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A phosphonium ylide as a visible light organophotoredox catalyst[†]

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A phosphonium ylide-based visible light organophotoredox catalyst has been designed and successfully applied to halohydrin synthesis using trichloroacetonitrile and epoxides. An oxidative quenching cycle by the ylide catalyst was established, which was confirmed by experimental mechanistic studies.

The field of phosphonium ylide chemistry, having a history of over 100 years, has contributed greatly to the development of organic synthesis.1 The C=C bond forming reaction using phosphonium vlides, known as the Wittig reaction, is a wellstudied transformation of carbonyl compounds to alkenes.² Not only the nucleophilic aspects of the carbanion but also the nature of the corresponding radical species have gained attention from researchers.3 In 1997, Janssen et al. reported methylenephosphorane-derived cation radicals that were prepared by one electron oxidation with the use of iodine, AgBF₄, or electrochemical methods.^{3a} Recently, Liu and co-workers were the first to use carbonyl-stabilized phosphonium ylides as reagents in photoredox catalysis, enabling (Z)-selective alkene synthesis or carbyne equivalent generation (Scheme 1a).^{3d,e} A carbon radical attached to the phosphonium ion is invoked as the key intermediate of the transformation. Therefore, it could be feasible to establish photoredox catalysis⁴ by phosphonium ylides if the photoexcited ylide is allowed to undergo photoinduced electron transfer (PET) to electron acceptors (A) utilizing light energy (Scheme 1b). PET is an initiative process in photoredox catalysis, and the excited state oxidation potential of the catalysts $[E^*_{ox}(cat^{\bullet^+}/cat^*)]$ is negative when the excited states act as reductants. Thermodynamically favorable PET is expected to occur favorably when $E^*_{ox}(cat^{\bullet+}/cat^*)$ is lower than the reduction potential of the acceptor $[E_{red}(A/A^{\bullet -})]$. To the best of our knowledge, however,

there are no examples of phosphonium ylides that serve as visible light organophotoredox catalysts.4a For this inquiry, we reasoned that a phosphonium ylide **1** with a π -conjugated system⁵ would be suitable due to the following points: (1) 1 bears no protons α to the phosphorus center, preventing undesired carbyne formation^{3d} by deprotonation from radical cation 1^{•+}; (2) the spin density delocalization and the steric hindrance of 1^{•+} may prevent undesired radical reactions; (3) the π -conjugated system is expected to increase the HOMO energy level of 1, enhancing reactivity for electron acceptors; (4) the system can lower the HOMO-LUMO energy gap of 1, which aids in visible light excitation. Herein, we describe the exploration of organophotoredox catalysis by 1. Recently, we reported a metal salts-catalyzed photodecomposition of CCl₃CN for halohydrin synthesis under visible light irradiation.^{6a} Since CCl₃CN is considered a good electron acceptor, this reaction was selected as the initial model reaction to validate the photoredox catalysis via oxidative quenching of 1*. Taking into account the mechanism of the •CCl2CN radical generation, the ylide catalysis was satisfactorily applied to trifluoromethylation reactions involving •CF₃ radical intermediate.⁷ In addition, the first example of



Scheme 1 Development of photoredox catalysis by phosphonium ylides.

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organocatalyzed direct C-H imidations of arenes under visible light irradiation was demonstrated since arylamines are ubiquitous in a range of biologically active compounds.⁸

We began our study with UV-vis absorption spectroscopy experiments (Fig. 1). CCl₃CN and epoxide 2a have no absorption bands in the visible light region, whereas phosphonium ylide 4 (λ_{abs} = 326 nm) exhibits an absorption band around 330 nm. In contrast, the band of 1 (λ_{abs} = 370 nm) extends past 400 nm, suggesting that blue LED irradiation can be utilized for photoreaction by 1. Next, the reducing power of 1 in the excited state [$E^*_{ox}(1^{\bullet+}/1^*)$] was estimated in accordance with eqn (1),

$$E^{*}_{\text{ox}}(\mathbf{1}^{\bullet^{+}}/\mathbf{1}^{*}) = E_{\text{ox}}(\mathbf{1}^{\bullet^{+}}/\mathbf{1}) - E_{0,0}$$
(1)

where E_{ox} is the oxidation potential in the ground state obtained from CV experiments (1: +0.72 V vs. SCE; 4: +1.12 V vs. SCE^{3d}) and $E_{0,0}$ is the excitation energy based on emission energy (hc/λ_{em}) obtained from the fluorescence spectra (1:436 nm; 4:481 nm). We therefore calculated the E^*_{ox} values of -2.36 V vs. SCE for 1* and -1.95 V vs. SCE for 4*.⁹ As expected, the reducing power of 1* was higher than that of 4*. It should be noted that the redox potential of 1* is similar to that of 10-phenylphenothiazine in the excited state.^{4a} Furthermore, the reduction potential of CCl_3CN was measured to be -0.28 V vs. SCE, revealing the feasibility of PET from 1 to CCl_3CN . We then investigated the Gibbs free energy change in the single electron transfer. The values of $\Delta G_{\rm ET}$ = +23.1 kcal mol⁻¹ (ground-state electron transfer) and $\Delta G_{\text{PET}} = -48.0 \text{ kcal mol}^{-1}$ (excited-state electron transfer) clearly indicated that the process could take place only when in the photoexcited state.¹⁰

Having elucidated the photochemical properties of **1**, we tested the HCl addition to epoxide **2a** *via* formation of the $^{\circ}$ CCl₂CN radical with the use of **1** and CCl₃CN as summarized in Table 1. The initial experiment was performed in a 99:1 mixture of MeCN and H₂O (0.1 M) with irradiation by blue LEDs (40 W Kessil lamp, 50 mW cm⁻²) under argon atmosphere at 25 °C for 6 h (Table 1, entry 1). This resulted in the desired halohydrin **3a** being obtained, albeit in low yield. Switching the solvent to **1**,4-dioxane/H₂O, DMF/H₂O or NMP/H₂O drastically improved the yield of **3a** (Table 1, entries 2–4). The amount of H₂O was important to achieve a higher yield (Table 1, entry 6). Notably, 17% of byproduct **5a** was observed in dry DMF, where



Fig. 1 UV-vis absorption spectra of ylide **1** (blue), epoxide **2a** (gray), CCl₃CN (red), and **4** (purple) in MeCN (2.0×10^{-4} M), and fluorescence emission spectra of **1** (green) and **4** (light green) in MeCN (5.0×10^{-5} M) at room temperature.

Table 1 Optimization of reaction conditions^a

1

	PhO	catalyst (10 mol %) CCl ₃ CN (3.0 equiv) PhO PhO	CI
	2a	25 °C, 6 h, blue LEDs 3a	
	Me	PPh ₃ PPh ₃ Me_N_CHC)
	1		
Entry	Catalyst	Solvent (0.1 M)	$\mathbf{3a}^{b}$ (%)
L	1	$MeCN: H_2O = 99:1$	33
2	1	$1,4$ -Dioxane: $H_2O = 99:1$	92
3	1	$DMF: H_2O = 99:1$	>95(91)
1	1	$NMP: H_2O = 99:1$	> 95
5	1	$DMA: H_2O = 99:1$	78
5	1	$DMF: H_2O = 9:1$	77
7	1	DMF	74 ^c
3	4	$DMF: H_2O = 99: 1$	54
Ð	None	$DMF: H_2O = 99: 1$	24
10^d	1	$DMF: H_2O = 99: 1$	0
$11^{d,e}$	1	$DMF: H_2O = 99: 1$	48
12^{f}	1	$DMF: H_2O = 99: 1$	86
13 ^g	1	$DMF: H_2O = 99: 1$	< 5
¹ Unless	otherwise no	ted all reactions were carried	lout with la

^{*a*} Unless otherwise noted, all reactions were carried out with **2a** (0.2 mmol), catalyst (10 mol%) and CCl₃CN (0.6 mmol) in 0.1 M solution at 25 °C for 6 h under blue LED irradiation. ^{*b*} Determined by ¹H NMR analysis (isolated yield is shown in parentheses). ^{*c*} 17% of **5a** was observed. ^{*d*} In dark. ^{*e*} At 100 °C. ^{*f*} CCl₄ was used instead of CCl₃CN. ^{*g*} CHCl₃ was used instead of CCl₃CN.

3a seemed to be coupled with DMF (Table 1, entry 7). A decreased yield was obtained with **4** (Table 1, entry 8). An attempt without catalysts resulted in low conversion (Table 1, entry 9), and the reaction under dark conditions led to recovery of **2a** (Table 1, entry 10). The thermal reaction at 100 °C gave **3a** in modest yield (Table 1, entry 11). CCl₄ ($E_{red} = -0.64 \text{ V vs. SCE}$) and CHCl₃ ($E_{red} = -0.90 \text{ V vs. SCE}$) were less effective, presumably due to their lower reduction potentials (Table 1, entries 12 and 13).¹¹

The scope of substrates is summarized in Table 2. The HCl addition to monoalkyl-substituted epoxides **2b–h** was first examined (Table 2, left box). Glycidyl ethers afforded the corresponding chlorohydrins **3b–f** in good yields. The regioisomer of **3g** was also observed in the reaction of **1**,2-epoxyhexane (**2g**). Enantiopure (*S*)-*N*-glycidyl phthalimide (**2h**) was smoothly converted to (*S*)-**3h** with high enantiomeric excess without stereochemical erosion. Oxirans **2i–k** bearing two or three substituents were tolerated to furnish **3i–k** with moderate to high yields (Table 2, center box). In the cases of indene oxide (**2l**) and styrene oxide (**2m**), the ring-opening regioselectivity was different from the alkyl ones (Table 2, right box). Owing to the aryl group, the chloride ion could attack the benzylic position of epoxides **2l** and **2m**.¹² The same tendency was observed for the reaction of aziridine **2n**.

We obtained intriguing outcomes from control experiments. The amount of HCl generated *in situ* can be estimated by Mohr's method, validating that 40% of CCl₃CN was converted to HCl under the standard conditions (Scheme 2a).^{6b} On the other hand, a radical trap experiment was successfully carried out (Scheme 2b). TEMPO adducts **6** and **7** were detected by ESI-TOF



^{*a*} Unless otherwise noted, all reactions were carried out with 2 (0.2 mmol), **1** (10 mol%), and CCl₃CN (0.6 mmol) in 0.1 M DMF/H₂O (99:1) at 25 °C for 6 h under blue LED irradiation. Isolated yields are shown. ^{*b*} Isolated after esterification. ^{*c*} In 0.5 M DMF. ^{*d*} **1** (20 mol%), CCl₃CN (5.0 equiv.) in 0.1 M 1,4-dioxane. ^{*e*} **1** (20 mol%), CCl₃CN (5.0 equiv.) in 0.1 M MeCN.

HRMS analysis, which supported the presence of radical cation 1^{\bullet^+} and an α -amino radical derived from DMF.

To gain more insight into the mechanism, we constructed Stern–Volmer plots based on quenching experiments (Fig. 2a). The excited state lifetime of 1 (τ_0) was measured at 2.0 ns in the absence of a quencher. The steady decrease in excited state lifetime was observed by increasing the amount of CCl₃CN, while epoxide **2a** did not strongly affect the lifetime (Fig. S8, ESI†). The Stern–Volmer constant (K_{SV}) of **1** was determined to be 1.81 M⁻¹ and thus, the quenching rate constant ($k_{q} = K_{SV}/\tau_0$) was estimated to be 9.16 × 10⁸ M⁻¹ s⁻¹. The diffusion-limited rate constant (k_{diff}) can be calculated as 1.9 × 10¹⁰ M⁻¹ s⁻¹ (MeCN, 25 °C) by using the Stokes–Einstein equation.¹³ In order for kinetic analysis of the





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Fig. 2 (a) Stern–Volmer plots for quenching of 1 by fluorescence lifetime measurements. (b) Proposed mechanism. (c) Spin density distributions (isoval = 0.002) in the radical cations $1^{\bullet+}$ and $4^{\bullet+}$ calculated by DFT.

electron transfer progress, $k_{\rm q}$ was corrected in accordance with eqn (2),

$$1/k_{\rm q} = 1/k_{\rm diff} + 1/k_{\rm act}$$
 (2)

where k_{act} is the rate constant for activated quenching.¹⁴ The $k_{\rm act}$ value was therefore determined to be 9.63 imes 10⁸ M⁻¹ s⁻¹, revealing that the rate of electron transfer is slower than that of diffusion. In bimolecular electron transfer reactions, an initial encounter complex is generated that leads to an active ion pair. Our kinetic study suggested that the electron transfer step is activation-controlled, while the formation of encounter complex [1*···CCl₃CN] proceeds as a diffusion-controlled process. Based on the experimental evidence, we proposed a mechanism for the catalytic HCl generation in DMF by 1 (Fig. 2b). First, visible light irradiation causes excitation of 1, leading to generation of •CCl₂CN and 1^{•+} through an electron transfer process. The generated •CCl₂CN abstracts a hydrogen atom from DMF to provide α -amino radical I, which in turn is oxidized by 1°+ to result in formation of iminium intermediate II and regeneration of 1.¹⁵ Hydrolysis of II generates HCl, whereas the reaction of II with halohydrin 3 gives byproduct 5. Moreover, DFT calculations with respect to radical cation 1. were performed to predict spin density distributions (Fig. 2c). Compared with 4^{•+}, spin densities of 1^{•+} can be delocalized over the π system and this could be deemed one of the key features for establishing the organophotoredox system.

Lastly, we attempted trifluoromethylation reactions to empower the ylide-based photoredox catalysis (Scheme 3 and Scheme S1, ESI†). Considering our mechanistic studies, electron acceptors having $E_{\text{red}}(\mathbf{A}/\mathbf{A}^{\bullet-})$ higher than $E^*_{\text{ox}}(\mathbf{1}^{\bullet+}/\mathbf{1}^*)$ are expected to undergo PET to release active radical species *via* an



oxidative quenching cycle. If the radical can be trapped by C—C bonds, various photoredox transformations might be accomplished. Hence, **8** ($E_{red} = -0.37 \text{ V} vs. \text{SCE}$)^{7c} was tested for performance validation of **1**. Indeed, trifluoromethylation of **9** provided **10** in 70% NMR yield (44% isolated yield after GPC). In addition, **11** underwent trifluoromethylative lactonization to afford **12** in 63% yield.^{7b} Further synthetic application was demonstrated in the direct arene C–H imidations using **13**, where •NPhth could be generated through reductive cleavage of the N–O bond by **1** under visible light irradiation (Scheme 3c).⁸ The imidations of 2,6-lutidine (**14a**), 2,4,6-collidine (**14b**), and mesitylene (**14c**) successfully proceeded to give **15a–c** in good yields. **1**,3,5-Trimethoxybenzene (**14d**) and benzene (**14e**) were also tolerated to furnish **15d** and **15e**, respectively.

In summary, we have developed a novel visible light organophotoredox catalyst. The catalytic system enabled not only HCl generation from CCl₃CN but also C–H functionalization reactions. **1** behaves as an excited-state reductant, which was unambiguously verified by mechanistic investigations. We believe that the potential utility of phosphonium ylides as photoredox catalysts will lead to fascinating visible lighttriggered transformations.

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Conflicts of interest

There are no conflicts to declare.

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