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Practical asymmetric synthesis of β-hydroxy-β-trifluoromethylated ketones *via* the first example of the *in situ* generation of trifluoroacetaldehyde and its successive asymmetric carbon–carbon bond formation reaction with chiral imines

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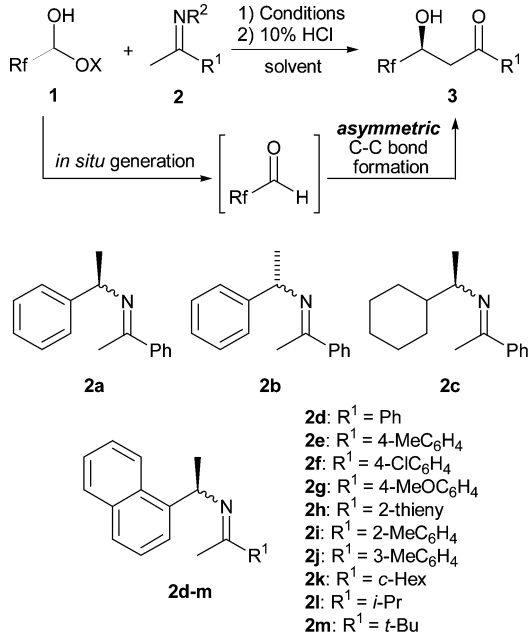
Not only trifluoroactaldehyde ethyl hemiacetal or hydrate but also other polyfluoroalkylaldehydes acetals or hydrates react with an equimolar amount of various chiral imines, followed by hydrolysis to produce the corresponding (*S*)-β-hydroxy-β-polyfluoroalkyl ketones in good yields with good enantioselectivities; furthermore, the ee of the products can be improved by simple recrystallization.

The enantioselective synthesis of α-trifluoromethylated alcohols or amines is of primary significance since these chiral synthons are among the most important and commonly found subunits in chiral drugs or materials.[1] Particularly, efficient and selective synthesis using trifluoroacetaldehyde or its hemiacetal as a C2 building block is an extremely useful approach toward functionalized trifluoromethylated compounds.[2] However, just before trifluoroacetaldehyde is employed, it should be generated from its hemiacetal or hydrate using an excess amount of conc. sulfuric acid under a high reaction temperature.[3] Moreover, careful treatment of the aldehyde is required due to its troublesome properties, such as its gaseous state at room temperature, high miscibility with moisture and high reactivity leading to self-polymerization.[3] Although the development of much more convenient and environmentally-benign methods has been investigated for some time, to the best of our knowledge, there is only one report on the generation of trifluoroacetaldehyde from its hemiacetal or hydrate *accompanied by a simultaneous asymmetric carbon–carbon bond formation reaction*, which has the serious disadvantage of extremely low enantioselectivity.[4] Recently, we have found that the enamines or imines are very effective for both the *in situ* generation of trifluoroacetaldehyde and its carbon–carbon bond formation reaction.[2]

Herein we wish to describe the first example of chiral imine-assisted *in situ* generation of trifluoroacetaldehyde from its hemiacetal and the successive asymmetric carbon–carbon bond formation reaction of the aldehyde with chiral imines to afford β-hydroxy-β-trifluoromethylated ketones with excellent enantioselectivities (Scheme 1).

The results of the reaction of trifluoroacetaldehyde ethyl hemiacetal **1a** with chiral imine **2a** derived from acetophenone and (*R*)-1-phenylethylamine under various conditions are summarized in Table 1. The reaction in hexane at room temperature for 7 h proceeded smoothly to give the ketone **3a** in 62% yield with good enantioselectivity (*S* : *R* = 80.1 : 19.9) (entry 1). Among other solvents examined, toluene is also usable for the reaction with a slight decrease of ee (entry 2). Employing dichloromethane (CH_2Cl_2) or acetonitrile (MeCN) reduced the ee of **3a** (entries 4 and 5). The reaction in THF was enormously sluggish to give an only trace amount of **3a** (entry 3). These results apparently suggest that less polar solvents such as hexane and toluene are more suitable for the reaction, giving higher yields as well as higher enantioselectivities of the product than polar solvents. When the reaction was performed with imine **2b** derived from (*S*)-1-phenylethylamine, the absolute configuration of the major isomer was completely reversed (entries 1 and 6). The (*R*)-1-cyclohexylethyl group of the imine **2c** brought about a higher yield, but with much lower selectivity (entry 7). The (*R*)-1-(1-naphthyl)ethyl group was the most effective chiral auxiliary for this reaction to provide **3a** in 66% yield with the best enantioselectivity (*S* : *R* = 85.5 : 14.5) (entry 8).

Carrying out the reaction at 0 °C afforded **3a** with higher selectivity, although a longer reaction time (7 d) is required (entry 9).† An even lower temperature (−15 °C) was not so effective in



Scheme 1

Table 1 The reaction of trifluoroacetaldehyde ethyl hemiacetal with chiral imines derived from acetophenone under various conditions

Entry[a]	Imine	Solvent	Conditions	Yield (%)[b]	Isomer ratio (*S* : *R*)[c]
1	**2a**	Hexane	rt, 7 h	62	80.1 : 19.9
2	**2a**	PhMe	rt, 7 h	64	77.6 : 22.4
3	**2a**	THF	rt, 7 h	8	73.3 : 26.7
4	**2a**	CH_2Cl_2	rt, 7 h	61	71.3 : 28.7
5	**2a**	MeCN	rt, 7 h	56	71.9 : 28.1
6	**2b**	Hexane	rt, 7 h	73	20.6 : 79.4
7	**2c**	Hexane	rt, 7 h	92	62.5 : 37.5
8	**2d**	Hexane	rt, 7 h	66	85.5 : 14.5
9	**2d**	Hexane	0 °C, 7 d	57	90.5 : 9.5
10	**2d**	Hexane	−15 °C, 7 d	48	89.3 : 10.7

[a] All the reactions were conducted with trifluoroacetaldehyde ethyl hemiacetal **1a** (0.5 mmol) and imine **2** (0.5 mmol). [b] Yields of isolated products. [c] Determined by HPLC analysis with CHIRALCEL OD (hexane : *i*-PrOH = 95 : 5).

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Table 2 The reaction of polyfluoroalkylaldehyde hemiacetal or hydrate **1** with various chiral imines **2**

Entry	1	Rf	X	Imine	R^1	Product	Yield (%)[b]	Enatiomer ratio (S : *R*)[c]	Ee[c]	Ee[c,d]
1	**1a**	CF_3	Et	**2d**	Ph	**3a**	57	90.5 : 9.5	81.0	92.8
2	**1b**	CF_3	H	**2d**	Ph	**3a**	57	89.1 : 10.9	78.2	—
3	**1a**	CF_3	Et	**2e**	4-MeC_6H_4	**3b**	68	89.4 : 10.6	78.8	>99.9
4	**1a**	CF_3	Et	**2f**	4-ClC_6H_4	**3c**	64	87.6 : 12.4	75.2	>99.9
5	**1a**	CF_3	Et	**2g**	4-$MeOC_6H_4$	**3d**	51	86.0 : 14.0	72.0	93.8
6	**1a**	CF_3	Et	**2h**	2-Thienyl	**3e**	37	90.3 : 9.7	80.6	>99.9
7	**1a**	CF_3	Et	**2i**	2-MeC_6H_4	**3f**	14	56.9 : 43.1	13.8	—
8	**1a**	CF_3	Et	**2j**	3-MeC_6H_4	**3g**	70	90.6 : 9.4	81.2	—
9	**1a**	CF_3	Et	**2k**	*c*-Hex	**3h**	73	93 : 7[e]	86	—
10	**1a**	CF_3	Et	**2l**	*i*-Pr	**3i**	59	88 : 12[e]	76	—
11	**1a**	CF_3	Et	**2m**	*t*-Bu	**3j**	24	92 : 8[e]	84	—
12	**1c**	CHF_2	Et	**2d**	Ph	**4a**	53	75.5 : 24.5	51.0	—
13	**1d**	CF_3CF_2	H	**2d**	Ph	**5a**	51	89.7 : 10.3	79.4	95.6

[a] All the reactions were carried out with **1** (0.5 mmol) and **2** (0.5 mmol) at 0 °C for 7 d. [b] Yields of isolated products. [c] Determined by HPLC analysis with CHIRALCEL OD (hexane : *i*-PrOH = 95 : 5). [d] After recrystallization. [e] Determined by ^{19}F NMR.

improving the selectivity, and ketone **3a** was obtained in 48% yield (entry 10).

The results of the reaction between hemiacetal **1a** and various chiral imines **2** under the optimized conditions are summarized in Table 2. The reaction of **1a** with chiral imines **2d–h,j** having 4- and 3-substituted phenyl groups as well as the thienyl one afforded the corresponding β-hydroxy-β-trifluoromethyl ketones **3a–e,g** in good yields with good enantioselectivities (entries 1,3–6 and 8). However, the use of chiral imine **2i** with a 2-methylphenyl group provided **3f** in only 14% yield with extremely low ee (entry 7). At the present stage, the exact reason for the low yield and selectivity is not clear. Chiral imines **2k–m** carrying aliphatic substituents, such as *c*-hexyl, *i*-propyl, and *t*-butyl group, underwent reaction with the hemiacetal **1a** to give the corresponding β-hydroxy-β-trifluoromethyl ketones **3h–j** with uniformly good enantioselectivities (entries 9–11). However, using imine **2m** with a *t*-butyl group produced **3j** in only 24% yield (entry 11).

The absolute configuration for **3a** with a phenyl group was determined as *S* by comparison with the reported optical rotation.[5] It is likely that the absolute configuration for the remaining products having other aromatic substituents can be assigned as the same by analogy. The absolute configurations and the ee values of **3g–i** with aliphatic groups were determined by the Mosher method.

The present protocol can be applied to trifluoroacetaldehyde hydrate as well as other polyfluoroalkylaldehyde acetals or hydrates. The use of trifluoroacetaldehyde hydrate **1b** in place of the hemiacetal **1a** gave the same yield (57%) of the ketone **3a** with similar enantioselectivity (entries 1 and 2). Compared with trifluoroacetaldehyde ethyl hemiacetal **1a**, the reaction of difluoroacetaldehyde ethyl hemiacetal **1c** with the imine **2d** provided a lower stereoselectivity of the product **4a** in 53% yield (entries 1 and 12). In contrast, treatment of pentafluoropropioaldehyde hydrate **1d** with the imine **2d** gave the corresponding β-hydroxy-β-pentafluoroethyl ketone **5a** in 51% yield with similar enantioselectivity to that of the trifluoromethylated one (entries 1 and 13).

Furthermore, simple recrystallization of the ketone **3a** using hot hexane (30 ml g^{-1} of **3a**) yields a highly enantioenriched product (92.8% ee). Ee values of other β-hydroxy-β-polyfluoroalkyl ketones **3,5** with aromatic substituents could also be improved by the same method (up to 99.9% ee). In the case of **3d**, changing the polarity of the solvent by using hexane–AcOEt (v/v = 50/1) (30 ml g^{-1} of **3d**) is required. Unfortunately, this method was not effective for difluoromethylated ketone **4** due to its lower melting point than those of the trifluoromethylated ones. Noteworthy is that higher ee values of the ketones are obtained from the mother liquor in all cases.[6]

In summary, we have achieved the stoichiometric *in situ* generation of trifluoroacetaldehyde as well as its simultaneous asymmetric carbon–carbon bond formation reaction with chiral imines, producing the corresponding β-hydroxy-β-trifluoromethyl ketones in good yields with high enantioselectivities. The major advantages of this process are good yields as well as high enantioselectivities, the absence of a generation step for the trifluoroacetaldehyde, the use of only stoichiometric amounts of chiral imines and the easy recovery of the chiral auxiliary.

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Notes and references

† To a solution of chiral imine **2d** (0.137 g, 0.5 mmol) in hexane (2 ml) was added trifluoroacetaldehyde ethyl hemiacetal **1a** (0.074 g, 0.5 mmol) at 0 °C under argon atmosphere. After being stirred at 0 °C for 7 d, the reaction mixture was hydrolyzed with 10% HCl aq. (4 ml) for 3 h, followed by extraction with Et_2O (30 ml × 3), drying over Na_2SO_4, and concentration under vacuum. The residue was chromatographed on silica gel using hexane–EtOAc, giving **3a** in 57% yield (0.062 g, 81.0% ee). The ee of the product was determined by chiral HPLC analysis (Daicel, CHIRALCEL OD, *n*-hexane : *i*-PrOH = 95 : 5, 0.8 ml min^{-1}, 254 nm). On the other hand, the aqueous layer and the precipitate at hydrolysis were treated with solid NaOH to make them alkaline, followed by extraction with Et_2O (30 ml × 3), drying over Na_2SO_4, and concentration under vacuum, (*R*)-1-(1-naphthyl)ethylamine was recovered in 88%. **3a**; $[\alpha]_D^{23}$ −20.3° (92.8% ee (S), *c* = 1.0, $CHCl_3$).

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