Rapid Multialkylation of Aqueous Ammonia with Alcohols by Heterogeneous Iridium Catalyst under Simple Conditions

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This paper reports the synthesis of tertiary and secondary amines from aqueous ammonia and benzylic alcohols by titania-supported iridium catalyst. It is a successful example of heterogeneous systems at moderate temperature without either additional solvent or high pressure. The catalytic system showed good tolerance to the atmosphere condition and performed rapidly to give tribenzylamine a yield of over 99% within 6 hours in argon. The crystal structure of titania supports for iridium catalysts strongly affected their activity. The catalysis smoothly proceeded on larger scales. The catalyst could be easily reused and run at least for 5 cycles without significant loss of activity. The highly-dispersed iridium species of less than 2 nm in diameter would be responsible for the excellent catalytic activity. This catalyst is well applicable in multi-alkylation of aqueous ammonia with various primary and secondary benzylic alcohols.

Ammonia is one of the chemicals products of the most output in the world with an annual production of 144 million tons.[1] On account of its readily available and low cost, ammonia has been intensively studied as a nitrogen source in the synthesis of high-value chemical products.[2–4] However, most of the reactions require the use of harmful and toxic alkyl halides as substrates.[5–9] It is noteworthy that with the rising of "green & sustainable chemistry",[10,11] the catalytic synthesis of amine from ammonia with alcohols has attracted significant attention due to its advantages of high atom efficiency and environmentally benign features.[4,12–14] The N-alkylation reaction possesses a high atomic utilization and does not produce toxic or wasteful by-products (only H_2O is outgrowth).[15–18] Up to now, the intensive research interests focus on developing homogeneous catalysed systems for the synthesis of organic amines using ammonia or its solution, and transition-metal homogeneous catalysis systems utilizing Ru,[19–24] Ir,[25–27] have been the most advanced strategy.[14] For example, Fujita et al. reported a water-soluble iridium catalyst [Cp*Ir(NH₃)₃][I]₂ for multialkylation of aqueous ammonia with primary and secondary alcohols, and selectively convert to tertiary and secondary amines, respectively. The catalyst could be recycled by a facile procedure maintaining high activity for at least 3 cycles.[25] Water-soluble iridium complex catalysts bearing N-heterocyclic carbene ligands that enable the selective N-monoalkylation of aqueous ammonia with a variety of alcohols were developed.[26] Meanwhile, heterogeneous catalysts using Ir,[28] Ni,[29–34] Ru,[35–37] Au–Pd,[38] and Rh-In[39] have newly emerged. Nevertheless, there are still some restrictions in the catalytic reactions such as indispensability of organic solvent, high-pressure atmosphere of hydrogen or ammonia, and high temperature. On the other hand, during previous studies by us and other researchers, a series of titania-supported iridium catalysts which showed excellent activity in the catalytic synthesis of nitrogen heterocycles from amines or diamine with alcohols under mild conditions has been developed.[40–45] Here, we report titania-supported iridium catalysts of high efficiency for the multi-alkylation of aqueous ammonia with alcohols without any additional solvent in the air or argon atmosphere. The TEM images reveal the highly dispersed iridium species of less than 2 nm in diameter. Whereas there are many reports for the heterogeneous catalytic synthesis of amines from ammonia with alcohols, the development of the catalytic synthesis procedure without organic solvent and high-pressure of H_2 (or NH₃) simultaneously at low temperature is highly desired. The catalysis smoothly proceeded on larger scales. In marked contrast to the traditional cognition, the desired product formed promptly within 6 h and gave a yield of over 99% in argon or over 85% in air, respectively.

The effects of various catalysts were compared in the N-alkylation of aqueous ammonia (28%) with benzyl alcohol (**1a**) to give tribenzylamine (**2a**) without additional solvents (bath temp; 140°C, 18 h, in atmospheric pressure of air). The results are shown in Table 1. The titania-supported iridium catalysts are all effective in the reaction (entries 1–3, 7). On the other hand, the iridium catalysts supported on other metal oxides such as silica, alumina, and ceria are inactive, implying the critical effects of titania supports for the present catalysis. The titanias

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Table 1. N-Alkylation of aqueous ammonia with benzyl alcohol by various catalysts..[a]

$$NH_3\ (aq)\ +\ HO\frown Ph \xrightarrow[140\ °C]{cat.} \ 2a$$

1a → **2a**

Entry	Catalysts[b]	Yield [%][c]
1	Ir/TIO-10 (A)[d]	71
2	Ir/TIO-6 (R) [d]	26
3	Ir/TIO-4 (A/R) [d]	60
4	Ir/SiO$_2$	trace
5	Ir/Al$_2$O$_3$	0
6	Ir/CeO$_2$	0
7	Ir/TIO-10 (A)[e]	66
8	[Ir(cod)Cl]$_2$[f]	0
9	Ir(acac)$_3$[f]	0
10	IrO$_2$	0
11	TIO-10 (A)	0
12	TIO-6 (R)	0
13	TIO-4 (A/R)	0
14	No catalyst	0

[a] Reaction conditions: NH$_3$ (0.5 mmol, 28% aqueous solution), **1a** (2.5 mmol), catalyst (3 mol% as Ir, 6 wt%, 50 mg), 140 °C, 18 h, in air. [b] JRC (Japan Reference Catalyst) titania designated as TIO-x (x = 4, 6, 10), (A): anatase, (R): rutile titania, (A/R): mixture of anatase and rutile, the catalysts were prepared using [Ir(cod)Cl]$_2$ as a precursor. [c] Yields were based on the amount of nitrogen in NH$_3$ and determined by GC analyses. [d] The BET surface areas of TIO-4, 6, and 10 are 50, 100, and 100 m^{2}g^{-1}, respectively. [e] The catalyst prepared using Ir(acac)$_3$ as a precursor. [f] [Ir(cod)Cl]$_2$ and Ir(acac)$_3$ were used as homogeneous catalysts.

Table 2. Optimization of the reaction conditions.[a].

$$NH_3\ (aq)\ +\ HO\frown Ph \xrightarrow{Ir/TIO-10}$$

1a → **2a**

Entry	Amount of Ir [mol%]	Bath temp. [°C]	Solvent [mL]	Time [h]	Yield[b] [%]
1	3	120	/	18	66
2	3	140	/	18	71
3	3	160	/	18	38
4[c]	3	140	/	18	90
5[d]	3	140	/	18	71
6[e]	3	140	/	18	69
7	3	140	Mesitylene [0.5]	18	64
8	3	140	/	2	28
9	3	140	H$_2$O [0.1]	2	18
10	3	140	H$_2$O [0.2]	2	24
11	3	140	H$_2$O [0.5]	2	0
12[f]	3	140	/	18	99
13[f]	2	140	/	18	82
14[f]	2	140	/	24	99
15[f]	1	140	/	18	72
16[f]	1	140	/	24	72
17[f][g]	3	140	/	24	(90)
18[f]	3	120	/	24	98
19[f]	3	100	/	24	78

[a] Reaction conditions: NH$_3$ (0.5 mmol, 28% aqueous solution), **1a** (2.5 mmol), catalyst (3 mol% as Ir, 6 wt%, 50 mg), 140 °C, 18 h, in air. [b] Yields were based on the amount of nitrogen in NH$_3$ and determined by GC analyses. Isolated yields are shown in the parenthesis. [c] 4-Fold reaction under the condition of NH$_3$ (2 mmol, 28% aqueous solution), **1a** (10 mmol), catalyst (3 mol% as Ir, 6 wt%, 200 mg). [d] Catalyst (3 mol% as Ir, 4 wt%, 75 mg). [e] Catalyst (3 mol% as Ir, 1 wt%, 300 mg). [f] The reaction was performed in argon. [g] NH$_3$ (1.5 mmol, 28% aqueous solution), **1a** (7.5 mmol).

of anatase and rutile phases were used for the supports (Figure S1). The anatase-supported catalyst showed excellent activity (entry 1), while the catalyst supported on rutile showed lower activity (entry 2). Our previous study reveals anatase-supported iridium catalysts show lower ability in CO uptake than that of rutile due to their strong metal-support interaction (SMSI) between iridium and anatase,[41] suggesting SMSI significantly affects the present catalytic system. The possible reason is that anatase supports with the higher surface area have a higher concentration of lattice defects which facilities the formation of TiOx species during reduction treatment.[46] When the precursor switch from [Ir(cod)Cl]$_2$ to Ir(acac)$_3$, the catalyst shows the good activity as well (entry 7). Whereas no formation of **2a** was observed using [Ir(cod)Cl]$_2$ or Ir(acac)$_3$ as a homogeneous catalyst (entries 8 and 9). The reaction did not proceed in the presence of IrO$_2$. Titania supports did not show any catalytic activity for the reaction without iridium species regardless of the crystal structure. Besides, the reaction of aqueous ammonia with **1a** never occurred in the absence of the catalyst.

In the next step, the effects of various reaction conditions were examined for the catalytic reaction in the presence of Ir/TIO-10 catalyst (Table 2). Entries 1–3 show the effect of the bath temperature on the catalytic reaction. The reaction carried out at 120 °C gave **2a** in high yield, while the yield of **2a** dramatically declined as the bath temperature increase to 160 °C. This result could be attributed to the high temperature accelerate the reflux of water which may impede the adsorption of ammonia onto the catalytically active sites. To our surprise,

the reaction more smoothly proceeded to a 90% yield of **2a** in the 4-fold catalytic reaction (entry 4). The catalysts with 1 and 4 wt% of metal loading levels show no real distinction in the yields at the same substrates to catalyst ratio (3 mol% to N). Interestingly, the TEM images (Figure S2) reveal the particle size of iridium species mainly distribute around 1 to 2 nm regardless of the increasing loading level. This could be the reason for the similar activity for the catalyst with different loading level. The addition of organic solvent did not contribute to the conversion of the desired product. The results shown in entries 8–11 testifies that the addition of water rather impedes the conversion of the substrates. The activity of the catalyst was further improved in an argon atmosphere as shown in entries 12–19. The substrates can be totally converted to the desired product with 2 or 3 mol% of Ir catalyst at 140 °C and an excellent yield can be achieved at lower temperatures of 120 °C and 100 °C.

The production of **2a** was completely stopped by the hot filtration of the solid catalyst using a PTFE filter (pore size 0.45 μm) after the reaction was allowed for 1 h (see Figure S3). The inductively coupled plasma atomic emission spectroscopy (ICP/AES) analysis shows that the presence of iridium in pure water and the filtrate (50 cm^3) were 0.087 and 0.110 ppm, respectively, suggesting the leaching of iridium to the solution is negligible. These results reveal that the catalysis of reaction is
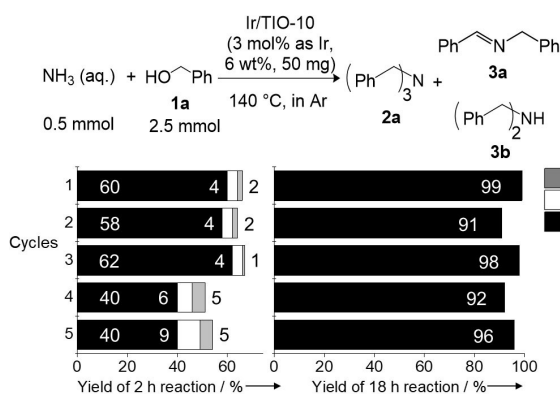
intrinsically based on the presence of the solid catalyst and proceeds heterogeneously. The present catalysts could be recycled by a simple method (Scheme 1). After the reaction was complete, the solid catalyst was separated from the reaction mixture by centrifugation and washed with THF, followed by calcination at 400 °C for 30 minutes and reduction at 500 °C for 30 minutes. The catalyst can stabilize the output yield of over 90 % for at least 5 cycles for 18 h reactions. To evaluate reaction rates at the intermediate conversion levels, recycling tests for 2 h reactions were also performed. During the first 3 cycles, the total yields of **2a** and the intermediate amines were in the range between 64 to 67 %, while the lower yields of 51 and 54 % were shown in the 4th and 5th cycles.

The catalyst was further characterized to understand the factors responsible for the high activity. The state of iridium species on titania was investigated by XPS, and the deconvolution pattern of the Ir 4f spectrum is shown in Figure S4. The Ir $4f_{7/2}$ binding energies assigned for Ir^{3+} (61.5 eV) and metallic Ir^0 (60.4 eV) are shown by vertical lines.[47] The contribution of IrO_2 (62.3 eV) was not confirmed in the fresh catalyst. The ratio of Ir^{3+} and Ir^0 was ca. 3 to 7, suggesting that a major part of the Ir species on the titania support are fully reduced after hydrogen reduction and a part of Ir species is in an intermediate oxidation state (3+). As shown in Figure S4, Ir^{3+} species are more predominant in anatase-supported catalysts, which show higher activity for the present reaction (see Table 1). Similar results have been reported in the related catalytic systems before.[40] Note that homogeneous catalysts based in the "Ir(III)Cp*" system were reported to be effective for the N-alkylation reactions.[25,26] These results suggest that the Ir^{3+} species could be responsible for the catalytic activity. Besides, the XP spectra of the recycled Ir/TIO-10 and Ir/TIO-6 catalysts recovered from the reaction mixture indicated that while the Ir^0 species were predominant in both catalysts, the surface Ir^{3+} species (and Ir^{4+} species in the Ir/TIO-10 catalyst) were also found. This suggests a partial oxidation of iridium species during the catalytic runs (Figure S4(c), (d)). Temperature-programmed desorption (TPD) profile of ammonia was performed to evaluate the acid strength of the catalyst (Figure S5). A strong peak at around 86 °C can be attributed to the desorption of ammonia on Ti sites which are saturated by hydroxyl groups. While the peak at 327.9 °C was assigned to the desorption of ammonia on free Ti sites due to the strong interaction between a relatively strong base (ammonia) with a Lewis acid site.[48] These results evidence that the catalyst possesses weak acid sites on the surface and the weak adsorption of ammonia could facilitate the conversion of the N-alkylation of benzylic alcohols.

The interactions between the surface of catalyst and substrate were further observed by in situ FTIR (Figure S6). CH_2 stretching (2948 cm^{-1}) and aromatic CH stretching (3100–3000 cm^{-1}) suggest benzyl alcohol strongly chemisorbs on the surface of the catalyst after heating at 140 °C for 30 min with evacuation. As ammonia gas (0.1 vol.% in He) was insufflated, NH_3 symmetric bending (930 and 965 cm^{-1})[49] and symmetric stretch of NH in proton-acceptor ammonia (3333 cm^{-1})[50] can be observed distinctly and increase cumulatively. The decreasing of O–H bending in benzyl alcohol (1209 cm^{-1})[51,52] shows the conversion of benzyl alcohol. Meanwhile, the formation of benzylamine was evidenced by the C–N stretching vibration cluster around 1180–1020 cm^{-1}[51] and N–H stretching vibration (3393 cm^{-1}) of primary amine.[53] Remarkably, the whole procedure performed as soon as the ammonia gas passed through.

As shown in Table 3, the effect of the present Ir/TIO-10 catalyst in large-scale reactions with representative benzylic alcohols was examined. This catalytic system possessed good tolerance to air and argon as well. Both primary benzylic alcohols containing electron-donating substituents and electron-withdrawing substituents undergo efficient conversion to corresponding benzylic tertiary amines in high yields. The reaction of ammonia with 1-octanol gave trioctylamine, but the yields were insufficient (entry 4). Moreover, the selective formation of secondary amines from secondary benzylic alcohol was also achieved (entry 5). The high yield of secondary amine
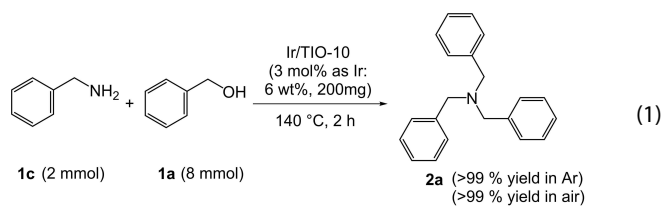
Table 3. Synthesis of tertiary and secondary amines from aqueous ammonia and benzylic alcohols by Ir/TIO-10 (6 wt %).[a]

Entry	Alcohol	Yield [%][b] Product	In air[c]	In Ar[d]
1			73	85 (80)
2			84	91 (85)
3			79	85 (74)
4			24	23
5			95	> 99 (82)[e]

[a] Reaction conditions: NH_3 (1.5 mmol, 28 % aqueous solution), alcohols (7.5 mmol), Ir/TIO-10 (6 wt %, 0.060 mmol as Ir), 140 °C. [b] The products were determined by GC-MS and NMR, the yields were based on the amount of nitrogen in NH_3 and determined by GC analyses. [c] Reactions run for 20 h. [d] Reactions run for 24 h. Isolated yields are shown in the parenthesis. [e] A mixture of diastereomers (meso/dl ca. 50 : 50 by NMR) was formed.

Scheme 1. Recycle of Ir/TIO-10 catalyst.

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even though using excess amounts of alcohol probably dues to the steric hindrance.[25,54]

$$\text{1c (2 mmol)} + \text{1a (8 mmol)} \xrightarrow[\text{140 °C, 2 h}]{\substack{\text{Ir/TIO-10}\\\text{(3 mol\% as Ir:}\\\text{6 wt\%, 200mg)}}} \text{2a} \quad (1)$$

1c (2 mmol)   **1a** (8 mmol)   **2a** (>99 % yield in Ar)
(>99 % yield in air)

The time course profiles for the yield over Ir/TIO-10 catalysed alkylation of ammonia with **1a** in both air and argon atmosphere are shown in Figure 1. The catalysis behaviours in air and argon are slightly different. When the reaction performed in air, the reaction proceeded slightly faster and gave the desired product in 19% yield in the initial hour. As the reaction proceeded, the yield of the product dramatically increased to 83% within 2 hours and then levelled off with further increases in the reaction time. In the following time, there was no substantial increase in production and finally achieved a 90% yield after 18 hours. As for the reaction in argon, the catalytic reaction gave the product in a yield of 47% in the initial hour. Then, the reaction proceeded smoothly and completed the conversion of all substrates within 6 hours. A separate experiment reveals that the formation of tribenzyl-amine from benzylamine and benzyl alcohol was rapidly finished in 2 hours both in air or argon atmosphere [Eq. (1)], suggesting the reaction rate hinges on the formation of benzylamine from benzyl alcohol and ammonia. As one possible reason for the different time course profiles in air or argon, the oxidation of benzyl alcohol to benzaldehyde by air and subsequent conversion to imines might accelerate the reaction at the early stage.[55–57] The further detailed study on the different behaviours in the reactions in air and argon is ongoing. Consequently, the presence of air is proved not to significantly hamper the reaction.

To understand the reaction mechanisms, a serial of separate experiments was performed. Since Ir/TiO₂ is well known for its high performance in the aerobic oxidation of **1a**,[55–57] we first investigated the conversion of **1a** in the presence of the catalyst for one hour in argon or air [Eq. (S1)]. The result shows that 36% or 27% of **1a** was converted to benzaldehyde and its dimers in argon or air, respectively. On the other hand, the alkylation of aqueous ammonia with free benzaldehyde was slow in the presence of the iridium catalyst [Eq. (S2)], probably because of the poisoning by benzaldehyde (see below). Without the catalyst the formation of **1c** as well as the corresponding imines were not detected under the present conditions, suggesting the present catalyst have a promotional role for this step. It is generally accepted that the hydrogen transfer pathway over heterogeneous[29,35] or homogeneous[19,25,58] cata-lyst proceeds via the oxidation of alcohol and the following amination of aldehyde. Also, the reaction of benzylamine **1c** and benzaldehyde **1b** gave N-benzylidenebenzylamine **3a** in low yield (19%), while the reaction in the absence of the catalyst smoothly proceeded [Eq. (S3)]. This suggests that the catalyst retarded the transformation from aldehyde to imine,
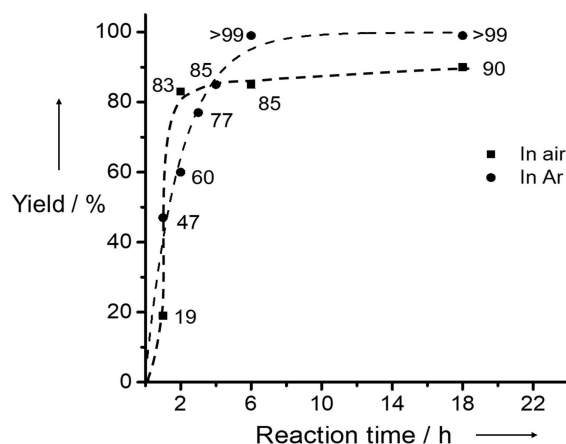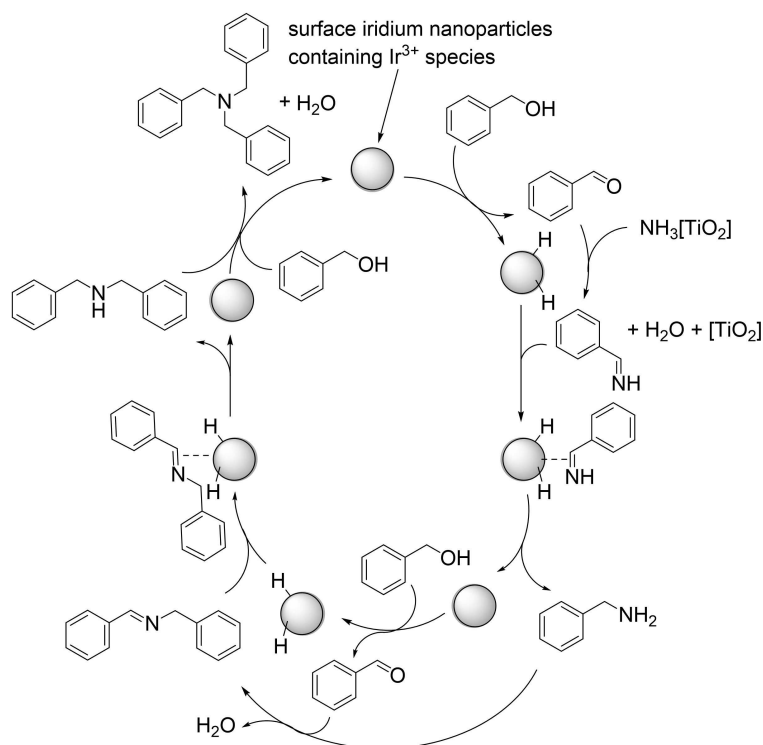

Figure 1. Time-course profiles of the yields (%) of **2a** from aqueous ammonia with **1a** over Ir/TIO-10 catalyst at 140 °C. The conditions of in air reactions: NH₃ (2 mmol, 28% aqueous solution), **1a** (10 mmol), catalyst (3 mol% as Ir, 6 wt%, 200 mg); The conditions of in argon reactions: NH₃ (0.5 mmol, 28% aqueous solution), **1a** (2.5 mmol), catalyst (3 mol% as Ir, 6 wt%, 50 mg).

probably due to the strong adsorption of benzaldehyde **1b** on the surface of the catalysts (see below). Note that the dehydrogenation of benzyl alcohol to benzaldehyde over titania-supported iridium catalyst was completely suppressed in the presence of an equimolar amount of benzaldehyde [Eq. (S4)] as previously reported by us in a similar catalytic system (see Figure S5 of [40]). This suggests that benzaldehyde poisons the active sites on the surface of the present catalyst. In the reactions shown in Eq. (S1) to Eq. (S4), the presence of a significant amount of benzaldehyde **1b** will hamper the reaction. In the present alkylation of ammonia by benzylic alcohols, the rapid transformation of aldehydes to imine would prevent the poisoning of the catalyst.

In addition, we further examined the reactivity of the possible intermediate, **3a** and **3b**. The reaction of **3a** or **3b** with benzyl alcohol **1a** produced a small amount of the desired product **2a** [Eq. (S5) and (S6)], while over 99% of product **2a** was rapidly achieved in 2-hours from **1c** and **1a** [Eq. (1)]. Again, the reaction of **3a** or **3b** with **1b** gave **2a** in low yields. These results suggest that the multi-alkylation proceeds via **3a** and **3b** kept in the coordination sphere of the surface iridium species rather than "free" **3a** or **3b**. The catalytic reaction of **1c** and **1d** smoothly proceeded to give corresponding tertiary amines **2b**, **2c**, and **2d** together with imine **3c** in a 2-hour reaction, and the formation of **3a** was not observed [Eq. (S7)]. This indicates the predominance of the dialkylation rather than the self-condensation of **1c**.[59] Therefore, the present catalytic transformation would proceed through hydrogen auto-transfer pathways as demonstrated in Scheme 2, which is based on that previously proposed for homogeneous catalysis.[25] The first N-alkylation proceeds via the rate-determining dehydrogenation of benzylic alcohols to aldehydes and hydride species on the surface of the iridium nanoparticles. The thus formed aldehyde would immediately react with ammonia, probably adsorbed on the weak acidic sites of the titania surface, to form an imine. The hydrogenation of imine by the surface hydride species

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Scheme 2. A possible mechanism for the N-alkylation of aqueous ammonia with benzyl alcohol.

would produce a corresponding primary amine. Subsequently, the hydrogen auto-transfer of an obtained primary amine with benzylic alcohol would proceed on the iridium sites through similar sequential processes to give a corresponding tertiary amine. The whole reaction process can be completed rapidly within 2 hours under the condition of adequate benzylic alcohol. The formation of small nanoparticles is generally preferable to achieve the excellent activity since it can maximize the area of the catalytically active surface of metallic species.[45] As evidenced by TEM study, the formation of iridium nanoparticles of less than 2 nm in diameter would be one reason for the excellent catalytic activity.

In conclusion, titania-supported iridium catalysts with simple reaction conditions and excellent activity for the synthesis of organic amines from aqueous ammonia have been developed. The catalytic system possesses a high tolerance in the reaction condition. No additional solvent is required, and the reaction can be performed readily in an air or argon atmosphere. The crystal structure of titania supports for iridium catalysts markedly affected their activities. The detailed characterization revealed that highly-dispersed partially-reduced iridium nanoparticles of less than 2 nm in diameter would be responsible for the excellent catalytic activity. Over Ir/TIO-10 catalyst, tertiary and secondary amines were synthesized by the multialkylation of aqueous ammonia with primary and secondary benzylic alcohols, respectively. The formation of the product smoothly proceeded in large-scale reactions. This catalytic system elucidates a green and simple method with high efficiency for the synthesis of organic amines.

Acknowledgements

Conflict of Interest

The authors declare no conflict of interest.

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COMMUNICATIONS

Solvent free! Titania-supported iridium catalyst achieved multialkylation of aqueous ammonia with alcohols without any additional solvent and give a yield over 99% within 6 hours. The reaction can be performed rapidly both in air and argon atmosphere.
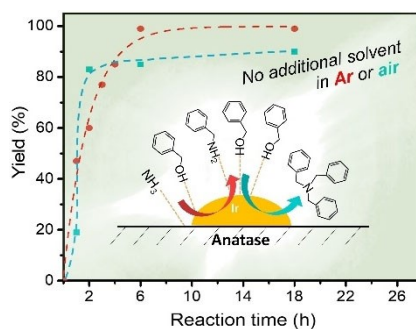
H. Yu, L. Ma, Prof. K. Wada*, Dr. R. Kurihara, Prof. Q. Feng, Prof. S. Uemura, Prof. K. Isoda

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Rapid Multialkylation of Aqueous Ammonia with Alcohols by Heterogeneous Iridium Catalyst under Simple Conditions