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Aminocatalysis of the Baylis–Hillman reaction: an important solvent effect

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Abstract—Examination of the aminocatalytic Baylis–Hillman reaction in the presence of proline and imidazole has revealed that water plays a crucial role in the acceleration of the reaction, allowing for excellent yields of the adduct between methyl vinyl ketone and a variety of aldehydes.

The recent interest in the discovery of new aminocatalytic procedures has been remarkable.[1] The development of new reliable synthetic procedures that proceed at ambient temperature in the presence of both moisture and air, frequently with excellent yield and enantioselectivity, has added a new set of powerful and robust methods to the synthetic chemists' tool box.[2]

In this broad field of research, the Baylis–Hillman reaction[3] has received significant attention due to the densely functionalised and potentially useful products that arise from the coupling of an electron deficient alkene and an aldehyde.[4] Numerous alternatives have been reported for the acceleration of this process using nitrogen, phosphorus and sulfur nucleophiles with good success.[5] A recent report from Shi et al. showed that a combination of 30 mol % imidazole in conjunction with 30 mol % proline promoted the reaction between methyl vinyl ketone and a series of aldehydes (Fig. 1).[6] It was proposed that formation of the iminium ion between methyl vinyl ketone **2** and proline **1** allowed for addition of imidazole **4** to give the enamine intermediate **5**. Addition to benzaldehyde **6**, elimination of imidazole and subsequent hydrolysis of the iminium ion then gave the observed product **8** together with regeneration of the two active species, proline **1** and imidazole **4** which could re-enter the catalytic cycle. Although low enantiomeric excess (<5%) was reported for each of the adducts described, given the recent levels of success achieved in aminocatalytic transformations with proline we thought this mechanistically intriguing process warranted further attention and sought to investigate alternative chiral secondary amines to accelerate the reaction. Within this Letter, we report the crucial role of water in the iminium ion catalysed Baylis Hillman reaction.

As a starting point, we investigated the reaction between methyl vinyl ketone **2** and 4-nitrobenzaldehyde **9** (Table 1). From the work of Shi, it was apparent that the polar solvent DMF was essential for catalytic activity. Using these conditions as a guide, DMF was used as the reaction medium in the presence of 10 mol % proline and imidazole, performing the reaction at 1 M concentration for 24 h.[7] This gave the expected adduct **10**, but in a disappointing 63% isolated yield, substantially lower than that reported (entry 1). Believing that this may have been due to the reduced catalyst loading, we performed the reaction using 30 mol % loading of imidazole and proline and once again observed a reduced yield to that expected (entry 2, 54%). In an attempt to rationalise this result, it was reasoned that the DMF used may have contained trace amounts of water and so performed the reaction in mixtures of DMF and water (entries 3–7). These experiments revealed that water was an important factor within the reaction with the optimal ratio of DMF:H_2O being 9:1 (entry 4).[8] Increasing the amount of water beyond this led to a gradual decrease in the yield observed.

Miller and co-workers has reported THF to be an effective solvent for the proline catalysed Baylis–Hillman reaction in the presence of a complex chiral base, the products being isolated in high yield and good enantiomeric

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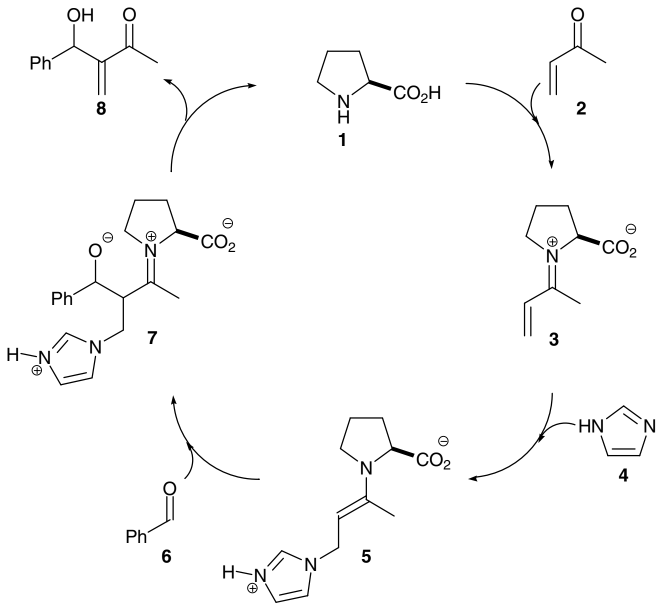
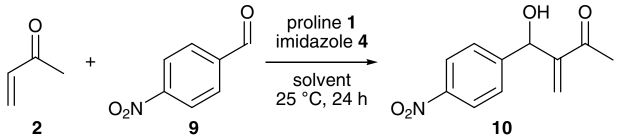


Figure 1. Shi's proline/imidazole catalysed Baylis–Hillman reaction.

Table 1. Baylis–Hillman reaction catalysed by imidazole and proline[a]



Entry	Solvent	**1** (mol %)	**4** (mol %)	Yield[b] (%)
1	DMF	10	10	61
2	DMF	30	30	54
3	DMF:H_2O 19:1	10	10	63
4	DMF:H_2O 9:1	10	10	80
5	DMF:H_2O 7.5:2.5	10	10	40
6	DMF:H_2O 1:1	10	10	30
7	H_2O	10	10	16
8	THF	10	10	27
9	THF:H_2O 19:1	10	10	62
10	THF:H_2O 9:1	10	10	30
11	THF:H_2O 1:1	10	10	32

[a] All reactions performed at 1 M concentration at 25 °C for 24 h.

[b] Isolated yield – reported yields are the average of two runs.

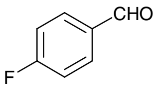
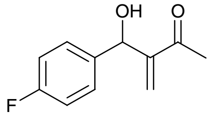
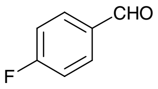
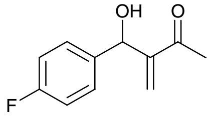
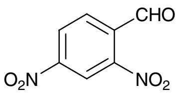
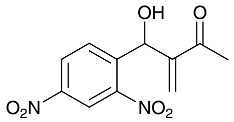
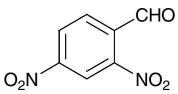
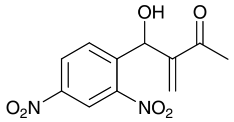
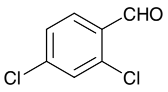
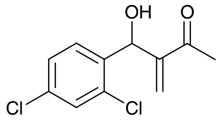
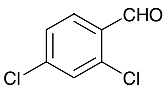
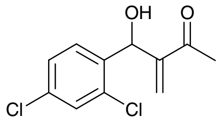
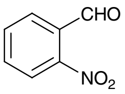
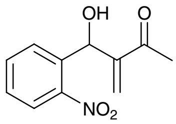
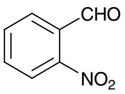
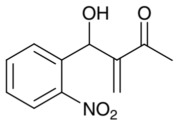
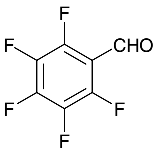
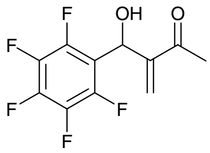
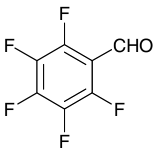
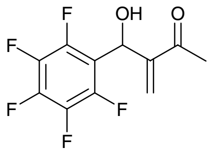
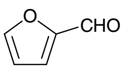
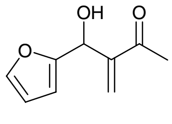
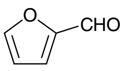
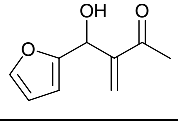
excess.[9] Given the practical convenience of THF when compared to DMF, we also examined this solvent (Table 1, entries 8–11). Once again the addition of water had a significant effect on the isolated yield of the reaction in the presence of 10 mol % proline and imidazole in a 19:1 mixture of THF:H_2O (entry 9). Increasing the amount of water beyond this level led to a lowering of the amount of isolated product.

The specific role of water in this complex mechanism is unclear at present, however, it has been noted in other iminium ion catalysed transformations that water is a crucial additive to bring about effective reaction rates. For example, in the Diels–Alder reaction of α,β-unsaturated aldehydes, MacMillan and co-workers has stated that in the absence of water, lower reaction rates were observed, with optimal reaction conditions involving a 19:1 MeOH:H_2O mixture.[10] Similar conclusions were also reported by Ogilvie and Lemay when monitoring the iminium ion catalysed Diels–Alder reaction between *trans*-cinnamaldehyde and cyclopentadiene.[11] In this Letter, it was shown that iminium ion formation was considerably more facile in a 19:1 mixture of nitromethane and water, when compared to nitromethane as the sole reaction solvent. From this it was proposed that the effect of water on iminium ion formation was due to an increase in the supply of available H^+, accelerating proton transfers involved in iminium ion formation. This may also be the case in the current work, whereby the activated iminium ion **3** is formed more rapidly in the presence of water, suggesting a general acid catalysed mechanism.

A specific advantage often cited within the literature of both iminium ion and enamine catalysis is that the reactions may be carried out in the presence of both moisture and air. It is entirely possible that this 'fortuitous' water is an essential element in bringing about the remarkable levels of catalyst activity observed and warrants further investigation in order to accurately define the catalytic cycle and design more efficient catalyst architectures.

Having established the advantages of water in the proline/imidazole catalysed Baylis–Hillman reaction of methyl vinyl ketone (**2**) and 4-nitrobenzaldehyde (**9**), we went on to investigate the generality of this phenomenon with alternative aldehydes (Table 2). Each reaction was performed in both anhydrous DMF and a mixture of DMF:H_2O (9:1) with 10 mol % of both **1** and **4**. In all cases, the substantial effect of water was confirmed; isolated yields increasing markedly using the DMF:H_2O mixture. The effect was most dramatic using pentafluorobenzaldehyde (Table 2, entries 9 and 10), whereby in the absence of water no Baylis–Hillman adduct was

Table 2. Generality of the reaction process[a]

Entry	ArCHO	Product	Yield
1[b]			67
2[c]			87
3[b]			42
4[c]			81
5[b]			56
6[c]			80
7[b]			58
8[c]			73
9[b]			0
10[c]			84
11[b,d]			33
12[c,d]			89

[a] All reactions performed at 1 M concentration at 25 °C for 24 h except entries 11 and 12.

[b] Reactions performed in DMF.

[c] Reactions performed in DMF:H_2O (9:1).

[d] Reactions performed for 90 h.

observed whereas in the DMF:H_2O mixture (9:1) the adduct was isolated in an excellent 84% yield. Less electron deficient aldehyde substrates were found to be slower, in line with the observations of others, the reaction of furfuraldehyde and methyl vinyl ketone taking 4 days to reach completion (Table 2, entry 12, 89%).

In accordance with the observations of Shi, examination of each of the adducts prepared in this study (Tables 1 and 2) by HPLC on a chiral stationary phase showed each to be racemic.

In summary, we have found that in the proline/imidazole catalysed Baylis–Hillman reaction between methyl vinyl ketone and aldehydes, the nature of the solvent is crucial for effective catalyst activity. Addition of small amounts of water brings about more effective reaction with a solvent mixture of DMF:H_2O (9:1) being optimal. This solvent mixture is effective with a variety of substrates within the reaction, with yields being substantially lower in the absence of water. Increasing or decreasing the amount of water present is detrimental to the observed yield. Due to the significant amount of interest in this type of Baylis–Hillman reaction and its potential for the development of an asymmetric variant, the incorporation of water in the reaction medium appears also to be an important factor in optimising catalyst activity.

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7. Anhydrous DMF used in this reaction was purified by stirring over phosphorus pentoxide for 48 h followed by distillation from calcium hydride under an atmosphere of nitrogen prior to use. Identical results could also be obtained using anhydrous DMF purchased from Aldrich Chemical Co., Inc.
8. *Typical experimental procedure for the Baylis–Hillman reaction*: 3-(Hydroxy(4-nitrophenyl)methyl)but-3-en-2-one **10**: To a solution of L-proline (12 mg, 0.1 mmol), imidazole (7 mg, 0.1 mmol) and 4-nitrobenzaldehyde (151 mg, 1 mmol) in DMF/water (9:1) (1 mL) was added methyl vinyl ketone (0.25 mL, 3 mmol) and the resulting solution was stirred for 24 h at 25 °C. The reaction was quenched with saturated sodium bicarbonate solution (5 mL) and extracted with dichloromethane (3 × 10 mL). The organic phase was washed with water (3 × 10 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica, eluting with ethyl acetate/light petroleum (3:7), to give the title compound (176 mg, 80%) as a pale yellow solid; mp = 79–81 °C; IR (nujol) 3419, 2922, 1732, 1660, 1652 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.17 (2H, d, $J = 8.9$ Hz), 7.54 (2H, d, $J = 8.9$ Hz), 6.30–6.22 (1H, m), 6.03 (1H, br s), 5.66 (1H, d, $J = 5.0$ Hz), 3.37 (1H, d, $J = 5.6$ Hz), 2.34 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 200.0, 149.0, 148.9, 147.3, 127.7, 127.2, 123.5, 72.2, 26.3; LRMS (CI, $[M+NH_4]^+$) m/z 239.1 (100%); HRMS (CI, $[M+NH_4]^+$): found 239.1028; ($C_{11}H_{15}N_2O_4$) requires 239.1026.
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