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A novel synthesis of fluorine-containing quaternary amino acid derivatives via palladium-catalyzed allylation reaction

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Abstract

The palladium-catalyzed allylation reaction of trifluoroalanine derivatives with various allyl carbonates was examined. When *N*-Cbz-protected alanine derivative was employed, the desired *C*-monoallylated product was obtained in good yield, together with *C*,*N*-diallylated and *N*-monoallylated ones. Changing the protecting group from Cbz to PMP group caused an exclusive formation of *C*-monoallylated products in high yields. The reaction with various types of allyl carbonates also proceeded smoothly. Based on the present palladium-catalyzed allylation reaction, the total synthesis of α-CF_3 leucine analogue was achieved.

Keywords: Fluorine-containing quaternary amino acids; Allylation; Palladium; Trifluoromethylated leucine analogue

1. Introduction

α-Trifluoromethyl α-amino acids, shown in Fig. 1, are powerful tools for bioorganic and medicinal chemists. The introduction of a trifluoromethyl group into the natural amino acid structure can impart dramatic effects on physical as well as chemical properties, such as high electronegativity, electron density, steric hindrance, and so on, resulting in the interesting biological activity [1]. Because of this fact, the amino acids and larger molecules containing them have enjoyed widespread popularity and use in applications, such as biochemical probes, alternate enzyme substrates, and enzyme inhibitors [2]. A consequence of this popularity is the existence of a large body of literature describing methods for the synthesis of these compounds [3]. Despite this progress, there still remains a strong demand for improved strategies and synthetic routes. Herein, we wish to describe the very mild synthetic methods for the preparation of α-trifluoromethyl α-amino acids derivatives via the allylation of α-CF_3 enolate with π-allylpalladium complex in detail [4].

2. Results and discussion

Initially, the reaction of **1a** [5] with allyl ethyl carbonate in the presence of $Pd(dppe)_2$ was examined, referring to literature [4] (Table 1). Thus, to a THF solution of **1a** in the presence of 5 mol% of $Pd(dppe)_2$ and MS 5A was added 1.0 equiv. of allyl ethyl carbonate **2a** at room temperature. The reaction was heated and refluxed for 6 h, the *C*-monoallylated adduct **3a** being produced in only 7% yield, along with *C*,*N*-diallylated **4a** in 92%. In order to improve the yield of **3a**, we examined the reaction employing various palladium catalysts. As shown in Entries 2–4, 8, and 9, dppe and PPh_3 were found to be the ligand of choice for the reaction proceeding smoothly, however, *C*,*N*-diallylated adduct was afforded preferentially. When a phosphine ligand was not used (Entry 5) or a bulky ligand, such as $(c\text{-Hex})_3P$ or $(o\text{-Tol})_3P$, was employed (Entries 6 and 7), the reaction did not proceed at all, the starting ester **1a** being recovered quantitatively.

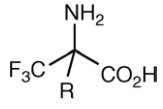

Fig. 1. α-CF_3-amino acids.

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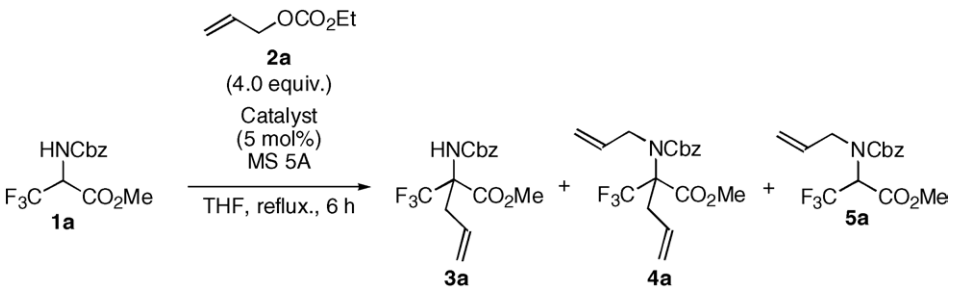
Table 1



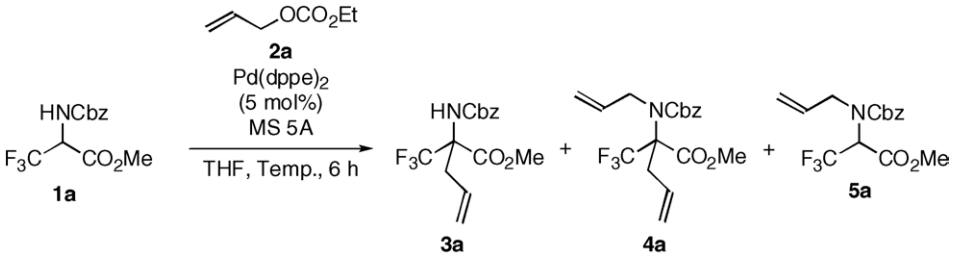
Entry	Catalyst (Pd = 5 mol%)	Yield[a] (%)			Recovery[a] (%) of **1a**
		3a	**4a**	**5a**	
1	$Pd(dppe)_2$	7	92	0	0
2	$1/2[\eta^3\text{-}CH_2\text{-}CHCH_2PdCl]_2 + 2dppe$	8	84	0	0
3	$Pd(PPh_3)_4$	12	86	0	0
4	$1/2[\eta^3\text{-}CH_2{=}CHCH_2PdCl]_2 + 4PPh_3$	10	80	0	0
5	$PdCl_2(PhCN)_2$	0	0	0	99
6	$Pd(OAc)_2 + 4(c\text{-Hex})_3P$	0	0	0	99
7	$Pd(OAc)_2 + 4(o\text{-Tol})_3P$	0	0	0	99
8	$Pd(OAc)_2 + 2(S)$-BINAP	29[b]	71	0	0
9	$1/2[\eta^3\text{-}CH_2{=}CHCH_2PdCl]_2 + 4PPh_3$	24	76	0	0

[a] Determined by ^{19}F NMR.
[b] The enantiomeric excess was not determined.

We next re-examined the reaction conditions, changing the temperature and an amount of **2a** as shown in Table 2. As shown in Entries 2–4, the use of MS 5A as well as a prolonged reaction time resulted in a significant increase of the yield, **3a** being produced preferentially. When 3 equiv. of **2a** was employed, the yield of **3a** increased up to 61%, along with 13% and 2% of **4a** and *N*-monoallylated **5a**, respectively (Entry 4). The reaction at the reflux temperature gave the desired product **3a** in 62% yield even when only 1.0 equiv. of **1a** was used. As shown in Entry 7, however, using 2 equiv. of **2a** caused the decrease of the yield of **3a** and the increase of the yield of **4a**.

We next investigated the allylation reaction by using *N*-PMP-protected amino esters **1b** or **1c** [6] as shown in Table 3. At first, we attempted the allylation of **1b** with 2.0 equiv. of **2a** under the refluxing conditions for 6 h. Interestingly, the *C*-monoallylated adduct **3b** was obtained quantitatively (Entry 1).

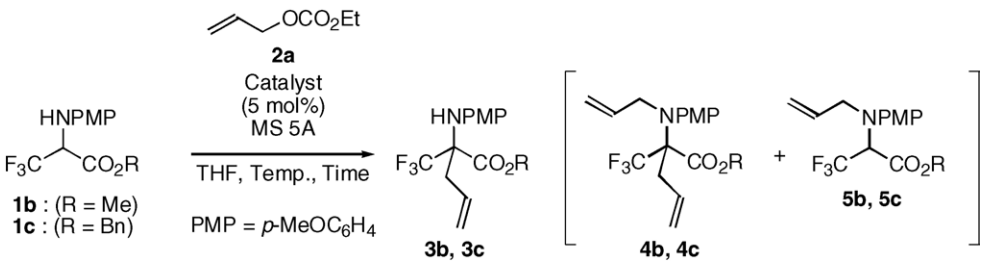
Table 2



Entry	Temperature	Equiv. of **2a**	Yield[a] (%)			Recovery[a] (%) of **1a**
			3a	**4a**	**5a**	
1	Reflux	4.0	7	92	0	0
2[b]	RT	1.0	18	1	6	73
3	RT	1.0	29	3	9	57
4[c]	RT	1.0	50	12	6	32
5[c]	RT	3.0	61	13	2	15
6	Reflux	1.0	62	14	1	23
7	Reflux	2.0	37	61	1	0

[a] Determined by ^{19}F NMR.
[b] MS 5A was not used.
[c] Carried out for 24 h.

Table 3

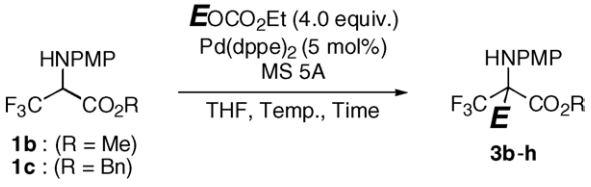


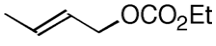
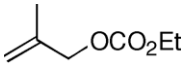
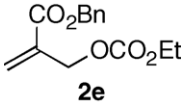
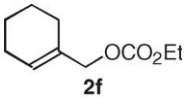
Entry	Catalyst	1	Temperature	Time	Equiv. of **2a**	Yield[a] (%) of **3**	ee[b] (%)	Recovery[a] (%) of **1**
1	$Pd(dppe)_2$	**1b**	Reflux	6	2.0	99 (97)	–	0
2	$Pd(dppe)_2$	**1b**	RT	12	1.2	99 (98)	–	0
3	$Pd(dppe)_2$	**1c**	RT	12	1.2	98 (96)	–	0
4[c]	$Pd(dppe)_2$	**1b**	RT	24	1.2	67	–	31
5	$Pd_2(dba)_3{\cdot}CHCl_3$ + 2(*S*)-BINAP	**1b**	RT	12	1.2	86	9	14
6	$Pd(OAc)_2$ + 2(*S*)-BINAP	**1b**	RT	12	1.2	13	–	87
7	$1/2[CH_2{=}CHCH_2PdCl]_2$ + 2(*S*)-BINAP	**1b**	RT	12	1.2	99 (96)	9	0
8	$1/2[CH_2{=}CHCH_2PdCl]_2$ + 2(*R*,*R*)-Chiraphos	**1b**	RT	12	1.2	63	4	37

[a] Determined by ^{19}F NMR. Values in parentheses are of isolated yields.
[b] Determined by HPLC (CHIRALPAC AD-H).
[c] One mol% of $Pd(dppe)_2$ was employed.

Any trace of *C*,*N*-diallylated or *N*-monoallylated product (**4b** or **5b**) was not detected at all. It was also found that the reaction using 1.2 equiv. of allyl ethyl carbonate at room temperature completed after 12 h, **3b** being produced quantitatively (Entry 2). Changing the substrate from **1b** to **1c** did not influence the reaction at all (Entry 3). However, the use of only 1 mol% of $Pd(dppe)_2$ caused a significant decrease of the yield (Entry 4).

Table 4



Entry	**1b** or **1c**	*E*OCO_2Et	Temperature	Time	Product	Yield[a] (%) of **3**	Recovery[a] (%) of **1**
1	**1b**		RT	12	**3b**	99 (98)	0
2	**1c**		RT	12	**3c**	98 (96)	0
3	**1b**		RT	12	**3d**	31	51
4	**1b**		Reflux	6		63 (59)	12
5	**1b**		RT	12	**3e**	44	49
6	**1b**		Reflux	6		95 (91)	0
7	**1b**		RT	12	**3f**	48	43
8	**1b**		Reflux	6		99 (84)	0
9	**1c**	**2d**	Reflux	6	**3g**	92 (86)	0
10	**1b**		RT	12	**3h**	0	96
11	**1b**		Reflux	6		37	61
12	**1b**	**2e**	Reflux	24		43 (40)	48
13	**1b**		RT	12		0	91
14	**1b**		Reflux	6	–	0	65
15	**1b**	**2f**	Reflux	24		0	51

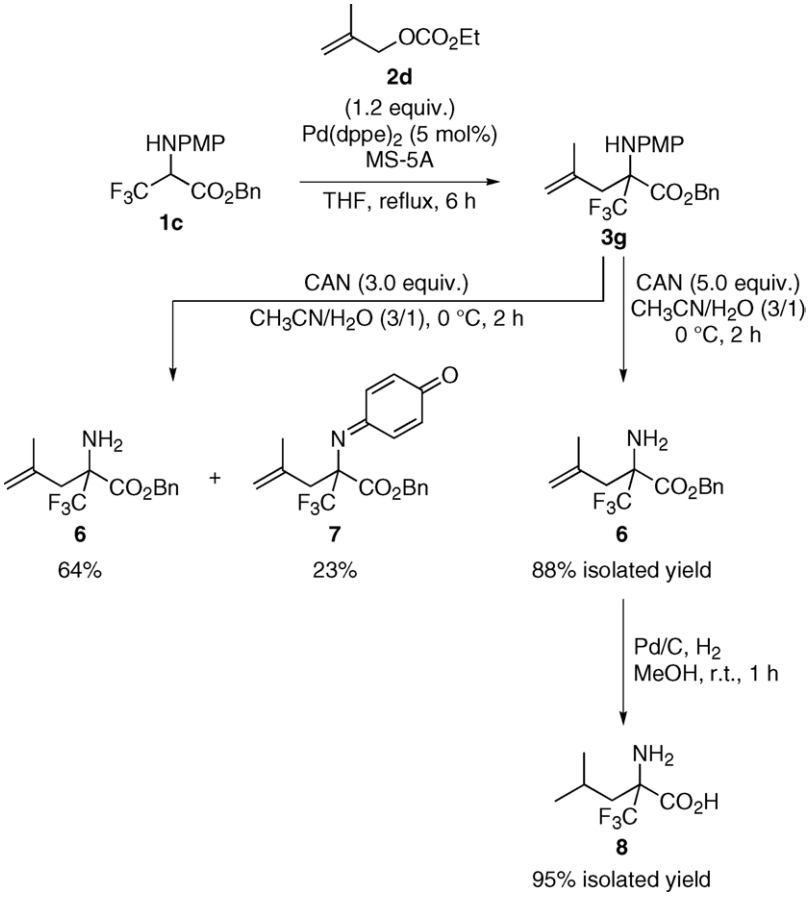
[a] Determined by ^{19}F NMR. Values in parentheses are of isolated yields.

We also attempted the reaction using a chiral ligand, such as (*S*)-BINAP or (*R*,*R*)-Chiraphos [7]. As shown in Entries 5, 7, and 8, the chiral catalysts prepared from $Pd_2(dba)_3{\cdot}CHCl_3$ or allylpalladium chloride dimer and the chiral ligands, were found to be very effective, the *C*-monoallylated adducts being afforded in good to high yields. However, the use of $Pd(OAc)_2$ resulted in a significant decrease of the yield, the starting material being recovered in 87% yield (Entry 6). Unfortunately, the enantioselectivity was not observed in these cases (4–9% ee).

With the optimum reaction conditions (Table 3, Entry 2), the allylation reactions of various types of allyl carbonates were examined. The results are summarized in Table 4. As shown in Entries 3, 5, and 7, the reaction with substituted allyl carbonate, such as crotyl, cinnamyl, and methallyl carbonates, at room temperature did not complete in 12 h, whereas the refluxing of the reaction mixture resulted in a smooth reaction, leading to the *C*-monoallylated adducts in good to excellent yields (Entries 4, 6, 8, and 9). As shown in Entries 10–12, β-ethoxycarbonyl allyl carbonate was not a good allylating reagent, the desired product being obtained in only 43% yield even when the reaction was conducted at the reflux temperature for 24 h. Additionally, **2f** was found to be completely inactive (Entries 13–15).

The reaction mechanism may be explained as follows, according to the literature [4]. Thus, the allyl ethyl carbonate **2** may add to the palladium oxidatively, followed by the subsequent elimination of carbon dioxide, π-allylpalladium complex **Int-1** being generated. The ethoxide may abstract α-proton of **1** to generate α-trifluoromethyl enolate **Int-2**, which could react readily with π-allylpalladium complex to give the desired α-allylated α-trifluoromethyl amino acid derivative **3**. In the case of *N*-Cbz-protected trifluoroalanine, the increase of the proton acidity at the amino group resulted in the facile proton abstraction by ethoxide to generate the corresponding amide **Int-3**, which reacted with π-allylpalladium complex to lead to *N*-allylated adduct, **4** or **5** (Fig. 2).

Next, our attention was directed to the synthesis of α-CF_3 leucine, based on the present allylation reaction. Thus, *C*-monoallylated adduct **3g**, which was obtained via the allylation of **1c** with ethyl methallyl carbonate in the presence of palladium catalyst, was treated with 3.0 equiv. of CAN (ammonium cerium(IV) nitrate) in CH_3CN/H_2O at 0 °C for 2 h. Unexpectedly, the desired free amine **6** was given in 64% yield, together with 23% of by-product **7**. After several attempts, we found that the use of 5.0 equiv. of CAN led to a smooth deprotection reaction, **6** being obtained in 88% isolated yield. Finally, the hydrogenation reaction took place smoothly to give the corresponding α-CF_3 leucine **8** in 95% yield (Scheme 1).



Scheme 1.

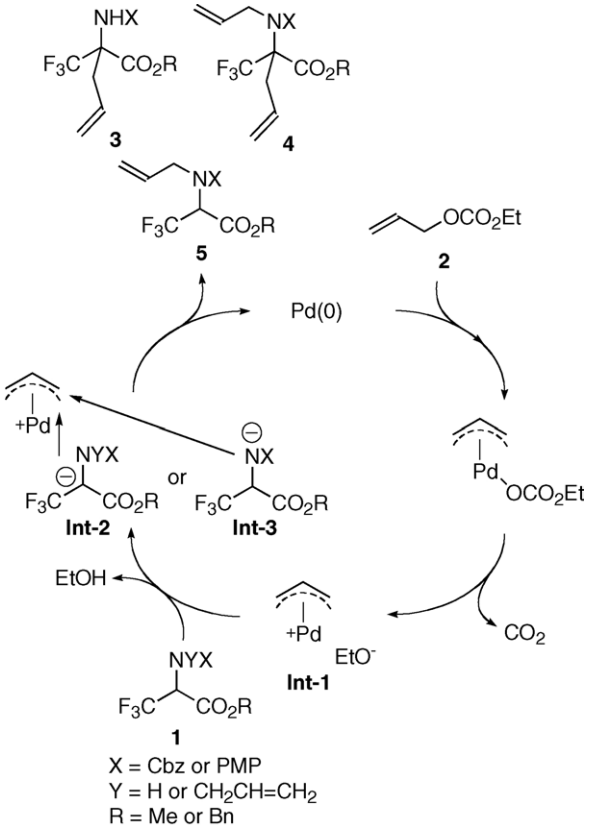


Fig. 2. The reaction mechanism.

3. Conclusion

In summary, we examined the palladium-catalyzed allylation reaction of trifluoroalanine derivatives for the synthesis of α-CF_3-α-amino acids in detail. *N*-Cbz-protected substrate **1a** led to *C*,*N*-bisallylated adduct preferentially due to a high acidity of the amino group, whereas *N*-PMP-protected ones (**1b** and **1c**) gave the corresponding *C*-monoallylated products exclusively. Additionally, various types of substituted allyl carbonates could be applied for the present reaction successfully. Based on the palladium-catalyzed allylation reaction, the efficient and convenient access to the α-CF_3 leucine was achieved.

4. Experimental

4.1. General experimental procedures

All reactions were performed under an argon atmosphere unless otherwise indicated. Flasks were flame-dried under a reduced pressure.

^{1}H NMR spectra were measured with a Bruker DRX (500.13 MHz) spectrometer in a chloroform-*d* ($CDCl_3$) solution with tetramethylsilane (Me_4Si) as an internal reference. ^{13}C NMR spectra were recorded on a Bruker DRX (125.77 MHz) spectrometer. A JEOL JNM-EX90 (84.21 MHz, FT) spectrometer was used for determining ^{19}F NMR spectra with an internal $CF_3C_6H_5$. $CFCl_3$ was used ($\delta_F = 0$) as an internal standard for ^{19}F NMR unless otherwise noted. Infrared spectra (IR) were recorded on a Shimadzu FTIR-8200A (PC) spectrophotometer. Mass spectra (MS) were taken on a JEOL JMS-700. Enantiomeric excesses were determined with high pressure liquid column chromatography (HPLC) using a CHIRALPAC AD-H column.

4.1.1. Materials

Anhydrous tetrahydrofuran (THF) and diethylether were purchased from Wako chemicals. All chemicals were of reagent grade and, if necessary, were purified in the usual manner prior to use. Thin layer chromatography (TLC) was done with Merck silica gel 60 F_{254} plates, and column chromatography was carried out with Wako gel C-200.

4.2. Synthetic procedures

4.2.1. Methyl 2-[(benzyloxycarbonyl)(prop-2-enyl)amino]-2-(trifluoromethyl)pent-4-enoate (*4a*)

Methyl 2-[*N*-(benzyloxycarbonyl)amino]-3,3,3-trifluoropropionate (64 mg, 0.220 mmol) was added to a solution of MS 5A (168 mg), $Pd(dppe)_2$ (9 mg, 0.010 mmol) and allyl ethyl carbonate (115 mg, 0.884 mmol) in 4.0 mL of THF and then reaction mixture was stirred for 6 h at reflux temperature. The reaction mixture was passed through silica gel short column. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (hexane:AcOEt = 5:1) to give methyl 2-[(benzyloxycarbonyl)(prop-2-enyl)amino]-2-(trifluoromethyl)pent-4-enoate (**4a**).

Yield 90% (isolated yield); ^{1}H NMR ($CDCl_3$) δ 1.85 (1H, m), 2.85 (1H, quint., $J = 3.3$ Hz), 3.75 (2H, dq, $J = 7.4$, 14.0 Hz), 3.75 (3H, br), 3.81 (2H, dd, $J = 5.0$, 18.0 Hz), 4.24 (1H, br), 5.15 (3H, br), 5.31 (1H, d, $J = 15.0$ Hz), 5.80 (2H, d, $J = 80.0$ Hz) 7.27–7.39 (5H, m); ^{13}C NMR ($CDCl_3$) δ 33.2, 53.0, 55.5, 67.1, 68.2 (q, $J = 26.1$ Hz), 114.3, 119.7, 124.6 (q, $J = 290.4$ Hz), 128.2, 128.4, 128.6, 129.9, 134.0, 135.5, 136.9, 154.2, 166.9, 168.2; ^{19}F NMR ($CDCl_3$) $\tilde{\delta}$ 72.63F, s; IR (neat) ν 2955, 1765, 1717, 1398, 1258, 1209, cm^{-1}; MS (FAB) calcd. for $C_{18}H_{21}F_3NO_4$ 372.1423 (M + H), found 372.1425.

4.2.2. Typical procedure for the allylic alkylation of 3,3,3-trifluoro alanine derivatives with carbonates

Methyl 2-[*N*-(anisyl)amino]-3,3,3-trifluoropropionate (**1b**) (123 mg, 0.467 mmol) was added to a solution of MS 5A (160 mg), $Pd(dppe)_2$ (21 mg, 0.023 mmol) and allyl ethyl carbonate (115 mg, 0.884 mmol) in 2.0 mL of THF and then reaction mixture was stirred for 6 h at reflux temperature. The reaction mixture was passed through silica gel short column. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (hexane:AcOEt = 5:1) to give methyl 2-[*N*-(anisyl)amino]-2-(trifluoromethyl)pent-4-enoate (**1b**) in 97% yield as a yellow liquid. The reaction proceeded even at room temperature (reaction time 12 h; yield 98%).

4.2.2.1. Methyl 2-[N-(anisyl)amino]-2-(trifluoromethyl)pent-4-enoate (3b). ^{1}H NMR ($CDCl_3$) δ 2.81 (1H, dd, $J = 8.1$,

14.5 Hz), 2.99 (1H, dd, J = 6.2, 14.5 Hz), 3.76 (3H, s), 3.84 (3H, s), 4.40 (1H, s), 5.10 (2H, m), 5.55 (1H, dt, J = 7.8, 16.9 Hz), 6.77 (2H, d, J = 9.0 Hz), 6.83 (2H, d, J = 9.0 Hz); ^{13}C NMR ($CDCl_3$) δ 34.6, 53.5, 55.5, 68.0 (q, J = 11.1 Hz), 114.3, 121.5, 130.2, 136.4, 154.8, 168.9; ^{19}F NMR ($CDCl_3$) $\tilde{\delta}$ 72.93F, s; IR (neat) ν 3375, 2957, 1747, 1514, 1443 cm^{-1}; MS (FAB) calcd. for $C_{14}H_{16}F_3NO_3$ 303.1082, found 303.1082.

*4.2.2.2. Benzyl 2-[N-(anisyl)amino]-2-(trifluoromethyl)pent-4-enoate (**3c**).* Benzyl 2-[*N*-(anisyl)amino]-3,3,3-trifluoropropionate (133 mg, 0.392 mmol) was used as a substrate (*condition*: allyl ethyl carbonate 1.2 equiv., reflux, 6 h; yield 91%) (*condition*: allyl ethyl carbonate 1.2 equiv., room temperature, 12 h; yield 96%). ^{1}H NMR ($CDCl_3$) δ 2.81 (1H, dd, J = 8.0, 14.6 Hz), 2.99 (1H, dd, J = 6.2, 14.6 Hz), 3.75 (3H, s), 4.39 (1H, s), 5.01 (1H, dd, J = 1.4, 17.0 Hz), 5.05 (1H, d, J = 10.2 Hz), 5.25 (2H, d, J = 2.8 Hz), 5.53 (1H, dt, J = 7.6, 16.8 Hz), 6.73 (2H, d, J = 9.0 Hz), 6.80 (2H, d, J = 9.0 Hz), 7.28–7.42 (5H, m); ^{13}C NMR ($CDCl_3$) δ 34.7, 55.5, 68.1 (q, J = 26.5 Hz), 68.6, 114.3, 120.7, 121.5, 124.6 (q, J = 288.1 Hz), 128.5, 128.6, 128.7, 129.9, 134.5, 136.5, 154.7, 168.2; ^{19}F NMR ($CDCl_3$) $\tilde{\delta}$ 72.73F, s; IR (neat) ν 3375, 2937, 1746, 1514, 1456 cm^{-1}; MS (FAB) calcd. for $C_{20}H_{20}F_3NO_3$ 379.1395, found 379.1400.

*4.2.2.3. (E)-Methyl 2-[N-(anisyl)amino]-2-(trifluoromethyl)-hex-4-enoate (**3d**).* Methyl 2-[*N*-(anisyl)amino]-3,3,3-trifluoropropionate (95 mg, 0.361 mmol) was used as a substrate (*condition*: crotyl ethyl carbonate 1.2 equiv., reflux, 6 h; yield 59%). ^{1}H NMR ($CDCl_3$) δ 1.61 (3H, d, J = 6.4 Hz), 2.74 (1H, dd, J = 8.0, 14.4 Hz), 2.90 (1H, dd, J = 6.3, 14.4 Hz), 3.76 (3H, s), 3.83 (3H, s), 4.35 (1H, s), 5.17 (1H, dt, J = 14.6, 7.2 Hz), 5.49 (1H, dq, J = 15.1, 6.5 Hz), 6.72–6.85 (4H, m); ^{13}C NMR ($CDCl_3$) δ 18.1, 34.0, 53.4, 55.5, 68.1 (q, J = 26.4 Hz), 114.3, 121.1, 122.3, 124.7 (q, J = 288.2 Hz), 131.8, 136.7, 154.6, 169.1; ^{19}F NMR ($CDCl_3$) $\tilde{\delta}$ 72.53F, s; IR (neat) ν 3375, 2957, 1747, 1514, 1443 cm^{-1}; MS (FAB) calcd. for $C_{15}H_{18}F_3NO_3$ 317.1239, found 317.1241.

*4.2.2.4. Methyl 2-[N-(anisyl)amino]-5-phenyl-2-(trifluoromethyl)pent-4-enoate (**3e**).* Methyl 2-[*N*-(anisyl)amino]-3,3,3-trifluoropropionate (101 mg, 0.384 mmol) was used as a substrate (*condition*: cinnamyl ethyl carbonate 1.2 equiv., reflux, 6 h; yield 91%). ^{1}H NMR ($CDCl_3$) δ 2.97 (1H, dd, J = 8.2, 14.6 Hz), 3.13 (1H, ddd, J = 1.2, 6.5, 14.6 Hz), 3.77 (3H, s), 3.85 (3H, s), 4.45 (1H, s), 5.88 (1H, dt, J = 15.4, 7.6 Hz), 6.37 (1H, d, J = 15.8 Hz), 6.79 (2H, d, J = 8.9 Hz), 6.87 (2H, d, J = 8.9 Hz), 7.20–7.32 (5H, m); ^{13}C NMR ($CDCl_3$) δ 33.9, 53.6, 55.5, 68.4 (q, J = 26.6 Hz), 114.4, 121.3, 121.9, 124.6 (q, J = 288.1 Hz), 126.3, 127.7, 128.5, 135.3, 136.5, 154.9, 168.9; ^{19}F NMR ($CDCl_3$) $\tilde{\delta}$ 72.93F, s; IR (neat) ν 3373, 2955, 1747, 1514 cm^{-1}; MS (FAB) calcd. for $C_{20}H_{20}F_3NO_3$ 379.1395, found 379.1400.

*4.2.2.5. Methyl 2-[N-(anisyl)amino]-4-methyl-2-(trifluoromethyl)pent-4-enoate (**3f**).* Methyl 2-[*N*-(anisyl)amino]-3,3,3-trifluoropropionate (127 mg, 0.483 mmol) was used as a substrate (*condition*: ethyl methallyl carbonate 1.2 equiv., reflux, 6 h; yield 84%). ^{1}H NMR ($CDCl_3$) δ 2.82 (1H, d, J = 15.5 Hz), 2.94 (1H, d, J = 15.6 Hz), 3.75 (3H, s), 3.84 (3H, s), 4.44 (1H, s), 4.87 (2H, d, J = 21.7 Hz), 6.75 (2H, d, J = 9.0 Hz), 6.81 (2H, d, J = 9.0 Hz); ^{13}C NMR ($CDCl_3$) δ 23.7, 36.5, 53.5, 55.5, 67.8 (q, J = 25.8 Hz), 114.2, 115.6, 121.1 (q, J = 1.5 Hz), 124.6 (q, J = 289.9 Hz), 136.7, 138.8, 154.5, 169.1; ^{19}F NMR ($CDCl_3$) $\tilde{\delta}$ 72.83F, s; IR (neat) ν 3387, 2957, 1747, 1514 cm^{-1}; MS (FAB) calcd. for $C_{15}H_{18}F_3NO_3$ 317.1239, found 317.1238.

*4.2.2.6. Benzyl 2-[N-(anisyl)amino]-4-methyl-2-(trifluoromethyl)pent-4-enoate (**3g**).* Benzyl 2-[*N*-(anisyl)amino]-3,3,3-trifluoropropionate (**1c**) (136 mg, 0.401 mmol) was used as a substrate (*condition*: ethyl methallyl carbonate 1.2 equiv., reflux, 6 h; yield 86%). ^{1}H NMR ($CDCl_3$) δ 1.61 (3H, s), 2.82 (1H, d, J = 15.6 Hz), 2.93 (1H, d, J = 15.6 Hz), 3.75 (3H, s), 4.84 (2H, s), 5.22 (1H, d, J = 12.2 Hz), 5.26 (1H, d, J = 12.2 Hz), 6.73 (2H, d, J = 9.0 Hz), 6.79 (2H, d, J = 9.0 Hz), 7.29–7.40 (5H, m); ^{13}C NMR ($CDCl_3$) δ 23.7, 36.7, 55.5, 67.8 (q, J = 26.0 Hz), 68.6, 114.2, 115.7, 121.1, 124.6 (q, J = 290.4 Hz), 128.5, 128.6, 128.6, 134.4, 136.7, 138.7, 154.5, 168.4; ^{19}F NMR ($CDCl_3$) $\tilde{\delta}$ 72.63F, s; IR (neat) ν 3383, 2910, 1744, 1514 cm^{-1}; MS (FAB) calcd. for $C_{21}H_{22}F_3NO_3$ 393.1552, found 393.1544.

*4.2.2.7. 5-Benzyl 1-methyl 2-[N-(anisyl)amino]-4-methylene-2-(trifluoromethyl)-dicarboxylate (**3h**).* Methyl 2-[*N*-(anisyl)amino]-3,3,3-trifluoropropionate (**1b**) (101 mg, 0.384 mmol) was used as a substrate (*condition*: ethyl (3-benzyloxycarbonyl-2-methylenepropyl) carbonate 1.2 equiv., reflux, 24 h; yield 40%). ^{1}H NMR ($CDCl_3$) δ 3.17 (2H, s), 3.71 (3H, s), 3.74 (3H, s), 4.75 (1H, s), 5.20 (2H, s), 5.73 (1H, s), 6.37 (1H, s), 6.68 (2H, d, J = 9.1 Hz), 6.73 (2H, d, J = 9.0 Hz), 7.27–7.39 (5H, m); ^{13}C NMR ($CDCl_3$) δ 33.2, 53.0, 55.5, 67.1, 68.2 (q, J = 26.1 Hz), 114.3, 119.7, 124.6 (q, J = 290.4 Hz), 128.2, 128.4, 128.6, 129.9, 134.0, 135.5, 136.9, 154.2, 166.9, 168.2; ^{19}F NMR ($CDCl_3$) $\tilde{\delta}$ 71.923F, s; IR (neat) ν 3379, 2955, 1747, 1717, 1514 cm^{-1}; MS (FAB) calcd. for $C_{22}H_{22}F_3NO_5$ 437.1450, found 437.1455.

4.2.3. Synthesis of α-trifluoromethyl leucine

*4.2.3.1. Benzyl 2-amino-4-methyl-2-(trifluoromethyl)pent-4-enoate (**6**).* Benzyl 2-[*N*-(anisyl)amino]-4-methyl-2-(trifluoromethyl)pent-4-enoate (**3g**) (128 mg, 0.325 mmol) (diluted with 6.5 mL of CH_3CN) was added to a solution of CAN (ammonium cerium(IV) nitrate) (948 mg, 1.64 mmol) in H_2O (6.5 mL) at room temperature and stirred for 2 h. The resulting solution was extracted with AcOEt and washed with brine. The collected organic layers were dried over anhydrous sodium sulfate, filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography on aluminum (hexane:AcOEt = 5:1 → 3:1) to give benzyl 2-amino-4-methyl-2-(trifluoromethyl)pent-4-enoate (**6**) (82 mg) in 88% yield as a yellow liquid. ^{1}H NMR ($CDCl_3$) δ 1.61 (3H, s), 1.82 (2H, s), 2.47 (1H, d, J = 14.0 Hz), 2.91 (1H, d, J = 14.0 Hz), 4.82 (1H, s), 4.94 (1H, t, J = 1.4 Hz), 5.21 (1H, d, J = 12.2 Hz), 5.27 (1H, d, J = 12.2 Hz), 7.28–7.40 (5H, m); ^{13}C

NMR ($CDCl_3$) δ 23.0, 40.0, 63.8 (q, J = 26.6 Hz), 68.4, 117.3, 124.9 (q, J = 285.6 Hz), 128.4, 128.6 (singlet peak × 2), 134.5, 138.4, 169.6; ^{19}F NMR ($CDCl_3$) δ 78.03F, s; IR (neat) ν 3412, 2953, 1746, 1611, 1456 cm^{-1}; MS (FAB) calcd. for $C_{14}H_{17}F_3NO_2$ 288.1211 (M + H), found 288.1207.

*4.2.3.2. α-Trifluoromethyl leucine (**8**).* Benzyl 2-amino-4-methyl-2-(trifluoromethyl)pent-4-enoate (**6**) (140 mg, 0.487 mmol) was added to a solution of Pd/C [102 mg (Pd 10%), 0.096 mmol] at room temperature and then the atmosphere was replaced with H_2 gas. After stirring for 1 h, the resulting solution was filtered off with MeOH. The solvent was removed under reduced pressure to give α-trifluoromethyl leucine (**8**) in 95% yield as a white powder. mp 161–165 °C; ^{1}H NMR (D_2O) δ 0.81 (3H, d, J = 6.6 Hz), 0.88 (3H, d, J = 6.7 Hz), 1.54–1.73 (1H, m), 1.81 (1H, dd, J = 3.9, 14.8 Hz), 2.00 (1H, dd, J = 9.2, 14.7 Hz); ^{13}C NMR (D_2O) δ 21.7, 23.4, 24.3, 38.5, 66.1 (q, J = 25.4 Hz), 124.5 (q, J = 283.8 Hz), 168.9; ^{19}F NMR (D_2O) δ 0.293F, s (internal standard: CF_3CO_2H); IR (KBr) ν 2968, 2878, 1651, 1620, 1539 cm^{-1}; MS (FAB) calcd. for $C_7H_{13}F_3NO_2$ 200.0898 (M + H), found 200.0899.

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