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Photochemical activity of a key donor–acceptor complex can drive stereoselective catalytic α-alkylation of aldehydes

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Asymmetric catalytic variants of sunlight-driven photochemical processes hold extraordinary potential for the sustainable preparation of chiral molecules. However, the involvement of short-lived electronically excited states inherent to any photochemical reaction makes it challenging for a chiral catalyst to dictate the stereochemistry of the products. Here, we report that readily available chiral organic catalysts, with well-known utility in thermal asymmetric processes, can also confer a high level of stereocontrol in synthetically relevant intermolecular carbon–carbon bond-forming reactions driven by visible light. A unique mechanism of catalysis is proposed, wherein the catalyst is involved actively in both the photochemical activation of the substrates (by inducing the transient formation of chiral electron donor–acceptor complexes) and the stereoselectivity-defining event. We use this approach to enable transformations that are extremely difficult under thermal conditions, such as the asymmetric α-alkylation of aldehydes with alkyl halides, the formation of all-carbon quaternary stereocentres and the control of remote stereochemistry.

Fascinated by the ability of natural photosynthetic systems to convert solar energy into chemical energy[1], the scientific community long ago recognized the potential of light-driven reactions (photochemistry) as a powerful approach to chemical synthesis[2]. From the high-energy intermediates generated by photoinduced excitation of organic molecules, unique reaction manifolds can be accessed that are generally unavailable to conventional thermal pathways. This explains why photochemical reactions considerably enrich the synthetic repertoire of modern organic chemists[3,4]. However, there has been very limited success in developing asymmetric catalytic photoreactions in solution that create chiral molecules with a well-defined three-dimensional spatial arrangement[5,6]. This has instilled the general perception that photochemistry is too unselective to parallel the impressive levels of efficiency reached by the asymmetric catalysis of thermal reactions[7]. Historically, two fundamental issues frustrated the development of asymmetric photochemical variants: (1) the inability of most organic molecules to absorb light in the visible spectrum, which calls on specialized apparatus for high-energy irradiation, and (2) the low-barrier, very rapid processes that proceed from short-lived electronic excited states. The latter condition challenges the ability of a chiral catalyst to bias and organize the molecular architecture of the fleetingly excited states of photoreactions, a prerequisite for high stereoinduction.

One effective catalytic strategy, among the very few reported so far[8], uses a chiral organic catalyst appropriately adorned with hydrogen-bonding motifs to bind a specific substrate selectively[9,10]. The catalyst, modified to act as a photosensitizer, excites the substrate via photoinduced electron transfer (ET), thus directing the resulting intramolecular cyclization towards a stereoselective pathway. The approach is limited by the intrinsic weakness of the hydrogen-bonding interactions[11], which complicates the geometrical organization of the catalyst–substrate assembly, and requires a specially tailored catalyst. Recently, a viable alternative was identified in that the photochemical activation step, which furnishes reactive radical species under the action of a photoredox catalyst[12,13], is differentiated clearly from the stereoselective ground-state process controlled by a distinct chiral catalyst.

Herein we describe how some of the effective tools available for catalytic asymmetric reactions in the ground state can be translated into the realm of photochemical activation to address the challenges of enantioselective photochemistry. We found that readily available chiral amines, with an established profile as catalysts of thermal asymmetric processes, can exert high stereocontrol in synthetically relevant intermolecular carbon–carbon bond-forming reactions driven by visible light. The catalysts do not contain any photosensitive unit, but rather they guide the photoactivation of the substrates by inducing the transient formation of photon-absorbing chiral electron donor–acceptor (EDA) complexes[14,15]. A mechanism (Fig. 1) that involves an in-cage radical combination as the stereodefining step is proposed and discussed based on diverse experimental evidence. To our knowledge this study constitutes the first example of photochemical asymmetric catalysis that involves an EDA complex of the reacting partners as the radiation acceptor.

Results and discussion

Our previous studies in asymmetric organocatalysis led us to wonder if the synthetic potential of this approach[16] could be expanded by combining it with the seemingly distinct field of photochemistry. It is well-established that chiral secondary amines of type **I** (Fig. 1) effectively condense with aldehydes to form reactive nucleophilic enamine intermediates **II**, and confer high stereoselectivity to their subsequent thermal reactions[17]. However, the enamine's potential to participate actively in the photoexcitation of substrates remains almost unexplored[18,19]. Still, the ability of tertiary amines to form EDA complexes with electron-accepting molecules of high electron affinity[15,20] suggests that the lone pair of the pyrrolidine ring in the enamine **II** (Fig. 1) could engage in such a molecular aggregation. A few precedents in the literature[18], and the low ionization potentials of the pyrrolidine-based enamines of type **II**

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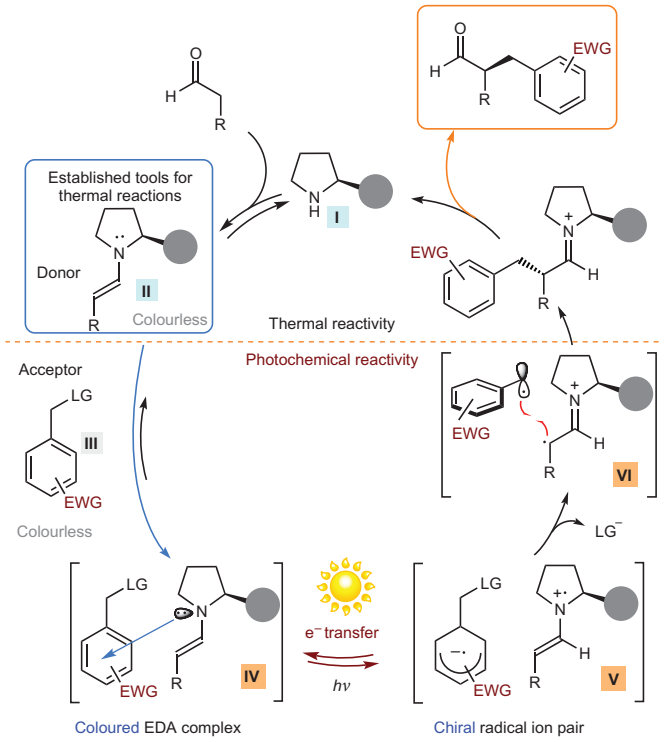


Figure 1 | Mechanistic proposal for asymmetric catalytic photochemical processes. Transient generation of chiral enamine-based EDA complexes **IV** exploited to access photochemical pathways. Central to this study is the possibility for substances that do not absorb visible light to become coloured on ground-state EDA association. EWG, electron-withdrawing group; LG, leaving group; filled grey circles represent the chiral fragment of the aminocatalyst scaffold.

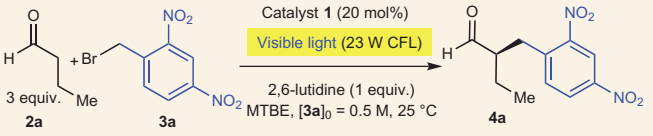
(for example, 1-(but-1-enyl)pyrrolidine has an ionization potential of 7.2 eV)[21], qualify them as potential donors for facilitating EDA associations in the ground state.

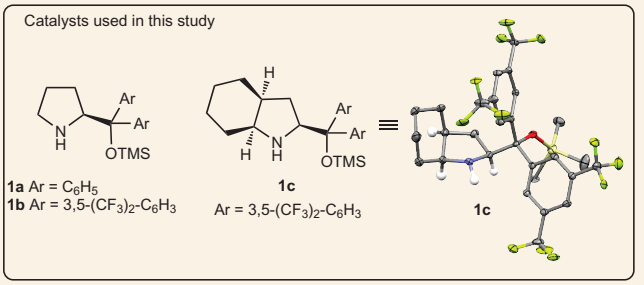
Typically, EDA complexes are characterized by the appearance of a weak absorption band, the charge-transfer band, associated with an ET transition from donor to acceptor[22]. In many cases, the energy of this transition lies within the visible-frequency range. This raises the tantalizing possibility of using easily managed visible light to activate substances that would not normally absorb in the visible spectrum. Surprisingly, although the photoexcitation of EDA complexes is studied extensively[23], their use in chemical synthesis is scarcely reported[24–26]. This is mainly because of an unproductive, fast reverse ET, which restores the ground-state EDA complex and thus renders any further reactivity improbable. Given these intrinsic difficulties, the question arises as to whether the enamine-based EDA complex **IV** could be harnessed to access a synthetically useful photochemical pathway. A viable path can be envisaged in that visible light irradiation of **IV** might induce ET to occur, and so produce the chiral contact radical ion pair **V**. As a critical factor, the presence of a suitable leaving group (LG in **V**) within the radical anion partner may trigger a fragmentation event rapid enough to compete with the reverse ET. This would productively render the positively charged intermediate pair **VI**, which brings two radicals within a geometrically restricted chiral space and in very close proximity. This condition should facilitate a stereocontrolled radical combination to form a new carbon–carbon bond and forge the stereogenic centre. This photochemical process would result in the asymmetric intermolecular α-alkylation of aldehydes with alkyl halides[12,13], a synthetically useful catalytic transformation that cannot be realized under thermal control[27].

We first examined the possibility of EDA associations between enamines **II** and electron acceptors by combining an excess of butanal (**2a**, 15 equiv.) and amines **1a** and **1b** (1 equiv.) in methyl *tert*-butyl ether (MTBE) with 2,4-dinitrobenzyl bromide (**3a**, 1 equiv., Table 1). The commercially available diarylprolinol silylether catalysts **1a** and **1b** were selected because of their potential to induce high enantioselectivity in thermal reactions of aldehydes that proceed through enamine formation[28]. The choice of the nitrobenzyl bromide **3a** was motivated by the low reduction potentials of nitroaromatics, which allow them to engage in EDA complexes with tertiary amines by means of $n \rightarrow \pi^*$ interactions[20]. The bromide would be the leaving group needed to originate a reactive benzylic radical within the chiral intermediate of type **VI**. Immediately after mixing with the bromide **3a**, the MTBE solution developed a marked yellow–orange colour, and its optical absorption spectrum showed a bathochromic displacement in the visible spectral region, diagnostic of an EDA complex (Fig. 2a). We recognized the formation of the coloured EDA complex **IV** and the tendency of alkyl bromide radical anions to dissociate[29] as key to developing an asymmetric catalytic photochemical strategy without the need for a photosensitizer.

Preliminary results (Table 1) revealed the feasibility of the approach. When using a household 23 W compact fluorescent light (CFL) bulb to irradiate an MTBE solution of **2a** (3 equiv.) and **3a** in the presence of catalysts **1a** and **1b**, we observed the quantitative formation of the desired α-benzylated product **4a** with a promising level of optical purity (Table 1, entries 1 and 2, 83% enantiomeric excess (e.e.) with catalyst **1b**). Analogous results were obtained using either 2,6-lutidine or sodium acetate as base (Table 1, entries 2 and 3, respectively). Careful exclusion of light or of the aminocatalyst completely inhibited the reaction, even on heating at 50 °C (Table 1, entries 4–6). The use of a blue light-emitting diode (LED) as a monochromatic light source ($\lambda_{max} = 460$ nm) reduced the reaction rate only slightly (Table 1, entry 7), which indicates that absorption in the visible

Table 1 | Explorative studies on the feasibility of the catalytic asymmetric photochemical process.





Entry	Catalyst	Light	Time	Yield (%)	e.e. (%) 4a
1	1a	ON	6 h	98	75
2	1b	ON	6 h	98	83
3*	1b	ON	6 h	94	82
4	1b	OFF	48 h	0	-
5	1b	OFF, 50 °C	48 h	0	-
6	-	ON	48 h	0	-
7	1b	ON, LED†	16 h	89	82
8	1b	ON, in air	40 h	78	84
9	1c	ON	48 h	87	92

*Reaction performed using 1 equiv. NaOAc instead of 2,6-lutidine. †460 nm LED, irradiance 13.8 W m^{-2}. TMS, trimethylsilyl.

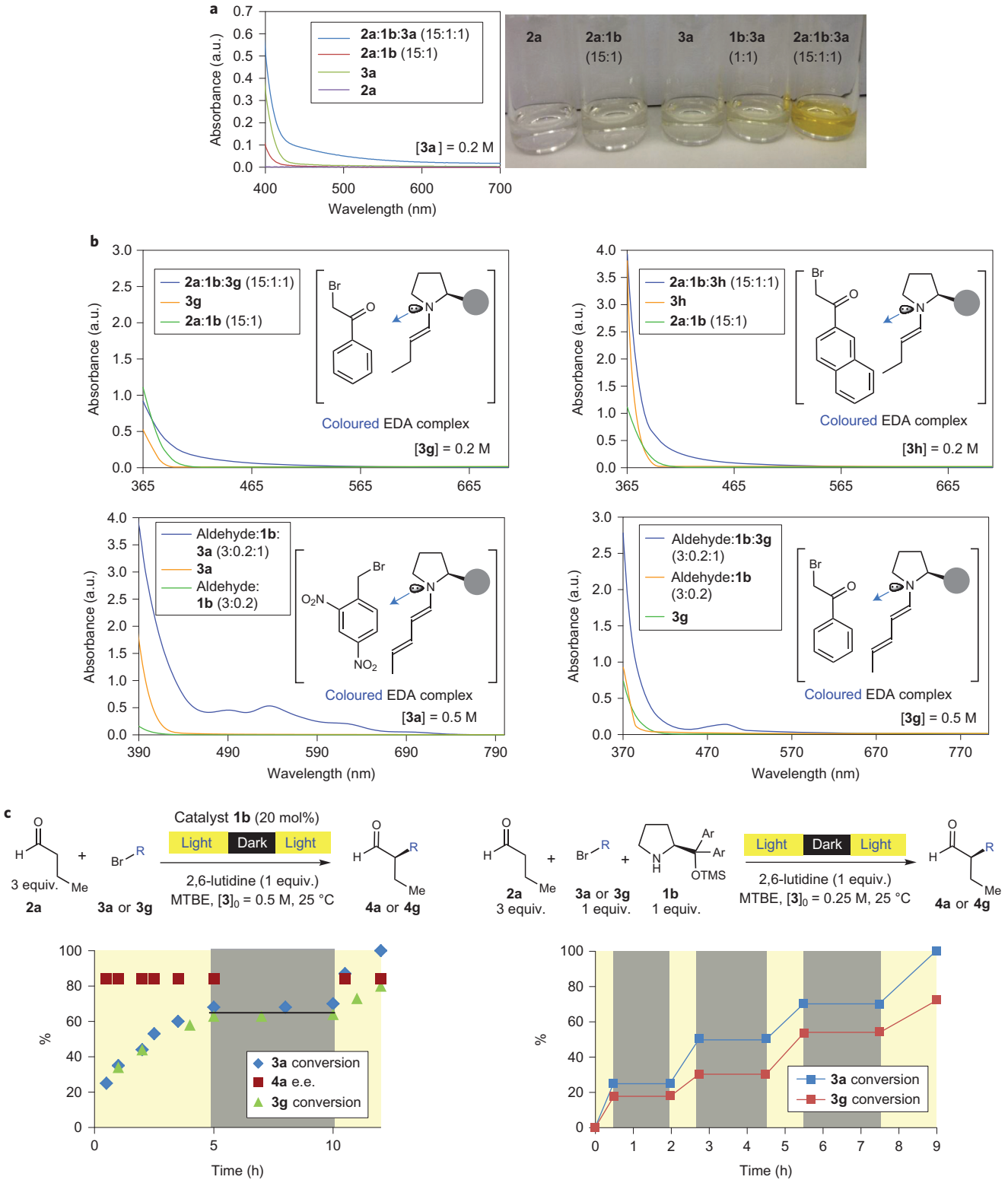
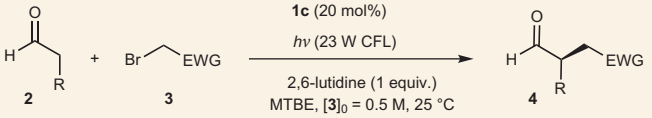


Figure 2 | Mechanistic investigations. a, Optical absorption spectra (recorded in MTBE in 1 mm path quartz cuvettes using a Shimadzu 2401PC UV-visible spectrophotometer) and visual appearance of the separate reaction components and of the coloured EDA complex. **b**, Representative optical absorption spectra of EDA complexes with enamines and extended enamines formed *in situ* (recorded in MTBE in 1 mm path quartz cuvettes using a Shimadzu 2401PC UV-visible spectrophotometer). **c**, Successive intervals of irradiation and dark periods for reactions of bromobenzyl **3a** and bromophenacyl **3g** promoted by 20 mol% (left) and 1 equiv. (right) of catalyst **1b**. a.u, arbitrary units.

region is sufficient for the reaction to occur. The reduced reactivity observed in the presence of oxygen (Table 1, entry 8) is consonant with a radical mechanism.

As for the stereoselectivity of the reaction, we found that it could be improved by using amine **1c** as catalyst (92% e.e., Table 1, entry 9). This is presumably because of the increased steric demand of the

Table 2 | Survey of the aldehydes and alkyl bromides that can participate in the catalytic asymmetric photochemical alkylation.



Entry	Substrate	Product	Entry	Substrate	Product
1	2b	4b 81% yield, 92% e.e.	7	3h	4h 70% yield, 86% e.e.
2	2c	4c 80% yield, 93% e.e.	8	3i	4i 94% yield, 86% e.e.
3	2d	4d 92% yield, 93% e.e.	9	3j	4j 86% yield, 86% e.e.
4	2e	4e 73% yield, 90% e.e.	10	3k	4k 70% yield, 83% e.e.
5	3f	4f 95% yield, 84% e.e.	11	3l	4l 96% yield, 87% e.e.
6*	3g	4g 89% yield, 94% e.e.	12	3m	4m 92% yield, 87% e.e.

Entries 1–4 were carried out in the presence of bromide **3a**; entries 5–12 were carried out in the presence of aldehyde **2a**. *Reaction performed under natural sunlight irradiation on the roof-top of the Institute of Chemical Research of Catalonia, Tarragona (Spain), on a partially cloudy day (27 Feb 2013, from 13:00 untill 18:00). TIPS, triisopropylsilyl.

catalyst's chiral fragment, which should impose greater conformational constraints on the short-lived diradical intermediate of type **VI** (Fig. 1).

As shown in Table 2, aldehydes that bear sterically hindered chains or heteroatom moieties were also benzylated stereoselectively in the presence of **3a** (Table 2, entries 1–4). Moreover, we found that other bromide-containing acceptors combined productively with chiral enamines in photon-absorbing EDA associations. In addition to electron-deficient benzylic systems (Table 2, entry 5), a broad array of phenacyl bromides participated effectively in the enantioselective alkylation of butanal **2a** (Table 2, entries 6–12, 70–96% isolated yield, 83–94% e.e.). The reaction protocol is operationally simple, conducted at ambient temperature with readily available substrates and catalysts, and using household CFL bulbs as the light source. Additionally, natural solar light effectively promoted the process: simply placing the reaction mixture in an ordinary Pyrex vessel on a rooftop effected the asymmetric catalytic alkylation of **2a** with phenacyl bromide **3g** (Table 2, entry 6, 5 hours reaction time, 89% yield, 94% e.e.).

The strategy also enabled transformations that are extremely difficult through thermal mechanisms. It forged all-carbon quaternary stereocentres with high fidelity, as demonstrated by the reaction of 2-phenylpropanal **5** with **3a** to afford the enantioenriched product **6** (86% e.e., Fig. 3a). In addition, this approach demonstrates a great potential for targeting stereocentres remote from the carbonyl moiety. The absorption spectra recorded for the EDA complexes of bromides **3a** and **3g** and the extended enamines, generated by condensation of the aminocatalyst with unsaturated aldehydes, are red shifted compared to those of the enamine of type **II**, and new bands in the visible region become well resolved (Fig. 2b). We found that the extended enamine intermediates efficiently initiated light-induced asymmetric alkylation setting a new stereocentre at a

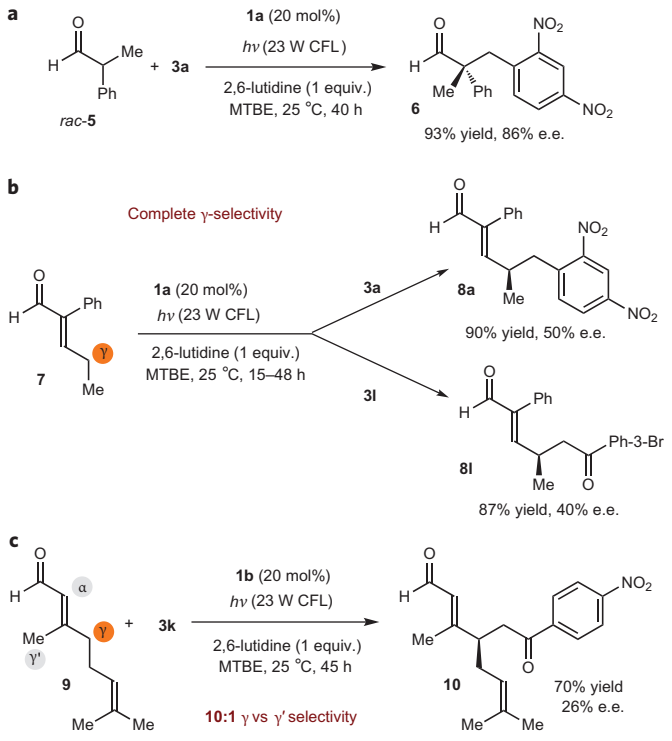


Figure 3 | Evaluating the scope and the strategy's potential to address synthetically relevant problems. a, Forging an all-carbon quaternary stereogenic centre. **b**, Remote stereocontrol and complete γ-site selectivity. **c**, Capacity to differentiate between three potential reactive centres.

distant position. Accordingly, treatment of the α-branched enal **7** with the benzyl bromide **3a** or phenacyl bromide **3l** enabled stereoselective alkylation exclusively at the aldehyde's γ-carbon (Fig. 3b, **8a** and **8l** formed in high yield and 50% and 40% e.e., respectively). The capacity for controlling the site selectivity was corroborated further by the experiments detailed in Fig. 3c, in which three possible reactive centres were partitioned. Citral **9** was functionalized at the more substituted γ-site position, with the enantioenriched adduct **10** being the main product detected (70% yield, 10:1 γ-regioselectivity). Our rationale for the observed site selectivity at the more distant position of polyunsaturated aldehydes relies on the preferential formation of the conjugated (rather than non-conjugated) radical iminium ion intermediates of type **VI**.

Mechanistic considerations. Our proposed mechanism (Fig. 1) involves highly organized EDA complexes[30] as critical intermediates that play an explicit role in determining the reactivity and the stereoselectivity. Control experiments performed for all the reactions presented here confirmed that the absence of the aminocatalyst **1** or of visible-light illumination suppressed the process completely. These observations suggest that the formation of a photon-absorbing enamine-derived EDA complex **IV** is necessary to initiate the photochemical process. On photoinduced ET, the intermediate **V** is formed. This contact radical ion pair is stabilized by Coulombic attractive forces that preserve the original well-defined mutual orientation. The alkyl radical generated on R–Br dissociative cleavage then undergoes combination with its chiral enamine radical cation partner in the solvent cavity of their origin (intermediate **VI**). A variety of data are consonant with radical combination that occurs prior to diffusive separation of the radical pair out of the solvent cage. For example, we did not detect any by-products derived from free radicals, such as hydrogen abstraction or dimerization derivatives. In addition, experiments with successive intervals of irradiation and dark periods were performed; these resulted in a total interruption of the reaction progress in the absence of light, and recuperation of reactivity on further illumination (Fig. 2c). These results demonstrate that light is a necessary component of the reaction. Although they do not definitively rule out a radical-chain mechanism, the data show that any chain-propagation process must be short-lived.

We conducted further experiments to challenge the possibility of an out-of-cage radical diffusion and subsequent chain propagation. An alternative mechanism, detailed in Fig. 4b, can be envisaged to proceed via a Kornblum–Russell $S_{RN}1$-type alkylation pathway[19,31–33], because both electron-poor benzyl[31] and phenacyl[32] bromides are suitable substrates. The process would proceed through a traditional enamine catalysis pathway, with the photoexcitation of the EDA complex (**IV** in Fig. 1) serving only to initiate a radical-chain mechanism. The radical anion within **V** would transpire out of the solvent cage to render, on facile fragmentation, a carbon-centred radical species **VIII**. That free radical could then add to the transiently generated enamine **II** to give an α-amino radical **IX**, which could be oxidized by compounds with low reduction potentials, such as the electron-poor alkyl bromide **III**. ET to **III** would regenerate the radical anion **VII**, and thus propagate the chain. Although in our proposed mechanism (Fig. 1 and Fig. 4a) the enamine radical cation within **V** is involved actively in the C–C bond-forming event, in the alternative mechanistic hypothesis, depicted in Fig. 4b, it would be an unproductive species.

We recognized that the implementation of a suitable radical clock-containing aldehyde substrate should allow us to better decipher the role played by the enamine radical cation within the ion

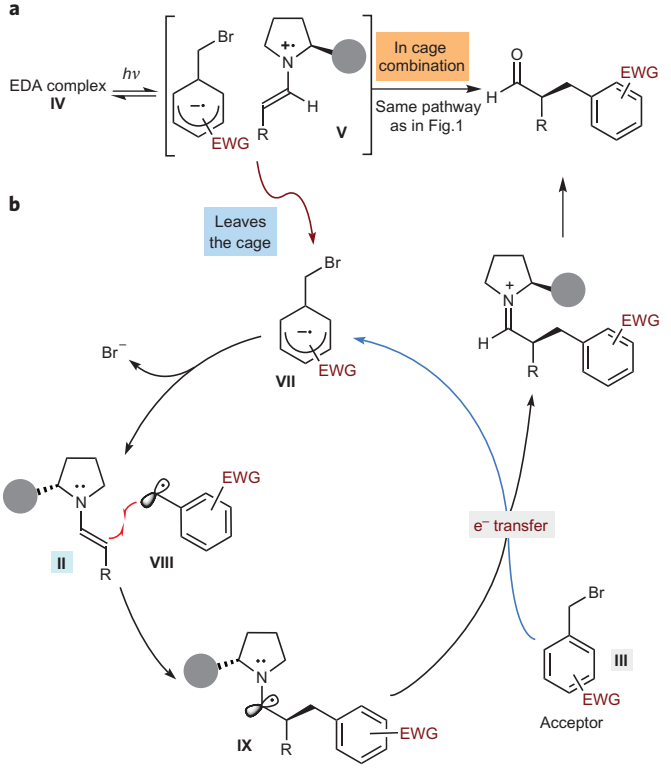


Figure 4 | Two possible reaction mechanisms. a, Our proposed mechanism based on the in-cage radical combination driven by EDA formation (see also Fig. 1). **b**, A plausible Kornblum–Russell alkylation pathway[31,32] via a radical-chain $S_{RN}1$ mechanism.

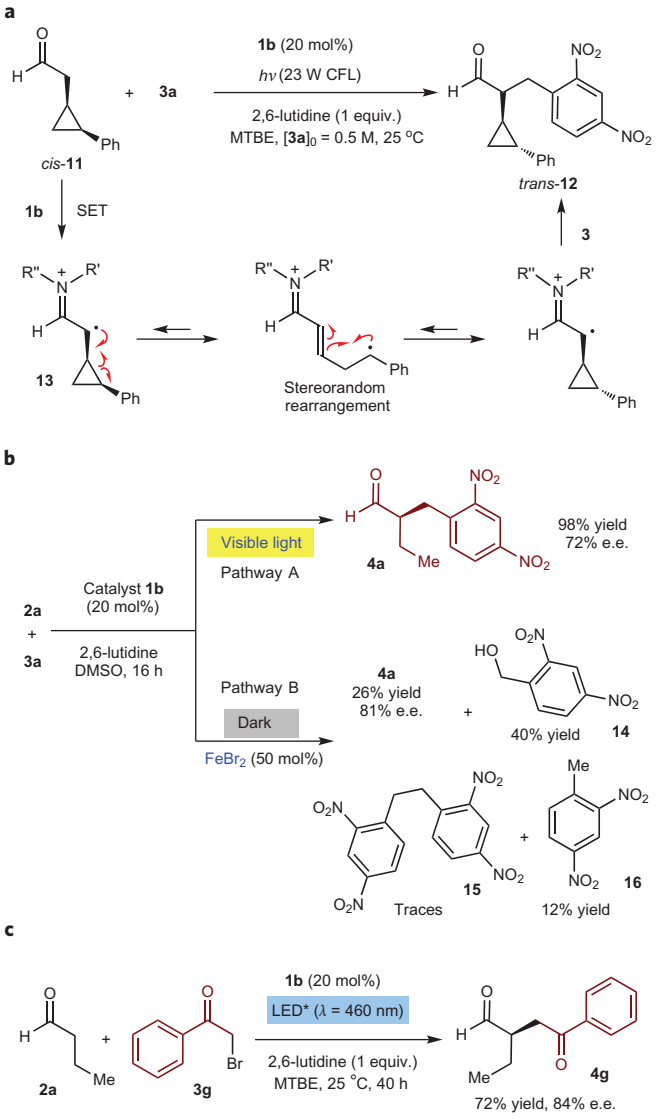


Figure 5 | Mechanistic investigations. a, Differentiating a radical cation-based pathway and enamine addition. **b**,**c**, Challenging the possibility of an $S_{RN}1$-type alkylation pathway (**b**) and of homolytic generation of carbon-centred radicals (**c**). LED: $\lambda = 460$ nm, irradiance = 13.8 W m^{-2} using an optical filter with a cutoff wavelength of 400 nm to prevent irradiation by ultraviolet harmonic frequencies.

pair **V**. When the *cis*-cyclopropyl-substituted aldehyde **11** was exposed to the alkylation protocol in the presence of bromide **3a**, the *trans*-substituted cyclopropane product **12** was formed exclusively (Fig. 5a). These observations provide evidence that the corresponding cyclopropylcarbinyl radical cation **13**, which undergoes ring opening/closing prior to productive C–C bond formation, is an intermediate along the main reaction pathway. Figure 5a shows the mechanism of cyclopropane stereomutation enabled by the radical enamine **13**, which led to the thermodynamically more stable *trans*-cyclopropyl product **12**[34]. In contrast, such radical intermediates are absent from the propagation steps of the enamine addition mechanism, as depicted in Fig. 4b. Therefore, *cis*-substituted cyclopropane products should be dominant if a radical-chain pathway prevails.

Also, we performed trapping experiments in the presence of radical scavengers (details are given in Supplementary Scheme S7). When 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO, 1 equiv.) was added to the reaction mixture of butanal **2a**, bromide **3a** and catalyst **1b**, the corresponding alkylation product **4a** was not detected after prolonged exposure to light (24 h). However, the oxyamination adducts of the aldehyde (TEMPO addition in the α position) and of the acceptor (trapping of the benzylic radical) were formed in a 1:1 ratio. Additionally, substoichiometric amounts of TEMPO (10 mol% with respect to **3a**) only retarded the commencement of the alkylation process, which then proceeded normally with a slight decrease in yield. A similar effect was observed with the galvinoxyl radical. Although this outcome is interesting *per se*, we do not wish to base the mechanistic proposal on this result. There is a plausible explanation, based on the behaviour of TEMPO as an electron donor in EDA complexes, that questions its validity as a trapping experiment (see Supplementary Scheme S8 for the alternative mechanism).

We then conducted the alkylation reaction in dimethyl sulfoxide (DMSO) in the presence of a substoichiometric amount of $FeBr_2$ (ref. 35), a one-electron transfer reagent (Fig. 5b). The reaction was performed under the rigorous exclusion of light to suppress completely a mechanism initiated by EDA complex excitation. Under these conditions, the ET from $FeBr_2$ to **3a**, leading to the radical anion **VII** depicted in Fig. 4b, is the only source of free radical intermediates amenable for a trapping event by the electron-rich enamine. This experiment mimics the conditions for an $S_{RN}1$-type chain mechanism. Accordingly, these conditions provided the alkylation adduct **4a** as a minor product (26% yield, 81% e.e.) together with large quantities of the by-products expected from diffusion-controlled free radical reactions, such as alcohol **14**, bibenzyl **15** and toluene derivative **16** (Fig. 5b, pathway B). This product distribution contrasts sharply with that obtained under illumination and excluding the ET reagent, in which none of these by-products were detected (Fig. 5b, pathway A). Interestingly, in the absence of $FeBr_2$ adduct **4a** was formed quantitatively (98% yield) in a lower optical purity (72% e.e.), which suggests that the stereoselectivity of this process is governed by a structurally different transition-state assembly.

Last, as depicted in Fig. 5c, aldehyde alkylation with phenacyl bromide **3g** under irradiation by a monochromatic LED ($\lambda_{max} = 460$ nm, irradiance 13.8 W m^{-2}) proceeded smoothly, which confirmed that residual near-ultraviolet light from the CFL source was not responsible for the observed reactivity. The use of low-energy monochromatic visible light excludes the possibility for homolytic generation of a carbon-centred radical as an initiation step because **3g** is stable under these conditions.

Taken together, our investigations support a mechanism that occurs predominantly through an enamine radical cation **VI**, the formation of which is triggered by an ET event within an EDA assembly and subsequent in-cage radical combination (Fig. 1). Although a radical-chain process cannot be ruled out completely, its contribution appears negligible. Continuing studies are aimed to further delineate the reaction mechanism and explore potential applications to other asymmetric catalytic photoreactions.

Conclusions

We found a bridge, the chiral EDA complex, to connect two powerful fields of molecule activation: asymmetric organocatalysis and photochemistry. Specifically, we demonstrate that chiral enamines, key intermediates in ground-state organocatalytic asymmetric processes, have the potential to participate actively in the photoexcitation of substrates, without the need for an external photosensitizer. The strategy differs from, but complements, the approach of photoredox catalysis[36], a rapidly developing area of modern chemical research. These findings are expected to open new avenues for reaction design in the field of asymmetric photochemical processes.

Methods

All reactions were performed under an argon atmosphere in oven-dried glassware using standard Schlenk techniques, unless otherwise noted. Synthesis-grade solvents were used as purchased and the reaction mixtures were deoxygenated by

three cycles of freeze–pump–thaw prior to illumination. Full experimental details and characterization data for all new compounds are included in the Supplementary Information.

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Author contributions

E.A. and I.D.J. were involved in the discovery and subsequent development of the light-driven alkylation reactions. E.A., I.D.J. and A.Á-F. performed the experiments. E.A., I.D.J., A.Á-F. and P.M. designed and analysed the experiments. P.M. conceived and directed the project and wrote the manuscript with contributions from E.A.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to P.M.

Competing financial interests

The authors declare no competing financial interests.