Integrating molecular switching and chemical reactivity using photoresponsive hexatrienes*

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Abstract: The use of photoresponsive hexatriene architectures to regulate chemical reactivity is described. The major focus of this report is how the two isomers of dithienylethene derivatives exhibit different steric and electronic properties. The ring-open form is structurally flexible, and the thiophene rings are electronically insulated from each other, while the ring-closed counterpart has a rigid structure, and there is a linear π-conjugated pathway along the molecular backbone. Representative examples that demonstrate how these photoswitches can be used to influence metal coordination, catalysis, and nucleophilicity are highlighted in this overview.

Keywords: molecular switches; photochromism; photochemistry; dithienylethenes; hexatrienes.

Molecular architectures that can be reversibly and predictably transformed between two isomers having properties unique to their structure have the potential to contribute to numerous materials science applications [1]. Compounds containing photoresponsive hexatriene substructures are particularly appealing, and the number of reports describing the use of these light-activated molecular switches in data processing and optical filter technologies has been growing rapidly [2]. One of the most promising hexatriene backbones is found in 1,2-dithienylethenes (DTEs), a class of photoswitches that can be toggled between two thermally stable and topologically distinct isomers when exposed to UV and visible light to induce ring-closing and ring-opening reactions, respectively (Fig. 1) [3]. Most reports focus on the photoregulation of the optical properties of DTE derivatives such as how they absorb, emit, refract, and rotate light, or on the changes in magnetism or charge transfer with the view of advancing controllable devices such as optical information processing, display materials, and molecular electronics [4]. In addition to the application of DTE derivatives to these technologies, our research interests involve harnessing the structural and electronic differences between the ring-open and ring-closed isomers of DTE derivatives to influence chemical reactivity. This underutilized behavior of DTEs has the potential to advance synthetic methods, photolithography, chemical sensing, and drug delivery. Our recent progress in this area is the focus of this overview.

The DTE backbone is well suited to modulate chemical reactivity and can be integrated into the design of photoactive catalysts and reagents, which will benefit from both the steric and electronic changes produced by the reversible ring-closing reactions. In its ring-open state (**DTE-*o*** in Fig. 1), there is relatively free rotation around the two carbon–carbon bonds joining the thiophene heterocycles to the

central cylopentene ring. This structural flexibility has two consequences on the groups labeled as "R" in the scheme: (1) they can converge toward each other and form a binding pocket (**DTE-*o'***) and (2) they are electronically insulated from each other and should be electronically independent. Photoinduced ring-closing generates a rigid structure (**DTE-*c***) containing a linearly conjugated π-electron pathway running along the DTE backbone. This transformation restricts bond rotation and forces any groups decorating the heterocycles to diverge away from each other, distorting the binding pocket in the ring-open state. It also creates a state where the ends of the conjugated pathway are in electronic communication and allows the groups labeled as "R" to sense the electronic nature of each other. Representative examples of both effects are described in this overview.
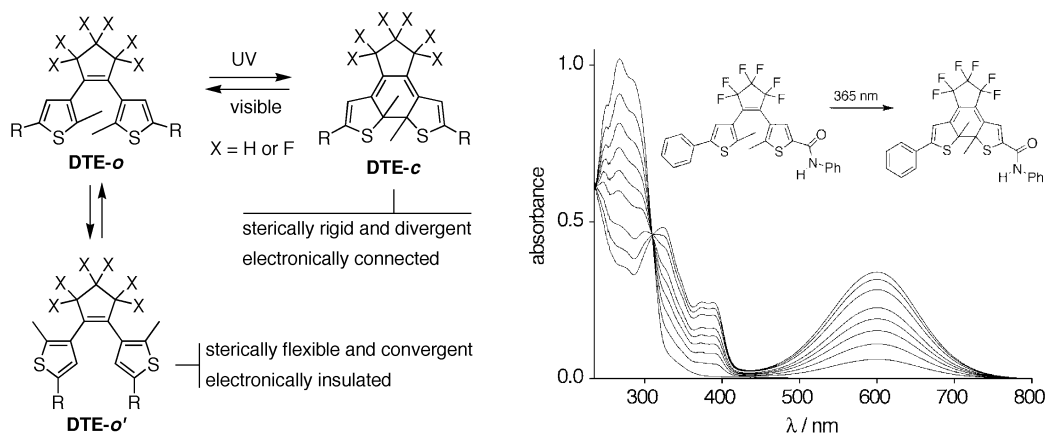

Fig. 1 Reversible light-induced cyclization of the generalized dithienylcyclopentene chromophore (left). Free rotation in the ring-open isomer results in a flexible, convergent, and electronically insulated state. The opposite is true for the ring-closed isomer. Irradiation of a representative example results in dramatic changes in the UV–vis absorption spectra (right) [5].

USING STERIC CHANGES TO REGULATE METAL BINDING AND CATALYSIS

The concept of regulating catalysis by artificial systems that take advantage of the changes in topology occurring after a photochemical event was introduced over two decades ago, and yet, it has not been extensively discussed in the literature. All the reported examples use the azobenzene structure as the switching elements and rely on the changes in molecular geometry that result from the light-induced *cis–trans*-isomerization reaction. For instance, Ueno and coworkers modified cyclodextrins with the photoswitchable azobenzene backbone to control ester hydrolysis [6]. In later reports, Rebek and Würthner [7] demonstrated that it was possible to influence amide formation in a hydrogen-bonded receptor by linking two adenine-binding surfaces by an azobenzene. A more recent example uses the azobenzene backbone as a photoresponsive spacer connecting two crown ether rings and shows that the bis(barium) complex acts as a phototunable catalyst for the ethanolysis of anilide derivatives [8]. Although, these elegant examples introduce and show the success of the concept of photomodulated catalysis, they are all limited by the thermal reversibility of the azobenzeme derivatives and cannot be used for practical applications.

Our approach takes advantage of the thermally irreversible photochemical ring-closing and ring-opening of catalysts built upon the DTE backbone and harnesses the differences in geometry of the two isomers to regulate metal-catalyzed reactions. Our first examples met with limited success [9]. Compounds **1** and **2** (Fig. 2) contain chiral oxazolines and were designed because bis(oxazoline) ligands that position transition metals in a C2-symmetric environment are commonly used as catalysts in

a wide variety of asymmetric processes [10]. Although the oxazoline ligands in the ring-open forms of compounds **1** and **2** seem to be too far apart to chelate a metal, this is an artifact of the way the structures are illustrated in the figure. The flexibility of the ring-open form of the DTE backbone allows the oxazoline rings to converge around the metal center (as shown for structure **DTE-o′** in Fig. 1). This prediction is supported by molecular modeling (Fig. 2, top left). The diverging oxazolines in the ring-closed form, on the other hand, are not appropriately positioned to chelate the metal or provide the C2-symmetric environment suitable for stereoselective catalysis.
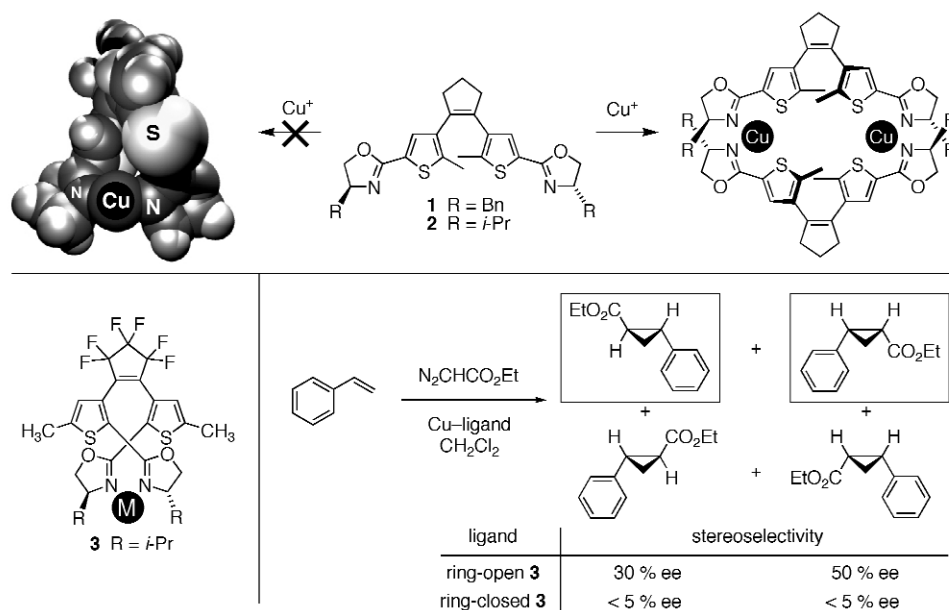
Fig. 2 Molecular model of the 1:1 complex formed when chiral bis(oxazoline) DTE derivatives **1** and **2** coordinate copper (top). This complex is not produced, and the optically pure binuclear helicate is the only product. Moving the oxazoline ligands to the C2-ring positions on the thiophenes prevents helicate formation and favors chelation by ligand **3** (bottom left). Stereochemical outcome of the copper-catalyzed cyclopropanation reaction of styrene using the ring-open and ring-closed isomers of **3** (bottom right). The major enantiomers are highlighted.

We chose the copper(I)-catalyzed cyclopropanation of styrene with ethyl diazoacetate as the model reaction to test the photoresponsive catalysts. This reaction produces four stereoisomers, two *trans*-enantiomers and two *cis*-enantiomers (Fig. 2, bottom right), and the ratio of these products is easily monitored by chiral high-performance liquid chromatography (HPLC) or gas chromatography (GC). However, the isomeric states of compounds **1** and **2** do not affect the stereoselectivity of the cyclopropanation reaction when they are used as ligands and neither the enantioselectivity nor the diastereoselectivity is systematically altered. In fact, in many cases, even the ring-open isomer does not generate consistent results when the reaction is repeated. These results are easily explained by the fact that the original prediction of the chelated structure shown in the upper left of Fig. 2 is not correct. The structure of the coordination compound of ring-open **1** and copper(I) in the single crystal reveals that it is a double helicate composed of two ligands wrapped around two metal centers (Fig. 2, top right) [9].

Moving the oxazoline rings from the "external" positions (at C5 on the thiophene rings) to the "internal" positions (at C2 on the thiophenes) prevents the formation of the double helicate in the flexible ring-open form and forces the metal to reside within the C2-chiral environment (Fig. 2, bottom left) [11]. When the ring-open form of compound **3** is used as the ligand in the cyclopropanation reaction, measurable enantioselectivities are observed, albeit they are low. The ring-closed counterpart does not
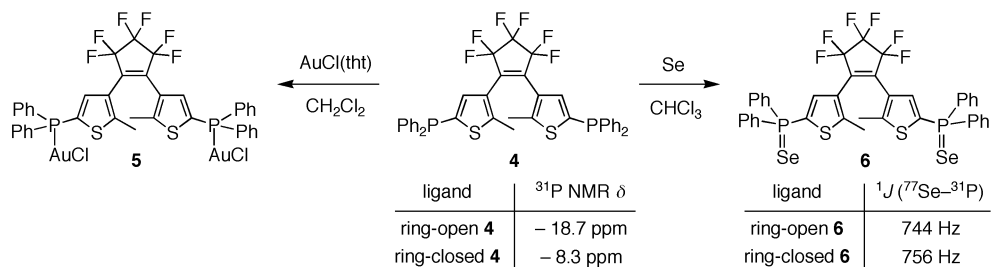
provide a suitable coordination environment for the metal owing to the more rigid architecture and, as anticipated, when a solution containing 97 % of the ring-closed isomer (produced by irradiating ring-open **3** with 313-nm light and isolating the ring-closed form by chromatography) is used as the ligand, the reaction shows insignificant stereoselectivity for both the *trans-* and the *cis*-products. The stereoselectivity can be increased by irradiating the reaction mixture with visible light (>434 nm) to regenerate the ring-open ligand.

USING ELECTRONIC CHANGES TO REGULATE METAL COORDINATION

Compound **3** represents the first example where the structure of a metal-binding pocket is reversibly altered to dictate the outcome of a stereoselective reaction using a DTE ligand as a photoresponsive catalyst. Our interests in photoregulating metal binding extends far beyond the modulation of catalysis, and we are designing other DTE-based ligands to take advantage of the rich variety of properties that metal complexes offer. Including metals in the molecular design enhances the ability to fine-tune the light-absorbing and -emitting behavior, it provides means to tailor energy and electron-transfer processes, and it is well documented that the properties of metal centers are highly sensitive to both the steric and electronic environment around the photoresponsive ligand [12].

Most of the reported examples of photoresponsive metal-DTE complexes focus on the formation of coordination compounds and polymers using nitrogen-based ligands (pyridine, bipyridine, and phenanthroline) [13]. Since it is well established that the electronic and steric environment around phosphorus ligands leads to marked changes in the properties and reactivity of both the free ligand and their metal complexes [14], it is surprising that, until recently, there were no reported examples of dithienylethenes decorated with phosphines.

We have designed a photoresponsive bis(phosphine) **4** as a bivalent ligand, have used it to prepare gold and selenium complexes (Scheme 1), and have demonstrated that the state of the ligand (ring-open or ring-closed) affects the nature of the two bound metals in the latter example [15]. The electronic differences between the two bis(phosphine) isomers **4** is best demonstrated using ^{31}P NMR spectroscopy where there is a 10-ppm downfield shift of the signal when the ring-open isomer is cyclized to its ring-closed counterpart using 313-nm light. The transfer of the differences in the electronic makeup of the ligand onto the metal centers is illustrated by the magnitude of the spin-spin coupling constants $^{1}J(^{77}Se-^{31}P)$ in the phosphine selenide compound **6**, where the increased electron-withdrawing nature of the ring-closed backbone leads to an increase in the coupling constant [16] (Scheme 1). This observation confirms that the ring-open isomer of **4** is a stronger nucleophile than its ring-closed counterpart and the magnitude of the change is similar to values observed when one of the phenyl groups of a triphenylphosphine ligand, is substituted by an alkyl group.


ligand	^{31}P NMR δ
ring-open **4**	– 18.7 ppm
ring-closed **4**	– 8.3 ppm

ligand	$^{1}J(^{77}Se-^{31}P)$
ring-open **6**	744 Hz
ring-closed **6**	756 Hz

Scheme 1

USING ELECTRONIC CHANGES TO REGULATE NUCLEOPHILICITY

It can be argued that the electronic differences between two similar molecules are best illustrated by how the molecules react or interact with others, and it is surprising that there are only a few literature precedents of photoresponsive systems that take advantage of the changes in electronic properties to modulate chemical reactivity. Kimura and coworkers [17] describe an example where the photochemical fragmentation of a bis(monoazacrowned) malachite green dye leads to the complete release of a cation owing to the electrostatic repulsion with the resulting positively charged nitrogen atom in the crown ether ring. Lehn and coworkers [18] have used the fact that the electronic communication between a phenol and an electron-withdrawing pyridinium group across a DTE backbone can be photochemically created or disrupted to modulate the acidity of the phenol. More recently, a modified version of this system was reported whereby an electron-donating methoxy group is introduced at the internal position of the thiophene bearing the phenol group leading to a more pronounced difference in pKa values between the ring-open and ring-closed isomers [19]. Irie and coworkers [20] have also demonstrated that the coordination geometry around a copper(II) ion can be photoregulated using the bis(pyridine) version of the DTE architecture.

One example from our research efforts focuses on how the differences in the π-conjugation between the ring-open **7** and the ring-closed **8** isomers of a mono-alkylated bis(pyridine) DTE derivative affects the nucleophilicity of the free nitrogen atom (Fig. 3) [21,22]. Because the two thiophenes in isomer **7** are electronically insulated from each other, the nucleophilic pyridine will not sense the electron-withdrawing behavior of the pyridinium group. Ring-closing creates the communication between the free pyridine and the electron-withdrawing pyridinium (shown in bold in **8** in Fig. 3) and reduces its nucleophilic strength. We have demonstrated the success of this concept by examining the rates at which the free pyridines in **7** and **8** are alkylated [21] and by how they selectively form coordination complexes with metalloporphyrins [22].
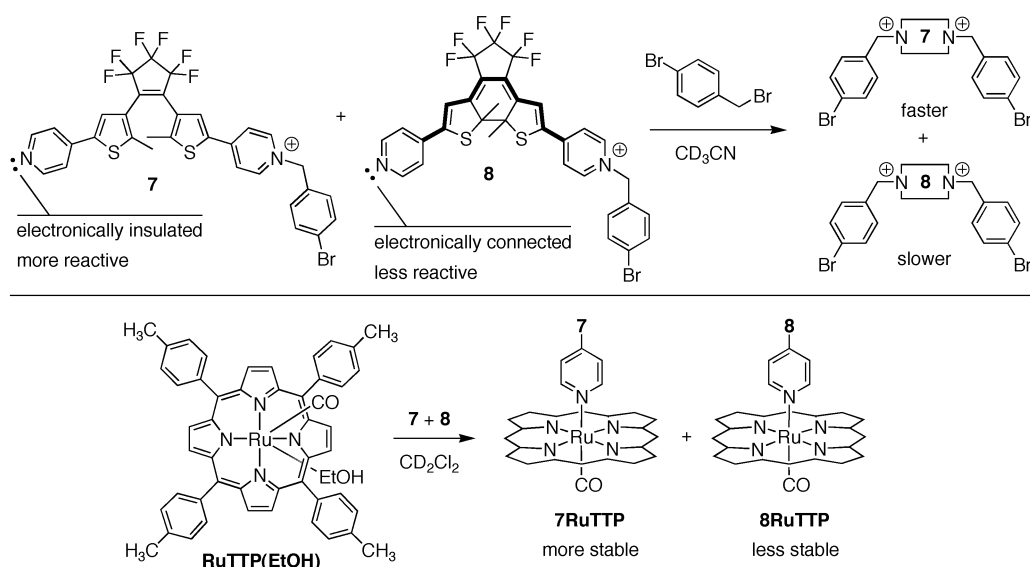

Fig. 3 Monocationic DTEs **7** and **8** display differing reactivity due to the changes in electronic communication between the two sides of the photoresponsive backbone (top) resulting in different rates of alkylation. The same electronic differences result in differing ability to coordinate to metalloporphyrins (bottom).

The reaction of an equimolar solution of ring-open **7** and ring-closed **8** monocations with an excess of 4-bromobenzyl bromide reveals that, as expected, the former compound is more reactive and forms its dication product first (Fig. 3, top). Subjecting each isomer independently to these pseudo-first-order conditions produces linear kinetic responses for both compounds and shows that **7** reacts 3 times faster than **8** [21].

Similar results can be obtained by examining the stability of axially substituted metalloporphyrin complexes prepared with **7** and **8** and Ru(TTP)(CO)(EtOH), a motif we have previously used to generate multicomponent supramolecular complexes [23]. Because the N–Ru binding is slow on the ^{1}H NMR time-scale [24], the presence of sharp and unchanging peaks corresponding to "free" and "bound" pyridines when less than one molar equivalent of Ru(TTP) (CO)(EtOH) is added to a 1:1 mixture of the ring-open **7** and ring-closed **8** isomers allows the quick assessment of the binding selectivity in a single NMR experiment. When the relative ratios of the peak integrals for the bound (**7RuTTP** and **8RuTTP**) to free (**7** and **8**) ligands (Fig. 3, bottom) are compared, it is clear that the ring-open isomer is approximately 1.5 times more effective as a ligand than its ring-closed counterpart [22]. This disappointingly low selectivity is due, in part, to the fact that the free pyridine ring is not completely coplanar with the conjugated backbone of **8** and will not feel the full effect of the electron-withdrawing pyridinium at the other end of the delocalized π-electron system. Other photochromic ligands may provide better selectivity.

Previous work from Yokoyama and coworkers [25] and our group [26] have independently established that replacing one of the thiophene heterocycles with a trisubstituted alkene produces a hexatriene system that retains its photoresponsive properties. We chose to investigate the differences in reactivity between the ring-open **9** and ring-closed **10** isomer of the dicyanoethylene-thienylethene (DCTE) architecture shown in Scheme 2.
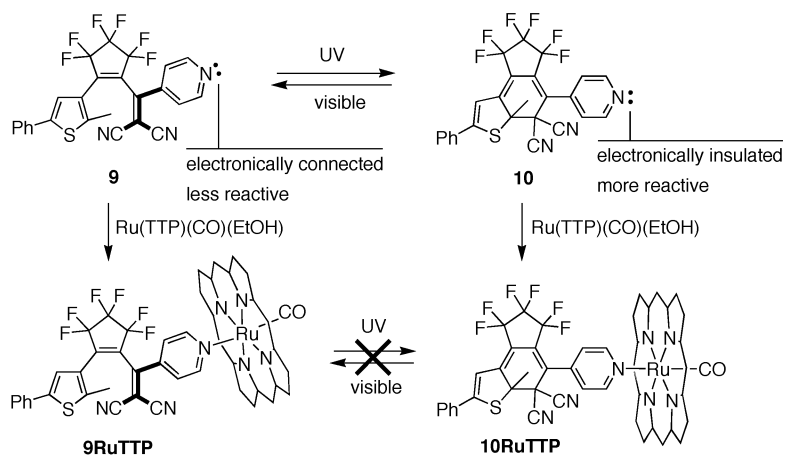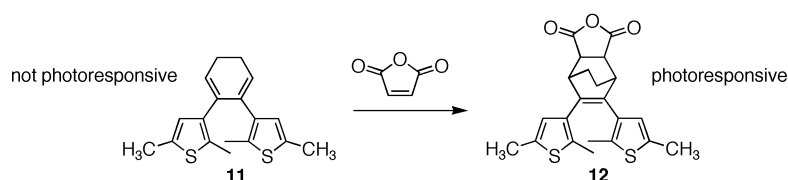

Scheme 2

In the ring-open form, the pyridine can sense the electronic pull of the electron-withdrawing dicyanoethylene group through the linear π-conjugated pathway (shown in bold in the scheme). Irradiation with UV light generates the ring-closed isomer **10**, where the pyridine is insulated from the dicyanoethylene group due to the change in hybridization of the carbon bearing the two nitrile functional groups from sp[2] to sp[3]. This photoinduced transformation should, therefore, lead to a compound that can act as a stronger coordinating ligand. When less than one molar equivalent of Ru(TTP)(CO)(EtOH) is added to a 1:1 mixture of **9** and **10**, the ^{1}H NMR spectra reveal that the ring-closed form acts as a stronger ligand for the metalloporphyrin and **10RuTTP** is the major product of the reaction. Unfortunately, it appears that the metalloporphrin has a detrimental effect on the photo-

chemistry of the organic ligand and, once either coordination complexes is formed, it no longer retains its photoresponsive behavior. We have observed similar effects with other complexes [27].

AN ALTERNATIVE APPROACH TO INTEGRATE CHEMICAL REACTIVITY AND PHOTOCHROMISM

All of the systems described so far in this overview are examples where the photochemistry regulates chemical reactivity by toggling the compounds between two isomers that have different properties. The alternative is reactivity-gated photochemistry. In this approach, the compounds do not contain an architecture that is suitable for photocyclization and are, therefore, not photoresponsive unless they first undergo a spontaneous chemical reaction to generate the hexatriene core. We have published an example of this concept and claim that it has significance in sensing and dosimetry applications [28]. This example is briefly described below to end this overview.

Scheme 3

Compound **11** does not contain a hexatriene, and irradiating with UV light does not induce a photocylization reaction. The compound does, however, contain a cyclic butadiene that can undergo Diels–Alder reactions with electron-deficient dienophiles such as maleic anhydride. The product of this thermal reaction (**12**) now contains a hexatriene as shown in Scheme 3 and closely resembles the dithienylcyclopentenes discussed throughout this overview. Compound **12** is photoresponsive, and irradiating it with 313-nm light induces the same ring-closing reaction as described for the other DTEs herein.

CONCLUSIONS AND PERSPECTIVES

Relating photoswitching and chemical reactivity in photoresponsive systems is a major goal in our research group. In this report, we have emphasized the versatile nature of the DTE backbone by showing specific examples where both the geometric and electronic properties of the ring-open and ring-closed photoisomers can be fine-tuned by rationally decorating the thiophene rings. It is critical that the group chosen to impart the desired steric or electronic effect does not interfere with the photoresponsive behavior of the system. Although these examples have successfully illustrated the concept of photoregulating reactivity, they are limited by the low selectivities and are not yet suitable for use in a practical setting. Further systems must be designed to improve the performance of the catalysts and reagents so that the ultimate goal of switching reactions on and off with light is achieved.

ACKNOWLEDGMENTS

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