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

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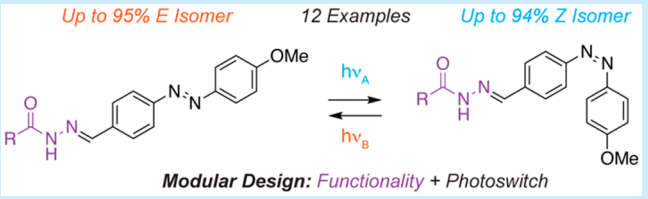
Supporting Information

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.



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).[1b,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 for separating the $n \rightarrow \pi^*$ bands of the two isomers have been reported.[5] Another approach to obtaining high $Z \rightarrow E$ conversion relies on rapid thermal relaxation of push−pull azobenzenes, so-called "pseudostilbenes".[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 azoextention 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 for introducing moieties of interest via hydrazide click chemistry.[7] However, access to azo-aldehydes 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*-indazoles[9] by *in situ* generation of an *o*-nitrosobenzaldehyde, primary amine condensation, and N−N bond-forming heterocyclization. Thus, we hypothesized that *p*-nitrosobenzaldehyde could be formed by treating *p*-nitrobenzyl

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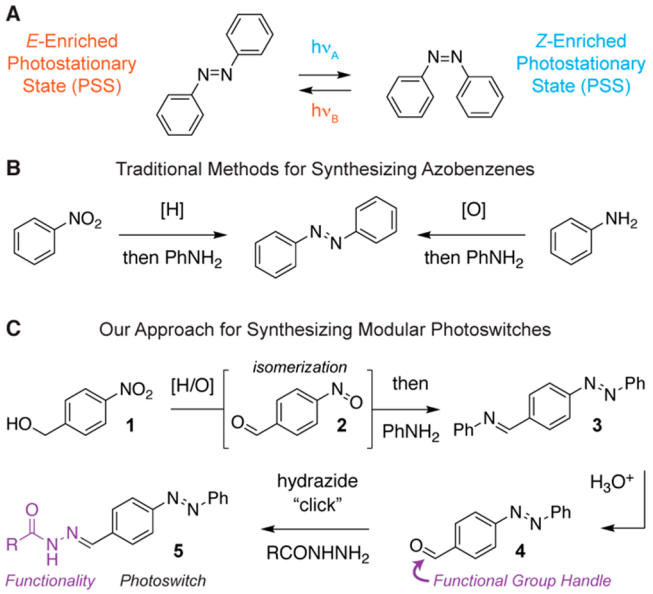


Figure 1. (A) Azobenzenes toggle between two PSSs depending on the irradiation wavelength. (B) Azobenzenes are traditionally synthesized via Mills reaction between an aniline and a nitrosoarene — derived by either reduction of a nitroarene or oxidation of an aniline. (C) Our redox isomerization strategy for preparing modular photoswitches.

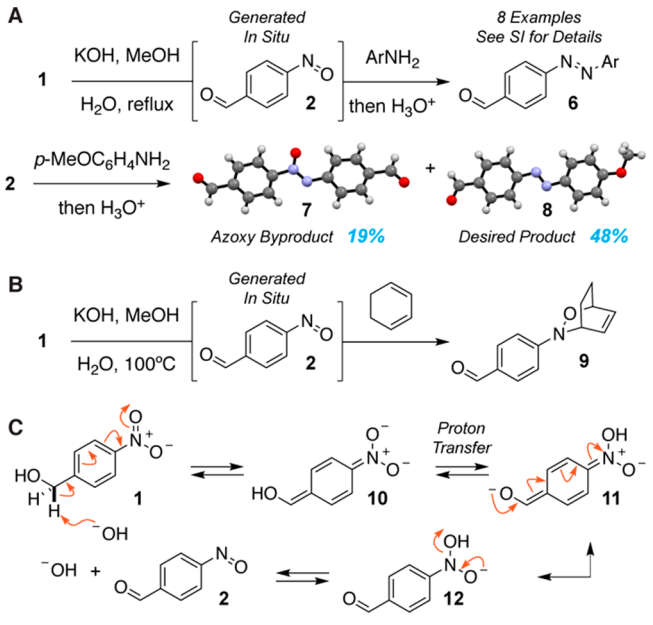
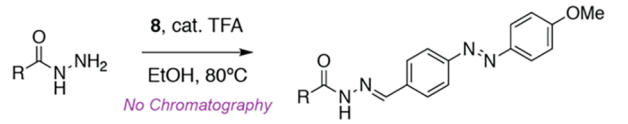


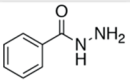
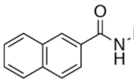
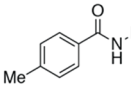
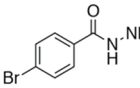
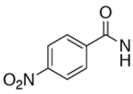
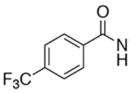
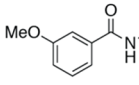
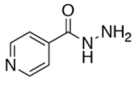
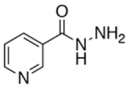
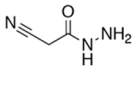
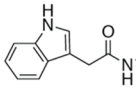
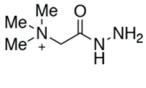
Figure 2. (A) A variety of *p*-formylazobenzenes can be accessed from *p*-nitrobenzyl alcohol. The X-ray structures of one such product (**8**) and the associated azoxy byproduct (**7**) are shown. (B) The nitroso-aldehyde can be trapped via a Diels–Alder reaction. (C) Proposed mechanism for redox isomerization of **1**.

alcohol with a base. Subsequent aniline condensation with the nitroso-aldehyde would furnish azo-imines that could be hydrolyzed 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.

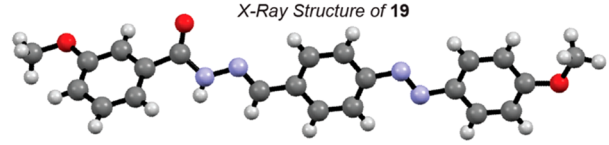
Treatment of *p*-nitrobenzyl alcohol (**1**) with KOH and an excess of commercially available anilines in a MeOH/H_2O

Table 1. Synthesis and PSSs of Modular Photoswitches[a]



hydrazide	product		365	405	470[b]	530	590	625	656
	**13**	*E*	12	18	68	75	86	93	95
	76%[c]	*Z*	88	82	32	25	14	7	5
	**14**	*E*	22	16	70	76	85	92	94
	65%	*Z*	78	84	30	24	15	8	6
	**15**	*E*	27	18	69	74	86	94	95
	79%	*Z*	73	82	31	26	14	6	5
	**16**	*E*	13	18	68	75	85	93	95
	88%	*Z*	87	82	32	25	15	7	5
	**17**	*E*	66	22	71	78	87	93	94
	95%	*Z*	34	78	29	22	13	7	6
	**18**	*E*	34	21	69	75	85	93	94
	75%	*Z*	66	79	31	25	15	7	6
	**19**	*E*	12	18	68	74	83	91	94
	83%	*Z*	88	82	32	26	17	9	6
	**20**	*E*	17	23	71	75	88	95	95
	73%	*Z*	83	77	29	25	12	5	5
	**21**	*E*	10	18	71	76	85	92	95
	71%	*Z*	90	82	29	24	15	8	5
	**22**	*E*	8	21	69	74	81	87	90
	94%[d]	*Z*	92	79	31	26	19	13	10
	**23**	*E*	9	16	70	75	84	94	95
	83%[d]	*Z*	91	84	30	25	16	6	5
	**24**	*E*	6	19	68	72	82	89	92
	76%[d]	*Z*	94	81	32	28	18	11	8

X-Ray Structure of **19**



[a]Photostationary states measured via ^{1}H NMR in DMSO-d_6 are reported at various wavelengths (nanometers). Quantification of a photostationary state consisting of >95% of a single isomer is challenging due to the signal-to-noise ratio of ^{1}H NMR. Therefore, a 95:5 ratio represents a maximally enriched photostationary state. [b]Upon sequential illumination from short to long wavelengths, 470

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Table 1. continued

nm light induces the largest change in the *Z*:*E* ratio. [c]Half-life ($t_{1/2}$) of 316 min at room temperature as determined by ^{1}H NMR in DMSO-d_6. [d]Rotomers observed.

mixture yields azo-imines. 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 the Supporting Information for a detailed discussion (Figure S1)]. Experimental evidence supports the intermediacy of a nitroso-aldehyde. Azoxy compound **7** was often observed,[10] 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 the formation of nitroso-aldehyde **2** is shown in Figure 2C. The pK_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 has a strong precedent,[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 ^{1}H 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 $\mathbf{13}^Z$ 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 suppressing the photoswitching performance. While individual photoswitches capable of

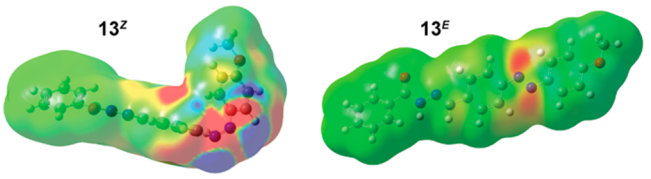
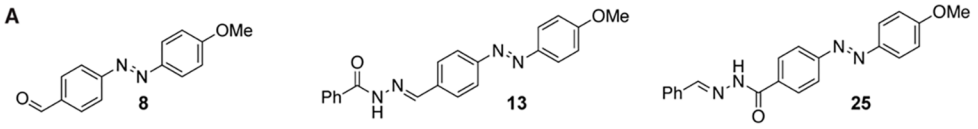


Figure 4. Calculated differential electron density surfaces (excited–ground state) predict localization of electron density changes over the azo functionality rather than the acylhydrazone. Red and blue indicate increased and decreased electron density, respectively, in the excited compared to the ground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



Compound		365 nm	405 nm	470 nm	530 nm	590 nm	625 nm	656 nm
8	*E*	37	35	75	73	79	86	89
	Z	63	65	25	27	21	14	11
13	*E*	12	18	68	75	86	93	95
	Z	88	82	32	25	14	7	5
25	*E*	40	39	64	68	70	72	72
	Z	60	61	36	32	30	28	28

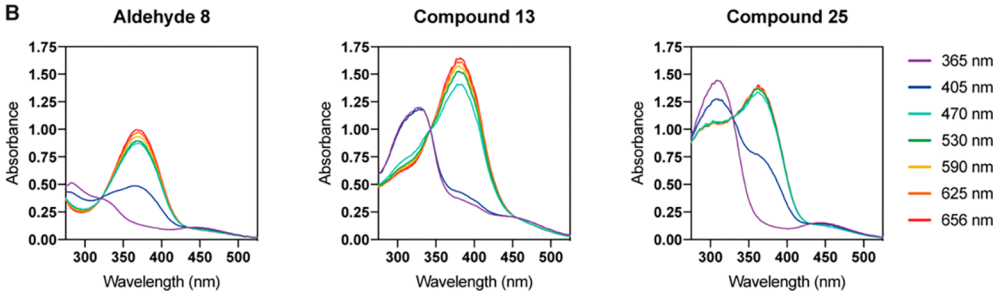


Figure 3. (A) Acylhydrazone-containing modular photoswitch **13** exhibits improved bidirectional photoconversion relative to that of parent aldehyde **8** or constitutional isomer **25**. Photostationary states measured via ^{1}H NMR in DMSO-d_6 are reported at various wavelengths (nanometers). The maximally enriched states for the *Z* and *E* isomers are colored 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 ^{1}H NMR. Therefore, a 95:5 ratio represents a maximally enriched photostationary state. (B) UV–vis spectra of **8**, **13**, and **25** (50 μM DMSO) after illumination with the indicated wavelengths for 10 min.

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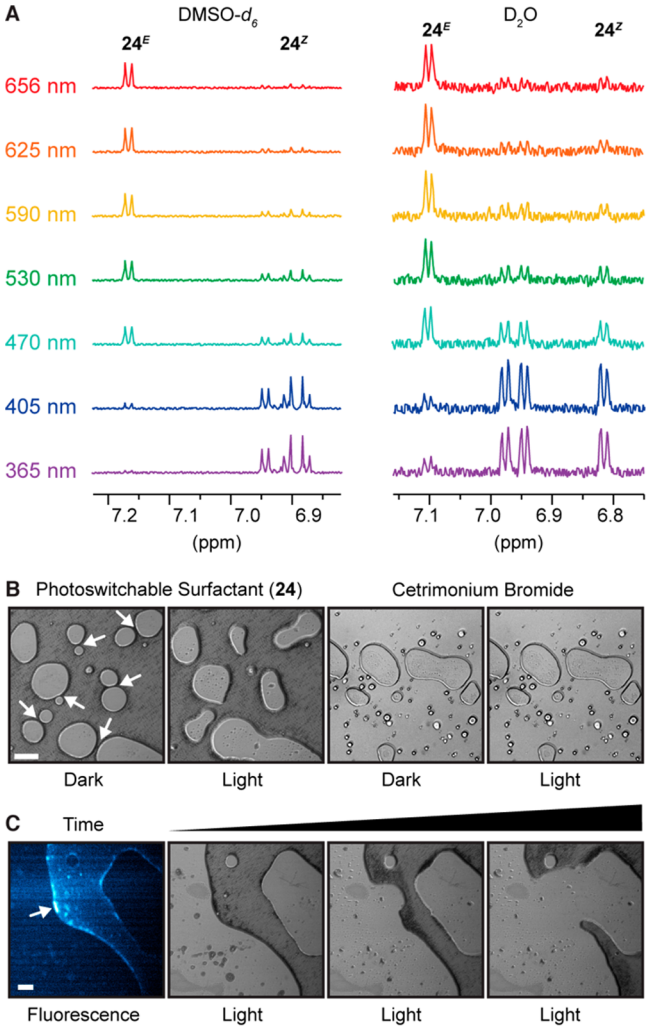

Figure 5. (A) Photoswitchable surfactant **24** can achieve PSSs in both DMSO-d_6 and D_2O that are highly enriched in either the *E* or *Z* isomers depending on the wavelength. (B) Light-induced phase separation occurs only in the presence of a photoswitchable surfactant (**24**) and not in the presence 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 panels B and C are 50 μm.

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 sp^3-hybridized atoms between the tethering group and the photoswitch are not ideal as they increase the degree of 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** than for *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 an increased level of 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 observe photoisomerization of only the azo group, not the acylhydrazone, even after extended irradiation. Time-dependent density functional theory (see SI for details) was used to predict differences in electron densities between ground and excited states for $\mathbf{13}^E$ and $\mathbf{13}^Z$ (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 headgroup 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 D_2O (88% *E* or 80% *Z*) (Figure 5A) with $Z \rightarrow E$ half-lives of 435 and 434 min, respectively. Dissolving **24** in water prior to addition of benzene gives an emulsion that can be readily controlled by light. Under 350 nm light, $\mathbf{24}^E$ photoisomerizes to the more polar $\mathbf{24}^Z$, resulting in droplet fusion and increased phase separation within 2 s (Figure 5B, left). To ensure that this was not due to heating upon irradiation, we used a nonphotoswitchable 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 wavelengths. The rapidity of this process is remarkable and contrasts sharply with the speed of other

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photoswitchable surfactants that require irradiation for minutes to hours for noticeable changes in emulsion properties.

To demonstrate spatial control, we sought to visualize the distribution of **24** in the emulsion. **24** is fluorescent upon being 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 s (Figure 5C and 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.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03387.

Figures S1 and S2, experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra (PDF)
Movie S1 (AVI)
Movie S2 (AVI)

Accession Codes

CCDC 1935827−1935829 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

J.S.Z., J.M.L., and R.J.T. contributed equally to this work. J.S.Z., J.M.L., S.R.B., and M.J.H. synthesized a majority of the compounds described in this paper. R.J.T. performed a 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.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For references related to biologically relevant photoswitches, see: (a) Hüll, K.; Morstein, J.; Trauner, D. In Vivo Photopharmacology. *Chem. Rev.* **2018**, *118*, 10710−10747. (b) Beharry, A. A.; Woolley, G. A. Azobenzene Photoswitches for Biomolecules. *Chem. Soc. Rev.* **2011**, *40*, 4422−4437. (c) Velema, W. A.; Szymanski, W.; Feringa, B. L. Photopharmacology: Beyond Proof of Principle. *J. Am. Chem. Soc.* **2014**, *136*, 2178−2191. (d) Fehrentz, T.; Schönberger, M.; Trauner, D. Optochemical genetics. *Angew. Chem., Int. Ed.* **2011**, *50*, 12156−12182. (e) Kramer, R. H.; Mourot, A.; Adesnik, H. Optogenetic pharmacology for control of native neuronal signaling proteins. *Nat. Neurosci.* **2013**, *16*, 816−823. (f) Szymański, W.; Beierle, J. M.; Kistemaker, H. A.; Velema, W. A.; Feringa, B. L. Reversible photocontrol of biological systems by the incorporation of molecular photoswitches. *Chem. Rev.* **2013**, *113*, 6114−6178.

(2) For references related to photoswitchable materials, see: (a) Russew, M.-M.; Hecht, S. Photoswitches: from molecules to materials. *Adv. Mater.* **2010**, *22*, 3348−3360. (b) Pianowski, Z. L. Recent Implementations of Molecular Photoswitches into Smart Materials and Biological Systems. *Chem. - Eur. J.* **2019**, *25*, 5128−5144. (c) Böckmann, M.; Doltsinis, N. L.; Marx, D. Azobenzene photoswitches in bulk materials. *Phys. Rev. E: Stat., Nonlinear, Soft Matter Phys.* **2008**, *78* (3), 036101.

(3) (a) Bandara, H. M.; Burdette, S. C. Photoisomerization in different classes of azobenzene. *Chem. Soc. Rev.* **2012**, *41*, 1809−1825. (b) Velema, W. A.; Szymanski, W.; Feringa, B. L. Photopharmacology: beyond proof of principle. *J. Am. Chem. Soc.* **2014**, *136*, 2178−2191.

(4) Merino, E.; Ribagorda, M. Control over molecular motion using the cis−trans photoisomerization of the azo group. *Beilstein J. Org. Chem.* **2012**, *8*, 1071−1090.

(5) (a) Bléger, D.; Schwarz, J.; Brouwer, A. M.; Hecht, S. o-Fluoroazobenzenes as readily synthesized photoswitches offering nearly quantitative two-way isomerization with visible light. *J. Am. Chem. Soc.* **2012**, *134*, 20597−20600. (b) Wegner, H. A. Azobenzenes in a new light-switching in vivo. *Angew. Chem., Int. Ed.* **2012**, *51*, 4787−4788. (c) Siewertsen, R.; Neumann, H.; Buchheim-Stehn, B.; Herges, R.; Nather, C.; Renth, F.; Temps, F. Highly efficient reversible Z-E photoisomerization of a bridged azobenzene with visible light through resolved S(1)(n pi*) absorption bands. *J. Am. Chem. Soc.* **2009**, *131*, 15594−15595. (d) Beharry, A. A.; Sadovski, O.; Woolley, G. A.

DOI: 10.1021/acs.orglett.9b03387
Org. Lett. XXXX, XXX, XXX−XXX

Azobenzene photoswitching without ultraviolet light. *J. Am. Chem. Soc.* **2011**, *133*, 19684−19687.
(6) (a) Broichhagen, J.; Frank, J. A.; Trauner, D. A Roadmap to Success in Photopharmacology. *Acc. Chem. Res.* **2015**, *48*, 1947−1960. (b) Morstein, J.; Awale, M.; Reymond, J. L.; Trauner, D. Mapping the Azolog Space Enables the Optical Control of New Biological Targets. *ACS Cent. Sci.* **2019**, *5*, 607−618.
(7) (a) Ganguly, T.; Kasten, B. B.; Bučar, D. K.; MacGillivray, L. R.; Berkman, C. E.; Benny, P. D. The hydrazide/hydrazone click reaction as a biomolecule labeling strategy for M(CO)3 (M = Re, (99m)Tc) radiopharmaceuticals. *Chem. Commun. (Cambridge, U. K.)* **2011**, *47*, 12846−12848. (b) Prescher, J. A.; Bertozzi, C. Chemistry in living systems. *Nat. Chem. Biol.* **2005**, *1*, 13−21.
(8) Molander, G. A.; Cavalcanti, L. N. Nitrosation of Aryl and Heteroaryltrifluoroborates with Nitrosonium Tetrafluoroborate. *J. Org. Chem.* **2012**, *77*, 4402−4413.
(9) (a) Haddadin, M. J.; Conrad, W. E. C.; Kurth, M. J. The Davis−Beirut Reaction: A Novel Entry into 2H-indazoles and Indazolones. Recent Biological Activity of Indazoles. *Mini-Rev. Med. Chem.* **2012**, *12*, 1293−1300. (b) Zhu, J. S.; Kraemer, N.; Li, C. J.; Haddadin, M. J.; Kurth, M. J. Photochemical Preparation of 1,2-Dihydro-3H-indazol-3-ones in Aqueous Solvent at Room Temperature. *J. Org. Chem.* **2018**, *83*, 15493−15498. (c) Zhu, J. S.; Kraemer, N.; Shatskikh, M. E.; Li, C. J.; Son, J.-H.; Haddadin, M. J.; Tantillo, D. J.; Kurth, M. J. N−N Bond Formation between Primary Amines and Nitrosos: Direct Synthesis of 2-Substituted Indazolones with Mechanistic Insights. *Org. Lett.* **2018**, *20*, 4736−4739.
(10) (a) Merino, E. Synthesis of azobenzenes: the coloured pieces of molecular materials. *Chem. Soc. Rev.* **2011**, *40*, 3835−3853. (b) Davey, M. H.; Lee, V. Y.; Miller, R. D.; Marks, T. J. Synthesis of Aryl Nitroso Derivatives by tert-Butyl Hypochlorite Oxidation in Homogeneous Media. Intermediates for the Preparation of High-Hyperpolarizability Chromophore Skeletons. *J. Org. Chem.* **1999**, *64*, 4976−4979.
(11) Bordwell, F. G.; Algrim, D.; Vanier, N. R. Acidities of anilines and toluenes. *J. Org. Chem.* **1977**, *42*, 1817−1819.
(12) Zhu, J. S.; Kraemer, N.; Shatskikh, M. E.; Li, C. J.; Son, J. H.; Haddadin, M. J.; Tantillo, D. J.; Kurth, M. J. N-N Bond Formation between Primary Amines and Nitrosos: Direct Synthesis of 2-Substituted Indazolones with Mechanistic Insights. *Org. Lett.* **2018**, *20*, 4736−4739.
(13) Wan, P.; Yates, K. Photoredox chemistry of nitrobenzyl alcohols in aqueous solution. Acid and base catalysis of reaction. *Can. J. Chem.* **1986**, *64*, 2076−2086.
(14) Banghart, M. R.; Trauner, D. A 1H NMR assay for measuring the photostationary States of photoswitchable ligands. *Methods Mol. Biol.* **2013**, *995*, 107−120.
(15) Weston, C. E.; Richardson, R. D.; Haycock, P. R.; White, A. J.; Fuchter, M. J. Arylazopyrazoles: azoheteroarene photoswitches offering quantitative isomerization and long thermal half-lives. *J. Am. Chem. Soc.* **2014**, *136*, 11878−11881.
(16) Stricker, L.; Fritz, E. C.; Peterlechner, M.; Doltsinis, N. L.; Ravoo, B. J. Arylazopyrazoles as Light-Responsive Molecular Switches in Cyclodextrin-Based Supramolecular Systems. *J. Am. Chem. Soc.* **2016**, *138*, 4547−4554.
(17) van Dijken, D. J.; Kovaříček, P.; Ihrig, S. P.; Hecht, S. Acylhydrazones as Widely Tunable Photoswitches. *J. Am. Chem. Soc.* **2015**, *137*, 14982−14991.
(18) (a) Bleger, D.; Dokic, J.; Peters, M. V.; Grubert, L.; Saalfrank, P.; Hecht, S. Electronic Decoupling Approach to Quantitative Photoswitching in Linear Multiazobenzene Architectures. *J. Phys. Chem. B* **2011**, *115*, 9930−9940. (b) Cisnetti, F.; Ballardini, R.; Credi, A.; Gandolfi, M. T.; Masiero, S.; Negri, F.; Pieraccini, S.; Spada, G. P. Photochemical and Electronic Properties of Conjugated Bis(Azo) Compounds: an Experimental and Computational Study. *Chem. - Eur. J.* **2004**, *10*, 2011−2021. (c) Bleger, D.; Liebig, T.; Thiermann, R.; Maskos, M.; Rabe, J. P.; Hecht, S. Light-Orchestrated Macromolecular "Accordions": Reversible Photoinduced Shrinking of Rigid-Rod Polymers. *Angew. Chem., Int. Ed.* **2011**, *50*, 12559−12563. (d) Galanti, A.; Santoro, J.; Mannancherry, R.; Duez, Q.; Diez-Cabanes, V.; Valášek, M.; De Winter, J.; Cornil, J.; Gerbaux, P.; Mayor, M.; Samorì, P. A New Class of Rigid Multi(azobenzene) Switches Featuring Electronic Decoupling: Unravelling the Isomerization in Individual Photochromes. *J. Am. Chem. Soc.* **2019**, *141*, 9273−9283.
(19) (a) Shinkai, S.; Matsuo, K.; Harada, A.; Manabe, O. Photocontrol of micellar catalyses. *J. Chem. Soc., Perkin Trans. 2* **1982**, *10*, 1261−1265. (b) Fujiwara, H.; Yonezawa, Y. Photoelectric response of a black lipid membrane containing an amphiphilic azobenzene derivative. *Nature* **1991**, *351*, 724. (c) Effing, J. J.; Kwak, J. C. Photoswitchable phase separation in hydrophobically modified poly (acrylamide)/surfactant systems. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 88−90. (d) Sakai, H.; Matsumura, A.; Yokoyama, S.; Saji, T.; Abe, M. Photochemical switching of vesicle formation using an azobenzene-modified surfactant. *J. Phys. Chem. B* **1999**, *103*, 10737−10740. (e) Liu, X. M.; Yang, B.; Wang, Y. L.; Wang, J. Y. New nanoscale pulsatile drug delivery system. *Chem. Mater.* **2005**, *17*, 2792−2795. (f) Sakai, H.; Orihara, Y.; Kodashima, H.; Matsumura, A.; Ohkubo, T.; Tsuchiya, K.; Abe, M. Photoinduced reversible change of fluid viscosity. *J. Am. Chem. Soc.* **2005**, *127*, 13454−13455. (g) Wang, Y.; Ma, N.; Wang, Z.; Zhang, X. Photocontrolled reversible supramolecular assemblies of an azobenzene-containing surfactant with α-cyclodextrin. *Angew. Chem., Int. Ed.* **2007**, *46*, 2823−2826. (h) Tabor, R. F.; Tan, D. D.; Han, S. S.; Young, S. A.; Seeger, Z. L.; Pottage, M. J.; Garvey, C. J.; Wilkinson, B. L. Reversible pH- and photocontrollable carbohydrate-based surfactants. *Chem. - Eur. J.* **2014**, *20*, 13881−13884. (i) Tabor, R. F.; Pottage, M. J.; Garvey, C. J.; Wilkinson, B. L. Light-induced structural evolution of photoswitchable carbohydrate-based surfactant micelles. *Chem. Commun. (Cambridge, U. K.)* **2015**, *51*, 5509−5512. (j) McCoy, T. M.; Liu, A. C.; Tabor, R. F. Light-controllable dispersion and recovery of graphenes and carbon nanotubes using a photo-switchable surfactant. *Nanoscale* **2016**, *8*, 6969−6974. (k) Adam, M. K.; Hu, Y.; Poisson, J. S.; Pottage, M. J.; Ben, R. N.; Wilkinson, B. L. Photoswitchable carbohydrate-based fluorosurfactants as tuneable ice recrystallization inhibitors. *Carbohydr. Res.* **2017**, *439*, 1−8. (l) Schnurbus, M.; Stricker, L.; Ravoo, B. J.; Braunschweig, B. Smart Air-Water Interfaces with Arylazopyrazole Surfactants and Their Role in Photoresponsive Aqueous Foam. *Langmuir* **2018**, *34*, 6028−6035. (m) Vialetto, J.; Anyfantakis, M.; Rudiuk, S.; Morel, M.; Baigl, D. Photoswitchable Dissipative Two-Dimensional Colloidal Crystals. *Angew. Chem., Int. Ed.* **2019**, *58*, 9145−9149.

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Org. Lett. XXXX, XXX, XXX−XXX