Heterogeneously Catalyzed One-pot Synthesis of Aldimines from Primary Alcohols and Amines by Supported Ruthenium Hydroxides

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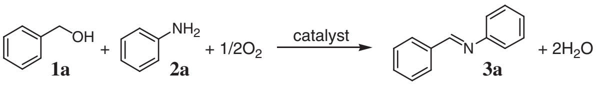
The one-pot synthesis of aldimines from primary alcohols and amines via sequential reactions of alcohol oxidation and dehydrative condensation could efficiently be promoted by supported ruthenium hydroxide catalysts, in particular $Ru(OH)_x/TiO_2$. The observed catalysis was truly heterogeneous and the retrieved catalyst could be reused without an appreciable loss of high catalytic performance.

Sequential catalysis that can mediate one-pot multistep synthesis has attracted much attention in both research and chemical industries.[1–3] In comparison with stepwise syntheses, one-pot synthesis can avoid the isolation of (unstable) intermediates and can reduce the production of chemical waste.[1–3] Although many transition-metal-based catalytic one-pot synthetic procedures have been developed, these systems have disadvantages of the recovery and reuse of (expensive) catalysts and/or the need for co-catalysts such as bases and stabilizing ligands.[1] Recently, focus has shifted from homogeneous to heterogeneous catalysis and several heterogeneously catalyzed efficient one-pot procedures have been reported.[2,3] Also, we have developed various heterogeneously catalyzed efficient functional group transformations including one-pot multistep syntheses by metal hydroxide catalysts.[3]

Imines (aldimines and ketimines) are an important class of chemicals that have widely been used as synthons for the organic synthesis, pharmaceuticals, and agricultural chemicals.[4] Very recently, one-pot procedures with heterogeneous catalysts such as manganese octahedral molecular sieves (K-OMS-2)[5a] and gold nanoparticles supported on hydroxyapatite (Au/HAP)[5b] for the synthesis of aldimines directly from primary alcohols and amines have been reported. However, the turnover frequencies (TOFs) are 1.3–83 h^{-1} and still low.[5] In this paper, we report the efficient one-pot syntheses of aldimines from primary alcohols and amines by supported ruthenium hydroxide catalysts.

First, the catalytic activities for the reaction of benzyl alcohol (**1a**) with aniline (**2a**) to produce *N*-benzylideneaniline (**3a**) were compared among various catalysts (Table 1). Supported ruthenium hydroxide catalysts such as $Ru(OH)_x/TiO_2$ and $Ru(OH)_x/Al_2O_3$ (see Supporting Information[6] for preparation and characterization) showed high catalytic activities for the synthesis of **3a**. In these cases, the corresponding secondary amine was not formed. No reaction proceeded in the absence of the catalysts, or in the presence of TiO_2 or Al_2O_3. In the presence of the catalyst precursor $RuCl_3 \cdot nH_2O$, the desired aldimine **3a** was not formed. Also, ruthenium complexes $RuCl_2(PPh_3)_3$, $RuCl_2(bpy)_2$, $[RuCl_2(p\text{-cymene})]_2$, $Ru(acac)_3$, and $Ru_3(CO)_{12}$ were not effective. The catalytic activities of supported ruthenium hydroxides were much higher than those of other heterogeneous catalysts such as Ru/C, Ru/HAP,[7] anhydrous RuO_2, and $Ru(OH)_x$. The reaction hardly proceeded in the presence of ruthenium chloride species supported on TiO_2 prepared without base pretreatment ($RuCl_x/TiO_2$, see Supporting Information[6] for preparation). Therefore, the generation of the active ruthenium hydroxide species on supports is very important to obtain high catalytic performance.

Table 1. The one-pot synthesis of **3a** by various catalysts[a]



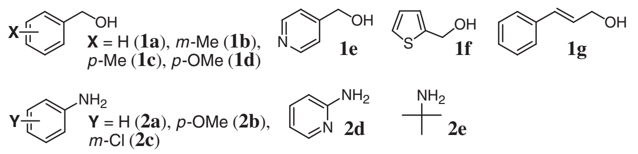
Entry	Catalyst	Yield of **3a**/%
1	$Ru(OH)_x/TiO_2$	95
2	$Ru(OH)_x/Al_2O_3$	44
3[b]	$Ru(OH)_x/Al_2O_3$	92
4	$RuCl_x/TiO_2$	<1
5	Ru/C	15
6	Ru/HAP	2
7	$Ru(OH)_x$	<1
8	anhydrous RuO_2	<1
9	$RuCl_3 \cdot nH_2O$	<1
10	$RuCl_2(PPh_3)_3$	2
11	$RuCl_2(bpy)_2$	<1
12	$[RuCl_2(p\text{-cymene})]_2$	<1
13	$Ru(acac)_3$	<1
14	$Ru_3(CO)_{12}$	<1
15[c]	TiO_2	<1
16[c]	Al_2O_3	<1
17	None	<1

[a]Reaction conditions: Catalyst (Ru: 2 mol %), **1a** (0.5 mmol), **2a** (0.75 mmol), toluene (2 mL), O_2 (1 atm), 100 °C, 60 min. Yields (based on **1a**) were determined by GC analyses. [b]180 min. [c]50 mg.

The $Ru(OH)_x/TiO_2$-catalyzed reaction of **1a** with **2a** was carried out under the conditions described in Table 1 and the catalyst was removed from the reaction mixture by hot filtration at ca. 40% conversion of **1a**. After removal of the catalyst, the reaction was again carried out with the filtrate under the same conditions. In this case, no further reaction proceeded (Figure S1).[6] In addition, it was confirmed by ICP-AES analysis that no ruthenium was detected in the filtrate (below detection limit of 7 ppb). These facts can rule out any contribution to the observed catalysis from ruthenium species that leached into the reaction solution and the observed catalysis is intrinsically heterogeneous.[8]

In the presence of the most active $Ru(OH)_x/TiO_2$ catalyst, various combinations of substrates (seven alcohols and five

Table 2. The one-pot synthesis of various aldimines[a]



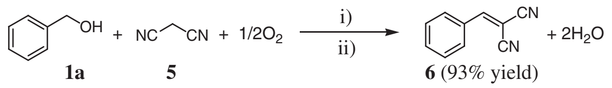
Entry	Alcohol	Amine	Time/min	Yield/%
1	**1a**	**2a**	60	95
2	**1a**	**2b**	180	91
3	**1a**	**2c**	90	87
4[b]	**1a**	**2d**	360	72
5[c]	**1a**	**2e**	60	74
6	**1b**	**2a**	75	98
7	**1c**	**2a**	60	95
8	**1d**	**2a**	60	95
9	**1e**	**2a**	180	91
10	**1f**	**2a**	360	62
11	**1g**	**2a**	180	91

[a]Reaction conditions: $Ru(OH)_x/TiO_2$ (Ru: 2 mol %), alcohol (0.5 mmol), amine (0.75 mmol), toluene (2 mL), O_2 (1 atm), 100 °C. Yields (based on alcohols) were determined by ^1H NMR or GC analyses. The chemical structures and data of products are shown in the Supporting Information. [b]$Ru(OH)_x/TiO_2$ (Ru: 4 mol %). [c]**2e** (1.5 mmol).

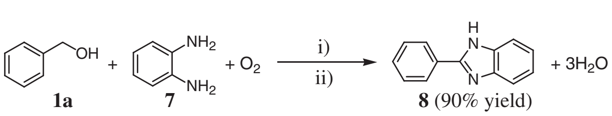
amines) have been investigated and all reactions efficiently proceeded to afford the corresponding aldimines in moderate to excellent yields (Table 2). Unfortunately, the reaction of the aliphatic alcohol 1-octanol with **2a** under the conditions described in Table 2 for 180 min gave the corresponding aldimine in only 5% yield. Notably, $Ru(OH)_x/TiO_2$ could be applied to the larger-scale production; the 10 mmol-scale reaction of **1a** with **2a** [**1a** (10 mmol), **2a** (15 mmol), $Ru(OH)_x/TiO_2$ (0.5 mol %), *p*-xylene (20 mL), O_2 (1 atm), 120 °C, 240 min] gave 80% yield of **3a**. In this case, the TOF (based on the initial rate) reached up to 182 h^{-1} and the value was higher than those of the previously reported heterogeneous systems (1.3–83 h^{-1}).[5] After the reaction was completed, the $Ru(OH)_x/TiO_2$ catalyst could easily be retrieved by filtration and the retrieved catalyst could be reused without an appreciable loss of its high catalytic performance (94% yield of **3a** for the reuse experiment).

The time courses for the reaction of **1a** with **2a** showed that benzaldehyde (**4**) was initially produced followed by the formation of **3a**. Therefore, the present transformation proceeds by sequential reactions, that is, the aerobic oxidation of alcohols to aldehydes followed by the dehydrative condensation to produce the corresponding aldimines. The reaction rate for the dehydrative condensation of **4** and **2a** in the presence of $Ru(OH)_x/TiO_2$ was 47 mM min^{-1} at 25 °C and was larger than that in the absence (21 mM min^{-1}),[6] suggesting that $Ru(OH)_x/TiO_2$ catalyzes not only the aerobic alcohol oxidation but also the dehydrative condensation.

Moreover, besides the synthesis of aldimines, the syntheses of benzylidenemalononitrile (**6**) (tandem reactions of alcohol oxidation and Knoevenagel condensation,[9] Scheme 1) and 2-phenylbenzimidazole (**8**) (tandem reactions of alcohol oxidation, double condensation, and amine oxidation, Scheme 2) could be realized in the presence of supported ruthenium hydroxide catalysts.[6]



Scheme 1. The tandem one-pot synthesis of **6**. Reaction conditions: i) $Ru(OH)_x/Al_2O_3$ (Ru: 1 mol %), **1a** (1 mmol), toluene (2 mL), O_2 (1 atm), 80 °C, 90 min, ii) followed by addition of 1,4-dioxane solution of **5** (1.2 M, 1 mL), air (1 atm), 80 °C, 20 min.



Scheme 2. The tandem one-pot synthesis of **8**. Reaction conditions: i) $Ru(OH)_x/TiO_2$ (Ru: 1 mol %), **1a** (1 mmol), toluene (2 mL), O_2 (1 atm), 80 °C, 60 min, ii) followed by addition of 1,4-dioxane solution of **7** (1 M, 2 mL), air (1 atm), 80 °C, 60 min.

In conclusion, supported ruthenium hydroxides could act as efficient heterogeneous catalysts for the above mentioned one-pot syntheses. The present system has the following significant advantages; i) higher TOF than those of the previously reported heterogeneous systems,[5] ii) applicability to various substrates, iii) no use of cocatalysts, iv) simple workup procedure, namely catalyst/product separation, and v) reusability of the catalyst.

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6 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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9 The reaction rate for the Knoevenagel condensation of **4** and **5** with $Ru(OH)_x/Al_2O_3$ was ca. ten times larger than that with $Ru(OH)_x/TiO_2$ (Table S1).[6] Thus, we used $Ru(OH)_x/Al_2O_3$ for this transformation (Scheme 1). The active site for the Knoevenagel condensation might be the basic site on Al_2O_3.