Gram-scale asymmetric synthesis of fluorinated amino acids using a chiral nickel(II) complex

Thomas Hohmann[1], Michael Dyrks[1], Suvrat Chowdhary[1], Manuela Weber[2], Duy Nguyen[1], Johann Moschner[1] and Beate Koksch[1]

Institute of Chemistry and Biochemistry, Freie Universität Berlin
[1]*Arnimallee 20, 14195 Berlin, Germany*
[2]*Fabeckstraße 34/36, 14195 Berlin, Germany*

Corresponding author:

Beate Koksch – *Institute of Chemistry and Biochemistry, Freie Universität Berlin*
[1]*Arnimallee 20, 14195 Berlin, Germany*
Email: beate.koksch@fu-berlin.de

Abstract

Fluorinated amino acids play an important role in the field of peptide and protein engineering. Although several different syntheses have been published in recent decades, obtaining fluorinated amino acids on a gram-scale still poses a challenge. Furthermore, the described pathways to obtain fluorinated amino acids are based on different synthetic strategies, making a uniform approach from similar starting materials highly interesting. Chiral Ni(II) complexes were introduced as powerful tools in the synthesis of non-canonical amino acids. In this work, we present a strategy for the synthesis of a diverse range of fluorinated amino acids from the corresponding Ni(II) complex on a gram-scale from which the products can be obtained in enantiopure form (>94%ee). In addition, we describe syntheses for alkyl iodide building blocks which are required for the alkylation reactions with the corresponding Ni(II) complex. Finally, we characterized the synthesized fluorinated amino acids with regard to their hydrophobicity and α-helix propensity.

Introduction

The element fluorine is a powerful tool in peptide and protein engineering and can be used to alter a broad range of properties such as thermal stability, metabolic stability, and proteolytic resistance.[1,2] Furthermore, fluorine can be used to direct and modify peptide self-assembly

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processes leading to the formation of fluorinated supramolecular structures.[3] In general, fluorine can be introduced into peptides and proteins using fluorinated amino acids as building blocks in solution or solid-phase peptide synthesis (SPPS).[4,5] For the syntheses of fluorinated variants of natural and non-natural amino acids, a large number of synthetic methods has been published such as the application of either commercially available fluorinated synthons or electrophilic or nucleophilic fluorinating reagents. Recently, our group has published a review about the diverse approaches for the synthesis of different classes of fluorinated amino acids.[6] One powerful synthetic strategy is the application of chiral nickel complexes. First introduced by Belokon et al.[7], a variety of chiral nickel complexes were established for the asymmetric synthesis of non-canonical amino acids or for the dynamic kinetic resolution (DKR) of racemic amino acid mixtures in the last twenty years.[8] Different reaction types such as alkylations with primary or secondary alkyl halides, Mannich reactions, and Michael additions can be used in this context.[8] The described Ni(II) complexes are constructed from a tridentate proline-derived Schiff base ligand and a canonical amino acid such as glycine or alanine. One crucial achievement was reported by the group of V. Soloshonok describing a trichlorinated version of the Ni(II) complex **1** which shows excellent stereoselectivities in reactions with alkyl halides.[9] Furthermore, the ligand can be recovered making this process atom-economical. Recently, a large-scale synthesis of the Soloshonok Ni(II) complex **1** was reported giving access to this important building block on a gram scale.[10–12]
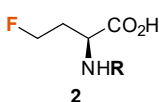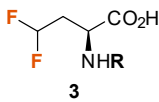
Han et al., 2019
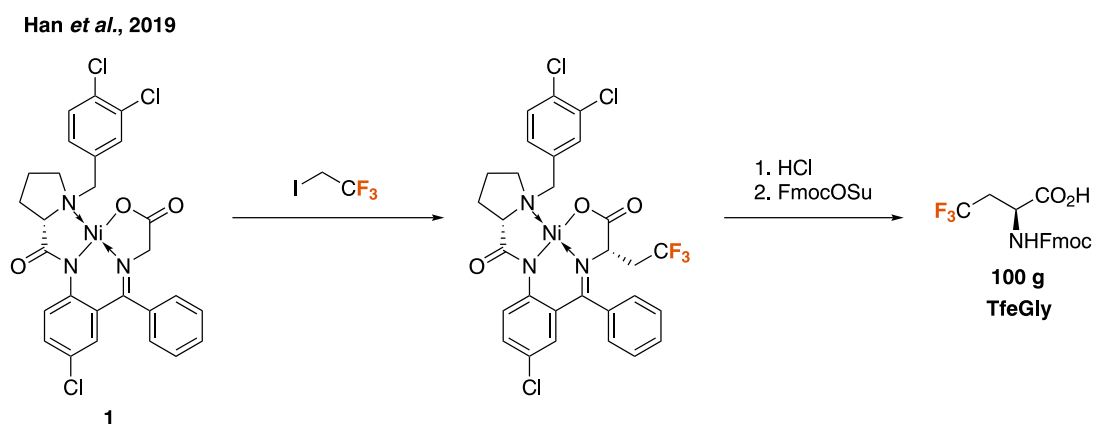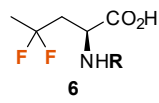
Scheme 1: Synthesis of TfeGly using the chiral Ni(II) complex **1**.

The described Ni(II) complex **1** was recently used in the asymmetric gram-scale preparation of trifluoroethylglycine (TfeGly) (**Scheme 1**).[13] These results indicated the great potential of the Ni(II) complex **1** in the synthesis of fluorinated amino acids.[13,14] In this work, we report on the

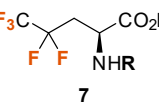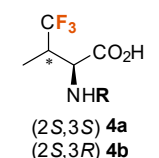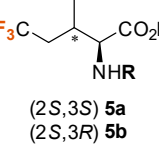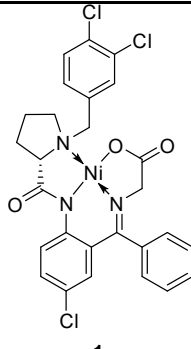development of a general procedure that enables access to a broad range of differently fluorinated amino acids based on the Ni(II) complex **1**.

Table 1: **Entries 1-6**: Fluorinated amino acids in the focus of this work and corresponding previous synthesis parameters. **Entry 7**: New strategy using the chiral Ni(II)-complex.

Entry	Amino acid	Overall yield [%]	R	Scale	Reaction steps	References
Previous work						
1	**2**	14-50	H, Fmoc	milligram	3-7	[15–17]
2	**3**	33	H	gram	5	[18]
3	**6**	22	H	milligram	7	[19]
4	**7**	38	H	milligram	4	[20]
5	(2*S*,3*S*) **4a** (2*S*,3*R*) **4b**	(3*S*) 13-96 (3*R*) 10-43	H, Boc, Fmoc	milligram	2-11	[21–25]
6	(2*S*,3*S*) **5a** (2*S*,3*R*) **5b**	(3*S*) 1-18 (3*R*) 4-16	H, Fmoc	milligram-gram	7-9	[26–28]
7	**1**			**2 steps** **good yields** **excellent enantiomeric purities** **gram-scale synthesis**		

We focused our work on the synthesis of three different classes of fluorinated amino acids (**Table 1**):

(1) the mono- and difluorinated variants of 2-aminobutyric acid; monofluoroethylglycine **2** [MfeGly], and difluoroethylglycine **3** [DfeGly] (**Table 1, entry 1-2**),
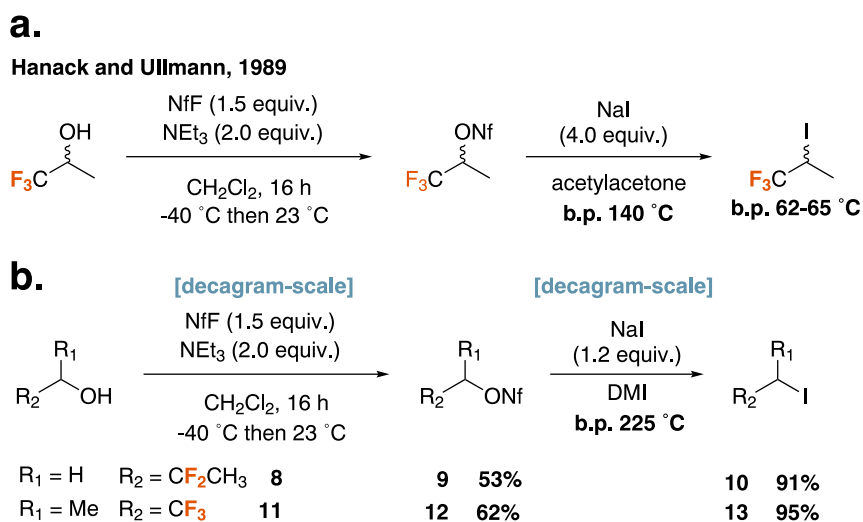
(2) the *β*-branched amino acids 2*S*, 3*S*-trifluorovaline **4a** [(2*S*, 3*S*)-TfVal], (2*S*, 3*R*)-trifluorovaline **4b** [(2*S*, 3*R*)-TfVal] (**Table 1, entry 5**), 5^3-(2*S*, 3*S*)-trifluorisoleucine **5a** [5^3-(2*S*, 3*S*)-TfIle], and 5^3-(2*S*, 3*R*)-trifluoroisoleucine **5b** [5^3-(2*S*, 3*R*)-TfIle] (**Table 1, entry 6**),

(3) the difluorinated and pentafluorinated variants of 2-aminopentanoic acid difluoropropylglycine **6** [DfpGly], and pentafluoropropylglycine **7** [PfpGly], (**Table 1, entry 3-4**).

Different synthetic methods were published in the last years to obtain the described compounds.[15–28] However, the described approaches are multi-step syntheses that require several chromatographic purification steps and follow different synthetic strategies. In addition, most of these amino acids could only be isolated on a milligram-scale. Usually, the synthesis of either *N*-unprotected or *N*-Boc-protected amino acids was described (**Table 1, Entry 2-5**). Herein, we present a uniform 2-step pathway from the Ni(II) complex **1** to obtain the desired fluorinated amino acids on a gram-scale in their Fmoc-protected form and, thus, prepared for their application in solid-phase peptide synthesis. Additionally, we describe the synthesis of several alkyl iodide building blocks that are employed in the alkylation step. Lastly, the synthesized fluorinated amino acids were characterized with respect to their hydrophobicity and *α*-helix propensity.

Results and Discussion

Synthesis of alkyl iodide building blocks   Alkyl iodides required for the syntheses of TfVal **4** and DfpGly **6** are not commercially available or are rather expensive. Our first goal was the establishment of a gram-scale synthesis of the corresponding alkyl iodides. The fluorinated alcohols **8** and **11** were used as starting materials since they are readily available and can easily be transformed into the desired compounds. We started our studies using 2-difluoropropan-1-ol **8**. First, several conditions such as Appel reaction, tosylation or mesylation with subsequent nucleophilic iodination, were employed without satisfying results since small highly fluorinated molecules are known to cause problems in nucleophilic substitution reactions.[29,30] This challenge was overcome by the introduction of a nonaflate leaving group. Hanack and Ullmann described the synthesis of 1-trifluoro-2-iodopropane **10** using the corresponding nonaflate as a powerful leaving group during the iodination step (**Scheme 2, a**).[30]

a.

Hanack and Ullmann, 1989

b.

| R₁ = H | R₂ = CF₂CH₃ | 8 | | 9 | 53% | | 10 | 91% |
| R₁ = Me | R₂ = CF₃ | 11 | | 12 | 62% | | 13 | 95% |

Scheme 2: a. Previously reported synthesis of 1-trifluoro-2-iodopropane **10**. **b.** Gram-scale synthesis of fluorinated alkyl iodide compounds from the corresponding fluorinated alcohols.

We applied the conditions reported by Hanack and Ullmann and could obtain both alkyl nonaflates **9** and **12** in good yields. To facilitate the purification of the alkyl iodide products **10** and **13** by distillation, the final step was modified. Several high-boiling solvents were screened showing that 1,3-dimethyl-2-imidazolidinone (DMI) is the most promising candidate (**Supporting Information, Table S1**). Finally, the desired alkyl iodides **10** and **13** could be isolated on a decagram-scale and in excellent yields.

Synthesis of MfeGly and DfeGly   Chiral Ni(II) complex **1** was synthesized according to the conditions published by Wang *et al.*[9] The alkylation step was carried out on a decagram scale using the reported conditions[14] (**Figure 3**). In addition, we looked more closely at the influence of the reaction temperature on the outcome of this conversion. Lower temperature (0 °C) resulted in slightly poorer yields but improved diastereoselectivity (**96%de**, **Supporting Information, Table S2**).
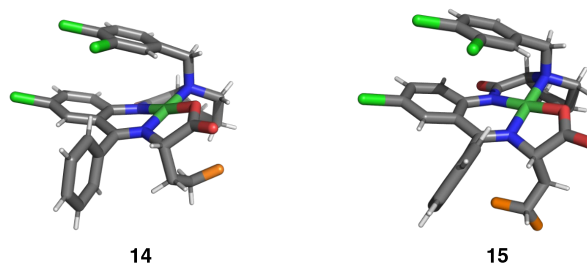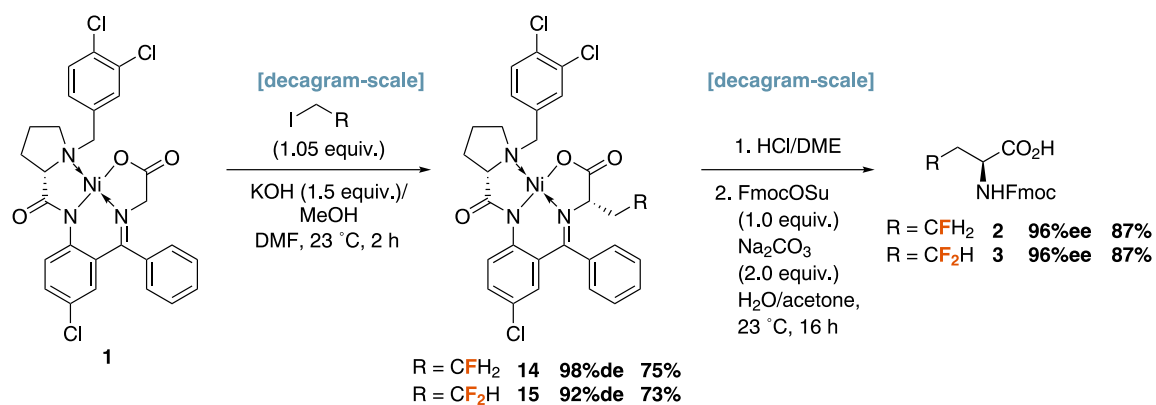
Scheme 3: Gram-scale synthesis of Fmoc-MfeGly **2** and Fmoc-DfeGly **3** using the chiral Ni(II) complex **1**. Ni(II) Schiff base complexes of MfeGly **14** and DfeGly **15** were further characterized by X-ray crystallography.

Both alkylated Ni(II) complexes **14** and **15** were obtained in great yields with high diastereomeric purities (**>92%de**) and Ni(II) complexes **14** and **15** were further characterized by X-ray crystallography. Subsequent one-pot hydrolysis of the complex and Fmoc-protection of the fluorinated amino acids led to the formation of the desired amino acids **2** and **3**. Both Fmoc-protected amino acids were isolated on a gram scale with high enantiomeric purities (**96%ee**).

Synthesis of β-branched fluorinated amino acids   We started our efforts with the alkylation reaction of the Ni(II) complex with 1-trifluoro-3-iodobutane. Employing the conditions reported by Soloshonok *et al.*[14] using KOH/MeOH led to unsatisfactory yields (**Table 1, Entry 3**).

Table 2: Screening conditions for the alkylation step using 1-trifluoro-3-iodobutane
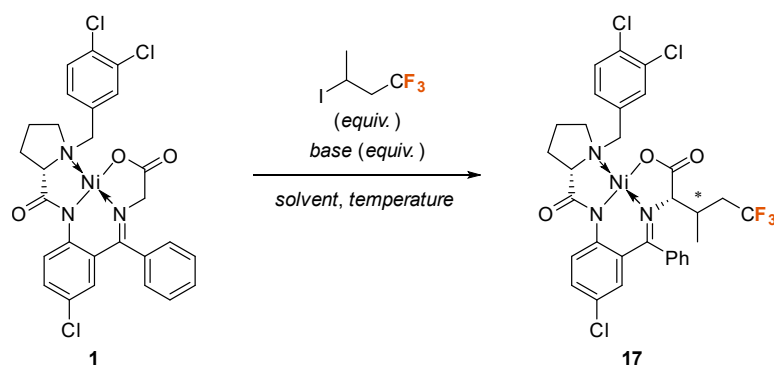
Entry	Base	Base [equiv.]	Side Chain [equiv.]	Solvent	Temperature [°C]	Yield [%]*
1	NaH	1.2	1.05	DMF	23	22
2	KOtBu	1.2	1.05	DMF	23	5
3	KOH/ MeOH	1.05	1.05	DMF	23	2
4	NaH	1.2	1.05	THF	23	11
5	NaH	1.2	1.05	MeCN	23	4
6	NaH	1.2	1.05	DMF/ THF	23	17
7	NaH	1.2	1.5	DMF	0	15
8	NaH	1.2	2.0	DMF	0	4
9	NaH	1.2	1.05	DMF	0	26
10	NaH	2.0	1.05	DMF	0	42
11	NaH	3.0	1.05	DMF	0	47
12	NaH	3.0	1.05	DMF	23	36
13	NaH	3.0	1.05	DMF	0	47
14	NaH	3.0	1.05	DMF	-20	15

*^{19}F-NMR yield using 2-chloro-4-fluorotoluene as an internal standard.

Therefore, we looked at different bases and screened a broad range of different reaction conditions including solvent and temperature (**Table 2**, for the complete screening summary, see **Supporting Information**, **Table S3**). The best results were obtained using sodium hydride at 0 °C (**Table 2, Entry 11**). Based on these optimized conditions, we were able to synthesize TfVal **4** and TfIle **5** in gram quantities (**Scheme 4**).
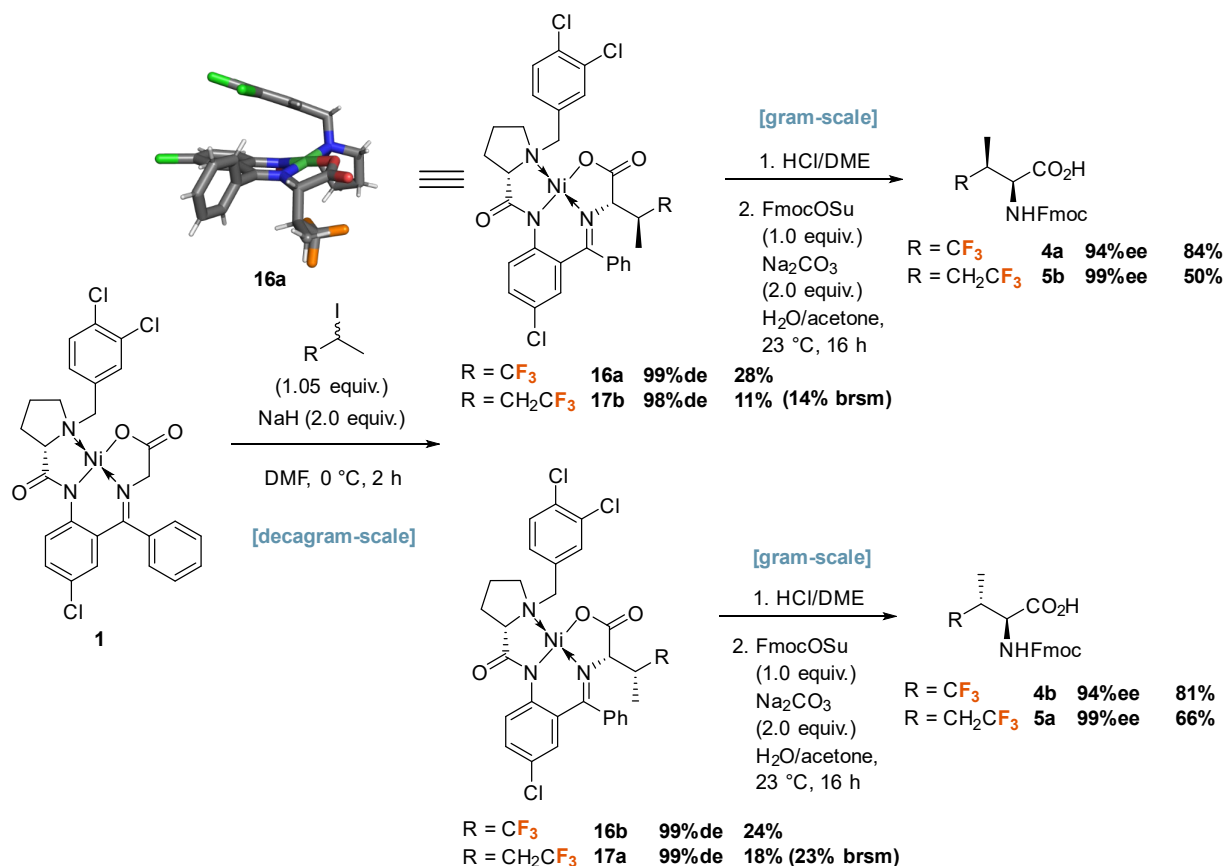
Scheme 4: Gram-scale synthesis of the TfVal **4** and TfIle **5** diastereomers using the chiral Ni(II) complex **1**. Stereochemistry of the Ni(II) complex of (2*S*, 3*S*)-TfVal **16a** was supported by X-ray crystallographic structure determination (for the sake of clarity, disordered atoms are not displayed).

The alkylated Ni(II) complexes **16** and **17** were obtained in moderate yields with high diastereomeric purities (**>98%de**). The corresponding diastereomers could be separated by flash column chromatography. Stereochemistry of the alkylated Ni(II) complexes was determined by X-ray diffraction or by 1D NOESY experiments (**Supporting Information**). After hydrolysis and Fmoc-protection both diastereomers of TfVal **4** and TfIle **5** were isolated with excellent enantiomeric purities (**>94%ee**).

Synthesis of fluorinated norvaline derivatives   For the synthesis of difluorinated **6** and pentafluorinated **7** variants of norvaline, we looked at different reaction conditions which

already showed good results in previous syntheses. Again, the use of KOH/MeOH during the alkylation reaction provided the targeted compounds in poor yields (**Supporting Information, Tables S5 and S6**). As previously reported for the synthesis of *β*-branched amino acids, the best results were observed using sodium hydride. Different base equivalents were screened showing that in contrast to TfVal **4** and TfIle **5** (2.0 equiv.) now only 1.3 equivalents were sufficient for both amino acids **6** and **7**.
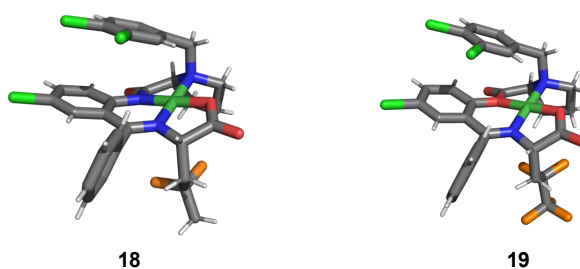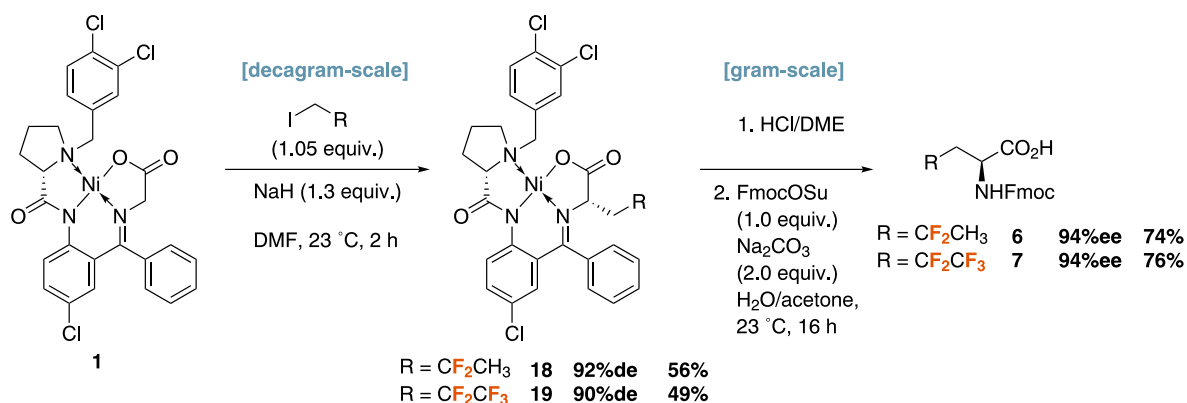
Scheme 5: Gram-scale syntheses of fluorinated norvaline variants using the chiral Ni(II) complex **1**. Ni(II) Schiff base complexes of DfpGly **18** and PfpGly **19** were further characterized by X-ray crystallographic structure determination.

The alkylated complexes **18** and **19** were isolated on a gram-scale in good yields and great diastereomeric purities (**>90%de**) and could be analyzed by X-ray diffraction (**Scheme 5**). The final hydrolysis of the Ni(II) complex was carried out using the previously reported conditions. Both Fmoc protected amino acids (DfpGly **6** and PfpGly **7**) were obtained in good yields and with high enantiomeric excess. To the best of our knowledge, the application of Fmoc-PfpGly **7** in the context of peptide chemistry has not yet been reported in the literature. To explore the properties of this highly fluorinated amino acid, we examined the hydrophobicity and α-helix propensity for this and all other fluorinated amino acids described in this work.

Hydrophobicity and helix propensity of fluorinated amino acids   We used an HPLC-based assay which is established in our laboratory to describe the hydrophobicity of PfpGly **7** (**Figure**

1, a).[31,32] The hydrophobicity of fluorinated Abu and valine analogs has been discussed thoroughly in previous publications.[31] Interestingly, the results for the fluorinated norvaline and isoleucine variants fit perfectly into prior results. Partial fluorination of the norvaline side chains (DfpGly **6**) lowers the hydrophobicity of the molecule, compared to the non-fluorinated norvaline, while pentafluorination strongly increases the retention time of PfpGly **7** which underlines its hydrophobicity (**Figure 1, a**).
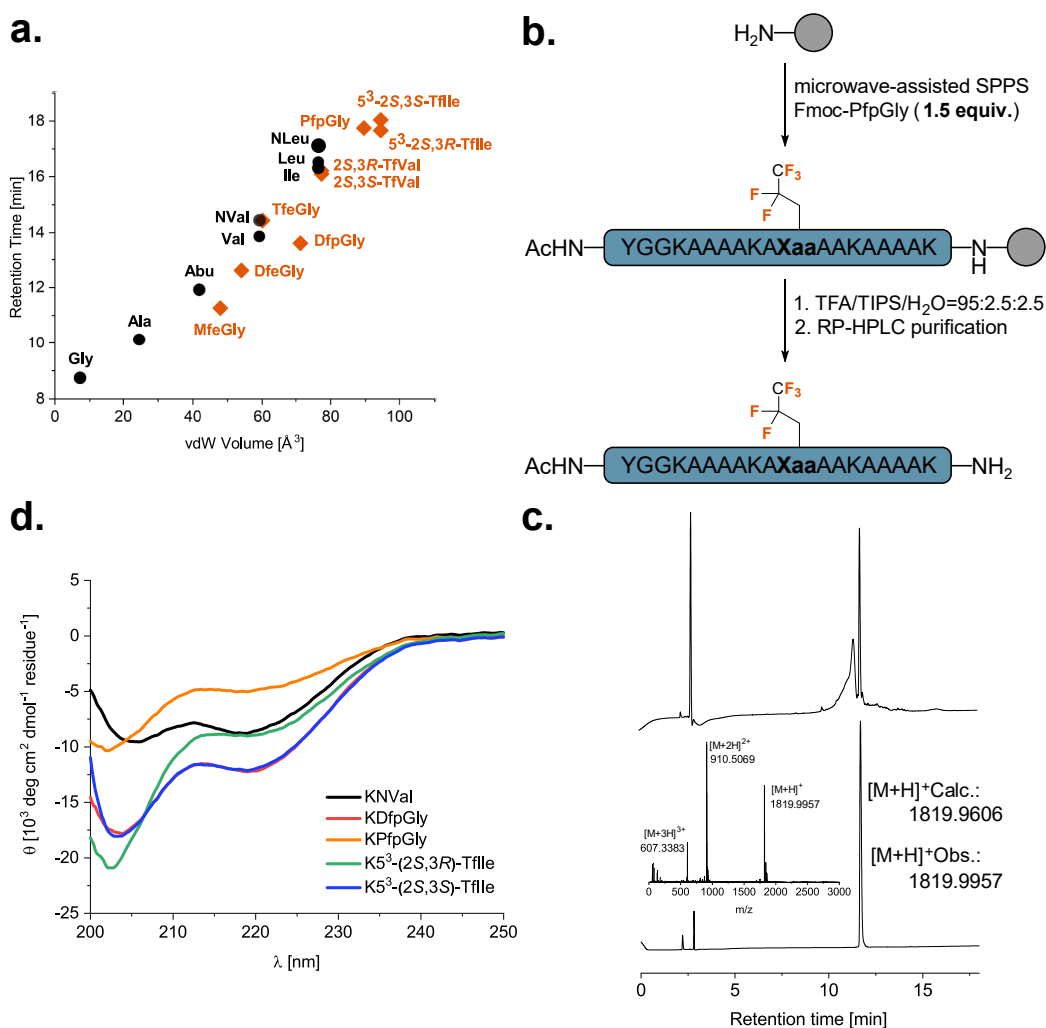
Figure 1: a. Retention times of amino acids plotted against the vdW volume of the side chains. **b.** SPPS of KPfpGly using only 1.5 equiv. of the pentafluorinated amino acid. **c.** HPLC chromatogram of the crude peptide after full cleavage (top) and HPLC chromatogram with the corresponding HRMS spectrum of the purified KPfpGly. **d.** CD spectra of KXaa peptides at 0 °C.

As expected, in the case of the fluorinated isoleucines, the fluorination of the side chains increases the hydrophobicity of the molecules. In contrast to TfVal **4**, the TfIle **5** diastereomers show a larger difference in their retention times. This clearly demonstrates that the influence of

fluorine on the hydrophobicity of amino acids depends on several factors, such as the degree of fluorination, position of fluorination, and the stereochemistry within the side chain.[33,34]

For the determination of the α-helix propensity, we used a circular dichroism (CD)-based assay which was introduced by Cheng et al.[35] The approach is based on a monomeric α-helical peptide with the sequence Ac-YGGKAAAAKA**Xaa**AAKAAAAK-NH$_2$ (KXaa). The amino acids to be studied regarding their structural properties are introduced into the peptide sequence at the Xaa position. Afterwards, corresponding α-helix propensity values can be calculated from the CD data. Our laboratory further expanded the data published by Cheng et al. continuously with new fluorinated amino acids.[31]

Table 3: Mean residue ellipticity (θ [222 nm]) and fraction helix (f_{helix}) values for a series of canonical and fluorinated amino acids. **Entry 1** was adapted from Cheng et al.[35] and **entries 2-8** were taken from Gerling et al.[31]

Entry	Fluorinated Amino Acid	Θ [222 nm]	f_{helix}	w
1	Abu	-18100±200	0.52±0.01	1.22±0.14[35]
2	Leu	-16814±379	0.50±0.01	0.99±0.09[31]
3	Val	-13969±569	0.38±0.01	0.41±0.04[31]
4	MfeGly	-7469±475	0.48±0.01	0.87±0.07[31]
5	DfeGly	-17457±465	0.40±0.02	0.50±0.06[31]
6	TfeGly	-13054±452	0.22±0.01	0.06±0.02[31]
7	(2S,3S)-TfVal	-2685±526	0.08±0.02	0[31]
8	(2S,3R)-TfVal	-3887±547	0.11±0.02	0[31]
9	NVal	-8006±622	0.23±0.02	0.09±0.03
10	DfpGly	-11541±213	0.33±0.01	0.31±0.02
11	PfpGly	-4621±23	0.13	0
12	5^3-(2S,3R)-TfIle	-8575±223	0.25±0.01	0.12±0.01
13	5^3-(2S,3S)-TfIle	-11372±709	0.33±0.02	0.30±0.06 (lit. 0.26)[27]

In the current work, NVal, DfpGly **6**, PfpGly **7**, 5^3-(2S,3R)-, and 5^3-(2S,3S)-TfIle **5** were analyzed using this approach (**Table 3, Entries 9-13**). The corresponding peptide sequences were synthesized by microwave-assisted SPPS. We were pleased to see, that PfpGly **7** could be incorporated using standard coupling conditions despite the highly fluorinated side chain (**Figure 1, b**). The trends for the helical propensity based on the degree of fluorination of NVal

are similar to those observed in the fluorination series of Abu (**Table 2, Entries 1, 4-6**). In this case, however, partial fluorination even increases the helical propensity of the amino acid (**Table 2, Entry 10**). As expected, pentafluorination leads to a loss of α-helix propensity compared to the non-fluorinated analog due to the increased size of the side chain and higher hydrophobicity (**Table 2, Entry 11**). The comparison between the values for TfVal **4** and TfIle **5** shows that the fluorinated analogs of Ile can stabilize the helix more effectively. This could be explained by the proximity of the CF_3-group to the backbone of the peptide. In the case of TfIle **4**, the sterically demanding fluorinated group is more distant from the backbone, which seems to allow a higher helical propensity. Finally, the results illustrate that α-helix propensities of fluorinated amino acids cannot only be explained by their hydrophobicity.[33,34] TfIle **5** diastereomers exhibit the highest hydrophobicity values of all fluorinated amino acids discussed in this work. However, the corresponding w values are higher than in the case of TfVal **4** indicating that other factors, such as proximity to the backbone and stereochemistry must contribute to the structural propensity of an individual amino acid.

Conclusion

We established a gram-scale synthesis for a series of different fluorinated amino acids. The syntheses described in this work are facile and can be carried out on a decagram-scale. All eight described fluorinated amino acids were synthesized from the same starting material in only two steps. The Fmoc protected amino acids were isolated with high enantiomeric purity (>94%ee). We also described a two-steps synthesis to obtain the desired linear and branched alkyl iodides as amino acid side chain precursors from the corresponding fluorinated alcohols on a gram-scale with good overall yields. Furthermore, to the best of our knowledge, we are the first to introduce the first synthesis of peptides containing the pentafluorinated variant of norvaline (Fmoc-PfpGly **7**) using microwave-assisted SPPS conditions. Finally, the hydrophobicity and the α-helix propensity of the synthesized amino acids were characterized using an HPLC-based assay and circular dichroism showing how the two intrinsic properties depend on several parameters such as the degree of fluorination, the fluorination position within the side chain, and the stereochemistry. This work provides a unified approach to a range of fluorinated amino acids, which vary widely in both sterics and degree of fluorination. The presented access to fluorinated amino acids on a gram-scale facilitates the utilization of these compounds in peptide chemistry and opens the door to their inclusion into biomaterial development.

Experimental Section

General information

All air- and hydrolysis-sensitive reactions were carried out under exclusion of air and water in Schlenk-vessels at a Schlenk unit/oil pump vacuum under nitrogen atmosphere. The stated reaction temperatures refer to the temperatures of the silicone oil heating bath. All reactions were stirred with an electric magnetic stirrer. **^{1}H-, ^{13}C- and ^{19}F-NMR** spectra were recorded at room temperature using a JEOL ECP 600 (JEOL, Tokyo, Japan). The depiction and analysis of the spectra was carried out with the program MestReNova Version 10.0.0 (Mestrelab Research S. L., Santiago de Compostela, Spain). The chemical shifts are given in parts per million (ppm). The ^{1}H- and ^{13}C-NMR chemical shifts were referenced against the specific internal solvent residual peaks (CDCl$_3$, CD$_3$OD) and given to trimethylsilane as internal standard (δ = 0.00 ppm). **High-resolution mass spectra (HRMS)** of the synthesized compounds were obtained on an Agilent 6220 ESI-TOF MS instrument (Agilent Technologies, Santa Clara,CA, USA). The dissolved samples were injected directly into the spray chamber using a syringe pump with flow rates of 10 to 40 µL/min. A spray voltage of 4 kV was used and the desolvation gas was set to 15 psi. All other parameters were optimized for maximal abundance of [M+H]$^+$, [M+Na]$^+$ or [M+K]$^+$. High-resolution electron ionization mass spectra (HR-EI-MS) were measured on a MAT 711 (Varian MAT, Bremen). Electron energy for EI was set to 70 eV. **Infrared spectra (IR)** were recorded on an ALPHA II (Bruker, Billerica, United States) spectrometer. Characteristic absorption bands are given in wavenumbers. **Elemental analysis (EA)** measurements were carried out on a VARIO EL (Elementar, Langenselbold, Germany). Qualitative **thin-layer chromatography (TLC)** was performed on silica gel 60 F$_{254}$ coated with aluminium plates from Merck. The analytes were indicated by irradiation of the TLC plates with UV light (λ = 254 nm) and UV absorption by the analyte. For flash chromatography, silica gel 60 M from Macherey-Nagel of grain size of 40-63 µm was used. The respective conditions are given in the form "(A:B = a:b)", where A:B indicates the solvents used as mobile phase and a:b their volume ratio. Purity of synthesized Fmoc-protected amino acids was determined by **analytical high performance liquid chromatography (HPLC)** on a Primaide™ DAD system (VWR/Hitachi, Germany). The system works with a low-pressure gradient containing a HPLC pump (1110) with a 6-channel solvent degaser, an organizer, an autosampler (1210) with a 100 µL sample loop, a column oven (1310) and a diode array detector (1430). A Kinetex™ C18 (2) column (5 µm, 250 Å x 4.6 mm, Phenomenex®, Torrance, CA, USA) was used. As eluents

H$_2$O and MeCN, both containing 0.1% (v/v) TFA were applied. For **chiral analytical HPLC**, a CHIRALPAK® ZWIX(-) column ((*R*,*R*)-ACHSA immobilized on 3 μm silica gel, 250 x 4 mm, Chiral Technologies Europe, Illkirch Cedex, France) was used. As eluents, MeCN/MeOH/H$_2$O with 50 mM formic acid and 25 mM diethylamine were used. A flow rate of 1.0 mL/min was used, and the column was heated to 24 °C. The UV-detection of the Fmoc-protected amino acids occurred at 280 nm. The data were analyzed with EZChrom ELITE software (version 3.3.2 SP2, Agilent). HPLC-based hydrophobicity assay was carried out on a LaChrom-ELITE-HPLC-System from VWR International Hitachi. The System contains an organizer, two HPLC-pumps (L-2130) with solvent degaser, an autosampler (L-2200), a diode array flow detector (L-2455), a fluorescence detector (L-2485) and a high-pressure gradient mixer. The data were analyzed with EZ Chrom ELITE software (version 3.1.7). A Capcell C18 column (Shiseido, Osaka Soda Co., LTD., Osaka, Japan) was used. As eluents, H$_2$O and MeCN, both containing 0.1% (v/v) TFA, were applied. A flow rate of 1 mL/min was used and the UV-detection occurred at 220 nm. Purification of synthesized peptides was performed on a Knauer low-pressure HPLC system (Knauer GmbH, Berlin, Germany) sold by VWR (Darmstadt, Germany), comprising a LaPrep Sigma preparative pump (LP1200), a ternary low-pressure gradient, a dynamic mixing chamber, a 6-port-3-channel injection valve with an automated preperative 10 mL sample loop, a LaPrep Sigma standard 1-channel-UV-detector (LP3101), a flow cell with 0.5 mm thickness and a 16-port LaPrep Sigma fractionation valve (LP2016). A Kinetex RPC18 endcapped (5 μM, 100 Å, 250 x 21.2 mm, Phenomenex®, USA) HPLC-column was used. A Security GuardTM PREP Cartridge Holder Kit (21.20 mm, ID, Phenomenex®, USA) served as pre-column. As eluents water and MeCN, both containing 0.1% (v/v) TFA were applied. HPLC runs were performed with a flow rate of 15 mL/min, UV-detection occurred at 220 nm for respective peptides. Deionized water was obtained using a Milli-Q Advantage® A10 Ultrapure Water Purification System (Millipore®, Billerica, MA, USA). Other chemicals were used without further purification and purchased from commercial sources.

X-ray diffractometry

Chiral Ni(II) complexes were crystallized by slow evaporation from MeOH (3 mg/mL). Low temperature x-ray diffraction data were acquired on a Bruker D8 Venture diffractometer fitted with a PhotonII CMOS detector. Crystal structures were solved using SHELXT and refined with SHELXL-2018.

Peptide synthesis

All peptides were synthesized according to standard Fmoc-chemistry on a 0.05 M scale using preloaded Fmoc-glycine Wang (0.19 mmol/g) resin on a Liberty Blue microwave-assisted peptide synthesizer (CEM GmbH, Matthews, USA). Fmoc deprotection was performed using 10% piperazine and 0.1 M HOBt (w/v) in EtOH:NMP=1:9 (1 min, 90 °C). Peptide couplings were carried out using 0.5 M DIC/0.5 M Oxyma/0.05 M DIPEA in DMF. The standard Fmoc-amino acids were coupled using 5 equiv. of amino acid (30 s, 75 °C). Fluorinated amino acids were introduced using only 1.5 equiv. of the amino acid with prolonged coupling times (2 min, 90 °C). For acetylation of the *N*-terminus of the synthesized peptides, the resin was treated with Ac_2O/DIPEA/DMF=1:1:8 (3x 5 mL, 10 min). Peptides were cleaved from the resin using TFA/TIPS/H_2O=95:2.5:2.5 (5 mL, 2 h). The synthesized peptides were purified by reversed-phase preparative HPLC and characterized by ESI-ToF HRMS. To lyophilize the synthesized peptides a laboratory freeze dryer ALPHA 1-2 LD (Christ Gefriertrocknungsanlagen GmbH, Osterode am Harz, Germany) was used.

α-helix propensity

Circular dichroism spectra were recorded with a Jasco J-810 spectropolarimeter using a quartz cuvette of 1 mm path length at 0 °C. For temperature control, a JACSO PFD-350S Peltier element was used. CD measurements were performed in 1 M NaCl, 1 mM sodium phosphate, 1 mM sodium citrate, and 1 mM sodium borate (pH=7) at peptide concentrations of 30, 50, and 80 mM. Each reported CD value represents the mean of at least three independent measurements. For each spectrum, the data was obtained at 0.2 nm intervals, 2 nm bandwidth, and 2 s response time. The nitrogen flow rate was set to 3.5 L/min. The spectra were recorded in the far-UV range (250-200 nm) and the signals of the blank solvent were subtracted. Ellipticity θ_{Obs} was normalized into molar ellipticity per residue using $[\theta]=\theta_{Obs}/10000\,l\,N\,c$ with l = path length [cm], N = number of residues, c = concentration [mol L^{-1}]. The fractional helical content of peptide (f_{helix}) was calculated from $[\theta]$ at 222 nm using $f_{helix}=[\theta]_{222nm}/(40\,000\,(1-2.5/N))$. The helix propensity *w* of the amino acid at the guest position was calculated from the f_{helix} of the corresponding peptide based on modified Lifson–Roig theory. For each amino acid, four different parameters are important: helix propensity (*w*), nucleation (*v*), N-terminal capping propensity (*n*), and C-terminal capping propensity (*c*). For all residues, v was set to 0.048, and c was set to 1. For the host amino acids, literature values were used for *w* and *n*. For the residue in the guest position, n was set to 1, and *w* was calculated numerically.

Size exclusion chromatography

Determination of the oligomerization state of KXaa peptides has been carried out using size exclusion chromatography (SEC) in combination with static light scattering (SLS). For the size exclusion analysis, a Superdex[TM] Peptide 10/300 GL column (10 x 310 mm, Cytiva) was used connected to a HPLC station (La Chrom, VWR, Hitachi, L-2130). The experiments were performed at a velocity of 0.5 mL min^{-1} in a 10 mM sodium phosphate buffer with 150 mM sodium chloride at pH 7.4. The sample concentration was between 500 and 600 mM and the injection volume was 100 µL. Dawn Heleos 8 light scattering photometer and an Optilab rEX refractive index detector (Wyatt Technology) were used for SLS experiments. Molecular weight values were calculated by using a dn/dc value of 0.185 mL g^{-1}. All data were analyzed with ASTRA software version 6.1 (Wyatt Technology).

HPLC-based hydrophobicity assay

The impact of fluorination on the hydrophobicity of fluorinated amino acids was investigated using a HPLC-based assay established by our group. The Fmoc-protected amino acids were dissolved in MeCN/H2O=4:6 (0.1 mM) with 0.1% TFA (v/v) and filtered over a syringe filter with 0.2 mm pore size. A linear gradient 40% to 70% MeCN in H_2O was used at room temperature and each measurement was carried out in triplicate. The obtained retention times were plotted against the van der Waals volumes of the corresponding side chains. The van der Waals volumes were calculated according to Zhao *et al*.[36]

General procedure A: Nonaflation of fluorinated alcohols

According to M. Hanack and J. Ullmann[30], the fluorinated alcohol (1.0 equiv.) was dissolved in dry CH_2Cl_2 (3.0 M) and NEt$_3$ (1.0 equiv.) was added at -40 °C under a nitrogen atmosphere. Perfluorobutanesulfonyl fluoride (1.375 equiv.) was added dropwise to the reaction solution at -40 C. After the addition, the reaction mixture was allowed to warm up to 23 °C. The reaction solution was stirred at this temperature for 16 h. Subsequently, CH_2Cl_2 was removed under reduced pressure. The crude product was purified by distillation.

General procedure B: Iodination of alkyl nonaflates

The nonaflate (1.0 equiv.) was dissolved in DMI (3 M) and sodium iodide (1.2 equiv.) was added to the solution. The reaction mixture was stirred at 23 °C for 24 h. The product was purified by high vacuum distillation (10^{-2} mbar) into a cooling trap (-78 °C).

General procedure C: Alkylation of chiral Ni(II) complex using KOH/MeOH

According to Z. Yin *et al.*[14], Ni(II) complex (1.0 equiv.) was dissolved in dry, degassed DMF (0.2 M) under a nitrogen atmosphere. Alkyl iodide (1.05 equiv.) and then KOH (1.05 equiv.) dissolved in dry, degassed MeOH were added to the solution at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. H_2O (3.2 v/w) was added to the solution and the reaction mixture was stirred for 1 h. An additional amount of H_2O (1.8 v/w) was added, and the reaction mixture was stirred for another 1 h. The precipitated product was filtered from the reaction mixture. The product was washed with DMF/H_2O=2:1 (1.8 v/w) and then with H_2O (2.0 v/w). The product was dried under high vacuum at 60 °C.

General procedure D: Alkylation of chiral Ni(II) complex using NaH

Ni (II) complex (1.0 equiv.) was dissolved in dry, degassed DMF (0.4 M) under a nitrogen atmosphere. Alkyl iodide (1.05 equiv.) and then NaH (1.3/2.0 equiv.) were added to the solution at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. H_2O (3.2 v/w) was added to the solution and the reaction mixture was stirred for 1 h. An additional amount of H_2O (1.8 v/w) was added, and the reaction mixture as stirred for another 1 h. The precipitated product was filtered from the reaction mixture. An additional amount of product precipitated from the filtrate after another addition of H_2O (2.0 v/w). The combined product was combined and dried under high vacuum at 60 °C.

General procedure E: Hydrolysis and Fmoc-protection

According to Z. Yin *et al.*, the alkylated Ni (II) complex (1.0 equiv.) was dissolved in dimethoxyethane (0.3 M) and 3 M aqueous HCl solution (5.0 equiv.) was added. The reaction mixture was stirred for 2 h at 60 °C. The reaction mixture was cooled to 23 °C and the precipitated ligand was filtered from the solution. The ligand was washed with H_2O (2.0 v/w)

and the filtrate was concentrated under reduced pressure (4.0 v/w). An additional amount of the ligand precipitated from the solution. The ligand was filtered and washed with H_2O (2.0 v/w). Both fractions of the ligand were combined and dried under high vacuum at 40 °C. MeCN (0.5 M) and EDTA Na_2 (1.0 equiv.) were added to the filtrate. The reaction mixture was stirred at 23 °C for 2 h. The pH of the solution was adjusted to 7 and subsequently Na_2CO_3 (2.0 equiv.) was added to the mixture. FmocOSu (1.0 equiv.) was dissolved in acetone (0.25 M) and added dropwise to the reaction solution. The mixture was stirred at 23 °C for 16 h. MeCN and acetone were removed under reduced pressure, additional amount of H_2O was added, and the aqueous solution was washed with Et_2O. The solution was acidified to pH=2 using a 6M aqueous HCl solution. The mixture was extracted with EtOAc, the combined organic phases were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by recrystallization from a hexane/EtOAc mixture.

*2,2-Difluoropropyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (**9**)*

According to **general procedure A**, 2,2-difluoropropan-1-ol (3.84 g, 3.3 mL, 40.0 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (13 mL), and NEt_3 (4.05 g, 5.6 mL, 40.0 mmol, 1.0 equiv.) and NfF (16.61 g, 9.9 mL, 55.0 mmol, 1.375 equiv.) were added at -40 °C under a nitrogen atmosphere. The desired product was purified by distillation (30 mbar, 70 °C) and obtained as colorless liquid (7.97 g, 53%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.55 (t, J = 10.8 Hz, 2H), 1.76 (t, J = 18.8 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 118.8 (t, J = 241.7 Hz), 118.0, 116.1, 114.6, 109.8, 74.0 (t, J = 36.7 Hz), 20.6 (t, J = 25.4 Hz). ^{19}F NMR (376 Hz, $CDCl_3$), δ -80.6 (t, J = 9.7 Hz), -99.4 (dtd, J = 29.1, 18.8, 10.8 Hz), -110.1, -121.2, -125.8. ATR-FTIR (neat) 1422, 1400, 1353, 1293, 1223, 1193, 1141, 1036, 1005, 980, 933, 913, 881, 849, 792, 749, 735, 699, 686, 653, 587, 532, 503 cm^{-1}. HRMS (EI, 70 eV) *m/z*: [M]$^{+\bullet}$ Calcd for $C_7H_5F_{11}O_3S$ 377.9784; Found 378.0275.

*1,1,1-Trifluoropropan-2-yl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (**12**)*

According to **general procedure A**, 1,1,1-trifluoropropan-2-ol (21.54 g, 17.1 mL, 188.8 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (63 mL), and NEt_3 (19.10 g, 26.2 mL, 188.8 mmol, 1.0 equiv.) and NfF (78.42 g, 46.7 mL, 259.6 mmol, 1.375 equiv.) were added at -40 °C under a nitrogen atmosphere. The desired product was purified by distillation (30 mbar, 62 °C) and obtained as colorless liquid (46.60 g, 62%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.14 (t, J = 12.2,

6.1 Hz, 1H), 1.65 (d, J = 6.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 122.1 (t, J = 241.7), 117.9, 116.3, 114.3, 109.8, 79.1 (q, J = 35.8 Hz), 14.6. ^{19}F NMR (376 Hz, CDCl$_3$), δ -78.7, -80.58 (t, J = 9.7 Hz), -109.58 – -111.30 (m), -120.89, -125.82. ATR-FTIR (neat) 1428, 1283, 1238, 1227, 1195, 1170, 1142, 1062, 1036, 1010, 939, 797, 786, 737, 700, 651, 590, 525 cm^{-1}. HRMS (EI, 70 eV) m/z: [C$_4$F$_9$SO$_3$CHCF$_3$]$^+$ Calcd for C$_4$F$_9$SO$_3$CHCF$_3$ 380.9455; Found 380.9859.

2,2-Difluoro-1-iodopropane (10)

According to **general procedure B**, difluoropropyl nonaflate (7.87 g, 20.8 mmol, 1.0 equiv.) was dissolved in DMI (7 mL) and sodium iodide (3.75 g, 25.0 mmol, 1.2 equiv.) was added to the solution. The product was obtained as colorless liquid (3.90 g, 91%). ^{1}H NMR (600 MHz, CDCl$_3$) δ 3.4 (t, J = 13.9 Hz, 2H), 1.8 (t, J = 17.8 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 120.4 (t, J = 239.8 Hz), 22.6 (t, J = 27.2 Hz), 4.9 (t, J = 32.0 Hz). ^{19}F NMR (376 Hz, CDCl$_3$) δ -87.5 – -87.7 (m). ATR-FTIR (neat) 1419, 1390, 1262, 1249, 1220, 1202, 1137, 1113, 1052, 958, 915, 816, 785, 647, 544, 497 cm^{-1}. HRMS (EI, 70 eV) m/z: [M]$^{+\bullet}$ Calcd for C$_3$H$_5$F$_2$I 205,9404; Found 205.9566.

1,1,1-Trifluoro-2-iodopropane (13)

According to **general procedure B**, trifluoro-*iso*-propyl nonaflate (46.37 g, 117.1 mmol, 1.0 equiv.) was dissolved in DMI (39 mL) and sodium iodide (21.1 g, 140.5 mmol, 1.2 equiv.) was added to the solution. The product was obtained as colorless liquid (24.90 g, 95%). ^{1}H NMR (600 MHz, CDCl$_3$) δ 4.25 (dq, J = 7.8, 7.4 Hz, 1H), 1.96 (d, J = 7.6 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 124.8 (q, J = 276.2 Hz), 21.8, 14.1 (q, J = 35.8 Hz). ^{19}F NMR (376 Hz, CDCl$_3$) δ -71.5 (d, J = 7.8 Hz). ATR-FTIR (neat) 1453, 1343, 1258, 1201, 1165, 1101, 1069, 1037, 973, 647 cm^{-1}. HRMS (EI-TOF) m/z: [M]$^{+\bullet}$ Calcd for C$_3$H$_4$F$_3$I 223.9310; Found 223.9519.

Ni(II)-Schiff base complex of MfeGly (14)

According to **general procedure C**, Ni(II) complex (20.00 g, 33.2 mmol, 1.0 equiv.) was dissolved in dry, degassed DMF (200 mL) under a nitrogen atmosphere. First alkyl iodide (6.06 g, 2.8 mL, 34.8 mmol, 1.05 equiv.) and then KOH (2.00 g, 34.8 mmol, 1.05 equiv.)

dissolved in dry, degassed MeOH (18 mL) were added to the solution at 0 °C and the mixture was stirred at 0 °C for 2 h. The product was obtained as orange solid (16.20 g, 75%). ^{1}H NMR (600 MHz, CD$_3$OD) δ 8.8 (d, J = 2.1 Hz, 1H), 8.2 (dd, J = 8.2, 2.1 Hz, 1H), 8.0 (d, J = 9.3 Hz, 1H), 7.6 (td, J = 7.6, 0.8 Hz, 1H), 7.6 (tt, J = 7.6, 1.3 Hz, 1H), 7.5 – 7.5 (m, 1H), 7.5 (d, J = 8.2 Hz, 1H), 7.4 (dt, J = 7.8, 1.7 Hz, 1H), 7.1 (dd, J = 9.3, 2.6 Hz, 1H), 7.0 (d, J = 7.8 Hz, 1H), 6.5 (d, J = 2.6 Hz, 1H), 4.9 – 4.6 (m, 2H), 4.2 (d, J = 12.6 Hz, 1H), 4.0 (dd, J = 8.2, 3.7 Hz, 1H), 3.6 – 3.5 (m, 2H), 3.4 – 3.3 (m, 2H), 2.7 – 2.5 (m, 2H), 2.3 – 2.1 (m, 3H), 2.1 – 2.0 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, CD$_3$OD) δ 181.3, 180.1, 171.3, 140.6, 136.6, 133.3, 133.0, 132.7, 132.7, 131.9, 131.7, 131.1, 130.8, 130.2, 129.2, 129.1, 127.8, 127.6, 127.0, 125.5, 124.2, 79.6 (d, J = 165.7 Hz), 71.4, 67.5, 62.6, 58.3, 34.8 (d, J = 19.8 Hz), 30.6, 23.0. ^{19}F NMR (376 Hz, CD$_3$OD), δ -218.3 – -218.6 (m). ATR-FTIR (neat) 1682, 1621, 1597, 1588, 1538, 1463, 1443, 1396, 1356, 1325, 1316, 1253, 1228, 1165, 1116, 1077, 1029, 927, 918, 893, 879, 816, 723, 706, 690, 666, 644, 591, 517, 507, 496, 464, 445, 421 cm^{-1}. HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for C$_{29}$H$_{25}$Cl$_3$FN$_3$NiO$_3$ 668.0197; Found 668.0186. Anal Calcd for C$_{29}$H$_{25}$Cl$_3$FN$_3$NiO$_3$: C, 53.79; H, 3.89; N, 6.49. Found: C, 55.39; H, 4.05; N, 6.52.

Ni(II)-Schiff base complex of DfeGly (15)

According to **general procedure C**, Ni(II) complex (20.00 g, 33.2 mmol, 1.0 equiv.) was dissolved in dry, degassed DMF (200 mL) under a nitrogen atmosphere. First alkyl iodide (6.68 g, 3.1 mL, 34.8 mmol, 1.05 equiv.) and then KOH (2.00 g, 34.8 mmol, 1.05 equiv.) dissolved in MeOH (18 mL) were added to the solution at 0 °C and the mixture was stirred at 0 °C for 2 h. The product was obtained as orange solid (16.1 g, 73%). ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.9 (s, 1H), 8.1 (d, J = 9.3 Hz, 1H), 7.8 – 7.7 (m, 1H), 7.6 – 7.4 (m, 3H), 7.4 – 7.3 (m, 1H), 7.3 – 7.2 (m, 1H), 7.1 (d, 1H), 6.9 – 6.8 (m, 1H), 6.6 (s, 1H), 6.1 (t, J = 55.7 Hz, 1H), 4.3 (d, J = 12.6 Hz, 1H), 4.1 – 4.0 (m, 1H), 3.6 – 3.4 (m, 2H), 3.4 – 3.3 (m, 1H), 3.2 (d, J = 12.7 Hz, 1H), 2.8 – 2.6 (m, 1H), 2.6 – 2.5 (m, 1H), 2.5 – 2.3 (m, 1H), 2.2 (d, J = 13.2 Hz, 1H), 2.1 – 2.0 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 180.1, 177.9, 171.7, 140.9, 134.9, 133.7, 133.7, 133.5, 132.9, 132.6, 132.4, 131.2, 130.7, 130.0, 129.7, 129.7, 127.2, 127.2, 127.0, 126.0, 124.3, 114.6 (t, J = 240.1 Hz), 71.4, 63.2, 58.6, 38.7 (t, J = 23.1 Hz), 30.9, 29.8, 23.8. ^{19}F NMR (376 Hz, CDCl$_3$), δ -114.0 (dddd, J = 287.8, 55.8, 15.0, 9.9 Hz), -116.0 (dddd, J = 287.8, 55.7, 23.9, 13.7 Hz). ATR-FTIR (neat) 1678, 1639, 1581, 1527, 1458, 1443, 1395, 1337, 1311, 1241, 1163, 1119, 1094, 1055, 1030, 917, 892, 872, 832, 819, 722, 707, 691, 684, 666, 597, 539, 516, 464, 439, 421 cm^{-1}. HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_{29}$H$_{24}$Cl$_3$F$_2$N$_3$NiO$_3$ 664.0285;

Found 664.0301. Anal Calcd for $C_{29}H_{24}Cl_3F_2N_3NiO_3$: C, 52.33; H, 3.63; N, 6.31. Found: C, 55.79; H, 4.40; N, 6.45.

Ni(II)-Schiff base complex of DfpGly (18)

According to **general procedure D**, Ni (II) complex (7.31 g, 12.2 mmol, 1.0 equiv.) was dissolved in dry, degassed DMF (30 mL) under a nitrogen atmosphere. Alkyl iodide (2.63 g, 1.35 mL, 12.8 mmol, 1.05 equiv.) and then NaH (60% dispersion in mineral oil, 632.0 mg, 15.8 mmol, 1.3 equiv.) were added to the solution at 0 °C and the reaction mixture was stirred at 0 °C for 2 h. The desired product was purified by recrystallization from EtOH and obtained as red solid (3.99 g, 48%). An additional amount of product (0.70 g, 8%) could be recovered from the recrystallization solution and was further purified by flash column chromatography (CHCl$_3$:acetone=30:1). ^{1}H NMR (600 MHz, CDCl$_3$) δ 9.15 (s, 1H), 8.36 (d, J = 9.3 Hz, 1H), 7.97 (d, J = 8.1 Hz, 1H), 7.88 – 7.66 (m, 3H), 7.65 – 7.44 (m, 2H), 7.33 (d, J = 9.3 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 6.78 (s, 1H), 4.51 (d, J = 12.7 Hz, 1H), 4.42 – 4.24 (m, 1H), 3.88 – 3.67 (m, 2H), 3.62 – 3.49 (m, 1H), 3.43 (d, J = 12.7 Hz, 1H), 3.09 – 2.94 (m, 1H), 2.88 – 2.72 (m, 1H), 2.60 – 2.44 (m, 1H), 2.43 – 2.17 (m, 3H), 1.82 (t, J = 18.6 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 180.1, 178.5, 171.2, 141.2, 135.1, 133.8, 133.5, 133.4, 133.4, 132.6, 132.2, 131.1, 130.5, 130.0, 129.6, 129.4, 127.7, 127.5, 127.0, 125.7, 124.2, 123.5 (t, J = 241.6 Hz), 71.8, 66.0, 63.3, 58.6, 40.2 (t, J = 24.9 Hz), 31.0, 24.6 (t, J = 26.8 Hz), 23.0. ^{19}F NMR (376 Hz, CDCl$_3$), δ -84.6 (d, J = 239.6 Hz), -86.6 (d, J = 240.4 Hz). ATR-FTIR (neat) 1673, 1636, 1589, 1532, 1461, 1395, 1362, 1337, 1312, 1273, 1245, 1229,1162, 1142, 1117, 1064, 1031, 905, 878, 844, 823, 706, 685, 488, 446 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{30}H_{26}Cl_3F_2N_3NiO_3$ 678.0441; Found 678,0468. Anal Calcd for $C_{30}H_{26}Cl_3F_2N_3NiO_3$: C, 53.02; H, 3.86; N, 6.18. Found: C, 53.09; H, 4.60; N, 6.26.

Ni(II)-Schiff base complex of PfpGly (19)

According to **general procedure D**, Ni (II) complex (9.07 g, 14.95 mmol, 1.0 equiv.) was dissolved in dry, degassed DMF (37 mL) under a nitrogen atmosphere. Alkyl iodide (4.08 g, 2.0 mL, 15.7 mmol, 1.05 equiv.) and then NaH (60% dispersion in mineral oil, 777.2 mg, 19.4 mmol, 1.3 equiv.) were added to the solution at 0 °C and the reaction mixture was stirred at 0 °C for 2 h. The desired product was purified by recrystallization from EtOH and obtained as red solid (4.86 g, 44%). An additional amount of product (0.59 g, 5%) could be recovered

from the recrystallization solution and was further purified by flash column chromatography (CHCl$_3$:acetone=30:1). ^{1}H NMR (600 MHz, CDCl$_3$) δ 9.14 (s, 1H), 8.37 (d, J = 9.3 Hz, 1H), 7.93 (d, J = 8.2 Hz, 1H), 7.85 – 7.67 (m, 3H), 7.57 (d, J = 8.1 Hz, 1H), 7.54 – 7.48 (m, 1H), 7.33 (d, J = 9.3 Hz, 1H), 7.08 (d, J = 7.7 Hz, 1H), 6.78 (s, 1H), 4.57 – 4.40 (m, 2H), 3.84 – 3.74 (m, 1H), 3.71 – 3.59 (m, 1H), 3.59 – 3.49 (m, 1H), 3.44 (d, J = 12.6 Hz, 1H), 3.02 – 2.91 (m, 1H), 2.86 – 2.60 (m, 2H), 2.42 – 2.32 (m, 1H), 2.31 – 2.15 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 180.2, 177.4, 172.4, 141.4, 135.0, 133.8, 133.6, 133.4, 133.2, 133.0, 132.3, 131.2, 130.9, 130.0, 129.8, 129.6, 127.5, 127.1, 126.7, 125.8, 124.3, 119.9 – 113.7 (m, 2C), 71.7, 64.2, 63.4, 58.6, 32.1 (t, J = 19.5 Hz), 31.0, 23.0. ^{19}F NMR (376 Hz, CDCl$_3$) δ -85.9, -112.3 (dd, J = 263.3, 34.3 Hz), -115.1 (dd, J = 260.9, 33.0 Hz). ATR-FTIR (neat) 1681, 1641, 1584, 1532, 1461, 1397, 1337, 1318, 1246, 1193, 1166, 1117, 1091, 1060, 1016, 977, 884, 825, 724, 707, 692, 667, 598, 518, 508, 494, 477, 450 cm^{-1}. HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_{30}$H$_{23}$Cl$_3$F$_5$N$_3$NiO$_3$ 732.0159; Found 732.0229. Anal Calcd for C$_{30}$H$_{23}$Cl$_3$F$_5$N$_3$NiO$_3$: C, 49.12; H, 3.16; N, 5.73. Found: C, 49.35; H, 3.56; N, 5.77.

Ni(II)-Schiff base complex of TfVal (16)

According to **general procedure D**, Ni (II) complex (20.00 g, 33.2 mmol, 1.0 equiv.) was dissolved in dry, degassed DMF (83 mL) under a nitrogen atmosphere. Alkyl iodide (7.82 g, 34.8 mmol, 1.05 equiv.) and then NaH (60% dispersion in mineral oil, 2.67 g, 66.5 mmol, 2.0 equiv.) were added to the solution at 0 °C and the reaction mixture was stirred at 0 °C for 2 h. The desired products were purified by flash column chromatography (CHCl$_3$:acetone=30:1) and obtained as red solids ((2S,3R)-isomer: 5.65 g, 24%; (2S,3S)-isomer: 6.50 g, 28%).

(2S,3S)-isomer 16a: ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.99 (d, J = 2.1 Hz, 1H), 8.17 (d, J = 9.3 Hz, 1H), 7.65 (dd, J = 8.2, 2.1 Hz, 1H), 7.62 – 7.54 (m, 2H), 7.52 (t, J = 7.4, 1.6 Hz, 1H), 7.36 – 7.27 (m, 2H), 7.10 (dd, J = 9.3, 2.6 Hz, 1H), 6.89 (d, J = 7.5 Hz, 1H), 6.56 (d, J = 2.6 Hz, 1H), 4.30 (d, J = 12.6 Hz, 1H), 3.98 (d, J = 3.6 Hz, 1H), 3.61 – 3.48 (m, 1H), 3.46 – 3.34 (m, 1H), 3.31 (dd, J = 10.6, 6.7 Hz, 1H), 3.17 (d, J = 12.6 Hz, 1H), 2.84 – 2.72 (m, 1H), 2.59 (dq, J = 13.4, 8.7 Hz, 1H), 2.34 – 2.20 (m, 1H), 2.16 – 1.96 (m, 2H), 1.01 (d, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 180.0, 175.7, 171.8, 141.4, 135.2, 133.9, 133.5, 133.4, 133.0, 133.0, 132.4, 131.1, 130.6, 129.9, 129.8, 129.6, 127.6, 127.3 (q, J = 282.3 Hz), 127.1, 127.0, 125.7, 124.0, 71.9, 69.4, 63.6, 58.6, 42.7 (q, J = 26.7 Hz), 30.9, 22.5, 11.8. ^{19}F NMR (376 Hz, CDCl$_3$) δ -64.9 (d, J = 9.1 Hz). ATR-FTIR (neat) 1677, 1638, 1579, 1571, 1527, 1458,

1395, 1335, 1315, 1265, 1240, 1180, 1163, 1134, 1111, 1089, 1080, 1054, 1031, 1014, 946, 877, 829, 724, 710, 691, 681, 665, 597, 550, 544, 506, 452, 441, 425 cm^{-1}. HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for C$_{30}$H$_{25}$Cl$_3$F$_3$N$_3$NiO$_3$ 718.0165; Found 718.0231. Anal Calcd for C$_{30}$H$_{25}$Cl$_3$F$_3$N$_3$NiO$_3$: C, 51.65; H, 3.61; N, 6.02. Found: C, 54.67; H, 3.91; N, 6.59.

(2S,3R)-isomer 16b: ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.99 (d, J = 2.1 Hz, 1H), 8.17 (d, J = 9.3 Hz, 1H), 7.65 (dd, J = 8.2, 2.1 Hz, 1H), 7.62 – 7.54 (m, 2H), 7.52 (t, J = 7.4, 1.6 Hz, 1H), 7.36 – 7.27 (m, 2H), 7.10 (dd, J = 9.3, 2.6 Hz, 1H), 6.89 (d, J = 7.5 Hz, 1H), 6.56 (d, J = 2.6 Hz, 1H), 4.30 (d, J = 12.6 Hz, 1H), 3.98 (d, J = 3.6 Hz, 1H), 3.61 – 3.48 (m, 1H), 3.46 – 3.34 (m, 1H), 3.31 (dd, J = 10.6, 6.7 Hz, 1H), 3.17 (d, J = 12.6 Hz, 1H), 2.84 – 2.72 (m, 1H), 2.59 (dq, J = 13.4, 8.0 Hz, 1H), 2.34 – 2.20 (m, 1H), 2.16 – 1.96 (m, 2H), 1.01 (d, J = 8.0 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 180.0, 175.2, 172.3, 141.1, 135.1, 133.8, 133.6, 133.5, 133.1, 132.7, 132.5, 131.2, 130.8, 129.90, 129.80, 129.5, 127.4, 127.3, 127.1, 126.0, 125.4 (q, J = 280.9 Hz) 123.9, 71.6, 68.5, 63.6, 58.4, 43.0 (q, J = 28.1 Hz), 31.0, 23.3, 10.1. ^{19}F NMR (376 Hz, CDCl$_3$) δ -69.5 (d, J = 9.2 Hz). ATR-FTIR (neat) 1694, 1629, 1589, 1536, 1460, 1395, 1351, 1333, 1315, 1276, 1246, 1176, 1164, 1133, 1104, 1059, 1021, 890, 829, 811, 740, 714, 703, 685, 668, 556, 543, 509, 451, 446, 425 cm^{-1}. HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for C$_{30}$H$_{25}$Cl$_3$F$_3$N$_3$NiO$_3$ 718.0165; Found 718.0230. Anal Calcd for C$_{30}$H$_{25}$Cl$_3$F$_3$N$_3$NiO$_3$: C, 51.65; H, 3.61; N, 6.02. Found: C, 49.61; H, 4.01; N, 5.77.

Ni(II)-Schiff base complex of TfIle (17)

According to **general procedure D**, Ni (II) complex (20.00 g, 33.2 mmol, 1.0 equiv.) was dissolved in dry, degassed DMF (200 mL) under a nitrogen atmosphere. Alkyl iodide (8.31 g, 34.9 mmol, 1.05 equiv.) and then NaH (60% dispersion in mineral oil, 2.67 g, 66.5 mmol, 2.0 equiv.) were added to the solution at 0 °C and the reaction mixture was stirred at 0 °C for 2 h. The desired products were purified by flash column chromatography (CHCl$_3$:acetone=30:1) and obtained as red solids ((2S,3R)-isomer: 2.63 g, 11% (brsm 14%); (2S,3S)-isomer: 4.31 g, 18% (brsm 23%)). An additional amount of starting material could be recovered (4.10 g, 26.4 mmol, 21%).

(2S,3R)-isomer 17b: ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.93 (s, 1H), 8.17 (d, J = 9.1 Hz, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.64 – 7.45 (m, 3H), 7.40 – 7.28 (m, 2H), 7.13 (d, J = 9.3 Hz, 1H), 6.86 (d, J = 7.6 Hz, 1H), 6.60 (s, 1H), 4.50 – 4.36 (m, 1H), 4.32 (d, J = 12.5 Hz, 1H), 3.88 – 3.77 (m, 1H), 3.60 – 3.47 (m, 1H), 3.46 – 3.26 (m, 2H), 3.22 (d, J = 12.6 Hz, 1H), 2.82 – 2.71 (m, 1H),

2.71 – 2.59 (m, 1H), 2.42 – 2.18 (m, 2H), 2.15 – 2.00 (m, 2H), 0.85 (d, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 180.0, 176.8, 171.9, 141.0, 134.9, 133.8, 133.7, 133.5, 133.0, 132.9, 132.6, 131.2, 130.5, 130.1 (q, J = 160.1 Hz), 129.8, 129.6, 129.5, 127.7, 127.2, 127.2, 126.0, 124.0, 74.1, 71.6, 63.1, 58.3, 35.9 (q, J = 28.1 Hz), 33.8, 31.0, 23.2, 17.0. ^{19}F NMR (376 Hz, CDCl$_3$) δ -63.1 (t, J = 11.2 Hz). ATR-FTIR (neat) 1673, 1650, 1581, 1528, 1461, 1396, 1336, 1311, 1277, 1244, 1166, 1138, 1117, 1075, 1053, 1031, 971, 884, 832, 823, 722, 707, 685, 664, 588, 541, 497, 472, 438, 416 cm^{-1}. HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_{31}$H$_{27}$Cl$_3$F$_3$N$_3$NiO$_3$ 710.0504; Found 710.0584. Anal Calcd for C$_{31}$H$_{27}$Cl$_3$F$_3$N$_3$NiO$_3$: C, 52.32; H, 3.82; N, 5.91. Found: C, 52.36; H, 3.97; N, 5.94.

(2S,3S)-isomer 17a: ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.97 (s, 1H), 8.16 (d, J = 9.3 Hz, 1H), 7.70 – 7.65 (m, 1H), 7.63 – 7.52 (m, 2H), 7.49 (t, J = 7.5 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.30 (d, J = 7.4 Hz, 1H), 7.12 (dd, J = 9.3, 2.6 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 6.58 (dd, J = 9.3, 2.6 Hz, 1H), 4.33 (d, J = 12.6 Hz, 1H), 3.99 (d, J = 3.4 Hz, 1H), 3.64 – 3.50 (m, 1H), 3.44 – 3.29 (m, 2H), 3.22 (d, J = 12.5 Hz, 1H), 2.83 – 2.69 (m, 1H), 2.69 – 2.53 (m, 1H), 2.25 – 2.13 (m, 4H), 2.13 – 1.96 (m, 3H), 1.96 – 1.85 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 180.0, 177.0, 171.8, 140.9, 135.1, 133.8, 133.6, 133.5, 132.8, 132.8, 132.5, 131.2, 130.5, 129.8, 129.6, 129.5, 127.5, 127.3, 126.9, 125.9, 124.8 (q, J = 157.0 Hz), 123.9, 73.1, 71.6, 63.6, 58.3, 36.8 (q, J = 28.1 Hz), 32.2, 31.0, 23.1, 16.1. ^{19}F NMR (376 Hz, CDCl$_3$) δ -64.4 (t, J = 11.1 Hz). ATR-FTIR (neat) 1669, 1636, 1584, 1532, 1461, 1395, 1351, 1335, 1316, 1276, 1247, 1166, 1137, 1062, 1033, 919, 882, 826, 748, 722, 708, 689, 663, 600, 548, 540, 499, 478, 441 cm^{-1}. HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_{31}$H$_{27}$Cl$_3$F$_3$N$_3$NiO$_3$ 710.0504; Found 710.0593. Anal Calcd for C$_{31}$H$_{27}$Cl$_3$F$_3$N$_3$NiO$_3$: C, 52.32; H, 3.82; N, 5.91. Found: C, 50.35; H, 4.10; N, 5.62.

(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-fluorobutanoic acid
(Monofluoroethylglycine, MfeGly) (2)

According to **general procedure E**, alkylated Ni (II) complex (16.00 g, 24.7 mmol, 1.0 equiv.) was dissolved in dimethoxyethane (82 mL) and 3M aqueous HCl solution (41.1 mL, 123.55 mmol, 5.0 equiv.) was added. After the recovery of the ligand (11.65 g, 90%), MeCN (49 mL) and EDTA Na$_2$ (9.20 g, 24.7 mmol, 1.0 equiv.) were added to the filtrate and the reaction mixture was stirred at 23 °C for 2 h. The pH of the solution was adjusted to 7 and subsequently Na$_2$CO$_3$ (5.24 g, 49.4 mmol, 2.0 equiv.) was added to the mixture. FmocOSu (8.34 g, 24.7 mmol, 1.0 equiv.) was dissolved in acetone (99 mL) and added dropwise to the

reaction solution. The desired product was obtained after recrystallization from hexane/EtOAc as colorless solid (7.42 g, 87%, 96% purity determined by analytical HPLC). ^{1}H NMR (600 MHz, CD$_3$OD) δ 7.76 (d, J = 7.6 Hz, 2H), 7.64 (t, J = 7.6 Hz, 2H), 7.36 (t, J = 7.5 Hz, 3H), 7.28 (t, J = 7.5 Hz, 2H), 4.58 – 4.40 (m, 2H), 4.39 – 4.25 (m, 3H), 4.19 (t, J = 7.0 Hz, 1H), 2.27 (dddt, J = 19.6, 14.1, 9.2, 5.0 Hz, 1H), 1.98 (dddt, J = 29.3, 14.1, 9.6, 4.7 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 174.0, 157.4, 143.9 (d, J = 21.2 Hz, 2C), 141.3 (2C), 127.5 (2C), 126.8 (d, J = 4.2 Hz, 2C), 124.9 (d, J = 2.9 Hz, 2C), 119.6 (2C), 80.1 (d, J = 165.1 Hz), 66.7, 50.5, 47.1, 32.1 (d, J = 20.5 Hz). ^{19}F NMR (376 Hz, CDCl$_3$) δ -222.5 – -222.8 (m). ATR-FTIR (neat) 3335, 2961, 1711, 1683, 1532, 1449, 1430, 1315, 1254, 1174, 1105, 1084, 1044, 1029, 977, 938, 894, 798, 783, 759, 736, 621, 584, 548, 485, 425 cm^{-1}. HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for C$_{19}$H$_{18}$FNO$_4$ 366.1118; Found 366.1091. Anal Calcd for C$_{19}$H$_{18}$FNO$_4$: C, 66.46; H, 5.28; N, 4.08. Found: C, 66.68; H, 5.28; N, 4.11. $[\alpha]_D^{25}$ = -0.5 (lit.:-0.6[17]) (c = 0.98, MeOH).

(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4,4-difluorobutanoic acid (Difluoroethylglycine, DfeGly) (3)

According to **general procedure E**, alkylated Ni (II) complex (16.00 g, 24.0 mmol, 1.0 equiv.) was dissolved in dimethoxyethane (80 mL) and 3 M aqueous HCl solution (40.0 mL, 120.2 mmol, 5.0 equiv.) was added. After the recovery of the ligand (10.95 g, 87%), MeCN (48 mL) and EDTA Na$_2$ (8.95 g, 24.0 mmol, 1.0 equiv.) were added to the filtrate and the reaction mixture was stirred at 23 °C for 2 h. The pH of the solution was adjusted to 7 and subsequently Na$_2$CO$_3$ (5.10 g, 48.1 mmol, 2.0 equiv.) was added to the mixture. FmocOSu (8.11 g, 24.0 mmol, 1.0 equiv.) was dissolved in acetone (96 mL) and added dropwise to the reaction solution. The desired product was obtained after recrystallization from hexane/EtOAc as colorless solid (7.55 g, 87%, 98% purity determined by analytical HPLC). ^{1}H NMR (600 MHz, CD$_3$OD) δ 7.75 (d, J = 7.6 Hz, 2H), 7.63 (t, J = 6.7 Hz, 2H), 7.35 (t, J = 7.5 Hz, 2H), 7.27 (t, J = 7.4 Hz, 2H), 5.92 (tt, J = 56.4, 4.7 Hz, 1H), 4.42 – 4.29 (m, 3H), 4.19 (t, J = 7.0 Hz, 1H), 2.44 – 2.32 (m, 1H), 2.27 – 2.14 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 172.8, 157.1, 143.9 (d, J = 18.2 Hz, 2C), 141.3 (2C), 127.5 (2C), 126.8 (2C), 124.9 (2C), 119.6 (2C), 115.7 (t, J = 238.1 Hz), 66.7, 49.1 (t, J = 6.3 Hz), 47.0, 35.7 (t, J = 22.8 Hz). ^{19}F NMR (376 Hz, CDCl$_3$) δ -117.5 – -119.0 (m). ATR-FTIR (neat) 3311, 2970, 1705, 1683, 1527, 1449, 1403, 1289, 1261, 1243, 1177, 1117, 1103, 1083, 1067, 1049, 1028, 908, 780, 758, 738, 645, 620, 588, 544, 509, 481, 426 cm^{-1}. HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for C$_{19}$H$_{17}$F$_2$NO$_4$

384.1024; Found 384.1026. Anal Calcd for $C_{19}H_{17}F_2NO_4$: C, 63.16; H, 4.74; N, 3.88. Found: C, 63.54; H, 4.87; N, 4.06. $[\alpha]_D^{25}$ = -21.8 (c = 1.01, MeOH).

(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4,4-difluoropentanoic acid (Difluoropropylglyine, DfpGly) (6)

According to **general procedure E**, alkylated Ni (II) complex (3.81 g, 5.6 mmol, 1.0 equiv.) was dissolved in dimethoxyethane (20 mL) and 3 M aqueous HCl solution (9.4 mL, 28.05 mmol, 5.0 equiv.) was added. After the recovery of the ligand (2.50 g, 85%), MeCN (11 mL) and EDTA Na$_2$ (2.09 g, 5.6 mmol, 1.0 equiv.) were added to the filtrate and the reaction mixture was stirred at 23 °C for 2 h. The pH of the solution was adjusted to 7 and subsequently Na$_2$CO$_3$ (1.19 g, 11.2 mmol, 2.0 equiv.) was added to the mixture. FmocOSu (1.89 g, 5.6 mmol, 1.0 equiv.) was dissolved in acetone (22 mL) and added dropwise to the reaction solution. The desired product was obtained after recrystallization from hexane/EtOAc as colorless solid (1.56 g, 74%, 98% purity determined by analytical HPLC). ^{1}H NMR (600 MHz, CD$_3$OD) δ 7.75 (d, J = 7.6 Hz, 2H), 7.63 (t, J = 6.6 Hz, 2H), 7.35 (t, J = 7.5 Hz, 2H), 7.27 (t, J = 7.5 Hz, 2H), 4.46 – 4.26 (m, 3H), 4.19 (t, J = 7.0 Hz, 1H), 2.48 (dtd, J = 16.3, 14.1, 3.5 Hz, 1H), 2.28 (dtd, J = 16.3, 15.0, 9.8 Hz, 1H), 1.59 (t, J = 18.0 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 173.2, 157.0, 143.9 (d, J = 16.6 Hz, 2C), 141.2 (2C), 127.4 (2C), 126.8 (2C), 124.9 (2C), 123.1 (t, J = 237.4 Hz), 119.6 (2C), 66.7, 49.5 (t, J = 5.0 Hz), 47.0, 38.6 (t, J = 26.3 Hz), 22.4 (t, J = 27.2 Hz). ^{19}F NMR (376 Hz, CDCl$_3$) δ -89.0 (dtq, J = 243.4, 34.2, 18.0 Hz), -90.7 (dtq, J = 243.4, 34.2, 18.0 Hz). ATR-FTIR (neat) 3314, 2968, 1696, 1545, 1525, 1450, 1421, 1396, 1310, 1277, 1252, 1229, 1170, 1119, 1080, 1057, 1039, 981, 946, 936, 915, 903, 859, 807, 757, 736, 646, 622, 587, 552, 523, 428 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ Calcd for $C_{20}H_{19}F_2NO_4$ 398.1180; Found 398.1200. Anal Calcd for $C_{20}H_{19}F_2NO_4$: C, 64.00; H, 5.10; N, 3.73. Found: C, 61.97; H, 5.68; N, 4.38. $[\alpha]_D^{25}$ = -18.8 (c = 0.97, MeOH).

(S)-2-(((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4,4,5,5,5-pentafluoropentanoic acid (Pentafluoropropylglycine, PfpGly) (7)

According to **general procedure E**, alkylated Ni (II) complex (4.62 g, 6.3 mmol, 1.0 equiv.) was dissolved in dimethoxyethane (22 mL) and 3 M aqueous HCl solution (10.5 mL, 31.5 mmol, 5.0 equiv.) was added. After the recovery of the ligand (2.84 g, 86%), MeCN (14 mL) and EDTA Na$_2$ (2.35 g, 6.3 mmol, 1.0 equiv.) were added to the filtrate and the

reaction mixture was stirred at 23 °C for 2 h. The pH of the solution was adjusted to 7 and subsequently Na$_2$CO$_3$ (1.34 g, 12.6 mmol, 2.0 equiv.) was added to the mixture. FmocOSu (2.13 g, 6.30 mmol, 1.0 equiv.) was dissolved in acetone (25 mL) and added dropwise to the reaction solution. The desired product was obtained after recrystallization from hexane/EtOAc as colorless solid (2.06 g, 76%, 94% purity determined by analytical HPLC). ^{1}H NMR (600 MHz, CD$_3$OD) δ 7.76 (d, J = 7.6 Hz, 2H), 7.64 (d, J = 5.4 Hz, 1H), 7.36 (t, J = 7.5 Hz, 2H), 7.27 (t, J = 7.3 Hz, 2H), 4.54 (dd, J = 9.8, 3.3 Hz, 1H), 4.32 (d, J = 7.2 Hz, 2H), 4.20 (t, J = 7.2 Hz, 1H), 2.86 – 2.70 (m, 1H), 2.69 – 2.52 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 171.9, 156.9, 143.9 (d, J = 4.8 Hz, 2C)), 141.2 (2C), 127.5 (2C), 126.8 (d, J = 2.6 Hz, 2C), 125.9-112.7 (m, 2C), 124.9 (2C), 119.6 (2C), 66.9, 48.2, 47.0, 31.4 (t, J = 20.7 Hz). ^{19}F NMR (376 Hz, CDCl$_3$) δ -87.3, -118.4 (ddd, J = 267.3, 28.4, 9.6 Hz), -119.5 (ddd, J = 267.3, 26.1, 8.5 Hz). ATR-FTIR (neat) 3339, 2940, 1720, 1696, 1529, 1447, 1429, 1346, 1295, 1274, 1234, 1214, 1202, 1187, 1119, 1104, 1055, 1025, 923, 914, 759, 739, 624, 587, 538, 471, 427 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ Calcd for C$_{20}$H$_{16}$F$_5$NO$_4$ 452.0897; Found 452.0931. Anal Calcd for C$_{20}$H$_{16}$F$_5$NO$_4$: C, 55.95; H, 3.76; N, 3.26. Found: C, 56.03; H, 3.50; N, 3.43. [α]$_D^{25}$ = -20.4 (c = 1.00, MeOH).

(2S,3S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4,4,4-trifluoro-3-methylbutanoic acid ((2S,3S)-Trifluorovaline, (2S,3S)-TfVal) (4a)

According to **general procedure E**, alkylated Ni (II) complex (6.33 g, 9.1 mmol, 1.0 equiv.) was dissolved in dimethoxyethane (32 mL) and 3 M aqueous HCl solution (15.1 mL, 45.35 mmol, 5.0 equiv.) was added. After the recovery of the ligand (4.39 g, 92%), MeCN (19 mL) and EDTA Na$_2$ (3.38 g, 9.1 mmol, 1.0 equiv.) were added to the filtrate and the reaction mixture was stirred at 23 °C for 2 h. The pH of the solution was adjusted to 7 and subsequently Na$_2$CO$_3$ (1.92 g, 18.1 mmol, 2.0 equiv.) was added to the mixture. FmocOSu (3.06 g, 9.1 mmol, 1.0 equiv.) was dissolved in acetone (36 mL) and added dropwise to the reaction solution. The desired product was obtained after recrystallization from hexane/EtOAc as colorless solid (2.98 g, 84%, 91% purity determined by analytical HPLC). ^{1}H NMR (600 MHz, CD$_3$OD) δ 7.76 (d, J = 7.6 Hz, 2H), 7.65 (d, J = 7.5 Hz, 2H), 7.36 (t, J = 7.5 Hz, 2H), 7.27 (t, J = 7.5 Hz, 2H), 4.79 – 4.72 (m, 1H), 4.33 (qd, J = 10.6, 7.2 Hz, 2H), 4.21 (t, J = 7.2 Hz, 1H), 3.04 – 2.92 (m, 1H), 1.16 (d, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 171.6, 157.3 (d, J = 8.6 Hz), 143.9 (d, J = 6.0 Hz, 2C), 141.2 (2C), 127.5 (2C), 127.2 (q, J = 279.9 Hz), 126.8 (d, J = 3.4 Hz, 2C), 125.0 (d, J = 2.7 Hz, 2C), 119.6 (2C), 66.9, 52.6, 47.0,

39.3 (q, $J = 26.6$ Hz), 7.3. ^{19}F NMR (376 Hz, CDCl$_3$) δ -72.3 (t, $J = 7.9$ Hz). ATR-FTIR (neat) 3304, 3067, 1730, 1694, 1539, 1391, 1373, 1338, 1321, 1261, 1242, 1236, 1223, 1186, 1164, 1133, 1106, 1084 1039, 1015, 981, 882, 754, 734, 685, 671, 663, 592, 529, 508, 445, 426 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ Calcd for C$_{20}$H$_{18}$F$_3$NO$_4$ 416.1086; Found 416.1124. Anal Calcd for C$_{20}$H$_{18}$F$_3$NO$_4$: C, 61.07; H, 4.61; N, 3.56. Found: C, 61.12; H, 4.76; N, 3.71. $[\alpha]_D^{25}$ = -14.5 (c = 1.07, MeOH).

(2S,3R)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4,4,4-trifluoro-3-methylbutanoic acid ((2S,3R)-Trifluorovaline, (2S,3R)-TfVal) (4b)

According to **general procedure E**, alkylated Ni (II) complex (5.43 g, 7.8 mmol, 1.0 equiv.) was dissolved in dimethoxyethane (27 mL) and 3 M aqueous HCl solution (13.0 mL, 38.9 mmol, 5.0 equiv.) was added. After the recovery of the ligand (3.84 g, 94%), MeCN (16 mL) and EDTA Na$_2$ (2.90 g, 7.8 mmol, 1.0 equiv.) were added to the filtrate and the reaction mixture was stirred at 23 °C for 2 h. The pH of the solution was adjusted to 7 and subsequently Na$_2$CO$_3$ (1.65 g, 15.6 mmol, 2.0 equiv.) was added to the mixture. FmocOSu (2.62 g, 7.8 mmol, 1.0 equiv.) was dissolved in acetone (31 mL) and added dropwise to the reaction solution. The desired product was obtained after recrystallization from hexane/EtOAc as colorless solid (2.48 g, 81%, 97% purity determined by analytical HPLC). ^{1}H NMR (600 MHz, CD$_3$OD) δ 7.76 (d, $J = 7.6$ Hz, 2H), 7.64 (t, $J = 6.4$ Hz, 2H), 7.36 (t, $J = 7.5$ Hz, 2H), 7.27 (t, $J = 7.5$ Hz, 2H), 4.47 (d, $J = 5.5$ Hz, 1H), 4.42 – 4.27 (m, 2H), 4.21 (t, $J = 7.1$ Hz, 1H), 3.01 – 2.90 (m, 1H), 1.17 (d, $J = 7.2$ Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 171.4, 157.2, 143.8 (d, $J = 25.4$ Hz, 2C), 141.3 (2C), 127.5 (2C), 127.3 (q, J = 280.4 Hz), 126.8 (2C), 124.9 (d, $J = 3.1$ Hz, 2C), 119.6 (2C), 66.9, 54.0, 47.0, 40.0 (q, $J = 25.7$ Hz), 10.0. ^{19}F NMR (376 Hz, CDCl$_3$) δ -70.3 (d, $J = 9.4$ Hz). ATR-FTIR (neat) 3301, 3070, 1723, 1698, 1542, 1447, 1371, 1312, 1266, 1235, 1182, 1163, 1134, 1105, 1087, 1033, 1016, 984, 942 883, 754, 734, 702, 669, 650, 636, 599, 559, 538, 480, 427 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ Calcd for C$_{20}$H$_{18}$F$_3$NO$_4$ 416.1086; Found 416.1130. Anal Calcd for C$_{20}$H$_{18}$F$_3$NO$_4$: C, 61.07; H, 4.61; N, 3.56. Found: C, 61.05; H, 4.69; N, 3.66. $[\alpha]_D^{25}$ = -6.4 (c = 1.02, MeOH).

(2S,3R)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5,5,5-trifluoro-3-methylpentanoic acid (5^3-(2S,3R)-Trifluoroisoleucine, 5^3-(2S,3R)-TfIle) (5b)

According to **general procedure E**, alkylated Ni (II) complex (2.53 g, 3.6 mmol, 1.0 equiv.) was dissolved in dimethoxyethane (13 mL) and 3 M aqueous HCl solution (5.9 mL, 17.8 mmol, 5.0 equiv.) was added. After the recovery of the ligand (1.59 g, 84%), MeCN (7.5 mL) and EDTA Na$_2$ (1.53 g, 3.6 mmol, 1.0 equiv.) were added to the filtrate and the reaction mixture was stirred at 23 °C for 2 h. The pH of the solution was adjusted to 7 and subsequently Na$_2$CO$_3$ (754.6 mg, 7.1 mmol, 2.0 equiv.) was added to the mixture. FmocOSu (1.20 g, 3.6 mmol, 1.0 equiv.) was dissolved in acetone (14 mL) and added dropwise to the reaction solution. The desired product was obtained after recrystallization from hexane/EtOAc as colorless solid (730.0 mg, 50%, 99% purity determined by analytical HPLC). ^{1}H NMR (600 MHz, CD$_3$OD) δ δ 7.76 (d, J = 7.7 Hz, 2H), 7.65 (t, J = 8.1 Hz, 2H), 7.35 (t, J = 7.5 Hz, 2H), 7.27 (t, J = 6.6 Hz, 1H), 4.43 – 4.35 (m, 2H), 4.33 (d, J = 4.1 Hz, 1H), 4.26 – 4.13 (m, 1H), 2.53 – 2.45 (m, 1H), 2.31 (dqd, J = 16.4, 11.6, 4.8 Hz, 1H), 2.04 – 1.87 (m, 1H), 0.99 (d, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 172.6, 157.7, 143.9 (d, J = 47.7 Hz, 2C), 141.3 (2C), 127.5 (d, J = 3.4 Hz, 2C), 127.2 (q, J = 276.9 Hz), 126.8 (d, J = 4.1 Hz, 2C), 124.9 (d, J = 4.8 Hz, 2C), 119.6 (d, J = 5.6 Hz, 2C), 66.6, 57.7, 47.2, 36.6 (q, J = 27.8 Hz), 30.1, 13.9. ^{19}F NMR (376 Hz, CDCl$_3$) δ -65.2 (t, J = 11.4 Hz). ATR-FTIR (neat) 3394, 3157, 1747, 1686, 1536, 1453, 1396, 1329, 1286, 1252, 1238, 1193, 1172, 1136, 1091, 1059, 1045, 1016, 976, 934, 816, 760, 742, 732, 681, 621, 579, 550, 524, 425 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ Calcd for C$_{21}$H$_{20}$F$_3$NO$_4$ 430.1242; Found 430.1243. Anal Calcd for C$_{21}$H$_{20}$F$_3$NO$_4$: C, 61.91; H, 4.95; N, 3.44. Found: C, 61.95; H, 4.99; N, 3.50. $[\alpha]_D^{25}$ = -4.5 (c = 0.95, MeOH).

(2S,3S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5,5,5-trifluoro-3-methylpentanoic acid (5^3-(2S,3S)-Trifluoroisoleucine, 5^3-(2S,3S)-TfIle) (5a)

According to **general procedure E**, alkylated Ni (II) complex (4.21 g, 5.9 mmol, 1.0 equiv.) was dissolved in dimethoxyethane (21 mL) and 3 M aqueous HCl solution (9.9 mL, 29.6 mmol, 5.0 equiv.) was added. After the recovery of the ligand (2.67 g, 86%), MeCN (12.5 mL) and EDTA Na$_2$ (2.20 g, 5.92 mmol, 1.0 equiv.) were added to the filtrate and the reaction mixture was stirred at 23 °C for 2 h. The pH of the solution was adjusted to 7 and subsequently Na$_2$CO$_3$ (755 mg, 7.1 mmol, 2.0 equiv.) was added to the mixture. FmocOSu (2.00 g, 5.9 mmol, 1.0 equiv.) was dissolved in acetone (24 mL) and added dropwise to the reaction solution. The desired product was obtained after recrystallization from hexane/EtOAc as colorless solid

(1.60 g, 66%, 93% purity determined by analytical HPLC). ^{1}H NMR (600 MHz, CD$_3$OD) δ 7.75 (d, J = 7.6 Hz, 2H), 7.63 (t, J = 7.6 Hz, 2H), 7.34 (t, J = 7.5 Hz, 2H), 7.27 (t, J = 7.4 Hz, 2H), 4.39 – 4.32 (m, 2H), 4.21 (d, J = 4.8 Hz, 1H), 4.19 (t, J = 6.9 Hz, 1H), 2.42 – 2.20 (m, 2H), 2.16 – 2.01 (m, 1H), 1.05 (d, J = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 172.6, 157.4, 143.9 (d, J = 35.4 Hz, 2C), 141.3 (2C), 127.5 (2C), 127.3 (q, J = 276.5 Hz), 126.8 (d, J = 3.8 Hz, 2C), 124.9 (d, J = 3.0 Hz, 2C), 119.6 (d, J = 3.4 Hz, 2C), 66.6, 58.4, 47.1, 35.7 (d, J = 27.7 Hz), 30.4, 15.5. ^{19}F NMR (376 Hz, CDCl$_3$) δ -65.0 (t, J = 11.6 Hz). ATR-FTIR (neat) 3391, 2977, 1747, 1737, 1684, 1540, 1451, 1396, 1330, 1290, 1251, 1236, 1193, 1175, 1138, 1088, 1060, 1045, 1016, 975, 934, 864, 857, 832, 814, 773, 759, 740, 731, 680, 641, 620, 583, 549, 541, 426 cm^{-1}. HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for C$_{21}$H$_{20}$F$_3$NO$_4$ 430.1242; Found 430.1308. Anal Calcd for C$_{21}$H$_{20}$F$_3$NO$_4$: C, 61.91; H, 4.95; N, 3.44. Found: C, 62.02; H, 5.01; N, 3.47. [α]$_D^{25}$ = -6.7 (c = 1.08, MeOH).

Associated content

Supporting information   The Supporting Information is available free of charge.

(Additional experimental details and methods)

(X-ray data, checkCIFs)

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

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