Iron-Catalyzed Unexpected Easy Access to Stereodefined Trimethylsilyl Vinyl Ketenes

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Stereodefined trimethylsilyl vinyl ketenes with polysubstitution have been synthesized highly regio- and stereoselectively via an iron-catalyzed reaction of 2-trimethylsilyl-2,3-allenoates with Grignard reagents in good to excellent yields. The reaction was believed to proceed via a conjugate addition and elimination mechanism. Applications of the products for the synthesis of stereodefined α -silyl- β , γ -unsaturated enones, a stereodefined triene, and polysubstituted phenols have been carefully demonstrated.

The utility of ketenes in organic synthesis has been well demonstrated in the past decades.¹ For example, vinyl ketenes could serve as both two- and four-carbon building blocks for the assembly of a variety of carbocyclic systems.² However, they are highly unstable and often generated as intermediates for *in situ* trapping, which greatly restrict their application. In 1980, Danheiser et al. reported the synthesis of trialkylsilyl vinyl ketenes by

the dehydrohalogenation of α -silyl- α , β -unsaturated acid chlorides (Scheme 1, route a).³ The presence of the silvl group could stabilize vinyl ketenes⁴ and allow them to serve as enophiles in [4 + 2] cycloadditions and reactive carbonyl compounds;⁵ in 1998, Danheiser et al. reported the photochemical Wolff rearrangement of α' -silvl- α' diazo- α , β -unsaturated ketones to afford trialkylsilyl vinyl ketenes (Scheme 1, route b);^{6a} in the same paper,^{6a} this type of vinyl ketenes was also prepared by heating the α -silyl cyclobutenone (Scheme 1, route c).⁶ Moreover, treatment of the Fischer-type chromium carbene complexes with silvl-substituted alkynes could also afford such vinyl ketenes (Scheme 1, route d).⁷ Herein, we present our recent unexpected observation for the synthesis of stereodefined trimethylsilyl vinyl ketenes via an iron-catalyzed reaction of 2-trimethylsilyl-2,3-allenoates with Grignard reagents (Scheme 1, route e).

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Scheme 1. Synthesis of Trimethylsilyl Vinyl Ketenes



2-Trimethylsilyl-2,3-allenoates could be easily prepared from the Pd-catalyzed methylcarboxylation of propargylic mesylates by the reported procedure (Scheme 2).⁸





During further study on iron-catalyzed conjugate addition of 2,3-allenoates with Grignard reagents,9 we accidentally found that the reaction of 2,3-allenoate 1a with 1.1 equiv of CH₃MgBr (3 M solution in Et₂O) in Et₂O at rt afforded an unknown new product 2a. Through careful spectroscopic analysis (¹H and ¹³C NMR, IR, and MS), 2a was confirmed to have a trimethylsilyl vinyl ketene unit! However, the Z/E selectivity (92:8) is poor. After extensive screening of the reaction conditions, we were glad to observe that when the reaction was conducted at -78 °C in the presence of 2 mol % of Fe(acac)₃ for 0.5 h followed by warming up to rt, the yield of Z-2a could be improved to 88% with excellent Z-stereoselectivity ($\geq 99/1$) (entry 3, Table 1). In the absence of catalyst the reaction afforded Z-2a in a lower yield (entry 4, Table 1). Other solvents such as THF, toluene, and CH₂Cl₂ also failed to afford better results (entries 5-7, Table 1). It is worth noting that when FeCl₃ was used instead of Fe(acac)₃, the ketene product could also be obtained in a considerable although somewhat lower yield (entry 8, Table 1). The use of $FeCl_3 \cdot 6H_2O$ as the catalyst also led to a lower yield of Z-2a with more Table 1. Optimization of the Reaction Conditions



	cat.	solvent	yield ^a (%)	
entry			Z -2a $(Z/E)^a$	Z -3a $(Z/E)^a$
1^b	Fe(acac) ₃	Et_2O	48 (92/8)	11 (≥98/2)
2^b	_	Et_2O	30 (95/5)	14 (90/10)
3^c	Fe(acac) ₃	Et_2O	88 (≥99/1)	3 (≥99/1)
4^c	_	Et_2O	49 (92/8)	4(79/21)
5^c	$Fe(acac)_3$	THF	48 (86/14)	8 (≥99/1)
6^c	$Fe(acac)_3$	toluene	69 (95/5)	$14 (\geq 98/2)$
$7^{c,d}$	$Fe(acac)_3$	CH_2Cl_2	45 (94/6)	$16 (\geq 99/1)$
8^c	$FeCl_3$	Et_2O	84 (≥99/1)	$4(\geq 99/1)$
9^c	$FeCl_3 \cdot 6H_2O$	Et_2O	65 (95/5)	$9(\geq 99/1)$
10^e	$\rm FeCl_3 \cdot 6H_2O$	Et_2O	75 (97/3)	$10 (\geq 99/1)$

^{*a*} Determined by NMR spectroscopy using dibromomethane as the internal standard based on the integral area of vinyl hydrogen. ^{*b*} The reaction was conducted at rt for 1 h. ^{*c*} The reaction was conducted at -78 °C for 0.5 h, followed by warming up to rt for 2 h. ^{*d*} Substrate **1a** was recovered in 14% yield. ^{*e*} CH₃MgBr (1.2 equiv) was used.

conjugate addition-protonation product **3a** due to the presence of H₂O in FeCl₃·6H₂O (entries 9 and 10, Table 1). Finally, we defined the reaction of 2-trimethylsilyl-2,3-allenoates with 1.1 equiv of Grignard reagents (solution in Et₂O) in Et₂O at -78 °C in the presence of 2 mol % of Fe(acac)₃ followed by warming to rt as the standard reaction conditions for the formation of trimethylsilyl vinyl ketenes Z-**2**.

The scope of this reaction was then investigated under the standard conditions (Table 2): the reaction is guite general and proceeded very smoothly with a variety of 2-trimethylsilyl-2,3-allenoates and Grignard reagents: primary, secondary, and tertiary alkyl groups are all well tolerated, affording corresponding trimethylsilyl vinyl ketenes Z-2a-Z-2m in moderate to excellent yields under standard conditions (entries 1-13, Table 2). However, it should be noted that when primary alkyl Grignard reagents other than CH₃MgBr, i.e., EtMgBr and n-C₅H₁₁MgBr, were used, slightly lower stereoselectivities and yields were observed (entries 6 and 7, Table 2). A tert-butyl Grignard reagent (1.3 equiv) was needed to complete the reaction with **1a** presumably due to the steric effect of the *tert*-butyl group (entry 13, Table 2). In addition to alkyl Grignard reagents, a phenyl Grignard reagent may also be used to afford corresponding trimethylsilvl vinvl ketenes Z-2n and Z-20 in slightly lower yields (entries 14-15, Table 2). When vinyl magnesium bromide (1.0 M solution in THF) was used, the reaction was conducted in toluene and warmed up to 30 °C instead of rt, after 1 h at -78 °C, affording a 65% yield (entry 16, Table 2). In addition, the reaction can be easily conducted at a scale of 3.0 mmol of the substrate 1d for a similar yield (entry 17, Table 2).

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 Table 2. Scope of the Reaction^a

$$\begin{array}{c} R^{1} \\ \hline TMS \\ CO_{2}CH_{3} \\ 1 \\ \end{array} + R^{2}MgX \text{ in } Et_{2}O \\ Et_{2}O, -78 \ ^{\circ}C (0.5-1 \ h) \\ \text{to rt} (2 \ h) \\ \end{array} + \begin{array}{c} TMS \\ R^{1} \\ R^{2} \\ Z-2 \\ \end{array}$$

entry	\mathbb{R}^1	\mathbb{R}^2	Z-2, yield ^b (%	
1	n-C ₄ H ₉ (1a)	CH_3	Z-2a , 77	
2	$n-C_{9}H_{19}(1\mathbf{b})$	CH_3	Z-2b , 81	
3	c-C ₆ H ₁₁ (1c)	CH_3	Z -2 \mathbf{c} , 78 c	
4	$CH_2 = CH(CH_2)_8 (\mathbf{1d})$	CH_3	Z-2d , 82	
5	$Ph(CH_2)_2$ (1e)	CH_3	Z-2e , 82	
6	$n-C_4H_9(\mathbf{1a})$	\mathbf{Et}	Z - 2f , 63^d	
7	$n-C_4H_9(\mathbf{1a})$	n-C ₅ H ₁₁	Z -2 g , 50 e	
8	$n-C_4H_9(\mathbf{1a})$	c-C ₆ H ₁₁	Z- 2h , 80	
9	n-C ₉ H ₁₉ (1b)	c-C ₆ H ₁₁	Z-2i , 83	
10	c-C ₆ H ₁₁ (1c)	c-C ₆ H ₁₁	Z-2j, 80 ^c	
11	$CH_2 = CH(CH_2)_8 (\mathbf{1d})$	c-C ₆ H ₁₁	Z-2k, 85	
12	t-C ₄ H ₉ (1f)	c-C ₆ H ₁₁	<i>Z-2</i> 1 , 91	
13^{f}	$n-C_4H_9(\mathbf{1a})$	t-C ₄ H ₉	Z-2m , 90	
14	$n-C_{9}H_{19}(1\mathbf{b})$	Ph	Z- 2n, 60	
15	c-C ₆ H ₁₁ (1c)	Ph	Z-20, 59	
16^g	n-C ₄ H ₉ (1a)	Vinyl	Z- 2p , 65	
17^h	$CH_2 = CH(CH_2)_8 (\mathbf{1d})$	CH_3	<i>Z-</i> 2d, 74	

^{*a*} The reaction was conducted with 0.6 mmol of 2,3-allenoates, 5 mL of Et₂O, and 1.1 equiv of RMgX in Et₂O (3.0 M solution for CH₃MgBr, 3.0 M solution for EtMgBr, 2.0 M solution for $n-C_5H_{11}$ MgBr, 2.0 M solution for $c-C_6H_{11}$ MgCl, 3.0 M solution for PhMgBr, and 1.7 M solution for $c^2C_6H_{11}$ MgCl, 3.0 M solution for PhMgBr, and 1.7 M solution for 'BuMgCl) or vinyl magnesium bromide (1.0 M solution in THF). $Z/E \ge 99/1$ unless other noted. ^{*b*} Isolated yield. ^{*c*} $Z/E \ge 98/2$. ^{*d*}Z/E = 96/4. ^{*e*}Z/E = 93/7. ^{*f*}t-BuMgCl (1.3 equiv) was used. ^{*g*} The reaction was conducted in toluene and warmed up to 30 °C instead of rt after 1 h at -78 °C. ^{*h*} The reaction was conducted with a 3.0 mmol scale (0.9261 g) of **1d**.

After careful study, it was observed that the reaction of **1a** with 1.1 equiv of CH₃MgBr (3 M solution in Et₂O) in Et₂O at rt also afforded the conjugate addition product allylsilane *Z*-**3a** in 11% yield, together with trimethylsilyl vinyl ketene *Z*-**2a** (entry 1, Table 1). Thus, we believed that after the formation of the magnesium 1,3-dienolate intermediate generated from the conjugate addition of 2-trimethylsilyl-2,3-allenoate **1a** with the Grignard reagent,⁹ elimination of the methoxy group would afford the trimethylsilyl vinyl ketene product *Z*-**2a** (Scheme 3).^{10,11}

Due to fact that such an elimination of ROLi from lithium ester enolates forming ketenes is known,⁹ reactions of 2-butyl-4-cyclohexyl-2,3-butadienoate 1g with CH₃MgBr under different conditions were conducted (Table 3). Under the standard conditions, the conjugate

Scheme 3. Rationale for the Formation of Trimethylsilyl Vinyl Ketene *Z*-2a



addition product Z-3b was afforded in 29% yield (entry 1, Table 3). No ketene or its related product was formed even when 2.4 equiv of CH₃MgBr were used⁹ (entry 2, Table 3; see also Scheme 3) or the temperature was raised up (entry 4, Table 3): the conjugate addition–protonation product Z-3b was formed in 49% or 51% yields, respectively, indicating the importance of the trimethylsilyl group in the current transformation.¹⁰

Since the trimethylsilyl vinyl ketenes are now easily available, in addition to what is already known,⁵ synthetic potentials have been further extensively explored:

(1) The resulting trimethylsilyl vinyl ketenes Z-2a and Z-2d could further react with primary, secondary, and tertiary alkyl organolithium reagents affording α -silyl- β , γ -unsaturated enones Z-4, which are synthetically very useful because of the allylic silane moiety,¹² yet difficult to prepare due to the presence of the nonconjugated C=C bond, ketone, and the silyl group (Scheme 4).

In addition, it was observed that the reaction between trimethylsilyl vinyl ketenes Z-2 and Grignard reagents is very slow; thus, the one-pot synthesis of product Z-4e from 2,3-allenoate 1c could be realized in a 50% yield by sequential addition of CH₃MgBr and *t*-BuLi, although the yield of the three-step synthesis of Z-4e without purification of the ketene intermediate is much higher (76%) (Scheme 5). Accordingly, the starting 2,3-allenoate 1 may be viewed as synthon A.

- (2) Further *in situ* trapping of the reaction intermediate with acyl chloride would afford polysubstituted triene 5(Z),7(Z)-5 highly stereoselectively (Scheme 6).
- (3) It could also be utilized as a four-carbon building block in the construction of polysubstituted phenol
 6 by a Diels-Alder reaction with highly electron-deficient DMAD.³ It is worth noting that the reaction may also proceed with ethyl propionate

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Table 3. Reactions of 2-Butyl-4-cyclohexyl-2,3-butadienoate 1g with CH₃MgBr under Different Conditions



entry	n	yield ^{<i>a</i>} of Z -3b (%) (Z/E) ^{<i>a</i>}
1	1.1	29 (≥98/2)
2	2.4	51 (≥99/1)
3^b	1.2	$90^c (\geq 96/4)$
4^d	1.2	49 (≥98/2)

^{*a*} Determined by NMR spectroscopy using dibromomethane as the internal standard. ^{*b*} The reaction was quenched directly at -78 °C instead of warming up to rt, and the conversion was 98%. ^{*c*} Isolated yield. ^{*d*} The reaction was conducted at -78 °C for 1 h, then warmed up to -20 °C by gradient heating (-60 °C, 1 h; then -40 °C, 2 h; then -20 °C, 2 h), and quenched at -20 °C.





to afford phenol 7 regiospecifically (Scheme 7).^{5a} It should be noted that the [1,5]-shift reaction of Z-2a was not observed probably due to the presence of an excess amount of the electron-deficient alkynes.¹³

In conclusion, we disclose here a convenient synthesis of trimethylsilyl vinyl ketenes by elimination of MeOMgX from the magnesium 1,3-dienolate intermediate generated *in situ* from the conjugate addition of Grignard reagents with the readily available 2-trimethylsilyl-2,3-allenoates.⁶ In addition, the resulting products could be easily converted to polysubstituted stereodefined α -silyl- β , γ -unsaturated enones, stereodefined triene, and phenols with high stereoselectivity. Considering the diversity of both starting materials and broad applications of the products, especially the presence of the silyl group, this protocol will be of high interest in organic chemistry and related disciplines.

Scheme 5. Synthesis of Z-4e from 1c



Scheme 6. Tandem Reaction of Trimethylsilyl Vinyl Ketene Z-2d, *n*-BuLi, and Acyl Chloride



Scheme 7. Synthesis of Phenols 6 and 7



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Supporting Information Available. General procedure and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

⁽¹³⁾ For the [1,5]-H shift of ketenes affording aldehydes, see: Pirkle, W. H.; Seto, W. H.; Turner, W. V. J. Am. Chem. Soc. **1970**, *92*, 6984.

The authors declare no competing financial interest.