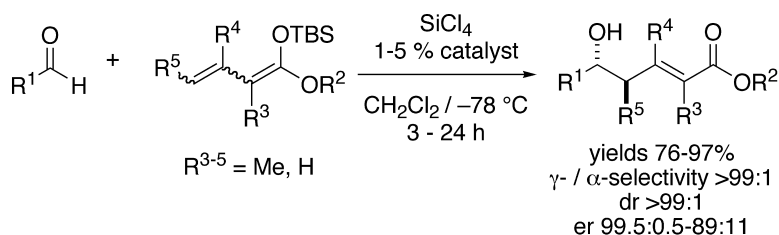


## Lewis Base Activation of Lewis Acids. Vinylogous Aldol Reactions

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## Lewis Base Activation of Lewis Acids. Vinylogous Aldol Reactions

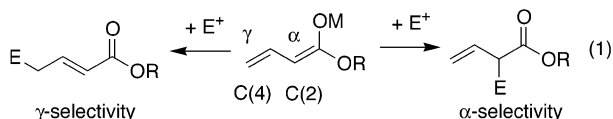
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In 1935, R. C. Fuson formulated the principle of vinylogy to provide a better understanding of the “anomalous” reactivity of some unsaturated compounds.<sup>1</sup> He recognized that when a functional group is attached to an unsaturated moiety, “the influence of (that) functional group might sometimes be propagated along the chain and make itself apparent at some remote point in the molecule.” Since then, this simple concept has been applied in countless reactions, extending the electrophilic or nucleophilic character of a functional group.

However, the possibility of reaction at a remote position does not guarantee that it will be favored or even observed. Reactions involving vinylogous systems must address regioselectivity, along with diastereo- and enantioselectivity. The problem is illustrated in the chemistry of dienolates, wherein reaction at the remote position is disfavored. Because of the high electron density at C(2) of a metallo-dienolate, reaction at the  $\alpha$ -position is favored kinetically over reaction at the  $\gamma$ -position (eq 1).<sup>2</sup>



The advantages of a vinylogous addition process involving dienolates, especially when an aldehyde is used as the electrophile, are considerable because the  $\gamma$ -addition product is a common motif that has found application in synthesis.<sup>3</sup> A strategy that has proven successful for overcoming the inherent  $\alpha$ -selectivity of metallo-dienolates involves steric differentiation of the reactive centers through the use of bulky modifiers that discriminate the enolate reactive sites.<sup>4</sup>

A different strategy that allows for high  $\gamma$ -selectivity is the use of Lewis acid catalysis in the addition of silyl dienol ethers. Unlike the reactions of metallo-dienolates, which are under electrostatic control, the reactions of silyl dienol ethers are under FMO control, therefore favoring reaction at C(4).<sup>2</sup> The application of Lewis acids in  $\gamma$ -selective aldol processes provides an attractive target for asymmetric catalysis. Indeed, Carreira,<sup>5</sup> Campagne,<sup>6</sup> and Scettri<sup>7</sup> have reported the use of Ti(IV) and Cu(II) complexes for the highly regio- and enantioselective additions of dioxanone- and simple ester-derived dienol ethers to a wide variety of aldehydes. Furthermore, Evans has employed a Cu(II) bisoxazoline catalyst in the addition of dienol ethers to  $\alpha$ -alkoxy aldehydes.<sup>8</sup> Although selectivities are generally high for these catalysts in the case of dioxanone-derived dienol ethers, simple ester-derived dienol ethers typically display lower yields and selectivities. We report herein a new method for catalytic enantioselective vinylogous aldol reactions that exhibits high regio-, diastereo-, and enantioselectivity for a number of dienol ether and aldehyde structures.

A previous disclosure from these laboratories demonstrated that the combination of a catalytic amount of the chiral bis-phosphoramidate (*R,R*)-**5**<sup>14</sup> and silicon tetrachloride (**2**) is able to promote a

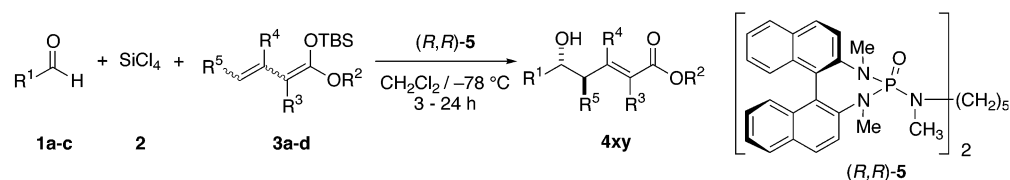
highly enantio- and diastereoselective addition of silyl ketene acetals to aldehydes.<sup>9</sup> In view of the exquisite sensitivity of this catalyst system to the steric demand of the substrates, we envisioned that reaction of a dienol ether would be favored at the less-substituted,  $\gamma$ -position. Initial investigations with the ethyl crotonate-derived dienol ether **3a**<sup>10</sup> and benzaldehyde **1a** reveal that the  $\gamma$ -addition product **4aa** can be obtained exclusively in the presence of **2** and only 1 mol % of (*R,R*)-**5** (Table 1, entry 1). The reaction of **3a** with cinnamaldehyde **1b** under similar conditions provided comparable yield and selectivity. The aliphatic aldehyde **1c**, often a problematic case in other SiCl<sub>4</sub>-promoted aldol processes,<sup>9</sup> also reacted to provide the product with high regio- and enantioselectivity. However, the use of 5 mol % of (*R,R*)-**5** and 5 mol % of diisopropylethylamine was required for consistently high yields. In all cases, the resulting enoate was exclusively of *E* configuration.

Extension of this method to other dienol ethers demonstrated the substrate scope of the **2**/phosphoramidate catalyst system. The methyl tiglate-derived dienol ether **3b**<sup>10</sup> yielded the  $\gamma$ -addition products **4ba** and **4bb** as single constitutional isomers with high enantioselectivity in the additions to **1a** and **1b** (entries 4 and 5). However, despite several attempts, **3b** did not react with **1c**. The ethyl senecioate-derived dienol ether **3c**<sup>10</sup> exclusively formed the  $\gamma$ -addition products with high enantioselectivity using all three aldehydes employed in the initial survey (entries 7–9).<sup>11</sup>

The use of a dienol ether bearing a substituent at the  $\gamma$ -position introduced the challenge of diastereoselectivity for the **2**/phosphoramidate catalyst system. Initial studies with an ethyl 2-pentenoate-derived dienol ether showed poor regioselectivities. However, increasing the size of the ester group led to a dramatic improvement. Thus, the *tert*-butyl 2-pentenoate-derived dienol ether **3d**<sup>10</sup> provided exclusively the  $\gamma$ -addition product **4da** (entry 10). This high regioselectivity is complemented by high anti diastereoselectivity and good enantioselectivity. Although high yields and good selectivities can be obtained in the additions of **3d** to **1a** and **1b**, this dienol ether is unreactive with **1c** (entry 12).

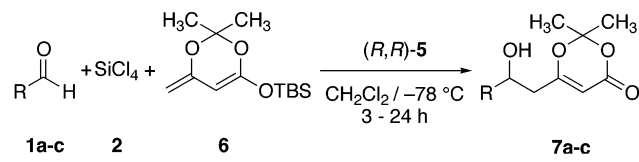
Reactions of the dioxanone-derived dienol ether **6**<sup>10</sup> formed only the  $\gamma$ -addition products **7a–c** in high yields and good enantioselectivities (Table 2). Interestingly, the observed trend in enantioselectivity for the additions of **6** is **1c** > **1b** > **1a**. This trend with respect to aldehyde is opposite to that observed in all other cases (Table 1, entries 1–3). The nucleophile consistently approaches the Re face of the aldehyde, generally forming the *5R* product.<sup>5a,6b,12</sup>

The extremely high selectivity of the catalyst for reaction at the  $\gamma$ -position of the dienol ether could be understood by examination of its reactivity patterns with simple silyl ketene acetals. ReactIR studies on the rates of addition of the methyl acetate-, methyl propanoate-, and methyl isobutyrate-derived silyl ketene acetals to **1a** revealed a striking kinetic dependence on the degree of  $\alpha$ -substitution: the acetate-derived silyl ketene acetal required <30 s to go to completion, and the propanoate-derived ketene acetal required 3 min.<sup>9</sup> Furthermore, the reaction of the isobutyrate-derived silyl ketene acetal required more than 12 h to reach completion!

**Table 1.** Vinylogous Aldol Reactions of Simple, Ester-Derived Dienolates **3a–d** with Aldehydes **1a–c**

entry	dienolate	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	product	yield, % <sup>a</sup>	γ/α <sup>b</sup>	dr <sup>b</sup>	er <sup>c</sup>
1	<b>3a<sup>d</sup></b>	Ph ( <b>1a</b> )	Et	H	H	H	<b>4aa</b>	89 <sup>e</sup>	>99:1		99:1
2	<b>3a<sup>d</sup></b>	PhCH=CH ( <b>1b</b> )	Et	H	H	H	<b>4ab</b>	84 <sup>e</sup>	>99:1		98:2
3	<b>3a<sup>f</sup></b>	PhCH <sub>2</sub> CH <sub>2</sub> ( <b>1c</b> )	Et	H	H	H	<b>4ac</b>	68 <sup>g</sup>	>99:1		95:5
4	<b>3b<sup>d</sup></b>	Ph ( <b>1a</b> )	Me	Me	H	H	<b>4ba</b>	93 <sup>e</sup>	>99:1		99.5:0.5
5	<b>3b<sup>d</sup></b>	PhCH=CH ( <b>1b</b> )	Me	Me	H	H	<b>4bb</b>	88	>99:1		99.5:0.5
6	<b>3b<sup>f</sup></b>	PhCH <sub>2</sub> CH <sub>2</sub> ( <b>1c</b> )	Me	Me	H	H	<b>4bc</b>		ND		ND
7	<b>3c<sup>d</sup></b>	Ph ( <b>1a</b> )	Et	H	Me	H	<b>4ca</b>	91 <sup>e</sup>	>99:1		96:4
8	<b>3c<sup>d</sup></b>	PhCH=CH ( <b>1b</b> )	Et	H	Me	H	<b>4cb</b>	97 <sup>h</sup>	>99:1		94:6
9	<b>3c<sup>f</sup></b>	PhCH <sub>2</sub> CH <sub>2</sub> ( <b>1c</b> )	Et	H	Me	H	<b>4cc</b>	73	>99:1		97.5:2.5
10	<b>3d<sup>d</sup></b>	Ph ( <b>1a</b> )	<i>t</i> -Bu	H	H	Me	<b>4da</b>	92 <sup>i</sup>	99:1	>99:1	94.5:5.5
11	<b>3d<sup>d</sup></b>	PhCH=CH ( <b>1b</b> )	<i>t</i> -Bu	H	H	Me	<b>4db</b>	71	99:1	>99:1	91:9
12	<b>3d<sup>f</sup></b>	PhCH <sub>2</sub> CH <sub>2</sub> ( <b>1c</b> )	<i>t</i> -Bu	H	H	Me	<b>4dc</b>		ND	ND	ND

<sup>a</sup> Yields of analytically pure material. <sup>b</sup> Determined by <sup>1</sup>H NMR analysis. <sup>c</sup> Determined by CSP-SFC. <sup>d</sup> Reactions employed 1.1 equiv of SiCl<sub>4</sub>, 1.2 equiv of dienolate, 0.01 equiv of (*R,R*)-**5** at 0.2 M in CH<sub>2</sub>Cl<sub>2</sub> at –78 °C for 3 h. <sup>e</sup> *R* absolute configuration. <sup>f</sup> Conditions as above with 0.05 equiv of (*R,R*)-**5**, 0.05 equiv of *i*-Pr<sub>2</sub>EtN at 0.2 M in CH<sub>2</sub>Cl<sub>2</sub> at –78 °C for 24 h. <sup>g</sup> *S* absolute configuration. <sup>h</sup> *E/Z*, 97:3. <sup>i</sup> 4*R*,5*R* absolute configuration.

**Table 2.** Vinylogous Aldol Reactions of Dioxanone-Derived Dienolate **6** with Aldehydes **1a–c**

entry	R	product	yield, % <sup>a</sup>	γ/α <sup>b</sup>	er <sup>c</sup>
1	Ph ( <b>1a</b> ) <sup>d</sup>	<b>7a</b>	92 <sup>e</sup>	>99:1	87:13
2	PhCH=CH ( <b>1b</b> ) <sup>d</sup>	<b>7b</b>	88 <sup>e</sup>	>99:1	89:11
3	PhCH <sub>2</sub> CH <sub>2</sub> ( <b>1c</b> ) <sup>f</sup>	<b>7c</b>	83 <sup>g</sup>	>99:1	94.5:5.5

<sup>a</sup> Yields after chromatography. <sup>b</sup> Determined by <sup>1</sup>H NMR analysis. <sup>c</sup> Determined by CSP-SFC. <sup>d</sup> Reactions employed 1.1 equiv of **2**, 1.2 equiv of dienolate, 0.01 equiv of (*R,R*)-**5** at 0.2 M in CH<sub>2</sub>Cl<sub>2</sub> at –78 °C for 3 h. <sup>e</sup> *R* absolute configuration. <sup>f</sup> Reactions employed 1.1 equiv of **2**, 1.2 equiv of dienolate, 0.05 equiv of (*R,R*)-**5**, 0.05 equiv of *i*-Pr<sub>2</sub>EtN at 0.2 M in CH<sub>2</sub>Cl<sub>2</sub> at –78 °C for 24 h. <sup>g</sup> *S* absolute configuration.

This reactivity trend is opposite to the scale of π-nucleophilicity determined by Mayr and co-workers.<sup>13</sup> It is possible that this trend is dictated by steric factors at the reaction center. In the case of the ethyl crotonate-derived dienol ether **3a**, the observed α/γ-selectivity represents favorable reaction at the less sterically demanding γ-position. In the 2-pentenoate derived-dienol ether **3d**, both reactive centers are monosubstituted. Introduction of a *tert*-butyl ester was required for high regioselectivity in the C–C bond forming reaction.

In conclusion, we have developed a highly regioselective, chiral-Lewis-base-catalyzed, vinylogous aldol reaction that provides γ-hydroxy enones in high enantio- and diastereoselectivities for a number of aldehyde and dienol ether structures. Low catalyst loadings (1 mol %) can be employed without compromising yields or selectivities. Further studies are underway to extend this method to ketone- and aldehyde-derived dienol ethers.

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**Supporting Information Available:** Full characterization of all dienol ethers and aldol products along with representative procedures for the addition reactions (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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