, 1 H), 3.33 (dd, J_1 = 9.2, J_2 = 7.5 Hz, 1 H), 3.19–3.12 (m, 1 H), 3.07 (dd, J_1 = 13.8, J_2 = 4.2 Hz, 1 H), 3.00 (dd, J_1 = 13.8, J_2 = 6.6 Hz, 1 H), 2.50–2.34 (m, 3 H), 1.98–1.89 (m, 1 H), 1.89–1.79 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.3, 177.5, 171.9, 151.0, 147.4 (q, J = 35 Hz), 143.0, 138.9, 134.9, 133.9, 133.5, 133.1, 132.8, 131.4 (2 C), 130.1, 129.4, 129.1, 128.9, 128.8 (2 C), 127.5, 127.1, 125.8, 123.5, 121.6 (q, J = 275 Hz), 120.7, 120.3, 70.3, 70.2, 63.3, 57.0, 37.0, 30.6, 23.2 ppm. HRMS (ESI) m/z calculated for $C_{34}H_{29}F_3N_4NaNiO_3$ [M + Na]$^+$ 679.1437, found 679.1452.

Ni^{II}-(*S*)-BPB/(*S*)-2-Amino-5-fluoropentanoic Acid Schiff Base Complex (4i): Yield 76%; red crystal (m.p. 201–203 °C). $[\alpha]_D^{21}$ = +3020 (c = 0.1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2970, 2929, 2880, 1675, 1639, 1589, 1544, 1441, 1335, 1259, 1166, 1062, 754, 706 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17–8.10 (m, 1 H), 8.08–8.02 (m, 2 H), 7.54–7.43 (m, 3 H), 7.37–7.31 (m, 2 H), 7.26–7.22 (m, 1 H), 7.19 (tt, J_1 = 7.5, J_2 = 1.3 Hz, 1 H), 7.13 (ddd, J_1 = 8.7, J_2 = 6.2, J_3 = 2.5 Hz, 1 H), 6.98–6.89 (m, 1 H), 6.69–6.60 (m, 2 H), 4.42 (d, J = 12.7 Hz, 1 H), 4.40–4.10 (m, 2 H), 3.86 (dd, J_1 = 9.1, J_2 = 3.4 Hz, 1 H), 3.66–3.50 (m, 2 H), 3.57 (d, J = 12.7 Hz, 1 H), 3.47 (dd, J_1 = 10.9, J_2 = 5.7 Hz, 1 H), 2.79–2.69 (m, 1 H), 2.59–2.45 (m, 1 H), 2.40–2.14 (m, 3 H), 2.11–2.02 (m, 1 H), 1.92–1.68 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.4, 179.1, 170.7, 142.3, 133.6, 133.3, 133.2, 132.3, 131.6 (2 C), 129.8, 129.1, 129.0 (2 C), 128.9 (2 C), 127.5, 127.1, 126.3, 123.8, 120.8, 82.9 (d, J = 166 Hz), 70.3,

69.6, 63.1, 57.1, 31.6 (d, J = 5 Hz), 30.8, 26.4 (d, J = 20 Hz), 23.8 ppm. HRMS (ESI) m/z calculated for $C_{30}H_{30}FN_3NaNiO_3$ [M + Na]$^+$ 580.1517, found 580.1528.

Ni^{II}-(*S*)-BPB/(*S*)- 2-Amino-6,6,6-trifluorohexanoic Acid Schiff Base Complex (4l): Yield 80%, red crystal (m.p. 201–203 °C). $[\alpha]_D^{21}$ = +2440 (c = 0.1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2962, 2930, 2874, 1674, 1636, 1588, 1544, 1440, 1334, 1257, 1165, 1132, 1060, 1025, 801, 753, 703 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19–8.11 (m, 1 H), 8.09–8.00 (m, 2 H), 7.56–7.49 (m, 2 H), 7.49–7.42 (m, 1 H), 7.39–7.31 (m, 2 H), 7.29–7.23 (m, 1 H), 7.22–7.17 (m, 1 H), 7.17–7.11 (m, 1 H), 6.95–6.88 (m, 1 H), 6.71–6.59 (m, 2 H), 4.43 (d, J = 12.7 Hz, 1 H), 3.89 (dd, J_1 = 8.4, J_2 = 3.5 Hz, 1 H), 3.58 (d, J = 12.7 Hz, 1 H), 3.55–3.49 (m, 2 H), 3.46 (dd, J_1 = 11.1, J_2 = 5.9 Hz, 1 H), 2.82–2.67 (m, 1 H), 2.59–2.46 (m, 1 H), 2.40–2.28 (m, 1 H), 2.22–2.12 (m, 1 H), 2.12–1.94 (m, 3 H), 1.90–1.76 (m, 2 H), 1.70–1.60 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.4, 178.8, 170.8, 142.4, 133.7, 133.2, 133.1, 132.3, 131.5 (2 C), 129.8, 129.0, 129.0, 128.9, 128.8 (2 C), 127.3, 127.1, 126.8 (q, J = 276 Hz), 126.3, 123.7, 120.8, 70.2, 69.5, 63.1, 57.0, 34.2, 33.1 (q, J = 29 Hz), 30.7, 23.6, 18.1 (q, J = 3 Hz) ppm. HRMS (ESI) m/z calculated for $C_{31}H_{30}F_3N_3NaNiO_3$ [M + Na]$^+$ 630.1485, found 630.1508.

Ni^{II}-(*S*)-BPB/(*S*)-2-Amino-6,6,7,7,7-pentafluoroheptanoic Acid Schiff Base Complex (4m): Yield 50%, red crystal (m.p. 101–103 °C). $[\alpha]_D^{24}$ = +2160 (c = 0.1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3067, 2963, 2926, 2867, 1723, 1670, 1636, 1588, 1544, 1440, 1334, 1258, 1194, 1166, 752, 704 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20–8.11 (m, 1 H), 8.08–8.02 (m, 2 H), 7.58–7.43 (m, 3 H), 7.39–7.31 (m, 2 H), 7.31–7.26 (m, 1 H), 7.23–7.17 (m, 1 H), 7.15 (ddd, J_1 = 8.7, J_2 = 6.5, J_3 = 2.2 Hz, 1 H), 6.96–6.88 (m, 1 H), 6.70–6.60 (m, 2 H), 4.43 (d, J = 12.7 Hz, 1 H), 3.90 (dd, J_1 = 8.2, J_2 = 3.3 Hz, 1 H), 3.58 (d, J = 12.7 Hz, 1 H), 3.56–3.48 (m, 2 H), 3.47 (dd, J_1 = 11.0, J_2 = 5.7 Hz, 1 H), 2.81–2.70 (m, 1 H), 2.60–2.48 (m, 1 H), 2.42–2.30 (m, 1 H), 2.22–2.12 (m, 1 H), 2.12–2.00 (m, 2 H), 1.96–1.80 (m, 2 H), 1.80–1.60 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.4, 178.9, 170.9, 142.4, 133.7, 133.3, 133.2, 132.4, 131.6 (2 C), 129.9, 129.1, 129.0, 129.0, 128.9 (2 C), 127.4, 127.2, 126.3, 123.8, 120.8, 119.0 (qt, J_1 = 285, J_2 = 35 Hz), 115.5 (tq, J_1 = 252, J_2 = 37 Hz), 70.3, 69.4, 63.2, 57.1, 34.6, 30.8, 29.9 (t, J = 22 Hz), 23.6, 16.5 ppm. HRMS (ESI) m/z calculated for $C_{32}H_{30}F_5N_3NaNiO_3$ [M + Na]$^+$ 680.1458, found 680.1505.

Ni^{II}-(*S*)-BPB/(*S*)-2-amino-6,6,7,7,8,8,8-heptafluorooctanoic Acid Schiff Base Complex (4n): Yield 63%, red crystal (m.p. 101–103 °C). $[\alpha]_D^{25}$ = +2296 (c = 0.1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3063, 2979, 2874, 1671, 1636, 1589, 1544, 1441, 1353, 1335, 1257, 1224, 1167, 1062, 752, 704 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20–8.10 (m, 1 H), 8.08–8.01 (m, 2 H), 7.57–7.48 (m, 2 H), 7.48–7.43 (m, 1 H), 7.38–7.31 (m, 2 H), 7.29–7.26 (m, 1 H), 7.22–7.17 (m, 1 H), 7.17–7.11 (m, 1 H), 6.95–6.87 (m, 1 H), 6.70–6.60 (m, 2 H), 4.43 (d, J = 12.7 Hz, 1 H), 3.91 (dd, J_1 = 8.4, J_2 = 3.6 Hz, 1 H), 3.58 (d, J = 12.7 Hz, 1 H), 3.55–3.49 (m, 2 H), 3.46 (dd, J_1 = 10.9, J_2 = 5.8 Hz, 1 H), 2.80–2.70 (m, 1 H), 2.59–2.46 (m, 1 H), 2.42–2.29 (m, 1 H), 2.20–2.02 (m, 3 H), 1.98–1.84 (m, 2 H), 1.80–1.60 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.4, 178.8, 170.9, 142.3, 133.6, 133.2, 133.1, 132.3, 131.5 (2 C), 129.8, 129.0, 129.0, 128.9, 128.8 (2 C), 127.3, 127.1, 126.3, 123.7, 120.8, 117.7 (qt, J_1 = 287, J_2 = 34 Hz), 117.4 (tt, J_1 = 253, J_2 = 31 Hz), 108.7 (ttq, J_1 = 263, J_2 = 36, J_3 = 35 Hz), 70.3, 69.4, 63.1, 57.0, 34.5, 30.7, 29.8 (t, J = 22 Hz), 23.6, 16.3 ppm. HRMS (ESI) m/z calculated for $C_{33}H_{30}F_7N_3NaNiO_3$ [M + Na]$^+$ 730.1421, found 730.1411.

Ni^{II}-(*S*)-BPB/(2*S*,3*S*)-2-amino-3-(cyanomethyl)-4,4,4-trifluorobutanoic Acid Schiff Base Complex (5j): Ni^{II} complex of glycine **1** (145 mg, 0.29 mmol), (cyanomethylene)tributylphosphorane **2** (153 μL, 0.58 mmol), and fluorinated alcohol **3** (85 μL, 1.16 mmol) were combined in toluene (0.3 mL). The red mixture was heated in a sealed tube at 120 °C for 64 h. The red solution was cooled to room temperature and purified by flash chromatography on silica gel using a CH_2Cl_2/acetone gradient (50:1 to 50:3) as eluent to afford a red crystals of **5j** (m.p. 289–291 °C). $[\alpha]_D^{25}$ = +3340 (c = 0.1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3063, 2979, 2942, 2253, 1675, 1636, 1584, 1542, 1469, 1439, 1368, 1335, 1255, 1163, 1120, 752, 703 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (dd, J_1 = 8.6, J_2 = 0.8 Hz, 1 H), 8.10–8.01 (m, 2 H), 7.64 (td, J_1 = 7.3, J_2 = 1.5 Hz, 1 H), 7.59 (tt, J_1 = 7.5, J_2 = 1.3 Hz, 1 H), 7.53 (td, J_1 = 7.3, J_2 = 1.5 Hz, 1 H), 7.38–7.29 (m, 3 H), 7.21–7.10 (m, 2 H), 6.96–6.86 (m, 1 H), 6.68–6.56 (m, 2 H), 4.34 (d, J = 12.8 Hz, 1 H), 4.30 (d, J = 4.3 Hz, 1 H), 3.55 (d, J = 12.8 Hz, 1 H), 3.51–3.44 (m, 1 H), 3.41 (dd, J_1 = 10.4, J_2 = 6.7 Hz, 1 H), 3.38–3.24 (m, 1 H), 3.11 (dd, J_1 = 16.8, J_2 = 10.3 Hz, 1 H), 2.85–2.72 (m, 1 H), 2.61–2.48 (m, 2 H), 2.44 (dd, J_1 = 16.8, J_2 = 4.7 Hz, 1 H), 2.11–1.98 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.2, 174.7, 173.1, 143.2, 133.5, 133.3, 133.2, 133.0, 131.4 (2 C), 130.6, 130.2, 129.4, 128.8 (2 C), 128.7, 127.1, 126.9, 125.8, 125.5 (q, J = 283 Hz), 123.5, 120.6, 115.3, 70.6, 65.5, 63.5, 57.1, 43.2 (q, J = 27 Hz), 30.4, 22.4, 14.8 (q, J = 3 Hz) ppm. HRMS (ESI) m/z calculated for $C_{31}H_{27}F_3N_4NaNiO_3$ [M + Na]$^+$ 641.1281, found 641.1291.

(*S*)-2-Amino-3-(3,4,5-trifluorophenyl)propanoic Acid Hydrochloride (10d): Yield 86%; white solid (m.p. 225–227 °C). $[\alpha]_D^{25}$ = +5 (c = 0.25, 2 M aq. HCl). IR (neat): $\tilde{\nu}$ = 3371, 3017, 3968, 2916, 1673, 1620, 1583, 1526, 1509, 1446, 1411, 1347, 1237, 1056, 1035, 864, 779, 650 cm^{-1}. ^{1}H NMR (400 MHz, D_2O): δ = 7.15–7.00 (m, 2 H), 4.00 (dd, J_1 = 7.6, J_2 = 5.6 Hz, 1 H), 3.26 (dd, J_1 = 14.7, J_2 = 5.6 Hz, 1 H), 3.14 (dd, J_1 = 14.7, J_2 = 7.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 173.2, 150.9 (ddd, J_1 = 248, J_2 = 10, J_3 = 4 Hz, 2 C), 138.9 (ddd, J_1 = 248, J_2 = J_3 = 15 Hz), 131.7 (ddd, J_1 = J_2 = 8, J_3 = 5 Hz), 113.6 (dd, J_1 = 16, J_2 = 6 Hz, 2 C), 55.5, 35.7 ppm. HRMS (ESI) m/z calculated for $C_9H_9F_3NO_2$ [M + H]$^+$ 220.0580, found 220.0581; Chiral HPLC: 95% *ee*, (Chirobiotic T, water/CH_3CN = 15:85, flow rate = 1.0 mL/min, 210 nm): major isomer (*S*): t_R = 11.6 min, minor isomer (*R*): t_R = 13.4 min.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR for all final compounds and chiral HPLC traces of compound **10d**.

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