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(Article begins on next page)

Application of Coumarin Dyes for Organic Photoredox Catalysis.

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Here we report the application of readily prepared and available coumarin dyes for photoredox catalysis able to mimic powerful reductant [Ir(III)] complexes. The coumarin derivatives 9 and 10 were employed as photoreductants in the pinacol coupling and in other reactions, in the presence of Et$_3$N as sacrificial reducing agent. As electronic, photophysical, and sterical properties of coumarins could be varied, a wide applicability to several classes of photoredox reactions is predicted.

Photoredox catalysis has become a hot topic in catalysis, due to the facility to generate active radical species in controlled and mild conditions, via electron or energy transfer from photocatalysts in their excited states to organic molecules.[1] In this context, organic dyes are attracting a great interest as photoredox catalysts (PC).[2,3,4] Although complexes of abundant and inexpensive metals have recently found some applications in photoredox catalysis,[5] organic dyes have been used as valid alternatives to the expensive, but widely used Ru(II)- and Ir(III)-complexes.[6] Several classes of suitable dyes have been explored in photocatalytic transformations.[2] As a prototypical example, the Fukuzumi catalyst (Figure 1, **1**) has been exploited in many interesting photoredox reactions, thanks to its strong oxidant ability in its lowest singlet excited state (E$_{1/2}$ = +2.06 V vs SCE, MeCN).[7] However, organic molecules behaving as strong reductants are much less common. Murphy described powerful organic reductants able to promote radical coupling and other reactions of substrates with reduction potentials < -1.8 V (vs SCE).[8] Unfortunately, these molecules are rather reactive and difficult to generate. Other organic photocatalysts used as reductants of substrates with reduction potentials in the range $-1.5 - -2.1$ V (vs SCE) are: 10-phenylphenothiazine **2**,[9a] perylene **3**,[9b] N-aryl phenoxazines **4**[9c] and *N,N*-diaryl dihydrophenazines **5**.[9d] These molecules contain electron-rich motifs which stabilize the radical cation formed in the photocatalytic process.[10]
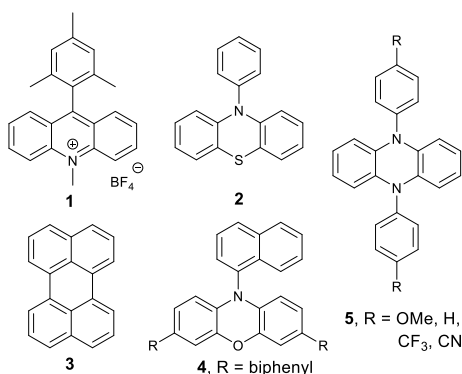

Figure. 1. Dyes employed in photocatalytic reactions.

Remarkably, although coumarins have been largely employed as fluorescent bio labels,[11a] laser dyes,[11b] emitting materials in organic light-emitting diodes (OLED)[11c] and dyes in solar cells,[11d] to the best of our knowledge, their systematic employment in photoredox reactions has not been yet explored. In addition, the low molecular weight and their straightforward synthesis[12] give the possibility to vary their photophysical and redox properties,[13] allowing to cover a wide range of photoredox potentials. With all these potentialities, the coumarin class attracted our interest for photoredox catalytic applications. Herein, we report the use of coumarins **9**[14] and **10** (see ESI for synthesis, details, and for evaluation of other coumarins in the model reaction) as powerful reductants in the photo-promoted radical coupling of carbonyls and imines,[15] and we illustrate the further possibility to apply coumarin dyes to many other photoredox reactions.

Quite recently, Rueping reported a photoredox mediated coupling of aldehydes, ketones, and imines mediated by Ir(III) photocatalyst, in the presence of Et$_3$N as sacrificial reductant.[16] Photoexcitation of the Ir(III) complex in the presence of Et$_3$N yielded the reduced Ir complex (E$_{1/2}$ = -1.69 V vs Fc), which is responsible for the reduction of carbonyl and imine groups. The so-formed radical cation Et$_3$N$^{•+}$, a Lewis acid, is supposed to coordinate to the carbonyl oxygen and to activate its reduction. This transformation is quite challenging for organic dye photocatalysts, due to the high negative potential necessary for the aldehyde reduction (e.g., benzaldehyde E$_{1/2}$ = -2.11 V vs Fc).[17] We commenced our investigation from the pinacol coupling of 4-chlorobenzaldehyde (**6a**, Scheme 1), as a model reaction, and investigating a series of coumarins readily prepared or commercially available.
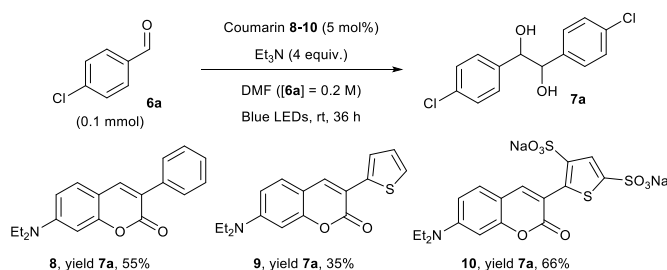
Scheme. 1. Reaction model for pinacol coupling (yields after chromatographic purification).

Table 1. Photophysical and electrochemical properties ($E_{1/2}$ in V vs SCE) of coumarins **8**, **9** and **10** in DMF solution at 298 K.

	Absorption		Emission				Electrochemistry	
	λ	ε	λ	Φ_{em}	τ	E_{00}	$E(A^+/A)$	$E(A^+/A^*)$
	(nm)	($M^{-1} cm^{-1}$)	(nm)		(ns)	(eV)	(V)	(V)
8	400	2.97	476	0.82	3.0	2.79	+0.92	−1.87
9	427	3.30	497	0.50	3.3	2.66	+0.79	−1.87
10	413	3.03	482	0.57	2.9	2.72	+0.83	−1.89

Among all the coumarins investigated (see ESI for more details) in the model reaction, only few coumarins were active, with coumarins **8**,[18] **9**, and **10** being the best performing photocatalysts. Coumarin **9** was readily obtained in 46% isolated yield from the reaction of diethylamino)-salicylaldehyde and thiophene acetic acid, performing the reaction with acetic anhydride and triethyl amine. The preparation of **10** is a straightforward sulfonylation of **9** with sulfur trioxide N,N-dimethylformamide complex in DMF, that gave the desired product **10** in 33% yields after purified by reverse phase chromatography. The reaction was further optimized in the presence of coumarin **10** by varying solvents, reductive reagents, and conditions (see SI for more details), as **10** was proved to be the most efficient catalyst.[19] The optimal conditions for the reaction were reached by using DMF as reaction solvent ([substrate] = 0.2 M) in the presence of 4 equiv. of Et_3N as sacrificial reductant. The generality of these conditions was investigated with different aldehydes: Scheme 2 reports the salient results. Other aldehydes were tested as well, but only low conversions or no reaction were observed (see ESI for further details). Only in the case of naphthyl aldehyde we have obtained excellent yields, and this could be due to the efficient formation of the ketyl radical coupled with an efficient reaction. Our conditions could also be applied to ketones without further optimization (Scheme 3 A). We were pleased to find that benzophenone **11a** ($E_{1/2}$ = −1.87 V vs. SCE)[16] and its derivatives were suitable substrates for the reaction. Imines were also proper substrates and under the standard reaction conditions, different benzyl and aryl imines react in satisfactory yields (Scheme 3B). Not only it is possible to use a cleavable benzyl as protecting group, but chiral benzylimines are suitable substrates and give access to chiral protected diamines.[20]
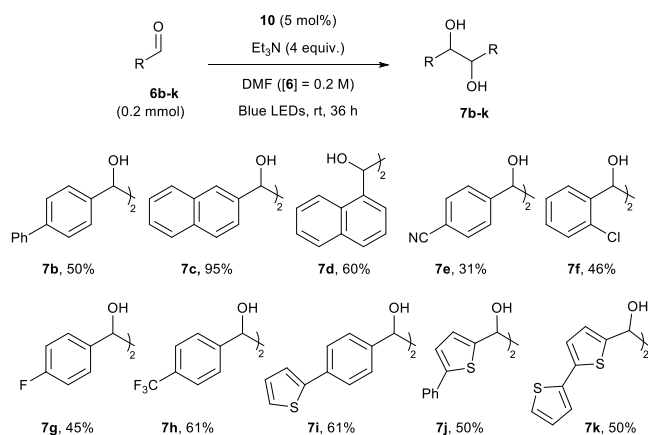

Scheme 2. Pinacol coupling of selected aldehydes (yields after chromatographic purification).
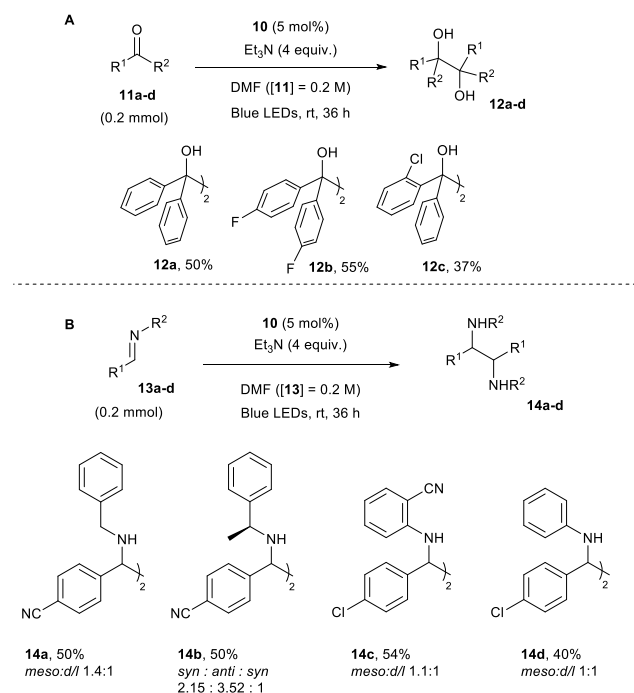
**Scheme 3.** Pinacol coupling of selected ketones and imines (yields after chromatographic purification).

To get insights into the mechanism of the pinacol reaction, a photochemical study was performed. The absorption spectrum of the photocatalyst is not significantly changed under the reaction conditions reported in Scheme 2 (ca. 1% degradation of coumarin **10** at the end of irradiation), demonstrating its significant photostability.

Fluorescence of coumarin **10** is not quenched by Et_3N (Figure S6, and comments), while it is quenched by aldehydes (Figure S7, and comments).[21] This behavior suggests a photoinduced oxidative quenching of the coumarin with direct formation of ketyl radicals. Indeed, energy transfer from the lowest excited state of coumarin to populate the lowest triplet excited state of aldehydes is ruled out, being endoergonic.[22] Based on the reduction potentials of aldehydes (Table S13) and of the S_1 excited state of coumarins (Table 1), oxidative quenching is exoergonic, apart from 4-chlorobenzaldehyde **6a**. However, as evident from data reported in Table S13, the presence of Lewis acids can substantially decrease the reduction potentials of aldehydes.[23] Under the conditions reported in Scheme 2, the radical cation $Et_3N^{\bullet+}$ can act as Lewis acid or Brønsted acid, as previously discussed by Rueping, making the investigated photoinduced electron transfer process exoergonic (see SI for more details). In the conditions reported by Rueping, the presence of 20 mol% K_2CO_3 or K_3PO_4 completely suppressed the pinacol coupling, due to the essential role of the Brønsted acidic α-ammonium radical in the C=O activation event. In our case, by performing the model reaction in the presence of 20 mol% K_2CO_3 and K_3PO_4, we observed a lower conversion, 16% and 12% respectivily, compare to the model reaction performed under standard conditions. In our case, the improved reduction potential of coumarin dyes respect to Ir complex (-1.89 V vs -1.69 V) is probably still favoring the reaction that was, however, less efficient, confirming the importance of the Brønsted acidic α-ammonium radical. We have also investigated cross-pinacol couplings, carring out the reaction of p-chlorobenzaldehyde in the presence of different aldehydes (naphylaldehyde, p-PhC_6H_4CHO, p-CNC_6H_4CHO, and p-$MeOC_6H_4CHO$; see SI for full details). Cross coupling products, as inseparable mixtures, were observed for the reactions with naphtylaldehyde and p-PhC_6H_4CHO but not with p-CN C_6H_4CHO, and p-$MeOC_6H_4CHO$, probably due to the major stabilization of the ketyl radicals. Based on the photochemical investigation we suggest the mechanism depicted in Scheme 4: aldehydes are directly reduced by the photocatalyst in the excited state (**I**) to form the ketyl radical (**III**), at variance with the reductive quenching of the Ir(III) photocatalyst reported by Rueping.[16] The ketyl radical is then coupled to another ketyl radical to give the pinacol product. In the case described by Rueping, and in other examples reported in literature, the photocatalyst in its photoexcited state is quenched by the sacrificial reductant (normally a tertiary amine) and then is able to perform the electron trasfer to the organic substrate in this reduced state. Remarkably, coumarins are able to directly transfer electrons to carbonyls, forming ketil radicals.
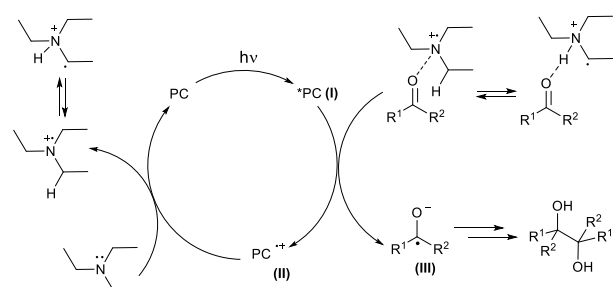

Scheme 4. Proposed reaction mechanism for the pinacol coupling reaction.

Recently, we have introduced BODIPY dyes for the atom transfer radical addition (ATRA) reaction.[24a] Investigating the coumarins **9** and **10** as possible catalyst for the ATRA reaction,[24b] we found quite promising results (Scheme 5), without the need of sacrificial Et₃N, or other reducing agent. It is noteworthy the possibility to use ethylbromoacetate (**16d**) for the ATRA reaction promoted by coumarin, a substrate quite challenging for other photocatalysts.[25]
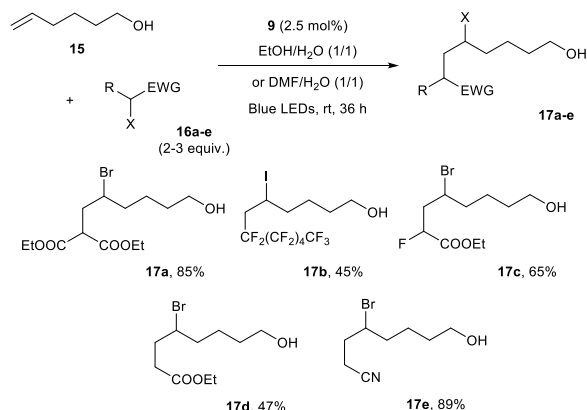
Scheme 5. ATRA reaction promoted by coumarin **9** (yields after chromatographic purification).

To further highlight the capability of coumarins **9** and **10** to promote a variety of different photoredox reactions, we have briefly investigated their use in: (i) the trifluoromethylation of alkenes by Umemoto reagent (Scheme 6, A),[26] (ii) the MacMillan stereoselective α-alkylation of aldehydes (Scheme 6, B),[27] promoted by the synergistic cooperation of photo- and enamine catalysis.[28] The enantiomeric excesses obtained for the reactions were in line with the reported values and the organic photocatalyst does not influence or reduce the enantiomeric excess of the reactions. It was also possible to use the coumarin catalyst in the reductive protonation of bromoketones, in the presence of the Hantzsch ester (Scheme 6, c).[29] These selected examples demonstrate that the potentiality of coumarins in photoredox catalysis could be explored in many different reactions, allowing the replacement of ruthenium(II) or iridium(III) complexes.
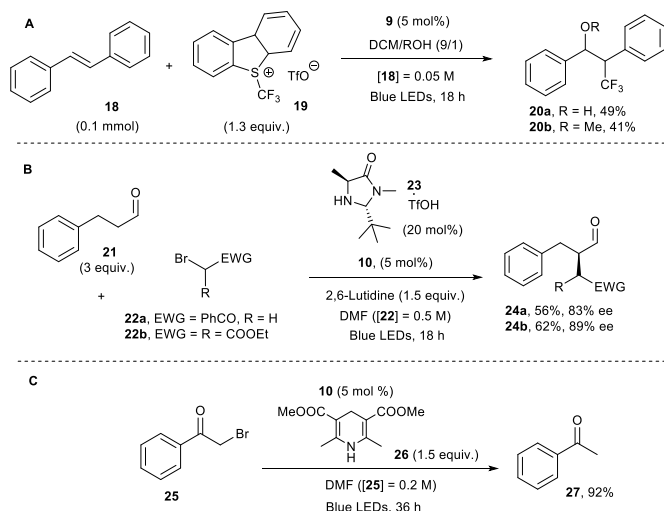
Scheme 6. Application of coumarins dyes **8** and **9** in different chemical reactions.

In summary, we have introduced coumarins dyes as powerful photoreductants in the photoredox catalysis arena. These new photo-reductive catalysts shown broad applicability and further studies about their application in other photoredox reactions are in progress. The possibility of tailoring redox and photophysical properties of coumarin dyes by introducing different functional groups, their simple synthesis and their affordable cost, can be useful for extending the application of these dyes to new photocatalytic transformations.

Acknowledgements

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