

# Highly Flexible Fibre-Optic ATR-IR Probe for Inline Reaction Monitoring

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## Abstract:

Near infrared (IR) applications have considerably profited from the use of flexible and robust fibre-optical probes. So far, a comparable technique for mid-IR was not available due to low stability and lack of robustness of the fibres. We report the use of a newly developed miniaturised diamond ATR-probe with high chemical resistance and pressure resistance based on robust fibre optics. The routine and convenient application in a glove box to highly air- and oxygen-sensitive reactions on a millilitre scale is reported, as well as the monitoring of a solventless reaction on a litre scale.

## Introduction

Inline reaction monitoring has turned out to be highly valuable for the efficient control of chemical processes and is a key tool in process analytical technology (PAT).<sup>1–5</sup> For obtaining real-time information on chemical composition, mid-IR spectroscopy has proven to be highly versatile, especially when performed with the attenuated total reflectance (ATR) technique.<sup>6–15</sup> Without the need for optical transmission paths, integration into existing experimental setups is easily achieved and not restricted by optical density. Here we report

the application of a highly flexible fibre optical ATR-IR probe for inline monitoring of reactions of current interest.

## Results and Discussion

A newly developed probe for IR measurements with the ATR technique based on previous designs<sup>16</sup> has been used for monitoring purposes (Figure 1).

As the internal reflection element (IRE), a diamond prism is welded to the gold plated Hastelloy body of the probe, giving rise to two internal bounces. The source light beam is conducted to the IRE and back by silver halide fibres. The connection of the fibres with the spectrometers is achieved by standard SMA plugs. Probes have been attached to VECTOR 22 and IRCube FTIR spectrometers (BrukerOptics, Ettlingen, Germany) and to Avatar 380 and Nexus 5700 FTIR spectrometers with a slightly modified MidIR Fiber-Port accessory (Thermo Inc., Waltham, MA, U.S.A.), demonstrating a broad compatibility with commercial equipment.

Due to the unique chemical properties of the diamond prism and of the gold layer covering the metal parts, the probe is resistant towards a broad variety of reaction media such as organic solvents, aqueous media, ionic liquids (ILs), and supercritical fluids. Moreover, pressures up to 300 MPa and temperatures up to 460 K have been applied without significant influence on the system performance. Sterilisation of the probe head with steam as required for pharmaceutical or biotechnological purposes is straightforward. The geometry allows the use of commercial fittings (Gyrlock- or Upchurch-type) for 1/4 in. tubing in order to achieve leak proof and gastight sealings.

With an overall transmission path of 0.6 to 4 m inside the light conductors and 2.6 mm inside the IRE, the residual spectral intensity in the wavenumber range between 4000 and 600 cm<sup>-1</sup> is by far sufficient for standard protocol measurements (Figure 2). Sensitivity is decreased between 2300 and 1900 cm<sup>-1</sup> due to the absorption of the diamond.

In order to illustrate the variety of possible applications, three types of reactions of current interest have been investigated: the solvent-free synthesis of ILs, the organo-catalysed aza-Baylis–Hillman reaction, and the transition metal-catalysed hydroamination.

**Solvent-Free Synthesis of Ionic Liquids.** 1-Ethyl-3-methylimidazolium ethyl sulfate ([EMIM]EtSO<sub>4</sub>) is an IL with a melting point below 208 K and an important

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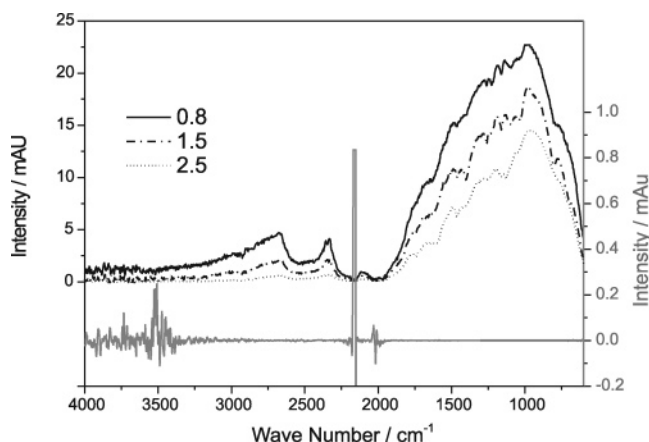
<sup>⊥</sup> infrared fiber sensors.

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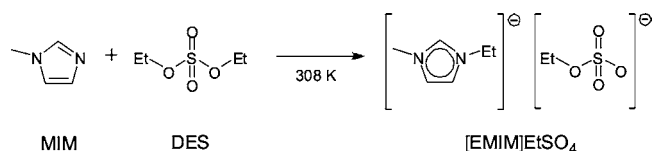
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**Figure 1.** Fibre probe by ifs-aachen with diamond prism as internal reflection element and a 1 Euro-coin (diameter 23 mm) for size relation.



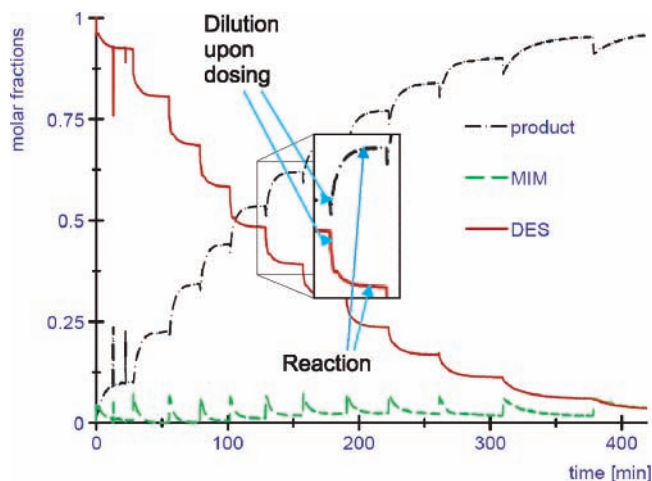
**Figure 2.** Single-channel spectrum of the ATR probe for different lengths of the fiber optics (0.8–2.5 m, left scale) and the resulting referenced transmission spectrum (gray, right scale) (32 scans, scan resolution: 4.0 cm<sup>-1</sup>, spectrometer: Bruker Vector 22)



**Figure 3.** Synthesis of [EMIM]EtSO<sub>4</sub> from MIM and DES. intermediate product for halide-free second-generation ILs.<sup>17</sup> It is accessible in a solvent-free synthesis via the *N*-alkylation of 1-methylimidazole (MIM) with diethyl sulfate (DES, Figure 3).<sup>18,19</sup> The reaction has been studied in a solvent-free fed-batch experiment.

In a typical experiment, DES was charged to a stainless steel reactor of 1.8 L total volume, and a stoichiometric amount of MIM was added in 12 consecutive injections.

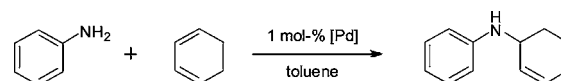
From the time-resolved spectra, quantitative information on the composition of the reacting mixture was gained by multivariate calibration with PLS (partial least-squares) algorithms implemented in the OMNIC software (Thermo Inc., Waltham, MA, USA). For calibration, spectra of binary and ternary mixtures of the involved compounds were subjected to a PLS regression in selected wavenumber



**Figure 4.** Molar fractions of reactants as a function of time during a fed-batch synthesis of [EMIM]EtSO<sub>4</sub>. (Inset) Two-step decrease in diethyl sulfate concentration.



**Figure 5.** Setup with the ATR-IR probe inside an argon purged glove box.



**Figure 6.** Hydroamination of 1,3-cyclohexadiene with aniline.

regions between 1650 and 650 cm<sup>-1</sup>. Thus, the molar fractions of the two substrates and the product can reliably be monitored (Figure 4).

The accuracy of the quantification even allows distinguishing between the decreases in molar fractions due to dilution and the reaction, showing that mixing times in the reactor are fast compared to times of reaction. Detailed kinetic investigations have been published elsewhere.<sup>20</sup>

**Palladium-Catalysed Hydroamination of Alkenes.** The kinetics of the Pd-catalysed hydroamination of 1,3-cyclohexadiene with aniline as developed by Hartwig<sup>21–23</sup> (Figure 6) have been investigated in small-scale batch experiments (typically 4 mL vessels) in a glove box setup (Figure 5).

The probe is introduced into the glove box via a dedicated fitting manufactured for both optical fibres with the spec-

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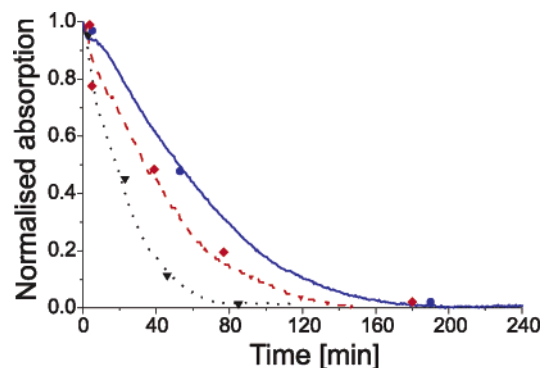
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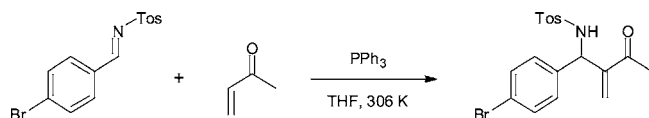
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**Figure 7.** Normalised residual concentration of aniline as a function of time at different reaction temperatures. Lines: normalised absorption at  $\tilde{\nu} = 1618 \text{ cm}^{-1}$ . Points: normalised residual concentrations from external analysis by gas chromatography (308 K: (●) solid line; 314 K: (◆) dashed line; 323 K: (▼) dotted line.



**Figure 8.** Aza-Baylis–Hillman reaction of *N*-(4-bromobenzylidene)-4-methyl-benzenesulfonamide with methylvinyl ketone.

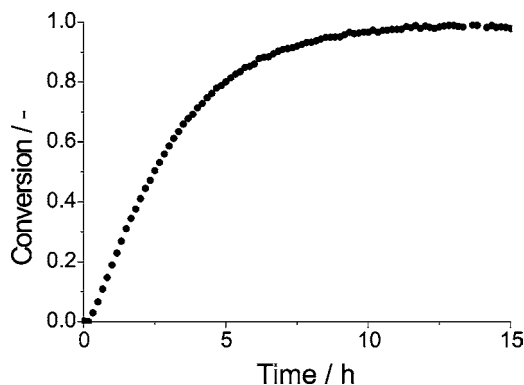
trometer being placed outside the box. This nicely illustrates the flexibility of the system, e.g. in its use for air and moisture sensitive reactions.

The intensity of the absorption at a wavenumber of  $\tilde{\nu} = 1618 \text{ cm}^{-1}$  was taken as a measure for the concentration of starting material (aniline). The decrease of intensity over time was in good agreement with gas chromatographic reference analyses (Figure 7). The reaction was characterised for temperature dependence, catalyst robustness, and concentration influences.<sup>24</sup>

Application of this technique revealed a pseudo-zero-order rate law with respect to both substrates up to conversions near 80% and a decrease in catalyst stability at elevated temperature.

**Organocatalytic Aza-Baylis–Hillman reaction.** The aza-Baylis–Hillman reaction, a Lewis-base-catalysed C–C coupling reaction between activated alkenes and imines (Figure 8), is of high interest for organic synthesis due to its densely functionalised reaction products.<sup>27–30</sup>

Kinetic studies of this reaction by NMR spectroscopy have recently been published independently by the groups of Jacobsen<sup>27</sup> and Leitner.<sup>30</sup> In both studies first-order dependence on both alkene and Lewis-base concentration was observed and a non-integer partial order was determined for the imine concentration. An external validation of the NMR spectroscopic monitoring was performed with IR spectroscopy.



**Figure 9.** Conversion vs time for the aza-Baylis–Hillman reaction at 306 K, derived from the normalised intensity of the product signal at  $\tilde{\nu} = 781 \text{ cm}^{-1}$ .

copy in the glove box setup described above. As a measure for product concentration, the absorption at a wavenumber of  $\tilde{\nu} = 781 \text{ cm}^{-1}$  was chosen (Figure 9).

Data from these measurements successfully cross validate the data obtained from NMR spectroscopy. This displays the potential of the presented ATR-IR setup for the monitoring of organocatalytic reactions.

## Conclusion and Outlook

The fibre-optic probe for ATR-IR spectroscopy presented here has proven its value for reaction monitoring and process control in a variety of applications. Results from kinetic studies in noncatalytic liquid–liquid synthesis, organocatalytic and transition metal-catalysed transformations have been externally validated with classical offline analytics (e.g., gas chromatography, NMR spectroscopy) and showed an excellent agreement. Reaction volumes range from 1 mL to litres, and time scales are covered from minutes to hours. Fibre optics allow usage in a glove box for rapid and convenient kinetic evaluation without sampling.

## Experimental

**Solvent-Free Synthesis of Ionic Liquids.** MIM and DES were provided by Solvent Innovation (Cologne/Germany), distilled under reduced pressure prior to use and stored under dry nitrogen. Typical protocol for a fed-batch experiment: DES (448 mL, 524 g, 3.40 mol) was charged into an HP 60 stainless steel tank reactor (Büchi Glas Uster, Uster/Switzerland) at 308 K. Via a thermostated dosing unit, MIM (281 mL, 290 g, 3.53 mol) was added in 12 consecutive injections (23 mL each).

**Transition-Metal Catalysed Hydroamination of Alkenes.** Reactions were carried out in a glove box (Braun, Munich, Germany) under an inert atmosphere of dry argon (purity 5.0). Typical protocol: A solution of cyclopentadienyl palladium allyl (17 mg, 0.080 mmol) in toluene (1.0 mL) was prepared in a 4 mL GC vial. A suspension of 3-(diphenylphosphino)benzoic acid (49 mg, 0.16 mmol) in cyclo-1,3-hexadiene (1.28 g, 1.52 mL, 16.0 mmol) was added and stirred for 15 min. The reaction was started by adding aniline (0.75 g, 0.72 mL, 8.0 mmol).

**Organocatalytic Aza-Baylis–Hillman Reaction.** *N*-(4-bromobenzylidene)-4-methylbenzenesulfonamide (42 mg,

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0.13 mmol) and triphenylphosphine (10 mg, 0.037 mmol) were dissolved in THF (2.0 mL). The reaction was started by addition of methylvinyl ketone (13  $\mu$ L, 11 mg, 0.15 mmol) at 306 K.

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