Switchable Catalysis

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# A Toggle Nanoswitch Alternately Controlling Two Catalytic Reactions**

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*Dedicated to Professor Christoph Rüchardt on the occasion of his 85th birthday*

***Abstract:*** *Reversible switching between two states of the triangular nanoswitch [Cu(**1**)]$^+$ was accomplished by alternate addition of 2-ferrocenyl-1,10-phenanthroline (**2**) and copper(I) ions. The two switching states regulate the binding and release of two distinct catalysts, piperidine and [Cu(**2**)]$^+$, in a fully interference-free manner and allow alternating on/off switching of two orthogonal catalytic processes. In switching state I, piperidine is released from the nanoswitch and catalyzes a Knoevenagel addition between 4-nitrobenzaldehyde and diethyl malonate (ON-1 and OFF-2), while in state II the released [Cu(**2**)]$^+$ catalyzes a click reaction between 4-nitrophenylacetylene and benzylazide (OFF-1 and ON-2). Upon addition of one equivalent of **2** to the (OFF-1 and ON-2)-state, both catalytically active processes are shut down (OFF-1 and OFF-2).*

Nature has often been a fruitful source of inspiration for chemists in their quest for promising research topics.[1] For decades, the mode of action of unusual enzymes, for example, ribonucleotide reductase,[2] has fascinated chemists spurring numerous model investigations. More recently, a paper by Fushinobu and co-workers[3] has drawn attention to another fascinating biological phenomenon: an enzyme that reorganizes its active site for catalyzing two distinct processes. Accordingly, the fructose-1,6-biphosphate aldolase/phosphatase (FBPA/P) is able to use a lysine residue in the active site for aldolase activity whereas when an alternative substrate is bound the enzyme undergoes major conformational rearrangments and the resulting magnesium aspartate complex displays phosphatase activity. As a result, the mentioned enzyme operates as a substrate-triggered switch with the effect that in state I (with substrate I) only catalysis I is ON, while catalysis II is OFF. Reciprocally, in state II only catalysis II is ON and catalysis I is OFF. Such clear-cut alternation between catalytic processes in biology is rare[4] and only demonstrated to a certain extent by other promiscuous enzymes.[5]

In FBPA/P,[3] the morphological changes at the enzyme's active site are brought about by a flip of the Schiff base loop while the lid loop and the C-terminal loop close. Extensive conformational reorganization that is linked to a change in functionality is reminiscent of artificial nanomechanical switches (here: nanoswitches) that have emerged only recently.[6,7] It occurred to us that the new family of triangular nanoswitches as developed by us over the past three years with their 2 nm reorganization at their switching arm[8,9] may be suitable to bring about an analogous dual alternating catalytic scenario using exclusively artificial components. At present, only a handful of nanomechanical switches are known that allow regulation of catalytic processes, for example, Rebek's light-controlled azobenzene–calixarene switch modulating a Knoevenagel condensation,[10] Mirkin's weak-link-controlled Diels–Alder cycloaddition,[11] Shibasaki's acylation,[12] Feringa's motor[13] and Leigh's rotaxane both of which catalyze a conjugate addition,[14] plus our large-amplitude ON/OFF nanoswitches controlling the catalysis of a Knoevenagel addition[8] as well as a *cis–trans* isomerization.[9]

Herein we describe how the chemically toggled nanoswitch [Cu(**1**)]$^+$[9] is able to alternately regulate two different catalyzed reactions—a Knoevenagel addition and a click reaction—depending on the respective switching state (Scheme 1). To the best of our knowledge such dual alternating catalysis employing an artificial nanoswitch is unprecedented. As such, it may only be remotely compared with a recent tandem reaction that was catalyzed by both an artificial host–guest complex and an enzyme.[15]

If one considers possible options for the design of a nanoswitch that administrates two catalytic reactions in an alternating manner, one has to bear in mind that both inputs for reversible switching between the two states as well as both catalytic processes have to operate in a fully orthogonal[16] manner at exactly the same temperature and during the same time. Quite obviously, the demands for the non-interference of all participants (two inputs for switching, two catalysts, two sets of reactants and products) severely limit the number of options and require high flexibility for the optimization of a two-state dual-catalytic system. Furthermore, one has to decide the fundamental issue of whether the switch itself will act as a catalyst[9] or whether the switch should regulate two catalytically active species by strong binding (inhibition) and release into solution (Scheme 2).[8] For the present paper, we have focused on the latter design because it is much more flexible toward probing a large variety of catalytic processes.

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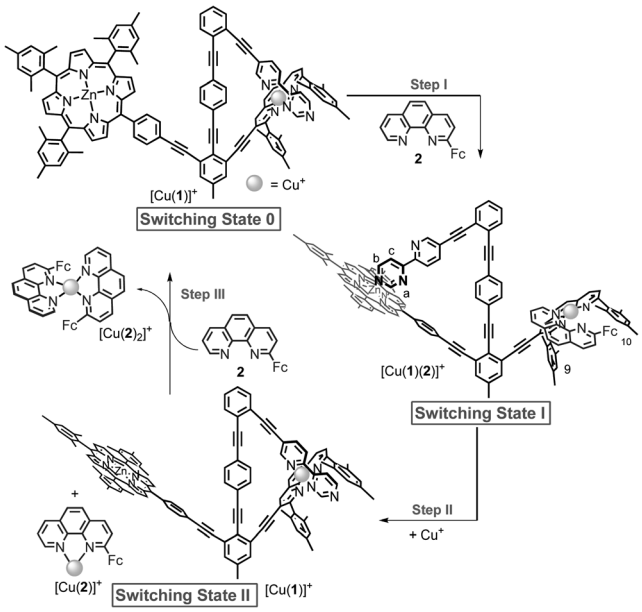
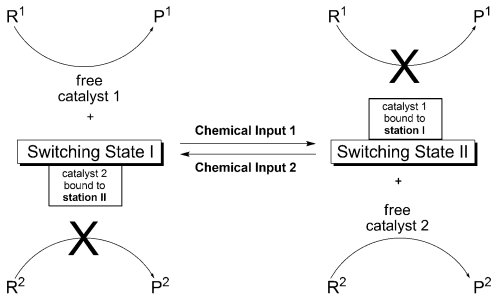


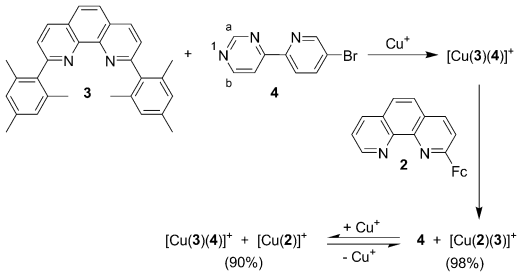

***Scheme 1.*** Toggling of nanoswitch **1** upon chemical input.




***Scheme 2.*** The principle of regulating two different catalytic processes by a nanoswitch with two stations. In switching state I, station II is used to firmly bind catalyst 2 thereby inhibiting its catalytic activity. At the same time, catalyst 1 is available in solution to catalyze process 1. After switching to state II, catalyst 2 separates from station II and thus reaction 2 is catalyzed in solution. Concurrently, catalyst 1 is inhibited by binding to station I.

First, we needed adequate chemical inputs suitable for both switching and catalysis. In our quest for electron-rich and thus strongly metal-ion-binding ligands we realized that after addition of 2-ferrocenylphenanthroline (**2**) to complex $[Cu(\mathbf{3})(\mathbf{4})]^+$ (Scheme 3),[17] which is isostructural to the metal complexation site in $[Cu(\mathbf{1})]^+$ (Scheme 1), self-sorting furnished a 1:1 mixture of $[Cu(\mathbf{2})(\mathbf{3})]^+$ and **4** in 98% yield (see Supporting Information: Figure S11. $\text{Log}\,K_2 = 3.9 \pm 0.2$ for $[Cu(\mathbf{3})]^+ + \mathbf{2}$). Notably, upon addition of a further equivalent of $Cu^+$, the mixture reshuffled in a second self-sorting to $[Cu(\mathbf{3})(\mathbf{4})]^+$ and $[(Cu(\mathbf{2})]^+$ in 90% yield (Figure S6).

Based on the above self-sorting, we selected the known nanoswitch[9] $[Cu(\mathbf{1})]^+$ as our starting point and phenanthroline **2** and $Cu^+$ as inputs to toggle the rotary arm. In $[Cu(\mathbf{1})]^+$—generated by adding one equivalent of $[Cu(CH_3CN)_4]PF_6$ to **1**[9] in [$D_2$]dichloromethane—the azabipyridine arm is anchored to the phenanthroline station in




***Scheme 3.*** Self-sorting of diimine ligands in the presence of copper(I) ions. Fc = ferrocenyl.

a heteroleptic copper(I) complex (Scheme 1).[18] Upon addition of one equivalent of 2-ferrocenylphenanthroline (**2**), the azabipyridine arm detaches from the phenanthroline station and binds to the zinc(II) porphyrin station. At the same time, **2** forms an intermolecular heteroleptic complex at the phenanthroline station (Scheme 1, step I), most likely driven by the stabilization gained in realizing the pyridine→zinc(II) porphyrin interaction. This switching process was documented by several spectroscopic techniques but it was also visible to the naked eye since the color of the solution immediately changed from deep pink to greenish violet. In the $^1$H NMR spectrum, for example, signals for protons a-H and b-H of the azabipyridine unit appear in the aliphatic region at 3.31 and 2.87 ppm, respectively, far upfield from their original positions at 7.30 ppm[9] in $[Cu(\mathbf{1})]^+$. Additionally, the appearance of new peaks for the mesityl protons 9-H and 10-H at 6.30, 6.16, 6.15, and 6.11 ppm (Figure 1b) and their concomitant disappearance at 6.37, 6.26, 6.16, and 5.93 ppm (Figure 1a) are indicative of the new complex. The involvement of ligand **2** in the complexation is evident as the $^1$H NMR signals of the ferrocenyl group at 5.24, 4.49, and 4.07 ppm (Figure S1) shifted and split, particularly in the

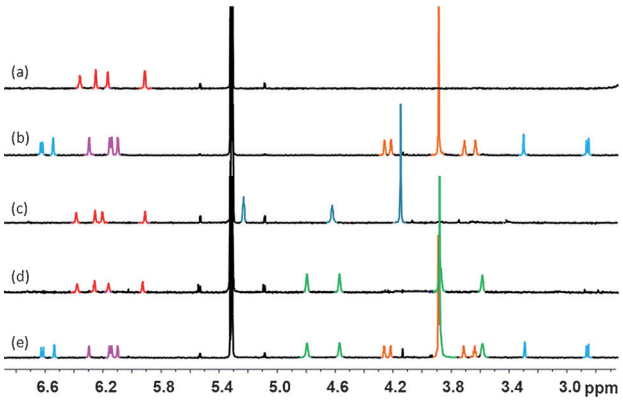



***Figure 1.*** Partial $^1$H NMR spectra (400 MHz, $CD_2Cl_2$, 298 K) of the switching process representing: a) $[Cu(\mathbf{1})]^+$ (red peaks); b) $[Cu(\mathbf{1})(\mathbf{2})]^+$ formed after addition of one equivalent of **2** to (a);* c) $[Cu(\mathbf{1})]^+$ and $[Cu(\mathbf{2})]^+$ (dark blue peaks) generated after addition of one equivalent of $[Cu(CH_3CN)_4]PF_6$ to (b); d) $[Cu(\mathbf{1})]^+$ and $[Cu(\mathbf{2})_2]^+$ (green peaks) formed after addition of one more equivalent of **2** to (c); e) addition of another equivalent of **2** to (d) regenerates spectrum (b) along with $[Cu(\mathbf{2})_2]^+$ as a byproduct. * The colors distinguish the proton signals of the azabipyridine (cyan), mesityl (magenta), and ferrocenyl (orange) units.

cyclopentadienyl ring attached to the phenanthroline, to 4.27, 4.23, 3.73, and 3.65 ppm, respectively (Figure 1b). The UV/Vis changes were equally conclusive as the Q-band at 550 nm shifted completely to 562 nm in a titration of $[Cu(\mathbf{1})]^+$ against **2** (Figure 2).

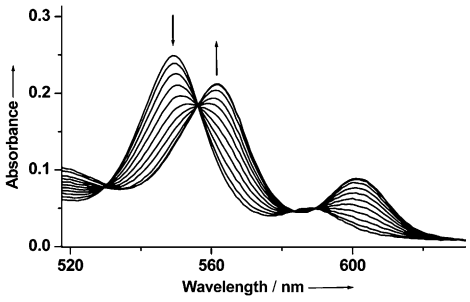



***Figure 2.*** UV/Vis titration of $[Cu(\mathbf{1})]^+$ with **2** (requires 4.5 equiv due to the low concentration of $10^{-5}$ M). The Q band completely shifts from 550 to 562 nm.

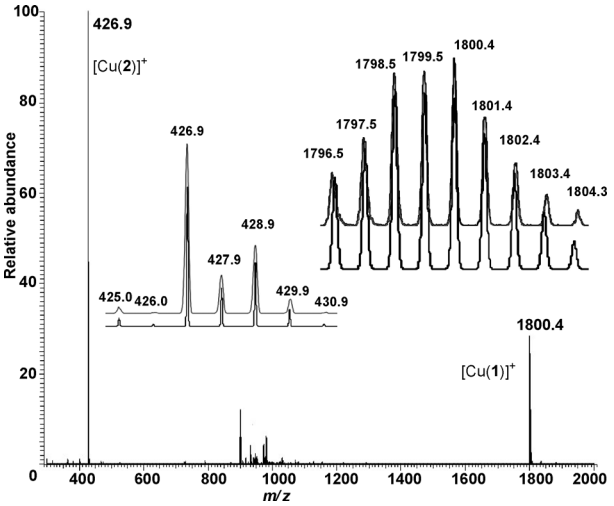



***Figure 3.*** ESI-MS of the mixture obtained in step II of the switching process. It contains $[Cu(\mathbf{1})]^+$ and $[Cu(\mathbf{2})]^+$. Inset: Experimental and theoretical (top) isotopic distribution.

Kinetic studies at room temperature on the switching of $[Cu(\mathbf{1})]^+$ with **2** were conducted at $2.5\times10^{-6}$ M with UV/Vis data being collected at 1 min intervals. The Soret band at 422 nm shifted completely to 429 nm within 26 min (Figure S12). The data for switching followed a first-order rate law at a half-life $t_{1/2}=233$ s (Figure S13). Due to the first-order behavior, the monomolecular breakup of complex $[Cu(\mathbf{1})]^+$ is the rate-determining step.

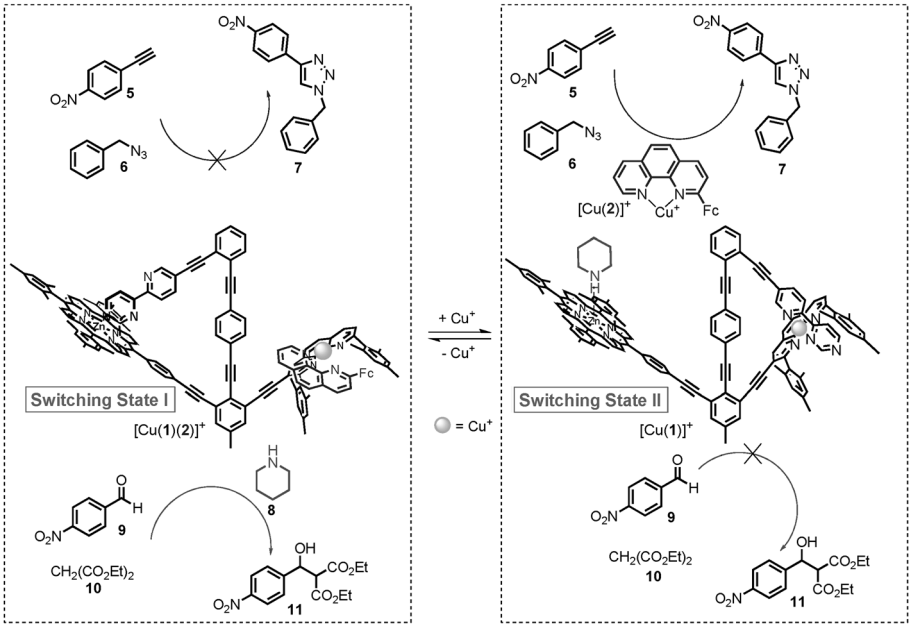
In step II of the switching process (Scheme 1), one equivalent of $Cu^+$ was added to complex $[Cu(\mathbf{1})(\mathbf{2})]^+$ in $[D_2]$dichloromethane, which quantitatively generated $[Cu(\mathbf{1})]^+$ and $[Cu(\mathbf{2})]^+$. In contrast to step I, this process, visible by the color change of from greenish violet to deep pink, was rather slow, so that the solution had to be heated for a few minutes at 40 °C. As a further sign of switching, the $^1$H NMR spectrum provided three types of characteristic shifts (Figure 1c): First, the signals of protons a-H and b-H of the azabipyridine arm are now shifted from 3.31 and 2.87 ppm to 7.30 ppm, clearly indicating that the unit is no longer in the shielding region of the zinc porphyrin. Second, a new set of signals for the mesityl protons appeared at 6.37, 6.26, 6.21, and 5.93 ppm, characteristic of the intramolecular complex $[Cu(\mathbf{1})]^+$.[9] Third, signals for the ferrocenyl protons now emerged at 5.24, 4.63, and 4.16 ppm, that is, at shifts that are distinctive for $[Cu(\mathbf{2})]^+$ (Figure S7). The UV/Vis spectrum showed a Q-band absorption at 550 nm, which precludes the possibility of axial coordination at the zinc porphyrin, as the latter would give rise to a band at 562 nm. The kinetics of switching was evaluated with UV/Vis spectroscopy at $5\times10^{-6}$ M. However, even after 3 h at room temperature there were no changes in the absorption. We then conducted the kinetic measurements at higher concentration (0.8 mM of both $Cu^+$ and $[Cu(\mathbf{1})(\mathbf{2})]^+$) using $^1$H NMR spectroscopy. The data revealed that the switching was almost complete (98%) within 13 min (Figure S9). The ESI-MS of the resultant complex showed molecular ion peaks at $m/z$ 426.9 for $[Cu(\mathbf{2})]^+$ and at $m/z$ 1800.4 for $[Cu(\mathbf{1})]^+$ (Figure 3). The theoretical isotopic distributions for both species match the experimental distributions. As a result, all data unambiguously indicate the full relocation of the azabipyridine arm from the zinc(II) porphyrin to the phenanthroline station. This switching can be performed reversibly by removing $Cu^+$ with a stronger binding ligand such as cyclam (Figure S10).

In step III (Scheme 1), addition of one further equivalent of **2** in $[D_2]$dichloromethane led to the formation of the homoleptic complex $[Cu(\mathbf{2})_2]^+$ without disturbing the nanoswitch $[Cu(\mathbf{1})]^+$. As expected, the azabipyridine arm did not change its position as the signals of the mesityl protons remained unaffected at 6.37, 6.26, 6.21, and 5.93 ppm (Figure 1d). The new peaks at 4.80, 4.58, and 3.60 ppm are indicative of the homoleptic copper complex $[Cu(\mathbf{2})_2]^+$, because they are identical to the NMR signals obtained when complex $[Cu(\mathbf{2})_2]^+$ was prepared individually from **2** and $[Cu(CH_3CN)_4]PF_6$ (2:1) (Figure S7). Thus, by the alternate addition of **2** and $Cu^+$ to state $0=[Cu(\mathbf{1})]^+$, the two states I and II of the nanoswitch **1** can be produced quantitatively. After adding one more equivalent of **2**, $[Cu(\mathbf{1})]^+$ (= state 0) is regenerated, however, with $[Cu(\mathbf{2})_2]^+$ as a byproduct (Figure 1e).

Having managed the reversible switching between the two states I and II by adding chemical inputs, we investigated the efficacy of the nanoswitch in regulating two different catalytic reactions by means of inhibition and release of catalysts. To set up two catalytic reactions in concurrent presence of all chemical inputs and reagents, we had to identify two non-interfering reaction systems compatible with the orthogonal inputs. After extensive exploration, we finally selected a $[Cu(\mathbf{2})]^+$-catalyzed click reaction and a piperidine-catalyzed Knoevenagel addition.

Analyzing the switching as depicted in Scheme 1, it is apparent that complex $[Cu(\mathbf{1})(\mathbf{2})]^+$ (= state I)—due to its intramolecular azabipyridine→zinc(II) porphyrin linkage—should not be able to harbor an additional guest like piperidine at the zinc(II) porphyrin. Added piperidine (**8**) should therefore be available as a catalyst for a Knoevenagel




***Scheme 4.*** Reversible switching controls two orthogonal catalytic reactions in two different switching states.

addition reaction (Scheme 4, left). In contrast, $[Cu(\mathbf{2})]^+$ is strongly bound in $[Cu(\mathbf{1})(\mathbf{2})]^+$. Upon addition of one equivalent of copper(I) ions to $[Cu(\mathbf{1})(\mathbf{2})]^+$ and generation of state II, the catalytic activity should switch because now piperidine is strongly bound to the liberated zinc(II) porphyrin station and hence Knoevenagel catalysis should stop. At the same time, $[Cu(\mathbf{2})]^+$ is detached and should be available to catalyze the click reaction (Scheme 4, right).

We first confirmed by NMR analysis that the reaction (55 °C, 3 h) between **9** (8.2 mM) and **10** (820 mM) in the presence of piperidine (**8**) was completely inhibited by zinc tetraphenylporphyrin (ZnTPP) (both 0.82 mM), whereas in absence of ZnTPP the Knoevenagel reaction product **11** was observed in (34 ± 2) % yield (Figure S16). Using the same concentrations and conditions,[19] we found that the reaction of **5** with **6** in the presence of $[Cu(\mathbf{2})]^+$ (10:10:1) produced the click product **7** in (55 ± 2) % yield (Figure S15), whereas the corresponding hetphen complex $[Cu(\mathbf{2})(\mathbf{3})]^+$ was unable to drive the above transformation (Figure S17). Furthermore, in a control experiment, the reaction of $[Cu(CH_3CN)_4]^+$ with **5** and **6** (1:10:10) afforded the click product (Figure S21), but at a much lower yield (25 %). The latter finding clearly proves that in concurrent presence of both phenanthroline **2** and $[Cu(CH_3CN)_4]^+$ (1:1) only complex $[Cu(\mathbf{2})]^+$ is the active catalyst.[20]

To evaluate the mutual compatibility of the Knoevenagel and click reactions in a shared solution and in the presence of all reagents (and of the later formed products), we firstly checked the catalysis triggered in switching state II (Scheme 4, right). Indeed, the reaction (55 °C, 3 h) of compounds **2**, **5**, **6**, **8**, **9**, **10**, $Cu^+$, and ZnTPP in a 1:10:10:1:10:1000:1:1 ratio gave rise to the click product **7** in (51 ± 2) % yield, but no Knoevenagel addition product (Figure S19). To evaluate state I, $Cu^+$ was masked as $[Cu(\mathbf{2})(\mathbf{3})]^+$ while piperidine was released (by mixing **2**, **3**, **5**, **6**, **8**, **9**, **10**, and $Cu^+$ in 1:1:10:10:1:10:1000:1). Here, the Knoevenagel addition product **11** formed in (34 ± 4) % yield while the click product was not detectable in the NMR spectrum (Figure S18).

Finally, the nanoswitch's potential to alternately control two catalytic processes had to be evaluated. For this, an NMR tube loaded with complex $[Cu(\mathbf{1})]^+$ (0.8 mM; = state 0) and compounds **5**, **6**, **8**, **9**, and **10** in a 1:10:10:1:10:1000 ratio was heated (55 °C for 3 h). No detectable amounts of products **7** or **11** were formed as evidenced by NMR spectroscopy (OFF-1 and OFF-2) (Figure S20a). After addition of one equivalent of **2** and thus formation of $[Cu(\mathbf{1})(\mathbf{2})]^+$, heating under the same conditions resulted in the Knoevenagel product **11** in (35 ± 4) % yield (Figure S20b), while the click reaction product **7** was not observed (ON-1 and OFF-2). After the addition of one more equivalent of $Cu^+$ to the above mixture,[21] the azabipyridine arm switched from the zinc porphyrin to the phenanthroline station releasing $[Cu(\mathbf{2})]^+$ into the solution. Simultaneously, $[Cu(\mathbf{1})]^+$ removed free piperidine (**8**) from the solution by the strong piperidine→zinc(II) porphyrin binding. When this mixture was heated, again at 55 °C for 3 h, it furnished the click reaction product **7** in (50 ± 2) % yield, while no further Knoevenagel addition reaction product **11** was formed, thus representing the OFF-1 and ON-2 mode of the dual alternating catalytic system (Figure S20c). Both catalytic processes were switched OFF by adding[22] one equivalent of **2** thus masking $[Cu(\mathbf{2})]^+$ as the homoleptic complex $[Cu(\mathbf{2})_2]^+$, while piperidine remained bound to state $[Cu(\mathbf{1})]^+$ (Figure S20d).

It can be seen that the complexity of the above system is far beyond that of previous artificial molecular switching processes, as in this ten-component reaction system all switching states, inputs, reactants, and products have to act orthogonally to one another. For instance, none of the prominent donor centers in **6**, **7**, **9**, and **10** is allowed to displace, even partly, the piperidine bound to $[Cu(\mathbf{1})]^+$ as otherwise the Knoevenagel reaction in state II (Scheme 4, right) would not remain switched OFF.

In conclusion, we present a new strategy to reversibly address the switching states of a two-state nanoswitch by adding phenanthroline **2** and copper(I) ions and thus to obtain control over ON/OFF regulation of two catalytic reactions. As nanoswitch **1** is able to up- and down-regulate two different catalytic reactions, one from each state, it mimics in a remote manner the operating principle of the FBPA/P aldolase/phosphatase. The reaction system presented in Scheme 4 serves as proof that ten components can

cooperate in an interference-free and functional manner within switching processes. It thus represents a fascinating example of the regulation of complex artificial systems and opens up new venues in systems chemistry.

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[19] The reactions were performed in $CDCl_3$ at 55 °C for 3 h.
[20] Free copper(I) ions liberated from $[Cu(\mathbf{2})]^+$ cannot be responsible for catalysis of the click reaction, because their equilibrium concentration and intrinsic catalytic efficiency are too low.
[21] To re-establish the starting conditions, the consumed aldehyde **9** was added.
[22] To re-establish the starting conditions, the consumed compounds **5** and **6** were added.

  