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## Diethylaluminum Iodide Promoted Morita–Baylis–Hillman Reaction of D-Glucose-Derived Densely *O*-Functionalized Cyclopentenone: Route to α-C-Branched Densely Functionalized Cyclic Enones

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Dedicated to Professor Y. D. Vankar<sup>[‡]</sup>

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Morita–Baylis–Hillman (MBH) reaction of D-glucose-derived highly O-functionalized cyclopentenone is described for the first time. The MBH reaction of cyclopentenone with different aldehydes in the presence of diethylaluminum iodide proceeded smoothly in moderate to good yields. Promoters such as organic, inorganic, or Lewis bases and an aqueous medium are not suitable conditions for the MBH reaction of highly O-functionalized cyclopentenones with aldehydes.

#### Introduction

The Morita–Baylis–Hillman (MBH) reaction, one of the most frequently used carbon–carbon bond-forming reactions, is basically the reaction of an aldehyde or ketone with an activated alkene or alkyne in the presence of a suitable catalyst to give highly functionalized MBH adducts.<sup>[1]</sup> The functionalities of the Morita–Baylis–Hillman adducts and their derivatives make them appropriate precursors for the strategic synthesis of several complex natural products or natural product like molecules.<sup>[2]</sup>

Normally nitrogen bases such as 1,4-diazabicyclo[2.2.2]octane (DABCO), DBU, DMAP, Et<sub>3</sub>N, imidazole, and so on are reported as catalysts in MBH reaction.<sup>[2]</sup> DABCO was found to be unsuccessful for cyclic enones in some cases.<sup>[3]</sup> Though self dimerization of cyclic enones was observed when DBU<sup>[4]</sup> or Et<sub>3</sub>N<sup>[5]</sup> was used as the catalyst, several successful  $\alpha$ -hydroxyalkylation reactions of simple cyclopentenones were reported by using DBU,<sup>[6]</sup> imidazole,<sup>[7]</sup> DMAP/MgI<sub>2</sub>,<sup>[8]</sup> triazoles,<sup>[9]</sup> and DABCO<sup>[10]</sup> as catalysts (Scheme 1). Systems such as NaOMe,<sup>[11]</sup> MgO<sub>2</sub>,<sup>[12]</sup> Ba(OH)<sub>2</sub>,<sup>[13]</sup> and Yb(OTf)<sub>3</sub><sup>[14]</sup> in combination with nitrogen bases have been used as activators in the MBH reactions of unfunctionalized cyclopentenone acting as an activated

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- [‡] On the occasion of his 62nd birthday.

alkene with various aldehydes. Lewis acids like  $TiCl_4$ ,<sup>[15]</sup>  $Et_2AII$ ,<sup>[16]</sup> and  $Me_3AI^{[17]}$  and Lewis bases like (dimethyl)(phenyl)phosphane<sup>[18]</sup> and tributylphosphane<sup>[19]</sup> were also successfully utilized as catalysts in MBH reactions of simple cyclopentenone. In some cases,  $MgI_2$  in combination with organometallic Fe complexes were also used (Scheme 1).<sup>[20]</sup>



Scheme 1. MBH reaction of simple cyclopentenone.

However, the MBH reactions of highly functionalized enones are seldom reported. Recently, we demonstrated the incorporation of the hydroxymethyl group at the  $\alpha$ -position of sugar-derived cyclohexenones by performing its MBH reaction with formaldehyde in the presence of DMAP as a catalyst, and it was observed that the protecting group played an important role in this reaction.<sup>[21]</sup> The use of the imidazole/NaHCO<sub>3</sub> system was not an appropriate combination for a catalyst in this transformation. Very recently, a highly diastereoselective C-2 hydroxyalkylation of sugarderived densely *O*-functionalized cyclohexenones with different aromatic aldehydes in the presence of diethylaluminum iodide (Et<sub>2</sub>AII) by using MBH chemistry has been disclosed by our group.<sup>[22]</sup>

To the best of our knowledge, the MBH reaction of sugar-derived, highly *O*-functionalized cyclopentenones has not been reported. In continuation of our study on the  $\alpha$ -functionalization of sugar-derived cyclic enones by involv-

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ing MBH chemistry, we wish to report herein our results on the MBH reaction of D-glucose-derived, highly O-functionalized cyclopentenone **2** as an activated alkene with both aliphatic and aromatic aldehydes.

#### **Results and Discussion**

Synthesis of activated alkene 2 commenced from methyl-6-deoxy-6-iodo-2,3-di-*O*-benzyl-α,D-glucopyranoside (6), which can easily be prepared from methyl a,D-glucopyranoside (7) in four steps in 62% yield.<sup>[23]</sup> Iodosugar 6, upon treatment with Zn dust in MeOH in the presence of a catalytic amount of cyanocobalamin at room temperature, yielded cyclic hemiacetal 5 (as an  $\alpha/\beta$  mixture).<sup>[24]</sup> Its Wittig methylenation with methyltriphenylphosphonium bromide in the presence of tBuOK afforded diene 4 (Scheme 2). Oxidation of the allylic alcohol in 4 was attempted by using oxidizing agents like MnO<sub>2</sub>, PCC, and PDC, but in each case, decomposition of the starting material was mainly observed with formation of the desired product in very poor yield (5–10%). Gratifyingly, oxidation with Dess-Martin periodinane (DMP) proceeded smoothly, and oxidized product 3 was obtained in 90% yield. Construction of the cyclopentenone core was then achieved by utilizing ringclosing metathesis. Thus, treatment of 3 with Grubbs second generation catalyst (5 mol-%) under refluxing conditions and an inert atmosphere furnished desired cyclopentenone 2 (Scheme 2). It is worth noting that Grubbs first generation catalyst was unsuccessful in this case.

After successful construction of 2, we wanted to explore the title reaction of 2 with 2-nitrobenzaldehyde by using conventional nitrogen bases like DABCO, DBU, and imidazole. Therefore, first we chose DABCO as a promoter for this reaction, but unfortunately, enone 2 decomposed completely. Other nitrogen bases such as imidazole and DBU showed the same result. MBH reaction of enone 2 in the presence of NaHCO<sub>3</sub> was also futile. Phosphane Lewis bases such as PPh<sub>3</sub> and PBu<sub>3</sub> were also tried, and in all of these cases, a complex reaction mixture was obtained with almost complete consumption of starting enone 2 (Table 1).

At this stage, we thought that a basic reaction medium (aqueous/nonaqueous) was not suitable for the MBH reaction of enone 2, and therefore, we decided to use a Lewis acid in this reaction. First, we tried the most widely used Lewis acid, TiCl<sub>4</sub>, but it did not deliver the expected MBH adduct; on the contrary, debenzylation of enone 2 took

Table 1. MBH reaction of enone **2** with 2-nitrobenzaldehyde under different conditions.

Entry	Promoter (equiv.)	Temp. [°C]	Time [h]	Result
1 <sup>[a,b]</sup>	DABCO (0.5-2)	-10 to 0	2	decomposition
$2^{[a,b]}$	imidazole $(0.5-2)$	-10 to 0	2	decomposition
3 <sup>[a,b]</sup>	NaHCO <sub>3</sub> (0.5–2)	-10 to 0	2	decomposition
4 <sup>[b,c]</sup>	DBU (0.5–2)	-10 to 0	12	decomposition
5 <sup>[b,d]</sup>	$PBu_{3}(1-2)$	-10 to 0	2	CM <sup>[e]</sup>
6 <sup>[b,d]</sup>	$PPh_{3}(1-2)$	-10 to 0	2	CM <sup>[e]</sup>
7 <sup>[d,f]</sup>	$TiCl_4$ (1.5–2)	-78	4	debenzylation
8[d,g]	$Et_2AlI (1.5-2)$	-78 to -55	4	MBH adduct 1a

[a] THF/H<sub>2</sub>O (1:1, 10 mL per 1 mmol of enone **2**) was used as the solvent. [b] The promoters were added at -10 °C, and then gradually the reaction was allowed to warm from 0 °C to room temperature for 2 h. [c] Reaction carried out both in neat DBU and in THF/H<sub>2</sub>O (1:1, 10 mL per 1 mmol of enone). [d] Dry DCM (10 mL per 1 mmol of enone) was used as the solvent. [e] CM = Complex mixture. [f] The reaction was performed at -78 °C. [g] The promoter was added to the reaction mixture at -78 °C, and the mixture was then allowed to stir at -55 °C.

place. Earlier, we had also noticed debenzylation of densely functionalized cyclohexenone in TiCl<sub>4</sub>-promoted MBH reactions.<sup>[22]</sup> Recently, we have successfully achieved the C-2 hydroxyalkylation of sugar-derived densely O-functionalized cyclohexenones with different aromatic aldehydes in the presence of Et<sub>2</sub>AlI.<sup>[22]</sup> Therefore, we preferred to choose Et<sub>2</sub>All as a Lewis acid promoter for the MBH reaction of enone 2 with 2-nitrobenzaldehyde to obtain the desired MBH adduct. Thus, performing the MBH reaction of enone 2 (1 equiv.) with 2-nitrobenzaldehyde (2 equiv.) in dry DCM at -78 °C by the dropwise addition of Et<sub>2</sub>AlI (1.5 equiv.) over 1 h led to the formation of the MBH adduct in 60% yield (Scheme 3). To further increase the yield, we modified our experimental protocol by adding Et<sub>2</sub>AlI (2 equiv.) at -78 °C over a period of 2 h, and stirring of the solution was continued at -55 °C. The complete disappearance of the starting material was noticed after 4 h, and the MBH adduct was obtained in 70% yield after column chromatographic purification (Table 2, entry 1).

Once the reaction conditions were optimized (Table 1), we wanted to explore the applicability of enone 2 as an activated alkene in the Et<sub>2</sub>AlI-mediated MBH reaction with various aldehydes. Thus, the title reaction of enone 2 with various aromatic aldehydes was also carried out under similar reaction conditions, and the adducts were obtained as diastereomeric mixtures in good to moderate yields



Scheme 2. Synthesis of cyclopentenone 2.

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Scheme 3. MBH reaction of cyclopentenone 2 with various aldehydes.

Table 2. MBH reaction of enone 2 with various aldehydes.

Entry	RCHO	Time	Product	Yield
		լոյ		[70]
1		4	1a	70
2	O2N CHO	4	1b	73
3	СІСІСІ	8	10	84
4	CHO	8	1d	75
5	CHO	8	le	80
6	NC CHO	8	1f	85
7	F F F	8	1g	81
8	CHO OCF3	8	1h	63
9	OCF <sub>3</sub>	8	1i	71
10	F3CO CHO	6	1j	61
11	СНО	8	1k	51
12	МеО	6	11	27
13	C <sub>8</sub> H <sub>17</sub> CHO	6	1m	79

(Scheme 3, Table 2). On the basis of our previous observations,<sup>[22]</sup> a plausible mechanistic pathway for the Et<sub>2</sub>AlI-induced MBH reaction of enone **2** involves a Michael-type addition of the iodide from Et<sub>2</sub>AlI to aluminum-coordinated enone **2a** (Figure 1) at the C-4 position with concomitant shifting of the 2,3-double bond to the 1,2-position to generate aluminum-coordinated oxyanion **2b** (Figure 1). In this case, formation of an orthoester intermediate is not possible, and therefore, the Et<sub>2</sub>AlI-coordinated approaching aldehyde cannot form a Zimmerman–Traxler-type closed transition state with oxyanion **2b**.<sup>[22]</sup> Thus, in this situation, the aldehyde can approach oxyanion **2b** from both sides leading to the formation of a mixture of diastereomeric adducts.



Figure 1. Structures of aluminum-coordinated enone **2a** and aluminum-coordinated oxyanion **2b**.

Encouraged by the mild reaction conditions and the reactivity of enone 2, we also carried out the title reaction of enone 2 with benzaldehyde and 4-methoxybenzaldehyde, and the desired adducts were obtained in 51 and 27% yield, respectively (Table 2, Entries 11 & 12). Further, the MBH reaction of enone 2 with the aliphatic aldehyde decanal was also successful under identical reaction conditions, and desired adduct 1m was obtained in 79% yield (Table 2, Entry 13).

### Conclusions

In summary, herein we have disclosed the Lewis acid (Et<sub>2</sub>AlI) promoted C-2 hydroxyalkylation of D-glucose-derived cyclic enone **2** involving MBH chemistry. To the best of our knowledge, the MBH reactions of highly *O*-functionalized cyclopentenone have not yet been reported. In each case of these reactions, a diastereomeric mixture of MBH adducts was obtained. It could be concluded here on the basis of the above experimental observations that reagents such as organic, inorganic, or Lewis bases and an aqueous medium are not suitable conditions for the MBH reactions of highly *O*-functionalized cyclopentenone with aldehydes.

### **Experimental Section**

General Procedure for the MBH Reaction of Sugar-Derived Enone and Aromatic Aldehydes: To a solution of enone (0.5 mmol) and aromatic aldehyde (1.0 mmol) in dry DCM (5 mL) under N<sub>2</sub> was added Et<sub>2</sub>AlI (1.0 mmol) at -78 °C over 2 h. The reaction mixture was warmed to -55 °C and stirred. After completion of the reaction (TLC), a saturated aqueous solution of NaHCO<sub>3</sub> (10 mL) was added to the mixture, which was then extracted with DCM (3× 10 mL). The combined organic layer was dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to a yellowish residue that was purified by column chromatography to give the MBH adduct.

**Supporting Information** (see footnote on the first page of this article): Experimental procedures and spectroscopic and HPLC data.

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#### Morita-Baylis-Hillman Reaction

Morita–Baylis–Hillman (MBH) reaction of carbohydrate derived highly O-functionalized cyclopentenone is described for the first time. The MBH reaction of cyclopentenone **2** with different aldehydes in the presence of diethylaluminum iodide (Et<sub>2</sub>AII) proceeded smoothly in moderate to good yields.



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Diethylaluminum Iodide Promoted Morita–Baylis–Hillman Reaction of D-Glucose-Derived Densely *O*-Functionalized Cyclopentenone: Route to α-C-Branched Densely Functionalized Cyclic Enones

Keywords: Aluminum / Aldehydes / Metathesis / Olefination