

Large-Scale Asymmetric Synthesis of Fmoc-(S)-2-Amino-6,6,6-Trifluorohexanoic Acid

Zizhen Yin,^[a] Hiroki Moriwaki,^{*,[b]} Hidenori Abe,^[b] Toshio Miwa,^[b] Jianlin Han,^{*,[a]} and Vadim A. Soloshonok^{*,[c, d]}

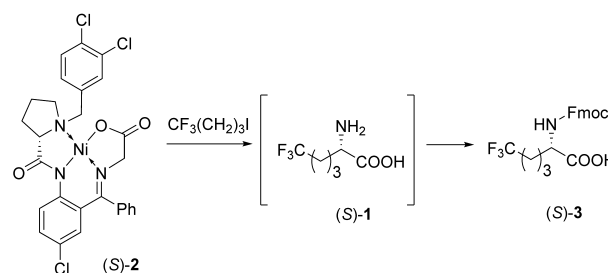
Here we report the first large-scale synthesis of Fmoc-(S)-2-amino-6,6,6-trifluorohexanoic acid via asymmetric alkylation of chiral Ni(II)-complex of glycine Schiff base with $\text{CF}_3(\text{CH}_2)_3\text{I}$. The synthesis was performed on over 100 g scale and can be recommended as the most advanced procedure for reliable preparation of large amounts of enantiomerically pure Fmoc-(S)-2-amino-6,6,6-trifluorohexanoic acid for protein engineering and drug design. Chiral auxiliary used in this protocol can be >90% recovered and reused.

Current trends in the design of new pharmaceuticals and drug formulations prominently feature application of fluorinated moieties as well as residues of tailor-made amino acids (AAs).^[1] In particular, the selective fluorination paradigm is widely used to control oxidative metabolic stability of drug molecules,^[2,3] while the incorporation of tailor-made amino AAs leads to more precise representation of the natural peptide-receptor interactions.^[4] One would agree, that fluorine-containing AAs, possessing both of these structural traits, represent an exciting class of biologically important compounds increasingly attracting attention of many synthetic research groups.^[5,6] Among structurally diverse fluorinated AAs currently used in the drug design,^[7] derivatives of (S)-2-amino-6,6,6-trifluorohexanoic acid **1** (Scheme 1) showed a plethora of useful biological properties^[8] and have been extensively used in de novo peptide/protein

engineering.^[9] In particular, fluoro-AA **1** was recently used in the design of new generation of antibiotics (Figure 1) derived from natural peptide teixobactin.^[9h]

Structurally, AA **1** is relatively simple and can be prepared by variety of general synthetic approaches including transformation of functional groups,^[10] including biomimetic transamination,^[11] and alkylation of glycine equivalents. The latter approach was particularly well-studied and known in asymmetric stoichiometric and catalytic versions.^[12] While the literature methods have apparent scientific interest, their application for economical large-scale preparation of target AA **1** is rather problematic. As part of a larger project focused on the development of a potential pharmaceutical drug, we needed a practically sounding access to large quantities of the corresponding Fmoc derivative of AA **3**. In this paper, we disclose our results on the development of >100 g -scale synthesis of our target product **3** via alkylation of a new generation of chiral nucleophilic glycine equivalent (S)-2.

Our interest in tailor-made AAs is rather broad, covering various structural motives,^[13] type of key functionalities^[14] and their chiroptical properties such as Self-Disproportionation of Enantiomers.^[15] However, our major interest in the field is related to the applications of Ni(II) complexes of AA Schiff bases as a general methodology for asymmetric synthesis of tailor-



Scheme 1. Approach for preparation of Fmoc derivative (S)-3 developed in this work.

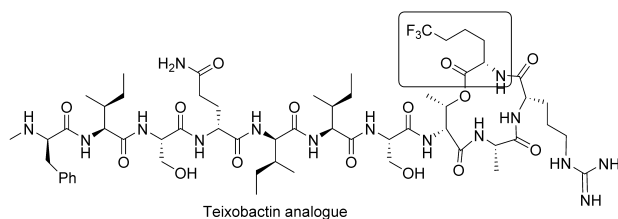


Figure 1. Structure of new peptide containing AA **1**.

[a] Z. Yin, Dr. J. Han
College of Chemical Engineering
Nanjing Forestry University
Nanjing, 210037, China
E-mail: hanjl@njfu.edu.cn

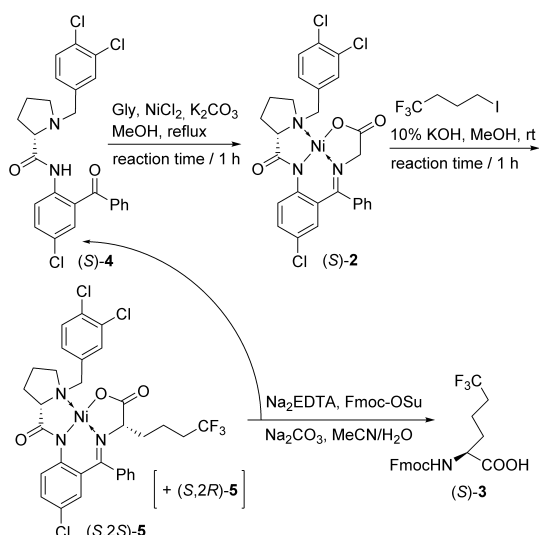
[b] Dr. H. Moriwaki, Dr. H. Abe, Dr. T. Miwa
Hamari Chemicals Ltd.
1-4-29 Kunijima, Higashi-Yodogawa-ku, Osaka 533-0024, Japan
E-mail: hiroki-moriwaki@hamari.co.jp

[c] Prof. Dr. V. A. Soloshonok
Department of Organic Chemistry I, Faculty of Chemistry
University of the Basque Country UPV/EHU
Paseo Manuel Lardizábal 3, 20018 San Sebastián, Spain
E-mail: vadymsoloshonok@ehu.es

[d] Prof. Dr. V. A. Soloshonok
IKERBASQUE, Basque Foundation for Science, María Díaz de Haro 3, Plaza Bizkaia, 48013 Bilbao, Spain

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Scheme 2. Large-scale synthesis of Fmoc derivative (S)-3 via alkylation of chiral nucleophilic glycine equivalent (S)-2.

made AAs.^[16] Using the modular design for the chiral tridentate ligands,^[17] we explored various structural ideas, featuring N–H functionality^[18] as well as elements helical chirality.^[19] One of the most recent developments is a tri-chloro-substituted ligand **4** (Scheme 2) rationally optimized to increase its stereocontrolling properties.^[20] So far, this new ligand was quite successfully used for the dynamic kinetic resolution of unprotected α -^[21] and β -AAs.^[22] On the other hand its application for asymmetric synthesis of tailor-made AAs via other approaches is virtually unstudied.^[23]

Proline-derived compounds (S)- or (R)-**4** are commercially available or can be expediently prepared on kilogram scale.^[24] The reaction of tridentate ligands of type **4** with glycine in the presence of base and source of Ni(II) is well-established procedure and was successfully used for preparation of glycine Schiff base complex (S)-**2**.^[24,25] In particular, similar to the previously reported synthesis^[23] in this work we selected quite inexpensive NiCl₂ and K₂CO₃, which were refluxed in MeOH along with (S)-**4** and glycine to afford complex (S)-**2** in excellent chemical yield. Taking advantage of our previous extensive experience with alkyl halide alkylations,^[26] we selected to use the homogeneous conditions, as versus to PTC,^[27] using DMSO or DMF as the reaction solvent.

Considering the goal of large-scale synthesis, optimization of the alkyl halide alkylation of the glycine moiety in complexes (S)-**2** was focused on both chemical and economic issues. In particular, we pursued adequate stoichiometry and minimum volume of solvents. As shown, for example in Table 1, the use of just one equivalent of KOH and CF₃(CH₂)₃I was quite sufficient to achieve over 99% conversion of the starting Ni(II) complex (S)-**2**. In general the alkylation reaction was robust, chemically rather clean and reliably reproducible. The undesirable diastereomer (S,2R)-**5** was observed in amounts not exceeding 1–2%, confirming our high expectation for excellent stereocontrolling ability of tri-chloro ligand (S)-**4**. The major technical problem

Table 1. Optimization of reaction conditions.^[a]

Entry	Time (min)	Solvent	2 (%) ^[b]	Product 5 (%) ^[b]	(S,2R)- 5 (%) ^[b]
1	10	DMF	0.36	86.34	1.87
2	60	DMF	0.33	87.21	1.73
3	120	DMF	0.30	88.49	1.55
4	120	dry DMF	0.09	96.49	0.35
5	10	deoxidized DMF	0.14	95.53	2.00
6	60	deoxidized DMF	0.12	94.44	1.76
7	120	deoxidized DMF	0.12	94.34	1.72
8	120	dry deoxidized DMF	0.10	98.46	0.47

[a] Reaction conditions: Ni-complex **2**, CF₃(CH₂)₃I (1.05 equiv), 10% KOH/MeOH (1.05 equiv), in DMF at room temperature under argon. [b] Determined by HPLC.

was found to be caused by oxidative decomposition of starting (S)-**2** and alkylated products **5** used strongly basic reaction conditions. These unwanted reactions were completely eliminated by using commercial deoxygenated (dry, oxygen-free) DMF.^[28] The final optimized condition were found to as follows; the use of 1.05 equiv. of 1,1,1-Trifluoro-4-iodobutane, 1.05 equiv. of 10% KOH/MeOH, with dry deoxidized DMF as solvent at 0–5 °C for 2 h under argon.

One of the important findings made in this work is that we were able to develop an economical procedure for isolation of virtually diastereomerically pure major product (S,2S)-**5**. Thus, taking into account that for the large-scale synthesis chromatographic purification is unacceptable and crystallization is undesirable, we focused our attention on a precipitation of major product (S,2S)-**5** directly from the reaction mixture. In particular, we found that two-step addition of water at ambient temperature results in gradual precipitation of target product (S,2S)-**5** of excellent chemical and diastereomeric purity (> 99% de).

Usually, the disassembly procedure of Ni(II) complexes of this type is performed in MeOH under the action of HCl.^[16] However, developing the large-scale synthesis, we found that this procedure would require detrimental amount of the solvent. Accordingly, we screened other reaction conditions and found that the use of dimethoxyethane (DME) allows to reach rather optimal solution. Despite incomplete solubility of (S,2S)-**5** on the initial stages of the process and partially biphasic system, the disassembly proceed quite well under heating at 50–60 °C. The red-orange color of (S,2S)-**5** was gradually changed to green (NiCl₂) within about 3 hrs of the reaction time. Upon cooling to the ambient temperature the hydrochloric salt of chiral ligand (S)-**4** was precipitated and conveniently isolated by filtration. It should be noted that chiral ligand (S)-**4** was recovered with total chemical yield of 98% (see

for details S1) and was shown to be stereochemically intact, underscoring economically attractive feature of this approach.

Upon evaporation of the aqueous solution, containing hydrochloric salt of (S)-1 and NiCl₂, the mixture was dissolved in acetonitrile and treated with ethylenediaminetetraacetic acid (EDTA) to chelate the Ni(II) ions. The resultant solution was treated with Fmoc-OSu, using rather standard Fmoc-protection reaction conditions. For the final purification of target product (S)-3, we resorted to a crystallization procedure. It was found that toluene serve as the solvent of choice allowing precipitation of Fmoc derivative (S)-3 of excellent purity.

Using this method product (S)-3 was prepared on 105.9 gram scale with total yield of 83.2% and of >99% enantiomeric purity.

In summary, the results reported in this work convincingly demonstrate that Ni(II) complex of amino acid Schiff bases methodology can be successfully applied for over 100 g-scale synthesis of pharmaceutically important Fmoc-(S)-2-amino-6,6,6-trifluorohexanoic acid. It should be emphasized that the application of new chiral ligand (S)-4 and the corresponding glycine equivalent (S)-2, providing for the enhanced reactivity and diastereo-control on the alkylation step, were vital for the successful realization of this approach on the large-scale. Excellent overall yield and enantiomeric purity of the final product coupled with operational convenience and attractive cost structure, bode well for widespread application of this methodology for large-scale synthesis of tailor-made amino acids.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: asymmetric synthesis · amino acids · fluorine · large-scale synthesis · stereochemical outcome

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