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A facile synthetic method of α -quaternary- β,γ -unsaturated aldehydes via the stereoselective 1,4-elimination and α -regioselective Ferrier reaction

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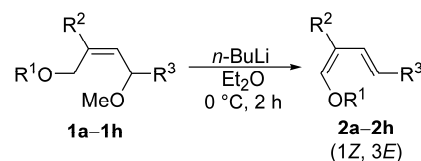
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Abstract— The 1,4-elimination reaction of 2-substituted-(*Z*)-4-methoxy-*O*-alkenyl acetals with *n*-butyllithium is shown to afford the 2-substituted-(1*Z*, 3*E*)-*O*-1,3-dienyl acetals in high stereoselectivities. The Ferrier reaction of the *O*-1,3-dienyl acetals thus obtained provides the corresponding α -quaternary- β,γ -unsaturated aldehydes in excellent yields with high α -regioselectivities. © 2013 Elsevier Science. All rights reserved

1-Alkoxy-1,3-dienes are useful synthetic intermediates that function as reactive diene components. Several applications for organic synthesis have been reported, e.g., dienolate equivalents for the vinylogous aldol reactions¹ and Ferrier-type reactions,² or as diene components for Diels–Alder reactions.³ We recently reported that a facile and stereoselective synthetic method of *O*-1,3-dienyl acetals via the 1,4-elimination of (*Z*)-4-methoxy-*O*-alkenyl acetals with *n*-butyllithium⁴ and the regioselective Ferrier reaction of *O*-1,3-dienyl acetals thus obtained by organoaluminum complexes to give α -substituted- β,γ -unsaturated aldehydes.^{2a} With this method in hand, we have now explored the feasibility of our reactions using 2- or 3-substituted-(*Z*)-4-methoxy-*O*-alkenyl acetals, which yield the 2- or 3-substituted-1,3-dienyl acetals by 1,4-elimination, and highly functionalized α -substituted- β,γ -unsaturated aldehydes by the regioselective Ferrier reaction.

First, we performed the reaction of (*Z*)-4-methoxy-2-methyl-1-(2'-tetrahydropyranyloxy)oct-2-ene (**1a**)⁵ with *n*-butyllithium (1.5 equiv) in diethyl ether at 0 °C (Table 1, entry 1). The corresponding 1,4-elimination product, 2-methyl-1-(2'-tetrahydropyranyloxy)oct-1,3-diene (**2a**) was obtained at 90% yield with high (1*Z*, 3*E*)-stereoselectivity [(1*Z*, 3*E*):(1*E*, 3*E*) = >20:1]. To define the scope and limitation of the 2-substituted-1,3-dienyl acetal forming reaction, we prepared a series of substrates **1b–1h** and

Table 1. 1,4-Elimination reaction of 2-substituted-(*Z*)-4-methoxy-*O*-alkenyl acetals **1**



entry	R ¹	R ²	R ³		yield (%) ^a
1	THP ^b	Me	<i>n</i> -C ₄ H ₉	a	90
2	THP ^b	<i>n</i> -C ₄ H ₉	<i>n</i> -C ₄ H ₉	b	94
3	EE ^c	Me	<i>n</i> -C ₄ H ₉	c	99
4	EE ^c	<i>n</i> -C ₄ H ₉	<i>n</i> -C ₄ H ₉	d	93
5	EE ^c	<i>n</i> -C ₄ H ₉	<i>i</i> -C ₃ H ₇	e	96
6	EE ^c	<i>n</i> -C ₄ H ₉	CH ₃	f	98
7	EE ^c	<i>n</i> -C ₄ H ₉	H	g	77
8	BOM ^d	<i>n</i> -C ₄ H ₉	<i>n</i> -C ₄ H ₉	h	72

^a Isolated yield. ^b THP = 2-tetrahydropyranyl. ^c EE = 1-ethoxyethyl.

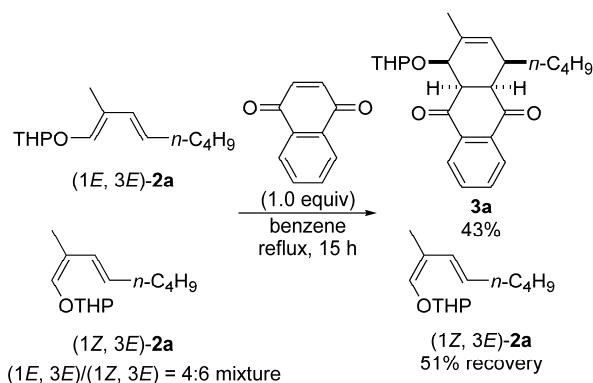
^d BOM = benzyloxymethyl.

carried out their reactions with *n*-butyllithium. The corresponding *O*-(2-tetrahydropyranyl)- or (1-ethoxyethyl)-1,3-dienyl acetals **2b–2f** were obtained with excellent yields and perfect levels of (1*Z*, 3*E*)-stereoselectivity (entries 2–6). Interestingly, the reaction of 4-unsubstituted substrate **1g** (entry 7) provided **2g** (77% yield) as derived by the initial deprotonation on the 1-ethoxyethoxy-bearing methylene in preference to the methoxy-bearing methylene. Our method is also useful for the preparation of *O*-benzyloxymethyl (BOM) derivative **2h** (entry 8).

Keywords: 1,4-Elimination; 1,3-Dienyl acetals; 1-Alkoxy-1,3-dienes; Ferrier reaction; α -Quaternary- β,γ -unsaturated aldehydes.

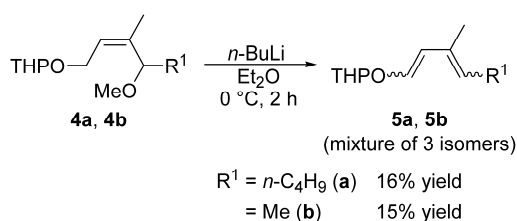
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The stereochemistry of **2a** was assigned by ^1H NMR comparison with an authentic sample, which was obtained by Diels–Alder reaction (Scheme 1). The Diels–Alder reaction of a 4:6 mixture of (1*E*, 3*E*)- and (1*Z*, 3*E*)-**2a**⁶ with 1,4-naphthoquinone was carried out in refluxing benzene for 15 h. One isomer resulted in the corresponding Diels–Alder adduct **3a** in 43% yield, whereas another isomer was recovered in 51% yield as an almost single stereoisomer. The stereochemistry of the reacted 1,3-dienyl acetal **2a** was assigned as (1*E*, 3*E*), and the recovered 1,3-dienyl acetal **2a** was assigned as (1*Z*, 3*E*).⁷ The stereochemistries of **2b–2h** were determined analogously to those of **2a**.



Scheme 1. Preparation of authentic sample (1*Z*, 3*E*)-**2a**.

Next, we prepared 3-substituted-(*ZZ*)-4-methoxy-*O*-alkenyl acetals **4** and performed their reactions with *n*-butyllithium to expand the scope of the present method (Scheme 2). However, the reactions were unsuccessful. The yields of the 1,3-dienyl acetal **5** were lowered compared to the 2-substituted substrate **2**. A three isomers mixture of 1,3-dienyl acetals **5** was obtained.⁸



Scheme 2. 1,4-Elimination reaction of 3-substituted-(*ZZ*)-4-methoxy-*O*-alkenyl acetals **4**.

Our previous studies determined that the (1*Z*, 3*E*)-stereoselective 1,4-elimination reaction of (*ZZ*)-4-methoxy-*O*-alkenyl acetals in ether proceeds via an initial precoordination of the two alkoxy-oxygens to *n*-butyllithium followed by E2-like elimination (Figure 1).⁴ The reaction of 2-substituted-(*ZZ*)-4-methoxy-*O*-alkenyl acetals **1** would proceed via the intermediate **A**, which leads to (1*Z*, 3*E*)-stereoisomers. However, in the case of the 3-substituted substrate **4**, the precoordination intermediate **B** would be sterically unfavorable because of the steric repulsion between 3-substituent (R³) and 4-substituent (R⁴). The 1,4-elimination of **4** may proceed through various types of unfavorable intermediates resulting in a mixture of 3 isomers.

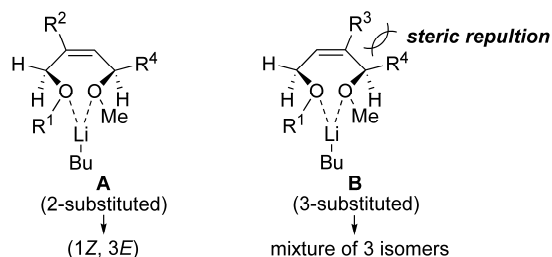
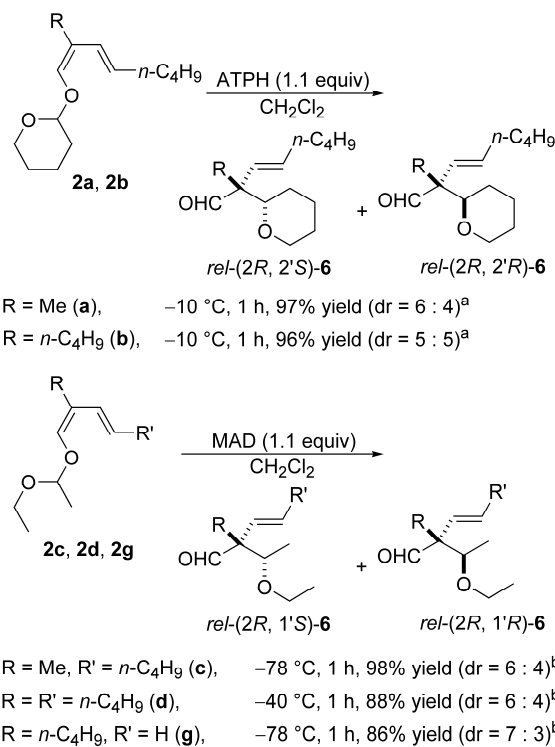


Figure 1. Proposed mechanism for 1,4-elimination of 2- and 3-substituted-(*ZZ*)-4-methoxy-*O*-alkenyl acetals.

Finally, we carried out the Ferrier reaction of 2-substituted-*O*-1,3-dienyl acetals **2** promoted by organoaluminum complexes such as aluminum tris(2,6-diphenylphenoxide) (ATPH) or methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) (Scheme 3). The reaction of **2a** in the presence of ATPH gave the corresponding α -quaternary- β,γ -unsaturated aldehyde **6a** in 97% yield [*rel*-(2*R*, 2'*S*)/*rel*-(2*R*, 2'*R*) = 6:4].¹⁰ Various types of α -quaternary- β,γ -unsaturated aldehydes **6b–d** were obtained in excellent yields with high α -regioselectivities.¹¹ Interestingly enough, 4-unsubstituted dienyl substrate **2g** also showed an equally high α -regioselectivity.



Scheme 3. Ferrier reaction of 2-substituted-*O*-1,3-dienyl acetals **2**: ^a *rel*-(2*R*, 2'*S*)/*rel*-(2*R*, 2'*R*). ^b *rel*-(2*R*, 1'*S*)/*rel*-(2*R*, 1'*R*).

In summary, the 1,4-elimination reaction of 2-substituted-(*ZZ*)-4-methoxy-*O*-alkenyl acetals with *n*-butyllithium proceeded to yield 2-substituted-1,3-dienyl acetals with high (1*Z*, 3*E*)-stereoselectivities. Application for the Ferrier reaction of the 2-substituted-1,3-dienyl acetals

afforded the corresponding α -quaternary- β,γ -unsaturated aldehydes in excellent yields with high α -regioselectivities.

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at XXX.

References and notes

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- Prepared by Horner–Wittig reaction of *trans*-oct-2-en-2-one and diethyl[(2-tetrahydropyranyloxy)methyl]phosphonate (45% overall yield): (i) LDA, THF, *trans*-oct-3-en-2-one, –78 °C to rt; (ii) *t*-BuOK, THF, rt. For more details, see Supplementary data.
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- The relative stereochemistry of **6c** was determined by ¹H NMR comparison with an authentic sample prepared via diastereoselective alkylation of α -substituted- β -hydroxyesters. The relative stereochemistries of **6a**, **6b**, **6d**, and **6g** were determined by analogy to the ¹H NMR chemical shifts of **6c**. For more details, see Supplementary data.
- ATPH is efficient for *O*-(2-tetrahydropyranyl) derivatives. For the *O*-(1-ethoxyethyl) derivatives, we used MAD because of the reasonable price. See also, ref 2a.