Synthesis of Isoxazolidines from Substituted Vinylnitrones and Conjugated Carbonyls via Visible-Light Photocatalysis

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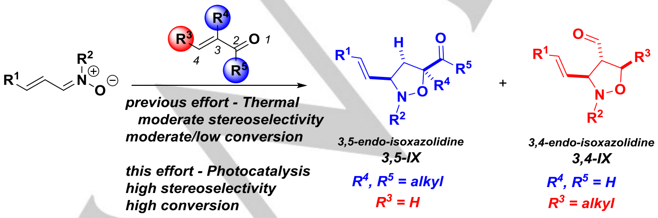
Abstract: Herein we report the first redox-neutral visible-light photocatalytic intermolecular dipolar cycloaddition for the diastereoselective synthesis of isoxazolidines. We have found that vinyl nitrones with a diverse substitution pattern undergo visible-light promoted cycloadditions with conjugated carbonyls in the presence of catalytic amounts of Ru(bpy)$_3$Cl$_2$ in high yields and high selectivities. These efforts indicate that a redox-neutral pathway is the primary photoredox mechanism for this transformation.

Introduction

Isoxazolidines are five-membered ring heterocycles containing connecting *N* and *O* atoms. This functional group is highly conserved among natural products, commercial drugs and provides conformational rigidity to serve as synthetic templates for the production of more complex heterocycles.[1] Isoxazolidines are also of great significance in drug discovery, due to their diverse pharmacological profiles based on their ability to mimic a wide range of natural molecular architectures.[2] As a consequence, the discovery of novel methods for the selective synthesis of stereochemically-dense isoxazolidines remains an important goal in the field of organic chemistry.[3]

The dipolar cycloaddition of nitrones with conjugated carbonyls has historically been the default approach for the construction of substituted isoxazolidines.[4] Due to the high energetic requirements for the thermal cycloaddition to be synthetically useful,[5] Lewis acid catalysis has also been employed as means to improve kinetics, conversions, scope, and stereoselectivities.[6] There is a large number of dipolar cycloaddition variants; however, few provide evidence for predictable regio- and diastereoselectivities.[7] Experimental and computational efforts indicate that there is a clear substrate bias for 3,5-isoxazolidines (*3,5-IX*) when using conjugated carbonyls with substituents in positions 2 and 3, and for 3,4-isoxazolidines (*3,4-IX*) when using conjugated carbonyls with substituents in position 4 only (**Scheme 1**).



Scheme 1. Dipolar cycloaddition of vinyl nitrones.

This trend has been observed under thermal and Lewis acid-promoted conditions and computational efforts have demonstrated a clear preference for *endo* products.[8] Marouka has found that changes on the steric bulk of the LA promoter are able to control the regioselectivity of the reaction irrespective of the substrate substitution patterns.[9] However, these methods still struggle with poor stereospecificity and stereoselectivity, thus superior methods for a highly stereoselective dipolar cycloaddition of vinyl nitrones and conjugated carbonyls continues to have great significance.

Photocatalysis has revolutionized the field of organic chemistry as the bridge towards new chemical reactions but also towards the development of otherwise inefficient or thermodynamically demanding transformations.[10] Moreover, visible-light-promoted photocatalysis has become a superior alternative to thermal methods by providing access to complex scaffolds with unprecedented efficiencies and selectivities.[11] From these, cycloaddition reactions have been extensively studied and several efforts have shown that dipolar cycloadditions are efficiently promoted by visible-light photocatalysis for the production of complex heterocycles.[12]

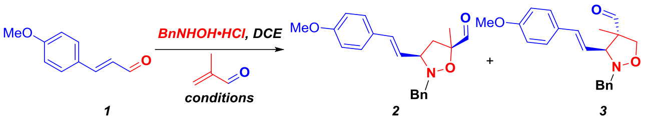
The Moura-Letts laboratory is focused on developing novel methods for the synthesis of complex nitrogen-containing heterocycles.[13] Recently, we discovered that vinyl nitrones undergo regioselective thermal intermolecular dipolar cycloaddition based upon the substitution pattern on the dipolarophile.[8] We also discovered that alkenylnitrones undergo visible-light promoted photocatalytic intramolecular dipolar cycloaddition to provide chromenoisoxazolidines with great efficiencies.[12a] Despite the success of thermal methods; the often observed moderate stereoselectivities, reduced scope and background decomposition pathways suggest that further reaction innovation is needed. Thus, the development of suitable photocatalytic reaction conditions is highly significant.

Redox-neutral processes has become recurrent among photocatalytic reactions. This preference is due to their access to stable radical cations and radical anions that do not undergo α-bond fragmentation to give neutral radicals.[12a,14] These intermediates are then poised to react with high degrees of productivity and specificity.[15] Thus, we aim to develop a visible-light promoted redox-neutral photocatalytic intermolecular dipolar cycloaddition for the synthesis of vinylisoxazolidines from vinyl nitrones and conjugated carbonyls.

Results and Discussion

Our previous studies on the thermal dipolar cycloaddition of vinyl nitrones reveal that a potential lower energy pathway may lead to higher reaction selectivities. Similar to the thermal process, we envisioned nitrones to form immediately upon reacting the enal substrate and benzylhydroxylamine hydrochloride. Thus, the reaction optimization is focused on the photocatalytic cycloaddition (**Table 1**).[8] These reactions were then set-up on a photo-reactor with a source of LED (105 watt, CFL bulb) white light. We found that the reaction outside the photo-reactor is very slow and produces **2** in very low yield, but in the absence of light no traces of **2** are found and if left by the windowsill for 4 days yield increases to 20% compared to the high yields obtained under heat (entries 1-4). Other variables known to alter visible-light promoted reactions (concentration, stoichiometry and solvent) allowed for the determination that CH_3CN at 0.05M in a 1:2 ratio provided **2** in 48% and in a much improved 25:1 *d.r* (entries 5-10).

Table 1. Reaction optimization.



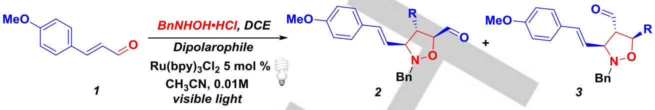
1 *2* *3*

Entry	Ratio[a]	Conditions	Solvent	Concentration (M)	t (°C)	%Yield of **2:3**[b]	d.r[c]
1	1:2	none	DCE	0.1	rt	5:1	12:1
2[d]	1:2	none	DCE	0.1	rt	0	-
3	1:2	none	DCE	0.1	80	88:4	15:1
4[e]	1:2	visible light	DCE	0.1	rt	20:4	20:1
5[f]	1:2	visible light	DCE	0.05	rt	30:4	20:1
6[f]	1:2.5	visible light	DCE	0.05	rt	30:5	20:1
7[f]	1:3	visible light	DCE	0.05	rt	29:8	20:1
8[f]	1:2	visible light	CH_3CN	0.05	rt	48:6	25:1
9[f]	1:2	visible light	benzene	0.05	rt	40:10	15:1
10[f]	1:2	visible light	Dioxane	0.05	rt	39:8	15:1
11[f]	1:2	$Ru(bpy)_3Cl_2$ 5 mol %	CH_3CN	0.05	rt	80:1	50:1
12[f]	**1:2**	**$Ru(bpy)_3Cl_2$ 5 mol %**	**CH_3CN**	**0.01**	**rt**	**98:1**	**50:1**
13[f]	1:2	$Ru(bpy)_3Cl_2$ 5 mol %	CH_3CN	0.005	rt	70:1	50:1
14[f]	1:2	$Ir(p\text{-}F\text{-}ppy)_3Cl_2$ 5 mol %	CH_3CN	0.01	rt	84:1	50:1
15[f]	1:2	$Ru(bpz)_3(PF_6)_2$ 5 mol %	CH_3CN	0.01	rt	74:1	50:1
16[f,g]	1:2	$Ir(L)_2(bpy)_3(PF_6)_2$ 5 mol %	CH_3CN	0.01	rt	69:1	50:1

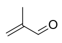
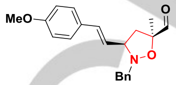
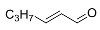
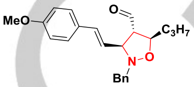
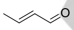
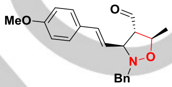
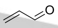
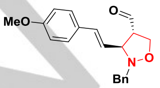
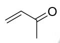
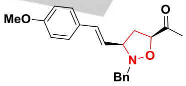
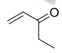
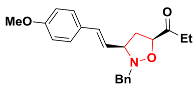
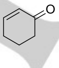
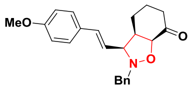
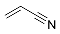
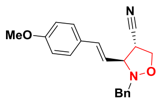
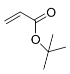
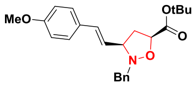
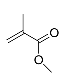
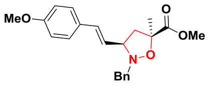
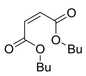
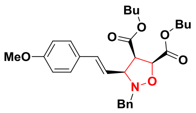
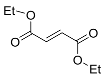
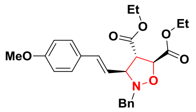
a. Ratio of enal:dipolarophile. b. Isolated yields. c. Ratio for the major isomer, measured by ^{1}H-NMR. d. In the absence of light (dark box). e. 4 days by the windowsill. f. White LED. g. L = $dfCF_3ppy$.

Based on our previous studies on photocatalysis, we decided to focus on inorganic photocatalysts.[12a] 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 and stereoselectivity to 50:1 *d.r* at 5 mol% and 0.01M (entries 11-13).[16] Other commercially available photocatalysts proved to be less efficient than $Ru(bpy)_3Cl_2$ (Entries-14-16). Having identified a suitable set of reaction conditions, we then focused on addressing the scope of this reaction. The steric effects of functional groups around the dipolarophile were hypothesized to provide an initial understanding of the reaction scope (**Table 2**). It was observed that hexenal, butenal, and acrolein provided **3** (*3,4-endo-IX*) with great conversion and very high stereoselectivities (entries 2-4). On the other hand, the introduction of groups on position 2 changed the selectivity to **2** (*3,5-endo-IX*) for methyl vinyl ketone, ethyl vinyl ketone and cyclohexenone with equally high stereoselectivities (entries 5-7). The focus then turned into addressing the effect of higher oxidation state carbonyls on the reaction. It was found that acrylonitrile provided **3** (*3,4-endo-IX*) with great selectivity (entry 8), but acroleyl t-butyl ester and methacroleyl methyl ester reacted with opposite selectivity to provide **2** (*3,5-endo-IX*) with very high selectivity (entries 9 and 10).

Table 2. Reaction scope.



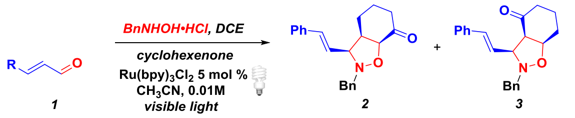
1 *2* *3*

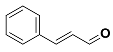
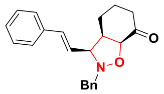
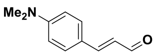
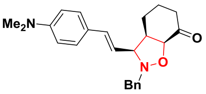
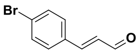
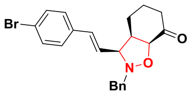
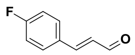
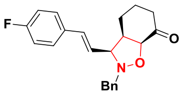
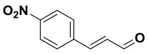
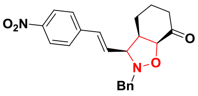
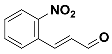
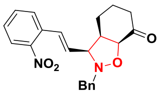
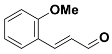
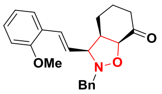
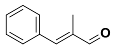
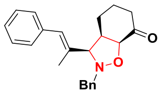
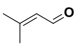
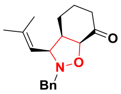
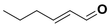
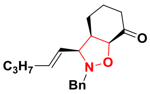
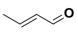
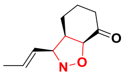
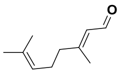
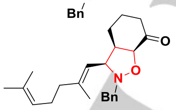
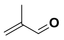
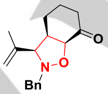
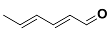
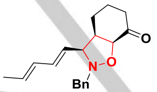
Entry[a]	Dipolarophile	Product	% of **2**[a]	% of **3**[c]	d.r.[c]
1			98	1	50:1
2			1	95	50:1
3			1	96	50:1
4			1	92	50:1
5			95	0	40:1
6			99	0	40:1
7			91	0	50:1
8			1	97	50:1
9			96	1	50:1
10			95	1	50:1
11			95		50:1
12			97		50:1

a. Reaction conditions: Enal (1 mmol) reacts with BnNHOHHCl (1.1 mmol) in DCE at rt for 1h. The solvent is removed and crude nitrone dissolved in CH_3CN (0.01M) and dipolarophile (2 mmol) and catalyst (0.05 mmol) are then added and stirred for 24h. b. Isolated yields. c. Measured by ^{1}H-NMR.

The stereospecificity of the reaction under photocatalysis was addressed by reacting *cis*-dibutylfumarate and *trans*-diethylfumarate. It was observed that the *cis* and the *trans* isomers conserved their relative stereochemistry for the corresponding products (entries 11 and 12). Given the sometimes radical nature of visible-light photocatalytic processes, the observed high stereospecificity is indicative of a redox-neutral photocatalytic process.

Table 3. Reaction scope.



Entry[a]	Enal	Product	% of 2[b]	% of 3[c]	d.r.[c]
1			98	0	50:1
2			96	0	50:1
3			92	1	44:1
4			90	1	44:1
5			86	3	40:1
6			89	3	40:1
7			91	2	50:1
8			84	0	50:1
9			93	0	50:1
10			95	0	44:1
11			90	0	50:1
12			84	0	40:1
13			96	0	50:1
14			91	0	48:1

a. Reaction conditions: Enal (1 mmol) reacts with BnNHOHHCl (1.1 mmol) in DCE at rt for 1h. The solvent is removed and crude nitrone dissolved in CH_3CN (0.01M) and dipolarophile (2 mmol) and catalyst (0.05 mmol) are then added and stirred for 24h. b. Isolated yields. c. Measured by ^{1}H-NMR.

These efforts also aimed at addressing the efficiency of visible-light photocatalysis on enals with different steric and electronic properties (**Table 3**). These examples were studied using cyclohexenone as the optimal dipolarophile due to its already high steric and energetic demands. It was observed that cinnamaldehyde and 4-dimethylaminocinnamldehyde reacted in very high yield and provided the expected product **2** (*3,5-endo-IX*) with great selectivities (entries 1and 2). Moreover, 4-bromo- and 4-fluoro-cinnamaldehydes provided **2** with similar high yields (entries 3 and 4). 4-Nitro, 2-nitro, 2-methoxy and α-methyl completed the cinnamaldehyde series with equal success (Entries 5-8). Additionally, 3-Methylbutenal and hexenal reacted to provide product **2** with unexpectedly high selectivities (entries 9 and 10). Butenal, citral, methacrolein and hexadienal completed the scope with similarly high conversions and selectivities despite the increased substitution patterns (entries 11-14). These results highlight the highly chemo-, regio- and diastereoseletive nature of this transformation, as only the vinyl nitrone participates during the photocatalytic process. Further validation of the method was obtained by performing a large scale (10 mmol) preparation of **T2A** (99% yield, >50:1 d.r). Moreover, **T2A** was further derivatized to the respective carbacycle[17] relying on an all-photocatalytic tandem dipolar cycloaddition sequence.[18]

The large scope obtained allowed us to shift the focus towards the study of the visible-light photocatalytic mechanism. It has been established that the *in-situ* formed *N-EDG* nitrone is a suitable candidate for photooxidation pathways due to their spin-trapping properties and less demanding oxidative pathways.[16]

As we have observed in our previous work, the reaction in the presence of only visible-light starts by slow excitation to the nitrone triplet state, followed by fast addition across the dipolarophile to then furnish the product. Under a photocatalytic redox-neutral mechanism the *in-situ* formed nitrone plays both reductant and oxidant roles (**Figure 1**).[12a] Thus, initial excitation of $Ru(bpy)_3^{+2}$ to $*Ru(bpy)_3^{+2}$ triggers single electron transfer oxidation of nitrone **1a** to form radical cation **4** and $Ru(bpy)_3^{+}$. Radical cation **4** then prompts intermolecular radical addition across the conjugated carbonyl to form isoxazolidine radical cation **5**. Despite the photocatalytic pathway, the regioselectivity for **5** is controlled by the steric effects of the substituents on the dipolarophile (**Scheme 1**). Then, intermediate **5** undergoes fast single electron reduction to provide **2** and $Ru(bpy)_3^{+2}$ to close the catalytic cycle.

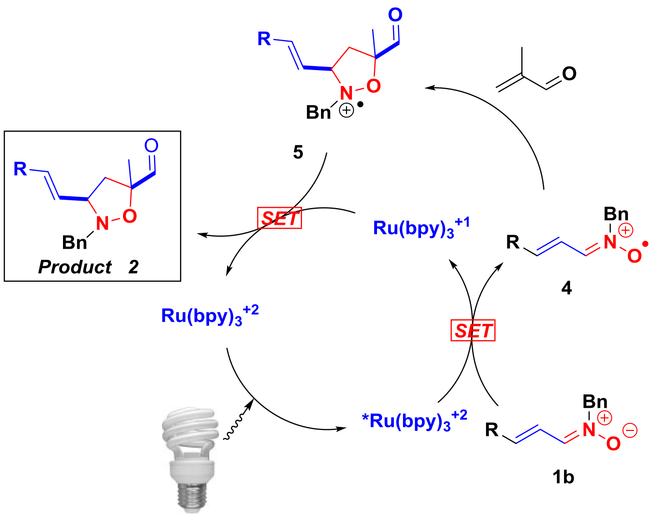


Figure 1. Photoredox-neutral proposed mechanism.

Further mechanistic evidence was obtained when no change in reaction outcome was observed upon using tertiary amines (Et_3N) as a sacrificial reductant. Radical-trapping experiments performed in the presence of a radical scavenger (TEMPO) displayed complete inhibition of the photoredox process. Stern-Volmer quenching experiments revealed that only nitrone **1b** is able to efficiently quench the photocatalyst. Morevoer, competition expeiments revealed that isomer **3** is not an intermediate for the formation of **2**. It was also found that the catalytic cycle could not be propagated in the absence of visible-light by ^{1}H-NMR monitoring. These experiments provide further evidence of a redox-neutral pathway (ESI).

Conclusion

In summary, we have developed the first general report for a redox-neutral visible-light photocatalytic intermolecular dipolar cycloaddition. The reaction works in great yields and very high stereoselectivities for a wide variety of substrates across enal and dipolarophile substrates. Future efforts will focus on developing enantioselective versions of this method and establishing novel photoredox reactions for the synthesis of other *N,O*-containing heterocycles.

Experimental Section

Essential Experimental Procedures and Spectroscopic Data for new and known compounds is in SI.

Acknowledgements

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Keywords: Photocatalysis • Dipolar Cycloadditions • Isoxazolidines • Vinyl nitrones • Complex Heterocycles

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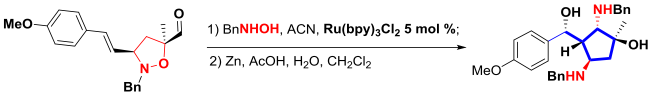
17. T2A undergoes further dipolar cycloadditition followed by *N-O* cleavage to provide carabcycle D1.



T2A

D1, 88% yield

18. P. Das, D. Almond, L. N. Tumbelty, B. E. Austin, G. Moura-Letts, *Org. Lett.* **2020**, *22* (14), 5491.

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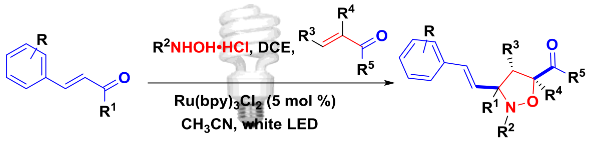

Redox-Neutral Cycloaddition - 26 examples, 84-98% yield

This effort highlights the first highly stereoselective photocatalytic dipolar cycloaddition of vinyl nitrones and conjugated carbonyls. This method allows for the synthesis of complex heterocycles under very mild conditions with great yields and selectivities. The data observed justifies a potential redox-neutral photocatalytic pathway for the observed products.