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A Redox Isomerization Strategy for Accessing Modular Azobenzene Photoswitches with Near Quantitative Bidirectional Photoconversion

Jie S. Zhu¹, Julio M. Larach¹, Robert J. Tombari¹, Phillip W. Gingrich¹, Stanley R. Bode¹, Jeremy R. Tuck¹, Hunter T. Warren¹, Jung-Ho Son¹, Whitney C. Duim¹, James C. Fettingner¹, Makhluif J. Haddadin², Dean J. Tantillo¹, Mark J. Kurth^{1,*}, David E. Olson^{1,3,4,*}

¹Department of Chemistry, University of California Davis, One Shields Avenue, Davis California 95616, United States

²Department of Chemistry, American University of Beirut, Beirut, Lebanon

³Department of Biochemistry & Molecular Medicine, School of Medicine, University of California, Davis, 2700 Stockton Blvd., Suite 2102, Sacramento, California 95817, United States

⁴Center for Neuroscience, University of California, Davis, 1544 Newton Ct., Davis, California 95618, United States

Abstract

Photoswitches capable of accessing two geometric states are highly desirable, especially if their design is modular and incorporates a pharmacophore tethering site. We describe a redox isomerization strategy for synthesizing *p*-formylazobenzenes from *p*-nitrobenzyl alcohol. The resulting azo-aldehydes can be readily converted to photoswitchable compounds with excellent photophysical properties using simple hydrazide click chemistry. As a proof of principle, we synthesized a photoswitchable surfactant enabling the photocontrol of an emulsion with exceptionally high spatiotemporal precision.

Graphical Abstract

*Corresponding Author: deolson@ucdavis.edu, mjkurth@ucdavis.edu.

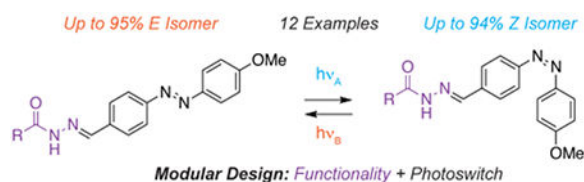
Author Contributions

J.S.Z., J.M.L. and R.J.T. contributed equally. J.S.Z., J.M.L., S.R.B., and M.J.H. synthesized the majority of the compounds described in the paper. R.J.T. performed the majority of the photoisomerization experiments. J.R.T. and H.T.W. synthesized and characterized **25**. P.W.G. and D.J.T. performed the computational experiments. J.-H.S. performed the high-resolution mass spectrometry experiments. J.C.F and J.-H.S. performed the X-ray crystallography experiments. W.C.D. assisted R.J.T. with the photoswitchable surfactant microscopy. M.J.K. and D.E.O. supervised experiments and wrote the manuscript with input from all authors. / All authors have given approval to the final version of the manuscript. / These authors contributed equally.

Supporting Information

Figure S1, Figure S2, Movie S1, Movie S2, Experimental procedures, characterization data, ¹H and ¹³C NMR spectra (PDF), and X-ray crystallography data (CIF).

The Supporting Information is available free of charge on the ACS Publications website.



The optical control of systems can be achieved by exploiting the photoisomerization of functional groups such as stilbenes, spiropyrans, diarylethenes, and fulgides.^{1,2} Of these, azobenzenes are prominent due to their large and rapid change in geometry, fatigue resistance, and tunability (Figure 1A).^{1,3} The greatest challenge associated with designing biologically relevant azobenzene photoswitches is ensuring that the two wavelengths of light used to induce photoisomerization are sufficiently red-shifted to maximize light penetration and minimize tissue damage, while achieving complete *E* and *Z* isomer conversion. Typically, irradiation of the *E* isomer with UV light induces isomerization to the *Z* isomer via a $\pi \rightarrow \pi^*$ transition, while visible light promotes *Z* \rightarrow *E* conversion via an $n \rightarrow \pi^*$ transition.⁴ The *Z* isomer $n \rightarrow \pi^*$ transition is symmetry allowed and more intense than that of the *E* isomer. However, the *E* and *Z* isomer $n \rightarrow \pi^*$ bands tend to overlap, making it challenging to achieve complete conversion to the *E* isomer, though strategies to separate the $n \rightarrow \pi^*$ bands of the two isomers have been reported.⁵ Another approach to obtain high *Z* \rightarrow *E* conversion relies on rapid thermal relaxation of push-pull azobenzenes, so-called “pseudo-stilbenes”.^{3a} The advantage is that their $\pi \rightarrow \pi^*$ transitions are red-shifted; however, this usually results in significant overlap of the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions, making it difficult to selectively irradiate one isomer and achieve highly enriched photostationary states (PSSs).

Challenges associated with azobenzene design often require these tools to be engineered on a case-by-case basis using azologization or azoextension strategies.⁶ This lack of modularity limits the ability of non-experts to design photoswitchable technologies. Therefore, we sought to design an azobenzene chromophore that could be conjugated to any pharmacophore or functional group through simple, robust chemistry to produce completely bidirectional photoswitches. We envisioned that an aldehyde would be an ideal handle to introduce moieties of interest via hydrazide click chemistry.⁷ However, access to azoaldehydes is not straightforward as most azobenzenes are constructed via the Mills reaction following nitroarene reduction or aniline oxidation (Figure 1B) to nitroso compounds — conditions not tolerated by redox-labile aldehydes. Alternatively, at the expense of step economy, *p*-nitrosobenzaldehyde can be synthesized via nitrosation of potassium trifluoroborates.⁸

Inspired by the Davis–Beirut Reaction (DBR), we envisioned a redox isomerization strategy for accessing *p*-formylazobenzenes from *p*-nitrobenzyl alcohol (**1**) (Figure 1C). The DBR delivers 2*H*-indazoles⁹ by N–N bond heterocyclization of *in situ* generated *o*-nitrosobenzaldehydes and ensuing primary amine condensation. Thus, we hypothesized that *p*-nitrosobenzaldehyde could be formed by treating *p*-nitrobenzyl alcohol with base. Subsequent aniline condensation with the nitroso-aldehyde would furnish azoimines hydrolysable to the desired azo-aldehydes. Herein, we report the synthesis of *p*-

formylazobenzenes through a redox isomerization strategy, their chromatography-free coupling to hydrazides, and the unique photophysical properties of the resulting modular photoswitches.

Treatment of *p*-nitrobenzyl alcohol (**1**) with KOH and an excess of commercially available anilines in MeOH/H₂O yields azoimines. Electron-rich anilines exhibit greater reactivity toward the transiently formed nitroso intermediate as compared to electron-deficient anilines. Selective imine to aldehyde hydrolysis is accomplished using aqueous acid. This procedure yields the desired *p*-formylazobenzenes in reasonable yields [~65% per step, Figure 2A; see Supporting Information for a detailed discussion (Figure S1)]. Experimental evidence supports the intermediacy of a nitroso-aldehyde: azoxy compound **7** was often observed¹⁰ and a Diels–Alder reaction with 1,3-cyclohexadiene can trap nitroso-aldehyde intermediate **2** producing **9** (20% yield, Figure 2B).

A proposed mechanism for formation of nitroso-aldehyde **2** is shown in Figure 2C. The p*K*_a of *p*-nitrotoluene is 20.4 in DMSO,¹¹ so benzylic deprotonation of *p*-nitrobenzyl alcohol (**1**) is a reasonable first step. Proton transfer yields **12** and hydroxide elimination furnishes **2**. While redox isomerization of *o*-nitrobenzyl alcohol is well precedented,¹² we report for the first time this transformation has been achieved using *p*-nitrobenzyl alcohol. However, *p*-nitrobenzyl alcohol is known to undergo redox isomerization following irradiation with light, generating the dimer of *p*-nitrosobenzaldehyde.¹³

Using hydrazide click chemistry,⁷ we were able to convert **8** into a variety of photoswitchable compounds in excellent yields (65–95%, Table 1). The simplicity of this procedure is of particular importance as it allows others without synthetic expertise to readily prepare novel photoswitchable tool compounds. Using ¹H NMR under constant sample irradiation,¹⁴ we characterized the PSSs of these modular photoswitches (Table 1). In general, moving from blue to red light resulted in PSSs more highly enriched in the *E* isomers. The half-life (*t*_{1/2}) for thermal isomerization of **13^Z** was 316 min at room temperature in DMSO-*d*₆. When a *Z*-enriched sample of **13** was illuminated sequentially from long to short wavelengths, photoisomerization was first observed at 625 nm, suggesting that the PSSs at 656 nm reported in Table 1 might be slightly impacted by thermal relaxation occurring during measurement of the PSSs.

While the isomeric enrichment of most azobenzene PSSs are typically only 70–80%, many compounds described here exhibited near quantitative bidirectional photoconversion regardless of what hydrazide was appended to the *p*-formylazobenzene. Our results suggest that the appended substrate does not influence the photophysical properties of the chromophore — thus, this chromophore can incorporate a variety of warheads without reducing photoswitching performance. While *individual* photoswitches capable of achieving near quantitative bidirectional photoconversion are known,^{5,15} most are not *modular* photoswitchable scaffolds. Ravoo and co-workers attempted to solve this problem by attaching a functionalizable carboxylic acid to the pyrazole nitrogen of an arylazopyrazole.¹⁶ However, flexible sp³-hybridized atoms between the tethering group and the photoswitch are not ideal as they increase conformational freedom tempering the stark structural differences between photoisomers.

While **13** undergoes nearly quantitative bidirectional photoconversion, its parent *p*-formylazobenzene **8** does not (Figure 3A). Inspection of their UV-Vis spectra reveals that more conjugated **13** absorbs more light at all wavelengths and exhibits a red-shifted λ_{max} for the $\pi \rightarrow \pi^*$ transition. Calculations predict a greater difference between the UV-Vis spectra of the *E* and *Z* isomers of modular photoswitch **13** as compared to *p*-formylazobenzene **8** at all wavelengths; this possibly explains why acylhydrazone containing **13** can achieve more highly enriched PSSs (Figure S2).

While **13** was derived from the reaction of an azoaldehyde with a hydrazide, we reasoned that modular photoswitches could also be prepared by reacting an azohydrazide with an aldehyde. Therefore, we synthesized **25** — a constitutional isomer of **13** resulting from the transposition of the acylhydrazone atoms. Surprisingly, **25** was unable to achieve highly enriched photostationary states (Figure 3) suggesting that it is not simply increased conjugation, but rather the specific array of atoms in the acylhydrazide that endows **13** with unique photophysical properties.

These photoswitches contain two potential photoswitchable groups — the azobenzene and the acylhydrazone.¹⁷ However, at biologically relevant wavelengths, we only observe photoisomerization of the azo group — not the acylhydrazone — even after extended irradiation. Time-dependent density functional theory was used to predict differences in electron densities between ground and excited states for **13^E** and **13^Z** (Figure 4). Differential electron density surfaces depict electron density primarily over the azo motif, with far less observed over the acylhydrazone motif.

This difference potentially explains why the *E* acylhydrazone configuration is retained during visible light-induced photoisomerization of the azo group. Furthermore, independent switching of two photoswitchable motifs is often not observed when the two functional groups are electronically coupled, as in **13**. However, through careful molecular design, photoswitchable functional groups within the same molecule can be electronically decoupled from each other to achieve independent photoswitching.¹⁸

Finally, we used our modular strategy to engineer **24** (see Table 1) — a compound with a polar cationic head group and a hydrophobic azobenzene tail capable of serving as a photoswitchable surfactant (Figure 5). A number of photoswitchable surfactants have been developed,¹⁹ as they enable colloidal system control, coordinated drug delivery, and the study of biological processes occurring at membranes. However, most photoswitchable surfactants have not demonstrated quantitative photoswitching and require long irradiation times (minutes to hours) to induce phase separation.

Compound **24** is a unique high performance photoswitchable surfactant. First, **24** achieves PSSs highly enriched in either the *E* or *Z* isomer in both DMSO-*d*₆ (93% *E* or 94% *Z*) and D₂O (88% *E* or 80% *Z*; Figure 5A) with half-lives of 435 and 434 minutes, respectively. Dissolving **24** in water prior to addition of benzene gives an emulsion that can be readily controlled by light. Under 350 nm light, **24^E** photoisomerizes to the more polar **24^Z**, resulting in droplet fusion and increased phase separation within 2 seconds (Figure 5B; left). To ensure that this was not due to heating upon irradiation, we used a non-photoswitchable

cationic surfactant (cetrimonium bromide) as a control. Irradiation of a benzene-water emulsion containing cetrimonium bromide did not lead to increased phase separation or changes in droplet morphology (Figure 5B; right). While light-induced phase separation is unidirectional, we demonstrated temporal control of this process by illuminating the edge of a benzene droplet with two distinct wavelengths of light. Under 350 nm irradiation, the benzene droplet begins to expand into the aqueous layer; this process can be instantly halted by switching to 560 nm light (Movie S1). Phase separation is initiated and halted by toggling between these two light wavelengths. The rapidity of this process is remarkable and contrasts sharply with other photoswitchable surfactants that require minutes to hours of irradiation for noticeable changes in emulsion properties.

To demonstrate spatial control, we sought to visualize the distribution of **24** in the emulsion — **24** is fluorescent when irradiated at 470 nm. As expected, the surfactant is localized to the benzene-water interface, with some areas possessing more surfactant than others. When the entire field of view was illuminated at 350 nm, regions of high surfactant density underwent the most drastic phase separation, which occurred in <2 seconds (Figure 5C/Movie S2). This is the first time a photoswitchable surfactant has been visualized at the interface between two immiscible liquids using fluorescence microscopy and highlights the importance of surfactant geometry for controlling surface tension.

In conclusion, we have developed a redox isomerization strategy inspired by the DBR. Our *p*-formylazobenzenes are easily functionalized with a variety of groups in high yields to produce *modular* photoswitches capable of achieving PSSs highly enriched in either the *E* or *Z* isomer depending on the wavelength of light employed. As a proof of principle, we developed a high performance photoswitchable surfactant enabling control of an emulsion with high spatial and temporal precision. The ease of this chemistry coupled with the exceptional photophysical properties of these modular photoswitches greatly expands the use of photoswitchable tools for applications in biology, materials science, and beyond.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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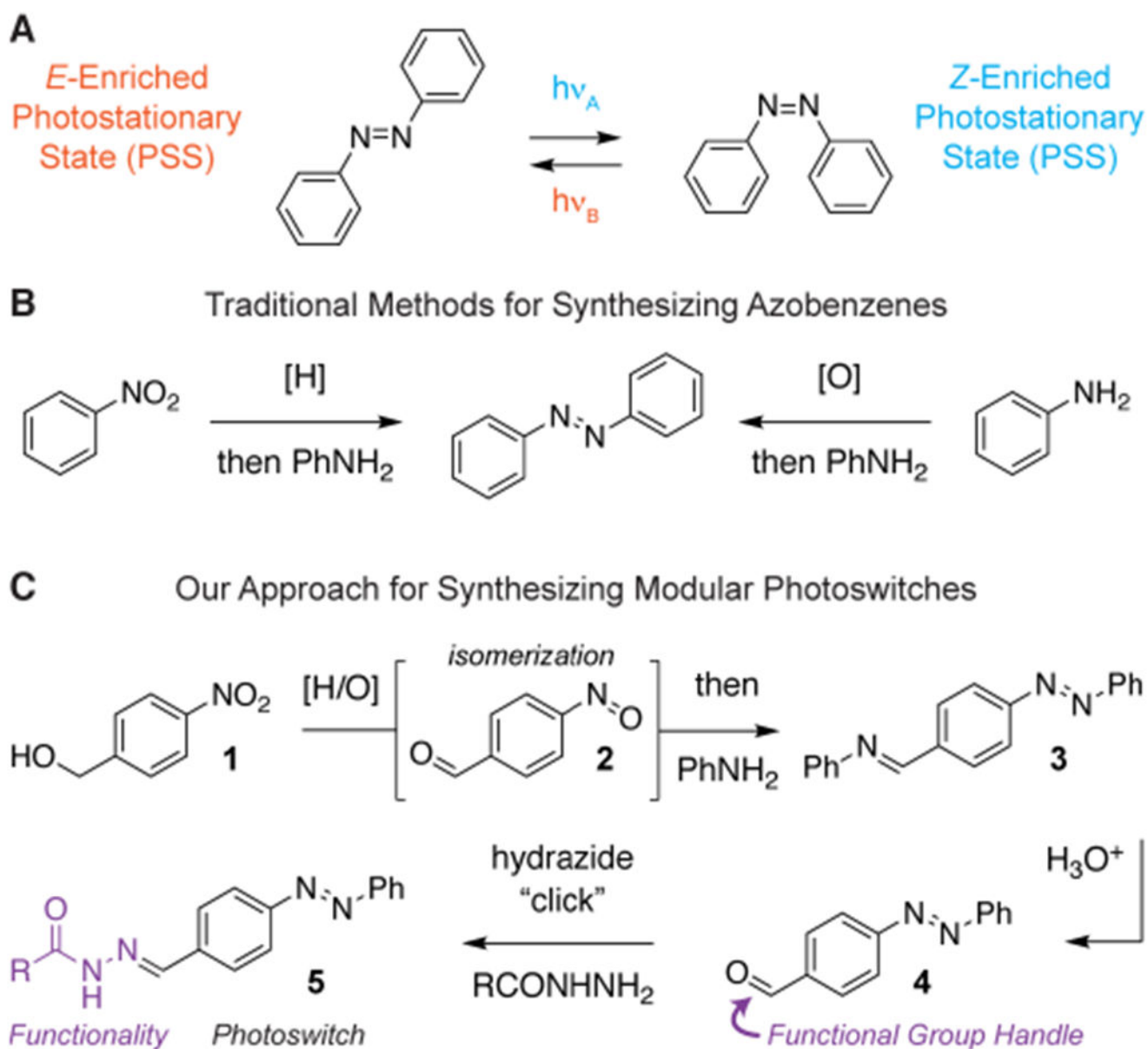
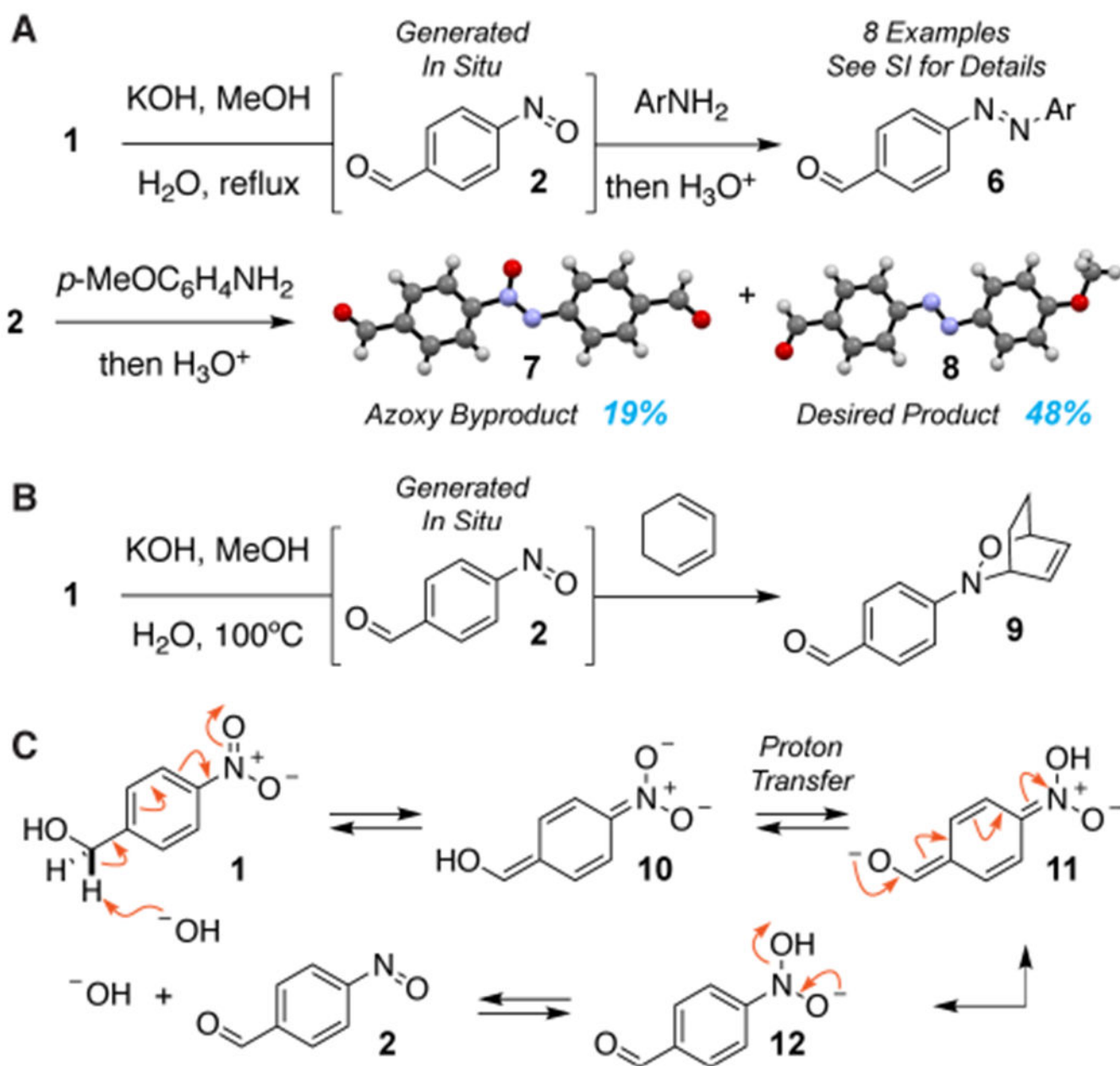
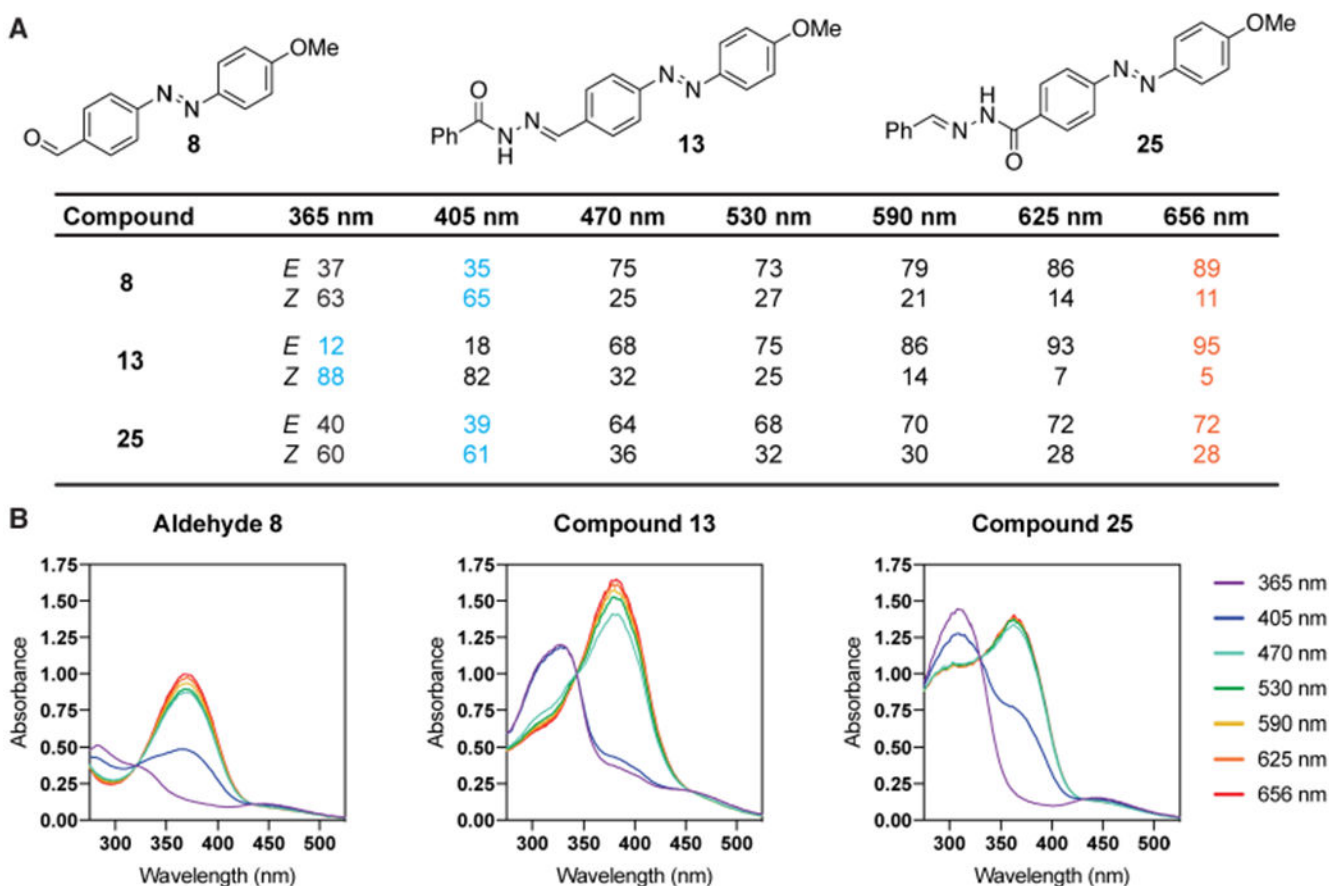


Figure 1. (A) Azobenzenes toggle between two PSSs depending on the irradiation wavelength. (B) Azobenzenes are traditionally synthesized via an aniline + nitrosoarene Mills reaction. (C) Our redox isomerization strategy modular photoswitch preparation.

**Figure 2.**

(A) A variety of *p*-formylazobenzenes can be accessed from *p*-nitrobenzyl alcohol. The X-ray structures of one such product (**8**) and the associated azoxy byproduct (**7**) are shown. (B) The nitroso-aldehyde can be trapped via a Diels–Alder Reaction. (C) Proposed mechanism for redox isomerization of **1**.

**Figure 3.**

(A) The acylhydrazone-containing modular photoswitch **13** exhibits improved bidirectional photoconversion relative to parent aldehyde **8** or constitutional isomer **25**. Photostationary states measured via ^1H NMR in $\text{DMSO-}d_6$ are reported at various wavelengths (nm). The maximally enriched states for the *Z* and *E* isomers are highlighted in blue and orange, respectively. Quantification of a photostationary state consisting of >95% of a single isomer is challenging due to the signal to noise ratio of ^1H NMR. Therefore, a ratio of 95:5 represents a maximally enriched photostationary state. (B) UV-Vis spectra for **8**, **13**, and **25** (50 μM DMSO) after illumination with the indicated wavelengths for 10 mins.

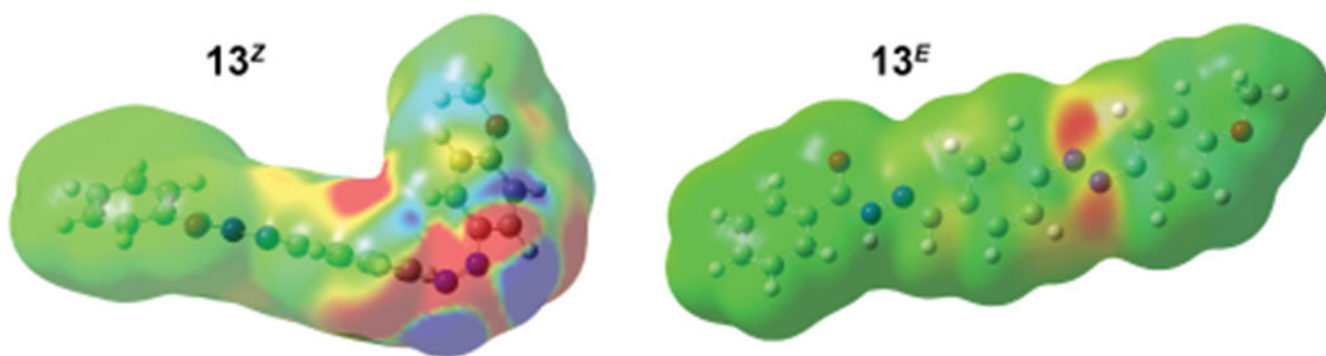


Figure 4. Calculated differential electron density surfaces (excited – ground state) predict localization of electron density changes over the azo functionality rather than the acylhydrazone. Red and blue indicate increased and decreased electron density in the excited compared to the ground states, respectively. Density calculations were performed for the lowest energy $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions for 13^E and 13^Z , respectively.

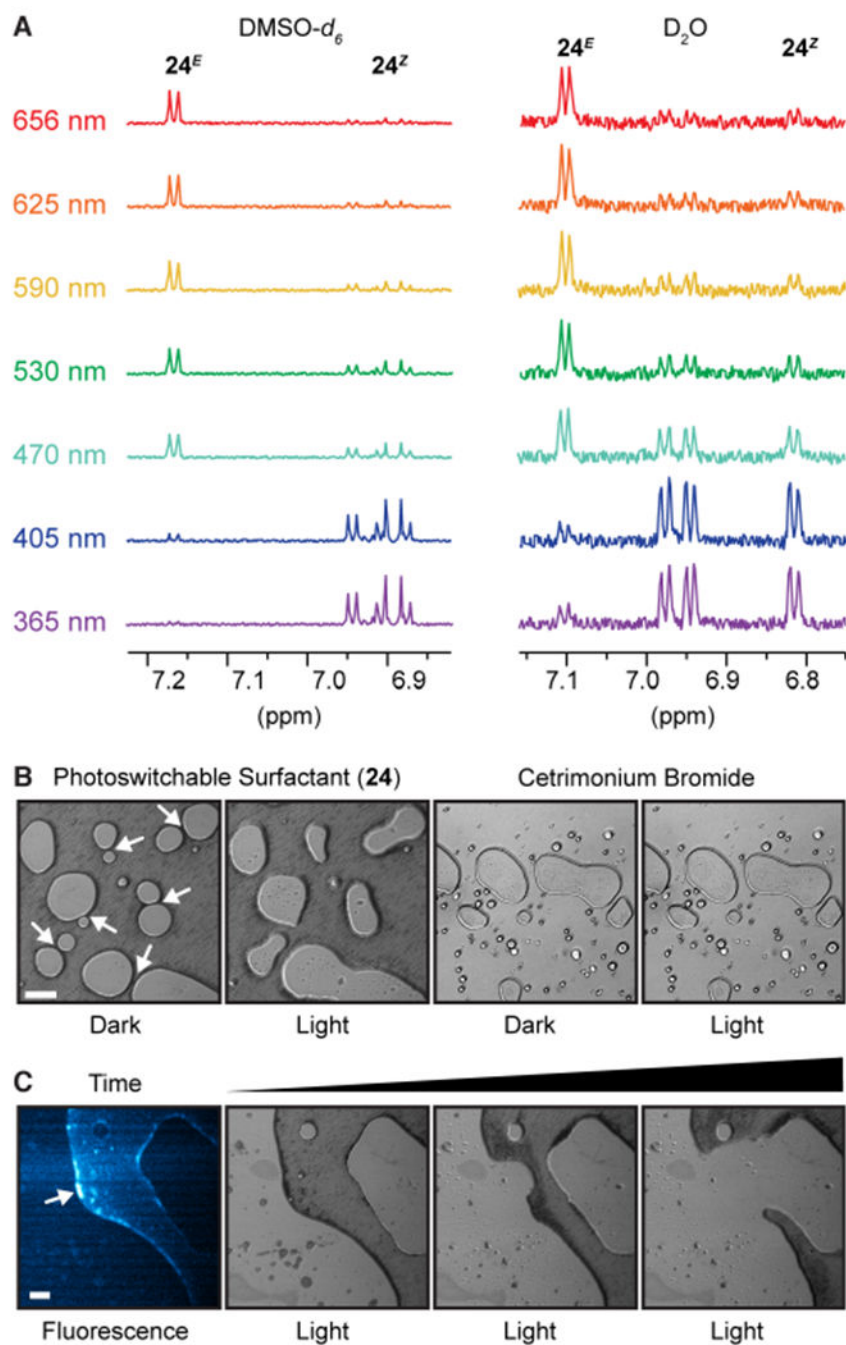


Figure 5. (A) The photoswitchable surfactant **24** can achieve PSSs in both DMSO- d_6 and D $_2$ O that are highly enriched in either the *E* or *Z* isomers depending on the wavelength. (B) Light-induced phase separation only occurs in the presence of a photoswitchable surfactant (**24**), and not in the presence of a surfactant lacking a photoswitchable functional group (cetrimonium bromide). White arrows indicate areas of photoinduced droplet fusion. (C) Fluorescence

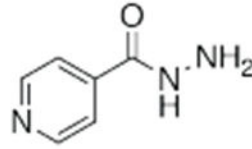
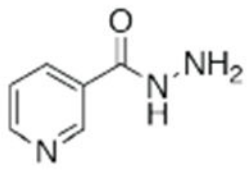
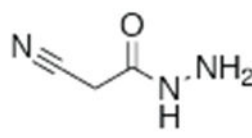
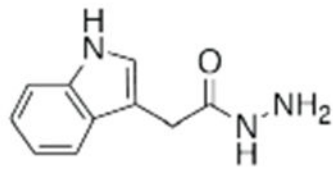
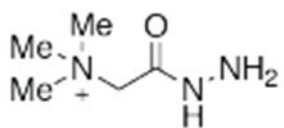
microscopy reveals that light-induced phase separation occurs at sites where the density of **24** is highest (indicated by a white arrow). Scale bars in B and C are 50 μm .

Table 1.

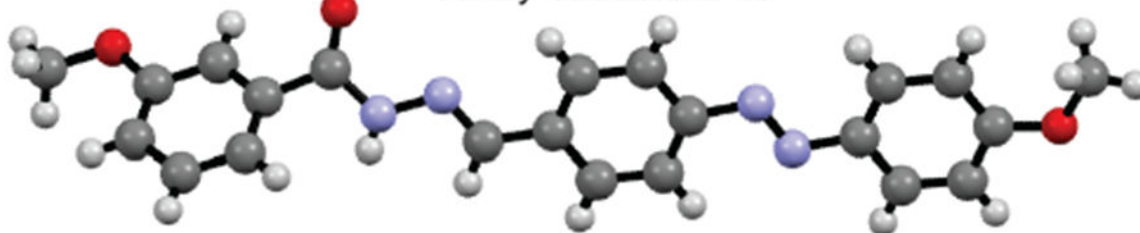
Synthesis and PSSs of Modular Photoswitches

Reaction scheme: $\text{R-CO-NH-NH}_2 \xrightarrow[\text{EtOH, 80}^\circ\text{C}]{\text{8, cat. TFA}} \text{R-CO-NH-N=N-CH}_2\text{-C}_6\text{H}_4\text{-N=N-C}_6\text{H}_4\text{-OMe}$
No Chromatography

hydrazide	product	36 5	40 5	47 0 ^a	53 0	59 0	62 5	65 6	
	13	<i>E</i>	12	18	68	75	86	93	95
	76% ^b	<i>Z</i>	88	82	32	25	14	7	5
	14	<i>E</i>	22	16	70	76	85	92	94
	65%	<i>Z</i>	78	84	30	24	15	8	6
	15	<i>E</i>	27	18	69	74	86	94	95
	79%	<i>Z</i>	73	82	31	26	14	6	5
	16	<i>E</i>	13	18	68	75	85	93	95
	88%	<i>Z</i>	87	82	32	25	15	7	5
	17	<i>E</i>	66	22	71	78	87	93	94
	95%	<i>Z</i>	34	78	29	22	13	7	6
	18	<i>E</i>	34	21	69	75	85	93	94
	75%	<i>Z</i>	66	79	31	25	15	7	6
	19	<i>E</i>	12	18	68	74	83	91	94
	83%	<i>Z</i>	88	82	32	26	17	9	6

	20	<i>E</i>	17	23	71	75	88	95	95
	73%	<i>Z</i>	83	77	29	25	12	5	5
	21	<i>E</i>	10	18	71	76	85	92	95
	71%	<i>Z</i>	90	82	29	24	15	8	5
	22	<i>E</i>	8	21	69	74	81	87	90
	94% ^c	<i>Z</i>	92	79	31	26	19	13	10
	23	<i>E</i>	9	16	70	75	84	94	95
	83% ^c	<i>Z</i>	91	84	30	25	16	6	5
	24	<i>E</i>	6	19	68	72	82	89	92
	76% ^c	<i>Z</i>	94	81	32	28	18	11	8

X-Ray Structure of 19



Photostationary states measured via ¹H NMR in DMSO-*d*₆ are reported at various wavelengths (nm). Quantification of a photostationary state consisting of >95% of a single isomer is challenging due to the signal to noise ratio of ¹H NMR. Therefore, a ratio of 95:5 represents a maximally enriched photostationary state.

^aWhen illuminating sequentially from short to long wavelengths, 470 nm light induces the largest change in the *Z* to *E* ratio.

^bHalf-life (*t*_{1/2}) = 316 min at room temperature as determined by ¹H NMR in DMSO-*d*₆.

^cRotomers observed.

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