JOC Note
pubs.acs.org/joc

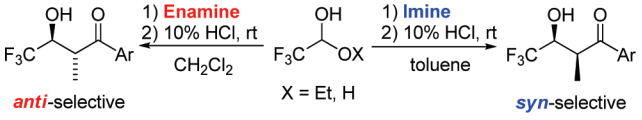
Reversal of Diastereoselectivity in Reactions of the Trifluoroacetaldehyde Ethyl Hemiacetal with Enamines and Imines: Metal-Free, Complementary *anti*- and *syn*-Selective Synthesis of 4,4,4-Trifluoro-1-aryl-3-hydroxy-2-methyl-1-butanones

Kazumasa Funabiki,* Kei Matsunaga, Hiroshi Gonda, Hitoshi Yamamoto, Takao Arima, Yasuhiro Kubota, and Masaki Matsui

Department of Materials Science and Technology, Faculty of Engineering, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan

funabiki@gifu-u.ac.jp

Received September 3, 2010

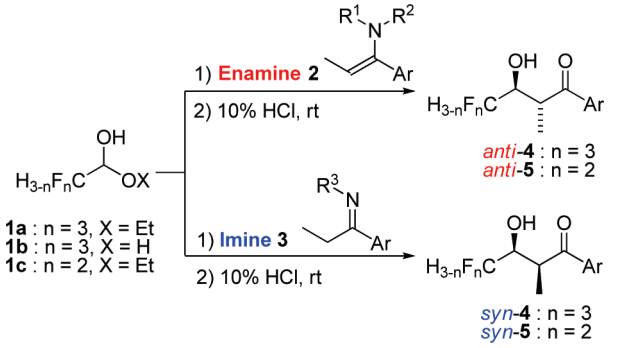


A complete reversal of diastereoselectivity was observed for reactions of the trifluoroacetaldehyde ethyl hemiacetal with enamines and imines, derived from propiophenones, that produce 4,4,4-trifluoro-1-aryl-3-hydroxy-2-methyl-1-butanones. This process serves as the first reliable, metal-free, complementary *anti*- and *syn*-selective method to prepare 4,4,4-trifluoro-1-aryl-3-hydroxy-2-methyl-1-butanones.

The development of diastereo- and enantioselective methods for the synthesis of β-hydroxy-α-methylated aldol products based on aldol reactions continues to be of crucial importance in organic syntheses, since these units appear in many natural products such as macrolide antibiotics. For this purpose, many complementary *anti*- and *syn*-selective aldol reactions that use metal-enolates to give the β-hydroxy-α-alkylated ketones, esters, and amides have been well studied.[1] Although *metal-free* or *organocatalytic* complementary diastereoselective direct aldol reactions are also of increasing interest, the substrates are limited to some aliphatic ketones[2] or aldehydes,[3] and there is no example that involves *aromatic ethyl* ketones.[4]

In recent investigations, we have explored reactions of the ethyl hemiacetal of trifluoroacetaldehyde (CF_3CHO) with various enamines and imines derived from methyl ketones as part of a regio-[5,6] and enantio-controlled[7] asymmetric methods for the synthesis of 1-aryl- and 1-alkyl-4,4,4-trifluoro-3-hydroxy-1-butanones. Furtheremore, recently, we reported the L-proline-catalyzed complementary *syn*- and *anti*-selective synthesis of 2-(2,2,2-trifluoro-1-hydroxyethyl)cycloalkanones via the direct aldol reaction of CF_3CHO hemiacetal with aliphatic cyclic ketones.[8] Below, we describe the first metal-free, complementary *anti*- and *syn*-selective method to prepare 4,4,4-trifluoro-1-aryl-3-hydroxy-2-methyl-1-butanones by the reactions of CF_3CHO hemiacetal with enamines or imines, derived from *aromatic ethyl ketones*, which should have a significant impact and basic information for the organocatalytic direct diastereoselective aldol reaction of *aromatic ethyl ketones*, leading to α-methylated aldol products (Scheme 1).

SCHEME 1. Complementary *anti*- or *syn*-Selective Synthesis of 4,4,4-Trifluoro- and 4,4-Difluoro-1-aryl-3-hydroxy-2-methyl-1-butanones (4, 5)



(1) A recent book, see: *Modern Aldol Reactions*;Mahrwald, R., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2004.

(2) For recent examples of α-methyl-, chloro-, and fluoro- alkoxy-, hydroxy-aliphatic ketones, *syn*-adducts, see: (a) Xu, X.-Y.; Wang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2007**, *9*, 4247. (b) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2007**, *129*, 288. (c) Ramasastry, S. S. V.; Albertshofer, K.; Utsumi, N.; Tanaka, F.; Barbas, C. F., III *Angew. Chem., Int. Engl.* **2007**, *46*, 5572. (d) Utsumi, N.; Imai, M.; Tanaka, F.; Ramasastry, S. S. V.; Barbas, C. F., III *Org. Lett.* **2007**, *9*, 3445. (e) Teo, Y.-C.; Chua, G.-L.; Ong C.-Y.; Poh, C.-Y. *Tetrahedron Lett.* **2009**, *50*, 4854. For *anti*-products, see: (f) Enders, D.; Grondal, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1210. (g) Suri, J. T.; Ramachary, D. B.; Barbas, C. F., III *Org. Lett.* **2005**, *7*, 1383. (h) Ibrahem, I.; Cordova, A. *Tetrahedron Lett.* **2005**, *46*, 3363.

(3) For recent examples of α-alkylated aldehydes, *syn*-adducts, see: (a) Li, J.; Fu, N.; Li, X.; Luo, S.; Cheng, J.-P. *J. Org. Chem.* **2010**, *75*, 4501. For *anti*-adducts, see: (b) Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 2152.

(4) For organocatalytic asymmetric direct aldol reaction of aromatic *methyl* ketones, see: (a) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983. (b) Mei, K.; Zhang, S.; He, S.; Li, P.; Jin, M.; Xue, F.; Luo, G.; Zhang, H.; Song, L.; Duan, W.; Wang, W. *Tetrahedron Lett.* **2008**, *49*, 2681. (c) Carpenter, R. D.; Fettinger, J. C.; Lam, K. S.; Kurth, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6407.

(5) For methyl ketones, see: (a) Funabiki, K.; Nojiri, M.; Matsui, M.; Shibata, K. *Chem. Commun.* **1998**, 2051. (b) Funabiki, K.; Matsunaga., K.; Matsui, M.; Shibata, K. *Synlett* **1999**, 1477. (c) Funabiki, K.; Matsunaga, K.; Nojiri, M.; Hashimoto, W.; Yamamoto, H.; Matsui, M.; Shibata, K. *J. Org. Chem.* **2003**, *68*, 2853. For aldehydes, see: (d) Funabiki, K.; Furuno, K.; Sato, F.; Gonda, H.; Kubota, Y.; Matsui, M. *Chem. Lett.* **2010**, *39*, 410.

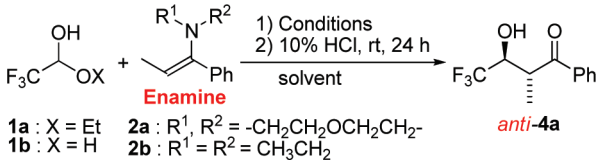
(6) Funabiki, K. In *Fluorine-Containing Synthons*; Soloshonok, V., Ed.; ACS Symposium Series 911; Oxford University Press/American Chemical Society: Washington, DC, 2005; p 342.

(7) Funabiki, K.; Hashimoto, W.; Matsui, M. *Chem. Commun.* **2004**, 2056.

(8) (a) Funabiki, K.; Yamamoto, H.; Nagaya, H.; Matsui, M. *Tetrahedron Lett.***2006**, *47*, 5507. (b) Funabiki, K.; Matsui, M. *Current Fluoroorganic Chemistry*; Soloshonok,V., Mikami, K., Yamazaki, T., Welch, J. T., Honek, J. F., Eds.; ACS Symposium Series 949; Oxford University Press/American Chemical Society: Washington, DC, 2007; p 141. Saito and Yamamoto also reported the same results of chloral with cycloalkanones; see ref 4a.

DOI: 10.1021/jo101733j Published on Web 12/03/2010

TABLE 1. Optimization of the Reaction Conditions for *anti*-Selective Synthesis of 4a[a]

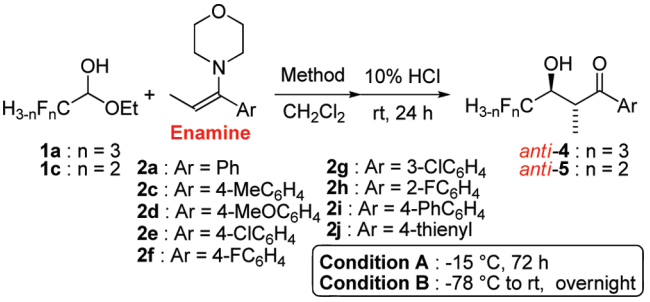


entry	1	2	solvent	temp (°C), time (h)	yield (%)[b]	(*syn*:*anti*)[c]
1	**1a**	**2a**	hexane	rt, 24	63	18:82
2	**1a**	**2a**	hexane	0, 48	39	11:89
3	**1a**	**2a**	hexane	−15, 120	27	9:91
4	**1a**	**2a**	hexane	−78 to rt[d]	21	10:90
5	**1a**	**2a**	toluene	−78 to rt[d]	43	19:81
6	**1a**	**2a**	CH_2Cl_2	−78 to rt[d]	63	**6:94**[e]
7[f]	**1a**	**2a**	CH_2Cl_2	−78 to rt[d]	70	**10:90**[e]
8[f]	**1a**	**2a**	CH_2Cl_2	−15, 72	71	**4:96**[e]
9	**1a**	**2b**[g]	CH_2Cl_2	−78 to rt[d]	13	17:83
10[f]	**1b**	**2a**	CH_2Cl_2	−78 to rt[d]	17	**4:96**[e]
11	**1b**	**2a**	CH_2Cl_2	−15, 72	24	**4:96**[e]

[a]Conditions: CF_3CHO ethyl hemiacetal **1a** or hydrate **1b** (1 mmol), enamine **2** (1 mmol, *E*/*Z* = 98/2), solvent (4 mL). [b]Yields of isolated products. [c]Determined by ^{19}F NMR analysis of the crude reaction mixture. [d]Overnight. [e]After column chromatography, the de of **4a** was >98%. [f]**1a** (3 equiv) was used. [g]*E*/*Z* = 89/11.

Initially, upon treatment of CF_3CHO ethyl hemiacetal **1a** with 1 equiv of enamine **2a** (*E*:*Z* = 98:2), prepared from propiophenone with morpholine, in hexane at room temperature for 24 h, followed by hydrolysis with 10% HCl aq at room temperature, 4,4,4-trifluoro-3-hydroxy-2-methyl-1-phenyl-1-butanone (**4a**) was obtained in 63% yield with *anti*-selectivity[9] (*syn*:*anti* = 18:82) (Table 1, entry 1). The results of the reaction of hemiacetal **1a** with enamines **2a** under various reaction conditions are summarized in Table 1. When reaction of CF_3CHO ethyl hemiacetal **1a** with the propiophenone enamine **2a** is performed at 0 and −15 °C for long time periods (48 and 120 h), the aldol product **4a** is generated in respective yields of 39% and 27% and with *syn*:*anti* diastereomer ratios of 11:89 and 9:91, respectively (entries 2 and 3). In addition, when hexane is used as solvent for this reaction carried out from −78 °C to room temperature overnight, **4a** is formed in yields and diastereoselectivities that are similar to those resulting from use of the shortest reaction time (entry 4). Among the solvents examined (hexane, toluene, and CH_2Cl_2), the use of CH_2Cl_2 for reaction of **1a** with enamines **2a** leads to formation of **4a** in a satisfactory yield (63%) and a high *anti*-selectivity (*syn*:*anti* = 6:94, entry 6). For the reaction in toluene, the aldol product **4a** is produced in 43% yield with a lower *anti*-selectivity than seen when either hexane or CH_2Cl_2 is employed as solvent (entry 5). When the amount of hemiacetal **1a** is increased to 3 equiv, the efficiencies for formation of fluorinated phenones **4a** are increased (entry 7). Importantly, reaction of enamine **2a** with 3 equiv of **1a** at −15 °C for 72 h gives **4a** in 71% yield with the highest observed diastereoselectivity (entry 8). Enamine **2b** carrying a diethylamino group in place of morpholino-substituted **2a** was not suitable for the reaction, because of decreasing diastereoselectivity (entry 9). Reactions of the hydrate of CF_3CHO **1b** with enamine **2a** under the optimized conditions produce **4a** in low yields (17−24%) but with high diastereoselectivities. The reason for the significant decrease in yield seen in reactions of the hydrate **1b** is not yet clear (entries 10 and 11).

TABLE 2. *anti*-Selective Synthesis of 4,4,4-Trifluoro- and 4,4-Difluoro-1-aryl-3-hydroxy-2-methyl-1-butanones 4, 5[a]



entry	1	2	condition	Ar	yield of 4, 5 (%)[b]	(*syn*:*anti*)[c]
1	**1a**	**2a**	A	Ph	**4a**: 71	4:96 (>98% de)
2	**1a**	**2a**	B	Ph	**4a**: 70	10:90 (>98% de)
3	**1a**	**2c**	A	4-MeC_6H_4	**4b**: 67	5:95 (>98% de)
4	**1a**	**2d**	A	4-$MeOC_6H_4$	**4c**: 87	7:93 (>98% de)
5	**1a**	**2e**	A	4-ClC_6H_4	**4d**: 86	7:93 (>98% de)
6	**1a**	**2f**	A	4-FC_6H_4	**4e**: 64	6:94 (>98% de)
7	**1a**	**2g**[d]	B	3-ClC_6H_4	**4f**: 72	10:90 (>98% de)
8	**1a**	**2h**[e]	B	2-FC_6H_4	**4g**: 76	10:90 (>98% de)
9	**1a**	**2i**[f]	B	4-PhC_6H_4	**4h**: 63	8:92 (>98% de)
10	**1a**	**2j**[g]	A	2-thienyl	**4i**: 74	7:93 (>98% de)
11	**1c**	**2a**	A	Ph	**5a**: 73	12:88

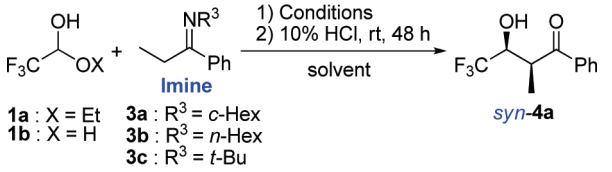
[a]Conditions: ethyl hemiacetal **1a,c** (3 mmol), enamine **2** (1 mmol, *E*/*Z* = 98/2), CH_2Cl_2 (4 mL). [b]Combined yields of isolated *anti*- and *syn*-products. [c]Determined by ^{19}F NMR analysis of the crude reaction mixture. Values in parentheses are the de of **4** after column chromatography. [d]*E*/*Z* = 97/3. [e]*E*/*Z* = 97/3. [f]*E*/*Z* = 99/1. [g]*E*/*Z* = 96/4.

The results of reactions between hemiacetal **1a,c** and various enamines **2** run under optimized conditions are summarized in Table 2.

Reactions of hemiacetal **1a** with various enamines **2a,c,d** derived from phenones containing phenyl, 4-methylphenyl, and 4-methoxyphenyl groups proceed smoothly to give the corresponding 4,4,4-trifluoro-3-hydroxy-2-methyl-1-aryl-1-butanones **4a,b,c** in 67−87% yields with high *anti*-selectivities under the optimized reaction conditions (entries 1−4). Other enamines, carrying 4-chlorophenyl, 4-fluorophenyl, 3-chlorophenyl, 2-fluorophenyl, and biphenyl groups also participated well in the reaction of **1a** to produce the corresponding 4,4,4-trifluoro-3-hydroxy-2-methyl-1-aryl-1-butanones **4d,e,f,g,h** in 63−86% yields with high *anti*-selectivities under either of the optimized reaction conditions (entries 5−9). The reactions of **1a** with enamine **2i** having a heteroaromatic group, such as a 2-thienyl substituent, at −15 °C for 72 h proceed smoothly to give the corresponding products **4i** in 74% yield and with high *anti*-selectivity (entry 10). Notably, in all cases of **4**, good to excellent *anti*-selectivities are observed, and the major diastereomers (>98% de) can be readily separated by using silica gel column chromatography. Finally, reaction of difluoroacetaldehyde (CHF_2CHO) ethyl hemiacetal **1c** with enamine **1a** generates the corresponding difluoromethyl-aldol product **5a** in 73% yield with slightly lower diastereoselectivity (*syn*:*anti* = 12:88) than is observed with the trifluoro-substituted analogue, due to the lower bulkiness of the difluoromethyl group compared with trifluoromethyl group (entry 11).[10] Unfortunately,

(9) The relative configurations were determined by NMR, according to the literature: (a) Ishii, A.; Kojima, J.; Mikami, K. *Org. Lett.* **1999**, *1*, 2013. (b) Ishii, A.; Mikami, K. *J. Fluorine Chem.* **1999**, *97*, 51.

TABLE 3. Optimization of the Reaction Conditions for *syn*-Selective Synthesis of 4a[a]



entry	1	3	solvent	temp (°C), time (h)	yield (%)[b]	(*syn*:*anti*)[c]
1	**1a**	**3a**	hexane	rt, 24	75	80:20
2	**1a**	**3a**	hexane	0, 48	27	84:16
3	**1a**	**3a**	hexane	−15, 120	tr	
4	**1a**	**3a**	hexane	−78 to rt[d]	45	84:16
5	**1a**	**3b**	hexane	−78 to rt[d]	30	72:28
6	**1a**	**3c**	hexane	−78 to rt[d]	63	88:12
7	**1a**	**3c**	toluene	−78 to rt[d]	68	**90:10**[e]
8	**1a**	**3c**	CH_2Cl_2	−78 to rt[d]	62	85:15[e]
9	**1b**	**3c**	toluene	−78 to rt[d]	62	92:8[e]

[a]Conditions: CF_3CHO ethyl hemiacetal **1a** (1 mmol), imine **3a** (1 mmol), solvent (4 mL). [b]Yields of isolated products. [c]Determined by ^{19}F NMR analysis of the crude reaction mixture. [d]Overnight. [e]After column chromatography, the de of **4a** was >98%.

the diastereomers of difluoro-substituted **5a** cannot be separated by using flash chromatography.

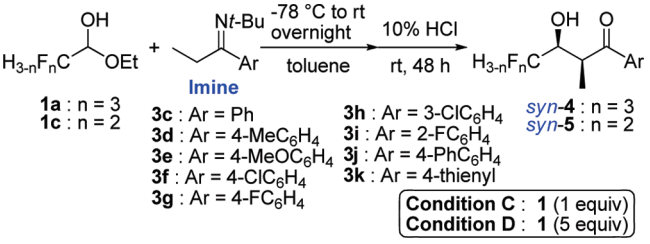
Next, treatment of CF_3CHO ethyl hemiacetal **1a** with 1 equiv of imine **3a**, prepared by the reaction of propiophenone with cyclohexylamine in hexane at room temperature for 24 h, followed by hydrolysis with 10% HCl aq at room temperature, gives rise to **4a** in 75% yield in a *syn*:*anti* ratio of 80:20 (Table 3, entry 1).

When lower reaction temperatures (0 or −15 °C) and longer reaction times (48 and 120 h) are employed, **4a** is formed in dramatically reduced yields and only slightly higher diastereoselectivity (*syn*:*anti* = 84:16, entries 2 and 3). When this reaction is performed using hexane as solvent from −78 °C to room temperature (overnight), the aldol product **4a** is generated in 45% yield with a *syn*:*anti* diastereoselectivity of 84:16 (entry 4). The findings of this effort show that substituents on the imine nitrogen strongly influence both the yields and isomer ratios seen in these processes (entries 4, 5, and 6). For example, imine **3b** that possesses a *n*-butyl group on nitrogen reacts with a decreased efficiency and a low diastereoselectivity (entry 5). In addition, reaction of hemiacetal **1a** with imine **3c**, carrying a *N*-*tert*-butyl group, gives product **4a** in 63% yield and with better diastereoselectivity (*syn*:*anti* = 88:12, entry 6). Finally, the effect of solvent on this reaction was examined. The use of toluene led to both the highest yield and diastereoselectivity (*syn*:*anti* = 90:10, entry 7). In contrast, reaction in CH_2Cl_2 was not effective since a slightly lower yield and a much lower diastereoselectivity (*syn*:*anti* = 85:15) were observed (entry 8). The CF_3CHO hydrate **1b** also reacts with imine **3c** to produce **4a** in 62% yield with the same high *syn*-selectivity (*syn*:*anti* = 92:8).

The results of reactions of hemiacetal of CF_3CHO or CHF_2CHO **1a,c** with various imines **3** under optimized conditions are also given in Table 4.

Imines **3d,e**, containing 4-methylphenyl and 4-methoxyphenyl substituents, participate in smooth reactions with 1 equiv of **1a** in toluene from −78 °C to room temperature

TABLE 4. *syn*-Selective Synthesis of 4,4,4-Trifluoro- and 4,4-Difluoro-1-aryl-3-hydroxy-2-methyl-1-butanones 4, 5[a]



entry	1	3	condition	Ar	yield of 4, 5 (%)[b]	(*syn*:*anti*)[c]
1	**1a**	**3c**	C	Ph	**4a**: 68	90:10 (>98% de)
2	**1a**	**3d**	C	4-MeC_6H_4	**4b**: 60	90:10 (>98% de)
3	**1a**	**3e**	C	4-$MeOC_6H_4$	**4c**: 63	91:9 (>98% de)
4	**1a**	**3f**	C	4-ClC_6H_4	**4d**: 64	82:18 (>98% de)
5	**1a**	**3g**	C	4-FC_6H_4	**4e**: 61	80:20 (>98% de)
6	**1a**	**3h**	D	3-ClC_6H_4	**4f**: 52	79:21 (>98% de)
7	**1a**	**3i**	D	2-FC_6H_4	**4g**: 64	86:14 (>98% de)
8	**1a**	**3j**	D	4-PhC_6H_4	**4h**: 31	70:30 (>98% de)
9	**1a**	**3k**	D	2-thienyl	**4i**: 58	80:20 (>98% de)
10	**1c**	**3c**	C	Ph	**5a**: 56	65:35

[a]Conditions: ethyl hemiacetal **1a,c**, imine **3** (1 mmol), toluene (4 mL). [b]Combined yields of isolated *anti*- and *syn*-products. [c]Determined by ^{19}F NMR analysis of the crude reaction mixture. Values in parentheses are the de of **4** after column chromatography.

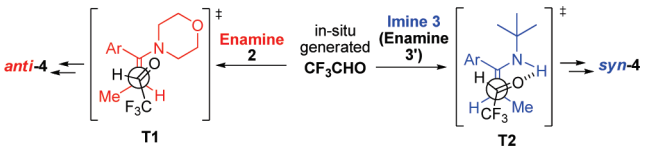


FIGURE 1. Proposed transition states.

overnight. These processes produce aldol products **4b,c** in 60−63% yields and with high *syn*-diastereoselectivities (*syn*:*anti* = 90:10−91:9) (entries 2 and 3). 4-Chlorophenyl and 4-fluorophenyl containing imines **3f,g** react with hemiacetal **1a** under the same conditions to give the corresponding products **4d,e** in similar good yields and lower *syn*-diastereoselectivities (entries 4 and 5). The reaction of imines **3 h,i,j,k** carrying the 3-chlorophenyl, 2-fluorophenyl, biphenyl, and 2-thienyl groups was achieved by the use of an excess amount (5 equiv) of hemiacetal **1a** to give the corresponding products **4f,g** in 31−64% yields with lower *syn*-diastereoselectivities (entries 6−9). Finally, reaction of CHF_2CHO ethyl hemiacetal **1c** with the imine **3c** also proceeds smoothly to give the corresponding difluoromethyl-aldol product **5a** in 56% yield, but with a lower diastereoselectivity (*syn*:*anti* = 65:35, entry 10).

For the reversal of diastereoselectivity in the reaction of hemiacetal **1a** with enamines **2** or imines **3**, it could be realized by the explanation that in situ generated CF_3CHO[5] reacts with enamine **2** or **3′** (MeCH=C(Ar)NH*t*-Bu), which is a tautomer of imine **3**, through the open transition state (**T1** or **T2**), as shown in Figure 1. According to the literature of not only the aldol reaction of CF_3CHO[11] but also chiral pyrrolidines or primary amines-catalyzed *anti*- or *syn*-selective asymmetric direct aldol reaction of fluorine-free aldehydes,[2,3] the trifluoromethyl group is situated in *antiperiplanar*

(10) Tafts, K. W., Jr *Steric Effects in Organic Chemistry*; Newman, M. S., Ed.; John Wiley & Sons: New York, 1956; p 556.

(11) Makino, M.; Iseki, K.; Fujii, K.; Oishi, S.; Hirano, T.; Kobayashi, Y. *Tetrahedron Lett.* **1995**, *36*, 6527.

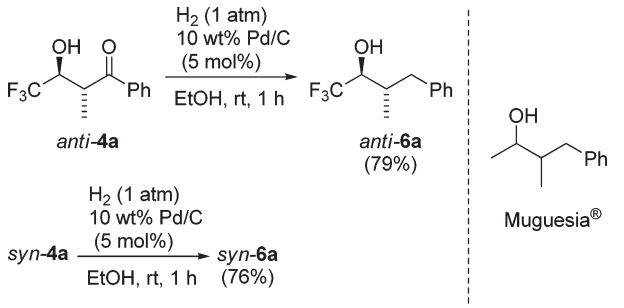


FIGURE 2. Synthesis of both diastereomers of the trifluoromethylated analogue of Muguesia.

of the carbon−carbon double bond of enamine **2**, because of electrostatic interaction of the trifluoromethyl group in **T1** and **T2**, which minimizes the gauche interaction between the trifluoromethyl and the methyl group on the forming bond. In **T2**, not only the steric interaction between the aryl and the methyl groups[2a,3a] but also hydrogen bonding between the oxygen atom and amino group are also important for *syn*-selectivities.

Unfortunately, 4-nitrobenzaldehyde as a fluorine-free aldehyde did not react with enamine **2a** or imine **3a** under the same conditions. The reaction of ethyl glyoxalate with enamine **2h** in toluene under the same conditions (condition B) occurred to give ethyl 4-(2-fluorophenyl)-2-hydroxy-3-methyl-4-oxobutanoate in 69% yield (*syn*:*anti* = 33:67). However, the reaction of imine **3i** with ethyl glyoxalate (condition D) gave ca. 40% yield of intermediate, followed by the hydrolysis to give a trace amount of the aldol product, since the retro-aldol reaction should occurr during the hydrolysis. These results indicate that the potent electron-withdrawing property and bulkiness of the trifluoromethyl group accelerates the metal-free carbon−carbon bond formation reaction with high diastereoselectivities.

Finally, synthesis of both diastereomers of trifluoromethylated analogue **6a** of Muguesia,[12] which is a kind of odorant, was carried out (Figure 2). Reductive decarbonylation of thus-obtained *anti*- and *syn*-**4a** in the presence of a catalytic amount (5 mol %) of Pd (10 wt %) on carbon with hydrogen (1 atm) in ethanol at room temperature for 1 h smoothly occurred without epimerization to give *anti*- and *syn*-1,1,1-trifluoro-3-methyl-4-phenylbutan-2-ol (**6a**) in 76−79% yields. Odor evaluation of racemic **6a** was not carried out at the present time.

In conclusion, a complete reversal of the diastereoselectivity has been observed for the carbon−carbon bond formation reactions of the ethyl hemiacetal of CF_3CHO with either enamines and imines, derived from propiophenones. These reactions, which produce 4,4,4-trifluoro-3-hydroxy-2-methyl-1-aryl-1-butanones, serve as the first reliable, metal-free, complementary *anti*- and *syn*-selective routes for the preparation of the aldol products. The extension of this method to the asymmetric complementary direct aldol reaction with aromatic ethyl ketones are currently being investigated.

(12) Abate, A.; Brenna, E.; Fuganti, C.; Gatti, F. G.; Giovenzana, T.; Malpezzi, L.; Serra, S. *J. Org. Chem.* **2005**, *70*, 1281.

Experimental Section

Typical Procedure (Condition A) for the Synthesis of *anti*-4,4,4-Trifluoro-3-hydroxy-2-methyl-1-aryl-1-butanones. To a solution of CF_3CHO ethyl hemiacetal **1a** (3 mmol, 0.432 g) in CH_2Cl_2 (4 mL) was added enamine **2a** (1 mmol, 0.203 g) at −15 °C under an argon atmosphere. After being stirred at −15 °C for 72 h, the mixture was hydrolyzed with 10% HCl aq (4 mL) at room temperature for 24 h, extracted with Et_2O (30 mL × 3), dried over Na_2SO_4, and concentrated under vacuum. After the distribution of the diastereomers was determined by ^{19}F NMR, the residue was subjected to chromatography on silica gel using hexane−EtOAc (10:1) give 4,4,4-trifluoro-3-hydroxy-2-methyl-1-phenyl-1-butanone (**4a**) (0.165 g, 71%). *anti*-4,4,4-Trifluoro-3-hydroxy-2-methyl-1-phenylbutan-1-one (*anti*-**4a**): IR (neat) 1682 (C=O), 3441 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (d, J = 7.32 Hz, 3H), 3.89 (dq, J = 7.32, 4.29 Hz, 1H), 4.20 (dquin, J = 7.64, 4.29 Hz, 1H), 4.73 (d, J = 8.29 Hz, 1H), 7.49−7.53 (m, 2H), 7.61−7.65 (m, 1H), 7.94−7.96 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 15.9 (s), 37.9 (s), 73.8 (q, J = 30.3 Hz), 125.0 (q, J = 283.4 Hz), 128.4 (s), 128.9 (s), 134.2 (s), 135.4 (s), 204.5 (s); ^{19}F NMR ($CDCl_3$, TFA) δ 0.99 (d, J = 7.64 Hz, 3F); HRMS (CI-FAB) found m/z 233.0788, calcd for $C_{11}H_{12}F_3O_2$ (M + H) 233.0790.

Typical Procedure (Condition C) for the Synthesis of *syn*-4. To a solution of **1a** (1 mmol, 0.144 g) in toluene (4 mL) was added imine **3c** (1 mmol, 0.189 g) at −78 °C under an argon atmosphere. After being stirred overnight from −78 °C to room temperature, the mixture was hydrolyzed with 10% HCl aq (4 mL) at room temperature for 48 h, extracted with Et_2O (30 mL × 3), dried over Na_2SO_4, and concentrated under vacuum. After the distribution of the diastereomers was determined by ^{19}F NMR, the residue was subjected to chromatography on silica gel using hexane−EtOAc (10:1) to give **4a** (0.158 g, 68%). *syn*-**4a**: IR (neat) 1684 (C=O), 3448 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (d, J = 7.28 Hz, 3H), 3.40 (br s, 1H), 3.77 (dq, J = 7.28, 3.54 Hz, 1H), 4.47 (dq, J = 6.83, 3.54 Hz, 1H), 7.40−7.46 (m, 2H), 7.53−7.58 (m, 1H), 7.84−7.91 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 11.8 (s), 40.0 (s), 70.1 (q, J = 30.9 Hz), 124.7 (q, J = 281.2 Hz), 128.6 (s), 129.0 (s), 134.0 (s), 134.7 (s), 203.0 (s); ^{19}F NMR ($CDCl_3$, TFA) δ 1.32 (d, J = 6.83 Hz, 3F); HRMS (CI) found m/z 233.0788, calcd for $C_{11}H_{12}F_3O_2$ (M + H) 233.0789.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research (C) (19550104) and Young Scientists (B) (14750665) of the Japan Society for the Promotion of Science (JSPS). We are grateful to Central Glass Co., Ltd., for the gift of CF_3CHO hemiacetal as well as for financial support. We thank not only Professors T. Ishihara and T. Konno of the Kyoto Institute of Technology but also Dr. Tomoko Yajima of Ochanomizu University for the HRMS measurements.

Supporting Information Available: Detailed procedures and characterization of all of the compounds; ^1H and ^{13}C NMR spectra for **4**, **5**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.