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Photoacid-Catalyzed Friedel−Crafts Arylation of Carbonyls

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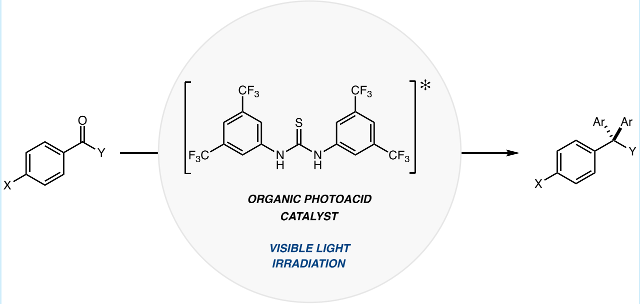
Supporting Information

ABSTRACT: In this report, we demonstrate that visible-light-induced thiourea photoacids catalyze C−C bond-forming reactions. Upon photoirradiation, Schreiner's thiourea [(*N*,*N*′-bis[3,5-bis(trifluoromethyl)phenyl]-thiourea] catalyzes the double Friedel−Crafts addition of indoles to aldehydes and isatins to form the corresponding triarylmethanes and 3,3′-diarylindolin-2-ones. This protocol is amenable to a wide range of aldehyde and isatin electrophiles, as well as a variety of electronically diverse indoles. Mechanistic studies show that light is required for reaction initiation.



The area of photocatalysis research has exhibited substantial growth in recent years,[1] and the development of new visible-light-driven catalytic methodology is fundamental for the improvement of green chemistry practices.[2] Recently, molecules that become orders of magnitude more acidic upon excitation with light, termed photoacids,[3] have emerged as a new class of small molecule hydrogen bond/proton donor organocatalysts. Although photoacids have been used in the context of polymerization reactions and to modulate the pH of biological systems,[4] their use in organic synthesis has only recently emerged as a viable strategy.[5] Small molecule hydrogen bond donor catalysts such as ureas and thioureas have been the focus of considerable research efforts,[6] and their catalytic efficacy is correlated to their relative acidity (pK_a).[7] In contrast to strong Brønsted acids or Lewis acidic metals, which have limited functional group compatibility or require air-free chemistry, photoacid catalysts can be attractive, since these catalysts are generally bench-stable weak acids in the absence of light and function as strong acids only upon photoactivation. Toshima and co-workers showed that Schreiner's thiourea (**1**) functions as an organophotoacid, becoming up to 10^3 times more acidic under long-wave UV (ultraviolet) irradiation to facilitate the glycosylation of alcohols (Figure 1).[8] As part of our research program on developing new photoacid catalysts, we questioned if this photoinduced thiourea-catalyzed process could be used to facilitate C−C bond-forming reactions. Here we show that upon irradiation with visible light (blue LEDs) thiourea **1** catalyzes the double addition of indoles to aldehydes and isatins to form the corresponding triarylmethanes and 3,3′-diarylindolin-2-ones. To the best of our knowledge, this represents the first example of thiourea photoacid catalysis in the context of a C−C bond-forming reaction.

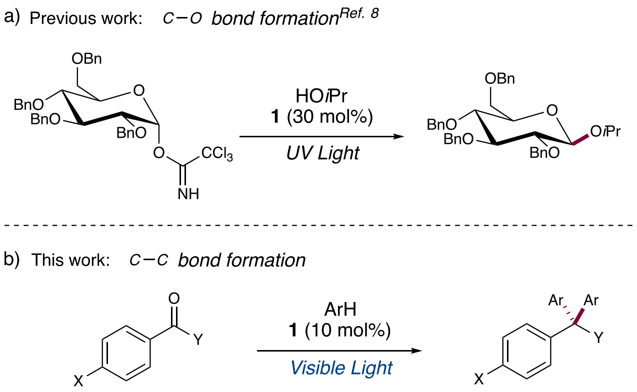


Figure 1. Photoinduced thiourea catalysis: (a) previous work and (b) this work.

We began our investigations using 4-(trifluoromethyl)benzaldehyde (**5**) and 1*H*-indole (**6**) to form 3,3′-((4-(trifluoromethyl) phenyl)methylene)bis(1*H*-indole) (**7**) (Table 1). In the absence of light and/or catalyst, no product was observed (entries 1−10). Heating to 65 °C in dioxane produced only trace product (<5%, entry 11). Irradiation with 40 W blue LEDs in the presence of 10 mol % **1** provided the desired product (entries 12−16), with dioxane being the optimal solvent (85% yield of **7**, entry 16). Switching to 370 nm LEDs also provided **7** in excellent yield (90%, entry 17). The reaction efficiency is affected by the catalyst loading; while lowering the catalyst loading to 5 mol % resulted in identical yield (90%, entry 18), decreasing further to 1 mol % catalyst resulted in a significant drop-off in reaction efficiency, 46% yield (entry 19). The trifluoromethyl substituents on the photoacid are not strictly required for catalysis, as *N*,*N*′-diphenylthiourea (**2**) is also an efficient photocatalyst, providing **7** in 84% yield. The enhanced acidity imparted by the sulfur of the thiourea is critical for reactivity, as both

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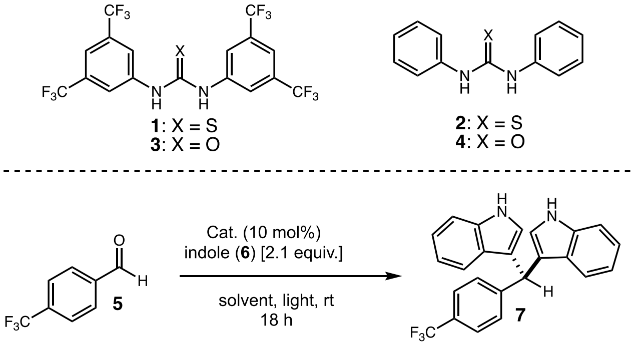
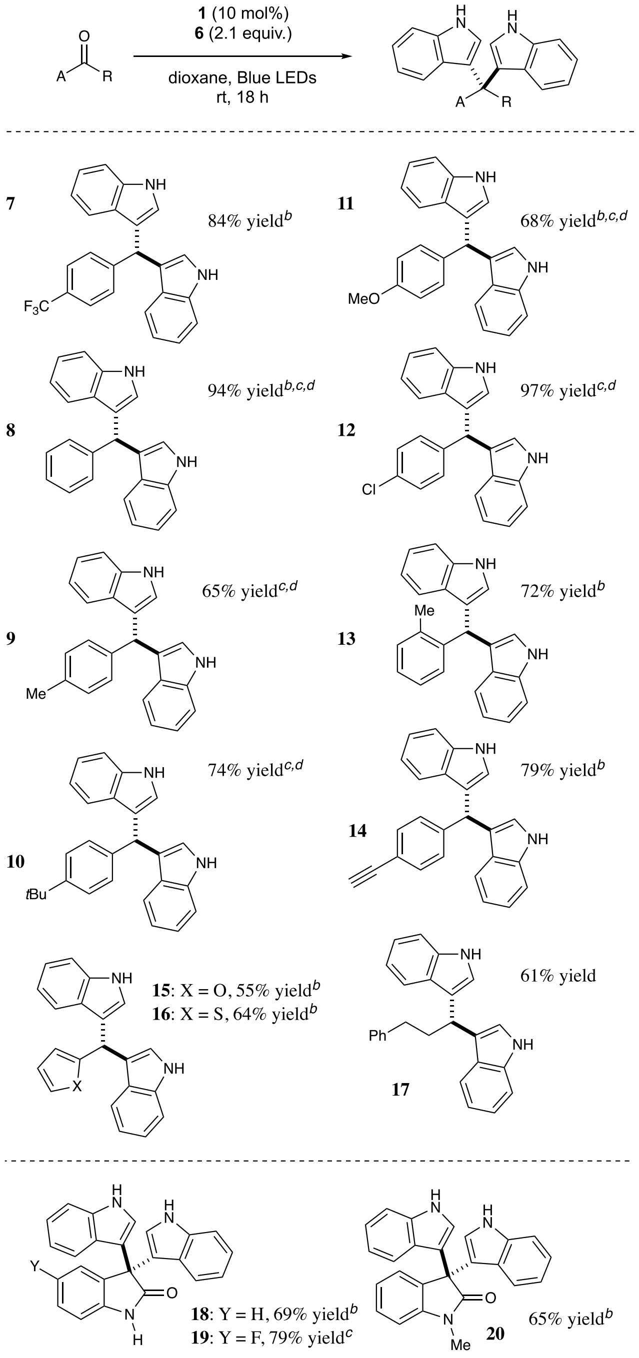
Table 1. Optimization for the Photoacid-Catalyzed Friedel–Crafts Arylation of Carbonyls



entry	solvent	catalyst	light	% yield[a]
1	DCM			0
2	1,4-dioxane			0
3	DCM		40 W blue LEDs	0
4	1,4-dioxane		370 nm LEDs	0
5	1,4-dioxane		40 W blue LEDs	0
6	DCM	1		0
7	DCE	1		0
8	ACN	1		0
9	THF	1		0
10	1,4-dioxane	1		0
11[b]	1,4-dioxane	1		<5
12	DCM	1	40 W blue LEDs	22
13	DCE	1	40 W blue LEDs	39
14	ACN	1	40 W blue LEDs	51
15	THF	1	40 W blue LEDs	75
16	1,4-dioxane	1	40 W blue LEDs	85
17	1,4-dioxane	1	370 nm LEDs	90
18[c]	1,4-dioxane	1	370 nm LEDs	90
19[d]	1,4-dioxane	1	370 nm LEDs	46
20	1,4-dioxane	2	370 nm LEDs	84
21	1,4-dioxane	3	370 nm LEDs	0
22	1,4-dioxane	4	370 nm LEDs	0

[a] % yields based on NMR using 5,6-dibromobenzo[*d*][1,3]dioxole as an internal standard. [b] Reaction run at 65 °C. [c] Using 5 mol % **1**. [d] Using 1 mol % **1**.

Scheme 1. Carbonyl Scope[a]



[a] Isolated yield. [b] Reaction run with 370 nm LEDs. [c] Reaction run with 4.2 equiv of **6**. [d] Run with dichloromethane as the solvent.

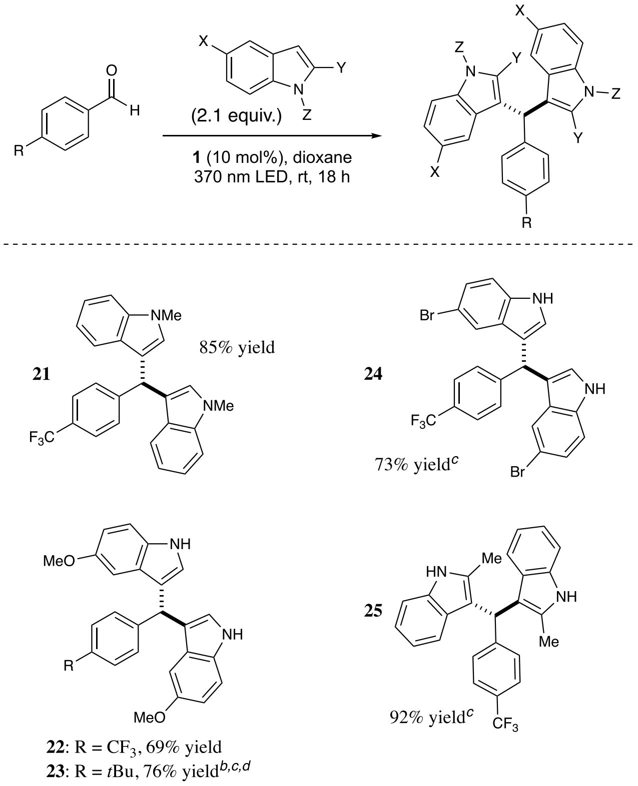
oxygen-containing urea catalysts **3** and **4** proved ineffective at inducing catalysis.[9]

(For complete catalyst evaluation details, see the Supporting Information.)

With optimized conditions in hand, we then investigated the scope for this photoacid-catalyzed process. A variety of substituted aryl aldehydes were tolerated (Scheme 1). Unsubstituted benzaldehyde provided double addition product **8** in an excellent 94% yield. Electron-donating groups at the *para*-position, including methyl, *t*-butyl, methoxy, and chloro are well tolerated (**9**–**12**). Interestingly, while either blue LEDs or 370 nm LEDs worked well for most substrates, select substrates performed slightly better using one or the other.[10] We observed a strong dependence on solvent choice for reaction efficiency. For example, using 370 nm LEDs, 4-methoxybenzaldehyde provided <10% product **11** in dioxane but resulted in 68% yield in DCM. Sterically hindered *o*-tolualdehyde was doubly arylated in good yield (72%, **13**), and an alkyne functional handle was well preserved in the course of the reaction (79% yield, **14**). The heteroaromatic aldehydes furfural and thenaldehyde afforded triarylmethane products **15** and **16** in 55 and 64% yields, respectively. Importantly, aryl substitution on the aldehyde was shown to be nonessential, as aliphatic aldehyde 3-phenylpropanal resulted in **17** in 61% yield. Isatins are also competent electrophiles for this photoacid-catalyzed process. Both *N*–H and *N*-methyl isatins gave the corresponding 3,3′-oxindoles in good yields (**18**–**20**, 65–79% yields).

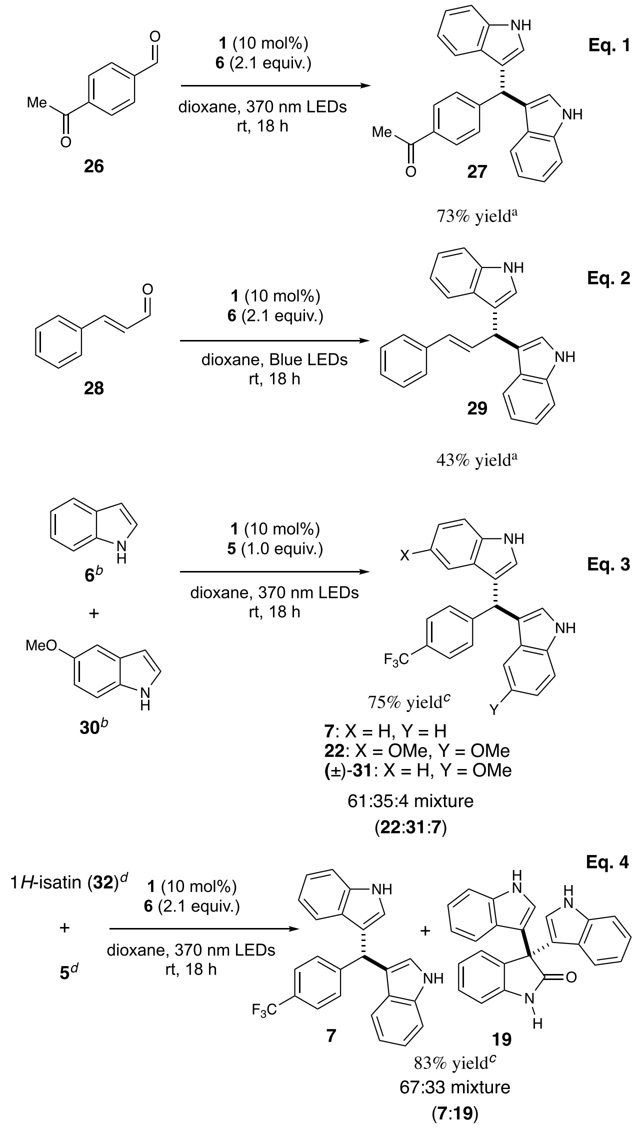
Next, we investigated the scope of indoles in this photoinduced protocol (Scheme 2). *N*-Methylindole provided triarylmethane product **21** in 85% yield. Varying the electronics on the indole was well tolerated. 5-Methoxyindole addition gave acute myelogenous leukemia (AML) inhibitors

Scheme 2. Indole Scope[a]



[a] Isolated yield. [b] Reaction run with blue LEDs. [c] Reaction run with 4.2 equiv of **6**. [d] Run with dichloromethane as the solvent.

Scheme 3. Competition Experiments[a]



[a] Isolated yield. [b] 2.1 equiv. [c] % yields based on NMR using 5,6-dibromobenzo[*d*][1,3]dioxole as an internal standard. [d] 1.0 equiv.

22 and **23** in good yields (69 and 76% yields, respectively).[11] Surprisingly, inductively deactivated 5-bromo indole provided **24** in good yield (73%). Sterically hindered 2-methylindole was also a competent nucleophile, providing access to **25** in 92% yield. Unfortunately, nucleophiles such as *N*,*N*-dimethyl-*m*-anisidine, skatole, and allyltriisopropylsilane provided only trace products.

A series of competition experiments revealed that this photoactivated protocol is selective for addition to aldehydes (Scheme 3). When 4-acetylbenzaldehyde (**26**) was employed under standard conditions, only addition to the aldehyde was observed, providing compound **27** in 73% yield, leaving the ketone intact (Scheme 3, eq 1). The reaction is selective for 1,2-addition to the aldehyde vs 1,4-conjugate addition, as demonstrated by the reaction with cinnamaldehyde (**28**), which provided exclusively **29**, albeit in diminished yield (43%, Scheme 3, eq 2).[12] When aldehyde **5** was exposed to a 1:1 mixture of 1*H*-indole (**6**) and 5-methoxy-1*H*-indole (**30**), the more electron-rich 5-methoxy indole outcompeted **6** to form a 61:35:4 mixture of triarylmethane products with **22** and chiral cross product (±)-**31** as the major products (75% yield, Scheme 3, eq 3). A competition between isatin **32** and **5** gave a 67:33 mixture of **7** to **19** in favor of addition to the aldehyde (83% yield, Scheme 3, eq 4).

Mechanistic studies for this photoinduced process demonstrate that light is required for reaction initiation. Under constant irradiation with 370 nm LEDs, the reaction between 1*H*-isatin (**32**) and 1*H*-indole (**6**) to form oxindole **19** reached 74% yield in 6 h (Figure 2A). Interestingly, when the reaction was irradiated for 1 h and then placed in the dark for 6 h, the reaction progress continued at a similar rate, reaching 81% yield (Figure 2B). One possible explanation for this observation is the photogeneration of an *in situ* formed acidic species which then catalyzes the arylation reaction.[5d,13,14] When catalyst **1** is irradiated for 1 h, followed by the addition of indole **6** and isatin **32**, the reaction only reaches 35% yield after 5 h in the absence of further light exposure (71% with light). However, if a combination of **1** and **32** or **1** and **6** is irradiated for 1 h, the reaction goes to completion after 5 h in the absence of further light exposure.[15] This result suggests that a complex composed of the thiourea and carbonyl (**33**) or indole (not shown) is critical for photoinitiation (Figure 2C). Addition of 5 mol % Na_2CO_3 to the reaction under standard conditions for the formation of **7** reduced the yield to 32%, and adding 5 mol % of a proton scavenger (2,6-di-*tert*-butyl-4-methylpyridine) had no effect on reaction efficiency (82% yield of **7**).[16] We observed a time-dependent initiation wherein irradiation of at least 10−30 min was required for the formation of oxindole **19** to progress in the dark (Figure 3). The molar absorption spectra for the reaction components for

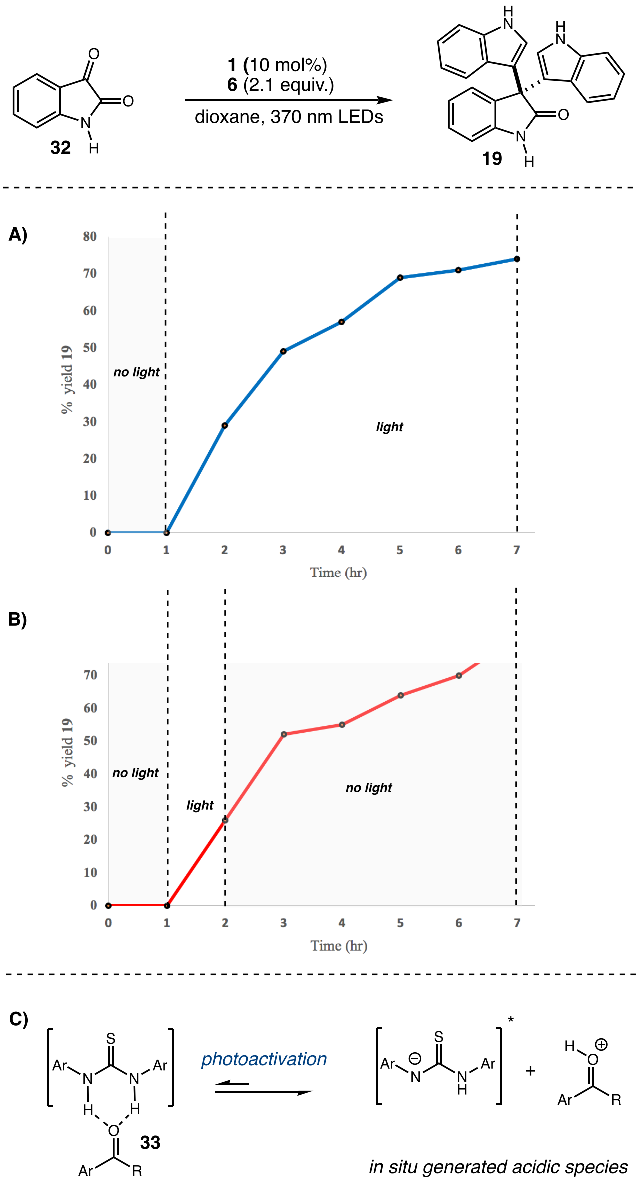


Figure 2. Reaction profile and photoacid activation. (A) Standard conditions for **19** formation with 1 h of no light, followed by light irradiation for 6 h. (B) Standard conditions for **19** formation with 1 h of no light, followed by 1 h of light irradiation and then 5 h of no light. (C) Photoexcitation of complex **33** and *in situ* generated acidic species.

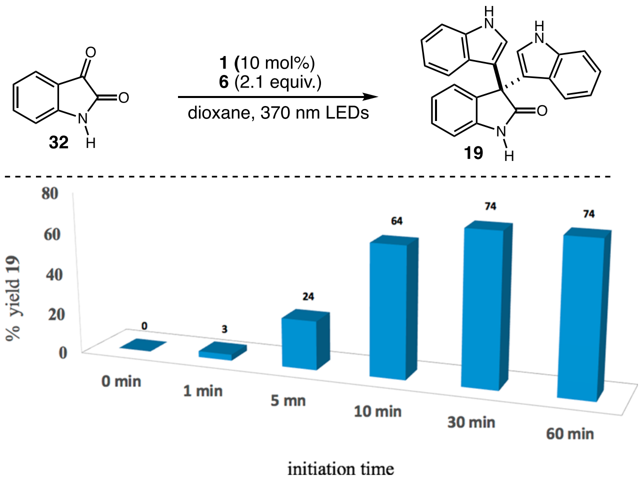


Figure 3. Time-dependent photoactivation. The reaction was irradiated for 0, 1, 5, 10, 30, or 60 min and placed in the dark. % yields based on NMR analysis at 7 h using 5,6-dibromobenzo[*d*]-[1,3]dioxole as an internal standard.

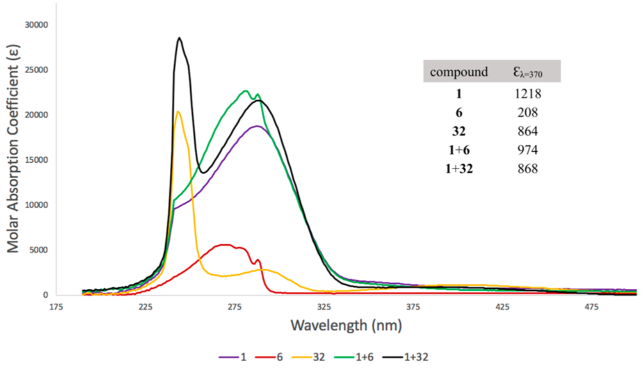


Figure 4. Molar extinction coefficients (ε) vs wavelength for **1**, **6**, **32**, and a 1:1 stochiometric mixture of **1** + **6** and **1** + **32**.

the formation of **19** are shown in Figure 4. All of the reaction components absorb 370 nm light, with catalyst **1** having the largest molar extinction coefficient ($\varepsilon_{\lambda=370}$) of 1218. It is also worth noting that the shape of the absorption spectra for the 1:1 mixture of **1** and **6** or **32** changes relative to their individual spectra (see the Supporting Information for LED emission spectra and additional details).

In conclusion, we have demonstrated that photoinduced thiourea catalysis facilitates a double Friedel–Crafts addition of indoles to aldehydes and isatins to form a wide range of triarylmethanes and 3,3′-diarylindolin-2-ones. Competition experiments show that this light-facilitated protocol is selective for addition to aldehydes over ketones, isatins, and Michael acceptors. Mechanistic studies show that light irradiation is critical for reaction initiation. Applications of this type of photoacid catalysis, as well as second-generation photoacids, are being studied in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02841.

Experimental procedures, characterization data, and copies of spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(10) Anywhere between 5 and 10% boost in efficiency depending on the substrate.

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(14) 10 mol % HF provided no product.

(15) Irradiation of **6** or **32** in the absence of catalyst produces no product.

(16) 10 mol % Na_2CO_3 resulted in <5% yield.