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Photoassisted Synthesis of Complex Molecular Architectures: Dearomatization of Benzenoid Arenes with Aza-*o*-xylylenes via an Unprecedented [2+4] Reaction Topology

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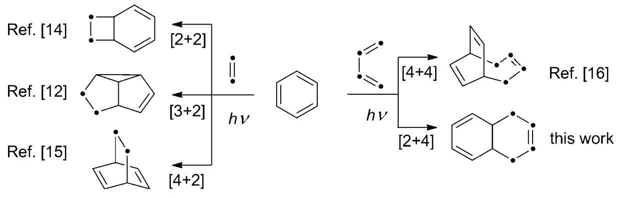
Abstract: *A new method was developed for the photoinduced dearomatization of arenes through an intramolecular cycloaddition with aza-o-xylylenes generated by excited-state intramolecular proton transfer (ESIPT) in the readily available photoprecursors. The [2+4] topology of this cycloaddition is unprecedented for photo-dearomatizations of benzenoid aromatic carbocycles. It provides rapid access to novel heterocycles, cyclohexadieno-oxazolidino-quinolinols, as valuable synthons for a broad range of post-photochemical transformations.*

Dearomatization of aryls provides an appealing preparative shortcut from ubiquitous aromatic hydrocarbons to complex *sp*^{3}-rich molecular topologies (see the excellent review by Porco),[1] offering access to vast areas of underexplored chemical space.[2] Dearomatization of electron-rich heterocycles such as indoles,[3] furans,[4] and pyrroles[5] have been reported, including our own recent contributions.[6,7]

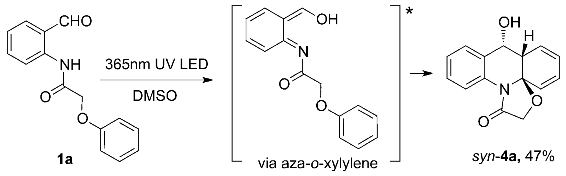
By contrast, the options for the ground-state dearomatization of carbocyclic benzenoid arenes are limited,[8] with a predominance of phenolic oxidation[9] and transition metal-assisted dearomatization.[10] Photocycloadditions to arenes nicely complement these methods to give diverse product topologies (Scheme 1).[11] Among these, [3+2] reactions[12] are often used as key steps in the synthesis of natural products,[13] while the [2+2],[14] [4+2],[15] and [4+4][16] cycloadditions of arenes remain somewhat underutilized. Furthermore, [2+4] photocycloadditions, with an arene acting as a 2π "dienophile", are unknown.[17] Instructively, such [2+4] reactions in the ground state are very rare.[18]



Scheme 1. Molecular topologies accessible through photochemical dearomatization of benzenoid arenes.

We now report a new photo-dearomatization of arenes via the missing [2+4] topology, resulting in the formation of unique cyclohexadiene-fused heterocycles as primary photoproducts, which are amenable to further growth of framework complexity through straightforward post-photochemical transformations.

As we have recently shown, cycloadditions of excited-state intramolecular proton transfer (ESIPT)-generated aza-xylylenes involve triplet species.[6d] The reaction is initiated by the electrophilic N-centered radical, with the overall process resembling a formal inverse-electron-demand Diels–Alder reaction. We hypothesized that a similar initial step should occur with donor-substituted benzenoid arenes. This indeed was the case: a readily available anilide of phenoxyacetic acid (**1a**) proved cycloaddition-competent, furnishing cyclohexadieno-quinolinol *syn*-**4a** upon irradiation with 365 nm LEDs (Scheme 2).



Scheme 2. A typical [2+4] cycloaddition of **1a**.

The scope of this cycloaddition was assessed with a matrix of amides comprised of three photoactive cores, *o*-aminobenzaldehyde **1**, aminoacetophenone **2**, and aminotetralone **3**, and twelve aromatic pendants: derivatives of phenoxyacetic- (**a**–**h**) and phenylpropanoic- (**i–k**) acids, and biphenyl **l** (Figure 1).

Optimization of the reaction conditions and solvent led to DMSO as the solvent of choice. The products resulting from irradiations of **1a**–**1c**, **1h**, **1j**, **2d**, **3d**, **3e**, and **3j** are summarized in Figure 2. For aldehyde-based precursors **1a**–**1c**, the *syn*-diastereomer was observed as the sole product, where "*syn*" refers to the relative position of the benzylic OH and the newly formed cyclohexadiene ring. The stereochemical assignment was based on analysis of proton spin–spin coupling constants (SSCC) and their comparison with values calculated with our relativistic force field (rff) DU8c method[19] (Table S1 in the Supporting Information).

Phenylpropanoic derivatives, such as **1j**, gave two regioisomers, *syn*-**4j** and *syn*-**4j′**, in a ratio approximately 2:1.

The reaction scope is not limited to photoprecursors derived from benzaldehyde. Compounds **2d**, **3d**, **3e**, and **3j**,

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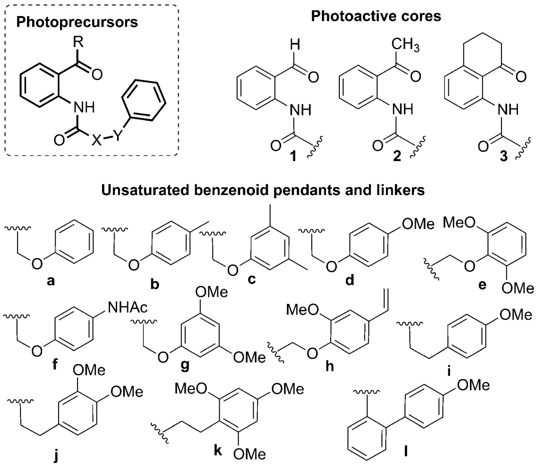


Figure 1. Substrate matrix.

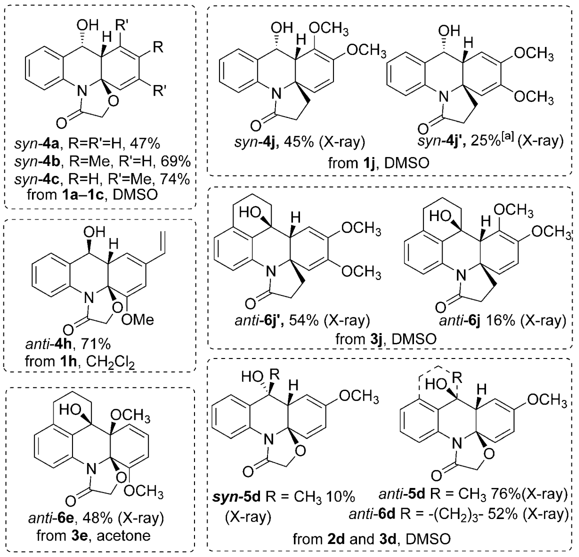
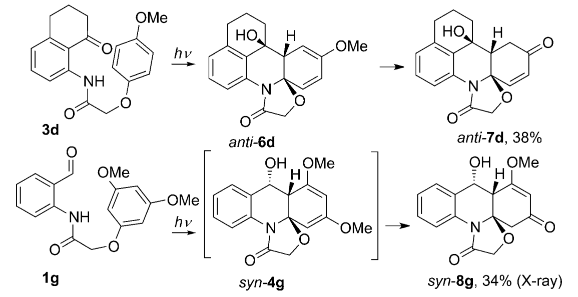


Figure 2. Primary photoproducts from anilides **1a**–**1c**, **1h**, **1j**, **2d**, **3d**, **3e**, and **3j**. Yields of isolated products after chromatographic separation of diastereomers are given. [a] 7% of *anti*-**4j**′ was additionally isolated.

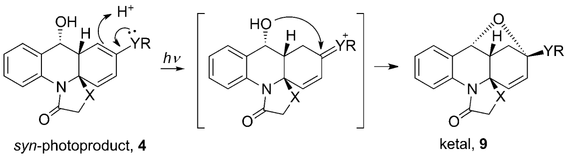
which contain acetophenone and tetralone-based photoactive cores, also underwent cycloaddition. The stereo- and regiochemistry of the cycloaddition for compounds *anti*-**6d**,**e**,**j** and **j**′, as well as *syn*- and *anti*-**5d**, was unambiguously confirmed by X-ray analysis.

In several cases, the methoxycyclohexadiene moiety in the primary photoproducts underwent hydrolysis into cyclohexenone. This reaction can be spontaneous as in the case of *syn*-**4g**, or can happen during the chromatography as in the case of *anti*-**6d** (Scheme 3).

A special case of interrupted post-photochemical hydrolysis is represented by *syn*-products **4** (YR = OMe or NHAc, Scheme 4 and Figure 3). After protonation of the vinyl ether moiety, the methoxyallyl cation is trapped by the benzylic hydroxy group to yield cyclic ketal **9**.



Scheme 3. Spontaneous hydrolysis of primary photoproducts. Yields of isolated product were calculated over two steps.



Scheme 4. Ketal formation from the *syn*-photoproducts.

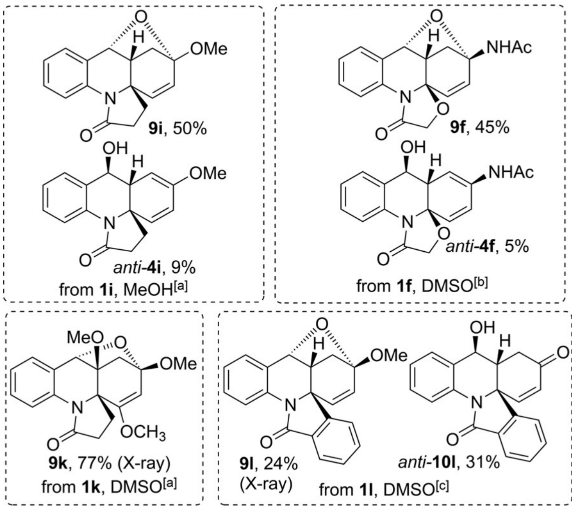
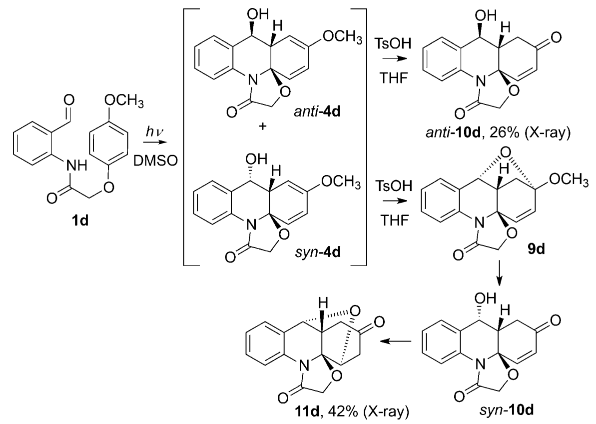


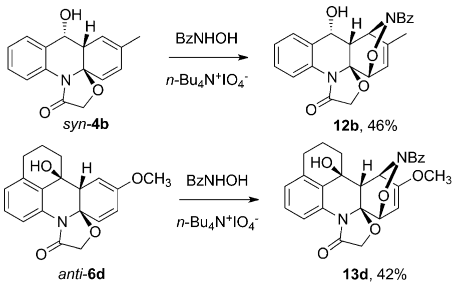
Figure 3. Formation of cyclic ketals. Conditions for ketal formation: [a] spontaneous; [b] HCl in ether, [c] *p*-TsOH·H_2O.

In this context, reaction of the aldehyde-based photoprecursor **1d** is instructive (Scheme 5). The initially formed *syn*- and *anti*-**4d** are unstable on the column. Upon the addition of tosic acid, *anti*-**4d** hydrolyzes to enone *anti*-**10d**. Product *syn*-**4d** initially undergoes cyclic ketalization to form **9d**, but its hydrolysis could be driven further to enone *syn*-**10d**, with subsequent acid-catalyzed nucleophilic capture of the benzylic hydroxy group by the α,β-unsaturated ketone to produce stable ether **11d**. The structure of ether **11d** was initially assigned based on NMR analysis, with the rff-calculated SSCCs matching the experimental data with high accuracy (rmsd = 0.09 Hz), and this was later confirmed by X-ray analysis.

Synthetically appealing post-photochemical modifications to diversify and grow the complexity of the resulting core scaffolds are not limited to ketalization. The primary photo-



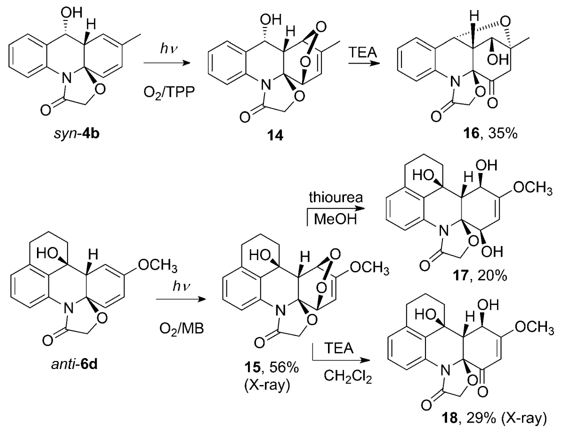
Scheme 5. Acid-catalyzed post-photochemical transformations. Ts = 4-toluenesulfonyl, THF = tetrahydrofuran.



Scheme 6. Hetero-Diels–Alder reaction of primary photoproducts. Bz = benzoyl.

products possess a reactive cyclohexadiene fragment that can be readily engaged in [4+2] cycloaddition, for example, hetero-Diels–Alder reactions with in situ generated benzoylnitroso compounds (Scheme 6).

Another prominent post-photochemical transformation is reaction with singlet oxygen to yield endoperoxides, such as **14** and **15** (Scheme 6). Peroxides are ubiquitous in natural products,[20] with many possessing antitumor, antibacterial, and antimalarial activity. Additionally, these endoperoxides can be ring-opened with urea or bases, thereby offering rapid access to complex pentasubstituted cyclohexenes fused to oxazolidino-quinolinol cores, for example ketal **16**, triol **17**, and enone **18** (Scheme 7).



Scheme 7. Reaction of primary photoproducts with singlet oxygen. Yields of isolated compounds **16**–**18** were calculated over two steps. TPP = tetraphenyl porphyrin, MB = methylene blue.

In conclusion, we have developed a new method for the dearomatization of benzenoid arenes, with the arene reacting as the 2π component—an unprecedented topology for a photochemical reaction of benzenoid aromatics. The primary photoproducts are cyclohexadieno-quinolinol fused heterocycles, which can be subjected to experimentally simple post-photochemical transformations to further grow scaffold diversity and complexity.

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Keywords: [2+4] reactions · aza-*o*-xylylenes · dearomatization · photochemistry · polyheterocycles

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