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Radical Cation Cycloadditions Using Cleavable Redox Auxiliaries

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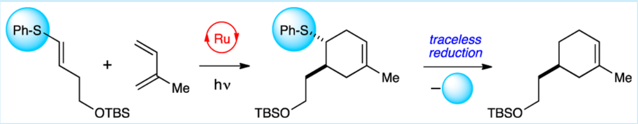
Supporting Information

ABSTRACT: The incorporation of an easily oxidized arylsulfide moiety facilitates the photocatalytic generation of alkene radical cations that undergo a variety of cycloaddition reactions with electron-rich reaction partners. The sulfide moiety can subsequently be reductively cleaved in a traceless fashion, affording products that are not otherwise directly accessible using photoredox catalysis. This approach constitutes a novel oxidative "redox auxiliary" strategy that offers a practical means to circumvent a fundamental thermodynamic limitation facing photoredox reactions.



Alkene radical ions are open-shell reactive intermediates that can participate in a wide variety of organic transformations. Many features of these reactions are synthetically attractive: they often proceed with very low activation barriers, and their regiochemical outcomes generally complement those involving closed-shell neutral alkenes.[1] In the past several years, there has been a renewed interest in the application of radical ion chemistry to synthesis, due in part to the recognition that photoredox catalysis offers a convenient means to access the distinctive reactivity of these odd-electron intermediates under relatively mild and convenient conditions.[2] Recent reports of synthetic transformations involving photogenerated alkene radical cations have included a variety of cycloaddition reactions[3] and anti-Markovnikov hydrofunctionalization reactions,[4] each of which would be challenging to accomplish using alternate synthetic strategies.

One limitation common to all photoredox reactions is that the scope of a given method is dictated by the thermodynamic feasibility of the initial photoinduced electron-transfer step; substantially endergonic photoredox steps result in poor overall reactivity. On the one hand, the availability of a large number of structurally varied photocatalysts spanning a range of excited state redox potentials can be exploited to broaden the scope of these reactions.[5] Nevertheless, a substrate's redox potential remains a fundamental thermodynamic constraint on the success of photoredox methods. For instance, simple mono- and disubstituted aliphatic alkenes have proven too difficult to oxidize (>+2.5 V vs SCE)[6] using even the most powerfully oxidizing photoredox catalysts in common usage and have not successfully been engaged in photooxidatively triggered transformations.

We recently described the concept of a "redox auxiliary," which we defined as an easily removable moiety that can be temporarily installed on a substrate to enable its activation by single-electron transfer processes.[7] Our initial demonstration of this concept was a radical anion [2 + 2] photoredox cycloaddition using 2-acylimidazoles as readily reducible analogues of enoate esters that would otherwise be resistant toward photoreductive activation. We wondered if a similar redox auxiliary strategy might be applied to facilitate photooxidatively initiated organic transformations. We imagined that installation of an electron-rich redox auxiliary onto an otherwise unactivated alkene would facilitate its one-electron oxidation; the resulting radical cations could subsequently be induced to undergo a number of characteristic alkene radical cation reactions, including Diels—Alder[3b,f,g] and [2 + 2] cycloadditions.[3a,d] Subsequent cleavage of the redox auxiliary group would afford the products of formal cycloadditions involving unactivated alkene substrates (Figure 1).[8,9]

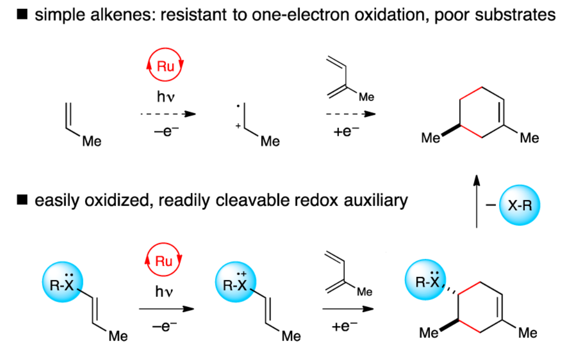


Figure 1. Traceless redox auxiliary strategy for radical cation reactions.

Very recently, Cooke and co-workers described an intriguing first step toward an alternate oxidative redox auxiliary strategy. They demonstrated that vinyl ferrocene is powerfully activated toward Diels—Alder and hydrothiolation reactions upon one-electron chemical oxidation.[10] This study verified that the incorporation of a reversibly oxidizable moiety onto an alkene can indeed be used to facilitate redox-promoted transformations. However, this strategy involves a separate activation step using stoichiometric chemical oxidant rather than an in situ redox

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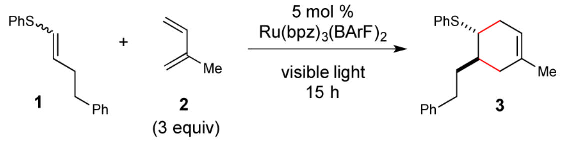
catalyst, and the requisite ferrocenyl moiety is not removable in a traceless fashion.

We imagined a different strategy utilizing a reversibly oxidizable sulfide moiety as a redox auxiliary (Figure 1). We were attracted to the use of vinyl sulfides in this context for a number of reasons. First, aryl vinyl sulfides generally possess oxidation potentials ranging from +1.1 V to +1.4 V vs SCE,[11] which are readily accessible using the well-characterized Ru(II) polypyridyl photoredox catalysts that are increasingly being utilized in synthetic chemistry. Second, Bauld has studied radical cation Diels–Alder cycloadditions of aryl vinyl sulfides using triarylaminium salts as chemical oxidants or aromatic nitriles as PET sensitizers.[11] This valuable precedent demonstrates that vinyl sulfide radical cations are indeed activated toward cycloaddition reactions. Finally, C–S bonds are relatively weak, and a variety of mild, operationally facile methods for their cleavage have been utilized in the synthesis of complex molecules.[12] We imagined that successful development of this sequence would enable the preparation of formal cycloaddition products of simple alkenes that are not amenable to direct activation by photoredox catalysis and would also be challenging to engage in classical thermal cycloaddition methods.

As a starting point for our investigations, we optimized conditions for the radical cation Diels–Alder cycloaddition of vinyl sulfide **1** with isoprene (**2**) (Table 1).[13] We first examined conditions adapted from our previous study of photocatalytic radical cation Diels–Alder cycloadditions with styrenic dienophiles, utilizing $Ru(bpz)_3(BArF)_2$ as a strongly oxidizing, organic-soluble photocatalyst. The yield of this model cycloaddition, however, was disappointingly low in a variety of solvents (entries 1–4). A study of additives quickly revealed a sensitivity of the reaction to the presence of water (entry 5). This observation led us to investigate the effect of dessicants such as $MgSO_4$, which resulted in a significant increase in the yield of the cycloaddition (entry 6), along with improved reproducibility. Intense blue LEDs are not required; the photocatalytic reaction proceeds using a less-intense CFL light bulb, albeit with slower rates (entry 7). Interestingly, although radical cation cycloaddition reactions of electron-rich styrenes can typically be conducted open to air, we observed diminished yields and poor mass balance when this Diels–Alder reaction was run under ambient atmosphere rather than in degassed solvent (entry 8), an observation we attribute to the sensitivity of sulfides toward reactive oxygen species.[14] Finally, consistent with the photocatalytic nature of this reaction, control experiments indicated that no product is formed either in the absence of $Ru(bpz)_3^{2+}$ or in the dark (entries 9 and 10).

Table 1. Optimization Studies for Vinyl Sulfide Radical Cation Diels–Alder Cycloadditions[a]

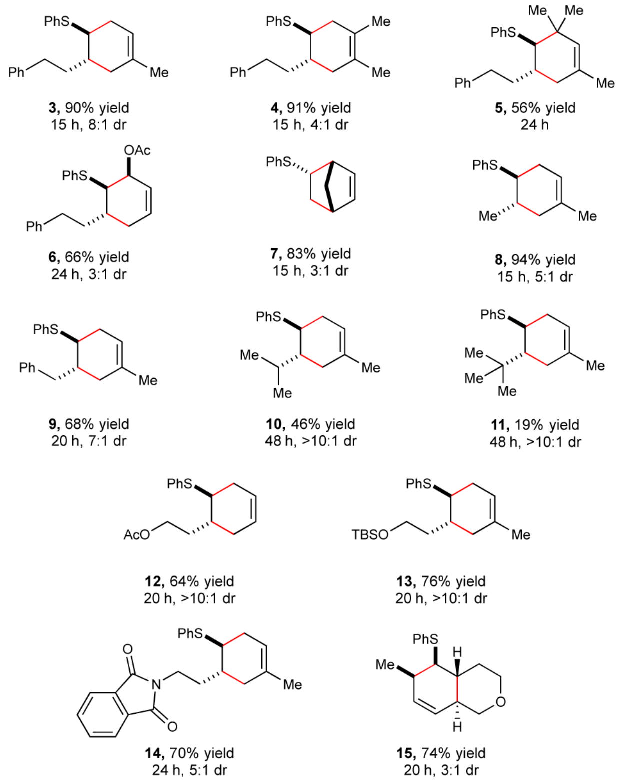


entry	solvent	light source	additive	yield (%)
1	MeCN	blue LED		40
2	CH_2Cl_2	blue LED		22
3	DMF	blue LED		0
4	DMSO	blue LED		0
5	MeCN	blue LED	H_2O (10 mol %)	11
6	MeCN	blue LED	$MgSO_4$	84
7	MeCN	23 W CFL	$MgSO_4$	44
8	MeCN	blue LED	$MgSO_4$, air	24
9	MeCN		$MgSO_4$	0
10[b]	MeCN	blue LED	$MgSO_4$	0

[a]Unless otherwise noted, reactions were conducted using 5 mol % $Ru(bpz)_3(BArF)_2$, 1 equiv of **1**, and 3 equiv of **2** in solvent degassed using three freeze/pump/thaw cycles. A 15 W blue LED was used as the irradiation source. [b]Reaction conducted without $Ru(bpz)_3(BArF)_2$.

Studies examining the scope of the radical cation Diels–Alder cycloaddition of vinyl sulfides under optimized photocatalytic conditions are summarized in Scheme 1. A range of simple cyclic and acyclic dienes participate readily in this process (**3**–**7**), though sterically bulky dienes require longer reaction times (**5**), and electron-rich dienes provide somewhat lower yields (**6**). Simple cyclic dienes (**7**), however, work well in this reaction. The structure of the vinyl sulfide partner can also be modified. An examination of simple alkyl-substituted dienophiles reveals a sensitivity to steric bulk; larger vinyl substituents result in substantially slower Diels–Alder reactions (**10** and **11**), and β,β-disubstituted vinyl sulfides do not provide any observable cycloadducts. However, the reaction tolerates various functional groups including esters, silyl ethers, and phthalimides (**12**–**14**). These conditions were also found to be applicable to intramolecular cycloadditions (**15**).[15]

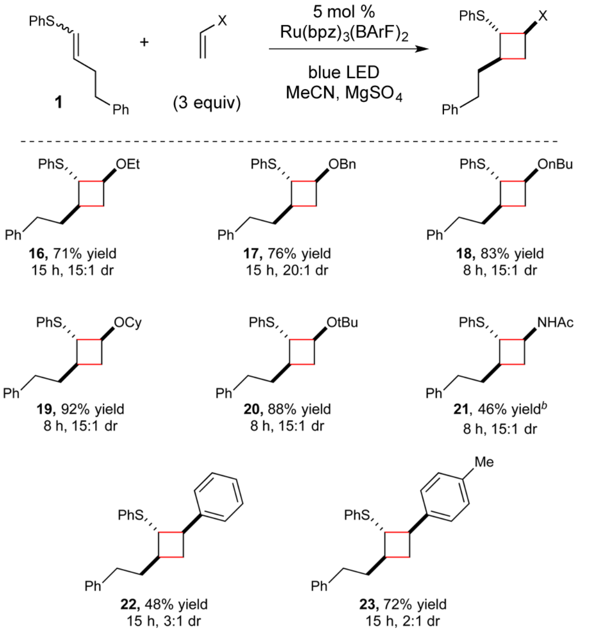
Scheme 1. Scope Studies for Photocatalytic Vinyl Sulfide Radical Cation Diels–Alder Cycloadditions[a]



[a]Reactions were conducted using 5 mol % $Ru(bpz)_3(BArF)_2$, 1 equiv of vinyl sulfide, 3 equiv of diene, and 2 weight equiv of $MgSO_4$ in degassed MeCN. A 15 W blue LED was used as the irradiation source.

These studies were premised on the hope that sulfide redox auxiliaries might be broadly applicable not only to Diels–Alder cycloadditions but also to a range of useful transformations involving alkene radical cations. As a first attempt to investigate the generality of this strategy, we studied the use of vinyl sulfides in intermolecular [2 + 2] cycloaddition reactions.[3d] We had previously investigated the factors controlling the crossed selectivity of such reactions involving electron-rich styrenes and were pleased to observe that similar considerations are applicable to [2 + 2] radical cation cycloadditions of vinyl sulfides (Scheme 2). Thus, when **1** is irradiated in the presence of electron-rich monosubstituted alkenes, the corresponding unsymmetrical cyclobutanes are produced in good yield. Vinyl ethers were excellent reaction partners in this reaction, affording good yields and excellent selectivities regardless of the steric bulk of the ether substituent (**16**–**20**).[16] An enamide also provided synthetically useful yields of the corresponding acetamide-substituted cyclobutane (**21**). Finally, although simple aliphatic olefins and vinyl esters did not participate in this reaction, styrenes are successful reaction partners (**22** and **23**), consistent with the stepwise radical mechanism expected for this cycloaddition.

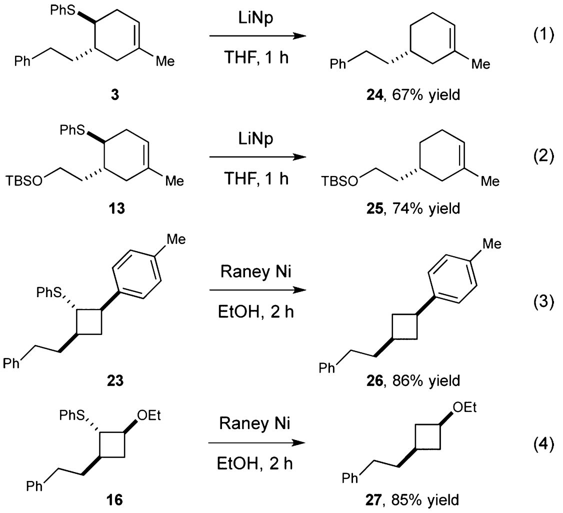
Scheme 2. Scope Studies for Photocatalytic Vinyl Sulfide Radical Cation [2 + 2] Cycloadditions[a]



[a]Unless otherwise noted, reactions were conducted using 5 mol % $Ru(bpz)_3(BArF)_2$, 1 equiv of vinyl sulfide, 3 equiv of alkene reaction partner, and 2 weight equiv of $MgSO_4$ in degassed MeCN. A 15 W blue LED was used as the irradiation source. [b]Reaction conducted using 10 equiv of *N*-vinylacetamide.

The concluding step in this redox auxiliary strategy requires the cleavage of the sulfide moiety, which can readily be accomplished using various reductive protocols (Scheme 3). First, treatment of [4 + 2] cycloadduct **3** with freshly prepared lithium naphthalenide rapidly affords the corresponding desulfurized product without competitive reduction of the alkene moiety (eq 1). Importantly, the resulting cyclohexene **24** would not be directly accessible using alternate thermal or redox-promoted Diels–Alder methods. Similarly, cycloadduct **13** bearing a TBS-protected primary alcohol undergoes desulfurization to afford **25** without cleavage of the silyl protecting group (eq 2). The reduction of [2 + 2] cycloadduct **23** can readily be accomplished by treatment with Raney nickel (eq 3), and the diastereomer ratio of the resulting cyclobutane (**26**) is identical to that of the starting material, indicating that epimerization does not occur under these conditions. The desulfurization of functionalized cycloadduct **16** occurs without observable cleavage or elimination of the alkoxy substituent. Thus, removal of these sulfide auxiliary groups can be accomplished under relatively mild conditions that tolerate a variety of common functional groups.

Scheme 3. Reductive Cleavage of the Redox Auxiliary Group



In conclusion, vinyl sulfides are easily activated by visible-light-promoted photooxidation and subsequently undergo cycloaddition reactions characteristic of alkene radical cations. The activating sulfide moiety can be tracelessly removed after the photoredox reaction to afford cycloadducts that could not be directly synthesized by reactions of simple unfunctionalized alkenes. These results, along with the reductive redox auxiliary strategy our group reported several years ago,[7] suggest that the use of redox auxiliary groups present a practical strategy to circumvent a fundamental limitation on the feasibility of photoredox reactions and could be used to significantly increase the scope of products that are available using this powerful mode of activation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03545.

Experimental details and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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(8) Yoshida pioneered the use of "electroauxiliaries" that are analogous to the concept that we propose here. Electroauxiliaries are generally Si, Sn, or S substituents that similarly facilitate the oxidation of organic substrates that are otherwise resistant to one-electron oxidation. In Yoshida's formualation, however, the electroauxiliary group is poised to undergo mesolytic cleavage upon oxidation, resulting in a cationic or radical reactive intermediate. In contrast, "redox auxiliaries," as we define them, are moieties that remain covalently bound throughout the net transformation, enabling the radical cation reactivity of the substrate to be directly exploited.

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(13) Both (*E*) and (*Z*) linear vinyl sulfides provide identical reaction rates and diastereomer ratios. Thus, the studies described herein were conducted using a mixture of geometric isomers arising from the synthesis of the substrates via photoinduced radical thiol-ene addition. See the Supporting Information for details.

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(16) We observe no evidence for competitive photooxidation of the vinyl ethers, presumably because their redox potentials (ca. +1.67 V vs SCE) are outside of the reasonable working range of the $Ru^*(bpz)_3^{2+}$ photocatalyst (+1.45 V vs SCE). See: (a) Koch, D.; Schäfer, H.; Steckhan, E. *Chem. Ber.* **1974**, *107*, 3640−3657. (b) Crutchley, R. J.; Lever, A. B. P. *J. Am. Chem. Soc.* **1980**, *102*, 7128−7129.