Chimia 57 (2003) 354–357
© Schweizerische Chemische Gesellschaft
ISSN 0009–4293

Thales Technologies AG

www.thalestech.com

Research Services for the Chemical Industries. How to Find the Needle in the Haystack and How to Find it FAST...

Daniel Wehrli* and Peter Chen

Abstract: Thales Technologies AG was founded as an ETH spinoff in 1999 and is situated at the Technopark in Zürich. The company supports the chemical industry with catalyst research, discovery, and development. Its patented and unique methodology allows the high-throughput screening of pooled libraries of highly sensitive organometallic catalysts.

Keywords: Combinatorial chemistry · Electrospray ionization · High-throughput-screening · Mass spectrometry · Organometallic catalysis · Thales Technologies AG

Introduction

More than 90% of chemicals produced today could not be manufactured without catalysts. There is a strong economic motivation for industry to develop better catalysts since faster, more selective reactions usually equate with more profit and in some cases new products would not even be possible without new catalysts. This is particular true in the polymer industry.

Better understanding of reaction mechanisms is leading to more advanced catalysts. In the past, trial and error has been the method to develop new catalysts. Even though catalyst design now starts at the computer, trial and error is still applied in the lab, albeit on a more select array of possibilities. Speeding up this discovery process leads to a faster time to market (Fig. 1). There are several approaches to cut resources spent on catalyst discovery. Whereas many depend on faster synthesis through robotics, the approach of Thales Technologies AG is unique.

Thales Technologies AG was founded as a spinoff company of the ETH Zürich in 1999 to bring a novel technology to market which was developed in Prof. Chen's group [1]. This new method allows the detection of substrate–catalyst complexes in the gas-phase by electrospray ionization mass spectrometry. A schematic representation of the tandem quadrupole electrospray MS is shown in Fig. 2. The ions are introduced into the MS *via* an ESI or APCI-source and can be selected (isolated) by the first quadrupole. MS-MS experiments on isolated ions can be performed in the collision cell. The second quadrupole serves to select the reaction products. Finally, the ions are detected with the assistance of an electron multiplier. Moreover, by introducing appropriate reactive collision gases in either the reaction cell or collision cell (or both), ion–molecule reactions with isolated catalytically active ions can be observed. As a consequence of the ability to isolate select ions with the MS, it is not necessary to have spatially separated libraries. In contrast to other library-screening methods, this solution does not rely on beats, wells or other markers, it is possible to utilize real combinatorial libraries. By avoiding cumbersome synthesis and especially isolation and purification steps of sensitive organometallic materials, the time used for the discovery, development and optimization of new catalysts can be reduced [2].

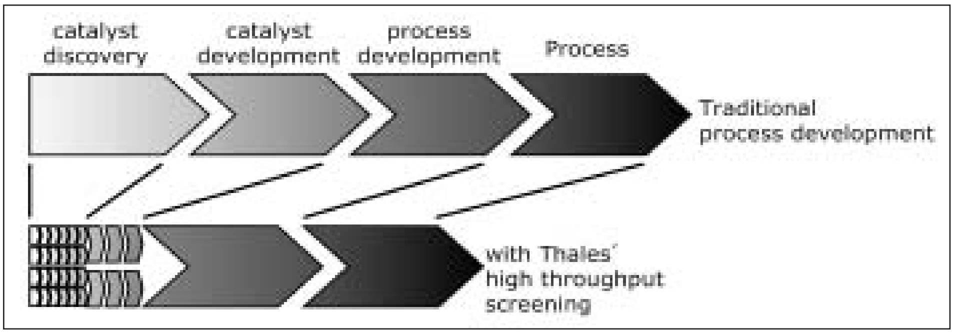


Fig. 1. Shorter time-to-market with Thales' screening method

---

*Correspondence: Dr. D. Wehrli
Thales Technologies AG
Technoparkstrasse 1
CH–8005 Zürich
Tel.: +41 1 445 12 16
Fax: +41 1 445 12 17
E-Mail: info@thalestech.com
www.thalestech.com

In support of the above statements, several examples are given in the following text. The first one illustrates the ability to screen catalyst libraries of organometallic species on the example of Brookhart's palladium system [3]. Thales has accumulated considerable experience screening catalyst libraries. Because of confidentiality agreements, the Brookhart system is the only 'publishable' example in this field to date. The next example of Thales' work demonstrates the wide scope of organometallic problems that can be investigated using this method. A longstanding problem of single site metallocene – MAO polymerization systems is that the number of 'active' metal centers is not known, but it is assumed that even in the presence of large excesses of MAO, only few of them are activated. Thales has introduced a new method to quantify the activation using ESI-MS. The last example shows the utility of the APCI-MS method in organometallic catalysis.

Screening Combinatorial Catalyst Libraries

To demonstrate the superiority of the Thales approach, a pooled library consisting of eight bis-imino palladium compounds was activated with AgOTf as shown in Scheme 1 and pressurized with ethylene (4 bar). The reaction was allowed to proceed for 1 h and was then quenched by the addition of DMSO. This mixture was subsequently submitted to ESI-MS analysis (Fig. 3). The spectrum shows the presence of several polymer-chain distributions. In all cases, the polymer chains are still attached to the palladium catalysts as can be shown by the isotopic distribution pattern of every signal. This is a prerequisite to screen pooled libraries, since this allows the clear assignment of a product to a particular catalyst. In this case, several products are assigned to a particular catalyst. For example, CID-analysis of all the ions with m/z > 2000 reveals that all these compounds derive from a single catalyst (Fig. 4). Moreover, based on the reaction mechanism introduced in Scheme 1, the distribution of the polymer chains allows the calculation of reaction rate constants for the initiation, the chain propagation and the chain transfer steps. This, in turn, allows the calculation of the M_w and M_w/M_n of the polymer formed by this catalyst *without* ever making any of the polymer. CID-analysis of the lower mass distributions present in the spectrum shown in Fig. 5 (m/z = 400–1300) reveals that several catalysts produce polymers in that mass range. The spectrum in Fig. 5 shows signals for three different pal-

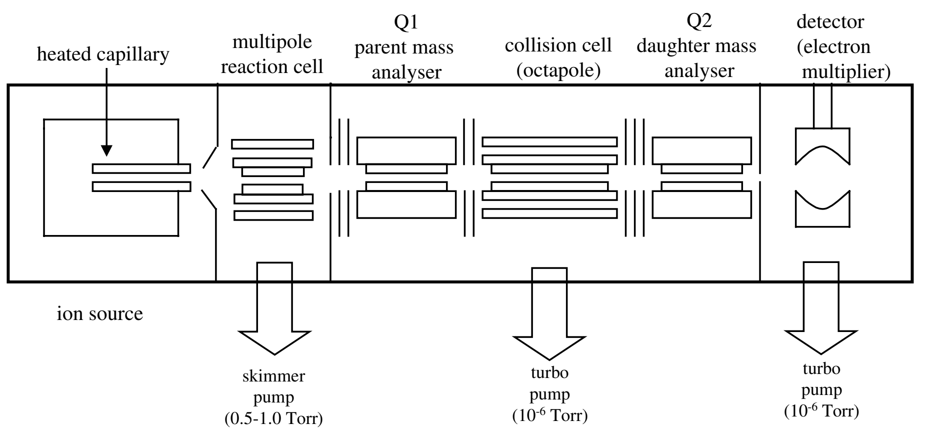
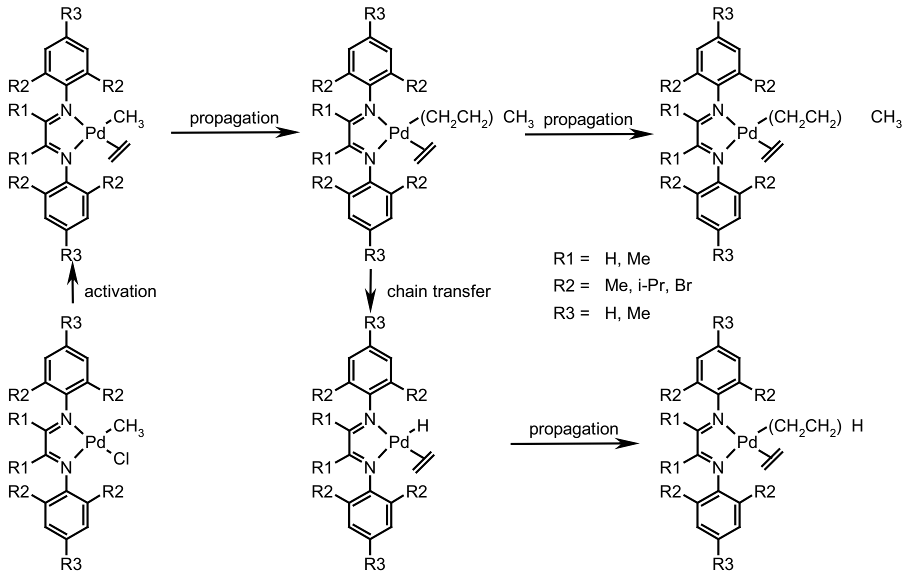


Fig. 2. Schematic description of a tandem-quadrupole MS



Scheme 1. Proposed reaction mechanism for a polymerization reaction

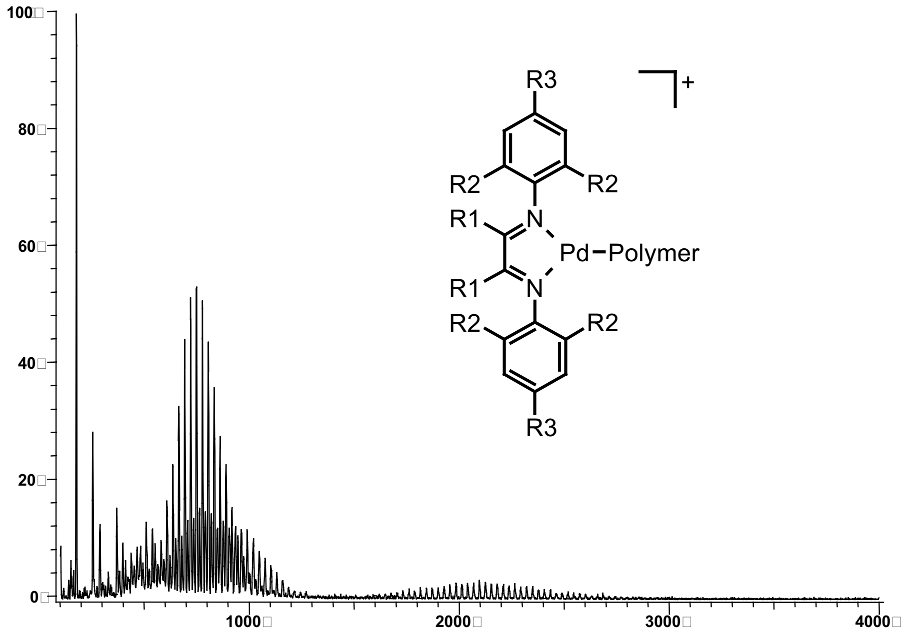


Fig. 3. ESI-MS spectrum after polymerization with a pooled catalyst library

ladium hydride species. The other signals present in this spectrum are due to the ligands (loss of Pd) and the fragmentation of the ligand (loss of Br). Performing parent ion scans on these fragment ions allows the assignment of the polymer distribution for every single catalyst. This is demonstrated on the example shown in Fig. 6, where the second quadrupole is locked on the signal at m/z = 399. The resulting distribution is due to all signals that form the fragment ion at m/z = 399 upon CID. Thus it is possible to determine the kinetic data and predict the polymer properties of every active catalyst in the pooled library present. Not only does this method allow the fast screening of pooled catalyst libraries, it can also provide detailed, quantitative information about the properties of these catalysts.

Quantification of Active Metallocene Species

A different area of interest at Thales is described here. Metallocene single site polymerization catalysts are activated most efficiently with aluminoxanes, such as MAO. Unfortunately, neither the exact structure nor its mode of action are known. Furthermore, up to 2000 equiv. of MAO have to be employed to obtain maximum activation of the catalyst. Our approach to quantify the active polymerization species *vs.* equiv. of MAO employed is outlined in Scheme 2. Upon activation with MAO, the metallocene catalyst presumably forms the methylated Zr-species shown. This is the initial active polymerization catalyst. To quantify the amount of active metallocene catalyst, the number of transferred methyl groups to an appropriate quencher was measured and compared to the amount of unreacted quencher left. Due to the high dynamic ratio of the MS and because of the special properties required of the quencher, ESI-MS is best suited to quantify this mixture.

This quencher must have following properties:

- It must contain a C–C double bond that can coordinate to the free coordination site of the Zr-metal center.
- After coordination, insertion into the Zr–Me bond must take place.
- The quencher must not polymerize (ideally, it contains a group that blocks the free coordination site after insertion).
- It must not react with MAO.

Fig. 7 shows our results with three different metallocene catalysts. It can clearly be seen that in all cases, only a small fraction of the metallocene is actually activated.

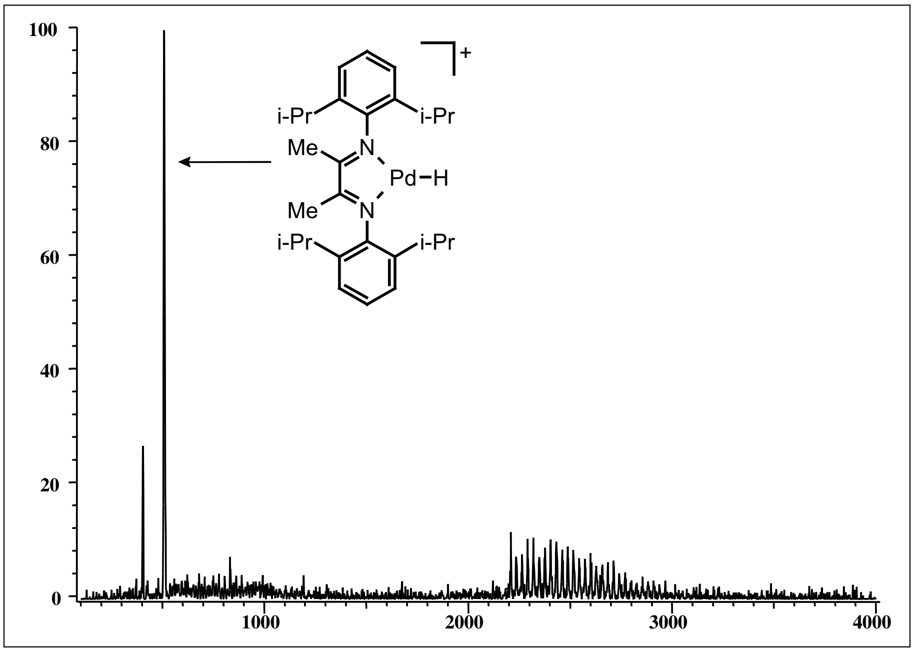


Fig. 4. CID experiment with signals at m/z > 2000

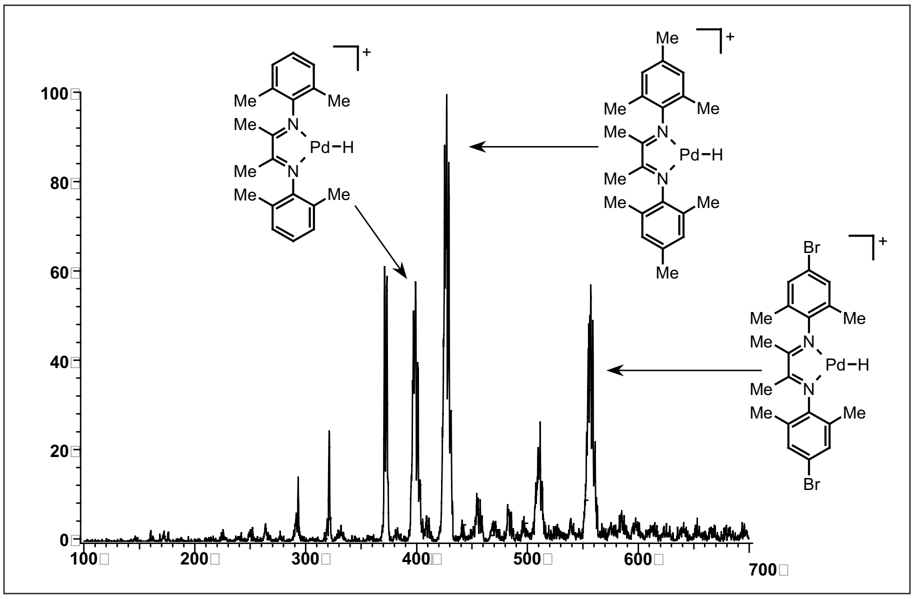


Fig. 5. CID experiments with the signals at m/z = 400–1300

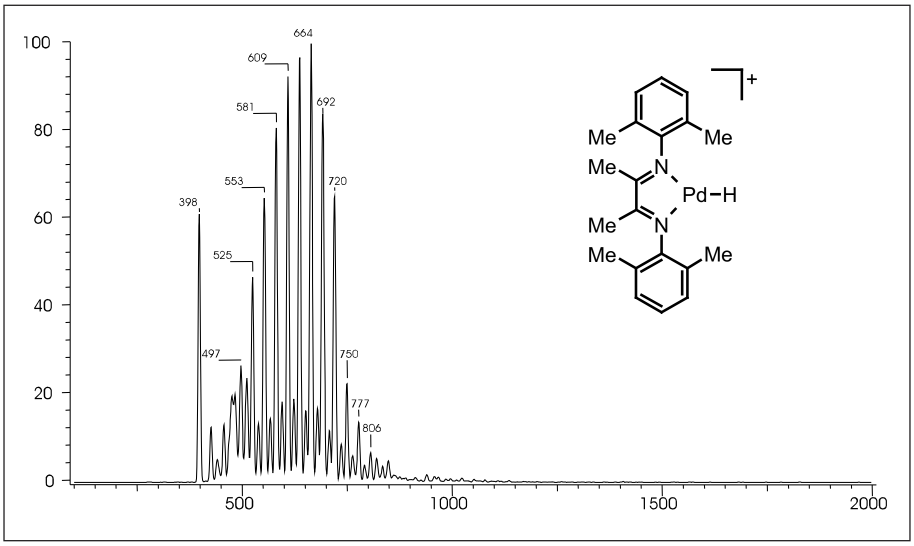


Fig. 6. Parent ion scan of the signal at m/z = 399

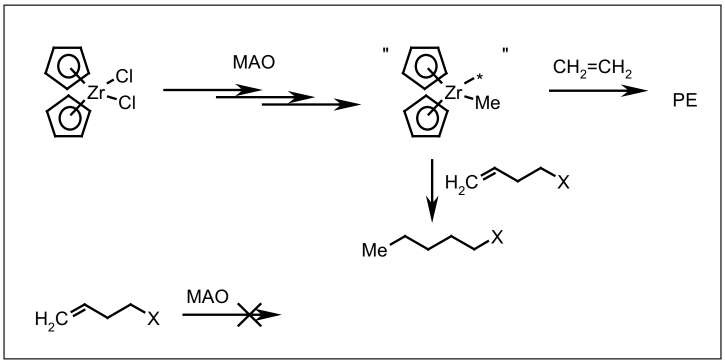
Detection of Highly Air-, Moisture-, and Lewis Base-Sensitive Organometallic Compounds

The mild electrospray ionization technique has the disadvantage that relatively polar solvents are required to generate the necessary spray. Many organometallic complexes are very sensitive to polar solvents and decay before analysis is possible. This effect is observed even more often when reactive intermediates are observed. Their reactive sites are often saturated with solvent molecules. To avoid this effect, Thales utilizes the less widely known atmospheric pressure chemical ionization technique (APCI) [4]. This method generates the spray by an ultrasonic nebulizer. The droplets are subsequently charged by a corona discharge. Although the sensitivity of this technique is lower than ESI, it allows the formation and detection of highly sensitive organometallic ions. This is exemplified by the detection of the activated zirconocene species depicted in Fig. 8. In this case, the highly air-, moisture-, and Lewis base-sensitive polymerization intermediate formed from zirconocene dichloride and MAO could be sprayed directly from the toluene solution in which its formation had taken place. This ion can be isolated by a quadrupole and its reactivity in the gas phase can be studied. This method is also applicable to other sensitive metal complexes, such as neodymium complexes.

Conclusions

Thales Technologies AG supports the chemical industry with a novel and unique tool for catalyst discovery and development based on ESI-MS. The method can be used to perform high-throughput screening of pooled libraries of organometallic compounds. Furthermore, quantification of active catalyst species as well as the detection of highly sensitive organometallic ions is possible.

Received: April 23, 2003



Scheme 2. Activation of single site metallocene catalysts with MAO

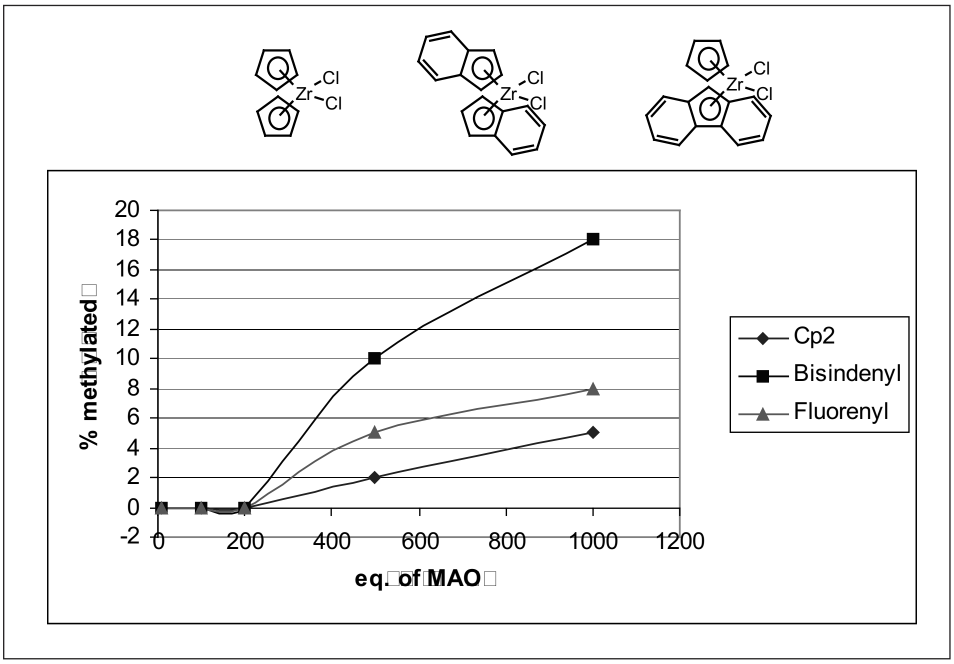


Fig. 7. Quantification of active polymerization catalyst

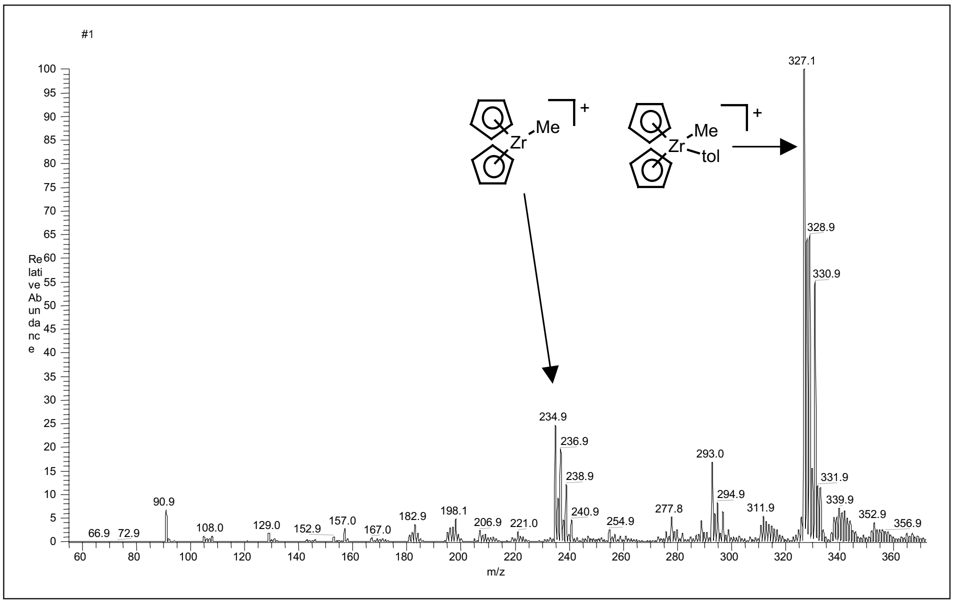


Fig. 8. Activated Zr-species sprayed using the APCI-source

---

[1] *E.g.* a) D. Feichtinger, D.A. Plattner, P. Chen, *J. Am. Chem. Soc.* **1998**, *120*, 7125; b) C. Hinderling, C. Adlhart, P. Chen, *Angew. Chem., Int. Ed.* **1998**, *37*, 2685; c) Y.-M. Kim, P. Chen, *Int. J. Mass Spectrometry* **1999**, *185/186/187*, 871; d) C. Hinderling, P. Chen, *Angew. Chem., Int. Ed.* **1999**, *38*, 2253; e) C. Hinderling, C. Adlhart, P. Chen, *Chimia* **2000**, *54*, 232.

[2] P. Chen, *Angew. Chem.* **2003**, *115*, (in press).

[3] a) a) L.K. Johnson, C.M. Killlian, M. Brookhart, *J. Am. Chem. Soc.* **1995**, *117*, 6414; b) L.K. Johnson, S. Mecking, M. Brookhart, *J. Am. Chem. Soc.* **1996**, *118*, 267; c) C.M. Killlian, D.J. Tempel, L.K. Johnson, M. Brookhart, *J. Am. Chem. Soc.* **1996**, *118*, 11664; d) B.L. Small, M. Brookhart, A.M.A. Bennet, *J. Am. Chem. Soc.* **1998**, *120*, 4049; e) B.L. Small, M. Brookhart, *Organometallics* **1999**, *32*, 2120.

[4] A.P. Bruins, in ‘Electrospray Ionization Mass Spectrometry’, Ed. R.B. Cole, John Wiley & Sons, Inc., New York, **1997**, Chapter 3, 107–136.