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PAPER

Electrospray mass spectrometry for detailed mechanistic studies of a complex organocatalyzed triple cascade reaction

M. Wasim Alachraf,[a] Peni P. Handayani,[a] Matthias R. M. Hüttl,[b] Christoph Grondal,[b] Dieter Enders[b] and Wolfgang Schrader*[a]

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The development of modular combinations of organocatalytic reactions into cascades has been shown to be an effective tool despite the fact that the mechanism of such a complex organocatalytic multistep cascade reaction still remains poorly understood. Here the detailed mechanistic studies of a complex organocatalytic triple cascade reaction for the synthesis of *tetra*-substituted cyclohexene carbaldehydes are reported. The investigation has been carried out using a triple quadrupole mass spectrometer with electrospray ionization. Important intermediates were detected and characterized through MS/MS studies. A detailed formation pathway is presented based on these characterized intermediates, and supporting the proposed mechanism of the formation of the substituted cyclohexene carbaldehydes.

Introduction

Until a few years ago, it was generally accepted that transition metal complexes and enzymes were the two main classes of efficient asymmetric catalysts. Since the year 2000, a third approach to the catalytic production of enantiomerically pure organic compounds has emerged – *organocatalysis*. These small chiral organic molecules are metal free, generally nontoxic, commercially available, and very often robust.[1]

Recently, amine-catalyzed reactions are gaining importance, particularly with chiral secondary amines, which belong to a class of organocatalysts that offer the capability of promoting several types of reactions through different activation modes. They either activate aldehyde and ketone substrates *via* enamine formation[1] or α,β-unsaturated aldehyde substrates *via* iminium-ion formation.[2] Consequently, chiral secondary amines are ideally suited for organocatalytic cascade reactions.[3–6] These cascades, also known as tandem or domino reactions, are complex reactions that combine several different steps in a one-pot synthesis without purification between each step and, in general, without changes in conditions. Thus, all reactants, substrates and catalysts are present from the beginning.

Therefore, this concept for the formation of carbon–carbon bonds with the control of multiple stereocenters in a one-pot synthesis has been a challenge in asymmetric catalysis. The design and implementation of organocatalytic cascade reactions are a powerful way for the construction of complex molecules from simple precursors.[7] Its efficiency can be judged by the number of bonds formed, the number of stereocenters generated and the increase in molecular complexity, as well as economy of time, labor, resource management, and waste generation. In addition, organocatalytic cascade reactions are advantageous as they proceed consecutively under the same reaction conditions.[8–10]

Although modular combinations of asymmetric organocatalytic reactions into cascades have become a fruitful concept in organic synthesis, detailed mechanistic studies of complex cascade reactions is largely unexplored due to different reasons. Multistep organocatalytic cascade reactions consist of several different substrates and catalysts hence the reaction mixture is becoming quite complex. Consequently, isolation and characterization of reaction intermediates can be problematic and time consuming and hence contradict the effect of a cascade reaction. Additionally, the short lived intermediates, often appearing only in minor concentrations, are generally not stable enough and amenable for isolation as they are rapidly transformed in the subsequent reactions.

For that reason, NMR and IR spectroscopy as the widely used tools to gain efficient information about structural parameters are not providing sufficient data to the mechanistic studies of complex organocatalytic cascade reactions. To date, the development of mass spectrometric ionization methods at atmospheric pressure (API) particularly electrospray ionization (ESI)[11–14] have opened up access to the investigation and detailed mechanistic studies of chemical reactions.[15–25]

ESI-MS and its tandem version ESI-MS/MS are rapidly becoming the preferred method for solution-phase mechanistic studies in chemistry due to the ability to select one specific ion and fragment it with *collision activated dissociation* (CAD) to obtain structural information concerning the molecular mass and structure of compounds in a reaction mixture. These combinations of techniques allow the study of not only reaction substrates and

[a]*Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 45470 Mülheim an der Ruhr, Germany. E-mail: wschrader@mpi-muelheim.mpg.de; Fax: +49 208 3062271*
[b]*Institut für Organische Chemie, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany; Fax: +49 241 8092127*

products, but even short-lived reaction intermediates as they are present in solution. These data provide novel insights into the mechanisms of many reactions.

ESI-MS and CAD can be useful to face the challenge of detailed mechanistic studies of a complex cascade reaction. Especially, the occurrence of side reactions can be troubling and a powerful method is needed to differentiate between the reaction steps and to help understand the mechanism. Continuing the previous successful work on the mechanistic investigation of organocatalytic reactions[26,27] by ESI-MS and ESI-MS/MS, we report here that these methods are also excellent tools for the interception and characterization of the reactive intermediates in a complex triple organocatalytic cascade reaction.

Secondary amines are capable of catalyzing organocatalytic cascade reactions *via* both enamine and iminium ion formation. List,[4] MacMillan[5] and Jorgensen[6] have developed cascade reactions by merging first iminium and then enamine activation. On the contrary, Enders[8] initiated a new reverse strategy using enamine activation of the first substrate to start a triple cascade. For the three-component (a linear aldehyde, a nitroalkene, an α,β-unsaturated aldehyde) cascade reaction diphenylprolinol trimethylsilyl ether as the catalyst is employed.

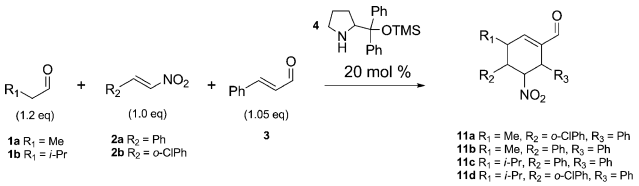
This cascade reaction is recognized as a powerful tool for the construction of *tetra*-substituted cyclohexene carbaldehydes with four stereogenic centers and its stereochemistry has been studied thoroughly.[28–31] Recently, in a related quadruple cascade reaction the intermediates have been characterized by ESI-MS.[32]

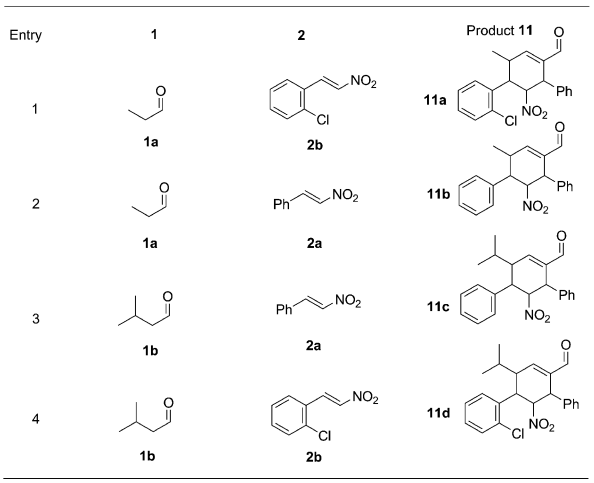
Results and discussion

The goal of this study was the investigation of an organocatalytic triple cascade reaction as has been reported by Enders.[28] For the mechanistic investigation of such a complex reaction it is necessary to observe the fast changes and the formation of small amounts of intermediate components. This was done here by using a high resolution triple quadrupole mass spectrometer with an electrospray ionization source. For a better understanding of the reaction and to study the influence of polyfunctional cyclohexene derivatives as the substrates, four different variations of the reaction have been carried out by varying the first and the second substrates, **1** and **2**, respectively which leads to changes in the mass spectral fingerprint. The experimental set up was kept the same for all reactions. The different reactions are illustrated in Scheme 1.

A first experimental overview is shown in Fig. 1 and 2, where spectra of reactions 1 and 3 are displayed, respectively, after different time intervals. The spectra indicate the progress of each reaction and show that the starting components make room at first for some intermediates and subsequently for the final product. In the case of reaction 3 the data showed that the reaction is much slower and some intermediates do not show the same response as in reaction 1 due to a different functional group. One of the most intense signals comes from the protonated catalyst [**4** + H]$^+$ at *m*/*z* 326. Other signals are also detected at *m*/*z* 366, 549, 440 and 681, respectively that could be assigned to putative intermediates. The details of their formation will be described in the following.

The mass spectra of reaction 3 using isovaleraldehyde **1b** and *E*-β-nitrostyrene **2a** after different reaction times are illustrated in Fig. 2. The signals at *m*/*z* 133 and 326 corresponding to





Scheme 1 The experimental set up of triple cascade reaction for the synthesis of *tetra*-substituted cyclohexene carbaldehydes **11a–d**.

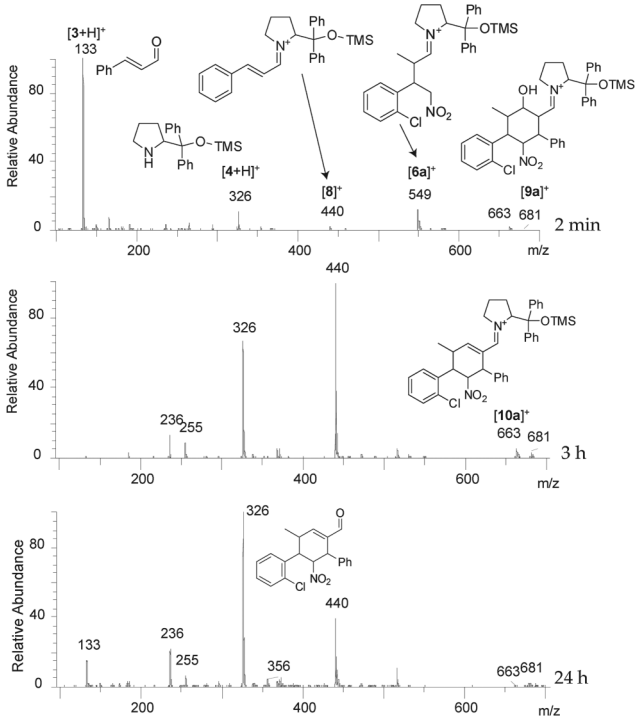


Fig. 1 Overview of the reaction mixture of propionaldehyde **1a** and 2-chloro-β-nitrostyrene **2b** after 2 min, 3 h and 24 h; displayed are ESI-(+)-MS spectra.

the protonated cinnamaldehyde [**3** + H]$^+$ and catalyst [**4** + H]$^+$, respectively, being some of the most intensive peaks. Other signals at *m*/*z* 440, 394, 543 and 675 that could be assigned to the putative intermediates are also recognized. These data show that there is no difference in the mechanism, as the intermediates

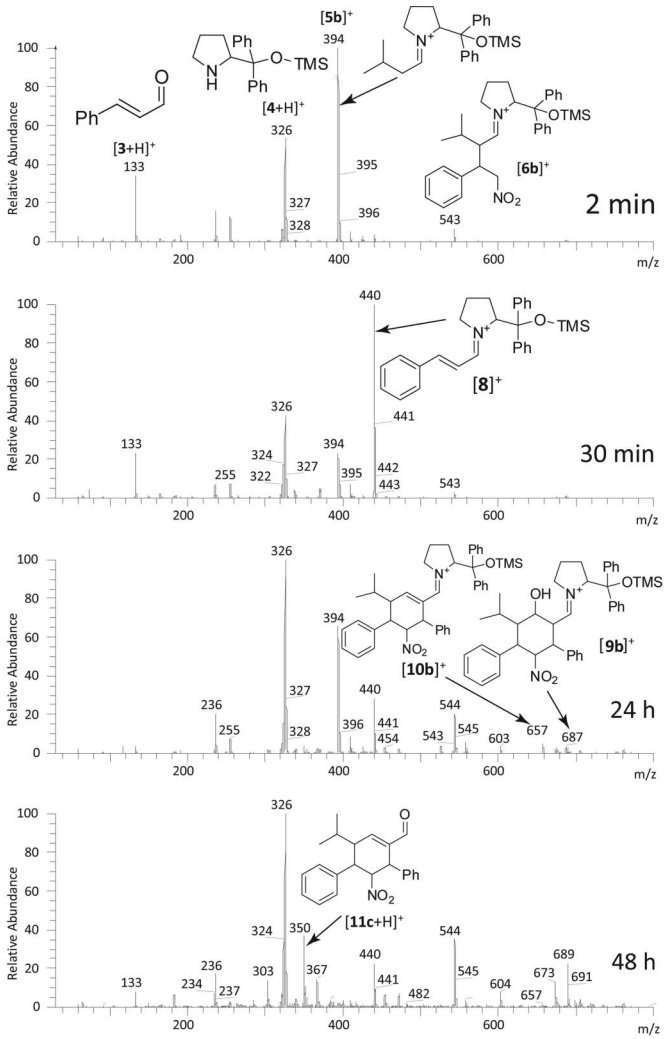
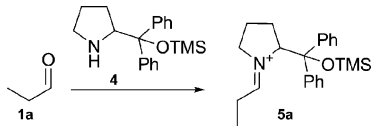


Fig. 2 ESI-(+)-MS spectrum of the reaction mixture of isovaleraldehyde **1b** and *trans*-β-nitrostyrene **2a** after 2, 30 min, 24 and 48 h.

that are being formed are corresponding to the same formation pathway. In general, it has to be noted, that most compounds show a significant signal that allows a detailed characterization of the reaction pathway. Nonetheless, there are some restrictions, as the product shows a very weak signal due to a bad response during electrospray ionization or to a short life time. To account for such problems additional studies were carried out using the atmospheric pressure chemical ionization (APCI) method. This ionization technique complements ESI measurements very well because APCI covers compounds that do not need to be as polar as they need to be for ESI and gives better signals for these compounds and intermediates.

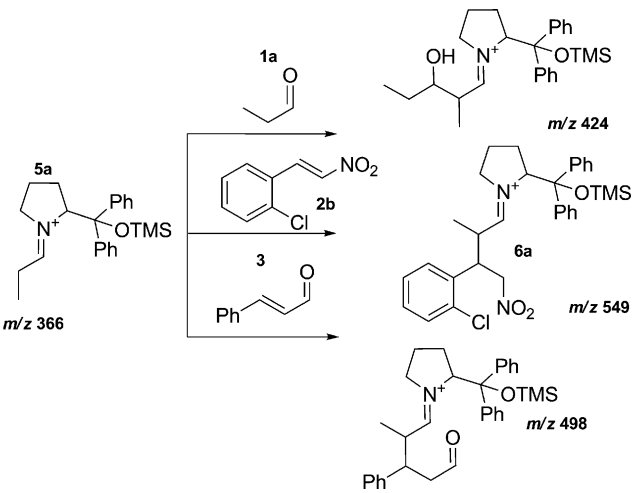
Since cascade reactions are combining a set of different organocatalytic reactions in subsequent steps, it is now important to follow the details of such a reaction as it progresses. Therefore, we use the reaction of propionaldehyde **1a**, (*E*)-2-chloro-β-nitrostyrene **2b** and cinnamaldehyde **3** with (*S*)-2-(diphenyl(trimethylsilyloxy)methyl)-pyrrolidine **4** as a catalyst as an example to describe the results of our mechanistic study of the investigated cascade reaction (Scheme 2).



Scheme 2 Catalytic activation of propionaldehyde **1a**.

The reaction begins with the activation of propionaldehyde **1a** by a proline-derived catalyst **4** *via* enamine formation to form the first intermediate **5a** at *m*/*z* 366.

At this point, it was not clear how the reaction proceeds since the enamine intermediate **5a** can react in three possible ways as described in Scheme 3. The first probable way would be a Michael addition of enamine intermediate **5a** to *trans*-2-chloro-β-nitrostyrene **2b** to form a nitroalkane **6a** which should be detectable at *m*/*z* 549. The second possible way is when the enamine intermediate **5a** reacts further with an excess of propionaldehyde **1a** and forms an iminium intermediate (*m*/*z* 424). The third probable path could proceed *via* Michael addition of enamine intermediate **5a** to cinnamaldehyde **3** for the generation of an iminium intermediate *m*/*z* 498 (Fig. 3).



Scheme 3 Three possible reaction pathways for the enamine intermediate **5**.

It is well-known that nitroalkenes are reactive Michael acceptors, as the nitro group is the best-known electron-withdrawing group.[33] This fact explains why the enamine **5a** reacts faster with **2b** than with **3**. The formation of **6a** was supported by MS/MS studies of *m*/*z* 549 as shown in Fig. 4 where the characteristic signals match the proposed structure ($C_{31}H_{38}N_2O_3SiCl$). Additionally, the signal from the first possibility at *m*/*z* 424 could not be detected during the reaction time.

To follow these mechanistic steps we have observed the individual steps outside of the cascade as well. The spectra are documented in Fig. 3, where the top spectrum shows the results of a reaction of substrate **1a** with catalyst **4**, while in Fig. 3b the results from the reaction of substrates **1a** and **2b** with catalyst **4** are shown. In Fig. 3c the results of the combination of **1a** and **3** with the catalyst **4** are displayed and in Fig. 3d the overall APCI spectrum of **1a** and **2b** in the presence of catalyst **4** shows the formation of **7a** which is only detectable by this ionization

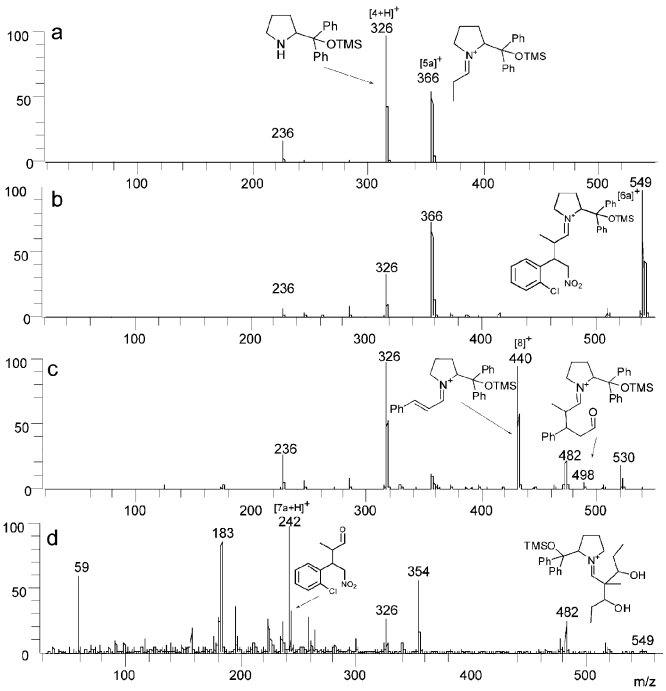


Fig. 3 a) ESI(+)-MS spectrum of **1a** and catalyst **4** in toluene after 5 min. b) ESI(+)-MS spectrum of **1a** and **2b** in the presence of catalyst **4** in toluene after 5 min. c) ESI(+)-MS spectrum of **1a** and **3** in the presence of catalyst **4** in toluene after 5 min. d) APCI(+)-MS spectrum of **1a** and **2b** in the presence of catalyst **4** in toluene after 24 h, **7a** is clearly detectable with APCI but not with ESI.

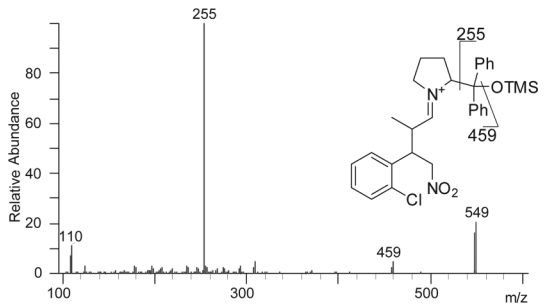


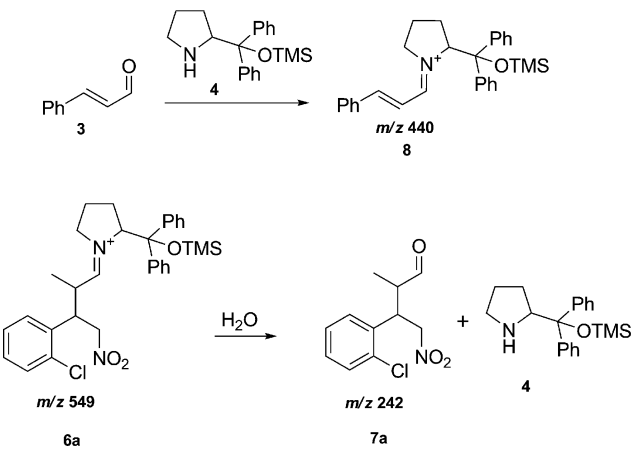
Fig. 4 ESI-(+)-MS/MS spectrum at *m/z* 549.

method in a sufficient intensity. All together these results confirm the mechanistic findings of the cascade reaction.

During the investigation a small signal of *m/z* 498 was detected which has a fragmentation pattern that fits the proposed structure in Scheme 3. To evaluate the conditions under which this intermediate forms different experiments were done. Especially helpful was a set of reactions where the reaction temperature was varied. An increase in temperature lead to an increase of *m/z* 498, which indicates that this intermediate is formed when the reaction temperature in higher. After recognizing this fact, the temperature during the MS studies was observed carefully but it was impossible to fully eliminate the formation of this intermediate. One additional signal appears at *m/z* 516.293 ($C_{32}H_{42}NO_3Si$, error 0.0 ppm) during later stages of the reaction. Here, MS/MS measurements and accurate mass data allowed us to propose that water was added to the double bond of *m/z* 498. Other than that no signals could be assigned that follow this reaction pathway, showing that these signals belong to side products of this reaction.

All these data allow us to conclude that the reaction proceeds *via* Michael addition of enamine intermediate **5a** to *E*-2-chloro-β-nitrostyrene **2b** in order to form a nitroalkane **6a** (*m/z* 549).

The iminium ion **8** (*m/z* 440.240, $C_{29}H_{34}NOSi$) is being formed early during the reaction, showing characteristic signals in the MS/MS spectrum as revealed in Fig. 5. Once the Michael adduct **6a** was formed, the subsequent steps took place relatively fast. The first step is a hydrolysis leading to **7a** (see Scheme 4) at *m/z* 242 which could not be detected directly during the reaction with ESI(+)MS but with APCI(+)MS (Fig. 3d).



Scheme 4 Reaction pathways of the hydrolysis step and the activation of cinnamaldehyde **3**.

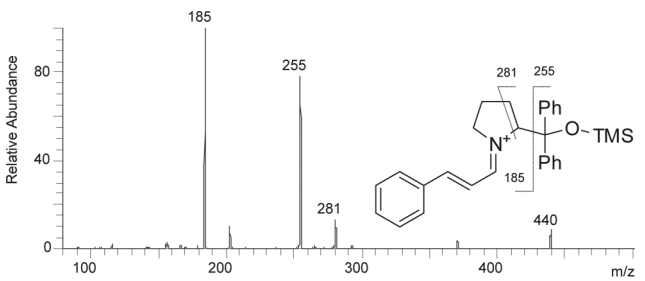
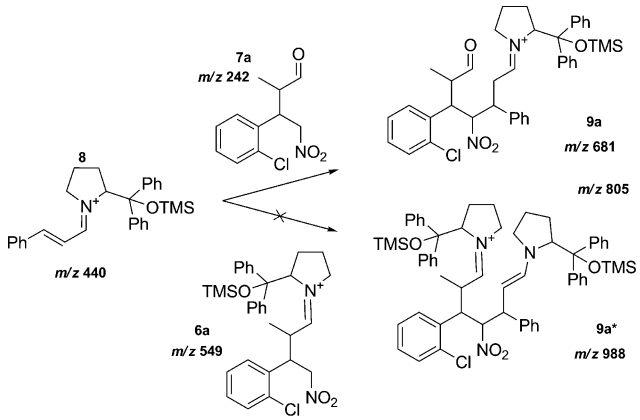


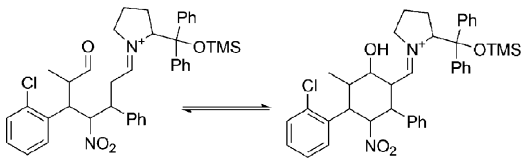
Fig. 5 ESI-(+)-MS/MS of *m/z* 440.

Afterwards, the reaction can proceed *via* two possible pathways. The first probable way is that the iminium ion intermediate **8** is attacked by nitroalkane **7a** in a Michael addition to yield an intermediate **9a** (*m/z* 681).

Another potential path would be that the iminium ion **8** reacts further with the intermediate **6a** to form an intermediate at *m/z* 988 as illustrated in Scheme 5. During the reaction time, the protonated ion at *m/z* 988 could not be detected. However the presence of protonated ion **9a** (*m/z* 681.292, $C_{40}H_{46}N_2O_4SiCl$) indicates that the reaction proceeded *via* the nitroalkane Michael addition. A posing question now is if the signal at *m/z* 681 is corresponding with the open iminium ion or with an iminium ion after ring closure according to Scheme 6. This is a difficult question to answer from mass spectrometric data. To try to get an answer to this question MS/MS measurements with increasing collision energies were undertaken.



Scheme 5 Reaction pathways of the second Michael addition.



Scheme 6 Intramolecular aldol reaction of *m/z* 681.

The MS/MS spectrum in Fig. 6 shows that even at higher collision energies only a few fragments can be detected, indicating that the structure is stable towards the collision activation. Spectra in the database from similar aliphatic structures show that defined fragments would be expected along the chain while a cyclic structure shows less fragments due to a higher stability. Here the fragments are very few, and although this is just an indirect indication, it seems that the signal at *m/z* 681 corresponds with the finished ring structure.

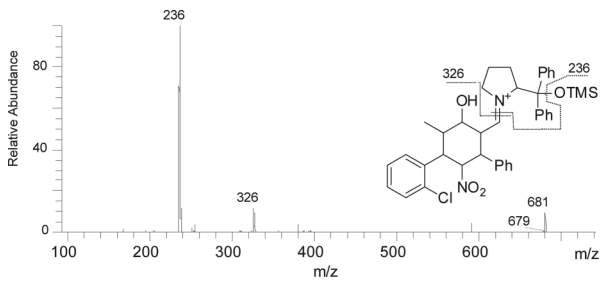
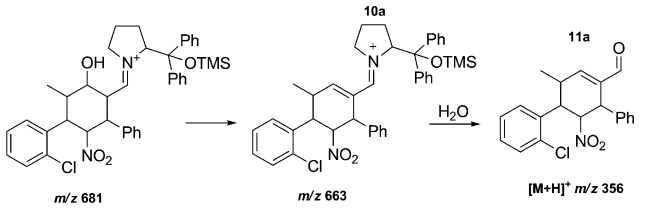


Fig. 6 ESI-(+)-MS/MS of *m/z* 681.

In the subsequent step, dehydration leads to **10a** (*m/z* 663.280, $C_{40}H_{44}N_2O_3SiCl$). Afterwards, the catalyst is released *via* hydrolysis step and the *tetra*-substituted cyclohexene carbaldehydes **11a** as the desired product is formed, as illustrated in Scheme 7.

For a better understanding and especially to characterize the unknown components of the reactions, all ions were also analyzed accurately for the calculation of elemental composition using FT-ICR MS. The data obtained from the reaction mixture 1 using propionaldehyde **1a** and 2-chloro-β-nitrostyrene **2b** after a reaction time of five minutes show the signal of the catalyst at *m/z* 326.194 which matches to formula $C_{20}H_{28}NOSi$ (error 1.0 ppm). The ions of other signals are revealed at *m/z* 366.225, 440.241, 549.234 and



Scheme 7 The hydrolysis process to form cyclohexene carbaldehyde product **11a**.

681.291, corresponding to formulas $C_{23}H_{32}NOSi$ (error 0.5 ppm), $C_{29}H_{34}NOSi$ (error 0.3 ppm), $C_{31}H_{38}N_2O_3SiCl$ (error 0.2 ppm), $C_{40}H_{46}N_2O_4SiCl$ (error 0.6 ppm), respectively. All the data fit well with the proposed intermediates.

In addition the same results can be obtained from the other reactions, an example is given in Fig. 7 that shows the mass spectrum from the reaction 1 using isovaleraldehyde **1b** and *E*-β-nitrostyrene **2a** after a reaction time of five minutes using FT-ICR MS. The spectrum shows the most important signals with their accurate masses and structural assignments from the catalyst at *m/z* 326.193 ($C_{20}H_{28}NOSi$) and from the putative intermediates at *m/z* 394.256 ($C_{25}H_{36}NOSi$), 440.241 ($C_{29}H_{34}NOSi$) and 543.304 ($C_{33}H_{43}N_2O_3Si$).

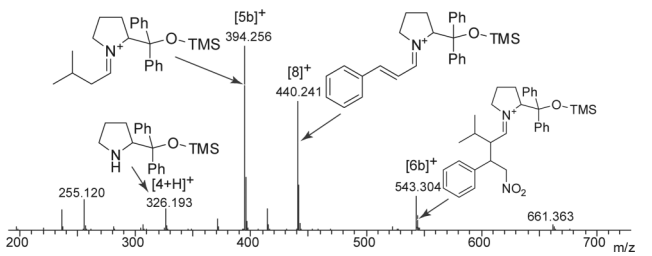


Fig. 7 ESI-(+)-MS spectrum from FT-ICR with the accurate mass data of the reaction mixture 3 of isovaleraldehyde **1b** and *E*-β-nitrostyrene **2a** after 5 min. (Note: Numbers are the same as with the components of reaction 1 to indicate the mechanism).

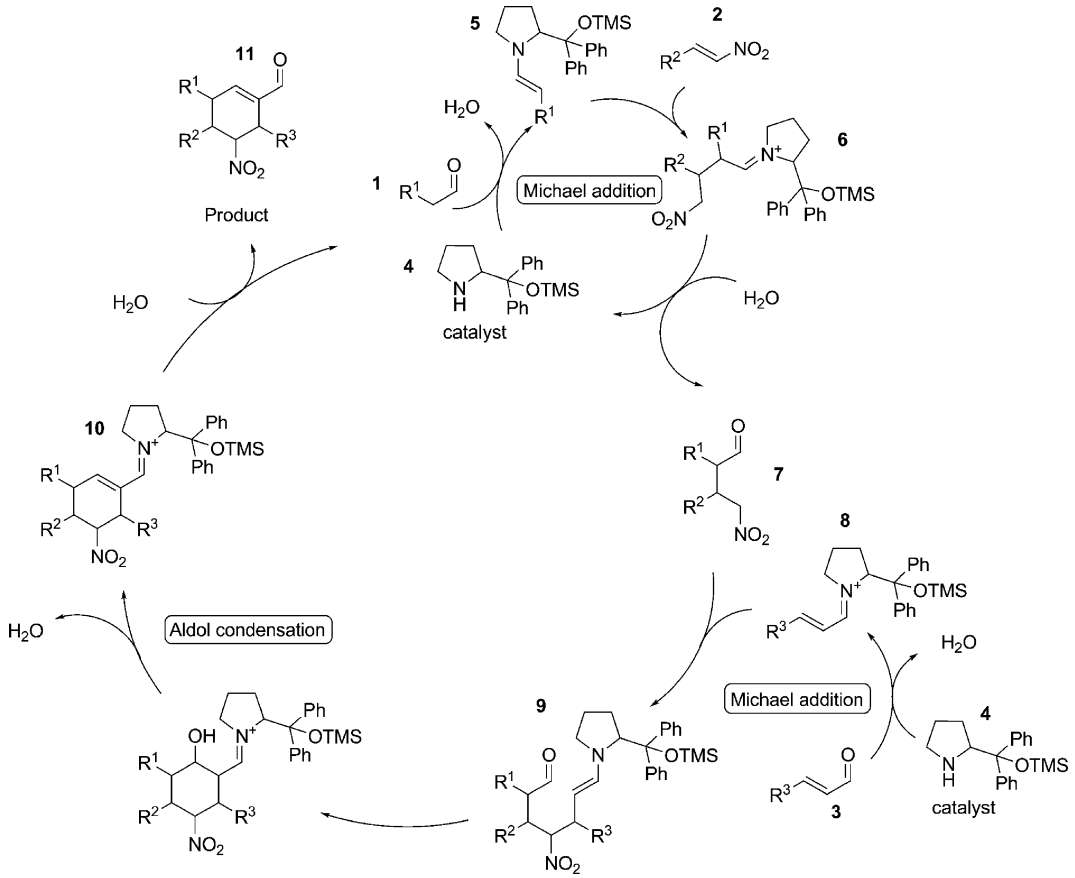
All the obtained results from ESI-MS and MS/MS experiments were supported by the data from accurate mass measurement by FT-ICR MS and the results from reaction 1 are summarized in Table 1.

Conclusions

Taking all the results into account, a complex triple organocatalytic cascade reaction for the stereoselective synthesis of *tetra*-substituted cyclohexene carbaldehydes has been successfully

Table 1 Accurate mass data from reaction 1, showing the results from most significant signals present

Species	Formula	Mass	Error [ppm]
[**4**+H]$^+$	$C_{20}H_{28}NOSi$	326.194	0.1
[**5a**]$^+$	$C_{23}H_{32}NOSi$	366.225	0.4
[**8**]$^+$	$C_{29}H_{34}NOSi$	440.241	0.0
[**6a**]$^+$	$C_{31}H_{38}N_2O_3SiCl$	549.234	0.3
[**10a**]$^+$	$C_{40}H_{44}N_2O_3SiCl$	663.280	0.8
[**9a**]$^+$	$C_{40}H_{46}N_2O_4SiCl$	681.292	1.6



Scheme 8 The proposed catalytic cycle for the complex organocatalyzed triple cascade reaction.

studied. The intermediates of an enamine-iminium-enamine activated triple cascade reaction have been intercepted through ESI-MS monitoring. Structural assignments were aided by using the accurate mass data from FT-ICR MS. ESI-MS, its tandem version MS/MS and the accurate mass determination are powerful methods to investigate complex organocatalyzed reactions by the interception, isolation, detection and structural characterization of important intermediates from the reaction, thus providing significant information about the proposed catalytic cycle of the reactions. Furthermore, the ability to isolate ions directly from crude reaction mixtures for further characterization of active species, reactive intermediates, and products without previous purification is an advantage.

The cascade starts with the activation of an aldehyde **1** by enamine formation thus allowing its addition to a nitroalkene **2** *via* a Michael reaction. The liberated catalyst from the hydrolysis process forms an iminium ion of an α,β-unsaturated aldehyde **3** to accomplish the conjugate Michael addition with the nitroalkane **7**. In subsequent steps, the enamine **9** leads to an intramolecular aldol condensation *via* **10**. The final product tetra-substituted cyclohexene carbaldehyde **11** is obtained after hydrolysis. The complete reaction cycle of the organocatalytic triple cascade reaction is displayed in Scheme 8. Further research concerning method development of mass spectrometry for the investigation of organocatalytic reactions is being pursued in our laboratory.

Experimental

The reaction mixtures were stirred between 0 °C and room temperature for 16–24 h in 1 ml of toluene. The analyte was taken directly from the reaction flask and was diluted in acetonitrile (1 : 100) before entry to the ESI source at a flow rate of 2 μL min^{-1}. The investigation was carried out by monitoring the reaction at specified intervals through ESI-MS. The reaction intermediates that appeared during the reaction were intercepted, detected and characterized with ESI-MS. MS/MS experiments were performed for structural confirmation using the product ion scan with the collision energy ranging from 10 to 50 eV, depending on the dissociation lability of the precursor ion. Additional data of accurate mass measurements were obtained with FT-ICR MS.

Instrumental

ESI-MS data were acquired using a Thermo TSQ Quantum Ultra AM triple quadrupole mass spectrometer equipped with an ESI source which was controlled by Xcalibur software. The spray voltages was set to 4000 V and 3000 V for positive and negative ions, respectively. The heated capillary temperature was adjusted to 270 °C. For MS/MS analysis, the collision energy was increased from 10 eV to 50 eV. The mass spectrometer was operated in the Q1 scan and product ion scan modes, with the mass width for Q1 set at 0.5 Da and for Q3 set at 0.7 Da. The collision cell, Q2,

contained argon and was adjusted to a pressure of 1.2 mTorr to induce CID. Spectra were collected by averaging 10 scans with a scan time of 1.5 s. The Mass range was adjusted between 50 and 1500 Da. Additional data were obtained using a Bruker APEX III FT-ICR MS with a 7 T actively shielded magnet operating with an Agilent ESI source. The analyte was introduced as a solution in acetonitrile 1 : 1 (v/v) dilution and injected in the infusion mode with a flow rate of 2 μL min^{-1} at an electrospray voltage of 4500 V. Scans was carried out from m/z 100 to 2400.

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