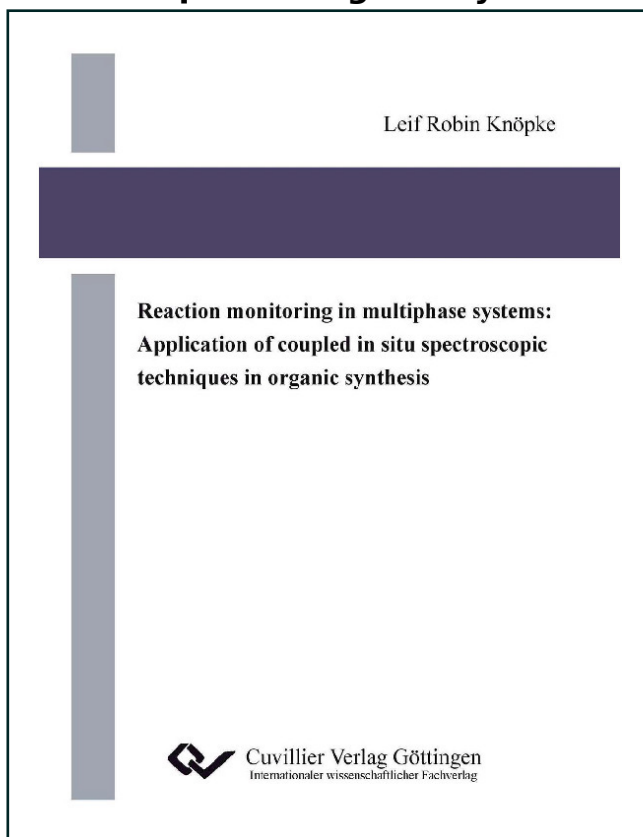




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**Reaction monitoring in multiphase systems:
Application of coupled in situ spectroscopic
techniques in organic synthesis**



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1. Motivation and Objectives

In situ spectroscopy is the only approach to derive reliable information on mechanisms and the role of intermediates in chemical reactions as well as on structure-reactivity relationships in catalysis [1-6].

In catalysis, the application of a variety of in situ methods has gained a lively development during the last two decades [1]. However, usually a complex network of reaction steps including interaction and conversion of reactants, formation of different intermediates as well as changes of the catalysts is passed during catalytic reactions which cannot be satisfactorily explored by applying only single spectroscopic in situ methods, since each of these techniques monitors only a restricted part of the overall reaction process.

Therefore, it is necessary to investigate chemical reactions by different in situ methods to obtain comprehensive information. If possible, a simultaneous coupling of such methods in the same experiment would be desirable to obtain most authentic results. An overview of opportunities is given in section 2. So far, there exist only few examples in which several in situ methods have been combined to analyse chemical reactions, under pressure or at temperatures below room temperature.

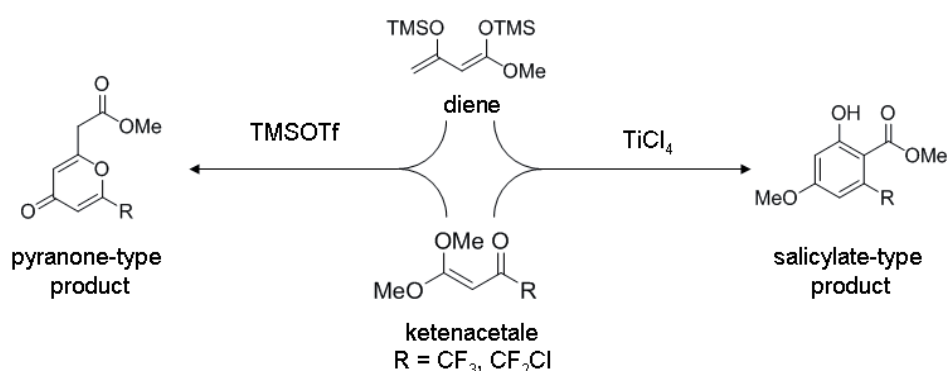
However, frequently chemical reactions have to be performed at elevated pressures or at low temperatures. This requires the use of special reactors that can be tempered and / or pressurised. The implementation of spectroscopic in situ methods in such reactor systems is still a widely unsolved problem and a true challenge.

It is the aim of this work to explore the potential of coupled in situ FTIR-ATR / UV-vis / Raman spectroscopy for applications at low temperature and higher pressures. This implies the development of sophisticated reactors with implemented spectroscopic probes. The following case studies have been selected to demonstrate the benefit of method coupling:

1. Elucidating the directing effect of the used Lewis acid on the reaction pathway in formal [3+3] cyclocondensation reactions
2. Heterogeneously catalysed asymmetric hydrogenation of imines: Reaction monitoring and mechanistic studies

In the first application example two different Lewis acids (TiCl_4 and TMSOTf) are utilised for the coupling of a 1,3-bis(silyloxy)-1,3-butadiene and a ketenacetale. Depending on the

applied acids, completely different products in form of salicylates or pyranones are obtained, although the same reaction conditions are applied (cf. Scheme 1) [7, 8]. In order to elucidate the driving force of the product selectivity of the [3+3] cyclisation reaction, the combined application of different spectroscopic methods becomes necessary [9]. Methods such as ATR-FTIR, UV-vis, and Raman spectroscopy are useful for studying the specific interactions between the Lewis acids TiCl_4 and TMSOTf with both reactants. Whereas ATR-FTIR and Raman spectroscopy reveal information of changes in terms of vibrations of characteristic bonds, UV-vis spectroscopy gives insight about changes of the electronic state of the molecules.



Scheme 1: Scheme of the Lewis acid mediated formal [3+3] cyclocondensation reaction; different products are obtained when TMSOTf or TiCl_4 are applied as mediating acid.

The obtained results from the in situ experiments shall be used as a basis for further investigations of this reaction type (cf. Figure 1). Thus, the possible utilisation of AlCl_3 , TiO_2 and Al_2O_3 as Lewis acids was proved. Furthermore, the nitrogen-containing N-salicylideneaniline was chosen as substrate.

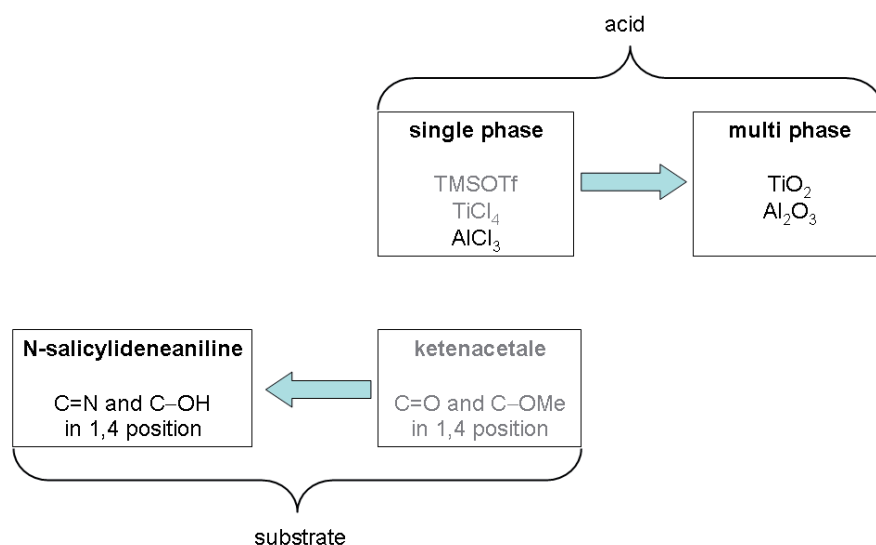


Figure 1: Transfer of the obtained results from the mechanistic investigations of the cyclocondensation reaction (grey) to similar systems (black).

In the second application example a new approach for the heterogeneously catalysed asymmetric hydrogenation of C=N double bonds is pursued using molecular hydrogen as hydrogen source. Supported noble metal catalysts are used for the activation of hydrogen. The implementation of chirality is effected by a suitable modifier like chiral phosphoric acid esters [10] (cf. Figure 2). First of all, the interaction between chiral modifier and solid catalyst are of interest. Only if the chiral modifier adsorbs with the right site on the surface of the catalyst, the modification of the surface will be successful. If the chiral modifier adsorbs with the wrong site or does not adsorb at all, the modification would be failed. The adsorption of the substrates and corresponding products is of interest, too, because adsorbates are important for the investigation of deactivation processes. Surface analysis combined with catalytic tests give insight if adsorbates deactivate the catalyst or not.

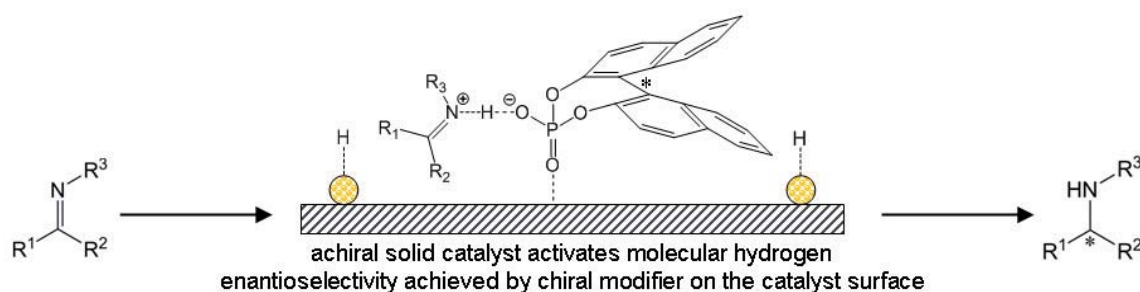


Figure 2: Principle of the heterogeneous catalyzed asymmetric hydrogenation of imines.

Although the interaction of imine and modifier shall occur at the surface of the catalyst, the interaction between both compounds have to be studied separately in liquid phase as well. The complexity of the system – substrate, modifier, catalyst, product, solvent – requires, besides the spectroscopic study of the single compounds, also studies of the mixtures. The main investigations will be focussed on the interaction between the imine and the chiral modifier because this is an essential step of the reaction.



2. State of the Art

2.1 Opportunities and limitations of common in situ methods

Numerous methods are suitable for in situ analysis. Several examples are known from magnetic resonance techniques, X-ray absorption and scattering methods, optical spectroscopy and even electron microscopy [1, 6, 11]. However, the field of application of most of these methods is determined by technical aspects.

NMR spectroscopy is not applicable to all nuclei and quenching problems may occur in the presence of paramagnetic species. On the other hand EPR spectroscopy can only detect systems with unpaired electrons. This limits the application potential for these methods. Furthermore, both methods require a homogeneous magnetic field. Therefore, the reactor geometry has to be narrow. Here, the application of small unstirred tube-type batch-reactors (e.g. NMR or EPR tubes) or of plug flow reactors (which require no stirring) is possible. The magnetic properties of the reactor wall materials have to be considered in every case. Even small impurities in the reactor material may cause fundamental perturbation of the analysis. Due to this fact the application of quartz glass reactors is essential in EPR spectroscopy because normal glass contains paramagnetic impurities which hinder a proper analysis. On the other hand all materials with high magnetic susceptibility constants cause problems when there are exposed to the magnetic fields of the spectrometers.

The application of X-ray methods is also limited referring to reactor geometry and materials. Common sample cells are rather narrow and a restrictive shielding to protect the operator and ambience from radiation is required. Due to the shielding manipulation of the reaction and monitoring of the running equipment inside the sample cell is often difficult. Optical control is commonly performed by cameras and all wires leading to control units have to pass special sewers through the shielding.

Discrete measurements inside the reaction mixture become necessary if the reaction conditions cannot be hold up in all locations in the reactor. For instance the vicinity of the walls is a critical zone referring to temperature and mixing. The analysis of inhomogeneous reaction mixtures requires proper spatial resolution. This can be archived by the implementation of probes which dip into the reaction mixture at the required point. Another problem is the analysis of pressure reactions inside stainless steel autoclaves. Therefore, aligned radiation and a sewer connection inside are required.

Contrary, to magnetic fields and X-ray beams optical radiation in form of ultraviolet, visible and infrared light can be aligned and routed easily. Classical tools for this are lenses, prisms and mirrors. These tools have in common that they can route beams straightforward only. But complex reactor geometries in narrow rooms require often flexible pathways and “beaming around the corner”. This can be achieved by using optical fibers. Typically, these fibers are made from quartz and can be used for transmission of ultraviolet and visible radiation. Such fibers are flexible, stable and well established for application in UV-vis and Raman spectrometers.

In contrast to this the transmission of infrared radiation is not possible with quartz fibers. In infrared spectroscopy the application of fibers made from chalcogenide or silver halogenide has been established in the last years [12-14]. Although these fibers are fragile and undergo ageing with time, there are no other alternatives. Silver halogenide fibers are beneficial because they are more stable and flexible than chalcogenide fibers.

Due to their fragility, fibers cannot be applied directly in the reaction medium. Generally they are connected to probe heads which are chemically inert and mechanically stable. Typical materials for the probe shafts are stainless steel or Hastelloy™. The other end of the probe head has a lens, a prism or any other kind of optical window which is chemically inert as well. Due to that the fibers are protected from but also connected to the chemical reaction.

Typical FTIR probes have a diamond prism which acts as internal reflection element and is suitable to perform ATR spectroscopic measurements [15]. Considering the diameter area of a 1/4” or 1/8” probe head the prism has to be small. Hence, the prism is just a single reflection element which is less considering the number of reflections in conventional ATR-IR prisms.

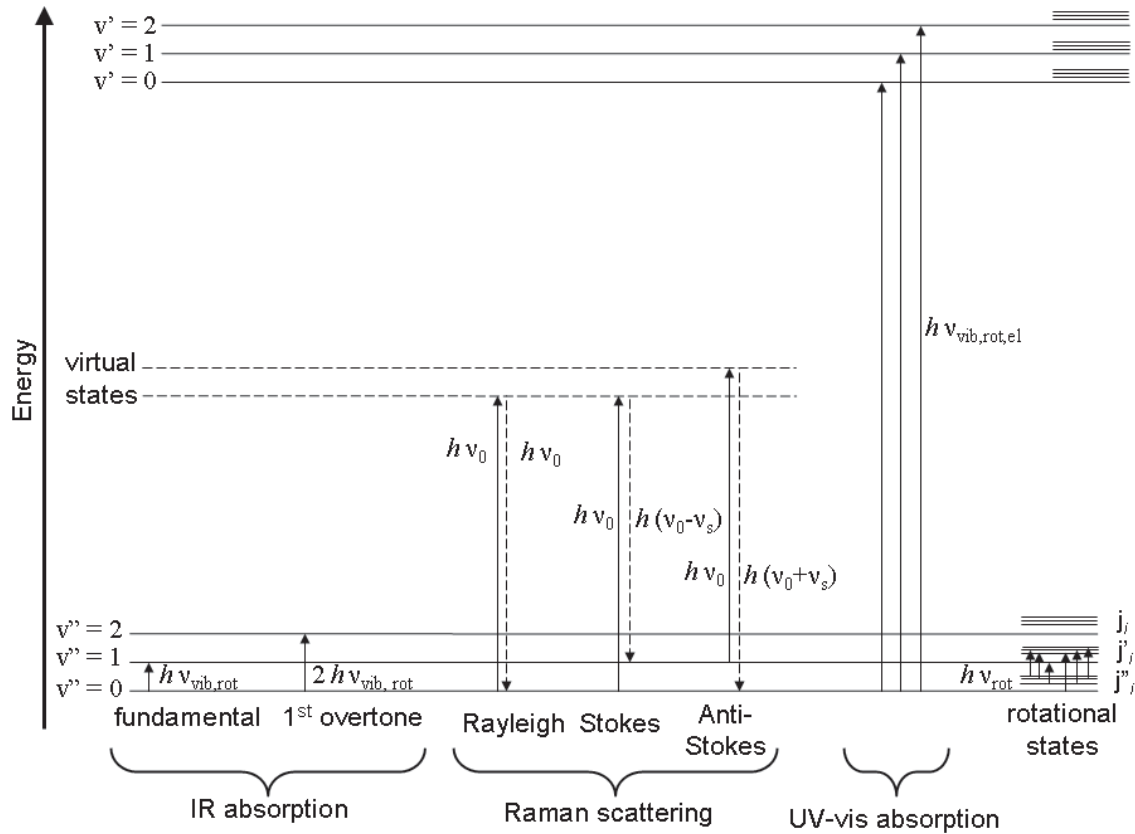
Modern Raman probes have a lens for the emission of the excitation laser at the end of the probe head. State of the art Raman spectrometers have detectors which enable the registration of Raman scattering in an angle of 180° relatively to the light source. For this reason the lens can be used for the detection of the scattered light, too. Illumination (send) and read (return) fiber can be located in parallel wires in the same cable. This setup is adequate to be used with 1/4” or 1/2” immersion probes as well as for contact-less measurements where the laser beam is focussed from outside through an optically transparent wall inside the reactor. In the latter case the focus is not directly in front of the lens but in a distinct distance and requires exact focusing on the sample with an optical bench [16].

Fiber probes for UV-vis spectroscopy are available for transmission as well as for reflection (UV-vis-DRS) spectroscopy. UV-vis transmission spectroscopy is usually applied to diluted solutions or – less common – to gaseous samples. Contrary, UV-vis-DRS spectroscopy is used for the analysis of powders and slurries. In a conventional system the illumination beam passes the sample which is stored in a transparent cuvette. A detector located on the other side receives the transmitted beam. The same principle is applied in the probes. Here the transmission probe has a gap which is filled with sample solution during the measurement. The illumination beam exits the illumination fibers, passes through the filled gap, gets reflected, passes through the gap again and is received by the read fiber. Due to the reflection the optical path is twice as the gap size. Contrary, reflection probes have no gap but an optical window. Here the probe has to be in intimate contact to the sample and the reflected light gets detected.

Nowadays the characterisation of organic and metal-organic compounds is mostly done by NMR spectroscopy, single crystal X-ray structure analysis and mass spectrometry. These methods provide information about the molecular structure of the sample in high-resolution. But as pointed out earlier the utilisation of these methods for in situ analysis is limited.

The molecular structures of organic and metal-organic compounds are mostly obtained by NMR spectroscopy and single crystal X-ray structure analysis. FTIR, Raman and UV-vis spectroscopy provide as well informations about the molecular structure but are mostly used as supplementary characterisation methods. FTIR and Raman spectroscopy is used for the observation of vibrational and rotational states of bonds between atoms and complete groups of a molecule. Especially the vibrations of functional groups like carbonyl groups are exhaustively documented. By means of respective band positions and intensities fundamental conclusions about the molecular structure are possible.

Although FTIR and Raman spectroscopy have similar scope of application, both methods provide rather complementary information. Scheme 2 shows that the transitions occurring during IR absorbance and Raman scattering are based on completely different mechanisms. This is due to the different selection rules occurring in both methods [17] (cf. Equation 1 and 2). FTIR spectroscopy requires groups with a permanent dipole moment. When the dipole moment of a certain group of a molecule or crystal is changed during its vibration, a certain amount of energy can be absorbed by this group.



Scheme 2. Schematic energy diagram of the common transitions occurring in IR, Raman and UV-vis spectroscopy referring to no special molecule; v : vibrational quantum numbers; j''_i, j''_f, j_i : rotational quantum numbers with $i = 0, 1, 2, \dots$; h : Planck constant; ν : frequency whereas: $\nu_{vib,rot} = \nu_{vib} + \nu_{rot}$, $\nu_{vib,rot,el} = \nu_{vib} + \nu_{rot} + \nu_{el}$, ν_{rot} = rotation, ν_{vib} = vibration, ν_{el} = electronic, ν_0 = excitation, ν_s = shifted emission; rotational niveaus shown for comparison; no rotational levels considered in the depictions of the vibronic transitions, no rotational and vibrational levels considered in the depictions of the electronic transitions; for the sake of clarity not all possible transitions are drawn in the scheme.

$$\frac{\partial \mu}{\partial r} \neq 0 \rightarrow IR\text{-active} \quad (1a)$$

$$\frac{\partial \alpha}{\partial r} \neq 0 \rightarrow Raman\text{-active} \quad (2a)$$

$$\frac{\partial \mu}{\partial r} = 0 \rightarrow IR\text{-inactive} \quad (1b)$$

$$\frac{\partial \alpha}{\partial r} = 0 \rightarrow Raman\text{-inactive} \quad (2b)$$

r = coordinate, μ = dipole moment, α = polarisability

Contrary, Raman spectroscopy requires groups in the molecule or crystal which can be polarised during vibration. Due to the polarisation the molecule group becomes anisotropic. If the polarised group is exposed to a laser beam, the incoming light is partly scattered at the electron shell. The major part of the scattered light is elastically scattered and has the same wavelength as the excitation light and is known as Rayleigh scattering. The rest of the incoming light is scattered inelastic and can be detected as Stokes-Raman and Anti-Stokes-Raman scattering. In this case the group interacts with a photon which causes energy transfer.

Stokes-Raman and Anti-Stokes-Raman scattering are shifted about the same amount to lower (Stokes scattering) or higher (Anti-Stokes) frequencies with respect to the Rayleigh radiation. The energy amount of the shifts is characteristic for the scattering group and can be used for structure elucidation. Usually only the Stokes scattering is used for the chemical analysis of samples with Raman spectroscopy.

As a result of the different selection rules certain vibrations of functional groups are active or inactive in IR or Raman spectra. Thus, the spectra of molecules like water or carbon monoxide show strong bands in the infrared spectra but only very weak bands in the Raman spectra. Otherwise, bands resulting from metal-non-metal vibrations can be observed well with Raman spectroscopy. The combination of both methods provides comprehensive information about the vibrational state of the sample.

While in common mid-infrared spectrometer vibrations below 400 cm^{-1} cannot be detected because the applied beam splitters are made from potassium bromide, Raman spectrometers do not have these limitations and can detect vibrations down to 100 cm^{-1} . But due to its nature Raman spectroscopy is very sensitive to fluorescence which can be emitted by the sample. Thus, the analysis of condensed aromatic systems can be perturbed by fluorescence and is difficult to perform with Raman spectroscopy [1, 3, 16].

UV-vis spectroscopy gives even less distinct information about the molecular structure than IR and Raman spectroscopy. Typically, the bands appearing in UV-vis spectra are no sharp absorption bands but rather broad band systems. This is due to the simultaneous excitation of rotational, vibrational and electronic transitions (cf. Scheme 2). This superposition of transitions causes the blurred broad bands. The fine structure arising from vibrational bands can be observed only in less common cases like in solid trans-stilbene [18] or in gaseous samples [19]. The bands appearing in UV-vis spectra are prominent for chromophores. These chromophores can be small parts of the sample molecule but in extreme case also the complete electronic shell of the sample molecule. Nevertheless, UV-vis spectroscopy is a powerful tool because it provides direct access to the electronic state of the molecules. Common UV-vis spectrometers allow to observe $\sigma \rightarrow \pi^*$, $\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$, $n \rightarrow \sigma^*$, $d \rightarrow d$ and charge transfer transitions. The appearance of $\sigma \rightarrow \sigma^*$ transitions shall be neglected at this point because these transitions appear mostly beyond the detection range of common UV-vis spectrometers. Thus, the electron withdrawing or pushing effects of distinct groups in the molecule, appearance of charged molecules, interactions of lone pairs with Lewis acids and interactions of transition metals with ligands as well as with other transition metals can be observed by this method.

The previous discussion shows that there is no master method which can cover all problems. Each method has its distinct advantages and disadvantages. Hence, the coupling of methods provides the possibility to obtain a more complex picture due to the increased amount of incoming information. Several examples have shown the benefit of methods coupling up to five methods to give comprehensive insight into the respective reaction [20-23]. The coupled methods should be applied in the same reactor in order to provide a maximum of comparability of the obtained results.

2.2 In situ studies by coupled techniques

Several examples are given in literature for the application of coupled in situ spectroscopic methods in gas-phase reactions [22]. Beale et al. [23] describe the deactivation of Mo/Al₂O₃ and Mo/SiO₂ catalysts during propane dehydrogenation by coupled XAFS / Raman / UV-vis spectroscopy and O'Brian et al. [24] reported the stability of iron molybdate catalysts monitored by coupled WAXS / XANES / UV-vis spectroscopy. The reaction behaviour of molybdate catalysts during methanol oxidation [25] and the phase variation and volatilisation during the reduction of MoO₃ [26] was investigated by coupled WAXS / Raman / UV-vis spectroscopy by the same research group. Coupled Raman / UV-vis spectroscopy has been used for studies about the dehydrogenation of propane over Cr/Al₂O₃ catalysts [27-30]. In these experiments the oxidation state of the chromium species were detected by UV-vis spectroscopy and structural changes in the catalyst with Raman spectroscopy. Mechanistic investigations on dimethyl carbonate formation by oxidative carbonylation of methanol over a CuY zeolithe with a combined SSITKA / DRIFTS / MS approach has been recently published by Engeldinger et al. [31]. The adsorbates on the catalyst have been detected by DRIFTS and those which occurred in gas-phase by mass spectrometry. It was demonstrated that the utilisation of the SSITKA technique enables the discrimination between active and spectator species by comparison of the isotopic exchange rate of surface and gas-phase species. Finally, the utilisation of in situ EPR spectroscopy for the investigation of catalytic reactions was promoted in the last decade by A. Brückner [32]. A coupled EPR/ UV-vis / Raman spectroscopy / GC setup was used for the elucidation of structure reactivity relationships of V/TiO₂ catalysts in the propane dehydrogenation [2]. The presence of isolated VO²⁺ and absence of Mo⁵⁺ was observed by EPR spectroscopy, UV-vis spectroscopy showed the d-d transitions of reduced vanadium species and Mo⁶⁺-V⁴⁺ IVCT transitions, Raman spectroscopy provided information about the bond states of metal-non-metal bonds and the conversion was analysed by gas chromatography. Coupled EPR / UV-vis / Raman spectroscopy was also used

by Janke et al. [33] for the investigation of the impact of phosphorous and nitrogen on the structure and catalytic performance of VZrPON oxynitrides in the ammoxidation of 3-picoline. Also in this study EPR and UV-vis spectroscopy are used for the investigation of the change of the valence states of vanadium species and Raman spectroscopy for the analysis of metal-non-metal bonds.

So far, the previous section showed that several examples exist for the application of coupled in situ spectroscopy for the investigation of gas-phase reactions but also for the monitoring of in organic preparation processes. But, there are only a few examples of using different spectroscopic methods or combinations of them for monitoring catalysed reactions in liquid phase under unusual conditions like higher pressure or low temperatures. Mul et al. [34] studied the esterification of 1-octanol and hexanoic acid over a Nafion/silica catalyst using a ReactIR system. It was shown that the concentration profile of the esterification reaction, as determined by real-time in situ IR spectroscopy, was in qualitative and quantitative agreement with that determined by conventional off-line GC analysis.

A similar ATR system was used by Pintar et al. [35] to investigate the hydrogenation of prochiral ketones over a Pd/C catalyst in a ternary system. Their in situ analysis showed the presence of a zwitterionic form of (S)-proline which is exclusively formed under working conditions. The coupling of ATR-FTIR/Raman/UV-Vis spectroscopy for studying the oxidation of veratryl alcohol with Co(salen) in aqueous solution under oxygen pressure was described by Kervinen et al. [36]. They illustrated the need of using different types of spectroscopy for different concentration levels. The complementary methods ATR-FTIR and Raman spectroscopy were used for higher concentration levels and UV-vis spectroscopy for the lower ones. The presence of molecular oxygen in the system could be studied by UV-vis spectroscopy. Nevertheless all spectroscopic measurements have been performed only under slightly elevated pressure by using the balloon technique for inserting oxygen. While immersion probes were used for ATR-FTIR and UV-vis spectroscopic measurements, Raman spectra were recorded by focusing the laser beam on the glass reaction vessel from outside.

Investigations of heterogeneously catalysed reactions in liquid phase are also known [37-40]. Bürgi [37] studied the reaction mechanism as well as the catalyst deactivation during alcohol oxidation reactions with coupled ATR-FTIR / UV-vis spectroscopy. The adsorbates on the catalyst and species dissolved in liquid phase were studied by ATR-FTIR spectroscopy and changes in the catalyst due to treatment with oxygen and hydrogen by UV-vis spectroscopy. Caravati et al. [38] applied coupled FTIR-transmission / ATR-FTIR

spectroscopy to get spectroscopic insights into the oxidation of benzyl alcohol. Here, they characterised the working catalyst immobilised on the ATR-crystal by ATR-FTIR spectroscopy and the conversion and product formation in liquid phase by transmission FTIR spectroscopy. In our group coupled EPR / Raman spectroscopy was used for the elucidation of the state of the $\text{Fe}_3(\text{CO})_{12}$ catalyst during the photocatalytic water reduction [39]. Another example from our group is the application of coupled ATR-FTIR / UV-vis / Raman spectroscopy to monitor the hydrogenation of imines [40].

Coupled in situ spectroscopic methods have also been applied for monitoring non-catalysed chemical reactions like catalyst preparations or polymerisation reactions. The monitoring of preparation processes for the synthesis of heterogeneous catalysts was described, for instance, by Kongmark et al. [41], Bentrup et al. [21] and Radnik et al. [42]. Kongmark et al. [41] showed the presence of different steps in the crystal growth of Bi_2MoO_6 by coupled XRD / XANES / Raman spectroscopy. Bentrup et al. [21] monitored a molybdate-based catalyst precursor synthesis by coupled WAXS / SAXS / Raman / ATR-FTIR / UV-vis spectroscopy. SAXS provided information about the particle size and shape and WAXS about occurring crystalline phases. UV-vis spectroscopy showed the charge transfer bands of $\text{Mo}^{6+}\text{-O}$ and $\text{Fe}^{3+}\text{-O}$ species, ATR-FTIR spectroscopy gave information about the nature of phosphate species and Raman spectroscopy showed the formation and changes of different molybdate phases. Radnik et al. [42] investigated the crystallisation process of solid catalysts from salt solutions in levitated droplets trapped in an ultra-sonic trap by synchrotron X-ray diffraction coupled with Raman spectroscopy in order to obtain deeper insight into processes which occur during spray-drying.

Examples for the reaction monitoring in organic chemistry are published by Quinebécche et al. [43] and Tolstoy et al. [44]. Quinebécche [43] determined kinetic parameters of the anionic copolymerisation of styrene and isoprene by means of coupled mid-IR and UV-vis spectroscopy which enables simultaneous measurements of the concentrations of monomers and active species in the anionic (co)polymerisation of above mentioned monomers. Tolstoy et al. [44] studied the geometries of strong hydrogen bonds of phenols with carboxylic acids using coupled UV-vis/NMR spectroscopy.

Considering all previously mentioned examples, the current state of the art of coupled in situ techniques can be summarised as follows:

1. The major field of research is the investigation of gas-phase reactions. These investigations focus mainly on the state of the working catalyst. Product analysis is usually performed by gas chromatography or mass spectrometry.
2. The investigation of catalytic reactions in liquid phase systems is focused on the utilisation of in situ ATR-FTIR spectroscopy. Coupled techniques are especially used in liquid phase systems for the monitoring of preparation processes where mainly the syntheses of solid inorganic catalysts were investigated. Only few examples exist for the monitoring of organic processes in liquid phase.
3. In situ investigations of pressure reactions are still less common. Especially the application of three different spectroscopic methods in the same reactor by utilising immersion probes has rarely performed.
4. Investigations at lower temperatures ($\approx -60^{\circ}\text{C}$) with coupled optical in situ spectroscopy have not been performed yet.

The current thesis will bridge these gaps. Organic preparation processes at low temperature as well as heterogeneous catalysed reactions in liquid phase under pressure will be analysed in situ by coupled ATR-FTIR / UV-vis / Raman spectroscopy using respective immersion probes.