

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

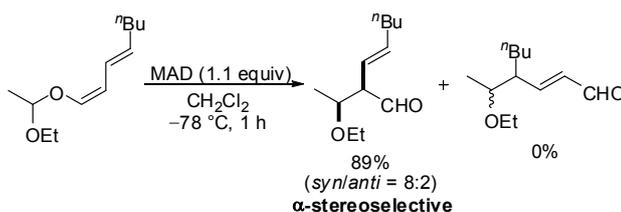
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ABSTRACT



The Ferrier reaction of *O*-1,3-dienyl acetals promoted by organoaluminum complexes such as MAD is shown to proceed with a high degree of regio- and stereoselectivity to afford the corresponding α -alkenyl-substituted β -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 reaction¹ of *O*-vinylic acetals (1-alkenyl 1-alkoxyalkyl ethers) is a useful synthetic transformation since it can easily convert the O–C bond into a new C–C bond to provide the corresponding β -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.² 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).³ 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-(*Z*)-alkenyl acetals with *n*-butyllithium.⁴ 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

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

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

high regioselectivity to afford the corresponding α -alkenyl-substituted β -alkoxy aldehydes (**2**).

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

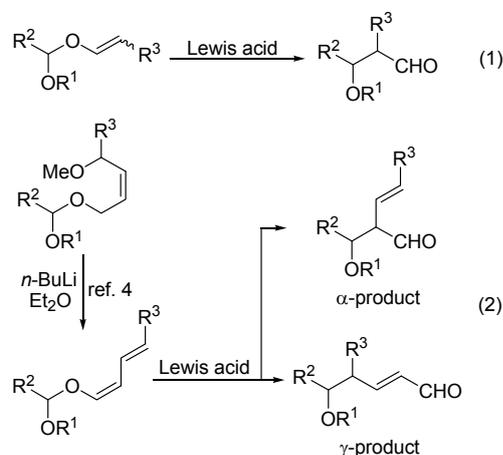
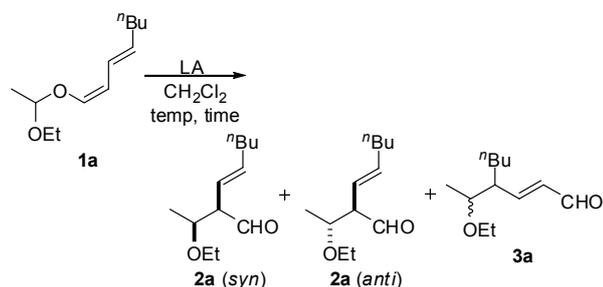


Table 1. Ferrier Reaction of *O*-1,3-Dienyl Acetal (**1a**) Promoted by Several Representative Lewis Acids (LA).

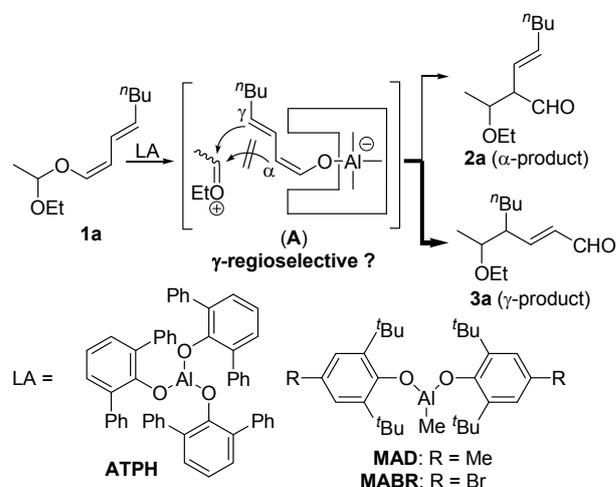


entry	LA (equiv)	temp, time (°C, h)	yield (%) ^a 2a (<i>syn/anti</i>) ^b	3a (dr) ^b
1	BF ₃ ·OEt ₂ (0.1)	-78, 1	75 (1:9)	9 (5:5)
2	SnCl ₄ (0.2)	-78, 1	80 (1:9)	18 (7:3)
3	TiCl ₄ (1.1)	-78, 1	51 (2:8)	33 (7:3)
4	MAD (1.1)	-78, 1	89 (8:2)	trace
5	MABR (1.1)	-78, 1	88 (8:2)	trace
6	ATPH (1.1)	-78, 2 to -10,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

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

Since 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 α - and γ -alkylation product as above mentioned. Thus the choice of the Lewis acid used is crucial for efficient regiocontrol. First, we examined the

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



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 trifluoride diethyl etherate (BF₃·OEt₂), tin tetrachloride (SnCl₄), and titanium tetrachloride (TiCl₄) was all found to provide a mixture of the α -product **2a** and γ -regioisomer **3a**, the former predominating (Table 1, entries 1–3). The α - or γ -regioisomer were assigned by ¹H NMR analysis (olefinic protons: 5.3–5.6 ppm for **2a**, 6.1–6.8 ppm for **3a**). The *syn/anti* stereochemistry of **2a** was determined by ¹H NMR comparison with an authentic sample.⁵ Next, we were intrigued by the use of bulky aluminum complexes⁶ such as MAD, methylaluminum bis(2,6-*tert*-butyl-4-bromophenoxide) (MABR), and aluminum tris(2,6-diphenylphenoxide) (ATPH) with the expectation that the aluminum dienolate involved would undergo the alkylation predominantly at the γ -position because the α -alkylation effectively suppressed by the bulky ligands (Scheme 2).⁷ Rather surprisingly, however, the stoichiometric use of MAD was found to result in the exclusive formation of the α -product **2a** in 89% yield, together with a high diastereoselectivity (Table 1, entry 4). Only a trace amount of γ -product **3a** was detected in the product mixture. Similar uses of MABR and ATPH provided equally high α -regioselectivities (entries 5 and

(5) The product **2a** (*syn/anti* = 8:2) was converted to 2-ethoxy-3-ethoxymethylnonane [(i) NaBH₄, MeOH, 0 °C to rt. (ii) H₂ (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. More details: see Supporting Information.

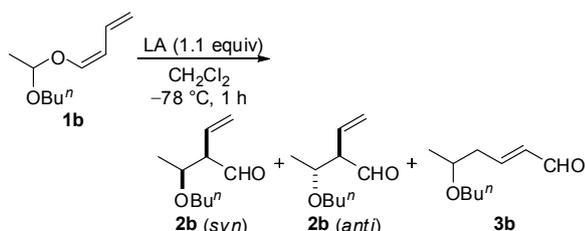
(6) For review: Miyaura, N.; Maruoka, K. In *Synthesis of Organometallic Compounds*; Komiyama, S., Ed.; John Wiley & Sons Ltd: Chichester, 1997; pp 364–390.

(7) ATPH-promoted conjugated addition to α,β -unsaturated aldehydes gave 1,4-adducts with high γ -regioselectivities, see: Maruoka, K.; Imoto, H.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 4131.

6), although the latter showed a slightly lowered diastereoselectivity.⁸

Significantly, the MAD-promoted Ferrier reaction of γ -unsubstituted dienyl substrate **1b** also showed a high α -regioselectivity, while BF₃- and TiCl₄-promoted reactions of **1b** provided higher γ -selectivities than those of the γ -substituted counterpart **1a** (Scheme 3).

Scheme 3. MAD-Promoted Ferrier Reaction of **1b**.^{a,b,c}



LA = BF₃·OEt₂ **2b**: 52% (*syn/anti* = 1:9), **3b**: 39%
 = TiCl₄ **2b**: 10% (*syn/anti* = 2:8), **3b**: 72%
 = MAD **2b**: 77% (*syn/anti* = 7:3), **3b**: trace

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

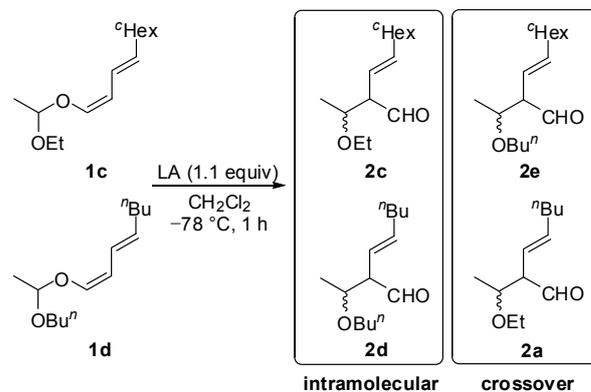
The question immediately arose as to what the mechanistic origin of the high α -regioselectivity observed with the bulky aluminum complexes. To answer the question, we performed crossover experiments to reconfirm the intramolecularity of the Lewis acid-promoted reactions concerned (Scheme 4). Thus, an equimolar mixture of substrates **1c** and **1d** was subjected to the BF₃- 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**),⁹ whereas the BF₃-promoted reaction provided the crossover products in ca. 50% yield.¹⁰ These observations suggest that the MAD-promoted reaction would proceed via the “contact ion pair”, thus leading to the high α -regioselectivity as actually observed, whereas the BF₃-promoted reaction would proceed via the “separate ion pair”, thus producing both α - and γ -products (Scheme 5).

(8) Use of trimethylaluminum (Me₃Al) did not induce the reaction at all (recovery of **1a** in 92% yield). Use of methylaluminum bis(phenoxide) [MeAl(OPh)₂] gave a complex mixture.

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

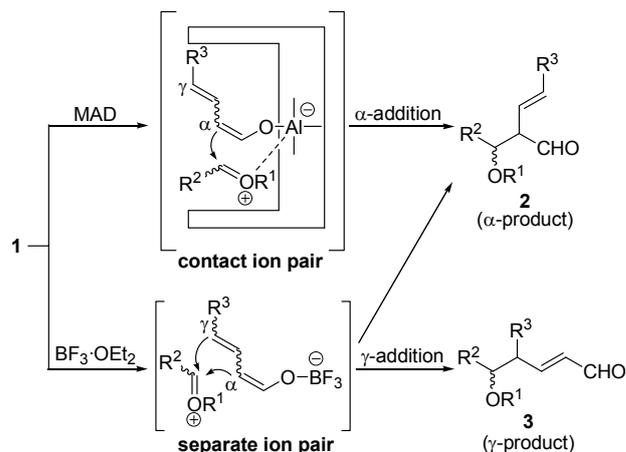
(10) For a few examples of the Ferrier reaction forming the crossover products, see ref. 2a and 2c.

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



LA = BF₃·OEt₂, 72%, **2c/2d/2e/2a** = 3:2:3:2 (50% crossover)
 = MAD, 76%, **2c/2d/2e/2a** = 5:5:0:0 (No crossover)

Scheme 5. Proposed Mechanism of α -Regioselective Ferrier Reaction.

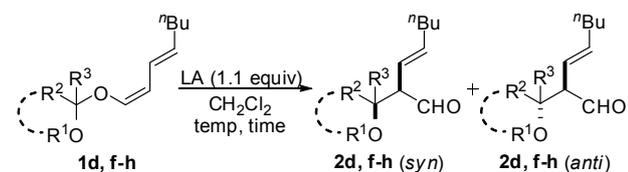


To further expand the scope of the present regioselective Ferrier reaction, we prepared a series of *O*-1,3-dienyl acetals and carried out their aluminum complex-promoted reactions (Table 2). In all cases, only α -products were obtained in high yields. It is interesting to note that ATPH is more efficient than MAD for the tetrahydropyranyl- (**1g**) and tetrahydrofuranyl- (**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 α -regioselectivity to afford the corresponding α -alkenyl-substituted β -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.

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



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

^a Isolated yield. ^b The ratios were determined by ¹H NMR assay.

^c The *syn/anti* stereochemistries were determined by analogy to chemical shifts and coupling constants of *syn*-**2a** or *anti*-**2a**. Details: see Supporting Information.

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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>.