Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 4, pp. 1205-1215, 1996

0957-4166/96 $15.00 + 0.00

S0957-4166(96)00127-9

Diastereoselective Bromodifluoromethylation and Difluoromethylation of Chiral Imide Enolates via Insertion of Difluorocarbene

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Abstract: Lithium enolates of chiral *N*-acyloxazolidinones reacted with dibromodifluoromethane and bromodifluoromethane to give α-bromodifluoromethyl and α-difluoromethyl carboximides, respectively, with good diastereomeric excess. These reactions proceed not via a radical mechanism but via an ionic chain mechanism involving insertion of difluorocarbene.

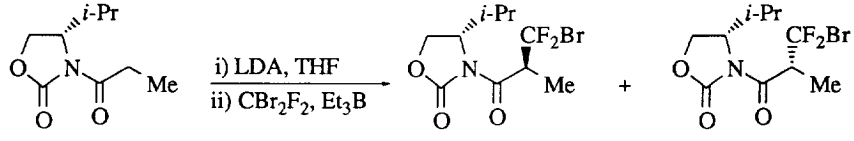
The synthesis of chiral fluoroorganic compounds is an important aspect of organofluorine chemistry in connection with biological and medicinal chemistry, due to the influence of the unique properties of fluorine on biological activity.[1] Recently, these compounds have become focal points of interest due to potential application to optoelectronic substances such as liquid crystals.[2] Fluorine-containing molecules with unexpected and generally unusual reactivity are often difficult to synthesize, and methodologies for synthesizing nonfluorinated chiral compounds are frequently impractical, giving rise to the term, "flustrate" by Seebach.[3] We previously established means for conducting the diastereoselective trifluoromethylation (CF_3),[4] (ethoxycarbonyl)difluoromethylation (CF_2CO_2Et)[5] and perfluoroalkylation[6] of chiral *N*-acyloxazolidinones **1** via a radical mechanism. This paper presents the diastereoselective bromodifluoromethylation[7] and difluoromethylation of **1** via an ionic chain mechanism involving insertion of difluorocarbene.

RESULTS AND DISCUSSION

Bromodifluoromethylation. *N*-Propionyloxazolidinone **1a** was used in the initial optimization since the stereochemistry of the major product **2a**[8] has been established (Table 1). This optimization was conducted by a modification of the standard procedure for trifluoromethylation which proceeds via a radical chain mechanism.[4] Thus, dibromodifluoromethane (CBr_2F_2) was added to the lithium enolate derived *in situ* from **1a** and lithium diisopropylamide (LDA) in tetrahydrofuran (THF) followed by the addition of 1 equiv of triethylborane (Et_3B, 1.0 M solution in hexanes) over 1 min at -78°C. The reaction system was allowed to warm to 0°C over 3 h. After workup in the usual manner, α-bromodifluoromethyl carboximides, **2a** and **3a**, were obtained with 61% diastereoselectivity but unfortunately, only in limited yields (9%) along with significant amounts (6%) of unexpected product **4a** (entry 1). It should be pointed out, however, that the products were obtained in 10% yield even *in the absence of* Et_3B (entry 2).[9] It was subsequently found that adjusting the concentration of lithium enolate solution by removing THF and diisopropylamine prior to

CBr_2F_2 addition *in vacuo* at -20°C affected the improvement of the product yield. The concentrated enolate was treated with CBr_2F_2 at -20°C and the reaction mixture was stirred at -20°C for 2 h to give the bromodifluoromethylated products in 43% yield and 69% de (entry 3). Dilution of the concentrated enolate with THF prior to CBr_2F_2 addition gave a better yield (51%, entry 4). The highest chemical yield and good diastereoselectivity were achieved using 1,2-dimethoxyethane (DME) as the diluent (59% yield and 68% de, entry 5). Treatment of the diluted enolate with CBr_2F_2 followed by the addition of 1 equiv of Et_3B did not affect the degree of diastereomeric excess nor chemical yield (68% de and 58% yield, entry 6). The addition of 5 equiv of diisopropylamine to the diluted enolate greatly suppressed bromodifluoromethylation (<1% yield, entry 7). In all cases, α-bromo carboximide **5a** was obtained as a by-product in a 0.8-8% yield, and diastereomeric excesses ranged from 34% to 68% by capillary GLC analysis.

Table 1. Bromodifluoromethylation of Imide **1a** under Various Conditions



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

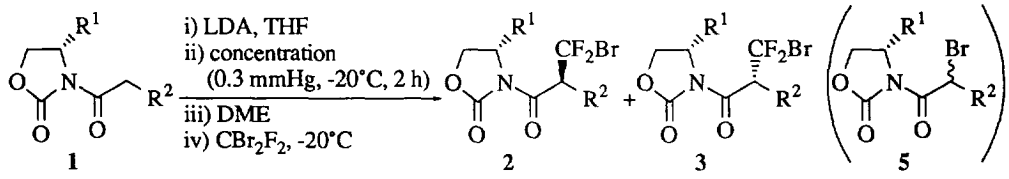
Entry	Reaction Conditions[a]	Solvent	Et_3B (equiv)	Product (**2a**, **3a**) % de[b]	Product (**2a**, **3a**) % yield (**2a** + **3a**)[c]	By-product **5a** % yield
1	A	THF	1.0	61	9 (30)	1
2	A	THF	0.0	60	10 (31)	1
3	B	none	0.0	69	43 (52)	<1
4	C	THF	0.0	66	51 (59)	6
5	C	DME	0.0	68	59 (66)	8
6	C	DME	1.0	68	58 (65)	6
7[d]	C	DME	0.0	66	<1 (5)	<1

a) In Method A, CBr_2F_2 was added to lithium enolate derived from **1a** and LDA in THF followed by the addition of Et_3B at -78°C. The reaction system was allowed to warm to 0°C over 3 h. In Method B, the lithium enolate solution was concentrated at 0.3 mmHg and -20°C for 2 h followed by the addition of CBr_2F_2. The system was stirred at -20°C for 1 h. In Method C, the concentrated enolate in Method B was diluted with THF or DME followed by the addition of CBr_2F_2. This solution was stirred in the presence or absence of Et_3B at -20°C for 1 h; b) Des were determined by capillary GLC. The major product was **2a**; c) Yields of all isolated compounds are indicated. Conversion yields are shown in parentheses; d) Diisopropylamine (5 equiv) was added to the diluted enolate prior to CBr_2F_2.

4a **5a**

Results of the diastereoselective bromodifluoromethylation of a variety of *N*-acyloxazolidinones **1** with CBr_2F_2 under optimal conditions (Table 1, entry 5) are summarized in Table 2. In all cases, our standard procedure afforded α-bromodifluoromethyl carboximides, **2** and **3**, in synthetically useful yields along with the recovery of the starting imides **1** (10-19%). All imides **1** showed good diastereoselectivity, and the diastereomeric excess (92% de) was attained with **1d** (R^1 = *i*-Pr, R^2 = *t*-Bu) bearing a bulky group (entry 4). α-Bromo carboximide **5** was obtained in a significant amount in all cases, especially **1d** giving **5d** in 20% yield. α-Bromodifluoromethyl carboximides **2** and their diastereomers **3** were separated by flash chromatography.

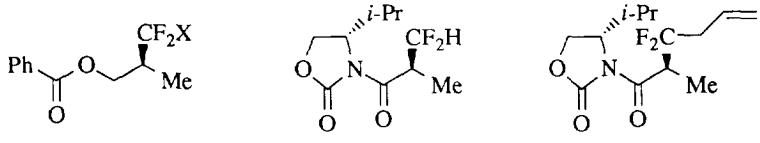
Table 2. Diastereoselective Bromodifluoromethylation of Lithium Enolates Derived from *N*-Acyloxazolidinones **1**



Entry	Imide **1**			Product **2**, **3**	
	R^1	R^2		% de[a]	% yield (**2** + **3**)[b]
1	*i*-Pr	Me	(**1a**)	68 (*S*)[c]	59 (66)
2	*i*-Pr	Bn	(**1b**)	67	52 (59)
3	*i*-Pr	*n*-Bu	(**1c**)	67	60 (68)
4	*i*-Pr	*t*-Bu	(**1d**)	92	42 (52)
5	Bn	Me	(**1e**)	71	55 (61)
6	*i*-Pr	OBn	(**1f**)	70	42 (48)
7	*i*-Pr	$N(Bn)_2$	(**1g**)	64	30 (34)

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

The reduction of α-bromodifluoromethyl carboximide **2a** with lithium borohydride ($LiBH_4$) in THF at room temperature followed by benzoylation of the resulting alcohol gave benzoate **6a** without racemization. Treatment of **2a** with tributyltin hydride (*n*-Bu_3SnH) and allyltributyltin in the presence of 2,2'-azobis(isobutyronitrile) (AIBN) under benzene reflux condition afforded **7a** and **8a** in 90% and 88% yields, respectively.



6a X = Br
10a X = H

7a

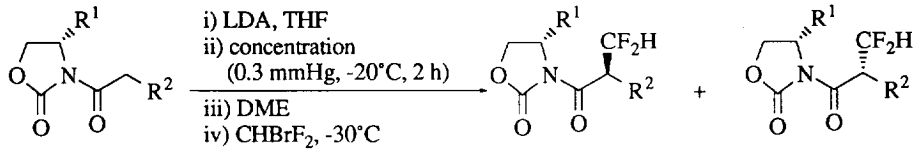
8a

Scheme 1

Difluoromethylation. Chiral compounds bearing a difluoromethyl group at the stereogenic center may exhibit unique physiological properties due to this group acting as a hydrogen bond donor,[10] potentially allowing interaction with biological molecules.[11] We next examined the difluoromethylation of *N*-acyloxazolidinones **1** with bromodifluoromethane ($CHBrF_2$). The lithium enolate solution derived *in situ* from **1a** and LDA in THF was concentrated *in vacuo* at -20°C for 2 h and diluted with DME followed by the addition of $CHBrF_2$ at -30°C. The reaction mixture was stirred at -30°C for 1-1.5 h prior to quenching with saturated aqueous NH_4Cl. These results are summarized in Table 3. Although the starting imides **1a-e** were recovered in 28-41%, α-difluoromethyl imides, **7** and **9**, were produced with moderate to good diastereoselectivity and in moderate yields (42-45%). The structure of imide **1** affected selectivity and **1d** (R^1=*i*-Pr, R^2 = *t*-Bu) appeared to react most favorably to give the greatest diastereomeric excess (93% de, entry 4). Reaction of **1a** without adjusting the concentration of the lithium enolate solution *in vacuo* gave

difluoromethyl carboximides, **7a** and **9a**, only in limited yields (2%). The addition of diisopropylamine (5 equiv) to the concentrated enolate prior to $CHBrF_2$ addition greatly suppressed product formation. α-Difluoromethyl carboximides **7** and their diastereomers **9** were separated by flash chromatography. The new asymmetric center of the major diasteremer **7a** (R^1 = *i*-Pr, R^2 = Me) was shown to have the (*S*)-configuration by comparison with the sample obtained by reduction of **2a** with *n*-Bu_3SnH. The reduction of **7a** with $LiBH_4$ in THF at room temperature followed by the benzoylation of the resulting alcohol gave (*S*)-3,3-difluoro-2-methylpropyl benzoate **10a** without racemization.

Table 3. Diastereoselective Difluoromethylation of Lithium Enolates Derived from *N*-Acyloxazolidinones **1**



1 **7** **9**

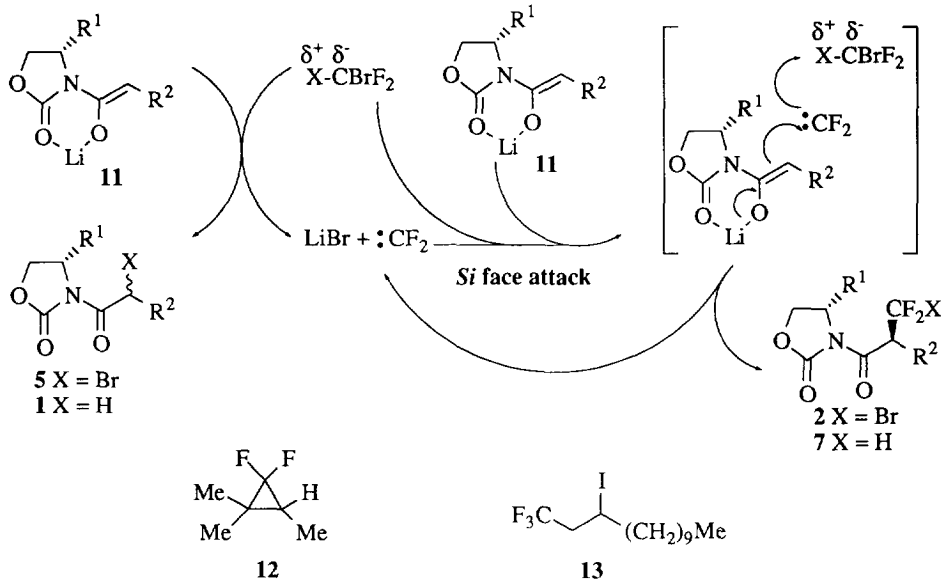
Entry	Imide **1**			Product **7**, **9**		Recovery of **1**
	R^1	R^2		% de[a]	% yield **7** + **9** [b]	%
1	*i*-Pr	Me	(**1a**)	61 (*S*)[c]	45 (62)	28
2	*i*-Pr	Bn	(**1b**)	62	45 (70)	36
3	*i*-Pr	*n*-Bu	(**1c**)	61	42 (71)	41
4	*i*-Pr	*t*-Bu	(**1d**)	93	42 (68)	38
5	Bn	Me	(**1e**)	51	43 (64)	34

a) Des were determined by ^{19}F NMR and capillary GLC; b) All yields are those of isolated compounds. Conversion yields are shown in parentheses; c) Configuration of the new asymmetric center of the major isomer.

Mechanism. The present bromodifluoromethylation and difluoromethylation may be explained by the ionic chain mechanism shown in Scheme 2. Reaction of Li-chelated *Z* enolate **11** with CBr_2F_2 ($CHBrF_2$) affords α-bromo carboximide **5** (starting imide **1**) and difluorocarbene (:CF_2) along with lithium bromide (LiBr). Difluorocarbene attacks other **11** with C(α)-*si*-face preference to yield α-bromodifluoromethyl carboximide **2** (α-difluoromethyl carboximide **7**) and reproduces difluorocarbene from CBr_2F_2 ($CHBrF_2$).

As reported previously by Oshima and Utimoto, Et_3B mediates the addition reaction of CBr_2F_2 to olefins and acetylenes via a bromodifluoromethyl radical.[9] But in contrast, the reaction of CBr_2F_2 with some carbon nucleophiles has been shown to proceed via insertion of difluorocarbene.[12] The present reactions would proceed not via radical mechanism but an ionic chain mechanism as illustrated in Scheme 2, based on the following observations: 1) The radical initiator, Et_3B, was not necessary, indicating a radical such as bromodifluoromethyl radical not to participate in the reactions.[9] 2) A significant amount of α-bromo carboximide **5** was obtained in bromodifluoromethylation, and difluoromethylation brought about the recovery of starting imide **1** in considerable yield. 3) The reactions were dramatically suppressed by the addition of diisopropylamine which inhibits the cyclopropanation of olefins with difluorocarbene. To a solution of triphenylphosphine (20 mmol) in triglyme (30 ml) was added CBr_2F_2 (20 mmol) at room temperature and, after 30 min at this temperature, 2-methyl-2-butene (20 mmol) and potassium fluoride (KF, 80 mmol) were added and the system was stirred at room temperature for 20 h to give difluorocyclopropane **12** in 44% yield. However, the addition of diisopropylamine (20 mmol) prior to 2-methyl-2-butene effectively inhibited the cyclopropanation to provide **12** only in a trace amount.[13] On the other hand, diisopropylamine failed to inhibit the addition of radicals to olefins mediated by triethylborane. Thus, a solution of 1-dodecene

(2 mmol), iodotrifluoromethane (CF_3I, 10 mmol), Et_3B (2 mmol) and diisopropylamine (2 mmol) in *n*-hexane (10 ml) was stirred at -30°C for 5 h and **13** was consequently obtained in 80% yield.[9a] These two experimental results would support the present reaction proceeded in an ionic fashion.



12

13

Scheme 2

CONCLUSION

The bromodifluoromethylation of lithium enolates of chiral *N*-acyloxazolidinones with CBr_2F_2 proceeded with good diastereomeric excess (64-92% de) and good yields. Reactions of the enolates with $CHBrF_2$ gave α-difluoromethyl carboximides with moderate to good diastereoselectivity and in synthetically useful yields. These reactions are considered to proceed via an ionic chain mechanism involving insertion of difluorocarbene. These reactions are presently being applied to the synthesis of important chiral fluoroorganic compounds.

EXPERIMENTAL

General. Reactions were run under an argon atmosphere with magnetic stirring in oven-dried glassware. THF and DME were freshly distilled from sodium benzophenone ketyl. 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. Analytical gas chromatography (GLC) was carried out using a GL Science (30-m x 0.25-mm) NEUTRABOND-1 capillary column with a thickness of 1.5 μm. GLC data were obtained for the mixture of diastereomers. Melting points are uncorrected. Optical rotations were measured at 589 nm using a 1.0-dm cell in total volume of 1 ml. Infrared spectra were obtained either as neat or KBr pellets. Absorption is expressed as reciprocal centimeters (cm^{-1}). ^1H NMR were recorded at 200 MHz and the chemical shifts were expressed in parts per million (ppm) downfield from TMS as the internal standard (δ). ^{19}F NMR spectra were measured at 188 MHz and the chemical shifts were given in parts per million (ppm) upfield from CCl_3F as the internal standard. Coupling constants are in hertz. $CDCl_3$ served as

solvent for ^1H and ^{19}F NMR. Low- and high-resolution mass spectral analyses were performed under 70 eV electron-impact (EI) conditions. Elemental analyses were conducted at Toray Research Center Inc., Tokyo.

Preparation of N-Acyloxazolidinone 1. (*S*)-4-Isopropyl-3-propionyl-2-oxazolidinone **1a** was purchased from Aldrich. (*S*)-4-Isopropyl-3-(3-phenylpropionyl)-2-oxazolidinone **1b**, (*S*)-3-hexanoyl-4-isopropyl-2-oxazolidinone **1c**, (*S*)-3-(3,3-dimethylbutanoyl)-4-isopropyl-2-oxazolidinone **1d**, (*S*)-4-benzyl-3-propionyl-2-oxazolidinone **1e** and (*S*)-3-(benzyloxyacetyl)-4-isopropyl-2-oxazolidinone **1f** were prepared by literature methods.[4b,14]

Preparation of (S)-3-(N,N-Dibenzylglycyl)-4-isopropyl-2-oxazolidinone 1g: A solution of (*S*)-3-(chloroacetyl)-4-isopropyl-2-oxazolidinone (6.13 g, 29.8 mmol), prepared from (*S*)-4-isopropyl-2-oxazolidinone and chloroacetyl chloride in analogy to **1b**, and dibenzylamine (6.3 ml, 32.8 mmol) in DME (20 ml) was heated at refluxing temperature for 2 h. The reaction mixture was poured into H_2O and extracted with ether. The combined extracts were washed with H_2O and brine, dried and filtered. After evaporation of the solvent, chromatography of the residue with *n*-hexane-EtOAc as eluent gave **1g** (6.4 g, 58.6%): colorless needles; mp 83.5-84.5°C (*n*-hexane-ether); $[\alpha]_D^{24}$ +54.0 (c 1.27, $CHCl_3$); IR (KBr) 1765, 1701, 1388, 1207, 732, 699; ^1H NMR 0.84 (d, *J* = 6.9, 3H), 0.91 (d, *J* = 7.0, 3H), 2.27-2.51 (m, 1H), 3.86 (s, 4H), 3.92 (s, 2H), 4.24-4.41 (m, 3H), 7.18-7.45 (m, 10H); MS *m/z* 366 [M$^+$], 275, 210, 181, 118, 91; HRMS Calcd for $C_{22}H_{26}N_2O_3$ [M$^+$] 366.194, found 366.193; Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.1; H, 7.2 N, 7.6 Found: C, 72.1; H, 7.2; N, 7.6.

General Procedure for Bromodifluoromethylation: **(2'*S*,4*S*)- and (2'*R*,4*S*)-3-(3'-Bromo-3',3'-difluoro-2'-methylpropionyl)-4-isopropyl-2-oxazolidinones, 2a and 3a.** To a solution of diisopropylamine (308 µl, 2.2 mmol) in THF (4 ml) at 0°C was added *n*-BuLi (1.57 M in hexanes, 1.4 ml, 2.2 mmol). After 30 min at 0°C, the solution was cooled to -78°C, followed by adding a solution of **1a** (370 mg, 2.0 mmol) in THF (6 ml). After 60 min at -78°C, the mixture was concentrated *in vacuo* (0.3 mmHg) at -78°C for 10 min and -20°C for 2 h. To the concentrated lithium enolate were added DME (10 ml) and CBr_2F_2 (0.91 ml, 10 mmol). After being stirred at -20°C for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The combined ethereal extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried and filtered. Diastereomeric excess was determined as 68% by capillary GLC analysis. After evaporation of the solvent, chromatography of the residue with *n*-hexane-CH_2Cl_2 and *n*-hexane-EtOAc as an eluent gave (2'*S*,4*S*)- 3-(3'-bromo-3',3'-difluoro-2'-methylpropionyl)-4-isopropyl-2-oxazolidinone **2a** (316 mg, 50.3%), (2'*R*,4*S*)-3-(3'-bromo-3',3'-difluoro-2'-methylpropionyl)-4-isopropyl-2-oxazolidinone **3a** (57 mg, 9.1%), α-bromo carboximide **5a** (43 mg, 7.8%) and starting material **1a** (38 mg, 10.2%): **2a** a colorless oil; $[\alpha]_D^{25}$ +22.3 (c 1.05, $CHCl_3$); IR (neat) 1775, 1708, 1389, 1245, 1205, 1121; ^1H NMR 0.90 (d, *J* = 6.9, 3H), 0.94 (d, *J* = 7.1, 3H), 1.45 (d, *J* = 6.9, 3H), 2.30-2.53 (m, 1H), 4.21-4.55 (m, 3H), 4.98-5.20 (m, 1H); ^{19}F NMR 48.76 (dd, *J* = 159.8, 11.2, 1F), 49.22 (dd, *J* = 159.8, 10.8, 1F); MS *m/z* 315 [M$^+$], 313 [M$^+$], 272, 270, 234, 190, 159, 157; HRMS Calcd for $C_{10}H_{14}BrF_2NO_3$ [M$^+$] 313.013, found 313.014; **3a** colorless needles; mp 66.2-67.4°C (*n*-hexane); $[\alpha]_D^{25}$ +95.2 (c 0.76, $CHCl_3$); IR (KBr) 1787, 1719, 1390, 1242, 1216, 1135; ^1H NMR 0.89 (d, *J* = 6.9, 3H), 0.93 (d, *J* = 7.1, 3H), 1.51 (d, *J* = 7.0, 3H), 2.38 (qqd, *J* = 7.1, 6.9, 4.0, 1H), 4.22-4.56 (m, 3H), 4.96 (ddq, *J* = 11.2, 10.8, 7.0, 1H); ^{19}F NMR 49.26 (dd, *J* = 160.8, 11.2, 1F), 49.52 (dd, *J* = 160.8, 10.8, 1F); MS *m/z* 315 [M$^+$], 313 [M$^+$], 272, 270, 234, 190, 159, 157; HRMS Calcd for $C_{10}H_{14}BrF_2NO_3$ [M$^+$] 313.013, found 313.014; Anal. Calcd for $C_{10}H_{14}BrF_2NO_3$: C, 38.2; H, 4.4; N, 4.5. Found: C, 38.3; H, 4.4; N, 4.4; **5a** a colorless oil; IR (neat) 1774, 1707, 1375, 1206; ^1H NMR 0.87-0.97 (m, 6H), 1.83 (d, *J* = 6.7, 2.2H), 1.86 (d, *J* = 6.7, 0.8H), 2.29-2.49 (m, 1H), 4.22-4.55 (m, 3H), 5.76 (q, J = 6.7, 1H); MS *m/z* 265 [M$^+$], 263 [M$^+$], 222, 220, 184, 137, 135; HRMS Calcd for $C_9H_{14}BrNO_3$ [M$^+$] 263.016, found 263.016.

(2'*S*,4*S*)- and (2'*R*,4*S*)-3-(2'-Benzyl-3'-bromo-3',3'-difluoropropionyl)-4-isopropyl-2-oxazolidinones, 2b and 3b. The general bromodifluoromethylation procedure was followed, using 523 mg (2.0 mmol) of (*S*)-4-isopropyl-3-(3-phenylpropionyl)-2-oxazolidinone **1b**. Diastereomeric excess was determined to be 67% by capillary GLC analysis. After evaporation of the solvent, chromatography of the residue with *n*-hexane-CH_2Cl_2 and *n*-hexane-EtOAc as an eluent gave the less polar isomer (70 mg, 9.0%), more polar isomer (337 mg, 43.2%) and starting material **1b** (63 mg, 12.0%): **less polar isomer** colorless needles; mp 92.0-92.6°C (*n*-hexane); $[\alpha]_D^{24}$ +17.2 (c 0.36, $CHCl_3$); IR (KBr) 1770, 1708, 1396, 1181, 1104; ^1H NMR 0.22 (d, *J* = 6.9,

3H), 0.74 (d, J = 7.1, 3H), 1.95 (qqd, J = 7.1, 6.9, 3.6, 1H), 3.27-3.31 (m, 2H), 4.04-4.46 (m, 3H), 5.71 (ddq, J = 11.3, 11.2, 6.9, 1H), 7.16-7.33 (m, 5H); ^{19}F NMR 47.51 (dd, J = 160.4, 11.2, 1F), 48.08 (dd, J = 160.4, 11.3, 1F); MS *m/z* 391 [M$^+$], 389 [M$^+$], 310, 260, 131, 91; HRMS Calcd for $C_{16}H_{18}BrF_2NO_3$ [M$^+$] 389.044, found 389.043; Anal. Calcd for $C_{16}H_{18}BrF_2NO_3$: C, 49.2; H, 4.6; N, 3.6. Found: C, 49.1; H, 4.6; N, 3.6; **more polar isomer** a colorless oil; $[\alpha]_D^{25}$ +103.9 (c 1.06, $CHCl_3$); IR (neat) 1782, 1707, 1387, 1202, 1107; ^{1}H NMR 0.84 (d, J = 6.7, 3H), 0.87 (d, J = 6.8, 3H), 2.31 (qqd, J = 6.8, 6.7, 4.0, 1H), 3.14-3.30 (m, 2H), 3.68-4.16 (m, 3H), 5.60 (ddq, J = 12.3, 10.4, 5.7, 1H), 7.15-7.34 (m, 5H); ^{19}F NMR 47.27 (dd, J = 159.3, 10.4, 1F), 49.01 (dd, J = 159.3, 12.3, 1F); MS *m/z* 391 [M$^+$], 389 [M$^+$], 310, 260, 131, 91; HRMS Calcd for $C_{16}H_{18}BrF_2NO_3$ [M$^+$] 389.044, found 389.043.

(2'*S*,4*S*)- and (2'*R*,4*S*)-3-[2'-(Bromodifluoromethyl)hexanoyl]-4-isopropyl-2-oxazolidinones, 2c and 3c. The general bromodifluoromethylation procedure was followed, using 455 mg (2.0 mmol) of (*S*)-3-hexanoyl-4-isopropyl-2-oxazolidinone **1c**. Diastereomeric excess was determined as 67% by capillary GLC analysis. After evaporation of the solvent, chromatography of the residue with *n*-hexane-CH_2Cl_2 and *n*-hexane-EtOAc as an eluent gave the less polar isomer (67 mg, 9.4%), more polar isomer (372 mg, 52.2%), α-bromo carboximide **5c** (68 mg, 11.1%) and starting material **1c** (50 mg, 11.1%): **less polar isomer** a colorless oil; $[\alpha]_D^{25}$ +50.9 (c 0.79, $CHCl_3$); IR (neat) 1782, 1708, 1388, 1200, 1102; ^{1}H NMR 0.88-0.98 (m, 3H), 0.90 (d, J = 7.0, 3H), 0.95 (d, J = 7.1, 3H), 1.16-1.50 (m, 4H), 1.80-2.20 (m, 2H), 2.39 (qqd, J = 7.1, 7.0, 3.7, 1H), 4.21-4.60 (m, 3H), 5.08-5.28 (m, 1H); ^{19}F NMR 46.70 (dd, J = 160.1, 11.0, 1F), 47.52 (dd, J = 160.1, 11.8, 1F); MS *m/z* 357 [M$^+$], 355 [M$^+$], 276, 232, 229, 227; HRMS Calcd for $C_{13}H_{20}BrF_2NO_3$ [M$^+$] 355.060, found 355.060; **more polar isomer** a colorless oil; $[\alpha]_D^{24}$ +44.4 (c 1.23, $CHCl_3$); IR (neat) 1779, 1705, 1386, 1200, 1102; ^{1}H NMR 0.82-0.99 (m, 3H), 0.91 (d, J = 6.8, 3H), 0.94 (d, J = 7.0, 3H), 1.15-1.45 (m, 4H), 1.76-2.15 (m, 2H), 2.43 (qqd, J = 7.0, 6.8, 3.5, 1H), 4.22-4.58 (m, 3H), 5.10-5.28 (m, 1H); ^{19}F NMR 46.28 (dd, J = 160.1, 11.1, 1F), 47.38 (dd, J = 160.1, 11.4, 1F); MS *m/z* 357 [M$^+$], 355 [M$^+$], 276, 232, 229, 227; HRMS Calcd for $C_{13}H_{20}BrF_2NO_3$ [M$^+$] 355.060, found 355.060; **5c** a colorless oil; IR (neat) 1776, 1707, 1370, 1210; ^{1}H NMR 0.87-0.97 (m, 9H), 1.20-1.52 (m, 4H), 1.91-2.27 (m, 2H), 2.31-2.50 (m, 1H), 4.20-4.55 (m, 3H), 5.62-5.71 (m, 1H); MS *m/z* 307 [M$^+$], 305 [M$^+$], 264, 262, 226; HRMS Calcd for $C_{12}H_{20}BrNO_3$ [M$^+$] 305.063, found 305.063.

(2'*S*,4*S*)- and (2'*R*,4*S*)-3-[2'-(Bromodifluoromethyl)-3',3'-dimethylbutanoyl]-4-isopropyl-2-oxazolidinones, 2d and 3d. The general bromodifluoromethylation procedure was followed, using 455 mg (2.0 mmol) of (*S*)-3-(3,3-dimethylbutanoyl)-4-isopropyl-2-oxazolidinone **1d**. Diastereomeric excess was determined to be 92% by capillary GLC analysis. Following evaporation of the solvent, chromatography of the residue with *n*-hexane-CH_2Cl_2 as an eluent gave the major isomer (69 mg, 9.7%), a mixture of isomers (227 mg, 31.9%), α-bromo carboximide **5d** (124 mg, 20.2%) and starting material **1d** (93 mg, 20.3%): **major isomer** colorless needles; mp 70.5-71.4°C (*n*-hexane); $[\alpha]_D^{25}$ +53.7 (c 2.17, $CHCl_3$); IR (KBr) 1780, 1698, 1389, 1202, 1110; ^{1}H NMR 0.96 (d, J = 6.2, 3H), 0.96 (d, J = 7.1, 3H), 1.15 (s, 9H), 2.51 (qqd, J = 7.1, 6.2, 3.3, 4H), 4.20-4.60 (m, 3H), 5.35-5.50 (m, 1H); ^{19}F NMR 38.88 (d, J = 144.3, 1F), 45.29 (dd, J = 144.3, 24.6, 1F); MS *m/z* 357 [M$^+$], 355 [M$^+$], 276, 220; HRMS Calcd for $C_{13}H_{20}BrF_2NO_3$ [M$^+$] 355.060, found 355.058; Anal. Calcd for $C_{13}H_{20}BrF_2NO_3$: C, 43.8; H, 5.7; N, 3.9. Found: C, 43.9; H, 5.5; N, 3.9; **5d** a colorless oil; IR (neat) 1775, 1707, 1367, 1217, 1112; ^{1}H NMR 0.87-0.96 (m, 6H), 1.19 (s, 9H), 2.34-2.50 (m, 1H), 4.19-4.55 (m, 3H), 5.80 (s, 1H); MS *m/z* 307 [M$^+$], 305 [M$^+$], 292, 290, 251, 249, 226; HRMS Calcd for $C_{12}H_{20}BrNO_3$ [M$^+$] 305.063, found 305.062.

(2'*S*,4*S*)- and (2'*R*,4*S*)-4-Benzyl-3-(3'-bromo-3',3'-difluoro-2'-methylpropionyl)-2-oxazolidinones, 2e and 3e. The general bromodifluoromethylation procedure was followed, using 467 mg (2.0 mmol) of (*S*)-4-benzyl-3-propionyl-2-oxazolidinone **1e**. Diastereomeric excess was determined to be 71% by capillary GLC analysis. After evaporation of the solvent, chromatography of the residue with *n*-hexane-CH_2Cl_2 and *n*-hexane-EtOAc as an eluent gave the less polar isomer (52 mg, 7.2%), more polar isomer (344 mg, 47.4%) and starting material **1e** (50 mg, 10.8%): **less polar isomer** colorless needles; mp 95.2-95.9°C (*n*-hexane); $[\alpha]_D^{24}$ +84.4 (c 0.56, $CHCl_3$); IR (KBr) 1765, 1705, 1395, 1224, 1113, 919; ^{1}H NMR 1.53 (d, J = 7.0, 3H), 2.81 (dd, J = 13.5, 9.5, 1H), 3.28 (dd, J = 13.5, 3.5, 1H), 4.20-4.33 (m, 2H), 4.69-5.04 (m, 2H), 7.18-7.41 (m, 5H); ^{19}F NMR 49.25 (d, J = 11.2, 1F), 49.33 (d, J = 10.8, 1F); MS *m/z* 363 [M$^+$], 361 [M$^+$], 282, 187, 185, 159, 157; HRMS

Calcd for $C_{14}H_{14}BrF_2NO_3$ [M+] 361.013, found 361.012; Anal. Calcd for $C_{14}H_{14}BrF_2NO_3$: C, 46.4; H, 3.9; N, 3.9. Found: C, 46.4; H, 3.8; N, 3.9; **more polar isomer** a colorless oil; $[\alpha]_D^{25}$ +13.8 (c 1.31, $CHCl_3$); IR (neat) 1774, 1707, 1389, 1213, 927; ^1H NMR 1.49 (d, J = 7.0, 3H), 2.76 (dd, J = 13.6, 9.9, 1H), 3.38 (dd, J = 13.6, 3.8, 1H), 4.17-4.30 (m, 2H), 4.94-5.15 (m, 1H), 5.05 (ddq, J = 11.2, 10.9, 7.0, 1H), 7.20-7.31 (m, 5H); ^{19}F NMR 48.81 (dd, J = 160.2, 11.2, 1F), 49.47 (dd, J = 160.2, 10.9, 1F); MS *m/z* 363 [M+], 361 [M+], 282, 187, 185, 159, 157; HRMS Calcd for $C_{14}H_{14}BrF_2NO_3$ [M+] 361.013, found 361.012.

(2'*S*,4*S*)- and (2'*R*,4*S*)-3-(2'-Benzyloxy-3'-bromo-3',3'-difluoropropionyl)-4-isopropyl-2-oxazolidinones, 2f and 3f. The general bromodifluoromethylation procedure was followed, using 554 mg (2.0 mmol) of (*S*)-3-(benzyloxyacetyl)-4-isopropyl-2-oxazolidinone **1f**. Diastereomeric excess was determined to be 70% by capillary GLC analysis. After evaporation of the solvent, chromatography of the residue with *n*-hexane-CH_2Cl_2 as an eluent gave the less polar isomer (51 mg, 6.3%), more polar isomer (288 mg, 35.5%) and starting material **1f** (75 mg, 13.5%): **less polar isomer** a colorless oil; $[\alpha]_D^{25}$ +60.7 (c 0.64, $CHCl_3$); IR (neat) 1783, 1717, 1389, 1202, 1121, 701; ^1H NMR 0.74 (d, J = 6.9, 3H), 0.89 (d, J = 7.0, 3H), 2.30 (qqd, J = 7.0, 6.9, 3.7, 1H), 4.20-4.48 (m, 3H), 4.77-4.95 (m, 2H), 6.02 (t, J = 8.2, 1H), 7.29-7.43 (m, 5H); ^{19}F NMR 55.89 (d, J = 8.2); MS *m/z* 326 [M-Br], 315, 313, 220, 91; HRMS Calcd for $C_{16}H_{18}F_2NO_4$ [M-Br] 326.120, found 326.120; **more polar isomer** a colorless oil; $[\alpha]_D^{24}$ +29.1 (c 0.53, $CHCl_3$); IR (neat) 1782, 1716, 1389, 1204, 1121, 715; ^1H NMR 0.81 (d, J = 7.0, 3H), 0.87 (d, J = 7.0, 3H), 2.21-2.37 (m, 1H), 4.02-4.26 (m, 3H), 4.65-4.96 (m, 2H), 6.01 (t, J = 8.2, 1H), 7.32-7.43 (m, 5H); ^{19}F NMR 55.88 (d, J = 8.2); MS *m/z* 408 [M+1], 406 [M+1], 325; HRMS Calcd for $C_{16}H_{19}BrF_2NO_4$ [M+H] 406.047, found 406.045.

(2'*S*,4*S*)- and (2'*R*,4*S*)-3-[3'-Bromo-2'-(*N*,*N*-dibenzylamino-3',3'-difluoropropionyl]-4-isopropyl-2-oxazolidinones, 2g and 3g. The general bromodifluoromethylation procedure was followed, using 732 mg (2.0 mmol) of (*S*)-3-[(*N*,*N*-dibenzylamino)acetyl]-4-isopropyl-2-oxazolidinone **1g**. Diastereomeric excess was determined to be 64% by capillary GLC analysis. After evaporation of the solvent, chromatography of the residue with *n*-hexane-CH_2Cl_2 and *n*-hexane-EtOAc as eluent gave the less polar isomer (54 mg, 5.4%), more polar isomer (244 mg, 24.7%) and starting material **1g** (88 mg, 12.0%): **less polar isomer** a colorless oil; $[\alpha]_D^{24}$ +7.5 (c 0.36, $CHCl_3$); IR (neat) 1781, 1704, 1386, 1204, 1105, 699; ^1H NMR 0.96 (d, J = 7.1, 3H), 0.98 (d, J = 6.9, 3H), 2.30-2.46 (m, 1H), 3.78-4.65 (m, 7H), 6.00 (dd, J = 13.8, 11.5, 1H), 7.15-7.40 (m, 10H); ^{19}F NMR 49.35 (dd, J = 157.4, 11.5, 1F), 51.15 (dd, J = 157.4, 13.8, 1F); MS *m/z* 496 [M+], 494 [M+], 405, 403, 340, 338; HRMS Calcd for $C_{23}H_{25}BrF_2N_2O_3$ [M+] 494.102, found 494.102; **more polar isomer** a colorless oil; $[\alpha]_D^{23}$ +61.7 (c 1.52, $CHCl_3$); IR (neat) 1784, 1698, 1391, 1214, 1115, 706; ^1H NMR 0.83 (d, J = 6.8, 3H), 0.86 (d, J = 7.0, 3H), 2.23-2.47 (m, 1H), 3.95-4.21 (m, 7H), 5.92 (dd, J = 13.8, 11.5, 1H), 7.15-7.38 (m, 10H); ^{19}F NMR 48.76 (dd, J = 157.8, 11.5, 1F), 51.69 (dd, J = 157.8, 13.8, 1F); MS *m/z* 496 [M+], 494 [M+], 405, 403, 340, 338; HRMS Calcd for $C_{23}H_{25}BrF_2N_2O_3$ [M+] 494.102, found 494.101.

General Procedure for Difluoromethylation: **(2'*S*,4*S*)- and (2'*R*,4*S*)-3-(3',3'-Difluoro-2'-methylpropionyl)-4-isopropyl-2-oxazolidinones, 7a and 9a.** To a solution of diisopropylamine (308 µl, 2.2 mmol) in THF (4 ml) at 0°C was added *n*-BuLi (1.55 M in hexanes, 1.4 ml, 2.2 mmol). After 30 min at 0°C, the solution was cooled to -78°C, and then to which was added a solution of **1a** (370 mg, 2.0 mmol) in THF (6 ml). After 60 min at -78°C, the mixture was concentrated *in vacuo* (0.3 mmHg) at -78°C for 10 min and -20°C for 2 h. The concentrated lithium enolate was cooled to -30°C and then treated with DME (10 ml) and $CHBrF_2$ (1.5 ml). After being stirred at -30°C for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The combined ethereal extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried and filtered. Diastereomeric excess was determined to be 61% by ^{19}F NMR. After evaporation of the solvent, chromatography of the residue with *n*-hexane-CH_2Cl_2 and *n*-hexane-EtOAc as an eluent gave (2'*S*,4*S*)- 3-(3',3'-difluoro-2'-methylpropionyl)-4-isopropyl-2-oxazolidinone **7a** (170 mg, 36.2%), (2'*R*,4*S*)-3-(3',3'-difluoro-2'-methylpropionyl)-4-isopropyl-2-oxazolidinone **9a** (42 mg, 8.9%) and starting material **1a** (103 mg, 27.7%): **7a** a colorless oil; $[\alpha]_D^{24}$ +60.5 (c 1.37, $CHCl_3$); IR (neat) 1780, 1704, 1389, 1207; ^1H NMR 0.88 (d, J = 7.1, 3H), 0.92 (d, J = 7.3, 3H), 1.30 (d, J = 7.0, 3H), 2.37 (qqd, J = 7.3, 7.1, 3.8, 1H), 4.18-4.53 (m, 4H), 6.04 (ddd, J = 56.8, 55.2, 5.7, 1H); ^{19}F NMR 118.64 (ddd, J = 282.9, 55.2, 9.6, 1F), 126.34 (ddd, J = 282.9, 56.8, 13.5, 1F); MS *m/z* 236 [M+1], 199; HRMS Calcd for $C_{10}H_{16}F_2NO_3$ [M+H] 236.110, found 236.110; **9a** colorless needles; mp 56.5-56.9°C (*n*-hexane-ether); $[\alpha]_D^{24}$ +100.5 (c 1.02,

$CHCl_3$); IR (KBr) 1795, 1769, 1698, 1389, 1216; ^1H NMR 0.96 (d, J = 6.9, 3H), 1.01 (d, J = 7.1, 3H), 1.45 (d, J = 7.1, 3H), 2.43 (qqd, J = 7.1, 6.9, 4.0, 1H), 4.20-4.60 (m, 4H), 6.12 (ddd, J = 56.4, 55.6, 6.3, 1H); ^{19}F NMR 118.38 (ddd, J = 284.3, 55.6, 10.5 1F), 127.91 (ddd, J = 284.3, 56.4, 10.7, 1F); MS *m/z* 236 [M+1], 199; HRMS Calcd for $C_{10}H_{16}F_2NO_3$ [M+H] 236.110, found 236.109; Anal. Calcd for $C_{10}H_{15}F_2NO_3$: C, 51.1; H, 6.4; N, 6.0. Found: C, 51.0; H, 6.4; N, 5.8.

(2'*S*,4*S*)- and (2'*R*,4*S*)-3-(2'-Benzyl-3',3'-difluoropropionyl)-4-isopropyl-2-oxazolidinones, 7b and 9b. The general difluoromethylation procedure was followed, using 523 mg (2.0 mmol) of (*S*)-4-isopropyl-3-(3-phenylpropionyl)-2-oxazolidinone **1b**. Diastereomeric excess was determined to be 62% by capillary GLC analysis. After evaporation of the solvent, chromatography of the residue with *n*-hexane-EtOAc as an eluent gave the less polar isomer (224 mg, 36.0%), more polar isomer (53 mg, 8.5%) and starting material **1b** (190 mg, 36.4%): **less polar isomer** colorless needles; mp 88.9-89.4°C (*n*-hexane-ether); $[\alpha]_D^{24}$ +134.9 (c 0.38, $CHCl_3$); IR (KBr) 1769, 1699, 1412, 1105; ^1H NMR 0.83 (d, J = 7.0, 3H), 0.87 (d, J = 7.1, 3H), 2.28 (qqd, J = 7.1, 7.0, 4.3, 1H), 2.98-3.17 (m, 2H), 3.80-4.23 (m, 3H), 4.81-5.03 (m, 1H), 6.06 (ddd, J = 56.4, 55.6, 5.8, 1H), 7.17-7.35 (m, 5H); ^{19}F NMR 118.89 (ddd, J = 285.7, 55.6, 11.5, 1F), 124.17 (ddd, J = 285.7, 56.4, 11.5, 1F); MS *m/z* 312 [M+1], 181; HRMS Calcd for $C_{16}H_{20}F_2NO_3$ [M+H] 312.141, found 312.140; Anal. Calcd for $C_{16}H_{19}F_2NO_3$: C, 61.7; H, 6.2; N, 4.5. Found: C, 61.8; H, 6.3; N, 4.4; **more polar isomer** colorless needles; mp 74.0-74.5°C (*n*-hexane-ether); $[\alpha]_D^{24}$ +9.2 (c 0.57, $CHCl_3$); IR (KBr) 1778, 1702, 1394, 1098; ^1H NMR 0.37 (d, J = 6.8, 3H), 0.78 (d, J = 7.0, 3H), 2.03 (qqd, J = 7.0, 6.8, 3.4, 1H), 3.08-3.16 (m, 2H), 4.06-4.45 (m, 3H), 4.90-5.12 (m, 1H), 5.97 (ddd, J = 56.2, 55.6, 6.2, 1H), 7.15-7.33 (m, 5H); ^{19}F NMR 119.09 (ddd, J = 285.6, 55.6, 11.8, 1F), 123.13 (ddd, J = 285.6, 56.2, 10.2, 1F); MS *m/z* 312 [M+1], 181; HRMS Calcd for $C_{16}H_{20}F_2NO_3$ [M+H] 312.141, found 312.140; Anal. Calcd for $C_{16}H_{19}F_2NO_3$: C, 61.7; H, 6.2; N, 4.5. Found: C, 61.7; H, 6.2; N, 4.6.

(2'*S*,4*S*)- and (2'*R*,4*S*)-3-[2'-(Difluoromethyl)hexanoyl]-4-isopropyl-2-oxazolidinones, 7c and 9c. The general difluoromethylation procedure was followed, using 455 mg (2.0 mmol) of (*S*)-3-hexanoyl-4-isopropyl-2-oxazolidinone **1c**. Diastereomeric excess was determined to be 61% by capillary GLC analysis. After evaporation of the solvent, chromatography of the residue with *n*-hexane-CH_2Cl_2 as an eluent gave the less polar isomer (45 mg, 8.1%), more polar isomer (186 mg, 33.6%) and starting material **1c** (188 mg, 41.4%): **less polar isomer** a colorless oil; $[\alpha]_D^{25}$ +53.5 (c 0.86, $CHCl_3$); IR (neat) 1783, 1698, 1388, 1203, 1102; ^1H NMR 0.83-1.00 (m, 3H), 0.89 (d, J = 6.9, 3H), 0.94 (d, J = 7.0, 3H), 1.17-1.93 (m, 6H), 2.26-2.48 (m, 1H), 4.20-4.57 (m, 4H), 5.99 (ddd, J = 56.6, 56.0, 6.5, 1H); ^{19}F NMR 117.96 (ddd, J = 285.3, 56.0, 11.5, 1F), 124.62 (ddd, J = 285.3, 56.6, 10.0, 1F); MS *m/z* 278 [M+1], 262; HRMS Calcd for $C_{13}H_{22}F_2NO_3$ [M+H] 278.157, found 278.157; **more polar isomer** a colorless oil; $[\alpha]_D^{25}$ +74.0 (c 1.63, $CHCl_3$); IR (neat) 1782, 1698, 1387, 1203, 1101; ^1H NMR 0.82-0.99 (m, 3H), 0.88 (d, J = 6.8, 3H), 0.92 (d, J = 7.0, 3H), 1.16-1.93 (m, 6H), 2.38 (qqd, J = 7.0, 6.8, 3.9, 1H), 4.20-4.62 (m, 4H), 5.98 (ddd, J = 56.6, 55.8, 6.0, 1H); ^{19}F NMR 118.36 (ddd, J = 284.6, 55.8, 11.1, 1F), 123.19 (ddd, J = 284.6, 56.6, 11.8, 1F); MS *m/z* 278 [M+1], 262; HRMS Calcd for $C_{13}H_{22}F_2NO_3$ [M+H] 278.157, found 278.156.

(2'*S*,4*S*)- and (2'*R*,4*S*)-3-[2'-(Difluoromethyl)-3',3'-dimethylbutanoyl]-4-isopropyl-2-oxazolidinones, 7d and 9d. The general difluoromethylation procedure was followed, using 455 mg (2.0 mmol) of (*S*)-3-(3,3-dimethylbutanoyl)-4-isopropyl-2-oxazolidinone **1d**. Diastereomeric excess was determined to be 93% by ^{19}F NMR. After evaporation of the solvent, chromatography of the residue with *n*-hexane-EtOAc as an eluent gave a mixture of isomers (232 mg, 41.8%) and starting material **1d** (173 mg, 38.1%). The mixture was purified by recrystallization to give pure major isomer: **major isomer** colorless needles; mp 72.5-73.5°C (*n*-hexane-ether); $[\alpha]_D^{23}$ +70.5 (c 1.38, $CHCl_3$); IR (KBr) 1786, 1690, 1398, 1208; ^1H NMR 0.87 (d, J = 7.0, 3H), 0.92 (d, J = 7.1, 3H), 1.10 (s, 9H), 2.38 (qqd, J = 7.1, 7.0, 3.8, 1H), 4.18-4.70 (m, 4H), 6.11 (ddd, J = 56.0, 55.8, 7.3, 1H); ^{19}F NMR 116.27 (ddd, J = 291.7, 55.8, 11.7, 1F), 118.36 (ddd, J = 291.7, 56.0, 9.6, 1F); MS *m/z* 277 [M+], 221, 149; HRMS Calcd for $C_{13}H_{21}F_2NO_3$ [M+] 277.149, found 277.150; Anal. Calcd for $C_{13}H_{21}F_2NO_3$: C, 56.3; H, 7.6; N, 5.1. Found: C, 56.1; H, 7.7; N, 5.0.

(2'*S*,4*S*)- and (2'*R*,4*S*)-4-Benzyl-3-(3',3'-difluoro-2'-methylpropionyl)-2-oxazolidinones, 7e and 9e. The general difluoromethylation procedure was followed, using 467 mg (2.0 mmol) of (*S*)-4-benzyl-3-propionyl-2-oxazolidinone (**1e**). Diastereomeric excess was determined to be 51% by ^{19}F NMR. After evaporation of the

solvent, chromatography of the residue with *n*-hexane-CH_2Cl_2 as an eluent gave the less polar isomer (59 mg, 10.4%), more polar isomer (183 mg, 32.3%) and starting material **1e** (157 mg, 33.7%): **less polar isomer** a colorless oil; $[\alpha]_D^{25}$ +71.7 (c 0.69, $CHCl_3$); IR (neat) 1783, 1698, 1388, 1202; ^1H NMR 1.38 (d, J = 7.1, 3H), 2.76-3.30 (m, 2H), 4.10-4.80 (m, 4H), 6.06 (ddd, J = 56.4, 55.6, 6.3, 1H), 7.17-7.40 (m, 5H); ^{19}F NMR 118.49 (ddd, J = 284.4, 55.6, 10.5, 1F), 127.39 (ddd, J = 284.4, 56.4, 10.9, 1F); MS *m/z* 284 [M+1], 193; HRMS Calcd for $C_{14}H_{16}F_2NO_3$ [M+H] 284.110, found 284.109; **more polar isomer** a colorless oil; $[\alpha]_D^{25}$ +57.0 (c 0.56, $CHCl_3$); IR (neat) 1782, 1701, 1392, 1215; ^1H NMR 1.34 (d, J = 7.0, 3H), 2.78-3.30 (m, 2H), 4.19-4.78 (m, 4H), 6.10 (ddd, J = 56.6, 55.6, 5.8, 1H), 7.15-7.40 (m, 5H); ^{19}F NMR 118.83 (ddd, J = 283.8, 55.6, 9.8, 1F), 127.08 (ddd, J = 283.8, 56.6, 13.2, 1F); MS *m/z* 284 [M+1], 193; HRMS Calcd for $C_{14}H_{16}F_2NO_3$ [M+H] 284.110, found 284.110.

Conversion of ***2a*** *to benzoate* ***6a****:* To a solution of **2a** (460 mg, 1.47 mmol) in THF (3 ml) was added $LiBH_4$ (2.0 M in THF, 2.2 ml) at 0°C. After 60 min at 0°C and 30 min at room temperature, the reaction mixture was poured into saturated aqueous NH_4Cl and extracted with ether. The combined extracts were washed with 0.5 N aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried and filtered. After evaporation of the solvent, the residue was dissolved in pyridine (5 ml) and then treated with benzoyl chloride (0.5 ml, 4.4 mmol). After stirring at room temperature for 18 h, the reaction mixture was diluted with ether, washed with 0.5 N aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried and filtered. After evaporation of the solvent, chromatography of the residue with *n*-hexane-EtOAc as an eluent gave **6a** (326 mg, 75.7%): a colorless oil; $[\alpha]_D^{25}$ -1.7 (c 1.04, $CHCl_3$); IR (neat) 1725, 1273, 1095; ^1H NMR 1.30 (d, J = 6.8, 3H), 2.69-2.90 (m, 1H), 4.32-4.58 (m, 2H), 7.41-8.10 (m, 5H); ^{19}F NMR 47.59-47.65 (m); MS *m/z* 294 [M^+], 292 [M^+], 213, 122, 107, 105; HRMS Calcd for $C_{11}H_{11}BrF_2O_2$ [M^+] 291.991, found 291.990.

Conversion of ***7a*** *to benzoate* ***10a****:* The procedure for **6a** was followed, using 82 mg (0.35 mmol) of **7a**. After evaporation of the solvent, chromatography of the residue with *n*-hexane-EtOAc as an eluent gave **10a** (51 mg, 69.1%): a colorless oil; $[\alpha]_D^{24}$ +7.2 (c 1.42, $CHCl_3$); IR (neat) 1724, 1274, 1114, 1088, 711; ^1H NMR 1.16 (d, J = 7.1, 3H), 2.28-2.61 (m, 1H), 4.36 (d, J = 6.2, 2H), 5.90 (ddd, J = 56.6, 56.2, 3.9, 1H), 7.40-8.10 (m, 5H); ^{19}F NMR 124.08 (ddd, J = 282.9, 56.2, 11.5, 1F), 127.06 (ddd, J = 282.9, 56.6, 17.5, 1F); MS *m/z* 214 [M^+], 122, 105, 77; HRMS Calcd for $C_{11}H_{12}F_2O_2$ [M^+] 214.081, found 214.080.

Reduction of ***2a*** *with n-*Bu_3SnH*:* A solution of **2a** (52 mg, 0.17 mmol), *n*-Bu_3SnH (0.2 ml, 0.74 mmol) and AIBN (3 mg, 0.018 mmol) in benzene (2 ml) was heated at reflux temperature for 2 h. After evaporation of the solvent, chromatography of the residue with *n*-hexane-EtOAc as an eluent gave **7a** (35 mg, 90.0%).

Allylation of ***2a*** *with allyltributyltin:* A solution of **2a** (52 mg, 0.17 mmol), allyltributyltin (0.25 ml, 0.81 mmol) and AIBN (3 mg, 0.018 mmol) in benzene (2 ml) was heated at reflux temperature for 7 h. After evaporation of the solvent, chromatography of the residue with *n*-hexane-EtOAc as an eluent gave **8a** (40 mg, 87.8%): a colorless oil; $[\alpha]_D^{24}$ +26.0 (c 0.64, $CHCl_3$); IR (neat) 1781, 1706, 1388, 1206, 993; ^1H NMR 0.89 (d, J = 7.0, 3H), 0.93 (d, J = 7.7, 3H), 1.31 (d, J = 7.0, 3H), 2.31-2.48 (m, 1H), 2.56-2.99 (m, 2H), 4.19-4.78 (m, 4H), 5.17-5.30 (m, 2H), 5.77-5.98 (m, 1H); ^{19}F NMR 98.54-102.77 (m); MS *m/z* 275 [M^+], 255, 214, 147, 126; HRMS Calcd for $C_{13}H_{19}F_2NO_3$ [M^+] 275.133, found 275.133.

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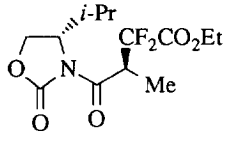
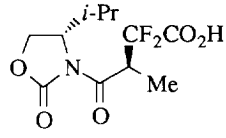
8. α-(Ethoxycarbonyl)difluoromethyl carboximide **14a** (See ref. 5) was converted to **2a** as follows. The hydrolysis of **14a** with $NaHCO_3$ in aqueous MeOH (room temperature, 12 h) gave the corresponding carboxylic acid **15a** which was then treated with Br_2 in CH_2Cl_2 in the presence of XeF_2 and NaF at room temperature for 6 h to afford **2a** in 42% overall yield.



14a



15a

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(*Received in Japan* 13 *February* 1996)