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Published in:
Chemistry

DOI:
[10.1002/chem.201602453](https://doi.org/10.1002/chem.201602453)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2016

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Vlatkovic, M., Collins, B. S. L., & Feringa, B. L. (2016). Dynamic Responsive Systems for Catalytic Function. *Chemistry*, 22(48), 17080-17111. <https://doi.org/10.1002/chem.201602453>

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■ Switchable Catalysts

Dynamic Responsive Systems for Catalytic Function

Matea Vlatković, Beatrice S. L. Collins, and Ben L. Feringa^{*[a]}

Abstract: Responsive systems have recently gained much interest in the scientific community in attempts to mimic dynamic functions in biological systems. One of the fascinating potential applications of responsive systems lies in catalysis. Inspired by nature, novel responsive catalytic systems have been built that show analogy with allosteric regulation of enzymes. The design of responsive catalytic systems allows

control of catalytic activity and selectivity. In this Review, advances in the field over the last four decades are discussed and a comparison is made amongst the dynamic responsive systems based on the principles underlying their catalytic mechanisms. The catalyst systems are sorted according to the triggers used to achieve control of the catalytic activity and the distinct catalytic reactions illustrated.

1. Introduction

Catalysis is a fundamental concept in chemistry and has drawn the attention of scientists since the late 18th century. Since the introduction of the principle of catalysis by Elizabeth Fulhame in 1794^[1] and its definition by Berzelius in the 19th century,^[2,3] chemists have developed numerous catalytic systems. Catalysts lower the activation energy of a chemical transformation and, as a consequence, catalyzed reactions occur faster or under milder conditions than uncatalyzed reactions. Nowadays, most industrial-scale processes are unimaginable without catalysts, ranging from polymer synthesis to the production of pharmaceuticals. With the development of modern synthetic chemistry, and the synthesis of complex molecular structures, the field of asymmetric catalysis has emerged. Numerous chiral catalysts, capable of inducing stereospecificity into the reactions they catalyze, have been developed over the last 50 years.

In the design of novel asymmetric catalysts, inspiration often comes from nature, where enzymes catalyze reactions with high conversions and reaction rates, as well as extremely high selectivities. Key to their catalytic capabilities, enzymes show high flexibility in their active site,^[4] which enables regulation of their activity by effector molecules. Effector molecules can increase or decrease the enzyme activity by specific binding. The regulation of enzymes by binding of effector molecules is crucial for the control of metabolic activity.

Making artificial responsive catalysts that can mimic the allosteric regulation of enzymes presents a major challenge. In recent years there has been increased interest in making stimuli-responsive dynamic catalysts that can switch their catalytic activity or selectivity.^[5,6,9–11] Upon exposure to external stimuli, catalysts undergo conformational changes, which can result in a change of their catalytic function (Scheme 1). In this overview, dynamic responsive catalysts that undergo reversible changes upon light stimuli, addition of ions or neutral molecules, or changes in oxidation state will be described.

Scheme 1. Dynamic conformational changes of an allosteric enzyme (a) and an artificial catalyst upon exposure to external stimuli (b).

2. Photoswitchable Dynamic Catalysts

Light presents one of the most attractive external stimuli,^[7–9] as it is noninvasive and offers the possibility of generating no waste. It also allows precise spatiotemporal control of the functions of catalysts containing a photochromic unit. To design an effective photoswitchable catalyst, it is important to choose a photochromic unit that shows efficient reversible switching and is fatigue resistant upon irradiation at specific wavelengths. Apart from having efficient, nearly quantitative switching, that is, high selectivity in the photoresponsive event, it is crucial that irradiation causes a significant change in the geometrical or electronic properties of the catalyst. Such changes should then result in different catalytic activities or selectivities.

2.1. Photoswitchable catalysts based on an azobenzene core

Azobenzenes are among some of the most studied photochromic switches and have gained a lot of attention in both fundamental studies and in applications towards responsive materials.^[10] Upon irradiation of azobenzenes, isomerization around the N=N bond takes place (Scheme 2), which causes a large change in geometry and dipole moment.

Pioneering studies on photoswitchable catalysis were performed by Ueno and co-workers in the early 1980s using an azobenzene photochromic moiety.^[11] Inspired by the principle of competitive inhibition of enzymes, they designed an artificial system to mimic this form of inhibition. The system utilized 4-carboxyazobenzene **1** as a photochromic inhibitor for the hy-

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Scheme 2. Photoisomerization of azobenzene.

drolysis of a phenolic ester by β -cyclodextrins (Scheme 3). In 1980, Ueno and co-workers reported that *E*-1 fits into the cavity of β -cyclodextrin (β -CD) and, as a consequence, inhibits the hydrolysis of 4-nitrophenyl acetate. *Z*-1 does not fit into the cavity of the β -CD, which then remains able to catalyze the hydrolysis of the phenolic ester; the hydrolysis reaction is thus accelerated upon irradiation of the reaction mixture. Although this represented the first proof of concept for photoswitchable catalysis, showing reversible control of reaction rate due to

competitive binding of a photoswitchable azobenzene, its efficiency was low since the catalyst and inhibitor concentrations exceeded the substrate concentration. A subsequent report described a more efficient system in which the photochromic moiety was covalently linked to the catalyst. Ueno and co-workers covalently attached 4,4'-bis-(carboxy)azobenzene to the smaller opening of β -CD (Scheme 3b).^[12] In this manner, the binding of the substrate into the β -CD cavity can be photoregulated by changing the depth of the hydrophobic pocket through photoinduced geometric changes of the azobenzene moiety. This allows catalyst **2** to adopt two distinct states comprising a more or less active configuration. The more compact *Z* isomer makes the cavity deeper with enhanced binding affinity, whereas the elongated *E* isomer closes the cyclodextrin more tightly and therefore causes the cavity to be shallower

Scheme 3. Regulation of the catalytic activity of a β -CD by light was achieved either by using an azobenzene moiety acting as a competitive inhibitor (a) or by incorporating the azobenzene photoswitchable moiety onto the β -CD macrocycle and directly controlling catalyst activity by steric shielding of the substrate (b and c).

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Prof. Dr. Ben L. Feringa obtained his Ph.D. degree in 1978 at the University of Groningen in the Netherlands under the guidance of Prof. Hans Wynberg. After working as a research scientist at Shell he was appointed full professor at the University of Groningen in 1988 and named the distinguished Jacobus H. van't Hoff Professor of Molecular Sciences in 2004. He has been elected foreign honorary member of the American Academy of Arts and Sciences and member of the Royal Netherlands Academy of Sciences. His research interests include stereochemistry, organic synthesis, asymmetric catalysis, molecular switches and motors, photopharmacology, self-assembly, and nanosystems.

and sterically less accessible. An irradiated sample that contained 38% of the *Z* isomer showed a 5.5-fold acceleration of hydrolysis compared to the sample that consisted exclusively of the *E* isomer. In this case, as in the first reported case of photoswitchable catalysis by the same group, there was a need for a large excess of catalyst with respect to the substrate due to product inhibition.

Use of β -CD with a covalently attached azobenzene in a truly catalytic manner, that is, with substoichiometric catalyst loadings, was achieved by Ueno and co-workers in 2001,^[13] by using a histidine linker for the covalent attachment (Scheme 3c). In the inactive state of catalyst **3**, the *E* isomer of the azobenzene moiety fills the CD cavity and prevents the binding of the substrate. Upon irradiation, the active state is obtained [the photostationary state (PSS) consists of 80% of the *Z* isomer]. The *Z* isomer does not fit into the cavity and therefore the substrate can bind inside the cavity and hydrolysis occurs. As in enzymes, in which histidine participates in catalytic triads for hydrolysis, the histidine moiety is also thought to aid catalysis when the catalyst is in its active state. The *Z* isomer was shown to catalyze the reaction and catalysis was successful even with low catalyst loadings of 2.5 mol%, whereas the *E* isomer displayed no catalytic activity.

The first example of an azobenzene template for photo-switchable catalysis was reported by Würthner and Rebek,^[14] who used an azobenzene scaffold derived from Kemp's triacid attached to a carbazole moiety (Scheme 4) to arrange two binding sites for the reacting molecules. The triacid motif is known to efficiently bind adenine moieties and thus, through the incorporation of a photoswitchable azobenzene moiety, the photocontrol of amide bond formation between substrates carrying adenine residues was achieved. The *E* isomer of recep-

tor **4** does not allow for favorable orientation of the substrates and has an insignificant effect on the reaction rate, whereas the tricomponent complex of both substrates with *Z*-**4**, in which reacting groups are arranged in greater proximity, shows an increase in the reaction rate. Upon irradiation of *E*-**4** at 366 nm, a PSS mixture containing 50% of the *Z* isomer was obtained and this caused a tenfold increase of the reaction rate. The rather low *E/Z* ratio in the PSS was attributed to the carbazole chromophore absorption in the wavelength region of the azobenzene absorption. This example shows that it is crucial to take into account photophysical properties of all the components of the catalyst during the design of a novel photoswitchable catalyst. Another drawback of Rebek's system is the structural similarity between substrates **5** and **6** and product **7**, leading to inhibition of the catalyst by the product, so that, for efficient substrate conversion, equimolar amounts of the template were required.

More than a decade later, Rebek and co-workers reported another interesting method for controlling catalytic activity upon photoirradiation.^[15] They designed a photoswitchable receptor system in which a covalently attached azobenzene moiety controls the binding of an organocatalyst (piperidine acetate) in the cavity of receptor **8** (Scheme 5). In this system, it is not the catalyst itself that is photoswitchable, but the catalytic activity of piperidine acetate could be increased by its binding into the photoswitchable receptor. By using light to induce structural changes in the receptor, control over the reaction rate of a Knoevenagel condensation was demonstrated. The receptor **8** with an *E*-azobenzene moiety binds piperidinium acetate with an association constant of 4300 M^{-1} . Upon irradiation at 365 nm, a high PSS of more than 95% *Z*-**8** is obtained. The photoisomerization causes a structural change that

Scheme 4. Photocontrol over amide bond formation by a photoswitchable catalyst.

Scheme 5. Photocontrol of the Knoevenagel condensation by a receptor/piperidinium complex.

allows the isopropyl group to point inside the cavity, ejecting the piperidinium acetate. In a catalytic system consisting of piperidinium acetate (5 mol%) and the *E* receptor (5–13 mol%), the reaction between malononitrile **10** and aromatic aldehydes is significantly accelerated compared to the uncatalyzed reaction. The presence of **E-8** causes a threefold increase in the initial reaction rate compared to the reaction with piperidinium acetate alone for a reaction between **9** and **10**. This example demonstrates how supramolecular regulation can be applied in controlling a catalytic reaction in a responsive way.

An interesting example of photoswitchable supramolecular catalysis was reported by Cacciapaglia and Mandolini in 2003 (Scheme 6).^[16] They showed that the activity of a bis-barium complex of azobis(benzo-18-crown-6) ether **12** could be regulated by light. Bis-barium crown complexes are known to catalyze ethanolysis of acetanilides, whereby one barium center serves as a binding point for the carboxylate group of the substrate and the other barium center makes the ethanoate species more nucleophilic and delivers it to the carbonyl moiety of the substrate. In the *Z* form obtained upon irradiation (high PSS with >95% of the *Z* isomer), the two metal centers are brought into proximity, enabling a two-point binding mode of the anilide **13**, enhancing the reaction rate of ethanolysis.

Due to the flexibility of the ether moieties, the extended *E* state is also observed to be active, albeit less so than for the *Z* state. As in the earlier studies by Ueno^[11,12] and Rebek,^[14]

owing to the structural similarity between the product **14** and substrate **13**, there is strong product inhibition and, as a consequence, equimolar amounts of catalyst had to be used to obtain efficient conversion.

By using a related approach, Imahori and co-workers designed an azobenzene-tethered bis(trityl alcohol) **15** (Scheme 7) that could function as a cooperative acid catalyst.^[17] Biaryltethered bis(trityl) alcohols have previously been reported as hydrogen-bond catalysts for the Diels–Alder reaction.^[18] It was anticipated that intramolecular hydrogen bonding between the two hydroxy groups of the catalyst in the *Z* isomer would enhance the acidity of one of the trityl alcohols. The catalyst activity was tested in a phosphine-catalyzed Morita–Baylis–Hillman reaction. Without catalyst, the product was obtained in 26% yield. Using 20 mol% of the *E* isomer gave 37% yield, whereas with the more active *Z* isomer the yield increased to 81%. Since each trityl group can contribute to catalytic activity (cooperative effect) the *Z* form of the catalyst shows a significant acceleration compared to the *E* form. The PSS mixture, containing 95% of the *Z* form, results in a reaction that is 82 times faster than with the *E* form. Such a dramatic effect was not observed when naphthyl or 3,5-dimethyl-4-fluorophenyl groups were used instead of the phenyl group in the bis(trityl alcohol) catalyst. The PSS was lower for the *Z* form of these catalysts. Interestingly, in the case of the catalyst containing 3,5-dimethyl-4-fluorophenyl groups, the *Z* and *E* forms showed similar activities; only 1.3-fold acceleration was observed on using a PSS mixture (*E/Z* = 15:85) compared to the inactive *E* form. The cooperativity effect in this more acidic derivative of the catalyst was not evident.

Scheme 6. Photocontrol over anilide ethanolysis with a photoresponsive catalyst.

Scheme 7. Photoswitchable bis(trityl alcohol) catalyst.

Cooperative activation by a photoresponsive catalyst was used recently in the design of a glycosidase mimic (Scheme 8).^[19] Azobenzene 3,3'-dicarboxylic acid **19** was designed as a catalyst for hydrolysis of glycosidic bonds. It was demonstrated that for *E*-**19** deprotonation of both carboxylic groups happens at the same pH, whereas for *Z*-**19**, obtained by photoirradiation (PSS composed of 70% *Z* isomer), it happens stepwise and two distinct pK_a values (4.7 and 6.5) were determined. Using the pH range in which the *Z* isomer of the catalyst is monodeprotonated, a rate enhancement of six orders of magnitude was observed for the hydrolysis of 4-nitrophenyl- β -D-glucopyranoside **20** compared to the *E* isomer.

Scheme 8. Controlling hydrolysis of 4-nitroxyphenyl- β -D-glucopyranoside with a photoresponsive catalyst.

An alternative approach was reported recently by Pericàs and co-workers,^[20] whereby they relied on antagonism, catalyst inactivation by attractive intramolecular interactions, as a new concept for the design of a photoswitchable catalyst. Their azobenzene-derived catalyst **22** contains a thiourea moiety (hydrogen-bond donor) on one side of the molecule and a hydrogen bond acceptor moiety (nitro, ester or amide) on the other. The catalyst was tested in the Michael addition of acetylacetone **24** to *m*-bromonitrostyrene **23**. Of the five synthesized derivatives of the catalyst, the one with a nitro group as the hydrogen-bond acceptor (Scheme 9) displayed the largest difference in activity between the *E* and *Z* forms. To demonstrate

that the rate difference was not simply a result of steric effects, the authors replaced the nitro group with a methyl group and found that the reactivity between the *E* and *Z* forms was not significantly different, suggesting that competitive intramolecular hydrogen bonding inhibits catalytic activity. In the Michael addition of acetylacetone **24** to *m*-bromonitrostyrene **23**, product yields differed by 75% when the reaction was conducted with *E*-**22** and the PSS mixture over 18 h. This effect is particularly impressive considering that the PSS mixture consists of only 56% of inactive *Z*-**22**. Other catalyst analogues displayed unsatisfactory PSS ratios upon irradiation at 365 nm and the low PSS ratio exhibited by the system prevents this responsive catalyst from being an efficient ON/OFF system.

Scheme 9. Photoswitchable thiourea catalyst that is inactivated in the *Z* form by intramolecular hydrogen bonding.

Another interesting example of photocontrol over catalyst activity was reported by Kawashima and co-workers,^[21] who were able to control the Lewis acidity of a catecholborane moiety by reversible switching of an azobenzene **26** (Scheme 10). Upon photoswitching, the coordination number of boron changed from four in the *E* isomer to three in the *Z* isomer, causing a change in Lewis acidity. This was demonstrated by the complexation ability of both of the azobenzene isomers of catecholborane with pyridine, for which a 300-fold difference in ligand binding was observed. Despite these large differences in ligand binding, this system was not employed in catalysis.

The first example of successfully employing a photoswitchable base as a catalyst was reported by Hecht and co-workers.^[22] The photoswitchable base **27** was derived from an *N*-alkylated piperidine in which the basic tertiary amine is shielded reversibly by a bulky azobenzene moiety. In the *E* form of the cata-

Scheme 10. Change of coordination number of boron and its Lewis acidity upon irradiation with light.

lyst, the nitrogen is sterically hindered.^[23] Upon photoisomerization with 366 nm light, the active *Z* isomer is obtained, in which the lone pair on nitrogen becomes sterically accessible, increasing the basicity of the catalyst by an order of magnitude ($\Delta pK_a = 0.8$). Catalyst **27** (Scheme 11) was successfully employed in the Henry reaction between nitroethane (**28**) and 4-nitrobenzaldehyde (**29**), in which *Z*-**27** caused a 30-fold increase of the reaction rate compared to *E*-**27**.

Scheme 11. Photoswitchable piperidine-derived catalyst.

Hecht and co-workers has also described the successful immobilization of this piperidine catalyst on silica gel by the attachment of monochlorosilane anchoring groups.^[24] The catalyst could be switched with fully reversibility, but the use of the immobilized catalyst in catalytic reactions has not yet been reported. In 2012, by using the same concept as in their first photoswitchable base catalyst,^[22] Hecht and co-workers reported the design of a photoswitchable guanidine catalyst,^[25] which was intended for the use in ring-opening polymerization (ROP) of lactide. Unfortunately the catalyst's basicity was not sufficient for the reaction and only a modest PSS ratio was obtained upon photoirradiation.

Using light to control the aggregation state of a catalyst also presents a possible method for regulating catalytic activity. This approach was utilized for the first time by Grzybowski and co-workers,^[26] who attached azobenzene moieties onto gold nanoparticles. These functionalized gold nanoparticles, comprising a mixed self-assembled monolayer of dodecylamine and azobenzene alkane thiols, were utilized in the hydrosilylation reaction of 4-methoxybenzaldehyde with diphenylsilane in toluene. Upon irradiation of the reaction mixture at 365 nm, causing isomerization of the azobenzene moieties to their *Z* form, the reaction slowed down dramatically due to aggregation of the catalyst (90 times slower). During aggregation, the solvent-exposed area of the catalyst decreases dramatically, which causes deactivation of the catalyst. Aggregates of the nanoparticles can be broken up after irradiation of the reaction mixture with visible light restoring the initial reaction rates. This process could be repeated up to three times on restoring

the initial dispersed catalyst. More cycles did not cause full aggregation of the nanoparticles, due to the high affinity of the substrates (benzaldehyde and diphenylsilane) for the gold surface.

More recently, Shibasaki and co-workers reported another example of photocontrol over the aggregation state of a catalyst.^[27] They designed a diamide **31** containing an azobenzene moiety and a nucleophilic pyridyl group, which varied its aggregation state depending on the geometry of the azobenzene (Scheme 12). With the azobenzene in the *Z* form, intermolecular alignment of the hydrogen-bond donors and acceptors is disrupted, making this catalyst more soluble in certain solvent systems than its *E* form. The PSS achieved upon irradiation of the catalyst at 365 nm in an *n*-hexane/propionitrile solvent mixture (4:1) was high, with 96% of the *Z* form. In this solvent mixture, the PSS mixture is soluble whereas the pure *E* isomer aggregates. The effect of aggregation was tested in two different catalytic reactions that could be accelerated by a nucleophilic pyridyl moiety. In the acylation reaction of 1-naphthol **32** and Boc_2O **33** employing 15 mol% of **31**, a large difference in activity was observed between the aggregated and dispersed forms. By using a PSS mixture upon irradiation at 365 nm, the product **34** could be obtained in 69% yield, whereas using the aggregated form of **31**, consisting of only the *E* form, gave **34** in only 11% yield. The difference in activity was even larger in the rearrangement of 2-acyloxybenzofuran **35** to 3-acyl-2-benzofuranone **36**. In this case, the product **36** was obtained in 80% yield when using the *Z* form of the catalyst and in 14% yield when using the aggregated form. This type of catalytic system is limited to specific solvents and the authors showed that, in solvents where both forms are soluble, there was almost no difference in catalytic activity.

2.2 Photoswitchable catalysts based on dithienylethene core

Dithienylethene (DTE)-based switches undergo reversible cyclization reactions when exposed to UV and visible light and the two isomers have distinct geometric and electronic properties (Scheme 13).^[28]

Switches based on the DTE core demonstrate high fatigue resistance in the ring-closing and ring-opening reactions; an aspect which has recently been studied in depth by Hecht and co-workers.^[29] They demonstrated that careful design of the substitution pattern can help in improving fatigue resistance. Unlike azobenzenes, which can interconvert upon exposure to heat as well as light, DTE switches almost exclusively switch between the two forms under irradiation with light. Upon ring closure and opening of DTE switches, there is a large change in the distribution of electron density. This property enables modulation of the electronic properties of the active site of a catalyst by light, provided that the active site of the catalyst is conjugated to the DTE unit. Although it has been demonstrated that the switching of electronic properties can cause changes in various chemical properties there have been only limited reports of the use of these systems in catalysis. The groups of Lehn,^[30] Irie,^[31] and Branda^[32] have all demonstrated the modulation of acidity upon changes in the electronic struc-

Scheme 12. Photocontrol over catalytic activity through aggregation/dissociation state of the catalyst.

Scheme 13. Photoisomerization of DTE switches.

ture. Branda and co-workers utilized changes in the electronic structure of the DTE core upon cyclization to affect the Lewis acidity of a boron center incorporated in the central ring of the switch.^[32] Unlike the Kawashima example (Scheme 10),^[21] where the Lewis acidity was changed due to different coordination of boron in different azobenzene isomers, here the acidity difference is caused exclusively by differences in electronic structure between the open and closed form of **37** (Scheme 14). In the open form *o*-**37**, the OFF form, the Lewis acidity of boron is low, since the *p*-orbital of boron is partially occupied with delocalized π electrons, as illustrated by the negligible binding of pyridine to the boron center. In the closed form *c*-**37**, the ON form, binding is strong, with a binding constant of $>7000\text{ M}^{-1}$. Despite these large differences in Lewis acidity of the boron in the open and closed forms, this system is yet to be employed in catalytic reactions.

Upon reversible ring opening and closing of DTE based switches, changes in stereoelectronic properties are observed that have been shown to cause changes of basicity,^[33] ligand coordination,^[34] hydrogen bonding,^[35] and reactivity in cycloaddition reactions.^[36]

Scheme 14. Regulating Lewis acidity of a boron atom with light.

The first example of using a DTE based switch in catalysis was reported by Branda and co-workers:^[37] a chiral bis(oxazoline) ligand with a DTE bridge unit was designed, which allowed the selectivity of a cyclopropanation reaction to be controlled with light. The approach exploited the differences in sterics between the open and closed forms, whereby in the open form, the two oxazoline moieties of the ligand **38** can bind Cu^I and moderate enantioselectivities of **41** (30–50% *ee*) were found in the cyclopropanation of **39** with **40** (Scheme 15). In the closed form (*c*-**38**) the two oxazolines are far apart, in an *anti* orientation, and cannot provide a bis-binding mode for the Cu^I atom. On using the ring-closed form, a significant drop in enantioselectivity of cyclopropanation was observed to 5% *ee*, although when a PSS mixture consisting of 23% of the closed form (*c*-**38**) was used in the cyclopropanation reaction, no significant drop in enantioselectivity was observed. This represents the first reported example of modulation of stereoselectivity of a copper-catalyzed reaction by light. Unfortunately, this system is not effective in switching the selectivity in situ due to the low PSS.

In 2008, Branda and co-workers reported the synthesis of nonsymmetric DTE switch **42**,^[38] which had a pyridine moiety on one side and a monobenzylated pyridine on the other side (Scheme 16). It was employed in catalytic reactions between dimethyl acetylenedicarboxylate (DMAD) **44** and 3-nitrobenzal-

Scheme 15. Photoswitching of a DTE-based oxazoline ligand that shows different stereoselectivities in the cyclopropanation of styrene.

Scheme 16. DTE pyridine-based catalyst for reaction between DMAD and 3-nitrobenzaldehyde

dehyde **45**, showing a 15% difference in conversion into **46** between the open and closed form. To achieve 20% conversion, 1 molar equivalent of the catalyst had to be employed, which presents a major disadvantage of the system so far.

More recently, Branda and co-workers used the difference in the electronic properties between the two isomers of DTE switches to design an ON/OFF catalytic system for the racemization of alanine (Scheme 17).^[39] Their design was inspired by the fact that the activity of pyridoxal 5-phosphate (PLP) in the racemization of alanine relies on the conjugation between the aldehyde and pyridinium functionalities. Upon condensation of an amino acid with PLP, the pyridinium group in the aldimine enhances the acidity of the amino acid α -hydrogen, facilitating deprotonation and subsequent racemization. In their PLP analogue **46**, the DTE switch contains a pyridinium and an aldehyde unit at the respective thiophenes. In the open form (o-**46**), there is no conjugation between the units and they are electronically insulated from each other and the system lacks catalytic activity. Upon UV irradiation a ring-closed form (c-**46**) is obtained, which results in a fully conjugated structure between the pyridinium and aldehyde groups, forming a PLP mimic. Upon condensation of an amino acid with the closed form of PLP mimic c-**46**, aldimine is obtained, which, upon removal of the amino acid α -hydrogen, results in a quinonoid intermediate. The catalytic ability of this PLP mimic was tested in the racemization of optically pure L-alanine in hydrogen/deuterium exchange experiments. Whereas the open form (o-**46**) led to minimal racemization, with less than 3% exchange at 40 °C over 140 h, after UV irradiation, the closed form (c-**46**; PSS consisted of 97% of the ring-closed form) resulted in significant acceleration of the reaction rate: at 40 °C during 140 h, 30% exchange was observed and nearly complete exchange (95%) could be reached after 230 h. It was thus demonstrated that the activity of the catalyst could be switched from the negligibly active form (OFF) to the more active form (ON) through alternate exposure to UV and visible light.

The use of electronic changes in DTE switches in photoresponsive catalysis was recently further explored by the Neilson and Bielawski (Scheme 18).^[40] A 4,5-dithienylimidazolium salt

Scheme 17. Photoswitchable PLP mimic for the racemization of L-alanine

(catalyst precursor) **47** was prepared, which underwent an electrocyclic ring-closing process under neutral and basic conditions upon exposure to UV radiation ($\lambda = 313$ nm). After exposure to visible light ($\lambda > 500$ nm), it could switch back to the open form nearly quantitatively. In the closed form, the electron density at the carbenoid center in the imidazolium salt pre-catalyst obtained with visible light was shown to catalyze a transesterification reaction between allyl alcohol **48** and vinyl acetate **49**. Similarly the amidation of ethyl acetate **51** with 2-aminoethanol **52** was accelerated. After exposure of the catalyst to UV light, the reaction rate dropped significantly, both for the transesterification ($k_{\text{vis}}/k_{\text{UV}} = 12.5$) and the amidation ($k_{\text{vis}}/k_{\text{UV}} = 100$) reaction. The switching between reaction rates in the amidation reaction was demonstrated upon alternating exposure to UV and visible light. Although the fatigue resistance of the catalyst **47** over many cycles has not been demonstrated, it was indicated that some (13%) decomposition of the catalyst to an unknown byproduct takes place after one cycle, limiting full reactivation of the catalyst by light.

The pre-catalyst **47** was also employed in controlling the ring-opening polymerization (ROP) of cyclic esters^[41] by light. For δ -valerolactone, the polymerization rate was much slower under UV light compared to visible light ($k_{\text{vis}}/k_{\text{UV}} = 59$) and by alternating exposure to UV and visible light, ROP could be reversibly activated and deactivated, representing the first reported example of a successful photoswitchable organocatalyst for ROP.

By using the same DTE core, a switchable NHC–Rh^I complex **55** was prepared and employed as an efficient catalyst for the hydroboration of alkenes and alkynes with pinacolborane (Scheme 18c).^[42] Upon exposure of the complex to UV light, the catalytic activity was diminished by an order of magnitude, although the PSS mixture after UV irradiation consisted of only

Scheme 18. Photoswitchable NHC catalyst and ligands: a) transesterification and transamidation; b) polymerization; c) rhodium-catalyzed hydroboration of alkenes and alkynes.

62% of the closed form (c-55). The effect on the rate constants is expected to be larger if quantitative ring closure could be achieved. Upon exposure to visible light, the open form (o-55) is almost completely restored (PSS consists of 97% of the open form). It was demonstrated that the hydroboration of styrene **56** with **57** could be switched ON and OFF multiple times with alternating UV and visible light. The crucial difference in reaction rates comes from the difference in ligand electron structure. In the closed form obtained after UV irradiation the NHC-ligand has decreased electron-donating ability, which results in inhibition of the rate-determining reductive elimination step.

An example of a photoswitchable organocatalyst **59** based on a DTE-linked imidazole was recently employed in the acylation of 2-decanol **60** with acetic anhydride **61** (Scheme 19).^[43] The open form o-59 proved to be an efficient catalyst, affording **62** in 72% yield after 24 h. Upon UV irradiation, the closed form c-59 is obtained, where the PSS consists of 89% of the closed form, and was demonstrated to be a less effective catalyst for the acylation reaction. The rate constants for the open and closed forms differ by one order of magnitude ($8.8 \times 10^{-4} \text{ M}^{-2} \text{ s}^{-1}$ vs. $6.9 \times 10^{-5} \text{ M}^{-2} \text{ s}^{-1}$), which is attributed to a distinct difference in the nucleophilicity of the imidazole groups. In the absence of the catalyst, a background reaction is ob-

served, affording the product in 11% yield after 24 h, which presents a drawback for building an efficient catalytic ON/OFF system. The closed form was not completely inactive, as it caused an increase in the reaction rate by two orders of magnitude compared to the noncatalyzed reaction. Another drawback is that upon alternative irradiation with UV and visible light some decomposition of the catalyst was observed, indicating that the full activity of the ring-opened form cannot be restored.

Scheme 19. Dithienylethene-linked imidazole as a photoswitchable catalyst for the acylation of decan-2-ol.

2.3 Photoswitchable catalysts based on a spiropyran core

Spiropyran photoswitches have found numerous applications in responsive materials,^[44] due to the large differences in properties between their isomers (Scheme 20). The isomers can be switched with various stimuli: light, solvent, pH and redox changes. Upon UV irradiation of the ring-closed form the ring-opened form is obtained through the cleavage of the C–O bond between the pyran oxygen and the spiro carbon. In the ring-closed form (spiropyran form), the two halves are orthogonal, whereas in the ring opened zwitterionic form (merocyanine) they are planar forming an extended conjugated system. Spiropyran compounds haven't been extensively studied in the area of photoswitchable catalysis, although in a pioneering study they have been used to modify enzyme activity.^[45] Biological applications have been explored, amongst others, by using spiropyran to achieve control over antigen–antibody interactions with light and for building photoresponsive enzyme-layered electrodes.^[46]

In 2007, Willner and co-workers reported a remarkable example of photoswitchable electrocatalyzed reduction of H_2O_2 and the generation of chemiluminescence at surfaces covered with a nitrospiropyran derivative in the presence of Pt nano-

Scheme 20. Photoswitching of spiropyran upon photoirradiation.

particles (Scheme 21).^[47] The nitrospiropyran derivative was attached to an indium tin oxide (ITO) electrode forming a monolayer. This monolayer does not attract the negatively charged Pt nanoparticles and is thus catalytically inactive towards the reduction of H_2O_2 . Upon irradiation with UV light ($380 > \lambda > 320 \text{ nm}$) photoisomerization of the spiropyran s-**63** in the monolayer occurs followed by protonation of the zwitterionic form resulting in a protonated merocyanine m-**63** monolayer. The positively charged monolayer attracts the Pt nanoparticles to the surface of the ITO electrode, leading to catalytic activity in the reduction of H_2O_2 . Irradiation of the monolayer with visible light ($\lambda > 475 \text{ nm}$) converted the merocyanine derivative back into the starting spiropyran moiety and led to detachment of the Pt nanoparticles and the re-formation of a catalytically inactive electrode. The electrocatalytic function of the ITO electrode was successfully switched upon alternate exposure to UV and visible light for ten cycles without significant degradation. The reaction could be followed electrochemically and by chemiluminescence generation.

Raymo and Credi reported an interesting photoswitchable catalytic system which could reversibly control the generation

Scheme 21. An electrode functionalized with a spiropyran monolayer allows the binding of Pt nanoparticles only in the open state of the spiropyran. Pt nanoparticles bound to the electrode catalyze the reduction of H_2O_2 to H_2O .

of singlet oxygen (Scheme 22).^[48] The system is composed of a merocyanine type photoacid m-**64** and an osmium polypyridine complex **65** acting as a singlet-oxygen sensitizer. Upon irradiation with near-visible light the merocyanine is converted into the spiropyran with release of protons into solution resulting in the protonation of the osmium polypyridine complex. In its protonated form the complex is not able to generate singlet oxygen. The activity of the complex could be restored upon leaving the solution in the dark at room temperature for five days.

2.4 Photoswitchable catalysts based on a stilbene core

Stilbenes are a widely studied class of photochromic switches,^[49,50] which, upon irradiation with UV light, undergo isomerization of the $\text{C}=\text{C}$ bond. They can exist in two stable geometrical isomers *E* and *Z*. Their application has been limited because of the common photodegradation that can occur in the presence of oxidants: *Z*-stilbene can undergo an electrocyclic reaction and in the presence of an oxidant the cyclized form can undergo irreversible dehydrogenation yielding a phenanthrene. This presents a major drawback for achieving photoswitchable catalysis or any other application, unless specifically designed stilbenes are used that avoid photocyclization (see below).

Despite these difficulties, a number of successful examples of employing the stilbene core in photoswitchable catalysts have been reported. In 1999, Inoue and co-workers designed a system in which stilbene derivative **66** was used for photoswitchable chemical fixation of CO_2 (Scheme 23).^[51] Their design was based on the observation that the bulky stilbene-derived ligand **66** (Scheme 23) can only coordinate efficiently to the aluminum porphyrin **67** in its *Z* configuration. Upon coordination with a nitrogen-containing base, the aluminum porphyrins are able to catalyze the transformation of CO_2 and 1,2-epoxypropylene into propylene carbonate. Switching from the *E* to the *Z* stilbene derivative by using UV light caused a tenfold acceleration of the reaction. A drawback of this catalytic system is that the reaction is slow; in 18 h, the conversion with *Z*-stilbene is 23%, whereas the reaction with *E*-stilbene **66** is

Scheme 22. Coupled operation of spiropyran photoacid system and osmium complex in generation of singlet oxygen

Scheme 23. A bulky stilbazole ligand can only coordinate to an aluminum porphyrin in the *Z* state, owing to steric hindrance that occurs upon binding of the *E* isomer. Once coordinated by stilbazole, the Al porphyrin complex catalyzes the reaction of CO₂ with 1,2-epoxypropane to propylene carbonate.

not completely suppressed (2% conversion obtained over the same time period).

Cacciapaglia et al. designed a bisbarium stilbenobis(18-crown-6) complex and showed how it works in a cooperative catalytic manner in the ethanolysis of esters.^[52] The *Z* complex was more efficient in ethanolysis of esters than its *E* analogue. It is worth noting that in situ acceleration of the reaction could be observed upon photoirradiation of the *E* catalyst. Unfortunately, the catalyst could not be reverted to the original, less active *E* state, by thermal or photochemical isomerization.

More recently Craig co-workers carried out systematic studies of a catalyst based on ligand **68** that consisted of a stilbene (1,1'-biindane) coupled to a chiral bis(phosphine) ligand (Scheme 24).^[53] They demonstrated that changes in the stilbene geometry influence the stereochemical outcome of palladium-catalyzed carbon-carbon bond-forming reactions. Upon irradiation of the *Z* ligand at 365 nm, a PSS mixture containing a 68:32 mixture of *Z* and *E* isomers was obtained. To compare their selectivity in catalysis, different isomers of the bisphosphine ligand were purified by column chromatography and used separately in asymmetric Heck reactions and Trost asymmetric allylic alkylations. Although, in all cases, the *Z* isomer demonstrated higher selectivity than the *E* isomer, reaction with either isomer resulted in the same major enantiomer of the product (despite differing degrees of enantioselectivity).

In 2011, Feringa and co-workers reported the first photo-switchable catalyst **78a** based on a molecular motor core that could be used to efficiently control stereoselectivity and activity of a thiol-enone Michael addition (Scheme 25).^[54] This catalytic system is based on an overcrowded alkene as a photochromic unit and it can exist in four states, unlike many other switches that can exist in only two isomeric forms. The motor bears a 4-dimethylaminopyridine (DMAP) group and a thiourea group which cooperatively catalyze the conjugate addition of thiols to enones. The relative orientation of these two catalytic units can be dictated by the unidirectional rotary cycle of the

Scheme 24. Different stereoselectivities of the product in asymmetric Heck reactions and Trost asymmetric allylic alkylations using the *Z* and *E* isomer of the biphenyl ligand.

molecular motor. In the *E* form, the two catalytic units are far apart, resulting in low catalytic activity. In the *Z* state, cooperativity between the two groups results in an increase of reaction rate. The helicity of the chiral molecular motor determines at which face of cyclohexenone **79** (*Si* or *Re*) attack of thiol **80** takes place and therefore which enantiomer of the product **81** is formed. With this design, a single chiral catalyst could form the racemate (from *E*-**78a**) of the addition product, as well as preferentially each enantiomer (from *Z*-**78a**). The switching between distinct catalysts is controlled by photochemical and thermal isomerization steps, whereas the sequence in which (*R,S*)-**81**, (*R*)-**81** or (*S*)-**81** product is obtained is governed by the chirality of motor unit. In 2014, our group reported another molecular motor-based organocatalyst **78b**, which differed from the original one by removal of the phenyl spacer between the motor core and the catalytic units.^[55] It proved a potent catalyst in the asymmetric Henry reaction, achieving ee values up to 71 %.

Recently, we reported a switchable chiral biphenyl ligand **78c**, based on a molecular motor core.^[56] Phosphine ligands were connected via amide bond linkers to the molecular motor core and used in a palladium-catalyzed desymmetrization of *meso*-cyclopent-2-en-1,4-diol bis(carbamate) **85**. This responsive catalyst resulted in 88% ee of one enantiomer of the product **86** with the (*P,P*)-*Z* state of the ligand and 87% ee of

Scheme 25. Molecular motor-based catalysts with 3 distinct active states: *trans*, which is least active and yields products with low levels of enantioenrichment, and two distinct *cis* states, which are pseudoenantiomers and are more active and result in the opposite enantiomers of the product. a) Bifunctional motor-based organocatalyst employed in a Michael reaction; b) bifunctional motor-based organocatalyst employed in the Henry reaction; c) phosphine motor-based ligand employed in a Pd-catalyzed desymmetrization reaction. DIPEA = diisopropylethylamine.

the opposite enantiomer of **86** with the (*M,M*)-*Z* state of the ligand. Therefore, by using the photoswitchable chiral biphosphine ligand it is possible to obtain both enantiomers of the product of a Pd-catalyzed reaction by using a single chiral ligand.

In summary, photoswitchable dynamic catalysis is a rapidly developing field that offers tremendous opportunities for non-invasive (light) control of catalytic transformations. An overview of current photoresponsive catalysts, including responsive

structural moieties, efficiency of switching processes, the principles underlying the responsive catalysis, and the various transformations used, is presented in Table 1.

3. Ion- and neutral molecule-switchable dynamic catalysts

Ions and small molecules are ubiquitous effectors of enzymes. Although many examples of artificial allosteric catalysts in-

Table 1. Overview of photoresponsive catalysts and comparison of principles underlying catalysis

Responsive core	PSS ratio ^[a]	Principle underlying responsive catalysis	Catalyzed reaction	Reference
azobenzene	$E_{\text{off}}/Z_{\text{on}} \approx 40:60$	competitive inhibition	hydrolysis of 4-nitrophenylacetate	[11]
azobenzene	$E_{\text{off}}/Z_{\text{on}} = 62:38$	steric shielding of the active catalyst site	hydrolysis of 4-nitrophenylacetate	[12]
azobenzene	$E_{\text{off}}/Z_{\text{on}} = 20:80$	combination of steric shielding and inhibition	hydrolysis of 4-nitrophenylacetate	[13]
azobenzene	$E_{\text{off}}/Z_{\text{on}} = 50:50$	catalyst template, ON state binds substrates increasing their local concentration	amide bond formation between aminoadenosine and <i>p</i> -nitro phenyl ester adenosine	[14]
azobenzene	$E_{\text{on}}/Z_{\text{off}} = 5:95$	supramolecular regulation by responsive receptor	Knoevenagel condensation	[15]
azobenzene	$E_{\text{off}}/Z_{\text{on}} = 5:95$	cooperative catalytic activation	ethanolysis of acetanilides	[16]
azobenzene	$E_{\text{off}}/Z_{\text{on}} = 5:95$	cooperative catalytic activation	Morita–Baylis–Hillman reaction	[17]
azobenzene	$E_{\text{off}}/Z_{\text{on}} = 30:70$	cooperative catalytic activation	hydrolysis of glucopyranoside	[19]
azobenzene	$E_{\text{on}}/Z_{\text{off}} = 44:56$	antagonism, catalyst inactivation by light	Michael addition	[20]
azobenzene	$E_{\text{off}}/Z_{\text{on}} = 39:61$	steric shielding	Henry reaction	[22]
azobenzene	No data	aggregation state of the catalyst	hydrosilylation reaction	[26]
azobenzene	$E_{\text{off}}/Z_{\text{on}} = 4:96$	aggregation state of the catalyst	acylation reaction and rearrangement of 2-acyloxybenzofuran	[27]
DTE ^[b]	$O_{\text{on}}/C_{\text{off}}^* = 77:23$	cooperative catalytic activation	cyclopropanation reaction	[37]
DTE	$O_{\text{off}}/C_{\text{on}}^* = 3:97$	difference in the electronic properties of DTE isomers	racemization of L-alanine	[39]
DTE	$O_{\text{on}}/C_{\text{off}}^* > 1:99$ UV det	difference in the electronic properties of DTE isomers	transamidation, transesterification, ROP, Rh-cat. hydroboration	[40, 41, 42]
DTE	$O_{\text{on}}/C_{\text{off}}^* = 11:89$	difference in the electronic properties of DTE isomers	acylation of decan-2-ol	[43]
spiropyran	no data	difference in charge between two isomers	reduction of H ₂ O ₂	[47]
spiropyran	no data	photogeneration of acid	singlet oxygen generation	[48]
stilbene	$E_{\text{off}}/Z_{\text{on}} = 77:23$	steric shielding	reaction of CO ₂ with 1,2-epoxypropane	[51]
overcrowded alkene	$E/Z = 32:68$	geometry change of the ligand	Trost allylic alkylation and Heck reaction	[53]
overcrowded alkene	$E/Z = 8:92$	cooperative catalytic activation	Michael thiol addition, Henry reaction, desymmetrization of <i>meso</i> -cyclopent-2-en-1,4-diol bis(carbamate)	[54, 55, 56]

[a] PSS = photostationary state. [b] DTE = dithienylethylene.

spired by enzymes have been reported, the reversibility of many of those systems has not been studied in detail.^[57] In this section, an overview of reversible systems will be given.

A remarkable example of cation-triggered switchable asymmetric catalysis was reported by Fan and co-workers.^[58] The authors designed a phosphoramidite ligand **87** modified with an

aza-crown ether and employed it in rhodium-catalyzed asymmetric hydrogenation of dehydroamino acid esters (Scheme 26). Due to the presence of the aza-crown ether moiety, the catalytic system is sensitive to alkali cations, especially sodium. In the absence of sodium, the catalytic system was completely inactive giving conversions with all tested sub-

strates below 1%. This is attributed to rhodium–aza-crown ether macrocycle interactions, which block the approach of the substrates to the metal catalytic center. Upon addition of sodium ions, which have much stronger interactions with the crown ether, the sandwich complex between the aza-crown ether and rhodium is broken and the catalytic center is no longer hindered for substrate binding. The ON state is thus obtained, with which full conversions in asymmetric hydrogenation can be obtained with excellent *ee* values (up to 98%). Switching back to the OFF state was achieved upon addition of two equivalents of cryptand[2,2,2], which exhibits stronger binding with sodium than the aza-crown ether moiety. It was demonstrated that during two switching cycles in the presence of only 1 mol% loading of the catalyst, conversions were unchanged and the *ee* was only slightly diminished by 1–2%. It was also shown that the cryptand sodium complex does not affect the catalysis and several cycles can be performed without reducing the catalytic activity of the switchable rhodium catalyst.

One of the first attempts at ion-responsive reversible catalysis was reported by Mirkin and co-workers (Scheme 27).^[59] A macrocyclic catalyst **90** was designed that consisted of two salen-type chromium catalytic centers and two rhodium centers incorporated into the macrocycle. The rhodium centers were crucial for achieving reversibility, since they were bound by weak thioether bonds that could be broken upon treatment with CO and chloride ions while the rhodium–phosphine bonds stayed intact. In this way, two different forms of the macrocycle **90** could be obtained: a tightly closed form **c-90** in which the rhodium atoms are bound between two bidentate ligands, thioether and phosphine, and a “looser” macrocyclic form in which the thioether bond is broken and, as a consequence, the rhodium atom is no longer in a tight sandwich complex but CO and chloride anion substitute the thioether ligands, resulting in a more flexible structure **o-90** (Scheme 27). When using this catalyst (0.16 mol% catalyst loading) in the ring-opening reaction of cyclohexene oxide by TMSN₃, the reaction rate increased twofold when bis(triphenylphosphoranyli-

dene) ammonium chloride (PPNCl) and CO were added as effectors. This implies that the more open form of the macrocycle is more active than the closed one. Unfortunately, the catalytic activity was not tested during several cycles and in situ switching was not demonstrated. In addition, enantioselectivities were not compared for the two different macrocyclic forms; only between the monomeric salen catalyst and the tightly closed one, where the *ee* was more than five times higher (68% *ee* with **c-90** compared to 12% *ee* with the monomeric form containing one chromium center).

Using the tetrametallic macrocyclic complex (**90**) described above, with zinc instead of Cr, resulted in an efficient catalytic system for acyl transfer reactions (Scheme 27b).^[60] With the closed form of the macrocycle, only slow background reaction between acetic anhydride and pyridyl carbinol (**94**) was observed. In its more active open form, a rate enhancement of approximately 25 times was achieved. It is proposed that in its open form catalysis in a bimetallic fashion is possible, whereas in the closed form the system is too sterically hindered for intramolecular activation of substrates. Acetic anhydride is activated by Zn^{II}–salen while in close proximity to a pyridyl carbinol molecule bound to the second Zn center. This system proved to be so sensitive that it could be used for the detection of chloride ions in solution under a CO atmosphere. Chloride ions triggered the opening of the macrocycle complex and the minimum concentration required to observe product formation could be quantified. This was achieved by using a pH-sensitive fluorophore, since acetic acid is a product of the reaction. Chloride concentrations as low as 800 nM could be detected with this coupled system. Acetate ions can also be used as effectors and their detection can be achieved by using the same system as used for chloride ions.^[61] By using a Zn^{II} porphyrin core instead of the salen unit, a rate enhancement in the acylation transfer reaction was observed using the less tight form of the macrocycle, but the enhancement was not as pronounced as with the salen moiety.^[62]

A related “tweezer” (Scheme 28) version of the catalyst, containing only one rhodium center, has also been developed.^[63]

Scheme 26. Sodium-triggered switchable rhodium catalyst employed in asymmetric hydrogenation of dehydroamino acid methyl ester.

Scheme 27. Responsive macrocyclic catalyst developed by Mirkin and co-workers. The geometry of the catalyst changes upon treatment with chemical triggers (CO and chloride or acetate) influencing its activity and selectivity. This responsive macrocyclic catalyst was employed in ring-opening of cyclohexene oxide (a) and acylation reaction between acetic anhydride and pyridyl carbinol (b).

The hemilability of the rhodium–thioether bond was used as part of the regulation of the reversible switching mechanism. Upon treatment with PPNCl and CO , an open form of the catalytic complex (o-96) is obtained. After subsequent removal of the solvent in vacuo or purging the solution with N_2 the system is switched back to the closed tweezer complex (c-96). The difference in shape upon opening and closing is much more pronounced than in the previous macrocyclic complex. The reversible switching of catalyst activity and selectivity was demonstrated in the same reaction as for the previous system, that is, the asymmetric ring opening of cyclohexene oxide by TMSN_3 . An impressively low catalyst loading of 0.2 mol% was used. The differences in selectivity between the open and closed forms of the catalyst were enhanced at lower catalyst concentrations (where intramolecular reactions play a greater role). By using a 7.2 mM concentration of the catalyst, an *ee* of 80% was obtained with the closed form, whereas the open form provided the product in 74% *ee*. With a lower catalyst concentration of 0.14 mM, *ee* values of 49 and 21% were obtained with the closed and open forms, respectively. In situ OFF switching was efficiently demonstrated by using CO at a pressure of 1 atm as a trigger. By alternating introduction and removal of CO , in situ switching of activity and selectivity was successfully demonstrated.

In 2007, Mirkin and co-workers reported the first example of artificial reversible allosteric control of phosphate ester hydrolysis.^[64] As in the previous examples, a labile thioether bond

Scheme 28. Responsive tweezer complex demonstrating different activity and selectivity in its two forms for the asymmetric ring opening of the epoxide.

was used in the design of a switchable tetrametallic system, which consisted of a macrocyclic structure in which the distance between two active zinc centers was controlled by cleavage of the thioether bond on the rhodium centers (Scheme 29). While in its closed form, the catalyst (**c-97**) was completely inactive, upon treatment with CO and chloride ions complete hydrolysis of 2-hydroxypropyl-*p*-nitrophenyl phosphate (**98**) was achieved in 40 min. This was the first demonstration of a completely inactive OFF state for an ion-responsive catalyst.

A remarkable example of achieving control over ring-opening polymerization of ϵ -caprolactone was reported in 2010 by Mirkin and co-workers employing a specially designed triple-layer catalyst **101** (Scheme 30).^[65] The catalyst consisted of a central core composed of an Al^{III} salen complex and outer layers composed of allosterically regulated rhodium ligands, which act as a steric barrier. Upon treatment with chloride, the Rh–N bonds break and the active central part of the catalyst is no longer hindered for approach of the substrate, and the catalyst is in its ON state. Upon removal of the chloride, the active Al catalytic component again becomes sterically shielded and catalysis ceases. The polymerization could be turned on and off in situ by opening and closing of the central part of the catalyst through addition and removal of chloride ions. With the active (open) form of the catalyst, conversion of the monomer was complete in 40 min, whereas the closed form was completely inactive (although it is noted that some activity was observed after 100 h, owing to decomposition of the catalyst). The catalyst could be reactivated in situ without significant loss of reactivity and reactivation of the catalyst led to an increase in the molecular weight of the polymer.

An interesting responsive system for controlled ring-opening polymerization (ROP), which is based on a CO₂-switchable or-

ganocatalytic system, was reported by Coulembier, Dubois, and co-workers.^[66] The small molecular trigger was carbon dioxide, which could deactivate an organocatalytic triazabicyclodecene (TBD)/1,8-diazabicycloundec-7-ene (DBU)/benzyl alcohol (BnOH; 10:1:1 mixture) system for ring-opening polymerization of ϵ -caprolactone and trimethylene carbonate. This deactivation is due to the three-component reaction of DBU, the primary alcohol, and CO₂, which leads to formation of the corresponding ionic iminium carbonate. In the absence of a primary alcohol to act as an initiator, TBD is unable to catalyze the ROP. Under a CO₂ atmosphere, the catalytic system is in its OFF state, whereas upon purging with nitrogen, removing the CO₂, the catalytic system can be reactivated. The cycle was repeated four times with only a slight loss of catalytic activity. This example shows that it is possible to control the activity of the catalyst through control of the atmosphere of the reaction.

Recently Mirkin and co-workers reported a chloride-responsive catalyst **102**, which is regulated by self-aggregation through competing intra- and intermolecular hydrogen bonding. The authors functionalized a bisaryurea with a labile phosphinoalkyl thioether moiety and incorporated it into a Pt^{II} tweezer complex (Scheme 31).^[67] In the absence of chloride ions, the bisurea moieties are able to catalyze a Diels–Alder reaction between cyclopentadiene (**103**) and methyl vinyl ketone (**104**) through hydrogen bonding and other noncovalent interactions. However, upon treatment with chloride ions the system becomes catalytically inactive. This is attributed to aggregation of the urea moieties. It is proposed that self-association of the urea moieties is prevented in the fully closed form due to the orientation of the carbonyl moieties (hydrogen bond acceptors) towards the Pt center. In this way, the carbonyl moiety is isolated from the hydrogen-bond-donating (NH) moieties and catalysis occurs. Successful in situ switching

Scheme 29. Zn–salen responsive catalyst, which is completely inactive in its tightly closed form. Upon opening after treatment with CO and TBACl it becomes highly active towards hydrolysis of HPNP (model substrate for RNA studies).

Scheme 30. Triple-layer responsive catalyst that demonstrates control over ring-opening polymerization of ε-caprolactone. In its closed form, it is completely inactive towards polymerization, whereas in its open form, obtained after treatment with a chloride source, it turns into the active open form.

was demonstrated by addition and removal of chloride ions. This represents a novel method for controlling the activity of a catalyst by modulating its self-aggregation.

Scheme 31. Tweezer-responsive catalyst containing bisurea moieties and a labile thioether linkage. The catalyst can be alternated between its inactive and active state by addition and removal of chloride ions, which influences self-aggregation of the catalyst and its catalytic properties.

Another elegant example of allosterically controlled self-aggregation of a catalyst was reported by Mirkin and co-workers a few months later.^[68] The authors designed a Pt^{II} complex containing the catalytically active hydrogen-bond-donating squaramide moiety and two hydrogen-bond-accepting ester moieties (Scheme 32). The hydrogen-bond-donating and -accepting moieties were connected to hemilabile ligands, which render the resulting Pt complex responsive towards chloride ions. The catalyst **106** could exist in the rigid, fully closed state (**c-106**) and the flexible semi-open state (**o-106**). Strong self-association was demonstrated in the semi-open state by FT-IR and ¹H DOSY NMR spectroscopy, indicating that intermolecular hydrogen bonding leads to tetrameric structures, preventing the substrate from binding to the catalyst. In its rigid form, obtained upon removal of chloride ions, hydrogen-bonding interactions are prevented by geometric constraints and the catalyst exists as the monomer in solution, as shown by ¹H DOSY NMR. The squaramide moiety is able to catalyze the Friedel-Crafts reaction between indole (**107**) and nitrostyrene (**108**) when the catalyst is in its fully closed state, whereas in the semi-open state no catalytic activity is observed. By employing 20 mol% of the catalyst **106**, the authors could achieve in situ deactivation and reactivation of the catalyst upon treatment with N(Bu)₄Cl and AgBAR^F, demonstrating the control of catalytic activity by regulation of the aggregation state of the catalyst.

In 2012, Schmittle and co-workers reported a switchable Zn complex **110** capable of controlling the organocatalytic activity of piperidine (Scheme 33).^[69] Piperidine, when free in solution, is able to catalyze the Knoevenagel reaction, but it becomes

Scheme 32. Squaramide catalyst, the catalytic activity of which can be switched by reversible control of its self-aggregation. In its monomeric form it is able to catalyze a Friedel–Crafts reaction.

catalytically inactive through binding to the Lewis acidic Zn porphyrin center. In the ON state of their Zn complex, an “inhibitory” 4-(2-pyridyl)pyrimidine arm is coordinated to the Zn porphyrin complex. In this way it prevents binding of any potential guest to the zinc and piperidine can’t coordinate to the Lewis acidic zinc center. Upon addition of Cu^+ along with a phenanthroline derivative, the complex switches to its OFF state, where the Zn center is free for guest coordination. The binding of piperidine to the Zn center causes its deactivation and it is no longer active as the organocatalyst for the Knoevenagel reaction. The system is completely reversible and in the OFF state, piperidine is completely catalytically inactive. The authors have successfully demonstrated three catalytic cycles of consecutively activating the system upon addition of Cu^+ and deactivating it upon removal of Cu^+ by addition of a strongly binding phenanthroline analogue.

Very recently, the same group reported an example of the regulation of two different reactions.^[70] The new system (Scheme 34) can exist in three states, each of which consists of two metal centers, copper and zinc, either of which can be blocked by coordination of the inhibitory arm. Employing the three possible states of the novel complex **114**, regulation of two different catalytic reactions—a Knoevenagel-type addition and a Huisgen-type click cycloaddition—was achieved. Starting from the initial state (State 1, Scheme 34) of the regulating switch, it was demonstrated that neither of the reactions were catalyzed (OFF state). Upon addition of one equivalent of 2-ferrocenylphenanthroline, the azapyridine arm moves from the

phenanthroline part of the switch and attaches to the Zn porphyrin. When the switch is in this state (State 2, Scheme 34), the Knoevenagel reaction proceeds, whereas the click reaction is not observed. Subsequent addition of one equivalent of Cu^+ to the reaction mixture causes the azapyridine arm to move back to the phenanthroline, resulting in the release of $[\text{Cu}(2\text{-ferrocenylphenanthroline})]^+$ into solution, which can effectively catalyze the click reaction. It must be noted here that the $[\text{Cu}(\text{CH}_3\text{CN})_4]^+$ complex added as a trigger is also able to catalyze the click reaction, but low yields were obtained in control experiments. Since the azapyridine arm moves from the Zn center, the newly formed complex (State 3, Scheme 34) scavenges the free piperidine from solution and no further Knoevenagel product formation is observed. Addition of one more equivalent of 2-ferrocenylphenanthroline (FcPhn) results in formation of State 1 (OFF state) of the complex. In this case, both reactions are switched off. This is the first artificial system capable of regulating two reactions in one pot. Even though more cycles were not demonstrated, owing to the complexity of the system, each step was proven to be reversible. Interestingly, this system is not a dynamic responsive catalyst itself, but it regulates the catalytic reaction in a dynamic fashion by interaction with the actual catalysts: piperidine and $[\text{Cu}(\text{FcPhn})]^+$. It can be regarded as a switchable, selective scavenger of the active forms of the catalyst.

Saito and co-workers reported amino organoboron compounds (**118**) that are capable of reversibly switching between monomeric (open) and dimeric (closed) forms upon addition

Scheme 33. Zn-based switchable complex that can control the Knoevenagel reaction by binding of the piperidine. When Zn is bound to the inhibitory arm, it cannot bind the piperidine and the reaction proceeds. When the inhibitory arm is removed from Zn, piperidine binds and the catalytic reaction is deactivated.

of acid and base (Scheme 35).^[71] Although they did not employ switching of this system directly in catalysis, they did, however, explore the equilibrium between the two species upon addition of various phenoxides and showed that, in the presence of more basic phenoxide, the open structure is more dominant at equilibrium. Since the open form was shown to be a more efficient catalyst than the closed form in the methanolysis of *N*-acyl oxazolidinone (**119**), the described system is conceptually close to a switchable catalyst, with the trigger being the change in basicity due to the phenoxide present in the mixture.

Leigh and co-workers employed acid and base as chemical triggers in switchable rotaxane organocatalysts (Scheme 36). Their first catalytic rotaxane system **121** consisted of a dibenzo[24]crown-8 macrocycle and an axle consisting of two triazolium groups and a central dibenzylamine moiety.^[72] In the initial state of the system, the macrocycle is situated on the triazolium ring; upon the treatment with an acid the dibenzylamine moiety is protonated and the macrocycle moves to the central part of the axle due to the formation of strong hydrogen bonds with the dibenzylammonium moiety. After treatment with aqueous sodium hydroxide, the dibenzylammonium moiety is deprotonated and the macrocyclic ring moves back to the triazolium ring. Acid–base-controlled positioning of the ring on the axle is thus achieved. Secondary amine/ammonium groups are known to participate in iminium catalysis over a variety of pH values. In the described system, the catalytic amine moiety could be sterically blocked, and thus unable to engage

in iminium catalysis, by positioning the macrocycle over it. Initially this system was utilized as a catalyst for the Michael addition of an aliphatic thiol to *trans*-cinnamaldehyde, a reaction known to be catalyzed by secondary amines. In its protonated form, the macrocyclic ring blocks the secondary amine and no conversion was observed over five days; upon treatment of the system with sodium hydroxide, complete conversion is achieved within one hour. The authors have also demonstrated the scope of catalyst **121** in a range of reactions catalyzed by iminium (β -sulfenylation of α,β -unsaturated carbonyl compounds, Michael addition of methylene compounds to α,β -unsaturated aldehydes) and enamine (α -chlorination of aldehydes and Michael addition of aldehydes to vinyl bisulfone) reactivity platforms, as well as in tandem iminium-enamine and trienamine catalysis (Diels–Alder reaction between 2,4-dienal **135** and cyanoester **136**).^[73] In iminium catalysis, high conversions with the ON state are observed, but the OFF state displayed some background activity for more activated substrates. In enamine-based reactions, lower conversions were achieved with the ON state, but the OFF state displayed no background activity.

Recently, the same group reported a switchable chiral rotaxane-based catalyst **138**,^[74] which incorporated an acyclic chiral secondary amine into the axle of the catalyst (Scheme 36b). The catalyst was used in the Michael addition of 1,3-diphenyl-1,3-propanedione (**140**) to crotonaldehyde (**139**). With 20 mol% of the inactive (protonated) form of the catalyst, no conversion into product **141** was observed. After treatment

Scheme 34. Switching of the zinc complex through 3 states. States 2 and 3 are able to control two orthogonal catalytic reactions.

with base, the chiral secondary amine is revealed and the ON state can be accessed to provide the desired Michael addition adduct in 70% yield with up to 88% ee.

Leigh and co-workers also recently reported a rotaxane catalyst **142** that, unlike the previously described rotaxane catalysts, contains two catalytic sites (Scheme 37).^[75] The axle of the rotaxane contains both catalytic centers: a dibenzylamine part capable of iminium catalysis, as in previous catalysts,^[72] and a novel catalytic center consisting of a squaramide unit that can activate electrophiles through hydrogen bonding. The macrocycle contains a pyridyl-2-6-dicarboxamide unit that can efficiently bind to the squaramide moiety and a crown ether region that can bind to the dibenzylammonium group. At low pH, the amine is protonated, resulting in stronger interactions with the crown ether, leaving the squaramide unit accessible and catalytically active. At higher pH, the interaction of the macrocycle with the unprotonated dibenzylamine is weak and the macrocycle moves to the squaramide unit, with

which it forms strong hydrogen bonds. This results in the deactivation of the squaramide, but allows the dibenzylamine to act as an organocatalyst. When the catalyst was present in a mixture of 1,3-diphenylpropane-1,3-dione **143** (Michael donor), crotonaldehyde **144** (Michael acceptor prone to iminium catalysis), and *trans*- β -nitrostyrene **145** (electrophilic Michael acceptor prone to the activation by hydrogen bonding), selective pH-dependent catalysis was observed. In the protonated form of the catalyst, when the macrocycle was blocking the dibenzylammonium group, 75% conversion into the addition product **146** with *trans*- β -nitrostyrene was observed. When the reaction mixture was treated with NaOH, 40% conversion into the addition product **147** with crotonaldehyde was achieved. With both forms of the catalyst, some undesired background reactions were also detected. Although the system is capable of controlling the two orthogonal reactions, selectivity was lower than with the Schmitt system,^[70] for which the background reactivity was negligible.

Scheme 35. Switchable aminoorganoboron compound that can be employed in methanolysis of *N*-acyl oxazolidinone.

During the last decade, dynamic catalysts triggered by neutral molecules and ions have shown their utility for control of various catalytic transformations. An overview of such systems, including trigger species, the principle underlying the responsive catalysis, and the various transformations used, is presented in Table 2.

4. Redox-Switchable Catalysts

Nature uses redox-active moieties, such as cofactors NADH and FADH, to control numerous processes. To mimic nature which is capable of catalyzing challenging multi-electron pro-

cesses, chemists have recently turned their attention to developing artificial systems relying on redox-active moieties.^[76] For achieving redox-switchable catalysis, the catalyst has to be able to change reversibly between oxidized and reduced forms. The presence of a redox-switchable moiety can affect the electronic and steric environment of the ligand bound to a metal center.

A pioneering work in the field of redox-switchable catalysis was reported by Wrighton and co-workers in 1995.^[77] A rhodium complex containing a cobaltocene-based ligand (reduced form) red-148 was designed and shown to undergo reversible oxidation and reduction (Scheme 38). The oxidized and re-

Table 2. Overview of ion- and/or molecule-triggered catalysts and comparison of principles underlying catalysis.

Trigger	Principle underlying responsive catalysis	Catalyzed reaction	Reference
Na ⁺	Steric shielding	Hydrogenation of dehydroamino acid methyl esters	[58]
CO, Cl [−]	Cooperative activation of the catalyst	Ring opening of cyclohexene oxide, acylation reaction	[59–63]
CO, Cl [−]	Steric shielding	HPNP ^[a] hydrolysis, ROP ^[b] of ε-caprolactone	[64, 65]
CO ₂	Trigger blocks catalytic activity by reaction with substrates	ROP of ε-caprolactone and trimethylene carbonate	[66]
Cl [−]	Aggregation of the catalyst	Diels–Alder reaction, Friedel–Crafts reaction	[67, 68]
Cu ⁺ Cu ⁺ , FcPhn ^[c]	Responsive complex that can block catalyst active site. Selective responsive scavenger of active forms of catalyst	Knoevenagel and Huisgen type cycloaddition	[69] [70]
HCl, NaOH	Steric shielding	Michael addition, β-sulfenylation, α-chlorination, Diels–Alder reaction	[72–75]

[a] HPNP = 2-hydroxypropyl-*p*-nitrophenyl phosphate. [b] ROP = ring-opening polymerization. [c] FcPhn = 2-ferrocenylphenanthroline.

Scheme 36. Rotaxane-based organocatalysts that can be switched between ON and OFF states upon treatment with base and acid: a) Achiral rotaxane organocatalyst able to control ON and OFF imine and enamine catalysis; b) chiral rotaxane organocatalyst switching between OFF state (completely inactive) to ON state upon treatment with base affording the product in up to 88 % ee.

duced forms showed different reactivity and selectivity; the reduced form (red-**148**) was a more efficient catalyst for the hydrogenation of cyclohexene and pent-1-ene, whereas the oxidized form (ox-**148**) was more efficient in the hydrosilylation of acetone and pent-1-ene. In situ switching between the two forms of the catalyst was demonstrated during the hydrogenation of cyclohexene: when using the in situ-generated reduced form of the catalyst, the reaction proceeds at 19 times higher rate than with the oxidized form of the catalyst. This is thought to be due to the higher basicity of the phosphine ligands in the reduced form, which in turns leads to increased electron

density at the rhodium center, which can promote the oxidative addition of hydrogen. For hydrosilylation, the oxidized form of the ligand accelerates the reaction 2.7 times compared to the reduced form, although it remains unclear why the oxidized form of the catalyst is more effective in this case. A drawback of this catalyst system is that, upon in situ reduction and oxidation of the catalyst, the catalytic activity cannot be completely recovered due to some decomposition of the catalyst during the switching process.

The most commonly used redox-active moiety in redox-switchable catalysis is ferrocene, which displays reversible

Scheme 37. Michael addition of 1,3-diphenylpropane-1,3-dione to either crotonaldehyde or *trans*-β-nitrostyrene, depending on which state of the rotaxane organocatalyst is used.

Scheme 38. Rhodium cobaltocene complex demonstrating different activity and selectivity, depending on which of its oxidation states is used for catalysis. In its reduced form, it displays high activity and selectivity for hydrogenation reactions, whereas in its oxidized form, it displays high activity and selectivity for hydrosilylation reaction.

redox switching and has a redox potential that can be varied over a large range by varying the substituents at the cyclopentadienyl rings.^[78] In 1997, Mirkin and co-workers reported a rhodium catalyst containing two ferrocenyl groups.^[79] Although in situ redox switching of the catalyst was not described, a significant difference between the oxidized and reduced forms of the catalyst was observed in the isomerization of an allyl ethyl ether. The observed rate of isomerization was 2–3 times faster with the doubly oxidized form of the catalyst than with the reduced or monooxidized forms.

A redox-switchable catalyst **149** that undergoes drastic solubility changes depending on the oxidation state of the ferrocenyl moieties was reported by Plenio and co-workers.^[80] They

incorporated two ferrocenyl moieties into a ruthenium-based Grubbs-type catalyst and demonstrated its catalytic properties in the ring-closing metathesis (RCM) of *N*-tosyl diallyl amide (Scheme 39). The catalyst is oxidized in situ by addition of two equivalents of the oxidant [FcCOCH₃][CF₃SO₃]. In its fully oxidized form, the catalyst (ox-**149**) does not display any significant activity due to its insolubility in the nonpolar solvent toluene. This property offers the possibility of stopping the reaction in situ upon treatment of the reaction mixture with an oxidant. Furthermore, the catalyst in its fully oxidized, insoluble form can be removed simply by filtration from the reaction mixture. The catalyst can also be reactivated in situ upon addition of the reducing agent FcMe₈. Later reports by Fleckenstein and Plenio and by Wang and co-workers have further investigated the development of catalysts that display redox-switchable solubility properties.^[81,82]

Hey-Hawkins and co-workers recently reported the preparation of ruthenium(II) complexes with monomeric and dendrimeric ferrocenylphosphine ligands.^[83,84] For the reduced forms of the catalysts, they demonstrated that the dendrimeric catalyst, which contained twelve ferrocene moieties, was more effective than the monomeric catalyst in the catalytic isomerization of 1-octene-3-ol (a sixfold acceleration in reaction rate was observed for the dendrimeric catalyst). In both cases, the reduced form showed greater activity than the oxidized form, in line with a decrease in basicity of the phosphines. The authors also performed an in situ oxidation–reduction cycle and showed that the in situ-reduced catalyst exhibited 96% of its original activity.

Gibson, White, and co-workers reported the first use of a redox-switchable catalyst in influencing polymerization reactions.^[85] Their catalyst **150** consisted of two ferrocenyl moieties

Scheme 39. Controlling the activity of a redox-switchable catalyst by the differences in the solubility between the oxidized and reduced forms in the reaction solvent.

attached to a titanium salen bis(isopropoxide) core (Scheme 40). With the reduced form of the catalyst, lactide ring-opening polymerization proceeds 30 times faster than with the oxidized dicationic form of the catalyst. The reversibility of the switching process was demonstrated in situ during the polymerization process upon addition of two equivalents of silver triflate (AgOTf) as an oxidant and subsequently two equivalents of $[\text{Cp}^*_2\text{Fe}]\text{OTf}$ as a reducing agent.

In 2011, Diaconescu and co-workers reported three novel redox-switchable catalysts containing ferrocenyl moieties (Scheme 41). The catalysts were employed in the ring-opening polymerization (ROP) of lactide and ϵ -caprolactone. The authors showed that yttrium (**151-Y**) and indium alkoxide phos-

fen catalyst (**151-In**) complexes containing a ferrocenyl unit could be reversibly switched in situ upon treatment with oxidizing or reducing agents.^[86] For the yttrium complex, the authors observed the same trend in reactivity as Gibson and co-workers^[85] had reported previously for a titanium complex (Scheme 40): upon oxidation of the ferrocenyl moiety, the catalyst became inactive. The polymerization stopped completely with the oxidized form but was restored upon addition of the reducing agent and in situ switching could be demonstrated through three cycles. Whereas the corresponding indium complex was not active for the ROP of lactide and ϵ -caprolactone in either of its forms, in the ROP of trimethylene carbonate the oxidized indium complex was more active than its reduced form (49% conversion vs. 2% conversion in 24 h at room temperature). Interestingly, the yttrium complex displayed the opposite reactivity in the same reaction, where the reduced form was more active. The exact reason for the difference in activity between the two complexes remains unclear. Diaconescu and co-workers also reported related cerium complexes and their efficiency in the ROP of L-lactide.^[87] In this case, the oxidation and reduction processes affect the catalytic metal center (cerium) instead of the ferrocenyl moiety. The reduced form of the complex showed much higher activity than its oxidized analogue. The complex containing the phosfen ligand was more active than the corresponding salen complex. The polymerization of 100 equivalents of L-lactide was achieved with 96% conversion within 30 min with the reduced form of the phosfen ligand, whereas the salen complex provided only 85% conversion in two hours under identical conditions. However, whereas the oxidized form of the cerium phosfen complex required approximately four hours to achieve 64% conversion in the ROP of lactide, the oxidized form of the cerium salen complex, ox-152, was completely inactive and thus, despite showing overall lower activity, could function as an ON/OFF switch—a desirable property in controlling polymerization growth.

Other examples of redox-switchable catalysts, in which the oxidation state of the central catalytic metal changes during

Scheme 40. Redox-switchable catalyst for ROP of *rac*-lactide, which shows high activity in its reduced form.

conversion of ROP of:		
catalyst	lactide	trimethylene carbonate
red-151-M		
M = Y	78 %	29 %
In	no data	2 %
Ce	96 %	100 %
ox-151-M		
M = Y	0 %	3.5 %
In	n.d.	49 %
Ce	64 %	no data
red-152	85 %	100 %
ox-152	0 %	no data

Scheme 41. Redox-switchable phosfen ferrocenyl yttrium, indium, and cerium catalysts and cerium salen catalyst for ROP of lactide, ϵ -caprolactone, and trimethylene carbonate.

an oxidation–reduction cycle, have been reported by the groups of Okuda, Byers, and Lang. Okuda and co-workers reported a redox-switchable cerium complex with a dithiabis(phenolate) ligand.^[88] They demonstrated that by using the reduced form of the complex, ROP of *meso*-lactide proceeds 60 times faster than the polymerization with the oxidized form. Three cycles of in situ switching were also demonstrated. These results are in agreement with those previously reported by Diaconescu,^[87] showing that cerium complexes in their reduced form are more active as polymerization catalysts.

In 2013, Byers and co-workers reported a ROP catalyst based on a bis(imino)pyridine iron diaryloxide complex **153** (Scheme 42).^[89] The iron(III) complex obtained upon oxidation was completely inactive in the polymerization of *rac*-lactide. The catalyst could be reduced back in situ by using [CoCp₂] to obtain a similar reaction rate to that with the original reduced form.

One year later, Lang and co-workers reported a redox-switchable iron catalyst **154** containing a bis(pyrazolyl)pyridine pincer ligand (Scheme 43).^[90] Their system required the use of an additional alcohol initiator to be able to catalyze ROP of ϵ -caprolactone. Interestingly, unlike the Byers catalyst, for which the oxidized form was completely inactive, in this case the oxidized form was active, whereas the reduced form was completely inactive under the same conditions.

Arguably the most impressive example of achieving control over ROP using a redox-switchable catalyst was reported in 2014 by Diaconescu and co-workers.^[91] They prepared zirconium and titanium alkoxide complexes containing a ferrocenyl moiety that demonstrated switchable selectivity towards the ROP of L-lactide and ϵ -caprolactone in their reduced and oxidized forms (Scheme 44). Following the pioneering work of Wrighton,^[77] this is the second reported case in which switchable substrate selectivity was observed. The complexes, specifically their ferrocenyl moieties, could be oxidized upon treatment with one equivalent of acetyl ferrocenium tetrakis-3,5-bis(trifluoromethylphenyl) borate and reduced back upon addition of one equivalent of [CoCp₂]. A zirconium salfan complex in its reduced form catalyzed the polymerization of L-lactide at 100 °C with high efficiency. By using this system, 90% conversion was achieved within two hours, whereas with the oxidized form less than 5% conversion was obtained. Similar behavior was observed for zirconium and titanium thiolan complexes. The opposite behavior was observed in the activity towards ROP of ϵ -caprolactone, where the oxidized forms of the complexes were more active. In situ switching for polymerization of L-lactide was demonstrated for the most active zirconium salfan complex. Unfortunately, an attempt to achieve controlled copolymerization of L-lactide and ϵ -caprolactone with the most active zirconium complex was unsuccessful, since upon in situ oxidation no polymerization of ϵ -caprolactone occurred. It was suggested that the strong coordination of the L-lactide to the oxidized form of the zirconium complex prevents the binding of ϵ -caprolactone, thus preventing copolymerization. In this regard, a breakthrough could be achieved using titanium thiolan complexes. First the L-lactide was polymerized with the reduced form of the catalyst com-

tion of the L-lactide to the oxidized form of the zirconium complex prevents the binding of ϵ -caprolactone, thus preventing copolymerization. In this regard, a breakthrough could be achieved using titanium thiolan complexes. First the L-lactide was polymerized with the reduced form of the catalyst com-

Scheme 42. Byers' switchable iron catalyst.

Scheme 43. Iron switchable precatalyst for ROP of ϵ -caprolactone.

plex until 58% conversion was reached, while no polymerization of ϵ -caprolactone was observed. Subsequently, the oxidizing reagent was added and, in two hours, 18% conversion of ϵ -caprolactone was achieved, whereas almost no conversion of L-lactide was observed. The block copolymer was isolated and described as poly[*block*-(LA-minorCL)-*block*-(CL-minorLA)]. Attempts to achieve higher conversions of ϵ -caprolactone resulted in a decrease in selectivity and incorporation of higher amount of L-lactide. Nevertheless, this represents the first reported example where in situ switching of the catalyst allowed in situ control over a copolymerization process.

Apart from ROP, redox-switchable catalysts have also been employed in atom-transfer radical polymerization (ATRP), as reported by Matyaszewski and co-workers through the external application of an electrochemical potential.^[92] A copper(I) catalyst could be reversibly activated by the reduction of an air-stable cupric species ($\text{Cu}^{\text{II}}\text{Br}_2/\text{Me}_6\text{TREN}$) (Me_6TREN = tris[2-(dimethylamino)ethyl]amine). By using an electrochemical method, the lower oxidation-state complex, the active Cu^{I} catalyst (ON state), could be reverted to the original higher oxidation state (OFF state) by shifting the applied potential to higher (more positive) values. The electrochemical reversibility

of their catalyst system was used in the polymerization of methyl acrylate showing that the polymerization rate could be controlled in situ by applying different potentials. Four cycles of complete ON/OFF switching were demonstrated. A linear increase in polymer molecular weight was also shown with monomer conversion, as expected for a living polymerization. This system represents a potent example of precise control of molecular weight of a polymer and polymerization rate by electrochemical methods.

Another impressive example of electrochemical control over reaction kinetics was reported recently by Hatton and co-workers.^[93] They used a heterogeneous catalyst system composed of porous carbon fiber coated with a redox-switchable polyvinylferrocene (PVF). In its ferrocenium form, the catalyst behaves as a Lewis acid and enhances the reaction rate, whereas the ferrocene form is catalytically inactive. By alternating the electrochemical potential during the Michael addition of ethyl-2-oxocyclopentane carboxylate to methyl vinyl ketone, the authors could regulate the activity of the catalyst. In the absence of an applied potential, the reaction was switched off, but could be switched on to proceed with the highest measured rate by applying a potential of 0.8 V (achieving a completely oxidized state). By applying potentials between these two values (0–0.8 V) they could obtain intermediate reaction rates. Interestingly, in the regulation of Michael reactions that involved neither ketoesters nor methyl vinyl ketone, no significant differences in reaction rates were observed by applying different potentials. The authors also managed to incorporate their system into a flow reactor and demonstrated high spatio-temporal control over reactant concentrations by changing the applied potentials. A similar system could be employed in controlling various reactions which are catalyzed by Lewis acids, especially those that are known to be catalyzed by iron(III) species.^[94]

Using an electrochemical potential to switch between two different states of catalyst is highly beneficial, since there is no need for additional workups or accumulation of chemical triggers.

Although redox-switchable catalysts are dominated by using the properties of the ferrocenium moiety, Bielawski and co-workers have recently designed *N*-heterocyclic carbene **156** containing redox active naphthoquinone moieties as the crucial part of a redox-switchable catalyst.^[95] By using a Ni complex with the redox-active NHC ligand, they achieved control over the Kumada cross-coupling between *p*-bromotoluene and PhMgCl (Scheme 45) and demonstrated that the reaction rate can be controlled in situ: on addition of two equivalents of the reducing agent $[\text{CoCp}_2]$, a decrease in reaction rate by one order of magnitude (from $4.7 \times 10^{-5} \text{ s}^{-1}$ to $2.7 \times 10^{-6} \text{ s}^{-1}$) was observed after two hours. Subsequently, on addition of $[\text{Fc}][\text{BF}_4]$ as the oxidant, an increase in the reaction rate was observed, although complete restoration of the initial reaction rate was not possible ($1.2 \times 10^{-5} \text{ s}^{-1}$ was attained), indicating that some decomposition of the catalyst occurs. An additional problem is caused by the fact that $[\text{Fc}]$

Scheme 44. Diaconescu's redox-switchable catalyst systems with difference in activity and selectivity towards the ROP of L-lactide and ϵ -caprolactone enabling controlled copolymerization.

Scheme 45. Control over the rate of the Kumada reaction with a redox-switchable NHC–Ni complex. Upon reduction, the NHC moiety is more electron-donating, rendering the metal center more electron-rich.

[BF₄] is able to partially oxidize one of the reactants, PhMgCl.

Bielawski and co-workers also succeeded in combining NHC and ferrocenyl groups to form *N*-ferrocenyl-substituted NHCs.^[96] Ruthenium complex **157** was utilized in the ring-closing metathesis of diethyl diallyl malonate. Upon addition of acetylferrocenium tetrafluoroborate as the oxidant, there was a 32-fold decrease in the reaction rate (Scheme 46). Upon addition of the reductant (decamethylferrocene), the reaction rate increased again, albeit only to 13% of its original value. The decrease in the catalytic activity of the reduced form depends on the duration of the period of oxidation. If the oxidation part of the switching cycle is shorter, a higher amount of the catalyst activity can be restored upon in situ reduction. Taking into account that the oxidation potentials between iron and ruthenium centers differ by only 380 mV the authors have related the diminishing activity to a partial oxidation of ruthenium, which leads to catalyst decomposition. For designing efficient redox-switchable catalysts the difference in oxidation potential between the redox-switchable ligand and the metal center should be as large as possible to avoid interference with each other. To increase the difference in potential, a pentamethylferrocene moiety was incorporated into the ligand. This substituted analogue is well established and known to have 300 mV lower potential than the original ferrocene analogue. In the new ruthenium complex, the measured difference between Fe and Ru oxidation potentials was increased to 660 mV. When this complex was used in the ring-closing metathesis, the reaction rate decreased fivefold upon oxidation (from 4.5×10^{-5} to $0.86 \times 10^{-5} \text{ s}^{-1}$). After subsequent reduction with decamethylferrocene the in situ generated reduced catalyst displayed 94% of its original catalytic activity.

In the same year Bielawski and co-workers reported a ruthenium complex **160** containing diaminocarbene–[3]ferrocenophane as a redox-switchable ligand (Scheme 47).^[97] This complex was able to catalyze ring-opening metathesis polymerization (ROMP) of 1,5-cyclooctadiene (COD), in which full conversion could be achieved at 80 °C in toluene in the presence of 0.1 mol% of catalyst **160** in one hour. Switching experi-

Scheme 46. Controlling RCM of diethyl diallyl malonate by changing oxidation state of iron in complex **157**.

ments were done at 60 °C in a 79:1 solvent mixture of deuterated toluene and DCM, with 0.04 mol% of the catalyst. Upon oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), the reaction rate was reduced 38-fold, whereas after in situ reduction with decamethylferrocene the reaction rate increased, although, as before, the original reaction rate could not be reached.

Scheme 47. Redox-switchable ROMP of *cis,cis*-1,5-cyclooctadiene.

The same authors attempted RCM and ROMP by using two commercially available ruthenium NHC complexes, [(SImes)(P-Cy₃)Cl₂Ru(=CHPh)] and [(SImes)Cl₂Ru(=CH-o-OrPrC₆H₄)] (SImes = 1,3-dimesitylimidazolin-2-ylidene), in which the ruthenium center would change oxidation state upon addition of an oxidant or reductant.^[98] Upon oxidation with DDQ, a significant decrease in reaction rate of both the RCM and the ROMP was observed. Following reduction, the authors encountered the same problem as in previous examples: after each cycle the reaction rate was lower than with the original reduced form.

None of the redox-switchable systems described above has allowed for the control of the stereochemical outcome of the reaction. The first reported redox-switchable chiral catalyst **163** was reported by Canary and co-workers (Scheme 48).^[99] They equipped a copper quinoline complex derived from L-methionine with catalytic bisurea moieties. This methionine complex was shown to undergo inner-sphere ligand rearrangement upon one-electron oxidation or reduction at copper. Depending on the oxidation state of the copper ion, the catalyst could be obtained in either helical form and the catalyst was used for the enantioselective addition of diethyl malonate to *trans*-

β -nitrostyrene. Depending on the oxidation state of the employed catalyst, different enantiomers of the product could be obtained in moderate yields. For example, when the Cu^{I} -quinoline complex was used, the desired addition product was obtained in 55% yield and 72% ee. Alternatively, use of the corresponding Cu^{II} complex gave the opposite enantiomer of the product **166** in 40% yield and 70% ee. The authors also demonstrated that, by using a reducing agent such as ascorbate, the Cu^{II} center could be reduced to Cu^{I} in situ, forcing the catalyst to adopt the opposite helicity. By using this Cu^{I} complex, the opposite product enantiomer to that obtained with the Cu^{II} complex was obtained. The yield was slightly lower but the ee of the product was identical to that obtained when using a preformed Cu^{I} complex.

Another redox-switchable system capable of tuning the stereochemical outcome of a reaction was recently reported by Wu and co-workers (Scheme 49).^[100] They demonstrated how the oxidation state of a ferrocenyl moiety can influence the activity of a covalently bound primary amine organocatalyst. The system takes advantage of the fact that, in its oxidized state, Fe^{III} is a potent Lewis acid, which can be beneficial in coordination of an electrophilic substrate. This novel amine organocatalyst **167** was utilized for catalyzing the aldol reaction. In the absence of an oxidant, the product of the reaction between *p*-nitrobenzaldehyde and cyclohexanone was obtained in low yield (38%) and with low stereoselectivity (*anti/syn* = 42:58, 24% ee). When an oxidant was used, excellent ee values were obtained (> 90%) but the diastereoselectivity was found to depend on the oxidant itself. The best results were obtained with the Lewis acidic oxidant $[\text{FeCp}_2]\text{BF}_4$. In situ switching between the oxidized and reduced form of the catalyst was also shown and the stereoselectivity could be tuned during the reaction depending on the oxidation state of the ferrocenyl moiety. Although this system provides neither complete ON/OFF switching nor complete switching of the stereochemical outcome of the reaction, it represents a remarkable example of responsive chiral catalysis.

Scheme 49. Primary amine organocatalyst bound to the ferrocenyl moiety, which is capable of tuning the stereochemical outcome of the aldol reaction depending on the oxidation state of the catalyst.

Redox-switchable catalysts have gained much attention lately, owing to the possibility of controlling reactions in time and space by applying different potential or enabling copolymerization, for example. An overview of such catalyst systems, including the various redox-active moieties, the principle underlying the responsive catalysis, and the various catalyzed transformations, is presented in Table 3.

5. Concluding remarks

Over the last 30 years, there have been remarkable advances in the design and synthesis of artificial dynamic responsive catalytic systems. Apart from the systems described herein, other responsive catalysts have also been reported such as solvent-dependent^[101] or magnetoresponsive^[102] systems, which are beyond the scope of this Review. Even though progress in this field has been remarkable, major barriers remain that need to be overcome. For example, a photoswitchable catalyst capable

Scheme 48. Redox-switchable catalyst based on copper-quinoline complex capable of controlling the stereochemical outcome of the addition of diethyl malonate to *trans*- β -nitrostyrene.

Table 3. Overview of redox-responsive catalysts and comparison of principles underlying catalysis.

Redox active species	Principle underlying responsive catalysis	Catalyzed reaction	Reference
cobaltocene	difference in the electronic properties of oxidized and reduced form of redox active moiety, influencing basicity of attached ligand	hydrogenation of cyclohexene and hydrosilylation of acetone	[80]
ferrocenyl	difference in the solubility of the catalyst	ring-closing metathesis of <i>N</i> -tosyldiallyl amide	[83]
ferrocenyl	difference in the electronic properties of oxidized and reduced form of redox active moiety and difference in solubility	isomerization of 1-octene-3-ol	[85,86]
ferrocenyl ferrocenyl and cerium	difference in electronic properties	ROP ^[a] of L-lactide and trimethylene carbonate	[88] [89]
cerium	difference in size and electronic properties of the catalyst	ROP of L-lactide and <i>meso</i> -lactide	[89,90]
iron	difference in steric and electronic properties	ROP of <i>rac</i> -lactide and ϵ -caprolactone	[91,92]
ferrocenyl Cu ⁺	difference in electronic properties difference in electronic properties	copolymerization of lactide and caprolactone ATRP ^[b] of methyl acrylate	[93] [94]
PVF ^[c]	difference in electronic properties, in ferrocenium form catalyst can act as Lewis acid	Michael addition of ethyl-2-oxocyclopentane carboxylate to methyl vinyl ketone	[95]
naphthoquinone	difference in electronic properties	Kumada coupling reaction	[97]
ferrocenyl	difference in electronic properties	ROMP ^[d] of 1,5-cyclooctadiene, RCM ^[e] of diethyl diallyl malonate	[98–99]
Ru	difference in electronic properties	ROMP of 1,5-cyclooctadiene, RCM of diethyl diallyl malonate	[100]
Cu	cooperative catalytic activation, two different helical structures of the catalyst can be obtained depending on the oxidation state of Cu	enantioselective addition of diethyl malonate to <i>trans</i> - β -nitrostyrene	[101]
ferrocenyl	difference in electronic properties	aldol reaction	[102]

[a] ROP = ring-opening polymerization. [b] ATRP = atom transfer radical polymerization. [c] PVF = polyvinylferrocene. [d] ROMP = ring-opening metathesis polymerization. [e] RCM = ring-closing metathesis.

of catalyzing two orthogonal reactions is yet to be reported. Unlike redox-switchable and ion-switchable systems, in which chemical waste is generated, photoswitchable systems offer major advantages, as they use a clean and noninvasive external trigger that allows spatiotemporal precision. Although Diaconescu and co-workers recently reported a remarkable example of the control of the composition of a polymer,^[91] their system suffers from low conversions of copolymerization and the use of chemical triggers. Further study of the photophysical properties of photochromic moieties will enable the design of more powerful systems, resistant to photodegradation and capable of performing tandem reactions, for example, by using two different wavelengths to control two orthogonal reactions. Redox-switchable catalysts also present a powerful tool for the future, where the application of different electrochemical potentials may enable better control over the performance of a catalyst. As demonstrated quite recently by Hatton and co-workers,^[97] this kind of system can be used for batch processing and controlling reaction rates *in situ*, offering potential opportunities in future industrial applications.

There are only few examples in which dual stereocontrol of chemical reactions (obtaining both enantiomers of the product on demand by using the same catalyst) can be achieved, although such systems are highly desirable in view of potential applications in the pharmaceutical industry. Multitasking responsive catalysts offer great prospects for the future of smart and adaptive chemical processes, in systems chemistry and complex chemistry reaction networks.

Acknowledgements:

This work was supported financially by the European Research Council (Advanced Investigator Grant No. 227897 to B.L.F.), the Netherlands Organization for Scientific Research (NWO-CW) and funding from the Ministry of Education, Culture and Science (Gravitation program No. 024.001.035) and the Royal Netherlands Academy of Arts and Sciences (KNAW).

Keywords: homogeneous catalysis • molecular switches • photochemistry • photoswitchable systems • redox chemistry

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Received: May 23, 2016

Published online on September 15, 2016