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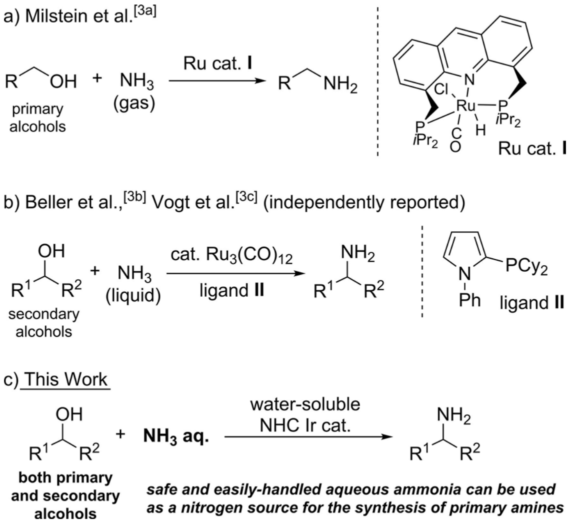
N-Alkylation of Aqueous Ammonia with Alcohols Leading to Primary Amines Catalyzed by Water-Soluble N-Heterocyclic Carbene Complexes of Iridium

Ken-ichi Fujita,* Shohichi Furukawa, Namino Morishima, Mineyuki Shimizu, and Ryohei Yamaguchi[a]

A new catalytic system for the N-monoalkylation of aqueous ammonia with a variety of alcohols was developed. Water-soluble dicationic complexes of iridium bearing N-heterocyclic carbene and diammine ligands exhibited high catalytic activity for this type of reaction on the basis of hydrogen-transfer processes without generating harmful or wasteful byproducts. Various primary amines were efficiently synthesized by using safe, inexpensive, and easily handled aqueous ammonia as a nitrogen source. For example, the reaction of 1-(4-methylphenyl)ethanol with aqueous ammonia in the presence of a water-soluble N-heterocyclic carbene complex of iridium at 150 °C for 40 h gave 1-(4-methylphenyl)ethylamine in 83 % yield.

Recently, much attention has been directed to the use of ammonia as a nitrogen source for organic synthesis, because of its abundance and low price.[1] To date, a number of reports on transition-metal-catalyzed reactions for the synthesis of organic amines by using gaseous (or liquid) ammonia or its solution in an organic solvent have appeared.[2] Because the selective catalytic synthesis of primary amine derivatives by the reaction of alcohol substrates with ammonia generates no harmful or wasteful byproducts (generating only H_2O as a coproduct), such a synthesis is considered important and desirable methodology in the field of synthetic organic chemistry.[3,4] The reaction is based on hydrogen-transfer processes, called “borrowing hydrogen” or “hydrogen autotransfer”.[5] For example, Gunanathan and Milstein reported the synthesis of primary amines from primary alcohols and pressurized gaseous ammonia under the catalysis of an acridine-based pincer complex of ruthenium (Scheme 1 a).[3a] Additionally, Beller et al. and Vogt et al. independently reported the synthesis of primary amines from secondary alcohols and liquid ammonia under the catalysis of the $Ru_3(CO)_{12}$/2-(dicyclohexylphosphino)-1-phenyl-1*H*-pyrrole system (Scheme 1 b).[3b,c]



Scheme 1. Selective catalytic synthesis of primary amines by N-alkylation of ammonia with alcohols.

Aqueous ammonia is an attractive nitrogen source considering its advantages in terms of safety and handling. Some systems involving the use of aqueous ammonia for the synthesis of organic amines have been reported. However, most of them required the employment of harmful organic halides as substrates.[6] On the other hand, during the course of our studies on hydrogen-transfer reactions catalyzed by iridium complexes,[7] we reported the synthesis of a water-soluble dicationic iridium–ammine complex, $[Cp^*Ir(NH_3)_3][I]_2$ (**1**) ($Cp^* = \eta^5$-pentamethylcyclopentadienyl), and its high catalytic activity for the multialkylation of aqueous ammonia with alcohols to give tertiary and secondary amines.[8] However, monoalkylation of aqueous ammonia with alcohols leading to primary amines has so far not been achieved.[9,10] Herein, we report the synthesis of new water-soluble iridium N-heterocyclic carbene (NHC) complexes and their high catalytic performance for the N-alkylation of aqueous ammonia with alcohols to give primary amines (Scheme 1 c).[11]

First, iridium NHC complexes **2**–**7** illustrated in Figure 1 were synthesized.[12] Details of the procedures for their synthesis and characterization (including single-crystal X-ray analysis of **4** and **5**) are described in the Supporting Information. All of these complexes were found to be stable in air, and dicationic complexes **1** and **4**–**7** were soluble in water.

The catalytic activities of these iridium NHC complexes for the monoalkylation of aqueous ammonia leading to primary amines were evaluated. Initially, the reaction of 1-(4-methylphenyl)ethanol with aqueous ammonia was investigated as a

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[a] *Prof. Dr. K. Fujita, S. Furukawa, N. Morishima, M. Shimizu,*
Prof. Dr. R. Yamaguchi
Graduate School of Human and Environmental Studies
Kyoto University
Sakyo-ku Kyoto 606-8501 (Japan)
E-mail: fujita.kenichi.6a@kyoto-u.ac.jp

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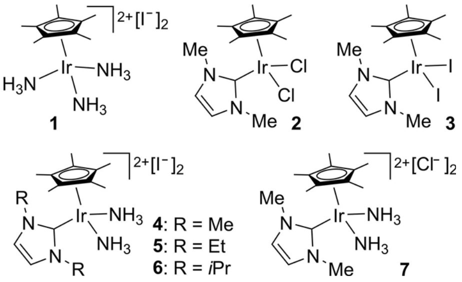
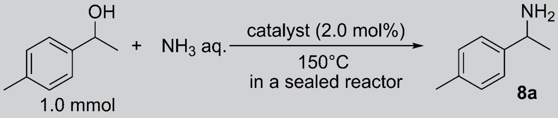


Figure 1. Iridium complexes **1**–**7** used in this study.

model reaction. The reactions were performed in a sealed reactor at 150 °C. The results are summarized in Table 1. Upon performing the reaction of 1-(4-methylphenyl)ethanol (1.0 mmol) with aqueous ammonia (28 %, 20 mmol) for 20 h in the presence of water-soluble triammine complex **1** (2.0 mol %) without an NHC ligand, 1-(4-methylphenyl)ethylamine (**8 a**) was obtained in only 3 % yield (Table 1, entry 1). On the other hand, dichloride complex **2**, bearing an NHC ligand, exhibited superior activity to give **8 a** in 37 % yield (Table 1, entry 2). Thus, the importance of the NHC ligand for the catalytic activity could be suggested. Upon using diiodide complex **3**, the yield of **8 a** was further improved to 46 % (Table 1, entry 3).[13] Moreover, water-soluble dicationic diammine complex **4** exhibited the highest catalytic activity to give **8 a** in 54 % yield (Table 1, entry 4). Complexes **5** and **6**, which have ethyl and isopropyl groups on the nitrogen atoms in the NHC ligands, respectively, showed lower catalytic activity (Table 1, entries 5 and 6). Additionally, complex **7** having chlorides as counteranions exhibited slightly lower catalytic activity than **4** (Table 1, entry 7). Increasing the amount of aqueous ammonia did not improve the yield of **8 a** (Table 1, entry 8). Increasing the reaction time (40 h) and catalyst loading (4.0 mol %) both improved the yield (Table 1, entries 9 and 10). Finally, the optimal reaction conditions were determined (Table 1, entry 11) to give **8 a** in 83 % yield.

To evaluate the scope of this catalytic system, reactions of various secondary alcohols with aqueous ammonia under the optimal conditions were conducted. The results are summarized in Table 2. The reactions of 1-arylethanols having electron-donating and electron-withdrawing substituents smoothly proceeded to give corresponding 1-arylethylamine derivatives **8 a**–**i** in good yields (Table 2, entries 1–9). 1-(Pyridin-2-yl)ethanol could also be used as a substrate to give 1-(2-pyridyl)ethylamine (**8 j**) in moderate yield (Table 2, entry 10). Moreover, cyclic secondary alcohols such as 1-indanol, 1,2,3,4-tetrahydro-1-naphthol, 1,2,3,4-tetrahydro-2-naphthol, and cyclohexanol were also converted into corresponding primary amines **8 k**–**n** in good yields (Table 2, entries 11–14). Additionally, noncyclic aliphatic secondary alcohols (e.g., 4-phenyl-2-butanol and 2-

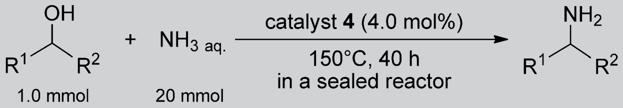
Table 1. Reaction of 1-(4-methylphenyl)ethanol with aqueous ammonia to give 1-(4-methylphenyl)ethylamine (**8 a**) under various conditions.

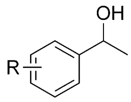
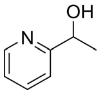
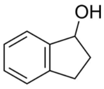
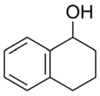
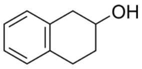
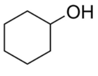
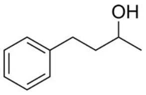
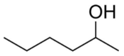


Entry	Catalyst	$NH_{3(aq)}$ [mmol]	*t* [h]	Conversion[a] [%]	Yield[a] [%]
1	**1**	20	20	17	3
2	**2**	20	20	54	37
3	**3**	20	20	66	46
4	**4**	20	20	74	54
5	**5**	20	20	65	44
6	**6**	20	20	55	33
7	**7**	20	20	68	50
8	**4**	40	20	47	35
9	**4**	20	40	85	70
10[b]	**4**	20	20	91	79
11[b]	**4**	20	40	96	83

[a] Conversion of the alcohol was determined by GC analysis. [b] Catalyst loading was 4.0 mol %.

Table 2. Reactions of various secondary alcohols with aqueous ammonia catalyzed by **4** to give primary amines.



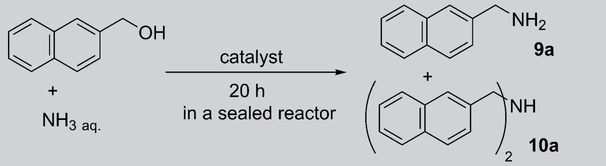
Entry	Alcohol	Product	Yield[a] [%]
			
1	R = H	**8 b**	(82)
2	R = 4-Me	**8 a**	63 (83)
3	R = 2-OMe	**8 c**	89
4	R = 3-OMe	**8 d**	88
5	R = 4-OMe	**8 e**	76
6	R = 2-Cl	**8 f**	88
7	R = 3-Cl	**8 g**	82
8	R = 4-Cl	**8 h**	73
9	R = 4-CF_3	**8 i**	73
10		**8 j**	56
11		**8 k**	83
12		**8 l**	70
13		**8 m**	72
14		**8 n**	(78)
15		**8 o**	70
16		**8 p**	(59)

[a] Yield of isolated product. Yield determined by GC is given in parentheses.

hexanol) were applied to this catalytic system, and they gave primary amines **8o** and **8p** in moderate to good yields (Table 2, entries 15 and 16).

The accomplishment of the synthesis of primary amines through the monoalkylation of aqueous ammonia with primary alcohols is a big challenge, as multialkylation leading to secondary and tertiary amines must be prevented. Thus, the reaction of (2-naphthyl)methanol with aqueous ammonia as a model reaction under various conditions was conducted. The results are summarized in Table 3. Upon performing the reaction of (2-naphthyl)methanol with aqueous ammonia (20 equiv.) in the presence of catalyst **4** (4.0 mol%) at 150 °C for 20 h (which were the optimal conditions for the reaction of secondary alcohols with aqueous ammonia to give primary amines), the desired primary amine, 1-(2-naphthyl)methanamine (**9a**), was obtained in only 27% yield. The major product under these conditions was the secondary amine bis(2-naphthalenylmethyl)amine (**10a**) (48% yield), which was formed by dialkylation of aqueous ammonia (Table 3, entry 1). In addition to increasing the number of equivalents of aqueous ammonia, the employment of catalyst **6**, which has more bulky isopropyl groups on the nitrogen atoms in the NHC ligand, improved the yield of **9a** to 56% (Table 3, entry 3). Finally, selective monoalkylation was accomplished by performing the reaction at 170 °C to give **9a** in 78% yield (Table 3, entry 4). Catalyst **6** was indispensable for selective monoalkylation in the reaction of a primary alcohol with aqueous ammonia, because a similar reaction using catalyst **4** resulted in lower yield of **9a** (Table 3, entry 5).[14]

Table 3. Reaction of (2-naphthyl)methanol with aqueous ammonia to give 1-(2-naphthyl)methanamine (**9a**) and bis(2-naphthalenylmethyl)amine (**10a**) under various conditions.

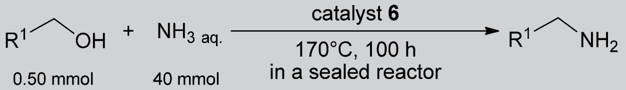


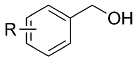
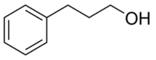
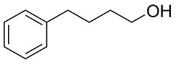
Entry	Alcohol [mmol]	$NH_{3(aq)}$ [mmol]	Catalyst [mol%]	*T* [°C]	Yield[a] [%] **9a**	**10a**
1	1.0	20	**4** (4.0)	150	27	48
2	1.0	20	**6** (4.0)	150	31	56
3	0.50	40	**6** (2.0)	150	56	22
4	0.50	40	**6** (2.0)	170	78	<5
5	0.50	40	**4** (2.0)	170	60	14

[a] Yield of isolated product.

Subsequently, reactions of various primary alcohols with aqueous ammonia catalyzed by **6** were conducted to investigate the substrate scope. The results are summarized in Table 4. The reactions of benzylic alcohols having electron-donating and electron-withdrawing substituents gave corresponding benzylamine derivatives **9b**–**g** in moderate to good yields (Table 4, entries 1–6). Besides, aliphatic primary alcohols (e.g., 3-phenyl-1-propanol and 4-phenyl-1-butanol) were also applied to this catalytic system, and they gave primary amines **9h** and **9i** in moderate to high yields (Table 4, entries 7 and 8).

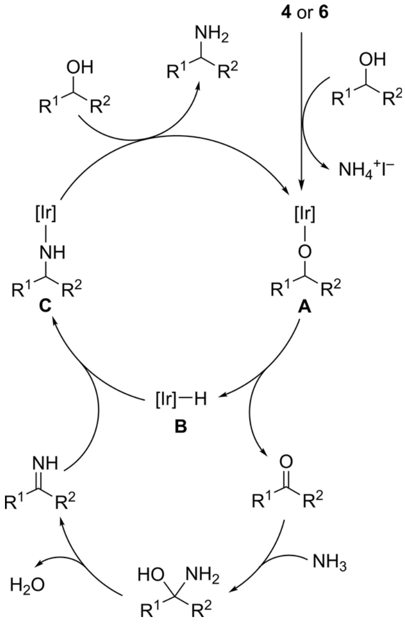
Table 4. Reactions of various primary alcohols with aqueous ammonia catalyzed by **6** to give primary amines.



Entry	Alcohol	Catalyst **6** [mol%]	Product	Yield[a] [%]
				
1	R=H	2.0	**9b**	(69)
2	R=3-OMe	2.0	**9c**	64
3	R=4-OMe	2.0	**9d**	45
4	R=4-tBu	2.0	**9e**	65
5	R=3-Cl	2.0	**9f**	(83)
6	R=4-Cl	2.0	**9g**	77
7		4.0	**9h**	88
8		4.0	**9i**	68

[a] Yield of isolated product. Yield determined by GC is given in parentheses.

We previously proposed mechanisms for the N-alkylation of amines with alcohols that were catalyzed by iridium complexes based on hydrogen-transfer processes.[7a–e] The catalytic reactions presented in this study would proceed through a similar mechanism, including three elementary steps (dehydrogenation of an alcohol, formation of an imine, and transfer hydrogenation of the imine), as shown in Scheme 2. The first step is



Scheme 2. Possible mechanism for the N-alkylation of aqueous ammonia with alcohols.

the formation of alkoxo–iridium species **A** by the reaction of catalyst **4** or **6** with an alcohol. Then, iridium hydride species **B** and the carbonyl intermediate (a ketone or an aldehyde) are formed by β-hydrogen elimination from **A**. Condensation between the carbonyl intermediate and ammonia occurs to afford an imine intermediate. Addition of iridium hydride species **B** to the C=N bond of the imine intermediate gives amido–iridium species **C**. Finally, amido–alkoxo exchange occurs to release a primary amine product, and this is accompanied by regeneration of alkoxo–iridium species **A**. The introduction of a strongly electron-donating NHC ligand enhances the process of **B** to **C** (addition of Ir–H to C=N) by increasing the nucleophilic character of the iridium hydride. Furthermore, for reactions of primary alcohols with aqueous ammonia (Table 4), the employment of catalyst **6** is important to accomplish the selective synthesis of primary amines, because the more bulky isopropyl groups of the NHC ligand in **6** prevent dialkylation to afford secondary amines by suppressing approach of the imine species, which might be generated by the reaction of a primary amine (product of the first catalytic cycle) with the aldehyde intermediate to the coordination sphere.[14]

In summary, we developed a new system for the selective synthesis of primary amines by N-alkylation of aqueous ammonia with alcohols catalyzed by new water-soluble N-heterocyclic carbene complexes of iridium. Various primary amines were efficiently synthesized by using safe, inexpensive, and easily handled aqueous ammonia as a nitrogen source.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alcohols · amines · carbene ligands · hydrogen transfer · iridium

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[9] In the reference 3a, Milstein et al. reported the synthesis of primary amines from alcohols and ammonia in water. However, pressurized (7.5 atm) gaseous ammonia has been used in their catalytic system.

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[12] Complexes **1** and **2** were prepared according to literature method: X.-Q. Xiao, G.-X. Jin, *J. Organomet. Chem.* **2008**, *693*, 3363–3368. See also reference 8.

[13] We have also performed the reaction in the presence of $[Cp^*IrI_2]_2$ (2.0 mol%Ir) under the same conditions as Table 1. In this case, the yield of **8a** was 11%, also indicating the importance of NHC ligand for high catalytic activity.

[14] We have attempted to prepare the Cp*Ir-NHC catalyst having more bulky *t*Bu groups on nitrogen atoms. However, it has not been successful so far.

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K. Fujita,* S. Furukawa, N. Morishima, M. Shimizu, R. Yamaguchi

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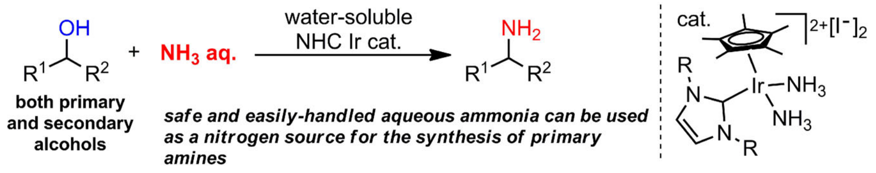
N-Alkylation of Aqueous Ammonia with Alcohols Leading to Primary Amines Catalyzed by Water-Soluble N-Heterocyclic Carbene Complexes of Iridium



Just once: A new catalytic system for the N-monoalkylation of aqueous ammonia with a variety of alcohols to give primary amines is developed. New water-soluble dicationic complexes of iridium bearing N-heterocyclic carbene (NHC) and diammine ligands exhibit high catalytic activities on the basis of hydrogen-transfer processes without generating harmful or wasteful byproducts.