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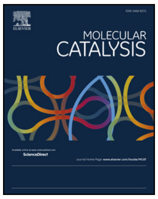

A remarkable solvent effect on reductive amination of ketones

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ABSTRACT

We report the first systematic study of solvent effect on reductive amination of ketones with ammonia and dihydrogen (H_2) over Ru/C, Rh/C, Pd/C and Pt/C catalysts. Protic (water, methanol, ethanol and isopropanol), aprotic polar (dioxane and tetrahydrofuran) and aprotic apolar (cyclohexane and toluene) solvents were investigated. Reaction kinetic model was built to reveal solvent-dependent reaction pathway and solvent-related rate constant for individual steps. Primary amine is produced via two distinct routes, i.e., hydrogenation of imine and hydrogenolysis of Schiff base adduct. These two routes co-exist in organic solvents, while the preference of which route to take heavily depends on the nature of the solvent. In contrast, the formation of imine and Schiff base are not favored in water, resulting in high selectivity towards alcohol. Methanol is identified as the best solvent for reductive amination of ketones, attributed to the highest rates for imine and Schiff base formation compared to other solvents, as well as high hydrogenation activity.

1. Introduction

Primary amines are important chemical intermediates with wide applications in the synthesis of polymers, drugs, dyes and pharmaceuticals [1–3]. Reductive amination of carbonyl compounds with ammonia (NH_3) and dihydrogen (H_2) to primary amines represents a more atom efficient synthetic method compared to other processes that use organic amines [4–7] and stoichiometric reductants (such as borohydride [8–10] and formate [11–13]). It is also a key reaction for renewable amine production from biomass [14,15]. The easy formation of side products, such as secondary amines, tertiary amines or corresponding alcohols, is the main problem encountered in reductive amination of carbonyl compounds [16–19]. Significant achievements have been made to overcome this obstacle over heterogeneous [17,20–30], homogeneous [31–33] and enzymatic catalysis [34,35]. Most efforts in the development of heterogeneous catalysts have so far been focused on Group VIII metals [22–26,28,29], to reveal the effect of the metal center and the support. For example, Lercher et al. reported that the catalyst selectivity in reductive amination of butyraldehyde was determined by the type of metal and the substrate: Ru- and Rh- based catalysts favored the formation of primary amine, while Pd- and Pt- based catalysts were more effective in producing secondary amine [23]. Nakamura et al. reported the amination of ketones with ammonia in o-xylene over Pt based catalysts, in which the authors claimed that the Lewis acid sites on the support played an important role in the synthesis of primary amine [24]. Dong et al. revealed that amphoteric supports were superior to purely basic and relative acidic supports for the transformation of heptaldehyde to 1-heptylamine [25].

In addition to catalysts, the choice of solvent often has a great effect on reaction activity [36–38]. To our knowledge, however, systematic study concerning solvent effect on reductive amination was not available [25]. Recently, Chatterjee et al. reported transformation of furfural to furfuryl amine in aqueous ammonia [26]. When commercial Ru/C was used as the catalyst, secondary amine (97.9% selectivity) was detected as the main product in water. However, Komanoya et al. found that in methanol a moderated yield of furfuryl amine (31%) was achieved over the same catalyst [28]. In another report, co-solvent (water-ethanol) was used to increase the yields of primary amines for some specific substrates using Ru/ZrO_2 catalyst [29]. It appears that the selectivity towards primary amine was not only based on the choice of catalysts, but also affected strongly by the selection of solvent. The reaction pathway in reductive amination is also under debate [19,26,28]. Whether the formation of primary amine results from the hydrogenation of imine or from hydrogenolysis of the adduct Schiff base is not clear. The apparent contradictory reports on reaction pathway may due to the different solvent system used in each study.

Since inspections into the literature suggest solvent may play a pivotal role, we conducted a detailed study on solvent effects in reductive amination of ketones with NH_3 and H_2 over Group VIII metal-based catalysts. Different solvents including protic (water, methanol, ethanol and isopropanol), aprotic polar (dioxane and tetrahydrofuran) and aprotic apolar (toluene and cyclohexane) solvents were investigated and compared. Using cyclohexnone as a model substrate, the reaction pathway and the reaction rate constants for individual steps in various

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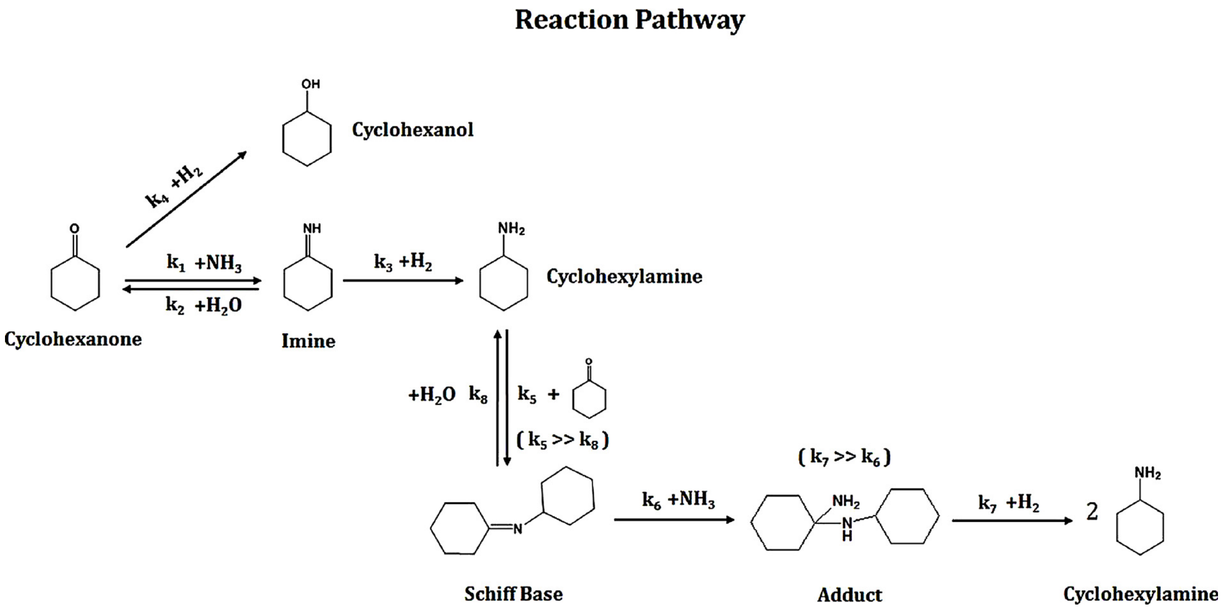

Scheme 1. Reaction pathway for reductive amination of cyclohexanone over the Ru/C catalyst.

solvents have been estimated based on experimental data and kinetic modelling.

2. Experimental

2.1. Chemicals

All chemicals were purchased from commercial suppliers: cyclohexanone (Sigma-Aldrich, > 99.0% purity), cyclohexanol (Sigma-Aldrich, 99% purity), cyclohexylamine (Sigma-Aldrich, > 99.9% purity), methanol (Sigma-Aldrich, 99.9% purity), ethanol (Sigma-Aldrich, 99.5% purity), toluene (Fisher Chemical, 99.9% purity), cyclohexane (Sigma-Aldrich, anhydrous, 99.5% purity), tetrahydrofuran (Sigma-Aldrich, anhydrous, > 99.9% purity), isopropanol (Sigma-Aldrich, anhydrous, 99.5% purity), dioxane (Sigma-Aldrich, anhydrous, 99.8% purity,) and ultra-pure water (Siemens Ultra-Clear TWF Water Purification Systems).

2.2. Catalysts

Commercial 5% Ru/C, 5% Rh/C and 5% Pt/C catalysts were purchased from Shaanxi Kaida Chemical Engineering Co., Ltd. 5% Pd/C catalyst was synthesized in our lab following a literature procedure [39]. Before reaction, the catalysts were treated with 5% H_2/N_2 at 673 K for 1 h with a ramping rate of 10 K/min, then cooled down to room temperature.

2.3. Catalytic reactions

The reductive amination of cylcohexanone was conducted in a 14 mL autoclave reactor with a magnetic stirrer (1000 rpm). Typically, 1 mmol cyclohexanone was added into 3 mL solvent, then 0.02 g catalyst was added and the autoclave was sealed and purged with 2 bar NH_3 ten times to remove the remaining air in the reactor. Each time, NH_3 was purged back to 2 bar when the pressure dropped to ca. 1 bar. After that, the NH_3 pressure was adjusted to 4 bar, and gas valve was closed. When the pressure decreased to atmosphere (since ammonia quickly dissolves in the solvent), the autoclave is further pressurized with H_2 and the final pressure was adjusted to 10 bar. Then, the reaction was conducted at room temperature (298 K) under stirring for certain times. After reaction, the catalyst was filtered by a PTEE membrane with a pore size of 0.45 μm. The liquid products were analyzed with GC (Agilent GC 7890A with a flammable ionization detector). Qualitative analysis of reaction products was conducted with GC–MS (GC–MS, an Agilent 7890A GC system and 5975C inert MSD with triple-axis detector) with column HP-5.

2.4. Kinetic modeling of the reaction

The concentration of dissolved gas in solvent was affected by temperature and gas partial pressure. The solubility of H_2 in selected solvents was limited based on the mole fraction of H_2 (X_{H2}) in Table S1, the calculated equations are listed as follow [40,41]:

$$X_{H_2} = \frac{n_{H_2}}{n_{H_2} + n_{liquid}}$$

$$C(H_2) = \frac{n_{H_2}}{V}$$

where n_{H2} is the moles of hydrogen dissolved in solvent, n_{liquid} is the moles of solvent, $C[H_2]$ is the mole concentration of H_2 in solvent and V is the volume of solvent at 298 K. The mole conversion of hydrogen was below 20% in all solvents. Therefore, the concentration of H_2 in all solvents was assumed to be a constant in the reaction kinetic model.

The solubility of ammonia in solvent is much higher than the solubility of hydrogen based on the mole fraction of NH_3 (X_{NH3}) shown in Table S1. The ammonia pressurized procedure is the same in all solvents, thus, $C[NH_3] = 2$ M was used in all solvents. The estimation is as follows: during 10 times purging, ca. 5 mmol NH_3 is dissolved in the solvent (0.5 mmol each time, based on ideal gas law). During the final charging of 4 bar NH_3, an additional 1.5 mmol NH_3 is dissolved. As such, the total amount of dissolved NH_3 is estimated to be 6.5 mmol, providing a NH_3 concentration of ca. 2 M considering the total volume is 3 mL. The conversion of NH_3 was also below 20%. Therefore, the concentration of NH_3 was assumed to be a constant in the reaction kinetic model.

The reaction pathway for reductive amination of cyclohexanone to cyclohexylamine was depicted in Scheme 1. *C*[*cyclohexanone*], *C*[*imine*], *C*[*cyclohexylamine*], *C*[*Schiff base*] and *C*[*cyclohexanol*] are used to represent the concentration of substrates, intermediates and products, respectively. NH_3 and H_2 are both in large excess so they are treated as pseudo-first-order. Moreover, the hydrogen pressure has a first order dependence on both C═O and C═N bond hydrogenation