

Rapid Photoassisted Access to N,O,S-Polyheterocycles with Benzoazocine and Hydroquinoline Cores: Intramolecular Cycloadditions of Photogenerated Azaxylylenes**

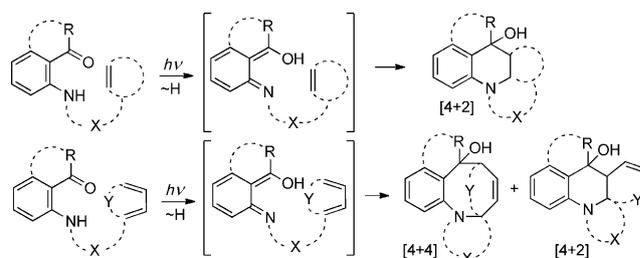
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o-Azaxylylenes have been known for half a century,^[1] but remained in relative synthetic obscurity until a decade ago, when Corey and Steinhagen reported their first preparation under simple mild conditions by base-induced elimination of hydrogen chloride from derivatives of *o*-chloromethylaniline.^[2] It was noted that “Surprisingly, simplest method possible for *o*-azaxylylene production ... has never been reported.”

Synthetically useful reactions of *o*-xylylenes (i.e. all-carbon *o*-quinodimethanes) are plentiful,^[3] and their generation from aromatic *o*-alkyl ketones by an intramolecular photoinduced hydrogen abstraction is well documented.^[4] Given this fact, it was surprising to us that the equally simple photogeneration of *o*-azaxylylenes from *o*-aminoketones by an excited-state intramolecular proton transfer (ESIPT)^[5] has never been utilized in synthetic chemistry.

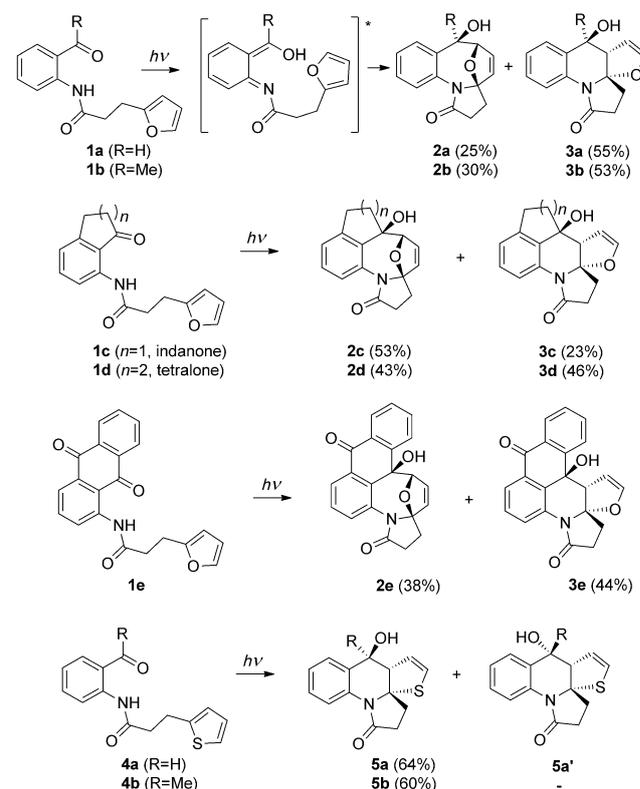
It is conceivable that such implementation was attempted but failed due to the fast back proton transfer successfully competing with bimolecular cycloadditions. Intramolecular proton transfers from one heteroatom to another (and back) are fast; a typical example is the much studied photophysics of salicylaldehyde or *o*-hydroxyacetophenone, although the elusive tautomeric form is not impossible to characterize.^[6] We, however, found that the *intramolecular* cycloaddition reactions of *o*-azaxylylenes photogenerated by excited-state proton transfer can successfully compete with the back proton transfer. Herein, we report the first example of [4 + 2] and [4 + 4] cycloaddition reactions of photogenerated azaxylylenes with unsaturated pendant groups; this reaction offers expeditious access to a diverse array of N,S,O-polyheterocycles with mostly unprecedented topologies (Scheme 1).

As the azaxylylenes are expected to act as acceptors in the inverse-electron-demand cycloaddition reactions, we synthesized photoactive azaxylylene precursors **1** and **4** by coupling



Scheme 1. Photogeneration of azaxylylenes and their intramolecular photocyclizations.

o-aminoketones with furan- or thiophenepropionic acid chlorides.^[7] These *o*-acylamido precursors have broad UV



Scheme 2. [4 + 2] and [4 + 4] cycloadditions of photogenerated azaxylylenes to the furan and thiophene pendant groups. **5'a** denotes the minor hydroxy epimer in the thiophene [4 + 2] cycloadduct. Yields of the isolated products are shown.

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[**] This work is supported by the NIH (GM093930). We thank Prof. Tarek Sammakia of University of Colorado Boulder for insightful discussion.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201103597>.

absorption with a maximum at 340–350 nm. Irradiations were carried out with a Rayonet broadband 300–400 nm UV source or Nichia 365 nm UV LEDs and gave stable polyheterocycles **2**, **3**, and **5**. The [4 + 2] photoadducts **3** and **5** possess unprecedented doubly fused furo[2,3-b]quinoline and pyrrolo[1,2-a]quinoline motifs and the [4 + 4] photoadducts **2** possess an O-bridged pyrrolo[1,2-a]benzazocine core (Scheme 2, for experimental details see the Supporting Information).

With regard to the chemoselectivity, the furan-based precursors (**1a–1e**) yielded both [4 + 4] and [4 + 2] cycloadducts **2** and **3** (Scheme 2). The ratio of the [4 + 4] to the [4 + 2] cycloadducts generally ranged from 1:1 to 2:3 (Table 1). In contrast, the thiophene derivatives **4a** and **4b** undergo mostly [4 + 2] cycloaddition forming dihydrothiophenes **5a** and **5b** (major products) and **5'a** (a minor hydroxy epimer observed for R = H). Cycloadditions of thiophenes, especially in the acetophenone series (**b**; R = Me), most efficiently occur upon heating the reaction mixture during irradiation.

The diastereoselectivity, that is the *syn/anti* configuration of the hydroxy group relative to the heteroatom in the annelated ring or the bridge, was high in this series, with predominant formation of the *anti* diastereomer of the [4 + 2] adducts and the *syn* diastereomer of the [4 + 4] adducts (Table 1). In some cases, the benzaldehyde derivatives produced a small amount of the minor hydroxy epimer (denoted with a prime). Ketones always reacted to yield exclusively the *anti* isomer of the [4 + 2] adducts and the *syn* isomer of the [4 + 4] adducts.

Mechanistically, the reaction with tetralone **1d**, which lacks a rotatable carbonyl group, pointed to the *endo* transition state (or intermediate) in both the [4 + 2] and [4 + 4] cycloadditions (Scheme 3). Our hypothesis is that benzaldehyde- or acetophenone-derived azaxylylenes also react with the furan or thiophene pendant groups via a similar *endo* transition state (or intermediate). In these cases, where the carbonyl group is rotatable, the minor hydroxy epimers potentially result from the out-hydroxy conformer of azaxylylene; at this point, however, we do not know whether the mechanism is concerted or stepwise.

While a detailed photophysical mechanistic study of these cycloadditions is ongoing, we suggest that these are excited-state reactions and not ground-state additions of the photogenerated azaxylylenes. All photoactive precursors possess two characteristic emission bands in their fluorescence spectra: the 400 nm fluorescence from the initial amide form, and the 540–550 nm band with a remarkably large Stokes shift. This second band is attributable to an excited-state intramolecular proton transfer (ESIPT), which in this particular case is due to the emission from the S₁ state of azaxylylene. Conceivably this band can be used in a fluorescence-quenching assay for high-throughput screening and optimization of the reaction conditions, an

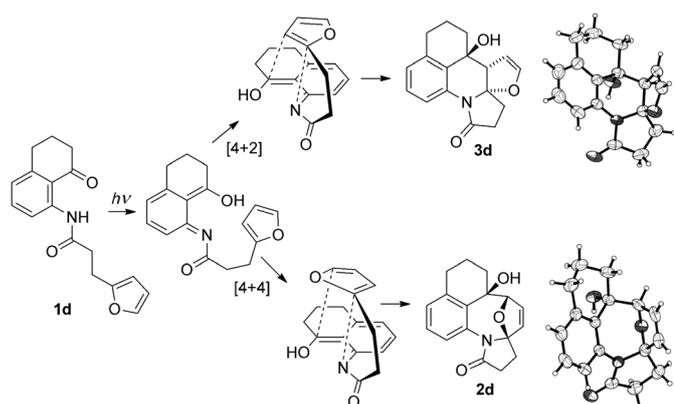
Table 1: Yields of the isolated products, reaction conditions, chemoselectivity and stereoselectivity of cycloadditions.^[a]

Precursor	Solvent	T [°C]	Yield [%] ^[b]	[4+4]/[4+2] ^[c]	d.r. ^[c,d]	
					[4+2]	[4+4]
1a	C ₆ H ₆	20	2a , 25 3a , 55	1:1	> 30:1	> 30:1
1b	C ₆ H ₆	20	2b , 30 3b , 53	0.7:1	> 30:1	> 30:1
1c	CH ₃ CN	20	2c , 53 3c , 23	2.1:1	> 30:1	> 30:1
1d	CH ₃ CN	20	2d , 43 3d , 46	1:1	> 30:1	> 30:1
1e	CH ₃ CN	20	2e , 38 3e , 44	1.2:1	> 30:1	> 30:1
4a	CH ₃ CN	20	5a , 64	1:9	> 30:1	> 30:1
4b	CH ₃ C ₆ H ₅	reflux	5b , 60	–	2:1	–
10a	CH ₃ CN	20	16a , 47 16'a , 33 19a , 9	12:1	1.5:1	> 30:1
11a	CH ₃ CN	reflux	17a/17'a 26	> 30:1	–	0.55:1
12a	CH ₃ CN ^[e]	0	18a ^[f]	> 30:1	–	> 30:1
13a	CH ₃ CN	20	21a , 32 21'a , 8 23a 33	1.1:1	> 30:1	4.3:1
13b	CH ₃ CN	20	21b , 59 23b ^[g]	4.6:1	> 30:1	> 30:1
14b	CH ₃ CN	20	22b , 57 24b , 28	2.6:1	> 30:1	> 30:1
15a	CH ₃ CN	20	25a , 46 25'a , 7 26a , 29	1.9:1	> 30:1	1:1.3
15b	CH ₃ CN	20	25b , 45 26b , 36	1.4:1	> 30:1	> 30:1
32c (X = CH ₂)	CH ₃ CN ^[h]	0	33 (X = CH ₂), 53	> 30:1	–	9:1
32s (X = S)	CH ₃ CN ^[h]	0	33 (X = S), 61 33' (X = S), 11	> 30:1	–	8:1
34a	C ₆ H ₆	20	35a , 30 35'a , 26 ^[i]	–	1:1	–
34b	C ₆ H ₆	20	35b , 38 35'b , 13 ^[j]	–	3:1	–
36a	C ₆ H ₆	20	38a , 87	–	> 30:1	–
36b	C ₆ H ₆	20	38b , 85	–	> 30:1	–
36f	C ₆ H ₆	20	38f , 47 ^[k]	–	> 30:1	–
37a	C ₆ H ₆	20	39a , 70	–	> 30:1	–

[a] Reaction carried out with 100–300 mg loading of the precursor. [b] Yields of the isolated products after column chromatography. [c] Determined by ¹H NMR spectroscopy. [d] *anti:syn* for [4 + 2] and *syn:anti* for [4 + 4]. [e] Two equivalents of HMPA. [f] Quantitative yield as determined by ¹H NMR spectroscopy (see the Supporting Information). **18a** decomposes during chromatography. [g] The [4 + 4] and [4 + 2] cycloadducts are not separable. [h] 5 vol % HMPA. [i] At 20 °C aminor **42a** (17%) was also formed. [j] At 20 °C aminor **42b** (30%) was also formed. [k] At 20 °C aminor **43f** (30%) was also formed.

assay similar to that reported by Porco, Jones, and co-workers^[8] for 3-hydroxyquinolines.

At this point, it was clear that we had uncovered a powerful photoassisted reaction that offers expeditious access to topologically unique N,O,S-polyheterocycles. The preparative potential of similar all-carbon [4 + 4] photoinduced cycloadditions of pyran-2-ones and pyridones to tethered furans, to access cyclooctane cores, is exemplified in the



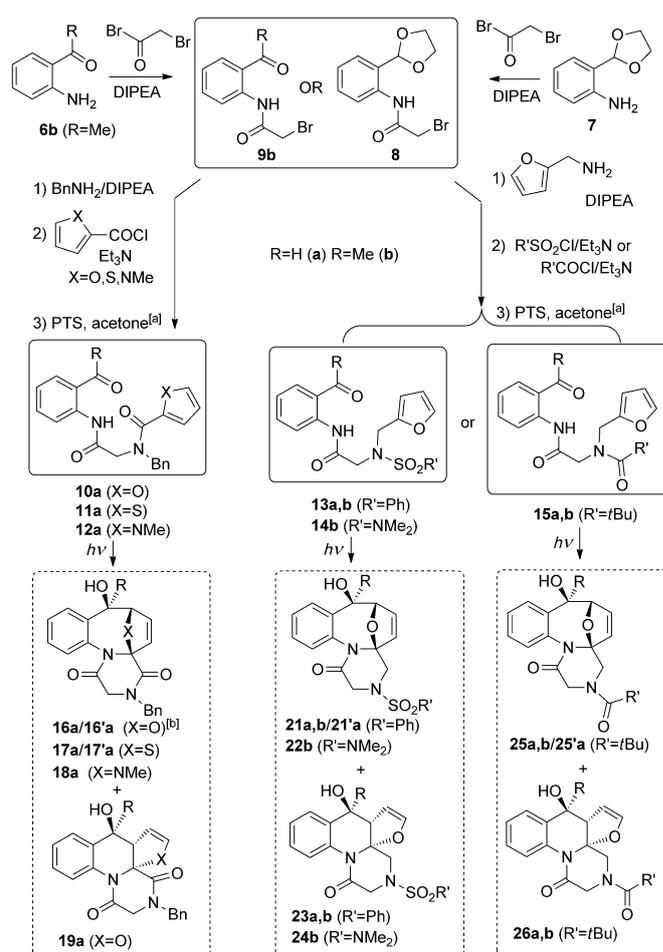
Scheme 3. Diastereoselective photocyclization of amidotetralone **1d**. X-ray structures of the [4+2] and [4+4] adducts are shown (thermal ellipsoids are set at 50% probability).^[12]

elegant synthetic work of West and co-workers,^[9] and Sieburth and co-workers.^[10] We evaluated the application of several simple and high-yielding reactions for the rapid assembly of the precursors, and implemented them as shown below. First, we developed a modular approach that is suitable for combinatorial synthesis with several diversity inputs. This approach is based on a bromoacetyl bromide linker, which was inspired by the readily automated peptoid synthesis.^[11] The overall reaction sequence is exemplified using protected *o*-aminobenzaldehyde (**7**) or unprotected *o*-aminoacetophenone (**6b**; Scheme 4).

First, the reaction with bromoacetyl bromide yielded bromoacetamides **8** and **9b** nearly quantitatively. These compounds were used without further purification and served as key intermediates in accessing monoketo- and diketopiperazino-fused quinolines and benzazacines **16–26**. In the left-hand series shown in Scheme 4, bromoacetamides **8** and **9b** were reacted with benzylamine and subsequently acylated with 2-furoyl, thienyl, or pyrroloyl chlorides to furnish the precursors **10–12**.

With regard to the chemoselectivity, azaxylylenes photo-generated from these precursors (**10a–12a**), in which the heteroaryl pendant group is conjugated to a carbonyl group, showed considerable bias toward the [4+4] cycloaddition (Table 1) especially in polar solvents (MeCN versus toluene and benzene). The pyrroloyl precursor **12a** forms the [4+4] cycloaddition product diketopiperazine **18a** exclusively (no [4+2] product was observed).

Diastereoselectivity was high for the [4+4] reactions, which gave the products with the benzylic hydroxy group positioned predominantly in the *syn* configuration relative to the endocyclic O, N, or S bridge. Nonpolar solvents not capable of hydrogen bonding (benzene, toluene) afforded higher d.r. values. Reactions were faster in acetonitrile, but at the expense of a somewhat reduced diastereoselectivity at ambient temperature. Lowering the temperature to 0°C generally improves the d.r. values. The reactions are further accelerated in acetonitrile in the presence of up to 5 vol % of HMPA. By analogy to the reported effect of HMPA on the lifetimes of all-carbon xylylenes, we attribute this result to the



Scheme 4. Peptoid-synthesis-inspired modular assembly of azaxylylene precursors and their cyclizations. [a] Acetal hydrolysis step is required only in the **a** (i.e. benzaldehyde) series. [b] Major diastereomer is shown, the minor hydroxy epimer (not shown) is denoted with a prime, **16'a** etc. Bn = benzyl, DIPEA = diisopropylethylamine, PTS = pyridinium *para*-toluenesulfonate.

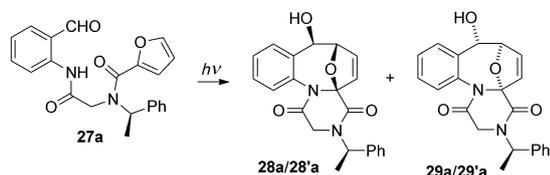
longer lifetimes of the excited azaxylylenes when they are hydrogen bonded to HMPA.^[4]

An alternative mode of the peptoid-inspired modular assembly of the precursors from bromoacetamides **8** and **9b** (Scheme 4, right-hand column) involved the reaction with furfuryl amine and a subsequent acylation with acyl chlorides, or sulfonylation with benzenesulfonyl or dimethyl sulfamoyl chlorides (as the last diversity input), thus furnishing the precursors **13–15**. In this series the furan or thiophene pendant group is tethered by a CH₂ bridge, not by a carbonyl group, as in **10–12**. This change appears to have a noticeable effect on the chemoselectivity, as the ratio of [4+4] to [4+2] products is decreased.

The diastereoselectivity of the photoinduced cycloadditions in the aminoketone series, that is, the *syn/anti* ratio for the [4+4] cycloadducts and *anti/syn* ratio for the [4+2] cycloadducts, is generally higher than for the benzaldehydes. On the contrary, as a rule the relative quantum yields of the cycloadditions are higher for the aldehydes.

All the [4+4] and the [4+2] cycloadducts shown in Scheme 4 are relatively stable and can be purified chromatographically, with the exception of pyrrole-based **18a**, which degraded on silica gel. The irradiations were carried out until quantitative conversion was achieved. For the preparative runs listed in Table 1 conversion of 100–300 mg of the precursor normally required 2–4 hours of irradiation for benzaldehyde and tetralone derivatives, and up to 12 hours for the slower reacting acetophenone-alkenyl dyads. The latter reactions can be accelerated to under 2–3 hours by carrying out the irradiation in toluene heated to reflux.

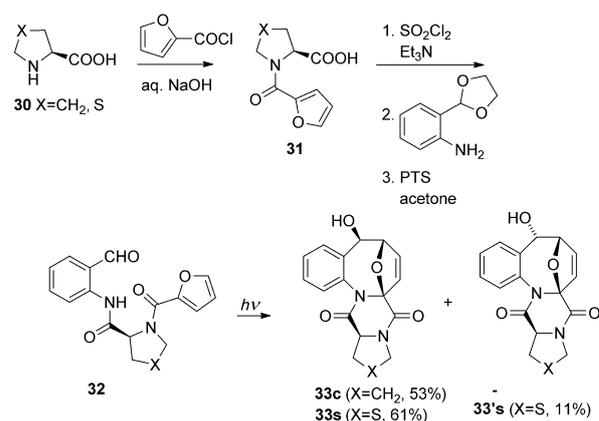
Enantiomerically pure precursor **27a** was synthesized from bromoacetamide **8** and optically active (*R*)-(+)- α -phenylethylamine in a procedure similar to the synthesis of **10a**. However, as shown in Scheme 5, this chiral auxiliary did not transfer chirality as the [4+4] diastereomeric cores of cycloadducts **28** and **29** were formed with low stereoselectivity, that is, the **28/29** ratio was nearly 2:1.



Scheme 5.

Conceivably, this lack of chirality transfer is because the chiral auxiliary is peripherally attached to the nitrogen atom of the tether linking the photoactive pendant group with the furan moiety, and therefore has little effect on the folding of the tether in the transition state. As expected the *syn* selectivity was high and only *syn* epimers **28a** and **29a** were observed at 0°C in acetonitrile. Irradiation at 25°C or in the presence of HMPA yielded small amounts of the *anti* epimers **28'a** and **29'a** (structures determined by X-ray crystallography).

We hypothesized that the incorporation of a cyclic amino acid such as L-proline or L-thiaproline into the tether should have a more pronounced effect on the stereocontrol of the photocyclization (and, at the same time, can serve as another opportunity to add molecular diversity). Photoprecursors **32** were therefore synthesized by acylating L-proline or L-thiaproline with furoyl chloride, and coupling it to a photoactive pendant group as shown in Scheme 6. At 0°C photocyclization of **32** occurred exclusively by the [4+4] pathway and gave adducts **33** (major) and their hydroxy epimers **33'** with d.r. of 12.5:1 for the proline derivative and 4:1 for the thiaproline derivative. The minor epimers **33'** are conceivably a result of the rotatable formyl group in **32**, which generates a small amount of the *out*-OH conformer of the azaxylylene. Note, however, that unlike the reaction of **27a**, the polyheterocyclic core in **33** and **33'** is formed in a stereospecific fashion (i.e. for the given stereochemistry of L-proline, the bridgeheads have *S,S* not *R,R* configuration), thus indicating full stereochemical control of the folding of the tether in the



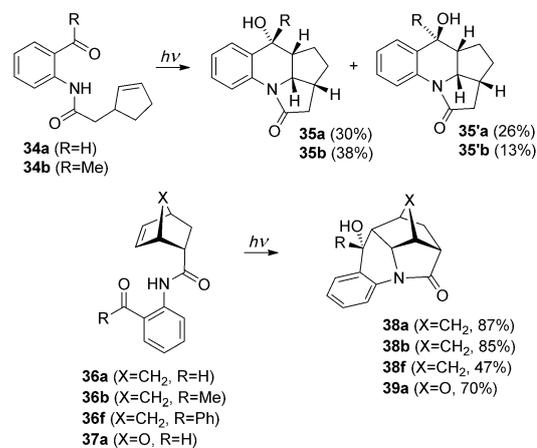
Scheme 6. Photoassisted synthesis of fused ketopiperazines in the L-proline and L-thiaproline series.

transition state by the (thia)proline moiety and 100% chirality transfer.

This example involved a modular assembly of precursors **32** by two trivial high yielding amide bond formations, that is the acylation of an amine with an acyl chloride. This was followed by a photoinduced step, which yielded **33**, an enantiomerically pure polyheterocycle with four stereogenic centers, one of which is quaternary, as the major product.

To evaluate the scope of the photoassisted reactions of azaxylylenes, we also prepared aminoketones (and amino-benzaldehyde) with alkenyl pendant groups. Irradiation of these precursors, **34**, **36**, and **37**, yielded the products of the [4+2] cycloaddition (Scheme 7).

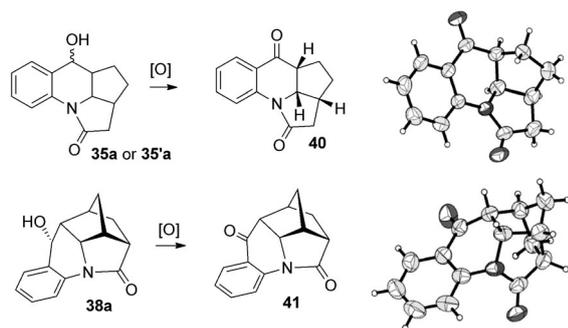
The [4+2] reactions shown in Scheme 7 were accelerated at elevated temperatures; an effect which is critical for the acetophenone derivatives (R = Me), for which high yields were achieved within 3 hours of irradiation in solvent heated to reflux. Reactions with the aldehyde precursors (R = H) were much faster and proceeded at ambient temperature, or at 0°C. Benzophenone derivatives (**f**) reacted very slowly with alkenes.



Scheme 7. [4+2] Cycloadditions to alkenyl pendant groups. Irradiations of precursors **b** (R = Me) were carried out in solvent heated to reflux.

Cycloaddition in acetophenone-based **34b** (cyclopentylacetic pendant group) showed moderate diastereoselectivity (Scheme 7). A d.r. value of 3:1 was observed for the benzylic epimers **35b** and **35'b**, whereas benzaldehyde-derived **35a** and **35'a** formed in nearly equal amounts.

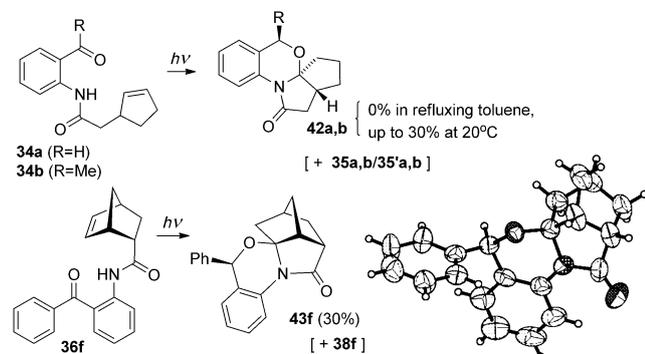
In most cases, the stereochemistry of the major diastereomers was unambiguously established by X-ray analysis (see the Supporting Information). The structure of the minor products was inferred from the ^1H NMR spectra, and in the benzaldehyde series it was confirmed by PCC oxidation of epimeric alcohols **35a** and **35'a**, which both gave the same ketone **40** (Scheme 8). The tetracyclic alcohol **38a** gave ketone **41**. X-ray structures were obtained for both ketones **40** and **41**.



Scheme 8. Oxidation of epimeric alcohols led to the same ketone. X-ray structures of **40** and **41** are shown (thermal ellipsoids are set at 50% probability).^[12]

Although the formation of two epimers of alcohol **35** is observed in Scheme 7, a concerted mechanism is still a possibility. Such concerted cycloaddition can be rationalized by invoking both the OH-in rotamer and the OH-out rotamer of azaxylylene. Alternatively, it may proceed by two different facial approaches of the cyclopentene moiety, resulting in the *endo* and *exo* transition states.

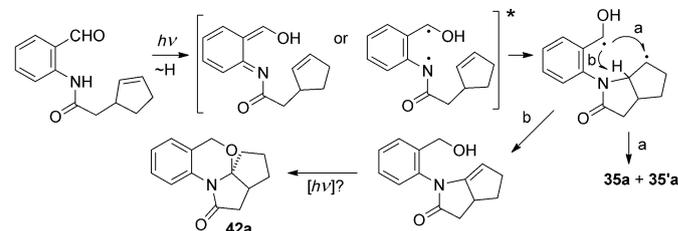
However, in the reactions of precursors **34a**, **34b**, and **36** at 20 °C we isolated aminals **42a**, **42b**, and **43f** (up to 30%; Scheme 9), thus indicating that the excited-state [4+2] cycloadditions of azaxylylenes to alkenes, transformations



Scheme 9. Aminals formed at lower temperatures. The X-ray structure of **43f** is shown (thermal ellipsoids are set at 50% probability).^[12]

which are formally not allowed by the orbital symmetry rules, may not be concerted at all.

Our mechanistic rationale for the aminal formation is shown in Scheme 10; this rationale is in keeping with the hypothesis of a nonconcerted cycloaddition. It involves attack



Scheme 10. Mechanistic rationale for the formation of aminals **42**.

of the nitrogen atom of the excited azaxylylene (alternatively depicted as a 1,4-diradical) on the double bond to form the initial 1,6-diradical. This 1,6-diradical can recombine to form both **35a** and **35'a** (Scheme 10, pathway a), or disproportionate by H abstraction to form a benzylic alcohol with an N-acyl enamine moiety and this alcohol can undergo a subsequent ground-state or photoinduced intramolecular alcohol addition to yield aminal **42a** (Scheme 10, pathway b).

The formation of aminals **42** and **43** is fully suppressed at elevated temperatures (irradiation + reflux), therefore, the aminal formation as a side product in slower reactions at 20 °C can be readily rectified and so is not an issue from the preparative standpoint. However, it provides indirect evidence for the nonconcerted pathway. It is also possible that a triplet state is involved in the product formation.

In view of these findings it is conceivable that the additions to the heterocyclic furanyl, thienyl, or pyrrolyl pendant groups may also occur by a nonconcerted singlet or triplet mechanism. Studies are under way in our laboratory to elucidate the detailed mechanism of these reactions.

In conclusion, we have discovered new cycloaddition reactions of *o*-azaxylylenes, generated by ESIPT from *o*-amido-substituted aldehydes or ketones; these reactions provide rapid access to conformationally constrained fused N,O,S-polyheterocycles with benzoazocine or hydroquinoline cores. The precursors for these reactions can be readily assembled by simple coupling reactions, making the overall sequence amenable to high throughput diversity-oriented synthesis.

Received: May 25, 2011

Published online: August 31, 2011

Keywords: cycloaddition · heterocycles · molecular diversity · *o*-azaxylylenes · photochemistry

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- [12] CCDC 826416 (**3d**), 826420 (**2d**), 826431 (**40**), 826432 (**41**), and 826433 (**43f**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.