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Synthesis of (2*S*,3*S*)-β-(trifluoromethyl)-α,β-diamino acid by Mannich addition of glycine Schiff base Ni(II) complexes to *N*-*tert*-butylsulfinyl-3,3,3-trifluoroacetaldimine

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ABSTRACT

A convenient access to (2*S*,3*S*)-β-(trifluoromethyl)-α,β-diamino acid is reported by using highly diastereoselective Mannich addition reactions of either chiral or achiral Ni(II) complexes derived from glycine Schiff bases to a chiral sulfinimine, *N*-*tert*-butylsulfinyl-3,3,3-trifluoroacetaldimine. Disassembly of the resultant Ni(II) complexes affords the target amino acid which was, for the first time, isolated in enantiomerically pure form and fully characterized.

1. Introduction

The design and synthesis of fluorine-containing amino acids and peptides [1] is a very active research field with major implications in chemistry and biology as well as the discovery of new drug candidates [2]. Thus, it is well-known that the selective fluorination of peptidic compounds usually contributes to an improvement of their chemical and thermal stabilities, and hence to their bioavailability. In particular, introduction of trifluoromethyl groups into amino acids is a common strategy in the quest for new bioactive compounds because of the unique characteristics of the CF_3 moiety. In recent years there has been a tremendous upsurge of synthetic methodologies for the convenient trifluoromethylation of organic compounds, especially on late stages of the synthetic processes without affecting sensitive functional groups [3]. Nonetheless, using CF_3-bearing building blocks as starting materials is still a valuable approach, provided that these small molecules are readily available, and preferably chiral [4].

Among amino acids, α,β-diamino acids constitute an important group of compounds widely found in nature as structural motifs of biologically relevant molecules [5]. However, the preparation of their fluorinated analogues is surprisingly a much underdeveloped area. In this context, it should be mentioned that the synthetic access to β-(trifluoromethyl)-α,β-diamino acid (2*S*,3*S*)-**5** was reported through the Mannich addition to PMP-protected imine **2** using Ni(II) complex (*S*)-**1** as a nucleophilic glycine equivalent (NGE) [6] (Scheme 1). Thus, when the reaction was conducted under conditions of kinetic control, the process took place with moderate diastereoselectivity to afford adduct (*S*)(2*S*,3*S*)-**3** as the major isomer. It should be emphasized that synthetic access to (*S*)-**1** is very straightforward from *N*-benzylproline, 2-aminobenzophenone, glycine and a Ni(II) salt [7]. Furthermore, its hydrolytic disassembly rendered the target compound (2*S*,3*S*)-**5** with quantitative recovery of the corresponding ligand (*S*)-**6**, that can be conveniently recycled in the production of complex (*S*)-**1**.

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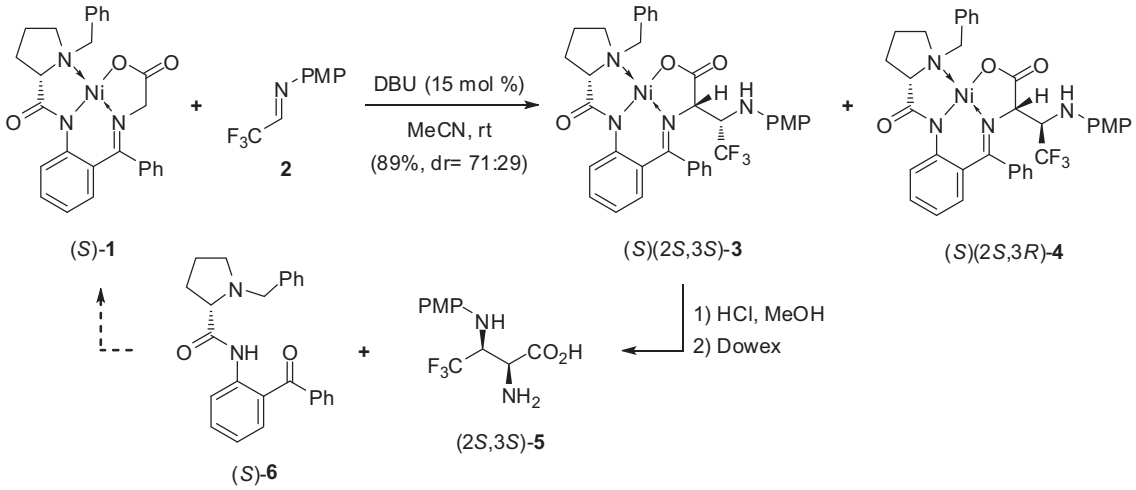


Scheme 1. Synthesis of CF_3-diamino acid (2*S*,3*S*)-**5** from chiral Ni(II) complex (*S*)-**1**.

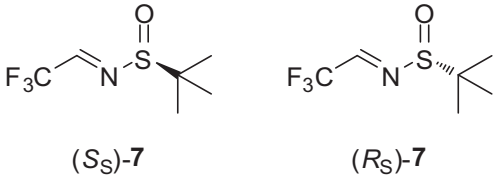


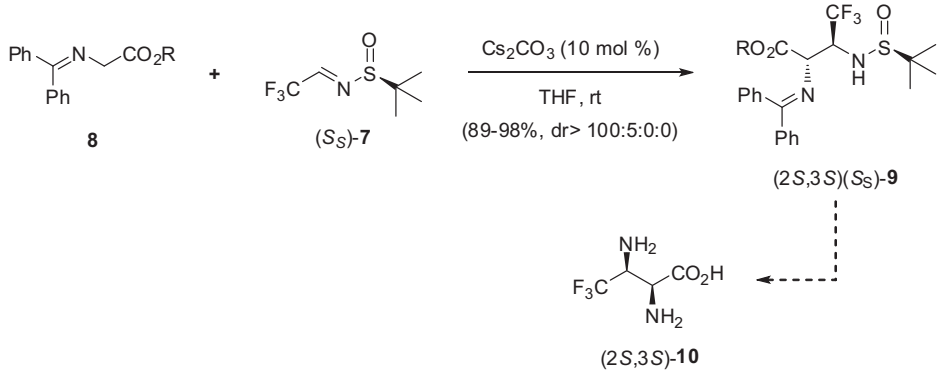
Fig. 1. Structures of sulfinimines (S_S)- and (R_S)-**7**.

Alternatively, *N*-*tert*-butylsulfinyl-3,3,3-trifluoroacetaldimine **7** is a chiral sulfinimine derived from trifluoroacetaldehyde (fluoral) and accessible in both enantiomeric forms [8] (Fig. 1). This compound has been employed for the expedient synthesis of a wide variety of α-(trifluoromethyl)amines [9]. For instance, several Mannich-type processes have been performed with (S_S)- or (R_S)-**7** by reaction with enolates derived from α-hydroxyesters [10], malonates [11] or indanones [12], as well as with other nucleophiles such as phosphites [13], lithium anions derived from phosphonates [14] or heterocycles [15].

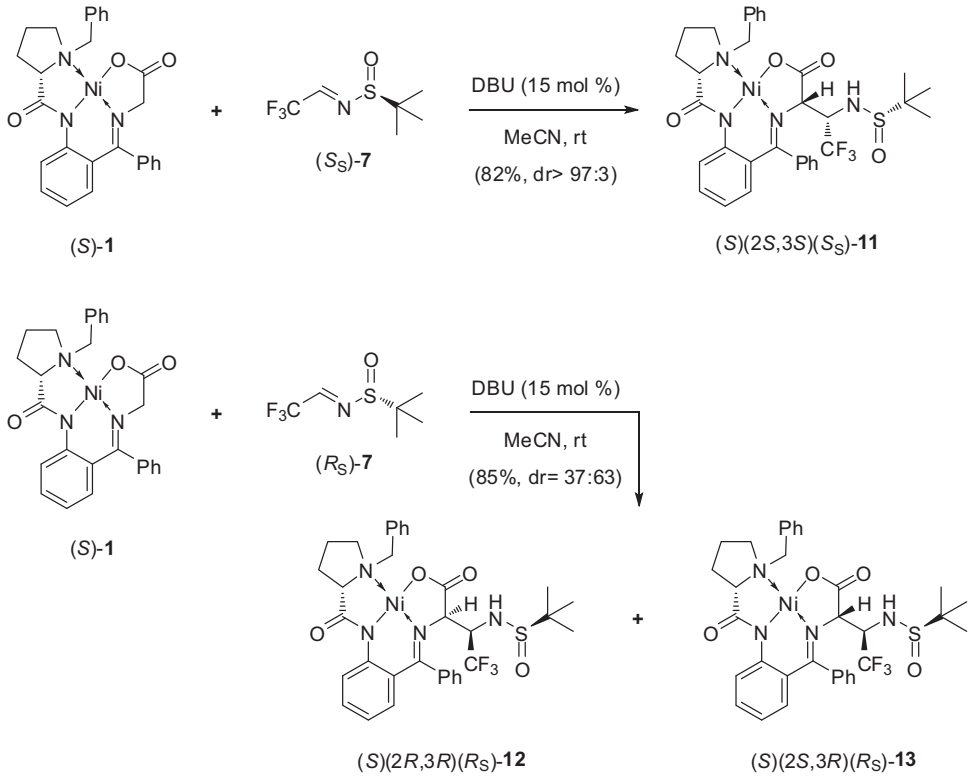
Recently, it was found that Mannich adducts (2*S*,3*S*)(S_S)-**9** were formed in very good yield and excellent diastereoselectivity upon reactions of sulfinimine (S_S)-**7** with benzophenone imines of glycine esters **8** [16] (Scheme 2). Nevertheless, implementation of this approach for the preparation of the corresponding free α,β-diamino acid (2*S*,3*S*)-**10** may not be feasible on a large scale due to the relative instability of NGEs **8**. It would be also desirable to take advantage of alternative types of NGEs which could be recovered and recycled after releasing the target amino acid molecule. As previously stated, these drawbacks can be circumvented by employing Ni(II) complexes derived from glycine Schiff bases such as (*S*)-**1**. Consistent with our interest in the synthesis of fluorine-containing biological relevant compounds in general [17] and in particular amino acids using the numerous applications of this class of NGEs [18–20], the aim of the current work is to explore the reactivity of different chiral and achiral Ni(II) complexes towards sulfinimine **7**, with the ultimate goal of accessing the previously unreported α,β-diamino acid (2*S*,3*S*)-**10** on a relatively large scale.

2. Results and discussion

Our investigation began with the Mannich reaction of chiral Ni(II) complex (*S*)-**1** and chiral sulfinimines (S_S)- or (R_S)-**7**. It would be anticipated that a pair of matched and mismatched reactions would emerge, according to the stereodirecting bias of both reactants. Thus, it is well established that kinetic control in the alkylation reactions of Ni(II) complex (*S*)-**1** usually affords up to 85:15 diastereoselectivity, favoring the corresponding (*S*) configuration at the α-carbon [21], and that was also the case in the previously shown example of a Mannich reaction with an achiral imine [6] (Scheme 1). On the other hand, the high facial selectivity displayed by chiral sulfinimine **7** was also demonstrated [9–15]. Therefore, the reaction of complex (*S*)-**1** with sulfinimine (S_S)-**7** constituted a perfectly matched case since essentially only one diastereomer (*S*)(2*S*,3*S*)(S_S)-**11** was observed (Scheme 3). In contrast, the analogous reaction using the enantiomeric sulfinimine (R_S)-**7** produced a mixture of two major diastereomers



Scheme 2. Mannich reaction between NGEs **8** and sulfinimine (S_S)-**7**.



Scheme 3. Mannich reactions between Ni(II) complex (*S*)-**1** and sulfinimines (S_S)- and (R_S)-**7**.

(*S*)(2*R*,3*R*)(R_S)-**12** and (*S*)(2*S*,3*R*)(R_S)-**13** in 63:37 ratio, along with traces of two minor ones. Diastereomers **12** and **13** were easily separated by column chromatography on silica gel.

Although we were unable to get suitable crystals for unambiguous *X*-ray structural determination, the stereochemical assignment of compounds **11–13** was carried out based on our previous experience on this type of transformations, in particular by correlation with known compounds **3** and **4** (Table 1). First of all, it should be mentioned that this class of compounds usually display high optical rotation values as a result of the inherent helical chirality associated, and in the case of (*S*)-configured α-monosubstituted Ni(II) complexes the $[\alpha]_D^{25}$ value always has a positive sign [22]. This trend was obeyed in complexes **3** and **4**, and this also served to establish the α-(*S*) configuration in compounds **11** and **13**, whereas complex **12**, showing a negative sign of $[\alpha]_D^{25}$ albeit in a much lower absolute value, should contain an (*R*)-configured α-carbon.

The second parameter studied was the chemical shift of the CF_3 group in the ^{19}FNMR spectra. It was previously observed for the *anti*/*syn* pair of diastereomers **3** and **4** that the lowest chemical shift (in absolute value) corresponded to the *syn* diastereomer **3** (referred to the orientation of both amino groups). Although the difference in chemical shifts in compounds **12** and **13** was reduced to only 1 ppm, the relative orientation was tentatively assigned as *syn* in compound **12** and consequently *anti* in **13**.

Finally, the ^{1}HNMR data provided more insights about the structural determination of these compounds, based again on the previously reported data of compounds **3** and **4**. For instance, the signal corresponding to the NH proton is always a doublet with a 10–12 Hz coupling constant. In the case of the *syn* diastereomer **3** this signal appear at 5.10 ppm, which is similar to what is also observed in *syn* Mannich adduct **9** (5.07 ppm, d, J = 10.7 Hz) derived from an achiral NGE. However, in the *anti* diastereomer **4** the corresponding peak came out at 4.11 ppm. When the signal corresponding to the NH proton was studied on compounds **11–13**, it was shown that compounds **11** and **12** had a much deshielded peak (5.59 and 5.67 ppm, respectively) compared to compound **13** (4.13 ppm). As a result, these data confirmed the *syn* relative relationship in complexes **11** and **12**, whereas compound **13** had *anti* disposition. Further evidence arose from the analysis of the signals corresponding to α- and β-protons matching those previously reported for complexes **3** and **4**.

Despite the good results obtained thus far, we were also willing to explore the reactivity in the case of achiral glycine Schiff base Ni(II) complexes of the new generation such as **14**, due to its enhanced chemical reactivity compared to complex (*S*)-**1** as well as

Table 1
Chiroptical and NMR data of compounds **3–4**, **11–13**.

Compound	Relative configuration	$[\alpha]_D^{25}$	^{19}FNMR	^{1}HNMR		
			δ CF_3	δ NH	δ CH-α	δ CH-β
(*S*)(2*S*,3*S*)-**3**	*syn*	+3030	−68.6	5.10 (d, J = 10.0 Hz)	4.21 (d, J = 5.0 Hz)	3.70 (m)
(*S*)(2*S*,3*R*)-**4**	*anti*	+5870	−72.4	4.11 (d, J = 12.2 Hz)	4.48 (s)	3.77–3.85 (m)
(*S*)(2*S*,3*S*)(S_S)-**11**	*syn*	+2197	−68.2	5.59 (d, J = 10.3 Hz)	4.12 (d, J = 4.9 Hz)	3.60–3.70 (m)
(*S*)(2*R*,3*R*)(R_S)-**12**	*syn*	−235	−68.5	5.67 (d, J = 10.3 Hz)	4.13 (d, J = 4.9 Hz)	3.54 (dd, J = 10.1, 4.8 Hz)
(*S*)(2*S*,3*R*)(R_S)-**13**	*anti*	+1563	−69.6	4.13 (d, J = 10.6 Hz)	4.28–4.40 (m)	

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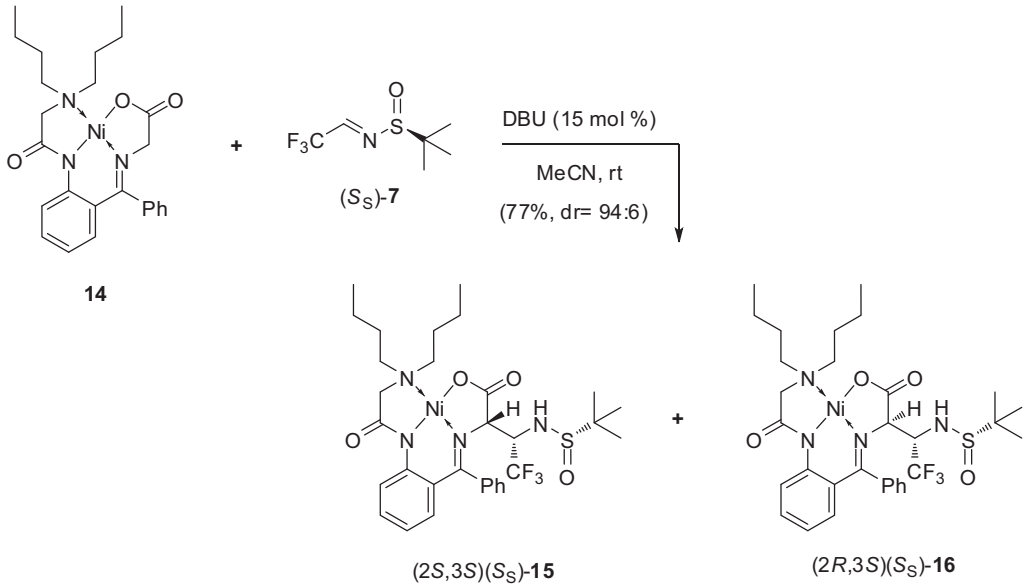


Scheme 4. Mannich reaction between Ni(II) complex (*S*)-**14** and sulfinimine (S_S)-**7**.

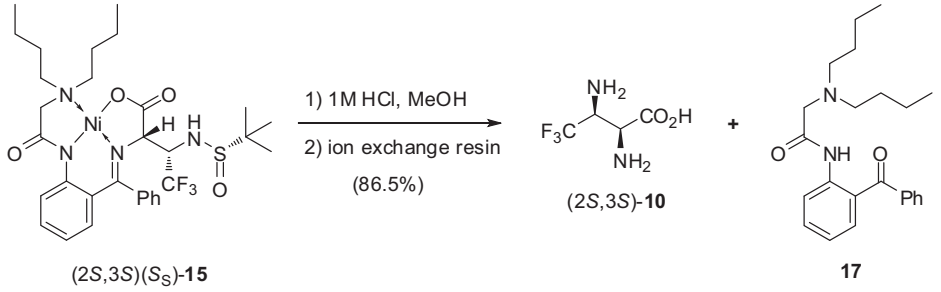
Table 2
Chiroptical and NMR data of compounds **15**–**16**.

Compound	Relative configuration	$[\alpha]_D^{25}$	^{19}FNMR	^{1}HNMR		
			δ CF_3	δ NH	δ CH-α	δ CH-β
(2*S*,3*S*)(S_S)-**15**	*syn*	+2247	−68.2	5.60 (d, *J* = 10.3 Hz)	4.10 (d, *J* = 4.9 Hz)	3.65–3.79 (m)
(2*R*,3*S*)(S_S)-**16**	*anti*	−1751	−70.3	4.19 (d, *J* = 11.1 Hz)	4.40 (d, *J* = 2.6 Hz)	4.04–4.14 (m)

its easier synthetic access through a modular assembly of four different units: 2-aminobenzophenone, 2-bromoacetyl bromide, di-*n*-butylamine and glycine [23] (Scheme 4). Remarkably, **14** reacted with chiral sulfinimine (S_S)-**7** to render a mixture of diastereomers in very high selectivity (94:6) that were separable by column chromatography on silica gel. The reaction could be easily and reliably scaled-up to 4.7 g without changes in the chemical yield or the diastereoselectivity.

Once again, the stereochemistry of adducts **15** and **16** was elucidated by matching their physical and spectroscopic characteristics with those of compounds **3** and **4** (Table 2) as well as the literature data. By observation of the optical rotation values and NMR data, it was concluded that major diastereomer **15** had *syn* relative orientation with an (*S*)-α-configured carbon, and therefore its absolute configuration was assigned as (2*S*,3*S*)(S_S). In the case of minor diastereomer **16**, all spectral and chiroptical data indicated its (2*R*,3*S*)(S_S) absolute configuration.

Finally, the synthetic relevance of this method was demonstrated by preparation of free α,β-diamino acid (2*R*,3*S*)-**10** by hydrolytic treatment (1 M HCl, MeOH) of the major diastereomeric complex (2*S*,3*S*)(S_S)-**15** (Scheme 5). Thus, diamino acid **10** was obtained in good yield after purification using an ion-exchange resin, and the corresponding organic ligand **17** was also recovered from the organic extracts and reused in the production of the starting complex **14**. In contrast to our previous experience on the synthesis of free amino acids by disassembly of Ni(II) complexes [24], this particular case proved to be somewhat difficult in order to isolate the final compound from the aqueous extracts, since some by-products (most likely coming from the hydrolysis of the sulfinimine moiety) were mixed with the target diamino acid and later on co-eluted during the resin purification. Therefore, a modified procedure was applied involving several extractions of the aqueous phase at different pHs.



Scheme 5. Synthesis of diamino acid (2*S*,3*S*)-**10**.

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3. Conclusions

In summary, we have developed a synthetically useful protocol for the addition to *N-tert*-butylsulfinyl-3,3,3-trifluoroacetaldimine **7**, employing glycine Schiff base Ni(II) complexes as Mannich donors. The process took place with complete diastereoselectivity using a chiral Ni(II) complex, provided that a matched pair of reactants was chosed, but also with high selectivity in the case of an achiral complex derived from *N*,*N*-di-*n*-butylamine, that resulted much cheaper and easier to produce. Isolation of the final (2*S*,3*S*)-β-(trifluoromethyl)-α,β-diamino acid **10** was accomplished on a relatively large scale by disassembly of the Ni(II) complex under acidic conditions, followed by purification on an ion-exchange resin.

4. Experimental

4.1. General procedure for the Mannich reaction of Ni(II) complexes to sulfinimines (S_S)- or (R_S)-7

DBU (15 mol %) was added to a solution of the corresponding Ni(II) complex (1 equiv.) and either (S_S)- or (R_S)-**7** (1.5 equiv) in MeCN (0.1 M). The mixture was stirred at room temperature for 30 min, and then H_2O was added. The crude was extracted with CH_2Cl_2, and the organic layer was dried over Na_2SO_4, concentrated at reduced pressure and purified on column chromatography on silica to render the corresponding Mannich adduct.

4.1.1. Mannich adduct (*S*)(2*S*,3*S*)(S_S)-11

According to the general procedure, from 105 mg (0.211 mmol) of (*S*)-**1**, 121 mg of (*S*)(2*S*,3*S*)(S_S)-**11** were obtained (82% yield). $[\alpha]_D^{25}$ = +2197.3 (*c* 0.166, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03 (s, 9H), 2.04–2.18 (m, 2H), 2.48–2.63 (m, 1H), 2.80–2.92 (m, 1H), 3.35–3.56 (m, 3H), 3.60–3.70 (m, 1H), 3.63 (d, *J* = 12.7 Hz, 1H), 4.12 (d, *J* = 4.9 Hz, 1H), 4.34 (d, *J* = 12.6 Hz, 1H), 5.59 (d, *J* = 10.3 Hz, 1H), 6.62 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.70 (ddd, *J* = 7.6, 6.8, 1.2 Hz, 1H), 7.00–7.05 (m, 1H), 7.18–7.27 (m, 2H), 7.26–7.32 (m, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.58–7.65 (m, 3H), 8.09 (d, *J* = 7.9 Hz, 2H), 8.31 (dd, *J* = 8.7, 1.1 Hz, 1H). ^{13}CNMR (75.5 MHz, $CDCl_3$): δ 22.0, 22.3, 30.4, 56.6, 57.1, 57.7 (q, $^2J_{CF}$ = 29.8 Hz), 63.4, 67.1, 70.6, 120.5, 123.4, 124.5 (q, $^1J_{CF}$ = 285.0 Hz), 125.6, 126.0, 127. 4, 128.6, 128.7, 129.4, 129.6, 130.2, 131.2, 132.9, 133.2, 133.3, 133.5, 143.1, 173.1, 176.1 and 180.2. ^{19}FNMR (376.4 MHz, $CDCl_3$): δ −68.2 (s, 3F). HRMS: calculated for $C_{33}H_{36}F_3N_4O_4SNi$ $[M+H]^+$ 699.1763, found 699.1772.

4.1.2. Mannich adducts (*S*)(2*R*,3*R*)(R_S)-12 and (*S*)(2*S*,3*R*)(R_S)-13

According to the general procedure, from 116 mg (0.233 mmol) of (*S*)-**1**, 47 mg of (*S*)(2*R*,3*R*)(R_S)-**12** (29% yield) and 92 mg of (*S*)(2*S*,3*R*)(R_S)-**13** (56% yield) were obtained. Data of (*S*)(2*R*,3*R*)(R_S)-**12**: $[\alpha]_D^{25}$ = −235.4 (*c* 0.081, $CHCl_3$). ^{1}HNMR (300 MHz, $CDCl_3$): δ 1.03 (s, 9H), 1.76–1.88 (m, 1H), 1.95–2.10 (m, 1H), 2.16–2.28 (m, 1H), 2.48 (ddd, *J* = 11.3, 9.9, 6.1 Hz, 1H), 2.66–2.83 (m, 1H), 3.54 (dd, *J* = 10.1, 4.8 Hz, 1H), 3.79–3.93 (m, 2H), 4.06 (d, *J* = 13.3 Hz, 1H), 4.13 (d, *J* = 4.9 Hz, 1H), 5.00 (d, *J* = 13.3 Hz, 1H), 5.67 (d, *J* = 10.3 Hz, 1H), 6.77 (ddd, *J* = 7.6, 6.8, 1.2 Hz, 1H), 6.87 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.17–7.30 (m, 2H), 7.33 (ddd, *J* = 7.8, 6.8, 1.8 Hz, 1H), 7.40–7.52 (m, 3H), 7.58–7.71 (m, 3H), 7.78–7.83 (m, 2H), 8.49 (dd, *J* = 8.8, 1.1 Hz, 1H). ^{13}CNMR (75.5 MHz, $CDCl_3$): δ 22.3, 23.6, 30.9, 56.5, 56.8, 58.5 (q, $^2J_{CF}$ = 29.6 Hz), 61.5, 67.7, 68.2, 120.9, 124.2, 124.6 (q, $^1J_{CF}$ = 285.3 Hz), 125.1, 126.1, 128.5, 128.9, 129.2, 129.5, 129.8, 130.3, 131.6, 132.1, 133.3, 133.7, 134.1, 143.6, 174.1, 176.6 and 182.5. ^{19}FNMR (376.4 MHz, $CDCl_3$): δ −68.5 (s, 3F). HRMS: calculated for $C_{33}H_{36}F_3N_4O_4SNi$ $[M+H]^+$ 699.1763, found 699.1760. Data of (*S*)(2*S*,3*R*)(R_S)-**13**: $[\alpha]_D^{25}$ = +1562.8 (*c* 0.018, $CHCl_3$). ^{1}HNMR (300 MHz, $CDCl_3$): δ 1.34 (s, 9H), 2.06–2.23 (m, 2H), 2.50–2.66 (m, 1H), 2.78–2.90 (m, 1H), 3.19–3.36 (m, 1H), 3.47–3.57 (m, 2H), 3.65 (d, *J* = 12.7 Hz, 1H), 4.13 (d, *J* = 10.6 Hz, 1H), 4.28–4.40 (m, 2H), 4.47 (d, *J* = 12.7 Hz, 1H), 6.67–6.71 (m, 2H), 7.10–7.22 (m, 3H), 7.28–7.38 (m, 3H), 7.49–7.64 (m, 3H), 8.01–8.07 (m, 2H), 8.39 (dt, *J* = 8.5, 0.9 Hz, 1H). ^{13}CNMR (75.5 MHz, $CDCl_3$): δ 22.1, 23.8, 30.4, 57.1, 57.9, 58.3 (q, $^2J_{CF}$ = 30.5 Hz), 63.7, 68.7, 70.4, 120.6, 123.2, 123.3 (q, $^1J_{CF}$ = 284.1 Hz), 125.4, 126.9, 128.3, 128.8, 128.9, 129.1, 129.4, 130.3, 131.4, 133.1, 133.1, 133.7, 134.0, 143.2, 173.6, 174.8 and 180.1. ^{19}FNMR (376.4 MHz, $CDCl_3$): δ −69.6 (s, 3F). HRMS: calculated for $C_{33}H_{36}F_3N_4O_4SNi$ $[M+H]^+$ 699.1763, found 699.1771.

4.1.3. Mannich adducts (2*S*,3*S*)(S_S)-15 and (2*R*,3*S*)(S_S)-16

According to the general procedure, from 4.7 g (9.79 mmol) of **14**, 4.8 g of (2*S*,3*S*)(S_S)-**15** (72% yield) and 0.3 g of (2*R*,3*S*)(S_S)-**16** (4% yield) were obtained. Data of **15**: $[\alpha]_D^{25}$ = +2246.8 (*c* 0.106, $CHCl_3$). ^{1}HNMR (300 MHz, $CDCl_3$): δ 1.02 (s, 9H), 1.04 (t, *J* = 7.3 Hz, 3H), 1.08 (t, *J* = 7.4 Hz, 3H), 1.24–1.68 (m, 4H), 1.79–1.95 (m, 1H), 2.21 (td, *J* = 12.3, 4.9 Hz, 1H), 2.53–2.70 (m, 5H), 2.94 (td, *J* = 12.4, 3.8 Hz, 1H), 3.04 (d, *J* = 16.4 Hz, 1H), 3.65–3.79 (m, 1H), 3.90 (d, *J* = 16.4 Hz, 1H), 4.10 (d, *J* = 4.9 Hz, 1H), 5.60 (d, *J* = 10.3 Hz, 1H), 6.73–6.83 (m, 2H), 7.07–7.12 (m, 1H), 7.28–7.32 (m, 1H), 7.38 (ddd, *J* = 7.6, 6.6, 2.1 Hz, 1H), 7.56–7.68 (m, 3H), 8.71 (dd, *J* = 8.7, 1.1 Hz, 1H). ^{13}CNMR (75.5 MHz, $CDCl_3$): δ 13.6, 13.7, 20.5, 20.6, 22.1, 26.6, 29.2, 56.7, 57.3, 57.9 (q, $^2J_{CF}$ = 29.6 Hz), 60.6, 62.0, 67.2, 120.9, 123.6, 124.6 (q, $^1J_{CF}$ = 285.3 Hz), 125.7, 126.1, 127.7, 129.5, 129.7, 130.3, 133.4, 133.7, 133.8, 143.3, 173.4, 176.0 and 177.4. ^{19}FNMR (376.4 MHz, $CDCl_3$): −68.2 (s, 3F). HRMS: calculated for $C_{31}H_{42}F_3N_4O_4SNi$ $[M+H]^+$ 681.2232, found 681.2241. Data of **16**: $[\alpha]_D^{25}$ = −1750.9 (*c* 0.087, $CHCl_3$). ^{1}HNMR (300 MHz, $CDCl_3$): δ 1.02 (t, *J* = 7.2 Hz, 3H), 1.09 (t, *J* = 6.2 Hz, 3H), 1.32–1.70 (m, 5H), 1.53 (s, 9H), 1.75–1.90 (m, 1H), 2.20–2.36 (m, 1H), 2.40–2.61 (m, 2H), 2.66–3.02 (m, 3H), 3.10 (d, *J* = 16.2 Hz, 1H), 4.01 (d, *J* = 16.2 Hz, 1H), 4.04–4.14 (m, 1H), 4.19 (d, *J* = 11.1 Hz, 1H), 4.40 (d, *J* = 2.6 Hz, 1H), 6.78–6.81 (m, 2H), 7.05–7.12 (m, 1H), 7.30–7.41 (m, 2H), 7.55–7.63 (m, 3H), 8.61 (dt, *J* = 8.6, 0.8 Hz, 1H). ^{13}CNMR (75.5 MHz, $CDCl_3$): δ 13.8, 13.9, 20.5, 20.8, 22.4, 24.7, 29.3, 56.3, 58.0, 59.1 (q, $^2J_{CF}$ = 30.7 Hz), 59.1, 63.3, 68.5, 121.1, 123.1 (q, $^1J_{CF}$ = 285.2 Hz), 123.6, 126.1, 126.8, 127.6, 129.4, 129.6, 130.4, 133.4, 133.5, 134.1, 143.1, 173.4, 174.5 and 176.3. ^{19}FNMR (376.4 MHz, $CDCl_3$): δ −70.3 (s, 3F). HRMS: calculated for $C_{31}H_{42}F_3N_4O_4SNi$ $[M+H]^+$ 681.2232, found 681.2245.

4.2. Synthesis of (2*S*,3*S*)-10

1 M HCl (17.4 mL, 17.4 mmol) was added to a solution of (2*S*,3*S*)(S_S)-**15** (1.7 g, 2.49 mmol) in MeOH (51 mL). The mixture was stirred at 50 °C for 4 h, and then concentrated in vacuo. The crude was partitioned between EtOAc (35 mL) and H_2O (35 mL), and the layers were separated. The organic layer was extracted with H_2O (34 mL) and 0.01 M HCl (17 mL), and the combined aqueous layers were adjusted to pH = 7.5–8 with conc. NH_4OH (0.9 mL), then washed twice with CH_2Cl_2 (34 mL and 17 mL). The aqueous layers were next adjusted to pH < 2 with 1 M HCl (10.5 mL) and washed with EtOAc (35 mL) and 2-methyl-1-propanol (8 mL, twice). The combined organic layers (EtOAc and CH_2Cl_2) were washed with sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated in vacuo to give recovered ligand **17** (789 mg, 86%). The combined aqueous layers were directly charged on a SK-1B column eluting with H_2O to 8% NH_4OH to afford diamino acid **10** (371.5 mg, 86.5%). $[\alpha]_D^{25}$ = −7.8 (*c* 0.98, H_2O). ^{1}HNMR (300 MHz, D_2O): δ 3.99 (d, *J* = 3.1 Hz, 1H), 4.05 (qd, *J* = 8.1, 3.1 Hz, 1H). ^{13}CNMR (50.3 MHz, D_2O): δ 53.4 (q, $^2J_{CF}$ = 29.3 Hz), 54.5, 125.9 (q, $^1J_{CF}$ = 280.0 Hz) and 171.2. ^{19}FNMR (376.4 MHz, D_2O): δ −75.0 (s, 3F). HRMS: calculated for $C_4H_8F_3N_2O_2$ $[M+H]^+$ 173.0538, found 173.0536.

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