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Research Note

Heterogeneously catalyzed selective *N*-alkylation of aromatic and heteroaromatic amines with alcohols by a supported ruthenium hydroxide

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ABSTRACT

The *N*-alkylation of aromatic and heteroaromatic amines with alcohols could efficiently be promoted by an easily prepared supported ruthenium hydroxide catalyst $Ru(OH)_x/Al_2O_3$. A variety of aromatic and heteroaromatic amines were selectively converted into the corresponding secondary amines in moderate to excellent yields without any co-catalysts such as bases and stabilizing ligands. The observed catalysis was intrinsically heterogeneous and the $Ru(OH)_x/Al_2O_3$ catalyst recovered after the reaction could be reused without an appreciable loss of its high catalytic performance for the *N*-alkylation.

1. Introduction

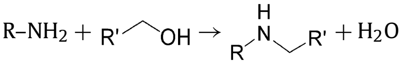
The *N*-alkylation of primary amines to secondary amines is of fundamental importance because secondary amines have widely been used as synthetic intermediates for pharmaceuticals, agrochemicals, bioactive compounds, polymers, and dyes [1,2]. In particular, the *N*-alkylation of aromatic amines is very important in industries [1,2]. The most frequently used procedure for the *N*-alkylation is the reaction of amines with alkyl halides in the presence of stoichiometric amounts of inorganic bases [1–3] [Eq. (1)]:

$$R\text{–}NH_2 + \underset{(X=Cl,Br,I)}{R'\text{–}X} \rightarrow RR'NH + HX \tag{1}$$

However, the selectivity to the desired secondary amines is generally low in the *N*-alkylation with alkyl halides because the nucleophilicity of amines is increased by the *N*-alkylation, resulting in the formation of undesired tertiary amines and alkylammonium halides as byproducts [1–3]. In addition, the above reaction produces large amounts of inorganic salts as wastes [1–3].

An alternative environmentally-benign approach to the synthesis of secondary amines is the *N*-alkylation with alcohols as alkylating reagents in the presence of transition metal catalysts [4–15]. The advantage of the procedure in comparison with the *N*-alkylation with alkyl halides is the high selectivity to the desired secondary amines. This is because it proceeds via a completely different mechanism [4–8]. In addition, the reaction produces only water as a byproduct [Eq. (2)]:

Until now, many homogeneous transition metal


(2)

$$R\text{–}NH_2 + R'CH_2OH \rightarrow R\overset{H}{N}CH_2R' + H_2O \tag{2}$$

catalysts, especially ruthenium- and iridium-based catalysts, have been reported to be active for the *N*-alkylation with alcohols [4–8]. However, these systems have disadvantages of the recovery and reuse of expensive catalysts and/or the indispensable use of co-catalysts such as bases and stabilizing ligands [4–8]. The development of easily recoverable and recyclable heterogeneous catalysts can solve the problems of the homogeneous systems and has received a particular research interest [16–20]. Although there are several reports on the *N*-alkylation using heterogeneous catalysts such as solid acids and transition metal-based catalysts, most of them require high reaction temperatures, the scope of substrates is limited, and turnover frequency (TOF) and turnover number (TON) are low [9–15]. Therefore, the development of widely usable heterogeneously catalyzed selective *N*-alkylation systems is still challenging.

Herein, we report the selective *N*-alkylation of aromatic and heteroaromatic amines with alcohols by an easily prepared supported ruthenium hydroxide catalyst $Ru(OH)_x/Al_2O_3$ [21–24]. The present system has the following significant advantages: (i) applicability to various aromatic and heteroaromatic amines, (ii) higher catalytic activity and selectivity than those of the previously reported heterogeneous systems [9–15], (iii) no use of co-catalysts,

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(iv) simple workup procedure, namely catalyst/product separation, (v) reusability of the $Ru(OH)_x/Al_2O_3$ catalyst, and (vi) use of an easily prepared $Ru(OH)_x/Al_2O_3$ catalyst.

2. Experimental

2.1. General

GC analyses were performed on Shimadzu GC-2014 using a flame ionization detector equipped with a TC-5 (internal diameter = 0.25 mm, length = 60 m) or a DB-WAX capillary column (internal diameter = 0.25 mm, length = 30 m). NMR spectra were recorded on JEOL JNM-EX-270. ^1H and ^{13}C NMR spectra were measured at 270 and 67.8 MHz, respectively, in $CDCl_3$ with TMS as an internal standard. ^2H NMR spectra were measured at 41.25 MHz using C_6D_6 as an external standard. Mass spectra were recorded on Shimadzu GCMS-QP2010 equipped with a TC-5HT capillary column (internal diameter = 0.25 mm, length = 30 m). The ICP-AES analyses were performed with Shimadzu ICPS-8100. Reagents and substrates were commercially obtained from Tokyo Kasei, Aldrich, and Fluka (reagent grade), and purified before the use [25]. Al_2O_3 (KHS-24, BET surface area: 160 $m^2\,g^{-1}$) was obtained from Sumitomo Chemical. Ru/C (Ru metal on active carbon, 5 wt%) and RuHAP [26] (Ru–Cl species on hydroxyapatite, 9.1 wt%) were purchased from NE Chemcat and Wako, respectively. The supported ruthenium hydroxide catalyst $Ru(OH)_x/Al_2O_3$ was prepared according to the procedure reported previously (see Supporting information) [21–24].

2.2. Procedure for the *N*-alkylation

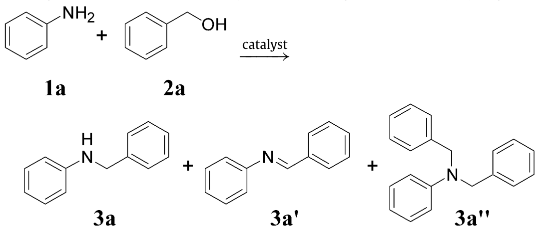
All operations for the *N*-alkylation were carried out in a glove box under Ar. A typical example is as follows. Into a Pyrex-glass vial were successively placed $Ru(OH)_x/Al_2O_3$ (Ru: 5 mol%), aniline (**1a**, 0.25 mmol), benzyl alcohol (**2a**, 0.375 mmol), and mesitylene (1 mL). A Teflon-coated magnetic stir bar was added and the reaction mixture was vigorously stirred (800 rpm) at 132 °C under 1 atm of Ar. The conversion and yield(s) were periodically determined by GC analyses. After the reaction was completed (11 h), the spent $Ru(OH)_x/Al_2O_3$ catalyst was separated by filtration, washed with an aqueous solution of NaOH (0.1 M) and water, and then dried in vacuo prior to being recycled. The product **3a** was isolated by a silica gel column chromatography (89% isolated yield).

3. Results and discussion

First, the catalytic activity and selectivity for the *N*-alkylation of **1a** with **2a** to the corresponding secondary amine **3a** were compared among various catalysts (Table 1). $Ru(OH)_x/Al_2O_3$ showed the highest catalytic activity and gave the corresponding secondary amine **3a** in 78% yield under the present conditions (entry 1). In this case, no formation of the tertiary amine **3a″** was observed. The reaction hardly proceeded in the absence of the catalyst, or in the presence of Al_2O_3 or Al_2O_3 treated with an aqueous NaOH solution (entries 12–14). In the presence of the catalyst precursor of $RuCl_3{\cdot}nH_2O$, the desired secondary amine **3a** was not produced (entry 7). Also, complexes of $[RuCl_2(p\text{-cymene})]_2$, $Ru(acac)_3$, and $Ru_3(CO)_{12}$ were not effective for the *N*-alkylation under the present conditions (entries 9–11). Although $RuCl_2(PPh_3)_3$ gave 66% yield of **3a**, the undesirable tertiary amine **3a″** was also produced to some extent (entry 8) [8]. The catalytic activity of $Ru(OH)_x/Al_2O_3$ was higher than those of other heterogeneous catalysts such as Ru/C, RuHAP, RuO_2 anhydrous, and $Ru(OH)_x$ (entries 3–6). The base pretreatment of the catalysts (see Supporting information) significantly increased the activity (entry 1 vs entry 2). This is likely because of the generation of the active ruthenium hydroxide species on the surface of Al_2O_3 by the reaction of ruthenium chloride species with NaOH [21–24].

Table 1

N-alkylation of aniline (**1a**) with benzyl alcohol (**2a**) by various catalysts:[a]



Entry	Catalyst	Conversion of **1a** (%)	Yield (%)		
			3a	**3a′**	**3a″**
1	$Ru(OH)_x/Al_2O_3$	96	78	18	nd
2	$RuCl_x/Al_2O_3$[b]	55	22	23	nd
3	Ru/C	88	50	21	nd
4	RuHAP	13	nd	13	nd
5	RuO_2 (anhydrous)	2	nd	2	nd
6	$Ru(OH)_x$	2	nd	2	nd
7	$RuCl_3{\cdot}nH_2O$	12	nd	3	nd
8	$RuCl_2(PPh_3)_3$	84	66	11	5
9	$[RuCl_2(p\text{-cymene})]_2$	12	3	6	nd
10	$Ru(acac)_3$	5	nd	2	nd
11	$Ru_3(CO)_{12}$	15	3	12	nd
12[c]	Al_2O_3	1	nd	1	nd
13[c]	Al_2O_3[d]	1	nd	1	nd
14	None	<1	nd	nd	nd

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.375 mmol), catalyst (Ru: 5 mol%), mesitylene (1 mL), 132 °C, 5 h, under 1 atm of Ar. Conversion and yield were based on **1a** and determined by GC. nd = not detected.

[b] Prepared without base pretreatment.

[c] 60 mg.

[d] Prepared by the treatment with an aqueous NaOH solution (0.1 M).

In order to verify whether the observed catalysis is derived from solid $Ru(OH)_x/Al_2O_3$ or leached ruthenium species, the *N*-alkylation of **1a** with **2a** was carried out under the conditions described in Table 1 and the $Ru(OH)_x/Al_2O_3$ catalyst was removed from the reaction mixture by filtration at ca. 50% conversion of **1a**. After removal of the catalyst, the reaction was again carried out with the filtrate under the same conditions. In this case, the reaction was completely stopped (Fig. S1). It was confirmed by ICP-AES analysis that no ruthenium was detected in the filtrate (below detection limit of 7 ppb). All 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 [27].

Next, the scope of the present $Ru(OH)_x/Al_2O_3$-catalyzed *N*-alkylation was examined (Table 2). Various combinations of substrates (six amines and four alcohols) have been investigated and all reactions efficiently proceeded to give the corresponding secondary amines in moderate to excellent yields without any co-catalysts such as bases and stabilizing ligands.[1] Especially, the reaction of aniline derivatives (**1a**–**1c**) with benzylic alcohols (**2a** and **2b**) efficiently proceeded; the reaction of **1a** with **2a** gave **3a** in 89% isolated yield (99% conversion of **1a**) under the present conditions, for example. In this case, the TOF (based on the initial rate) and the TON reached up to 4 h^{-1} and 18, respectively, and these values were higher than those of the previously reported heterogeneous systems so far (TOF: 0.1–0.9 h^{-1}, TON: 0.2–9.1) [9–15]. Not only aniline derivatives but also heteroaromatic amines (**1d** and **1f**) gave high yields of the corresponding

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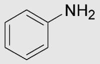
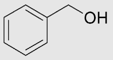
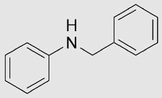
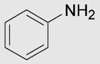
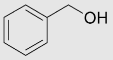
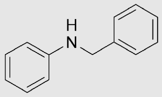
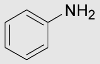
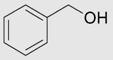
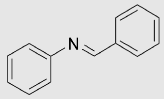
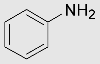
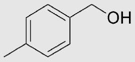
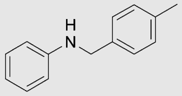
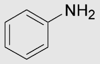
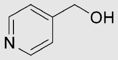
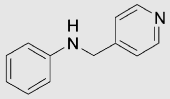
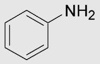
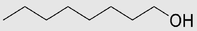
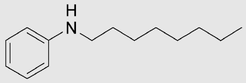
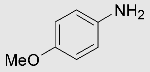
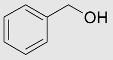
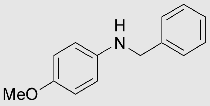
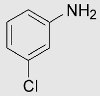
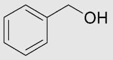
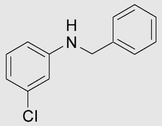
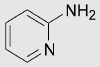
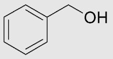
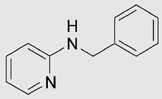
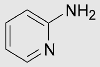
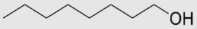
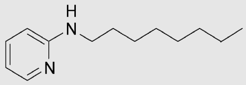
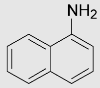
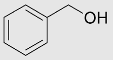
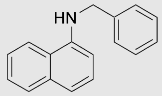
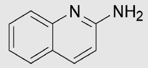
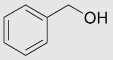
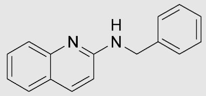
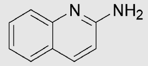
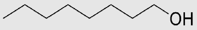
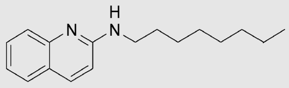
[1] The *N*-alkylation of *tert*-butylamine with **2a** gave the corresponding secondary amine in 60% yield for 11 h under the conditions described in Table 2.

Table 2
Scope of the present $Ru(OH)_x/Al_2O_3$-catalyzed *N*-alkylation.[a]

Entry	Amine		Alcohol		Time (h)	Product		Conv. of amine (%) (Yield (%))
1		**1a**		**2a**	11		**3a**	99 (89[b])
2[c]		**1a**		**2a**	11		**3a**	98 (87)
3[d]		**1a**		**2a**	0.17		**3a′**	98 (98)
4[d]		**1a**		**2b**	11		**3b**	>99 (90)
5		**1a**		**2c**	24		**3c**	>99 (95[b])
6		**1a**		**2d**	24		**3d**	89 (75)
7		**1b**		**2a**	24		**3e**	>99 (83)
8		**1c**		**2a**	11		**3f**	95 (76)
9		**1d**		**2a**	24		**3g**	>99 (99)
10		**1d**		**2d**	24		**3h**	66 (60)
11		**1e**		**2a**	24		**3i**	98 (96)
12		**1f**		**2a**	24		**3j**	98 (90)
13		**1f**		**2d**	24		**3k**	66 (65)

[a] Reaction conditions: Amine (0.25 mmol), alcohol (0.375 mmol), $Ru(OH)_x/Al_2O_3$ (Ru: 5 mol%), mesitylene (1 mL), 132 °C, under 1 atm of Ar. Conversion and yield were based on the starting amine and determined by GC and ^1H NMR.

[b] Isolated yield.

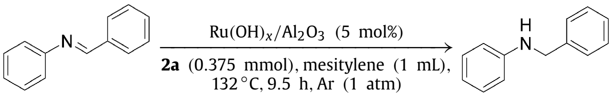
[c] Recycling experiment.

[d] Under 1 atm of O_2.

secondary amines. Benzylic (**2a** and **2b**) as well as heteroaromatic (**2c**) and aliphatic alcohols (**2d**) worked well as reaction partners of aromatic and heteroaromatic amines. After the reaction was completed, the $Ru(OH)_x/Al_2O_3$ catalyst could be easily recovered by filtration and the spent catalyst could be reused without an appreciable loss of its high catalytic performance (entry 2 in Table 2).

The reaction profiles for the $Ru(OH)_x/Al_2O_3$-catalyzed *N*-alkylation of **1a** with **2a** (Fig. 1) showed that **3a′** was initially formed followed by the formation of **3a**. Under aerobic conditions, the reaction of **1a** with **2a** exclusively gave **3a′** without the formation of **3a** (entry 3 in Table 2). It was confirmed in a separate experiment that the hydrogenation of imines to amines in the presence of alcohols (MPV-type reduction [23,24]) efficiently proceeded with the $Ru(OH)_x/Al_2O_3$ catalyst; the hydrogenation of **3a′** readily proceeded to give **3a** in 77% yield in the presence of **2a** as a hydrogen donor [Eq. (3)]:

Therefore, the



3a′ (0.25 mmol) **3a**, 77% yield (3)

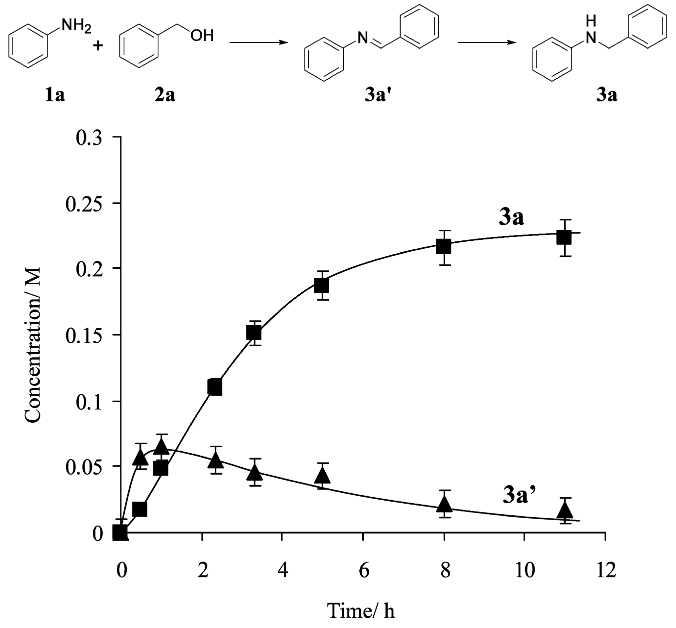


Fig. 1. Reaction profiles for the *N*-alkylation of **1a** with **2a**. Reaction conditions: **1a** (0.25 mmol), **2a** (0.375 mmol), $Ru(OH)_x/Al_2O_3$ (Ru: 5 mol%), mesitylene (1 mL), 132 °C, under 1 atm of Ar.

present *N*-alkylation likely proceeds via the following three sequential reactions. First, the oxidative dehydrogenation of an alcohol to a carbonyl compound proceeds[2] with the *transitory* formation of the ruthenium hydride species [4–8,21–24].[3] Then, the carbonyl compound readily reacts with a starting amine to form the corresponding imine. Finally, the hydrogen transfer reaction from the hydride species to the imine proceeds to afford the corresponding secondary amine. In the present $Ru(OH)_x/Al_2O_3$-catalyzed *N*-alkylation, the formation of the imine intermediate is not possible starting from the secondary amine. Therefore, it seems that the high selectivity toward the corresponding secondary amine is a specific feature that derives from the above-mentioned reaction mechanism.

4. Conclusion

The supported ruthenium hydroxide $Ru(OH)_x/Al_2O_3$ could act as an efficient heterogeneous catalyst for the *N*-alkylation of aromatic and heteroaromatic amines with alcohols. The *N*-alkylation could be performed with high conversion and selectivity, giving the corresponding secondary amines. Furthermore, the catalyst/product separation could be easily carried out and the $Ru(OH)_x/Al_2O_3$ was recyclable.

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Supporting information

The online version of this article contains additional supporting information.

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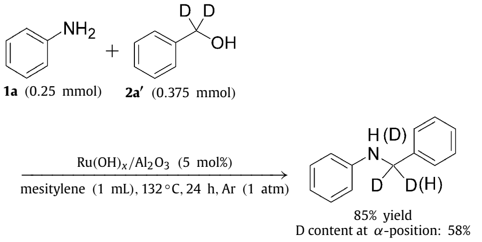
[2] The corresponding aldehydes were detected in the present *N*-alkylation, albeit in small amounts with most substrates tested (below 10% based on alcohols).

[3] Since the detailed mechanistic studies for the $Ru(OH)_x/Al_2O_3$-catalyzed oxidative dehydrogenation of alcohols and MPV-type reduction of carbonyl compounds (including imines) suggest the formation of ruthenium hydride species [21–24], the present *N*-alkylation consisting of the dehydrogenation of alcohols and MPV-type reduction probably proceed via the metal hydride mechanism. For the metal hydride mechanism two different pathways have been reported depending on the kinds of metal hydride species [28]. The metal monohydride species can be formed only from the α-hydrogen of an alcohol substrate, while the metal dihydride species can be formed from both the α-hydrogen and hydroxyl proton of an alcohol substrate. In the case of monohydride mechanism, the α-hydrogen is directly transferred to the imine carbon [28]. In contrast, two hydrogens are completely scrambled and lose their identity in the case of dihydride mechanism [28]. When the *N*-alkylation of **1a** with α,α-dideuteriobenzyl alcohol **2a′** was carried under the conditions described in Table 2, the corresponding secondary amine was obtained in 85% yield for 24 h [Eq. (4)]. The deuterium content at the α-position of the corresponding amine was 58% [Eq. (4)], suggesting the formation of ruthenium dihydride species during the present *N*-alkylation [23,28]:



1a (0.25 mmol) **2a′** (0.375 mmol)

85% yield
D content at α-position: 58%

(4)