Asymmetric synthesis with high stereoselectivity and yield remains a fundamental challenge in organic chemistry. Optimization of reaction parameters requires universal methods for fast and accurate characterization of chiral reaction products and intermediates with low sample consumption. In the present work, a gas-phase method for online monitoring of enantiomeric ratios is developed. The asymmetric synthesis is performed on a microfluidic chip reactor coupled to a cryogenic ion trap triple mass spectrometer. The chiral analyte is transferred from solution to the gas phase by electrospray ionization, where it is thermalized to room temperature and then interacts with a chiral selector molecule. Diastereomeric complexes are formed, and the gas phase vibrational spectra of the mass-selected complexes are recorded in the O-H and N-H stretching region. Differences in the position and intensity of the modes allow differentiation and quantification of the enantiomers.

The method is first demonstrated for mixtures of L- and D-alanine. Diastereomeric complexes are formed with one to three 2-butanol molecules. For a fast determination of the diastereomeric ratio, a smaller spectral region (60 cm\(^{-1}\)) of the vibrational spectrum of the complex with two 2-butanol molecules is recorded. Evaluation of the data with cosine similarity matching shows that the ratio of the diastereomeric complexes determined using this method is directly transferable to the enantiomeric ratio in solution. The method is then used to optimize the parameters of an on-chip transfer hydrogenation. The influence of reaction parameters, such as the nature of the solvent and acid, on the selectivity of the reaction is optimized using this method. The influence of varying the chiral selector is also studied.