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Synthetic feasibility of oxygen-driven photoisomerizations of alkenes and polyenes

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Abstract

This review describes O_2-dependent photoreactions for possible routes to double-bond isomerizations. *E,Z*-isomerizations triggered by O_2 and visible light are a new area of potential synthetic interest. The reaction involves the reversible addition of O_2 to form a peroxy intermediate with oxygen evolution and partial regeneration of the compound as its isomer. Targeting of O_2-dependent photoisomerizations also relates to a practical use of visible light, for example the improved light penetration depth for visible as opposed to UV photons in batch sensitized reactions. This review is intended to draw a link between visible-light formation of a peroxy intermediate and its dark degradation with O_2 release for unsaturated compound isomerization. This review should be of interest both to photochemists and synthetic organic chemists, as is ties together mechanistic and synthetic work, drawing attention to an overlooked subject.

1. Introduction

This review describes oxygen-dependent photoisomerizations in organic chemistry. It takes into account results in the field of photooxidation, in which a peroxy intermediate is likely formed (Figure 1). Even though the peroxy intermediate is short-lived, isomerization is feasible with O_2 departure. The motivation for this review is to encourage the further use of O_2-mediated photoisomerization in organic chemistry.

Previous reviews on UV-based photoisomerizations have been published.[1-3] *Oxygen-free* UV-based isomerization are extremely common, we focus on oxygen-mediated photoisomerizations. *Oxygen-induced* photoisomerizations have emerged (albeit in fewer cases) for its ability to isomerize compounds, and can be triggered with visible light. Thus, in this review, O_2-based photoisomerization and its potential utility in synthesis will be summarized in an effort to help validate it.

In the 1970s, reports started to emerge on C=C double bond isomerization as a byproduct of photooxidation.[4] Polyene isomerization was observed in addition of $^1O_2$ to a double-bond to weaken it to single-bond character and enable the isomerization. For a review that summarizes oxygen-based photoisomerization, a brief discussion is needed of mechanism and what makes the substrate susceptible to isomerization (Figure 2). Visible-light sensitized production of oxygen radicals (type I) and singlet oxygen (type II, $^1O_2$)[5] are potentially useful for double-bond isomerizations. Direct irradiation and O_2 uptake is a third reaction path. Experimental design can distinguish between these mechanistic paths. Zwitterion **A** or diradical **B** peroxy are interpreted as probable intermediates for rotation to reach the isomer by O_2 unmasking, as compared to oxygenated products by O_2 retention.

The review is intended to be of interest to photochemists and synthetic organic chemists, where photoisomerizations represent the uptake and release of oxygen. No coverage yet exists for the topic in the formation of natural products and related compounds. The next portions of the review have been organized into four sections (sections 2-5).

In sections 2-4, C=C bond isomerization is discussed where $^1O_2$ and oxygen radicals are key intermediates. The O_2-based photoisomerization of cyclic and acyclic monoalkenes, dienes, and polyenes are discussed where formation of the peroxy intermediate is a key step. Notably, the peroxy intermediate responsible for the *E,Z* isomerization is in the ground state, *not* the excited state. Some of the isomerized products are reachable by singlet oxygen, but not with $^1O_2$ mimics, such as the enophiles DEAD and MTAD as will be discussed (section 3). In section 5, mechanistic facets on the role of O_2 in photoisomerizations will be described.

Our review is up-to-date where sections 2-5 cover oxygen's participation in double bond isomerization. Because there are reviews on synthetic photooxidation chemistry,[6-11] this literature will not be explicitly covered. Charge-transfer and non-covalent pairs of oxygen with unsaturated groups, such as exciplexes, will also not be covered due to preexisting reviews.[12,13] Organic and biological studies have been carried out with direct substrate photoisomerizations in O_2-free conditions,[14,15] will also not be covered. The review will emphasize the interplay between visible-light and formation of a peroxy intermediate to establish oxygen with the formation of isomerized compounds in mind. Finally, the review fits into a broader picture that oxygen-photoassistance in bond isomerization reactions of not only alkenes and polyenes, the former is relevant in the first example in section 2.

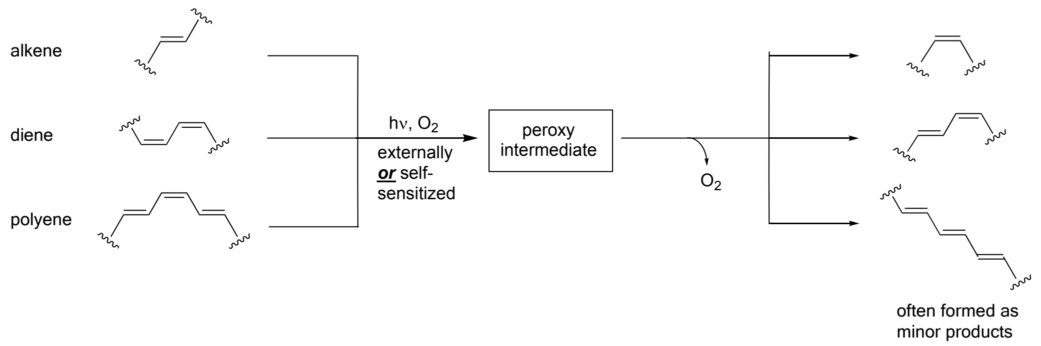


Figure 1. Oxygen-dependent photochemical paths for alkene, diene, and polyene bond isomerizations. The peroxy intermediate is important in a context for isomerization of selected substrates, not only for its formation, but also the needed O_2 release step.

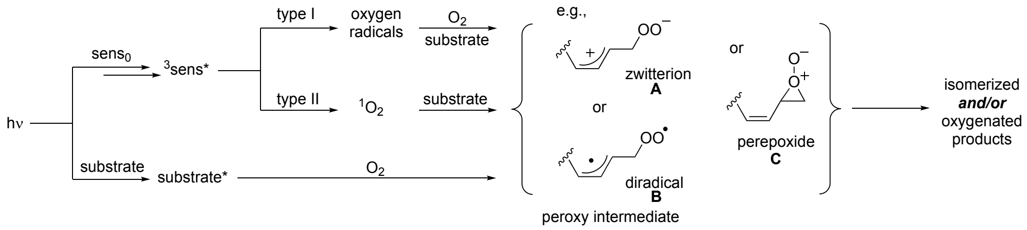
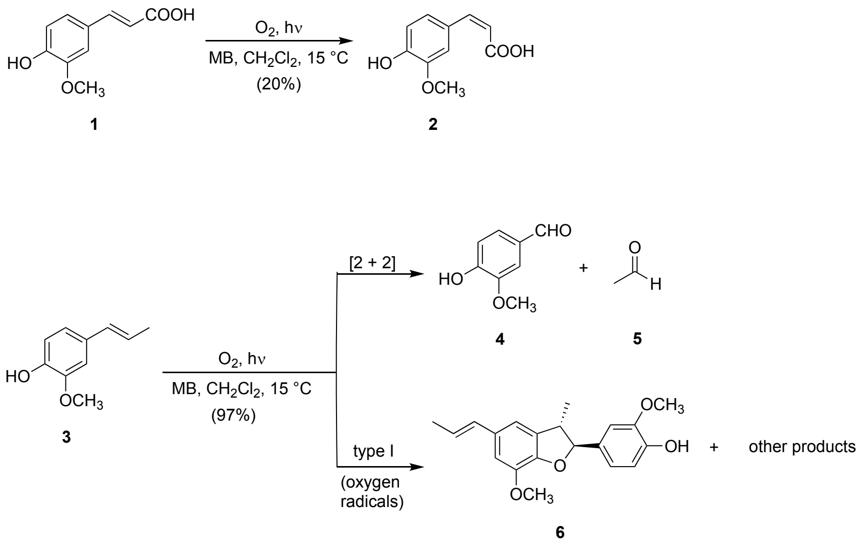


Figure 2. Three mechanistic possibilities of the O_2-dependent isomerization involving unsymmetrical, asynchronous formation of a zwitterion **A** or diradical **B** peroxy intermediate, and/or ring closure to form perepoxide **C**. The first two paths involve irradiation of $Sens_0$ to $^3Sens^*$ to produce oxygen radicals (type I) and singlet oxygen (type II, $^1O_2$). The third path involves direct substrate excitation and uptake of O_2.

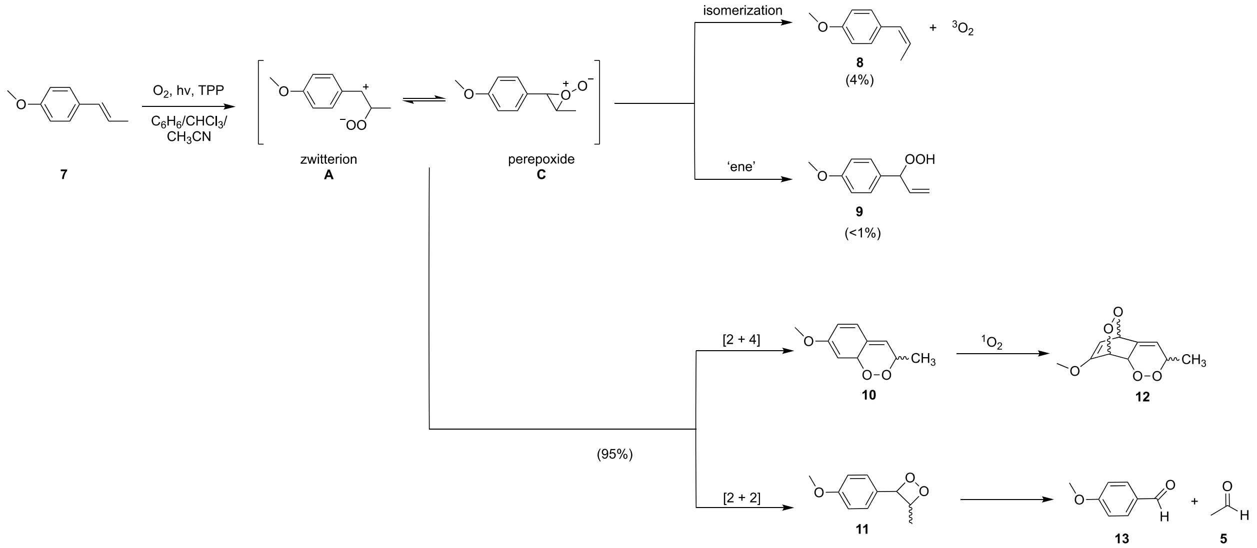
2. Alkene isomerization

We have located 4 studies: first, an approach reported in 2008 features a MB-sensitized oxygen-dependent photoisomerization of *trans*-ferulic acid **1** to give *cis*-ferulic acid **2** in 20% yield (Scheme 1).[16] A proposed mechanism for the isomerization was not reported, but the involvement of a peroxy intermediate is likely. In contrast to *trans*-ferulic acid **1**, the photooxidation of isoeugenol **3** led to oxidized products and no reported isomerized starting material. Isoeugenol **3** underwent a [2 + 2] cycloaddition of $^1O_2$ led initially to a dioxetane species, which cleaved apart to vanillin **4** and acetaldehyde **5**, along with a reaction to form dehydroisoeugenol **6**. Dehydroisoeugenol **6** and other products were thought to arise from a type I photosensitized oxidation with oxygen radical intermediates.



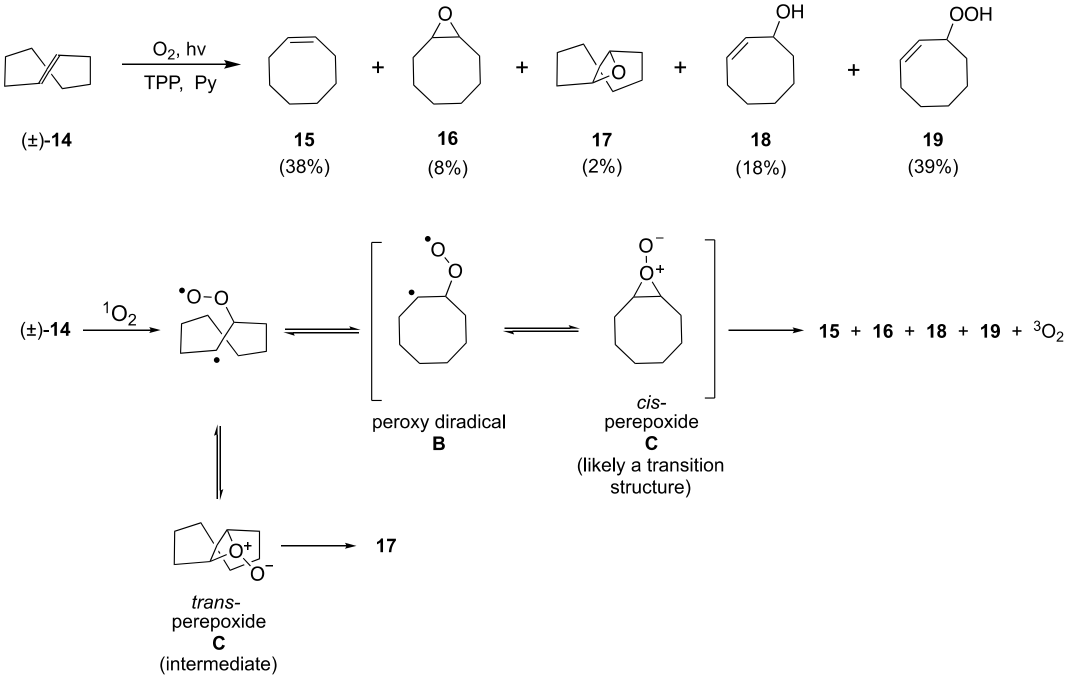
Scheme 1. Oxygen-dependent photoisomerization of *trans*-ferulic acid **1** to *cis*-**2**, and the photooxidation reaction of isoeugenol **3**.

Second, a 2000 report describes the TPP-sensitized oxygen-mediated photoisomerization of *trans*-4-propenylanisole **7** to furnished *cis*-4-propenylanisole **8** in 4% yield (Scheme 2).[17] To reach *cis*-**8**, rotation of a zwitterionic peroxy intermediate **A** is thought to be involved. The intermediacy of $^1O_2$ (and not oxygen radicals from a type I sensitized oxidation) was confirmed by the use of 1,4-dimethylnaphthlene endoperoxide as a chemical source of $^1O_2$, leading to the same isomerization and oxidation product yields as the oxygen-mediated TPP-photosensitized reaction. Hydroperoxide **9**, endoperoxide **10**, dioxetane **11** (based upon its decomposition products *p*-MeO-C_6H_4CHO **13** and acetaldehyde **5**), and diendoperoxide **12** were also formed.



Scheme 2. Oxygen-dependent photoisomerization of *trans*-4-propenylanisole **7** to *cis*-**8**, and formation of oxygenated products.

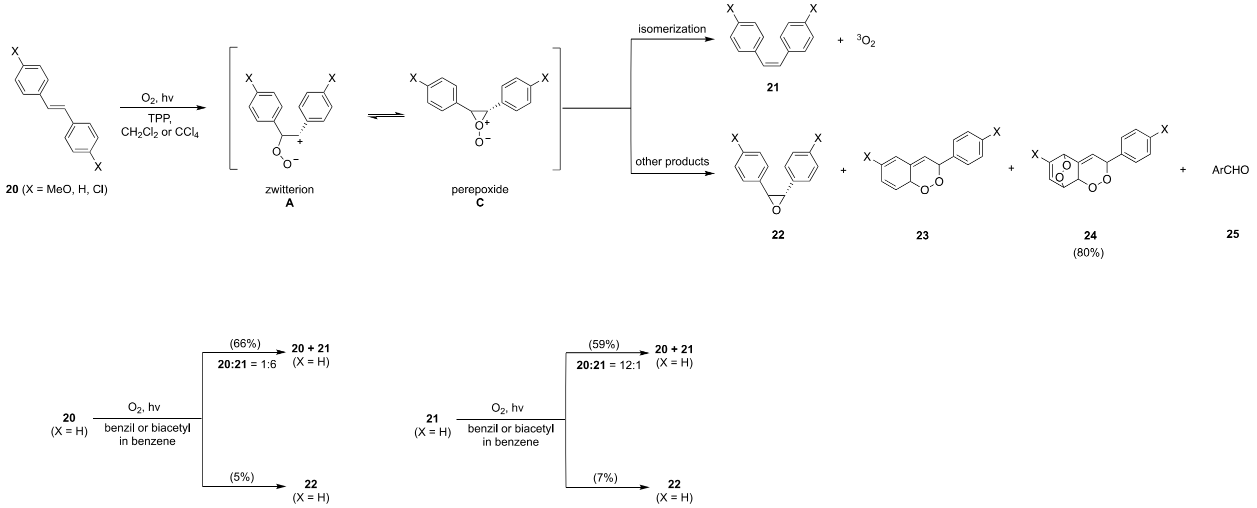
Third, we have located a 1995 report which describes the TPP-sensitized O_2-based photoisomerization of a *trans*-cyclooctene **14** to furnish *cis*-cyclooctene **15** (Scheme 3).[18] After irradiation for 30 min, the percent yield of *cis*-**15** is 38%, but diminishes after 90 min (to 8%) and after 150 min (to 0.3%). Lower reaction times yielded greater amounts of *cis*-**15**, as it is formed initially, but then consumed in a secondary $^1O_2$ reaction. Mechanistically, a perepoxide intermediate was proposed followed peroxy intermediate rotation about the former C=C bond along with deoxygenation. The intermediacy of $^1O_2$ (more so than oxygen radicals from a type I sensitized oxidation) in the isomerization process was evident based on using a chemical source of $^1O_2$, and the radical trap (2,6-di-*tert*-butylphenol). *Cis*-epoxide **16**, *trans*-epoxide **17**, allylic alcohol **18**, and hydroperoxide **19** were also formed. Computational results were also reported for the reaction of *trans*-cyclooctene **14** with $^1O_2$ with B3LYP/6-31G(d) and CASMP2/6-31G(d) calculations.[19] The reaction proceeds initially by an activation barrier of 19.5 kcal/mol, to reach peroxy intermediate **B**. Rotation about the C–C bond in **B** is a low-energy 4.2 kcal/mol process to isomerize the cycloooctene with a path for O_2 release. Notably, the calculations predict involvement of a *trans*-perepoxide intermediate **C**, which contrasts with simple alkenes such as tetramethylethylene with DFT models that predict a two-step no-intermediate mechanism.[20] Perepoxides are generally not minima due to residing up on the caldera region of potential energy surfaces. However, *trans*-cyclooctene **14** is unique where the allylic hydrogens are inaccessible so that the H-abstraction in the $^1O_2$ 'ene' reaction is unfavorable, and thus a potential well develops for the perepoxide.



Scheme 3. O_2-dependent photoisomerization of *trans*-cyclooctene **14** to *cis*-**15**, and formation of oxygenated products.

Fourth, a 1988 report describes the TPP-sensitized oxygen-mediated photoisomerization of *p*-substituted *trans*-stilbenes **20** (X = MeO, H, and Cl) to produce *cis*-stilbenes **21** (percent yield not reported).[21] Unsymmetrical or symmetrical attack on the π-bond of the alkene carbons was proposed considering the formation of the zwitterion peroxy intermediate **A** and perepoxide **C**, and the products provide a degree of support for their intermediacy. In addition to *cis*-**21**, the epoxide **22**, endoperoxide **23**, diendoperoxide **24**, and aldehyde **25** were also formed. Due to long irradiation times, the diendoperoxide **24** was the major product in 80% yield. A 1976 report[22] describes the benzil- or biacetyl-sensitized oxygen-mediated photoisomerization of *trans*-stilbene **20** to *cis*-**21**. Irradiation of *trans*-**20** yielded a mixture of *cis*-**21** in 66% yield and recovered *trans*-**20** in a product ratio of **20**:**21** = 1:6. However, under identical reaction conditions, the *cis*-**21** isomer gave a mixture of *trans*-**20** in 59% yield and recovered *cis*-**21** in a product ratio of **20**:**21** = 12:1.

The report[22] posits that the results obtained is indicative of initial energy transfer to *trans*-stilbene **20**. Once the photochemical *trans-cis* isomerization is complete, *cis*-stilbene is available for epoxidation as a high triplet excitation energy makes it difficult for it to act as a rapid energy acceptor or quencher of the triplet excited sensitizer. The isomerization might proceed via the excited triplet, the epoxidation step involves a zwitterionic[21] or diradical[22] intermediate where rotation from the *cis* to *trans* form is probable. Relatedly, an oxygen-dependent *cis*- to *trans*-photoisomerization of *trans*-α-methyl stilbene has also been reported.[23]

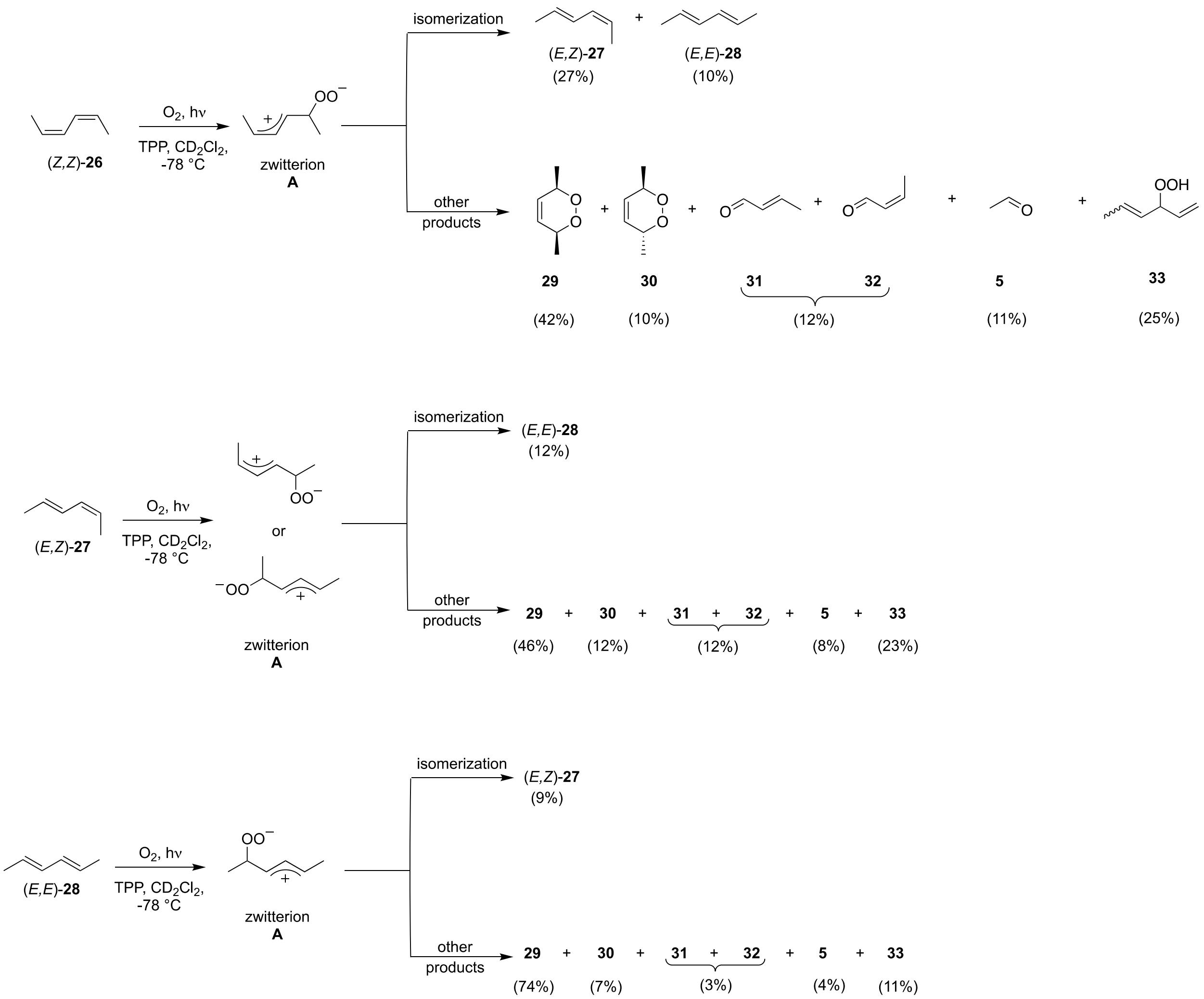


Scheme 4. Oxygen-dependent photoisomerization of *p*-substituted *trans*-stilbene **20** to *cis*-**21**, and formation of oxygenated products.

3. Diene isomerization

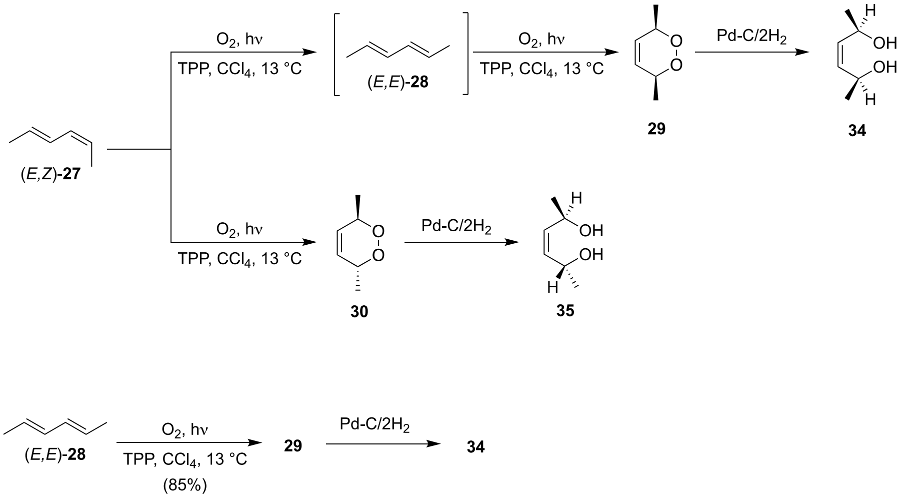
Two reports are reviewed here. First, a 1988 study describes the TPP-sensitized oxygen-dependent photoisomerization of (*Z,Z*)-, (*E,Z*)-, and (*E,E*)-2,4-hexadiene (**26**, **27**, and **28**, respectively).[24] (*Z,Z*)-**26** led to isomerized (*E,Z*)-**27** (27% yield) and (*E,E*)-**28** (10% yield). (*E,Z*)-

27 led to isomerized (*E,E*)-**28** (12% yield) and (*Z,Z*)-**26** (0% yield) (Scheme 5). (*E,E*)-**28** led to isomerized (*E,Z*)-**27** in 9% yield. The reaction time influences the isomer yield (as was also seen in section 2). After irradiation for 5-10 min, the percent yield of isomers was highest, but diminished after 20-60 min (to 0%). A mechanism which involves an unsymmetrical attack of $^1O_2$ on one of the hexadiene carbons and formation of the zwitterion peroxy intermediate **A** is consistent with the results. The intermediacy of $^1O_2$ in the isomerization reaction was evident since deuterated solvents increased yields, and different sensitizers furnished similar product distributions. Furthermore, inclusion of a radical trap (2,6-di-*tert*-butylphenol) had no influence on the isomerization suggesting that type I oxygen radicals are not involved. That the (*Z,Z*)-**26** had the highest yield of isomers speaks to its restricted rotation to the *s*-cis rotamer, reducing access to the Diels-Alder [2 + 4] path. *Cis*-endoperoxide **29**, *trans*-endoperoxide **30**, (*E*)-butenal **31**, (*Z*)-butenal **32**, acetaldehyde **5**, and hydroperoxide **33** were also formed. A reported thermal isomerization of (*E,*Z)- to (*E,E*)-1,4-diphenylbutadiene by a zirconocene η^4-complex has also been published.[25]

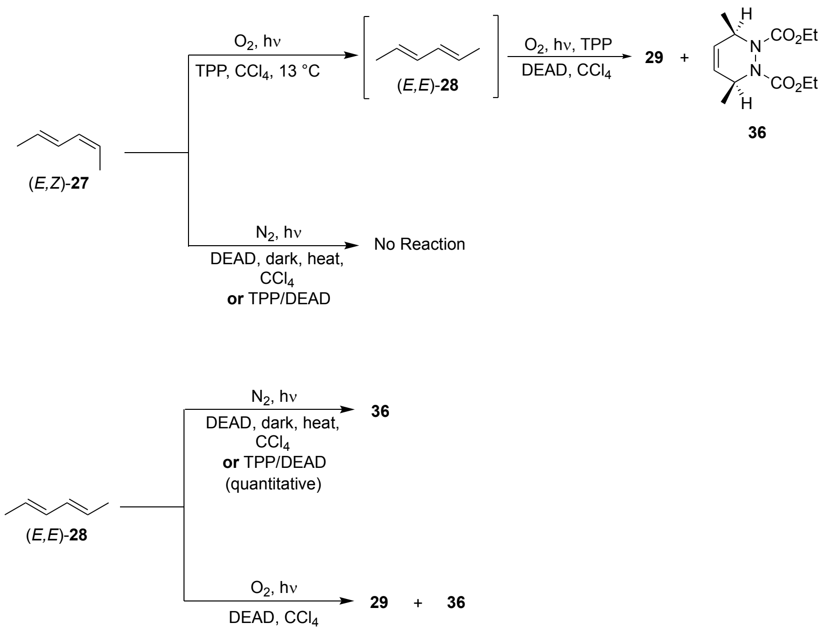


Scheme 5. Oxygen-dependent photoisomerization of *(Z,Z)*-**26**, *(E,Z)*-**27**, and *(E,E)*-**28**, and formation of oxygenated products.

Second, a 1983 report describes the TPP-sensitized O_2-based photoisomerization of (*E,Z*)- and (*E,E*)-2,4-hexadiene (**27** and **28**, respectively) (Scheme 6).[26] The (*E,Z*)-**27** formed two endoperoxides **29** and **30** with a yield of 72% and a product (**29**:**30**) ratio of 83:17, whereas (*E,E*)-**28** produced the endoperoxide **29** in 85% yield. This product profile points to isomerization of (*E,Z*)-**27** to (*E,E*)-**28** prior to formation of endoperoxide **29**. The percent yield and ratio of endoperoxides **29** and **30** were determined upon catalytic reduction with H_2, which provided the ring-opened diols **34** and **35**, respectively. The isomerization reaction was ascribed to a $^1O_2$ process. That the (*E,E*)-**28** had the highest yield of endoperoxide speaks to its ease of rotation to *s*-cis compared to (*E,Z*)-**27**, analogous to the photooxidation of (*E,E*)- and (*E,Z*)-1-aryl-1,3-pentadienes in selectively generating *cis*-endoperoxides.[27] The 1983 report[26] also describes the use of the singlet oxygen mimic, DEAD (Scheme 7). The reaction of (*E,E*)-**28** with DEAD was found to form the Diels-Alder product **34** in quantitative yield. The reaction of (*E,E*)-**28** with DEAD in the presence of TPP and light in the absence of oxygen produced **34** with similar yields, but (*E,Z*)-**27** was unreactive with DEAD itself.



Scheme 6. Oxygen-dependent photoisomerization of *(E,Z)*-**27** to *(E,E)*-**28**, and formation of endoperoxide and alcohol products.

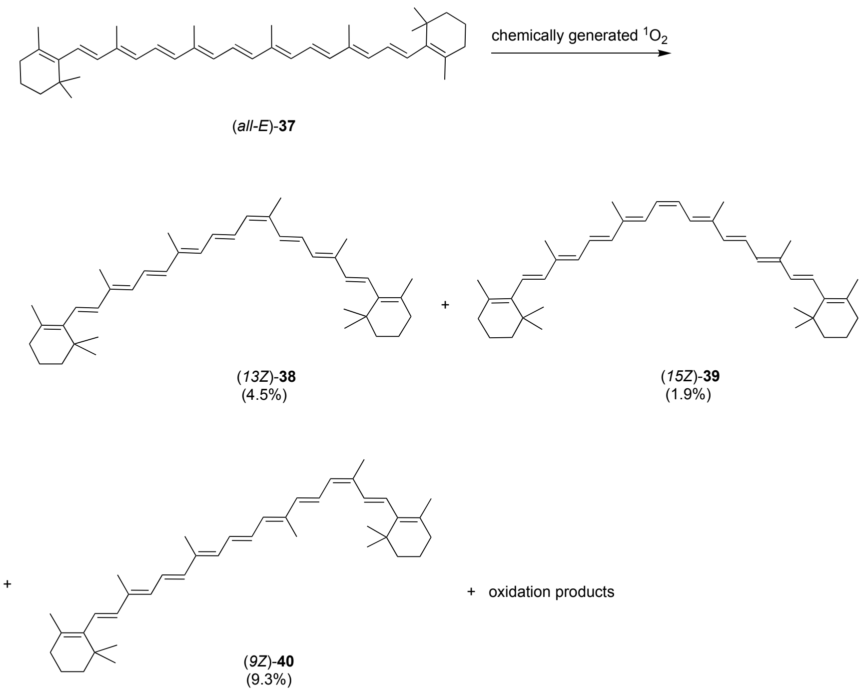


Scheme 7. Oxygen-dependent photoisomerization of *(E,Z)*-**27** to *(E,E)*-**28**, in the presence and absence of DEAD.

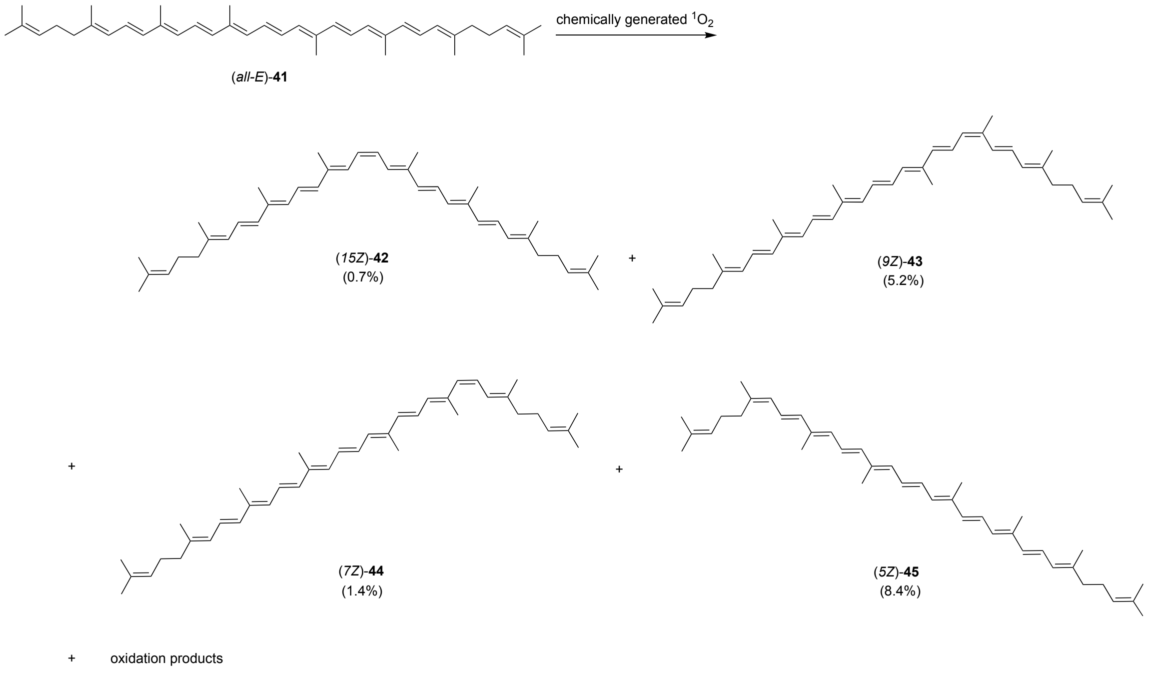
Similar to DEAD, MTAD is a poor mimic of $^1O_2$ in terms of its potential for C=C double bond isomerization, as was seen in the photoreaction of *trans*- and *cis*-methyl urocanate.[28] The reaction of *trans*- and *cis*-methyl urocanate with MTAD proceeded with a [2 + 4] stereoselective cycloaddition that involved both the olefinic side chain and the C=C bond of the imidazole ring, instead of reacting in a [2 + 4] manner with the imidazole ring itself. Relatedly, external and internal influences, such as encapsulation and sterics can enhance $^1O_2$ [2 + 4] cycloaddition.[29-33] Moving on from DEAD and MTAD reactions, we now describe the isomerization of natural product carotenes and lycopenes.

4. Polyene isomerization

There are reports of oxygen-dependent photoisomerization, as well as, $^1O_2$–based isomerization of polyenes. That $^1O_2$ can be quenched in essentially a diffusion-controlled rate by polyenes, such as β-carotene by energy transfer quenching,[3] indicates the reaction will depend on details as outlined below. A 2015 report[34] describes the reaction of (*all-E*)-β-carotene **37** with a $^1O_2$-based isomerization (in which $^1O_2$ was chemically generated by release from 1,4-dimethylnaphthalene-1,4-endoperoxide) furnished (*13Z*)-**38**, (*15Z*)-**39**, and (*9Z*)-**40** in 4.5%, 1.9%, and 9.3% yields, respectively (Scheme 8). Of note is a study from 1970[4] on the MB-sensitized oxygen-mediated photoisomerization of (*15Z*)-**39**, to furnish (*all-E*)-β-carotene **37** in 89% yield. The use of NaOCl/H_2O_2 as a chemical source of $^1O_2$ led to the isomerization of **39** to **37** in 36% yield, fully a 53% reduction to the MB-sensitized oxygen-dependent route. ^{3}MB also contributed to the isomerization of **39** to **37**. Furthermore, on storage in the dark for weeks or months, **39** also isomerizes to **37** in ~10% yield. Thus, the isomerization reaction results from mechanisms of oxygen radicals (type I reaction), $^1O_2$ (type II reaction), as well as ^{3}MB and slow processes in the dark. Relatedly, the reaction of (*all-E*)-β-lycopene **41** with $^1O_2$-based isomerization (in which $^1O_2$ was chemically generated) furnished (*15Z*)-**42**, (*9Z*)-**43**, (*7Z*)-**44**, and (*5Z*)-**45** in 0.7%, 5.2%, 1.4%, and 8.4% yields, respectively (Scheme 9). Furthermore, a reaction of the radical probe ABTS with H_2O_2 suggested that oxygen radicals were also played a role in the isomerization process of **37** and **41**. Polyene photoreactions are reported to physically quench $^1O_2$ and scavenge oxygen radicals, and in some cases form oxidized products.[35-40] Oxidation products were formed in cases of **37** and **41** albeit in higher amounts in the lycopene–$^1O_2$ reaction.



Scheme 8. Singlet oxygen-mediated isomerization of (*all-E*)-**37**, (*13Z*)-**38**, (*15Z*)-**39**, and (*9Z*)-**40**.



Scheme 9. Singlet oxygen-mediated isomerization of (*all-E*)-**41**, (*15Z*)-**42**, (*9Z*)-**43**, (*7Z*)-**44** and (*5Z*)-**45**.

5. Mechanism: On the Role of Oxygen in Photoisomerization

The isomerization in the above examples require an open peroxy intermediate. Many cases involved primary photochemical reactions, and isomerization itself is a dark event arising after O_2 is bound as a peroxy intermediate. Oxygen likely departs as $^3O_2$ and not $^1O_2$ due to the stepwise nature of the reaction, although studying oxygen context dependencies is still needed. A challenging problem that awaits exploration is the perturbation of substrates for unsymmetrical oxygen addition. For example, encapsulation may enable temporary storage pools of bound O_2 in cases other than known naphthalene and anthracene derivatives,[41-44] to make this isomerization path potentially attractive synthetically.

The reaction time is also an issue when consumption of the primarily-formed (isomerized) compound undergoes a secondary photooxidation reaction. One example in Scheme 3, the primary product *cis*-cyclooctene **15** is competitively consumed over time with its $^1O_2$ chemical quenching rate constant (k_r) 31% greater than that of *trans*-cyclooctene **14** [cf. 1.7×10^4 M^{-1} s^{-1} for **15** and 1.3×10^4 M^{-1} s^{-1} for **14** (*cis* effect)].[45] Studies of short and long irradiation times would show more clearly the isomerization reaction to afford greater amounts of isomer, but it is unlikely for a clean isomerization reaction to be taken to 100% conversion.

In summary, oxygen-based photoisomerizations have not yet been found as useful alternatives to the commonly used direct UV-irradiation methods. O_2-based photoisomerizations have mainly been of mechanistic interest, where their synthetic utility remains to be established. As we saw, type I (oxygen radicals) and type II ($^1O_2$), and excited substrate–$^3O_2$ reactions can lead to *E,Z* isomerization. There are advantages over conventional UV photolysis conditions. The use of UV photolysis in batch sensitized reactions suffer from limited depth of photon penetration into solution from inner-filter effects. Further, speaking to the virtues of visible and NIR light use in synthetic chemistry[46-48] and flow systems,[6,49] longer irradiation wavelengths with sensitization is appealing for unsaturated compounds with poor chromophores.

6. Conclusion

The review describes—for the first time—oxygen-mediated photoisomerization reactions in organic chemistry. Photoisomerized C=C bonds were highlighted in cases where oxygen was required. Hydroperoxides, epoxides, dioxetanes, endoperoxides, and related oxidized compounds were also observed products, which represents a shortcoming for its potential use solely for isomerization. Although a large body of photoisomerization literature is available using direct-light absorption, the fraction that we focus on is O_2-driven, where its broader synthetic utility has not yet been established.

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Conflicts of interest

There are no conflicts of interest to declare.

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Abbreviations

ABTS	2,2′-azino-*bis*(3-ethylbenzothiazline-6-sulfonic acid)
DEAD	diethyl diazenedicarboxylate
MB	methylene blue
MTAD	*N*-methyltriazolinedione
NIR	near infrared
Py	pyridine
RB	rose bengal
TPP	tetraphenylporphyrin

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Table of Contents graphic:

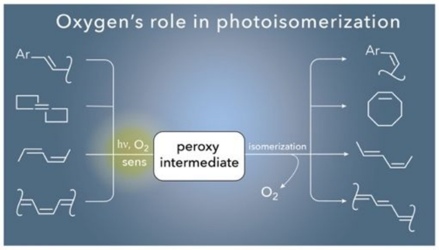

Table of Contents entry:

Photogeneration of a peroxy intermediate leads to oxygen evolution along with regeneration of the compound as its isomer. The review is *arranged* to probe patterns of isomer *arrangements* (pun intended).