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Enantioselective Organocatalytic Alkylation of Aldehydes and Enals Driven by the Direct Photoexcitation of Enamines

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Supporting Information

ABSTRACT: Disclosed herein is a photo-organocatalytic enantioselective α- and γ-alkylation of aldehydes and enals, respectively, with bromomalonates. The chemistry uses a commercially available aminocatalyst and occurs under illumination by a fluorescent light bulb in the absence of any external photoredox catalyst. Mechanistic investigations reveal the previously hidden ability of transiently generated enamines to directly reach an electronically excited state upon light absorption while successively triggering the formation of reactive radical species from the organic halides. At the same time, the ground state chiral enamines provide effective stereochemical induction for the enantioselective alkylation process.

Despite their synthetic potential, it is challenging to develop enantioselective catalytic variants of visible light-driven photochemical reactions.[1,2] Complications stem from the inability of most organic molecules to absorb light in the visible spectrum. In addition, the involvement of short-lived electronically excited states inherent to any photochemical pattern challenges the ability of a chiral catalyst to dictate the stereochemistry of the reaction products. A viable strategy has recently been identified in that the photochemical activation of substrates, which furnishes reactive radical species under the action of a visible light-active photoredox catalyst,[3] is differentiated from the stereoselective ground state process, controlled by a distinct chiral catalyst. Such dual catalytic systems[4] served to effectively access chiral molecules in an asymmetric fashion.[5]

Recently, we discovered that chiral enamines, key intermediates in ground state organocatalytic asymmetric processes,[6] can actively participate in the photoexcitation of substrates.[7] The resulting strategy differed from photoredox enantioselective catalytic approaches[5] in that the enamine served to both photogenerate the radical and induce the stereocontrolled formation of the chiral products, without the need for an external photosensitizer.[8] The metal-free process relied upon the formation of photon-absorbing electron donor—acceptor (EDA) complexes,[9] generated in the ground state upon association of the electron-rich enamine **I** (Figure 1a) with electron-deficient benzyl and phenacyl bromides **II**. Visible light irradiation of the colored EDA complex **III** induced a single electron transfer (SET), allowing access to radical species under mild conditions. This reactivity enabled the development of a light-driven stereoselective α-alkylation of carbonyl compounds.[7]

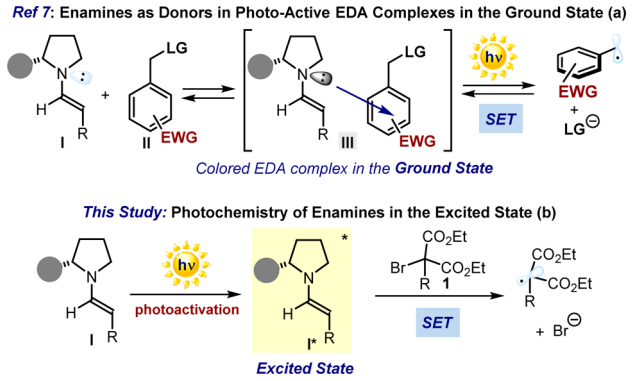

Figure 1. Mechanisms that enamines can use to drive the photochemical generation of radicals: (a) by inducing ground state EDA complex formation; (b) acting as a photosensitizer upon direct photoexcitation. The enamine radical cation, resulting from the SET, is not shown. The gray circle represents the chiral organocatalyst scaffold.

Herein, we demonstrate that the photochemical activity of chiral enamines and their potential for light-induced radical generation is not limited to the formation of ground state EDA complexes. This study unveils the to date hidden ability of enamines, generated by condensation of aldehydes with a commercially available chiral secondary amine catalyst, to reach an electronically excited state upon simple light absorption and then to act as effective photosensitizers (Figure 1b). At the same time, such photochemical behavior conjugates with the enamine ability of stereoselectively intercepting the reactive radicals generated from the sensitization of organic halides. This novel photo-organocatalytic mechanism overcomes the need for an external photoredox catalyst. We used it to develop the enantioselective alkylation of aldehydes with bromomalonates **1**, a transformation that served as a benchmark for developing enantioselective dual photoredox—organocatalytic systems.[5a,10]

Our initial explorations focused on the reaction between butanal **2a** and diethyl bromomalonate **1a** (Table 1). When adding the aminocatalyst **A**[11] (20 mol %) to an MTBE solution under irradiation by a household 23 W compact florescent light (CFL) bulb, the alkylation product **3a** was formed in high yield and enantioselectivity after 4 h (94% yield, 83% ee, entry 1). The careful exclusion of light completely suppressed the process, confirming the photochemical nature of the reaction (entry 2). The inhibition of the reactivity was also observed under an

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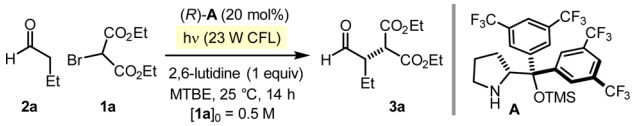
Table 1. Initial Studies on the Model Reaction[a]



entry	deviation from standard conditions	% yield	% ee[b]
1	4 h reaction time	94[c]	83
2	in the dark	<5	
3	in air	<5	
4	TEMPO (1 equiv)	<5	
5	2 h, 10 mol % **A**	33	83
6	2 h, 10 mol % **A**, 0.5 mol % $Ru(bpy)_3^{2+}$	74	83
7[d]	cut off @ 385 nm	>95[e]	83
8[d]	band-pass @ 400 nm	>95[e]	83
9[d]	band-pass @ 450 nm	<5	

[a]TMS: trimethylsilyl. Reactions performed on a 0.1 mmol scale using 3 equiv of **2a** and a 23 W CFL bulb to illuminate the reaction vessel. [b]Enantiomeric excess determined by HPLC analysis on a chiral stationary phase. [c]Yield of **3a** determined after isolation by chromatography. [d]Using a 300 W xenon lamp. [e]NMR yield of **3a** determined using 1,1,2-trichloroethene as the internal standard.

aerobic atmosphere (entry 3) or in the presence of TEMPO (1 equiv, entry 4), the latter experiment being indicative of a radical mechanism. The results in entries 5 and 6 indicate that the addition of an external photosensitizer significantly increases the reactivity,[12] in consonance with the occurrence of an additional photoinduced electron transfer pathway.[5a,10]

In analogy with our previous studies on the enantioselective photochemical alkylation of aldehydes with benzyl and phenacyl bromides (Figure 1a),[7] we anticipated the intermediacy of a photoactive EDA aggregation between the transient enamine and **1a** as being crucial for reactivity. However, we did not observe any color change of the solution, which remained achromatic during the reaction progression. The absence of any photoabsorbing ground state EDA complex was further confirmed by the optical absorption spectrum of the reaction mixture (blue line in Figure 2a), which perfectly overlaid the absorption of the enamine, generated upon condensation of the catalyst **A** with **2a** (red line in Figure 2a). In a separate experiment, we observed how the addition of a large excess of **1a** to a solution of enamines did not change the absorption spectra, further excluding any EDA association in the ground state (details in Figure S17 within the Supporting Information, SI). This puzzling observation prompted us to evaluate other possible pathways for the photochemical activation of **1a**. We recently demonstrated the ability of aromatic aldehydes, opportunely excited under CFL illumination, to generate a carbon-centered radical from **1a** by a light-driven energy transfer mechanism.[13] The possibility of a similar pattern in the model reaction triggered by the photoactivity of **2a** was excluded by experiments conducted using a 300 W xenon lamp equipped with a cutoff filter at 385 nm and a band-pass filter at 400 nm (irradiation at $\lambda \geq 385$ nm and $\lambda = 400$ nm, respectively; entries 7 and 8, Table 1). Under these conditions, the reactivity of the model reaction remained unaltered, in spite of the inability of **2a** to absorb light (orange line in Figure 2a). Clearly, a different mechanism was at the basis of the photochemical process.

A closer inspection of the absorption spectrum indicated that the only photoabsorbing compound at 400 nm was the enamine[14] (red line in Figure 2a, absorption band until 415 nm). Thus, the suggestive prospect arose that the direct

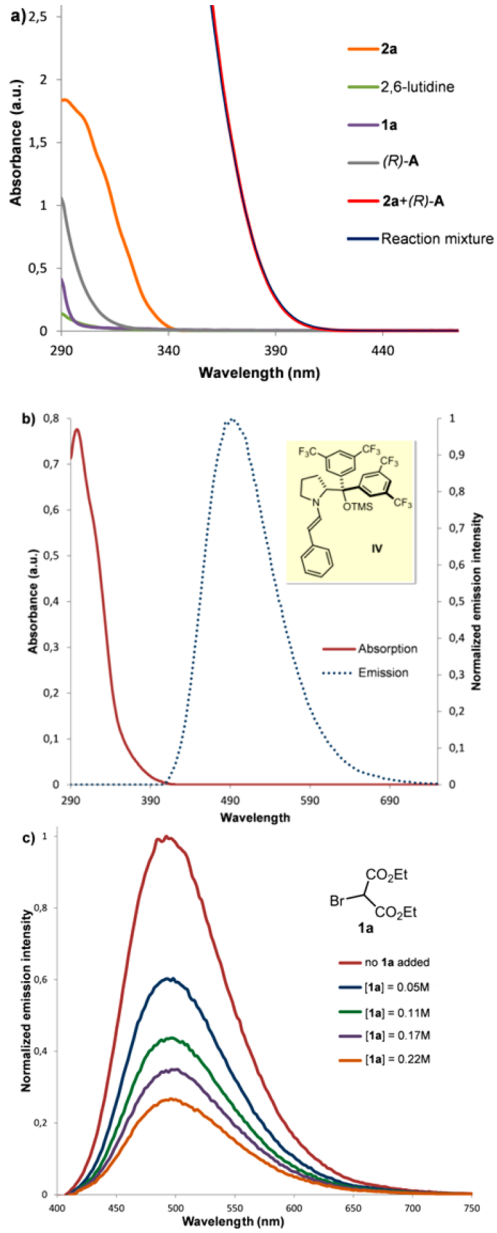


Figure 2. (a) Optical absorption spectra acquired in MTBE in 1 cm path quartz cuvettes: [**2a**] = 1.5 M; [2,6-lutidine] = 0.5 M; [**1a**] = 0.5 M; [(*R*)-**A**] = 0.1 M. (b) Absorption and emission spectra (excitation at 365 nm) of the preformed enamine **IV** ([**IV**] = 5×10^{-5} M in toluene). (c) Quenching of the enamine **IV** emission ([**IV**] = 5×10^{-5} M in toluene) in the presence of increasing amounts of bromomalonate **1a**.

photoexcitation of the enamine could trigger the radical generation from **1a**. This mechanistic scenario was consonant with the experiment performed using a band-pass filter at 450 nm (a wavelength that could not be absorbed by the enamine) since a complete inhibition of the reaction was observed (entry 9).[15]

To further examine the possible implication of the enamine within the photochemical regime, we investigated the photophysical behavior of enamine **IV**, prepared by condensation of catalyst **A** and 2-phenylacetaldehyde[16] in the presence of molecular sieves. Figure 2b shows the absorption spectra and, more importantly, the emission spectra of **IV** recorded upon excitation at 365 nm. A series of Stern–Volmer quenching studies was performed (Figure 2c), which revealed that bromomalonate **1a** effectively quenched the excited state of **IV**.

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On the basis of these observations, we propose the mechanism depicted in Figure 3. The enamine **I**, upon light absorption, can

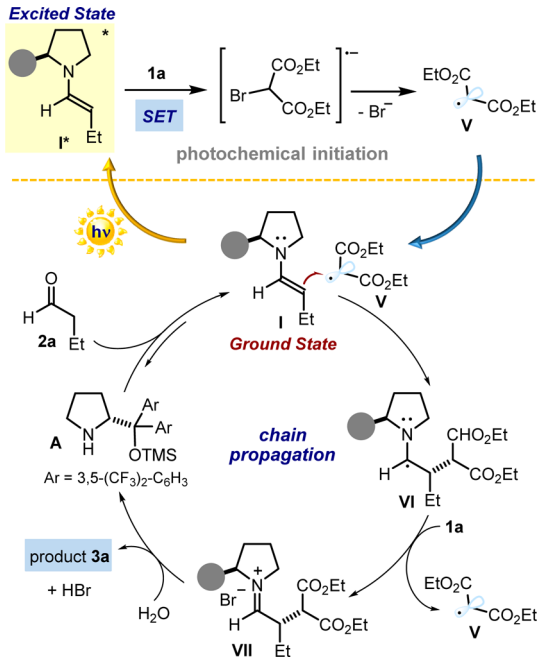

Figure 3. Proposed mechanism: exploiting the dichotomous reactivity profile of enamines in the ground and excited states.

reach an electronically excited state (**I***) and act as a photoinitiator triggering the formation of the electron deficient radical **V** through the reductive cleavage of the bromomalonate C–Br bond via a single electron transfer (SET) mechanism.[17] The redox potential of the excited enamine was estimated as −2.50 V (vs Ag/AgCl, NaCl sat) on the basis of electrochemical and spectroscopic measurements (see SI for details).[18] Considering the consolidated ability of **I** to infer high stereoselectivity in enamine-mediated polar reactions,[11] the addition of the radical **V** to the ground state **I** proceeds in a stereocontrolled fashion. Since α-aminoalkyl radicals are known to be strong reducing agents,[19] the intermediate **VI** would induce the reductive cleavage of bromomalonate **1a** through an outersphere SET process, thereby regenerating the radical **V**.[20] This path provides a bromide-iminium ion pair **VII**, which eventually hydrolyzes to release the product **3a** and the aminocatalyst **A**. Overall, the reaction proceeds through a radical chain propagation pathway. It is of note that, within the photochemical regime, the excited enamine **I*** serves as a sacrificial initiator of the chain mechanism, with the enamine radical cation resulting from the SET event (structure not shown) lying outside of the productive manifold.[21]

We then evaluated the synthetic potential of the photo-organocatalytic strategy. As detailed in Figure 4a, variously substituted bromomalonates effectively participated in the enantioselective alkylation of butanal **2a** (products **3a–d**). Aldehydes bearing a long alkyl fragment, an internal olefin, or a heteroatom moiety were also alkylated stereoselectively to afford **3e–g**. Additionally, natural solar light effectively promoted the process: simply placing the reaction mixture in ordinary Pyrex glass vessels on a rooftop effected the asymmetric catalytic alkylation with diethyl 2-bromo-2-methylmalonate **1b** (product **3b**, 98% yield, 91% ee).

This photo-organocatalytic alkylation approach demonstrated potential for targeting stereocenters remote from the carbonyl moiety.[22] We found that extended enamine intermediates, formed from α-branched enals **4**, could efficiently trap the photogenerated radical while setting a new stereocenter at a distant γ-position (Figure 4b). The capacity for controlling the site selectivity was further corroborated by the experiment detailed in Figure 4c, where hepta-2,4-dienal **6**, which may potentially react at the α- and γ-positions too, was exclusively alkylated at the more remote ε-carbon, albeit at the expense of stereocontrol.

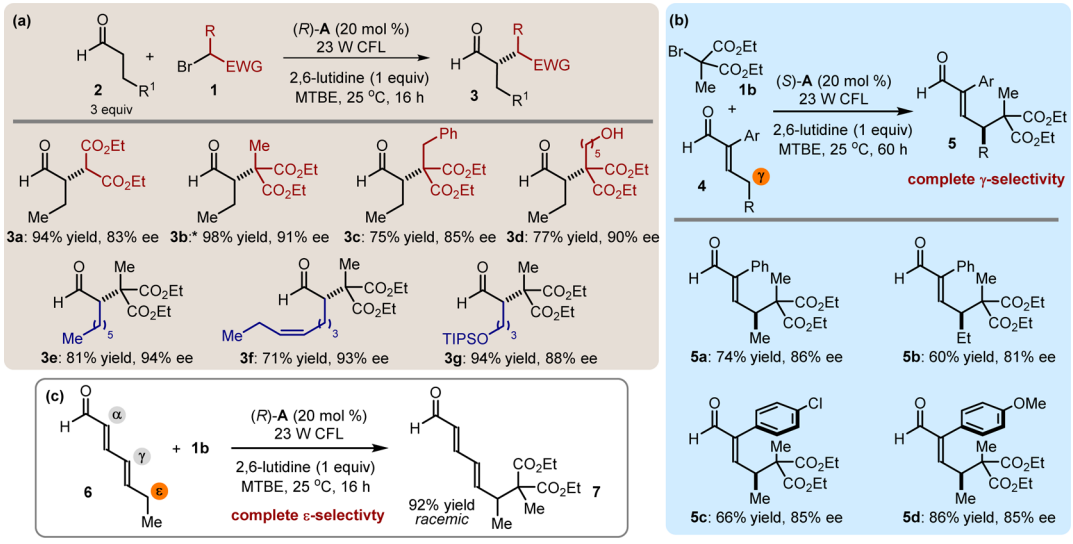

Figure 4. Photo-organocatalytic enantioselective alkylation of aldehydes and enals. (a) Survey of the bromomalonate derivatives and aldehydes that can participate in the catalytic asymmetric ATRA reaction. Evaluating the strategy's potential to address relevant synthetic problems: (b) remote stereocontrol and complete γ-site selectivity; (c) capacity to differentiate between three potential reactive centers. For all entries, omission of light resulted in no reaction. *Reaction performed under natural sunlight irradiation on the roof-top of the ICIQ, Tarragona, Spain (10 Oct. 2012; from 9 a.m. to 6 p.m.).

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In summary, this study establishes the ability of chiral enamines to act as photosensitizers upon excitation by simple light irradiation and to trigger the formation of reactive open-shell species under mild conditions. At the same time, the ground state enamines provide effective asymmetric induction for the enantioselective alkylation of aldehydes and enals. This novel photo-organocatalytic strategy, which capitalizes upon the dichotomous reactivity profile of enamines in the ground and the excited states, can offer new opportunities for designing photochemical enantioselective transformations.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) The increase in reactivity becomes larger in polar solvents, where $Ru(bpy)_3^{2+}$ is completely soluble, details in Table S1 of the SI.

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(14) For an additional example of an enamine, formed upon condensation of an aliphatic aldehyde and a secondary amine, which weakly absorbs in the visible region, see: González-Béjar, M.; Peters, K.; Hallett-Tapley, G. L.; Grenier, M.; Scaiano, J. C. *Chem. Commun.* **2013**, *49*, 1732.

(15) In sharp contrast, under the same conditions ($\lambda_{irradiation}$ = 450 nm), the reactivity of the photo-organocatalytic alkylation of aldehydes with benzyl and phenacyl bromides remained unaltered (ref 7a) since the enamine-based EDA complexes could absorb such low-energy photons.

(16) 2-Phenylacetaldehyde is a competent substrate of the photo-organocatalytic reaction with **1a**, providing full conversion into the corresponding product under the conditions set out in Table 1. Low enantioselectivity was, however, observed (below 30% ee), a consequence of the lability of the resulting benzylic stereocenter.

(17) For examples of photoinduced reductive cleavage of C−X bonds in electron-poor alkyl halides via a SET from excited substrates, see: (a) Rico, I.; Cantacuzene, D.; Wakselman, C. *Tetrahedron Lett.* **1981**, *22*, 3405. (b) Iwasaki, T.; Sawada, T.; Okuyama, M.; Kamada, H. *J. Phys. Chem.* **1978**, *82*, 371. (c) Barata-Vallejo, S.; Flesia, M. M.; Lantaño, B.; Argüello, J. E.; Peñéñory, A. B.; Postigo, A. *Eur. J. Org. Chem.* **2013**, 998.

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(22) For a review on vinylogous organocatalytic strategies for achieving remote stereocontrol, see: Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Chem. Sci.* **2013**, *4*, 2287.

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