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# Diastereoselective Trifluoromethylation of Chiral Imide Enolates with Iodotrifluoromethane Mediated by Triethylborane

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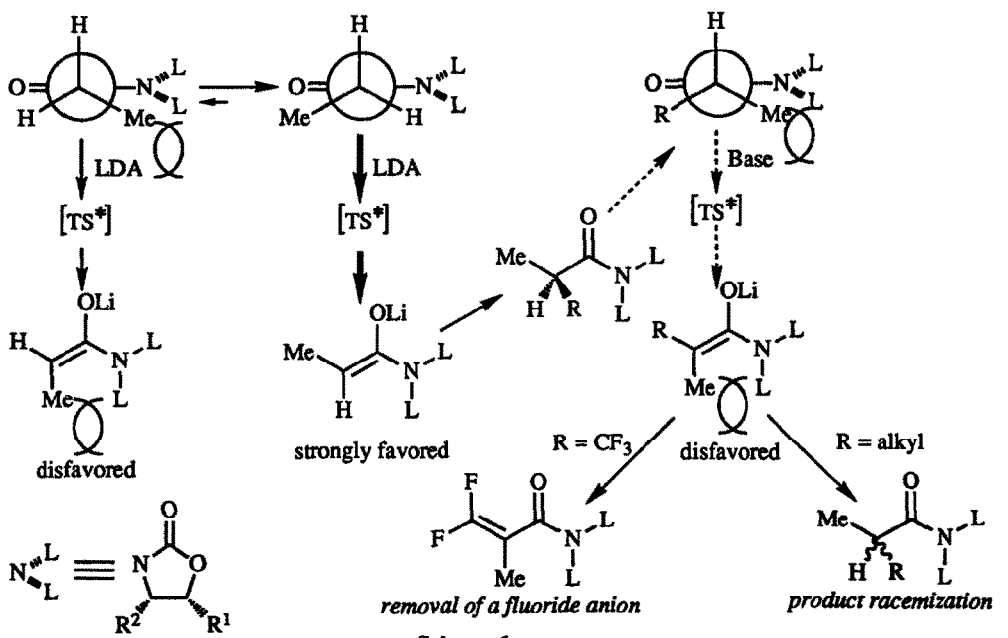
***Abstract:*** *The trifluoromethylation of lithium enolates of chiral N-acyloxazolidinones with iodotrifluoromethane mediated by triethylborane proceeds with good diastereomeric excess.*

## Introduction

The synthesis of chiral trifluoromethylated molecules is now an important aspect of organofluorine chemistry in connection with analytical and medicinal chemistry and opto-electric substances such as liquid crystals.[1] However, little research has been conducted on asymmetric trifluoromethylation for the optically active compounds.[2] The diastereoselective trifluoromethylation of chiral enolates, which would certainly be useful for the synthesis of chiral α-trifluoromethylalkanoic acids and β-trifluoromethylalkanols, has so far been considered quite difficult since the trifluoromethylation of achiral enolates easily gives β,β-difluoro-α,β-unsaturated carbonyl compounds *via enolization of the corresponding trifluoromethylated product and subsequent removal of a fluoride anion.*

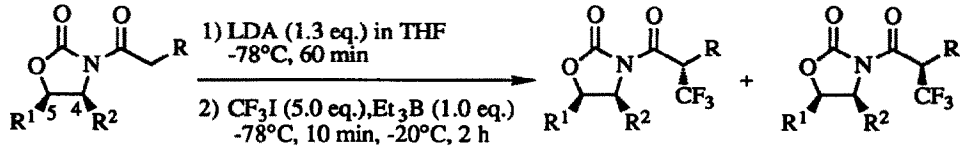



**Scheme 1**

D. A. Evans *et al.* reported the highly diastereoselective alkylation of enolates derived from *N*-acyloxazolidinones.[3] In regard to stereoselectivity, they considered that allylic strain conformational control elements should give *Z*-enolates preferentially and prevent product racemization (*via enolization*) during bond formation (Scheme 1).[4] From this, the possibility of stereoselective trifluoromethylation, ***without removal of a fluoride anion***, of Evans imide enolates was evident to us. The details of this trifluoromethylation with iodotifluoromethane mediated by triethylborane are presented in the following.[5]

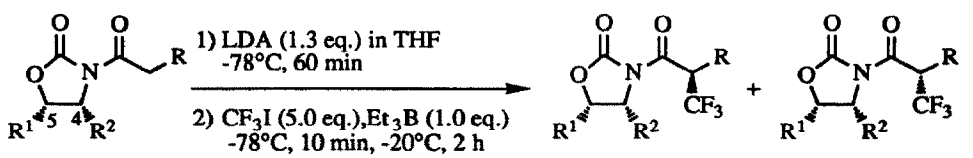
**Results and Discussion**

**Table 1.** Diastereoselective Trifluoromethylation of Lithium Enolates Derived from *N*-Acyloxazolidinones (1)




1 2 3

| Entry | Imide 1 | | | | Product (2, 3) | | |
|---|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | R | | % de[a] | % yield(2 + 3)[b] | |
| 1 | H | *i*-Pr | Me | (1a) | 64 (*S*)[c] | 70 (87) | (2a, 3a) |
| 2 | H | *i*-Pr | Bn | (1b) | 74 | 61 (80) | (2b, 3b) |
| 3 | H | *i*-Pr | Ph | (1c) | 67 (*S*)[c] | 45 (73) | (2c, 3c) |
| 4 | H | *i*-Pr | *n*-Bu | (1d) | 76 | 75 (85) | (2d, 3d) |
| 5 | H | *i*-Pr | *t*-Bu | (1e) | 86 | 67 (83) | (2e, 3e) |
| 6 | H | Bn | Me | (1f) | 72 (*S*)[c] | 70 (78) | (2f, 3f) |



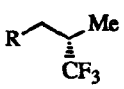

1 2 3

| Entry | Imide 1 | | | | Product (2,3) | | |
|---|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | R | | % de[a] | % yield(2 + 3)[b] | |
| 7 | Ph | Me | Me | (1g) | 44 | 29 (39) | (2g, 3g) |
| 8 | H | *i*-Pr | OBn | (1h) | 57 (*R*)[c] | 45 | (2h, 3h) |

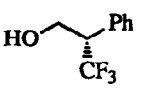
a) Des were determined by capillary GLC. b) All yields are those of isolated compounds. Values in parentheses are conversion yields. c) Configuration of the new asymmetric center of the major isomer.

Triethylborane induces the trifluoromethylation of acetylenes, olefins, silyl enol ethers and ketene silyl acetals with iodotrifluoromethane, as previously reported by Oshima and Utimoto.[6] Although this method has not been applied to enolates,[6] the present authors intend to do so for lithium enolate prepared from *N*-acyloxazolidinone **1**. Several Evans imides (**1b-f**) were synthesized according to the literature,[7] and **1h** was

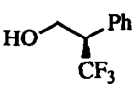
prepared in the same manner as **1b**. After initial studies, acceptable yields were obtained under our standard conditions. Imide **1** was first treated with 1.3 equiv of LDA at -78°C to obtain the lithium enolate. After stirring the solution at the same temperature for 60 min, 5.0 equiv of gaseous iodotrifluoromethane were added with a cannula followed by 1.0 equiv of triethylborane (1.0 M in hexanes) over 1 min. After stirring at -78°C for 10 min and at -20°C for 2 h, the reaction mixture was quenched with saturated ammonium chloride. α-Trifluoromethyl carboximides **2** and their diastereomers **3** were isolated by flash choromatography. The results are summarized in Table 1. Although the starting imides (**1a-g**) except **1h** were partially recovered in the range of 10-38% (entries 1-7), the trifluoromethylated imides (**2**, **3**) were produced in synthetically useful yields. In all cases, significant diastereoselectivity, as determined by GLC analysis of the crude product, was from 44 to 86% de. The structure of imide **1** affected selectivity, and **1e** (R = *t*-Bu) appeared to react most favorably to give the greatest diastereomeric excess (86% de, entry 5). Imide **1g** showed poor selectivity and gave small amounts (2.6%) of *5R*-isomers, along with **2g** and **3g** (entry 7).[8] Stereochemical assignments of minor isomers **3a** and **3h** were made by X-ray crystallography.[9] Relative and absolute stereochemical assignments of the major isomers, **2a**, **2c** and **2h**, were firmly established by conversion to known compounds. The reduction of **2a** with $LiBH_4$, followed by tosylation of the resulting alcohol **4**, gave **5**. Tosylate **5** was converted to benzoate **6** by a 5-step sequence of cyanation, hydrolysis, esterification, reduction and benzoylation. The hydrolysis of **6** afforded the known primary alcohol **7**.[10] The reduction of **2c** with $LiBH_4$ gave **9**, the enantiomer of alcohol **10**.[11] The reduction of **2h** with the same reducing agent gave **11**, which was converted to **12** by Jones oxidation and esterified to afford enantiomer **13** of ester **14**.[12] Primary alcohols, **4**, **9** and **11**, were confirmed enantiomerically pure by $^1H$ and $^{19}F$ NMR spectra of the corresponding Mosher esters. The Mosher ester converted from **2f** was identical with **8** from **2a**.



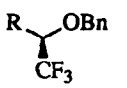

**4** R = OH
**5** R = OTs
**6** R = $CH_2OBz$
**7** R = $CH_2OH$
**8** R = O-(*R*)-MTPA



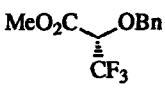

**9**




**10**



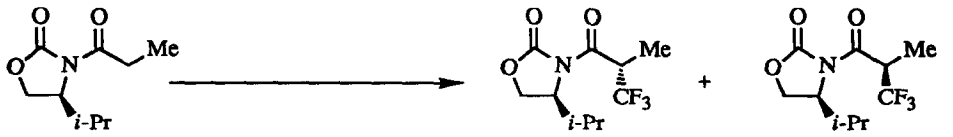

**11** R = $CH_2OH$
**12** R = $CO_2H$
**13** R = $CO_2Me$




**14**

The effects of variation in the trifluoromethylation of imide **1a** shown in Table 2 were determined in terms of diastereoselectivity and chemical yield. Boron enolate (entry 1) decreased diastereomeric excess and chemical yield, compared to standard conditions (Table1, entry 1). The lack of reaction in the absence of triethylborane (entry 2) is evidence that this trifluoromethylation occurs through attack of the trifluoromethyl radical on the lithium enolate.[6] Entry 3 shows decrease in triethylborane to have virtually no effect on diastereoselectivity and the reaction to proceed sufficiently at -78°C. Use of the radical scavenger, galvinoxyl, greatly suppressed trifluoromethylation (entry 4). The reaction was completely inhibited under an argon atmosphere from which all oxygen was removed (entry 5).[13] Entries 4 and 5 present additional evidence for the proposed trifluoromethyl radical mechanism.

**Table 2.** Variation in Conditions for the Trifluoromethylation of Imide **1a**

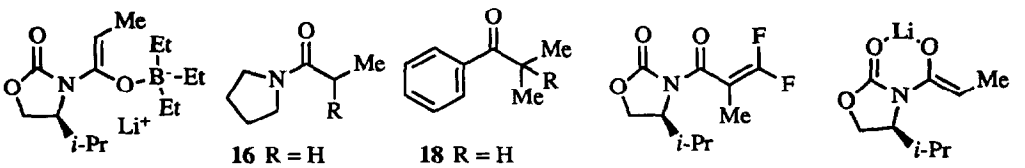


**1a** **2a** **3a**

| Entry | Base | $Et_3B$ (eq) | Additive | Temp.[a] | Product (2, 3) % de[b] | Product (2, 3) % yield(2 + 3)[c] |
|---|---|---|---|---|---|---|
| 1 | *n*-$Bu_2BOTf$-$Et_3N$ | 1.0 | - | A | 23 (*S*)[d] | 10 (12) |
| 2 | LDA | - | - | A | - | - |
| 3 | LDA | 0.2 | - | B | 62 (*S*)[d] | 86 (92) |
| 4 | LDA | 0.2 | galvinoxyl[e] | B | 50 (*S*)[d] | 22 (88) |
| 5 | LDA | 0.2 | without $O_2$[f] | B | - | - |

a) After adding triethylborane, the reaction system was stirred under conditions A (10 min at -78°C and 2 h at -20°C) or B (15 min at -78°C) prior to quenching. b) Des were determined by capillary GLC. c) All yields are those of isolated compounds. Values in parentheses are conversion yields. d) Configuration of the new asymmetric center of the major isomer. e) Twenty mol% of galvinoxyl was used based on **1a**. f) Oxygen was completely removed from argon by passage through a column with BASF R-11 copper pellets. See Experimental Section.

Methylenes adjacent to negatively charged boron atoms show absorption between δ -0.3 and 0.3 in the $^1H$ NMR spectra of tetravalent boron compounds.[14] Treatment of the lithium enolate of **1a** with triethylborane at -78°C showed no absorption in this area, indicating the trifluoromethylation does not proceed via lithium borate **15**.[15]

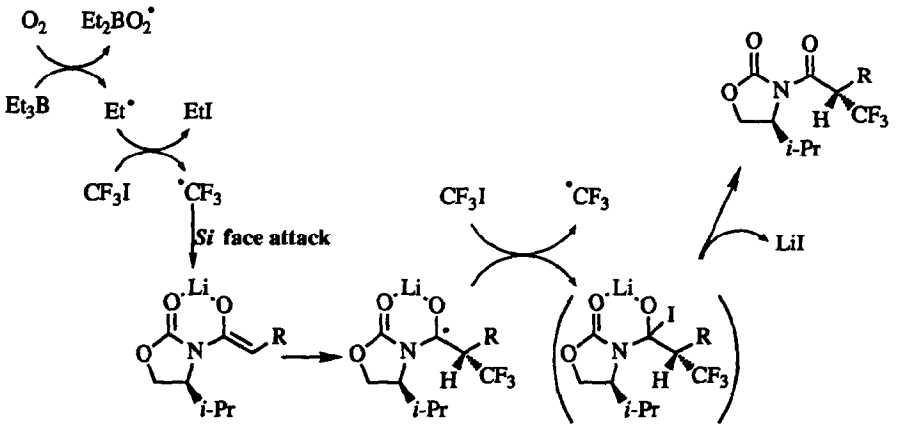


**15** **16** R = H, **17** R = $CF_3$ **18** R = H, **19** R = $CF_3$ **20** **21**

A control experiment with *N*-propionylpyrrolidine **16** under standard conditions failed to provide a trace of the desired product **17**. The rapid enolization of **17** and subsequent removal of a fluoride anion may have given rise to complicated reactions. The lithium enolate of isobutyrophenone **18**, which was recovered in large amount, was converted to a significant yield of the desired product **19**. Treatment of **3a** with 1.5 equiv of LDA at -78°C for 10 min gave a 1:1 mixture of **3a** and β,β-difluoro-α,β-unsaturated imide **20** but no trace of **2a**. After being warmed to -20°C, GLC analysis of the solution showed **3a**:**20** of 1:8.5. Treatment of **3a** with 1.4 equiv of the lithium enolate **21** gave rise to no peaks containing **2a** and **20**, except for **1a** and **3a** in GLC even after stirring at -20°C for 2 h. Thus, during trifluoromethylation, enolization of **2** and **3** would thus appear not to occur. These results support our hypothesis that in the reaction conditions employed the Evans imide system

prevents the trifluoromethylated product from removal of a fluoride anion. The mechanism in Scheme 2 is consistent with the present results. The trifluoromethyl radical reacts on the *Si* face of the lithium imide.

In conclusion, the triethylborane-mediated reaction of the lithium enolate derived from **1** with iodotrifluoromethane makes possible easy access to trifluoromethylated imides **2a-h** with 44-86% diastereoselectivity. Although stereoselectivity in this reaction is not satisfactory, products **2** and **3**, can be easily purified by chromatography to give access to synthetically useful β-trifluoromethyl alcohols of very high enantiomeric purity via reduction with $LiBH_4$.




**Scheme 2**

**Experimental Section**

**General.** Reactions were run under an argon atmosphere with magnetic stirring in flame- or oven-dried glassware. THF and ether were freshly distilled under an argon atmosphere from sodium benzophenone ketyl prior to use. Methylene chloride was distilled under an argon atmosphere from $CaH_2$ immediately before use. Other solvents and reagents were used as supplied or purified. Anhydrous magnesium sulfate was used as the drying agent. Silica gel 60 (Merck, 230-400 mesh) was used for column chromatography. TLC analysis was conducted on a Merck silica gel 60F-254 (0.25 mm, precoated on glass). Analytical gas chromatography (GLC) was carried out on a Shimadzu GC-14A instrument using a GL Science (30-m x 0.25-mm) NEUTRABOND-1 capillary column with a film thickness of 1.5 μm. GLC data were obtained on the mixture of isomers produced by trifluoromethylation.

Melting points were determined with a Yanaco MP-500D hot stage microscope and are not corrected. Optical rotations were measured on a JASCO DIP-370 polarimeter at a wavelength of 589 nm (Na D line) using a 1.0-dm cell with a total volume of 1 ml. Infrared spectra were obtained on a Perkin Elmer 1600 FT-IR either neat or in KBr pellets. Absorption was expressed as reciprocal centimeters ($cm^{-1}$). $^1H$ NMR were recorded at 200 MHz on a Varian Gemini-200 instrument and indicated in parts per million (ppm) downfield from tetramethylsilane as the internal standard (δ) (unless otherwise stated: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad). $^{19}F$ NMR spectra were measured at 188 MHz on a Varian Gemini-200 instrument and given in parts per million (ppm) upfield from $CCl_3F$ as the internal standard. $CDCl_3$ served as solvent for $^1H$ and $^{19}F$ NMR, unless otherwise specified. NOESY spectra were recorded at 500 MHz on a Brucker AMX 500

spectrometer. Low- and high-resolusion mass spectral analyses were performed under 70 eV electron-impact (EI) conditions on a Kratos CONCEPT-1H double focusing magnetic sector spectrometer. Elemental analyses were made at Toray Research Center, Inc., Tokyo. GC-MS analyses were carried out on a Shimadzu GC-14A gas chromatograph coupled with a Shimadzu QP 2000GF mass selective detector using a Shimadzu (30-m x 0.32-mm) CBJ1 capillary column with a film thickness of 0.25 μm.

**Preparation of *N*-Acyloxazolidinones (1).** (*S*)-4-Isopropyl-3-propionyl-2-oxazolidinone (**1a**) and (4*R*,5*S*)-4-methyl-5-phenyl-3-propionyl-2-oxazolidinone (**1g**) were purchased from Aldrich and Fluka. (*S*)-4-Isopropyl-3-(3-phenylpropionyl)-2-oxazolidinone (**1b**), (*S*)-4-isopropyl-3-(2-phenylacetyl)-2-oxazolidinone (**1c**), (*S*)-3-hexanoyl-4-isopropyl-2-oxazolidinone (**1d**), (*S*)-3-(3,3-dimethylbutanoyl)-4-isopropyl-2-oxazolidinone (**1e**) and (*S*)-4-benzyl-3-propionyl-2-oxazolidinone (**1f**) were prepared by literature methods.[7] (*R*)-3-(2-Benzyloxyacetyl)-4-isopropyl-2-oxazodinone (**1h**) was obtained from (*R*)-4-isopropyl-2-oxazolidinone and benzyloxyacetyl chloride in analogy to **1b**. **1h**: colorless needles; mp 83.5-84.8°C (*n*-hexane-$CH_2Cl_2$); $[\alpha]_D^{23}$ -71.6 (c 2.97, $CH_2Cl_2$); IR (KBr) 1764, 1709, 1388, 1128; $^1$H NMR 0.88 (d, $J$ = 7.0 Hz, 3H), 0.93 (d, $J$ = 7.1 Hz, 3H), 2.44 (qqd, $J$ = 7.1, 7.0, 3.8 Hz, 1H), 4.26 (dd, $J$ = 8.9, 3.4 Hz, 1H), 4.34 (dd, $J$ = 8.9, 7.9 Hz, 1H), 4.46 (ddd, $J$ = 7.9, 3.8, 3.4 Hz, 1H), 4.67 (s, 2H), 4.71 (s, 2H), 7.26-7.48 (m, 5H); MS *m/z* 276 [M$^+$-1], 259, 247, 229, 220, 204, 186, 171, 107, 91; HRMS Calcd for $C_{15}H_{18}NO_4$ [M$^+$-H] 276.124, found 276.123; Anal. Calcd for $C_{15}H_{19}NO_4$: C, 65.0; H, 6.9; N, 5.1. Found: C, 64.8; H,7.1; N, 5.1.

**General Procedure for Trifluoromethylations with Lithium Enolates of 1: (2′*S*,4*S*)- and (2′*R*,4*S*)-4-Isopropyl-3-(3′,3′,3′-trifluoro-2′-methylpropionyl)-2-oxazolidinone (2a, 3a).** To a solution of LDA, prepared from diisopropylamine (2.6 mmol, 0.37 ml) and *n*-BuLi (2.39 M in hexanes, 2.6 mmol, 1.1 ml) in THF (3 ml) at 0°C, was added a solution of (*S*)-4-isopropyl-3-propionyl-2-oxazolidinone (**1a**, 370 mg, 2.0 mmol) in THF (3 ml) at -78°C. After 60 min at the same temperature, gaseous iodotrifluoromethane ($CF_3I$, 9.9 mmol, 0.8 ml at -42°C) was added with a cannula followed by triethylborane (1 M in hexanes, 2.0 mmol, 2.0 ml) over 1 min. After stirring at -78°C for 10 min and at -20°C for 2 h, the reaction mixture was quenched with saturated ammonium chloride and extracted with ether. The combined ethereal extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried and filtered. After evaporation of the solvent, chromatography of the residue with *n*-hexane-$CH_2Cl_2$ (2:1) as eluent gave the less polar isomer (**3a**, 55 mg, 10.9%), more polar isomer (**2a**, 299 mg, 59.1%) and starting material **1a** (72 mg, 19.5%): **(2′*R*,4*S*)-4-Isopropyl-3-(3′,3′,3′-trifluoro-2′-methylpropionyl)-2-oxazolidinone (3a, less polar isomer)** colorless prisms; mp 48.6-50.0°C (*n*-hexane); $[\alpha]_D^{23}$ +86.5 (c 4.51, $CHCl_3$); IR (KBr) 2974, 1789, 1699, 1248, 1174; $^1$H NMR 0.89 (d, $J$ = 6.9 Hz, 3H), 0.96 (d, $J$ = 7.0 Hz, 3H), 1.23 (d, $J$ = 7.1 Hz, 3H), 2.37 (qqd, $J$ = 7.0, 6.9, 3.9 Hz, 1H), 4.25 (dd, $J$ = 9.1, 3.3 Hz, 1H), 4.33 (dd, $J$ = 9.1, 7.8 Hz, 1H), 4.51 (ddd, $J$ = 7.8, 3.9, 3.3 Hz, 1H), 4.73 (qq, $J$ = 7.6, 7.1 Hz, 1H); $^{19}$F NMR 69.67 (d, $J$ = 7.6 Hz); MS *m/z* 253 [M$^+$], 210, 197, 167, 125, 97, 86, 69; HRMS Calcd for $C_{10}H_{14}NO_3F_3$ [M$^+$] 253.093, found 253.092; Anal. Calcd for $C_{10}H_{14}NO_3F_3$: C, 47.4; H, 5.6; N, 5.5. Found: C, 47.1; H, 5.5; N, 5.6; **(2′*S*,4*S*)-4-Isopropyl-3-(3′,3′,3′-trifluoro-2′-methylpropionyl)-2-oxazolidinone (2a, more polar isomer)** a viscous oil; $[\alpha]_D^{22}$ +63.7 (c 5.49, $CHCl_3$); IR (KBr) 2968, 1782, 1708, 1244, 1174; $^1$H NMR 0.88 (d, $J$ = 6.9 Hz, 3H), 0.93 (d, $J$ = 7.1 Hz, 3H), 1.42 (d, $J$ = 7.0 Hz, 3H), 2.39 (qqd, $J$ = 7.1, 6.9, 4.0 Hz, 1H), 4.25 (dd, $J$ = 9.1, 4.0 Hz, 1H), 4.32 (dd, $J$ = 9.1, 7.8 Hz, 1H), 4.50 (ddd, $J$ = 7.8, 4.0, 4.0 Hz, 1H), 4.90 (qq, $J$ = 8.0, 7.0 Hz, 1H); $^{19}$F NMR 69.58 (d, $J$ = 8.0 Hz); MS *m/z* 253 [M$^+$], 210, 167, 125, 97, 86, 69; HRMS Calcd for $C_{10}H_{14}NO_3F_3$ [M$^+$] 253.093, found 253.091.

**(2′*S*,4*S*)- and (2′*R*,4*S*)-3-(2′-Benzyl-3′,3′,3′-trifluoropropionyl)-4-isopropyl-2-oxazolidinone (2b, 3b).** The general trifluoromethylation procedure was followed, using 522 mg (2.0 mmol) of (*S*)-4-isopropyl-3-(3-phenylpropionyl)-2-oxazolidinone (**1b**). Chromatography of the residue with *n*-hexane-ethyl acetate (10:1) as eluent gave the less polar isomer (42 mg, 6.4%), more polar isomer (357 mg, 54.2%) and starting material **1b** (124 mg, 23.8%): **less polar isomer** colorless prisms; mp 107.4-108.8°C (*n*-hexane); $[\alpha]_D^{24}$ -12.1 (c 0.60, $CHCl_3$); IR (KBr) 1771, 1711, 1247, 1166; $^1H$ NMR 0.27 (d, *J* = 6.9 Hz, 3H), 0.75 (d, *J* = 7.0 Hz, 3H), 1.84-2.10 (m, 1H), 3.19 (dd, *J* = 13.1, 5.7 Hz, 1H), 3.28 (dd, *J* = 13.1, 10.5 Hz, 1H), 4.09 (dd, *J* = 9.1, 2.9 Hz, 1H), 4.20 (dd, *J* = 9.1, 8.1 Hz, 1H), 4.42 (ddd, *J* = 8.1, 3.4, 2.9 Hz, 1H), 5.37-5.60 (m, 1H), 7.10-7.33 (m, 5H); $^{19}F$ NMR 67.87 (d, *J* = 8.0 Hz); MS *m/z* 329 [M+], 260, 201, 172, 131, 91, 69; HRMS Calcd for $C_{16}H_{18}NO_3F_3$ [M+] 329.124, found 329.123; Anal. Calcd for $C_{16}H_{18}NO_3F_3$: C, 58.4; H, 5.5; N, 4.3. Found: C, 58.4; H, 5.6; N, 4.2; **more polar isomer** colorless prisms; mp 54.6-55.3°C (*n*-hexane); $[\alpha]_D^{24}$ +145.9 (c 0.50, $CHCl_3$); IR (KBr) 1780, 1765, 1713, 1249, 1165; $^1H$ NMR 0.83 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H), 2.15-2.40 (m, 1H), 3.16 (dd, *J* = 13.0, 6.0 Hz, 1H), 3.24 (dd, *J* = 13.0, 10.1 Hz, 1H), 3.84 (dd, *J* = 9.1, 8.4 Hz, 1H), 4.06 (dd, *J* = 9.1, 2.7 Hz, 1H), 4.19 (ddd, *J* = 8.4, 4.0, 2.7 Hz, 1H), 5.28-5.51 (m, 1H), 7.13-7.35 (m, 5H); $^{19}F$ NMR 67.75 (d, *J* = 7.9 Hz); MS *m/z* 329 [M+], 260, 201, 172, 131, 91, 69; HRMS Calcd for $C_{16}H_{18}NO_3F_3$ [M+] 329.124, found 329.124; Anal. Calcd for $C_{16}H_{18}NO_3F_3$: C, 58.4; H, 5.5; N, 4.3. Found: C, 58.3; H, 5.7; N, 4.3.

**(2′*S*,4*S*)- and (2′*R*,4*S*)-4-Isopropyl-3-(3′,3′,3′-trifluoro-2′-phenylpropionyl)-2-oxazolidinone (2c, 3c).** The general trifluoromethylation procedure was followed, using 494 mg (2.0 mmol) of (*S*)-4-isopropyl-3-(2-phenylacetyl)-2-oxazolidinone (**1c**). Chromatography of the residue with *n*-hexane-ethyl acetate (10:1) as eluent gave the less polar isomer (**3c**, 49 mg, 7.8%), more polar isomer (**2c**, 235 mg, 37.3%) and starting material **1c** (190 mg, 38.5%): **(2′*R*,4*S*)-4-Isopropyl-3-(3′,3′,3′-trifluoro-2′-phenylpropionyl)-2-oxazolidinone (3c, less polar isomer)** a viscous oil; $[\alpha]_D^{22}$ -45.6 (c 0.94, $CHCl_3$); IR (neat) 1780, 1712, 1157; $^1H$ NMR 0.47 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), 2.27 (qqd, *J* = 7.0, 6.9, 3.6 Hz, 1H), 4.15 (dd, *J* = 9.2, 3.4 Hz, 1H), 4.31 (dd, *J* = 9.2, 8.6 Hz, 1H), 4.56 (ddd, *J* = 8.6, 3.6, 3.4 Hz, 1H), 5.92 (q, *J* = 8.3 Hz, 1H), 7.35-7.60 (m, 5H); $^{19}F$ NMR 67.12 (d, *J* = 8.3 Hz); MS *m/z* 315 [M+], 295, 186, 159, 109, 86, 69; HRMS Calcd for $C_{15}H_{16}NO_3F_3$ [M+] 315.108, found 315.108; **(2′*S*,4*S*)-4-Isopropyl-3-(3′,3′,3′-trifluoro-2′-phenylpropionyl)-2-oxazolidinone (2c, more polar isomer)** colorless needles; mp 71.0-72.2°C (*n*-hexane-ether); $[\alpha]_D^{21}$ +151.9 (c 1.03, $CHCl_3$); IR (KBr) 1771, 1708, 1256, 1154; $^1H$ NMR 0.93 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H), 2.38-2.61 (m, 1H), 4.11-4.23 (m, 2H), 4.30 (ddd, *J* = 7.2, 4.0, 4.0 Hz, 1H), 6.03 (q, *J* = 8.5 Hz, 1H), 7.30-7.60 (m, 5H); $^{19}F$ NMR 67.16 (d, *J* = 8.5 Hz); MS *m/z* 315 [M+], 295, 186, 159, 109, 86, 69; HRMS Calcd for $C_{15}H_{16}NO_3F_3$ [M+] 315.108, found 315.108; Anal. Calcd for $C_{15}H_{16}NO_3F_3$: C, 57.1; H, 5.1; N, 4.4. Found: C, 57.1; H, 5.3; N, 4.4.

**(2′*S*,4*S*)- and (2′*R*,4*S*)-4-Isopropyl-3-[2′-(trifluoromethyl)hexanoyl]-2-oxazolidinone (2d, 3d).** The general trifluoromethylation procedure was followed, using 454 mg (2.0 mmol) of (*S*)-3-hexanoyl-4-isopropyl-2-oxazolidinone (**1d**). Chromatography of the residue with *n*-hexane-$CH_2Cl_2$ (2:1) as eluent gave the less polar isomer (60 mg, 10.2%), more polar isomer (381 mg, 64.6%) and starting material **1d** (55 mg, 12.1%): **less polar isomer** a viscous oil; $[\alpha]_D^{22}$ +44.7 (c 0.92, $CHCl_3$); IR (neat) 2965, 1783, 1709, 1241, 1166; $^1H$ NMR 0.86-0.95 (m, 3H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H), 1.20-1.50 (m, 4H), 1.75-2.13 (m, 2H), 2.39 (qqd, *J* = 7.0, 7.0, 3.5 Hz, 1H), 4.24 (dd, *J* = 9.2, 3.5 Hz, 1H), 4.32 (dd, *J* = 9.2, 7.7 Hz, 1H), 4.53 (ddd, *J* = 7.7, 3.5, 3.5 Hz, 1H), 4.84-5.07 (m, 1H); $^{19}F$ NMR 67.52 (d, *J* = 8.2 Hz); MS *m/z* 295 [M+], 276, 252, 239, 196, 167, 86, 69; HRMS Calcd for $C_{13}H_{20}NO_3F_3$ [M+] 295.140, found 295.138; **more polar isomer** a viscous

oil; $[\alpha]_D^{20}$ +83.6 (c 1.33, $CHCl_3$); IR (neat) 2937, 1782, 1709, 1239, 1168; $^1H$ NMR 0.88 (d, $J$ = 7.0 Hz, 3H), 0.90 (t, $J$ = 7.0 Hz, 3H), 0.93 (d, $J$ = 7.1 Hz, 3H), 1.15-1.50 (m, 4H), 1.70-2.11 (m, 2H), 2.40 (qqd, $J$ = 7.1, 7.0, 3.8 Hz, 1H), 4.24 (dd, $J$ = 9.2, 3.8 Hz, 1H), 4.31 (dd, $J$ = 9.2, 7.7 Hz, 1H), 4.53 (ddd, $J$ = 7.7, 3.8, 3.8 Hz, 1H), 4.87-5.09 (m, 1H); $^{19}F$ NMR 67.57 (d, $J$ = 8.1 Hz); MS *m/z* 295 [$M^+$], 276, 252, 239, 196, 167, 86, 69; HRMS Calcd for $C_{13}H_{20}NO_3F_3$ [$M^+$] 295.140, found 295.140.

**(2′*S*,4*S*)- and (2′*R*,4*S*)-3-[3′,3′-Dimethyl-2′-(trifluoromethyl)butanoyl]-4-isopropyl-2-oxazolidinone (2e, 3e).** The general trifluoromethylation procedure was followed, using 454 mg (2.0 mmol) of (*S*)-3-(3,3-dimethylbutanoyl)-4-isopropyl-2-oxazolidinone (**1e**). Chromatography of the residue with *n*-hexane-$CH_2Cl_2$ (2:1) as eluent gave the less polar isomer (30 mg, 5.1%), more polar isomer (368 mg, 62.3%) and starting material **1e** (87 mg, 19.1%): **less polar isomer** a viscous oil; $[\alpha]_D^{21}$ +46.9 (c 0.86, $CHCl_3$); IR (neat) 2968, 1764, 1708, 1251, 1155; $^1H$ NMR 0.90 (d, $J$ = 6.9 Hz, 3H), 0.95 (d, $J$ = 7.0 Hz, 3H), 1.19 (s, 9H), 2.38 (qqd, $J$ = 7.0, 6.9, 3.4 Hz, 1H), 4.23 (dd, $J$ = 9.2, 3.4 Hz, 1H), 4.30 (dd, $J$ = 9.2, 7.5 Hz, 1H), 4.56 (ddd, $J$ = 7.5, 3.4, 3.4 Hz, 1H), 5.03 (q, $J$ = 9.3 Hz, 1H); $^{19}F$ NMR 60.43 (d, $J$ = 9.3 Hz); MS *m/z* 295 [$M^+$], 252, 239, 196, 167, 151, 130, 86, 69; HRMS Calcd for $C_{13}H_{20}NO_3F_3$ [$M^+$] 295.140, found 295.137; **more polar isomer** colorless needles; mp 65.4-66.2°C (*n*-hexane); $[\alpha]_D^{21}$ +89.6 (c 1.24, $CHCl_3$); IR (KBr) 2968, 1774, 1707, 1250, 1154; $^1H$ NMR 0.88 (d, $J$ = 6.9 Hz, 3H), 0.93 (d, $J$ = 7.1 Hz, 3H), 1.15 (s, 9H), 2.46 (qqd, $J$ = 7.1, 6.9, 3.9 Hz, 1H), 4.18-4.36 (m, 2H), 4.53 (ddd, $J$ = 6.6, 4.3, 3.9 Hz, 1H), 5.09 (q, $J$ = 9.5 Hz, 1H); $^{19}F$ NMR 60.43 (d, $J$ = 9.5 Hz); MS *m/z* 295 [$M^+$], 239, 196, 167, 151, 130, 86, 69; HRMS Calcd for $C_{13}H_{20}NO_3F_3$ [$M^+$] 295.140, found 295.138; Anal. Calcd for $C_{13}H_{20}NO_3F_3$: C, 52.9; H, 6.8; N, 4.7. Found: C, 52.7; H, 7.0; N, 4.7.

**(2′*S*,4*S*)- and (2′*R*,4*S*)-4-Benzyl-3-(3′,3′,3′-trifluoro-2′-methylpropionyl)-2-oxazolidinone (2f, 3f).** The general trifluoromethylation procedure was followed, using 466 mg (2.0 mmol) of (*S*)-4-benzyl-3-propionyl-2-oxazolidinone (**1f**). Chromatography of the residue with *n*-hexane-$CH_2Cl_2$ (2:1) as eluent gave the less polar isomer (**3f**, 63 mg, 10.5%), more polar isomer (**2f**, 360 mg, 59.8%) and starting material **1f** (47 mg, 10.1%): **(2′*R*,4*S*)-4-Benzyl-3-(3′,3′,3′-trifluoro-2′-methylpropionyl)-2-oxazolidinone (3f, less polar isomer)** a viscous oil; $[\alpha]_D^{21}$ +60.3 (c 1.16, $CHCl_3$); IR (neat) 1792, 1716, 1141; $^1H$ NMR 1.49 (d, $J$ = 7.1 Hz, 3H), 2.81 (dd, $J$ = 13.3, 9.4 Hz, 1H), 3.23 (dd, $J$ = 13.3, 3.3 Hz, 1H), 4.19-4.34 (m, 2H), 4.60-4.84 (m, 2H), 7.18-7.42 (m, 5H); $^{19}F$ NMR 69.63 (d, $J$ = 7.9 Hz); MS *m/z* 301 [$M^+$], 210, 190, 160, 125, 91, 86; HRMS Calcd for $C_{14}H_{14}NO_3F_3$ [$M^+$] 301.093, found 301.092; **(2′*S*,4*S*)-4-Benzyl-3-(3′,3′,3′-trifluoro-2′-methylpropionyl)-2-oxazolidinone (2f, more polar isomer)** a viscous oil; $[\alpha]_D^{21}$ +53.6 (c 1.25, $CHCl_3$); IR (neat) 1772, 1718, 1072; $^1H$ NMR 1.46 (d, $J$ = 7.1 Hz, 3H), 2.80 (dd, $J$ = 13.5, 9.5 Hz, 1H), 3.31 (dd, $J$ = 13.5, 3.3 Hz, 1H), 4.19-4.31 (m, 2H), 4.75-4.77 (m, 1H), 4.82 (qq, $J$ = 7.9, 7.1 Hz, 1H), 7.15-7.40 (m, 5H); $^{19}F$ NMR 69.51 (d, $J$ = 7.9 Hz); MS *m/z* 301 [$M^+$], 257, 210, 190, 160, 125, 91, 86; HRMS Calcd for $C_{14}H_{14}NO_3F_3$ [$M^+$] 301.093, found 301.093.

**(2′S,4*R*,5*S*)- and (2′S,4*R*,5*S*)-4-Methyl-5-phenyl-3-(3′,3′,3′-trifluoro-2′-methylpropionyl)-2-oxazolidinone (2g, 3g).** The general trifluoromethylation procedure was followed, using 466 mg (2.0 mmol) of (4*R*,5*S*)-4-methyl-5-phenyl-3-propionyl-2-oxazolidinone (**1g**). Chromatography of the residue containing four isomers on a Kusano CPS-HS-221-1 silica gel column using *n*-hexane-ethyl acetate (30:1) as eluent gave the less polar isomer of (4*R*,5*S*)-ones (49 mg, 8.1%), more polar isomer of (4*R*,5*S*)-ones (124 mg, 20.6%), less polar isomer of (4*R*,5*R*)-ones (13 mg, 2.2%), more polar isomer of (4*R*,5*R*)-ones (2.9 mg, 0.5%) and starting material **1g** (122 mg, 26.2%): **less polar isomer of (4*R*,5*S*)-ones** a viscous oil; $[\alpha]_D^{23}$ +21.6 (c 0.56, $CHCl_3$); IR (neat) 1790, 1714, 1247, 1156; $^1H$ NMR 0.92 (d, $J$ = 6.6 Hz, 3H), 1.48 (d, $J$ = 7.1 Hz, 3H), 4.75 (qq, $J$ =

8.0, 7.1 Hz, 1H), 4.83 (qd, $J$ = 7.1, 6.6 Hz, 1H), 5.73 (d, $J$ = 7.1 Hz, 1H), 7.27-7.50 (m, 5H); $^{19}$F NMR 69.62 (d, $J$ = 8.0 Hz); MS $m/z$ 301 [M$^+$], 282, 257, 231, 176, 125, 107, 97; HRMS Calcd for $C_{14}H_{14}NO_3F_3$ [M$^+$] 301.093, found 301.092; **more polar isomer of (4*R*,5*S*)-ones** a viscous oil; $[\alpha]_D^{21}$ +26.8 (c 1.68, $CHCl_3$); IR (neat) 1790, 1715, 1246, 1156; $^1$H NMR 0.92 (d, $J$ = 6.6 Hz, 3H), 1.47 (d, $J$ = 7.1 Hz, 3H), 4.70-4.98 (m, 2H), 5.71 (d, $J$ = 7.5 Hz, 1H), 7.27-7.50 (m, 5H); $^{19}$F NMR 69.64 (d, $J$ = 8.0 Hz); MS $m/z$ 301 [M$^+$], 282, 257, 231, 176, 125, 107, 97; HRMS Calcd for $C_{14}H_{14}NO_3F_3$ [M$^+$] 301.093, found 301.094; **less polar isomer of (4*R*,5*R*)-ones** a viscous oil; IR (neat) 1774, 1718, 1216, 1136; $^1$H NMR 1.43 (d, $J$ = 7.1 Hz, 3H), 1.57 (d, $J$ = 6.2 Hz, 3H), 4.44 (qd, $J$ = 6.2, 4.9 Hz, 1H), 4.83 (qq, $J$ = 8.0, 7.1 Hz, 1H), 5.12 (d, $J$ = 4.9 Hz, 1H), 7.27-7.50 (m, 5H); $^{19}$F NMR 69.68 (d, $J$ = 8.0 Hz); MS $m/z$ 301 [M$^+$], 257, 231, 176, 125, 107, 97; HRMS Calcd for $C_{14}H_{14}NO_3F_3$ [M$^+$] 301.093, found 301.092; **more polar isomer of (4*R*,5*R*)-ones** a viscous oil; IR (neat) 1780, 1712, 1253, 1146; $^1$H NMR 1.48 (d, $J$ = 7.1 Hz, 3H), 1.57 (d, $J$ = 6.4 Hz, 3H), 4.48 (qd, $J$ = 6.4, 4.0 Hz, 1H), 4.82 (qq, $J$ = 7.9, 7.1 Hz, 1H), 5.10 (d, $J$ = 4.0 Hz, 1H), 7.24-7.50 (m, 5H); $^{19}$F NMR 69.64 (d, $J$ = 7.9 Hz); MS $m/z$ 301 [M$^+$], 257, 231, 176, 125, 107, 97; HRMS Calcd for $C_{14}H_{14}NO_3F_3$ [M$^+$] 301.093, found 301.094. NOESY of the (4*R*,5*R*)-isomer showed association between 4-$CH_3$ and 5-H, while that of the (4*R*,5*S*)-one did not show such association.

**(2′*R*,4*R*)- and (2′*S*,4*R*)-3-(2′-Benzyloxy-3′,3′,3′-trifluoropropionyl)-4-isopropyl-2-oxazolidinone (2h, 3h).** The general trifluoromethylation procedure was followed, using 554 mg (2.0 mmol) of (*R*)-3-(2-benzyloxyacetyl)-4-isopropyl-2-oxazodinone (**1h**). Chromatography of the residue with *n*-hexane-ethyl acetate (10:1) as eluent gave the less polar isomer (**3h**, 74 mg, 10.7%) and more polar isomer (**2h**, 237 mg, 34.4%): **(2′*S*,4*R*)-3-(2′-Benzyloxy-3′,3′,3′-trifluoropropionyl)-4-isopropyl-2-oxazolidinone (3h, less polar isomer)** colorless needles; mp 57.7-60.2°C (*n*-hexane-ether); $[\alpha]_D^{21}$ -26.5 (c 1.06, $CHCl_3$); IR (KBr) 1801, 1780, 1703, 1253, 1202, 1148; $^1$H NMR 0.76 (d, $J$ = 6.8 Hz, 3H), 0.90 (d, $J$ = 7.0 Hz, 3H), 2.32 (qqd, $J$ = 7.0, 6.8, 3.5 Hz, 1H), 4.24 (dd, $J$ = 9.0, 3.5 Hz, 1H), 4.31 (dd, $J$ = 9.0, 7.6 Hz, 1H), 4.45 (ddd, $J$ = 7.6, 3.5, 3.5 Hz, 1H), 4.78 (d, $J$ = 11.6 Hz, 1H), 4.85 (d, $J$ = 11.6 Hz, 1H), 5.93 (q, $J$ = 6.1 Hz, 1H), 7.21-7.45 (m, 5H); $^{19}$F NMR 73.71 (d, $J$ = 6.1 Hz); MS $m/z$ 254 [M$^+$-Bn], 239, 196, 107, 91, 69; HRMS Calcd for $C_9H_{11}NO_4F_3$ [M$^+$-Bn] 254.064, found 254.064; Anal. Calcd for $C_{16}H_{18}NO_4F_3$: C, 55.7; H, 5.3; N, 4.1. Found: C, 55.9; H, 5.3; N, 4.0; **(2′*R*,4*R*)-3-(2′-Benzyloxy-3′,3′,3′-trifluoropropionyl)-4-isopropyl-2-oxazolidinone (2h, more polar isomer)** a viscous oil; $[\alpha]_D^{20}$ -74.0 (c 1.27, $CHCl_3$); IR (neat) 1783, 1716, 1250, 1149; $^1$H NMR 0.82 (d, $J$ = 7.0 Hz, 3H), 0.88 (d, $J$ = 7.1 Hz, 3H), 2.31 (qqd, $J$ = 7.1, 7.0, 3.9 Hz, 1H), 4.07-4.22 (m, 2H), 4.26 (ddd, $J$ = 8.1, 3.9, 3.9 Hz, 1H), 4.70 (d, $J$ = 11.5 Hz, 1H), 4.85 (d, $J$ = 11.5 Hz, 1H), 5.96 (q, $J$ = 6.1 Hz, 1H), 7.30-7.43 (m, 5H); $^{19}$F NMR 73.75 (d, $J$ = 6.1 Hz); MS $m/z$ 254 [M$^+$-Bn], 239, 196, 107, 91, 69; HRMS Calcd for $C_9H_{11}NO_4F_3$ [M$^+$-Bn] 254.064, found 254.064.

**Absolute Configuration of (2′*S*,4*S*)-4-Isopropyl-3-(3′,3′,3′-trifluoro-2′-methylpropionyl)-2-oxazolidinone (2a): (*S*)-3,3,3-Trifluoro-2-methyl-*O*-(*p*-toluenesulfonyl)propanol (5).** To a solution of $LiBH_4$ (103 mg, 4.7 mmol) in ether (5 ml) at 0°C was added dropwise a solution of **2a** (1.0 g, 3.95 mmol) in the same solvent (5 ml). After 2 h at 0°C, the reaction mixture was quenched with 2 N aqueous HCl and saturated ammonium chloride and extracted with ether. The combined ethereal extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried and filtered. After careful removal of ether, the residue was dissolved in pyridine (5 ml) and *p*-toluenesulfonyl chloride (1.1 g, 5.8 mmol) was added at 0°C. After 60 min at the same temperature, the reaction mixture was brought to and left at room temperature for 18 h, diluted with water and extracted with ether. The combined ether extracts were washed with 2 N aqueous HCl, saturarated

aqueous $NaHCO_3$ and brine, dried and filtered. After evaporation of the solvent, chromatography of the residue with *n*-hexane as eluent gave **5** (837 mg, 75.1%): a colorless oil; IR (neat) 1599, 1367, 1259, 1178, 993; $^1H$ NMR 1.17 (d, $J$ = 7.1 Hz, 3H), 2.46 (s, 3H), 2.58 (m, 1H), 3.97 (dd, $J$ = 10.3, 6.8 Hz, 1H), 4.16 (dd, $J$ = 10.3, 5.3 Hz, 1H), 7.37 (d, $J$ = 8.0 Hz, 2H), 7.80 (d, $J$ = 8.0 Hz, 2H); $^{19}F$ NMR 72.03 (d, $J$ = 8.4 Hz).

**(*S*)-*O*-Benzoyl-4,4,4-trifluoro-3-methylbutanol (6).** A mixture of **5** (836 mg, 2.96 mmol), KCN (856 mg, 13.1 mmol), 18-Crown-6 (72 mg, 0.27 mmol) and acetonitrile (1.6 ml) was refluxed for 46 h and diluted with ether and $H_2O$. The organic layer was washed with $H_2O$ and brine, dried and filtered. After evaporation of the solvent, the residue was resolved in 47% aqueous HBr (10 ml), and the mixture was refluxed for 18 h and extracted with ether. The ethereal extracts were washed with $H_2O$ and brine, dried and filtered. Afer evaporation of the solvent, the residue was resolved in ether, and the mixture was treated with a solution of diazomethane in the same solvent at 0°C until the light yellow color ceased to fade. The reaction mixture was quenched with formic acid and extracted with ether. The combined ethereal extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried and filtered. After removal of the solvent, the residue was dissolved in ether (5 ml). The ethereal solution was added dropwise to $LiAlH_4$ (112 mg, 2.96 mmol) in the same solvent (2 ml) at 0°C. The reaction mixture was stirred at room temperature for 3 h, quenched with 2 N $H_2SO_4$ and extracted with ether. The ethereal extracts were washed with $H_2O$, saturated aqueous $NaHCO_3$ and brine, dried and filtered. After evaporation of the solvent, the residue was resolved in pyridine (2 ml), and benzoyl chloride(490 mg, 3.49 mmol) was added at 0°C. After 30 min at the same temperature, the reaction mixture was stirred at room temperature for 4 h, diluted with $H_2O$ and extarcted with ether. The combined ether extracts were washed with 2 N aqueous HCl, saturarated aqueous $NaHCO_3$ and brine, dried and filtered. After evaporation of the solvent, chromatography of the residue with *n*-hexane-ethyl acetate (30:1) as eluent gave **6** (59 mg, 8.1%): a colorless oil; $^1H$ NMR 1.21 (d, $J$ = 7.0 Hz, 3H), 1.67-1.86 (m, 1H), 2.14-2.58 (m, 2H), 4.22-4.51 (m, 2H), 7.41-7.63 (m, 3H), 8.00-8.09 (m, 2H); $^{19}F$ NMR 73.82 (d, $J$ = 8.9 Hz); MS *m/z* 246 [$M^+$], 178, 122, 105, 77, 69; HRMS Calcd for $C_{12}H_{13}O_2F_3$ [$M^+$] 246.087, found 246.087.

**(*S*)-4,4,4-Trifluoro-3-methylbutanol (7).** To a solution of **6** (54 mg, 0.22 mmol) in methanol-$H_2O$(1:1, 0.5 ml) at room temperature was added anhydrous KOH (50 mg, 0.89 mmol). The reaction mixture was stirred at the same temperature for 60 min and diluted with ether and water. The organic layer was washed with brine, dried and filtered. After evaporation of the solvent, the bulb-to-bulb distillation of the residue gave **7** (12 mg, 38.5%): a colorless oil; $[\alpha]_D^{23}$ -16.5 (c 0.56, $CHCl_3$), [lit. $[\alpha]_D^{26}$ -13.8 (c 0.94, $CHCl_3$)].[10a] This mterial was identical by IR and $^1H$ NMR with a racemic 4,4,4-trifluoro-3-methylbutanol.[10b]

**Mosher Ester of (*S*)-3,3,3-Trifluoro-2-methylpropanol (8).** To a solution of $LiBH_4$ (15 mg, 0.69 mmol) in ether (2 ml) at 0°C was added dropwise a solution of **2a** (137 mg, 0.54 mmol) in the same solvent (2 ml). After 2 h at 0°C, the reaction mixture was quenched with 2 N aqueous HCl and saturated ammonium chloride and extracted with ether. The combined ethereal extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried, and filtered. After careful removal of ether, the residue was dissolved in pyridine (2 ml), and (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (410 mg, 1.62 mmol) was added at 0°C. After 60 min at 0°C, the reaction mixture was brought to and left at room temperature for 18 h, diluted with water and extarcted with ether. The combined ether extracts were washed with 2 N aqueous HCl, saturarated aqueous $NaHCO_3$ and brine, dried and filtered. After evaporation of the solvent, chromatography of the residue with *n*-hexane-ethyl acetate (20:1) as eluent gave **8** (134 mg, 72.1%): a colorless oil; $^1H$ NMR 1.16 (d, $J$ = 7.1 Hz, 3H), 2.50-2.79 (m, 1H), 3.55 (br s, 3H), 4.29 (dd, $J$ = 11.5, 6.1 Hz, 1H), 4.50 (dd, $J$ = 11.5, 5.6 Hz, 1H),

7.30-7.60 (m, 5H); $^{19}$F NMR 72.02 (s, 3F), 72.16 (d, $J$ = 8.6 Hz, 3F); MS *m/z* 344 [M$^+$], 325, 314, 275, 189, 158, 127, 77, 69; HRMS Calcd for $C_{14}H_{14}O_3F_6$ [M$^+$] 344.085, found 344.085.

**Absolute Configuration of (2′*S*,4*S*)-4-Isopropyl-3-(3′,3′,3′-trifluoro-2′-phenylpropionyl)-2-oxazolidinone (2c).** To a solution of $LiBH_4$ (44 mg, 2.0 mmol) in ether (5 ml) at 0°C was added dropwise a solution of **2c** (516 mg, 1.64 mmol) in the same solvent (5 ml). After 6.5 h at room temperature, the reaction mixture was quenched with 2 N aqueous HCl and saturated ammonium chloride and extracted with ether. The combined ethereal extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried and filtered. After evaporation of the solvent, chromatography of the residue with *n*-pentane-ether (3:1) as eluent gave (*S*)-3,3,3-trifluoro-2-phenylpropanol (**9**, 243 mg, 78.1%). Recrystallization from *n*-pentane-ether at -20°C gave a crystalline solid: mp 51.9-52.1°C; $[\alpha]_D^{22}$ -37.3 (c 2.29, $CHCl_3$), [lit. (*R*)-3,3,3-trifluoro-2-phenylpropanol mp 51-52°C; $[\alpha]_D^{24.4}$ +37.79 (c 5.08, $CHCl_3$)].[11]

**Absolute Configuration of (2′*R*,4*R*)-3-(2′-Benzyloxy-3′,3′,3′-trifluoropropionyl)-4-isopropyl-2-oxazolidinone (2h): (*R*)-2-Benzyloxy-3,3,3-trifluoropropanol (11).** To a solution of $LiBH_4$ (24 mg, 1.1 mmol) in ether (5 ml) at 0°C was added dropwise a solution of **2h** (300 mg, 0.87 mmol) in the same solvent (5 ml). After 60 min at 0°C, the reaction mixture was quenched with 2 N aqueous HCl and saturated ammonium chloride and extracted with ether. The combined ethereal extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried and filtered. After evaporation of the solvent, chromatography of the residue with *n*-hexane-ethyl acetate (5:1) as eluent gave **11** (95 mg, 49.7%): a colorless oil; IR (neat) 3418, 1171, 1139; $^1$H NMR 1.85-1.92 (m, 1H), 3.67-3.98 (m, 3H), 4.66 (d, $J$ = 11.7 Hz, 1H), 4.93 (d, $J$ = 11.7 Hz, 1H), 7.38 (br s, ,5H); $^{19}$F NMR 75.04 (d, $J$ = 6.4 Hz); MS *m/z* 220 [M$^+$], 149, 107, 91; HRMS Calcd for $C_{10}H_{11}O_2F_3$ [M$^+$] 220.071, found 220.070.

**Methyl (*R*)-2-Benzyloxy-3,3,3-trifluoropropionate (13).** To a solution of **11** (83 mg, 0.38 mmol) in ether (5 ml) at 0°C was added dropwise a solution of anhydrous $CrO_3$ (1.0 g) and $H_2SO_4$ (1.1 ml) in water (5 ml). After stirring at 0°C for 8 h and at room temperature for 18 h, the reaction mixture was extracted with ether. The ethereal extracts were washed with water, saturated aqueous $NaHCO_3$ and brine, dried and filtered. Afer evaporation of the solvent, the residue was resolved in ether, and the mixture was treated with a solution of diazomethane in the same solvent at 0°C until the light yellow color ceased to fade. The reaction mixture was quenched with formic acid and extracted with ether. The combined ethereal extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried and filtered. After evaporation of the solvent, chromatography of the residue with *n*-hexane-ethyl acetate (20:1) as eluent gave **13** (65 mg, 69.5%) as a colorless oil: The $^1$H and $^{19}$F NMR spectra of this material were in agreement with the literature data of the (*S*)-isomer. $[\alpha]_D^{22}$ -59.1 (c 1.97, $CHCl_3$), [lit. methyl (*S*)-benzyloxy-3,3,3-trifluoropropionate $[\alpha]_D$ +65.1 (c 1.00, $CHCl_3$)].[12]

**Absolute Configuration of (2′*S*,4*S*)-4-Benzyl-3-(3′,3′,3′-trifluoro-2′-methylpropionyl)-2-oxazolidinone (2f).** To a solution of $LiBH_4$ (16 mg, 0.73 mmol) in ether (2 ml) at 0°C was added dropwise a solution of **2f** (163 mg, 0.54 mmol) in the same solvent (2 ml). After 2 h at 0°C, the reaction mixture was quenched with 2 N aqueous HCl and saturated ammonium chloride and extracted with ether. The combined ethereal extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried and filtered. After careful removal of ether, the residue was dissolved in pyridine (5 ml), and (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (1.1 g, 4.4 mmol) was added at 0°C. After 60 min at the same temperature, the reaction mixture was brought to and left at room temperature for 18 h, diluted with water and extarcted with ether. The combined ether extracts were washed with 2 N aqueous HCl, saturated aqueous

$NaHCO_3$ and brine, dried and filtered. After evaporation of the solvent, chromatography of the residue with *n*-hexane-ethyl acetate (20:1) as eluent gave **8** (126 mg, 67.6%).

**Trifluoromethylation with the Boron Enolate of 1a.** To a solution of **1a** (185 mg, 1.0 mmol) in $CH_2Cl_2$ (2 ml) at -78°C were added *n*-$Bu_2BOTf$ (395 mg, 1.4 mmol, prepared according to T. Mukaiyama *et al.*)[16] and $Et_3N$ (220 μl, 1.5 mmol). After stirring at -78°C for 30 mim and at 0°C for 60 min, the solution was cooled to -78°C and gaseous iodotrifluoromethane ($CF_3I$, 5.0 mmol, 0.4 ml at -42°C) was added with a cannula followed by triethylborane (1 M in hexanes, 1.0 mmol, 1.0 ml) over 1 min. After 2 h at -78°C and 10 h at -20°C, the reaction mixture was poured into methanol (3 ml) followed by the addition of pH 7.0 phosphate buffer (0.1 M, 1.5 ml). The resultant mixture was allowed to warm to 0°C, and 30% $H_2O_2$-methanol (1.5 ml-4.5 ml) was added. After stirring at room temperature for an additional 60 min, the mixture was concentrated in vacuo. The residue was diluted with 10% aqueous $NaHCO_3$ and extracted with $CH_2Cl_2$. The combined organic extracts were washed with brine, dried and filtered. After evaporation of the solvent, chromatography of the residue with *n*-hexane-$CH_2Cl_2$ (2:1) as eluent gave **3a** (7.5 mg, 3.0%), **2a** (18.3 mg, 7.2%) and starting material **1a** (27.3 mg, 14.7%).

**Trifluoromethylation of the Lithium Enolate of 1a with 0.2 equivalents of Triethylborane at -78°C.** To a solution of LDA, prepared from diisopropylamine (2.6 mmol, 0.37 ml) and *n*-BuLi (2.39 M in hexanes, 2.6 mmol, 1.1 ml) in THF (3 ml) at 0°C, was added a solution of **1a** (370 mg, 2.0 mmol) in THF (3 ml) at -78°C. After 60 min at the same temperature, gaseous iodotrifluoromethane ($CF_3I$, 9.9 mmol, 0.8 ml at -42°C) was added with a cannula followed by triethylborane (1 M in hexanes, 0.4 mmol, 0.4 ml) over 1 min. After 15 min at -78°C, the reaction mixture was quenched with saturated ammonium chloride and extracted with ether. The combined ethereal extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried and filtered. After evaporation of the solvent, chromatography of the residue with *n*-hexane-$CH_2Cl_2$ (2:1) as eluent gave **3a** (84 mg, 16.6%), **2a** (351 mg, 69.4%) and starting material **1a** (24.8 mg, 6.7%).

**Trifluoromethylation of the Lithium Enolate of 1a in the Presence of Galvinoxyl.** To a solution of LDA, prepared from diisopropylamine (1.3 mmol, 0.15 ml) and *n*-BuLi (2.39 M in hexanes, 1.3 mmol, 0.54 ml) in THF (1.5 ml) at 0°C, was added a solution of **1a** (185 mg, 1.0 mmol) in THF (1.5 ml) at -78°C. After 60 min at -78°C, iodotrifluoromethane ($CF_3I$, 5.0 mmol, 0.4 ml at -42°C), galvinoxyl (84 mg, 0.2 mmol) and triethylborane (1 M in hexanes, 0.2 mmol, 0.2 ml) were slowly added. After 15 min at -78°C, the reaction mixture was quenched with saturated ammonium chloride and extracted with ether. The combined ethereal extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried and filtered. After evaporation of the solvent, chromatography of the residue with *n*-hexane-$CH_2Cl_2$ (2:1) as eluent gave **3a** (12 mg, 4.7%), **2a** (44 mg, 17.4%) and starting material **1a** (139 mg, 75.1%).

**Trifluoromethylation of the Lithium Enolate of 1a under Complete Removal of Oxygen.** The reaction was carried out using 185 mg (1.0 mmol) of **1a** according to the general trifluoromethylation procedure except for the following: 1) The reaction was carried out using standard Schlenk and vacuum line techniques under argon from which all oxygen was removed by passage through a column with BASF R-11 copper pellets activated with $H_2$ prior to use. 2) All solutions and reagents were degassed by three consecutive freeze-pump-thaw cycles. Chromatography of the residue with *n*-hexane-$CH_2Cl_2$ (2:1) as eluent recovered starting material **1a** (168 mg, 90.8%).

**Trifluoromethylation of the Lithium Enolate of *N*-Propionylpyrrolidine (16).** The general trifluoromethylation procedure was followed, using **16** (254 mg, 2.0 mmol). The reaction gave an unseparable complex mixture, and $^{19}F$ NMR showed no $CF_3$ peak.

**Trifluoromethylation of the Lithium Enolate of Isobutyrophenone (18).** The general trifluoromethylation procedure was followed, using **18** (296 mg, 2.0 mmol). Chromatography of the residue with *n*-hexane-$CH_2Cl_2$ (10:1) as eluent gave 3,3,3-trifluoro-2,2-dimethylpropiophenone (**19**, 86 mg, 19.9%) and recovered **18** (470 mg, 79.4%): **3,3,3-Trifluoro-2,2-dimethylpropiophenone (19)** a colorless oil; IR (neat) 1686, 1127; $^1H$ NMR 1.56 (s, 6H), 7.37-7.57 (m, 3H), 7.62-7.70 (m, 2H); $^{19}F$ NMR 73.06 (s); MS *m/z* 216 [$M^+$], 201, 147, 105, 77, 69; HRMS Calcd for $C_{11}H_{11}OF_3$ [$M^+$] 216.076, found 216.076.

**Treatment of (2′*R*,4*S*)-4-Isopropyl-3-(3′,3′,3′-trifluoro-2′-methylpropionyl)-2-oxazolidinone (3a) with LDA.** To a solution of LDA (0.1 mmol) in THF (140 µl) was added a solution of **3a** (16.5 mg, 65 µmol) in THF (0.5 ml) at -78°C. After 10 min at -78°C, analytical gas chromatography (GLC) showed a 1:1 mixture of **3a** and (*S*)-3-(3,3-difluoro-2-methylpropenoyl)-4-isopropyl-2-oxazolidinone (**20**). After the reaction mixture allowed to warm to -20°C, GLC alalysis showed a ratio of 1:8.5. **(*S*)-3-(3,3-difluoro-2-methylpropenoyl)-4-isopropyl-2-oxazolidinone (20)** was determined by $^1H$ NMR, $^{19}F$ NMR and GC-MS: $^1H$ NMR 0.90 (t, $J$ = 6.9 Hz, 3H), 0.93 (t, $J$ = 7.1 Hz, 3H), 1.88 (dd, $J$ = 2.9, 2.9 Hz, 3H), 2.39 (qqd, $J$ = 7.1, 6.9, 4.3 Hz, 1H), 4.21 (dd, $J$ = 8.5, 4.3 Hz, 1H), 4.32 (dd, $J$ = 8.5, 8.5 Hz, 1H), 4.52 (ddd, $J$ = 8.5, 4.3, 4.3 Hz, 1H); $^{19}F$ NMR 78.04 (dq, $J$ = 22.5, 2.9 Hz, 1F), 83.51 (dq, $J$ = 22.5, 2.9 Hz, 1F); MS *m/z* 233 [$M^+$], 190, 165, 105.

**Treatment of 3a with the Lithium Enolate of 1a.** To a solution of LDA (0.13 mmol) in THF (180 µl) was added a solution of **1a** (18.5 mg, 0.1 mmol) in THF (0.5 ml) at -78°C. After 60 min at -78°C, a solution of **3a** (18 mg, 71 µmol) in THF (0.5ml) was added. The reaction mixture was stirred at -78°C for 10 min and at -20°C for 2 h. After quenching with saturated ammonium chloride and extraction with ether, analytical gas chromatography (GLC) did not show any peak except **1a** and **3a**.

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8. This partial epimerization at C5 during reaction may have proceeded through a tertiary benzyl radical.
9. X-ray structure analysis was conducted by Dr. M. Shiro of Rigaku Corporation, Tokyo, Japan. Crystal data for **3a**: $C_{10}H_{14}NO_3F_3$, 253.22, colorless prism, 0.35 x 0.35 x 0.35 mm, orthorhombic, space group $P2_12_12_1$; $a$ = 9.883 (1) Å, $b$ = 18.314 (2) Å, $c$ = 6.638 (1) Å; $V$ = 1201.4 (2) Å$^3$; $Z$ =4; $D_{calc}$ = 1.40 g/cm$^3$; F (000) = 528. The diffraction data were collected on a Rigaku AFC5R diffractometer at 23°C in the $\omega$-$2\theta$ mode using Cu-$K_\alpha$ radiation ($\mu$ = 11.34 cm$^{-1}$, $\lambda$ = 1.54178 Å) to a maximum $2\theta$ value of 120°. The structure was solved by direct methods. The final cycle of full-matrix least-squares refinement was based on 977 unique reflections ($I > 3\sigma(I)$) and 155 variable parameters and converged with unweighted and weighted agreement factor of $R$ = 0.048 ($R_w$ = 0.070). All calculation were performed using the TEXSAN crystallographic software package of Molecular Structure Corporation. Crystal data for **3h**: $C_{16}H_{18}NO_4F_3$, 345.32, colorless prism, 0.3 x 0.3 x 0.3 mm, orthorhomic, space group $P2_12_12_1$; $a$ = 9.920 (2) Å, $b$ = 31.374 (3) Å, $c$ = 5.333 (2) Å; $V$ = 1659.6 (7) Å$^3$; $Z$ = 4; $D_{calc}$ = 1.38 g/cm$^3$; F (000) =720; $\mu$ (Cu-$K_\alpha$) = 10.46 cm$^{-1}$; $\lambda$ = 1.54178 Å. The structure was solved by direct methods and refined by a full-matrix least-squares procedure to $R$ = 0.041 and $R_w$ = 0.058 for 1163 unique reflections ($I > 3\sigma(I)$).
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