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A Versatile Approach to 2-Substituted 3-Trifluoromethyl-1,3-diols Based on the Reaction of Trifluoroacetaldehyde Ethyl Hemiacetal with Enamines Derived from Aldehydes

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Treatment of trifluoroacetaldehyde ethyl hemiacetal with various enamines, derived from various aldehydes, at room temperature, followed by hydrolysis with 10% HCl aqueous solution and reduction with sodium borohydride in ethanol, gave 2-substituted 3-trifluoromethyl-1,3-diols in good yields with fair to good diastereoselectivities.

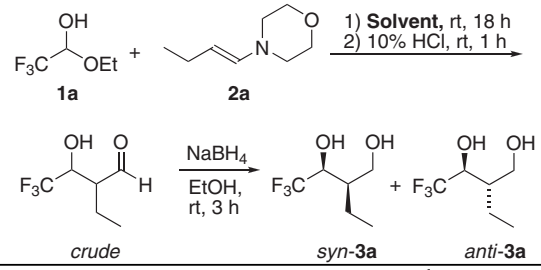
Much attention has been given to the development of a general, convenient, effective, and stereoselective method for the synthesis of substituted 1,3-diols in organic synthesis, because substituted 1,3-diols are fundamental units contained in many naturally occurring compounds.[1] Although 4,4,4-trifluorobutan-1,3-diol is essential for the synthesis of an *anti*-depressant (befloxatone), which could be easily prepared by reduction of commercially available ethyl 4,4,4-trifluoro-3-oxobutanoate,[2] there are very limited examples of a general and convenient synthetic route to 2-substituted 3-trifluoromethyl-1,3-diols.[3] We describe here a versatile new approach to 2-substituted 3-trifluoromethyl-1,3-diols based on the carbon–carbon bond-formation reaction of commercially available trifluoroacetaldehyde (CF_3CHO) ethyl hemiacetal with enamines derived from aldehydes without any additives, such as Lewis or Brønsted acids as well as bases.[4]

Treatment of CF_3CHO ethyl hemiacetal **1a** with an equiv of enamine **2a**, prepared from butanal and morpholine,[5] in dichloromethane (CH_2Cl_2) at room temperature for 18 h in the absence of any additives, followed by hydrolysis with 10% HCl aqueous solution, extraction with diethyl ether, drying with sodium sulfate (Na_2SO_4), concentration under vacuum, and reduction with sodium borohydride ($NaBH_4$) in ethanol at room temperature for 3 h, gave 2-ethyl-4,4,4-trifluorobutan-1,3-diol (**3a**) in 50% ^{19}F NMR yield as a mixture of diastereomers with a *syn*:*anti* ratio of 33:67 (Table 1, Entry 3).[6] Other solvents, such as hexane, toluene, acetonitrile, and tetrahydrofuran (THF), were less suitable solvents than CH_2Cl_2 and gave the diol **3a** in yields of 11–42% with lower diastereoselectivities (Entries 1, 2, 4, and 5). The use of 2 equiv of CF_3CHO hemiacetal **1a** resulted in a slight increase in the yield of the product **3a** as well as an increase in diastereoselectivity (Entry 6).

A versatile approach to 2-substituted 3-trifluoromethyl-1,3-diols **3** based on the reactions of CF_3CHO ethyl hemiacetal **1a** with enamines **2** is summarized in Table 2.

Other enamines **2b**–**2f** carrying phenyl, benzyl, *n*-butyl, *n*-hexyl, and *n*-decyl groups, derived from various aldehydes, such as 2-phenylacetaldehyde, 3-phenylpropanal, hexanal, octanal, and dodecanal, also successfully participated in carbon–carbon bond-forming reactions with CF_3CHO hemiacetal **1a**, followed by hydrolysis and reduction with $NaBH_4$, to produce the corresponding 2-substituted 3-trifluoromethyl-1,3-diols **3b**–**3f** in good yields (Entries 2–6). Although use of the isopropyl bearing enamine **2g**, derived from 3-methylbutanal, resulted in a significant decrease in the yield (24% ^{19}F NMR yield, *syn*:*anti* = 10:90) of the product **3g** under the same conditions (Entry 7), an increase in the amount (5 equiv) of CF_3CHO hemiacetal **1a** improved the yield of **3g** (Entry 8). Treatment of difluoroacetaldehyde ethyl hemiacetal **1b** with enamine **2c** under the same reaction conditions gave 2-ethyl-4,4-difluorobutan-1,3-diol (**4c**) in 50% ^{19}F NMR yield (Entry 9). In all cases, the diastereomers can be readily separated by using silica gel column chromatography. Moderate to good overall yields could be attributed to the steps of in situ generation of CF_3CHO and a successive carbon–carbon bond-formation reaction with enamines.

Table 1. Screening of the conditions



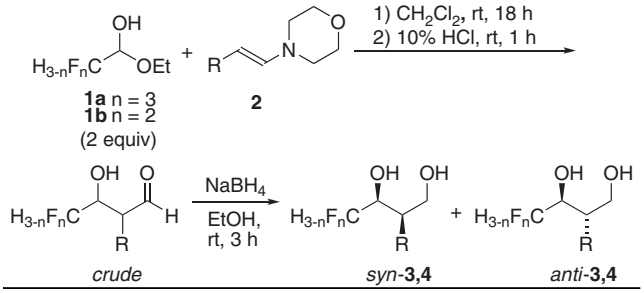
Entry[a]	**1a** (equiv)	Solvent	Overall yield[b]/%	*syn*:*anti*[c]
1	1	Hexane	42	38:62
2	1	Toluene	33	39:61
3	1	CH_2Cl_2	50	33:67
4	1	MeCN	31	46:54
5	1	THF	11	42:58
6[d]	2	CH_2Cl_2	59 (43)	24:76

[a]All the reaction was carried out with trifluoroacetaldehyde ethyl hemiacetal **1a** (2 mmol) and aldehyde enamine **2a** (2 mmol) in solvent (8 mL). [b]^{19}F NMR yields using benzotrifluoride. Values in parentheses stand for isolated yields. [c]Determined by ^{19}F NMR of the reaction mixture. [d]**1a** (2 equiv) was used.

The relative stereochemistries of the 2-substituted 3-trifluoromethyl-1,3-diols **3c** were determined from the vicinal coupling constants of the 1,3-dioxane **5c** in ^{1}H NMR after conversion of the trifluoromethylated 1,3-diol **3c** with acetone dimethylacetal in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) into 1,3-dioxane **5c**, as shown in Scheme 1. *syn*-1,3-Dioxolane **5c**, which has vicinal protons at C-4 and C-5 in a *syn* arrangement, has a smaller coupling constant ($^3J_{Hax–Heq} = 2.66$ Hz) than that ($^3J_{Hax–Hax} = 9.78$ Hz) of *anti*-**5c**, according to the reported values.[3b]

Stereochemical assignments of the other 1,3-diols **3** and **4** were made by the comparison of the chemical shifts to those of *syn*- and *anti*-**3c** in ^{19}F NMR.

Table 2. A versatile synthesis of 2-substituted 3-trifluoromethyl- or difluoromethyl-1,3-diols **3** and **4**



Entry	1	Enamine 2, R	Product 3, 4	Overall yield/%[a]	*syn*:*anti*[b]
1	**1a**	**2a**, CH_3CH_2	**3a**	59 (43)	24:76
2	**1a**	**2b**, Ph	**3b**	70 (64)	40:60
3	**1a**	**2c**, $PhCH_2$	**3c**	65 (65)	27:73
4	**1a**	**2d**, $CH_3(CH_2)_3$	**3d**	63 (58)	34:66
5	**1a**	**2e**, $CH_3(CH_2)_5$	**3e**	79 (75)	31:69
6	**1a**	**2f**, $CH_3(CH_2)_9$	**3f**	76 (74)	25:75
7	**1a**	**2g**, $(CH_3)_2CH$	**3g**	24	10:90
8[c]	**1a**	**2g**, $(CH_3)_2CH$	**3g**	55 (50)	14:86
9	**1b**	**2c**, $PhCH_2$	**4c**	50 (40)	45:55

[a] ^{19}F NMR yields. Values in parentheses stand for isolated yields. [b]Determined by ^{19}F NMR before isolation. [c]CF_3CHO ethyl hemiacetal **1a** (5 equiv) was used.

As described in Scheme 2, CF_3CHO, generated in situ by the reaction of CF_3CHO ethyl hemiacetal **1a** with enamine **2**,[4a] reacts with enamine **2** through the open transition state (T1). According to the literature,[7] the trifluoromethyl group is situated in *antiperiplanar* of the carbon–carbon double bond of enamine **2**, because of electrostatic interaction of the trifluoromethyl group in the T1, which minimizes the gauche interaction between the trifluoromethyl and R groups on the forming bond. The effect of the solvents on the diastereoselectivity is not clear at the present time.

In conclusion, we have developed a new versatile approach to 2-substituted 3-trifluoromethyl-1,3-diols **3** based on the tandem effective in situ generation of CF_3CHO and a successive carbon–carbon bond-formation reaction with enamines without any additives, such as acids or bases, derived from aldehydes, followed by hydrolysis and reduction with $NaBH_4$.

Organocatalytic asymmetric synthesis of 2-substituted 3-trifluoromethyl-1,3-diols based on the in situ generation of CF_3CHO and successive stereoselective carbon–carbon bond-formation is currently being investigated in our laboratory.

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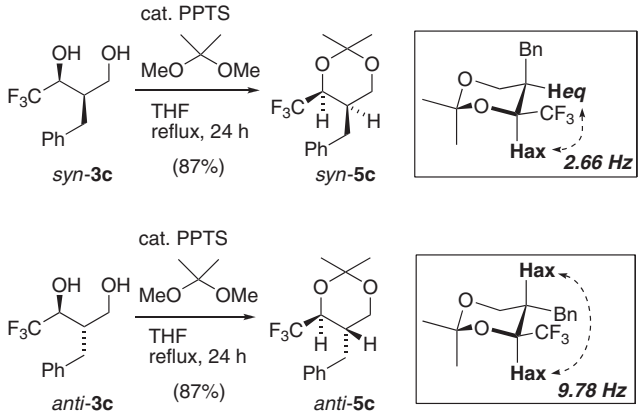
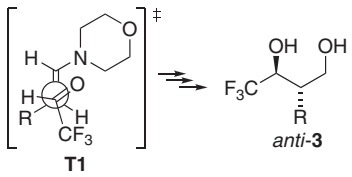
References and Notes

1 A recent review, see: S. E. Bode, M. Wolberg, M. Müller, *Synthesis* **2006**, 557.



Scheme 1. Determination of the relative configurations of **3**.



Scheme 2. Proposed transition state.

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6 The intermediate aldol products could be isolated. However, in this reaction the aldol products were used as crude products in next reduction step. Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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