Catalytic asymmetric C–C cross-couplings enabled by photoexcitation

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Enantioselective catalytic processes are promoted by chiral catalysts that can execute a specific mode of catalytic reactivity, channeling the chemical reaction through a certain mechanistic pathway. Here, we show how by simply using visible light we can divert the established ionic reactivity of a chiral allyl-iridium(III) complex to switch on completely new catalytic functions, enabling mechanistically unrelated radical-based enantioselective pathways. Photoexcitation provides the chiral organometallic intermediate with the ability to activate substrates via an electron transfer manifold. This redox event unlocks an otherwise inaccessible cross-coupling mechanism, since the resulting iridium(II) center can intercept the generated radicals and undergo a reductive elimination to forge a stereogenic center with high fidelity. This photochemical strategy enables difficult-to-realize enantioselective alkyl-alkyl cross-coupling reactions between allylic alcohols and readily available radical precursors, which are not achievable under thermal activation.

Asymmetric catalysis is widely used to prepare single enantiomer chiral compounds in academia[1] and industry[2]. Over the last 60 years, major advances have been spurred by the identification of a few generic catalytic modes of substrate activation and stereochemical induction, exerted by a variety of chiral catalysts[3]. The power of a mode of catalytic reactivity[4] is that the intermediate formed upon activation of the substrate by the chiral catalyst can participate in many reaction types with consistently high stereoselectivity. An intrinsic limit of this approach is that it allows the design of new but mechanistically related enantioselective processes (Fig. 1a, left panel).

Recent studies have demonstrated that photoexcitation can expand the potential of generic modes of catalytic activation beyond their established ground-state reactivity, providing a new force for innovation in asymmetric catalysis (Fig. 1a, right panel). For example, we recently found that excitation of chiral organocatalytic intermediates with visible light can turn on novel catalytic functions that are unavailable to conventional ground-state organocatalysis[5-7]. Specifically, on excitation, these intermediates can activate substrates via single-electron transfer (SET) mechanisms and initiate stereocontrolled radical reactions. This photochemical strategy was also successfully applied in enantioselective biocatalysis, since Hyster demonstrated that photoexcitation of common biological cofactors allows enzymes to catalyze completely different processes than those for which they evolved[8,9]. Moreover, chiral Lewis acids have been successfully used to trigger photochemical asymmetric radical processes upon formation of photoactive intermediates by coordination of carbonyl substrates[10-13]. In contrast, the possibility of using light to draw out new reactivity modes from chiral organometallic catalytic complexes, which diverge from their established ground-state chemistry, has been far less investigated. Recently, there have been a few reports on the excitation of achiral organometallic intermediates for promoting non-asymmetric processes[14-17]. The sole stereocontrolled method using this concept has been developed by Peters and Fu[18], who recently designed a copper-based catalytic system that, on excitation, could drive enantioselective radical-based C-N cross-couplings unachievable under thermal conditions. This method required the identification of a specific chiral phosphine-based copper(I)-amido complex to ensure reactivity and stereocontrol, which had no previous application in polar enantioselective catalysis.

Herein, we demonstrate that visible light excitation can upgrade the well-established ground-state reactivity of a chiral organometallic complex to switch on completely new catalytic functions, enabling mechanistically unrelated radical-based enantioselective pathways (Fig. 1b). This photochemical strategy enabled the development of enantioselective alkyl-alkyl cross-coupling reactions, which are highly valuable but difficult-to-realize processes for making chiral molecules[19]. Specifically, we found that the chiral (η^3-allyl)iridium(III) complex (**Ir-1**), which has a well-established electrophilic character in the ground state[20], acquires on excitation the ability to trigger SET pathways and empower cross-coupling mechanisms. Complex **Ir-1**, generated upon coordination of the iridium(I)-precatalyst $[Ir(cod)Cl]_2$ with the chiral phosphoramidite-olefin ligand (*S*)-**L** followed by acid-assisted oxidative addition into allylic alcohols **1**[21], has been originally reported by Carreira[22]. **Ir-1** is widely recognized as a privileged organometallic

intermediate to promote enantioselective catalytic allylic substitution reactions[20], which are fundamental and venerable transformations in asymmetric catalysis[23,24]. Complex **Ir-1** promotes the addition of a large variety of nucleophiles to easily accessible racemic branched allylic alcohols **1** with consistently high stereocontrol and regioselectivity in favour of the branched products. We found that this established reactivity can be diverted by simply using weak blue light (460 nm), since excitation provides **Ir-1** with the ability to activate non-nucleophilic substrates **2**, adorned with suitable redox-active moieties, via an SET oxidation pathway. The photo-induced SET unlocks an otherwise inaccessible cross-coupling mechanism, since the resulting iridium(II) center can intercept the generated radicals to afford an iridium(III) complex. The latter intermediate (not shown in Fig. 1b) finally promotes a reductive elimination to forge a stereogenic center within the final branched product **3**. This photochemical strategy enables the enantioselective C(sp^3)-C(sp^3) cross-coupling of racemic allylic alcohols with stable radical precursors, which is not achievable under thermal activation. Sparse examples of enantioselective transition-metal-catalyzed cross-coupling methods that proceed via interception of photochemically generated radicals have been reported, but they all required the use of external photoredox catalysts to generate the open-shell species[25-27].

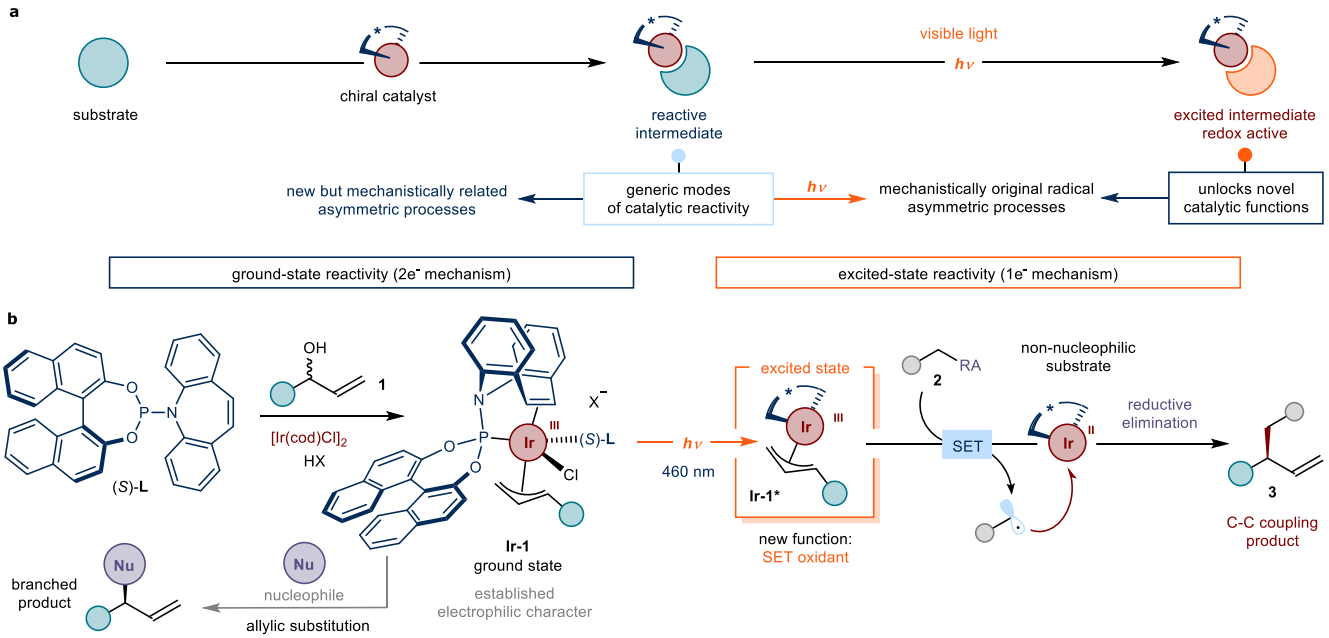


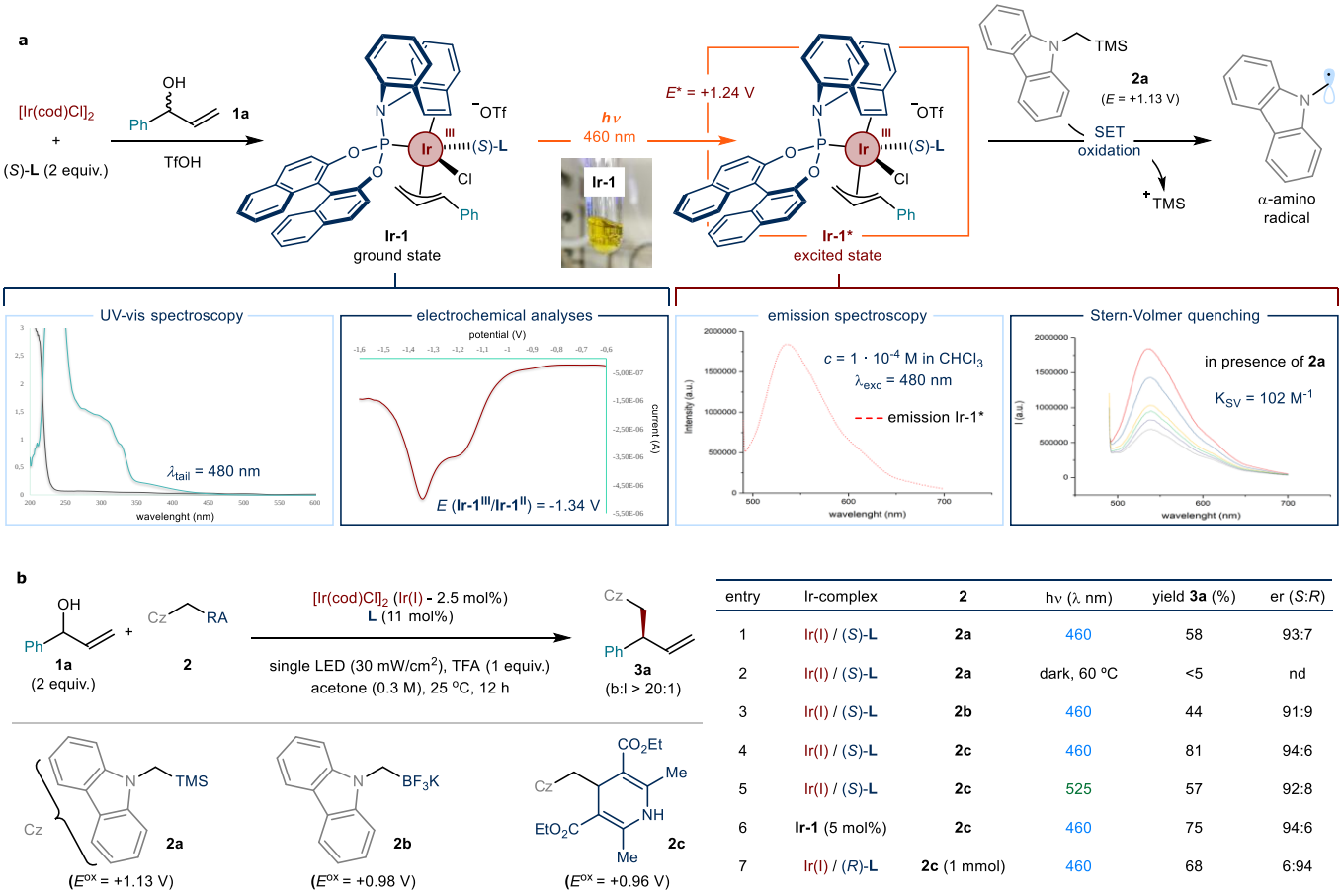
Figure 1 | Enhancing the potential of generic modes of catalytic reactivity with light. **a,** Asymmetric catalysis generally relies on a few established catalytic modes of substrate activation (left panel) to promote enantioselective processes via ground-state two-electron reactivity. Photoexcitation (right panel) offers a new force of innovation[5-13] by providing chiral catalytic intermediates with the ability to activate substrates via electron transfer and trigger stereocontrolled radical pathways that diverge from the innate ground-state reactivity. **b,** Visible light excitation of the chiral (η^3-allyl)iridium(III) complex **Ir-1** diverts its established catalytic reactivity for allylic substitution reactions turning an electrophilic intermediate into an oxidant. This strategy enables otherwise inaccessible stereocontrolled alkyl-alkyl cross-couplings between allylic alcohols **1** and non-nucleophilic substrates **2**. SET, single-electron transfer; RA, redox auxiliary.

Results and discussion

Design Plan. We started our studies by characterizing the photophysical and electrochemical properties of the chiral (η^3-allyl)iridium(III) complex (**Ir-1**, Fig. 2a). The complex was prepared by mixing $[Ir(cod)Cl]_2$ with two equivalents of phosphoramidite-olefin (*S*)-**L** in the presence of racemic 1-phenylprop-2-en-1-ol **1a** and trifluoromethanesulfonic acid[21]. The isolated **Ir-1** showed an intense orange coloration, which indicated its ability to absorb light in the visible region. This observation prompted us to explore if photoexcitation could divert the innate propensity of **Ir-1** to act as an electrophile in polar pathways towards mechanistically divergent radical-based reaction patterns. Ultraviolet-visible (UV-vis) spectroscopic analysis established that **Ir-1** could absorb until 480 nm (ε = 930 $M^{-1}\cdot cm^{-1}$ at 460 nm). Using differential pulse voltammetry, we determined the redox properties of the complex in the ground state (E (**Ir-1**(III)/**Ir-1**(II)) = -1.34 V vs Ag/Ag^+ in CH_2Cl_2). On the basis of these electrochemical and spectroscopic measurements, we applied the Rehm-Weller formalism[28,29] to estimate the redox potential of the allyl-iridium complex in the excited state (E^* (**Ir-1**(III)*/**Ir-1**(II)) = +1.24 V). This redox value implies that photoexcitation turns the electrophilic ground-state complex **Ir-1** into a good SET oxidant.

We then wondered if the new catalytic function acquired by **Ir-1*** upon excitation could be useful to activate, by means of electron transfer mechanisms, non-nucleophilic substrates that would not react under thermal conditions. Trimethylsilyl carbazole **2a** was selected as the model substrate. This choice was informed by the redox potential of **2a** (E (**2a**$^{\bullet+}$/**2a**) = +1.13 V vs Ag/Ag$^+$ in CH_3CN), which implies an exergonic SET oxidation from the excited **Ir-1***, and the presence of a trimethylsilyl (TMS) electro-auxiliary group[30], which should facilitate radical formation upon electron transfer. In addition, asymmetric processes that install the carbazole moiety within the chiral products are valuable because this structural motif is widespread in materials[31] and biorelevant molecules[32]. We used luminescence quenching analysis to evaluate the feasibility of the excited allyl-iridium complex **Ir-1*** to interact with **2a**. We recorded the emission spectrum of **Ir-1*** upon excitation at 480 nm (emission centered at 535 nm, red dotted line in Fig. 2a). A series of Stern-Volmer quenching experiments revealed that silane **2a** effectively quenched the excited state of **Ir-1***, confirming **2a** as a potential substrate.

Method optimization. After proving the ability of the Ir(III)-π-allylic system to absorb visible light, reach an excited state, and interact with **2a**, we aimed to translate these findings into the implementation of a catalytic asymmetric C(sp^3)-C(sp^3) cross-coupling (Fig. 2b). We found that irradiation of allylic alcohol **1a** and silane **2a** in acetone for 12 hours in the presence of trifluoroacetic acid and catalytic amounts of $[Ir(cod)Cl]_2$ and (*S*)-**L** provided the cross-coupling product **3a** in 58% yield, 93:7 enantiomeric ratio (er), and with complete regioselectivity for the branched adduct (entry 1). The process was performed at ambient temperature and under illumination by a blue-light-emitting diode (LED, λ_{max} = 460 nm). Control experiments revealed that the reactivity is completely inhibited in the dark, even when heating the mixture at 60 °C for 12 hours (entry 2), or in the presence of a radical scavenger (TEMPO; interception of the α-amino radical was observed, results detailed in section F2 of the Supplementary Information). Swapping the redox auxiliary group of the radical precursor from TMS to the easier-to-oxidize potassium trifluoroborate (**2b**, E (**2b**$^{\bullet+}$/**2b**) = +0.98 V vs Ag/Ag$^+$ in CH_3CN) slightly affected the efficiency of the process (entry 3), while the use of 1,4-dihydropyridine **2c** (E (**2c**$^{\bullet+}$/**2c**) = +0.96 V vs Ag/Ag$^+$ in CH_3CN) secured a better chemical yield and a similar stereocontrol (entry 4). The reaction was also promoted by green light (λ_{max} = 525 nm, entry 5), although with somehow reduced efficiency. This result is mechanistically relevant since the only intermediate capable of absorbing green light is the Ir(III)-π-allylic complex **Ir-1**, thus excluding any photoactivity of substrate **2c** (see section F2 in the Supplementary Information for further details). The preformed complex **Ir-1** (5 mol%, entry 6) provided similar catalytic activity and stereocontrol, which confirmed its catalytic competence. The use of (*R*)-**L** ligand secured access to the opposite enantiomer of the cross-coupling product *ent*-**3a**. This reaction was conducted on a 1 mmol scale and smoothly delivered the product (0.2 g, entry 7).



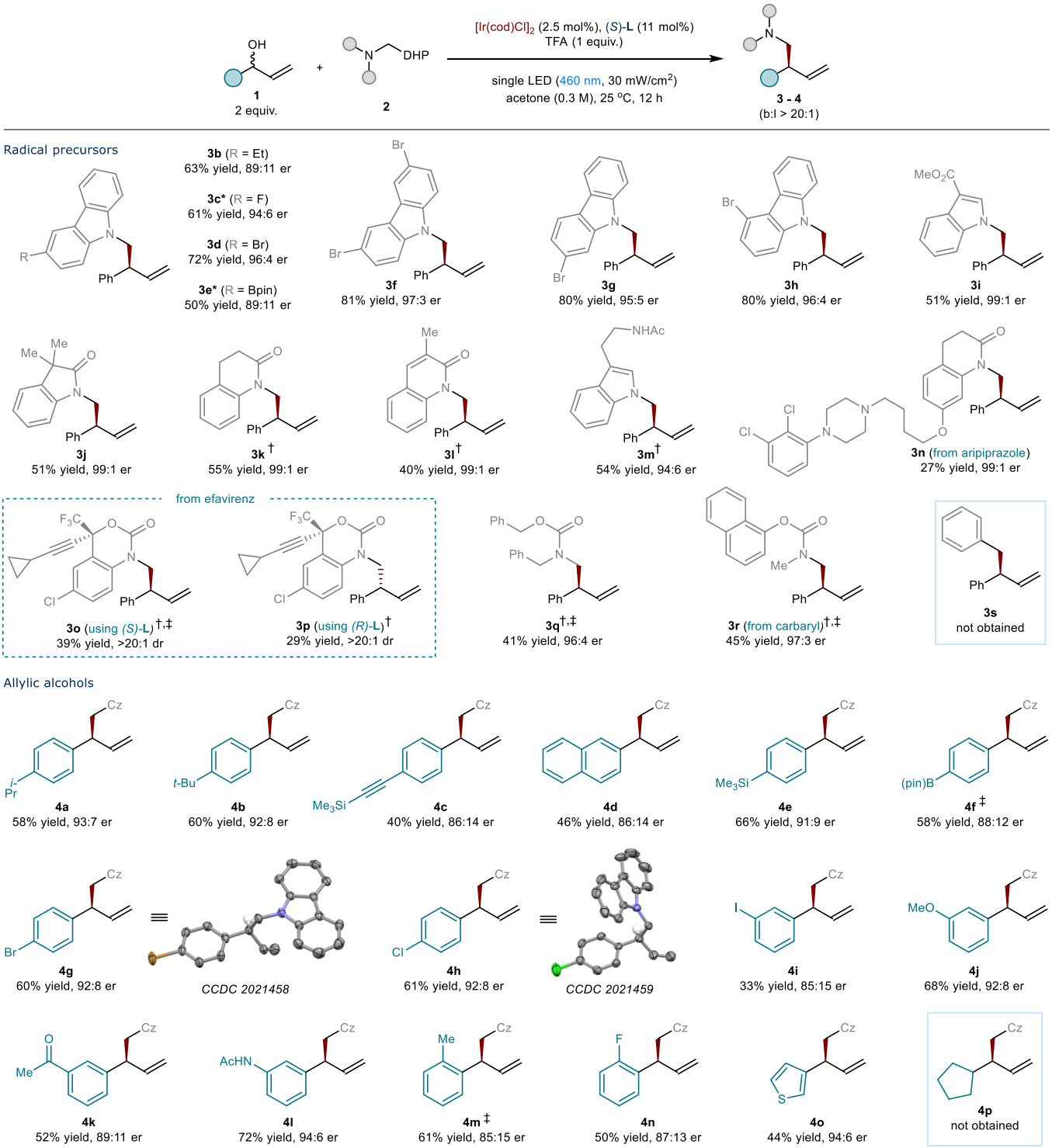
b

entry	Ir-complex	2	hν (λ nm)	yield **3a** (%)	er (*S*:*R*)
1	Ir(I) / (*S*)-**L**	**2a**	460	58	93:7
2	Ir(I) / (*S*)-**L**	**2a**	dark, 60 °C	<5	nd
3	Ir(I) / (*S*)-**L**	**2b**	460	44	91:9
4	Ir(I) / (*S*)-**L**	**2c**	460	81	94:6
5	Ir(I) / (*S*)-**L**	**2c**	525	57	92:8
6	**Ir-1** (5 mol%)	**2c**	460	75	94:6
7	Ir(I) / (*R*)-**L**	**2c** (1 mmol)	460	68	6:94

Figure 2 | Characterization and light-induced catalytic activity of the (η³-allyl)iridium(III) complex Ir-1. a, Photophysical and electrochemical studies to define the ground-state and excited-state properties of **Ir-1**. UV-vis spectroscopy and electrochemical analysis indicated that **Ir-1** in the excited state can act as a good SET oxidant, while the Stern-Volmer quenching experiments established its ability to interact with **2a**. **b,** Optimization of the catalytic asymmetric C-C cross-coupling enabled by the visible light excitation of **Ir-1**; reactions performed on a 0.1 mmol scale. Cz, carbazolyl; TMS, trimethylsilyl; RA, redox auxiliary.

Scope of the method. Adopting the conditions described in Fig. 2b, entry 4, we then evaluated the generality of the photochemical asymmetric cross-coupling. First, we examined the ability of the Ir(III)-π-allylic complex **Ir-1**, derived from alcohol **1a**, to drive the coupling reaction of different radical precursors **2** (Table 1, upper part). 1,4-Dihydropyridines bearing a wide range of substituents at the carbazole core, including alkyl, halogen and boron functionalities, were competent substrates, delivering the corresponding products **3b-h** in high yield and enantioselectivity. The use of α-amino radical precursors enabled the stereoselective installation of *N*-heterocyclic fragments of pharmaceutical interest within products **3**, such as an indole, an oxindole, a 3,4-dihydroquinolone, and a quinolone moiety (adducts **3i-l**). In addition, a tryptamine unit and the antipsychotic *aripiprazole* scaffold could be installed in products **3m** and **3n**, respectively. The use of a chiral substrate adorned with the *efavirenz* core (HIV/AIDS treatment) provided access to derivative **3o** as a single diastereoisomer. Performing the reaction with ligand (*R*)-**L** afforded the opposite diastereomer **3p**, indicating that the chiral catalyst fully governs the stereoselectivity of the process. Acyclic carbamates, including a derivative of the insecticide *carbaryl*, also participated in the coupling process, leading to products **3q** and **3r**. One limitation of the system is that a 4-benzyl-1,4-dihydropyridine derivative did not offer the desired cross-coupling product **3s** (see Figure S1 in the Supporting Information, which includes a list of moderately successful and unsuccessful substrates).

Table 1 | Substrate scope for the asymmetric photochemical C-C cross-coupling.



Survey of the radical precursors (products **3**) and the allylic alcohols (products **4**) that can participate in the reaction. Reactions performed on a 0.1 mmol scale; yields and enantiomeric ratios (er) of the isolated products are indicated below each entry (average of two runs per substrate). *Using the trimethylsilane radical precursor **2**. †Performed in $CHCl_3$. ‡Using the pre-formed complex **Ir-1** as the catalyst (5 mol%). DHP, 1,4-dihydropyridine; b:l, branched:linear ratio; Cz, carbazolyl moiety.

We then evaluated the allylic alcohols **1** suitable for the photochemical cross-coupling with 1,4-dihydropyridine **2c** (Table 1, lower part). Aromatic substrates adorned with a broad range of functional groups at their phenyl ring successfully participated to the stereocontrolled process. In addition to alkyl moieties (**4a-b**), the protocol tolerates functionalities at the *para*-position suitable for further derivatization, including alkynyl- (**4c**), silyl- (**4e**), boron- (**4f**), and halogenated (**4g-h**) groups. Crystals from adducts **4g** and **4h** were suitable for X-ray crystallographic analysis, which established their absolute configuration. Halogen-, alkoxy-, keto-, and amino-substituents could also be included at

the *meta*-position of the arene ring (compounds **4i-l**), while an *ortho*-substitution pattern delivered products **4m** and **4n** with a slightly reduced enantioselectivity. Finally, we established the possibility of using a thienyl-containing allylic alcohol to generate a photoactive (η^3-allyl)iridium(III) complex, leading to product **4o**. In contrast, the presence of an alkyl fragment within the alcohol **1** completely inhibited the reaction (adduct **4p**). Interestingly, for some of the products (**3o, 3q-r**, **4f**, and **4m**), slightly improved results were obtained using the preformed complex **Ir-1** as the catalytic entity.

Mechanistic investigations. To glean insights into the overall mechanism, we examined the key steps of the photochemical cross-coupling process. First, we performed two reactions using the enantiopure allylic alcohol (*S*)-**1a** and the antipodes of the phosphoramidite-olefin ligand **L**, which afforded the cross-coupling product **3a** with similar reactivity and enantioselectivity but opposite absolute configuration (Fig. 3a). These experiments indicate that any three-dimensional information translated from substrate (*S*)-**1a** into the ground-state allyl-iridium(III) **Ir-1** via oxidative addition is inconsequential and eventually overwritten during the reaction. Overall, the chiral ligand **L** is the sole responsible to dictate the stereochemical outcome.

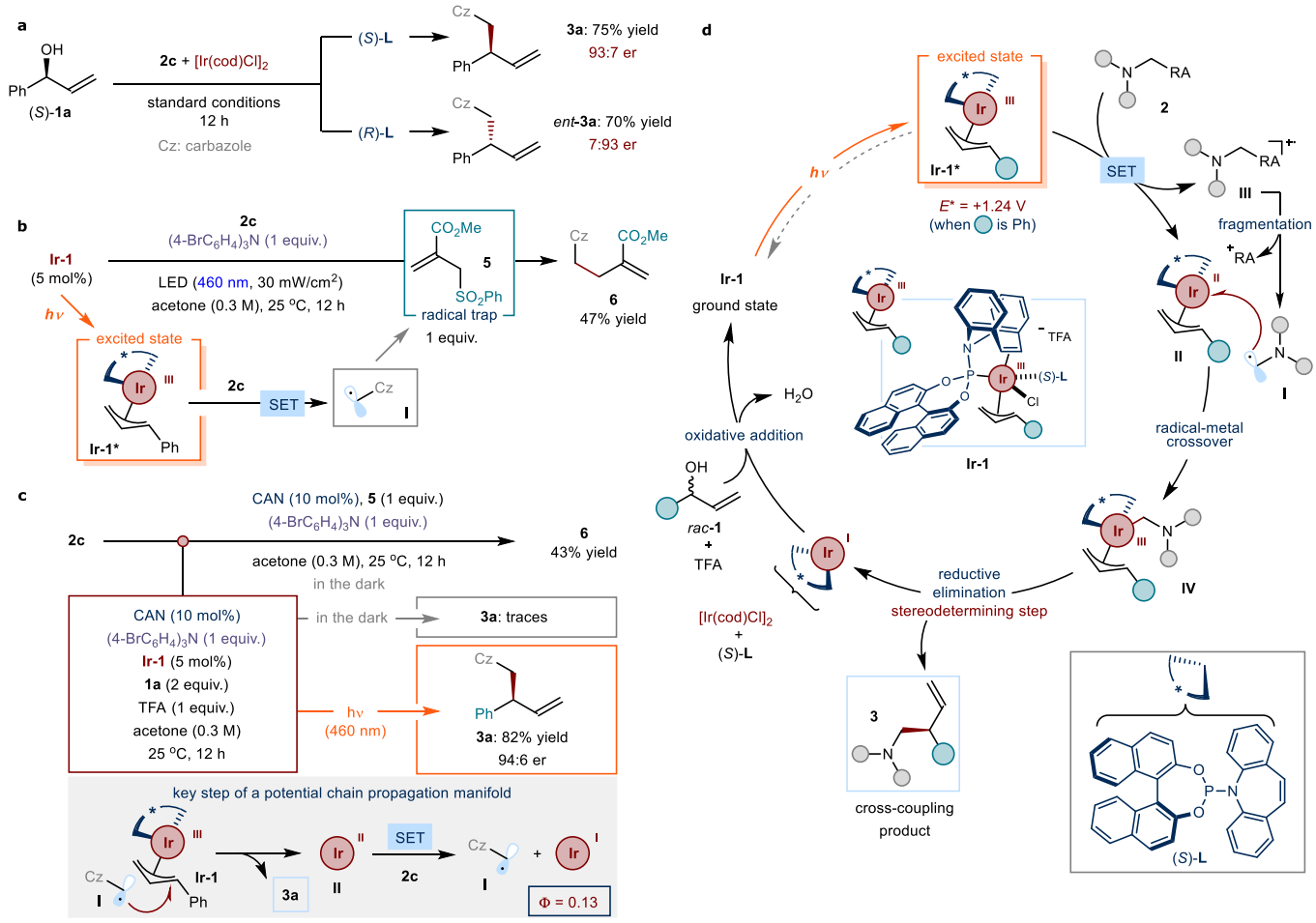


Figure 3 | Mechanistic considerations. **a,** Investigating the origin of stereoselectivity: the experiment establishes that the chiral ligand **L** governs the stereoselectivity of the process. **b,** Ability of preformed **Ir-1** to generate radicals from **2c** upon photoexcitation and trigger an allylation process of **5** leading to product **6** via a radical addition-desulfonylation sequence. **c,** Evaluating a possible radical chain propagation mechanism: the absence of reactivity when using a thermal system (CAN as the oxidant in the dark) to generate radicals from **2c** along with the low measured quantum yield indicate that a radical-chain process triggered by the radical addition to the ground-state **Ir-1** is unlikely. **d,** Proposed mechanism for the enantioselective photochemical C(sp^3)-C(sp^3) cross-coupling. CAN, cerium ammonium nitrate; RA, redox auxiliary; TFA, trifluoroacetic acid.

One crucial aspect of our proposed mechanism is the ability of complex **Ir-1** to generate, upon photoexcitation, radicals via SET oxidation of substrates **2**. To unambiguously prove this pathway, we used 5 mol% of the preformed **Ir-1** to promote the addition of radical **I**, generated from dihydropyridine **2c**, to allyl sulfone **5**, which served as a radical trap (Fig. 3b). This radical addition-desulfonylation process[33] was performed in the presence of tris(4-bromophenyl)amine (TBPA) as a redox mediator[34] and required visible light in order to afford product **6**. We also found

that the same reactivity could be obtained in the dark when using cerium ammonium nitrate (CAN) as the oxidant instead of **Ir-1** (Fig. 3c). These thermal conditions provided a way to generate radicals from **2c** (a competent substrate in our cross-coupling protocol) in the absence of light. We therefore could evaluate if a radical addition to the ground-state electrophilic Ir(III)-π-allyl complex **Ir-1** could be the key C-C bond forming step of the model reaction. In order for this step to be operative in our photochemical system, the ensuing Ir(II)-species **II**, generated together with product **3a**, should be capable of oxidizing substrate **2c**. This SET event would be needed to regenerate the active Ir(I) precatalyst and radical **I** (inset in Fig. 3c), thus feeding a self-propagation radical process where the photoactivity of complex **Ir-1** would solely serve as an initiation. We used the CAN/TBPA system to mimic the radical initiation step in the absence of light. However, as depicted in Fig. 3c, the model reaction between **1a** and **2c** conducted in the dark provided only traces of product **3a**. This result indicates that, even if radical **I** might add to the ground-state Ir(III)-intermediate **Ir-1**, this event does not generate an organometallic species suitable for sustaining a radical chain propagation. We also confirmed that the CAN/TBPA system is compatible with complex **Ir-1**, since the same experiment conducted under blue light irradiation performed normally (**3a** obtained in 82% yield and 94:6 er). Finally, we measured the quantum yield of the Ir-catalyzed photochemical coupling reaction between **1a** and silane **2a**, which was found to be 0.13[29]. Collectively, these results indicate that a radical-chain process triggered by the radical addition to the ground-state complex **Ir-1** is highly unlikely.

Overall, our mechanistic investigations support the catalytic cycle depicted in Fig. 3d. Acid-promoted oxidative addition of the chiral Ir(I) precatalyst, generated from $[Ir(cod)Cl]_2$ and two equivalents of ligand **L**, to allylic alcohol **1** delivers the (η^3-allyl)iridium(III) complex **Ir-1**. Upon visible light absorption, the excited **Ir-1*** activates the radical precursors **2** via SET oxidation. This redox step switches on a unique reaction pattern, since it triggers the simultaneous formation of radical **I**, upon fragmentation of the radical cation **III**, and of the iridium(II) center **II**. The latter fleeting intermediate then intercepts **I** via radical-metal crossover[35] to afford a more stable iridium(III) complex **IV**. A regio- and stereo-determining reductive elimination eventually forges the C(sp^3)-C(sp^3) bond within product **3** while restoring the active Ir(I)-catalyst.

Conclusion

The results presented here demonstrate that chiral organometallic intermediates with an established thermal reactivity can be repurposed to mediate mechanistically different enantioselective processes using simple light excitation. Specifically, we used the photoexcitation of a stereodefined allyl-iridium complex to generate radicals and an elusive transition metal species (intermediate **II**), whose reactivity triggers a difficult-to-realize enantioselective alkyl-alkyl cross coupling process. These findings may serve as a blueprint to further expand the established potential of asymmetric transition-metal catalysis using photoexcitation.

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

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Author contributions G.E.M.C. and P.M. conceived and supervised the project. All authors contributed to the experimental design and the interpretation of data. G.E.M.C. and P.M. directed the research and wrote the manuscript with input from all authors.

Author information Crystallographic data for compounds **4g** and **4h** have been deposited with the Cambridge Crystallographic Data Centre, accession numbers CCDC 2021458 and 2021458, 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).

Data availability Materials and methods, experimental procedures, useful information, mechanistic studies, ^{1}H NMR spectra, ^{13}C NMR spectra and mass spectrometry data are available in the Supplementary Information. Raw data are available from the corresponding author on reasonable request.

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