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COMMUNICATION

Photoacid-Catalyzed Acetalization of Carbonyls with Alcohols

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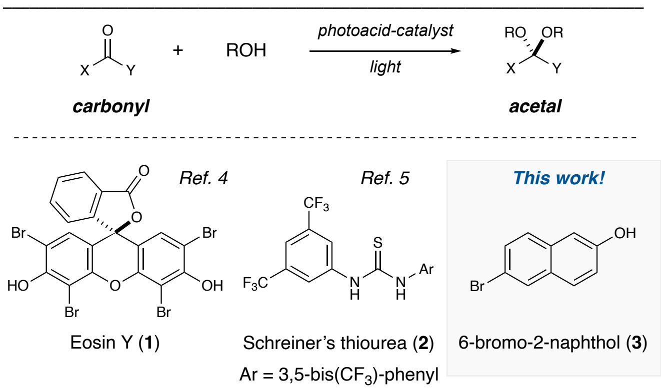
In this report, we demonstrate that visible light photoactivation of 6-bromo-2-naphthol facilitates the photoacid-catalyzed acetalization of carbonyls with alcohols. We also demonstrate that 2-naphthol when coupled to a photosensitizer provides acetylated products from electron-deficient aldehydes. In addition, the S_1 excited state pKa for 6-bromo-2-naphthol in water was determined and shown to have increased excited-state acidity relative to 2-naphthol.

Photoacid-catalyzed processes have recently emerged as a useful strategy for organic synthesis using visible light as a mild way to modulate chemical reactivity.[1,2] Photoacids are bench stable weak acids in the absence of light irradiation and only upon irradiation become strongly acidic and thus catalytically active. The acetalization of carbonyl compounds is an important protecting group strategy for the multi-step synthesis of complex molecules and natural products. Many acetalization reactions involve the use of strong Brønsted acids or Lewis acidic metals.[3] Recent reports by Lei and Kokotos have shown that the direct excitation of photoacids **1** and **2** provide access to acetylated materials from aldehydes and ketones (Figure 1).[4-6] In this report we show that using visible light irradiation, 6-bromo-2-naphthol (**3**) functions as a photoacid catalyst for the synthesis of acetals.[7,8] We also demonstrate that photosensitization of 2-naphthol in the presence of a photosensitizer facilitates the acetalization of electron-deficient aldehydes. In addition, the S_1 excited-state pKa for 6-bromo-2-naphthol was determined and shown to exhibit enhanced excited-state acidity relative to 2-naphthol in water.

We choose to begin our investigations using bromo-substituted naphthols due to their propensity to undergo intersystem crossing (ISC) into long lived triplet excited states. Excitingly, irradiation of benzaldehyde (**6**) and 10 mol% 6-bromo-2-naphthol (**3**) with 40W Blue LEDs in methanol provides acetal **7** in 90% yield (Table 1, Entry 4). In the absence of catalyst and/or light no product is observed (Entries 1-3). Importantly, when 456 nm LEDs are used, **7** is formed in 94% yield (Entry 5). Using 370 nm or 390 nm LEDs gives **7** in 44% and 76% yield, respectively (Entries 6 and 7). The yield drops to 36% using 5 mol% **3** and only trace product is observed when 1 mol% **3** is employed (Entries 8 and 9). The bromine atom is essential for catalyst activation, 7-bromo-2-naphthol (**4**) provides **7** in 84% yield and unsubstituted 2-naphthol (**5**) is inactive (Entries 10 and 11). It is worth noting that in the case of benzaldehyde (**6**) aerobic photoirradiation (reaction run open to air) in the absence of catalyst, provides **7** in 81% efficiency (Entry 12).[9] It is possible that benzoic acid is being photogenerated when the rection is left open to air, however, when 10 mol% benzoic acid was used with and without light only 40 and 50% yield was observed, respectively (Entries 13 and 14). When 5 mol% sodium bicarbonate is added the reaction shuts down, supporting the formation of a Brønsted acid under the reaction conditions (Entry 15). Importantly, catalyst **3** can be recovered in up to 96% without the need for column chromatography and used in subsequent reactions without loss of efficiency.

With optimized conditions in hand, we proceeded to elucidate the scope of this photoacid catalyzed protocol (Table 2). Aromatic aldehydes containing both electron-donating and electron-withdrawing groups produced acetals **7**-**17** in 25-94% yield. Interestingly, photoirradiation of halogenated aldehydes provided acetals **10**-**12** with or without catalyst **3** (64-98% yield). Acetal **18**, containing an alkyne functional handle forms in 78%

Figure 1: Previous examples of photoacid-catalyzed acetalization of carbonyls.



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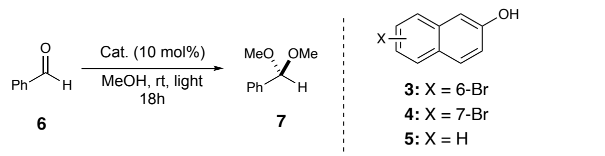
yield and ortho-substituted acetal **20** forms in 50% yield. Both heteroaromatics **22** and **23**, and α,β-unsaturated system **21** form acetals in good yields (64-92% yield). Importantly, aliphatic acetal **24** and cyclohexanone-derived acetal **25** form in 62 and 75% yield, respectively. Benzophenone produced no product. We also investigated a range of alcohols for this photoacid-catalyzed protocol. Ethoxy acetals **26** and **27** formed in 64 and 70%, respectively. Cyclic acetals derived from ethylene glycol **28** and pinacol **29** formed in good yield, 62 and 67%, respectively. Chloroethanol derived acetal **30** formed in 53% yield, for a comparison when 10 mol% **2** is used **30** forms in 78% yield. In some cases, substrate optimization was performed, and the use of 20 mol% **3**, 370 nm LEDs, and/or the use of 1,4-dioxane as a cosolvent was required for higher levels of efficiency.

Table 1: Optimization for the photoacid-catalyzed acetalization of carbonyls.[a]



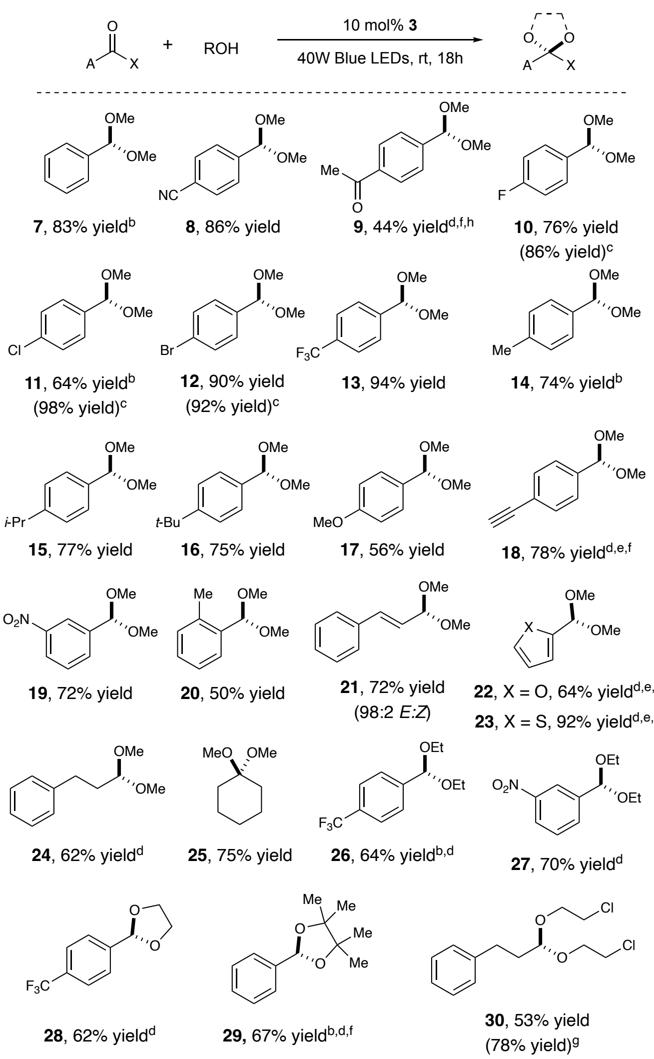
entry	catalyst	light	% yield[b]
1	--	--	0
2	--	40W Blue LEDs	0
3	3	--	0
4	**3**	**40W Blue LEDs**	**90**
5	3	456 nm LEDs	94
6	3	370 nm LEDs	44
7	3	390 nm LEDs	76
8[c]	3	40W Blue LEDs	36
9[d]	3	40W Blue LEDs	<5
10	4	40W Blue LEDs	84
11	5	40W Blue LEDs	0
12[e]	--	40W Blue LEDs	81
13	$PhCO_2H$	--	50
14	$PhCO_2H$	40W Blue LEDs	40
15[f]	3	40W Blue LEDs	0

[a]Conditions: **6** (0.5 mmol) in MeOH (0.5 M), under argon atmosphere. [b]% yields based on ^{1}H NMR using an internal standard: 5,6-dibromo-1,3-benzodioxole. [c]Run with 5 mol% **3**. [d]Run with 1 mol% **3**. [e]Reaction run open to air. [f]Run with 5 mol% $NaHCO_3$.

Finally, it is worth noting that we observed inconsistent results depending on the batch of methanol used, it was ultimately determined that freshly distilled methanol worked best (See supporting information).

It is noted that the bromine atom of **3** is critical for photoacid catalysis to occur, unsubstituted 2-naphthol (**5**) is completely inactive. For comparison, we determined both the ground state acidity (pKa) and excited-state acidity (pKa*) for both **3** and **5** (Figure 2, A).[10] The pKa of **5** was determined to be 9.75 and the pKa of **3** was determined to be 9.84, to the best of our knowledge this represents the first time the pKa for **3** has been determined in water.[11] The pKa* of **3** and **5** were determined to be 1.98 and 3.26, respectively. Interestingly, although the ground state pKa of **3** and **5** differ by only 0.09 pKa units, the pKa* of **3** was found to be $10^{1.4}$ times more acidic than the pKa* of **5**, shifting by 10^7 orders of magnitude. The excited state (S_1) lifetimes for both **3** and **5** were also determined, τ = 0.049 ns (4.9 ps) and τ = 6.8 ns, respectively. The substantially shorter lifetime of **3** is attributed to rapid intersystem crossing (ISC) facilitated by the heavy atom effect of bromine into a triplet excited state.[12] It is worth noting that the pKa, pKa*, and S_1 lifetime values determined for **5** are in good agreement with Tolbert and Haubrich.[13] Importantly, the direct excitation with visible light (Blue LEDs) activates photoacid catalyst **3** to facilitate acetalization. To better understand this, we measured the UV-Vis spectra for both **3** and **5** before and after 18 h irradiation (Figure 2, B). Catalyst **3** develops a prominent new feature at ~220 nm after irradiation, **5** remains largely unchanged. Catalyst **3** absorbs lower-energy light (340-360 nm) and with higher efficiency when compared to **5**, however, neither

Table 2: Scope for the photoacid-catalyzed acetalization of carbonyls.[a]



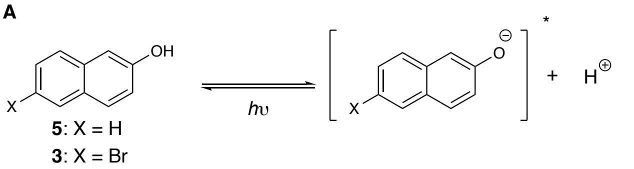
[a]Conditions: carbonyl compound (0.5 mmol) in the corresponding alcohol (0.5 M), under argon atmosphere, % yields based on ^{1}H NMR using an internal standard: 5,6-dibromo-1,3-benzodioxole. [b]isolated yield. [c]Run with no catalyst. [d]Run with 20 mol% **3**. [e]Run with 370 nm LEDs. [f]Run in 0.33 M MeOH:dioxane (2:1). [g]Run with 10 mol% **2**. [h]Reaction run with 0.25 mmol aldehyde.

3 nor 5 significantly absorbs light in the blue region of the electromagnetic spectrum (450-485). The 40W Blue LEDs used in this study emit strongly from 408-535 nm with weak emission from 372-390 nm.[14]

Initiation studies suggest that a 2 h induction period is required before the reaction begins and that if sufficient photoactivation is achieved the acetalization reaction proceeds in the absence of further light irradiation, suggesting the formation of a persistent in situ generated acidic species is responsible for catalysis.[4,15] Interestingly if 10 mol% **3** in methanol is irradiated overnight, followed by the addition of **6** and placement in the dark, the reaction finishes in 1 vs 6 h (See supporting information). The addition of 5 mol% triethylamine or sodium bicarbonate completely shuts down the standard reaction of **6** to **7** in the presence of 10 mol% **3**.

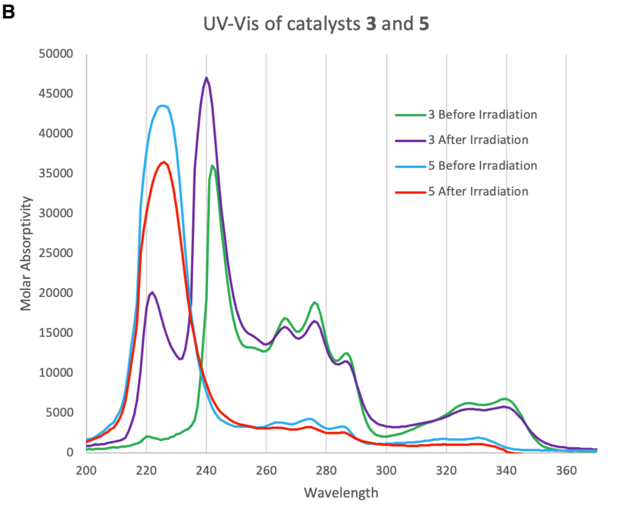
Figure 2: Excited-state acidity and lifetime determination and UV-Vis for catalysts **3** and **5**.

A



X	λ_{max} (nm)	τ_{S1} (ns)	pK_a (H_2O)	pK_a^* (H_2O)
H	330	6.8 (8.6)*Ref. 13*	9.75 (9.45)*Ref. 13*	3.26 (2.8)*Ref. 13*
Br	340	0.049	9.84	1.98

B



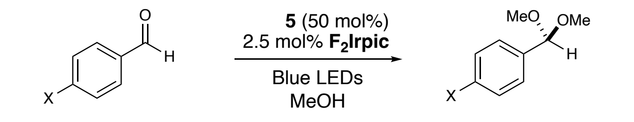
A) Excited-state pKa and lifetime determination for catalysts **3** and **5**. B) UV-vis spectra for **3** and **5** before and after 18 h irradiation with Blue LEDs (5 mM in MeOH).

Interestingly, we have also shown that unsubstituted 2-naphthol (**5**) in the presence of a photosensitizer **F₂Irpic** [bis[2-(4,6-difluorophenyl)pyridinato-C2,N](picolinato)iridium(III)]

facilitates the reaction of electron deficient aldehydes to form acetals **8** and **13** (Figure 3, A). When the sensitizer **F₂Irpic** alone is used the reaction only reaches up to 25% yield. However, when both **F₂Irpic** (2.5 mol%) and **5** (50 mol%) are employed the rection reaches 70-74% yield. Emission quenching studies showed that **F₂Irpic** emission was 34% quenched in the presence of 2-naphthol (**5**) with and without 4-trifluoromethyl benzaldehyde, suggesting efficient energy transfer between **F₂Irpic** and **5**. No **F₂Irpic** emission quenching was observed in the presence of aldehyde in the absence of **5**. Based on reports by Hanson and Protti, a possible mechanism for acetal formation is shown in Figure 3, B.[16,17] Photoexcitation of **F₂Irpic** results in formation of singlet **¹F₂Irpic***, intersystem crossing (ISC), and metal to ligand charge transfer (MLCT) gives rise to triplet excited state **³F₂Irpic***. Triplet energy transfer (TET) from **³F₂Irpic*** to **5**, gives rise to **5*** which is sufficiently acidic to protonate aldehyde **31** to afford oxonium **32**.

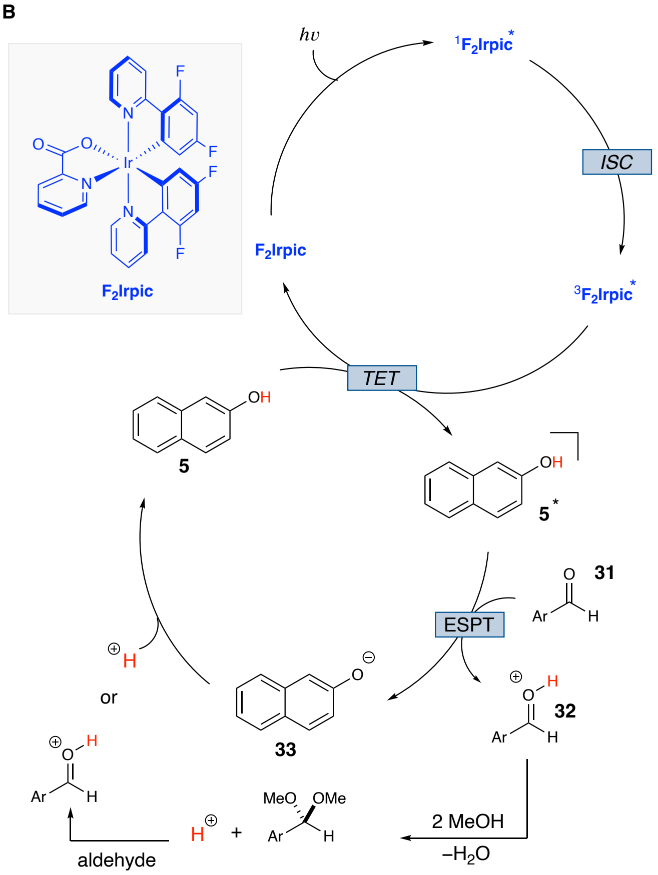
Figure 3: Photosensitization of 2-naphthol.[a]

A



5	F₂Irpic	%yield (8, X = CN)	%yield (13, X = CF₃)
×	×	0	0
√	×	0	0
×	√	0	25
√	√	***70***	***74***

B



[a]Conditions: Reaction run with (0.5 mmol) aldehyde in methanol (0.5 M), under argon atmosphere, % yields based on ¹H NMR using an internal standard: 5,6-dibromo-1,3-benzodioxole. ESPT =Excited State Proton Transfer.

Subsequent reaction of **32** with 2 equivalents of methanol results in acetal formation and regenerates a proton. The resulting in situ generated proton can either protonate an additional equivalent of aldehyde or protonate **33** to reconstitute **5**. The addition of 5 mol% sodium bicarbonate shut down acetal formation in the presence of **F_2Irpic** with and without **5**, supporting that the reaction involves generation of a Brønsted acid. It was observed that electron-withdrawing groups are required for the sensitization reaction to proceed, and that the reaction does not proceed in the absence of light irradiation. The photosensitization reaction shuts down if left open to air. Efforts to expand the scope of this TET process and mechanistic studies to better understand the selectivity for electron-withdrawing aldehydes are ongoing in our laboratory (See supporting information).

Conclusions

In conclusion, we have demonstrated that visible light irradiation of 6-bromo-2-naphthol (**3**) facilitates the photoacid-catalyzed synthesis of acetals. We have also shown that 2-naphthol in the presence of a photosensitizer facilitates the acetalization of electron-deficient aldehydes. In addition, the pKa, pKa*, and S_1 lifetime for 6-bromo-2-naphthol were determined. Catalyst **3** was shown to exhibit enhanced excited-state acidity relative to 2-naphthol in water. The development of new photoacids and their use as catalysts for organic synthesis is ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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