Preparation of α,α-Disubstituted Trifluoromethyl Ketones via Suzuki Reaction of Bromoenamines

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Abstract: Palladium-catalyzed cross-coupling reaction of β-amino-β-trifluoromethylvinyl bromides **7** and **8** with boronic acids has been achieved to afford new stable β,β-disubstituted α-trifluoromethyl enamines **12** and **13**, which can be used as masked ketones. The ketone function can be released in acidic medium.

Key words: vinyl bromides, cross-coupling, boronic acids, enamines, trifluoromethyl ketones, hydrolysis

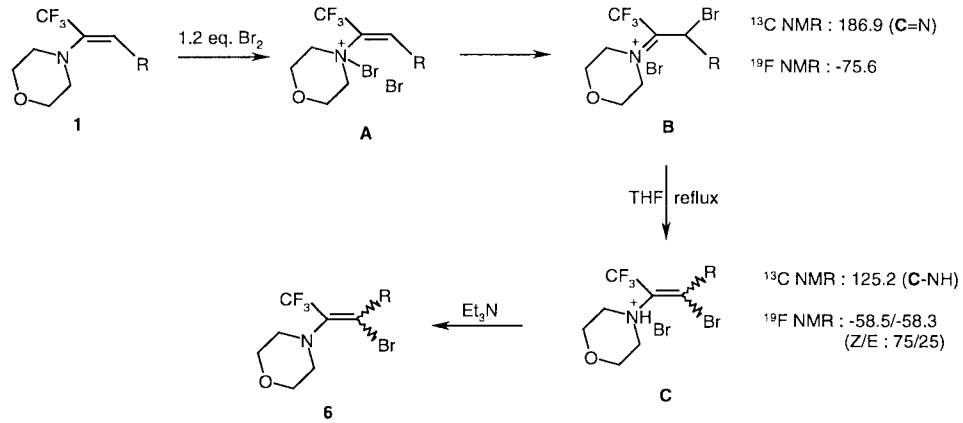
Trifluoromethyl ketones are molecules of great interest as synthetic intermediates in the preparation of more complex molecules and because of their properties as enzyme inhibitors.[1] Among them, simple trifluoromethyl alkyl ketones are selective inhibitors of esterases such as juvenile hormone esterases.[2] In recent years, great improvements in the synthesis of fluoroalkyl ketones have been reported.[1,3] Most of these methods are not efficient for the preparation of α,α-dialkyl trifluoromethyl ketones. Furthermore α,α-disubstituted ketones, and particularly α,α-diaryl ketones are very sensitive to traces of nucleophilic and basic agents.[4] To overcome this problem, we envisioned to prepare β,β-disubstituted trifluoromethyl enamines as masked ketones (Figure).

Figure β,β-Disubstituted trifluoromethyl enamines as masked ketones

Our previously described methods of preparation of trifluoromethyl enamines by Wittig reaction[5] and by the reaction of lithium amides with enol ethers[6] cannot be applied to the formation of β,β-dialkyl trifluoromethyl enamines. Thus, we envisaged palladium-catalyzed cross-coupling reaction performed on β-CF_3 vinyl bromides. This reaction is one of the most straightforward method for C−C bond formation[7] and has been applied to α-CF_3 vinyl bromides.[8,9] Recently, we have successfully described the Suzuki cross-coupling arylation, alkylation reaction of β-ethoxy β-CF_3 vinyl bromides.[10] This prompted us to investigate this reaction with parent trifluoromethyl enamines. To our knowledge, only one example of cross-coupling reaction has been performed with enamines.[11] We report here the preparation of β-amino-β-trifluoromethylvinyl bromides and their coupling with boronic acids.

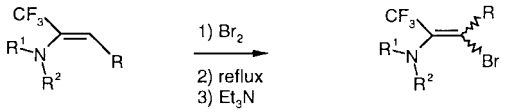
Trifluoromethyl enamines **1-5** were prepared by Wittig reaction with morpholinotrifluoroacetamide[5] or by reaction of lithium amides with enol ethers.[6] Our previous studies on the bromination/dehydrobromination of trifluoromethyl enamines showed that this classical method of preparation of vinyl bromides was not straightforward in the case of trifluoromethyl enamines.[12] Problem arose from the relative stabilities of intermediate iminium and enammonium salts (Scheme).

Thus we reinvestigated this reaction in detail. It was performed by reacting **1** with Br_2 in THF at 0 °C. We noticed that more than one equivalent of bromine was required. With only one equivalent, the starting enamine was recovered after neutralization with triethylamine. This suggests that the first step of the reaction is a *N*-bromination lead-



Scheme

Table 1 Bromination of Enamines **1**–**5**



Substrate	R^1, R^2	R	Product[a]	Yield[b] (%)	*Z*/*E*
1	$(CH_2)_2O(CH_2)_2$	$(CH_2)_5CH_3$	**6**	95	75:25
2	$(CH_2)_2O(CH_2)_2$	Ph	**7**	90	70:30
3	$(CH_2)_2O(CH_2)_2$	$(CH_2)_2Ph$	**8**	89	90:10
4	$(CH_2)_5$	Ph	**9**	51	70:30
5	Bn	Ph	**10**	82	90:10

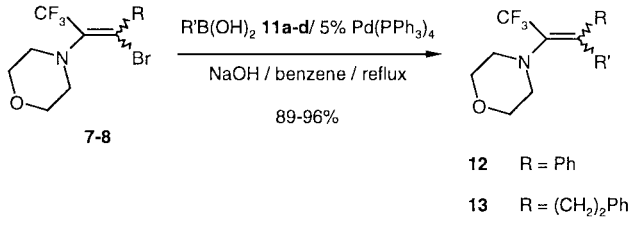
[a] No satisfactory microanalysis obtained.
[b] Yield of isolated products.

ing to salt **A** and not a bromination of the double bond. Furthermore, with 1.2 equivalent of Br_2 a stable salt was obtained, identified by NMR as the iminium salt **B**. This salt cannot undergo dehydrobromination with triethylamine. However, it could be totally isomerized into the enamonium salt **C** by heating. Neutralization with triethylamine could provide the expected vinyl bromides only at this stage. Under these conditions, enamines **1**−**5** could be converted in high yields into **6**−**10** as a mixture of *Z*/*E* isomers (Table 1).

The stereochemistry of **7** was unambiguously determined by ^{1}H NMR experiments. For the minor isomer of **7**, the irradiation of CH_2N entailed a NOE (8%) on the signal of the ortho proton of the phenyl group, indicating their spatial proximity. Thus, the major isomer has a *Z*-configuration. Stereochemistry of **6**, **8**−**10** has been determined by comparison of their ^{19}F NMR chemical shifts with those of **7**.

The Suzuki reaction was performed under the conditions optimized for β-ethoxy vinyl bromides.[10] β-Amino-β-trifluoromethylvinyl bromides **7** and **8** were treated in the presence of NaOH with boronic acids **11a**−**d** under $Pd(PPh_3)_4$ catalysis in benzene. In all cases compounds of cross-coupling were obtained after 2−6 hours in very high yields (Table 2). Ratio of isomers is always the same as in starting enamines. Due to the great number of aromatic protons, determination via ^{1}H NMR spectroscopy was difficult. However, in **12b** the presence of methoxy group differentiated the ortho protons, and the above described NOESY analysis confirmed the 70:30 mixture of *Z*/*E*-isomers. Unfortunately in these series examination of ^{19}F NMR chemical shifts did not allow the determination of *Z*/*E* ratio for other compounds. In the ^{1}H NMR spectra of **13a**−**c**, although signals of CH_2O are well differentiated in both isomers (0.4 ppm) assignment cannot be done unambiguously. Considering the stereospecificity of the Suzuki reaction, we assumed the *Z*/*E* values reported in the experimental section for **12a**, **c**−**d**, **13a**−**d**. Thus, we have shown that the Suzuki reaction is very efficient to introduce a β-substitution to trifluoromethyl enamines. Enamines **12** and **13** are very stable and can be stored for months at 0 °C.

Table 2 Reaction of Aryl- or Alkenylboronic Acids **11a**–**d** with Vinyl Bromides **7**–**8**



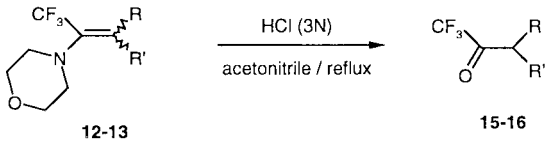
Vinyl Bromide	**R**	Boronic Acid **11** R'	Time (h)	Product	Yield[a] (%)
7	Ph	**a** : 4-C_6H_4F	4	**12a**	89
7	Ph	**b** : 4-C_6H_4OMe	6	**12b**	95
7	Ph	**c** : α-naphthyl	2.5	**12c**	95
7	Ph	**d** : CH=CHPh	3	**12d**	72
8	$(CH_2)_2Ph$	**a** : 4-C_6H_4F	4	**13a**	90
8	$(CH_2)_2Ph$	**b** : 4-C_6H_4OMe	4.5	**13b**	96
8	$(CH_2)_2Ph$	**c** : α-naphthyl	2.5	**13c**	95
8	$(CH_2)_2Ph$	**d** : CH=CHPh	4	**13d**	85

[a] Yield of isolated products.

Although the amino group has to be removed in view of ketone preparation, we have checked the influence of the amino group in the cross-coupling reaction with **11c**. Preliminary results showed that the coupling was also efficient from **9** when the amino substituent is a piperidine, leading to **14c** (70:30), but failed in the case of the dibenzylamine parent compound **10**.

In order to liberate the ketone function, the hydrolysis of enamines **12** and **13** has been investigated in acidic conditions. At room temperature, in acetonitrile with 2 equivalents of HCl (3 N), no reaction occurred after 24 hours. At reflux of the solvent, enamines **12a**−**c** and **13a**−**c** could be hydrolyzed under these conditions, to provide the crude ketones **15a**−**c** and **16a**−**c**, respectively, in good yields. However they could not be purified due to their instability.

Table 3 Hydrolysis of Enamines **12, 13**



Enamines	Time (min)	Product[a]	Yield[b] (%)
12a	15	**15a**	87
12b	15	**15b**	80
12c	15	**15c**	78
13a	60	**16a**	90
13b	60	**16b**	87
13c	60	**16c**	91

[a] Products **15**, **16** obtained have less than 5% impurity.
[b] Yield of crude products.

In conclusion, we have developed a preparation of β-amino-β-trifluoromethylvinyl bromides which could easily undergo Suzuki cross-coupling reactions and provide highly substituted-α-CF_3-enamines. These stable enamines are masked α,α-disubstituted trifluoromethyl ketones whose access through classical routes is limited due to their instability.

^{19}F NMR, ^{13}C NMR, ^{1}H NMR spectra were recorded on a 200 MHz multinuclear spectrometer. Chemichal shifts (δ) are given in ppm relative to $CFCl_3$ for ^{19}F NMR, and relative to TMS for ^{1}H NMR and ^{13}C NMR spectra. Coupling constants are given in Hz. In all NMR measurements $CDCl_3$ was used as a solvent. GC analyses were performed using a SE 30 capillary column (12 m). Boronic acids **11a**−**c** are commercially available. Enamines **1**−**3, 5**,[5,6] the bromoenamine **7**,[12] boronic acid **11d**,[13] $Pd(PPh_3)_4$[14] and ketones **15a**,**b**[15] were prepared according to the literature procedure. Petroleum ether used had bp 40-65 °C.

(*Z*)-1-Phenyl-2-piperidino-3,3,3-trifluoroprop-1-ene (4)

2-Ethoxy-1-phenyl-3,3,3-trifluoroprop-1-ene[5b] (1 g, 4.6 mmol) was added at −78 °C under argon to the *N*-lithiated amine prepared at −30 °C from BuLi (9.2 mmol, 1.6 M in hexane) and piperidine (861 mg, 10 mmol) in THF (15 mL). The colored solution was stirred for 15 min at −78 °C and then was allowed to warm to 0 °C over a period of 1 h. After 3 h, the brown solution was poured into satd aq NH_4Cl solution, the layers were separated and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) and evaporated to afford after chromatography on silica gel (pentane), pure (*Z*)-enamine **4** as a yellow oil; yield: 1.05 g (90%).

^{19}F NMR: δ = −63 (s, CF_3).

^{1}H NMR: δ = 1.6 (m, 6 H, 3 CH_2), 2.9 (m, 4 H, 2 CH_2N), 6.5 (s, 1 H), 7.2-7.4 (m, 3 H), 7.7 (d, *J* = 7.9 Hz, 2 H).

^{13}C NMR: δ = 24.0, 26.3, 51.4, 121.5 (q, $^{3}J_{C\text{-}F}$ = 5 Hz, CF_3C=*C*), 123.4 (q, $^{1}J_{C\text{-}F}$ = 281 Hz, CF_3), 128.2, 129.7, 134.4, 137.5 (q, $^{2}J_{C\text{-}F}$ = 28 Hz, CF_3*C*).

Anal. calcd for $C_{14}H_{16}F_3N$ (255.3): C, 65.87; H, 6.32; N, 5.49. Found: C, 65.75; H, 6.28; N, 5.29.

(*Z*/*E*)-1-Bromo-2-morpholino-1-phenyl-3,3,3-trifluoroprop-1-ene (7); Typical Procedure

To a solution of enamine **2** (400 mg, 1.55 mmol) in THF (20 mL) at 0 °C was added Br_2 (0.1 mL, 1.86 mmol). After 0.5 h at reflux of the solvent, Et_3N (0.3 mL, 3.1 mmol) was added at 0 °C, stirred for a further 10 min and then poured into an aq satd NH_4Cl solution (20 mL). The layers were separated and the aqueous phase extracted with Et_2O (3 × 10mL). The combined organics phases were dried ($MgSO_4$) and evaporated to afford, after chromatography on silica gel (petroleum ether/EtOAc, 90:10), pure vinyl bromide **7** as a yellow oil; yield: 479 mg (90%).

(*Z*/*E*)-3-Bromo-2-morpholino-1,1,1-trifluorononon-2-ene (6)

^{19}F NMR: δ = −56.9 (*Z*)/−58.1 (*E*) (75:25) (s, CF_3).

^{1}H NMR: δ = 0.9 (m, 3 H), 1.2 (m, 8 H), 1.9 (m, 2 H), 2.6 (*E*)/2.9 (*Z*) (m, 4 H), 3.4 (*E*)/3.7 (*Z*) (m, 4 H).

^{13}C NMR: δ = 13.7, 22.2, 27.9, 31.0, 36.9, 44.2, 49.5/50.5 (*Z*), 61.7 (*Z*)/67.2, 123.0 (q, $^{1}J_{C\text{-}F}$ = 283 Hz, CF_3), 134.6 (q, $^{2}J_{C\text{-}F}$ = 29 Hz, *C*CF_3), 139.1 (q, $^{3}J_{C\text{-}F}$ = 3.8 Hz).

(*Z*/*E*)-3-Bromo-2-morpholino-1,1,1-trifluoropent-2-ene (8)

^{19}F NMR: δ = −57.3 (*Z*)/−58.0 (*E*) (90:10) (s, CF_3).

^{1}H NMR: δ = 2.8 (m, 8 H), 3.6 (m, 4 H), 7.1 (m, 7 H).

^{13}C NMR: δ = 35.3 (*Z*), 39.4, 49.7, 67.4, 122.9 (q, $^{1}J_{C\text{-}F}$ = 283 Hz, CF_3), 126.5, 128.5, 135.5 (q, $^{2}J_{C\text{-}F}$ = 30 Hz, *C*CF_3), 137.5 (q, $^{3}J_{C\text{-}F}$ = 3.8 Hz), 139.9.

(*Z*/*E*)-1-Bromo-1-phenyl-2-piperidino-3,3,3-trifluoroprop-1-ene (9)

^{19}F NMR: δ = −57.1 (*Z*)/−61.8 (*E*) (70:30) (s, CF_3).

^{1}H NMR: δ = 1.4 (*Z*)/1.7 (*E*) (m, 6 H, 3 CH_2), 2.5 (*E*)/3.0 (*Z*) (t, 2 CH_2N), 7.2−7.4 (m, 5 H).

^{13}C NMR: δ = 23.7 (*E*)/34.1 (*Z*), 26.3 (*E*)/26.5 (*Z*), 51.1 (*Z*)/53.2 (*E*), 122.7 (q, $^{1}J_{C\text{-}F}$ = 287 Hz, CF_3), 128.0, 128.2, 128.4 (q, $^{5}J_{C\text{-}F}$ = 1.9 Hz), 129.2 (q, $^{3}J_{C\text{-}F}$ = 3.9 Hz, CF_3C=*C*), 137.8 (q, $^{2}J_{C\text{-}F}$ = 29 Hz, CF_3*C*=C), 138.5.

(*Z*/*E*)-2-Dibenzylamino-1-bromo-1-phenyl-3,3,3-trifluoroprop-1-ene (10)

^{19}F NMR: δ = −56.3 (*Z*)/−59.4 (*E*) (90:10) (s, CF_3).

^{1}H NMR: δ = 3.7 (*E*)/4.2 (*Z*) (s, 4 H, 2 CH_2), 6.9−7.4 (m, 15 H, 3 C_6H_5).

^{13}C NMR: δ = 56.2 (*Z*)/56.8 (*E*), 123.2 (q, $^{1}J_{C\text{-}F}$ = 283 Hz, CF_3), 127.7, 128.1, 128.4, 128.5, 129.3, 129.5, 132.3 (q, $^{3}J_{C\text{-}F}$ = 3.4 Hz, CF_3C=*C*), 136.4 (q, $^{2}J_{C\text{-}F}$ = 29 Hz, CF_3*C*=C), 138.0, 138.5.

(*Z*/*E*)-2-Morpholino-1-(4-fluorophenyl)-1-phenyl-3,3,3-trifluoroprop-1-ene (12a); Typical Procedure

A solution of vinyl bromide **7** (1 g, 2.7 mmol) and $(Ph_3P)_4Pd$ (162 mg, 0.14 mmol) in benzene (30 mL) was stirred for 15 min under argon. A solution of **11a** (546 mg, 3.5 mmol) in benzene (10 mL) and 2 M aq NaOH (1.8 mL, 5.4 mmol) were added and the mixture was refluxed for 4 h (the reaction was monitored by GC). After washing with aq satd NH_4Cl solution, the organic phase was extracted with Et_2O (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to give, after chromatography on silica gel (petroleum ether/EtOAc, 90:10), pure enamine **12a** as a white solid; yield: 939 mg (89%).

^{19}F NMR: δ = −58.7 (*Z*)/−58.9 (*E*) (70:30) (s, CF_3), −113.8 (*Z*)/−114.6 (*E*) (70:30) (m, C_6H_4F).

^{1}H NMR: δ = 2.6 (m, 4 H), 3.4 (m, 4 H), 6.8−7.3 (m, 9 H).

^{13}C NMR: δ = 53.5 (*Z*)/53.7, 68.3, 116.2 (d, $^{2}J_{C\text{-}F}$ = 22 Hz, *C*HCF), 123.0 (q, $^{1}J_{C\text{-}F}$ = 294 Hz, CF_3), 128.7, 128.9, 129.3, 130.2, 130.9 (d, $^{3}J_{C\text{-}F}$ = 8 Hz), 135.1 (q, $^{2}J_{C\text{-}F}$ = 29 Hz, CF_3*C*=C), 137.3 (d, $^{4}J_{C\text{-}F}$ = 4.5 Hz), 139.6, 140.2 (q, $^{3}J_{C\text{-}F}$ = 3 Hz, CF_3C=*C*), 141.2, 162.5 (d, $^{1}J_{C\text{-}F}$ = 248 Hz, CF).

Anal. calcd for $C_{19}H_{17}F_4NO$ (351.3): C, 64.95; H, 4.88; N, 3.99. Found: C, 64.90; H, 4.87; N, 3.98.

(*Z*/*E*)-2-Morpholino-1-(4-methoxyphenyl)-1-phenyl-3,3,3-trifluoroprop-1-ene (12b)

^{19}F NMR: δ = −58.8 (*Z*)/−59.0 (*E*) (70:30) (s, CF_3).

^{1}H NMR: δ = 2.7 (m, 4 H), 3.58 (m, 4 H), 3.79/3.81 (*Z*) (s, OCH_3), 6.85−7.3 (m, 9 H).

^{13}C NMR: δ = 52.7 (*Z*)/52.9, 55.1 (*Z*)/55.2, 67.4, 113.7/114.2 (*Z*), 123.7 (q, $^{1}J_{C\text{-}F}$ = 290 Hz, CF_3), 127.4, 127.6, 129.0 (*Z*) (q, $^{5}J_{C\text{-}F}$ = 2 Hz), 130.5/130.3 (*E*) (q, $^{5}J_{C\text{-}F}$ = 2 Hz), 133.5, 133.7, 134.3 (q, $^{2}J_{C\text{-}F}$ = 29 Hz, CF_3*C*=C), 140.2, 140.9 (q, $^{3}J_{C\text{-}F}$ = 2.3 Hz, CF_3C=*C*), 141.8, 159.2/159.3 (*Z*).

Anal. calcd for $C_{20}H_{20}F_3NO_2$ (363.4): C, 66.11; H, 5.55; N, 3.85. Found: C, 66.21, H, 5.60; N, 3.83.

***(Z/E)*-2-Morpholino-1-naphthyl-1-phenyl-3,3,3-trifluoroprop-1-ene (12c)**

^{19}F NMR: δ = −58.8 (*Z*)/−58.9 (*E*) (70:30) (s, CF_3).

^{1}H NMR: δ = 2.6 (m, 4 H), 3.5 (m, 4 H), 7.0−7.7 (m, 12 H).

^{13}C NMR: δ = 52.8 (*Z*)/52.9, 67.4 (*Z*)/67.5, 123.5 (q, $^{1}J_{C\text{-}F}$ = 292 Hz, CF_3), 126.3−128.6, 129.4 (q, $^{5}J_{C\text{-}F}$ = 2 Hz), 132.8, 133.1, 135.4 (q,

$^2J_{C-F}$ = 29 Hz, CF_3C=C), 138.9, 139.8, 141.1 (q, $^3J_{C-F}$ = 3 Hz, CF_3C=*C*).

Anal. calcd for $C_{23}H_{20}F_3NO$ (383.4): C, 72.05; H, 5.26; N, 3.65. Found: C, 71.67; H, 5.31; N, 3.61.

(*E*,*E*/*Z*,*E*)-4-Morpholino-1,3-diphenyl-5,5,5-trifluoropenta-1,3-diene (12d)

^{19}F NMR: δ = −55.5 (s) (*E*,*E*)/−58.6 (s) (*Z*,*E*) (70:30).

^{1}H NMR: δ = 2.6 (*Z*,*E*)/3.1 (E,E) (t, *J* = 4.3 Hz, 4 H), 3.4 (*Z*,*E*)/3.9 (*E*,*E*) (t, *J* = 4.6 Hz, 4 H), 6.1 (*E*,*E*)/6.2 (*Z*,*E*) (d, *J* = 16 Hz, 1 H), 7.1−7.5 (m, 10 H), 7.8 (d, *J* = 16 Hz, 1 H).

^{13}C NMR: δ = 51.5 (*E*,*E*)/52.0 (*Z*,*E*), 67.2 (*Z*,*E*)/67.8 (*E*,*E*), 123.5 (q, $^1J_{C-F}$ = 280 Hz, CF_3), 126.4, 127.9, 128.3, 128.5, 128.7, 128.8, 129.1 (q, $^5J_{C-F}$ = 2.0 Hz), 134.0 (q, $^2J_{C-F}$ = 28 Hz, CF_3C=C), 136.0, 136.9, 142.1 (q, $^3J_{C-F}$ = 3.6 Hz, CF_3C=*C*).

Anal. calcd for $C_{21}H_{20}F_3NO$ (359.4): C, 70.18; H, 5.61, N, 3.90. Found: C, 70.88, H, 5.40; N, 3.58.

(*Z*/*E*)-3-(4-Fluorophenyl)-2-morpholino-5-phenyl-1,1,1-trifluoropent-2-ene (13a)

^{19}F NMR: δ = −54.8 (*E*)/−59.0 (*Z*) (10:90) (s, CF_3), −114.5 (*E*)/−116.0 (*Z*) (10/90) (m, C_6H_4F).

^{1}H NMR: δ = 2.5(*Z*)/2.9 (m, 4 H), 2.6 (m, 4 H), 3.4 (*Z*)/3.7 (m, 4 H), 6.9−7.3 (m, 9 H).

^{13}C NMR: δ = 33.3/34.7 (*Z*), 35.9 (*Z*)/37.1, 51.0/51.8 (*Z*), 67.2 (*Z*)/67.6, 115.4 (d, $^2J_{C-F}$ = 21.7 Hz, *C*HCF), 123.5 (q, $^1J_{C-F}$ = 281 Hz, CF_3), 126.2, 128.3, 128.4, 129.7 (d, $^3J_{C-F}$ = 7.3 Hz, *C*HCF), 135.3 (q, $^2J_{C-F}$ = 29 Hz, CF_3C=C), 136.4 (d, $^4J_{C-F}$ = 3.8 Hz, *C*CF), 141.1, 143.2 (q, $^4J_{C-F}$ = 2.2 Hz, CF_3C=*C*), 162.5 (d, $^1J_{C-F}$ = 247 Hz, *C*HCF).

Anal. calcd for $C_{21}H_{21}F_4NO$ (379.4): C, 66.48; H, 5.58; N, 3.69. Found: C, 66.46; H, 5.60; N, 3.58.

(*Z*/*E*)-3-(4-Methoxyphenyl)-2-morpholino-5-phenyl-1,1,1-trifluoropent-2-ene (13b)

^{19}F NMR: δ = −54.8 (*E*)/−59.4 (*Z*) (10:90) (s, CF_3).

^{1}H NMR: δ = 2.5 (*Z*)/2.9 (m, 4 H), 2.65 (m, 4 H), 3.5 (*Z*)/3.75 (m, 4 H), 3.8 (s, OCH_3), 6.7−7.4 (m, 9 H).

^{13}C NMR: δ = 33.4/34.9 (*Z*), 36.2 (*Z*)/37.2, 51.1/52.6 (*Z*), 55.3, 67.3 (*Z*)/67.7, 113.5/113.7 (*Z*), 124.3 (q, $^1J_{C-F}$ = 281 Hz, CF_3), 126.0, 128.3, 128.4, 129.3, 132.5, 134.5 (q, $^2J_{C-F}$ = 29 Hz, CF_3-*C*=C), 141.5, 143.1 (q, $^3J_{C-F}$ = 1.8 Hz, CF_3C=*C*), 159.1.

Anal. calcd for $C_{22}H_{24}F_3NO_2$ (391.4): C, 67.51; H, 6.18; N, 3.58. Found: C, 67.51; H, 6.26; N, 3.51.

(*Z*/*E*)-2-Morpholino-3-naphthyl-5-phenyl-1,1,1-trifluoropent-2-ene (13c)

^{19}F NMR: δ = −54.8 (*E*)/−59.3 (*Z*) (10:90) (s, CF_3).

^{1}H NMR: δ = 2.5 (*Z*)/3.0 (m, 4 H), 2.65 (m,4 H), 3.3 (*Z*)/3.7 (m, 4 H), 6.9−7.8 (m,12 H).

^{13}C NMR: δ = 33.5/34.9 (*Z*), 36.0 (*Z*)/37.2, 51.1/51.9 (*Z*), 67.2 (*Z*)/67.8, 123.9 (q, $^1J_{C-F}$ = 281 Hz, CF_3), 125.8−128.6, 132.8, 133.2, 135.3 (q, $^2J_{C-F}$ = 29 Hz, CF_3C=C), 138.1, 141.3, 143.8 (q, $^3J_{C-F}$ = 2.1 Hz, CF_3C=*C*).

Anal. calcd for $C_{25}H_{24}F_3NO$ (411.5): C, 72.98; H, 5.88; N, 3.40. Found: C, 72.82; H, 5.90; N, 3.30.

(*E*,*E*/*Z*,*E*)-4-Morpholino-1-phenyl-3-(2-phenylethyl)-5,5,5-trifluoropenta-1,3-diene (13d)

^{19}F NMR: δ = −56.0 (*Z*,*E*)/−61.8 (*E*,*E*) (90:10) (s, CF_3).

^{1}H NMR: δ = 2.8 (m, 4 H, 2 CH_2), 3.0 (m, 4 H, 2 CH_2), 3.9 (t, *J* = 4.4 Hz, 4 H, 2 CH_2), 6.9 (d, *J* = 16 Hz, 1 H), 7.1−7.6 (m, 10 H), 7.8 (d, *J* = 16 Hz, 1 H).

^{13}C NMR: δ = 29.8 (*Z*,*E*)/30.8(*E*,*E*), 35.5(*E*,*E*)/36.4(*Z*,*E*), 50.9(*E*,*E*)/52.1(*Z*,*E*), 66.9(*E*,*E*)/67.8(*Z*,*E*), 124.7 (q, $^1J_{C-F}$ = 278 Hz, CF_3), 126.5, 127.0, 128.4, 128.7, 128.8, 129.0, 132.6, 132.9, 134.7 (q, $^2J_{C-F}$ = 29 Hz, CF_3C=C), 137.2, 137.5, 141.4 (q, $^3J_{C-F}$ = 3.6 Hz, CF_3C=*C*).

Anal. calcd for $C_{23}H_{24}F_3NO$ (387.4): C, 71.30; H, 6.24; N, 3.62. Found: C, 71.90; H, 6.19; N, 3.55.

(*Z*/*E*)-1-Naphthyl-1-phenyl-2-piperidino-3,3,3-trifluoroprop-1-ene (14c)

^{19}F NMR: δ = −58.8 (*Z*)/−58.9 (*E*) (70:30) (s, CF_3).

^{1}H NMR: δ = 1.5 (m, 6 H, 3 CH_2), 2.8 (m, 4 H, 2 CH_2), 7.0−8.1 (m, 12 H).

^{13}C NMR: δ = 24.0 *(Z)*/24.1*(E)*, 26.5 (*Z*)/26.6 (*E*), 53.8 (*Z*)/53.9 (*E*), 126.1−128.3, 129.5, 132.5, 132.9, 136.8 (q, $^2J_{C-F}$ = 29 Hz, CF_3C=C), 137.7, 140.2. CF_3 (not observed)

3-(4-Fluorophenyl)-3-phenyl-1,1,1-trifluoropropan-2-one (15a); Typical Procedure

To a solution of enamine **12a** (200 mg, 0.57 mmol) in MeCN (5 mL) was added 3 N HCl (0.38 mL, 1.1 mmol). After 15 min at reflux of the solvent, the mixture was neutralized with aq 1 N $NaHCO_3$ solution (1.1 mL). The organic phase was extracted with Et_2O (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to give crude ketone **15a** (140 mg, 87%).

^{19}F NMR: δ = −77.3 (s, CF_3), −114.0 (m, C_6H_4F).

^{1}H NMR: δ = 5.6 (s, 1 H), 6.9−7.5 (m, 10 H).

^{13}C NMR: δ = 57.1, 116.0 (d, $^2J_{C-F}$ = 22 Hz), 116.1 (q, $^1J_{C-F}$ = 293 HZ, CF_3), 128.3, 128.8, 129.2, 130.5 (d, $^3J_{C-F}$ = 8.5 Hz), 131.5 (d, $^4J_{C-F}$ = 3.0 Hz), 135.4, 162.6 (d, $^1J_{C-F}$ = 247 Hz), 149.9 (q, $^2J_{C-F}$ = 34 Hz, CF_3CO).

IR (CH_2Cl_2): $\nu_{C=O}$ = 1756 cm^{-1}.

3-(4-Methoxyphenyl)-3-phenyl-1,1,1-trifluoropropan-2-one (15b)

^{19}F NMR: δ = −77.3 (s, CF_3).

^{1}H NMR: δ = 3.8 (s, 3 H), 5.5 (s, 1 H), 6.8−7.5 (m, 9 H).

^{13}C NMR: δ = 55.2, 57.2, 114.6, 116.1 (q, $^1J_{C-F}$ = 293 Hz, CF_3), 127.4, 128.1, 128.8, 129.0, 130.1, 136.1, 159.5, 190.2 (q, $^2J_{C-F}$ = 33 Hz, CF_3CO).

IR (CH_2Cl_2): $\nu_{C=O}$ = 1729 cm^{-1}.

3-Naphthyl-3-phenyl-1,1,1-trifluoropropan-2-one (15c)

^{19}F NMR: δ = −77.4 (s, CF_3).

^{1}H NMR: δ = 5.7 (s, 1 H), 7.2−8.2 (m, 12 H).

^{13}C NMR: δ = 58.0, 116.2 (q, $^1J_{C-F}$ = 293, CF_3), 125.8−129.1, 132.9, 133.0, 133.4, 138.5, 189.6 (q, $^2J_{C-F}$ = 34, CF_3CO).

IR (CH_2Cl_2): $\nu_{C=O}$ = 1763 cm^{-1}.

3-(4-Fluorophenyl)-5-phenyl-1,1,1-trifluoropentan-2-one (16a)

^{19}F NMR: δ = −77.4 (s, CF_3), −113.8 (m, C_6H_4F).

^{1}H NMR: δ = 2.1 (m, 1 H), 2.5 (m, 3 H), 4.0 (t, *J* = 7.0 Hz, 1 H), 7.0−7.5 (m, 9 H).

^{13}C NMR: δ = 32.9, 34.0, 51.3, 115.8 (q, $^1J_{C-F}$ = 293 Hz, CF_3), 116.2 (d, $^2J_{C-F}$ = 22 Hz, *C*HCF), 126.4, 128.3, 128.6, 130.2 (d, $^3J_{C-F}$ = 8 Hz), 130.8 (d, $^4J_{C-F}$ = 4 Hz), 140.3, 162.5 (d, $^1J_{C-F}$ = 245 Hz, CF), 191.5 (q, $^2J_{C-F}$ = 31 Hz, CF_3CO).

3-(4-Methoxyphenyl)-5-phenyl-1,1,1-trifluoropentan-2-one (16b)

^{19}F NMR: δ = −76.9 (s, CF_3).

^{1}H NMR: δ = 2.1 (m, 1 H), 2.4 (m, 1 H), 2.5 (m, 2 H), 3.8 (s, 3 H, OCH_3), 3.95 (t, *J* = 7.0, 1 H), 6.9−7.5 (m, 9 H).

^{13}C NMR: δ = 33.0, 33.9, 51.4, 55.2, 114.7, 115.8 (q, $^1J_{C-F}$ = 293 Hz, CF_3), 126.3, 126.8, 128.4, 128.6, 129.8, 140.7, 159.6, 191. 5 (q, $^2J_{C-F}$ = 33 Hz, CF_3CO).

3-Naphthyl-5-phenyl-1,1,1-trifluoropentan-2-one (16c)
^{19}F NMR: δ = −77.0 (s, CF_3).

^{1}H NMR: δ = 2.2 (m, 1 H), 2.5 (m, 3 H), 4.1 (t, *J* = 7 Hz, 1 H), 7.0−7.8 (m, 12 H).

^{13}C NMR: δ = 33.0, 34.0, 52.3, 116.5 (q, $^1J_{C\text{-}F}$ = 293 Hz, CF_3), 125.8-129.2, 132.4, 133.0, 133.6, 140.5, 192.0 (q, $^2J_{C\text{-}F}$ = 34 Hz, CF_3*CO*).

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