Enhancing the potential of enantioselective organocatalysis with light

Mattia Silvi[1] & Paolo Melchiorre[2,3]*

Catalysis mediated by small chiral organic molecules is a powerful technology for enantioselective synthesis, which has found extensive applications within traditional ionic, two-electron-pair reactivity domains. Recently, organocatalysis has been successfully combined with photochemical reactivity to unlock previously inaccessible reaction pathways, thereby creating new synthetic opportunities. Here, we critically describe the historical context, scientific reasons, and landmark discoveries that were essential to expanding the functions of organocatalysis to include one-electron-mediated chemistry and excited-state reactivity.

For synthetic chemists, preparing chiral molecules with a well-defined three-dimensional spatial arrangement is a central and by no means trivial task. Enantioselective organocatalysis offers powerful solutions[1]. This strategy, which uses purely small organic molecules as chiral catalysts, has greatly enriched the synthetic toolbox, complementing traditional metal-based and enzymatic approaches to enantioselective catalysis[2]. Although sporadic examples of organic-catalyst-mediated processes were documented in the twentieth century[3-6], enantioselective organocatalysis gained prominence from 2000 onwards[7,8]. A seminal review[9] published in this journal in 2008 argued that the organocatalysis field had blossomed so dramatically in a relatively short period of time thanks to the identification of a few generic mechanisms of substrate activation and stereochemical induction (detailed in Box 1), which provided powerful tools for reaction invention. At that time[9], organocatalysis was almost exclusively applied within traditional two-electron-pair reactivity domains, and reached high levels of efficiency, as testified to by applications in the total synthesis of natural products[10,11]. Because of this progress, the general perception within the chemistry community was that it would be difficult to further expand the synthetic potential of organocatalysis. But this perception was challenged by later developments, which saw the merging of organocatalysis and photochemical reactivity[12], two powerful strategies of molecule activations that have before remained largely unrelated.

Herein we outline the historical context and the scientific reasons that motivated the combination of photocatalysis[13] and organocatalysis. Instead of providing an exhaustive list of reactions, this review critically describes developments since 2008, charting the essential ideas, serendipitous observations, and landmark discoveries that were crucial to moving organocatalysis beyond the established patterns of polar reactivity. A selection of pioneering studies will demonstrate how the merging of organocatalysis and light-mediated chemistry has profoundly influenced other fields of chemical research, such as radical chemistry[14] and enantioselective photochemistry[15]. In terms of stereoselectivity, impressive results have been achieved in many one-electron-mediated transformations, dispelling the notion that the high reactivity of radicals limits their use in enantioselective catalysis[16]. Similarly, some of the organocatalytic tools have been used to enforce high stereocontrol in photochemical processes, challenging the previously accepted idea that photochemistry is too unselective to enable efficient preparation of chiral molecules. This review will also highlight the strong connections and ancestral lineage between organocatalysis and the rapidly growing field of visible-light-mediated photoredox catalysis[17].

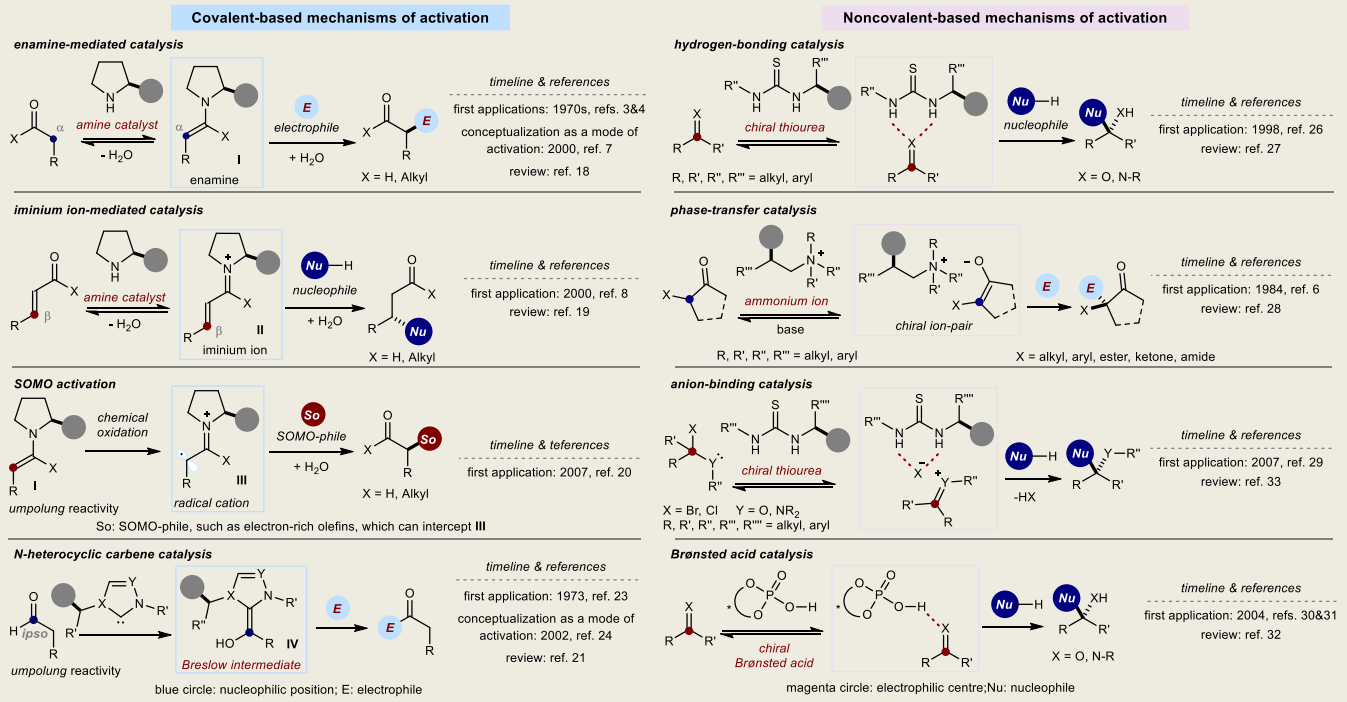
1 – School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, United Kingdom.
2 – *ICIQ,* Institute of Chemical Research of Catalonia - the Barcelona Institute of Science and Technology, Avinguda Països Catalans 16 – 43007, Tarragona, Spain.
3 – *ICREA,* Catalan Institution for Research and Advanced Studies, Passeig Lluís Companys 23 – 08010, Barcelona, Spain.
*email: pmelchiorre@iciq.es

BOX 1

Generic mechanisms of organocatalytic reactivity. Organic catalysts can exert their functions by following two different substrate activation patterns.

Covalent-based modes of activation exploit the ability of an organic catalyst to covalently bind a substrate in a reversible fashion and form a reactive intermediate that can participate in many reaction types with consistently high enantioselectivity. Chiral primary and secondary amines belong to this class, activating carbonyl substrates via formation of nucleophilic enamines **I**[7,18] (generated from enolisable aldehydes and ketones), electrophilic iminium ions **II**[8,19] (from unsaturated carbonyl compounds), and α-iminyl radical cation intermediates **III**[20] (generated upon single-electron oxidation of enamines by a chemical oxidant). N-heterocyclic carbene (NHC) catalysts[21] offer an alternative activation mechanism for aldehydes, inferring an inverted (umpolung) reactivity to the normally electrophilic carbonyl carbon atom upon formation of the Breslow intermediate **IV**[22], which acts as an acyl anion equivalent[23,24]. These activation modes, which rely on strong, directional interactions, provide for the stereoselective functionalisation of unmodified carbonyl compounds at the ipso, α, and β positions.

Non-covalent approaches are based on the cooperation of multiple weak attractive interactions between the catalyst and a basic functional group of the substrates[25]. Although the catalyst/substrate interactions are generally weaker and less directional than their covalent counterparts, they operate in concert to ensure a high level of transition state structural organisation, resulting in a high degree of enantioselectivity. Hydrogen-bonding activation[26,27], phase-transfer catalysis[6,28], anion-binding activation[29], and Brønsted acid catalysis[30-32] are other useful organocatalytic strategies for making chiral molecules[33].

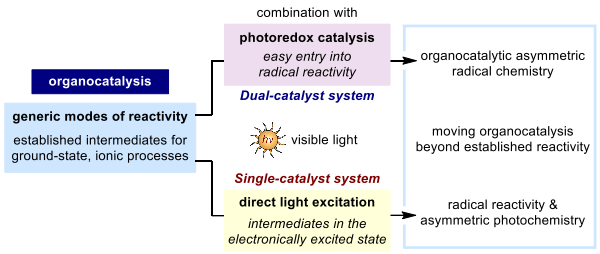


BOX 2

Light in organocatalysis. Two main strategies, the dual- and the single-catalyst approach, have been used to successfully combine organocatalysis and photochemical reactivity. This review is organised in terms of the mechanistic frameworks underpinning the two approaches.

In the *dual-catalyst approach*, the activity of a photoredox catalyst[17] synergistically combines with the generic mechanisms of activation, which define the ground-state reactivity of chiral organocatalytic intermediates. This approach exploits the ability of visible light-absorbing metal or organic photocatalysts, upon excitation, to either remove an electron from or donate an electron to simple organic substrates. This single-electron transfer (SET) mechanism facilitates access to radical species under mild conditions[34]. The unique reactivity of such photocatalytically generated open-shell intermediates allows the expansion of the organocatalytic functions from a *polar* to a *radical* reactivity domain. Overall, the field of photoredox catalysis, which is a fast-moving area of modern synthetic chemistry[17], has led to the development of many novel synthetic methodologies.

- The *single-catalyst approach* exploits the ability of organocatalytic intermediates to directly reach an excited state upon light absorption, and to participate in the activation of substrates, without using external photocatalysts. At the same time, the chiral organocatalyst ensures effective stereochemical control. This approach demonstrates that the synthetic potential of organocatalytic intermediates is not limited to the ground-state domain, but can be expanded by exploiting their *photochemical activity*. By bringing an organocatalytic intermediate to an electronically excited-state, light excitation unlocks reaction manifolds that are unavailable to conventional ground-state organocatalysis.



Merging Organo- & Photoredox Catalysis – Motivations and Historical Context

Why was organocatalysis combined with photochemical reactivity? What were the scientific motivations for exploring beyond the established boundaries of two-electron-pair reactivity? As it is often the case in science, progress was spurred by a specific goal that could not be achieved with the available technologies. Here, that goal was the intermolecular enantioselective α-alkylation of carbonyl substrates with alkyl halides (Fig. 1a) using an enamine-mediated catalytic pattern. It is important to understand why this simple transformation greatly attracted the interest of the enantioselective catalysis community[35]. The α-alkylation of carbonyl compounds is among the most important classical synthetic reactions[36]. Generally, the process requires the preformation of stoichiometric metal enolate nucleophiles that undergo a S_N2-type reaction with alkyl halides[37]. Developing an enantioselective catalytic version, however, has proven difficult, with the few reported methodologies being limited in scope[38,39]. Clearly, it was ambitious to seek to develop catalytic asymmetric methods that could directly functionalise unmodified carbonyl substrates. Enamine-based chemistry was considered the most promising approach here. This goes back to Gilbert Stork's fundamental studies[40] in the 1960s, which taught organic chemists that stoichiometric enamines could react with alkyl halides via S_N2 manifolds. With the advent of enamine-mediated catalysis, heralded by a seminal report published in 2000[7], it was thought that implementing general strategies for the direct stereoselective intermolecular α-alkylation of aldehydes would be not only feasible, but also straightforward. However, this synthetic target turned out to be much more difficult than expected[41]. The main reason was the modest reactivity of alkyl halides, which complicates the ionic alkylation step while favouring side processes, e.g. N-alkylation of the Lewis basic amine catalysts and self-aldol condensation.

In 2008, the group of David MacMillan[42] realised that the main hurdle to overcome was intrinsic to the ionic S_N2 path. Therefore, they used alkyl bromides not as electrophiles but as precursors for generating radicals. The underlying idea was to exploit the innate tendency of electron-deficient radicals to rapidly react with π-rich olefins, thus allowing the formation of difficult-to-make carbon-carbon bonds[43]. A ruthenium-based polypyridyl photocatalyst **5** ($Ru(bpy)_3^{2+}$ where bpy is 2,2′-bipyridine) was used to easily generate open-shell species from α-bromo carbonyl compounds **2** (Fig. 1b). Photocatalyst **5** had a rich history as a SET catalyst for facilitating inorganic applications[44], but had found limited use in synthetic chemistry up to that point[45].

The reaction mechanism, as detailed in Fig. 1c, is based on the integration of two independent catalytic cycles. On one side, the photoredox cycle proceeded through the reductive cleavage of **2**, instigated by SET reduction from the Ru(I) intermediate ($Ru(bpy)_3^{+}$, **7**), to afford the electrophilic radicals **8**. Concurrently, the organocatalytic pathway provided for the generation of the nucleophilic enamine **Ia** upon condensation of organocatalyst **4** with aldehydes **1**. Then, the ground-state chiral enamine stereoselectively trapped the radical **8** to forge the stereogenic centre within the α-amino radical **9** with high fidelity. In the original study, it was proposed that this electron-rich intermediate **9** was finally oxidised by the excited state of the Ru(II) photocatalyst ($^*Ru(bpy)_3^{2+}$, **6**), a SET event which closed the photoredox cycle while affording the iminium ion **10**. Hydrolysis of the latter species furnished the α-alkylation product **3** while regenerating the catalyst **4**. Luminescence quenching studies revealed that the reducing

$Ru(bpy)_3^{+}$ species **7** was initially generated by oxidation of a sacrificial amount of enamine **Ia** by the excited *Ru(II) catalyst **6**. Later, mechanistic investigations established a radical chain manifold as the main reaction path (Fig. 1d)[46]. Thus, the photoredox catalyst initiates a self-propagating radical process which is sustained by the ability of the α-amino radical **9** to regenerate the radical **8** by directly reducing the organic bromide **2**. The same reaction can be conducted replacing the ruthenium photocatalyst with organic dyes[47] or different metal-based polypyridyl complexes[48].

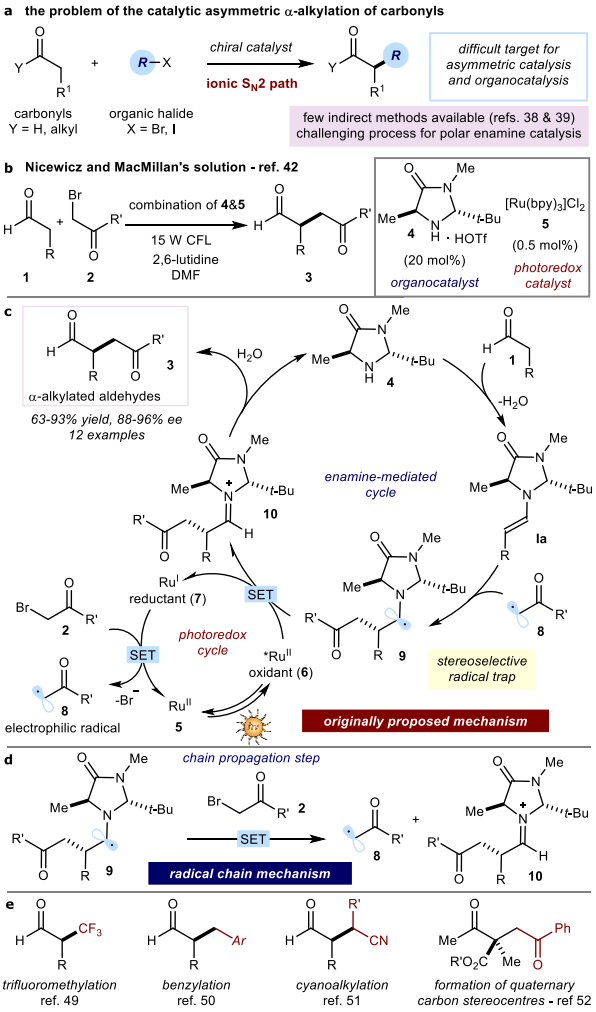


Figure 1 | **Merging photoredox and enamine catalysis. a,** The synthetic challenge of developing an intermolecular catalytic enantioselective α-alkylation of unmodified carbonyl substrates with alkyl halides via an ionic S_N2 path. **b,** The solution provided by the combination of enamine-mediated catalytic reactions and photoredox catalysis. **c,** The originally proposed closed catalytic cycle. **d,** The key propagation step of the radical chain mechanism. **e,** Further synthetic applications of this dual catalytic strategy for the direct stereocontrolled α-alkylation of aldehydes. CFL: compact fluorescence lamp; SET: single-electron transfer.

This study has had many far-reaching implications. Synthetically, by combining enamine-mediated catalysis with the action of a photoredox catalyst, it was possible to develop mechanistically related enantioselective α-alkylation reactions (Fig. 1e), including trifluoromethylation[49], benzylation[50], and cyanoalkylation[51] processes. It also allowed the enantioselective α-alkylation of 1,3-dicarbonyl substrates, which forged synthetically useful yet difficult-to-form quaternary carbon stereocentres[52]. However, the main synthetic impact was the demonstration that radical intermediates could be generated from readily available precursors and at ambient temperature, simply by using a photocatalyst activated by visible light. This meant that the tools and the mechanisms of stereocontrol of enantioselective organocatalysis, which require mild conditions for optimal efficiency, could be successfully applied within radical reactivity patterns. These studies, along with other investigations dealing with non-stereocontrolled transformations[53,54], also laid the foundations for the development of the field of photoredox catalysis[17]. Today, synthetic chemists are exploring the benefits of integrating the activity of photoredox catalysts with other catalytic systems, including metal-based catalysis[55] and chiral Lewis acid catalysis[56], though these aspects fall out of the scope of the review.

Other Dual-Catalyst Systems using Covalent Organocatalysis

After enamines, other well-established chiral organocatalytic intermediates have been used in synergy with redox-active photocatalysts.

Merging SOMO activation & photoredox catalysis

The example of singly-occupied molecular orbital (SOMO) activation illustrates how the combination with photoredox catalysis could lead to unconventional transformations. This mode of organocatalytic reactivity was introduced in 2007[20]. It exploits the SET oxidation of chiral enamines **I** by a chemical oxidant, which renders an electrophilic α-iminyl radical cation **III** amenable to a range of open-shell reactions. Since **III** can be stereoselectively intercepted by electron-rich functionalised olefins (e.g. allyl silanes), the resulting α-alkylation products result from umpolung reactivity. The main drawback of this strategy is that it requires an excess of stoichiometric oxidant. This issue was solved using a light-activated catalyst that could trigger the key SET oxidation of enamines to access the intermediate **III** (Fig. 2a)[57]. The milder radical-generation conditions offered the possibility of intercepting **III** with unactivated olefins, such as simple styrenes, in a stereocontrolled fashion (path (*i*) in Fig. 2a)[58]. By avoiding the use of organic halides, this approach further expanded the potential of the organocatalytic intermolecular α-alkylation technology. The chemistry required the combination of organocatalysis with both an iridium photoredox catalyst[59], which generated intermediate **III**, and a hydrogen atom transfer (HAT)[60] thiol catalyst, which reduced the intermediate **V** emerging from the radical addition to the styrene.

The chemistry of α-iminyl radical cation **III**, generated under photoredox conditions, is not limited to radical addition manifolds. It can be expanded to realise unconventional and difficult-to-achieve transformations, such as the direct β-arylation of unsaturated carbonyl substrates[61] (path (*ii*) in Fig. 2a). The allylic C–H bonds in intermediate **III** are sufficiently weakened to allow for proton abstraction by a suitable base,

such as DABCO (1,4-diazabicyclo[2.2.2]octane), giving the β-enaminyl radical intermediate **VI**. This species can undergo radical coupling with the long-lived radical anion **13**, generated upon SET reduction of 1,4-dicyanobenzene **12** from an iridium (III) photocatalyst. This bond-forming event, which is governed by the persistent radical effect[62], forms a new carbon-carbon bond at the original carbonyl β-position. The strategy is synthetically appealing, given the lack of alternative methods for the direct β-functionalization of carbonyl substrates bearing saturated alkyl chains. However, only a single enantioselective example has been reported. Still, this study provided an initial demonstration that classical organocatalytic tools, such as the chiral amine catalyst **14**, could serve to control the stereochemical outcome of a radical coupling event, which is greatly complicated by its intrinsic high rate[63].

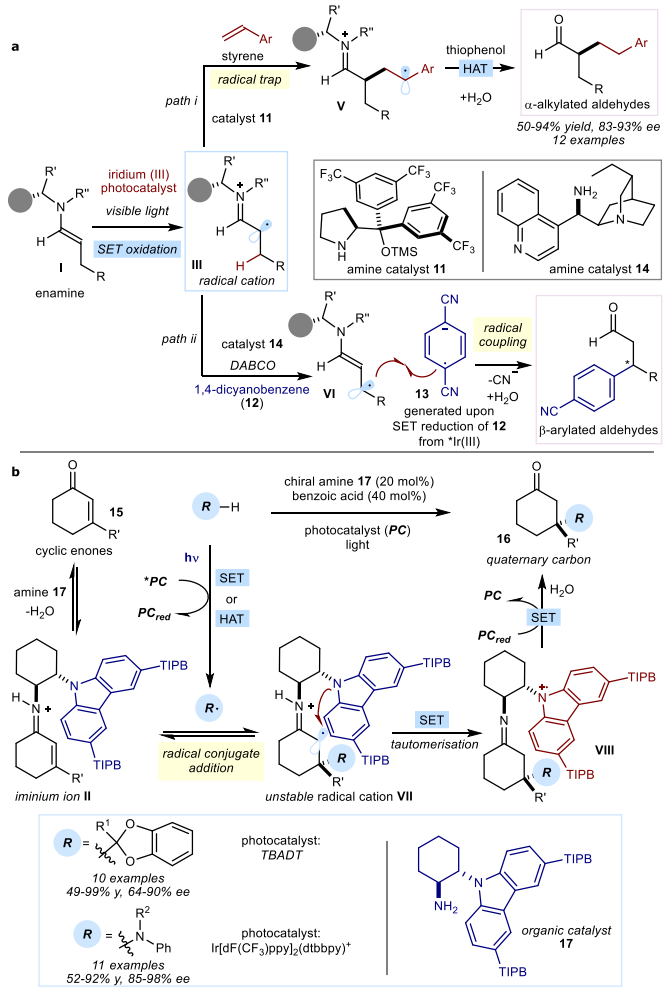


Figure 2 | Merging photoredox and covalent organocatalysis. a, Irradiation of an iridium (III) photocatalyst generates an excited state that can take an electron from the enamine **I** to afford the radical cation **III**. The chiral intermediate **III** can follow two different reaction manifolds: *i*) it can be intercepted by styrenes to eventually afford α-homobenzylated aldehydes; *ii*) it can be deprotonated to furnish the β-enaminyl radical intermediate **VI**, which can then engage in a radical coupling with the radical anion **13**. In both cases, the stereo-defining event is controlled by a chiral open-shell organocatalytic intermediate. **b,** To implement an enantioselective iminium-ion-catalysed conjugate addition of radicals, the short-lived radical intermediate **VII** must be bypassed. This is achieved by intramolecular reduction from the electron-rich carbazole moiety within catalyst **17**. HAT: hydrogen atom transfer; TMS: trimethylsilyl; LED: light-emitting diode; DABCO:1,4-diazabicyclo[2.2.2]octane; TIPB: triisopropylbenzene; TBADT: tetrabutylammonium decatungstate; $TBABF_4$: tetraethylammonium tetrafluoroborate; PC: photoredox catalyst; PC_{red}: reduced photocatalyst.

Overall, the studies detailed in Fig. 2a indicate that the native reactivity of an established organocatalytic intermediate (i.e. enamines) can be switched from a closed-shell to an open-shell manifold with a light-activated photoredox catalyst. They also highlight the ability of traditional chiral organic catalysts, generally used in enantioselective ionic processes, to control the geometry of the ensuing radical intermediates (such as **V** and **VI**) while creating a suitable chiral environment for stereocontrolled bond formation.

Merging iminium ion & photoredox catalysis

Iminium ion activation has found many applications in ionic domains, facilitating the conjugate additions of soft nucleophiles to the β-carbon atom of unsaturated carbonyl compounds. However, it has not been trivial to develop a stereoselective trap of nucleophilic radicals. This is because the addition of radicals to a cationic iminium ion **II** creates a reactive α-iminyl radical cation **VII** (Fig. 2b), an unstable intermediate with a high tendency to undergo β-scission[64] and reform the more stable iminium ion **II**. Recently, a strategy was reported that enabled enantioselective radical conjugate additions to β,β-disubstituted cyclic enones **15** in order to set quaternary carbon stereocentres with high fidelity[65]. To bypass the species **VII**, an electron-rich carbazole moiety was tethered at a strategic position of the chiral primary amine catalyst **17**, where it is poised to undergo a rapid intramolecular SET reduction of the unstable **VII**, preventing it from breaking down. A fast tautomerisation of the nascent enamine intermediate (not shown) leads to the more stable imine **VIII**, thus avoiding a possible competitive back-electron transfer (BET). Finally, the long-lived carbazole radical cation in **VIII**, emerging from the intramolecular SET, undergoes single-electron reduction from the reduced photoredox catalyst (***PC**red* in Fig. 2b). This restores the neutral carbazole moiety while yielding the quaternary product **16**. Notably, a photocatalyst (***PC***) both creates the nucleophilic radical and promotes the final redox process, which was identified as being the turnover-limiting step of the overall reaction[66].

The process provides a way to construct quaternary carbon stereocentres in an enantioselective manner and exploits the tendency of radicals to connect structurally congested carbons because their reactivity is only marginally affected by steric factors[67]. However, radical-based catalytic enantioselective strategies had previously found limited application to construct quaternary carbon sterecenters[52], and were not mentioned in a recent comprehensive survey of available methods[68]. It appears that organocatalysis, in combination with photoredox catalysis, may offer effective tools to better exploit the intrinsic merits of radical reactivity.

Also N-heterocyclic carbene (NHC) catalysis could be used in conjunction with photoredox catalysts[69]. Although this approach has not yet been used to stereoselectively trap photochemically generated radicals, this target appears feasible.

Dual-Catalyst Systems using Noncovalent Organocatalysis

Noncovalent modes of organocatalytic reactivity have also been used with photoredox catalysis. To date, there have been few reports, but these have offered solutions to synthetically meaningful problems. Initial approaches used photochemical strategies to in situ generate reactive closed-shell species (e.g. iminium ions[70], singlet oxygen[71]), which were successively intercepted by chiral organocatalytic intermediates. The first application of noncovalent organocatalysis in light-mediated radical chemistry provided a strategy to perform an asymmetric aza-pinacol cyclisation (Fig. 3a)[72]. The combination of the chiral phosphoric acid catalyst **20** and an iridium photoredox catalyst promoted the intramolecular reductive coupling between the ketone and hydrazone moieties within substrate **18** to furnish the *syn* 1,2-amino alcohol derivatives **19** with high enantioselectivity. The process was triggered by the formation of the ketyl radical intermediate **21**, which was generated by a concerted proton-coupled electron transfer (PCET) process[73] driven by the cooperation of the photoredox and organic catalyst. PCET uses the simultaneous transfer of a proton and an electron in a single elementary step to allow processes that would be precluded via sequential, discrete proton and electron transfer steps. In this specific case, the direct SET reduction of the aryl ketone in **18** by the iridium photocatalyst alone would not be feasible. The ketyl radical **21**, generated by PCET, was primed to cyclise into the hydrazone. Subsequent hydrogen atom transfer (HAT) from a terminal reductant (Hantzsch dihydropyridine) to the emerging hydrazyl radical led to the final product **19**. The high level of enantiocontrol indicated that the neutral ketyl radical **21** could maintain a meaningful association, via tight hydrogen-bonding interactions, with the coordinating phosphate anion of the chiral Brønsted acid **20** during the course of the stereo-defining cyclisation. This study established the possibility of using concerted PCET to realise enantioselective radical processes by streamlining the preparation of radicals that are otherwise difficult to achieve. It also suggested the somewhat unexpected finding that the weak interactions inherent to noncovalent organocatalysis are suited to selectively binding radical intermediates while channelling the resulting processes toward stereoselective manifolds.

Recently, Takashi Ooi expanded on by using chiral P-spiro tetraaminophosphonium ion **25**, which could selectively bind the anion-radical **26** via ion-pairing interactions (Fig. 3b)[74]. The system required the concomitant action of an iridium photoredox catalyst to reduce the N-sulfonyl aldimines **22** and oxidise N,N-arylaminomethanes **23**. The radical coupling of **26** and **27**, governed by the chiral ion pair, gave the amine product **24** in high enantioselectivity. This study further demonstrated that organocatalysis can provide effective approaches to address issues in enantioselective radical chemistry that were previously considered unattainable, such as the precise stereocontrol of radical coupling processes[63].

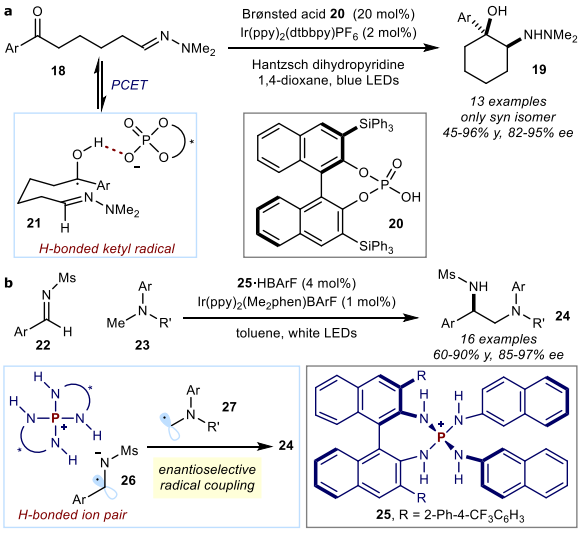


Figure 3 | Merging photoredox and noncovalent organocatalysis. a, The synergistic action of a chiral Brønsted acid and an iridium (III) photoredox catalyst facilitates both the formation of the neutral ketyl radical **21**, by concerted proton-coupled electron transfer (PCET), and the ensuing stereocontrolled aza-pinacol cyclisation. **b,** The chiral ion pair, formed between the cationic catalyst **25** and the photochemically generated radical anion **26**, governs an enantioselective radical coupling to afford products **24**. Ms: methanesulfonyl; BArF: tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

Organocatalysis in the Excited State

The great potential of combining photoredox catalysis and organocatalysis lies mainly in the possibility of accessing open-shell species whose unique reactivity allows transformations not accessible through polar pathways. A different strategy has recently emerged, which offers possibilities to expand the field of organocatalysis. Researchers are exploring the potential of some chiral organocatalytic intermediates to directly reach an excited state upon visible-light absorption to turn on new catalytic functions. The chemical reactivity of electronically excited molecules differs fundamentally from that in the ground state[75]. For example, an excited-state molecule is both a better electron-donor (i.e. a better reductant) and electron-acceptor (i.e. a better oxidant) than in the ground state[76]. This explains why, on excitation, some chiral organocatalytic intermediates can activate substrates via SET manifolds without the need for an external photocatalyst. At the same time, the chiral intermediate can provide effective stereochemical control over the ensuing bond-forming process. In this strategy, stereoinduction and photoactivation combine in a single chiral organocatalyst.

Photochemistry of enamines

The reaction in Fig. 1b was also instrumental in the discovery that the synthetic potential of chiral enamines is not limited to the ground-state domain, and can be expanded by exploiting their photochemical activity. During investigations on the direct α-alkylation of aldehydes with electron-deficient alkyl bromides **28** using the organocatalyst **11** (Fig. 4a), a control experiment revealed that the reaction could be efficiently conducted in a stereoselective fashion under light illumination but without the need for any external photoredox catalyst[77].

Mechanistic studies revealed the ability of enamines **Ib** to trigger the photochemical formation of radicals from alkyl bromides using two different photochemical mechanisms, depending on the substrate. The first mechanism[77] relied on the formation of visible-light-absorbing electron donor-acceptor (EDA) complexes[78,79], generated in the ground state upon association of the electron-rich enamine **Ib** with the electron-deficient dinitro-benzyl bromide **28a** (Fig. 4a, path *i*). Irradiation of the coloured EDA complex **IX** induced a SET event, allowing access to the radical intermediate **30a**. A second radical generation mechanism[80] (Fig. 4a, path *ii*) exploited the ability of the chiral enamine **Ib** to directly reach an electronically excited state (**Ib***) upon light absorption and then act as a potent single-electron reductant. SET reduction of the bromomalonate **28b** induced the formation of the radical **30b**. Mechanistic studies[81] established that both enamine-mediated photochemical alkylations proceeded through a self-propagating radical chain mechanism (Fig. 4a, right panel)[82], in analogy to the processes performed in the presence of a photoredox catalyst (Fig. 1d). This implies that the photochemical activity of enamines, which generates radicals by either EDA complex activation or direct excitation, serves as an initiation to sustain a chain process.

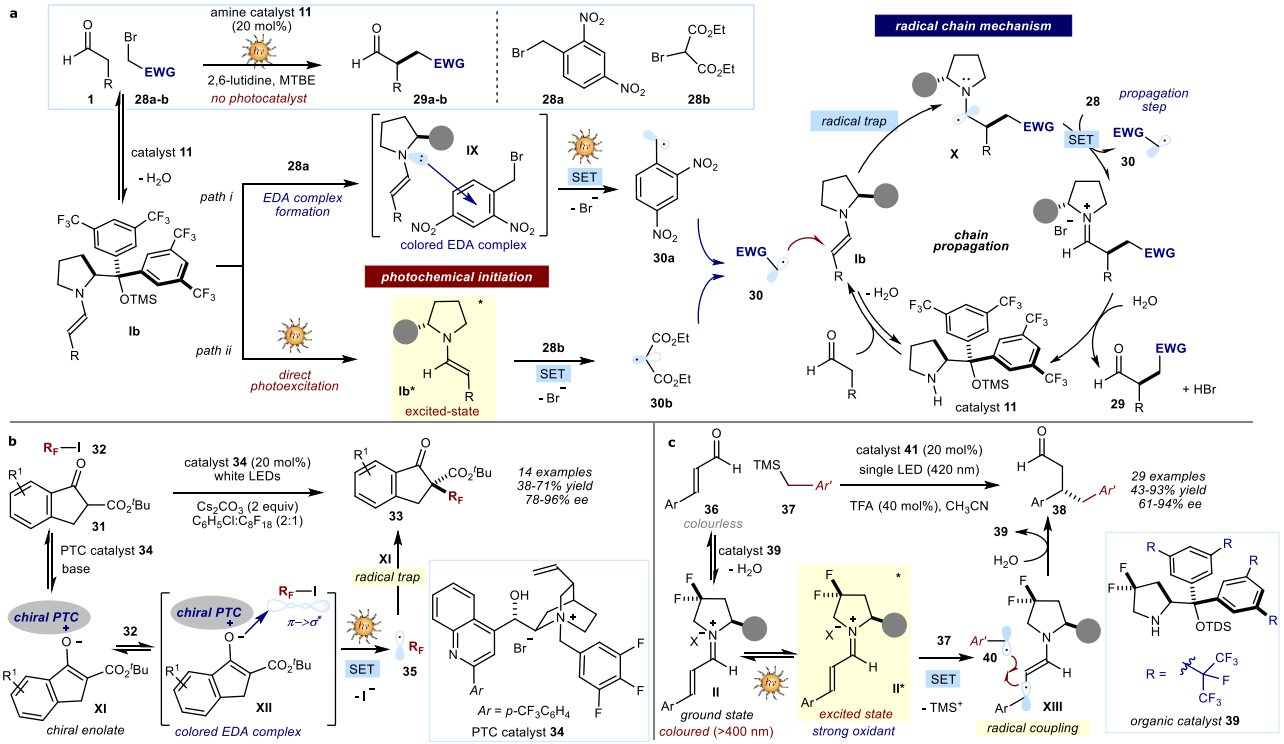


Figure 4 | **Excited-state reactivity of chiral organocatalytic intermediates. a,** Light-driven enantioselective α-alkylation of aldehydes: the photochemical activity of the enamines, either by EDA complex formation (path *i*) or direct photoexcitation (path *ii*), generates the electrophilic radicals **30** from electron-poor organic bromide **28**. The stereoselective radical trap, which is governed by the ground-state chiral enamine **Ia**, triggers a chain propagation mechanism. **b,** Phase-transfer-catalysed enantioselective perfluoroalkylation of β-ketoesters, driven by the photoactivity of the enolate-based EDA complex **XII**. **c,** Exploiting the direct photoexcitation of chiral iminium ions **II** to enable stereocontrolled β-alkylation of enals with non-nucleophilic alkyl silanes **37**; the chiral β-enaminyl radical **XIII**, emerging from the SET reduction of the excited iminium ion **II***, which acts as a strong oxidant, governs the stereocontrolled radical coupling to afford products **38**. The filled grey circle represents a bulky substituent on the chiral amine catalyst; PG: protecting group; TFA: trifluoroacetic acid; TDS: thexyl-dimethylsilyl; R_F: perfluoroalkyl fragment.

These studies demonstrated that light excitation can turn enamines (which behave as nucleophiles in the ground state) into reductants and trigger the formation of radicals. At the same time, ground-state enamines control the stereochemical course of the radical trapping event. This strategy was expanded to develop mechanistically related enantioselective α-functionalization reactions, including phenacyl alkylation[77], amination[83], and arylsulfonyl alkylation[84] of aldehydes and the alkylation of cyclic ketones[85].

Photochemistry of other organocatalytic intermediates

The discovery that the catalytic functions of enamines can be expanded by using their excited-state reactivity[77] motivated the quest for other chiral organocatalytic intermediates that could use similar photochemical mechanisms. The electronic similarities with enamines suggested the use of enolates of type **XI**, generated in situ under PTC conditions[28] (see Box 1) by deprotonation of cyclic β-ketoesters **31**, as suitable donors to facilitate the formation of photoactive ground-state EDA complexes (Fig. 4b)[86]. Perfluoroalkyl iodides (R_FI **32**) served as electron-accepting substrates, leading to the formation of the coloured EDA complex **XII**. A visible-light-promoted SET triggered the formation of the perfluoralkyl radical **35** ($R_F^•$) through the reductive cleavage of the C–I bond. The electrophilic nature of $R_F^•$ allowed the stereoselective trap by the chiral enolate **XI**, generated using the cinchonine-derived PTC catalyst **34**. The chemistry provided access to enantio-enriched ketoester products **33** bearing either a perfluoroalkyl- or a trifluoromethyl-containing quaternary stereocentre.

Recently, it was also established that chiral iminium ions participate in photochemistry (Fig. 4c)[87]. Condensation of the chiral amine catalyst **39** with aromatic enals **36** converts an achromatic substrate into a coloured iminium ion **II**. Selective excitation with a violet-light-emitting diode (LED) forms an electronically excited state (**II***). This turns an electrophilic species into a strong oxidant[88], which can trigger the formation of radicals through SET oxidation of organic silanes **37**. The latter event furnishes the chiral β-enaminyl radical intermediate **XIII** along with the radical **40**, which is generated upon irreversible fragmentation of the carbon–silicon bond. A stereocontrolled intermolecular coupling of the chiral β-enaminyl radical **XIII** and **40** then forms the stereogenic centre in the β-functionalised aldehyde product **38**. The silane reagents **37** are non-nucleophilic substrates, which are recalcitrant to classical conjugate addition manifolds. Thus, in contrast to other examples of excited-state organocatalytic intermediates, the excitation of chiral iminium ions enables transformations that could not be realised by conventional catalytic asymmetric methodologies. A further difference is that stereoselectivity is dictated by the chiral radical intermediate **XIII**, which governs the radical coupling event, and not by the ground-state iminium ion. Given the high oxidation potential of the excited iminium ion **II*** (E_{red}^* estimated as ≈+2.3 V *vs* Ag/Ag^+ in CH_3CN), this strategy holds potential for the development of other stereocontrolled enal β-functionalisations driven by light.

Noncovalent organocatalysis in enantioselective photochemistry

The photochemical organocatalytic strategies discussed so far all relied on the stereoselective interception of photogenerated radicals or radical ions in their ground states. But organocatalysis can also provide effective tools for catalytic stereocontrol in reactions of electronically excited intermediates. This is a difficult target because it requires the control of a photochemical process in a high-energy hypersurface, where the action of a catalyst is greatly complicated by the absence of significant activation barriers. Hydrogen-bonding catalysis[27], which relies on multiple weak interactions to activate the substrates, has provided effective solutions. Chiral ketones, properly adorned with hydrogen-bonding motifs[89], were used to catalyse light-triggered stereocontrolled cyclisations[90]. The ketone-based organic catalysts effectively bind the substrate through a directional double H-bond interaction, thus enabling the selective photoexcitation of a chiral catalyst-substrate complex. This ensured that the substrate resided in a suitable chiral environment when reaching an excited-state. This strategy was successfully used in both photo-induced redox processes and energy-transfer-induced photochemical reactions. In an example of the latter (Fig. 5a)[91], a visible-light-absorbing thioxanthone moiety was incorporated within the catalyst **43**. The lactam functionality of **43** was essential for binding the substrate **41** via a double hydrogen-bond interaction. Meanwhile, the thioxanthone, upon light-excitation, activated the substrate within the complex **44** via a proximity-driven Dexter energy transfer mechanism[75] and directed the [2+2] cyclization in the triplet energy hypersurface. The final product **42** was obtained with excellent enantioselectivity.

Other strategies for the enantioselective catalysis of photochemical processes[15,92] have been successively developed. For example, it was demonstrated that a mechanistically similar intramolecular [2+2] photocycloaddition is promoted with high stereoselectivity by chiral thiourea catalysts[93], traditional ground-state hydrogen-bonding organocatalysts[94].

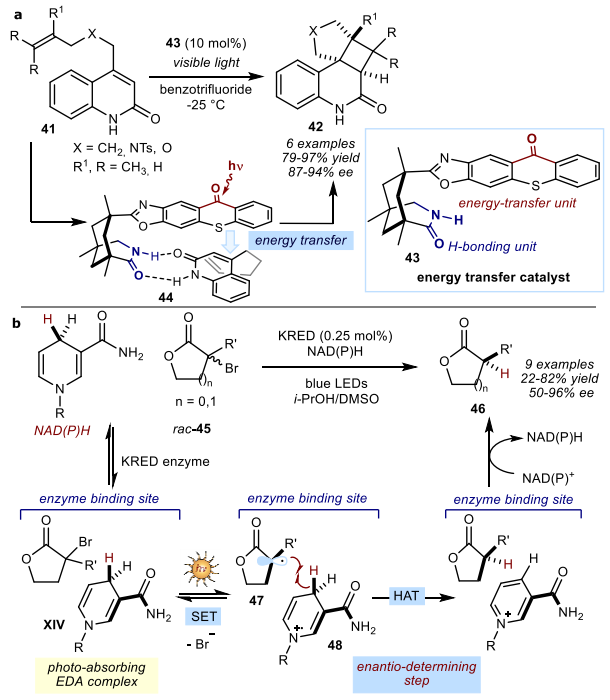


Figure 5 | a, Hydrogen-bonding catalysis of enantioselective photochemical [2+2] cycloaddition via triplet energy-transfer mechanism. **b,** Photoexcitation of a NAD(P)H-dependent enzyme enables a non-natural reactivity, allowing an enantioselective debromination of **45**. KRED: nicotinamide-dependent ketoreductase.

Photoexcitation of enzyme cofactors

Recently, a strategy has been reported that uses the excited-state reactivity of common biological cofactors to allow enzymes to catalyse completely different processes than those for which they evolved. The natural reactivity of nicotinamide-dependent ketoreductases (KREDs) can be altered upon light excitation of the NADH/NADPH cofactor, which is bound into the enzyme active site[95]. KREDs have found extensive use in the preparation of chiral alcohols upon reduction of ketones[96]. This native polar reactivity is enabled by the ability of such enzymes to simultaneously bind, through noncovalent weak interactions, a carbonyl compound and the cofactor, and the tendency of NADH (or NADPH) to serve as a hydride (H^-) source. Visible-light excitation, however, switches on a completely distinct reactivity, for the NAD(P)H becomes a strong reducing agent[97], allowing access to radical manifolds (Fig. 5b). This photochemical behaviour was used to perform an enantioselective dehalogenation of racemic α-bromo lactones **45**. Once the NAD(P)H and the substrate **45** are brought into close proximity in the enzyme active site, they can form a visible-light-absorbing EDA complex **XIV**, which triggers the formation of the prochiral radical intermediate **47** upon reductive cleavage of the substrate C-Br bond. The cofactor radical cation **48** drives the formation of the reduced chiral product **46**.

This brief detour in enzymatic catalysis[98] highlights how the power of photochemistry to unlock unconventional reactivity is influencing other established fields of catalytic enantioselective synthesis, including metal catalysis[99].

Conclusions and outlook

Over the last decade, the combination with light has created exciting opportunities for expanding the scope of organocatalysis beyond conventional two-electron reactivity. Groundbreaking developments have taught synthetic chemists how to translate the generic mechanisms of activation, which govern the success of enantioselective polar organocatalysis, into the realm of excited-state reactivity and radical chemistry. The resulting light-driven methodologies are greatly expanding the way chemists think about making chiral molecules sustainably.

Major developments are probably still to come. This prediction is motivated by the fast-growing stream of innovation in photoredox catalysis, which is continuously offering powerful new ways to generate radicals, and by the fact that the potential of excited-state organocatalytic reactivity is far from being fully revealed. Novel synthetic developments are expected to arise from the combination of photoredox catalysis and the activation mechanisms of ground-state organocatalysis. Considering the powerful photoredox methods available for generating radicals upon selective C–H activation of unactivated substrates (i.e. PCET and HAT mechanisms), the development of challenging enantioselective C(sp^3)- C(sp^3) coupling strategies will likely set an ambitious target. Efforts will also be devoted to the use of continuous flow photoreactors, which may enable the scale-up of photochemical organocatalytic asymmetric methods[100]. Another central goal for the continued expansion of organocatalysis will be to fully explore the unique modes of reactivity enabled by excitation of organocatalytic intermediates. Along these lines, traditional photosensitisers could provide a reliable support for facilitating, by means of energy transfer mechanisms, the generation of excited-state chiral intermediates that cannot be accessed by direct light absorption. This approach will require a deep understanding of the photophysical properties of the organocatalytic intermediates. It is expected that the combination of conventional physical organic chemistry tools with photophysical investigations will play an increasingly relevant role for the rational design of new catalysts and new reactions. Another force for innovation may arise by integrating the photochemical activity of chiral organocatalytic intermediates within metal-mediated catalytic cycles, which could enable unconventional mechanisms for stereocontrolled bond-formation. Finally, we expect great strides in the development of photochemical radical cascade processes, where the unique excited-state organocatalytic reactivities can be combined to provide powerful transformations for the one-step synthesis of complex chiral molecules[10].

Given the many innovative reactivity concepts identified in the last decade, and their impact on other research fields, such as radical and photo-chemistry, the future of enantioselective organocatalysis looks bright.

Acknowledgements P.M. thanks the Generalitat de Catalunya (CERCA Program), MINECO (CTQ2016-75520-P), and the European Research Council (ERC 681840 - CATA-LUX) for financial support. M.S. thanks the EU for a Marie Skłodowska-Curie Fellowship (grant no. 744242).

Author contributions P.M. outlined the content of the review and defined its scope. M.S. and P.M. worked together to prepare and edit the manuscript, figures, and references.

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