Chem Soc Rev

REVIEW ARTICLE

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View Journal | View Issue

Cite this: *Chem. Soc. Rev.*, 2014, **43**, 1982

Remote-controlling chemical reactions by light: Towards chemistry with high spatio-temporal resolution

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Received 28th October 2013

DOI: 10.1039/c3cs60383k

www.rsc.org/csr

The foundation of the chemical enterprise has always been the creation of new molecular entities, such as pharmaceuticals or polymeric materials. Over the past decades, this continuing effort of designing compounds with improved properties has been complemented by a strong effort to render their preparation (more) sustainable by implementing atom as well as energy economic strategies. Therefore, synthetic chemistry is typically concerned with making specific bonds and connections in a highly selective and efficient manner. However, to increase the degree of sophistication and expand the scope of our work, we argue that the modern aspiring chemist should in addition be concerned with attaining (better) control over *when* and *where* chemical bonds are being made or broken. For this purpose, photoswitchable molecular systems, which allow for external modulation of chemical reactions by light, are being developed and in this review we are covering the current state of the art of this exciting new field. These "remote-controlled synthetic tools" provide a remarkable opportunity to perform chemical transformations with high spatial and temporal resolution and should therefore allow regulating biological processes as well as material and device performance.

Introduction

The creative force of chemistry is primarily evident through the emergence of new substances and materials with unprecedented functions. They are typically the result of designing and synthesizing new molecules that exhibit specific properties, ranging from biological activity (pharmaceuticals) all the way to device performance (materials). Hence, the impact of chemistry on society largely depends on the success of making new molecules in an environmentally benign and sustainable manner. For this

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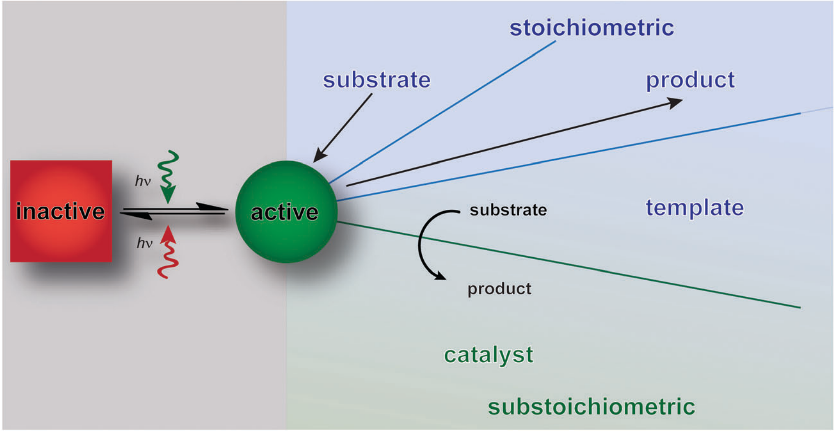


Fig. 1 Controlling chemical reactions with photoswitches: Toggling a photochrome between two forms of different reactivity in their ground states enables external control over covalent bond formation (and scission). The photoswitchable system can be exploited either using stoichiometric processes (serving as the substrate, product or template) or substoichiometric processes (serving as the catalyst).

reason over the past decades, chemical research, in particular in industry, has been primarily concerned with developing new chemical transformations and applying them to generate new drugs, scaffolds, and polymers. These endeavors have been complemented by a more recent surge to perform "green" chemical reactions, which has led to better atom economy and energy efficiency, facilitated by the development of (recyclable) catalysts with boosted efficiency and selectivity as well as advanced reaction engineering (micro-reactors, reaction media such as supercritical CO_2 or ionic liquids) and improved purification methods. Today, the research in this field continues to flourish and there are many tools developed by and available to the synthetic chemists.

However, besides being concerned with *what* and *how* to make, we argue that it will become increasingly important for chemists to control *when* and *where* chemical reactions take place. The ultimate goal is to perform chemical processes with high temporal and spatial resolution, which would allow one to time reactions, for example in simple cascades or complex chemical networks, and to localize them, for example in 2D patterns for array chip technologies. Ideally, control over time and space of the chemical transformation of choice is provided by an entity, the gate, which upon the action of an external stimulus acts as a "remote control".

Regarding the quest to attain the best possible control, superior spatial resolution is clearly provided by an STM tip, which can be used to induce chemical reactions on the nanoscale.[1] A clear drawback of using an STM is the slow speed, rather serial processing, and limited scale-up. Other stimuli such as temperature or mechanical forces suffer from poor spatial resolution besides other limitations and offer little parallelization capability.[2] It is generally accepted that light serves by far as the best stimulus to operate the gate entity. While the choice of the wavelength and intensity allows for precise triggering of a specific photoreaction, the exposure can be carried out using modern optics thereby enabling highly parallel processes. In addition to providing superb temporal control over illumination, spatial resolution that is traditionally limited due to the law of diffraction has recently been improved significantly by super-resolution techniques[3] and two-photon processes.[4]

To use light for gating a chemical reaction, the gate entity can either undergo an irreversible or a reversible photoreaction. While the first allows for a singular activation or de-activation event in a *fuse*-like fashion only, the latter provides the opportunity to toggle between two states multiple times allowing us to *switch* the system and hence the entire chemical process. Therefore, only reversible photoreactions, which are typically associated with the phenomenon of photochromism, provide true "remote-control" over the chemical process by light.

Here, we cover the increasing number of such photoswitchable systems, which display external control over thermal (ground-state) chemical reactions (Fig. 1). After describing key design criteria for merging photochromic and reactive units, we first discuss approaches that utilize the photoswitch in a stoichiometric manner, for example to control substrate, product or template of a reaction, followed by a survey of photoswitchable catalytic systems.[2,5] Finally, we identify future challenges and opportunities of this exciting and rapidly developing field.

General design considerations

In order to design photoswitchable systems that are capable of controlling ground-state, *i.e.* thermal chemical reactions, suitable photochromic gates[6] have to be incorporated into the system in a manner that the structural differences between their two switching states are translated into different chemical reactivity. Therefore, one has to optimize the intrinsic switching properties of the photochrome itself as well as the way it is intersecting with the gated chemical reaction.

The performance of a photochrome is best described by the efficiency and robustness of the light-induced forward and backward switching. The degree of attainable photoconversion,

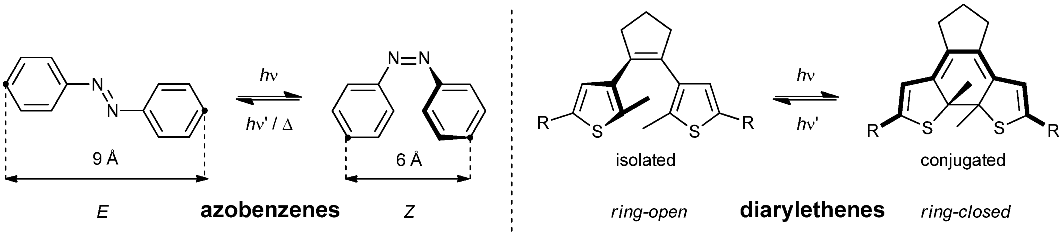


Fig. 2 Molecular structure changes upon either *E*/*Z*-isomerization of azobenzene or 6π-electrocyclization of diarylethene photoswitches.

i.e. the composition of the photostationary states (PSSs) for forward (and backward) switching, is governed by the ratio of the absorption of both switching forms (typically geometrical isomers or valence tautomers) at the used irradiation wavelength multiplied by the ratio of the quantum yields of the forward and backward photochemical reactions. Ideally, only one form of the switch can be selectively excited and undergoes the respective photochemical reaction with a high quantum yield. Note that there are cases in which the quantum yield is dependent on the irradiation wavelength. Furthermore, it is generally accepted that the sum of the quantum yields for both forward and backward reactions amounts at best to unity. In addition to efficiency, the repeated operation of the switch requires clean and highly reversible photochemistry, which can be attained by suppressing irreversible side reactions by molecular design as well as by removing oxygen from the solvent, thereby giving rise to high fatigue resistance. Depending on the photochrome used, either both switching forms are thermally stable and can only be interconverted by light (P-type photochrome, such as diarylethenes shown in Fig. 2, right) or one of them is meta-stable and reverts back thermally to the more stable form (T-type photochrome, such as azobenzenes shown in Fig. 2, left). While the first necessitates the use of two different irradiation wavelengths, *i.e.* light sources, to toggle the system between its ON and OFF forms, the latter is only ON (or OFF) when being irradiated (assuming a fast dark reaction to the OFF (or ON) state).

The ON state is associated with a higher reactivity as compared to the OFF state and clearly the reactivity difference of the switching states is the handle for remote-controlling the chemical process of choice. To translate molecular changes during the course of photoswitching into reactivity differences, the photochrome should undergo significant geometrical and/or electronic changes (Fig. 2). Large geometrical changes are typically achieved *via E–Z* photoisomerization reactions of azobenzene (or stilbenes), leading to largely reduced distances between the phenyl termini in the bent, non-planar *Z*-configuration when compared to the extended, planar *E*-configuration. Complementary to the systems with large geometrical changes, the electrocyclic ring-closing/ring-opening reactions of 1,3,5-hexatriene systems, for example in diarylethenes (or spiropyranes/spirooxazines or fulgides) result in substantially different electronic properties of the ring-closed isomer as compared to the ring-opened form. It is important to maintain the switching behavior throughout the reaction and therefore the excitation of the photochromic moiety should be selective and local, without interfering quenching processes by energy or electron transfer.[7]

The photochromic gate can be incorporated either directly, *i.e.* by covalent connection to one of the components participating in the reaction, or indirectly, *i.e.* by non-covalent interaction with the same. This review will focus on the former as covalent constructs offer the advantage that they operate (more) independently of concentration as opposed to supramolecular approaches. For an overview regarding the non-covalent interactions of switches on reactivity-controlling entities the reader is referred to the existing literature.[2] In general, the coupling of a photochromic system to gate another thermal reaction can be realized using various concepts depending on the particular geometrical and/or electronic alteration of the switch and the point of interference. Such interference can occur either at the level of the substrate, product or template, leading to stoichiometric processes with maximum overall quantum yields of unity ($\Phi \leq 1$), or at the level of the catalyst or effector, giving rise to an amplification of the light stimulus and overall quantum yields exceeding unity ($\Phi > 1$). All examples have been classified according to the general approach used and are being discussed in the next two sections.

Photoswitchable stoichiometric processes

The introduction of light as a gating stimulus means enabling manipulation of one reaction component in a way that it can be switched from an unreactive state to a reactive state or *vice versa*. This can be achieved through three different approaches. (i) Switching one of the starting materials from an inactive to an active form allows the respective compound to participate in the reaction and to form the desired product on demand (starting material control). (ii) Switching the reaction product from an active form into an inactive form removes the compound from the initial equilibrium between the reactants and thus locks the product in an unreactive state (product control). (iii) Switching neither substrate(s) nor product but a ‘‘reaction mediator’’, namely a template, from an inactive to an active form and thereby controlling conversion by supramolecular complexation (template control).

Starting material control

The photoreversible activation of a starting material allowing it to participate in a chemical reaction is conceptually depicted in Fig. 3. As opposed to photocaging, true reversibility can only be

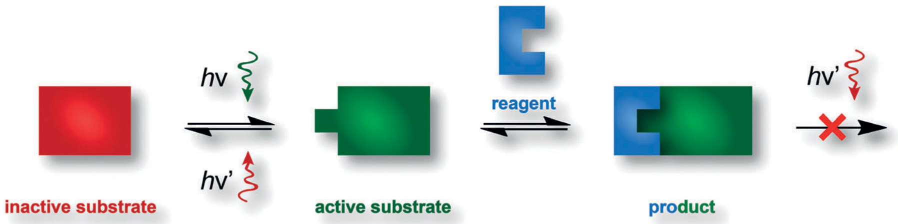
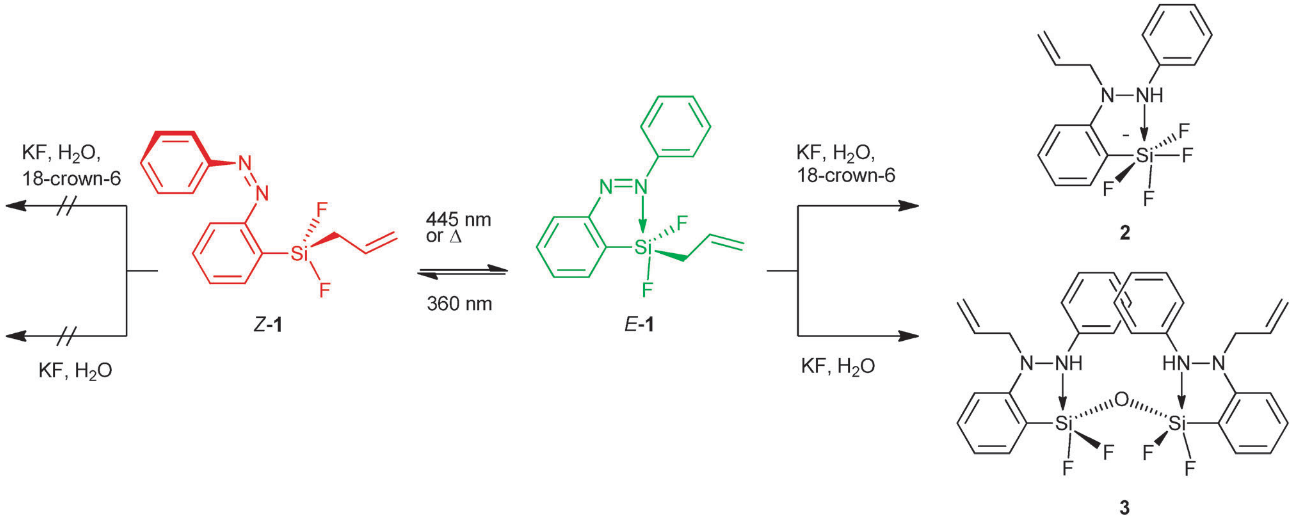


Fig. 3 Concept of starting material control: Photoswitching a substrate between inactive and active forms allows for controlled feeding or removal of a starting material to or from a dynamic covalent equilibrium.

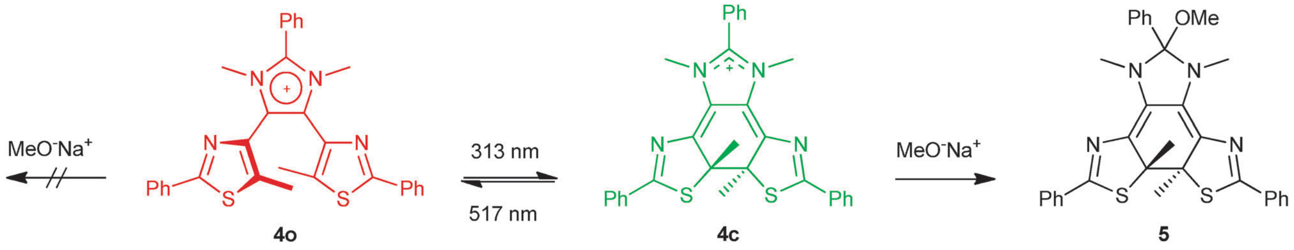
achieved if the photodynamic reaction is coupled to a dynamic thermal equilibrium, *i.e.* the starting material can be reformed thermally and subsequently deactivated by light.

First, Kawashima and coworkers reported silicon fluoride derivatives bearing a covalently attached azobenzene ligand as early as 2001.[8] Photochemical isomerization of the azobenzene from the *Z*- to the *E*-form could reversibly change the complex from the pentacoordinate to the hexacoordinate geometry. The group then transferred this reversible geometry change to an azobenzene substituted allyldifluorosilane **1**.[9] Photoisomerization of *Z*-**1** to *E*-**1** followed by subsequent treatment with 18-crown-6 and potassium fluoride induces an allyl-shift to the azobenzene reducing it to diphenylhydrazine **2** (Scheme 1). However, the original *Z*-isomer is unreactive under those reaction conditions. Further work on this system enabled photocontrol not only over the allyl-shift but also over disiloxane formation (**3** in Scheme 1)[10] and intermolecular hydrosilylation and desilylation reactions.[11] The latter is an exceptional example, as it not only allows the ON/OFF-switching of a reaction but offers the choice between two different reaction types.

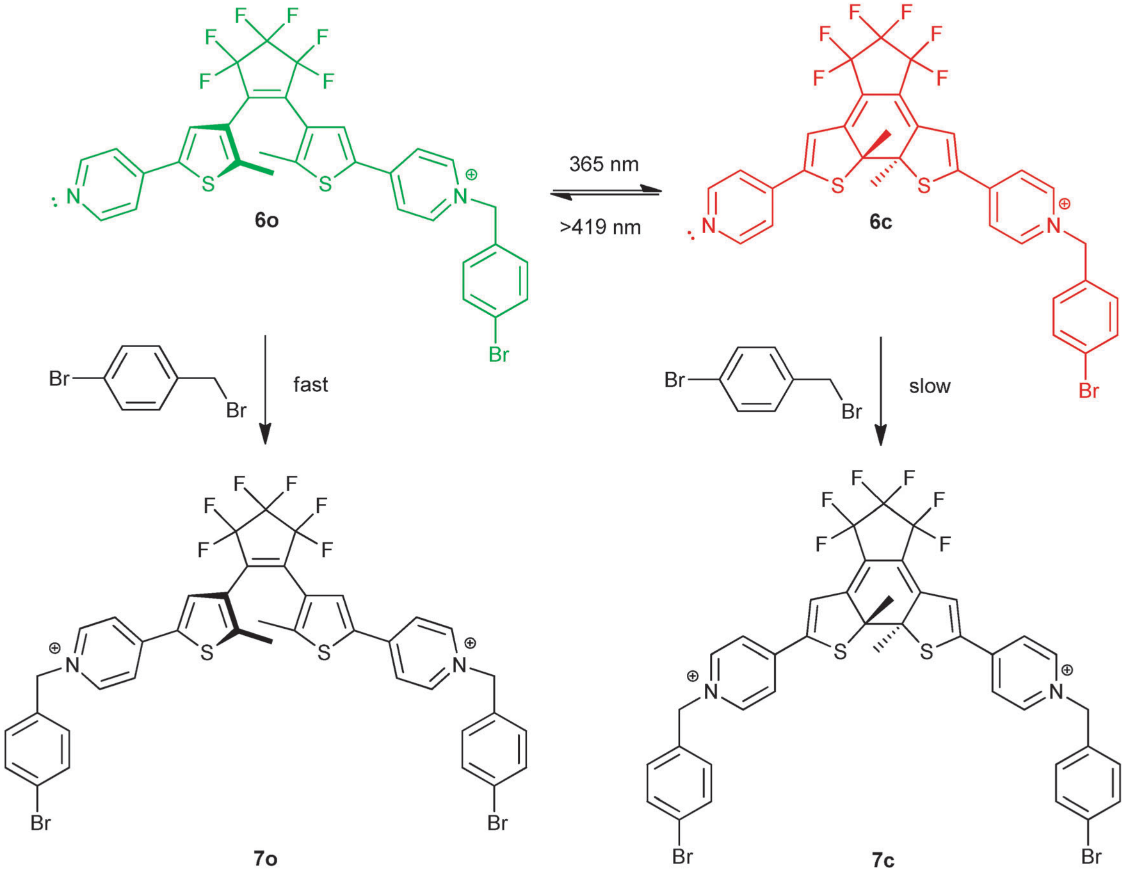
Another elaborate example is the incorporation of an aromatic imidazolium moiety into the bridge position of diarylethene **4o** reported by Kawai and coworkers (Scheme 2).[12] Due to its aromatic stabilization, the imidazolium ion is not prone to nucleophilic addition of methoxide. However, upon photocyclization to **4c** the bridge moiety is transformed into an imidazolinium ion removing the crucial double bond as well as the aromatic stabilization. The closed-form switch can then react reversibly to yield the methanol adduct **5**.



Scheme 1 Photocontrolled allyl transfer reaction of silyl azobenzenes with fluoride yielding hydrazine rearrangement products.[9]



Scheme 2 Photocontrolled addition of methanol to imidazol(in)ium ions embedded in a diarylethene framework.[12]



Scheme 3 Photomodulation of a nucleophilicity by switchable coupling to an acceptor moiety through a diarylethene bridge.[15]

Kawai and coworkers further exploited the combination of photoswitching and aromatic stabilization in benzothienyl substituted terarylenes.[13] The crucial methyl substituent in the 2-position of the aryl moieties was omitted on one benzothiophene and replaced by a methoxy-group on the other. UV-induced photocyclization of this switch to the dihydrophenanthrene derivative enables the elimination of methanol under acidic conditions while generating the aromatically stabilized phenanthrene derivative. This system could be tuned to the point where the authors were also able to achieve photocontrol over the elimination of ethanol and reversible nucleophilic addition–elimination cascades.[14]

Photomodulation of nucleophilicity could be achieved by Branda and coworkers, who reported diarylethene **6** incorporating a pyridyl substituent into one aryl moiety and an electron withdrawing pyridinium group into the other (Scheme 3).[15] In the ring-open form **6o** the two aryl moieties are not in conjugation and thus the nucleophilicity of the pyridyl-lone pair is unbiased in a reaction with *p*-bromobenzyl bromide to **7o**. However, upon UV-induced photocyclization of **6o** to **6c** a conjugation pathway between the two aryl-moieties is opened up and electron density is removed from the pyridyl-lone pair lowering its nucleophilic character and hampering the reaction with *p*-bromobenzyl bromide to **7c** severely.

Product control

In an analogous manner to switching ON the starting materials of a covalent chemical reaction, switching OFF a reaction product crucially demands for the thermal reaction to be in a dynamic equilibrium. Only in this way can the reaction products be removed from the initial reaction mixture and locked in an unreactive state (Fig. 4).

Branda and coworkers synthesized a number of pro-diarylethenes incorporating a *cisoid* diene moiety that can undergo a Diels–Alder reaction with the corresponding dienophile. Upon adduct formation, a 6π-electron system is generated and photocyclization can be induced by UV light removing the diarylethene adduct from the chemical equilibrium and locking it in an unreactive state.

The first work employing this concept relied on a hexadiene motif in the bridge position of a pro-diarylethene that could undergo the Diels–Alder reaction with maleic anhydride to yield the target photochrome.[16] Since the equilibrium was shifted to the product side, this system proved to be especially useful for gating photochromism through chemical reactivity. However, the potential of the overall concept was quickly recognized and a publication followed that evolved the bridge motif of pro-diarylethene **8** to the photochromically more advantageous fulvenyl moiety.[17] Reaction of this pro-photochrome with dicyanofumarate yielded the respective diarylethene **9o** that could undergo photocyclization to **9c** locking it in its unreactive state (Scheme 4).

However, the equilibrium between diene and dienophile was lying strongly on the starting materials side at room temperature.

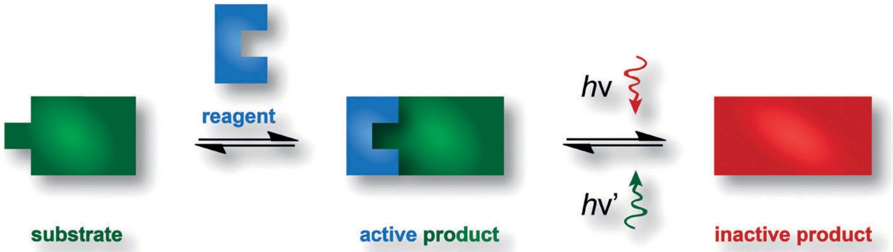
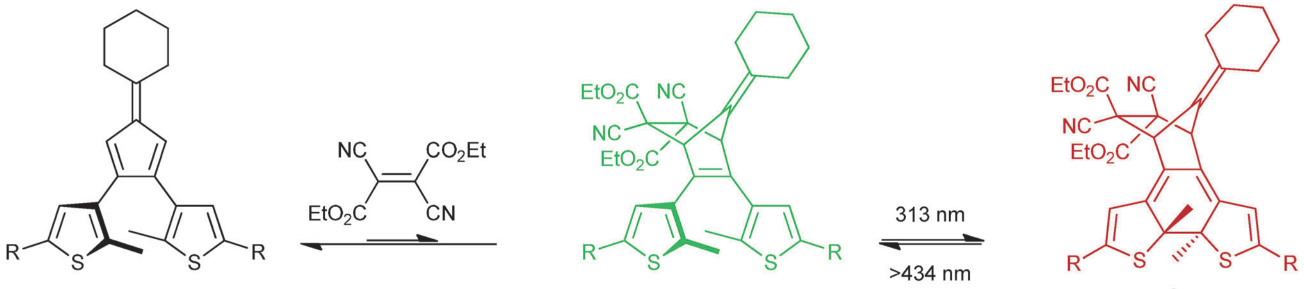
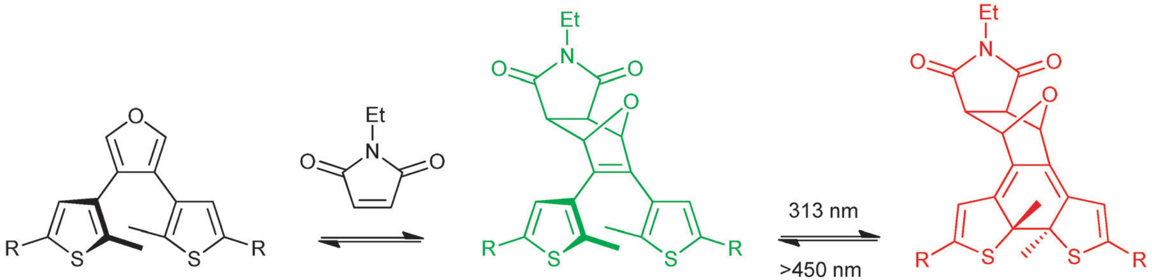


Fig. 4 Concept of product control: Photoswitching a product to an inactive "locked" form removes it from a dynamic covalent equilibrium, while switching it back into its active "unleashed" form and re-introduces it to the system.



8 **9o** **9c**

Scheme 4 Photoswitching locks the Diels–Alder adduct (**9o** → **9c**) and removes it from the dynamic equilibrium (**8** → **9o**).[17]



10 **11o** **11c**

Scheme 5 Photoswitching locks the Diels–Alder adduct (**11o** → **11c**) and removes it from the dynamic equilibrium (**10** → **11o**).[17]

This allows for exploitation of the design for photo-release of the dicyanofumarate from the pure locked Diels–Alder adduct **9c**, which was isolated beforehand. Only recently the scope was expanded by incorporating a furyl moiety in the bridge position as the diene in pro-dithienylethene **10** enabling the use of maleimide derivatives as dienophiles (Scheme 5).[18] Since the furan–maleimide couple exists in a highly reversible regime under ambient conditions, the system could be exploited far beyond the simple photorelease from adduct **11o** to **10** adding new potential applications for the light controlled adduct-locking in materials sciences and biological environments.

Template control

Substrate switching offers convenient possibilities of enabling or disabling a chemical reaction. However, since the photoswitchable unit has to be incorporated into one of the reaction partners, its inherent disadvantage lies in the lack of flexibility in choosing the substrates. Template switching addresses this issue by outsourcing the photocontrollable unit from the substrate to an external molecule that pre-arranges the reactive centers of the starting materials so that a previously inhibited reaction can take place (Fig. 5).

The first photoswitchable template was synthesized as early as 1995 by Würthner and Rebek.[19] They designed a complex biscarbazolylimide terminated azobenzene **12** (Scheme 6). In the *E*-form this template is inactive and shows no conversion in the coupling reaction between aminoadenosine **13** and *p*-nitrophenyl ester **14** to amide **15**, whereas upon UV-induced isomerization to *Z*-**12** the formed cavity acts as an ideal host to promote the coupling reaction. However, the coupling product remains bound to the host upon bond formation, thereby not completely fulfilling the ambitious task of designing a photoswitchable catalyst. The authors later showed that product inhibition as well as inhibition by competitive binders are observed during the reaction and neither photochemical nor thermal *Z* → *E* isomerization could be induced into the host while being bound to the coupled product.[20]

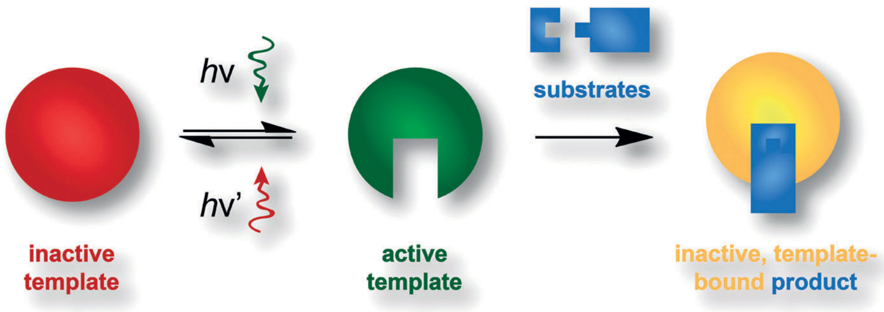
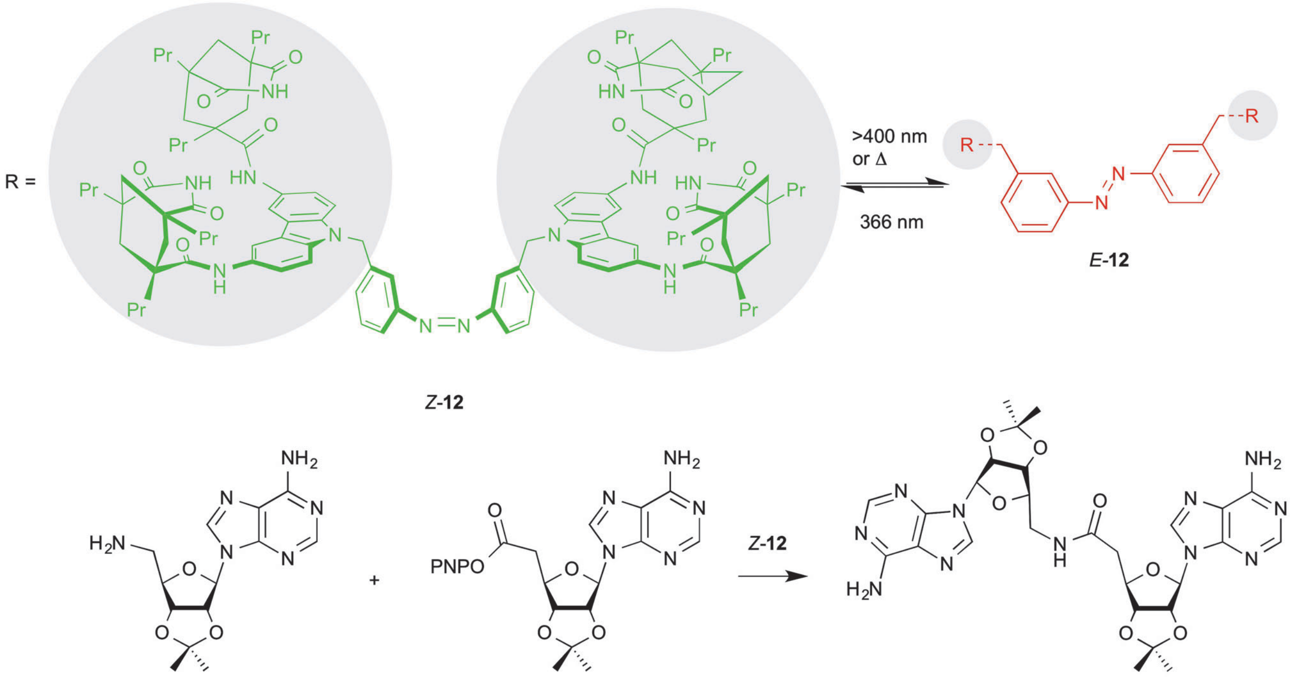


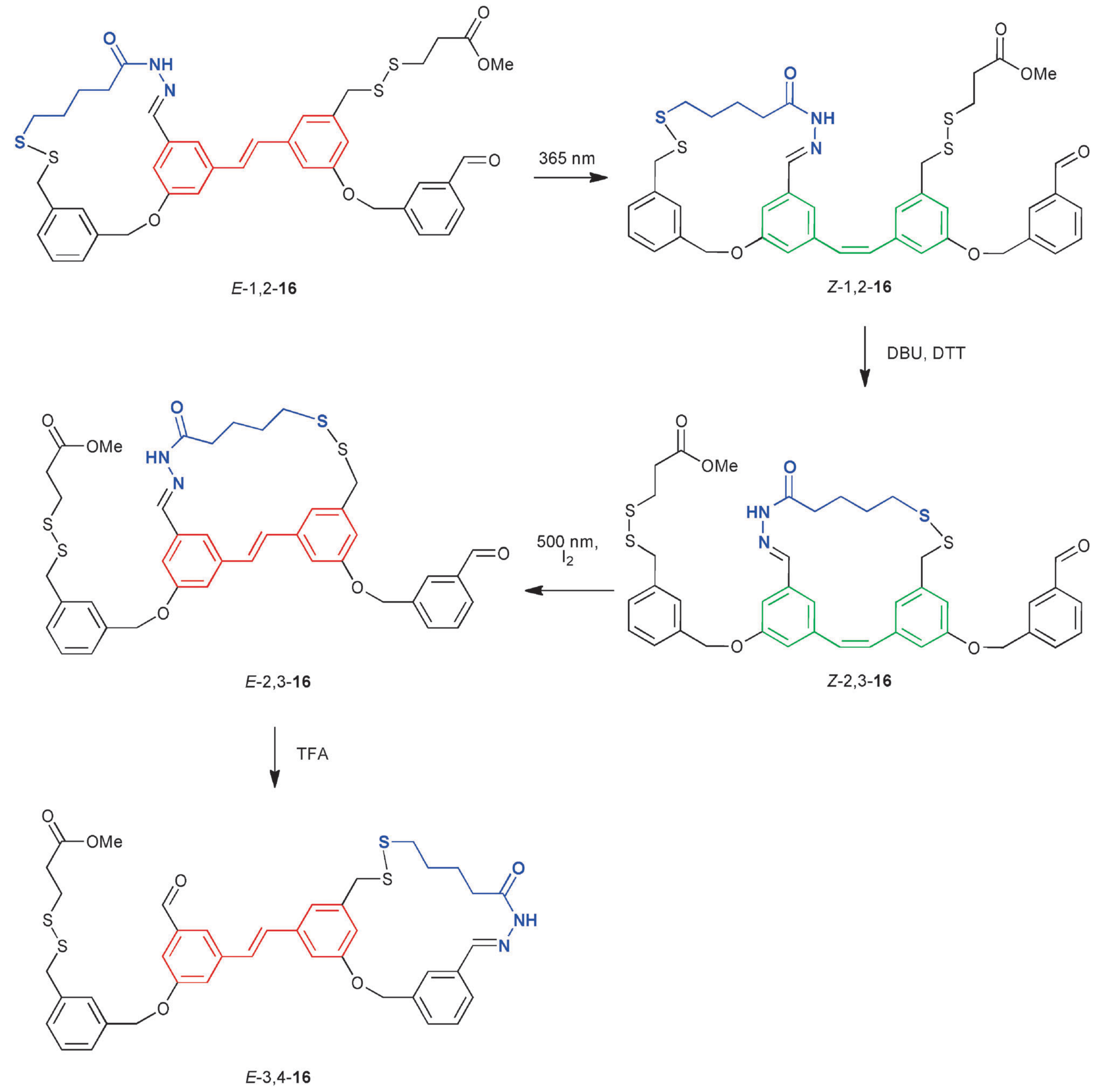
Fig. 5 Concept of template control: Photoswitching a template between inactive and active forms allows for control of conversion of starting materials to products.



Scheme 6 Photoswitchable template **12**, which in its *Z*-isomer enabling the coupling of amine **13** and activated acid **14** to amide **15**.[19]

Switching of the template can, in a broader sense, also be achieved by manipulating the track of a molecular walker by light.[21] Leigh and coworkers synthesized walker-track conjugate **16** offering different possibilities for hydrazone and disulfide binding (Scheme 7). The key step in the movement of the walker is the isomerization of the stilbene moiety incorporated into the center of the track. Upon UV-induced isomerization from *E*-1,2-**16** to *Z*-1,2-**16** the equilibrium between disulfide formation on the first position and the third position is highly biased toward the latter position and the walker moves along the track to form *Z*-2,3-**16**. Subsequent vis-light induced back isomerization from *Z*-2,3-**16** to *E*-2,3-**16** shifts the equilibrium between the hydrazone formation on the second and fourth position towards the fourth position to form *E*-3,4-**16**. Overall, the walker was moved successfully along the track by dynamically breaking and forming covalent bonds and biasing the associated equilibria by photoisomerization.

Besides directly switching the template ON or OFF, the assembly of the template itself can be dynamic and controlled by light (Fig. 6). As opposed to the switching of a stable and inert template molecule, the formation of the template itself can be rendered photoswitchable by coupling the template-assembly to dynamic covalent chemistry. Typically, a dynamic constitutional library consists of a large number of equilibrated host structures, derived from a number of building blocks connected *via* reversible covalent bonds, and the equilibria present in the library can be biased towards one or few particular structures by stabilizing non-covalent interactions with a certain guest molecule, thereby leading to a selection and amplification of the best binder. If one of the building blocks of the library consists of a photochrome, one should be able to modulate the initial composition of the unbiased library and therefore also the selection and amplification process by light.



Scheme 7 In a molecular walker-track conjugate, a photoswitchable stilbene moiety in the track guides the walker (shown in blue) along the track by biasing the individual dynamic covalent equilibria for disulfide and hydrazone formation.[21]

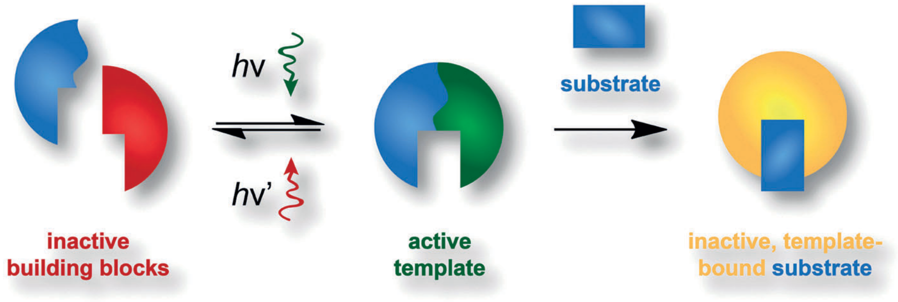
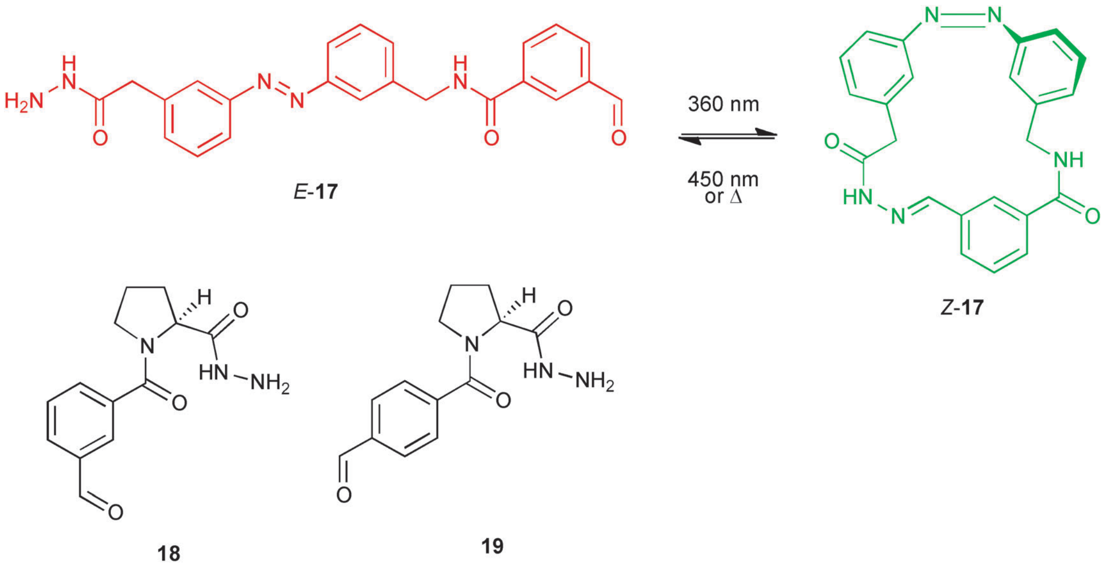


Fig. 6 Concept of dynamic template control: Photoswitching a building block of a dynamic constitutional library between reactive and non-reactive forms allows for the assembly of an active template, which facilitates the conversion of starting materials to products.



Scheme 8 Photoswitching the composition of a dynamic constitutional library by incorporating a photochromic building block leads to a change of the host distribution in the presence of an oligoproline guest.[22]

Such a system has been described by Waters and Ingerman, who employed a dynamic constitutional library consisting of one azobenzene *E*-**17** and two proline (**18** and **19**) building blocks (Scheme 8).[22] The library was equilibrated in the presence of an oligoproline guest and yielded a distinct distribution of host molecules. However, upon UV-induced isomerization of building blocks *E*-**17** to *Z*-**17** the distribution amongst the possible macrocycles changed significantly, therefore amplifying macrocyclic *E*-**17** by more than 60%. This shows that in addition to switching the template ON or OFF, it is also possible to switch between different receptor states.

Photoswitchable catalytic processes

All of the above examples suffer from the drawback that they need a stoichiometric amount of a photoswitch to achieve complete conversion. The previously mentioned system by Würthner and co-workers for example shows that a template can be used to reversibly control a reaction, but due to product inhibition a stoichiometric amount of template was needed to reach full conversion. This of course has an impact on the photoefficiency with which the reaction can take place. In order to achieve full conversion each template molecule needs to be switched, which leads to problems when trying to address the photoresponsive groups *in situ*. Most reactions take place at a reasonable rate only at concentrations which exceed the ones typically employed in photochemistry by several orders of magnitude. This problem can be overcome to a certain extent by using a photoresponsive catalyst, which lowers the overall concentration of the absorbing photochrome in the reaction mixture. Furthermore with a photoresponsive catalyst it is possible to amplify the light stimulus in the system, since the photoreaction that is needed to isomerize the catalyst molecule triggers multiple chemical conversions (turnover).

Reaction control in catalysis can be divided into two different approaches, one is to control the activity of the catalyst and the other is to control the selectivity. In this review both of these concepts are covered.

Activity control

Almost all photoswitchable catalyst systems reported to date focus on modulating the catalytic activity. For this a catalytically active molecule is functionalized with a photoswitchable entity. Ideally, the difference in catalytic activity between the two forms of the photochrome differs significantly enough, so it leads to an ON/OFF switching of the catalyst (Fig. 7). There are several strategies that can be employed to achieve control over the activity of a catalyst. Herein, we will focus on the control of cooperative effects, steric shielding of the active site, and modulation of the electronic properties of a catalyst, which are the more promising approaches. For additional approaches using photochromic effector molecules, activating or inhibiting the catalyst system, the reader is referred to previous reviews.[2,5]

Cooperative effects play an important role in biological and synthetic catalytic systems and have therefore also been exploited to photomodulate reactivity. The basic principle relies on a large geometrical change during the isomerization process that allows the variation of the distance between to catalytically active sites. Cacciapaglia *et al.* reported the first successful use of a photoswitchable cooperative effect in catalysis.[23] The bis-barium complex of an azobis(benzo-18-crown-6) ether **20** was used to catalyze the basic ethanolysis of tertiary anilides (Scheme 9). By reversible *E*/*Z* isomerization of the azobenzene spacer the catalytic activity could be phototuned. The thermodynamically more stable *E*-**20** has only a low catalytic activity. Photoswitching the azobenzene moiety into the *Z*-form changes the geometry of the bis-barium complex into a more favorable concave conformation in which the two barium centers are in close proximity to each other. In the catalytically

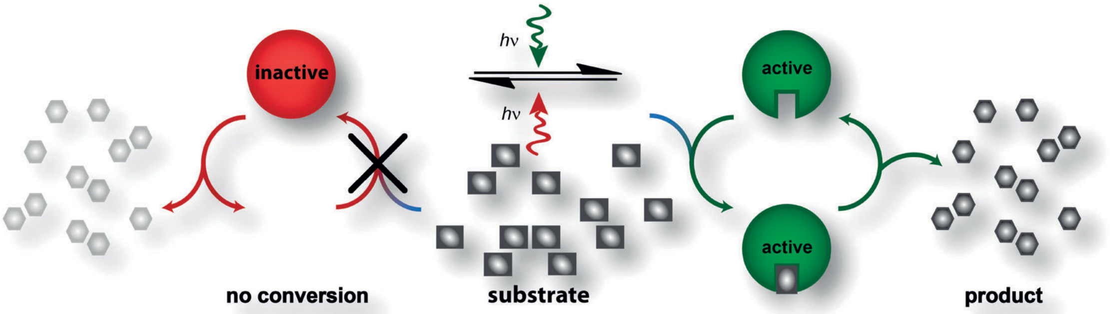
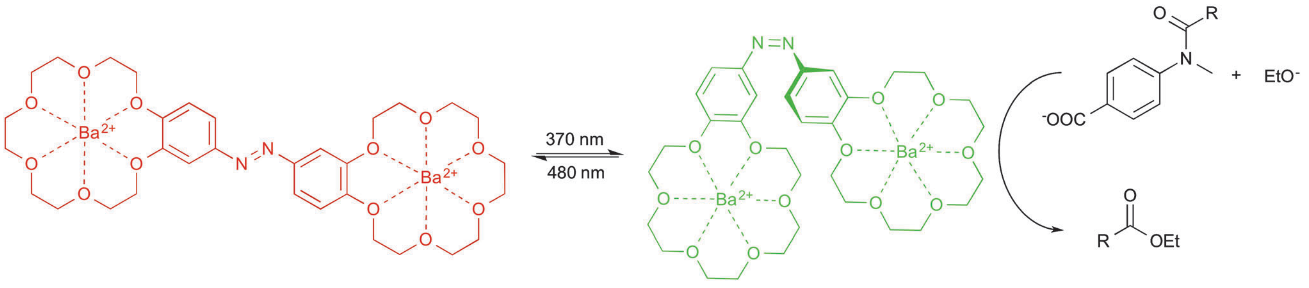


Fig. 7 Concept of photoswitching the activity of a catalyst: photoswitching converts a catalyst from an inactive to an active form, which turns the substrate over to the product, while the inactive form shows no conversion (turnover). Thereby, one switching event can lead to the formation of many product molecules (amplification).



E-**20**

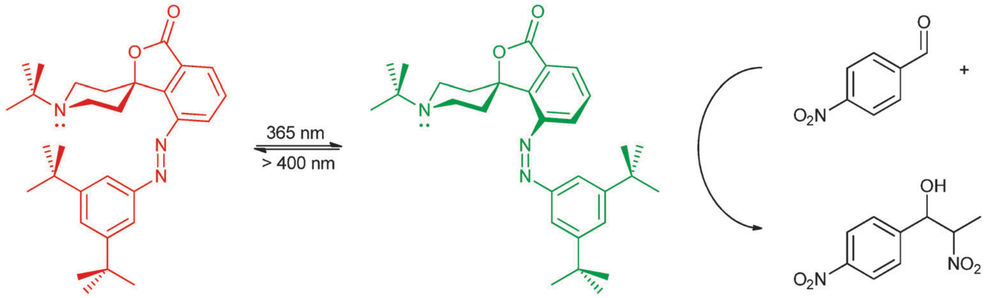
Z-**20**

Scheme 9 In the photoswitchable cooperative catalyst **20**, *E* → *Z* photoisomerization brings both barium centers and hence the two coordinated starting materials into close proximity to catalyze the ethanolysis of tertiary anilides.[23]

active complex one barium center serves as a binding site for a carboxylate anchoring group on the anilide substrate while the other barium center binds a nucleophilic ethoxide ion. The close proximity of these two pre-organized starting materials gives rise to an increased catalytic activity of the *Z*-isomer.

Cooperative effects have also been used in a similar way to photoreversibly control the Morita–Baylis–Hillman reaction.[24] A bifunctional cooperative acid catalyst was functionalized by Imahori and coworkers with an azobenzene moiety to activate or deactivate the cooperative effect, which led to a reversible control of the reaction rate.

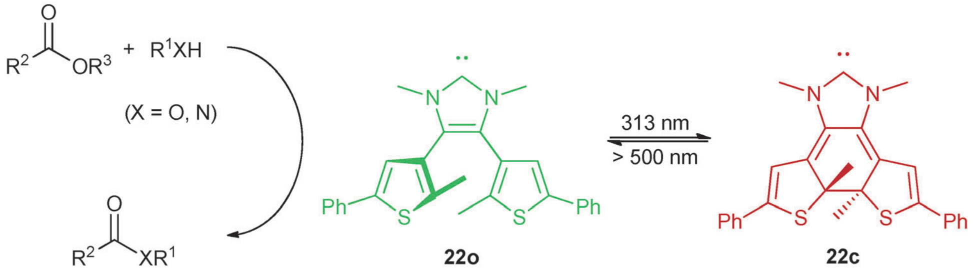
Steric effects can influence the activity as well as selectivity of a catalyst for a given reaction. To gain control over the activity of a catalyst using this concept, a photoswitch is needed that induces a large geometrical change to shield or deshield the substrate binding site of the catalyst. An approach where this concept was successfully used has been reported previously by our group.[25] The lone pair of the *N*-alkylated piperidine base **21** can reversibly be shielded by *E*/*Z* isomerization of a rigidly connected azobenzene ''wiper'' (Scheme 10). It was shown using titration experiments that the piperidine base has a lower basicity in the resting state *E*-**21**. Switching the azobenzene moiety into the *Z*-configuration deshields the piperidine electron lone-pair, which leads to an increase in basicity. The different basicities were used to photocontrol the conversion of a base-catalyzed nitroaldol (Henry) reaction. Later on, a related catalyst



E-**21**

Z-**21**

Scheme 10 *E*/*Z*-photoisomerization of an azobenzene moiety controls the accessibility of a piperidine base, which can be used to catalyze a nitroaldol (Henry) reaction.[25]



Scheme 11 Ring-open N-heterocyclic carbene (NHC) **22o** catalyzes transesterification, amidation as well as ring-opening polymerization reactions yet upon irradiation its corresponding ring-closed isomer **22c** exhibits significantly reduced catalytic activity.[27,29]

was immobilized on various solid surfaces, such as silica gel or silicon wafers, to prevent the loss of spatial resolution due to diffusion of the catalyst in solution.[26]

Electronic effects can significantly influence the active site and hence electronic fine-tuning constitutes one of the main strategies in catalyst design. Therefore, it is no surprise that efforts were put into photomodulation of the electronic properties of a catalyst. The basic concept is founded on breaking or forming a conjugated system between the active site and an electronically activating group. Recently Bielawski and Neilson used this concept to control the activity of a catalyst.[27] An N-heterocyclic carbene (NHC) functionality was incorporated into the backbone of a dithienylethene (DTE) backbone **22** (Scheme 11). The length of the conjugated π-system modulates the electronic properties of the NHC-functionality. In the presence of visual light and a base the NHC **22o** catalyzes transesterification and amidation reactions. Upon irradiation with UV-light to the ring-closed derivative **22c** the rate of a transesterification and an amidation reaction was significantly decreased. This process was reversibly switched several times between a slow and a fast reaction rate. On the basis of NMR-experiments with an isotopic label at the C2 "carbene" carbon, the authors could rationalize the observed activity differences by showing that the ring-open form **22o** exists as an imidazolium species while the ring-closed species **22c** forms the less active alcohol adduct.

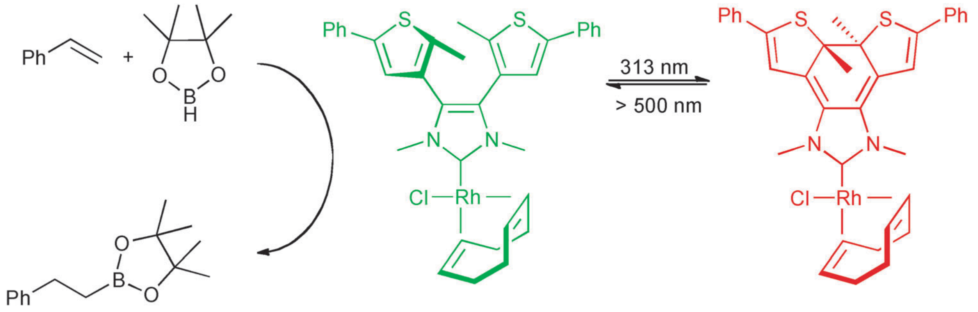
This photomodulation of the nucleophilicity of the NHC center was further used to switch the activity of a Rh(I)-complex **23** (Scheme 12).[28] It was shown that the Rh-metal center functionalized with the photochromic NHC ligand **23o** can catalyze the hydroboration of various alkenes, such as styrene, with modest activity differences between the two different switching forms. In this case the rate-determining reductive elimination step was attenuated by the lower donor capability of the NHC-ligand in its ring-closed form.

Recently Bielawski and coworkers were also able to show the first photoswitchable attenuation for the ring-opening polymerization (ROP) of δ-valerolactone as well as ε-caprolactone using their dithienylethene-based NHC **22** (see Scheme 11).[29]

Selectivity control

The previous examples impressively show how much progress has been made in the field of photoinduced activity control of catalysts. Although efforts toward activity control have thus far been the main focus, approaches to photoswitch the selectivity of catalysts are equally important. For this a catalytically active entity is combined with a photoswitch that leads to a difference of chemo-, regio-, and stereo-selectivity between the two forms (Fig. 8). Until now efforts have been limited to reversible switching of the catalyst's chirality thereby trying to modulate its stereoselectivity.

The first successful approach to photochemically switch the stereoselectivity of a catalyst was reported by Branda and coworkers.[30] Their dithienylethene-based chiral bis(oxazoline) ligand **24** is only able to chelate to the catalytically active copper center in its more flexible ring-open form (Scheme 13). This complexation generates a chiral environment around the copper center and thereby allows a cyclopropanation reaction to take place stereoselectively. Hence, in the open form **24o** an ee of 30–50% was observed whereas the closed form **24c**, where the rigidity of the



23o **23c**

Scheme 12 Photoswitching of a dithienylethene-based N-heterocyclic carbene (NHC) ligand modulates the activity of the derived Rh(I)-complex in the hydroboration of styrene.[28]

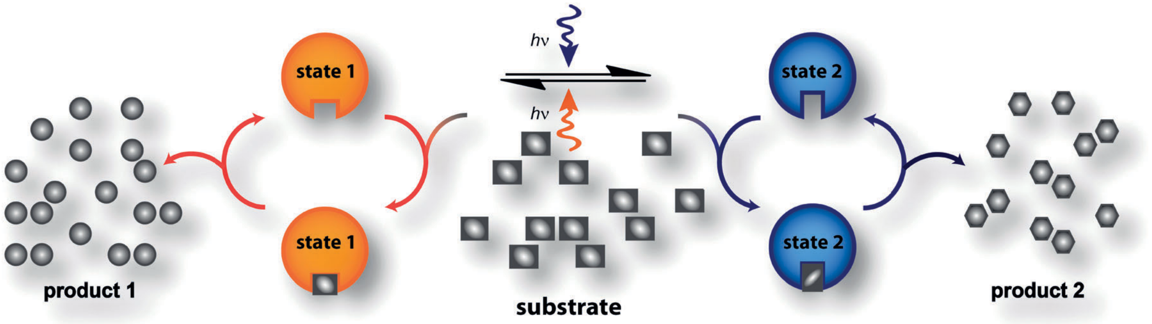
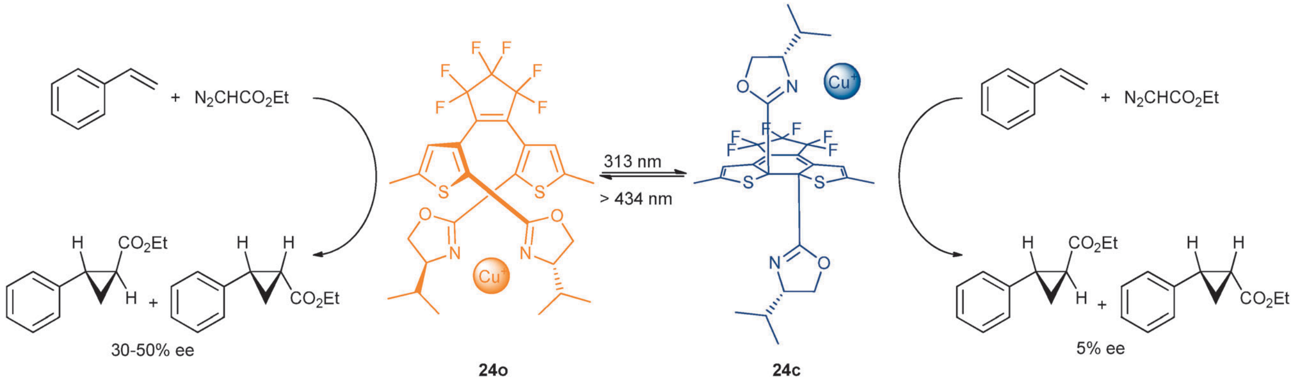


Fig. 8 Concept of photoswitching the selectivity of a catalyst: Photoswitching interconverts a catalyst between two forms exhibiting different selectivity in a given transformation. Again, one switching event can lead to the formation of many product molecules (amplification).



Scheme 13 Photoswitching of a dithienylethene-based bisoxazoline ligand leads to modulation of its chelation ability and hence chirality of the corresponding copper complexes, which display different degrees of stereoselectivity for the cyclopropanation of styrene.[30]

ligand prevents chelation, only showed a very low ee of 5%. Irradiating the sample with visible light led to recovery of the original chiral information and gave an ee of 11–37%.

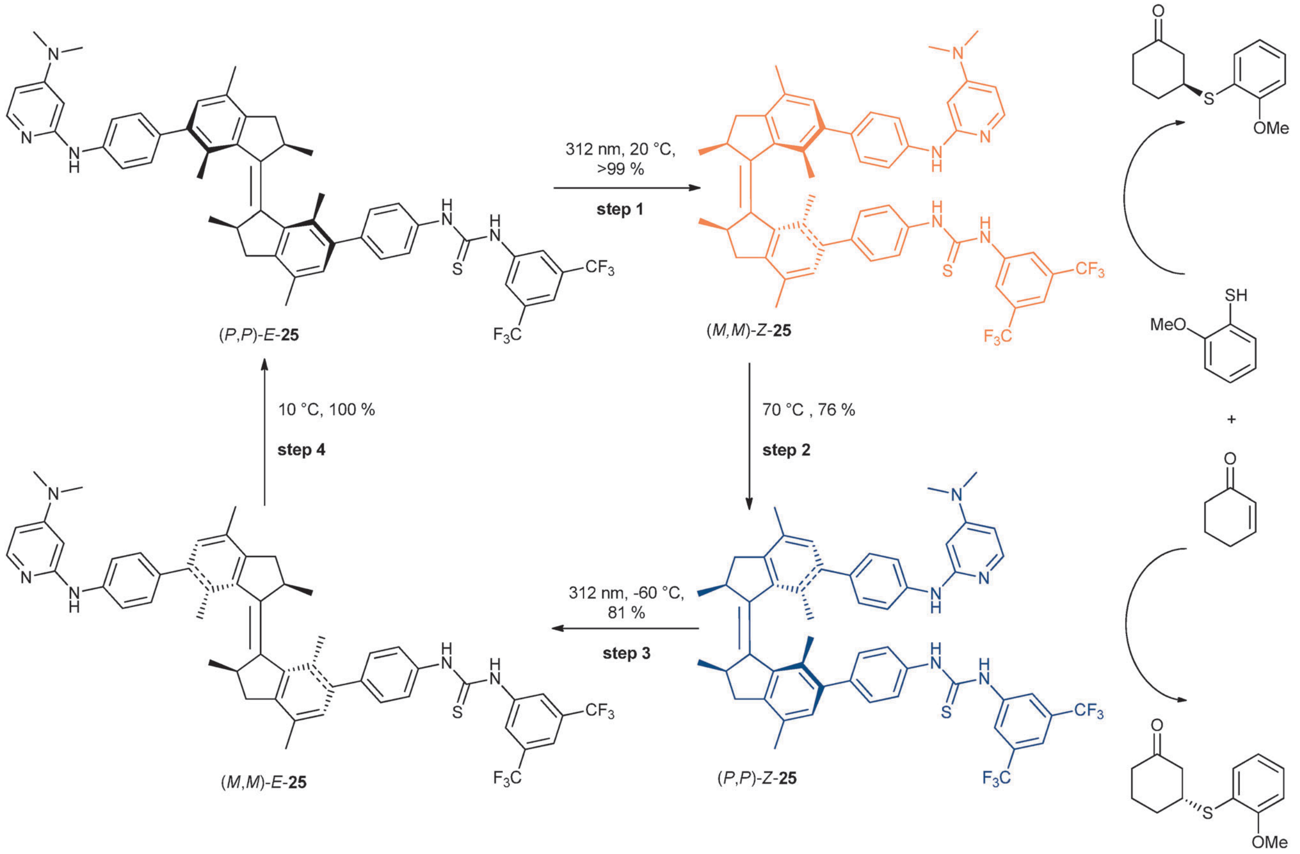
Feringa and Wang combined both of the two concepts of photoswitching activity and selectivity (Scheme 14).[31] For this purpose, their rotatory molecular motor was transformed into a photoswitchable bifunctional organocatalyst by attaching a Brønsted base and a thiourea hydrogen-bonding donor group, which are known to cooperate in the catalysis of Michael additions, among other reactions. The thermodynamically stable (*P*,*P*)-*E*-**25** isomer shows a negligible catalytic activity with no stereoselectivity (*e.r.*, *S* : *R* = 49 : 51) in the Michael addition. However, upon irradiation helix inversion takes places and the (*M*,*M*)-*Z*-**25** isomer is formed, which shows a higher activity in the Michael addition and forms the product in considerable enantiomeric excess (*e.r.*, *S* : *R* = 75 : 25). Heating the (*M*,*M*)-*Z*-**25** isomer to 70 °C triggers a thermal isomerization step that forms the (*P*,*P*)-*Z*-**25** isomer, which also catalyzed the Michael addition but yielding the opposite stereoisomer (*e.r.*, *S* : *R* = 23 : 77). Subsequent photochemical and thermal isomerization gives rise to reformation of the original (*P*,*P*)-*E*-**25** isomer *via* (*M*,*M*)-*E*-**25**.

Outlook

In this review we have summarized the existing body of literature in the field of photoswitchable gating of chemical reactions and arranged the examples according to the different conceptual approaches explored thus far. The various designs have been divided into two main categories depending on the stoichiometric or substoichiometric use of the photochrome (and hence the incoming photons). After discussing all of the specific examples we want to seize this opportunity to point out some general drawbacks, emphasize remaining challenges, and highlight grand opportunities. Please be aware that this future vision of the field is naturally based on our own personal and current perspective.

To realize the full potential of photoswitches to gate chemical processes there are a number of critical issues, which have to be addressed:

In situ switching has to be accomplished by carefully engineering the entire reaction set-up. The reader will have noticed that most studies are typically performed using both forms of the photoswitch for reactivity studies only after they have been isolated. While such *ex situ* experiments establish the theoretically achievable ON/OFF reactivity ratios of both switching forms, the practically accessible window may be much narrower due to non-quantitative photochemical interconversion yielding a PSS mixture and non-productive absorbance of other components in the reaction mixture. This resulting "window of opportunity" has to be used in real *in situ* switching experiments to exploit the desired advantages of "remote-controlling" chemical reactions. For this purpose, several parameters have to be



Scheme 14 Modulation of the relative orientation of a pyridine basic and a thiourea hydrogen-bonding site embedded in a molecular motor leads to a photoswitchable bifunctional organocatalyst, which allows for control over the activity and stereoselectivity of a Michael reaction.[31]

optimized to ensure instant and complete exposure of the entire sample volume to light. For example, both the optical density (dictated by the concentration of the absorbing photochrome) at the irradiation wavelength (potentially exciting at the absorption edge, not the maximum) as well as the sample thickness should be minimized to allow for maximum light penetration. While the first aspect clearly shows the advantage of using catalytic approaches because the amount or loading of absorbing photochrome can be much lower, the second point illustrates the attractiveness of working with monolayers at interfaces, for example SAMs.

Increasing the overall efficiency and robustness of the light-controlled chemical process is an important ongoing effort in the design of photochromes with ever-improving switching characteristics. The PSS compositions (given by the ratio of extinction coefficients of both switching forms at the applied excitation wavelength multiplied by the ratio of the quantum yields) dictate the population difference of both switches associated with different reactivities. Therefore to optimize the photoswitching behavior and achieve quantitative photoconversions, the absorption spectra of both switching forms have to be separated to ensure that selective excitation and the quantum yields have to be maximized. In addition to improving the efficiency of the switching process, which also enhances the system's sensitivity particularly when coupled to a catalytic amplification mechanism, it is important to design reliable and hence robust switches. The necessary high reversibility of both photochemical reactions associated with the photochromicity requires that all other competing side reactions, in particular if irreversible (so called fatigue), have to be shut down effectively. Although there has been a lot of progress made over the years for designing fatigue-resistant switches in the context of optical data storage,[32] we want to emphasize here that there is an ongoing need to improve photochromic performance with regard to this key criterion, which is often overlooked in academic research. Last but not least, we would like to point out that T-type photochromes, which typically are not valued highly by most people in the community, are very interesting as gates. By engineering the half-lives of their metastable forms, which we assume to exhibit higher reactivity (ON), to allow for the chemical transformation yet otherwise reverting quickly back to the less reactive OFF form, only one light source in needed to control the reaction. Such a combination of light-induced ON-switching and fast thermal OFF-switching should prove increasingly important for many applications (even beyond the gating of reactivity).

Maximizing the reactivity differences of the two switching forms is equally important for optimizing their population changes accessible by illumination. This aspect is perhaps the least straightforward to engineer and is primarily tied to the creative force of the chemist. With regard to the stoichiometric use of photochromes, it is rather obvious to integrate it into a chemical reaction, which is sensitive to the structural or geometrical changes during the photochromic reaction. Due to the available portfolio of photoswitches and the myriads of known chemical reactions, there clearly is a lot of room for exploring along this broad direction. More difficult to achieve and much harder to predict is the interaction of photochromes with catalysts. The most obvious approach will be based on an established catalyst structure, ideally using a mechanism known in great detail, and merging it with a known photochrome. From our own experience and keeping in mind that a low catalyst loading is necessary to enhance the penetration of light through the sample, we have found it more promising to render a highly active catalyst less active (ON → OFF) as compared to the opposite approach (OFF → ON).[25] However, the reader should be reminded that there is plenty of room for higher reactivity differences (ON/OFF-ratios) and qualitatively new, creative designs are needed.

Controlling bimolecular reactions is an important prerequisite in order to use photoswitches to gate connections between separate (different) chemical entities or building blocks. In contrast to controlling unimolecular reactions, the difficulty arises from the much narrower operating concentration window, which is not only dependent on the optimal optical density to assure full exposure of the sample but also the optimal concentration of the reaction partners. Photoswitching bimolecular connections would enable the control over polymerization processes, for example by the covalent connection (and disconnection) of monomers to linear chains or crosslinking of polymer chains into networks. However, thus far there has been only Bielawski's work on photoswitchable catalysts for the ROP of lactones.[29] Another important area would be the control over covalent surface functionalization, for example to allow for dynamic patterning of SAMs. In this context, the work by Kawai on photoswitching reversible NHC-adduct formation (see Scheme 2) could prove useful.[12–14] Without doubt, such photoswitchable bimolecular connection reactions will provide ample opportunities in the field of soft matter materials science.

At this point we want to return to our initial motivation to develop photoswitchable reactive systems as ''remote-controlled synthetic tools'' and critically reflect on their (potential) capability to carry out chemical processes with high spatial and temporal resolution. Clearly, the achievable spatial resolution has physical limitations inherent to the wavelength of the light used and it furthermore requires ''defocussing'' pathways, such as delocalization of excitation as well as diffusion, to be shut down. The first point is most readily achieved by removing, or at least sufficiently separating, all possibly interfering energy and electron transfer quenching pathways. The latter point necessitates immobilization of (one of) the reactants (and the product) either directly or *via* the photochrome or in the absence of any solvent. Taking these aspects into consideration, patterning of surfaces or even structuring in 3D with spatial resolution characteristic for (non-linear) optical techniques should be achieved. While the spatial resolution achievable with light is limited to length-scales that are much larger than individual molecules, the temporal resolution provided by modern laser technology easily allows for individual chemical reactions to be followed in real time. Therefore, the potential of the ''remote-controls'' described herein lies perhaps more in their superior temporal resolution, which in principle should allow us to *time* individual successive reaction steps. Such unprecedented control over the sequence of chemical events should have a large impact on our ability to prepare complex chemical structures, in particular (bio)-macromolecules. This is perhaps most readily illustrated by considering a photoswitchable polymerization catalyst. By toggling between its ON and OFF state, one should be able to program a sequence of blocks with exact control over their individual length (activity), their monomer composition (chemoselectivity), and their tacticity (stereoselectivity), thereby creating completely new and otherwise inaccessible polymer architectures.

When considering the opportunities in this field, it is clear that we have to continue to design improved photoswitchable reactive systems and exploit their unique features to precisely and externally control chemical processes in time and space. Such high-resolution, remote-controlled chemical tools will prove extremely powerful in basic research, ranging from synthetic chemistry to molecular cell biology, and have a tremendous impact on future materials applications. In the long run, such systems could in fact become tiny molecular machines with the ability to assemble chemical entities, somewhat different, yet reminiscent of Drexler's ''molecular assembler'',[33] and chemists, who create and operate them, will have a bright future!

Acknowledgements

We are grateful to our dedicated coworkers and collaborators, who have contributed to this research endeavor over the past years. Generous support by the European Research Council (*via* ERC-2012-STG_308117 ''Light4Function'') is gratefully acknowledged.

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