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A Modular Approach to Arylazo-1,2,3-triazole Photoswitches

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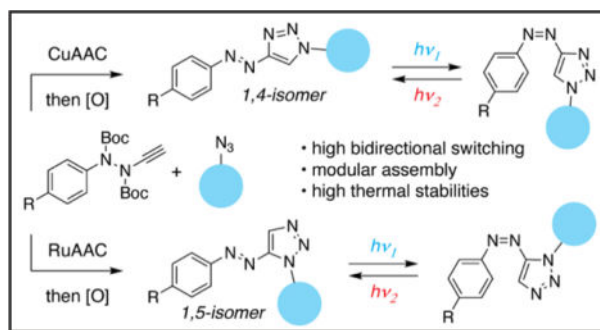
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Abstract

Azoheteroarenes are an emerging class of photoswitchable compounds with unique photophysical properties and advantages over traditional azobenzenes. Therefore, methods to synthesize azoheteroarenes are highly desirable. Here, we utilize azide-alkyne click chemistry (AAC) to access arylazo-1,2,3-triazoles, a previously unexplored class of azoheteroarenes that exhibit high thermal stabilities and near quantitative bidirectional photoconversion. Controlling the catalyst or 1,3-dipole grants access to both regioisomeric arylazotriazoles as well as arylazoisoxazoles, highlighting the versatility of our approach.

Graphical Abstract



Photoswitchable compounds capable of toggling between two distinct isomeric states have applications ranging from materials science to biology owing to the precise spatial and temporal control that they can impart to a variety of systems.^{1,2,3,4,5,6,7,8} Azobenzenes have emerged as the most widely studied and utilized class of photoswitchable molecules due to

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Author Contributions

JRT and RJT contributed equally to this work. JRT and RJT synthesized the majority of the compounds described in this paper, with help from NY. JRT performed the majority of the photoisomerization experiments. DEO supervised experiments and wrote the manuscript with input from all authors.

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, characterization data, and ¹H and ¹³C NMR spectra (PDF)

their remarkable photostability, large and rapid geometric change following $E \rightarrow Z$ diazene isomerization, and highly tunable photophysical properties.^{9,10,11} While these properties make azobenzenes attractive photoswitches, significant challenges still exist in the design of optimized azobenzene-based photoswitches a priori.

Currently, complex asymmetric azobenzene photoswitches must be engineered on a case-by-case basis utilizing azologization or azoextension strategies,^{12,13} and they often require extensive optimization to achieve high degrees of bidirectional photoconversion, ideal thermal half-lives of the Z isomer, and acceptable photoswitching wavelengths for a given application. Optimization of any one of these parameters is often at the expense of another. For example, push-pull electronic systems are often utilized to red-shift the $\pi \rightarrow \pi^*$ transition of the E isomer, but this can lead to greater overlap with the $n \rightarrow \pi^*$ transition of the Z isomer causing incomplete photoswitching. As it is often difficult to predict how azobenzene modification might impact a range of photophysical properties, arduous empirical optimization is often required.¹³

Azoheteroarenes have sparked significant interest as alternative photochromic systems with many potential advantages over traditional azobenzenes.¹⁴ Of these, photoswitches comprised of five-membered nitrogenous heterocycles have shown the greatest promise (Figure 1). Herges and co-workers demonstrated that arylazoimidazoles can undergo near-quantitative $E \rightarrow Z$ photoconversion and exhibit thermal half-lives of several weeks. However, these molecules were unable to completely photoconvert back to the E isomer.¹⁵ Significant advancements came from Fuchter's group with the development of arylazopyrazoles—compounds with unique photophysical properties including near quantitative bidirectional photoconversion and exceptionally long thermal half-lives (~1000 days).¹⁶ The vast majority of common nitrogenous heterocycles have been incorporated into azoheteroarenes and investigated in depth, with many possessing interesting photophysical characteristics.^{17,18} Additionally, arylazoisoxazole photoswitches were recently reported that can achieve >90% photoconversion to either the E or Z isomer and exhibit high Z isomer thermal stability, demonstrating the utility of oxygen heterocyclic photoswitches.^{19,20}

Given the challenges associated with photoswitch optimization, several groups have developed methods for appending a pre-optimized photoswitchable module to any structural element of interest (Figure 1). Ravoo and co-workers added a level of modularity to previously reported arylazopyrazoles by installing an extended carboxylic acid linker as a tethering site on an existing azoheteroarene scaffold.²¹ Similarly, Yu, Li, and co-workers developed arylazopyrazole photoswitches with both phenol and ester tethering sites, enabling bifunctionalization.²² In 2019, our group developed a modular azobenzene scaffold that could be attached to a wide variety of groups via hydrazide click chemistry.²³ Despite these advances, we still lack a general method for directly connecting any structural motif of interest to a photoswitchable module with pre-optimized photophysical properties.

Inspired by these discoveries, we decided to explore arylazo-1,2,3-triazoles—a previously unknown class of azoheteroarenes—as we reasoned that they might possess favorable photophysical properties while being readily accessed in a modular fashion through robust copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reactions. Arylazo-1,2,4-triazoles

have been described previously,¹⁷ however the relative position of the three nitrogen atoms excludes them from the modularity and synthetic ease associated with CuAAC chemistry. We envisioned constructing the photoswitch through reaction of an arylazoalkyne-equivalent synthon with an azide pre-attached to any structure of interest. The robustness of CuAAC click chemistry and the associated wealth of methodology available for accessing azide-functionalized molecules^{24,25,26} made this strategy quite attractive. Moreover, we anticipated that the tethered group would be electronically decoupled from the photoswitchable module due to a lack of π -conjugation between the two components, and thus, would not impact the photochemistry. Unlike previous modular photoswitchable scaffolds, the tethered group of arylazotriazoles would be directly attached to the photoswitch, which would reduce the degrees of freedom and increase the likelihood that the two isomers would possess differential functional properties.

To access arylazotriazoles with diverse electronic properties, we first coupled di-*tert*-butyl hydrazodiformate (**1**) with a variety of aryl iodides under copper catalysis (Scheme 1).²⁷ The resulting bis-Boc arylhydrazines proved challenging substrates for a variety of alkylation reactions including standard ynamide-forming cross-coupling reactions with silyl-protected bromoalkynes²⁸ and a recently reported CuCl₂-catalyzed silyl-acetylene oxidative ynamide coupling.²⁹ Fortunately, we were able to access **4a–4d** in good to excellent yields through a very robust 2-step sequence involving dichlorovinylolation followed by alkyl lithium-mediated elimination and lithium halogen exchange (Scheme 1).³⁰

The method used to synthesize **4a–d** was not amenable to the synthesis of **4e**, so we took an alternative approach. The addition of lithiated silyl-acetylene to di-*tert*-butyl azodicarboxylate produced **5** in 48% yield.³¹ Copper-catalyzed cross-coupling of **5** with *N*-(4-iodophenyl) acetamide yielded **6** in moderate yield, which was readily deprotected with TBAF (Scheme 1). We successfully employed this method with other aryl halides, and thus, it seems to be general. However, we favor the dichlorovinylolation/elimination sequence in most scenarios given its simplicity and robustness.

To access a series of model arylazotriazoles, we reacted compounds **4a–4e** with benzyl azide under CuAAC conditions followed by Boc group removal and oxidation of the hydrazine (Scheme 2). We opted to take the bis-protected hydrazines into the cycloaddition reaction given that unprotected ynamines are known to be relatively unstable and readily tautomerize to reactive ketenimines which undergo rapid hydration to form the corresponding hydrazides.^{32,33} Cascade deprotection-oxidation strategies using acid were unsuccessful given that acid can catalyze the rearrangement of hydrazo compounds to benzidines, diphenylenes, and semidines.³⁴ Thermal deprotection of the Boc groups only produced the desired azo compounds in low yields. Ultimately, we found that Boc group deprotection with TMSI^{35,36} followed by hydrolysis of the resulting trimethylsilyl carbamates in an oxygenated atmosphere afforded the desired benzyl substituted arylazo-1,2,3-triazoles **8a–e** in good overall yields (Scheme 2).

Next, we performed constant illumination NMR experiments^{23,37} to establish the PSSs of these electronically diverse model arylazotriazoles under a variety of wavelengths (Figure 2A–B). The electron withdrawn photoswitch **8a** underwent near near-quantitative conversion

to the *Z* isomer when irradiated with 365 nm light but was unable to fully isomerize back to the *E* isomer under any wavelength tested. The unsubstituted photoswitch **8b** also did not possess ideal photophysical properties as it was unable to reach highly enriched *E* or *Z*PSSs under any wavelength tested and displayed a diminished extinction coefficient in the UV-Vis spectrum, as compared to other arylazotriazole photoswitches.

Fortunately, the methoxy substituted **8c** can access a PSS quantitatively enriched in the *Z* isomer under 365 nm light with longer wavelengths achieving approximately 80% photoconversion to the *E* isomer (Figure 2B). Increasing the electron donating ability of the para substituent further as in **8d** appeared to be detrimental, likely due to rapid thermal relaxation due to the strong push-pull effect. Compound **8e**, chosen for its electronic similarity to **8c**, achieved near-quantitative conversion to the *Z* isomer at 365 nm, and >85% photoconversion to the *E* isomer at longer wavelengths. Interestingly, unlike push-pull azobenzenes which typically experience rapid thermal relaxation, compounds **8c** and **8e** are exceptionally stable as their *Z* isomers. Their thermal stabilities, defined as the percentage of *Z* to *E* relaxation in the dark after 1 week measured via ¹H NMR integration ratios, were observed to be 13% and 18%, respectively. The observed *Z* isomer stability may be rationalized through a favorable H- π interaction between the triazole and phenyl component, as proposed by Fuchter in regards to the *Z* isomer stability of similar azoheteroarenes.¹⁷

Due to the desirable photophysical properties of **8c** and **8e**, we reacted a variety of alkyl and aryl azides with **4c** and **4e** followed by deprotection/oxidation to produce arylazo-1,2,3-triazole photoswitches (note: care must be taken when working with organic azides as they are potentially explosive). Ambient temperature was suitable for a majority of the deprotection sequences, but the reactions of aromatic tethered compounds **10–13** were low yielding under these conditions. This issue was resolved by using extended reaction times and/or heating during the deprotection step. As expected, the tethered group had minimal impact on the photophysical properties of the photoswitchable module with all arylazotriazoles achieving high bidirectional photoconversion (Figure 3). Additionally, we investigated the UV-Vis spectral properties of photoswitches based on **4c** with various alkyl and aromatic functional groups and found that the electronic transitions were comparable regardless of direct aryl or alkyl attachment to the photoswitch scaffold (Figure S1). Photoswitches derived from **4c** were preferred to those derived from **4e** given that **4c** can easily be prepared on gram scale.

Having demonstrated the exceptional photophysical properties of 1,4-substituted triazoles derived from **4c**, we were interested in accessing the regioisomeric 1,5-substituted triazoles. Fortunately, we were able to access **18**, simply by switching from copper(I)- to ruthenium(II)-catalysis³⁸ (Figure 4). Like its regioisomer **8c**, **18** was able to achieve high bidirectional photoconversion. The ability to access two structural distinct photoswitches from the same starting materials is a hallmark of our approach and should prove exceptionally useful when optimizing for functional properties. Finally, we constructed arylazoisoxazole photoswitch **19** through dipolar cycloaddition of **4c** with a nitrile oxide derived from benzyl hydroximoyl chloride (Figure 4).³⁹ While 4-arylazoisoxazole photoswitches have been described recently,^{19,20} this new class of 5-arylazoisoxazole can only be accessed via the specialized arylynehydrazides presented here. Like the

arylazotriazoles, compound **19** achieved high bidirectional photoconversion (>90% enrichment of either the *E* or *Z* isomer). However, the thermal stabilities of **8c**, **18**, and **19** were quite different. While **8c** was so stable that we were unable to reliably measure a half-life (13% conversion in 1 week as measured by ¹H NMR), the half-lives of **18** and **19** were measured to be 35.2 h and 25.5 min, respectively (as measured by UV-Vis).

In conclusion, we have discovered arylazo-1,2,3-triazoles—a new class of azoheteroarenes that possess exceptional photophysical properties and can be easily prepared in a modular fashion. Furthermore, our strategy enables the synthesis of both arylazotriazole regioisomers as well as arylazoisoxazoles simply by controlling the catalyst or 1,3-dipole. Given the availability of their azide precursors, the predictability of their photophysical properties, and the ease of their synthesis, we anticipate that arylazotriazoles will find great utility as light-responsive molecular switches for a variety of applications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

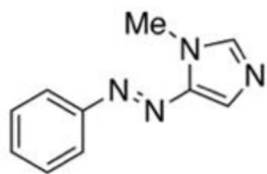
This work was supported by funds from the National Institutes of Health (NIH) (R01GM128997 to DEO; T32GM113770 to RJT), a Provost's Undergraduate Fellowship (NY), an R. Bryan Miller Graduate Fellowship (RJT), and a Francesca Miller Undergraduate Research Award (NY). Funding for NMR spectrometers was provided by the National Science Foundation (Grants DBI0079461 and DBI-0722538). Analysis for this project was performed in the UC Davis Campus Mass Spectrometry Facilities, with instrument funding provided by the NIH (Grant 1S10OD025271).

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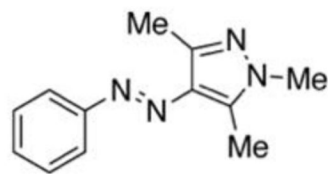
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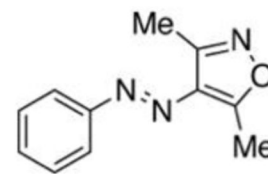
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A Azoheteroarene Photoswitches

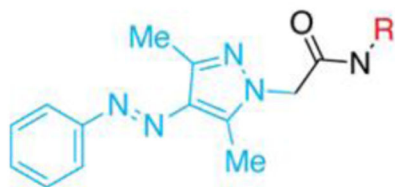
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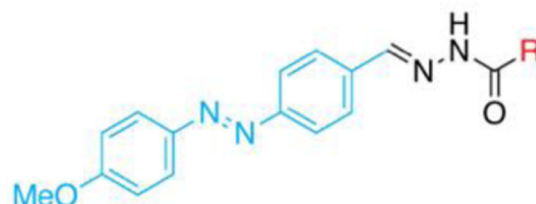
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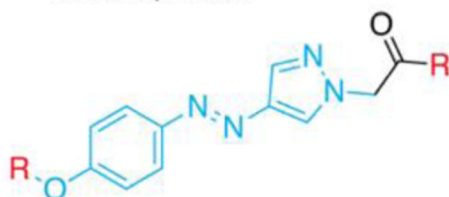
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B Modular Azo Scaffolds

Ravoo, 2016



Olson, 2019



Yu and Li, 2019



This Work

Figure 1.

(A) Azoheteroarenes have emerged as attractive alternatives to traditional azobenzene photoswitches due to their useful photophysical properties. (B) Several modular photoswitch scaffolds are shown. The photoswitch module is depicted in blue and the appended structural motif in red.

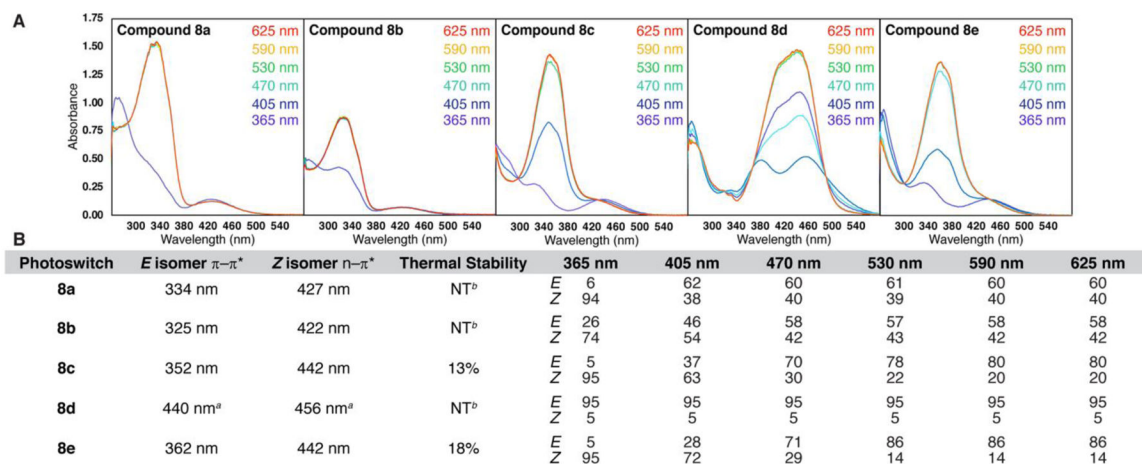


Figure 2.

(A) UV-Vis spectra of model arylazotriazole photoswitches (50 μM in DMSO) under various wavelengths of light. (B) Photophysical properties as determined via UV-Vis spectroscopy (electronic transitions) and constant illumination NMR (thermal stability and PSSs).

Thermal stability indicates the percentage of *Z* isomer that reverts to the *E* isomer after 1 week in the dark as measured by ^1H NMR. ^aThe $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions for the *E* and *Z* isomers, respectively, overlap. NT = not tested. ^bNot determined due to an inability to achieve highly enriched PSS states.

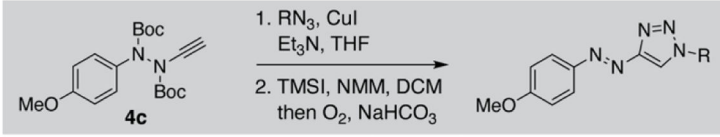
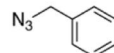
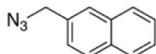

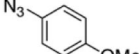
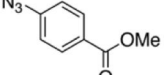
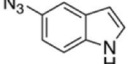

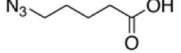
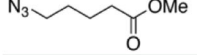
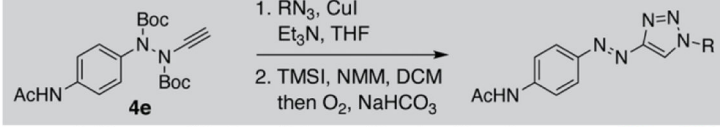
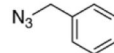

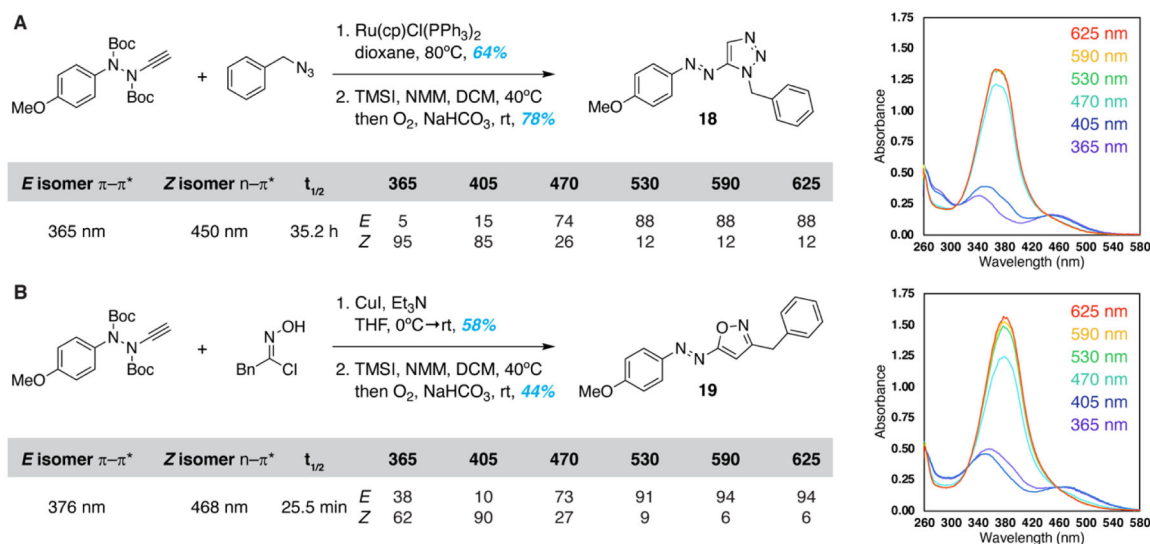
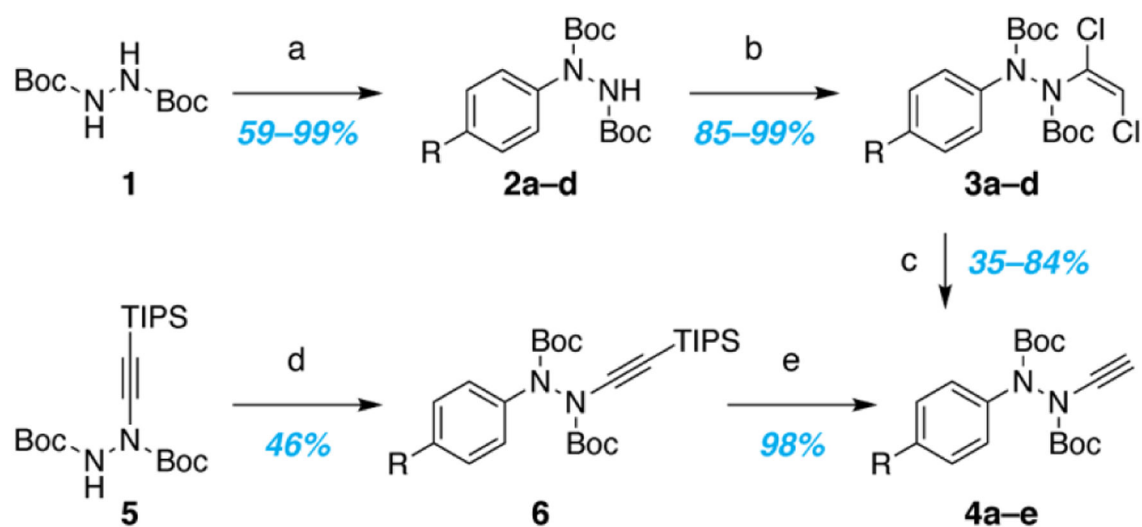
					
Azide	Photoswitch	Step 1	Step 2	365	530
	8c	94%	64%	<i>E</i> 5 <i>Z</i> 95	78 22
	9	93%	63%	<i>E</i> 5 <i>Z</i> 95	84 16
	10	81%	74%	<i>E</i> 5 <i>Z</i> 95	88 12
	11	99%	82%	<i>E</i> 5 <i>Z</i> 95	77 23
	12	97%	30%	<i>E</i> 5 <i>Z</i> 95	90 10
	13	96%	70%	<i>E</i> 5 <i>Z</i> 95	88 12
	14	74%	85%	<i>E</i> 5 <i>Z</i> 95	85 15
	15	75%	52%	<i>E</i> 5 <i>Z</i> 95	78 ^a 22
	16	82%	49%	<i>E</i> 5 <i>Z</i> 95	86 14
					
Azide	Photoswitch	Step 1	Step 2	365	530
	8e	83%	49%	<i>E</i> 5 <i>Z</i> 95	86 14
	17	94%	36%	<i>E</i> 5 <i>Z</i> 95	85 15

Figure 3. Synthesis and properties of arylazotriazoles. PSSs at 365 nm (most *Z*-enriched) and 530 nm (most *E*-enriched) are shown. 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 95:5 ratio represents a maximally enriched photostationary state. ^aPhotoswitch **15** achieves the most *E*-enriched PSS (78%) at 470 nm, not 530 nm.

**Figure 4.**

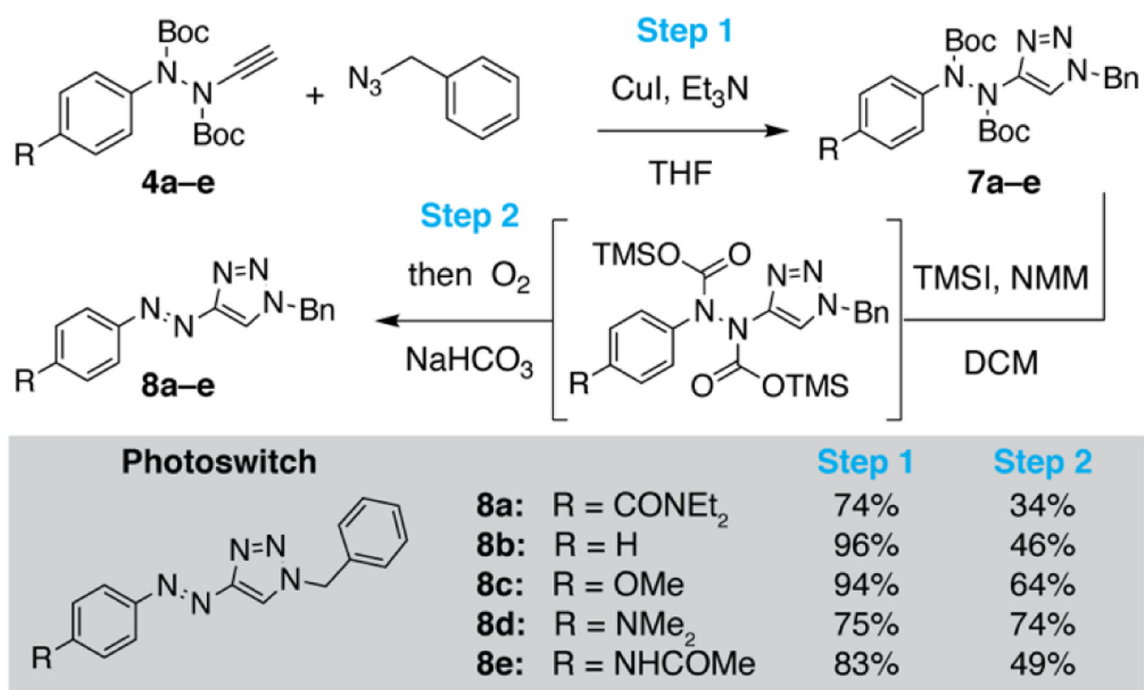
(A) Synthesis of 1,5-substituted triazole **18**. (B) Synthesis of 3,5-substituted isoxazole **19**. PSSs at 365–625 nm are shown. UV-Vis spectra for **18** and **19** are shown to the right (50 μM in DMSO) under various wavelengths of light. Half-lives (t_{1/2}) were measured by UV-Vis spectroscopy.



Compound	Yield	a	b	c	d	e
4a: R = CONEt ₂		94%	98%	35%	–	–
4b: R = H		98%	94%	71%	–	–
4c: R = OMe		99%	99%	84%	–	–
4d: R = NMe ₂		59%	85%	72%	–	–
4e: R = NHAc		–	–	–	46%	98%

Scheme 1. Synthesis of a masked arylalkyne module

Reagents and conditions. (a) aryl iodide, copper (I) iodide, 1,10-phenanthroline, Cs₂CO₃, DMF, 80°C. (b) NaH, DMF, then trichloroethylene. (c) *n*-BuLi, THF, –78°C to room temperature, then *n*-BuLi, –78°C followed by H₂O. (d) *N*-(4-iodophenyl)acetamide, copper (I) iodide, 1,10-phenanthroline, Cs₂CO₃, DMF, 90°C. (e) TBAF, THF, 0°C.



Scheme 2.
Preparation of model arylazotriazoles