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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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Abstract—The 1,4-elimination reaction of 2-substituted-(2*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.

1-Alkoxy-1,3-dienes are useful synthetic intermediates that function as reactive diene components. Several applications for organic synthesis have been reported, for example, dienolate equivalents for the vinylogous aldol reactions[1] 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 (2*Z*)-4-methoxy-*O*-alkenyl acetals with *n*-butyllithium[4] 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-(2*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 (2*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**–**h** and carried out their reactions with *n*-butyllithium. The corresponding *O*-(2-tetrahydropyranyl)- or (1-ethoxyethyl)-1,3-dienyl acetals **2b**–**f** 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).

The stereochemistry of **2a** was assigned by ^{1}H 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**–**h** were determined analogously to those of **2a**.

Next, we prepared 3-substituted-(2*Z*)-4-methoxy-*O*-alkenyl acetals **4** and performed their reactions with *n*-butyllithium to expand the scope of the present

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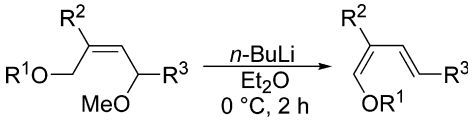
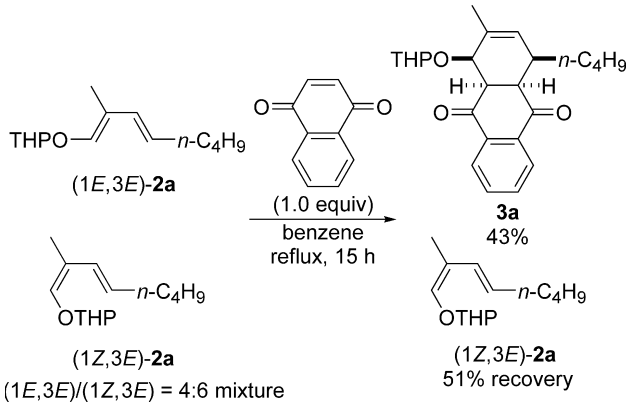
Table 1. 1,4-Elimination reaction of 2-substituted-(2*Z*)-4-methoxy-*O*-alkenyl acetals **1**

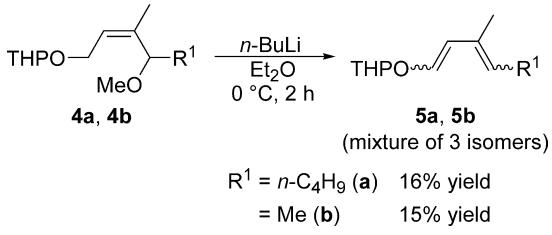


Entry	R^1	R^2	R^3		Yield[a] (%)
1	THP[b]	Me	n-C_4H_9	**a**	90
2	THP[b]	n-C_4H_9	n-C_4H_9	**b**	94
3	EE[c]	Me	n-C_4H_9	**c**	99
4	EE[c]	n-C_4H_9	n-C_4H_9	**d**	93
5	EE[c]	n-C_4H_9	i-C_3H_7	**e**	96
6	EE[c]	n-C_4H_9	CH_3	**f**	98
7	EE[c]	n-C_4H_9	H	**g**	77
8	BOM[d]	n-C_4H_9	n-C_4H_9	**h**	72

[a] Isolated yield.
[b] THP = 2-tetrahydropyranyl.
[c] EE = 1-ethoxyethyl.
[d] BOM = benzyloxymethyl.



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



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

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]

Our previous studies determined that the (1*Z*, 3*E*)-stereoselective 1,4-elimination reaction of (2*Z*)-4-methoxy-*O*-alkenyl acetals in ether proceeds via an initial

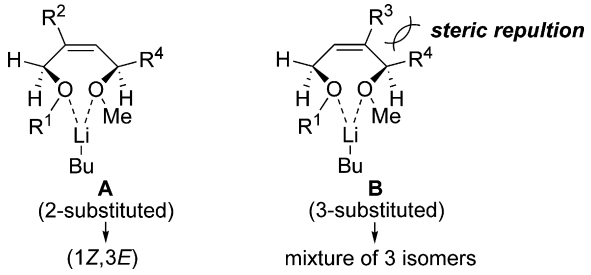
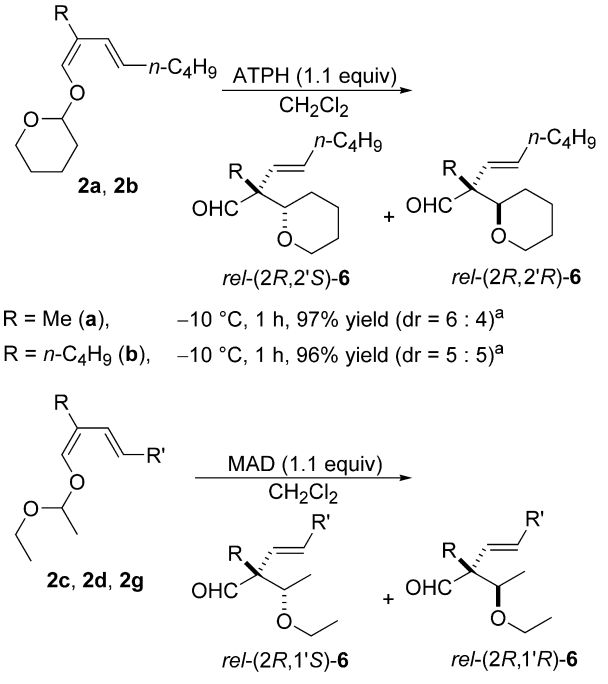


Figure 1. Proposed mechanism for 1,4-elimination of 2- and 3-substituted-(2*Z*)-4-methoxy-*O*-alkenyl acetals.

precoordination of the two alkoxy-oxygens to *n*-butyllithium followed by E2-like elimination (Fig. 1).[4] The reaction of 2-substituted-(2*Z*)-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 (R^3) and 4-substituent (R^4). The 1,4-elimination of **4** may proceed through various types of unfavorable intermediates resulting in a mixture of three isomers.

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).



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*).

The reaction of **2a** in the presence of ATPH gave the corresponding α-quaternary-β,γ-unsaturated aldehyde[9] **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.

In summary, the 1,4-elimination reaction of 2-substituted-(2*Z*)-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.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.049.

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5. Prepared from tetrahydro-2-(2-propynyloxy)-2*H*-pyran (50% overall yield): (i) *n*-BuLi, THF, ClCOOEt, −78 to −10 °C; (ii) Me_2CuLi, THF, −78 °C; (iii) Red–Al, toluene, 0 °C; (iv) MnO_2, hexane, rt; (v) *n*-BuLi, THF, −78 °C; (vi) NaH, MeI, THF, 0 °C to rt.
6. 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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8. Similar yields and selectivities were observed using 3-butyl or *O*-(1-ethoxyethyl) derivatives.
9. For preparations of α-quaternary-β,γ-unsaturated aldehydes: (a) Deng, X.-M.; Sun, X.-L.; Tang, Y. *J. Org. Chem.* **2005**, *70*, 6537–6540; (b) Mino, T.; Fukui, S.; Yamashita, M. *J. Org. Chem.* **1997**, *62*, 734–735; (c) Hiroi, K.; Nakazawa, K. *Chem. Lett.* **1980**, *9*, 1077–1080.
10. The relative stereochemistry of **6c** was determined by ^{1}H 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 ^{1}H NMR chemical shifts of **6c**. For more details, see Supplementary data.
11. 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.