Molecular Switches

Photoswitching of Stereoselectivity in Catalysis Using a Copper Dithienylethene Complex**

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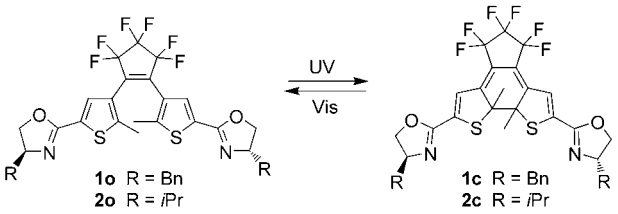
Harnessing the changes in molecular structure and function that occur when photoresponsive compounds are reversibly toggled between thermally stable isomers is becoming increasingly important to the development of molecular devices containing switching elements.[1] Compounds that undergo reversible photochemical transformations have been investigated for use in optoelectronic technologies and to a lesser extent, in influencing chemical reactivity. Although the concept of using the geometric changes that accompany a photoreaction to regulate chemical reactivity and catalysis was introduced over 20 years ago, only a few examples have been reported,[2–5] and all rely on azobenzene units as the photoresponsive structure. The large molecular movements that result from the *cis–trans* isomerization were shown to influence ester hydrolysis within modified cyclodextrins[2] or crowns ethers,[3] and amide formation in hydrogen-bonded receptors.[4,5] Although they remain elegant examples of the concept of photocontrolling catalysis, the photoresponsive azobenzene derivatives are plagued by thermal reversibility, which will significantly limit their practical use.

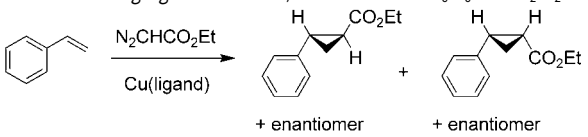
Compounds constructed from the 1,2-dithienylethene backbone represent a significant improvement over most other photoresponsive structures primarily because they undergo thermally irreversible photochemical ring-closing and ring-opening reactions.[6] Our goals include using the structural differences between the two photoisomers to influence the outcome of metal-catalyzed reactions. We prepared the chiral bis(oxazoline) ligand **1** with the expectation that it can only chelate to a metal when the photoswitch is in its flexible ring-open state, **1o** (Scheme 1).[7] This complexation places the metal center within a chiral environment ready to perform stereoselective reactions.[8] Irradiation with UV light will generate the ring-closed form, **1c**, which cannot chelate the metal because the photochemically produced rigid backbone forces the two oxazolines to exist in a divergent relationship to each other.



Scheme 1. Interconversion of ring-open (**o**) and ring-closed (**c**) isomers of **1** and **2**.

Our original work proved this anticipated metal-binding mode to be incorrect and instead of forming a chelated complex with copper(I), **1o** forms a double helicate, [Cu_2-(**1o**)$_2$], where two ligands are wrapped around two metals in a stereospecific manner.[7] This result helps to explain why there is no observable stereoselectivity when a metal-catalyzed reaction (cyclopropanation, see entry 1 in Table 1) is carried out using the *iso*-propyl version of bis(oxazoline) **2o** as the ligand (10 to 25 mol%).[9] However, the fact that **2o** may not be conformationally well-defined around the metal center so as to provide an appropriate chiral catalytic environment cannot be ruled out.[10]

Table 1: Results of the cyclopropanation reactions of styrene with ethyl diazoacetate using ligands **2** and **3**, and CuOTf·0.5 C_6H_6 in CH_2Cl_2.[a]



Entry	Ligand	*ee* [%][b]		d.r.[c]
		trans	*cis*	
1	**2o**	0	0	–
2	**3o**	30	50	55:45
3	23% **3c**[d]	11	37	70:30
4	97% **3c**[e]	5	5	63:37

[a] All values are averages of multiple runs using 10 mol% catalyst.[13] [b] Determined by HPLC analysis using a CHIRACEL-OD column. The values for the *cis* isomer are estimates owing to significant peak overlap in the HPLC traces. [c] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. The *trans* isomer was always found to be the major product. [d] Represents the photostationary state generated by irradiating a solution of the ligand with 313 nm light for 15 min. [e] Isolated from the photostationary state by centrifugal chromatography using 0.5% CH_3OH in CH_2Cl_2. The remaining 3% is **3o**.

One of the appealing features of photoresponsive dithienylethene compounds is the versatility with respect to what can be attached onto the thiophene heterocycles. Relocating the oxazoline groups onto the internal positions (thiophene C2) provides ligand **3o** that, according to computer modeling, cannot form a helicate with metal ions such as copper(I). This ligand is prepared from the known oxazoline **4** (Scheme 2) by taking advantage of the oxazoline to direct the lithiation to the C3 position on the thiophene.[11] Scheme 2 also illustrates the significant differences between the metal-binding pocket in the ring-open **3o** and ring-closed **3c** forms.

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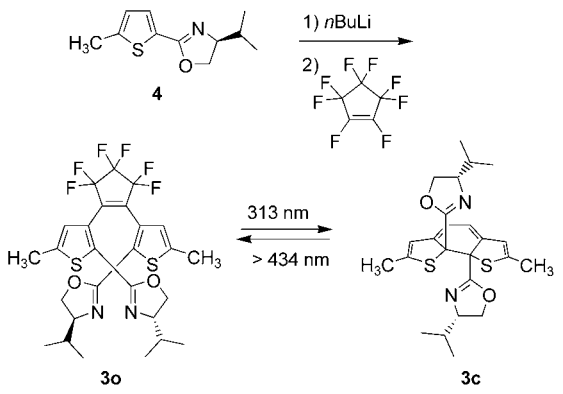

Scheme 2. Synthesis and photochemical cyclization of bis(oxazoline) **3o**.

Bis(oxazoline) **3o** can be toggled between its ring-open and ring-closed isomers by alternate irradiation with appropriate wavelengths of light as is best demonstrated using UV/Vis absorption spectroscopy (Figure 1). Irradiation of a

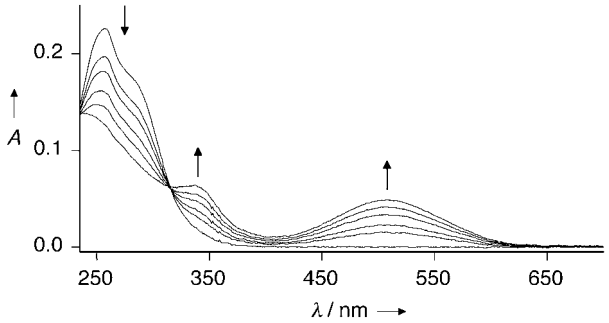

Figure 1. Changes in the UV/Vis absorption spectra of **3o** upon irradiation with 313 nm light. Irradiation periods are 0, 5, 10, 20, 30, and 60 s.

CH_2Cl_2 solution of **3o** with 313 nm light[12] results in the appearance of an absorption band in the visible spectral region ($\lambda_{max} = 510$ nm) and a visual change from colorless to deep red owing to the generation of the ring-closed isomer, **3c**. Irradiation of **3c** at wavelengths greater than 434 nm triggers the ring-opening photoreaction and the regenerates the original absorption spectrum corresponding to **3o**.

One reaction involving bis(oxazolines) as chelating ligands is the copper-catalyzed cyclopropanation of olefins with diazoesters, and is a good reaction to illustrate our concept because is provides a simple model reaction with an easy to analyze and well characterized product distribution. The results from the stereoselective cyclopropanation reactions of styrene with ethyldiazoacetate using bis(oxazolines) **2** and **3** are listed in Table 1.[13]

The low enantioselectivities observed when **3o** is used as the ligand (entry 2) and copper(I) trifluoromethanesulfonate ($CuOTf{\cdot}0.5\,C_6H_6$) as the metal source (10 mol% of each) are a result of the flexibility of the ligand around the metal center and are adequate to evaluate the efficacy of the bis(oxazoline) as a photoresponsive catalyst. When a solution of the **3o** is irradiated with 313 nm light to form the photostationary state[12] and the catalytic reaction is repeated using this solution as the ligand source, the enantioselectivities drop (entry 3). The small magnitude of the changes can be explained by the fact that the photostationary state generated under these conditions consists of 23% of the ring-closed isomer, **3c**, as identified by ^{1}H NMR spectroscopy. Although this low photostationary state is a temporary drawback, future generations of photoswitchable ligands based on the 1,2-dithienylethene scaffold will circumvent this limitation by taking advantage of the electronic tuning that can be tailored into the structure. Photostationary states containing a greater amount of the ring-closed isomer can be expected to display more significant differences in the product distribution when used as ligands in catalytic reactions. This assumption is confirmed when a purified sample of the ring-closed isomer, **3c**, is used as the ligand, in this case the enantioselectivities are insignificant (entry 4). The enantioselectivities can be turned back on by converting the ring-closed isomer back into its ring-open counterpart by irradiating the reaction mixture containing all the ingredients with light of wavelength greater than 434 nm[12] before the cyclopropanation reaction has finished. When this experiment is performed, the original values for the enantio- and diastereoselectivity are regenerated as a result of the photoinduced ring-opening reaction to regenerate **3o**, (**3c**→**3o**). This observation clearly demonstrates the in situ photoswitching of stereoselective catalysis and is the first example of its kind.

The photoinduced ring-closing reaction (**3o**→**3c**), however, is inhibited when the metal is present and irradiation of CH_2Cl_2 solutions of ligand **3o** and $CuOTf{\cdot}0.5\,C_6H_6$ results in no changes in the color or in the observed stereoselectivities. This inhibition is caused by the copper being too tightly bound within the ligand's chelation site to allow for photoswitching. The presence of the copper center prevents the ligand from undergoing the necessary geometric changes during the photoreaction. This problem is overcome by adding a small amount (5%) of the more competitive coordinating solvent CH_3CN to the CH_2Cl_2 solutions. When the cyclopropanation reactions are repeated using this solvent mixture, the outcome of the reaction can be photoregulated. For example, the enantioselectivity of the *trans* isomer of the cyclopropane product can be decreased from 23% to 10% by irradiating the CH_3CN/CH_2Cl_2 reaction mixture containing **3o** and $CuOTf{\cdot}0.5\,C_6H_6$ with 313 nm light to convert the ring-open isomer into the photostationary state.

Herein we have described the first example of photoregulation in metal catalysis using the established 1,2-dithienylethene photoswitch. Future reports will focus on expanding the range of reactions that will benefit from this molecular-level control as well as optimizing the photochemistry to afford more versatile catalysts.

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[9] It was originally anticipated that the ring-open isomer **2o** would induce a greater amount of stereoselectivity in the cyclopropanation reactions than the ring-closed isomer **2c**. However, when using **2o** resulted in no observable stereoselectivity, **2c** was never tested as a ligand.
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[12] Standard lamps used for visualizing thin-layer chromatography (TLC) plates (Spectroline E-series, 470 $\mu W\,cm^{-2}$) were used to carry out the ring-closing reaction of **3o** to **3c** with and without copper(I). The ring-opening reactions were carried out using the light of a 150-W tungsten source that was passed through a 434 nm cutoff filter to eliminate higher energy light.
[13] In a typical reaction, the oxazoline ligand (7.6 mg; 1.1 equiv) was dissolved in CH_2Cl_2 (1 mL) and $CuOTf{\cdot}0.5\,C_6H_6$ (5.5 mg; 1 equiv, 10 mol%; $OTf = [CF_3SO_3]^-$) was added. The solution was cooled to 0 °C in an ice bath and stirred for 30 min at which time an excess of styrene (100 μL) was added. After stirring for an additional 30 min, ethyl diazoacetate (10 μL) in CH_2Cl_2 (1 mL) was added using a syringe pump over 4–6 h while maintaining the solution at 0 °C. The solution was stirred overnight at room temperature, then filtered through a small plug of silica (CH_2Cl_2). The excess styrene was removed by gradient flash chromatography (silica, hexanes to 1:1 hexanes/ethyl acetate). The purity and identity of both diastereoisomers was verified with ^1H NMR spectroscopy. Both the *cis* and *trans* enantiomeric mixtures were analyzed by chiral HPLC using a CHIRACEL-OD chiral column (0.5 $mL\,min^{-1}$, 95:5 hexanes:2-propanol). Detection was adjusted at 220 nm, which is a maximum in the absorption spectrum of the *trans* isomers. A solution of *trans* enantiomers gave two peaks separated in their retention time by 3.7 min. The *cis* isomers were only separated by 0.4 min and were not baseline separated. It was however possible to distinguish both maxima and by deconvoluting the data using the software provided with the HPLC, the separate peak areas were obtained. The amount of catalyst can be lowered to 1 mol% with respect to the ethyl diazoacetate to produce 120 mg (63%) of the cyclopropanated products as a mixture of stereoisomers after workup and isolation by centrifugal chromatography (2% ethyl acetate/hexanes).

