Emergence of Stimuli-Controlled Switchable Bifunctional Catalysts

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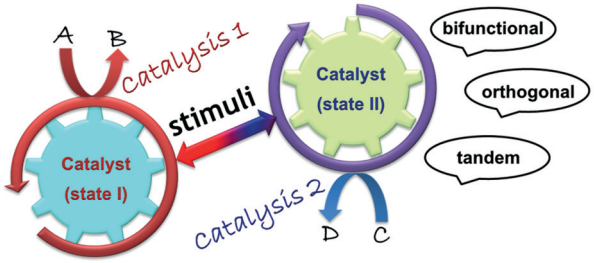
Dedicated to Professor Milko E. van der Boom on the occasion of his 48th birthday



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Abstract Can a single catalyst perform more than one 'type' of reaction? If we consider traditional design of catalysts, then the answer would probably be 'no'. However, with the advancement of catalyst design concepts, chemists have been able to demonstrate the above task, thanks to '*stimuli-switchable bifunctional catalysts*'. Within the nascent research area of '*artificial switchable catalysis*', this new type of system offers the potential to achieve complex functions which are otherwise difficult or impossible. This Synpacts article highlights the rise of these new-generation catalysts.

1 Introduction
2 Key Advances
3 Conclusion

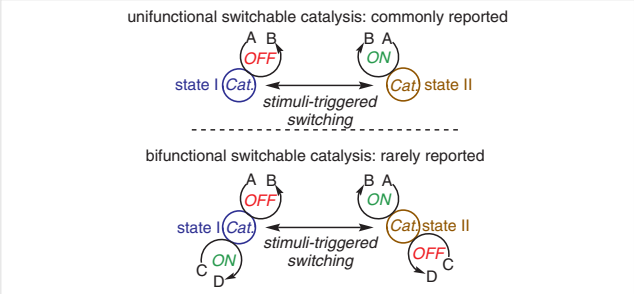
Key words switchable catalysis, stimuli, pH, redox, light, orthogonal reactions, tandem catalysis

Joyanta Choudhury (right) obtained his PhD in 2006 from IIT Kharagpur, India working under Professor Sujit Roy on the development of well-defined Ir–Sn heterobimetallic complexes for electrophilic aromatic C–H functionalization reactions. He then moved to The Scripps Research Institute, Florida, USA for postdoctoral work with Professor Roy A. Periana in the field of alkane functionalization chemistry. In 2008, he received the prestigious Marie Curie International Incoming Fellowship from the European Union and went to the Weizmann Institute of Science, Israel for a second postdoctoral posting with Professor Milko E. van der Boom conducting research on coordination-driven molecular assemblies on solid surfaces. In April of 2011, he joined the Department of Chemistry, IISER Bhopal, India as an Assistant Professor. Currently, he is an Associate Professor in the same department. His research focusses on (a) small-molecule activation and functionalization including CO_2, H_2, alkanes, arenes, and H_2O to address renewable energy and fuel related problems, and (b) design of smart multifunctional switchable catalysts for addressing complex chemical reactions. His research work on 'switchable catalysis' has been highlighted in the popular Chemistry magazine, *ChemistryWorld*. Recently, he has been featured as '*Movers & Shakers*' by the industry-leading magazine '*The Catalyst Review*', published by The Catalyst Group (TCG), PA, USA.
Shrivats Semwal (left) obtained his BSc and MSc degrees from H. N. B. Garhwal University, Uttarakhand, India in 2009 and 2011, respectively. After that, in 2013 he joined the group of Dr. Joyanta Choudhury at IISER Bhopal, India for his doctoral studies. He works on tunable and switchable catalysis, transfer hydrogenation, hydrogenation and dehydrogenation, and CO_2 conversion chemistry.

1 Introduction

The ability to control the behavior (property and/or reactivity) of chemical species with the help of an external trigger or stimulus offers the opportunity to mimic enzymatic functions, at least to some extent. The idea of designing such 'enzyme-like' artificial smart systems intrigues chemists, which eventually led to the inception of a challenging research field of '*artificial switchable catalysis*'.[1] This field is multifaceted and connects to the '*artificial molecular machines*' also, which garnered the 2016 Nobel Prize in Chemistry.[2] Catalysis plays a vital role in the world of chemical and material synthesis and promises to offer advanced and controllable output in accordance with the trend and demand. From this point of view, switchable catalysis holds a tremendous potential to deliver. In the past few years, the researchers in this area have witnessed fervent efforts from a number of research groups to develop

some fascinating catalysts demonstrating a range of unparalleled tasks in contrast to the traditional approaches.[1] The main advantage of stimuli-controlled catalysts is the freedom of choosing one or more external stimuli such as light, heat, acid/base, redox event, metal coordination, etc. in creating a dynamic, switchable platform to toggle between two distinct reactivity of the catalytic site. This sophisticated chemistry, therefore, can equip the system with a high level of 'control' over the output of catalytic reactions.

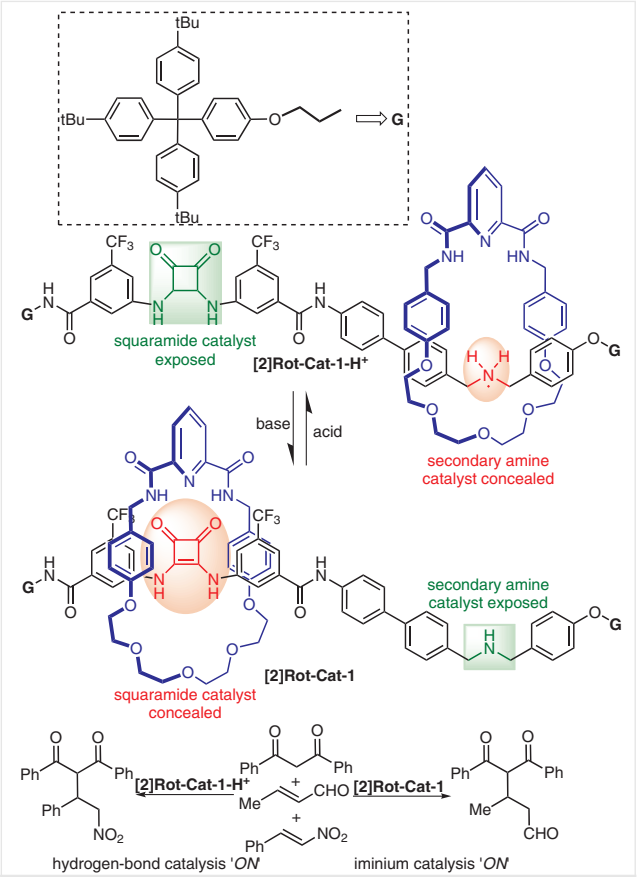


Scheme 1 Concept of stimuli-controlled unifunctional and bifunctional switchable catalysis

Generally, the output of a chemical catalysis can be expressed in terms of rate of the reaction, substrate selectivity, yield of the desired product, or/and chemo-/regio-/stereoselectivity of the products. Controlling these parameters at will, with a definite and constructive purpose, has been the primary goal of the first-generation artificial switchable catalysts. However, in majority of these systems, 'control' on rate (up-regulation or down-regulation) or other stereochemical property of *only one specific reaction* has been the most common, reportedly achieved so far.[1] Systems which show more advanced control such as orthogonal control *of two or more different catalytic processes* and preprogrammed (multi)stimuli-triggered *tandem reactions* are rarely reported (*vide infra*) (Scheme 1). The grand challenge here is to incorporate the requisite feature of switchable bi/multifunctionality into the design of the desired catalytic system as well as the experimental compatibility of the applied stimuli. Nevertheless, with the help of accrued knowledge, and imagination, chemists have been drawing inspiration to develop new systems for addressing the above challenges, too. In this Synpacts article, we highlight on this aspect including our efforts.

2 Key Advances

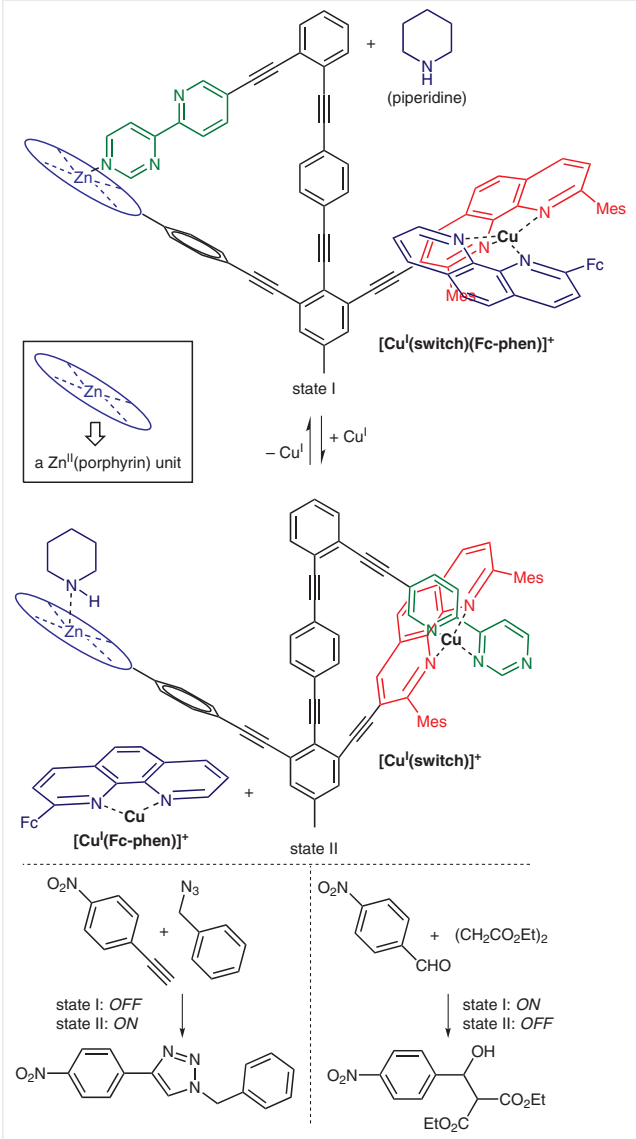
One such development appeared as recently as in the year 2015 involving a switchable [2]rotaxane system,[3] although switchable catalysis with these systems was long known.[1] This new system, reported by Leigh and co-workers, was inherently a dual-function catalyst as two different, function-specific catalytic stations were constructed deliberately on the axle.[3] Thus the macrocycle ring was reversibly positioned in an alternate manner over either of the secondary amine and squaramide catalytic units controlled by acid and base as stimuli, respectively. In effect, two different catalytic Michael addition reactions (such as a hydrogen-bond catalysis by squaramide and an iminium catalysis by secondary amine) could be run selectively, from a mixture of three substrates, in two different states of this interlocked system, depending on which catalyst was exposed and which one was concealed (Scheme 2). The significance of the concept lied on the fact that both the catalytic reactions were interference-free and highly selective under the switchable mode. Soon after this discovery, Leung and co-workers demonstrated a similar [2]rotaxane catalyst for switching thiourea catalysis and amine catalysis *ON* and *OFF* alternately with pH as stimulus.[4]



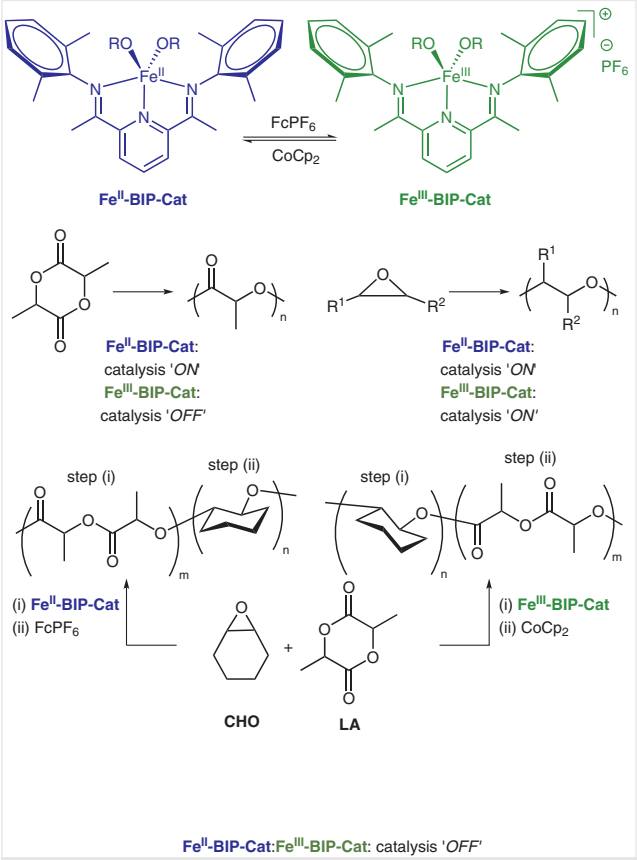
Scheme 2 pH-switchable [2]rotaxane-based dual-function catalyst[3]

Conceptually similar strategy was also discovered by Schmittel and co-workers by employing a nonrotaxane nanomechanical switch as the platform to regulate two orthogonal catalytic processes.[5] However, unlike the rotaxane system, this one did not hold the two catalysts within the nanoswitch itself through permanent bonds. Instead, the switch was toggled between two states by chemical trigger to trap or release two external catalysts alternately, so that

the respective catalyst-specific organic reactions could be realized in solution. They chose a Cu^{I}(Fc-phen)-catalyzed click reaction and a piperidine-catalyzed Knoevenagel addition for the demonstration of the above concept (Scheme 3). Thus in switching **state I**, piperidine catalyst remained free because of inability of the azabipyridine-coordinated Zn^{II} porphyrin to bind it. At the same time, Cu^{I}(Fc-phen) was bound at the switch in this state. Therefore, **state I** resulted in Knoevenagel addition reaction *ON* but click reaction *OFF*. Addition of one more equivalent of Cu^{I} to the **state I** forced the azabipyridine ligand to bind this Cu^{I} at the switch by releasing the Cu^{I}(Fc-phen) catalyst simultaneously. However, this time, the piperidine catalyst got bound at the azabipyridine-decoordinated $zinc^{II}$ porphyrin site. Thus



Scheme 3 Metal-ion coordination-triggered bifunctional nanoswitch catalyst[5]

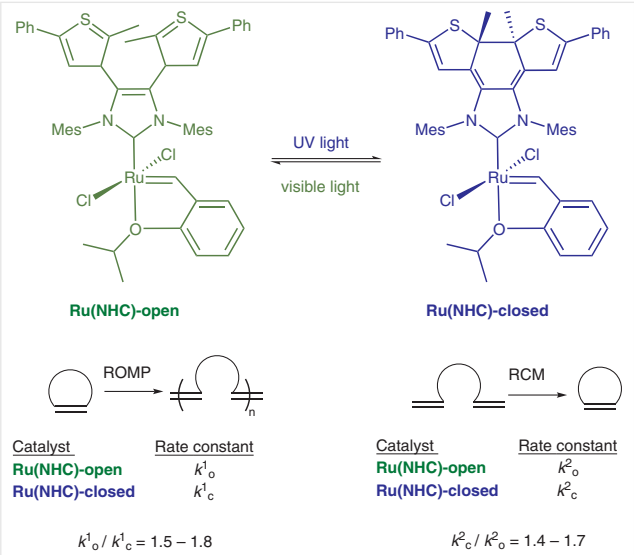


Scheme 4 Redox-switchable bifunctional polymerization catalyst[7]

in this switching **state II**, the click reaction was *ON* but the Knoevenagel addition was *OFF*. The key scientific principle of this system relied on the delicate balance of metal–ligand binding to achieve a highly selective self-sorting, required for running two orthogonal catalytic events in a fully interference-free manner. Recently, the same group networked two nanoswitches in a smart way by applying Fe^{II} ion and a special terpyridine as chemical stimuli and Cu^{I} as a second messenger that was reversibly translocated between the two nanoswitches.[6] Although, in this case, one catalytic reaction, namely, *N*-methylpyrrolidine-catalyzed conjugate addition was regulated, but this type of networking is highly relevant to the field of molecular cybernetics to regulate molecular communication and thereby complex functions.

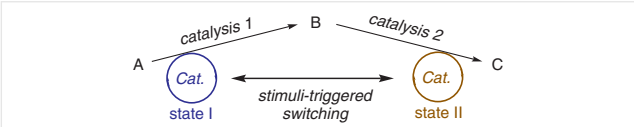
Two popular fields of catalysis research – polymerization and olefin metathesis, recently witnessed stimuli-switchable orthogonal activity of two reactions achieved by a single molecular bifunctional catalyst. In these cases, unlike the previous ones, the catalytic molecule contained only one active site (a metal center), whose stereoelectronic feature was switched between two states to induce different catalytic behavior by the same molecule. With this operational concept, Byers and co-workers applied redox

stimulus to switch a molecular iron complex between cationic Fe^{III} and neutral Fe^{II} states.[7] Interestingly, the cationic Fe^{III} state was found to be active in epoxide polymerization but inactive in lactide polymerization. On the other hand, the neutral Fe^{II} state showed exactly opposite behavior. Therefore, in situ oxidation and reduction of the catalyst center by $FcPF_6$ and $CoCp_2$, respectively, allowed to conduct two orthogonal polymerization sequentially (Scheme 4). They applied this promising strategy in copolymerization reaction to yield block copolymers with a different property than the corresponding homopolymers. In the other work, Bielawski and co-workers designed a Ru^{II} olefin metathesis catalyst by using a dithienylethene-functionalized N-heterocyclic carbene (NHC) ligand.[8] Light stimulus was used in this system to carry out reversible ring-closing and ring-opening photoisomerization of the ligand backbone. The steric and electronic perturbation at the catalytic metal center created from such photostimulated structural changes within the molecule rendered it a dual character toward catalyzing ring-closing metathesis (RCM) and ring-opening metathesis polymerization (ROMP) of some selected substrates. The rate of RCM reaction was observed to be faster with the dithienylethene ring-closed catalyst than with the ring-opened version by about 1.4 to 1.7 times. On the contrary, the ring-opened catalyst exhibited much faster rate in ROMP reaction than its ring-closed counterpart by about 1.5 to 1.8 times (Scheme 5). Mechanistic studies conducted in this work disclosed some useful insight. It was found that the electron-donating effect of the NHC ligand controlled the activation barrier in case of RCM reaction, and the ring-opened catalyst having strong donor NHC showed a higher barrier for the rate-determining retro-[2+2] cycloaddition step, than the ring-closed one. In case of ROMP, the controlling factor was substrate-dependent and steric or electronic effect guided the corresponding activation barrier. In either case, the ring-opened catalyst exhibited a lower barrier for the rate-determining step and hence was a better catalyst. Although the difference of activity by the two states of the catalyst in the two catalysis processes was only modest, the principle of orthogonal responses induced by simple stimuli-control worked well. This initial success set the stage to further develop orthogonal catalyst-pair for attaining at least close to 'true' *ON*/*OFF*-type control in suitable catalytic processes.



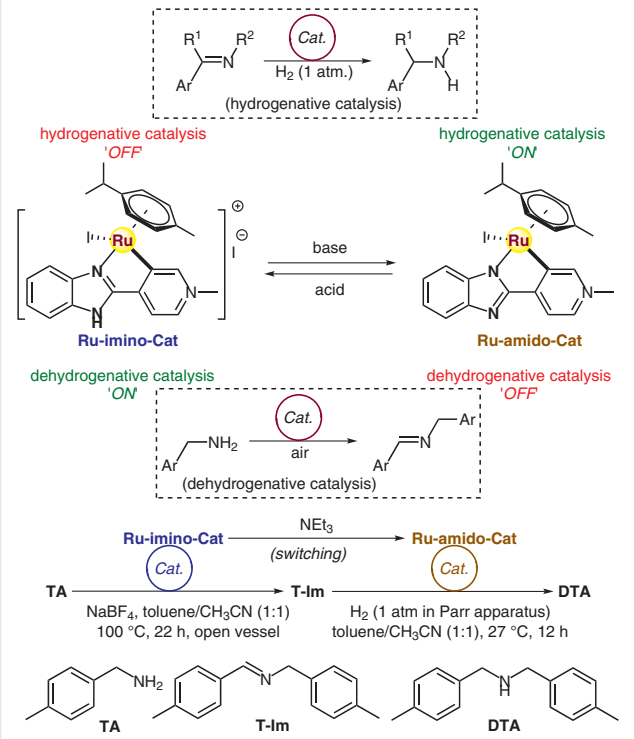
Scheme 5 Photoswitchable bifunctional olefin-metathesis catalyst[8]

Success in achieving stimuli-triggered two orthogonal catalytic processes from the **states I** and **II** of a catalyst, in principle, could offer the possibility to couple the two processes in a tandem manner within the same reaction pot. By definition, this type of smart process is called '*assisted tandem catalysis*' (Scheme 6).[9] Assisted tandem catalysis is known but only a few examples can be found in literature,[9,10] probably because of issues associated with reagent/substrate compatibility and complexity in designing such single 'multitasking' catalyst. Notably, all of the reported catalysts were converted from **state I** into **state II** by causing a trigger-induced permanent/irreversible structural change within the catalyst backbone. In this context, although unexplored so far, the idea of using switchable catalyst might strengthen the potentiality of this underdeveloped strategy. The key to the success of the same would be to incorporate such a function-regulatory feature which provides a fully reversible nature of the stimuli-induced change in the catalyst's state. In 2016, we developed a conceptually different type of acid/base-switchable catalyst to gain full control on the reversible nature of the two states of an iridium-based catalyst.[11] This switchable catalyst was utilized for highly efficient and controllable *ON*/*OFF* switching of a catalytic imine hydrogenation reaction based on acid/base input. Inspired by this successful concept, recently we upgraded this design by replacing the catalytic Cp^*Ir^{III} center with a (*para*-cymene)Ru^{II} center to explore as a bifunctional bistate catalyst and effectuate a pair of switchable orthogonal catalytic reactions – catalytic imine hydrogenation and catalytic dehydrogenative coupling of amines.[12] The catalyst switch was based on acid/base-controlled molecular coordination switch possessing two distinct metal-coordination modes in its two states. A (*para*-cymene)Ru^{II} unit bound to a hybrid pyridylidene–benzimidazole ligand was used to design the catalyst, wherein the benzimidazole functionality was the key for acid/base-controlled reversible coordination (Scheme 7). Thus, **state I** with a benzimidazole–Ru^{II} species (neutral imino-type N-



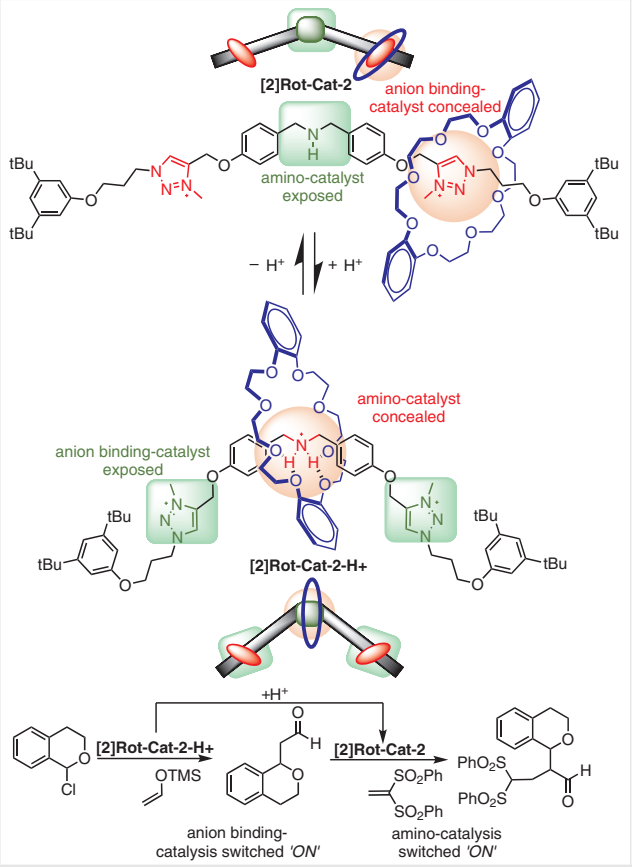
Scheme 6 Conceptual design of '*assisted tandem catalysis*'

coordination) and **state II** with a benzimidazolate–Ru^{II} species (anionic amido-type N–Ru bonding) were achieved with acid and base stimulus, respectively. The distinctly different nature of the metal–ligand bonding in two forms of the switch eventually furnished a bifunctional molecule which operated as a bistate catalyst to switch two different reactions in a complimentary manner. The base-triggered ruthenium–amido-containing **state II** was active (switched *ON*) in catalytic imine hydrogenation while the acid-triggered ruthenium–imino containing **state I** was switched *OFF* in this reaction. Conversely, **state I** and **state II** were switched *ON* and *OFF*, respectively, in the catalytic dehydrogenative coupling of amines. Of course, the reaction conditions such as temperature and the presence/absence of an additive ($NaBF_4$) were also changed accordingly for optimum catalytic activity in both the reactions. Significantly, we successfully demonstrated the *ON*/*OFF* switching behavior of this catalyst multiple times without any loss of efficacy in on-going catalysis reactions. Lastly, we applied this success to achieve a higher-level application by manifesting a one-pot-assisted tandem catalysis, through connecting a dehydrogenative coupling of amine followed by hydrogenation of the resulting imine, triggered by alternate input of acid and base stimuli, respectively (Scheme 7).



Scheme 7 Acid/base-switchable molecular coordination-based bifunctional and assisted tandem catalyst[12]

Soon after this report, Leigh and co-workers published an elegant work where they utilized a pH-switchable new [2]rotaxane-based catalytic system to perform not only two orthogonal catalytic reactions, similar to their previously reported one, but also a two-step tandem catalytic process by concealing/revealing the two catalysts in a sequential manner.[13] Like their earlier system,[3] here also they installed two catalytic stations, but this time, an amino catalyst and an anion-binding catalyst (a pair of triazolium groups) on the thread. Thereafter, two different catalytic processes – anion-binding-catalyzed Ritter reaction and amino-catalyzed nucleophilic reaction – were successfully promoted in an orthogonal and selective manner depending on the exposure or concealment of the respective catalytic units as a function of acid/base stimuli. Finally, they extended the orthogonal catalytic responses to demonstrate a preprogrammed-assisted tandem process via the pH-controlled sequential switching of anion-binding catalysis and thereafter amino catalysis (Scheme 8).



Scheme 8 pH-switchable [2]rotaxane-based dual-function and assisted tandem catalyst[13]

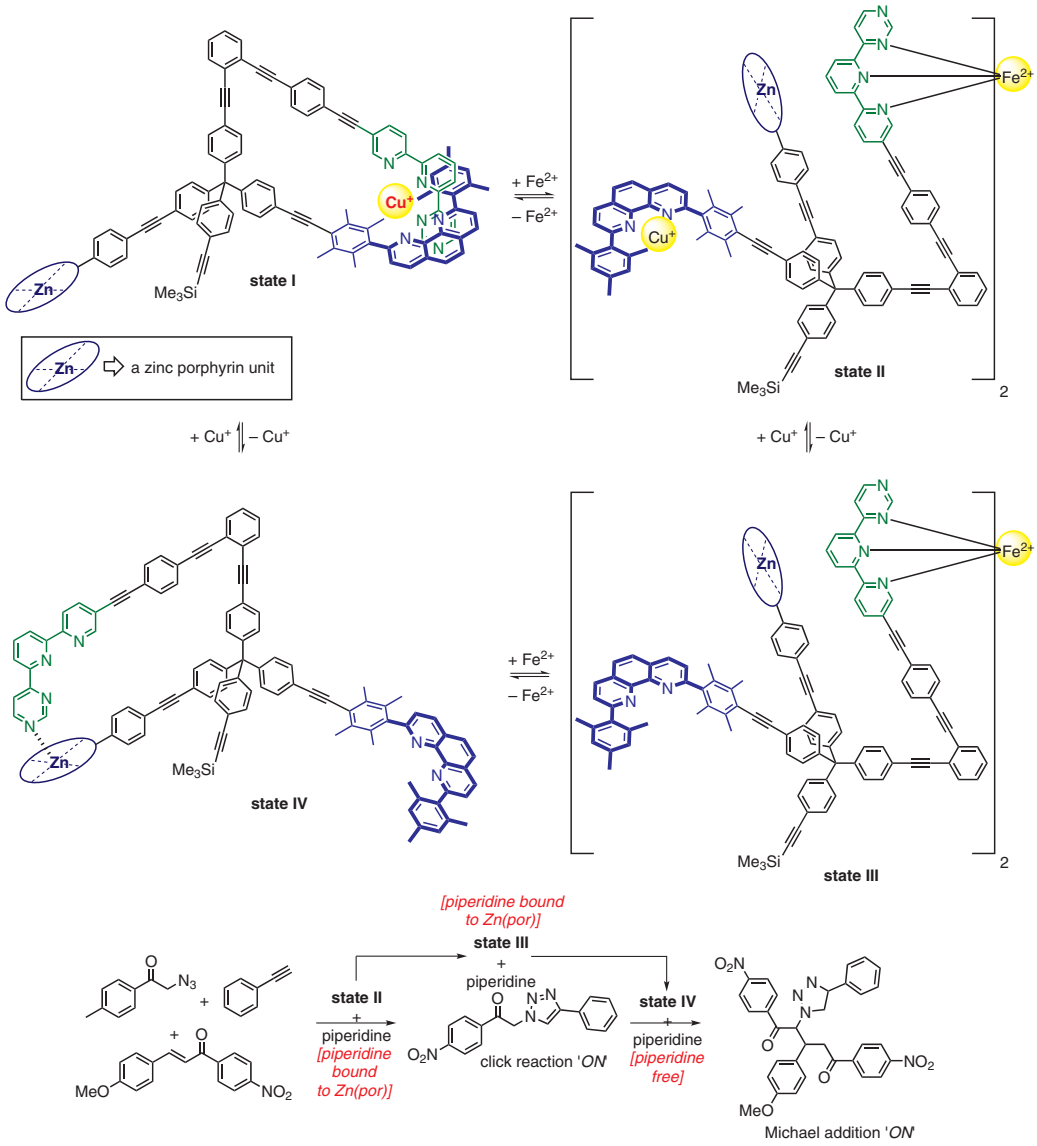
In another interesting development, Schmittel and co-workers upgraded their previously reported two-state nanomechanical switch into a four-state one, regulated via reversible addition or removal of Fe^{II} and Cu^{I} ions as inputs to achieve a tandem catalysis involving a click reaction followed by a Michael addition maintaining a high degree of orthogonality (Scheme 9).[14] Thus the four **states I–IV** of the

switch were found to be interconvertible as shown in the scheme. This system along with piperidine (as Michael addition catalyst) was used as catalyst for the above tandem reaction. **State II** was active in click reaction due to the presence of $[Cu(phen)]^+$ moiety within the switch but inactive in Michael addition because the catalyst piperidine was firmly bound to the zinc(porphyrin) site. Later on, **state IV** was activated toward the second step of the tandem catalysis, i.e., the Michael addition by making the piperidine catalyst free through strong coordination of the zinc(porphyrin) unit by the aza-terpyridine ligand within the switch as shown in Scheme 9.

These latest developments exemplified a high level of sophistication to achieve 'biolike' control in chemical catalysis and therefore can potentially stimulate further research for developing new-generation multifunctional switchable catalysts for addressing complex problems.

3 Conclusion

In summary, this article highlighted the emanation of a new trend to sophisticate artificial molecular catalysts with dual or multiple 'personalities' and thereby achieve unique functions which are otherwise difficult or impossible to acquire. Judicious incorporation of desirable stimuli-responsive, function-regulatory features within the same molecu-



Scheme 9 Metal-ion triggered four-state nanomechanical switch for tandem Click reaction–Michael addition catalysis[14]

lar catalyst is the main 'art and craft' for successful development of such unconventional bi-/multifunctional systems. The state-of-the-art accentuated herein is believed to inspire contemporary chemists in this area to be able to address the existing and future challenges related to the scope of application as well as nature and library of catalysts. Some of the key areas to be targeted with switchable bi-/multifunctional catalysts are asymmetric synthesis, energy storage, and systems chemistry. Similarly, suitably designed and fully compatible multistimuli-responsive catalysts could help to minimize the step of traditional multistep synthetic methodologies.

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