JOC Notes

In Situ Generation of 3,3,3-Trifluoropropanal and Its Use for Carbon−Carbon Bond-Forming Reactions

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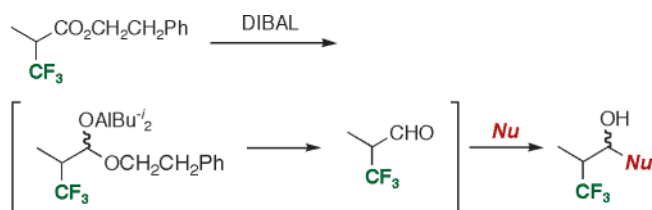
The DIBAL reduction of 2-phenylethyl 3,3,3-trifluoro-2-methylpropionate **2** at −78 °C afforded the aluminum acetal **3**, and this intermediate, on worming up to 0 °C, was found to slowly decompose into the corresponding aldehyde **4**, which smoothly reacted with appropriate nucleophiles in a one-pot manner in good to excellent yields with up to 93% diastereoselectivity.

Taking the strong electron-withdrawing properties of a trifluoromethyl (CF_3) group into account,[1] it is not difficult to understand that the lability of the hydrogen atom α to the carbonyl moiety in 3,3,3-trifluoropropanals is due to the double activation by both the CF_3 and C=O groups. In fact, abstraction of this hydrogen atom was readily performed even by relatively

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(1) The electron-withdrawing nature of a CF_3 group is sometimes compared with the one of an ester functional group. For example, the pK_a values of CHF_2CF_3 and CHF_2CO_2Me were reported to be 28.2 and 25, respectively. See: Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3. Moreover, pK_a values of CF_3CO_2H and HO_2CCO_2H were 0.5 and 1.271. *Lange's Handbook of Chemistry*, 14th ed.; Dean, J. A., Ed.; McGraw-Hill: New York, 1992; Section 8.

SCHEME 1
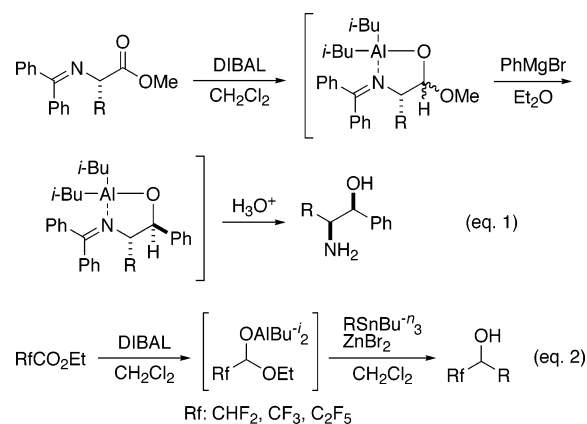
weak bases such as tertiary amines,[2] and the resultant anionic intermediates usually follow the smooth delivery of a fluoride ion to furnish 3,3-difluoroprop-2-enal. The fate of this unstable intermediate is most likely to lose all fluorine atoms by a repetitive addition−elimination sequence of appropriate nucleophiles at the highly positively charged terminal sp^2 carbon atom possessing two fluorine atoms.[3]

Our interest in stereoselective construction of trifluorinated aldol structures,[4] R^1-CH(CF_3)-CH(OH)-R^2, prompted us to investigate the utilization of 2-substituted 3,3,3-trifluoropropanals as substrates that apparently open the direct access to these targets by just a single-step reaction with various types of enolates or their equivalents. In connection with the fact that the corresponding 3,3,3-trifluoropropionates are relatively more stable and readily synthesized by various methods,[5] we envisaged the application of the procedure by Polt and co-workers (Scheme 1, eq 1),[6] which allowed us to utilize the in situ generated aluminum acetals for the reaction with appropriate nucleophiles. However, despite its usefulness, to the best of our knowledge, only limited examples could be found in the

(2) $C_nF_{2n+1}CH_2CHO$ was found to follow dehydrofluorination only by treating with Et_3N to give (Z)-$C_{n-1}F_{2n-1}CF$=CHCHO stereoselectively. Lévêque, L.; Le Blanc, M.; Pastor, R. *Tetrahedron Lett.* **1998**, *39*, 8857. A similar situation was noticed under 1 mol/L NaOH/EtOH conditions. Hedhli, A.; Baklouti, A.; Cambon, A. *Tetrahedron Lett.* **1994**, *35*, 6877.
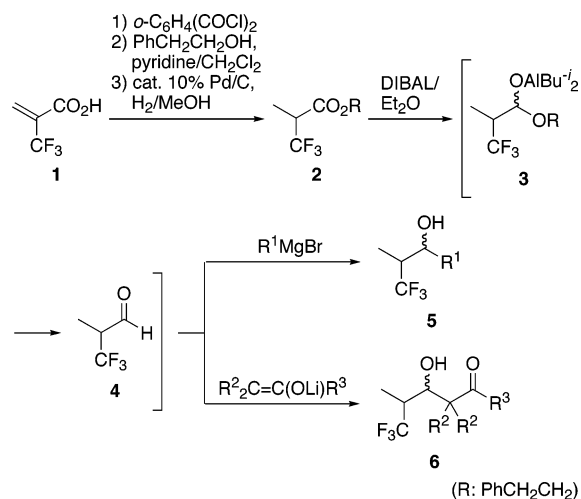
(3) The F_2C=C carbon is known to possess strongly positive charges. See: (a) Ueki, H.; Chiba, T.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **2004**, *69*, 7616. (b) Ichikawa, J.; Wada, Y.; Fujiwara, M.; Sakoda, K. *Synthesis* **2002**, 1917.

(4) These targets were successfully prepared by a very few research groups. (a) Hanamoto, T.; Fuchikami, T. *J. Org. Chem.* **1990**, *55*, 4969. (b) Angert, H.; Czerwonka, R.; Reissig, H.-U. *Liebigs Ann.* **1997**, 2215. (c) Iseki, K.; Kuroki, Y.; Nagai, T.; Kobayashi, Y. *Chem. Pharm. Bull.* **1996**, *44*, 477. (d) Konno, T.; Yamazaki, T.; Kitazume, T. *Tetrahedron* **1996**, *52*, 199. (e) Konno, T.; Umetani, H.; Kitazume, T. *J. Org. Chem.* **1997**, *62*, 137. (f) Loh, T.-P.; Li, X.-R. *Eur. J. Org. Chem.* **1999**, 1893.

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SCHEME 2

(R: PhCH₂CH₂)

TABLE 1. Reaction of Various Nucleophiles to in Situ Prepared Aldehyde 4[a]

Pro[b]	R[1]	R[2]	R[3]	isolated yield (%)	diastereomer andi:syn
5a[c]	Ph(CH₂)₂			complex	
5a[d]	Ph(CH₂)₂			78	83:17
5a[e]	Ph(CH₂)₂			75	83:17
5b[f]	Ph			50	86:14
5c	PhC≡C[g]			66	72:28
6a		H	Ph	84	61:39
6b		H	EtO	64	71:29
6c[e,h]		Mw	Me	76	90:10
6c[h]		me	Me	71	93:7
6d[h]		H	Me₂N	41	65:35
6e		me	Me	63	87:13

[a] To an ethereal solution of **2** was added 1.05 equiv of DIBAL and the mixture was stirred at −78 °C for 0.5 h, when 2 equiv of a nucleophile was added at the same temperature and the mixture was stirred at 0 °C for 1.5 h. [b] Product. [c] THF was employed as the solvent. [d] Reaction temperature at −78 and −40 °C after addition of a nucleophile furnished the product **5a** in 22% and 68% NMR yields, respectively. [e] The commercially available aldehyde **4** was employed instead of the in situ generated aluminum acetal. [f] See ref 11. [g] The corresponding Li salt was used. [h] Their *anti* preference was assumed from the other results.

literature for direct employment of these intermediary acetals,[7] mainly because success of this partial reduction is highly substrate-dependent.[8]

On the other hand, it is well-known that poly- and perfluorinated aldehydes show clear tendency to form the stable hydrate structure by their significantly electron-withdrawing nature, which effectively decreases the LUMO energy level and thus strongly increases the nucleophile-accepting ability of the carbonyl group.[9] For example, the efficient C−C bond formation of trifluoroacetate-based aluminum acetals was recently realized by Ishihara's group[9b] using allylic stannanes in the presence of appropriate Lewis acids at 40 °C, which is in sharp contrast to the case of the Polt procedure proceeding at −78 °C (Scheme 1, eq 2). At this stage, we anticipated that insertion of an additional CH₂ group between CF₃ and carbonyl moieties would render the thermodynamic stability of the corresponding aluminum acetals lower. If this is the case, these intermediates such as **3** would be converted into the aldehyde **4** at higher temperature, allowing smooth reaction with appropriate nucleophiles. Realization of this pathway provides ready access to the desired CF₃-containing aldol structure without need to isolate such unstable fluorinated aldehydes.[10]

Throughout the text, 2-phenylethyl 3,3,3-trifluoro-2-methyl-propionate **2** was employed as the representative substrate because it is readily accessible in a simple three-step procedure starting from the commercially available trifluorinated methacrylic acid **1**[11] (Scheme 2). Partial reduction of this ester **2** was performed at −78 °C using a slight excess (1.05 equiv) of DIBAL in Et₂O, and the TLC analysis of the reaction mixture after 0.5 h at that temperature clearly demonstrated the production of 2-phenylethanol and total disappearance of **2**. This

experimental evidence was interpreted as the result of the smooth half reduction of **2** by DIBAL, and the resultant aluminum acetal **3** was, as our expectation, stable enough at temperatures as low as −78 °C. If this is not the case, decomposition of **3** would mainly produce **4**, which should predominantly consume DIBAL, leading to incomplete conversion of **2** under the conditions employed.

At the next stage, successfully generated aluminum acetal intermediate **3** was reacted with PhCH₂CH₂MgBr as the representative nucleophile. It appeared that the desired transformation occurred more cleanly in Et₂O rather than in THF. After 30 min of DIBAL reduction at −78 °C, this Grignard reagent was added, and the temperature was raised to 0 °C just by changing the dry ice−acetone bath to an ice bath. Stirring for a further 1.5 h eventually furnished the desired product **5a** in 78% isolated yield in a diastereomeric ratio of *anti*:*syn* = 83:17. Less clean reaction in THF would be mainly due to its higher coordinating ability to Al, which rendered the Al−O bond weaker, resulting in destabilization of the acetal **3**.

As we have successfully disclosed this optimized condition at the steps of the acetal formation and its reaction with the Grignard reagent, various nucleophiles were employed for proving the usefulness of this process by way of the unique intermediate **3**, whose results were collected in Table 1. Good to excellent chemical yields were attained in every instance with good to excellent levels of diastereoselectivity.

Relative stereochemistries of the adducts **5** and **6** were unambiguously determined by chemical correlation (Scheme 3) except for the adduct **5b**, which was already reported previously.[4a] Chromatographic purification of **6a** enabled us to partially resolve the diastereomer mixture, and the fraction collected was found to be composed of a 95:5 mixture of *anti* and *syn* isomers. Because this sample was fortunately solidified and recrystallization afforded a good quality of crystal, the X-ray crystallographic analysis was carried out to clearly demonstrate that the major isomer of **6a** possessed an *anti* relative stereochemical relationship between the hydroxy- and CF₃-attached carbon atoms. At the next stage, the carbonyl group in **6a** and the C−C triple bond in **5c** were independently reduced[12] to yield the same compound **5a**, whose NMR comparison led to the conclusion

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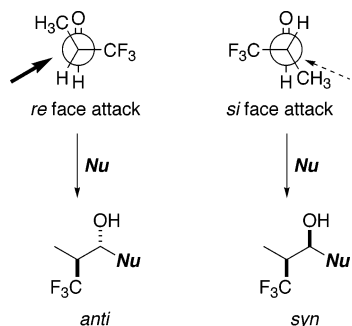
(10) Ishihara also used 3,3,3-trifluoro-2-(tosyloxy)propionate as the substrate, and the aluminum acetal generated was reacted with allylic stannanes. Ishihara, T. *J. Synth. Org. Chem. Jpn.* **1999**, *57*, 313.

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SCHEME 3

SCHEME 4

re face attack   *si* face attack

anti   *syn*
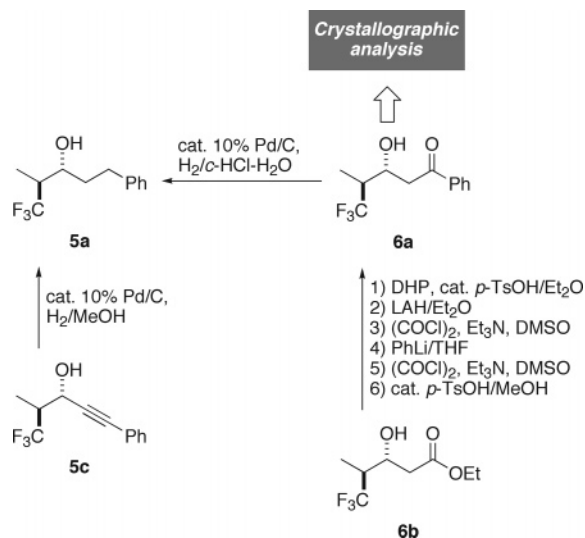
that all **5a** synthesized from **5c** and **6a** and directly obtained from **2** were totally identical. Thus, it was clarified that **5a** and **5c** were also constructed in an *anti* preferential fashion. The major isomer of **6b** was also proved to be *anti* as the result of its elaborated transformations into **6a**.

For obtaining mechanistic support, the commercially available aldehyde **4** was employed for the reaction with PhCH$_2$CH$_2$MgBr and the enolate from isobutyrate under the same conditions. As shown in Table 1, results were obtained that were basically identical in terms of both the chemical yields and diastereo-selectivities to the ones by way of the in situ generated reactive species **3**. In connection with the various *anti*:*syn* ratios recorded in the same table (from 61:39 to 93:7),[13] it is highly expected for this reaction to proceed by way of the aldehyde **4** by slow conversion of the intermediary acetal **3** during increase of the reaction temperature.

As described above, the major diastereoisomers in Table 1 possessed an *anti* relative stereochemical relationship, and this selectivity was consistently explained by the well-accepted Felkin−Anh transition state models (Scheme 4).[14] Thus, the most electron-withdrawing and sterically demanding CF$_3$ group[15]

would reasonably occupy a position perpendicular to the carbonyl group. The incoming nucleophile would encounter the unfavorable steric interference with the methyl group when it approaches to the carbonyl *si* face, and as a result energetically more favorable attack from the *re* face led to the predominant production of the *anti* stereoisomers in every instance. Entry of two methyl groups to R^2 in enolates resulted in higher *anti* preference, which is understood by an increase of steric bulkiness at the reaction site to more effectively differentiate the two diastereomeric transition states. The opposite is also true when lithium acetylide from phenylacetylene was used. The selectivity dropped since this molecule possesses sterically less bulky linear structure.

In this note, we have shown a novel carbon−carbon bond-forming method by utilization of in situ generated α-CF$_3$-aldehyde **4** for reaction with organometallic species as well as various types of enolates. Avoidance of any direct handling of the usually labile aldehydes such as **4** is one of the most important advantages of our process, which will widely open the way to construct unique CF$_3$-containing aldol structures whose general preparation procedure has not established yet.

Experimental Section

General Procedure for Reaction of 2-Phenylethyl 2-Methyl-3,3,3-trifluoropropionate 2 by Way of Aluminum Acetal Intermediate 3. To an ethereal solution (5 mL) of 2-phenylethyl 2-methyl-3,3,3-trifluoropropionate **2**[16] (246 mg, 1.00 mmol) was added at −78 °C a 1 mol/L hexane solution of DIBAL (1.05 mL, 1.05 mmol), and the mixture was stirred for 0.5 h at that temperature. An appropriate nucleophile (2.00 mmol), preformed alkylmetals or enolates by the conventional methods, was added to this solution, and after changing the dry ice−acetone bath to an ice bath, the whole solution was stirred for 1.5 h at 0 °C. The reaction was quenched by addition of 3 mol/L aqueous HCl, then the resultant crude materials were extracted with Et$_2$O twice, and the ethereal layer was dried over anhydrous MgSO$_4$. Evaporation of the volatiles was performed, and the resultant crude oil was purified by silica gel column chromatography to give the final product as a diastereoisomeric mixture.

(2*S**,3*R**)-1,1,1-Trifluoro-2-methyl-5-phenylpentan-3-ol (5a): 78% yield as a separable 83:17 *anti*:*syn* diastereomer mixture. Major isomer: R_f 0.53 (Hex/AcOEt = 10:3); ^{1}H NMR δ 1.16 (3 H, d, *J* = 7.1 Hz), 1.62 (1 H, d, *J* = 4.7 Hz), 1.65−1.76 (1 H, m), 1.84−1.97 (1 H, m), 2.22 (1 H, dqq, *J* = 2.3, 7.3, 9.5 Hz), 2.67 (1 H, ddd, *J* = 6.7, 9.5, 13.7 Hz), 2.85 (1 H, ddd, *J* = 5.2, 9.8, 13.7 Hz), 4.04 (1 H, dddd, *J* = 2.0, 4.5, 4.6, 9.1 Hz), 7.18−7.33 (5 H, m); ^{13}C NMR δ 6.4 (q, *J* = 2.8 Hz), 32.2, 36. 5, 42.9 (q, *J* = 24.1 Hz), 67.9 (q, *J* = 2.6 Hz), 125.8, 127.8 (q, *J* = 279.7 Hz), 128.2, 128.3, 141.2; ^{19}F NMR δ 91.5 (d, *J* = 9.5 Hz); IR (neat) ν 3579, 3449, 3022, 2950, 2552, 1604, 1498, 1458, 1270, 1137, 937, 700 cm^{-1}. Anal. Calcd for C$_{12}$H$_{15}$F$_3$O: C, 62.06; H, 6.51. Found: C, 61.72; H, 6.65. Minor isomer: R_f 0.44 (Hex/AcOEt = 10:3); ^{1}H NMR δ 1.13 (3 H, d, *J* = 7.1 Hz), 1.72−1.96 (3 H, m), 2.38 (1 H, dqq, *J* = 5.5, 7.3, 9.3 Hz), 2.68 (1 H, ddd, *J* = 6.9, 9.6, 13.7 Hz), 2.85 (1 H, ddd, *J* = 5.0, 9.4, 14.4 Hz), 3.85 (1 H, ddt, *J* = 2.9, 5.5, 9.6 Hz), 7.18−7.33 (5 H, m); ^{13}C NMR δ 8. 9 (q, *J* = 2.9 Hz), 32.0, 34.8, 43.9 (q, *J* = 23.9 Hz), 69.5 (q, *J* = 2.0 Hz), 125.7, 127.5 (q, *J* = 279.9 Hz), 128.1, 128.5, 141.4; ^{19}F NMR δ 93.3 (d, *J* = 9.5 Hz); IR (neat) ν 3421, 3027, 2932, 2364, 1943, 1869, 1752, 1604,

(12) Burdeska, K. *Synthesis* **1982**, 940.

(13) When the intermediate **3** was treated with trimethylsilyl trifluoromethanesulfonate (TMSOTf) in the presence of pyridine, formation of 2-phenylethyl trimethylsilyl acetal **7** was observed by ^{1}H and ^{19}F NMR as a diastereomeric mixture in a range of 65:35 to 70:30 (due to its inherent instability, we have not successfully isolated it yet). This is clearly supported that the present reaction is not the S$_N$2-type process.

(14) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191.

(15) This group is considered to possess a volume similar to that of the nonfluorinated isobutyl group on the basis of the revised Taft's E_s value, $E_s{}'$. See: MacPhee, J. A.; Panaye, A.; Dubois, J.-E. *Tetrahedron* **1978**, *34*, 3553.

(16) Yamazaki, T.; Ichige, T.; Kitazume, T. *Collect. Czech. Chem. Commun.* **2002**, *67*, 1479.

1497, 1380, 1266, 1175, 1136, 1046, 938, 750, 699 cm^{-1}. Anal. Calcd for $C_{12}H_{15}F_3O$: C, 62.06; H, 6.51. Found: C, 62.04; H, 6.92.

Reactions of Nucleophiles with 2-Methyl-3,3,3-trifluoropropanal. An appropriate nucleophile (2 mmol) was added to an ethereal solution (5 mL) containing 2-methyl-3,3,3-trifluoropropanal **4** (0.127 g, 1.000 mmol) freshly distilled with a few drops of BF$_3$· OEt$_2$ at −78 °C, and the whole solution was stirred for 1.5 h at 0 °C. Usual workup and purification by silica gel furnished the adduct, whose physical properties were consistent with those obtained by way of the aluminum acetal as shown above.

Determination of Relative Stereochemistry. Transformation of 6a into 5a. To a mixture of concentrated HCl (60 mg) and H$_2$O (0.84 mL) containing 10% Pd/C (21 mg) was added **6a** (0.049 g, 0.199 mmol; major:minor = 95:5), and the whole mixture was stirred overnight at room temperature under H$_2$ atmosphere. Filtration and evaporation of this mixture afforded a crude material from which **5a** (0.042 g, 0.181 mmol; major:minor = 95:5) was isolated by column chromatography in 90% yield. The physical properties of the obtained material were consistent with those of **5a** as shown above.

Transformation of 5c into 5a. To a MeOH solution (3 mL) containing 10% Pd/C (6 mg) was added **5c** (0.160 g, 0.701 mmol; major:minor = 78:22), and the whole mixture was stirred overnight at room temperature under H$_2$ atmosphere. Filtration and evaporation of this mixture afforded a crude material from which **5a** (0.151 g, 0.650 mmol; major:minor = 80:20) was isolated by column chromatography in 93% yield. The physical properties of the obtained material were consistent with those of **5a** as shown above.

Transformation of 6b into 6a. To an Et$_2$O solution (10 mL) containing a catalytic amount of *p*-TsOH were successively added **6b** (0.214 g, 0.999 mmol; major:minor = 76:24) and dihydropyran (0.170 g, 2.021 mmol), and the whole mixture was stirred for 4 h at room temperature. After quenching with saturated aqueous NaHCO$_3$, the usual workup gave a crude material that was used for the next step without further purification. The resultant crude THP ether was reduced with LAH (28.5 mg, 0.75 mmol) in Et$_2$O (10 mL) at 0 °C, and the reaction was continued for 3 h at room temperature. The reaction was stopped by the addition of saturated aqueous NaSO$_4$, and the usual workup gave a crude alcohol that was subjected to the usual Swern oxidation conditions. To this aldehyde was added at −78 °C PhLi (1.05 mmol) in THF (5 mL), and the stirring was continued for 1 h at the same temperature. After addition of H$_2$O the workup gave a crude alcohol that was again oxidized to the corresponding ketone by way of the Swern procedure, and the THP protection was removed by the conventional method (cat. *p*-TsOH in MeOH) to give the crude material. Purification by column chromatography afforded 0.056 g (0.227 mmol, 23% total yield) of **6a** as a 76:24 diastereomer mixture. The physical properties of the obtained material were consistent with those for **6a** as shown above.

Supporting Information Available: Experimental details and spectral data for the compounds **5b,c**, **6a**−**e**, and **7** and Cartesian coordinates of the compound **6a** obtained by X-ray crystallographic analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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