

Chemical Photocatalysis with 1-(*N,N*-Dimethylamino)pyrene

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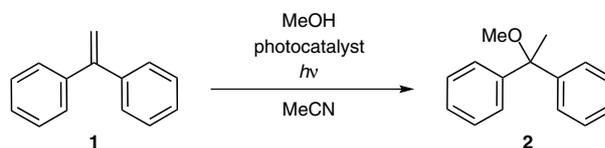
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Abstract: 1-(*N,N*-Dimethylamino)pyrene was applied as chemical photocatalyst for two different organic reactions: Both the photocatalytically driven nucleophilic addition of methanol to 1,1-diphenylethylene and the photocatalytic deprotection of *N*-phenylsulfonylindole gave the corresponding products in good yields and in a highly sustainable way after short irradiation with high-power LED. This concept can potentially be transferred to other photochemical reactions.

Key words: pyrene, chromophore, electron transfer, alkene, indole

Chemical photocatalysis in the organic-chemical context can be applied in such a way that a redox active chromophore, upon irradiation with light, induces an electron transfer to the substrate.^{1–7} This photophysical process (charge separation) is coupled to a subsequent chemical reaction. The absorbed light energy contributes to the overall energy balance of the reaction and thereby increases its sustainability. The photocatalysis should work in the UV-A/Vis range in order to increase sustainability by applying high-power light-emitting diodes (LED) as a cheap and reliable source for irradiation. This concept drives our search for new photocatalytic methods which can be accomplished by rethinking photochemical reactions that have been known for decades. Herein, we describe our efforts to develop photocatalytic versions of two simple, but synthetically important reactions. Both reactions have in common that a photoinduced electron-transfer step is the initial photochemical step.

Photochemical addition of amines to styrenes and stilbenes were first reported by Cookson⁸ and Kawanishi.⁹ Lewis and co-workers elucidated exciplex states as key intermediates for this kind of reactions.¹⁰ On the other hand, photohydration of aromatic alkenes requires the direct excitation of the alkene component by energy-rich UV light.¹¹ The first attempt to perform this type of reaction by photosensitization was published by Arnold and Maroulis.¹² They applied naphthalene derivatives to achieve the nucleophilic addition of methanol to alkenes. However, this process is still not compatible with irradiation by LED. Hence, we wanted to develop a new photocatalytic version of this reaction and used 1,1-diphenylethylene (**1**) as test substrate to avoid a prochiral center (Scheme 1).



Scheme 1 Photocatalytic nucleophilic addition to **1** as test reaction

First, we tested common aromatic chromophores as potential photocatalysts based on naphthalene (as previously published),¹² and additionally anthracene and pyrene derivatives (Table 1). For this screening, irradiation was performed by a conventional 200 W Hg(Xe) lamp (ozone-free) without monochromator. This, in the photochemical sense rather unselective irradiation was to cover the broad

Table 1 Chromophore Screening for the Nucleophilic Addition to **1** Yielding **2**^a

Entry	Photocatalyst	Yield (%) ^b
1	naphthalene	0
2	1-methylnaphthalene	3
3	1-methoxynaphthalene	12
4	1,4-dimethoxynaphthalene	56
5	2,6-dimethoxynaphthalene	37
6	2-(methylthio)naphthalene	49
7	1-(<i>N,N</i> -dimethylamino)naphthalene	17
8	1,5-di(<i>N,N</i> -dimethylamino)naphthalene	63
9	anthracene	2
10	9-methylanthracene	3
11	9,10-dimethylanthracene	9
12	9,10-dimethoxyanthracene	24
14	pyrene	4
15	1-(<i>N,N</i> -dimethylamino)pyrene	29
16 ^c	1-(<i>N,N</i> -dimethylamino)pyrene	33
17 ^c	1-(<i>N,N</i> -dimethylamino)pyrene ^d	75

^a Reaction conditions: **1** (2 mM), photocatalyst (2 mM), in MeCN–MeOH (7:3; 4 mL), argon atmosphere, 15 h, r.t., 200 W Hg(Xe) arc lamp, cut-off filter $\lambda < 305$ nm, reactants identified by GC–MS, quantified by GC–FID.

^b Averaged yield from at least two independent reactions.

^c With LED illuminator $\lambda = 365$ nm.

^d With 5% (v/v) Et₃N.

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excitation range of all applied chromophores by one lamp, and makes sense in the context of preparative organic photocatalysis to compare yields under comparable reaction conditions. The starting material **1** absorbs light in the range below 300 nm; hence it was important to equip the lamp with a 305 nm cut-off filter. The samples had to be degassed very carefully in order to avoid the formation of benzophenone as an undesired side product. The screening reactions were performed in an acetonitrile–methanol mixture (7:3), stopped after 15 hours irradiation time, and analyzed by GC–MS.

It is clear that the yields reflect the different extinction coefficients of the different chromophores above 305 nm to a certain extent. Nevertheless, from these results it became obvious that electron-donating groups are crucial for successful photocatalysis. This indicates an electron-transfer mechanism which will be further discussed below. In fact, the best yields of 1,1-diphenyl-1-methoxyethane (**2**) were obtained with those photocatalysts that carry two methylated hydroxyl or amino groups (Table 1, entries 4, 5, 8, 12, and 15). Among the most promising photocatalysts in the test reactions, 1-(*N,N*-dimethylamino)pyrene (**D**) has the highest extinction in the range around 350–370 nm. High-power LED are available for distinct excitation at these wavelengths. Beside this, **D** represents also a powerful reductant with a reduction potential of -2.16 V.¹³ Together with the reduction potential of -2.08 V (vs. NHE)¹⁴ for **1**, the Rehm–Weller equation gives a small ΔG of approximately 100 meV for the initial electron-transfer step. Hence, we further investigated this photocatalytic reaction using a special illuminator that contains 250 mW (optical output) high-power LED for irradiation at 365 nm, a Peltier temperature control element and a stirrer. Using this apparatus, the reaction in entry 15 (Table 1) could now reach completion in three hours. The yield, however, was not significantly increased (Table 1, entry 16). An important observation in the latter reaction was found in the GC–MS analysis: The photocatalyst **D** degrades during the photochemical reaction and thereby limits the photocatalytic conversion from **1** into **2**. Assuming an electron transfer from **D** to the substrate **1** as the initial step for the photocatalysis it was reasonable to add Et₃N to get better recovery of the oxidized radical cation of **D** (**D**⁺) to ground state **D**. In fact, in the presence of 5% (v/v) Et₃N product **2** could be obtained in 75% yield. In order to get more insight into the kinetic behavior of this reaction, aliquots were taken every ten minutes during irradiation and were analyzed by GC–FID. The data plot (Figure 1, top) showed clear conversion from **1** into **2** which is finished after ca. three hours.

Careful analysis of the GC–MS/GC–FID data revealed, however, a second product **3** which is formed concomitantly with the main product **2**, but only in the presence of Et₃N. It was identified to be 1,1-diphenylethane (**3**). The addition of Et₃N as an additional electron shuttle in this photocatalytic reaction offers the possibility to use **D** in substoichiometric amounts. These reactions were tested down to 0.1 equivalents **D** (Figure 1, bottom) to achieve

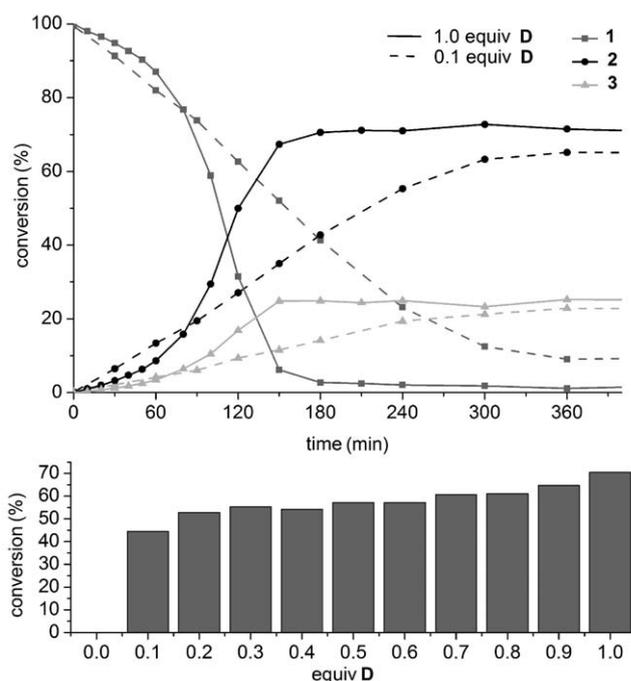
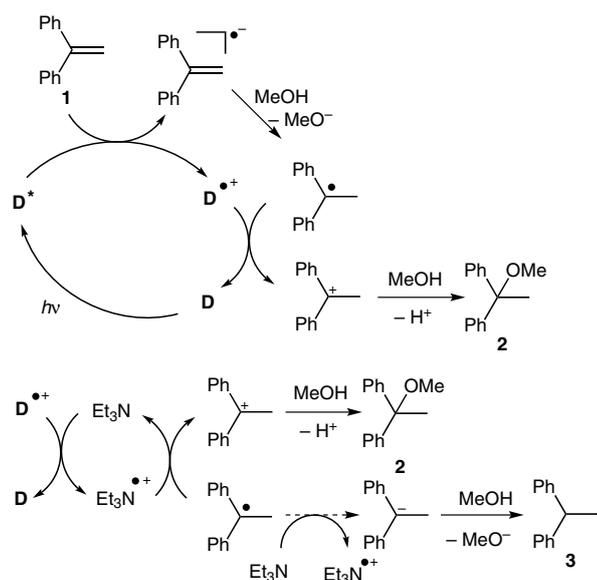


Figure 1 Top: Time-dependent analysis of the photocatalytic conversion of **1** into **2** in the presence of 1.0 (straight line) and 0.1 equiv **D** (dashed line); **1** (2 mM), in MeCN–MeOH (7:3, 4 mL), 5% (v/v) Et₃N, r.t., LED illuminator $\lambda = 365$ nm. Bottom: Yields obtained with stoichiometric and substoichiometric amounts of **D**; **1** (2 mM), in MeCN–MeOH (7:3, 4 mL), 5% (v/v) Et₃N, 3 h, 25 °C, LED illuminator $\lambda = 365$ nm.

true chemical photocatalysis. After three hours irradiation the yields decreased from 71% (with 1 equiv **D**) down to 45% of product **2** in the presence of 0.1 equivalent **D**. The detailed kinetic analysis (Figure 1, top, dashed lines) revealed that the latter reaction just needs more time (ca. 6 h) to reach completion with only slightly diminished yield (65% vs. 71%). The control experiment without any photocatalyst **D** showed no conversion at all. It is important to point out additionally that all reactions with the LED illuminator did not require degassing of the reaction samples.

Arnold and Maroulis proposed an electron-transfer mechanism for the nucleophilic addition. In fact, a Stern–Volmer plot indicates fluorescence quenching of **D** in the presence of **1** (data not shown). Hence, we assume a similar electron-transfer mechanism for the conversion of **1** into **2** that is photocatalyzed by **D** in the absence of Et₃N. Based on the observed degradation of **D** during this reaction, the most critical step of this mechanistic cycle seems to be the back electron transfer from the protonated (neutral) diphenylethyl radical to the photocatalyst **D**. Obviously, Et₃N represents the electron donor better than the substrate radical, since degradation of **D** is significantly reduced. Moreover, addition of Et₃N increases the yield of **2** significantly. This implies the idea that Et₃N closes the cycle and gets regenerated by oxidation of the diphenylethyl radical. Thereby an additional electron shuttle is provided by Et₃N for the improved back electron transfer. On the other hand, this makes the formation of side product **2** very plausible, since the diphenylethyl radical cannot only

be oxidized by the Et_3N radical cation but also reduced by Et_3N itself; subsequent protonation of the diphenylethyl radical anion gives the saturated product **3**.



Scheme 2 Proposed mechanism for the photocatalytic nucleophilic addition of MeOH to **1** in the absence of Et_3N (top) and in the presence of Et_3N (bottom)

To support the proposed role of Et_3N as an electron shuttle we performed additional photocatalytic experiments with different amounts of Et_3N (0–180 equiv) and three hours irradiation time by LED (Figure 2). At low Et_3N concentrations the photocatalyst **D** gets degraded, as already mentioned above. Thus, product **2** is formed only in lower yield (ca. 30%). Additionally, benzophenone is formed as a significant and undesired side product. On the other hand, 180 equivalents Et_3N are enough to keep the photocatalyst **D** active until complete conversion of **1** takes place. If the photocatalytic experiment with 40 equivalents Et_3N is compared to the reaction with 180 equivalents it becomes obvious that higher concentrations of

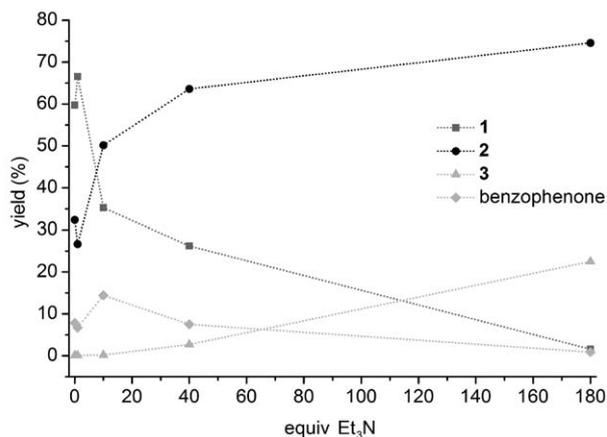
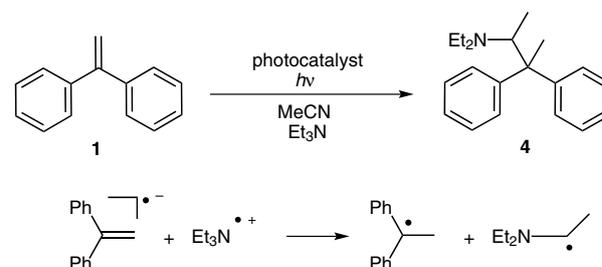


Figure 2 Photocatalytic conversion of **1** into **2** with different amounts of Et_3N . Conditions: **1** (2 mM), **D** (2 mM), in MeCN–MeOH (7:3; 4 mL), 3 h, 25 °C, LED illuminator.

Et_3N give rise to the amount of side product **3**. This observation supports additionally the proposed mechanism (Scheme 2).

It is remarkable that in the absence of MeOH as nucleophile for the photocatalytic addition, product **4** is obtained in yields of 62–67% (Scheme 3) by addition of Et_3N . No product **3** is obtained in these reactions. Based on the proposed role of Et_3N as described above it seems to be very plausible that electron transfer to the substrate **1** and generation of the photocatalyst **D** (from D^*) by oxidation of Et_3N yields a radical ion pair, that (upon proton transfer) recombines simply to product **4**.

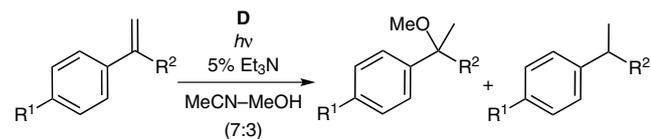


Scheme 3 Top: Photocatalytic addition of Et_3N to **1** in the absence of MeOH; **1** (2 mM), **D** (2 mM), in MeCN (4 mL), 5% (v/v) Et_3N , 3 h, 25 °C, LED illuminator 265 nm. Bottom: Proposed mechanism for this reaction.

The substrate scope of this photocatalytic addition was elucidated with several α -phenylstyrenes and styrenes (Table 2). It became obvious that electron-withdrawing groups are required for this reaction (Table 2, entries 1–4 and 7); methoxy-substituted α -phenylstyrene (Table 2, entry 5) and unsubstituted styrene (Table 2, entry 6) showed no significant amounts of products. This result is due to the small driving force for the initial photoinduced electron-transfer step as already discussed above in the case of **1**.

In a last set of experiments we wanted to extend the scope of this photocatalytic concept and method to a completely different reaction that is initiated by a photoinduced electron transfer which is the deprotection of sulfonylated indoles. The phenylsulfonyl protecting group is used very often for amines, especially aromatic amines, such as indole.¹⁵ The disadvantage of this group, however, is its high stability which requires harsh basic or acidic conditions to remove it.^{16,17} This limits the synthetic usefulness of this kind of protecting group. Photodesulfonylation of sulfonamides¹⁸ and amines¹⁹ was achieved by direct excitation of the substrate. Excitation of indoles at 254 nm induced an electron transfer to Et_3N and gave deprotected indoles in moderate yield and accompanied by a couple of side products.²⁰ We applied nearly the same reaction conditions that were previously elucidated for the conversion of **1** into **2** for the deprotection of *N*-phenylsulfonylindole (**5**) to indole (**6**, Scheme 4).

In the absence of Et_3N , degradation of the photocatalyst **D** was so fast and efficient that no deprotection of **5** could be achieved at all by excitation at 365 nm with LED (Table

Table 2 Photocatalytic Addition Reactions of α -Phenylstyrenes and Styrenes^a

Entry	R ¹	R ²	Yield (%) addition	Yield (%) reduction
1	H	H	75 ^b	23
2	CO ₂ Me	Ph	68 ^b	31
3	CN	Ph	35 ^b	65
4	F	Ph	34 ^c	2
5	MeO	Ph	5 ^d	1
6	Ph	H	0 ^c	0
7	CO ₂ Me	H	58 ^b	42

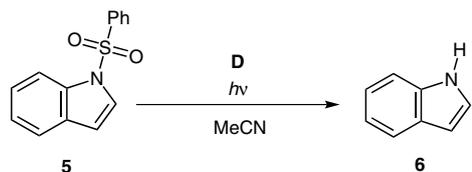
^a Conditions: substrate (2 mM), MeCN–MeOH (7:3, 4 mL), 5% (v/v) Et₃N, r.t., LED illuminator $\lambda = 365$ nm, reactants identified and quantified by GC–MS.

^b Nearly complete conversion.

^c Conversion 36%.

^d Conversion 6%.

^e No conversion.

**Scheme 4** Photocatalytic deprotection of *N*-sulfonylated indole 4

3, entry 1). The situation changed completely after addition of Et₃N; good yield (77%, Table 3, entry 2) was obtained for the deprotected indole **6** in the presence of an equimolar amount of **D** (Table 3, entry 2). An even better yield (87%, Table 3, entry 4) was achieved in the presence of only 0.5 equivalents photocatalyst. The reaction with

Table 3 Photocatalytic Deprotection of **5** to **6**^a

Entry	D (mM)	Et ₃ N (equiv)	Yield (%) ^b
1	2	–	0
2	2	200	77 ^c
3	–	200	0
4	1	200	87 ^c
5	0.5	200	30

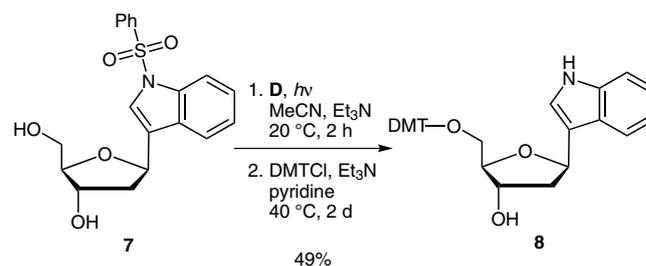
^a Conditions: **5** (2 mM), **D**, Et₃N, in MeCN (1 mL), 2 h, 25 °C, 250 mW LEDs output at 365 nm, reactants identified by GC–MS, quantified by GC–FID.

^b Averaged yield from at least two independent reactions.

^c Conversion 100%.

0.1 equivalents **D** gave only 30% yield (Table 3, entry 5), but conversion was not complete in two hours, similar to the corresponding photocatalytic nucleophilic addition that was discussed above (Figure 1, bottom). These results demonstrate that the photocatalytic reaction conditions elucidated for the conversion of **1** into **2** can be transferred to other photochemical problems, such as the deprotection of **5** to **6**.

In order to test this methodology representatively in ‘real’ synthesis we used it for deprotection of *N*-sulfonylated indole nucleoside **7** that was synthesized according to the literature (Scheme 5).²¹ Without any workup after deprotection of **7**, the 5'-hydroxy group was protected with DMT which is needed for later DNA building-block chemistry. The reaction on a 100 mg scale (compound **7**) yielded 49% of the desired indole nucleoside **8**.

**Scheme 5** Photocatalytic deprotection of *N*-sulfonylated indole nucleoside **7**

Our results show clearly that it is worth to revisit known photochemical reactions and develop photocatalytic versions. Better yields were obtained for both types of photocatalytic processes that are presented herein. The irradiation in the UV-A/Vis range increases the sustainability significantly by applying energy-efficient high-power LED as a cheap and reliable source for light. The mild and nonacidic and nonbasic conditions make this type of photocatalysis a promising alternative for organic synthesis including protecting-group chemistry. This principal concept and type of methodology will certainly be applicable for other organic reactions in the future.

Synthesis of **8**

In a cuvette with a stir bar, **7**¹⁹ (100 mg, 268 μ mol, 1 equiv) was dissolved in MeCN (1.20 mL) and Et₃N (1.80 mL, 20.1 mmol, 75 equiv). **D** (65.7 mg, 268 μ mol, 1 equiv) was added and the solution was irradiated for 2 h (365 nm, 20 °C). The deprotection was observed by TLC [CH₂Cl₂–MeOH (10:1), *R_f* = 0.35]. The solvents were removed under vacuum. The crude product was dissolved in anhydrous pyridine (1.5 mL). Et₃N (40 μ L, 536 μ mol, 1 equiv) and DMTCI (118 mg, 349 μ mol, 1.3 equiv) were added, and the mixture was stirred over night at 40 °C. The reaction was observed by TLC [CH₂Cl₂–MeOH (25:1), *R_f* = 0.60]. Et₃N (40 μ L, 536 μ mol, 1 equiv) and DMTCI (118 mg, 349 μ mol, 1.3 equiv) were added again, and the mixture was stirred for another night at 40 °C. The solvents were removed under vacuum. The remaining pyridine was lyophilized out of benzene. The dried crude product was purified by column chromatography [silica gel, CH₂Cl₂–acetone (25:1), 1% Et₃N] yielding a brown solid (49%). The spectroscopic data was in agreement with the literature.¹⁹

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