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Organic base catalyzed carbonyl allylation of methyl trifluoropyruvate with activated alkenes

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ABSTRACT

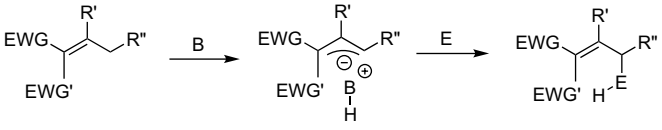
The carbonyl allylation of methyl trifluoropyruvate (MeTFP) with activated alkenes has been investigated in detail using organic bases as catalysts. Organic bases, such as DMAP, Et_3N, DABCO, NMM, Et_2NH, and quinine, could deprotonate the allylic hydrogen of activated alkenes and furnish nucleophilic species to undergo the addition reaction with methyl trifluoropyruvate and afford versatile homoallylic alcohols with CF_3 group in excellent yields. The ^{19}F NMR monitoring indicated that the isomerization induced by base gave two separable diastereoisomers in an equilibrium ratio of 1:3. The relative configuration of hydroxy and the neighboring alkyl group in the major diastereoisomer was determined as *syn*-configuration by X-ray diffraction analysis.

1. Introduction

The ever-growing pharmaceutical and agrochemical interests and applications of fluorine-containing compounds have attracted much attention on the exploitation of new highly efficient synthons and practical synthetic methods.[1] The building block strategy using simple fluorinated substrates, which are relatively easily available and display appropriate reactivity, is one of general ways for the introduction of fluorinated group into the target molecule.[2]

Carbonyl allylation represents an important C–C bond forming process, which provides a very efficient approach to the preparation of functionalized homoallylic alcohols.[3] The allyl sources utilized for the carbonyl allylation include stoichiometric allylic metal or semimetal reagents, such as those containing zinc, tin, indium, boron, and silicon.[4] Recently, the approach employing allyl acetates, alcohols, halides, allenes or dienes as allyl donors has attracted more attentions.[5] Additionally, carbonyl-ene reaction also affords a product of carbonyl allylation, which generally involves the use of alkene and Lewis acid as the catalyst.[6] However, to our best knowledge, no report has addressed the carbonyl allylation with activated alkene catalyzed by organic base.

In some very recent publications, it has been identified that the acidity of allylic hydrogen can be greatly enhanced when some strong electron-withdrawing groups are attached to C=C bond, which allows the easy generation of nucleophilic species by in situ deprotonation under mild conditions, as shown in Scheme 1.[7] On the other hand, 3,3,3-trifluoropyruvates have been used as efficient fluorinated building blocks in the synthesis of some trifluoromethylated compounds with special biological properties.[8] Because of the concurrent influence of two electron-withdrawing groups, 3,3,3-trifluoropyruvates are highly electrophilic. Therefore, we are motivated to perform the carbonyl allylation of trifluoropyruvate (MeTFP) with alkenes catalyzed by organic bases and hope to provide a practical method for the preparation of polyfunctional homoallylic alcohols with trifluoromethyl group.



Scheme 1. Organic base catalyzed deprotonation of allylic hydrogen and addition to electrophile.

2. Results and discussion

To establish the experimental conditions for the carbonyl allylation, our investigation started with the reaction of alkylidene cyanoacetate **1a** and MeTFP catalyzed by several kinds of organic bases. As shown in Table 1, *N*,*N*-4-dimethylaminopyridine (DMAP),

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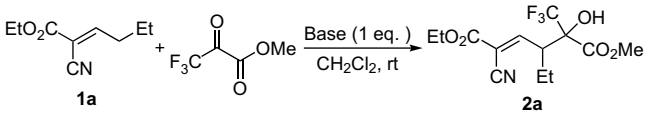
Table 1
Screening of catalysts and reaction conditions for the allylic addition of MeTFP



1a 2a

Entry	Catalyst	pK_a (BH^+) (in water)	Time (h)	Yield[a] (%)	dr[a]
1	NMM	7.41[b]	72	95	1.1:1
2	DMAP	9.7[c]	24	93	1:3.1
3	Quinine	7.73[d]	72	92	1:2.4
4	Et_2NH	10.98[b]	24	88	1:3.0
5	DABCO	8.8[c]	24	83	1:3.0
6	Et_3N	10.65[b]	48	84	1:3.1
7	DBU	23.9[e]	0.5	40	1:2.8
8	Pyridine	5.14[d]	24	0[f]	—
9	DMAP	9.7	0.1	77	1:0.8
10	DMAP	9.7	1	87	1:1.3
11	DMAP	9.7	6	90	1:2.6
12	DMAP	9.7	10	90	1:2.8
13	DMAP	9.7	22	92	1:3.1
14	DMAP	9.7	50	92	1:3.0

[a] Determined by ^{19}F NMR spectra of the crude reaction mixture.
[b] Ref. 9a.
[c] Ref. 9b.
[d] Ref. 9c.
[e] Ref. 9d, pK_a (BH^+) in acetonitrile.
[f] Only hydrated MeTFP was detected.

N-methylmorpholine (NMM), quinine, and Et_2NH afforded excellent yields (Table 1, entries 1–4). 1,4-Diazabicyclo[2.2.2]octane (DABCO) and Et_3N gave moderate yields, and lower than 50% yield was obtained in the case of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Table 1, entries 4–6). However, no addition product was isolated when pyridine was used as catalyst (Table 1, entry 7). The experiment results were presumably ascribed to the strength of the bases. The stronger base caused more side-reactions, whereas the weaker base could not deprotonate the allylic hydrogen (the base strength was evaluated by the pK_a value of its conjugate acid, as shown in Table 1).

The ^{19}F NMR spectrum of product **2a** showed two single signals at −73.5 ppm and −75.0 ppm, indicating that the reaction gave a mixture of two expected diastereoisomers. Interestingly, the observed diastereomeric ratios changed with the reaction time. During initial hours, the ratio was close to 1:1, which was in agreement with the expected ratio of non-stereocontrolled addition reaction. However, the ratio changed and reached a stable value of approximate 1:3 after 22 h (Table 1, entries 8–13). It is reasonable to postulate that this is due to thermodynamically controlled isomerization of the chiral center under the basic reaction condition. The two diastereoisomers could be isolated by column chromatography. The 'less polar' minor diastereoisomer with low melting point was corresponding to −73.5 ppm in the ^{19}F NMR spectrum, and the 'more polar' major diastereoisomer with high melting point was corresponding to −75.0 ppm.

To further demonstrate the thermodynamic equilibrium, the following experiment was conducted. A sample of major diastereoisomer of **2a** was treated with 1.0 equiv DMAP under the same condition and monitored by ^{19}F NMR. The new equilibrium could be reached again with the ratio of 1:3, which represented the thermodynamic equilibrium position. It is worth noting that we did not observe the interconversion of the two diastereoisomers in the presence of NMM at room temperature. The dr value still remained about 1:1 even after 96 h.

The relative configuration of the major diastereoisomer of **2a** was determined by X-ray crystallography.[10] As shown in Figure 1, the ethyl and hydroxy group are *syn* to each other.

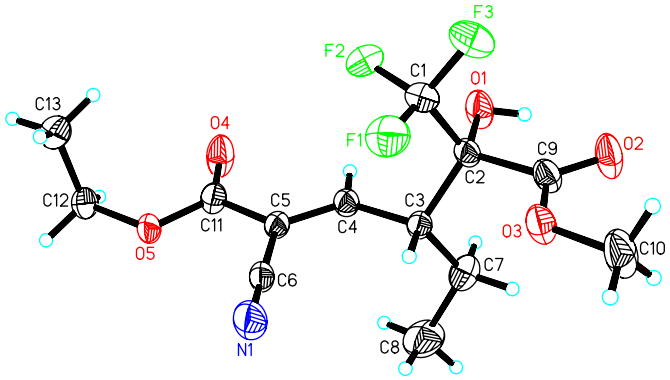
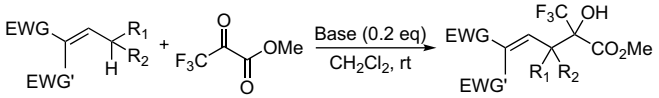


Figure 1. X-crystal structure of the major diastereoisomer of **2a**.

Table 2
The reaction of activated alkenes with trifluoropyruvate



1 2

Entry	1	EWG	EWG′	R^1	R^2	2	Base	Time (h)	Yield[a] (%)	dr[b]
1	**1a**	CO_2Et	CN	H	Et	**2a**	DMAP	24	88	1:3.0
2	**1b**	CO_2Et	CN	H	Me	**2b**	DMAP	13	84	1:2.7
3	**1c**	CO_2Et	CN	H	*i*-Pr	**2c**	DMAP	72	76	1:3.6
4[c]	**1d**	CO_2Et	CN	Me	Me	**2d**	DMAP	24	78	—
5[d]	**1e**	COMe	COMe	H	Et	**2e**	DMAP	16	52	1:1.3
6	**1f**	CN	CN	H	Et	**2f**	NMM	24	68	1:2.4
7[d]	**1g**	CO_2Me	CO_2Me	H	*i*-Pr	**2g**	DBU	1	49	1:1.4

[a] Isolated total yield.
[b] The diastereomeric ratio was determined by ^{19}F NMR spectra of the crude reaction mixture.
[c] 0.5 equiv catalyst was used.
[d] 1.0 equiv catalyst was used.

Decreasing the catalyst loading from 1.0 equiv to 0.5 and 0.2 equiv, the yields did not drop obviously when DMAP was used.

To extend the scope of the reaction, a series of different substituted alkylidenes were chosen to react with MeTFP in CH_2Cl_2 using organic bases as catalyst. The results are summarized in Table 2. The alkyl substituents at the γ-position of alkylidenes consistently gave good yields with similar diastereoselectivities when 0.2 equiv of DMAP was used as base (Table 2, entries 1–4). Comparing the ^{19}F NMR spectra and the polarity on the silica gel column with those of **2a**, we assigned the major diastereoisomers of **2b** and **2c** as *syn*-configuration.

When the two electron-withdrawing groups were changed to two acetyl groups, the yield of addition product dropped obviously (Table 2, entry 5). In the case of more activated dicyano alkene **1f**, a satisfactory yield was obtained in the presence of 0.2 equiv NMM (Table 1, entry 6). The major diastereoisomer of **2f** was *syn*-configuration according to ^{19}F NMR spectra and the polarity on the silica gel column, which showed similar diastereoselectivity to **2a**. For the less activated alkene **1g**, 1.0 equiv of DBU was used for better result (Table 1, entry 7). Because the yield dropped obviously with increasing the reaction time, we could not get a dr value at the equilibrium position of isomerization. Furthermore, the two diastereoisomers of **2g** could not be separated by column chromatography.

3. Conclusion

In summary, we have demonstrated a mild organic base catalyzed carbonyl allylation of trifluoropyruvate with activated alkenes, which provides a convenient access to polysubstituted homoallylic alcohols with trifluoromethyl group. Base-induced isomerization of the products under the reaction conditions favored to form *syn*-configuration diastereoisomer when the reaction reached thermodynamical equilibrium. Although the precise driving force for the *syn*-selectivity is unclear at present, it should be noted that the carbonyl allylation reaction is diastereoselective under the basic reaction condition. We believe that the present results will motivate more interests in the exploitation of carbonyl allylation catalyzed by organic bases.

4. Experimental

4.1. General

All manipulations were performed under a nitrogen atmosphere using standard Schlenk techniques. Solvents were freshly distilled using general method to remove water. Column chromatography was performed on silica gel employing petroleum ether–ethyl acetate mixture as eluant. (*E*)-Activated alkenes **1a**–**1g** were prepared following the literature procedures.[11]

Melting points were uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker AM-300 spectrometer (300 MHz) with TMS as internal standard. ^{19}F NMR spectra were taken on a Bruker AM-300 (282 MHz) spectrometer using $CFCl_3$ as external standard. ^{13}C NMR spectra were taken on a Bruker AM-400 (100 MHz) spectrometer. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Mass spectra were obtained on a Finnigan GC–MS 4021 spectrometer. High-resolution mass data were obtained on a high-resolution mass spectrometer in the EI mode.

4.2. Typical procedure

Methyl trifluoropyruvate (62 mg, 0.4 mmol) was added to a solution of alkylidene cyanoacetate **1a** (67 mg, 0.4 mmol) and *N*,*N*-4-dimethylaminopyridine (10 mg, 0.08 mmol) in dichloromethane (4 mL) at room temperature. The reaction mixture was stirred for 24 h. After removal of the volatile solvents under vacuum, the crude product was purified by chromatography on silica gel column (petroleum ether/ethyl acetate=9:1) to give two diastereoisomers **2a** (TLC, petroleum ether/ethyl acetate=7:1, R_f of minor diastereomer is 0.45, R_f of major diastereomer is 0.4).

4.2.1. (*E*)-1-Ethyl 6-methyl 2-cyano-4-ethyl-5-hydroxy-5-(trifluoromethyl)hex-2-enedioate **2a**

Minor diastereomer: colorless oil, yield 22%; IR (film): ν 3468, 2982, 2237, 1740, 1631, 1443, 1245, 1158, 1020 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, J=7.5 Hz, 3H), 1.37 (t, J=7.2 Hz, 3H), 1.55–1.63 (m, 1H), 1.94–2.05 (m, 1H), 3.38 (dt, J_1=11.4 Hz, J_2=3.6 Hz, 1H), 3.96 (s, 3H), 4.01 (s, 1H), 4.34 (q, J=7.2 Hz, 2H), 7.46 (d, J=11.4 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −73.5 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2, 160.4, 158.0, 122.8 (q, J=288.0 Hz), 112.9, 112.7, 78.7 (q, J=28.7 Hz), 63.0, 54.8, 46.9, 20.5, 14.0, 11.4; MS (*m*/*z*, %): 323 (M$^+$, 7.07), 138 (100.00); HRMS calcd for $C_{13}H_{16}F_3NO_5$ [M$^+$]: 323.0981, found: 323.0992.

Major diastereomer: white solid, yield 66%; mp: 95–98 °C; IR (KBr): ν 3450, 2978, 2235, 1726, 1634, 1465, 1373, 1268, 1146, 1102, 1019 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, J=7.5 Hz, 3H), 1.26–1.42 (m, 1H), 1.38 (t, J=7.2 Hz, 3H), 1.55–1.66 (m, 1H), 3.42 (dt, J_1=11.1 Hz, J_2=3.3 Hz, 1H), 3.99 (s, 3H), 4.10 (s, 1H), 4.35 (q, J=7.2 Hz, 2H), 7.58 (d, J=11.1 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −75.0 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 160.5, 158.0, 122.7 (q, J=287.6 Hz), 113.4, 112.1, 79.4 (q, J=28.5 Hz), 62.8, 54.8, 45.7, 21.0, 14.0, 11.1; MS (*m*/*z*, %): 323 (M$^+$, 5.47), 94 (100.00); HRMS calcd for $C_{13}H_{16}F_3NO_5$ [M$^+$]: 323.0981, found: 323.0967.

4.2.2. (*E*)-1-Ethyl 6-methyl 2-cyano-5-hydroxy-4-methyl-5-(trifluoromethyl)hex-2-enedioate **2b**

Minor diastereomer: white solid, yield 23%; mp: 64–67 °C; IR (KBr): ν 3464, 2989, 2237, 1742, 1633, 1442, 1253, 1164, 1093, 1002 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25–1.39 (m, 6H), 3.58–3.64 (m, 1H), 3.94 (s, 3H), 4.08 (s, 1H), 4.33 (q, J=7.2 Hz, 2H), 7.50 (d, J=11.1 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −73.8 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2, 160.5, 158.7, 122.8 (q, J=287.6 Hz), 112.6, 110.8, 78.3 (q, J=29.5 Hz), 63.0, 54.8, 39.8, 14.0, 13.4; MS (*m*/*z*, %): 309 (M$^+$, 2.61), 148 (100.00); HRMS calcd for $C_{12}H_{14}F_3NO_5$ [M$^+$]: 309.0824, found: 309.0813.

Major diastereomer: white solid, yield 61%; mp: 107–109 °C; IR (KBr): ν 3452, 2995, 2234, 1758, 1725, 1633, 1462, 1260, 1091, 1013 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (d, J=6.9 Hz, 3H), 1.37 (t, J=7.2 Hz, 3H), 3.58–3.69 (m, 1H), 3.99 (s, 1H), 4.23 (s, 1H), 4.34 (q, J=7.2 Hz, 2H), 7.71 (d, J=10.8 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −75.4 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.9, 160.6, 159.4, 122.7 (q, J=287.6 Hz), 112.9, 110.2, 79.0 (q, J=29.5 Hz), 62.8, 54.8, 38.8, 14.1, 14.0; MS (*m*/*z*, %): 310 (M$^+$+1, 13.93), 124 (100.00); HRMS calcd for $C_{12}H_{14}F_3NO_5$ [M$^+$]: 309.0824, found: 309.0828.

4.2.3. (*E*)-1-Ethyl 6-methyl 2-cyano-5-hydroxy-4-isopropyl-5-(trifluoromethyl)hex-2-enedioate **2c**

Minor diastereomer: white solid, yield 19%; mp: 66–68 °C; IR (KBr): ν 3446, 2968, 2237, 1735, 1629, 1374, 1249, 1162, 1040 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97–1.03 (m, 6H), 1.38 (t, J=7.2 Hz, 3H), 2.44–2.54 (m, 1H), 3.44 (dd, J_1=11.7 Hz, J_2=3.6 Hz, 1H), 3.95 (s, 3H), 4.08 (s, 1H), 4.34 (q, J=7.2 Hz, 2H), 7.63 (d, J=11.7 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −73.7 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 160.3, 156.3, 122.8 (q, J=287.9 Hz), 113.4, 113.0, 79.3 (q, J=29.2 Hz), 62.9, 54.8, 49.6, 28.9, 22.8, 17.5, 14.0; MS (*m*/*z*, %): 338 (M$^+$+1, 19.70), 236 (100.00); HRMS calcd for $C_{14}H_{18}F_3NO_5$ [M$^+$]: 337.1137, found: 337.1135.

Major diastereomer: white solid, yield 57%; mp: 72–74 °C; IR (KBr): ν 3431, 2973, 2235, 1730, 1627, 1376, 1255, 1144, 1040 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96–1.01 (m, 6H), 1.38 (t, J=7.2 Hz, 3H), 1.86–1.92 (m, 1H), 3.43 (dd, J_1=11.7 Hz, J_2=3.0 Hz, 1H), 4.00 (s, 3H), 4.15 (s, 1H), 4.35 (q, J=7.2 Hz, 2H), 7.75 (d, J=11.7 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −75.3 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 160.5, 157.3, 122.6 (q, J=288.4 Hz), 113.5, 112.4, 80.2 (q, J=28.2 Hz), 62.8, 54.8, 48.1, 31.1, 22.6, 18.6, 14.0; MS (*m*/*z*, %): 338 (M$^+$+1, 6.89), 236 (100.00); HRMS calcd for $C_{14}H_{18}F_3NO_5$ [M$^+$]: 337.1137, found: 337.1129.

4.2.4. (*E*)-1-Ethyl 6-methyl 2-cyano-5-hydroxy-4,4-dimethyl-5-(trifluoromethyl)hex-2-enedioate **2d**

Colorless oil, yield 78%; IR (film): ν 3468, 2989, 2234, 1737, 1626, 1442, 1371, 1259, 1186, 1019 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 (t, J=7.2 Hz, 3H), 1.48 (s, 3H), 1.54 (s, 3H), 4.00 (s, 3H), 4.26 (s, 1H), 4.34 (q, J=7.2 Hz, 2H), 7.98 (s, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −70.8 (s, 3F); MS (*m*/*z*, %): 324 (M$^+$+1, 20.01), 43 (100.00). Anal. Calcd for $C_{13}H_{16}F_3NO_5$: C, 48.30; H, 4.99; N, 4.33. Found: C, 48.30; H, 5.09; N, 4.40.

4.2.5. Methyl 5-acetyl-3-ethyl-2-hydroxy-6-oxo-2-(trifluoromethyl)hept-4-enoate **2e**

First fraction on the column: white solid, yield 26%; mp: 63–65 °C; IR (KBr): ν 3473, 2974, 2259, 1755, 1673, 1440, 1236, 1183, 1100, 1029 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, J=7.5 Hz, 3H), 1.25–1.33 (m, 1H), 1.47–1.55 (m, 1H), 2.32 (s, 3H), 2.39 (s, 3H), 3.15 (dt, J_1=10.8 Hz, J_2=3.6 Hz, 1H), 3.94 (s, 3H), 4.15 (s, 1H), 6.61 (d, J=10.8 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −74.6 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.5, 197.6, 169.5, 146.6, 142.4, 123.0

(q, J=289.4 Hz), 79.7 (q, J=27.7 Hz), 54.6, 42.3, 31.1, 26.3, 21.9, 11.3; MS (m/z, %): 293 (M^+-H_2O+1, 0.52), 43 (100.00); HRMS calcd For $C_{13}H_{17}F_3O_5$ [M^+]: 310.1028, found: 310.1023.

Second fraction on the column: colorless oil, yield 26%; IR (film): ν 3464, 2968, 1752, 1674, 1440, 1382, 1234, 1179, 1023 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.82 (t, J=7.5 Hz, 3H), 1.41–1.52 (m, 1H), 1.79–1.87 (m, 1H), 2.24 (s, 3H), 2.27 (s, 3H), 2.96 (dt, J_1=11.1 Hz, J_2=3.3 Hz, 1H), 3.86 (s, 3H), 4.02 (s, 1H), 6.41 (d, J=11.1 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −73.0 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.1, 197.2, 169.7, 147.4, 141.2, 123.0 (q, J=287.9 Hz), 79.1 (q, J=29.1 Hz), 54.6, 43.8, 31.4, 26.3, 20.9, 17.8; MS (m/z, %): 293 (M^+-H_2O+1, 0.99), 43 (100.00); HRMS calcd for $C_{13}H_{15}F_3O_4$ [M^+-H_2O+1]: 292.0922, found: 292.0930.

4.2.6. Methyl 5,5-dicynao-3-ethyl-2-hydroxy-2-(trifluoromethyl)-pent-4-enoate **2f**

Minor diastereoisomer: white solid, yield 20%; mp: 80–82 °C; IR (KBr): ν 3489, 3062, 2242, 1739, 1443, 1241, 1182, 1127, 1092 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.94 (t, J=7.2 Hz, 3H), 1.47–1.58 (m, 1H), 2.01–2.07 (m, 1H), 3.35 (dt, J_1=11.4 Hz, J_2=3.6 Hz, 1H), 3.99 (s, 3H), 4.10 (s, 1H), 7.24 (d, J=11.4 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −73.8 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.4, 164.7, 122.5 (q, J=287.9 Hz), 111.5, 110.3, 91.8, 79.2 (q, J=28.9 Hz), 55.1, 46.5, 21.8, 11.1; MS (m/z, %): 276 (M^+, 1.48), 119 (100.00); HRMS calcd for $C_{11}H_{11}F_3N_2O_3$ [M^+]: 276.0722, found: 276.0714.

Major diastereoisomer: white solid, yield 48%; mp: 81–83 °C; IR (KBr): ν 3486, 3047, 2244, 1751, 1441, 1297, 1243, 1147, 1091 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.94 (t, J=7.5 Hz, 3H), 1.41–1.45 (m, 1H), 1.56–1.63 (m, 1H), 3.40 (dt, J_1=11.4 Hz, J_2=3.9 Hz, 1H), 4.00 (s, 3H), 4.25 (s, 1H), 7.31 (d, J=11.4 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −75.2 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.6, 164.6, 122.6 (q, J=287.2 Hz), 111.5, 110.0, 92.6, 78.5 (q, J=29.3 Hz), 55.1, 47.9, 20.7, 11.4; MS (m/z, %): 276 (M^+, 2.10), 119 (100.00); HRMS calcd for $C_{11}H_{11}F_3N_2O_3$ [M^+]: 276.0722, found: 276.0730.

4.2.7. Trimethyl 5,5,5-trifluoro-4-hydroxy-3-isopropylpent-1-ene-1,1,4-tricarboxylate **2g**

White solid, yield 49%; IR (KBr): ν 3460, 2964, 1739, 1440, 1247, 1156, 1068 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.88–1.03 (m, 6H), 1.73–1.81 (m, 0.53H), 2.32–2.39 (m, 0.47H), 3.18 (dd, J_1=11.7 Hz, J_2=3.0 Hz, 0.53H), 3.34 (dd, J_1=11.7 Hz, J_2=3.0 Hz, 0.47H), 3.80–3.84 (m, 6H), 3.88 (s, 1.59H), 3.95 (s, 1.41H), 4.05 (s, 1H), 7.01 (d, J=11.7 Hz, 0.53H), 7.15 (d, J=11.7 Hz, 0.47H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −73.3 (s, 1.59F), −75.2 (s, 1.41F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0, 169.9, 165.3, 165.0, 164.0, 163.6, 143.8, 141.9, 131.6, 130.4, 123.1 (q, J=287.9 Hz), 122.8 (q, J=287.9 Hz), 80.5 (q, J=28.8 Hz), 79.7 (q, J=28.8 Hz), 54.6, 54.4, 52.6, 52.5, 52.3, 52.2, 46.6, 45.0, 30.4, 28.3, 22.8, 22.5, 18.5, 17.6; MS (m/z, %): 357 (M^++1, 23.34), 223 (100.00); HRMS calcd for $C_{14}H_{19}F_3O_7$ [M^+]: 356.1083, found: 356.1093.

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References and notes

1. (a) Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Chemistry: Principle and Commercial Applications*; Plenum: New York, NY, 1994; (b) Hiyama, T. *Organofluorine Compounds: Chemistry and Application*; Springer: Berlin, 2000; (c) Filler, R.; Kobayashi, Y.; Yagupolskii, L. M. *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Elsevier: Amsterdam, 1993; (d) Ojima, I.; McCarthy, J. R.; Welch, J. T. *Biomedical Frontiers of Fluorine Chemistry*; American Chemical Society: Washington, DC, 1996.
2. Soloshonok, V. A. *Fluorine-Containing Synthons*; American Chemical Society: Washington, DC, 2005.
3. For recent review, see: (a) Marek, I.; Sklute, G. *Chem. Commun.* **2007**, 1683–1691; (b) Hall, D. G. *Synlett* **2007**, 1644–1655; (c) Denmak, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763–2793.
4. For respective examples, see: (a) Ren, H.; Dunet, G.; Mayer, P.; Knochel, P. *J. Am. Chem. Soc.* **2007**, *129*, 5376–5377; (b) Marek, I.; Sklute, G. *J. Am. Chem. Soc.* **2006**, *128*, 4642–4649; (c) Kennedy, J. W. J.; Hall, D. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4732–4739; (d) Ishiyama, T.; Ahiko, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414–12415; (e) Waltz, K. M.; Gavenonis, J.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3697–3699.
5. For recent examples, see: (a) Kim, I. S.; Ngai, M. Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6340–6341; (b) Shibahara, F.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6338–6339; (c) Bower, J. F.; Skucas, E.; Patman, R. L.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 15134–15135; (d) Miller, J. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 2752–2753, and references therein.
6. (a) Yuan, Y.; Zhang, X.; Ding, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 5478–5480; (b) Okachi, T.; Fujimoto, K.; Onaka, M. *Org. Lett.* **2002**, *4*, 1667–1669; (c) Koh, J. H.; Larsen, A. O.; Gagné, M. R. *Org. Lett.* **2001**, *3*, 1233–1236; (d) Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936–7943; (e) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325–335; (f) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021–1050.
7. (a) Xue, J. W.; Chen, W.; Li, R.; Zeng, M.; Du, W.; Yue, L.; Chen, Y.-C.; Wu, Y.; Zhu, J.; Deng, J.-G. *Angew. Chem., Int. Ed.* **2007**, *46*, 389–392; (b) Liu, T.-Y.; Cui, H. L.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *J. Am. Chem. Soc.* **2007**, *129*, 1878–1879; (c) Bell, M.; Frisch, K.; Jørgensen, K. A. *J. Org. Chem.* **2006**, *71*, 5407–5410; (d) Xie, J.-W.; Yue, L.; Xue, D.; Ma, X.-L.; Chen, Y.-C.; Wu, Y.; Zhu, J.; Deng, J.-G. *Chem. Commun.* **2006**, 1563–1565; (e) Poulsen, T. B.; Bell, M.; Jørgensen, K. A. *Org. Biomol. Chem.* **2006**, *4*, 63–70; (f) Xue, D.; Chen, Y.-C.; Wang, Q.-W.; Cun, L.-F.; Zhu, J.; Deng, J.-G. *Org. Lett.* **2005**, *7*, 5293–5296; (g) Poulsen, T. B.; Alemparte, C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 11614–11615.
8. For recent papers using trifluoropyruvate as building blocks, see: (a) Ogawa, S.; Shibata, N.; Inagaki, J.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 8666–8669; (b) Shibata, N.; Fujimoto, H.; Mizuta, S.; Ogawa, S.; Ishiuchi, Y.; Nakamura, S.; Toru, T. *Synlett* **2006**, 3484–3488; (c) Deb, I.; Dadwal, M.; Mobin, S. M.; Namboothiri, I. N. N. *Org. Lett.* **2006**, *8*, 1201–1204; (d) Zhao, J.-L.; Liu, L.; Sui, Y.; Liu, Y.-L.; Wang, D.; Chen, Y.-J. *Org. Lett.* **2006**, *8*, 6127–6130; (e) Chaume, G.; Severen, M.-C. V.; Marinkovic, S.; Brigaud, T. *Org. Lett.* **2006**, *8*, 6123–6126; (f) Skarpos, H.; Vorob'eva, D. V.; Osipov, S. N.; Odinets, I. L.; Breuer, E.; Roeschenthaler, G.-V. *Org. Biomol. Chem.* **2006**, *4*, 3669–3674; (g) Abid, M.; Torok, B. *Adv. Synth. Catal.* **2005**, *347*, 1797–1803; (h) Takikawa, G.; Katagiri, T.; Uneyama, K. *J. Org. Chem.* **2005**, *70*, 8811–8816; (i) Sibgatulin, D. A.; Volochnyuk, D. M.; Kostyuk, A. N. *Synlett* **2005**, 1907–1911; (j) Toeroek, B.; Abid, M.; London, G.; Esquibel, J.; Toeroek, M.; Mhadgut, S. C.; Yan, P.; Prakash, G. K. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3086–3089; (k) Lyle, M. P. A.; Draper, N. D.; Wilson, P. D. *Org. Lett.* **2005**, *7*, 901–904.
9. (a) Hall, H. K., Jr. *J. Am. Chem. Soc.* **1957**, *79*, 5441–5444, and references therein; (b) Faltin, C.; Fleming, E. M.; Connon, S. J. *J. Org. Chem.* **2004**, *69*, 6496–6499, and references therein; (c) Braude, E. A.; Nachod, F. C. *Determination of Organic Structures by Physical Methods*; Academic: New York, NY, 1955; (d) Streitwieser, A.; Kim, Y.-J. *J. Am. Chem. Soc.* **2000**, *122*, 11783–11786, and references therein.
10. Crystal data: $C_{13}H_{16}F_3NO_5$; M=323.27; monoclinic, $P2(1)/n$; a=11.381 Å, b=9.051 Å, c=15.904 Å; α=90.00, β=108.945(4), γ=90.00, V=1549.5 $Å^3$; Z=4; 3021 reflections; R_{int}=0.1761; R_1=0.0659, and wR_2=0.1685. Crystallographic data for the structures of **2a** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC 689148). Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, United Kingdom (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.uk).
11. (a) Popp, F. D.; Catala, A. *J. Org. Chem.* **1960**, *26*, 2738–2740; (b) Verhé, R.; Kimpe, N.; Courtheyn, D.; Buyck, L.; Schamp, N. *Tetrahedron* **1982**, *38*, 3649–3660; (c) Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Ginaotti, M.; Tolomelli, A. *Synth. Commun.* **2003**, *33*, 1587–1594.