Chapter 4 Tandem mass spectrometry of silver-adducted ferrocenyl catalyst complexes.
Abstract

Ferrocene is a popular template in material science due to its exceptional characteristics that offer the ability to optimize the selectivity and activity of catalysts by the addition of carefully selected substituents. In combinatorial catalyst development, the high susceptibility to electrophilic substitution reactions offers the opportunity for the rapid introduction of molecular diversity. Mass spectrometry (MS)-based continuous-flow systems can be applied to rapidly evaluate catalyst performance as well as to (provisionally) identify the introduced catalyst complexes. Herein, we describe the fragmentation characteristics of the [ferrocenyl bidentate + Ag]^+ catalyst complexes in dedicated (high-resolution) MSn experiments. The investigation of the fragmentation patterns of a selected number of catalyst classes is accompanied with a density functional theory investigation of fragmentation intermediates in order to assess the viability of a selected fragmentation mechanism.
Introduction

Since the discovery of ferrocene,[1-3] there has been an increasing interest in this exceptional iron-containing sandwich structure and its derivatives. The unique combination of properties of ferrocene include the special geometry, the ability to create structurally diverse derivatives by the high susceptibility to electrophilic substitution reactions, the possibility to adjust chemical and electronic properties by altering the redox state, the high tolerance to moisture and oxygen, the high (thermo) stability in different solvents and the low price of the ferrocene backbone.[4] In addition, ferrocene compounds have proven to be exceptionally useful in asymmetric catalysis.[5] Our interest in ferrocene derivatives, and especially silver-coordinated bis(diphenylphosphine)-ferrocene complexes, stems from their potential as homogeneous catalysts in organic synthesis. The amenability for substitution of the ferrocene backbone makes this compound class an ideal candidate to be synthesized with combinatorial chemistry approaches where different substituents are used to alter the associated selectivity. Recently, we reported a mass spectrometry (MS)-based continuous-flow reaction detection system that enables rapid evaluation of homogeneous catalyst performance in synthetic conversions.[6,7] Such a system enables the rapid activity assessment of Lewis-acid catalysts[6] in combination with (combinatorial produced) catalyst complexes, such as ferrocenyl bidentates in multi-component reactions.[7] In that case, the MS can be used to combine the sensitive detection of the formed product with the (provisional) identification of introduced catalyst complexes. MS, and especially electrospray ionization (ESI)-MS, is extensively used for the molecular mass determination and the study of solution-phase chemical properties of various ferrocenyl compounds.[8-10] In the current study, the neutral ferrocenes are complexed with Ag⁺ to form [ferrocenyl bidentate + Ag⁺] adduct ions. Over the years, Ag⁺ adduct formation in ESI-MS, also called coordination electrospray (or ionspray), has been reported for a
variety of compounds, not readily amenable to regular ESI-MS.\cite{11} Coordination ESI-MS with Ag\(^+\) has been used in the analysis of, among others, amines,\cite{12,13} and (unsaturated) lipids.\cite{14} Fragmentation of silver-adducted lipids in tandem mass spectrometry (MS/MS) resulted in losses of both RCOOH (fatty acid) and RCOOAg (fatty acid, silver salt). In the fragmentation of silver-adducted alkyl amines, competition was found between the loss of H\(_2\) and of silver hydride, AgH\(_2\).\cite{12,13} Recently, it was demonstrated that this loss of AgH involves a 1,2-elimination leading to the formation of a stable immonium fragment ion.\cite{15} Here, we study the fragmentation of [ferrocenyl bidentate + Ag\(^+\)]\(^+\) catalyst complexes using MS\(^n\) experiments with high-resolution quadrupole-time-of-flight (Q-TOF) and ion-trap-time-of-flight (IT-TOF) hybrid instruments. The investigation is accompanied with a density functional theory (DFT) investigation of exemplary fragmentation intermediates in order to assess the feasibility of proposed fragmentation mechanisms. The investigated ferrocene library consisted of eight in-house synthesized ligands\cite{16} and various Solvias ligands from the Josiphos, Taniaphos and Walphos compound classes.\cite{17}
Experimental

Chemicals

The silver in the catalyst complexes was obtained by dissolving 200 μM silver trifluoromethanesulfonate (silver triflate, AgOTf, >98%) from Fluka in methanol (MeOH, absolute ULC/MS grade) that was purchased from Biosolve (Valkenswaard, The Netherlands). The ferrocene ligand library comprises five compound classes. Class-1 (Scheme 4.1: 1–6) and Class-2 (Scheme 4.1: 7 and 8) ferrocene ligands were synthesized in-house in six steps starting from ferrocene carboxaldehyde, according to a procedure described by Hayashi and Yamazaki.\[16\] This synthesis procedure together with NMR and high-resolution MS-based confirmation is previously described.\[7\] In addition, ferrocene ligands from Taniaphos (Class-3, Scheme 4.1: 9 and 10), Josiphos (Class-4, Scheme 4.1: 11) and Walphos (Class-5, Scheme 4.1: 12) compound classes were studied. These ferrocene ligands were purchased from Sigma–Aldrich. The employed catalyst complex solutions were prepared by mixing 200 μM AgOTf with 200 μM of the ferrocene ligand (in MeOH) (1:1, v/v) yielding catalyst complex solutions of 100 μM.

High-resolution MS\(^2\) systems

For the detailed fragmentation study of silver-adducted catalyst complexes, an Agilent Technologies Model 1100 (Walbronn, Germany) LC system and autosampler was utilized to inject the catalyst complexes in 100% MeOH (flow rate of 200 μl/min). For the investigation of catalyst complex fragmentation, MS and MS\(^2\) experiments were conducted by utilizing a Bruker Daltonics MicrOTOF-Q mass spectrometer (Bremen, Germany), equipped with an ESI source operated in the positive ion mode. The MicrOTOF-Q instrument was operated...
Scheme 4.1 The ferrocenyl bidentate library of compounds that coordinate with silver to form the applied catalyst complexes. In addition to the structures, the molecular formulae and the \( m/z \) of the silver-coordinated complex ions are presented. Class I and II are in-house produced ligands while Class III (Taniaphos), Class IV (Josiphos) and Class V (Walphos) are commercially available ligands.
with a probe voltage of 4.5 kV, a nebulizer flow of 1.6 bar and a drying gas-flow and drying temperature of 8.0 l/min and 200 °C, respectively. Spectra were acquired in the range of $m/z$ 50–3000 in MS mode and $m/z$ 100–1000 in MS$^2$ mode. The default setting of the isolation width was applied (~6 $m/z$ units around the center of gravity of the isotope cluster). Although some variation was studied, the typical collision energy was 10 eV in most experiments. The instrument provided a resolution, measured as ($m/z$)/FWHM, ranging between 8800 and 10 000 for [M + Ag]$^+$ in MS mode, and between 9900 and 11 000 for the fragment ion with $m/z$ 581 in MS$^2$ mode. For additional MS$^2$, MS$^3$ and MS$^4$ experiments, a Shimadzu LC-IT-TOF (‘s-Hertogenbosch, the Netherlands) was utilized using the catalyst complex introduction system previously described. This hybrid mass spectrometer was equipped with an ESI source and operated in the positive ion mode. The MS was operated with an interface voltage of 4.5 kV, an interface temperature of 50 °C, a curved desolvation line (CDL) temperature of 250 °C and a 1.5 L/min nebulizing gas flow. Mass spectrometric fragmentation experiments of the catalyst complex library were performed in the full-scan mode (MS$^1$) and automatic multiple-stage fragmentation scan modes (MS$^2$–MS$^4$) over a mass scan range of $m/z$ 100–1000. The instrument provided a resolution ranging between 9500 and 10300 for [M + Ag]$^+$ in MS mode, and of 10200 for the fragment ion with $m/z$ 581 in MS$^2$ mode. With both instruments, external calibration on sodium trifluoroacetate clusters was applied.
Chapter 4

Computational methods

In order to compare energy levels of Class-1 and Class-2 silver-coordinated ferrocene bidentate catalyst complexes, DFT\cite{18} calculations were utilized using the Amsterdam Density Functional (ADF) program.\cite{19} To determine the feasibility of the fragmentation hypothesis, the silver coordination energy levels were calculated using the BLYP density functional,\cite{20,21} in combination with the high-quality TZ2P basis set. The BLYP functional is widely used and has been benchmarked for a number of Pd[0] (iso-electronic to Ag\(^+\)) complexes.\cite{22-25} Moreover, relativistic effects, especially important for silver, were accounted for using the zeroth-order regular approximation (ZORA).\cite{26} This approach should provide us with accurate relative energies for the complexes discussed in this paper. Equilibrium geometries were fully optimized using analytical gradient techniques. All structures were verified by frequency calculations, where all normal modes have real frequencies.
Results and Discussion

MS based flow injection analysis system

In the development of our continuous-flow reaction detection system, the applicability of both APCI and ESI MS detection was investigated.\[^{6,7}\] Mass spectra that were accordingly acquired illustrate the inherent characteristics of the two ionization methods when silver-adducted ferrocenyl bidentate ligands are introduced. In the ESI MS spectrum, a very intense [M+Ag]\(^+\) adduct ion is observed while the APCI MS spectrum shows only a minor [M+Ag]\(^+\) adduct ion next to extensive fragmentation. In order to adequately elucidate the fragmentation pattern of the different catalyst classes in the studied ferrocenyl bidentate library, the system was temporarily equipped with a high-resolution MS\(^n\) instrument, either a quadrupole–time-of-flight hybrid (Q-TOF) or an ion-trap–time-of-flight hybrid (IT-TOF) instrument.

In MS\(^n\) studies, precursor ion selection was performed with a \(~6\ m/z\) units wide window, as to include the complete isotope pattern of the silver-coordinated ferrocenyl bidentate complex. This feature greatly facilitated the interpretation of the fragmentation, especially in terms of determination of elemental composition. Information from the isotope pattern of the fragment ion was useful to decide whether Ag\(^+\) and/or Fe\(^{2+}\) ions were still present in the fragments. Silver shows a characteristic isotope pattern due to \(^{107}\)Ag (106.905 Da, 100% relative abundance) and \(^{109}\)Ag (108.905 Da, 92.9%), whereas iron also shows a characteristic isotope pattern due to \(^{54}\)Fe (53.940, 6.4% relative abundance), \(^{56}\)Fe (55.935, 100%), and \(^{57}\)Fe (56.935, 2.3%). In Figure 4.1A, the isotope patterns of catalyst complex 5 are presented when the spectrum is zoomed-in. Good agreement is observed with a theoretically predicted spectrum of the theoretical molecular formula (shown in Figure 4.1B). In addition, the Bruker Daltonics software facilitates the calculation and evaluation of elemental
compositions of ions with a molecular formula predictor that ranks proposed compositions based on i.e. the nitrogen rule, mass defect, isotope pattern, H/C element ratio, double bond equivalent and electron configuration. This information is condensed in a single sigmAFIT value that is described by Ojanpera et al.\textsuperscript{[27]} For the spectrum in Figure 4.1A, the sigmaFit value of 20 is ranked first. Similar sigmaFit values were obtained for the other complexes. For the fragment ions, the isotope patterns were carefully compared to the theoretically predicted patterns as well.

\textbf{Figure 4.1} Simulated (B) and experimentally obtained high-resolution MS zoom spectra (A) of ferrocenyldentate complex 5. The diamond indicates the ion that is selected for MS/MS experiments (precursor ion selection window ~6 m/z units wide).
Fragmentation of Class-1 ferrocenyl bidentate catalyst complexes

The structures of the Class-1 ferrocenyl bidentate catalysts investigated are presented in Scheme 4.1 (1-6). The ESI MS$^2$ spectra of 5 acquired with (see B in Figure 4.2) and without (A in Figure 4.2) complexation with Ag$^+$ prior to introduction are shown in Figure 4.2.

Figure 4.2 High-resolution MS/MS spectra of ferrocenyl bidentate complex 5 (A= MS/MS of the protonated catalyst complex, B = MS/MS of the silver-adducted catalyst complex). Fragment numbers correspond to the structures presented in Scheme 2.
As is evident from this figure, the complexation with silver significantly increases the number of MS² fragments that are observed. Since all the major MS² fragments of the [M+H]^+ spectrum are also encountered in the [M+Ag]^+, the latter fragmentation will be described in detail first. For the silver-coordinated Class-1 complexes, 9 characteristic fragments are observed (Table 4.1 and Scheme 4.2). For most fragments, a mass accuracy within 5 ppm of the calculated m/z value is observed, although for some of the low-abundant fragments, especially F3 and F7, relatively poor mass accuracy is achieved (see below). The fragmentation pattern is presented in Scheme 4.2 accompanied with elemental composition and calculated m/z.

Most of the fragments of 5 are found to be class-specific fragments, that is: the 6 fragments F3-F8 (see Scheme 4.2) are found with the same m/z throughout the entire compound class. In addition, three compound-specific fragments (F1, F2 and F9) were observed. In the synthesis of the ferrocene based catalysts, the last step involves the addition of the amine group to the ferrocene template taking advantage of a highly regioselective reactivity. In order to be able to distinguish between the different catalysts, amine substituent related fragmentation of the complexes has to be observed.

Interestingly, aside the intact silver-coordinated catalyst complex ([M+Ag]^+), only two silver-adducted fragments (F3 and F4) are observed, both with relatively low intensity. In the other fragments, the adducted silver is lost, apparently in different ways as discussed below.
Scheme 4.2 Exemplary fragmentation pattern of ferrocenyl bidentate complex 5. Selective fragmentation of the silver-adducted ferrocenyl compound yields 9 major fragments.

The two silver-adducted fragments are actually related to the loss of the catalyst-specific amine substituent, which in complex 5 correspond to the loss of either 1-piperideine (F3 with m/z 689) or 1-vinylpiperidine (F4 with m/z 661). The complementary fragment of the latter reaction in complex 5 is the 1-ethyldenedepiperidinium ion with m/z 112 (F9). With other members of Class-1 ferrocenyl bidentate ligands, the m/z value of F9 is obviously different (see Table 4.1).
Table 4.1 Overview of fragment ions of the Class-I ferrocenyl bidentate ligand library given as m/z (mass error in ppm).

<table>
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<tr>
<th>Catalyst Complex</th>
<th>[M-H]</th>
<th>P1</th>
<th>P9</th>
<th>F3 551.2031</th>
<th>F4 551.2032</th>
<th>F5 306.0719</th>
<th>F6 212.0205</th>
<th>F7 306.0719</th>
<th>F8 306.0719</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>760.1149 (x.7)</td>
<td>652.2005 (3.9)</td>
<td>100.1123 (2.7)</td>
<td>8.5</td>
<td>2.5</td>
<td>0.8</td>
<td>2.3</td>
<td>9.5</td>
<td>6.4</td>
</tr>
<tr>
<td>2</td>
<td>795.1429 (x.8)</td>
<td>681.2278 (4.9)</td>
<td>129.1398 (4.9)</td>
<td>12.3</td>
<td>3.4</td>
<td>2.9</td>
<td>3.8</td>
<td>10.0</td>
<td>5.4</td>
</tr>
<tr>
<td>3</td>
<td>803.1558 (x.1)</td>
<td>688.2462 (2.3)</td>
<td>145.1554 (4.1)</td>
<td>9.8</td>
<td>0.2</td>
<td>0.4</td>
<td>1.6</td>
<td>9.5</td>
<td>0.8</td>
</tr>
<tr>
<td>4</td>
<td>820.1343 (x.4)</td>
<td>712.2191 (1.5)</td>
<td>160.1393 (3.4)</td>
<td>18.8</td>
<td>1.5</td>
<td>2.9</td>
<td>3.6</td>
<td>13.7</td>
<td>6.1</td>
</tr>
<tr>
<td>5</td>
<td>772.1129 (x.6)</td>
<td>684.1995 (2.3)</td>
<td>112.1350 (3.4)</td>
<td>3.0</td>
<td>1.7</td>
<td>1.3</td>
<td>2.6</td>
<td>6.7</td>
<td>5.7</td>
</tr>
<tr>
<td>6</td>
<td>774.0938 (x.4)</td>
<td>688.1789 (2.0)</td>
<td>114.0677 (7.1)</td>
<td>3.9</td>
<td>1.9</td>
<td>3.5</td>
<td>4.3</td>
<td>9.0</td>
<td>4.4</td>
</tr>
</tbody>
</table>
Careful inspection of the MS² spectra of Class-1 ligands showed that the major peak due to the loss of an imine (the low-abundant fragment F3 with m/z 689), that is the loss of 1-piperideine with 5, is accompanied by a minor peak due to the loss of the corresponding amine (“F3–2”, a fragment ion with m/z 687), that is the loss of piperidine with 5. The ratio between imine and amine loss appears to be somewhat compound dependent, but was not studied in more detail. For Class-1 compounds, the loss of imine was always more abundant than the loss of amine under the studied conditions. This fragmentation behavior adversely affects the obtained mass accuracy of the F3 fragment (Table 4.1). The ion with m/z 689 is actually an unresolved mixture of F3 with ¹⁰⁷Ag and “F3–2” with ¹⁰⁹Ag or ¹³C₂.

The loss of adducted silver from the complexes during MS² is an interesting phenomenon. Grewal et al. studied the elimination of AgR (R= H, CH₃, C₆H₅) from [M+Ag]⁺ adduct ions of amines. [15] The hypothesis of this unexpected elimination was substantiated with DFT calculations that proved that the mechanism is energetically feasible. They also found that the hydrogen originated from the α-position and the loss of AgH results in the formation of a stable immonium ion. More recently, Schäfer et al. also reported the loss of AgH from [M+Ag]⁺ adduct ions of tertiary amines and aminocarboxylic acids involving hydrogen abstraction from the nitrogen carrying α-methylene to form the most effectively stabilized immonium ion as demonstrated with deuterium labeling. [20] In the current study, a similar process of AgH elimination is observed to form fragment F1 (Scheme 4.2). The fragmentation was confirmed by accurate-mass determination and the absence of the silver characteristic isotopic pattern in fragment F1. Furthermore, the formation of a stabilized immonium ion F9 is encountered after the loss of the catalyst complex backbone, that is the formation of the 1-ethylidenepiperidinium ion F9 with 5. A combination of the loss of AgH and 1-piperideine results in the generally more abundant fragment F5 with m/z 581. For most of the Class-1 ligands, next to the loss of AgH, a minor peak due to the loss of AgCH₃ is observed, which in agreement with Schäfer et al. [19] and
Grewal et al.\textsuperscript{[15]} would involve the methyl group at the $\alpha$-position, relative to the $N$, and also results in an immonium ion fragment (F2 in Scheme 2).

Next to the two fragmentation pathways outlined above, two additional pathways are observed. The first one involves the formation of fragments F6 and F7 (Scheme 2). Fragment F6, a radical cation with $m/z$ 396, can be described as a secondary fragment of fragment F5 due to the loss of a diphenylphosphine radical ($\text{C}_{12}\text{H}_{10}\text{P}$). It is thus formed from the [M+Ag]$^+$ adduct ion of 5 by the losses of 1-piperideine, AgH and the diphenylphospine radical. Fragment F6 can further show the loss of dibenzophosphazole ($\text{C}_{12}\text{H}_{9}\text{P}$) after hydrogen rearrangement, to fragment F7 with $m/z$ 212. The latter was previously also reported in a study by Wu et al., who investigated the oxidative impurity of 1,1'-bis(diphenylphosphino)-ferrocene (DPPF).\textsuperscript{[12]}

To further elucidate the fragmentation mechanism of Class-1 catalysts, additional MS$^n$ experiments were conducted using an IT-TOF hybrid mass spectrometer. The results for complex 3 are presented in Figure 4.3. Similar results were achieved for the other complexes. All potential fragmentation routes in this pathway are illustrated in Scheme 4.3. The fragmentation in ion-trap MS$^2$ is similar to the fragmentation in Q–TOF MS$^2$, previously discussed. However, low $m/z$ fragment ions were significantly less abundant in the ion-trap MS/MS investigation due to its characteristic unfavorable ion-trapping capabilities for low $m/z$ ions (typical $< 25$-30\% of the $m/z$ of the precursor ion). For instance, fragment-ion F9 with $m/z$ 143 (that is $\sim 20$\% of the precursor), which is the result of a precursor between $m/z$ 700-850, is not observed.
Figure 4.3 High-resolution MS$^3$ mass spectra of the silver-adducted ferrocenyl bidentate complex 3 (A) MS$^2$ of m/z 805, (B) = MS$^2$ of m/z 581 and (C) MS$^3$ of m/z 396. Fragment numbers correspond to the structures presented in Scheme 2.
The IT-TOF data confirm the fragmentation route described above, that is the loss of both AgH and 1-piperideine to form fragment F5 with \( m/z \) 581, with F3 with \( m/z \) 689 as a possible intermediate, the subsequent loss of a diphenylphosphine radical to fragment F6 with \( m/z \) 396, and finally the dissociation of the ferrocene structure itself, leading to fragment F8 with \( m/z \) 305.

Scheme 4.3 Fragmentation scheme of the silver-adducted catalyst complex 3. The possible fragment routes of the abundant fragments F5, F6 and F8 are indicated with A – F. The dashed lines indicate fragmentation routes that are not observed in dedicated fragmentation experiments.
The feasibility of the generation of fragments F5, F6, and F8 via the pathways A, B, and C in Scheme 4.3 is thereby confirmed. The MS\textsuperscript{3} experiments, where fragment F5 is investigated, confirms the formation of F6 with m/z 396 as secondary fragmentation of F5 (fragmentation route D in Scheme 4.3). Interestingly, these MS\textsuperscript{3} experiments also show that fragment F8 with m/z 305 is not formed as a fragment of F5 with m/z 581 (fragmentation route E in Scheme 4.3), but is only generated from the intact silver-adducted catalyst complex indicating that fragmentation route E (Scheme 3) is not possible. Wu et al. reported that DPPF, in contrast to its oxidative impurity, did not fragment via bond cleavage between Fe(II) and the cyclopentadiene ring.\textsuperscript{12} The absence of the oxygen, which is believed to be essential for the promotion of $\pi$-cation interactions, results in the necessity to retain the cyclopentadiene ring and to undergo the loss of the diphenylphosphine radical. In the present study, the ethyl substituent of the cyclopentadiene ring appears to have a similar function in the formation of F8 from the intact catalyst complex. This claim is further substantiated with the MS\textsuperscript{4} fragmentation of F6 where F8 was not generated through fragmentation route F either (Scheme 4.3). Both the MS\textsuperscript{3} fragmentation of F5 and the MS\textsuperscript{4} fragmentation of F6 confirm that the formation of F7 with m/z 212 after the loss of dibenzophosphazole can be considered as secondary fragmentation of F6.

In fact, an additional fragment is found for Class-1 compounds with a non-cyclic amine substituent (compounds 2-4 in Scheme 4.1). These compounds show a fragment consistent with the loss of C\textsubscript{19}H\textsubscript{18}PAg, that is the loss of AgCH\textsubscript{3}, dibenzophosphazol (C\textsubscript{12}H\textsubscript{9}P) and benzene (or AgCH\textsubscript{3}, a phenyl and dibenzophosphine radical). A proposed structure for this fragment (see supplementary information) could be described as a ring closure of the amine substituent to the pentadienyl ring. However, this would implicate the loss of the dibenzophosphine group from the other cyclopentadienyl ring than in the fragments F6 and F7 in Scheme 4.2. The ring closure is not possible with compounds 5 and 6 (Scheme 4.1), which serves as an explanation why this
fragmentation pathway is not observed with these two compounds. However, this does not clarify the absence of this pathway in the fragmentation experiments concerning catalyst complex 1.

Substantial attention was paid to the fragments observed in the MS² spectra of Class-1 compounds, especially because to the best of our knowledge hardly any MS² data and interpretation have been reported for various classes of ferrocenyl bidentate ligands used in homogeneous catalysis. For the provisional identification of related structures, the m/z values of the [M+Ag]⁺ adduct ion and of the fragments F3, F5 and F9 are most relevant. Most of the other fragment ions discussed either confirm the conclusions that can be drawn from this information or provide further confirmation of the ferrocenyl backbone. The latter is not especially important in a library of related structures, differing only in the amine substituent.

As indicated above, the MS² fragmentation of [M+H]⁺ of Class-1 and Class-2 compounds in MS² was also studied. The major fragment ions of [M+H]⁺ were identical to the fragment ions observed for [M+Ag]⁺ adduct ions, that is fragment ions F5 with m/z 581 and F6 with m/z 396. In addition, a series of minor fragments are observed, most of which can be considered as secondary fragments of the odd-electron ion F6, thus involving losses of radicals, that is an ion with m/z 381 due to the loss of a methyl radical, m/z 331 due to the loss of a cyclopentadienyl radical, and m/z 319 due to the loss of a phenyl radical. Finally, two minor fragments are observed involving the dissociation of the ferrocene structure, that is F8 with m/z 305 and an ion with m/z 288, which is not understood. The most likely formula for the latter (C₁₄H₁₉FeNP⁺) is not consistent with its formation also from Class-2 compounds as they do not contain N. It was somewhat surprising that although for Class-1 compounds the loss of the amine substituent is observed (fragment F5), no fragment ions were observed consistent with charge retention at the amine part (comparable to fragment F9) in MS² of [M+H]⁺. As such, the MS² spectra based on [M+H]⁺ provide less compound-specific information than those based on [M+Ag]⁺.
Note, that the observation of the fragment ion with m/z 331 indicates that the diphenylphosphine radical in the formation of F6 with m/z 396 from F5 with m/z 581 indeed is lost from the nonsubstituted cyclopentadienyl ring, as assumed in drawing Scheme 4.2. This also explains why fragment F8 with m/z 305 as such cannot be formed from F6 with m/z 396.
Dissimilarities in fragmentation between Class-1 and Class-2 ferrocenyl bidentate catalyst complexes

The Class-2 compounds (structures 7 en 8 in Scheme 1) were also synthesized in-house. They have identical structures to the Class-1 compounds except that the amine substituent is replaced by a methoxy (7) or an acetoxy (8) substituent. Markedly, most of the characteristic fragments of the Class-1 compounds (cf. Scheme 4.2) are not observed for the Class-2 compounds. Whereas for Class-1 compounds, the amine side chain is preferentially lost as an imine (fragment F3 in Scheme 4.2) rather than an amine (fragment “F3-2”, mentioned above), the loss of methanol (instead of formaldehyde) and acetic acid is observed for the two Class-2 compounds 7 and 8, respectively. Characteristic fragments of Class-1 compounds involving the loss of AgH are not observed, although fragments with m/z 212 (F7 in Scheme 4.2) and m/z 305 (F8 in Scheme 4.2) are observed for Class-2 compounds as well. Some additional fragments are observed for Class-2 compounds, for which it is difficult to propose a structure consistent with the elemental composition and common fragmentation routes.

In order to clarify the different fragmentation behavior of Class-1 and Class-2 catalyst complexes, DFT calculations were conducted. These were performed on model representations of the Class-1 and Class-2 ferrocenyl bidentate complexes with all major substituents removed to allow feasible (and reliable) calculations. Grewal et al. reported that AgH elimination involves migration of the silver atom from the nitrogen to the hydrogen atom on the α-carbon. [15] In the ferrocenyl bidentates catalyst complexes, this process is only achievable when the AgH elimination is preceded by the transformation of the bisphosphine ligated complex into a silver complex where only one of the phosphines and the amine (or ether/ester) of the substituent are involved.
Table 4.2 Schematic structures, complexation energies and entropy effects (enthalpy, entropy and Gibbs free energies at 298 K) of Class-1 (top) and Class-2 (bottom) models of silver-coordinated bidentate catalysts, also including the AgH elimination product associated with fragment F1. Geometrical parameters are distances in Angstrom and angles in degrees.

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<th>ΔH</th>
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<td>-79.2</td>
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<td>d(P-Ag)</td>
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<td>2.512</td>
<td>-</td>
<td>-</td>
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<tr>
<td>d(Ag²⁻P)</td>
<td>2.447</td>
<td>2.464</td>
<td>2.384</td>
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<td>⟨P/N-Ag⁻²⁻P⟩</td>
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<td>Class-1</td>
<td>-91.3</td>
<td>-92.4</td>
<td>-78.6</td>
<td>-40.5</td>
</tr>
<tr>
<td>Class-2</td>
<td>-88.9</td>
<td>-89.9</td>
<td>-76.5</td>
<td>-44.0</td>
</tr>
<tr>
<td>ΔS</td>
<td>-34.5</td>
<td>-33.1</td>
<td>-31.6</td>
<td>7.4</td>
</tr>
<tr>
<td>ΔG</td>
<td>-81.0</td>
<td>-82.5</td>
<td>-69.2</td>
<td>-42.7</td>
</tr>
<tr>
<td>d(P-Ag)</td>
<td>2.440</td>
<td>2.438</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>d(Ag²⁻P)</td>
<td>2.444</td>
<td>2.434</td>
<td>2.371</td>
<td>-</td>
</tr>
<tr>
<td>d(O-Ag)</td>
<td>-</td>
<td>2.908</td>
<td>2.241</td>
<td>-</td>
</tr>
<tr>
<td>⟨P/O-Ag⁻²⁻P⟩</td>
<td>125</td>
<td>125</td>
<td>144</td>
<td>-</td>
</tr>
</tbody>
</table>

In kcal mol⁻¹ (for ΔS in cal mol⁻¹ K⁻¹), computed at: ZORA-BLYP/TZ2P.

The relative stability of this complexation provides information on the relative viability/probability of the hydrogen abstraction pathway in Class-1 and Class-2 ferrocenyl bidentate catalysts. Table 4.2 shows schematic structures and energies for various silver complexation possibilities of the model Class-1 and Class-2 compounds. In Table 4.2, it is illustrated that transformation of the model Class-1 and Class-2 complex from a bidentate phosphine into a complex that
involves all three donating-capable moieties is energetically favorable. However, these most stable conformers are mainly biphosphine type complexations with relatively little contributions from the other moiety, especially in the case of the ether/ester group. Further alteration involves the conversion to a bidentate that loses one phosphine coordination. Although this conformer is energetically less favorable, required transformation energies are only a fraction of the energy involved in typical MS$^2$ experiments.

The Class-1 model complex, where both an amine and the phosphine are involved, is almost as stable as the biphosphine ligated complex. In contrast, for the model Class-2 compound, the ether/ester and phosphine complexation is more than 12 kcal mol$^{-1}$ less stable compared to the biphosphine ligated complex. In addition, we have also calculated the energy of the AgH elimination production related to the generation of the F1 fragment, also shown in Table 4.2. From this data we see that the formation of the AgH elimination product is over 12 kcal mol$^{-1}$ more stable for Class-1 compared to Class-2. Although a full analysis would require the incorporation of the entire fragmentation pathway (as reported by Grewal et al.\cite{15}), the energies calculated strongly indicate a much higher probability for the AgH elimination reaction to take place in Class-1 than in Class-2 compounds.

**Fragmentation of Class-3 ferrocenyl bidentate ligand complexes**

With the presence of a dimethylamine substituent at the α-carbon relative to one of the cyclopentadienyl rings, the two Class-3 ligands (commercially available Taniaphos ligands, one with two diphenylphosphine substituents (structure 9 in Scheme 4.1) and one with two dicyclohexylphosphine substituents (10 in Scheme 1) are most similar to the Class-1 compounds. This similarity is also reflected in the fragmentation pattern. The exemplary MS$^2$ spectrum of 9 and an associated fragmentation scheme is provided in the supporting information.
Based on the discussion of the fragmentation of the Class-1 compounds, one would expect the loss of the imine (H₂C=N–CH₃) to a structure similar to F₃ (Scheme 4.2) as well as the loss of both AgH and the imine to a structure similar to F₅. Both these fragment ion are observed for 9 and 10. However, the loss of the imine side chain appears to be a bit more complex for the Taniaphos ligands than for the Class-1 ligands. In fact, a cluster of peaks is present, indicating that there is a competition between the loss of dimethylamine (C₂H₆N), the loss of the dimethylamine radical (C₂H₅N•), and the loss of the imine (C₂H₅N). The loss of the radical appears to lead to the most abundant fragment ions for 9 and 10. Loss of AgH and imine from [M+Ag]⁺ of aminoalkylferrocenyl phosphines was also reported by Henderson and Olsen [10], although it is not clear whether the fragment reported by them is actually due to the loss of dimethylamine from [M+H]⁺ or due to the combination of AgH and imine from [M+Ag]⁺. In their experiments with deliberately added Ag⁺, no such fragment was observed.

In the current study on Class-3 ligands, fragment ions that originate from the loss of just AgH are absent, but fragment ions due to the loss of AgH and P-phenyl-dibenzo[phosphazene (C₁₈H₁₃P), which have a structure very similar to the immonium ion of F₁ in Scheme 4.2, and of AgH and the imine (see above, similar to F₅) are observed. The loss of the imine itself is also observed (similar to F₃). For 9, a fragment ion with a proposed structure similar to F₆ is also observed, that is the ion with m/z 458, which like fragment F₆ for Class-1 ligands is consistent with the loss of AgH, the imine and a diphenylphosphine radical. Fragments similar to the fragments F₇ and F₈ are not observed for this compound class.

In addition to the fragment ions similar to the Class-1 compounds, some additional fragments were observed for Class-3 compounds. Two of these appeared to be class-specific for the Class-3 (Taniaphos) ligands.

The first class-specific fragment is due to a neutral loss of 165.025 Da. The isotope pattern of the fragments indicates the presence of Ag, but suggests the loss of Fe. For 9, the elemental composition of the resulting fragment ion with
Chapter 4

$m/z$ 629.075 was calculated to be $C_{36}H_{28}AgP_2^+$ (3.1 ppm), which indicates the loss of $C_7H_{11}FeN$, thus the loss of Fe, cyclopentadiene, ($C_5H_6$), and the imine ($C_2H_5N$). The fragmentation mechanism involved is unclear. The same neutral loss with 10 results in a fragment ion with $m/z$ 653.263.

The other class-specific fragment ion is observed with $m/z$ 383 for 9 and with $m/z$ 395 for 10. The mass difference of 12 Da suggest the loss of one of the two phosphine groups, diphenylphosphine for 9 and dicyclohexylphosphine for 10. This is consistent with the calculated elemental composition of these fragments ($C_{23}H_{32}FeP^+$ for 9 and $C_{23}H_{32}FeP^+$ for 10). In fact, these fragments can be explained by the loss of AgH, the imine, and $P$-phenyl-dibenzophosphazole ($C_{19}H_{13}P$) or $P$-phenyl-dicyclohexylphosphazole ($C_{19}H_{25}P$) for 9 and 10, respectively.

Another (apparently compound-specific) fragment of 9 is an ion with $m/z$ 337, for which elemental composition calculation indicates the loss of Fe. The calculated elemental composition of $C_{24}H_{18}P^+$ (3.4 ppm) would be consistent with the loss of AgH and dibenzophosphazole from the fragment ion with $m/z$ 629 (see above). However, in principle, an alternative elemental composition of $C_{20}H_{21}NP^{**}$ (2.5 ppm) can be calculated for this ion. Given the relation to the fragment with $m/z$ 629, the former interpretation is considered more likely. No attempts were made to further elucidate the identity of any of these fragments by MS$^n$ experiments in the IT-TOF instrument.

**Fragmentation of other classes of ferrocenyl bidentate ligand complexes**

In the course of the development of the continuous-flow reaction detection system for the evaluation of homogeneous catalysts performance, two other compound classes of ferrocenyl bidentate ligands were studied, that is some of the commercially available Josiphos and Walphos ligands $^{[21]}$. As part of the current studies, the fragmentation in MS$^2$ of at least two members of each of these compound classes was evaluated. The results of these studies are briefly
discussed in this section, with an emphasis on similarities and dissimilarities to the fragmentation of Class-1 compounds.

For the Class-4 ligands studied (Josiphos ligands, example structure (11) in Scheme 4.1), the most abundant fragment ions are the radical ions with m/z 396 (F6 in Scheme 2) and 212 (F7 in Scheme 2). For compound 11, the fragment ion with m/z 396 results from the losses of AgH and the di(t-butyl)phosphine radical from the [M+Ag]^+ adduct ion. In addition, a fragment ion with m/z 503 is observed, which is consistent with the loss of di(t-butyl)phosphine, that is a bit similar to the minor fragments due to the loss of an amine rather than an imine (fragment “F3–2”, cf. Scheme 4.2 and the discussion above).

The losses of di(substituent)phosphine to a fragment ion with m/z 579 and of AgH and diphenylphosphine to a fragment ion with m/z 473 are also observed for the Class-5 ligands studied (Walphos ligands, example structure 12 in Scheme 4.1). In addition, a number of other fragment ions are observed, which do no longer contain the Ag^+ ion. Some of these fragments, which show the same m/z for the two Walphos ligands studied, are readily understood, whereas some others are more difficult to interpret.
Conclusion

The fragmentation patterns of 5 different classes of silver-adducted ferrocenyl bidentates based Lewis acid catalysts were investigated using Q–TOF and IT–TOF hybrid mass spectrometers. The majority of the fragment ions for Class-1 compounds proved to be class specific, that is the fragments showed the same $m/z$ value through the entire compound class. However, some compound-specific fragments were also observed, thereby offering the possibility to identify specific substituents to the ferrocene backbone. Similarities and dissimilarities in the fragmentation patterns observed for the other four compound classes were elucidated. Density functional theory calculations were performed to understand some of the fragmentation characteristics of the Class-1 compounds as well as some of dissimilarities in the fragmentation between Class-1 and Class-2 compound.
Acknowledgement

This work was financially supported with an ECHO grant of the Dutch Scientific Society NWO. Dr. Marek Smoluch (VU University – Faculty of Sciences) is thanked for his assistance in acquiring the high-resolution MS–MS data. Solvias is acknowledged for providing Josiphos, Walphos, Mandyphos and Taniaphos ferrocene catalyst ligands. Niels Elders and Romano Orru (Department of Organic and Inorganic Chemistry, VU University – Faculty of Sciences) are thanked for the synthesis of the Class I and Class II ferrocene catalysts ligands.
References


Chapter 4  Tandem mass spectrometry of silver-adducted ferrocenyl catalyst complexes.

Supporting Information

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Fragmentation of Class-3 ferrocenyl bidentate ligand complexes

For clarity, some text from the previous chapter is repeated, but references to the structures in the fragmentation scheme below have been added.

Based on the discussion of the fragmentation of the Class-1 compounds, one would expect the loss of the imine (H₂C=N–CH₃) to a structure similar to F3 (Scheme 2) as well as the loss of both AgH and the imine to a structure similar to F5. Both these fragment ion are observed for 9 and 10 (SF3 and SF5A in the Scheme S1 below). However, the loss of the imine side chain appears to be a bit more complex for the Taniaphos ligands than for the Class-1 ligands. In fact, a cluster of peaks is present, indicating that there is a competition between the loss of dimethylamine (C₂H₇N) (“SF3-2”), the loss of the dimethylamine radical (C₂H₆N⁺) (“SF3-1”), and the loss of the imine (C₂H₅N) (SF3). The loss of the radical appears to lead to the most abundant fragment ions for 9 and 10. Loss of AgH and imine from [M+Ag]⁺ of aminoalkylferrocenyl phosphines was also reported by Henderson and Olsen [9], although it is not clear whether the fragment reported by them is actually due to the loss of dimethylamine from [M+H]⁺ or due to the combination of AgH and imine from [M+Ag]⁺. In their experiments with deliberately added Ag⁺, no such fragment was observed.

In the current study on Class-3 ligands, fragment ions that originate from the loss of just AgH are absent, but fragment ions due to the loss of AgH and P-phenyl-dibenzophosphazole (C₁₈H₁₃P), which have a structure very similar to the immonium ion of F1 in Scheme 2 (SF1 or SF5B), and of AgH and the imine (see above, similar to F5) (SF5A) are observed. The loss of the imine itself is also observed (similar to F3) (SF3). For 9, a fragment ion with a proposed structure similar to F6 is also observed, that is the ion with m/z 458 (SF6), which like fragment F6 for Class-1 ligands is consistent with the loss of AgH, the imine and a diphenylphosphine radical. Fragments similar to the fragments F7 and F8 are not observed for this compound class.
In addition to the fragment ions similar to the Class-1 compounds, some additional fragments were observed for Class-3 compounds. Two of these appeared to be class-specific for the Class-3 (Taniaphos) ligands.

The first class-specific fragment is due to a neutral loss of 165.025 Da (SF10). The isotope pattern of the fragments indicates the presence of Ag, but suggests the loss of Fe. For 9, the elemental composition of the resulting fragment ion with \( m/z \) 629.075 was calculated to be \( \text{C}_{36}\text{H}_{28}\text{AgP}_2^+ \) (3.1 ppm), which indicates the loss of \( \text{C}_7\text{H}_{11}\text{FeN} \), thus the loss of Fe, cyclopentadiene, (\( \text{C}_5\text{H}_6 \)) and the imine (\( \text{C}_2\text{H}_5\text{N} \) (SF10). The fragmentation mechanism involved is unclear. The same neutral loss with 10 results in a fragment ion with \( m/z \) 653.263.

The other class-specific fragment ion is observed with \( m/z \) 383 for 9 (SF11) and with \( m/z \) 395 for 10. The mass difference of 12 Da suggest the loss of one of the two phosphine groups, diphenylphosphine for 9 and dicyclohexylphosphine for 10. This is consistent with the calculated elemental composition of these fragments (\( \text{C}_{23}\text{H}_{30}\text{FeP}^+ \) for 9 and \( \text{C}_{23}\text{H}_{32}\text{FeP}^+ \) for 10). In fact, these fragments can be explained by the loss of AgH, the imine, and P-phenyl-dibenzophosphazole (\( \text{C}_{18}\text{H}_{13}\text{P} \) (SF11) or P-phenyl-dicyclohexylphosphazole (\( \text{C}_{18}\text{H}_{25}\text{P} \) for 9 and 10, respectively.

Another (apparently compound-specific) fragment of 9 is an ion with \( m/z \) 337, for which elemental composition calculation indicates the loss of Fe. The calculated elemental composition of \( \text{C}_{24}\text{H}_{18}\text{P}^+ \) (3.4 ppm) (SF12) would be consistent with the loss of AgH and dibenzophosphazole from the fragment ion with \( m/z \) 629 (see above). However, in principle, an alternative elemental composition of \( \text{C}_{20}\text{H}_{21}\text{NP}^{++} \) (2.5 ppm) can be calculated for this ion. Given the relation to the fragment with \( m/z \) 629, the former interpretation is considered more likely. No attempts were made to further elucidate the identity of any of these fragments by MS\(^n\) experiments in the IT-TOF instrument.
Scheme S1 Exemplary fragmentation pattern of ferrocenyl bidentate complex 9.
Proposed ring-closure of ferrocenyl bidentate ligand complexes

As is stated in the manuscript, an additional fragment is found for Class-1 compounds with a non-cyclic amine substituent (compounds 1-4 in Scheme 1). These compounds show a fragment consistent with the loss of C\textsubscript{19}H\textsubscript{18}PAg, that is the loss of AgCH\textsubscript{3}, dibenzophosphazole (C\textsubscript{12}H\textsubscript{9}P) and benzene (or AgCH\textsubscript{3}, a phenyl and diphenylphosphine radical). A proposed structure for this fragment (products of this ring closure are presented in Figure S1) could be described as a ring closure of the amine substituent to the pentadienyl ring. However, this would implicate the loss of the dibenzophosphine group from the other cyclopentadienyl ring than in the fragments F\textsubscript{6} and F\textsubscript{7} in Scheme 2. The ring closure is not possible with compounds 5 and 6 (Scheme 1), which serves as an explanation why this fragmentation pathway is not observed with these two compounds. However, this does not clarify the absence of this pathway in the fragmentation experiments concerning catalyst complex 1.

**Figure S1** The products that are the result of the proposed ring closure of catalyst complexes with a non-cyclic amine substituent.