

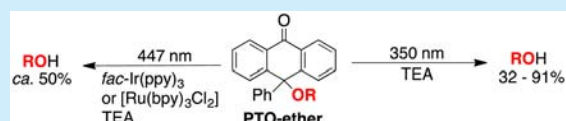
## Uncaging Alcohols Using UV or Visible Light Photoinduced Electron Transfer to 9-Phenyl-9-tritylone Ethers

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## Supporting Information

**ABSTRACT:** The clean and efficient photorelease of primary and secondary alcohols is reported from the deprotection of a new photoremovable protecting group, the 9-phenyltritylone (PTO) group. Deprotection is initiated by 350 nm excitation of the PTO chromophore in the presence of triethylamine or using 447 nm light in the presence of a visible light absorbing photocatalyst and triethylamine. Laser flash photolysis results are reported in support of a proposed deprotection mechanism for the release of alcohols on a ca. 20  $\mu$ s time scale.



Interest in spatiotemporal control of molecular concentrations has motivated the development of photoremovable protecting groups (PPGs).<sup>1</sup> Photorelease strategies have found applications in several areas: synthesis of complex molecules,<sup>2</sup> photolithography,<sup>3</sup> time-resolved studies of enzymatic and cellular processes,<sup>4</sup> controlled release of drugs,<sup>5</sup> optogenetics,<sup>6</sup> photoimaging,<sup>7</sup> and the development of light driven self-assembly of supramolecular structures.<sup>8,20b</sup> Recent developments include the coumaryl group,<sup>9</sup> BODIPY derivatives,<sup>10</sup> phenacyl groups,<sup>11</sup> fluorescein analogues,<sup>12</sup> and meta-substituted arylmethyl groups.<sup>13</sup>

All of these PPGs provide excellent options for the protection and photorelease of relatively good leaving groups such as phosphates, sulfonates, carboxylates, etc. In the case of less labile leaving groups such as alcohols, there are fewer options. One approach is to protect the OH group as a mixed carbonate ester and rely on the spontaneous decarboxylation of the mono-carbonic ester to release the alcohol.<sup>9a-c</sup> Other avenues for alcohol release include photoisomerization and intramolecular cyclization of silyl<sup>14a</sup> and cinnamate<sup>14b</sup> derivatives, photoenolization,<sup>15</sup> naphthylenyl derivatives,<sup>16</sup> and the direct photolysis of trityl ethers.<sup>17</sup>

While photorelease of alcohols can be effected using ultraviolet (UV) light, there is particular interest in the development of PPGs capable of using visible or near-infrared light. High wavelengths are particularly valuable in situations where the OH group is part of a structure that contains other chromophores. For example, 55 (36.7%) of the top 150 small molecule pharmaceutical products (2012 retail sales)<sup>18</sup> contain primary or secondary OH groups. In contrast, the CO<sub>2</sub>H group, which has dominated PPG development, is only observed in 16.7% of that group. Additionally, of the 55 primary and secondary OH containing drugs, 49 had aromatic rings or  $\alpha,\beta$ -unsaturated carbonyl moieties capable of absorbing UV. Thus, the development of new PPGs for alcohols utilizing high wavelength light is an important endeavor.

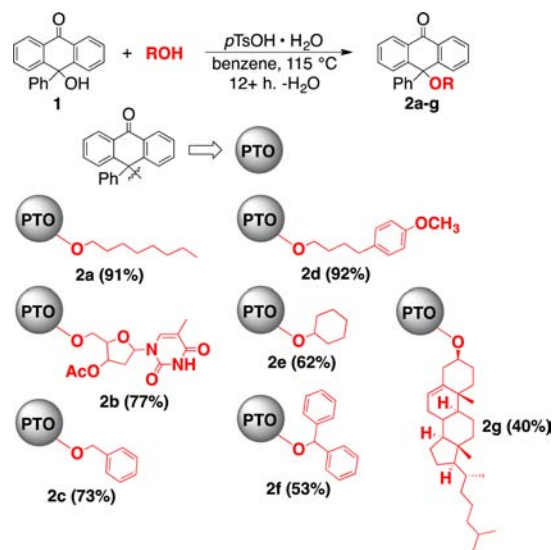
Herein, is described the 9-phenyl-9-tritylone (PTO) group, which releases alcohols via photoinduced electron transfer (PET). PET systems provide a means for decoupling the light-

absorbing step from the bond-breaking chemistry allowing for broad spectral response (UV and visible light). Successful examples include phenacyl<sup>19</sup> and NAP groups,<sup>20</sup> triplet sensitized nitrophenyl groups,<sup>21</sup> and phenethyl alcohol systems.<sup>22</sup> This report describes the simple release of alcohols in good yields under 350 or 447 nm light. Laser flash photolysis and product analysis experiments help identify intermediates and products driving the mechanism proposed for the photochemical deprotection of alcohols using the PTO group.

$$\Delta G_{ET} \approx 23.06(E_{ox} - E_{red}) - E_{00} - S \quad (1)$$

The PTO-ethers, shown in Scheme 1, were prepared through acid-catalyzed condensation of 9-hydroxy-9-phenyltritylone **1** with the corresponding alcohols. As with previous reports, we

## Scheme 1. Synthesis and Scope of PTO-Ethers



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find that primary alcohols are most readily protected in the best yields, whereas secondary alcohols are less reactive and provide lower yields of PTO-ether. We, and previous investigators,<sup>23</sup> were unsuccessful in attempts to protect tertiary alcohols.

While the PTO group has been previously described as a protecting group for alcohols,<sup>24</sup> the behavior of the PTO-ethers toward PET has not been reported. Using previously reported<sup>25</sup> reduction potentials for PTO-ethers ( $E_{\text{red}} = -1.30$  to  $1.36$  V vs Ag/AgCl), and assuming PTO has the same triplet state energy as benzophenone,<sup>26</sup> eq 1 predicts that PET from triethylamine (TEA,  $E_{\text{ox}} = +1.15$  V vs SCE)<sup>27</sup> to the PTO-ethers is exergonic by ca. 13 kcal/mol.<sup>28</sup> It was further anticipated that the resulting PTO radical anion would undergo C–O bond-breaking leading to the deprotection and recovery of the alcohol. The photolysis experiments summarized in Table 1 confirm this hypothesis.

**Table 1. Yield of Released Alcohols Following 240 min of 350 nm Irradiation As Analyzed by GC**

ether	[ether], mM	[TEA], mM	solvent(s) <sup>b</sup>	% yield <sup>c</sup>
2a	11.4	21.5	MeOH	91.0 ± 1.82
2b <sup>a</sup>	2.80	5.38	MeOH	82.3 ± 1.56
2c	8.99	26.9	MeOH/dioxane	92.2 ± 1.59
2d	11.8	21.5	MeOH/dioxane	31.6 ± 0.63
2e	11.9	21.5	MeOH/dioxane	82.3 ± 3.63
2f	7.24	17.9	MeOH/dioxane	63.7 ± 1.68
2g	5.75	17.9	MeOH/dioxane	77.4 ± 5.12

<sup>a</sup>25 min photolysis; analyzed by HPLC. <sup>b</sup>1,4-Dioxane (25% v/v except ether 2d where 12.5% was used) added to help solubilize ether at concentrations used. <sup>c</sup>Photolysis reactions were performed in triplicate.

Photolysis of ethers 2a–g at 350 nm in the presence of TEA cleanly releases the alcohol. 3'-O-Acetylthymidine, benzyl alcohol, cyclohexanol, benzhydrol, and cholesterol were all released in satisfactory yields. A potential limitation of this process is illustrated by the low yield of 4-(4'-methoxyphenyl)-1-butanol from 2d. In this case the readily oxidized anisyl group can act as an electron donor, competing with TEA for reduction of the triplet state PTO group. Apparently, undesired products resulting from intramolecular PET limit the yield from 2d under UV conditions. However, when visible light is used (see below), the yield increases to 66%. This supports the notion of intramolecular PET acting as a nonproductive pathway.

To understand how solvent and donors affect the overall deprotection process, ether 2a was photolyzed under various conditions (Table 2). These experiments were carried out at modest conversions (ca. 70% under standard conditions) so that small changes in yields or photolysis rates would be apparent. Yields of 1-octanol are normalized to entry 1 conditions which facilitated the best deprotection results.

The best yields are obtained in polar solvents (MeOH, MeCN), while increasing the donor concentration above 15 mM had no significant effect on the yield or efficiency. Two donors, *N,N*-dimethylaniline (DMA) and *N,N,N*-triphenylamine (TPA), provided lower yields of the alcohol. This can be attributed to competing light absorption in the 320–380 nm range by the donor (see Supporting Information, SI). In principle, excited singlet amines should be able to donate electrons to ground state PTO. However, this process is expected to be of lower efficiency due to the short lifetimes of the amine singlet states. A bridgehead amine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), was examined to determine the importance of secondary proton

**Table 2. Relative Yields of 1-Octanol in the 60 min Photolysis at 350 nm of 2a and a Donor in Various Solvents**

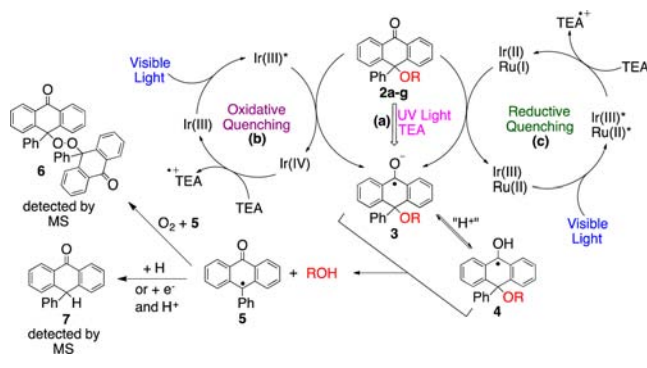
[2a], mM	donor	[donor], mM	solvent	relative yield <sup>c</sup>
11.3	TEA	28.7	MeOH	1.00 ± 1.00
11.3	TEA	14.3	MeOH	0.98 ± 0.65
11.3	TEA	5.65	MeOH	0.84 ± 1.80
10.4 <sup>a</sup>	TEA	27.0	MeOH	0.38 ± 0.21
10.4 <sup>b</sup>	DMA	28.4	MeOH	0.40 ± 0.27
10.4	DBU	29.5	MeOH	0.64 ± 1.08
10.4	anisole	27.3	MeOH	0.79 ± 2.19
10.8	TEA	28.7	1,4-dioxane	0.63 ± 0.55
11.0	TPA	28.7	1,4-dioxane	0.37 ± 0.76
11.8	TEA	28.7	MeCN	0.98 ± 3.26
10.9	TEA	28.7	benzene	0.52 ± 0.53
10.0	TEA	32.6	<i>tert</i> -BuOH	0.59 ± 0.46

<sup>a</sup>Purged with O<sub>2</sub>. <sup>b</sup>Average of two runs; peaks of donor and ROH not well resolved. <sup>c</sup>Photolysis reactions were performed in triplicate.

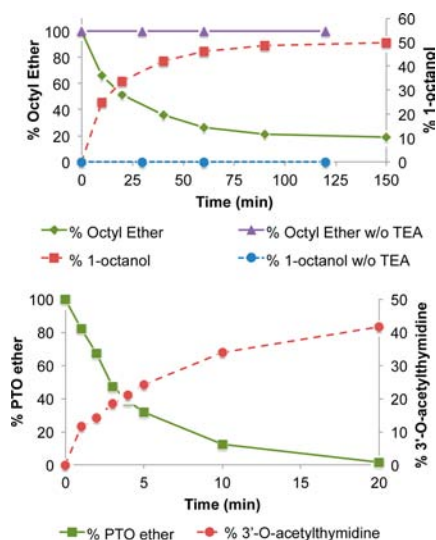
transfers from the oxidized donor. The bicyclic structure of DBU inhibits proton transfer from DBU<sup>+</sup>. Indeed DBU provides a lower yield, suggesting that such proton transfers play a role in the release mechanism. Finally, product yields can be inhibited using a triplet quencher (ground state O<sub>2</sub>). We attribute this decrease in photochemical efficiency to triplet energy transfer from excited state PTO competing with the desired PET pathway.

These results above imply that formation of the PTO anion radical 3 is sufficient for the desired C–O bond scission. Thus, it should be possible to initiate the reaction using visible light absorbing sensitizers as outlined in Scheme 2. In this case, rather

**Scheme 2. Proposed Mechanism for the Release of Alcohols under (a) Direct UV Irradiation, (b) Oxidative, and (c) Reductive Visible Light Irradiation**



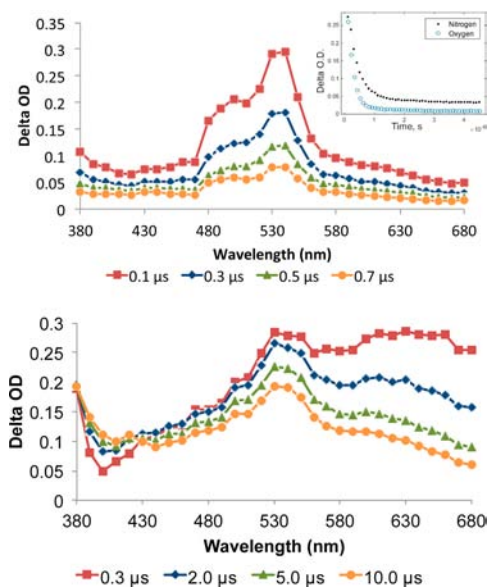
than using UV light to excite the PTO group, two photocatalysts, *fac*-(tris(2,2'-phenylpyridine))iridium(III) (*fac*-Ir(ppy)<sub>3</sub>) and tris(bipyridine)ruthenium(II) chloride ([Ru(bpy)<sub>3</sub>]Cl<sub>2</sub>), were excited using visible light (CW diode laser, 1 W, 447 nm). As indicated in Figure 1, with added TEA both photocatalysts trigger photorelease of 2a and 2b with a ca. 50% yield of alcohol. Release occurs through PET from TEA to the photocatalysts generating either *fac*-Ir(ppy)<sub>3</sub><sup>2+</sup> or [Ru(bpy)<sub>3</sub>]Cl<sub>2</sub><sup>+</sup>. Both species are strong reducing agents ( $E_{\text{red}} = -2.19$  V<sup>29</sup> and  $-1.33$  V<sup>30</sup> vs SCE respectively) that are able to reduce the PTO group. Using [Ru(bpy)<sub>3</sub>]Cl<sub>2</sub> in comparison to *fac*-Ir(ppy)<sub>3</sub> provided the ability to monitor the photocatalyst during the photolysis reaction due to its characteristic absorption band at 450 nm. Over the course of the reaction a decrease in this band could be observed (see SI)



**Figure 1.** Photolysis of octyl ether **2a** ( $\sim 10$  mM), TEA ( $\sim 93$  mM), and *fac*-Ir(ppy)<sub>3</sub> ( $\sim 200$   $\mu$ M) (top) and photolysis of **2b** (0.832 mM), TEA (0.108 mM), and [Ru(bpy)<sub>3</sub>]Cl<sub>2</sub> (2.11 mM) (bottom). Both photolyses done using a 447 nm 1 W laser.

suggesting degradation of photocatalyst as a reason why moderate yields of alcohol are obtained under the visible light conditions stated above.

Laser flash photolysis (LFP) experiments were conducted on ether **2c** to identify intermediates in the reaction. Figure 2 shows



**Figure 2.** Transient absorption spectrum of benzyl ether **2c** in benzene with decay profile monitored at 530 nm under N<sub>2</sub> and O<sub>2</sub> (top) and MeCN with TEA under N<sub>2</sub> (bottom).

transient spectra obtained at various times following 355 nm pulsed laser excitation (355 nm, 10 mJ, 7 ns) of **2c** in benzene, a solvent presumed to be inert to H atom transfer reactions. Under these conditions a short-lived band with  $\lambda_{\text{max}} = 540$  nm appears immediately following the nanosecond laser pulse. This species decays in a first-order manner with a rate constant of  $2.63 \times 10^6$  s<sup>-1</sup>. This signal is quenched by O<sub>2</sub>, with the decay rate constant increasing to  $4.87 \times 10^6$  s<sup>-1</sup> in an air-equilibrated sample. The transient species observed under these conditions is similar to the

triplet state of the benzophenone chromophore.<sup>31</sup> On the basis of these observations, this species shown in the top of Figure 2 is assigned to the triplet state of PTO.

When an electron donor (TEA) is added, two new transient species are formed. Figure 2 shows spectra from LFP of **2c** in the presence of TEA in CH<sub>3</sub>CN. Immediately following the laser pulse, two features appear: a broad band with an indistinct peak near 620 nm and a sharper feature at 530 nm. The former decays rapidly, leaving a longer-lived transient with a maximum at ca. 530 nm. The signal at 620 nm decays in a biexponential manner having a rapid phase rate constant of  $4.03 \times 10^5$  s<sup>-1</sup> and a slower phase of  $4.75 \times 10^4$  s<sup>-1</sup>. This behavior is very similar to what has been observed when benzophenone is excited in the presence of amine donors.<sup>32</sup> In that case the anion radical, which absorbs in the 600–700 nm region, decays via protonation to form the neutral ketyl radical, which absorbs at ca. 530 nm. On the basis of that precedent, we attribute the 620 nm peak to the PTO anion radical **3** and the 530 nm peak to the ketyl radical **4**. While the 530 nm signal overlaps significantly with the signal assigned to the triplet state, the two species can be distinguished on the basis of their different lifetimes. Quenching of the signals assigned to **3** and **4** by O<sub>2</sub> provides further support for these assignments.

Following the decay of **4** (530 nm) additional transient absorptions in the 370–420 nm and 470–570 nm region are seen (see SI). These persist, without detectable decay for >0.5 ms following the laser pulse. Such long-lived signals are consistent with what would be expected for the highly conjugated tritylonyl radical **5**. While additional work will be done to verify the formation of **5**, further evidence is provided by mass spectrometry. Aerobic photolysis leads to an M + 1 peak corresponding to peroxide **6**. Alternatively, anaerobic photolysis generates an M + 1 peak consistent with reduction product **7**.

The above experiments demonstrate clean and rapid photo-release of alcohols from photolysis of PTO-ethers under electron transfer conditions. These conditions can be realized through UV (350 nm) excitation of the PPG chromophore in the presence of electron donors or through mediated electron transfer using visible light (447 nm). LFP and product analysis studies present a picture consistent with the mechanisms shown in Scheme 2. Under direct UV irradiation, the triplet PTO chromophore abstracts an electron from the TEA donor generating **3**. Subsequent proton transfer generates the ketyl species **4**. The latter releases alcohol on a 20  $\mu$ s time scale generating the radical **5**. Presumably under visible light conditions, the same intermediates can be formed. However, the electron source for the formation of anion radical **3** in these cases is reduced *fac*-Ir(ppy)<sub>3</sub> and [Ru(bpy)<sub>3</sub>]Cl<sub>2</sub>. Several details of the mechanism such as (1) whether the C–O bond scission releases an alkoxide anion or whether it is coupled to a proton transfer and (2) whether **4** releases the alcohol directly or via **5** are not clearly established with current data. Future efforts aim to elucidate the details of the release mechanism, verify relevant intermediates, optimize the chemical yields, and explore applications of this protecting group with emphasis on visible light deprotection.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02924.

Detailed synthetic procedures, characterization data, photolysis methods, and laser studies (PDF)



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## Notes

The authors declare no competing financial interest.

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