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Pyrrolidine as an efficient organocatalyst for direct aldol reaction of trifluoroacetaldehyde ethyl hemiacetal with ketones

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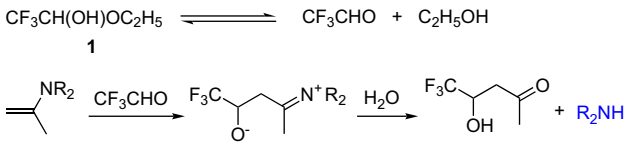
Abstract—Pyrrolidine-catalyzed aldol reaction of trifluoroacetaldehyde ethyl hemiacetal (**1**) with ketones or aldehydes was described. In the presence of 20 mol % of pyrrolidine, the reaction proceeded smoothly at room temperature to afford the aldol products in good to excellent yields (up to 95%). Pyrrolidine showed a much higher catalytic activity than piperidine in the reaction with less reactive ketones. GC analysis clearly indicated that the catalyst and the enamine intermediates were kept at extremely low concentration during the reaction. Based on these observations, we suggested that formation of the enamine would be a rate-determining step for the catalytic aldol reaction. In addition, the asymmetric aldol reaction of **1** with cyclohexanone catalyzed by L-proline derivatives was also discussed.

1. Introduction

Trifluoroacetaldehyde ethyl hemiacetal (**1**) as a useful building block has been widely used for preparing various trifluoromethyl carbinols.[1] Its aldol reaction usually utilized the ketone or aldehyde surrogates such as enamines or silyl enolates as the starting materials.[2] The reaction with enamines was suggested to undergo along with the following mechanism (Scheme 1):



Scheme 1.

Apparently, the secondary amine would be released when the aldol product was generated through nucleophilic addition and subsequent hydrolysis. Thus we realized that a secondary amine might act as a catalyst for the aldol reaction between **1** and ketones with α-hydrogen atom. We are interested in the direct aldol reactions of **1** with ketones or aldehydes in the presence of a secondary amine. Recently, a great deal of success has been achieved in the field of organocatalytic aldol reactions.[3] In many cases, addition of a certain amount of an organic weak acid or introduction of an acidic group in the amine molecule could accelerate the amine-catalyzed aldol reactions to a great extent.[4]

In our recent work, piperidine and L-prolinamide have been successfully used to catalyze the direct cross-aldol reaction between chloral and aliphatic aldehydes.[5] As a continuous work, the organocatalytic direct aldol reaction of **1** with aliphatic ketones and aldehydes has been recently examined. We found that the catalytic activity of piperidine was rather low for the reaction with cyclohexanone. A similar observation was reported by Funabiki and co-workers several months ago.[6] In their work, a moderate yield of aldol product was obtained by using 1 equiv of piperidine and acetic acid (50 mol %) as the catalyst, and acetic acid or the introduction of a carboxyl group in amine molecules[7] seemed to be necessary. In addition, a large excess amount of ketone was always added. However, we found that pyrrolidine was an ideal catalyst to improve the aldol reaction of **1** in our experiments, in which additional weak organic acid was not needed at all. It should be emphasized that this acid-free catalytic reaction has the following advantages: (1) using only 1 equiv of ketone; (2) giving the aldol products in a high yields; (3) appropriate for a wide scope of ketones; (4) less limited for the solvent used. The details about this catalytic reaction are discussed as follows.

2. Results and discussion

Reaction of trifluoroacetaldehyde ethyl hemiacetal (**1**) with cyclohexanone was chosen as a model system for screening

Keywords: Pyrrolidine; Organocatalysis; Aldol reaction; Trifluoroacetaldehyde ethyl hemiacetal.
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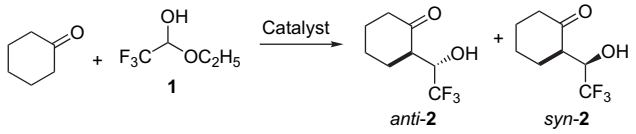
Table 1. Catalytic aldol reaction of the hemiacetal **1** with cyclohexanone[a]

Entry	Catalyst	Temperature	Yield of **2** (%)	*anti*/*syn*
1	Piperidine	rt	8	36:64
2	Morpholine	rt	<5	/
3	Piperazine	rt	<2	/
4	Diethylamine	rt	<2	/
5	Pyrrolidine	rt	92	31:69
6	Pyrrolidine/AcOH	rt	30	73:27
7	Pyrrolidine/TFA	rt	<1	/
8	Cyclohexylamine	rt	16	64:36

[a] Cyclohexanone (1.0 mmol) and **1** (1.0 mmol) in 2 mL CH_2Cl_2 for 24 h.

the catalysts. Several commercially available secondary amines listed in Table 1 are examined. Their catalytic activity was assessed by the model reaction of hemiacetal **1** (1.0 mmol) with cyclohexanone (1.0 mmol) in dichloromethane (2 mL) at room temperature in the presence of 20 mol % of various amines based on the amount of cyclohexanone that was used (Scheme 2). Product analysis was conducted under the following GC conditions: the carrier gas was N_2 and the column temperature was from 55 to 180 °C, which was programmed to rise in 15 °C/min. Retention times (minutes) of the main compounds were 2.385 min for **1**, 2.850 min for pyrrolidine, 6.460 min for cyclohexanone, 8.101 min for its enamine, and 10.179 min and 10.366 min for *anti*-**2** and *syn*-**2**, respectively. The stereoisomers were easily distinguished from each other according to the different chemical shifts for the proton of CF_3CHOH group.[7] Yields for the products were calculated based on the starting material added. The *anti*/*syn* ratio was determined by GC and confirmed by ^1H NMR spectra.



Scheme 2.

Among the amines given in Table 1, pyrrolidine is found to be the most efficient catalyst for the model reaction. In this case, aldol product **2** was afforded in 92% yield (entry 5). When an equivalent amount of acetic acid or trifluoroacetic acid was added, however, its catalytic activity was markedly decreased (entries 6 and 7). The aldol reaction catalyzed by other secondary amines was rather sluggish, yielding small amount of **2** (entries 1–4). In addition, cyclohexylamine, a primary amine, also showed a rather low catalytic efficiency in the reaction (entry 8).

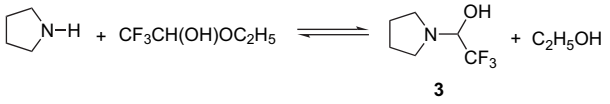
Next, effect of the catalyst loading on the reaction was assessed at room temperature. When less than 5 mol % of pyrrolidine was added, the reaction gave **2** in a low yield (Table 2). A satisfactory result was obtained when about 20 mol % of pyrrolidine was used.

Table 2. Effect of the catalyst dosage on the reaction[a]

Catalyst (mol %)	2.0	5.0	10.0	15.0	20.0	25.0	30.0
Yield of **2** (%)	11	62	89	92	94	95	95

[a] Cyclohexanone (1.0 mmol) and **1** (1.0 mmol) in 2 mL of CH_2Cl_2 for 36 h.

In order to understand the details of this process, we have followed the formation of product **2** and the disappearance of **1** and hemiaminal **3** generated in situ by GC analysis. In the presence of 20 mol % of pyrrolidine, the reaction of **1** with cyclohexanone proceeded readily. When **1** was mixed in advance with 20 mol % of pyrrolidine in dichloromethane and stirred for 30 min at room temperature, less than 1% of pyrrolidine could be detected in the mixture, whereas the hemiaminal **3** was yielded predominantly, indicative of the occurrence of a rapid reaction between **1** and pyrrolidine. During the aldol reaction, the disappearance of **1** was accompanied with the formation of **2**, but the amount of **3** was almost kept constant until **1** was exhausted. The amount of **3** started to slowly decrease when **1** was completely consumed. Simultaneously, a further increase in the yield of **2** was observed. Apparently, a decomposition of the hemiaminal **3** generated in situ would happen through a reversible process as illustrated in Scheme 3, although its dissociation rate was markedly slower than that of **1** (Scheme 1). The yield of **2** would reach up to 95% if the reaction time was prolonged to 48 h. In a parallel experiment, the aldol reaction was obviously accelerated and almost completed after 6 h when 25 mol % of pyrrolidine was added (Table 3, data in parentheses). Moreover, it was difficult to detect pyrrolidine in the reaction mixture at the initial stage, but about 3% of pyrrolidine was actually detected after 3 h by GC.



Scheme 3.

Another interesting observation resulted from the stereochemistry change for product **2**. Initially, the reaction preferentially gave aldol product *anti*-**2** (Table 3, entry 1). Unexpectedly, *anti*-**2** was gradually converted in situ into *syn*-**2** during the progress of the reaction (entries 2–7). The final molar ratio of *anti*-**2**/*syn*-**2** was maintained to be about 30:70 (entry 9). Based on these observations, we believe that formation of the *anti*-**2** was kinetically favored and the driving force for initiating its isomerization might be attributed to the formation of a relatively thermodynamically stable *syn*-**2**. Generally, the isomerization might proceed via the enolization of **2**, which could be accelerated in the presence of pyrrolidine.

Table 3. Reaction of the hemiacetal **1** with cyclohexanone at rt[a]

Entry	Time (h)	**1** (%)	**3** (%)	Yield of **2**[b] (%)	*anti*/*syn*
1	0.1	71	19	9 (17)	90:10
2	0.5	53	19	25 (65)	87:13
3	1.0	42	19	36 (83)	85:15
4	2.0	15	19	64 (93)	76:24
5	3.0	7	18	73	60:40
6	6.0	3	18	78 (95)	36:64
7	12.0	/	13	86	31:69
8	24.0	/	8	92	30:70
9	48.0	/	4	95	30:70

[a] Cyclohexanone (1.0 mmol), **1** (1.0 mmol), and pyrrolidine (0.20 mmol) in 2 mL of CH_2Cl_2.
[b] Data in parentheses were the yields using 0.25 mmol of pyrrolidine.

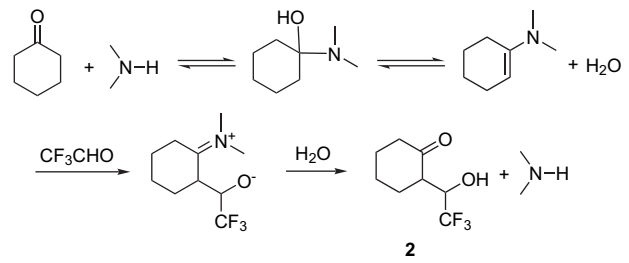
Table 4. Solvent effect on the aldol reaction with cyclohexanone[a]

Entry	Solvent	Yield of **2** (%)		*anti*-**2**/*syn*-**2**	
		3 h	24 h	3 h	24 h
1	*c*-C_6H_{12}	84	95	36:64	24:76
2	$PhCH_3$	92	95	62:38	28:72
3	CH_2Cl_2	73	92	60:40	31:69
4	$CHCl_3$	75	93	87:13	41:59
5	CH_3CN	35	86	84:16	45:55
6	Et_2O	21	85	89:11	66:34
7	THF	9	67	86:14	69:31
8	DMSO	5	39	60:40	54:46
9	DMF	4	24	77:23	71:29
10	NMP	<1	9	/	45:55

[a] Cyclohexanone (0.5 mmol), **1** (0.5 mmol), and pyrrolidine (0.1 mmol) in 2 mL of solvent at 15 °C.

Ten solvents with different polarities were next examined in the reaction. The results are summarized in Table 4. The ideal result was obtained when a nonpolar or weakly polar solvent such as cyclohexane, toluene, and dichloromethane was used. There was a significant decrease in the yield of **2** when the reaction was carried out in an aprotic polar solvent like DMSO or NMP. In addition, the reaction rate and the molar ratio of *anti*-**2**/*syn*-**2** were also affected by the property of solvent to some extent. From the product distributions determined individually at the times of 3 and 24 h, we can see that in most cases, the *anti*-**2** was preferentially afforded. Although the molar ratio of *anti*-**2**/*syn*-**2** gradually decreased during the reaction until 24 h, the isomerization rate was greatly dependent on the solvent property. For example, the isomeric ratio was still kept to be 87:13 in chloroform even if the yield of **2** was so high as to 75%, whereas it fell down to 36:64 in cyclohexane at 3 h. The *anti*-**2** was still the main product after 24 h when the reaction was carried out in a highly polar solvent like THF. All the results demonstrated that the isomerization proceeded more easily in nonpolar solvents than in polar solvents.

Although the aldol reaction usually underwent along with the pathways as illustrated in Scheme 3, it cannot fully explain the experimental results presented above. One is why the catalytic activity of pyrrolidine was much higher than other secondary amines such as piperidine and morpholine. Another is why the reaction could still occur readily in the presence of pyrrolidine at a very low concentration. Furthermore, we wonder if the aldol reaction would take place via the general base catalyzed route. For this reason, direct reaction between cyclohexanone and pyrrolidine or piperidine has been followed by GC analysis. When cyclohexanone (1.0 mmol) was mixed with 1 equiv of pyrrolidine in dichloromethane and stirred at room temperature, 6.5 and 15.5% of the corresponding enamine **5** was detected at the time of 24 and 48 h, respectively. In the case of piperidine, 1.8 and 4.3% of the enamine **6** was given under the same conditions, respectively. This result was consistent with the common opinion that pyrrolidine is more nucleophilic than piperidine toward ketones. The problem is, however, whether the enamine was really yielded in this reaction since pyrrolidine was almost converted into the hemiaminal **3** under the reaction conditions. Actually, there was no **5** detected during the reaction by GC. The possibility for the general base catalysis was therefore assessed by investigating the aldol reaction of the hemiacetal **1** with cyclohexanone in the presence of a tertiary amine like nicotine **7**, which resembles the hemiaminal **3** in structure. In fact, no reaction occurred at all under these conditions. Thus the possibility along with the general base catalysis could be excluded. Based on the above analysis, we believe that the pyrrolidine-catalyzed aldol reaction would proceed via a pathway shown in Scheme 4, where the formation of enamine was the rate-determining step (Fig. 1).



Scheme 4.

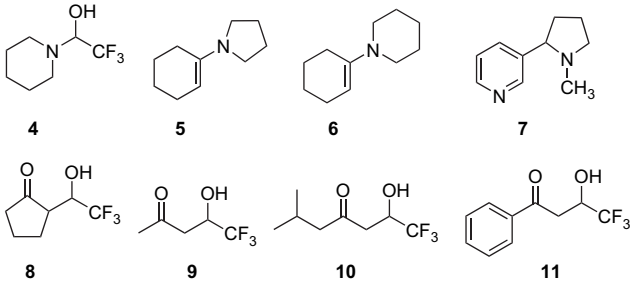


Figure 1.

The above interesting findings enabled us to extend our study to the reaction with different ketones. In order to compare the relative reactivity of cyclic ketones, a competitive reaction was performed by stirring the mixture of **1** (2.0 mmol), cyclohexanone (2.0 mmol), cyclopentanone (2.0 mmol), and pyrrolidine (0.50 mmol) in dichloromethane at room temperature. The reaction was almost completed within 3 h, and about 6% of cyclohexanone and 44% of cyclopentanone were converted into the corresponding aldol products **2** and **8**. This clearly indicated that cyclopentanone was much reactive in comparison with cyclohexanone. In an individual reaction with cyclopentanone, 81% of the product **8** was yielded in dichloromethane, wherein the molar ratio of *anti*/*syn* was 19:81.

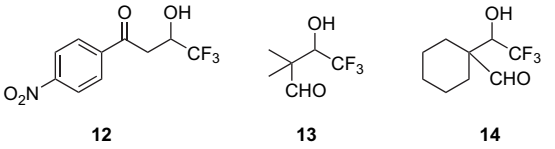
Pyrrolidine was also used to catalyze the aldol reaction with acyclic ketones. In the presence of 20 mol % of pyrrolidine, **1** smoothly reacted with excess of anhydrous acetone, yielding 87% of the aldol product **9**. Our concern in regioselectivity promoted us to evaluate the aldol reaction with 4-methylpentan-2-one. As shown in Table 5, the reaction proceeded slowly and provided only 7.3% of the aldol product **10** after 2 h. A satisfactory yield was obtained when the reaction time was prolonged to 48 h. Interestingly, the aldol reaction took place only at the site of methyl group. Moreover, it was worth noting that there was no obvious change in the amount of the hemiaminal **3** until the hemiacetal **1** was almost consumed in this case. This indicated that the dissociation rate of **3** was considered to be much slower than that of **1**.

Table 5. Reaction of **1** with 4-methylpentan-2-one at rt[a]

Entry	Time (h)	**1** (%)	**3** (%)	Yield of **10** (%)
1	0.1	76	24	0.3
2	1.0	73	24	3.2
3	2.0	68	24	7.3
4	4.0	62	24	14
5	6.0	56	24	20
6	8.0	46	24	30
7	24	20	21	58
8	48	<2	12	84

[a] Ketone (2.0 mmol), **1** (2.0 mmol), pyrrolidine (0.5 mmol) in 2 mL of CH_2Cl_2.

As a representative of alkyl aryl ketones, acetophenone was also used to react with **1**. In the presence of 20 mol % of pyrrolidine, product **11** was afforded in a rather low yield (36%) when equivalent amounts of the ketone and **1** were mixed and refluxed in THF for 24 h. The yield of **11** could be raised to 62% by adding 40 mol % of pyrrolidine. In addition, the introduction of electron-withdrawing group in benzene ring greatly favored the occurrence of aldol reaction. For example, the reaction of **1** with 4′-nitroacetophenone gave **12** in 75% yield under the same conditions (Fig. 2).



12 **13** **14**

Figure 2.

The cross-aldol reaction of **1** with aliphatic aldehydes was also studied. A moderate yield (62%) of cross-aldol product **13** was detected by GC in the reaction of **1** with isobutyraldehyde in dichloromethane, although it was quite difficult to purify the product **13** by silica gel column chromatography. A successful example was the reaction with cyclohexanecarbaldehyde in dichloromethane, in which 81% of cross-aldol product **14** was yielded by stirring a mixture of **1** (1.0 mmol), the aldehyde (1.0 mmol), and pyrrolidine (0.2 mmol) at room temperature for 24 h.

From the above experimental results, we realized that cyclopentanone was the most reactive among all the ketones used in this work. An interesting question was thus raised whether piperidine, a poor catalyst, could catalyze the aldol reaction of **1** with cyclopentanone. Therefore, the reaction between cyclopentanone and **1** was carried out in dichloromethane using 25 mol % of piperidine as the catalyst (Table 6). Eventually, 60% of the aldol product **8** was obtained. The *anti* and *syn* isomers formed in a ratio of about 15:85 as characterized by ^{1}H NMR and GC analysis. This finding further assured us that the formation of enamine was the key step in the organocatalytic aldol reaction of the hemiacetal **1**.

For our interest in asymmetric catalytic reaction, several optically pure catalysts **15** derived from L-proline have been studied in the model reaction of the hemiacetal **1** (1.0 mmol) with cyclohexanone (1.0 mmol) in dichloromethane. The result is given in parentheses in Table 7, little amount of aldol product **2** was detected when L-proline and its derivatives **15b** and **15c** were used as catalysts under these conditions. Obviously, their catalytic activity was extremely lower than that of pyrrolidine except L-prolinamide. According to the conditions reported in Ref. 7b, we carried out this reaction by stirring cyclohexanone (1.0 mL), the hemiacetal **1** (1.0 mmol), and the catalyst (0.2 mmol) at 15 °C for 36 h. As a result, **15b** and **15c** showed much higher catalytic activity than L-proline (Table 7, entries 2–4), and **15d** was the worst (entry 5). The *anti*-**2**/*syn*-**2** ratio and the ee value were determined by chiral GC analysis with a DIKMA Chirasil-DEX CB (25 m×0.25 mm) column. The conditions are: from 80 to 150 °C at a rate of 0.9 °C/min, then isotherm for 20 min at 150 °C. Retention times were 32.3 min (major) and 33.9 min (minor) for *anti*-**2**, and 44.3 min (major) and 45.3 min (minor) for *syn*-**2**. The results clearly indicated that the *anti*-**2** was the main product in the cases of L-proline and L-prolinamide, whereas the *syn*-**2** became the main product in the cases of pyrrolidine and L-methyl prolinate. Moreover, the reaction catalyzed by L-prolinamide gave the product **2** in much higher enantioselectivity than that catalyzed by L-proline and its ester **15b** under these conditions (Fig. 3).

Table 6. Piperidine-catalyzed aldol reaction with cyclopentanone[a]

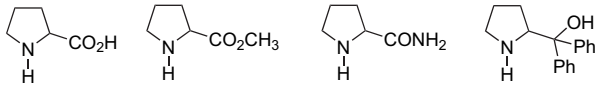
Entry	Time (h)	**1** (%)	**4** (%)	Yield of **8** (%)	*anti*/*syn*
1	0.1	75	24	<1	/
2	0.5	67	24	7	15:85
3	1.0	61	23	13	15:85
4	3.0	42	23	40	15:85
5	4.0	24	23	49	15:85
6	6.0	3	23	56	16:84
7	24.0	/	12	60	16:84

[a] Cyclopentanone (2.0 mmol), and **1** (2.0 mmol) in 2 mL of CH_2Cl_2.

Table 7. Reaction of the hemiacetal **1** with cyclohexanone catalyzed by L-proline derivatives[a]

Entry	Catalyst	Yield of **2**[b] (%)	*anti*/*syn*	ee[c] (*anti*-2/*syn*-2)
1	Pyrrolidine	95 (95)	26:74 (28: 72)	/
2	**15a**	57 (<1)	66:34	35:10
3	**15b**	95 (<1)	21:79	12:13
4	**15c**	92 (65)	90:10 (43:57)	88:56 (24:25)
5	**15d**	<1	/	/

[a] Cyclohexanone (1.0 ml), **1** (1.0 mmol), and the catalyst (0.2 mmol), and stirred at 15 °C for 36 h.
[b] Yields in parentheses were determined in the reaction of cyclohexanone (1.0 mmol), **1** (1.0 mmol), and the catalyst (0.2 mmol) in 1 mL of CH_2Cl_2, and stirred at 15 °C for 24 h.
[c] Determined by chiral GC.



15a **15b** **15c** **15d**

Figure 3.

3. Conclusion

In summary, pyrrolidine was an efficient catalyst for the direct aldol reaction of trifluoroacetaldehyde ethyl hemiacetal with various ketones or aldehydes. Its catalytic reaction did not need any additional assistant acids. This was a convenient

and environmentally friendly route to prepare β-hydroxy-β-trifluoromethyl carbonyl compounds in good to excellent yields. The key step for the catalytic aldol reaction seemed to be the formation of enamine intermediates. The utility of nonpolar or weakly polar solvents would be helpful for the reaction.

4. Experimental

4.1. General

^{1}H NMR spectra were measured on Bruker AC 200E (400 MHz) spectrometer at ambient temperature. Data were recorded by using TMS as the internal standard on the δ scale. ^{13}C NMR spectra were recorded on Bruker AC 200E (100 MHz) spectrometer at ambient temperature. Chemical shifts are recorded from the solvent resonance employed as the internal standard (deuterated chloroform at 77.07 ppm). The crude products were purified by preparative column chromatography on silica gel with 100–200 mesh. All the reagents including trifluoroacetaldehyde ethyl hemiacetal, amines, ketones, and aldehydes were all commercially available and used without further purification.

4.2. A typical procedure for pyrrolidine-catalyzed aldol reaction of the hemiacetal 1

A typical procedure was as follows: to a solution of the hemiacetal **1** (1.0 mmol) in dichloromethane (2 mL), pyrrolidine (0.20 mmol) was added and the resulting mixture was stirred at room temperature for 30 min. Then cyclohexanone (1.0 mmol) was poured into the solution. The reaction mixture was stirred at room temperature for a specified period. The solvent was evaporated under a reduced pressure and the residue was subjected to flash silica gel column chromatography (eluting with *n*-hexane/ethyl acetate, 10:1 v/v) to give **2** as a colorless oily liquid in 80% yield.

4.3. Spectrum data for the aldol products

4.3.1. *anti*-2-(1′-Hydroxy-2′,2′,2′-trifluoroethyl)cyclohexanone (*anti*-2).[7b] Yield: 55% (isolated yield from the reaction in chloroform); ^{1}H NMR (TMS, $CDCl_3$): δ 4.33 (1H, br s, O*H*), 4.03–4.07 (1H, m, *CH*CF_3), 2.74–2.78 (1H, m, C_2–H), 2.40–2.48 (2H, m), 2.23–2.24 (1H, m), 2.14–2.18 (1H, m), 1.95–1.98 (1H, m), 1.68–1.78 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 213.6, 124.7 (*C*F_3, q, J_{CF}=280 Hz), 71.7 (*C*HCF_3, q, J_{CF}=31 Hz), 50.4, 43.0, 31.6, 28.1, 24.9.

4.3.2. *syn*-2-(1′-Hydroxy-2′,2′,2′-trifluoroethyl)cyclohexanone (*syn*-2). Yield: 49% (isolated yield from the reaction in dichloromethane); ^{1}H NMR (TMS, $CDCl_3$): δ 4.70 (1H, q, J=8.0 Hz, *CH*CF_3), 2.96 (1H, br s, O*H*), 2.73 (1H, dd, J_1=12.8 Hz, J_2=5.6 Hz, C_2–H), 2.50 (1H, d, J=13.6 Hz, C_6–*H*), 2.33–2.41 (1H, m, C_6–*H*), 2.23–2.27 (1H, d, C_5–*H*), 2.13–2.15 (1H, m), 1.97–1.99 (1H, m), 1.83–1.93 (1H, m), 1.67–1.77 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.2, 125.0 (*C*F_3, q, J_{CF}=280 Hz), 67.5 (*C*HCF_3, q, J_{CF}=31 Hz), 50.4, 42.2, 27.3, 26.2, 24.5.

4.3.3. *syn*-2-(1′-Hydroxy-2′,2′,2′-trifluoroethyl)cyclopentanone (8).[7a] Yield: 62% (isolated yield from the reaction in dichloromethane); ^{1}H NMR (TMS, $CDCl_3$): δ 4.55 (1H, dq, J_1=7.2 Hz, J_2=1.6 Hz, *CH*CF_3), 3.41 (1H, br s, O*H*), 2.36–2.45 (2H, m), 2.07–2.20 (4H, m), 1.74–1.86 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 218.9, 125.2 (*C*F_3, q, J_{CF}=280 Hz), 67.6 (*C*HCF_3, q, J_{CF}=32 Hz), 49.3, 38.0, 22.4, 20.6. ^{1}H NMR data observed for its *anti* isomer: δ 4.16 (1H, dq, J_1=9.2 Hz, J_2=6.4 Hz, *CH*CF_3).

4.3.4. 5,5,5-Trifluoro-4-hydroxypentanone (9).[6] Yield: 76% (isolated yield from the reaction in excess acetone); ^{1}H NMR (TMS, $CDCl_3$): δ 4.45–4.53 (1H, m, *CH*CF_3), 3.60 (1H, br s, O*H*), 2.87 (1H, dd, J_1=18.0 Hz, J_2=9.4 Hz, *CH*C═O), 2.77 (1H, dd, J_1=18.0 Hz, J_2=2.8 Hz, *CH*C═O), 2.25 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.4, 124.7 (*C*F_3, q, J_{CF}=279 Hz), 66.4 (*C*HCF_3, q, J_{CF}=32 Hz), 42.8, 30.6.

4.3.5. 1,1,1-Trifluoro-2-hydroxy-6-methylheptan-4-one (10).[8] Yield: 68% (isolated yield from the reaction in dichloromethane); ^{1}H NMR (TMS, $CDCl_3$): δ 4.48–4.53 (1H, m, *CH*CF_3), 3.71 (1H, br s, O*H*), 2.82 (1H, dd, J_1=17.6 Hz, J_2=9.2 Hz, *CH*C═O), 2.71 (1H, dd, J_1=17.6 Hz, J_2=2.4 Hz, *CH*C═O), 2.37 (2H, d, J=6.8 Hz, CH_2CO), 2.13–2.19 (1H, m, *CH*), 0.94 (3H, d, J=6.6 Hz, CH_3), 0.93 (3H, d, J=6.6 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.6, 124.7 (*C*F_3, q, J_{CF}=279 Hz), 66.5 (*C*HCF_3, q, J_{CF}=32 Hz), 52.6, 42.3, 24.5, 22.4, 22.3.

4.3.6. 4,4,4-Trifluoro-3-hydroxy-1-phenylbutanone (11).[2b] Mp 79.4–79.8 °C (recrystallized from hexane/ethyl acetate); yield: 49% (isolated yield from the reaction in THF); ^{1}H NMR (TMS, $CDCl_3$): δ 7.98 (2H, d, J=7.6 Hz, *ortho*), 7.64 (1H, t, J=7.6 Hz, *para*), 7.51 (2H, t, J=7.6 Hz, *meta*), 4.68–4.72 (1H, m, *CH*CF_3), 3.51 (1H, br s, O*H*), 3.39 (1H, dd, J_1=18.0 Hz, J_2=9.0 Hz, *CH*C═O), 3.33 (1H, dd, J_1=18.0 Hz, J_2=3.2 Hz, *CH*C═O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 136.0, 134.2, 128.9, 128.2, 124.5 (*C*F_3, q, J_{CF}=278 Hz), 67.1 (*C*HCF_3, q, J_{CF}=32 Hz), 38.3.

4.3.7. 4,4,4-Trifluoro-3-hydroxy-1-(4-nitrophenyl)-1-butanone (12).[2b] Mp 104.5–105.0 °C (recrystallized from hexane/ethyl acetate); yield: 55% (isolated yield from the reaction in THF); ^{1}H NMR (TMS, $CDCl_3$): δ 8.35 (2H, d, J=8.8 Hz, *meta*), 8.14 (2H, d, J=8.8 Hz, *ortho*), 4.71–4.79 (1H, m, *CH*CF_3), 3.47 (1H, dd, J_1=18.0 Hz, J_2=9.6 Hz, *CH*C═O), 3.32 (1H, dd, J_1=18.0 Hz, J_2=2.4 Hz, *CH*C═O), 3.18 (1H, br s, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.6, 150.9, 140.3, 129.3, 124.6 (*C*F_3, q, J_{CF}=278 Hz), 66.8 (*C*HCF_3, q, J_{CF}=32 Hz), 39.1.

4.3.8. 1-(2,2,2-Trifluoro-1-hydroxyethyl)cyclohexanecarbaldehyde (14). Yield: 61% (isolated yield from the reaction in dichloromethane); ^{1}H NMR (TMS, $CDCl_3$): δ 9.72 (1H, s, C*H*O), 3.99 (1H, q, J=8.0 Hz, *CH*CF_3), 3.47 (1H, br s, O*H*), 2.01–2.09 (2H, m), 1.58–1.68 (4H, m), 1.30–1.46 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.3, 124.7 (*C*F_3, q, J_{CF}=283 Hz), 74.9 (*C*F_3, q, J_{CF}=29 Hz), 50.6, 28.6, 28.0, 25.0, 21.9, 21.8.

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