

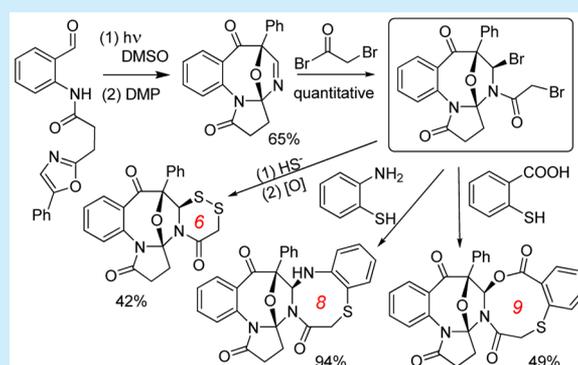
# Photoassisted Diversity-Oriented Synthesis: Intramolecular Cycloadditions of Photogenerated Azaxilylenes with Oxazole Pendants, and Subsequent Postphotochemical Multicomponent Modifications

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**S** Supporting Information

**ABSTRACT:** Photogenerated aza-*o*-xylylenes undergo intramolecular cycloaddition reactions to tethered oxazoles, with primary photoproducts featuring a reactive cyclic imine moiety suitable for multicomponent postphotochemical transformations. For example, the reaction of these imine photoproducts with bromoacetyl bromide leads to a key 1,4-dielectrophilic synthon, offering access to diverse polyheterocyclic molecular architectures. This reaction sequence is accompanied by rapid growth complexity in a very few simple synthetic steps, and is in keeping with the philosophy of diversity-oriented synthesis (DOS).

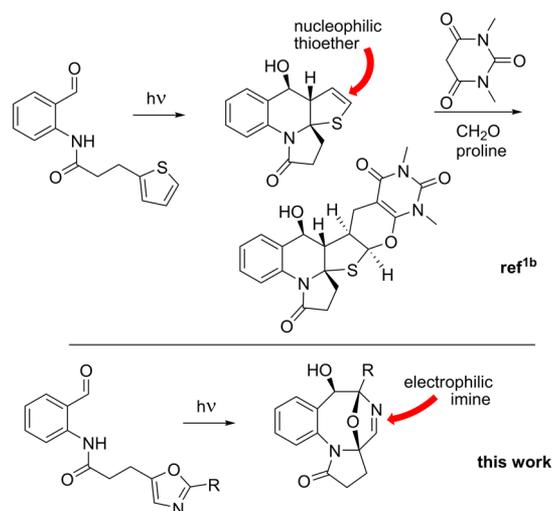


Intramolecular cycloadditions of aza-*o*-xylylenes photogenerated via excited state intramolecular proton transfer (ESIPT) in aromatic aminoketones is developing into a general methodology for photoassisted synthesis of complex polyheterocycles.<sup>1</sup> The scope of this reaction is rather broad: we have demonstrated that photoprecursors with unsaturated pendants from simple alkenes to dienic heterocycles such as furans, thiophenes, or pyrroles are cycloaddition-competent. In these cases, the initial photoproducts possess a newly installed electron-rich reactive double bond, amenable to postphotochemical transformations with electrophiles to further grow the complexity of primary photoproducts. For example, hetero-Diels–Alder or Povarov-type reactions offer rapid access to rather complex polyheterocyclic molecular architectures<sup>1b</sup> (Scheme 1, top, illustrates this point with the oxa-Diels–Alder modification of the initially formed reactive electron-rich dihydrothiophene moiety).

Whether or not the excited aza-*o*-xylylenes are capable of intramolecular cycloadditions to heterodienic unsaturated pendants with *two* heteroatoms (e.g., oxazoles) is an important question, as the primary photoproducts in this case are expected to contain an *electrophilic* reactive moiety, such as an imine (Scheme 1, bottom).

In this Letter, we report that *oxazoles*,<sup>2</sup> tethered to the photoactive core of aromatic amino-ketones, are indeed cycloaddition-competent with photogenerated aza-*o*-xylylenes, offering rapid photoassisted access to reactive photoproducts containing a cyclic imine moiety. The primary photoproducts are potentially suitable for a variety of subsequent *postphotochemical transformations*, including multicomponent cycliza-

**Scheme 1.** Intramolecular Cycloaddition of Aza-*o*-xylylenes Generated via ESIPT: Primary Photoproducts with the Newly Installed Reactive Nucleophilic Thioether (Top); vs Electrophilic Imine (Bottom)



tions, to further expand the diversity of resulting polyheterocyclic scaffolds.

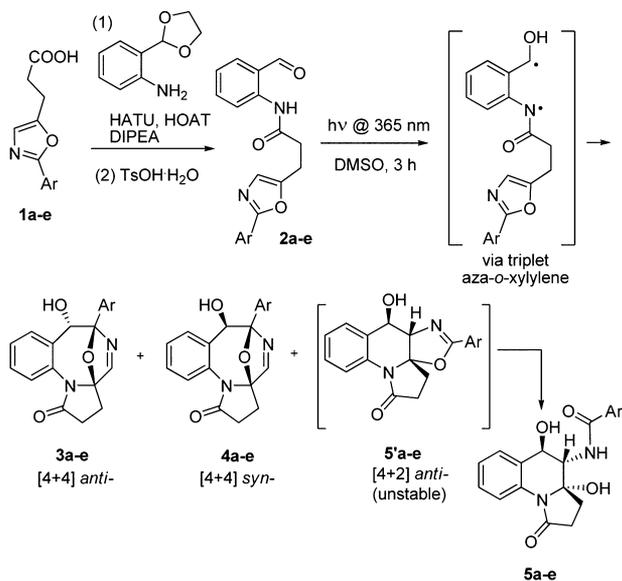
3-(Oxazol-5-yl)propanoic acids **1a–e**, in which the oxazole moiety is tethered through position 5, were readily synthesized

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as described in the literature<sup>3</sup> and outfitted with photoactive *o*-aminobenzaldehyde cores to yield photoprecursors **2a–e** as shown in Scheme 2. Upon UV-irradiation with 365 nm UV

### Scheme 2. Synthesis of Oxazole-5-yl Based Photoprecursors and Their Photoinduced Cyclization via ESIPT/Aza-*o*-xylylene



LEDs, oxazoles **2** underwent ESIPT-mediated [4 + 4] and [4 + 2] formal photocyclizations to form primary photoproducts **3–5**. As we reported earlier,<sup>1f</sup> the cycloaddition reaction most likely occurs via the triplet aza-*o*-xylylenes, which are better represented by the 1,4-diradicaloid structure shown in Scheme 2. Unlike the outcome of similar reactions with tethered furanpropanoyl pendants, the diastereoselectivity of photolysis of oxazoles **2** was low for the two isomeric [4 + 4] products, *syn*- (**3**) and *anti*- (**4**). Oxazoles **2** also yielded the minor products of [4 + 2] cycloaddition, oxazolino-quinolinols **5'**. However, they were unstable and hydrolyzed during workup and chromatographic purification to amido-diols **5**. Table 1 summarizes the isolated yields and gives legends for the aromatic substituents.

The combined isolated yield of the diastereomers of the major [4 + 4] photoproducts was 60–70%. As we were aiming to introduce the newly formed cyclic imine functionality into postphotochemical transformations, we elected to oxidize the

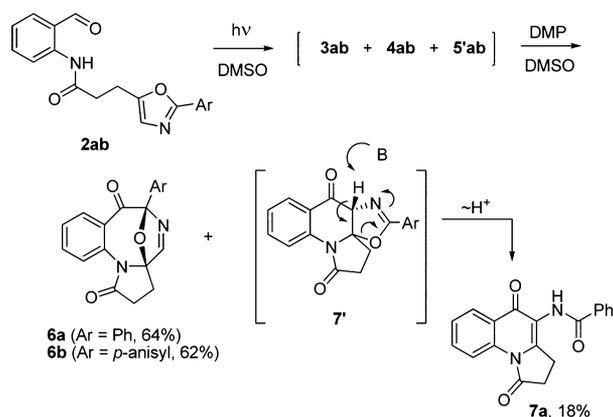
**Table 1. Isolated Yields for Primary Photoproducts in the Reaction of 5-Tethered Oxazoles**

Ar	yield <sup>a</sup> (%)		
	3a–e ( <i>anti</i> -)	4a–e ( <i>syn</i> -)	5a–e (diol) <sup>b</sup>
2a Ph-	34	32	14
2b <i>p</i> -anisyl-	27	34	15
2c 2-furyl-	39 <sup>c</sup>	31	17
2d 2-thienyl-	23	43	16
2e 5-oxazolyl-	62	– <sup>d</sup>	– <sup>d</sup>

<sup>a</sup>Isolated yields of photoproducts. <sup>b</sup>The primary [4 + 2] products **5'** are unstable and hydrolyze during workup and column purification via oxazoline ring opening to give isolable dihydroxy benzamides. <sup>c</sup>Structure is determined by X-ray crystallography; see Supporting Information <sup>d</sup>Minor **4e** and **5e** were not isolated; detected by NMR.

reaction mixture before isolation of the [4 + 4] product to convert benzylic alcohol into the keto group. This helps avoid complications in subsequent transformations, prevents retrocyclization, and reduces the number of diastereomers to just one. As Scheme 3 illustrates, the one-pot irradiation/oxidation

### Scheme 3. Two-Step One-Pot Photocyclization–Oxidation Sequence



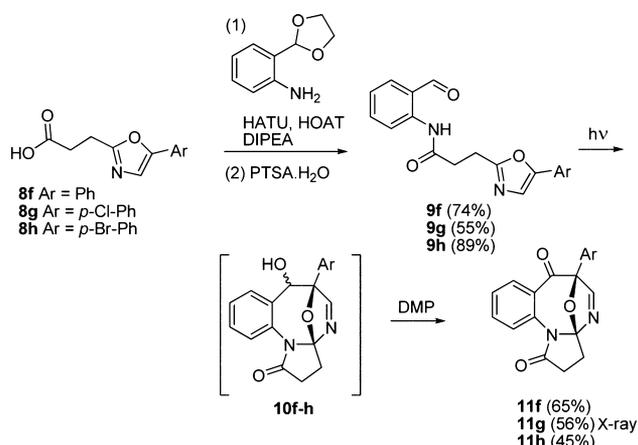
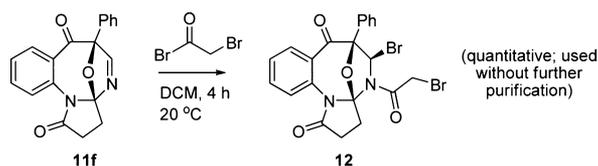
procedure worked nicely. For phenyl- or *p*-anisyl-oxazoles the yields of keto-imines **6** derived from the [4 + 4] photoproducts were 64% and 62% respectively, over the two steps. Oxidation of the minor [4 + 2] cycloadduct was accompanied by the oxazoline ring opening to yield benzamido-quinolone **7a**. This is expected as the initial phenone produced by oxidation of the primary [4 + 2] photoproduct **5'** has an acidic enolizable proton and should be prone to elimination with subsequent oxazoline ring opening, as shown in Scheme 3. The minor quinolinone **7a** is a peculiar diamidoenone and is photoactive itself.<sup>4</sup>

Photoprecursors **9** possessing the oxazole pendants tethered through position 2 (i.e., not 5) are also readily “assembled” in a modular fashion. Their photochemistry is similar to that of 5-substituted oxazoles **2**, although they do not form the [4 + 2] photoproducts, only [4 + 4], conceivably because the [4 + 2] photoproducts in this case are hemiaminals of aromatic aldehydes.

The two-step one-pot irradiation/oxidation procedure, starting with **9**, gives imines **11** topologically similar to imines **6** except for the placement of the imine nitrogen atom in the diazacane ring, Scheme 4.

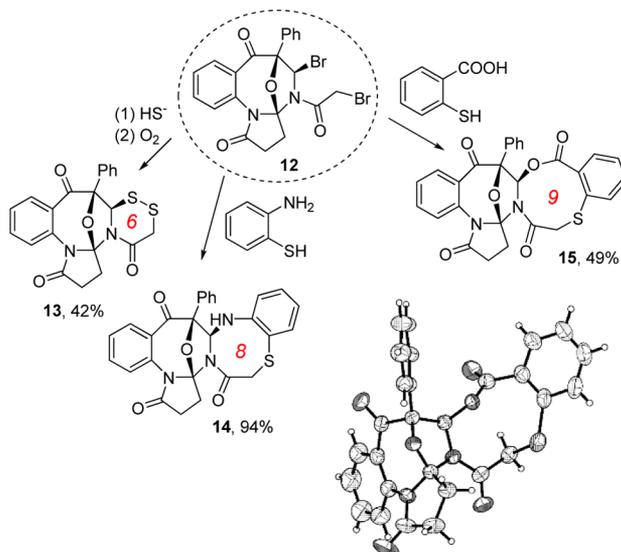
At this point it was abundantly clear that this new photoinduced cycloaddition reaction of aza-*o*-xylylenes with oxazole pendants is rather general in its scope. We therefore surveyed known multicomponent reactions of imines suitable for postphotochemical diversification of the polyheterocyclic imine-containing scaffolds **6** and **11**. This work is in progress, and the full account will be reported elsewhere. In this Letter we wish to report a new three-component reaction involving bromoacetyl bromide.

We have found that imine **6** or **11** reacts cleanly with bromoacetyl bromide producing reactive synthons, latent acyl iminium salts with two 1,4-electrophilic centers.<sup>5</sup> Scheme 5 shows the formation of dibromide synthon **12** from imine **11f** (Ar = Ph). Under the optimized conditions (equimolar reagent, 4 h in dichloromethane at 20 °C), dibromide **12** is formed at a 95% purity and does not require further purification.<sup>6</sup>

Scheme 4. Photocyclization/Oxidation Sequence in Oxazole-2-yl Tethered Photoprecursors **9**Scheme 5. *In Situ* Generation of 1,4-Dibromo Synthone **12**

Synthone **12** is a versatile reactive 1,4-dibromide, which can be engaged by various dinucleophiles under mild conditions to append the pyrrolidino-benzodiazacane core of the primary [4 + 4] photoproducts with an additional heterolactam ring as large as one that is nine-membered, as in the case of thiosalicylic acid<sup>7</sup> (its X-ray structure is shown), **Scheme 6**.

To summarize, we have demonstrated that photogenerated aza-*o*-xylylenes are capable of intramolecular cycloadditions with tethered oxazole pendants. Unlike previously reported reactions with the furan-, thiophene-, or pyrrole-based unsaturated pendants, which give primary photoproducts containing reactive *nucleophilic* double bonds, the photoinduced

Scheme 6. Further Diversification of the Primary Photoproducts via the Reactions of 1,4-Dibromo Synthone **12** with Dinucleophiles; ORTEP Drawing of **15** Is Shown

reactions of oxazole pendants offer access to strained cyclic imines, i.e. reactive *electrophilic* moieties, potentially suitable for postphotochemical transformations via existing multicomponent reactions. Additionally, a new three-component reaction was developed, which involves *in situ* generation of 1,4-dielectrophilic species,  $\alpha,\alpha'$ -dibromo amide **12**, upon treatment of the primary photoproducts with bromoacetyl bromide, and subsequent reaction with dinucleophiles to yield fused (hetero) lactams of varied ring sizes, further diversifying the resulting polyheterocyclic cores.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03503.

Experimental details and NMR spectra (PDF)

Crystallographic data for **3c** (CIF)

Crystallographic data for **11g** (CIF)

Crystallographic data for **15** (CIF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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- (4) Photochemistry of minor diamidoenones **7** will be addressed elsewhere. In this Letter we will focus on the major photoproduct possessing a 1,3-diazacane core.

(5) Similar reactions of chloroacetyl chloride with imines are known: (a) Golding, B. T.; Hall, D. R. *J. Chem. Soc., Perkin Trans. 1* **1975**, *13*, 1302. (b) Lidert, Z.; Gronowitz, S. *Synthesis* **1980**, *1980*, 322. (c) Venkov, A.; Nikolova, M.; Mollov, N. *Synthesis* **1982**, *1982*, 216. (d) Schwarze, W.; Drauz, K.; Martens, J. *Chemiker-Zeitung* **1987**, *111*, 149.

(6) Stereochemical assignment in **12** (*exo*-Br vs *endo*-Br) was challenging as there are no useful proton–proton coupling constants which can be used for stereoassignment. We assigned the *exo*-Br stereochemistry based on DFT calculations: according to B3LYP/6-31+G(d,p) the *exo*-isomer is 4.5 kcal/mol more stable than the *endo*-isomer. We hypothesize that there exists an *exo*–*endo* equilibration mechanism through ionization of the C–Br bond and formation of transient iminium ion. The experimental <sup>1</sup>H NMR spectrum does not show any evidence for the presence of the second stereoisomer, which is in keeping with the DFT results which would predict less than 0.05% of the minor *endo*-isomer.

(7) The *exo*-stereochemistry of the carboxylate, as clearly demonstrated by the X-ray structure, is also in keeping with the hypothesis of a transient acyliminium intermediate in an S<sub>N</sub>1-like substitution at the iminium carbon.