

## Diethylaluminum Ethoxide Mediated Crossed Aldol Reaction of Enol Esters with Carbonyl Compounds

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Crossed aldol reaction of enol esters, stable carbon nucleophiles, with carbonyl compounds is effectively performed by the promotion of diethylaluminum ethoxide under mild conditions. This reaction is applicable not only to simple enol esters but also to lactones such as  $\alpha$ -angelicalactone.

Effective carbon-carbon bond forming reaction is successfully carried out by the combination of stable and weakly nucleophilic carbon species and carbonyl compounds in the presence of a Lewis acid. The aldol reaction of enol silyl ethers with carbonyl compounds promoted by Lewis acids has been, for example, applied to a wide variety of carbon skeleton constructions. Though the aldol reaction generally takes place smoothly and gives the adducts in satisfactory yields, typical Lewis acid catalysts sometimes induce the side reactions such as cleavage of protecting groups, isomerization and rearrangement when the carbonyl compounds which have acid-sensitive functionalities. Therefore, it is still desirable to explore a new and effective catalyst which promotes aldol reaction without the accompanying side reactions.

There are many reports concerning aldol reaction by using enol esters under basic conditions, and generation of lithium enolates from the enol esters with methyllithium is one of the most popular examples.<sup>1</sup> To date, there are a few reports on the aldol reaction which proceeds under weakly acidic or neutral conditions by using enol esters though the esters are readily prepared and considered as stable carbon nucleophiles.<sup>2</sup> Recently,  $\text{Et}_2\text{AlOEt}$ -mediated Diels-Alder reaction of  $\alpha,\beta$ -unsaturated ketones and 1-acetoxybutadienes was reported from our laboratory.<sup>3</sup> It was shown there that 1-acetoxybutadienes were activated by a nucleophilic attack of the ethoxy group of  $\text{Et}_2\text{AlOEt}$  to acetyl groups of the dienes after coordination of the aluminum reagent to the ketones. Because the above mentioned 1-acetoxybutadiene is considered as a kind of enol ester, it was anticipated that the aluminum reagent also promotes the nucleophilic reactions of various enol esters. Here, we would like to describe the  $\text{Et}_2\text{AlOEt}$ -mediated aldol reaction of enol esters with carbonyl compounds.

In the first place, the aldol reaction of isopropenyl acetate (**1**), an enol ester of acetone, with various carbonyl compounds was examined. Toluene was a suitable solvent for the previously reported Diels-Alder reaction, but in the present aldol reaction, THF was proved to be the best. The reactions of both aldehydes and ketones proceeded to give the corresponding aldols in good yields as summarized in Table 1. Interestingly, 1,2-adduct was a main product when  $\alpha,\beta$ -unsaturated ketone was employed while Michael adduct is preferentially obtained by Lewis acid mediated aldol reaction using enol silyl ethers (Entry 7). Even in the cases of the aldol reaction with an aldehyde **3** having *tert*-butyldimethylsiloxy, benzyloxy and *p*-methoxybenzyloxy groups,<sup>4</sup> and a ketone **4** having an acetoxy group, these functionalities were not affected and the desired aldol was

**Table 1.** Yields of adducts by the aldol reaction of enol esters with various carbonyl compounds<sup>a</sup>

Entry	Enol Ester	Electrophile	Product	Yield / %
1	<b>1</b>	PhCHO		74
2	<b>1</b>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> CHO		70
3	<b>1</b>	<i>p</i> -BnOC <sub>6</sub> H <sub>4</sub> CHO		78
4 <sup>b</sup>	<b>1</b>	OHCCH <sub>2</sub> Ph		56
5	<b>1</b>	OHCCH=CHPh		74
6	<b>1</b>			72
7	<b>1</b>			61
8	<b>1</b>			76
9	<b>1</b>			78 <sup>c</sup>
10	<b>1</b>			82
11	<b>2</b>			45
12	<b>2</b>			72 <sup>d</sup>

<sup>a</sup>Isolated yield. All reactions were carried out at 0 °C in THF. Molar ratio of enol ester / electrophile /  $\text{Et}_2\text{AlOEt}$  was 5 / 1 / 5. <sup>b</sup>Ethanol (5 eq.) was added to the reaction mixture. <sup>c</sup>C<sub>4</sub>,C<sub>6</sub>-syn / C<sub>4</sub>,C<sub>6</sub>-anti = 3 / 2. <sup>d</sup>Diastereomeric ratio = 3 / 2.

obtained in good yield (Entry 9 or 10). On the other hand, the Lewis acid promoted aldol reaction of 2-(trimethylsiloxy)propene using  $\text{MgBr}_2$  or  $\text{Et}_2\text{AlCl}$  with the polyoxy aldehyde **3** accompanied side reactions such as cleavage of protecting groups. When vinyl acetate (**2**), an enol ester of acetaldehyde, was used in the reaction with several carbonyl compounds, chemical yields were rather low because the products still contained aldehyde moieties which were further attacked by **2** to give oligomeric products (Entries 11 and 12).

A typical experimental procedure is described for the reaction of isopropenyl acetate (**1**) with benzaldehyde: To a solution of benzaldehyde (53 mg, 0.50 mmol) and **1** (0.28 mL, 2.5 mmol) in THF (3 mL) at 0 °C was added a solution of diethylaluminum ethoxide in hexane (1.0 M, 2.5 mL, 2.5 mmol). After the reaction mixture was stirred for 4 h at 0 °C, saturated aqueous potassium sodium tartrate and ethyl acetate were added at that temperature, and the mixture was further stirred for an additional 30 min at room temperature. After usual work-up, the crude product was submitted to silica gel chromatography to afford the corresponding aldol (61 mg, 74%) as a colorless oil (Table 1, Entry 1).

When benzaldehyde was added to the pre-treated mixture of isopropenyl acetate and  $\text{Et}_2\text{AlOEt}$ , reaction rate was nearly the same to that of the above three components reaction while it proceeded rapidly by treating benzaldehyde with the aluminum enolate, prepared from 2-(trimethylsiloxy)propene, at 0 °C. It was further observed by  $^1\text{H}$  NMR measurement that the formation of ethyl acetate was very slow when two components, isopropenyl acetate and  $\text{Et}_2\text{AlOEt}$ , were treated in  $\text{THF-d}_8$  at 0 °C. These results indicate that the complex of three components (isopropenyl acetate,  $\text{Et}_2\text{AlOEt}$  and carbonyl compound) was formed initially and then it was converted synchronously to the aldol by internal nucleophilic replacement accompanied with formation of ethyl acetate as sketched in Figure 1.

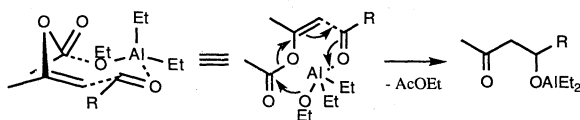


Figure 1. Proposed reaction mechanism.

Table 2. Yields of adducts by the aldol reaction of lactones with several carbonyl compounds<sup>a</sup>

(1.2 eq.)	(1.0 eq.)	ester	trans-lactone	cis-lactone	
Entry	R	ester	syn / anti	trans-lactone	trans / cis
1	Ph	trace	ca. 1 / 1	74	>20 / 1
2 <sup>b</sup>	PhCH <sub>2</sub> CH <sub>2</sub>	trace	ca. 1 / 1	61	>20 / 1
3	PhCH=CH	0	-	72	>20 / 1

(1.2 eq.)	(1.0 eq.)	ester	trans-lactone	cis-lactone	
Entry	R	ester	syn / anti	trans-lactone	trans / cis
4	Ph	40	ca. 1 / 1	50	>20 / 1
5	PhCH <sub>2</sub> CH <sub>2</sub>	24	0 / 100	70	>20 / 1

<sup>a</sup>Isolated yield. Relative configuration was determined by  $^1\text{H}$  NMR.<sup>5</sup> <sup>b</sup>The reaction was carried out at -10 °C. Molar ratio of **5** / 3-phenylpropanal /  $\text{Et}_2\text{AlOEt}$  was 2 / 1 / 0.6.

In the next place, the reactions of 5-methyl-2(3*H*)-furanone ( $\alpha$ -angelicalactone) (**5**) and 3,4-dihydro-6-methyl-2*H*-pyran-2-one (**6**) with aldehydes were tried and the results are shown in Table 2. These lactones are similarly considered as nucleophiles in the present aldol reaction because they contain enol ester parts.

The reaction of furanone **5** with several aldehydes proceeded smoothly to give separable *trans*- and *cis*-lactones with small amounts of mixtures of *syn*- and *anti*-esters. In this case, the aluminum reagent worked catalytically as illustrated in the following Figure 1. The reaction took place diastereoselectively and gave the *trans*-lactones as major products (*trans* / *cis* = >20 / 1).<sup>5</sup> When dihydropyranone **6** was employed as a nucleophile in this reaction, *trans*- and *cis*-lactones were similarly formed with high diastereoselectivities though yields of these lactones were lower than those of the above reaction using **5**, and a mixture of *syn*- and *anti*-esters (Entry 4) or only *anti*-ester (Entry 5) was obtained in rather high yield. Like the case of the reaction of furanone **5**, the *trans*-lactones were mainly formed from the corresponding *syn*-esters.

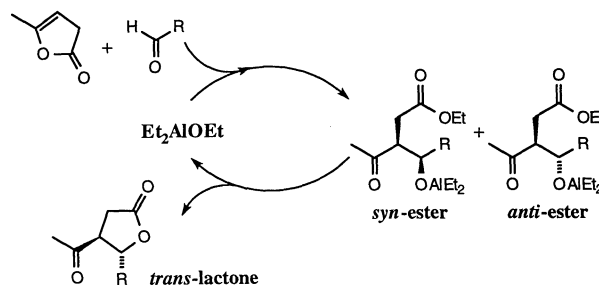


Figure 2. Proposed catalytic cycle forming the *trans*-lactones.

It is noted that crossed aldol reaction of enol esters, stable carbon nucleophiles, with carbonyl compounds was carried out effectively by the promotion of  $\text{Et}_2\text{AlOEt}$  under mild conditions.

## References and Notes

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- A series of NOEs of the minor lactone including strong one between H3 $\beta$  and H4 $\beta$  was observed as shown below. Therefore, it is indicated that the relative configuration of minor lactone is *cis* and the major lactone has *trans* configuration though it was once reported as *cis* (ref 2f).

