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Microfluidic chip reactor and the stereoselective hydrogenation of methylacetoacetate over (*R*)-Ru-BINAP in the $[N_{8222}][Tf_2N]$/methanol/water mixed phase

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ABSTRACT

Homogeneous asymmetric catalysts represented by organometallics of transition elements reveal very high activity and stereoselectivity in asymmetric hydrogenation of β-ketoesters. Recently, it appeared efficient to use ionic liquids of the $[N_{R222}][Tf_2N]$ type for accommodation of the chiral catalytic complex. Even on the industrial scale it is becoming attractive to carry out hydrogenations with such immobilised complexes in a continuous regime in microreactors. Attention was paid to the stereoselective hydrogenation of methylacetoacetate (MAA) to isomeric (*R*)–(+) or (*S*)–(−)-methyl-3-hydroxybutanoates over a chiral ([RuCl((*R*)-BINAP)(*p*-cymene)]Cl) complex immobilised in the mixed $[N_{8222}][Tf_2N]$/methanol/water solvent phase, and performed inside of a microfluidic chip reactor. It was shown that the reaction could be successfully carried out in such an arrangement with a very high enantioselectivity (above 99%) and at very high conversion of MAA (above 97%). It was proven that the participation of a specific solvent (methanol or the mixture $[N_{8222}][Tf_2N]$/methanol/water) essentially influences the mechanism of the reaction. The solvents actively participate in the re-coordination of the catalytic complex in a series of reactions which is reflected in the values of reaction enthalpies. The specific process output was also evaluated.

1. Introduction

Industrial production of fine chemicals with chiral centres requires involvement of stereoselective reactions as a principal condition. The process usually starts with a racemic mixture or with achiral compounds which are then transformed to optically pure products, and the asymmetric (stereoselective) catalysis represents a standard tool [1–3]. The major advantage comprises a multiple enantioresolution on a single chiral active centre [1]. Homogeneous asymmetric hydrogenation catalysts represented by various types of organometallics of transition elements typically reveal very high activity and stereoselectivity [2,4,5]. There is one major drawback regarding their practical utilisation – a complicated separation for a repeated use. A recent alternative comprised the utilisation of ionic liquids for selective accommodation of the chiral catalytic complex [6–8]. Even on the industrial scale it is becoming potentially attractive to carry out these transformations in a continuous regime inside of a micro-channel reactor [9–11]. It is common with certain fine chemicals that the yearly produced amounts are very low in comparison with the standard bulk chemicals. It is due to their high chemical or biological activity even at very low concentrations (low amounts are needed), or their market demand is low from other diverse reasons. In such cases the production platform based on the continuously operated microreactor technology represents a newly appearing option.

During the last few years we have been focusing on the research of novel integrated microreactors of various types for in principle different catalytic chemical reactions. Attention has been paid to slit microphotoreactors, microtubular continuous flow reactors, and to microfluidic chips incorporated into a characteristic microreactor platform [12–15]. The third technology is also believed as potentially well suited for the stereoselective hydrogenation of β-ketoesters over a chiral Ru-BINAP complex

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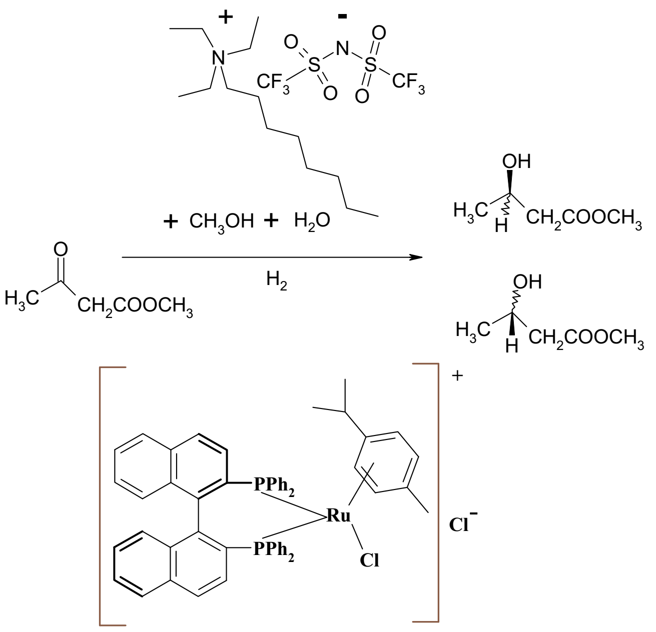

Fig. 1. Stereoselective course of the methylacetoacetate hydrogenation over chiral Ru-BINAP in the $[N_{8222}][Tf_2N]$/methanol/water mixed solvent system.

([RuCl((*R*)-BINAP)(*p*-cymene)]Cl) immobilised in the ionic liquid phase (Fig. 1).

The concept of stereoselective hydrogenation of β-ketoesters with chiral organometallics in the mixed phase with ionic liquids was repeatedly proven as feasible [16–21]. However, such reactions have never been reported to be performed in the confined space of the microfluidic chip. To attempt these reactions successfully (in the microfluidic space) it requires a profound system validation aiming at flow properties of reaction mixtures of various compositions, phase behaviour and viscosities. In the recent past we performed such a step-by-step validation [15] involving a specific microfluidic chip for selected mixed phases with characteristic $[N_{R222}][Tf_2N]$ ionic liquids. It should be emphasized that the choice of a convenient ionic liquid (IL) is essential for such systems. Depending on the ions (their molecular structures) a particular IL may reveal selective properties towards the catalytic complex. It leads to conformation modifications of an active centre and/or to blocking/promoting the substrate access [20–23]. These factors then significantly contribute to the magnitude of the parameter of enantioselectivity (preferential formation of one of the enantiomers).

The ionic liquid serves for selective accommodation of the homogeneous catalytic complex. However, in hydrogenations it may also negatively affect the reaction since the hydrogen solubility in such liquids is generally low. From this reason a main organic solvent is always present [6,7,19,21,24] (typically methanol or other aliphatic alcohols). For β-ketoesters hydrogenations in the presence of methanol a temporary formation of acetals must be also expected. This unwanted side reaction could be effectively supressed by addition of certain amount of water [25]. The solvent mixture for the reaction thus contained methanol, ionic liquid, and water. Dilution of $[N_{8222}][Tf_2N]$ with methanol was also necessary to diminish its viscosity which would be in flow contradiction with the very narrow curved channel space available in the microfluidic reactor chip [15,26–29].

To summarize, in this communication we report on the stereoselective hydrogenation of achiral methylacetoacetate (MAA) over optically pure [RuCl((*R*)-BINAP)(*p*-cymene)]Cl complex to isomeric (*R*)–(+) or (*S*)–(−)-methyl-3-hydroxybutanoates (MHB) in the $[N_{8222}][Tf_2N]$/methanol/water phase. The novelty comprises the performance of this asymmetric reaction with many reaction mixture components of specific properties inside of the confined space of a microfludic chip. The chip is incorporated in the microreactor platform. To the best of our knowledge a comparable treatment of this topic has not been published yet.

2. Experimental part

2.1. Chemicals

Water and methanol were of HPLC grades and were both supplied by Sigma-Aldrich. The ionic liquid (IL) was octyltriethylammonium bis(trifluoromethylsulfonyl)imide ($[N_{8222}][Tf_2N]$, Fig. 1) and it was purchased from IoLiTech (>99%). Methylacetoacetate (MAA, Fig. 1)) and (*R*)–(+) or (*S*)–(−)-methyl-3-hydroxybutanoates (MHB, Fig. 1) were all of Aldrich origin in the 99.99% purity. [RuCl((*R*)-BINAP)(*p*-cymene)]Cl complex (Ru-BINAP, Fig. 1) was supplied by Aldrich in a 99.5% optical purity. The hydrogen 3.0 of a purity >99.9% was supplied by Linde Gas.

2.2. The hydrogenation microreactor platform

The experimental setup (Fig. 2) was based on the Labtrix (Chemtrix) platform. The platform accommodated a glass microchip reactor (either Chemtrix 3222 type or Chemtrix 3223 type, Fig. 3) supplied with the linear pump (Fusion 200, Chemyx Inc.), the temperature sensor (Pt100) and the pressure sensor (M 11, WIKA).

The setup core element was a chemically etched glass microchip (Fig. 3) with a channel of the width 300 μm and 120 μm of the height (common for 3222 and 3223). Its length was either 151.9 mm (3222) or 303.9 mm (3223). The channel cross-section *A* was 32910 μm^2 and the channel circumference *P* was 737 μm. Hydraulic equivalent radius of the channel $R_H = 2A/P$ was 89.3 μm (all common for 3222 and 3223). The microchips

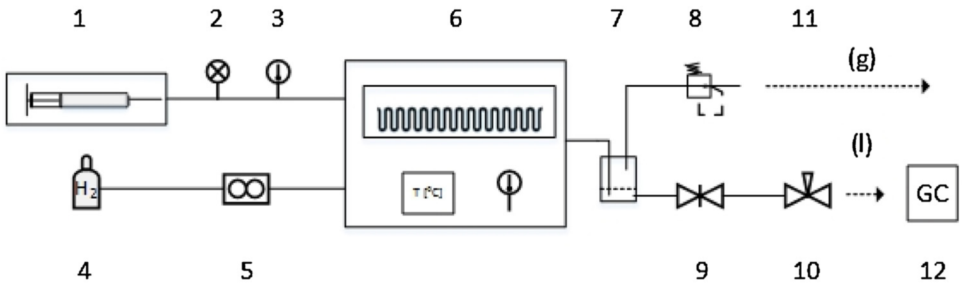

Fig. 2. The experimental setup: 1–linear pump, 2–pressure sensor, 3–temperature sensor, 4–hydrogen reservoir, 5–gas flow-meter/controller, 6–microfluidic chip, 7–(g-l) separator, 8–back pressure valve, 9–shut off valve, 10–micro metering valve, 11–gas outlet, 12–gas chromatography and data acquisition station.