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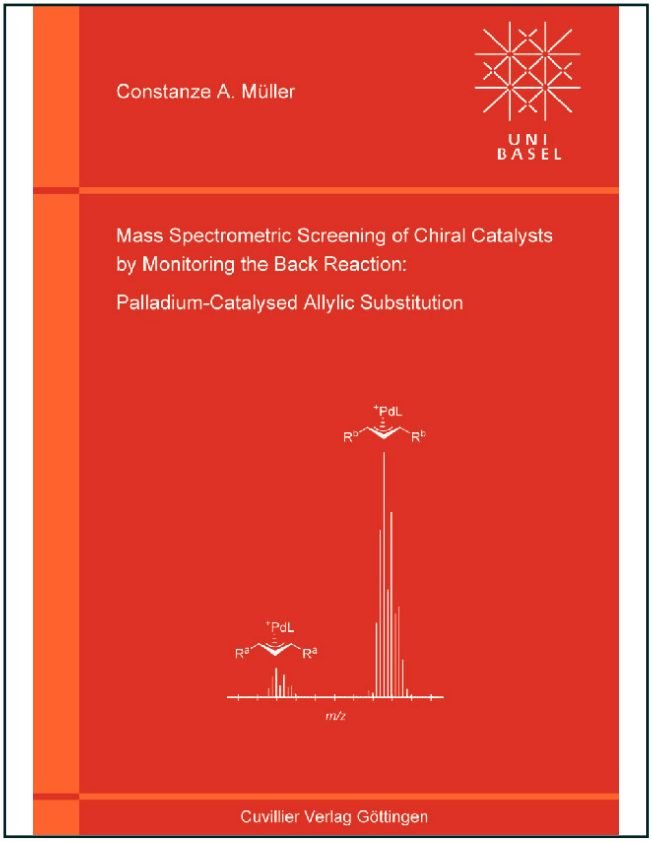
Mass Spectrometric Screening of Chiral Catalysts



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1 Introduction

Asymmetric catalysis is one of the most important methods for the synthesis of enantiomerically enriched compounds.[1-3] The development and fine-tuning of chiral catalysts, which provide efficient asymmetric induction for a specific transformation, is often a labour-intensive, costly, and time-consuming process. Therefore, screening methods that accelerate the identification and optimisation of new ligands are of considerable importance and increasing amount of research has been devoted to the development of high-throughput techniques in the last few years.[4, 5]

The enantioselectivity of a chiral catalyst is usually determined by measuring the enantiomeric excess of the reaction product it produces. However, the value obtained in this fashion does not necessarily reflect the intrinsic enantioselectivity of the respective catalyst. A competing unselective background reaction, catalytically active impurities, or the dissociation of a chiral ligand from the metal centre might lead to low enantiomeric purity of the product, despite the high selectivity of the catalyst itself.

In our group, a method based on quasienantiomeric substrates and electrospray ionisation mass spectrometry (ESI-MS) was developed, allowing for the determination of a catalyst´s intrinsic enantioselectivity.[6] This approach relies on the quantification of charged reaction intermediates and does not require product analysis. As a first application, the kinetic resolution of racemic allyl esters by palladium-catalysed allylic substitution was studied.

1.1 Electrospray Ionisation Mass Spectrometry

Electrospray ionisation (ESI), which originated in the paint and coatings industry, was first applied to mass spectrometry in the late 1960's. Dole realised that electrospraying of a polymer solution into an evaporation chamber resulted in the formation of intact macroions in the gas phase.[7] The method was considerably improved by Fenn, who coupled an electrospray source to a quadrupole mass analyser, thus enabling the mass spectrometric analysis of thermally fragile polar molecules such as proteins and peptides.[8-10] For this contribution Fenn was awarded the Nobel Prize for Chemistry in 2002, along with Tanaka, who introduced matrix assisted laser desorption (MALDI) in mass spectrometry.[11, 12]

Electrospay ionisation (ESI) is a mild technique that allows for transfer of intact molecular ions from a dilute solution directly into the gas phase.[13-15] The charged compounds being analysed can either be transient species, or protonated/deprotonated forms or ion adducts of neutral species.

The spraying process can be described with relative simplicity.[16] The solution containing the analyte is pumped through a charged capillary. The high voltage generates a mist of charged droplets (nebulisation), which pass through a potential and pressure gradient towards the analyser of the mass spectrometer.[17] The solvent in these droplets is evaporated by a warm flow of drying gas, usually nitrogen. As a consequence, the charge density increases to a point at which electrostatic repulsion becomes of the same order of magnitude as the surface tension.[18] At this point the droplet fragments in what is termed a 'Coulomb explosion', producing many daughter droplets, which in turn undergo the same process.[19] Whether or not this iterative process finally produces the bare analyte ions is still a subject of debate. Alternatively ions can 'evaporate' from the droplet's surface.[20] Whatever the exact mechanism might be, electrospray ionisation is a very 'soft' means of ionisation, that causes little or no fragmentation of the analyte. Proteins can be ionised without denaturation and noncovalent receptor-ligand complexes remain intact. The method can even be used for the examination of charged non-covalent and non-volatile organometallic complexes, which are usually not compatible with most ionisation techniques.[21]

1.2 Mass Spectrometric Detection of Reaction Intermediates

Electrospray ionisation as a tool for the analysis of ionic transition metal complexes was first described by Chait for bipyridyl (bpy) and 1,10-phenanthroline complexes of ruthenium in 1990.[22] A dilute solution of $[Ru(II)(bpy)_3]^{2+}$ in acetonitrile was analysed and the signal for the intact cation detected. The collision energy was found to be an adjustable parameter, which controls the extent of desolvation and fragmentation. Under mild conditions, the mass spectrum exhibited additional peaks resulting from the attachment of one to four acetonitrile molecules to the ruthenium centre, whereas at higher energies the doubly charged ion dissociated and signals for the fragments $[Ru(II)(bpy)_2]^{2+}$and $[Ru(II)(bpy)]^{2+}$ were observed. Fragmentation of the complex by collisional activation is a characteristic feature for mass spectra of coordination compounds.[23] Typically, the loss of an intact ligand occurs rather than its fragmentation. This is particularly helpful for the identification and structural assignment of signals in the mass spectra and can be used for the characterisation of organometallic complexes.[21]

During the last two decades there has been considerable growth in the applications of electrospray ionisation mass spectrometry as a tool for mechanistic investigations, especially for homogeneous transition metal-catalysed reactions.[24-26] The great utility of ESI-MS can be

ascribed to its ability to transfer ions of many different types, charges, and broad mass ranges from the reaction solution directly to the gas phase and to characterise these ions quickly, sensitively, and selectively. The gentle ion transfer ensures a close relation between the detected gas-phase ion and the actual species in solution.[24] The opportunity to directly analyse dilute solutions is a major advantage, as catalytically active species often exist only under these conditions and can not be isolated as pure compounds. The optimal concentration range (0.001-10 mM) for ESI-MS corresponds to typical catalyst concentrations of many reactions. The ability of ESI-MS to selectively 'fish' for ionic species[27] allows to analyse the course of various transformations by interception, characterisation, and reactivity investigations of charged intermediates.

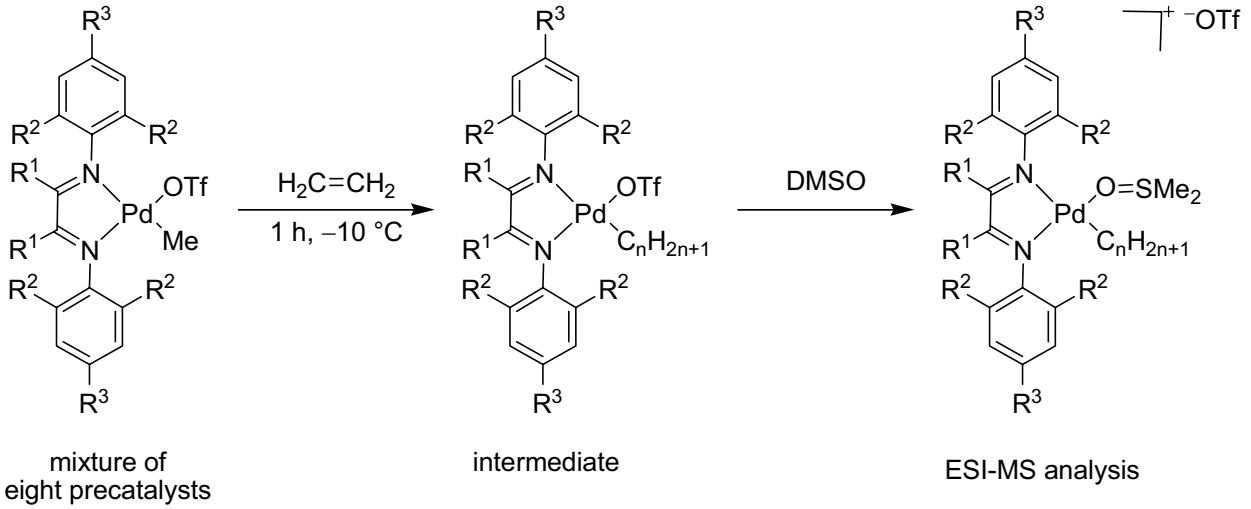
Pioneering work in this field was accomplished by Chen, who also advanced ESI-MS as a tool for the mechanistic investigation of transition metal-catalysed reactions by the development of more sophisticated instruments. The interests of Chen's group have included catalytic hydrogenations with rhodium,[28] iridium,[29] and ruthenium complexes,[30, 31] C-H activation reactions with iridium(III),[32, 33] and platinum(II),[34-36] olefin metatheses,[37-41] Ziegler-Natta polymerisations using zirconocene catalysts,[42, 43] the olefination of aldehydes with high-valent rhenium compounds,[44] and the palladium-catalysed polymerisation of ethene.[45, 46]

Furthermore, ESI-MS has been applied by other groups to study additional palladium-catalysed transformations such as Heck,[47] Suzuki,[48, 49] and Stille reactions,[50] the oxidative homocoupling of arylboronic acids,[51] and allylic substitution reactions.[52, 53] Its usefulness for studying reactions involving other metal ions has been demonstrated for nickel-catalysed C-C couplings,[54] catalytic epoxidations with oxomanganese(V) complexes,[55, 56] iridium-catalysed hydrosilylations of terminal alkynes,[57] and cobalt-mediated Pauson-Khand reactions.[58]

Along with a variety of transition metal-catalysed reactions, ESI-MS has become a major tool for the detection of reaction intermediates in organocatalytic transformations. These species are mostly either charged (e.g. iminium ions) or can be easily protonated by protic solvents. The first study in this field was reported by Eberlin, who investigated the Baylis-Hillman reaction catalysed by 1,4-diazabicyclo[2,2,2]octane (DABCO).[59] More recently, the analysis of direct Mannich-type α-methylenation of ketoesters was described.[60] Metzger used ESI-MS as an analytical tool to study the respective reaction mechanisms for electron transfer-initiated Diels-Alder reactions,[61] proline-catalysed aldol reactions,[62] and the direct organocatalytic α-halogenation of aldehydes.[63]

The variety of transformations analysed by ESI-MS to date demonstrates the enormous potential of this method for mechanistic studies. Beyond this, several applications in reactivity screenings for the discovery and development of catalysts were described.[24]

An elegant evaluation of different Brookhard-type catalysts was reported by Chen.[45] The polymerisation of ethene was carried out in the presence of a simultaneously synthesised mixture of eight different precatalysts.



Scheme 1. Polymerisation of ethene using eight different Brookhard-type catalysts in one pot.

The ESI-MS analysis of the reaction mixture after the addition of dimethylsulfoxide provided a complex spectrum. Several overlapping series of oligo- and polymeric ions corresponded to each catalyst with zero to hundred attached ethylene units. The most efficient catalyst, carrying the longest polymer chain, was identified by a collision induced dissociation (CID) experiment. A series of intermediates with $m/z > 2200$ was filtered out and fragmented by xenon collision. The β-hydride elimination of the hydrocarbon chain, induced in this manner, generated a palladium hydride, which allowed for identification of the most effective catalyst.

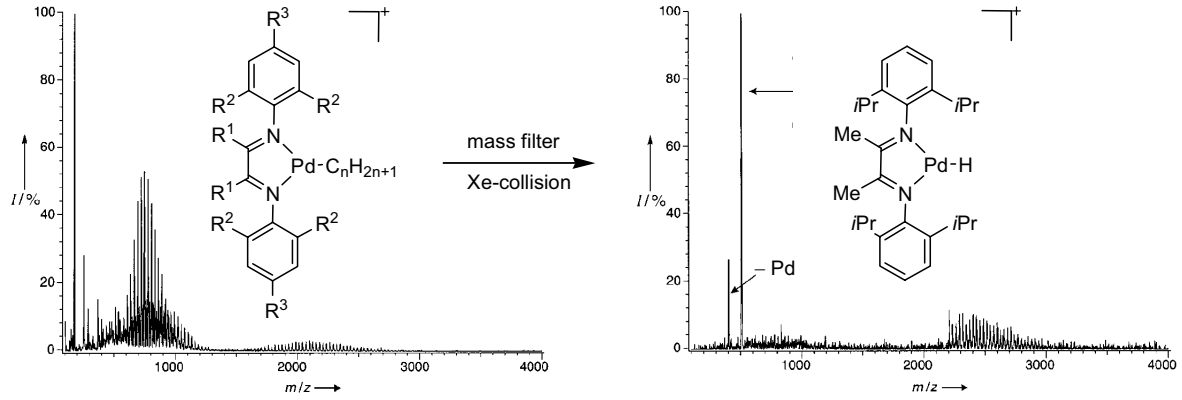


Figure 1. Mass spectrometric screening for reactivity.

1.3 Quasienantiomers in Mass Spectrometry

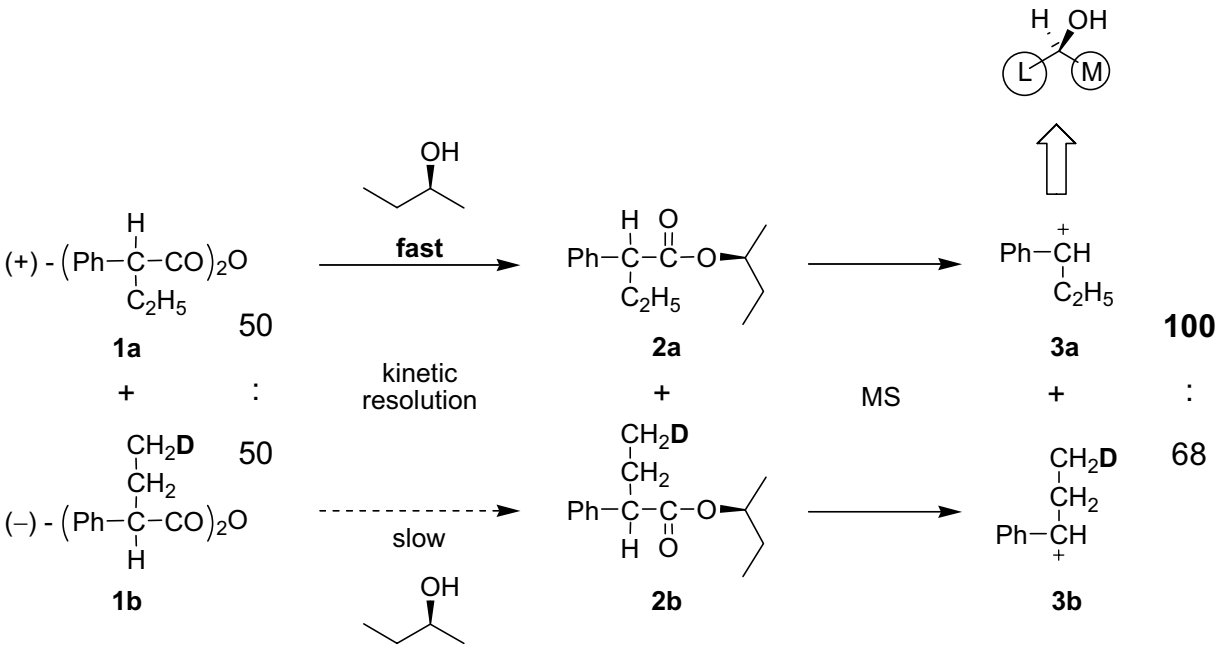
Mass spectrometry is an attractive analytical method for high-throughput applications due to its wide scope (many types of molecules can be detected), sensitivity, tolerance of impurities (peaks other than the masses of interest can be ignored), and speed. However no stereo information is provided by this technique, because enantio- or diastereomeric compounds can not be distinguished as they have the same mass.

In the last two decades several methods for distinction of stereoisomers by mass spectrometry have been developed,[64] including the kinetic method based on the dissociation of cluster ions,[65-67] the formation of diastereomeric host guest adducts, [68-71] and the collision-induced dissociation (CID) of diastereomeric adducts of the analyte and a chiral reference in a MS/MS experiment.[72]

An elegant method, introduced by Horeau in 1990, is based on the use of mass labels to determine the absolute configuration of secondary alcohols by mass spectrometry.[73]

An equimolar mixture of chiral anhydrides **1a** and **1b** was used for the acylation of an enantiomerically pure secondary alcohol of unknown configuration (Scheme 2). The transformation proceeds by kinetic resolution to give the diastereoisomeric esters **2a** and **2b**. The anhydrides **1a** and **1b** differed not only in their absolute configuration but also in mass. By the introduction of a deuterium label, the resulting esters **2a** and **2b** could be distinguished through mass spectrometry. After the reaction mixture had been subjected to electron impact ionisation spectrometry, the relative peak intensities of species **3a** and **3b**, formed by

fragmentation, were compared. Based on the more abundant species, the absolute configuration could be unambiguously assigned.



Scheme 2. Assignment of the absolute configuration of secondary alcohols according to Horeau.

An extension of this methodology to determine the enantiomeric excess of secondary alcohols was described by Finn.[74] The approach uses chiral mass-labelled *N*-acylprolines as the acylating agents, which differ in a substituent remote to the stereogenic centre. The validation of this so-called 'mass spectrometry enantiomeric excess determination' (MSEED) analytical method was performed by screening a family of chiral phosphite P,N-ligands for the rhodium-catalysed asymmetric hydrosilylations of ketones.[75] The catalysts were tested in the reduction of several substrates (Scheme 3). The obtained silyl ethers **5** were reacted with mass-labelled acylprolines **6a** and **6b** to give a mixture of diastereomeric esters **7a** and **7b**, which could then be distinguished by mass spectrometry. Based on the ratio of these derivatives the enantiomeric excesses of the hydrosilylation products were estimated. For comparison aliquots of the silyl ethers **5** were hydrolysed to the corresponding alcohols **8**, which were then analysed by HPLC on a chiral column. The values obtained from both methods were quite similar (within ± 10% *ee* for all examples). Phosphite **9** was identified as the most selective ligand in this screening with enantioselectivities of up to 94%.