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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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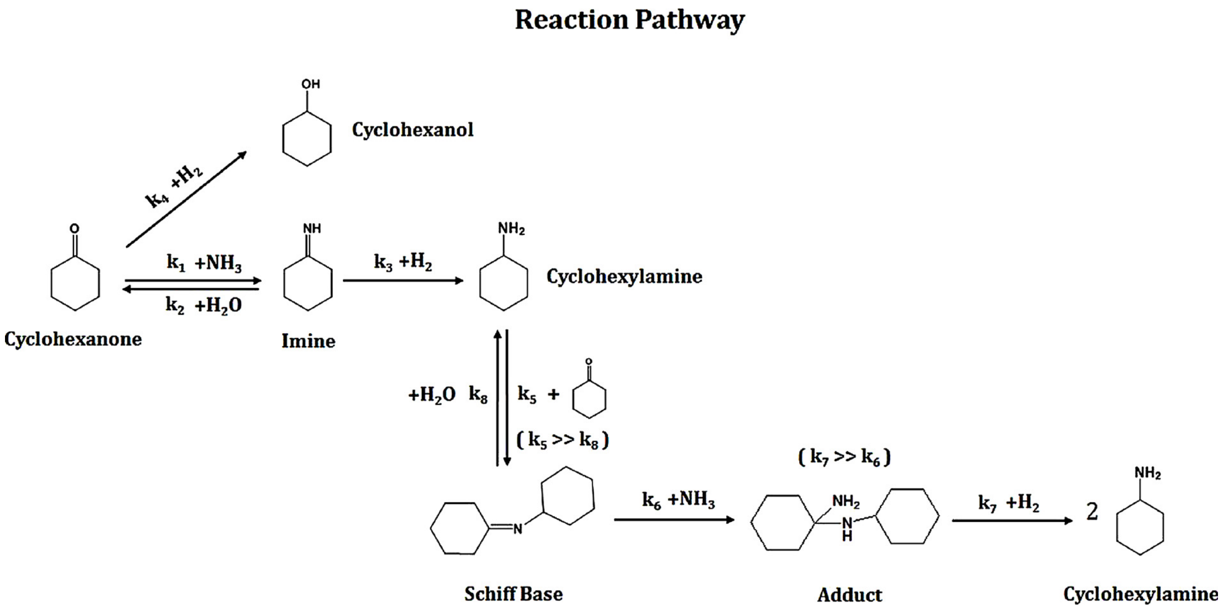


Scheme 1. Reaction pathway for reductive amination of cyclohexanone over the Ru/C catalyst.

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

(Table S2). As such, first-order reaction was assumed for all steps involved in Scheme 1. The number of catalyst active sites was assumed to keep constant in the entire reaction process [42,43]. Based on the Scheme 1 and these assumptions, kinetic equations are listed as follows:

$$\frac{dC\,[cyclohexanone]}{dt} = -k_1{*}C\,[cyclohexanone]{*}C\,[NH_3] - k_4{*}C\,[cyclohexanone]{*}C\,[H_2] - k_5{*}C\,[cyclohexanone]{*}C\,[cyclohexylamine] + k_2{*}C\,[imine]{*}C\,[H_2O]$$

$$\frac{dC\,[imine]}{dt} = k_1{*}C\,[cyclohexanone]{*}C\,[NH_3] - k_3{*}C\,[imine]{*}C\,[H_2] - k_2{*}C\,[imine]{*}C\,[H_2O]$$

$$\frac{dC\,[cyclohexylamine]}{dt} = k_3{*}C\,[imine]{*}C\,[H_2] - k_5{*}C\,[cyclohexanone]{*}C\,[cyclohexylamine] + 2{*}k_6{*}C\,[Schiff\ base]{*}C\,[H_2]{*}C\,[NH_3]$$

$$\frac{dC\,[Schiff\ base]}{dt} = k_5{*}C\,[cyclohexanone]{*}C\,[cyclohexylamine] - k_6{*}C\,[Schiff\ base]{*}C\,[H_2]{*}C\,[NH_3]$$

$$\frac{dC\,[cyclohexanol]}{dt} = k_4{*}C\,[cyclohexanone]{*}C\,[H_2]$$

Water is produced from the dehydration steps, and the concentration of water is equal to the amounts of nitrogen-containing compounds based on Scheme 1 (except for water as solvent), as shown below:

$$C\,[H_2O] = C\,[imine] + C\,[cyclohexylamine] + C\,[Schiff\ base]$$

The yield of cyclohexylamine from imine hydrogenation was calculated based on the equation shown below. The equation of $C[imine]$ was generated by the curve fitting toolbox of MATLAB based on simulated concentration data.

$$Yield\ \ of\ \ cyclohexylamine\ \ from\ \ imine\ \ hydrogenation = \int_0^t k_3{*}C\,[H_2]{*}C\,[imine]\,dt$$

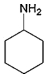
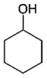
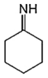
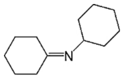
The time-on-stream concentration of substrate, intermediates and products in different solvents were used to simulate the reaction kinetic constants. Reaction kinetic parameters were simulated based on the least squares fitting algorithm of MATLAB lsqcurvefit [43–48]. Several constraints have been used to make sure that the fitting curve is reasonable.

3. Results and discussion

3.1. Solvent effects on reductive amination of cyclohexanone with ammonia and H_2

Reductive amination of cyclohexanone with NH_3 and H_2 over Ru/C catalyst was chosen as a model reaction to investigate the solvent effects [16,17]. Eight solvents including protic solvents (water, methanol, ethanol and isopropanol), aprotic polar solvents (dioxane and tetrahydrofuran) and aprotic apolar solvents (cyclohexane and toluene) were investigated at 298 K for 2 h. The results were summarized in Table 1. The highest conversion was obtained with methanol as solvent (entry 1, 100%), followed by water and other alcohols (entries 2–4, ~80–90%), then aprotic apolar solvents (entries 7–8, ~60–70%), and finally aprotic polar solvents (entries 5–6, ~30–40%). Cyclohexylamine or Schiff base were the main products in alcohols and aprotic apolar solvents, while imine was the main product in aprotic polar solvents. In water, on the other hand, the main product was cyclohexanol. These results clearly highlighted a critical influence of solvent in both substrate conversion and product distribution. Prompt by this, we established a solvent dependent reaction pathway and reaction kinetic profile, to provide rationales for the observed solvent effect.

Table 1
Reductive amination of cyclohexanone in different solvents over Ru/C catalysts.

Entry	Solvent	Con. (%)	Product distributions (%)			
						
1	Methanol	100	87.8	7.8	0	4.4
2	Ethanol	91.8	36.1	5.9	18.7	39.3
3	Isopropanol	82.1	8.9	2.1	40.6	48.4
4	Water	89.5	25.7	74.2	0	0.1
5	THF	36.1	0	0	97.0	3.0
6	Dioxane	30.9	0	0	100	0
7	Toluene	67.9	61.3	12.2	4.9	21.6
8	Cyclohexane	69.8	27.4	15.6	3.8	53.2

Reaction conditions: Cyclohexanone 1 mmol, catalyst 0.02 g (Ru:cyclohexanone = 1:100), solvent 3 mL, H_2 = 9 bar, T = 298 K, agitator speed = 1000 rpm, time = 2 h.

3.2. Modeling of reaction kinetics

Based on GC–MS analysis of product mixtures and a previous report [19], a reaction pathway for the reductive amination of cyclohexanone over Ru/C catalyst was depicted in Scheme 1. Cyclohexanone first reacts with ammonia to form imine, and further hydrogenation of imine affords the desired product cyclohexylamine. However, cyclohexylamine is not inert in the system; it reacts with cyclohexanone to form a Schiff base, as often observed as an intermediate in reductive amination [21]. The Schiff base further reacts with ammonia to form an adduct, and then converts to two molecules of cyclohexylamine via hydrogenolysis [23]. This means, cyclohexylamine is first produced from imine hydrogenation, and additionally from a self-propagation process where one amine molecule becomes two via Schiff base as an intermediate. In the literature, the Schiff base may be directly reduced to a secondary amine by hydrogenation [18]. Nevertheless, only trace amount of secondary amine was detected in all reactions, in accordance with a previous finding that the hydrogenation of the Schiff base was not favored over Ru-based catalysts [23]. As such, formation of secondary amine is not further analyzed in the kinetic modeling, and we only consider direct hydrogenation of cyclohexanone to cyclohexanol as the main side reaction.

Reaction kinetic model has been established based on the reaction pathway (Scheme 1), where first-order reaction was assumed for all steps. The adduct (addition of ammonia to Schiff base) was undetectable, indicating that reaction rate constant k_7 was much larger than k_6. Therefore, the rate constant of Schiff base to adduct (k_6) was used to represent the rate constant of Schiff base to cyclohexylamine. The reversed reaction rate constant of Schiff base formation, i.e., Schiff base reacts with water, and decomposes into cyclohexanone and cyclohexylamine (correspond to rate constant k_8) was much lower than k_5 according to modeling results. Thus, k_8 was ignored in the reaction kinetic model. All kinetic equations for reactant, intermediates and products are listed in Experimental Section 2.4. On the basis of experimental data in selected solvents, reaction rate constants for each step calculated from the kinetic model in Scheme 1 were summarized in Table 2. The fitting curves were shown in Figs. 1–5, which well captured the key features of the concentration of various species as a function of time for selected solvents (methanol, ethanol, water, toluene and dioxane).

The fitting curves for methanol were shown in Fig. 1. The rate constant of cyclohexanone to imine (k_1) was three times higher than the rate constant of cyclohexanone to cyclohexanol (k_4), which was consistent with the fact that imine was observed as the major product in the

Table 2
Reaction rate constants (min^{-1}) calculated from the kinetic model in Scheme 1.

Solvent	k_1	k_2	k_3	k_4	k_5	k_6
Methanol	0.229 ± 0.064	0.737 ± 0.364	0.726 ± 0.137	0.081 ± 0.140	5.000 ± 3.194	0.255 ± 0.048
Ethanol	0.023 ± 0.004	0.104 ± 0.045	0.264 ± 0.052	0.049 ± 0.029	1.299 ± 0.810	0.149 ± 0.030
Water	$k = k_1 * k_3 / k_2 = 15.193 \pm 3.944$			1.584 ± 0.201	–	–
Toluene	0.005 ± 0.001	0.793 ± 0.533	1.132 ± 0.287	0.043 ± 0.009	0.122 ± 0.026	0.522 ± 0.107
Dioxane	0.123 ± 0.073	3.880 ± 1.963	0.023 ± 0.009	0.003 ± 0.002	0.015 ± 0.004	0.201 ± 0.082

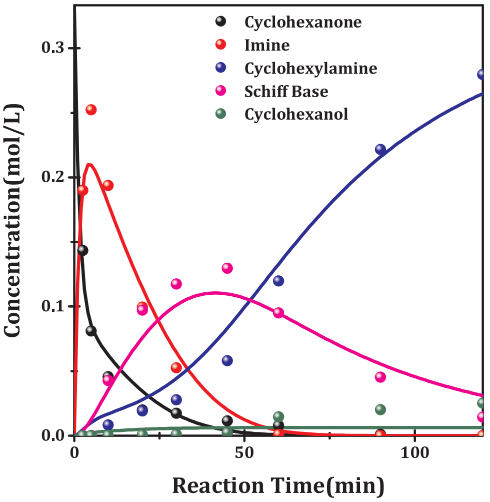


Fig. 1. Experimental (cycles) and modeled (solid lines) concentration of cyclohexanone and products in the reductive amination of cyclohexanone with methanol as solvent over Ru/C catalysts.

first twenty minutes (Fig. 1b). The rate constant of imine to cyclohexanone (k_2) was comparable with that of imine to cyclohexylamine (k_3), but k_2 is less than 20% of the rate constant of cyclohexanone with cyclohexylamine to Schiff base (k_5). As such, a large amount of cyclohexanone has been consumed in the initial five minutes, and further suppressed the formation of cyclohexanol.

The fitted curve for the yield of cyclohexylamine against reaction time exhibited an inflection point at 40–50 min. The slope of the curve gradually increased to a peak value until the concentration of the Schiff base reached its maximum. Afterwards, the slope of the curve decreased as the concentration of the Schiff base decreased. Accordingly to the reaction network, cyclohexylamine is produced via two routes, including the hydrogenation of imine and the hydrogenolysis of Schiff base adduct. MATLAB was employed to identify the percentage of cyclohexylamine from each route (detailed in experimental section). In methanol, approximately 50% of cyclohexylamine originated from the hydrogenation of imine, and the rest was produced from the hydrogenolysis of Schiff base adduct (Table S4).

The yield trends of products (Fig. 2) were similar in ethanol to that in methanol (Fig. 1), but the reaction rate constants were drastically different. The biggest difference lay in k_1, which was almost ten times lower in ethanol, well justifies that the inferior activity was due to the much slower formation rate of imine from cyclohexanone. Other steps were inhibited as well. From Table 2, the reaction rate constants of k_2 to k_6 in ethanol were 2–6 times smaller than that in methanol. This induced a significantly enhanced percentage of intermediates in the product mixture after 3 h reaction. Nonetheless, the ratio of cyclohexylamine from the hydrogenolysis of Schiff base adduct was close to 50% with ethanol as solvent, which was similar to that in methanol (Table S4).

Two major products were identified using water as the solvent, namely cyclohexylamine and cyclohexanol (Fig. 3). Imine was not detected, not unexpected though, due to the instability of imine in water.

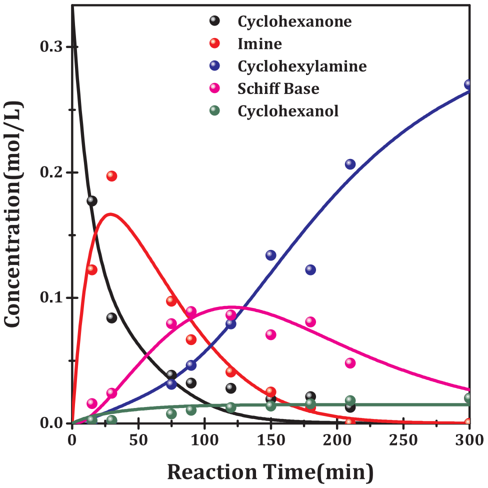


Fig. 2. Experimental (cycles) and modeled (solid lines) concentration of cyclohexanone and different products in the reductive amination of cyclohexanone with ethanol as solvent over Ru/C catalyst.Figure 3. Experimental (cycles) and modeled (solid lines) concentration of cyclohexanone and different products in the reductive amination of cyclohexanone with water as solvent over Ru/C catalyst.

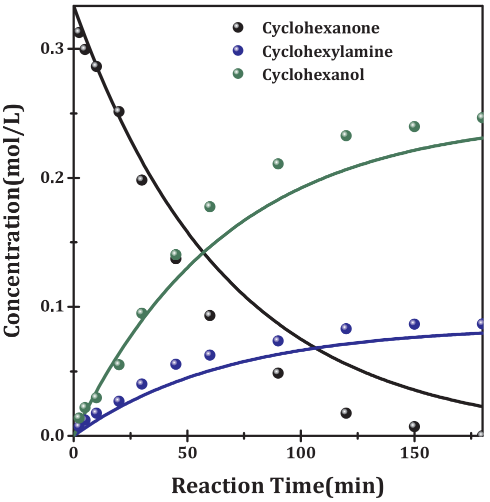


Fig. 3. Experimental (cycles) and modeled (solid lines) concentration of cyclohexanone and different products in the reductive amination of cyclohexanone with water as solvent over Ru/C catalyst.

Therefore, $k = k_1 * k_3 / k_2$ was used to represent the formation rate from cyclohexanone to cyclohexylamine (detailed equations provided in the Supporting Information). Only a trace amount of the Schiff base (< 0.1% yield) was detected during the entire reaction process suggesting the formation of the Schiff base is not favored. We further conducted a control experiment where cyclohexanone and cyclohexylamine were added into aqueous ammonia (Table S3). The yield of the Schiff base was only 1%, indisputably highlighted the strong inhibition

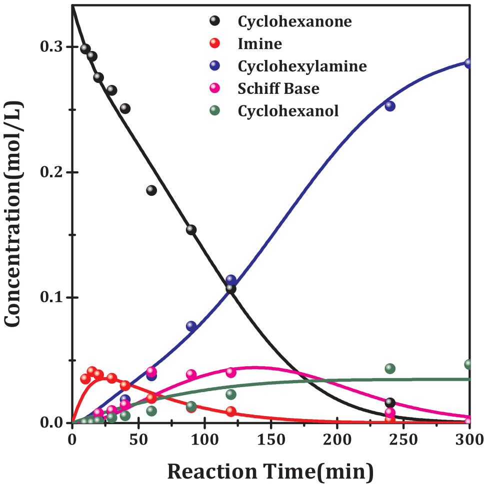


Fig. 4. Experimental (cycles) and modeled (solid lines) concentration of cyclohexanone and different products in the reductive amination of cyclohexanone with toluene as solvent over Ru/C catalyst.

effect of water for the formation of Schiff base. Thus, the rate of cyclohexanone with cyclohexylamine to Schiff base (k_5) was ignored in the kinetic model. After these simplification, we obtained the rate constant of cyclohexanone to cyclohexanol (k_4), as well as that for cyclohexanone to cyclohexylamine (k). Strikingly, k_4 in water is 20 times and 30 times more than that in methanol and ethanol, respectively, suggesting hydrogenation of C=O double bond to alcohol is greatly enhanced. This is an important discovery, implying that the low selectivity towards amine products in water is not only due to the instability of imine, but also due to the remarkably enhanced ability of the catalyst in C=O double bond hydrogenation.

Toluene was chosen as an example of apolar aprotic solvents, and the fitting result was shown in Fig. 4. The conversion of cyclohexanone was slower than earlier cases. In the first 45 min, imine was observed as the main product, but the concentration was significantly lower than that in alcohols. Indeed, the k_1 value in toluene is at least one order of magnitude lower than that in other solvents (except water). At the same time, the reaction rate constant of Schiff base (k_5) in toluene was a few to ten percent compared to the values in alcohols, in accordance with control experiments on Schiff base formation in different solvents where toluene was the second worst solvent after water (Table S3). Despite these disadvantages, the rate constant of imine hydrogenation (k_3) was the largest, while the rate constant of cyclohexanone hydrogenation was the second smallest in toluene. For these reasons, the yield of cyclohexylamine was 85 mol% at full conversion of cyclohexanone, comparable to that in methanol (88 mol%) and in ethanol (86 mol%). In toluene, close to 70% of cyclohexylamine originated from Schiff base (Table S4), which was different with that in protic solvents.

The simulated result for an aprotic polar solvent, dioxane, was shown in Fig. 5. A strong inhibition was observed for both cyclohexanone and imine hydrogenation (Table 1). Therefore, the percentage of amine formation from imine hydrogenation was very small (16% based on fitting results, see Table S4). A dominant portion of the product came from the hydrogenolysis of Schiff base adduct, more significant than that in toluene, and entirely different from reactions in alcohols and water.

Based on reaction kinetic research, we conclude that there are different reaction pathways in various solvents for reductive amination. Cyclohexylamine is the major final product in organic solvents. In alcohols, cyclohexylamine is produced equally from the hydrogenation of imine and hydrogenolysis of Schiff base adduct. In aprotic solvents, cyclohexylamine is mainly produced from the hydrogenolysis of Schiff base adduct with a much slower overall rate. In water, the formation of cyclohexanol is dominate.

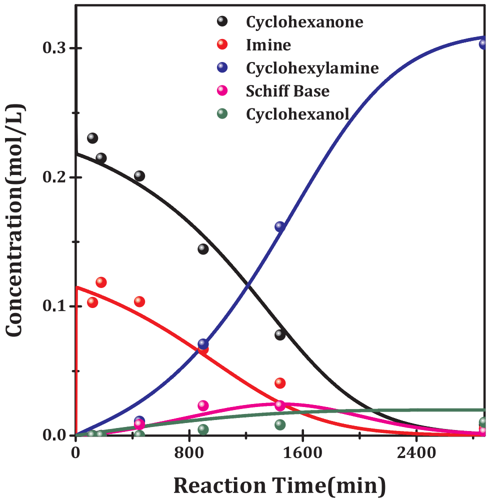


Fig. 5. Experimental (cycles) and modeled (solid lines) concentration of cyclohexanone and different products in the reductive amination of cyclohexanone with dioxane as solvent over Ru/C catalyst.

3.3. Nature of solvent effects on reductive amination of cyclohexanone

Hildebrand-Hansen and Kamlet-Taft parameters are two common sets of parameters used to explain the solvent effects [49–51]. We first attempted to associate catalytic performance with solvent properties, but no clear correlations between solvent parameters and cyclohexylamine yield can be observed (as shown in Fig. S1 and Fig. S2). Therefore, the remarkable solvent effect on reductive amination cannot be simply attributed to the intrinsic properties of the solvent as described by Hilderbrand-Hansen or Kamlet-Taft parameters. Instead, solvent has a profound influence on the catalyst and substrates resulting in a modification of specific reactivity.

In aprotic polar solvents, such as dioxane and tetrahydrofuran, the main product was imine (Table 1, entry 5 and 6). The higher selectivity towards imine implied that hydrogenation of imine was inhibited, which was further testified by the small hydrogenation rate constants (k_3 and k_4 in dioxane, see Table 2). Such an inhibition effect in hydrogenation, plausibly, is due to the strong adsorption of the solvent molecules on the catalysts blocking the accessibility of the active sites [52]. For protic and aprotic apolar solvents, the solvent-catalyst interaction is weaker so that the hydrogenation reaction is not inhibited. Indeed, comparable hydrogenation rate constants (k_3 and k_4) were found in methanol, ethanol and toluene (Table 2). Therefore, the drastically different product distributions in these solvents was a result of solvent-dependant imine and Schiff base formation rate. Protic solvents are more active promoting the reaction between ammonia and ketone, as well as reaction between imine and ketone than aprotic apolar solvents. The lowest selectivity of cyclohexylamine observed in water is due to two reasons: 1) the instability of imine and Schiff base in water, which is well known, and 2) the significantly enhanced C=O double bond hydrogenation activity. One explanation for the second factor is that water directly participated in the reaction by acting as a hydrogen donor, which has been suggested by DFT calculations for C=O hydrogenation under basic conditions [53].

To identify whether the solvent effects observed on Ru catalysts are extendable to other metal catalysts, reductive amination of cyclohexanone over Pt/C, Rh/C and Pd/C catalysts in methanol and water were investigated (Fig. 6, Ru/C data were included for easier comparison). The exact trend observed over Ru/C catalysts, i.e., the selectivity toward cyclohexylamine in methanol was substantially higher than that in water, was also observed over Pt/C (10% vs 0.8%), Rh/C (89% vs 42%) and Pd/C (72% vs 13%) catalysts, suggesting the drastic solvent effect in amination is not specific to Ru, but is a general phenomenon.

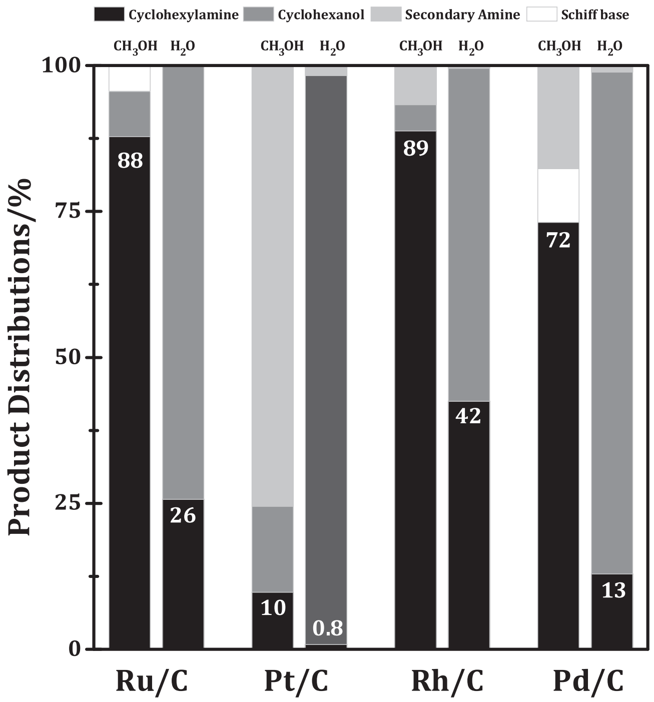


Fig. 6. Product distributions of reductive amination of cyclohexanone over Group VIII metal-based catalysts in methanol and water. Reaction conditions: Cyclohexanone 1 mmol, catalyst 0.02 g, solvent 3 mL, H_2 = 9 bar, T = 298 K, agitator speed = 1000 rpm, time = 2 h.

Recycling experiments of cyclohexanone reductive amination over Ru/C catalyst were conducted. The conversion of cyclohexanone decreased from 94.8% to 87.7% after five cycles. The yield of imine increased, while the yields of Schiff base, cyclohexylamine and cyclohexanol decreased (as shown in Fig. S3). These suggest that the Ru/C catalyst is reusable and reasonably stable in methanol.

4. Conclusion

In organic chemistry, the solvent effect is well established and widely practiced. This was not the case for either gas-liquid-solid three phase catalytic reactions in general, or metal catalyzed reductive amination reaction in particular. In this study, we report a dramatic solvent effect on reductive amination of ketones over metal catalysts in protic, aprotic polar and aprotic apolar solvents. A complete, solvent-dependent reaction network was established and quantitatively analyzed. Imine and Schiff base are two key intermediates for amine formation, while direct hydrogenation of ketone to alcohol is the major side reaction. In alcohols, cyclohexylamine is produced equally from the hydrogenation of imine and hydrogenolysis of Schiff base adduct while in toluene and dioxane, cyclohexylamine is mainly originated from hydrogenolysis of Schiff base adduct.

Water is not a preferable solvent, since it prevents imine/Schiff base formation while promotes undesired C═O hydrogenation. Aprotic polar solvents have strong solvent-catalyst interactions that inhibit the hydrogenation activity of the catalyst, resulting in a slow overall reaction rate towards amine. The major issue with aprotic apolar solvents is that the formation of two key intermediates, i.e., imine and Schiff base, is sluggish. Methanol is the most suitable solvent due the highest rates for imine and Schiff base formation compared to other solvents, and a high rate for hydrogenation. This study highlights the critical role of solvents in determining the activity and selectivity in reductive amination, which should not be neglected in designing new catalytic systems and rationalizing catalyst performance.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.mcat.2018.05.017.

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