Efficient and convenient entry to  $\beta$ -hydroxy- $\beta$ -trifluoromethyl- $\beta$ substituted ketones and 2,6-disubstituted 4-trifluoromethylpyridines based on the reaction of trifluoromethyl ketones with enamines or imines PERKIN

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The reactions of trifluoromethyl ketones with enamines or imines are described. The reaction of trifluoroacetone with enamines or imines followed by hydrolysis gave the corresponding  $\beta$ -hydroxy- $\beta$ -trifluoromethyl- $\beta$ -methyl ketones in good yields. The reaction of trifluoromethylated  $\beta$ -diketones with enamines in the presence of ammonium acetate gave 4-trifluoromethylated pyridines exclusively in good yields, without any detectable amount of regioisomers.

The trifluoromethyl group is one of the most attractive functional groups in organic chemistry, since trifluoromethylcontaining organic molecules can serve as liquid crystals,<sup>1</sup> catalysts,<sup>2</sup> and inhibitors,<sup>3</sup> and these properties often confer excellent physical and biological activities. Therefore, efficient introduction of a trifluoromethyl group is a topic of growing interest in organofluorine chemistry and many approaches to such compounds have been investigated recently.<sup>4</sup> Among them, *a*-trifluoromethylated carbonyl compounds are most useful and applicable building blocks for the synthesis of organofluorine compounds.<sup>5</sup>

Recently, we have demonstrated that enamine- or imineassisted facile generation of trifluoroacetaldehyde from trifluoroacetaldehyde ethyl hemiacetal or hydrate and sequential carbon–carbon bond formation lead to  $\beta$ -hydroxy- $\beta$ -trifluoromethyl ketone derivatives in the absence of additives.<sup>6</sup> In this paper we describe the reaction of trifluoromethyl ketones with various enamines or imines followed by hydrolysis affording  $\beta$ -hydroxy- $\beta$ -trifluoromethyl- $\beta$ -substituted ketones in good yields as well as the application for the reaction of trifluoromethylated  $\beta$ -diketones with enamines in the presence of ammonium acetate towards the regioselective synthesis of 4trifluoromethylated pyridines.

#### **Results and discussion**

# Reaction of trifluoromethyl ketones with enamines leading to $\beta$ -hydroxy- $\beta$ -trifluoromethyl- $\beta$ -substituted ketones

The reactions of trifluoroacetone **1** with 1 equiv. of enamine, prepared from acetophenone and morpholine, in hexane at room temperature for 3 h, followed by hydrolysis with 10% HCl solution, gave the corresponding  $\beta$ -hydroxy- $\beta$ -methyl- $\beta$ -trifluoromethyl ketones **2a** in 68% yield (Scheme 1, Table 1, entry 1).

Elevated temperature gave only a small amount of ketone 2a because of the low boiling point of the starting ketone (22 °C). Employment of 3 equiv. of trifluoroacetone at ambient temperature afforded the corresponding ketone 2a in 90% yield (entry 3). Toluene and dichloromethane are also usable as reac-



Scheme 1 Reagents and conditions: i, rt, 1–3 h; ii, 10% HCl aq. rt, 0.5 h.

tion solvents (entries 4 and 5). Some enamines with *p*-tolyl, *p*-chlorophenyl and thienyl groups participated well in the reaction to give the corresponding  $\beta$ -hydroxy- $\beta$ -methyl- $\beta$ -trifluoromethyl ketones **2** in good to excellent yields (entries 6–8). The reaction of trifluoroacetone with an enamine with a *c*-hexyl group did not occur efficiently and gave only 32% of the corresponding ketone **2e**. This is probably owing to the lack of stabilization of the iminium ion species by a  $\pi$ -system (entry 9).

Treatment of hexafluoroacetone trihydrate **3** with enamine, prepared from acetophenone and morpholine, at room temperature for 3 h, followed by hydrolysis with 10% HCl, gave the corresponding  $\beta$ -hydroxy- $\beta$ , $\beta$ -bis(trifluoromethyl) ketone **4** in only 8% yield (Scheme 2). The yield was not improved even if



Scheme 2 Reagents and conditions: i, rt, 3 h; ii, 10% HCl aq. rt, 0.5 h.

reflux temperature or an excess amount of enamine was used. Probably, the tetrahedral intermediate is too stable to generate hexafluoroacetone effectively on account of the electronwithdrawing properties of the two trifluoromethyl groups. On the other hand, enamine reacted with hexafluoroacetone, generated from hexafluoroacetone trihydrate **3** and conc.  $H_2SO_4$ , followed by hydrolysis using 10% HCl, giving **4** in 31% yield.

It is significant that the reaction of acetone with enamine under the same conditions did not proceed at all.

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Entry	1 (equiv.)	R <sup>1</sup>	Temp.	Time/h	Product	Yield <sup>a</sup> (%)
1	1	Ph	rt	3	2a	68 <sup>b</sup>
2	1	Ph	rt	1	2a	16 <sup>b</sup>
3	3	Ph	rt	3	2a	90
4 <sup>c</sup>	3	Ph	rt	3	2a	80
5 <sup>d</sup>	3	Ph	rt	3	2a	79
6	3	4-MeC <sub>6</sub> H₄	rt	3	2b	77
7	3	4-ClC <sub>6</sub> H <sub>4</sub>	rt	3	2c	94
8	3	2-Thienyl	rt	3	2d	89
9	3	c-Hex	rt	3	2e	32

<sup>a</sup> Yields of isolated products. <sup>b</sup> Yields were determined by <sup>19</sup>F NMR. <sup>c</sup> Toluene was used as reaction solvent. <sup>d</sup> Dichloromethane was used as reaction solvent.

	Table 2	Reaction	of trif	luoromethy	l ketones 1	l with	imines
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Entry	R <sup>1</sup>	Addition temp.	Time/h	Hydrolysis acid	Temp.	Time/h	Yield <sup><i>b</i></sup> of <b>2</b> (%)	Yield <sup><i>b</i></sup> of <b>5</b> (%)
1	Ph	rt	3	Α	rt	0.5	<b>2a</b> (7)	<b>5a</b> (39)
2	Ph	rt	3	А	rt	24	<b>2a</b> (35)	5a (22)
3	Ph	rt	3	В	rt	24	<b>2a</b> (36)	5a (trace)
4	Ph	rt	24	В	rt	24	<b>2a</b> $(55)^d$	5a (trace)
5	Ph	Reflux	1	В	rt	24	<b>2a</b> (7)	5a (trace)
6	4-ClC <sub>6</sub> H₄	rt	24	В	rt	24	$2c(65)^d$	5c (trace)
7	c-Hex	rt	24	В	rt	24	<b>2d</b> (10)	5d (trace)
8	t-Bu	rt	24	В	rt	24	2e (trace)	5e (trace)

<sup>*a*</sup> All the reactions were carried out with trifluoroacetone **1** (3 mmol) and imine (1 mmol) in hexane (4 ml). <sup>*b*</sup> Yields were determined by <sup>19</sup>F NMR. <sup>*c*</sup> A: 10% HCl (4 ml). B: conc. HCl (1 ml), SiO<sub>2</sub> (1 g) and EtOH (2 ml). <sup>*d*</sup> Yields of isolated products.

# Reaction of trifluoroacetone with imines leading to $\beta$ -hydroxy- $\beta$ -methyl- $\beta$ -trifluoromethyl ketones 2

Treatment of imine ( $\mathbb{R}^1 = \mathbb{P}h$ ) with 3 equiv. of trifluoroacetone **1** under the same conditions as the reaction of enamine, gave a trace amount of the corresponding  $\beta$ -hydroxy- $\beta$ -methyl- $\beta$ -trifluoromethyl ketone **2a** together with 39% of  $\beta$ -hydroxy- $\beta$ -methyl- $\beta$ -trifluoromethyl imine **5a** (Scheme 3, Table 2, entry 1).<sup>7</sup>



Scheme 3 Reagents and conditions: i, 1-24 h; ii, hydrolysis.

Surprisingly, 10% HCl was not so effective for hydrolysis (24 h), giving the mixture of ketone **2a** and imine **5a** in 35% and 22% yields, respectively (entry 2). Hydrolysis using conc. HCl-adsorbed silica gel<sup>8</sup> and EtOH in place of 10% HCl occurred smoothly to provide only ketone **2a** in 36% yield (entry 3). Longer time (24 h) for the reaction between **1** and enamine resulted in good yield (55%) of **2a** (entry 4).

At reflux temperature for 1 h the reaction did not proceed smoothly giving only a trace amount of 2a (entry 5). A couple of aromatic enamines reacted readily with trifluoroacetone 1 at room temperature to provide the corresponding ketones 2a, c in good yields (entries 4 and 6). However, aliphatic enamines carrying *c*-hexyl or *tert*-butyl groups did not react well giving a small or trace amount of products (entries 7 and 8).

# Regioselective synthesis of 4-trifluoromethyl-2,6-disubstituted pyridines by the reaction of $\beta$ -trifluoromethyl- $\beta$ -diketones with enamines in the presence of ammonium acetate<sup>9</sup>

The reaction of enamine, prepared from acetophenone and morpholine, with trifluoromethylated  $\beta$ -diketone **6a** in the presence of 2 equiv. of ammonium acetate for 0.5 h provided 4-trifluoromethyl-2,6-diphenylpyridine (**7a**) in 32% yield (Scheme 4, Table 3, entry 1). The other regioisomer of the pyridine **7a** was not detected in the reaction mixture.



Scheme 4 Reagents and conditions: i,  $NH_4OAc$ , solvent, reflux, 0.5-3 h.

Among the solvents, such as hexane, acetonitrile, ethanol, propan-1-ol, diglyme, triglyme and DMF, triglyme gave the best result (entry 7). Prolonged reaction time (3 h) did not improve the yield of **7a** (entry 4). Use of 2 equiv. of enamine in triglyme afforded **7a** in 71% yield (entry 9). Other trifluoromethylated  $\beta$ -diketones **6** as well as other enamines participated well in the reaction to afford 4-trifluoromethyl-2,6-disubstituted pyridine derivatives **7** in good yields (Scheme 5, Table 4, entries 2–8).



Scheme 5 Reagents and conditions: i, NH<sub>4</sub>OAc, triglyme, reflux, 0.5 h.

Table 3Screening for the synthesis of 2,6-diphenyl-4-trifluoromethyl-<br/>pyridine  $(7a)^a$ 

Entry	Enamine (equiv.)	Solvent	Time/h	Yield <sup>b</sup> (%)
1	1.1	Hexane	0.5	32
2	1.1	MeCN	0.5	37
3	1.1	EtOH	0.5	33
4	1.1	EtOH	3	37
5	1.1	n-PrOH	0.5	42
6	1.1	Diglyme	0.5	52
7	1.1	Triglyme	0.5	58
8	1.1	DMF	0.5	49
9	2	Triglyme	0.5	71

<sup>*a*</sup> The reaction was carried out with diketone **4a**, enamine and  $NH_4OAc$  (2 equiv.) in solvent at reflux. <sup>*b*</sup> Yields of isolated products.

 Table 4
 Synthesis of 2,6-disubstituted 4-trifluoromethylpyridines (7)<sup>a</sup>

Entry	R <sup>1</sup>	R <sup>2</sup>	Product	Yield <sup>b</sup> (%)
1	Ph	Ph	7a	71
2	4-ClC <sub>6</sub> H <sub>4</sub>	Ph	7b	75
3	4-MeOC <sub>6</sub> H <sub>4</sub>	Ph	7c	73
4	2-Thienyl	Ph	7d	72
5	Ph	4-ClC <sub>6</sub> H <sub>4</sub>	7b	75
6	Ph	4-MeC <sub>6</sub> H <sub>4</sub>	7e	74
7	Ph	4-MeOC <sub>6</sub> H <sub>4</sub>	7c	70
8	Ph	2-Thienyl	7d	71

<sup>*a*</sup> The reaction was carried out with diketone **6** (1 mmol), enamine (2 mmol) and  $NH_4OAc$  (2 mmol) in triglyme (2 ml) at reflux for 0.5 h. <sup>*b*</sup> Yields of isolated products.



Scheme 6 Reagents and conditions: i, NH4OAc, triglyme, reflux, 0.5 h.

To make a regiochemical assignment of 7, the reaction as described in Scheme 6 was carried out under the same conditions; the reaction of  $\alpha$ , $\beta$ -unsaturated trifluoromethyl ketone 8 with 2 equiv. of enamine in the presence of 2 equiv. of ammonium acetate in triglyme at reflux temperature gave 6-trifluoromethylated pyridine 9 in 13% yield.

The chemical shift (-68.64 ppm) of **9** in <sup>19</sup>F NMR appeared at higher field than that of **7a** (-63.04 ppm). This tendency is entirely consistent with our previous report.<sup>9e</sup> Furthermore, the spectral data, <sup>1</sup>H, <sup>13</sup>C and <sup>19</sup>F NMR, of **7c**, which was produced from the reaction between  $\beta$ -diketone **6c** and an enamine with a phenyl group, are identical with those of the product from the reaction between  $\beta$ -diketone **6a** and an enamine with a *p*methoxyphenyl group (entries 3 and 7). According to these results, regiochemical assignment of pyridines **7** can be made as 4-trifluoromethylated compounds.

A plausible reaction mechanism for the formation of **7** is described in Scheme 7. Trifluoromethylated  $\beta$ -diketones **6** exist nearly exclusively as enols.<sup>10</sup> The enol **6'** and/or  $\beta$ -amino- $\alpha$ , $\beta$ -unsaturated ketones **10**, which can be obtained from **6'** and ammonia, will react with an enamine *via* Michael addition,<sup>11</sup> followed by cyclisation to give the intermediate **12** or **13**. These intermediates **11**, **11'**, **12** and/or **13** would react with ammonia, followed by elimination of NHR<sub>2</sub> and XH<sub>2</sub> leading to 4-trifluoromethylated pyridines **7**.

In summary, we have demonstrated that trifluoroacetone reacts with enamines or imines, followed by hydrolysis, to give the corresponding  $\beta$ -trifluoromethylated- $\beta$ -methyl ketones in good yields. We also show that one trifluoromethyl



Scheme 7 A plausible reaction mechanism for the formation of 7.

group accelerates the addition reaction of enamines or imines, affording the first example for the convenient synthesis of  $\beta$ -trifluoromethylated- $\beta$ -methyl ketones. In addition, we have described the reaction of trifluoromethylated  $\beta$ -diketones with enamines in the presence of NH<sub>4</sub>OAc which give the corresponding 4-trifluoromethylated 2,6-disubstituted pyridines regioselectively in good yields.

#### Experimental

## General

Melting points were obtained on a Shimadzu MM-2 micro point determination apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Shimadzu IR-400 spectrometer. <sup>1</sup>H NMR spectra were measured with a JEOL  $\alpha$ -400 (400 MHz) FT-NMR spectrometer in deuteriochloroform (CDCl<sub>3</sub>) solutions with tetramethylsilane (Me<sub>4</sub>Si) as the internal standard. <sup>13</sup>C NMR spectra were obtained on a JEOL  $\alpha$ -400 (100 MHz) FT-NMR spectrometer in CDCl<sub>3</sub> solutions relative to CDCl<sub>3</sub> (77.0 ppm). <sup>19</sup>F NMR spectra were recorded on a JEOL  $\alpha$ -400 (376 MHz) FT-NMR in CDCl<sub>3</sub> solutions using trifluoroacetic acid as the external standard and converted to the CFCl<sub>3</sub> standard by the calculation of  $\delta$ (CFCl<sub>3</sub>) =  $-[77.0 - \delta(\text{TFA})]$ . Mass spectra (MS) were taken on a Hitachi-80B spectrometer operating at an ionization potential of 70 eV. Elemental analyses were made on a Yanaco MT-5 CHN corder. The isolation of pure products was carried out by column chromatography using silica gel (Wakogel C-200, 100–200 mesh, Wako Pure Chemical Ind. Ltd.).

## Typical procedure for the reaction of trifluoroacetone with enamine

To a hexane (2 ml) solution of trifluoroacetone, **1** (0.336 g, 3 mmol) was slowly added 4-(1-phenylethenyl)morpholine (0.189 g, 1 mmol) at room temperature. After the reaction mixture was stirred at room temperature for 3 h under an argon atmosphere, 10% HCl solution (4 ml) was added, and left at this temperature for 30 min. The resultant mixture was quenched with brine (30 ml), extracted with diethyl ether (30 ml  $\times$  3), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The residual oil was chromatographed on silica-gel and using benzene as an eluent afforded analytically pure **2a** (0.201 g, 86%) as a white solid.

#### Typical procedure for the reaction of trifluoroacetone with imine

To a hexane (2 ml) solution of trifluoroacetone, **1** (0.336 g, 3 mmol) was slowly added *N*-(1-phenylethylidene)cyclohexylamine (0.201 g, 1 mmol) at room temperature. After the reaction mixture was stirred at room temperature for 3 h under an argon atmosphere, conc. HCl (1 ml)-adsorbed silica gel (1 g) and EtOH (2 ml) were added, and left at this temperature for 24 h. The resultant mixture was quenched with brine (30 ml), extracted with diethyl ether (30 ml × 3), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The residual oil was chromatographed on silica-gel and using benzene as an eluent afforded analytically pure **2a** (0.125 g, 54%) as a white solid.

**4,4.4-Trifluoro-3-hydroxy-3-methyl-1-phenylbutan-1-one 2a.** Mp 40.8–41.7 °C (hexane);  $\nu_{max}$ (KBr)/cm<sup>-1</sup> 1672.9 (C=O), 3424.0 (OH);  $\delta_{\rm H}$  1.51 (3H, s, CH<sub>3</sub>), 3.11 (1H, d, *J* 17.08, CH<sub>A</sub>CH<sub>B</sub>), 3.51 (1H, d, *J* 17.08, CH<sub>A</sub>CH<sub>B</sub>), 5.27 (1H, s, OH), 7.49–7.53 (2H, m, aryl H), 7.63–7.66 (1H, m, aryl H), 7.95–7.97 (2H, m, aryl H);  $\delta_{\rm C}$ (CDCl<sub>3</sub>) 22.08 (s), 40.19 (s), 73.40 (q, *J* 28.67), 125.67 (q, *J* 285.05), 128.27 (s), 128.90 (s), 134.31 (s), 136.45 (s), 200.16 (s);  $\delta_{\rm F}$  (CDCl<sub>3</sub>) –81.97 (3F, s, CF<sub>3</sub>); MS (EI) *m*/*z* (rel intensity) 232 (M<sup>+</sup>; 45.7%), 214 (33.0), 163 (28.1), 145 (32.3), 77 (100.0); Found: C, 56.91; H, 4.79. C<sub>11</sub>H<sub>11</sub>F<sub>3</sub>O<sub>2</sub> requires C, 56.90; H, 4.77%.

**4,4.4-Trifluoro-3-hydroxy-3-methyl-1-(4-methylphenyl)butan-1-one 2b.** Mp 53.0–53.6 °C (hexane);  $v_{max}$ (KBr)/cm<sup>-1</sup> 1681.0 (C=O), 3486.7 (OH);  $\delta_{\rm H}$ (CDCl<sub>3</sub>) 1.49 (3H, s, CH<sub>3</sub>), 2.44 (3H, s, CH<sub>3</sub>), 3.07 (1H, d, J 16.84,  $CH_{\rm A}CH_{\rm B}$ ), 3.46 (1H, d, J 16.84, CH<sub>A</sub>CH<sub>B</sub>), 5.40 (1H, s, OH), 7.30 and 7.85 (4H, AB quartet, J 8.29, aryl H);  $\delta_{\rm C}$ (CDCl<sub>3</sub>) 21.73 (s), 22.11 (s), 39.91 (s), 73.40 (q, J 29.22), 125.68 (q, J 285.05), 128.44 (s), 129.59 (s), 134.00 (s), 145.50 (s), 199.80 (s);  $\delta_{\rm F}$  (CDCl<sub>3</sub>) -81.95 (3F, s, CF<sub>3</sub>); MS (EI) *m*/*z* (rel intensity) 246 (M<sup>+</sup>; 21.3%), 231 (19.2), 134 (36.0), 119 (100.0), 91 (100.0), 77 (15.0), 65 (94.4); Found: C, 58.54; H, 5.34. C<sub>12</sub>H<sub>13</sub>F<sub>3</sub>O<sub>2</sub> requires C, 58.54; H, 5.32%.

**1-(4-Chlorophenyl)-4,4,4-trifluoro-3-hydroxy-3-methylbutan-1-one 2c.** Mp 40.0–40.6 °C (hexane);  $v_{max}$ (KBr)/cm<sup>-1</sup> 1686.5 (C=O), 3485.9 (OH);  $\delta_{\rm H}$ (CDCl<sub>3</sub>) 1.51 (3H, s, CH<sub>3</sub>), 3.05 (1H, d, *J* 17.08, CH<sub>A</sub>CH<sub>B</sub>), 3.49 (1H, d, *J* 17.08, CH<sub>A</sub>CH<sub>B</sub>), 5.06 (1H, s, OH), 7.49 and 7.90 (4H, AB quartet, *J* 8.30, aryl H);  $\delta_{\rm C}$ (CDCl<sub>3</sub>) 22.04 (s), 40.27 (s), 73.36 (q, *J* 28.67), 125.59 (q, *J* 284.50), 129.26 (s), 129.69 (s), 134.74 (s), 140.97 (s), 198.74 (s);  $\delta_{\rm F}$  (CDCl<sub>3</sub>) -81.88 (3F, s, CF<sub>3</sub>); MS (EI) *m*/*z* (rel intensity) 268 (M + 2; 0.5%), 266 (M<sup>+</sup>; 1.3), 154 (26.1), 139 (100.0), 111 (100.0), 75 (60.1), 69 (15.1); Found: C, 49.55; H, 3.81.  $C_{11}H_{10}ClF_3O_2$  requires C, 49.55; H, 3.78%.

**4,4,4-Trifluoro-3-hydroxy-3-methyl-1-(2-thienyl)butan-1-one 2d.**  $v_{max}(film)/cm^{-1}$  1647.6 (C=O), 3422.4 (OH);  $\delta_{H}(CDCl_{3})$  1.50 (3H, s, CH<sub>3</sub>), 3.05 (1H, d, J 16.59, CH<sub>A</sub>CH<sub>B</sub>), 3.41 (1H, d, J 16.59, CH<sub>A</sub>CH<sub>B</sub>), 5.15 (1H, s, OH), 7.18–7.20 (1H, m, aryl H), 7.76–7.78 (2H, m, aryl H);  $\delta_{C}(CDCl_{3})$  21.89 (s), 41.11 (s), 73.36 (q, J 29.22), 125.55 (q, J 285.05), 128.55 (s), 135.87 (s), 143.43 (s), 192.15 (s);  $\delta_{F}$  (CDCl<sub>3</sub>) –81.81 (3F, s, CF<sub>3</sub>); MS (EI) m/z (rel intensity) 238 (M<sup>+</sup>; 63%), 126 (99), 111 (100.0), 97 (21.7), 83 (42.2).

**1-Cyclohexyl-4,4-trifluoro-3-hydroxy-3-methylbutan-1-one 2e.**  $v_{max}(film)/cm^{-1}$  1696.0 (C=O), 3406.2 (OH);  $\delta_{H}(CDCl_3)$ 1.12–1.29 (6H, m, CH<sub>2</sub> × 3), 1.31 (3H, s, CH<sub>3</sub>), 1.61–1.80 (4H, m, CH<sub>2</sub> × 2), 2.26–2.32 (1H, m, CH), 2.50 (1H, d, *J* 17.08, CH<sub>A</sub>CH<sub>B</sub>), 2.90 (1H, d, *J* 17.08, CH<sub>A</sub>CH<sub>B</sub>), 5.33 (1H, s, OH);  $\delta_{C}(CDCl_3)$  22.04 (s), 25.30 (d, *J* 6.62), 25.56 (s), 27.71 (d, *J* 8.72), 42.27 (s), 52.17 (s), 73.14 (q, *J* 28.67), 125.62 (q, *J* 85.60), 214.97 (s);  $\delta_{F}$  (CDCl<sub>3</sub>) –81.79 (3F, s, CF<sub>3</sub>); MS (EI) *m/z* (rel intensity) 238 (M<sup>+</sup>; 1.8%), 196 (1.7), 183 (8.0), 169 (2.8), 155 (3.3), 111 (21.7), 83 (100.0)

1,1,1-Trifluoro-4-(cyclohexylimino)-2-methyl-4-phenylbutan-

**2-ol 5a.**  $v_{\text{max}}(\text{film})/\text{cm}^{-1}$  1649.2 (C=N), 3060.7 (OH);  $\delta_{\text{H}}(\text{CDCl}_3)$ 1.12–1.70 (10H, m, CH<sub>2</sub> × 5), 1.44 (3H, s, CH<sub>3</sub>), 2.66 (1H, d, *J* 17.08, CH<sub>A</sub>CH<sub>B</sub>), 2.88 (1H, d, *J* 17.08, CH<sub>A</sub>CH<sub>B</sub>), 3.22–3.29 (m, 1H, CH), 7.10–7.13 (2H, m, aryl H), 7.26–7.28 (1H, m, aryl H), 7.37–7.45 (2H, m, aryl H);  $\delta_{\text{C}}(\text{CDCl}_3)$  22.70 (s), 23.84 (s), 25.45 (s), 33.44 (s), 41.69 (s), 59.64 (s), 73.77 (q, *J* 27.57), 126.44 (q, *J* 286.16), 125.57 (s), 128.77 (s), 137.55 (s), 168.27 (s);  $\delta_{\text{F}}$  (CDCl<sub>3</sub>) –80.96 (3F, s, CF<sub>3</sub>); MS (CI) *m*/*z* (rel intensity) 244 (5.4), 202 (96.0), 186 (100.0), 172 (24.1), 158 (45.7), 146 (44.6), 130 (25.5), 124 (15.2), 120 (70.9), 104 (69.7), 91 (15.7), 77 (23.9); HRMS (CI) Found: 314.1713 (M + H). C<sub>17</sub>H<sub>23</sub>F<sub>3</sub>NO requires 314.1733.

#### Preparation of 4,4,4-trifluoro-3-hydroxy-3-methyl-1-phenyl-3trifluoromethylbutan-1-one (4)

To a hexane (4 ml) solution of hexafluoroacetone trihydrate (0.673 g, 3 mmol) was slowly added 4-(1-phenylethenyl)morpholine (0.189 g, 1 mmol) at room temperature. After the reaction mixture was stirred at room temperature for 24 h under an argon atmosphere, conc. 10% HCl solution (4 ml) was added, and left at this temperature for 0.5 h. The resultant mixture was quenched with brine (30 ml), extracted with diethyl ether (30 ml × 3), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The residual oil was chromatographed on silica-gel and using benzene as an eluent afforded analytically pure **4** (0.022 g, 8%).

#### 4,4,4-Trifluoro-3-hydroxy-3-methyl-1-phenyl-3-trifluoro-

methylbutan-1-one 4.  $\delta_{\rm H}$ (CDCl<sub>3</sub>) 7.08 (1H, s, OH), 7.46–7.53 (2H, m, CH<sub>2</sub>), 7.61–7.65 (1H, m, aryl H), 7.89–7.91 (2H, m, aryl H);  $\delta_{\rm F}$  (CDCl<sub>3</sub>) –77.31 (6F, s); MS (EI) *m/z* (rel intensity) 286 (M<sup>+</sup>; 1.5%), 267 (1.6), 249 (1.4), 217 (1.1), 201 (0.8), 105 (100.0), 77 (100.0), 69 (33.9).

#### Typical procedure for the synthesis of 4-trifluoromethylpyridines

After the triglyme (2 ml) solution of 4-(1-phenylethenyl)morpholine (2 mmol, 0.379 g), diketone **6a** (1 mmol, 0.216 g) and ammonium acetate (2 mmol, 0.154 g) was refluxed for 0.5 h, the resultant mixture was quenched with saturated NaHCO<sub>3</sub> solution, extracted with diethyl ether (30 ml × 3), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The residue was purified by column chromatography on silica gel eluting with hexane–benzene = 1 : 1, giving **7a** (0.212 g, 71%) as a white solid. **2,6-Diphenyl-4-trifluoromethylpyridine** 7a. Mp 85.1–85.9 °C (hexane);  $\delta_{\rm H}$ (CDCl<sub>3</sub>) 7.46–7.55 (6H, m, aryl H), 7.88 (2H, s, aryl H), 8.16–8.18 (4H, m, aryl H);  $\delta_{\rm C}$ (CDCl<sub>3</sub>) 114.01 (q, *J* 3.31), 123.16 (q, *J* 272.92), 127.09 (s), 128.86 (s), 129.80 (s), 138.14 (s), 139.97 (q, *J* 33.08), 158.15 (s);  $\delta_{\rm F}$  (CDCl<sub>3</sub>) –63.04 (s, 3F); MS (EI) *m/z* (rel intensity) 298 (M<sup>+</sup>; 100.0%), 280 (36.7), 258 (20.2), 230 (100.0), 202 (54.5), 77 (71.0).

**2-(4-Chlorophenyl)-6-phenyl-4-trifluoromethylpyridine 7b.** Mp 89.8–90.3 °C;  $\delta_{\rm H}$ (CDCl<sub>3</sub>) 7.47–7.56 (3H, m, aryl H), 7.50 and 8.12 (4H, AB quartet, *J* 8.54, aryl H), 7.84 (1H, s, aryl H), 7.88 (1H, s, aryl H), 8.10–8.16 (2H, m, aryl H);  $\delta_{\rm C}$ (CDCl<sub>3</sub>) 55.38 (s), 113.22 (s), 114.20 (s), 123.27 (q, *J* 273.75), 127.05 (s), 128.45 (s), 128.83 (s), 129.72 (s), 130.77 (s), 138.31 (s), 139.86 (q, *J* 33.08), 157.77 (s), 157.97 (s);  $\delta_{\rm F}$  (CDCl<sub>3</sub>) –63.88 (3F, s, CF<sub>3</sub>); *m/z* (EI) 335 (M<sup>+</sup> +2, 32%), 333 (M<sup>+</sup>, 100).

**2-(4-Methoxyphenyl)-6-phenyl-4-trifluoromethylpyridine** 7c. Mp 81.5–82.0 °C;  $\delta_{\rm H}$ (CDCl<sub>3</sub>) 3.89 (3H, s, OCH<sub>3</sub>), 7.04 and 8.14 (4H, AB quartet, *J* 8.78, aryl H), 7.45–7.55 (3H, m, aryl H), 7.81 (2H, s, aryl H), 8.12–8.17 (2H, m, aryl H);  $\delta_{\rm C}$ (CDCl<sub>3</sub>) 113.77 (q, *J* 3.30), 114.32 (q, *J* 3.31), 121.69 (q, *J* 273.74), 127.09 (s), 128.35 (s), 128.93 (s), 129.09 (s), 129.97 (s), 136.05 (s), 136.56 (s), 137.96 (s), 140.17 (q, *J* 33.63), 156.95 (s), 158.35 (s);  $\delta_{\rm F}$  (CDCl<sub>3</sub>) –63.88 (3F, s, CF<sub>3</sub>); *m/z* (EI) 329 (M<sup>+</sup>, 100), 286 (25).

**2-Phenyl-6-(2-thienyl)-4-trifluoromethylpyridine 7d.** Mp 110.5–111.0 °C;  $\delta_{\rm H}$ (CDCl<sub>3</sub>) 7.16 (1H, dd, *J* 5.1 and 3.7, aryl H), 7.46–7.54 (3H, m, aryl H), 7.47 (1H, dd, *J* 5.1 and 0.98, aryl H), 7.74 (1H, s, aryl H), 8.12–8.15 (2H, m, aryl H);  $\delta_{\rm C}$ (CDCl<sub>3</sub>) 112.32 (q, *J* 3.30), 113.48 (q, *J* 3.31), 121.66 (q, *J* 273.17), 125.66 (s), 127.00 (s), 128.16 (s), 128.80 (s), 128.85 (s), 129.92 (s), 137.60 (s), 139.90 (q, *J* 33.63), 143.99 (s), 153.43 (s), 158.02 (s);  $\delta_{\rm F}$  (CDCl<sub>3</sub>) –64.04 (3F, s, CF<sub>3</sub>); *m*/*z* (EI) 305 (M<sup>+</sup>, 100%).

**2-(4-Methylphenyl)-6-phenyl-4-trifluoromethylpyridine** 7e. Mp 95.3–96.0 °C (hexane);  $\delta_{\rm H}$ (CDCl<sub>3</sub>) 7.33 and 8.07 (4 H, AB quartet, *J* 8.30, aryl H), 7.46–7.55 (3H, m, aryl H), 7.85 (2H, s, aryl H), 8.16–8.18 (2H, m, aryl H);  $\delta_{\rm C}$ (CDCl<sub>3</sub>) 21.34 (s), 113.71 (s), 123.20 (q, *J* 274.58), 126.97 (s), 127.09 (s), 128.86 (s), 129.60 (s), 129.75 (s), 135.43 (s), 138.29 (s), 139.90 (q, *J* 33.08), 140.00 (s), 158.19 (s);  $\delta_{\rm F}$  –63.99 (3F, s, CF<sub>3</sub>); MS (EI) *m/z* (rel intensity) 312 (M<sup>+</sup>; 100.0), 244 (18.9), 91 (43.5); Anal. Calcd for: C, 72.83; H, 4.50: N, 4.47. Found: C, 72.99; H, 4.61; N, 4.49%.

**2,4-Diphenyl-2-trifluoromethylpyridine 9.** Mp 93.0–94.1 °C (hexane);  $\delta_{\rm H}$ (CDCl<sub>3</sub>) 7.45–7.57 (6H, m, aryl H), 7.69 (6H, m, aryl H), 7.81 (1H, d, *J* 1.3, aryl H), 8.09 (1H, d, *J* 1.3, aryl H), 8.10–8.13 (2H, m, aryl H);  $\delta_{\rm F}$  (CDCl<sub>3</sub>) –68.64 (s, 3F); MS (EI) *m*/*z* (rel intensity) 299 (M<sup>+</sup>; 100.0%), 230 (86.0).

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