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Preparation and Synthetic Application of a Novel Ketene Silyl Acetal of Methyl Trifluoropyruvate

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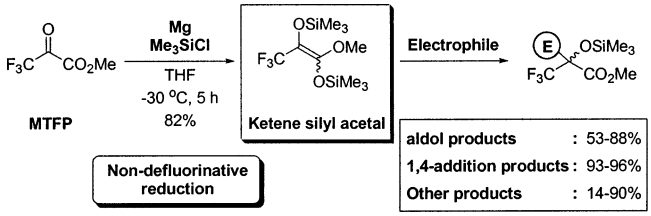
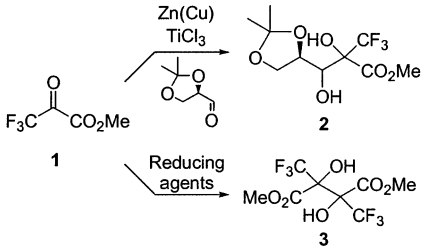


A novel trifluoromethyl ketene silyl acetal (**4**) of methyl trifluoropyruvate (**1**) was prepared in 82% yield by metal Mg reduction in a (TMS)Cl/THF system. Subsequent carbon−carbon bond formation such as Mukaiyama aldol, Michael addition, and other nucleophilic reactions of **4** at the trifluoromethylated carbon with various electrophiles gave various coupling products in high yields.

Introduction

Trifluoropyruvates and their derivatives have been widely used in the fields of medicinal, agricultural, and advanced materials.[1] Their molecular transformations have been extensively investigated. In particular, carbon−carbon bond formation at the α-carbon to the CF_3 group is an efficient route to quaternary trifluoromethylated compounds. Nonetheless, such carbon−carbon bond formations have been mostly attained by reactions with nucleophiles: alkylation with Grignard reagents[2] or acetylene anion,[3] ene reaction with alkenes,[4] aldol reaction with enolates,[5] and Friedel−Crafts reactions.[6] On the other hand, only two reactions of **1** with electrophiles have been reported: Zn(Cu)-promoted cross-coupling of **1** with protected glyceraldehyde to give diol **2**[7] and reductive pinacol coupling of **1**, leading to diols **3** (Scheme 1).[8−10]

SCHEME 1. Nucleophilic Addition of Trifluoropyruvates



It is quite relevant from the viewpoint of synthetic organofluorine chemistry to exploit the strategic variations for the utilization of **1** as a nucleophile. To attain such a purpose, dipole inversion of either substrates or reagents with infusion of electrons would be necessary for carbon−carbon bond formation of **1** with electrophiles. Fortunately, the pyruvate **1** has a low-lying LUMO, due

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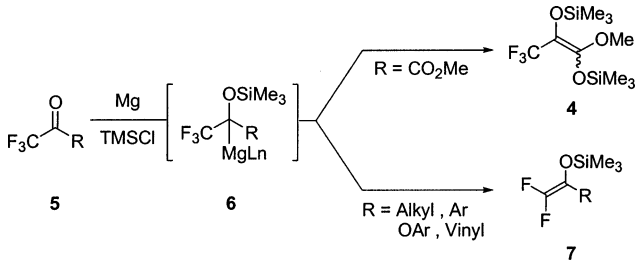
SCHEME 2. Strategy for Preparation of Ketene Silyl Acetal



to the electron-withdrawing effect of the CF_3 group, and easily accepts electrons. Moreover, we have developed a facile method to infuse electrons to carbonyl moieties by the use of a Mg−(TMS)Cl (chlorotrimethylsilane) system.[11] On this basis, we are interested in the idea that the ketene silyl acetal **4** is a reduced pyruvate, a potential anion equivalent of **1**, which can react with electrophiles at the keto carbonyl carbon.

Ketene silyl acetals are, in general, prepared by base-catalyzed enolization of esters followed by trapping of the enolates with (TMS)Cl.[12] However, α-keto esters have never been used for this purpose. Our key idea relies on a practical synthesis of ketene silyl acetal **4** from **1** by Mg metal reduction and utilization of **4** as a trifluoromethyl synthetic block.

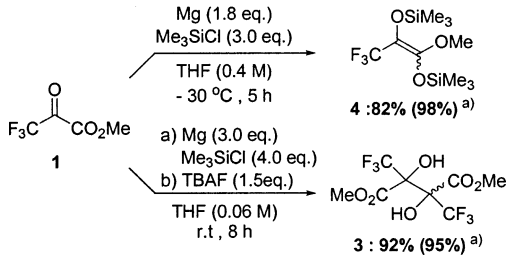
The magnesium−(TMS)Cl system has been used for C−F bond activation of the trifluoromethyl group attached to π-electron systems such as carbonyl, iminyl, and phenyl groups. Trifluoromethyl ketones,[13] imines,[14] esters,[15] and aromatic compounds[16] can be transformed to difluoro enol silyl ethers, difluoro enamines, α-silyl acetates, and difluorobenzylsilanes, respectively. We were interested in seeing whether the Mg-promoted C−F bond activation of trifluoromethyl ketones could be applicable for nondefluorinative functionalization of **5**. Namely, attachment of the carboalkoxy group on the trifluoroacetyl moiety as an anion-stabilizing group would retard defluorination and thus promote the formation of ketene silyl acetal, although trifluoroacetyl derivatives **5** bearing alkyl, aryl, phenoxy, and vinyl groups undergo defluorination exclusively, leading to **7** via **6**, on treating them with metal Mg (Scheme 2).

We describe here a new preparation of a novel CF_3-substituted ketene silyl acetal (**4**) by reductive transformation of **5** (R = CO_2Me) in a Mg−(TMS)Cl/THF system, and nucleophilic additions of **4** with various electrophiles.

Results and Discussion

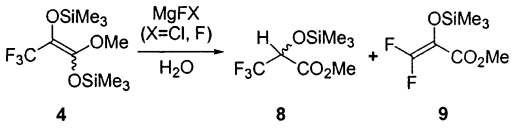
Mg(0)-Promoted Preparation of Ketene Silyl Acetal 4 from Methyl Trifluoropyruvate (MTFP, 1). 1 was at first subjected to Mg-promoted reduction (Scheme 3). Contrary to the conventional reactions of trifluoromethylated ketones, a defluorination product was not obtained. Instead, pinacol **3** was produced selectively as a diastereomeric mixture at room temperature in 92% isolated yield with a diastereomeric ratio of 56:44. The reaction at −30 °C gave ketene silyl acetals **4** selectively in 82% yield as a mixture of stereoisomers.

SCHEME 3. Mg-Promoted Transformation of MTFP (1)



[a] Isolated yield. The yield in parentheses was analyzed by ^{19}F NMR integration of product **4** relative to hexafluorobenzene as an internal standard.

SCHEME 4. Formation of Byproducts 8 and 9 from 4



The ^{19}F NMR analyses of the crude reaction mixture suggested a quantitative production of **4** at a reaction temperature of −30 °C. However, ketene silyl acetal **4** was found to be both moisture- and oxygen-sensitive under acidic conditions so that about 20% of the product **4** was lost during the workup procedure. For the effective isolation of **4**, exposure of the products to water, oxygen, and Lewis acid must be carefully avoided. In particular, $MgCl_2$ generated in the reaction should be completely removed from ketene silyl acetal **4**; otherwise, the yield of **4** is drastically lowered. The addition of 1,4-dioxane for complexation with magnesium salt to form an insoluble $MgCl_2$−dioxane complex polymer, followed by Celite filtration under an argon atmosphere, was found to be effective in removing the $MgCl_2$ salt.[17] Complete removal of $MgCl_2$ made the purification of **4** very easy. The condensed crude ketene silyl acetals **4** were finally purified by distillation. The pure ketene silyl acetals **4** are stable even on distillation at 120 °C and on being kept in a mixture of benzene and water at room temperature for 1 h. Unless $MgCl_2$ was completely removed, a large amount of **4** was transformed to a mixture of byproducts **8** and **9**, and the isolated yield of **4** was poor (Scheme 4).

Optimization of the Mukaiyama Aldol Reaction of 4. The chemically pure **4** was successfully prepared, which was usable for further reactions. First, the effect of Lewis acid in the Mukaiyama aldol reaction of **4** was optimized, and the results are summarized in Table 1.

Mukaiyama aldol reaction of **4** with aldehydes was successfully conducted under conventional (TMS)OTf-promoted conditions, and the desired aldol compounds were obtained in high yields. The silyl acetal **4** was

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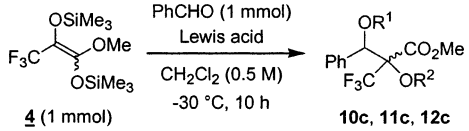
TABLE 1. Effects of a Lewis Acid on the Mukaiyama Aldol Reaction of 4[a]



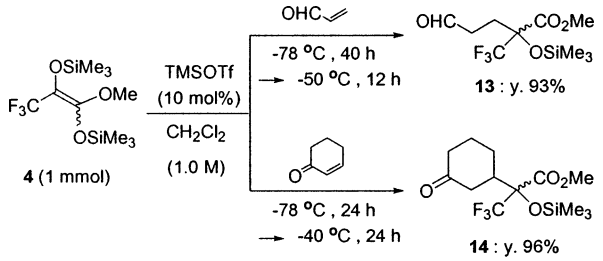
entry	Lewis acid (equiv)	results (yield, %)[b] 10c[c]	11c[c]	12c[c]	8	9
1	(TMS)OTf (0.05)	94	5	ND	1	ND
2	$ZnBr_2$ (1.2)	60	2	ND	31	3
3	ZnI_2 (1.3)	54	trace	ND	33	1
4	$AlCl_3$ (1.2)	26	45	23	1	4
5	$SnCl_4$ (1.2)	trace	38	ND	20	39
6	$TiCl_4$ (1.1)			decomp		

[a] ND means not detected. [b] After workup, the yields were analyzed by ^{19}F NMR and were calculated by ^{19}F NMR integration of the product relative to hexafluorobenzene as an internal standard. [c] **10c**, $R^1 = R^2 = SiMe_3$; **11c**, $R^1 = H$, $R^2 = SiMe_3$; **12c**, $R^1 = R^2 = H$.

converted to **10c** under Mukaiyama aldol reaction conditions with $ZnBr_2$, ZnI_2, and $AlCl_3$, but the products were, somewhat, complicated. The starting substrate was easily hydrolyzed to give a silylated lactate (**8**) via desilylative protonation when $ZnBr_2$ and ZnI_2 were used. The hydrolysis of **4** would be promoted by water, which probably comes from the moisture-contaminated zinc halides. Complete removal of such water from $ZnBr_2$ and ZnI_2 by the conventional drying method is difficult. In the reaction with $AlCl_3$, desilylation occurred without regioselectivity on workup of the reaction mixture. Monosilylated aldol compound **11c** easily underwent retro-aldol reaction when **11c** was submitted to silica gel chromatography for isolation. The reaction of **4** with $SnCl_4$ gave a partial formation of protonated **8** and a considerable amount of defluorinated compound **9**. The reaction with $TiCl_4$ was so strong that the reaction resulted in complete decomposition of ketene silyl acetal **4**, and no desired compound was obtained. On the basis of these results, (TMS)OTf was found to be the best of the Lewis acids so far examined for the Mukaiyama aldol reaction with various electrophiles.

Scope of the Mukaiyama Aldol Reaction with Aldehydes. Next, the scope of the aldehyde electrophiles in the Mukaiyama aldol reaction of ketene silyl acetals **4** was examined. The results are summarized in Table 2.

SCHEME 5. Results of the Mukaiyama–Michael Reaction

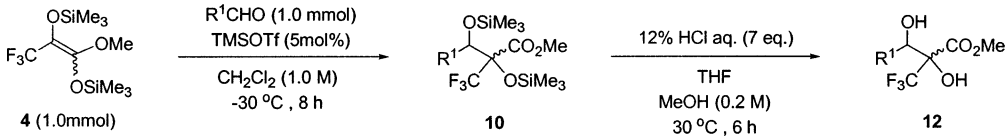


The desired cross-aldol compounds were obtained as diastereomeric mixtures in high yields. Disilylated aldol products of **10a** and **10b** were stable under neutral conditions and easily isolable by column chromatography with neutralized silica gel. However, disilylated compounds **10c–e** were hydrolyzed in part and **10f–h** were mostly hydrolyzed, when isolated. They seemed to be converted into monosilylated compounds during the silica gel chromatographic isolation process. The monosilylated compounds were also unstable and decomposed gradually via retro-aldol reaction. **10a–h** were converted to the stable desilylated diols **12a–h** under hydrolysis conditions in a homogeneous MeOH–THF–HCl(aq) system. The desilylation in a heterogeneous system such as CH_2Cl_2–HCl(aq) proceeded very slowly, thus promoting retro-aldol reaction, which resulted in a low yield of the desired diols. Aldol products **10g** and **10h** from aliphatic aldehydes were not isolated due to easy desilylation and retro-aldol reaction. The NMR, GC–MS, and GC analyses of the reaction mixture obviously indicated that aldol compounds were once formed.

Mukaiyama–Michael Reaction with α,β-Unsaturated Carbonyl Compounds. Next, 1,4-additions of ketene silyl acetals **4** to α,β-unsaturated carbonyl compounds were studied. The results are shown in Scheme 5.

A lower reaction temperature was found essential to avoid unfavorable double Mukaiyama–Michael reaction and to improve the yields of the target compounds **13** and **14**. Thus, a longer reaction time was needed. However,

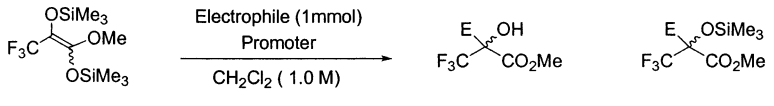
TABLE 2. Results of the Mukaiyama Aldol Reaction of 4 with Aldehydes



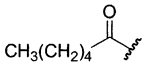
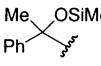
entry	R^1	product **10**, yield[a] (%)	[THF] (M)	product **12**, yield[b] (%)
1	4-$CH_3OC_6H_4$	**10a**, 97 (98)	0.2	**12a**, 87
2	3-ClC_6H_4	**10b**, 86 (98)	0.3	**12b**, 79
3	Ph	**10c**, 60 (94)	0.4	**12c**, 79
4	4-$CF_3C_6H_4$	**10d**, 58 (87)	0.5	**12d**, 68
5	furyl	**10e**, 50 (87)	0.5	**12e**, 73
6	4-$CH_3C_6H_4$	**10f**, 20 (88)	0.5	**12f**, 88
7	$Ph(CH_2)_2$	**10g** (57)[c]	0.2	**12g**, 53
8	$CH_3CH{=}CH$	**10h** (76)[c]	0.5	**12h**, 64

[a] Isolated yield. Yields in parentheses are GC yields, which were calculated by the percentage of GC integration of products **10**. [b] Isolated yield. Yields of compounds **12** were overall yields from **4** without isolation of **10**. [c] The disilyl compounds **10g** and **10h** were too unstable to be purified, so they were converted to diols **12g** and **12h** without a purification process.

TABLE 3. Reaction with Various Electrophiles



4 (1 mmol) **15** **16**

entry	electrophile (1mmol)	promoter (mol%)	additive	conditions (°C , time)	product	yield (%)[a]
1	PhCOCl	TBAF (120)	MS-3A	-20 , 10 min	 **: 15a**	86
2	$CH_3(CH_2)_4COCl$	TBAF (120)	MS-3A	-20 , 10 min	 **: 15b**	72
3	$PhCH(OMe)_2$	TMSOTf (10)	-	-20 , 2 h	 **: 16a**	90
4	PMPCH=NMs [b]	$B(C_6F_5)_3$ (0.02)	-	20 , 48 h	 **: 16b**	15
5	$PhCOCH_3$	$B(C_6F_5)_3$ (0.01)	-	20 , 48 h	 **: 16c**	14

[a] Isolated yield. [b] PMP means 4-$CH_3OC_6H_4$.

in the reaction of other Michael acceptors such as acrylonitrile, methyl acrylate, and crotonaldehyde, Michael addition products were not obtained. The rate of polymerization of these Michael acceptors seemed to be faster than that of the reaction with **4** under a wide range of temperature conditions.

Nucleophilic Reactions of 4 with Other Electrophiles. Nucleophilic reactions of **4** with other electrophiles were examined. The results are summarized in Table 3.

Acylation with acyl halides proceeded quite smoothly by TBAF in the presence of molecular sieves 3A (MS-3A), and α,α-disubstituted β-keto esters **15a** and **15b** were readily obtained in high yields (entries 1 and 2). In the absence of MS-3A, the reaction gave β-keto esters in low yield with byproduction of a large amount of hydrolyzed compound **8**. Mukaiyama-type aldol reaction with benzaldehyde dimethyl acetal gave coupling compound **16a** in 90% yield. However, Mannich-type coupling with an aldimine as an electrophile proceeded very slowly under the usual conditions using (TMS)OTf as Lewis acid. Here, tris(pentafluorophenyl)borane was found to be effective for this reaction of **4** with the electrophiles; the desired compound **16b** was obtained in 15% yield. (TMS)OTf did not promote the Mukaiyama aldol reaction of **4** with acetophenone, but the use of $B(C_6F_5)_3$ enabled preparation of **16c** in 14% yield.

Conclusion

Reduction of methyl trifluoropyruvate (**1**) with Mg metal provided novel ketene silyl acetal **4** at −30 °C in 82% yield, while giving pinacol compound **3** at room temperature selectively, but no difluoro enol silyl ether **9** was obtained. Ketene silyl acetals **4** could be used for C−C bond formation by nucleophilic addition to electrophiles such as aldehydes, acyl halides, and aldimines. The simple preparation of silyl acetal **4** and the scope of its applications for C−C bond formation with various electrophiles suggested the high potential of **4** as a trifluoromethyl-substituted building block which behaves as a synthetic equivalent of a carbanion species at the keto carbonyl group of trifluoropyruvate.

Experimental Section

Preparation of a Pinacol (2,3-Dihydroxy-2,3-bistrifluoromethylsuccinic Acid Dimethyl Ester, 3). A suspension of (TMS)Cl (0.5 mL, 4.0 mmol) in freshly distilled THF (9 mL) and Mg (73 mg, 3.0 mmol) was kept at 20−30 °C under an argon atmosphere, MTFP (**1**; 156 mg, 1.0 mmol) in dry THF (1 mL) was added dropwise with a cannula (1 h) at 20−30 °C under an argon atmosphere. The reaction mixture was stirred for an additional 7 h at 20−30 °C. After removal of excess (TMS)Cl and THF in vacuo (ca. ∼30 mmHg), the reaction mixture was poured into 20 mL of 10% HCl(aq) at 0 °C. Then, the resulting mixture was extracted with Et_2O (10 mL × 3), and the organic layer was washed with brine. After removal of the Et_2O in vacuo (ca. ∼50 mmHg), 3 mL of THF and 0.5 mL of 10% HCl(aq) were added to the resulting oil. To the solution was added TBAF in THF (1.5 mL, 1.5 mmol) dropwise with a cannula (10 min) at 10−20 °C, and the reaction mixture was stirred for an additional 1 h at 20−30 °C. After evaporation of most of the THF, 5 mL of 10% HCl(aq) was added to the residue, the reaction mixture was extracted with Et_2O (10 mL × 6), and the organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, purification of the crude product by chromatography on silica gel (*n*-hexane: Et_2O = 8:1) afforded **3** (144 mg, 92%) as a white solid: diastereomeric mixture (56:44 by ^{19}F NMR); mp 102−104 °C; IR (KBr) 3510, 3000, 1750, 1455 cm^{-1}; ^1H NMR (300 MHz) δ 3.98 (s, 6H, major), 4.00 (s, 6H, minor), 4.52 (s, 2H, minor), 4.53 (s, 2H, major); ^{19}F NMR (282 MHz) δ 88.6 (s, 3F, minor), 88.9 (s, 3F, major); EI MS *m/z* (relative intensity) 255 (M^+ − 59, 9), 158 (70), 69 (61), 59 (100). Anal. Calcd for $C_8H_8F_6O_6$: C, 30.59; H, 2.57. Found: C, 30.44; H, 2.67.

Preparation of Ketene Silyl Acetals (1-Methoxy-1-trimethylsilyloxy-2-trifluoromethyl-2-trimethylsilyloxy-

ethene, 4). Under an argon atmosphere, a mixture of Mg (turnings) (2.8 g, 115.3 mmol) and (TMS)Cl (20.9 g, 192.2 mmol) was treated by ultrasound irradiation prior to the reaction. To the mixture of Mg and (TMS)Cl in dry THF (180 mL) was added **1** (10.0 g, 64.1 mmol) in dry THF (20 mL) dropwise with a cannula (1 h) at −30 °C under an argon atmosphere, and the reaction mixture was stirred for an additional 4 h at −30 °C. To the reaction mixture was added 1,4-dioxane (40 mL) at −30 °C, and then the reaction mixture was stirred for an additional 1 h at room temperature. Residual magnesium and dioxane−$MgCl_2$ salt were separated by filtration under an argon atmosphere through completely dried Celite with an argon atmosphere pressure, and the filtrate was washed with freshly dried *n*-heptane (200 mL). THF, *n*-heptane, (TMS)Cl, and a half amount of 1,4-dioxane were removed under reduced pressure (15 mmHg) at 0 °C, and a solution of *n*-heptane (50 mL) was added. The resulting salt was removed by filtration under an argon atmosphere through completely dried Celite. Evaporation of the filtrate and distillation (1 mmHg, 45−55 °C) provided a colorless oil of **4** (15.9 g, 82%) as a mixture of *E*/*Z* isomers (62:38 by ^{19}F NMR): IR (neat) 2968, 2900, 2850, 1698, 1450 cm^{-1}; ^{1}H NMR (300 MHz) (*E* isomer) δ 0.19 (s, 9H), 0.25 (s, 3H), 3.64 (s, 3H), (*Z* isomer) δ 0.19 (s, 9H), 0.27 (s, 9H), 3.60 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) (*E* isomer) δ 97.1 (s, 3F), (*Z* isomer) δ 97.8 (s, 3F); ^{13}C NMR (151 MHz, C_6D_6) (*E* isomer) δ −0.6, −0.2, 56.0, 112.4 (q, J = 35.1 Hz), 123.7 (q, J = 270.1 Hz), 150.5, (*Z* isomer) δ −0.3, −0.1, 57.6, 113.6 (q, J = 35.7 Hz), 123.9 (q, J = 270.1 Hz), 151.0; EI MS *m*/*z* (relative intensity) 302 (M^+, 5), 195 (60), 73 (100). Anal. Calcd for $C_{10}H_{21}F_3O_3Si_2$: C, 39.71; H, 7.00. Found: C, 39.76; H, 7.00.

Typical Procedure for (TMS)OTf-Catalyzed Mukaiyama Aldol Reactions of Ketene Silyl Acetals 4 with Aldehydes. To a mixture of **4** (302 mg, 1.0 mmol) and aldehyde (1.0 mmol) in dichloromethane (1 mL) which was cooled to −30 °C under an argon atmosphere was added (TMS)OTf (11 mg, 5 mol %), and then the resulting mixture was stirred for an additional 8 h. Then, the reaction mixture was poured into 2% $NaHCO_3$(aq), and the organic products were extracted with diethyl ether (Et_2O; 20 mL × 2). The organic layer was washed with brine and dried over Na_2SO_4. Purification of the product by silica gel column chromatography (*n*-hexane:Et_2O = 20:1) afforded **10**.

Data for 3,3,3-trifluoro-2-[phenyl(trimethylsilyloxy)-methyl]-2-trimethylsilyloxypropanoic acid methyl ester (10c): 60% yield; colorless oil; diastereomeric mixture (68:32 by ^{19}F NMR); IR (neat) 3040, 2968, 2908, 1772, 1763, 1498, 1456 cm^{-1}; ^{1}H NMR (300 MHz) δ −0.05 (s, 9H, minor), 0.01 (s, 9H, major), 0.05 (s, 9H, major), 0.21 (s, 9H, minor), 3.73 (s, 3H, major), 3.87 (s, 3H, minor), 5.24 (s, 1H, minor), 5.28 (s, 1H, major), 7.27−7.39 (m, 5H × 2, major and minor mixed); ^{19}F NMR (282 MHz, $CDCl_3$) δ 87.6 (s, 3F, minor), 89.8 (s, 3F, major); EI MS *m*/*z* (relative intensity) 393 (M^+ − 15, trace), 302 (trace), 179 (100), 73 (55). Anal. Calcd for $C_{17}H_{27}F_3O_4Si_2$: C, 49.98; H, 6.66. Found: C, 50.07; H, 6.87.

Data for 3,3,3-trifluoro-2-(1′-phenylhydroxymethyl)-2-trimethylsilyloxypropanoic acid methyl ester (11c): 5% yield; white powder; mp 69−70 °C; IR (neat) 3598, 3000, 2945, 1770, 1510, 1470, 1455 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.17 (s, 9H), 2.62 (d, J = 8.4 Hz, 1H), 3.90 (s, 3H), 5.15 (d, J = 8.1 Hz, 1H), 7.32−7.40 (m, 5H); ^{19}F NMR (282 MHz) δ 89.2 (s, 3F); EI MS *m*/*z* (relative intensity) 336 (M^+, trace), 320 (10), 230 (75), 214 (100), 195 (58), 138 (34), 107 (77), 77 (60), 73 (38). Anal. Calcd for $C_{14}H_{19}F_3O_4Si$: C, 49.99; H, 5.69. Found: C, 50.14; H, 5.49.

Typical Procedure for Desilylation of Mukaiyama Aldol Compounds. To a mixture of **10** (without purification, 1.0 mmol) in MeOH (5 mL) and THF (2−5 mL) was added 12% HCl(aq) (2.1 mL, 7 mmol), and then the resulting mixture was stirred for an additional 6 h at 30 °C. After evaporation of most of the MeOH and THF, the resulting residue was extracted with Et_2O (10 mL × 6). The organic layer was washed with brine and dried over Na_2SO_4. Purification of the product by silica gel column chromatography (*n*-hexane:Et_2O = 3:1) afforded **12**.

Data for 3,3,3-trifluoro-2-hydroxy-2-(1′-phenylhydroxymethyl)propanoic acid methyl ester (12c): 79% yield; white powder; diastereomeric mixture (66:34 by ^{1}H NMR); mp 88−90 °C; IR (neat) 3515, 3055, 2990, 1755, 1505, 1463, 1456 cm^{-1}; ^{1}H NMR (300 MHz) δ 2.53 (d, J = 9.0 Hz, 1H, minor), 2.84 (d, J = 8.4 Hz, 1H, major), 3.71 (s, 3H, major), 3.92 (s, 1H, major), 4.00 (s, 3H, minor), 4.14 (s, 1H, minor), 5.21 (d, J = 7.2 Hz, 1H, minor), 5.26 (d, J = 8.1 Hz, 1H, major), 7.32−7.49 (m, 5H × 2, major and minor mixed); ^{19}F NMR (282 MHz) δ 83.9 (s, 3F × 2, major and minor mixed); EI MS *m*/*z* (relative intensity) 247 (M^+ − 17, trace), 187 (8), 107 (100), 79 (91), 77 (48). Anal. Calcd for $C_{11}H_{11}F_3O_4$: C, 50.01; H, 4.20. Found: C, 50.30; H, 4.45.

(TMS)OTf-Catalyzed Mukaiyama−Michael Reaction of Ketene Silyl Acetal 4 with an α,β-Unsaturated Aldehyde (5-Oxo-2-trifluoromethyl-2-trimethylsilyloxypentanoic Acid Methyl Ester, 13). To a mixture of **4** (302 mg, 1.0 mmol) and acrolein (56 mg, 1.0 mmol) in dichloromethane (1 mL) which was cooled to −78 °C under an argon atmosphere was added (TMS)OTf (22 mg, 10 mol %), and then the resulting mixture was stirred for an additional 40 h. After being stirred at −50 °C for 12 h, the resulting mixture was poured into 2% $NaHCO_3$(aq), and the organic products were extracted with Et_2O (20 mL × 2). The organic layer was washed with brine and dried over Na_2SO_4. The residue was purified by silica gel column chromatography (*n*-hexane:Et_2O = 10:1) to afford **13** in 93% yield as a colorless oil: diastereomeric mixture (the diastereomeric ratio could not analyzed by ^{1}H NMR, ^{19}F NMR, and GC); IR (neat) 2968, 2905, 2850, 2740, 1762, 1730, 1444 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.17 (s, 9H × 2, major and minor mixed), 2.17−2.35 (m, 2H × 2, major and minor mixed), 2.42−2.64 (m, 2H × 2, major and minor mixed), 3.82 (s, 3H × 2, major and minor mixed), 9.74 (t, J = 0.9 Hz, 1H × 2, major and minor mixed); ^{19}F NMR (282 MHz) δ 84.9 (s, 3F × 2, major and minor mixed); EI MS *m*/*z* (relative intensity) 271 (M^+ − 15, trace), 211 (82), 89 (100), 77 (92), 73 (93), 59 (52). Anal. Calcd for $C_{10}H_{17}F_3O_4Si$: C, 41.95; H, 5.98. Found: C, 41.82; H, 5.76.

(TMS)OTf-Catalyzed Mukaiyama−Michael Reaction of Ketene Silyl Acetal 4 with an α,β-Unsaturated Ketone (3,3,3-Trifluoro-2-(3-oxocyclohexyl)-2-trimethylsilyloxypropanoic Acid Methyl Ester, 14). To a mixture of **4** (302 mg, 1.0 mmol) and 2-cyclohexen-1-one (96 mg, 1.0 mmol) in dichloromethane (1 mL) which was cooled to −78 °C under an argon atmosphere was added (TMS)OTf (22 mg, 10 mol %), and then the resulting mixture was stirred for an additional 24 h. After being stirred at −40 °C for 24 h, the resulting mixture was poured into 2% $NaHCO_3$(aq), and the organic products were extracted with Et_2O (20 mL × 2). The organic layer was washed with brine and dried over Na_2SO_4. The residue was purified by silica gel column chromatography (*n*-hexane:Et_2O = 10:1) to afford **14** in 96% yield as a colorless oil: diastereomeric mixture (75:25 by ^{19}F NMR); IR (neat) 2964, 2900, 2875, 1766, 1724, 1454, 1440 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.18 (s, 9H, minor), 0.19 (s, 9H, major), 1.38−1.69 (m, 3H × 2, major and minor mixed), 1.90−2.57 (m, 6H × 2, major and minor mixed), 3.79 (d, J = 0.3 Hz, 3H, minor), 3.82 (d, J = 0.9 Hz, 3H, major); ^{19}F NMR (282 MHz) δ 89.8 (s, 3F, major), 90.1 (s, 3F, minor); EI MS *m*/*z* (relative intensity) 311 (M^+ − 15, 92), 283 (52), 89 (100), 77 (74), 73 (93), 69 (68). Anal. Calcd for $C_{13}H_{21}F_3O_4Si$: C, 47.84; H, 6.49. Found: C, 47.62; H, 6.48.

Typical Procedure for TBAF-Promoted Preparation of Trifluoromethylated β-Keto Esters. To a mixture of **4** (302 mg, 1.0 mmol), dried MS-3A (400 mg), and acyl chloride (1.0 mmol) in dichloromethane (1 mL) which was cooled to −20 °C under an argon atmosphere was added TBAF/THF (1 mol/L solution, 1.2 mL, 1.2 mmol), and then the resulting mixture was stirred for an additional 10 min. After removal of MS-3A, the filtrate was poured into 5% HCl(aq), and the organic

products were extracted with Et_2O (20 mL × 2). The organic layer was washed with brine and dried over $MgSO_4$. Pure **15a** and **15b** were obtained as a clear and colorless oil from silica gel column chromatography (*n*-hexane:Et_2O = 10:1) as a diastereomeric mixture.

Data for 2-benzoyl-3,3,3-trifluoro-2-hydroxypropanoic acid methyl ester (15a): 86% yield; diastereomeric mixture (50:50 by ^{19}F NMR); colorless oil; IR (neat) 3090, 2968, 1775, 1748, 1700, 1610, 1592, 1460, 1445 cm^{-1}; ^1H NMR (600 MHz) δ 3.89 (s, 3H), 5.71 (q, J = 7.2 Hz, 1H), 7.50 (m, 2H), 7.65 (m, 1H), 8.12 (m, 2H); ^{19}F NMR (282 MHz) δ 88.2 (s, 3F), 88.3 (s, 3F); EI MS *m/z* (relative intensity) 262 (M^+, 12), 105 (100), 77 (44), 51 (20). Anal. Calcd for $C_{11}H_9F_3O_4$: C, 50.39; H, 3.46. Found: C, 50.30; H, 3.65.

(TMS)OTf-Catalyzed Mukaiyama-Type Aldol Reaction of Ketene Silyl Acetal 4 with Benzaldehyde Dimethyl Acetal (3,3,3-Trifluoro-2-[(1′-phenyl)methoxymethyl]-2-trimethylsilyloxypropanoic Acid Methyl Ester, 16a). To a mixture of **4** (302 mg, 1.0 mmol) and benzaldehyde dimethyl acetal (156 mg, 1.0 mmol) in dichloromethane (1 mL) which was cooled to −20 °C under an argon atmosphere was added (TMS)OTf (22 mg, 10 mol %), and then the resulting mixture was stirred for an additional 2 h. The resulting mixture was poured into 2% $NaHCO_3$(aq), and the organic products were extracted with Et_2O (20 mL × 2). The organic layer was washed with brine and dried over Na_2SO_4. The residue was purified by silica gel column chromatography (*n*-hexane:Et_2O = 15:1) to afford **16a** in 90% yield as a colorless oil: diastereomeric mixture (74:26 by ^{19}F NMR); IR (neat) 3100, 3060, 2990, 2940, 2855, 1780, 1765, 1508, 1468, 1450 cm^{-1}; ^1H NMR (300 MHz) δ 0.01 (s, 9H, major), 0.16 (s, 9H, minor), 3.16 (s, 3H, minor), 3.26 (s, 3H, major), 3.76 (s, 3H, major), 3.89 (s, 3H, minor), 4.71 (s, 1H, minor), 4.78 (s, 1H, major), 7.26−7.35 (m, 5H × 2, major and minor mixed); ^{19}F NMR (282 MHz) δ 88.4 (s, 3F, minor), 90.2 (s, 3F, major); EI MS *m/z* (relative intensity) 335 (M^+ − 15, trace), 187 (5), 121 (100), 77 (19). Anal. Calcd for $C_{15}H_{21}F_3O_4Si$: C, 51.41; H, 6.04. Found: C, 51.47; H, 5.96.

$B(C_6F_5)_3$-Catalyzed Mannich-Type Reaction of Ketene Silyl Acetal 4 with an Aldimine (3,3,3-Trifluoro-2-[(1′-methanesulfonylamino)(4-methoxyphenyl)methyl]-2-trimethylsilyloxypropanoic Acid Methyl Ester, 16b). To a mixture of $B(C_6F_5)_3$ (10 mg, 0.02 mol %) and *N*-(4-methoxybenzylidene)methanesulfonamide (213 mg, 1.0 mmol) in CH_2Cl_2 (1 mL) was added **4** (302 mg, 1.0 mmol), and then the resulting mixture was stirred for an additional 48 h at 20 °C. The resulting mixture was poured into 2% $NaHCO_3$(aq), and the organic products were extracted with CH_2Cl_2 (10 mL × 5). The organic layer was washed with brine and dried over Na_2SO_4. The residue was purified by silica gel column chromatography (*n*-hexane:Et_2O = 10:10) and recrystallization (*n*-hexane/Et_2O) to afford **16b** in 15% yield as a white powder: mp 173−175 °C; IR (KBr) 3310, 3050, 3000, 2940, 2880, 2855, 1780, 1625, 1526, 1455, 1430 cm^{-1}; ^1H NMR (300 MHz) δ 0.17 (s, 9H), 2.58 (s, 3H), 3.67 (s, 3H), 3.80 (s, 3H), 5.11 (d, J = 9.9 Hz, 1H), 5.45 (d, J = 9.9 Hz, 1H), 6.85 (dd, J = 2.1 Hz, J = 6.6 Hz, 1H), 7.20 (dd, J = 2.1 Hz, J = 6.6 Hz, 1H); ^{19}F NMR (282 MHz) δ 90.0 (s, 3F); EI MS *m/z* (relative intensity) 428 (M^+ − 15, trace), 214 (100), 134 (24), 77 (25). Anal. Calcd for $C_{16}H_{24}F_3NO_6SSi$: C, 43.33; H, 5.45; N, 3.16. Found: C, 43.41; H, 5.35; N, 3.26.

$B(C_6F_5)_3$-Catalyzed Mukaiyama Aldol Reaction of Ketene Silyl Acetal 4 with a Ketone (3-Phenyl-2-trifluoromethyl-2,3-bis(trimethylsilyloxy)butyric Acid Methyl Ester, 16c). To a mixture of $B(C_6F_5)_3$ (5 mg, 0.01 mol %) and acetophenone (120 mg, 1.0 mmol) in CH_2Cl_2 (1 mL) was added **4** (302 mg, 1.0 mmol), and then the resulting mixture was stirred for an additional 48 h at 20 °C. The resulting mixture was poured into 2% $NaHCO_3$(aq), and the organic products were extracted with Et_2O (20 mL × 2). The organic layer was washed with brine and dried over Na_2SO_4. The residue was purified by silica gel column chromatography (*n*-hexane:Et_2O = 20:1) in 14% yield as a colorless oil: diastereomeric mixture (60:40 by ^{19}F NMR); IR (KBr) 3140, 3100, 3000, 1770, 1515, 1462, 1454 cm^{-1}; ^1H NMR (300 MHz) δ −0.04 (s, 9H, major), 0.08 (s, 9H, major), 0.11 (s, 9H, minor), 0.16 (s, 9H, minor), 1.76 (s, 3H, minor), 1.85 (q, J = 2.1 Hz, 3H, major), 3.66 (s, 3H, major), 3.83 (s, 3H, minor), 7.23−7.46 (m, 5H × 2, major and minor mixed); ^{19}F NMR (282 MHz) δ 92.4 (s, 3F, minor), 92.9 (s, 3F, major); EI MS *m/z* (relative intensity) 363 (M^+ − 59, trace), 193 (100), 73 (61). Anal. Calcd for $C_{18}H_{29}F_3O_4Si_2$: C, 51.16; H, 6.92. Found: C, 51.14; H, 7.04.

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Supporting Information Available: ^1H and ^{19}F NMR, IR, and MS spectral and elemental analysis data of **10a,b**, **10d**−**f**, **12a,b**, **12d**−**h**, and **15b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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