An I_2-catalyzed, Visible-Light Photoredox-Mediated Radical Conversion of α-Nitrocarbonyls to Nitrile Oxides. Catalytic Access to Isoxazolines and Isooxazoles from Alkenes and Alkynes

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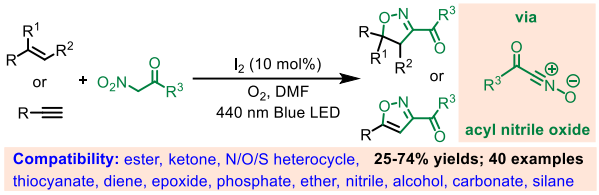
Supporting Information Placeholder

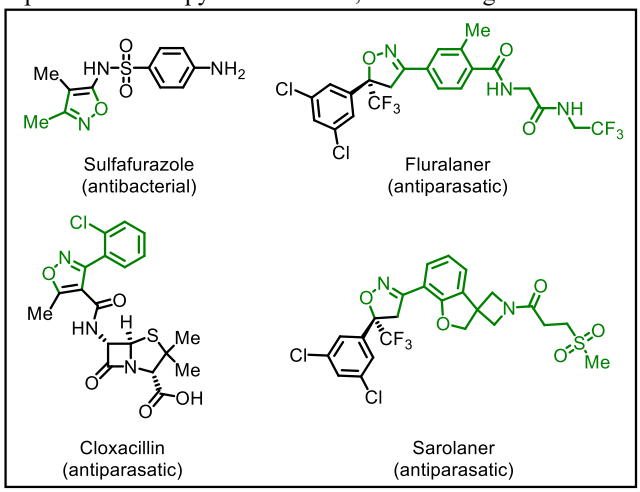


ABSTRACT: A visible light-mediated, I_2-catalyzed intermolecular transformation of alkenes, conjugated dienes, styrenes and alkynes to isooxazoline and isoxazole motifs with α-nitrocarbonyls and analogs is reported. The reaction is also applicable to 1,1-disubstituted terminal, 1,2-disubstituted internal and trisubstituted alkenes, and tolerates a range of functional groups including epoxides, heterocycles, phosphates, free alochols and thiocyanates. Mechanistic studies reveal that α-nitrocarbonyls are first converted to α-carbonyl radicals followed by their conversion to acyl nitrile oxides, which subsequently undergo [3 + 2] dipolar cycloaddition reactions with the unsaturated molecules.

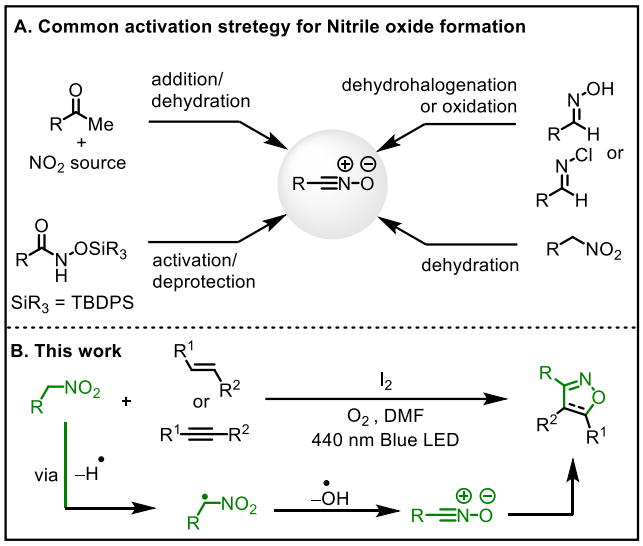
The omnipresent nature of isooxazole moiety in many natural products, pharmaceuticals, agrochemicals, and bio-active compounds has made it an important class of heterocycles (Scheme 1).[1-4] The presence of nitrogen and oxygen in the core structure offers important functions like H-bonding, weak London dispersion forces, $\pi - \pi$ stacking with enzymes and biological receptors.[5-7] The isoxazole-contianing molecules also exhibit remarkable anti-parasatic and anti-bacterial property.[8] Therefore, a number of marketed human and veterinary drugs like Afoxoianer, Cloxacilin, Sarolaner and Fluralaner contain an isooxazole motif.[9] Isoxazoles also serve as chiral ligands in many chemical reactions,[10] and versatile synthons for valuable feedstock like β-hydroxy oximes, γ-amino alcohols, β-lactams and β-hydroxy nitriles.[11] Given the importance, significant efforts have been dedicated for the development of methods to create the isooxazole core. For example, isoxazoles are synthesized intramolecularly from one-pot oxidation/cyclization from propargyl-amines,[12] cycloisomerization of α,β-acetylenic oximes,[13] cyclocondensation of hydroxylamine with β-diketones,[14] transition-metal-catalyzed oximes,[15] and thermal decomposition of *o*-azidocarbonyl compounds.[16]

Alternatively, the intermolecular 1,3-dipolar cycloaddition of nitrile oxides with alkenes or alkynes is an atom-economic and step-efficient approach for the synthesis of isooxazoles.[17] Classically, nitrile oxides are generated by dehydrohalogenation of hydroximoyl chlorides from corresponding aldolxime with oxidant like t-BuOCl, t-BuOI, m-CPBA, $ArI(OAc)_2$, DMDO, NXS, NaClO, Chloramine-T and bases like 2,6 lutidine and Et_3N (Scheme 2A).[18-22] Likewise, α-nitro compounds aer also dehydrated to nitrile oxides with dehydrating agents such as phenyl isocyanate and $POCl_3$, acetic ahydride and $ClCO_2Et$ in presence of a base.[23-25] Silyl hydroxamate also serve as a reagent for generating nitrile oxide through its activation with acylating or sulfonylating reagents and followed by

deprotection with pyridium acetate, or the Hunig's base.[26] Recently, nitrosyl transfer reagent like $Cu(NO_3)_2$, N-nitrosuccinimide and



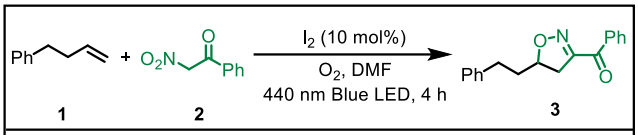
Scheme 1. Marketed veterinary drugs with isooxazoles



Scheme 2. Common methods of generating nitrile oxides and the current approach

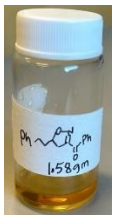
tBuONO have been shown to serve to generate nitrile oxide in situ from akynes, ketones and diazo precursors.[27-30] Herein, we report an unprecedented radical approach to generate nitrile oxides in situ under the blue LED photoredox condition with a catalytic amount of I_2 in the presence of O_2 (Scheme 2B). These radically generated nitrile oxides readily undergo 1,3-dipolar cycloaddition with unactivated and activated alkenes as well as alkynes to produce variously functionalized isooxazolines and isoxazoles, respectively.

Table 1. Optimization of reaction conditions[a]



1 2 3

entry	deviation from standard condition	yield (%)
1	None	81 (74)[b]
2	without blue LED at RT and at 60 °C[c]	0
3	without O_2[d]	0
4	without I_2	12
5	neat reaction[e]	0
6	DCM, THF, MeCN, H_2O	0-10
7	with 20 mol% I_2	78
8	with 5mol% I_2	20
9	with $PhI(OAc)_2$[e]	12
10	*t*-butyl peroxide instead of O_2[e]	60
11	hydrogen peroxide instead of O_2[e]	54



[a]Reactions were run at 0.10 mmol scale unless stated otherwise. [b]Isolated yield from a 7.6 mmol scale reaction in parenthesis. [c]Reaction vial was wrapped with aluminum foil. [d]Reaction was run with 0.50 mmol of ethylnitroacetate. [e]Reactions run under N_2.

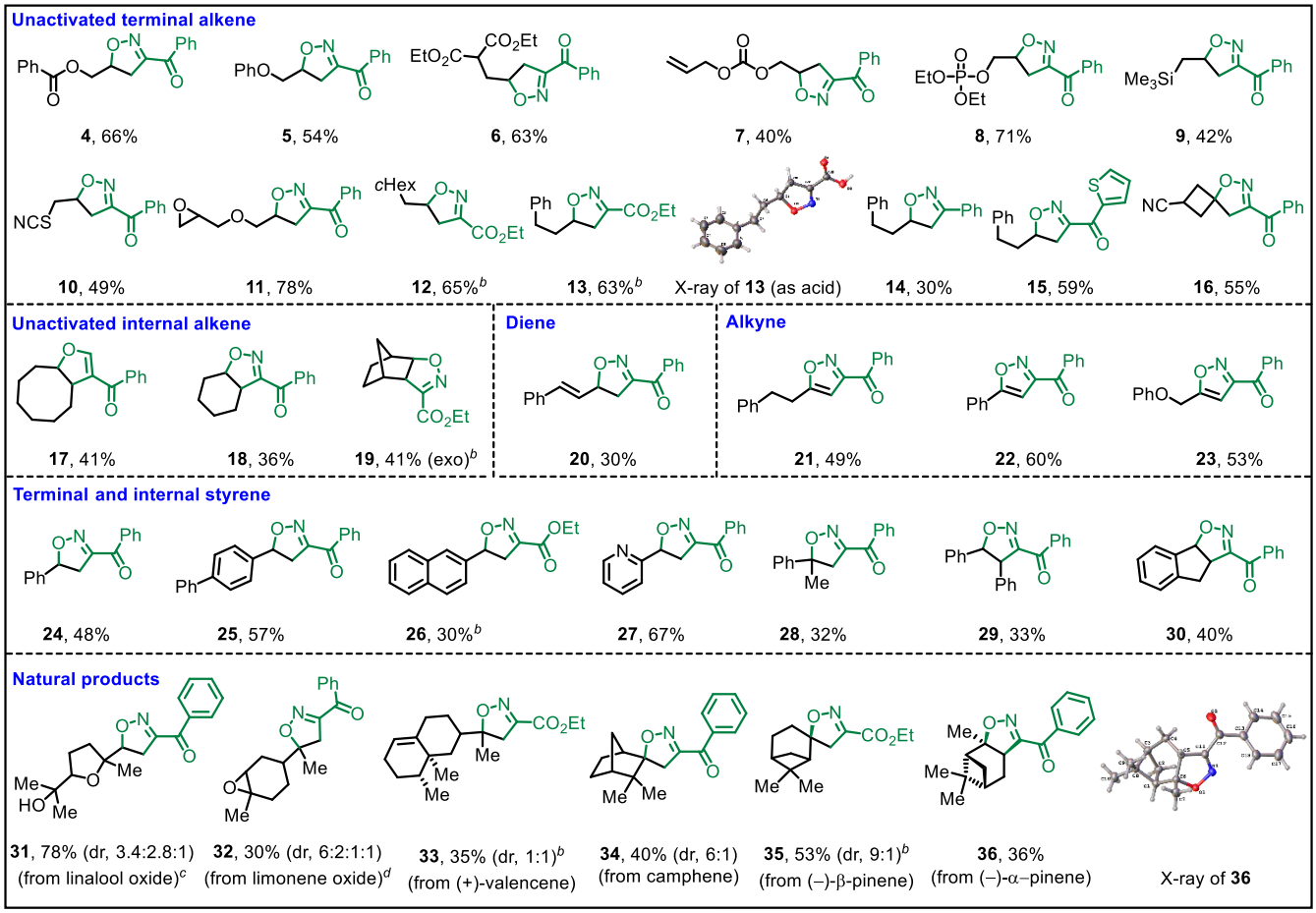
During our studies on photoredox alkene difunctionalization, we observed the formation of isooxazoline **4** in 81% yield when 4-phenylbutene **1** reacted with α-nitroacetophenone **2** as an active methylene compound in the presence of catalytic amount of I_2 under oxygen and blue LED in DMF (Table 1, entry 1). This reaction can be scaled up to gram quantity (7.6 mmol scale, 1.58g, 74% isolated). Control experiments revealed that the reaction didn't proceed in the absence of blue LED at rt and even at an elevated temperature (60 °C) (entry 2). While the reaction afforded no product in the absence of O_2 (entry 3), 12% product could still be obtained in the absence of I_2 (entry 4). Solvent DMF is critical for the success of the reaction since reactions run either neat (no solvent) or with other solvents such as DCM, THF, MeCN and H_2O generated no product to a small amount (entries 5-6). 10 mol % I_2 as a catalyst remained optimal since lowering its concentration decreased the yield although higher amount didn't affect the yield significantly (entries 7-8). The reaction could also be performed with other oxidants such as *t*-butyl peroxide and hydrogen peroxide, which afforded the product **3** in moderate yields, although $PhI(OAc)_2$ generated the product **3** only in 12% (entries 9-11).

After optimizing the reaction parameters, we examined the scope of the reaction (Table 2). We first examined the scope of unactivated terminal alkenes bearing monoester, diester and ether functional groups, which formed the products with α-nitroacetophenone **2** in good yields (**4**-**6**). A carbonate functional group is also well tolerated as shown by the selective formation of mono-isooxazoline on diallyl carbonate (**7**). The reaction also tolerates some of the most sensitive functional groups like phosphates, silanes, thiocyanates and allyl epoxy ethers, which generate the products in good to excellent yields (**8**-**11**). Isoxazolines are also generated from other types of α-nitrocarbonyls and analogs such as ethyl nitroacetate, α-nitrotoluene and 2-(nitroacetyl)thiophene (**12**-**15**). The structure of compound **13** was confirmed by a single crystal X-ray crystallography. In addition, isoxazolines can be constructed on 1,1-disubstituted unactivate alkenes such as the one present in 3-methylenecyclobutane-1-carbonitrile (**16**). Similarly, 1,2-disubstituted cyclic internal alkenes can be readily converted into bicyclic isoxazolines (**17**-**19**) as demonstrated by the reactions of cyclooctene, cyclohexene and norbornene with α-nitroacetophenone and ethyl nitroacetate.

In addition to unactivated alkenes, the reaction is also compatible with conjugated dienes, alkynes and styrenes (Table 2). For example, the terminal alkene in *trans*-phenyl-1,3-butadiene was selectively converted to isooxazoline while the internal alkene remained intact (**20**). The terminal alkynes in 4-phenyl-1-butyne, phenylacetylene and 3-phenoxy-1-propyne were readily converted to isoxazoles (**21**-**23**) upon reaction with α-nitroacetophenone. The reaction conditions were also applicable for the conversion of terminal and internal alkenes in a wide range of styrene and indene derivatives. For example, the terminal alkenes in styrene, 4-phenylstyrene and 2-vinylnaphthalene were readily converted to their corresponding isoxazolines (**24**-**26**) upon their reaction with α-nitroacetophenone and ethyl nitroacetate. The reaction is also compatible with pyridine heterocycle as shown by the reaction of 2-vinylpyridine with α-nitroacetophenone, which afforded the corresponding isoxazoline in good yield (**27**). The 1,1-disubstituted alkene in α-methylstyrene and the 1,2-disubstituted internal alkenes in *trans*-stilbene and indene also reacted well with α-nitroacetophenone to generate their isooxazoline derivatives (**28**-**30**).

Lastly, we examined the effectiveness of the method in coverting alkenes in complex natural products to isoxazolines (Table 2). For example, the terminal alkene attached to a *tert*-carbon center in linalool oxide, which contains a tetrahydrofuran ring and a free *tert*-hydroxy groups, was efficiently converted an isooxazoline ring in excellent yield (**31**). Similarly, the 1,1-

Table 2. Scope with alkenes, dienes, styrenes, alkynes and α-nitrocarbonyls[a]



Conditions. Reactions were run at 0.50 mmol scale in 2.5 mL DMF for 4 h at ambient temperature. The percentage numbers are the yields of the isolated products. [b]Reactions were run for 12 h. cPrepared from linalool oxide as a mixture of isomers. [d]Prepared from (+)-limolene oxide as a mixture of *cis* and *trans* isomers.

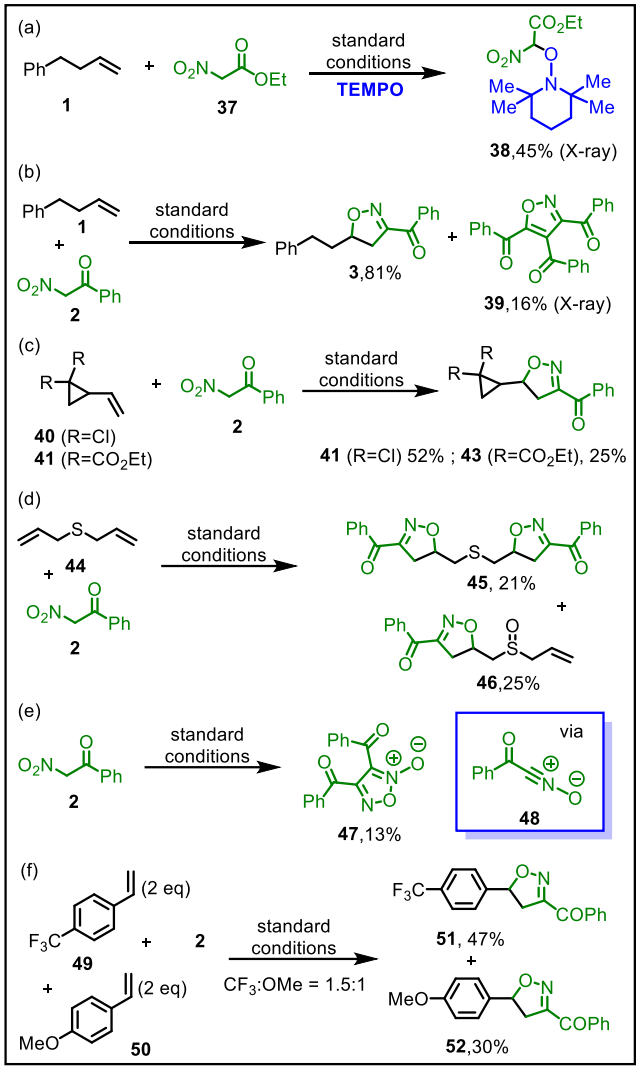
disubstituted alkenes in limonene oxide, valencene, camphene and β-pinene, which respectively contain a cyclohexyl ring with an epoxide, a decalin ring with a trisubstituted alkene and sterically congested [2.2.1] and [3.1.1] bridged bicyclic rings, were also transformed into isoxazolines with α-nitroacetophenone (**32**-**34**). Most importantly, the sterically encumbered trisubstituted alkene in the [3.1.1] bridged bicyclic ring in α-pinene could also be converted to its corresponding isooxazoline ring (**36**). These examples demonstrate the robustness of the current method for its use in complex molecular architectures.

Encouraged by its wide scope, we decided to understand the mechanism of the reaction (Scheme 3). Since our previous cyclopropanation reaction under similar reaction conditions generated α-carbonyl radicals from dicarbonyl compounds,[31] we used 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as a radical interceptor to intercept the α-carbonyl radicals in the reaction of 4-phenylbutene **1** with α-nitroacetophenone **2** under the standard reaction conditions (Scheme 3a). Indeed, we were also able intercept the α-carbonyl radical, and isolate and characterize the TEMPO-adduct **38**. The structure of the adduct **38** was also confirmed by a single crystal X-ray crystallography (Fig. 1). In addition, we isolated the trimer **39** of α-nitroacetophenone **2** in 16% yield from the standard reaction as a side product along with the isooxazoline product **3** in 81% yield (Scheme 3b). The structure of the trimer **39** was confirmed by a single crystal X-ray crystallography (Fig. 1). The trimer of α-nitroacetophenone **2** is generated from its corresponding α-carbonyl radicals. Chracterization of the TEMPO-adduct **38** and the isolation of the trimer **39** confirmed the formation of α-carbonyl radicals from α-nitroacetophenone in the reaction.

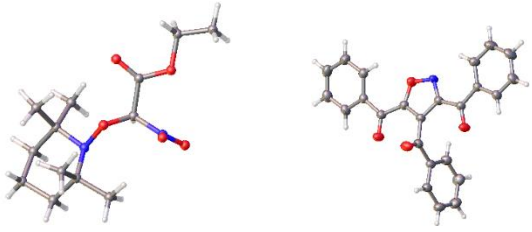
Next, we conducted radical clock experiments to deduce if the α-carbonyl radicals reacted with alkenes and alkynes by a radical addition process. The reactions of two radical clocks, 1,1-dichloro-2-vinylcyclopropane (**40**) and diethyl 2-vinylcyclopropane-1,1-dicarboxylate (**41**), with α-nitroacetophenone generated the corresponding isooxazoline products **42** and **43** in 52% and 25%, respectively, and no ring-opening product was observed (Scheme 3c). We also utilized diallyl sulfide (**44**) as a radical clock and conducted its reaction with α-nitroacetophenone **2** (Scheme 3d). This reaction generated a mixture of mono- and di-isoxazoline products **45** and **46**, and no cyclized tetrahydrothiopene derivative was observed. These experiments suggested that α-nitroacetophenone **2** generates α-carbonyl radicals but these radicals are not added to alkenes and alkynes by a radical process (Scheme 4, Path A).

Based on the radical clock studies, we speculated that α-nitroacetophenone **2** could generate an acyl nitrile oxide via its α-cabonyl radical by the loss of HO$^{\bullet}$ under the photoredox conditions. Indeed, we isolated the dimer **47**, which is derived from the dimerization of the acyl nitrile oxide **48**, in 13% yield from the reaction of α-nitroacetophenone **2** under the standard reaction conditions but in the absence of an alkene (Scheme 3e).[32] Consequently, the isooxazoline and isoxazole products are generated by a [3 + 2] cycloaddition

reaction of the acyl nitrile oxide **55** with an alkene or alkyne (Scheme 4, Path B). A competitive study between two electronically different styrenes containing *p*-CF_3 (**49**) and *p*-OMe (**50**) generated the corresponding isooxazoline products **51** and **52** in 1.5:1 ratio, respectively (Scheme 3f). The faster rate for the reaction of more electron deficient styrene (**49**) than the electron rich styrene (**50**) is also consistent with the electronic demand for a [3 + 2] dipolar cycloaddition reaction involving a nitrile oxide since a negative charge built at the transition state is stabilized by the electron-withdrawing group.

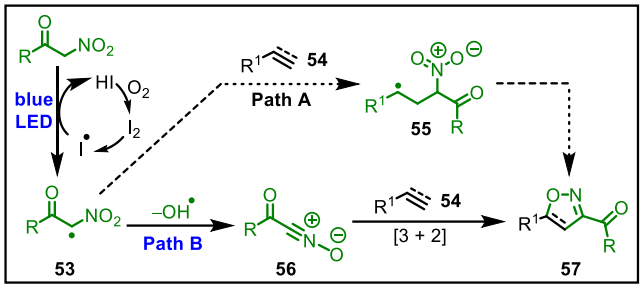


Scheme 3. Mechanistic studies



Adduct **38** Trimer **39**

Fig. 1. X-ray structures of **38** and **39**.



Scheme 4. Proposed mechanism

In summary, we have developed an unprecedented method for the conversion of α-nitrocarbonyl compounds to their corresponding acyl nitrile oxide via visible light photoredox under blue LED in the presence of catalytic amount of I_2. The acyl nitrile oxides then react with a wide variety of unactivated alkenes, conjugated dienes, styrenes and alkynes to form isoxazolines and isoxazoles. The reaction is compatible with a range of functional groups and works well with mono- and 1,1-disubstituted terminal alkenees, and 1,2-disubstituted and trisubstituted internal alkenes. Mechaistic studies by radical clock experiments, trapping of α-carbonyl radicals, dimerization, trimerization and electronic competition studies suggest that the acyl nitrile oxides are generated via a radical process while their subsequent addition to alkenes and alkynes is attained by a non-radical [3 + 2] dipolar cycloaddition reactions.

ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge at https://pubs.acs.org/

CCDC numbers 2381201 (compound **38**), 2381202 (compound **39**), 2381203 (compound **36**) and 2381204 (compound **13**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via https://www.ccdc.cam.ac.uk/

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