

# Regio- and Stereoselective Ferrier Reaction of *O*-1,3-Dienyl Acetals Promoted by Organoaluminum Complexes

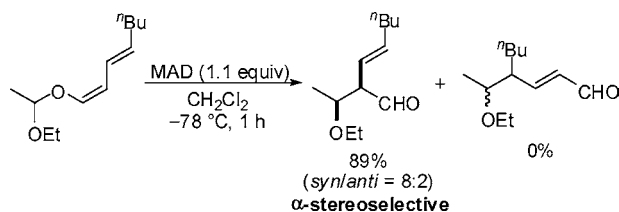
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## ABSTRACT

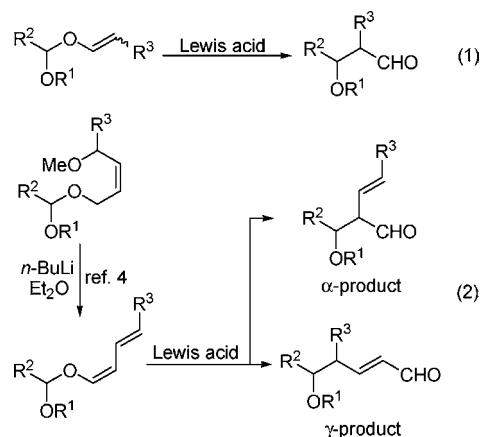


The Ferrier reaction of *O*-1,3-dienyl acetals promoted by organoaluminum complexes such as methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) is shown to proceed with a high degree of regio- and stereoselectivity to afford the corresponding  $\alpha$ -alkenyl-substituted  $\beta$ -alkoxy aldehydes in good yields. The mechanistic origin of the high regiocontrolling ability of MAD is elucidated. This method, coupled with the easy availability of the requisite substrates, expands the synthetic scope of the Ferrier reaction.

The Ferrier reaction<sup>1</sup> of *O*-vinylic acetals (1-alkenyl 1-alkoxyalkyl ethers) is a useful synthetic transformation because it can easily convert the *O*–C bond into a new C–C bond to provide the corresponding  $\beta$ -alkoxyaldehydes (Scheme 1, eq 1) and hence has found wide application (as a kind of formal aldol-type reaction) for the synthesis of oxygen-containing heterocycles such as tetrahydropyranyl derivatives and *C*-glycosides.<sup>2</sup> However, little attention has been paid to the *O*-1,3-dienyl version of the Ferrier reaction which might pose the regiochemical problem (Scheme 1, eq 2).<sup>3</sup> Very recently, we have developed an efficient synthetic method for *O*-1,3-

dienyl acetals (1-alkoxyalkyl 1,3-dienyl ethers) based on the 1,4-elimination of the *O*-4-methoxy-(2*Z*)-alkenyl acetals with

**Scheme 1.** Ferrier Reaction of *O*-Vinylic Acetals (1) and *O*-1,3-Dienyl Acetals (2)



(1) (a) Ferrier, R. J. *Chem. Rev.* **1993**, *93*, 2779. (b) Ferrier, R. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1455.

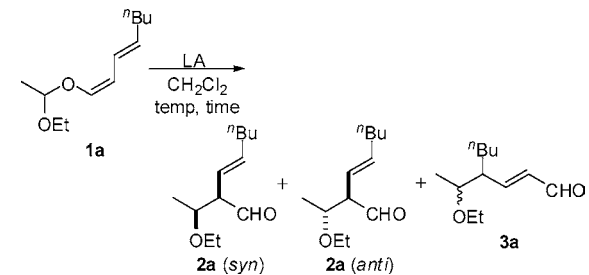
(2) (a) Shenoy, S. R.; Woerpel, K. A. *Org. Lett.* **2005**, *7*, 1157. (b) Suzuki, T.; Inui, M.; Hosokawa, S.; Kobayashi, S. *Tetrahedron Lett.* **2003**, *44*, 3713. (c) Zhang, Y.; Reynolds, N. T.; Manju, K.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 9720. (d) Dixon, D. J.; Ley, S. V.; Tate, E. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2385. (e) Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett.* **1996**, *37*, 141. (f) Takahashi, M.; Suzuki, H.; Moro-oka, Y.; Ikawa, T. *Tetrahedron Lett.* **1982**, *23*, 4031. (g) Takahashi, M.; Suzuki, H.; Moro-oka, Y.; Ikawa, T. *Tetrahedron Lett.* **1982**, *23*, 1079.

(3) An example of Ferrier reaction of 1,3-dienyl acetals: Inui, M.; Hosokawa, S.; Nakazaki, A.; Kobayashi, S. *Tetrahedron Lett.* **2005**, *46*, 3245.

*n*-butyllithium.<sup>4</sup> With various *O*-dienyl acetals in hand, our interest was now directed toward the regio- and stereochemistry in the Lewis acid promoted Ferrier reaction thereof. We now wish to report that the Ferrier reaction of *O*-1,3-dienyl acetal (**1**), when promoted by bulky organoaluminum complexes such as methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD), proceeds with a remarkably high regioselectivity to afford the corresponding  $\alpha$ -alkenyl-substituted  $\beta$ -alkoxy aldehydes (**2**).

Because the Lewis acid promoted Ferrier reaction in general is believed to proceed via the ionic cleavage forming the enolate and carbocationic species followed by their recombination, the Ferrier version now concerned might involve the dienolate species and hence might provide the  $\alpha$ - and  $\gamma$ -alkylation products as mentioned above. Thus, the choice of the Lewis acid used is crucial for efficient regiocontrol. First, we examined the regiochemistry of the reaction of *O*-1,3-dienyl acetal **1a** in dichloromethane at  $-78$  °C using typical Lewis acids (Table 1). The use of boron

**Table 1.** Ferrier Reaction of the *O*-1,3-Dienyl Acetal (**1a**) Promoted by Several Representative Lewis Acids (LA)



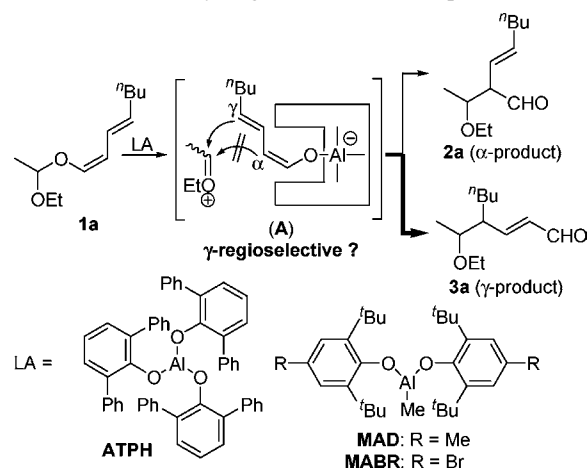
entry	LA (equiv)	temp, time (°C, h)	yield (%) <sup>a</sup> of <b>2a</b> (syn/anti) <sup>b</sup>	<b>3a</b> (dr) <sup>b</sup>
1	BF <sub>3</sub> ·OEt <sub>2</sub> (0.1)	-78, 1	75 (1:9)	9 (5:5)
2	SnCl <sub>4</sub> (0.2)	-78, 1	80 (1:9)	18 (7:3)
3	TiCl <sub>4</sub> (1.1)	-78, 1	51 (2:8)	33 (7:3)
4	MAD (1.1)	-78, 1	89 (8:2)	trace
5	MABR (1.1)	-78, 1	88 (8:2)	trace
6	ATPH (1.1)	-78, 2 to -10, 1	91 (5:5)	trace

<sup>a</sup> Isolated yield. <sup>b</sup> The diastereomeric ratios of **2a** (syn/anti) and **3a** (dr) were determined by <sup>1</sup>H NMR assay.

trifluoride diethyl etherate (BF<sub>3</sub>·OEt<sub>2</sub>), tin tetrachloride (SnCl<sub>4</sub>), and titanium tetrachloride (TiCl<sub>4</sub>) was found to provide a mixture of the  $\alpha$ -product **2a** and  $\gamma$ -regioisomer **3a**, with the former predominating (Table 1, entries 1–3). The  $\alpha$ - and  $\gamma$ -regioisomers were assigned by <sup>1</sup>H NMR analysis (olefinic protons: 5.3–5.6 ppm for **2a** and 6.1–6.8 ppm for **3a**). The syn/anti stereochemistry of **2a** was determined by <sup>1</sup>H NMR comparison with an authentic sample.<sup>5</sup> Next, we were intrigued by the use of bulky aluminum complexes<sup>6</sup> such as MAD, methylaluminum bis(2,6-di-*tert*-butyl-4-bromophenoxide) (MABR), and aluminum tris(2,6-diphenylphenoxide) (ATPH) with the expecta-

tion that the aluminum dienolate involved would undergo the alkylation predominantly at the  $\gamma$ -position because the  $\alpha$ -alkylation was effectively suppressed by the bulky ligands (Scheme 2).<sup>7</sup> Rather surprisingly, however, the stoichiometric

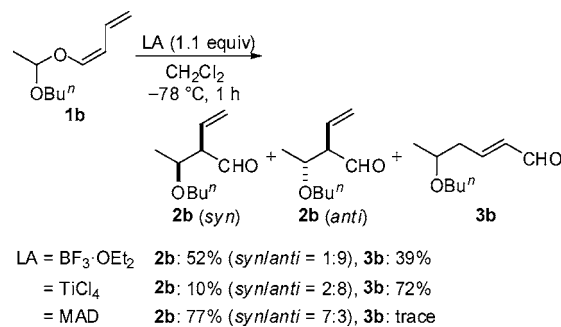
**Scheme 2.** Hypothesis for the Ferrier Reaction of **1a** Promoted by Organoaluminum Complexes



use of MAD was found to result in the exclusive formation of the  $\alpha$ -product **2a** in 89% yield, together with a high diastereoselectivity (Table 1, entry 4). Only a trace amount of  $\gamma$ -product **3a** was detected in the product mixture. Similar uses of MABR and ATPH provided equally high  $\alpha$ -regioselectivities (entries 5 and 6), although the latter showed a slightly lowered diastereoselectivity.<sup>8</sup>

Significantly, the MAD-promoted Ferrier reaction of  $\gamma$ -unsubstituted dienyl substrate **1b** also showed an equally high  $\alpha$ -regioselectivity, whereas BF<sub>3</sub>- and TiCl<sub>4</sub>-promoted reactions of **1b** provided higher  $\gamma$ -selectivities than those of the  $\gamma$ -substituted counterpart **1a** (Scheme 3).

**Scheme 3.** MAD-Promoted Ferrier Reaction of **1b**<sup>a-c</sup>



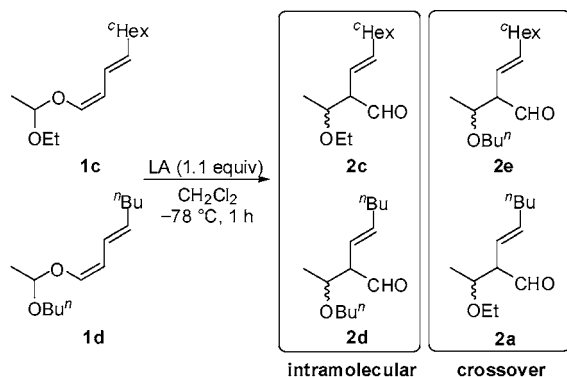
<sup>a</sup>The yields were determined by <sup>1</sup>H NMR analysis using 1,4-bis(trifluoromethyl)benzene as an internal standard. <sup>b</sup>The syn/anti stereoselectivities were determined by <sup>1</sup>H NMR assay. <sup>c</sup>The syn/anti stereochemistry was determined by analogy to the chemical shifts and coupling constants of *syn*-**2a** or *anti*-**2a**. For details, see Supporting Information.

The question of the mechanistic origin of the high  $\alpha$ -regioselectivity observed with the bulky aluminum complexes

(4) Tayama, E.; Sugai, S. *Synlett* **2006**, 849.

immediately arose. To answer the question, we performed crossover experiments to reconfirm the intramolecularity of the Lewis acid promoted reactions concerned (Scheme 4).

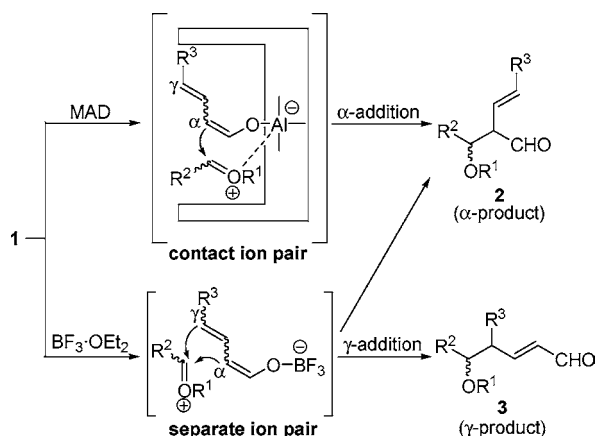
**Scheme 4.** Crossover Reaction of **1c** and **1d**



LA =  $\text{BF}_3 \cdot \text{OEt}_2$ , 72%, **2c/2d/2e/2a** = 3:2:3:2 (50% crossover)  
 = MAD, 76%, **2c/2d/2e/2a** = 5.5:0:0 (No crossover)

Thus, an equimolar mixture of substrates **1c** and **1d** was subjected to the  $\text{BF}_3$ - and MAD-promoted reaction. Interestingly enough, product analyses revealed that the MAD-promoted reaction did not produce any detectable amount of the crossover products (**2e** and **2a**),<sup>9</sup> whereas the  $\text{BF}_3$ -promoted reaction provided the crossover products in ca. 50% yield.<sup>10</sup> These observations suggest that the MAD-promoted reaction would proceed via the “contact ion pair”, thus leading to the high  $\alpha$ -regioselectivity as actually observed, whereas the  $\text{BF}_3$ -promoted reaction would proceed via the “separate ion pair”, thus producing both  $\alpha$ - and  $\gamma$ -products (Scheme 5).

**Scheme 5.** Proposed Mechanism of  $\alpha$ -Regioselective Ferrier Reaction



To further expand the scope of the present regioselective Ferrier reaction, we prepared a series of *O*-1,3-dienyl acetals and carried out their aluminum complex-promoted reactions (Table 2). In all cases, only  $\alpha$ -products were obtained in high yields. It is interesting to note that ATPH is more efficient

**Table 2.** Ferrier Reaction of Various Types of *O*-1,3-Dienyl Acetals and Ketal **1**

entry	LA	temp, time (°C, h)	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	yield (%) <sup>a</sup> (syn/anti) <sup>b,c</sup>	
1	MAD	-78, 1	<b>d</b>	<sup>n</sup> Bu	Me	H	88 (7:3)
2	MAD	-78, 1	<b>f</b>	Me	Me	Me	90
3	ATPH	-78, 1 to -20, 1	<b>g</b>	-(CH <sub>2</sub> ) <sub>4</sub>	H	H	92 (7:3)
4	ATPH	-78, 2 to -20, 3	<b>h</b>	-(CH <sub>2</sub> ) <sub>3</sub>	H	H	78 (5:5)

<sup>a</sup> Isolated yield. <sup>b</sup> The ratios were determined by <sup>1</sup>H NMR assay. <sup>c</sup> The syn/anti stereochemistries were determined by analogy to chemical shifts and coupling constants of *syn*-**2a** or *anti*-**2a**. For details, see Supporting Information.

than MAD for the tetrahydropyranyl (**1g**) and tetrahydrofuranly (**1h**) derivatives.

In summary, we have demonstrated that the Ferrier reaction of *O*-1,3-dienyl acetals in the presence of aluminum complexes such as MAD proceeds with high  $\alpha$ -regioselectivity to afford the corresponding  $\alpha$ -alkenyl-substituted  $\beta$ -alkoxy aldehydes in good yields and high diastereoselectivities. The high regioselectivity is suggested to arise from the contact ion pair type intermediate. This method, coupled with the easy availability of the requisite substrates, expands the synthetic scope of the Ferrier reaction. Further work to make the reaction catalytic is in progress in our laboratory.

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**Supporting Information Available:** Experimental procedures and characterization data of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(5) The product **2a** (syn/anti = 8:2) was converted to 2-ethoxy-3-ethoxymethylnonane [(i)  $\text{NaBH}_4$ , MeOH, 0 °C to rt; (ii)  $\text{H}_2$  (1 atm), Pd-C, EtOAc, rt; (iii) EtI, NaH, THF, 0 °C to reflux], and the anti authentic sample was prepared from *n*-octanoic acid BHT ester via the known anti-selective aldol reaction with acetaldehyde. For more details, see Supporting Information.

(6) For review: Miyaura, N.; Maruoka, K. In *Synthesis of Organometallic Compounds*; Komiya, S., Ed.; John Wiley & Sons Ltd.: Chichester, 1997; pp 364–390.

(7) ATPH-promoted conjugate addition to  $\alpha,\beta$ -unsaturated aldehydes gave 1,4-adducts with high  $\gamma$ -regioselectivities. See: Maruoka, K.; Imoto, H.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 4131.

(8) Use of trimethylaluminum ( $\text{Me}_3\text{Al}$ ) did not induce the reaction at all (recovery of **1a** in 92% yield). Use of methylaluminum bis(phenoxy) [ $\text{MeAl}(\text{OPh})_2$ ] gave a complex mixture.

(9) The product ratios were determined by 500 MHz <sup>1</sup>H NMR analysis. All possible stereoisomers were prepared independently as authentic samples.

(10) For a few examples of the Ferrier reaction forming the crossover products, see refs 2a and 2c.