

The “Borrowing Hydrogen Strategy” by Supported Ruthenium Hydroxide Catalysts: Synthetic Scope of Symmetrically and Unsymmetrically Substituted Amines

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Abstract: The *N*-alkylation of ammonia (or its surrogates, such as urea, NH_4HCO_3 , and $(\text{NH}_4)_2\text{CO}_3$) and amines with alcohols, including primary and secondary alcohols, was efficiently promoted under anaerobic conditions by the easily prepared and inexpensive supported ruthenium hydroxide catalyst $\text{Ru}(\text{OH})_x/\text{TiO}_2$. Various types of symmetrically and unsymmetrically substituted “tertiary” amines could be synthesized by the *N*-alkylation of ammonia (or its surrogates) and amines with “primary” alcohols. On the other hand, the *N*-alkylation of ammonia sur-

rogates (i.e., urea and NH_4HCO_3) with “secondary” alcohols selectively produced the corresponding symmetrically substituted “secondary” amines, even in the presence of excess amounts of alcohols, which is likely due to the steric hindrance of the secondary alcohols and/or secondary amines produced. Under aerobic conditions, nitriles could be synthesized directly

from alcohols and ammonia surrogates. The observed catalysis for the present *N*-alkylation reactions was intrinsically heterogeneous, and the retrieved catalyst could be reused without any significant loss of catalytic performance. The present catalytic transformation would proceed through consecutive *N*-alkylation reactions, in which alcohols act as alkylating reagents. On the basis of deuterium-labeling experiments, the formation of the ruthenium dihydride species is suggested during the *N*-alkylation reactions.

Keywords: alcohols • alkylation • amines • heterogeneous catalysis • hydrogen • ruthenium

Introduction

Nitrogen-containing compounds (for example, tertiary and secondary amines) are an important class of chemicals that have been used as dyes, color pigments, electrolytes, extractants, stabilizers, and synthons for pharmaceuticals, agricultural chemicals, bioactive compounds, and functionalized materials.^[1] In the past decade, a number of procedures (including catalytic and noncatalytic processes) have been developed for the synthesis of tertiary and secondary amines. As for the synthesis of *N*-alkylated amines, alkyl halides

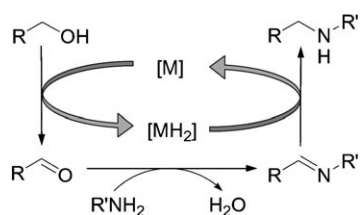
have traditionally been utilized as alkylating reagents.^[1] However, the selectivity toward the desired tertiary or secondary amines is generally low in *N*-alkylation reactions with alkyl halides because the nucleophilicity of amines is increased by *N*-alkyl substitution, thus resulting in the formation of undesired ammonium halides and/or tertiary amines as byproducts.^[1] Moreover, alkyl halides are toxic and their use in *N*-alkylation reactions produces large amounts of inorganic waste, which is not desirable from the standpoint of green chemistry.^[2]

Recently, much attention has been paid to the use of alcohols as alkylating reagents for the *N*-alkylation of amines (including ammonia) because alcohols are readily available and inexpensive and theoretically only produce water as a byproduct. Although the direct use of alcohols as alkylating reagents is very difficult due to their poor electrophilicity, this can be overcome by the strategy of borrowing hydrogen in the presence of appropriate transition-metal-based catalysts (Scheme 1).^[3] In this strategy, the dehydrogenation of an alcohol initially proceeds to give a much more reactive (electrophilic) aldehyde, followed by the formation of an imine through dehydrative condensation. The imine is hydrogenated by the transitory formed metal hydride species,

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Scheme 1. The “borrowing hydrogen strategy” in the *N*-alkylation of an amine with an alcohol. M = metal center.

thus affording the desired *N*-alkylated product. This strategy was first introduced independently by the groups of Grigg^[4a] and Watanabe^[4b] in 1981. Until now, many efficient catalytic procedures for the *N*-alkylation of amines with alcohols have been developed (including homogeneous and heterogeneous processes).^[4,5] Very recently, we also reported that supported ruthenium hydroxide (i.e., Ru(OH)_x/Al₂O₃) could act as an efficient reusable heterogeneous catalyst for the *N*-alkylation of aniline and heteroaromatic amine derivatives with primary alcohols.^[5g]

Ammonia and its surrogates, such as urea and ammonium salts, are attractive nitrogen sources for many functional-group transformations.^[6–11] Despite their cost, and from an atom-economy point of view, there are only a few reports for the selective catalytic synthesis of symmetrically substituted tertiary and secondary amines with ammonia or its surrogates; for example, 1) the palladium-catalyzed *N*-arylation of ammonia with aryl halides,^[8] 2) the iridium-catalyzed *N*-alkylation of ammonium salts such as CH₃COONH₄ and NH₄BF₄ with alcohols,^[9] 3) the gas-phase *N*-alkylation of ammonia with alcohols,^[10] and 4) the photocatalytic *N*-alkylation of ammonia with alcohols.^[11]

Recently, we developed efficient heterogeneous catalysts for various functional-group transformations.^[12–14] Our strategy to design efficient heterogeneous catalysts is based on a highly dispersed metal hydroxide species on an appropriate support.^[12–14] The metal hydroxide species would possess both Lewis acid and Brønsted base sites in the same metal site, and various functional-group transformations are likely to be promoted by the concerted activation of the Lewis acid and Brønsted base sites.^[12–14] The *N*-alkylation of ammonia (or its surrogates) with alcohols as alkylating reagents is likely to be promoted by the concerted activation of the Lewis acid and Brønsted base sites through the strategy of borrowing hydrogen (Scheme 1).^[3] Therefore, various kinds of supported metal hydroxide catalysts (on Al₂O₃) were prepared and tested for the *N*-alkylation of urea (**1a**) with benzyl alcohol (**2a**). The transformation proceeded efficiently to give tribenzylamine (**3a**) in a high yield with the supported ruthenium hydroxide catalysts (see later) and we reported the results for the synthesis of symmetrically substituted amines with **1a** as a nitrogen source.^[15] Herein, we report the details of the *N*-alkylation reaction, for example, the effects of the catalysts and nitrogen sources (including ammonia and its surrogates, such as urea and ammonium salts) and the extension of the synthetic scope of symmetri-

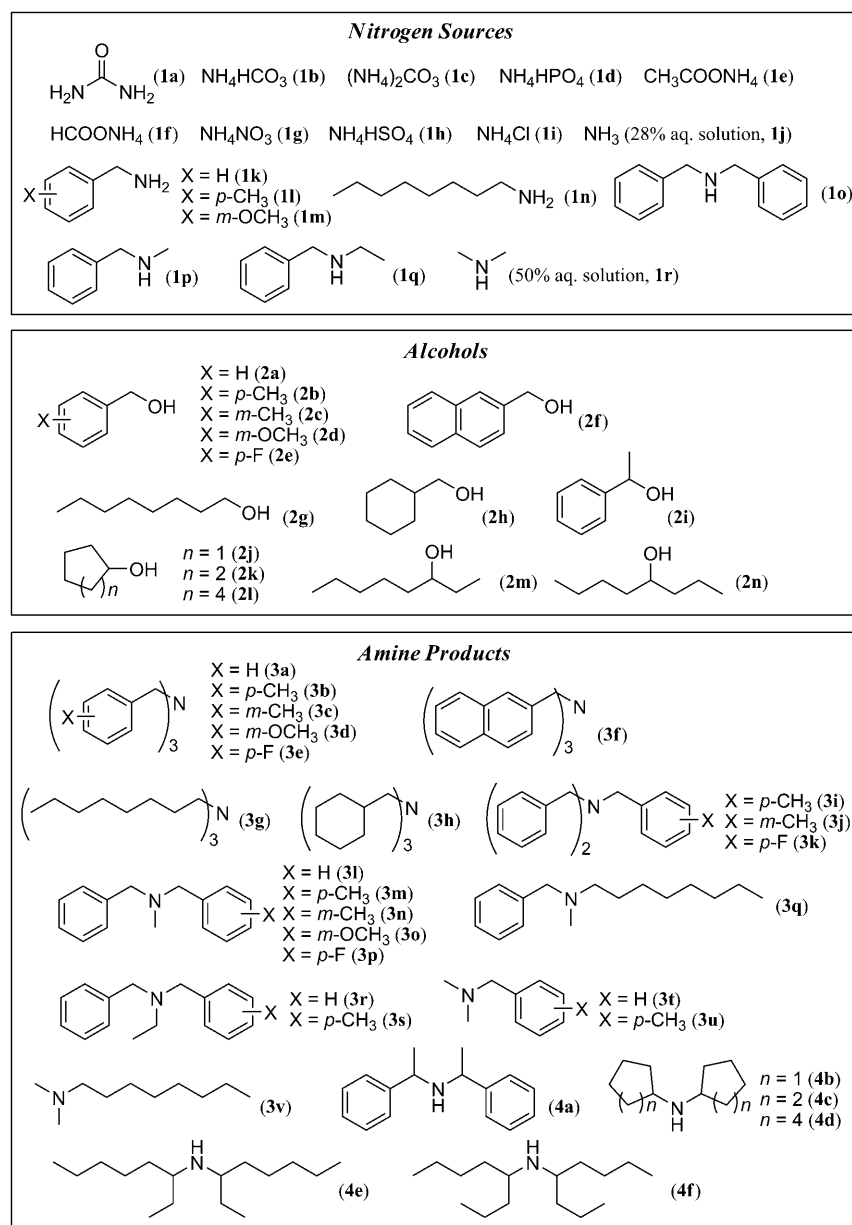
cally substituted amines (Scheme 2). Furthermore, the applicability of the supported ruthenium hydroxide catalysts to the synthesis of unsymmetrically substituted amines is examined (Scheme 2). In addition, we report efficient oxidative nitrile synthesis directly from alcohols and ammonia surrogates with molecular oxygen (air) as an oxidant. The possible reaction mechanism for the present *N*-alkylation reaction is also discussed in more detail.

Results and Discussion

Effects of catalysts and nitrogen sources on the *N*-alkylation of urea with benzyl alcohol: Initially, we examined several reaction conditions to improve the catalytic activity and selectivity for the *N*-alkylation of **1a** with **2a** to the desired tertiary amine **3a** in the presence of the supported ruthenium hydroxide on TiO₂ (Ru(OH)_x/TiO₂) under argon.^[16] Changing the **2a**/nitrogen (in **1a**) ratio from 1:3 to 5:1 resulted in an improvement in the selectivity toward the desired tertiary amine **3a** (Table 1, entries 1–5). Among the solvents examined, nonpolar mesitylene was a good solvent and gave a high yield of **3a** (Table 1, entry 5). In contrast, no reaction proceeded in polar aprotic and protic solvents, such as DMSO, DMF, and water, because of their strong coordination to the active center(s) (Table 1, entries 6–8). Thus, all reactions hereafter were carried out in mesitylene with the alcohol/nitrogen ratio of 5:1 under argon (unless otherwise noted).

Various kinds of supported metal hydroxide catalysts on Al₂O₃ (including ruthenium, palladium, rhodium, platinum, and iridium) were prepared and applied to the *N*-alkylation of **1a** with **2a** to **3a** (Figure 1). Among the metal hydroxide catalysts examined, Ru(OH)_x/Al₂O₃ showed the highest catalytic activity and selectivity for the transformation (Figure 1). Catalyst Pd(OH)_x/Al₂O₃ exclusively gave *N*-benzylidenebenzylamine (**1o'**) because of the poor catalytic activity for the hydrogenation with alcohols as hydrogen sources. Indeed, the Meerwein–Ponndorf–Verley-type (MPV-type) reduction of carbonyl compounds with 2-propanol (as a hydrogen source) hardly proceeded in the presence of Pd(OH)_x/Al₂O₃. Catalyst Rh(OH)_x/Al₂O₃ gave dibenzylamine (**1o**) as a major product. The catalytic activities of Pt(OH)_x/Al₂O₃ and Ir(OH)_x/Al₂O₃ were intrinsically very low.

The effect of the catalyst support was significant; for example, the rate of formation of **3a** with Ru(OH)_x/TiO₂ was larger than with Ru(OH)_x/Al₂O₃ (Table 2, entries 1 and 2).^[17] Judging from the Ru K-edge extended X-ray absorption fine structure (EXAFS) analysis, the ruthenium species in Ru(OH)_x/TiO₂ (the coordination number (CN) of the nearest neighbor Ru atoms was 0.76 ± 0.21) were more highly dispersed than in Ru(OH)_x/Al₂O₃ (CN = 0.91 ± 0.20).^[12d] In addition, we very recently reported that the catalytic activities of Ru(OH)_x/TiO₂ (with more highly dispersed ruthenium species) for the oxidative dehydrogenation of alcohols and hydrogen-transfer reactions (for example, an



Scheme 2. Nitrogen sources, alcohols, and amine products.

MPV-type reduction with alcohols and racemization of chiral secondary alcohols) were higher than those activities of $\text{Ru}(\text{OH})_x/\text{Al}_2\text{O}_3$.^[12i,j] Therefore, the more highly dispersed ruthenium species would show a high catalytic activity for the present *N*-alkylation reaction composed of dehydrogenation and hydrogenation reactions (Scheme 1; see later).^[17]

A simple mixture of $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (catalyst precursor) and TiO_2 (support) was not effective for the *N*-alkylation reaction (Table 2, entry 14). In addition, the reaction hardly proceeded in the presence of the ruthenium chloride species supported on TiO_2 ($\text{RuCl}_3/\text{TiO}_2$) prepared without treatment with a base (Table 2, entry 3; see the Supporting Information for the preparation); that is, treatment of the catalyst with aqueous NaOH upon preparation, which significantly

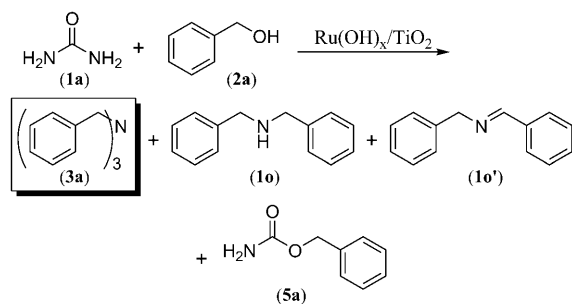
increased the activity (Table 2, entry 1 vs. 3). This outcome is likely because of the generation of the active ruthenium hydroxide species on TiO_2 by the reaction of the ruthenium chloride species with NaOH.^[12]

The catalytic activities of various kinds of ruthenium-based catalysts were compared. In the presence of the catalyst precursor of $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$, **3a** was not formed (Table 2, entry 4). Ruthenium complexes such as $[\text{RuCl}_2(\text{PPh}_3)_3]$ and $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ gave moderate yields (20–39%) of **3a** with the formation of the undesirable benzyl carbamate (**5a**) as a by-product through the condensation of **1a** and **2a** (Table 2, entries 5 and 6). Other ruthenium complexes, such as $[\text{RuCl}_2(\text{bpy})_2]$ ($\text{bpy} = 2,2'$ -bipyridine, $[\text{Ru}(\text{acac})_3]$ ($\text{acac} = \text{acetylacetonate}$), and $[\text{Ru}_3(\text{CO})_{12}]$ were not effective for the *N*-alkylation reaction (Table 2, entries 7–9). The catalytic activities of $\text{Ru}(\text{OH})_x/\text{TiO}_2$ and $\text{Ru}(\text{OH})_x/\text{Al}_2\text{O}_3$ were much higher than those of other commonly used ruthenium-based heterogeneous catalysts, such as a ruthenium chloride species supported on hydroxyapatite (RuHAP)^[18] and Ru^0 species supported on active carbon (Ru/C ; Table 2, entries 10 and 11, respectively). The *N*-alkylation reaction hardly proceeded in the presence of anhydrous RuO_2 and $\text{Ru}(\text{OH})_x \cdot n\text{H}_2\text{O}$

(Table 2, entries 12 and 13).^[17] Notably, the catalytic activity of a physical mixture of $\text{Ru}(\text{OH})_x \cdot n\text{H}_2\text{O}$ and TiO_2 powders was comparable to that of $\text{Ru}(\text{OH})_x \cdot n\text{H}_2\text{O}$ (except for the low yield of **5a**) and much lower than that of $\text{Ru}(\text{OH})_x/\text{TiO}_2$ (Table 2, entry 15), thus indicating that the highly dispersed ruthenium hydroxide species is essential for a high catalytic performance.^[17]

In the absence of the catalyst, the desired tertiary amine **3a** was not formed and **5a** was formed as a by-product (Table 2, entry 18). In the presence of just TiO_2 or Al_2O_3 , no formation of **3a** was observed (Table 2, entries 16 and 17). In contrast to the transformation without the catalyst, **5a** was hardly observed with TiO_2 or Al_2O_3 . It was confirmed in separate experiments that **1a** hydrolytically decomposed

Table 1. Optimization of reaction conditions for the synthesis of **3a**.^[a]



Entry	2a/nitrogen	Solvent	Yield [%]			
			3a	1o	1o'	5a
1	1:3	mesitylene	n.d.	n.d.	n.d.	30
2	1:1	mesitylene	n.d.	4	14	n.d.
3	3:1	mesitylene	35	27	17	n.d.
4	4:1	mesitylene	81	4	6	n.d.
5	5:1	mesitylene	93	1	1	n.d.
6	5:1	DMSO	n.d.	n.d.	n.d.	n.d.
7	5:1	DMF	n.d.	n.d.	n.d.	n.d.
8 ^[b]	5:1	water	n.d.	n.d.	n.d.	n.d.

[a] Reaction conditions: **1a** (0.25 mmol for entries 3–8), **2a** (0.5 mmol for entries 1 and 2), catalyst (Ru: 3 mol% with respect to the limited reagent), mesitylene (0.5 mL), 141 °C, 12 h, 1 atm of Ar; the yields are based on the limited reagent (amount of nitrogen in **1a** or **2a**). [b] 141 °C (bath temperature). DMSO = dimethyl sulfoxide, n.d. = not detected (below 1% yield).

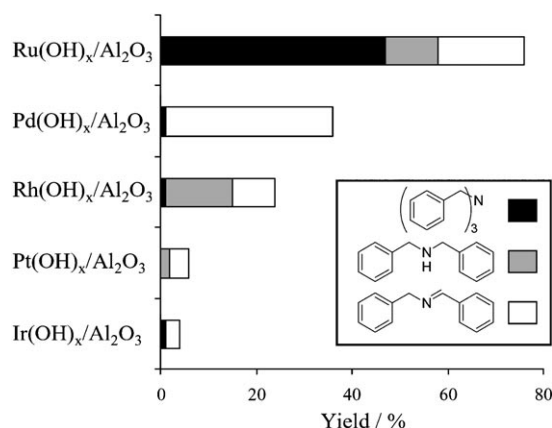
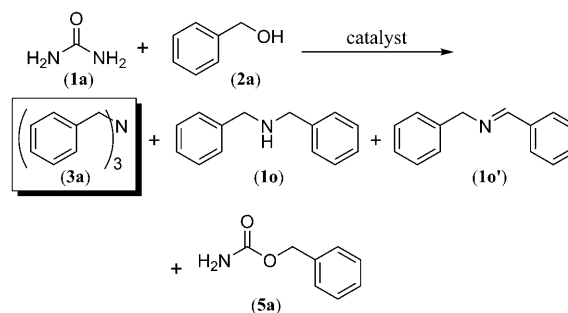


Figure 1. Synthesis of **3a** from **1a** and **2a** catalyzed by various platinum-group metal hydroxides supported on Al₂O₃. Reaction conditions: **1a** (0.25 mmol), **2a** (2.5 mmol), catalyst (metal: 15 μmol), mesitylene (0.5 mL), 141 °C, 12 h, 1 atm of Ar. The yields are based on the amount of nitrogen in **1a**.

to ammonia in the presence of TiO₂ or Al₂O₃ under similar conditions (Table 2) and that the decomposition hardly proceeded in the absence of TiO₂ or Al₂O₃. The supports would take part in the generation of ammonia in situ through the hydrolytic decomposition of **1a** with water contained in the catalysts (or supports) and/or water produced through the dehydrative condensation of the carbonyl compounds and amines (including ammonia) generated in situ.^[19] Therefore, other ammonia surrogates are likely to be usable as nitrogen

Table 2. Effect of catalysts on the synthesis of **3a**.^[a]



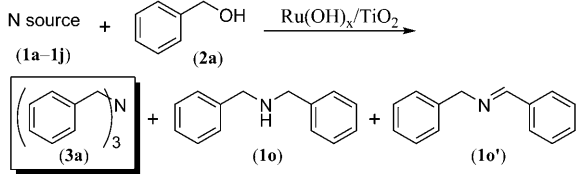
Entry	Catalyst	Yield [%]			
		3a	1o	1o'	5a
1	Ru(OH) _x /Al ₂ O ₃	47	11	18	n.d.
2	Ru(OH) _x /TiO ₂	93	1	1	n.d.
3	RuCl _x /TiO ₂	n.d.	2	4	n.d.
4	RuCl ₃ ·nH ₂ O	n.d.	n.d.	n.d.	21
5	[RuCl ₂ (PPh ₃) ₃]	39	n.d.	n.d.	40
6	[[RuCl ₂ (<i>p</i> -cymene)] ₂]	20	7	6	37
7	[RuCl ₂ (bpy) ₂]	n.d.	n.d.	n.d.	50
8	[Ru(acac) ₃]	1	5	7	30
9	[Ru ₃ (CO) ₁₂]	n.d.	2	3	31
10	RuHAP	n.d.	1	3	33
11	Ru/C	18	2	6	29
12	Ru(OH) _x ·nH ₂ O	n.d.	n.d.	2	34
13	Ru ₂ O ₃ anhydrous	n.d.	n.d.	n.d.	50
14 ^[b]	RuCl ₃ ·nH ₂ O + TiO ₂	n.d.	n.d.	1	n.d.
15 ^[b]	Ru(OH) _x ·nH ₂ O + TiO ₂	n.d.	n.d.	1	1
16 ^[b]	TiO ₂	n.d.	1	4	2
17 ^[b]	Al ₂ O ₃	n.d.	1	1	1
18	none	n.d.	n.d.	n.d.	44

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (2.5 mmol), catalyst (Ru: 15 μmol), mesitylene (0.5 mL), 141 °C, 12 h, 1 atm of Ar; the yields are based on the amount of nitrogen in **1a**. [b] TiO₂ or Al₂O₃ (75 mg). n.d. = not detected (below 1% yield)

sources for the present amine synthesis (if they can be decomposed to ammonia in situ).

Next, the synthesis of **3a** was carried out with various ammonia surrogates. Besides **1a**, NH₄HCO₃ (**1b**), and (NH₄)₂CO₃ (**1c**; a mixture of ammonium bicarbonate and ammonium carbamate) could act as effective nitrogen sources for the present reaction, thereby giving **3a** in yields of 61 and 62%, respectively (Table 3, entries 2 and 3). It was confirmed in separate experiments that **1b** and **1c** thermally decomposed to ammonia under the conditions described in Table 3. In contrast, other ammonium salts, such as NH₄HPO₄ (**1d**), CH₃COONH₄ (**1e**), HCOONH₄ (**1f**), NH₄NO₃ (**1g**), NH₄HSO₄ (**1h**), and NH₄Cl (**1i**), were not effective because these salts hardly decomposed to ammonia under these conditions (Table 3, entries 4–9). It is noted that aqueous ammonia (**1j**; 28% aq. solution) could be directly utilized for the present *N*-alkylation reaction. When the transformation was carried out with **1j**, the desired tertiary amine **3a** was obtained in 87% yield (over 6 h; Table 3, entry 10).

Catalytic performance of Ru(OH)_x/TiO₂: The scope of the Ru(OH)_x/TiO₂-catalyzed synthesis of symmetrically substi-

Table 3. Effect of nitrogen source on the synthesis of **3a**.^[a]


Entry	Nitrogen source	Yield [%]		
		3a	1o	1o'
1	1a	93	1	1
2	1b	61	5	12
3	1c ^[b]	62	7	27
4	1d	17	4	23
5	1e	5	6	31
6	1f	n.d.	n.d.	n.d.
7 ^[c]	1g	n.d.	2	25
8	1h	n.d.	n.d.	n.d.
9	1i	4	1	7
10 ^[d]	1j	87	2	3

[a] Reaction conditions: Nitrogen source (amount of nitrogen: 0.5 mmol), **2a** (2.5 mmol), catalyst (Ru: 15 μ mol), mesitylene (0.5 mL), 141 °C, 12 h, 1 atm of Ar; the yields are based on the amount of nitrogen in the nitrogen sources. [b] A mixture of ammonium bicarbonate and ammonium carbamate. [c] **1g** (0.5 mmol); the yields are based on **1g**. [d] 6 h. n.d. = not detected (below 1% yield).

tuted tertiary amines was examined first. We have already reported the synthesis of symmetrically substituted tertiary amines from **1a** and primary alcohols.^[15] The scope of this investigation was extended and thirteen new entries were added (Table 4). The *N*-alkylation of **1a** with primary benzylic alcohols containing electron-donating and electron-withdrawing substituents (**2a–f**) efficiently proceeded to afford the corresponding benzylic tertiary amines in high yields (Table 4, entries 1–6). Aliphatic primary alcohols (**2g, h**) could act as effective alkylating reagents for the *N*-alkylation of **1a**, thus giving the corresponding aliphatic tertiary amines in high yields (Table 4, entries 7 and 8). In the *N*-alkylation of **1j** (as a nitrogen source), primary benzylic and aliphatic alcohols could also be utilized as alkylating reagents for the synthesis of symmetrically substituted tertiary amines (Table 4, entries 9–14). Besides **1a** and **1j**, primary and secondary amines could be utilized as nitrogen sources for the present Ru(OH)_x/TiO₂-catalyzed synthesis of symmetrically substituted tertiary amines (Table 4, entries 15–19). In addition, Ru(OH)_x/TiO₂ showed high catalytic activity for the reductive *N*-alkylation of an *N*-alkyl imine (Table 4, entry 20).

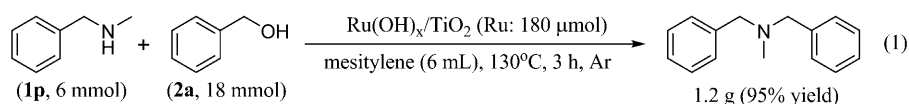
To demonstrate the usefulness of the present system, we explored the synthesis of unsymmetrically substituted tertiary amines. In the presence of Ru(OH)_x/TiO₂, the *N*-alkylation of dibenzylamine (**1o**), *N*-methylbenzylamine (**1p**), and *N*-ethylbenzylamine (**1q**) with various kinds of structurally diverse primary alcohols, including benzylic and aliphatic alcohols, efficiently proceeded to afford the corresponding un-

Table 4. Synthesis of various symmetrically substituted tertiary amines.^[a]

Entry	Nitrogen source	Alcohol	Time [h]	Product	Yield [%]
1	1a	2a	12	3a	89
2	1a	2b	16	3b	95
3	1a	2c	24	3c	94
4	1a	2d	20	3d	93
5	1a	2e	24	3e	76
6	1a	2f	24	3f	86
7	1a	2g	15	3g	87
8	1a	2h	24	3h	97
9	1j	2a	6	3a	87
10	1j	2b	6	3b	82
11	1j	2c	12	3c	68
12	1j	2d	10	3d	80
13	1j	2e	6	3e	71
14	1j	2g	8	3g	88
15	1k	2a	6	3a	88
16	1l	2b	12	3b	87
17	1m	2d	12	3d	81
18	1n	2g	12	3g	80
19	1o	2a	3	3a	93
20	1o'	2a	3	3a	85

[a] Reaction conditions: Nitrogen source (amount of nitrogen: 0.5 mmol), alcohol (2.5 mmol for entries 1–14; 1.5 mmol for entries 15–20), Ru(OH)_x/TiO₂ (Ru: 15 μ mol for entries 1 and 9–20; 20 μ mol for entries 2–8), mesitylene (0.5 mL for entries 1, 7, 9, and 11–20; 0.8 mL for entries 2–6, 8, and 10), 141 °C, 1 atm of Ar; the yields are based on the amount of nitrogen in the nitrogen sources.

symmetrically substituted tertiary amines in high yields (Table 5, entries 1–13). Notably, an aqueous solution of dimethylamine (**1r**; 50%) could be utilized as a nitrogen source and the corresponding tertiary amines could be obtained in high yields (Table 5, entries 14–16). The larger-scale *N*-alkylation of **1p** with **2a** (scaled up 12-fold) was also effective and 1.2 g of **3l** could be obtained [Eq. (1)].



When secondary alcohols were used as alkylating reagents (**1a** and **1b** were used as nitrogen sources), the corresponding secondary amines could selectively be obtained. Various types of secondary alcohol, including benzylic (**2i**), aliphatic cyclic (**2j–l**), and aliphatic linear alcohols (**2m, n**), could be converted into the corresponding secondary amines in high yields, even in the presence of excess amounts of secondary alcohols (Table 6). In addition, it was confirmed that the *N*-alkylation of secondary amines **1o** and **1p** with secondary alcohols **2i** and **2j** hardly proceeded under similar reaction conditions. Similar selectivities to secondary amines reported in the [[Cp*IrCl₂]₂]-catalyzed (Cp* = pentamethylcyclopentadienyl) *N*-alkylation of NH₄BF₄ with secondary alcohols are explained by the steric hindrance of the secondary alcohols and/or secondary amines produced.^[9]

Table 5. Synthesis of various unsymmetrically substituted tertiary amines.^[a]

Entry	Nitrogen source	Alcohol	Time [h]	Product	Yield [%]
1	1o	2b	3	3i	82
2	1o	2c	5	3j	65
3	1o	2e	3	3k	74
4	1p	2a	3	3l	97
5 ^[b]	1p	2a	3	3l	81
6 ^[b]	1p	2a	3	3l	72
7	1p	2b	3	3m	86
8	1p	2c	3	3n	90
9	1p	2d	3	3o	87
10	1p	2e	3	3p	97
11	1p	2g	7	3q	79
12	1q	2a	3	3r	75
13	1q	2b	3	3s	77
14 ^[c]	1r	2a	5	3t	82
15 ^[c]	1r	2b	5	3u	81
16 ^[c]	1r	2g	5	3v	75

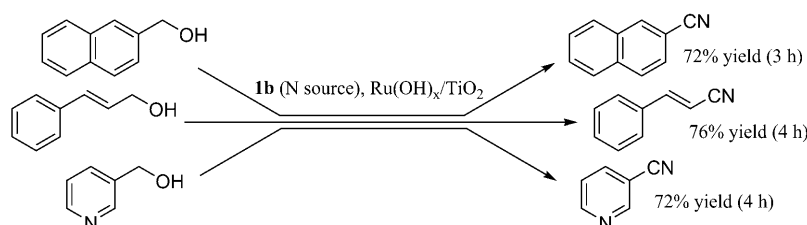
[a] Reaction conditions: Nitrogen source (0.5 mmol), alcohol (1.5 mmol), Ru(OH)_x/TiO₂ (Ru: 15 μmol), mesitylene (0.5 mL), 130 °C, 1 atm of Ar; the yields are based on the nitrogen sources. [b] Reuse experiments: the first reuse (entry 5) and the second reuse (entry 6). [c] 140 °C.

Table 6. Synthesis of various symmetrically substituted secondary amines.^[a]

Entry	Nitrogen source	Alcohol	Time [h]	Product	Yield [%]
1	1a	2i	24	4a	92 ^[b]
2	1a	2j	24	4b	80
3	1a	2k	16	4c	92
4 ^[c]	1a	2k	16	4c	90
5	1a	2l	24	4d	85
6	1a	2m	20	4e	98 ^[b]
7	1a	2n	20	4f	95 ^[b]
8	1b	2j	12	4b	67
9	1b	2k	12	4c	86

[a] Reaction conditions: Nitrogen source (amount of nitrogen: 0.5 mmol), alcohol (2.5 mmol), Ru(OH)_x/TiO₂ (Ru: 20 μmol), mesitylene (0.8 mL), 141 °C, 1 atm of Ar; yields are based on the amount of nitrogen in **1a**. [b] A mixture of diastereomers (the ratio was not determined.). [c] Reuse experiment.

Notably, the present system could be applied to oxidative nitrile synthesis directly from alcohols and ammonia surrogates by using molecular oxygen (air) as an oxidant.^[20] Benzylic, allylic, and heteroaromatic alcohols could be converted into the corresponding nitriles under the optimized reaction conditions (Scheme 3). In the transformation of an allylic alcohol, the corresponding unsaturated nitrile could be



Scheme 3. Oxidative nitrile synthesis from alcohols and **1b** (as a nitrogen source). Reaction conditions: **1b** (1.5 mmol), alcohol (0.5 mmol), catalyst (Ru: 10 mol% with respect to alcohols), mesitylene (2 mL), 140 °C (bath temperature), 6 atm of air. The yields are based on the alcohols.

obtained selectively without hydrogenation and isomerization of the double bond.

After the *N*-alkylation reaction was completed, the Ru(OH)_x/TiO₂ catalyst could be easily retrieved from the reaction mixture by simple filtration (or centrifugation). The retrieved catalyst could be reused for *N*-alkylation reactions without any significant decrease in its catalytic performance (Table 5, entries 5 and 6, and Table 6, entry 4).

To verify whether the observed catalysis is derived from solid Ru(OH)_x/TiO₂ or leached ruthenium species, *N*-alkylation of **1a** (or **1j**) with **2a** was carried out under the conditions described in Table 4 and the catalyst was removed from the reaction mixture by filtration at approximately 40–50% yield of **3a**. After removal of the catalyst, **1a** (or **1j**; 0.25 mmol) was newly added to the filtrate and the reaction was carried out again with the resulting filtrate under the conditions described in Table 4. In this case, no further production of **3a** was observed. For the *N*-alkylation of **1p** with **2a**, the reaction was also completely stopped by the removal of Ru(OH)_x/TiO₂ by filtration. In addition, it was confirmed by inductively coupled plasma atomic emission spectroscopic (ICP-AES) analysis that no ruthenium was detected in the filtrate (below the detection limit). All these results can rule out any contribution to the observed catalysis from ruthenium species that leached into the reaction solution; therefore, the observed catalysis is intrinsically heterogeneous.^[21]

Reaction scheme: The addition of radical scavengers, such as hydroquinone and 2,6-di-*tert*-butyl-*para*-cresol (one equivalent with respect to the ruthenium species in Ru(OH)_x/TiO₂), did not change the reaction rate and product selectivity of the *N*-alkylation of **1a** with **2a**, thus suggesting that free-radical intermediates are not involved in the present Ru(OH)_x/TiO₂-catalyzed *N*-alkylation reaction.

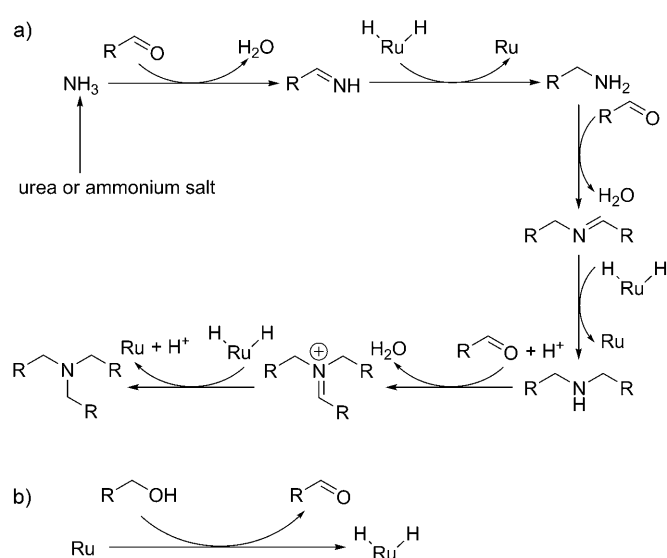
The reaction profiles of the Ru(OH)_x/TiO₂-catalyzed *N*-alkylation of **1a** with **2a** showed the formation of **1o'** (*N*-alkyl imine) and **1o** (secondary amine) as major reaction intermediates (see Figure S1 in the Supporting Information). In addition to the formation of *N*-alkyl imines and secondary amines, *N*-unsubstituted imines, primary amines, and iminium cations could be detected during the *N*-alkylation of **1a**, albeit in only small amounts (i.e., below 1% yield as determined by GC–MS analysis; see Figure S2 in the Supporting Information).^[22] As mentioned above, the Ru(OH)_x/TiO₂-

catalyzed *N*-alkylation of **1k** (primary amine; Table 4, entry 15), **1o'** (*N*-alkyl imine; Table 4, entry 20), and **1o** (secondary amine; Table 4, entry 19) with **2a** efficiently proceeded to give the corresponding tertiary amine **3a**. In the absence of **2a**, the desired tertiary amine **3a** was not produced.

The $\text{Ru}(\text{OH})_x/\text{TiO}_2$ -catalyzed competitive dehydrogenation of *para*-substituted benzyl alcohols gave the following order of reactivity: *p*- OCH_3 ($R_X/R_H=2.4$) > *p*- CH_3 (1.6) > *p*- H (1.0) > *p*- Cl (0.95) (the values in the parentheses were the relative rates and the rate of **2a** was taken as a unity). The relative rates ($\log(R_X/R_H)$) are plotted against the heterolytic benzylic C–H bond dissociation energies of *para*-substituted benzyl alcohols (see Figure S3 in the Supporting Information). A good linear correlation was observed, thus suggesting the formation of the ruthenium hydride species through a carbocation-type transition state (β -hydride elimination). The formation of the ruthenium hydride species was evidenced by the fact that $\text{Ru}(\text{OH})_x/\text{TiO}_2$ showed a high-catalytic performance for the hydrogen-transfer reactions, such as the MPV-type reduction of carbonyl compounds with 2-propanol and racemization of chiral secondary alcohols.^[12f,i]

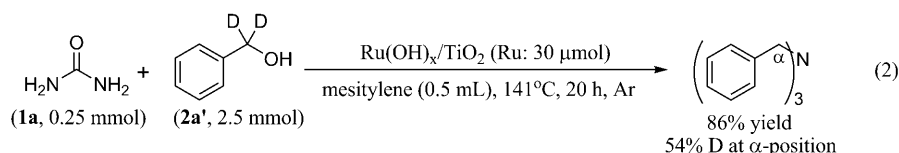
On the basis of the above-mentioned experimental results, the present catalytic transformation would proceed through consecutive *N*-alkylation reactions, in which alcohols act as alkylating reagents (Scheme 4). In the first *N*-alkylation reaction in the transformation of ammonia (or its surrogates, in which case ammonia is generated in situ), the dehydrogenation of an alcohol to the corresponding carbonyl compound initially proceeds with the “transitory formation of the ruthenium hydride species”.^[12,22] The carbonyl compound readily reacts with ammonia to form corresponding *N*-unsubstituted imines. Finally, the hydrogen-transfer reaction from the hydride species to the *N*-unsubstituted imine proceeds to afford the corresponding primary amine.^[23] The second and third *N*-alkylation reactions should proceed through similar sequential processes, which comprise dehydrogenation of an alcohol, dehydrative condensation of the carbonyl compound generated in situ to yield an *N*-alkyl imine (or an iminium cation), and hydrogenation of the *N*-alkyl imine (or the iminium cation). The reaction rate for the dehydrative condensation of benzaldehyde and aniline in the presence of $\text{Ru}(\text{OH})_x/\text{TiO}_2$ was 47 mmol min^{-1} (at 25°C), which was larger than when the reaction was carried out in the absence $\text{Ru}(\text{OH})_x/\text{TiO}_2$ (21 mmol min^{-1}), thus suggesting that $\text{Ru}(\text{OH})_x/\text{TiO}_2$ catalyzes not only the hydrogen-transfer reactions (dehydrogenation and hydrogenation) but also the dehydrative condensations.^[24]

For the mechanism that involves the metal hydride, two different pathways have been reported that depend on the type of metal hydride species (monohydride or dihydride).^[25] The metal monohydride species can be formed only from the α -hydrogen atom of an alcohol, whereas the metal dihydride species can be formed from both the α -hydrogen atom and hydroxy proton of an alcohol.^[25] In the case of the mechanism for the monohydride species, the α -hydrogen atom is directly transferred to the imine (or imini-

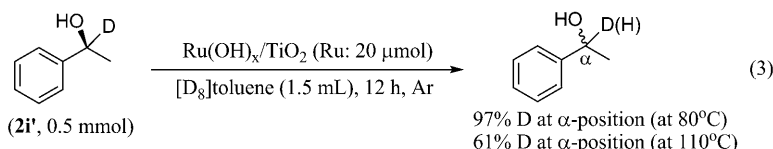


Scheme 4. a) A possible reaction pathway and b) a formation of the dihydride species.

um) carbon atom.^[25] In contrast, two hydrogen atoms are completely scrambled and lose their identity in the case of the mechanism for the dihydride species.^[25] When the *N*-alkylation of **1a** with α,α -dideuteriobenzyl alcohol (**2a'**, 98% D at the α -position) was carried out, the corresponding tertiary amine was obtained in 86% yield over 20 h [Eq. (2)]. The (average) deuterium content at the α -position of the corresponding tertiary amine was 54% [Eq. (2)], thus suggesting the formation of the ruthenium dihydride species during the present *N*-alkylation reaction.^[26]



The type of hydride species formed on the $\text{Ru}(\text{OH})_x/\text{TiO}_2$ catalyst (monohydride or dihydride) was dependent on the reaction temperature. When the $\text{Ru}(\text{OH})_x/\text{TiO}_2$ -catalyzed racemization of (*S*)-1-deuterio-1-phenylethanol (**2i'**; >99% *ee*, >99% D at the α -position) was carried out at below 80°C , the deuterium atoms were almost retained at the α -position of the racemic alcohol after complete racemization [Eq. (3)]. This behavior means that the “monohydride species” is mainly formed at below 80°C (see Figure S4 in the Supporting Information). In contrast, the deuterium atoms at the α -position were scrambled with the hydroxy protons of the alcohol, water, and/or the catalyst when the racemization of **2i'** was carried out at above 110°C [Eq. (3)]. This behavior means that the “dihydride species” is mainly formed at above 110°C (see Figure S4 in the Supporting Information).



Conclusion

$\text{Ru}(\text{OH})_x/\text{TiO}_2$ could act as an efficient heterogeneous catalyst for the *N*-alkylation of ammonia (or its surrogates) and amines with alcohols as alkylating reagents. Various kinds of symmetrically and unsymmetrically substituted amines could be synthesized in high yield. In addition, $\text{Ru}(\text{OH})_x/\text{TiO}_2$ could be applied to the oxidative synthesis of nitriles directly from alcohols and ammonia surrogates with molecular oxygen (air) as an oxidant. The catalyst/product separation could be easily carried out by simple filtration (or centrifugation) and $\text{Ru}(\text{OH})_x/\text{TiO}_2$ was recyclable. The transformation proceeded through sequential *N*-alkylation reactions, in which a ruthenium dihydride species plays a key role. The present $\text{Ru}(\text{OH})_x/\text{TiO}_2$ -catalyzed system has the following significant advantages: 1) applicability to various nitrogen sources (i.e., ammonia, including its surrogates, and amines) and alkylating reagents (various kinds of structurally diverse primary and secondary alcohols); 2) high catalytic activity and selectivity; 3) no use of cocatalysts and additives; 4) a simple workup procedure, namely, catalyst/product separation; and 5) reusability of the catalyst. The results demonstrated herein will open up a new avenue for the green amine synthesis, which can completely avoid the use of conventional hazardous reagents, such as organic halides and the formation of inorganic byproducts.

Experimental Section

General: The GC analyses were performed on a Shimadzu GC-2014 machine using a flame ionization detector (FID) equipped with a DB-WAX ETR capillary column (internal diameter: 0.25 mm, length: 30 m), a TC-WAX capillary column (internal diameter: 0.25 mm, length: 30 m), a TC-1 capillary column (internal diameter: 0.25 mm, length: 30 m), or a TC-5 capillary column (internal diameter: 0.25 mm, length: 60 m). The mass spectra were recorded on a Shimadzu GCMS-QP2010 machine equipped with a TC-5HT capillary column (internal diameter: 0.25 mm, length: 30 m). The NMR spectra were recorded on a JEOL JNM-EX-270 spectrometer. The ^1H and ^{13}C NMR spectra were measured at 270 and 67.8 MHz, respectively, in CDCl_3 with trimethylsilane (TMS) as an internal standard. The ^2H NMR spectra were measured at 41.25 MHz with $[\text{D}_6]$ benzene as an external standard. The ICP-AES analyses were performed on a Shimadzu ICPS-8100 machine. The ESR measurements (X-band) were performed on a JEOL JES-RE-1X spectrometer at -150°C in an argon atmosphere.

Reagents: Substrates (alcohols and amines) and solvents were commercially obtained from Tokyo Kasei, Aldrich, and Fluka (reagent grade) and were purified before use.^[27] Compound **2a'** (98% D at the α -position) was obtained from Isotec and used as received. Ammonium salts and urea were commercially obtained from Nacalai Tesque, Aldrich, and Wako Pure Chemical Industries (reagent grade) and were used as received. Ruthenium salts and complexes were obtained from Wako Pure Chemical Industries, Kanto Chemical Co., and Tokyo Kasei (reagent

grade) and were used as received. TiO_2 (anatase, JRC-TIO-1, BET surface area: $73\text{ m}^2\text{ g}^{-1}$) and Al_2O_3 (KHS-24, $160\text{ m}^2\text{ g}^{-1}$) were obtained from the Catalysis Society of Japan and Sumitomo Chemical, respectively. Ru/HAP (ruthenium chloride species supported on hydroxyapatite; 9.1 wt%) and Ru/C (Ru(0) species supported on activated

carbon; 5 wt%) were purchased from Wako Pure Chemical Industries and NE Chemcat Corp., respectively. Compound **2i'** (>99% ee; >99% D at the α -position) was synthesized according to a reported procedure.^[12a] Supported metal hydroxide catalysts were prepared according to a reported procedure (see the Supporting Information).^[12]

Procedure for the synthesis of amines: All the operations for the synthesis of amines were carried out in a glovebox under argon. $\text{Ru}(\text{OH})_x/\text{TiO}_2$, an alcohol, nitrogen source, and mesitylene were successively placed into a pyrex-glass screw-cap vial (volume: ca. 20 mL). A teflon-coated magnetic stirring bar was added, and the reaction mixture was vigorously stirred (800 rpm) under argon (1 atm; see Tables 1–6 for the detailed reaction conditions). The yields of the products were periodically determined by GC analyses. After the reaction was completed, the spent $\text{Ru}(\text{OH})_x/\text{TiO}_2$ catalyst was separated by filtration (or centrifugation), washed with mesitylene and 2-propanol, and dried in vacuo prior to being recycled. The products were isolated by column chromatography on silica gel (eluent: *n*-hexane until elution of mesitylene, then ethyl acetate or diethyl ether). The products were confirmed by ^1H and ^{13}C NMR spectroscopic and/or GCMS analyses.^[5,9,28] For nitrile synthesis, the reactions were carried out under air (6 atm) with a teflon-coated autoclave (volume: ca. 15 mL).

Dehydrative condensation of benzaldehyde and aniline: Benzaldehyde (1 mmol), aniline (1 mmol), toluene (3 mL), and $\text{Ru}(\text{OH})_x/\text{TiO}_2$ (50 mg, or without the catalyst) were successively placed into a glass vial. The reaction mixture was stirred at 25°C under air (1 atm). The conversion and yield were periodically determined by GC analysis. The reaction rates were determined from the slopes of the reaction profiles (plots of $[\text{benzaldehyde}]_0 - [\text{benzaldehyde}]_t$ vs. time) at low conversions of benzaldehyde (<10%; the initial-rate method).

Acknowledgements

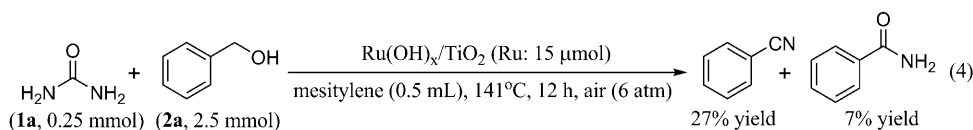
This work was supported in part by the Core Research for Evolutional Science and Technology (CREST) program of the Japan Science and Technology Agency (JST), the Global COE Program (Chemistry Innovation through Cooperation of Science and Engineering), and Grants-in-Aid for Scientific Researches from Ministry of Education, Culture, Sports, Science and Technology.

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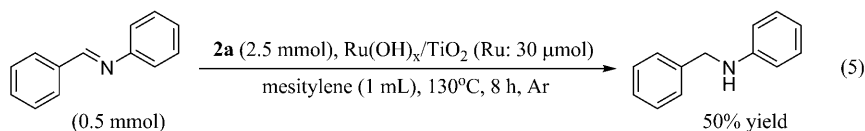
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major nitrogen-containing products without the formation of **3a**; the yields are based on nitrogen in **1a** [Eq. (4)].



- [17] The coordination number (CN) of nearest neighbor Ru atoms for $\text{Ru(OH)}_x \cdot n\text{H}_2\text{O}$ was 1.4 ± 0.2 ;[12i] the formation rate of **3a** monotonically increased with the decrease in coordination number (see Figure S5 in the Supporting Information), thus suggesting that the highly dispersed ruthenium hydroxide species are effective in the present transformation.
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