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Visible-light excitation of iminium ions enables the enantioselective catalytic β -alkylation of enals

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Chiral iminium ions, generated upon condensation of α,β -unsaturated aldehydes and amine catalysts, are used extensively by chemists to make chiral molecules in enantioenriched form. In contrast, their potential to absorb light and promote stereocontrolled photochemical processes remains unexplored. This is despite the fact that visible-light absorption by iminium ions is a naturally occurring event that triggers the mechanism of vision in higher organisms. Herein we demonstrate that the direct excitation of chiral iminium ions can unlock unconventional reaction pathways, enabling enantioselective catalytic photochemical β -alkylations of enals that cannot be realised via thermal activation. The chemistry uses readily available alkyl silanes, which are recalcitrant to classical conjugate additions, and occurs under illumination by visible light-emitting diodes. Crucial to success was the design of a chiral amine catalyst with well-tailored electronic properties that can generate a photo-active iminium ion while providing the source of stereochemical induction. This strategy is expected to offer new opportunities for reaction design in the field of enantioselective catalytic photochemistry.

Enantioselective organocatalysis has emerged in recent years as a powerful technology in the realm of chiral molecule synthesis¹. This strategy uses chiral small organic molecules as catalysts to trigger and control a chemical reaction via generic mechanisms of substrate activation and induction². One such mode of activation exploits the capacity of secondary amines of type **1** to reversibly condense with enals **2** to form iminium ion intermediates **I** (Fig. 1a). The electronic redistribution within **I**, by lowering the energy of the lowest unoccupied molecular orbital (LUMO), facilitates conjugate additions of nucleophiles to the β -carbon atom³. Over the past 15 years, the ground-state reactivity of electron-poor iminium ions has found a myriad of applications in the stereoselective β -functionalisation of enals **1**, effectively complementing established metal-based asymmetric strategies for conjugate additions to unsaturated carbonyl compounds⁴.

Iminium ions also play a crucial role in biological systems. Nature uses these ions' capacity for absorbing visible light to trigger the primary photochemical event underlying visual transduction^{5,6}. The mechanism of vision in vertebrates is initiated by light excitation of the iminium ion formed upon condensation of 11-*cis*-retinal with the ϵ -amino group of a lysine residue within opsins (Fig. 1b). Crucially, 11-*cis*-retinal undergoes a bathochromic absorption shift from the ultraviolet (~370 nm) to the visible region (>400 nm) upon formation of the iminium ion⁷. Although the photoexcitation of iminium ions is a well-established biochemical process, it is largely underused by the organic chemistry community. In the 1980's, Mariano exploited the photoactivity of preformed cyclic non-conjugated iminium ions in chemical synthesis⁸⁻¹¹. However, to the best of our knowledge, this light-driven strategy remains unexplored in the realm of enantioselective catalysis.

We recently questioned whether the synthetic potential of iminium ion catalysis could be expanded from the established ground-state domain into the seemingly distinct fields of excited-state reactivity¹² and asymmetric photochemistry¹³. We were motivated by our recent studies demonstrating that chiral enamines¹⁴⁻¹⁶, key intermediates in thermal organocatalytic enantioselective processes¹⁷, could directly participate in the photoexcitation of substrates while inducing the stereocontrolled formation of chiral products (Fig. 1c). Specifically, we showed that electron-rich enamines, which are primarily understood as nucleophiles in their ground state, could become strong reductants upon light excitation and trigger the formation of radicals through the SET reduction of electron-poor organic halides. At the same time, the ground-state chiral enamines provided effective stereochemical control over the enantioselective radical trapping process. That strategy, where stereoiduction and photoactivation merged in a sole chiral organocatalytic intermediate, enabled light-driven enantioselective transformations that could not be realised using the thermal reactivity of enamines. For the present study, we thus surmised that using light excitation to bring the electron-poor iminium ion **I** to an electronically excited state **I*** could provide further opportunities for reaction inventions. Since an excited state possesses much higher electronic affinity (i.e. it is a better electron acceptor) than the ground state¹⁸, we hypothesised that the photoexcited iminium ion **I*** could function as a strong oxidant, affording reactive open-shell intermediates upon SET oxidation of electron-rich substrates of type **3** (Fig. 1d). If successful, this strategy would complement the photochemical activity of enamines by using a completely different series of radical precursors. In addition, it would unlock unique reaction manifolds that are unavailable to conventional ground-state iminium ion chemistry. Herein, we document how this ideal was translated to experimental reality, demonstrating that visible-light excitation of catalytically generated chiral iminium ions **I** enables highly stereoselective β -alkylations of enals **2** that cannot be realised via thermal activation. More specifically, non-nucleophilic and readily available organic

trimethylsilane reagents **3**, which are recalcitrant to classical conjugate addition manifolds, have been successfully used as coupling partners for photochemical enal functionalisations.

Results and discussion

Design Plan. Figure 2 presents a detailed description of our proposed mechanism for the photochemical β -alkylation of enals **2** with alkyl silanes **3**, enabled by iminium ion excitation. We anticipated that, in analogy with the biological mechanism of vision (Fig. 1b), the condensation of a chiral secondary amine catalyst **1** with enal **2** would convert an achromatic substrate into a coloured iminium ion **I**. Visible-light excitation (>400 nm) would then provide an electronically excited state **I*** through a $\pi\pi^*$ transition, which could function as a strong oxidant in single-electron transfer (SET) processes. Specifically, we hoped that an SET from the electron-rich alkyl trimethylsilane **3** to the photo-excited iminium ion **I*** would occur to furnish the 5π -electron β -enaminy radical intermediate **II** along with the silyl radical cation **III**. Mechanistically, the choice of organic silanes **3** as redox partners is motivated by (i) their relatively low oxidation potential (E_{ox}), which facilitates their SET oxidation¹⁹, and (ii) the tendency of the resulting **III** to undergo rapid desilylation in the presence of weak nucleophiles, including solvents such as acetonitrile (CH_3CN)²⁰. Such irreversible fragmentation of the carbon–silicon bond in **III** is critical because, by hampering an unproductive back-electron transfer (BET), it would trigger the generation of neutral radical intermediates **IV** along with a formal trimethylsilyl cation (TMS^+). At this juncture, we presumed that a stereocontrolled intermolecular coupling of the chiral β -enaminy radical **II** and **IV** would form a new carbon–carbon bond while forging the stereogenic centre. The resulting enamine intermediate **V**, upon hydrolysis, would regenerate the catalyst **1** while liberating the β -functionalised aldehyde **4**.

From the outset, we recognised the choice of the chiral secondary amine **1** as key to realising our design plan. Indeed, the electronic properties of catalyst **1** must be adequately tuned to chemically enable four critical steps, including (i) the generation of an iminium ion **I** that can absorb visible light to reach an excited state **I***, and (ii) the effective SET reduction of **I*** from the silane **3**. The last step requires the catalyst to confer a high oxidising capability to the excited iminium ion **I***, for the thermodynamic facility of photoinduced SET is determined by the difference between the donor oxidation potential ($E_{\text{ox}}(\mathbf{3}^+/\mathbf{3})$) and the acceptor excited state reduction potential ($E_{\text{red}}^*(\mathbf{I}^*/\mathbf{I}^-)$). At the same time, since a secondary amine may be prone to SET oxidation²¹, catalyst **1** should (iii) not be electron-rich enough to outcompete **3** as a redox donor in the reduction of **I*** - i.e. $E_{\text{ox}}(\mathbf{1}^+/\mathbf{1})$ should be higher than $E_{\text{ox}}(\mathbf{3}^+/\mathbf{3})$. Finally, the chiral catalyst should (iv) enforce high levels of enantiocontrol in the coupling of the planar 5π -electron β -enaminy radical **II** with alkyl radicals **IV**. With respect to this carbon-carbon bond-forming event, it was recently demonstrated that β -enaminy radicals of type **II**, generated through a completely different approach^{22,23}, are generally prone to radical-radical coupling mechanisms, albeit not through stereocontrolled manifolds.

Photochemical enantioselective β -benzylation of cinnamaldehyde. We tested the feasibility of our photochemical strategy by exploring the reaction between cinnamaldehyde **2a** and benzyl trimethylsilane **3a** (Table 1). The choice of **3a** was motivated by its established tendency toward a SET oxidation-desilylation sequence to afford a benzyl radical²⁴, which is facilitated by the presence of the trimethylsilyl (TMS) electroauxiliary group¹⁹ and the relatively low oxidation potential ($E_{\text{ox}}(\mathbf{3a}^+/\mathbf{3a}) = +1.74$ V vs Ag/Ag^+ in CH_3CN). We first confirmed that the condensation of the colourless **2a** with the commercially available imidazolidinone catalyst **1a**³ generated an iminium ion **Ia** absorbing until 440 nm (blue line, Fig. 3a). With the aim of selectively exciting the transient chiral iminium ion **Ia**, we conducted the explorative experiments detailed in Table 1 in CH_3CN under irradiation by a single high-power visible-light-emitting diode (LED, $\lambda_{\text{max}} = 420$ nm). Gratifyingly, 20 mol% of catalyst **1a** provided the desired β -benzylated aldehyde product **4a** with a chemical yield as high as 79% after 4 hours, albeit with a low level of enantiomeric excess (e.e., entry 1, Table 1). No product formation was detected in the absence of catalyst **1a** or light (entries 2 and 3), demonstrating that both components are needed for this photochemical protocol. The inhibition of the reactivity was also observed under an aerobic atmosphere and in the presence of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO, 1 equivalent), the latter experiment being indicative of a radical mechanism.

To unambiguously establish the implication of the iminium ion within the photochemical regime, we investigated the photophysical behaviour of preformed **Ia**. The reduction potential of the excited iminium ion ($E_{\text{red}}^*(\mathbf{Ia}^*/\mathbf{Ia}^-)$), which was estimated as +2.3 V (vs Ag/Ag^+ in CH_3CN) on the basis of electrochemical and spectroscopic measurements (details in Section F4 within the Supplementary Information), establishes the thermodynamic feasibility of the SET oxidation of **3a**. In addition, we recorded the emission spectrum of **Ia** upon excitation at 400 nm (red dotted line in Fig. 3a). A series of Stern-Volmer studies, detailed in Supplementary Figure 29, revealed that benzylsilane **3a** effectively quenched the excited state of **Ia**, in consonance with the SET mechanism triggered by the iminium ion-photoactivity proposed in Fig. 2.

Catalyst optimisation. We then focused on identifying a chiral amine catalyst that could enforce a high level of stereocontrol. The diarylprolinol silylether **1b**, generally used in stereoselective iminium ion-catalysed thermal reactions²⁵, provided greatly improved enantioinduction but at the expense of reactivity (28% yield, 76% e.e., entry 4, Table 1). The poor catalytic activity of **1b** was rationalised on the basis of its electron-rich nature, which imparted an oxidation potential ($E_{\text{ox}}(\mathbf{1b}^+/\mathbf{1b})$) of +1.57 V vs Ag/Ag^+ in CH_3CN , a slightly lower value than the E_{ox} of benzyl silane **3a**. This situation makes catalyst **1b** prone to a SET oxidation from the photoexcited iminium ion ($E_{\text{red}}^*(\mathbf{Ib}^*/\mathbf{Ib}^-) = +2.3$ V vs Ag/Ag^+ in CH_3CN), an event which would trigger the formation of an unstable and highly reactive amine radical cation²⁶, resulting in an undesired catalyst degradation path. This scenario was confirmed by NMR analysis, which revealed that the overall amount of amine **1b** constantly decreased during the reaction (see Section F1 in the Supplementary Information). These observations prompted us to modify the electronic properties of the diarylprolinol catalyst **1b** in order to enhance stability towards oxidation by attenuating its electron-donor ability. The incorporation of electron-withdrawing fluorine atoms is widely used in medicinal chemistry to lower the susceptibility of nearby moieties to enzymatic oxidation²⁷. In addition, it is known that fluorine introduction strongly reduces amine basicity²⁸. These considerations provided a rationale for the higher oxidation potential measured for the *gem*-difluorinated catalyst **1c** ($E_{\text{ox}}(\mathbf{1c}^+/\mathbf{1c}) = +2.20$ V vs Ag/Ag^+ in CH_3CN), and its excellent catalytic activity in the photochemical reaction (entry 5, Table 1, product **4a** formed in 83% yield and

85% e.e.). To better investigate the effect of amine **1c**, we synthesised tetrafluoroborate salts of the iminium ion **Ic**, generated upon condensation with substrate **2a**, which were characterised by X-ray single-crystal analysis (Fig. 3a). Interestingly, the *gem*-difluorine atoms induce a strong conformational control over the pyrrolidine ring, as triggered by stereoelectronic effects and charge-dipole interactions²⁹, which has no counterpart in the structure of iminium ion **Ib**, thus providing a possible rationale for the increased level of stereoselectivity. A final cycle of catalyst optimisation established amine **1d**, possessing bulkier perfluoro-isopropyl groups on the arene scaffold, as suitable for improving enantiocontrol while preserving the catalytic activity (entry 6, Table 1).

Importantly, this photochemical process furnishes the enantioenriched β -benzylated aldehyde **4a**, a synthetically useful chiral compound that cannot be easily accessed by other direct stereoselective methods. In the polar domain, the intrinsic instability of benzyl-metallic derivatives³⁰, along with the competing 1,2-addition manifold, generally complicates the development of metal-catalysed conjugate additions. This is why, to our knowledge, no catalytic asymmetric conjugate additions of benzyl-metallic reagents to enals have been reported, aside from non stereoselective³¹ or indirect variants³². In addition, thermal enantioselective iminium ion chemistry has been successful for only a specific class of highly activated nitro-toluene substrates³³⁻³⁴. In the realm of open-shell reactivity, it is well-known that the large resonance stabilisation of benzyl radicals makes their addition to electron-poor olefins difficult³⁵⁻³⁶, a situation which generally favours the formation of dimeric bibenzyl derivatives instead. This is why successful strategies for benzyl radical addition to electron-poor alkenes, aside from a recently reported exception³⁷, have largely relied upon SET reduction of the acceptor to form an alkene radical anion, which is a much better trap for benzyl radicals^{9-10,38}. As depicted in Fig. 2, our strategy is based upon a similar mechanistic pattern, the coupling between the β -enaminy radical **II** and the benzyl radical **IVa** providing the desired adduct **4a**. A variety of data are consistent with this radical-radical combination mechanism. First, we did not observe the formation of bibenzyl. In addition, we measured the quantum yield of the process catalysed by amine **Ic**, which was found to be 0.05 ($\lambda = 400$ nm in CH₃CN). Although these data do not completely rule out a radical-chain process triggered by the conjugate addition of benzyl radical **IVa** to the ground-state iminium ion **I**, a chain propagation mechanism is unlikely for several reasons: (i) the already-mentioned poor nucleophilicity of benzyl radicals³⁵, (ii) the low tendency of iminium ions to trap radicals³⁹, and (iii) the endergonic SET between the benzyl silane **3a** and the α -iminyl radical cation **VI** (Fig. 3c), which would ensue from the radical addition to **I**. The last SET process, which would be essential for a chain propagation manifold by regenerating the benzyl radical **IVa**, is highly disfavoured when considering the redox potentials of the intermediates.

Scope of enantioselective photochemical β -alkylations of enals. Adopting the optimised conditions described in Table 1, entry 6, we then demonstrated the generality of the photochemical β -benzylation process by evaluating a variety of enals **2** and benzyl trimethylsilanes **3**. The results are reported in Table 2. Different substitution patterns at the aromatic moiety of **2** were well tolerated, regardless of their electronic and steric properties and position on the phenyl ring (products **4a-i**). The method is synthetically useful, with a good efficiency maintained when running the reaction on a 1 mmol scale (product **4a**). One limitation of the system is that the presence of a β -alkyl fragment in **2** completely inhibits the reaction (**4j**). Experiments to probe the scope of the benzyl silane component **3** revealed that a wide range of substituents are tolerated on the aryl ring (adducts **4k-q**). The presence of a *gem*-dimethyl substituent at the benzylic position provides the corresponding product **4r** bearing a quaternary carbon, while monosubstituted benzyl silanes afford compounds **4s-t**, having two vicinal stereogenic centres, with high enantiomeric purity, albeit with a poor diastereomeric ratio. Notably, heteroaryl frameworks can also be included in the product, as shown for the indolyl- and benzothienyl-substituted adducts **4u** and **4v**, respectively.

We next wondered if the photoexcitation of iminium ions could provide a widely applicable mechanism of substrate activation suitable for a broad range of stereocontrolled enal β -functionalisations. On the basis of our mechanistic proposal, the simple use of well-established physical properties should permit the predictable and rational identification of competent substrates. In theory, any organic silane possessing an appropriate oxidation potential (i.e., E_{ox} lower than **3a**) should have the capability to serve as a viable coupling partner. Following this reasoning, we found that α -silyl thioethers, α -silyl amines, and α -silyl ethers could productively engage in the photochemical asymmetric process. This is because the silyl group at the α -position of the heteroatom imparts an adequately low oxidation potential to these substrates through $\sigma \rightarrow n$ orbital interactions¹⁹. As a result, chiral aldehydes **5a-h** bearing a methylene-heteroatom fragment at the β -position could be synthesised with moderate to high stereoselectivity (products depicted in the last row of Table 2). Crystals from a derivative of compound **5a** were suitable for X-ray analysis, which secured the absolute configuration of the products.

Conclusions

In summary, we have developed a new and simple strategy to control the stereochemical outcome of catalytic photochemical reactions driven by visible light. Specifically, our studies demonstrate that chiral iminium ions, key intermediates in thermal enantioselective organocatalytic processes, can unlock previously inaccessible reactivities when reaching an excited state upon visible-light absorption, while inducing effective stereochemical control over the ensuing carbon-carbon bond-forming event. These findings are expected to open new avenues for reaction design in the field of enantioselective photochemical processes.

Data availability X-ray crystallographic data for amine **1c**, iminium ion **Ic**, and a derivative of compound **5a** are freely available from the Cambridge Crystallographic Data Centre, accession numbers CCDC 1494740, 1494741, and 1494742, respectively.

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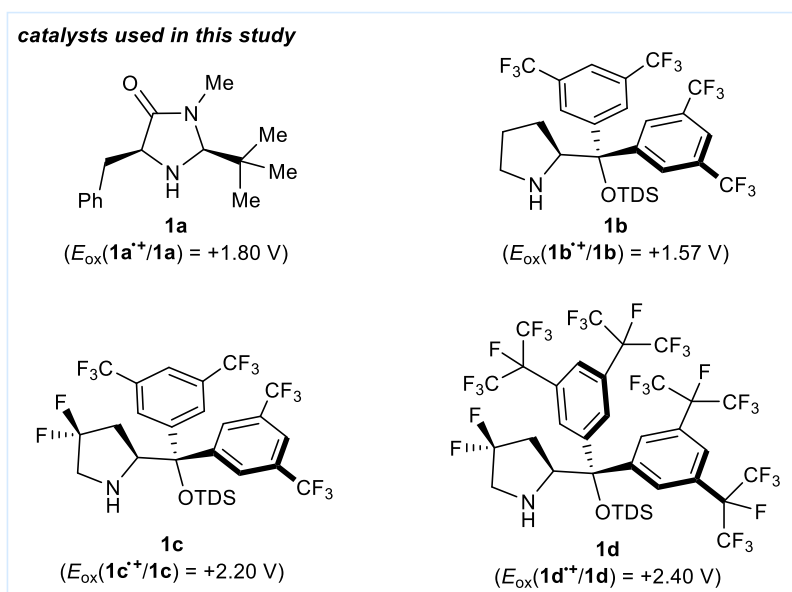
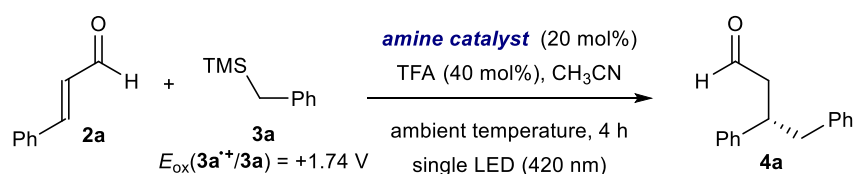
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Author contributions M.S. was involved in the discovery and initial development of the light-driven reactions. C.V. and Y.P.R. designed and synthesised the catalysts. C.V., Y.P.R., and L.B. performed the experiments. All the authors analysed the data and designed the experiments. P.M. directed the project and wrote the manuscript with contributions from all the authors.

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. (pmelchiorre@icq.es).

Competing financial interests The authors declare no competing financial interests.

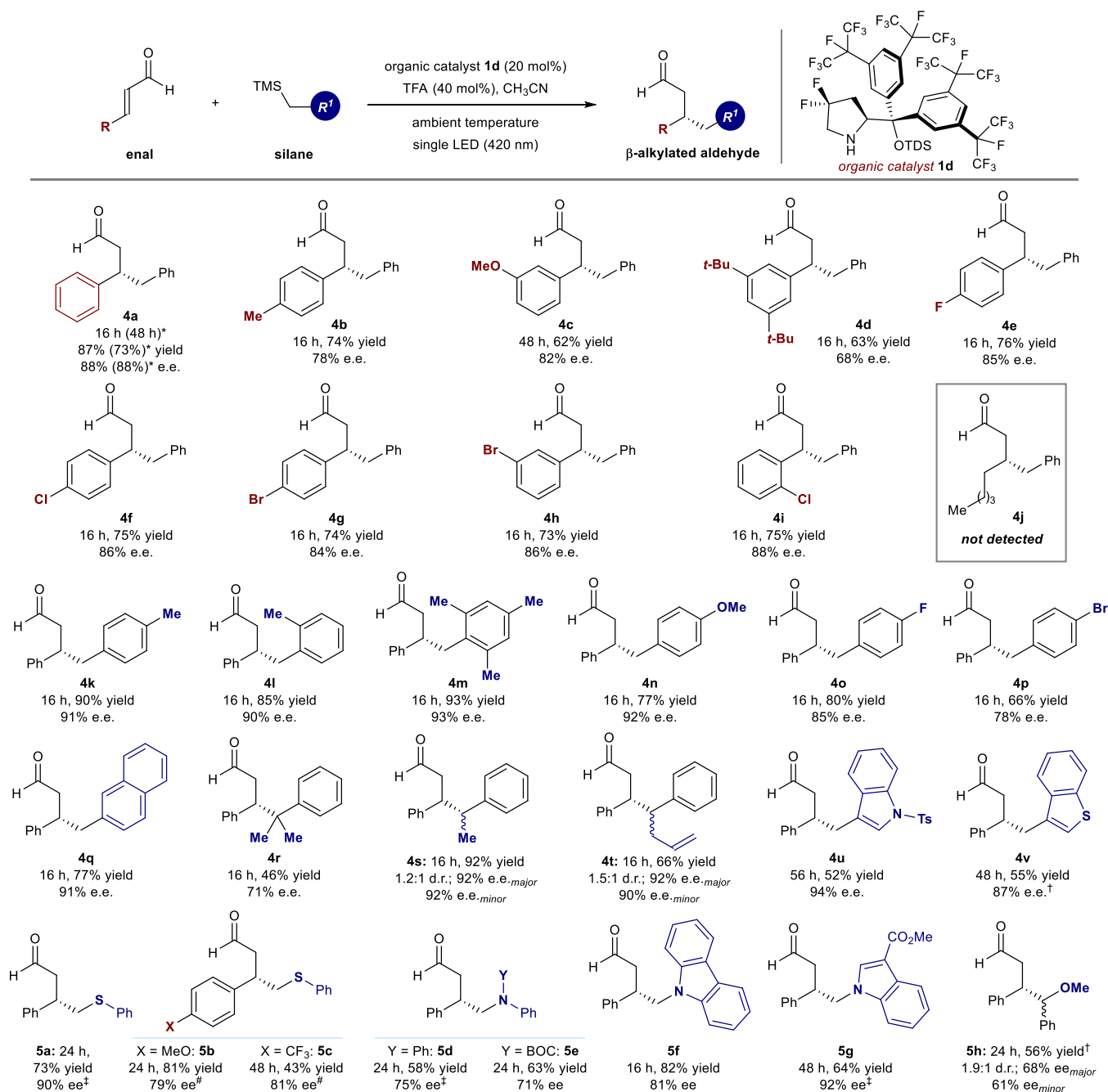
Table 1 | The model reaction and the chiral catalysts evaluated[‡].



Entry	Catalyst	Light	3a yield (%)	e.e. (%)
1	1a	ON	79	30
2	none	ON	0	-
3	1a	OFF	0	-
4	1b	ON	28	76
5	1c	ON	83	85
6	1d	ON	87	88

[‡] E_{ox} for catalysts **1** measured by cyclic voltammetry vs Ag/Ag⁺ in CH₃CN

Table 2 | Substrate scope for the photochemical β -alkylation of enals[§].



[§]Survey of the α,β -unsaturated aldehydes (products **4a-j**), the benzylsilane derivatives (products **4k-v**), and the α -silyl thioethers (products **5a-c**), α -silyl amines (products **5d-g**), and α -silyl ethers (product **5h**) that can participate in the reaction. Reactions performed on a 0.1 mmol scale using 3 equivalents of enals; the excess of enal secured a more effective iminium ion formation. Reaction time, yields, and enantiomeric excesses of the isolated products are indicated below each entry (average of two runs per substrate). Generally, full consumption of the limiting silane substrate was observed at the end of the reaction. *Performed on a 1 mmol scale; [†]using catalyst **1c**; [‡]using catalyst **1b** in a 3:1 CH₃CN/H₂O solvent mixture; [#]using catalyst **1c** in a 3:1 CH₃CN/H₂O solvent mixture. TFA: trifluoroacetic acid; TDS: thexyl-dimethylsilyl; Ts: 4-toluenesulfonyl; BOC: *tert*-butoxycarbonyl; TMS: trimethylsilyl.

Figure Legends

Figure 1 | Reactivities of iminium ions in biological systems and enantioselective catalytic synthesis. **a**, Established ground-state reactivity of chiral iminium ions **I** as electrophiles in enantioselective conjugate additions. **b**, In biological systems, the visible-light excitation of the iminium ion, formed upon condensation of 11-*cis*-retinal with a lysine residue of opsins, is the primary photochemical event of vision. **c**, Our previous studies demonstrated that chiral enamines, which are primarily understood as nucleophiles in their ground state, can become potent single-electron reductants upon light excitation and trigger the generation of radicals through the SET reduction of electron-poor organic halides, thus promoting enantioselective α -alkylation of aldehydes. **d**, Proposed strategy to unlock reaction manifolds unavailable to conventional ground-state iminium ion chemistry: enantioselective β -alkylation of enals with non-nucleophilic alkyl silanes **3** driven by the visible-light excitation of iminium ions **I**, which act as chiral photo-oxidants to afford reactive open-shell intermediates upon SET oxidation of **3**. TMS: trimethylsilyl; EWG: electron-withdrawing group; SET: single-electron transfer; filled grey circle represents a bulky substituent on the chiral amine catalyst.

Figure 2 | Design plan and mechanistic proposal: exploiting the direct photoexcitation of transiently generated chiral iminium ions **I** to enable stereocontrolled photochemical processes. Central to this study is the high oxidising capability of the excited iminium ion **I*** that can drive, by SET oxidation of **3**, the formation of alkyl radicals **IV** and the chiral β -enaminy radical intermediate **IV**, which are primed for the ensuing enantiocontrolled radical coupling reaction. H-X: organic acid; TMS: trimethylsilyl; SET: single-electron transfer; BET: back-electron transfer; filled grey circle represents a bulky substituent on the chiral amine catalyst; *Solv*: nucleophilic solvent, such as CH₃CN or water.

Figure 3 | Photophysical and structural characterisation of iminium ions and mechanistic investigations. **a**, Absorption of cinnamaldehyde **2a** (black line) and the preformed iminium ion **Ia** (blue line) and emission of **Ia** (excitation at 400 nm, red dotted line) in CH₃CN. **b**, X-ray crystal structure of the iminium ion **Ic**. E_{red}^* vs Ag/Ag⁺ in CH₃CN for the excited iminium ions **I*** estimated on the basis of electrochemical and spectroscopic measurements. **c**, Assessing the feasibility of a radical chain propagation mechanism: the photochemical activity of the excited iminium ion **I** would serve as an initiation event, generating the benzyl radical **IVa** which could be trapped by a ground-state iminium ion **I**. The endergonicity of the SET between **3a** and the α -iminyl radical cation **VI**, which would be essential to sustain a chain propagation manifold by regenerating **IVa**, means that this process is thermodynamically disfavoured. E_{red} (**VIa/Va**) measured by cyclic voltammetry vs Ag/Ag⁺ in CH₃CN of an analogue of enamine **Va**, see Supplementary Figure 1 for details and a comprehensive picture of this mechanism. TFA: trifluoroacetic acid; TDS: hexyl-dimethylsilyl; TMS: trimethylsilyl.

Table of Contents Summary

Chiral iminium ions **I**, generated from an amine catalyst **1** and enals **2**, are key organocatalytic intermediates in thermal asymmetric processes. Here we show that visible-light excitation of **I** can turn these ions into strong oxidants to enable enantioselective photochemical β -alkylations of enals with silanes **3**, which are unachievable via conventional ground-state pathways