Catalytic Organic Molecular Transformations Involving Iridium-Mediated Hydride Transfer as a Key Step: An Application for Dehydrogenation and Borrowing Hydrogen Reaction

Jaeyoung Jeong

Acknowledgement

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The Lord is my strength and my shield; my heart trusts in him, and he helps me. My heart leaps for joy, and with my song I praise him (Psalm 28:7 in Bible). First of all, the author is grateful to The Almighty God for protecting my health, family and saving all my life during studying abroad.

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Jaeyoung Jeong

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Chapter 1

General Introduction

1.1. Introduction

Sustainable Development Goals (SDGs)[1] are aims to achieve a better world for people and the planet. The United Nations (UN) announced the SDGs, at the 70th General Assembly in 2015, due to the global concerns over achieving sustainable economic development in the future and solving universal social problems. The development of technology has made human beings more comfortable and improved quality of life. However, many problems such as food shortages, resource depletion, and environmental pollution remain. Solutions have been suggested for these problems with the SDGs proposing specific plans to tackle these issues faced by modern society and how to achieve them. The SDGs are divided into five areas: people, planet, prosperity, peace, and partnership. It consists of 17 detailed goals to be achieved by 2030 (Figure 1).[2]

Figure 1. The 17 goals for sustainable development.

Goal 6, 7, 12, 13, 14, and 15 are closely related to environmental issues illustrating why sustainable development needs to consider the environment. Chemistry has a tremendous impact on industry and how future developments will affect the environment. It is the study

of the structure, properties, and interaction of the elements and compounds that make up matter. A wide variety of chemical products have been developed to make human life more comfortable and affluent, with modern society evolving along with the chemicals industry. The development of appropriate synthetic methods to supply chemical raw materials are of great importance in academia and industry. Classical synthetic methods designed reactions to obtain the desired product in high yields. These reaction process have environmental problems due to the large amount of waste generated and resource depletion due to dependence on fossil resources. Modern chemistry aims to achieve the SDGs by solving problems faced by conventional synthetic methods. The concept of green chemistry is making a significant contribution to the achievement of these SDGs to reduce the environmental impact of all chemical processes. The 12 principles of green chemistry were described by Paul T. Anastas and John C. Warner in 1998 (Figure 2).[3]

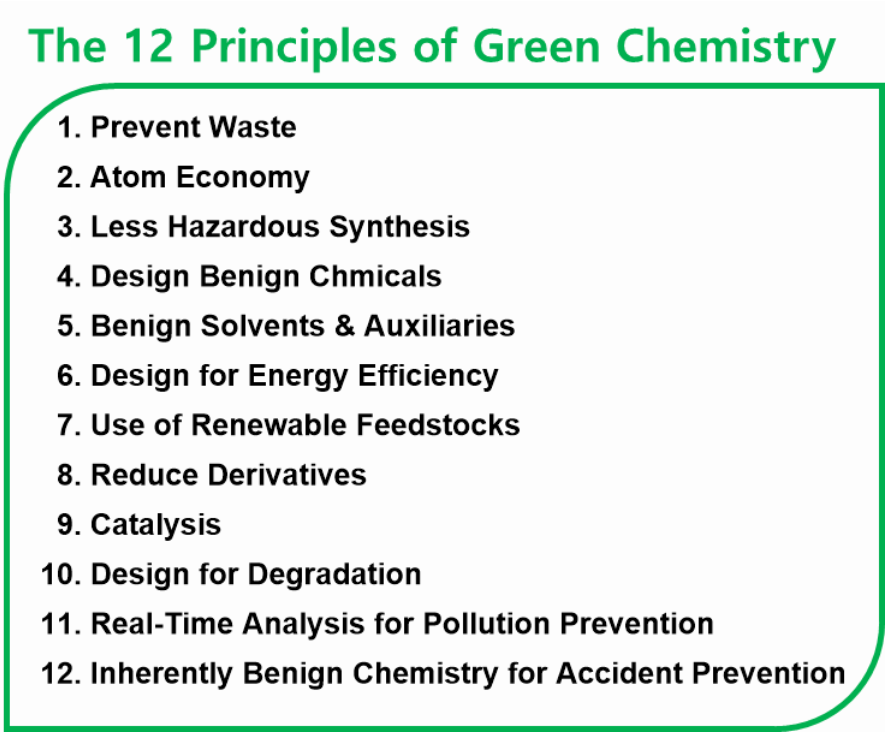


Figure 2. The 12 principles of green chemistry by Paul T. Anastas and John C. Warner.

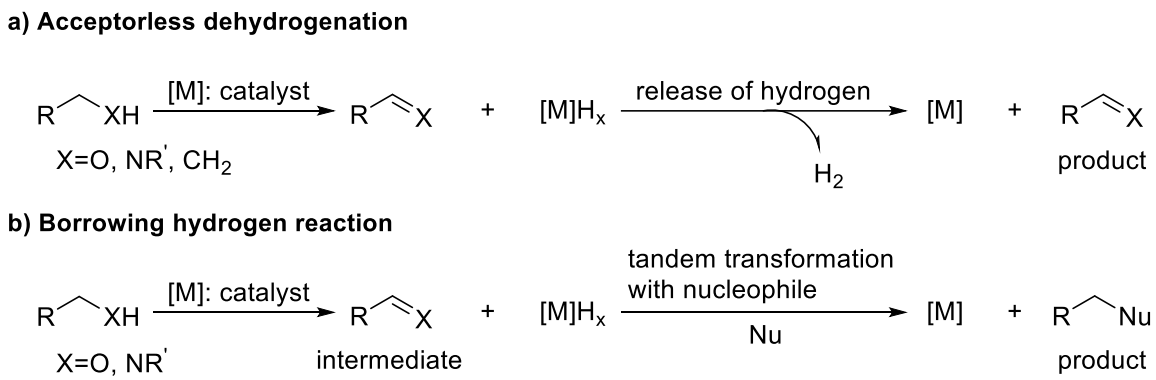
To meet these requirements various synthetic methods have been developed for environmentally friendly and effective molecular transformation. Catalytic organic reactions

using transition metal complex enable selective and efficient molecular transformations by appropriate selection of starting materials and design of reaction pathways. This has led to many catalytic reactions being developed to solve the problems of conventional synthetic methods; the use of toxic reagents, low selectivity, and waste. In this thesis, the author investigates catalytic organic molecular transformation involving transition-metal mediated hydride transfer. Hydride is a hydrogen atom with a negative formal charge and often exists in the form of metal hydride bound to metals. They are utilized in many organic synthetic reactions due to their high reactivity characteristics. Reducing agents such as LiH, (*i*-$Bu_2AlH)_2$, and $LiAlH_4$ are some of the typically known forms of alkali-metal hydride.[4] These possess high chemical reactivity and are especially useful for effective molecular transformations in a chemical structure. Using alkali-metal hydrides as reducing agents in synthetic method involving direct hydride transfer has raised concerns in green chemistry due to their low atom efficiency, low selectivity, low safety factor, and adverse environmental issues due to waste production.[5] Molecular transformation reactions involving the hydride transfer utilizing metal-hydride species generated by catalytic processes have been developed instead of using alkali-metal hydrides directly.[5a,6] These catalytic reactions involve metal-hydride species as an active intermediate using transition metal-based catalysts. Hydride transfer is the process of transferring a hydrogen atom from one molecule to another in the form of hydride in a chemical reaction.[7] During the reaction, the hydrogen atom is bonded to the transition metal to form a transition metal-hydride species that enables efficient hydride transfer. Metal-mediated hydride transfer is a key step in many organic synthesis reactions leading to researchers utilizing it to achieve efficient molecular transformations.[8] Most attention has been given to catalytic dehydrogenation and borrowing hydrogen reaction, involving metal-mediated hydride transfer.

Catalytic alcohol activation has been utilized for molecular transformations including dehydrogenation and borrowing hydrogen reactions.[9] One of the most atom economic reactions is catalytic acceptorless alcohol dehydrogenation. This simultaneously produces carbonyl compounds and hydrogen gas without oxidant or hydrogen acceptor (Scheme 1a).[10] Metal-mediated hydride transfer allows dehydrogenation of alcohols with relative thermodynamic stability (Chapter 1.2). The transition metal-hydride species derived from the reaction effectively liberates hydrogen by protonolysis, cleaving the chemical bond with an

acidic proton (H^+). There has been a lot of scientific exploration into catalysts with different reaction conditions to achieve dehydrogenation of alcohols. Catalytic dehydrogenation occurs with alcohols and other organic compounds (e.g., amine and alkane), meaning that catalysis using organic molecules has been developed as a hydrogen storage medium (e.g., organic hydride, Chapter 1.3).[11]

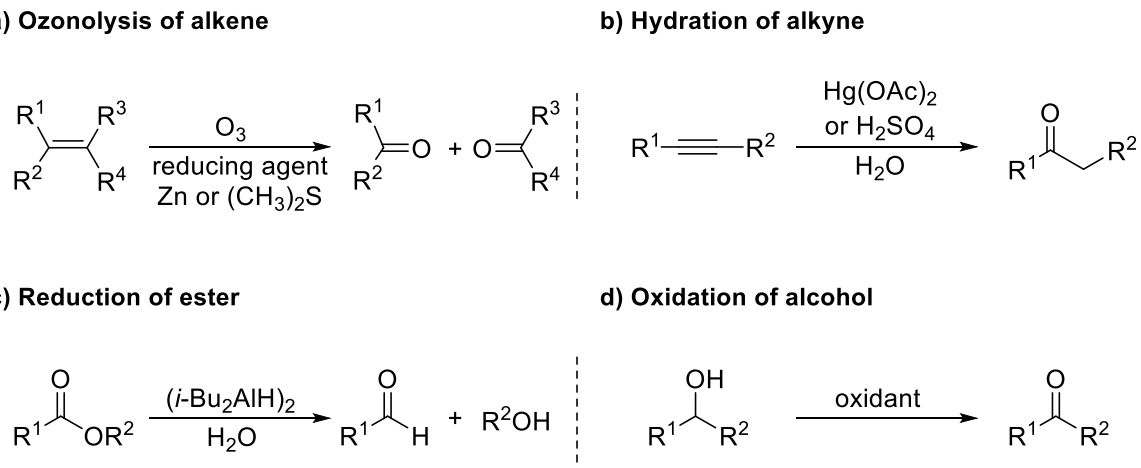
Carbonyl compounds generated as an intermediate via the activation of alcohol can be functionalized through tandem transformation with an additional nucleophile. The metal-hydride species obtained from the dehydrogenation step of alcohol can perform transfer hydrogenation of unsaturated compounds. This is the borrowing hydrogen reaction or hydrogen autotransfer reaction (Scheme 1b).[12] Borrowing hydrogen processes consists of consecutive dehydrogenation, dehydrative condensation, and transfer hydrogenation, occuring without additional hydrogen gas or oxidant. Water is the only by-product generated in this process. This makes the process highly environmentally friendly and atom economic. Many studies have been conducted using an alcohol starting material to allow the borrowing of hydrogen in a chemical reaction. A similar methodology has been used to invesitgate *N*-alkylation to synthesize amines (Chapter 1.4).



Scheme 1. Dehydrogenative activation involving metal-mediated hydride transfer.

1.2. Alcohol Oxidation

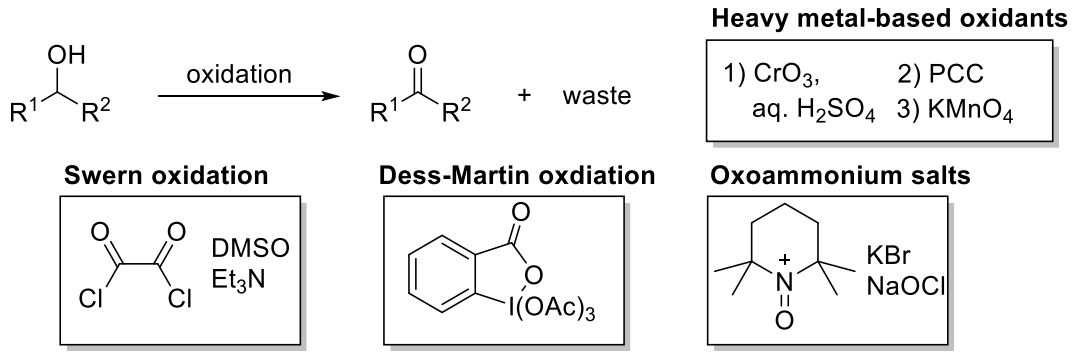
Organic carbonyl compounds with a carbon-oxygen double bond (C=O) are commonly found in ubiquitous molecules. Carbonyl compounds are used in industry and academic fields as solvents and substrates for organic synthesis. Aldehyde and ketone are included in a wide variety of natural products and biologically active substances.[13] They are widely used in pharmaceutical industries, food and processing industries (for sweetening and flavoring), and polymer material industries. They show nucleophilic (oxygen) and electrophilic (carbon) characteristics and hence are used as precursors for synthesizing various useful compounds due to these versatile properties. Various methods, such as ozonolysis of alkene (Scheme 2a),[14] hydration of alkyne (Scheme 2b),[15] and reduction of ester (Scheme 2c)[16] using alkali-metal hydride reagents, have been developed for effectively synthesizing aldehyde and ketone. Various other synthetic methods such as oxidation of alcohol, one of the most convenient methods to synthesize aldehyde and ketone, have also been developed (Scheme 2d).[17] A massive amount of alcohol is industrially produced through the Ziegler process or hydration of alkene (cracking oil) or fermentation of biomass.[15,18,19] Synthetic methods using alcohols as starting materials have become prominent due to low production cost, minimal toxicity, and availability.



Scheme 2. Conventional method for synthesis of aldehyde and ketone.

1.2.1. Traditional Alcohol Oxidation

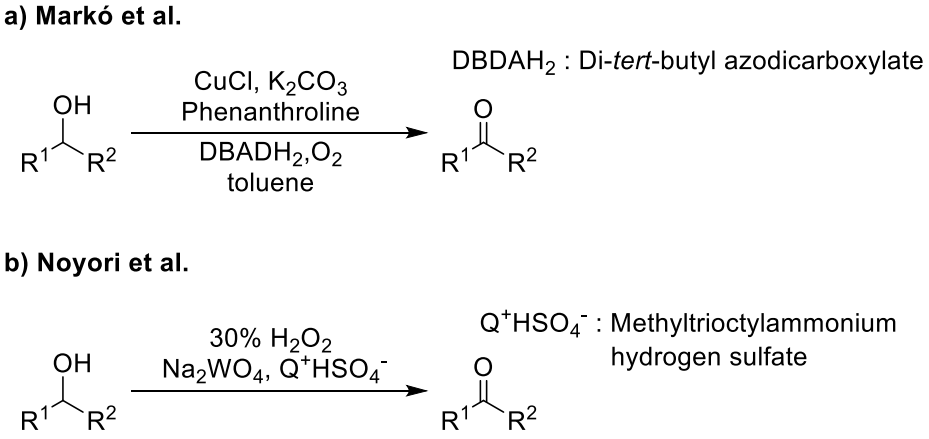
Dehydrogenation of less reactive alcohols involves an uphill thermodynamic reaction. Stoichiometric amounts of oxidants are required in traditional oxidation of alcohol (Scheme 3). The highly reactive Jones reagent (CrO_3, aq. H_2SO_4),[20] PCC (pyridinium chlorochromate),[21] and $KMnO_4$[22] are widely used oxidants. Heavy metal-based oxidants have issues of high toxicity, overoxidation, low selectivity, and large amounts of waste products. There are organic reactions that don't use heavy metals: the Swern oxidation,[23] the Dess-Martin oxidation,[24] and oxoammonium salt oxidation[25]. These organic reactions also require stoichiometric amounts of oxidants. Making the production of large amounts of by-products is a concern. Analyzing these facts illustrates the requirement for an environmentally benign and atom economical alcohol oxidation process.



Scheme 3. Traditional method for alcohol oxidation using additives.

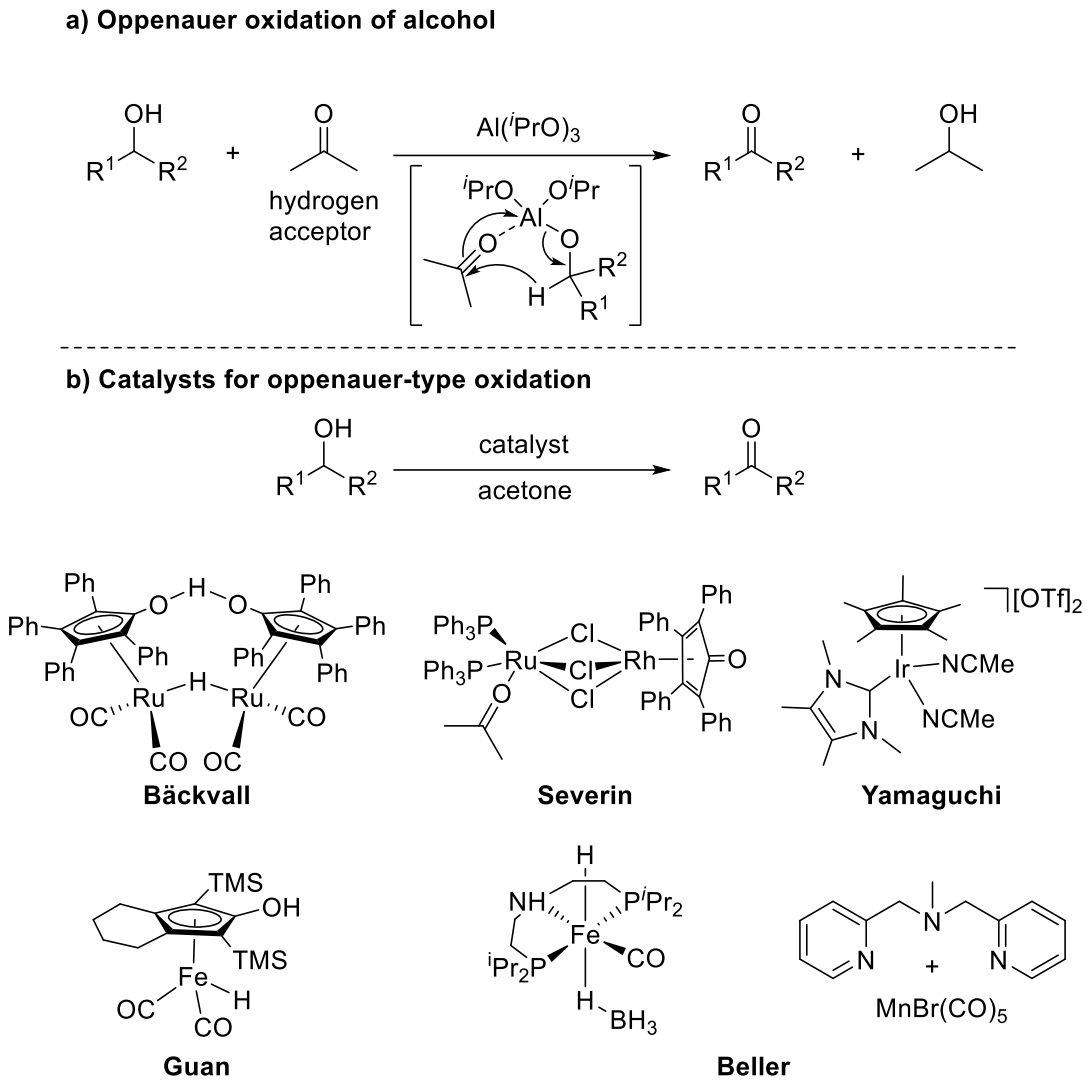
1.2.2. Catalytic Oxidation of Alcohol Using Hydrogen Acceptor

Environmentally favorable oxidants are developed for catalytic oxidation of alcohol to overcome the drawbacks of traditional oxidants (e.g., low selectivity, waste, and toxicity). Marko et al. reported the copper-catalyzed alcohol oxidation with oxygen as an oxidant, producing H_2O as the only by-product (Scheme 4a).[26a] Noyori et al. reported the tungstate-catalyzed oxidation of alcohol using aqueous hydrogen peroxide as an oxidant and generating H_2O as the only by-product (Scheme 4b).[26b]



Scheme 4. Catalytic alcohol oxidation using environmentally favorable oxidant.

The efforts of such researchers lead to exploring more environmentally benign alcohol oxidation processes. The catalytic Oppenauer oxidation using a hydrogen acceptor without use of an oxidant has been developed. The Oppenauer oxidation is the reverse reaction derived from the Meerwein–Pondorf–Verley reduction. This reaction accomplishes the synthesis of ketone from secondary alcohol by a hydrogen transfer reaction using acetone as the solvent and a hydrogen acceptor. Alkoxide species are formed with aluminum isopropoxide and secondary alcohols. The hydride is transferred to acetone (hydrogen acceptor) to drive the synthesis of ketone (Scheme 5a).[27] Many catalysts for Oppenauer-type oxidation of alcohol have been developed and the scope of substrates was also expanded. Aldehyde has also been successfully synthesized using primary alcohols. Catalysts composed of precious metals such as Ru, Rh, and Ir have been explored (Scheme 5b).[28] Oppenauer-type oxidations have been developed using catalysts comprised of earth-abundant metals such as Fe and Mn (Scheme 5b).[29] These transition metal catalysts use the hydrogen transfer reaction including formation of metal hydride species produced by alcohol activation. The Oppenauer-type oxidation reaction is a reversible reaction where the equilibrium is moved to the product side by using a large amount of hydrogen acceptor. This indicates that further improvements in atomic efficiency are required.

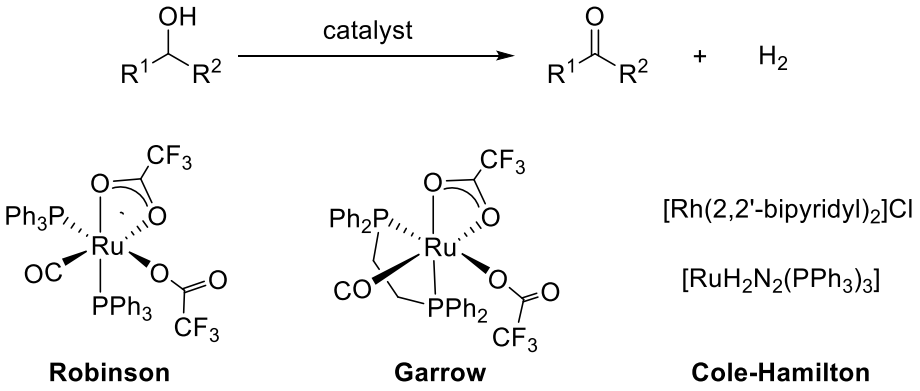


Scheme 5. Catalytic Oppenauer-type oxidation of alcohol with hydrogen acceptor.

1.2.3. Acceptorless Dehydrogenative Oxidation of Alcohol

Acceptorless alcohol dehydrogenation (AAD) is an oxidation process developed by many researchers. AAD has hydrogen gas as the only by-product making it an environmentally benign alcohol oxidation. This transformation of the organic molecule forms carbonyl compound and metal hydride species through catalytic alcohol activation without oxidant and hydrogen acceptor. Residual metal-hydride species generates hydrogen gas by protonolysis completing the reaction (Scheme 1a). Catalytic dehydrogenation is an important method for green sustainable chemistry because of its high atom efficiency. Hydrogen

produced in this reaction has been regarded as an ideal energy carrier for the future. Dehydrogenation of alcohol is not thermodynamically favorable as it is an endothermic reaction requiring high temperature.[30] This implies that to stop hydrogen release, the reversible reactions between the dehydrogenation and hydrogenation reactions must be avoided. Many transition metal catalysts have been developed to overcome this limitation by achieving dehydrogenation of alcohol under mild conditions. Robinson et al [31] reported the Ru catalyst for dehydrogenation of alcohol. Garrou et al.[32] and Cole-hamilton et al.[33] independently reported Ru and Rh catalysts enabling dehydrogenation (Scheme 6). Classical catalysts for dehydrogenation cause several problems: activity by deactivation, narrow scope of substrates, and low selectivity by side reaction.



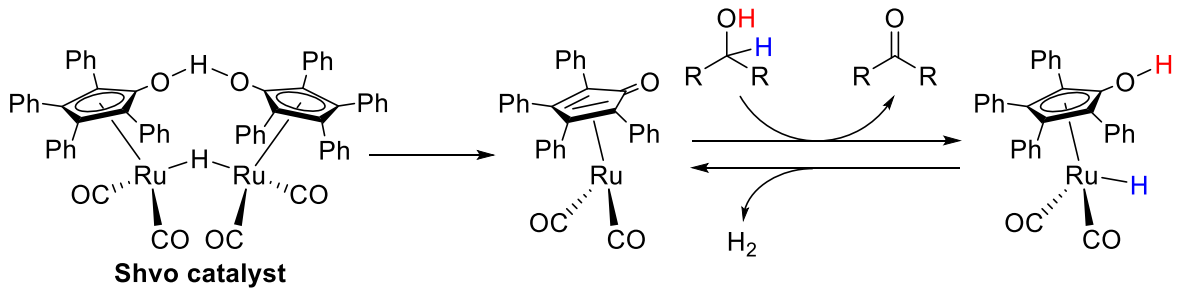
Scheme 6. Classical homogeneous catalysts for dehydrogenation of alcohols.

1.2.4. Catalytic Dehydrogenation via Metal-Ligand Cooperation

Conventional catalytic dehydrogenations of alcohol occur following the inner-sphere mechanism through *β*-hydrogen elimination of alcohol at the vacant site in a metal. The ligand around the metal center controls the environment of the catalyst through steric and electronic effects. The design of an appropriate ligand can be expected to enable advanced molecular transformation. Many catalysts for dehydrogenation have been developed through the design of ligands. Bifunctional catalysts via metal-ligand cooperation pathway have gained a lot of attention.[10b,34] A well-designed functional ligand has the capability to directly

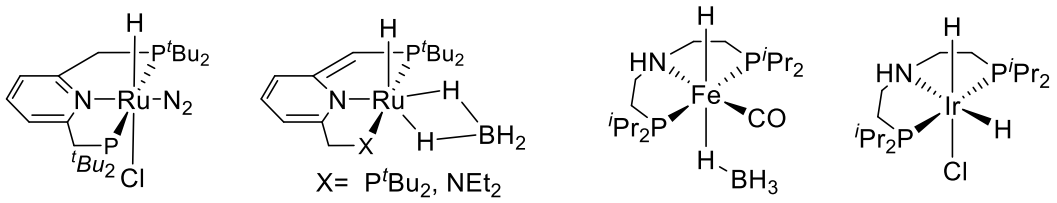
participate in a catalytic reaction by changing its structure plus steric and electronic effects. Many ligands and catalysts based on metal-ligand cooperation have been developed as it could result in a dehydrogenation reaction at a relatively low thermodynamic energy. Some typical examples are described as follows.

In 1985, Shvo et al. reported dehydrogenative homocoupling of alcohols for the synthesis of esters catalyzed by a dinuclear ruthenium complex. The Shvo catalyst is a precatalyst that contains hydroxycyclopentadienyl ligand bridged by a pair of ruthenium metals via a strong hydrogen bond and a hydride. Dehydrogenation of alcohol is proceeded by 16 electron active ruthenium species bearing a cyclopentadienone ligand produced via the dissociation of dinuclear complex. Hydride transfer occurs in the electrophilic metal center via alcohol. A proton of OH is transferred to the cyclopentadiene ligand to produce the aldehyde and ketone. The generated hydride species liberates hydrogen by protonolysis (Scheme 7).[35]



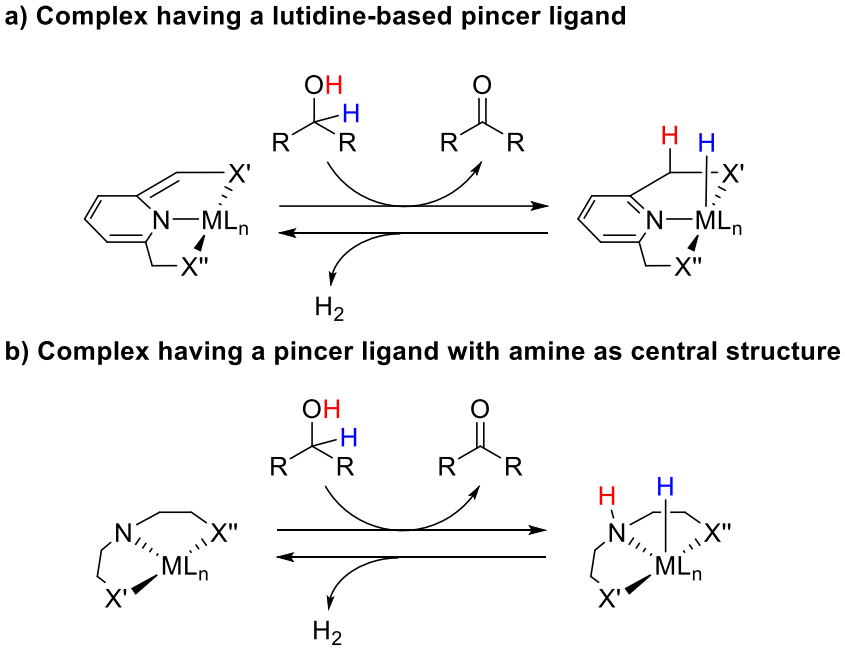
Scheme 7. Proposed mechanism for dehydrogenation of alcohols by the Shvo Ru catalyst.

Many researchers have tried to synthesize catalysts exhibiting high catalytic activity and selectivity with Pincer-type complexes gaining the most attention. Pincer-type ligands have three binding sites that can coordinate with metal, leading to structural stability of the catalyst. They have been widely used in organic synthesis reactions.[36] Various explorations have been carried out on molecular transformation of pincer catalysts. Milstein et al.[37] and Beller et al.[38] have reported a variety of pincer-type ligands and catalysts for dehydrogenation of alcohol following metal-ligand cooperation (Scheme 8).



Scheme 8. Pincer complexes for dehydrogenation of alcohols.

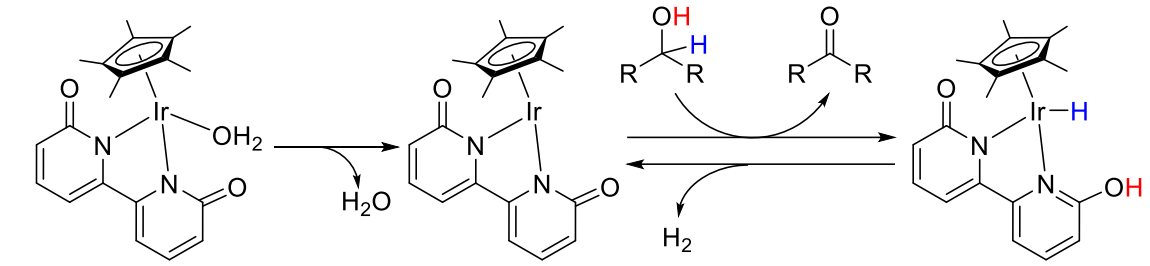
Scheme 9a shows a Pincer catalysts bearing an *N*-heterocyclic compound (pyridine) as a central coordinating group to conduct dehydrogenation alcohol through metal-ligand cooperation by aromatization-dearomatization.[39] A catalyst with pincer ligands using amine as a central structure carring out the alcohol activation by interconversion between amine and amide is shown in Scheme 9b.[40]



Scheme 9. Metal-ligand cooperation in pincer-type metal complexes.

Our research group has studied iridium complexes bearing a functional ligand and succeeded in catalytic dehydrogenation of alcohols using these complexes.[41] Iridium catalysts have an α-pyridonate-based functional ligand that exhibits high catalytic

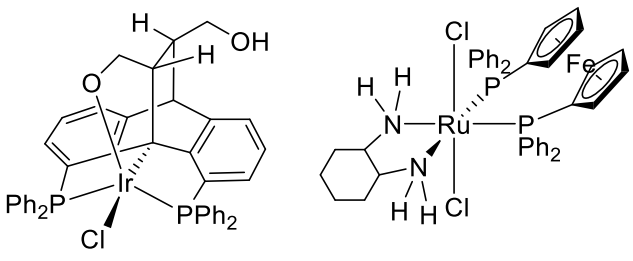
performance. For the activation of alcohol, an α-pyridonate ligand accepts a proton, whereas iridium accepts hydride to produce aldehyde and ketone. The dehydrogenation step proceeds through protonolysis of hydride species alongside α-pyridonate changing into α-hydroxypyridine (Scheme 10).[42]



Fujita and Yamaguchi

Scheme 10. Proposed mechanism for dehydrogenation of alcohol using iridium catalysts bearing a functional α-pyridonate ligand.

Catalysts with various functional ligands have been reported as many researchers continue to synthesize novel catalysts with high activity and special functions (Scheme 11).[43] The design of ligands around the metal center of catalyst is expected to enable more advanced molecular transformations and catalytic activity.

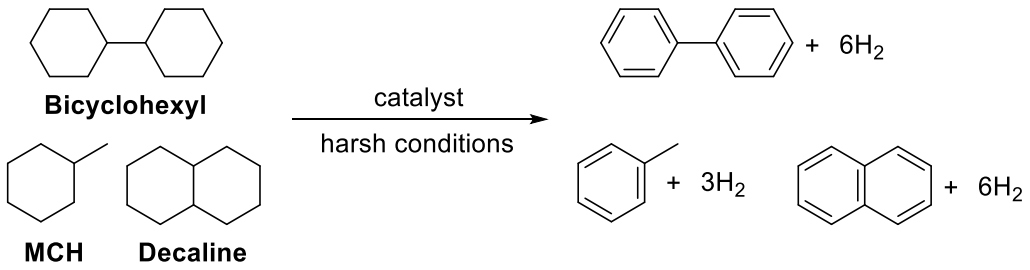


Gelman Baratta

Scheme 11. Other type catalysts following metal-ligand cooperation in dehydrogenation.

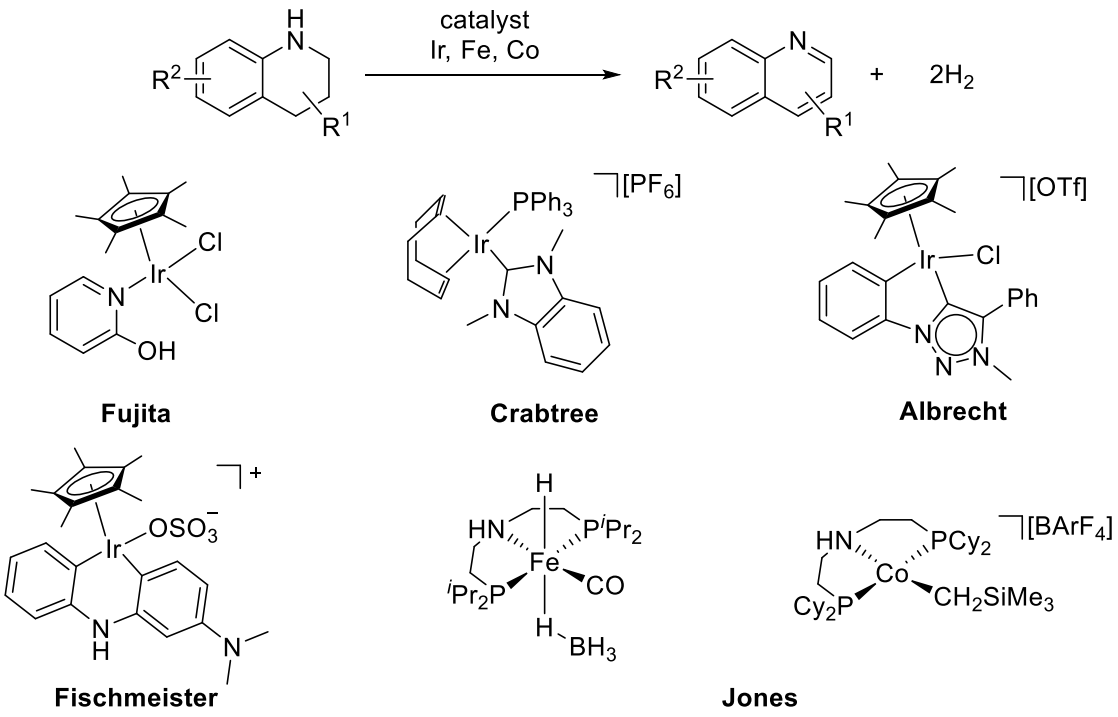
1.3. Catalytic Dehydrogenation of *N*-Heterocycles

Catalytic dehydrogenations to render hydrogen from various organic compounds have been developed for a low carbon future.[44] Hydrogen is regarded as the most promising clean energy carrier because of its advantageous properties: High mass energy density; easy transformation into electrical energy in fuel cells, and generation of non-toxic water upon utilization of stored energy. As hydrogen is flammable it is necessary to establish a safe and efficient hydrogen storage system. Organic hydrides, using organic compounds, are a desirable storage medium to overcome this safety issue. This type of hydrogen storage system is easy and safe way to handle explosive hydrogen by covalently storing the hydrogen in organic hydride molecules. Cycloalkanes such as methylcyclohexane (MCH), decaline, and bicyclohexyl are well known as representative organic hydrides and are being actively researched (Scheme 12). However, the catalytic dehydrogenations using cyclic carbon compounds as an organic hydride require high temperatures (above 200 °C).[45]



Scheme 12. Catalytic dehydrogenation of cycloalkanes.

Catalytic dehydrogenations using *N*-heterocyclic compounds have been developed to require a lower thermodynamic energy than organic hydrides such as carbon cyclic compounds. Similar to these examples, our group had reported the iridium-catalyzed dehydrogenation of 2-methyl-1,2,3,4-tetrahydroquinoline.[46] Studies of many catalysts used for the dehydrogenation of *N*-heterocyclic compounds based on the tetrahydroquinoline structure have been carried out. Initial catalysts used Ir as the central metal but recently inexpensive earth-abundant metal catalysts using iron, and cobalt have been developed (Scheme 13).[47] Catalytic dehydrogenations of *N*-heterocycles with higher hydrogen storage capacity were also developed and various other catalysts were also synthesized to render such reactions (Table 1).[48]



Scheme 13. Catalysts for dehydrogenation of tetrahydroquinoline derivatives.

Table 1. *N*-Heterocycles with relatively high hydrogen storage capacity.

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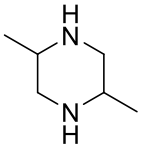
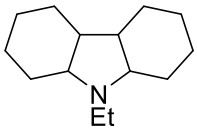
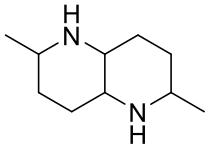
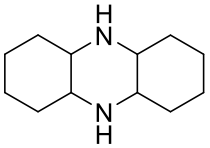
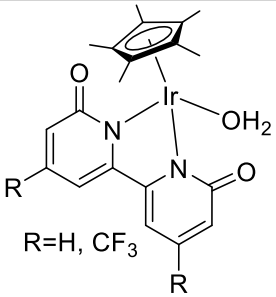
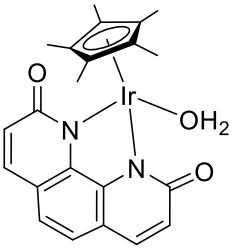
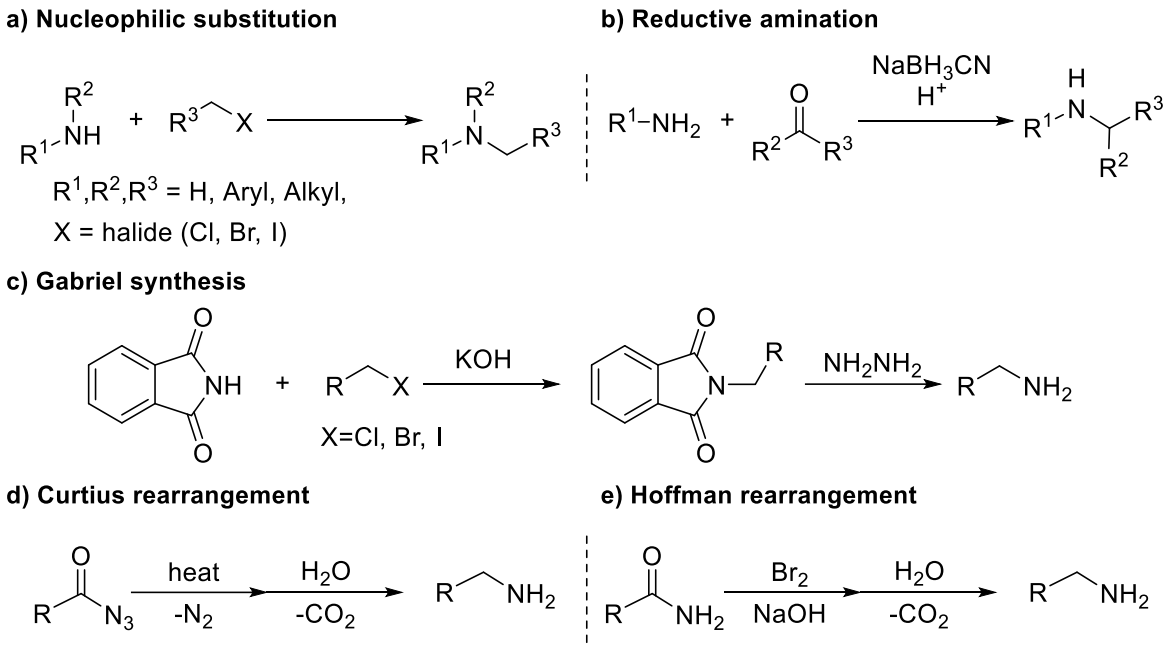
				
H_2 storage capacity	5.3 wt%	5.8 wt%	6.0 wt%	7.3 wt%
catalyst		$Pd/LiAlO_2$		$Pd_2Ru@SiCN$

1.4. Catalytic *N*-Alkylation of Amines with Alcohols through Borrowing Hydrogen Strategy

The catalytic dehydrogenative activation of alcohol has allowed study into the synthetic method of obtaining valuable compounds using alcohol as a starting material via borrowing hydrogen and hydrogen autotransfer processes (Scheme 1b). Catalytic *N*-alkylation through borrowing hydrogen pathway has become one of the most important reactions for the synthesis of amines.[12,49] It is important for green chemistry to synthesize useful compounds by utilizing more stable alcohols instead of highly reactive alkyl halide or alkyl tosylate. The borrowing hydrogen reaction is viewed to be an innovative method that could incorporate relatively low reactivity alcohols. The reactive intermediate aldehyde produced by alcohol dehydrogenation step results in functionalized compounds by reacting with external substrates. Amine compounds containing nitrogen with a lone pair of electrons are classified into primary, secondary, and tertiary amines according to the number of organic substituents existing in various forms. Amines are a representative scaffold of bioactive compounds included in organisms such as plants and animals and they are utilized in pharmaceutical drugs, agrochemicals, dyes, and polymers.[50] Efficient methods for synthesizing amine have been developed as it is used as a precursor in many organic syntheses.

1.4.1. Conventional Amine Synthesis

Many synthetic methods use alkylating agents and amine or ammonia as a nitrogen source. Nucleophilic substitution[49a,51] using alkyl halides are some representative synthetic methods used to obtain amines (Scheme 14a). Reductive amination[52] using aldehydes or ketones, as alkylating agents with reducing agents has been utilized both in industrial and academic fields (Scheme 14b). Other general amine synthesis methods are Gabriel synthesis[53] with phthalimide, Curtius rearrangement[54] with acyl azide, and Hoffman rearrangement[55] with amide (Scheme 14c-e).

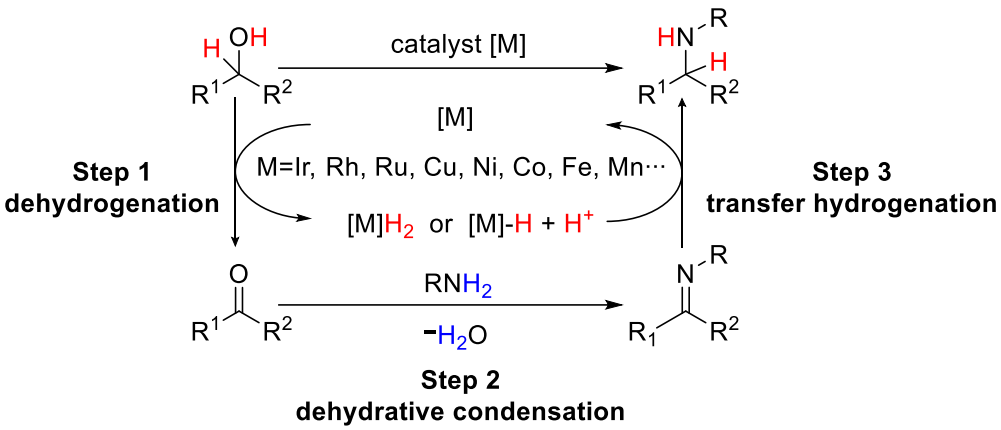


Scheme 14. Representative methods for synthesis of amine.

These conventional methods contain significant drawbacks: low selectivity, usage of excess stoichiometric amounts of toxic reagents, and waste. The toxic reagents in conventional methods have an adverse impact on the environment. Borrowing hydrogen reactions are promising, effective, and environmentally friendly processes when using inexpensive and low toxic alcohol.

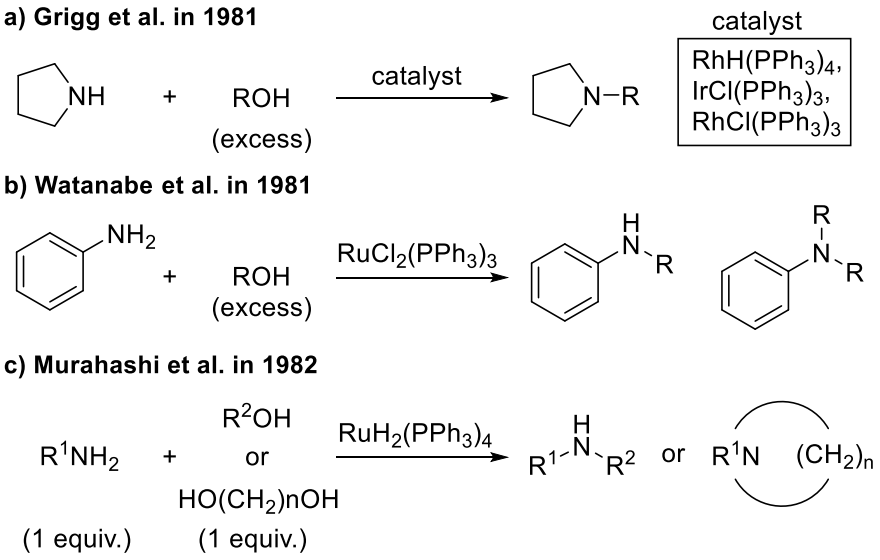
1.4.2. Catalytic *N*-Alkylation of Amines Using Alcohols

Catalytic *N*-alkylation uses the borrowing hydrogen processes: consecutive dehydrogenation, dehydrative condensation (forming imine), and transfer hydrogenation (Scheme 15).[9b,12] In this reaction, amine is the single target product and the only by-product is water. This makes *N*-alkylation via the borrowing hydrogen strategy an atom economic and environmentally benign method for synthesis of amine. The process of dehydrogenative activation of alcohol forms the intermediate carbonyl product and hydride species.



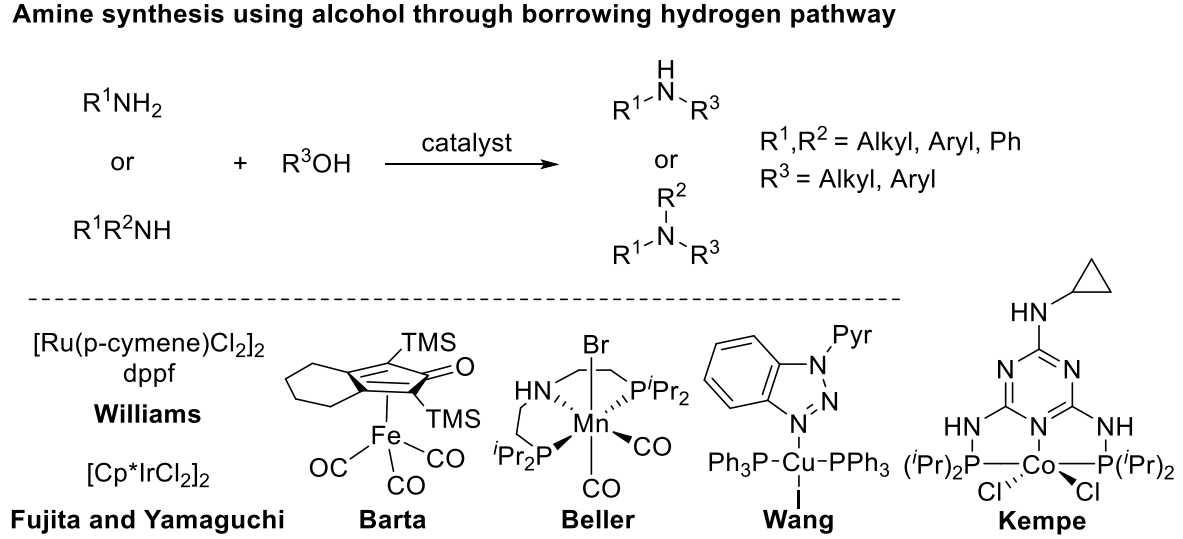
Scheme 15. General proposed mechanism for *N*-alkylation using amine and alcohol through borrowing hydrogen reaction involving metal-mediated hydride transfer.

This hydride species is reused in hydrogenation step through metal-mediated hydride transfer. Hydride transfer becomes important in this catalytic system to effectively transport hydrogen atom. *N*-alkylation using alcohols has been extensively explored over two decades. The pioneering works of Grigg et al. and Watanabe et al. in 1981 independently reported the catalytic *N*-alkylation of amines with excess amounts of alcohols (Scheme 16a,b).[56a,b] Murahashi et al. achieved *N*-alkylation using equimolar mixture of alcohol and amine in contrast to previous works (Scheme 16c).[56c]



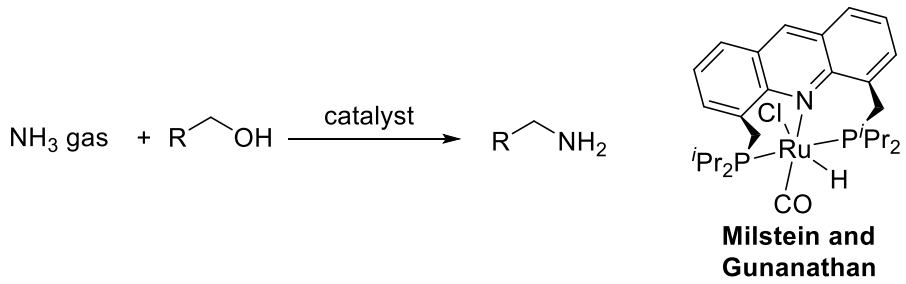
Scheme 16. First reports of *N*-alkylation of amines with alcohols.

Early examples of this catalytic system used precious metal-based catalysts: Rh, Ru, and Ir. Earth-abundant transition metal-based complexes including Cu, Ni, Mn, Fe, and Co have been recently synthesized for *N*-alkylation (Scheme 17).[57]



Scheme 17. Catalysts for synthesis of various amines by *N*-alkylation through borrowing hydrogen.

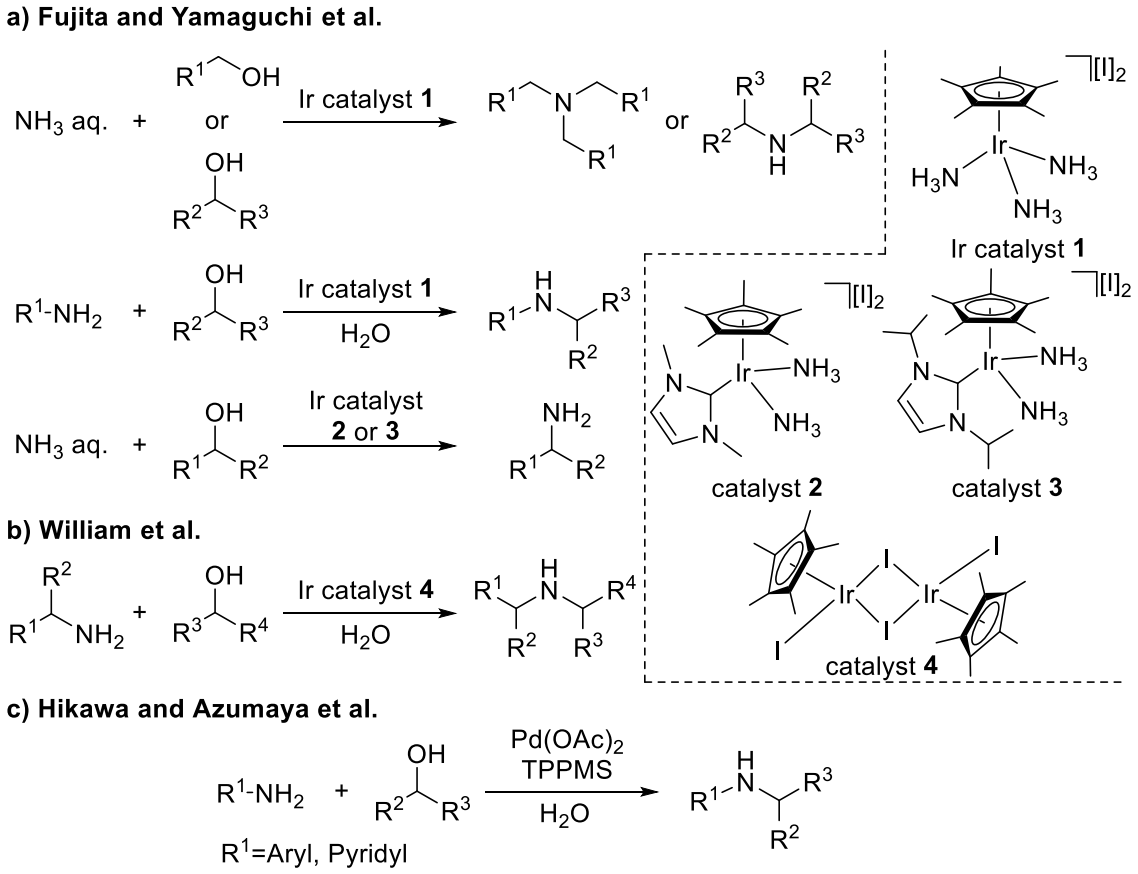
N-alkylation has been developed using various alcohols and amines as starting materials.[58] The range of products have also been increased. *N*-Alkylation of less nucleophilic ammonia as a nitrogen source has been developed. Milstein and Gunanathan (in 2008) reported ruthenium-catalyzed *N*-alkylation for synthesis of primary amines using ammonia gas and alcohols (Scheme 18).[59] This initiated further research and development into catalytic *N*-alkylations using ammonia.[60]



Scheme 18. Ruthenium-catalyzed *N*-alkylation for synthesis of primary amines using ammonia gas and alcohols.

1.4.3. *N*-Alkylation Under Aqueous Conditions

Environmentally friendly organic synthesis has gained appreciation around the globe. Synthetic methods using water as a solvent are being promoted to reduce damage to the environment. Reactions using transition metal catalysts under aqueous conditions are rare due to low solubility and deactivation caused by instability. Our group achieved iridium-catalyzed multialkylation using alcohol and an aqueous solution of ammonia with no requirement of other organic solvents. This showed that iridium triammine catalyst were stable under aqueous conditions and exhibited high catalytic activity (Scheme 19a).[61] An iridium catalysts with *N*-heterocyclic carbene (NHC) ligands was shown to be stable under aqueous solution (Scheme 19a).[62] Few other catalysts are known to achieve *N*-alkylation under aqueous conditions (Scheme 19b,c).[63] Synthetic methods for obtaining various amines in aqueous conditions are still being investigated.

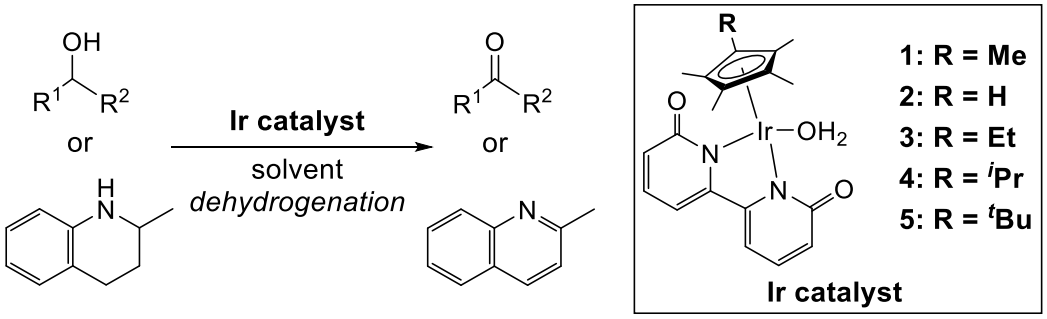


Scheme 19. Catalytic *N*-alkylation for synthesis of amine under aqueous conditions.

1.5. Overview

Hydride transfer is utilized as a key step in many organic synthetic reactions. Catalytic dehydrogenation and borrowing hydrogen reaction enable effective molecular transformation through metal-mediated hydride transfer. For this study, the author has focused on the design of the iridium catalyst for dehydrogenation and synthetic method for amines through borrowing hydrogen pathway.

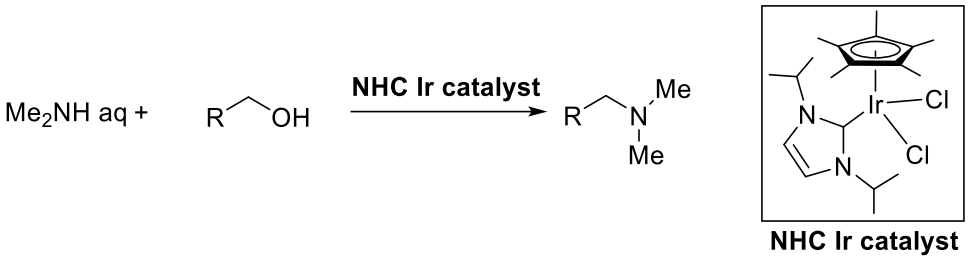
The second chapter describes the design of the iridium catalyst bearing cyclopentadienyl and bipyridonate ligand for acceptorless dehydrogenation (Scheme 20). Cyclopentadienyl ligands with various electronic and steric properties are applied in the synthesis of a new catalyst. A previously reported theoretical study suggests that charge transfer from pentamethylcyclopentadienyl ligand to iridium center contributes to the stabilization of active species. This could lead to the development of a catalyst with higher activity through tuning the substituents of the cyclopentadienyl ligand. In chapter 2 the author develops methods to synthesize new iridium complexes having cyclopentadienyl ligands with a series of alkyl substituents. The catalytic activity of new complexes for the dehydrogenation of alcohols and 2-methyl-1,2,3,4-tetrahydroquinoline were investigated.



Scheme 20. Design of new iridium catalysts and dehydrogenation of alcohols and an *N*-heterocycle.

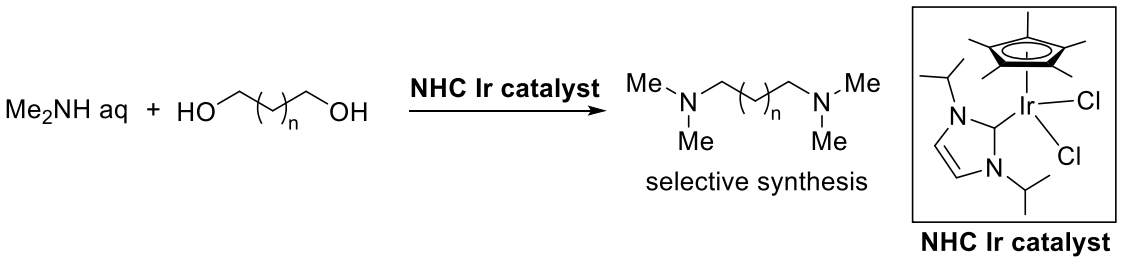
In Chapter 3, the author reports a new iridium catalytic system for the synthesis of *N,N*-dimethylamine derivatives using primary alcohol and an aqueous solution of dimethylamine, without an additional organic solvent (Scheme 21). This reaction utilizes the atom economic and environmentally benign hydrogen borrowing processes. In this catalytic system, the iridium catalyst bearing *N*-heterocyclic carbene (NHC) ligand exhibited high activity under

aqueous conditions. The author has attempted to synthesize a variety of *N,N*-dimethylamine derivatives, including pharmaceutical drug and alkaloid, using inexpensive and less toxic alcohols.



Scheme 21. Iridium-catalyzed dimethylamination of primary alcohols and an aqueous solution of dimethylamine.

In chapter 4, the author describes the selective synthesis of bisdimethylamine derivatives from diols and an aqueous solution of dimethylamine (Scheme 22). Diols are less toxic and easily obtained from relatively cheap feedstocks making bisdimethylamination of diols a promising process for bisdimethylamine derivatives. There are very few examples for synthesis of bisdimethylamine compounds through the borrowing hydrogen pathway. The formation of aminoalcohol as a by-product is a problem in these processes. Current research only reports on iridium-catalyzed bisdimethylamination from diol for selective bisdimethylamine derivatives without the accompanying aminoalcohols. The author conducted synthesis of valuable bisdimethylamine derivatives for application in many fields (e.g., polymer and organic synthesis). To accompany this work, attempts were made to achieve trimethylamination, bismonoamination, and site-selective monoamination processes.



Scheme 22. Iridium-catalyzed bisdimethylamination for synthesis of bisdimethylamine derivatives from diols and an aqueous solution of dimethylamine through borrowing hydrogen processes.

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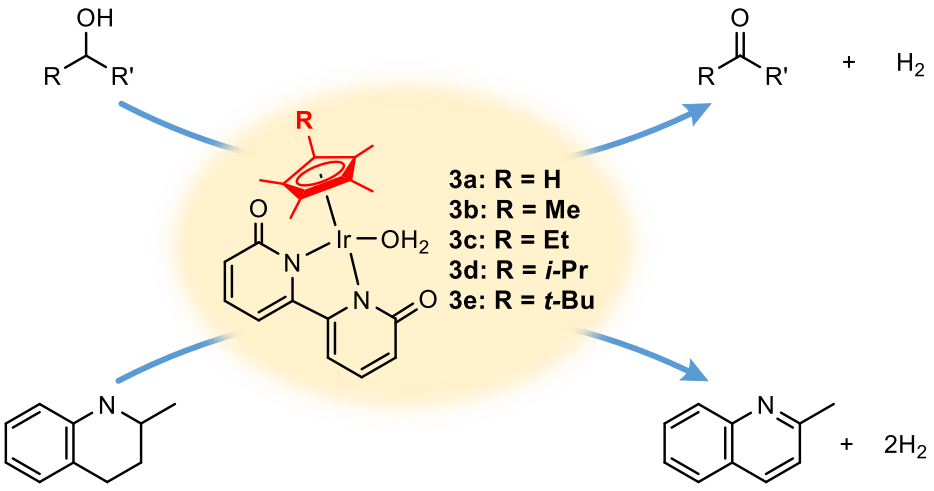
Chapter 2

Effect of a Substituent in Cyclopentadienyl Ligand on Iridium-Catalyzed Acceptorless Dehydrogenation of Alcohols and 2-Methyl-1,2,3,4-tetrahydroquinoline

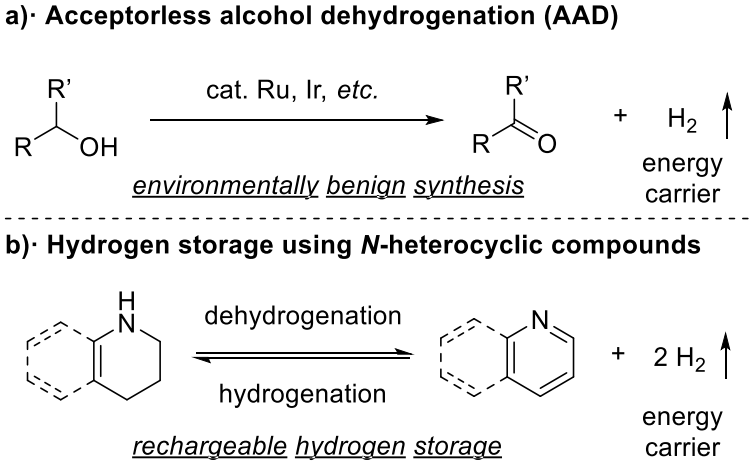
Abstract

New iridium(III)-bipyridonate complexes having cyclopentadienyl ligands with a series of alkyl substituents were synthesized for the purpose of tuning the catalytic activity for acceptorless dehydrogenation reactions. A comparison of the catalytic activity was performed for the reaction of alcoholic substrates such as 1-phenylethanol, 2-octanol, and benzyl alcohol. The *t*-butyl-2,3,4,5-tetramethylcyclopentadienyl iridium complex exhibited the best performance, which surpassed that of the 1,2,3,4,5-pentamethylcyclopentadienyl (Cp*) iridium catalyst in the dehydrogenation reaction of alcohols. The catalytic activity in the dehydrogenation of 2-methyl-1,2,3,4-tetrahydroquinoline was also examined. The highest efficiency was obtained in the reaction catalyzed by the same *t*-butyl-substituted cyclopentadienyl iridium complex.



2.1. Introduction

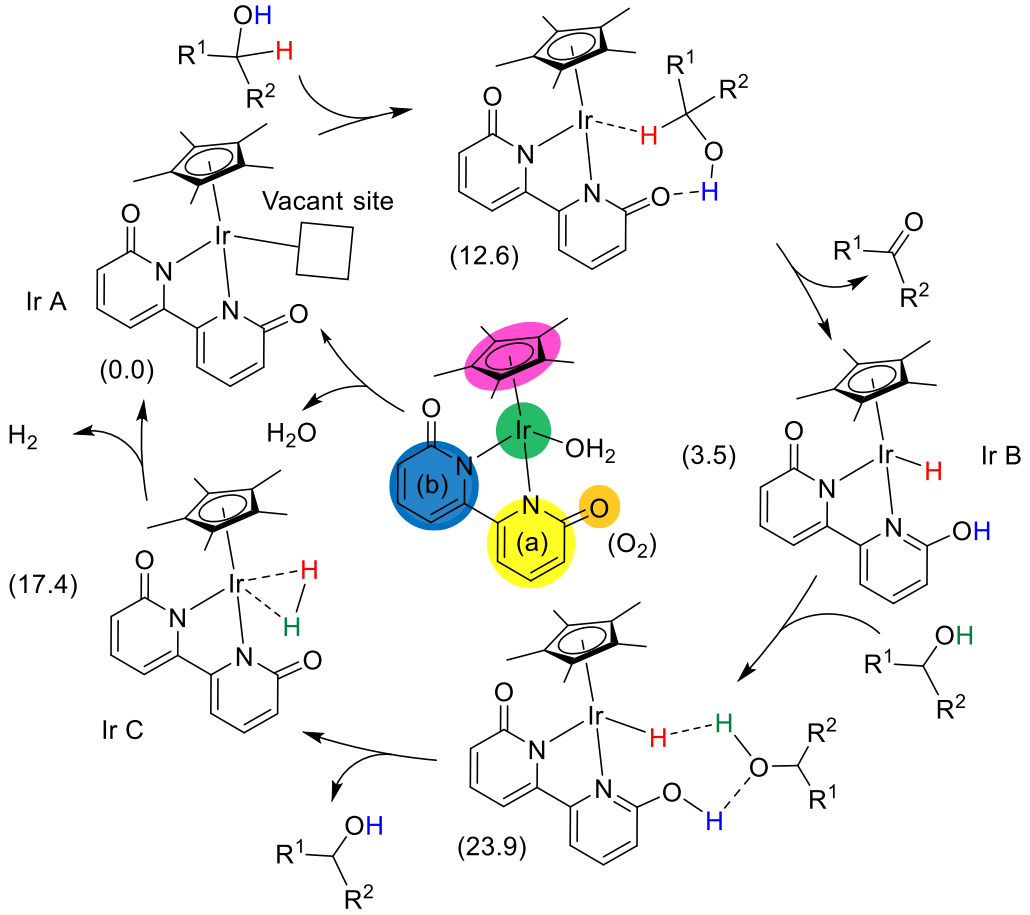
Dehydrogenation of small organic molecules without using external oxidants (i.e., acceptorless dehydrogenation) is an attractive transformation reaction from the viewpoint of excellent atomic efficiency.[1] Avoidance of the use of harmful oxidants without generating stoichiometric amounts of waste (other than hydrogen gas) meets the requirements of green chemistry. Moreover, the resulting hydrogen gas can be used as a promising energy carrier owing to its high weight energy density and carbon neutrality. These characteristics make the significance of acceptorless dehydrogenation much greater in the field of organic synthesis as well as energy science.[1d,2] Owing to the catalytic activity of ruthenium complexes in dehydrogenation reactions of alcohols,[3] considerable efforts have been made to improve catalytic systems with the development of complexes such as pincer-type ruthenium or iridium complexes with non-innocent behavior of the pincer ligands (Scheme 1a).[4] Recently, a catalytic system has been applied to the dehydrogenation reaction of *N*-heterocyclic compounds for use in hydrogen storage (Scheme 1b).[5] The search for a highly efficient catalytic dehydrogenation system remains a challenging task.



Scheme 1. Catalytic dehydrogenation of alcohols and *N*-heterocycles.

Our research group has consistently studied the catalytic activity of pentamethylcyclopentadienyl (Cp*) iridium complexes for the hydrogen transfer process of alcoholic substrates.[6] By combining hydroxypyridine or dihydroxybipyridine derivatives as non-innocent ligands, the Cp* iridium complex shows an extremely high catalytic activity in acceptorless dehydrogenation reactions of alcoholic substrates and *N*-heterocyclic

compounds.[7] Mechanism for dehydrogenation of alcohol using iridium catalyst bearing a functional α,α'-bipyridonate ligand is described in Scheme 2.



Scheme 2. Mechanism for acceptorless alcohol dehydrogenation using iridium catalyst with non-innocent α,α'-bipyridonate ligand and gibbs energy (kcal/mol) in parentheses.

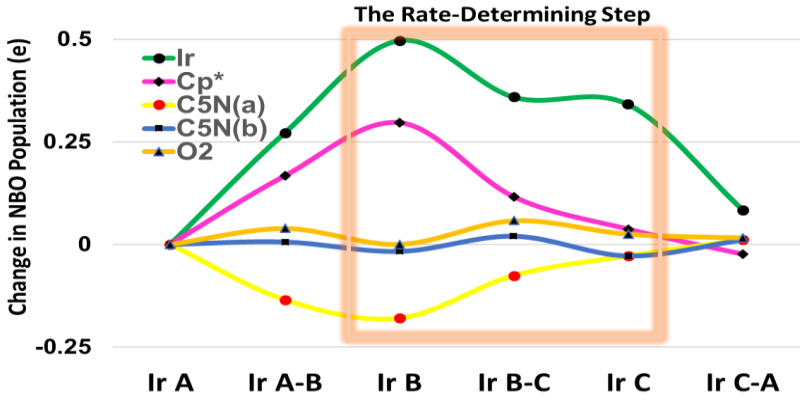
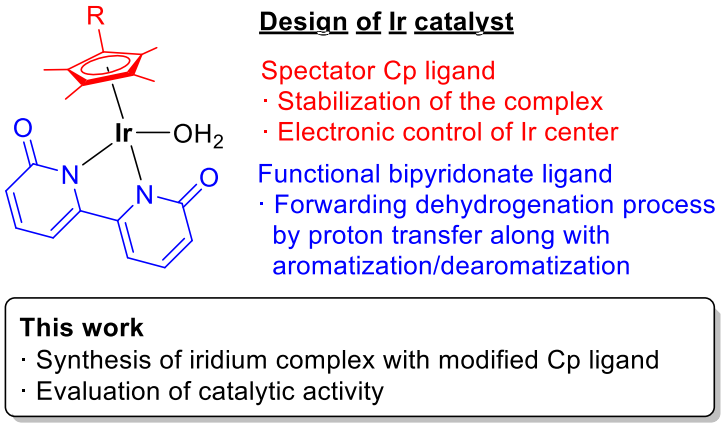


Figure 1. Natural bond orbital (NBO) population charges of elements in Cp*Ir-bypridonate complex.

Theoretical studies suggest that the spectator Cp* ligand contributes to the stabilization of catalytically active species and to the milder electron-population change on the iridium center during the reaction, which decreases the overall reaction barrier (Figure 1).[8]

In general, a cyclopentadienyl (Cp) ligand donates six electrons to a metal center with tridentate coordination mode, which results in stable complexes that are widely used as catalysts. The incorporation of substituents on the Cp ring allows both electronic and steric perturbation on the Cp metal complexes.[9] Well-modified Cp ligands have been used to improve the potential catalytic activity and reaction selectivity of transition metal complexes.[10] Thus, a systematic study of the modified Cp-ligated iridium complex should provide significant insight for the development of a more active catalytic system for acceptorless dehydrogenation reactions.

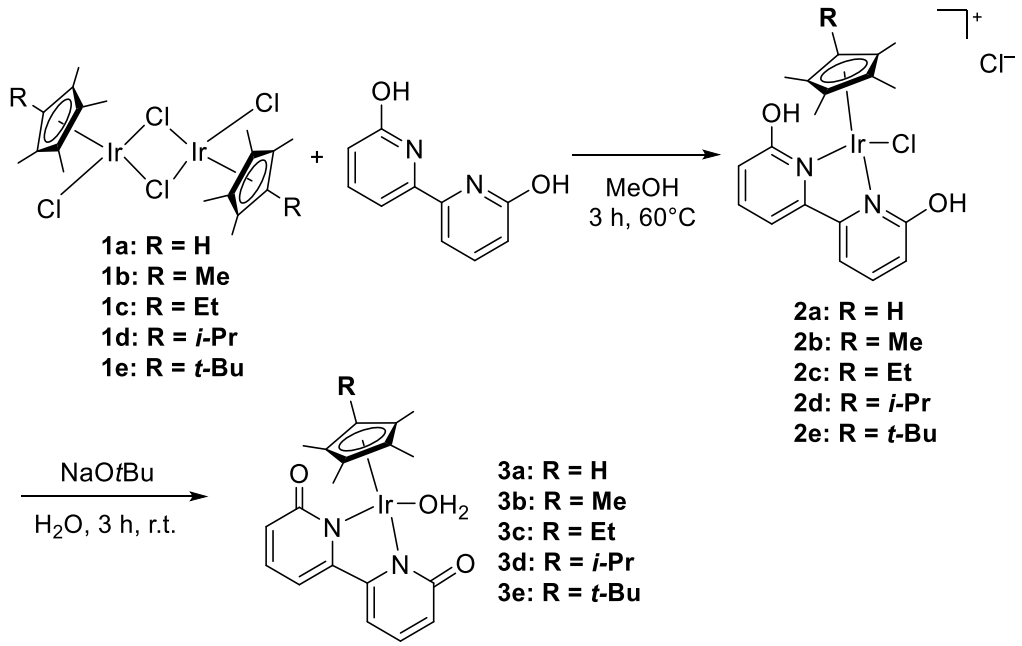


Scheme 3. Design of the Ir catalyst bearing Cp and bipyridonate ligand.

Herein, the author synthesized a series of bipyridonate-coordinated iridium(III) complexes bearing Cp ligands with various alkyl substituents to reveal the trend of catalytic activity in the dehydrogenation of alcohols and 2-methyl-1,2,3,4-tetrahydroquinoline (Scheme 3). The 1-*tert*-butyl-2,3,4,5-tetramethylcyclopentadienyl iridium complex exhibited higher activity.

2.2. Results and Discussion

On the basis of our previous studies, in which Cp* iridium complexes exhibited excellent catalytic activity,[7] the author attempted to modify one methyl group in the Cp* ligand to hydrogen, ethyl, isopropyl, and *t*-butyl groups in order to improve the catalytic properties (Scheme 4).



Scheme 4. Synthesis of bipyridonate iridium complexes with a Cp ligand bearing a series of alkyl groups.

Cp* ligand and Me_4Cp ligand reagents are commercially available, and Cp ligand with other substituents was synthesized by Grignard reaction using 2,3,4,5-tetramethyl-2-cyclopentenone and alkyl magnesium halide (RMgX, X=halide) according to the literature. A series of cyclopentadienyl-ligated iridium dichloride dimers **1a-1e** including new iridium dichloride dimer **1e** were synthesized by the reaction of iridium trichloride with parent cyclopentadiene derivatives.[11] The structure of novel complex **1e** was successfully identified by X-ray crystallographic analysis. The coordination reactions of **1a-1e** with 6,6'-dihydroxy-2,2'-bipyridine in methanol at 60 °C gave cationic complexes **2a-2e** which were converted into neutral aquo complexes **3a-3e** by treatment with NaO*t*Bu in water. The structures of cationic bipyridine complexes **2** and neutral bipyridonate complexes **3** were fully

characterized by ^{1}H and ^{13}C NMR and elemental analysis. X-ray crystallographic analysis could be performed for **2a** and **2e** to provide unambiguous structural information (Figure 2). Tetramethylcyclopentadienyl ligand of **2a** is located where the steric demand for hydroxy group of the hydroxybipyridine ligand becomes small (Figure 2, left). The *t*-butyl group of **2e** is located at the trans position to the chloro ligand probably owing to its steric demand. Complexes **2a** and **2e** showed similar structural parameters around the iridium center (Figure 2, right). Additionally, the distance between carbon in cyclopentadienyl ring and iridium was investigated. The average distance between carbon of cyclopentadienyl ring of **2a** and iridium was 2.170 Å, and that of **2e** was 2.180 Å (Table 1). The torsion angles of the cyclopentadienyl ring on complexes **2a** and **2e** were also investigated. The average absolute value of the torsion angle of the cyclopentadienyl ring of **2a** was 2.68° and that of **2e** was 3.06° (Table 2.). Both are confirmed to be close to near planar.

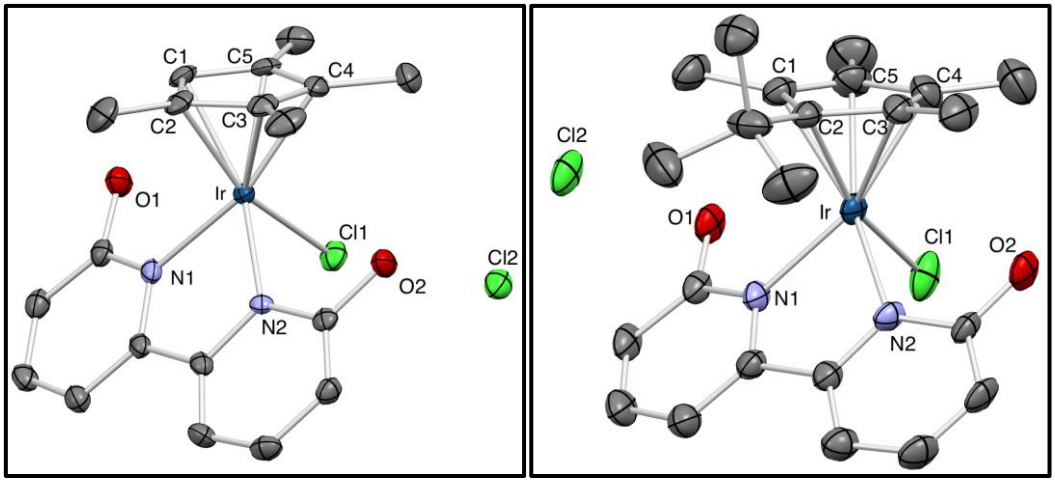


Figure 2. ORTEP illustrations of complexes **2a** (left) and **2e** (right) at the 50% probability level. Solvent molecules and hydrogen atoms are omitted for clarity.

Table 1. Distance between carbon of cyclopentadienyl ring and iridium on complexes **2a** and **2e**.

Ir complex **2a**	distance between C and Ir (Å)	Ir complex **2e**	distance between C and Ir (Å)
C1-Ir	2.158(5)	C1-Ir	2.190(7)
C2-Ir	2.157(5)	C2-Ir	2.164(9)
C3-Ir	2.200(5)	C3-Ir	2.190(7)
C4-Ir	2.172(5)	C4-Ir	2.177(7)
C5-Ir	2.166(4)	C5-Ir	2.177(7)
average	2.170	average	2.180

Table 2. Torsion angles of cyclopentadienyl ligand on complexes **2a** and **2e**.

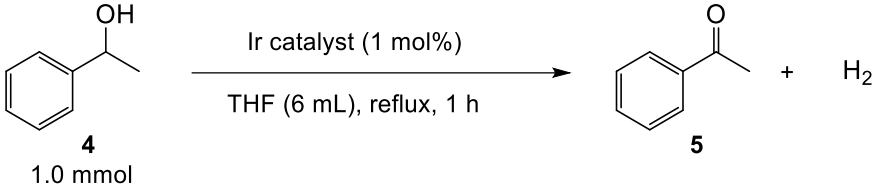
Ir complex **2a**	torsion angle (°)	Ir complex **2e**	torsion angle (°)
C1-C2-C3-C4	-4.11	C1-C2-C3-C4	-4.67
C2-C3-C4-C5	3.43	C2-C3-C4-C5	2.99
C3-C4-C5-C1	-1.37	C3-C4-C5-C1	0.00
C4-C5-C1-C2	-1.22	C4-C5-C1-C2	-2.99
C5-C1-C2-C3	3.28	C5-C1-C2-C3	4.67
average[a]	2.68	average	3.06

[a]Average absolute value

After obtaining a series of iridium catalysts **3**, their catalytic activities in the dehydrogenation of 1-phenylethanol (**4**), which is a model substrate that our research group previously studied in detail, were investigated (Table 3). To ensure full solubility of iridium complexes, reactions were performed in THF under reflux conditions. The yield of dehydrogenated product acetophenone (**5**) after 1 h was determined by gas chromatography (GC) analysis to evaluate initial catalytic activity. To avoid mistake of catalytic activity evaluation, the author use average of three runs. In the presence of tetramethylcyclopentadienyl complex **3a**, the dehydrogenation reaction proceeded to give acetophenone in 35% yield (Table 3, entry 1). Cp* complex **3b**, ethyltetramethylcyclopentadienyl complex **3c**, and isopropyltetramethylcyclopentadienyl complex **3d** exhibited higher catalytic activities than **3a** to produce **5** in similar yields (Table 3, entries 2-4). The *t*-butyltetramethylcyclopentadienyl complex **3e** exhibited the highest catalytic activity (Table 3, entry 5). Although the difference in catalytic activity between **3b**-**3d** was not large, the

observed trend indicated that a stronger electron-donating cyclopentadienyl ligand leads up to higher catalytic activity. This conclusion is based on the observation that **3a** was least active while **3e** showed the highest catalytic activity. After 24 h, the complete conversion of starting alcohol was achieved, which suggests that the obtained results originated only from the catalytic activity and not from the deactivation of catalysts.

Table 3. Catalytic activity of iridium complexes **3** in dehydrogenation of 1-phenylethanol (**5**).

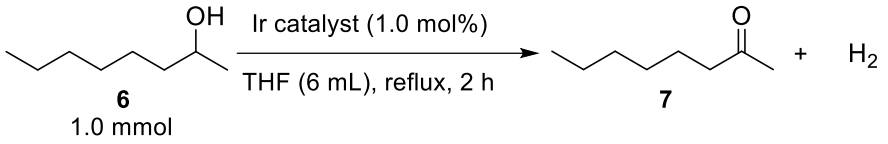


entry	catalyst	conv.(%)[a,b]	yield(%)[a,b]
1	**3a**	35	35
2	**3b**	57	57
3	**3c**	53	53
4	**3d**	55	55
5	**3e**	64	64

[a]Conversions and yields were determined by GC using undecane as an internal standard. [b] Average of three runs.

The catalytic abilities of iridium complexes **3** were also examined in the dehydrogenation reaction of 2-octanol (**6**) as an aliphatic alcohol in refluxing THF (Table 4). Catalyst **3a** exhibited the lowest catalytic activity to give 2-octanone (**7**) with an 18% yield after 2 h (Table 4, entry 1). Catalyst **3b** exhibited moderate performance and produced a dehydrogenated product with a 49% yield (Table 4, entry 2). The highest catalytic ability was achieved by **3e**, which produced **7** with a 57% yield (Table 4, entry 3). The trend of catalytic ability is consistent with that of the dehydrogenation reaction of 1-phenylethanol (**4**), which is shown in Table 3.

Table 4. Catalytic activity of iridium complexes **3** in dehydrogenation of 2-octanol (**7**).

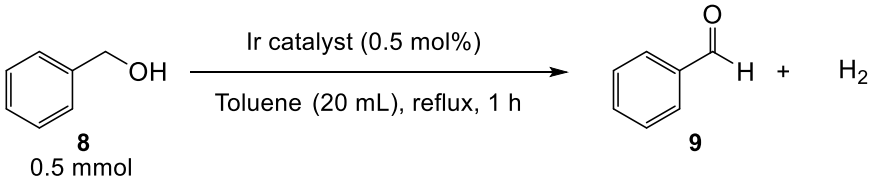


entry	catalyst	conv.(%)[a,b]	yield(%)[a,b]
1	**3a**	19	18
2	**3b**	49	49
3	**3e**	57	57

[a]Conversions and yields were determined by GC using biphenyl as an internal standard.

However, compared with the dehydrogenation of secondary alcohols, no significant difference in catalytic activity was observed for the primary alcohol (Table 5). The reactions were performed under more diluted conditions than those for secondary alcohols to suppress undesired side reactions, such as self-condensation leading to ester product. Dehydrogenation reaction of benzyl alcohol (**8**) in refluxing toluene was carried out in the presence of 0.5 mol% of iridium catalyst to produce benzaldehyde (**9**). Catalyst **3a** exhibited a slightly lower performance compared with catalyst **3b** and **3e** (Table 5, entries 1-3). Catalysts **3b** and **3e** showed similar catalytic activities.

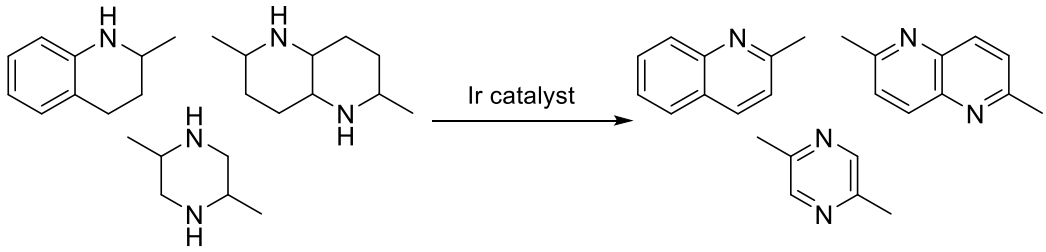
Table 5. Catalytic activity of iridium complexes **3a**, **3b**, and **3e** in dehydrogenation of benzyl Alcohol (**8**).



entry	catalyst	yield(%)[a,b]
1	**3a**	41
2	**3b**	46
3	**3e**	48

[a]Conversions and yields were determined by GC using biphenyl as an internal standard.

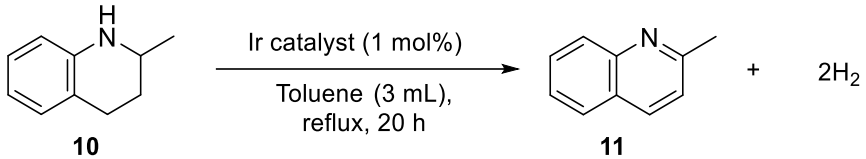
Our research group has previously reported that the dehydrogenation of a cyclic amine, which leads to aromatized *N*-heterocycles, is also catalyzed by the same iridium complex used for the dehydrogenation of alcoholic substrates (Scheme 5).[7j-7l]



Scheme 5. Our previously reported dehydrogenation of *N*-heterocycles using iridium catalyst.

Hence, the author also examined the catalytic activity of a series of iridium complexes **3** in the dehydrogenation of 2-methyl-1,2,3,4-tetrahydroquinoline (**10**) as a model substrate (Table 6).

Table 6. Catalytic activity of iridium complexes **3** in dehydrogenation of 2-methyl-1,2,3,4-tetrahydroquinoline (**10**).



10
1.0 mmol

11

entry	catalyst	conv.(%)[a,b]	yield(%)[a,b]
1	**3a**	55	55
2	**3b**	91	91
3	**3c**	83	83
4	**3d**	62	62
5	**3e**	99	99

[a]Conversions and yields were determined by GC using undecane as an internal standard.

Considering the relatively slower reaction rate for the dehydrogenation of cyclic amines than that of alcohols, the reactions were performed under toluene reflux conditions for 20 h.

Catalyst **3a** exhibited moderate catalytic activity to produce the dehydrogenated product 2-methylquinoline (**11**) with a 55% yield (Table 6, entry 1). Catalyst **3b** exhibited high performance with a 91% yield (Table 6, entry 2). The reactions in the presence of catalysts **3c** and **3d** were somehow significantly less effective than the reaction catalyzed by **3b** (Table 6, entries 3, 4). Similar to the dehydrogenation of alcoholic substrates, the highest catalytic ability was achieved by catalyst **3e** (Table 6, entry 5).

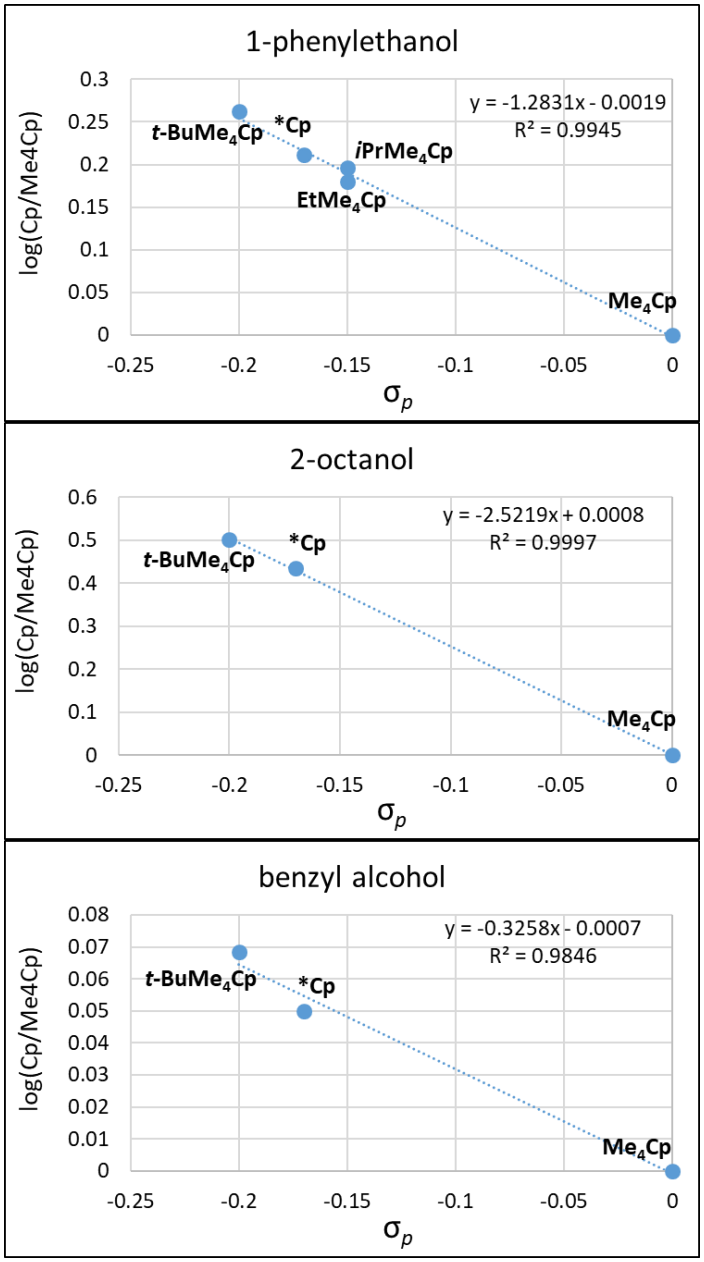


Figure 3. Hammett Plot based on the yield of dehydrogenation of alcohols.

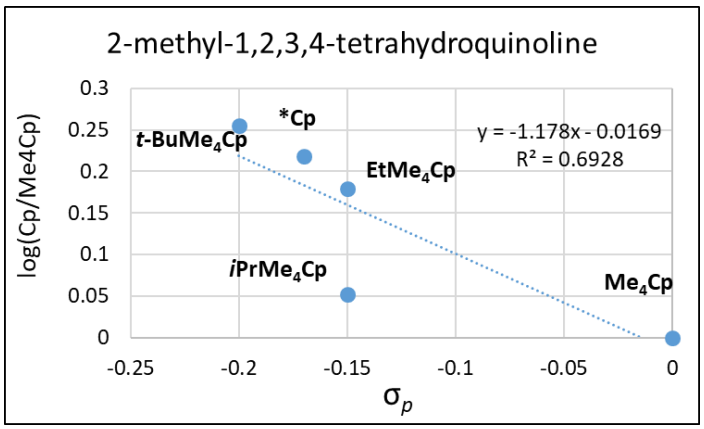


Figure 4. Hammett Plot based on the yield of dehydrogenation of 2-methyl-1,2,3,4-tetrahydroquinoline.

To gain insights into the effect of substituents on cyclopentadienyl ligand, Hammett study based on the yield of dehydrogenation was conducted. The negative slope of Hammett plot was represented.[12] Hammett plot was analyzed with yield of dehydrogenation of alcohols for several substituents resulting in a good correlation (Figure 3). The yield of dehydrogenation of 2-methyl-1,2,3,4-tetrahydroquinoline also showed a good correlation except for **3d** (Figure 4). Therefore, this investigation indicated that the electron-donating effect of a substituent on cyclopentadienyl ligand is important in dehydrogenation reaction. For this reason, the author expects that 1-*tert*-butyl-2,3,4,5-tetramethylcyclopentadienyl iridium complex **3e** exhibited higher activity.

2.3. Conclusions

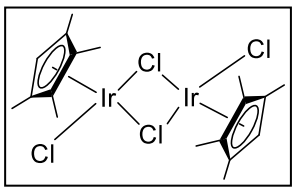
In conclusion, the author successfully synthesized new iridium complexes **1-3** having cyclopentadienyl ligands with various alkyl substituents. The *t*-butyl-substituted cyclopentadienyl complex **3e** exhibited a slightly higher catalytic activity than other complexes in the dehydrogenation of alcohols and 2-methyl-1,2,3,4-tetrahydroquinoline. Based on Hammett plot correlation, it is expected that this trend is due to the relatively larger electron-donating effect of *t*-butyl substituents on cyclopentadienyl ligand than others. Although computational studies on the relationship between the effect of the cyclopentadienyl ligand on iridium complexes and their catalytic activity is unclear, this study provides systematic information on the effect of substituents on the cyclopentadienyl ligand in a catalytic dehydrogenation reaction. These results indicate that the activity of a catalyst can be controlled by tuning the ligand, and it can be said that the design of ligands enables the synthesis of catalysts with higher activity.

2.4. Experimental Section

^{1}H and ^{13}C 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). Elemental analyses were carried out at the Microanalysis Center of Kyoto University. Melting point was measured by a Yanaco MP-500D under air. Dehydrated solvent was used in reaction. HCp^{*Ethyl}(5-ethyl-1,2,3,4-tetramethylcyclopentadiene),[13] HCp^{*iPr}(5-isopropyl-1,2,3,4-tetramethylcyclopentadiene),[11c,13] HCp^{*tBu}(5-*tert*-butyl-1,2,3,4-tetramethylcyclopentadiene),[14] [Cp*Ir(6,6'-dihydroxy-2,2'-bipyridine)Cl]Cl (**2b**),[15] Cp*Ir(2.2'-bipyridine-6,6'-dionato)H_2O (**3b**),[16] and 6,6'-dihydroxy-2,2'-bipyridine[17] were prepared according to the literature method. All other reagents are commercially available and were used as received.

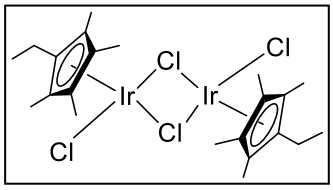
Procedure for the syntheses of $[Cp^{R}IrCl_2]_2$

$[(\eta^5\text{-}C_5Me_4H)IrCl_2]_2$ (1a)[18]



Under an atmosphere of argon, $IrCl_3 \cdot 5H_2O$ (998.2 mg, 2.57 mmol) was placed in 50 mL two-neck flask equipped with a Dimroth condenser and three-way cock. Methanol (19.7 mL) and 1,2,3,4-tetramethylcyclopentadiene (1271.3 mg, 10.37 mmol) were added, and the mixture was stirred for 48 h at 90 °C. After cooled to r.t., orange precipitate was filtered with a glass filter, washed with Et_2O (15 mL), and then dried under vacuum to give the title compound as an orange solid (355.5 mg, 0.463 mmol, 36%). ^{1}H NMR (400 MHz, $CDCl_3$, r.t.) δ 5.24 (s, 2H, CpH), 1.66 (s, 12H, $CpCH_3$), 1.61 (s, 12H, $CpCH_3$). ^{13}C NMR (100.5 MHz, $CDCl_3$, r.t.) δ 92.1 (CpC), 86.4(CpC), 68.0 (CpC), 11.1 ($CpCH_3$), 9.4 ($CpCH_3$).

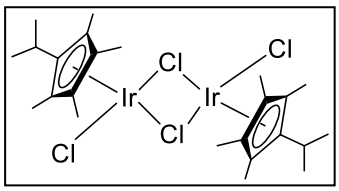
$[Cp^{*Ethyl}IrCl_2]_2$ (1c)[13]



Under an atmosphere of argon, $IrCl_3 \cdot 5H_2O$ (645.6 mg, 1.66 mmol) was placed in 50 mL two-neck flask equipped with a Dimroth condenser and three-way cock. Methanol (13.0 mL) and 5-ethyl-1,2,3,4-tetramethylcyclopentadiene (996.3 mg, 6.63 mmol) were added, and the mixture was stirred for 72 h at 90 °C. After cooled to r.t., the solvent was

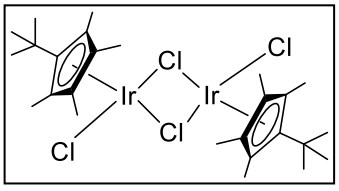
slightly removed by vacuum and orange precipitate was filtered with a glass filter, washed with Et_2O (15 mL), and then dried under vacuum to give the title compound as an orange solid (458.2 mg, 0.519 mmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$, r.t.) δ 2.13 (q, 4H, J = 7.6 Hz, CH_2), 1.58 (s, 12H, $CpCH_3$), 1.56 (s, 12H, $CpCH_3$), 1.05 (t, 6H, J = 7.6 Hz, CH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$, r.t.) δ 89.2 (CpC), 86.6 (CpC), 86.2 (CpC), 17.7 (CH_2), 11.8 (CH_3), 9.4 ($CpCH_3$), 9.2 ($CpCH_3$).

[Cp*$^{i\mathrm{Pr}}$IrCl$_2$]$_2$ (1d)[11c,13]



Under an atmosphere of argon, $IrCl_3 \cdot 5H_2O$ (840.2 mg, 2.16 mmol) was placed in 50 mL two-neck flask equipped with a Dimroth condenser and three-way cock. Methanol (16.6 mL) and 5-isopropyl-1,2,3,4-tetramethylcyclopentadiene (1440.7 mg, 8.77 mmol) were added, and the mixture was stirred for 48 h at 90 °C. After cooled to r.t., orange precipitate was filtered with a glass filter, washed with Et_2O (20 mL), and then dried under vacuum to give the title compound as an orange solid (783.8 mg, 0.919 mmol, 85 %). ^{1}H NMR (400 MHz, $CDCl_3$, r.t.) δ 2.46 (sept, 2H, J = 7.2 Hz, CH), 1.66 (s, 12H, $CpCH_3$), 1.58 (s, 12H, $CpCH_3$), 1.26 (d, 12H, J = 7.2 Hz, CH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$, r.t.) δ 90.4 (CpC), 86.3 (CpC), 86.1 (CpC), 25.3 (CH), 20.7 ($CH(CH_3)_2$), 10.4 ($CpCH_3$), 9.6 ($CpCH_3$).

[Cp*$^{t\mathrm{Bu}}$IrCl$_2$]$_2$ (1e)

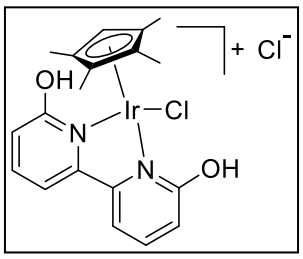


Under an atmosphere of argon, $IrCl_3 \cdot 5H_2O$ (546.5 mg, 1.41 mmol) was placed in 50 mL two-neck flask equipped with a Dimroth condenser and three-way cock. Methanol (11.1 mL) and 5-*tert*-butyl-1,2,3,4-tetramethylcyclopentadiene (1010.0 mg, 5.66 mmol) were added, and the mixture was stirred for 144 h at 90 °C. After cooled to r.t., orange precipitate was filtered with a glass filter, washed with Et_2O (10 mL), and then dried under vacuum to give an orange solid (276.8 mg, 0.314 mmol, 45 %); m.p. > 277.6 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$, r.t.) δ 1.79 (s, 12H, $CpCH_3$), 1.61 (s, 12H, $CpCH_3$), 1.37 (s, 18H, $C(CH_3)_3$). ^{13}C NMR (100.5 MHz, $CDCl_3$, r.t.) δ 92.1 (CpC), 87.4 (CpC), 84.8 (CpC), 33.8 (CMe_3), 30.9 ($C(CH_3)_3$), 13.3 ($CpCH_3$), 10.1 ($CpCH_3$). Anal. Calcd for

$C_{26}H_{42}Cl_4Ir_2$: C, 35.45; H, 4.81. Found: C, 35.05; H, 4.69.

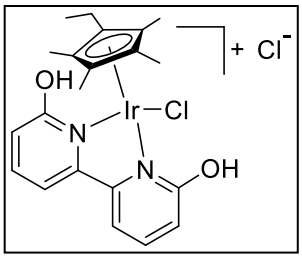
Procedure for the syntheses of [Cp^{R}Ir(6,6'-dihydroxy-2,2'-bipyridine)Cl]Cl

[(η^5-C_5Me_4H)Ir(6,6'-dihydroxy-2,2'-bipyridine)Cl]Cl (2a)



Under an atmosphere of argon, [(η^5-C_5Me_4H)$IrCl_2$]$_2$ (**1a**) (49.8 mg, 0.065 mmol), 6,6'-dihydroxy-2,2'-bipyridine (24.4 mg, 0.130 mmol), methanol (1.1 mL) were placed in 10 mL two-neck test tube flask equipped with a Dimroth condenser and three-way cock. The mixture was stirred for 3 h at 60 °C. After cooled to r.t., the solvent was removed under reduced pressure and the residue was dried under vacuum to give the title compound as a yellow solid (59.3 mg, 0.1036 mmol, 80%); m.p. > 344.9 °C (decomp.); ^{1}H NMR (500 MHz, CD_3OD, r.t.) δ 7.99 (t, 2H, *J* = 7.5 Hz, aromatic), 7.93 (d, 2H, *J* = 7.5 Hz, aromatic), 7.12 (d, 2H, *J* = 8.0 Hz, aromatic), 5.87 (s, CpH), 1.73 (s, $Cp(CH)_3$), 1.68 (s, $Cp(CH)_3$). ^{13}C NMR (100.5 MHz, CD_3OD, r.t.) δ 165.4 ($C_{aromatic}$), 156.1 ($C_{aromatic}$), 143.3 ($C_{aromatic}$), 116.4 ($C_{aromatic}$), 113.9 ($C_{aromatic}$), 92.3 (CpC), 91.9 (CpC), 77.3 (CpC), 10.7 (CH_3), 10.0 (CH_3). Anal. Calcd for $C_{19}H_{21}Cl_2IrN_2O_2$: C, 39.86; H, 3.70; N, 4.89. Found: C, 39.69; H, 3.68; N, 4.77.

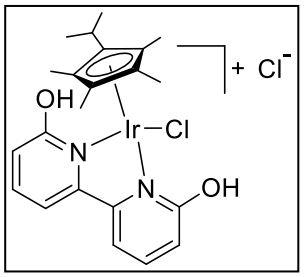
[Cp*^{Ethyl}Ir(6,6'-dihydroxy-2,2'-bipyridine)Cl]Cl (2c)



Under an atmosphere of argon, [Cp*^{Ethyl}$IrCl_2$]$_2$ (**1c**) (106.1 mg, 0.13 mmol), 6,6'-dihydroxy-2,2'-bipyridine (48.7 mg, 0.26 mmol), methanol (2.0 mL) were placed in 10 mL two-neck test tube flask equipped with a Dimroth condenser and three-way cock. The mixture was stirred for 3 h at 60 °C. After cooled to r.t., the solvent was removed under reduced pressure and the residue was dried under vacuum to give the title compound as a yellow solid (121 mg, 0.201 mmol, 78 %); m.p. > 344.7 °C (decomp.); ^{1}H NMR (400 MHz, CD_3OD, r.t.) δ 7.97 (t, 2H, *J* = 8.0 Hz, aromatic), 7.89 (d, 2H, *J* = 7.8 Hz, aromatic), 7.07 (d, 2H, *J* = 8.2 Hz, aromatic), 2.12 (q, 2H, *J* = 7.6 Hz, CH_2), 1.67 (s, 6H, $Cp(CH)_3$), 1.66 (s, 6H, $Cp(CH)_3$), 1.05 (t, 3H, *J* = 8.0 Hz, CH_3). ^{13}C NMR (100.5 MHz, CD_3OD, r.t.) δ 164.1 ($C_{aromatic}$), 154.5 ($C_{aromatic}$), 142.0 ($C_{aromatic}$), 114.8 ($C_{aromatic}$), 112.7 ($C_{aromatic}$), 91.2 (CpC), 89.6 (CpC), 88.9 (CpC), 17.3 (CH_2), 11.0 (CH_3), 8.4 ($CpCH_3$), 8.3

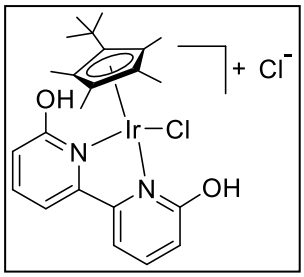
(CpCH$_3$). Anal. Calcd for $C_{21}H_{25}Cl_2IrN_2O_2$: C, 42.00; H, 4.20; N, 4.66. Found: C, 41.90; H, 4.38; N, 4.53.

[Cp*$^{i\mathrm{Pr}}$Ir(6,6'-dihydroxy-2,2'-bipyridine)Cl]Cl (2d)



Under an atmosphere of argon, [Cp*$^{i\mathrm{Pr}}$IrCl$_2$]$_2$ (**1d**) (101.6 mg, 0.12 mmol), 6,6'-dihydroxy-2,2'-bipyridine (44.8 mg, 0.24 mmol), and methanol (2.0 mL) were placed in 10 mL two-neck test tube flask equipped with a Dimroth condenser and three-way cock. The mixture was stirred for 3 h at 60 °C. After cooled to r.t., the solvent was removed under reduced pressure and the residue was dried under vacuum to give the title compound as a yellow solid (121.3 mg, 0.197 mmol, 83 %); m.p. > 342.3 °C (decomp.); ^{1}H NMR (400 MHz, CD$_3$OD, r.t.) δ 7.97 (t, 2H, *J* = 7.6 Hz, aromatic), 7.90 (d, 2H, *J* = 7.8 Hz, aromatic), 7.08 (d, 2H, *J* = 8.2 Hz, aromatic), 2,38 (sept, 1H, *J* = 7.6 Hz, CH), 1.79 (s, 6H, CpCH$_3$), 1.73 (s, 6H, CpCH$_3$), 0.99 (d, 6H, *J* = 7.2 Hz, CH$_3$). ^{13}C NMR (100.5 MHz, CD$_3$OD, r.t.) δ 165.5 (C$_{\mathrm{aromatic}}$), 156.1 (C$_{\mathrm{aromatic}}$), 143.4 (C$_{\mathrm{aromatic}}$), 116.1 (C$_{\mathrm{aromatic}}$), 114.1 (C$_{\mathrm{aromatic}}$), 98.2 (CpC), 88.3 (CpC), 86.9 (CpC), 26.8 (CH), 20.5 (CH$_3$), 11.6 (CpCH$_3$), 9.4 (CpCH$_3$). Anal. Calcd for $C_{22}H_{27}Cl_2IrN_2O_2$: C, 43.00; H, 4.43; N, 4.56. Found: C, 42.60; H, 4.74; N, 4.42.

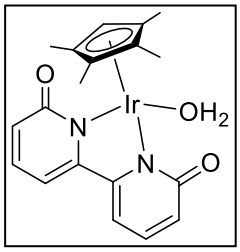
[Cp*$^{t\mathrm{Bu}}$Ir(6,6'-dihydroxy-2,2'-bipyridine)Cl]Cl (2e)



Under an atmosphere of argon, [Cp*$^{t\mathrm{Bu}}$IrCl$_2$]$_2$ (**1e**) (36.3 mg, 0.04 mmol), 6,6'-dihydroxy-2,2'-bipyridine (15.7 mg, 0.08 mmol), and methanol 0.7 mL were placed in 10 ml two-neck test tube flask equipped with a Dimroth condenser and three-way cock. The mixture was stirred for 3 h at 60 °C. After cooled to r.t., the solvent was removed under reduced pressure and the residue was dried under vacuum to give the title compound as a yellow solid (44.2 mg, 0.0703 mmol, 86 %); m.p. > 344.6 °C (decomp.); ^{1}H NMR (400 MHz, CD$_3$OD, r.t.) δ 7.99 (t, 2H, *J* = 7.6 Hz, aromatic), 7.94 (d, 2H, *J* = 8.0 Hz, aromatic), 7.08 (d, 2H, *J* = 8.0 Hz, aromatic), 1.88 (s, 6H, CpCH$_3$), 1.82 (s, 6H, CpCH$_3$), 0.93 (s, 9H, CH$_3$). ^{13}C NMR (100.5 MHz, CD$_3$OD, r.t.) δ 165.4 (C$_{\mathrm{aromatic}}$), 156.2 (C$_{\mathrm{aromatic}}$), 143.5 (C$_{\mathrm{aromatic}}$), 116.1 (C$_{\mathrm{aromatic}}$), 114.2 (C$_{\mathrm{aromatic}}$), 101.8 (CpC), 88.9 (CpC), 84.4 (CpC), 34.3 (CMe$_3$), 30.3 (CH$_3$), 15.0 (CpCH$_3$), 9.6 (CpCH$_3$).

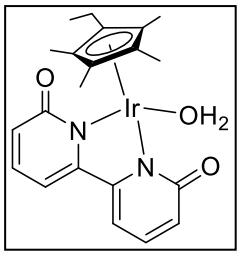
Procedure for the syntheses of $Cp^{R}Ir$(2.2'-bipyridine-6,6'-dionato)H_2O

(η^5-C_5Me_4H)Ir(2,2'-bipyridine-6,6'-dionato)H_2O (3a)



Under an atmosphere of argon, [(η^5-C_5Me_4H)$IrCl_2$]$_2$ (**1a**) (203.8 mg, 0.27 mmol), 6,6'-dihydroxy-2,2'-bipyridine (99.8 mg, 0.53 mmol), methanol 6.4 mL were placed in 30 mL two-neck round flask equipped with a Dimroth condenser and three-way cock. The mixture was stirred for 3 h at 60 °C. After cooled to r.t., the solvent was removed under reduced pressure and the residue was dried under vacuum overnight to give a yellow solid. Sodium *tert*-butoxide (102.6 mg, 1.07 mmol) and degassed H_2O (9.3 mL) were added to the same flask and stirred for 3 h at r.t.. After the reaction, the precipitate was filtered by cannulation through glass filter under argon atmosphere and dried under vacuum. CH_2Cl_2 (35 mL) was added to dissolve the solid. Solution was collected in flask and the solvent was evaporated. CH_2Cl_2 (1 mL) was added, followed by the addition of hexane (15 mL) for reprecipitation. Resulted solid was filtered with glass filter and washed with H_2O (10 mL), affording the title compound as a green yellow solid (158.3 mg, 0.306 mmol, 57%) after drying under vacuum. m.p. > 288.9 °C (decomp.); ^{1}H NMR (400 MHz, CD_3OD, r.t.) δ 7.45 (br t, 2H, J = 8.0 Hz, aromatic), 6.71 (br d, 2H, J = 7.2 Hz, aromatic), 6.51 (br d, 2H, J = 6.8 Hz aromatic), 5.85 (br s, 1H, CpH), 1.72 (br s, 6H, $CpCH_3$), 1.52 (br s, 6H, $CpCH_3$). ^{1}H NMR (500 MHz, CD_3OD, 60 °C) δ 7.23 (t, 2H, , J = 12 Hz, aromatic), 6.92 (d, 2H, J = 9.0 Hz, aromatic), 6.64 (br, 2H, aromatic), 5.60 (br, 1H, CpH), 1.59 (s, 6H, $CpCH_3$), 1.43 (s, 6H, $CpCH_3$). ^{13}C NMR (100.5 MHz, CD_3OD, 60 °C) δ 171.4 ($C_{aromatic}$), 157.7 ($C_{aromatic}$), 139.7 ($C_{aromatic}$), 118.5 ($C_{aromatic}$), 107.5 ($C_{aromatic}$), 92.0 (CpC), 88.7 (CpC), 74.4 (CpC), 10.7 ($CpCH_3$), 9.9 ($CpCH_3$). Anal. Calcd for $C_{19}H_{21}IrN_2O_3$: C, 44.09; H, 4.09; N, 5.41. Found: C, 43.84; H, 3.96; N, 5.39.

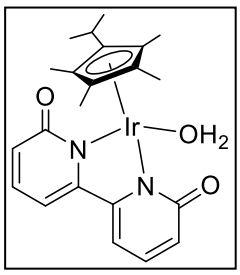
$Cp^{*Ethyl}Ir$(2,2'-bipyridine-6,6'-dionato)H_2O (3c)



Under an atmosphere of argon, [$Cp^{*Ethyl}IrCl_2$]$_2$ (**1c**) (198.2 mg, 0.24 mmol), 6,6'-dihydroxy-2,2'-bipyridine (90.4 mg, 0.48 mmol), and methanol (5.8 mL) were placed in 30 mL two-neck round flask equipped with a Dimroth condenser and three-way cock. The mixture was stirred for 3 h at 60 °C. After cooled to r.t., the solvent was removed under reduced pressure and the residue was dried under vacuum overnight to give a yellow solid.

Sodium *tert*-butoxide (92.3 mg, 0.96 mmol) and degassed H_2O (8.4 mL) were added to the same flask and stirred for 3 h at r.t. After the reaction, the precipitate was filtered by cannulation through glass filter under argon atmosphere and dried under vacuum. CH_2Cl_2 (35 mL) was added to dissolve the solid. Solution was collected in flask and the solvent was evaporated. CH_2Cl_2 (1 mL) was added, followed by the addition of hexane (15 mL) for reprecipitation. Resulted solid was filtered with glass filter and washed with H_2O (8 mL). The title compound was obtained as a green yellow solid (141.3 mg, 0.259 mmol, 57%) after drying under vacuum. m.p. > 272.3 °C (decomp.); ^{1}H NMR (400 MHz, CD_3OD, 60 °C) δ 7.42 (t, 2H, J = 6.5 Hz, aromatic), 6.90 (d, 2H, J = 6.5 Hz, aromatic), 6.52 (br s, 2H, aromatic), 1.95 (br s, 2H, CH_2), 1.47 (s, 12H, $CpCH_3$), 0.93 (br s, 3H, CH_3). ^{13}C NMR (100.5 MHz, CD_3OD, 60 °C) δ 171.3 ($C_{aromatic}$), 157.2 ($C_{aromatic}$), 139.5 ($C_{aromatic}$), 118.3 ($C_{aromatic}$), 106.7 ($C_{aromatic}$), 90.0 (CpC), 88.2 (CpC, two peaks may be overlapped), 18.7 (CH), 11.9 (CH_3), 9.7 ($CpCH_3$, two peaks may be overlapped). Anal. Calcd for $C_{21}H_{25}IrN_2O_3$: C, 46.23; H, 4.62; N, 5.13. Found: C, 46.13; H, 4.56; N, 5.11.

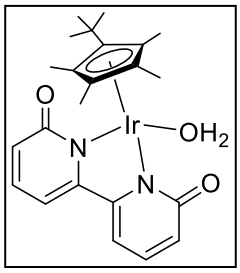
Cp*$^{i\mathrm{Pr}}$Ir(2,2'-bipyridine-6,6'-dionato)H_2O (3d)



Under an atmosphere of argon, [Cp*$^{i\mathrm{Pr}}$$IrCl_2$]$_2$ (**1d**) (159.3 mg, 0.19 mmol), 6,6'-dihydroxy-2,2'-bipyridine (70.8 mg, 0.38 mmol), and methanol (4.4 mL) were placed in 30 ml two-neck round flask equipped with a Dimroth condenser and three-way cock. The mixture was stirred for 3 h at 60 °C. After cooled to r.t., the solvent was removed under reduced pressure and the residue was dried with vacuum overnight to give a yellow solid. Sodium *tert*-butoxide (71.8 mg, 0.75 mmol) and degassed H_2O (6.6 mL) were added to the same flask and stirred for 3 h at r.t.. After the reaction, the precipitate was filtered by cannulation through glass filter under argon atmosphere and dried under vacuum. $CHCl_3$ (35 mL) was added to dissolve the solid. The solution was collected in flask and solvent was evaporated. $CHCl_3$ (1 mL) was added, followed by the addition of hexane (10 mL) for reprecipitation. Resulted solid was filtered with glass filter and washed with H_2O (8 mL). Title compound was obtained as a green yellow solid (87 mg, 0.155 mmol, 42 %) after drying under reduced pressure. m.p. > 274.7 °C (decomp.); ^{1}H NMR (400 MHz, CD_3OD, r.t.) δ 7.43 (t, 2H, J = 7.6 Hz, aromatic), 6.93 (d, 2H, J = 6.0 Hz, aromatic), 6.42 (d, 2H, J = 7.2 Hz,

aromatic), 2.16 (br sept, 1H, J = 3.6 Hz CH), 1.83 (br s, 6H, $CpCH_3$), 1.71 (br s, 6H, $CpCH_3$), 0.94 (br d, 6H, J = 6.4 Hz, CH_3). ^{1}H NMR (400 MHz, CD_3OD, 60 °C) δ 7.40 (t, 2H, J = 10.5 Hz, aromatic), 6.88 (d, 2H, J = 9.0 Hz, aromatic), 6.43 (br s, 2H, J = 11.0 Hz, aromatic), 2.22 (sept, 1H, J = 9.0 Hz, CH), 1.77 (s, 6H, $CpCH_3$), 1.70 (s, 6H, $CpCH_3$), 0.97 (d, 6H, J = 9.0 Hz, CH_3). ^{13}C NMR (100.5 MHz, CD_3OD, 60 °C) δ 171.2 ($C_{aromatic}$), 157.6 ($C_{aromatic}$), 139.6 ($C_{aromatic}$), 118.2 ($C_{aromatic}$), 106.4 ($C_{aromatic}$), 94.5 (CpC), 89.0 (CpC), 81.5 (CpC), 26.8 (CH), 20.1 (CH_3), 11.2 ($CpCH_3$), 9.7 ($CpCH_3$). Anal. Calcd for $C_{22}H_{27}IrN_2O_3$: C, 47.21; H, 4.86; N, 5.01. Found: C, 47.41; H, 4.98; N, 4.90.

Cp*$^{t\mathrm{Bu}}$Ir(2,2'-bipyridine-6,6'-dionato)H_2O (3e)



Under an atmosphere of argon, $[Cp^{t\mathrm{Bu}}IrCl_2]_2$ (**1e**) (146.5 mg, 0.17 mmol), 6,6'-dihydroxy-2,2'-bipyridine (63.2 mg, 0.34 mmol), and methanol (4.0 mL) were placed in 30 mL two-neck round flask equipped with a Dimroth condenser and three-way cock. The mixture was stirred for 3 h at 60 °C. After cooled to r.t., the solvent was removed under reduced pressure and dried under vacuum overnight to give a yellow solid. Sodium *tert*-butoxide (65.5 mg, 0.68 mmol) and degassed H_2O (6.6 mL) were added to the same flask and stirred for 3 h at r.t.. After the reaction, the precipitate was filtered by cannulation through glass filter under argon atmosphere and dried under vacuum. $CHCl_3$ (55 mL) was added to dissolve the solid. The solution was collected in flask and solvent was evaporated. $CHCl_3$ (1 mL) was added, followed by the addition of hexane (15 mL) for reprecipitation. Resulted solid was filtered with glass filter and washed with H_2O (10 mL). The title compound was obtained as a green yellow solid (121.1 mg, 0.211 mmol, 63.6 %) after drying under vacuum. m.p. > 280.2 °C (decomp.); ^{1}H NMR (400 MHz, CD_3OD, r.t.) δ 7.43 (t, 2H, J = 7.6 Hz, aromatic), 6.96 (d, 2H, J = 6.8 Hz, aromatic), 6.43 (br d, 2H, J = 4.8 Hz), 1.93 (s, $CpCH_3$), 1.80 (s, $CpCH_3$), 0,90 (s, CH_3), ^{13}C NMR (100.5 MHz, CD_3OD, r.t.) δ 170.7 ($C_{aromatic}$), 157.8 ($C_{aromatic}$), 140.0 ($C_{aromatic}$), 118.1 ($C_{aromatic}$), 106.8 ($C_{aromatic}$), 100.2 (CpC), 90.6 (CpC), 74.5 (CpC), 33.7 (CH), 29.8 (CH_3), 14.8 ($CpCH_3$), 10.1 ($CpCH_3$), Anal. Calcd for $C_{23}H_{29}IrN_2O_3$: C, 48.15; H, 5.10; N, 4.88. Found: C, 48.36; H, 5.15; N, 4.90.

Investigation of catalytic activity in dehydrogenation of 1-phenylethanol (4)

Under an atmosphere of argon, Ir catalyst (1.0 mol%), THF (6.0 mL), 1-phenylethanol (**4**) (1.0 mmol) were placed in 50 mL two-neck round flask equipped with a Dimroth condenser and three-way cock. It was stirred for 1 h at 106 °C (oil bath temperature) under the reflux. After the reaction, THF (24 mL) and undecane (internal standard) were added and stirred. Conversion and yield were determined by GC. Average of three runs are shown.

Investigation of catalytic activity in dehydrogenation of benzyl alcohol (6)

Under an atmosphere of argon, Ir catalyst (0.5 mol%), toluene (20 mL), benzylalcohol (**6**) (0.5 mmol) were placed in 50 mL two-neck round flask equipped with a Dimroth condenser and three-way cock. It was stirred for 1 h at 131 °C (oil bath temperature) under the reflux. After the reaction, toluene (10 mL) and biphenyl (internal standard) were added and stirred. Conversion and yield were determined by GC.

Investigation of catalytic activity in dehydrogenation of 2-octanol (8)

Under an atmosphere of argon, Ir catalyst (1.0 mol%), THF (6 mL), 2-octanol (**8**) (1.0 mmol) were placed in 30 mL two-neck round flask equipped with a Dimroth condenser and three-way cock. It was stirred at 131 °C (oil bath temperature) under the reflux. After reaction, toluene (14 mL) and biphenyl (internal standard) were added and stirred. Conversion and yield were determined by GC.

Investigation of catalytic activity in dehydrogenation of 2-MeTHQ (10)

Under an atmosphere of argon, Ir catalyst (1.0 mol%), toluene (3 mL), 2-methyl-1,2,3,4-tetrahydroquinoline (**10**) (1.0 mmol) were placed in 30 mL two-neck round flask equipped with a Dimroth condenser and three-way cock. It was stirred for 20 h at 131 °C (oil bath temperature) under the reflux. After reaction, toluene (14 mL) and undecane (internal standard) were added and stirred. Conversion and yield were determined by GC.

X-ray crystallographic analyses

Crystallographic data of **1e** was collected on a Rigaku/R Axis Rapid diffractometer with CrystalClear (Rigaku). Crystallographic data of **2a** and **2e** were collected on a Rigaku/Saturn

70 CCD diffractometer and processed with CrystalClear (Rigaku). Calculations for **1e** was performed with the CrystalStructure software package (Rigaku). Calculations for **2a** and **2e** were performed with the Olex2 software package (Rigaku).

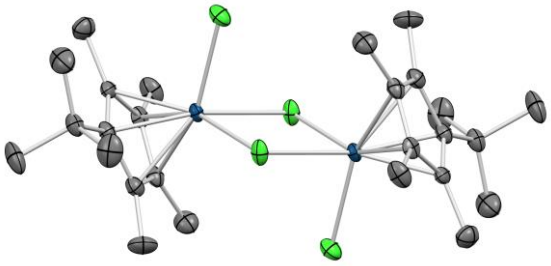


Figure S1. ORTEP illustration of **1e**. Hydrogen atoms are omitted for clarity.

Table S1. Crystal data of 1e.

Empirical Formula	$C_{26}H_{42}Cl_4Ir_2$
Formula Weight	880.87
Crystal Color, Habit	orange, block
Crystal System	triclinic
Lattice Parameters	
a (Å)	8.3751(10)
b (Å)	9.2021(9)
c (Å)	9.6358(11)
α (°)	102.832(3)
β (°)	99.083(4)
γ (°)	100.880(3)
V (Å ^{3})	695.41(13)
Space Group	P-1 (#2)
Z value	1
D_{calc} (g cm^{-3})	2.103
F_{000}	420.00

Radiation	MoKα (λ = 0.71075 Å) graphite monochromated
Temperature (°C)	–100.0
Max 2θ (°)	54.9
No. of Reflections Measured	Total: 6650
Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares on F^2
No. Observations (All reflections)	3092
No. Variables	166
Reflection/Parameter Ratio	18.63
Residuals: R_1; wR_2	0.0296; 0.0389
Residuals: *R* (All reflections)	0.0304
Goodness of Fit Indicator	1.003
Max Shift/Error in Final Cycle	0.000
Maximum peak in Final Diff. Map (e^- Å^{-3})	2.24
Minimum peak in Final Diff. Map (e^- Å^{-3})	–2.18

Table S2. Crystal data of 2a.

Empirical Formula	$C_{20}H_{25}Cl_2N_2O_3Ir$
Formula Weight	604.52
Crystal Color, Habit	yellow, platelet
Crystal System	orthorhombic
Lattice Parameters	
a (Å)	16.891(2)
b (Å)	14.4978(18)
c (Å)	17.310(2)
V (Å ^{3})	4238.8(9)
Space Group	P*bca* (#61)
Z value	8
D_{calc} (g cm^{-3})	1.895
F_{000}	2352.0
Radiation	MoKα (λ = 0.71075 Å) graphite monochromated
Temperature (℃)	–100.0
Max 2θ (°)	55.0
No. of Reflections Measured	Total: 32707
Structure Solution	Direct Methods (SHELXT Version 2015)
Refinement	Full-matrix least-squares on F^2
No. Observations (All reflections)	4852
No. Variables	261
Reflection/Parameter Ratio	18.59
Residuals: R_1; wR_2	0.0416; 0.1070
Residuals: *R* (All reflections)	0.0450
Goodness of Fit Indicator	1.033
Max Shift/Error in Final Cycle	0.002
Maximum peak in Final Diff. Map (e$^-$ Å $^{-3}$)	2.371
Minimum peak in Final Diff. Map (e$^-$ Å $^{-3}$)	–4.090

Table S3. Crystal data of 2e.

Empirical Formula	$C_{47}H_{62}Cl_4N_4O_5Ir_2$
Formula Weight	1289.20
Crystal Color, Habit	yellow, platelet
Crystal System	orthorhombic
Lattice Parameters	
a (Å)	13.240(3)
b (Å)	11.975(2)
c (Å)	32.330(6)
V (Å^3)	5125.9(18)
Space Group	P*nma* (#62)
Z value	4
D_{calc} (g cm^{-3})	1.671
F_{000}	2536.0
Radiation	MoKα (λ = 0.71075 Å) graphite monochromated
Temperature (°C)	–130.0
Max 2θ (°)	55.0
No. of Reflections Measured	Total: 40989
Structure Solution	Direct Methods (SHELXT Version 2015)
Refinement	Full-matrix least-squares on F^2
No. Observations (All reflections)	6136
No. Variables	312
Reflection/Parameter Ratio	19.67
Residuals: R_1; wR_2	0.0584; 0.1362
Residuals: *R* (All reflections)	0.0628
Goodness of Fit Indicator	1.170
Max Shift/Error in Final Cycle	0.001
Maximum peak in Final Diff. Map (e$^-$ Å^{-3})	2.961
Minimum peak in Final Diff. Map (e$^-$ Å^{-3})	–2.022

The data for Hammett plot based on the yield of dehydrogenation of 1-phenylethanol.[12]

catalyst	σ_p	Cp(yield)	log(Cp/Me$_4$Cp)
3a	0	35	0
3d	-0.15	55	0.180208
3b	-0.17	57	0.211807
3c	-0.15	53	0.196295
3e	-0.20	64	0.262112

The data for Hammett Plot based on the yield of dehydrogenation of 2-octanol.[12]

catalyst	σ_p	Cp(yield)	log(Cp/Me$_4$Cp)
3a	0	19	0
3b	-0.15	49	0.434924
3e	-0.20	57	0.500602

The data for Hammett Plot based on the yield of dehydrogenation of benzyl alcohol.[12]

catalyst	σ_p	Cp(yield)	log(Cp/Me$_4$Cp)
3a	0	41	0
3b	-0.15	46	0.049974
3e	-0.20	48	0.068457

The data for Hammett Plot based on the yield of dehydrogenation of 2-methyl-1,2,3,4-tetrahydroquinoline.[12]

catalyst	σ_p	Cp(yield)	log(Cp/Me$_4$Cp)
3a	0	55	0
3d	-0.15	62	0.052029
3b	-0.17	91	0.218679
3c	-0.15	83	0.178725
3e	-0.20	99	0.255273

2.5. References

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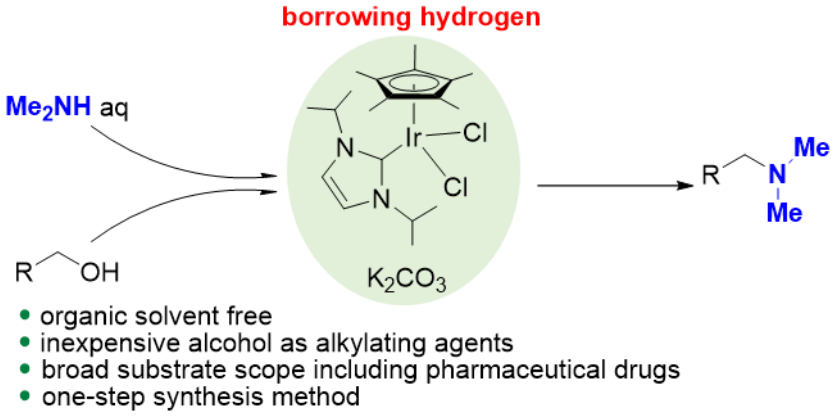
Chapter 3

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

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.



3.1. 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.

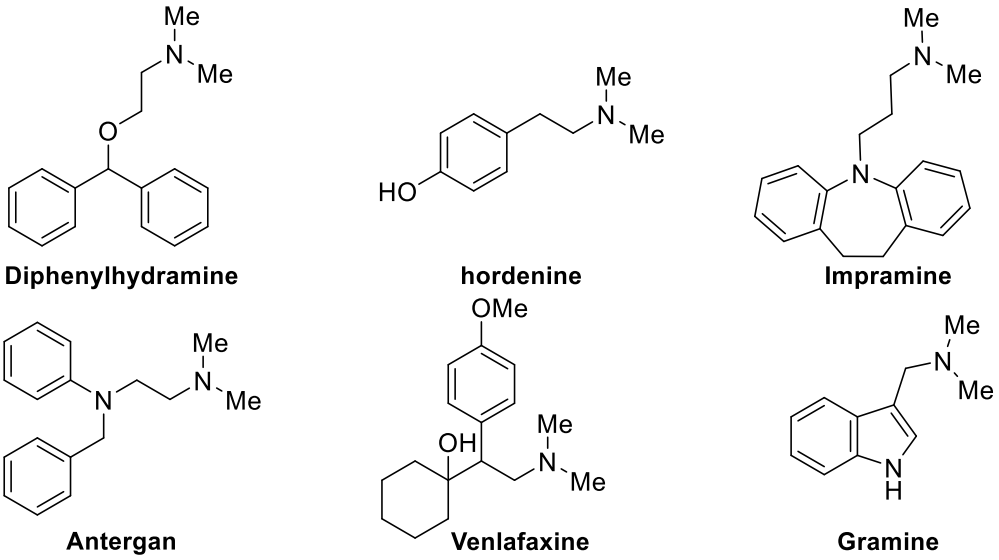
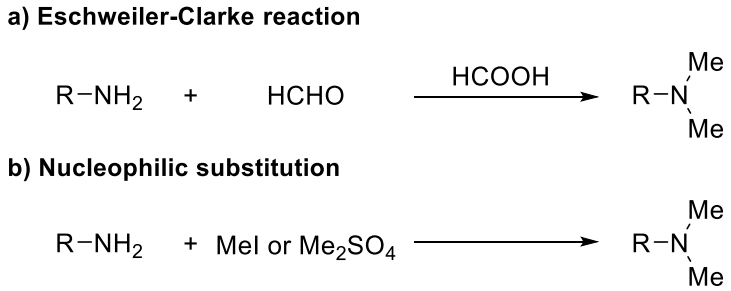


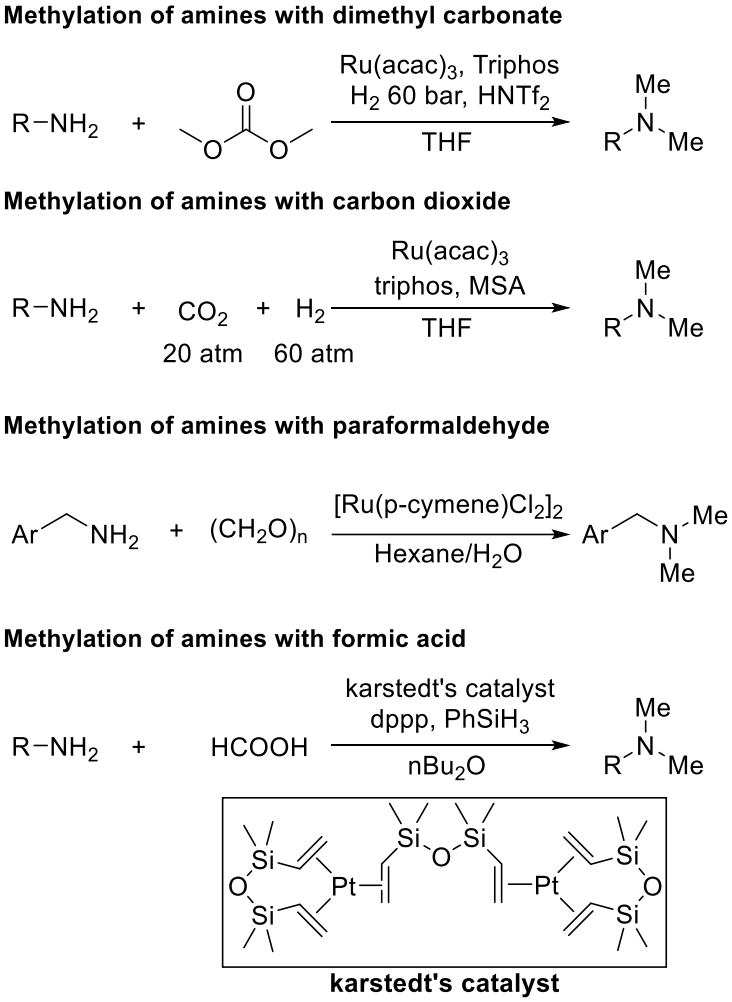
Figure 1. Representative drugs containing the *N,N*-dimethylamine moiety.

The Eschweiler-Clarke reaction, which achieves *N*-methylation using amine and formaldehyde, has been established as a conventional synthetic method in the industry (Scheme 1a).[2] Furthermore, nucleophilic substitution using methyl halide[3] or dimethyl sulfate[4] is well known (Scheme 1b). However, these reactions have significant disadvantages as they use toxic reagents, produce a large amount of waste, and in many cases, suffer from low selectivity.



Scheme 1. Conventional synthetic methods for *N,N*-dimethylamine derivatives.

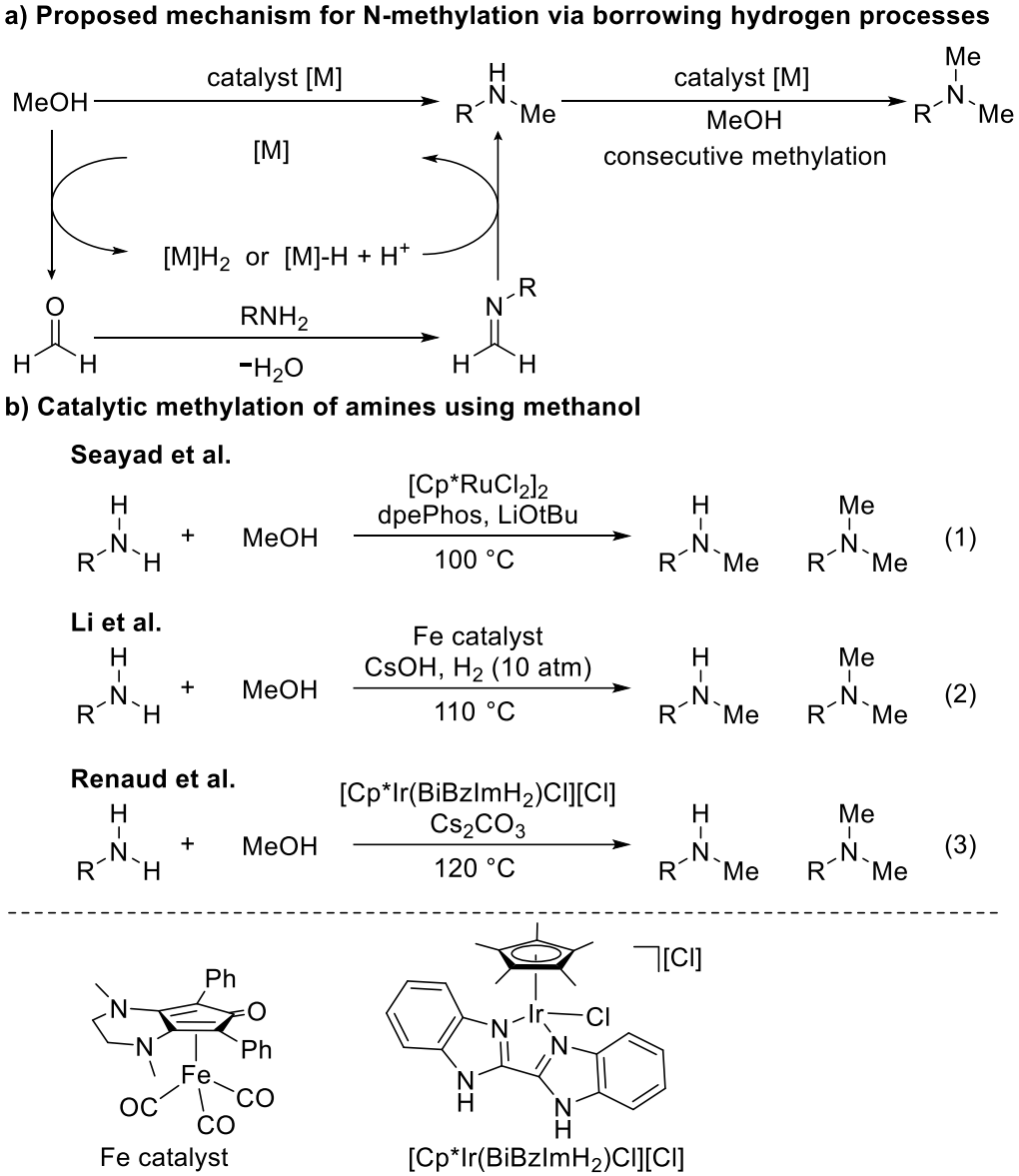
To overcome these drawbacks, transition-metal-catalyzed *N*-methylation of amines utilizing methyl reagents[5] such as dimethyl carbonate,[5a] carbon dioxide,[6] paraformaldehyde,[7] or formic acid[8] has been successfully developed (Scheme 2). However, these reactions require a reductant, are performed under harsh conditions (high temperature and pressure), and have low selectivity.



Scheme 2. Catalytic methylation for synthesis of *N,N*-dimethylamine derivatives using several methylation reagents.

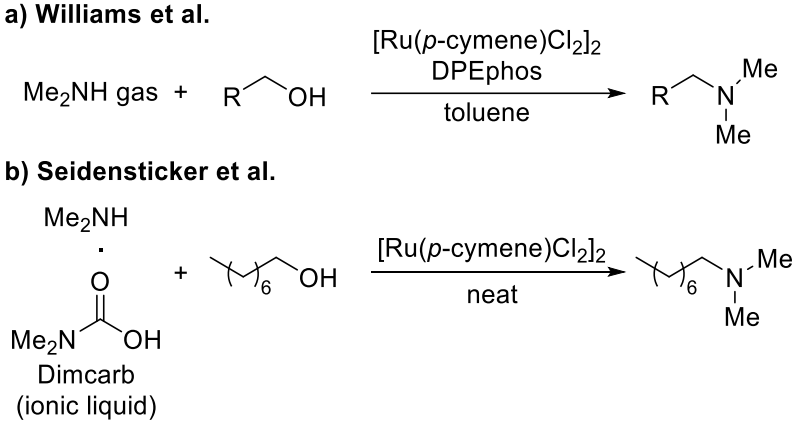
Thus, the construction of a C−N bond through a catalytic "borrowing hydrogen strategy," using amines and alcohols, has been regarded as a clean and atom-efficient method.[9] The overall reaction consists of several consecutive processes including dehydrogenation, imine formation, and transfer hydrogenation (Scheme 3a). 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 (Scheme 3b).[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.[11]



Scheme 3. Catalytic methylation of amines using methanol.

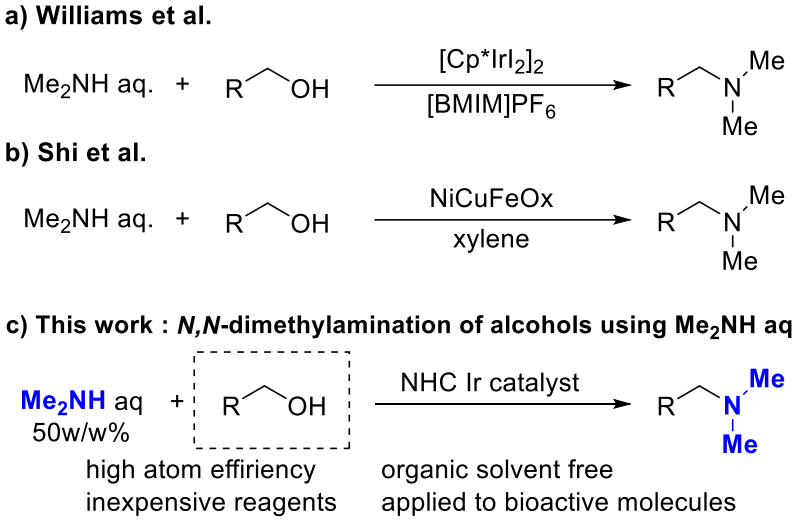
By contrast, *N,N*-dimethylamination utilizing alcohols, via borrowing hydrogen processes, is an efficient method to obtain dimethylamine derivatives.[12] Alcohols are good alkylating reagents considering their low toxicity, price, and availability. Therefore, *N,N*-dimethylamination using alcohol and 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 (Scheme 4). 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] For example, in 2009, Williams et al succeeded in ruthenium-catalyzed *N,N*-dimethylamination of alcohols with dimethylamine gas (Scheme 4a). In addition, recently, Seidensticker et al. also reported *N,N*-dimethylamination of alcohols with dimcarb ionic liquid (*N,N*-dimethylammonium-*N,N*-dimethyl carbamate) as dimethylamine source (Scheme 4b).



Scheme 4. Catalytic *N,N*-dimethylamination utilizing alcohols with dimethylamine gas or dimethylammonium salt.

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. As works using an aqueous solution of dimethylamine, Williams reported dimethylamination with an aqueous solution of dimethylamine, but it is necessary to use ionic liquid as a solvent (Scheme 5a). Shi et al. also developed heterogeneous catalysis for synthesis of *N,N*-dimethylamine derivatives using an aqueous solution of dimethylamine and xylene as a solvent (Scheme 5b).



Scheme 5. Dimethylamination of alcohols with an aqueous solution of dimethylamine.

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]

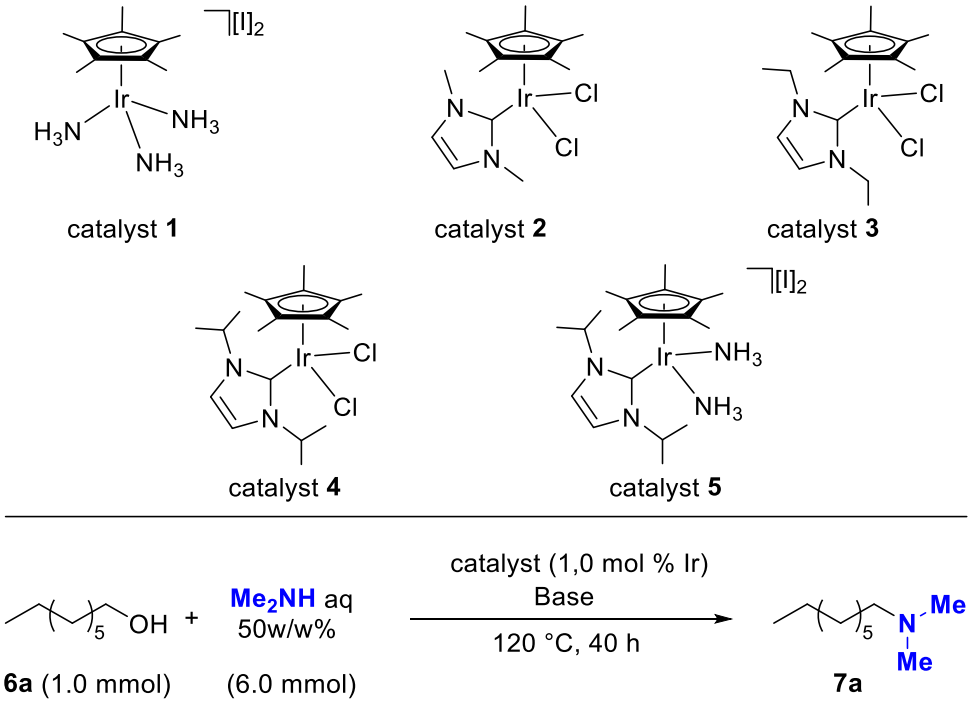
Our research group (Fujita and Yamaguchi) has previously developed and reported *N*-alkylation using alcohols and a series of efficient catalysts.[15] In this study, the aurthor discovered that an iridium catalyst with an *N*-heterocyclic carbene (NHC) ligand exhibited good catalytic activity in the *N,N*-dimethylamination of alcohols using commercially available aqueous dimethylamine (Scheme 5c). Moreover, an environmentally benign synthetic method was developed based on organic solvent-free reaction system. Based on this, the author examined synthetic methods for obtaining valuable dimethylamine derivatives with important applications.

3.2. Results and Discussion

To obtain dimethylamine derivatives, the author 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, the author expected that an iridium catalyst including an NHC ligand would be effective for *N,N*-dimethylamination by aqueous 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 **4**, which has dichloride ligand, exhibited the best performance and resulted in a 91% (Table 1, entry 6). The author 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.

Table 1. Optimization of conditions for *N,N*-dimethylamination of 1-octanol with aqueous dimethylamine.[a]

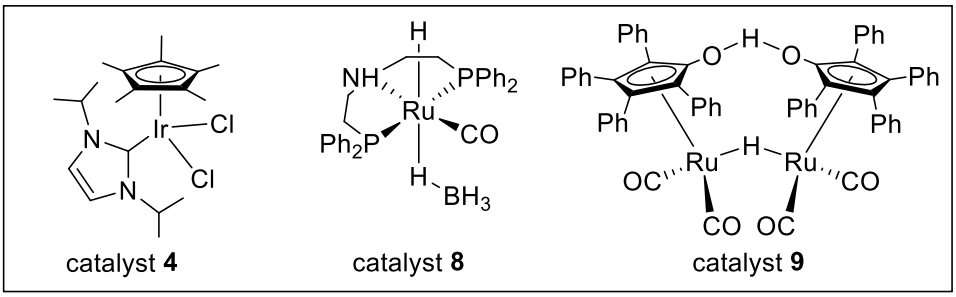


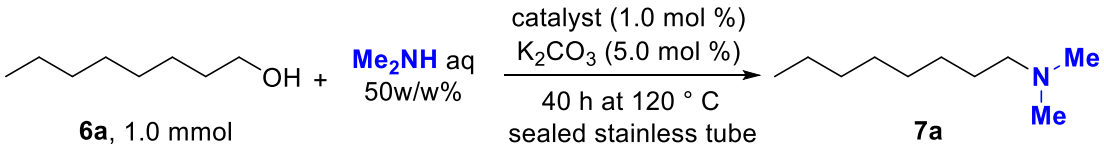
entry	catalyst	base (mol %)	conv. (%)[b]	yield (%)[b]
1	$[Cp^*IrCl_2]_2$	K_2CO_3 (5)	18	13
2	$[IrCl(cod)]_2$	K_2CO_3 (5)	8	8
3	**1**	K_2CO_3 (5)	24	15
4	**2**	K_2CO_3 (5)	35	35
5	**3**	K_2CO_3 (5)	82	77
6	**4**	K_2CO_3 (5)	92	91
7	**5**	K_2CO_3 (5)	92	85
8	**4**	none	63	62
9	**4**	K_2CO_3 (2.5)	86	83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

In addition to this, other catalysts having activity for borrowing hydrogen reaction were also explored (Table 2).

Table 2. Investigation for *N,N*-dimethylamination with other catalysts.[a]





6a, 1.0 mmol

7a

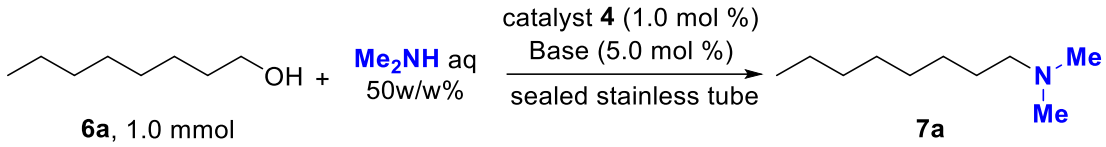
entry	catalyst	conv. (%)[b]	yield (%)[b]
1	**4**	92	91
2	$[Cp^*RhCl_2]_2$	1	0
3	$Co(acac)_2$	0	0
4	$PdCl_2$/dppe	0	0
5	**8**	64	54
6	**9**	28	33
7	$[Ru(p\text{-cymene})Cl_2]_2$	11	11
8	$RuCl_2(PPh_3)_3$	30	27

[a]Reaction was carried out with 1-octanol (1.0 mmol), dimethylamine (6.0 mmol), K_2CO_3 (5 mol %), and the catalyst (1.0 mol % metal) at 120 °C for 40 h. [b]Determined by GC analysis using biphenyl as an internal standard.

When $[Cp^*RhCl_2]_2$, $Co(acac)_2$, $PdCl_2$/dppe were used, *N,N*-dimethyloctylamine was not obtained (Table 2, entry 2-4). On the other hand, ruthenium complexes showed catalytic activity (Table 2, entry 5-8). In particular, when Ru-MACHO catalyst **8** and Shvo catalyst **9** were used, the yield was increased, but they showed lower activity than Ir catalyst **4**. The

author speculates that the reason for the high activity of catalyst **4** is due to the stability of the NHC ligand and solubility in water. The author additionally investigated the dimethylamine amounts (Table 3, entry 1-4), temperatures (Table 3, entry 5 and 6), reaction times (Table 3, entry 7), and bases (Table 3, entry 8-13). Then, optimized condition was determined.

Table 3. Optimization of the amount of dimethylamine, reaction time and temperatures, and bases.



6a, 1.0 mmol **7a**

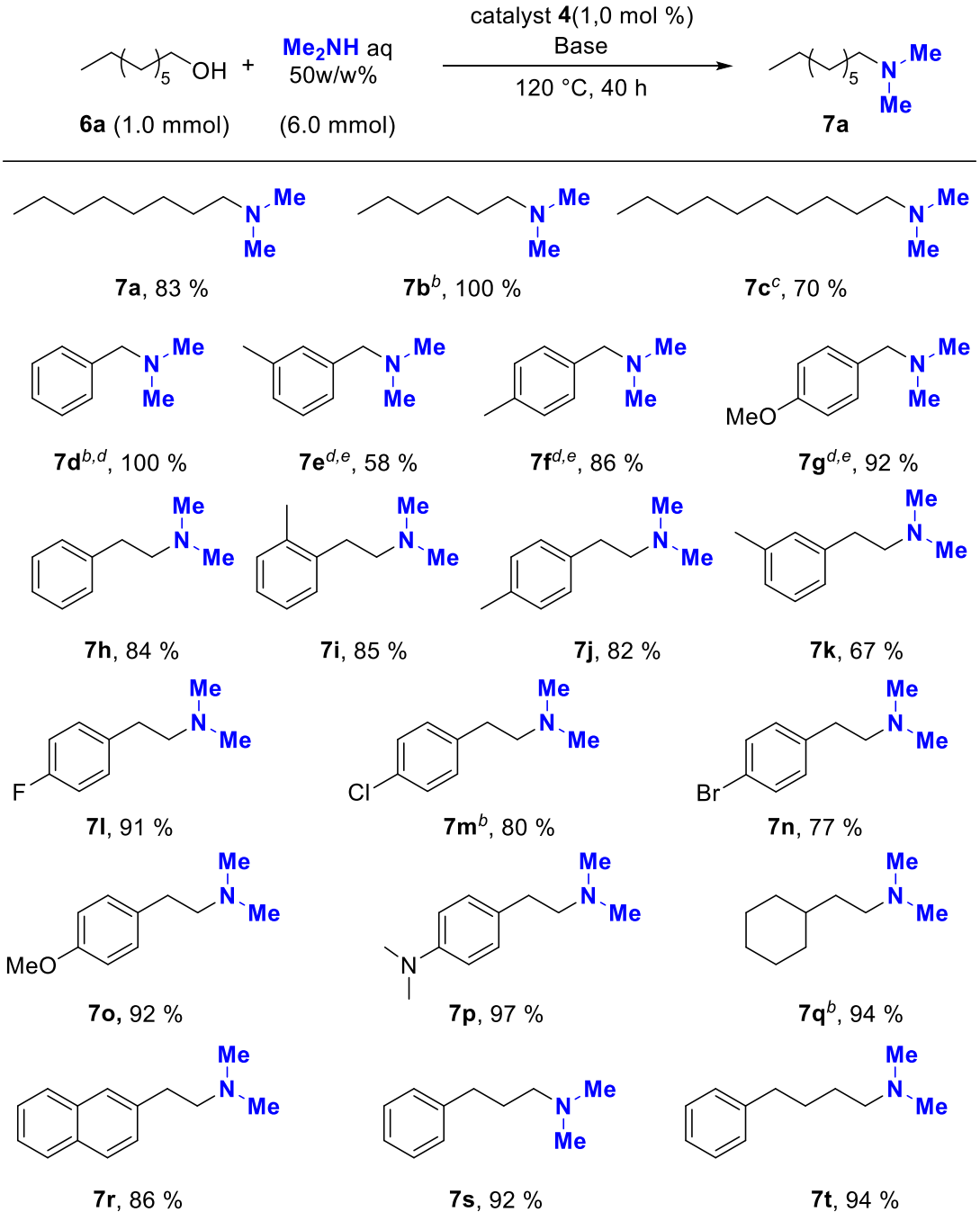
entry	Me_2NH (mmol)	base	*t* (h)	temp. (°C)	conv. (%)[b]	yield (%)[b]
1	6	K_2CO_3	40	120	92	91
2	2	K_2CO_3	40	120	76	70
3	4	K_2CO_3	40	120	83	80
4	8	K_2CO_3	40	120	93	92
5	6	K_2CO_3	40	100	75	74
6	6	K_2CO_3	40	140	96	92
7	6	K_2CO_3	20	120	78	78
8	6	None	40	120	63	62
9	6	$NaHCO_3$	40	120	68	65
10	6	Cs_2CO_3	40	120	93	90
11	6	Na_2CO_3	40	120	93	89
12	6	MeONa	40	120	89	89
13	6	^{t}BuOK	40	120	90	87

[a]Reaction was carried out with 1-octanol (1.0 mmol), dimethylamine (2.0-8.0 mmol), base (0-5 mol %), and the catalyst (1.0 mol % metal) at 100-140 °C for 20-40 h. [b]Determined by GC analysis using biphenyl as an internal standard.

After identifying suitable conditions for the reaction, the author 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 **4**, 120 °C, 40 h). The obtained dimethylamine derivatives are illustrated in Scheme 6. 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, the author 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** and **7j**). Moreover, phenethylalcohol with an electron-withdrawing group such as a halogen and phenethylalcohol with an electrondonating methoxy or dimethylamino group afforded the desired products (**7l**−**7p**). Interestingly, saturated cyclic alcohol (2-cyclohexylethanol) and 2-naphthalene ethanol were also tolerated as substrates (**7q** and **7r**). 3-Phenyl-1-propanol 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.

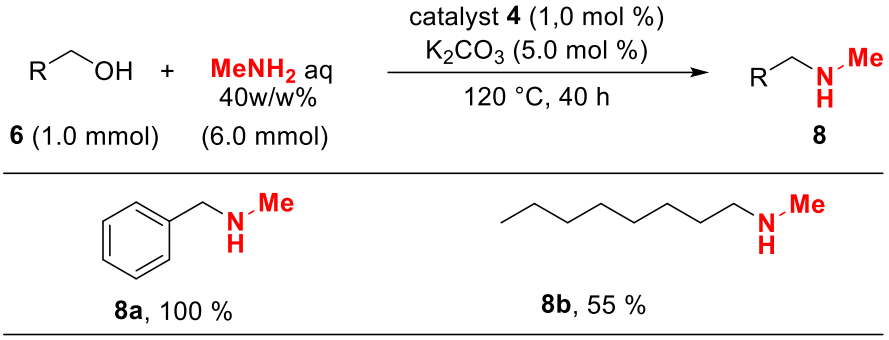
Scheme 6. *N,N*-Dimethylamination of various primary alcohols.[a]



[a]Reaction was carried out with primary alcohol (1.0 mmol), dimethylamine (6.0 mmol), catalyst **4** (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 **4** (0.5 mol %) was used. Isolated yields are shown.

The author 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 7, **8a** and **8b**). These results were expected that this catalyst system would be applied in synthesis of *N*-monomethylamine derivatives.

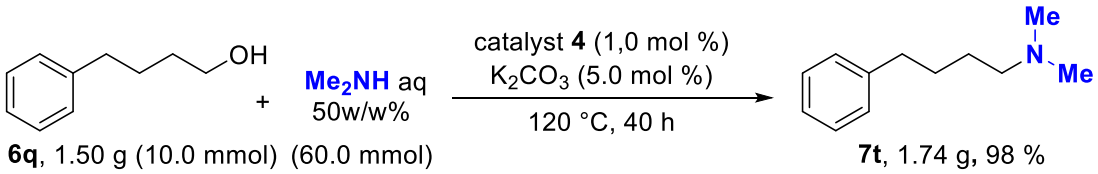
Scheme 7. Investigation of *N*-monomethylamination using aqueous methylamine solution.[a]



[a]Reaction was carried out with primary alcohol (1.0 mmol), methylamine (6.0 mmol), catalyst **4** (1.0 mol %), and K_2CO_3 (5.0 mol %) at 120 °C for 40 h. Yields were determined by GC analysis.

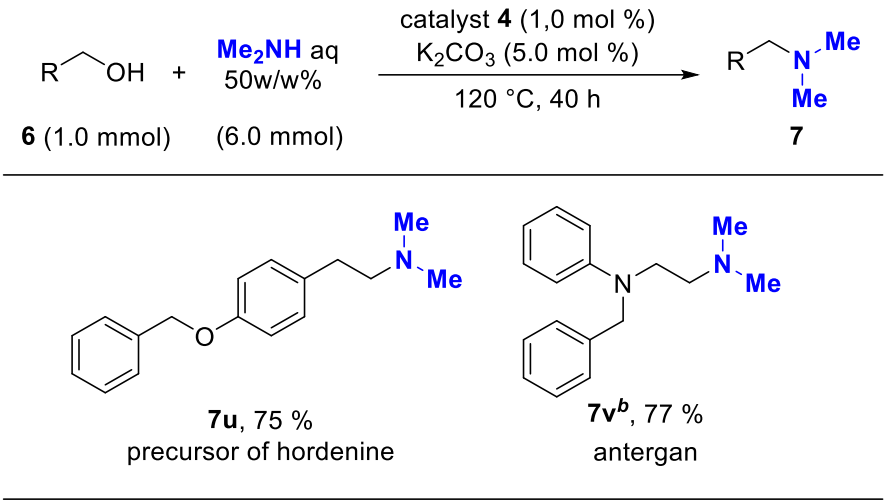
To evaluate the practical utility of our reaction scheme, a gram-scale reaction with phenylbutyl alcohol (10 mmol) and aqueous dimethylamine was carried out. Catalyst **4** exhibited good performance and the product was obtained in an excellent isolated yield (Scheme 8).

Scheme 8. Gram-scale reaction.



Finally, the author attempted the synthesis of drugs, including a biologically active compound containing a dimethylamine moiety, using this methodology (Scheme 9). 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**).

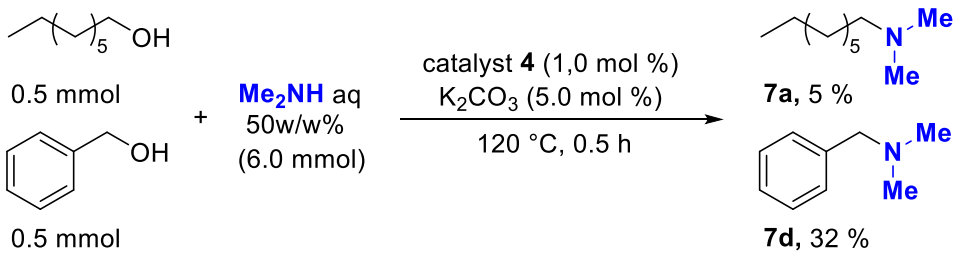
Scheme 9. Synthesis of pharmaceutical drugs via *N,N*-dimethylation using aqueous dimethylamine.[a]



[a]Reaction was carried out with primary alcohol (1.0 mmol), dimethylamine (6.0 mmol), catalyst **4** (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.

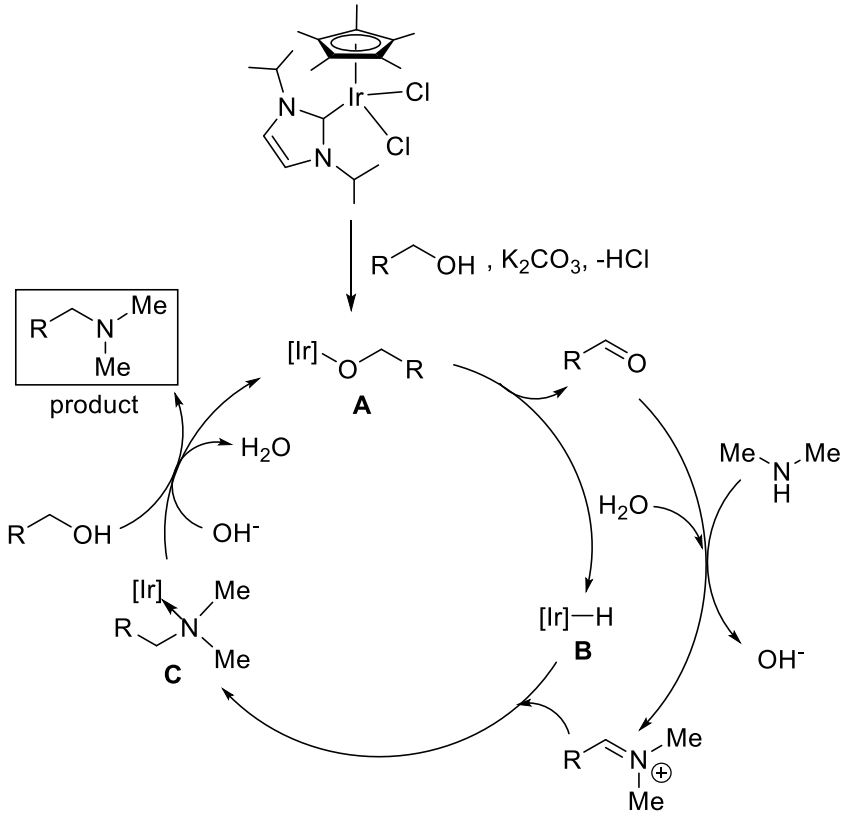
To compare the reactivity between benzyl alcohol and longchained aliphatic alcohol, a reaction using a 1:1 mixture of benzyl alcohol (0.5 mmol) and 1-octanol (0.5 mmol), aqueous dimethylamine (6.0 mmol), catalyst **4** (1.0 mol %), and K_2CO_3 (5.0 mol %) at 120 °C for 0.5 h was carried out. By this competitive experiment, *N,N*-dimethylbenzylamine was obtained in a higher yield than *N,N*-dimethyloctylamine (Scheme 10). This result indicates that benzyl alcohol is more reactive than 1-octanol.

Scheme 10. Competitive experiment[a]



Based on a previously reported mechanism for amination using a secondary amine and alcohol,[15f,19] a plausible mechanism for the reactions investigated in this study is described in Scheme 11. Alkoxo-iridium species **A** is formed by the reaction of alcohol and catalyst **4**.

Then, an aldehyde and hydrido-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 hydrido-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.

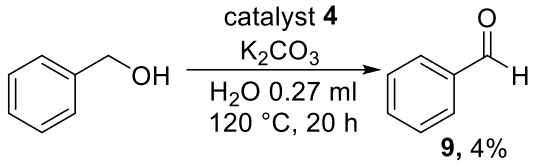


Scheme 11. Possible mechanism for the *N,N*-dimethylamination of primary alcohols with dimethylamine.

In order to obtain information about the reaction pathway, mechanistic experiments were conducted. Catalytic amination of secondary amine with primary alcohol through borrowing hydrogen pathway would include three steps as follows: 1) transfer dehydrogenation of primary alcohol giving an aldehyde, 2) formation of an iminium ion via condensation of the aldehyde with a secondary amine, and 3) transfer hydrogenation of the iminium ion by metal hydride species. Catalytic dehydrogenation of benzyl alcohol was examined. The reaction was carried out with benzyl alcohol (1.0 mmol), catalyst **4** (1.0 mol%), K_2CO_3 (5.0 mol%),

and H_2O (0.27 ml) at 120 °C for 20 h without adding an aqueous solution of dimethylamine. This catalytic dehydrogenation proceeded to give benzaldehyde (4%), proving the first step of the catalytic mechanism (Scheme 12). The low yield might be due to the absence of a hydrogen acceptor.

Scheme 12. Dehydrogenation of benzyl alcohol catalyzed by **4**.



In order to observe the active species of catalyst **4** working in the reaction, ^{1}H NMR spectra were also analyzed under several conditions. A dichloride iridium catalyst **4** bearing an *N*-heterocyclic carbene ligand with isopropyl substituent was founded to be insoluble in water (Figure 2a). When a base (K_2CO_3) was added, catalyst **4** become dissolved in water (Figure 2b). Although the detailed structure is unclear, this indicates that catalyst **4** is changed to a water-soluble iridium active species by reaction with a base. The ^{1}H NMR spectrum of the iridium active species remained unchanged after the addition of an aqueous solution of dimethylamine. Therefore, dimethylamine would not be coordinated to the catalyst at room temperature (Figure 2c). When benzyl alcohol was added, no change in the ^{1}H NMR spectrum of the iridium active species was observed, confirming that the alcohol is also not coordinated at room temperature (Figure 2d). Based on NMR analysis, the structure of the active species is expected to be a complex with a hydroxide ligand coordinated instead of a chloride ligand. In order to get evidence for the existence of hydrido-iridium species as a key intermediate in borrowing hydrogen reaction, the reaction was conducted with catalyst **4**, K_2CO_3, and benzyl alcohol at 80 °C for 7 h. The signal due to hydride-iridium species was observed at -16.5 ppm and -16.7 ppm in NMR analysis (Figure 2e). At high temperatures (80 °C), changes in the ^{1}H NMR spectrum was monitored compared to the conditions of the absence of benzyl alcohol (Figure 2e and 2f). Based on these NMR analyses, this catalytic system is also very likely to generate alkoxo-iridium species at high temperatures, and aldehyde and hydrido-iridium species through *β*-hydrogen elimination.

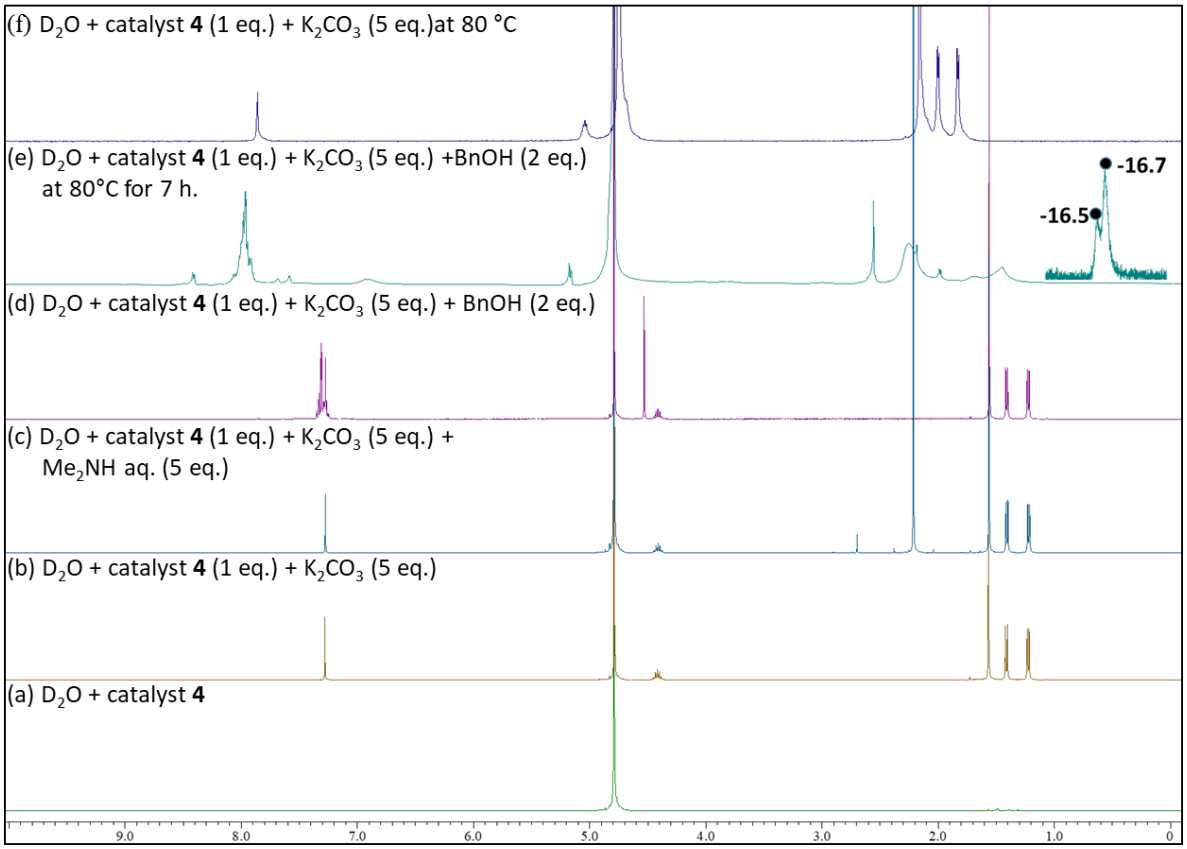
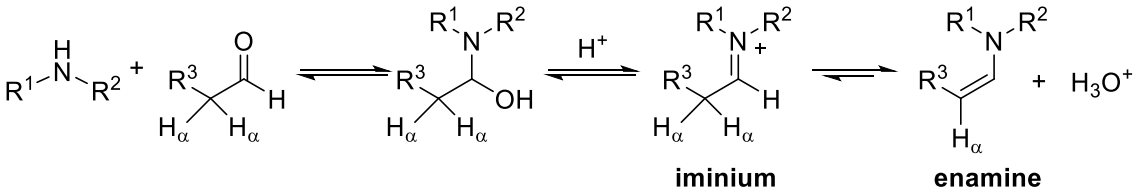


Figure 2. ^{1}H NMR spectrum showing the formation of catalyst **4** in several conditions.

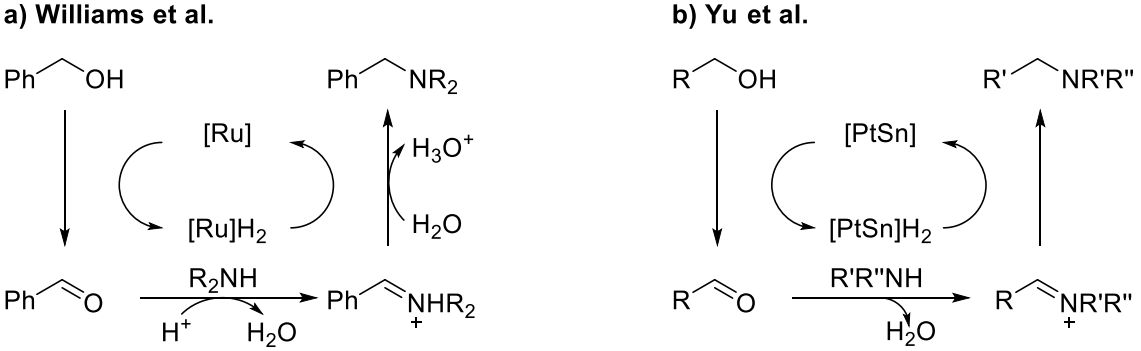
Finally, the author attempted to isolate or observe the iminium ion, which is considered to be a key intermediate. However, unfortunately, it was not successful to isolate or spectroscopically observe the iminium ion due to its structural instability. Thus, transfer hydrogenation of iminium ion was not carried out. Additionally, there is a possibility that enamine would be generated by the reaction of aldehyde having α-hydrogen with dimethylamine, which is in equilibrium with iminium (Scheme 13).[20] Whereas the reduction of the C=C bond of enamine is not favored, it has been reported that the rearrangement of enamine in the presence of a proton source produces iminium ions, which can be reduced.[21] Owing to the presence of a proton source in this catalytic reaction, the author expects the reaction would proceed by transfer hydrogenation from iminium ions rather than reduction of the C=C bond of enamine.

Scheme 13. Reaction of aldehyde having α-hydrogen with secondary amine.



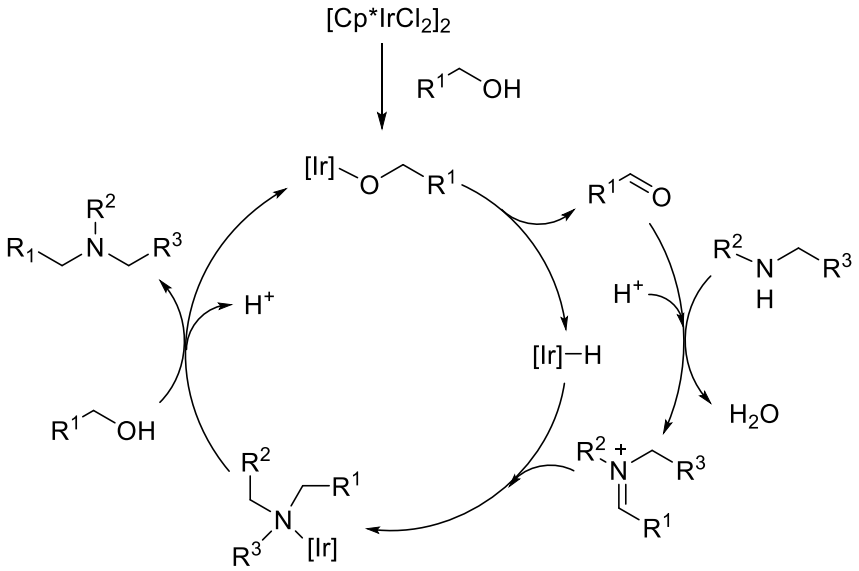
In the borrowing hydrogen reaction, the involvement of iminium ions rather than enamines has been widely proposed in the mechanism for the synthesis of tertiary amines using secondary amine with primary alcohol. Williams et al. reported a ruthenium-catalyzed system for tertiary amines using secondary amine and primary alcohol through borrowing hydrogen pathway (Scheme 14a).[22] Yu et al. also reported heterogeneous Pt-Sn/γ-Al_2O_3 catalyzed *N*-alkylation of secondary amine with primary alcohol and succeeded in the synthesis of tertiary amine (Scheme 14b).[23]

Scheme 14. Previously proposed mechanism for synthesis of tertiary amines using secondary amine with primary alcohol.

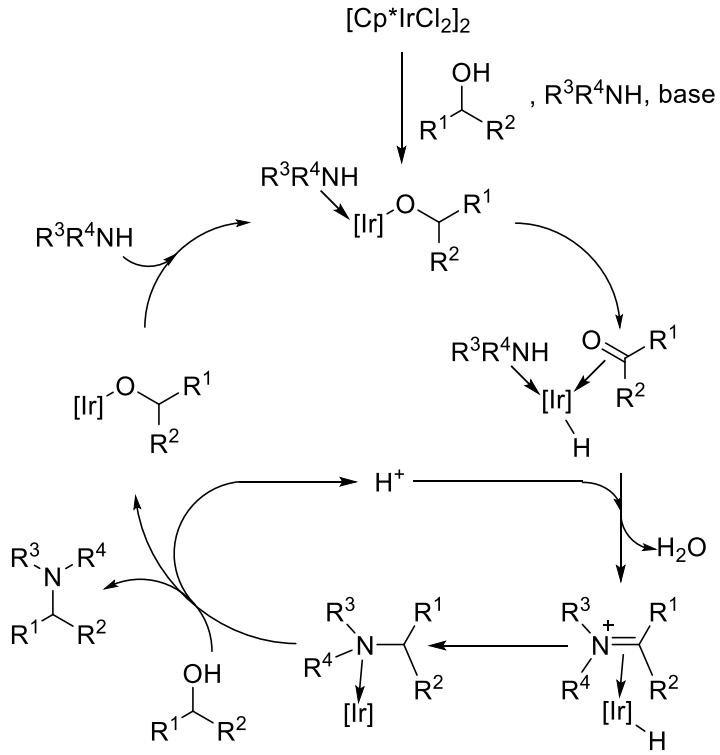


Chen et al. reported a mechanism for the synthesis of tertiary amines from secondary amines and primary alcohol using iridium catalyst (Scheme 15).[24] In our previous paper, a mechanism for *N*-alkylation of secondary amine with alcohol catalyzed by the iridium complex was also proposed (Scheme 16).[15f]

Scheme 15. Mechanism for iridium-catalyzed *N*-alkylation of secondary amine with primary alcohol.



Scheme 16. Our previously proposed mechanism for iridium-catalyzed *N*-alkylation of secondary amine with alcohol.



These reports suggested that iminium ion as intermediate is produced in the mechanism for *N*-alkylation of secondary amines and alcohols through borrowing hydrogen pathway. Additionally, in this catalytic reaction, dimethylamination using alcohol that produces aldehyde having no α-hydrogen also proceeded successfully. It is expected that the reaction is very likely to be through hydrogenation of iminium ion. Based on these considerations, the possibility of hydrogenation of enamine is very low. Therefore, the catalytic reaction using this secondary amine and primary alcohol catalyzed by **4** is also expected to generate iminium ion species and would also allow for transfer hydrogenation. These mechanistic experiments and backgrounds strongly support the proposed mechanism in Scheme 11.

3.3. Conclusion

In summary, the author 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 an aqueous solution of dimethylamine.

3.4. Experimental Section

General information

All reactions were performed in a sealed stainless tube. ^{1}H and $^{13}C\{^{1}H\}$ 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**,[25] **3**,[26] **4**,[10h] **5**, [15e] and $[Cp^*IrCl_2]_2$[27] were prepared according to the literature method. 2-(4-Benzyloxyphenyl) ethanol[28] and *N*-benzyl-2-anilinoethanol[29] were prepared 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.

Procedure for optimization of catalyst shown in Table 2.

In a stainless tube, the catalyst (1.0 mol % metal), K_2CO_3 (5 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.

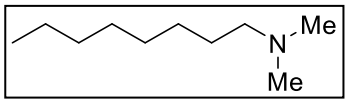
Procedure for optimization of the amount of dimethylamine, reaction time and temperatures, and bases shown in Table 3.

In a stainless tube, the catalyst **4** (1.0 mol %), Base (0-5 mol %), 1-octanol (1.0 mmol), and a 50% aqueous solution of dimethylamine (2.0-8.0 mmol) were added and sealed. The mixture was stirred for 20-40 h at 100-140 °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 6.**

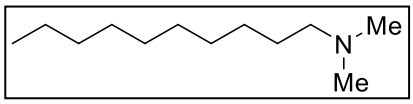
In a stainless tube, the iridium catalyst **4** (0.5−1.0 mol %), K_2CO_3 (5 mol %), primary alcohol (1.0 mmol), and a 50% aqueous solution of dimethylamine (0.66 mL, 6.0 mmol) were added and sealed. The mixture was stirred for 20−40 h at 120−130 °C using an aluminum block heater. On completion of the 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 6, 7a).[10h]**



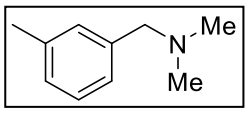
The product was isolated by silica gel chromatography eluting with $CHCl_3$/Et_3N (50:1) to give **7a** as a pale yellow oil, 130.0 mg (0.826 mmol, 83%). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 2.20−2.09 (m, 8H, $CH_2N(CH_3)_2$), 1.43−1.37 (m, 2H, CH_2), 1,28−1.10 (m, 10H, $(CH_2)_5$), 0.84−0.81 (t, 3H, J = 7.0 Hz, CH_3). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 60.1 ($CN(CH_3)_2$), 45.6 ($N(CH_3)_2$), 31.9 (CH_2), 29.7 (CH_2), 29.4 (CH_2), 27.9 (CH_2), 27.6 (CH_2), 22.8 (CH_2), 14.2 (CH_3).

***N,N*-Dimethyldecylamine (Scheme 6, 7c).[30]**



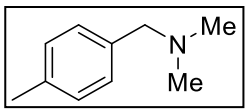
The product was isolated by silica gel chromatography eluting with $CHCl_3/Et_3N$ (50:1) to give **7c** as a pale yellow oil, 129.2 mg (0.699 mmol, 70%). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 2.27−2.17 (m, 8H, $CH_2N(CH_3)_2$), 1.45−1.42 (m, 2H, CH_2), 1.31−1.18 (m, 14H, $(CH_2)_7$), 0.87(t, 3H, J = 6.9 Hz, CH_3). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 60.2 ($CN(CH_3)_2$), 45.7 ($N(CH_3)_2$), 32.1 (CH_2), 29.79 (CH_2), 29.77 (CH_2), 29.75(CH_2), 29.5 (CH_2), 28.0 (CH_2), 27.7 (CH_2), 22.8 (CH_2), 14.3 (CH_3)

***N,N*-Dimethyl-(3-methylphenyl)methanamine (Scheme 6, 7e).[10h]**



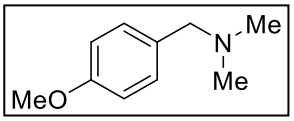
The product was isolated by silica gel chromatography eluting with an organic solvent (EtOAc/hexane/Et_3N = 1:50:1 to $CHCl_3/Et_3N$ = 30:1) to give **7e** as a pale yellow oil, 87.0 mg (0.583 mmol, 58%). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.21 (t, 1H, J = 8.0 Hz, aromatic), 7.14 (s, 1H, aromatic), 7.08 (t, 2H, J = 7.5 Hz, aromatic), 3.38 (s, 2H, CH_2). 2.35 (s, 3H, CH_3), 2.24 (s, 6H, $N(CH_3)_2$). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 138.9 ($C_{aromatic}$), 138.0 ($C_{aromatic}$), 129.9 ($C_{aromatic}$), 128.2 ($C_{aromatic}$), 127.9 ($C_{aromatic}$), 126.3 ($C_{aromatic}$), 64.6 (CH_2), 45.6 ($N(CH_3)_2$), 21.5 (CH_3).

***N,N*-Dimethyl-(4-methylphenyl)methanamine (Scheme 6, 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, aromatic), 7.13 (d, 2H, J = 8 Hz, aromatic), 3.38 (s, 2H, CH_2), 2.34 (s, 3H, CH_3), 2.23 (s, 6H, $N(CH_3)_2$). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 136.7 ($C_{aromatic}$), 135.9 ($C_{aromatic}$), 129.2 ($C_{aromatic}$), 129.0 ($C_{aromatic}$), 64.2 (CH_2), 45.4 ($N(CH_3)_2$), 21.2 (CH_3).

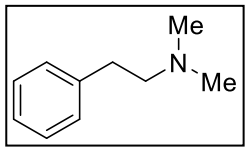
***N,N*-Dimethyl-(4-methoxylphenyl)methanamine (Scheme 6, 7g).[10h]**



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, aromatic), 6.85 (d, 2H, J = 9 Hz, aromatic),

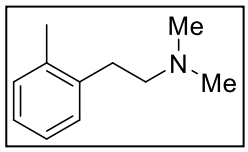
3.80 (s, 3H, OCH_3), 3.35 (s, 2H, CH_2), 2.22 (s, 6H, $N(CH_3)_2$). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 158.8 ($C_{aromatic}$), 131.1 ($C_{aromatic}$), 130.4 ($C_{aromatic}$), 113.7 ($C_{aromatic}$), 63.9 (CH_2), 55.4 (OCH_3), 45.3 ($N(CH_3)_2$).

_N,N_-Dimethylphenethylamine (Scheme 6, 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 7.33−7.28 (m, 2H, aromatic), 7.23−7.19 (m, 3H, aromatic), 2.81−2.56 (m, 2H, CH_2), 2.56−2.50(m, 2H, CH_2), 2.31 (s, 6H, $N(CH_3)_2$). $^{13}C\{1H\}$ NMR (126 MHz, CDCl3, r.t.) δ 140.4 ($C_{aromatic}$), 128.6 ($C_{aromatic}$), 128.4 ($C_{aromatic}$), 126.0 ($C_{aromatic}$), 61.6(CH_2N), 45.5($N(CH_3)_2$), 34.5(CH_2).

2-(2-Methylphenyl)-_N,N_-dimethylethanamine (Scheme 6, 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, aromatic), 2.81−2.77 (m, 2H, CH_2), 2.49−2.46 (m, 2H, CH_2), 2.33 (s, 3H, $N(CH_3)_3$). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 138.6 ($C_{aromatic}$), 136.1 ($C_{aromatic}$), 130.3 ($C_{aromatic}$), 129.3 ($C_{aromatic}$), 126.3 ($C_{aromatic}$), 126.1 ($C_{aromatic}$), 60.4 (CH_2N), 45.6 ($N(CH_3)_2$), 31.8 (CH_2), 19.4 ($ArCH_3$). 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.

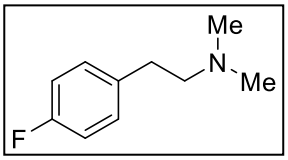
2-(4-Methylphenyl)-_N,N_-dimethylethanamine (Scheme 6, 7j).[31]

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, 5H, aromatic), 2.77−2.73 (m, 2H, CH_2), 2.53−2.50 (m, 2H, CH_2), 2.32 (s, 3H, $ArCH_3$), 2.30 (s, 6H, $N(CH_3)_2$). $^{13}C\{1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 137.4 ($C_{aromatic}$), 135.5 ($C_{aromatic}$), 129.2 ($C_{aromatic}$), 128.6 ($C_{aromatic}$), 61.9 (CH_2N), 45.6 ($N(CH_3)_2$), 34.1 (CH_2), 21.1 ($ArCH_3$).

2-(3-Methylphenyl)-*N*,*N*-dimethylethanamine (Scheme 6, 7k).

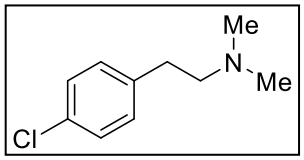
The product was isolated by silica gel chromatography eluting with $CHCl_3/Et_3N$ (50:1) to give **7k** as a pale yellow oil, 109.7 mg (0.672 mmol, 67%). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.21−7.17 (m, 1H, aromatic), 7.02−7.01(m, 3H, aromatic), 2.77−2.73 (m, 2H, CH_2), 2.54−2.51 (m, 2H, CH_2), 2.33 (s, 3H, $ArCH_3$), 2.30 (s, 6H, $N(CH_3)_2$). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 140.4 ($C_{aromatic}$), 138.1 ($C_{aromatic}$), 129.6 ($C_{aromatic}$), 128.4 ($C_{aromatic}$), 126.9 ($C_{aromatic}$), 125.8 ($C_{aromatic}$), 61.8 (CH_2N), 45.6 ($N(CH_3)_2$), 34.4 (CH_2), 21.5 ($ArCH_3$). 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 6, 7l).[32]



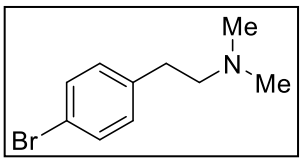
The product was isolated by silica gel chromatography eluting with $CHCl_3/Et_2NH$ (50:1) to give **7l** as a pale yellow oil, 151.8 mg (0.908 mmol, 91%). ^1H NMR (500 MHz, $CDCl_3$, r.t.) 7.16−7.14 (m, 2H, aromatic), 6.98−6.94 (m, 2H, aromatic), 2.76−2.73 (m, 2H, CH_2), 2.51−2.48 (m, 2H, CH_2), 2.28 (s, 6H, $N(CH_3)_2$). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 161.5 (d, J = 244.1 Hz, $FC_{aromatic}$), 136.1 (d, J = 2.4 Hz, $C_{aromatic}$), 130.1 (d, J = 7.1 Hz, $C_{aromatic}$), 115.3 (d, J = 20.4 Hz, $C_{aromatic}$), 61.7 (CH_2N), 45.6 ($N(CH_3)_2$), 33.7 (CH_2).

2-(4-Chlorophenyl)-*N*,*N*-dimethylethanamine (Scheme 6, 7m).



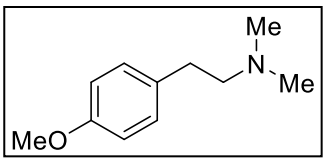
The product was isolated by silica gel chromatography eluting with $CHCl_3/Et_2NH$ (50:1) to give **7m** as a pale yellow oil, 147.8 mg (0.805 mmol, 80%). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.23 (d, 2H, J = 8.6 Hz, aromatic), 7.12 (d, 2H, J = 8.3 Hz, aromatic), 2.75−2.72 (m, 2H, CH_2), 2.51−2.47 (m, 2H, CH_2), 2.27 (s, 6H, $N(CH_3)_2$). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 138.9 ($C_{aromatic}$), 131.8 ($C_{aromatic}$), 130.1 ($C_{aromatic}$), 128.6 ($C_{aromatic}$), 61.4 (CH_2N), 45.6 ($N(CH_3)_2$), 33.8 (CH_2). 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 6, 7n).[33]



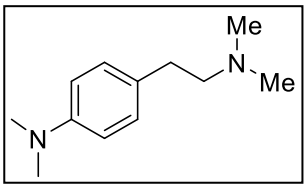
The product was isolated by silica gel chromatography eluting with $CHCl_3/Et_2NH$ (50:1) to give **7n** as a pale yellow oil, 176.4 mg (0.773 mmol, 77%). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.39 (d, 2H, J = 8.5 Hz, aromatic), 7.07 (d, 2H, J = 8.5 Hz, aromatic), 2.74−2.71 (m, 2H, CH_2), 2.51 (m, 2H, CH_2), 2.28 (s, 6H, $N(CH_3)_2$). $^{13}C\{1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 139.5 ($C_{aromatic}$), 131.5 ($C_{aromatic}$), 130.5 ($C_{aromatic}$), 119.9 ($C_{aromatic}$), 61.4 (CH_2N), 45.6 ($N(CH_3)_2$), 33.9 (CH_2).

2-(4-Methoxyphenyl)-*N,N*-dimethylethanamine (Scheme 6, 7o).[34]



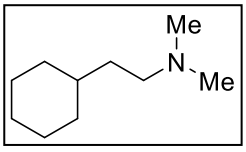
The product was isolated by silica gel chromatography eluting with $CHCl_3/Et_3N$ (100:1) to give **7o** as a pale yellow oil, 164.1 mg (0.915 mmol, 92%). ^1H NMR (500 MHz, CDCl3, r.t.) δ 7.2 (d, 2H, J = 8.5 Hz, aromatic), 6.82 (d, 2H, J = 8.5 Hz, aromatic), 3.78 (s, 3H, CH_3O) 2.74−2.70 (m, 2H, CH_2), 2.51−2.47 (m, 2H, CH_2), 2.29 (s, $N(CH_3)_2$). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 158.0 ($C_{aromatic}$), 132.6 ($C_{aromatic}$), 129.6 ($C_{aromatic}$), 113.9 ($C_{aromatic}$), 62.0 (CH_2N), 55.4 (CH_3O), 45.6 ($N(CH_3)_2$) 33.6 (CH_2).

2-(4-Dimethylaminophenyl)-*N,N*-dimethylethanamine (Scheme 6, 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, aromatic), 6.70 (d, 2H, J = 8.5 Hz, aromatic), 2.91 (s, 6H, $(CH_3)_2NAr$), 2.71−2.68 (m, 2H, CH_2), 2.51−2.47 (m, 2H, CH_2), 2.29 (s, 6H, $N(CH_3)_2$). $^{13}C\{1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 149.3 ($C_{aromatic}$), 129.3 ($C_{aromatic}$), 128.6 ($C_{aromatic}$), 62.1 (CH_2N), 45.6 ($N(CH_3)_2$), 41.0 ($ArN(CH_3)_2$), 33.5 (CH_2). 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.

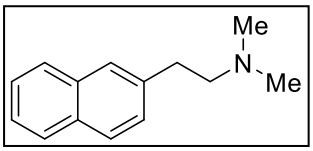
2-Cyclohexyl-*N,N*-dimethylethanamine (Scheme 6, 7q).[35]



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, CH_2),

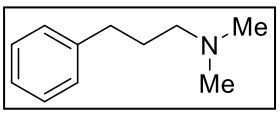
2.15 (s, 6H, $N(CH_3)_2$), 1.70−0.87 (m, 13H, $((CH_2)_5CH)CH_2$). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 57.8 (CH_2N), 45.7 ($N(CH_3)_2$), 36.1 (CH_2), 35.6 (C_{Cy}), 33.6 (C_{Cy}), 26.8 (C_{Cy}), 26.4 (C_{Cy}).

***N,N*-Dimethyl-2-Naphthaleneethanamine (Scheme 6, 7r).**



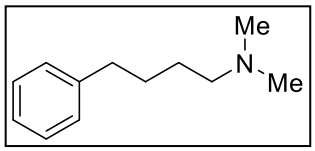
The product was isolated by silica gel chromatography eluting with $CHCl_3/Et_2NH$ (50:1) to give **7r** as a pale yellow oil, 171.2 mg (0.859 mmol, 86%). 1H NMR (500 MHz, CDCl3, r.t.) δ 7.82−7.78 (m, 3H, aromatic), 7.66 (s, 1H, aromatic), 7.46−7.35 (m, 3H, aromatic), 2.98-2.92 (m, 2H, CH_2), 2.65−2.62 (m, 2H, CH_2), 2.34 (s, 6H, $N(CH_3)_2$). $^{13}C\{^1H\}$ NMR (126 MHz, CDCl3, r.t.) δ 138.1 ($C_{aromatic}$), 133.7 ($C_{aromatic}$), 132.2 ($C_{aromatic}$), 128.0 ($C_{aromatic}$), 127.7 ($C_{aromatic}$), 127.54 ($C_{aromatic}$), 127.53 ($C_{aromatic}$), 126.9 ($C_{aromatic}$), 126.0 ($C_{aromatic}$), 125.3 ($C_{aromatic}$), 61.6 (CH_2N), 45.7 ($N(CH_3)_2$), 34.7 (CH_2). 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 6, 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, aromatic), 7.21 (m, 3H, aromatic), 2.64 (t, 2H, J = 7.9 Hz, CH_2), 2.30 (t, J = 7.4 Hz, CH_2), 2.23 (s, 6H), 1.80 (q, 2H, J = 7.5 Hz, CH_2). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 142.4 ($C_{aromatic}$), 128.5 ($C_{aromatic}$), 128.4 ($C_{aromatic}$), 125.8 ($C_{aromatic}$), 59.4 (CH_2N), 45.6 ($N(CH_3)_2$), 33.8 (CH_2), 29.6 (CH_2).

***N,N*-Dimethyl-3-phenylbutan-1-amine (Scheme 6, 7t).[36]**

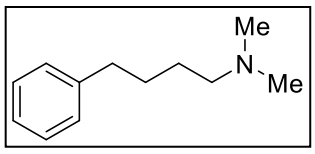


The product was isolated by silica gel chromatography eluting with $CHCl_3/Et_3N$ (50:1) to give **7t** as a pale yellow oil, 167.7 mg (0.946 mmol, 94%). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.30−7.26 (m, 2H, aromatic), 7.19−7.16 (m, 3H, aromatic), 2.63 (t, 2H, J = 7.7 Hz, CH_2), 2.27 (t, 2H, J = 7.6 Hz, CH_2), 2.21 (s, 6H, CH_3), 1.68−1.62 (m, 2H, CH_2), 1.54−1.48 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 142.6 ($C_{aromatic}$), 128.5 ($C_{aromatic}$), 128.3 ($C_{aromatic}$), 125.7 ($C_{aromatic}$), 59.8 (CH_2N), 45.7 ($N(CH_3)_2$), 36.0 (CH_2), 29.4 (CH_2), 27.6 (CH_2).

Investigation of *N*-monomethylamination using an aqueous methylamine solution in Scheme 7.

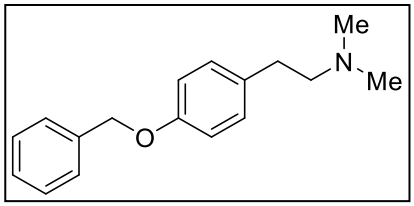
In a stainless tube, the iridium catalyst **4** (1.0 mol %), K_2CO_3 (5 mol %), primary alcohol (1.0 mmol), and a 40% aqueous solution of methylamine (0.50 mL, 6.0 mmol) were added and sealed. The mixture was stirred for 40 h at 120 °C using an aluminum block heater. On completion of the reaction, it 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 in Scheme 8.



In a stainless tube, the iridium catalyst **4** (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%). ^{1}H NMR (400 MHz, $CDCl_3$, r.t.) δ 7.30−7.25 (m, 2H, aromatic), 7.19−7.15 (m, 3H, aromatic), 2.63 (t, 2H, J = 7.2 Hz, CH_2), 2.27 (t, 2H, J = 7.2 Hz, CH_2), 2.20 (s, 6H, $N(CH_3)_2$), 1.70−1.60 (m, 2H, CH_2), 1.54−1.47 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100.5 MHz, $CDCl_3$, r.t.) δ 142.7 ($C_{aromatic}$), 128.5 ($C_{aromatic}$), 128.4 ($C_{aromatic}$), 125.8 ($C_{aromatic}$), 59.9 (CH_2N), 45.7 ($N(CH_3)_2$), 36.0 (CH_2), 29.4 (CH_2), 27.6 (CH_2).

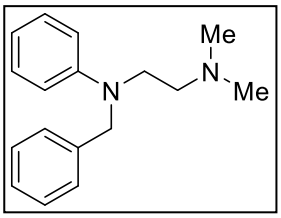
2-(4-Benzyloxyphenyl)-*N,N*-dimethylethanamine (Scheme 9, 7u).



In a stainless tube, the iridium catalyst **4** (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, aromatic), 7.13 (d, 2H, J = 10.5 Hz, aromatic), 6.91 (d, 2H, J = 10.5 Hz, aromatic), 5.04 (s, 2H, CH_2O), 2.75−2.71 (m, 2H, CH_2), 2.52−2.48 (m, 2H, CH_2), 2.29 (s, 6H, $N(CH_3)_2$). $^{13}C\{^1H\}$ NMR (100.5 MHz, $CDCl_3$, r.t.) δ 157.3 ($C_{aromatic}$), 137.3 ($C_{aromatic}$), 132.9 ($C_{aromatic}$), 129.7 ($C_{aromatic}$) , 128.7 ($C_{aromatic}$), 128.0 ($C_{aromatic}$), 127.6 ($C_{aromatic}$), 114.9 ($C_{aromatic}$), 70.2 (CH_2O), 62.0 (CH_2), 45.6 ($N(CH_3)_2$), 33.7 (CH_2). 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 9, 7v).[13e]



In a stainless tube, the iridium catalyst **4** (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, aromatic), 7.25-7.16 (m, 5H, aromatic), 6.71-6.66 (m, 3H, aromatic), 4.57 (s, 2H, $ArCH_2N$), 3.55 (t, 2H, J = 7.6 Hz, CH_2), 2.55 (t, 2H, J = 8.0 Hz, CH_2), 2.28 (s, 6H, $N(CH_3)_2$).. $^{13}C\{^1H\}$ NMR (100.5 MHz, $CDCl_3$, r.t.) δ 148.5 ($C_{aromatic}$), 139.0 ($C_{aromatic}$), 129.4 ($C_{aromatic}$), 128.7 ($C_{aromatic}$), 126.9 ($C_{aromatic}$), 126.7 ($C_{aromatic}$), 116.4 ($C_{aromatic}$), 112.2 ($C_{aromatic}$), 56.5 (CH_2), 54.9 (CH_2), 49.7 ($ArCH_2$), 46.1 ($N(CH_3)_2$).

Competitive experiment in Scheme 10.

In a stainless tube, the iridium catalyst **4** (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.

Dehydrogenation of benzyl alcohol catalyzed by 4 in Scheme 12.

In a stainless tube, the iridium catalyst **4** (1.0 mol %), K_2CO_3 (5 mol %), benzyl alcohol (1.0 mmol), and H_2O 0.27 mL were added and sealed. The mixture was stirred for 20 h at 120 °C using an aluminum block heater. On completion of the reaction, it was cooled to room temperature. The crude mixture was diluted with tetrahydrofuran (THF) (50 mL). The product yield was determined by GC analysis using biphenyl as an internal standard.

^{1}H NMR spectrum showing the formation of catalyst 4 in several conditions in Figure 2.

(a) In a 5 mL vial, catalyst **4** (0.01 mmol) and D_2O (2 mL) were added and sealed. Sonication was conducted for 20 mins. The mixture was transferred to NMR tube. It was analyzed by ^{1}H NMR.

(b) In a 5 mL vial, catalyst **4** (0.01 mmol), K_2CO_3 (0.05 mmol) and D_2O (2 mL) were added and sealed. Sonication was conducted for 20 mins. Then, the mixture was transferred to NMR tube. It was analyzed by ^{1}H NMR.

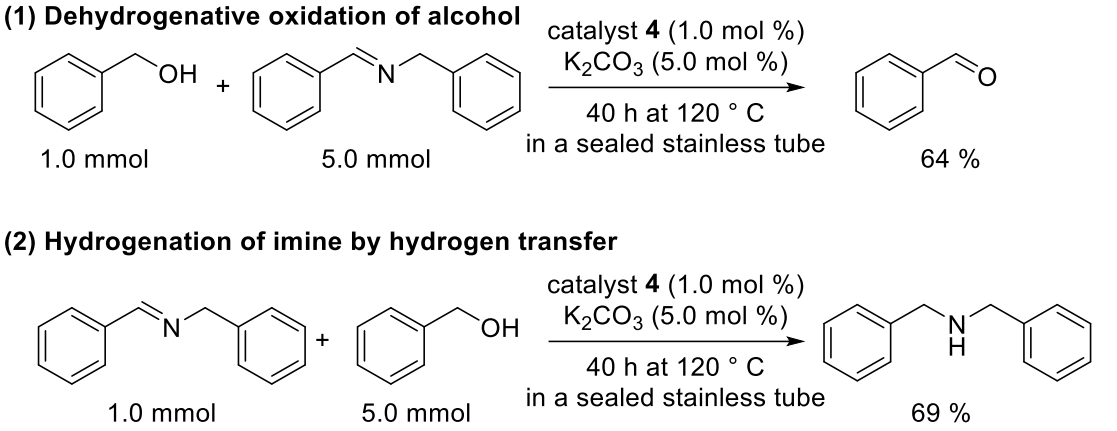
(c) In a 5 mL vial, catalyst **4** (0.01 mmol), an aqueous solution of dimethylamine (0.05 mmol) and D_2O (2 mL) were added and sealed. Sonication was conducted for 20 mins. Then, the mixture was transferred to NMR tube. Ir was analyzed by ^{1}H NMR analysis.

(d) In a 5 mL vial, catalyst **4** (0.01 mmol), benzyl alcohol (0.02 mmol) and D_2O (2 mL) were added and sealed. Sonication was conducted for 20 mins. Then, the mixture was transferred to NMR tube. Ir was analyzed by ^{1}H NMR.

(e) In a 5 mL vial, catalyst **4** (0.01 mmol), K_2CO_3 (0.05 mmol), benzyl alcohol (0.02 mmol) and D_2O (2 mL) were added and sealed. Sonication was conducted for 20 mins. Then, the mixture was transferred to NMR tube. The tube was placed into the NMR apparatus and temperature was raised to 80 °C. The tube was left in the spectrometer at the same temperature for 7 h. Then, ^{1}H NMR spectra were measured.

(f) In a 5 mL vial, catalyst **4** (0.01 mmol), K_2CO_3 (0.05 mmol) and D_2O (2 mL) were added and sealed. Sonication was conducted for 20 mins. Then, the mixture was transferred to NMR tube and temperature was raised to 80 °C. It was analyzed by ^{1}H NMR.

Scheme 17. Mechanistic investigations.[a]



[a]The yields were determined by GC analysis.

In order to obtain the information about the catalytic mechanism, first of all, the author attempted to isolate or observe the iminium ion, which is considered to be a key intermediate. However, unfortunately, it was not successful to isolate or spectroscopically observe the iminium ion due to its structural instability. Instead, catalytic transfer dehydrogenation of benzyl alcohol using an imine (*N*-benzylidenebenzylamine) as a hydrogen acceptor was examined. This reaction proceeded successfully to give benzaldehyde (64%), proving the first step of the catalytic mechanism. Additionally, catalytic transfer hydrogenation of the imine (*N*-benzylidenebenzylamine) using an alcohol (benzyl alcohol) as a hydrogen donor was examined. This reaction also proceeded successfully to give dibenzylamine (69%), proving the final step of the catalytic mechanism.

(1) Dehydrogenative oxidation of alcohol

In a stainless tube, the catalyst **4** 5.6 mg (0.01 mmol), K_2CO_3 7.0 mg (0.05 mol), benzyl alcohol 108.4 mg (1.0 mmol) and *N*-Benzylidenebenzylamine 976.3 mg (5.0 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 THF (50 ml). The yield of benzaldehyde was determined by GC analysis using biphenyl 60.7 mg (0.39 mmol) as an internal standard.

(2) Hydrogenation of imine by hydrogen transfer

In a stainless tube, the catalyst **4** 5.6 mg (0.01 mmol), K_2CO_3 7.0 mg (0.05 mol), benzyl alcohol 540.8 mg (5.0 mmol) and *N*-Benzylidenebenzylamine 195.4 mg (1.0 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 THF (50 ml). The yield of *N,N*-dibenzylamine was determined by GC analysis using biphenyl 60.6 mg (0.39 mmol) as an internal standard.

3.5. Reference

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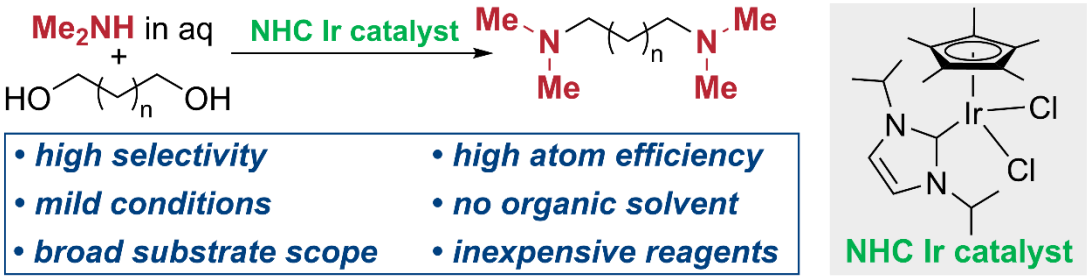
Chapter 4

Selective Synthesis of Bisdimethylamine Derivatives from Diols and an Aqueous Solution of Dimethylamine through Iridium-Catalyzed Borrowing Hydrogen Pathway

Abstract

Bisdimethylamine derivatives are an important class of compounds in the polymer and pharmaceutical industries. However, existing methods for the synthesis of these compounds have several drawbacks such as low selectivity, use of toxic reagents, and generation of waste. In this study, a new system was developed for the selective synthesis of bisdimethylamine derivatives using a diol and dimethylamine as starting materials and an iridium complex bearing an *N*-heterocyclic carbene ligand as catalyst. The starting materials were easily available, less toxic, inexpensive, and easy to handle. The reaction proceeded efficiently through a borrowing hydrogen pathway under aqueous conditions, without any additional organic solvent, to afford various bisdimethylamine derivatives in good to excellent yields.



4.1. Introduction

Bisdimethylamine derivatives with dimethylamino groups at the two terminal sites are an important class of compounds in the polymer industry as foaming agents[1] or cross-linkers.[2] In addition, bisdimethylamine derivatives have been utilized as pincer-type ligands, which impart distinct functionalities to organometallic compounds. They have been used in combination with metals for the development of homogeneous catalytic systems.[3,4] Furthermore, bisdimethylamine derivatives are precursors of bioactive compounds[5] such as antimicrobials,[5a,b] antibiotics,[5c,d] and anticancer drugs.[5e,f] Consequently, bisdimethylamine derivatives are highly valuable compounds from the viewpoint of synthetic organic chemistry (Figure 1).

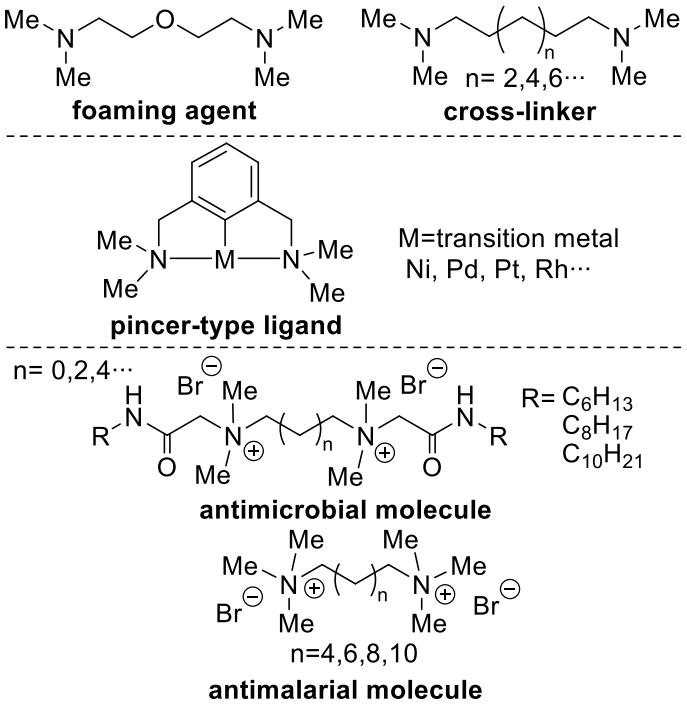
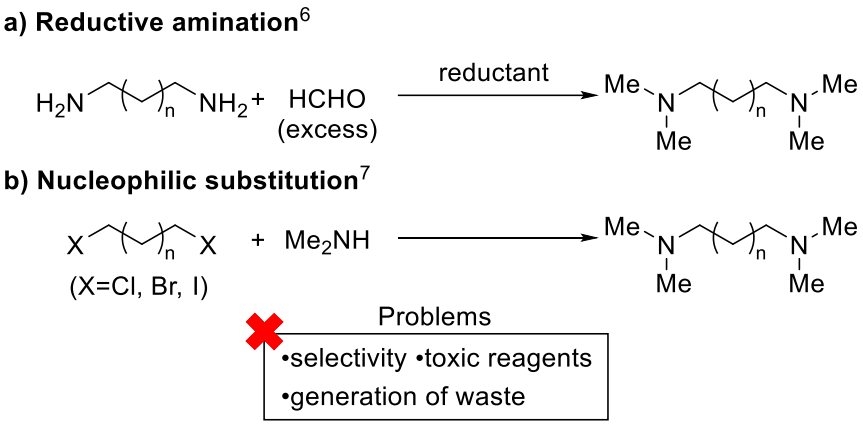


Figure 1. Application of bisdimethylamine derivatives

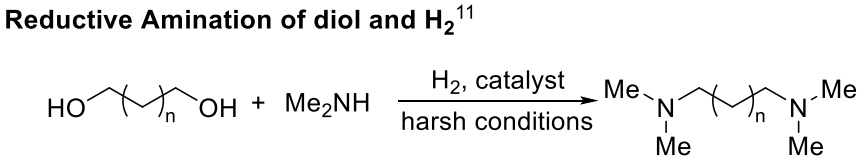
Conventionally, bisdimethylamine derivatives are synthesized via reductive methylation using unsubstituted diamines as the starting material and formaldehyde as methylation reagent (Scheme 1a).[6] Alternatively, nucleophilic substitution using hydrocarbons with two halogen substituents at the two terminals and dimethylamine as a dimethlyamination reagent is also commonly employed (Scheme 1b).[7]



Scheme 1. Conventional synthetic method of bisdimethylamine derivatives.

However, the selectivity for the target product is poor in these reactions, and they also require more than the stoichiometric amount of reducing agent. Most importantly, the existing protocols may have a detrimental effect on the environment due to use of excess toxic reagents and generation of waste.[8] Considering these limitations, the development of catalytic systems for the highly efficient synthesis of bisdimethylamine derivatives has received significant attention in recent years. In other words, it is essential to develop a catalytic system that does not generate harmful byproducts and uses sustainable, easily available, and inexpensive compounds as starting materials.[9]

Diols are less toxic and can be easily obtained by derivatization from relatively inexpensive feedstocks, including biomass.[10] This suggests that bisdimethylamination of diols using dimethylamine as the nitrogen source is a promising strategy for the safe, convenient, and cost-effective synthesis of bisdimethylamine derivatives. Studies on the synthesis of bisdimethylamine derivatives using diols and dimethylamine as starting materials have been already reported.

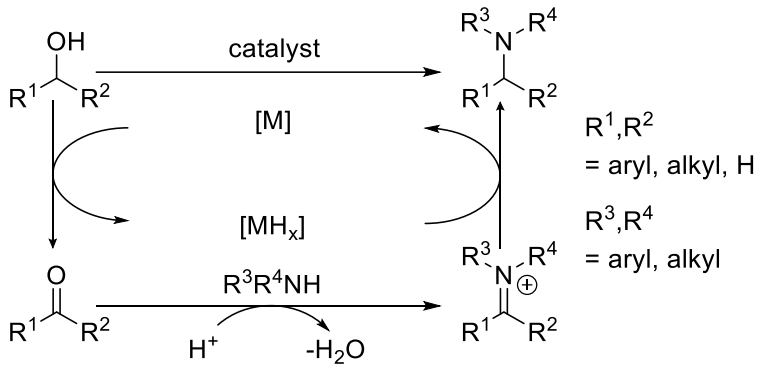


Scheme 2. Bisdimethylamination using diol with hydrogen gas as a reducing agent.

However, the reported synthetic protocols require a high temperature, and consequently, a

high energy input (Scheme 2). Furthermore, the requirement of high-pressure hydrogen as a reducing agent renders the synthesis inconvenient. Additionally, in many cases, it was also a significant problem that the formation of aminoalcohols as byproducts could not be avoided rather than selective formation of bisdimethylamine derivatives, which is the target product.[11]

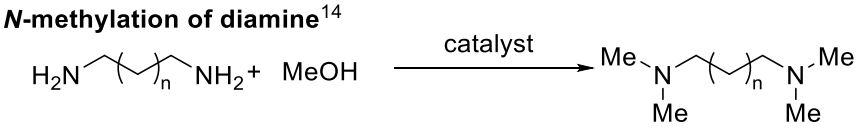
Meanwhile, over the last several decades, transition-metal-catalyzed carbon-nitrogen bond formation reactions using alcohols and amines through borrowing hydrogen processes have attracted much attention.[12] In these processes, the catalytic conversion of alcohols to carbonyl intermediates, formation of imines or iminium species by dehydrative condensation of amines and carbonyl intermediates, and catalytic hydrogenation of imines occur sequentially (Scheme 3).



Scheme 3. Mechanism for synthesis of tertiary amine through borrowing hydrogen process.

The surplus hydrogen atoms in the first step are consumed in the third step, and accordingly, this is known as the borrowing hydrogen strategy.[13] In this process, water is the only non-organic by-product. Thus, this strategy is highly environment-friendly and atom-economical.

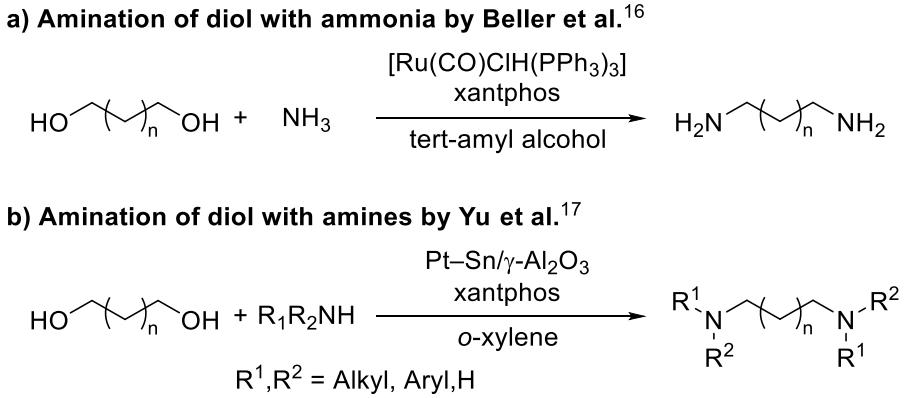
Recently, *N*-methylation reactions for synthesizing bisdimethylamine derivatives, based on the borrowing hydrogen strategy using unsubstituted diamines as raw materials and methanol as a methylating agent, have been reported (Scheme 4).[14]



Scheme 4. Catalytic *N*-methylation for synthesis of bisdimethylamine compounds.

This is an effective method for synthesizing bisdimethylamine derivatives. However, because methanol is used as the methylating agent, a total of four methylation reactions must occur continuously to afford the bisdimethylamine derivative. Owing to this, it is difficult to obtain the desired product selectively, and the reaction is limited by special starting materials. In addition, unsubstituted diamines are relatively expensive because they are usually synthesized through multi-step reactions from simple nitrogen-containing compounds.[15] Therefore, the development of a synthetic method based on a simple nitrogen source (e.g., dimethylamine) and an inexpensive and easily available raw material (e.g., diol) is highly desirable.

Diamination of diols as feedstocks, based on the borrowing hydrogen strategy, can be a new method for addressing the limitations of the previous protocols. However, there are very few examples of the diamination of diols. Beller et al.[16] and Yu et al.[17] independently reported the synthesis of diamines from diols; however, no bisdimethylamine derivatives were produced (Scheme 5).[18]

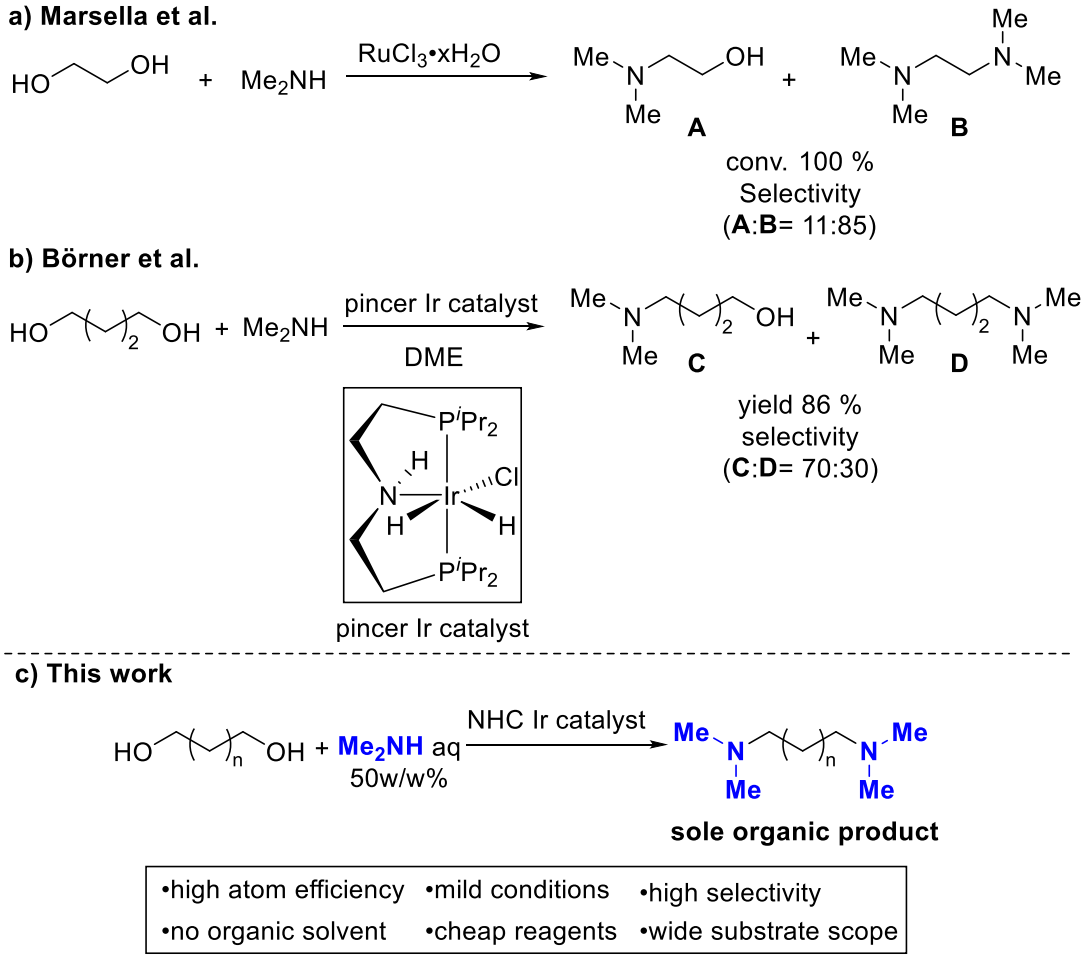


Scheme 5. Catalytic diamination of diol with amine or ammonia.

Moreover, as shown in Scheme 6, Marsella et al.[19] and Börner et al.[20] independently reported catalytic reactions based on the borrowing hydrogen strategy using various diols and dimethylamines as starting materials (Scheme 6a,b). However, they have not yet developed a reaction for the selective synthesis of bisdimethylamine derivatives. To the best of our knowledge, only a few research groups have succeeded in developing catalytic synthetic methods for bisdimethylamine derivatives based on the borrowing hydrogen strategy.

In this study, the author has developed a highly efficient and selective method for the

transition-metal catalyzed synthesis of bisdimethylamine derivatives using an aqueous solution of dimethylamine and a safe and easily available diol under mild conditions; as described before, this has been extremely challenging thus far. Considering the impact of the synthetic protocol on the environment, an aqueous solution of dimethylamine was used; no other organic solvents were used for this reaction. Incidentally, our research group have previously developed carbon-nitrogen bond-forming reactions based on the borrowing hydrogen strategy using alcohols and amines.[21] Recently, our reaserch group reported iridium catalysts that exhibited high activity for carbon-nitrogen bond formation reactions in water.[22] Based on this, the author successfully developed a new catalytic system for the synthesis of a range of bisdimethylamine derivatives using various diols and dimethylamine as starting materials. The reaction proceeded under relatively mild conditions (120 °C) in the presence of an iridium complex as catalyst (Scheme 6).



Scheme 6. Catalytic bisdimethylamination of diol with dimethylamine.

4.2. Results and Discussion

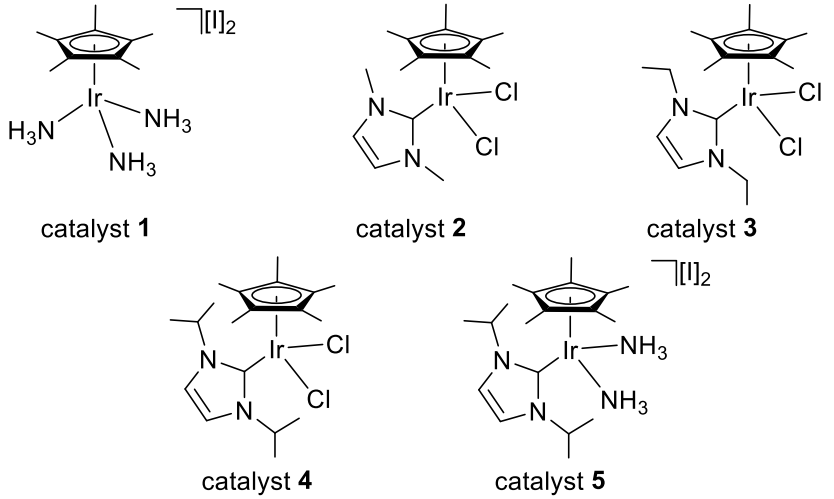
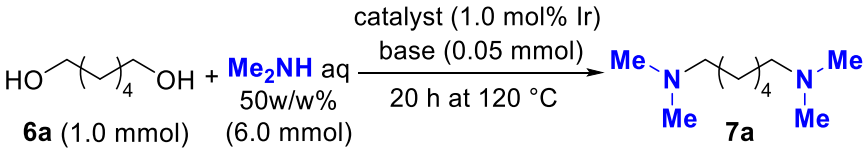


Figure 2. Iridium complexes **1**-**5** used in this study.

The structures of the series of iridium complexes used as catalysts are illustrated in Figure 2. As a model reaction, the reaction of 1,6-hexanediol (**6a**) and dimethylamine to produce *N,N,N′,N′*-tetramethylhexanediamine (**7a**) was investigated. As mentioned before, an aqueous solution of dimethylamine was used, and no other organic solvents were required for this reaction. Various experimental conditions were screened to determine the optimum reaction conditions (Table 1). The reaction between **6a** (1.0 mmol) and aqueous dimethylamine (6.0 mmol) was conducted in a stainless tube under argon atmosphere in the presence of iridium catalyst (1.0 mol% Ir) and potassium carbonate (0.05 mmol) at 120 °C for 20 h. When $[IrCl(cod)]_2$ and $[Cp^*IrCl_2]_2$, commonly used monovalent and trivalent iridium catalysts, respectively, were used, no target product **7a** was obtained (entries 1 and 2). Interestingly, no target product was obtained when iridium-based dicationic catalyst **1** (entry 3), which our research group previously reported to be highly active for carbon-nitrogen bond formation in water,[22d,e] was used. However, the scenario changed when a nitrogen-heterocyclic carbene (NHC) ligand was introduced in the iridium catalyst. In the presence of catalyst **2**, which has methyl groups on the nitrogen atoms of the NHC ligand, the target product **7a** was formed in 7% yield (entry 4). To examine the effect of substituents on the nitrogen atoms of the NHC ligand, the same reaction was carried out using catalysts **3** and **4**, bearing ethyl and isopropyl groups, respectively. The yields increased to 79% and 92%

(entries 5 and 6), respectively, in the presence of these catalysts. Furthermore, when dicationic catalyst **5**, which exhibits high activity for carbon-nitrogen bond formation in water,[22a] was used, the yield of **7a** was 89% (entry 7), i.e., the yields obtained with catalysts **4** and **5** were almost similar. Reducing the dimethylamine concentration to 4.0 mmol decreased the yield of **7a** to 82% (entry 8). Increasing the amount of dimethylamine to 8.0 mmol did not raise the yield of **7a** (entry 9). In addition, effect of the amount of catalyst **4** and the reaction temperature were examined (entries 10 and 11). When the catalyst loading was reduced to 0.33 mol%, the yield of **7a** decreased to 64% (entry 10). Lowering the reaction temperature to 90 °C resulted in 60% yield of **7a** (entry 11). Next, the effect of base on the yield of **7a** was investigated. In the absence of base, the yield of **7a** was 56% (entry 12). When sodium carbonate and cesium carbonate were used as the base, the yield of **7a** was 92% (entries 16 and 17). Thus, sodium carbonate, cesium carbonate, and potassium carbonate were suitable bases for this reaction (entries 6, 16, and 17). On the other hand, when sodium bicarbonate, sodium methoxide, or potassium *tert*-butoxide was used as the base, the yield of **7a** decreased (entries 13-15). For the reaction corresponding to entry 17, the pure target product was obtained in 83% isolated yield upon purification using silica gel column chromatography. Based on these results, **4** was determined to be the optimum iridium catalyst. Although any one of sodium, potassium, or cesium carbonate could be suitably used as a base for this reaction, the author chose to use sodium carbonate in the subsequent experiments considering the cost and ease of handling.

Table 1. Optimization of the reaction conditions for bisdimethylamination of 1,6-hexanediol with an aqueous solution of dimethylamine.[a]

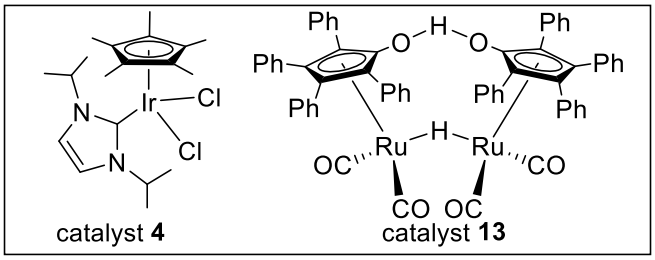


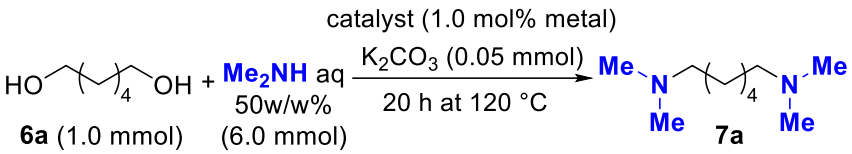
entry	catalyst	base	conv. (%)[b]	yield (%)[b]
1	$[IrCl(cod)]_2$	K_2CO_3	7	0
2	$[Cp^*IrCl_2]_2$	K_2CO_3	34	0
3	**1**	K_2CO_3	33	0
4	**2**	K_2CO_3	41	7
5	**3**	K_2CO_3	100	79
6	**4**	K_2CO_3	100	92
7	**5**	K_2CO_3	100	89
8[c]	**4**	K_2CO_3	100	82
9[d]	**4**	K_2CO_3	100	92
10[e]	**4**	K_2CO_3	100	64
11[f]	**4**	K_2CO_3	100	60
12	**4**	none	100	56
13	**4**	$NaHCO_3$	100	59
14	**4**	NaOMe	100	89
15	**4**	^{t}BuOK	100	86
16	**4**	Cs_2CO_3	100	92
17	**4**	Na_2CO_3	100	92(83[g])

[a]Reaction was conducted with 1,6-hexanediol (**6a**, 1.0 mmol), dimethylamine (6.0 mmol), base (0.05 mmol) and catalyst (1.0 mol% Ir) at 120 °C for 20 h. [b]Conversion and yield were determined by GC analysis using biphenyl as an internal standard. [c]4.0 mmol of dimethylamine was used. [d]8.0 mmol of dimethylamine was used. [e]catalyst **4** (0.33 mol%) was used. [f]reaction was conducted at 90 °C. [g]Isolated yield.

Additional experiments using other transition metal catalysts were also carried out, and the results are provided in Table 2. None of the catalysts showed higher activity than iridium catalyst **4** having NHC ligands with isopropyl substituents on nitrogen

Table 2. Additional investigation of other catalysts for bisdimethylamination.[a]





entry	catalyst	yield (%)[b]
1	**4**	92
2	$Co(acac)_2$	0
3	$PdCl_2$/dppe	0
4	$[Ru(p\text{-cymene})Cl_2]_2$	0
5[c]	$[Ru(p\text{-cymene})Cl_2]_2$	0
6[d]	$[Ru(p\text{-cymene})Cl_2]_2$	4
7	$RuCl_2(PPh_3)_3$	6
8	**13**	3

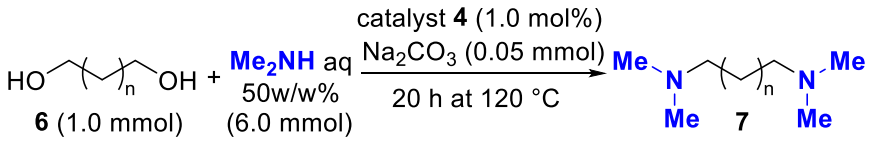
[a]Reaction was conducted with 1,6-hexandiol (1.0 mmol), dimethylamine (6.0 mmol), K_2CO_3 (0.05 mmol) and catalyst (1.0 mol% metal) at 120 °C for 20 h. [b]yields were determined by GC analysis using biphenyl as an internal standard. [c]The reaction was conducted without addition of base. [d]The reaction was conducted using DPEphos (1.0 mol%) without addition of base.

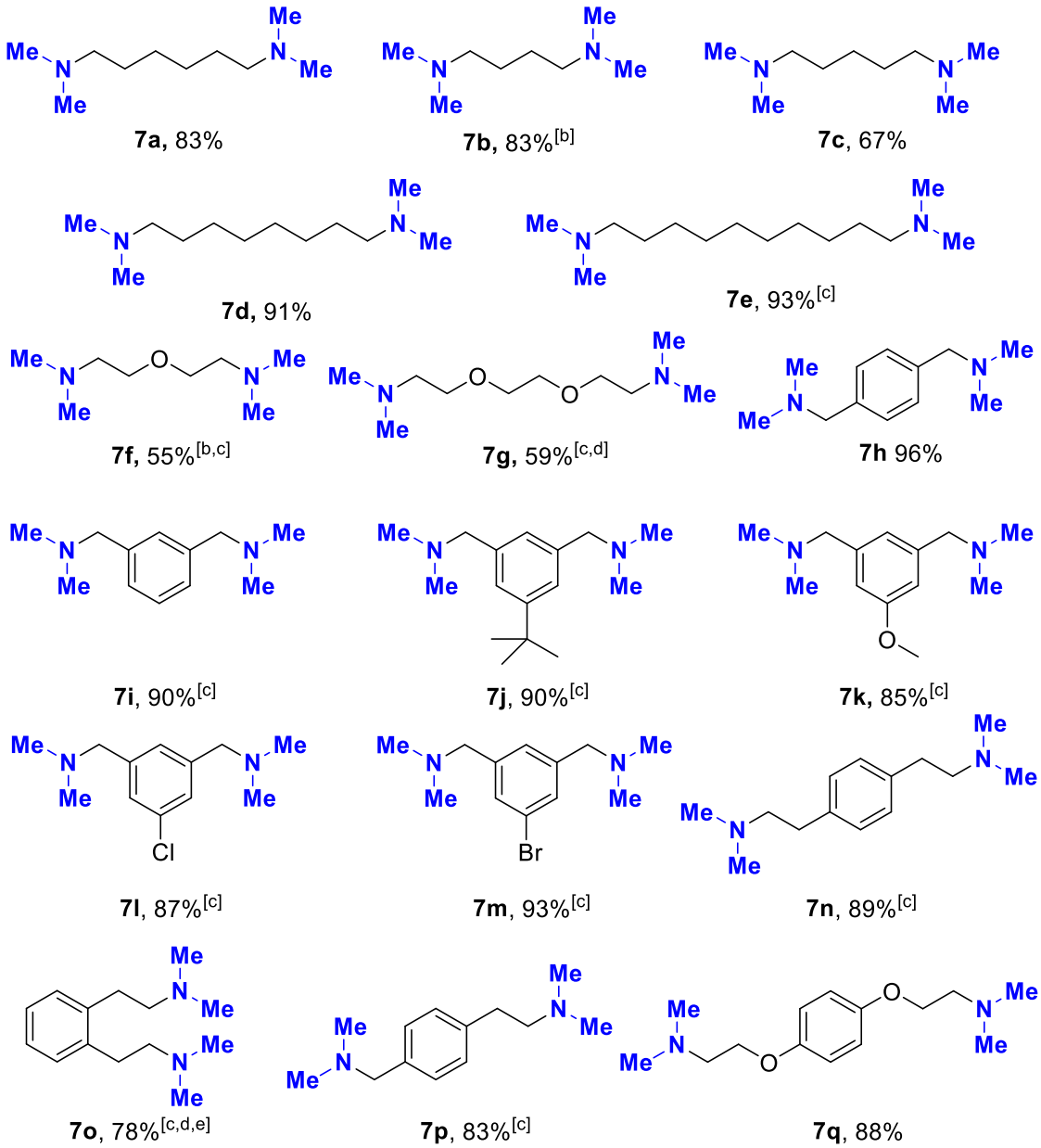
The scope of the reaction was investigated under the optimum reaction conditions. The reaction was performed inside a stainless tube under argon atmosphere by reacting various diols (1.0 mmol) with aqueous dimethylamine (6.0 mmol) in the presence of iridium catalyst **4** (1.0 mol%), and sodium carbonate (0.05 mmol) at 120 °C for 20 h. The isolated yields are shown in Table 3.[23] First, the author performed the synthesis of linear compounds containing

dimethylamino groups at both ends. These products are often utilized as foaming agents in urethane synthesis, as cross-linking agents in polymer synthesis, and as precursors for synthesizing bioactive substances and surfactants.[1-3] *N,N,N′,N′*-Tetramethyl-1,6-hexanediamine (**7a**) was obtained in good isolated yields of 83%. The yields of bisdimethylamines **7b** and **7c** with relatively short alkyl chains (C4 and C5) were 83% and 67%, respectively. On the other hand, the yields of **7d** and **7e** with long alkyl chains were 91% and 93%, respectively. Products **7f** and **7g** containing ether moieties could be synthesized using the corresponding diols as starting materials.

Next, the author investigated the syntheses of bisdimethylamine derivatives containing a benzene skeleton, which is useful from the viewpoint of synthetic chemistry. Using 1,4-benzenedimethanol as the starting material, bisdimethylaminated product **7h** was obtained in a very high yield (96%). In addition, the syntheses of compounds **7i-m**, which are important NCN pincer ligands in the fields of organometallic chemistry and catalysis, were investigated. The reaction of 1,3-benzenedimethanol gave **7i** in 90% yield. Compound **7j** with bulky *tert*-butyl groups on the benzene ring was also obtained in a high yield. The synthesis of **7k** with an electron-donating methoxy group was also feasible. Further, the syntheses of **7l** and **7m** with chloro and bromo groups, respectively, proceed smoothly. These results will not only be useful for the syntheses of pincer-type ligands with electron-withdrawing substituents but will also be important from the viewpoint of their utilization as intermediates for the conversion into other derivatives. Compounds **7n** and **7o**, which contain two ethylene chains attached to the benzene ring with dimethylamino groups at their termini, were synthesized in good yields. The synthesis of the unsymmetrical compound **7p**, in which ethylene and methylene chains were connected to a benzene ring, proceed smoothly. The synthesis of 1,4-bis(2-dimethylaminoethoxy)benzene (**7q**) can be easily conducted using this catalytic system. Thus, bisdimethylamine derivatives can be synthesized using the corresponding diols as starting materials.

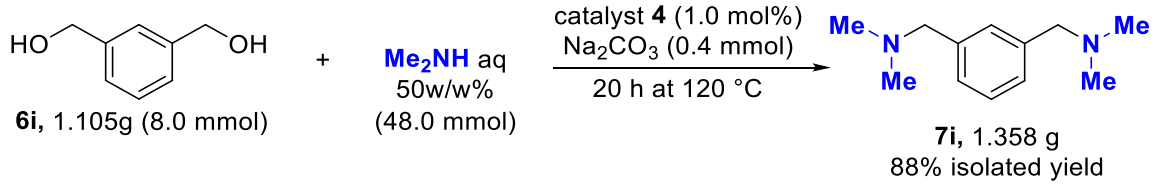
Table 3. Bisdimethylamination of various diols with an aqueous solution of dimethylamine.[a]





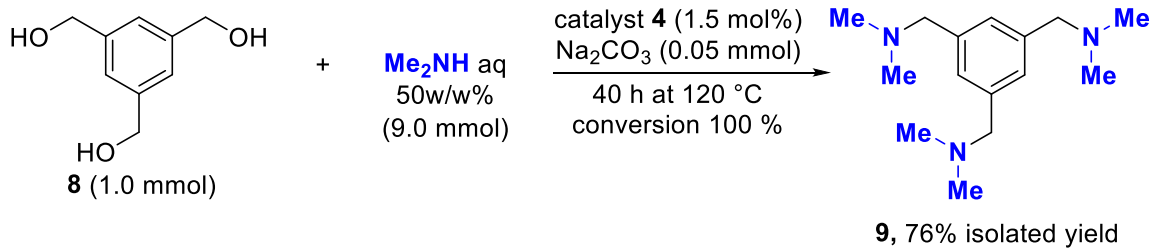
[a]Reaction was conducted with diol (1.0 mmol), dimethylamine (6.0 mmol), Na_2CO_3 (0.05 mmol) and catalyst **4** (1.0 mol%) at 120 °C for 20 h. Isolated yields are shown. [b]Determined by GC analysis. [c] Reaction was conducted for 40 h. [d] Catalyst **4** (1.5 mol%) was used. [e]Reaction was conducted at 130 °C.

From the viewpoint of practical organic synthesis, the author next performed the gram-scale reaction (Scheme 7). Indeed, **7i**, a potential NCN pincer ligand, was obtained in 88% yield (1.358 g) using 1.105 g of 1,3-benzenedimethanol and 5.28 mL of an aqueous solution of dimethylamine (50% w/w). Conventionally, **7i** is synthesized via a multi-step reaction using expensive starting materials and/or highly toxic reagents. Using the new catalytic system, analogous promising NCN pincer ligands can be conveniently synthesized on a large scale.



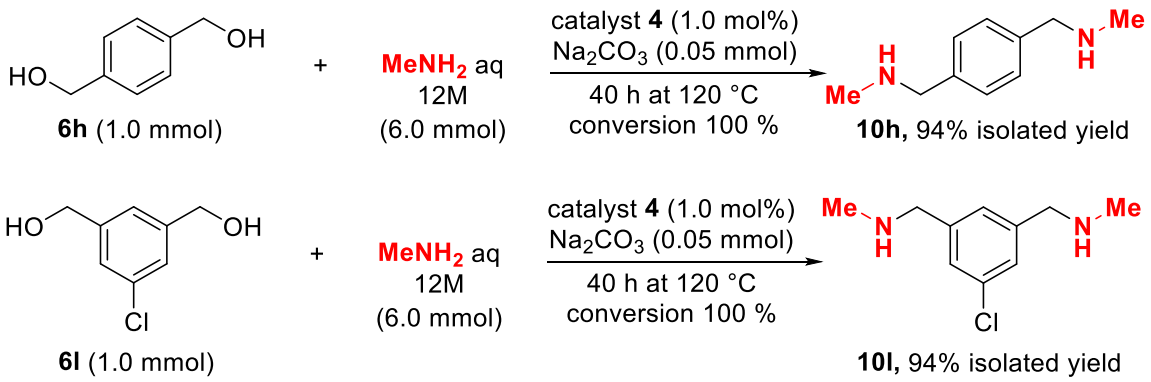
Scheme 7. Investigation for gram-scale reaction.

The catalytic system developed here could be applied for the synthesis of other amino compounds. First, the trisdimethylamination of a triol **8** with aqueous dimethylamine was examined. Consequently, 1,3,5-tris(dimethylaminomethyl)benzene (**9**) was obtained in 76% yield (Scheme 8). Product **9** is used as a foaming agent, an electrolytic solution, and a photosensitive compound; therefore, the single-step synthesis of this compound from readily available starting materials will be of significant practical importance.[24]



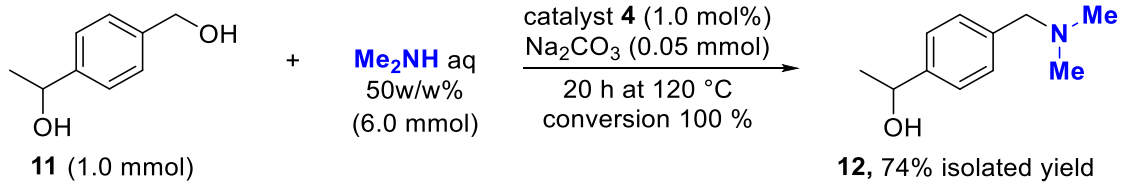
Scheme 8. Trisdimethylamination of triol.

Next, the reactions were conducted using an aqueous solution of monomethylamine instead of dimethylamine. As illustrated in Scheme 9, bismethylamination of **6h** and **6l** proceeded under these conditions to afford good yields of **10h**,[25] which can be used as monomers in polymer synthesis and new compound **10l**.



Scheme 9. Bismethylamination with an aqueous solution of methylamine.

In addition, diol **11**, which contains both primary and secondary alcohol groups, was reacted with aqueous dimethylamine. Dimethylamination proceeded selectively at the sterically unhindered primary alcohol site to give product **12** in 74% yield without dimethylamination at sterically hindered secondary alcohol site (Scheme 10). Thus, the present catalytic system could be effective for the preferential dimethylamination of primary alcohols. Based on this, the developed strategy is expected to be useful for site-selective amination to synthesize natural products and pharmaceuticals.

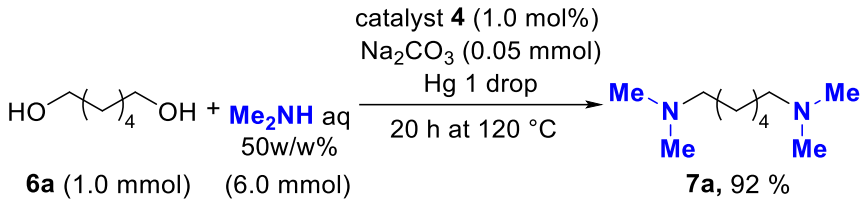


Scheme 10. Site-selective mono-amination of diol.

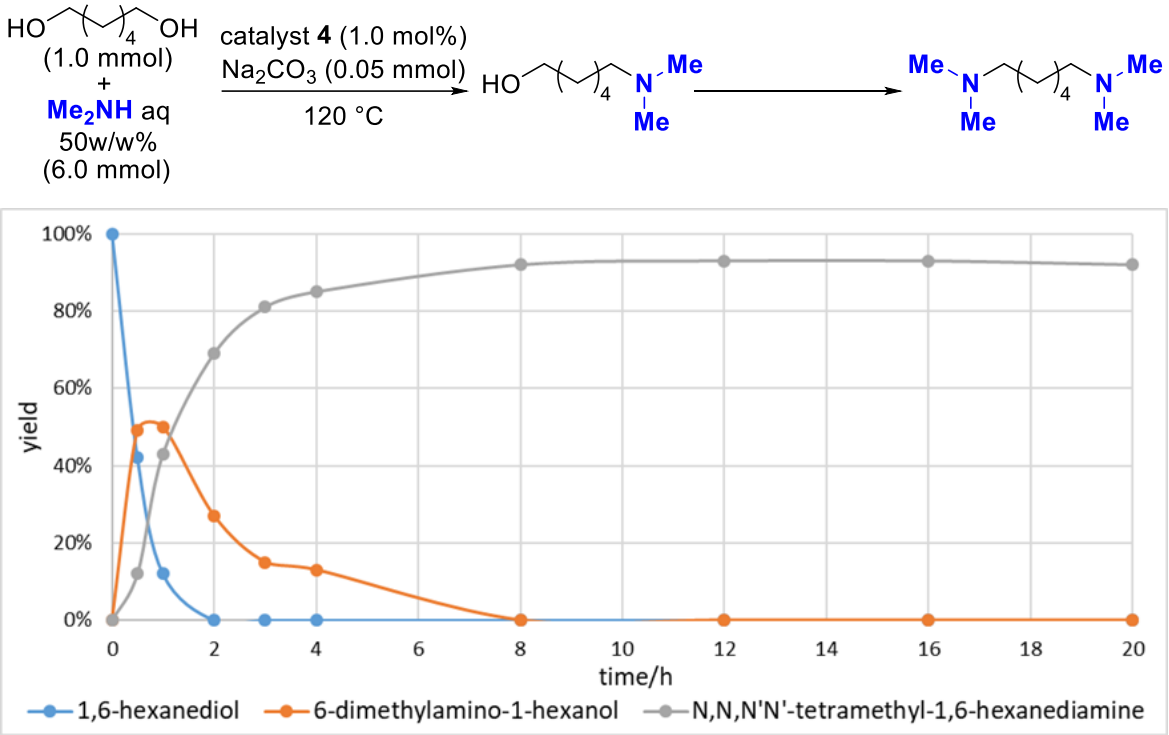
To gain insights into the mechanism for bisdimethylamination, the author conducted the mercury poisoning test, which is the method to distinguish between the homogeneous catalyst and heterogeneous catalyst. In the case of heterogeneous catalysts, the addition of mercury poisons the catalyst, leading to suppressing catalytic activity. When the reaction was conducted with 1,6-hexanediol (**6a**, 1.0 mmol), an aqueous solution of dimethylamine (6.0 mmol), Na_2CO_3 (0.05 mmol), catalyst **4** (1.0 mol%) and 1 drop of mercury at 120 °C for 20 h, *N,N,N′,N′*-tetramethylhexanediamine (**7a**) was obtained in 92% yield. Then, the mercury poisoning test showed no influence of the yield of bisdimethylamination, suggesting that this

catalytic reaction is homogeneous.

Scheme 11. Mercury poisoning experiment.

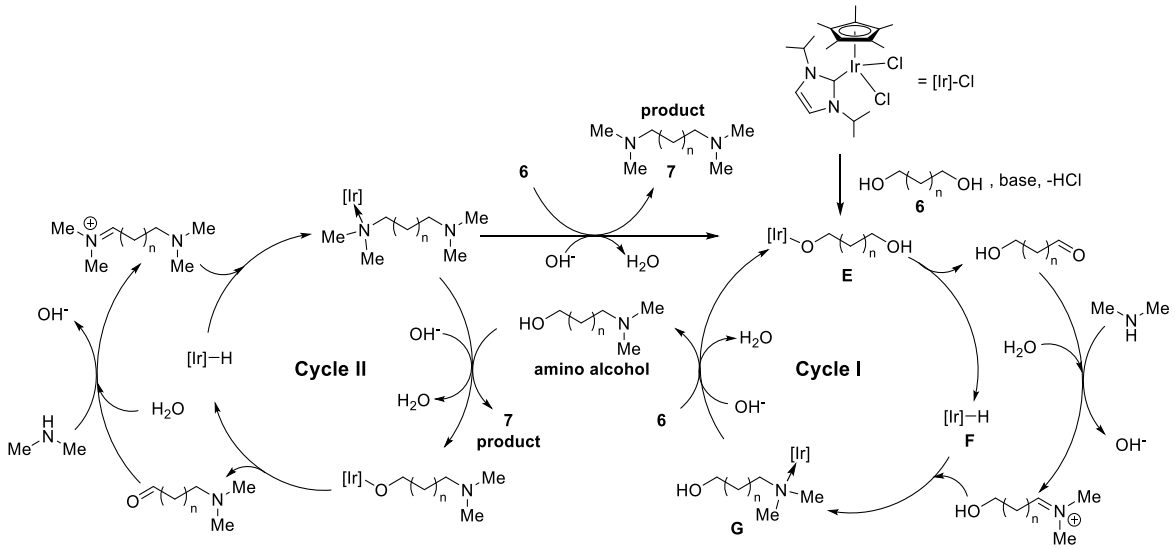


Additionally, the author investigated the time-resolved profile of bisdimethylamination of 1,6-hexanediol. Product yields were determined by GC analysis (Scheme 12). This catalytic reaction was found to be a successive reaction that produced 6-dimethylamino-1-hexanol. 1,6-hexanediol is quickly consumed in the initial step of the reaction to form 6-dimethylamino-1-hexanol. Continuously, *N,N,N′,N′*-tetramethyl-1,6-hexanediamine was also rapidly produced without accumulation of 6-dimethylamino-1-hexanol. This time-resolved profile indicates that the production of 1,6-hexanediol and 6-dimethylamino-1-hexanol do not interfere with each other and the dimethylamination reaction proceeds simultaneously.



Scheme 12. Time-resolved profile of the yield for bisdimethylation of 1,6-hexanediol catalyzed by **4**.

In contrast to previous reports obtained as a mixture with dimethylamino alcohols (Scheme 6), this catalytic system accomplished the reaction to give bisdimethylamine derivatives effectively without catalyst deactivation. Our research group has previously proposed the mechanism for the *N*-alkylation of amines with alcohols[21,22] and the author discussed the iridium-catalyzed *N,N*-dimethylamination of primary alcohols[22c] through borrowing hydrogen strategy in chapter 3. Based on these mechanisms and experimental evidence, a plausible mechanism for the present reaction is illustrated in Scheme 13. Catalytic bisdimethylamination involves the dimethylamination of diol to afford aminoalcohol (Cycle l), followed by the successive dimethylamination of the alcoholic moiety of aminoalcohol (Cycle II). In Cycle l, alkoxo-iridium species **E** is formed by the reaction of catalyst **4** with diol **6** in the presence of a base (Na_2CO_3). Then, the hydrido-iridium species **F** and an aldehyde are formed by *β*-hydrogen elimination. The aldehyde reacts with dimethylamine to afford iminium ions via dehydrative condensation. Next, transfer hydrogenation of the iminium ion with the hydrido-iridium species **F** proceeds to give amine coordination complex **G**, which would be subjected to the release of aminoalcohol. In Cycle II, the aminoalcohol intermediate is dimethylaminated to give bisdimethylamine as the final product (**7**) through dehydrogenation, formation of iminium ion, and transfer hydrogenation, similar to that in Cycle I.



Scheme 13. Plausible mechanism for bisdimethylamination of diol and dimethylamine.

In order to support the proposed mechanism, the author tried to observe the hydride species which is the important active species in borrowing hydrogen reaction. The reaction of catalyst **4**, 1,6-hexanediol, and Na_2CO_3 at 50 ℃ for 8 hours was performed, resulting in the observation of a signal due to hydrido-iridium species at -17.2 ppm in ^1H NMR analysis (Figure 3). This result strongly supports the proposed mechanism, although the detailed structure of hydrido-iridium species has not been clarified at this stage.

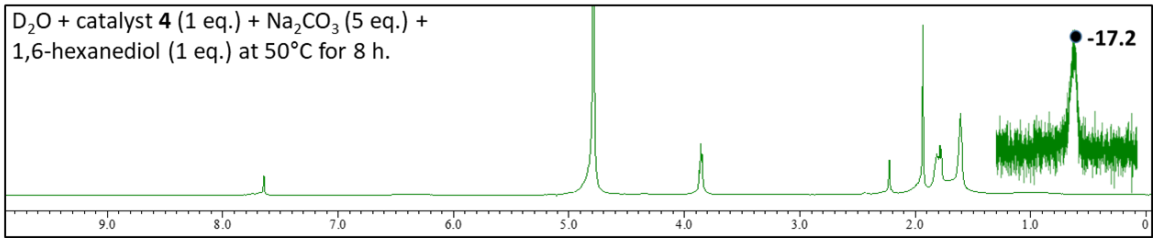


Figure 3. ^1H NMR spectra showing the formation of catalyst **4** with Na_2CO_3 and 1,6-hexanediol at 50 °C.

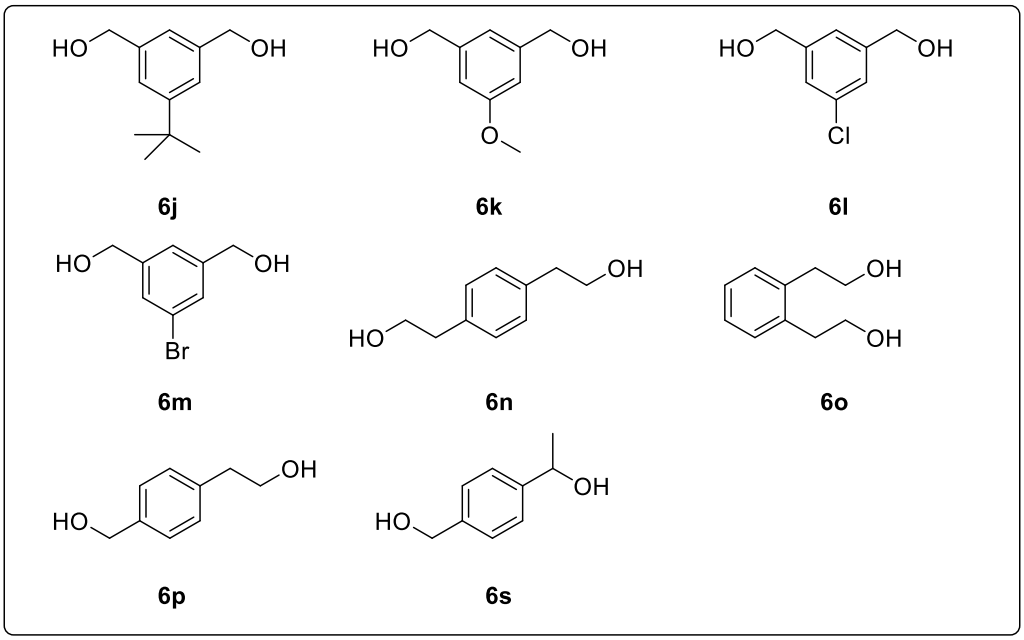
4.3. Conclusion

In summary, the author successfully developed a new iridium-catalyzed system for the selective synthesis of bisdimethylamines using diol and aqueous dimethylamine. The reaction followed the borrowing hydrogen pathway and proceeded under environmentally benign conditions, without requiring additional organic solvents, expensive ligands, high temperatures, or high pressures. Using this catalytic system, various valuable bisdimethylamine derivatives could be selectively synthesized. Furthermore, trisdimethylamination, bismethylamination, and site-selective monoamination were feasible using this catalytic system.

4.4. Experimental Section

All reactions were performed in a sealed stainless tube using aluminum block heater. ^{1}H and $^{13}C\{^{1}H\}$ 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 (GL-Science, Tokyo, Japan) with a capillary column (InertCap for Amines and InertCap Pure WAX) and a flame ionization detector (FID). GC oven temperature was programmed (the initial temperature was 50 °C, held for 10 min and raised at 5 °C/min to 250 °C, held for 10 min.). Elemental analyses were carried out at the Microanalysis Center of Kyoto University. Flash column chromatography was conducted with a Wako-gel C-200. An aqueous dimethylamine solution (50%) is commercially available and was used as received from FUJIFILM Wako Pure Chemical Corporation. an aqueous methylamine solution (40%) is commercially available and was used as received from Tokyo Chemical Industry. $[Cp^*IrCl_2]_2$[26] (Cp^*: η^5-pentamethylcyclopentadienyl), the complexes **1**,[22d] **2**,[27] **3**,[28] **4**,[21d] and **5**[22a] were prepared according to the literature method. All other reagents are commercially available and were used as received from Tokyo Chemical Industry, Sigma-Aldrich, Acros Organics, Nacalai Tesque, BLD Pharm, FUJIFILM Wako Pure Chemical Corporation, and Oakwood Chemical.

Preparation of diols



(1) Preparation of 5-*tert*-butyl-1,3-benzenedimethanol (6j)[29]: Under an atmosphere of argon, stirrer bar, 5-*tert*-Butylisophthalic acid (1560.8 mg, 7.0 mmol) and THF (28.0 mL) were placed to two-neck round flask equipped with a three-way cork. BH_3-THF (1M in THF) (28.0 mL, 28.0 mmol) was added dropwise and the mixture was stirred overnight at room temperature. After the reaction, it was carefully quenched with H_2O (50 mL) and extracted with diethyl ether (50 mL x 3). The separated solution was washed with brine and dried with $MgSO_4$. After evaporation, the product was purified by silica gel chromatography eluting with organic solvent (hexane/EtOAc =1:1 to 1:4) to give **6j** as a white solid in 89% yield (1209.9 mg, 6.2 mmol). ^{1}H NMR (400 MHz, $CDCl_3$, r.t.) δ 7.29 (s, 2H, aromatic), 7.17 (s, 1H, aromatic), 4.64 (s, 4H, C*H*$_2$OH), 2.24 (s, 2H, O*H*), 1.32 (s, 9H, C(C*H*$_3$)$_3$). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, r.t.) δ 152.1 (*C*$_{aromatic}$), 141.0 (*C*$_{aromatic}$), 123.5 (*C*$_{aromatic}$), 123.1 (*C*$_{aromatic}$), 65.6 (*C*H$_2$), 34.9 (*C*(CH$_3$)$_3$), 31.5 (C(*C*H$_3$)$_3$).

(2) Preparation of 5-methoxy-1,3-benzenedimethanol (6k)[30]: Under an atmosphere of argon, stirrer bar, 5-methoxy-Butylisophthalic acid (1380.0 mg, 7.1 mmol) and THF (28.0 mL) were placed to two-neck round flask equipped with a three-way cork. BH_3-THF (1M in THF) (28.9 mL, 28.9 mmol) was added dropwise and the mixture was stirred overnight at room temperature. After the reaction, it was carefully quenched with H_2O (50 mL) and extracted with diethyl ether (50 mL x 3). The separated solution was washed with brine and dried with $MgSO_4$. After evaporation, the product was purified by silica gel chromatography eluting with organic solvent (hexane/EtOAc =1:1 to 1:4) to give **6k** as a white solid in 57% yield (686.7 mg, 4.1 mmol). ^{1}H NMR (500 MHz, $CDCl_3$, r.t.) δ 6.92 (s, 1H, aromatic), 6.83 (s, 2H, aromatic), 4.65 (s, 4H, C*H*$_2$), 3.81 (s, 3H, OC*H*$_3$), 1.98 (s, 2H, O*H*). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, r.t.) δ 160.3 (*C*$_{aromatic}$), 142.9 (*C*$_{aromatic}$), 117.6 (*C*$_{aromatic}$), 111.7 (*C*$_{aromatic}$), 65.3 (*C*H$_2$), 55.5 (O*C*H$_3$).

(3) Preparation of 5-chloro-1,3-benzenedimethanol (6l): Under an atmosphere of argon, stirrer bar, 5-chloro-Butylisophthalic acid (1403.7 mg, 7.0 mmol) and THF (28.0 mL) were placed to two-neck round flask equipped with a three-way cock. BH_3-THF (1M in THF) (28.0 mL, 28.0 mmol) was added dropwise and the mixture was stirred overnight at room temperature. After the reaction, it was carefully quenched with H_2O (50 mL) and extracted

with diethyl ether (50 mL x 3). The separated solution was washed with brine and dried with $MgSO_4$. After evaporation, the product was purified by silica gel chromatography eluting with organic solvent (hexane/EtOAc =1:1 to 1:4) to give **6l** as a white solid in 85% yield (1025.3 mg, 5.94 mmol). ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.28 (s, 2H, aromatic), 7.23 (s, 1H, aromatic), 4.67 (s, 4H, C*H*$_2$), 1.83 (s, 2H, O*H*). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, 50 °C) δ 143.3 (*C*$_{aromatic}$), 134.9 (*C*$_{aromatic}$), 126.2 (*C*$_{aromatic}$), 123.3 (*C*$_{aromatic}$), 64.7 (*C*H$_2$). ^{1}H NMR (500 MHz, CD_3OD, r.t.) δ 7.26 (s, 1H, aromatic), 7.24 (s, 1H, aromatic), 4.59 (s, 4H, C*H*$_2$). ^{13}C{^{1}H} NMR (126 MHz, CD_3OD, r.t.) δ 145.3 (*C*$_{aromatic}$), 135.2 (*C*$_{aromatic}$), 126.4 (*C*$_{aromatic}$), 124.3 (*C*$_{aromatic}$), 64.3 (*C*H$_2$). Elemental analysis calcd for $C_8H_9ClO_2$: C 55.67, H 5.26, found: C 55.47, H 5.19.

(4) Preparation of 5-bromo-1,3-benzenedimethanol (6m)[31]: Under an atmosphere of argon, stirrer bar, 5-bromo-Butylisophthalic acid (1707.7 mg, 7.0 mmol) and THF (28.0 mL) were placed to two-neck round flask equipped with a three-way cock. BH_3-THF (1M in THF) (28.0 mL, 28.0 mmol) was added dropwise and the mixture was stirred overnight at room temperature. After the reaction, it was carefully quenched with H_2O (50 mL) and extracted with diethyl ether (50 mL x 3). The separated solution was washed with brine and dried with $MgSO_4$. After evaporation, the product was purified by silica gel chromatography eluting with organic solvent (hexane/EtOAc =1:1 to 1:4) to give **6m** as a white solid in 71% yield (1678.7 mg, 5.0 mmol). ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ 7.45 (s, 2H, aromatic), 7.29 (s, 1H, aromatic), 4.68 (d, 4H, *J* = 5.5 Hz, C*H*$_2$), 1.71 (s, 2H, O*H*). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, 50 °C) δ 143.6 (*C*$_{aromatic}$), 129.2 (*C*$_{aromatic}$), 123.9 (*C*$_{aromatic}$), 123.0 (*C*$_{aromatic}$), 64.6 (*C*H$_2$).

(5) Preparation of 1,4-benzenediethanol (6n)[32]: Under an atmosphere of argon, stirrer bar, 1,4-Phenylenediacetic Acid (1401.0 mg, 7.2 mmol) and THF (28.0 mL) were placed to two-neck round flask equipped with a three-way cock. BH_3-THF (1M in THF) (28.0 mL, 28.0 mmol) was added dropwise and the mixture was stirred overnight at room temperature. After the reaction, it was carefully quenched with H_2O (50 mL) and extracted with diethyl ether (50 mL x 3). The separated solution was washed with brine and dried with $MgSO_4$. After evaporation, the product was purified by silica gel chromatography eluting with organic

solvent (hexane/EtOAc =1:1 to 1:4) to give **6n** as a white solid in 62% yield (746.5 mg, 4.5 mmol). ^{1}H NMR (400 MHz, $CDCl_3$, r.t.) δ 7.17 (s, 4H, aromatic), 3.80–3.85 (t, 4H, J = 5.6 Hz, CH_2OH), 2.81–2.85 (t, 4H, J = 5.6 Hz, ArCH_2), 1.66–1.69 (t, 2H, J = 5.6 Hz, OH). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, r.t.) δ 136.8 ($C_{aromatic}$), 129.4 ($C_{aromatic}$), 63.7 (CH$_2$OH), 38.9 (ArCH$_2$).

(6) Preparation of 1,2-benzenediethanol (6o)[33]: Under an atmosphere of argon, stirrer bar, 1,2-Phenylenediacetic Acid (1094.6 mg, 5.6 mmol) and THF (23.0 mL) were placed to two-neck round flask equipped with a three-way cock. BH_3-THF (1M in THF) (23.0 mL, 23.0 mmol) was added dropwise and the mixture was stirred overnight at room temperature. After the reaction, it was carefully quenched with H_2O (50 mL) and extracted with diethyl ether (50 mL x 3). The separated solution was washed with brine and dried with $MgSO_4$. After evaporation, the product was purified by silica gel chromatography eluting with organic solvent (hexane/EtOAc =1:1 to 1:4) to give **6o** as a white solid in 75% (706.8 mg, 4.3 mmol). ^{1}H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.18 (s, 4H, aromatic), 3.79–3.81 (t, 4H, J = 7.0 Hz, CH_2OH), 2.89–2.92 (t, 4H, J = 6.5 Hz, ArCH_2), 2.85 (brs, 2H, OH). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, r.t.) δ 137.3 ($C_{aromatic}$), 130.1 ($C_{aromatic}$), 129.8 ($C_{aromatic}$), 126.8 ($C_{aromatic}$), 63.5 (CH$_2$OH), 35.6 (ArCH$_2$).

(7) Preparation of 4-(Hydroxymethyl)benzeneethanol (6p)[34]: Under an atmosphere of argon, stirrer bar, 4-Carboxybenzeneacetic acid (1256.1 mg, 7.0 mmol) and THF (28.0 mL) were placed to two-neck round flask equipped with a three-way cock. BH_3-THF (1M in THF) (28.0 mL, 28.0 mmol) was added dropwise and the mixture was stirred overnight at room temperature. After the reaction, it was carefully quenched with H_2O (50 mL) and extracted with diethyl ether (50 mL x 3). The separated solution was washed with brine and dried with $MgSO_4$. After evaporation, the product was purified by silica gel chromatography eluting with organic solvent (hexane/EtOAc =1:1 to 1:4) to give **6p** as a white solid in 65% yield (693.2 mg, 4.6 mmol). ^{1}H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.29–7.31 (d, 2H, J = 8.0 Hz, aromatic), 7.20–7.22 (d, 2H, J = 8.0 Hz, aromatic), 4.64 (s, 1H, ArCH_2OH), 3.82 (brs, 2H, CH$_2$CH_2OH), 2.84–2.86 (t, 2H, J = 6.5 Hz, ArCH_2CH$_2$), 1.98 (brs, 1H, ArCH$_2$OH), 1.68 (brs, 1H, OH). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, r.t.) δ 139.2 ($C_{aromatic}$), 138.1 ($C_{aromatic}$), 129.3

($C_{aromatic}$), 127.3 ($C_{aromatic}$), 65.2 (ArCH_2OH), 63.7 (CHCH_2OH), 38.9 (ArCH_2CH_2).

(8) preparation of 1-(4-(Hydroxymethyl)phenyl)ethanol (6s)[35]: Under an atmosphere of argon, 4-Acetylbenzoic acid (1459.0 mg, 8.89 mmol) and THF (120.0 mL) were placed to two-neck round flask equipped with a Dimroth condenser, a three-way cock and a drop funnel. Stirrer bar and $LiAlH_4$ 2010.0 mg (53.0 mmol) were placed in drop funnel and added dropwise. the mixture was stirred at 90 °C overnight. After the reaction, it was carefully quenched with 6 M NaOH (10 mL) and solution was separated with glass filter packed with celite. After evaporation, the product was purified by silica gel chromatography eluting with organic solvent (hexane/EtOAc =1:1) to give **6s** as a white solid in 80% yield (1086.2 mg, 7.14 mmol). ^{1}H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.31–7.28 (m, 4H, aromatic), 4.85–4.82 (q, 1H, *J* = 6.0 Hz, C*H*), 4.59 (s, 2H, CH_2), 2.51 (s, 2H, ArCH_2O*H,* CH*OH* two peak may be overlapped), 1.45–1.44 (d, 3H, *J* = 6.5 Hz, CH_3). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, r.t.) δ 145.3 ($C_{aromatic}$), 140.1 ($C_{aromatic}$), 127.2 ($C_{aromatic}$), 125.7 ($C_{aromatic}$), 70.2 (*C*H), 64.9 (*C*H_2), 25.3 (*C*H_3).

Procedure for optimization of the reaction conditions for bisdimethylamination of 1,6-hexanediol with an aqueous solution of dimethylamine in Table 1.

In a stainless tube (5 mL), stirrer bar, the catalyst (0.33-1.0 mol%Ir), base (0-0.05 mmol), 1,6-hexanediol (**6a**, 1.0 mmol) and a 50w/w% aqueous solution of dimethylamine (0.44 mL-0.88 mL, 4.0-8.0 mmol) were added and sealed. The mixture was stirred for 20 h at 90-120 °C using aluminum block heater. After the reaction, it was cooled to room temperature. The crude mixture was diluted with tetrahydrofuran (THF) (50 mL). the conversion of 1,6-hexanediol (**6a**) and the yield of *N,N,N',N'*-tetramethylhexanediamine (**7a**) were determined by GC analysis using biphenyl as an internal standard.

Procedure for optimization of additional catalyst in Table 2.

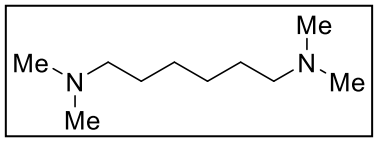
In a stainless tube (5 mL), stirrer bar, the catalyst (1.0 mol%), K_2CO_3 (0.05 mmol), 1,6-hexanediol (1.0 mmol) and a 50w/w% aqueous solution of dimethylamine (0.66 mL, 6.0 mmol) were added and sealed. The mixture was stirred for 20 h at 120 °C using aluminum block heater. After the reaction, it was cooled to room temperature. The crude mixture was

diluted with tetrahydrofuran (THF) (50 mL). the conversion of 1,6-hexanediol (**6a**) and the yield of *N,N,N',N'*-tetramethylhexanediamine (**7a**) were determined by GC analysis using biphenyl as an internal standard.

Procedure for bisdimethylamination of various diols with an aqueous solution of dimethylamine shown in Table 3.

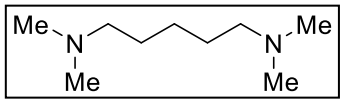
In a stainless tube (5 ml), stirrer bar, the catalyst **4** (1.0-1.5 mol%), Na_2CO_3 (0.05 mmol), diol (1.0 mmol) and a 50w/w% aqueous solution of dimethylamine (0.66 mL, 6.0 mmol) were added and sealed. The mixture was stirred for 20-40 h at 120-130 °C using aluminum block heater. After the reaction, it was cooled to room temperature. The crude mixture was transferred to round bottom flask with dichloromethane. After evaporation, the product was isolated by silica gel column chromatography. The yields of **7b** and **7f** were determined by by GC analysis using biphenyl as an internal standard. Identification of **7b** and **7f** were done by comparison of retention time with commercially available standards.

***N,N,N',N'*-Tetramethyl-1,6-hexanediamine (7a)**:[14c] The product was isolated by silica gel



chromatography eluting with MeOH/EtOAc/Et_2NH (10:100:1) to give **7a** as a pale yellow oil in 83% yield (143.1 mg, 0.583 mmol). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 2.25–2.15 (m, 16H, C*H*$_2$N(C*H*$_3$)$_3$), 1.46–1.42 (m, 4H, C*H*$_2$CH$_2$N(CH$_3$)$_2$), 1.31–1.28. (m, 4H, C*H*$_2$CH$_2$CH$_2$N(CH$_3$)$_2$). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 60.0 (*C*H$_2$N(CH$_3$)$_2$), 45.7 (N(*C*H$_3$)$_2$), 27.9 (*C*H$_2$CH$_2$N(CH$_3$)$_2$), 27.6 (*C*H$_2$CH$_2$CH$_2$N(CH$_3$)$_2$).

***N,N,N',N'*-Tetramethyl-1,5-pentanediamine (7c)**:[36] The product was isolated by silica gel



chromatography eluting with MeOH/EtOAc/Et_2NH (10:100:1) to give **7c** as a pale yellow oil in 67% yield (105.1 mg, 0.583 mmol). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 2.26–2.15 (m, 16H, *CH*$_2$N(C*H*$_3$)$_3$), 1.49–1.42 (m, 4H, C*H*$_2$CH$_2$N(CH$_3$)$_2$), 1.30–1.29. (m, 2H, C*H*$_2$CH$_2$CH$_2$N(CH$_3$)$_2$). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 60.0 (*C*H$_2$N(CH$_3$)$_2$), 45.7 (N(*C*H$_3$)$_2$), 27.9 (*C*H$_2$CH$_2$N(CH$_3$)$_2$), 25.5 (*C*H$_2$CH$_2$CH$_2$N(CH$_3$)$_2$).

***N,N,N′,N′*-Tetramethyl-1,8-octanediamine (7d)**:[37] The product was isolated by silica gel chromatography eluting with MeOH/EtOAc/ Et_2NH (10:100:1) to give **7e** as a pale yellow oil in 91% yield (182.6 mg, 0.911 mmol). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 2.25–2.16 (m, 16H, $CH_2N(CH_3)_3$), 1.46–1.42 (m, 4H, $CH_2CH_2N(CH_3)_2$), 1.29–1.26. (m, 8H, $CH_2CH_2CH_2CH_2CH_2CH_2N(CH_3)_2$). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 60.1 ($CH_2N(CH_3)_2$), 45.7 ($N(CH_3)_2$), 29.7 ($CH_2CH_2N(CH_3)_2$), 27.9 ($CH_2CH_2CH_2N(CH_3)_2$), 27.6 ($CH_2CH_2CH_2CH_2N(CH_3)_2$).

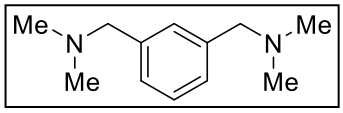
***N,N,N′,N′*-Tetramethyl-1,10-decanediamine (7e)**:[37] The product was isolated by silica gel chromatography eluting with $CHCl_3/Et_2NH$ (50:1) to give **7e** as a pale yellow oil in 93% yield (212.3 mg, 0.929 mmol). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 2.22–2.19 (m, 16H, $CH_2N(CH_3)_3$), 1.44–1.41 (m, 4H, $CH_2CH_2N(CH_3)_2$), 1.34–1.26. (m, 12H, $CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2N(CH_3)_2$). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 60.1 ($CH_2N(CH_3)_2$), 45.7 ($N(CH_3)_2$), 29.75 ($CH_2CH_2N(CH_3)_2$), 29.69 ($CH_2CH_2CH_2N(CH_3)_2$), 27.9 ($CH_2CH_2CH_2CH_2N(CH_3)_2$), 27.6 ($CH_2CH_2CH_2CH_2CH_2N(CH_3)_2$).

1,2-Bis(2-dimethylaminoethoxy)ethane (7g):[38] The product was isolated by silica gel chromatography eluting with MeOH/EtOAc/Et_2NH (5:100:1) to give **7g** as a pale yellow oil in 59% yield (120.3 mg, 0.588 mmol). ^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 3.62 (s, 4H, OCH_2CH_2O), 3.57. (t, J = 6.0 Hz, 4H, OCH_2CH_2N). 2.52–2.49 (t, 4H, J = 6.0 Hz, CH_2N). 2.26 (s, 12H, $N(CH_3)_2$). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 70.5 (OCH_2CH_2O), 69.4 (OCH_2CH_2N), 58.9 (CH_2N), 46.0 ($N(CH_3)_2$).

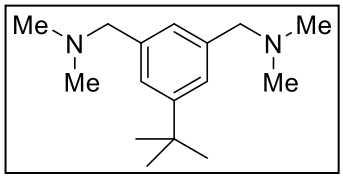
1,4-Bis(dimethylaminomethyl)benzene (7h):[14d] The product was isolated by silica gel chromatography eluting with MeOH/EtOAc/Et_2NH (10:100:1) to give **7h** as a pale yellow oil in 96% yield (185.3 mg, 0.964 mmol).^1H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.24 (s, 4H, aromatic), 3.39. (s, 4H, CH_2N). 2.22 (s, 12H, $N(CH_3)_2$). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, r.t.) δ 137.8

($C_{aromatic}$), 129.1 ($C_{aromatic}$), 64.3 (CH_2), 45.5 (N(CH_3)$_2$).

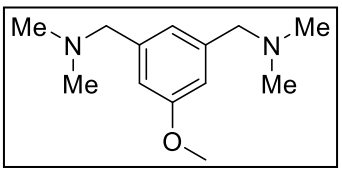
1,3-Bis(dimethylaminomethyl)benzene (7i):[4e] The product was isolated by silica gel chromatography eluting with MeOH/EtOAc/Et_2NH (10:100:1) to give **7i** as a pale yellow oil in 90% yield (172.7 mg, 0.898 mmol). ^{1}H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.28–7.18 (m, 4H, aromatic), 3.40. (s, 4H, CH_2). 2.23 (s, 12H, N(CH_3)$_2$). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, r.t.) δ 139.0 ($C_{aromatic}$), 130.0 ($C_{aromatic}$), 128.3 ($C_{aromatic}$), 128.0 ($C_{aromatic}$), 64.5 (CH_2N), 45.5 (N(CH_3)$_2$).



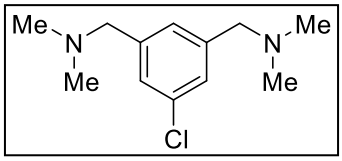
3-*tert*-Butyl-1,5-bis(dimethylaminomethyl)benzene (7j):[39] The product was isolated by silica gel chromatography eluting with MeOH/EtOAc/Et_2NH (5:100:1) to give **7j** as a pale yellow oil in 90% yield (224.7 mg, 0.905 mmol). ^{1}H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.20 (s, 2H, aromatic), 7.04 (s, 1H, aromatic), 3.40 (s, 4H, CH_2N). 2.23 (s, 12H, N(CH_3)$_2$), 1.32 (s, 9H, C(CH_3)$_3$) ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, r.t.) δ 151.2 ($C_{aromatic}$), 138.4 ($C_{aromatic}$), 127.3 ($C_{aromatic}$), 125.0 ($C_{aromatic}$), 64.8 (CH_2), 45.5 (N(CH_3)$_2$), 34.7 (C(CH$_3$)$_3$), 31.6 (C(CH_3)$_3$).



5-Methoxy-1,3-bis(dimethylaminomethyl)benzene (7k): The product was isolated by silica gel chromatography eluting with $CHCl_3$/Et_2NH (50:1) to give **7k** as a pale yellow oil in 85% yield (183.5 mg, 0.848 mmol). ^{1}H NMR (400 MHz, $CDCl_3$, r.t.) δ 6.83 (s, 1H, aromatic), 6.76 (s, 2H, aromatic), 3.80 (s, 3H, OCH_3). 3.40 (s, 4H, CH_2N), 2.22 (s, 12H, N(CH_3)$_2$) ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, r.t.) δ 159.8 ($C_{aromatic}$), 140.5 ($C_{aromatic}$), 122.3 ($C_{aromatic}$), 113.3 ($C_{aromatic}$), 64.5 (CH_2), 55.4 (OCH_3), 45.6 (N(CH_3)$_2$). Elemental analysis calcd for $C_{13}H_{22}N_2O$: C 70.23, H 9.97, 12.60 found: C 70.11, H 9.84, N 12.53.

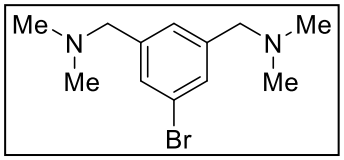


1-Chloro-3,5-bis(dimethylaminomethyl)benzene (7l): The product was isolated by silica gel chromatography eluting with MeOH/EtOAc/Et_2NH (5:100:1) to give **7l** as a pale yellow oil in 87% yield (195.5 mg, 0.865 mmol). ^{1}H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.20 (s, 2H,



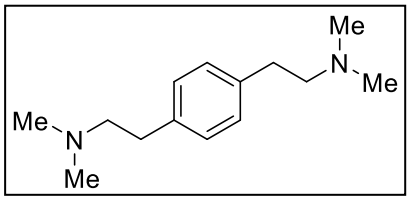
aromatic), 7.12 (s, 1H, aromatic), 3.36 (s, 4H, CH_2N). 2.22 (s, 12H, N(CH_3)$_2$). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, r.t.) δ 141.1 ($C_{aromatic}$), 134.2 ($C_{aromatic}$), 127.8 ($C_{aromatic}$, two peak may be overlapped), 63.9 (CH_2), 45.5 (N(CH_3)$_2$). Elemental analysis calcd for $C_{12}H_{19}N_2Cl$: C 63.56, H 8.45, 12.35 found: C 63.50, H 8.58, N 12.39.

1-Bromo-3,5-bis(dimethylaminomethyl)benzene (7m):[40] The product was isolated by



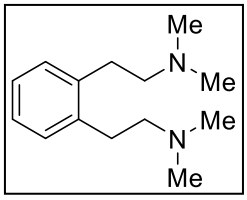
silica gel chromatography eluting with MeOH/EtOAc/Et_2NH (5:100:1) to give **7m** as a pale yellow oil in 93% yield (252.8 mg, 0.932 mmol). ^{1}H NMR (400 MHz, $CDCl_3$, r.t.) δ 7.36 (s, 2H, aromatic), 7.17 (s, 1H, aromatic), 3.36 (s, 4H, CH_2N). 2.22 (s, 12H, N(CH_3)$_2$). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, r.t.) δ 141.4 ($C_{aromatic}$), 130.7 ($C_{aromatic}$), 128.3 ($C_{aromatic}$), 122.5 ($C_{aromatic}$), 63.8 (CH_2), 45.5 (N(CH_3)$_2$).

1,4-bis(dimethylaminoethyl)Benzene (7n): The product was isolated by silica gel



chromatography eluting with $CHCl_3$/Et_2NH (50:1) to give **7n** as a pale yellow oil in 89% yield (196.6 mg, 0.892 mmol). ^{1}H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.12 (s, 4H, aromatic), 2.76–2.72 (m, 4H, ArCH_2), 2.52–2.28 (m, 4H, CH_2N). 2.28 (s, 12H, N(CH_3)$_2$). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, r.t.) δ 138.1 ($C_{aromatic}$), 128.8 ($C_{aromatic}$), 61.8 (ArCH_2), 45.6 (N(CH_3)$_2$), 34.1 (CH_2N). Elemental analysis calcd for $C_{14}H_{24}N_2$: C 76.31, H 10.98, N 12.71 found: C 76.21, H 10.87, N 12.51.

1,2-bis(dimethylaminoethyl)Benzene (7o): The product was isolated by silica gel



chromatography eluting with $CHCl_3$/Et_2NH (50:1) to give **7o** as a pale yellow oil in 78% yield (171.0 mg, 0.776 mmol). ^{1}H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.17–7.13 (m, 4H, aromatic), 2.82–2.79 (m, 4H, ArCH_2), 2.51–2.48 (m, 4H, CH_2N). 2.32 (s, 12H, N(CH_3)$_2$). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, r.t.) δ 138.3 ($C_{aromatic}$), 129.8 ($C_{aromatic}$), 126.5 ($C_{aromatic}$), 61.4 (ArCH_2), 45.6 (N(CH_3)$_2$), 31.1 (CH_2N). Elemental analysis calcd for $C_{14}H_{24}N_2$: C 76.31, H 10.98, N 12.71 found: C 75.93, H 10.91, N 12.51.

4-(2-(Dimethylamino)ethyl)-*N,N*-dimethylaminomethylbenzene (7p): The product was isolated by silica gel chromatography eluting with $CHCl_3/Et_2NH$ (50:1) to give **7p** as a pale yellow oil in 83% yield (171.2 mg, 0.830 mmol). ^{1}H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.22–7.20 (d, 2H, J = 8.0 Hz, aromatic), 7.16–7.14 (d, 2H, J = 8.0 Hz, aromatic), 3.37 (s, 2H, ArCH_2N) 2.78–2.74 (m, 2H, ArCH_2), 2.53–2.50(m, 2H, CH_2N). 2.29 (s, 6H, $ArCH_2N(CH_3)_2$), 2.22 ($ArCH_2CH_2N(CH_3)_2$). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, r.t.) δ 139.3 ($C_{aromatic}$), 136.7 ($C_{aromatic}$), 129.3 ($C_{aromatic}$), 128.6 ($C_{aromatic}$), 64.2 (ArCH_2N), 61.8 (CH_2N), 45.6 ($ArCH_2N(CH_3)_2$), 45.5 ($ArCH_2CH_2N(CH_3)_2$) 34.2 (CH_2CH_2N). Elemental analysis calcd for $C_{13}H_{22}N_2$: C 75.68, H 10.75, N 13.58 found: C 75.52, H 10.56, N 13.37.

1,4-Bis(2-(dimethylamino)ethoxy)benzene (7q): The product was isolated by silica gel chromatography eluting with MeOH/EtOAc/Et_2NH (5:100:1) to give **7q** as a pale brown solid in 88% yield (223.0 mg, 0.884 mmol). ^{1}H NMR (500 MHz, $CDCl_3$, r.t.) δ 6.84 (s, 4H, aromatic), 4.03–3.98 (m, 4H, OCH_2), 2.71–2.68 (m, 4H, CH_2N). 2.32 (s, 12H, $N(CH_3)_2$). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, r.t.) δ 153.2 ($C_{aromatic}$), 115.6 ($C_{aromatic}$), 66.7 (OCH_2), 58.5 (CH_2N), 46.0 ($N(CH_3)_2$). Elemental analysis calcd for $C_{14}H_{24}N_2O_2$: C 66.63, H 9.59, N 11.10 found: C 66.46, H 9.51, N 11.03.

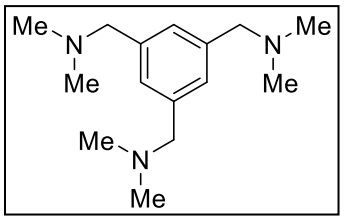
Investigation for gram-scale reaction in Scheme 7.

In a stainless tube (20 ml), stirrer bar, the catalyst **4** (1.0 mol%), Na_2CO_3 (0.40 mmol), 1,3-benzenedimethanol (**6i**, 8.0 mmol) and a 50w/w% aqueous solution of dimethylamine (5.28 ml, 48.0 mmol) were added and sealed. The mixture was stirred for 40 h at 120 °C using aluminum block heater. After the reaction, it was cooled to room temperature. The crude mixture was transferred to round bottom flask with dichloromethane. After evaporation, the product was isolated by silica gel column chromatography eluting with $CHCl_3/Et_2NH$ (100:1) to give **7i** as a pale yellow oil in 88% yield (1358.2 mg, 7.06 mmol). ^{1}H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.27–7.18 (m, 4H, aromatic), 3.40 (s, 4H, CH_2), 2.22 (s, 12H, $N(CH_3)_2$). ^{13}C{^{1}H}

NMR (126 MHz, $CDCl_3$, r.t.) δ 139.0 ($C_{aromatic}$), 129.9 ($C_{aromatic}$), 128.2 ($C_{aromatic}$), 127.9 ($C_{aromatic}$), 64.4(CH_2), 45.5 (N(CH_3)$_2$).

Trisdimethylamination of triol in Scheme 8.

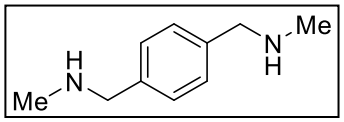
1,3,5-Tris(dimethylaminomethyl)benzene (9):[41] In a stainless tube (5 mL), stirrer bar, the



catalyst **4** (1.5 mol%), Na_2CO_3 (0.05 mmol), 1,3,5-benzenetrimethanol (**8**, 1.0 mmol) and a 50w/w % aqueous solution of dimethylamine (0.88 mL, 9.0 mmol) were added and sealed. The mixture was stirred for 40 h at 120 °C using aluminum block heater. After the reaction, it was cooled to room temperature. The crude mixture was transferred to round bottom flask with dichloromethane. After evaporation, the product was isolated by silica gel column chromatography eluting with MeOH/EtOAc/Et_2NH (5:100:1) to give **9** as a pale yellow oil in 76% yield (189.5 mg, 0.760 mmol). ^{1}H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.13 (s, 3H, aromatic), 3.39 (s, 6H, CH_2), 2.22 (s, 18H, N(CH_3)$_2$). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, r.t.) δ 139.0 ($C_{aromatic}$), 128.8 ($C_{aromatic}$), 64.4 (CH_2), 45.6 (N(CH_3)$_2$).

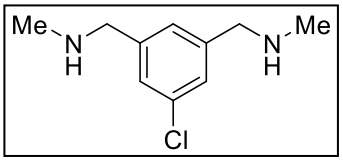
Bismethylamination with an aqueous solution of methylamine in Scheme 9.

1,4-Bis(methylaminomethyl)benzene (10h):[42] In a stainless tube (5 mL), stirrer bar, the



catalyst **4** (1.0 mol%), Na_2CO_3 (0.05 mmol), 1,4-benzenedimethanol (**6h**, 1.0 mmol) and a 12 M 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 aluminum block heater. After the reaction, it was cooled to room temperature. The crude mixture was transferred to round bottom flask with dichloromethane. After evaporation, the product was isolated by silica gel column chromatography eluting with $CHCl_3$/ Et_2NH (100:1) to give **10h** as a pale yellow oil in 94% yield (153.9 mg, 0.937 mmol). ^{1}H NMR (400 MHz, $CDCl_3$, r.t.) δ 7.27 (s, 4H, aromatic), 3.73 (s, 4H, CH_2), 2.45 (s, 6H, NCH_3), 1.32 (s, 2H, NH). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, r.t.) δ 139.0 ($C_{aromatic}$), 128.3 ($C_{aromatic}$), 56.0 (CH_2), 36.2 (NCH_3).

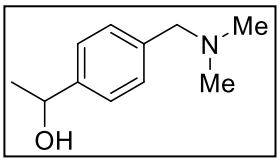
1-Chloro-3,5-bis(methylaminomethyl)benzene(10l): In a stainless tube (5 mL), stirrer bar,



the catalyst **4** (1.0 mol%), Na_2CO_3 (0.05 mmol), 5-chloro-1,3-benzenedimethanol (**6l**, 1.0 mmol) and a 12 M 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 aluminum block heater. After the reaction, it was cooled to room temperature. The crude mixture was transferred to round bottom flask with dichloromethane. After evaporation, the product was isolated by silica gel column chromatography eluting with $CHCl_3$/Et_2NH (50:1) to give **10l** as a pale yellow oil in 97% yield (193.0 mg, 0.971 mmol). ^{1}H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.19 (s, 2H, aromatic), 7.14 (s, 1H, aromatic), 3.70 (s, 4H, C*H*$_2$), 2.43 (s, 12H, NC*H*$_3$), 1,34 (s, 2H, N*H*). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, r.t.) δ 142.4 (*C*$_{aromatic}$), 134.3 (*C*$_{aromatic}$), 126.9 (*C*$_{aromatic}$), 126.1 (*C*$_{aromatic}$), 55.6 (*C*H$_2$), 36.2 (N*C*H$_3$). Elemental analysis calcd for $C_{10}H_{15}N_2Cl$: C 60.45, H 7.61, N 14.10 found: C 60.11, H 7.54, N 13.82.

Site-selective mono-amination of diol in Scheme 10.

1-(4-(Dimethylaminomethyl)phenyl)ethan-1-ol (12):[43] In a stainless tube (5 mL), stirrer



bar, the catalyst **4** (1.0 mol%), Na_2CO_3 (0.05 mmol), 1-(4-(Hydroxymethyl)phenyl)ethanol (**11**, 1.0 mmol) and a 50w/w % aqueous solution of dimethylamine (0.66 mL, 6.0 mmol) were added and sealed. The mixture was stirred for 20 h at 120 °C using aluminum block heater. After the reaction, it was cooled to room temperature. The crude mixture was transferred to round bottom flask with dichloromethane. After evaporation, the product was isolated by silica gel column chromatography eluting with Hexane/EtOAc/Et_2NH (40:10:1) to give **12** as a pale yellow oil in 74 % (133.2 mg, 0.743 mmol). ^{1}H NMR (500 MHz, $CDCl_3$, r.t.) δ 7.32–2.25 (m, 4H, aromatic), 4.89–4.85 (q, 1H, *J* = 6.5 Hz, C*H*), 3.39 (s, 2H, C*H*$_2$), 2.22 (s, 6H, N(C*H*$_3$)$_2$), 1.49–1.48 (d, 3H, *J* = 6.5 Hz, C*H*$_3$). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, r.t.) δ 144.9 (*C*$_{aromatic}$), 138.1 (*C*$_{aromatic}$), 129.4 (*C*$_{aromatic}$), 125.5 (*C*$_{aromatic}$), 70.3 (*C*H), 64.2 (N(*C*H$_3$)$_2$), 45.5 (*C*H$_2$), 25.3 (*C*H$_3$).

Mercury poisoning experiment in Scheme 11.

In a stainless tube (5 mL), stirrer bar, the catalyst **4** (1.0 mol%), Na_2CO_3 (0.05 mmol), 1,6-hexanediol (1.0 mmol), a 50w/w% aqueous solution of dimethylamine (0.66 ml, 6.0 mmol) and 1 drop of mercury were added and sealed. The mixture was stirred for 20 h at 120 °C using aluminum block heater. After the reaction, it was cooled to room temperature. The crude mixture was diluted with tetrahydrofuran (THF) (50 mL). the conversion of 1,6-hexanediol (**6a**) and the yield of *N,N,N',N'*-tetramethylhexanediamine (**7a**) were determined by GC analysis using biphenyl as an internal standard.

Time-resolved profile of the yield for bisdimethylation of 1,6-hexanediol catalyzed by 4 in Scheme 12.

In a stainless tube (5 mL), stirrer bar, the catalyst **4** (1.0 mol%), Na_2CO_3 (0.05 mmol), 1,6-hexanediol (1.0 mmol) and a 50w/w% aqueous solution of dimethylamine (0.66 ml, 6.0 mmol) were added and sealed. The mixture was stirred for 0.5h-20 h at 120 °C using aluminum block heater. After the reaction, it was cooled to room temperature. The crude mixture was diluted with tetrahydrofuran (THF) (50 mL). the conversion of 1,6-hexanediol (**6a**) and the yield of *N,N,N',N'*-tetramethylhexanediamine (**7a**) were determined by GC analysis using biphenyl as an internal standard.

^{1}H NMR spectra showing the formation of catalyst 4 with Na_2CO_3 and 1,6-hexanediol at 50 °C in Figure 3.

In a 5 mL vial, catalyst **4** (0.01 mmol), 1,6-hexanediol (0.01 mmol), Na_2CO_3 (0.05 mmol) and D_2O 2 mL were added and sealed. The mixture was dissolved by sonication and transferred to NMR tube. The tube was placed into the NMR apparatus and temperature was raised to 80 °C. The tube was left in the spectrometer at the same temperature for 8 h. Then, ^{1}H NMR spectra were measured.

4.5. Reference

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Chapter 5

Conclusion

Chapter 2 represented “Effect of a Substituent in Cyclopentadienyl Ligand on Iridium-Catalyzed Acceptorless Dehydrogenation of Alcohols and 2-Methyl-1,2,3,4-tetrahydroquinoline”. In this study, the author succeeded in synthesis of new iridium(III)-bipyridonate complexes having cyclopentadienyl ligands with a series of alkyl substituents. A comparison of the catalytic activity was carried out for dehydrogenation reactions of several alcohols and 2-methyl-1,2,3,4-tetrahydroquinoline to obtain an insight into the design of a more active catalyst. The *t*-butyl-2,3,4,5-tetramethylcyclopentadienyl iridium complex exhibited the best performance, which is superior to that of previously reported 1,2,3,4,5-pentamethylcyclopentadienyl iridium complex. On the other hand, hydrogen-substituted cyclopentadienyl complex showed least results. The author performed the Hammett study based on the yield of dehydrogenation for a series of substituents of cyclopentadienyl ligand. Reaction of alcohols showed a good correlation, although there was one exception in the case of 2-methyl-1,2,3,4-tetrahydroquinoline. These results indicate that the activity of a catalyst can be controlled by tuning the ligand, and it can be said that the design of ligands enables the synthesis of catalysts with higher activity. For example, in Chapter 3 and Chapter 4, the author used iridium catalysts having pentamethylcyclopentadienyl ligand and an *N*-heterocyclic carbene ligand for amination of alcohols through borrowing hydrogen pathway. The electron-donating effect of the ligand is very important in the transfer hydrogenation of the iminium ion by hydrido-iridium species. Therefore, introduction of a *t*-butyl-2,3,4,5-tetramethylcyclopentadienyl ligand with a large electron-donating effect would improve the catalytic activity.

Chapter 3 reported “Dimethylamination of Primary Alcohols Using a Homogeneous Iridium Catalyst: A Synthetic Method for *N,N*-Dimethylamine Derivatives”. The reactions proceed via borrowing hydrogen processes. In this catalytic system, an aqueous solution of dimethylamine was used, and no other organic solvents were required. Iridium catalyst bearing an *N*-heterocyclic carbene (NHC) ligand showed good performance without deactivation under aqueous conditions. The author synthesized valuable *N,N*-dimethylamine derivatives, including biologically active and pharmaceutical molecules using relatively inexpensive alcohols. In addition, monomethylamination with an aqueous solution of monomethylamine was also achieved. A variety of *N,N*-dimethylamine derivatives can be simply obtained using cheap and commercial available starting materials through this

catalytic system.

Chapter 4 described “Selective Synthesis of Bisdimethylamine Derivatives from Diols and an Aqueous Solution of Dimethylamine through Iridium-Catalyzed Borrowing Hydrogen Pathway”. The author developed bisdimethylamination of diols with an aqueous solution dimethylamine in the absence of additional organic solvents. Moreover, various bisdimethylamine derivatives were synthesized without accompanying aminoalcohols as a by-product. Furthermore, trisdimethylamination, bismethylamination, and site-selective monoamination were succeeded using this catalytic system. It is expected to be an effective method to obtain useful bisdimethylamine derivatives used in the polymer industry and synthetic organic chemistry.

As explained above, the author has studied the catalytic organic molecular transformations involving iridium-mediated hydride transfer as a key step. Hydride transfer reactions for transferring a hydrogen atom is an important process in organic synthetic chemistry. In particular, dehydrogenation and borrowing hydrogen reaction were explored. Iridium catalysts used in this study enabled high atom-economy and effective organic molecular transformation. In addition, such catalytic reactions have achieved the goals of green chemistry as an environmentally friendly synthetic method which produce water or hydrogen gas as the only byproduct. Through the design of catalytic reactions, the author aims to develop clean synthetic methods to effectively afford valuable chemicals for the future society adhering to the SDGs. Therefore, such synthetic methods are of great importance in both academia and industry. This study achieved catalytic dehydrogenation, and amination through borrowing hydrogen involving iridium-mediated hydride transfer and it provides significant insights into the design of complexes to improve catalytic activity and the synthesis of valuable amine derivatives.

Lists of publications

Chapter 2. "Effect of a Substituent in Cyclopentadienyl Ligand on Iridium-Catalyzed Acceptorless Dehydrogenation of Alcohols and 2-Methyl-1,2,3,4-tetrahydroquinoline"
Jaeyoung Jeong, Takuya Shimbayashi, Ken-ichi Fujita.
*Catalyst*s **2019**, *9*, 846. doi: 10.3390/catal9100846

Chapter 3. "Dimethylamination of Primary Alcohols Using a Homogeneous Iridium Catalyst: A Synthetic Method for *N,N*-Dimethylamine Derivatives"
Jaeyoung Jeong, Ken-ichi Fujita.
J. Org. Chem. **2021**, *86*, 4053. doi: 10.1021/acs.joc.0c02896

Chapter 4. "Selective Synthesis of Bisdimethylamine Derivatives from Diols and an Aqueous Solution of Dimethylamine through Iridium-Catalyzed Borrowing Hydrogen Pathway"
Jaeyoung Jeong, Ken-ichi Fujita.
ChemCatChem, **2021**. In press, doi.org/10.1002/cctc.202101499

Publications not included in this thesis

"Anti-Markovnikov Hydroamination of Alkenes with Aqueous Ammonia by Metal-Loaded Titanium Oxide Photocatalyst"
Soyeong Park, Jaeyoung Jeong, Ken-ichi Fujita, Akira Yamamoto, Hisao Yoshida.
J. Am. Chem. Soc. **2020**, *142*, 12708. doi: 10.1021/jacs.0c04598

"Iridium Complex Catalyzed Hydrogen Production from Glucose and Various Monosaccharides"
Ken-ichi Fujita, Takayoshi, Inoue, Toshiki Tanaka, Jaeyoung Jeong, Shoichi Furukawa, Ryohei Yamaguchi.
Catalysts **2021**, *11*, 891. doi: 10.3390/catal11080891

※著作権等

Effect of a Substituent in Cyclopentadienyl Ligand on Iridium-Catalyzed Acceptorless Dehydrogenation of Alcohols and 2-Methyl-1,2,3,4-tetrahydroquinoline Jeong, Jaeyoung; Shimbayashi,Takuya; Fujita, Ken-ichi. Catalysts, 2019, 9, 846. DOI.10.3390/catal9100846

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