Polymer Synthesis

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External Regulation of Controlled Polymerizations

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Polymer chemists, through advances in controlled polymerization techniques and reliable post-functionalization methods, now have the tools to create materials of almost infinite variety and architecture. Many relevant challenges in materials science, however, require not only functional polymers but also on-demand access to the properties and performance they provide. The power of such temporal and spatial control of polymerization can be found in nature, where the production of proteins, nucleic acids, and polysaccharides helps regulate multicomponent systems and maintain homeostasis. Here we review existing strategies for temporal control of polymerizations through external stimuli including chemical reagents, applied voltage, light, and mechanical force. Recent work illustrates the considerable potential for this emerging field and provides a coherent vision and set of criteria for pursuing future strategies for regulating controlled polymerizations.

1. Introduction

The most profound developments in modern polymer chemistry have arisen from a combination of controlled polymerization techniques and precision polymer functionalization. This dual strategy has and will continue to lead to advanced materials with applications in microelectronics, biotechnology, energy, defense, and the developing world. Starting almost two decades ago with the introduction of controlled radical polymerization (CRP) methods,[1–3] this renaissance has facilitated the rational design of polymers with predictable molecular weights and narrow polydispersities traditionally accessible only through ionic mechanisms. CRP approaches have the advantage of being tolerant towards many functional groups, amenable to a wide range of monomers, able to easily produce copolymers, and practically simple to execute. These techniques, as well as important advances in organocatalytic ring-opening polymerization,[4] chain-walking coordination polymerization,[5] and ring-opening metathesis polymerization,[6] have made it commonplace to produce well-defined polymers with control over functional group identity, placement, and polymer architecture. Furthermore, with the ever-shrinking gap between organic and polymer chemistry,[7] material scientists now have a number of reliable methods to post-functionalize these polymeric materials using the robust, efficient, and orthogonal "click" family of reactions.[8]

With such powerful tools available to synthesize polymers of almost infinite variety, architecture, and functionality, what fundamental innovations can synthetic polymer chemists continue to provide that will contribute to solving the grand challenges[9] in materials science? Nature generously provides the necessary inspiration. For example, our synthetic methods pale in comparison to the ribosome, which is able to produce flawless polymers of exceedingly high molecular weights that fold into pre-programmed secondary, tertiary, and quaternary structures. Perhaps the most impressive part of this synthetic machinery, however, is our body's ability to provide temporal and spatial control over these polymerizations. For instance, the initiation, chain-growth, and crosslinking of actin, the cell's most important resource for mechanical support and directed movement, is regulated by over 100 accessory proteins, providing precise control over a variety of processes including membrane permeability, cell replication, and cell motility.[10]

Emulating the spatial and temporal control over polymerization exhibited by natural systems is a formidable challenge for polymer chemists. The potential of such

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technology is self-evident considering the myriad of high-value applications associated with (irreversible) temporal control over polymer initiation. This seemingly simple development has spawned billion-dollar industries in commodity materials such as coatings, thermosets, foams, and adhesives. Further, this technology has made its way into sophisticated materials such as photocured dental resins and complex chip manufacturing processes that employ photolithography.[11]

The prospect of in-situ, reversible polymer initiation and termination would build on the already realized living polymerization techniques and post-functionalization methods to introduce new and innovative applications through external control of the viscosity, mechanical properties, structure, and function of macromolecules. The development of such chemistry would allow the programming of functional units in discrete locations along the polymer backbone, providing the technology necessary to tune the secondary interactions of polymer chains by precisely modifying their primary structure. Further, combining spatially and temporally controlled polymerizations with concepts such as templation and compartmentalization has the potential to create multicomponent systems where numerous functions and/or reactions can be individually addressed externally, with the ultimate goal of creating systems that are fully self-regulatory.

In order to provide a set of criteria for future work in this area and compare previous contributions, this Minireview focuses on processes which have the ability to reversibly turn polymerizations *both* “on” and “off” through the use of added reagents, applied voltage, light, or mechanical force (Figure 1). In an ideal system, the propagating polymer chain should switch between an active and a dormant state quickly, quantitatively, and be fully reversible under external stimulation. In addition, the active state should show the qualities of a living polymerization (minimal termination and/or chain-

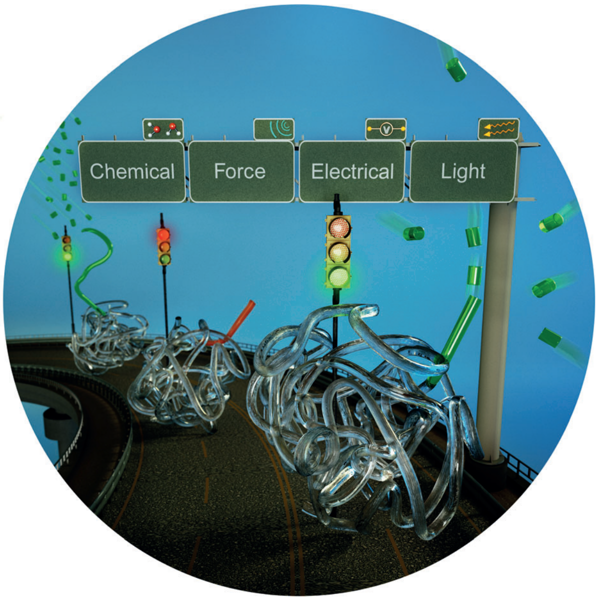


Figure 1. Temporally controlled polymerizations can be regulated by a variety of stimuli to reversibly start and stop polymerizations.

transfer, linear increase in molecular weight with conversion, and low polydispersity), switching should not compromise the polymerization rate, and the system should be tolerant to a diversity of monomers and functional groups.

Realizing the potential of spatial and temporal control of polymerization will require the expertise of many traditional chemical disciplines, including organometallic chemistry, organic synthesis, catalysis, and polymer chemistry. This Minireview is intended to emphasize the on-going work in these sometimes disparate disciplines and show the significant promise of this exciting area. Mimicking Nature's spatial and temporal control of polymerization provides dynamic control of material synthesis, opening opportunities to not only enhance properties but also create new applications for functional materials.

2. Selected External Stimuli

2.1. Allosteric Control

Biologists have long strived to understand how living systems are able to reversibly control the synthesis of biopolymers, such as polypeptides, polynucleotides, and polysaccharides. For example, production of the multi-branched polysaccharide glycogen from glucose lowers human blood glucose levels after meals, storing energy for periods of starvation. The sophisticated control system for glycogen production is essential to prevent toxicity to peripheral tissues in response to prolonged hyperglycaemia or loss of consciousness due to hypoglycaemia. It has been known for more than 50 years that insulin regulates glycogen synthase, the enzyme that progressively lengthens the glycogen polymer, but despite decades of intensive research, the molecular mechanisms remained controversial. Only recently has genetic engineering been able to show conclusively that the primary mechanism for activation of glycogen synthase is allosteric binding of glucose-6-phosphate, the production of which is stimulated by insulin.[12]

Allosteric control of catalyst activity by the reversible binding of an effector to a location remote from the catalytically active site is one of nature's main enzyme regulation mechanisms. Synthetically, the most prominent examples of allosteric systems have been based on bimetallic catalysts where binding of the effector changes the distance between two metal sites, thereby altering the rate of reaction.[13–15] In 2010, Mirkin and co-workers reported the first example of allosteric control of a polymerization catalyst through their weak-link approach (WLA).[16] The triple-layer architecture uses an $\mathrm{Al^{III}}$-salen polymerization catalyst hinged to aromatic groups by $\mathrm{Rh^{I}}$ complexes. The "open" form (**1**) polymerizes ε-caprolactone, reaching complete conversion after 40 h at 90 °C with good control over molecular weight (PDI of 1.10–1.20). However, the catalyst can be almost completely deactivated in situ by the addition of two equivalents of NaBArF (BArF = tetrakis[3,5-trifluoromethylphenyl]borate) or $\mathrm{LiB(C_6F_5)\cdot 4\,Et_2O}$, which abstracts $\mathrm{Cl^-}$ from the $\mathrm{Rh^{I}}$ hinge, quantitatively converting the complex to its "closed" form ($\mathbf{1^{2+}}$) within 20 min. The "closed" complex is essentially inactive as a polymerization catalyst due to the aromatic groups which π-stack above and below the salen catalyst, blocking access to the active site. It should be noted that the inactive state will decompose to the active form over time (ca. 7 % conversion after 100 h). Furthermore, the linear dependence of the molecular weight (M_n) on percent conversion is maintained through closing and reopening (Figure 2), confirming that the activity of the catalyst is unaffected by allosteric regulation.

This work provides a critical proof-of-principle and with careful choice of the catalyst system, blocking groups, and

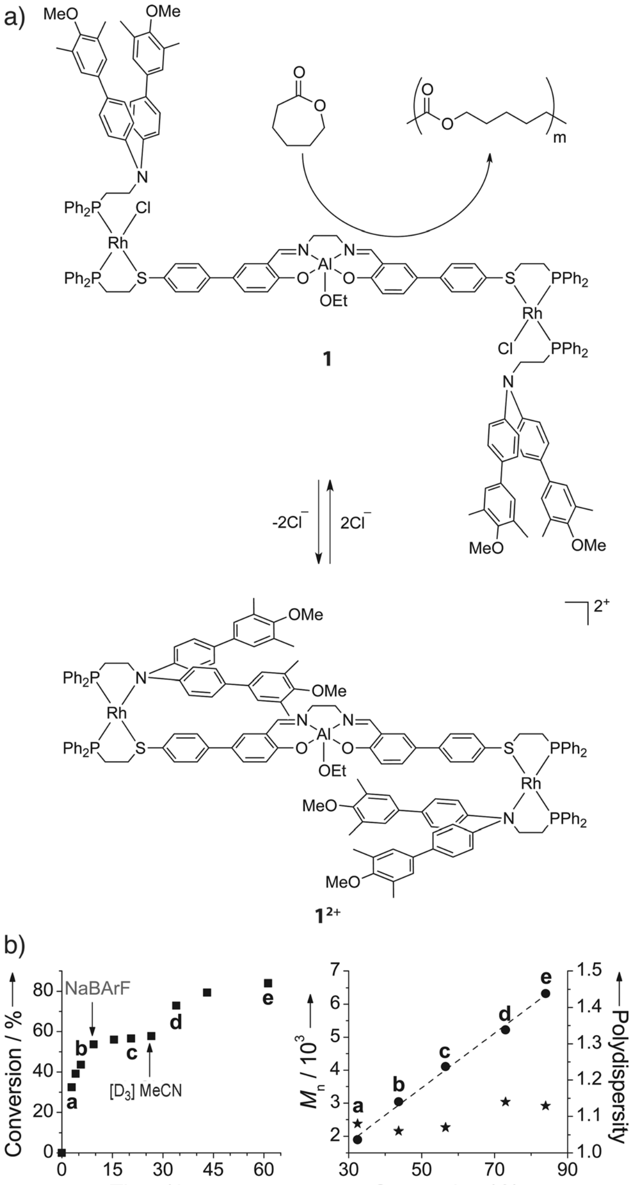


Figure 2. The triple-layer complex allosterically regulates the polymerization of ε-caprolactone by reversibly switching between the active (**1**) "open" and the inactive ($\mathbf{1^{2+}}$) "closed" forms. The formation of the product was monitored at various times (a–e) during the reaction using a) ^{1}H NMR spectroscopy and b) gel permeation chromatography (GPC) (for M_n and PDI). (Part (b) adapted with permission from reference [16] and reprinted with permission from AAAS.)

allosteric effectors, the triple-layer approach could be extended to control other polymerization processes. Additionally, employing metals other than rhodium would further increase the generality of this allosteric system. Many other architectures, including supramolecular assemblies, may also be amenable to allosteric regulation and could allow polymerization of a diverse range of monomers. An even more impressive target is to utilize small molecules as allosteric effectors, mimicking natural, self-regulating allosteric systems through feedback from downstream product polymers or feedforward from upstream monomer or oligomer substrates.

2.2. Chemical Control

In addition to allosteric regulation, which relies on binding of an external effector, many reversible chemical transformations may afford temporal control over polymerization. Of these, redox-active systems were the first to be exploited, and a number of polymerization catalysts have been reported to reversibly switch between two stable oxidation states that have different catalytic efficiencies.[17–19]

The first redox-modulated polymerization catalyst was reported by Gibson, Long and co-workers in 2006 and was based on a Ti^{IV}-salen complex where the ligand was symmetrically conjugated to two ferrocene groups (Figure 3 a).[17] Ferrocene was selected as the redox-active switch because it is a highly reversible redox agent and its chemical and electronic properties are well understood. Though the ferrocene units are distant from the catalytic metal center, the neutral form of the complex (**2**) catalyzes the ring opening polymerization of *rac*-lactide 30 times faster than the oxidized form **2·OTf**, demonstrating that the ligand relays an electronic effect to the metal, a finding that is consistent with other Ti-salen complexes substituted with electron-withdrawing groups.[20] Further, both **2** and **2·OTf** give a single atactic chain per metal center, and their resulting polymers have polydispersities below 1.20, indicating that propagation is well controlled.

Reversible redox control of the rate of *rac*-lactide polymerization was demonstrated by addition of two equivalents of the one electron oxidant AgOTf during polymerization, which markedly slowed monomer conversion. Subsequent addition of two equivalents of the one electron reductant Cp*$_2$Fe returned the activity to approximately the same level as for the virgin catalyst ($k_{app} = 4.98 \times 10^{-6}\ s^{-1}$, cf. $k_{app} = 4.73 \times 10^{-6}\ s^{-1}$ before oxidation) (Figure 3 b).[17] Though reversible control of the polymerization rate was demonstrated with **2**, polymerization cannot be completely halted by oxidation, as both the neutral and oxidized forms of the Ti-salen complex polymerize *rac*-lactide.

In an effort to develop greater redox control of polymerization, Diaconescu and co-workers examined a series of lactide polymerization catalysts based on a new redox-active phosfen ligand, **3-M**.[18,19] Similar to Gibson and Long's system, the phosfen ligand incorporates ferrocene, but dependent on whether yttrium,[18] indium,[18] or cerium[19] is used as the catalytic center, either the ferrocene ligand or the active metal-center is oxidized upon addition of the oxidizing agent ferrocenium tetrakis(3,5-bis(trifluoromethyl)phenyl) borate (FcBArF). Subsequent reduction by CoCp$_2$ returns the catalysts to their original states.

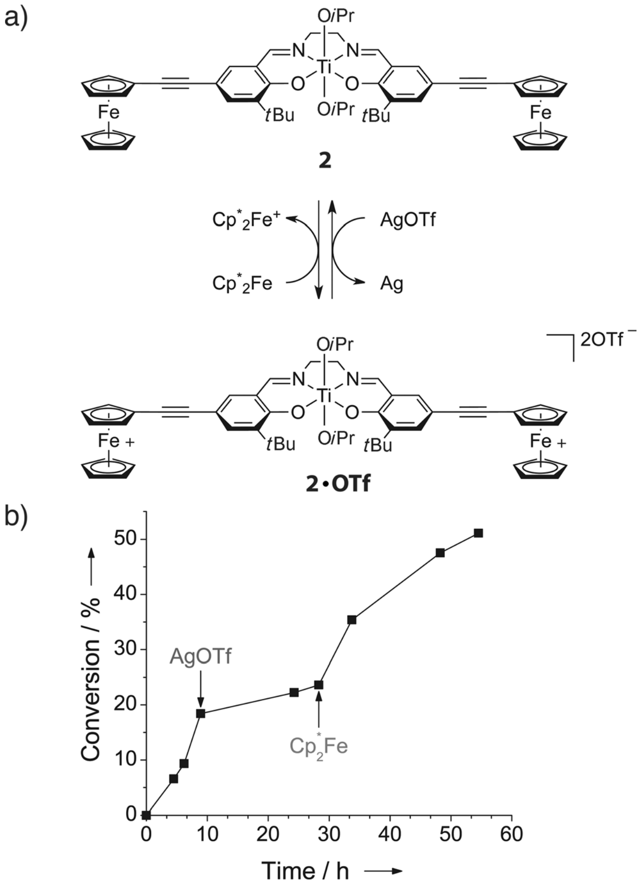
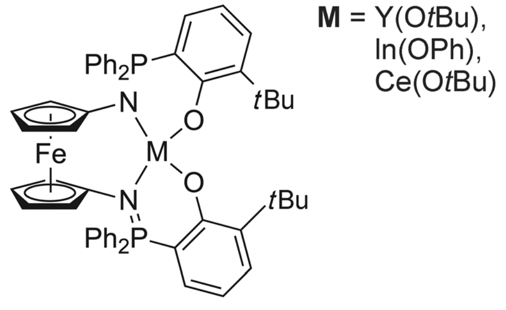


Figure 3. A plot of conversion versus time for the polymerization of *rac*-lactide with in situ redox-switching between the neutral, active form **2** and the less active, oxidized species **2·OTf.** (Adapted with permission from reference [17]. Copyright 2006 American Chemical Society.)

In the case of the yttrium *tert*-butoxide phosfen complex **3-Y**,[18] reaction with one equivalent of FcBArF produces the oxidized form **3-Y·BArF** within minutes. X-ray absorption near edge structure (XANES) and Mössbauer spectroscopy supported the assignment of ferrocene as the redox-active group with the relative polymerization efficiencies of the two forms being compared at room temperature using 100 equivalents of L-lactide in THF. Whilst the neutral complex reached 74% conversion in three hours, no conversion was observed for the oxidized form. The inactivity of the oxidized form allowed polymerization to be halted in situ by addition of FcBArF. Addition of one equivalent of the reducing agent CoCp$_2$ was then able to revert the oxidized complex back to its neutral form within minutes. The polymerization resumed at the same rate as before oxidation with the PDI of the final polymer being below 1.06, indicating that the polymerization remained controlled through switching. Three consecutive cycles of in situ oxidation and reduction were completed (Figure 4) illustrating how the careful choice of an external oxidant and reductant can allow a controlled polymerization to be reversibly switched "off" and "on."



3–M

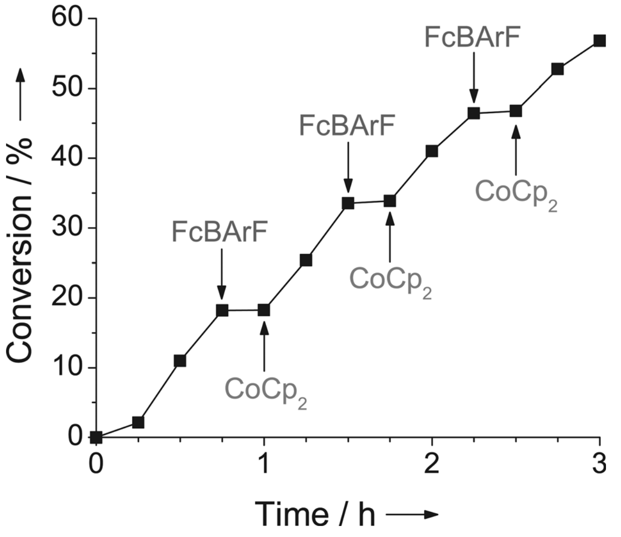


Figure 4. Redox active polymerization catalysts based on phosfen **3** [M = Y(O*t*Bu), In(OPh) or Ce(O*t*Bu)]. A plot of conversion (%) versus time for the controlled polymerization of L-lactide using **3** [M=Y(O*t*Bu)]. The system was redox-switched three times in situ via oxidation with FcBArF and reduction with $CoCp_2$. (Adapted with permission from reference [18]. Copyright 2011 American Chemical Society.)

An intriguing feature of this system is that significant changes in the polymerization behavior of the species are observed on replacement of the yttrium *tert*-butoxide with indium phenoxide in the phosfen complex.[18] Though Mössbauer spectroscopy supports the assignment of ferrocene again being the redox-active species, both the neutral **3-In** and oxidized forms **3-In·BArF** are slow to polymerize either L-lactide or ε-caprolactone. However, room temperature polymerization of trimethylene carbonate demonstrated that oxidized **3-In·BArF** was the more active species, as it reached 49% conversion in 24 h as compared to 2% conversion for **3-In**. In contrast to the yttrium complex, increasing the electron withdrawing nature of the ligand by oxidizing ferrocene leads to an increase in the rate of polymerization. The opposite switching behavior of the yttrium and indium complexes demonstrates the degree of regulation that can be achieved in these chemically controlled systems with the effect of the ferrocene redox-switch being dependent on the identity of the metal.

Diaconescu and co-workers also prepared a Ce^{III}-salen species that required around eight times longer than its phosfen analogue to reach similar L-lactide conversion levels and the PDI was marginally higher (1.34 at 93% conversion).[19] The Ce^{IV}-salen complex produced by FcBArF oxidation was also inactive towards L-lactide polymerization, allowing reversible in situ redox-control of polymerization. Almost no loss of activity was observed before ($k_{app} = 1.96 \times 10^{-2}$) and after ($k_{app} = 1.73 \times 10^{-2}$) switching, though the PDI of the product polymer (1.73 at 90% conversion) was higher than when the oxidation state of the cerium was not changed, indicating some loss in polymerization control by redox-switching. The cerium-phosfen and -salen complexes demonstrate that, although the ligand does not participate in the direct-metal redox-switch, it remains a crucial component of the system and has a marked influence on catalytic activity.

These results demonstrate that external chemical modulation is an effective method for regulating ring-opening polymerizations in situ, and with further developments, including expanding its applicability to other polymerization mechanisms, significant opportunities exist. One of the most powerful outcomes from this work however, is the clear correlation between catalyst design and performance. The incorporation of a highly reversible redox-switch, such as ferrocene, into the ligand allows two stable oxidation states to be reversibly accessed and exploited, while the nature of the metal center also plays an important role. Developing new systems offers opportunities for effective control of polymerization depending on the appropriate choice of catalyst system, oxidant, reductant, and monomer. Future research directions include exploring lanthanides as the redox-active metal. In this case, the 4f valence shells have only a small contribution to bonding and, unlike transition metals, redox-switching has a mainly electrostatic influence on their coordination sphere.

2.3. Electrochemical Control

In terms of remote regulation, electrochemical stimulus offers a number of attractive attributes, including functional group tolerance and easily adjustable parameters for manipulating polymerization rate. Other attractive features include the orthogonality of electrochemical conditions to many common polymerization strategies, such as radical procedures, and the simple automation of electrochemical cells.

Matyjaszewski and co-workers recently reported the first electrochemically-mediated controlled radical polymerization.[21] Their process is based on the well-developed atom transfer radical polymerization (ATRP) mechanism, which relies on the reversible oxidation of a catalytic Cu^I species to generate an alkyl radical. Subsequent reduction of the Cu^{II} species regenerates Cu^I and end-caps the growing polymer chain. Such a mechanism is ideally suited for electrochemical control,[22] as the system can initially be charged with a catalytic amount of air stable Cu^{II}. Application of a cathodic current then reduces the catalyst to active Cu^I, which starts polymerization. Reoxidizing the complex *via* an anodic current yields the catalytically inactive Cu^{II} species and stops further polymer formation.

The resulting electrochemical process is efficient, as application of a cathodic current to a system containing initiator, monomer, an amine-based ligand, and Cu^{II} results in almost 80% monomer conversion in only two hours.[21] The polymerization displayed all the characteristics of a living process, including a linear relationship between M_n and conversion, a good agreement between theoretical and obtained molecular weight, and a low PDI. Further, the polymerization rate was sensitive and responsive to the applied potential. More negative potentials enhanced the polymerization rate while maintaining living polymerization characteristics. The power of electrochemically mediated ATRP (*e*ATRP) is most apparent in its temporal control, where repeated cycling of the potential from one that favors formation of Cu^{I} at the electrode, and thus polymerization, to one that favors Cu^{II} and no polymerization (Figure 5).

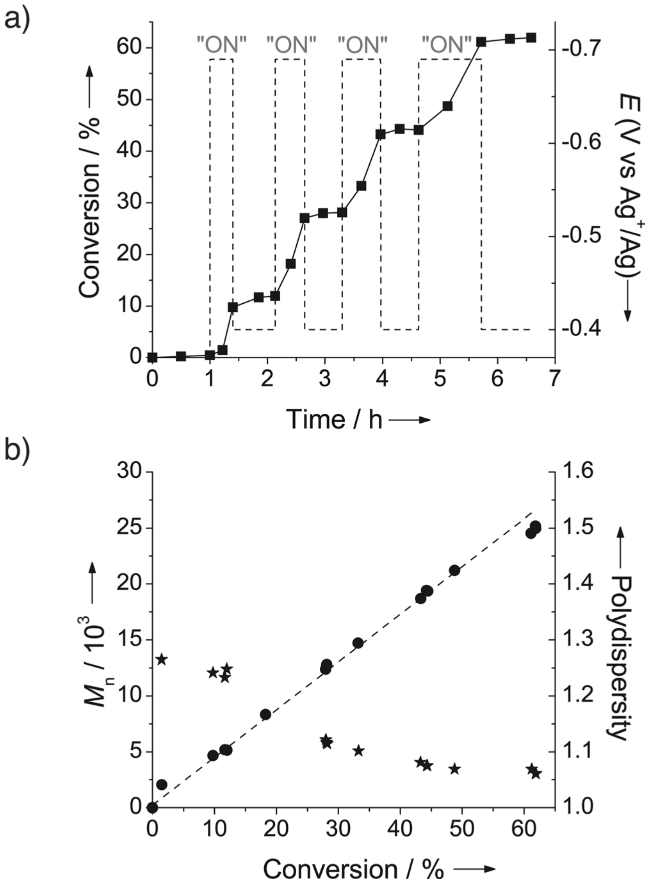


Figure 5. Temporal control of *e*ATRP demonstrated by the switching of polymerization "on" and "off" in response to applied voltage (a) while still showing the characteristics of a living polymerization (b). (Adapted with permission from reference [21] and reprinted with permission from AAAS.)

*e*ATRP fulfills many of the criteria for an ideal system for temporal control of polymerization. It switches efficiently and reversibly between an active and a dormant state, shows the qualities of a living polymerization when in its active state, and, although only the polymerization of acrylates and methacrylates has been reported,[21,23] *e*ATRP should be broad in terms of monomer selection and functional group tolerance. Challenges for the future include improving the slow response time for deactivation of polymerization, which takes nearly 20 min for polymerization to completely stop after the potential change. Further, the current system is restricted to working in an electrochemical cell which could hinder the ability to scale-up reactions due to problems with mass transport to the working electrode and will make it difficult to provide coincident temporal and spatial control of polymerization. Given these accomplishments, *e*ATRP is a powerful system for the temporal control of polymerization that will push polymer chemists in new directions and provide novel application drivers for the synthesis of complex materials.

2.4. Photochemical Control

Of the various stimuli employed to provide in situ control over the reversible activation and deactivation of polymerizations, the inherent properties of light provide most of the necessary characteristics for an ideal system. Light is a widely available, non-invasive, and environmentally benign reagent that provides opportunities for both spatial and temporal control of polymerization. In addition to reversibly switching processes by simply turning the light "on" or "off," light further facilitates precise control over reaction kinetics by modulating the intensity of irradiation.

The well-recognized advantages of light as a stimulus are manifested in many practical and important processes, such as ultraviolet (UV) photocuring, photolithography, etc., that have resulted from photoinitiated radical and cationic polymerizations.[24] The infrastructure and knowledge currently associated with photochemical processes also adds significantly to the potential impact of photochemical mediation of controlled polymerizations. Current approaches are, however, fundamentally limited by using light to control only the initiation step of the polymerization process. In addressing this challenge, three strategies have made significant progress toward achieving such a system, including employing light to activate the monomer,[25,26] the polymer chain-end,[27] or a catalyst.[28]

The group of Manners and co-workers has reported a successful strategy for controlling anionic polymerizations based on monomer activation, where a silicon-bridged ferrocenophane monomer is the key component (Figure 6).[25,26] Irradiation of these cyclic monomers with UV light induces an excited state, thereby selectively weakening the Fe-cyclopentadienyl (Cp) bond and allowing for displacement of a Cp ligand by a weak nucleophilic initiator (NaCp). This initiation event forms an anionic Cp chain-end that can subsequently propagate with additional excited monomers. Propagation, therefore, relies on continued photoirradiation to excite the cyclic monomers and polymerization stops when the light is turned off. Polymerization proceeds in a controlled manner and displays the characteristics of a living system, affording well-defined polymers (PDI < 1.10) with theoretical molecular weights matching experimental observations. This excellent control further allowed the synthesis of block copolymers. The dynamic control and well-defined polymerization make this system almost ideal; however, the limitation

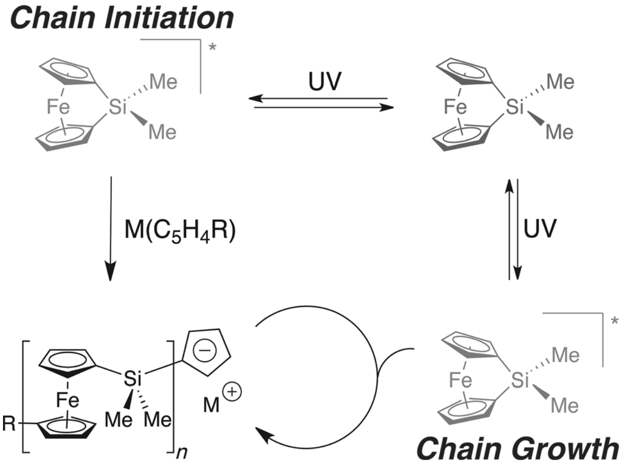


Figure 6. Monomer activation: anionic polymerization of silicon-bridged ferrocenophanes mediated by monomer excitation with UV light.

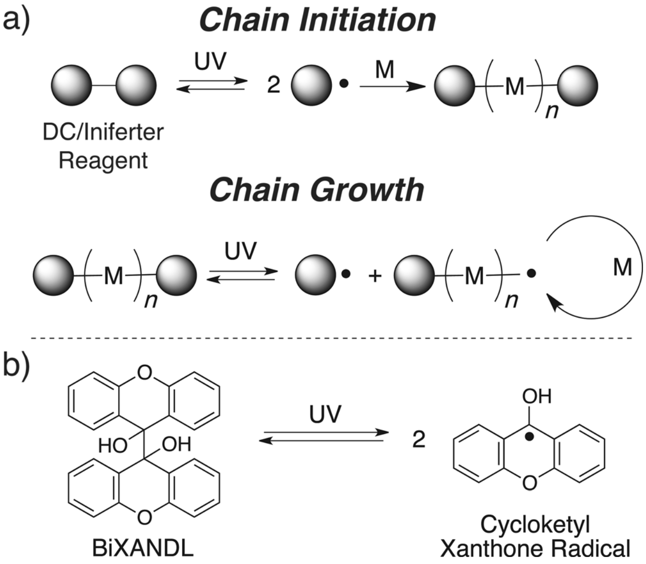


Figure 7. Chain-end activation: a) general mechanism for DC polymerization (M = monomer); b) the DC reagent BiXANDL and its light mediated fragmentation to give cycloketyl xanthone radicals.

of using only specialized, strained ferrocene monomers limits the potential of this specific system. Nevertheless, this strategy of photochemical monomer activation holds great promise and clearly defines the development of other activatable monomers as a future direction.

Photoactivation of the polymer chain-end is potentially a more synthetically accessible approach, with light-sensitive alkoxyamines for nitroxide mediated radical polymerization,[29–32] iniferter (initiator-transfer agent-terminator)[33] or dissociation/combination (DC)[34] reagents being developed in an effort to control radical polymerizations. Although promising, light-activated alkoxyamines have not led to a system that provides controlled polymerizations. Related to these alkoxyamine studies, preliminary work on the photolysis of organotellurium functionalized polymers also holds considerable promise, although the dynamic nature of these systems has not yet been reported.[35,36]

Iniferter and DC polymerizations, which were pioneered by Otsu[33] and Braun,[34] involve homolytic cleavage of an initiator into two radical species upon exposure to UV light (Figure 7). In this system, one radical initiates polymerization and the second acts as a reversible terminating agent to give the dormant polymer. Ideally, further exposure to UV irradiation would homolytically cleave the chain-end, thus allowing continued propagation. This reversible homolysis and termination then affords a photocontrolled polymerization process. The most successful system based on this concept comes from Yang and co-workers employing a new DC reagent, 9,9′-bixanthene-9,9′-diol (BiXANDL).[27] Upon photolysis, BiXANDL fragments into two cycloketyl xanthone radicals. These stabilized, yet reactive radicals are able to efficiently initiate polymerization as well as reversibly terminate the chain-end. Moderate control over the observed molecular weight and molecular weight distributions (PDI = 1.25–1.82) has been demonstrated for the polymerization of acrylates, methacrylates and a styrenic monomer. Further, the polymerization can be reversibly activated or deactivated by cycling exposure to UV irradiation. Although a significant advance, this system suffers from thermal instability of the polymer chain-end and poor control over molecular weight and PDI.

The direct photoactivation of a catalyst holds perhaps the greatest potential for regulating controlled polymerizations with light, as one only needs to control ppm levels of a catalytic species and not every monomer or every chain end. The past few years have witnessed an explosion of literature mediating small molecule organic transformations by visible light using photoredox catalysts,[37] although the temporal control of such processes remains largely unexplored. In an innovative report employing these photoredox catalysts for photocontrolled polymerization, Hawker and co-workers have developed a living free radical polymerization of methacrylates that is efficiently controlled by visible light.[28] The power of this process is a result of controlled polymerization under irradiation and the highly responsive, efficient, and reversible chain termination upon removal of the light (Figure 8a). Mechanistically, an Ir-based catalyst undergoes excitation with a photon to afford an $Ir^{III}*$ species (Figure 8b). The excited catalyst is highly reducing and reacts with an alkyl bromide to give the desired alkyl radical, which initiates polymerization. The resulting Ir^{IV} can then oxidize the alkyl radical chain-end back to the dormant alkyl bromide and the entire process can be repeated with an additional photon of light. The final result is a controlled/living radical polymerization process that leads to polymers with control over molecular weight and low molecular weight distributions (PDI = 1.19–1.25). More importantly, the polymerization can be reversibly, and in a highly responsive manner, activated or deactivated by light and has been extended to produce block copolymers.

While initial work demonstrated the polymerization of only methacrylate monomers, this mechanism should be applicable to a range of monomer systems in analogy to traditional ATRP processes.[2,38] Further, the extension of this temporal control to provide spatial control through standard

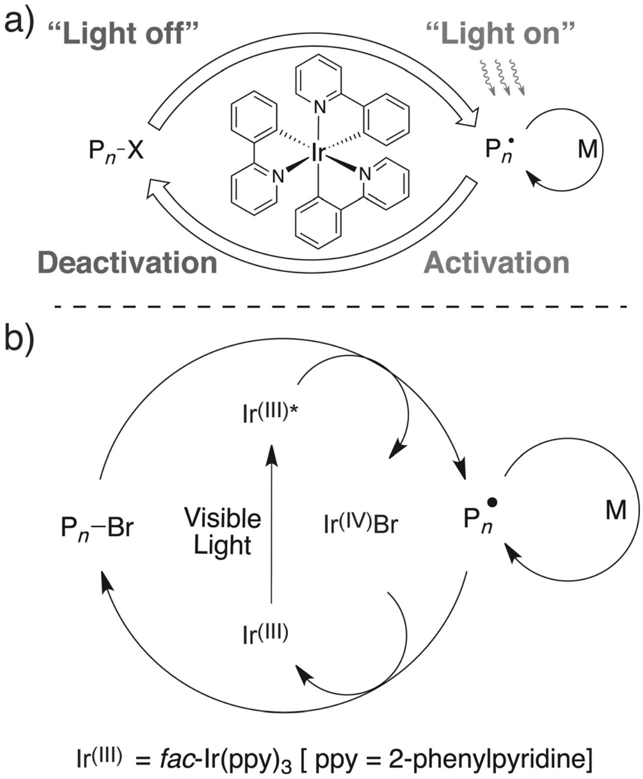


Figure 8. Catalyst activation: a) a schematic illustration of the photoredox radical polymerization concept and b) a detailed mechanism of a living radical polymerization controlled by light using a photoredox catalyst. (Adapted with permission from reference [28].)

photomasks is highly relevant and requires no major changes to this photochemically controlled, living radical process. Future challenges entail exploring the full range of polymerizable monomers and moving away from exotic metals, such as iridium, as the catalytic species and the preparation of functional macromolecules (i.e. block copolymers) with external command of final structure, architecture, and sequence.

2.5. Mechanochemical Control

In contrast to the previously described external methods for control, the application of mechanical force is a newer concept and has been proposed as a novel stimulus to affect chemical reactivity.[39] In these processes, mechanical stresses can trigger a variety of chemistries, including bond cleavage,[40,41] retrocycloadditions,[42,43] and can even enable thermally inaccessible reaction pathways.[44,45] During such "mechanochemistry", polymer chains usually act as actuators, gathering and translating externally applied energy to the site of chemical transformation, which is often termed the mechanophore. Sonication is one of the most efficient methods to apply mechanical force in solution with strong shear-forces being created around collapsing cavitation bubbles, stretching linear polymers and accumulating significant stress midchain.[46]

While reversible bond scission is key to mechanochemical control of polymerization, most recent work in this field has focused on enabling discrete, irreversible chemical reactions.[39] However, these studies illustrate the potential for this approach and seminal work from Sijbesma and co-workers has demonstrated the first example of the reversible mechanochemical cleavage of metal-ligand bonds.[47] Extending this concept to an organometallic catalyst, they subsequently demonstrated control of polymerization through the application of mechanical force.[48] A ruthenium alkylidene complex was synthesized with axial N-heterocyclic carbene (NHC) ligands that are known to require elevated temperatures ($>80\,°C$) to dissociate, leading to catalytic activity (Figure 9).[49] Both NHC ligands were substituted with long polytetrahydrofuran chains to act as actuators, enabling mechanochemical cleavage of the Ru-NHC bond upon sonication. Significantly, GPC and NMR studies found that complete scission required sonication for 75 min (when M_n (pTHF) = 17k) and bond dissociation was irreversible. The catalyst was then used for the ring-opening polymerization of cyclooctene, reaching almost 90% conversion after sonication for two hours at low temperature (20 °C). Mechanochemical catalyst activation was confirmed by control experiments with minimal conversion being observed in the absence of sonication, or with sonication in the presence of a catalyst with butyl groups in place of the polymer actuators. Slow catalyst activation is a significant challenge for this system, leading to reduced control over molecular weight (PDI of 1.6 at 90% conversion). Further, as the latent catalyst is not regenerated after mechanochemical cleavage, interruption in sonication, therefore, causes only a pause in polymer initiation and does not reinitiate established polymer chains.

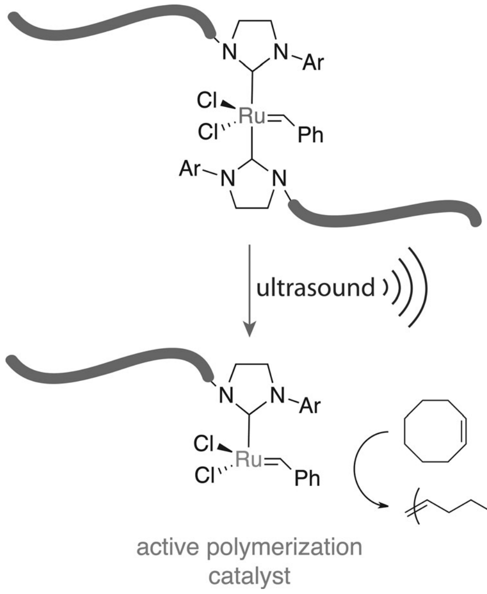


Figure 9. The mechanochemical scission of a Ru–NHC bond and the subsequent ROMP of cyclooctene.

Subsequent work using a highly strained norbornene system proved the existence of the active ring opening metathesis polymerization (ROMP) catalyst well after cessation of sonication, confirming that sonication only provides polymer initiation with catalyst decomposition being the primary mode of termination, not reformation of the latent complex.[50] Another limitation of this system results from the mechanochemical scission of the polymers being formed from ROMP. Lastly, addition of the polymer chain to the NHC ligand negatively affects catalyst activity of the Ru catalyst, as the second order rate constant for ROMP of norbornene derivatives by the polymer-bound catalyst is 20 times lower than for the corresponding small molecule, third-generation Grubbs catalyst.[50]

Bielawski and co-workers took a conceptually different approach to mechanochemically controlling polymerization. They utilized the dissociated ligand instead of the metal as an initiator for the polymerization of α-trifluoromethyl-2,2,2-trifluoroethyl acrylate in solution.[51] Their system, which is based on the mechanochemical cleavage of a pyridine ligand from a palladium pincer complex, shows reversibility of ligand binding after mechanochemical cleavage. A base-mediated mechanism was therefore employed to irreversibly initiate polymerization, where the free pyridine ligand released upon sonication initiated polymerization. Once the ligand reacts with a monomer, however, it cannot rebind the metal and therefore control of chain growth is not possible.

Whilst mechanochemical control of polymerization using sonication will be limited by the rate of ligand scission and the potential for scission of covalent bonds in high molecular weight product polymers, the evaluation of different metal-ligand systems and the possibility of activating catalysts in a thermally inaccessible manner holds significant potential.[52] A challenge for the future involves development of a system that combines the reversible ligand scission demonstrated by Bielawski with the use of a polymerization catalyst by Sijbesma. Such a mechanochemically controlled polymerization strategy would allow dynamic control of polymerization and could be applied to amplify mechanical stresses in materials and enable self-healing or diagnostic reporting of damage.

3. Outlook and Future Directions

Dynamic regulation of polymer synthesis, as evidenced by this Minireview, is a burgeoning field with potential to uncover fundamentally new chemistry with unexpected applications. To date, the most successful methods for temporally controlling polymerizations, as shown by *e*ATRP and visible light mediated polymerization, rely on switching the activity of the polymerization catalyst "on" and "off." These approaches allow for the use of well-understood commodity monomers, polymerization mechanisms, and offer the greatest opportunities to approach an ideal system. Further, the ease and efficiency of these methodologies allow for their quick adoption in academic and industrial laboratories.

The ability to regulate catalyst activity in situ, however, is understandably underdeveloped. Synthetic chemists have traditionally focused their efforts on making catalysts with exceedingly high activity, chemoselectivity, and enantioselectivity, without an express need to turn a reaction "off". As modern chemistry looks more to multicomponent systems in order to solve pressing challenges in interdisciplinary areas, a number of research groups have started to look at how they can manipulate the activity and structure of catalysts to respond to applied stimuli.[53] The following examples are not only instructive for future catalyst design, but also provide a number of unique conceptual approaches for the dynamic control of reactivity in material systems.

Drawing inspiration from both organic chemistry and natural systems, chain folding holds significant potential for temporally controlled polymerizations.[54] An early example comes from the work of Dervan and co-workers, who designed a peptide derivative containing a crown ether-type structure that bind metal ions such as Ba^{2+} or Sr^{2+}.[55] Upon metal binding, the peptide fragment folds into a conformation primed for DNA complexation and cleavage (Figure 10 a).

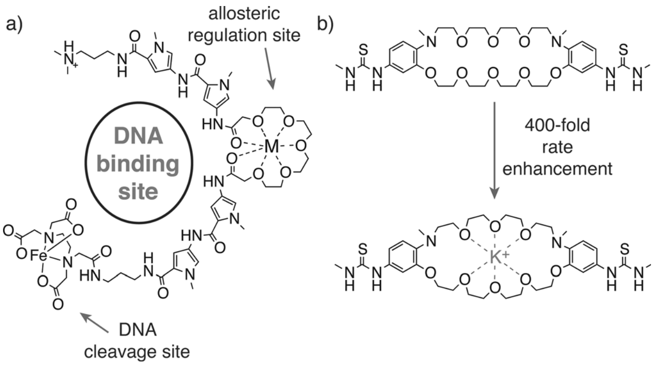


Figure 10. Examples of synthetic allosteric catalyst systems that show a large rate increase upon metal binding to crown ether-like moieties.

Employing a similar concept with a bisthiourea based organic catalyst, Kubo and co-workers relied on K^+ binding to bring the two organocatalytic moieties into close proximity, thus achieving a 400-fold rate enhancement for phosphate diester cleavage (Figure 10 b).[56] Similar strategies can be envisaged for the external control of polymerization reactions and as described above, arguably the most successful application of allosteric catalysis in synthetic systems has been the WLA of Mirkin and co-workers.[15,57] They have developed tweezer, sandwich, and triple-layer geometries for a number of transformations that rely on the weak binding of Lewis acidic moieties to metal centers (See section 2.1 for mechanistic details). Although all of the synthetic allosteric systems reported thus far have used metal-ligand chemistry to trigger a switch in catalyst geometry, conformation changes initiated by binding organic "signaling" molecules would be advantageous for spatially and temporally controlling polymerizations.

The potential also exists to use multiple stimuli in order to impact catalyst activity or reaction rate. Perhaps the simplest example of this strategy involves modulating the macroscopic solubility properties of a catalyst through an external stimuli (i.e. chemical oxidation, light, or pH), which in turn alters reactivity. Grubbs-type ruthenium metathesis catalysts have served as a platform for these efforts with Plenio and Süßner pioneering this concept through the synthesis of diferrocenyl-tagged Ru catalysts (Figure 11 a).[58] In this case, the neutral ligand is a highly active catalyst in toluene; however, addition of two equivalents of an oxidant leads to formation of cationic ferrocenyl complexes, causing the Ru catalyst to precipitate from solution, thus stopping catalysis. Addition of a reductant reformed the neutral and soluble catalyst, allowing the reaction to resume. In a complementary system, a change in solubility was externally controlled through irradiation of a spiropyran photoswitch appended to a Ru metathesis catalyst (Figure 11 b).[59] UV light causes a ring-opening of the spiropyran to its zwitterionic form, whereas thermal relaxation of the spiropyran reforms the hydrophobic, neutral species. This solubility switch allows light to be used as a switchable phase transfer mediator, enabling temporal control of the reaction. Lastly, a number of groups have designed systems wherein pH changes affect the rate of reactivity. This concept has been employed to alter the ligand environment of a catalyst to control hydrolysis[60] and epoxidation[61] reactions. Further, Dunbar et al. altered the rate of ROMP through the protonation of amine containing ligands on ruthenium metathesis catalysts.[62,63] Both solubility and pH switches hold promise as bulk property switches that can control polymerization rate, which is attractive for dynamic control of a number of large-scale systems.

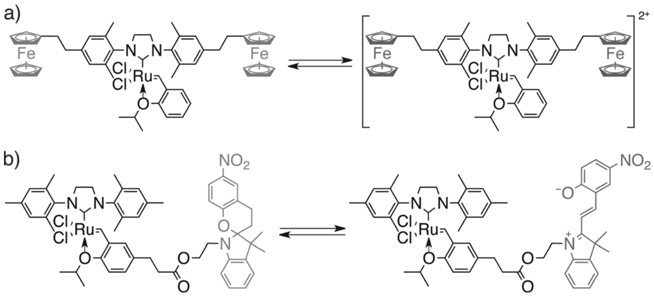


Figure 11. Solubility switches control catalysis by either oxidation of diferrocenyl units (a) or the photoswitching on spiropyran (b).

Similar to the spiropyran mentioned previously, small molecule photoswitches have also provided a practical method for externally controlling a number of chemical processes. In a seminal report on catalysis, Hecht and co-workers extended the use of the azobenzene photoswitch toward reversibly modulating the activity of an organic catalyst.[64,65] As shown in Figure 12 a, the tertiary amine organic catalyst is sterically inaccessible from substrates in its resting state. Upon irradiation with UV light, the *trans* to *cis* isomerization of azobenzene allows substrates to access the organocatalytic amine, thus catalyzing a nitroaldol (Henry) reaction. Recently, Bielawski and co-workers reported a photoswitchable NHC through the use of a diarylethene scaffold (Figure 12 b).[66] Significantly, photoswitching modulated the electronic properties of the NHC organocatalyst, leading to a 100 fold rate increase for the more electron rich, open form of the NHC in amidation reactions.[67] In a complementary manner, Feringa and co-workers used a light induced photoswitch not to activate or deactivate a process, but instead to determine the stereochemical outcome of a reaction—a fascinating glimpse into the future of tacticity control for macromolecules in general (Figure 12 c).[68] Such reversible, external control of a catalyst through photoswitching remains an under-developed concept and while Feringa and Hecht both employed photoswitches to sterically block a catalyst, other modes of regulation including competitive inhibition, reversible ligand binding, and catalyst proximity can be envisaged.[69]

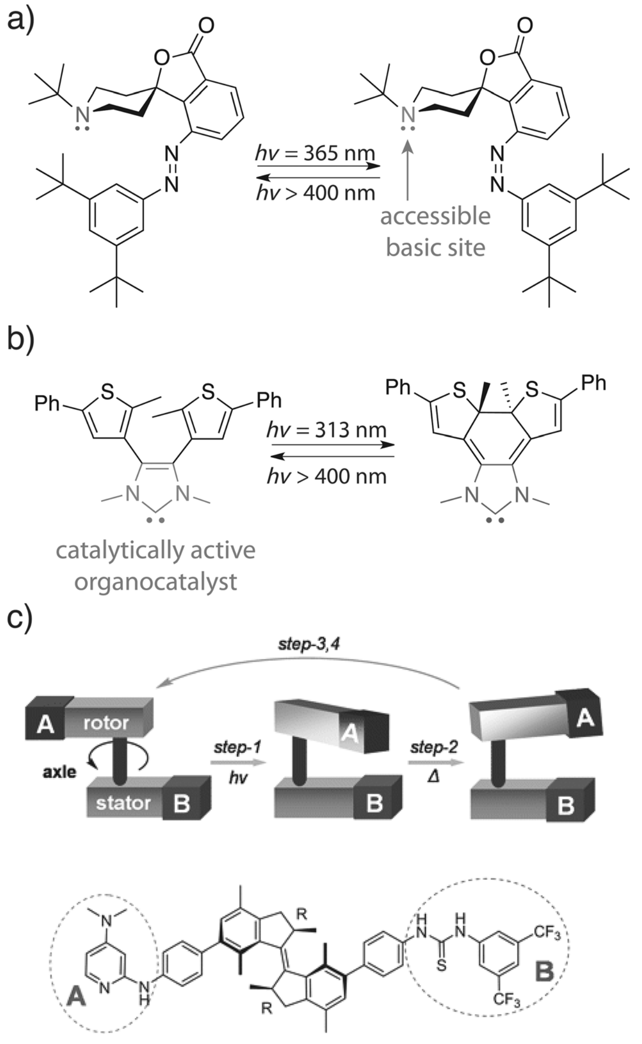


Figure 12. Light regulated catalyst systems based on photoswitches can dynamically a) regulate basicity, b) change the electronic properties of a catalyst or c) modulate the location of an intramolecular cocatalyst (Part (c) adapted from reference [68] and reprinted with permission from AAAS.)

In order to realize the full potential of temporal control, again Nature provides insights into future directions. Dynamically controlling not only polymerization but also depolymerization is a fascinating concept that microtubules employ to regulate cellular processes. Further, similar to the mechanism of the ribosome, combining temporal control with the concepts of compartmentalization and multi-component systems would allow control over not only when a polymerization takes place, but could also allow segregation from other reactions and/or processes occurring simultaneously.[70,71] Pausing a polymerization would also allow the addition and templation of a desired monomer type or monomer sequence. Unifying the spatial and temporal control of reactivity with template directed polymerizations similar to the systems of O'Reilly[72] and Sleiman[73] and/or with the work on sequence controlled polymerizations being pursued by Lutz[74,75] and Sawamoto,[76–78] will provide synergistic complex systems that move toward the grand challenges of dictating the primary structure of polymers and creating self-regulatory and "smart" processes.

4. Conclusions

The impact of controlled polymerization and orthogonal, "click" chemistry on modern polymer chemistry cannot be overstated. These advances have allowed an unprecedented level of control and functional group tolerance to be combined with the necessity to make these systems simple, user-friendly and available to non-experts in various fields. Ideas, concepts and applications for these advances have been drawn from organic chemistry, materials science, and biology, leading to a vibrant and evolving research area. It is this ability to look beyond the narrow confines of a single discipline that is one of the strengths of modern polymer chemistry and many parallels can be found in the burgeoning field of temporal and spatial regulation of controlled polymerizations. With this in mind, the significant potential provided by the development of an ideal dynamic and externally controlled polymerization process is a relevant and timely challenge for both chemists and material scientists. Success in expanding the palette of controlled polymerizations that can be regulated by external stimuli will allow the concept of "on-demand" preparation of well-defined functionalized macromolecules to be fully realized and new applications, structures, and physical properties discovered.

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