Reaction Mechanisms

Probing the Mechanism of the Baylis–Hillman Reaction by Electrospray Ionization Mass and Tandem Mass Spectrometry**

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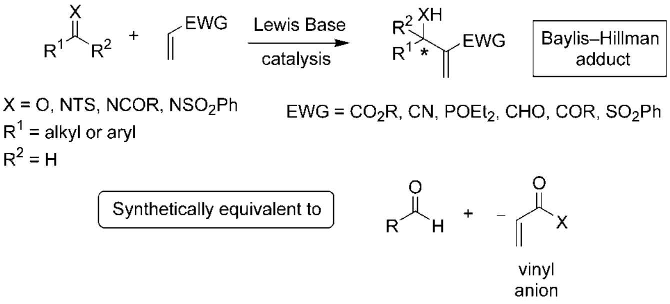
The search for efficient methodologies to form C–C bonds continues to challenge chemists who face the construction of organic molecules of increasing complexity and functions. Multifaceted functional-group transformations and the creation and control of new asymmetric centers are key steps in the total synthesis of organic molecules, with special emphasis on catalytic activation.[1] Atom economy and high chemo-, regio-, and stereoselectivity are also essential requisites of new, efficient synthetic reactions.[2]

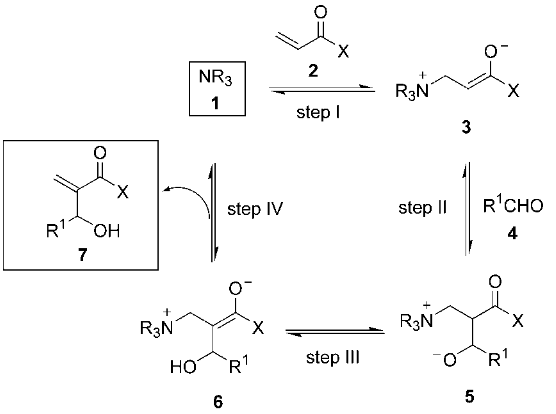
Within this scenario, the Baylis–Hillman reaction (Scheme 1) has recently experienced an enormous growth in importance and use.[3] This versatile multicomponent reaction was first described by Morita et al.[4] and later, in a German patent, by Baylis and Hillman.[5] The reaction leads to the straightforward formation of new σ C–C bonds in a single step, and yields densely functionalized molecules (α-methylene-β-hydroxy derivatives), which are then conveniently manipulated as key synthons in the synthesis of a variety of natural and nonnatural products.[6]



Scheme 1. General scope of the Baylis–Hillman reaction.

The Baylis–Hillman reaction can be broadly defined as a coupling reaction between an alkene activated by an electron-withdrawing group and an electrophile (Scheme 1) that occurs under Lewis base catalysis, with 1,4-diazabicyclo[2.2.2]octane (DABCO) normally used as the base.[3] Formally, the reaction is synthetically equivalent to the addition of a vinyl anion to an aldehyde.

Several mechanistic considerations and kinetic studies led to the general acceptance of the Baylis–Hillman catalytic cycle summarized in Scheme 2. This mechanism was initially proposed by Hill and Isaacs,[7a] and later refined by others.[7b–d]



Scheme 2. Currently accepted catalytic cycle for the Baylis–Hillman reaction.

According to Scheme 2, the first reaction step I consists of the 1,4-addition of the catalytic tertiary amine **1** to the activated alkene **2** (α,β-unsaturated carbonyl compounds), which generates the zwitterion intermediate **3**. In step II, **3** adds to aldehyde **4** by an aldolic addition reaction to yield intermediate **5**. Step III involves an intramolecular prototropic shift within **5** to form intermediate **6**, which in step IV forms the final Baylis–Hillman adduct **7** through E2 or E1cb elimination in the presence of a Lewis base. The last step IV returns catalyst **1** to the catalytic cycle. The reaction rate seems to be determined by step II because the dipole moment is increased by further charge separation.

Despite its increasing importance and use, up to now only a single experimental study has collected evidence for the catalytic cycle of the Baylis–Hillman reaction. Drewes et al.[8] carried out the reaction of methyl acrylate with 2-hydroxybenzaldehyde in dichloromethane at 0 °C in the presence of DABCO (Scheme 3), isolated a type-**6** intermediate (Scheme 2) as a coumarin salt, and characterized the salt by X-ray crystallography.

Molecular analysis by mass spectrometry (MS) has greatly benefited from the development of electrospray ionization (ESI),[9] since molecules and supramolecules[10] of high polarity, molecular complexity, and/or mass can be easily ionized by ESI for investigation by MS. ESI is an interesting "ion-

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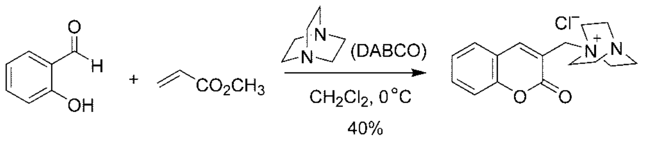
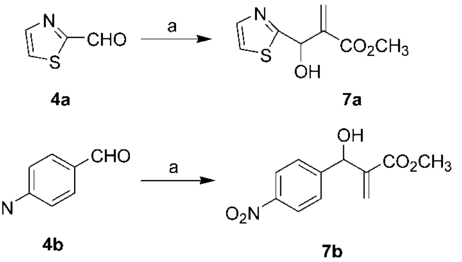


Scheme 3. The single Baylis–Hillman intermediate so far isolated and characterized by X-ray crystallography.

fishing” technique, since it gently transfers preformed ions directly from solution to the gas phase. ESI-MS (and its tandem version ESI-MS/MS) is rapidly becoming the technique of choice for solution mechanistic studies in chemistry and biochemistry[11], and in high-throughput screening of homogeneous catalysis reactions.[12]

Several neutral zwitterionic intermediates are involved in the currently accepted mechanism for the Baylis–Hillman reaction of acrylates with aldehydes catalyzed by DABCO (Scheme 2). However, these neutral species are expected to be in equilibrium with their protonated forms in methanolic solution. ESI-MS/MS appears therefore to be the ideal technique to probe the Baylis–Hillman reaction mechanism and catalytic cycle, since ESI could “fish” (with high sensitivity) such cationic intermediates directly from solution to the gas phase for their unprecedented MS interception, mass analysis, and MS/MS structural characterization. Herein, we describe the results of an ESI-MS/MS study aimed at detecting and structurally characterizing the putative intermediates of the Baylis–Hillman reaction.

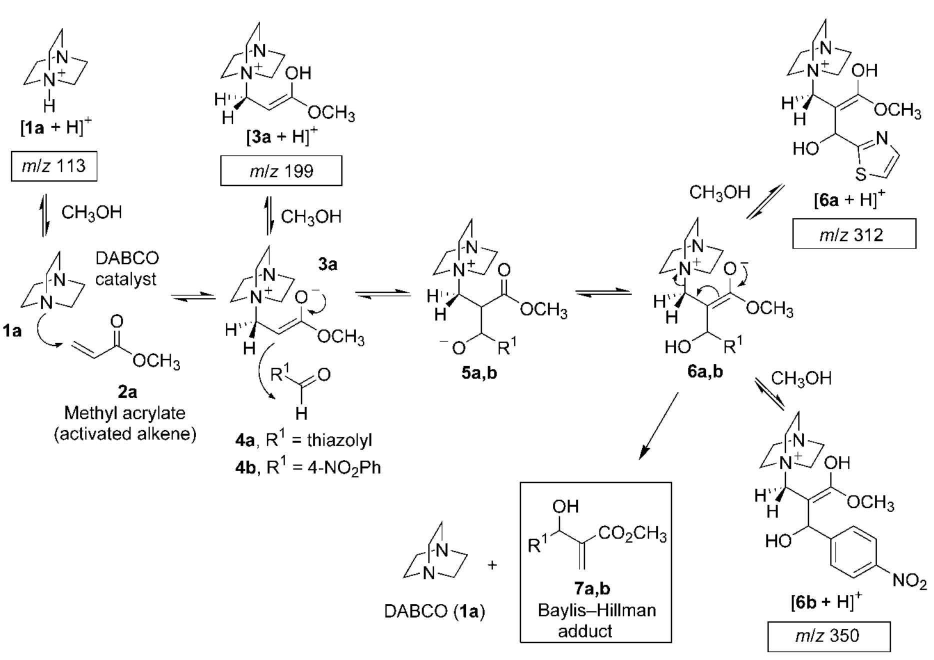
Our investigation began with the ESI-MS monitoring[13] of the reaction of methyl acrylate with two aldehydes (**4a** and **4b**, Scheme 4) catalyzed by DABCO in methanol.[14] The aim was to intercept the cationic species resulting from the proton-exchange equilibrium with methanol using ESI-MS in the positive-ion mode (Scheme 5). ESI is known for its ability to transfer ions to the gas phase without inducing undesirable side reactions,[9] and the composition of ESI-generated ions often closely reflects that in solution.[10,15] We then mixed DABCO (0.65 equiv), methyl acrylate (1.30 equiv), and the respective aldehyde (1.00 equiv) in methanol (2 mL), and monitored the reaction by ESI-MS using a microsyringe pump to deliver the methanol solution directly to the ESI source at flow rates of 0.01 mL min^{-1}.



Scheme 4. Baylis–Hillman reactions monitored by ESI(+)-MS/MS. Reagents and conditions: a) DABCO (**1a**), methyl acrylate (**2a**), MeOH, RT.

The cationic reaction intermediates are likely to be in equilibrium with their respective neutral zwitterionic forms in methanolic solutions, and even disfavored equilibria could be useful because of the high sensitivity of ESI-MS analysis. Indeed, the ESI-MS spectra collected for such reactions are extraordinarily clean and mechanistically enlightening. Shortly after one to five minutes of reaction of aldehyde **4a**, three covalently bonded cationic species directly related to the proposed Baylis–Hillman catalytic cycle (Scheme 5) are detected as major ions (Figure 1a): [**1a**+H]$^+$ of *m*/*z* 113, [**3a**+H]$^+$ of *m*/*z* 199, and [**6a**+H]$^+$ of *m*/*z* 312. The ESI-MS spectrum for the reaction of aldehyde **4b** (Figure 1b) shows two of the same major ions, [**1a**+H]$^+$ of *m*/*z* 113 and [**3a**+H]$^+$ of *m*/*z* 199 but, as expected, [**6a**+H]$^+$ of *m*/*z* 312 from aldehyde **4a** was replaced by [**6b**+H]$^+$ of *m*/*z* 350 from aldehyde **4b** (Scheme 5). The formation of covalent species is indicated by the relatively high kinetic energy of gas-phase ions transferred from the ESI source into the mass spectrometer (acceleration cone voltage of 40–45 V), and the optimized declustering properties of the ESI source. Under such conditions, loosely bonded species should not survive.

All these intermediates, so gently transferred to the gas phase by ESI in their intact protonated forms, were then individually mass-selected by quadrupole Q1 for collision-induced dissociation (CID) with nitrogen in quadrupole q2, and were structurally characterized by tandem mass spectro-



Scheme 5. Baylis–Hillman reaction of methyl acrylate and aldehydes catalyzed by DABCO. The protonated species expected to be intercepted and structurally characterized by ESI(+)-MS/MS, with their respective *m*/*z* ratios.

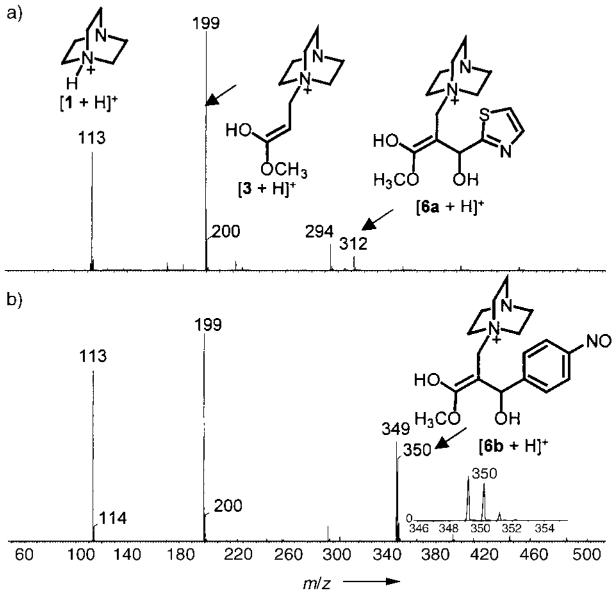


Figure 1. ESI(+)-MS spectra for the Baylis–Hillman reaction of methyl acrylate with aldehydes a) **4a** and b) **4b** catalyzed by DABCO. Other unidentified ions are likely to correspond to either impurities (favorably ionized under positive-ion ESI) or side-reaction products.

metric (MS/MS) analysis.[13] The relatively high resistance toward CID (15–30 eV collisions with nitrogen were needed to promote dissociation) and the diverse dissociation chemistry displayed by such ionic products cause loosely bonded adducts, such as proton-bonded dimers $[M_1\cdots H\cdots M_2]^+$, to be discarded. Noncovalently bonded adducts would dissociate exclusively or nearly exclusively to form either M_1H^+ or M_2H^+, or both.[16] The ESI-MS/MS spectra show that protonated DABCO [**1a**+H]$^+$ of *m/z* 113 loses an ethyl radical to form the fragment ion of *m/z* 84 (Figure 2a). Intermediate [**3a**+H]$^+$ of *m/z* 199 also loses an ethyl radical, probably from the DABCO moiety, to form the fragment ion of *m/z* 170 (Figure 2b). However, the main dissociation routes of [**3a**+H]$^+$ lead to ionized DABCO of *m/z* 112, which dissociates in turn by the loss of a methyl radical to form the ion of *m/z* 97.

Intermediate [**6b**+H]$^+$ of *m/z* 350 dissociates nearly exclusively by the loss of neutral **7b** to yield protonated DABCO [**1a**+H]$^+$ of *m/z* 113 (Figure 2d). Therefore, there is an interesting close analogy between this CID process and the final Baylis–Hillman reaction step that affords **7b** by the release of neutral DABCO (Scheme 5). The analogue intermediate [**6b**+H]$^+$ of *m/z* 312 also dissociates by the loss of neutral **7a** to yield [**1a**+H]$^+$ of *m/z* 113 (Figure 2c), but several other dissociation channels are available to [**6a**+H]$^+$ for which R^1 = thiazolyl. This ion can dissociate by the loss of neutral thiazole to form the fragment ion of *m/z* 227, which dissociates in turn by the loss of neutral DABCO and then water to give ions of *m/z* 200 and 182, respectively.

In conclusion, the proposed intermediates for the catalytic cycle of the Baylis–Hillman reaction (**3**–**5**/**6**, Schemes 2 and 5) have been successfully intercepted and structurally characterized for the first time using electrospray ionization with mass and tandem mass spectrometry. Strong evidence for the currently accepted mechanism has been collected, thus confirming the proposals initially made by Isaacs and Hill and refined later by others. Studies aimed at intercepting key cationic intermediates of Baylis–Hillman reactions catalyzed by Lewis acids, such as those described by Aggarwal et al.,[17] and of reactions performed in ionic liquids as solvents for which contradictory conclusions have been reached,[18] are under way.

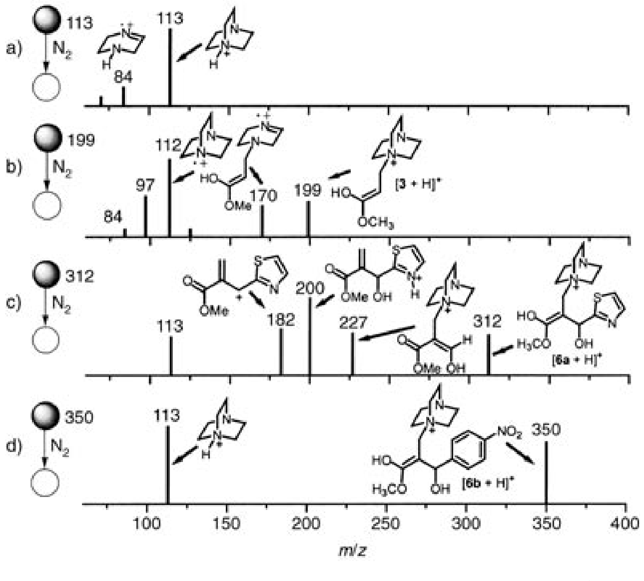


Figure 2. ESI(+)-MS/MS spectra of a) protonated DABCO [**1**+H]$^+$ and intermediates, b) [**3**+H]$^+$, c) [**6a**+H]$^+$, and d) [**6b**+H]$^+$. In the terminology used to describe the tandem mass spectrometric experiments, the circle represents a mass analyzer that transmits either an ion with a fixed *m/z* ratio (filled circle) or variable *m/z* ratio (open circle). The arrow indicates the ion course, with mass changes being caused by dissociative collisions with a neutral gas (N_2). For more details, see reference [19].

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