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A New Photolabile Protecting Group for Release of Carboxylic Acids by Visible-Light-Induced Direct and Mediated Electron Transfer

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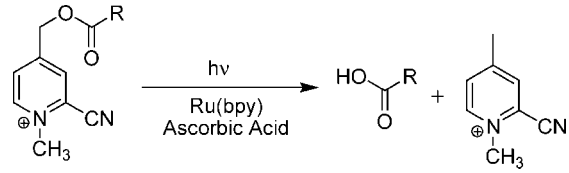

A new aqueous-compatible photoinduced electron transfer based photolabile protecting group has been developed for the release of carboxylic acids. The reduction potential of this group is more positive than previous systems, thereby allowing the use of sensitizers with modest oxidation potentials. Release of several carboxylic acids has been demonstrated using tris(bipyridyl)ruthenium(II) as both a direct sensitizer and a mediator for electron transfer between a good donor and the protecting group.

Introduction

Photoremovable protecting groups (PRPGs) have become broadly applicable for convenient and controlled release of functional molecules in a variety of environments.[1,2] Some of the more interesting applications include photolithography,[3−6] the "caging" and release of biologically significant compounds,[7−9] and organic synthesis.[10,11] Many PRPGs have been developed around a rearrangement and/or radical bond fragmentation process that occurs within a chromophore upon excitation. Examples of such PRPGs include the *o*-nitrobenzyl esters and ethers,[12−14] benzoin,[15−18] phenacyl ester,[19−21] and coumarin[22−24] derivatives. Several wavelength-addressable multiple PRPG systems have also been investigated.[25−27] Ideally, a PRPG would be stable before excitation, have fast rates of release, high quantum yields of release (Φ_{rel}), solubility in a wide range of solvents, and produce benign side products. Additionally, it would be convenient for the release to be initiated by low-energy light such as visible or infrared irradiation. Unfortunately, a large number of the aforementioned PRPGs absorb ultraviolet (UV) light, which can present a problem if other UV-active compounds are included in the system. Through the selection of

(1) Wirz, J.; Pelliccioli, A. P. *Photochem. Photobiol.* **2002**, *1*, 441–458.
(2) Bochet, C. G. *J. Chem. Soc., Perkin Trans. 1* **2002**, 125–142.
(3) MacDonald, S. A.; Willson, C. G.; Frechet, J. M. J. *Acc. Chem. Res.* **1994**, *27*, 151–158.
(4) Sabongi, G. J. *Chemical Triggering: Reactions of Potential Utility in Industrial Processes*; Plenum: New York, 1987.
(5) Lockhart, D. J.; Dong, H.; Byrne, M. C.; Follettie, M. T.; Gallo, M. V.; Chee, M. S.; Mittmann, M.; Wang, C.; Kobayashi, M.; Horton, H.; Brown, E. L. *Nat. Biotechnol.* **1996**, *14*, 1675–1680.
(6) Pirrung, M. C.; Fallon, L.; McGall, G. *J. Org. Chem.* **1998**, *63*, 241–246.
(7) Kalbag, S. M.; Roeske, R. W. *J. Am. Chem. Soc.* **1975**, *97*, 440–441.
(8) Pirrung, M. C.; Rana, V. S. *Dyn. Stud. Biol.* **2005**, 341–368.
(9) Il'ichev, Y. V.; Schwoerer, M. A.; Wirz, J. *J. Am. Chem. Soc.* **2004**, *126*, 4581–4595.
(10) Pillai, V. N. R. *Synthesis* **1980**, 1–26.
(11) Yoon, U. C.; Jin, Y. X.; Oh, S. W.; Park, C. H.; Park, J. H.; Campana, C. F.; Cai, X.; Duesler, E. N.; Mariano, P. S. *J. Am. Chem. Soc.* **2003**, *125*, 10664–10671.
(12) Kaplan, J. H.; Forbush, B.; Hoffman, J. F. *Biochemistry* **1978**, *17*, 1929–1935.
(13) Patchornik, A.; Amit, B.; Woodward, R. B. *J. Am. Chem. Soc.* **1970**, *92*, 6333–6335.
(14) Dussy, A.; Meyer, C.; Quennet, E.; Bickle, T. A.; Giese, B.; Marx, A. *ChemBioChem* **2002**, *3*, 54–60.
(15) Corrie, J. E. T.; Trentham, D. R. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2409–2417.
(16) Cameron, J. F.; Willson, C. G.; Frechet, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2429–2442.
(17) Sheehan, J. C.; Wilson, R. M. *J. Am. Chem. Soc.* **1964**, *86*, 5277–5281.
(18) Baldwin, J. E.; McConnaughie, A. W.; Moloney, M. G.; Pratt, A. J.; Shim, S. B. *Tetrahedron* **1990**, *46*, 6879–6884.
(19) Givens, R. S.; Athey, P. S.; Matuszewski, B.; Kueper, L. W.; Xue, J. Y.; Fister, T. *J. Am. Chem. Soc.* **1993**, *115*, 6001–6012.
(20) Banerjee, A.; Falvey, D. E. *J. Org. Chem.* **1997**, *62*, 6245–6251.
(21) Sheehan, J. C.; Umezawa, K. *J. Org. Chem.* **1973**, *38*, 3771–3774.
(22) Furuta, T.; Torigai, H.; Sugimoto, M.; Iwamura, M. *J. Org. Chem.* **1995**, *60*, 3953–3956.
(23) Suzuki, A. Z.; Watanabe, T.; Kawamoto, M.; Nishiyama, K.; Yamashita, H.; Ishii, M.; Iwamura, M.; Furuta, T. *Org. Lett.* **2003**, *5*, 4867–4870.
(24) Shembekar, V. R.; Chen, Y.; Carpenter, B. K.; Hess, G. P. *Biochemistry* **2007**, *46*, 5479–5484.
(25) Blanc, A.; Bochet, C. G. *Org. Lett.* **2007**, *9*, 2649–2651.
(26) Blanc, A.; Bochet, C. G. *J. Org. Chem.* **2002**, *67*, 5567–5577.
(27) Bochet, C. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 2071–2073.

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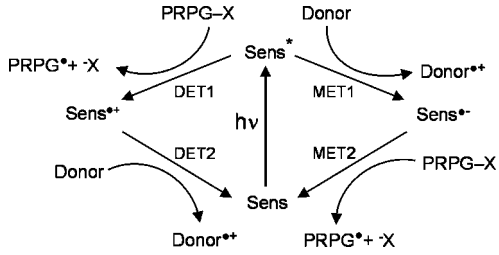
SCHEME 1. Direct Electron Transfer (DET) versus Mediated Electron Transfer (MET) Deprotection[40]



new visible-light (VIS)-absorbing chromophores[28,29] or by modifying existing PRPGs to red-shift their absorption profiles,[30−32] deprotection reactions can be initiated using visible light. Unfortunately, finding new chromophores with a predictable and reproducible bond fragmentation can be exceedingly difficult, and modification of existing PRPGs often has the unintended consequence of negatively altering the efficiencies and rates of the release reaction or other properties such as solubility.

One approach to address this dilemma is to separate the light absorption step from the bond-breaking step by using a sensitizer to activate a protecting group through energy or electron transfer.[33] Our group has protected carboxylic acids and carbamates using the phenacyl[20,34,35] and *N*-alkyl-4-picolinium (NAP)[36−39] groups that undergo a bond scission reaction upon simple one electron reduction through photoinduced electron transfer (PET) from a photoexcited donor. Deprotection can be accomplished by direct electron transfer (DET) or mediated electron transfer (MET) (Scheme 1). DET occurs through donation of an electron from the excited-state chromophore (Sens*) to the protecting group (DET1, Scheme 1). If a donor is present in the system, the oxidized chromophore may abstract an electron to regenerate the original chromophore (DET2, Scheme 1), assuming the oxidized state is stable for a sufficient period of time. MET proceeds through the donation of an electron from a ground-state donor to the excited chromophore (MET1, Scheme 1) followed by reduction of the protecting group (MET2, Scheme 1). The redox potentials of all components are a critical design consideration to ensure that electron transfer from the sensitizer to the PRPG and from the donor to the sensitizer are favorable processes. The judicious selection of an appropriate donor is also essential to prevent undesirable thermal or photochemical reactions that are not part of the desired phototriggered deprotection. We have previously reported the successful use of VIS-absorbing laser dyes for direct sensitization and release of NAP-protected carboxylic acids.[37] Mediated sensitization has also been investigated using UV-absorbing dyes and VIS-absorbing gold nanoparticles in the presence of a good electron donor.[38,41] Since direct sensitization often leads to the degradation of the chromophore, the mediated scheme offers a significant improvement in that the chromophore is regenerated by the end of the deprotection process. Thus, it is possible to use substoichiometric amounts of potentially expensive sensitizer to fully deprotect a solution of NAP-protected compounds. Additionally, mediated PET deprotection has frequently demonstrated higher quantum yields of release and faster overall deprotection compared to direct sensitization.

To further improve upon all of the benefits of the mediated systems previously mentioned, it would be desirable to be able to use a wider variety of readily available VIS-absorbing chromophores so that this deprotection strategy may utilize a broader range of irradiation wavelengths. A great number of inorganic dyes exist that possess beneficial properties, i.e., strong molar absorptivities in the visible, aqueous solubility, and high stability under irradiation, that make them promising candidates for use in these systems. Tris(bipyridyl)ruthenium(II) (Ru(bpy)) is one such dye that we have chosen as our focus. Ru(bpy) is widely available and has been heavily studied across many disciplines due to its strong VIS-absorption, relative stability under irradiation, and unique optoelectronic properties applicable to photosensitization, imaging, and solar energy conversion, among others.[42−45] Unfortunately, Ru(bpy), along with many other dyes, has fairly modest redox potentials, $E(Ru^{2+/+}(bpy)) = -1.33$ V vs SCE and $E(Ru^{2+/3+}(bpy)) = 1.29$ V vs SCE.[44] As such, electron transfer to the NAP group ($E_{red} = -1.1$ V vs SCE) is less favorable under our standard conditions. In order to tune the redox potentials to make the PET reaction more favorable, the electronics of either Ru(bpy) or the NAP group must be altered. Since we wish to preserve Ru(bpy) in its widely available form, we must therefore alter the NAP group to make it a better electron acceptor even though this may have an influence on the efficiency of deprotection as previously discussed. In this work, we report the development of a modified version of the NAP group that allows the use of Ru(bpy) and, presumably, a wider array of inorganic and organic sensitizers for PET deprotection reactions. The deprotection reactions can be initiated by either a direct or mediated PET process using visible light. In the presence of a good electron donor, mediated PET is effective in initiating deprotection using substoichiometric amounts of Ru(bpy).

Results and Discussion

It was expected that substitution of the existing NAP group with a strongly electron-withdrawing substituent would adjust the reduction potential to more positive values. Toward this goal, 4-methyl-2-pyridinecarbonitrile was methylated to act as a model for the NAP group with a 2-cyano substitution. Using cyclic voltammetry, a value of −0.63 V (vs SCE, in MeCN, taken

(28) Chen, Y.; Steinmetz, M. G. *J. Org. Chem.* **2006**, *71*, 6053–6060.
(29) Shembekar, V. R.; Chen, Y.; Carpenter, B. K.; Hess, G. P. *Biochemistry* **2005**, *44*, 7107–7114.
(30) Conrad, P. G.; Givens, R. S.; Weber, J. F. W.; Kandler, K. *Org. Lett.* **2000**, *2*, 1545–1547.
(31) Aujard, I.; Benbrahim, C.; Gouget, M.; Ruel, O.; Baudin, J.-B.; Neveu, P.; Jullien, L. *Chem.−Eur. J.* **2006**, *12*, 6865–6879.
(32) Stensrud, K. F.; Heger, D.; Sebej, P.; Wirz, J.; Givens, R. S. *Photochem. Photobiol.* **2008**, *7*, 614–624.
(33) Falvey, D. E.; Sundararajan, C. *Photochem. Photobiol.* **2004**, *3*, 831–838.
(34) Banerjee, A.; Lee, K.; Falvey, D. E. *Tetrahedron* **1999**, *55*, 12699–12710.
(35) Lee, K.; Falvey, D. E. *J. Am. Chem. Soc.* **2000**, *122*, 9361–9366.
(36) Sundararajan, C.; Falvey, D. E. *Org. Lett.* **2005**, *7*, 2631–2634.
(37) Sundararajan, C.; Falvey, D. E. *J. Am. Chem. Soc.* **2005**, *127*, 8000–8001.
(38) Sundararajan, C.; Falvey, D. E. *Photochem. Photobiol.* **2006**, *5*, 116–121.
(39) Sundararajan, C.; Falvey, D. E. *J. Org. Chem.* **2004**, *69*, 5547–5554.
(40) See Supporting Information for an alternate representation of Scheme 1.
(41) Borak, J. B.; Lopez-Sola, S.; Falvey, D. E. *Org. Lett.* **2008**, *10*, 457–460.
(42) Balzani, V.; Barigelletti, F.; De Cola, L. *Top. Curr. Chem.* **1990**, *158*, 31–71.
(43) Meyer, T. J. *Pure Appl. Chem.* **1986**, *58*, 1193–1206.
(44) Kalyanasundaram, K. *Coord. Chem. Rev.* **1982**, *46*, 159–244.
(45) Kalyanasundaram, K. *Photochemistry of Polypyridine and Porphyrin Complexes*; Academic Press: London, U.K., 1992.

SCHEME 2. Synthesis of mPCN-Protected Esters

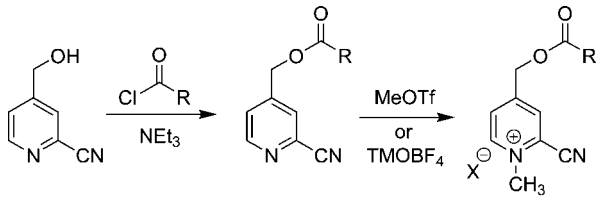


TABLE 1. Synthesized mPCN Esters and Their Respective Reduction Potentials

compound	R	X	E_{red} (V)[a]
3aBF$_4$	phenyl	BF_4	−0.50
3bBF$_4$	4-bromobenzyl	BF_4	−0.51
3cOTf	4-*tert*-butylbenzyl	OTf	−0.52

[a] Versus SCE, in acetonitrile, taken from the half-maximum current of an irreversible wave.

from the half-maximum current of an irreversible wave) was obtained for the reduction potential of this model compound, a substantial shift to less negative potentials compared to the previously used NAP group. The driving force for the direct electron transfer reaction between Ru^{2+}(bpy) and the modified NAP group (DET1, Scheme 1) can be estimated from eq 1 where E_{ox} is the oxidation potential of the $Ru^{2+/3+}$(bpy) couple, E_{red} is the reduction potential of the modified NAP group, and E_{oo} is the energy of the triplet metal−ligand charge transfer excited state of Ru(bpy) (^{3*}MLTC) equal to 48.9 kcal/mol.[44] The driving force for mediated electron transfer from Ru^{+}(bpy) to the modified NAP group (MET2, Figure 1) can be estimated from eq 2 where E_{ox} now represents the ground-state oxidation potential for the $Ru^{2+/+}$(bpy) couple.

$$\Delta G = 23.06(E_{ox} - E_{red}) - E_{oo} \quad (1)$$

$$\Delta G = 23.06(E_{ox} - E_{red}) \quad (2)$$

A value of −4.6 kcal/mol is obtained for DET1 and −16.1 kcal/mol for MET2, suggesting that both the direct and mediated pathways should be favorable. Thus, several simple 2-cyano-NAP (mPCN) esters were prepared for further experimentation (Scheme 2).

2-Substitution of 4-(hydroxymethyl)pyridine is accomplished using a modified procedure by El Hadri and Leclerc[46] to generate 4-((*tert*-butyldimethylsilyloxy)methyl)picolinonitrile, which is subsequently deprotected using aqueous acid. Coupling of 4-(hydroxymethyl)picolinonitrile (PCN) to a carboxylic acid is accomplished by simply using the respective acid chloride. Due to the increased electron deficiency of the pyridine ring by the cyano group, *N*-methylation must be completed using a strong methylating reagent: methyl triflate (MeOTf) and trimethyloxonium tetrafluoroborate ($TMOBF_4$) were both employed to create the respective methylated PCN (mPCN) ester salts. Three simple mPCN esters have been synthesized by this method (Table 1). Cyclic voltammetry of each ester revealed an irreversible reduction wave that is approximately 100 mV more positive than the model compound, which subsequently decreases ΔG_{DET1} to approximately −7 kcal/mol and ΔG_{MET2} to approximately −19 kcal/mol (Table 1).

An unusual observation noted when these compounds are dissolved in very polar solvents, such as acetonitrile, is the gradual formation of one broad absorption band around 350 nm followed by subsequent reduction of that band concurrent with the growth of a second longer wavelength band around 510 nm (see Supporting Information). The second band persists, and there are no apparent changes in the NMR spectrum over the course of these color changes. Irradiation of this band does not result in any significant amount of deprotection products. The formation of these bands appears to be a consequence of deprotonation at the benzylic position of the mPCN group. In comparison to the unsubstituted NAP group, the mPCN group possesses greater electron-withdrawing ability, thus increasing the acidity of the benzylic protons. Trace amounts of base may be sufficient for deprotonation. The increased acidity of these protons is evidenced by NMR studies of **3bBF$_4$** in CD_3CN/D_2O in which deuterium incorporation occurs at the benzylic position slowly over the course of 24 h and more rapidly in the presence of a catalytic amount of triethylamine. Studies of **3bBF$_4$** prepared in acetonitrile/methanol (1/1) with varying concentrations of triethylamine also support this suggestion, as all samples exhibited the 350 nm absorption band to varying degrees proportional to the concentration of base. After several minutes, the 350 nm band was diminished and the 510 nm band had begun to develop. Samples of **3bBF$_4$** prepared in the presence of varying concentrations of sulfuric acid remained stable and colorless for several days. Upon acidification of the basic solutions with excess sulfuric acid, the 510 nm band is diminished and a persistent weakly absorbing broadband at ca. 380 nm develops (see Supporting Information). Thus, it is clear that the deprotonation of a benzylic proton contributes to the formation of these colored species. However, the behavior is more complex than a simple acid/base reaction, and the identities of each absorption are not known with certainty. It is likely that the deprotonated mPCN group is participating in a slow, irreversible side reaction to a certain degree that results in the persistent 380 nm absorption. Since the color changes are not observed for at least several hours in acetonitrile/methanol (1/1), photolysis solutions were prepared in this solvent for preliminary experimentation.

At first, deprotection photolysis experiments were carried out on systems containing only Ru(bpy) and one of the esters (i.e., direct electron transfer). Representative data for these experiments are found in Table 2. Surprisingly, photolysis yields peak at 0.5 equiv of Ru(bpy) (compared to ester concentration). Decreasing the concentration of Ru(bpy) from this point subsequently reduces the yield for a given irradiation time period. Increasing the concentration to 1 equiv actually has the effect of reducing the yield of free acid.

Control solutions that lacked Ru(bpy) or light resulted in an insignificant yield of the free acid product (≤5%). One of the advantages of the triflate salts of the PCN esters is their aqueous compatibility (with mild warming and stirring); however, these solutions develop the same long wavelength absorption band within minutes. In an effort to develop a more robust system that does not form the long wavelength band, it was determined that the mPCN esters are soluble and stable in 0.5 M acetate buffer at pH 4.0. The development of the long wavelength absorption band is delayed by several hours to 1 day and does not seem to occur during photolysis experiments. Direct photolysis of the esters with Ru(bpy) in acetate buffer results in clean release of the free acid (Table 2, entries 4−8) in yields similar to those in the acetonitrile/methanol (1/1) solvent system.

(46) El Hadri, A.; Leclerc, G. *J. Heterocycl. Chem.* **1993**, *30*, 631–635.

TABLE 2. Selected Data for DET Deprotection Experiments

entry	ester	[ester] (mM)	[Ru(bpy)] (mM)	conditions	% yield[a]	% conversion[a]
1	**3bBF$_4$**	4.8	0.24	1 h, MeCN/MeOH (1/1)	9.9	21.7
2	**3bBF$_4$**	4.8	2.4	1 h, MeCN/MeOH (1/1)	23.9	28.5
3	**3bBF$_4$**	4.8	4.8	1 h, MeCN/MeOH (1/1)	15.1	13.8
4	**3bOTf**	4.8	0.24	1 h, acetate buffer[b]	12.8	23.5
5	**3bOTf**	4.8	2.4	1 h, acetate buffer[b]	15.8	20.7
6	**3bOTf**	4.8	4.8	1 h, acetate buffer[b]	14.1	22.1
8	**3bOTf**	0.6	0.3	30 min, acetate buffer[b]	29.7	42.1

[a] Determined by HPLC, relative to [ester] in a dark control sample, corrected for any dark deprotection, estimated error <5%. [b] 0.5 M acetate buffer, pH 4.0.

TABLE 3. Selected Data for MET Deprotection Experiments

entry	ester	donor[a]	[ester] (mM)	[Ru(bpy)] (mM)	[donor] (mM)	conditions	% yield[b]	% conversion[b]
1	**3bBF$_4$**	DMA	4.8	2.4	9.6	1 h, MeCN/MeOH	38.4	48.1
2	**3bBF$_4$**	DMA	4.8	2.4	24	1 h, MeCN/MeOH	53.8	70.4
3	**3bBF$_4$**	DMA	4.8	2.4	24	3 h, MeCN/MeOH	96.2	96.9
4	**3bBF$_4$**	DABCO	0.6	0.3	1.2	10 min, MeCN/MeOH	6.7	15.2
5	**3bBF$_4$**	DABCO	0.6	0.3	60	10 min, MeCN/MeOH	35.1	52.2
6	**3bOTf**	ASC	0.6	0.3	3	10 min, acetate buffer	28.7	40.2
7	**3bOTf**	ASC	0.6	0.3	6	10 min, acetate buffer	35.6	62.1
8	**3bOTf**	ASC	0.6	0.3	60	10 min, acetate buffer	89	94.2

[a] DMA = *N*,*N*-dimethylaniline, DABCO= 1,4-diazabicyclo[2.2.2]octane, ASC = ascorbic acid. [b] Determined by HPLC, relative to [ester] in a dark control sample, corrected for any dark deprotection, estimated error <5%.

In order to deprotect the esters using mediated photolysis, a donor must be chosen that is visible-light-transparent and has an E_{ox} low enough to donate an electron to the photoexcited Ru(bpy), MET1 (Scheme 1). The driving force for this reaction can be estimated using eq 1 by substituting the oxidation potential of the donor for E_{ox} and the redox potential for the $Ru(bpy)^{2+/+}$ couple for E_{red}. Two amine donors were initially chosen for experimentation because of their low oxidation potentials: *N*,*N*-dimethylaniline (DMA) and 1,4-diazabicyclo-[2.2.2]octane (DABCO) with oxidation potentials of 0.81[47] and 0.57 V,[48] respectively (vs SCE, in MeCN). Both DMA and DABCO have been observed to quench the luminescence of the $Ru(bpy)^{2+}$ ^{3*}MLCT. Mediated deprotection photolysis experiments were performed in a manner similar to the direct photolysis experiments but included an excess amount of donor. A large increase in the free acid yield can be seen in these experiments compared to the direct photolysis experiments for a given irradiation period (Table 3, entries 1−5). Nearly full deprotection is observed using 5 equiv of DMA after 3 h of irradiation (Table 3, entry 3). Using DABCO as the donor demonstrated similar results but generally with higher yields of free acid for a shorter irradiation period. Unfortunately, a significant amount of deprotection occurs in the dark control sample for the DABCO and DMA systems, generating yields of free acid as high as 50% in some cases. Furthermore, the dark free acid yield seems to be proportional to the concentration of donor. The dark electron transfer reaction between either donor and ester is predicted to be disfavored by about 30 kcal/mol; however, it is possible that base-catalyzed hydrolysis or methanolysis by the amine donors is a competitive side reaction under these conditions. Additionally, in both systems, the slow formation of a long wavelength band over the course of the irradiation period is observed that competes with Ru(bpy) for light absorption. It is likely that this band originates from

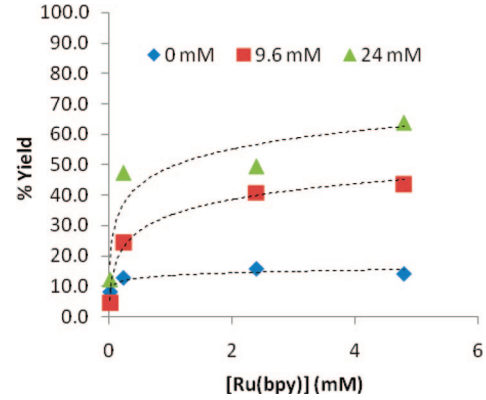


FIGURE 1. Effect of increasing concentration of Ru(bpy) or ascorbic acid on the yield of free acid from ester **3bOTf** (4.8 mM across all data points).

deprotonation at the benzylic position of the mPCN group as discussed above by DMA or DABCO since its appearance is accelerated in the presence of these donors.

Ascorbic acid was chosen for use as an aqueous soluble donor in a mediated deprotection scheme due to its low oxidation potential (0.29 V vs SCE, taken from the half-maximum current of an irreversible wave). The yields observed for these experiments (Table 3, entries 6−8) are comparable to those using DMA as the donor. Faster release with the use of less Ru(bpy) can be achieved in this system by increasing the concentration of ascorbic acid. In fact, 89% yield of the free acid is observed after 10 min using 100 equiv of ascorbic acid and 0.5 equiv of Ru(bpy) (Table 3, entry 8). Figure 1 demonstrates the general trend observed upon increasing concentration of Ru(bpy) and/or ascorbic acid.

The stability of this system is far greater compared to the DMA or DABCO systems as the dark control solution exhibited very low deprotection over time (less than 3% over 18 h) and did not seem to be affected by the concentration of ascorbic acid.

The proposed mechanism for mediated deprotection, shown in Scheme 1, is supported by luminescence quenching and laser

(47) Kitamura, N.; Kim, H. B.; Okano, S.; Tazuke, S. *J. Phys. Chem.* **1989**, *93*, 5750–5756.
(48) Ruiz, G.; Rodriguez-Nieto, F.; Wolcan, E.; Feliz, M. R. *J. Photochem. Photobiol., A* **1997**, *107*, 47–54.

TABLE 4. Observed Rate Constants and Quantum Yields of Release for Mediated Deprotection

ester	donor	k_q (MET1) (M^{-1} s^{-1})	k_{obs} (MET2) ($M^{-1}s^{-1}$)	Φ_{rel}
3bBF$_4$	DMA	1.05×10^8	3.17×10^9	0.02
3bBF$_4$	DABCO	2.40×10^6	*a*	0.002
3bOTf	ascorbic acid	3.84×10^7	1.77×10^9	0.01

[a] Unable to determine due to interference from long wavelength absorption band.

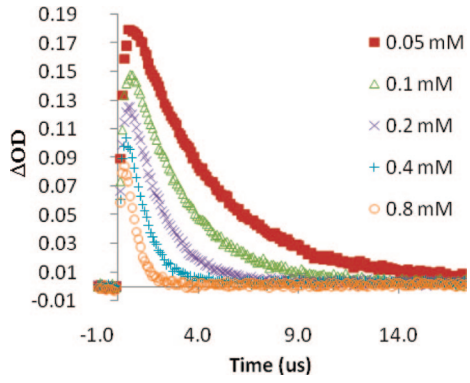


FIGURE 2. Time-dependent absorption signals at 510 nm from pulsed laser photolysis (532 nm, 100−200 mJ, 6 ns) of 0.4 mM Ru(bpy) + 1 M ascorbic acid + varying [**3bOTf**] in N_2-purged acetate buffer (0.5 M, pH 4.0).

flash photolysis (LFP) experiments. Luminescence of the Ru(bpy) ^{3*}MLCT was reduced upon addition of any of the three donors and upon addition of the esters. Quenching rate constants were determined for MET1 and are presented in Table 4. The quenching rate constant (k_q) for DET1 in the direct photolysis experiments was also determined to be 5.18×10^8 M^{-1} s^{-1}. Transient absorption spectra of samples containing Ru(bpy) and a large excess of any of the donors exhibited a broad signal centered at 510 nm characteristic of Ru^+(bpy), thereby providing further evidence for the MET1 process.[44,49,50] Upon addition of esters **3bBF$_4$** or **3bOTf**, the signal at 510 nm is reduced in intensity and its rate of decay increases. This indicates that the esters can quench $Ru(bpy)^+$, suggesting the MET2 process is occurring (Figure 2). Decay rate constants (k_{obs}) were determined at various ester concentrations by second-order analysis of the time dependent absorption signals and are presented in Table 4. Rate constants for MET2 for both the DMA and ascorbic acid systems are near the diffusion limit. A rate constant could not be determined for the DABCO system because of the rapid thermal formation of the long wavelength absorption band during the LFP experiment. Surprisingly, k_q for DET1 is larger than all of the MET1 rate constants despite the longer irradiation time required for the DET experiments to produce an equal amount of free acid. This suggests that the mechanistic pathway in the MET experiments may actually follow the DET mechanism for a certain percentage of deprotection events and the predominating pathway is ultimately determined by the relative concentrations of donor and ester. The reduced mPCN group could not be directly observed by LFP experiments in either the DET or the MET systems using Ru(bpy). The expected signal (410 nm) is likely bleached by the strong absorption of Ru(bpy) in that region, but it has been observed using the UV-absorbing sensitizer 9-methylcarbazole (see Supporting Information).

Quantum yields of release, Φ_{rel}, of the free carboxylate for each system were determined (Table 4) using monochromatic irradiation at 450 nm (±10 nm). Despite the modest irradiation times required for full deprotection, it appears that processes that compete with the productive MET1 and MET2 steps are fairly fast and efficient, as evidenced by the very low Φ_{rel} values for all systems. In comparison to the previously used NAP system, substitution of the pyridinium ring with the cyano group in the current system likely alters the energetics of the deprotection bond fragmentation; however, it is unclear to what extent this may contribute to overall efficiencies.

Conclusions

We have demonstrated successful deprotection of a new photoinduced electron transfer based PRPG using the widely available Ru(bpy) dye in both direct and mediated photolysis. As a result of the more positive reduction potential of the mPCN group, it should be possible to use a wider variety of sensitizers to initiate deprotection reactions. Additionally, this system is particularly compelling because of (1) the use of visible light, (2) the use of substoichiometric amounts of Ru(bpy), and (3) compatibility in aqueous media. Fluorescence quenching and transient spectroscopy experiments support the proposed direct and mediated electron transfer mechanisms. The selection of donors that have suitable oxidation potentials and do not participate in undesirable side reactions is critical for a well-behaved and predictable system. The medium in which these systems are prepared is another important consideration as slightly acidic solutions tend to allow more dependable behavior in which the formation of the long wavelength absorbing species is suppressed. Although the deprotection photolysis experiments generally require a modest irradiation period for full deprotection, quantum yields of release are low possibly due to fast back electron transfer or a decreased bond fragmentation efficiency as a result of the cyano substituent. Future work will focus on identifying derivatives of the mPCN group that will be more broadly applicable.

Experimental Section

Cyclic Voltammetry. All electrochemical experiments were performed on a voltammetry analyzer with $[Bu_4N]$-$[PF_6]$ as the supporting electrolyte. A carbon working electrode, a platinum auxiliary electrode, and an Ag/AgCl reference electrode were used to take measurements. The voltammograms were taken at a scan rate of 100 mV/s in dry acetonitrile after purging with nitrogen for 15 min. Measurements were taken in reference to the ferrocene/ferrocenium couple found at ca. 536 mV vs SCE.

Luminescence Quenching. Luminescence quenching experiments were performed using a luminescence spectrometer. Samples were prepared in a 1 cm quartz cuvette, sealed with a rubber septum, and purged with N_2 for 10 min. Sensitizer concentrations were prepared such that the optical density of the sensitizer at the excitation wavelength was between 0.1 and 0.3. Quencher concentrations were prepared such that a linear relationship was obtained with respect to $I°/I$.

Deprotection Photolysis. A solution containing 0.6−4.8 mM ester and 0.024−4.8 mM Ru(bpy) was prepared in 5 mL of methanol/acetonitrile (1/1) when using the tetrafluoroborate salts and in 5 mL of 0.5 M acetate buffer at pH 4.0 when using the triflate salts. In mediated photolysis experiments, 0.6−2.4 mM

(49) Rivarola, C. R.; Bertolotti, S. G.; Previtali, C. M. *Photochem. Photobiol.* **2006**, *82*, 213–218.
(50) Mulazzani, Q. G.; Emmi, S.; Fuochi, P. G.; Hoffman, M. Z.; Venturi, M. *J. Am. Chem. Soc.* **1978**, *100*, 981–983.

DMA, DABCO, or ascorbic acid was included in the solution. An aliquot of the solution was set aside as a dark control, and a 2 mL aliquot was added to a thermostatted water-jacketed test tube that was sealed with a rubber septum and purged with N_2 for 10 min. The solution was irradiated for various periods of time with continuous stirring and maintained at 20 °C (±1°). The irradiation source consisted of a 300 W tungsten/halogen lamp the output of which was passed through a 330 nm cutoff filter and a Kopp 7093 IR-absorbing filter to ensure visible-light irradiation only. Dark control and irradiated sample mixtures were analyzed using an HPLC system equipped with an analytical C_{18} reversed-phase column. Gradient elution using an acetonitrile/acetate buffer (100 mM, pH 4.0) mixture that adjusts from 25% acetonitrile to 70% acetonitrile over 20 min at a flow rate of 0.5 mL/min was sufficient to resolve the starting material and free acid peaks, monitored at 254 nm. Yields of free acid in the irradiated samples were calculated relative to the amount of unreacted ester plus any amount of free acid detected in the dark control sample.

Laser Flash Photolysis. An Nd:YAG laser capable of 532, 355, and 266 nm pulses between 4−6 ns duration was used as the excitation source. A 350 W Xe arc lamp was used as the probe beam passed through a monochromator to a PMT detector. A 350 MHz digital oscilloscope was used to observe the signals. Samples were prepared such that the optical density at the excitation wavelength, 532 nm, was between 0.1 and 0.5. The samples were placed in a 1 cm quartz cuvette, sealed with a rubber septum, and purged with N_2 for 10 min. Samples were stirred continuously during photolysis. Full transient spectra were obtained using a flow-cell setup to continuously refresh the photolysis solution over the course of the experiment.

Quantum Yield Determination. Solutions were irradiated with the light output from a 1000 W Hg−Xe lamp passed through a spectral energy monochromator with a 10 nm bandpass, set at the λ_{max} of Ru(bpy). Solutions were prepared as optically thick samples (optical density greater than 3) using a substoichiometric amount of sensitizer and a large excess of donor, where applicable. Samples were placed in a 1 cm quartz cuvette and purged with nitrogen for 10 min. A variety of irradiation periods were selected such that deprotection yields fell below 30%. Deprotection yields were determined by HPLC analysis as described for the deprotection photolysis experiments. Light intensities were measured by a radiometer calibrated by ferrioxalate actinometry.

Synthesis of 4-(Hydroxymethyl)picolinonitrile, 1. 4-((*tert*-Butyldimethylsilyloxy)methyl)picolinonitrile (15.0 g, 60.5 mmol) was prepared from literature procedures[46] and was dissolved in methanol (100 mL). H_2SO_4 (2 N, 30 mL) was added slowly, and the mixture was stirred at room temperature for 1 h. TLC (1/1 EtOAc/hexanes) after 1 h showed no visible sign of the starting material. The solvent was evaporated, and water (250 mL) was added to the residue. The crude product was extracted with EtOAc (1 × 250 mL), and the solvent was removed to yield a yellow solid. The compound was dissolved in EtOAc/hexanes (1/1) and passed through silica to yield a white crystalline solid (6.0 g, 74%).

General Procedure for Synthesis of PCN Esters, 2. The esters were prepared by modification of previously reported procedures.[39] Compound **1** (20 mmol) was dissolved in a minimal amount of benzene/acetonitrile. Triethylamine (36 mmol) was added, and the mixture was stirred for several minutes. The respective acid chloride (32 mmol) was added slowly, and the mixture was allowed to stir at room temperature for several hours until TLC (50/50 EtOAc/hexanes) showed the absence of starting material. The solvent was evaporated, and benzene was added (250 mL). The mixture was washed with water (1 × 250 mL), and the organic layer was separated, concentrated, and dried. Purification of each ester was accomplished with flash column chromatography.

General Procedure for Synthesis of Methylated Esters, 3. Tetrafluoroborate Salts. A portion of the ester **2** (8.3 mmol) was dissolved in a minimal amount of acetonitrile or acetone. Trimethyloxonium tetrafluoroborate was added (16.6 mmol), and the mixture was stirred for several hours until analysis by TLC (50/50 EtOAc/hexanes) showed the absence of starting material. The precipitate was filtered off and washed with cold methanol. If no precipitate formed, the solvent was removed and the residue was recrystallized from hot pentane/acetone (9/1).

Triflate Salts. A portion of the ester **2** (11 mmol) was dissolved in a minimal amount of dry dichloromethane. Methyl trifluoromethane sulfonate (14.3−16.5 mmol) was added slowly, and the mixture was stirred for several hours under nitrogen atmosphere until analysis by TLC (50/50 EtOAc/hexanes) showed the absence of starting material. The solvent was evaporated in vacuo, and the residue was recrystallized from hot ethanol.

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Supporting Information Available: Full synthetic procedures; compound characterization; copies of ^1H and ^{13}C NMR of **2a−c**, **3aBF$_4$**, **3bBF$_4$**, **3aOTf**, **3bOTf**, and **3cOTf**; luminescence data; laser flash photolysis data; cyclic voltammograms; and UV spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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