



## Digest paper

## Recent development of vinylogous Mukaiyama aldol reactions

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## ABSTRACT

The vinylogous Mukaiyama aldol reaction (VMAR) is a powerful tool of polyketide synthesis, which constructs a large size structure by simultaneous introduction of the stereogenic center(s) and the  $\alpha,\beta$ -unsaturated carbonyl group. A variety of stereocontrolled VMARs have been developed and applied to natural product synthesis. This review is focused on recent development of the vinylogous Mukaiyama aldol reaction using *s-trans* silyl dienolates.

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## Introduction

The vinylogous Mukaiyama aldol reaction (VMAR)<sup>1</sup> provides large polyketide segments by the simultaneous induction of the stereogenic center(s) and the  $\alpha,\beta$ -unsaturated carbonyl group. Therefore, the VMAR has been employed as a powerful tool of polyketide synthesis. Since the first report in 1975, the VMAR has been developed and excellent reviews have been presented.<sup>1–7</sup>

This review is focused on the recent vinylogous Mukaiyama aldol reactions using *s-trans* silyl dienol ethers. The VMARs using franone-derived silyl dienol ethers, not included in this review, also have been well-investigated, which are summarized in recent reviews.<sup>8–10</sup>

## Stereoselective VMAR with chiral aldehydes

The VMAR with chiral aldehydes and non-chiral silyl dienolates in the presence of non-chiral Lewis acids has been utilized in natural product synthesis. At the beginning, the aldehyde-depending stereoselective VMARs are briefly reviewed. Kalesse group reported on VMAR using the chiral aldehyde **1** and vinylketene silyl acetal **2** (Fig. 1).<sup>11</sup> They found that BPh<sub>3</sub> promoted the reaction stereoselectively, while BF<sub>3</sub>·OEt<sub>2</sub> gave the adducts in moderate selectivity. The stereoselectivity of this reaction was rationalized by the Felkin-Ahn model. Interestingly, B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> gave the protected adduct **4** in good yield with high selectivity.

Kalesse group also reported that VMAR using *Z,Z*-vinylketene silyl acetal **5** proceeded to give *syn* adduct **6** in the presence of B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> (Fig. 2).<sup>12</sup> All-*syn* products **7** and **8** were obtained stereoselectively by the Felkin-Ahn control. **9** was also the Felkin-Ahn

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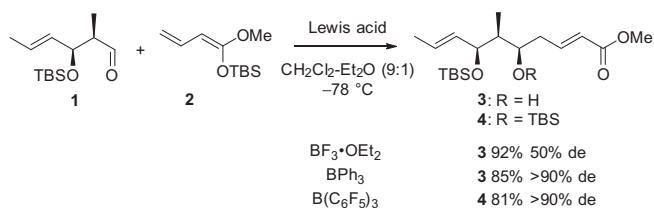


Fig. 1. The Boron-mediated VMAR with aldehyde **1**.

product, while the reaction proceeded in moderate selectivity on Felkin-Ahn control. This chemistry was applied to the total synthesis of tetradolide.<sup>13,14</sup>

Kalesse group achieved the tandem Jung reaction-VMAR by using epoxy alcohol **10** and vinylketene silyl acetal **11** in the presence of two equivalents of TBSOTf (Fig. 3).<sup>15</sup> Epoxy alcohol **10** underwent the O-silylation and the semi-pinacol rearrangement to provide the activated aldehyde **13** which reacted with **11** to afford all-*syn* adduct **12** by the Felkin-Ahn control.

Kalesse group also accomplished the stereodivergent VMAR by using PMB-protected Roche aldehyde **15** (Fig. 4).<sup>16</sup> The MgBr<sub>2</sub>-mediated VMAR produced 4,5-*syn*-5,6-*anti* adduct **16** in high stereoselectivity. ZnCl<sub>2</sub> promoted the reaction in the presence of *i*-PrOH to afford **17** in good selectivity, and Cy<sub>2</sub>BCl-mediated VMAR proceeded to give all-*syn* product **18** in excellent stereoselectivity. The favored transition states of VMARs promoted with MgBr<sub>2</sub>, ZnCl<sub>2</sub>, and Cy<sub>2</sub>BCl were proposed as **19**, **20**, and **21**, respectively.

### Stereoselective VMAR with the chiral vinylketene silyl *N,O*-acetals

Kobayashi and Hosokawa group developed the stereoselective vinylogous Mukaiyama aldol reactions using vinylketene silyl *N,O*-acetals possessing the chiral oxazolidinone (Fig. 5).<sup>17</sup> The VMAR

using vinylketene silyl *N,O*-acetal **22** took place stereoselectively to give  $\delta$ -hydroxy- $\alpha,\beta$ -unsaturated imide **23** (eq 1). The 1,7-asymmetric induction was carried out in excellent stereoselectivity. Vinylketene silyl *N,O*-acetal **24** also worked to give *anti* adduct **25** stereoselectively (eq 2). These reactions have been widely used in natural product syntheses.<sup>7,18–20</sup> The stereodivergent synthesis of reduced polypropionates was also achieved based on the reaction using **24**.<sup>21</sup> The transition state of this reaction was proposed as shown in Fig. 6 by the conformational analysis of **24** using X-ray crystallography and NOE correlation in CDCl<sub>3</sub>.<sup>17</sup>

Kobayashi group reported that the addition of H<sub>2</sub>O accelerated the VMARs without decreasing yield and stereoselectivity (Fig. 7).<sup>22</sup> The reaction of **22** with hexanal under the original conditions took 7 h, while the reaction with 10 mol% H<sub>2</sub>O completed in 45 min. The reaction of **24** also accelerated to give *anti* adduct **27** in 45 min in quantitative yield. On the acceleration they tentatively proposed two possibilities including H<sub>2</sub>O-mediated dissociation of TiCl<sub>4</sub> and the double activation of the carbonyl group of the aldehyde by both TiCl<sub>4</sub> and proton of a plausible hydrated TiCl<sub>4</sub>. This method was utilized in the total synthesis of fomitellic acid **B**.<sup>23,24</sup>

Yang group reported that AgSbF<sub>6</sub> was identified as an efficient agent to reverse the facial selectivity of the TiCl<sub>4</sub>-mediated VMAR with vinylketene silyl *N,O*-acetal **28** and glyoxylate **29** (Fig. 8).<sup>25</sup> Without silver(I) cation the VMAR proceeded to afford **30** as the major product, while the reaction with AgSbF<sub>6</sub> generated **31** in high yield with excellent selectivity. They accounted the stereoselectivity of the VMARs with and without silver salt as follows: As shown in Fig. 9, in the absence of silver(I) cation, TiCl<sub>4</sub>-aldehyde **29** complex could be approached from the upper face of the diene as **32** to avoid the electric repulsion between the ester carbonyl oxygen and the oxazolidinone carbonyl oxygen, thus, the adduct **30** turned out to be the major product. On the other hand, in the presence of AgSbF<sub>6</sub>, the resulting TiCl<sub>4</sub><sup>+</sup> might form the hexacoordinated complex **33** with **28** and **29**. As the result, the adduct **31** was

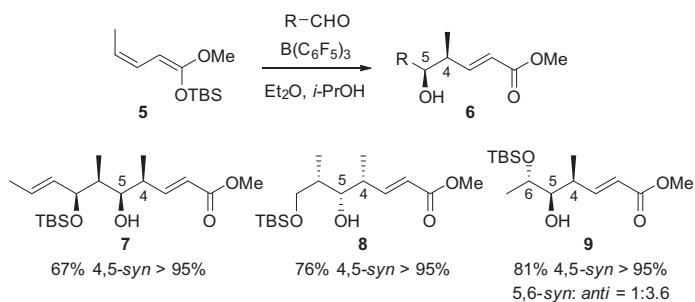


Fig. 2. The B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub>-mediated VMAR with *Z,Z*-vinylketene silyl *N,O*-acetal **5**.

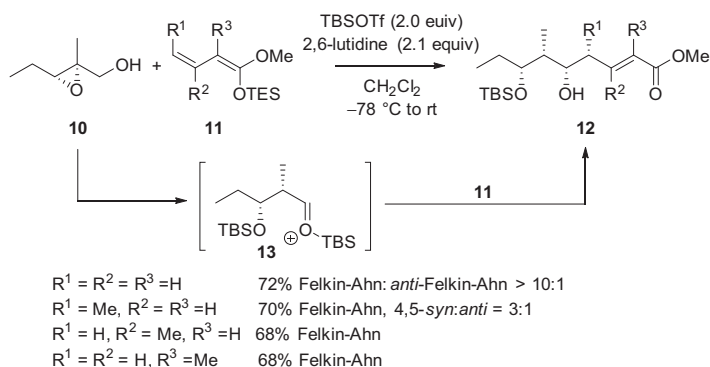


Fig. 3. The tandem Jung reaction-vinylogous Mukaiyama aldol reaction.

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