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Dualistic Nature of the Mechanism of the Morita−Baylis−Hillman Reaction Probed by Electrospray Ionization Mass Spectrometry

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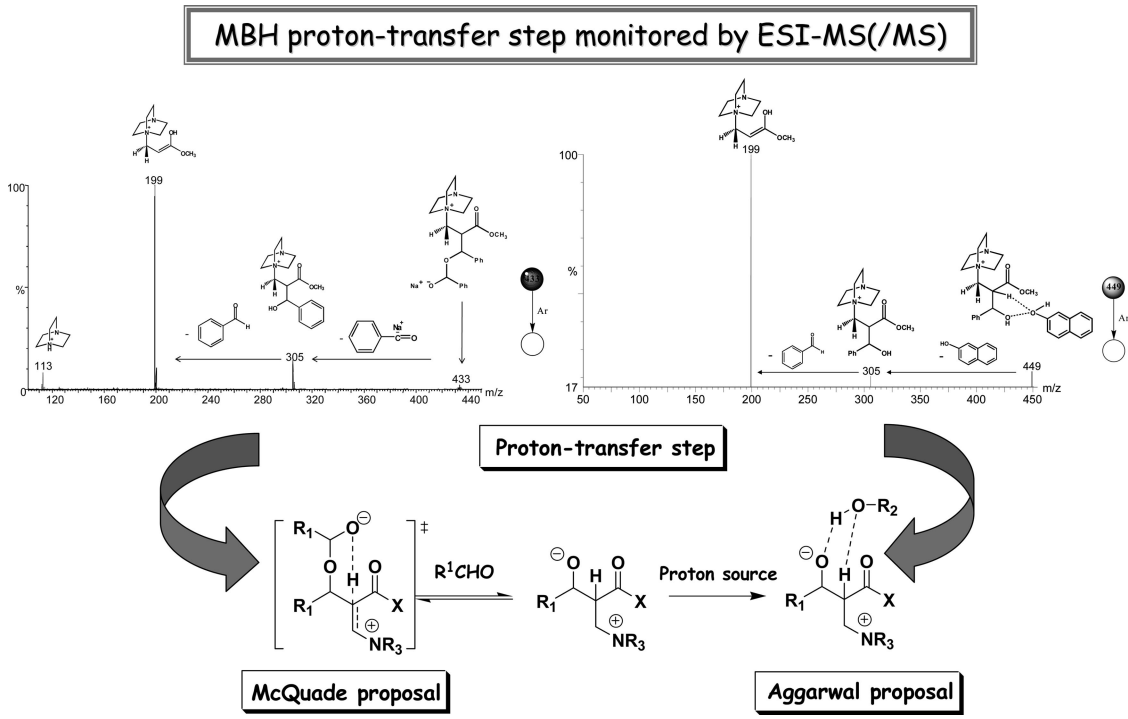

The Morita−Baylis−Hillman (MBH) reaction allows chemists to form new σ C−C bonds in a single-step straightforward manner and thus to construct densely functionalized molecules for further chemical manipulation. Using electrospray ionization for transferring ions directly from solution to the gas phase, and mass (and tandem mass) spectrometry for mass and structural assignments, new key intermediates for the rate-determining step of the MBH reaction have been successfully intercepted and structurally characterized. These ESI-MS data provide experimental evidence supporting recent suggestions, based on kinetic experiments and theoretical calculations, for the dualist nature of the proton-transfer step of the MBH mechanism.

Introduction

The Morita−Baylis−Hillman (MBH) reaction (Scheme 1) constitutes a broad range, synthetically useful chemical transformation allowing chemists to construct, via efficient formation of new C−C σ bonds, a myriad of densely functionalized α-methylene-β-hydroxy derivatives.[1−3]These derivatives are known as MBH adducts and are formed by coupling an electrophile (an aldehyde or an imine) with an activated

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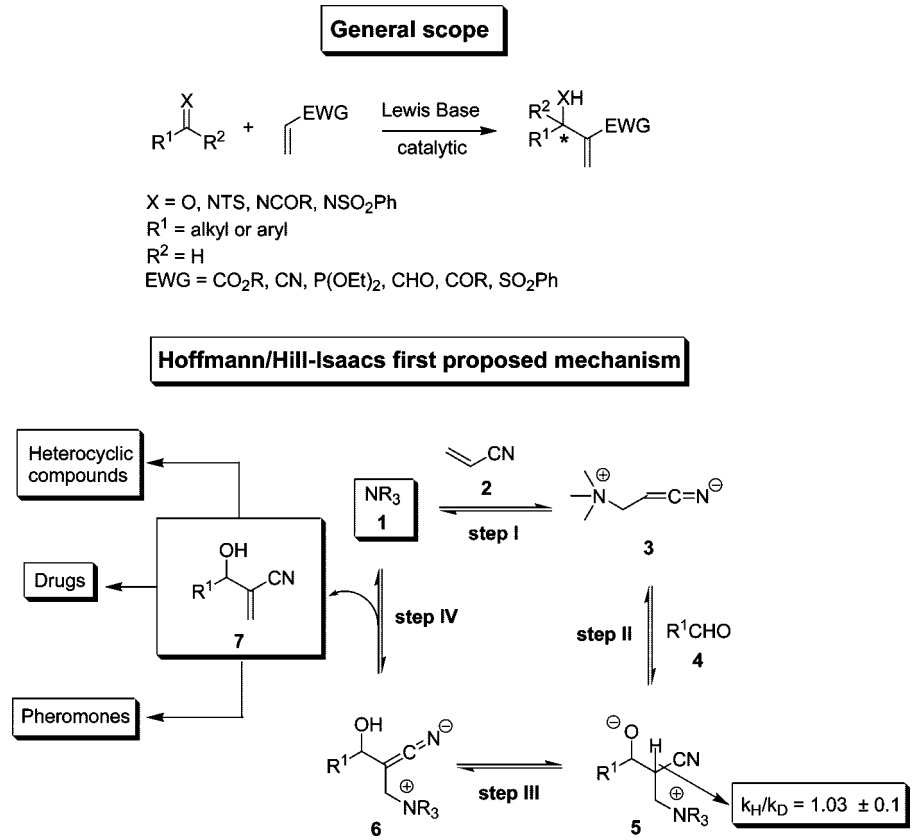
SCHEME 1. General Scope and First Catalytic Cycle Proposed by Hoffmann/Hill and Isaacs for the Morita−Baylis−Hillman Reaction



(normally with an electron-withdrawing group) alkene in the presence of a Lewis base catalyst (most often DABCO). The MBH reaction has been used to form building blocks for the total synthesis of many heterocycles, natural products, and drugs.[4] Based on its atom economy and feasibility, the MBH reaction is currently regarded as one of the most efficient transformations in organic chemistry.[5]

Hoffmann, in 1983, was the first to propose a mechanism for the MBH reaction,[6] which was refined from kinetic data by Hill and Isaacs[7a] and others (Scheme 1).[7b,c] The first reaction step **I** involves 1,4-addition of the catalytic tertiary amine **1** to the activated alkene **2** (α,β-unsaturated carbonyl compounds, nitriles, ect.) to generate the *zwitterionic* aza-enolate **3**. In step **II**, **3** forms intermediate **5** by adding to aldehyde **4** via an aldolic addition reaction. Step **III** involves intramolecular proton shift within **5** to form **6**, which in step **IV** forms the final MBH adduct **7** via E2 or E1cb proton-transfer in the presence of a Lewis base. The last step **IV** returns **1** to the catalytical cycle. Due to the low kinetic isotopic effect (KIE = 1.03 ± 0.1, using acrylonitrile as nucleophile for the MBH reaction) measured by Hill and Isaacs and the dipole increase by charge separation, **II** was initially considered as the MBH rate-determining step (RDS, Scheme 1).

Recently, McQuade et al.[8] and Aggarwal et al.[9] re-evaluated the MBH mechanism using kinetics and theoretical studies, focusing on the proton-transfer step. According to McQuade, the MBH reaction is second order relative to the aldehyde and shows significant kinetic isotopic effect (KIE: $k_H/k_D = 5.2 \pm 0.6$ in DMSO). Interestingly, regardless of the solvents (DMF, MeCN, THF, $CHCl_3$), the KIE were found to be greater than 2, indicating the relevance of proton abstraction on the rate-determining step. Based on these new data, McQuade et al. proposed a new mechanism view for the proton-transfer step (Scheme 2), suggesting **IV** as the RDS. Soon after, Aggarwal, also on the basis of kinetic studies, proposed that the reaction kinetic is second order in relation to the aldehyde but only at its beginning (≤20% of conversion), then becoming autocatalytic. Apparently, the MBH adducts **7** may act as a proton donor

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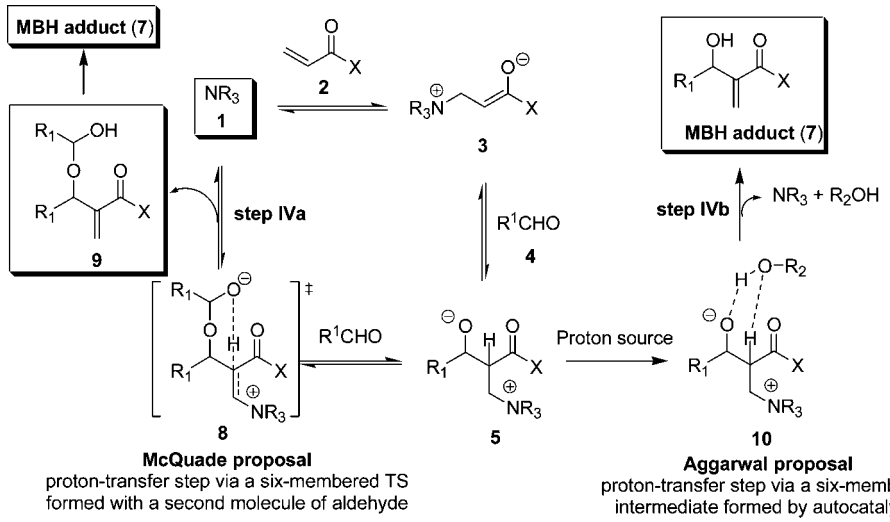
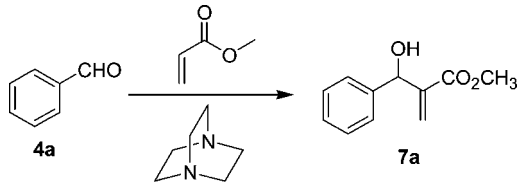
SCHEME 2. New Mechanistic Proposals from for the Proton-Transfer Step IV of the MBH Reaction



SCHEME 3. Morita−Baylis−Hillman Reaction Monitored by ESI-MS(/MS)



and therefore can assist the proton-transfer step via a six-membered intermediate (Scheme 2).

This new kinetic evidence has stimulated further theoretical studies on the MBH mechanism conducted initially by Xu[10] and Sunoj.[11] Aggarwal performed recently an extensive theoretical study which has supported both their own kinetic observations as well as those of McQuade about the proton-transfer step.[12] They suggested that step **IV** can proceed via two pathways: (a) in the absence of a proton source, proton shift is assisted by a second molecule of aldehyde (**8**), as proposed by McQuade, or (b) in the presence of a proton source such as an alcohol; however, the proton shift proceeds via intermediate **10** or similar species (Scheme 2).

To investigate the MBH mechanism, we have used electrospray ionization mass spectrometry, ESI-MS(/MS), and have been able to characterize key MBH reaction intermediates.[13] Using ESI-MS(/MS), we also shed light on the cocatalyst role of ionic liquids in MBH reactions.[14] ESI-MS[15] is a gentle, fast, and high-sensitivity technique that may allow even short-lived or loosely bounded intermediates[16] to be transferred efficiently from the reaction solution to the gas phase. ESI-MS has provided therefore consistent snapshots of the ionic composition of reaction solutions,[16−18] thus functioning as an interesting "ion-fishing" plus ion characterization technique and a major technique for solution mechanistic studies in chemistry[19] and biochemistry.[20] The mechanistically important new propositions about the proton-transfer step of the MBH reaction just discussed have therefore stimulated us to perform complementary investigations on the MBH reaction mechanism via ESI-MS(/MS) aiming to intercept and characterize the new intermediates postulated for the dualist nature of the key RDS proton-transfer step.

Results and Discussion

Our investigation began with the ESI-MS monitoring of the reaction of methyl acrylate with an excess of benzaldehyde (**4a**, Scheme 3) catalyzed by DABCO without solvent.[21]

DABCO (1 equiv), methyl acrylate (1 equiv) and benzaldehyde (3 equiv) were mixed without additional solvent. Aliquots of the reaction medium (0.05 μL) were taken, diluted in acetonitrile with a trace of formic acid, and injected directly to the ESI source. Although neutral zwitterionic species participate in MBH reactions, in solution they are in equilibrium with their protonated or cationized forms and in such cationic forms may be detected by ESI-MS.[13] Just after mixing the reagents for the reaction outlined in Scheme 3, an aliquot was taken and the reaction stopped by addition of 100 μL of acetonitrile acidified with traces of formic acid. As before,[13] the ESI-MS (Figure 1a) of such a reaction solution intercepts three covalently bonded cationic species directly related to the MBH catalytic cycle (Scheme 4): [**1a** + H]$^+$ of *m*/*z* 113, [**3a** + H]$^+$ of *m*/*z* 199, and [**6a** + H]$^+$ of *m*/*z* 305. But for the first time, due to high concentration, two new species are also intercepted and putatively assigned to [**11** + K]$^+$ of *m*/*z* 323 and [**12** + K]$^+$ of *m*/*z* 409.[22] The formation of covalent species is indicated by the relatively high kinetic energy set for the extraction of gas-phase ions from the ESI source into the mass spectrometer (acceleration cone voltage of 20−30 V) and the optimized declustering properties of the ESI source. Under such conditions, loosely bonded species should not survive.

The ions of *m*/*z* 113 [**1a** + H]$^+$ and *m*/*z* 199 [**3a** + H]$^+$ have been fully characterized in our previous investigation (see also

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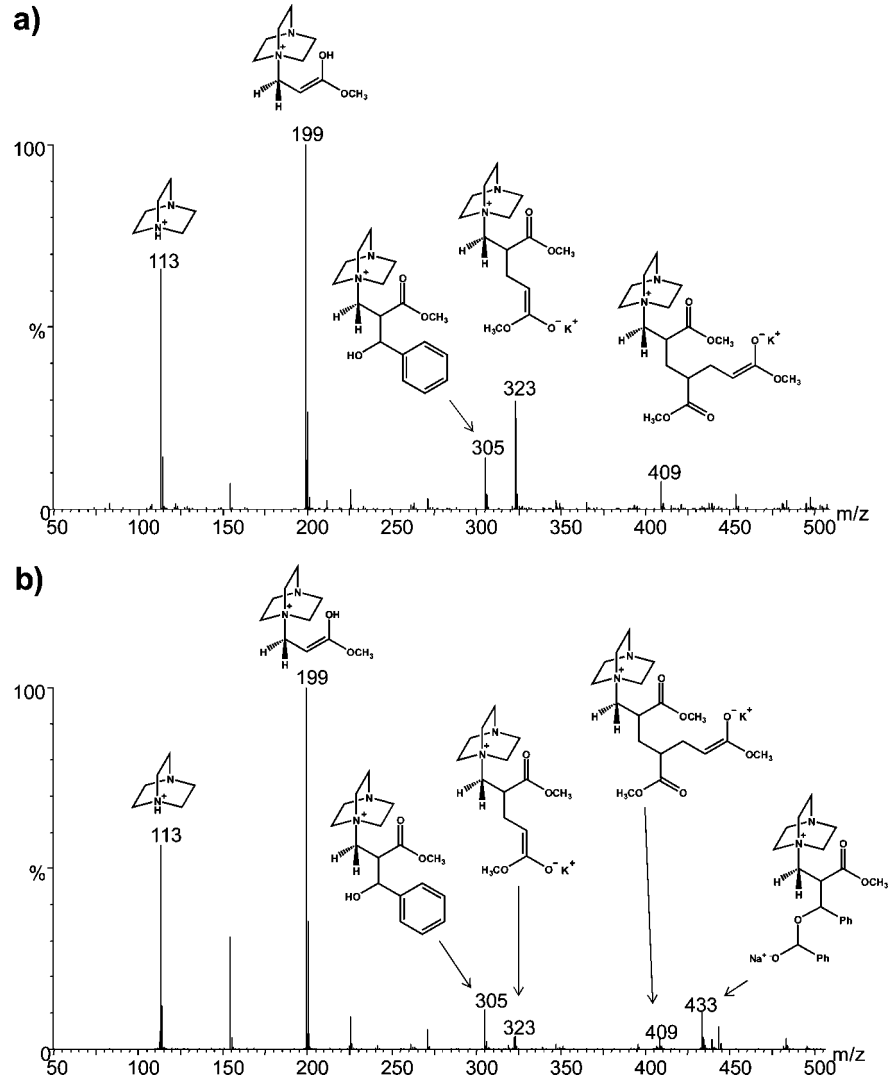


FIGURE 1. ESI(+)-MS of the MBH reaction of methyl acrylate with benzaldehyde: (a) $t = 0$ min; (b) $t = 10$ min.

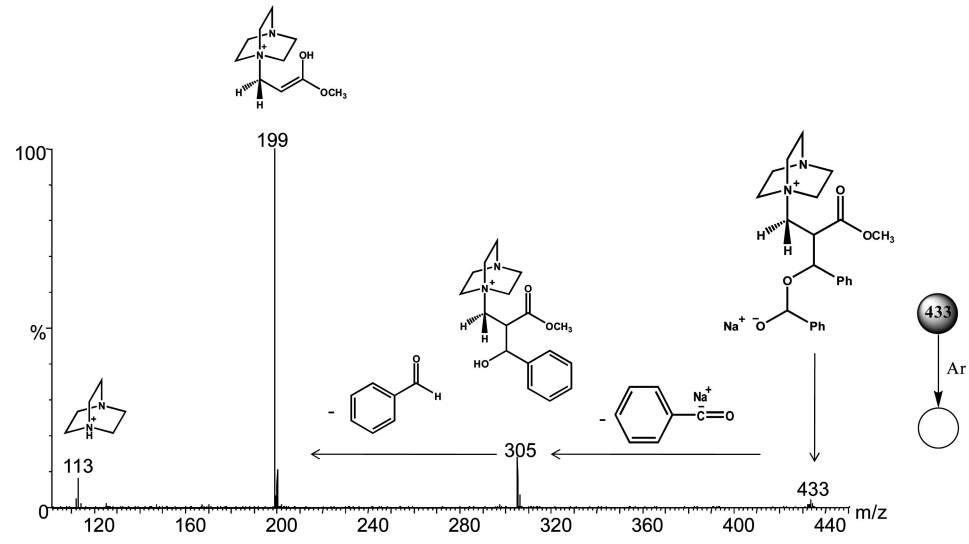
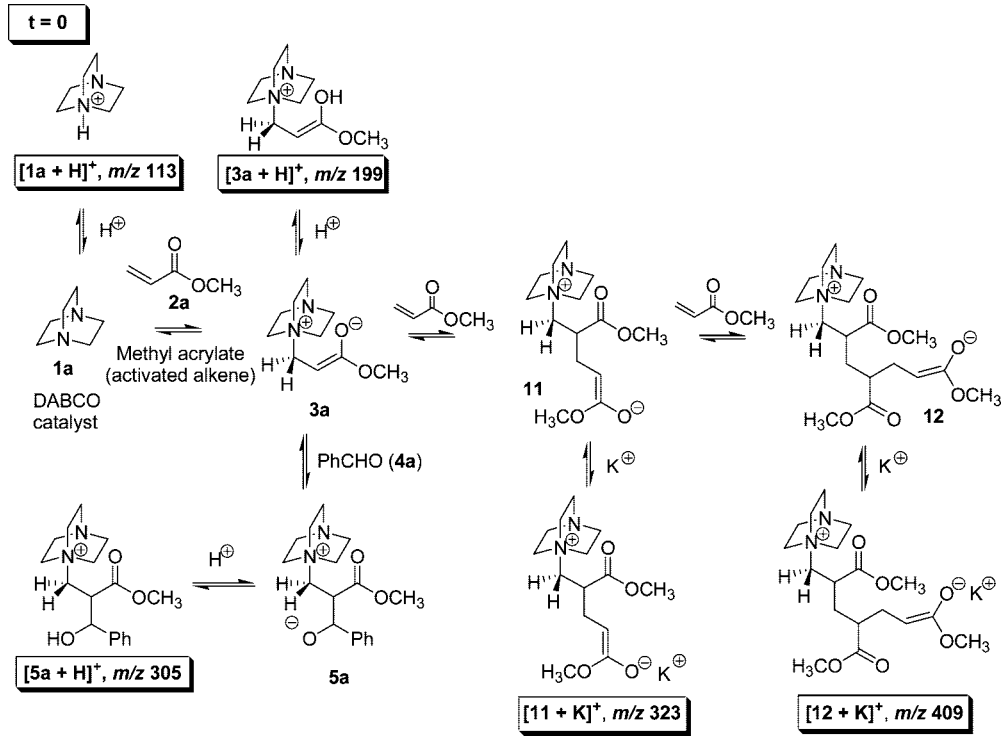


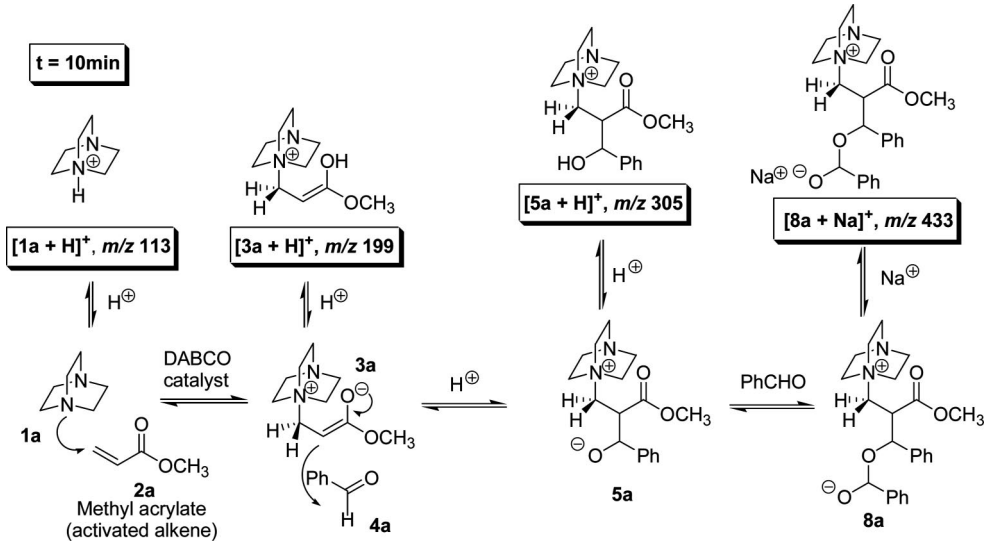
FIGURE 2. ESI-MS(/MS) of the ion of *m*/*z* 433 (**8a**).

the Supporting Information for their ESI-MS(/MS)).[13] For structural characterization of the new species, the ions of *m*/*z* 323, *m*/*z* 305, and *m*/*z* 409 were individually selected for collision-induced dissociation (CID) with argon via tandem mass spectrometric (ESI-MS(/MS)) experiments (Figure S1, Supporting Information). The $[\mathbf{11} + K]^+$ ion of *m*/*z* 323 forms the

SCHEME 4. MBH Reaction for Methyl Acrylate and Benzaldehyde Catalyzed by DABCO, Showing the Protonated or Cationized Species Intercepted and Structurally Characterized by ESI-MS and ESI-MS(/MS)



SCHEME 5. MBH Reaction Monitored after 10 min



fragment ion of *m*/*z* 211 by losing a molecule of DABCO (Figure S1a, Supporting Information) and protonated DABCO of *m*/*z* 113 by losing a neutral species of 210 Da, characterized as the K^+ adduct of the anionic product resulting of a Michael addition of the *aza*-enolate **3a** on the acrylate. Note the close analogy of this CID process to that of the final MBH reaction step (Scheme 2). The ion [**12** + K]$^+$ of *m*/*z* 409 dissociates predominantly by the loss of the neutral species of 210 Da to yield protonated *aza*-enolate [**3a** + H]$^+$ of *m*/*z* 199 (Figure S1b). The key MBH intermediate [**5a** +H]$^+$ of *m*/*z* 305 dissociates, as observed before, mainly by the loss of the MBH adduct **7a** of 192 Da to form protonated DABCO of *m*/*z* 113 (Figure S1c, Supporting Information).

After 10 min, another aliquot of the MBH reaction solution was diluted in acetonitrile and its ESI-MS collected (Figure 1b). To our delight, it seems that ESI-MS intercepted now intermediate **8a** proposed by McQuade[9] from the nucleophilic attack of the MBH alkoxyde to the aldehyde (Scheme 5) as the [**8a** + Na]$^+$ ion of *m*/*z* 433. Using freshly distilled benzaldehyde, the analogous protonated species of *m*/*z* 411 was also detected and characterized by ESI-MS(/MS) (see the Supporting Information).

Ion [**8a** + Na]$^+$ of *m*/*z* 433 shows a characteristic and unique dissociation pattern via ESI-MS(/MS). It loses (most probably) PhC═O$^-$Na$^+$ (128 Da) and PhCHO (106 Da) to afford the protonated form of the *aza*-enolate of *m*/*z* 199 as well as forms protonated DABCO of *m*/*z* 113 (Figure 2).[23]

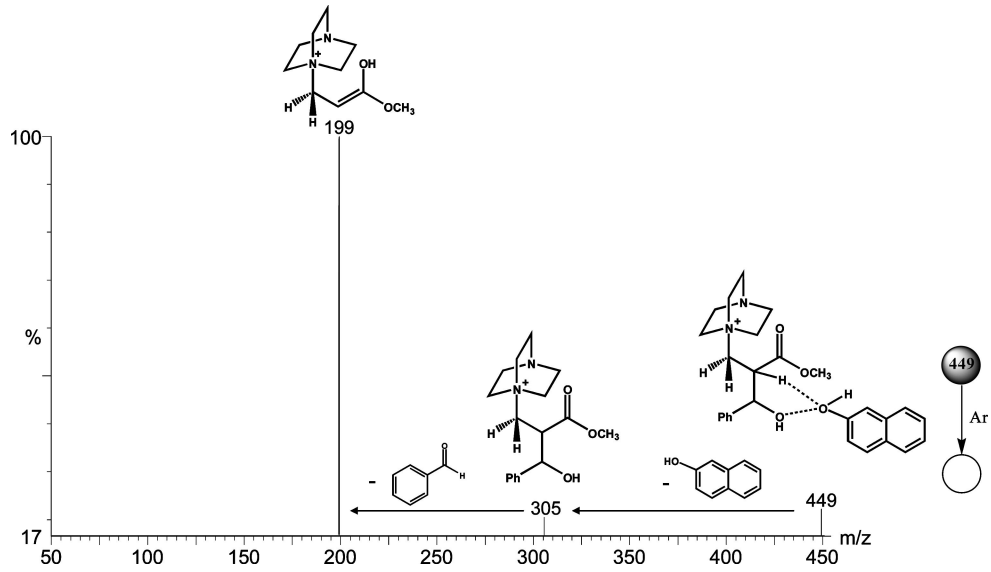


FIGURE 3. ESI-MS(/MS) of the ion of *m*/*z* 449.

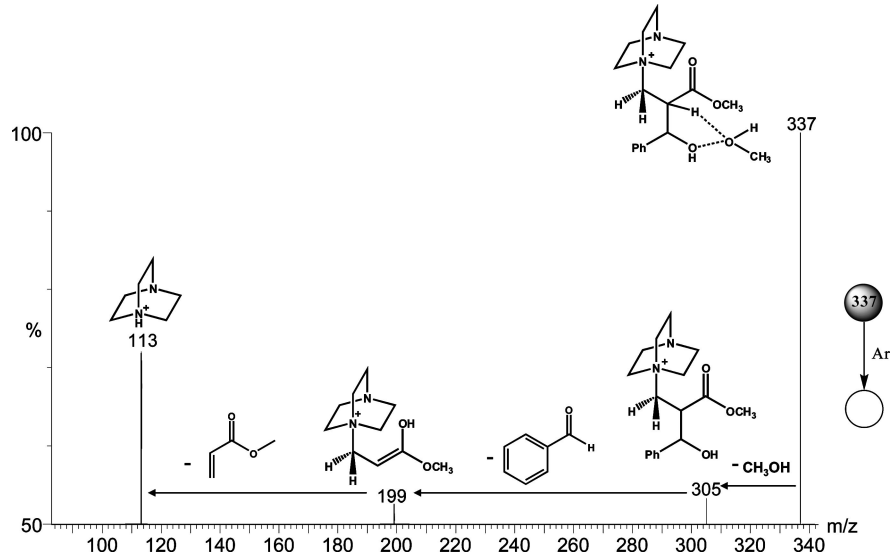


FIGURE 4. ESI-(+)-MS(/MS) spectrum of the ion of *m*/*z* 337.

Considering Aggarwal's proposal for proton sources,[9] we monitored the MBH reaction performed with the same experimental protocol but added an additional 3 equiv of β-naftol (an external proton source). Immediately after the reagents were mixed, an aliquot of the reaction solution was subjected to ESI-MS (Figure S2, Supporting Information), and again a new species [**10a** + H]$^+$ of *m*/*z* 449 was detected whereas the ions of *m*/*z* 305 and 433 were nearly absent. The ESI-MS(/MS) of this new ionic species of *m*/*z* 449 was collected (Figure 3), showing the ion to dissociate by the sequential losses of β-naftol and benzaldehyde to afford [**3a** + H]$^+$of *m*/*z* 199. The interception and characterization of [**10a** + H]$^+$ agrees therefore with Aggarwal's proposition that a proton source participates in the proton-transfer step by assisting the removal of the base.

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To collect additional evidence for the action of an external proton source, we repeated the MBH reaction using methanol as solvent. Just after the reagents were mixed, an aliquot of the reaction solution was subject to ESI-MS (Figure S3, Supporting Information). A new ion of *m*/*z* of 337 [**10b** + H]$^+$ was intercepted and characterized via ESI-MS(/MS) (Figure 4). As expected from its more loosely bonded nature, the ion lost methanol to yield the fragment of *m*/*z* 305, which subsequently dissociated by the loss of benzaldehyde and methyl acrylate to form protonated DABCO of *m*/*z* 113.

Conclusions

New intermediates of the MBH reaction (**8a**, **10a**−**b**, **11**, and **12**) have been, for the first time, successfully intercepted and structurally characterized via ESI-MS(/MS) monitoring. Intermediates **8a** and **10a**−**b** provide the first structural evidence supporting the mechanistic propositions recently made by McQuade et al.[9] and Aggarwal et al.[10] for the key RDS proton-transfer step **IV** of MBH reactions. The "fishing" and structural characterization of these key intermediates exemplifies the complex equilibrations occurring during MBH reactions, and the interception of intermediates **8a** and **10a**−**b** confirms the dualistic nature of the RDS proton-transfer step. These findings may also help develop general asymmetric versions of MBH reactions, which should consider all major equilibria and use a fast and efficient proton-transfer promoter.

Experimental Section

General Procedures. All reagents were used without purification. ESI mass and tandem mass spectra in the positive-ion mode were acquired using a Micromass (Manchester, UK) QTof instrument of ESI-QTof configuration with 5.000 mass resolution and 50 ppm mass accuracy in the TOF mass analyzer. The following typical operating conditions were used: 3 kV capillary voltage, 8 V cone voltage, and desolvation gas temperature of 100 °C. Tandem ESI-MS/MS were collected after 4−32 eV collision-induced dissociation (CID) of mass-selected ions with argon. Mass-selection was performed by Q1 using a unitary *m*/*z* window, and collisions were performed in the rf-only hexapole collision cell, followed by mass analysis of product ions by the high-resolution orthogonal reflectron TOF analyzer.

The monitored Morita−Baylis−Hillman was carried out as follows: To a mixture of benzaldehyde (70 mg, 0.66 mmol) and DABCO (25 mg, 0.22 mmol) was added methyl acrylate (19 mg, 0.22 mmol). The resulting mixture was stirred at room temperature for 6 h. Aliquots from this reaction medium were taken at different times and diluted in a mixture of acetonitrile with a tiny amount of formic acid.

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Supporting Information Available: ESI-MS/MS for products intercepted in the MBH reaction of methyl acrylate with benzaldehyde (Figure S1); ESI-MS of the Morita−Baylis−Hillman reaction in the presence of β-naftol (Figure S2); ESI-MS of the Morita−Baylis−Hillman reaction in the presence of methanol (Figure S3); ESI-MS(/MS) of the ion of *m*/*z* 423 obtained in the Morita−Baylis−Hillman reaction carried out with benzaldehyde-d_6 (Figure S4); ESI-MS/MS of the ion of *m*/*z* 311 obtained in the Morita−Baylis−Hillman reaction carried out with benzaldehyde-d_6 (Figure S5); ESI-MS(/MS) of the ion of *m*/*z* 411 obtained in the Morita−Baylis−Hillman reaction carried out with distilled benzaldehyde and recrystallized DABCO (Figure S6). This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Benzaldehyde is stabilized by 2 ppm of a potassium salt; hence, it may function as the K^+ source.

(23) Additional information regarding the structure of this intermediate (detected as the sodiated form of *m*/*z* 433) came from reactions using Na^+ and K^+ free benzaldehyde and benzaldehyde-d_6. The analogous protonated species of *m*/*z* 411 and 423 were intercepted, and their ESI-MS/MS are shown in Figures S4 and S6 (see the Supporting Information).