

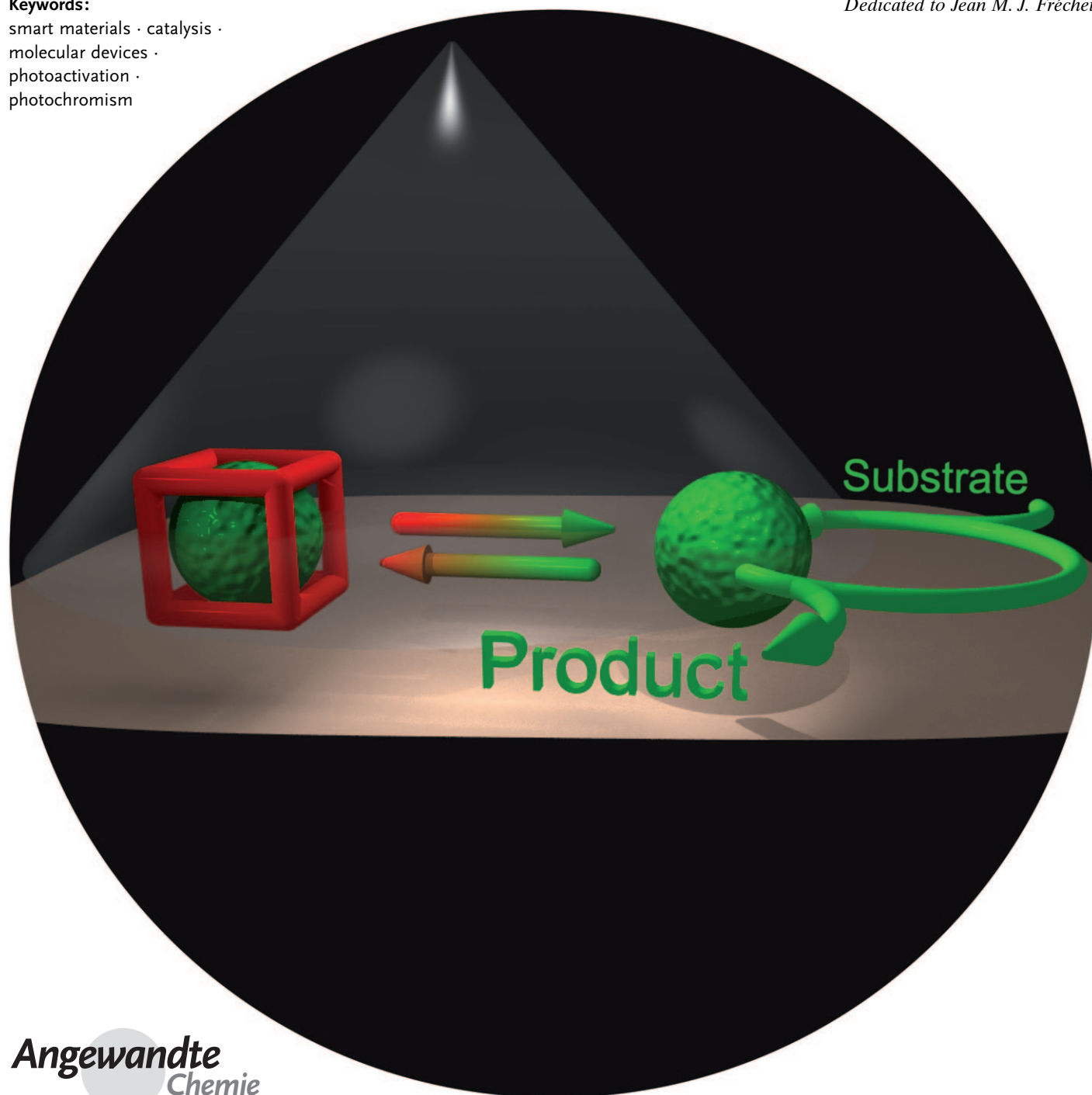
Artificial Light-Gated Catalyst Systems

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Dedicated to Jean M. J. Fréchet



Having control over an entity or even an entire process is arguably the ultimate demonstration of its understanding and it will enable its potential to be fully exploited. With this in mind, chemists have not only been creating and optimizing a myriad of different catalysts for most (relevant) chemical reactions over the past decades, but have recently started to implement controlling elements into the catalyst design. These incorporated gates operate upon exposure to suitable control stimuli, and light represents perhaps the scientifically and technologically most attractive stimulus. In principle, irradiation can thereby induce activity and selectivity in a given catalyst system with high spatial and temporal control, leading to an overall localization and amplification of an optical signal and translation into chemical action. While nature has developed and utilized this concept, in particular in the processes of vision and photomovement, such artificial photocontrolled catalyst systems offer unique opportunities and have high potential for future applications. In this Review, we outline the general concept of light-gated catalysis based on photocaged and also photoswitchable systems, and discuss relevant examples of the past and recent literature.

“What a man’s mind can create, man’s character can control.”

Thomas A. Edison

1. Introduction

All essential functions of living organisms in nature, such as energy harvesting and conversion, internal and external communication, and growth and reproduction are governed by highly sophisticated biological machinery that is founded on a truly molecular basis. These processes are managed by complex interconnected networks of functional units—usually associated with proteins—that can be regulated in their activity by internal and external stimuli. Similarly, in man-made materials it is critical to control and manipulate structure at the molecular and higher hierarchy levels to realize advanced and responsive functions. For this purpose, functional molecular units need to be created whose functions can be controlled by suitable stimuli.^[1] Commonly, stimuli-triggered intra- and intermolecular structure-reorganization processes involving folding and aggregation are exploited to control important functions, including mechanical behavior, mass and charge transport, optoelectronic and magnetic properties, and chemical reactivity. The latter in particular is appealing, as even small alterations in chemical reactivity induced by a stimulus can be amplified in the overall system by means of one or more catalytic cycles. Arguably, implementing such exquisite control over catalytic function in a synthetic system will open the door to new intriguing properties and attractive future applications. From a chemist’s viewpoint, it certainly constitutes an appealing idea to be able to temporally and spatially modulate any given catalyst’s activity and selectivity.

From the Contents

1. Introduction	5055
2. Photocaged Catalyst Systems	5057
3. Photoswitchable Catalyst Systems	5062
4. Outlook	5071

Best possible control requires a critical analysis of the types of available stimuli. In nature, the majority of biological processes are regulated by chemical stimuli, such as proton or ion concentrations and interactions with specific small molecules acting as effectors or inhibitors. Arguably, the chemical potential is elegantly manipulated by electrochemical means, which allows for precise tuning and

dosing of the required energy input. However, in the context of controlling catalysis, few successful examples have been reported to date.^[2] It should be noted that this stimulus is necessarily confined to the interfaces dictated by the electrodes’ surfaces and furthermore requires the presence of a suitable electrolyte and thus a polar medium.

Further to changing the chemical potential, the rather trivial stimulus encoded in temperature changes can lead to very effective and nonlinear catalytic responses, reflected for example in the use of DNA polymerase from thermophiles for the polymerase chain reaction. Even subtle conformational changes, which can be caused by temperature changes in combination with statistical fluctuations, can have dramatic effects on enzyme activity.^[3] Temperature effects are of course well-known from latent catalyst systems, and some impressive examples have been reported recently.^[4] Although there are several ways to introduce thermal energy into the system—homogeneously and inhomogeneously by conventional heating, microwave heating, or sonication—a precise control over location and time is hard to achieve and is further hampered by rapid heat dissipation.

In contrast to temperature, mechanical forces constitute an unconventional alternative stimulus, which however is rather common in nature, as manifested in the senses of touching and hearing. Owing to the ability to precisely measure small forces and to manipulate individual molecules,

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thermodynamic reaction parameters, for example bond strengths, have been successfully correlated to mechanical forces.^[5] However, mechanochemistry^[6] has only recently been successfully used to induce chemical transformations by applying macroscopic mechanical forces.^[7]

Last but by no means least, electromagnetic radiation^[8] is known to induce chemical processes. Light is perhaps the most advantageous stimulus as it can be conveniently manipulated by modern optics, potentially enabling the setup of highly parallel processes. Most importantly, precise selection of the appropriate wavelength for electronic excitation allows controlled induction of chemical reactivity. Although the utilized energy quanta enable a very high temporal resolution, the spatial resolution that can be achieved is traditionally limited by the law of diffraction (directly proportional to the wavelength λ of the light used).^[9]

Conversion of light energy into chemical energy is most apparent in the process of photosynthesis, which constitutes the (historical) basis for the world's energy supply. During photosynthesis, light is used to drive charge separation, thereby providing the thermodynamic driving force for production of high-energy biological fuels. On average, eight solar photons are needed to either release one O₂ molecule or to fix one CO₂ molecule.^[10] Apart from conversion of light energy into chemical energy, a light stimulus may be amplified by means of catalysis.^[11] This is impressively manifested in the process of vision, during which capture of few photons is translated into a chemical signal that is further amplified by a biochemical cascade, finally leading to firing of neurons associated with the visual perception.^[12] Primary biological processes, such as light-directed movement and growth in plants (phototaxis, photonasty, and phototropism),^[13] constitute other astonishing examples for the importance of photoresponsive

systems in nature, which are realized by catalytic systems coupled to light stimuli.

From these examples, it becomes obvious that it is highly attractive to mimic such systems and create artificial light-gated catalytic systems.^[14,15] Such systems can be realized by several conceptually rather different approaches, including photocatalysis and photocontrolled thermal catalysis (Figure 1) and also photoinduced chain reactions. It should be noted that there are considerable differences in the nomenclature of processes involving catalysis in combination with light, and the reader is referred to representative overviews of the field.^[16]

In the process of photocatalysis (Figure 1 a), the excited state of the catalyst, which has no activity in its ground state, participates in the catalytic cycle usually associated with an electron transfer event; that is, photoinduced electron transfer (PET). Therefore, the excited state that is generated provides the chemical potential to realize otherwise endothermic processes. Besides the already-mentioned biological benchmark of photosynthesis, photocatalysis involves inorganic photocatalysts and their nanoparticles^[17] as well as organic photocatalysts, ranging from singlet-oxygen sensitizers,^[18] for example in photodynamic therapy,^[19] to catalysts for

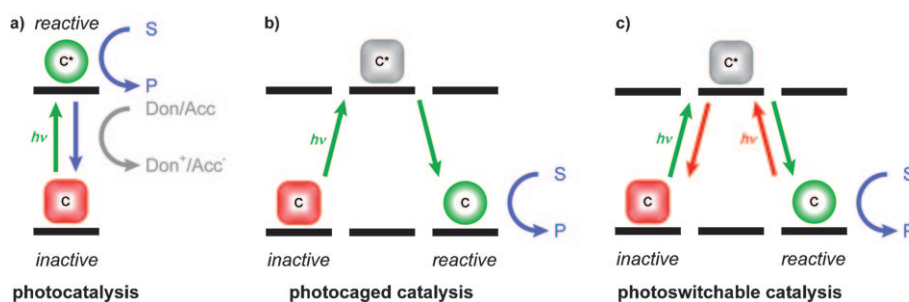


Figure 1. General approaches towards photocontrol of catalytic activity. a) True photocatalysts, which react from their transient excited state, b) photocaged catalysts, which in the course of a photochemical event irreversibly generate the catalytically active species, and c) photoswitchable catalysts, which can reversibly toggle between their inactive and reactive forms by means of suitable photochromes. In (b) and (c), which are the topic of this review, catalytic activity originates from a ground-state species. The inactive species (OFF state of the catalyst system) is depicted in red, and the active species (ON state of the catalyst system) is shown in green. This red/green color coding, and the abbreviations for catalyst (C), substrate (S), and product (P), are used throughout this review.



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light-driven biocatalytic oxidations^[20] and advanced enantioselective PET catalysts.^[21] A general feature, however, of photocatalysis is the stoichiometric use of photons associated with quantum yields $\Phi \leq 1$. Note that quantum yields exceeding unity are not necessarily associated with catalytic processes, as exemplified by photoinduced chain reactions often encountered in various photoinduced polymerization processes.

In contrast to photocatalysis, photocontrolled thermal catalysis involves light-gating of ground state reactivity of a given catalyst. This concept is in theory applicable to any thermal catalyst and thus much broader in scope, provided a suitable interface between the catalyst and the light stimulus is available. Such an interface is provided by a gating photoreaction ($\Phi \leq 1$), unleashing the catalyst activity, which turns over substrate into product molecules, thereby leading an amplification of the light stimulus and thus an overall quantum yield exceeding unity ($\Phi > 1$). In the case of an irreversible photoreaction, the masked dormant catalyst system is referred to as “caged”^[22] (Figure 1 b) and is activated by light only once.^[23] In contrast, photoswitchable systems (Figure 1 c) rely on reversible photoreactions, enabling repetitive toggling of the catalyst between its active and inactive forms.

Photocontrolled thermal catalysis is clearly an appealing yet challenging concept that offers great potential for the realization of smart catalysts. Recently, there has been a surge in attempts to construct such sophisticated systems, and first encouraging results point to an exciting future in the field, where one day synthetic chemists may be able to control both the activity and the selectivity of a given catalyst with a ray of light.^[24] Herein, we review the field of artificial^[25] light-gated catalyst systems, focusing on photocaged and photoswitchable (thermal) homogenous catalysis. We will present general design considerations and discuss their realization on the basis of the most prominent examples from the literature.

2. Photocaged Catalyst Systems

2.1. General Design Approaches

In the case of photocaged catalysis, irradiation triggers an irreversible photoreaction, which transforms an inactive catalyst precursor into an active species that is capable of catalyzing a given chemical reaction (Figure 1 b). The coupling of the photoreaction with the generation of a catalytically active entity can be achieved by various conceptually different approaches (Figure 2).

In biochemistry, the light-induced cleavage of a suitable photolabile protecting group^[25b,26] “un-cages” an activating small molecule, such as a co-factor, which typically activates the biological catalyst, for example an enzyme (Figure 2 a). While this strategy is rather uncommon for artificial systems, the reverse process involving light-induced removal of an inhibiting moiety, such as a ligand, from the active site to generate the active catalyst, for example a metal complex, has been more frequently realized (Figure 2 b). In a slight variation of this concept, photoinduced cleavage can occur

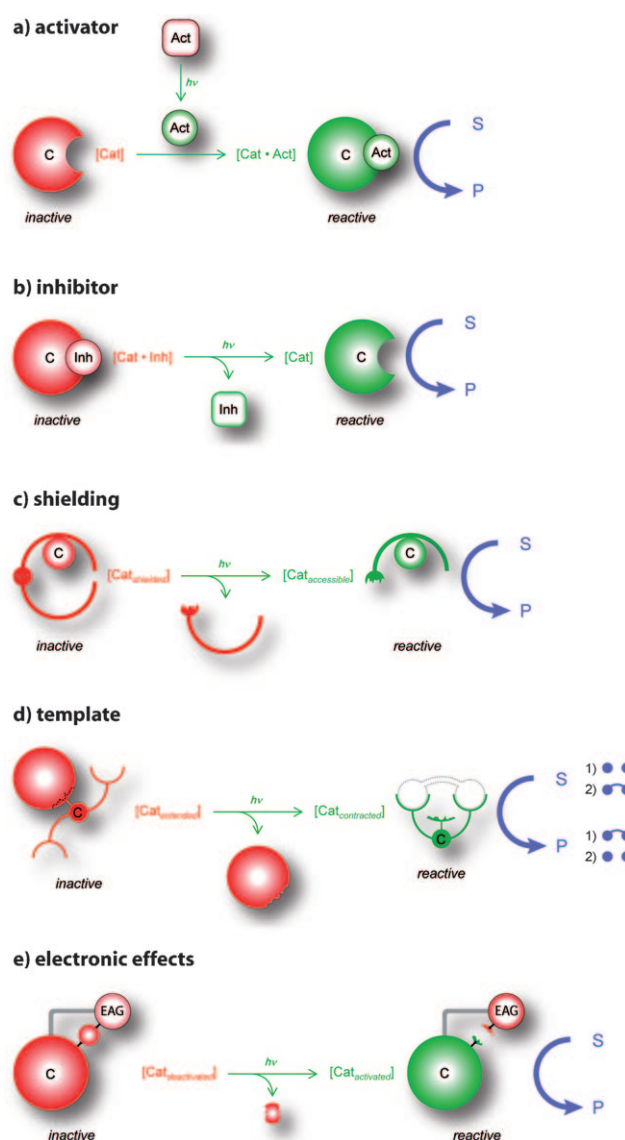


Figure 2. Conceptual approaches to the design of photocaged catalysts in which the light stimulus triggers an irreversible activation of the catalytically active species. a) Photochemical release of an activator from a caged derivative, b) photochemically induced cleavage of an inhibitor (or ligand) from its complex with the catalyst, c) photochemical removal of parts of the catalyst remote from the active site leading to an effective deshielding event, d) photorearrangement, for example by cleavage of a bulky group, to yield a template, which due to reactant pre-organization can catalyze either bond making (1) or breaking (2), and e) photochemically induced alteration of the electronic characteristics of the active site, for example by disrupting communication, that is, π conjugation with an electronically active group (EAG; electron-donating or electron-accepting moiety).

in the vicinity of the active site leading to a de-shielding of the catalyst, allowing the substrate to productively interact with the catalyst (Figure 2 c). A more complicated scenario involves pre-organization of the substrate (or substrates) with the aid of a catalyst template, which is generated by a geometrical rearrangement occurring in the course of the photoreaction (Figure 2 d). Finally, the photoreaction may lead to a modulation of electronic communication between an

activating or deactivating substituent and the catalytically active site. This modulation could in principle be caused by photodissociation leading to an interruption of the electronic interaction (Figure 2e) or by photoaddition or photorearrangement causing changes in π -conjugation.

Although all of the above approaches should in principle enable the construction of photocaged catalysts, almost all examples described in the literature to date exclusively rely on the unleashing of an inhibited catalyst (Figure 2b); we will cover the most prominent examples in the following three subsections.

2.2. Photocaged Brønsted Acids

The photoinduced generation of Brønsted acids, that is, protons, constitutes the technologically most relevant area of photocaged catalysis owing to the enormous impact of photolithography on current semiconductor industry. Photolithography and photography both utilize the ability of light to induce chemical transformations with spatial resolution, leading to marked differences of physical properties within the exposed and unexposed regions of a thin film. In the case of photography, these property differences encode a pre-defined geometrical pattern, which is typically developed by dissolution of parts of the resist and subsequently transferred to the flat substrate (usually the semiconductor) by an etching process, in which the remaining parts of the resist protect the underlying surface (Figure 3, bottom). While conventional photoresists rely on solubility differences generated in the course of a reaction, which requires a stoichiometric amount of photons, the advent of photoacid generators^[27] (PAGs, Scheme 1) in combination with well-established general acid catalysis has led to the development of chemically amplified resists (Figure 3) by Ito, Willson, and Fréchet.^[28] It should be noted that PAGs irreversibly yield protons and thus differ from photoacids and superphotoacids, in which ultrafast proton transfer occurs in the excited state, followed by recombination.^[29]

Upon irradiation, PAGs, which are usually onium salts or protected sulfonic acids^[27] (Scheme 1), undergo bond scission to reactive fragments, which recombine under the liberation of protons. In combination with weakly coordinating counteranions, strong acids can therefore be generated. The generated protons are able to catalyze a chemical transformation associated with large solubility differences, for example, the acid-catalyzed deprotection of polymer-bound phenols (Figure 3a). Catalysis is key to the efficiency of the process, as one proton on average leads to liberation of approximately 1000 phenolic groups.^[28b,30] Thus by exploiting the light-triggered catalytic cycle, very few photons are capable to achieve pronounced solubility differences during the development process using aqueous base. The thus largely increased sensitivity of the photolithographic process translates directly into high quality replication of the features of the original mask, which is impressively illustrated by today's highly sophisticated chip architectures (Figure 3b).

Although the concept of combining photoinitiation with a catalytic cycle has increased sensitivity in resist systems

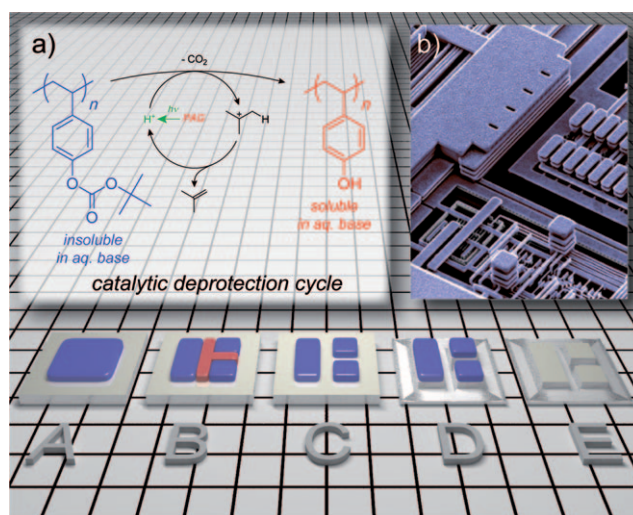
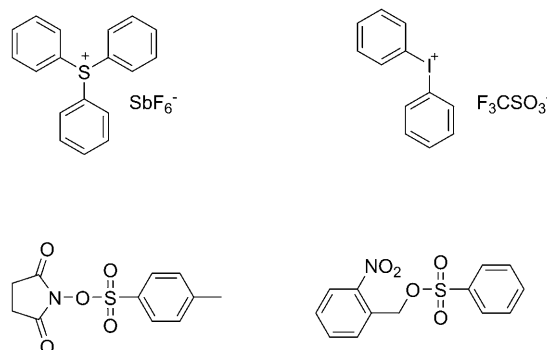


Figure 3. Chemically amplified resist technology.^[28] Thin films of photoresist material (A, bottom) are exposed to deep UV light (currently $\lambda_{\text{irr}} = 193$ nm from an ArF laser) through a mask to yield a desired pattern (B), which can be transferred after removal of the exposed regions (C, the case of a so-called positive tone resist), and subsequent etching of the underlying silicon surface (D) to yield the desired nanostructured semiconductor surface (E). a) Chemical amplification and thus increased sensitivity can be achieved by a photo-triggered catalytic deprotection cycle utilizing photoacid generators (PAGs, see Scheme 1), that is, caged protons, which catalyze a chemical transformation leading to large solubility differences between exposed and unexposed regions. b) A microchip as an example of sophisticated integrated circuitry, which was produced by many repeated lithographic steps (A–E).



Scheme 1. Photoacid generators (PAGs) commonly employed in photolithography (see Figure 3).^[27]

tremendously, it cannot overcome physical boundaries dictated by the law of diffraction, that is, feature sizes are inevitably governed by the wavelength of irradiation used^[9] and are primarily bound to two dimensions within one photolithographic step. However, the general concept of two-photon excitation leads to enhanced resolution and, more importantly, has successfully been extended to the third dimension, enabling the laser-assisted production of nano-scale features in the bulk.^[31]

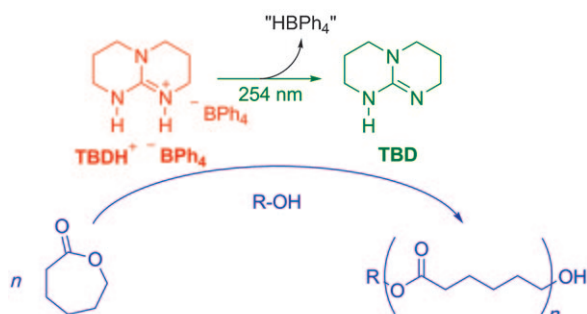
Although the above example utilizes the photogenerated proton directly as the catalyst, it can also be exploited to

activate another catalyst by a stoichiometric acid–base reaction, as discussed in Section 2.4 for latent olefin metathesis catalysts. Complementary photobase generators,^[27b,32] leading to the liberation of amine bases upon irradiation, have also been developed, but their potential to serve in general base catalysis has been less exploited to date. Although the above example shows that general acid (and base) catalysis can be used to efficiently carry out light-induced chemical transformations, it would be clearly beneficial to photocage more sophisticated metal-free as well as metal-containing catalysts or catalyst systems.

2.3. Photocaged Organocatalysts

The overwhelming majority of the work in the field of organocatalysis is concerned with small-molecule transformations and their associated selectivities, in particular enantioselectivity, while much less attention has been paid to organocatalysts that are able to catalyze the transformation of small molecule monomers into a growing polymer chain.^[33] However, polymerization catalysis would most obviously benefit from the ability of photocontrol, as the usually fast kinetics of photoreactions enable rapid initiation in well-defined reaction loci. Light could therefore be used to trigger the synthesis of polymers at a precise point in time and space, which shows great promise for future materials applications.

As shown in the pioneering work of Hedrick, Waymouth, and co-workers, the ring-opening polymerization of lactides and various cyclic lactones can be accomplished in a living fashion using nucleophilic organocatalysts, such as 4-dimethylaminopyridine (DMAP)^[34] and various N-heterocyclic carbenes (NHCs),^[35] as well as bifunctional hydrogen-bonding organocatalysts such as thiourea–amine systems,^[36] 1,5,7-triaza-bicyclo[4.4.0]dec-5-ene (TBD),^[37] and fluorinated alcohols.^[38] In one remarkable case, the authors could exploit the thermally induced reversible dissociation of a dormant NHC–alcohol adduct to turn the polymerization activity of the NHC catalyst on and off using temperature.^[4a] The first and to date only realization of a photocaged organocatalyst capable of inducing polymerization was reported by the group of Wang (Scheme 2).^[39]



Scheme 2. UV irradiation of acid–base adducts of 1,5,7-triaza-bicyclo[4.4.0]dec-5-ene (TBD) with tetraphenylboric acid releases TBD, which catalyzes the living ring-opening polymerization of ϵ -caprolactone.^[39]

The authors prepared the salt of TBD and tetraphenylboric acid, which shows no activity as a polymerization catalyst owing to protonation of the bifunctional guanidine moiety of TBD. Irradiation with UV light (254 nm) led to formation of free TBD. The tetraphenylborate counterion is essential for the photodeprotonation process, as the related TBD·HCl adduct exhibits no photoactivity. The authors suggest that upon excitation, the tetraphenylborate anion undergoes a rearrangement and subsequently abstracts the proton from the guanidinium moiety with an overall quantum efficiency of 18% at 254 nm excitation. Once the TBD is photogenerated in bulk ϵ -caprolactone, a living ring-opening polymerization occurs to yield well-defined poly(ϵ -caprolactone) (Scheme 2). Furthermore, the ability of TBD to catalyze transesterification reactions was exploited as a means to photo-cross-link poly(methyl methacrylate) with 2-hydroxyethylcellulose. A photo-cross-linking polymer system was also designed by incorporation of both necessary functional groups, that is, ester and hydroxy groups, into the same polymer. Note that in all cases, initial short periods of irradiation (few minutes), associated with photoactivation, were followed by prolonged periods of “dark” reactions (several hours), which are necessary for thermal polymerization and cross-linking, respectively. From a practical standpoint, the photocaged TBD catalyst offers the advantage that it can be conveniently stored at room temperature in the dark without losing its photoactivity. Importantly, adduct formation with tetraphenylboric acid seems to constitute a general way to photocage various organic bases, as exemplified by photocaging a phosphazene base, which has shown independently to promote the stereoselective ring opening of lactides.^[40]

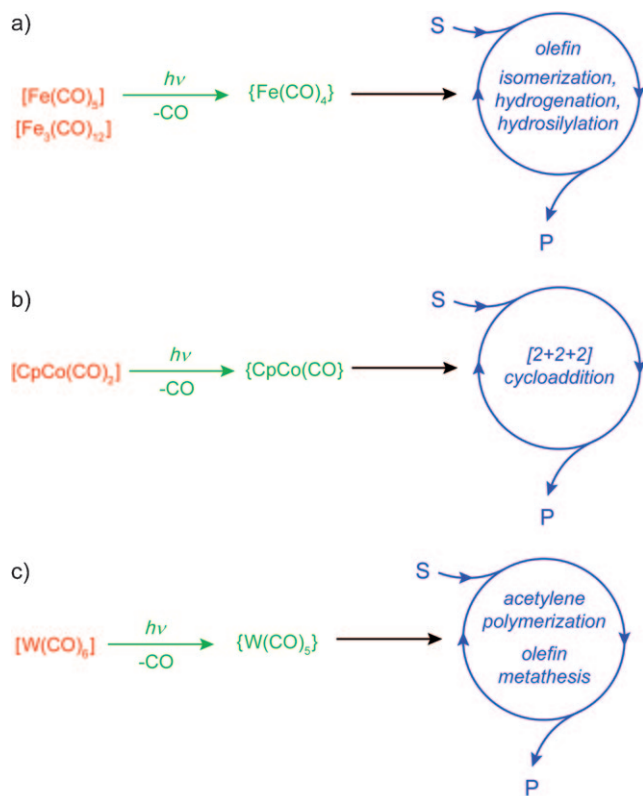
Surprisingly, there have been few other successful examples of photocaged organocatalysts reported to date in the literature. It could be speculated that this absence is associated with the rather high energies required to excite common photolabile protecting groups and their potential interference with the organocatalyst. In contrast, organocatalysis has recently been merged with photoredox catalysis,^[41] utilizing ruthenium trisbipyridine complexes [Ru(bpy)₃], which can be excited in the visible region of the spectrum, thereby providing a means to light-driven—but not light-gated—(organo)catalysis.^[21]

2.4. Photocaged Transition Metal Catalysts

One way to overcome the problem of high-energy excitation is to shift the wavelength necessary for photodissociation to longer wavelengths. This can successfully be realized with the aid of transition metal complexes exhibiting low-lying electronic transitions, such as metal–ligand charge-transfer (MLCT) transitions, which can be utilized in the aforementioned [Ru(bpy)₃]²⁺ complex. In many examples, it has been shown that irradiation can lead to acceleration of ligand-exchange processes by many orders of magnitude. In these processes, photoexcitation leads to population of antibonding orbitals and thus facilitates ejection of a bound ligand to generate a vacant site at the metal center. Such

photochemically assisted organometallic chemistry and catalysis^[16a] has most frequently been performed using carbonyl complexes.^[42]

Perhaps one of the oldest examples dates back to work by Asinger and co-workers in the early 1960s, in which they could demonstrate the beneficial effect of UV irradiation on the catalytic activity of iron carbonyl complexes in the isomerization of long-chain olefins (Scheme 3a).^[43] The



Scheme 3. Catalytically active transition metal fragments generated by photoinduced dissociation of carbon monoxide from carbonyl complexes for various organic transformations: a) iron carbonyls,^[43–47] b) cobalt carbonyls,^[48] and c) tungsten carbonyls.^[50–53]

authors found a much faster conversion to the thermodynamically equilibrated mixture of the five possible *n*-undecenes in the case of UV exposure, thus indicating accelerated formation of the $\{Fe(CO)_4\}$ fragment, which subsequently initiates the catalytic cycle. Subsequent detailed studies by Wrighton and co-workers revealed a quantum efficiency of $\Phi_{366nm} \approx 500$ for 1-pentene to 2-pentene isomerization using the $[Fe(CO)_5]$ photocatalyst, which exhibited turnover numbers (TON) of over 1000.^[44] Their findings clearly show that light-induced but thermally driven catalysis is operating in their system. The authors could extend the scope of the photocatalysis to olefin hydrogenation using H_2 under mild conditions (25 °C, 1 atm)^[44] and also hydrosilylation,^[45] and furthermore they were able to shift the required irradiation wavelength to the visible region by employing clusters, such as $[Fe_3(CO)_{12}]$ or $[Ru_3(CO)_{12}]$.^[46] They found that $[Fe(CO)_5]$ and $[Fe_3(CO)_{12}]$ constitute photochemical precursors to extremely active and fast homogenous catalysts.^[47]

This concept of photochemically induced transition metal catalysis has been utilized for even more challenging organic transformations, such as the cobalt-catalyzed [2+2+2] cycloadditions of alkynes, olefins, and nitriles developed by Vollhardt and co-workers (Scheme 3b).^[48] The catalyst precursors $[Co_2(CO)_8]$ and in particular $[CpCo(CO)_2]$ (Cp = cyclopentadienyl) showed markedly enhanced activities under (continuous) irradiation. However, as the thermal catalytic process necessitates elevated temperatures, considerable thermal background reactivity was observed, because CO dissociation is not only aided by irradiation but can also be accomplished by heating.

Reactive fragments of other transition metals, in particular molybdenum and tungsten, are well-known for their ability to form carbene and carbyne complexes,^[49] which show catalytic activity for various transformations involving alkenes and alkynes. Again, carbonyl complexes, that is, $[Mo(CO)_6]$ and $[W(CO)_6]$, have typically been used as the photochemical precursors of the thermally active catalysts. For example, Masuda et al. described the UV-induced polymerization of various acetylenes using $[W(CO)_6]$ as the catalyst precursor (Scheme 3c).^[50] Either the active catalyst was generated by irradiating $[W(CO)_6]$ in the presence of CCl_4 prior to addition of the phenylacetylene monomer, or it was generated by irradiation of $[Mo(CO)_6]$ in the presence of 2-chloro-1-phenylacetylene, indicating that chlorine abstraction is required for catalyst formation. In both cases, the photochemical initiation (30 min) was followed by extended periods (24 h) of polymerization in the dark, giving rise to polyacetylenes with high molecular weights ($M_w \approx 80\,000$ – $400\,000$). Later, Geoffroy and co-workers could alleviate the need for halocarbon solvents or monomers by conducting photolysis of $[W(CO)_6]$ in hexane in the presence of the appropriate monomer.^[51] Interestingly, in the case of acetylene, irradiation initiated the polymerization, which then proceeded in the dark, whereas in the case of phenylacetylene, polymerization ceased once irradiation was stopped. Most likely, the catalyst formed in-situ from acetylene shows a much higher reactivity as compared to its phenyl-substituted analogue; furthermore, the authors provided evidence that the active carbene catalyst is generated via an alkyne-vinylidene rearrangement.

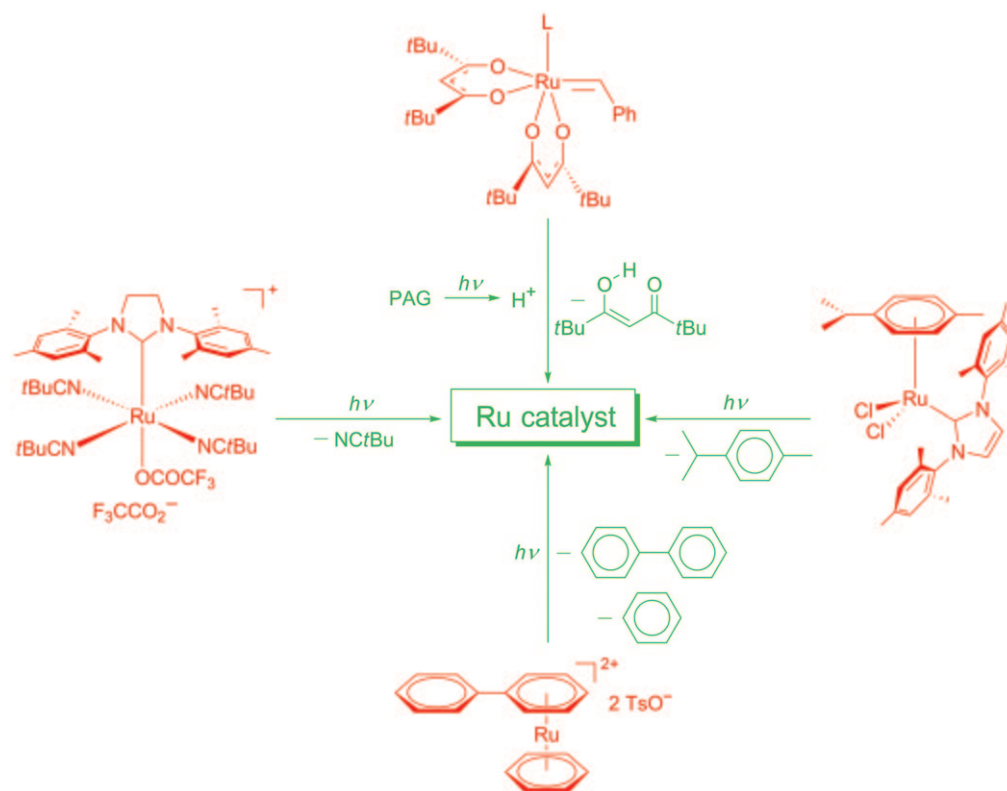
Early work by McNelis and by Dubois showed that by irradiation of the $[W(CO)_6]/CCl_4$ system, catalysts for olefin metathesis can be generated that however displayed rather low activities.^[52] Later, Schaaf et al. presented a well-defined Schrock-type olefin metathesis catalyst, which could be generated by photoinduced α -H abstraction from a $[L_xW(CH_2SiMe_3)_2]$ precursor.^[53] The catalytic activity of the generated tungsten carbene complex was demonstrated by polymerization of dicyclopentadiene and was monitored by differential scanning calorimetry.

The development of well-defined ruthenium-based catalysts enabled olefin metathesis of various types, such as ring-closing and cross metathesis (RCM and CM) and ring-opening and acyclic diene metathesis polymerizations (ROMP and ADMET), with unprecedented functional group tolerance.^[54] Based on these developments, several groups reported approaches to photoinitiate latent versions of

these catalysts^[55] for polymerizations (Scheme 4) and also for small-molecule transformations (Scheme 5).

In the context of polymerization catalysis employing latent olefin metathesis catalysts, Mühlebach and co-workers could demonstrate the beneficial effect of light on polymerization activity.^[56] They found that photochemical activation in the absence of monomer was most efficient for ruthenium arene sandwich complexes (Scheme 4, bottom). These com-

plexes generated coordinatively unsaturated ruthenium centers with high catalytic activity in the ROMP of various strained bicyclic olefins subsequently added to the irradiated reaction mixture.



Scheme 4. Photolabile precursors of ruthenium carbene complexes that catalyze the ring-opening metathesis polymerization (ROMP) of various cyclic olefins. Photoinitiation is caused by dissociation of labile ligands, such as arenes (bottom),^[56–58] *p*-cymene (right),^[59] and nitriles (left).^[62] In combination with photoacid generators (PAGs), displacement of hexamethylacetylacetonate (Me₆acac) ligands can be accomplished by light-triggered protonation (top).^[63]

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As the photocaged ruthenium-based catalysts of the type [Ru(*p*-cymene)Cl₂PR₃] showed significant activity even prior to irradiation, Hafner and co-workers exchanged the ruthenium center for osmium.^[57] The resulting less-active osmium-based catalysts do not initiate thermal ROMP of norbornene; however, after UV irradiation (200 W Hg lamp, 5 min), active ROMP catalysts were obtained. This effect was only observed when the auxiliary phosphine ligand carried bulky substituents (R = Cy or *i*Pr) leading to large cone angles;^[58] catalysts with sterically less-demanding phosphine derivatives showed very poor or no polymerization activity.

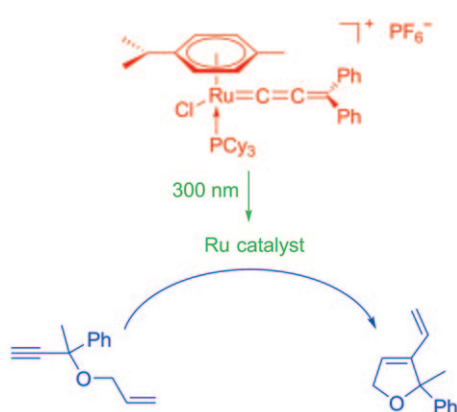
Another means to reduce the thermal activity of ruthenium-based metathesis catalysts involves tuning their ligand

environment. In this context, NHCs^[59] have received tremendous attention^[60] and proved to be extremely useful to modulate both the electronic and the steric properties at the metal center. In one relevant example, the group of Noels reported [Ru(*p*-cymene)Cl₂NHC] complexes (Scheme 4, right) for the polymerization of cyclooctene.^[61] Upon irradiation with light from ordinary 40 W “cold-white” fluorescent tubes or light bulbs, practically quantitative monomer conversion could be achieved, leading to polymers with molecular weights M_w of more than 500 000. For comparison, polymerizations run in the dark gave only 22 % monomer conversion and $M_w \approx 21\,000$, indicating residual thermal catalytic activity. Interestingly, the polymers obtained upon irradiation of the catalysts displayed narrower polydispersities (PDI = 1.33 as compared to PDI = 1.53) and reduced *cis*-olefin content (less than 20 % compared to 36 %). It is reasonable to assume that excitation leads to dissociation of the η^6 -bound cymene ligand and formation of the highly reactive Ru–NHC fragment. The substitution pattern influences the electronic transition responsible for cymene dissociation (450 nm) and thus visible light can be employed for photogenerating the active catalyst.

To increase the spatial resolution for potential surface patterning applications, Buchmeiser and co-workers used UV irradiation (254 nm Hg lamp or 172 nm Xe₂ excimer laser) to photogenerate ruthenium catalysts for the ROMP of various norbornene-type monomers and of cyclooctene.^[62] For this purpose, they utilized cationic Ru–NHC complexes carrying four equatorial *tert*-butylnitrile ligands (Scheme 4, left), one of which is cleaved upon irradiation, leaving the desired coordinately unsaturated Ru–NHC fragment. Notably, shorter wavelengths of irradiation led to faster initiation and quantitative monomer conversion, yielding polymers with $40\,000 < M_w < 880\,000$ and rather broad PDIs. Importantly, no reaction was observed upon mixing monomers and catalyst precursors, and therefore the large difference in reactivity between dark and illuminated regions could successfully be utilized to prepare photopatterned polymer coatings on glass substrates.

Recently, Grubbs and co-workers described a rather broadly applicable and conceptually new approach of using PAGs for photoinduced ligand displacement in ruthenium carbene complexes (Scheme 4, top).^[63] In their system, the photogenerated protons seem to facilitate displacement of both Me₆acac ligands for chloride ions. Substitution for chloride ions seems to be a necessary prerequisite for obtaining a reactive catalyst since no replacement of the counterion with the non-nucleophilic nonaflate ion (nonaflate = perfluoro-1-butanedisulfonate) does not give a reactive catalyst upon irradiation. Therefore, two equivalents of PAG per catalyst equivalent are needed for complete activation. The photogenerated reactive ruthenium intermediates are capable of either catalyzing RCM of various diolefin substrates in excellent conversions, or ROMP of a number of functional norbornene monomers and also cyclooctene. Interestingly, the molecular weights obtained were consistently higher ($8500 < M_w < 187\,000$) than those predicted from the monomer to initiator/catalyst ratio, pointing to incomplete catalyst activation even upon continuous irradiation of the reaction mixture. Trapping experiments employing (2-isopropylalkoxy)-*trans*- α -methylstyrene led to the tentative formulation of a highly reactive 14-electron intermediate, which is also encountered in the catalytic cycle observed with the parent Grubbs I type catalyst. It should be emphasized that, in contrast to the previous examples involving ruthenium precatalysts, the photochemical step (acid generation) is mechanistically well-separated from catalyst activation (ligand displacement). This constitutes a conceptually new and rather versatile approach towards light-gated catalysts, as a variety of ligand substitution reactions can in principle be exploited to unleash a catalytically active species from a dormant transition metal precatalyst.

The ability to photoactivate ruthenium carbene complexes for small-molecule transformations, especially RCM, has already been exploited by the groups of Dixneuf (Scheme 5)^[64] and Fürstner.^[65] Dixneuf and co-workers used an 18-electron cationic ruthenium allenylidene complex,^[66] which is known to catalyze the RCM of α,ω -dienes with up to a C₁₇ tether, and could show that its catalytic activity was greatly increased upon initial irradiation for 0.5 h followed by



Scheme 5. Photodissociation of a *p*-cymene ligand from a photocaged ruthenium carbene complex generates an efficient catalyst for the ring-closing metathesis (RCM) of α,ω -enynes.^[64]

thermal reaction carried out at 80 °C over the reaction run under the same conditions but in the dark. The authors could successfully use these light-activated catalysts for the formation of a range of dihydrofuran derivatives from various allyl propargyl ethers in good to very good yields. As indicated in the previously discussed examples,^[56a,57] it was assumed that the *p*-cymene ligands dissociate upon excitation. Later, Fürstner and Ackermann described a more practical approach using in-situ formation of the active metathesis catalyst by reaction of the ruthenium dimer $[\text{Ru}(\textit{p}\text{-cymene})\text{Cl}_2]_2$ in the presence of PCy₃ and the α,ω -diene substrate in a “well-illuminated hood”.^[65] Clearly, a remarkably efficient photochemical generation of the active ruthenium species takes place that catalyzes RCM to yield various cyclic olefins with medium to large ring sizes ($5 \leq n \leq 21$).

More recently, Ru–NHC complexes have also been exploited in small-molecule transformations using light-induced olefin metathesis. Whereas Dixneuf and co-workers used $[\text{Ru}(\textit{p}\text{-cymene})\text{Cl}_2\text{NHC}]$ to catalyze both the RCM of dienes and also the CM of styrenes,^[67] Lemcoff and co-workers described Ru–NHC complexes carrying a chelating carbene–sulfide ligand to catalyze RCM of dienes and ROMP of various cyclic olefins.^[68] In both cases, irradiation caused improved catalytic performance. In the first case, light most likely induces *p*-cymene ligand dissociation, whereas in the latter case, irradiation induces a structural rearrangement associated with the generation of a vacant coordination site by breaking the Ru–S bond.

3. Photoswitchable Catalyst Systems

3.1. General Design Approaches

In contrast to photocaged catalysts, in photoswitchable catalyst systems irradiation is used to trigger a reversible photoreaction, which gates a thermal catalytic cycle. In order to realize this process, photochromic moieties^[69] have to be incorporated into the catalyst system.^[70] The reactivity of the photoswitchable catalyst can be gated by light of different wavelengths and the interface between system and stimulus is provided by a suitable photochrome. The state of higher reactivity is commonly referred to as the ON state, whereas the state of lower reactivity is referred to as the OFF state. A switchable catalyst system is best characterized by the ON/OFF ratio k_{rel} , which is given by the ratio of rate constants for substrate conversion^[71] by the ON and OFF states; that is, $k_{\text{rel}} = k_{\text{ON}}/k_{\text{OFF}}$. A high activity ratio not only implies high reactivity associated with the ON state, but also a low OFF state reactivity to avoid undesirable background reactivity, that is, substrate conversion by the OFF state, over long periods of time. Several prerequisites are mandatory for achieving high ON/OFF ratios to efficiently modulate and hence switch the catalytic activity.

The first pre-requisite is a significant population of the desired catalyst species, as manifested in high attainable photostationary states (PSSs) for the forward and backward photochemical reactions. This illustrates the importance of a proper choice of photochrome, and in fact all other chromo-

phores present in the system. While the photochrome should combine advantageous characteristics, including (almost) quantitative and efficient switching in both directions using distinct wavelengths and photochemical stability (fatigue resistance), excitation should be localized on the photochromic part, thus prohibiting competing dissipation processes (energy and electron transfer to or from the catalyst).^[72] In principle, two scenarios are conceivable: one employing P-type photochromes, necessitating two different excitation wavelengths for switching the catalyst. In the other scenario, which utilizes T-type photochromes, a thermal back-reaction occurs, adding another possible means to gate the catalyst system besides photochemical switching. While in the first case, the catalyst is turned ON by irradiation at one specific wavelength and operates until it is turned OFF by irradiating at another wavelength, the catalyst in the latter case is only active when being irradiated (assuming a fast thermal back-reaction to the OFF state). In the case of a sufficiently long half live of the thermodynamically less-stable isomer, both thermal and photochemical deactivation of the catalyst is possible.

A second prerequisite is that the altered geometrical and/or electronic properties of the photochrome have to strongly influence the catalyst performance in order to translate molecular changes during the course of photoswitching into favorable activity differences. In general, large structural changes can be achieved using *E*–*Z* isomerization reactions of olefins and azo compounds carrying aromatic substituents, such as stilbene and azobenzene, leading to much shorter distances between the aryl termini in the non-planar *Z* configuration ($d_{4-4'} \approx 6$ Å) as compared to the planar *E* configuration ($d_{4-4'} \approx 9$ Å). Complementary electrocyclic ring-closing/ring-opening reactions of 1,3,5-triene systems, such as spiropyranes/spirooxazines, diarylethenes, and fulgides, result in substantially different electronic properties (such as absorption and emission, dipole moment, and redox potential) of the ring-closed isomer as compared to the acyclic form. The coupling of photochromic reactivity and catalytic activity can conceptually be achieved by various approaches (Figure 4), depending on the particular geometrical or electronic alteration of the photoswitch.

Implementation of the photochromic elements necessary to gate the activity of the catalyst system is possible either by direct incorporation of the photochrome into the catalyst framework or by intermolecular interaction of a suitable photochromic additive with the active site. Considering the latter case, the photochromic additive in one of its switching states could either act as an activator (Figure 4a), conceptually resembling naturally occurring catalyst regulation by co-factors, or as an inhibitor (Figure 4b). Thus, switching of the photochromic inhibitor leads to its dissociation and “unleashes” the catalytically active species, whereas switching of the photochromic activator leads to formation of a reactive catalyst-activator complex.

Covalent attachment of the photochrome to the catalyst offers the advantage that the interaction between both units is independent of their concentration, as opposed to the inhibitor/activator approaches outlined above. Note that in a biological context, photoswitchable affinity labels devel-

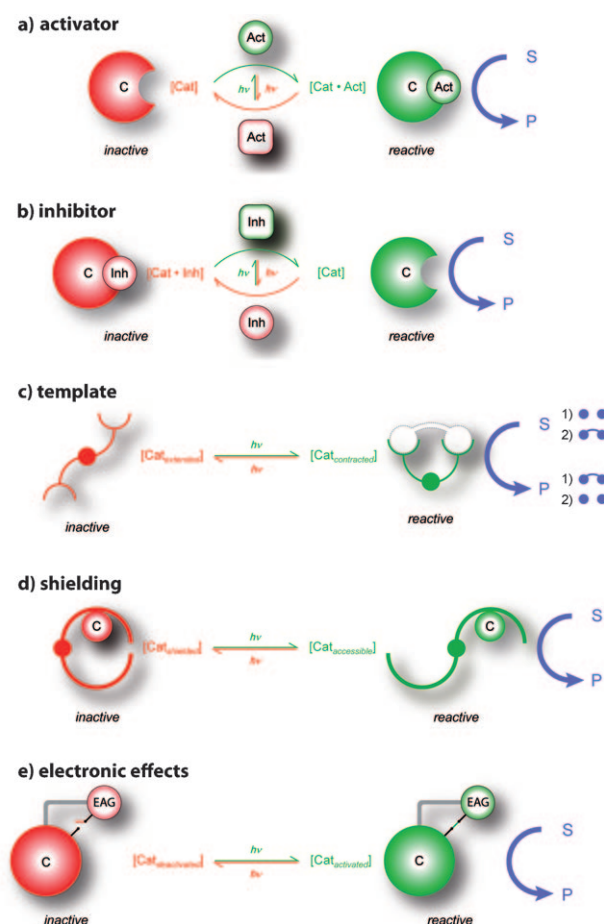


Figure 4. Conceptual approaches to the design of photoswitchable catalysts in which two different light stimuli reversibly shuttle the catalytic system between an active ON state and an inactive OFF state. a) A photochromic activator is switched between a deactivated unbound and an activating bound form. b) A photochromic inhibitor is switched between a deactivating bound and an activated unbound form. c) A photochromic template is switched to allow for reactant pre-organization and hence catalysis of either bond making (1) or breaking (2). d) A photochromic shield is switched to block access to the active site in one switching state and to grant it in the other. e) Photochrome-mediated alteration of the electronic characteristics of the active site, for example by enabling electronic communication; that is, π -conjugation with an electronically active group (EAG; electron-donating or electron-accepting moiety).

oped by Trauner and co-workers^[73] offer a rather general approach for covalent modification of an enzyme and have been successfully exploited to render endogeneous ion channels photoswitchable.^[74] When exploiting geometrical changes of the photochromic unit, typically associated with *E*–*Z* isomerizations, two approaches can be distinguished: one leads to change of the catalyst’s active site by rearranging multiple substrate binding sites to template product formation (Figure 4c), whereas in the other, accessibility to the active site is modulated by steric shielding (Figure 4d).

The first case employing photochromic templates is based on the preorganization of reactants, which is frequently encountered in enzymatic reactions and in bifunctional catalysis, and requires suitable binding sites for the recog-

nitration and orientation of the substrate(s). When two substrate molecules are bound to the active template, the high local concentration (effective molarity) in combination with a forced arrangement, which structurally resembles the transition state, leads to facilitated bond formation (Figure 4c, case 1). However, inhibition, caused by multivalent binding of the product formed, can diminish catalytic turnover. On the contrary, multivalent binding of a given substrate can be used for activation and thus accelerated bond cleavage (Figure 4c, case 2).

The second case utilizes a photochromic steric shield, which controls the access of the substrate to the active site of the catalyst (Figure 4d). In the OFF state a blocking group is fixed in the proper orientation to intercept substrate approaching the active site, while moving away the blocking group to provide free access to the active site in the ON state. Highly efficient shielding is necessary to completely shut down catalytic activity in order to realize high ON/OFF ratios.

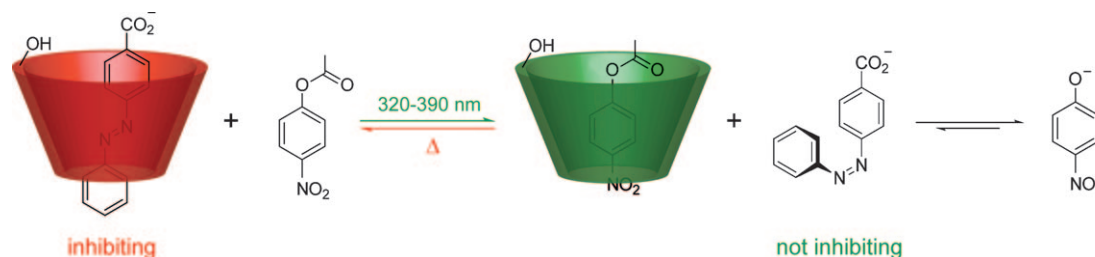
Besides sufficient accessibility of the catalytically active site, its electronic nature is of outmost importance for the performance of a catalyst system, and manipulating the electronics of a catalyst thus constitutes a very fundamental way to control its activity (Figure 4e). In particular photochromes that are based on electrocyclic ring-opening/ring-closing reactions could provide a suitable interface to gate the interplay of electron donating/electron withdrawing groups with the active site. Switching could either couple or decouple the electronically active group to the active site to achieve activation of the catalyst. Although this approach is very promising, it is more than fair to state that it is by no means trivial to design such electronically modulated systems. In the following four subsections, the realization of the design concepts detailed above will be described.

3.2. Photochromic Additives

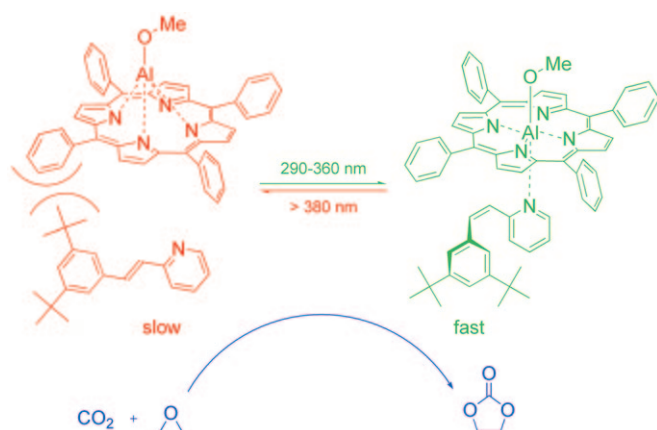
The first example of a photoswitchable catalyst system was described by Ueno and co-workers as early as in 1980 (Scheme 6).^[75] β -Cyclodextrin (β -CD) is known to aid the hydrolysis of phenolic ester derivatives by providing a host for the hydrophobic aryl residue of the ester, thereby facilitating nucleophilic attack from one of the nearby peripheral hydroxy groups at the ester moiety. This system was rendered photoswitchable by introduction of 4-carboxyazobenzene as a photochromic inhibitor. β -CD is only able to bind the

extended *E*-isomer of the inhibitor, whereas the kinked *Z*-isomer does not fit into the cyclodextrin cavity.^[76] Systems comprised of β -CD, the 4-carboxylazobenzene inhibitor, and the 4-nitrophenyl acetate substrate showed decreased hydrolysis activity before irradiation compared to irradiated samples in buffered solution (pH 8.7). From control experiments, the authors reasoned that the excess *E*-azobenzene efficiently competes with the phenolic ester for the binding pocket of β -CD, whereas the photogenerated *Z*-isomer is not able to compete owing to steric reasons, and thus ester hydrolysis is accelerated upon irradiation. However, it should be noted that the system does not provide turnover, as the catalyst and inhibitor concentrations exceed the substrate concentration by one and by roughly two orders of magnitude, respectively, and yet the overall effect is still rather small.

Photocontrol of catalysis utilizing a photochromic activator was described by Inoue and co-workers.^[77] Aluminum porphyrins are known to catalyze the reaction of carbon dioxide and propylene oxide to yield cyclic propylene carbonate.^[78] However, conversion is only observed in the presence of axial nitrogen-based ligands, such as *N*-methylimidazole or pyridine. Photocontrol over the rate of conversion was achieved by replacing the pyridine moiety with a photochromic stilbazole derivative acting as a photoswitchable activator (Scheme 7). Steric interactions between the 3,5-di-*tert*-butylphenyl moiety of the *E*-stilbazole and the porphyrin macrocycle presumably prevent efficient coordination of the stilbazole pyridine moiety to the aluminum center, thereby inhibiting conversion in the OFF state. Switching the stilbazole to the sterically less demanding *Z*-isomer enables its coordination to the aluminum center of the porphyrin framework, rendering the overall catalyst system active. Indeed, upon UV irradiation, a tenfold rate acceleration based on propylene carbonate formation was observed under catalytic conditions employing 5 mol% of the aluminum-porphyrin catalyst (with presumably the same amount of stilbazole derivative). Exposure to visible light led to a slowing of product formation, which was presumably due to photochemical *Z*→*E* isomerization and decomplexation associated with deactivation. Although the rates after UV and after visible irradiation approached those measured for the ex-situ prepared systems using isolated *Z*- or *E*-stilbazole, the switching response observed was rather slow and the overall performance of the catalyst system was low, as substantial conversion could only be achieved over the course of several days. Interestingly, photoisomerization of



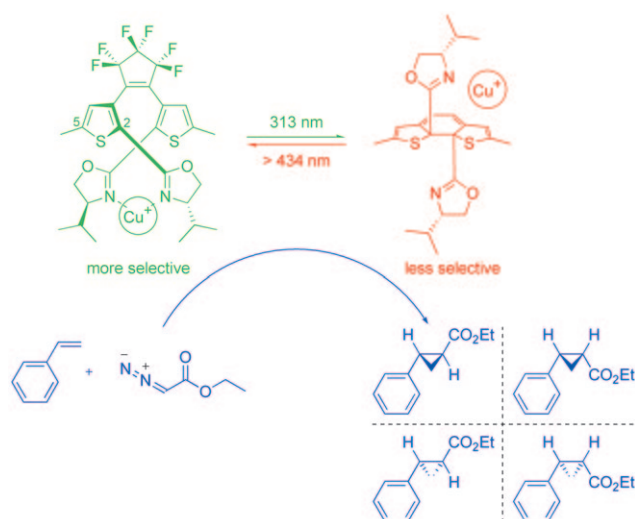
Scheme 6. A photoswitchable azobenzene additive acting as an inhibitor of ester hydrolysis in its *E* configuration by binding to the interior of a β -cyclodextrin (left), whereas the corresponding *Z* isomer does not inhibit substrate binding, and ester hydrolysis is facilitated (right).^[75]



Scheme 7. A photoswitchable ancillary stilbazole ligand controls the activity of an aluminum tetraphenylporphyrin catalyst for carbon dioxide activation by selective axial coordination to the aluminum center in its Z configuration.^[77]

the stilbazole ligand (in both directions) was not hampered by the presence of the aluminum porphyrin complex, which is in line with previous mechanistic studies in related systems.^[79,80]

Successful photocontrol of the stereochemical outcome of a cyclopropanation reaction was demonstrated by Branda and co-workers utilizing chiral dithienylethene (DTE) ligands (Scheme 8).^[81] Classification of this system according to the concepts given in Section 3.1 is not straightforward. When considering the assembly of the catalyst from a Cu^I center and the chiral DTE (see below), the ligand is viewed as a photochromic additive, which influences the stereochemical outcome of the cyclopropanation reaction. However, classifying the ligand as a photochromic template that induces either a chiral or achiral environment also seems appropriate. It should be emphasized that the authors describe switching of



Scheme 8. A photoswitchable bis(oxazoline) ligand with a dithienylethene core shows altered diastereo- and enantioselectivity in the copper(I)-catalyzed cyclopropanation of styrene owing to changes in the ligand geometry, facilitating chelation in the ring-opened form (left) whilst hindering chelation in the ring-closed form (right).^[81]

selectivity rather than reactivity, clearly separating their system from other examples reported in the literature. In light of possible applications, switching of selectivity offers completely different opportunities than switching of reactivity, as the latter allows to change the connectivity of atoms whereas selectivity switching allows to control the relative orientation of atoms within compositionally identical molecular entities (see Section 4).

Structural changes associated with the ring-closure/ring-opening of DTEs are small when considering substitution in 5 and 5' positions, which are easily substituted without far-reaching influence on the switching behavior. However, a substantial structural difference is observed for substituents in the 2 and 2' positions of the thiophene moieties as their spatial separation is increased considerably upon conrotatory ring closure due to the resulting *anti* orientation. (Scheme 8, top). Exploiting these structural differences between the ring-closed and ring-opened isomers, it was possible to photocontrol the stereoselectivity in the cyclopropanation of styrene catalyzed by copper(I) complexes derived from chiral, bis(2-oxazoline)-substituted DTE ligands and a copper(I) source (Scheme 8).

Complexes generated from the ring-opened ligand and a copper(I) source are able to transfer the chiral information of the ligand to the styrene substrate employing a diazoester carbene source, leading to modest enantio- and diastereoselectivities (30% *ee* for the *anti* diastereomer, 50% *ee* for the *syn* diastereomer, 55:45 *anti:syn* diastereomeric ratio). On the other hand, in the ring-closed isomer, both oxazoline moieties cannot bind to the same copper center (no chelation possible), which most likely influences complex formation and stability and also the C₂ symmetry necessary to efficiently transfer chirality to the substrate. Thus, employing the purified ring-closed ligand (97% after chromatographic isolation in presence of residual 3% ring-opened isomer) leads to a significant drop in enantioselectivity (5% *ee* for the *anti* diastereomer, 5% *ee* for the *syn* diastereomer) with slightly increased diastereoselectivity (63:37 *anti:syn* diastereomeric ratio). However, ring-closure of the ligand in presence of copper(I) leads only to a weak drop in enantioselectivity (11% *ee* for the *anti* diastereomer, 37% *ee* for the *syn* diastereomer, 70:30 *anti:syn* diastereomeric ratio) because the PSS is comprised of only 23% of the ring-closed isomer. This result could be reproduced by assembly of the catalyst from a PSS mixture of the ligand and a copper(I) source.

Although these observations showing modest selectivity changes for the two isomers are a first proof of concept, the system suffers from the drawback of limited photoswitchability. The 2,2'-disubstitution pattern of the DTE system imposes a steric hindrance upon the ring-closure event, leading to only a minor amount of ring-closed isomer being present in the PSS, in line with earlier findings by Irie and co-workers.^[82,83] Furthermore, reversibility of photoswitching is hampered by the tight binding of the ligand to the copper center, and only addition of acetonitrile as competitive ligand to the dichloromethane solution enables some degree of reversible ring closure and ring opening associated with a $\Delta ee = 13\%$ (23% *ee* for ring-opened and 10% *ee* for the PSS

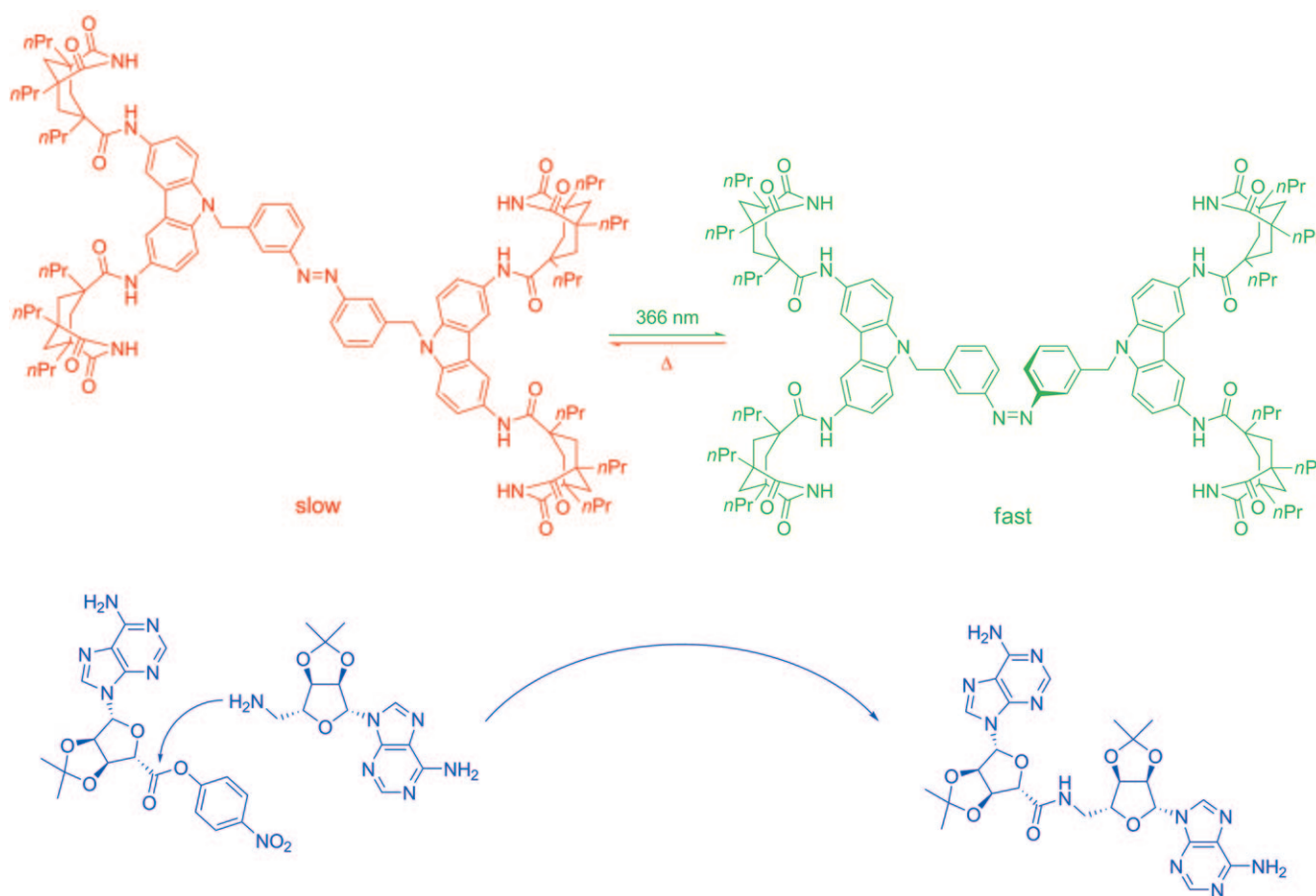
mixture in case of the *anti* diastereomer). Apart from low conversion to the ring-closed isomer, the ring-opened ligand displays rather low enantioselectivities, which is presumably due to the substantial flexibility and thus the larger number of accessible conformations compared to other well-established rigid bis(oxazoline) ligands.^[84] Another factor is the suboptimal fit of the metal ion into the binding site of the ligand; therefore the possible selectivity differences are intrinsically rather limited.

3.3. Photochromic Templates

The first example of a photochromic template was described by Würthner and Rebek, who exploited an azobenzene scaffold to arrange two substrate binding sites (Scheme 9).^[85] They utilized carbazole-based receptors derived from Kemp's triacid, which is known to efficiently bind adenine moieties, and connected them by a photochromic azobenzene core. This strategy enabled successful photocontrol of amide bond formation between substrates carrying the necessary adenine residues. In the complex of both substrates with the kinked *Z*-azobenzene receptor, the reactive groups (the amine nucleophile and 4-nitrophenylester electrophile) are arranged in close proximity, leading to a

significant increase of the effective concentration of the substrates. This accelerates the rate of amide bond formation compared to the more extended *E*-isomer, which does not allow for such favorable orientation of the reactants. Indeed, upon irradiation at 366 nm and formation of ca. 50 % *Z* isomer, a circa tenfold rate acceleration could be observed, whereas the *E* isomer showed only a small rate acceleration of 1.2. By determining the binding constants of the substrate to the templates and calculating the concentrations of the termolecular complexes, the authors deduced that the *Z* isomer is approximately 50 times more active in catalysis than its corresponding *E* isomer.

However, even in the absence of catalyst, the rate of amide formation is relatively fast, limiting the accessible ON/OFF ratio. Furthermore, product inhibition^[86] is a severe drawback for this and in fact many templating systems due to the close structural relation between substrates and product. Equimolar amounts of template are therefore required for efficient substrate conversion. However, due to the unfavorable PSS composition, which comprises only 50 % of reactive *Z* isomer, the effective loading of ON state catalyst is only 50 %, and one-half of potential catalytic activity is therefore neglected. The low content of *Z* isomer in the PSS is attributed to the marked carbazole absorption in the wavelength region of azobenzene absorption and underlines the



Scheme 9. A photoswitchable template with an azobenzene core and two terminal nucleoside receptors enables control by light over amide bond formation by proper pre-organization of both bound substrates in the *Z* configuration.^[85]

importance of proper catalyst design, not only taking geometrical considerations into account, but also the photo-physical characteristics of all catalyst components (see Section 3.1). Furthermore, suitable reactants have to be equipped with adenine residues, which are essential for binding to both receptor sites of the photochromic template.

A related template approach was devised by Cacciapaglia et al. to photocontrol the rate for ethanolsysis of 4-carboxy-acetanilides in basic solution (Scheme 10).^[87] Dinuclear alkaline-earth-metal ion complexes of bis-crown ethers connected by a suitable spacer unit are known to catalyze the ethanolsysis of acetanilides that carry a distal carboxylate group to ensure binding to both metal ions. The metal centers need to be in close proximity to ensure a two-point binding mode of the anilide. In conceptual analogy to the work by Shinkai^[88] and Ueno,^[89] the authors realized that an *E*-azobenzene spacer would be too extended to allow for two-point binding, whereas the more contracted *Z* isomer should favor this binding mode. Molecular models confirmed the intended close proximity of both metal centers in the ON state catalyst that is ideal for the necessary two-point binding of the acetanilide substrate (Scheme 10, bottom). Indeed, when comparing irradiated with thermally equilibrated samples, activity ratios between the *Z* and *E* isomers of 5 to 6 were observed for the ethanolsysis of two different types of acetanilide substrates. Note that the PSS for *E*→*Z* switching is comprised of 95 % *Z* isomer, ensuring an efficient generation of ON-state catalyst, while photochemical *Z*→*E* switching leads to PSS mixtures composed of 81 % *E* isomer and

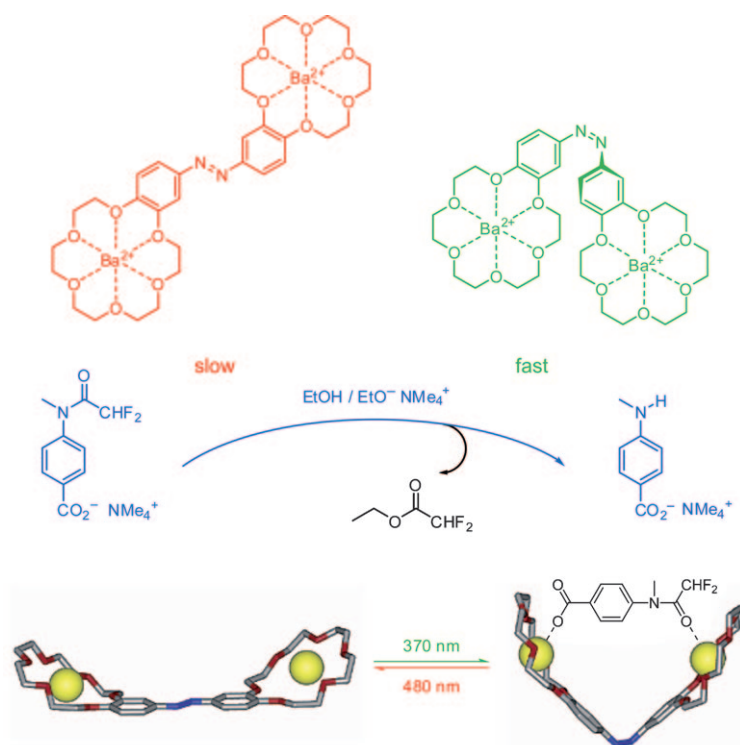
19 % *Z* isomer. Taking these numbers into account, the practically accessible ON/OFF ratio is approximately 3. The authors could successfully switch their catalyst system several times in situ, leading to an alternating activity profile. Furthermore, they were able to demonstrate control over conversion by changing either irradiation wavelength or exposure time.

Similar to other systems discussed above, the catalyst performance is hampered by a substantial OFF-state reactivity (the authors thus label this state the “LOW state”), which can be attributed to the high flexibility of the crown ether moieties that allow activating binding events to occur even in the extended *E* isomer. Furthermore, as expected from the close structural relation of substrate and product, product inhibition comes into play at higher conversions. Therefore, equimolar amounts of catalyst had to be employed for efficient catalysis, and the system does not exhibit turnover. Furthermore, the strict structural requirements needed for fitting the substrate into the activating binding pocket significantly narrow the scope of the system to the hydrolysis of specific tertiary aromatic amides that was investigated, and an extension to a broader class of catalyzed chemical transformations is hardly conceivable.

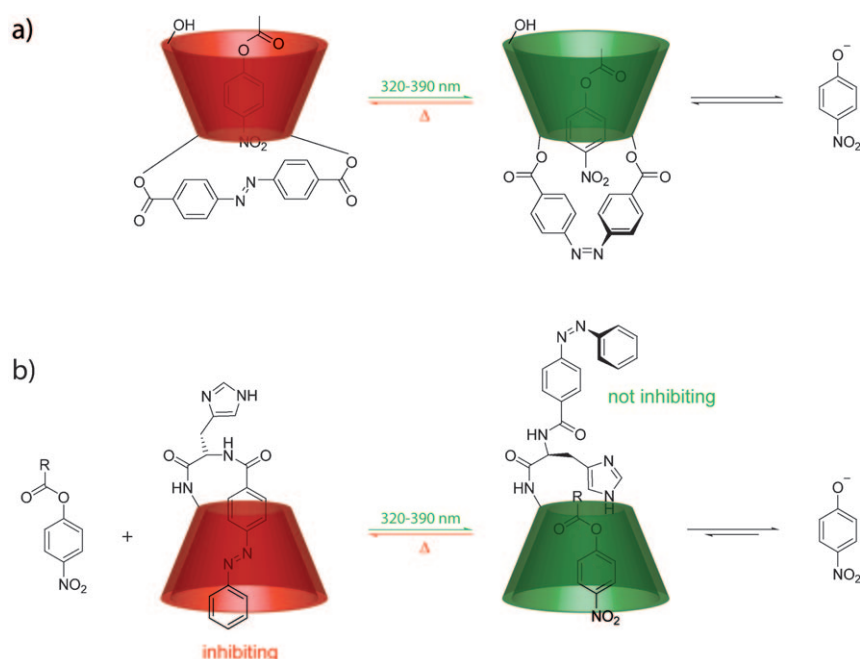
3.4. Reversible Steric Shielding

The development of photoswitchable catalysts based on β -CDs by Ueno and co-workers (see Section 3.2 and Scheme 6)^[75] was complemented by covalently linking the photochromic azobenzene with the catalytically active macrocycle.^[90,91] Capping the smaller opening of the β -CD with a 4,4'-bis-(carboxy)azobenzene allowed the binding behavior to be photomodulated by dictating the depth and thus size of the hydrophobic pocket via the photochromic bridge (Scheme 11a).^[90] The more extended *E* isomer closes the cyclodextrin tightly and provides a rather shallow cavity, whereas the bent *Z* isomer leaves considerably more space at the base, thereby opening a deeper cavity with enhanced binding affinity. As the substrate binding behavior and thus catalytic activity is modulated by steric means, the system is classified as a reversible steric-shielding approach.

Irradiation with UV light gave solutions having a different content of the *Z* isomer, depending on concentration, which were used for the hydrolysis of 4-nitrophenyl acetate in buffered solution (pH 8.7). A maximum 5.5-fold rate acceleration was observed for an irradiated sample containing 38 % of *Z* isomer compared to the same sample in thermal equilibrium, that is, solely composed of the *E* isomer. Although detailed kinetic analysis proved difficult due to the presence of both isomers in solution and their varying ratios at different concentrations, applying the Michaelis–Menten catalytic scheme revealed that two opposing effects are operating in this system: The *Z* isomer leads to



Scheme 10. A photoswitchable template with an azobenzene core and two terminal barium-ion-containing crown ethers allows for photocontrol over ethanolsysis of acetanilides by proper pre-organization of the substrate in the *Z* configuration.^[87]



Scheme 11. Photoswitchable azobenzene-capped β -cyclodextrin macrocycles.^[90,91] a) $E \rightarrow Z$ photoisomerization leads to a deeper cavity and enhanced substrate binding that overcompensates a slightly reduced hydrolysis rate for 4-nitrophenyl acetate.^[90] b) While the E -azobenzene derivative acts as a tethered inhibitor (left), its corresponding Z isomer enables substrate binding and presents a catalytically active imidazole moiety (right).^[91]

enhanced substrate binding by roughly one order of magnitude owing to the deeper hydrophobic pocket that is provided compared to the E isomer. However, once the substrate is bound to the cyclodextrin host, the E isomer is able to catalyze the hydrolysis about twice as fast as the Z isomer, which is presumably due to a more favored orientation to yield the tetrahedral intermediate. As the increased substrate binding outweighs the slowed hydrolysis rate for the Z isomer, an overall rate acceleration was observed upon irradiation. It should be noted that the system also does not exhibit turnover, because an excess of catalyst over substrate was necessary to compensate for unfavorable product inhibition.

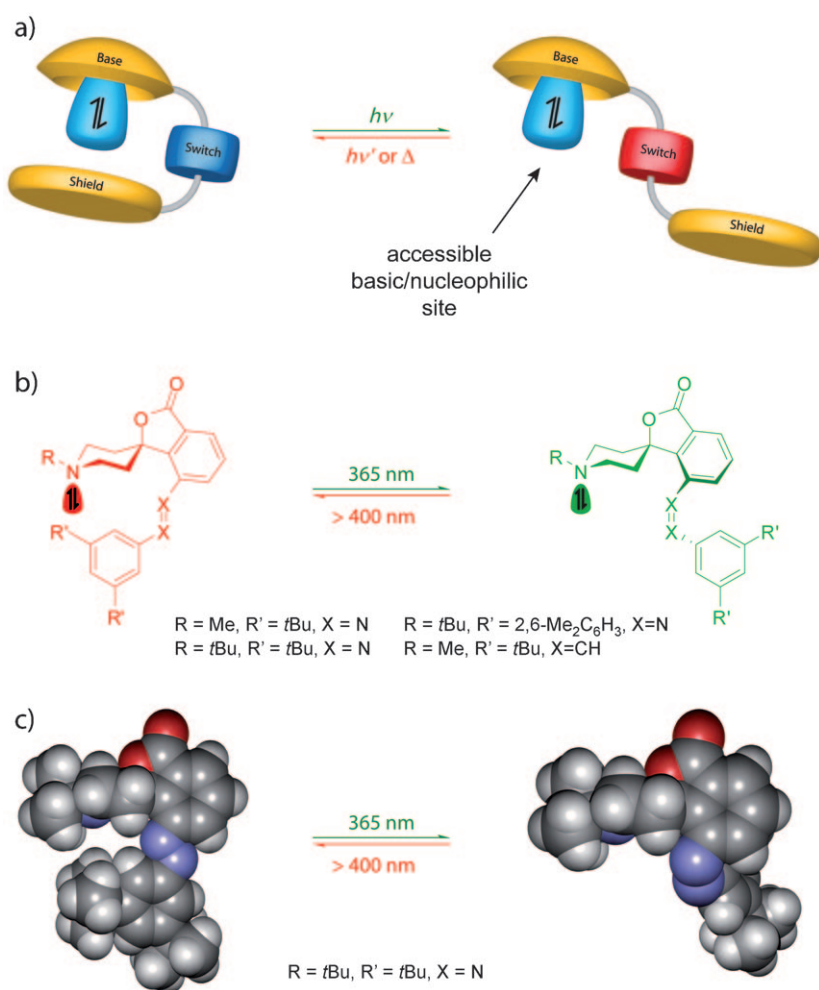
More than two decades later, the group of Ueno reported a similar design, which more closely resembled a covalent version of their initial photochromic inhibitor concept (see Section 3.2 and Scheme 6).^[75] The authors covalently attached an azobenzene moiety to the smaller opening of β -CD via a histidine linker (Scheme 11b).^[91] In the OFF state, the E isomer of the azobenzene occupies the cavity and prevents binding of the substrate. However, in the ON state, the kinked Z isomer does not fit into the β -CD cavity and the substrate can bind. Importantly, the imidazole residue of the histidine linker aids the catalysis in a similar fashion as in the catalytic triads of naturally occurring proteases. Upon irradiation, about 80 % of Z isomer was formed, and the catalytic activity of dark and irradiated samples in the hydrolysis of various 4-nitrophenolic esters in buffered solution (pH 7.2) was investigated. Detailed kinetic analysis with catalyst loadings as low as 2.5 mol % showed that only the Z isomer catalyzed the reaction, whilst the E isomer displayed no catalytic activity in

the Michaelis–Menten sense as no substrate binding was observed. However, the Z isomer showed a largely reduced enantioselectivity for hydrolysis of Boc-protected L- and D-configured 4-nitrophenolalanine compared to a suitable reference compound carrying no azobenzene moiety. This result may be explained by interaction of the substrate with the Z -azobenzene moiety, which seems to remain in close contact to the rim of the cyclodextrin, as shown by induced circular dichroism.

While the previous two examples are based on photocontrolled steric shielding of the substrate binding site, that is, the cyclodextrin cavity, another approach followed by our group is the photocontrolled shielding of the reactive functionality of the catalyst, that is, the active site. After initial attempts to render metalloporphyrins photoswitchable by sterically blocking access to their metal centers failed due to detrimental energy transfer from the azobenzene blocking groups to the porphyrin core,^[72] we focused on photo-

physically innocent organocatalysts.^[92] We therefore sought to reversibly shield one of the most general reactive functionalities, the lone pair of a nitrogen atom, thus impairing both its basicity and its nucleophilicity (Scheme 12a). Our initial design was based on a piperidine scaffold, in which a spiro junction enables attachment of a sterically bulky photochromic azobenzene shield in a rigid and orthogonal fashion (Scheme 12b).^[93] The conformation of the catalyst in the OFF state (E isomer) is largely restricted, thus efficiently shielding the trajectories leading to the reactive lone pair of the piperidine. This was shown by single-crystal structural analyses for three different derivatives (one selected example is shown in Scheme 12c, left) and also extensive NMR studies in solution using residual dipolar couplings.^[94] Upon irradiation, $E \rightarrow Z$ isomerization is induced, leading to a relative movement of the 3,5-disubstituted azobenzene terminus away from the piperidine moiety and therefore granting access to the basic/nucleophilic nitrogen atom. In one case, single crystals of the Z isomer could be grown, and the X-ray analysis revealed the structural basis of our photoswitchable catalysts (Scheme 12c). It should be noted that in all cases, almost quantitative conversion to the Z isomers could be achieved; these showed significantly enhanced thermal half-lives of up to 20 days, which is in strong contrast to the parent azobenzene with a half life of 16 h at room temperature.^[95]

The structural reorganization upon $E \rightarrow Z$ isomerization is clearly manifested in the different reactivity of both switching states. Acid–base titration experiments in acetonitrile reveal a difference in pK_a values of approximately one unit, which corresponds to an enhancement of the Z -isomer basicity by almost one order of magnitude: from 15.9 for the E isomer to



Scheme 12. Photoswitchable azobenzene-based piperidines as light-controlled general base catalysts.^[93,94] a) Concept of light-triggered reversible steric shielding of a basic/nucleophilic site. b) Chemical structures of investigated azobenzene and stilbene derivatives with optimized substitution pattern to achieve high ON/OFF ratios. c) Structural comparison between shielded *E* isomer (left) and accessible *Z* isomer (right) based on single crystal X-ray structures (van der Waals radii shown).

16.7 in the case of the *Z* isomer (Scheme 12c). Considering that the proton is the smallest possible electrophile, these changes seem rather remarkable, and more pronounced effects are expected for interactions with bulkier electrophiles. Consequently, the photoswitchable piperidines were exploited as general base catalysts in a nitroaldol (Henry) addition of nitroethane to 4-nitrobenzaldehyde. Optimizing the structure of the catalyst by introducing suitable substituents at the piperidine N atom to prevent N-inversion and at the 3,5-positions of the azobenzene terminus to more efficiently block the pyridine nitrogen atom led to an enhancement of the ON/OFF ratio to more than 35. Although replacement of the azobenzene by a stilbene moiety led to P-type photochromicity and a remarkable PSS composed of 97% *Z* isomer, photochemical *Z*→*E* isomerization could only recover 23% of the *E* isomer and the catalyst displayed a disappointing ON/OFF ratio of 2.^[94]

Due to the mediocre activity of the piperidine catalysts, necessitating catalyst loadings of 10 mol%, all catalysis

experiments were performed with ex-situ-prepared and separated *E* and *Z* isomers, as the large optical density of the reaction mixture (due to the relatively high concentration) prevented efficient switching in solution. To overcome this rather technical issue and to truly harness the spatial resolution possible by irradiation, we engaged in immobilizing the catalyst on a solid substrate surface (Scheme 13).^[96] In addition to immobilization, true confinement of reactivity to the irradiated areas is furthermore needed to prevent product diffusion processes, either by catalyzing living polymerizations and/or by working in thin films.

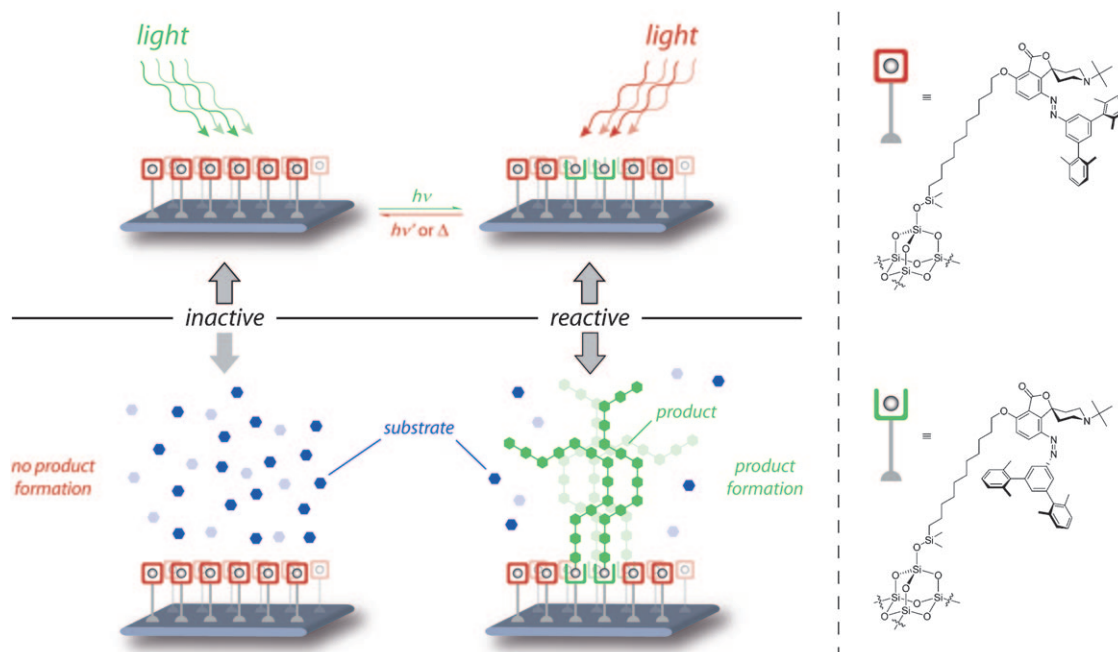
Introduction of a monochlorosilane functionality to the piperidine catalyst scaffold enabled its immobilization on silica gel. Several successful and fully reversible switching cycles at the surface were demonstrated by UV/Vis absorption spectroscopy of suspensions in dichloromethane. Notably, the pH of a suspension of these functionalized silica particles in water could be photo-modulated by approximately 0.3 units, which might after optimization lead to interesting applications in the context of photocontrolling natural systems by reversible light-induced pH changes.

Although these examples illustrate the power of structure-based optimization, the system suffers from the low intrinsic activity of the piperidine lead structure, which limits the general scope of the catalyst system and the attainable ON/OFF ratios. Furthermore, the localization of catalytic activity achieved by immobilization is lost in the course of small-molecule reactions due to facile product diffusion (see Section 4).

3.5. Switching of Electronic Characteristics

It is surprising that no example of successful reactivity switching by a photochrome-mediated electronic modulation of a catalyst's active site has been described to date. The only exception is the photocontrol of CO₂ fixation by utilizing an aluminum porphyrin complex in combination with an activating stilbazole ligand acting as a photochromic activator, which has already been described in Section 3.2 (see Scheme 7).^[77] There is no apparent reason for the lack of examples involving electronic modulation of the active site, and we are convinced that in the future this approach will become very powerful, in a similar fashion to classical physical organic chemistry exploring linear free-energy relationships over the past decades.

An encouraging example that does not involve catalysis but demonstrates the feasibility of electronic modulation has recently been reported by Branda and co-workers, who

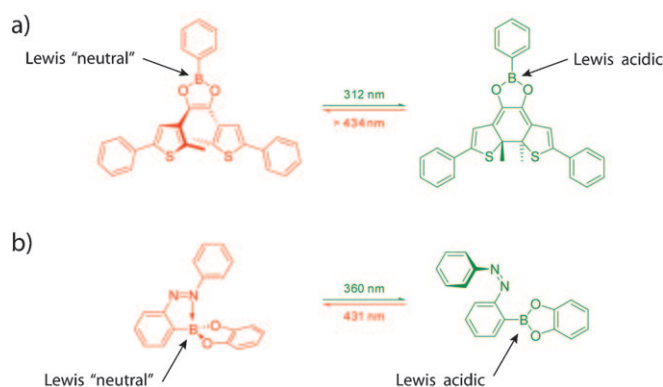


Scheme 13. Immobilizing photoswitchable azobenzene-based piperidines on silica gel (right) to prevent diffusion and associated loss of spatial resolution, potentially enabling spatial control over polymerization processes (left).^[96]

designed a DTE photoswitch carrying a central dioxaborole bridge (Scheme 14a).^[97] In the ring-opened form, the vacant p orbital of the boron atom is part of the planar aromatic system containing $4n + 2$ ($n = 1$) π electrons and thus displays very low Lewis acidity. Upon irradiation however, the borate group becomes cross-conjugated with the linearly π -conjugated DTE backbone and therefore the Lewis acidity of the boron atom is remarkably increased. The intended and computationally predicted alteration of Lewis acidity upon photoswitching has been verified experimentally by means of Lewis acid–base titration experiments monitored by ^1H NMR. While in the presence of large excess of pyridine

no signal shifts and thus negligible binding were observed for the ring-opened isomer, in the case of the ring-closed isomer, significant NMR shifts were found and these were fitted to a binding constant of approximately 7000 L mol^{-1} . Clearly, the ring-closed isomer interacts much more strongly with the Lewis base pyridine than its ring-opened counterpart. Furthermore, the authors found that the photochromic performance of the DTE system could be retained upon bridge substitution (the PSS reached after 12 s is composed of 81 % of the ring-closed isomer) and in the presence of pyridine (the rate of ring-opening is only about four times slower in the presence of pyridine as compared to its absence). Therefore, the pyridine could be released upon ring-opening. In an alternative approach the Branda group has exploited a pyridine DTE derivative to photomodulate its nucleophilicity, and first results on preliminary catalysis studies have been presented.^[98]

Earlier Kawashima and co-workers reported another system in which the Lewis acidity is affected by changing the coordination number of a boron center with the aid of a nearby azobenzene moiety (Scheme 14b).^[99] The authors explored *ortho*-substituted azobenzenes extensively to photocontrol the coordination environment of various main group elements (B, Si, P)^[99,100] and thus their reactivity. In the *E* isomer, the remote nitrogen atom of the azo group can engage in efficient σ donation to the boron center. Upon light-induced *E* \rightarrow *Z* isomerization, this intramolecular Lewis acid–base interaction disappears and the empty p orbital on boron can interact in an intermolecular fashion with an external Lewis base, such as pyridine. This is reflected in the 300-fold increased binding constant of the *Z* isomer to pyridine compared to the corresponding *E* isomer. The stabilizing Lewis acid–base interaction present in the



Scheme 14. Photoswitchable boron-derived Lewis acids:^[97,99] a) Upon photochemical ring closure of a dithienylethene (DTE), the aromaticity within the integrated dioxaborole bridge is lost and the central boron atom becomes more Lewis acidic.^[97] b) An appended photochromic azobenzene moiety is an efficient donor in the *E*-configuration forming a stabilizing B–N bond, where the corresponding *Z* isomer cannot yield such adduct and the boron atom becomes more Lewis acidic.^[99]

E isomer detrimentally affects the *E*→*Z* photoisomerization, as only 51 % of the *Z* isomer could be obtained even after prolonged irradiation times. It should be noted that to date, neither Branda's nor Kawashima's system have been used as photoswitchable Lewis acids to control any chemical transformation, for example as activators, reagents, or catalysts, as they suffer from the severe drawback of substantial instability towards oxidation.

Apart from Lewis acids, Brønsted acids can also be generated reversibly by proton-transfer reactions, for example involving *ortho*-nitrobenzyl derivatives,^[101] whereas Brønsted bases can be formed in the course of the ring-opening of spiropyranes^[102] and spirooxazines. The latter system has been used to introduce light sensitivity to a variety of supramolecular systems by the groups of Raymo and Credi.^[103] In one case they reported the reversible light-induced activation of a singlet-oxygen-sensitizing osmium bisterpyridine complex with appended protonated pyridyl functions, which does not generate singlet oxygen in the presence of the spiropyran form.^[104] Photochemical ring-opening to the merocyanine form yielded the basic phenoxide, which immediately led to deprotonation of the complex, thereby unleashing the active singlet oxygen sensitizer. Although this example certainly represents an example of a photoswitchable catalyst system, the subsequent process of singlet oxygen generation takes place on the excited state potential energy surface and thus requires stoichiometric amounts of photons.

4. Outlook

In the previous sections, we outlined the different conceptual approaches to achieve light-gating of homogeneous chemical reactions by using a well-designed catalyst. The various designs were divided into photocaged and photoswitchable catalysts and catalyst systems enabling either irreversible or reversible gating processes, and the most important (and often the only known) examples were discussed in view of their mode of action, their advantages and drawbacks, and their potential for various applications. While we have tried to convey the excitement over the rapid development of the field and the great potential of remotely controlling chemical processes by means of such sophisticated catalysts, the careful reader has undoubtedly noticed eminent problems, potential drawbacks, and remaining challenges. In this final section, we therefore try to address some of these critical points and sketch some future vision of the field, both of course coming from our own current perspective.

Beyond activity control: Throughout this review we have focused on catalytic activity, encoding the ability of the catalyst to enable and speed up an otherwise unfeasible chemical reaction. However, one of the inherent challenges in catalyst research is not only the mere enabling of a given chemical transformation but also the complete control over its outcome by developing suitable catalysts to dictate chemoselectivity, regioselectivity, and stereoselectivity of the reaction. Applying these features to polymerization processes would be particularly beneficial in this context, as

polymers allow to maintain the localization of a spatially resolved light stimulus (see Section 3.4 and below). Thus it would be possible to have control over practically all important aspects of polymer architecture:^[105] temporal control over activity would relate to chain length (and polydispersity, assuming rapid initiation/termination), control over chemoselectivity would relate to monomer composition (block versus gradient versus random), control over regioselectivity would relate to monomer connectivity (linear versus branched), and control over stereoselectivity would relate to tacticity. This illustrates the great potential of photoswitchable polymerization catalysts, which could enable the control over one and ideally all of these features.

Increasing complexity and implementing regulation: Integration of several features, for example activity and selectivity control, into one catalytic entity would lead to dual-mode catalysts, which could be controlled by two different stimuli, for example two different wavelengths or one wavelength in combination with temperature or pH changes. Combination of various different stimuli, either orthogonal or additive,^[106] should enable the programmed production of complex yet defined polymer products and small-molecule product mixtures. Furthermore, the photocontrolled generation of activators or inhibitors during the course of the reaction should impart advanced regulative functions, that is, positive and negative feedback loops, respectively.

Photocontrolling relevant processes: The key advantage of light-gated catalytic systems lies in the ability to precisely address them in time and space and thus any future impact of this field has to exploit this unique feature. While for biological investigations and medical applications locally induced biochemical reactions are desirable to trigger various processes in certain compartments of a cell or an organism, in the case of materials applications, such small-molecule transformations suffer from the drawback of dissipating the localized stimulus by diffusion and thus the loss of spatial resolution. Clearly, the control over where and when a reaction product is formed has to be harnessed, and for this purpose either living polymerization events or supramolecular polymerizations are attractive processes to control. The first grow covalently bound polymer chains at the site of the catalyst, whose position dictates the site of action, whereas the latter induce non-covalent association events leading to phase transitions, thereby preventing diffusion of the self-assembled entities. For example, highly active catalysts for polymerization processes, such as ruthenium-based ROMP catalysts (see Section 2.4), present attractive current targets to exploit the potential of photoswitchable catalysts in general, and for surface patterning in particular. Furthermore, immobilization of photoswitchable catalysts (see Section 3.4)^[96] could provide a means to the construction of sophisticated flow systems that allow light-controlled (local) concentrations of chemical species.^[87]

Exploiting light-gated catalysis: From an applications perspective, light-gated catalysts have already been successfully implemented in current technology (see Section 2.2). They are the basis of most patterning processes, which typically involve some sort of photolithographic step, but are also particularly interesting for optimizing coating and

gluing processes. Furthermore, photocaging is an important method in chemical biology to study biochemical pathways.^[25] All of the commonly applied systems are classified as photocaged catalysts (see Section 2) and feature a light-induced irreversible one-way activation, as there is typically no need to deactivate the catalyst afterwards.

In these systems, decomposition of the catalyst during the reaction typically terminates the catalytic cycle. The more sophisticated photoswitchable catalysts (see Section 3) offer the unique feature of reversible activation, allowing the triggering of several catalytic cycles, but promising applications that exploit this aspect have yet to be developed. For example, surface patterning should benefit from the ability to grow polymers of defined composition at defined places and times, enabling the creation of gradient surfaces.^[107] Furthermore, periodic switching based on lattice commensurability could provide a means to introduce patterning on the nanoscale using a photochromic surface array.^[108] In the case of biological studies as well, the ability to cycle between two states and thus improve the signal-to-noise ratio in highly sensitive optical measurements is attractive to investigate various processes.

The next steps to take: From a scientific perspective, there is a need to develop light-gated catalysts with broad substrate scope for general and useful transformations (see above) and with high ON/OFF ratios. In particular, high activity differences (ON/OFF ratios) are still difficult to achieve. For this purpose, the most promising ingredients should be combined in the overall system, necessitating an integrative interdisciplinary research approach. On one hand, homogeneous catalysts based on privileged types of transition metal catalysts and general acid/base and nucleophilic organocatalysts should be targeted and rendered light-gated. In particular, bifunctional catalysts involving dual activation of the substrate(s) should provide effective means to implement photoswitchability. The proper design of active and inactive forms of the catalyst system will dictate its ON/OFF ratio. On the other hand, there is a need for improved gating moieties. Photocaging moieties (photoremovable protecting groups) and photoswitches should be optimized with regard to required wavelengths, stabilities, and the efficiency of decaging or switching. Furthermore, the means of exposing the system to the controlling light stimulus should be optimized, for example by utilizing masks, two-photon techniques,^[31] or hybrid systems.^[109,110] To realize a more general approach to photocontrolled catalysts, it seems attractive to use light to gate the accessibility to a given reaction compartment in which the catalyst(s) of choice are located, for example by integrating the light-responsive component into the micellar structure or vesicle walls.^[69g,88,111] The light-responsive component might even be included in biological channels, as demonstrated by Feringa and co-workers when rendering large pore-forming mechanosensitive channel proteins, and thus the access to the hosting liposomes, photoswitchable.^[112] Alternatively, photoswitchable foldamer hosts^[113] might be equipped with internal catalytic functionalities.^[114] Ideally, one suitable photoresponsive host system could thereby be applied in combination with a variety of compatible catalysts to catalyze various and perhaps subsequent transforma-

tions.^[115] These concepts constitute photocontrolled versions of supramolecular catalysis,^[116] which can be furthermore regulated by allosteric effects.^[117]

Turn on the lights! Of course, we are not limited to our expanding yet limited organic chemist's toolbox, and it seems highly desirable to equip biological machinery, such as the ribosome, with a light-gated remote control. Furthermore, promising new catalytic environments and vehicles, such as porous materials, most notably metal and covalent organic frameworks,^[118] but also viruses, cells, and even entire organisms^[119] are attractive targets for photocontrol of their action, which would enable many exciting possibilities. In view of the emerging global energy shortage, the future will witness an ever-increasing demand to exploit light as a stimulus and energy source.^[120] Modern communication technologies for example already rely on photon signals and their optical manipulation. Chemistry is in the unique position to provide a suitable interface as it can create smart (macro)-molecules and supramolecular assemblies thereof and thereby advance these technologies even further. In our view, artificial light-gated catalyst systems are one, yet only one, important component in future advanced materials and devices. Clearly, as progress continues there is a constant need for new stimulating concepts and thrilling ideas and we are only limited by our imagination!

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