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Asymmetric Synthesis of Sterically and Electronically Demanding Linear ω-Trifluoromethyl Containing Amino Acids via Alkylation of Chiral Equivalents of Nucleophilic Glycine and Alanine

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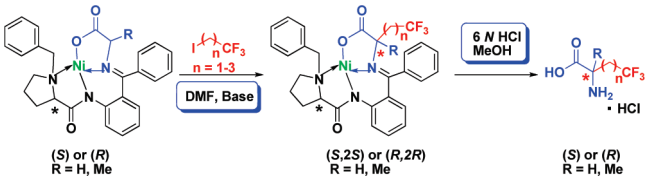

An operationally convenient, scalable asymmetric synthesis of linear, ω-trifluoromethyl-containing amino acids, which were not previously produced in their enantiomerically pure form, has been developed via alkylation of chiral equivalents of nucleophilic glycine and alanine. The simplicity of the experimental procedures and high stereochemical outcome (yields up to 90% and diastereoselectivity up to 99%) of the presented method render these fluorinated amino acids readily available for systematic medicinal chemistry studies and de novo peptide design.

Due to the extraordinary characteristics of fluorine, such as size, electronegativity, polarization, and energy of chemical bonds, fluorine substitution for hydrogen results in profound changes in a parent molecule giving rise to new modes of physical properties,[1] chemical reactivity,[2] and chiral recognition.[3] It is generally recognized that the ability to induce and control these desired physicochemical properties via selective fluorination of organic compounds holds quite an inspiring, creative potential in many areas of modern science and technology.[1,2] On the other hand, as it has been recently emphasized,[4] fluoroorganic methodology is considerably underdeveloped to match the ever-increasing demand for fluorinated products. Consequently, the development of practical methods for the preparation of rationally designed fluorine-containing compounds constitutes a strategically important area of contemporary organic chemistry.[1−3,5]

In the recent decade, fluorine-containing analogues of natural compounds have become privileged targets in bioorganic and medicinal chemistry aimed at the rational design of potent and highly selective biologically active compounds.[5,6] One of the noticeable accomplishments in this area is the development of "Fluorine-Scan" allowing for predictable improvement of metabolic stability of pharmaceuticals and agrochemicals.[7] Thus, about 40% of marketed drugs and an estimated 80% of current drug-candidates contain at least one fluorine atom.[4a,7] Due to the special role of amino acids in various areas of health-related sciences, synthesis of fluorinated α-[8] and β-amino acids[9] has been of particular importance.[10] In particular, it has been demonstrated, most notably by the groups of Kumar,[11] Koksch,[12] Ulrich,[13] and Seebach,[14] that selective

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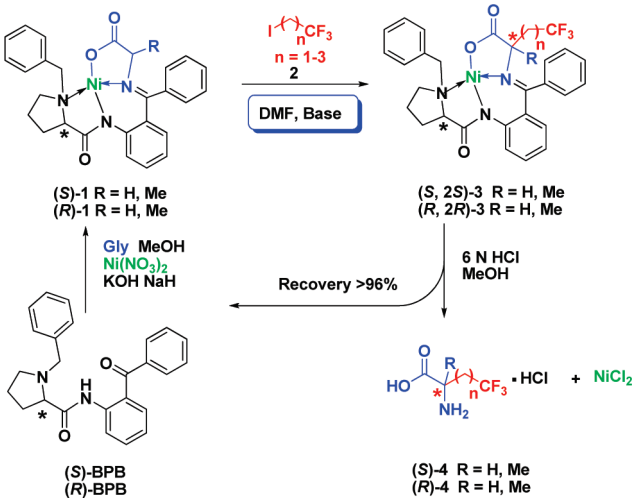
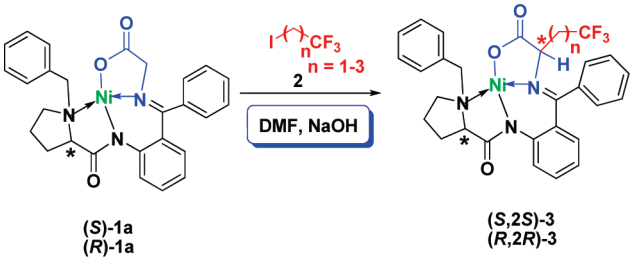
SCHEME 1. Asymmetric Synthesis of Linear ω-Trifluoromethyl-Containing Amino Acids via Chiral Nickel(II) Complexes Alkylation with Alkyl Halides



incorporation of fluorinated amino acids allows for remarkable opportunities to study and control the dynamics of peptide secondary structure and folding. It is assumed that further progress in this area of research might depend on availability of various structural and functional types of fluorinated amino acids. Thus, substantial progress has been made in the development of general approaches for preparation of fluorine-containing amino acids in enantiomerically pure form.[5,6,8,9,15] One particular type, linear ω-trifluoromethyl-containing α-amino acids **4** (Scheme 1), is of considerable interest for peptide design due to the strong steric[16] and electrostatic[17] requirements of a trifluoromethyl group. However, asymmetric synthesis of this type of amino acids features rare for synthetic methods operational convenience and based on readily available and inexpensive starting materials.[18] Herein, we describe results of our study on the asymmetric alkylation reactions between the nickel(II) complex of the Schiff base of glycine and alanine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone **1** and ω-trifluoromethyl alkyl iodides **2**, allowing for an efficient access to enantiomerically pure, linear ω-trifluoromethyl-containing amino acids **4** (R = H) as well as previously unknown α-methyl derivatives **4** (R = Me).

TABLE 1. Asymmetric Alkylation of Chiral Nickel(II) Complexes (*S*)- and (*R*)-1a with Alkyl Halides 2a−c[a]



entry	product	Ni(II) complex	alkyl iodide	yield (%)	de[b] (%)
1	(*S*,2*S*)-**3a**	(*S*)-**1a**	$CF_3CH_2CH_2CH_2I$	90	97
2	(*S*,2*S*)-**3b**	(*S*)-**1a**	$CF_3CH_2CH_2I$	84	99
3	(*S*,2*S*)-**3c**	(*S*)-**1a**	CF_3CH_2I	81	96
4	(*R*,2*R*)-**3a**	(*R*)-**1a**	$CF_3CH_2CH_2CH_2I$	91	99
5	(*R*,2*R*)-**3b**	(*R*)-**1a**	$CF_3CH_2CH_2I$	83	96
6	(*R*,2*R*)-**3c**	(*R*)-**1a**	CF_3CH_2I	82	94

[a]Reactions were run with 0.20 mmol of **1**, 0.24 mmol of **2** in 10 mL of DMF with 0.22 mmol of NaOH for 0.5 h. [b]Determined by chiral HPLC analysis (see the Supporting Information for details).

The nickel(II) complex of the chiral Schiff base of glycine[19] has been widely used to synthesize enantiopure amino acids via aldol,[20] Michael addition,[21] Mannich reaction,[22] and C-alkylation reactions.[23] Notable merits of the nickel(II) complex's methods are the following: (1) predictable stereochemical outcome and high level of enantio- and/or diastereoselectivity; (2) inexpensive cost-structure and ready availability of nickel(II) complexes;[24] (3) operationally convenient reaction procedures; (4) high overall reaction yields and reproducibility; and (5) easy and virtually complete recovery of chiral ligands, rivaling catalytic methods in terms of consumption of the stereocontrolling reagents. These unique features render this method an attractive strategy for practical synthesis of various α-amino acids, in particular, on relatively large scale.[25] In this paper, we describe a successful application of chiral nickel(II) complexes of glycine and alanine for preparative, simple two-step synthesis of linear ω-trifluoromethyl-containing amino acids.

Considering the most general and successful reactions previously reported,[23−25] we decided to study the reactions of chiral (*S*)-nickel(II) complex of glycine **1a** with the 1,1,1-trifluoro-4-iodobutane **2a** as a model substrate for optimizing reaction

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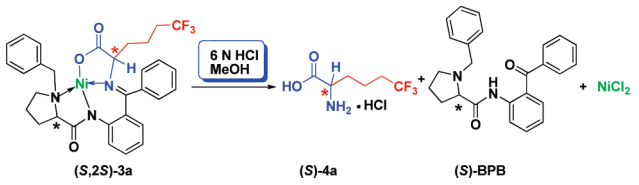
SCHEME 2. Disassembling of Nickel(II) Complex To Release Free Amino Acid and Recovery of the Ligand (*S*)-BPB



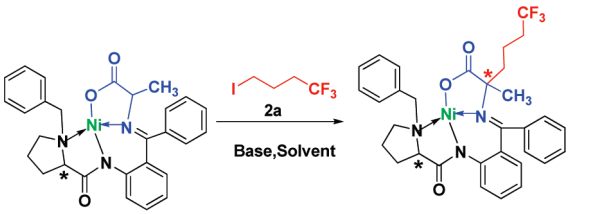
conditions. After a series of experiments in which bases, solvents, and reaction temperatures were varied, the alkylation was performed by using the following protocol: (*S*)-**1a** was treated with 1,1,1-trifluoro-4-iodobutane **2a** (1.2 equiv) in the presence of sodium hydroxide (1.1 equiv) at ambient temperature in *N*,*N*-dimethylformamide for half an hour to afford the alkylation adduct (*S*,2*S*)-**3a** in high yield and diastereoselectivity (entry 1). The (*S*)-absolute configuration of the major diastereomeric product was confirmed by single crystal X-ray analysis (Figure S1 in the Supporting Information). Next we explored alkylation reactions of complex (*S*)-**1a** with the other alkyl iodides: 1,1,1-trifluoro-3-iodopropane **2b** and 1,1,1-trifluoro-2-iodoethane **2c** bearing shorter chain alkyl groups (entries 2 and 3). As it follows from the results reported in Table 1, the alkylation products (*S*,2*S*)-configured products (*S*,2*S*)-**3b**, and (*S*,2*S*)-**3c** were obtained with the same high diastereoselectivity. On the other hand, the chemical yields decreased gradually with alkyl chain length, indicating the increasing electronic effect of the trifluoromethyl group in the series **2a**−**c**.

To provide the corresponding (*R*)-enantiomers of the target amino acids, we also studied the alkylations of (*R*)-configured complex **1a** with alkyl halides **2a**−**c**. The reactions conducted under the same conditions (entries 4−6) showed a similar stereochemical outcome as compared with that obtained from the alkylation of complex (*S*)-**1a**.

Taking advantage of the fact that the data for the diastereomerically pure (*S*)-2-amino-6,6,6-trifluorohexanoic acid are available from the literature,[18] we decided to decompose product (*S*,2*S*)-**3a** to afford the corresponding amino acid. The standard procedure for the disassembly of the chiral ligand (*S*)-BPB is performed by heating a suspension of (*S*,2*S*)-**3a** in methanol/6 N HCl to afford the target amino acid (*S*)-2-amino-6,6,6-trifluorohexanoic acid **4a** in 96% yield. Furthermore, the ligand (*S*)-BPB (Scheme 2) is quantitatively recovered and can be reused.

Quite unexpectedly, the alkylation reactions of the chiral nickel(II) complex of the Schiff base of alanine (*S*)-**1b** with alkyl halides **2a**−**c** proceeded very sluggishly resulting in noticeable amounts of decomposition products (Table 2). The observed outcome is most likely due to negative, combined stereoelectronic effects of both alanine derived complex **1b** and iodides **2a**−**c**. Thus, application of the reaction conditions optimized for the alkylation of the glycine complex **1a**, 3.0 equiv of NaOH in DMF, ambient temperature (entry 1), did not result in formation of detectable amounts of desirable product **3d**. To overcome this problem, other bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), potassium hydroxide (KOH), sodium hydride (NaH), and potassium *tert*-butoxide (*t*BuOK) were screened at room temperature (entries 2−5). Importantly, application of strong and non-nucleophilic base *t*BuOK provided the highest yield and diastereoselectivity (entry 5). The effect of

TABLE 2. Optimization of the Reaction Conditions for Alkylation of Alanine Derived Complex 1b[a]



entry	base	solvent	temp (°C)	yield (%)
1	NaOH	DMF	23	
2	DBU	DMF	23	trace
3	KOH	DMF	23	15
4	NaH	DMF	23	23
5[b]	*t*BuOK	DMF	23	74
6	*t*BuOK	CH_2Cl_2	23	trace
7	*t*BuOK	CH_3CN	23	33
8	*t*BuOK	THF	23	24
9	*t*BuOK	Toluene	23	trace
10	*t*BuOK	*t*BuOH	23	47
11	*t*BuOK	DMF	60	77
12	*t*BuOK	DMF	0	62
13	*t*BuOK	DMF	−20	59
14	*t*BuOK	DMF	−40	57
15	*t*BuOK	DMF	−60	52

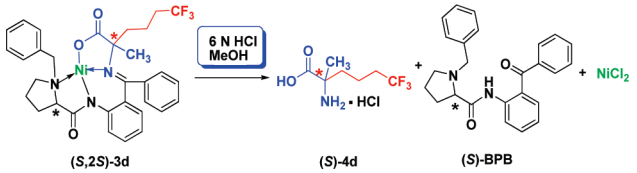
[a]Reactions were run with 0.20 mmol of (*S*)-**1b**, 0.5 mmol of **2a** in 10 mL of DMF with 0.60 mmol of *t*BuOK for 1 h. [b]Determined by chiral HPLC analysis, de >99% (see the Supporting Information for details).

solvent was also investigated (entries 7−10). Unfortunately, no improvement was achieved indicating that *N*,*N*-dimethylformamide should be used as the most effective solvent (entry 5) for this alkylation reaction. Finally, the effect of the reaction temperature was studied. Interestingly, we found that yield of the target product can be improved by conducting the alkylation reaction at a higher temperature (60 °C). In contrast, lowering the reaction temperature resulted in lower yields (entries 11−15). After optimizing the reaction conditions, the alkylation was performed by using the following protocol: (*S*)-**1b** was treated with 1,1,1-trifluoro-4-iodobutane **2a** in the presence of *t*BuOK (3.0 equiv) at ambient temperature in *N*,*N*-dimethylformamide for 1 h to afford the product (*S*,2*S*)-**3d** in 74% yield and with virtually complete diastereoselectivity. We also studied the chiral (*R*)-nickel(II) complex of alanine **1b** with the 1,1,1-trifluoro-4-iodobutane **2a**; the reaction conducted under the same conditions showed a similar yield (72%) and diastereoselectivity (de >97%). Unfortunately, application of 1,1,1-trifluoro-3-iodopropane **2b** and 1,1,1-trifluoro-2-iodoethane **2c**, containing a shorter alkyl chain, did not allow for synthetically useful preparation of the corresponding products, indicating limitations of this method.

Disassembly of the diastereomerically pure complex (*S*,2*S*)-**3d** under the previously described standard conditions afforded the target (*S*)-2-amino-6,6,6-trifluoro-2-methylhexanoic acid **4d** in 96% yield and the quantitative recovery of the (*S*)-BPB (Scheme 3).

In summary, we have developed a simple and highly efficient method for the synthesis of linear ω-trifluoromethyl-containing amino acid derivatives. The asymmetric alkylation reaction of the chiral nickel(II) complexes of the Schiff

SCHEME 3. Disassembling of Nickel(II) Complex To Release Target Amino Acid and Recovery of the Ligand (*S*)-BPB



base of glycine and alanine (*S*)-**1** and alkyl iodides **2** were performed at room temperature under operationally convenient conditions. Appreciable chemical and stereochemical outcomes of the alkylation step render this approach immediately useful for the preparation of this type of fluorinated amino acids and the systematic exploration of their biological applications.

Experiment Section

General Procedure for the Synthesis of (*S*,2*S*)-3a. The nickel(II) complex of glycine (*S*)-**1a** (200 mg, 0.40 mmol) was dissolved in DMF (2 mL). Sodium hydroxide (19.2 mg, 0.48 mmol) was added at ambient temperature. Next 1,1,1-trifluoro-4-iodobutane **2a** (104 mg, 0.44 mmol) was added and the reaction mixture was stirred for 0.5 h. The reaction was quenched by pouring the crude reaction mixture over 30 mL of aq. sat. NH_4Cl. The suspension was extracted with ethyl acetate (3 times). The combined organic layers were dried with $MgSO_4$, concentrated, and purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1/1) to give (*S*,2*S*)-**3a** as a red solid.

Ni(II)-(*S*)-BPB/(*S*)-2-Amino-6,6,6-trifluorohexanoic Acid Schiff Base Complex 3a. Mp 183−185 °C; $[\alpha]^{24}_{D}$ +1667 (*c* 0.3 g/100 mL, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.13 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 7.5 Hz, 2H), 7.55−7.43 (m, 3H), 7.35 (t, J = 7.5 Hz, 2H), 7.29−7.26 (m, 1H), 7.22−7.11 (m, 2H), 6.92 (d, J = 6.6 Hz, 1H), 6.70−6.62 (m, 2H), 4.42 (d, J = 12.6 Hz, 1H), 3.90 (dd, J_1 = 8.4 Hz, J_2 = 3.6 Hz, 1H), 3.60−3.44 (m, 4H), 2.78−2.70 (m, 1H), 2.58−2.49 (m, 1H), 2.37−2.31 (m, 1H), 2.22−1.94 (m, 6H), 1.90−1.79 (m, 2H), 1.73−1.62 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.0, 23.5, 30.6, 33.0 (q, J = 28.7 Hz), 34.0, 57.0, 63.1, 69.4, 70.2, 120.7, 123.6, 125.3, 126.2, 126.7 (q, J = 274.9 Hz), 127.0, 127.2, 128.8, 128.9, 129.8, 131.4, 132.2, 133.1, 133.5, 142.2, 170.8, 178.8, 180.3 ppm. LRMS (EI) $[M]^+$ found m/z 607. HRMS (EI) $[M]^+$ found m/z 607.1593, calcd for $C_{31}H_{30}F_3N_3NiO_3$ 607.1598. HPLC (Chiralpak IA, isopropanol/*n*-hexane = 40/60, flow rate 1.0 mL/min, λ = 254 nm), t_{minor} = 6.0 min, t_{major} = 12.2 min, de = 97%.

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Supporting Information Available: Experiment procedures, analytical and spectral characterization data for all compounds, and crystallographic information files (CIF) of **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.