SHORT PAPER

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The Baylis-Hillman reactions of aldehydes with methyl vinyl ketone in the presence of imidazole, binol and silica gel

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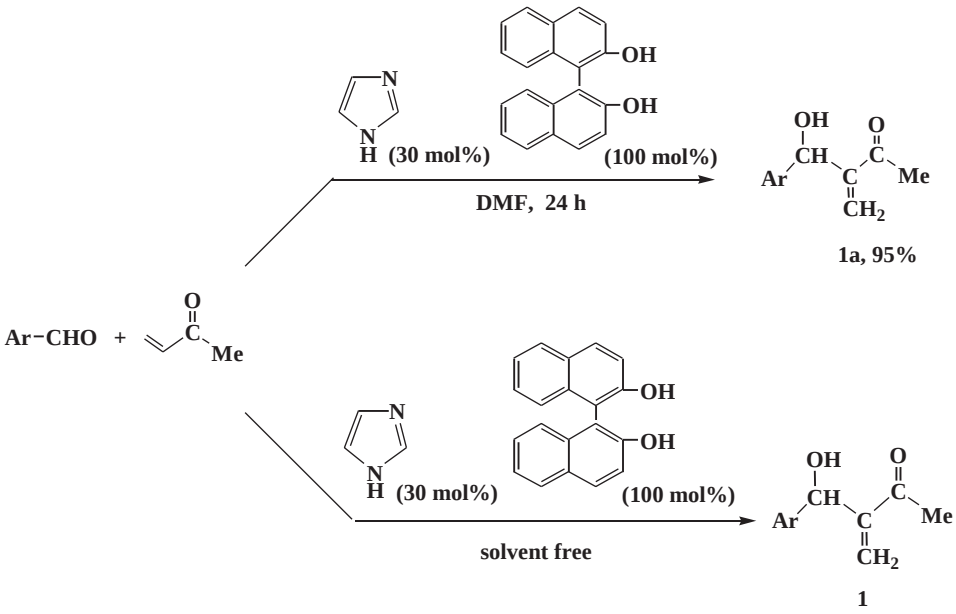
In the Baylis–Hillman reaction of aldehydes with methyl vinyl ketone, we found that, in the presence of a stoichiometric amount of binol and silica gel (SiO_2), a weak *Lewis* base such as imidazole can promote the reaction to give the normal Baylis–Hillman adduct under good yields under heterogeneous reaction conditions.

Keywords: imidazole, binol, Baylis–Hillman reaction, silica gel, heterogeneous reaction conditions

Great progress has been made in the application of the Baylis–Hillman reaction,[1] for which a catalytic asymmetric version has been published,[2] since Baylis and Hillman first reported the reaction of acetaldehyde with ethyl acrylate and acrylonitrile in the presence of catalytic amounts of strong Lewis bases such as 1,4-diazabicyclo[2.2.2]octane (DABCO) in 1972.[3] Our own investigation on this very simple and useful reaction, have provided novel results.[4] Recently we reported that, in the reaction of arylaldehydes with methyl vinyl ketone (MVK), weak Lewis bases such as imidazole and Et_3N can promote this reaction in the presence of L-proline to give high yields of **1**.[5] In that paper, we first disclosed that imidazole (30 mol%) and Et_3N (30 mol%) as weak Lewis bases cannot promote the reaction of arylaldehydes with MVK by themselves. But, we found that, in the presence of L-proline (30 mol%), this reaction takes place smoothly to give high yields of **1**.[5]

In the present paper, we report another version of such a combination, namely that this reaction can also be promoted in the presence of imidazole and binol.[6]

First, we used *p*-nitrobenzaldehyde and MVK as the substrate to examine the Baylis–Hillman reaction in the presence of imidazole and racemic binol (Scheme 1). As a result, we found that, in the presence of imidazole (30 mol%) and binol (100 mol%), the corresponding Baylis–Hillman adduct **1a** can be obtained in 97% in DMF within 24 h. But except for *o*-nitrobenzaldehyde and 3-pyridylaldehyde, the Baylis–Hillman reaction of other aldehydes with MVK does not take place under the same conditions (Table 1). In this version of the Baylis–Hillman reaction, we believe that the binol acted as a Lewis acid through hydrogen-bonding with the carbonyl group of the aldehyde. In order to explore suitable reaction conditions for a larger series of aldehydes using imidazole and binol in a co-catalysed system, we performed a heterogenous Baylis–Hillman reaction of aldehydes with MVK in the presence of imidazole



a: R=*p*-$NO_2C_6H_4$; b: R=*m*-$NO_2C_6H_4$; R=*o*-$NO_2C_6H_4$; R=*p*-BrC_6H_4; e: R=*p*-ClC_6H_4; f: R=*p*-FC_6H_4; g: R=C_6H_5; h: R=3-pyridyl; i: R=$C_6H_5CH{=}CH$; j: R=$C_6H_5CH_2CH_2CH_2$; k: R=*p*-$C_6H_5OC_6H_4$.

Scheme 1

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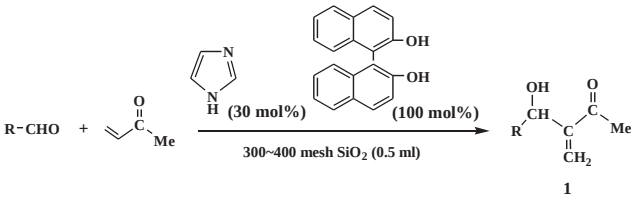
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Reactions of aldehyde (1.0 equiv) with MVK (2.0 equiv) in the presence of imidazole (0.3 equiv) and binol (1.0 equiv) in DMF

Entry	RCHO	Time /h	Produce /%[a]
	R		1
1	*o*-$NO_2C_6H_4$	24	**1c,** 69
2	*p*-BrC_6H_4	72	–
3	*p*-ClC_6H_4	72	–
4	*m*-FC_6H_4	72	–
5	3,5-$(CF_3)_2C_6H_3$	48	Trace
6	C_6H_5	48	–
7	*m*-$CH_3C_6H_4$	48	–
8	3-pyridyl	48	**1h,** 17
9	$C_6H_5CH{=}CH$	72	–
10	$C_6H_5CH_2CH_2$	72	–

[a]Yields of isolated products.



Scheme 2
a: R=*p*-$NO_2C_6H_4$; b: R=*m*-$NO_2C_6H_4$; c: R=*o*-$NO_2C_6H_4$; d: R=*p*-BrC_6H_4; e: R=*p*-ClC_6H_4; f: R=*p*-FC_6H_4; g: R=C_6H_5; h: R=3-pyridyl; i: R=$C_6H_5CH{=}CH$; j: R=$C_6H_5CH_2CH_2$; k: R=*p*-$C_6H_5OC_6H_4$.

(30 mol%) and binol (100 mol%) (Scheme 2). A mixture of *p*-nitrobenzaldehyde (1.0 equiv), imidazole (0.3 equiv), and binol (1.0 equiv) was ground in an agate mortar with a pestle, mixed with MVK (2.0 equiv) and kept in a capped sample tube at room temperature for 2–4 days. The mixture was extracted with CH_2Cl_2 and separated by column chromatography to afford **1a**. As shown in Table 2, *p*-nitrobenzaldehyde and *p*-chlorobenzaldehyde reacted with MVK very well in the presence of imidazole and binol to give the Baylis–Hillman adduct **1** in good yield (Table 2, entry 1,2). However for benzaldehyde, the yield was still low (Table 2, entry 3).

In order to improve the efficiency of this version of the Baylis–Hillman reaction under heterogeneous reaction conditions, we then performed the same reaction in the presence of silica gel (SiO_2 300–400 mesh). We believe that SiO_2 can act as a Lewis acid in this reaction (Scheme 2).[7] A mixture of aldehyde (1.0 mmol), imidazole (0.3 mmol), racemic binol (1.0 mmol) and SiO_2 (0.5 ml) was ground in an agate mortar with pestle. Then, MVK (2.0 mmol) was added into the solid mixture in a capped sample tube and the mixture was kept at room temperature for 2–4 days. The mixture was extracted with CH_2Cl_2 and separated by column chromatography to afford the corresponding Baylis–Hillman adduct **1**. Under these reaction conditions, we found that for many aldehydes, **1** can be obtained in good yields (Table 3, entry 1–5 and 7–9). However, for aliphatic aldehydes and arylaldehydes with a strong electron-donating group, the yield was low (Table 3, entry 6, 10–11).

Concerning the additives used for the Baylis–Hillman reactions, $LiClO_4$ and $NaBF_4$ have been used as Lewis acids together with Lewis bases DABCO and pyrrolizidine, respectively, to accelerate the reaction rate.[8] In these systems, DABCO or pyrrolizidine alone are able to promote the reaction. In our system, the coexistence of imidazole and binol is required to promote the Baylis–Hillman reaction, although, the yields are not very high.

In conclusion, we have found that, in the Baylis–Hillman reaction of aldehydes with methyl vinyl ketone (MVK), the weak Lewis base imidazole can promote the reaction in the presence of binol and silica gel under heterogeneous reaction conditions. It should be emphasised here that, using chiral (*R*)-(+)-1,1'-bi-2-naphthol as a co-catalyst, the Baylis–Hillman adducts **1** were obtained with very low optical activity (2–3% ee). Nevertheless, we believe that this finding may open up a new way for the design and synthesis of chiral ligands that will catalyse the asymmetric version of the Baylis–Hillman reaction under heterogeneous reaction conditions. Efforts are underway to elucidate the mechanistic details of this reaction and to discover its scope and limitations.

Table 2 Reactions of aldehyde (1.0 equiv) with MVK (2.0 equiv) in the presence of imidazole (0.3 equiv) and binol (1.0 equiv) in solid phase

Entry	RCHO	Time /h	Produce /%[a]
	R		**1**
1	*p*-$NO_2C_6H_4$	24	**1a,** 66
2	*p*-ClC_6H_4	48	**1e,** 56
3	C_6H_5	72	**1g,** <5

[a]Yields of isolated products.

Table 3 Reactions of aldehyde (1.0 equiv) with MVK (2.0 equiv) in the presence of imidazole (0.3 equiv) and binol (1.0 equiv) in the presence of SiO_2 (0.5 ml) in solid phase

Entry	RCHO	Time /h	Produce /%[a]
	R		1
1	*p*-$NO_2C_6H_4$	24	**1a,** 47
2	*m*-$NO_2C_6H_4$	24	**ab,** 47
3	*o*-$NO_2C_6H_4$	24	**1c,** 88
4	*p*-BrC_6H_4	24	**1d,** 57
5	*p*-ClC_6H_4	24	**1e,** 70
6	*p*-FC_6H_4	24	**1f,** <5
7	C_6H_5	24	**1g,** 47
8	3-pyridyl	24	**1h,** 34
9	$C_6H_5CH{=}CH$	24	**1i,** 26
10	$C_6H_5CH_2CH_2$	24	**1j,** <5
11	*p*-$C_6H_5OC_6H_4$	24	**1k,** <5

[a]Yields of isolated products.

Experimental section

General: M.p.s were obtained with a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer for solutions in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard; *J*-values are in Hz. Mass spectra were recorded with a HP-5989 instrument and HRMS was measured by a Finnigan MA+ mass spectrometer. Organic solvents were dried by standard methods when necessary. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with Huanghai GF_{254} silica gel coated plates. Flash column chromatography was carried out using 200–300 mesh silica gel at increased pressure.

The spectroscopic data of the corresponding Baylis–Hillman adducts are shown below. The yields of **1f**, **1j** and **1k** were very low and therefore, we were unable to obtain their spectroscopic data.

Representative experimental procedure: A mixture of *p*-nitrobenzaldehyde (151 mg, 1.0 mmol), imidazole (20.4 mg, 0.3 mmol), binol (302 mg, 1.0 mmol), and silica gel (200–300 mesh) (0.5 ml) was ground in an agate mortar with a pestle. Then, methylvinylketone (2.0 mmol) was added to the solid mixture in a capped sample tube. The reaction mixture was kept at room temperature for 2–4 d. The mixture was extracted with CH_2Cl_2 (10 ml) and separated by column chromatography (SiO_2, petroleum ether/AcOEt 1/4) to afford the corresponding Baylis–Hillman adduct **1a** as a colourless solid.

The Baylis–Hillman adduct **1a**: m.p. 76–77 °C; IR (KBr) ν 3483 (O–H), 2935, 1658 (C=O), 1305, 856 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.37 (3H, s, Me), 3.34 (1H, d, *J* = 5.3 Hz, OH), 5.69 (1H, d, *J* = 5.3 Hz), 6.04 (1H, s), 6.28 (1H, s), 7.56 (2H, d, *J* = 8.6 Hz, Ar), 8.25 (2H, d, *J* = 8.6 Hz, Ar); MS (EI) *m/e* 220 (M^+-1, 20.9), 204

(M^+-17, 100), 174 (M^+-47, 88.1); [Found: HRMS (EI) *m/z* 222.0749 $(M+1)^+$; $C_{11}H_{12}O_4N$ requires M+1, 222.0766].

The Baylis–Hillman adduct **1b**: 55 mg, 50%; a colourless solid; m.p. 79–80 °C; IR (KBr) ν 3431 (O–H), 2930, 1654 (C=O), 1585, 834 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.37 (3H, s, Me), 3.35 (1H, d, *J* = 5.4 Hz, OH), 5.68 (1H, d, *J* = 5.4 Hz), 6.09 (1H, s), 6.30 (1H, s), 7.56 (1H, dd, *J* = 8.0, 8.0 Hz, Ar), 7.78 (1H, d, *J* = 8.0 Hz, Ar), 8.16 (1H, d, *J* = 8.0 Hz, Ar), 8.26 (1H, s, Ar); MS (EI) *m/z* 221 (M^+, 5.0), 220 (M^+–1, 43.0), 204 (M^+-17, 85.4), 77 (M^+-144 , 36.8), 43 (M^+-178, 100); [Found: HRMS (EI) *m/z* 222.0766 $(M+1)^+$, $C_{11}H_{12}O_4N$ requires M+1, 222.0774].

The Baylis–Hillman adduct **1c**: a colourless solid; 92 mg, 83%; m.p. 75–76 °C; IR (KBr) ν 3362 (O–H), 2961, 1663 (C=O), 1571, 859 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.39 (3H, s, Me), 3.53 (1H, d, *J* = 4.1 Hz, OH), 5.80 (1H, s), 6.19 (1H, s), 6.25 (1H, d, *J* = 4.1 Hz, CH), 7.50 (1H, dd, *J* = 7.1, 7.1 Hz, Ar), 7.70 (1H, dd, *J* = 7.6, 7.6 Hz, Ar), 7.79 (1H, d, *J* = 7.6 Hz, Ar), 8.0 (1H, d, *J* = 8.2 Hz, Ar); MS (EI) *m/z* 204 (M^+-17, 31.0), 162 (M^+-59, 100), 144 (M^+-77, 26.5), 43 (M^+-178, 86.6); [Found: HRMS (EI) *m/z* 222.0766 $(M+1)^+$, $C_{11}H_{12}O_4N$ requires M+1, 222.0771].

The Baylis–Hillman adduct **1d**: a colourless oily compound; 65 mg, 51%; IR (KBr) ν 3423 (O–H), 2963, 1676 (C=O), 1487, 822 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.33 (3H, s, Me), 3.20 (1H, d, *J* = 4.8 Hz, OH), 5.58 (1H, d, *J* = 4.8 Hz, CH), 5.99 (1H, s), 6.22 (1H, s), 7.25 (2H, d, *J* = 8.4 Hz, Ar), 7.48 (2H, d, *J* = 8.4 Hz); MS (EI) *m/z* 255 (M^+, 38.5), 239 (M^+-17, 10.3), 175 (M^+-80, 100), 157 (M^+-98, 45.1), 77 (M^+-178, 42.6), 43 (M^+-212, 54.7); [Found: HRMS (EI) *m/z* 253.9946 (M^+), $C_{11}H_{11}O_2Br$ requires M, 253.9942].

The Baylis–Hillman adduct **1e**: a colourless oily compound; 65 mg, 62%; IR (KBr) ν 3434 (O–H), 2936, 1676 (C=O), 1490, 827 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.37 (3H, s, Me), 3.23 (1H, d, *J* = 4.9 Hz, OH), 5.59 (1H, d, *J* = 4.9 Hz, CH), 5.99 (1H, s), 6.23 (1H, s), 7.33 (4H, s, Ar); MS (EI) *m/z* 210 (M^+, 9.6), 193 (M^+-17, 15.1), 175 (M^+-35, 100), 77 (M^+-133, 70.2), 43 (M^+-167, 76.4); [Found: HRMS (EI) *m/z* 222.0448 (M^+). $C_{11}H_{11}O_2Cl$ requires M, 222.0428].

The Baylis–Hillman adduct **1g**: a colourless oily compound; 64 mg, 73%; IR (KBr) ν 3427 (O–H), 3031, 1673 (C=O), 1492, 840 cm^{-1} ; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.38 (3H, s, Me), 3.20 (1H, d, *J* = 4.3 Hz, OH), 5.62 (1H, d, *J* = 4.3 Hz, CH), 6.0 (1H, s), 6.23 (1H, s), 7.30–7.40 (5H, m, Ar); MS (EI) *m/z* 176 (M^+, 22.0), 157 (M^+-1, 100.0), 77 (M^+ - 99, 33.0), 43 (M^+-133, 49.0); [Found: HRMS (EI) *m/z* 176.0837 (M^+), $C_{11}H_{12}O_2$ requires M, 176.0826].

The Baylis–Hillman adduct **1h**: a colourless solid 62 mg, 70%; m.p. 85–86 °C; IR (KBr) ν 3354 (O–H), 2930, 1714 (C=O), 896 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.33 (3H, s, Me), 3.88 (1H, br., s, OH), 5.65 (1H, s, CH), 6.09 (1H, s), 6.27 (1H, s), 7.20–7.30 (1H, m, Ar), 7.73 (1H, dd, *J* = 8.0, 1.5 Hz, Ar), 8.46 (1H, dd, *J* = 8.0, 6.2 Hz, Ar), 8.50 (1H, d, *J* = 5.9 Hz, Ar); MS (EI) *m/z* 177 (M^+, 14.2), 160 (M^+-17, 100), 43 (M^+-134, 52.7); [Found: HRMS (EI) *m/z* 177.0786 (M^+), $C_{10}H_{11}O_2N$ requires M, 177.0788].

The Baylis–Hillman adduct **1i**: a colourless oily compound; 58 mg, 57%; IR (KBr) ν 3438 (O–H), 2924, 1672 (C=O), 1575, 852 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.40 (3H, s, Me), 3.10 (1H, d, *J* = 5.9 Hz, OH), 5.69 (1H, t, *J* = 5.9 Hz, CH), 6.13 (1H, s), 6.17 (1H, s), 6.31 (1H, dd, *J* = 16.3, 6.2 Hz, CH), 6.68 (1H, d, *J* = 16.3 Hz), 7.26–7.41 (5H, m, Ar); MS (EI) *m/z* 202 (M^+, 42.5), 184 (M^+-18, 50.3), 70 (M^+-132, 66.2), 43 (M^+-159, 100); [Found: HRMS (EI) *m/z* 202.1006 (M^+), $C_{13}H_{14}O_2$ requires M, 202.0994].

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