



Ir Catalysis

Ir(bis-NHC)-Catalyzed Direct Conversion of Amines to Alcohols in Aqueous Glycerol

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Abstract: Sustainable catalytic conversion of amines to alcohols was realized in the presence of iridium catalysts and aqueous glycerol. Iridium catalysts involving bis-N-heterocyclic carbene (bis-NHC) show good reactivity and stability in the conversion of amines into alcohols in aqueous glycerol. The reaction was initiated with the dehydrogenation of amines and followed

Introduction

Transition-metal-catalyzed borrowing hydrogen reactions, in which alcohols undergo dehydrogenation to form carbonyl compounds, followed by the nucleophilic addition of amines, and hydrogenation to afford amines (Scheme 1), have been employed in the conversion of alcohols to amines.^[1,2] In contrast to the conversion of alcohols to amines, the reverse reaction is rarely studied; KOH-mediated reaction at high temperature^[3] and Ru-catalyzed direct conversion of amines to alcohols^[4] are a few examples. The conversion of amines to alcohols should include the dehydrogenation of amines to form imines, which undergo hydrolysis to produce carbonyl compounds along with the release of ammonia. Then, carbonyl compounds undergo hydrogenation to give alcohols. It is known that the conversion of amines to alcohols is challenging, because 1) dehydrogenation of amines is slower than that of alcohols and 2) imines formed via dehydrogenation undergo facile re-addition of amines to induce transamination because of the high nucleophilicity of amines.^[5] To promote the conversion of amines to alcohols, efficient catalysts facilitating the dehydrogenation of amines and the reduction of intermediate carbonyl compounds are required.

Bio-waste-derived glycerol is considered a renewable feed stock.^[6] Glycerol is non-toxic, non-volatile, biodegradable, and highly-functionalized with hydroxy groups, and a variety of glycerol applications from chemical feedstocks to solvents have been reported because of these attractive attributes. In particular, glycerol has been used as a reducing agent in metal-catalyzed transfer hydrogenation, where a hydrogen atom from

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by hydrolysis and reduction. Iridium catalysts play dual roles in both the dehydrogenation and reduction steps. By employing glycerol as a solvent and hydrogen source, the final reduction was facilitated. The synthesis and characterization of various Ir(bis-NHC) complexes are described along with the catalytic reaction results of the amine into alcohol conversion.





Scheme 1. Reaction between alcohols and amines.

glycerol is delivered to the metal center to generate hydrogen gas or reduce organic compounds.^[7] In the iridium-catalyzedconversion of amines to alcohols in glycerol, glycerol acts as a hydrogen source generating iridium-hydrides for efficient reduction as well as a green solvent.

Ir complexes possessing a bis-N-heterocyclic carbene (NHC) ligand show excellent reactivity in the hydrogenation and transfer hydrogenation of various π -systems.^[8–10] The reactivity and stability of Ir-NHC catalysts in hydrogenation or transfer hydrogenation are increased with assistance from strong electron-donating carbene ligands.^[11] Considering the reaction of Ir(bis-NHC) complexes with alcoholic solvents to form Ir–H during transfer hydrogenation, Ir(bis-NHC) complexes may promote: 1) the dehydrogenation of amines to initiate the conversion of amines to alcohols and 2) the reduction of intermediate aldehydes to produce alcohols to complete this conversion. In this work, we present a catalytic protocol for the amine to alcohol conversion, employing efficient iridium catalysts possessing various bis-NHC ligands and a sustainable aqueous glycerol solvent.

Results and Discussion

We began optimizing the conversion of 4-methoxy benzylamines **1a** to 4-methoxy benzyl alcohols **1b** with Crabtree's Ir^{III} complex **A** (Table 1). The reactions of **1a** (1 mmol) with catalyst **A** (0.35 mol-%) and KOH (1 equiv.) in a solvent mixture of glycerol (1 mL) and H₂O (0.5 mL) at 120 °C to 150 °C to afford **1b** with 55 % to 62 % yields, respectively (entries 1–3). The reaction

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D available on the WWW under https://doi.org/10.1002/ejoc.201900042.





of entry 1 (Table 1) was monitored by ¹H NMR, showing clear conversion of amines to alcohols (see supporting information). During the reaction, trace amount of amides and imines derived from the reaction of aldehydes and amines were observed by ¹H NMR, but they were not isolated (see supporting information). Upon changing the amount of KOH, the yield was increased to 70 % (entries 4-6). Next, other inorganic bases and an organic base were examined; they showed a good yield of 1b with NaOH (entries 7–10). The effect of solvents was also investigated (entries 11-16). Without water, the yield of 1b decreased slightly (55 %, entry 11). In the absence of an alcoholic solvent, the reaction did not proceed to form **1b** (entry 12). Propylene glycol (PG), ethylene glycol (EG), 1,3-propandiol (PD), and 2-propanol (IPA) were employed to show low yields of 1b (entries 13-16). Glycerol showed the best result in this reaction. Presumably, glycerol delivers hydrogen to iridium catalysts in a more efficient manner than other alcoholic solvents.^[12] In the absence of iridium catalysts, the reaction did not proceed (entry 17).

Table 1. Optimization of the conversion of amines to alcohols.



[a] Isolated Yield. [b] Reaction time: 8 h. [c] No iridium catalyst. PD (1,3-propanediol), IPA (2-propanol) Reaction conditions: 1a (1 mmol), **A** (3.5 μ mol), and bases in the indicated solvent were heated for 16 h.

Using the conditions optimized for the conversion of **1a** to **1b**, shown in Table 1, various iridium complexes modified on anionic ligands and wingtips were examined (Scheme 2). The complex **A** reported by Crabtree was prepared as described previously.^[10a,10b] Complexes **B**–**D** containing benzoate, *p*-OH benzoate, and *o*-OH benzoate, and complex **E** containing a modified NHC ligand^[10c] were prepared in a manner analogous to the synthesis of **A**. The coordination mode of ligands on iridium metal ion in compounds **B**–**E** was determined by the analogy of the NMR spectra of **A** and X-ray crystallographic data (Figure 1). Single crystals of **C** and **D** were obtained via slow evaporation of acetone/hexane mixture solutions at -20 °C. Iridium catalysts **B**–**D** were examined for the conversion of amines to alcohols to form **1b** at yields of 72 %, 68 %, and 68 %, respectively. Complex **E** involving a wingtip-modified bis-NHC ligand participated in this reaction to afford **1b** with 58 % yield.



Scheme 2. Comparison of the reactivities of various Ir(NHC) complexes.



Figure 1. (a) X-ray structure of complex \bm{C} and (b) X-ray structure of complex $\bm{D}^{[13]}_{\cdot}$

The scope of this transformation involving alcohol formation from amines was examined (Figure 2). The compounds 3- and 2-methoxy substituted benzylamines participated in this reaction to form desired alcohols **2b** (70 %) and **3b** (69 %), respectively. Compounds 4-methyl and 4-Cl substituted benzylamines were transformed to alcohols **4b** and **5b** with 51 % and 60 % yields, respectively. Piperonylamine was subjected to reaction conditions to afford **6b** with 67 % yield. *N*-phenylethane-1,2-





diamine participated in the reaction to form desired alcohol product **7b** with 22 % yield. (*1S,2S*)-1,2-diphenyl ethylenediamine was subjected to reaction conditions to form pyrazine **8b** with 50 % yield. Instead of alcohol formation, vicinal diamines underwent facile cycloaddition with pyruvic aldehyde which is formed from glycerol.^[14]



<u>Reaction conditions</u>: Amines (1 mmol), A (3.5 µmol), and KOH (2 mmol) in a solvent mixture of glycerol and water were heated at 120 °C for 16 h. The indicated yields are isolated yields.

Figure 2. Substrate scope.

The proposal of the reaction mechanism is based on control experiments (Scheme 3). A mixture of 1a and 4-methyl benzyl alcohol was subjected to the optimized conditions, resulting in the formation of **1b** (72 % yield) and the decomposition of 34 % of 4-methyl benzyl alcohol (Equ. 1). This result implies that the conversion rate of amines to alcohols is fast enough to form alcohols as a major product of this reaction, but the decomposition of alcohols was unavoidable. To probe the destination of alcohols, alcohol **1b** was exposed to standard conditions in the presence of aniline for reductive amination (Equ. 2). The expected reductive amination of oxidized alcohols (aldehydes) occurred at a very low yield (2 %). These results also indicate that iridium catalyst A promotes the conversion of amines to alcohols, not vice versa. Next, the reaction mechanism involving the borrowing hydrogen concept was investigated. If the borrowing hydrogen mechanism is the major pathway, deuterium of deuterio-1a should remain in deuterio-1b (Equ. 3). Based on the

amount of deuterium of **1b**, the α -hydrogens of **1b** are speculated to have come from glycerol. Subsequent to the dehydrogenation of glycerol, it could be transformed to lactate, which was observed in this reaction.^[15] The reaction in a mixture of glycerol and H¹⁸O formed the mixture of ¹⁸O- and ¹⁶O-labelled **1b**, suggesting that KOH and H₂O are the oxygen source of **1b** (Equ. 4).



Scheme 3. Control experiments.

Conclusion

This work describes the successful Ir-catalyzed conversion of amines to alcohols. Ir(bis-NHC) catalysts show great activity in the conversion of amines to alcohols with the assistance of glycerol as a hydrogen source and solvent, in which the conventional dehydrogenation-reductive amination of alcohols was suppressed. Various anion-modified and wingtip-modified iridium complexes were examined to show good yields of alcohol formation. According to mechanistic studies using deuterated amines, the α -hydrogens of alcohols are derived from α -hydrogens of glycerol.

Experimental Section

Representative Procedure for Iridium Complexes: A mixture of 3,3'-methylene-bis(1-methyl-1*H*-imidazol-3-ium) iodide (300 mg, 0.694 mmol), [Ir(COD)CI]₂ (233 mg, 0.347 mmol), KI (230 mg, 1.39 mmol) and sodium acetate (342 mg, 2.78 mmol) was stirred in MeCN (15 mL, 0.05 M) for 16 h with reflux. The gradient column chromatography (CH₂Cl₂/acetone, 8:2) gave **A** as an orange solid in 40 % yield.

Representative Procedure for Catalytic Reactions: 4-Methoxybenzylamine (1a) (130 μ L, 1 mmol), KOH (112 mg, 2 mmol), iridium





catalysts (0.0035 mmol), H_2O (0.5 mL) and glycerol (1 mL, 13.7 mmol) were put into a pressured tube. The mixture was heated at 120 °C for 16 h. Then, the reaction mixture was cooled to ambient temperature, purified by column chromatography (ethyl acetate/hexane, 1:9) to afford 4-methoxybenzyl alcohol (**1b**).

Acknowledgments

This study was supported by the next generation carbon upcycling project (No. 2017M1A2A2043141) through NRF funded by the Ministry of Science and ICT, Ajou University, and the Human Resources Program in Energy Technology (No. 20154010200820) of the Korea Institute of Energy Technology Evaluation and Planning (KETEP), which receives financial resources from the Ministry of Trade, Industry & Energy, Republic of Korea.

Keywords: Iridium · Dehydrogenation · Amines · Alcohols · Glycerol

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Received: January 10, 2019







Iridium catalysts including biscarbene ligands were employed to transform amines into alcohols with an assistance of aqueous glycerol. The synthesis and characterization of various Ir(bis-NHC) complexes are described.

DOI: 10.1002/ejoc.201900042