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# On the mechanism of the *aza*-Morita–Baylis–Hillman reaction: ESI-MS interception of a unique new intermediate†

**Thais Regiani,[ab] Vanessa G. Santos,[b] Marla N. Godoi,[b] Boniek G. Vaz,[b] Marcos N. Eberlin*[b] and Fernando Coelho*[a]**

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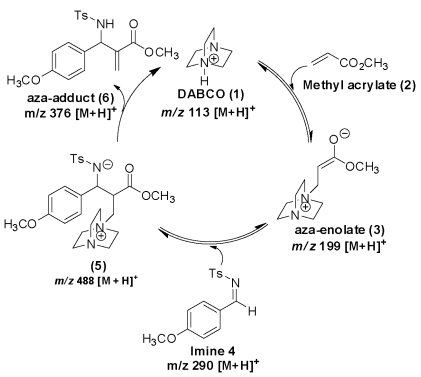
**Solutions of *aza*-Morita–Baylis–Hillman (*aza*-MBH) reactions were directly monitored by ESI(+)-MS(/MS) spectrometry to obtain information on their mechanism. A unique bis-sulfonamide intermediate was intercepted and characterized and, based on this novel species, a mechanism that rationalizes the uniqueness of *aza*-MBH reactions is proposed.**

The Morita–Baylis–Hillman reaction (MBH)[1,2] is a highly efficient transformation that has been used widely in organic synthesis.[3] The MBH reaction occurs between an aldehyde and an olefin activated by an electron withdrawing group.[4] In the *aza* version, the aldehyde is replaced by an imine, yielding α-methylene-β-amino carbonylated derivatives that have been used as versatile synthons in organic synthesis.[5,6] The mechanism and synthetic relevance of the classical MBH reaction particularly for natural products have been extensively scrutinized.[7,8] In contrast, the *aza*-MBH reaction has received much less attention most particularly with regard to its mechanism.[9,10] Most of the studies have explored theoretical[10] or kinetical features and only a single *aza*-MBH intermediate has been isolated so far.[10] For the classical MBH mechanism, we have intercepted and characterized several of its key intermediates by electrospray ionization mass (ESI-MS) and tandem mass spectrometry (ESI-MS/MS).[8] These intermediates provided new insights or supported mechanistic aspects of the reaction as the McQuade *et al.*[11] and Aggarwal *et al.*[12] proposal that the rate-determining step (RDS) of classical MBH reactions is their proton transfer step with dualistic behaviour.[13] For the *aza*-MBH reaction, it is commonly assumed that its mechanism is similar to that of the classical MBH reaction. Contrary to the classical version, however, successful and general approaches have been reported for asymmetric versions of *aza*-MBH[14] reactions pointing therefore to the existence of unique features of their mechanism. *aza*-MBH equilibria seems also to be unique.[10] This communication describes our investigation of the *aza*-MBH reaction mechanism *via* direct ESI-MS(/MS) monitoring. This technique has been established as a major tool for mechanistic studies,[15] allowing one to monitor reaction substrates, products and, most interestingly, intermediates. Even transient reaction intermediates have been intercepted and transferred directly from solution to the gas phase by ESI for MS and MS/MS characterization. The technique thus provides continuous snapshots of the changing composition of reaction solution and hence insights into its actual mechanism.

Scheme 1 depicts the accepted reaction cycle for the *aza*-MBH reaction. In the first step, Michael-type nucleophilic addition of the DABCO (**1**) on the activated double bond (**2**) provides an *aza*-enolate (**3**) intermediate, which promotes nucleophilic attack on the imine electrophilic carbon (**4**). Proton transfer followed by DABCO elimination forms the final *aza*-MBH adduct (**6**). The two initial steps are reversible whereas the proton transfer step is normally the RDS.[10]

As a test case for an *aza*-MBH reaction, we selected the reaction between methyl acrylate (1 equiv.) and *N*-(4-methoxy-benzylidene)-4 methyl-benzenesulfonamide[16] (3 equiv.) in the presence of DABCO (1 equiv.) using acetonitrile as solvent. Aliquots of the reaction medium (1.0 μL) were taken, diluted in acetonitrile (1 mL) with a trace of formic acid and the MS data were immediately recorded.

Fig. 1 shows typical ESI(+)-MS of the reaction solution at $t = 0$ and $t = 30$ min. Note the detection in protonated forms of key players of the *aza*-MBH reaction cycle: DABCO (**1**) of $m/z$ 113, the zwitterionic *aza*-enolate (**3**) of $m/z$ 199, and **5** of $m/z$ 488 (from **3** plus the imine **4**). Intermediate **7**




**Scheme 1** Accepted mechanism for the *aza*-MBH reaction.

[a] *Laboratory of Synthesis of Natural Products and Drugs, University of Campinas-UNICAMP, Campinas, SP, Brazil. E-mail: coelho@iqm.unicamp.br*
[b] *ThoMSon Mass Spectrometry Laboratory, University of Campinas-UNICAMP, Campinas, SP, Brazil. E-mail: eberlin@iqm.unicamp.br*

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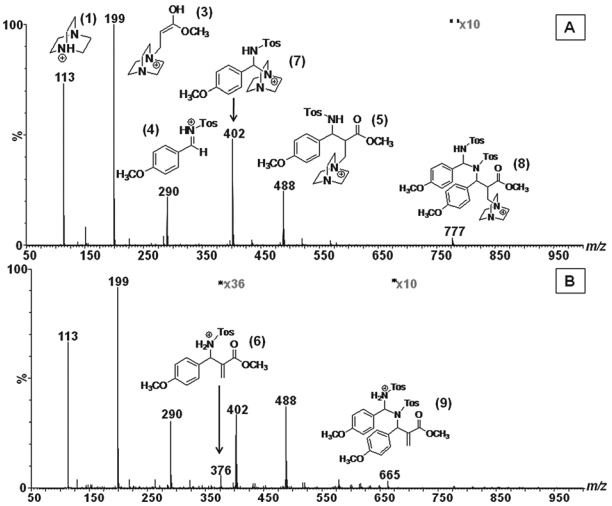


**Fig. 1** ESI(+)-MS of the prototype *aza*-MBH reaction solution at (A) $t = 0$ min and (B) $t = 30$ min.

of $m/z$ 402 was also detected, and identified as the product of the nucleophilic attack of DABCO on **4** ($m/z$ 290). The final *aza*-MBH adduct **6** of $m/z$ 376 was also intercepted. The concentration in the reaction solution of the most transient intermediates should be the lowest and hence they are likely to be detected, if at all, as minor ions. In their search, spectra were therefore expanded paying special attention to the $m/z$ 650–850 region. Fig. 1A shows that ESI(+)-MS, due to its high detectability, was able to intercept a unique new intermediate of $m/z$ 777, which was characterized as the bis-sulfonamide intermediate **8** resulting from the nucleophilic attack of the *N*-tosyl anion on the electrophilic carbon of **4**.[17] This unprecedented intermediate intrigued us. The *N*-tosyl anion should have a low nucleophilicity due to the electron withdrawing effect of the tosyl group. But perhaps, this low nucleophilicity could be compensated by the high electrophilicity exhibited by the *N*-tosyl imine **4**.

After 30 min of reaction, **8** was no longer detected and a new intermediate **9** of $m/z$ 665 resulting from the elimination of DABCO from **8** was intercepted. The key intermediates **5**, **6** and **9** (Fig. S4, S5 and S7, ESI†) and **8** (Fig. 2) were characterized *via* ESI(+)-MS/MS with dissociation chemistries in accordance with proposed structures.

We argue that the transient but well characterized intermediate **8** may play an important role in the *aza*-MBH mechanism. It seems, for instance, to explain the greater speed of the *aza*-version of MBH reactions. In the RDS proton-transfer step, **8** could facilitate intramolecular proton transfer *via* a stable six-membered intermediate (Scheme 2). Based on theoretical calculations Sunoj *et al.*[10] suggested that a six membered TS speeds the rate of *aza*-MBH reactions with additives such as formic acid or even water (Fig. 3).

Asymmetric *aza*-MBH reactions normally give adducts in moderate to good enantiomeric excesses and reasonable yields. Unlike what was observed for an analog dioxanone intermediate found in some classical MBH reactions,[18] the *aza*-intermediate **8** does not cyclize to a pyrimidinone derivative (**11**). A resolution step is therefore avoided, which could increase the enantiomeric excess of the *aza*-version of MBH reactions.

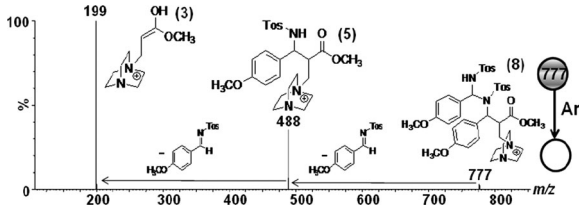
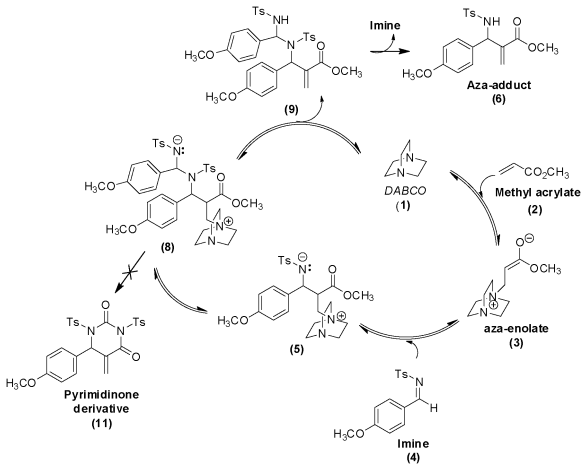


**Fig. 2** ESI(+)-MS(/MS) of **8** of $m/z$ 777.




**Scheme 2** Mechanistic cycle proposed for the *aza*-MBH reaction based on the interception of the bis-sulfonamide intermediate **8** and its analogues **14** and **22**.

The ESI-MS/MS of **5** was also revealing. This intermediate of $m/z$ 488 was found to undergo a retro-*aza*-MBH reaction with the loss of the neutral imine forming the *aza*-enolate **3** of $m/z$ 199. Raheem and Jacobsen observed a similar behavior when recording the NMR spectrum of a similar molecule.[10] The spectra were accompanied by resonances related to an acrylate and an imine in different concentrations due to a retro-*aza* MBH reaction.

Two other variants of *aza*-MBH reactions were also monitored by ESI(+)-MS. First, DABCO was replaced by quinuclidine (**12**), which is known as one of the most efficient bases for MBH reactions.[19] Second, methyl acrylate was replaced by hexafluoroisopropyl acrylate, which should facilitate the formation of a dioxanone ring due to the efficiency of hexafluoroisopropanoxide as a leaving group.[18] Fig. 4 shows the two corresponding ESI(+)-MS (for details see ESI†).

In both reactions, bis-sulfonamide intermediate analogues to **8** were again detected: **14** and **22**. When hexafluoroisopropyl acrylate was used, **22** of $m/z$ 913 was detected now as a relatively high abundant ion and was promptly observed even at $t = 0$ min. We have meticulously investigated all regions of this particular spectrum carefully searching for an ion related to the pyrimidinone derivative similar to **11**,[20] but no signs of it were noted. The deviation from the pyrimidinone route may therefore explain the successful developments of asymmetric versions of the *aza*-MBH reaction since the low nucleophilicity of the sulfonylated nitrogen ion may have a crucial role in the *aza*-MBH reaction. Its nucleophilicity may be sufficiently high to promote intermolecular proton transfer *via* **8** through a six membered transition state (Fig. 3), but low enough to prevent the intramolecular nucleophilic attack on the carbonyl of the

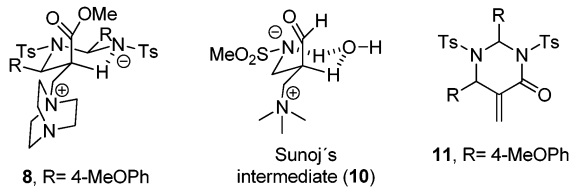



**Fig. 3** Analogy between intermediate **8** intercepted by ESI(+)-MS and that proposed by Sunoj (**10**), based on theoretical calculations, and a hypothetical intermediate (**11**) for *aza*-MBH reactions.

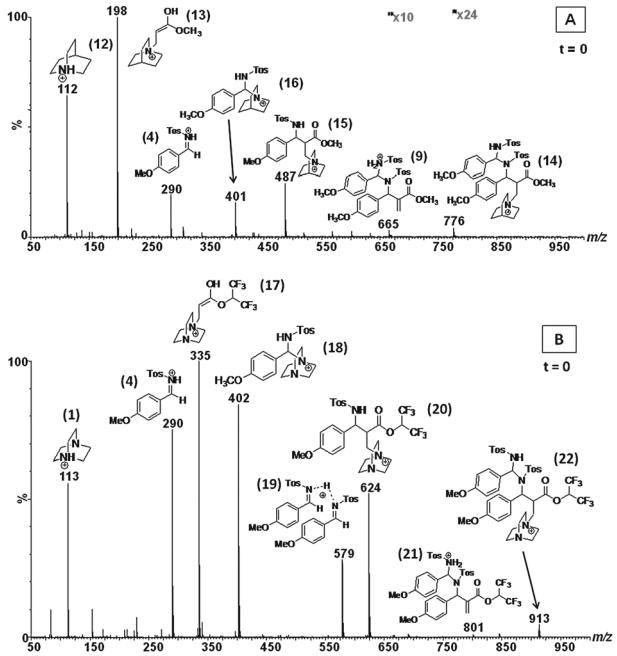



**Fig. 4** ESI(+)-MS at $t = 0$ min of the *aza*-MBH reaction solution (A) in the presence of quinuclidine and (B) with hexafluoroisopropyl acrylate.

hexafluoroisopropyl acrylate that would afford the pyrimidinone intermediate. This unique behavior of the *aza*-MBH reaction would suppress the resolution step which leads to an important but undesirable equilibrium in asymmetric versions of the classical MBH reaction.[18] Based on the interpretation of the unique intermediate **8** and its analogues **14** and **22**, a unique mechanistic cycle for *aza*-MBH reactions could be proposed (Scheme 2).

ESI(+)-MS(/MS) monitoring of prototype *aza*-MBH reactions provided important insights into their mechanistic cycle by revealing the participation of a transient but crucial bis-sulfonamide intermediate. Its participation in the key and RDS proton transfer step seems to provide a rationale for the much greater efficiency of asymmetric *aza*-versions of MBH reactions. Knowing the effects governing the efficient asymmetrical *aza*-MBH reactions may help the development of efficient asymmetric versions also for classical MBH reactions.

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20 The ESI-MS interception of no *aza* analog of dioxanone does not eliminate the possibility of its existence. However the low nucleophilicity of an anionic sulfonylated nitrogen atom would tend to hamper its formation.