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Asymmetric Hydrogenation of 3-Chloro-1-phenylpropan-1-one Catalyzed by Ruthenium Complexes[1]

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Abstract—A ruthenium complex modified with (1*S*,2*S*)-1,2-diphenyl-1,2-ethanediamine efficiently catalyzes asymmetric hydrogenation of 3-chloro-1-phenylpropan-1-one in the presence of potassium hydroxide solution in isopropyl alcohol, specific optical rotation of the synthesized products reaching –24.6°. Effects of the reaction time, hydrogen pressure, and the alkali concentration on the reaction course have been elucidated.

Keywords: asymmetric hydrogenation, ketone; ruthenium catalysts

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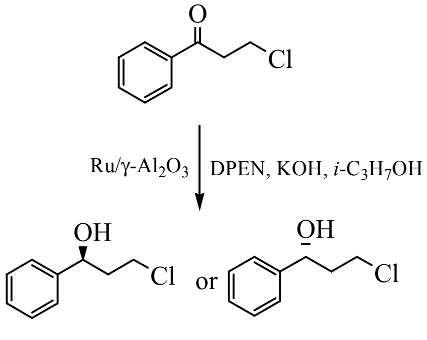
Hydrogenation of carbonyl compounds has recently attracted much interest due to promising applications of the products in the field of medicine [1]. Asymmetric hydrogenation of simple ketones provides an efficient approach to prepare chiral (optically active) secondary alcohols, important organic synthesis intermediates [2].

Catalytic asymmetric hydrogenation is among industrially used reactions due to its simplicity and material efficiency [3]. In particular, asymmetric hydrogenation of simple ketones occurring under mild conditions to yield chiral alcohols has received a portion of attention [4]. A number of transition-metal complexes have revealed catalytic activity towards hydrogenation of ketones; however, only rhodium and iridium complexes have efficiently catalyzed asymmetric hydrogenation with pronounced enantioselectivity [5]. A recent report has also demonstrated the potential of ruthenium complexes [6]; on top of the promising catalytic promising, ruthenium compounds are better available and cheaper than rhodium or iridium ones. Several chiral triarylphosphine ligands have been successfully applied in asymmetric hydrogenation processes [7, 8].

Although many highly selective chiral catalysts have been successfully used for ketones hydrogenation, their industrial applications have been complicated by requirement to remove traces of the toxic metals from the product [9]. In order to overcome the problem, catalytic asymmetric reactions catalyzed by heterogeneous catalysts have been recently investigated, heterogeneous catalysts allowing for better reaction control and being easier separated off and recycled [10].

Herein, we report on preliminary studies on asymmetric hydrogenation of 3-chloro-1-phenylpropan-1-one catalyzed with γ-Al_2O_3-loaded DPEN-modified Ru/TPP complex [TPP standing for triphenylphosphine and DPEN standing for (1*S*,2*S*)-1,2-diphenyl-1,2-ethanediamine] [11].



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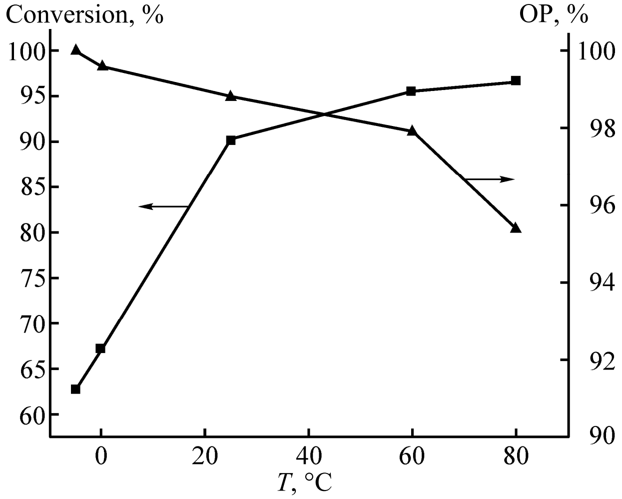

Fig. 1. The reaction conversion and the product optical purity as function of temperature. Hydrogen pressure 1.2 MPa; reaction time 180 min; $RuCl_3$: DPEN : ketone 1 : 1 : 100 (mol/mol/mol).

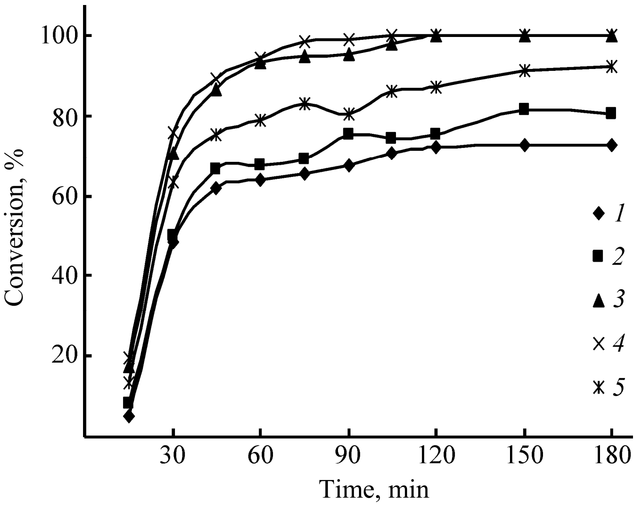

Fig. 2. The reaction kinetics at different hydrogen pressures. T 60°C; $RuCl_3$: DPEN : ketone 1 : 1 : 100 (mol/mol/mol).

In detail, we have examined effects of the reaction time, hydrogen pressure, and alkali concentration on the yield and specific optical rotation of the products.

Effect of temperature on the reaction conversion and the product specific rotation is shown in Fig. 1. As seen from the data, the prepared Ru/TPP/DPEN/γ-Al_2O_3 catalyst revealed good activity towards 3-chloro-1-phenylpropan-1-one enantioselective hydrogenation into 3-chloro-1-phenylpropan-1-ol under mild temperature and moderate hydrogen pressure of 1.2 MPa. The substrate conversion increased with the reaction temperature to reach a maximum of 97% at 80°C. Optical purity of the product decreased upon heating; however, remaining moderately high up to 60°C.

We further studied the effect of hydrogen pressure on the reaction course and the product properties. The reaction was accelerated with hydrogen pressure increasing up to 1.2 MPa; however, further increase of hydrogen pressure to 1.4 MPa somewhat slowed the hydrogenation down (Fig. 2). The effect is better documented in Fig. 3 displaying the reaction outcome after 180 min. Interestingly, the optical purity of the product increased with the conversion as hydrogen pressure increased to 1.2 MPa, whereas decrease of the conversion at hydrogen pressure of 1.4 MPa was accompanied with steep decrease of the optical purity. Hence, the reaction conditions optimized in terms of reaction time, hydrogen pressure, and temperature were as follows: T 60°C, hydrogen pressure 1.2 MPa, the reaction time 90–180 min. Under those conditions, the substrate conversion was of 100%, and the product optical purity was of 98%.

The effect of potassium hydroxide concentration, other conditions being the same (hydrogen pressure 1.2 MPa, T 60°C, reaction time 90 min, and Ru : DPEN : ketone ratio 1 : 1 : 100 mol/mol/mol) on the reaction conversion and the product optical purity are documented in Fig. 4. The results indicated that the reasonably high yield of the pure enantiomer required the presence of certain amount of the alkali in isopropanol medium. In particular, fairly low yield of a mixture of enantiomers was found in the absence of KOH; both the reaction conversion and the optical purity of the product went up with the alkali concentration increasing in the range of 0.02–0.08 mol/L, and further increase of the alkali amount resulted in somewhat decreased product yield of lower optical purity.

To conclude, a Ru/TPP complex modified with DPEN and applied on γ-Al_2O_3 support has revealed excellent catalytic activity towards conversion of 3-chloro-1-phenylpropan-1-one into the corresponding alcohol. All the altered reaction conditions (reaction time, temperature, hydrogen pressure, and alkali concentration) should be chosen properly in order to attain the high product yield and the high optical purity. In detail, the best conditions have been optimized

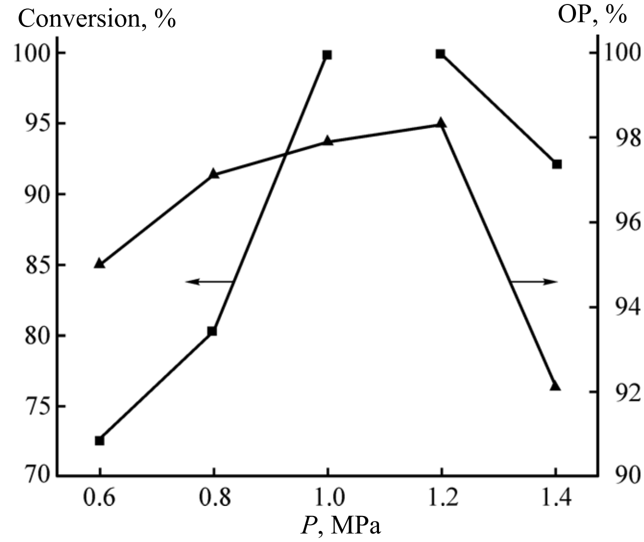

Fig. 3. The reaction conversion and the product optical purity as function of hydrogen pressure. T 60°C; reaction time 180 min; $RuCl_3$: DPEN : ketone 1 : 1 : 100 (mol/mol/mol).

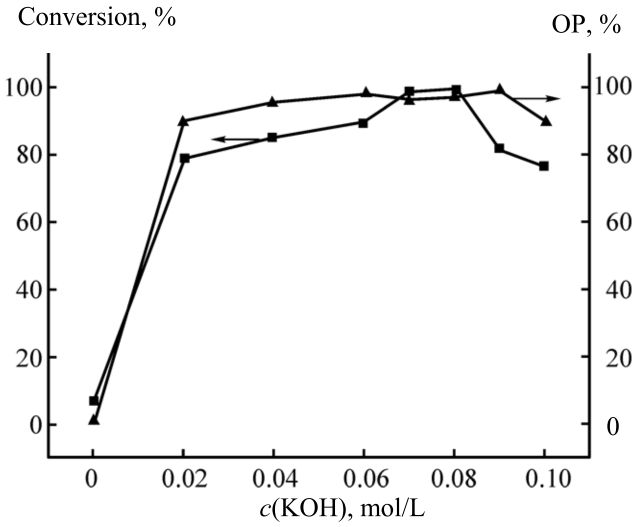

Fig. 4. The reaction conversion and the product optical purity as function of KOH concentration. T 60°C; hydrogen pressure 1.2 MPa; reaction time 90 min; $RuCl_3$: DPEN : ketone 1 : 1 : 100 (mol/mol/mol).

as follows: T 60°C; hydrogen pressure 1.2 MPa, KOH concentration 0.08 mol/L, and reaction time 90 min. Further work is being run to elucidate the reaction mechanism and broadening the range of substrates of the reported asymmetric hydrogenation process.

EXPERIMENTAL

3-Chloro-1-phenylpropan-1-one, (1*S*,2*S*)-diphenyl-1,2-ethylenediamine, (1*R*,2*R*)-diphenyl-1,2-ethylenediamine, and isopropanol were used as received from the supplier.

The ruthenium complex catalyst Ru/TPP/γ-Al_2O_3 was prepared as described elsewhere [11].

The hydrogenation reaction was performed in a 50 mL stainless steel autoclave equipped with a magnetic stirring bar. The prepared catalyst, the substrate 3-chloro-1-phenylpropan-1-one (0.2 g, 1.2 mmol), and required amounts of DPEN modifier and KOH were dissolved in 15 mL of isopropyl alcohol. The solution was placed into the autoclave; the latter was fed with hydrogen up to the desired pressure and incubated at the experiment temperature. After suction filtration of the solids and evaporation off the solvent on a rotary evaporator, the product was purified by recrystallization from cyclohexane to form white solid powder.

3-Chloro-1-phenylpropan-1-ol. ^{1}H NMR spectrum (500 MHz, $CDCl_3$, TMS), δ_H, ppm: 7.371 d ($^3J_1$ 4.5 Hz, 4H), 7.307 m ($^3J_1$ 4.0 Hz, 1H), 4.951 m (1H), 3.721–3.770 m (1H), 3.543–3.588 m (1H), 2.209–2.278 m, (1H), 2.063–2. 129 m (1H), 1.884 s (1H); ^{13}C NMR spectrum, δ_C, ppm: 143.943, 128.916, 128.176, 126.011, 71.599, 41.950, 41.697. GC-MS (EI, 70 eV) 170 (MH^+).

The reaction conversion was determined from gas chromatography–mass spectrometry data. Specific rotation of the product was determined by polarimetry and reflected the optical purity (OP) of the product:

$$\mathrm{OP} = \frac{[\alpha]_{\mathrm{exp}}}{[\alpha]_{\mathrm{theor}}} \times 100\%.$$

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