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The Baylis–Hillman condensation of α,β-conjugate cycloketones with aldehydes using diethylaluminum iodide alone as the promoter†

Wei Pei, Han-Xun Wei and Guigen Li*
Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, TX 79409-1061, USA.
E-mail: qeggl@ttu.edu

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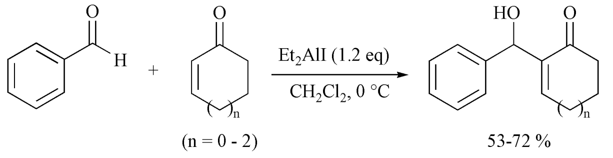
The Baylis-Hillman condensation of three types of α,β-conjugate cycloketones with aldehydes was successfully performed by using diethylaluminum iodide as the Lewis acid promoter alone without the direct use of a Lewis base. The reaction proceeded to completion at 0 °C in CH_2Cl_2 within 24 h to give modest to good yields (53–72%).

The Baylis–Hillman and related processes have become increasingly important in synthetic organic chemistry because the resulting adducts have an array of multifunctional groups which can be subjected to numerous transformations.[1] These reactions usually require the direct use of Lewis bases, such as DABCO, Ph_3P and chalcogen species.[2–5] Recently, we found that the Baylis–Hillman-type reaction of α,β-unsaturated cycloketones with aldehydes can occur in the presence of $TiCl_4$ without the use of any Lewis bases.[6,7] Unfortunately, this reaction is limited to the use of aliphatic aldehydes or those aromatic aldehydes with strong electron withdrawing groups (*e.g.*, $–NO_2$, $–CF_3$). The limitation also exists for α,β-unsaturated Michael acceptors. For example, when the reaction substrates were changed to α,β-unsaturated acyclic ketones, the reaction resulted in (*Z*)-2-(halomethyl)vinyl ketones.[3a] The later reactions were also confirmed by using Lewis acid/Lewis base co-promoters under different conditions.[8]

In the past few years, we have made many efforts to overcome the above serious limitations. In this communication we would like to report that the Baylis–Hillman condensation of three types of α,β-conjugate cycloketones with aldehydes which failed to give any products under the previous $TiCl_4$-based conditions can now be successfully performed by using diethylaluminum iodide as the Lewis acid promoter alone, without the direct use of a Lewis base. The three types of α,β-conjugate cycloketones include α,β-unsaturated 2-cyclopeten-1-one, 2-cyclohexen-1-one and 2-cyclohepten-1-one, as described in Scheme 1.

The reaction was carried out under the protection of nitrogen gas, and is easy to run by simply adding the dichloromethane solution of diethylaluminium iodide into the mixture of aldehyde and α,β-unsaturated cycloketone. The reaction proceeded to completion at 0 °C in dichloromethane within 24 h to give Baylis–Hillman adducts in modest to good chemical yields which are summarized in Table 1.

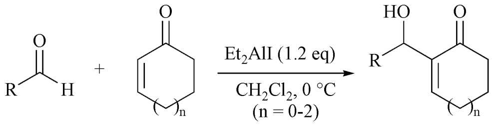
As revealed in Table 1, the current reaction showed the good scope of substrates for both Michael-type acceptors and electrophiles. The electrophiles to react with aluminum enolate intermediates derived from conjugate addition of Et_2AlI onto α,β-unsaturated cycloketones can be both aromatic and aliphatic aldehydes. Meanwhile, all three common kinds of α,β-unsaturated cycloketones (2-cyclopeten-1-one, 2-cyclohexen-1-one and 2-cyclohepten-1-one) proved to be the effective Michael-type acceptors giving good yield (up to 69%, entries 1–4). As measured by GC or TLC, these α,β-unsaturated cycloketones showed similar reaction rates. When α,β-unsaturated acycloketones were employed, the reaction stopped at the stage of halo aldols under current conditions. Regarding aromatic aldehydes, both electron-withdrawing and electron-donating substrates showed similar effectiveness. It is noteworthy that the strong electron-donating *p*-methoxybenzaldehyde can give 53% yield (entry 5). As anticipated, the electron-withdrawing property of *p*-nitrobenzaldehyde benefits the chemical yield (72%, entry 6).

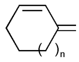
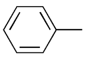
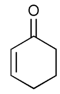
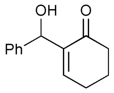
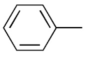
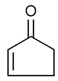
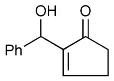
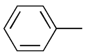
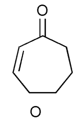
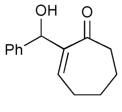
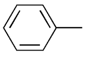
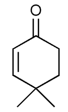
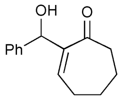
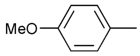
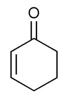
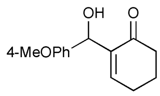
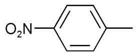
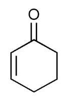
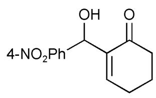
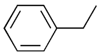
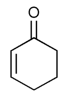
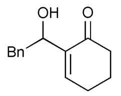


Scheme 1

A slightly excess amount of α,β-unsaturated cycloketones was found necessary to achieve the complete consumption of aldehydes and optimized yields. There was no improvement on

Table 1 Results of Et_2AlI-mediated B-H type reaction[11]



Entry	R-		Product		Yield (%)
1				**1**	65
2				**2**	56
3				**3**	69
4				**4**	61
5				**5**	53
6				**6**	72
7				**7**	61

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† Electronic supplementary information (ESI) available: experimental details. ^1H NMR data for compounds **1–7**. See http://www.rsc.org/suppdata/cc/b2/b206736f/

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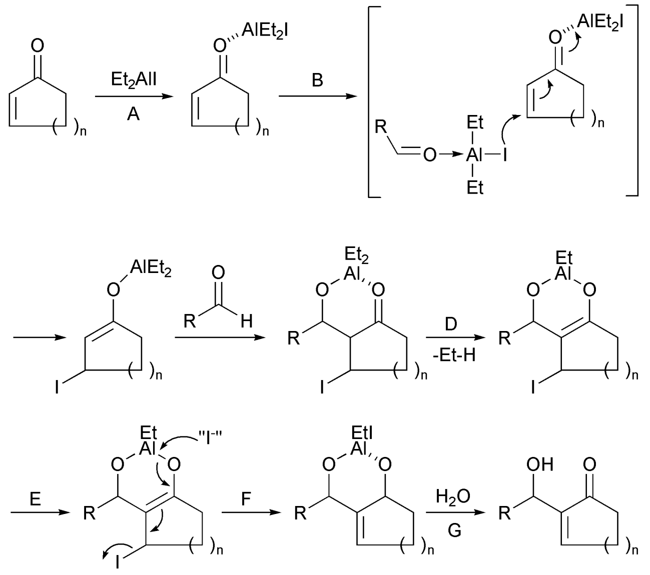
yields by loading more α,β-unsaturated cycloketones. Attempts to use a substoichiometric amount of diethylaluminium iodide (0.25 and 0.5 equiv. respectively) proved to be unsuccessful due to the slow reaction rate: a considerable amount of aldehyde remained even after a long period (> 24 h). In addition, keeping the reaction temperature low (0 °C) is also crucial. In fact, when the reaction was carried out at room temperature, more unknown side products were generated.

Unlike our previous $TiCl_4$-based system, this effective reaction is attributed to the irreversible deprotonation step during the reaction process (step D of Scheme 2). The release of CH_3CH_3 acts as a strong driving force and makes the reaction irreversible. This step conceivably benefits both the chemical yields and the reaction rate. This hypothesis can distinguish diethylaluminium iodide[9] from most other Lewis acids which have been examined so far. Similarly to our $TiCl_4$-promoted system, the first step proceeded *via* the intermolecular Michael-type pathway, which is governed by the rigid characteristic of α,β-unsaturated cycloketones. In contrast, the Et_2AlI-promoted reaction using α,β-unsaturated thioester as the substrate is more likely to occur through an intramolecular pathway in the Michael-type addition step due to the flexible structure of the α,β-unsaturated thioester.[10] The later intramolecular pathway is similar to that of haloaldol reaction promoted by $TiCl_4$–*n*Et_4NI as proposed by Oshima.[8a]

This mechanism can also account for the observation that a substoichiometric amount of diethylaluminium iodide failed to drive the reaction to completion. Other two factors which could benefit the reaction include the stability of the resulting cyclic α,β-conjugate Baylis–Hillman structures and the greater reactivity of halogeno aluminum enolates than their titanium counterparts. The use of acyclic ketones for this reaction under new conditions will be investigated later.



Scheme 2

In summary, the Baylis–Hillman-type reaction of α,β-unsaturated cycloketones with various aldehydes has been smoothly performed by using diethylaluminium iodide as the promoter without the direct use of any Lewis bases. The reaction showed the extended scope for both aldehydes and α,β-unsaturated cycloketones.

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