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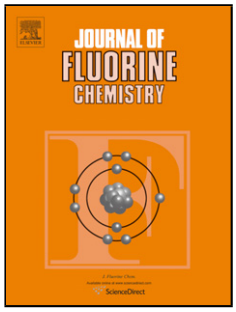

Convenient synthesis of racemic 4,4-difluoro glutamic acid derivatives via Michael-type additions of Ni(II)-complex of dehydroalanine Schiff bases

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Convenient synthesis of racemic 4,4-difluoro glutamic acid derivatives via Michael-type additions of Ni(II)-complex of dehydroalanine Schiff bases.

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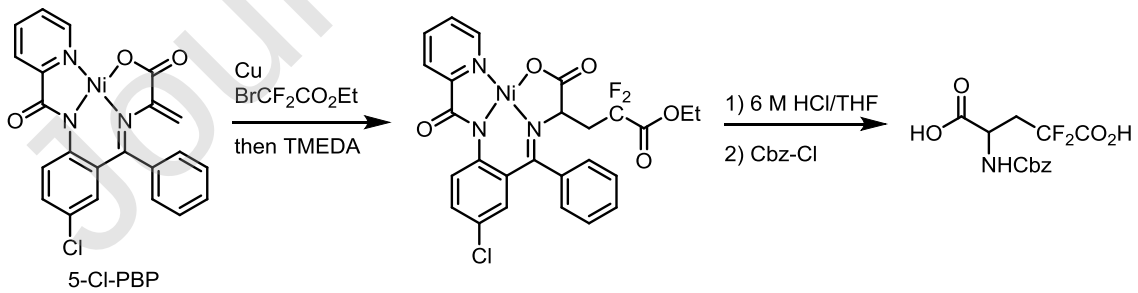
Keywords: tailor-made amino acids, fluorine-containing amino acids, Michael-type additions, organometallic, Ni(II)-complexes

Dedication: This paper is dedicated to Professor Norio Shibata on the occasion of receiving the 2019 ACS Award for Creative Work in Fluorine Chemistry.

Graphical abstract



Research highlights

- An efficient, operationally convenient and scalable synthesis of racemic 4,4-difluoroglutamic acid derivatives was developed.
- The synthesis is based on the Michael-type addition reactions of an in-situ derived Cu-reagent to a Ni(II)-complex of dehydroalanine Schiff bases.
- It was revealed that these Ni(II)-complexes are stable in the presence of Cu(II) ions and have sufficient activation of the dehydroalanine moiety for the corresponding addition reactions.

Abstract

Michael-type addition reactions of Ni(II)-complex of a dehydroalanine Schiff base and ethyl bromodifluoroacetate in the presence of copper for the synthesis of racemic 4,4,-difluoroglutamic acid derivatives were developed. These reactions proceeded smoothly and gave the desired product in 80% yield. Furthermore, this procedure is of low cost-structure, operationally convenient, and scalable.

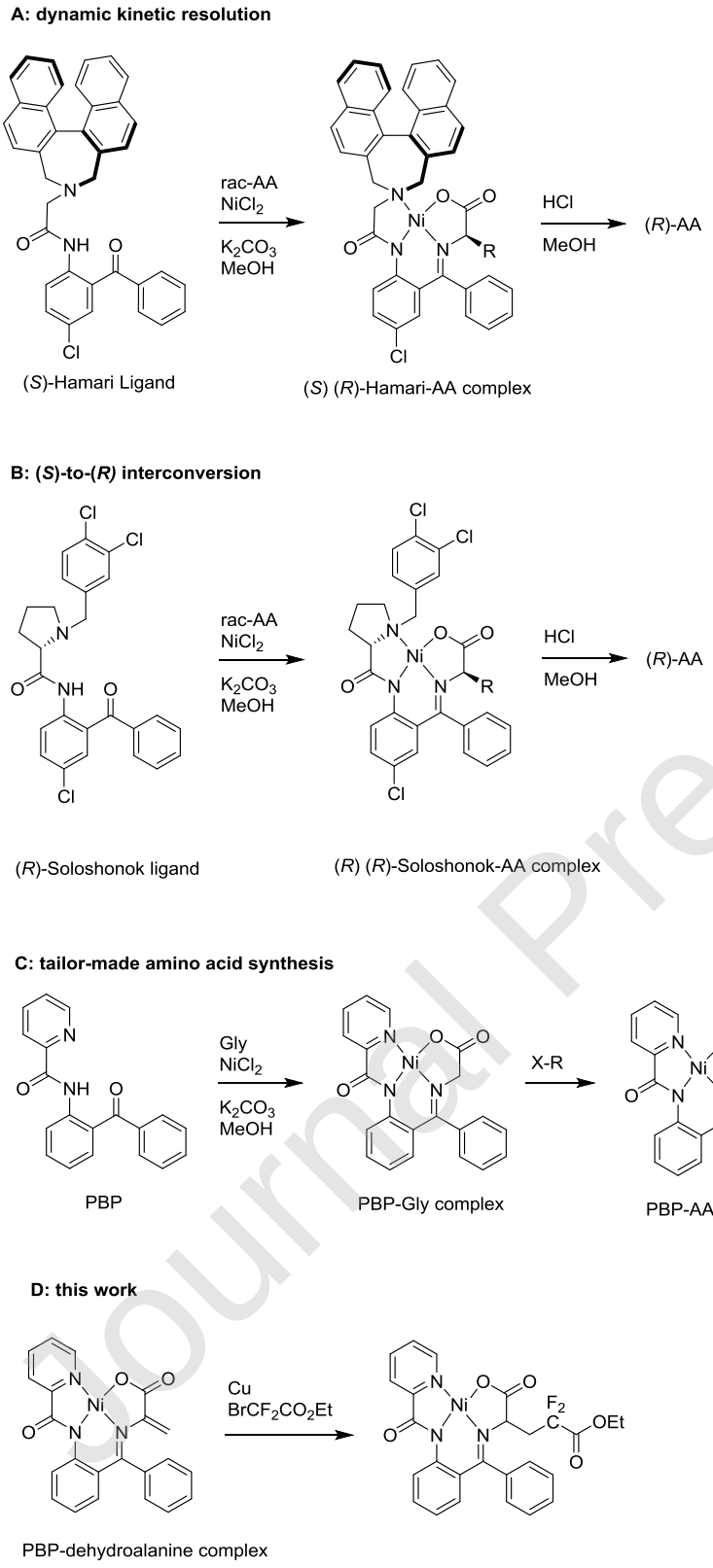
1. Introduction

Fluorinated compounds have some great potential in numerous industrial fields. Above all, fluorinated amino acids can exert significant effect on drug discovery [1], peptide chemistry [2], and supramolecular science [3]. For this reason, the development of synthetic methods for the preparation of fluorine-containing amino acids has been the focus of many research groups [4, 5]. Nevertheless, efficient synthetic protocols for the

preparation of fluorinated amino acids are still in great demand. For example, it is especially difficult to introduce the CF_2 unit into amino acids. For example, difluorinated glutamic acid derivatives, promising amino acid, are highly sought targets [6]. 4,4-Difluoroglutamic acid can be easily converted into 4,4-difluoroornithine and 4,4-difluoroglutamine, Glu derivatives being important compounds in mechanistic studies for glutamic decarboxylase and hydrolase enzyme [7]. Taguchi's group reported the first synthesis of 4,4-difluoroglutamic acid (**1**) via a Michael-type addition of 2,3-difluoroketene silyl acetal with α,β-carbonyl compounds, followed by introducing the amino function into the α-position of the fluorinated compound [6a]. In 2013, photo-induced radical hydroperfluoroalkylation of *N*-phthalimide-dehydroalanine derivative was published by Yajima [6b]. Haufe's group developed many excellent methods including desulfurization-fluorination [6c] and copper-mediated Michael-type additions [6d-f]. However, these methods have problems with the cost of starting materials, the preparation of substrates, and the flexibility of amino acid derivatives that can be synthesized. In order to solve this problem, we considered the Michael-type addition reaction of a Ni(II)-complex of dehydroalanine and ethyl bromodifluoroacetate in the presence of copper. Although this Michael-type addition reaction was originally developed by Kumadaki *et al*. [8], it was Kondratov's group that showed this to be

applicable to dehydro amino acids [6d-f]. On the other hand, Ni(II)-complexes of benzophenone derivatives with amino acids are reported to be suitable for the synthesis of many amino acids, including unusual, specially designed, tailor-made amino acids [9]. So far, the Hamari ligands [9a] with axial chirality, the Soloshonok ligands [9b-d] developed recently, and PBP (pyridine-2-carboxylic acid (2-benzoyl-phenyl)-amide) [9e-g] as achiral ligands have been synthesized. These ligands have had great success in dynamic kinetic resolution [9b, d], (*S*)-to-(*R*) interconversion of α or β amino acids [9c], and tailor-made amino acid synthesis using electrophiles (A-C, Scheme 1) [9h-i]. The advantages of these ligands are that they are inexpensive, scalable, easily to make, and recyclable and reused [9j-l]. However, this approach for the synthesis of tailor-made amino acid mainly uses the Ni(II)-complex of a ligand and an amino acid as a nucleophile, and few examples exist where the complex is used as an electrophile (D, Scheme 1) [9m-n]. On the other hand, it is unknown if these Ni(II) complexes can be used in the presence of Cu(II) ions, as the latter can easily replace the former. Furthermore, it is suggested by Kondratov [6f] that the electrophilicity of dehydroalanine is very important for this reaction. Consequently, it remains unknown if the activation provided by the Ni(II)-complexes structure would be sufficient for these reactions to proceed at all. Therefore, it is necessary to investigate if these Ni complexes have sufficient stability and reactivity to

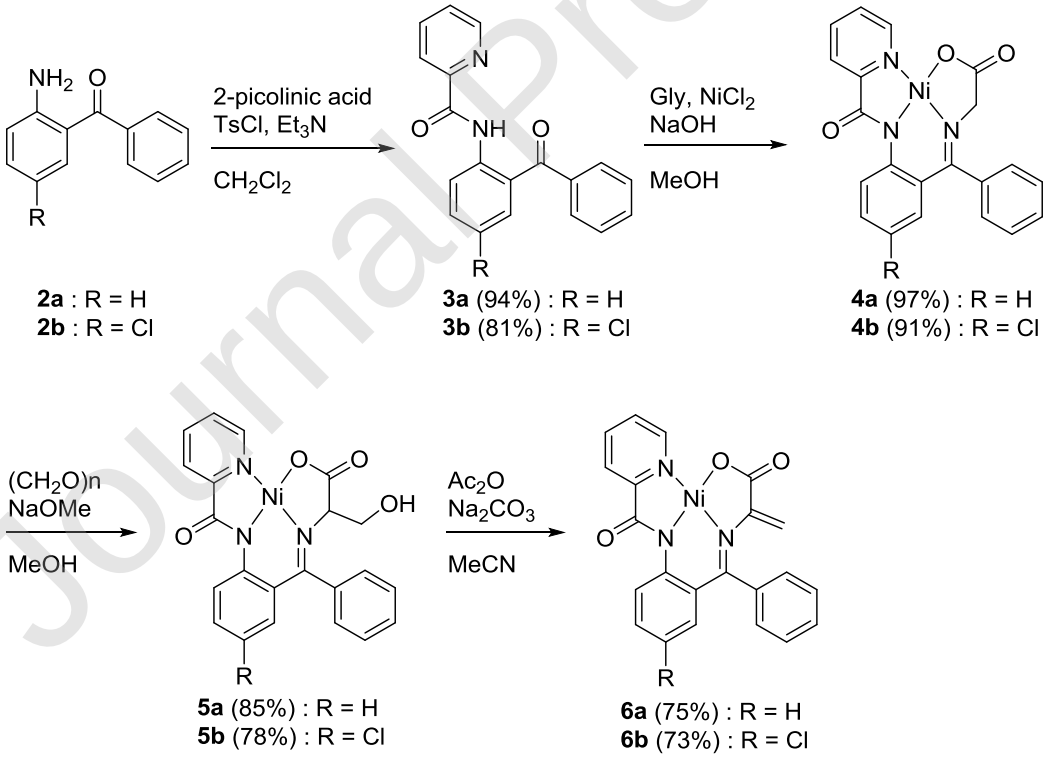
be used as the substrates in Cu-mediated additions. To avoid additional complications with the issues of formation of diastereomers and focus solely on chemical suitability and reactivity, we decided to dedicate a separate study using achiral tridentate ligands. We believe the Michael-type addition reactions of achiral Ni(II)-complexes reported herein provide a simple, operationally convenient method for preparation of difluorinated-glutamic acid derivatives and open up a new chapter in the application of Ni(II)-complexes of dehydroalanine for the preparation of various tailor-made amino acids.



Scheme 1. Application of Ni(II)-complex for amino acid synthesis and this work

2. Result and Discussion

The PBP/dehydroalanine Schiff base complex (**6a**) (Scheme 2) was efficiently synthesized starting from 2-aminobenzophenone (**2a**) by a known method [10]. 5-Cl-PBP/dehydroalanine (**6b**) was also obtained from 5-chloro-2-amino-benzophenone (**2b**) in the same way. To reiterate, previous studies suggest that the electrophilicity of dehydroalanine derivatives is important in this reaction. Therefore, in order to increase the electrophilicity of the substrate, 5-Cl-BPB, which was available at low cost, was prepared [6f].



2a : R = H
2b : R = Cl

3a (94%) : R = H
3b (81%) : R = Cl

4a (97%) : R = H
4b (91%) : R = Cl

5a (85%) : R = H
5b (78%) : R = Cl

6a (75%) : R = H
6b (73%) : R = Cl

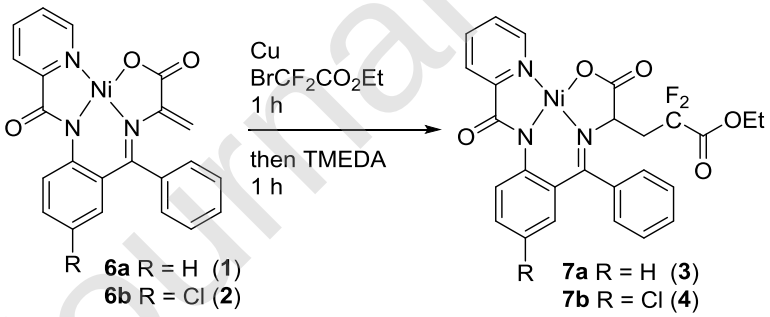
Scheme 2. Preparation for PBP-dehydroalanine complex (**6a**) and 5-Cl-PBP

dehydroalanine complex (**6b**)

The results of condition optimization for Michael-type addition of **6a** or **6b** with ethyl bromodifluoroacetate are summarized in Table 1. First, the reaction was performed using 6 equivalents of activated Cu powder, 3 equivalents of bromodifluoroacetate, and 3.6 equivalents of tetramethylene ethylendiamine (TMEDA) in THF, but the chemical yield was moderate (45%) because of several byproducts (entry 1). Reducing the amounts of reagents to prevent the byproduct formation, the reaction did not proceed completely (entry 2). The reaction in CH_3CN gave almost the same result as using THF (entry 3). It was found that the order of addition of reagents had an important influence on the reaction. When the Ni(II)-complex was added to the mixture after all reagents except the complex were mixed at reflux for 0.5 h, a lot of byproducts were observed (entry 4). To confirm the stability of complex (**6a**) under the reaction conditions, we tried to work without bromide reagents to get recovery yields 61% (entry 5). Taking into account that the low recovery rate could be a result of replacement of Ni by a Cu ion, $NiCl_2$ was added to the reaction mixture, which indeed allowed us to improve the recovery rates (entry 6). However, it was found that $NiCl_2$ interrupted the Michael-type addition under the conditions where all reagents, including the bromide, were added (entry 7). The

temperature is also one of the important factors, since this reaction proceeded smoothly to give desired product **7a** in 67% yield at 70 °C (entry 8-10). When 5-Cl-PBP complex (**6b**) was used (entry 11-14), 70 °C was the most suitable temperature, the yield was better than when the PBP complex (**6a**) was used (entry 8 and 12). From TLC, it was observed that the Cl-PBP complex (**6b**) is highly active and disappeared within 20 min. As the reaction time was reduced, the decomposition of the compound also decreased, and the yield was improved to 80% (entry 15). The decrease in the amount of reagents caused an incomplete progress of the reaction (entry 16), but this reaction can also be used for the gram-scale (entry 17). Finally, we tried this reaction in the absence of copper.

Table 1. Condition optimization for Cu-mediated Michael-type addition

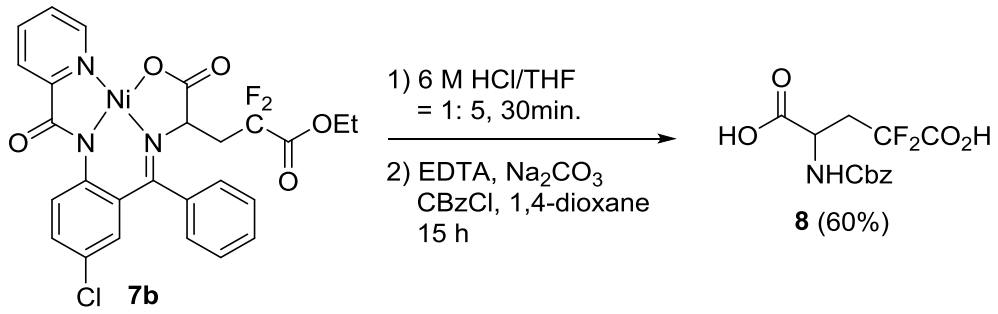


entry	R	Reagent	solvent	temp. (°C)	Yield
1	H	Cu (6), bromide (3), TMEDA (3.6)	THF	reflux	45%
2	H	Cu (2.2), bromide (1.1), TMEDA (2.2)	THF	reflux	20%
3	H	Cu (6), bromide (3), TMEDA (0.9)	CH_3CN	reflux	46%
4[a]	H	Cu (6), bromide (3), TMEDA (0.9)	CH_3CN	reflux	5%
5[b]	H	Cu (6), bromide (0), TMEDA (0.9)	CH_3CN	reflux	-
6[c]	H	Cu (6), bromide (0), TMEDA (0.9), $NiCl_2$	CH_3CN	reflux	-

		(6)			
7	H	Cu (6), bromide (3), TMEDA (0.9), $NiCl_2$ (6)	CH_3CN	reflux	0%
8	H	Cu (6), bromide (3), TMEDA (0.9)	CH_3CN	70	67%
9	H	Cu (6), bromide (3), TMEDA (0.9)	CH_3CN	50	41%
10	H	Cu (6), bromide (3), TMEDA (0.9)	CH_3CN	r.t.	0%
11	Cl	Cu (6), bromide (3), TMEDA (0.9)	CH_3CN	reflux	38%
12	Cl	Cu (6), bromide (3), TMEDA (0.9)	CH_3CN	70	70%
13	Cl	Cu (6), bromide (3), TMEDA (0.9)	CH_3CN	60	63%
14	Cl	Cu (6), bromide (3), TMEDA (0.9)	CH_3CN	r.t.	0%
15	Cl	Cu (3), bromide (1.5), TMEDA (0.9)	CH_3CN	70	43%
16[d]	Cl	Cu (6), bromide (3), TMEDA (0.9)	CH_3CN	70	80%
17[d,e]	Cl	Cu (6), bromide (3), TMEDA (0.9)	CH_3CN	70	65%
18[f]	Cl	Cu (0), bromide (3), TMEDA (0.9)	CH_3CN	70	0%

a: After copper, bromide ($BrCF_2CO_2Et$), and TMEDA were mixed for 60 min, **6a** was added to the mixture and stirred for 1h. b: 61% **6a** was recovered. c: 83% **6a** was recovered. d: After adding TMEDA, the mixture was stirred for 20 min. e: The reaction was conducted on a gram-scale. f: 93% **6a** was recovered.

Next, we tried the disassembly of the final complex (**7b**) and Cbz-protection of difluoro amino acid (Scheme 3). The procedure was attempted by using 6 M HCl/THF (1:5) at room temperature. After the 5-Cl-PBP (**3b**) ligand was removed by a separation operation, EDTA, Na_2CO_3, and Cbz-Cl were added to the aqueous layer, and Cbz-4,4-difluoro glutamic acid (**8**) was obtained by hydrolysis of the ethyl ester. The total overall yield was 20% over 7 steps, and 51% 5-Cl-PBP (**3b**) was recovered. This method is highly efficient for this 4,4-difluoroglutamic acid derivative.



Scheme 3. Synthesis of Cbz-4,4-difluoroglutamic acid (**8**).

3. Conclusion

We successfully accomplished the Michael-type addition reaction of Ni(II)-complex of dehydroalanine and ethyl bromodifluoroacetate in the presence of copper. The reaction was easily scaled up for a quite efficient synthesis of 4,4-difluoro glutamic acid and its N-protected derivatives.

4. Experimental

General. IR spectra of samples were obtained as films with a Thermo Avatar 370 FT-IR spectrometer. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), and ^{19}F NMR (376 MHz) spectra were recorded on a JNM-ECX400 spectrometer. Chemical shifts are reported in ppm with reference to tetramethylsilane [^{1}H NMR: $CDCl_3$ (0.00)], or solvent signals [^{1}H NMR: $CDCl_3$ (7.26), CD_4CN (1.94); ^{13}C NMR: $CDCl_3$ (77.16), CD_4CN (1.32), ^{19}F NMR: $CFCl_3$ (0.00)]. High-resolution mass spectra were recorded on a JEOL AccuTOF JMS-

T100LC spectrometer (ESI-MS).

5-Chloro-2-(picolinoylamino) benzophenone (3b)

To a solution of picolinic acid (12.9 mmol, 1.59 g) in CH_2Cl_2 was added Et_3N (32.4 mmol, 4.52 ml), TsCl (12.9 mmol, 2.46 g), and 5-Cl-benzophenone **2b** (10.8 mmol, 2.5 g) while being held in an ice/water bath. After 15 min, the mixture was stirred at 50 ^oC for 12 h. The mixture was quenched with 5% AcOH, and the organic layer was washed with H_2O three times and evaporated in vacuo. The residue was washed with ether to give the title compound (**3b**) (2.95 g, 8.76 mmol, 81%) as a pale purple solid.

IR (film) νmax: 1685, 1641, 1597, 1571, 1512, 1463, 1448, 1429, 1399, 1320, 1291, 1255, 1181, 1155, 1143, 1131, 1096, 1086, 997, 995, 940, 897, 839, 832, 814, 806, 744, 712, 692, 661, 641, 620, 530, 462. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.45-7.63 (6H, m), 7.76-7.78 (2H, m), 7.88 (1H, td, *J* = 8.0, 2.0 Hz), 8.26 (1H, ddd, *J* = 7.6, 1.2, 1.2 Hz), 8.73 (1H, ddd, *J* = 4.8, 1.6, 1.2 Hz), 8.86 (1H, d, *J* = 8.8 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 122.8, 123.2, 126.3, 126.7, 127.7, 128.6, 130.2, 132.6, 133.0, 133.7, 137.6, 138.1, 138.3, 148.8, 150.0, 163.6, 197.7 ppm. HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{19}H_{14}ClN_2O_2$:337.0744; found:337.0738.

Ni(II)-5-chloro-2-(picolinoylamino) benzophenone/glycine Schiff base complex (4b)

A solution of 5-chloro-2-(picolinoylamino) benzophenone **2b** (2.95 g, 8.76 mmol), Gly (43.8 mmol, 3.29 g), $NiCl_2$ (17.5 mmol, 2.27 g), NaOH (61.3 mmol, 2.45 g) in MeOH was stirred at 60 ^oC for 4 h and at ambient temperature for 12 h. The reaction mixture was quenched with ice/water and AcOH (6 ml). The precipitate was filtered off and washed with petroleum ether to give the title compound **4b** (3.60 g, 7.99 mmol, 91%) as a red powder.

IR (film) νmax : 3443, 1678, 1633, 1606, 1537, 1485, 1464, 1447, 1393, 1357, 1328, 1304, 1294, 1277, 1263, 1231, 1169, 1108, 815, 755, 714, 700, 676. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.81 (1H, d, *J* = 2.0 Hz), 6.83 (1H, d, *J* = 2.0 Hz), 7.11 (2H, d, *J* = 6.0 Hz), 7.30 (1H, dd, *J* = 9.2, 1.6 Hz), 7.45 (1H, t, *J* = 6.4 Hz), 7.54-7.58 (3H, m), 7.88 (1H, d, *J* = 7.6 Hz), 8.00 (1H, dd, *J* = 7.2, 7.2 Hz), 8.26 (1H, d, *J* = 4.8 Hz), 9.01 (1H, d, *J* = 9.2 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 62.3, 124.3, 125.6, 126.0, 126.5, 127.0, 127.4, 130.1, 130.3, 133.2, 133.4, 134.1, 140.9, 142.1, 147.2, 153.1, 170.7, 172.5, 177.2 ppm. HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{21}H_{16}ClN_3NiO_3$: 450.0155; found:450.0150.

Ni(II)-5-chloro-2-(Picolinoylamino) benzophenone/serine Schiff base complex (5b)

To a solution of 5-Cl-BPB/Gly complex **4b** (7.99 mmol, 3.60 g) in CH_3OH (30.0 ml)

were added 25 wt% CH_3ONa (7.40 ml) and $(CH_2O)n$ (22.4 mmol, 672 mg). The mixture was stirred under reflux for 2 h. The reaction mixture was cooled down to r.t. and quenched with 5% AcOH. The precipitate was filtered off and washed with water and dried. A solution of the product in $CHCl_3$ was stirred at r.t. for 1 h. The precipitate was filtered off and dried to give **5b** (3.01 g, 6.26 mmol, 78%). IR (film) νmax: 3354, 3079, 2958, 1656, 1607, 1533, 1464, 1443, 1400, 1333, 1306, 1276, 1270, 1259, 1234, 1173, 1112, 1073, 837, 768, 708, 682. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.80 (1H, dd, *J* = 10.8, 4.0 Hz), 3.92 (1H, dd, *J* = 11.6, 6.8 Hz), 4.08 (1H, dd, *J* = 6.0, 3.6 Hz), 6.74 (1H, d, *J* = 2.8 Hz), 7.12 (1H, dd, *J* = 6.8, 1.6 Hz), 7.28 (1H, overlapped), 7.31 (2H, dd, *J* = 9.6, 2.8 Hz), 7.45 (1H, t, *J* = 6.0 Hz), 7.54-7.58 (3H, m), 7.90 (1H, d, *J* = 7.6 Hz), 8.00 (1H, ddd, *J* = 8.0, 8.0, 1.2 Hz), 8.21 (1H, d, *J* = 5.6 Hz), 8.96 (1H, d, *J* = 9.2 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = ppm. HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{22}H_{17}ClN_3NiO_4$:480.0261; found:480.0256.

Ni(II)-5-chloro-2-(Picolinoylamino) benzophenone/dehydroalanine Schiff base complex (6b)

To a solution of 5-Cl-BPB/Ser complex **5b** (6.24 mmol, 3.0 g) in CH_3CN (23 ml) was added Ac_2O (5.1 ml), and the mixture was stirred at reflux for 1 h. Na_2CO_3 (18.7 mmol,

1.98 g) was added to the mixture, and the reaction mixture was stirred at the same temperature for 2 h. The reaction mixture was cooled down to r.t. and quenched with H_2O. The precipitate was filtered off and washed with water and dried. A solution of the product in MeOH was stirred at reflux for 1h. The precipitate was filtered and dried to give the title compound (**6b**) (2.00 g, 4.32 mmol, 69 %).

IR (film) νmax: 3416, 1671, 1646, 1610, 1564, 1520, 1486, 1455, 1391, 1328, 1303, 1274, 1259, 1229, 1200, 1155, 1139, 1102, 925, 888. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.21 (1H, d, *J* = 1.2Hz), 5.65 (1H, s), 6.93 (1H, d, *J* = 2.4 Hz), 7.20 (2H, d, *J* = 6.8 Hz), 7.27 (1H, dd, *J* = 9.2, 2.4 Hz), 7.43-7.56 (4H, m), 7.87 (1H, d, *J* = 7.2 Hz), 7.99 (1H, ddd, *J* = 8.8, 7.6, 1.2 Hz), 8.20 (1H, d, *J* = 5.6 Hz), 8.91 (1H, d, *J* = 10.0 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 117.1, 124.4, 124.7, 126.3, 127.4, 128.2, 128.7, 129.7, 130.8, 134.0, 134.1, 135.1, 140.9, 143.0, 147.0, 147.2, 152.9, 169.9, 170.0, 170.4 ppm. HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{22}H_{15}ClN_3NiO_3$:462.0155; found:462.0150.

Ni(II)-5-chloro-2-(picolinoylamino)benzophenone/4-amino-2,2-difluoropentane-1,5-dioic acid 5-ethyl ester Schiff base complex (7b)

A solution of dehydroalanine complex **6b** (100 mg, 0.216 mmol), activated Cu [10] powder (1.30 mmol, 82 mg), and ethyl bromodifluoroacetate (0.639 mmol, 84.0 μl) in

acetonitrile (10.0 ml) was stirred at 70 ºC for 1 h. TMEDA (0.194 mmol, 29.0 μl) was added to the mixture, which was stirred at the same temperature for 20 min. The reaction mixture was quenched with 5% AcOH, and the aqueous layer extracted twice with CH_2Cl_2. The organic layer was washed with H_2O and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography ($CHCl_3$) to give the title compound (**7b**) (101 mg, 0.172 mmol, 80%) as a red powder.

IR (film) νmax: 3416, 1671, 1646, 1610, 1564, 1520, 1486, 1455, 1391, 1328, 1303, 1274, 1259, 1229, 1200, 1155, 1139, 1102, 925, 888, 817, 808, 762, 709, 696, 687, 540. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (3H, t, *J* = 7.2 Hz), 2.47 (1H, ddd, *J* = 28.8, 14.8, 2.4 Hz), 2.61-2.75 (1H, m), 4.17-4.23 (3H, m), 6.74 (1H, d, *J* = 2.4 Hz), 7.21-7.22 (1H, m), 7.26-7.31(2H, m), 7.46 (1H, td, *J* = 5.6, 1.2 Hz), 7.57-7.60 (3H, m), 7.89 (1H, d, *J* = 7.6 Hz), 8.01 (1H, t, *J* = 7.6 Hz), 8.21 (1H, d, *J* = 5.2 Hz), 8.99 (1H, d, *J* = 9.2 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 37.2 (t, *J* = 20.1 Hz), 63.5, 66.6 (t, *J* = 5.7 Hz), 114.8 (dd, *J* = 254.5, 248.7 Hz), 124.3, 125.0, 126.3, 126.8, 127.5, 127.7, 128.0, 129.5, 129.8, 130.8, 133.1, 133.5, 133.8, 140.9, 142.3, 147.2, 152.9, 163.4 (t, *J* = 31.6 Hz), 170.3, 173.6, 178.0 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -103.56 (ddd, *J* = 274.1, 19.6, 15.0 Hz), -96.5 (dt, *J* = 2743.4, 13.2 Hz) ppm. HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{26}H_{21}ClF_2N_3NiO_5$:586.0491; found:586.0486.

Ni(II)-2-(picolinoylamino) benzophenone/4-amino-2,2-difluoropentane-1,5-dioic acid 5-ethyl ester Schiff base complex (7a)

A solution of dehydroalanine complex **6a** (100 mg, 0.234 mmol), activated Cu [11] powder (1.40 mmol, 89.0 mg), and ethyl bromodifluoroacetate (0.639 mmol, 83.0 μl) in acetonitrile (10.0 ml) was stirred at 70 °C for 1 h. TMEDA (0.211 mmol, 31.0 μl) was added to the mixture, and stirring was continued at the same temperature for 1 h. The mixture was quenched with 5% AcOH, and the aqueous layer was extracted twice with CH_2Cl_2. The organic layer was washed with H_2O and brine, dried over magnesium sulfate, filtered, and then evaporated in vacuo. The residue was purified by column chromatography ($CHCl_3$) to give the title compound (**7a**) (86.0 mg, 0.156 mmol, 67%) as a red powder.

IR (film) νmax: 3458, 2984, 1762, 1681, 1642, 1605, 1590, 1546, 1471, 1440, 1377, 1329, 1274, 1259, 1237, 1192, 1168, 1110, 1059, 1021, 776, 754, 713, 682. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (3H, t, *J* = 7.2 Hz), 2.47 (1H, dd, *J* = 28.4, 14, 2.8 Hz), 2.65-2.79 (1H, m), 4.18 (2H, q, *J* = 6.8 Hz), 4.23 (1H, dd, *J* = 8.0, 2.8 Hz), 6.76-6.83 (2H, m), 7.20-7.23 (1H, m), 7.27-7.29 (1H, m), 7.36 (1H, ddd, *J* = 8.4, 6.4, 1.6 Hz), 7.44 (1H, ddd, *J* = 6.8, 5.6, 0.8 Hz) 7.54-7.57 (3H, m), 7.90 (1H, d, *J* = 7.2 Hz), 8.00 (1H, ddd, *J* = 7.6, 7.6, 0.8

Hz), 8.21 (1H, d, *J* = 5.6Hz), 8.97 (1H, d, *J* = 8.8 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 37.4 (t, *J* = 23.8 Hz), 63.5, 66.0 (d, *J* = 5.7 Hz), 114.76 (dd, *J* = 255.7, 247.9 Hz), 121.6, 123.7, 124.3, 126.5, 126.9, 127.2, 128.2, 129.2, 129.6, 130.4, 133.8, 134.1, 135.0, 140.7, 143.6, 147.1, 153.3, 163.5 (t, *J* = 31.4 Hz), 170.2, 174.3, 178.0 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -103.97 (ddd, *J* = 274.5, 21.4, 14.3 Hz), -96.12 (dt, *J* = 274.5, 12.8 Hz) ppm. HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{26}H_{22}F_2N_3NiO_5$:552.0881; found:552.0875.

Cbz-4,4-difluoro-Glu-OH (8)

To a solution of complex **7b** (250 mg, 0.426 mmol) in THF (2 ml) was added 6 M HCl (0.4 ml) at room temperature, and the mixture was stirred for 30 min. The mixture was distilled with H_2O, and the aqueous layer was washed twice with AcOEt. EDTA disodium salt dihydrate (0.426 mmol, 159 mg), Na_2CO_3 (500 mg), Cbz-Cl (1.70 mmol, 0.243 ml), and 1,4-dioxane (6 ml) were added to the aqueous solution, and the mixture was stirred at room temperature for 12 h. Et_2O was added to the mixture and the aqueous phase was washed with Et_2O twice. To the aqueous phase was added 2M HCl and extracted with AcOEt three times. The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give the amino acid **8** (81 mg, 0.255 mmol, 60%) as

a white solid.

The analytical data are in a good agreement with those from the publication.

Conflict of Interest

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[11] activated Cu

A solution of Cu powder in 2% I_2/acetone was stirring at room temperature for 10 minutes. Cu powder was filtered off and washed with acetone. The resulting Cu was added to 50% 12 M HCl/acetone and stirred for 5 minutes. The activated copper was obtained by filtering again, washing with acetone and drying.