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Hydrogenation and Dehydrogenation of *N*-Heterocycles Under Cp*Co(III)-Catalysis

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Pardeep Dahiya,^a Nidhi Garg,^a Rinaldo Poli,^{b,c} and Basker Sundararaju*,^a

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To realize the goal of a carbon-free energy economy, it is crucial to discover reactions that utilizes sustainable resources as an alternatives to fossil feedstocks. In this study, a well-defined, air-stable Cp*Co(III)-catalyst for transfer hydrogenation of quinolines derivatives and oxidative dehydrogenation of cyclic amines in water is developed. While the former reaction is promoted by formic acid as transfer hydrogenating reagent, the latter is mediated by molecular oxygen as the sole oxidant. These processes provide new avenues for the investigation of air-stable cobalt catalysts for environmentally benign hydrogenation and dehydrogenation reactions.

The demand for efficient catalysts for the bidirectional hydrogenation-dehydrogenation (BHD) of suitable organic molecules is of considerable significance within the context of research on alternative energy sources, as it has the potential to be considered as a liquid organic hydrogen carrier (LOHC).^{1–6} In this regard, formic acid, oxidized hydrocarbons (e.g. alcohols) or amines including heterocycles were considered as LOHCs, and explored for BHD process as it can be performed under mild conditions which will have a direct implication to replace fuels based on fossil resources.^{7,8} In addition to alternate fuel research, indole, quinoline and ketones or its hydrogenated derivatives were served as important framework in pharmaceuticals and fine chemicals.^{9–11} Hence, environmentally benign process for hydrogenation and dehydrogenation using non-toxic hydrogen carrier or O₂ as oxidant will be ideal for BHD processes. In this context, hydrogenation of heterocycles into their saturated cyclic

amines are widely explored,^{12–16} however the reverse reaction by removal of hydrogen from saturated *N*-heterocycles is a thermodynamically uphill process requiring high temperature or stoichiometric amount of chemical oxidant, partly because of the high energy barrier for C(sp³)-H metalation, however the presence of an N atom in the ring system decreases the endothermicity of the reaction.^{17–20} The development of a single bifunctional catalyst able to carry out both oxidative dehydrogenation (ODH) and the Catalytic Transfer Hydrogenation (CTH) of *N*-heterocycles under mild conditions is challenging. The use of O₂ as oxidant in ODH is a fascinating alternative over strong oxidants (e.g. 2,3-Dichloro-5,6-Dicyano-1,4-benzoQuinone (DDQ), metal oxides, *Tert*-ButylHydroPeroxide (TBHP), sulfur etc.) and does not produce any toxic by-products. In CTH, formic acid (FA) is a low-flammability H⁺/H⁻ transfer agent, obtained from biomass. Thus, it avoids the use of pressurized hydrogen gas and special equipment.²¹ The implementation of reactions in aqueous media falls under the criteria of green chemistry and constitutes meaningful research work.^{22,23} Nowadays, scientists are intensely searching ways to replace traditional non eco-friendly volatile organic solvents with the inexpensive, greener, and abundant water.

A plethora of unidirectional heterogeneous^{24–29} and homogeneous^{30,31} catalysts are reported in the literature that are capable of doing either hydrogenation or dehydrogenation reactions of heterocycles, however only a handful of them are known to catalyze both processes. For example, Iridium-based catalysts are quite predominant in this bidirectional hydrogenation-dehydrogenation (BHD) chemistry. In 2009, Fujita and co-workers demonstrated that an iridium complex homogeneously catalyzes both the acceptorless dehydrogenation of THQs and the reverse quinoline hydrogenation under 1 atm of hydrogen pressure.³² Various advances were subsequently made in BHD chemistry.^{33–36} However, the rarity of noble metals on the earth crust makes it imperative to design earth-abundant, less toxic base-metal

^a Department of chemistry, Indian Institute of Technology Kanpur, Kanpur, Uttar Pradesh, India – 208 016. Email: basker@iitk.ac.in

^b CNRS, LCC (Laboratoire de Chimie de Coordination), Université de Toulouse, UPS, INPT, 205 Route de Narbonne, BP 44099, F-31077, Toulouse Cedex 4, France.

^c Institut Universitaire de France, 1, rue Descartes, 75231 Paris Cedex 05, France.

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complexes that exhibit this dual-functionality. In 2014, Jones and co-workers reported the Fe-(PNP)-catalyzed BHD of N-heterocycles, which required however the presence of a strong base and 5-10 atm of hydrogen pressure to perform the hydrogenation of quinolines.³⁷ In 2015, the same group explored cobalt pincer catalysts to perform reversible hydrogenation/dehydrogenation.³⁸ Later, Rueping and co-workers demonstrated the Mn-(PNP) catalyzed dehydrogenation and hydrogenation of N-heteroarenes under milder temperature conditions, which required the presence of KO^tBu and very high hydrogen pressure.³⁹ Ma and co-workers also explored the potential of heterogeneous Co@NCNTs nanoparticles in BHD.⁴⁰

Although these developments are impressive, there is room for the exploration of BHD process under mild conditions in view of a possible implementation at the industrial level. Encouraged by the activity exhibited by the above-mentioned base metals, we planned to further explore their potential by rationally designing the coordination environment.⁴¹ In our continuous efforts for a targeted exploration of the hydrogenation and dehydrogenation potential of cobalt complexes,⁴² we focused our attention on synthesizing well-defined bench-stable cobalt complexes with bidentate ligands and to study their catalytic behavior for the hydrogenation/dehydrogenation of N-heterocycles. In this contribution, we report the synthesis of the simple and highly stable [Cp*Co(N^A N)]⁺ (N^A N = 8-aminoquinoline) complex and its high activity in the aqueous-phase BHD of THQs/quinolines in the absence of any base/additive. To the best of our knowledge, this work is the first report on homogeneous

[Cp*Co]-catalyzed BHD in water under environmentally benign conditions, in complete harmony with green chemistry principles. Complexes **D-E** were synthesised directly from Cp*Co(CO)I₂ (**A**) or CpCo(CO)I₂ (**B**) monomer with 8-aminoquinoline in dichloromethane at room temperature for 24 hours, yielding 88% (**D**) and 47% (**E**) of the expected cationic cobalt(III) complexes, respectively (Scheme 1, (i)). The dicationic complex [Cp*Co(NH₃)₃]²⁺, 2I⁻ (**F**) was obtained by mixing aqueous ammonia with a methanolic solution of [Cp*Co]₂ dimer (**C**) for one hour, affording 96% of complex [Cp*Co(NH₃)₃]²⁺, 2I⁻ (**F**) (Scheme 1, (ii)). X-ray crystallography corroborates the structure of the complexes **D-F**.

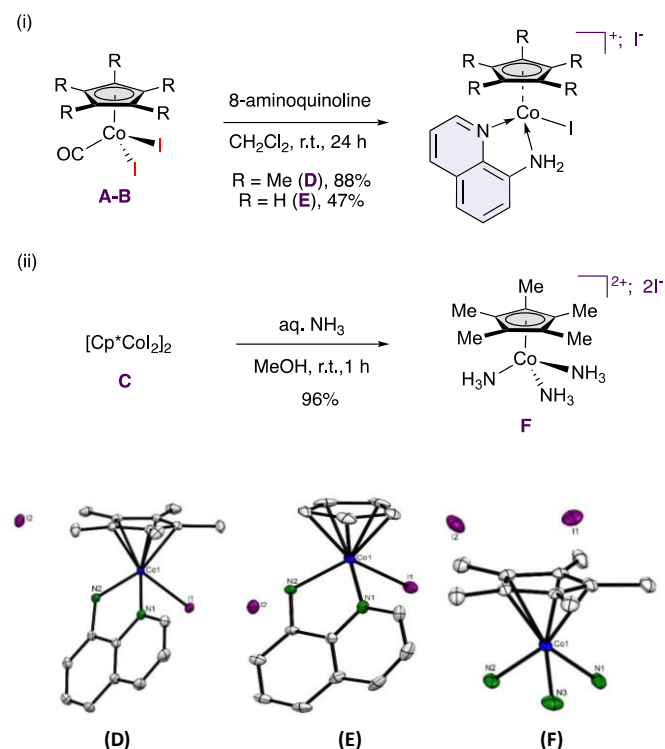
With the isolated complexes in hand, we commenced hydrogenation of N-heterocyclic compounds, using quinoline **1a** as the model substrate. The catalytic transfer hydrogenation was investigated at 80°C in the presence of various hydrogen donors with 5 mol% cobalt catalyst **D** and water as the solvent. Among the hydrogen surrogates screened, formic acid provides complete conversion (entries 1-3, **Table 1**). The formation of THQ is negligible when the reaction is performed in any solvent other than water (See ESI for details). The expected product **2a** was obtained at a yield of 88% when the temperature was reduced to 60°C, while only trace amounts were found at ambient temperature (entries 4-5). Further reaction optimization revealed that employing only 3 mol % of catalyst is sufficient in obtaining the complete conversion (entry 6), while dropping the catalyst loading to 1 mol% resulted in only a 33% yield (entry 7).

Table 1: Optimization studies^[a]

Entry	Catalyst (mol%)	H ₂ donor (equiv)	Yield (%) ^[b]
1	Cat D (5)	HCO ₂ NH ₄ (10)	6
2	Cat D (5)	NH ₃ .BH ₃ (10)	26
3	Cat D (5)	HCO ₂ H (10)	>99
4	Cat D (5)	HCO ₂ H (10)	88 ^[c]
5	Cat D (5)	HCO ₂ H (10)	2 ^[d]
6	Cat D (3)	HCO ₂ H (10)	>99
7	Cat D (1)	HCO ₂ H (10)	33
8	Cat D (3)	HCO ₂ H (8)	>99 ^[e]
9	Cat E (3)	HCO ₂ H (8)	n.d.
10	Cat F (3)	HCO ₂ H (8)	n.d.
11	Cat A (3)	HCO ₂ H (8)	n.d.
12	Cat B (3)	HCO ₂ H (8)	n.d.

^[a]All the reactions were carried out under argon atmosphere unless otherwise stated using **1a** (0.2 mmol), [Co]-cat (0.01 mmol), H₂ donor (2 mmol) in water (1 mL) at 80°C for 16 h. ^[b]NMR yield using anisole as internal standard. ^[c]Reaction performed at 60°C. ^[d]Reaction performed at room temperature. ^[e]Reaction performed for 4 h. n.d. = not determined.

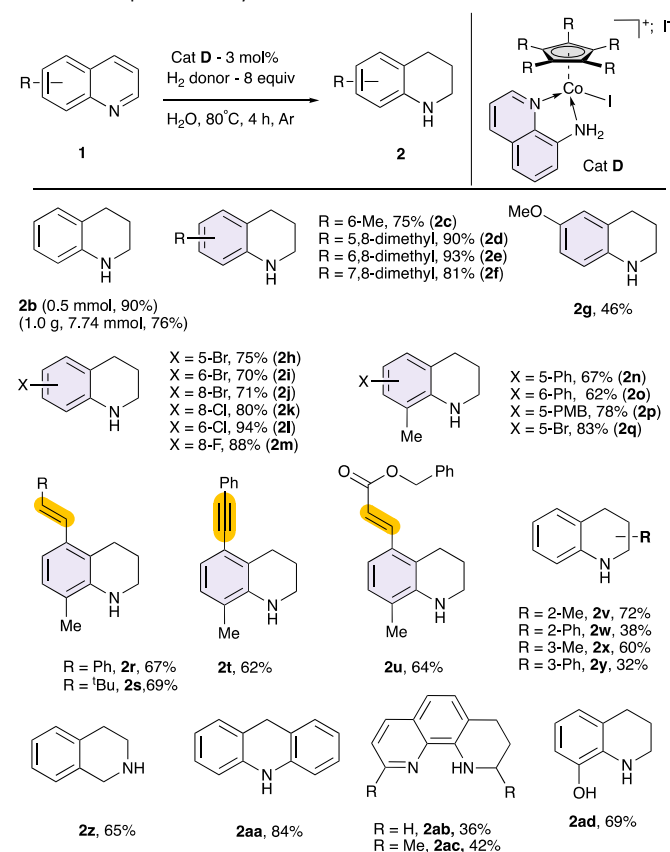
Scheme 1. Synthesis of complexes **D-F** and their x-ray crystal structures.



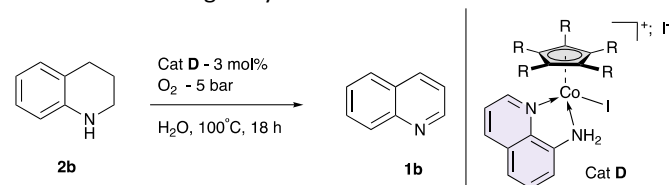
Interestingly, lowering the reaction period to 4 hours with a 3 mol% catalyst loading and 8 equivalents of formic acid in 4 hours resulted in >99% product formation (Entry 8). Under the optimized conditions, other isolated complexes **A-C** and **E-F** were tested. Unfortunately, none of them are effective for transfer hydrogenation of **1a** using formic acid, suggesting that 8-aminoquinoline ligand and Cp* is necessary to obtain the transfer hydrogenation product (entries 9-12). Control experiments without catalyst/formic acid produced no desired product (See ESI for details), confirming the need of both components.

After finding the optimum conditions for the transfer hydrogenation of **1a** to the saturated cyclic amine **2a**, we investigated a variety of substituted quinolines and isolated the corresponding products in moderate-to-excellent yields, as outlined in Scheme 2. To test the practical utility of this protocol, reactions were performed in both 0.5 mmol and gram-scale, and the expected product **2b** was isolated in 90% and 76% yield respectively after 4 h. Electron-donating groups such as (-CH₃, -OMe) at various positions of the aromatic ring (non-pyridyl ring) resulted in an excellent yield of the hydrogenated product, except when -OMe is located at the C-6 position of quinoline (**2c-2g**). Furthermore, the presence of valuable halogen groups at various positions of arenes and disubstituted arenes is well tolerated and excellent mass conversion was achieved by transfer hydrogenation (**2h-2q**). Notably, the introduction of other reducible moieties such as alkene, alkyne, and α - β unsaturated ester does not interfere,

Scheme 2. Scope of heterocycles.



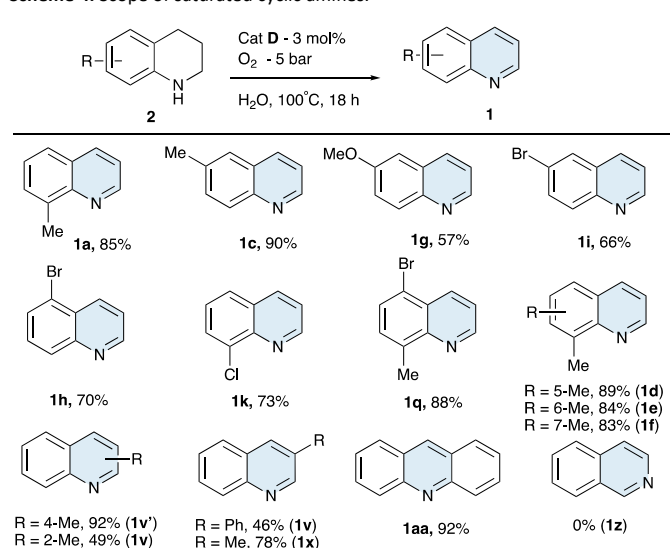
and the heteroarenes were transfer hydrogenated smoothly and chemoselectively, resulting in moderate-to-high yields of the desired products (**2r-2u**). Although the protocol provides good conversion for the transfer hydrogenation substituted heteroarenes, the substitutions at the C-2 and C-3 position of the heteroarenes do influence the conversion rates, indicating that the steric plays a crucial role in the transfer of hydride to the substrate (**2v-2y**). The protocol can be extended to transfer hydrogenation of other heterocycles such as isoquinoline, acridine, and phenanthroline, as well as 8-hydroxyquinoline, to their corresponding saturated amine derivatives (**2z, 2aa-2ad**) with moderate-to-good yield.



Scheme 3. Cobalt-catalyzed oxidative dehydrogenation of THQ.

We next turned our attention to study the possibility of achieving oxidative dehydrogenation with isolated cobalt complex **D**. A brief screening the reaction parameters revealed that the complete conversion of the tetrahydroquinoline **2b** was achieved with the isolated yield of 94% in water under 5 bar pressure of O₂ at 100 °C for 18 h (Scheme 3). Lowering the catalyst loading had a influence in the product outcome and the control experiments revealed that the reaction occur only in water in the presence of 5 bar oxygen pressure (See the ESI for more details). Subsequently, the scope of the THQs for dehydrogenation using oxygen as sole oxidant as shown in Scheme 4. Both electron rich substituents (Me-, MeO-) and electron withdrawing substituents (Br, Cl) at various position of the arene (1a-1c, 1g-i, 1k) afforded the desired products in moderate-to-good yields. The same trend extended when more than one substituent present at the arene ring (**1q, 1d-1f**). Improved yields were obtained when substituents present at the pyridine ring in contrast with hydrogenation (**1v, 1v', 1x-y**).

Scheme 4. Scope of saturated cyclic amines.



The strategy is applied to dehydrogenate dibenzopiperidine into the acridine under the optimized conditions and isolated **1aa** in excellent yield. However, to our surprise, THIQ **2z** did not undergo dehydrogenation to isoquinoline **1z** even at higher pressure or higher catalyst loading.

In summary, we successfully synthesized molecularly defined cationic cobalt-based catalytic system bearing commercially available 8-aminoquinoline as ligand exhibit excellent catalytic activities towards transfer hydrogenation and dehydrogenation of nitrogen-based heterocycles. While the former utilizes formic acid as transfer hydrogenating agent and latter achieved under 5 bar oxygen pressure in water to afford a range of respective products. We are currently investigating the detailed mechanistic studies for the hydrogenation and dehydrogenation reaction, and further efforts to isolate the reactive intermediates involved in the catalytic cycle.

Conflicts of interest

There are no conflicts to declare.

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