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Dimethylamination of Primary Alcohols Using a Homogeneous Iridium Catalyst: A Synthetic Method for *N,N*-Dimethylamine Derivatives

Jaeyoung Jeong and Ken-ichi Fujita*

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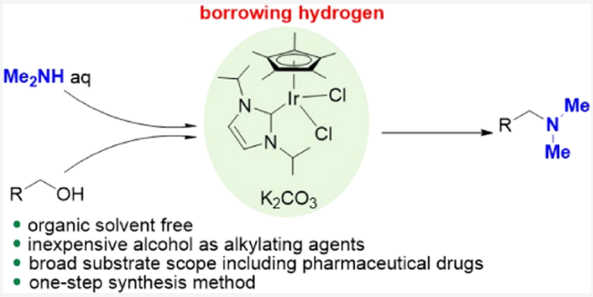
ABSTRACT: A new catalytic system for *N,N*-dimethylamination of primary alcohols using aqueous dimethylamine in the absence of additional organic solvents has been developed. The reaction proceeds via borrowing hydrogen processes, which are atom-efficient and environmentally benign. An iridium catalyst bearing an *N*-heterocyclic carbene (NHC) ligand exhibited high performance, without showing any deactivation under aqueous conditions. In addition, valuable *N,N*-dimethylamine derivatives, including biologically active and pharmaceutical molecules, were synthesized. The practical application of this methodology was demonstrated by a gram-scale reaction.



INTRODUCTION

N,N-Dimethylamine derivatives are a representative building block of bioactive compounds and natural products that are applied in various fields such as agrochemicals, materials, and pharmaceuticals (Figure 1).[1] Therefore, the synthesis of valuable *N,N*-dimethylamine compounds has attracted much attention.

The Eschweiler−Clarke reaction, which achieves *N*-methylation using amine and formaldehyde, has been established as a conventional synthetic method in the industry (Scheme 1, (1)).[2] Furthermore, nucleophilic substitution using methyl halide[3] or dimethyl sulfate[4] is well known (Scheme 1, (2)). However, these reactions have significant disadvantages as they

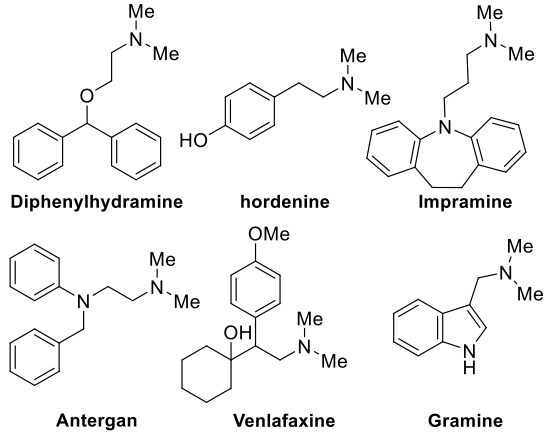
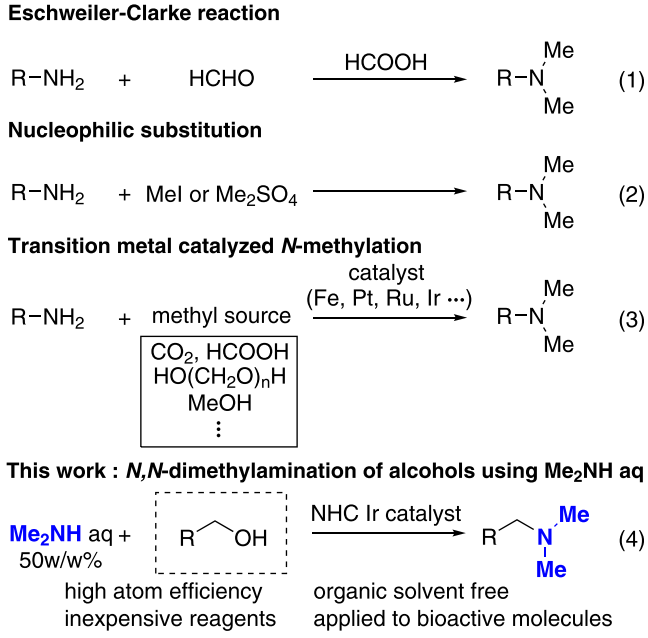


Figure 1. Representative drugs containing the *N,N*-dimethylamine moiety.

Scheme 1. Synthetic Method for *N,N*-Dimethylamine Compounds



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use toxic reagents, as well as because of producing a large amount of waste, in many cases, these reactions suffer from low selectivity.

To overcome these drawbacks, transition-metal-catalyzed *N*-methylation of amines utilizing methyl reagents[5] such as carbon dioxide,[6] paraformaldehyde,[7] or formic acid[8] has been successfully developed (Scheme 1, (3)). However, these reactions require a reductant, are performed under harsh conditions (high temperature and pressure), and have low selectivity. Thus, the construction of a C−N bond through a catalytic "borrowing hydrogen strategy," using amines and alcohols, has been regarded as a clean and atom-efficient method.[9] The overall reaction consists of several consecutive processes including dehydrogenation, imine formation, and transfer hydrogenation. The only generated byproduct, H_2O, is harmless. Based on this protocol, there have been many reports of catalytic *N*-methylation using methanol to obtain *N,N*-dimethylamine derivatives.[10] However, for dehydrogenation, compared to other alcohols, methanol demands that a higher activation energy barrier should be overcome. Furthermore, selectivity for *N,N*-dimethylation over *N*-methylation is poor. Moreover, amines used as raw materials are usually synthesized from nitrogen compounds such as ammonia, imines, and amides, which are relatively expensive substrates.[1g,11]

By contrast, *N,N*-dimethylamination utilizing alcohols, via borrowing hydrogen processes, is an efficient method to obtain dimethylamine derivatives (Scheme 1, (4)).[12] Alcohols are good alkylating reagents considering their low toxicity, price, and availability. Therefore, *N,N*-dimethylamination using alcohol and dimethylamine has the advantage of being more efficient than methylation of amines using methylation reagents. Nevertheless, there are few examples using dimethylamine for the synthesis of *N,N*-dimethylamine derivatives. Since dimethylamine is gaseous at room temperature, it is difficult to handle without special instrumentation. For this reason, only a few methods using a mixture of organic solvents or using dimethylammonium salts have been reported.[13]

In general, commercially available *N,N*-dimethylamine derivatives are more expensive than the corresponding alcohols with the same skeletons, although there are some exceptions. Thus, the development of a new method for dimethylamination of alcohols is important because it would provide a means of producing valuable compounds starting from inexpensive raw materials. Thus, such a method has the potential to become an important protocol in the field of synthetic organic chemistry. In addition, *N,N*-dimethylamine compounds can be simply synthesized using an aqueous dimethylamine solution. The reaction using methylating agents requires relatively costly amines and two cycles of methylation. Therefore, any synthetic method using aqueous dimethylamine is a simpler and more economically favorable process. However, in the absence of additional organic solvents, catalytic *N,N*-dimethylamination of alcohols using commercial aqueous dimethylamine via a borrowing hydrogen strategy has so far remained a challenge. In particular, in aqueous conditions, reactions using a metal catalyst are rare because of the ease of deactivation and low solubility.[14]

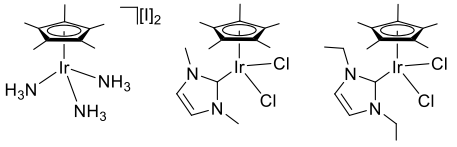
We have previously developed and reported *N*-alkylation using alcohols and a series of efficient catalysts.[15] In this study, we discovered that an iridium catalyst with an *N*-heterocyclic carbene (NHC) ligand exhibited good catalytic activity in the *N,N*-dimethylamination of alcohols using commercially available aqueous dimethylamine. Moreover, an environmentally benign synthetic method was developed based on organic-solvent-free reaction system. Based on this, we examined synthetic methods for obtaining valuable dimethylamine derivatives with important applications.

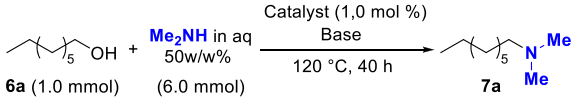
RESULTS AND DISCUSSION

To obtain dimethylamine derivatives, we examined efficient and environmentally benign iridium catalytic *N,N*-dimethylamination of a range of primary alcohols, using aqueous dimethylamine in the absence of additional organic solvents. First, optimization studies were carried out with aqueous dimethylamine and 1-octanol as a model reaction in the presence of an iridium catalyst (1.0 mol %) and K_2CO_3. All reactions were conducted in a sealed stainless tube, and the results are summarized in Table 1. First of all, catalysts previously demonstrated as effective for the *N*-alkylation of alcohols were investigated. When iridium catalysts without an NHC ligand—such as $[Cp^*IrCl_2]_2$, $[IrCl(cod)]_2$, and a water-soluble triammine catalyst **1**—were used, *N,N*-dimethyloctylamine was obtained with low yield under aqueous conditions (Table 1, entries 1−3).

However, in the presence of catalyst **2**, which has an NHC ligand with methyl substituents, catalytic activity slightly increased to give 35% yield (Table 1, entry 4). Therefore, we expected that an iridium catalyst including an NHC ligand would be effective for *N,N*-dimethylamination by aqueous

Table 1. Optimization of Conditions for *N,N*-Dimethylamination of 1-Octanol with Aqueous Dimethylamine[a]





entry	catalyst	base (mol %)	conv. (%)[b]	yield (%)[b]
1	$[Cp^*IrCl_2]_2$	K_2CO_3 (5)	18	13
2	$[IrCl(cod)]_2$	K_2CO_3 (5)	8	8
3	**1**	K_2CO_3 (5)	24	15
4	**2**	K_2CO_3 (5)	35	35
5	**3**	K_2CO_3 (5)	82	77
6	**4**	K_2CO_3 (5)	92	85
7	**5**	K_2CO_3 (5)	92	91
8	**5**	none	63	62
9	**5**	K_2CO_3 (2.5)	86	83
10	**5**	K_2CO_3 (10)	90	89

[a]Reaction was carried out with 1-octanol (1.0 mmol), dimethylamine (6.0 mmol), K_2CO_3 (0−10 mol %), and the catalyst (1.0 mol % Ir) at 120 °C for 40 h. [b]Determined by GC analysis using biphenyl as an internal standard.

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J. Org. Chem. 2021, 86, 4053−4060

dimethylamine. The yield was improved to 77% when catalyst **3**, bearing NHC ligands with ethyl groups was used (Table 1, entry 5). Among all of the catalysts examined, catalysts **4** and **5**, having NHC ligands with isopropyl substituents on nitrogen, demonstrated the highest activity, with the greatest conversion and yield percentages being achieved using these catalysts (Table 1, entries 6 and 7). In particular, NHC catalyst **5**, which has dichloride ligand, exhibited the best performance and resulted in a 91% (Table 1, entry 7). We also optimized the amount of a base (Table 1, entries 8−10). In the absence of a base, the yield was reduced to 62% (entry 8). When a 2.5 or 10 mol % amount of K_2CO_3 was added, the yield was increased (entries 9 and 10), but a 5 mol % amount of K_2CO_3 gave the best results. In addition to this, other bases, catalysts, temperatures, reaction times, and the dimethylamine amounts were explored (see the Supporting Information, Tables S1−S3). After identifying suitable conditions for the reaction, we investigated the substrate scope for this reaction.

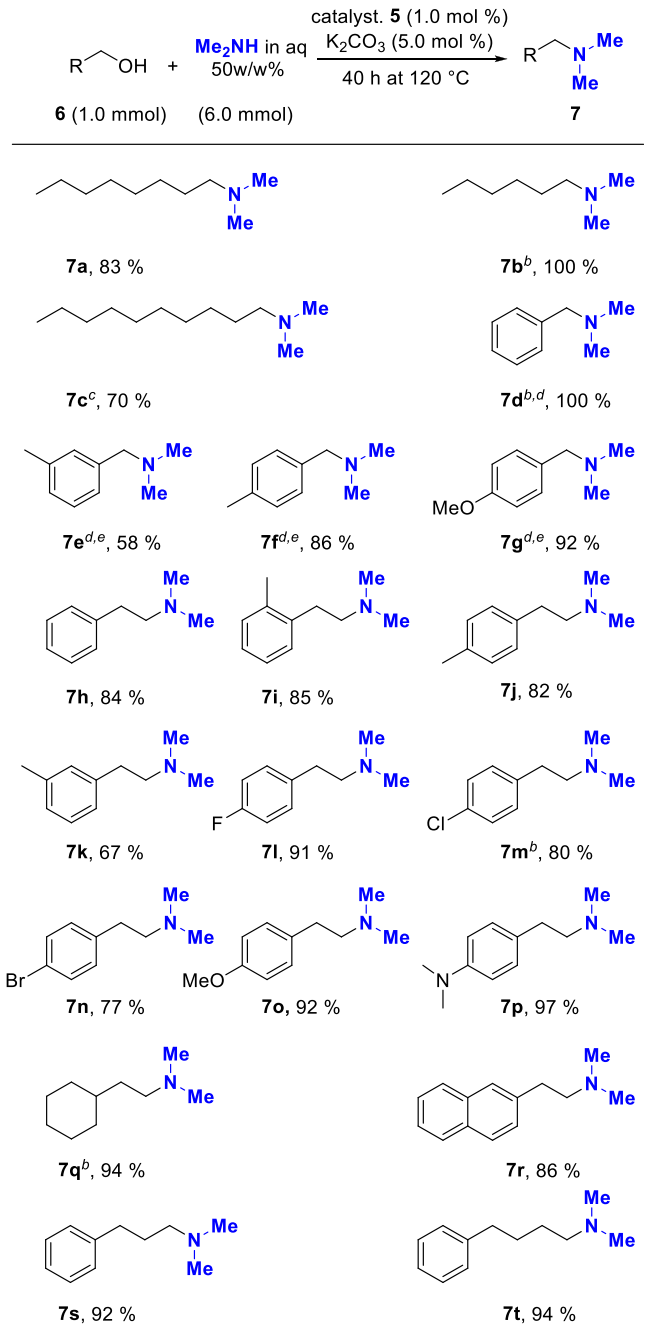
N,N-Dimethylamination with aqueous dimethylamine of various primary alcohols was conducted under the optimized conditions (5 mol % K_2CO_3, 1.0 mol % catalyst **5**, 120 °C, 40 h). The obtained dimethylamine derivatives are illustrated in Scheme 2. Good yields were obtained for these derivatives. Interestingly, trace amounts of monomethylamine byproducts were confirmed by nuclear magnetic resonance (NMR) spectroscopy in some cases. *N,N*-Dimethylamine derivatives having various alkyl chains, such as octyl, hexyl, and decyl, were observed in good yields (**7a**−**7c**). *N,N*-Dimethylbenzylamine products with methyl or methoxy aromatic substituents (**7d**−**7g**) were also obtained in good yields. In addition, we attempted to synthesize some of the expensive *N,N*-dimethylphenethylamines used in various fields, including as supplements and flavorings (**7h**−**7p**).[16] Phenethylalcohol gave the corresponding dimethylamine product with an isolated yield of 84% (**7h**). Although a *meta*-methyl substituent on phenethylalcohol resulted in the slightly reduced yield (**7k**), *ortho*- or *para*-methyl phenethylalcohols also produced *N,N*-dimethylaminated derivatives in good yields (**7i**, **7j**). Moreover, phenethylalcohol with an electron-withdrawing group such as a halogen and phenethylalcohol with an electron-donating methoxy or dimethylamino group afforded the desired products (**7l**−**7p**). Interestingly, saturated cyclic alcohol (2-cyclohexylethanol) and naphthalene ethanol were also tolerated as substrates (**7q** and **7r**). 3-Phenyl-1-propyl alcohol and 4-phenyl-1-butanol, having elongated carbon chains, resulted in excellent yields for their *N,N*-dimethylamino derivatives (**7s** and **7t**). Additionally, the reactions of cinnamyl alcohol and 3-phenyl-2-propyn-1-ol with dimethylamine were attempted. However, desired *N,N*-dimethylamino products were not detected at all.

We also conducted *N*-monomethylamination with aqueous methylamine and alcohols. Interestingly, *N*-monomethylamines were obtained. Benzyl alcohol and 1-octanol gave the corresponding *N*-monomethylamine products (Scheme 3, **8a** and **8b**).

To evaluate the practical utility of our reaction scheme, a gram-scale reaction with phenylbutyl alcohol (10 mmol) and aqueous dimethylamine was carried out. Catalyst **5** exhibited good performance and the product was obtained in an excellent isolated yield (Scheme 4). Finally, we attempted the synthesis of drugs, including a biologically active compound containing a dimethylamine moiety, using this methodology (Scheme 5). Hordenine,[17] a natural alkaloid, was obtained in the form of a precursor with an isolated yield of 75% (**7u**). Antergan[18] is an antihistamine possessing a dimethylamine moiety and this was prepared in good yield (77%) (**7v**).

To compare the reactivity between benzyl alcohol and long-chained aliphatic alcohol, a reaction using a 1:1 mixture of benzyl alcohol (0.5 mmol) and 1-octanol (0.5 mmol), aqueous dimethylamine (6.0 mmol), catalyst **5** (1.0 mol %), and K_2CO_3 (5.0 mol %) at 120 °C for 0.5 h was carried out. By this

Scheme 2. *N,N*-Dimethylamination of Various Primary Alcohols[a]



[a]Reaction was carried out with primary alcohol (1.0 mmol), dimethylamine (6.0 mmol), catalyst **5** (1.0 mol %), and K_2CO_3 (5.0 mol %) at 120 °C for 40 h. Isolated yields are shown. [b]Yield was determined by GC analysis. [c]Reaction was carried out at 130 °C. [d]Reaction was carried out for 20 h. [e]Catalyst **5** (0.5 mol %) was used. Isolated yields are shown.

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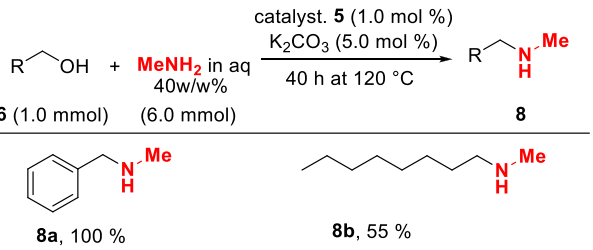
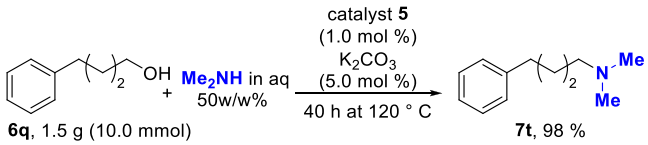
J. Org. Chem. 2021, 86, 4053−4060

Scheme 3. Investigation of *N*-Monomethylamination Using an Aqueous Methylamine Solution[a]



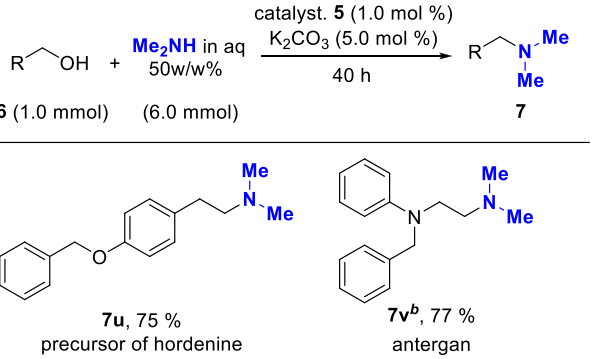
[a]Reaction was carried out with primary alcohol (1.0 mmol), methylamine (6.0 mmol), catalyst **5** (1.0 mol %), and K_2CO_3 (5.0 mol %) at 120 °C for 40 h. Yields were determined by GC analysis.

Scheme 4. Gram-Scale Reaction[a]



[a]Reaction was carried out with phenylbutyl alcohol (10.0 mmol), dimethylamine (60.0 mmol), catalyst **5** (1.0 mol %), and K_2CO_3 (5.0 mol %) at 120 °C for 40 h. Isolated yields are shown.

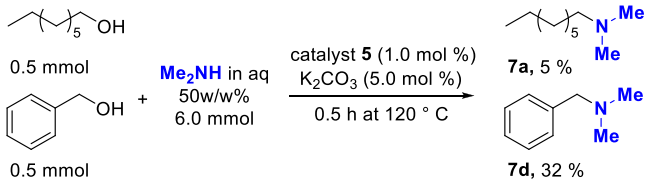
Scheme 5. Synthesis of Pharmaceutical Drugs via *N,N*-Dimethylation Using Aqueous Dimethylamine[a]



[a]Reaction was carried out with primary alcohol (1.0 mmol), dimethylamine (6.0 mmol), catalyst **5** (1.0 mol %), and K_2CO_3 (5.0 mol %) at 120 °C for 40 h. Isolated yields are shown. [b]Reaction was carried out at 130 °C.

competitive experiment, *N,N*-dimethylbenzylamine was obtained in a higher yield than *N,N*-dimethyloctylamine (Scheme 6).

Scheme 6. Competitive Experiment[a]

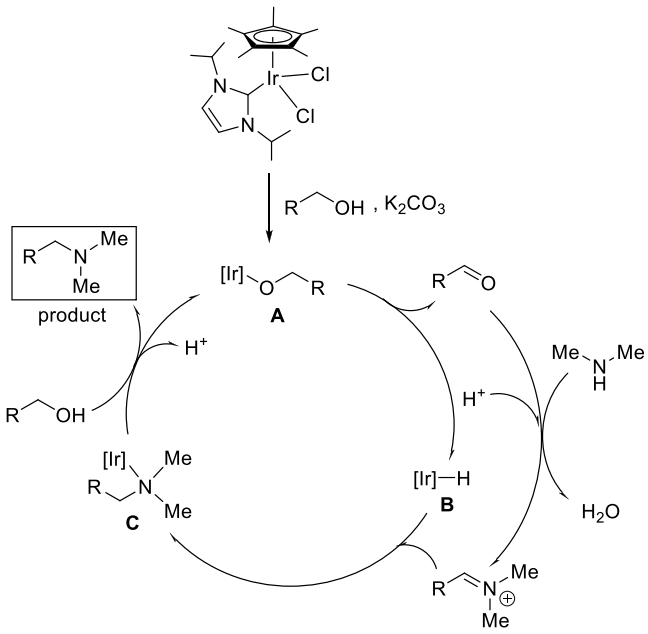


[a]Reaction was carried out with benzyl alcohol (0.5 mmol) and 1-octanol (0.5 mmol), aqueous dimethylamine (6.0 mmol), catalyst **5** (1.0 mol %), and K_2CO_3 (5.0 mol %) at 120 °C for 0.5 h. Yield was determined by GC analysis.

This result indicates that benzyl alcohol is more reactive than 1-octanol.

Based on a previously reported mechanism for *N,N*-dimethylamination using a secondary amine and alcohol,[15f,19] a plausible mechanism for the reactions investigated in this study is described in Scheme 7. Alkoxo-iridium species **A** is

Scheme 7. Possible Mechanism for the *N,N*-Dimethylamination of Primary Alcohols With Dimethylamine



formed by the reaction of alcohol and catalyst **5**. Then, an aldehyde and hydride-iridium species **B** is formed through *β*-hydrogen elimination. The aldehyde is transformed into an iminium ion by condensation with dimethylamine. Next, the iminium ion is coordinated to the metal in hydride-iridium species **B** and an amino complex **C** is formed. The product is released through the recovery of alkoxo-iridium species **A** and the catalytic cycle is completed.

CONCLUSIONS

In summary, we developed an efficient and environmentally benign method for the *N,N*-dimethylamination of various primary alcohols using aqueous dimethylamine, without any additional solvent, via borrowing hydrogen and hydrogen autotransfer processes. A dichloride iridium catalyst bearing an *N*-heterocyclic carbene ligand with isopropyl substitutes exhibited good performance under aqueous conditions. Valuable dimethylamine derivatives including a simple pharmaceutical drug were synthesized from relatively inexpensive primary alcohols and aqueous dimethylamine.

EXPERIMENTAL SECTION

General Information. All reactions were performed in a sealed stainless tube. ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on JEOL ECX-500 (500 MHz) and ECS-400 (400 MHz) spectrometers. Gas chromatography (GC) analyses were performed on a GC-4000Plus with a capillary column (InertCap for Amines and InertCap Pure WAX). The complexes **1**,[15c] **2**,[20] **3**,[21] **4**,[15e] **5**,[10h] and $[Cp^*IrCl_2]_2$[22] were prepared according to the literature method. 2-(4-Benzyloxyphenyl) ethanol[23] and *N*-benzyl-2-anilinoethanol[24] were prepared

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J. Org. Chem. 2021, 86, 4053−4060

according to the literature method. An aqueous dimethylamine solution (50%) and an aqueous methylamine solution (40%) are commercially available and were used as received. Flash column chromatography was carried out using a Wako-gel C-200. All other reagents are commercially available and were used as received from Tokyo Chemical Industry, Sigma-Aldrich, Acros Organics, BLD Pharm, FUJIFILM Wako Pure Chemical Corporation, and Oakwood Chemical.

Procedure for Optimization Under the Various Conditions Shown in Table 1. In a stainless tube, the catalyst (1.0 mol %), K_2CO_3 (0−10 mol %), 1-octanol (1.0 mmol), and a 50% aqueous solution of dimethylamine (0.66 mL, 6.0 mmol) were added and sealed. The mixture was stirred for 40 h at 120 °C using an aluminum block heater. On completion of the reaction, it was cooled to room temperature. The product was extracted with tetrahydrofuran (THF) (50 mL). The conversion of 1-octanol and the yield of *N,N*-dimethyloctylamine (**7a**) were determined by GC analysis using biphenyl as an internal standard.

***N,N*-Dimethylamination of Various Primary Alcohols with Aqueous Dimethylamine Catalyzed by 5 Given Dimethylamine Derivatives Shown in Scheme 2.** In a stainless tube, the iridium catalyst **5** (0.5−1.0 mol %), K_2CO_3 (5 mol %), primary alcohol (1.0 mmol), and a 50% aqueous solution of dimethylamine (0.66 mL, 6.0 mmol) were added and sealed. The mixture was stirred for 20−40 h at 120−130 °C using an aluminum block heater. On completion of the reaction, it was cooled to room temperature. The product was extracted with dichloromethane. After evaporation of the solution, the product was isolated by silica gel chromatography. Quantitative analysis of **7b** and **7d** were carried out by GC using biphenyl as an internal standard. Identification of **7b** and **7d** was done by comparison of retention time with commercially available standards.

*N,N-Dimethyloctylamine (Scheme 2, **7a**).*[10h] The product was isolated by silica gel chromatography eluting with $CHCl_3/Et_3N$ (50:1) to give **7a** as a pale yellow oil, 130.0 mg (0.826 mmol, 83%). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 2.20−2.09 (m, 8H), 1.43−1.37 (m, 2H), 1.28−1.10 (m, 10H), 0.84−0.81 (t, 3H, J = 7.0 Hz). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 60.1, 45.6, 31.9, 29.7, 29.4, 27.9, 27.6, 22.8, 14.2.

*N,N-Dimethyldecylamine (Scheme 2, **7c**).*[25] The product was isolated by silica gel chromatography eluting with $CHCl_3/Et_3N$ (50:1) to give **7c** as a pale yellow oil, 129.2 mg (0.699 mmol, 70%). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 2.27−2.17 (m, 8H), 1.45−1.42 (m, 2H), 1.31−1.18 (m, 14H), 0.87 (t, 3H, J = 6.9 Hz) $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 60.2, 45.7, 32.1, 29.79, 29.77, 29.75, 29.5, 28.0, 27.7, 22.8, 14.3.

*N,N-Dimethyl(3-methylphenyl)methanamine (Scheme 2, **7e**).*[10h] The product was isolated by silica gel chromatography eluting with an organic solvent (EtOAc/hexane/Et_3N = 1:50:1 to $CHCl_3/Et_3N$ = 30:1) to give **7e** as a pale yellow oil, 87.0 mg (0.583 mmol, 58%). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.21 (t, 1H, J = 8.0 Hz), 7.14 (s, 1H), 7.08 (t, 2H, J = 7.5 Hz), 3.38 (s, 2H). 2.35 (s, 3H), 2.24 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 138.9, 138.0, 129.9, 128.2, 127.9, 126.3, 64.6, 45.6, 21.5.

*N,N-Dimethyl(4-methylphenyl)methanamine (Scheme 2, **7f**).*[10h] The product was isolated by silica gel chromatography eluting with $CHCl_3/Et_3N$ = 30:1 to give **7f** as a pale yellow oil, 128.4 mg (0.860 mmol, 86%). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.19 (d, 2H, J = 7.5 Hz), 7.13 (d, 2H, J = 8 Hz), 3.38 (s, 2H), 2.34 (s, 3H), 2.23 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 136.7, 135.9, 129.2, 129.0, 64.2, 45.4, 21.2.

*N,N-Dimethyl(4-methoxylphenyl)methanamine (Scheme 2, **7g**).*[10h] The product was isolated by silica gel chromatography eluting with an organic solvent (EtOAc/hexane = 1:50 to $CHCl_3/Et_3N$ = 50:1) to give **7g** as a pale yellow oil, 150.2 mg (0.919 mmol, 92%). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.21 (d, 2H, J = 9 Hz), 6.85 (d, 2H, J = 9 Hz), 3.80 (s, 3H), 3.35 (s, 2H), 2.22 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 158.8, 131.1, 130.4, 113.7, 63.9, 55.4, 45.3.

*N,N-Dimethylphenethylamine (Scheme 2, **7h**).*[13b] The product was isolated by silica gel chromatography eluting with $CHCl_3/Et_3N$ (50:1) to give **7h** as a pale yellow oil, 126.1 mg (0.844 mmol, 84%). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.31−7.28 (m, 2H), 7.23−7.19 (m, 3H), 2.81−2.78 (m, 2H), 2.56−2.53 (m, 2H), 2.31 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 140.4, 128.6, 128.4, 126.0, 61.6, 45.5, 34.5.

*2-(2-Methylphenyl)-N,N-dimethylethanamine (Scheme 2, **7i**).* The product was isolated by silica gel chromatography eluting with $CHCl_3/Et_3N$ (50:1) to give **7i** as a pale yellow oil, 137.9 mg (0.847 mmol, 85%). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.20−7.10 (m, 4H), 2.81−2.77 (m, 2H), 2.49−2.46 (m, 2H), 2,34 (s, 3H), 2.33(s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 138.6, 136.1, 130.3, 129.3, 126.3, 126.1, 60.4, 45.6, 31.8, 19.4. Anal. calcd for $C_{11}H_{17}N$: C, 80.92; N, 8.58; H, 10.50. Found: C, 80.74; N, 8.49; H, 10.67.

*2-(4-Methylphenyl)-N,N-dimethylethanamine (Scheme 2, **7j**).*[26] The product was isolated by silica gel chromatography eluting with $CHCl_3/Et_3N$ (50:1) to give **7j** as a pale yellow oil, 132.9 mg (0.814 mmol, 82%). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.15−7.08 (m, 4H), 2.77−2.73 (m, 2H), 2.53−2.50 (m, 2H), 2.32 (s, 3H), 2.30 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 137.4, 135.5, 129.2, 128.6, 61.9, 45.6, 34.1, 21.1.

*2-(3-Methylphenyl)-N,N-dimethylethanamine (Scheme 2, **7k**).* The product was isolated by silica gel chromatography eluting with $CHCl_3/Et_3N$ (50:1) to give **7k** as a pale yellow oil, 109.7 mg (0.672 mmol, 67%). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.21−7.17 (m, 1H), 7.02−7.01 (m, 3H), 2.77−2.73 (m, 2H), 2.54−2.51 (m, 2H), 2.33 (s, 3H), 2.30 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 140.4, 138.1, 129.6, 128.4, 126.9, 125.8, 61.8, 45.6, 34.4, 21.5. Anal. calcd for $C_{11}H_{17}N$: C, 80.92; N, 8.58; H, 10.50. Found: C, 80.68; N, 8.34; H, 10.71.

*2-(4-Fluorophenyl)-N,N-dimethylethanamine (Scheme 2, **7l**).*[27] The product was isolated by silica gel chromatography eluting with $CHCl_3/Et_2NH$ (50:1) to give **7l** as a pale yellow oil, 151.8 mg (0.908 mmol, 91%). ^1H NMR (500 MHz, $CDCl_3$, r.t.) 7.16−7.13 (m, 2H), 6.99−6.94 (m, 2H), 2.76−2.73 (m, 2H), 2.51−2.48 (m, 2H), 2.28 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 161.5 (d, J = 244.1 Hz), 136.1 (d, J = 2.4 Hz), 130.1 (d, J = 7.1 Hz), 115.3 (d, J = 20.4 Hz), 61.7, 45.6, 33.7.

*2-(4-Chlorophenyl)-N,N-dimethylethanamine (Scheme 2, **7m**).* The product was isolated by silica gel chromatography eluting with $CHCl_3/Et_2NH$ (50:1) to give **7m** as a pale yellow oil, 147.8 mg (0.805 mmol, 80%). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.23 (d, 2H, J = 8.6 Hz), 7.12 (d, 2H, J = 8.3 Hz), 2.75−2.72 (m, 2H), 2.51−2.47 (m, 2H), 2.27 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 138.9, 131.8, 130.1, 128.6, 61.4, 45.6, 33.8. Anal. calcd for $C_{10}H_{14}NCl$: C, 65.29; N, 7.63; H, 7.68. Found: C, 64.99; N, 7.50; H, 7.66.

*2-(4-Bromophenyl)-N,N-dimethylethanamine (Scheme 2, **7n**).*[28] The product was isolated by silica gel chromatography eluting with $CHCl_3/Et_2NH$ (50:1) to give **7n** as a pale yellow oil, 176.4 mg (0.773 mmol, 77%). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.39 (d, 2H, J = 8.5 Hz), 7.07 (d, 2H, J = 8.5 Hz), 2.74−2.71 (m, 2H), 2.51−2.48 (m, 2H), 2.28 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 139.5, 131.5, 130.5, 119.9, 61.4, 45.6, 33.9.

*2-(4-Methoxyphenyl)-N,N-dimethylethanamine (Scheme 2, **7o**).*[29] The product was isolated by silica gel chromatography eluting with $CHCl_3/Et_3N$ (100:1) to give **7o** as a pale yellow oil, 164.1 mg (0.915 mmol, 92%). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.2 (d, 2H, J = 8.5 Hz), 6.82 (d, 2H, J = 8.5 Hz), 3.78 (s, 3H) 2.74−2.70 (m, 2H), 2.51−2.47 (m, 2H), 2.29 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 158.0, 132.6, 129.6, 113.9, 62.0, 55.4, 45.6, 33.6.

*2-(4-Dimethylaminophenyl)-N,N-dimethylethanamine (Scheme 2, **7p**).* The product was isolated by silica gel chromatography eluting with $CHCl_3/Et_3N$ (100:3) to give **7p** as a pale yellow oil, 185.8 mg (0.966 mmol, 97%). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.08 (d, 2H, J = 8.5 Hz), 6.70 (d, 2H, J = 8.5 Hz), 2.91 (s, 6H), 2.71−2.68 (m, 2H), 2.51−2.47 (m, 2H), 2.29 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 149.3, 129.3, 128.6, 62.1, 45.6, 41.0, 33.5. Anal. calcd for $C_{12}H_{20}N_2$: C, 74.95; N, 14.57; H, 10.48. Found: C, 74.74; N, 14.35; H, 10.59.

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J. Org. Chem. 2021, 86, 4053−4060

*2-Cyclohexyl-N,N-dimethylethanamine (Scheme 2, **7q**).*[30] The product was isolated by silica gel chromatography eluting with $CHCl_3/Et_2NH$ (100:1) to give **7q** as a pale yellow oil, 145.9 mg (0.940 mmol, 94%). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 2.25−2.22 (m, 2H), 2.15 (s, 6H), 1.70−0.87 (m, 13H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 57.8, 45.7, 36.1, 35.6, 33.6, 26.8, 26.4.

*N,N-Dimethyl-2-Naphthaleneethanamine (Scheme 2, **7r**).* The product was isolated by silica gel chromatography eluting with $CHCl_3/Et_2NH$ (50:1) to give **7r** as a pale yellow oil, 171.2 mg (0.859 mmol, 86%). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.82−7.78 (m, 3H), 7.66 (s, 1H), 7.48−7.35 (m, 3H), 2.98−2.92 (m, 2H), 2.65−2.62 (m, 2H), 2.34 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 138.1, 133.7, 132.2, 128.0, 127.7, 127.53 (two peaks may be overlapped), 126.9, 126.0, 125.3, 61.6, 45.7, 34.7. Anal. calcd for $C_{14}H_{17}N$: C, 84.37; N, 7.03; H, 8.60. Found: C, 84.22; N, 6.88; H, 8.80.

*N,N-Dimethyl-3-phenylpropan-1-amine (Scheme 2, **7s**).*[13e] The product was isolated by silica gel chromatography eluting with $CHCl_3/Et_3N$ (50:1) to give **7s** as a pale yellow oil, 150.2 mg (0.920 mmol, 92%). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.3−7.26 (m, 2H), 7.21−7.17 (m, 3H), 2.64 (t, 2H, J = 7.9 Hz), 2.30 (t, 6H, J = 7.4 Hz), 2.23 (s, 6H), 1.80 (q, 2H, J = 7.5 Hz). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 142.4, 128.5, 128.4, 125.8, 59.4, 45.6, 33.8, 29.6.

*N,N-Dimethyl-3-phenylbutan-1-amine (Scheme 2, **7t**).*[31] The product was isolated by silica gel chromatography eluting with $CHCl_3/Et_3N$ (50:1) to give **7t** as a pale yellow oil, 167.7 mg (0.946 mmol, 94%). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.30−7.26 (m, 2H), 7.19−7.16 (m, 3H), 2.63 (t, 2H, J = 7.7 Hz), 2.27 (t, 2H, J = 7.6 Hz), 2.21 (s, 6H), 1.68−1.62 (m, 2H), 1.54−1.48 (m, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 142.6, 128.5, 128.3, 125.7, 59.8, 45.7, 36.0, 29.4, 27.6.

Investigation of *N*-Monomethylamination Using an Aqueous Methylamine Solution (Scheme 3). In a stainless tube, the iridium catalyst **5** (1.0 mol %), K_2CO_3 (5 mol %), primary alcohol (1.0 mmol), and a 40% aqueous solution of methylamine (0.50 mL, 6.0 mmol) were added and sealed. The mixture was stirred for 40 h at 120 °C using an aluminum block heater. On completion of the reaction, it was cooled to room temperature. The product yield was determined by GC analysis using biphenyl as an internal standard.

Gram-Scale Reaction to Synthesize *N,N*-Dimethyl-3-phenylbutan-1-amine (Scheme 4). In a stainless tube, the iridium catalyst **5** (55.1 mg (1.0 mol %)), K_2CO_3 (69.2 mg (5 mol %)), 4-phenyl-1-butanol (1501.1 mg (10.0 mmol)), and a 50% aqueous solution of dimethylamine (5403.7 mg (6.60 mL, 60.0 mmol)) were added and sealed. The mixture was stirred for 40 h at 120 °C using an aluminum block heater. On completion of the reaction, it was cooled to room temperature. The product was extracted with dichloromethane. After evaporation of the solution, the product was isolated by silica gel chromatography eluting with $CHCl_3/Et_3N$ (50:1) to give **7t** as a pale yellow oil, 1742.9 mg (9.83 mmol, 98%). ^1H NMR (400 MHz, $CDCl_3$, r.t.) δ 7.30−7.25 (m, 2H), 7.19−7.15 (m, 3H), 2.63 (t, 2H, J = 7.2 Hz), 2.27 (t, 2H, J = 7.2 Hz), 2.20 (s, 6H), 1.70−1.60 (m, 2H), 1.54−1.47 (m, 2H). $^{13}C\{^1H\}$ NMR (100.5 MHz, $CDCl_3$, r.t.) δ 142.7, 128.5, 128.4, 125.8, 59.9, 45.7, 36.0, 29.4, 27.6.

2-(4-Benzyloxyphenyl)-*N,N*-dimethylethanamine (Scheme 5, 7u). In a stainless tube, the iridium catalyst **5** (5.5 mg (1.0 mol %)), K_2CO_3 (7.1 mg (5 mol %)), 2-(4-benzyloxyphenyl) ethanol (227.8 mg (1.0 mmol)), and a 50% aqueous solution of dimethylamine (543.6 mg (0.66 mL, 6.0 mmol)) were added and sealed. The mixture was stirred for 40 h at 120 °C using an aluminum block heater. On completion of the reaction, it was cooled to room temperature. The product was extracted with dichloromethane. After evaporation of the solution, the product was isolated by silica gel chromatography eluting with $CHCl_3/Et_3N$ (100:1) to give **7u** as a pale yellow oil, 190.3 mg (0.745 mmol, 75%). ^1H NMR (400 MHz, $CDCl_3$, r.t.) δ 7.44−7.30 (m, 5H), 7.13 (d, 2H, J = 10.5 Hz), 6.91 (d, 2H, J = 10.5 Hz), 5.04 (s, 2H), 2.75−2.71 (m, 2H), 2.52−2.48 (m, 2H), 2.29 (s, 6H). $^{13}C\{^1H\}$ NMR (100.5 MHz, $CDCl_3$, r.t.) δ 157.3, 137.3, 132.9, 129.7, 128.7, 128.0, 127.6, 114.9, 70.2, 62.0, 45.6, 33.7. Anal. calcd for $C_{17}H_{21}NO$: C, 79.96; N, 5.49; H, 8.29. Found: C, 79.77; N, 5.44; H, 8.33.

Antergan (Scheme 5, 7v).[13e] In a stainless tube, the iridium catalyst **5** (5.6 mg (1.0 mol %)), K_2CO_3 (7.1 mg (5 mol %)), *N*-benzyl-2-anilinoethanol (227.9 mg (1.0 mmol)), and a 50% aqueous solution of dimethylamine (537.4 mg (0.66 mL, 6.0 mmol)) were added and sealed. The mixture was stirred for 40 h at 130 °C using an aluminum block heater. On completion of the reaction, it was cooled to room temperature. The product was extracted with dichloromethane. After evaporation of the solution, the product was isolated by silica gel chromatography eluting with $CHCl_3/Et_3N$ (50:1) to give **7v** as a pale yellow oil, 195.2 mg (0.767 mmol, 77%). ^1H NMR (400.0 MHz, $CDCl_3$, r.t.) δ 7.31−7.29 (m, 2H), 7.25−7.16 (m, 5H), 6.71−6.66 (m, 3H), 4.57 (s, 2H), 3.55 (t, 2H, J = 7.6 Hz), 2.55 (t, 2H, J = 8.0 Hz), 2.28 (s, 6H). $^{13}C\{^1H\}$ NMR (100.5 MHz, $CDCl_3$, r.t.) δ 148.5, 139.0, 129.4, 128.7, 126.9, 126.7, 116.4, 112.2, 56.5, 54.9, 49.7, 46.1.

Competitive Experiment (Scheme 6). In a stainless tube, the iridium catalyst **5** (1.0 mol %), K_2CO_3 (5 mol %), benzyl alcohol (0.5 mmol), 1-octanol, and a 50% aqueous solution of dimethylamine (6.0 mmol) were added and sealed. The mixture was stirred for 0.5 h at 120 °C using an aluminum block heater. On completion of the reaction, it was cooled to room temperature. The product yield was determined by GC analysis using biphenyl as an internal standard.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02896.

Investigation of additional conditions such as catalysts, bases, temperature, reaction times, and the amount of the aqueous dimethylamine solution and copies of ^1H and $^{13}C\{^1H\}$ NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Ken-ichi Fujita − *Graduate School of Human and Environmental Studies, Kyoto University, Kyoto 606-8501, Japan;* orcid.org/0000-0002-8362-2694; Email: fujita.kenichi.6a@kyoto-u.ac.jp

Author

Jaeyoung Jeong − *Graduate School of Human and Environmental Studies, Kyoto University, Kyoto 606-8501, Japan*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c02896

Notes

The authors declare no competing financial interest.

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