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Supporting Information

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

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(I) Experimental

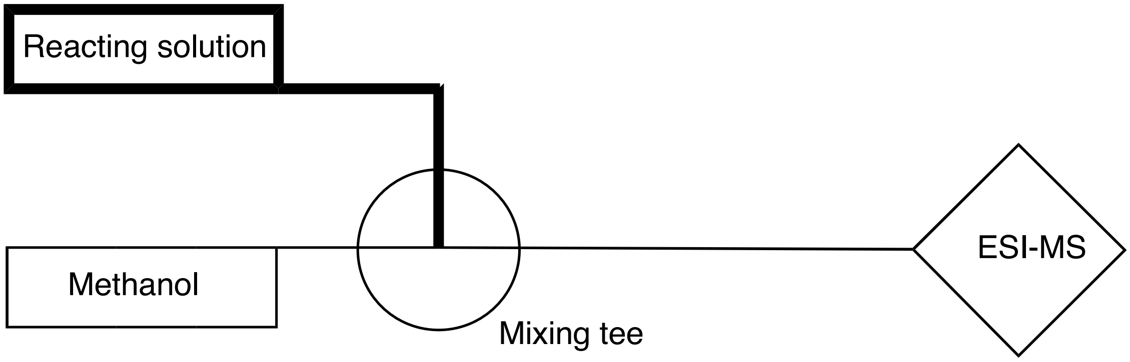
The mass spectrometric measurements were performed on the quadrupole-time of flight (Q-Tof) instrument Micromass Premier (Waters, Manchester) equipped with a standard ESI ion source containing a stainless steel spray capillary (127μm inner diameter, 229μm outer diameter, 181mm of length). A capillary voltage of 500V, and source and desolvation temperature of 40°C were used as standard ESI-MS operation conditions. The collision-induced dissociation (CID, collision gas argon) was performed in the collision cell region, using a capillary voltage of 2.5kV, source and desolvation temperature of 40°C, and collision energy of 8a.u. as standard ESI-MS/MS operation conditions.

Butanal **1**, N-chlorosuccinimide (NCS), N-bromosuccinimide (NBS), N-iodosuccinimide (NIS), N-methyl-Lproline, L-prolinamide **3**, methanol, and CH_2Cl_2 were obtained from Aldrich (Steinheim, Germany). All chemicals were used without further purification but NCS, NBS that were purified by recrystallization from water, and NIS, recrystallized from a mixture of 1,4-dioxan/CCl_4. Them three were dried afterwards in vacuum using P_2O_5 as drying agent. CH_2Cl_2 was dried before used using CaH_2 as drying agent.

(II) General Procedures

*a) On-going reaction MS experiments***.**

Two syringes assembled in different pumps, one containing the on-going reaction and the other containing a diluting solvent, *e.g.*, methanol, were allowed to feed a mixing tee (Techlab, PEEK mixing tee) directly connected to the ESI or APCI source (see graphic S1). The reacting solution was this way diluted before entering the ion source. When any of the reactants was present in suspension, the reaction was let to take place in a vessel. Samples of the reacting mixture were then collected at different intervals, diluted with methanol, and injected directly into the ESI source.



Graphic S1. Schematic setup for the on-going reaction MS experiments.

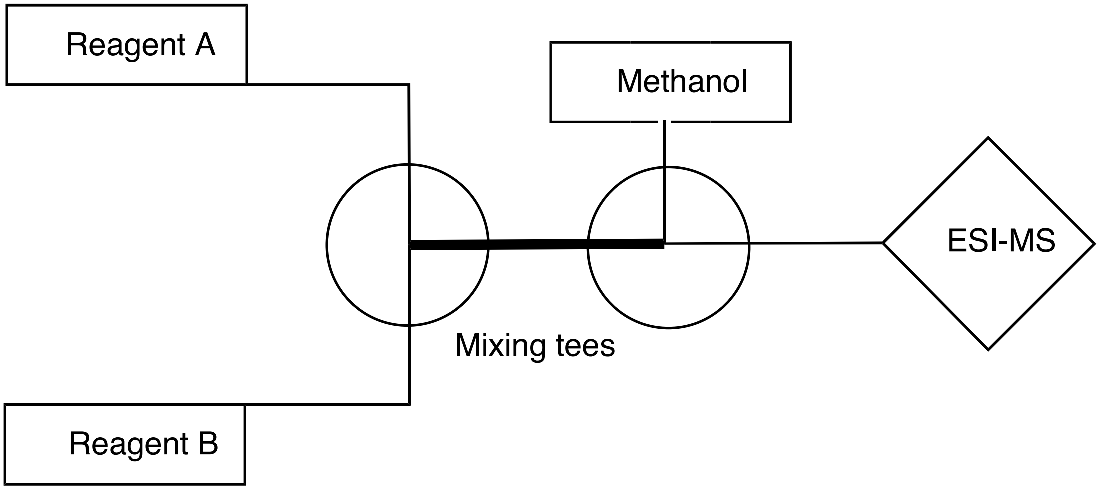
A solution of **1** (45μL, 0.5M), **3** (5.7mg, 50mM), and N-halosuccinamide (X=Br and I, 1M) in 1mL CH_2Cl_2 was prepared. With the help of the assembly above described, this mixture was injected into the ESI source. An injection speed of 0.1μLmin^{-1} was settled for the reactants solution, and 40μLmin^{-1} for the methanol.

NCS did not dissolve completely in these conditions, remaining in part as a suspension. In the experiments performed with it, samples of 5μL of the reacting mixture were collected at different intervals, diluted with 1mL methanol, and injected directly into the ESI source.

The intermediates **5** and **6** where intercepted and analyzed using this assembly. For the detection of **T1** and **T3**, a mixture of methanol/water (1:1, v/v) was used as diluent instead of methanol.

b) *Continuous-flow MS experiments.*

Two syringes containing solutions of the different reagents were allowed to feed a mixing tee. A second mixing tee was attached between that and the ionization source to reduce the final sample concentration entering the mass spectrometer (see graphic below). The reaction volume (0.75μL, bold in graphic S2) for bimolecular processes was then that of the capillary connecting both mixing tees; the volume of the metal spray capillary is rendered negligible after the strong dilution process in the second mixing tee. The reaction time was controlled by the flow rate set up on the different pumps.

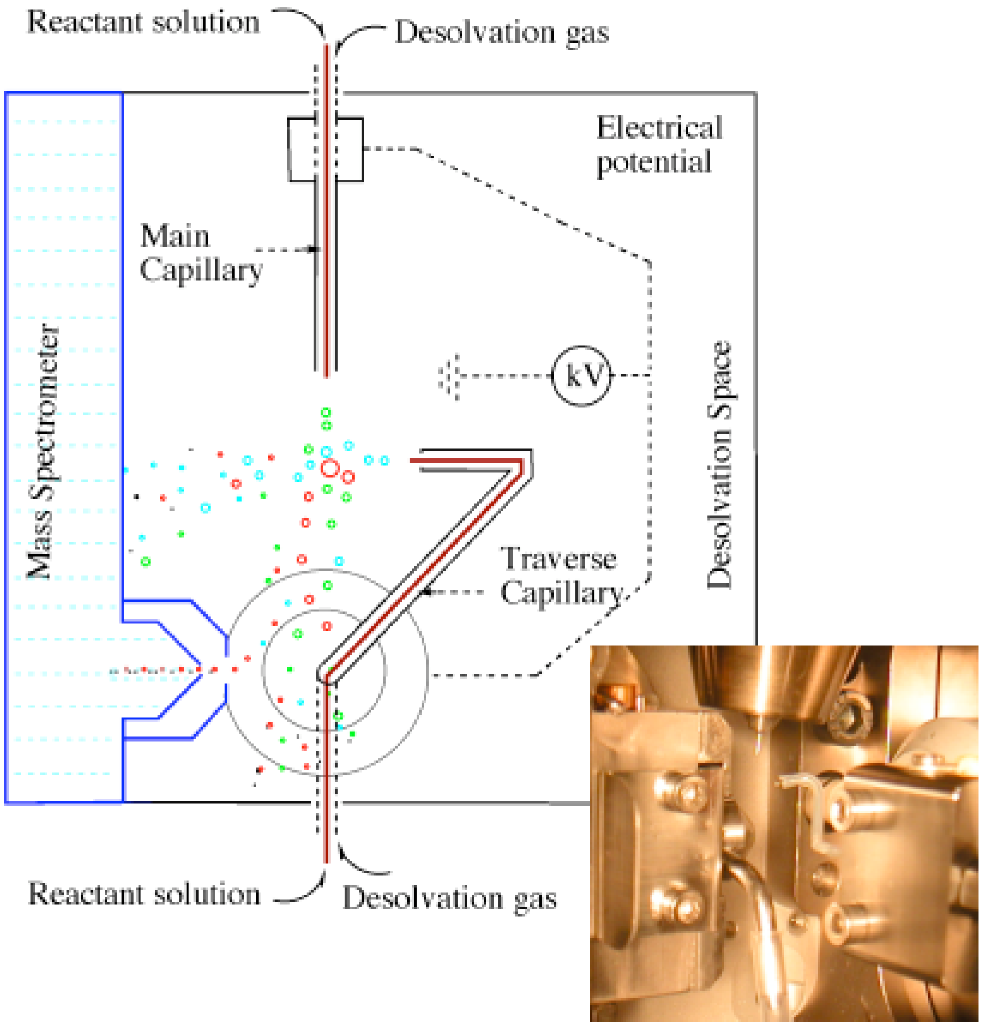


Graphic S2. Schematic setup for the continuous-flow MS experiments.

Two solutions were prepared, the first containing **1** (4.5μL, 50mM) and NXS (50mM) in 1mL dried CH_2Cl_2 (Reagent A), and the second **3** (0.57mg, 0.5mM) in 1mL dried CH_2Cl_2 (Reagent B). These two solutions were transfer to syringes and allowed to react by using the assembly described above. An injection speed of 5μLmin^{-1} was settled for the reactants solutions, and 40μLmin^{-1} for the methanol. These conditions allowed the study of the medium ~1s after initiating the reaction. Other times were achieved by varying the flow speed in the pumps. The evolution in time of **5**, **T2/6**, and their homologues using NBS and NIS were analyzed using this assembly.

c) *Halogens 1,3-shift MS experiments.*

A solution of **1** (4.5μL, 50mM) and **3** (0.57mg, 0.5mM) in 1mL dried CH_2Cl_2 was prepared in the presence of molecular sieves (Reagent A), and in a different vessel, a solution of NXS (50mM) in 1mL dried CH_2Cl_2 (Reagent B). These two solutions were transfer to syringes and allowed to react by using the microreactor system. An injection speed of 90μLmin^{-1} was settled for the reactants solutions. These conditions allowed the study of the medium ~1s after initiating the reaction. For the experiments performed on the Dual ESI, reagent A was sprayed using the main capillary of the Q-Tof, while reagent B was sprayed using the traverse capillary. The Dual ESI assembly is depicted below (graphic S3).



Graphic S3. Schematic representation and picture of the Dual ESI assembly used.

(III) Selected Spectra.

a) Atmospheric Pressure Chemical Ionization.

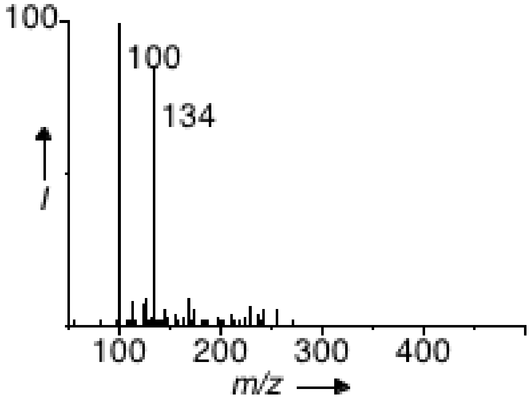


Figure S1. APCI-MS spectrum of the reaction of **1** and NCS catalyzed by **3** after 30min.

b) *Kinetics.*

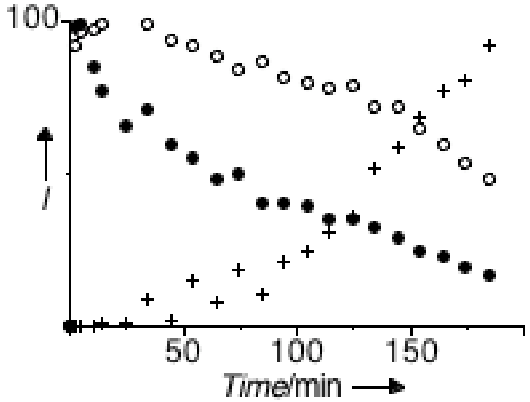


Figure S2. Evolution in time for the intermediates **4** and **5**•H$^+$ (●), **6** (○) –from ESI-MS experiments–, and the ratio between NHS•H$^+$ and NCS•H$^+$ (+) –from APCI-MS experiments–.

c) *Reaction Intermediates*.

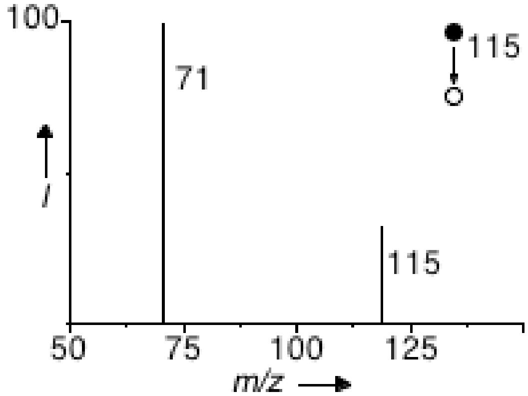


Figure S3. ESI-MS/MS of **3**•H$^+$.

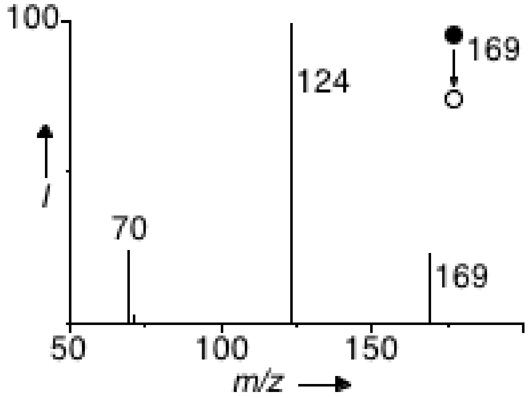
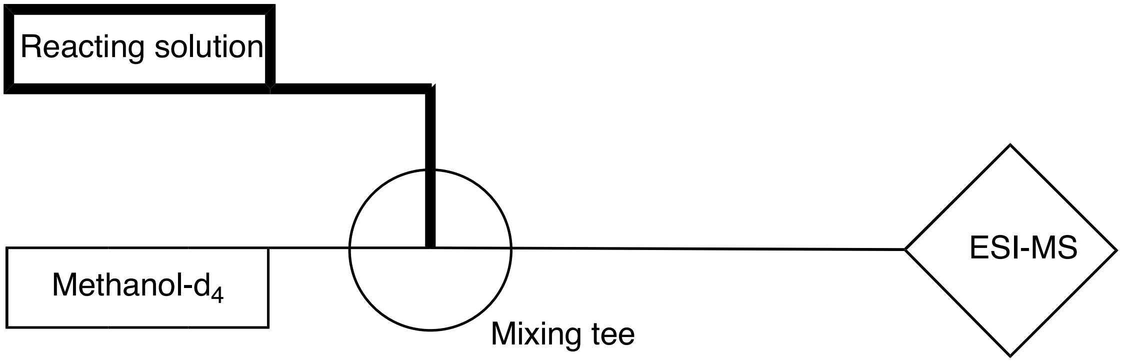


Figure S4. ESI-MS/MS of the ion signal corresponding to **4** and **5**•H$^+$ (m/z 169).

(IV) Iminium ion (4)/ enamine (5•D$^+$) differentiation

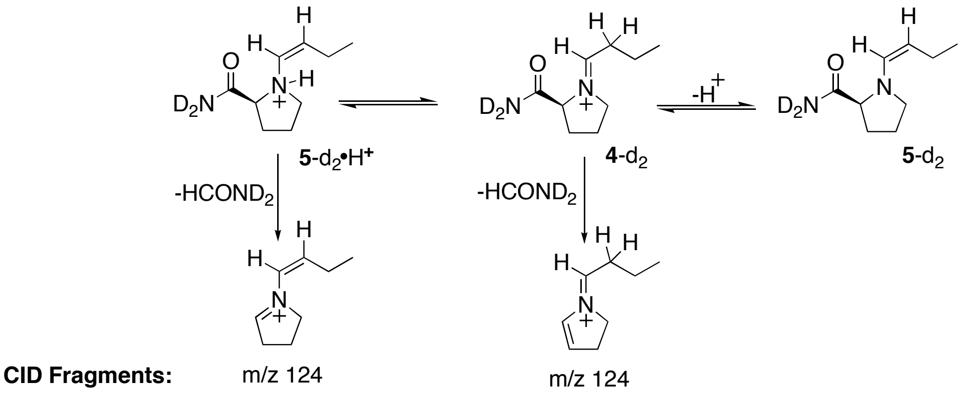
Ions **4** and **5**•H$^+$ can be distinguished by using a deuterated medium. A mixture of **1** (50mM) and **3** (0.5mM) in *per*-deuterated methanol was prepared and allowed to react during 30 minutes (see graphic S4).



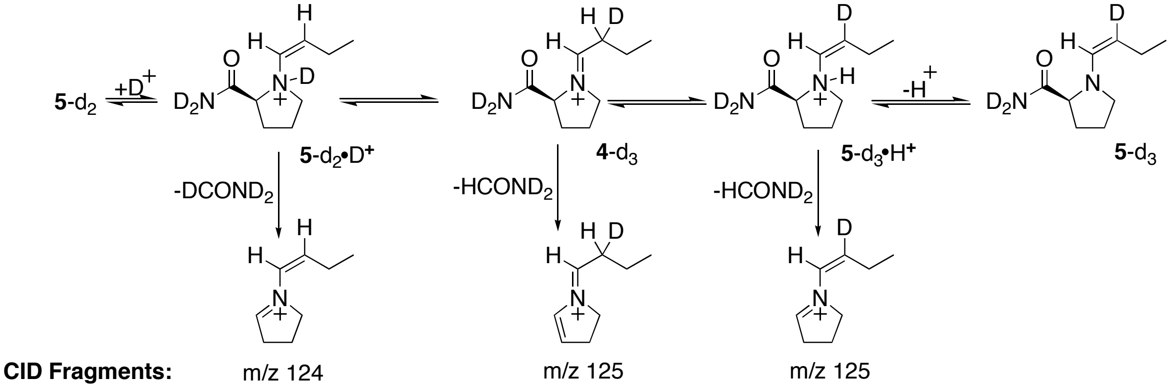
Graphic S4. Schematic setup for the iminium ion / enamine differentiation experiments.

With the help of the assembly above described, this mixture was injected into the ESI source. An injection speed of 0.1μLmin^{-1} was settled for the reactants solution, and 40μLmin^{-1} for the per-deuterated methanol. Scheme S1 shows the different species and the m/z ratios expected for the main CID fragment ions.

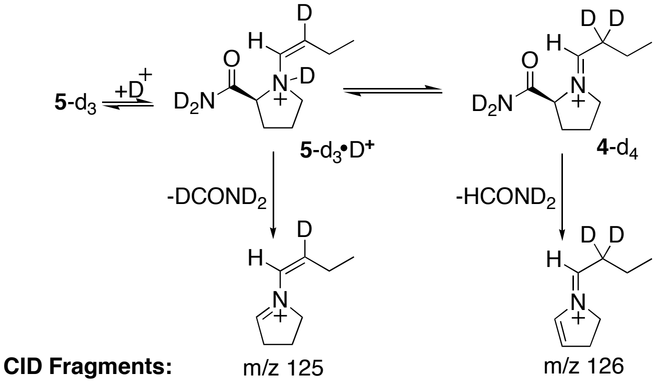
m/z 171, corresponding to 5-d$_2$•H$^+$ and 4-d$_2$:



m/z 172, corresponding to 5-d$_2$·D$^+$, 4-d$_3$, and 5-d$_3$·H$^+$:



m/z 171, corresponding to 5-d$_3$·D$^+$ and 4-d$_4$:



Scheme S1. Different species and the m/z ratios expected for the main CID fragment ions for the iminium ion / enamine differentiation.

According with the scheme depicted above, the ion with m/z 171 is not suitable for the calculation of the signal ratio enamine/iminium since both enamine (**5**-d$_2$•H$^+$) and iminium (**4**-d$_2$) fragment to produce the same ion with m/z 124. In the case of the ion with m/z 172, it is not suitable either; the fragment with m/z 125 corresponds to the enamines (**5**-d$_2$•D$^+$, **5**-

d_3•H^+) and the iminium (**4**-d_3). However, the fragments observed for the ion with m/z 173 allows a rough estimation for the ratio enamine/iminium, since the enamine (**5**-d_3•D^+) only fragments to m/z 125, meanwhile the iminium (**4**-d_4) only to 126. From the spectra studied (shown below), and considering only the ratio of the intensities of the ions m/z 125 and m/z 126 observed in the MS/MS spectrum of ion m/z 173, an enamine/iminium ratio of 10:1 is estimated.

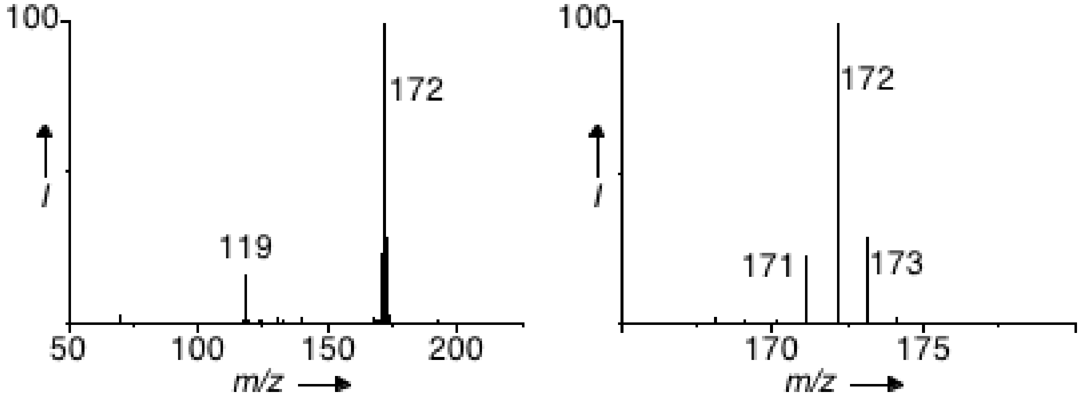


Figure S5. ESI-MS spectrum of the reaction of **1** (50mM) and **3** (0.5mM) in *per*-deuterated methanol after 30min. The signal with m/ 119 corresponds to **3-**d_3•D^+. On the right, the same spectrum expanded in the m/z range corresponding to the deuterated products **4** and **5**•D^+.

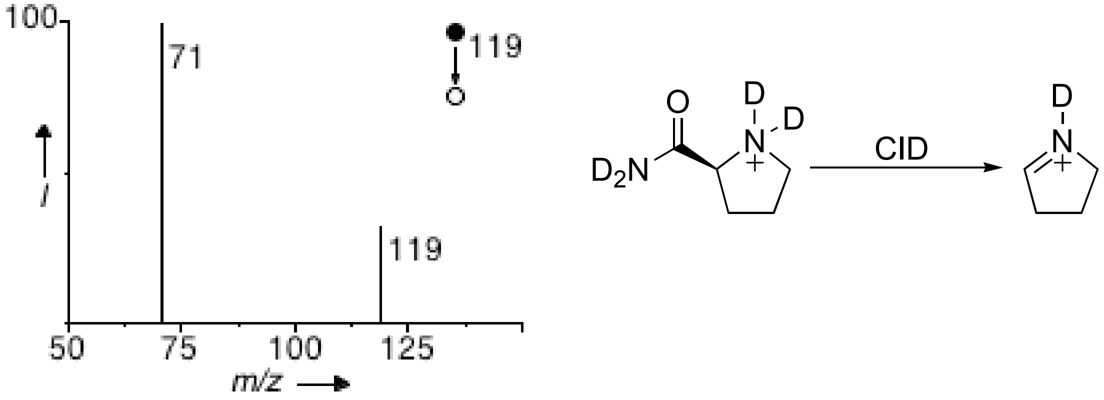


Figure S6. ESI-MS/MS spectrum for the ion with m/z 119 in the same experiment.

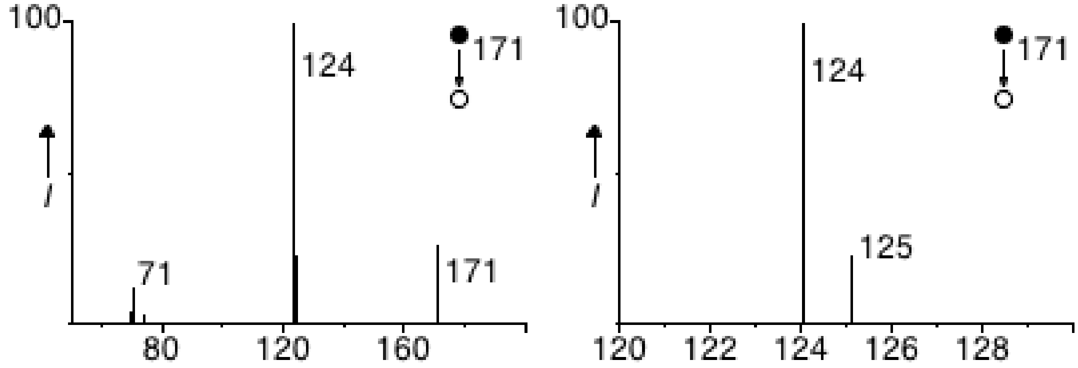


Figure S7. ESI-MS/MS spectrum for the ion with m/z 171, corresponding to **5**-d_2•H^+ and **4**-d_2. On the right, the same spectrum expanded in the m/z range corresponding to the main fragmentation.

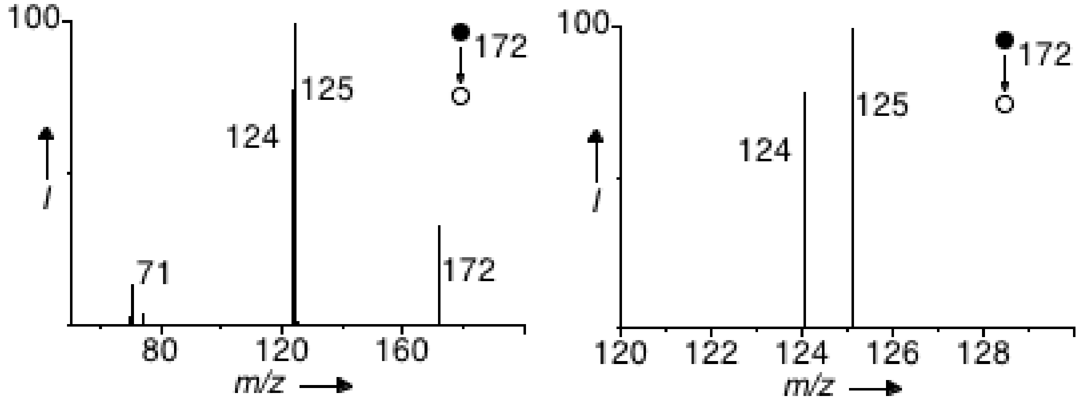


Figure S8. ESI-MS/MS spectrum for the ion with m/z 172, corresponding to **5**-d_2•D^+, **5**-d_3•H^+, and **4**-d_3. On the right, the same spectrum expanded in the m/z range corresponding to the main fragmentation.

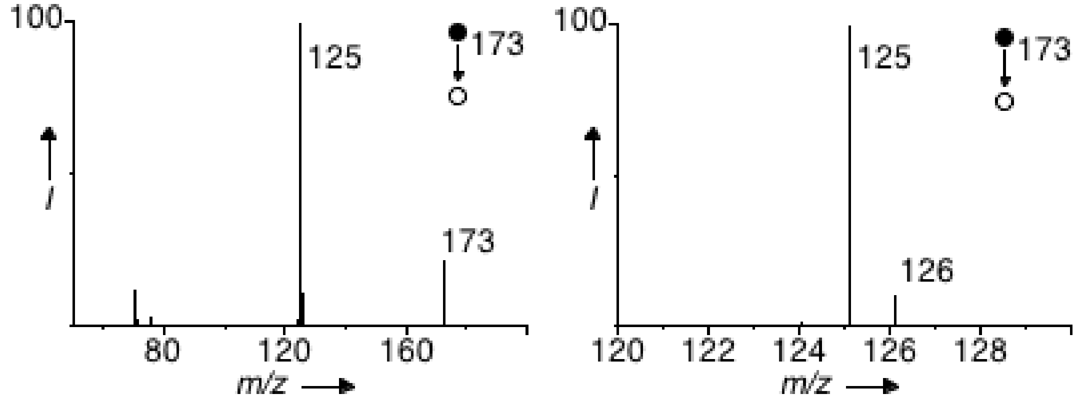


Figure S9. ESI-MS/MS spectrum for the ion with m/z 173, corresponding to **5**-d_3•D^+ and **4**-d_4. On the right, the same spectrum expanded in the m/z range corresponding to the main fragmentation.

(V) Fragmentation Patters.

a) *N-halo-L-prolinamides.*

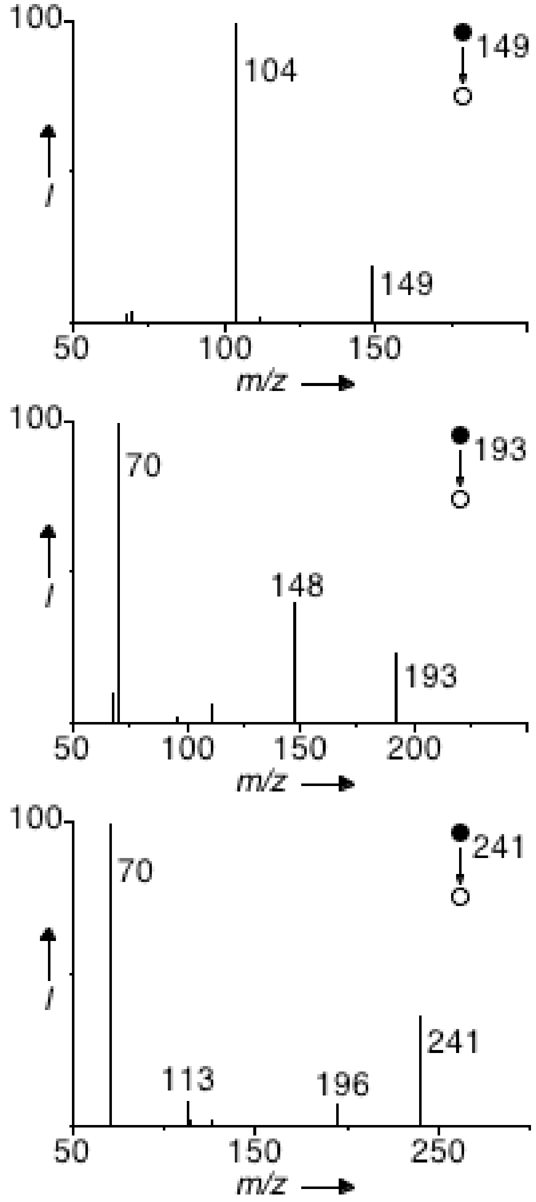


Figure S10. ESI-MS/MS of the reaction of **3** (2.5mM) and NXS in dried CH_2Cl_2 (2.5mM, X=Cl, Br, and I respectively). Notice that N-chloro-L-prolinamide fragments to release $HCONH_2$. However, when the amine hydrogen is replaced by a methyl group (see below), the fragmentation Cl-$CONH_2$ is favored. For NBS and NIS, the main fragmentation is that to release X-$CONH_2$, forming the ion with m/z=70.

b) *N-methyl-N'-halo-L-proline*.

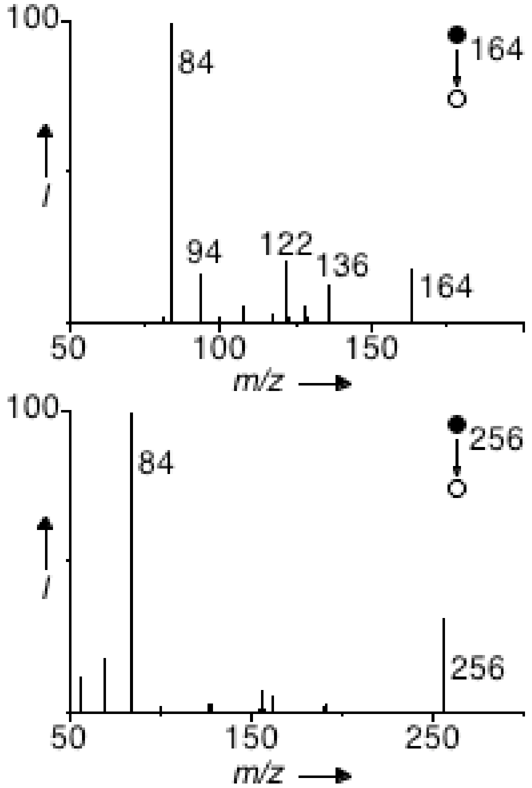


Figure S11. ESI-MS/MS of the reaction of N-methyl-L-proline (2.5mM) and NXS (2.5mM, X=Cl, and I respectively). The halogenation is not favored in any case, but clear spectra could be achieved from signals at noise level in case of NCS and NIS. No clear spectrum could be obtained for NBS. The main fragmentation is that to release X-CONH$_2$, producing the fragment ion with m/z=84.

c) *Synthesized **6**-type compounds (L-prolinamide + haloketones).*

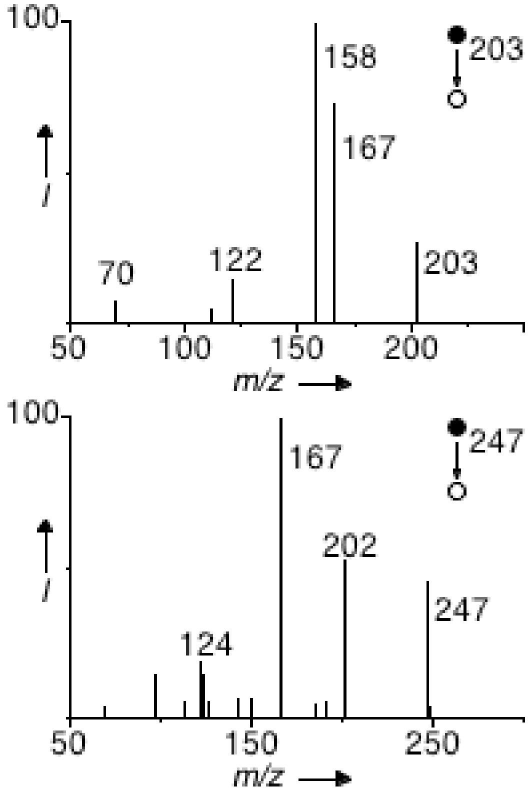


Figure S12. ESI-MS/MS of the reaction in dried CH_2Cl_2 of **3** (2.5mM) and 3-chloro-2-butanone (2.5mM), and the reaction of **3** (2.5mM) and 1-bromo-2-butanone (2.5mM) respectively. Notice that the release of formamide (ion signals at m/z 158 and 202 respectively) and HX (m/z 167 in both cases) are predominant in both cases.