Hydrogenation

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Switch in Catalyst State: Single Bifunctional Bi-State Catalyst for Two Different Reactions

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Abstract: *Disclosed here is a molecular switch which responds to acid-base stimuli and serves as a bi-state catalyst for two different reactions. The two states of the switch serve as a highly active and poorly active catalyst for two catalytic reactions (namely a hydrogenation and a dehydrogenative coupling) but in a complementary manner. The system was used in an assisted tandem catalysis set-up involving dehydrogenative coupling of an amine and then hydrogenation of the resulting imine product by switching between the respective states of the catalyst.*

Simplification of complexity in chemical systems is a difficult task, yet entertained by chemists. For example, enzymes, a class of smart catalysts gifted by nature, regulate a myriad of highly sophisticated and extremely complex catalytic processes with the required level of precision over the desirable outcome.[1] Mimicking such smart activity by artificial man-made molecules is an incessant quest for modern chemists. Recently, artificial switchable catalysts have been constructed through judicious incorporation of reversibly responsive, function-regulatory feature(s) controlled by various external stimuli.[2] However, almost all of the developed switchable catalysts show an activity-switching or stereo/chemoselectivity-switching behavior for only one catalytic reaction (S→P, Figure 1A).[2,3] The next generation of smart catalysts is intended to be more sophisticated by featuring switching activity and facilitating two different reactions (S1→P1 and S2→P2, Figure 1B).[4] Such a bifunctional bistate catalyst having single active site to regulate two state-specific catalytic reactions is rare, even in biology. A system close to having the above-described sophistication has been recently uncovered by Fushinobu et al. They discovered that the enzyme fructose-1,6-biphosphate aldolase/phosphatase (FBPA/P) catalyzes two chemically distinct reactions (a reversible aldol condensation and a dephosphorylation reaction) within a single catalytic domain by substrate-induced active-site metamorphosis.[5] The concept of this orthogonal catalytic behavior has recently found application in electro-splitting of water, albeit with nanoparticulate material, thus catalyzing a hydrogen evolution reaction (HER) and oxygen evolution reaction (OER) through a switch in the catalyst state.[6] Only two such systems, involving a synthetic catalyst having a single active site, have been reported. That is, a redox-switchable and photoswitchable catalyst as reported by the groups of Byers[7a] and Bielawski,[7b] respectively. The rarity of examples emphasizes the challenge in devising a simple yet ideal switchable, bifunctional bi-state catalyst which fulfills the following prerequisites: a) ability to catalyze two different synthetically important reactions through tiny structural/electronic changes; b) sustainable, robust, selective, and recyclable; and c) at least two orders of magnitude rate difference between the reactions catalyzed by either catalyst form and still remain switchable. Toward this end, herein, we present a successful design of a bi-state molecule which catalyzes two contrasting reactions by switching between its two states. The working principle of this new switchable catalyst is different from that of either the natural or artificial systems described earlier. The design works on an acid/base-controlled molecular switch involving two interconvertible metal coordination modes (state I and state II), each of which shows fast and slow catalysis in two contrasting reactions, namely, a catalytic imine hydrogenation and a dehydrogenative coupling of an amine (Figure 1C). The system exhibits excellent switching between outputs for the catalytic activity during the actual

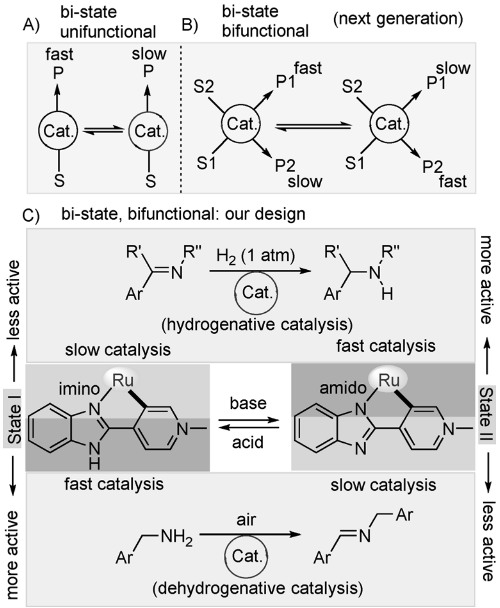

Figure 1. Design of stimuli-active switchable catalysis: A) Present generation bi-state, unifunctional catalyst. B) Target design of next-generation bi-state, bifunctional switchable catalyst. C) The design adopted in this work based on acid-base triggered molecular coordination switch.

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both reactions, which are triggered by simple acid/base inputs. Finally, the switch was effectively utilized to construct an assisted tandem catalysis[8] involving the dehydrogenative coupling of an amine followed by hydrogenation of the resulting imine, in one pot, and it was achieved by alternatively triggering a change in the catalyst state.

A hybrid pyridylidene-benzimidazole ligand (**L**), bound to a catalytic [Ru^{II}(*para*-cymene)] center, was utilized to exploit the acid/base control switch of the coordination (states I and II) through the benzimidazole functionality, and to provide a robust metal-ligand platform. The Ru–C(pyridylidene) bonding seemed to be crucial for the success of the system as this covalent binding of the ligand to the metal center assured that the ligand would not dissociate from the metal center, not even at high reaction temperatures. The complex switches between an acid-stimulated Ru^{II}–benzimidazole coordination mode featuring a neutral imino-type σ-donating N→Ru coordination (state I) and a base-stimulated Ru^{II}–benzimidazolate coordination mode consisting of anionic σ- and π-donating amido-type N–Ru covalent bonding (state II). The complexes **1** and **2**, that is, states I and II, respectively, were synthesized according to the reactions as shown in Figure 2 A, and characterized fully by several spectroscopic and single-crystal X-ray diffraction techniques (Figure 2 B and the Supporting Information).

After successfully verifying the smooth interconversion between **1** and **2** in solution with acid-base inputs (Figure 2 C), the two complexes were used for the catalytic hydrogenation of imines with molecular hydrogen under ambient conditions (1 atm H_2 at 40 °C) in 2,2,2-trifluoroethanol (TFE; Figure 3). TFE is a highly polar and coordinating solvent which facilitates removal of the iodide ligand from the metal coordination sphere of the catalysts, as required for subsequent activation of H_2. It was observed that **2** was highly active (product yield 69 to 88 %), whereas **1** was almost inactive (product yield 1 % to 5 %) in this reaction, as it was tested for a range of substrates.

Next, the catalyst switch was utilized for a complementary reaction. The activity of **1** and **2** was reversed for the dehydrogenative coupling of a series of benzylic amines to the corresponding imines performed in the presence of $NaBF_4$ in acetonitrile/toluene at 100 °C under open-flask conditions (Figure 3). In this reaction, $NaBF_4$ was used for removal of the iodide ligand to facilitate substrate binding. Herein, **1** was more efficient (product yield 78 to 94 %) than **2** (product yield 2 % to 25 %).

This type of orthogonal catalytic response of the **1**↔**2**-based switch for the two reactions was further explored for online temporal control of the switch during the progress of the reactions. Thus, when a model hydrogenation reaction was started with the less effective catalyst **1**, no product formation was observed in the first 2 hours of catalysis. Addition of NEt_3 (1 equiv with respect to catalyst) generated the active catalyst **2**, which afforded fast reaction and 26 % yield of the product in the next 2 hours. The activity of **2** was drastically slowed down by adding 1 equivalent of CF_3COOH, and it was restored again with addition of NEt_3. Three representative cycles were performed without any loss of activity of the catalyst, thus showing 0–2 % of product yield in the slow state and incremental yields of 19–22 % in the fast state for every 2 hour period (Figure 4 A). Similarly, switchability of the system was successfully verified for the dehydrogenative catalysis starting with the less active catalyst **2**, which furnished only 4 % of the product within the initial 3 hour period. After addition of CF_3COOH (1 equiv with respect to catalyst) the more active catalyst **1** was generated and accelerated the reaction to provide 17 % yield of the product in the next 3 hours. Addition of NEt_3 stopped the catalysis and to restore it acid was added. Three representative cycles were tested and exhibited 4–8 % yield in the slow state and 17–24 % yield in the fast state for alternating 3 hour periods (Figure 4 B).

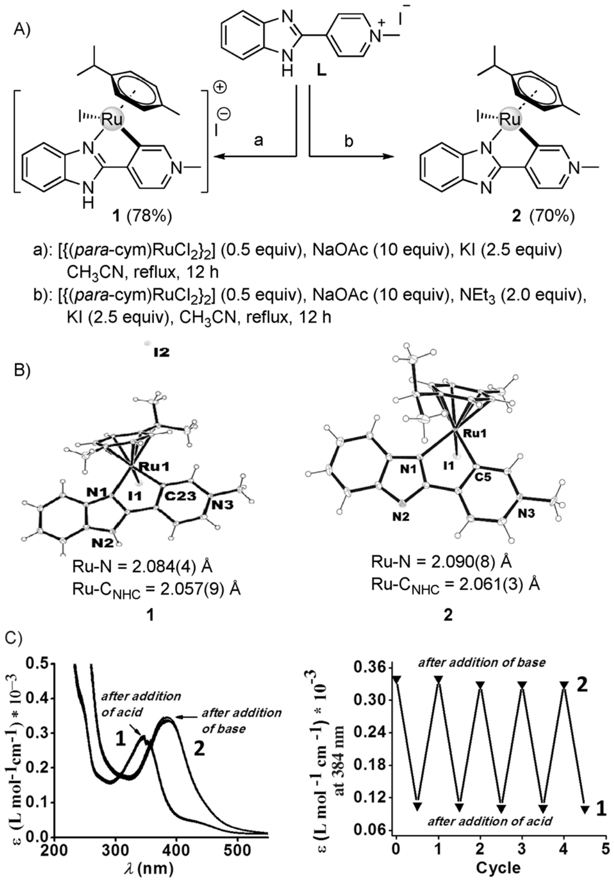

Figure 2. A) Synthesis (A) and ORTEP[9] representation (B) of solid-state molecular structures of **1** and **2**. The thermal ellipsoids are shown at 30 % probability. C) Acid-base triggered **1**↔**2** interconversion monitored by UV/Vis spectroscopic method in solution.

After successful demonstration of the switchable catalysis, the power of the method was further tested for an assisted tandem catalysis[8] (such as A→B→C) by switching on the correct catalyst state (I or II) for each step by using the appropriate stimulus. Finding common but compatible reaction conditions (solvent, temperature etc.) for both of the catalyses in a single pot was challenging. To demonstrate proof-of-concept, however, we compromised the activity to some extent and chose a preliminary reaction set-up as described below. At first, the dehydrogenative coupling of 4-methylbenzylamine (**5 f**) was started with the less active

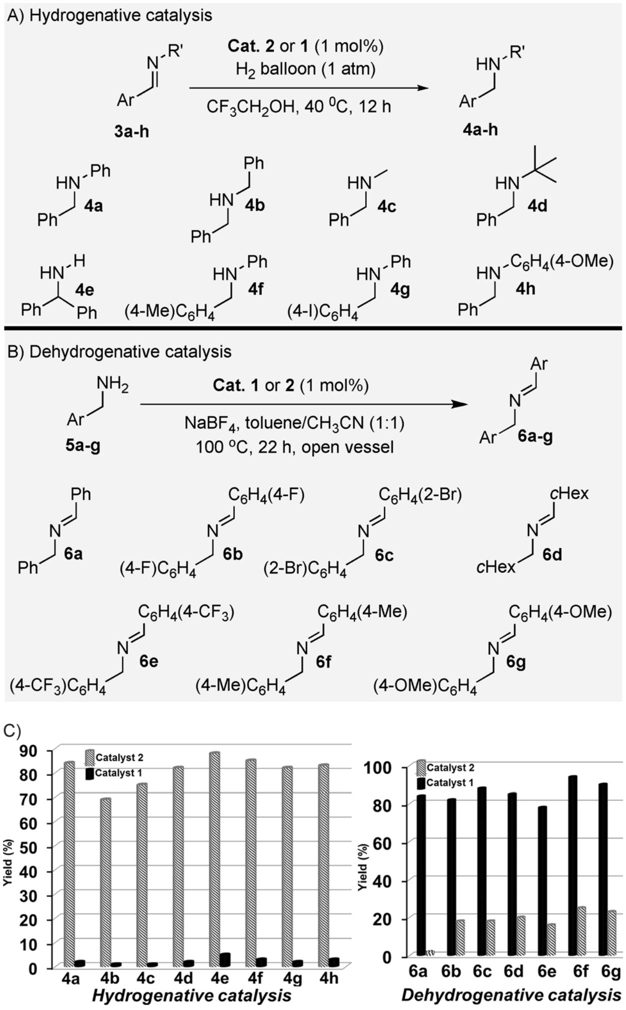

Figure 3. Examples of hydrogenative (A) and dehydrogenative (B) catalysis performed by **1** and **2**. C) Yields [%] of the products depicted in (A and B).

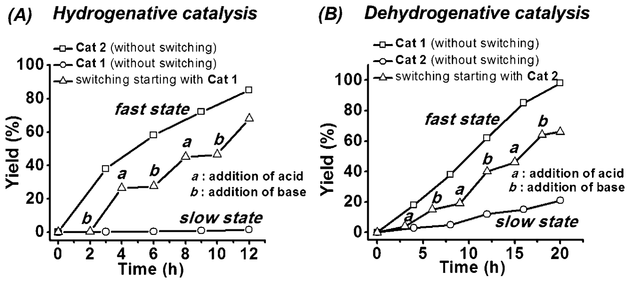

Figure 4. Switches of reactivity throughout hydrogenation of *N*-benzylideneaniline (A) and dehydrogenative coupling of benzylamine (B).

catalyst **2** (1.5 mol %) under the reaction conditions as applied previously (Figure 5 A). As expected, yield of the imine product (**6 f**) was low (18 %) after 22 hours of reaction (step i; Figure 5 B). In the next step, the acid stimulus (1 equiv of CF_3COOH with respect to catalyst) was added to the reaction to generate the more active catalyst **1**, and the reaction was continued. A high yield (96 %) of **6 f** was obtained after 22 hours (step ii; Figure 5 B). Then, a modified hydrogenation reaction was applied in the same pot as shown in Figure 5 A, and the reaction was again left to continue. As **1** was less active in the hydrogenation reaction, the corresponding amine product **4 i** was formed in only 8 % yield after 12 hours (step iii; Figure 5 B). At this stage, the required stimulus, that is, base (1 equiv of NEt_3 with respect to catalyst), was added to switch **1** into **2**, which was supposed to be highly active in hydrogenation. After 12 hours of further reaction under the same reaction conditions, 55 % yield of the desired amine product was recorded (step iv; Figure 5 B), thus demonstrating successful and fast hydrogenation catalysis, by **2**, for **6 f**, which was formed in the first reaction. An overall 70 % yield of **4 i** was achieved after 24 hours of total reaction time (step v; Figure 5 B). Notably, the activity of **2** under these modified but somewhat compromised reaction conditions involving a one-pot multicomponent set-up was comparable to the original activity as shown in Figure 3. This assisted tandem catalysis was further performed successfully for a large-scale set-up as well (see the Supporting Information).

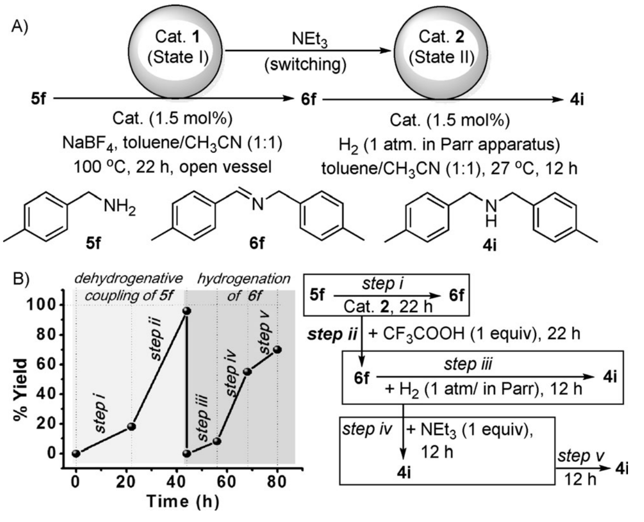

Figure 5. Design of an assisted tandem catalysis set-up (**5 f**→**6 f**→**4 i**) based on the **1**↔**2** switch: A) Reaction conditions applied for dehydrogenative coupling of **5 f** to **6 f**, followed by hydrogenation of **6 f** to **4 i**. B) Time versus yield profile of the assisted tandem catalysis involving consecutive **5 f**→**6 f** and **6 f**→**4 i** conversions by the respective active and dormant states of the catalyst.

Next we sought an acceptable explanation of our hypothesis on the above bifunctional, bi-state catalyst. We believe that the difference in activity of **1** and **2** in the hydrogenative catalysis is due to the nature of the ligand sphere and its influence on the activation of H_2, in line with our previous investigation involving similar iridium-based complexes (see Scheme S5).[10] The basic amido ligand in **2** is highly efficient in metal–ligand cooperative activation of H_2 to generate Ru-H species and facilitate hydride insertion and subsequent hydrogenation. In contrast, the imino ligand in **1** is unable to play any such cooperative role to activate H_2 and the catalysis is promoted via a coordinated dihydrogen species from which the hydride delivery is extremely poor.[11] To gain insight into the differential activity of **1** and **2** in the dehydrogenative catalysis, mechanistic investigations, including evaluation of rate law by initial-rate kinetics, kinetic deuterium isotope effects (KDIEs), and substrate (amine) coordination/decoordination equilibrium constants for both **1** and **2** were conducted (see the Supporting Information). Based on the experimental results, two different catalytic cycles were proposed (see Schemes S6 and S7) and provide an explanation for the observed fast and slow dehydrogenative catalysis with **1** and **2**, respectively. Most importantly, efficient substrate (amine) coordination to the electron-poor ruthenium center in **1**[12] [$K_{\text{asso}} = 875.09\,\text{M}^{-1}$ for **1** was much higher compared to that for **2** ($2.06\times10^{-3}\,\text{M}^{-1}$)], and amine-assisted rate-determining substrate N−H bond cleavage ($k_H/k_D = 3.44$ for **1**) suggested higher activity in the **1**-catalyzed reaction.[13] In contrast, poor substrate (amine) coordination to the π-donating amido-ligand-bound electron-rich ruthenium center in **2**[12] ($K_{\text{asso}} = 2.06\times10^{-3}\,\text{M}$ for **2**, and $k_H/k_D = 0.89$ for **2**) in the rate-limiting amine association step resulted in sluggish dehydrogenative catalysis with **2**. A detailed study, including DFT calculations, will be undertaken in future to either validate the above or to discover other possibilities.

In summary, a ruthenium(II)-based bi-state molecular switch, which is responsive to acid/base stimuli, was designed and exhibits highly reversible metal–ligand coordination modes. The modes are either a neutral imino-type σ-donating N→Ru coordinate bonding state or an anionic σ/π-donating amido-type N-Ru covalent bonding state. The switch between modes presents a bifunctional bi-state catalyst for two different reactions. The "Ru-amido state" is highly active in catalytic hydrogenation of various imine substrates while the "Ru-imino state" remains poorly active in this reaction. On the contrary, for the catalytic dehydrogenative coupling of amines, the "Ru-imino state" was much more efficient compared to the "Ru-amido state". Furthermore, modulation of rates by switching between fast/slow catalysis of during the hydrogenative and dehydrogenative reactions was also achieved by simply applying acid/base inputs into the system. In both the applications, the system featured a large difference in reaction rates, and demonstrated high switchability and robustness. Extending the concept further, the switch was also utilized effectively to demonstrate an assisted tandem catalysis involving the dehydrogenative coupling of an amine followed by hydrogenation of the resulting imine, in one pot, all triggered by acid and base stimuli in an alternating manner. The work may be considered a step forward to develop more sophisticated next-generation multifunctional switchable catalysts. Efforts are ongoing to upgrade the present system in this direction.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

Keywords: hydrogenation · imines · ligand effects · ruthenium · synthetic methods

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[11] To correlate with the previous investigations (Ref. [9]), kinetic studies and NMR analyses were performed. See the Supporting Information for details.

[12] The Ru^{2+}/$^{3+}$ redox potential in **1** was found to be 72 mV higher than that in **2** (for **1**: 1020 mV; for **2**: 948 mV vs. saturated calomel electrode). See the Supporting Information for details.

[13] When a control catalysis experiment was performed using a model complex in which the N-H group in **1** was replaced with N-CH$_3$ group, no product formation was observed, thus suggesting the key role of the N-H group in **1** during substrate activation and/or other steps. See the Supporting Information for details.

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Communications

Hydrogenation

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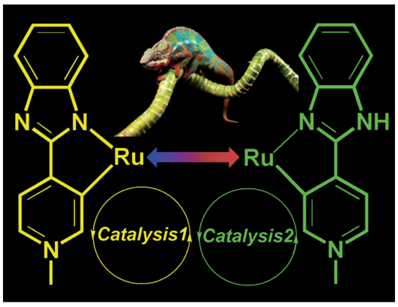
Switch in Catalyst State: Single Bifunctional Bi-State Catalyst for Two Different Reactions



In a state: An acid-base responsive bi-state catalyst controls the rates of two different catalytic processes in a complementary manner. This concept was used in an assisted tandem catalysis by switching between catalyst states to achieve the desired reaction sequence.