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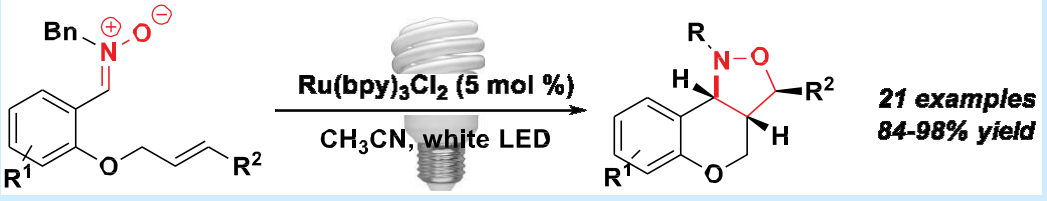
Synthesis of Chromenoisoxazolidines from Substituted Salicylic Nitrones via Visible-Light Photocatalysis

Graham Haun, Alyson N. Paneque, David W. Almond, Brooke E. Austin, and Gustavo Moura-Letts*

Department of Chemistry and Biochemistry, Rowan University, 201 Mullica Hill Road, Glassboro, New Jersey 08028, United States

Supporting Information



ABSTRACT: This effort reports the first redox-neutral visible-light photocatalytic intramolecular dipolar cycloaddition for the diastereoselective synthesis of chromenoisoxazolidines. The authors have found that alkenylphenyl nitrones with a diverse substitution pattern on the aromatic ring and the alkenyl substituent undergo visible-light-promoted cycloadditions in the presence of catalytic amounts of $Ru(bpy)_3Cl_2$ in high yields and selectivities. Evidence indicates that the proposed redox-neutral pathway is the predominant photoredox mechanism for this transformation.

The dipolar cycloaddition reaction has long been among the most influential organic transformations due to its ability to furnish a variety of highly substituted five-membered heterocycles.[1] The scaffolds obtained through this reaction are important intermediates in the preparation of natural products and commercial drugs.[2] Moreover, up to three continuous stereocenters can be formed through this reaction, and the challenge of controlling regio-, diastereo-, and enantioselectivities has attracted much attention in recent years.[3] Although some selective methods are available, high regio- and diastereoselectivities remain elusive.[4] Intramolecular dipolar cycloadditions between nitrones and unactivated alkenes are poised to provide high selectivities, although reported efforts rely on high heat or harsh reagents to achieve high reaction efficiencies.[5] Thus, more efficient and milder methods remain goals in the field of organic chemistry.

Photocatalysis has emerged in the last 15 years as a promising approach toward the development of otherwise inefficient or thermodynamically demanding transformations.[6] Visible-light-promoted photocatalysis exploits its inexpensive and mild nature to promote a variety of novel transformations, thus becoming an emerging field in organic synthesis.[7] Among these, cycloaddition reactions have received considerable attention, and several efforts have shown that dipolar cycloadditions are efficiently promoted by visible-light photocatalysis for the synthesis of five-membered heterocycles.[8] Despite the significant developments, many of these reactions rely on complex substrates and suffer from poor generality.[9] Thus, further development of more efficient and general visible-light-promoted photocatalytic methods is of fundamental importance to this field.

Chromenoisoxazolidines are important molecular scaffolds in drug discovery for their properties as antidepressants, antipsychotics, and antianxiolytics.[10] These can also be used as templates for the synthesis of more complex molecules.[11] However, the few available methods rely on the intramolecular cycloaddition of alkenylnitrones through high temperatures or harsh reagents to achieve moderate efficiencies.[5] Moreover, available methods for their synthesis suffer from substrate scope, thus severely limiting their applicability. Thus, more efficient and general methods for the synthesis of such important scaffolds remain an important synthetic goal.

We are focused on developing novel methods for the synthesis of complex nitrogen-containing heterocycles.[12] Recently we discovered that nitrones undergo regioselective intermolecular dipolar cycloaddition based upon the substitution pattern on the dipolarophile. However, inter- and intramolecular unactivated dipolarophiles are highly unreactive and therefore poised for the development of suitable photocatalytic reaction conditions.[13]

Among the variety of visible-light photocatalytic processes, redox-neutral photocatalysis may be employed to access stable radical cations and radical anions that do not provide fragmentation to give neutral radicals.[14] These intermediates possess reactivity that is inherently different from that of their ground state, thus providing access to otherwise unprecedented transformations.[15] We envisioned a visible-light-promoted redox-neutral photocatalytic dipolar cycloaddition for the synthesis of chromenoisoxazolidines from alkenylnitrones.

Based on our efforts toward better understanding the selectivity of nitrone cycloadditions, we discovered that 2-allyloxyphenyl-*N*-benzylnitrone undergoes very slow conver-

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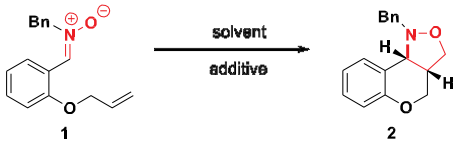
Table 1. Reaction Optimization



entry	additive	solvent	t (°C)	concentration (M)	yield (%)[a]
1[b]	none	toluene	rt	0.01	0
2[b]	none	toluene	60	0.01	32
3[b]	none	toluene	100	0.01	88
4[c]	visible light	benzene	rt	0.01	18
5[d]	visible light	CH_2Cl_2	rt	0.01	20
6[d]	visible light	CH_3CN	rt	0.01	32
7[d]	visible light	MeOH	rt	0.01	28
8[d]	visible light	CH_3CN	rt	0.02	18
9[d]	visible light	CH_3CN	rt	0.03	15
10[d]	visible light	CH_3CN	rt	0.05	32
11[d]	visible light	CH_3CN	rt	0.005	42
12[d]	$Ru(bpy)_3Cl_2$ 5 mol %	CH_3CN	rt	0.005	98
13[d]	$Ru(bpy)_3Cl_2$ 1 mol %	CH_3CN	rt	0.005	44
14[d]	$Ru(bpy)_3Cl_2$ 10 mol %	CH_3CN	rt	0.005	65
15[d]	$Ir(p\text{-}F\text{-}ppy)_3Cl_2$ 5 mol %	CH_3CN	rt	0.005	71
16[d]	$Ru(bpz)_3(PF_6)_2$ 5 mol %	CH_3CN	rt	0.005	64
17[d,e]	$Ir(L)_2(bpy)_3(PF_6)_2$ 5 mol %	CH_3CN	rt	0.005	75
18[d]	methyl viologen	CH_3CN	rt	0.005	14

[a]Isolated yields. [b]In the absence of light (dark box). [c]3 days by the windowsill. [d]White LED. [e]L = $dfCF_3ppy$.

sion to the respective chromenoisoxazolidines in 18% yield over 3 days by the windowsill. Analysis of the reaction indicated complete selectivity for the cis diastereomer. A survey of the literature revealed few reports focused on visible-light-promoted cycloaddition of nitrones, and among those none had focused on the intra- or intermolecular visible-light-promoted dipolar cycloaddition of nitrones with unactivated dipolarophiles.[9]

Thus, we decided to focus on the optimization of this transformation under the proposed reaction conditions (Table 1). The initial discovery highlighted the potential for visible-light-promoted transformations for this type of substrate. We found that in the absence of light no conversion was observed at room temperature (entry 1). However, in the absence of light and at 60 °C the yield increased to 32% and at 100 °C to 88% (entries 2 and 3, respectively). Although the thermal transformation is known to work, difficult purifications and mediocre scopes due to decomposition and lack of functional group tolerance are unavoidable, thus rendering this approach inefficient. We then assessed the effect of solvent on the proposed visible-light transformation. These reactions were then setup on a photoreactor with a source of white LED. As a result, different solvents proved a slight preference for polar aprotic CH_3CN at 0.01 M by providing the product in 32% yield (entry 6; other solvents entries 4, 5, and 7). Despite the low conversions and relative independence on solvent, the substrate undergoes slow excitation with fast cyclization to provide the expected chromenoisoxazolidine. Further efforts revealed that the productivity is moderate even at lower concentrations, providing a slightly better 42% yield at 0.005 M (entry 11; other concentrations entries 8−10). Other efforts for comparable reactions have revealed the need of organic or inorganic photocatalyst for the efficient promotion of such transformations.[16] These efforts led to the discovery that well-known photocatalyst $Ru(bpy)_3Cl_2$ was able to significantly increase the reaction productivity to 98% yield at 5 mol % (entry 12).[17] However, at 1 or 10 mol % the yield decreased to moderate yields (44 and 55%, entries 13 and 14, respectively). Other commercially available photocatalysts proved to be less efficient than $Ru(bpy)_3Cl_2$ (entries 15−18).

Based on the high conversions and diastereoselectivities, the next step forward focused on assessing the scope of the transformation across multiple diversification points. We anticipated that functional group electronic and steric effects around the salicylic aromatic ring would provide a thorough understanding of the reaction scope (Table 2). Moreover, substituted salicylaldehydes and acetophenones proved ideal at condensing with benzylhydroxylamine to provide the required nitrones. Thus, 3-allyl and naphthyl substrates proved to convert to the corresponding product in very high yields and with similar high diastereoselectivities for the cis isomer (entries 2 and 3, 97 and 92% yield, respectively). Dihalogeneted substrates (diiodo, dichloro, and dibromo) also reacted in very high yields and provided the respective chromenoisoxazolidines as single diastereomers (entries 4−6; 95, 94, and 91% yield, respectively). Other substitution patterns around the nitrone aromatic ring provided the desired heterocycle in similar high yields (entries 7 and 8, 92 and 96% yield, respectively). Further exploration of the reaction scope led to the discovery that phenone-derived nitrones with a variety of substitution patterns undergo equally high yielding reactions for the respective cis-chromenoisoxazolidines as single diastereomers (entries 9−12; 93, 95, 96, and 90% yield, respectively).

This study also aimed at assessing the efficiency of the visible-light-promoted process on substrates with sterically demanding allyl ethers (Table 3). As expected, diastereoselectivities across the fused ring remain highly selective for the cis product.[18] Substitution at the allylic carbon led to the production of the expected heterocycle as a 12:1 mixture of

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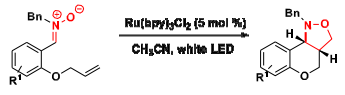
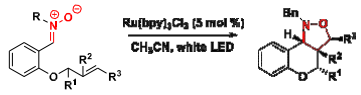
Table 2. Reaction Scope



entry	nitrone	product[c]	yield (%)[a,b]
1	1a	2a	98
2	1b	2b	97
3	1c	2c	92
4	1d	2d	95
5	1e	2e	94
6	1f	2f	91
7	1g	2g	92
8	1h	2h	96
9	1i	2i	93
10	1j	2j	95
11	1k	2k	96
12	1l	2l	90

[a]Reaction conditions: ntrone (0.1 mmol) and $Ru(bpy)_3Cl_2$ (0.005 mmol) in CH_3CN 0.005 M for 24 h. [b]Isolated yields. [c]Reaction crude was purified by automated chromatography. [d]Nitrone 1a is particularly sensitive and high purity is required to avoid hydrolysis.

Table 3. Reaction Scope



entry	nitrone	product[c]	yield (%)[a,b]
1	1m	2m	91
2	1n	2n	92
3	1o	2o	89
4	1p	2p	87
5	1q	2q	91
6	1r	2r	88
7	1s	2s	86
8	1t	2t	85
9	1u	2u	84

[a]Reaction conditions: Nitrone (0.1 mmol) and $Ru(bpy)_3Cl_2$ (0.005 mmol) in CH_3CN 0.005 M for 24 h. [b]Isolated yields. [c]Reaction crude was purified by automated chromatography.

diastereomers at the chiral allylic position. The stereoselectivity observed highly correlates with an expected all-pseudoequatorial transition state for this substrate. Moreover, the reaction yield and overall conversion were not affected by the added substitution (entry 1, 91% yield). Substrates with methyl substituents at the 2- and 3-carbon were also very successful at providing the respective chromenoisoxazolidine in high yields and diastereoselectivities (entries 2 and 3, 92 and 89% yield, respectively). Trisubstituted 3,3-dimethylallyl nitrone provided the product in similar high yields with a slightly prolonged reaction time (entry 4, 87% yield).

Similarly, sterically demanding 3-phenylallyl and geranyl nitrones also provided the respective product in high yields and stereoselectivities (entries 5 and 6, 91 and 88% yield,

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respectively). Tetrasubstituted and bulkier trisubstituted allyl nitrones failed to react to provide the respective highly substituted chromenoisoxazolidines in synthetically useful yields (not shown in the table).

Diversification at the N-alkyl position showed similar success as N-cyclohexyl, N-phenyl, and N-methyl nitrones provided the desired heterocycles in similar high yields and selectivities (entries 7−9, 86, 85, and 84% yield, respectively). Nitrones with N-bound electron-withdrawing groups (Boc, Cbz) displayed very low conversion under the proposed reaction conditions.

The encouraging results shifted the focus toward the study of the reaction mechanism. Nitrones derived from aromatic aldehydes are good spin-trapping agents, making them suitable candidates for photoxidation pathways.[19] Moreover, aldonitrones with electron-donating groups as the proposed substrate are reported to undergo less demanding oxidation pathways.[20]

Mechanistically, the reaction in the absence of a photocatalyst must be promoted by the slow excitation of the substrate to the nitrone triplet state, followed by fast cyclization and then relaxation to the ground state. Under a photocatalytic redox-neutral mechanism the substrate plays both reductant and oxidant roles (Figure 1). Thus, upon

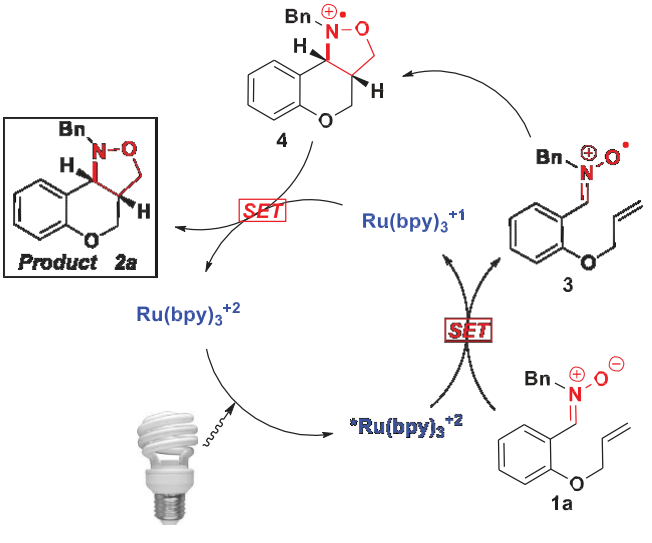

Figure 1. Proposed photoredox-neutral mechanism.

excitation of $Ru(bpy)_3^{+2}$ to $^*Ru(bpy)_3^{+2}$, nitrone 1a undergoes single electron transfer oxidation to form the respective radical cation 3 and $Ru(bpy)_3^{+}$. The radical cation intermediate then undergoes intramolecular radical addition across the pendant alkene to form chromenoisoxazolidine radical cation 4. This intermediate quickly undergoes single electron transfer reduction to produce product 2a and return the catalyst to the ground state. In an effort to fully understand the dominant pathway, tertiary amines were used as potential additives, and it was discovered that no significant change was observed, thus eliminating any potential need for a sacrificial reductant and further validating a redox-neutral pathway. Next, radical-trapping experiments showed that in the presence of TEMPO there was complete shutdown of the photoredox pathway, and no product was observed. This key experiment provided further evidence of a predominant SET mechanism.

It was also discovered that the proposed photoredox process could not be propagated in the absence of visible light by ^1H NMR monitoring, thus providing further evidence of a redox-neutral pathway (SI).

In conclusion, we have developed the first general report for a redox-neutral visible-light photocatalytic intramolecular dipolar cycloaddition. The reaction works in high yields for a wide variety of substrates with multiple diversification points under very mild conditions. Additionally, the reaction appears to be highly diastereoselective and stereospecific for the cis isomer and tolerant for a wide degree of substitution patterns around the aromatic ring and pendant alkenyl group. Efforts will continue to focus on further elucidating the proposed redox-neutral mechanism and establishing novel photoredox reactions for the synthesis of complex N-containing heterocycles.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00097.

Experimental protocols and spectroscopic data for each chromenoisoxazolidine are provided (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: moura-letts@rowan.edu.

ORCID

Gustavo Moura-Letts: 0000-0001-8156-151X

Notes

The authors declare no competing financial interest.

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(17) General protocol for synthesis of chromenoisoxazolidines from nitrones: In an oven-dried 250 mL round-bottom flask, nitrone (1 mmol, 1 equiv) and $Ru(bpy)_3Cl_2$ (0.05 mmol, 0.05 equiv, 5 mol %) were dissolved in CH_3CN (200 mL) 0.005 M under N_2 atmosphere. The resulting mixture was then stirred at room temperature in a photoreactor with a white LED bulb for 24 h. The resulting crude was then dried under reduced pressure, and the residue was loaded directly onto a silica gel column for automated purification.

(18) The isomers isolated in this reaction were characterized by 1D and 2D ^{1}H NMR. The cis stereochemistry was assigned based on coupling constant and NOE analysis.

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