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Redesign of a Pyrylium Photoredox Catalyst and Its Application to the Generation of Carbonyl Ylides

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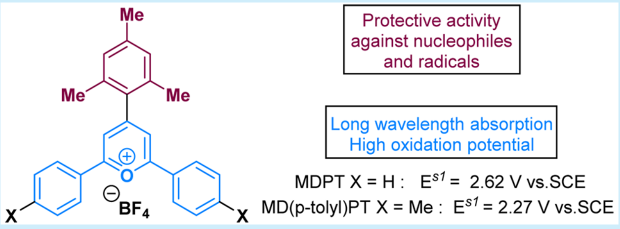
Supporting Information

ABSTRACT: We report the exploration into photoredox generation of carbonyl ylides from benzylic epoxides using newly designed 4-mesityl-2,6-diphenylpyrylium tetrafluoroborate (MDPT) and 4-mesityl-2,6-di-*p*-tolylpyrylium tetrafluoroborate (MD(*p*-tolyl)PT) catalysts. These catalysts are excited at visible wavelengths, are highly robust, and exhibit some of the highest oxidation potentials reported. Their utility was demonstrated in the mild and efficient generation of carbonyl ylides from benzylic epoxides that otherwise could not be carried out by current common photoredox catalysts.



Photoredox catalysis has become a valuable tool for the synthesis of building blocks and biologically relevant scaffolds. The ability to produce open shell intermediates under low concentration and mild conditions has enabled numerous elusive transformations, changing the way synthetic chemists consider bond construction.[1] Most notable are the catalysts that use visible light to promote this reactivity, as UV light can cause unproductive pathways to occur. In particular, organic dyes have become a popular choice for photoredox reactions, offering a metal-free alternative, lower cost, and high oxidation potentials that are not available to their metal counterparts.[2] Therefore, there has been a great deal of interest in the discovery of organic photoredox catalysts that can both absorb longer wavelengths of light and promote thermodynamically challenging redox processes.[3]

We became interested in methods for the photoredox generation of carbonyl ylides from benzylic epoxides. Such reactions could be used to rapidly access cyclic ethers, which are present in many biologically active natural products (Figure 1a).[4] Carbonyl ylides are highly versatile intermediates which can be generated from silicon-based 1, 3 eliminations, samarium reduction, and photochemical reactions.[5] The most common approach relies on carbonyl interception of transient carbenoids.[5d] These methods often suffer from issues such as use of precious metals, superstoichiometric amounts of reagents, toxicity, designed substrates, and poor yields. Thus, we felt that a general and mild method to access carbonyl ylides from benzylic epoxides would have broader application.

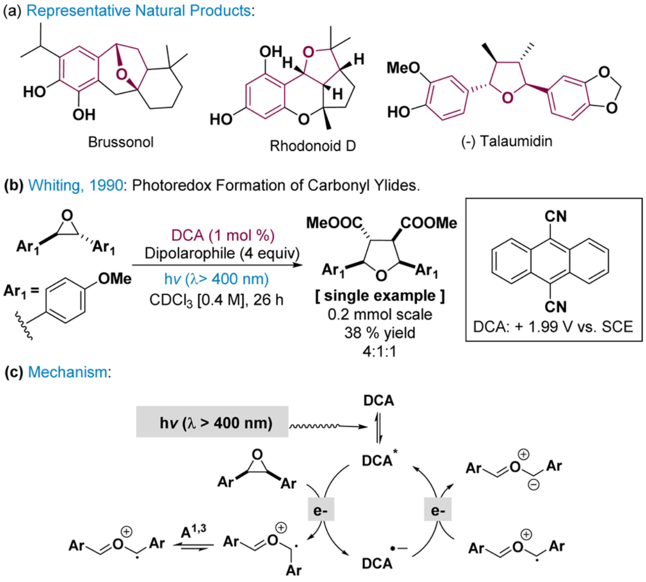


Figure 1. (a) Representative natural products. (b) Previous work by Whiting on the photoredox formation of carbonyl ylides. (c) Mechanism proposed by Arnold and Albini.

Early accounts of the photochemical formation of carbonyl ylides from stilbene oxide and their cycloaddition to a wide variey of dipolarophiles were reported by Arnold and Albini,[6] Griffin,[7] and others.[8] Later, Whiting[9] demonstrated that a carbonyl ylide from an electron-rich epoxide could only be obtained when 9,10-anthracenedicarbonitrile (DCA) (E^{s1}_{red} = +1.99 V vs SCE), a visible light absorbing catalyst, was employed (Figure 1b). This finding was critical because it avoided direct excitation of the epoxide which leads to poor yields. Although successful, this reaction was only demonstrated on a single example, required super stoichiometric amounts of the dipolarophile, and used degassed solvent due to the formation of superoxide, generated by DCA, which led to

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undesired side products.[10] The reaction mechanism is proposed to proceed through single electron transfer (SET) from the epoxide to the excited DCA, forming both a reduced DCA and a radical cation which rearranges to an oxonium radical (Figure 1c).[6] A subsequent back electron transfer furnishes the desired carbonyl ylide. Independent of the epoxide relative configuration, the *cis* product is favored, likely to avoid allylic-1,3 ($A_{1,3}$) interaction in the oxonium radical intermediate. Therefore, use of *cis* epoxide usually leads to higher diastereoselectivity.

Since the dipolarophile scope has been well explored and the carbonyl ylide formation from epoxides had only been demonstrated on a very limited number of diaryl substrates, we began investigating this [3 + 2] dipolar cycloaddition by trapping acetylenedicarboxylate (DMAD). Early experiments revealed that DCA and Fukuzumi's catalyst (Mes-Acr-Me) (E^{s1}_{red} = +2.18 V vs SCE) could catalyze the desired cycloaddition of stilbene oxide and DMAD (Figure 2a). After optimization using DCA as the catalyst, we began probing electron-rich diaryl epoxides in a preparative scale (Figure 2b). These include examples having chlorine and alkyl ethers incorporated in them (**1**−**2**). Additionally, an example bearing naphthalene and an *ortho* electron-donating group was well tolerated and the desired product (**3**) was isolated in excellent yield. Heterocycles such as furan (**4**) and thiophene (**5**) proceeded in moderate to excellent yields. Overall, diastereomeric ratios >4:1 were consistently obtained when using the *cis* epoxide. The reactions with moderate yields were due to a competing reaction, wherein C−O cleavage and subsequent aryl migration afforded diaryl acetaldehyde (**6**).[9] Unfortunately, DCA and Mes-Acr-Me failed with electron-deficient epoxides under several conditions (Figure 2a). However, when higher oxidizing 2,4,6-triphenylpyrylium tetrafluoroborate (TPT) (E^{s1}_{red} = +2.55 V vs SCE) was used conversion to the desired product could be observed, but major decomposition of the catalyst limited this method (Figure 2a).

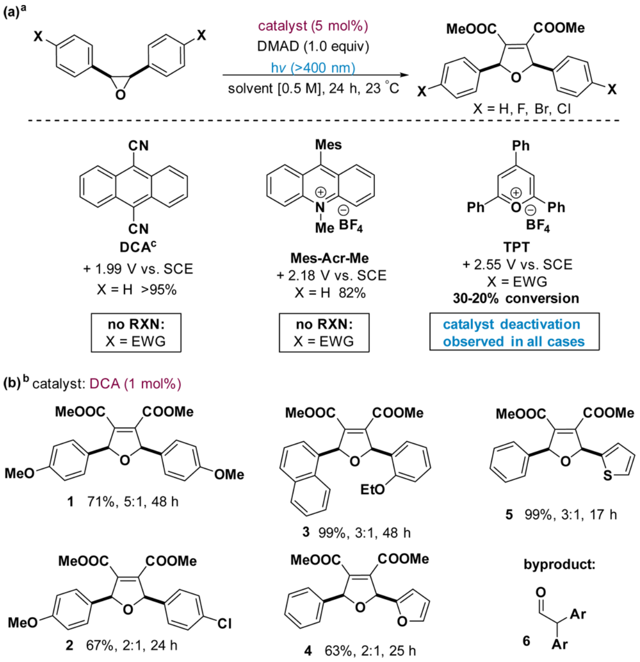

Figure 2. Evaluation of photoredox catalyst for the [3 + 2] dipolar cycloaddition and the scope when using DCA. [a] Standard conditions: 0.05 mmol of catalyst, 0.1 mmol of DMAD, 0.12 mmol of epoxide, acetonitrile (MeCN) 0.5 M. [b] 0.01 mmol of DCA, 1 mmol of DMAD, 1.2 mmol of epoxide, 0.5 M degassed Chloroform ($CHCl_3$). [c] $CHCl_3$ instead of MeCN.

Although TPT has a higher oxidation potential than Mes-Acr-Me, the latter and its derivatives, made popular by Nicewicz and co-workers, have recently received more attention.[11] This is, in part, due to the protective nature of the orthogonal mesityl group, which minimizes undesirable reactivity with exogenous nucleophiles and transient radicals at the acridinium chromophore.[12] This unique feature has allowed a method in which even highly reactive fluoride anions were employed.[13] Unfortunately, TPT is deactivated by homocoupling of its pyranyl form or by nucleophile and radical addition to its pyrylium core, limiting its synthetic use.[14] We considered whether chemical modification of TPT could lead to a more robust catalyst with an oxidation potential suitable for more challenging reactions requiring higher oxidation potentials, such as the carbonyl ylide formation of electron-deficient substrates. TPT is known to possess two independent chromophores, the 4-arylpyrylium moiety which absorbs UV light and the 2,6-diarylpyrylium that absorbs visible light. The latter is responsible for the activity most often associated with TPT mediated photoredox processes. We hypothesized that replacing the 4-aryl moiety with a mesityl group will give TPT a protective environment, while maintaining the photophysical properties attributed to the 2,6-diarylpyrylium chromophore (Figure 3a). If successful, this will allow us to access a catalyst with greater stability and high oxidation potential.

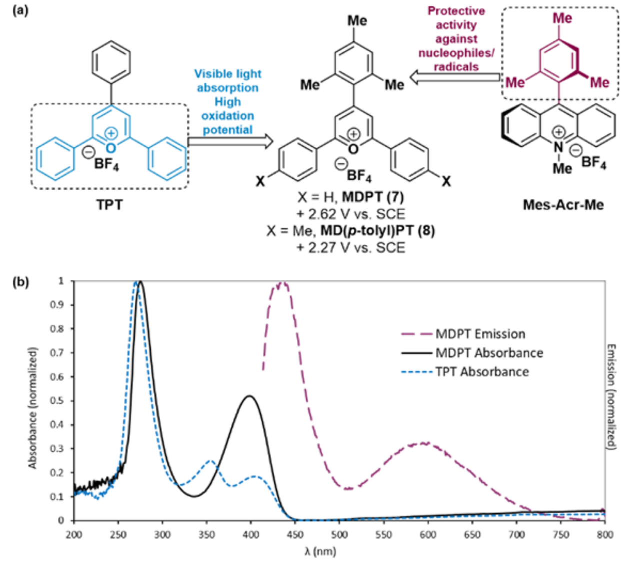

Figure 3. (a) Rationalization for the synthesis of MDPT. (b) Emission and absorbance spectra of MDPT and absorbance spectrum of TPT.

After considerable experimentation, we were able to synthesize the desired 4-mesityl-2,6-diphenylpyrylium tetrafluoroborate (**7**, MDPT). Photophysical analysis of MDPT revealed that it exhibits two well-defined maximums in its absorbance spectra, an overlap peak of the mesityl and benzene groups, and the 2,6-diarylpyrylium chromophore, located at 274 and 399 nm, respectively (Figure 3b). Interestingly, MDPT lacks the 4-arylpyrylium chromophore commonly present in TPT due to restricted rotation about the mesityl pyrylium bond

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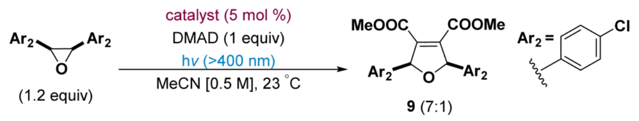
(Figure 3b). More striking is the emission spectrum which features two maximums, the first ascribed as the singlet transition at 438 nm and a broader, yet well-defined, peak at 590 nm (Figure 3b).[15] From these spectroscopic data the singlet excited state energy, at one-half the Stokes shift, is 2.96 V. Furthermore, cyclic voltammetry (CV) experiments were conducted and MDPT was found to have an irreversible reduction peak at $E_{p/2} = -0.34$ V vs SCE in acetonitrile. Taking together this data, with the Gibbs free energy of photoinduced electron transfer equation, we have estimated the singlet excited state redox potential of MDPT to be $E^{s1}_{red} = +2.62$ V vs SCE.[16] These physical attributes make MDPT one of the strongest visible light photoredox oxidants reported to date.[17]

We also synthesized 4-mesityl-2,6-di-*p*-tolylpyrylium tetrafluoroborate (**8**, MD(*p*-tolyl)PT) with the goal of creating a more red-shifted absorbing catalyst.[16] This catalyst exhibits absorbance and emission maximums at 420 and 479 nm, respectively, and its singlet excited state redox potential is $E^{s1}_{red} = +2.27$ V vs SCE. This provides evidence that, like TPT, the electronic properties of the catalyst can be tuned via structural modifications.

The stage was now set for the investigation of the [3 + 2] dipolar cycloaddition with a more electron-deficient system such as 2,3-bis(4-chlorophenyl)oxirane. Simply by switching the solvent to acetonitrile (MeCN) and maintaining the same stoichiometry, MDPT promoted the cycloaddition to give **9** in excellent yields with no apparent photobleaching observed over 24 h (Table 1, entry 1). Under the same conditions, TPT also promoted the cycloaddition, but in low yields (Table 1, entry 2). This result validates our original hypothesis and shows the significant improvement of the catalyst's robustness over TPT. It is important to note that at this stage we cannot be sure which excited state of the catalyst is responsible for the initial SET; however, we are currently conducting detailed photophysical characterization of MDPT to better understand the mechanism.[18]

Table 1. Investigation of the [3 + 2] Dipolar Cycloaddition with an Electron-Deficient Epoxide[a]



entry	catalyst	yield (%)
1	MDPT, 24 h	93[b]
2	TPT, 24 h	11[b]
3	Mes-Acr-Me (5 mol %) or DCA (5 mol %)	0
4	MD(*p*-tolyl)PT, 1 h	>95[b]
5	MD(*p*-tolyl)PT, 1 h (not degassed)	>95[b]
6	no light or no catalyst	0

[a] Standard conditions: 0.1 mmol of DMAD, 0.12 mmol of epoxide, MeCN 0.5 M. [b] Average isolated yield of two reactions.

Under these optimized conditions DCA and Mes-Acr-Me failed to produce the desired product (Table 1, entry 3). We also used MD(*p*-tolyl)PT and found that it promoted the cycloaddition at a significantly faster rate, likely due to its greater molar absorptivity in the optical window of use (Table 1, entry 4). Moreover, no degassing or drying of the MeCN is needed with these catalysts (Table 1, entry 5). Control experiments demonstrated that both light and catalyst are needed to promote the cycloaddition (Table 1, entry 6).

We proceeded to explore the scope of this reaction (Figure 4a) and found that a variety of electron-deficient and -neutral substrates can now undergo the reaction when using MD(*p*-tolyl)PT. Halogenated and alkyl-containing compounds were well tolerated (**9**–**16**). Examples with substitution at the *para* and *ortho* positions reacted much faster than that of the *meta*. We observed no dehalogenation in the crude reaction mixture for any of these substrates. Higher diastereomeric ratios were obtained for *ortho* substituted substrates (**14**–**15**), likely due to enhanced $A^{1,3}$-interaction. It was found that a tetrasubstituted epoxide afforded a single regioisomer (**17**). A nonsymmetric example bearing a trifluoromethyl group was obtained in good yields and selectivity (**18**). Furthermore, a *bis*-halogenated substrate, bearing orthogonal groups appropriate for iterative cross-coupling reactions, afforded dihydrofuran (**19**) in good yield.

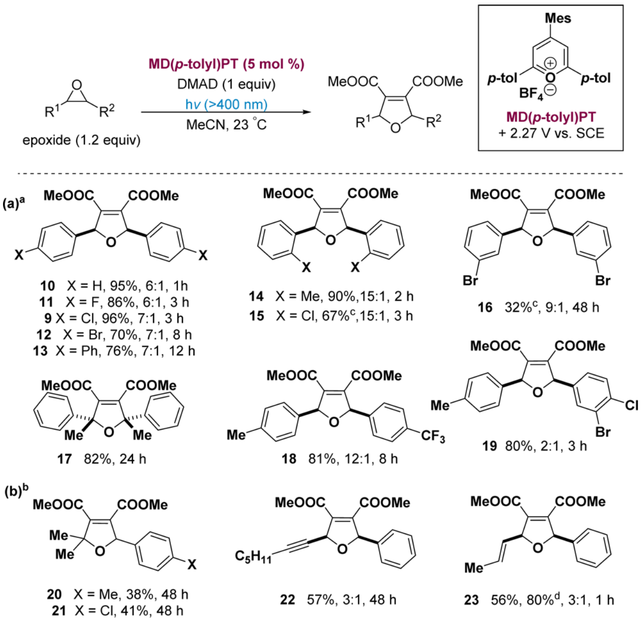


Figure 4. Scope of the [3 + 2] dipolar cycloaddition. [a] 0.005 mmol of MD(*p*-tolyl)PT, 0.1 mmol of DMAD, 0.12 mmol of epoxide, MeCN. [b] 0.05 mmol of MDP(*p*-tolylPT), 1 mmol of DMAD, 1.2 mmol of epoxide, 0.5 M MeCN. [c] 1 mmol scale. [d] 1 mmol of epoxide and 5 mmol of DMAD.

After identifying a complementary method to access carbonyl ylides from both electron-rich and -deficient diaryl epoxides, we began exploring substrates that lacked one aryl substituent, which have not been reported to participate in the reaction. We were excited to observe that epoxides bearing dialkyl and aryl substitution (Figure 4b) proceeded in moderate yields (**20**–**21**). We then proceeded to investigate an alkynyl aryl epoxide. Indeed, it underwent the desired cycloaddition with modest yield and selectivity (**22**). These examples reacted much slower, needing reaction times of 48 h.[19] Even a vinyl aryl epoxide afforded the cycloaddition (**23**) with modest yield and selectivity and reacted much faster than all the previously shown examples. Thus, in an effort to trap the carbonyl ylide faster we made the epoxide the limiting reagent and we were able to obtain the cycloaddition in good yields. Remarkably, no isomerization of the olefin was observed. It is important to note that DCA could not catalyze any of these aforementioned examples. Overall, we found that careful choice of catalyst must be considered when targeting a particular product. When dihydrofuran **1** was irradiated with 5 mol % of MD(*p*-tolyl)PT, major decomposition was observed, providing evidence that the products can be redox active.[20]

In summary, we have significantly expanded the scope of the formation of carbonyl ylides from epoxides. Overcoming current limitations led to the development of powerful organo photoredox catalysts that are robust and possess some of the highest oxidation potentials reported. These pyrylium catalysts could find immediate application in already established methods where more common catalysts such as Mes-Acr-Me failed to produce a single electron transfer.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01222.

> Experimental procedures for synthesis of substrates and catalysts and for photoredox reactions; full characterization data and NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(15) Currently, we do not have sufficient data to assign this transition. We speculate it may be a charge transfer state due to the similarities to Fukuzumi's catalyst.

(16) See Supporting Information for details.

(17) Other organic photoredox catalysts that possess higher oxidation potentials absorb UV light. See ref 2 for a thorough inquiry.

(18) It is possible that the triplet excited state redox potential of MDPT and MD(*p*-tolyl)PT, which would have a longer lifetime, could be oxidizing enough to generate the desired carbonyl ylides.

(19) The epoxide and DMAD could be detected in the crude material after the 48 h irradiation period.

(20) ^{1}H NMR analysis of the crude material showed peaks corresponding to DMAD and byproduct **10**.