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A novel and expedient synthesis of optically active fluoroalkylated amino acids via palladium-catalyzed allylic rearrangement and Ireland–Claisen rearrangement

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Abstract—The allylic substitution reactions of various chiral α-fluoroalkylated mesylates with carboxylic acids in the presence of a palladium catalyst proceeded smoothly to give γ-fluoroalkylated allyl esters in excellent yields. The esters were subsequently subjected to Ireland–Claisen rearrangement without isolation, leading to the corresponding homochiral α-fluoroalkylated-β,γ-unsaturated amino acids in good yields. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Fluorine-containing amino acids are an especially important class of non-proteinogenic amino acids displaying a broad spectrum of interesting and potent biological activities imparted by the fluorine atom. Therefore, various approaches to the synthesis of this class of amino acids have been developed during the last few decades.[1] In particular, β-fluoroalkylated-γ,δ-unsaturated amino acids **1**, shown in Fig. 1, have attracted much attention in recent years because non-fluorinated-γ,δ-unsaturated amino acids are of great importance not only as potent enzyme inhibitors[2] but also as intermediates for the synthesis of complex amino acids and peptides.[3]

Recently, we have succeeded in developing the stereospecific palladium-catalyzed allylic substitution reaction of homochiral fluorinated mesylates with various carboxylic acids leading to the corresponding optically active γ-fluoroalkylated allyl esters in excellent yields.[4] This success and our recent results on [3,3]-sigmatropic rearrangement[5] prompted us to examine the possibility of preparing β-fluoroalkylated-γ,δ-unsaturated amino acids **1** by combination of the palladium-catalyzed allylic substitution reaction[6] and Ireland–Claisen rearrangement reaction.[7] Herein, we wish to report a new expedient method for the synthesis of the enantiomerically enriched compounds from α-fluoroalkylated mesylates in a one-pot procedure.

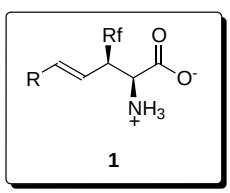

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Figure 1. Fluorine-containing amino acids.

2. Results and discussion

We first investigated the reaction of trifluoromethylated allyl mesylate **2a** with *N*-protected glycine in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) (Scheme 1). The mesylate **2a**, prepared readily from ethyl trifluoroacetate in three steps,[4] was treated with 5 mol% of $Pd(PPh_3)_4$ at 0°C for 10 min, followed by addition of 1.2 equiv. each of *N*-Boc glycine and triethylamine at the same temperature. After stirring the reaction mixture at rt for 1 h, *N*-Boc glycine γ-trifluoromethyl allyl ester **3a** was obtained as the sole product in quantitative yield. Neither the regioisomer **4a**, the stereoisomer **5a** nor the allylamine derivative **6a** (which may be produced by attack of the nitrogen atom

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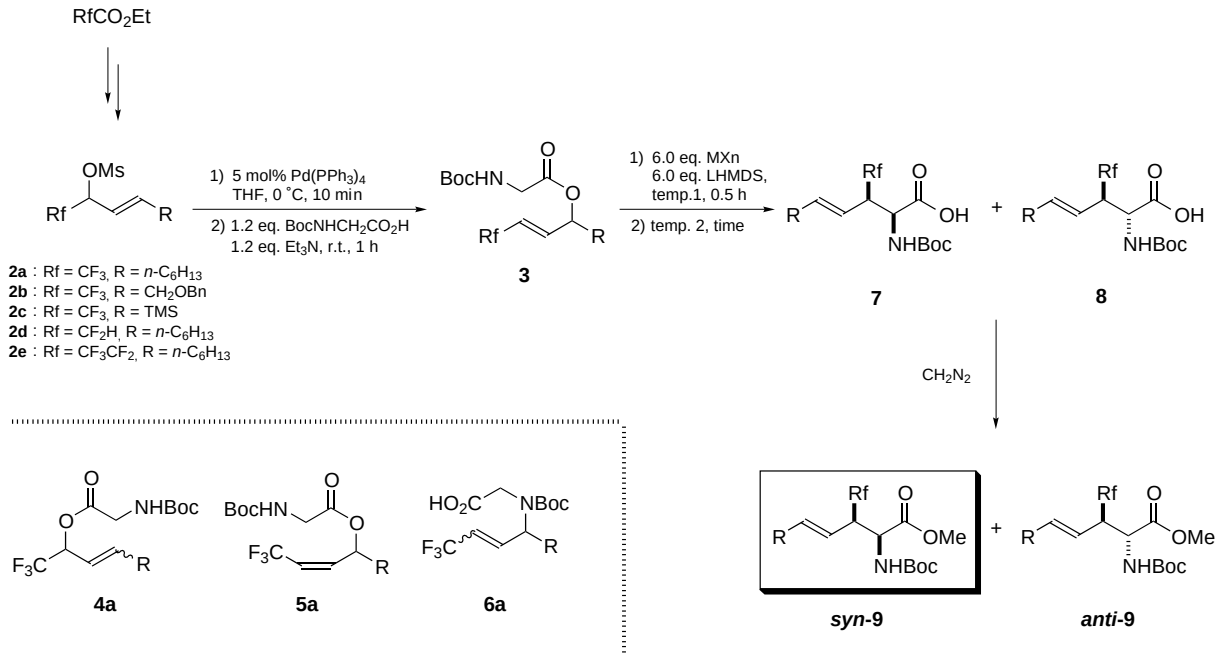


Scheme 1.

of the amide moiety to the π-allylpalladium complex) were detected in the reaction mixture. This result strongly encouraged us to undertake the one-pot synthesis of the fluorine-containing amino acids by direct Ireland–Claisen rearrangement of **3a**. The glycine allyl ester **3a**, generated in situ by the above-described reaction, was allowed to react with TMSCl and LHMDS at −78°C, followed by warming of the reaction mixture to rt. ^{19}F NMR analysis of the reaction mixture revealed that the desired rearrangement products, **7a** and **8a**, were formed in 48% yield, along with 44% of the unreacted **3a**. In view of the findings of Bartlett and Barstow that the Ireland–Claisen rearrangement of non-fluorinated glycine crotyl ester proceeds stereoselectively (d.s. = ca. 9:1) to give the corresponding amino acid in good yield,[8] it is very surprising that the products **7a** and **8a** were formed as a diastereomeric mixture in a ratio of 62:38. Thus, the reaction conditions for the [3,3]-rearrangement were examined in detail. These results are summarized in Table 1. As shown in entry 2, prolonging the reaction time for the [3,3]-rearrangement (20 h) did not lead to a dramatic change in either the yield or stereoselectivity. When the reaction mixture was stirred under reflux for 6 h, the desired products were obtained in excellent yield (94%), but the diastereomeric ratio was still only 73:27 (entry 3). Excellent diastereoselectivity (**7a**:**8a** = 100:0) was observed in the reaction without TMSCl (entry 4). In this case, however, the yield of the rearranged product was not high (49%) and the allyl ester **3a** was recovered in 23% yield.

It was observed that generation of the enolate of **3a** and its trapping with TMSCl at 0°C improved the diastereoselectivity of the reaction. As shown in entry 5, at room temperature over 20 h, the desired product was obtained in 62% yield with high diastereoselectivity (**7a**:**8a** = 96:4) and 32% of **3a** still remained unreacted. Therefore, the in situ generated silyl ketene acetal was subjected to reflux conditions for 6 h to afford **7a** and

Table 1. Investigation of the reaction conditions

Entry	MX_n	Temp. 1 (°C)	Temp. 2 (°C)	Time (h)	Yield[a] (%) of **7a**, **8a**	Yield[a] (%) of **3a**	Diastereomeric ratio **7a**:**8a**
1	TMSCl	−78	Rt	6	48	44	62:38
2	TMSCl	−78	Rt	20	45	55	54:46
3	TMSCl	−78	Reflux	6	94	2	73:27
4	None	−78	Rt	20	49	23	100:0
5	TMSCl	0	Rt	20	62	32	96:4
6	TMSCl	0	Reflux	6	84	9	91:9
7	TMSCl	0	Reflux	15	84	11	90:10
8[b]	TMSCl	0	Reflux	6	79	4	94:6
9	$ZnCl_2$	0	Reflux	6	82	14	100:0
10	$ZnCl_2$·TMEDA	0	Reflux	6	71	22	100:0

[a] Determined by ^{19}F NMR.
[b] Z-Glycine was used instead of Boc-glycine.

8a in 84% combined yield with high diastereoselectivity (**7a**:**8a** = 91:9). Prolonged refluxing (entry 7) and use of Cbz instead of Boc as a protecting group (entry 8) did not affect the yield or the diastereoselectivity. Kazmaier et al. reported that bidentate chelation in the enolate by using $ZnCl_2$ leads to a marked enhancement of the thermal stability, and that the rearrangement often proceeds with a high degree of stereoselectivity due to the fixed geometry of the enolate.[9] Therefore, we attempted the use of the zinc enolate prepared with anhydrous zinc chloride ($ZnCl_2$). On treating the in situ formed **3a** with $ZnCl_2$ and LHMDS at 0°C for 0.5 h, followed by heating the mixture under reflux for 6 h, the desired amino acid **7a** was obtained in 82% yield as a single isomer (entry 9). The $ZnCl_2$·TMEDA complex was also examined instead of anhydrous $ZnCl_2$ because $ZnCl_2$ was somewhat difficult to handle due to its high moisture-sensitivity. However, the use of $ZnCl_2$·TMEDA led to a slightly decrease in the yield of **7a** (entry 10).

With the best reaction conditions in hand, we next applied the present protocol for various types of fluorinated mesylates. The results are summarized in Table 2.

When the mesylate **2b** with a benzyloxymethyl group as the side chain R was employed, the reaction proceeded sluggishly to give the corresponding trifluoromethylated amino acid derivative in moderate yield, together with 29% of the allyl ester **3b** and 11% of the starting material **2b**. In the case of **2c** bearing a TMS group as R, the first allylic substitution reaction did not take place at all. It is highly possible that both CF_3 and TMS groups were so bulky[10] that the palladium complex could not coordinate to the double bond due to high steric repulsion. On the other hand, the mesylates with difluoromethyl and pentafluoroethyl Rf groups, **2d** and **2e**, could participate in the present reaction to give the corresponding rearranged products *syn*-**9d** and *syn*-**9e** in 53 and 62% isolated yields, respectively, after esterification with diazomethane.

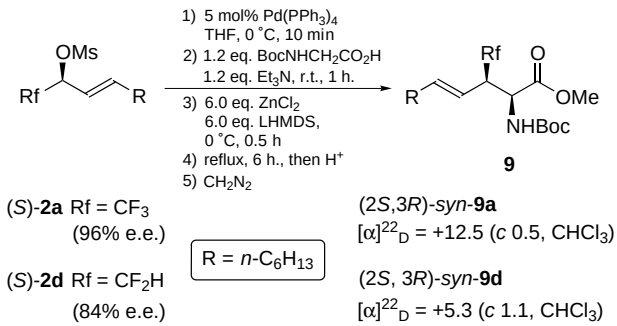
Next, our interest was directed toward the stereoselective synthesis of chiral fluorinated amino acids (Scheme 2). The chiral mesylates, (*S*)-**2a** and (*S*)-**2d**, prepared readily according to the literature,[11] were subjected to the same reaction conditions as described above, and the enantiomerically enriched products *syn*-**9a** and *syn*-**9d** were obtained in 60 and 53% yields, respectively. The rearranged product *syn*-**9a**, produced from trifluoromethylated mesylate with 96% enantiomeric excess, was treated with a mixture of TFA and CH_2Cl_2 (v:v = 1:1) at 0°C for several hours to remove the Boc group (Scheme 3). The TFA salt **10a** was treated with (*S*)-MTPA-Cl and DMAP to give the corresponding MTPA-amide **11a**,[12] whose diastereomeric excess was determined by ^{19}F NMR. It was found that the amide **11a** had 92% diastereomeric excess strongly suggesting that, within observational error, the reaction proceeded without any loss of enantiomeric purity through the two successive rearrangements.

Table 2. Syntheses of fluorine-containing amino acids with various fluoroalkyl groups

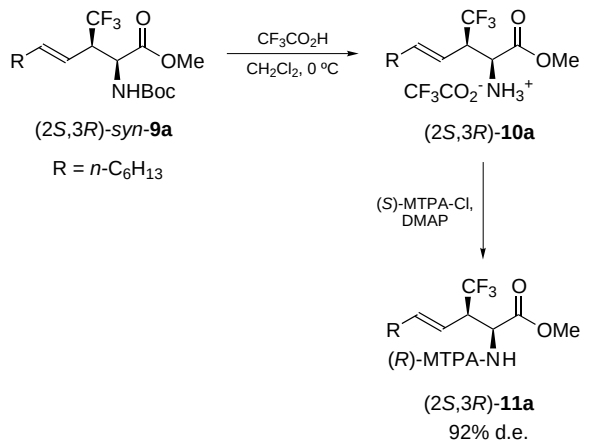
Entry	Substrate	Product	Yield[a] (%) of *syn*-**9**
1	**2a**	*syn*-**9a**	60 (82)
2	**2b**	*syn*-**9b**	–[b] (60)
3	**2c**	–	0
4	**2d**	*syn*-**9d**	53 (64)
5	**2e**	*syn*-**9e**	62 (65)

[a] Isolated yields. Values in parentheses show the ^{19}F NMR yields of **7**.

[b] Not determined because *syn*-**9b** could not be separated from the unidentified products.



Scheme 2.



Scheme 3.

The stereochemical assignment was carried out as follows: the relative stereochemistry of *syn*-**9a** and *anti*-**9a** was assigned by comparison of the chemical shifts in ^{19}F NMR with those of diethyl *N*-(diphenylmethylene)-2-trifluoromethyl glutamates **12a** and **13a** (Fig. 2).[13] It is reported that the signal of the *syn*-isomer **12a** (δ 7.65) appears at lower field than that of the *anti*-isomer **13a** (δ 5.77) in ^{19}F NMR (standard: trifluoroacetic acid). The difference of the chemical shifts is qualitatively analogous to the situation in *syn*-**9a** (δ 7.93) and *anti*-**9a** (δ 6.36). Therefore, the major isomer was assigned as *syn*-**9a** and the minor isomer *anti*-**9a**.

Although the absolute configuration of **7** has not been determined yet, the *syn* isomer **7** may be assumed to

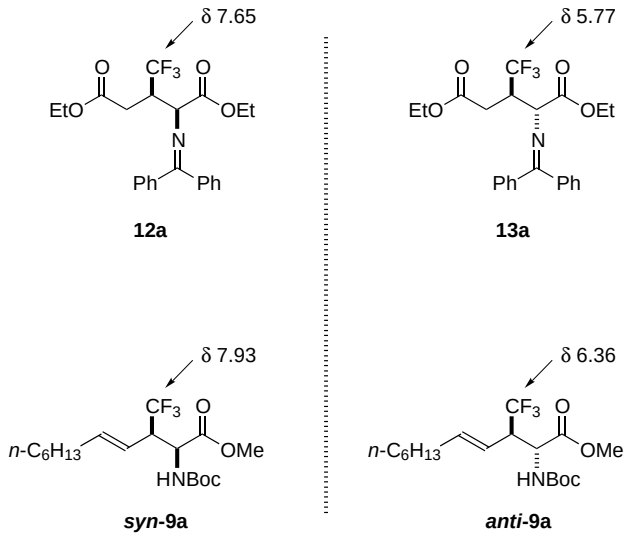
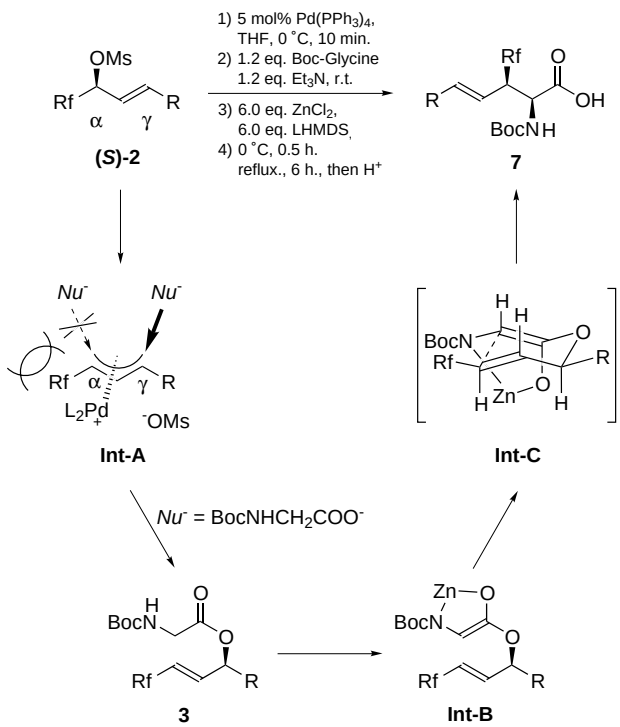


Figure 2. Stereochemical assignment.

have (2*S*,3*R*)-configuration on the basis of our preceding results[14] and the mechanism of the Ireland–Claisen rearrangement described in Scheme 4. Thus, when the Pd complex coordinates with the face of the olefin distal to the mesyloxy group, the Pd species displaces the mesylate with inversion to give a π-allyl complex (**Int-A**). The carboxylate nucleophile then attacks the complex on the face opposite to that occupied by Pd and this double inversion results in net retention for these processes.[15] In this case, the Pd moiety might be closer to the Rf group than the R group due to the electron-withdrawing effect of the Rf group. Therefore, the nucleophile attacks preferentially at the less hindered γ-carbon to give the γ-fluoroalkylated allylic ester **3**. Treatment of this allylic ester with $ZnCl_2$/LHMDS results in the stereoselective formation of (*Z*)-enolate (**Int-B**), which undergoes the stereoselective Ireland–Claisen rearrangement via an energetically stable six-membered cyclic transition state (**Int-C**), where the R group occupies the equatorial position, to give the desired amino acid with (2*S*,3*R*)-configuration.



Scheme 4.

3. Conclusions

In summary, we have investigated sequential allylic and Ireland–Claisen rearrangements, leading to the development of a novel synthesis of the optically active fluoroalkylated amino acid derivatives. This reaction can also serve as a general method for the preparation of chiral non-racemic amino acids with various types of fluoroalkyl groups such as CF_2H, CF_3, and CF_3CF_2 groups.

4. Experimental

4.1. General

Infrared spectra (IR) were recorded on a Shimadzu FTIR-8200A (PC) spectrophotometer. ^1H and ^{13}C NMR spectra were measured with a Bruker DRX 500 (500.13 MHz in ^1H NMR, 125.75 MHz in ^{13}C NMR) spectrometer in a chloroform-*d* ($CDCl_3$) solution with tetramethylsilane (Me_4Si) as an internal reference. A JEOL JNM-EX90F (84.21 MHz, FT) spectrometer was used for determining ^{19}F NMR spectra in a CH_2Cl_2 solution with internal TFA (trifluoroacetic acid). TFA was used ($\delta_F = 0$) as an internal standard for ^{19}F NMR. High resolution mass spectra (HRMS) were taken on a Hitachi M-80B mass spectrometer operating at an ionization potential of 70 eV. The optical rotation was measured by HORIBA SEPA-200.

4.2. Materials

Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone kethyl. *n*-Butyllithium (a 1.6 mol/L hexane solution) was commercially available from Wako Co. Et_3N and HMDS were distilled over calcium hydride and stored under argon. All chemicals were of reagent grade and, if necessary, were purified in the usual manner prior to use. Thin layer chromatography (TLC) was carried out with Merck silica gel 60 F_{254} plates, and column chromatography was carried out with Wako gel C-200. All reactions were carried out under an atmosphere of argon. ^{19}F NMR yield was calculated from the peak area ratio of a sample to hexafluorobenzene as an internal reference.

4.3. Typical procedure for the preparation of allyl mesylates 2

To a solution of α-fluoroalkylated allylic alcohol[11] (1 mmol) and methansulfonyl chloride (1.2 mmol) in CH_2Cl_2 (5 mL) was added dropwise triethylamine (1.2 mmol) at 0°C. The reaction mixture was allowed to

warm to room temperature and stirred for several hours. Then, the reaction mixture was poured into satd NH_4Cl aq. and the whole mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude materials were purified by silica gel column chromatography to give the corresponding allyl mesylate in over 90% yield.

4.3.1. (1*S*)-1-(Trifluoromethyl)-(2*E*)-nonenyl methanesulfonate (*S*)-2a. ^{1}H NMR δ 0.88 (t, J=5.1 Hz, 3H) 1.20–1.50 (m, 8H), 2.10–2.20 (m, 2H), 3.08 (s, 3H), 5.24 (dq, J=8.1, 6.3 Hz, 1H), 5.54 (dd, J=8.4, 15.6 Hz, 1H), 6.17 (dt, J=15.3, 6.5 Hz, 1H); ^{13}C NMR δ 13.94, 2.46, 28.08, 28.58, 31.45, 32.22, 39.45, 77.80 (q, J=34.1 Hz) 122.25 (q, J=279.9 Hz), 144.10; ^{19}F NMR δ −1.19 (d, J=6.6 Hz, 3F); IR (neat) ν 1670, 1373 cm^{-1}; $[\alpha]_D^{20}$= +38.9 (c 0.82, $CHCl_3$) (82% e.e.); anal. calcd for $C_{11}H_{19}F_3O_3S$: C, 45.82; H, 6.64. Found: C, 45.47; H, 6.59%.

4.3.2. 4-Benzyloxy-1-(trifluoromethyl)-(2*E*)-butenyl methanesulfonate 2b. ^{1}H NMR δ 3.10 (s, 3H) 4.11 (d, J=3.5 Hz, H), 4.55 (s, 2H), 5.33 (quint., J=6.5 Hz, 1H), 5.89 (dd, J=7.5, 15.5 H, 1H), 6.25 (dt, J=16.0, 4.0 Hz, 1H), 7.28–7.40 (m, 5H); ^{13}C NMR δ 39.40, 68.53, 72.72, 76.78 (q, J=34.9 Hz) 118.77, 122.18 (q, J=280.8 Hz), 127.72, 127.86, 128.47, 137.58, 138.49; ^{19}F NMR ($CDCl_3$) δ −0.98 (d, J=6.6 Hz); IR (neat) ν 1690, 1315 cm^{-1}; HRMS (M^+) calcd for $C_{19}H_{17}F_3O_3$, 350.1130. Found 350.1137.

4.3.3. 1-(Difluoromethyl)-(2*E*)-nonenyl methanesulfonate (*S*)-2d. ^{1}H NMR δ 0.85 (t, J=6.6 Hz, 3H) 1.20–1.42 (m, 8H), 2.05–2.15 (m, 2H), 3.02 (s, 3H), 5.04 (ddt, J=3.3, 8.4, 10.8 Hz, 1H), 5.49 (dd, J=8.1, 15.3 Hz, 1H), 5.77 (dt, J=3.6, 54.9 Hz, 1H), 6.07 (dt, J=6.6, 15.3 Hz, 1H); ^{13}C NMR δ 13.96, 22.47, 28.24, 28.64, 31.48, 32.31, 39.29, 79.62 (t, J=26.7 Hz) 112.84 (t, J=246.6 Hz) 118.75, 142.81; ^{19}F NMR δ −50.14 (ddd, J=8.8, 55.0, 288.3 Hz, 1F) −44.12 (ddd, J=8.8, 52.8, 288.2 Hz, 1F); IR (neat) ν 1670, 1366 cm^{-1}. $[\alpha]_D^{21}$=+31.3 (c 0.93, $CHCl_3$) (84% e.e.).

4.3.4. (1*S*)-1-(Pentafluoroethyl)-(2*E*)-nonenyl methanesulfonate 2e. ^{1}H NMR δ 0.88 (t, J=6.5 Hz, 3H) 1.20–1.34 (m, 6H) 1.38–1.45 (m, 2H) 2.16 (q, J=7.0 Hz, 2H) 5.34 (q, J=10.5 Hz, 1H) 5.56 (d, J=8.5 Hz, 1H) 6.17 (dt, J=15.5, 6.6 Hz, 1H); ^{13}C NMR δ 13.95, 22.50, 28.14, 28.61, 31.49, 32.29, 39.66, 7.49 (d, J=96.8, 111.2 Hz) 110.0–114.0 (m), 18.40 (tq, J=35.1, 286.70 Hz), 117.53, 144.68; ^{19}F NMR δ −47.94 (dd, J=8.8, 22.03 Hz, 2F) −5.47 (s, 3F); IR (neat) ν 1670, 1373 cm^{-1}; (96% e.e.); anal. calcd for $C_{12}H_{19}F_5O_3S$: C, 42.60; H, 5.66. Found: C, 42.57; H, 5.60%.

4.4. General procedure for the synthesis of fluorine-containing amino acid derivatives

To a solution of $Pd(PPh_3)_4$ (22 mg, 0.0019 mmol, 5 mol%) in THF (4 mL) was added trifluoromethylated allylic mesylate (0.100 g, 0.374 mmol) at 0°C. After stirring the mixture for 10 min, the reaction mixture was treated with Boc-glycine (0.073 g, 0.449 mmol) and Et_3N (0.06 mL, 0.449 mmol) at 0°C. The resulting mixture was allowed to warm to rt and stirred for 1 h to afford the corresponding *N*-Boc glycine γ-trifluoromethyl allyl ester. In the case of the compound with *n*-hexyl as a side chain, the spectral and analytical data are as follows.

4.4.1. (1-*n*-Hexyl-3-(trifluoromethyl)propen-2-yl) *N*-(*t*-butoxycarbamoyl)acetate 3a. ^{1}H NMR δ 0.87 (3H, t, J=6.8 Hz), 1.27–1.29 (10H, m), 1.45 (9H, s), 1.66 (1H, m) 3.94 (2H, dd, J=4.0, 18.5 Hz), 5.02 (1H, m), 5.41–5.42 (1H, m), 5.79–5.42 (1H, m), 6.28–6.33 (1H, m); ^{13}C NMR δ 13.97, 22.48, 24.65, 28.23, 28.85, 31.51, 33.67, 42.45, 72.77, 80.14, 119.57 (q, J=34.6 Hz), 122.65 (q, J=269.7 Hz) 137.44 (q, J=6.2 Hz), 155.67, 169.50; ^{19}F NMR δ 11.36 (3F, d, J=8.8 Hz); IR (neat) ν 1716, 1508 cm^{-1}; MS (CI) m/z (rel. intensity) 368 (M+H, 3), 312 (100), 120 (80); HRMS (CI) calcd for $C_{17}H_{29}F_3NO_4$, m/z 368.2049. Found: 368.2020.

In other cases, the intermediate, allyl esters were not isolated and were used for the subsequent Ireland–Claisen rearrangement without purification. Thus, to the reaction mixture was added anhydrous zinc chloride (0.284 g, 2.24 mmol) and lithium hexamethyldisilazide (LHMDS) (0.545 M solution, 3.82 mL, 2.24 mmol), which was prepared from hexamethyldisilazane (HMDS) and *n*-BuLi, at 0°C. The mixture was stirred at that temperature for 30 min and allowed to warm to reflux temperature of THF and stirred under reflux for 6 h. Saturated aqueous NH_4Cl was poured into the mixture, which was extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The residue was dissolved in ether (4.0 mL) and the solution was cooled to 0°C. To this solution was added dropwise an ethereal solution of diazomethane at 0°C. After stirring for 1 h, the reaction was quenched with AcOH, and the mixture was concentrated in vacuo. Purification by silica gel column chromatography gave the corresponding amino acid derivative.

4.4.2. Methyl 2-(*t*-butoxycarbamoyl)-3-trifluoromethyl-(4*E*)-undecenoate (2*S*,3*R*)-*syn*-9a. Yield: 60%. ^{1}H NMR δ 0.88 (3H, t, J=6.5 Hz), 1.20–1.40 (8H, m), 1.44 (9H, s), 2.06 (2H, q, J=7.0 Hz), 3.30 (1H, m), 3.74 (3H, s), 4.22 (1H, dd, J=4.5, 9.5 Hz), 5.07 (1H, d, J=9.5 Hz), 5.32 (1H, dd, J=9.5, 15.0 Hz), 5.79 (1H, dt, J=7.0, 15.0 Hz); ^{13}C NMR δ 13.94, 22.49, 28.12, 28.58, 31.53, 32.42, 49.53 (q, J=26.2 Hz), 52.45, 52.88, 80.40, 118.45, 125.45 (q, J=281.0 Hz), 140.35, 155.01, 170.34; ^{19}F NMR δ 7.93 (3F, d, J=8.8 Hz); IR (neat) ν 1751, 1720 cm^{-1}; MS (CI) m/z (rel. intensity) 382 (M+H, 10), 326 (100); HRMS (CI) calcd for $C_{18}H_{31}F_3NO$ m/z 382.2206. Found 382.2196; $[\alpha]_D^{22}$=+12.5 (c 0.5, $CHCl_3$) (92% e.e.).

4.4.3. Methyl 6-benzyloxy-2-(*t*-butoxycarbamoyl)-3-trifluoromethyl-(4*E*)-hexenoate (2*S,3*R**)-*syn*-9b**. Yield 60% (determined by ^{19}F NMR). ^{1}H NMR δ 1.44 (9H, s), 3.43 (1H, m), 3.76 (3H, s), 4.04 (2H, d, J=4.50 Hz),

4.51 (2H, s), 4.68 (1H, dd, $J=4.5$, 9.5 Hz), 5.13 (1H, d, $J=9.5$ Hz), 5.67 (1H, dd, $J=9.5$, 15.5 Hz), 5.94 (1H, dt, $J=4.5$, 15.5 Hz), 7.26–7.35 (5H, m); ^{13}C NMR δ 28.18, 49.20 (q, $J=26.7$ Hz), 52.68, 68.41, 72.15, 80.61, 121.37, 127.69, 127.75, 128.39, 129.80 (q, $J=268.7$ Hz), 135.70, 137.90, 155.11, 170.15; ^{19}F NMR δ 8.40 (3F, d, $J=11.0$ Hz); IR (neat) ν 1720 cm^{-1}.

4.4.4. Methyl 2-(*t*-butoxycarbamoyl)-3-difluoromethyl-(4*E*)-undecenoate (2*S*,3*R*)-*syn*-9d. Yield 53%. ^{1}H NMR δ 0.87 (3H, t, $J=7.0$ Hz), 1.25–1.37 (8H, m), 1.44 (9H, s), 2.04 (2H, q, $J=7.0$ Hz), 2.89 (1H, m), 3.74 (3H, s), 4.55 (1H, m), 5.09 (1H, d, $J=7.5$ Hz), 5.23 (1H, dd, $J=9.5$, 15.5 Hz), 5.71 (1H, dt, $J=7.00$, 15.5 Hz), 5.86 (1H, dt, $J=4.5$, 56.0 Hz); ^{13}C NMR δ 14.02, 22.54, 28.20, 28.66, 28.80, 31.59, 32.61, 49.94 (t, $J=86.8$ Hz), 52.38, 53.06, 80.35, 115.94 (t, $J=251.5$ Hz), 119.54, 139.49, 155.08, 171.00; ^{19}F NMR δ −46.95 (dd, $J=15.4$, 56.0 Hz); IR (neat) ν 1720 cm^{-1}; MS (CI) m/z (rel. intensity) 364 (M+H, 3), 308 (100). HRMS (CI) calcd for $C_{18}H_{32}F_2NO_4$ m/z 364.2300. Found 364.2287; $[\alpha]_D^{22}=+5.3$ (c 1.1, $CHCl_3$).

4.4.5. Methyl 2-(*t*-butoxycarbamoyl)-3-pentafluoroethyl-(4*E*)-undecenoate (2*S,3*R**)-*syn*-9e**. Yield 62%. ^{1}H NMR δ 0.87 (3H, t, $J=7.0$ Hz), 1.26–1.38 (8H, m), 1.45 (9H, s), 2.06 (2H, q, $J=7.00$ Hz), 3.33 (1H, m), 3.75 (3H, s), 4.68 (1H, dd, $J=5.5$, 9.5 Hz), 5.09 (1H, d, $J=9.0$ Hz), 5.30 (1H, dd, $J=5.5$, 9.5 Hz), 5.75 (1H, dt, $J=7.0$, 15.0 Hz); ^{13}C NMR δ 14.00, 22.53, 28.19, 28.62, 31.58, 32.42, 47.27 (t, $J=20.3$ Hz), 52.54, 52.81, 80.48, 114.10–122.15 (m), 118.39, 140.33, 154.94, 170.40; ^{19}F NMR δ −7.09 (3F, s), −42.90 (2F, dq, $J=25.3$, 270.6 Hz); IR (neat) ν 1724 cm^{-1}; MS (CI) m/z (rel. intensity) 432 (M+H, 7), 376 (100); HRMS (CI) calcd for $C_{19}H_{31}F_5NO_4$ m/z 432.2174. Found 432.2157.

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