CYCLOADDITIONS WITH SINGLET OXYGEN MECHANISM AND SUBSTITUENT DIRECTING EFFECTS

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INTRODUCTION

In 1867 Fritzsche reported the first instance of a singlet oxygen reaction when he observed that a precipitate forms in a solution of 2,3-benzanthracene exposed to air and ambient light.[1] At the time, the nature of the reagent and product were unknown and the reaction did not elicit further interest until the work by Dufraisse[2] and Windaus[3] sixty years later. The structure of singlet oxygen remained the subject of debate until Foote unequivocally established its identity in 1968.[4] In its ground state, oxygen has two degenerate LUMOs which each contain an unpaired electron. In this triplet state, oxygen displays diradical character. Singlet oxygen is an excited form in which both electrons are paired in the same LUMO. This form is 22 kcal / mol higher in energy and displays double bond character between the oxygens. It is a synthetically useful reagent because it is readily available and provides access to a number of polyoxidized compounds, including a number of endoperoxides with antibiotic or antimalarial properties.[5] This report presents recent mechanistic investigations and the effect of substituents in diastereoselective cycloadditions.

SINGLET OXYGEN GENERATION

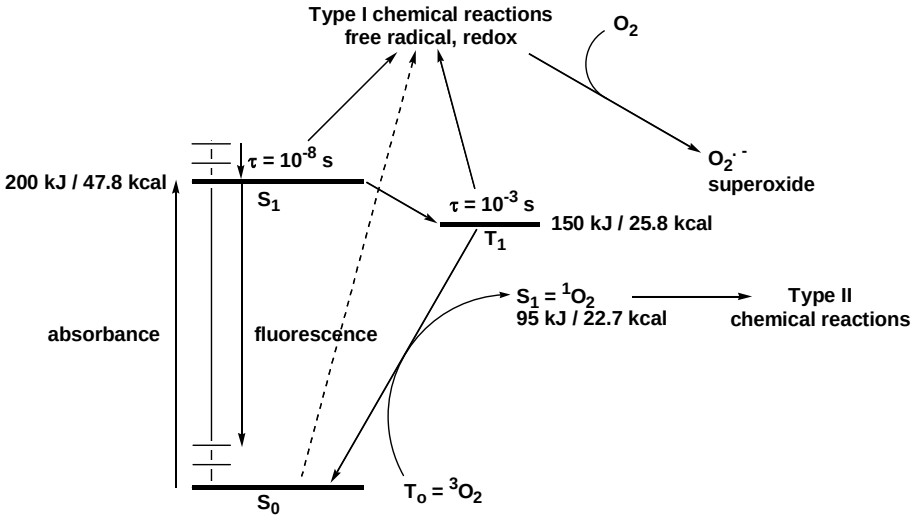


Figure 1. Photosensitizer mechanism

The most common method of generating singlet oxygen in organic solvents has been the use of dyes in solution with the reagents.[6] The irradiation of the solution with a bright lamp excites the dyes to a higher singlet state, which then undergoes intersystem crossing to the longer lived triplet state (Figure 1). This state transfers its energy to form singlet oxygen from the triplet ground state. Commonly used dyes include Rose Bengal (**1**), methylene blue (**2**) and tetraphenylporphyrin (**3**) shown in Figure 2. The choice of dye is based on high absorbance in the visible region, the half-life and energy of the triplet state, and the efficiency at exciting oxygen in the reaction solvent. Although the

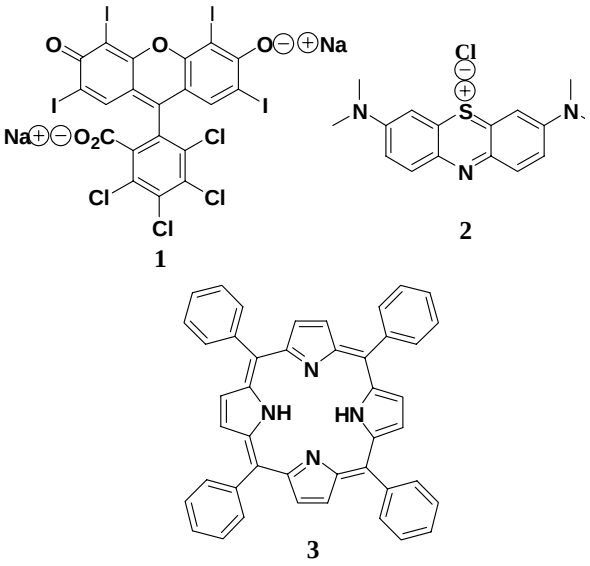


Figure 2. Dye structures.

dyes are catalytic, they are slowly degraded by singlet oxygen in a photobleaching process and longer photooxygenation require higher dye loading to be efficient. As a result, this technique is not amenable to large scale reactions and alternative photooxidations methods have been investigated.

Fréchet has reported the use of dendrimers as catalysts for singlet oxygen reactions.[7] The dendrimer structure shown in Figure 3 contains a hydrophobic core with a photosensitizing moiety. Nonpolar reagents diffuse into the reaction core while polar products diffuse back into solution. This method would be expected to work best when there is a large polarity difference between product and reactant. Cyclopentadiene was reacted with singlet oxygen in the presence of the dendrimer and reduced *in situ* with thiourea to afford the *syn* cyclopentene diol. After 50 minutes, the conversion to product was 35 %. Benaglia and coworkers have fixed 5,10,15,20-tetrakis(4-hydroxyphenyl)porphyrin onto polyethylene glycol resins to generate a catalyst that is soluble in methylene chloride.[8] Upon reaction completion, the catalyst may be precipitated with the addition of diethyl ether, filtered and recycled up to six times without activity loss. Polymer-bound photosensitizers show higher stability toward photobleaching and minimize dye decomposition and solution contamination. Free and polymer-bound dyes exhibit the same product selectivity and comparable yields.

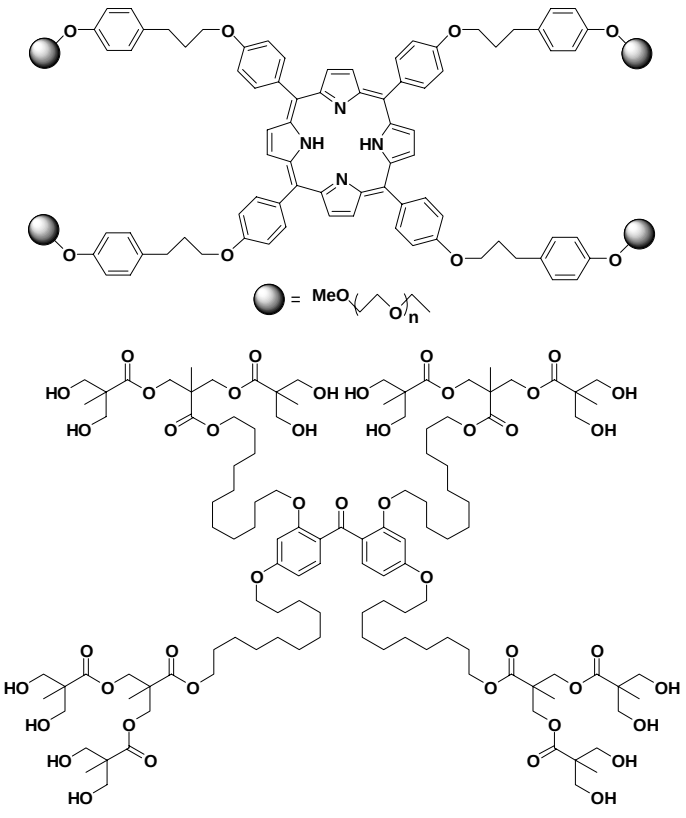


Figure 3. Polymer-supported dye and dendrimer for photooxygenation.

Alternatively, singlet oxygen can be "stored" for several weeks in the form of calcium peroxide diperoxohydrate ($CaO_2 \cdot 2H_2O_2$) at -80 ^oC.[9] $CaO_2 \cdot 2H_2O_2$ can be made by reacting H_2O_2 with $CaCl_2$ or

$CaO_2 \cdot 8H_2O$. The yield of $^1O_2$ from the calcium salt upon thermolysis at 50 ^oC is observed to be 25 % by titration with a reactive cyclic diene, α-terpinene. This method is most efficient for compounds that readily undergo photooxygenation. However, when physical and chemical quenching become important, longer reaction times and higher calcium peroxide diperoxohydrate loading are required.

REACTION MECHANISM

The early observation of 6-membered endoperoxides initially suggested a reaction pathway analogous to a Diels-Alder reaction. In 1976, Dewar calculated that a reaction pathway through a perepoxide intermediate would be lower in energy than the concerted cycloaddition transition state.[10] Stephenson and coworkers studied the kinetic isotope effects associated with the ene reaction between singlet oxygen and a number of deuterium-labeled tetramethylethylenes.[11] While the results were inconsistent with a concerted mechanism, they could be reconciled with a stepwise pathway in which formation of the perepoxide intermediate was the rate-determining step. Delogu and coworkers observed that the reaction of bisdialine with oxygen in the presence of light with tetraphenylporphyrin as a sensitizer gave primarily the *anti* cycloadduct with little of the expected *syn* product (Figure 4).[12] Since a concerted cycloaddition seemed unlikely, a stepwise mechanism was proposed in which perepoxide intermediate **4** could open up to the zwitterions **5** and **6** which respectively gave the *syn* and *anti* isomers. The *anti* isomer was presumably more stable thermodynamically since it was the major product observed. Once formed, the two endoperoxides did not interconvert. The preferential formation of the *anti* cycloadduct was unique to singlet oxygen because other dienophiles such as maleic anhydride and N-phenylmaleimide proceeded to give *syn* products with bisdialine.

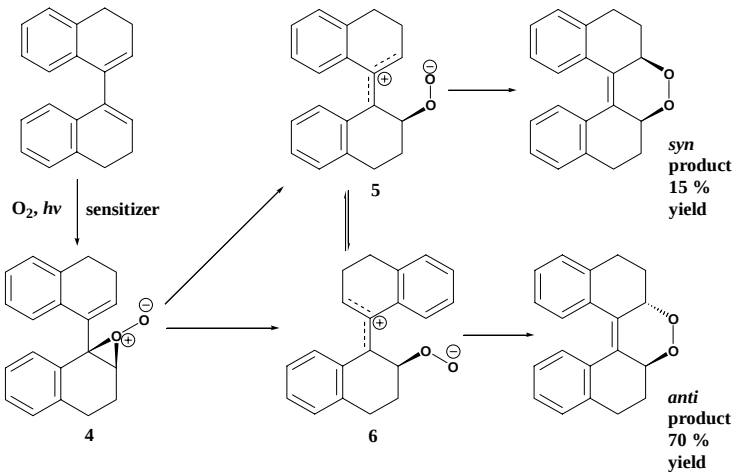


Figure 4. The reaction of bisdialine with singlet oxygen.

Carpenter reported a cycloaddition that appeared to proceed with singlet oxygen approaching from the more hindered side of a cyclic diene (Figure 5).[13] To explain this unexpected result, two perepoxides were proposed to be intermediates from the approach of singlet oxygen. The approach to the less hindered face led to perepoxide **7**, in which the oxygen removed a hydrogen from the tertiary carbon to afford the ene product **8**. Perepoxide **9** was formed by the more hindered approach but this intermediate rearranged to endoperoxide **10** faster because there was no hydrogen that might be easily abstracted by the oxygen to form an ene product.

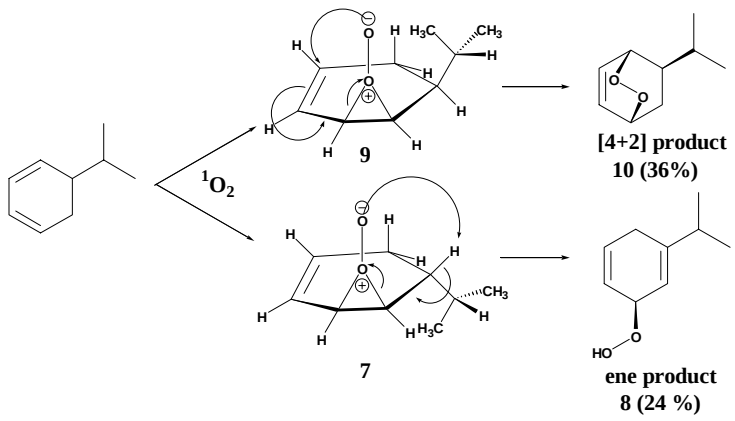


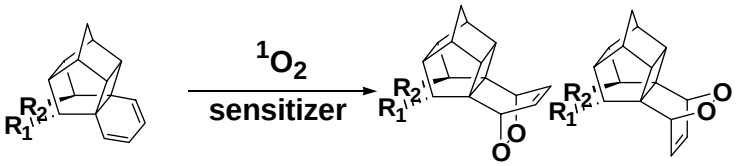
Figure 5. Common perepoxide for ene and [4+2] reactions.

More recently, computational work by Tonachini and coworkers proposed an alternative mechanism.[14] Calculations performed on ethylene, methyl vinyl ketone and butadiene suggested that the formation of a perepoxide could not occur directly from singlet oxygen and an olefin, but instead had to proceed through a diradical intermediate. In addition, the barrier between the perepoxide and the dioxetane product was very high, indicating that while the perepoxide could form, it was probably not an intermediate located on the reaction pathway. Proceeding from the diradical to the dioxetane product was predicted to be lower in energy. However, these calculations have only been performed on simple systems and might not be representative of the reactivity of larger compounds. Thus far, mechanistic experiments have not been able to rule out either pathway. Trapping reactions run with trimethyl phosphite gave epoxides, which were the reduction products of the intermediates. However, these experiments are inconclusive as reduction of the diradical and perepoxide would be predicted to lead to the same epoxide.[15]

CONTROLLING SINGLET OXYGEN APPROACH

Mehta and coworkers have studied 1,3-dienes attached to polycyclic systems which fix the conformation and found that protecting groups can control stereoselectivity (Table 1).[16-18] The reaction with singlet oxygen proceeded to give **11** or **12** depending on the face of attack. Many dienophiles such as maleic anhydride attacked exclusively from the less sterically hindered bottom face to give **11**. With carbonyls

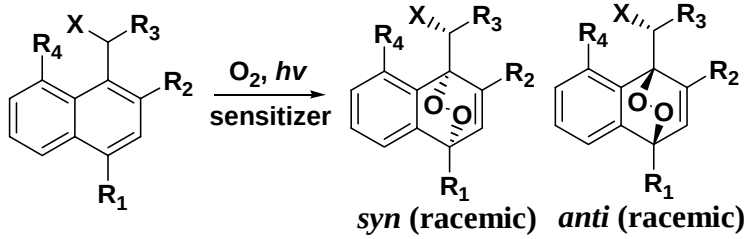
Table 1. Influence of protecting groups on stereochemistry



R_1	R_2	**11** / **12**	Yield (%)
=O	=O	78 / 22	88
—OCH_2CH_2O—	—OCH_2CH_2O—	3 / 97	91
OH	**OH**	79 / 21	80
OAc	**OAc**	79 / 21	80
OMe	**OMe**	0 / 100	80
—$SCH_2CH_2CH_2S$—	=O	0 / 100	81

at R_1 and R_2, singlet oxygen displayed the same steric preference. However, converting the carbonyls to acetals induced singlet oxygen to attack from the contrasteric side to give **12**, presumably due to repulsion between $^1O_2$ and the acetal lone pairs. In the case of hydroxyl or acetate groups, the preference for product **11** was again observed. In the case of acetate, crystallographic studies indicated that this preference could be attributed to a favorable interaction between singlet oxygen and the electrophilic carbonyl carbons of the acetate groups. In the case of the alcohols, a hydrogen bond with singlet oxygen was invoked.

Table 2. Hydroxyl directing in chiral naphthalenes.



Entry	X	R^1	R^2	R^3	R^4	*Syn* / *anti*	Yield (%)
1	OH	Me	H	Me	H	85:15	>95
2	OH	Me	H	tBu	H	87:13	>95
3	OH	OMe	H	Me	H	79:21	96
4	OH	H	OMe	Me	H	91:9	>95
5	OH	H	H	Me	Me	>95:5	25
6	OH	H	Me	Me	H	6:94	>95
7	OAc	Me	H	Me	H	56:44	>95
8	COOH	Me	H	Me	H	10:90	>95

Hydroxyl group direction of singlet oxygen approach has been extensively studied by Adam and coworkers. This effect was first observed in the ene reaction of chiral allylic alcohols with $^1O_2$.[19] One important component of the system was the 1,3-allylic strain with the stereogenic center which provided stereodiffentiation between the two faces. In order to study this effect in [4+2] cycloadditions, naphthyl alcohols were chosen because their endoperoxides were well documented (Table 2).[20] The photooxidation was found to be diastereoselective and was directed by the minimization of *peri* strain between R_3 and R_4. For entries 1 and 2, transition state **O** was lower in energy since *ortho* strain between R_2 and R_3 was minimized while transition state **P** was destabilized by *peri* strain. The *syn* diasteromer was obtained by hydroxyl group direction to the same face (Figure 6). Steric bias

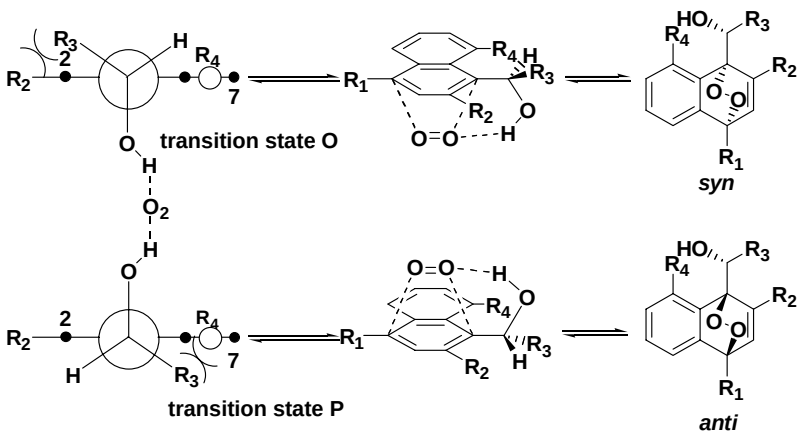


Figure 6. Transition states for the naphthyl system.

was not the main cause of selectivity since the *tert-butyl* group at R_3 did not increase *syn / anti* selectivity (entry 2).[21] Entries 3 and 4 seemed to support a stepwise mechanism. With R_1=OMe, the electron-rich olefin was farther from the directing hydroxyl group and a decreased selectivity was observed. When the methoxy group was placed in the *ortho* position, the selectivity was increased because singlet oxygen bonded to the electron-rich olefin first and was closer to the directing hydroxyl. Larger R_4 groups increased the *peri* strain in the transition state **P** which resulted in better *syn* selectivity (entry 5). Substituents at the R^2 position introduced *ortho* strain and thus destabilized transition state **O**, effectively reversing the selectivity (entry 6).[22] The existence of a hydrogen bond interaction was supported by the decrease in selectivity in more polar solvents (not shown). Additionally, acetylating the alcohol eliminated oxygen coordination and no diastereoselectivity was observed (entry 7). Further expansion to carbon-containing substituents showed that an ester or acid functionality directed the oxygen to the opposite face to give *anti* product (entry 8).[23] While a carboxylic acid could form hydrogen bonds, the repulsion between the carbonyl oxygen lone pairs and singlet oxygen was presumably stronger.

The use of singlet oxygen is usually complicated by the competition between the ene reaction and the cycloadditions. The presence of allylic hydrogens next to a diene usually results in preferential formation of a hydroperoxide via an ene reaction instead of a [4+2] cycloadduct. However, the reaction mode of $^1O_2$ is also subject to substituent directing effects as competition with the ene reaction may be eliminated if no allylic hydrogens are accessible. Matsumoto and coworkers observed that in styrene derivative **13** the allylic oxygen atom directed singlet oxygen to the molecule face with no allylic hydrogens and [2+2] cycloaddition predominated to give **14** in 89 % yield.[24] In the methylene analogue **15** with no such directing oxygen, a mixture of [2+2] cycloadduct **16** and ene product **17** was obtained in a ratio of 56:44. In the case of adamantylidene-substituted allylic alcohols, acetylation of the alcohol led to exclusive ene reaction instead of [2+2] cycloaddition by elimination of the the hydrogen bond directing effect.[25]

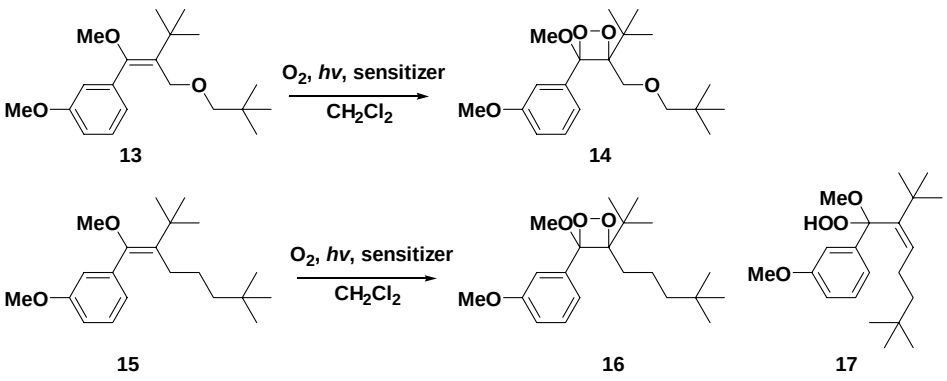
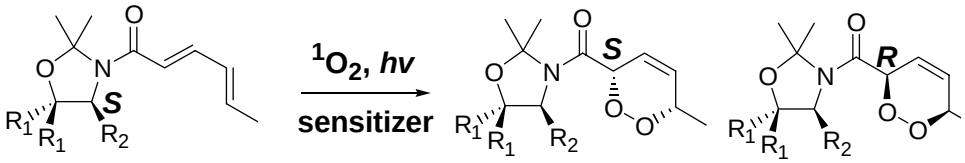


Figure 7. Oxygen directing effects favor cycloaddition.

CHIRAL AUXILIARIES

Since a "built-in" directing functional group is not always available, chiral auxiliaries have been recently investigated. Sorbic acid derivatives were attached to optically active 2,2-dimethyloxazolidines to conduct diastereoselective [4+2] cycloadditions with singlet oxygen (table 3).[26] A large R_1 group on the oxazolidine was required to achieve selectivity since the dienophile was so small. Moreover, the difficult conditions needed to cleave the auxiliary were unfavorable for synthetic applications as they could lead to product degradation. To improve on this, enecarbamates with Evans' chiral oxazolidinones were used (Table 4).[27] Diastereoselective [2+2] cycloadditions predominated in the case of *Z* alkenes.[28] The nitrogen directed the oxygen approach to the side without any allylic hydrogens so the ene reaction could not occur. *Z*-Enecarbamates showed good selectivity with a range of steric bulk on the oxazolidinone. Inversion of oxazolidinone chirality also led to a diastereoselectivity reversal (entry 5).[29] It was noted that the stereochemistry of the C-3 center did not affect the dioxetane stereoselectivity. The chiral auxiliary could then be cleaved off under reductive conditions and the dioxetanes could be elaborated to diols or ketones.

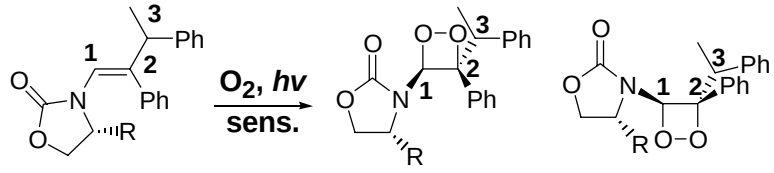
Table 3. Use of chiral oxazolidine with sorbic acid.



Entry	R_1	R_2	*S* / *R*	Yield (%)
1	H	CH_2Ph	68 / 32	> 95
2	H	CH_2Nph [a]	67 / 33	> 95
3	H	*i*-Pr	76 / 24	> 95
4	H	Ph	91 / 9	> 95
5	Me	CH_2Ph	> 95 / 5	> 95

a. Nph = 2-Naphthyl

Table 4. Using Evans' oxazolidinone to control [2+2] stereoselectivity in ene-carbamates.



R oxazolidinone 1*S*, 2*S* 1*R*, 2*S*

Entry	R	Product dr
1	H	50:50
2	(*R*)-Me	>95:5 [1*S*,2*S*]
3	(*R*)-iPr	>95:5 [1*S*,2*S*]
4	(*R*)-iPr	>95:5 [1*S*,2*S*]
5	(*S*)-iPr	>95:5 [1*R*,2*R*]

CONCLUSIONS

Chemists have recently gained more insight into the singlet oxygen cycloaddition. The stepwise nature of the mechanism has been determined based on a number of unexpected products observed such as in the case of bisdialine. At this point, the preferred mechanism is the formation of a perepoxide

intermediate which then rearranges to either a [4+2] or [2+2] cycloadduct, but a diradical mechanism cannot be ruled out. Substituent directing effects and reactions using chiral auxiliaries have been demonstrated by experiments. While there is still much room for progress, these methods shows promise for the future use of singlet oxygen in selective organic processes instead of more toxic and expensive oxidizing agents.

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