LETTER

Enantioselective catalytic construction of quaternary carbons by iminium ion trapping of photochemically generated radicals

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A central goal of modern organic chemistry is to develop novel catalytic enantioselective carbon-carbon bond-forming strategies for forging quaternary stereogenic centres[1]. While considerable advances have been achieved in the realm of polar reactivities, radical transformations have found very limited application[2]. This is despite the fact that open-shell intermediates are intrinsically primed for connecting structurally congested carbons, as their reactivity is only marginally affected by steric factors[3]. Herein we demonstrate how the combination of photoredox[4] and asymmetric organic catalysis[5] enables enantioselective radical conjugate additions to β,β-disubstituted cyclic enones to set quaternary carbon stereocentres with high fidelity. Key to success was the design of a chiral organic catalyst, purposely adorned with a redox-active carbazole moiety, which drives the stereoselective interception of photochemically-generated carbon-centred radicals by means of an electron-relay mechanism. We demonstrate the generality of this organocatalytic radical-trapping strategy with two sets of open-shell intermediates, formed through unrelated light-triggered pathways from readily available substrates and photoredox catalysts. To the best of our knowledge, this method represents the first applicable use of iminium ion activation[6] (a successful catalytic strategy for enantioselective polar chemistry) within the realm of radical reactivity.

Organic chemists generally rely on polar reactivities to address the challenge of forging quaternary carbon stereocentres in a catalytic enantioselective fashion[1]. Of the synthetic methods available, metal-catalysed conjugate additions of organometallic nucleophilic species to trisubstituted unsaturated carbonyl substrates have recently emerged as a powerful technology[7-10] (Fig. 1a). These are reliable and stereoselective processes, but they require harsh reaction conditions and pre-formed organometallic reagents. In contrast, there has been limited success in developing analogous transformations with nucleophilic carbon-centred radicals. While a few examples of metal-catalysed enantioselective radical conjugate additions have been reported[11-14], none of these approaches provide for the formation of sterically demanding quaternary carbons. Our herein-reported work was prompted by the desire to address this gap in catalytic enantioselective methodology.

Our initial motivation stems from the notion that, due to the long carbon-carbon forming bond in the early transition state[15], additions of radicals to electron-deficient olefins are rather insensitive to steric hindrance[3]. This makes radical reactivity particularly suited to connecting structurally complex carbon fragments while forging quaternary carbons, as testified to by literature synthesis of natural products facilitated by radical conjugate additions[16].

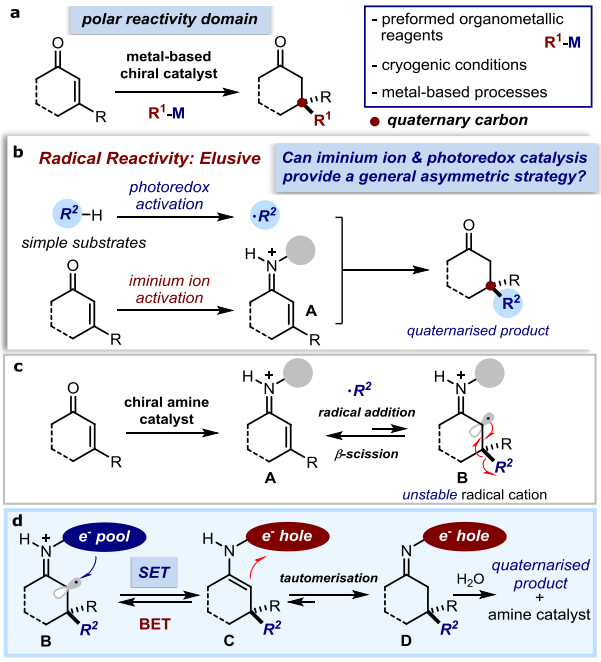

Figure 1 | Conjugate addition technology for forging quaternary stereocentres. a, Established metal-catalysed enantioselective conjugate additions of organometallic reagents (R-M) via classical polar pathways. **b**, Design plan for dual photoredox and iminium ion catalysis of radical conjugate additions; the grey circle represents the chiral organic catalyst scaffold. **c**, Challenges associated with implementing iminium ion-catalysed conjugate addition of radicals ($\cdot R_2$). **d**, Our electron-relay strategy to bypass the short-lived α-iminyl radical **B** by intramolecular reduction, and the role of tautomerisation to prevent back electron transfer. SET = single electron transfer. BET = back electron transfer. The blue circle represents an electron rich, reducing moiety, while the magenta circle represents a stable oxidising species.

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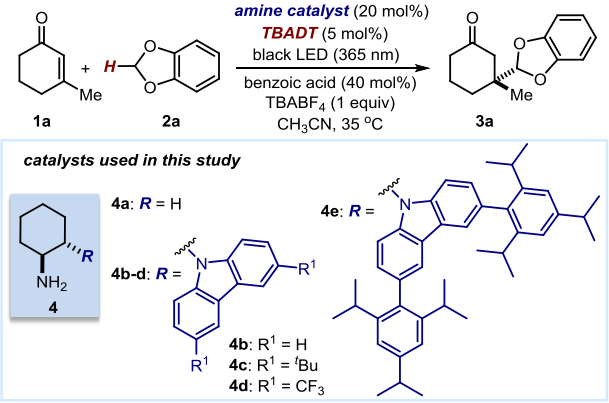
We also recognised that the emerging field of light-mediated photoredox catalysis[4] had recently provided an effective way of generating radical intermediates from readily available, bench-stable precursors and under mild conditions. As a result, novel synthetic transformations have been invented that capitalise upon non-traditional open-shell mechanisms[17]. We sought to combine this effective radical generation strategy, which requires no purposely functionalised reactant, with a suitable chiral catalyst that could drive the stereoselective trap of photogenerated carbon-centred radicals while setting quaternary stereocentres. If successful, this combination would provide direct access to chiral molecules that could not be synthesised using polar conjugate additions. In this Letter, we report the realisation of this goal.

We used the iminium ion activation strategy[6] to attack the problem of identifying a suitable chiral catalyst. This chemistry exploits the electrophilic nature of the chiral iminium ion **A** (Fig. 1b), transiently generated upon condensation of chiral amine catalysts and unmodified α,β-unsaturated ketones, to facilitate enantioselective conjugate additions of carbon nucleophiles. This catalytic platform has found many applications in the polar domain over the last 15 years[5,6]. However, to date, chiral iminium ions **A** have never been used to trap nucleophilic radicals. This is most surprising, given the high tendency of open-shell species to react with electron-deficient olefins[3]. We reasoned that this dearth of applications could stem from the nature of the radical intermediate **B**, generated upon the carbon-carbon forming event (Fig. 1c). Generally, olefinic radical traps are electrically neutral and, as such, afford long-lived, neutral radical intermediates. In contrast, radical addition to the cationic iminium ion **A** generates a short-lived and highly reactive α-iminyl radical cation **B**, which, in consonance with the classical behaviour of radical ions[18], has a high tendency to undergo radical elimination (β-scission)[19] thus reforming the more stable conjugated iminium ion **A**.

Recognising the instability of **B** as the main obstacle to productive radical conjugative addition to iminium ions, we knew it would be necessary to bypass this troublesome intermediate (Fig. 1d). As a mechanistic blueprint, we considered the possibility of reducing the α-iminyl radical cation **B** *in situ* to generate the corresponding closed shell enamine **C**, which can be turned over in a facile manner to release both the catalyst and the conjugate addition product. From the outset, we identified three design elements as key to realising this goal. First, the high reactivity of **B** requires a very rapid single electron transfer (SET) reduction. We hypothesised that using a chiral amine catalyst adorned with a redox active, electron-rich moiety (electron pool unit) would secure a fast, proximity-driven intramolecular reduction of **B**. This idea finds support in the mechanism of electron transfer within biological systems, where even endergonic redox processes can be achieved via electron tunnelling if the redox centres are in close proximity[20]. Second, we needed to identify a rapid process to interrupt a possible reversible electron transfer between **B** and the nascent enamine **C**. Since secondary enamines are known to exist mainly as tautomeric electron poor imines **D**[21], the use of a chiral primary amine catalyst potentially offered an efficient mechanism to preclude the back electron transfer (BET) by triggering a tautomeric equilibrium which converts **C** into **D**. Last, the oxidised centre (electron hole unit in Fig. 1d), arising from the intramolecular SET event, had to be stable enough to engage in subsequent redox processes with the photoredox catalysts (as detailed in Figure 2a), restoring the redox-active moiety while facilitating productive catalysis. Achieving a high level of stereocontrol further complicated matters.

To test the feasibility of this electron-relay strategy[22], we explored the reaction between the commercially available β-methyl cyclohexenone **1a** and benzodioxole **2a** (Table 1). We used the inorganic photocatalyst tetrabutylammonium decatungstate[23] (TBADT, 5 mol%) because, upon light excitation, it can easily photogenerate a nucleophilic carbon-centred radical by homolytically cleaving the inactive methylene C-H bond in **2a**[24] via a hydrogen transfer mechanism (*HAT*). The experiments were conducted at 35 °C in acetonitrile (CH_3CN) and under irradiation by a single black-light-emitting diode (black LED, λ_{max} = 365 nm).

Table 1 | Exploratory studies on the feasibility of the electron-relay strategy.



entry	catalyst	time	$E_{1/2}$ vs Ag/AgCl	**3a** yield (%)	ee (%)
1	none	48 h	-	traces	-
2†	**4a**	48 h	-	4	0
3	**4b**	48 h	+1.22 V	33	82
4†*	**4a**	48 h	-	5	0
5	**4c**	48 h	+1.22 V	35	84
6	**4d**	48 h	+1.22 V	xx	83
7	**4e**	48 h	+1.22 V	46	93
8	**4e**	84 h	+1.22 V	75	93

†Using 40 mol% of trifluoroacetic acid (TFA) instead of benzoic acid. *Using 20 mol % of exogenous *N*-cyclohexyl-3,6-di-*tert*-butyl-carbazole.

We observed a negligible racemic background process in the absence of any amine catalyst, which is a necessary condition for realising a stereoselective process (entry 1). We then focused on identifying a redox-active moiety that, when installed within the chiral primary amine catalyst, could provide for a fast intramolecular oxidation of the transient α-iminyl radical cation of type **B** and thus trigger the entire radical conjugate addition. We identified carbazole as a suitable scaffold because of *i*) its excellent electron-donating capabilities, which would provide the electron pool unit, and *ii*) the high stability of the long-lived carbazole radical cation[25], which makes it a possible electron hole moiety. These properties form the basis of the wide application of carbazole derivatives in hole-transport materials for light-emitting diodes[26] and photovoltaic cells[27]. Gratifyingly, the

chiral cyclohexylamine scaffold **4b** adorned with the carbazole moiety provided the desired product **3a** with good appreciable yield and stereoselectivity (33 yield, 82% ee, entry 3). In consonance with the proposed electron-relay mechanism, the reaction could not be catalysed by cyclohexylamine **4a**, which mimics the catalyst's **4b** scaffold while lacking the redox-active moiety (entry 2; for other primary amines which failed to promote the radical process, see Figure S1 in the Supplementary Information, SI). An equimolar combination of **4a** and exogenous *N*-cyclohexyl 3,6-di-*tert*-butyl-carbazole (20 mol%) also proved unsuitable for catalysis, suggesting the importance of a proximity-driven intramolecular SET process. We then modified the carbazole scaffold within the amine catalyst by introducing substituents at the 3- and 6-positions. It is known that this substitution pattern can further stabilise the carbazole radical cation[25]. Indeed, we could isolate and characterise a shelf-stable carbazoliumyl radical cation salt when treating *N*-cyclohexyl-3,6-di-*tert*-butyl-carbazole with $SbCl_5$, as detailed in Section F3 within the SI. Concurrently, the increased steric hindrance carried the additional benefit of inferring a higher stereocontrol. These considerations provide a rationale for the better yield and enantioselectivity achieved when using the chiral primary amine catalyst **4e** (entry 8, product **3a** formed in 75% yield and 93% ee). Notably, the presence of an electron-withdrawing group, which lowers the oxidising tendency of the carbazole unit, resulted in reduced reactivity (catalyst **4d**, entry 6). Finally, no product formation was detected in the absence of TBADT, organic catalyst **4e**, or light, demonstrating that all these components are needed for this catalytic protocol.

We then undertook studies to better investigate the role of the active intermediates in the electron-relay mechanism (Fig. 2a). We could synthesise stable tetraborofluorate salts of the chiral iminium ion **A-1**, generated upon condensation of catalyst **4c** and substrate **1a**, which were characterised by X-ray single-crystal analysis (Fig. 2b). Interestingly, the unusual stability of the secondary iminium ion **A-1** and the well-defined (*Z*)-configuration of the C=N double bond originate from a stabilising intramolecular charge transfer π-π interaction between the electron-rich carbazole nucleus and the electron-deficient iminium ion. As a result, the measured interatomic separation in the solid state between the carbazole nitrogen and the sp^2 α-carbon of the iminium ion (3.10 Å) is significantly less than the van der Waals distance.

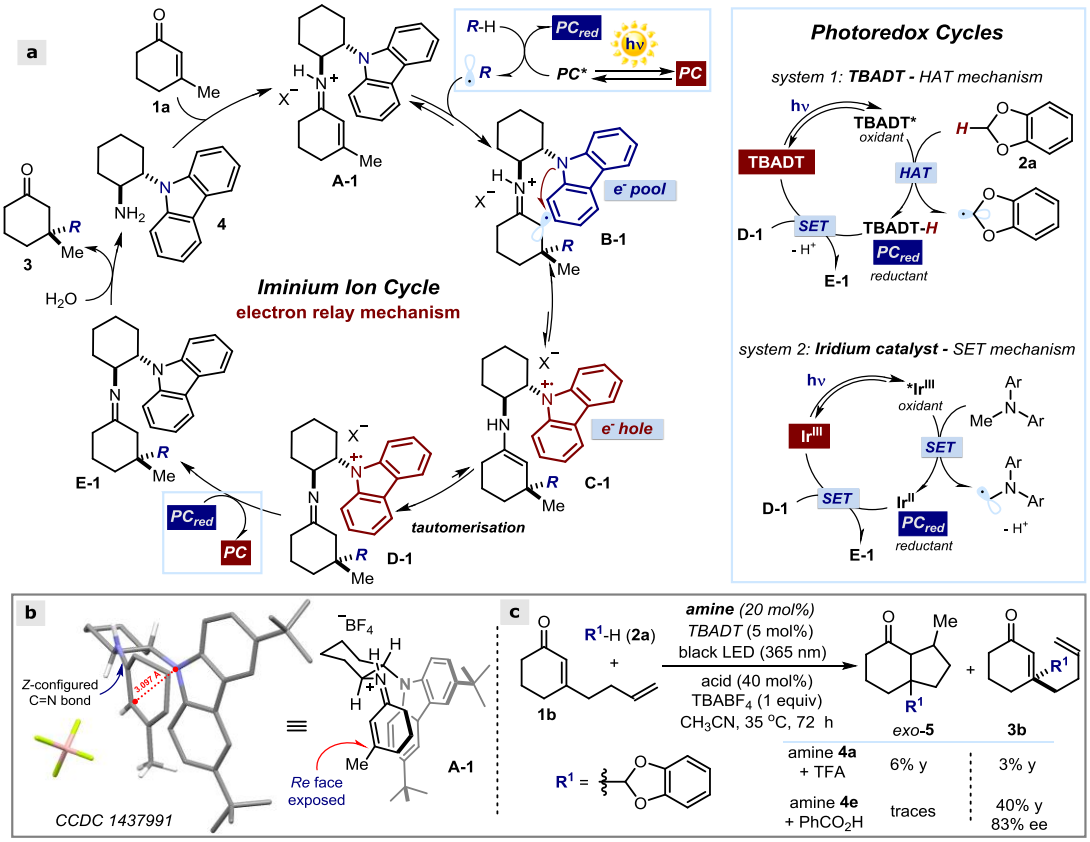


Figure 2 | Proposed mechanism and mechanistic investigations. **a,** Synergistic activities of the iminium ion and the photoredox catalytic cycles to realise the enantioselective radical conjugate addition to enone **1a**. Upon radical addition to the iminium ion **A-1**, the electron-relay mechanism bypasses the unstable radical cation **B-1** producing a carbazoliumyl radical cation **C-1**, which is prevented from undergoing back-electron transfer by tautomerisation of the secondary enamine to the corresponding imine **D-1**. Regeneration of the photocatalyst (***PC***) is achieved by reduction of the carbazoliumyl radical cation in **D-1**, while the aminocatalyst **4** is liberated upon hydrolysis of imine **E-1**. **b,** X-ray crystal structure of the carbazole-based iminium ion **A-1**: the distance between the carbazole nitrogen and the sp^2 α-carbon of the cyclohexene moiety is highlighted. **c,** Cyclisation experiments indicating that the α-iminyl radical intermediate **B-1** has been bypassed when using the carbazole-based catalyst **4e**.

This highly organised topology of the iminium ion **A-1**, which NMR spectroscopic analyses confirmed to be dominant in solution also, plays a critical dual role in the efficiency of the system. On the one hand, it governs the stereocontrol in the radical conjugate addition, since the bulky carbazole unit is positioned in such a way as to effectively

shield the *Si* face of the iminium ion, leaving the *Re* face exposed for enantioselective bond formation. Importantly, the sense of asymmetric induction observed in the model reaction is consistent with this stereochemical model (Fig. 2b). On the other hand, the three-dimensional assembly of **A-1** suggests that the α-iminyl radical cation **B-1**, arising from the iminium ion trap of the radical, is generated in close proximity to the electron-rich carbazole (electron pool), allowing for a fast, proximity-driven[20,28] intramolecular reduction[29]. Once the carbazoliumyl radical cation (electron hole) is generated, the fast tautomerisation of the secondary enamine **C-1** to afford the electron-poor imines **D-1** precludes the back electron transfer. At this point, the long-lived carbazoliumyl radical cation in **D-1** can be reduced by the photocatalyst (***PC***), closing the photoredox cycle (Fig. 2a, right panel). The iminium ion cycle terminates with the imine **E-1** hydrolysis to regenerate the organic catalyst **4** while liberating the quaternary ketone product **3** (Fig. 2a, left panel).

To gain further evidence supporting the proposed electron-relay mechanism, we used the enone **1b**, bearing a β-homoallyl substituent, to trap the radical photogenerated from benzodioxole **2a** (Fig. 2c). The reaction catalysed by cyclohexylamine **4a** provides preferentially the cyclised *exo*-adduct **5** (**5**:**3b** in a 2:1 ratio). This is because of the propensity of the electrophilic transient α-iminyl radicals, emerging from the radical addition, to undergo cyclisation with unactivated olefins. In sharp contrast, the process catalysed by the amine **4e** almost exclusively affords the conjugate addition product **3b** (40% yield, 83% ee, **3b**:**5** in a >10:1 ratio). This result is consonant with a fast redox process, governed by the carbazole-based catalyst, which bypasses the α-iminyl radical **B-1** intermediate preventing cyclisation.

With a clearer mechanistic picture in mind and adopting the optimised conditions described in Table 1, entry 8, we demonstrated the generality of the radical conjugate addition by evaluating a variety of cyclic enones **1** and benzodioxoles **2** (Figure 3). The presence of a methyl substituent at the methylene position of the radical precursor **2** provides the corresponding product **3c**, bearing two adjacent tetrasubstituted carbons, with nearly perfect enantioselectivity. This experiment further illustrates the propensity of radical reactivity for connecting structurally congested carbons. Experiments to probe the scope of the cyclic enone component revealed that a wide range of carbocycles and β-olefin substituents are well tolerated. For example, high levels of stereocontrol are achieved with ring systems that incorporate different β-alkyl groups (products **3d**,**f**), while the radical conjugate addition performs well for a diverse range of ring sizes, including cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl architecture (adducts **3a**, **3f**-**h**). One limitation of the system is that the presence of an aromatic β-substituent completely inhibits the reaction. As for the benzodioxole substrates **2**, different substituents can be installed at the aromatic ring without compromising the efficiency of the reaction (adducts **3i**-**k**). Crystals from compound **3i** were suitable for X-ray analysis, which secured the absolute configuration of the products.

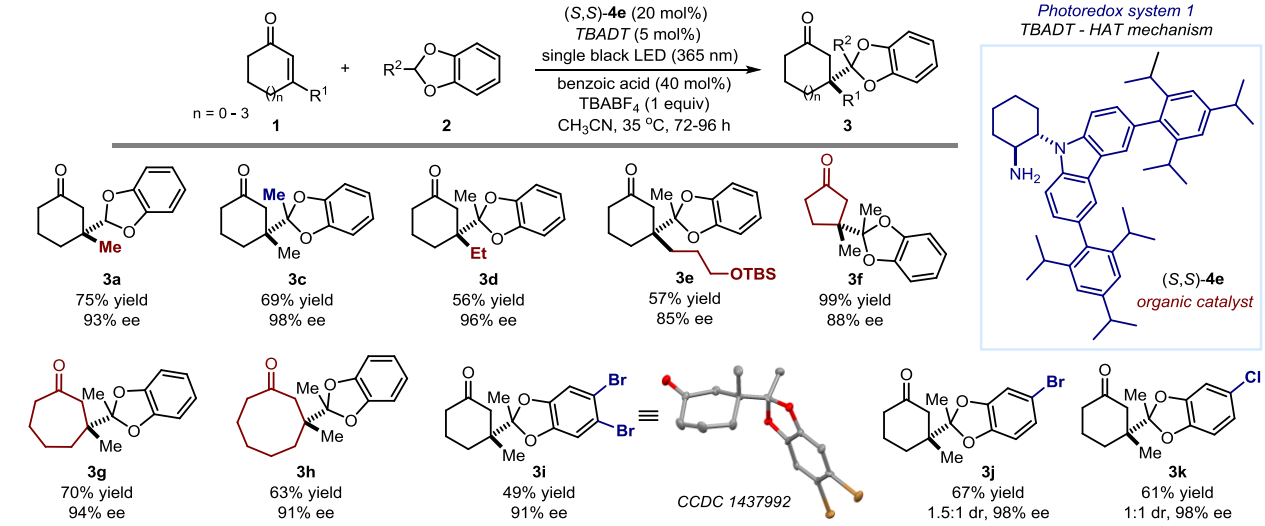


Figure 3 | Substrate scope for the enantioselective trap of benzodioxole-derived radicals via the dual photoredox organocatalytic strategy. Survey of the cyclic enones **1** and substituted benzodioxoles **2** that can participate in the organocatalytic asymmetric radical conjugate addition to forge quaternary stereocentres. Reactions performed on a 0.2 mmol scale; yields and enantiomeric excesses of the isolated products are indicated below each entry. Details of the TBADT-mediated photoredox cycle to produce carbon-centred radicals from **2** via a HAT mechanism are reported in Figure 2a. TBS: *tert*-butyldimethylsilyl; $TBABF_4$: tetraethylammonium tetrafluoroborate.

The general applicability of a chemical strategy is crucial for evaluating its usefulness. We wondered if the synthetic utility of the chiral amine carbazole catalyst **4e** could be expanded to successfully trap other carbon-centred radicals, formed through an unrelated light-triggered mechanism, while forging quaternary stereocentres. Specifically, we used the commercially available photocatalyst $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (**8**) which, upon absorption of visible light, can generate α-amino radicals directly from simple tertiary amines **6** via single electron oxidation[17] (SET mechanism). Gratifyingly, the conjugate addition adducts **7** were provided with high stereoselectivity by using the combination of catalysts (*R*,*R*)-**4e** and **8** while conducting the reactions with enones **1** at 15 °C in toluene and under irradiation by a white LED (λ_{emiss} > 400 nm) (Fig. 4a). We next sought to explore the scope of both substrates in this dual

photoredox organocatalytic strategy. As highlighted in Fig. 4b, cyclic enones of different ring sizes (**7c**-**e**) and bearing alkyl β-substituents (products **7a**,**b**) are suitable substrates. We found that both mixed *N*-alkyl-*N*-aryl (adducts **7a**, **7f**-**g**) and *N*,*N*-diaryl tertiary amines (**7h**-**j**) efficiently participated in the radical conjugate addition, while aliphatic amines remained completely unreacted. Substituents of different electronic nature were easily accommodated at the aryl *para* (**7f**-**g**, **i**) or *ortho* position (**7j**), without affecting the efficiency of the process, while the use of a cyclic amine afforded compound **7k**, bearing two vicinal stereogenic centres, with high enantiomeric purity, albeit with a 2:1 diastereomeric ratio. For this enantioselective trap of α-amino radicals, we have determined a quantum yield (Φ) of 0.4 (λ = 400 nm), while Stern–Volmer fluorescence quenching experiments have demonstrated that the excited state of the iridium photocatalyst **8** is quenched by the amine **6**. Both experiments are consistent with the electron-relay mechanism depicted in Fig. 2a. Notably, the radical conjugate addition can be performed without any metal when replacing the photocatalyst **8** with the benzophenone derivative **9**, which can generate the radical acting as an organic photosensitiser (Fig. 4c).

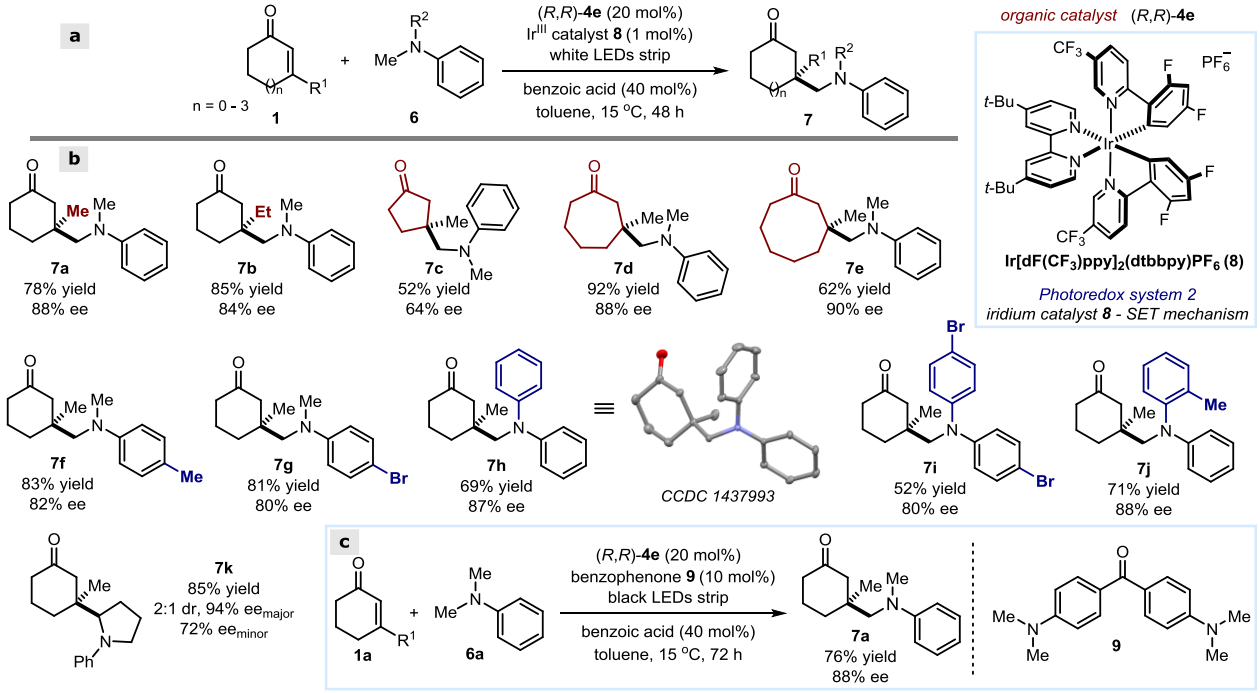


Figure 4 | Substrate scope for the enantioselective trap of α-amino radicals via the dual photoredox organocatalytic strategy. a, The photochemical organocatalytic radical conjugate addition developed to forge quaternary stereocentres. **b,** Survey of the cyclic enones **1** and tertiary amines **6** that can participate in the reaction. Reactions performed on a 0.2 mmol scale; yields and enantiomeric excesses of the isolated products are indicated below each entry. Details of the iridium-mediated photoredox cycle to produce carbon-centred radicals via a SET mechanism are reported in Figure 2a. **c,** Fully organocatalytic enantioselective radical conjugate addition using the benzophenone photocatalyst **9**.

In summary and to the best of our knowledge, we have developed the first catalytic strategy that allows quaternary carbon stereocentres to be set with high fidelity using an enantioselective radical conjugate addition manifold. The approach, which relies on the mechanistic merger of photoredox and organic catalysis, requires mild conditions and readily available unfunctionalised substrates. This effectively complements established polar conjugate addition technologies based on preformed organometallic reagents. Our studies also established the possibility of expanding the versatility of iminium ion activation, a powerful catalytic strategy for enantioselective polar chemistry, within the realm of radical reactivity.

Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

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Author contributions J.J.M., D.B., and S.P. performed the experiments and analysed the data. J.J.M., D.B., S.P., M.F., and P.M. designed the experiments. M.F. and P.M. conceived the project. P.M directed the project and wrote the manuscript with contributions from all the authors.

Author information Crystallographic data for the iminium ion **A-1** and for compounds **3i** and **7h** have been deposited with the Cambridge Crystallographic Data Centre, accession numbers CCDC 1437991, 1437992, and 1437993, respectively. Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Correspondence and requests for materials should be addressed to P.M. (pmelchiorre@iciq.es).

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29. By using cyclic voltammetry, we found that the carbazole within the catalyst **4e** undergoes a fully reversible oxidation at $E_{1/2}$ +1.12 V (vs. Ag/AgCl) in acetonitrile to produce the carbazoliumyl radical cation. However, we could not measure the redox potential of the secondary enamines generated upon catalyst condensation with cyclohexanone, because of the unfavourable imine/enamine tautomeric equilibrium. Given that tertiary enamines have ionization potentials in the range of 0.7-0.8 V (see Ref. 30), a slightly endergonic intramolecular redox process, facilitated by the close proximity of the redox centres in **B-1**, is likely taking place during the electron-relay mechanism.
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