Amine Synthesis

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Efficient Catalytic Synthesis of Tertiary and Secondary Amines from Alcohols and Urea**

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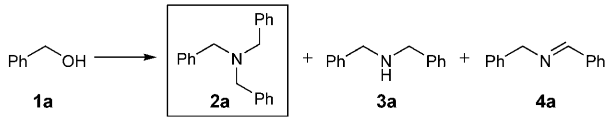
The synthesis of tertiary and secondary amines is of great importance because they have been used as dyes, color pigments, electrolytes, extractants, stabilizers, and synthons for pharmaceuticals, agricultural chemicals, herbicides, polymers, and functionalized materials.[1] A number of catalytic and non-catalytic procedures,[1c] for example, 1) N-alkylation of amines with alkyl halides or alcohols,[2] 2) reductive amination of carbonyl compounds,[3] 3) amination of aryl halides,[4] and 4) hydroamination of unsaturated hydrocarbons with amines,[5] have been developed for the synthesis of tertiary and secondary amines.[1c] However, these conventional procedures suffer significant disadvantages: 1) the use of environmentally unfriendly halides, 2) use of expensive amines as starting materials, 3) production of large amounts of wasteful salts, and 4) low selectivities.[1–5] Therefore, the development of more efficient and green catalytic synthetic procedures is a challenging subject in the modern organic synthesis.

Ammonia and its related compounds, such as urea and ammonium salts, are attractive nitrogen sources for the synthesis of amines.[6–8] Until now, many efficient catalytic procedures using copper, ruthenium, rhodium, and iridium complexes have been reported for the synthesis of primary amines using ammonia or its related compounds as nitrogen sources.[7] As for the selective catalytic synthesis of tertiary and secondary amines using ammonia or its related compounds, there are only a few reports;[8,9] for example, 1) palladium-catalyzed N-arylation of ammonia with aryl halides[8a] and 2) iridium-catalyzed N-alkylation of ammonium salts such as NH_4OAc and NH_4BF_4 with alcohols.[8b] Most of these reported procedures for the catalytic synthesis of amines (including primary, secondary, and tertiary amines) are homogeneous systems and have shortcomings in the catalyst/product separation and recycling of expensive platinum group metal catalysts.[10]

Recently, we have developed a series of metal hydroxide catalysts for various functional group transformations promoted by the "concerted activation" of the Lewis acid and Brønsted base sites on these catalysts.[11,12] During the course of our investigations, we have now discovered that the synthesis of tertiary and secondary amines from alcohols and urea could be realized in the presence of the ruthenium hydroxide catalyst supported on titanium dioxide, $Ru(OH)_x/TiO_2$. Whereas there are many procedures (including catalytic and non-catalytic) for the synthesis of amines,[2–9] nothing has been reported for the catalytic selective synthesis of tertiary and secondary amines from alcohols and urea.

First, the catalytic activity and selectivity for the reaction of benzyl alcohol (**1a**) and urea to give tribenzylamine (**2a**) were compared by using various catalysts (Table 1). The supported ruthenium hydroxide catalysts such as $Ru(OH)_x/TiO_2$ and $Ru(OH)_x/Al_2O_3$ showed high catalytic activities for the transformation;[13] in particular, the transformation with

Table 1: Synthesis of **2a** from **1a** and urea.[a]



Entry	Catalyst	Yield [%][b]			
		2a	**3a**	**4a**	others[c]
1	$Ru(OH)_x/TiO_2$	93(19)	1	1	n.d.
2	$Ru(OH)_x/Al_2O_3$	47(9)	11	18	n.d.
3	$RuCl_x/TiO_2$	n.d.	2	4	n.d.
4	$Ru(OH)_x$	n.d.	n.d.	2	34
5	RuO_2 anhydrous	n.d.	n.d.	n.d.	50
6	RuHAP	n.d.	1	3	33
7	Ru/C	18(4)	2	6	29
8	$RuCl_3 \cdot n H_2O$	n.d.	n.d.	n.d.	21
9	$[RuCl_2(PPh_3)_3]$	39(8)	n.d.	n.d.	40
10	$[\{RuCl_2(p\text{-cymene})\}_2]$	20(4)	7	6	37
11	$[RuCl_2(bpy)_2]$	n.d.	n.d.	n.d.	50
12	$[Ru(acac)_3]$	1(0.2)	5	7	30
13	$[Ru_3(CO)_{12}]$	n.d.	2	3	31
14[d]	TiO_2	n.d.	1	4	2
15	none	n.d.	n.d.	n.d.	44

[a] Reaction conditions: **1a** (2.5 mmol), urea (0.25 mmol), catalyst (Ru: 0.015 mmol), mesitylene (0.5 mL), 141 °C, 12 h, under 1 atm of Ar. [b] Yields were based on the amount of nitrogen in urea and determined by GC analyses. Values in the parentheses are yields based on alcohols. n.d. = not detected (below 1 % yield). [c] The main by-product was benzyl carbamate. [d] Used 75 mg of TiO_2. bpy = 2,2′-bipyridine, acac = acetylacetonate.

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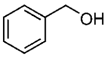
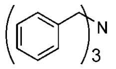
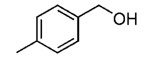
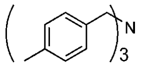
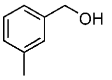
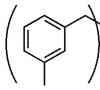
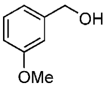
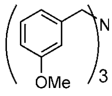
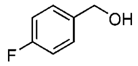
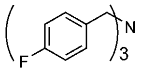
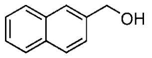
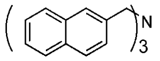
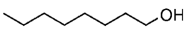
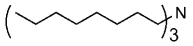
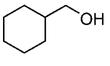
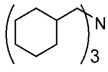
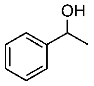
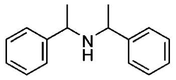
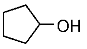
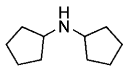
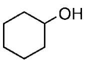
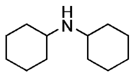
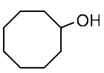
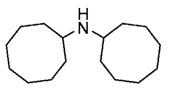
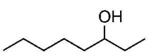
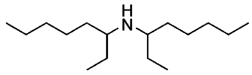
$Ru(OH)_x/TiO_2$ gave **2a** in 93 % yield (based on the amount of nitrogen in urea) with high selectivity (Table 1, entry 1).[14] In the absence of the catalyst, the desired tertiary amine **2a** was not formed and benzyl carbamate was formed as a major by-product through the condensation of **1a** and urea (Table 1, entry 15). No formation of **2a** was observed in the presence of just TiO_2 (Table 1, entry 14). In contrast to the transformation without the catalyst, benzyl carbamate was hardly observed with TiO_2. We confirmed, in separate experiments, that urea was hydrolytically decomposed to ammonia by the presence of TiO_2 under the conditions described in Table 1[15] and that the decomposition hardly proceeded in the absence of TiO_2. Therefore, the TiO_2 support takes part in the in situ generation of ammonia from urea during the reaction.

In the presence of the catalyst precursor of $RuCl_3{\cdot}n\,H_2O$, the desired tertiary amine **2a** was not produced (Table 1, entry 8). Complexes of $[RuCl_2(bpy)_2]$, $[Ru(acac)_3]$, and $[Ru_3(CO)_{12}]$ were not effective (Table 1, entries 11–13), and although $[RuCl_2(PPh_3)_3]$ and $[\{RuCl_2(p\text{-cymene})\}_2]$ gave moderate yields of **2a**, the undesirable benzyl carbamate was also produced as a by-product (Table 1, entries 9 and 10). The catalytic activity of $Ru(OH)_x/TiO_2$ was much higher than those of other ruthenium-based heterogeneous catalysts such as $Ru(OH)_x$,[11d] RuO_2 anhydrous, RuHAP (HAP = hydroxyapatite),[16] and Ru/C (Table 1, entries 4–7). The transformation hardly proceed in the presence of ruthenium chloride species supported on TiO_2 ($RuCl_x/TiO_2$) prepared without the base treatment (Table 1, entry 3). The base treatment of the catalyst with an aqueous NaOH solution during the preparation significantly increased the activity (Table 1, entry 1 versus entry 3). This increased activity is likely because of the generation of the active ruthenium hydroxide species on the surface of TiO_2 by the reaction of ruthenium chloride species with NaOH.[11]

To verify whether the observed catalysis is derived from solid $Ru(OH)_x/TiO_2$ or leached ruthenium species, the transformation of **1a** into **2a** was carried out under the conditions described in Table 1 and the catalyst was removed from the reaction mixture by filtration to give a 50 % yield of **2a**. After removal of the catalyst, urea (0.25 mmol) was newly added to the filtrate and the solution was again heated at 141 °C under 1 atm of Ar. In this case, no additional production of **2a** was observed. It was confirmed by the inductively coupled plasma atomic emission spectroscopy (ICP/AES) analysis that no ruthenium was detected in the filtrate. All these results rule out any contribution to the observed catalysis from ruthenium species that leached into the reaction solution and the observed catalysis is intrinsically heterogeneous.[17]

Next, the scope of the present $Ru(OH)_x/TiO_2$-catalyzed system with regard to various kinds of structurally diverse primary and secondary alcohols was examined. $Ru(OH)_x/TiO_2$ showed high catalytic performance for the transformation of benzylic, aliphatic liner, and aliphatic cyclic alcohols, as summarized in Table 2. The transformation of primary benzylic alcohols (**1a**–**1f**) containing electron-donating as well as electron-withdrawing substituents efficiently proceeded to afford the corresponding benzylic tertiary amines in high yields (Table 2, entries 1–6). In the transformation of aliphatic primary alcohols (**1g** and **1h**), the corresponding aliphatic tertiary amines could be obtained (Table 2, entries 7 and 8). Secondary alcohols including benzylic (**1i**), cyclic (**1j**–**1l**), and acyclic (**1m**) alcohols were selectively converted into the corresponding secondary amines in high yields, even in the presence of excess amounts of the secondary alcohol (Table 2, entries 9–14), which is likely to result from the steric hindrance of

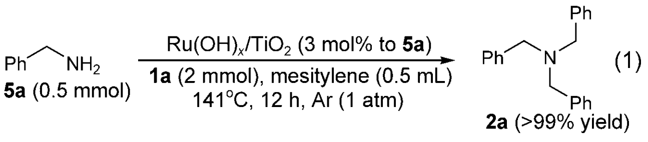
Table 2: Synthesis of tertiary and secondary amines from alcohols and urea catalyzed by $Ru(OH)_x/TiO_2$.[a]

Entry	Substrate		*t* [h]	Product		Yield [%][b]
1[c,d]		**1a**	12		**2a**	89(18)
2		**1b**	16		**2b**	95(19)
3		**1c**	24		**2c**	94(19)
4		**1d**	20		**2d**	93(19)
5		**1e**	24		**2e**	76(15)
6		**1f**	24		**2f**	86(17)
7[c]		**1g**	15		**2g**	87(17)[e]
8		**1h**	24		**2h**	97(19)
9		**1i**	24		**3i**	92(18)[f]
10		**1j**	24		**3j**	80(16)
11		**1k**	16		**3k**	92(18)
12		**1l**	24		**3l**	85(17)
13		**1m**	20		**3m**	98(20)[g]

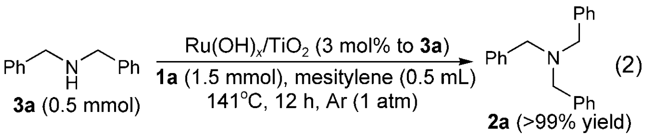
[a] Reaction conditions: Alcohol (2.5 mmol), urea (0.25 mmol), $Ru(OH)_x/TiO_2$ (Ru: 0.02 mmol), mesitylene (0.8 mL), 141 °C, under 1 atm of Ar. [b] Yields of isolated product are based on the amount of nitrogen in urea. Values in the parentheses are yields of the isolated product based on alcohols. [c] Mesitylene (0.5 mL). [d] Used $Ru(OH)_x/TiO_2$ (Ru: 0.015 mmol). [e] Yield determined by GC analysis. [f] A mixture of diastereomers (meso/*dl* = 77:23). [g] A mixture of diastereomers (the ratio was not determined.).

secondary alcohols or secondary amines produced.[18] After the transformation was completed, the $Ru(OH)_x/TiO_2$ catalyst could easily be retrieved from the reaction mixture by simple filtration (or centrifugation). The retrieved catalyst could be reused without a significant loss of its catalytic performance; for example, 90% yield of **3k** was obtained in the transformation of **1k** for the recycling experiment with the retrieved catalyst.

The reaction profiles for the $Ru(OH)_x/TiO_2$-catalyzed transformation of **1a** into **2a** showed that the initially formed **4a** was hydrogenated to **3a** with subsequent N-alkylation to produce **2a** (see Figure S1 in the Supporting Information). In addition, benzaldehyde and benzylamine (**5a**, below 1% yield) could be detected during the reaction, albeit in only small amounts. Furthermore, it was confirmed by the separate experiments that the $Ru(OH)_x/TiO_2$-catalyzed N-alkylation of **5a** [Eq. (1)] and **3a** [Eq. (2)] with **1a** efficiently proceeded to afford the corresponding tertiary amine **2a** in quantitative yields (based on starting amines). In the absence of **1a**, the desired tertiary amine **2a** was not produced under the conditions described in Equation (1) and (2).[19] Therefore, the present catalytic transformation would proceed through the three (or double) N-alkylation reactions, in which alcohols act as alkylating reagents. In the first N-alkylation, the oxidative dehydrogenation of an alcohol into the corresponding carbonyl compound initially proceeds with the transitory formation of the ruthenium hydride species.[11a,b,d] Then, the carbonyl compound readily reacts with ammonia[20] (produced through the hydrolytic decomposition of urea) to form the corresponding imine.[11e] Finally, the hydrogen transfer reaction from the hydride species to the imine proceeds to afford the corresponding primary amine. The second and third N-alkylations would proceed through the similar sequential processes (see the Scheme in Figure S1 in the Supporting Information), that is, 1) the oxidative dehydrogenation of an alcohol, 2) formation of an imine (or an iminium cation), and 3) hydrogenation of the imine (or the iminium cation).



(1)



(2)

In conclusion, $Ru(OH)_x/TiO_2$ serves as an efficient heterogeneous catalyst for the synthesis of tertiary and secondary amines directly from alcohols and urea. The observed catalysis was truly heterogeneous and the catalyst was reusable. The more detailed mechanistic studies are now in progress.

Experimental Section

The supported ruthenium hydroxide catalysts ($Ru(OH)_x/TiO_2$ and $Ru(OH)_x/Al_2O_3$), $RuCl_x/TiO_2$, and $Ru(OH)_x$ were prepared according to the reported procedures (see the Supporting Information for the preparation).[11] A procedure for the synthesis of amines was as follows: All operations for the synthesis of amines were carried out in a glove box under Ar. $Ru(OH)_x/TiO_2$ (Ru: 1.5–2 mol% with respect to urea), an alcohol (2.5 mmol), urea (0.25 mmol), and mesitylene (0.5–0.8 mL) were successively placed into a Pyrex-glass screw cap vial (volume: ca. 20 mL). A Teflon-coated magnetic stir bar was added and the reaction mixture was vigorously stirred (800 rpm) at 141 °C under 1 atm of Ar. The product yields were periodically determined by GC analyses. After the reaction was completed, the spent $Ru(OH)_x/TiO_2$ catalyst was separated by filtration (or centrifugation), washed with mesitylene and 2-propyl alcohol, and then dried in vacuo prior to being recycled. The products (tertiary and secondary amines) were isolated after a silica gel column chromatography (initial: *n*-hexane, after mesitylene was eluted: ethyl acetate). The isolated products were characterized by ^1H and ^{13}C NMR and GC mass analyses.[8,21]

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Keywords: alcohols · amines · heterogeneous catalysis · ruthenium hydroxide · urea

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[13] The preparation of highly dispersed, supported ruthenium hydroxide catalysts with SiO_2 and MgO was unsuccessful because SiO_2 and MgO supports were somewhat soluble in the ruthenium solution during the catalyst preparation.

[14] Judging from the Ru K-edge EXAFS and ESR analyses, ruthenium species on TiO_2 ($Ru(OH)_x/TiO_2$, the coordination number of nearest neighbor Ru atoms ($CN = 0.76 \pm 0.21$) were more highly dispersed than that on Al_2O_3 ($Ru(OH)_x/Al_2O_3$, $CN = 0.91 \pm 0.20$).[11d] We have very recently reported that the catalytic activities of $Ru(OH)_x/TiO_2$ with more highly dispersed ruthenium species for the oxidative dehydrogenation and hydrogen transfer reactions were higher than those of $Ru(OH)_x/Al_2O_3$.[11d,f]

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[18] Similar selectivities to secondary amines reported for the $[\{Cp^*IrCl_2\}_2]$-catalyzed N-alkylation of NH_4BF_4 with secondary alcohols are explained by the steric hindrance.[8b]

[19] In the transformation of **5a** without **1a** under the conditions described in Equation (1), a small amount of the secondary amine **3a** was produced (4 % yield based on **5a**).

[20] When the reaction of **1a** was carried out with ammonia (0.5 mmol, 28 % aqueous solution of ammonia) instead of urea under the reaction conditions described in Table 1 (for 6 h), the desired tertiary amine **2a** was obtained in 87 % yield (based on ammonia).

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