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Lewis acid-promoted reaction of β,γ-unsaturated α,α-dimethoxy esters with silyl nucleophiles

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ABSTRACT

The Lewis acid-promoted reaction of β,γ-unsaturated α,α-dimethoxy esters, which are easily prepared by the acetalization of β,γ-unsaturated α-keto esters, with silyl nucleophiles is presented. By employing trimethylsilyl enolate and allyltrimethylsilane as nucleophiles, the BF_3-promoted reactions of a series of β,γ-unsaturated α,α-dimethoxy esters bearing aromatic and aliphatic substituents proceeded at the γ-position in an S_N2' manner to furnish γ-substituted α,β-unsaturated α-methoxy esters in good yields with high regioselectivity. In contrast, the reaction using trimethylsilyl cyanide predominantly occurred at the α-position, and the reaction of silyl hydride resulted in a mixture of α- and γ-regioisomers in favor of the γ-substitution products.

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In recent years, there has been considerable interest in the utilization of β,γ-unsaturated α-keto esters as versatile reaction partners in organic synthesis because a variety of highly functionalized structures can be easily constructed using these building blocks. For instance, they have been utilized as substrates in asymmetric aldol reactions,[1] reactive Michael acceptors,[2] electrophiles in Friedel–Crafts type reactions,[3] oxo-diene units in hetero-Diels–Alder reactions,[4] and components in other cycloaddition reactions.[5]

In earlier reports, we described an efficient method for preparing β,γ-unsaturated α-keto esters via the BF_3-mediated aldol reaction of 2-(trimethylsiloxy)acrylate esters with acetals,[6] and we utilized this procedure for several synthetic processes, including the chiral auxiliary-induced stereoselective reduction[7] and the addition of organometallic compounds to the α-carbonyl moieties.[8] As a continuation of our efforts in this field, we proposed examining a Lewis acid-promoted reaction of β,γ-unsaturated α-keto esters with silyl nucleophiles. Although the Lewis acid-mediated conjugate additions of silyl nucleophiles to α,β-unsaturated carbonyl compounds has been analyzed in previous studies as fundamental reactions in organic synthesis,[9] to our knowledge, no reports about a similar reaction of β,γ-unsaturated α-keto esters have appeared to date. Consequently, we initially examined the Lewis acid-promoted conjugate addition of silyl nucleophiles to β,γ-unsaturated α-keto esters. However, the reaction of methyl (*E*)-2-oxo-4-phenyl-3-butenoate (**1a**) with silyl nucleophiles in the presence of $BF_3{\cdot}OEt_2$ resulted in poor or moderate yield of the Michael adduct even after several attempts.[10] At this stage, we envisaged that if the dimethyl acetal derivatives of β,γ-unsaturated α-keto esters could be activated by Lewis acids, the addition of silyl nucleophiles might result in α-substituted β,γ-unsaturated α-methoxy esters (α-product) or γ-substituted α,β-unsaturated α-methoxy esters (γ-product), as shown in Scheme 1. The α-alkoxy acrylate moieties of the γ-products exist in several natural and synthetic products,[11] and compounds that possess the α-alkoxy acrylate moiety have been employed as key intermediates for the synthesis of biologically important compounds.[11b,12a,d,f,g,13] Several general methods are available for the preparation of α,β-unsaturated α-methoxy esters and most of them rely either on the Horner–Wadsworth–Emmons reaction using α-alkoxyphosphonoacetates[12] or on the condensation of alkoxyacetates with aldehydes under basic conditions.[11b,13] More recently, the $CrCl_2$-mediated Reformatsky-type reaction of 2,2-dichloro-2-methoxyacetate with aldehydes has been reported by Falck et al. for the facile preparation of α,β-unsaturated α-methoxy esters.[14] Herein, we report a novel approach for the preparation of α,β-unsaturated α-methoxy esters via addition of silyl nucleophiles to dimethyl acetal **2** in the presence of Lewis acid (Scheme 1).

The starting dimethyl acetals **2a–g** were prepared as *E*-isomers by treating (*E*)-β,γ-unsaturated α-keto esters **1a–g** with 2.4 equiv of trimethyl orthoformate and a catalytic amount of $TsOH{\cdot}H_2O$ in refluxing MeOH (Table 1).[15] *p*-Nitrophenyl-substituted β,γ-unsaturated α-keto ester **1e** showed lower reactivity though an improvement in yield was achieved by prolonging the reaction time. The reaction of alkyl-substituted β,γ-unsaturated α-keto esters **1f** and

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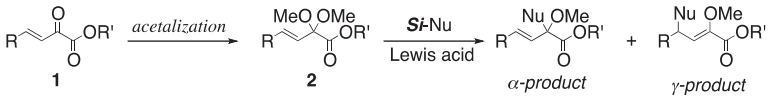


Scheme 1. Lewis acid-promoted reaction of β,γ-unsaturated α,α-dimethoxy esters with silyl nucleophiles.

1g resulted in moderate yields because of the formation of unidentified by-products.

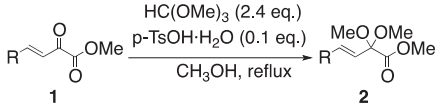
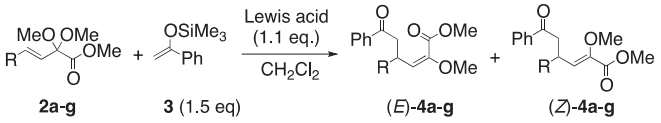


Table 1
Preparation of acetals **2a–g**

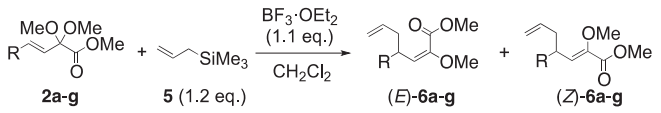
Entry	R	Time (h)	Product	Yield[a] (%)
1	C_6H_5	4.5	**2a**	91
2	*p*-$MeOC_6H_4$	1	**2b**	98
3	*p*-MeC_6H_4	3	**2c**	92
4	*p*-ClC_6H_4	1.5	**2d**	95
5	*p*-$NO_2C_6H_4$	47	**2e**	88
6	$PhCH_2CH_2$	5.5	**2f**	53
7	*c*-C_6H_{11}	6	**2g**	59

[a] Isolated yields.

We initiated our experiment by screening suitable Lewis acids for the reaction of methyl (*E*)-2,2-dimethoxy-4-phenyl-3-butenoate (**2a**) with silyl enolate **3**. Several representative results are summarized in Table 2, entries 1–4. Each reaction afforded only γ-product **4a** and no α-regioisomer was observed. Among the Lewis acids examined, $BF_3{\cdot}OEt_2$ was identified as the most effective, providing γ-product **4a** in 91% yield as a mixture of *E*/*Z* isomers (Table 2, entry 1).[16] In contrast, $TiCl_4$ and trimethylsilyl trifluoromethanesulfonate (TMSOTf) were not sufficiently reactive and were ineffective in promoting the addition reaction. With the optimal reaction conditions using $BF_3{\cdot}OEt_2$, we then tested the substrate scope of the reaction by varying the γ-substituent of the unsaturated acetals. γ-Aryl-substituted β,γ-unsaturated α,α-dimethoxy esters **2b–e** having both electron-donating and electron-withdrawing substituents were effective substrates in this transformation (entries 4–8). γ-Alkyl-substituted β,γ-unsaturated α,α-dimethoxy esters **2f** and **2g** were also good substrates for the reaction, but the primary-alkyl substituent resulted in a moderate yield (entry 9). The *E*/*Z* ratios of products **4a–g** were confirmed on the basis of the integration of appropriate proton absorptions by ^1H NMR analysis (vide infra).



We next turned our attention to surveying several other silyl nucleophiles to enhance the scope of this regioselective γ-substitution reaction and initially focused on allyltrimethylsilane (**5**).[17] The results of the reactions using unsaturated acetalderivatives **2a–g** are summarized in Table 3. It is noteworthy that $TiCl_4$ and a catalytic amount of TMSOTf as well as $BF_3{\cdot}OEt_2$ promoted the substitution reaction smoothly to furnish the γ-products in high yields. Interestingly, depending on the promoter used, the *E*/*Z*-ratios for product **6a** varied from approximately 1:1 ($BF_3{\cdot}OEt_2$) to 1:4 ($TiCl_4$) and 4:1 (TMSOTf). Again, substrates **2b–d** with *p*-substituted phenyl groups or alkyl groups at the γ-position were good substrates in the reaction with allylsilane **5** in the presence of $BF_3{\cdot}OEt_2$ to give γ-products **6b–g** in moderate to excellent yields (Table 3, entries 5–10).



The reaction was also conducted using silyl cyanide and silyl hydride as nucleophiles. The substitution reaction employing TMSCN, however, occurred predominately at the α-position to form (*E*)-β,γ-unsaturated ester **8** in 86% yield along with 9% yield of (*E*)-α-methoxy-α,β-unsaturated ester **7**. The reaction of Et_3SiH also afforded a significant amount of (*E*)-α-substitution product **10**, though γ-substitution product **9** was the major product. The use of more bulky Ph_3SiH improved selectivity for

Table 2
Reactions of acetals **2a–g** with trimethylsilyl enolate **3**

Entry	Acetal	Lewis acid	Conditions	Product	Yield[a] (%)	*E*/*Z* Ratio[b]
1	**2a**	$BF_3{\cdot}OEt_2$	−78–0 °C for 2 h, then 0 °C, 2 h	**4a**	91	56:44
2	**2a**	$TiCl_4$	−78–0 °C for 2 h, then 0 °C, 20 h	**4a**	5	100:0
3	**2a**	TMSOTf[c]	0 °C, 3 h	**4a**	11	—[d]
4	**2a**	TMSOTf	0 °C, 3 h	**4a**	48	65:35
5	**2b**	$BF_3{\cdot}OEt_2$	−78–0 °C for 2 h, then 0 °C, 5 h	**4b**	98	64:36
6	**2c**	$BF_3{\cdot}OEt_2$	−78–0 °C for 2 h, then 0 °C, 4 h	**4c**	92	85:15
7	**2d**	$BF_3{\cdot}OEt_2$	−78–0 °C for 2 h, then 0 °C, 4 h	**4d**	81	68:32
8	**2e**	$BF_3{\cdot}OEt_2$	−78–0 °C for 2 h, then 0 °C, 4 h	**4e**	92	80:20
9	**2f**	$BF_3{\cdot}OEt_2$	−78–0 °C for 2 h, then 0 °C, 20 h	**4f**	37[e]	89:11
10	**2g**	$BF_3{\cdot}OEt_2$	−78–0 °C for 2 h, then 0 °C, 4 h	**4g**	85	96:4

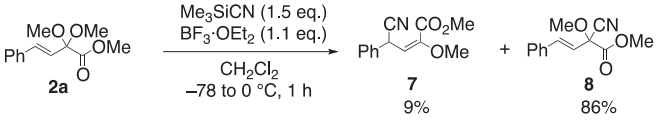
[a] Isolated yields.
[b] Determined by ^1H NMR.
[c] The reaction was carried out using 0.1 equiv of TMSOTf.
[d] This ratio was not determined.
[e] The corresponding α-product was also obtained in 11% yield.

Table 3
Reactions of acetals **2a–g** with allyltrimethylsilane **5**

Entry	Acetal	Lewis acid	Conditions	Product	Yield[a] (%)	*E*/*Z* Ratio[b]
1	**2a**	$BF_3{\cdot}OEt_2$	−78–0 °C for 2 h, then 0 °C, 2 h	**6a**	93	46:54
2	**2a**	$TiCl_4$	−78 °C, 25 min	**6a**	90	23:77
3	**2a**	TMSOTf[c]	−78 °C 3 h, then 0 °C, 2 h	**6a**	92	80:20
4	**2a**	TMSOTf[c]	0 °C, 2 h	**6a**	94	67:33
5	**2b**	$BF_3{\cdot}OEt_2$	−78–0 °C for 2 h, then 0 °C, 1 h	**6b**	95	59:41
6	**2c**	$BF_3{\cdot}OEt_2$	−78–0 °C for 2 h, then 0 °C, 3 h	**6c**	84	38:62
7	**2d**	$BF_3{\cdot}OEt_2$	−78–0 °C for 2 h, then 0 °C, 1 h	**6d**	92	52:48
8	**2e**	$BF_3{\cdot}OEt_2$	−78–0 °C for 2 h, then 0 °C, 6 h	**6e**	82	83:17
9	**2f**	$BF_3{\cdot}OEt_2$	−78–0 °C for 2 h, then 0 °C, 20 h	**6f**	69	94:6
10	**2g**	$BF_3{\cdot}OEt_2$	−78–0 °C for 2 h, then 0 °C, 3 h	**6g**	86	86:14

[a] Isolated yields.
[b] Determined by ^{1}H NMR.
[c] The reaction was carried out using 0.1 equiv of TMSOTf.

the γ-substitution product (entry 2 in Table 4). This result implies that the regioselectivity of the substitution of the silyl nucleophiles is dependent on the steric effects of the nucleophiles used.



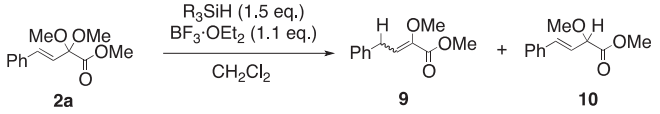


Table 4
Reactions of acetal **2a** with silyl hydride

Entry	R_3SiH	Conditions	Yield of **9**[a]	*E*/*Z* Ratio[b]	Yield of **10**[a] (%)
1	Et_3SiH	−78–0 °C, 6 h	69	86:14	21
2	Ph_3SiH	−78–0 °C, 1 h	86	86:14	12

[a] Isolated yields.
[b] Determined by ^{1}H NMR.

γ-Substituted α,β-unsaturated α-methoxy esters were obtained as *E*/*Z*-mixtures with variable ratios. The assignment of the *E*- and *Z*- isomers was established on the basis of the chemical shift (δ) value of the vinyl proton in the ^{1}H NMR spectra and NOE experiments. The representative δ value for **4a** is depicted in Figure 1. Generally, the δ values of the vinyl protons in the *Z*-isomers of α-alkoxy-2-alkenoates are larger than those of the vinyl protons in the corresponding *E*-isomers by approximately 1 ppm.[18] In addition, NOE measurements on the *E*-isomer of **4a** revealed a clear enhancement between the vinyl proton and the neighboring methoxy group.

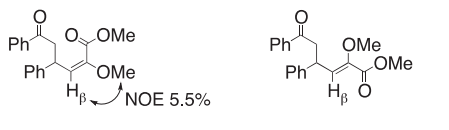


Figure 1. Assignment of the *E*- and *Z*-isomers for compound **4a**.

In summary, we have successfully developed the Lewis acid-promoted γ-substitution reaction of β,γ-unsaturated α,α-dimethoxy esters with silyl nucleophiles. The reactions using silyl enolate and allylsilane proceed smoothly to provide γ-substituted α,β-unsaturated α-methoxy esters in excellent yields with various *E*/*Z*-ratios. In contrast, the reactions using silyl cyanide and silyl hydride resulted in mixtures of α- and γ-substitution products. The regioselectivity seems to be dependent on the steric bulk of the silyl nucleophiles. Further, attempts to extend this reaction to other silyl nucleophiles and to render the reaction sequence asymmetric are currently being pursued in our laboratory.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.078. These data include MOL files and InChiKeys of the most important compounds described in this article.

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10. For example, the BF_3-mediated reaction of methyl (*E*)-2-oxo-4-phenyl-3-butenoate (**1a**) with allyltrimethylsilane in CH_2Cl_2 at 0 °C for 6 h afforded the corresponding Michael adduct in only 8% yield along with 70% yield of recovered **1a**. As another example using TMS enolate as a silyl nucleophile, treatment of **1a** with 1-(trimethylsiloxy)styrene in CH_2Cl_2 at 0 °C for 4 h in the presence of $BF_3{\cdot}OEt_2$ furnished a mixture of 1,4- and 1,2-adducts in 60% and 8% yields, respectively.
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15. *A representative procedure for acetalization of* ***1a***: To a solution of **1a** (3.17 g, 16.7 mmol) in dry MeOH (4.4 mL) and $HC(OMe)_3$ (4.4 mL, 40 mmol) was added *p*-$TsOH{\cdot}H_2O$ (0.31 g, 1.7 mmol), and the mixture was refluxed for 5 h. The solution was cooled to rt, neutralized with satd $NaHCO_3$ aq, and extracted with Et_2O (2×30 mL). Combined organic layers were dried and then concentrated under reduced pressure to give crude product, which was purified by silica gel column chromatography. Elution of the column with hexane/AcOEt (4:1) mixture gave **2a** (3.74 g, 95%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.35 (s, 6H), 3.81 (s, 3H), 6.11 (d, *J* = 16 Hz, 1H), 6.97 (d, *J* = 16 Hz, 1H), 7.30–7.36 (m, 3H), 7.40–7.44 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 50.4, 52.9, 100.6, 124.4, 126.9, 128.6, 128.6, 135.3, 135.3, 169.0.
16. *A representative procedure for the substitution reaction of* ***2a*** *with 1-(trimethylsiloxy)styrene* ***3***: To a solution of **2a** (318 mg, 1.34 mmol) and **3** (0.402 g, 2.09 mmol) in dry CH_2Cl_2 (13 mL) was added $BF_3{\cdot}OEt_2$ (0.200 mL, 1.47 mmol) at −78 °C under Ar. The mixture was gradually warmed to 0 °C and continued to stir at 0 °C for 2 h. After completion of the reaction (TLC), it was quenched with satd $NaHCO_3$ aq and extracted with CH_2Cl_2 (2×10 mL). Combined organic layers were dried and then concentrated under reduced pressure to give crude product, which was purified by silica gel column chromatography. Elution of the column with hexane/AcOEt (95:5) mixture gave (*E*)-**4a** (224 mg, 51%) and (*Z*)-**4a** (176 mg, 40%), respectively. (*E*)-isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.35 (dd *J* = 7.3, 16.0 Hz, 1H), 3.51 (dd, *J* = 6.4, 16.0 Hz, 1H), 3.54 (s, 3H), 3.75 (s, 3H), 5.06 (ddd, *J* = 6.4, 7.3, 10.1 Hz, 1H), 5.34 (d, *J* = 10.1 Hz, 1H), 7.19 (t, *J* = 7.3 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 2H), 7.3 (d, *J* = 7.3 Hz, 2H), 7.41 (t, *J* = 7.3 Hz, 2H), 7.51 (t, *J* = 7.3 Hz, 1H), 7.91 (d, *J* = 7.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 38.0, 45.8, 51.9, 55.3, 115.7, 126.4, 127.1, 127.9, 128.4, 128.5, 132.8, 136.7, 143.7, 145.3, 163.3, 197.8; (*Z*)-isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.43 (dd, *J* = 7.8, 17.0 Hz, 1H), 3.46 (dd, *J* = 6.4, 17.0 Hz, 1H), 3.64 (s, 3H), 3.70 (s, 3H), 4.61 (ddd, *J* = 6.4, 7.8, 10.1 Hz, 1H), 6.40 (d, *J* = 10.1 Hz, 1H), 7.16–7.32 (m, 5H), 7.38–7.42 (m, 2H), 7.48–7.53 (m, 1H), 7.90–7.94 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 37.3, 44.3, 51.6, 59.6, 126.6, 127.2, 127.8, 128.4, 128.5, 129.8, 132.9, 136.5, 142.4, 145.1, 163.8, 197.2.
17. *A representative procedure for the substitution reaction of* ***2a*** *with allyltrimethylsilane* ***5***: To a solution of **2a** (124 mg, 0.52 mmol) and **5** (0.10 mL, 0.60 mmol) in dry CH_2Cl_2 (5 mL) was added $BF_3{\cdot}OEt_2$ (0.070 mL, 0.55 mmol) at −78 °C under Ar. The mixture was gradually warmed to 0 °C and continued to stir at 0 °C for 2 h. After completion of the reaction (TLC), it was quenched with satd $NaHCO_3$ aq and extracted with CH_2Cl_2 (2×10 mL). Combined organic layers were dried and then concentrated under reduced pressure to give crude product, which was purified by silica gel column chromatography. Elution of the column with hexane/AcOEt (95:5) mixture gave (*E*)-**6a** (55 mg, 43%) and (*Z*)-**6a** (65 mg, 50%), respectively. (*E*)-isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.40–2.47 (m, 1H), 2.48–2.55 (m, 1H), 3.51 (s, 3H), 3.72 (s, 3H), 4.48 (ddd, *J* = 5.0, 7.8, 10.1 Hz, 1H), 4.93 (d, *J* = 10.1 Hz, 1H), 5.01 (d, *J* = 16.0 Hz, 1H), 5.26 (d, *J* = 10.1 Hz, 1H), 5.67 (ddt, *J* = 6.8, 10.1, 16.0 Hz, 1H), 7.12–7.30 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 41.3, 41.3, 51.5, 55.0, 116.1, 116.9, 125.9, 127.0, 128.1, 135.7, 144.1, 144.8, 163.3; (*Z*)-isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ:2.42–2.48 (m, 1H), 2.50–2.56 (m, 1H), 3.61 (s, 3H), 3.74 (s, 3H), 3.96 (ddd, *J* = 5.0, 8.2, 10.1 Hz, 1H), 4.99 (dd, *J* = 0.9, 10.1 Hz, 1H), 5.04 (dd, *J* = 1.3, 17.0 Hz, 1H), 5.70 (ddt, *J* = 7.3, 10.1, 17.0 Hz, 1H), 6.38 (d, *J* = 10.1 Hz, 1H), 7.17–7.32 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 40.1, 41.7, 51.8, 59.9, 116.6, 126.5, 127.3, 128.5, 131.0, 135.6, 142.8, 145.1, 164.0.
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