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Practical and Robust Method for Regio- and Stereoselective Preparation of (*E*)-Ketene *tert*-Butyl TMS Acetals and *β*-Ketoester-derived *tert*-Butyl (1*Z*,3*E*)-1,3-Bis(TMS)dienol Ethers

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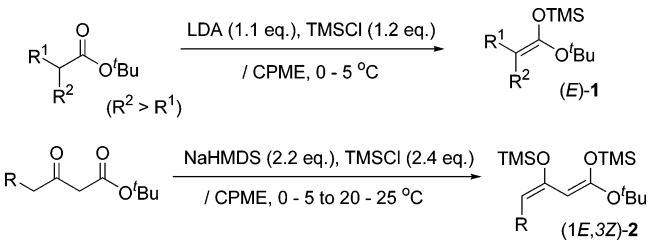


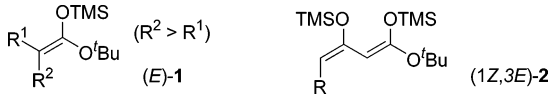
We developed an efficient, practical, robust method for the regio- and stereoselective preparation of (*E*)-ketene trimethylsilyl acetals (KSAs) derived from *tert*-butyl esters **1**. The reaction was performed under convenient reaction conditions; LDA−TMSCl, 0−5 °C, and cyclopentyl methyl ether (CPME) solvent. Two kinds of (*Z*)- and (*E*)-KSAs derived from α-oxygen and α-nitrogen-substituted *tert*-butyl esters, respectively, were also obtained in good yield. The present protocol was successfully applied to a stereocontrolled preparation of useful, but highly reactive (less accessible) *β*-ketoester-derived *tert*-butyl (1*Z*,3*E*)-1,3-bis(TMS)dienol ethers **2**.

Ketene silyl acetals (KSAs) are well recognized as highly useful, activated ester derivatives and are employed as reactive precursors in a wide range of organic syntheses, such as the Mukaiyama aldol and Michael reactions, Ireland−Claisen rearrangement, Diels−Alder reaction, etc.[1] *β*-Ketoester-derived 1,3-bis(TMS)enol ethers, important reactive derivatives of KSAs, also serve as useful and elaborate 1,3-dicarbonyl building blocks.[2] Despite the remarkable utility of the KSAs (in particular, TMS derivatives), there is a high demand for a practical, robust, and cost-effective preparative method of KSAs from the recent standpoint of process chemistry.

The most conventional method is performed by the *O*-silylation of alkali metal ester enolates with TMSCl.[1,3a,b] There are two other useful, but less accessible methods; a related *O*-silylation using TMSOTf−Et_3N reagent[4] and an Rh(I)-catalyzed hydrotrimethylsilylation of α,*β*-unsaturated esters.[5] The former method lacks substrate generality and requires the use of expensive reagents. The latter method requires hard to handle gaseous $HSiMe_3$ for trimethylsilylated KSAs and involves the critical problem of *O*- and *C*-silylation regioselectivity.

Even for traditional *O*-silylations of ester enolates with TMSCl, there are some tedious procedures that restrict large-scale preparation; (i) a low temperature (−78 °C) is generally required to suppress two undesirable side reactions, that is thermodynamically preferred *self*-Claisen condensation between esters and/or competitive *C*-trimethylsilylation; and (ii) a more careful operation is required compared with a related preparation of enol silyl ethers from ketones or aldehydes, due to the instability of KSAs against acids and bases (Scheme 1).

In close connection with our continued studies on practical silylation and desilylation reactions of alcohols, aldehydes, and ketones,[6] and *crossed*-Claisen condensations utilizing KSAs,[7] we present here a practical, robust, regio- and stereocontrolled method for the preparation of not only (*E*)-ketene *tert*-butyl TMS acetals **1**, but also highly reactive, hence less accessible, *β*-ketoester-derived *tert*-butyl (1*Z*,3*E*)-1,3-bis(TMS)dienol ethers **2**.



The stereochemistry (*E* or *Z*) of KSAs is of primary importance due to the successive diastereo and enantioselective C−C bond-forming reactions. Extensive and systematic studies, reported by Ireland,[3c,e] Heathcock,[3d] Corset,[3f] Otera,[3g] and their co-workers, have revealed that the *E*- or *Z*-selectivity depends upon subtle reaction conditions, such as molar ratio, temperature, alkali amide, and solvent. Consequently, the *E*-isomer is a

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SCHEME 1. General Preparation of KSA

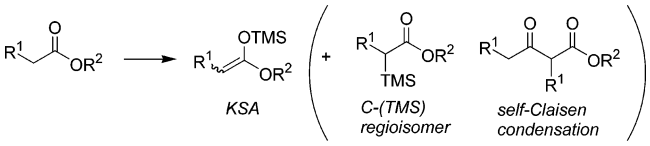
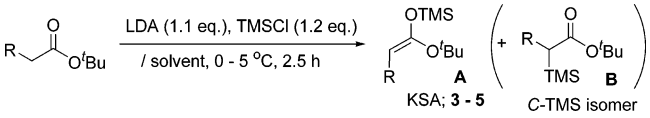


TABLE 1. Screening of Ether Solvents for the Preparation of KSAs



entry	R	solvent	product	yield of A (%)[a]	ratio of A/B[b]	*E*/*Z*[a]
1	Me	Et_2O	**3**	65[a]	60:40	>99:1
2		THF		49[b]	69:31	96:4
3		dioxane		46[a]	66:34	95:5
4		DME		trace[a]	−	−
5		*t*-BuOMe		43[a]	90:10	98:2
6		CPME		69[b]	97:3	>99:1
7	*t*-Bu	*t*-BuOMe	**4**	63[a]	90:10	98:2
8		CPME		80[b]	98:2	>99:1
9	Oct	*t*-BuOMe	**5**	76[a]	89:11	99:1
10		CPME		76[b]	97:3	>99:1

[a] Determined by ^{1}H NMR of the crude product. [b] Isolated.

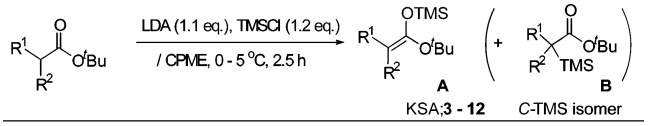
kinetic product, and the *Z*-isomer is a thermodynamic product. Taking their findings into account, we focused our attention on the preparation of analogous *tert*-butyl trimethylsilylated KSA based on two promising features: (i) the expected use of a practically accessible reaction temperature (from −20 to 20 °C), because *tert*-butyl ester enolates are more stable among alkyl esters to suppress undesirable *self*-Claisen condensation, and (ii) the bulky *tert*-butyl group enhances *E*-selectivity, based generally on Otera's study.[3g]

The initial solvent-screening was guided using three *tert*-butyl alkanoates for the preparation of KSAs **3**−**5**: a *tert*-butyl alkanoate was treated with LDA (1.1 equiv) to generate the Li enolate at 0−5 °C, followed by trapping with TMSCl (1.2 equiv) for 2.5 h using some ether solvents. Table 1 lists the results. When KSAs **3** were used, Et_2O, THF, dioxane, and DME solvents resulted in poor regioselectivity accompanying undesirable *C*-silylation (entries 1−3). Although DME gave disappointing results (entry 4), *tert*-BuOMe increased the regioselectivity (entry 5). The best result was obtained using cyclopentyl methyl ether (CPME)[8] with regard to both yield and regioselectivety (≥97:3) for the preparation of all KSAs **3**−**5** (entries 6, 8, 10). Notice that the *E*-stereoselectivity of KSAs **3**−**5** was excellent (*E*/*Z* = >99:1). CPME solvent has recently attracted attention from the standpoint of process chemistry, due to the superiority to traditional ether solvents.

Using the optimized conditions shown in Table 1, several KSAs **3**−**12** were prepared (Table 2). The salient features are as follows. (i) In every case examined, KSAs **3**−**12** were obtained in good yield (69−83%) with excellent regio- (>96:4) and *E*-stereoselectivity (>99:1 except for **9** and **10**). (ii) α,α-

(8) CPME was recently launched by the Zeon group and applied the useful ether solvent in the place of THF, dioxolane, DME, etc. Watanabe, K.; Yamagiwa, N.; Torisawa, Y. *Org. Process Res. Dev.* **2007**, *11*, 251. Appropriate bp 106 °C, low solubility in water (high separation property), low formation of peroxides, relative stability under acidic and basic conditions, formation of azeotropes with water, a narrow explosion range.

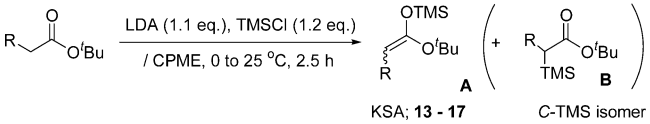
TABLE 2. Regio- and (*E*)-Selective Preparation of Various KSAs



Entry	R^1, R^2	Product	Yield of **A** (%)[a]	Ratio of **A**/**B**[b]	*E* / *Z*[b]
1	Me, H	**3**	69	97 : 3	>99 : 1
2	*n*-Bu, H	**4**	80	98 : 2	>99 : 1
3	$CH_3(CH_2)_7$, H	**5**	78	97 : 3	>99 : 1
4	*i*-Pr, H	**6**	73	>99 : 1	>99 : 1
5	 , H	**7**	78	96 : 4	>99 : 1
6	Me, Me	**8**	79[c]	>99 : 1	-
7	Et, Me	**9**	83[c]	>99 : 1	-[d]
8	*n*-Bu, Et	**10**	68[c]	>99 : 1	-[d]
9	$-(CH_2)_5-$	**11**	76[c]	>99 : 1	-
10	H, H	**12**	35 (63)[e]	>99 : 1	-

[a] Isolated. [b] Determined by ^{1}H NMR of the crude product. [c] 0−25 °C. [d] *E*/*Z* ratios were not determined. [e] Use of KHMDS instead of LDA.

TABLE 3. Preparation of α-Oxygen or α-Nitrogen Substituted KSAs



entry	R	product	yield of A (%)[a]	ratio of A/B[b]	*E*/*Z*[b]
1	TBSO−	**13**	59	>99:1	20:80
2	BnO−	**14**	58	81:19	3:97
3	MOMO−	**15**	66	>99:1	2:98
4	$(allyl)_2N-$	**16**	51	>99:1	89:11
5	Bn_2N-	**17**	95	>99:1	>99:1

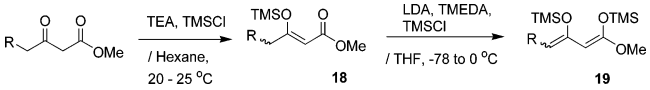
[a] Isolated. [b] Determined by ^{1}H NMR of the crude product.

Dialkylated esters also underwent the desired reaction (entries 6−9). (iii) In the case of CH_3CO_2t-Bu, a higher yield was obtained using NaHMDS. (iv) Highly carcinogenic and hazardous HMPA, a frequently used cosolvent for the preparation of KSA, was not necessary. (v) A 10 g-scale synthesis was performed for the preparation of **3**.

Next, we investigated the reaction using α-oxygen- or α-nitrogen-substituted *tert*-butyl esters (lactates and glycinates) because these *O*-and *N*-protected KSAs are useful substrates for important acyclic stereocontrolled synthesis. Table 3 lists the successful results. The desired KSAs **13**−**17** were successfully obtained in moderate to excellent yield (51−95%) with complete regioselectivity (>99:1), except for the case of **14**. With regard to the stereoselectivity, KSAs **13**−**15** derived from lactates showed *Z*-selectivity, whereas KSAs **16** and **17** derived from glycinates switched to *E*-selectivity.

To further demonstrate the utility of the present protocol, we next focused our attention on a practical and robust preparation of β-ketoester-derived 1,3-bis(TMS)-KSAs **2**. Langer's group extensively studied the utilization of various 1,3-bis(TMS)dienol ethers of β-dicarbonyl compounds and reviewed the impressive

SCHEME 2. General Preparation of Methyl (1*Z*)-1,3-Bis(TMS)dienol Ethers 19



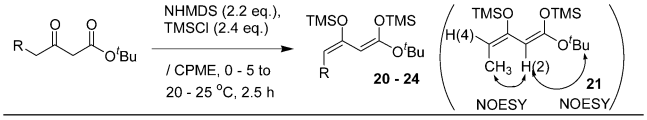
progress in this area.[2] β-Ketoester-derived *methyl* (1*Z*)-1,3-bis-(TMS)dienol ethers **19** are recognized as highly reactive and useful precursors for the Mukaiyama aldol,[9] cyclopentannulation,[10] benzannulation,[11] oxabicyclo[3.2.1]octan-3-one formation,[12] tetrahydrofuran formation,[13] furanone formation,[14] Michael addition,[15] [4+2]-cycloaddition,[16] and Claisen-type reactions.[17]

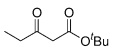
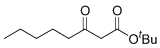
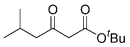
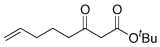
The most general method for the preparation of **19** involves a two-step sequence; the starting methyl β-ketoesters are converted to enol silyl ethers **18** using the $Et_3N-TMSCl$ reagent, and then transformed to the desired dienol ethers **19** using the LDA−TMSCl reagent at −78 °C (Scheme 2).[11,18] Another one-pot method utilizing the $2Et_3N-2TMSOTf$ reagent lacks substrate generality.[19] Because purification and handling procedures of 1,3-bis(TMS)-KSAs require caution due to their high inherent reactivity, a more robust preparative method is desired.

On the basis of the successful preparation of KSAs, we speculated that the *tert*-butyl analogue of 1,3-bis(TMS)-KSAs **2** was a promising candidate for this purpose. *tert*-Butyl β-ketoesters were directly converted to desired **2** using two equivalents of the NaHMDS−TMSCl reagent.

Table 4 lists the successful results, and the salient features are as follows. (i) NaHMDS was the best amide reagent with regard to yield for the production of **20** (entry 1), compared with other amides such as LDA (trace), LiHMDS (trace), and KHMDS (16%). (ii) Despite the instability of **2**, the reaction was performed under practically accessible conditions (0−25 °C in CPME solvent) in a similar manner as for the preparation of **1**. (iii) The reaction proceeded in good to excellent yield. (iv) (1*Z*,3*E*)-isomers **21**−**24** were obtained with high stereoselectivity, and to the best of our knowledge, this is the first example of a stereoselective preparation of **2**. The ^1H NMR chemical shifts of the two olefinic protons were characteristic: H(2) and H(4) of the (1*Z*,3*E*)-isomers located at 4.41−4.47 and 4.57−4.63, respectively, and those for the (1*Z*,3*Z*)-isomers were located at 4.27−4.29 and 4.98−5.04, respectively. The configuration of **21** was determined using the NOESY spectrum between −C*H*═ and CH_3CH═, and between −C*H*═ and (CH_3)$_2$(*t*-Bu)O−. The stereochemistry of other analogs **22**−**24** were deduced on the basis of the chemical shift data of **21**.

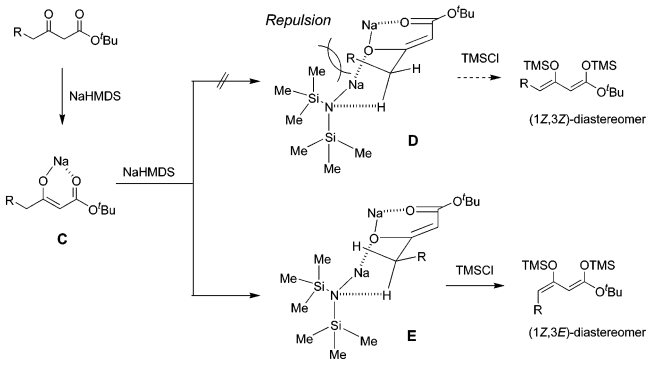
TABLE 4. Preparation of *tert*-Butyl (1*Z*,3*E*)-1,3-Bis(TMS)dienol Ethers



Entry	β-Ketoester	Product	Yield (%)[a]	(1*Z*, 3*E*) / (1*Z*, 3*Z*)[b]
1		**20**	76	-
2		**21**	90	96 : 4
3		**22**	75	97 : 3
4		**23**	67	97 : 3
5		**24**	75	96 : 4

[a] Isolated. [b] Determined by ^1H NMR of the crude product.

SCHEME 3. Proposed Mechanism



A proposed mechanism to account for the (1*Z*,3*E*)-stereoselectivity is depicted in Scheme 3. A *tert*-butyl β-ketoester is converted to sodium monoenolate **C**, which is subsequently transformed into bicyclic disodium dienolate transition-state **D** or **E**. Steric repulsion between the R group and the bulky hexamethyldisilazane group favors the production of **E**, which is reacted with 2TMSCl to give the (1*Z*,3*E*)-diastereomer.

In conclusion, we developed an efficient, practical, regio-, and stereoselective preparation of various (*E*)-KSAs **1** and 1,3-bis(TMS)-KSAs **2**, derived from *tert*-butyl esters and *tert*-butyl β-ketoesters, respectively. The present robust method will

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provide an easy access to these KSAs for process research and natural product synthesis.

Experimental Section

(1*E*)-*tert*-Butoxy-1-(trimethylsiloxy)propene (3).[20] BuLi (1.59 M in hexane, 55.0 mL, 88 mmol) was added to a stirred solution of *i*-Pr_2NH (13.5 mL, 96 mmol) in cyclopentyl methyl ether (CPME; 60 mL) at 0−5 °C under an argon atomosphere, and the mixture was stirred at the same temp for 30 min *tert*-Butyl propanoate (10.42 g, 80 mmol) in CPME (20 mL) was added to the mixture at the same temp during 15 min.

After being stirred for 30 min, TMSCl (12.18 mL, 96 mmol) was added to the mixture at the same temp during 5 min, followed stirring for 1.5 h. The mixture was poured into ice water and hexane, which was extracted with hexane. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by distillation to give the desired product **3** (10.24 g, 69%).

Colorless oil; bp 49−53 °C/5.6 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.20 (9H, s), 1.32 (9H, s), 1.49 (3H, d, J = 6.9 Hz), 3.89 (1H, d, J = 6.9 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ −0.1, 10.7, 29.1, 78.1, 85.4, 152.0; IR (neat) 2978, 2932, 1680, 1253, 1209, 1153, 1051, 929, 873, 846, 758 cm^{-1}.

C-TMS isomer of **3**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.07 (9H, s), 1.12 (3H, d, J = 7.2 Hz), 1.44 (9H, s), 1.94 (1H, q, J = 7.2 Hz), 7.17−7.31 (3H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ −2.8, 10.9, 28.3, 31.0, 79.2, 175.6.

1-*tert*-Butoxy-1-(trimethylsiloxy)ethylene (12).[21] *tert*-Butyl acetate (3.48 g, 30 mmol) in CPME (7 mL) was added to a stirred solution of KHMDS (0.5 M in toluene, 72 mL, 36 mL) in CPME (23 mL) at 0−5 °C during 7 min under an argon atomosphere, and the mixture was stirred at the same temp for 30 min. TMSCl (4.95 mL, 39 mmol) was added to the mixture during 3 min, followed by being stirred for 30 min. The mixture was warmed up to room temp and stirred at the same temp for 2 h. The mixture was poured into ice water and hexane, which was extracted with hexane. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by distillation to give the desired product **12A** (3.56 g, 63%).

Colorless oil; bp 61−63 °C/20 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.23 (9H, s), 1.34 (9H, s), 3.41 (1H, d, J = 1.4 Hz), 3.44 (1H, d, J = 1.4 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ −0.1, 28.5, 71.7, 78.1, 157.5; IR (neat) 2978, 2905, 1715, 1476, 1252, 1163, 1047, 848, 760 cm^{-1}.

1,3-Bis(trimethylsiloxy)-1-*tert*-butoxybuta-1,3-diene (20).[22] *tert*-Butyl 3-oxobutanoate (791 mg, 5 mmol) was added to a stirred solution of NaHMDS (1.0 M in THF, 11.0 mL, 11.0 mmol) in CPME (5 mL) at 0−5 °C during 5−8 min under an Ar atmosphere, and the reaction mixture was stirred at the same temperature for 30 min. TMSCl (1.52 mL, 12.0 mmol) was added to the mixture during 3−5 min, followed by being stirred for 30 min. The mixture was warmed up to room temp and stirred at the same temperature for 1.5 h. The mixture was poured into ice water and hexane, which was extracted with hexane. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by distillation to give the desired product **20** (1.15 g, 76%).

Colorless oil; bp 65 − 67/0.5 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.20 (9H, s), 0.24 (9H, s), 1.36 (9H, s), 4.21 (1H, d, J = 1.0 Hz), 4.25 (1H, d, J = 1.0 Hz), 4.54 (1H, s); ^{13}C NMR (75 MHz; $CDCl_3$): δ 0.2, 0.6, 28.4, 79.7, 89.2, 91.0, 153.2, 153.7; IR (neat) 2963, 1649, 1602, 1368, 1344, 1252, 1132, 1045, 1026, 847, 756 cm^{-1}.

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Supporting Information Available: Experimental details for the preparation of (*E*)-ketene *tert*-butyl TMS acetals **4**−**11**, **13**−**17**, and *tert*-butyl (1*Z*,3*E*)-1,3-bis(TMS)dienol ethers, **21**−**24**. This material is available free of charge via the Internet http://pubs.acs.org.

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