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Communication

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Oxazolines as Dual-Function Traceless Chromophores and Chiral Auxiliaries: Enantioselective Photoassisted Synthesis of Polyheterocyclic Ketones

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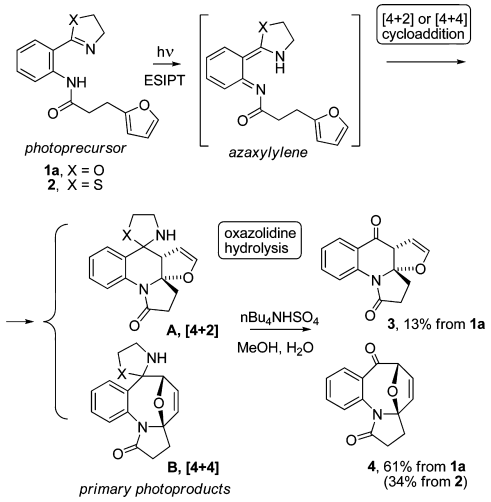
Supporting Information

ABSTRACT: 2-(*o*-Amidophenyl)oxa- and -thiazolines undergo excited-state intramolecular proton transfer (ESIPT), generating aza-*o*-xylylenes capable of intramolecular [4+2] and [4+4] cycloadditions with tethered unsaturated pendants. Facile hydrolysis of the primary photoproducts, spiro-oxazolidines and thiazolidines, under mild conditions unmasks a phenone functionality. Variations in linkers allow for access to diverse core scaffolds in the primary photoproducts, rendering the approach compatible with the philosophy of diversity-oriented synthesis. Chiral oxazolines, readily available from the corresponding amino alcohols, yield enantioenriched keto-polyheterocycles of complex topologies with enantiomeric excess values up to 90%.

Significant progress has been made in chiral photochemistry,[1] yet its scope is largely limited to enantioselective Paternò–Büchi reactions[2] and other [2+2] cycloadditions,[3] with modest forays into [4+2] and [4+4] cycloadditions, as well as electrocyclic reactions and photorearrangements.[4] This may be partially attributable to the limited variety of chiral catalysts or chiral auxiliaries traditionally used in photochemical reactions (mostly esters or acetals), although recent advances in enantioselective photoredox chemistry help fill the void with either chiral auxiliaries adopted from the ground-state radical chemistry or novel chiral photoredox catalysts.[5]

Recently we developed a novel photoassisted synthetic methodology involving excited-state intramolecular proton transfer (ESIPT) to generate reactive aza-*o*-xylylenes from aromatic amino ketones[6] or imines.[7] It allows for rapid access to complex polyheterocyclic molecular architectures in a very few simple synthetic steps. We rationalized that such reactions with structurally not dissimilar chromophores, 2-*aryloxazolines*, could be a valuable addition to the synthetic applications of this methodology as the generated aza-*o*-xylylenes in this case would have the carbon terminus substituted with two heteroatoms, N and O, Scheme 1. Their primary photoproducts possess readily hydrolyzable aminals, rendering these oxazoline chromophores *traceless*. We aimed to augment them with a chiral auxiliary to devise a dual-purpose traceless chromophore/auxiliary, especially in view of the fact that in the ground-state chemistry—ever since the pioneering work of Meyers[8]—*oxazolines* are universally recognized as versatile chiral auxiliaries in asymmetric C–C bond formations, ligands for chiral catalysts[9] and as building blocks for organocatalysts.[10]

Scheme 1. Model Photocycloaddition Reactions with Oxazoline and Thiazoline Photoprecursors 1a and 2 (Isolated Yields over Two Steps Are Shown)



In this Communication we demonstrate that 2-(*o*-aminophenyl)oxazolines undergo ESIPT leading to cycloaddition-competent push–pull aza-*o*-xylylene intermediates and that chiral oxazolines indeed serve as effective dual function traceless chromophores/chiral auxiliaries.

Initially we examined the reactions of achiral photoprecursors **1** and **2** containing unsubstituted oxa- and thiazolines (Scheme 1), prepared from readily accessible 2-(4,5-dihydrooxazol-2-yl)aniline and 2-(4,5-dihydrothiazol-2-yl)aniline (see SI for synthetic details). Compounds **1** and **2** have broad UV absorption with the maximum around 320–330 nm. Irradiations at ambient temperature were carried out in a broadband 300–400 nm Rayonet photoreactor (12 × 16 W) with dichloromethane (DCM) as a solvent, resulting in the clean formation of both [4+2] and [4+4] photoproducts. The primary photoproducts, spiro oxazolidines or thiazolidines **A** and **B**, were hydrolyzed without isolation in aqueous methanol with PPTS or *n*-Bu_4NHSO_4 to corresponding ketones **3** and **4**.

Instructively, the quantum yield of the photocyclization with the oxazoline chromophore was three times higher than that with thiazoline, which decided the further use of *oxa*- and not *thia*zolines in the subsequent studies.

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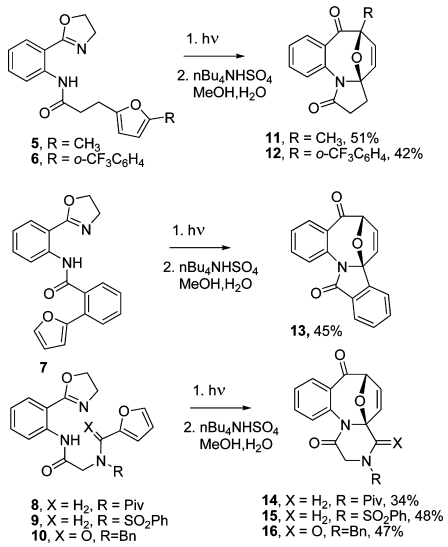
Photophysics of the close relatives of oxazolines—benzoxazoles, benzothiazoles, and benzimidazoles—was documented in the literature,[11] and 2-(2′-hydroxyphenyl)benzoxazoles and -thiazoles found use in biosensors[12] and sensitizers.[13] To the best of our knowledge, no synthetic applications of these processes have been reported; further, no experimental data are available on ESIPT in oxazolines or thiazolines.

We also synthesized a *benzo*thiazole-based photoprecursor, because of benzothiazole's ready availability and a strong red-shifted absorption band. Although ESIPT in o-benzothiazolylanilines is known,[14] the benzothiazole-based photoprecursor failed to cyclize. Since it cannot serve as a dual-function *chiral* chromophore anyway, its lack of photoreactivity was not disappointing.

The scope of the reaction was probed by varying the length and the nature of the linker between the 2-(*o*-aminophenyl)-4,5-dihydrooxazole photoactive core and the unsaturated pendant (i.e., the furan moiety), which also allowed for assessing the reaction tolerance to the functional groups in the potential diversity inputs, Scheme 2. All photoprecursors were synthesized by amide coupling of 2-(4,5-dihydrooxazol-2-yl)aniline with the corresponding acid.[15]

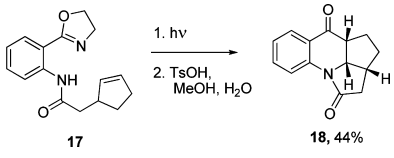
Scheme 2. Scope of Photocycloadditions with Furanoyl and Furanyl Pendants Tethered via Aliphatic or Aromatic Linkers



Simple cycloalkene pendants were also shown to react. Cyclopentenyl photoprecursor **17** (Scheme 3) underwent the [4+2] photocyclization, as the [4+4] channel is not available for alkenes. Oxazolidines initially formed from **17** proved to be somewhat more stable than their dihydrofuran-containing counterparts and required TsOH to hydrolyze.

Encouraged by this success in the model achiral systems we then proceeded with synthesis of chiral oxazolines **1b**–**1g**

Scheme 3. Photoreaction of Cyclopentene-Containing Precursor 17



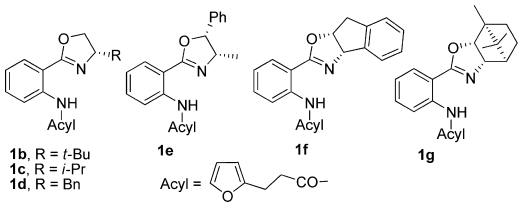


Figure 1. Chiral oxazoline-based photoprecursors **1b**–**g**.

(Figure 1) with the goal of accessing enantiopure photoproducts. In the context of ESIPT-generation of azaxylylenes, combining the roles of a chromophore and a chiral auxiliary in the same oxazoline moiety necessarily places its stereogenic center in the close proximity of the reaction center, which should arguably provide a greater control of the stereochemical outcome.

Compounds **1b**–**1f** can be readily prepared from commercially available 2-aminoalcohols;[16] camphor-based **1g** was obtained as described from camphorquinone.[17] The optimization runs (solvent/temperature/chiral auxiliary) are shown in Table 1 and Figure 2. At 20 °C, the enantiomeric excess (*ee*) values in DMSO were slightly better than in DCM, but low temperature clearly had an overriding advantage, making DCM the solvent of choice, as DMSO does not allow for any substantial cooling. Efficient temperature control was essential; thus, the photoinduced cycloadditions at low temperature were conducted in a Pyrex Dewar with a clear window and a medium-pressure 200 W Hanovia lamp. Primary photoproducts—

Table 1. Optimization of Reaction Conditions for Chiral Photoprecursors

		de (%) by NMR[a]			*ee* (%) by HPLC[b]	
	T (°C)/ solv.	[4+2]	[4+4]	**B**:**A** ratio	**3**, [4+2]	**4**, [4+4]
1b	20/DCM	11	72	4.5	17	54
1b	20/DMSO	–[c]	–	–[c]	37	68
1b	0/DCM	51	71	4.5	41	69
1b	−20/DCM	48	69	3.7	37	69
1b	−40/DCM	38	72	3.4	51	75
1b	−78/DCM	57	88	2.9	60	86
1e	−78/DCM	36	18	2.3	43	25
1d	−78/DCM	12	63	2.1	8	57
1c	−78/DCM	61	75	3.0	65	84
1f	−78/DCM	34	84	3.7	30	84[d]
1g	−78/DCM	31	96	2.3	–	86

[a]Before hydrolysis. [b]By chiral HPLC after hydrolysis into ketones. [c]Partial hydrolysis occurs during the photoreaction; calculation of de or **B**:**A** ratio is not possible. [d]1-Amino-2-hydroxyindanone-based auxiliary produced reversed ratio of enantiomers.

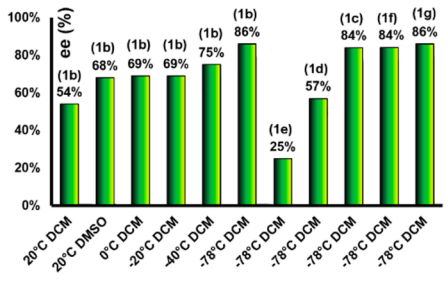


Figure 2. Optimization of *ee*'s for the [4+4] ketone product.

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oxazolidines **A** and **B**—are formed as two diastereomers, distinguishable by NMR. This enabled calculation of diastereomeric excess prior to the workup of the reaction. After the completion of the irradiation as determined by NMR, hydrolysis was performed, and the mixture was analyzed by chiral HPLC (Chiracel AD) using compounds **3** and **4** as racemic chromatography standards. The results of this optimization are shown in Table 1.

Figure 2 illustrates in a graph form the final *ee* values determined by chiral HPLC for the optimization runs in the [4+4] cycloadducts. Of commercially available amino alcohols *tert*-leucinol-based photoprecursor **1b** (first six vertical bars) performed the best. Compound **1g** exhibited similar performance, but was not commercially available. We thus selected the *tert*-leucinol-based photoactive cores. As follows from Table 1, the diastereomeric excess (de) values for the primary photoproducts of types **A** and **B** (columns 2 and 3 in Table 1) generally correlated with the final *ee* values for the hydrolyzed products **3** and **4**. One instructive observation (see Table 1) was that the [4+4] products generally exhibited higher *ee*'s than the [4+2] products. Our mechanistic rationale for this is presented in Figure 3.

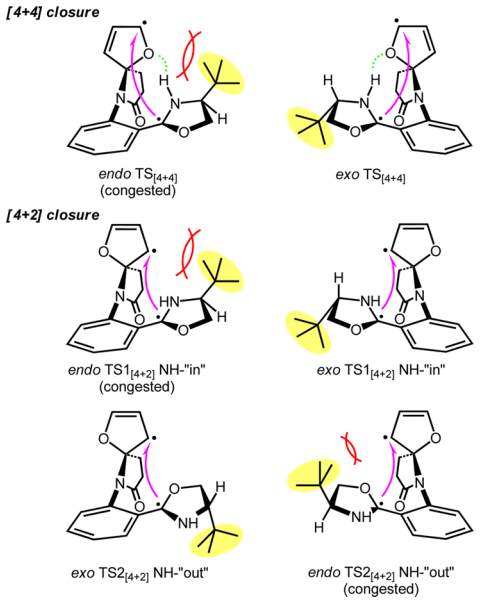


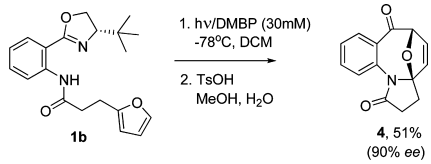
Figure 3. Plausible mechanistic rationale for tighter stereocontrol in the TS leading to [4+4] photoproducts.

We hypothesize that the stereodifferentiation either does not occur at all or occurs only to a minor extent at the initial attack of the N-radical center of the triplet aza-*o*-xylylene on the tethered furan moiety. Rather, the stereochemical outcome is controlled at the recombination step (after the intersystem crossing, ISC, to the singlet ground state) in the diradical species produced by this initial attack, Figure 3. For the [4+4] closure, the hydrogen bond (green dotted line) between the furan oxygen and the NH moiety locks the rotation of oxazolidinyl radical limiting the conformational space to only one rotamer—either *endo* $TS_{[4+4]}$ or *exo* $TS_{[4+4]}$. In the *endo* $TS_{[4+4]}$, the collapse of the diradical species after ISC is obstructed by the *tert*-butyl group while there is no such steric clash in the *exo* $TS_{[4+4]}$—hence, the higher *ee* values.

The [4+2] cycloadducts are formed via a similar radical recombination, but at the other terminus of the allylic radical (the alternative *resonance* structure for the dihydrofuryl radicals illustrates this in Figure 3). The rotamers leading to the [4+2] closure lack the hydrogen bond with furan's oxygen, so the NH moiety is free to assume both "in" and "out" conformation in the aryl-conjugated oxazolidinyl radical. This implies that all four combinations, *exo/endo* and *NH-in/NH-out*, are feasible, thus lowering the *ee* values for the [4+2] products. The fact that the [4+2] reaction is still stereoselective may point to a weak hydrogen bond between the NH and the γ-lactam moiety, which biases the system toward the NH-"in" rotamer, *exo* $TS1_{[4+2]}$. The overall regioselectivity of the addition, i.e., [4+4] vs [4+2], is conceivably governed by the intrinsic differences of spin density in the allylic radical and the average distance between the radical centers, which is slightly greater for the [4+4] recombination. The better orbital overlap for the [4+2] channel and the fact that the [4+4] to [4+2] ratio decreases at lower temperatures (Table 1, *tert*-leucinol-based **1b**) indicates that [4+2] is a kinetic product.

Preparative scale low temperature irradiations always present additional challenge as the Hanovia medium pressure mercury lamps deposit considerable amount of energy into the reaction flask. UV LEDs offer well-conditioned "cool" UV light, but currently only 360 nm (and higher) LEDs are powerful enough to be practical for the preparative runs. Yet the absorption maximum of oxazolines **1b–g** is blue-shifted to 320–330 nm as compared with 350–360 nm absorption of the corresponding *o*-aminoketones. Our earlier mechanistic studies in the ketone series indicated that these cycloadditions occur in the triplet manifold.[18] Thus, our solution to this challenge was to employ a triplet sensitizer, which allowed for the utilization of a linear array of 365 nm UV-LEDs (4 × 250 mW). Several sensitizers were tested (aminobenzonitrile, methyl anthranilate, benzophenone, 4-methoxybenzophenone, 4,4′-dimethylbenzophenone, 4,4′-difluorobenzophenone, 4,4′-dimethoxybenzophenone, thioxanthone), and 4,4′-dimethoxybenzophenone (DMBP) was identified as the sensitizer of choice. The preparative scale (~100 mg) irradiation at −78 °C with a 10 mol% sensitizer proceeded smoothly and, after hydrolysis and chromatographic purification, gave [4+4] cycloadduct **4** with 51% isolated yield and 90% *ee* (average of two experiments, Scheme 4).

Scheme 4. Preparative-Scale Photolysis for *tert*-Leucinol-Based Photoprecursor 1b



In conclusion, we report the first example of the photoinduced intramolecular cycloadditions of 2-(2-amidophenyl)oxazolines via ESIPT. The photoprecursors are amenable to modular assembly, rendering the method compatible with the philosophy of diversity-oriented synthesis. The reaction is tolerant to a variety of linkers and proceeds smoothly with both furyl and alkenyl unsaturated pendants. The facile hydrolysis of the primary photoproducts, spiro-oxazolidines, cleanly unmasks a ketone functionality. The use of readily accessible chiral oxazolines results in the formation of enantioenriched heterocyclic ketones with high *ee*'s. Given a variety of postphotochemical transformations available to further grow

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complexity of the primary photoproducts of azaxylylene cyclizations,[6,7] one can readily envision how rather complex polyheterocyclic molecular architectures could be obtained in an enantiopure form.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b12690.

Experimental procedures and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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