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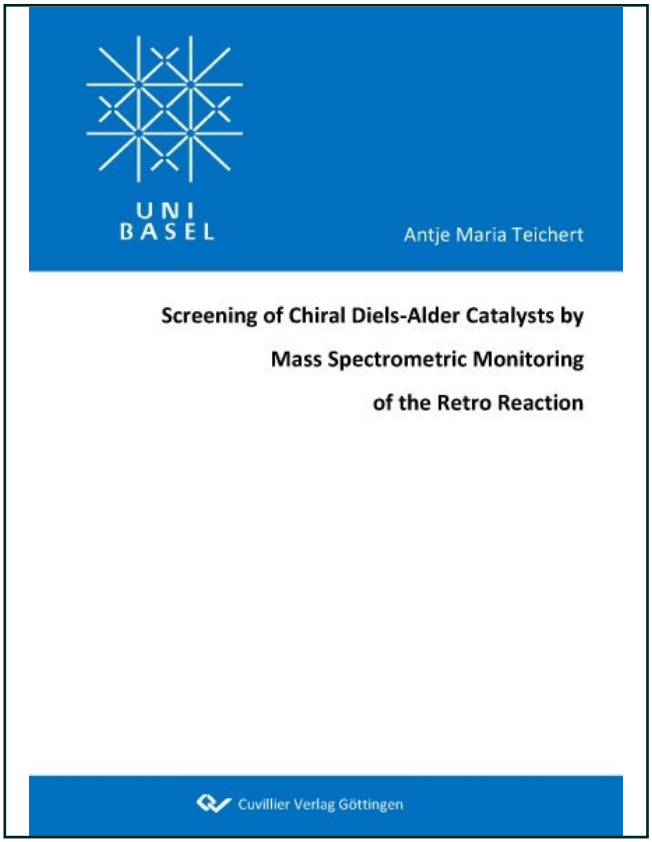
Screening of Chiral Diels-Alder Catalysts by Mass Spectrometric Monitoring of the Retro Reaction



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1 Introduction

The importance of asymmetric catalysis for the synthesis of enantiomerically enriched compounds has been highlighted by awarding SHARPLESS, NOYORI and KNOWLES the 2001 Nobel Prize in Chemistry.[1-3]

The discovery of new, highly efficient chiral catalysts is often costly and time-consuming. In recent years, many high-throughput screening methods have been developed for a variety of catalysed transformations.[4-8] Analysis is usually product-based, which has potential pitfalls as the enantioselectivity of a reaction is often lower than the catalyst's intrinsic selectivity. MARKERT and PFALTZ developed a screening method for determining the intrinsic enantioselectivity of a catalyst using ESI MS. This method was used to rapidly evaluate enantioselective catalysts for the palladium-catalysed kinetic resolution of allylic esters.[9] This work was based on an ESI MS screening method by CHEN, which allowed identification of the most effective catalyst in a palladium-catalysed polymerisation (Section 1.1.5).[10, 11]

1.1 Electrospray Ionisation Mass Spectrometry

1.1.1 Historical Perspective and Development

Electrospray ionisation (ESI) allows the transfer of low-volatile and decomposable organic compounds "gently" from solution into the gas-phase, enabling analysis of large fragile biomolecules and organometallic complexes.[12, 13] ESI is not an ionisation technique in the sense that neutral species become charged. Instead ions from solution are transferred to the gas-phase by nebulisation.[14]

The electrospray process was developed more than 80 years ago for applications ranging from painting to printing. In the late 1960's DOLE realised that electrospraying of a polymer solution into an evaporation chamber resulted in production of intact gaseous macroions.[15] This pioneering work by DOLE led FENN and co-workers, 15 years later, to considerably improve the method by coupling an ESI source with a quadrupole mass analyser.[16, 17] In contrast to classical techniques ions were transferred to the gas-phase without fragmentation and therefore allowed analysis of the intact molecules.[16] Before the implementation of ESI MS biomolecules could not accurately be analysed as their molecular weight exceeded

the mass range of most mass analysers. FENN discovered that under electrospray conditions large, non-volatile biomolecules such as proteins ("molecular elephants", FENN[18]) became multiple charged ions leading to mass-to-charge ratios below $m/z \leq 2000$.[12] Application of a deconvolution algorithm made analysis of molecules with up to 100 000 kDa possible.[18]

FENN was awarded the 2002 Nobel Prize in Chemistry for his contributions along with TANAKA, who introduced MALDI (matrix assisted laser desorption ionisation), another "soft" ionisation technique in mass spectrometry.[18, 19]

ESI MS is not limited to the analysis of large biomolecules. This method can also be used for the analysis of non-covalent and non-volatile organometallic complexes, usually not amenable to standard ionisation techniques.[20-22] Recently, ESI MS has become a powerful tool in probing the reaction mechanism of transition metal- and organocatalysed reactions (see Sections 1.1.3 and 1.1.4). As the ions are transferred directly from solution to the gas-phase, this technique is ideal to monitor short-lived reaction intermediates.

1.1.2 Electrospray Ionisation Process

In ESI MS a dilute solution of an analyte is pumped through a capillary at continuous flow. A high voltage (2-5 kV) is applied to the capillary. The resulting electric field gradient between the capillary and the counter electrode leads to the formation of the so-called "TAYLOR cone"[23] of the emerging liquid. If the imposed field is high enough, the protruding liquid is dispersed in a fine spray of charged droplets towards the counter electrode. An excess of anions or cations, depending on the applied field, accumulates on the surface of the droplets resulting in a conical spray of charged species due to COULOMB repulsion.[24] Evaporation of the solvent molecules by a counter-flow of an inert gas leads to accumulation of charge density in the droplets up to the point where the magnitude of the charge is sufficient to overcome the surface tension holding the droplet together, termed the "RAYLEIGH limit".[25] The droplet then fragments into smaller daughter ions, referred to as "COULOMB explosion" (Figure 1.1).

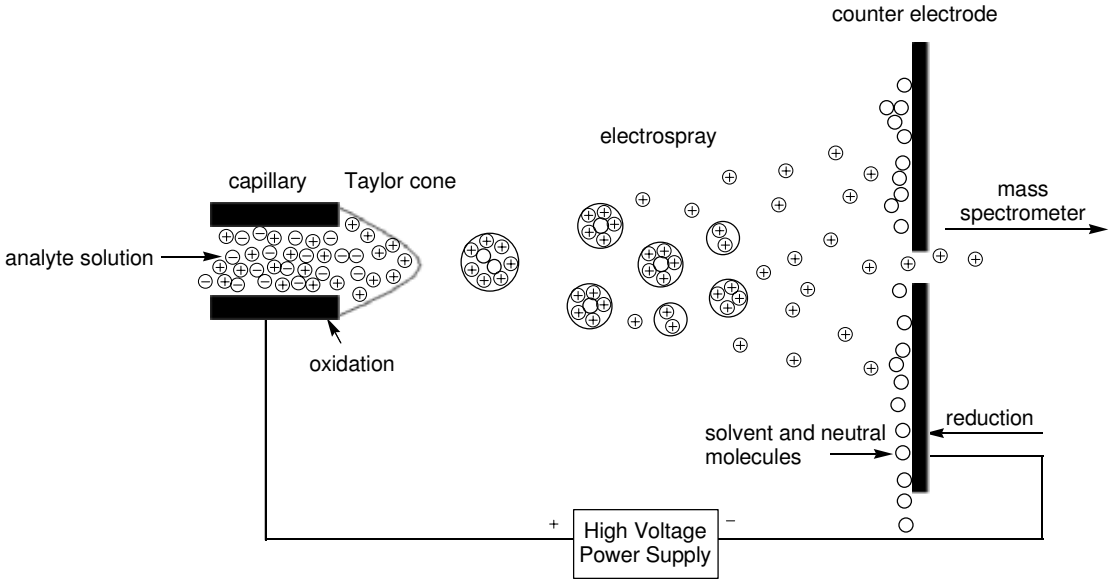


Figure 1.1: *Schematic representation of the electrospray ionisation process.*

Generation of bare, gaseous analyte ions has been proposed to occur by two possible pathways (Figure 1.2): 1) Continuous COULOMB explosions and evaporation of solvent molecules eventually result in the formation of droplets containing only a single ion. This is called the "charged residue model (CRM)" and was first proposed by DOLE.[15] 2) Two meteorologists, IRIBANE and THOMSON, suggested that before the droplets become small enough to contain only one analyte ion, the field strength of the droplet surface becomes strong enough to "evaporate" a surface ion from the droplet into the gas-phase. This is referred to as "ion evaporation model (IEM)".[26] The relative importance of the CRM and IEM remains a topic of discussion as both proposed models have yet to be confirmed by experimentation.

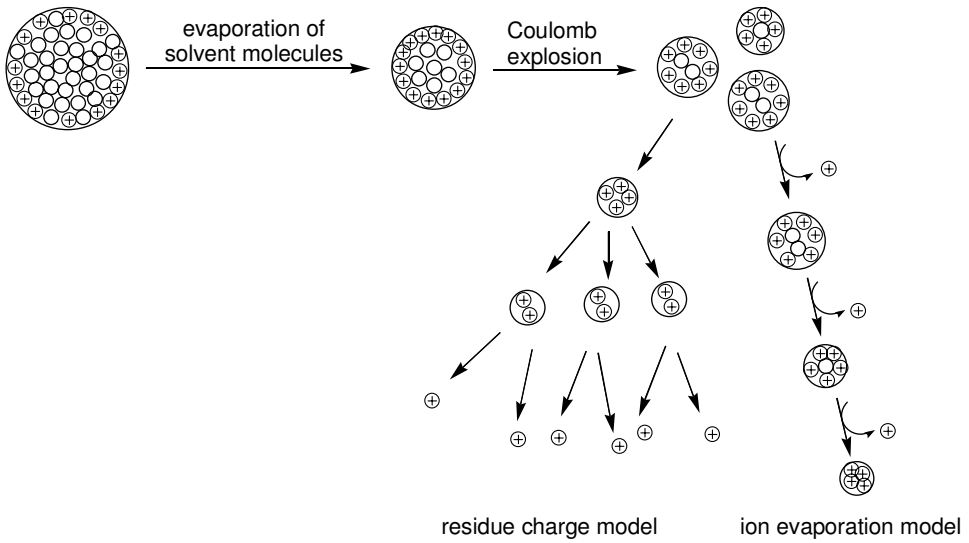


Figure 1.2: *After solvent evaporation Coulomb explosion leads to fragmentation of the droplets. The two proposed models for the transfer of single ions from the liquid to the gas-phase are shown.*

The continuous flow of charged ions from the capillary to the counter electrode leads to an accumulation of ions of the opposite charge, which must be charged balanced for the electrospray process continually to operate. KEBARLE and co-workers have described the ES ion source as "an electrolytic cell of a somewhat special kind".[27, 28] Electrochemical reactions are therefore likely to occur during the electrospray process and can have an influence on the analyte solution. This is of special importance when examining organometallic complexes as the oxidation state of the metals can be affected.[29]

1.1.3 Detection of Organometallic Reaction Intermediates by ESI MS

When using ESI MS the analyte has to be injected into the mass spectrometer as a liquid. This allows direct investigation of reaction products and/or reaction intermediates. To allow detection of intermediates the species must be charged and have a sufficiently long lifetime. The relatively gentle transfer of ions from the liquid to the gas-phase ensures a close relation between the gas-phase ion and solution species.[30]

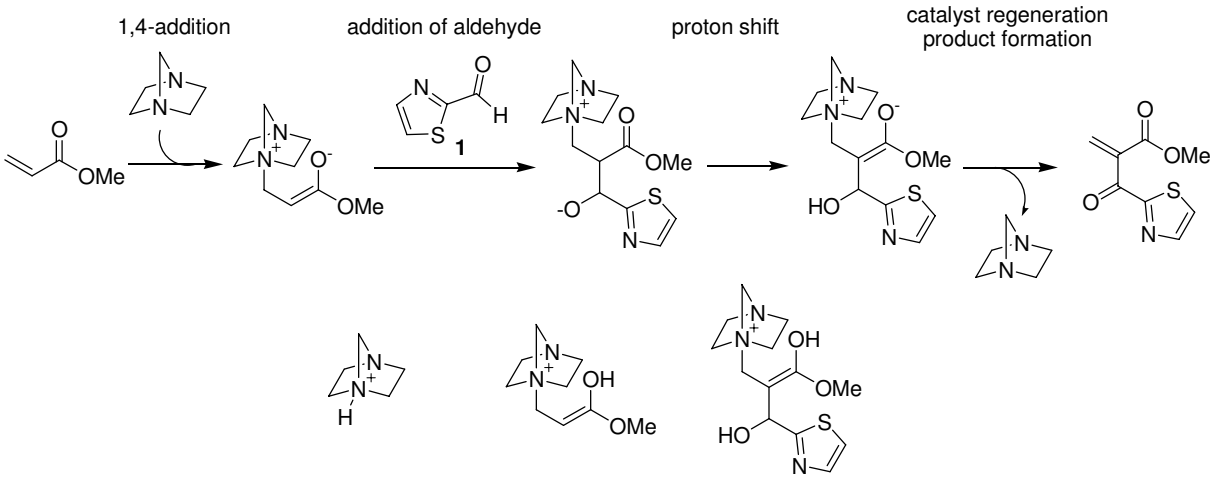
Early ESI MS investigations of ionic reaction intermediates were conducted for phosphine-mediated Wittig, Mitsunobu and Staudinger reactions.[31] Ionic intermediates were detected and used to confirm the proposed mechanisms. The disappearance and appearance of ionic species further allowed the reaction progress to be studied.

As ionic reaction intermediates are often involved in homogeneous transition metal catalysed reactions, ESI MS has become the technique of choice for mechanistic investigations and high-throughput screenings of such reactions.[30] WILSON and WU reported one of the first investigations involving the detection of nickel(I)-derived complexes in Raney-nickel catalysed C-C-coupling reactions.[32] Since then ESI MS has been widely applied in the study of palladium-catalysed transformations such as the Heck reaction, [33] the Suzuki-reaction,[34] the Stille-reaction,[35] oxidative coupling of arene- and arylboronic acids,[36, 37] polymerisation of ethane[10, 11] and the allylic substitution reaction.[9] Furthermore its broad applicability has been demonstrated by investigating different transition metal catalysed processes such as C-H activation reactions with iridium(III)[38, 39] and platinum(II),[40] catalytic hydrogenation reactions with rhodium[41, 42] and ruthenium complexes,[43, 44] olefin metathesis,[45, 46] catalytic oxidative epoxidation,[47, 48] aldehyde olefination with high-valent rhenium compounds,[49] Ziegler-Natta polymerisation using an alkylzirconocene catalyst[50, 51] and the cobalt-mediated Pauson-Khand reaction.[52]

The variety of transition metal complexes and reaction types analysed by ESI MS demonstrates the enormous potential of this fast analytical method. The fact that also catalysed reactions can be successfully studied highlights that even low-concentration species can be selectively monitored by this technique. As CHEN has studied many transition metal catalysed processes with ESI MS and developed more sophisticated instruments, he can certainly be regarded as the pioneer in this area of research.[30]

1.1.4 ESI MS as Tool for Detection of Reaction Intermediates in Organocatalysis

The first study of an organocatalytic reaction by ESI MS was reported by EBERLIN and co-workers.[53] The 1,4-diazabicyclo[2.2.2]octane (DABCO) catalysed Baylis-Hillman reaction was investigated to detect and structurally characterise the reaction intermediates. Although neutral species were expected from the proposed catalytic cycle (Scheme 1.1), these species were assumed to be in equilibrium with their protonated forms in methanolic solution. The reaction was monitored by directly pumping the reaction mixture into the ESI MS source. Reaction intermediates were observed with collision-induced dissociation (CID) measurements, which provided strong evidence for the proposed mechanism.[54, 55]

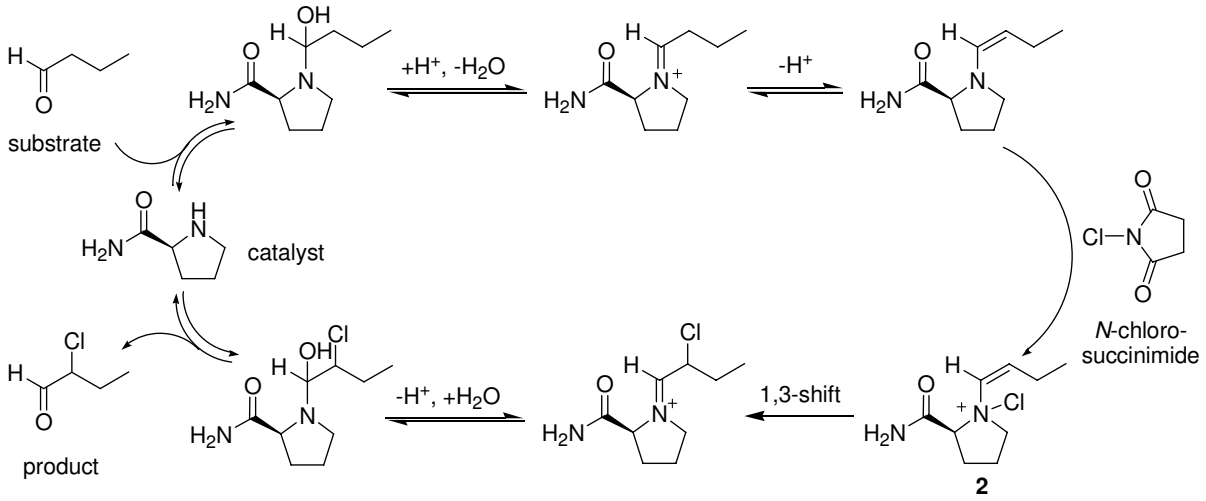


Scheme 1.1: *Catalytic cycle for the Baylis-Hillman reaction using methyl acrylate and aldehyde **1** with DABCO and observed intermediates by ESI MS.*

METZGER and co-workers recently reported an ESI MS study on the proline-catalysed aldol reaction. They characterised all proposed reaction intermediates and also followed the reaction progress over time.[56] A more sophisticated application of the technique is their recently developed "dual ESI MS".[57] By spraying the substrate and reagent solution independently in the reaction chamber, dual ESI MS allows observation of reaction intermediates after a few milliseconds. Using this technique, METZGER and co-workers were

able to clarify whether the organocatalysed α-halogenation of aldehydes proceeded via N-chlorination or direct C-chlorination of the enamine intermediate (Scheme 1.2). After reaction time of milliseconds, fragment ions resulting from CID measurements were unambiguously identified for intermediate **2**, providing evidence for the mechanism to proceed via N-chlorination.

ESI MS has also led to the confirmation of the mechanism in the conjugate *umpolung* reaction.[58]



Scheme 1.2: *Proposed mechanism of the L-prolineamide-catalysed α-chlorination of butanal. By performing CID experiments intermediate* ***2*** *was identified to be relevant in the catalytic cycle.*

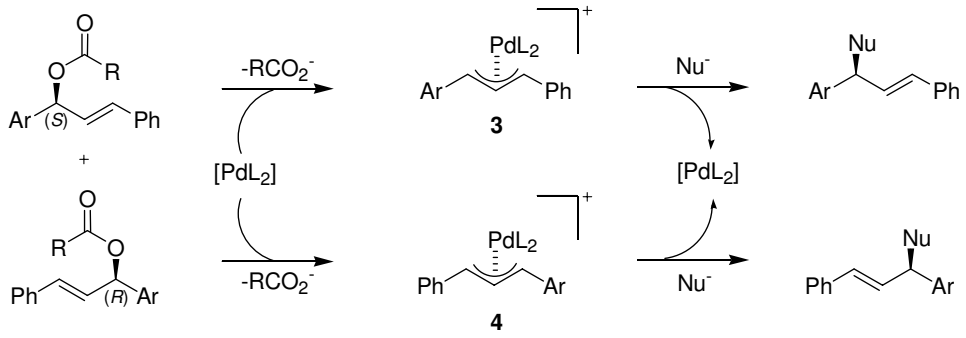
Intermediates in organocatalysis are generally charged (for example iminium ions) or are easily transformed into charged species by protic solvents (such as methanol or water), which makes them amenable to ESI MS detection. In this growing area of research useful methods are needed to aid reaction development and mechanistic understanding. As ESI MS is a very fast and practical technique with instruments available at most research institutes, it can be a very important tool for the investigation of organocatalytic reactions.

1.1.5 ESI MS Screening

HINDERLING and CHEN demonstrated an elegant application of ESI MS for the rapid screening of homogeneous polymerisation catalysts.[10] ESI MS analysis of a mixture of eight simultaneously synthesised Brookhart-type palladium(II)-olefin polymerisation catalysts and ethylene showed a complex mass spectrum. Multiple, overlapping series of oligo- and polymeric ions corresponded to each catalyst with between zero and one hundred ethylene units added. As the most effective catalyst carries the longest polymer chain, ions of the

highest molecular masses were selected and subjected to CID measurments. They underwent β-hydride elimination of the hydrocarbon chain producing ions corresponding to the most effective catalyst.

Based on that work, MARKERT and PFALTZ developed a screening method for the intrinsic enantioselectivity of chiral catalysts.[9] By examining charged catalyst-reactant complexes by ESI MS they were able to rapidly identify highly selective ligands in the palladium-catalysed kinetic resolution of allylic esters. The first step in the catalytic cycle for the kinetic resolution reaction gives palladium-allyl complexes **3** and **4**. As nucleophilic attack of these species is rate limiting, the cationic intermediates **3** and **4** exist in sufficient concentration to be detected by ESI MS (Scheme 1.3).



Scheme 1.3: *Kinetic resolution of allylic esters.*

Intermediates **3** and **4** are enantiomers and therefore cannot be distinguished by mass spectrometry. By introducing mass labels at the *para* aryl-position, which is sufficiently far removed from the reactive centre, the molecules become distinguishable by mass spectrometry (Figure 1.3). If an equimolar mixture of these "quasienantiomers" was treated with an achiral palladium catalyst, the catalytic intermediates **5** and **6** were detected with a 50:50 ratio as expected (Figure 1.3, catalyst **7**). If an equimolar mixture of quasienantiomers was subjected to a chiral catalyst, a higher reactivity for one of the quasienantiomers would be expected. This was the case when performing the experiment with the palladium-catalyst derived from ligand **8** (Figure 1.3). Using these screening conditions the most selective ligand to date was identified, illustrating the potential of this method.