# Investigating organocatalytic reactions: mass spectrometric studies of a conjugate *umpolung* reaction

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**An organocatalyzed conjugate *umpolung* reaction has been studied in detail using electrospray mass spectrometry, which allows to support the catalytic cycle by intercepting intermediates.**

The development of electrospray ionization (ESI)[1] has strongly changed the applicability of mass spectrometry and analytical chemistry of organic compounds. This method allows to convert low volatile and decomposable organic compounds "softly" from solution into the gas phase and is so gentle that even electrostatic complexes or intermediates can be ionized and subsequently analyzed.[2] A wide variety of analytical problems solved by using ESI-MS include mostly bioanalytical[3] applications but also more exotic problems such as measurements of silicate oligomers.[4]

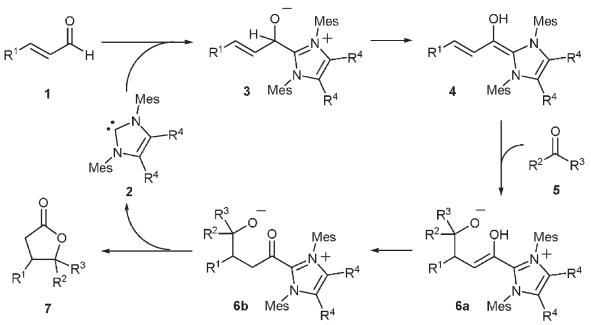
ESI-MS is especially useful for the investigation of catalytic reactions. For a better understanding of the mechanism and the catalytic cycle a thorough determination of the formed species is necessary. Some of the reactions investigated include the Heck reaction,[5] Mannich type reactions[6] or aromatic Claisen rearrangement.[7] Very helpful in this approach is the use of the MS/MS technique, where one specifically selected ion can be subjected to fragmentation with gas molecules by using collision activated dissociation (CAD). The fragment spectrum gives direct information about structural aspects of the investigated ion and can provide efficient information about mechanistic properties.[8] In combination with accurate mass data that allow to calculate the elemental composition from detected ions using a Fourier Transform Ion Cyclotron Resonance Mass Spectrometer[9] (FT-ICR MS) gives further confidence to the obtained data.

One of the growing fields of catalytic research is organocatalysis where toxic catalysts are substituted with more environmental friendly compounds.[10] Most recently, the first studies of organocatalytic reactions using ESI-MS have been reported. Santos *et al.*[11] described an organocatalytic approach to the Baylis–Hillman reaction in which most intermediates could be observed using ESI-MS. Marquez and Metzger[12] coupled a micro reactor to an ESI mass spectrometer to investigate an L-proline catalyzed aldol reaction.

One of the more thrilling reactions in organic synthesis are *umpolung* reactions, which reverse the natural polarity of a functional group. Usually, catalytic *umpolung* reactions of aldehydes are performed using cyanide or thiazolium carbenes.[13] Possible pathways lead to aromatic aldehydes (benzoin condensation)[14] or olefins (Stetter reaction).[15] In addition, it is possible to convert α,β-unsaturated aldehydes into nucleophiles by using the "conjugate" *umpolung*. Very recently two groups, Burstein *et al.*[16] and Sohn *et al.*,[17] simultaneously introduced an organocatalytic approach to the conjugate *umpolung* reaction.[18]

In the reaction studied here an α,β-unsaturated aldehyde **1** is activated by addition of the carbene catalyst **2** to the aldehyde group. The resulting conjugate enamine attacks another electrophilic carbonyl compound **5**. As a consequence of an intramolecular cyclization the γ-lactone product **7** is formed. A formal catalytic cycle has been proposed (see Scheme 1).[16,17] For an experimental verification and a better understanding of the mechanism an investigation of this conjugate *umpolung* reaction was launched in order to characterize the formed intermediates. This was done by studying four different reactions as described in Scheme 1. The reaction solution was diluted with $CH_3CN$ and subsequently injected into the ESI source.

The mass spectrum of reaction (1) using cinnamaldehyde and 4-chlorobenzaldehyde after 1.5 h of reaction time is shown in Fig. 1. The most intense peaks of *m*/*z* 153 and 305 correspond to DBU and the catalyst, respectively. The signal of **1** (*m*/*z* 133) and the intermediates **3**/**4** and **6** (*m*/*z* 437 and 577) are also detected. The signal of the product (*m*/*z* 273) has lower concentration and is barely seen. Other signals in the spectrum, *i.e.* at *m*/*z* 445, 599, *etc* are connected to side products (SP) and are described in detail in Table 1. The accurate mass data from FT-ICR MS allow the calculation of the elemental composition with high accuracy. In this case the ions of the potential intermediates were detected at *m*/*z* 437.2584 and 577.2614 corresponding to formulas $C_{30}H_{33}N_2O$ (error 0.4 ppm) and $C_{37}H_{38}N_2O_2Cl$ (error 0.3 ppm), respectively, which fit exactly for the proposed intermediates.




**Scheme 1** Proposed mechanism of the investigated reaction. The data shown in this work are the results from reaction (1), for conditions see ref. 19.

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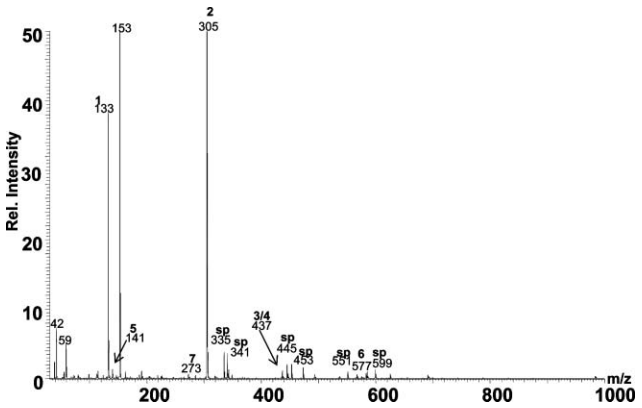
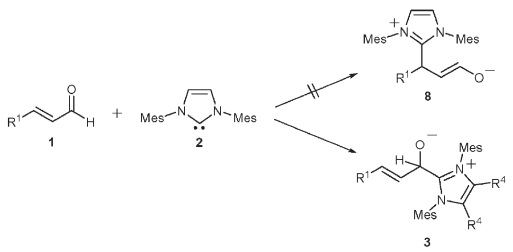



**Fig. 1** Overview MS spectrum of reaction (1) (after 1.5 h).

The first result verifies that the activation of **1** occurs at the aldehyde group. Another possibility, an addition of the catalyst at the double bond as shown in Scheme 2 that would form **8** can not be observed. The fragments that would correspond to such a structure are not present in the MS/MS spectrum (see Fig. 2). On the contrary, fragments at *m*/*z* 91, 103 and 133, respectively, indicate an activation at the aldehyde function. It should be noted

**Table 1** Potential side products found during MS studies of reaction (1); formulas correspond with the respective positively charged ion[20]

| Accurate Mass | Formula | Error/ppm | Structure |
|---|---|---|---|
| 285,196000 | $C_{18}H_{25}N_2O_1$ | 0,5 | |
| 437,258413 | $C_{30}H_{33}N_2O_1$ | 0,5 | |
| 445,204030 | $C_{28}H_{30}N_2O_1Cl_1$ | 0,2 | |
| 453,253523 | $C_{30}H_{33}N_2O_2$ | 0,3 | |
| 551,306017 | $C_{39}H_{39}N_2O_1$ | 0,6 | |
| 565,284247 | $C_{39}H_{37}N_2O_2$ | 1,2 | |
| 567,301098 | $C_{39}H_{39}N_2O_2$ | 0,9 | |
| 569,316679 | $C_{39}H_{41}N_2O_2$ | 0,8 | |
| 577,261436 | $C_{37}H_{38}Cl_1N_2O_2$ | 0,3 | |




**Scheme 2** Catalytic activation of **1**: the attack of the catalyst at the double bond was not observed in MS/MS results.

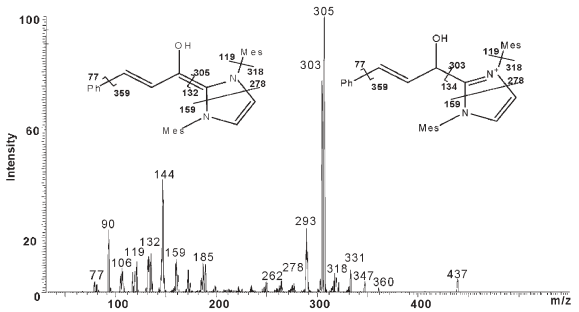



**Fig. 2** MS/MS spectrum of *m*/*z* 437.

that all MS/MS spectra were obtained with an isolation width between 0.25 and 0.5 Da, isolating just one isotopic signal.

Although the fragment pattern is complicated, it shows characteristic fragments. It should be noted that the data suggest the presence of two different structures from the ion at *m*/*z* 437. The first structure would correspond to the protonated ion **3** while the second structure would be a protonated conjugated dienamine **4**. Both structures can be explained by the fragmentation, especially the major signals at *m*/*z* 303 and 305, respectively. This results are supported by LC/MS measurements that show two different signals at *m*/*z* 437, although with very small intensities.

The second intermediate **6** is formed from the reaction of **4** with substrate **5**, which can be either an aldehyde or a ketone. Both possibilities have been investigated and show no difference in the mechanism. In this case, the formed intermediate can be detected at *m*/*z* 577 and the corresponding MS/MS spectrum is shown in Fig. 3.

The originally proposed mechanism suggests the formation of an alcoholate **6a** that is isomeric to the corresponding tautomer **6b**. MS/MS results from the ion at *m*/*z* 577 indicate that the proposed intermediate is present. The fragmentation pattern suggests the presence of at least the alcoholate structure. However, additional signals indicate that there is an underlying structure present as well that is similar to the structure found for **4**. It seems that the second

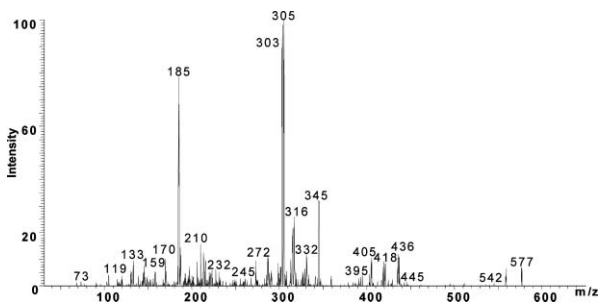
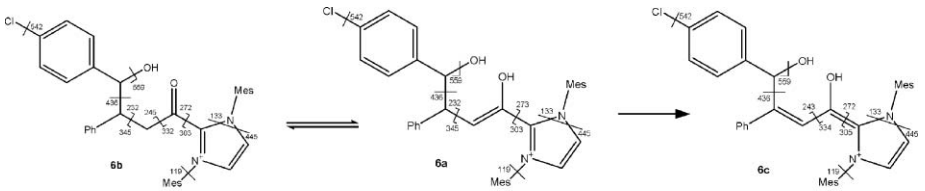



**Fig. 3** MS/MS spectra of *m*/*z* 577.




**Scheme 3** Proposed structures for intermediate at *m*/*z* 577.

intermediate also shows a protonated conjugated dienamine structure **6c** as is shown in Scheme 3. This can be explained by the removal of an acidic hydrogen and the formation of the double bond. This formation can explain the appearance of some double signals in the mass spectrum, especially at *m*/*z* 303 and 305. While compounds **6a** and **6b** are imidazolium cations, the deprotonation results in neutral **6c** (M = 576 Da). However, since all molecules are subjected to ionization in the ESI source the neutral molecule would be ionized forming an $[M + H]^+$-ion, which would be detected at *m*/*z* 577.

The reaction continues from **6a** to the product, a γ-lactone **7**, by an intramolecular cyclization at the carbonyl group. Accordingly, the catalyst is released in this step.

This conjugate *umpolung* reaction was studied using four different setups as are described in Scheme 1. All results show the same intermediates, albeit at different *m*/*z* values, but in agreement with the proposed mechanism.

Additionally, some minor side products were recorded during the observation of the reaction and structures are suggested. One of the major side products is formed from the addition of another molecule of **1** to the already activated **3**. The catalytically activated substrate can therefore also react with the same species and form some kind of a dimer. The respective signals were detected and accurate mass data in connection with MS/MS fragmentation data suggest that the formed dimer eliminates water to form an additional product. The data are summarized in Table 1 while all signals are also observed in the spectrum shown in Fig. 1. Considering all data allows to assign tentative structures for those products, and are described also in Table 1.

Taking all data into account, ESI-MS has shown to be an exceptional tool for the investigation of organocatalytic reactions. It was possible to intercept important intermediates of this reaction and provide substantial experimental background to the proposed catalytic cycle, which could be confirmed. One point of emphasis for such studies is the utilization of fragmentation experiments (CAD) that allow insights into potential structures of intermediates. In this case the data suggest that the bonding of the intermediates is fairly strong, since the collision energies required for both intermediates were in the upper range (between 25 and 50 eV). In connection with accurate mass data, important information of catalytic reactions can be obtained by such an approach.

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19 We studied the reaction of cinnamaldehyde **1** (1 equiv.) which is activated by addition 10 mol% of the 1,3-dimesityl-2,3-dihydro-1*H*-imidazol-2-ylidene (IMES) catalyst **2** and 10 mol% 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The reaction solution was diluted with 3 ml of $CH_3CN$ for each equivalent of cinnamaldehyde and stirred at ambient temperature for 16 h. As a consequence of an intramolecular cyclization, the γ-lactone product **7** is formed. For a better understanding of the mechanism and experimental verification of the reaction, three other different reactions were run under the same condition as described above. The reaction solution was diluted with $CH_3CN$ (1 : 100) before injection into the MS in different time intervals for time dependent analysis.
20 The structures are tentative assignments based on the experimental data. Due to weak signals, especially from the MS/MS measurement, the *keto–enol* tautomerism can not be described precisely.

 