Stereoselective Synthesis of *anti*-α-(Difluoromethyl)-*β*-amino Alcohols by Boronic Acid Based Three-Component Condensation. Stereoselective Preparation of (2*S*,3*R*)-Difluorothreonine

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Received December 3, 2001

Starting from optically active 3,3-difluorolactaldehyde, an alkenyl or aryl boronic acid, and an amine, a one-step three-component methodology was developed for the stereoselective preparation of *anti*-α-(difluoromethyl)-*β*-amino alcohols. *β*-Furyl-substituted *anti*-α-(difluoromethyl)-*β*-amino alcohol was further elaborated to form (2*S*,3*R*)-difluorothreonine in high yield and ee.

Introduction

The scarcity of fluorinated molecules in nature together with their increasing use in new materials and new pharmaceuticals has inspired chemists to develop efficient methodologies for their synthesis. Among the most important applications of organofluorine compounds is in medicinal chemistry.[1] A noteworthy example is the use of fluoroalkyl groups in peptidyl fluoroalkyl ketones, which can serve as protease inhibitors[2] and are characterized by high oral activity and bioavailability.

In recent years, we have developed several nucleophilic trifluoromethylation methods,[3] which allow the efficient incorporation of fluorine into organic molecules. These processes have found wide use in the preparation of various types of bioactive compounds. Our most recent advances in this area include direct preparation of trifluoromethylated amines[4] and amino alcohols.[5] Unlike trifluoromethylated compounds, their difluoromethylated[6] congeners provide further opportunity for interaction with the solvent and biological molecules[7] due to their ability to serve as hydrogen bond donors. Also the $-CF_2H$ group is isosteric with an −OH group. Difluoromethylated amino alcohols, therefore, are significant synthetic targets because they feature important functional handles (Figure 1) that allow diverse interaction within biologically active molecules.

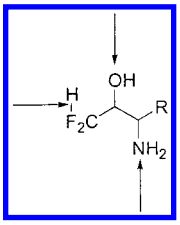

Figure 1.

In this paper we disclose a new convenient methodology for the preparation of difluoromethylated amino alcohols using a novel three-component reaction strategy (Scheme 1).[8] This approach is based on our recently reported chemistry involving the one-step three-compo-

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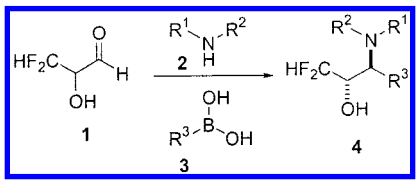
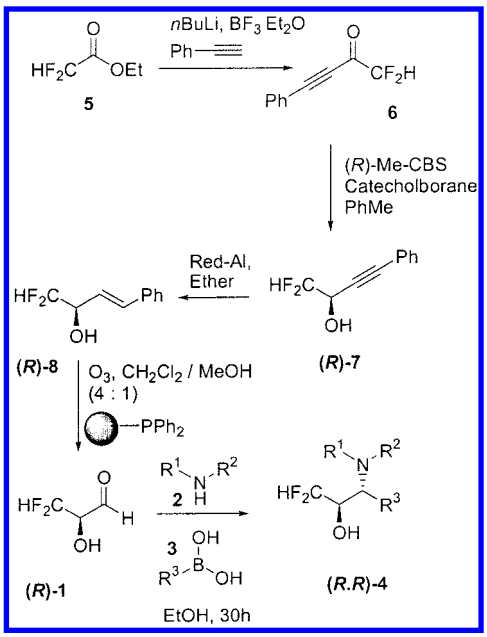
10.1021/jo011116w CCC: $22.00
Published on Web 04/27/2002

Scheme 1



Scheme 2

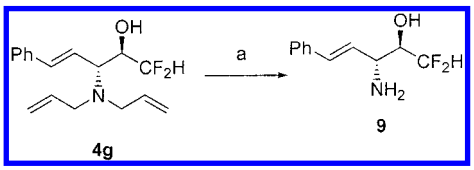


nent reaction among a carbonyl compound, an amine, and an organoboronic acid. We have previously reported the use of this novel process for the synthesis of amino acids[8a,b] and amino alcohols[8c,d] including trifluoromethylated derivatives[5] as well as the synthesis of aminopolyols.[8f] The application described herein involves the one-step reaction among difluorolactaldehyde (**1**), an amine (**2**), and an alkenyl or aryl organoboronic acid (**3**) to form directly *anti*-α-(difluoromethyl)-β-amino alcohols **4**.[9]

Results and Discussion

No literature precedence exists for the preparation and properties of **1**, the envisioned precursor for our three-component condensation reaction. We have now achieved its convenient preparation as outlined in Scheme 2 starting from ethyl difluoroacetate (**5**). The acetylenic alcohol **7** was synthesized according to a literature procedure.[10] However, instead of using the chloroborane protocol for its asymmetric reduction, we relied on Corey's CBS reduction using (*R*)- as well as (*S*)-methyloxazaborolidine.[11] This resulted in a significantly increased ee. The

Scheme 3[a]



[a] Reagents and conditions: (a) $D(PPh_3)_4/CH_2Cl_2$, dimethylbarbituric acid, Δ, or $Rh(PPh_3)_3Cl$, H_2O, CH_3CN, Δ.

alkynyl alcohol **(*R*)-7** thus obtained was converted to alkenyl alcohol **(*R*)-8** using Red-Al without any stereochemical loss. Ozonolysis of **(*R*)-8** in a 4:1dichloromethane/methanol mixture provided quantitatively the hydroxyaldehyde **(*R*)-1** in an oligomeric form.[12] The corresponding **(*S*)-1** was prepared similarly.

Hydroxyaldehyde **1** (in its oligomeric form[12]) was used directly in the coupling reaction, without further purification. Alkenyl, aryl, and heteroaryl boronic acids participated very well in this process. In general, the coupling products were obtained in good yields in the presence of secondary amines (Table 1). Under these reaction conditions, however, the primary amine **2c** afforded the coupling product **4h** in only moderate yield, albeit in a high de (>99%) and ee as well. It should be mentioned that the commercially available boronic acids gave higher yields of the coupling products only upon purification by recrystallization.

The overall enantiomeric excess (% ee) was similar to the one observed during the ketone reduction step (Scheme 2), and no loss of enantiomeric purity was observed during the ozonolysis (Scheme 2) and coupling reaction, as confirmed by comparing the ee values of the amino alcohols with that of the alcohol precursor. The ee values of the amino alcohols were determined by ^{19}F NMR using Mosher's chloride and compared with the corresponding Mosher's derivatives of the racemic compounds.

The unprotected amino alcohol derivatives can also be prepared by the present method, using diallylamine as the amine component, followed by catalytic deallylation, as we have previously reported.[8f] This is exemplified with the efficient synthesis of compound **9** from the diallylamino alcohol **4g** via deallylation in the presence of a catalytic amount of $Pd(Ph_3)_4$ using dimethylbarbituric acid as the allyl group scavenger (Scheme 3).[13]

Enantioselective Preparation of (2*S*,3*R*)-Difluorothreonine (13). Having developed a general method for the preparation of difluoromethylated amino alcohols, we subsequently investigated their possible conversion to biologically important compounds, such as fluorinated amino acids.[1,14] In addition to being employed as chemotherapeutic agents, these molecules are also used in the

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(9) The *anti* stereochemical assignment was made on the basis of the analogy with our previous finding (see ref 8c) as well as comparison of the coupling constant of the proton H4 of the oxazolidinone **11** and with that of a similar system. Begue, J.-P.; Bonnet-Delpon, D.; Fischer-Durand, N. *Tetrahedron: Asymmetry* **1994**, *5*, 1099−1110.

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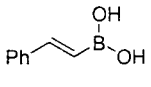
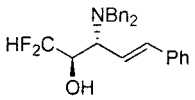
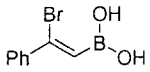
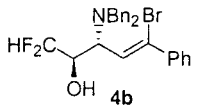
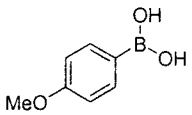
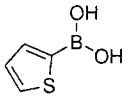
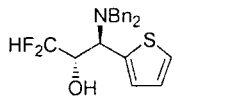
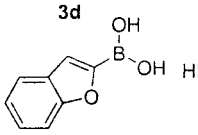
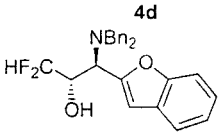
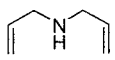
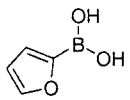
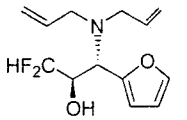
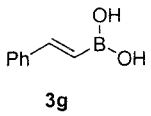
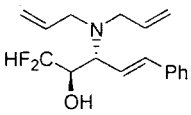
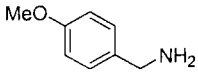
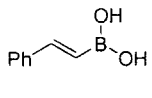
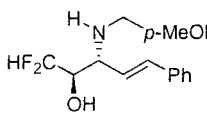
Table 1. Synthesis of *anti*-α-(Difluoromethyl)-*β*-amino Alcohols

Aldehyde	Amine	Boronic Acid	Amino Alcohol[a]	ee (%)	Yield (%)
					
(*R*)-1	**2a**	**3c**	**4c**	>99	60
					
(*R*)-1	**2a**	**3b**	**4b**	94	63
					
(*R*)-1	**2a**	**3c**	**4c**	92	55
					
(*S*)-1	**2a**	**3d**	**4d**	92	57
					
(*S*)-1	**2a**	**3e**	**4e**	>99	65
					
(*R*)-1	**2b**	**3f**	4f	86	90
					
(*R*)-1	**2b**	**3g**	**4g**	92	75
					
(*R*)-1	**2c**	**3h**	**4h**	96	30

[a] All the amino alcohols were obtained in >99% de.

study of biosynthetic pathways and as conformational modifiers in physiologically active enzymes.[14a] Consequently, several studies have been directed for their synthesis.[14] The reports on difluoromethylated amino acids are, however, fewer, since feasible enantioselective synthetic strategies for these compounds have been limited.[7,15] Although some enzymatic routes have been described[15] for the synthesis of (2*S*,3*S*)- as well as (2*R*, 3*R*)-difluorothreonine, there have been no reports on the asymmetric synthesis of *anti*-difluorothreonine. To employ the synthetic concept described herein to the synthesis of *anti*-difluorothreonine, the group incorporated via the boronic acid component had to be an appropriate precursor for a carboxyl or carbonyl group. Thus, furyl derivative **4f** was investigated (Scheme 4). Compound **4f** was first deallylated and subsequently converted to the oxazolidinone[8f,17] **11** using Boc_2O in 90% yield. Although oxidation of the furyl group of the oxazolidinone **11** was successful with the $RuCl_3/NaIO_4$ system,[16] the extreme water solubility of **12** led us to search for an alternative nonaquatic methodology. Thus, ozonolytic oxidation[18] of the furyl moiety of **11** gave the acid **12** in 75% isolated yield, which was hydrolyzed using 6 N HCl to the *anti*-difluorothreonine (2*S*,3*R*)-**13.**

In summary, we have developed a facile and efficient multicomponent methodology for the stereoselective synthesis of *anti*-α-(difluoromethyl)-*β*-amino alcohols **4**. The method was extended to the enantioselective preparation of **13** in high yield and high ee.

(15) For the synthesis of difluorothreonine see: (a) Shimizu, M.; Yokota, T.; Fujimori, K.; Fujisawa, T. *Tetrahedron: Asymmetry* **1993**, *4*, 835−838. (b) Yamazaki, T.; Haga, J.; Kitazume, T. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 271−276.

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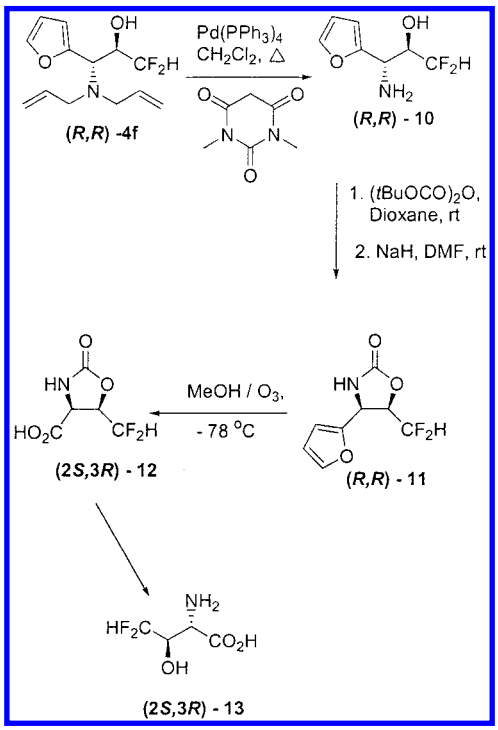
(17) Begue, J.-P.; Bonnet-Delpon, D.; Fischer-Durand, N. *Tetrahedron: Asymmetry* **1994**, *5*, 1099−1110.

(18) Demir, A. S. *Pure Appl. Chem.* **1997**, *69*, 105−108.

Scheme 4



Experimental Section

General Procedures. Unless otherwise mentioned, all the reagents were purchased from commercial sources. THF was distilled under nitrogen from sodium/benzophenone ketyl prior to use. Flash chromatography was carried out using Merck 60 230−400 mesh silica gel. Diastereoselectivities were determined directly from a crude reaction mixture by ^{19}F NMR. Chemical shifts are reported relative to those of internal chloroform (δ 7.24), methanol (δ 4.78), or tetramethylsilane (δ 0.0) for ^{1}H, chloroform (δ 77.0) or methanol (δ 49.0) for ^{13}C, and $CFCl_3$ (δ 0.0) for ^{19}F. The ^{1}H NMR shifts of the −OH groups are not shown because of their dependence on concentration. Optical rotations were measured at ambient temperature. Enantioselectivities were determined from ^{19}F NMR of the corresponding (*S*)-MTPA derivatives.

Reduction of 2 to 3: (*R*)-(+)-1,1-Difluoro-4-phenyl-3-butyn-2-ol (7). In a flame-dried flask containing **2** (0.962 g, 5.34 mmol, azeotropically dried with toluene) in 5 mL of toluene was placed (*R*)-methyl-CBS-oxazaborolidine (0.534 mmol). The reaction mixture was cooled to −78 °C, 0.768 g (6.4 mmol) of catecholborane in 4.4 mL of toluene was added slowly down the side of the flask over 30 min, and the reaction mixture was stirred for 20 h. Methanol was added at the end of the reaction, and the solution was warmed to room temperature, diluted with ether, and washed with buffer (pH 13, 1 N NaOH/saturated $NaHCO_3$, 2:1) until the aqueous phase became colorless. The aqueous phase was extracted twice with ether. The combined organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography (10% ethyl acetate in hexanes) provided 0.850 g (87%) of (*R*)-**3** in 90% ee: $[\alpha]^{20}_D$ + 17.2 (*c* 0.96 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.54 (1H, d, J = 6.7 Hz), 4.75 (1H, m), 5.83 (1H, dt, J = 55.5, 3.16 Hz), 7.30−7.39 (3H, m), 7.46−7.48 (2H, m); ^{13}C NMR ($CDCl_3$) δ 63.5 (t, $^{2}J_{C-F}$ = 27 Hz), 82.1, 87.9, 113.8 (t, $^{1}J_{C-F}$ = 247 Hz), 121.3,128.4, 129.3, 131.9; ^{19}F NMR ($CDCl_3$) δ −128.5 (1F, dd, J = 51.9, 5.4 Hz).

Preparation of (*R*)-4: (*R*)-(+)-1,1-Difluoro-4-phenyl-3-buten-2-ol (8). To a solution of 0.664 g (3.65 mmol) of (*R*)-**3** in 25 mL of ether under an argon atmosphere was added 1.63 mL (5.47 mmol) of Red-Al at 0 °C. The resulting solution was warmed to room temperature and stirred for 20 h. Subsequently, the solution was cooled in an ice bath and cautiously decomposed by adding dilute aqueous H_2SO_4 dropwise. The aqueous phase was separated and extracted twice with ether. The combined ether extract was washed with saturated $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated to afford 0.670 g (99%) of (*R*)-**4**. $[\alpha]^{20}_D$ +14.5 (*c* 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.41 (1H, d, J = 4.76 Hz), 4.44 (1H, m), 5.70 (1H, dt, J = 60.4, 4.76 Hz), 6.19 (1H, d, J = 14.6 Hz), 6.2 (1H, dd, J = 16.1 Hz), 7.24−7.41 (5H, m); ^{13}C NMR ($CDCl_3$) δ 72.2 (t, $^{2}J_{C-F}$ = 25.3 Hz), 115.7 (t, $^{1}J_{C-F}$ = 245 Hz), 122.5(t, $^{1}J_{C-F}$ = 3.97 Hz), 126.7,128.4, 128.7, 134.8, 135.7; ^{19}F NMR ($CDCl_3$) δ −128.4 (1F, ddd, J = 285, 57.1, 11.0), −129.8 (1F, ddd, J = 285, 57, 10.5 Hz).

Preparation of Difluoromethylactaldehyde (1). A flame-dried tube containing (*R*)-**8** (152 mg, 0.75 mmol) in 31 mL of a dichloromethane/methanol mixture (25 mL of dichloromethane and 6 mL of methanol) was cooled to −78 °C and a stream of ozone bubbled through the solution until the blue color of ozone persisted. Oxygen was passed to remove the excess ozone from the solution. At this point polymer-bound triphenylphosphine (280 mg, 0.85 mmol) was added, and the reaction mixture was stirred for 10 min at −78 °C. Subsequently, the solution was warmed to 0 °C and stirred for 10 min. Then the reaction mixture was warmed to room temperature and stirred for an additional 10 min. The reaction mixture was filtered through a plug of Celite and concentrated. This crude difluoromethylactaldehyde (in its oligomeric form[12]) was taken directly for the coupling reaction.

Typical Procedure for the Synthesis of Amino Alcohol. To a 25 mL round-bottom flask containing 0.5 mmol of difluoromethylactaldehyde and 0.5 mmol of amine in 5 mL of ethanol was added boronic acid. The reaction mixture was stirred for 24−48 h at room temperature. Evaporation of solvent gave a crude oil that was purified by flash chromatography (5−10% ethyl acetate in hexanes) to afford 60−90% amino alcohols.

Data for (2*R*,3*R*)-3-Dibenzylamino-1,1-difluoro-5-phenyl-4-penten-2-ol (4a): $[\alpha]^{20}_D$ −166.7 (*c* 1.1 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.43 (1H, m), 3.49 (2H, d, J = 13.7 Hz), 3.92 (2H, d, J = 13.7 Hz), 4.02 (1H, m), 5.94 (1H, t, J = 52.9 Hz), 6.30 (1H, dd, J = 15.8, 6.6 Hz), 6.55 (1H, d, J = 16.0 Hz), 7.22−7.44 (15H, m); ^{13}C NMR ($CDCl_3$) δ 55.2, 62.1, 71.6 (t, $^{2}J_{C-F}$ = 22.7 Hz), 115.0 (t, $^{1}J_{C-F}$ = 243 Hz), 122.5, 126.6, 127.3, 128.1, 128.5, 128.6, 128.7, 136.3, 136.9, 139.0; ^{19}F NMR ($CDCl_3$) δ −129.8 (1F, ddd, J = 284, 55, 6.7 Hz), −135.2 (1F, ddd, J = 285, 57.2, 17.4 Hz); HRMS (DCI, NH_3) *m*/*z* 394.1971 [M^+], calcd for $C_{25}H_{26}F_2NO$ 394.1982.

Data for (2R,3R)-5-Bromo-3-dibenzylamino-1,1-difluoro-5-phenyl-4-penten-2-ol (4b): obtained as a colorless oil by flash chromatography (5% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$) δ 3.62 (2H, d, J = 13.5 Hz), 3.96 (2H, d, J = 13.5 Hz), 4.0−4.11 (2H, m), 5.86 (1H, td, J = 55.5, 3.2 Hz), 6.47 (1H, d, J = 9.3 Hz), 7.25−7.59 (15H, m); ^{13}C NMR ($CDCl_3$) δ 55.7, 61.9, 72.2 (t, $^{2}J_{C-F}$ = 21.7 Hz), 114.8 (t, $^{1}J_{C-F}$ = 243 Hz), 125.1, 127.3, 127.9, 128.4, 128.5, 128.8, 129.2, 131.2, 138.9, 139.4; ^{19}F NMR ($CDCl_3$) δ −128.5 (1F, ddd, J = 281, 57.0, 6.5 Hz), −133.9 (1F, ddd, J = 289, 57, 19.9 Hz); HRMS (DCI, NH_3) *m*/*z* 472.1070 [M^+], calcd for $C_{25}H_{25}BrF_2NO$ 472.1087.

Data for (1*R*,2*R*)-1-Dibenzylamino-3,3-difluoro-1-(4-methoxyphenyl)propan-2-ol (4c): $[\alpha]^{20}_D$ −81.3 (*c* 0.3 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.49 (2H, d, J = 13.5 Hz), 3.92 (6H, m), 4.40 (1H, m), 6.20 (1H, dt, J = 55.0, 2.0 Hz), 6.80−7.52 (14H, m); ^{13}C NMR ($CDCl_3$) δ 54.8, 55.3, 62.7, 70.3 (t, $^{2}J_{C-F}$ = 22 Hz), 113.8, 115.3 (t, $^{1}J_{C-F}$ = 240 Hz), 125.0, 127.3, 128.5, 131.0, 138.8, 159.4; ^{19}F NMR ($CDCl_3$) δ −129.6 (1F, ddd, J = 283, 58, 9.0 Hz), −136.6 (1F, ddd, J = 280, 54.9, 15.5 Hz); HRMS (DCI, NH_3) *m*/*z* 398.1922 [M^+], calcd for $C_{24}H_{26}F_2NO_2$ 398.1931.

Data for (1*R*,2*S*)-1-Dibenzylamino-3,3-difluoro-1-thiophen-2-ylpropan-2-ol (4d): $[\alpha]^{20}_D$ −117.7 (*c* 1.26 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.27 (2H, d, J = 13.6 Hz), 3.87 (2H, d, J = 13.7 Hz), 4.20 (1H, d, J = 8.2 Hz), 4.29 (1H, m), 6.04 (1H. dt, J = 55.6, 2.43 Hz), 7.0 (1H, d, J = 3.0 Hz), 7.10 (1H, m), 7.21−7.37 (11H, m); ^{13}C NMR ($CDCl_3$) δ 55.2, 58.9, 71.7 (t, $^{2}J_{C-F}$ = 21.3 Hz), 114.8 (t, $^{1}J_{C-F}$ = 243 Hz), 125.7, 126.7, 127.4, 128. 3, 128.5, 128.8, 135.9, 138.7; ^{19}F NMR ($CDCl_3$) δ −129.7 (1F, ddd, J = 284, 57.5, 6.4 Hz), −136.5 (1F, ddd, J = 284, 54.8, 17.0

Hz); HRMS (DCI, NH_3) *m/z* 374.1384 [M^+], calcd for $C_{21}H_{22}F_2NOS$ 374.1390.

Data for (1*R*,2*S*)-1-Benzofuran-2-yl-1-dibenzylamino-3,3-difluoropropan-2-ol (4e): $[\alpha]^{20}_D$ −184.6 (*c* 1.26 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.29 (2H, d, J = 13.6 Hz), 3.97 (2H, d, J = 13.6 Hz), 4.08 (1H, d, J = 9.6 Hz), 4.49 (1H, m), 6.22 (1H, t, J = 55.0 Hz), 6.70 (1H, s), 7.21−7.36 (12H, m), 7.53 (1H, d, J = 8.0 Hz), 7.61 (1H, d, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 55.7, 57.7, 69.7 (t, $^2J_{C-F}$ = 21 Hz), 107.8, 111.4, 114.7 (t, $^1J_{C-F}$ = 243 Hz), 121.1, 123.0, 124.4, 127.4, 127.9, 128.5, 128.9, 138.6, 152.5, 154.9; ^{19}F NMR ($CDCl_3$) δ −130.4 (1F, ddd, J = 281, 54, 5.2 Hz), −137.8 (1F, ddd, J = 281, 54, 18.7 Hz); HRMS (DCI, NH_3) *m/z* 408.1767 [M^+], calcd for $C_{25}H_{24}F_2NO_2$ 408.1775.

Data for (1*S*,2*R*)-1-Diallylamino-3,3-difluoro-1-furylpropan-2-ol (4f): $[\alpha]^{20}_D$ −104.9 (*c* 1.05 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.74 (2H, dd, J = 14.9, 8.6 Hz), 3.32 (2H, m), 4.05 (1H, d, J = 1.2 Hz), 4.31 (1H, m), 5.15 (3H, m), 5.20 (1H, m), 5.73 (2H, m), 6.10 (1H, dt, J = 55.0, 2.0 Hz), 6.27 (1H, d, J = 3.2 Hz), 6.38 (1H, dd, J = 3.6, 2.0 Hz), 7.43 (1H, m); ^{13}C NMR ($CDCl_3$) δ 54.1, 57.3, 69.7 (t, $^2J_{C-F}$ = 20.9 Hz), 110.1, 110.4, 115.0 (t, $^1J_{C-F}$ = 239 Hz), 117.8, 135.7, 142.4, 150.1; ^{19}F NMR ($CDCl_3$) δ −131.6 (1F, ddd, J = 290, 56.4, 6.9 Hz), −138.8 (1F, ddd, J = 280, 51.5, 17.5 Hz).

Data for (2*R*,3*R*)-3-Diallylamino-1,1-difluoro-5-phenyl-4-penten-2-ol (4g): ^1H NMR ($CDCl_3$) δ 3.05 (2H, dd, J = 14.0, 7.9 Hz), 3.35 (dd, 2H, J = 14.9, 5.7 Hz), 3.51 (1H, m), 3.99 (1H, m), 5.19 (4H, m), 5.74−6.07 (3 H, m), 6.20 (1H, dd, J = 15.4, 9.7 Hz), 6.57 (1H, d, J = 15.4 Hz), 7.25−7.42 (5H, m); ^{13}C NMR ($CDCl_3$) δ 53.5, 62.7, 70.8 (t, $^2J_{C-F}$ = 20 Hz), 115.5 (t, $^1J_{C-F}$ = 241 Hz), 117.8, 123.0, 126.5, 128.0, 128.6, 135.5, 136.2, 136.3; ^{19}F NMR ($CDCl_3$) δ −130.8 (1F, ddd, J = 277, 54, 9.5 Hz), −134.2 (1F, ddd, J = 285, 52.4, 13.9 Hz).

Data for (2*R*,3*R*)-1,1-Difluoro-3-(4-methoxybenzylamino)-5-phenylpent-4-en-2-ol (4h): $[\alpha]^{20}_D$ −73.7 (*c* 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.5 (1H, m), 3.65 (1H, d, J = 12.2 Hz), 3.80−3.95 (5H, m), 5.74 (1H, dt, J = 55.5, 4.34 Hz), 6.15 (1H, dd, J = 16.0, 8.68 Hz), 6.56 (1H, d, J = 16.4 Hz), 6.80 (2H, d, J = 8.67 Hz), 7.20−7.41 (7H, m); ^{13}C NMR ($CDCl_3$) δ 50.2, 55.3, 60.3, 71.6 (t, $^2J_{C-F}$ = 22 Hz), 113.9, 116.0 (t, $^1J_{C-F}$ = 244 Hz), 125.5, 126.5, 128.1, 128.6, 129.4, 131.4, 134.5, 136.0; ^{19}F NMR ($CDCl_3$) δ −128.46 (1F, ddd, J = 289, 54.7, 12.1 Hz), −130.3 (1F, ddd, J = 292, 54.7, 9.0 Hz); HRMS (DCI, NH_3) *m/z* 334.1617 [M^+], calcd for $C_{19}H_{22}F_2NO_2$ 334.1617.

(*R*,*R*)-2-Amino-1-difluoromethyl-4-phenyl-3-(*E*)-butenol (9). 4g (147 mg, 0.501 mmol) was dissolved in 13 mL of acetonitrile and water (84:16). A Claisen adapter fitted with a reflux condenser and addition funnel on one arm and with a short-path distillation head on the other was then attached to the reaction flask. The addition funnel was charged with excess acetonitrile/water (84:16), the system flushed with argon, and 27 mg of $(PPh_3)_3RhCl$ added at room temperature. The orange mixture was brought to vigorous boiling, and fresh solvent was added to replace the volume of liquid swept out the distillation head and into a cooled trap (−78 °C) by a slow stream of argon. After 1.5 h the reaction was judged complete according to TLC and the solvent removed in a vacuum. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 10:1; R_f = 0.15), yielding 66 mg (62%) of **9**: $[\alpha]^{20}_D$ −17.3 (*c* 1.0 $CHCl_3$); ^1H NMR (CD_3OD) δ 3.58 (dd, J = 8.1, 3.6 Hz, 1H), 3.77 (m, 1H), 5.68 (ddd, J = 56.4, 55.2, 5.4 Hz, 1H), 6.30 (dd, J = 15.9, 8.1 Hz, 1H), 6.57 (d, J = 15.9 Hz, 1H), 7.18−7.48 (m, 5H); ^{13}C NMR (CD_3OD) δ 55.38 (dd, J = 6.0, 2.4 Hz), 74.74 (dd, J = 24.5, 20.6 Hz), 117.44 (t, J = 242 Hz), 127.51 (2C), 128.73, 129.13, 129.60 (2C), 133.38, 138.19; ^{19}F NMR ($CDCl_3$) δ −127.99 (ddd, J = 310, 55.4, 6.6 Hz), −129.9 (ddd, J = 310, 56.6, 15.0 Hz); HRMS (DCI, NH_3) *m/z* 214.1046 [M^+], calcd for $C_{11}H_{14}F_2NO$ 214.1043.

(1*S*,2*R*)-1-Amino-3,3-difluoro-1-furan-2-ylpropan-2-ol (10). **8f** was deallylated according to the reported procedure. Thus, a solution of 0.681 g (2.63 mmol) of **8f** in 7 mL of dry degassed dichloromethane was added to a flask containing 0.06 g (0.051 mmol, 10^{-2} mmol/allylic group) of the catalyst (tetrakis(triphenylphosphino)palladium and 1.23 g (7.89 mmol, 3 mmol/allylic group) of *N*,*N*′-dimethylbarbituric acid under an argon atmosphere. The reaction mixture was stirred for 3 h at 35 °C. The orange-red heterogeneous reaction mixture was cooled to room temperature and evaporated to dryness. The crude reaction mixture was redissolved in 100 mL of ether and extracted twice with 20 mL of saturated aqueous Na_2CO_3. This amine-containing ethereal solution was washed with 20 mL of water and dried with $MgSO_4$. Evaporation of ether followed by column chromatography with 1:10 methanol/dichloromethane provided 0.388 g (82%) of the deallylated amine: $[\alpha]^{20}_D$ −8.4 (*c* 0.95 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.99 (1H, m), 4.20 (1H, d, J = 4.4 Hz), 5.66 (1H, dt, J = 55.7, 4.0 Hz), 6.29 (1H, d, J = 2.7 Hz), 6.36 (1H, dd, J = 3.8, 2.0 Hz), 7.40 (1H, m); ^{13}C NMR ($CDCl_3$) δ 50.2, 72.7 (t, $^2J_{C-F}$ = 20.3 Hz), 107.0, 110.4, 115.0 (t, $^1J_{C-F}$ = 243 Hz), 142.3, 154.0; ^{19}F NMR ($CDCl_3$) δ −128.8 (1F, ddd, J = 290, 54.5, 5.7 Hz), −131.2 (1F, ddd, J = 289, 54.6, 15.0 Hz).

(4*S*,5*R*)-5-Difluoromethyl-4-furan-2-yloxazolidin-2-one (11). A mixture of 0.384 g (2.17 mmol) of **10** and 0.568 g (1.2 equiv) of di-*tert*-butyl dicarbonate in dry dioxane was stirred for 24 h at room temperature. Dioxane was evaporated, and the residue was dissolved in ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$. Evaporation under reduced pressure followed by column chromatography using 20% ethyl acetate/hexanes yielded *N*-Boc-protected **10** as a white solid: $[\alpha]^{20}_D$ −38.0 (*c* 0.94 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.44 (9H, s), 3.33 (1H, m), 4.08 (1H, m), 5.06 (1H, m), 5.39 (1H, m), 5.60 (1H, t, J = 55.2 Hz), 6.34 (2H, d, J = 9.8 Hz), 7.39 (1H, s); ^{13}C NMR ($CDCl_3$) δ 28.2, 49.4, 72.9 (t, $^2J_{C-F}$ = 22.5 Hz), 80.7, 108.4, 110.5, 114.8 (t, $^1J_{C-F}$ = 244 Hz), 142.6, 150,2, 155.5; ^{19}F NMR ($CDCl_3$) δ −128.0 (1F, ddd, J = 295, 54.4, 4.0 Hz), −131.0 (1F, ddd, J = 293, 55.8, 13.2 Hz); HRMS (DCI, NH_3) *m/z* 278.1202 [M^+], calcd for $C_{12}H_{18}F_2NO_4$ 278.1203. A flame-dried flask containing sodium hydride (1.1 equiv, 0.079 g, 60% dispersion in mineral oil) in 5 mL of DMF was cooled to −78 °C under an inert atmosphere, and a solution of 0.497 g of *N*-Boc-protected **10** in 3 mL of DMF was added quickly. The heterogeneous mixture was warmed to room temperature and stirred for 7 h. The clear homogeneous solution thus obtained was diluted with ethyl acetate and washed several times with water. The organic phase was dried over $MgSO_4$ and concentrated to give an oil that was purified by column chromatography using 35% ethyl acetate/hexanes to afford 0.273 g (75%) of **11**: $[\alpha]^{20}_D$ −16.6 (*c* 1.06 MeOH); ^1H NMR ($CDCl_3$) δ 4.82 (1H, m), 5.12 (1H, d, J = 8.5 Hz), 5.57 (1H, dd, J = 55.7, 5.6 Hz), 6.43 (2H, m), 7.47 (1H, m); ^{13}C NMR (CD_3OD) δ 52.0, 77.8 (t, $^2J_{C-F}$ = 23.6 Hz), 110.5, 111.8, 114.2 (t, $^1J_{C-F}$ = 240 Hz), 144.9, 149.9, 159.9; ^{19}F NMR ($CDCl_3$) δ −126.5 (1F, ddd, J = 309, 54.0, 9.6 Hz), −128.9 (1F, ddd, J = 309, 55.4, 6.7 Hz); HRMS (DCI, NH_3) *m/z* 221.0735 [M^+], calcd for $C_8H_{11}F_2N_2O_3$ 221.0737.

(4*S*,5*R*)-5-Difluoromethyl-2-oxooxazolidine-4-carboxylic Acid (12). In a 100 mL tube 0.05 g (0.245 mmol) of **11** in 20 mL of methanol was cooled to −78 °C, and ozone was passed until the blue color persisted. The reaction was stopped and N_2 gas bubbled to remove the excess ozone. Evaporation of solvent gave the crude product as a white solid that was purified by flash chromatography (7:2.5:0.5 ethyl acetate/methanol/ammonium hydroxide) to afford 0.032 g (72%) of **12**: $[\alpha]^{20}_D$ −34.4 (*c* 1.07 MeOH); ^1H NMR (CD_3OD) δ 4.45 (1H, d, J = 9.2 Hz), 6.18 (1H, dt, J = 54.9, 2.9 Hz); ^{13}C NMR (CD_3OD) δ 58.1, 76.7 (t, $^2J_{C-F}$ = 21.1 Hz), 114.4 (t, $^1J_{C-F}$ = 245 Hz), 160.7, 173.7; ^{19}F NMR (CD_3OD) δ −127.0 (1F, ddd, J = 294, 53.3, 6.5 Hz), −132.4 (1F, ddd, J = 295, 55.4, 18.6 Hz); HRMS (DCI, NH_3) *m/z* 182.0267 [M^+], calcd for $C_5H_6F_2NO_4$ 182.0264.

(2*S*,3*R*)-2-Amino-4,4-difluoro-3-hydroxybutyric Acid (13). In a 25 mL single-neck, round-bottom flask equipped with a magnetic stirring bar and a reflux condenser were placed 0.032 g of **12** and 10 mL of 6 N HCl, and the mixture was refluxed at 100 °C for 8 h. Evaporation of the reaction mixture gave a brown solid that was purified by flash chromatography (6:3.5:0.05 ethyl acetate/methanol/ammonium hydroxide) to afford 0.025 g (92%) of **13** as a white solid: $[\alpha]^{20}_D$ +7.0 (*c* 1.0 MeOH); ^1H NMR (CD_3OD) δ 4.15 (1H, m), 4.22 (1H, m), 6.05

(1H, dt, $J = 56.2$, 6.07 Hz); ^{13}C NMR (CD_3OD) δ 54.8, 70.8 (t, $^2J_{C-F} = 28.0$ Hz), 116.3 (t, $^1J_{C-F} = 241$ Hz), 168.1; ^{19}F NMR (CD_3OD) δ −127.1 (2F, ddd, $J = 56.1$, 21.9, 11.0 Hz); HRMS (DCI, NH_3) m/z 156.0471 [M^+], calcd for $C_4H_8F_2NO_3$ 156.0472.

Acknowledgment. The support of our work by the Loker Hydrocarbon Research Institute is gratefully acknowledged. N.A.P. also thanks the National Institutes of Health (Grant GM 45970) for its support.

Supporting Information Available: ^{1}H, ^{13}C, and ^{19}F NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO011116W