Mechanism of the Photorelease of Alcohols from the 9-Phenyl-9-tritylone Protecting Group

ARTICLE

Mechanism of the Photorelease of Alcohols from the 9-Phenyl-9-tritylone Protecting Group

Andrea N. Zeppuhar, Kevin Hill-Byrne, and Daniel E. Falvey[*]

The 9-phenyl-9-tritylone photoremovable protecting group was examined using both photoproduct analysis and laser flash photolysis in order to determine the details of its mechanism of alcohol release. It is shown that formation of the tritylone anion radical is required for alcohol release. Attempts to trigger release via intramolecular photoinduced electron transfer were unsuccessful due to rapid back electron transfer reactions of the triplet diradical anion.

1. Introduction

Photoreleasable protecting groups (PPGs) provide means for unmasking stable molecules under mild conditions and with a high degree of spatiotemporal control.[1] Successful application of PPG strategies in total synthesis,[2] drug release,[3, 4] optogenetics,[5, 6] photolithography,[7] photoimaging,[8] and other areas has inspired efforts at designing new PPGs with expanded capabilities.

There have been many developments in the field of PPGs when it comes to the photorelease of good leaving groups, such as carboxylates and sulfonates. However, with less labile leaving groups such as alcohols, there are fewer examples. Some approaches to alcohol release include intramolecular cyclization of silyl[9] and cinnamate[10] protecting groups, lactonization employed with a quinone trimethyl lock,[11] photoenolization,[12] and the use of carbamate esters that rely on decarboxylation to effect alcohol release.[13]

A recent report[14] described the 9-phenyl-9-tritylone (PTO) group as a PPG capable of clean and efficient release of primary and secondary alcohols through a photoinduced electron transfer (PET) mechanism. PET is advantageous because it allows for decoupling of the light absorbing step from release which allows for optimization of the chromophore without changing its mechanism. Excitation of PTO ethers with UV light in the presence of strong ground state electron donors (e.g. triethylamine) could effect release of alcohols in good yields, with polar solvents (methanol, acetonitrile) providing better yields than nonpolar solvents (benzene). Alternatively, visible light photolysis of a strong excited state donor (e.g. Ir(ppy)$_3$) in the presence of PTO ethers also caused release. In addition, preliminary laser flash photolysis (LFP) studies of these reactions confirmed that photoinduced electron transfer from the donor to the PTO group was responsible for release (Scheme 1). However, the latter experiments show that both the PTO anion radical **2**, as well as its conjugate acid, ketyl radical **3**, form under the

Scheme 1. Previously proposed mechanism for the photorelease of alcohols under PET conditions
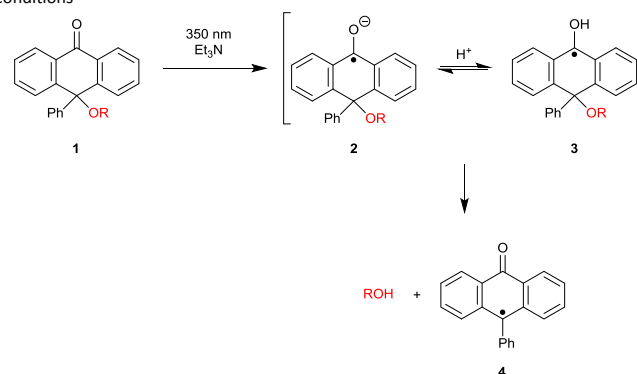
standard photorelease conditions.

However, less clear was if **2**, **3**, or both, lead to substrate release. The possibility that **3** could lead directly to substrate release was intriguing as it forms readily in simple solvents with modestly reactive C–H bonds (e.g. methanol, 1,4-dioxane). Such a pathway could allow for the application of PTO release without an additional electron donor, and thus greatly expand its applicability. In fact, some early control experiments showed photoconversion of the PTO-ethers was occurring in the absence of strong electron donors.

The work herein describes a series of mechanistic and spectroscopic studies designed to support further development of the PTO group and similar PPGs. Specifically, the behavior of PTO-ethers will be probed under direct photolysis conditions, i.e. in the absence of an electron donor, in order to determine the details of the release mechanism. These studies will show that (a) while **3** forms readily, it is **2** that is necessary for the desired C—O bond scission; (b) the C—O bond scission is relatively slow, having a time constant of approximately 1 ms; (c) the PTO group can be modified in a way to allow intramolecular electron transfer however, a more rapid bond scission step is needed to compete with back electron transfer.

Department of Chemistry and Biochemistry, University of Maryland, College Park, MD 20742, USA
falvey@umd.edu

2. Experimental

2.1 General Procedures

UV-Vis spectra were collected on a Shimadzu UV-1800 spectrometer using UVProbe 2.43 software. Samples were scanned using a fast scanning speed and a sampling interval of 1.0 nm. Each sample was blanked with the solvent of choice used in solvating the compound. All ^{1}H NMR were obtained on a Bruker 400 MHz instrument. Mass spectrometry experiments were performed on a JEOL AccuTOF-CS-ESI-TOF. Kinetic growth and decay curves were fitted using MATLAB software.

2.2 Gas Chromatography Analysis

Gas chromatography analysis was done using a Shimadzu GC-17A, containing a RTX-5 stationary phase column (length = 15 m, inner diameter (i.d.) = 0.25 mm, film thickness = 0.25 μm), equipped with a FID detection system, and using the following method specifications: column temperature = 60°C, injection temperature = 280°C, and detector temperature = 300°C, with a temperature/pressure profile for injection of: 67 kPa, 3.0 minutes, 3.9 mL/minute, 98 kPa, 9.0 minutes, column of: 60°C, 3 minutes, 30 mL/minute, 300°C, 9.0 minutes, injector pressure of 60 kPa, total flow of 31 mL/min., column flow of 1.45 mL/min., and a linear velocity of 39.1 cm/s. For yield determination, a calibration curve was generated (see SI).

2.3 Steady-State Photolysis

Benzyl ether was photolyzed in an RPR-600 Rayonet reactor (8-bulb, 36 watt, ~33°C operating temperature, 350 nm max output) supplied by Southern New England Ultraviolet. 1 mL of a 9 mM photolysis solution was placed in a quartz cuvette and purged with nitrogen in both the solution (minimum of 15 minutes) and the headspace (minimum of 3 minutes). The samples were irradiated at 350 nm for up to 3 hours. Upon completion of photolysis time, 60 μL of the sample was transferred into a GC vial and then acidified by adding 10 μL of 0.1M acetic acid. 2 μL of this solution was injected into the GC for analysis.

2.4 Laser Flash Photolysis

Laser flash photolysis studies were conducted using a Nd:YAG laser (355 nm output) supplied by Continuum with pulses 4-6 ns in duration as the excitation source. The probe beam used was a 350 W Xe arc lamp that passed through a monochromator to a PMT detector. Solutions were purged with N_2, both in the solution (minimum of 15 minutes) and the headspace (minimum of 3 minutes). Samples were prepared such that the absorption at 355 nm was between 1.0 and 2.0. When obtaining a full spectrum, a fresh supply of the reaction mixture into the cuvette was attained by setting up a standard N_2 purged flow cell connecting the cuvette to the stock solution via a double-headed needle. The photolysate was then drained from the cuvette into a waste vessel. This setup prevents accumulation of photoproducts and avoids the depletion of the substrate during the experiment.

2.5 Synthesis

Synthetic procedures as well as characterization data for new compounds can be found in the SI.

3. Results and Discussion

As outlined in Scheme 2, the PTO-ether chosen for these studies was benzyl ether **5** which, upon photolysis, releases benzyl alcohol **6**. This ether was chosen due to its ease of synthesis as well as ease of product analysis.

Scheme 2. Direct photolysis of benzyl ether **5** to generate benzyl alcohol **6**
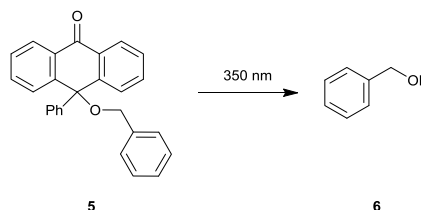
In order to understand the role of solvent in the release mechanism, **5** was photolyzed at 350 nm in various solvents under direct photolysis conditions. The depletion of **5** (Figure 1, top) as well as formation of **6** (Figure 1, bottom) was monitored by gas chromatography.
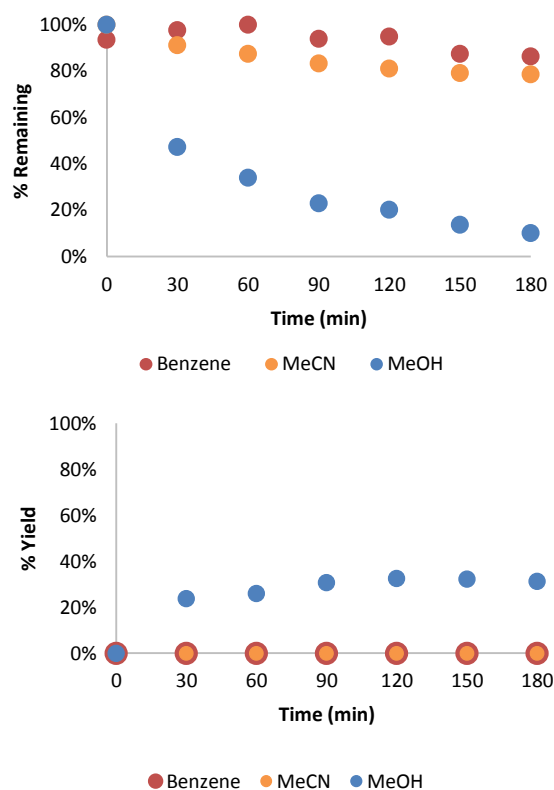

Figure 1. Top: Monitoring conversion of **5** during direct photolysis in various solvents. Bottom: Monitoring yield of **6** during direct photolysis in various solvents

In benzene and acetonitrile there was very little depletion of **5** and no formation of **6**. This is due to these solvents being

poor hydrogen atom donors, which is supported by the bond dissociation energies (BDE) for hydrogen atom abstraction. The C—H bond BDEs for these solvents are 112.9 kcal/mol and 97.0 kcal/mol, respectively.[15] The BDE of benzene is too large and benzene is considered inert as a hydrogen atom donor. While acetonitrile is more thermodynamically favored for hydrogen atom transfer, it is not kinetically favored due to the electron withdrawing cyano group. This electron deficient C—H bond does not allow for a rapid reaction with the excited state triplet. Therefore, in these solvents, the excited state triplet is formed which returns to ground state without releasing the alcohol. However, when a better hydrogen atom donating solvent, such as methanol, is used, depletion of **1** is observed. Methanol has a BDE of 96.1 kcal/mol and has a more electron rich C—H bond allowing for a more kinetically favorable hydrogen atom abstraction. In this case, there is some formation of benzyl alcohol observed but in poor yields. The belief is that, when in the presence of a good hydrogen atom donor, the excited state triplet can abstract a hydrogen atom to form the ketyl radical **3**. From **3**, chemistry can begin to occur. Since the yield of **5** is poor, it is believed that release from **3** is a minor pathway and depletion of the **5** is due to other nonproductive pathways.

Formation of these intermediates is further confirmed by laser flash photolysis (LFP), which is a technique used to identify short-lived intermediates. Figure 2 (top) displays the transient absorption spectrum resulting from 355 nm pulsed photolysis of **5** in benzene. A short-lived peak with λ_{max} = 540 nm forms immediately after the pulse. Previous studies[14] have assigned this peak to be the triplet state of PTO due to its resemblance to the triplet state of the structurally similar benzophenone chromophore.[16] The band at 440 nm that persists beyond the triplet lifetime is attributed to the tritylonyl radical **4** that would form as a result of homolytic cleavage of the C—O bond of **5**. Additionally, this band displays an increase in decay rate when exposed to oxygen which is also consistent with the formation of a tritylonyl radical. It is believed that this bond cleavage from the triplet state, while not very efficient, does explain the small amount of conversion of **5** observed in benzene. However, in the absence of any radical scavengers, the radicals that result from homolytic cleavage simply recombine. Figure 2 (bottom) displays the transient absorption spectrum resulting from 355 nm pulsed photolysis of **5** in methanol. This spectrum displays a sharp peak with λ_{max} = 530 nm which has a half-life that exceeds 350 µs. Previous work[14] has assigned this peak to the PTO ketyl radical **3**. This is in agreement with the previous data that indicates **3** is necessary for chemistry to occur as depletion of **5** was observed in methanol but not in benzene.

These results led to the hypothesis that alcohol release occurs through the anion radical intermediate **2**. In order to confirm this, studies were conducted in methanol with the addition of a base. In methanol **3** would form and then would be deprotonated by the base in order to form **2**. It is from here that C—O bond scission is expected to occur and release the alcohol. When using a strong base, such as hydroxide, alcohol release was observed. As shown in Table 1, as the concentration of hydroxide increases from 0-1 mM, the yield of alcohol also increases. However, for reasons that are not yet clear, when the base concentration is greater than 1.5 mM the yields start to drop. It is important to note that the yield of alcohol under direct photolysis conditions is significantly less than those reported under PET conditions[14] indicating that, from a practical standpoint, direct photolysis is not the most beneficial route for alcohol deprotection.
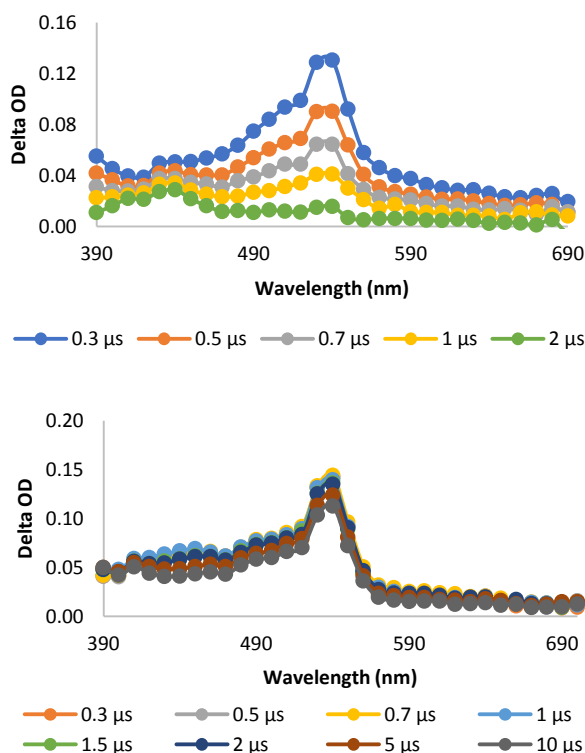
Table 1. Yields of **6** in the 3-hour photolysis at 350 nm with varying concentrations of sodium hydroxide. Starting ether concentration is 9 mM

[NaOH] (mM)	% Yield Alcohol[a, b]
0.0	43.8 ± 0.96
0.1	68.4 ± 8.46
0.5	74.5 ± 6.51
1.0	77.5 ± 17.74
1.5	55.9 ± 11.73
2.0	46.7 ± 2.22
2.5	47.5 ± 2.81

[a]Error bars are the result of triplicate experiments
[b]Yields are corrected to reflect amount of starting material that converted

Figure 2. Transient absorption spectra from 355 nm pulsed photolysis of **5**, Top: in benzene, Bottom: in 3:1 methanol: 1,4-dioxane

To test the hypothesis that complete deprotonation of **3** is required for release, experiments were also performed using a weaker base. For this, pyridine was chosen since it can act as a base but it is a poor electron donor meaning it is not likely to undergo PET. Under these conditions, depletion of **5** was observed but there was no release of alcohol. Using previous estimates on similar radicals, we estimate that ketyl radical **3** has a pKa ≈ 9[17] meaning pyridine is not a strong enough base for deprotonation.

Further confirmation that **2** is formed when adding hydroxide is provided by LFP experiments. Upon addition of sodium hydroxide, a change in the spectrum is observed as shown in Figure 3. In the 550-650 nm region, a new broad band grows in. Previous work[14] has assigned this band to be anion radical **2**. Formation of **2** is due to deprotonation of **3** by sodium hydroxide. The isosbestic point at 530 nm is due to simultaneous formation of **2** as **3** is decaying.
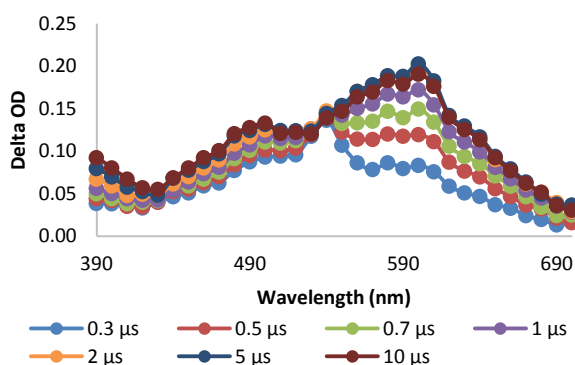

Figure 3. Transient absorption spectrum obtained from 355 nm pulsed photolysis of **5** in 3:1 methanol: 1,4-dioxane with the addition of 1 mM sodium hydroxide

Upon observing that the yields of alcohol were improved with increasing concentrations of base, LFP studies were performed to determine the effect of base concentration on the formation of **2**. As shown in Figure 4, as the concentration of base is increased, the rate at which **2** forms also increases. Using these data, a pseudo-first order analysis was done in order to determine the second-order rate constant for proton transfer between the **3** and base. The rate constant was determined to be 1.84×10^9 M^{-1}s^{-1}.
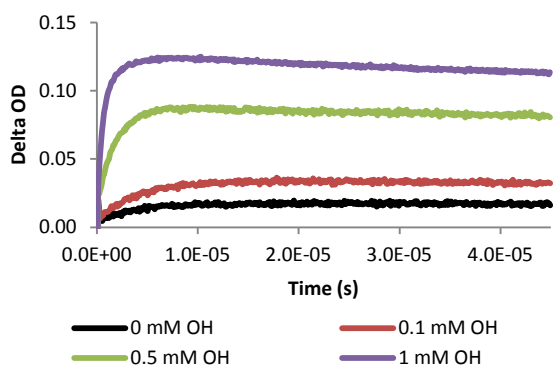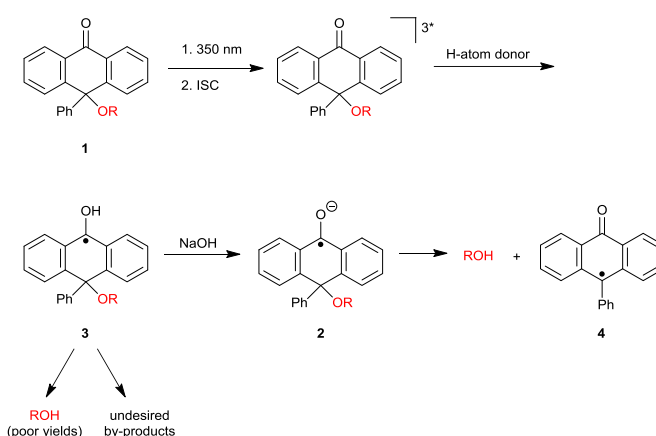

Figure 4. Growth of anion radical **2** at 620 nm with changing concentration of hydroxide. Starting ether concentration is 9 mM

Scheme 3. Proposed mechanism for the photorelease of alcohols under direct photolysis conditions

With these data, the mechanism of photorelease under direct conditions can be proposed, as shown in Scheme 3. Upon excitation with 350 nm light, the PTO-ether is excited to its singlet state. Because benzophenone forms triplet rapidly and with unit quantum yield[18], we assume the PTO-ethers behave in a similar way and that the observed photochemistry occurs exclusively from the triplet state. In the presence of a good hydrogen atom donor, the triplet state abstracts a hydrogen atom to form the ketyl radical **3**. From **3**, some alcohol is released but in poor yields along with a complex mixture of other by-products, the most likely being various isomers formed from dimerization of **3**. Similar products have been observed in systems where the structurally similar benzophenone ketyl radical is formed.[19] When **3** is generated in the presence of a base, it is deprotonated to form the anion radical **2** and it is from **2** that C—O bond scission occurs to cleanly release the alcohol. Previous studies[14] have demonstrated that the alcohol is released as an anion and the PTO chromophore is left behind as radical **4** which abstracts a hydrogen atom or combines with oxygen. The absorption of **2** can be fitted to first-order decay, and from that we derive a lifetime of ca. 1-2 ms. This is near the upper limit of lifetimes that can be accurately determined with our current LFP setup as mixing of irradiated solution with dark areas is also occurring on this timescale.

Knowing that release occurs through the anion radical, attempts were made to improve the PTO group. Modifications were made in an effort to have intramolecular electron transfer thus eliminating the need for an external electron donor. As shown in Scheme 4, the phenyl group in **1** was replaced with a 4-phenol group to make compound **7**. We anticipated that, upon deprotonation, the phenoxide anion would donate an electron to the excited tritylone moiety to

Scheme 4. Proposed reaction for intramolecular electron transfer for alcohol release
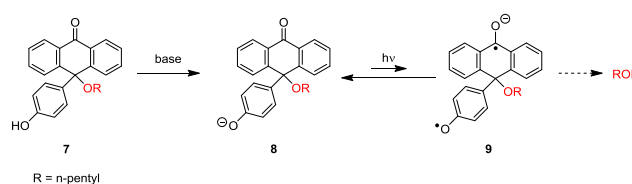
form the anion diradical **9**, which would subsequently release alcohol.

As shown in Figure 5, deprotonation of the pentyl ether derivative of **7** leads to a new absorption band with a maximum at 362 nm and tail extending out to nearly 500 nm. This new high wavelength absorption is not present in either the simple tritylone group or the isolated phenoxide anion (λ_{max} at 290 nm, see SI) and is therefore attributed to charge transfer absorption from the phenoxide group to the tritylone moiety.
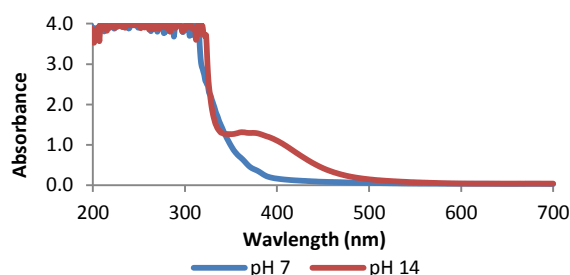

Figure 5. UV-Vis spectrum of **7** in acetonitrile

Unfortunately, extended photolysis (20 hrs) in basic acetonitrile of the pentyl ether derivative of **7** at 350 nm does not release 1-pentanol to any appreciable extent. Apparently, back electron transfer to restore the ground state occurs more rapidly than alcohol release. This can be further confirmed by LFP. As displayed in Figure 6, LFP of **7** in basic acetonitrile, provides two transient absorption bands, one at 420 nm and the other at 510 nm. These signals can be tentatively assigned to the triplet anion diradical **9**.
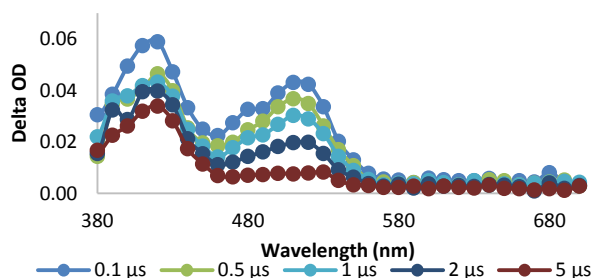

Figure 6. Transient absorption spectrum from 355 nm pulsed photolysis of **7** in basic acetonitrile

This assignment is made on the basis of the following considerations. First, prolonged photolysis of **6** provides little or no decomposition. Thus, the transient species could not be a radical or ionic fragment of **7**. Second, the transient absorption bands from **7** differ in both position and shape from the simple tritylone-localized triplet state derived from **5** shown in Figure 2 (top). Simple, localized tritylone ketyl radical and anion radical are also excluded due to lack of resemblance to the corresponding spectra derived from **5** (bottom of Figure 2 and Figure 3, respectively) Third, the observation of the charge transfer absorption in the steady-state UV-Vis spectrum (Figure 5) indicates **9** forms directly upon light absorption. Finally, we note that the signal at 510 nm is quenched by O_2

leaving a longer-lived signal at 420 nm. The latter is characteristic of an isolated phenoxy radical which has an absorption at ca. 400 nm.[20] The 510 nm transient species is further assigned to the triplet diradical due its relatively long lifetime of 2.5 μs (in the absence of O_2). This long lifetime is unusual for a covalently linked diradical species. Additional characterization through computational modeling and ultrafast spectroscopy will be undertaken in due course.

4. Conclusions

The above experiments provide further insight into the mechanism of alcohol photorelease from PTO-ethers. LFP and product analysis studies have confirmed that while the ketyl radical intermediate **3** is formed during photolysis, it is from the anion radical **2** that C—O bond scission occurs. However, under these conditions, alcohol release is relatively slow, on the order of ca. 1 ms. In an effort to eliminate the need for an external electron donor, modifications were made to the PTO-ether in an effort to allow for intramolecular electron donation. Unfortunately, even with extended photolysis, this derivative did not demonstrate efficient alcohol release likely due to back electron transfer being more rapid than alcohol release.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Notes and references

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A mechanistic investigation of the 9-phenyl-9-tritylone photoremovable protecting group for alcohols revealed that the anion radical is the key intermediate required for clean deprotection.