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Redox Control over Acyl Hydrazone Photoswitches

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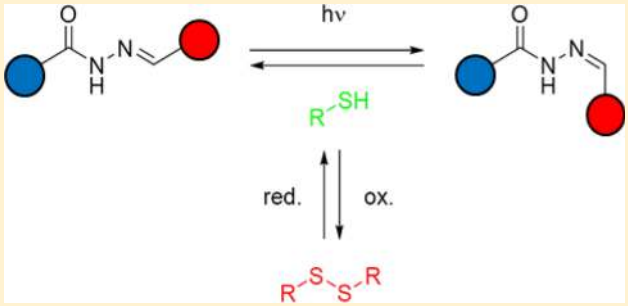
Supporting Information

ABSTRACT: Photoisomerization provides a clean and efficient way of reversibly altering physical properties of chemical systems and injecting energy into them. These effects have been applied in development of systems such as photoresponsive materials, molecular motors, and photoactivated drugs. Typically, switching from more to less stable isomer(s) is performed by irradiation with UV or visible light, while the reverse process proceeds thermally or by irradiation using another wavelength. In this work we developed a method of rapid and tunable $Z \rightarrow E$ isomerization of C=N bond in acyl hydrazones, using aromatic thiols as nucleophilic catalysts. As thiols can be oxidized into catalytically inactive disulfides, the isomerization rates can be controlled via the oxidation state of the catalyst, which, together with the UV irradiation, provides orthogonal means to control the E/Z state of the system. As a proof of this concept, we have applied this method to control the diversity of acyl hydrazone based dynamic combinatorial libraries.



INTRODUCTION

Photoisomerization, relying solely on the input of energy in form of light, is one of the cleanest ways of inducing changes in the physical properties of chemical systems. Photoswitches are relevant in areas ranging from materials science to pharmacology and have been applied in a broad range of systems, including responsive materials,[1] molecular receptors,[2] catalysts,[3] reaction networks,[4] molecular motors,[5] and photoactivated drugs.[6] For full control over switching, both the activation and deactivation processes must be controllable externally. While activation is typically performed by irradiation with visible or UV light, the reverse process often relies on thermal isomerization, the rates of which predominantly depend on the molecular design of the system. Dependence on the design of the system can be overcome by using E/Z isomerization catalysts, which has been demonstrated on olefins, diazenes, and hydrazones.[7] Besides that, electrochemistry and supramolecular chemistry have also recently been used to effect isomerization in photoswitches.[8] Nevertheless, the use of catalysts for the inversion of photoswitches has been underutilized.

Hydrazones, especially acyl-derived ones, have long had an important place in systems chemistry.[9] They have been used both for their ability to take part in dynamic combinatorial chemistry (DCC), by (acyl) hydrazone exchange,[7e,10] and for the (photo)switchability of their C=N bonds.[11] While their use in DCC is somewhat limited due to slow exchange rates, especially in macrocyclic systems,[12] they have nevertheless been one of the major tools to establish a new class of polymers, now known as dynamers,[13] in which dynamic covalent bonds allow for emergent properties such as self-healing. The isomerization of their C=N bonds has been applied in design of responsive materials[11d,j,k] or networks,[11b,c] and even in design of the first molecular robotic arm.[14] Besides that, acyl hydrazones have recently been recognized as a new class of photoswitches.[15]

As in other photoswitchable systems, $E \rightarrow Z$ isomerization in hydrazones is typically a light-driven process, while the reverse reaction can proceed thermally, through different mechanisms,[16] or by irradiation at a different wavelength. The thermal isomerization rates and absorption wavelength maxima can, in principle, be tuned, but such tuning usually requires changing the structure of the molecules. The question how to independently tune the thermal isomerization rates for a given system remains largely unanswered. In principle, altering global parameters like temperature or pH should affect isomerization rates, but is unlikely to only have impact on one of the isomerization steps. We decided to approach the problem in a more specific way, by using nucleophilic catalysts. Our approach was designed considering the formation mechanism of the hydrazones (Scheme 1a).[17] For acyl hydrazones the product is thermodynamically much more stable than both the starting materials and the carbinol intermediate, and the last dehydration step is fast in neutral and acidic aqueous environment. We assumed that the reversible acid-assisted addition of nucleophiles could lead to quick equilibration between the E and Z isomers without affecting the overall stability of the hydrazones (Scheme 1b, for the effect of pH upon isomerization see also Figure S27d). Moreover, if the nucleophile catalyst could be reversibly converted into a non-nucleophilic species, this conversion could be used as a handle to externally control the isomerization rates and therefore the overall state of the (photo)switchable system. Specifically, oxidation of nucleophilic thiols converts them into non-

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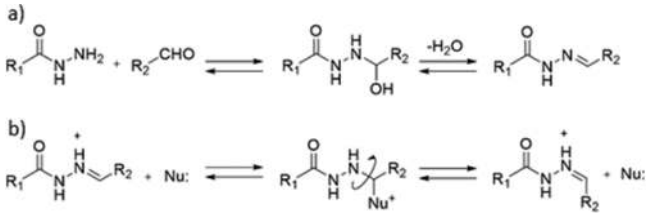
Scheme 1. (a) Key Steps in Formation of Acyl Hydrazones: Formation of Carbinol and Dehydration, and (b) Acid-Assisted Nucleophilic Catalysis of *E*/*Z* Isomerization[a]



[a]When an adduct is formed, the C=N bond becomes single and the rotation becomes possible, thus enabling isomerization.

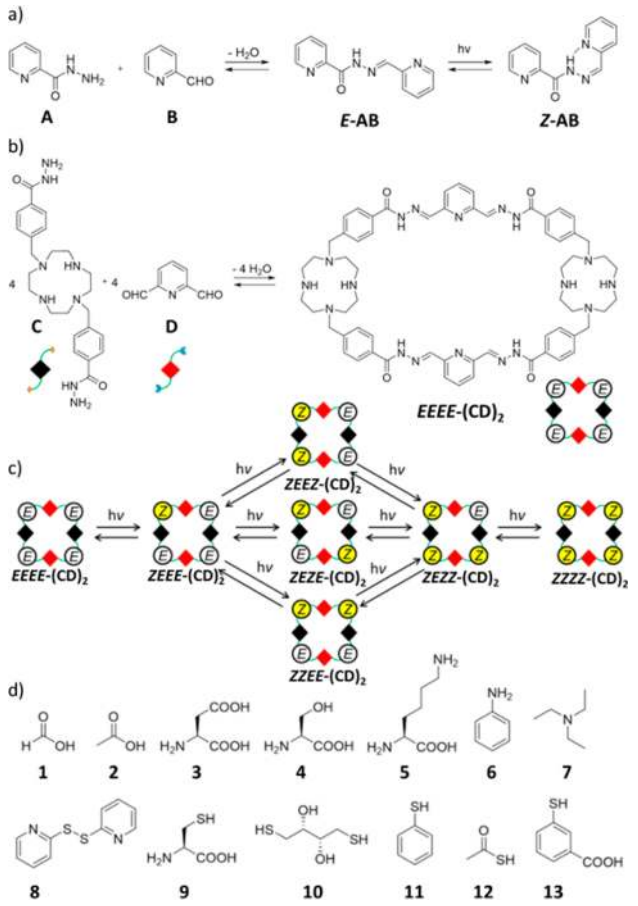
nucleophilic disulfides while reduction may be used to liberate the thiols again.

Using irradiation and switchable catalysts to control the composition of a photodynamic library is in fact a two-way control of the system. Catalyst decreases the activation energy but has no effect upon the relative energies of the products and therefore cannot influence the equilibrium composition of the library. However, photostationary states are not equilibria. Microscopic reversibility is broken, and now the catalyst can act selectively on the thermal step, i.e., the reverse reaction, leaving the photoisomerization step unaffected. This way orthogonal means of controlling the state of the system are achieved—light works in one direction and the catalyst in the other one, without mutual interference. Effectively, any point between the equilibrium and photostationary state of the system is thus reachable by activating one and deactivating the other input.

We decided to test our hypotheses using two different hydrazone systems, a linear one (**AB**, Scheme 2a) and a macrocyclic one (**CD**, Scheme 2b). In both cases, the *Z*-isomers are stabilized by intramolecular hydrogen bonds. For the linear hydrazone only one *E*/*Z* isomerization step can occur, thus enabling simple analysis of the catalytic efficiencies of the nucleophiles. The bifunctional hydrazide **C** and aldehyde **D** can form macrocycles of various sizes. Each of these macrocycles, by isomerization of their C=N bonds, could yield a family of stereoisomers (for $(\mathbf{CD})_2$ see Scheme 2c), for which the number of possible isomers grows rapidly with the size of the macrocycle, i.e., with the number of C=N bonds (3 for **CD**, 7 for $(\mathbf{CD})_2$, 16 for $(\mathbf{CD})_3$, 40 for $(\mathbf{CD})_4$, and so on). This means that combinatorial diversity originating from the different macrocycle sizes can be enhanced by the introduction of molecular isomerism. This concept has so far only been employed by using diazo compounds and sulfoxides,[18] while the isomerizable C=N bond in hydrazone-based dynamic combinatorial libraries (DCLs) has until now only been used as a linking moiety.[7e,10]

We explored nucleophilic catalysis of *Z*→*E* isomerization for a broad range of nucleophiles, including several carboxylic acids, amines, amino acids, and thiols (Scheme 2d). For example, we expected that aniline would catalyze the isomerization, since it has been successfully used as a hydrazone formation catalyst.[19] Also, it has been reported that thiols can catalyze *E*/*Z* isomerization in semicarbazones, compounds structurally similar to acyl hydrazones.[20] However, no systematic study of isomerization catalysts for acyl hydrazones has been reported.

Scheme 2. Materials Used for the Isomerization Experiments (a) Formation of Linear Hydrazone AB from Its Building Blocks and Its Isomerization,[a] **(b) Formation of E_4-$(CD)_2$ as a Characteristic Representative of the Macrocyclic System, (c) Possible Products of Isomerization of C=N Bonds in the $(CD)_2$ Macrocycles,**[b] **and (d) Nucleophiles Tested as *E*/*Z* Isomerization Catalysts: Formic Acid (1), Acetic Acid (2), Aspartic Acid (3), Serine (4), Lysine (5), Aniline (6), Triethylamine (7), 2,2′-Dipyridyldisulfide (8), Cysteine (9), Dithiothreitol (10), Thiophenol (11), Thioacetic Acid (12), and 3-Mercaptobenzoic Acid (13)**



[a]Note the N–H···N hydrogen bond stabilizing the *Z*-isomer. [b]Due to loss of molecular symmetry after the first isomerization step, three different isomers can be formed in the second step.

RESULTS AND DISCUSSION

Our experiments were performed in three phases. First we prepared, characterized, and tested the hydrazones for their photoswitching properties, using UPLC(-MS) and UV/vis spectroscopy for the analyses. After that we compared the catalytic efficiencies of the selected nucleophiles for *Z*→*E* isomerization both in the linear and macrocyclic hydrazones. Last, after finding the optimal isomerization catalyst, we used it to develop a method of quick and controllable *Z*→*E* isomerization of acyl hydrazone C=N bond. As the aromatic thiols were found to be the best catalysts, we decided to control the isomerization rates using the oxidation state of their sulfur atoms, since thiols are nucleophilic while disulfides are not.

Both the linear and macrocyclic hydrazones were prepared *in situ* prior to the isomerization experiments, by mixing equimolar solutions of the corresponding hydrazides (**A** or

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C) and aldehydes (**B** or **D**) in ammonium acetate buffer (pH = 4.0). Aside from lowering the pH to enable quick hydrazone formation, buffer was also used to control the protonation state of the hydrazones and therefore the isomerization rates (see Scheme 1b), thus excluding any catalytic effects via changes in acidity or basicity. For the preliminary experiments solid hydrazones were also used. When prepared *in situ*, both hydrazones formed within minutes, the linear one predominantly as the *E*-isomer (***E*-AB**; Figure 1a), later equilibrating to

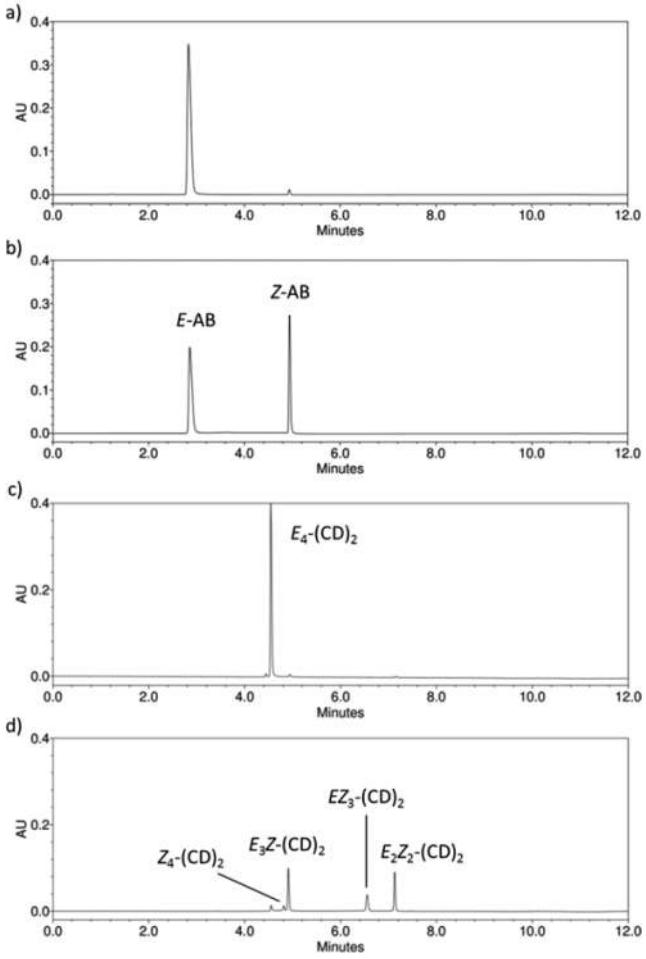

Figure 1. Chromatograms of the hydrazones prior to UV irradiation and in photostationary states: **AB** isomers prior to UV isomerization (a) and in photostationary state (b) (1.0 mM **AB** in water, irradiated with 365 nm UV light for 3 h); **CD** system at equilibrium, with E_4-$(\mathbf{CD})_2$ as the dominant species (c), and in the photostationary state, with five different isomers present (d) (0.15 mM $(\mathbf{CD})_2$ in water, pH adjusted to 4 using 1 M HCl, irradiated with 365 nm UV light for 55 min). For the kinetic profile of the photoisomerization see Figure S25, and for the reverse reactions see Figure S26.

E:*Z* ratio of 90:10, and the macrocyclic system first appearing as a mixture of isomers of various macrocycles, and later equilibrating into mostly E_4-$(\mathbf{CD})_2$ (Figure 1c; see also Figures S2−S23 for details on identification of the oligomers). No polymers were observed in the mixture, most likely due to the fact that it is entropically favorable to produce a large number of small molecules over a small number of large molecules. The dominance of $(\mathbf{CD})_2$ isomers over the smaller macrocycle **CD** is attributed to the strain resulting from the mismatch in distance between the two hydrazide groups in **C** relative to the two aldehyde groups in **D**.

Upon exposure to UV irradiation (365 nm) ***E*-AB** was converted to ***Z*-AB**, reaching *E*:*Z* ratio of 52:48 in the photostationary state (Figure 1b; for the changes in UV/vis spectrum during the irradiation see Figure S24a). The macrocycle $(\mathbf{CD})_2$, due to four isomerizable C═N bonds present in its molecules, showed more complex behavior upon irradiation (365 nm), being converted into a mixture of five isomers (Figure 1d; for the changes in the UV/vis spectrum during the irradiation see Figure S24b). The kinetic profile of the reaction (Figure S25b), aided by a simple kinetic model (see SI, section 6), suggested that the appearance of the $(\mathbf{CD})_2$ isomers follows the order shown in Scheme 2c, with either two E_2Z_2 isomers not appearing, or their peaks overlapping in the chromatogram. The multitude of C═N bonds in $(\mathbf{CD})_2$ also accounts for the small amount of the E_4-$(\mathbf{CD})_2$ remaining in the photostationary state, compared to the nearly 1:1 *E*:*Z* ratio in **AB**. First, four isomerizable bonds increase the E_3Z:E_4 ratio by 4-fold, as compared to the *E*:*Z* ratio in **AB**, and the subsequent isomerization steps further decrease the amount of E_4. The final distribution in the photostationary state is E_4:E_3Z:E_2Z_2:EZ_3:Z_4 = 3.5:22.9:42.2:26.4:5.1. The total *E*-to-*Z* ratio in the cyclic **CD** system is therefore 48:52, which is comparable to the 52:48 ratio observed for the linear **AB** system, suggesting that the hydrazone bonds photoswitch essentially independently from each other. Altogether, these results confirmed that, even for relatively small macrocycle sizes, combinatorial diversity can be significantly increased by using photoisomerization.

Isomerization catalysis experiments were first performed for the linear hydrazone **AB**, using 1.0 mM hydrazone solution in 20 mM ammonium acetate buffer (pH = 4.0), prepared from 2.0 mM photostationary solution of **AB**. Along with this solution, which also served as the reference system, a series of solutions was prepared that contained one of a range of nucleophiles (three amines **6**−**8**, two aliphatic thiols **9** and **10**, one aromatic thiol **11**, and thioacetic acid **12**; Scheme 2d). Immediately after the preparation, the composition of the mixtures, i.e., the ratio of the two isomers, was monitored by UPLC while irradiation was discontinued. The results (Figure 2a) show that thioacetic acid and thiophenol dramatically increase the rate of isomerization, while the amines and aliphatic thiols do not alter it significantly relative to the buffer. This strongly suggested that sulfur nucleophiles, fully or partially deprotonated, are superior catalysts for the *E*/*Z* isomerization of acyl hydrazones.

Subsequently, experiments with the macrocyclic system were performed, using a similar experimental approach, but now with a broader scope of nucleophiles (Figure 2b,c; note the different catalyst concentrations). Due to the combined effect of four isomerization steps instead of one and the rigidity of the macrocycle, the reverse isomerization in macrocyclic hydrazone was roughly an order of magnitude slower than that of the linear **AB** system, but the same trend in catalytic efficiency was observed. As with the linear hydrazone, again the most efficient catalysts were thioacetic acid and aromatic thiols, while amines could only show a comparable effect when added in 50-fold excess. The same was the case for carboxylates, which, compared to the isomerization rate in water acidified with HCl ("blank" in Figure 2b), explains the rather fast isomerization of the linear hydrazone in ammonium acetate buffer. Addition of isomerization catalyst to photoirradiated samples

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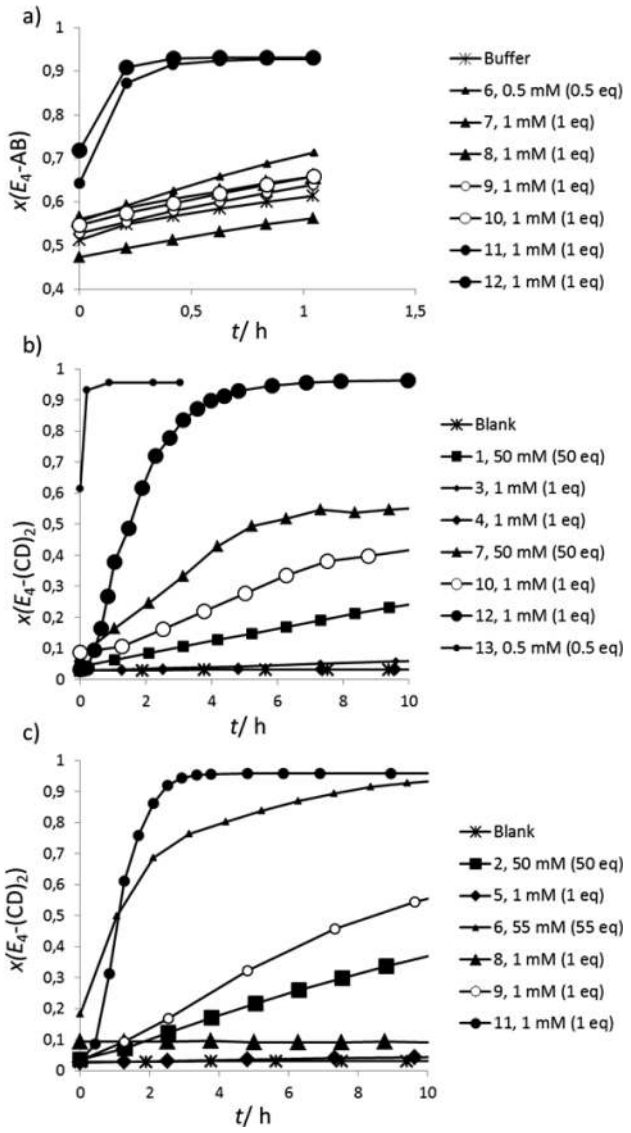

Figure 2. Comparison of various nucleophiles as $E \rightarrow Z$ isomerization catalysts for (a) linear hydrazone **AB** (1.0 mM **AB** in 20 mM aqueous ammonium acetate buffer, pH = 4.0) and (b,c) macrocycles $(\mathbf{CD})_2$ (0.25 mM $(\mathbf{CD})_2$ in 50 mM aqueous ammonium acetate buffer, pH = 4.0, except for blank, performed in water, pH set to 4 with HCl, and **1**, performed in 50 mM ammonium formate buffer, pH = 4.0). For clarity, in (a) only the amount of *E*-**AB** is shown, while in (b) and (c) only the amount of E_4-$(\mathbf{CD})_2$ is shown. Catalyst loading is shown in parentheses, after concentration, in equivalents relative to the total concentration of hydrazone groups. Large deviations in the starting fractions of the all-*E* isomers with the more efficient catalysts occur because of the conversion happening between the addition of the catalyst and the first sampling.

caused the isomer composition to return to ratios similar to those observed before photoirradiation (Table S2).

Having found that aromatic thiols and thioacetic acid are the best catalysts for *E*/*Z* isomerization in acyl hydrazones, we developed methodology that allowed controlling the isomerization rates via the oxidation state of the catalyst. It is well established that the nucleophilicity of thiols can be reversibly nullified by oxidizing them into disulfides. For our further experiments we chose 3-mercaptobenzoic acid (**13**), as it is better water-soluble than thiophenol, non-hydrolyzable in contrast to thioacetic acid, and, in contrast to both of these, it bears no detestable odor. Moreover, this thiol proved to be much more effective than any other tested nucleophile, being able to drastically increase isomerization rates (up to a factor 6300), retaining activity even when added in 10 μM concentration (1.0% catalyst loading; see Figure S27a and Table S3 for quantitative comparisons between catalysts and loadings).

To control the isomerization rates efficiently through the oxidation state of thiols, it is essential to achieve rapid oxidation and reduction, so that thiols can be quickly transformed into disulfides and *vice versa*. For that purpose we decided to employ iodine as the oxidizing agent and tris(2-carboxyethyl)phosphine (TCEP) as the reducing agent. Iodine (dissolved in aqueous KI solution) was chosen over commonly used peroxides for its much faster reaction rates with thiols, no formation of side products (peroxides tend to slowly overoxidize thiols), and the fact that it does not decompose over time.[21] Also, neither iodine nor iodide interferes with hydrazone chemistry, and a KI/I_2 solution did not show any catalytic activity in hydrazone isomerization (Figure S27b). TCEP was selected predominantly due to its quick and clean reaction with disulfides, while the fact that it is also a moderate isomerization catalyst (Figure S27c and Table S3) was not expected to affect the experimental outcome, as it is much less efficient than **13**.

In the first experiment (Figure 3a; see also Figure S28 for more details) restorability of the catalyst was tested. First, a sample of photostationary 0.25 mM library of $(\mathbf{CD})_2$ isomers was monitored by UPLC for about an hour, and then 1.0% **13** (final concentration 2.5 μM) was added. Immediately after the addition, a sharp increase of the isomerization rate was observed. After another hour, 1 equiv of iodine was added to oxidize **13** into the corresponding disulfide. This reduced the isomerization rate close to the initial level. In the last step, 1 equiv of TCEP was added to the solution, which was promptly followed by an increase in the isomerization rate. As TCEP was shown not to strongly affect the isomerization rates when present in 20 μM concentration (Figure S27c), the increase of the isomerization rate was evidently due to the reduction of **13** disulfide into the thiol. In addition, we performed an experiment in which **13** in various states of oxidation was added to the photostationary **CD** library. Again, the isomerization rates reflected the concentration of thiol groups, i.e., the oxidation state of the system, and not the initial concentration of **13** added (see Figure S29). These experiments confirmed that it is possible to control the rates of *E*/*Z* isomerization of acyl hydrazones solely by controlling the oxidation state of the (aromatic) thiols present in the solution.

For the full control over the *E*/*Z* state of the system, however, it is necessary to be able to switch the hydrazones in both directions. To confirm that the system can be again brought to the photostationary state without destroying the catalyst, we irradiated the sample with UV light after inactivating the catalyst (Figure 3b; see also Figure S30 for more details). Similarly to the previous experiment, first a 0.25 mM library in its photostationary state was monitored by UPLC for about an hour, and then 2.0% **13** (final concentration 5.0 μM) was added to the sample. The isomerization rate first increased rapidly and slowed down after 1 equiv of iodine was added. Next, instead of direct addition of TCEP, the sample was irradiated by 365 nm UV light in two 10 min sessions, which brought the system back to the photostationary state. Finally, after 1 h of monitoring the photostationary sample, 1 equiv of TCEP was added, and promptly the isomerization rate

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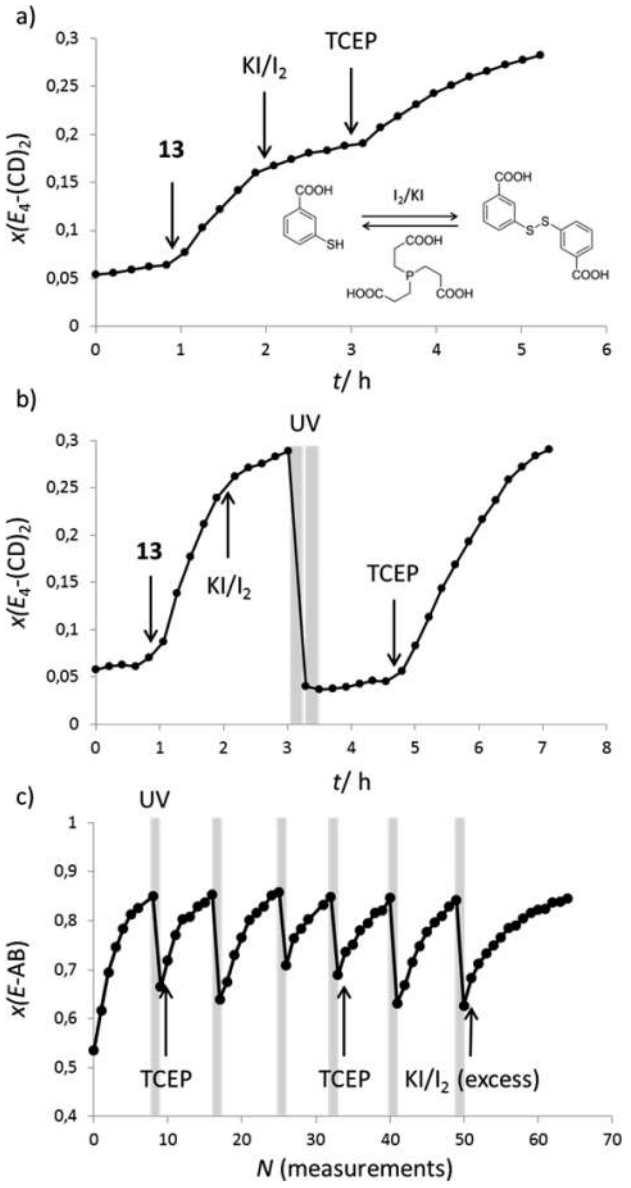

Figure 3. Control of E/Z state of hydrazones by UV and oxidation state of the isomerization catalyst. (a) Isomerization is enhanced by addition of **13** and retarded by oxidizing **13** with I_2. After the disulfide is reduced to thiol by TCEP, the isomerization is restarted (inset: oxidation and reduction of **13** by I_2 and TCEP, respectively). (b) Isomerization is enhanced by addition of **13** and retarded by addition of I_2. Irradiation by UV light (shaded) brings the system to the photostationary state, and the rapid isomerization can again be restarted by adding TCEP as a reducing agent. For clarity, only the amount of E_4-$(\mathbf{CD})_2$ is shown. Experiments were performed with 0.25 mM $(\mathbf{CD})_2$ in 20 mM aqueous ammonium acetate buffer, pH = 4.0. (c) Isomerization cycles on **AB** (1.0 mM in 20 mM ammonium acetate buffer, pH = 4) in the presence of active catalyst. Time intervals between two measurements are 10 min, except before the additions of TCEP, which was done after the sample was irradiated (indicated by gray shading) overnight.

was restored close to the value after the addition of **13**. This means that the disulfide, i.e., the inactivated catalyst (known to be photosensitive), is not destroyed by UV irradiation and can be reactivated by reduction at any time, without the need to add more of it. Thus, the thiol−disulfide system acts as a switchable catalyst for a molecular switch, in this case the acyl hydrazone system. This result was corroborated by a similar experiment with **AB** (Figure 3c) in which **13** was added to a photostationary solution of **AB** to start the quick isomerization. After approaching equilibrium the solution was irradiated to bring it again to a photostationary state (now different, due to the presence of active catalyst). This cycle was repeated six times. Finally oxidant was added to switch off catalysis by the thiols, which reduced the $Z\rightarrow E$ isomerization rate, although this reaction still proceeded, in part due to accumulation of catalytically active TCEP (which was used to reactivate **13** oxidized by atmospheric oxygen over time). Thus, these two experiments demonstrate the full compatibility between the (photo)switchable hydrazone, nucleophilic catalysis, and oxidation/reduction subsystems.

CONCLUSIONS

We have found that aromatic thiols are highly effective in catalyzing the E/Z isomerization in acyl hydrazones and that they (together with thioacetic acid) are far more efficient than any of the other tested nucleophiles (amines, carboxylic acids, aliphatic thiols). We have applied this finding in dynamic combinatorial chemistry, by controlling the distribution of macrocyclic $(\mathbf{CD})_2$ isomers in a small acyl hydrazone library, thus effectively controlling the diversity of the system. Thus, it is possible to influence product distributions of dynamic combinatorial libraries through catalysis in a non-trivial sense. Note that this is not normally possible, as product distributions in regular dynamic combinatorial libraries are under thermodynamic control and therefore unaffected by catalysis (catalysis only affects energies of transition states but does not change relative energies of starting materials and products). The concept works in this photodynamic system because photostationary states are not equilibria; microscopic reversibility is broken (catalysis can now act selectively on the thermal step, without affecting the reverse photochemical step).

Finally, we have shown that the thiol catalyst can be reversibly deactivated and reactivated by oxidation into disulfide and reduction therefrom, thus acting as a switchable controller[22] for hydrazone isomerization. In this way we have connected three subsystems: thiol/disulfide chemistry, nucleophilic catalysis of $Z\rightarrow E$ isomerization, and photochemical $E\rightarrow Z$ isomerization. Note that, when considering E/Z isomerization, disulfide and hydrazone chemistry are now interacting rather than orthogonal as we and others reported previously.[23]

These results have broader implications for systems chemistry and for photopharmacology. For the latter field, it is important to realize that cells can contain significant quantities of nucleophiles (human intracellular glutathione levels are in the millimolar range) which may counteract photoactivation. Conversely, intracellular nucleophiles could potentially be harnessed to reactivate photoinactivated drugs. In the context of systems chemistry, the newly established connection between thiol and hydrazone chemistries may also have utility for the design of complex systems containing feedback loops, far-from-equilibrium systems, or even systems mimicking switching between aerobic and anaerobic regimes. As E/Z isomerization constitutes an intramolecular motion, combination of light-driven isomerization and thiol-driven reverse isomerization could lead to new types of molecular motors or spatially controlled delivery of energy.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b03724.

Experimental details, MS spectra, additional experiments, and detailed kinetic profiles, including Schemes S1 and S2, Tables S1−S4, and Figures S1−S31 (PDF)

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Notes

The authors declare no competing financial interest.

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