Organocatalytic Halogenation

DOI: 10.1002/anie.200700266

Electrospray Ionization Mass Spectrometric Study on the Direct Organocatalytic α-Halogenation of Aldehydes**

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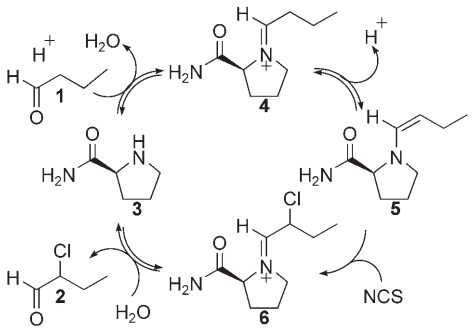
The mechanism of reactions in solution can be studied using electrospray ionization mass spectrometry (ESI-MS).[1] We recently conducted an ESI-MS study on the aldol reaction catalyzed by L-proline where we were able not only to follow the reaction over time, but to isolate and characterize all the reaction intermediates by tandem mass spectrometry (MS/MS).[2] Herein we present a mechanistic study on the organocatalytic α-halogenation (Cl, Br, I) of aldehydes, which is a compelling method for obtaining optically active halogen-containing compounds highly valuable as synthetic intermediates.[3–5] The catalytic cycle currently accepted for the organocatalytic α-chlorination of aldehydes is shown in Scheme 1 for the reaction of butanal (**1**) and *N*-chlorosuccinimide (NCS) catalyzed by L-prolinamide (**3**) to produce 2-chlorobutanal (**2**). The reaction proceeds via the formation of the iminium ion **4**, which releases a proton to form the enamine intermediate **5**. This enamine is halogenated by NCS to produce an intermediate cation **6**, with a succinimidyl counterion. Reaction with water yields the product **2** and succinimide (NHS).[5]



Scheme 1. Mechanism of the L-prolinamide-catalyzed α-chlorination of butanal with NCS.

Recently, an electrophilic N-chlorination of the enamine intermediate instead of a direct C-chlorination has been proposed based on isotope effects, nonlinear effects, kinetic studies, and DFT calculations.[5] The interception and characterization of the possible reactive $N{-}X^+$ intermediate in solution is an important challenge. Marigo and Jørgensen discussed quite recently the organocatalytic direct asymmetric α-heteroatom functionalization of aldehydes and ketones.[6]

The ESI-MS spectrum of an on-going reaction of **1** and NCS in the presence of **3** under the experimental conditions described by Halland et al.[4,5] reveals the presence of **3**·H^+ (*m*/*z* 115), and the formation of the intermediates **4** and **5**·H^+ (both *m*/*z* 169), and **6** (*m*/*z* 203; Figure 1).[7] Aldehydes such as **1** and **2** are not easily protonated under standard operational conditions, and are not detected in the ESI spectrum. Ions **4** and **5**·H^+ are observed from the first moments of reaction. They can be distinguished by using deuterated methanol as the medium, which allows the ratio of [**4**]/[**5**·D^+] in solution to be estimated as 1:10.[8]

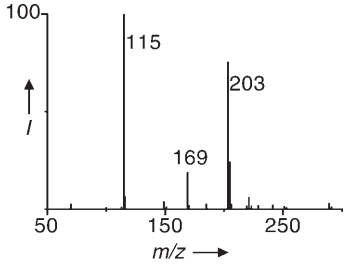


Figure 1. ESI-MS (positive mode) spectrum of the reaction after 30 minutes of **1** and NCS catalyzed by L-prolinamide.

The intensity of the *m*/*z* 169 signal (**4** and **5**·H^+) reaches a maximum early on in the reaction process, and has a fast decay that leads to a maximum concentration of **6** (*m*/*z* 203) after approximately 30 minutes reaction time.[8] The formation of NHS and the disappearance of NCS can be followed over time by monitoring the reaction by atmospheric pressure chemical ionization mass spectrometry (APCI-MS). The ratio of the signal intensities of the protonated forms of NHS and of NCS is representative of the reaction progress, and corresponds to that between **2** and **1**.[8] Interestingly, this ratio evolved much slower than the formation of intermediates **5** and **6**. The slow reaction of intermediate **6** with water to give product **2** and the catalyst **3** is the rate-determining step of the catalytic cycle, which is in accordance with the results obtained by Halland et al. in their study on the influence of water and acid on the reaction rate.[5]

The addition of water before the reacting solution enters the ESI source allowed for the interception of the protonated

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[**] We thank the German Research Association (DFG) for their financial support of this project (SSP 1179).

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

transients **T1** and **T3** (Scheme 2), and their concentration rises to an observable level. Their predominant fragmentations result in the formation of both precursors and products in the cycle, which allows noncovalent adducts, which could have the same mass, to be eliminated as being responsible for the signals (Figure 2). **T1** could be observed directly after a reaction time of less than 1 ms by using the recently developed dual electrospray ionization mass spectrometry (dual ESI-MS) methodology.[8]

Halland et al. hypothesized that the electrophilic halogenation of **5** might proceed through an initial, kinetically controlled formation of an N–Cl bond in transient **T2** (Scheme 2) which rapidly undergoes a [1,3] sigmatropic shift to produce the thermodynamically favored ion **6**. The isomers **T2** and **6** (*m*/*z* 203) should give different MS/MS spectra. We investigated the reaction of the previously formed enamine **5** with *N*-halosuccinimide (NXS, X = Cl, Br, and I) after about 1 s by using a microreactor and at very short reaction times of about 1 ms by using dual ESI-MS[8] (Figure 3).

The MS/MS spectrum of **5**·Cl^+ (*m*/*z* 203) at 1 s and after longer reaction times shows the expected fragmentation of ion **6:** scission of HCl to give *m*/*z* 167 and of $HCONH_2$ to give *m*/*z* 158. The formation of the fragment ion at *m*/*z* 70 ($C_4H_7NH^+$) is a common fragment ion in the collision-induced dissociation (CID) of protonated proline and prolinamide. After reaction times of milliseconds we observed high intensity signals for additional fragments at *m*/*z* 124 that arise from the scission of $ClCONH_2$ and a significant fragment $C_4H_7NCl^+$ at *m*/*z* 104; the latter fragment can be attributed unambiguously to the primary formed N–Cl intermediate **T2** (Figure 3 a).[9]

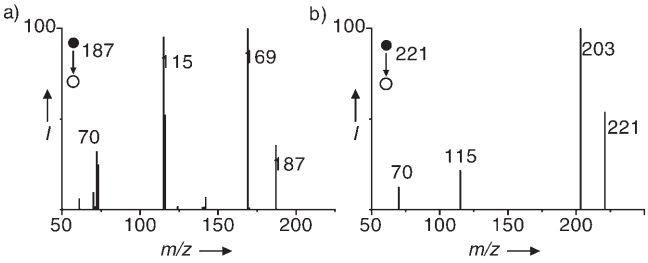
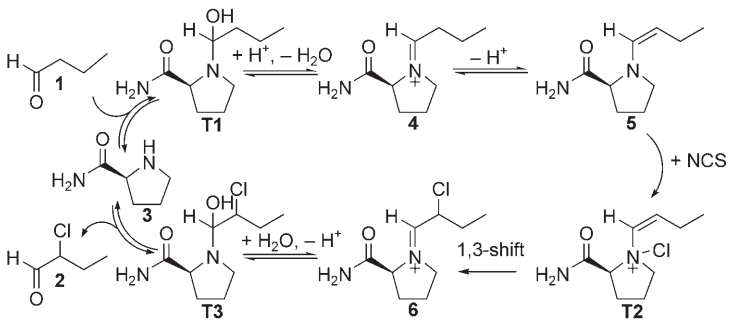


Figure 2. a) Dual ESI-MS/MS spectrum of **T1** (*m*/*z* 187). b) ESI-MS/MS spectrum of **T3** (*m*/*z* 221).



Scheme 2. Proposed mechanism of the L-prolinamide-catalyzed α-chlorination of butanal.

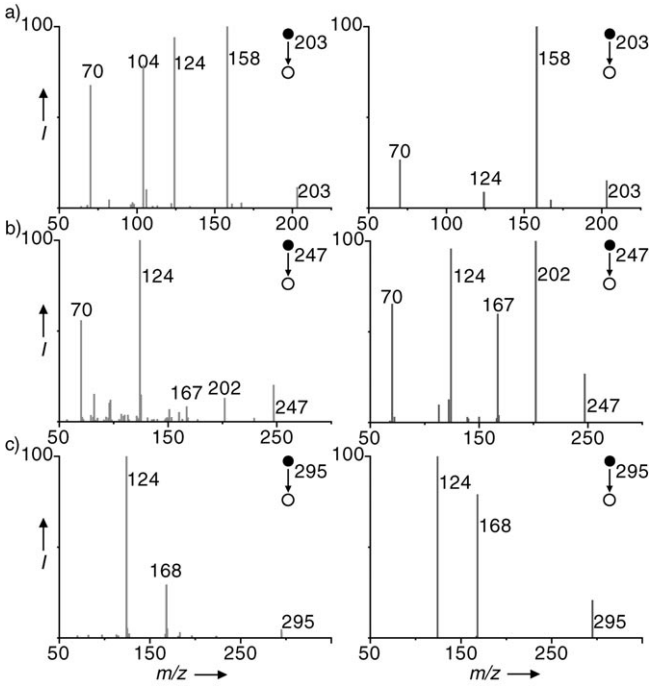


Figure 3. a) MS/MS spectra of the ion with *m*/*z* 203, which corresponds to **T2** and/or **6**, at reaction times of milliseconds (left, dual ESI) and 1 s (right, microreactor). The fragment with *m*/*z* 104, which corresponds to $C_4H_7NCl^+$, disappears with time. b) Same experiment but using NBS (*m*/*z* 247). c) Same experiment but using NIS (*m*/*z* 295).

Remarkably, the CID fragmentation pattern varies with the halogen used. The bromo and the iodo intermediates do not change with reaction time (Figure 3 b and c respectively). Most importantly, the fragment ions $C_4H_7NBr^+$ (*m*/*z* 148) and $C_4H_7NI^+$ (*m*/*z* 196) are not observed on the millisecond timescale. The intermediate **T2** is formed only with X = Cl and not with X = Br, I. This finding is most remarkable and may be rationalized as follows: Enamine **5** will be attacked by a hard electrophile such as Cl^+ preferentially at the harder nitrogen atom and by the softer electrophiles Br^+ and I^+ preferentially at the softer carbon atom.

In summary, the time-dependent interception and characterization not only of the intermediates assumed to participate in the catalytic cycle, but also of transients **T1**–**T3** allows a more detailed understanding of the process (Scheme 2). Moreover, the halogen effect observed by ESI-MS in the halogenation of enamine **6** provides a deeper knowledge of the reaction mechanism of the direct organocatalytic α-halogenation of aldehydes.

Received: January 19, 2007
Revised: June 30, 2007
Published online: August 7, 2007

Keywords: α-halogenation · mass spectrometry · organocatalysis · reactive intermediates · rearrangement

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[7] The accuracy observed in the *m*/*z* value of the molecular ion of the species analyzed in this study was less than 2 ppm in all cases.
[8] See the Supporting Information.
[9] For example, the fragmentation patterns observed for *N*-halo-prolinamide and *N*-halo(*N*-methyl)proline—both resembling **T2**—correspond mainly to the release of X-$CONH_2$ and X-COOH, respectively. In contrast, compounds similar to **6** prepared by the reaction of L-prolinamide with 3-chloro-2-butanone or 1-bromo-2-butanone fragment to release mainly $HCONH_2$ and HX.

