Summary
One of the exciting developments in synthetic organic chemistry is the transfer from traditional batch-wise synthesis platforms to flowing systems. In Chapter 1, an overview of the major components and developments of flow-chemistry methods and techniques is presented emphasizing on innovative developments especially related to (direct) reaction monitoring.

In continuous-flow or flow-chemistry approaches, static synthesis setups are replaced by an in-flow alternative where reactants are fed into an online reactor (or a series of sequential reactors) and the reaction product is collected after a fixed reactor residence time. In recent years, (continuous-) flow-chemistry has emerged as an exciting technique that utilizes automation and miniaturization to increase reaction efficiencies, optimization throughput and to reduce the cost per compound and the consumption of resources, energy and the production of waste.

The key advantages of performing reactions in a flow-chemistry system stems from the enhanced parameter control compared to batch synthesis. The reaction conditions such as flow speed, associated reaction time and the reactor temperature and pressure can be very accurately controlled with the components used in such systems. Because of the reduced volume, these process conditions are also more consistent across the entire reaction and the associated reaction homogeneity is reported to be responsible for enhanced product purities.

Despite the remarkable progress in flow-chemistry, in the majority of the applications the analysis of most laboratory-scale flow-chemistry reaction products is currently performed by (manual or automated) collection of effluent and subsequent offline analysis using NMR or HPLC with UV detection, eventually after a sample pre-concentration procedure. The advantage of this approach is that after collection, the effluent containing the product of interest can be optimally prepared for careful identification and quantification. However, to correctly determine conversion kinetics, meticulous quenching of the reaction mixture is obligatory. As a result, the workflow for optimization of such a flow-
chemistry system is at least as tedious and time-consuming as the workflow in batch synthesis optimization strategies.

An attractive alternative is to incorporate a flow-through detection device to directly monitor reactants and products in the flow-chemistry system. A wide variety of suitable detection systems are commercially available, as such flow-through detectors are also widely applied as detector in liquid chromatography and other flow-system approaches. In this perspective, mass spectrometry (MS) offers exceptional specificity and selectivity for the sensitive detection of (multiple) selected target molecules in complex matrixes.

From a flow-chemistry point-of-view, the integration of a detection system after the reactor offers several advantages of which significant saving of time and labor intensity are most prominent. Besides monitoring the product generation, direct reaction monitoring provides the ability to more accurately and efficiently control the reaction process, e.g., by terminating reactions when substrates or reagents are consumed, and eventually control of important reaction parameters (flow-rates, temperatures, etc) via a feedback system. Online real-time reaction monitoring in flow-chemistry allows instrument parameters to be adapted during conversions, thus providing a system that can automatically optimize reaction conditions for optimal product formation or reduced conversion into impurities. Depending on the detection principle chosen, some challenge in direct reaction-monitoring approaches is related to possible interferences related to solvents, substrates/reagents, and catalysts.

The high-throughput experimental syntheses and screening methods that were first introduced in the pharmaceutical industry to accelerate the discovery process have also been applied for catalyst development. The high information density libraries that are created with these combinatorial techniques are composed of a large number of different homogeneous catalyst analogues. In order to assess the activity of such large pools of potential catalysts, sophisticated high-throughput screening methods are essential. Flow-chemistry systems that are equipped with direct reaction monitoring provide an ideal
assessment platform to determine catalyst activity towards a synthetic conversion on-the-fly. **Chapter 2** concerns the development of a flow-chemistry system for the online screening of homogeneous catalyst performance using reaction detection mass spectrometry. In this chapter, a novel integrated approach to achieve high sample throughput for the screening of homogeneous catalysts is described. In traditional catalyst performance methods, the catalysts are rated based on an elevated slope of the initial rate period. In order to obtain kinetic data, the product formation has to be determined at several time intervals. In the present concept, the ranking of different homogeneous catalysts was performed by determining the peak area of formed product shortly after the online synthesis reaches the initial rate period. The increased throughput is thus accomplished by reducing the number of data points that are required to characterize catalyst performance. This concept is only feasible when the methodology allows for the quantification of small amounts of synthesis product with high accuracy. In the presented online system, all system parameters (i.e., sampling time, reaction time, reaction pressure, and reaction temperature) are either fixed or accurately controlled, and therefore, a very high system repeatability and reproducibility can be achieved. In this first proof-of-principle study, a limited number of Lewis acid catalysts were screened for activity toward the synthesis of a highly substituted 2-imidazoline. When the continuous-flow screening method is utilized, the assessment of homogeneous catalysts for the selected synthesis requires 4 min of analysis time per sample. Compared to the traditional bench-scale catalyst assessments, a considerable time advantage is achieved. Other virtues of our automated continuous-flow system are the low sample consumption, high sensitivity, and broad solvent, substrate, and product applicability. The results obtained with the screening method are in good agreement with a traditionally applied bench-scale experiment and demonstrate the power of the methodology for the screening of homogeneous catalysts.

Another key issue when applicability of a screening system is concerned is the ruggedness of the applied methodology. In mass spectrometry, the ruggedness
is mainly limited by the introduction of non-volatiles into the mass spectrometer. The ruggedness of the current screening system was investigated by the repetitive injecting of silver triflate catalyst every 4 min for 24 h. The analysis of successive catalyst injections is presented in Figure 4. In 1440 min, the system was capable of performing 305 silver triflate analyses with a peak area variation within 7% residual standard deviation (RSD). The high intraday repeatability and the ruggedness demonstrate the potential of this new method.

In Chapter 3, the applicability of the novel continuous-flow reaction detection methodology was further explored by the investigation of high-throughput reaction optimization and activity screening of Ferrocene-based Lewis acid–catalyst complexes by using the same continuous-flow reaction detection MS system.

Ferrocene is an exceptional iron-containing sandwich structure which unique combination of properties 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, the low price of the ferrocene backbone and the proven applicability in asymmetric catalysis. Our interest in ferrocene derivatives, and especially silver-coordinated bis(diphenylphosphine)-ferrocene complexes, stems from their potential as homogeneous catalysts in the synthesis of substituted imidazolines. 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.

We demonstrated that with the accurately controlled system parameters in our system, the fast optimization of reaction parameters could straightforwardly be achieved. After optimization, the flexibility of the system was demonstrated by employing the same MS based flow-chemistry system for the screening of
catalyst libraries for activity. Minute amounts of reactants and catalysts were used, without the necessity of altering any system parameters.

In the previous two applications, the MS detector that is incorporated in the flow-chemistry system was primarily employed for the sensitive detection of product. Although the advantages of direct detection in flow-chemistry systems is increasingly reported, the ability to use the incorporated detector for a provisional identification of introduced compounds is untapped. In order to enlarge the applicability, it was investigated if this online reaction-monitoring tool could also be employed for the investigation of introduced moieties being reagents, catalysts or catalyst ligand complexes. Due to the possibility for substitution of the ferrocene backbone, this compound class is an ideal template to be synthesized with combinatorial chemistry approaches where different substituents are used to alter catalyst selectivity and activity. Therefore, these analogous catalyst ligands are used as a model to assess the concept of utilizing the MS based flow system for simultaneous identification and activity screening. The attractiveness of this novel concept stems from the amount of potential candidates that can be created with combinatorial approaches and the time that is required to assess activities and to characterize these new formed entities by using traditional methodologies. Combining activity screening and identification in one system, with the previous reported repetition rates of four minutes, allows for the assessment of much more entities in the reaction development phase.

In Chapter 4, the fragmentation of [ferrocenyl bidentate + Ag]\(^{+}\) catalyst complexes was investigated using MS\(^{n}\) experiments with a flow system equipped 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 (Class-1 and Class-2) and various Solvias ligands from the Josiphos, Taniaphos and Walphos compound classes.
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 for 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 also elucidated. DFT calculations were also 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 compounds.

The results in Chapter 4 indicate that a flow system equipped with high-resolution MS is able to identify and/or confirm introduced catalyst complexes that are created with combinatorial synthesis approaches. In Chapter 5, the ability to characterize [ferrocenyl bidentate+Ag]+ catalyst complexes in a system equipped with a low-resolution single-stage quadrupole MS under synthesis conditions is investigated by comparing in-source fragmentation with the previously determined MS^n fragmentation patterns. Moreover, in this chapter, the detailed (fragmentation) investigation regards a variety of solvent systems with APCI and ESI MS and the fragmentation of these complexes in APCI MS is compared to that in ESI MS^n. The potential of a flow-chemistry reaction detection system equipped with single-stage quadrupole MS is evaluated with respect to its ability to screen for catalyst performance and to (provisionally) identify the (active) catalysts in a combinatorial synthesized library. In order to optimize the information content of the mass spectrometric detection, the potential of ESI in a dedicated ESI source, APCI, no-discharge APCI (ND-APCI), and rapid switching between APCI and ND-APCI in a dedicated APCI source, as well as rapid switching between ESI and APCI in a dual-ESI/APCI source was investigated.

Although the obtained in-source fragmentation with APCI MS was significantly less profound than the fragmentation with dedicated (high-resolution) MS^n instruments, comparison of the fragmentation with the previously elucidated fragmentation patterns results in the ability to characterize the introduced catalyst
complexes from APCI MS spectra acquired on a single-stage quadrupole MS system, especially if APCI is performed in combination with ND-APCI to determine the intact [M+Ag]$^+$. 