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N-Alkylation of Amines with Alcohols Catalyzed by a Water-Soluble Cp*Iridium Complex: An Efficient Method for the Synthesis of Amines in Aqueous Media

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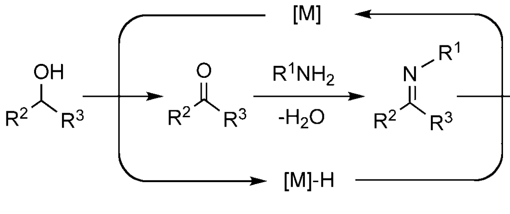
Abstract: An efficient and environmentally benign catalytic system for the synthesis of various organic amines catalyzed by the water-soluble and air-stable (pentamethylcyclopentadienyl)-iridium-ammine iodide complex, $[Cp^*Ir(NH_3)_3][I]_2$ (Cp* = pentamethylcyclopentadienyl), has been developed. A wide variety of secondary and tertiary amines were synthesized by the *N*-alkylation reactions of theoretical equivalents of amines with alcohols in water under air without a base. The synthesis of cyclic amines was also achieved by the *N*-alkylation of benzylamine with diols. Furthermore, the recycle use of the present water-soluble Cp*Ir catalyst was accomplished.

Keywords: alcohols; alkylation; amines; iridium; water-soluble catalyst

Introduction

Organic amines are widely used as synthetic intermediates for the production of pharmaceuticals, fine chemicals, agrochemicals, bioactive compounds, polymers, and dyes. Thus, the development of practical methods for the synthesis of amines has been one of the most important subjects in synthetic organic chemistry.[1]

As an environmentally benign approach to the synthesis of amines, much attention has been paid to the transition metal-catalyzed *N*-alkylation of amines or ammonia with alcohols as alkylating agents based on the catalytic hydrogen transfer process (Scheme 1).[2] This reaction sequence would start with the dehydrogenation of an alcohol to generate a corresponding aldehyde or ketone. Subsequently, an imine or iminium intermediate is formed through dehydrative condensation between an amine and the carbonyl intermediate, followed by transfer hydrogenation with the transiently formed metal hydride species, affording the desired *N*-alkylated amine.

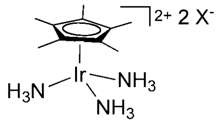


Scheme 1. Reaction pathway for the *N*-alkylation of amines with alcohols through a catalytic hydrogen transfer process.

Compared to the *N*-alkylation of amines with alkyl halides[1,3] and reductive amination with carbonyl compounds,[4] the reactions using alcohols as alkylating agents are more attractive and promising, because such reactions do not generate harmful and wasteful by-products (they generate only H_2O as a co-product). Additionally, less toxic and readily available alcohols can be employed as starting materials.

To date, a number of homogeneous catalytic systems for the *N*-alkylation of amines with alcohols has been studied using iridium,[5,6,8a] ruthenium,[7] and other transition metal catalysts.[8] However, most of these catalytic reactions have to be performed in organic solvents, which might cause the production of a large amount of auxiliary waste. Most of the organic solvents are associated with hazard risks, and might lead to environmental pollution. Therefore, it should be important to develop a new catalytic system which can be performed in a greener solvent such as water.[9,10] There are many advantages of replacing organic solvents with water for organic synthesis. Obviously, water is the most inexpensive, safe and environmentally friendly solvent. In this context, the development of water-tolerant and water-soluble catalysts has become an active area of research.

Recently, we have reported the synthesis of the novel water-soluble Cp*Ir-ammine complexes $[Cp^*Ir(NH_3)_3][X]_2$ (**1**: X = Cl, **2**: X = Br, **3**: X = I) and the high catalytic performance of **3** in the *N*-alkylation of aqueous ammonia with alcohols.[11] A variety of tertiary and secondary amines was synthesized by the multialkylation of aqueous ammonia with primary and secondary alcohols. Since we are interested in the potential and scope of synthetic organic chemistry in water solvent, we began to investigate the *N*-alkylation of other lower amines with alcohols using water as a solvent.[12]



1: X = Cl
2: X = Br
3: X = I

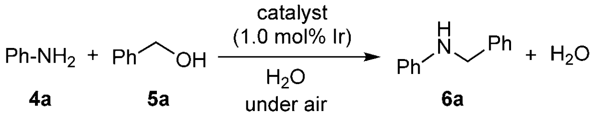
We report here an efficient catalytic system for the *N*-alkylation of primary and secondary amines with a variety of alcohols in water catalyzed by water-soluble Cp*Ir-ammine complex **3**. The operational convenience of this system is noteworthy because the reaction can be performed in water under air. In addition, the recycle use of the water-soluble Cp*Ir catalyst has also been demonstrated.

Results and Discussion

N-Alkylation of Aniline with Benzyl Alcohol in Water: Optimization of the Reaction Conditions

Initially, the reaction of aniline (**4a**) with benzyl alcohol (**5a**) was investigated as a model reaction. The reactions were performed in the presence of Cp*Ir complexes as catalysts in water under air. The results are summarized in Table 1. The reaction of **4a** with **5a** does not occur in the absence of catalyst (entry 1). When the reaction of equimolar amounts of **4a** with **5a** was carried out in the presence of water-insoluble $[Cp^*IrCl_2]_2$ (1.0 mol% Ir) and $NaHCO_3$ (1.0 mol%) in water under reflux for 4 h, only a trace amount of *N*-benzylaniline (**6a**) was formed (entry 2). The yield of **6a** was improved by the employment of water-soluble catalysts (entries 3–5), and the catalyst **3** having iodide as counteranion exhibited the highest performance, giving **6a** in 80% yield (entry 5).[13] The reaction proceeded smoothly using water as solvent without a base, and resulted in the selective formation of monoalkylated aniline **6a** besides a very small amount (4%) of an imine (*N*-benzylideneaniline). It should be noted that the reaction under air gave a similar result to that of the reaction under argon atmosphere (entry 6). The desired product could be obtained in good yield (86%) with a lower loading of the catalyst (0.50 mol%), although a longer reaction time (24 h) was required (entry 7). The reaction also proceeded at 80 °C (entry 8). An excellent yield (95%) of **6a** was obtained by the reaction for 6 h (entry 9), giving the optimal result. It should be noted that the present catalytic system produces the desired product **6a** in an excellent yield by employing theoretical equivalents of starting materials in water under air without additional base and harmful organic solvents.

Table 1. *N*-Alkylation of aniline (**4a**) with benzyl alcohol (**5a**) catalyzed by Cp*Ir complexes under various conditions.[a]



Entry	Catalyst	Temp.	Time [h]	Yield [%][b]
1	none	reflux	4	0
2[c]	$[Cp^*IrCl_2]_2$	reflux	4	trace
3	**1**	reflux	4	8
4	**2**	reflux	4	14
5	**3**	reflux	4	80
6[d]	**3**	reflux	4	79
7[e]	**3**	reflux	24	86
8	**3**	80 °C	4	51
9	**3**	reflux	6	95

[a] The reaction was carried out with **4a** (2.0 mmol), **5a** (2.0 mmol), and the catalyst (1.0 mol% Ir) in water (0.2 mL) under reflux.

[b] Determined by GC.

[c] $NaHCO_3$ (1.0 mol%) was added as a base. When the similar reaction catalyzed by $[Cp^*IrCl_2]_2/NaHCO_3$ was carried out in toluene, **6a** was obtained in 44% yield.

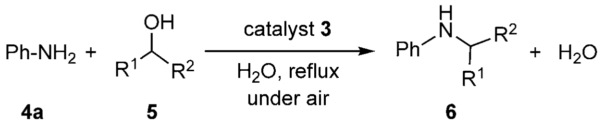
[d] Under an argon atmosphere.

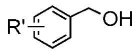
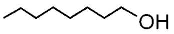
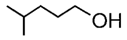
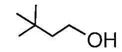
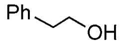
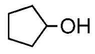
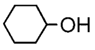
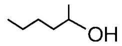
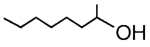
[e] Catalyst **3** (0.50 mol%) was used.

N-Alkylation of Aniline with Various Alcohols in Water under Air

We next explored the scope of the reaction. The results of the reaction of aniline (**4a**) with various alcohols are summarized in Table 2. The *N*-alkylation reactions of **4a** with benzyl alcohols bearing electron-donating and electron-withdrawing substituents at the aromatic ring proceeded smoothly to give the corresponding *N*-alkylated products in good to high yields (entries 1–9). Methoxy, chloro, bromo, trifluorometh-

Table 2. *N*-Alkylation of aniline (**4a**) with various primary and secondary alcohols affording secondary amines in water under air.[a]



Entry	Alcohol		Cat. 3 [mol%]	Time [h]	Yield [%][b]
					
1	R' = H	**5a**	1.0	6	92
2	R' = 2-OMe	**5b**	1.0	6	90
3	R' = 3-OMe	**5c**	1.0	6	92
4	R' = 4-OMe	**5d**	1.0	6	93
5	R' = 4-Cl	**5e**	1.0	6	92
6	R' = 4-Br	**5f**	1.0	6	90
7	R' = 4-CF$_3$	**5g**	1.0	14	83
8	R' = 4-NO$_2$	**5h**	3.0	14	88
9	R' = 4-CO$_2$Me	**5i**	1.0	14	93
10		**5j**	1.0	6	89
11		**5k**	1.0	6	89
12		**5l**	1.0	6	92
13		**5m**	3.0	14	94
14		**5n**	2.0	24	82
15		**5o**	1.0	6	93
16		**5p**	3.0	24	80
17		**5q**	3.0	24	81

[a] The reaction was carried out with **4a** (2.0 mmol), **5** (2.0 mmol), and the catalyst **3** (1.0–3.0 mol%) in water (0.2 mL) under reflux.

[b] Isolated yield.

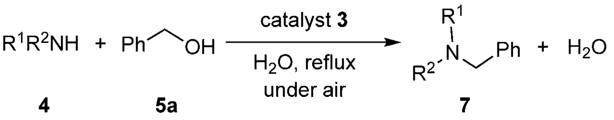
yl, nitro, and methoxycarbonyl substituents were tolerated in the present catalytic system (entries 2–9). The reaction with sterically demanding 2-methoxybenzyl alcohol (**5b**) gave the corresponding product in high yield (entry 2). Aliphatic primary and secondary alcohols could also be used as alkylating agents (entries 10–17). All of these reactions resulted in the selective formation of the monoalkylated aniline in good to high yields.

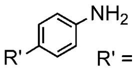
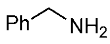
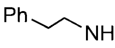
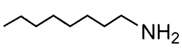
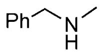
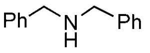
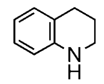
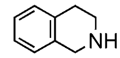
N-Alkylation of Various Amines with Benzyl Alcohol and Other Alcohols in Water under Air

To investigate the substrate scope regarding amines, reactions of several substituted anilines and other various primary and secondary amines with benzyl alcohol (**5a**) were conducted. As shown in Table 3, a variety of primary and secondary amines can be utilized for the present *N*-alkylation system, giving good results. Anilines bearing electron-donating and electron-withdrawing substituents at the aromatic ring and other aliphatic primary amines were successfully alkylated with benzyl alcohol (entries 1–9). It is noteworthy that halo-substituted anilines were well tolerated (entries 3 and 4), which can be used for further transformations. Furthermore, the *N*-alkylation of secondary amines with alcohols also proceeded to give tertiary amines in good to excellent yields, while a relatively longer reaction time was required (entries 10–13). Cyclic secondary amines such as 1,2,3,4-tetrahydroquinoline (**4m**) and 1,2,3,4-tetrahydroisoquinoline (**4n**) were also applicable in this catalytic system (entries 12 and 13).

The *N*-alkylation of aliphatic primary amines with aliphatic alcohols was also examined. The reaction of

Table 3. *N*-Alkylation of various primary and secondary amines with benzyl alcohol (**5a**) affording secondary and tertiary amines in water under air.[a]



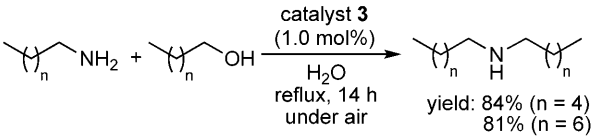
Entry	Amine			Cat. 3 [mol%]	Time [h]	Yield [%][b]
1		R' = OMe	**4b**	1.0	6	93
2		R' = Me	**4c**	1.0	6	80
3		R' = Cl	**4d**	1.0	6	89
4		R' = Br	**4e**	1.0	14	88
5		R' = CO$_2$Me	**4f**	2.0	24	77
6[c]		R' = CN	**4g**	3.0	24	74
7			**4h**	1.0	6	91
8			**4i**	1.0	24	86
9			**4j**	1.0	14	82
10			**4k**	1.0	6	83
11			**4l**	1.0	24	92
12			**4m**	2.0	24	91
13			**4n**	2.0	24	93

[a] The reaction was carried out with **4** (2.0 mmol), **5a** (2.0 mmol), and the catalyst **3** (1.0–3.0 mol%) in water (0.2 mL) under reflux.

[b] Isolated yield.

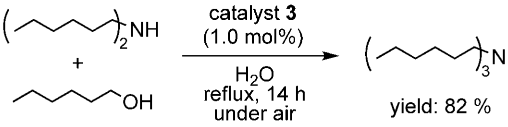
[c] The reaction was conducted using a sealed vessel at 110 °C for 24 h.

hexylamine with 1-hexanol in the presence of the catalyst **3** (1.0 mol%) for 14 h gave dihexylamine in 84% yield [Eq. (1)]. The reaction of octylamine with 1-octanol also gave dioctylamine in good yield.



(1)

Furthermore, the *N*-alkylation of an aliphatic secondary amine with a primary alcohol was successfully accomplished. The reaction of dihexylamine with 1-hexanol gave trihexylamine in 82% yield [Eq. (2)].



(2)

As shown above, the present catalytic system has a broad substrate scope: aromatic and aliphatic amines as well as primary and secondary amines could be alkylated in water under milder conditions using a variety of alcohols as alkylating agents. In addition, the reactions proceed sufficiently with the use of equimolar amounts of starting materials, providing a highly atom-economical method for the synthesis of amines.

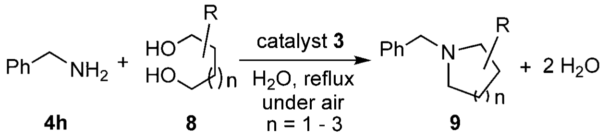
N-Alkylation of Benzylamine with Diols in Water under Air: Synthesis of Cyclic Amines

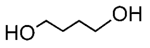
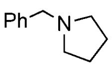
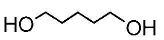
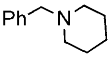
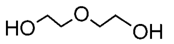
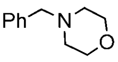
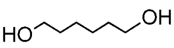
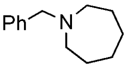
The development of efficient methods for the synthesis of N-heterocyclic compounds is very important because their skeletons are found in a variety of physiologically active molecules.[14] The present catalytic system was further applied to the synthesis of cyclic amines from benzylamine and diols, as shown in Table 4. The reactions of benzylamine (**4h**) with 1,4-butanediol (**8a**), 1,5-pentanediol (**8b**), and 1,6-hexanediol (**8d**) gave five-, six-, and seven-membered cyclic amines in good yields (entries 1, 2, and 4). The morpholine skeleton could be synthesized successfully by the use of diethylene glycol (**8c**) as a diol (entry 3). Thus, synthesis of various N-heterocyclic compounds was achieved from inexpensive and readily available starting materials along with water as a co-product.

Recycle Use of the Water-Soluble Cp*Ir Catalyst

Next, our attention turned to the recycle use of the catalyst in the present alkylation system. Use of water-soluble catalysts made it easy to separate the organic product from the catalyst **3**. The isolation of produced amine and the recovery of **3** were achieved by a simple phase separation (see the Experimental Section). The recovered catalyst **3** was then subjected to the second and third runs, as shown in Table 5. It should be noted that the recovered catalyst maintained its high activity at least until the third run.

Table 4. Synthesis of various N-heterocyclic compounds.[a]



Entry	Diol	Cat. 3 [mol%]	Product	Yield [%][b]
1	 **8a**	3.0	 **9a**	74
2	 **8b**	1.0	 **9b**	94
3	 **8c**	3.0	 **9c**	88
4	 **8d**	1.0	 **9d**	90

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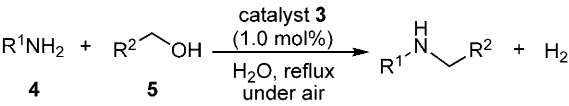
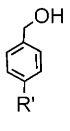
[a] The reaction was carried out with **4h** (2.0 mmol), **8** (2.0 mmol), and the catalyst **3** (1.0–3.0 mol%) in water (0.2 mL) under reflux for 24 h.

[b] Isolated yield.

Table 5. Recycle use of the catalyst **3** in the *N*-alkylation of primary amines with primary alcohols.[a]



Entry	Amine	Alcohol		Yield [%][b]	
			1st	2nd	3rd
1	$PhNH_2$ **4a**	 R' = H **5a**	98[c]	95[c]	90[c]
2	**4a**	R' = Me **5r**	94	89	86
3	**4a**	R' = OMe **5d**	96	92	88
4	$PhCH_2NH_2$ **4h**	R' = H **5a**	94	90	85

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[a] The reaction was carried out with **4** (2.0 mmol), **5** (2.2 mmol), and the catalyst **3** (1.0 mol%) in water (0.2 mL) under reflux for 6 h. After the reaction was completed, the recovered catalyst was subjected to the next run (see the Experimental Section).

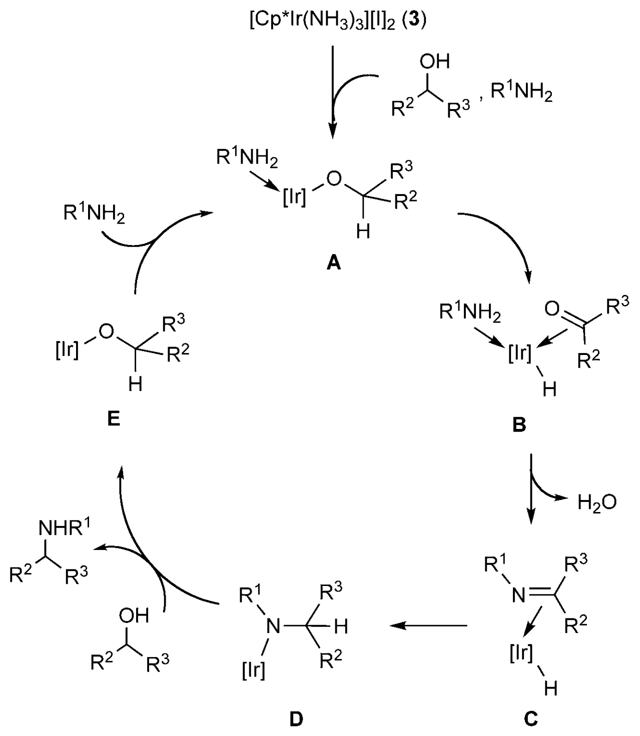
[b] Determined by ^1H NMR.

[c] Determined by GC.

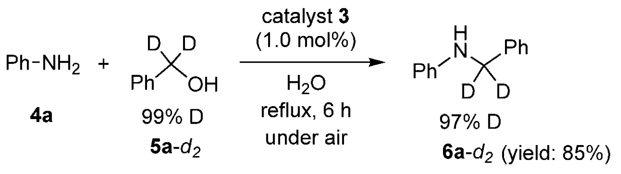
Mechanistic Consideration of the *N*-Alkylation of Amines with Alcohols Catalyzed by a Water-Soluble Cp*Ir Complex

In our previous papers, we have proposed a mechanism for the intra- and intermolecular *N*-alkylation of amines with alcohols catalyzed by the $[Cp^*IrCl_2]_2$/base system.[6] The present catalytic reactions would proceed through similar processes, which include three elementary steps (dehydrogenation, formation of imine, and transfer hydrogenation) as shown in Scheme 2. The initial step of the reaction would involve the formation of the alkoxo-iridium species **A** coordinated with an amine through the reaction of catalyst precursor **3** with an alcohol. Then, a hydrido-iridium species **B** coordinated with the amine and the aldehyde (or ketone) would be formed by β-hydrogen elimination of alkoxo moiety.[15] Condensation between the amine and the aldehyde (or ketone) in the coordination sphere of iridium would lead to the formation of an imine-coordinated iridium hydride **C** through elimination of water. Addition of the transient hydrido-iridium moiety to the C=N bond in **C** would occur to give an amido-iridium intermediate **D**. Amido-alkoxo exchange[16] accompanied by the release of the product would produce an alkoxo-iridium species **E**, from which **A** would be regenerated by the coordination of the amine.[17]

To obtain information concerning the reaction pathway, a labelling experiment was carried out. The reaction of **4a** with **5a**-d_2 (99% D) catalyzed by **3** (1.0 mol%) in water under reflux for 6 h gave an *N*-alkylated product **6a**-d_2 containing deuterium atoms at the benzylic position (97% D) in 85% yield [Eq. (3)], supporting the proposed mechanism.[18,19]

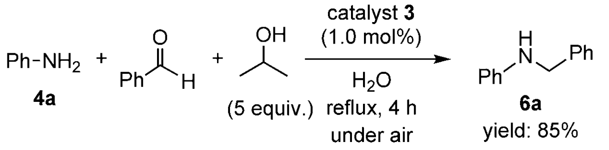


Scheme 2. A plausible mechanism.

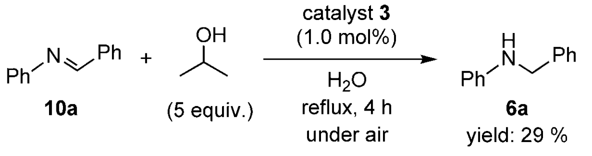


(3)

Furthermore, the reaction of an amine with an aldehyde in the presence of a hydrogen donor (2-propanol) under the catalytic conditions was conducted: the reaction of **4a** with benzaldehyde in the presence of 2-propanol (5 equiv.) catalyzed by **3** (1.0 mol%) in water under reflux for 4 h gave **6a** in 85% yield [Eq. (4)], strongly supporting the proposed mechanism based on hydrogen transfer. On the other hand, the reaction of the corresponding imine (*N*-benzylideneaniline) **10a** with 2-propanol catalyzed by **3** (1.0 mol%) in water under reflux for 4 h gave **6a** in a relatively low yield (29%) [Eq. (5)]. These results indicate that the transfer hydrogenation of an uncoordinated imine catalyzed by **3** could be slow, and the formation of an iminic intermediate would predominantly occur in the coordination sphere of iridium through the species **B** as shown in Scheme 2.



(4)



(5)

Conclusions

In summary, we have developed a practical and highly efficient catalytic system for the *N*-alkylation of amines with alcohols which can be performed in water under air. It has a broad substrate scope, and provides the desired product selectively in good to high yields. By means of the present catalytic system, various acyclic and cyclic amines have been synthesized under mild and harmless conditions without producing wastes.

Experimental Section

General Methods

^{1}H and ^{13}C NMR spectra were recorded on JEOL ECX-500, ECS-400 and EX-270 spectrometers. Gas chromatographic (GC) analyses were performed on a GL-Sciences GC353B gas chromatograph with a capillary column (GL-Sciences InertCap 5 and TC-17). Silica-gel column chromatography was carried out by using Wako-gel C-200. $[Cp^{*}IrCl_2]_2$[20] and $[Cp^{*}Ir(NH_3)_3][X]_2$ (**1**: X=Cl, **2**: X=Br, **3**: X=I)[11] were prepared according to the literature method. All other reagents are commercially available and were used as received.

General Procedure for the *N*-Alkylation of Aniline (4a) with Various Primary and Secondary Alcohols Affording Secondary Amines in Water under Air

In a round-bottom flask, catalyst **3** (1.0–3.0 mol%), aniline (**4a**) (2.0 mmol), alcohol (2.0 mmol), and water (0.2 mL) were placed under air. The mixture was heated under reflux in an oil bath for 6–24 h. The product was extracted with dichloromethane (30 mL). After evaporation of the solvent, the products were isolated by column chromatography on silica gel (eluent: ethyl acetate/hexane).

General Procedure for the *N*-Alkylation of Various Primary and Secondary Amines with Benzyl Alcohol (5a) Affording Secondary and Tertiary Amines in Water under Air

In a round-bottom flask, catalyst **3** (1.0–3.0 mol%), amine (2.0 mmol), benzyl alcohol (**5a**) (2.0 mmol), and water (0.2 mL) were placed under air. The mixture was heated under reflux in an oil bath for 6–24 h. The product was extracted with dichloromethane (30 mL). After evaporation of the solvent, the products were isolated by column chromatography on silica gel (eluent: ethyl acetate/hexane).

General Procedure for the Synthesis of Various N-Heterocyclic Compounds

In a round-bottom flask, catalyst **3** (1.0–3.0 mol%), benzylamine (**4h**) (2.0 mmol), diol (2.0 mmol), and water (0.2 mL) were placed under air. The mixture was heated under reflux in an oil bath for 24 h. The product was extracted with dichloromethane (30 mL). After evaporation of the solvent, the products were isolated by column chromatography on silica gel (eluent: ethyl acetate/hexane).

Procedure for the Recycle Use of Catalyst 3 in the *N*-Alkylation of Primary Amines with Primary Alcohols

In a round-bottom flask, catalyst **3** (1.0 mol%), amine (2.0 mmol), alcohol (2.2 mmol), and water (0.2 mL) were placed under air. The mixture was heated under reflux in an oil bath for 6 h. The product was extracted with dichloromethane (30 mL). The yield of product was calculated by the integration in ^{1}H NMR spectra measured in chloroform-*d* using 1,3,5-trimethoxybenzene as an internal standard. Then, the solvent was removed under reduced pressure. To the residue was added 28% aqueous ammonia (10 mL) and the mixture stirred for 30 min at room temperature. Dichloromethane (30 mL) was added again. 28% aqueous ammonia (10 mL) was then added to the aqueous phase again, and the mixture was stirred for 30 min at room temperature. After removal of the water under vacuum, the resultant yellow powder was collected and 20 mol% of ammonium iodide was added. This mixture was used as a catalyst for the next run.

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[13] We have previously reported the similar effect of counteranions (ref.[11]). The superiority of the catalyst **3** having iodide (I$^-$) as a counteranion among the catalysts **1**–**3** could be attributed to the differences of activities for the transfer hydrogenation of the iminic intermediate (see the plausible mechanism shown in Scheme 2). There have been many examples that iodide exhibits a positive effect in the transition metal-catalyzed hydrogenation of imines; a) F. Spindler, B. Pugin, H.-U. Blaser, *Angew. Chem.* **1990**, *102*, 561–562; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 558–559; b) Y. N. C. Chan, J. A. Osborn, *J. Am. Chem. Soc.* **1990**, *112*, 9400–9401; c) A. Togni, *Angew. Chem.* **1996**, *108*, 1581–1583; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1475–1477; d) D. Xiao, X. Zhang, *Angew. Chem.* **2001**, *113*, 3533–3536; *Angew. Chem. Int. Ed.* **2001**, *40*, 3425–3428; e) E. Guiu, B. Muñoz, S. Castillón, C. Claver, *Adv. Synth. Catal.* **2003**, *345*, 169–171.

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[19] The substoichiometric reaction of **3** with **4a** and **5a** was also investigated. After the reaction of **3** with **4a** and **5a** (**3**:**4a**:**5a** = 1:10:10) in water under reflux for 0.5 h had been conducted, chloroform-*d* was added to the reaction mixture, and the organic phase and the aqueous phase were separated. Analysis of the organic phase by ^{1}H NMR revealed the formation of the reaction intermediates; benzaldehyde (9%), *N*-benzylideneaniline (6%), and the product *N*-benzylaniline (8%) along with a hydrido-iridium complex ($\delta = -13.15$), supporting the proposed mechanism shown in Scheme 2.

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