



# Synthesis and hydrogenation of (*E*)- $\gamma$ -aryl- $\gamma$ -morpholino- $\alpha$ -trifluoromethylated allyl alcohols through the reaction of trifluoroacetaldehyde ethyl hemiacetal with enamines

Kazumasa Funabiki<sup>a,\*</sup>, Yoshihiro Murase<sup>a</sup>, Yudai Furuno<sup>a</sup>, Yasuhiro Kubota<sup>a</sup>, Masahiro Ebihara<sup>b</sup>, Masaki Matsui<sup>a</sup>

<sup>a</sup> Department of Materials Science and Technology, Faculty of Engineering, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan

<sup>b</sup> Department of Chemistry, Faculty of Engineering, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan

## ARTICLE INFO

### Article history:

Received 18 December 2009

Received in revised form 4 March 2010

Accepted 4 March 2010

Available online 10 March 2010

### Keywords:

Trifluoroacetaldehyde

Hemiacetal

Enamine

Hydrogenation

Reductive deamination

## ABSTRACT

Treatment of trifluoroacetaldehyde ethyl hemiacetal with enamines, derived from acetophenone derivatives, at room temperature gave (*E*)-1,1,1-trifluoro-4-morpholino-4-aryl-but-3-en-2-ols, which are intermediates for preparation of the  $\beta$ -trifluoromethylated aldol products, 4,4,4-trifluoro-3-hydroxy-1-aryl-butan-1-ones. The structure of the intermediate (*E*)-1,1,1-trifluoro-4-morpholino-4-(4-nitrophenyl)-but-3-en-2-ols could be assigned by <sup>1</sup>H, <sup>13</sup>C NMR, IR, and X-ray crystallography. Furthermore, hydrogenation and reductive deamination of the intermediate (*E*)-1,1,1-trifluoro-4-morpholino-4-aryl-but-3-en-2-ols with hydrogen in the presence of a catalytic amount (10 mol %) of palladium on carbon in trifluoroethanol proceeded smoothly at room temperature to give 1,1,1-trifluoro-4-aryl-2-butanols in good to excellent yields.

© 2010 Elsevier Ltd. All rights reserved.

## 1. Introduction

Trifluoroacetaldehyde (CF<sub>3</sub>CHO) is one of the most important building blocks for the construction of  $\alpha$ -trifluoromethylated alcohols.<sup>1,2</sup> However, CF<sub>3</sub>CHO normally exists as a hydrate or hemiacetal, due to the strong electron-withdrawing properties of the trifluoromethyl group.<sup>3</sup> Therefore, the direct use of commercially available CF<sub>3</sub>CHO ethyl hemiacetal with some reagents, such as Grignard reagents, lithium reagents, and enolates, is sometimes not suitable for the preparation of  $\alpha$ -trifluoromethylated alcohols, due to the difficulty of the elimination of the  $\alpha$ -trifluoromethylated alkoxide resulting in the generation of CF<sub>3</sub>CHO, although Kitazume et al. reported that  $\alpha$ -difluoromethylated alcohols can be synthesized by the direct use of difluoroacetaldehyde ethyl hemiacetal with Grignard reagents and lithium acetylide.<sup>4</sup>

There are scattered examples of the direct reaction of CF<sub>3</sub>CHO ethyl hemiacetal with some nucleophiles, such as nitroalkane,<sup>5</sup> anilines,<sup>6</sup> phenols,<sup>7</sup> hydrazones,<sup>8</sup> and so on.<sup>9</sup> Some of these methods suffer from a need of a strong base or acid, a high reaction temperature, low regioselectivities, low stereoselectivities, and low

versatility for introduction of the functional groups. Therefore, there is still a need for the development of effective, stereo- and/or regio-selective, and atom-economical methods for the direct use of CF<sub>3</sub>CHO hemiacetal in carbon–carbon bond-forming reactions.

Recently, we reported that an equimolar amount of enamine promoted the efficient in situ generation of CF<sub>3</sub>CHO under mild reaction conditions and the successive carbon–carbon bond-forming reaction with regenerated enamines without any additives, followed by hydrolysis with 10% HCl aqueous solution to give the corresponding  $\beta$ -hydroxy- $\beta$ -trifluoromethylated ketones in good to excellent yields.<sup>10</sup> However, before hydrolysis, the exact structures of the intermediate products, produced by reacting CF<sub>3</sub>CHO ethyl hemiacetal and enamine, have not yet been assigned. This information should be worthwhile to develop the organo-catalytic direct aldol reactions of CF<sub>3</sub>CHO ethyl hemiacetal with ketones.<sup>11</sup>

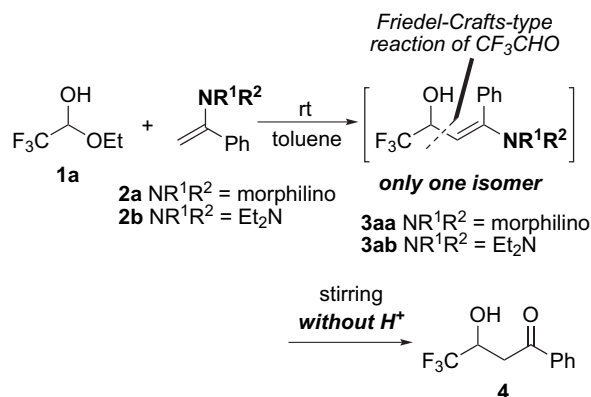
In this paper, we report the structure of the intermediate (*E*)-1,1,1-trifluoro-4-morpholino-4-aryl-but-3-en-2-ols based on NMR, IR, and X-ray data, which were obtained by reacting CF<sub>3</sub>CHO ethyl hemiacetal with enamine derived from acetophenone derivatives, as well as the reactivities, such as not only hydrolysis but successive hydrogenation and reductive deamination of the intermediate (*E*)-1,1,1-trifluoro-4-morpholino-4-aryl-but-3-en-2-ols, which represents a convenient method for the one-pot synthesis of 1,1,1-trifluoro-4-aryl-2-butanols.

\* Corresponding author. Tel.: +81 293 2599; fax: +81 293 2794; e-mail address: [funabiki@gifu-u.ac.jp](mailto:funabiki@gifu-u.ac.jp).

## 2. Results and discussion

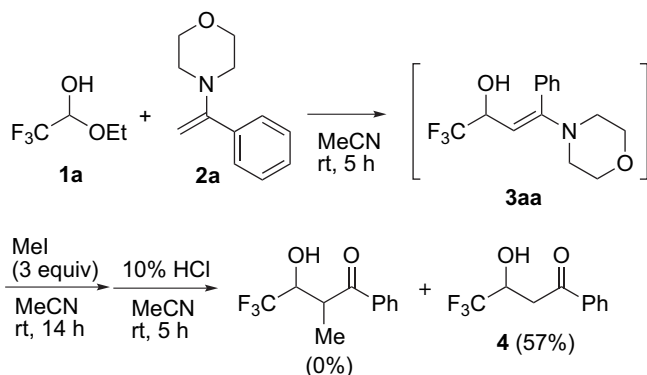
### 2.1. Assignment of the structure and reactivity of the intermediate product by reacting CF<sub>3</sub>CHO ethyl hemiacetal **1a** with enamine **2** derived from acetophenones

When CF<sub>3</sub>CHO ethyl hemiacetal **1a** was treated with an equimolar amount of enamine **2a** or **2b**, prepared from acetophenone and morpholine or diethylamine, in toluene at room temperature, 1,1,1-trifluoro-4-morpholino-4-phenyl-but-3-en-2-ol (**3aa**) or 1,1,1-trifluoro-4-diethylamino-4-phenyl-but-3-en-2-ol (**3ab**) was observed after 1 h. The products **3aa** and **3ab** could be produced by a Friedel–Crafts-type reaction of enamine, as in the reaction of the enol silyl ether or vinyl ether with CF<sub>3</sub>CHO.<sup>10,p</sup> Notably, the product **3aa** and **3ab** were each observed as only single isomer in the crude reaction mixture, by <sup>1</sup>H, <sup>13</sup>C, and <sup>19</sup>F NMR (Scheme 1), although the *E/Z* ratios of the product obtained by reacting enol silyl ether and enol methyl ether with CF<sub>3</sub>CHO ranged from 33/67 to 14/86. The reason for complete *E*-selectivity of is not clear at the present time.



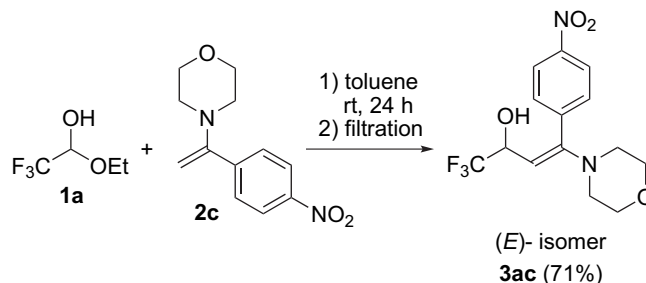
The reactivities of thus-obtained products **3aa** and **3ab** were examined by simple stirring without addition of any acids or bases. As a result, hydrolysis of the intermediate (*E*)-1,1,1-trifluoro-4-diethylamino-4-aryl-but-3-en-2-ols (**3ab**) occurred after 50 h to give the corresponding aldol product **4** in 75% yield, together with **3ab** in 9% yield, probably due to the high acidity of the hydroxyl group attached by the trifluoromethyl group. Compared with this result, the hydrolysis of 4-morpholino-substituted **3aa** is much slower than that of the diethylamino-substituted **3ab**, and gave **4** in 69% yield, together with the remaining **3aa**, even after 11 days. Thus, the morpholino-substituted product **3aa** is much more stable than the diethylamino-substituted **3ab** under this conditions.<sup>12</sup>

As another reaction of **3aa**, methylation using iodomethane (3 equiv) was carried out in acetonitrile as shown in Scheme 2.



However, methylation did not occur at all, followed by hydrolysis to give the corresponding aldol product **4** in 57% yield.

To confirm the exact structure of **3**, including the stereochemistry of the carbon–carbon double bond, the following reaction was carried out. Treatment of CF<sub>3</sub>CHO ethyl hemiacetal **1a** with enamine **2c** carrying a nitro group on the phenyl group in toluene at room temperature for 24 h gave (*E*)-1,1,1-trifluoro-4-morpholino-4-(4-nitrophenyl)but-3-en-2-ol (**3ac**) in 71% yield in the form of a solid as a single isomer, as shown in Scheme 3.



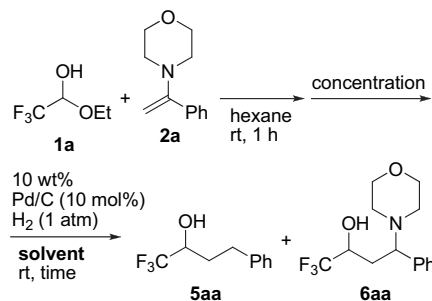
The structural assignment of the isolated **3ac** was based on the results of <sup>1</sup>H, <sup>13</sup>C, and <sup>19</sup>F NMR, IR, and X-ray crystallography,<sup>13</sup> where the morpholino and 1-hydroxy-2,2,2-trifluoroethyl groups are situated trans to each other.

### 2.2. Synthesis and hydrogenation of (*E*)-γ-aryl-γ-morpholino-α-trifluoromethylated allyl alcohols through the reaction of CF<sub>3</sub>CHO ethyl hemiacetal and enamine to give 4-aryl-1,1,1-trifluoro-2-butanols (**5**)

The oily intermediate (*E*)-1,1,1-trifluoro-4-morpholino-4-aryl-but-3-en-2-ols (**3**) could not be purified by flash chromatography on silica gel, because **3** was easily hydrolyzed during the chromatography to give the corresponding aldol products **4**. Therefore (*E*)-γ-aryl-γ-morpholino-α-trifluoromethylated allyl alcohols were used as crude products for next hydrogenation reaction.

The mixture of CF<sub>3</sub>CHO ethyl hemiacetal **1a** with enamine **2a** was stirred in hexane at room temperature, followed by concentration in vacuum, the addition of trifluoroethanol (TFE) as a solvent, and hydrogenation with hydrogen in the presence of a catalytic amount (10 mol %) of palladium on carbon (Merck Ltd., loading: 10 wt %) at room temperature for 1 h to give 1,1,1-trifluoro-4-phenylbutan-2-ol

**Table 1**  
Screening of the hydrogenation

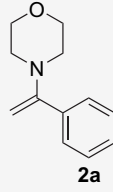
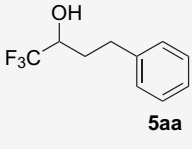
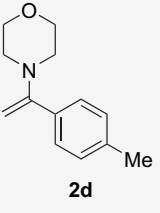
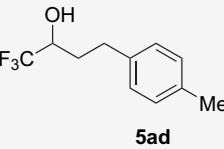
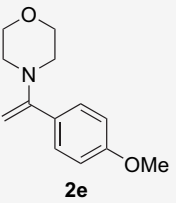
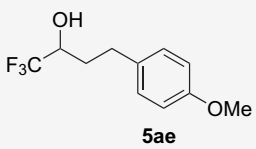
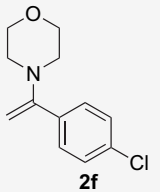
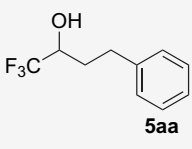
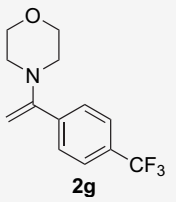
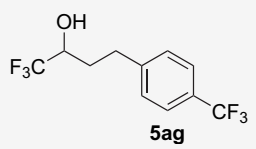
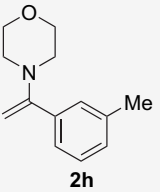
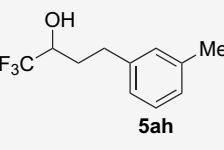


Entry	Solvent	Time (h)	5aa, yield <sup>a</sup> (%)	6aa, yield <sup>b</sup> (%), dr
1	TFE	1	62	23 (18:82)
2	TFE	18	84	—
3	THF	18	55	38 (16:84)
4	EtOH	18	65	23 (10:90)
5	Hexane	18	57	23 (12:88)

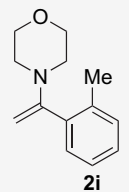
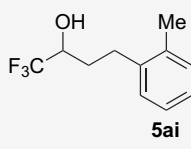
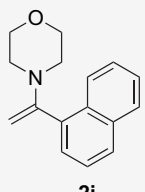
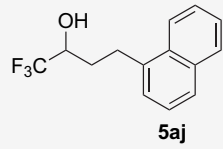
<sup>a</sup> All reaction was carried out with hemiacetal **1a** (1 mmol) and enamine **2a** (1 mmol).

<sup>b</sup> <sup>19</sup>F NMR yields.

**Table 2**  
Synthesis of 4-aryl-1,1,1-trifluoro-2-butanols **5**

$\text{F}_3\text{C}-\text{CH}(\text{OH})-\text{OEt} + \text{Enamine } \mathbf{2} \xrightarrow[\text{H}_2 (1 \text{ atm}), \text{ TFE}, \text{ rt}, 18 \text{ h}]{\begin{matrix} 1) \text{ hexane, rt, 1 h} \\ 2) \text{ concentration} \\ 3) 10 \text{ wt\% Pd/C (10 mol\%)} \end{matrix}} \text{F}_3\text{C}-\text{CH}(\text{OH})-\text{CH}_2-\text{CH}_2-\text{R}$			
Entry	Enamine <b>2</b>	Product <b>5</b>	Yield <sup>a</sup> (%)
1			84 (70)
2			76 (68)
3			90 (89)
4			86 (64)
5			94 (92)
6			79 (66)

**Table 2 (continued)**

Entry	Enamine <b>2</b>	Product <b>5</b>	Yield <sup>a</sup> (%)
7			87 (75)
8			65 (63)

<sup>a</sup> <sup>19</sup>F NMR yields. Values in parentheses stand for yields of isolated products.

(**5aa**) in 62% NMR yield and 1,1,1-trifluoro-4-morpholino-4-phenylbutan-2-ol (**6aa**) in 23% NMR yield (Table 1, entry 1).

An increase in the reaction time from 1 h to 18 h for hydrogenation resulted in an increased yield of trifluoromethylated alcohol **5aa** as well as the disappearance of amino alcohol **6aa**. Among the solvents examined, which included ethanol, tetrahydrofuran (THF), hexane, and TFE, the use of TFE gave the best yield of the product **5aa** (entry 2).<sup>14</sup> Ethanol, THF, and hexane were also used as a solvent, but were not as effective in the deamination of amino alcohol **6aa** (entries 3–5).

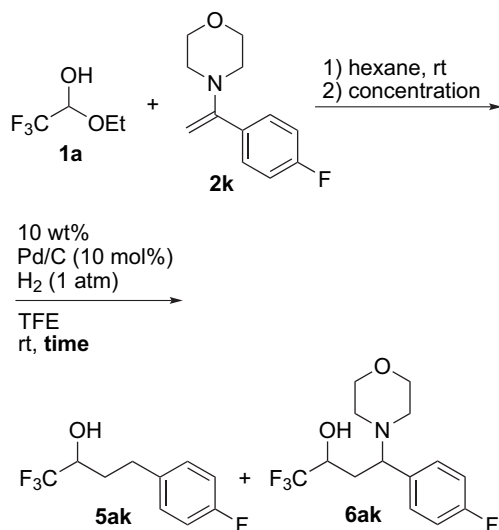
The results of hydrogenation leading to 4-aryl-1,1,1-trifluoro-2-butanols (**5**) are summarized in Table 2.

Other enamines **2d–j**, derived from 4', 3', and 2'-substituted acetophenones as well as 1-acetonaphthone, successfully participated in the one-pot three-components coupling reactions to give the corresponding 1,1,1-trifluoro-4-(4', 3', and 2'-substituted aryl)-2-butanols **5aa**, **5ad**, **5ae**, **5ag**, **5ah**, **5ai**, and **5aj** in good to excellent yields. The reaction of enamine **2f** carrying a 4-chlorophenyl group also proceeded smoothly to give not 4-chlorophenylated alcohol **5af** but rather phenylated alcohol **5aa** in 64% yield, which could be obtained by the reduction of the chlorine atom on the phenyl group (entry 4).

As shown in Scheme 4, in the case of enamine **2k**, reductive deamination was very sluggish under the same reaction conditions, due to the effect of the fluorine atom on the phenyl group.<sup>15</sup> A prolonged reaction time (five days) was required to obtain the product **5ak** in good yield.

When difluoroacetaldehyde ethyl hemiacetal **1b** was treated with enamine **2j** in hexane at room temperature and hydrogenated in the presence of a catalytic (10 mol%) amount of palladium on carbon at room temperature, 1,1-difluoro-4-(naphthalen-1-yl)butan-2-ol (**5bj**) was obtained in 53% yield, together with a compound, that is, dehydroxylated at the  $\alpha$ -carbon of the difluoromethyl group, 1-(4,4-difluorobutyl)naphthalene (**7**), and a defluorinated compound, 1-butylnaphthalene (**8**), in respective yields of 9% and 7% (Scheme 5). Comparable dehydroxylated and defluorinated compounds were not detected in the case of CF<sub>3</sub>CHO ethyl hemiacetal **1a**. The weaker bond energy of the carbon–fluorine bond of the difluoromethylated group as well as carbon–oxygen bond, compared with that of the trifluoromethyl group, may cause the dehydroxylation as well as defluorination of the product **5bj**.<sup>16</sup>

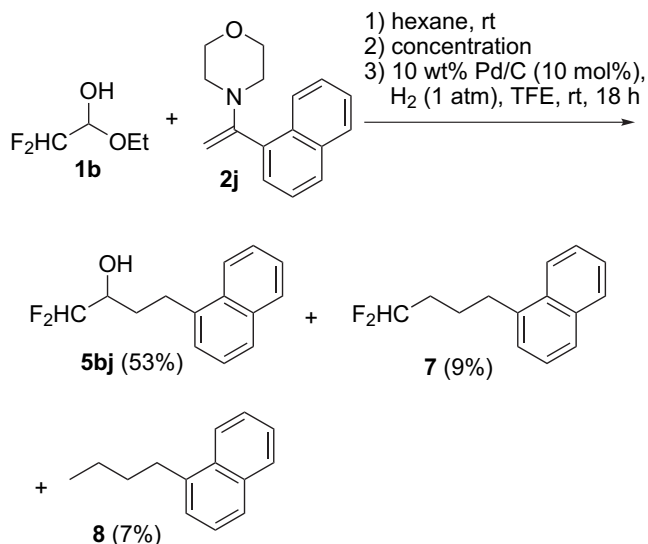
Hydrogenation of the product, which was obtained by the reaction of trifluoroacetaldehyde ethyl hemiacetal **1a** with enamine **2l** derived from cyclohexanone, was carried out under the same reaction conditions. Consequently, hydrogenation of the carbon–carbon double bond smoothly proceeded. But reductive deamination did not occur at all to give amino alcohol **6al** in 47% yield (Scheme 6).



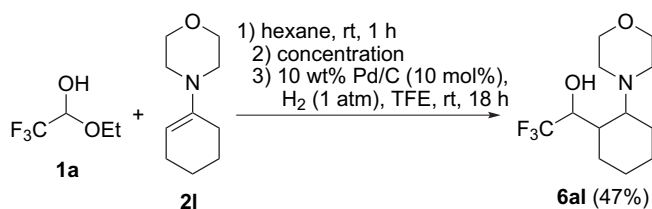
time	5ak, yield (%) <sup>a</sup>	6ak, yield (%) <sup>a</sup> , <i>dr</i> <sup>b</sup>
18 h	39 (23)	46 (39), 91 : 9
5 days	71 (50)	24 (15), 79 : 21

<sup>a</sup> Measured by <sup>19</sup>F NMR. Values in parentheses stand for the yields of isolated products.  
<sup>b</sup> Determined by <sup>19</sup>F NMR before isolation.

**Scheme 4.** Reaction of **1a** with enamine **2k** carrying a fluorine atom on the phenyl group.

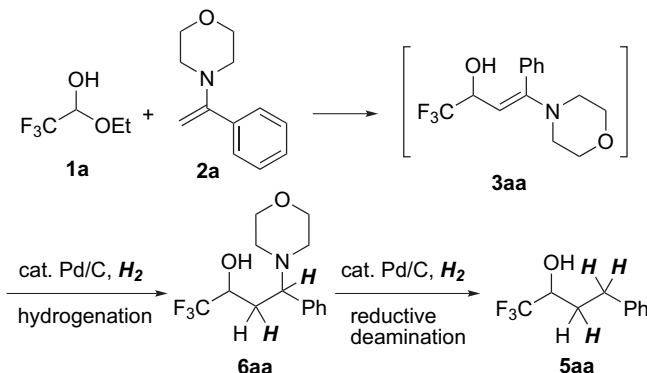


**Scheme 5.** Reaction of difluoroacetaldehyde ethyl hemiacetal **1b** with enamine **2j**.



**Scheme 6.** Reaction of **1a** with enamine **2l**.

Based on these findings, we can propose the following reaction mechanism. As shown in **Scheme 7**, the reaction of CF<sub>3</sub>CHO ethyl hemiacetal **1a** with enamine **2a** gives the oily intermediate, 1,1,1-trifluoro-4-morpholino-4-phenylbut-3-en-2-ol (**3aa**), as a single isomer. The intermediate **3aa** is hydrogenated with hydrogen in the presence of a catalytic amount (10 mol %) of palladium on carbon to give the amino alcohol **6aa**. The amino alcohol **6aa** undergoes palladium-catalyzed deamination at the benzyl position with hydrogen to produce 1,1,1-trifluoro-4-phenylbutan-2-ol (**5aa**). TFE was effective in the deamination process of **6**.



**Scheme 7.** Proposed reaction mechanism.

### 3. Conclusion

In conclusion, the structure of the intermediate (*E*)-1,1,1-trifluoro-4-morpholino-4-(4-nitrophenyl)but-3-en-2-ol (**3ac**), obtained by reacting CF<sub>3</sub>CHO ethyl hemiacetal **1a** with enamine **2** derived from acetophenones, could be assigned based on the results of an X-ray analysis. Furthermore, we have developed a new method for the synthesis of 4-aryl-1,1,1-trifluoro-2-butanols based on the tandem effective in situ generation of CF<sub>3</sub>CHO and successive carbon–carbon bond-formation reactions with enamines, followed by hydrogenation and deamination with hydrogen in the presence of a catalytic amount (10 mol %) of palladium on carbon at room temperature. The use of a fluorine atom or a trifluoromethyl group gave interesting results: (1) In the step of deamination, trifluoroethanol (TFE) was more effective than other usual organic solvents. (2) A fluorine atom on the phenyl group apparently disturbed the deamination process at the benzyl positions of the intermediates. The diastereoselective and enantioselective synthesis of  $\alpha$ -trifluoromethylated alcohol based on this hydrogenation reaction is currently being investigated in our laboratory.

### 4. Experimental section

#### 4.1. General

Melting points were obtained on a Yanagimoto MP-S2 micro melting point apparatus and are uncorrected. IR spectra were recorded on a SHIMADZU FT-IR 8100A spectrometer. <sup>1</sup>H (400 MHz) or <sup>13</sup>C (100 MHz) NMR spectra were measured with a JEOL  $\alpha$ -400 FT NMR spectrometer in deuteriochloroform (CDCl<sub>3</sub>) solutions with tetramethylsilane (Me<sub>4</sub>Si) as an internal standard. <sup>19</sup>F NMR (376 MHz) spectra were recorded on a JEOL  $\alpha$ -400 FT NMR in CDCl<sub>3</sub> solutions using trichlorofluoromethane (CFCl<sub>3</sub>) as an external standard. HRMS were measured on a JEOL JMS-700 mass spectrometer. Pure products were isolated by column chromatography using Silica Gel 60 (spherical, 270–325 mesh, KANTO CHEMICAL CO., INC.) or Wakogel C200 (100–200 mesh, Wako Pure Chemical Ind., Ltd.). Analytical TLC was performed on Merck precoated (0.25 mm) silica gel 60 F<sub>254</sub> plates. All chemicals were of reagent



grade and, if necessary, purified in the usual manner prior to use. Palladium on carbon was purchased from Merck Ltd. (loading: 10 wt %). Anhydrous tetrahydrofuran (THF), dichloromethane, and diethyl ether were purchased from Kanto Chemical Co.

## 4.2. Preparation of (E)-1,1,1-trifluoro-4-morpholino-4-(4-nitrophenyl)but-3-en-2-ol (**9j**)

To a toluene (2 ml) solution of enamine **2c** (0.234 g, 1 mmol) was slowly added CF<sub>3</sub>CHO ethyl hemiacetal **1a** (0.144 g, 1 mmol) at room temperature. After the mixture was stirred for one day, the precipitate was filtered, and washed with toluene (1 ml) to give (E)-1,1,1-trifluoro-4-morpholino-4-(4-nitrophenyl)but-3-en-2-ol (**3ac**) in 71% yield.

**4.2.1. (E)-1,1,1-trifluoro-4-morpholino-4-(4-nitrophenyl)but-3-en-2-ol (**3ac**).** Mp 155–156 °C; IR (KBr) 3391 (OH), 1628 (C=C), 1524, and 1350 (NO<sub>2</sub>), cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.31 (1H, s), 2.83–2.85 (4H, m), 3.71–3.73 (4H, m), 4.02–4.11 (1H, m), 4.83 (1H, d, J=9.9 Hz), 7.61, and 8.32 (4H, AB quartet, J=8.7 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 48.9 (s), 66.5 (s), 68.8 (q, J=32.8 Hz), 97.1 (s), 123.3 (s), 124.7 (q, J=281.8 Hz), 130.5 (s), 142.1 (s), 148.2 (s), 155.1 (s); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -78.4 (3F, d, J=6.1 Hz); HRMS (EI) found: *m/z* 332.0989, calcd for C<sub>14</sub>H<sub>15</sub>F<sub>3</sub>O<sub>4</sub>N<sub>2</sub>, 332.0985.

## 4.3. A typical procedure

To a solution of 4-(1-phenylvinyl)morpholine (**2a**) (0.189 g, 1 mmol) in hexane (2 ml) was added CF<sub>3</sub>CHO ethyl hemiacetal **1a** (0.144 g, 1 mmol) at room temperature under argon. After stirring at room temperature for 1 h, the reaction mixture was concentrated by distillation under reduced pressure. To a resultant reaction mixture was added of a catalytic amount (10 mol %, 0.106 g) of palladium on carbon (Merck, loading: 10 wt %) and trifluoroethanol (10 ml). After replacement of air with hydrogen, the mixture was vigorously stirred at room temperature under ordinary hydrogen pressure (balloon) for 18 h. The reaction mixture was filtered using Celite® 545RVS and the filtrate was concentrated under pressure to provide 1,1,1-trifluoro-4-phenylbutan-2-ol (**5aa**). After the measurement of the residue by <sup>19</sup>F NMR using benzotrifluoride (**5aa**:84%), purification by flash chromatography on silica gel (hexane–EtOAc=10:1) gave 1,1,1-trifluoro-4-phenylbutan-2-ol (**5aa**) (70%, 0.143 g).

**4.3.1. 1,1,1-Trifluoro-4-phenylbutan-2-ol (**5aa**)**<sup>17</sup>. *R<sub>f</sub>* 0.20 (hexane–EtOAc=10:1); IR (NaCl) 3399 (OH) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.80–1.99 (2H, m), 2.42 (1H, s), 2.65 (1H, dt, J=13.9, 8.2 Hz), 2.83 (1H, ddd, J=13.9, 8.7, 5.3 Hz), 3.79 (1H, ddq, J=9.9, 6.5, 3.2 Hz), 7.11–7.24 (5H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 30.7 (s), 30.9 (s), 69.5 (q, J=31.1 Hz), 125.2 (q, J=281.8 Hz), 126.3 (s), 128.4 (s), 128.6 (s), 140.4 (s); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -79.8 (3F, d, J=6.9 Hz); HRMS (EI) found: *m/z* 204.0755, calcd for C<sub>10</sub>H<sub>11</sub>F<sub>3</sub>O, 204.0762.

**4.3.2. 1,1,1-Trifluoro-4-morpholino-4-phenylbutan-2-ol (**6aa**).** *R<sub>f</sub>* 0.20 (hexane–EtOAc=10:1); IR (NaCl) 3375 (OH) cm<sup>-1</sup>; HRMS (EI) found: *m/z* 289.1293, calcd for C<sub>14</sub>H<sub>18</sub>F<sub>3</sub>O<sub>2</sub>N: M–H, 289.1290; major isomer <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.82 (1H, ddd, J=14.3, 2.7, 2.7 Hz), 2.34 (2H, s), 2.48 (1H, ddd, J=14.3, 11.8, 11.1 Hz), 2.67–2.72 (2H, m), 3.68 (4H, m), 3.89 (1H, dd, J=11.8, 2.7 Hz), 4.24–4.33 (1H, m), 7.14–7.41 (6H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 27.6 (s), 66.9 (s), 68.5 (s), 71.5 (q, J=31.1 Hz), 124.5 (q, J=280.2 Hz), 128.3 (s), 128.6 (s), 134.3 (s); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -80.8 (3F, d, J=6.9 Hz); minor isomer <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.99 (1H, ddd, J=5.4, 4.6, 3.1 Hz), 2.39 (2H, s), 2.50 (1H, ddd, J=15.3, 11.2, 4.6 Hz), 2.62–2.67 (2H, m), 3.68–3.74 (4H, m), 4.08 (1H, dd, J=11.2, 3.1 Hz), 4.23–4.32 (1H, m), 7.18–7.20 (2H, m), 7.32–7.40 (4H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 27.5 (s), 49.6 (s), 66.2 (s), 66.9 (s), 69.5 (q, J=30.3 Hz), 125.7 (q, J=282.6 Hz), 128.3

(s), 128.4 (s), 128.5 (s), 134.9 (s); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -77.6 (3F, d, J=7.6 Hz).

**4.3.3. 1,1,1-Trifluoro-4-*p*-tolylbutan-2-ol (**5ad**).** *R<sub>f</sub>* 0.23 (hexane–EtOAc=6:1); IR (NaCl) 3435 (OH) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.96–2.14 (2H, m), 2.43 (3H, s), 2.79 (1H, dt, J=13.9, 8.2 Hz), 2.97 (1H, ddd, J=13.9, 8.7, 5.3 Hz), 3.96 (1H, ddq, J=16.4, 6.5, 3.2 Hz), 7.19–7.24 (4H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 20.9 (s), 30.3 (s), 31.0 (s), 69.5 (q, J=31.1 Hz), 125.2 (q, J=281.8 Hz), 128.3 (s), 129.3 (s), 135.8 (s), 137.2 (s); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -79.9 (3F, d, J=6.5 Hz); HRMS (EI) found: *m/z* 218.0916, calcd for C<sub>11</sub>H<sub>13</sub>F<sub>3</sub>O: M–H, 218.0919.

**4.3.4. 1,1,1-Trifluoro-4-(4-methoxyphenyl)butan-2-ol (**5ae**).** *R<sub>f</sub>* 0.17 (hexane–EtOAc=6:1); IR (NaCl) 3436 (OH) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.83–2.04 (2H, m), 2.66 (1H, ddd, J=14.0, 8.3, 8.2 Hz), 2.84 (1H, ddd, J=14.0, 8.8, 8.7 Hz), 3.78 (3H, s), 3.85 (1H, ddq, J=16.4, 6.5, 3.3 Hz), 6.82–7.13 (4H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 29.8 (s), 31.1 (s), 55.2 (s), 69.4 (q, J=31.1 Hz), 114.0 (s), 125.0 (q, J=281.8 Hz), 129.4 (s), 132.5 (s), 158.0 (s); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -79.7 (3F, d, J=6.5 Hz); HRMS (EI) found: *m/z* 234.0873, calcd for C<sub>11</sub>H<sub>13</sub>F<sub>3</sub>O<sub>2</sub>: M–H, 234.0868.

**4.3.5. 1,1,1-Trifluoro-4-(4-(trifluoromethyl)phenyl)butan-2-ol (**5ag**).** *R<sub>f</sub>* 0.18 (hexane–EtOAc=6:1); IR (NaCl) 3390 (OH) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.91–2.07 (2H, m), 2.26 (1H, dd, J=5.8, 5.8 Hz), 2.81 (1H, ddd, J=13.9, 8.3, 8.2 Hz), 2.98 (1H, ddd, J=13.9, 8.8, 5.3 Hz), 3.89 (1H, ddq, J=16.0, 6.5, 3.3 Hz), 7.33, and 7.57 (4H, AB quartet, J=8.1 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 30.6 (s), 69.4 (q, J=31.1 Hz), 124.9 (q, J=281.8 Hz), 125.5 (s), 125.6 (s), 128.8 (q, J=32.8 Hz), 144.5 (s); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -62.3 (3F, s), -79.8 (3F, d, J=6.5 Hz); HRMS (EI) found: *m/z* 272.0647, calcd for C<sub>11</sub>H<sub>10</sub>F<sub>6</sub>O: M–H, 272.0636.

**4.3.6. 1,1,1-Trifluoro-4-*m*-tolylbutan-2-ol (**5ah**).** *R<sub>f</sub>* 0.20 (hexane–EtOAc=6:1); IR (NaCl) 3408 (OH) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.97–2.10 (2H, m), 2.38 (3H, s), 2.61 (1H, s), 2.73 (1H, ddd, J=13.9, 8.5, 8.3 Hz), 2.92 (1H, ddd, J=13.9, 8.8, 5.3 Hz), 3.91 (1H, ddq, J=9.9, 6.5, 3.3 Hz), 7.04–7.26 (4H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 21.2 (s), 30.7 (s), 30.9 (s), 69.5 (q, J=31.1 Hz), 125.2 (q, J=281.8 Hz), 125.4 (s), 127.1 (s), 128.5 (s), 129.2 (s), 138.2 (s), 140.3 (s); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -79.9 (3F, d, J=6.5 Hz); HRMS (EI) found: *m/z* 218.0911, calcd for C<sub>11</sub>H<sub>13</sub>F<sub>3</sub>O: M–H, 218.0919.

**4.3.7. 1,1,1-Trifluoro-4-*o*-tolylbutan-2-ol (**5ai**).** *R<sub>f</sub>* 0.28 (hexane–EtOAc=8:1); IR (NaCl) 3389 (OH) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.91–2.11 (2H, m), 2.42 (3H, s), 2.73 (1H, s), 2.81 (1H, ddd, J=14.0, 9.4, 7.5 Hz), 3.00 (1H, ddd, J=14.2, 9.4, 5.0 Hz), 4.00, (1H, m), 7.11–7.24 (4H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 19.1 (s), 28.2 (s), 29.7 (s), 69.9 (q, J=31.1 Hz), 125.2 (q, J=281.8 Hz), 126.1 (s), 126.5 (s), 128.8 (s), 130.4 (s), 136.0 (s), 138.6 (s); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -79.8 (3F, d, J=6.9 Hz); HRMS (EI) found: *m/z* 218.0924, calcd for C<sub>11</sub>H<sub>13</sub>F<sub>3</sub>O: M–H, 218.0919.

**4.3.8. 1,1,1-Trifluoro-4-(naphthalen-1-yl)butan-2-ol (**5aj**).** *R<sub>f</sub>* 0.15 (hexane–CH<sub>2</sub>Cl<sub>2</sub>=7:1); IR (NaCl) 3419 (OH) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.89–2.08 (2H, m), 2.45 (1H, s), 3.04 (1H, ddd, J=14.1, 8.3, 8.2 Hz), 3.28 (1H, ddd, J=14.1, 9.2, 5.1 Hz), 3.83 (1H, ddq, J=20.0, 6.8, 3.3 Hz), 7.23–7.93 (7H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 27.9 (s), 30.3 (s), 69.8 (q, J=31.1 Hz), 125.2 (q, J=281.8 Hz), 123.4 (s), 125.5 (s), 125.6 (s), 126.2 (s), 127.2 (s), 128.9 (s), 131.7 (s), 133.9 (s), 136.5 (s); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -79.6 (3F, d, J=6.8 Hz); HRMS (EI) found: *m/z* 254.0926, calcd for C<sub>14</sub>H<sub>13</sub>F<sub>3</sub>O: M–H, 254.0919.

**4.3.9. 1,1,1-Trifluoro-4-(4-fluorophenyl)butan-2-ol (**5ak**).** *R<sub>f</sub>* 0.23 (hexane–EtOAc=8:1); IR (NaCl) 3389 (OH) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.92–2.09 (2H, m), 2.77 (1H, ddd, J=14.0, 8.3, 8.2 Hz), 2.86

(1H, s), 2.95 (1H, ddd,  $J=14.0, 8.3, 5.1$  Hz), 3.93 (1H, m), 7.01–7.24 (4H, m);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  30.0 (s), 31.0 (s), 69.4 (q,  $J=31.1$  Hz), 115.2 (s), 115.4 (s), 125.1 (q,  $J=281.8$  Hz), 129.8 (s), 129.9 (s), 136.0 (s), 161.5 (d,  $J=244.1$  Hz);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  –117.0 (1F, ddt,  $J=8.4, 5.3, 5.3$  Hz), –79.9 (3F, d,  $J=6.1$  Hz); HRMS (EI) found:  $m/z$  222.0671, calcd for  $\text{C}_{10}\text{H}_{10}\text{F}_4\text{O}$ : M–H, 222.0668.

**4.3.10. 1,1,1-Trifluoro-4-(4-fluorophenyl)-4-morpholinobutan-2-ol (6ak).**  $R_f$  0.04 (hexane–EtOAc=8:1); IR (NaCl) 3375 (OH)  $\text{cm}^{-1}$ ; HRMS (EI) found:  $m/z$  307.1203, calcd for  $\text{C}_{14}\text{H}_{17}\text{F}_4\text{O}_2\text{N}$ : M–H, 307.1196; major isomer  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.84 (1H, ddd,  $J=15.2, 5.2, 3.1$  Hz), 2.16–2.31 (2H, m), 2.34–2.43 (1H, m), 2.49–2.59 (2H, m), 3.56–3.65 (4H, m), 3.98 (1H, dd,  $J=11.3, 3.1$  Hz), 4.13–4.23 (1H, m), 6.97–7.11 (4H, m);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  27.9 (s), 49.3 (s), 65.1 (s), 66.9 (s), 69.1 (q,  $J=31.1$  Hz), 115.1 (s), 125.7 (q,  $J=283.5$  Hz), 130.1 (s), 130.2 (s), 130.8 (s), 162.4 (d,  $J=47.4$  Hz);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  –113.7–(–113.6) (1F, m), –77.7 (3F, d,  $J=7.6$  Hz); minor isomer  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.72 (1H, ddd,  $J=14.4, 2.8, 2.7$  Hz), 2.16–2.31 (2H, m), 2.34–2.43 (1H, m), 2.49–2.59 (2H, m), 3.56–3.65 (4H, m), 3.80 (1H, dd,  $J=11.3, 3.1$  Hz), 4.23–4.33 (1H, m), 6.97–7.11 (4H, m);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  27.9 (s), 49.3 (s), 66.8 (s), 67.6 (s), 71.2 (q,  $J=31.1$  Hz), 115.3 (s), 124.5 (q,  $J=280.2$  Hz), 130.0 (s), 130.1 (s), 130.4 (s), 162.5 (d,  $J=47.4$  Hz);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  –113.4–(–113.3) (1F, m), –80.7 (3F, d,  $J=6.9$  Hz).

**4.3.11. 1,1-Difluoro-4-(naphthalen-1-yl)butan-2-ol (5bj).**  $R_f$  0.18 (hexane– $\text{CH}_2\text{Cl}_2=7:1$ ); mp 56–58 °C; IR (KBr) 3371 (OH)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 1.84–2.03 (2H, m), 2.72 (1H, s), 3.08 (1H, ddd,  $J=14.0, 9.2, 7.3$  Hz), 3.32 (1H, ddd,  $J=14.0, 9.4, 5.1$  Hz), 3.68–3.77 (1H, m), 5.54 (1H, dt,  $J=56.0, 4.1$  Hz), 7.29–8.04 (7H, m);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) 27.9 (s), 30.8 (s), 60.4 (t,  $J=22.9$  Hz), 116.3 (t,  $J=244.1$  Hz), 123.5 (s), 125.5 (s), 126.0 (s), 126.1 (s), 126.9 (s), 128.8 (s), 131.6 (s), 133.9 (s), 137.0 (s);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ) –129.3 (1F, dd,  $J=56.0, 9.9$  Hz), –129.3 (1F, dd,  $J=56.0, 12.2$  Hz); HRMS (EI) found:  $m/z$  236.1008, calcd for  $\text{C}_{14}\text{H}_{14}\text{F}_2\text{O}$ : M–H, 236.1013.

**4.3.12. 1-(4,4-Difluorobutyl)naphthalene (7).**  $R_f$  0.68 (hexane– $\text{CH}_2\text{Cl}_2=7:1$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.90–1.97 (4H, m), 3.13 (2H, t,  $J=7.2$  Hz), 5.82 (1H, tt,  $J=57.0, 4.1$  Hz), 7.24–8.01 (7H, m);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  23.0 (s), 32.2 (s), 33.9 (t,  $J=20.5$  Hz), 117.2 (t,  $J=239.2$  Hz), 123.5 (s), 125.5 (s), 125.5 (s), 125.9 (s), 126.1 (s), 127.0 (s), 128.8 (s), 131.7 (s), 133.9 (s), 137.3 (s);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  –116.0–(–115.7) (2F, m); HRMS (EI) found:  $m/z$  220.1060, calcd for  $\text{C}_{14}\text{H}_{14}\text{F}_2$ : M–H, 220.1064.

**4.3.13. 1-Butylnaphthalene (8)<sup>18</sup>.**  $R_f$  0.83 (hexane– $\text{CH}_2\text{Cl}_2=7:1$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.97 (3H, dd,  $J=7.5, 7.4$  Hz), 1.41–1.51 (2H, m), 1.70–1.78 (2H, m), 3.07 (2H, dd,  $J=7.7, 7.7$  Hz), 7.31–8.06 (7H, m);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  14.0 (s), 22.9 (s), 32.8 (s), 33.0 (s), 123.9 (s), 125.3 (s), 125.5 (s), 125.6 (s), 125.8 (s), 126.4 (s), 128.7 (s), 131.9 (s), 133.9 (s), 139.0 (s); HRMS (EI) found:  $m/z$  184.1257, calcd for  $\text{C}_{14}\text{H}_{16}$ , 184.1253.

**4.3.14. 2,2,2-Trifluoro-1-(2-morpholinocyclohexyl)ethanol (6al).**  $R_f$  0.18 (hexane–EtOAc=4:1); IR (KBr) 3441 (OH)  $\text{cm}^{-1}$ ; LRMS (EI) found:  $m/z$  267.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.81–1.62 (8H, m), 1.79–1.87 (2H, m), 2.16 (1H, br), 2.39–2.42 (2H, m), 2.80 (1H, br), 3.58–3.81 (4H, m), 4.26 (1H, qd,  $J=8.94, 7.00$  Hz), 8.97 (1H, br);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  20.1 (s), 24.0 (s), 25.2 (s), 27.3 (s), 31.2 (s), 49.2 (s), 51.7 (s), 66.7 (s), 67.2 (2C, s), 70.4 (q,  $J=28.7$  Hz), 125.9 (q,  $J=283.5$  Hz);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  –2.71 (3F, d,  $J=7.00$  Hz).

## Acknowledgements

We are grateful to Central Glass Co., Ltd., for the gift of  $\text{CF}_3\text{CHO}$  ethyl hemiacetal and trifluoroethanol as well as for financial

support. We thank Professors T.I. and T. Konno of the Kyoto Institute of Technology for the HRMS measurements.

## Supplementary data

Supplementary data associated with this articles can be found in the online version, at doi:10.1016/j.tet.2010.03.019.

## References and notes

- For the reaction with boron enolates, see: (a) Iseki, K.; Oishi, S.; Kobayashi, Y. *Chem. Pharm. Bull.* **1996**, *44*, 2003–2008; (b) Iseki, K.; Oishi, S.; Kobayashi, Y. *Tetrahedron* **1996**, *52*, 71–84; (c) Makino, Y.; Iseki, K.; Oishi, S.; Fujiki, K.; Hirano, T.; Kobayashi, Y. *Tetrahedron Lett.* **1995**, *36*, 6527–6530; For with a lithium enolate, see: (d) Qian, C.-P.; Liu, Y.-Z.; Tomooka, K.; Nakai, T. *Org. Synth.* **1999**, *76*, 151–158; (e) Qian, C. P.; Nakai, T.; Dixon, D. A.; Smart, B. E. *J. Am. Chem. Soc.* **1990**, *112*, 4602–4604; (f) Patel, D. V.; Rielley-Gauvin, K.; Ryono, D. E.; Free, C. A.; Smith, S. A.; Petrillo, E. W. *J. Med. Chem.* **1993**, *36*, 2431–2447; (g) Patel, D. V.; Rielley-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* **1988**, *29*, 4665–4668; (h) Seebach, D.; Juaristi, E.; Miller, D. D.; Schickli, C.; Weber, T. *Helv. Chem. Acta* **1987**, *70*, 237–261; (i) Yamazaki, T.; Takita, K.; Ishikawa, N. *Nippon Kagaku Kaishi* **1985**, 2131–2139; (j) Tius, M. A.; Savariar, S. *Tetrahedron Lett.* **1985**, *26*, 3635–3638; For with a zinc enolate, see: (k) Watanabe, S.; Sakai, Y.; Kitazume, T.; Yamazaki, T. *J. Fluorine Chem.* **1994**, *68*, 59–61; (l) Kitazume, T. *Ultrasonics* **1990**, *28*, 322–325; For with a nickel enolate, see: (m) Soloshonok, V. A.; Kukhar, V. P.; Galushko, S. V.; Svistunova, N. Y.; Avilov, D. V.; Kuz'mina, N. A.; Raevski, N. I.; Struchkov, Y. T.; Pysarevsky, A. P.; Belokon, Y. N. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3143–3155; For with ketene silyl acetal, see: (n) Mikami, K.; Yajima, T.; Takasaki, T.; Matsukawa, S.; Terada, M.; Uchimarui, T.; Maruta, M. *Tetrahedron* **1996**, *52*, 85–98; For with enol silyl ether, see: (o) Ishii, A.; Kojima, J.; Mikami, K. *Org. Lett.* **1999**, *1*, 2013–2016; For with vinyl ether, see: (p) For titanium enolate, see Ishii, A.; Mikami, K. *J. Fluorine Chem.* **1999**, *97*, 51–55; (q) Itoh, Y.; Yamanaka, M.; Mikami, K. *Org. Lett.* **2003**, *5*, 4807–4809; For with enamines, see: (r) Molines, H.; Wakselman, C. *J. Fluorine Chem.* **1980**, *16*, 97–101.
- For with sodium cyanide, see: (a) Kitazume, T. *J. Fluorine Chem.* **1987**, *35*, 287–294 For with active methylene-compounds, see: (b) Hager, C.; Miethchen, R.; Reinke, H. *J. Fluorine Chem.* **2000**, *104*, 135–142; (c) Uneyama, K.; Itano, N. *Denki Kagaku* **1994**, *62*, 1151–1153; (d) Cen, W.; Dai, X.; Shen, Y. *J. Fluorine Chem.* **1993**, *65*, 49–52; (e) Ogoshi, H.; Mizushima, H.; Toi, H.; Aoyama, Y. *J. Org. Chem.* **1986**, *51*, 2366–2368; For with lithium or zinc reagents, see: (f) Steves, A.; Oestreich, M. *Org. Biomol. Chem.* **2009**, *7*, 4464–4469; (g) Tomoyasu, T.; Tomooka, K.; Nakai, T. *Synlett* **1998**, 1147–1149; (h) Obrecht, D.; Gerber, F.; Sprenger, D.; Masqelin, T. *F. Helv. Chim. Acta* **1997**, *80*, 531–537; (i) Kitazume, T.; Lin, J. T.; Yamazaki, T. *J. Fluorine Chem.* **1989**, *43*, 177–187; (j) Hanzawa, Y.; Ishizawa, S.; Kobayashi, Y. *Chem. Pharm. Bull.* **1988**, *36*, 4209–4212; (k) Ishikawa, N.; Koh, M. G.; Kitazume, T. *J. Fluorine Chem.* **1984**, *24*, 419–430; For with vinyl aluminum reagents, see: (l) Ramachandran, P. V.; Reddy, M. V. R.; Rudd, M. T.; De Alaniz, J. R. *Tetrahedron Lett.* **1998**, *39*, 8791–8794; (m) For boron reagents, see Ramachandran, P. V.; Reddy, M. V. R.; Rudd, M. T. *Chem. Commun.* **1999**, 1979–1980; (n) Ramachandran, P. V.; Chatterjee, A. *Org. Lett.* **2008**, *10*, 1195–1198; (o) Ramachandran, P. V.; Padiya, K. J.; Rauniyar, V.; Reddy, M. V. R.; Brown, H. C. *Tetrahedron Lett.* **2004**, *45*, 1015–1017; (p) Ramachandran, P. V.; Padiya, K. J.; Reddy, M. V. R.; Brown, H. C. *J. Fluorine Chem.* **2004**, *125*, 579–583 For Morita–Baylis–Hillman Reaction, see: (q) Reddy, M. V. R.; Rudd, M. T.; Ramachandran, P. V. *J. Org. Chem.* **2002**, *67*, 5382–5385; For Friedel–Crafts reaction, see: (r) Shermolovich, Y. G.; Yemets, S. V. *J. Fluorine Chem.* **2000**, *101*, 111–116; For asymmetric Friedel–Crafts reaction, see: (s) Ishii, A.; Soloshonok, A. V.; Mikami, K. *J. Org. Chem.* **2000**, *65*, 1597–1599 For ene reaction, see: (t) Hayashi, E.; Takahashi, Y.; Itoh, H.; Yoneda, N. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 3040–3043; (u) Ogawa, K.; Nagai, T.; Nonomura, M.; Takagi, T.; Koyama, M.; Ando, A.; Miki, T.; Kumadaki, I. *Chem. Pharm. Bull.* **1991**, *39*, 1707–1712; (v) Pautrat, R.; Marteau, J.; Cheritat, R. *Bull. Soc. Chim. Fr.* **1968**, 1182–1186; For asymmetric ene reaction for with alkenes see: Ref. 1n and with vinyl sulfides see: (w) Mikami, K.; Yajima, T.; Siree, N.; Terada, M.; Suzuki, Y.; Kobayashi, I. *Synlett* **1996**, 837–838; For Hetero Diels–Alder reaction, see: (x) Leveque, L.; Le Blanc, M.; Pastor, R. *Tetrahedron Lett.* **1997**, *38*, 6001–6002; (y) Jeong, I. H.; Kim, Y. S.; Cho, K. Y.; Kim, K. J. *Bull. Korean Chem. Soc.* **1991**, *12*, 125–126; For Asymmetric Hetero Diels–Alder reaction, see: (z) Mikami, K.; Yajima, T.; Matsukawa, S.; Terada, M. 72nd National Meeting of the Chemical Society of Japan, Tokyo, March, 1997; Abstr. No. 4H332.
- (a) Landge, S. M.; Borkin, D. A.; Török, B. *Tetrahedron Lett.* **2007**, *48*, 6372–6376; (b) Mimura, H.; Watanabe, A.; Kawade, K. *J. Fluorine Chem.* **2006**, *127*, 519–523; (c) Ishii, A.; Terada, Y. *J. Synth. Org. Chem. Jpn.* **1999**, *57*, 898–900; (d) Braid, M.; Iserson, H.; Lawlor, F. E. *J. Am. Chem. Soc.* **1954**, *76*, 4027; (e) Henne, A. L.; Pelley, R. L.; Alm, R. M. *J. Am. Chem. Soc.* **1950**, *72*, 3370; (f) Shechter, H.; Conrad, F. *J. Am. Chem. Soc.* **1950**, *72*, 3371–3373.
- Kaneko, S.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **1993**, *58*, 2302–2312.
- For selected examples, see: (a) Guenter, S. *Chem. Ber.* **1973**, *106*, 2960–2968; (b) Ogoshi, H.; Mizushima, H.; Toi, H.; Aoyama, Y. *J. Org. Chem.* **1986**, *51*, 2366–2368; (c) Iwata, S.; Ishiguro, Y.; Utsugi, M.; Mitsuhashi, K.; Tanaka, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2432–2435; (d) Molteni, M.; Consonni, R.; Giovenzana, T.; Malpezzi, L.; Zanda, M. *J. Fluorine Chem.* **2006**, *127*, 901–908.
- Gong, Y.; Kato, K.; Kimoto, H. *Synlett* **1999**, 1403–1404.

7. Gong, Y.; Kato, K.; Kimoto, H. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 377–383 and Ref. 5.
8. Fernández, R.; Martín-Zamora, E.; Pareja, C.; Alcarazo, M.; Martín, J.; Lassaletta, J. M. *Synlett* **2001**, 1158–1160.
9. (a) Petrov, V. A.; Davidson, F.; Smart, B. E. *J. Fluorine Chem.* **2004**, *125*, 1543–1552; (b) Gong, Y.; Kato, K.; Kimoto, H. *J. Heterocycl. Chem.* **2001**, *38*, 25–27; (c) Shirai, K.; Onomura, O.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **2000**, *41*, 5873–5876; (d) Kuwano, R.; Miyazaki, H.; Ito, Y. *J. Organomet. Chem.* **2000**, *603*, 18–29; (e) Gong, Y.; Kato, K.; Kimoto, H. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 249–250; (f) Loh, T.-P.; Li, X.-R. *Tetrahedron* **1999**, *55*, 5611–5622; (g) Sakumo, K.; Kuki, N.; Kuno, T.; Takagi, T.; Koyama, M.; Ando, A.; Kumadaki, I. *J. Fluorine Chem.* **1999**, *93*, 165–170; (h) Loh, T.-P.; Xu, K.-C.; Ho, D. S.-C.; Sim, K.-Y. *Synlett* **1998**, 369–370; (i) Omote, M.; Ando, A.; Takagi, T.; Koyama, M.; Kumadaki, I. *Tetrahedron* **1996**, *52*, 13961–13970; (j) Ishihara, T.; Hayashi, H.; Yamanaka, H. *Tetrahedron Lett.* **1993**, *34*, 5777–5780; (k) Kubota, T.; Iijima, M.; Tanaka, T. *Tetrahedron Lett.* **1992**, *33*, 1351–1354; (l) Guy, A.; Lobgeois, A.; Lemaire, M. *J. Fluorine Chem.* **1986**, *32*, 361–366.
10. (a) Funabiki, K.; Nojiri, M.; Matsui, M.; Shibata, K. *Chem. Commun.* **1998**, 2051–2052; (b) Funabiki, K.; Matsunaga, K.; Nojiri, M.; Hashimoto, W.; Yamamoto, H.; Shibata, K.; Matsui, M. *J. Org. Chem.* **2003**, *68*, 2853–2860.
11. For asymmetric direct aldol reaction, see: (a) Funabiki, K.; Yamamoto, H.; Nagaya, H.; Matsui, M. *Tetrahedron Lett.* **2006**, *47*, 5507–5510; (b) Funabiki, K.; Matsui, M. Current Fluoroorganic Chemistry: New Synthetic Directions, Technology, Materials, and Biological Applications. In *ACS Symposium Series* 949; Soloshonok, V. A., Mikami, K., Yamazaki, T., Welch, J. T., Honek, J. F., Eds.; Oxford/American Chemical Society: Washington DC, 2007; pp 141–355; (c) For direct aldol reaction, see Torii, H.; Nakada, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983–1986; (d) Funabiki, K.; Nagaya, H.; Ishihara, M.; Matsui, M. *Tetrahedron* **2006**, *62*, 5049–5053; (e) Zhang, F.; Peng, Y.; Liao, S.; Gong, Y. *Tetrahedron* **2007**, *63*, 4636–4641; For direct observation of an enamine intermediate in amine catalyst, see: (f) Zhu, X.; Tanaka, F.; Lerner, R. A.; Barbas, C. F., III; Wilson, I. A. *J. Am. Chem. Soc.* **2009**, *131*, 18206–18207.
12. (a) Kempf, B.; Hampel, N.; Ofial, A. R.; Mayr, H. *Chem.—Eur. J.* **2003**, *9*, 2209–2218; (b) Mayr, H.; Kemps, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66–77.
13. Crystallographic data has been deposited with Cambridge Crystallographic Data Center (12, Union Road, Cambridge, CB2 1FZ, UK; fax: 44 1223 336033; e-mail: [deposit@ccdc.cam.ac.jp](mailto:deposit@ccdc.cam.ac.jp)); Deposition number CCDC-761515. **Supplementary data** is also described of crystal data and structure refinement.
14. (a) Abe, H.; Amii, H.; Uneyama, K. *Org. Lett.* **2001**, *3*, 313–315; (b) Suzuki, A.; Mae, M.; Amii, H.; Uneyama, K. *J. Org. Chem.* **2004**, *69*, 5132–5134.
15. Kanai, M.; Yasumoto, M.; Kuriyama, Y.; Inomiya, K.; Katsuhara, Y.; Higashiyama, K.; Ishii, A. *Chem. Lett.* **2004**, *33*, 1424–1425.
16. Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, 2006; p 23 and 56.
17. For a recent example, see Yamazaki, T.; Terajima, T.; Kawasaki-Takasuka, T. *Tetrahedron* **2008**, *64*, 2419–2424.
18. For a recent example, see Xu, H.; Ekoue-Kovi, K.; Wolf, C. J. *Org. Chem.* **2008**, *73*, 7638–7650.