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Oxazoline−Oxazinone Oxidative Rearrangement. Divergent Syntheses of (2*S*,3*S*)-4,4,4-Trifluorovaline and (2*S*,4*S*)-5,5,5-Trifluoroleucine

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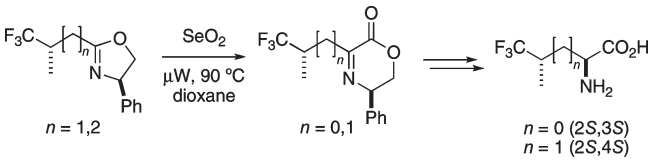

Stereoselective syntheses of the valuable fluorinated amino acids (2*S*,3*S*)-4,4,4-trifluorovaline and (2*S*,4*S*)-5,5,5-trifluoroleucine have been achieved starting from 4,4,4-trifluoro-3-methylbutanoic acid by using a conceptually simple transformation: conversion to a chiral oxazoline, SeO_2-promoted oxidative rearrangement to the dihydro-2*H*-oxazinone, and face-selective hydrogenation of the C=N bond, followed by hydrogenolysis−hydrolysis. The transformation is limited by the tendency of the intermediate β-trifluoromethyldihydrooxazinone to undergo imine−enamine isomerization. Both amino acids were obtained as configurationally pure hydrochloride salts identical in all respects with those in literature reports.

Introduction

Fluorinated amino acids have attracted attention as enzyme inhibitors[1] and antitumor and antibacterial agents.[2] Trifluoro analogues of proteinogenic amino acids (e.g., diastereomers of L-4,4,4-trifluorovaline and L-5,5,5-trifluoroleucine) have attracted particular interest in protein structural biology[3] owing to their isosteric compatibility with their natural counterparts, incorporation into proteins under control of cellular ribosomal protein assembly, and their ability to induce altered secondary structure.[3c,4] For example, fluorinated leucine participates in leucine coiled coil motifs that favor homologous association by attractive fluorous forces.[4f] Most protein biosynthesis studies use commercially available, unresolved mixed isomers of trifluorovaline and trifluoroleucine for incorporation studies. Although it has been shown that only the (2*S*,3*R*)-isomer of 4,4,4-trifluorovaline is selected by Val *t*-RNA in protein biosynthesis,[4d] it is not clear that this selection would be preserved in nonribosomal peptide syntheses that generate natural product peptides. In our biosynthetic studies of marine natural product peptides, we required diastereomerically pure isomers of fluorinated valine and leucine. Syntheses of trifluorovaline and trifluoroleucine has been reported by several research groups,[5] including Kumar and co-workers, who resolved all four diastereomers of both amino acids using a combination of chromatography and lipase-mediated hydrolysis of the corresponding *N*-acyl amino acids.[5a,5b]

In this paper, we present a flexible approach to the synthesis of (2*S*,3*S*)-4,4,4-trifluorovaline (**1**) and (2*S*,4*S*)-5,5,5-trifluoroleucine (**2**) through a conceptually simple transformation (Figure 1): carboxylic acids **i** to amino acids

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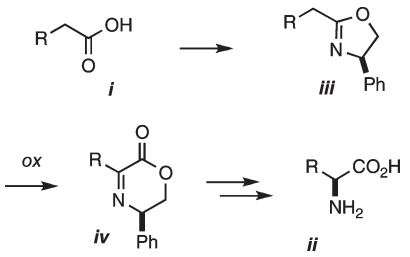


FIGURE 1. Generalized approach to amino acids via oxazoline−oxazinone rearrangement.

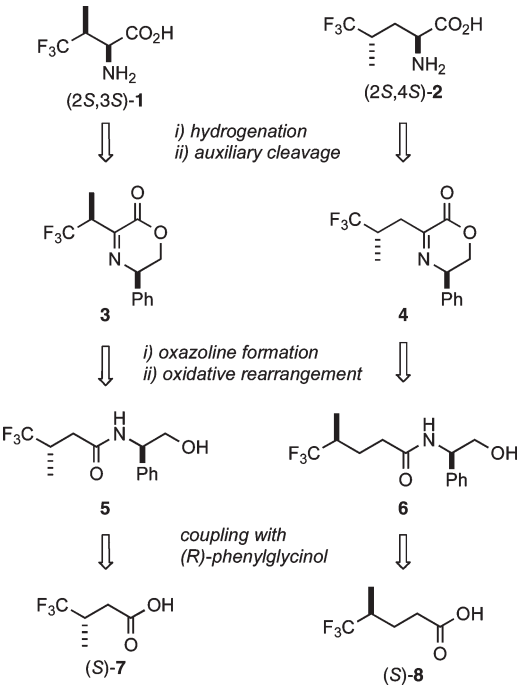
ii, via our previously reported[6] oxidative rearrangement of oxazolines **iii** to dihydro-2*H*-oxazinones **iv** (hereafter, referred to as "oxazinones"), followed by hydrogenolysis−hydrolysis.

The use of phenylglycinol-derived oxazinones, morpholinones (dihydro-**iv**), and 5,6-diphenylmorpholinones as chiral auxiliaries for amino acid syntheses have been widely reported.[7] Whereas the preparations of oxazinone auxiliaries in several of these reports required 4−6 step syntheses for *each desired* α*-amino acid*,[7g,7h] the transformation of **iii** to **iv** via the oxazoline−oxazinone rearrangement gives facile access to the requisite morpholinone after hydrogenation of **iv**. The advantage offered by this approach is maximum flexibility for the synthesis of virtually *any* nonpolar α-amino acid starting with a simple alkanoic acid. Since both the oxidative rearrangement and hydrogenation steps are particularly efficient in the preparation of *β*-branched amino acids,[6a,7k] it was attractive to investigate their utility in the preparation of fluorinated analogues of the nonpolar amino acids valine and leucine.

Results and Discussion

The antithetical work flow for the preparation of (2*S*,3*S*)-**1** and (2*S*,4*S*)-**2** is outlined in Scheme 1. The α-stereocenter of **1** and **2** is installed by face-selective hydrogenation[7j,7k] of oxazinones **3** and **4**, respectively, directed by a phenylglycinol-derived auxiliary. Oxazinones **3** and **4** can be obtained by SeO_2-mediated oxidative rearrangement[6] of the corresponding oxazolines. The oxazolines, in turn, originate from

SCHEME 1. Retrosynthetic Analysis of 1 and 2



amides **5** and **6** derived from (*R*)-phenylglycinol and optically enriched carboxylic acids (*S*)-**7**[8] and (*S*)-**8**, respectively.

The preparation of the common precursor to the optically active carboxylic acids (*S*)-**7** and (*S*)-**8** is depicted in Scheme 2. *N*-Acylation of Oppolzer's (−)-sultam (**10**)[9] using the acid chloride derived from commercially available (*E*)-4,4,4-trifluoro-3-methylbut-2-enoic acid (**9**) provided **11**[9d] in 49% yield.[10] The CF_3 stereocenter was then introduced by hydrogenation of **11** under heterogeneous catalysis (Pd−C, H_2, 6 atm, EtOH, 1.5 h). However, the major isomer (3*S*)-**12** was obtained with only moderate diastereoselectivity (dr 4:1) in contrast to hydrogenation of the nonfluorinated *N*-crotonyl sultam (dr 20:1).[11] The configuration of the newly established stereocenter was proved by reductive cleavage of the sultam auxiliary ($LiAlH_4$)[12] to provide known alcohol (−)-(*S*)-**13** ($[\alpha]^{22}_D$ −8.9, *c* 2.0, $CHCl_3$, 60% ee; lit.[5e] $[\alpha]^{20}_D$ −7.3, *c* 1.3, $CHCl_3$, 42% ee).

Attempts were made to improve the diastereoselectivity of the reduction of *N*-acyl sultam **11** (see Table 1) under other conditions. Changing the solvent gave no significant improvement (entries 1 and 2), while 1,4-conjugate reduction with either *L*-Selectride or $LiAlH_4/CoCl_2$[11] also gave

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SCHEME 2. Synthesis of *N*-Acyl Sultam 12

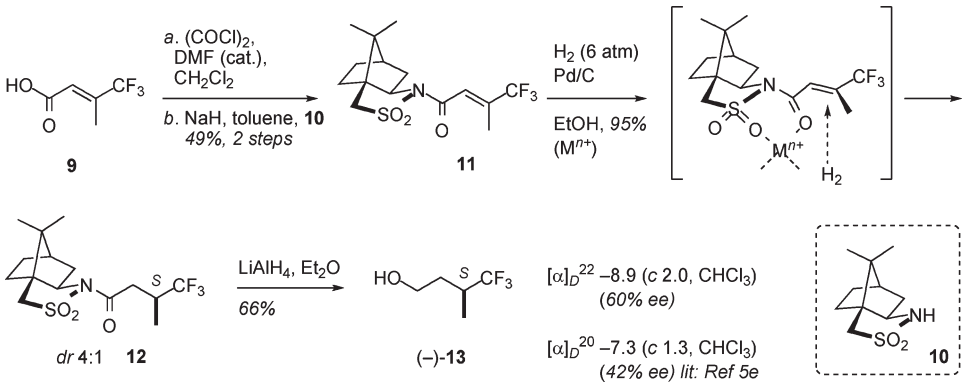
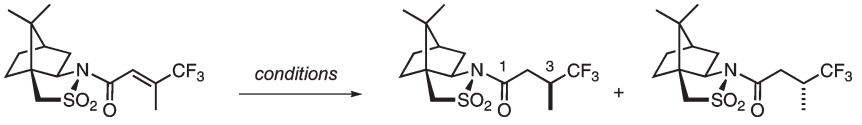


TABLE 1. Reductions of *N*-Acyl Sultam 11



entry	conditions	temp	time (h)	conversion[a]	dr 3*S*:3*R*[b]
1	H_2, Pd/C, CF_3CH_2OH[c]	rt	1.5	100	4.2:1
2	H_2, Pd/C, hexanes[c]	rt	1.5	100	1.7:1
3	H_2, Pd/$BaSO_4$, EtOH[c]	rt	1.5	100	5.0:1
4	$CeCl_3 \cdot 7H_2O$ (5 equiv), H_2, Pd/C, EtOH[c]	rt	2.0	100	9.6:1
5	$CoCl_2 \cdot 6H_2O$ (5 equiv), H_2, Pd/C, EtOH[c]	rt	1.5	100	8.8:1
6	$MgCl_2$ (5 equiv), H_2, Pd/C, EtOH[c]	rt	1.5	100	7.2:1
7	L-Selectride (1.2 equiv), THF[d]	−78 to −40 °C	1.2	59	1:1.4[f]
8	$CoCl_2$ (2.4 equiv), $LiAlH_4$ (1.2 equiv), THF[e]	−78 °C to rt	12.0	52	2.8:1[f]
9	$NaBH_4$ (10 equiv), THF	−20 °C	0.5	100[g]	---
10	$NiCl_2 \cdot 6H_2O$ (2 equiv), $NaBH_4$ (10 equiv), MeOH	−20 °C	0.5	100	9.8:1
11	$NiCl_2 \cdot 6H_2O$ (2 equiv), $NaBH_4$ (10 equiv), MeOH	−50 °C	0.5	100	4.4:1
12	$NiCl_2 \cdot 6H_2O$ (2 equiv), $NaBH_4$ (10 equiv), MeOH	−5 °C	0.2	100	8.5:1

[a] Conversions were calculated from NMR integration of the crude product. [b] Diastereoselectivity was determined from chiral HPLC; see the Supporting Information for full details. [c] 6 atm of H_2. [d] L-Selectride (1.2 equiv) and $BF_3 \cdot OEt_2$ (1.2 equiv) did not improve the dr or conversion. [e] Significant amide bond cleavage was observed. No improvement in dr was found by replacing THF with Et_2O. [f] The dr and conversion were determined by ^{19}F NMR; see the Supporting Information for details. [g] Cleavage of the amide bond was the main product; only 10% of **12** was observed (dr 1:1).

unsatisfactory results (entries 7 and 8). The use of metal ion additives in heterogeneous catalytic hydrogenation was investigated (entries 3−6). Hydrogenation of **11** over Pd/$BaSO_4$ led to complete conversion but only a modest improvement in diastereoselectivity (dr 5:1). Further improvement was observed upon catalytic hydrogenation over Pd−C in the presence of salts of Ce^{III}, Co^{II}, and Mg^{II} with the greatest diastereoselectivity obtained in the case of $CeCl_3 \cdot 7H_2O$ (dr 9.6:1, entry 4). Enhanced selectivity of reduction of **11** was also achieved with "nickel boride" generated in situ ($NiCl_2 \cdot 6H_2O$, $NaBH_4$,[13] entries 10−12) with optimum diastereoselectivity observed at a temperature of −20 °C (dr 9.8:1, entry 10). While the highest diastereoselectivity was observed with the latter reagent, separation of the diastereomers was not possible under practical preparative conditions. For convenience of through-put, compound **12** with the 4:1 diastereomeric composition obtained under catalytic hydrogenation was carried forward in the syntheses of the target amino acids.

Sultam 3*S*-**12** (dr 4:1) served as the common starting material for preparation of both **1** and **2** as illustrated in Schemes 3 and 4, respectively. Hydrolysis of **12** afforded enantiomerically enriched carboxylic acid (*S*)-**7**, which was immediately coupled with optically pure (*R*)-phenylglycinol **14**[14] to give amide **5** in 75% yield as a 4:1 mixture of diastereomers at the CF_3 stereocenter. Partial separation of the mixture (silica flash chromatography) provided the major isomer **5** (56%) that was carried through the remainder of the sequence.

Treatment of **5** with DAST[15] gave oxazoline **15** in good yield and without loss of stereochemical integrity. Oxidative rearrangement of **15** in the presence of SeO_2[6a] in refluxing 1,4-dioxane gave oxazinone **3** as a 7:1 mixture of diastereomers. The cause of the partial epimerization at the α-stereocenter is likely the presence of adventitious acid formed during the oxidative transformation (e.g., H_2SeO_3) that may catalyze the imine−enamine (**16**) isomerization.

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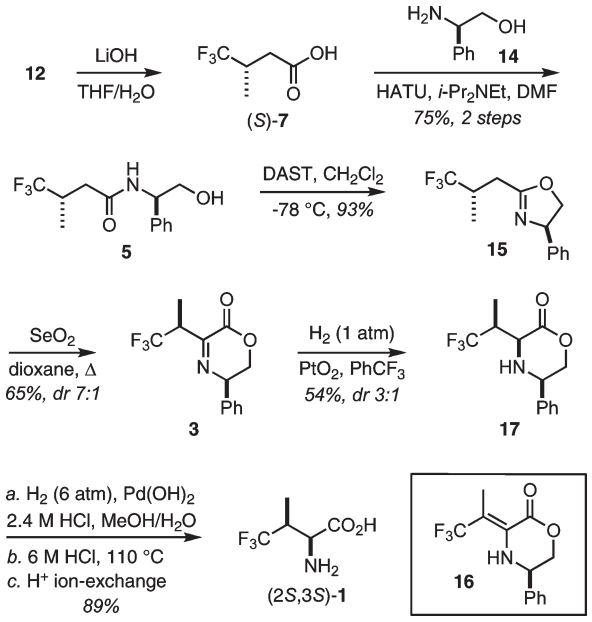
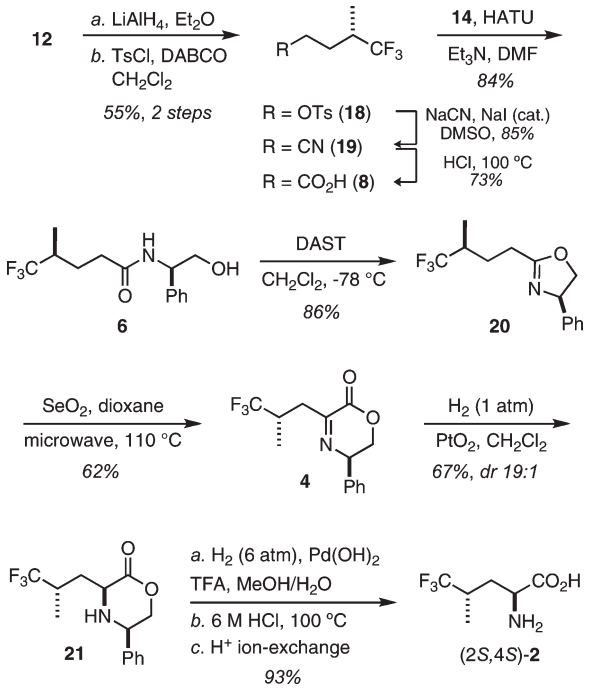
SCHEME 3. Synthesis of (2*S*,3*S*)-1



SCHEME 4. Synthesis of (2*S*,4*S*)-2



The enamine (**16**) was isolated in small amounts from the reaction mixture and assigned based on evidence from ^{1}H NMR data and mass spectrometry. Attempted conversion of **15** to **3** in either 1,4-dioxane or THF with MgO as an additive resulted in lower yields (30−40%), albeit with less epimerization (dr 10:1). Substitution of the solvent (EtOAc, $CHCl_3$) also gave lower yields of **3** (40−50%), with no change in the dr.

Exposure of **3** (dr 7:1) to H_2 (1 atm) and PtO_2[7j] in α,α,α-trifluorotoluene gave a 54% yield of **17**, which could be separated from the more polar minor diastereomers by flash chromatography. To estimate the diastereoselectivity of this reaction, a small sample of pure **3**, obtained as a single diastereomer by HPLC purification, was exposed to the hydrogenation conditions described above. HPLC analysis of the crude reaction showed a dr of 3:1 favoring **17**. The low diastereoselectivity for this hydrogenation compared to literature precedents (e.g., dr >15:1 when the trifluoroisopropyl group is replaced by *tert*-butyl)[7k] is likely the result of dipole effects exerted by the proximal CF_3 group. It appears the strong trifluoromethyl group dipole erodes stereoselectivity in both the catalytic reduction of **3** and **11**. Hydrogenolysis of **17** at elevated pressure, followed by treatment of the crude product with 6 M HCl gave the hydrochloride salt of **1**, which matched literature data in every respect.[5a,5b] Ion-exchange chromatography (strong cationic resin, H^+ form, elution with 2 M NH_4OH) provided amino acid (2*S*,3*S*)-**1** in 89% yield from **3**.

The synthesis of **2** follows a similar sequence as **1** but requires the homologous carboxylic acid **8** (Scheme 4). The camphor sultam 3*S*-**12** (dr 4:1) was reductively cleaved ($LiAlH_4$)[12] to provide alcohol (*S*)-**13**,[5e] which was subsequently activated as the tosylate ester **18** (55%, 2 steps). S_N2 displacement of **18** with NaCN gave nitrile **19** in good yield (85%). Direct conversion of nitrile **19** to oxazoline **20** with (*R*)-phenylglycinol (**14**) in the presence of $ZnCl_2$[16] in refluxing dichlorobenzene gave **20** in only 15% yield, while reaction in the presence of $Zn(OTf)_2$[17] did not provide **20** at all. Consequently, nitrile **19** was hydrolyzed (conc HCl) to the carboxylic acid (*S*)-**8** and coupled with **14** to afford amide **6** in 84% yield. Cyclization of **6** (DAST, Et_3N, CH_2Cl_2) gave oxazoline **20** (86%).

SeO_2-mediated oxidative rearrangement of **20** under the standard conditions (1,4-dioxane, 100 °C)[6a] gave only traces of oxazinone **4**. The ^{1}H NMR spectrum of the crude product showed a complex mixture of compounds, including small peaks corresponding to desired product **4**. A dramatic improvement in the oxidative rearrangement of **20** was realized under microwave irradiation conditions. Following a procedure for microwave-promoted SeO_2-mediated allylic oxidations,[18] **20** was heated to 110 °C with SeO_2 in 1,4-dioxane for 10 min, filtered, and purified by column chromatography. While **4** was obtained in only 14% yield as a mixture of inseparable diastereomers, the crude product was cleaner and suggested that the low yield was a result of over-oxidation at the α-CH_2 group of oxazinone **4**.[19] Optimal conditions were found by lowering the temperature to 90 °C and keeping the reaction time to only 5 min, which provided oxazinone **4** in 62% yield. The dr of **4** (4:1) was unchanged from **12** suggesting no racemization of the CF_3-substituted stereocenter in **4**, in contrast to the more activated stereocenter in **3**.

The diastereomeric purity of imine **4** was enriched by HPLC purification (dr >20:1) prior to hydrogenation by

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(18) Zou, Y.; Chen, C.-H.; Taylor, C. D.; Foxman, B. M.; Snider, B. B. *Org. Lett.* **2007**, *9*, 1825.

(19) The ^{1}H NMR of a mixture of side products from the reaction lacked the CH_2 signals adjacent to the C=N bond, suggesting that a second oxidation took place at this position at higher temperature and longer reaction times. Reaction times of less than 5 min returned only starting material, suggesting a short induction period.

using the Harwood conditions[7j] to afford the desired morpholinone with high diastereoselectivity ((2*S*,4*S*)-**21**, dr 19:1 by HPLC, 67% yield). Operationally, it was more convenient to hydrogenate unenriched **4** (dr 4:1) since the epimers of **21** were now readily separated by flash chromatography, in contrast to **4**.

Cleavage of the auxiliary was performed in two steps. Hydrogenolysis (H_2, 6 atm) in the presence of CF_3CO_2H and $Pd(OH)_2$[20] followed by subjection of the crude material to stronger hydrolysis conditions (6 M HCl, reflux, 14 h) provided the HCl salt of **2**. The salt was purified by ion-exchange chromatography (strong cationic resin, H^+ form, elution with 2 M NH_4OH) to provide enantiomerically pure free amino acid, (2*S*,4*S*)-trifluoroleucine (**2**), after removal of the volatiles. The ^1H and ^{19}F NMR data and optical rotations of both the free amino acid and the hydrochloride salt of **2** matched the corresponding literature values.[5a,5e]

Comparison of the syntheses of amino acids **1** and **2** reveals both advantages of the oxazoline−oxazinone rearrangement approach and liabilities when the CF_3 group is close to the α-carbon. The dipole associated with the CF_3 group diminishes diastereoselectivity in the heterogeneous catalytic reduction of both trifluoromethyl-substituted alkene **11** and imine **3**.

In addition, the electron-withdrawing effect of a β-CF_3 group appears to promote acid-catalyzed imine−enamine equilibration of **3**, which further erodes the configurational composition at the β-stereocenter. These effects are absent in the synthesis of **2** where the CF_3 group is removed to the γ-position and insulated from the α-center by a CH_2 group. Nevertheless, with judicious choice of conditions it may be possible to exploit the enamine−imine equilibration in **3** for additional reactions, including dynamic kinetic resolution, incorporation of isotopic label (e.g., ^2H, ^3H) at the β-center, or additional C−C bond forming reactions for preparation of homologated trifluorovaline analogues. Finally, it should be mentioned that both **1** and **2** appear to have good configurational stability upon exposure to standard hydrolytic conditions for amino acids (6 M HCl, 110 °C).

In summary, the stereoselective syntheses of amino acids (2*S*,3*S*)-**1** and (2*S*,4*S*)-**2** have been achieved from a common precursor (3*S*)-**12**, derived from commercially available (*E*)-4,4,4-trifluoro-3-methylbut-2-enoic acid (**9**). This method is applicable to the synthesis of any of the four diastereomers of **1** and **2** by appropriate choice of configurations of the chiral auxiliaries: the Oppolzer sultam to control the CF_3-substituted stereocenter (Scheme 2) and the phenylglycinol to control the C2 stereocenter (Schemes 3 and 4).

Experimental Section

For general procedures and experimental data for all new compounds, refer to the Supporting Information.

(*R*)-5-Phenyl-3-((*S*)-1,1,1-trifluoropropan-2-yl)-5,6-dihydro-2*H*-1,4-oxazin-2-one (3). A solution of oxazoline **15** (110 mg, 0.428 mmol) in 1,4-dioxane (1.4 mL) was added to a suspension of SeO_2 (94.9 mg, 0.855 mmol) in 1,4-dioxane (1.4 mL) and the mixture was heated at reflux for 50 min. The reaction mixture was cooled to rt and then filtered through magnesium silicate (200 mesh). Evaporation of the solvent under reduced pressure gave the crude product, which was purified by flash chromatography (SiO_2, 3:37 EtOAc:hexanes) to give oxazinone **3** (75.6 mg, 65%, dr 7:1) as a yellow oil; FTIR (ATR, neat) ν 3065, 3033, 3000, 2952, 2894, 1742, 1645, 1497, 1456, 1384, 1342, 1308, 1260, 1224, 1172, 1115, 1078, 1049, 1037, 1030, 1001, 984, 920, 870, 819, 795, 758, 697, 670, 662 cm^{-1}; $[\alpha]^{20}_D$ −110 (*c* 1.20, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.46−7.29 (m, 5H), 5.06 (dd, *J* = 9.2, 4.4 Hz, 1H), 4.64 (dd, *J* = 11.6, 4.4 Hz, 1H), 4.31 (dd, *J* = 11.6, 9.2 Hz, 1H), 4.16 (m, 1H), 1.49 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 159.0 (C), 154.6 (C), 136.2 (C), 129.4 (CH), 128.8 (CH), 127.2 (CH), 126.1 (q, *J* = 281 Hz, CF_3), 71.4 (CH_2), 59.9 (CH), 41.1 (q, *J* = 28.2 Hz, CH), 12.7 (CH_3); HREIMS *m*/*z* $[M]^+$ 271.0812, calcd for $C_{13}H_{12}F_3NO_2$ 271.0815.

(3*S*,5*R*)-5-Phenyl-3-((*S*)-1,1,1-trifluoropropan-2-yl)morpholin-2-one (17). A mixture of oxazinone **3** (dr 7:1, 16.6 mg, 61.2 μmol) and PtO_2 (9.7 mg, 39.6 μmol) in $PhCF_3$ (1.5 mL) was evacuated twice and then stirred under 1 atm of H_2 for 1.5 h. The reaction mixture was filtered through cotton wool and concentrated under reduced pressure to give the crude product. Purification by flash chromatography (SiO_2, 1:19 → 1:9 EtOAc:hexanes) gave morpholinone **17** (9.1 mg, 54%) as a colorless oil; FTIR (ATR, neat) ν 3338, 3065, 3033, 2989, 2952, 2917, 2848, 1737, 1497, 1458, 1407, 1389, 1371, 1323, 1288, 1260, 1208, 1178, 1154, 1118, 1092, 1069, 1040, 996, 977, 920, 875, 802, 782, 760, 701, 665 cm^{-1}; $[\alpha]^{20}_D$ −57.6 (*c* 2.755, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6) δ 7.04−7.02 (m, 3H), 6.96−6.94 (m, 2H), 3.86 (m, 1H), 3.68 (td, *J* = 10.6, 1.8 Hz, 1H), 3.61 (dq, *J* = 10.6, 3.0 Hz, 1H), 3.34 (m, 1H), 3.27 (m, 1H), 1.44 (br s, 1H), 1.11 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3 (C), 137.1 (C), 129.0 (CH), 128.9 (CH), 127.7 (q, *J* = 278 Hz, CF_3), 127.1 (CH), 74.9 (CH_2), 58.5 (d, *J* = 2.3 Hz, CH), 56.7 (CH), 40.5 (q, *J* = 25.8 Hz, CH), 8.37 (d, *J* = 2.3 Hz, CH_3); HREIMS *m*/*z* $[M]^+$ 273.0970, calcd for $C_{13}H_{14}F_3NO_2$ 273.0971. HPLC analysis (silica 5 μm, 250 × 4.6 mm, 3:7 Et_2O:hexanes, flow rate = 1 mL/min, UV detection at λ = 210, 220 nm) showed a retention time of t_R = 5.7 min for **17**. Repeating the reaction with **3** as a single diastereomer gave a mixture of products that was analyzed under the HPLC conditions described above. Integration of the peaks for **17** (t_R = 5.7 min) and 3-*epi*-**17** (t_R = 13.7 min) indicated a dr of 3:1.

(2*S*,3*S*)-4,4,4-Trifluorovaline (1). A mixture of morpholinone **17** (51.5 mg, 0.188 mmol), $Pd(OH)_2$ (20% Pd content, 25.1 mg, 0.0471 mmol), and 2.4 M HCl (314 μL, 0.753 mmol) in MeOH (6 mL) and H_2O (0.4 mL) contained in a thick-walled flask was shaken under 90 psi (6 atm) of H_2 for 2 h with use of a Parr hydrogenation apparatus. The reaction mixture was filtered through a pad of diatomaceous earth and concentrated under reduced pressure, then redissolved in 6 M HCl (6 mL) and heated at 110 °C for 20 h. The reaction mixture was again concentrated under reduced pressure to give **1**·HCl (40.0 mg) as an orange solid; $[\alpha]^{24}_D$ +7.0 (*c* 1.0, 1.0 N HCl) (lit.[5a,5b] $[\alpha]^{24}_D$ + 7.2 (*c* 0.75, 1.0 N HCl)); ^1H NMR (500 MHz, D_2O) δ 4.33 (d, *J* = 2.6 Hz, 1H), 3.25 (m, 1H), 1.21 (d, *J* = 7.4 Hz, 3H); ^{19}F NMR (471 MHz, D_2O/1% CF_3CO_2H) δ −71.62 (s) (lit.[5a] ^{19}F NMR (283 MHz, D_2O/CF_3CO_2H) δ −71.69 (d, *J* = 9.3 Hz)). Ion-exchange chromatography (strong cation-exchange resin, 200−400 dry-mesh, H^+ form, eluting with 2.0 M NH_4OH) gave amino acid (2*S*,3*S*)-**1** (28.7 mg, 89%) as a white solid; $[\alpha]^{22}_D$ + 0.22 (*c* 1.0, H_2O); ^1H NMR (500 MHz, D_2O) δ 4.08 (d, *J* = 2.3 Hz, 1H), 3.16 (m, 1H), 1.18 (d, *J* = 7.5 Hz, 3H); HRESIMS *m*/*z* $[M + H]^+$ 172.0579, calcd for $C_5H_9F_3NO_2$ 172.0580.

(*R*)-5-Phenyl-3-((*R*)-3,3,3-trifluoro-2-methylpropyl)-5,6-dihydro-2*H*-1,4-oxazin-2-one (4). SeO_2 (40.9 mg, 369 μmol) was added to oxazoline **20** (50.0 mg, 184 μmol) in 1,4-dioxane (1.8 mL) in a 10 mL microwave reaction vessel with cap and heated at 90 °C under microwave irradiation for 5 min. The reaction was cooled to 60 °C and then filtered through magnesium silicate (200 mesh) with Et_2O. The filtrate was concentrated and directly purified by flash chromatography (SiO_2, 8:92→ 12:88 → 15:85 EtOAc:hexanes) to provide oxazinone **4** (32.8 mg,

(20) Harwood, L. M.; Tyler, S. N. G.; Anslow, A. S.; MacGilp, I. D.; Drew, M. G. B. *Tetrahedron: Asymmetry* **1997**, *8*, 4007.

62%, dr 4:1) as a pale yellow oil. The major diastereomer could be separated by HPLC (SiO_2, 250 × 10 mm, 12:88 Et_2O:hexanes, flow rate = 3 mL/min, t_R(major) = 20.7 min, t_R(minor) = 21.3 min, with some partial peak overlap) but resulted in only 40% recovery of the desired product. The following data are for the 4:1 diastereomeric mixture: $[\alpha]^{21}_D$ −178.7 (*c* 1.0, $CHCl_3$); R_f 0.33 (1:4 EtOAc:hexanes); FTIR (ATR, neat) ν 1737, 1644 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45−7.41 (m, 2H), 7.40−7.32 (m, 3H), 4.93−4.88 (m, 1H), 4.58 (dd, *J* = 11.4, 4.6 Hz, 1H), 4.21 (dd, *J* = 11.8, 11.2 Hz, 1H), 3.10 (ddd, *J* = 16.6, 5.2, 2.8 Hz, 1H), 3.03−2.93 (m, 1H), 2.83 (ddd, *J* = 16.5, 8.3, 2.6 Hz, 1H), 1.20 (d, *J* = 6.8 Hz, 3H); signals of the minor diastereomer are partially resolved: δ 4.22 (dd, *J* = 11.4, 11.4 Hz, 1H), 1.24 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0 (C), 155.2 (C), 136.6 (C), 129.1 (CH), 128.6 (CH), 128.1 (q, *J* = 278.1 Hz, CF_3), 127.1 (CH), 71.4 (CH_2), 59.9 (CH), 35.0 (q, *J* = 26.4 Hz, CH), 34.3 (CH_2), 13.3 (q, *J* = 2.4 Hz, CH_3); HRESIMS m/*z* $[M + H]^+$ 286.1052, calcd for $C_{14}H_{15}F_3NO_2$ 286.1049.

(3*S*,5*R*)-5-Phenyl-3-((*S*)-3,3,3-trifluoro-2-methylpropyl)morpholin-2-one (21). A mixture of PtO_2 (3.3 mg, 15 μmol) and diastereomerically pure oxazinone **4** (9.3 mg, 33 μmol) in CH_2Cl_2 (650 μL) was purged with H_2 before stirring under 1 atm of H_2 for 2 h. The mixture was filtered and concentrated to a colorless oil. HPLC separation of the crude material (SiO_2, 250 × 10 mm, 2:3 Et_2O/hexanes, flow rate = 3 mL/min, t_R(major) = 18.63 min, t_R(minor) = 23.15 min) provided the major isomer, morpholinone **21** (6.3 mg, 67%). Integration of the peaks for the major and minor products showed the dr to be 19:1. Major diastereomer, **21**: $[\alpha]^{23.3}_D$ −82.8 (*c* 1.0, $CHCl_3$); R_f 0.22 (1:4 EtOAc:hexanes); FTIR (ATR, neat) ν 3315 (br), 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42−7.34 (m, 5H), 4.40 (dd, *J* = 16.8, 10.4 Hz, 1H), 4.31−4.25 (m, 2H), 3.87 (br dd, *J* = 11.2, 5.6 Hz, 1H), 2.60−2.49 (m, 1H), 2.11 (t, *J* = 6.8 Hz, 2H), 1.78 (br s, 1H), 1.20 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6 (C), 137.5 (C), 129.2 (CH), 129.0 (CH), 128.3 (q, *J* = 279.0 Hz, CF_3), 127.2 (CH), 74.7 (CH_2), 57.3 (CH), 56.1 (CH), 34.9 (q, *J* = 27.0 Hz, CH), 33.4 (CH_2), 12.8 (CH_3); HRESIMS *m*/*z* $[M + H]^+$ 288.1208, calcd for $C_{14}H_{17}F_3NO_2$ 288.1211.

(2*S*,4*S*)-5,5,5-Trifluoroleucine (2). A mixture of morpholinone **21** (5.0 mg, 17 μmol), $Pd(OH)_2$ (20% Pd content, 3.0 mg, 4.3 μmol), and TFA (5.2 μL, 68 μmol) in MeOH/H_2O (10:1, 870 μL) contained in a thick-walled flask was shaken under 90 psi (6 atm) of H_2 for 12 h with use of a Parr hydrogenation apparatus. The reaction was filtered through diatomaceous earth and concentrated to give the crude product, which was redissolved in 6 M HCl (870 μL) and heated at 100 °C for 14 h. After concentration, the crude material was purified by ion-exchange chromatography (strong cation-exchange resin, 200−400 dry-mesh, H^+ form, elution with 2.0 M NH_4OH) to provide amino acid (2*S*,4*S*)-**2** as a pale yellow solid (3.0 mg, 93%). ^1H NMR (500 MHz, D_2O) δ 3.74 (dd, *J* = 9.4, 5.2 Hz, 1H), 2.55−2.44 (m, 1H), 2.11 (ddd, *J* = 14.9, 9.4, 4.6 Hz, 1H), 1.94 (ddd, *J* = 14.9, 9.8, 5.2 Hz, 1H), 1.18 (d, *J* = 6.8 Hz, 3H); HR ESI-TOFMS *m*/*z* $[M + H]^+$ 186.0738, calcd for $C_6H_{11}F_3NO_2$ 186.0736. A sample of **2**, obtained after treatment with 6 M HCl (500 μL) and evaporation of the volatiles gave enantiomerically pure **2**·HCl as a pale yellow solid: $[\alpha]^{21.7}_D$ −3.2 (*c* 1.0, 1 N HCl) (lit.[5e] $[\alpha]^{20}_D$ −4.5 (*c* 1.0, 1 N HCl)); ^1H NMR (500 MHz, D_2O) δ 4.01 (dd, *J* = 9.2, 5.8 Hz, 1H), 2.59−2.49 (m, 1H), 2.14 (ddd, *J* = 14.8, 8.8, 4.8 Hz, 1H), 2.02 (ddd, *J* = 14.9, 9.2, 5.8 Hz, 1H), 1.13 (d, *J* = 6.8 Hz, 3H); ^{19}F NMR (471 MHz, D_2O/1% CF_3CO_2H) δ −74.13 (s) (lit.[5a] ^{19}F NMR (283 MHz, D_2O/CF_3CO_2H) δ −74.11 (s)).

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Supporting Information Available: General experimental procedures, experimental details, characterization data, and copies of spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.