Enantioselective diversification of alkene radical anions

Bin Zhang[1], Min Jiang[2], Zhi-Han Zhang[1], Ke Zhao[1], Wen-Yuan Qu[1], Wen-Jing Xiao[1,*], Jia-Rong Chen[1,*]

[1]CCNU-uOttawa Joint Research Centre, Key Laboratory of Pesticides & Chemical Biology Ministry of Education, College of Chemistry, Central China Normal University, 152 Luoyu Road, Wuhan, Hubei 430079, P. R. China

[2]College of Materials, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 310036, P. R. China

*wxiao@mail.ccnu.edu.cn; chenjiarong@mail.ccnu.edu.cn

Alkene radical ions constitute an integral and unique class of reactive intermediates for the synthesis of valuable compounds, because they have both unpaired spins and charge. However, relatively few synthetic applications of alkene radical anions have emerged, due to a dearth of generally applicable and mild radical anion generation approaches. Precise control over the chemo- and stereoselectivity in alkene radical anion-mediated processes represents another long-standing challenge due their high reactivity. To overcome these issues, here, we develop a new redox-neutral strategy that seamlessly merges photoredox and copper catalysis to enable the controlled generation of alkene radical anions and their orthogonal enantioselective diversification via distonic-like species. This new strategy enables highly regio-, chemo- and enantioselective hydrocyanation, deuterocyanation, and cyanocarboxylation of alkenes without stoichiometric reductants or oxidants under visible light irradiation. This work demonstrates the power of photochemistry in expanding new chemical space and overcoming persistent challenges in radical anion chemistry.

Introduction

Organic radical cations and anions, generated from neutral parent molecules by a chemical, electrolytic, or photolytic single electron transfer (SET) event, are currently recognized as members of an integral class of reactive intermediates in many areas (*1-3*). Such radical ions possess both unpaired spins and charge, and they often exhibit unique chemical reactivities and facilitate distinctive types of bond construction that are difficult to achieve with other more conventional types of reactive intermediates (*4,5*). In particular, the use of alkene radical ions represents a powerful and attractive approach for synthesizing valuable organic compounds from alkene feedstocks. Extensive research on the synthetic chemistry of alkene radical cations has been reported in the last few decades (*6-9*); however, relatively few synthetic applications of alkene radical anions have been reported (Fig. 1A) (*10-12*), mainly because of the dearth of generally applicable and mild methods for the controllable SET-based reduction of alkenes.

The most commonly used methods for the generation of alkene radical anions involve sacrificial electrode systems (*13-15*) or superstoichiometric reducing agents such as SmI_2 (*16*) and dissolved metals (*17,18*). However, these systems often result in overreduction, yielding complex mixtures of reduction and reductive dimerization products; poor functional group compatibility; and limited reaction scope. To achieve a more practical and sustainable approach, a nonsacrificial metal system is highly desirable. Pioneering works in the literature (*19-22*) have demonstrated that the problematic overreduction

associated with electrolytic techniques and metallic reagents can be avoided by the use of photochemical SET processes, although most photochemical methods are currently limited to more easily reducible stilbenes and enones or require high-energy irradiation. To overcome these limitations, visible-light photoredox catalysis (*23-24*) has recently been demonstrated to be a powerful tool for the generation of various reactive species, including alkene radical anions. For instance, the Yoon group revealed that $Ru(bpy)_3Cl_2$ serves as an efficient photocatalyst for generating radical anions from activated alkene-aryl enones under visible light irradiation, and developed efficient intra- and intermolecular [2+2] enone cycloadditions (*25,26*). Quite recently, Polyzos (*27*) and Nicewicz (*28*) reported breakthrough discoveries involving the application of photoexcited reduced species of $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ and acridinum salt as super SET donors towards the reduction of styrenes and conjugated alkenes to the corresponding radical anions upon multiphoton excitation using stoichiometric *N*,*N*-diisopropylethylamine (DIPEA) as a sacrificial electron donor. The resultant nucleophilic radical anions can then be added to ketones in an intra- or intermolecular manner, followed by further SET-reduction and protonation to yield reductive hydrofunctionalization products. Yu revealed that the alkene radical anions generated by a visible-light-driven reductive quenching process in the presence of DIPEA could undergo a sequential process of CO_2 trapping, SET-reduction and additional CO_2 trapping to yield reductive dicarboxylation products (*29*). Despite being promising, these processes still require the use of sacrificial SET donors, and often leads to overreduction and limits the reaction scope, as the resultant oxidized radical species can further function not only as oxidants but also as hydrogen atom donors. The development of highly reducing photocatalyst systems that do not require sacrificial additives is highly desirable for addressing these issues. Another long-standing challenge related to the generation and synthetic application of alkene radical anions is that there are still few strategies that provide precise control over the regio-, chemo- and stereoselectivity in chiral product construction, particularly in the context of intermolecular multicomponent variants. Despite improvements in the generation of alkene radical anions (*30*), associated catalytic strategies to achieve enantioselective alkene radical anion-based synthetic transformations, particularly orthogonal enantioselective diversification at both the charge and radical sites, are conspicuously lacking.

Although most alkenes possess very negative onset reduction potentials outside the redox window of commonly used photoredox catalysts (Fig. 1B), we hypothesized that controlled SET-reduction of alkenes by a photoexcited catalyst might be kinetically facilitated if the resultant alkene radical anions could be intercepted via a fast electrophilic trap at the charged site, and that the resultant neutral radical species could then be efficiently trapped by another chiral catalyst to achieve radical cross-coupling (Fig. 1C). Considering this, we sought to develop a process based on a dual catalysis strategy by combining photoredox chemistry with chiral copper-catalysed radical coupling (*31*). We postulated that successful reactivity would be achieved by merging three fundamental reactivity concepts, as illustrated in Fig. 1D:

(i) A direct SET from an excited-state photocatalyst to an alkene generates an alkene radical anion together with an oxidized photocatalyst, and this step might be achieved under mild conditions by means of visible-light irradiation in the absence of a sacrificial electron donor. As such, complex side reactions arising from overreduction, reductive homocoupling, or hydrogen-atom transfer (HAT), which are often encountered in electrochemical or reductive-quenching photocatalysis, would be avoided.

(ii) The alkene radical anion generated in (i) is nucleophilic in nature and could therefore be trapped by an electrophile to form a neutral radical species, which can undergo further SET-reduction, self-dimerization, or HAT-based hydrogenation. However, we envisage that the efficient trapping of such intermediates by a chiral transition metal catalyst such as copper complex might unlock a new

reactivity-radical cross-coupling.

(iii) Balancing the rates of the radical anion- and neutral radical-forming reactions in (i) and (ii) together with trapping by metal catalysts should enable the desired radical cross-coupling to afford orthogonal diversification products. To avoid undesired side reactions of neutral carbon radicals, such as SET reduction, self-dimerization, HAT based hydrogenation, or oxidation to carbocations (*32*), we sought to a chiral copper catalyst to trap the neutral carbon radical and catalyze the desired enantioselective cross-coupling reaction (*33,34*).

Here, we report a new strategy that seamlessly merges organic photoredox catalysis and copper catalysis to enable the controlled generation of alkene radical anions and orthogonal enantioselective diversification of intermediates acting as formal "distonic" species (Fig. 1E).

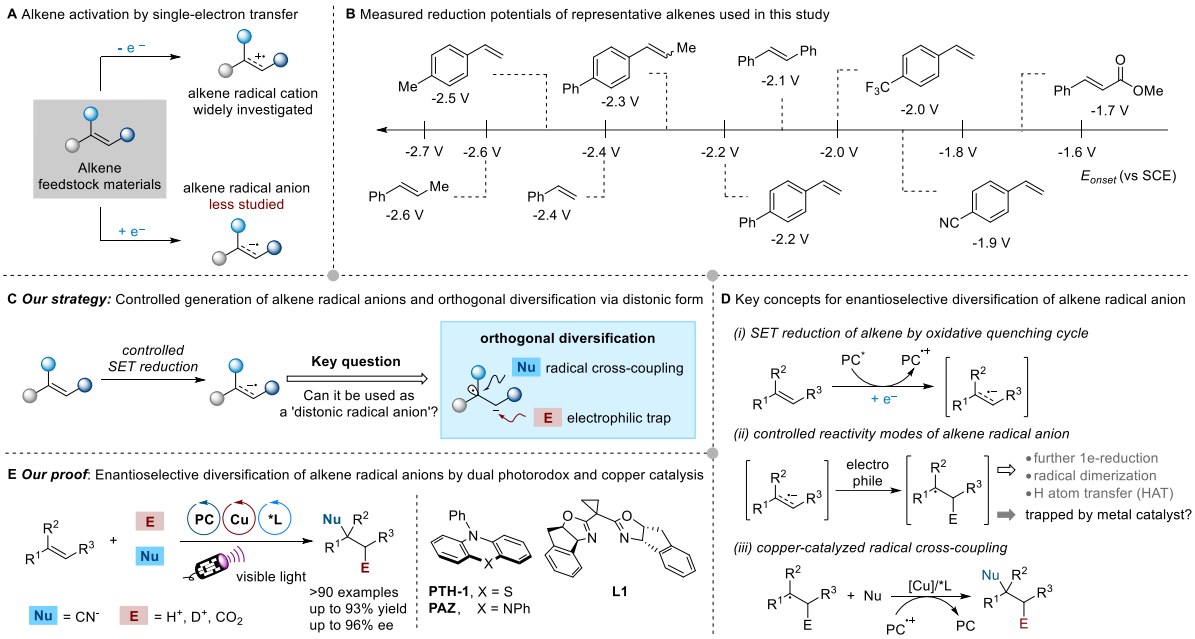
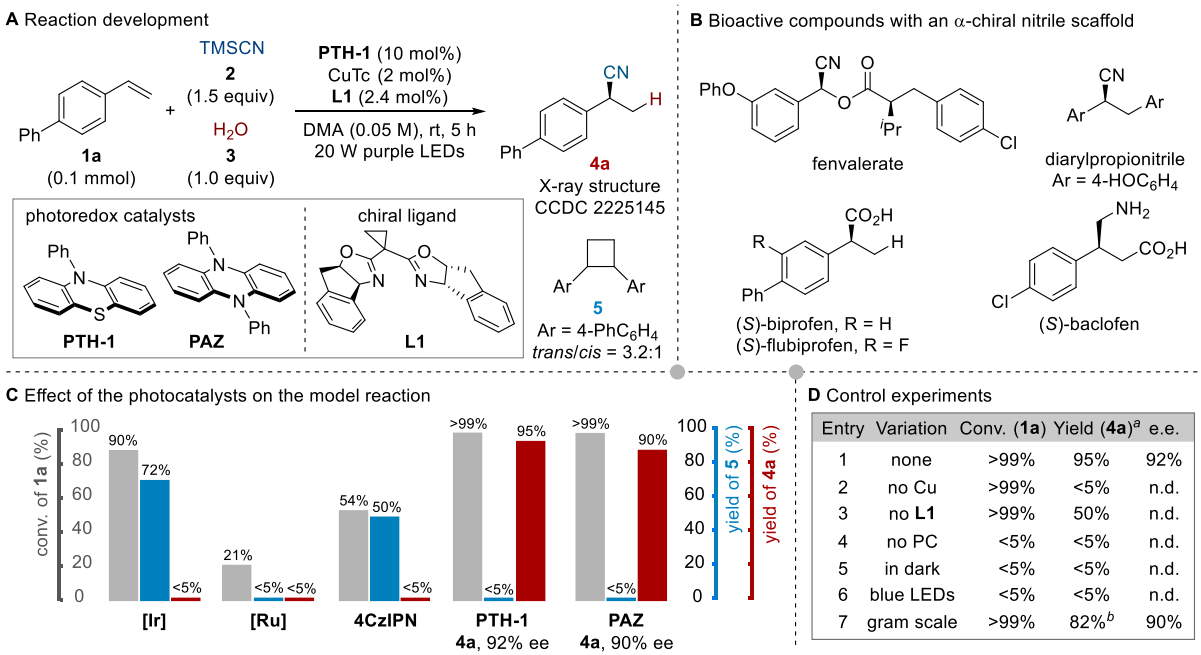


Fig. 1. Background, envisaged strategy, and reaction design of alkene radical anions. (**A**) Activation modes of alkenes by single-electron transfer (SET). (**B**) Measured reduction potentials of representative alkenes used in this study (vs. SCE in DMA). (**C**) Our strategy of controlled generation of alkene radical anions and reaction design. (**D**) Key concepts that underlie orthogonal enantioselective diversification of alkene radical anions. (**E**) Our proof of strategy-enantioselective diversification of alkene radical anions. SET, single-electron transfer; PC, photocatalyst.

Many organic photoredox catalysts have demonstrated high reducing power in their excited states even in the absence of sacrificial electron donors, and have been extensively applied in the reductive activation of various carbon-halogen bonds (*35-39*). Liu and Stahl first developed an oxidative asymmetric cyanation of benzylic C-H bonds for the construction of chiral nitriles by a copper-catalysed radical relay strategy (*40*). Inspired by this work, Xu (*41*) and Liu and Wang (*42*) recently independently developed a means of oxidative highly enantioselective photoelectrocatalytic benzylic C(sp^3)-H cyanation by replacing the oxidant *N*-fluorobenzenesulfonylimide (NFSI) with 2e$^-$ anode oxidation. Moreover, Lin and DiStasio devised a dual electrocatalysis strategy to combine Co-mediated HAT and Cu-mediated radical cyanation, and achieved a highly enantioselective hydrocyanation of conjugated alkenes using 2e$^-$ anode oxidation (*43*). Despite being powerful, these chemical and electrolytic 2e$^-$ oxidation methods rely on stoichiometric oxidants or anode oxidation, which can sometimes lead to overoxidation of the key benzylic radical

intermediates or erosion of enantiomeric excess. With the above information in mind, we hoped to combine the potent excited-state reducing potential of organic photocatalysts with the stereo-inducing ability of chiral copper complexes to initially validate our hypothesis on the asymmetric radical hydrocyanation reaction of alkenes, as the products are important chiral nitriles. In contrast to the abovementioned studies, our strategy provides a distinct alternative for developing redox-neutral and practical asymmetric radical cyanation reactions that could appreciably expand the scope of α-chiral nitriles and the subsequent synthetic utility (*44*).



Entry	Variation	Conv. (**1a**)	Yield (**4a**)[a]	e.e.
1	none	>99%	95%	92%
2	no Cu	>99%	<5%	n.d.
3	no **L1**	>99%	50%	n.d.
4	no PC	<5%	<5%	n.d.
5	in dark	<5%	<5%	n.d.
6	blue LEDs	<5%	<5%	n.d.
7	gram scale	>99%	82%[b]	90%

Fig. 2. Reaction development and optimization. (**A**) Development of asymmetric hydrocyanation of alkene by dual photoredox and copper catalysis. (**B**) Selected bioactive molecules featuring an α-chiral nitrile scaffold. (**C**) Effects of photocatalysts on the model reaction. (**D**) Control experiments. [a]Yield based on ^{1}H NMR analysis. [b]5.0 mmol, isolated yield. [Ir] = *fac*-Ir(ppy)$_3$; [Ru] = Ru(bpy)$_3$(PF$_6$)$_2$; DMA, *N*,*N*-dimethylacetamide; CuTc, copper(I) thiophene-2-carboxylate; 4CzIPN, 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene.

Results and Discussion

To proof our strategy of controlled generation of alkene radical anions and enantioselective diversification, we first investigated the asymmetric hydrocyanation of 4-phenyl styrene **1a** using TMSCN as a cyanide source and H_2O as a proton source to generate α-chiral nitrile **4a** (Fig. 2A), as most alkene analogues are commercially available and α-chiral nitriles are prevalent in many bioactive molecules (Fig. 2B) (*45,46*). In addition, the products of α-chiral nitrile hydrolysis, namely, α-aryl carboxylic acids, are also privileged pharmacophores that are components of many commercial drugs.

Optimization studies showed that the initial major challenge was the chemoselectivity, which varied significantly especially when different photocatalysts were used (Fig. 2C). For instance, the photocatalyst *fac*-Ir(ppy)$_3$ promoted full conversion of **1a** but led only to dimerization side product **5** in good yield; this side product was likely produced via triplet energy transfer-mediated [2+2] photocycloaddition of substrate **1a** (*47*). The use of Ru(bpy)$_3$(FP$_6$)$_2$ led to moderate conversion of **1a**, but neither side product **5** nor desired hydrocyanation product **4a** was detected. Although the organic photocatalyst 4CzIPN gave rise only to side product **5**, both **PTH-1** and 5,10-diphenyldihydrophenazine (**PAZ**), with highly reducing excited

states, enabled complete conversion of **1a** and produced **4a** in excellent yield with excellent enantioselectivity (92% and 90% ee). These results showed that the overall performance was not dependent only on the reducing power of the photoexcited states of these photocatalysts, indicating that the second SET process between the oxidized photocatalyst and the copper catalyst might also play an important role in the reaction. Remarkably, no alkene hydrogenation products were observed during our reaction owing to the redox-neutral conditions and the lack of a need for a sacrificial electron donor.

After extensive optimization (Supplementary Tables S1-S8), we obtained **4a** at an optimal yield of 95% with 92% ee when we irradiated the reaction mixture of **1a**, **2**, and **3** in DMA with purple LEDs at room temperature for 5 hours using the organic photocatalyst 10-phenylphenothiazine (**PTH-1**) and the chiral catalyst CuTc/**L1** (Fig. 2D, entry 1). A range of control experiments were conducted to evaluate the significance of each reaction parameter. Notably, no product was formed in the absence of copper (entry 2), and omission of chiral bisoxazoline ligand **L1** resulted in substantially lower yield (entry 3). These findings also implied that balancing the rate of alkene radical anion formation with that of the subsequent asymmetric radical coupling is critical to the reaction. No product was obtained when the reaction was conducted without light or photocatalyst or under irradiation with blue LEDs (entries 4-6). The asymmetric radical hydrocyanation could also be performed on a gram scale with high yield and excellent enantioselectivity (entry 7, 82% yield and 90% ee).

Reaction scope and application.

Under the optimized conditions, we first explored a wide range of structurally diverse and highly functionalized styrene derivatives (Fig. 3A). The array of vinylbiphenyls **1a-f** with a neutral, electron-donating (e.g., Me, *t*-Bu) or electron-withdrawing (e.g., OAc, F, CF_3) group at the *para*-position of the 4-phenyl substituent underwent hydrocyanation efficiently, affording the corresponding products **4a-f** in good yields (53-96%) and with high enantioselectivities (85-92% ee). Thus, the efficiency of the reaction appeared to be relatively independent of the electronic properties of the 4-aryl substituent. Substrates with 2-naphthyl or 2-thienyl substituents at the *para*-position of the aromatic ring also proved to be suitable for the reaction, as shown in the cases of **4g** and **4h**. Moreover, variation in the substitution patterns and steric hindrance of the 4-phenyl styrene analogues **4i-n** had no deleterious effects on the enantioselectivity (87-95% ee). For substrates with two vinyl substituents (**1o**, **1p**), only one vinyl group (specifically the sterically less hindered one) selectively participated in the hydrocyanation reaction with good enantioselectivity. We further examined the substituent effect of phenyl ring substituents by incorporating an internal alkynyl moiety at the *para*-position of the phenyl ring. Alkenes **1q-v** with an alkynyl moiety containing various functionalized alkyl chains, heteroatom functionalities, or (hetero)aromatic rings all proved to be excellent substrates, generating products **4q-v** in good yields and with excellent enantioselectivity (90-92% ee). Notably, the reaction of **1n** on a 5-mmol scale also afforded product **4n** with a comparable outcome (90% ee), demonstrating the preparative utility of this methodology.

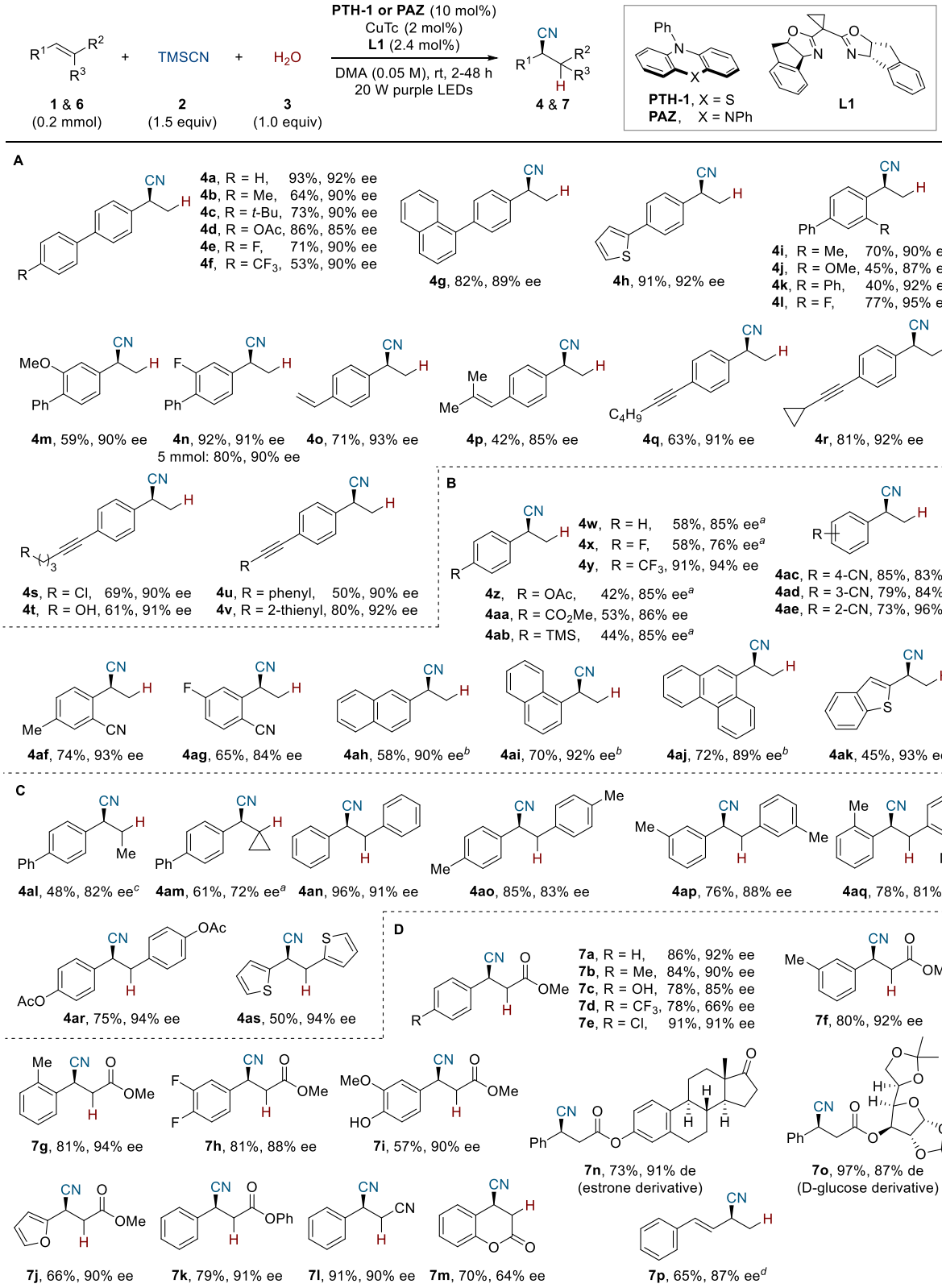


Fig. 3. Substrate scope. (**A**) Scope of styrene derivatives with *para*-sp^2 and sp substituents. (**B**) Scope of functionalized simple styrene derivatives. (**C**) Scope of internal alkenes. (**D**) Scope of conjugated alkenes. Conditions: alkene (0.2 mmol), TMSCN (0.3 mmol, 1.5 equiv.), H_2O (0.2 mmol), **PTH-1** (10 mol%), CuTc (2 mol%), **L1** (2.4 mol%), DMA (4 mL), 20 W purple LEDs (λ_{max} = 395 nm, distance approx. 3 cm) at room temperature under Ar. Isolated yields. [a]With **PAZ** (10 mol%) as a photocatalyst. [b]With $Cu(MeCN)_4PF_6$ (2

mol%). [c]With **PTH-1** (20 mol%), CuTc (5 mol%), and **L1** (6 mol%) for 24 hours. [d]With CuBr (2 mol%), **PTH-1** (2 mol%), MeCN, and 10 W purple LEDs. DMA, *N*,*N*-dimethylacetamide.

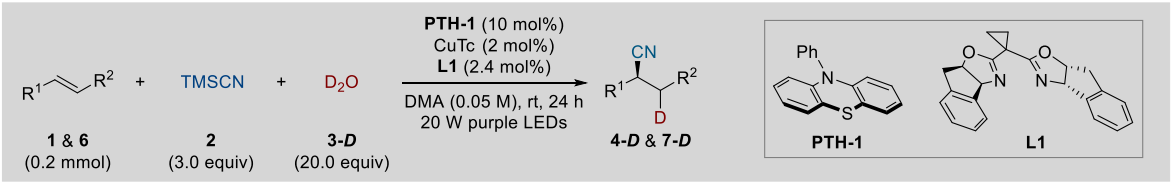
To further examine the applicability of our dual photoredox/copper catalytic system, we also tested this reaction with various functionalized but more challenging vinylarenes, most of which are commercially available feedstock materials (Fig. 3B). Simple parent styrene (**1w**) and its derivatives (**1x-ab**) with common functional groups (F, CF_3, OAc, CO_2Me, TMS, CN) at the *para*-position of the phenyl ring were all suitable for this approach, affording the expected products **4w-ab** in moderate to good yields (42-91%) with high enantioselectivities (76-94% ee). Notably, vinylarenes with a cyano group at different positions of the aromatic ring (**1ac-ae**) as well as those with multiple substituents (**1af**, **1ag**) all reacted well, generating products **4ac-ag**, some of which are challenging to synthesize by oxidative photoelectrochemical cyanation reactions (*41*), in synthetically useful yields and enantioselectivities. The fused aromatic or heteroaromatic group-substituted substrates **1ah-ak** reacted equally well, affording hydrocyanation products **4ah-ak** in 45-72% yields with satisfactory enantioselectivities (89-93% ee). Thus, our developed catalytic system is also applicable to these more challenging vinylarenes.

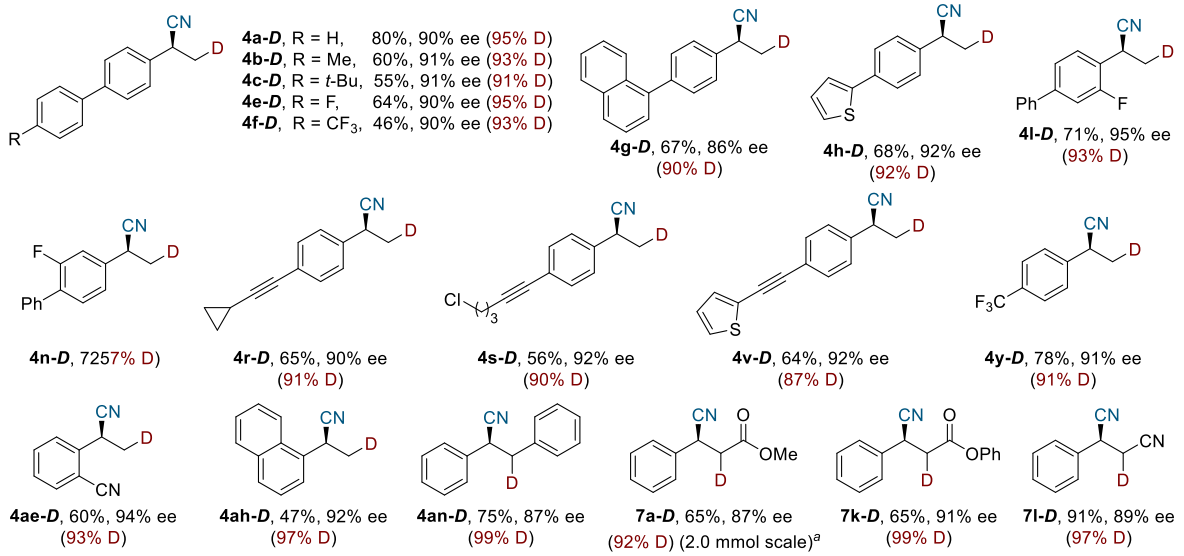
Next, we evaluated the applicability of our reaction to internal alkenes (Fig. 3C), which have previously been reported as challenging substrates in transition metal-catalysed ionic pathway-based enantioselective hydrocyanation reactions due to their low reactivity (*48*). With our catalytic system, 1,2-disubstituted alkene **1al** and bulky 1,2,2-trisubstituted alkene **1am** both reacted smoothly, affording products **4al** and **4am** with good results. In particular, stilbene derivatives such as **1an-as** that are susceptible to intramolecular cyclization to phenanthrenes under photochemical conditions (*49*) also readily underwent hydrocyanation to generate valuable chiral 2,3-diaryl propionitriles with synthetically useful yields and enantioselectivities. Note that Ac-protected (*R*)-diarylpropionitrile **4ar** is an oestrogen receptor β-selective ligand, and other diaryl propionic acids and propionamides that can be derived from these products have been used in the treatment of pulmonary embolism or as antiobesity agents (*50*). As the geometry of the starting alkene does not affect the reaction efficiency or enantioselectivity, it was found that an *E*/*Z*-mixture of isomers can be used in this hydrocyanation reaction (e.g., **4ao**, **4aq**).

Next, we explored the application of our approach to other electron-deficient internal alkenes (Fig. 3D), which can easily undergo triplet energy transfer-mediated [2+2] photocycloaddition (*47*) or reductive dimerization, a characteristic reaction of activated alkene-derived radical anions. Methyl cinnamate **6a** and the series of derivatives **6b-e** with weak electron-donating (Me) or electron-withdrawing (OH, CF_3, Cl) substituents at the *para*-position of the phenyl ring were well accommodated, affording hydrocyanation products **7a-e** in good yields and with good enantioselectivities (66-92% ee). Moreover, as shown in the cases of **7f** to **7i**, the substitution pattern and steric hindrance of the aromatic ring moiety had no deleterious effects on enantioselectivity (88-94% ee). Asymmetric hydrocyanation was also achieved for substrates with 2-furyl (**6j**) and phenyl cinnamate (**6k**) moieties, with products **7j** and **7k** obtained with 90% and 91% ee, respectively. Note that both cinnamonitrile (**6l**) and coumarin (**6m**) were also suitable for this hydrocyanation reaction. These results revealed that our reaction can serve as a general alternative to the ionic enantioselective Michael addition to generate analogous products in terms of its practicability. Cinnamoyl-type esters **7n** and **7o** that contain complex biologically active scaffolds could also undergo highly stereoselective hydrocyanation, indicating the potential of our protocol for the derivatization of cinnamoyl side chain-containing natural products and their related precursors (e.g., Taxol and phyllanthocin). Notably, linear diene **6p**, which can easily undergo electrochemical $2e^-$ reduction, underwent selective mono-hydrocyanation at the terminal alkene moiety to generate product **7p** with

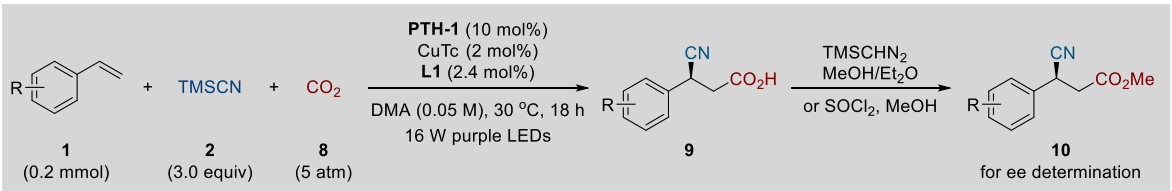
high enantioselectivity under our redox-neutral conditions. Thus, the current protocol can be successfully extended to other electron-deficient internal alkenes. In addition to representing a conceptual advance in the chemistry of alkene radical anions, our dual photoredox/copper-catalysed asymmetric radical hydrocyanation is synthetically valuable and provides access to various α-chiral nitriles.

A Catalytic asymmetric deuterocyanation of styrenes and internal alkenes





B Catalytic asymmetric cyanocarboxylation of styrenes



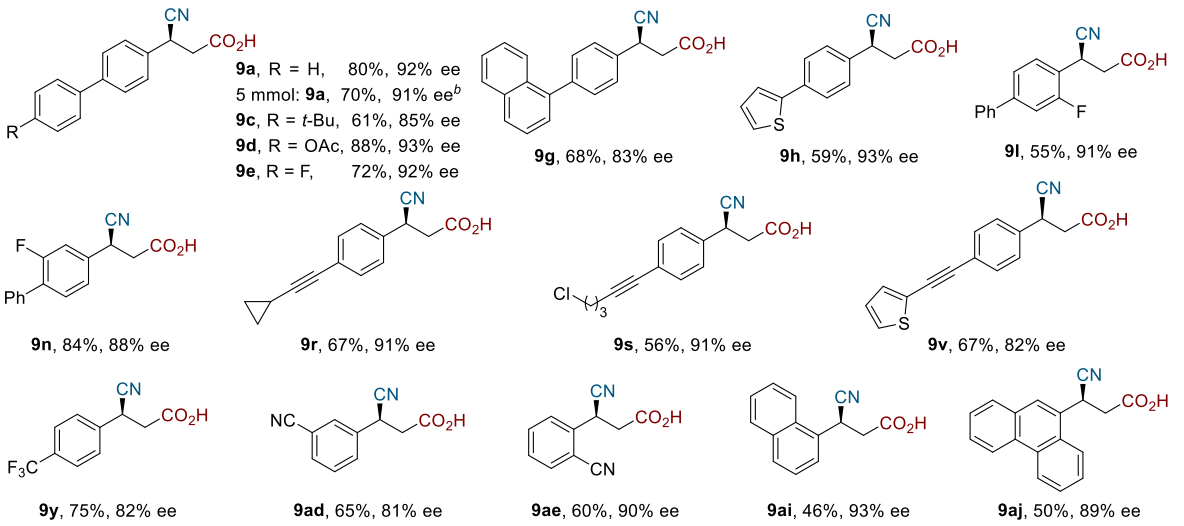


Fig. 4. Further reaction design and substrate scope. (**A**) Catalytic asymmetric deuterocyanation of alkene radical anions. Conditions: alkene (0.2 mmol), TMSCN (0.6 mmol, 3.0 equiv.), D_2O (4 mmol, 20 equiv.), **PTH-1** (10 mol%), CuTc (2 mol%), **L1** (2.4 mol%), DMA (4 mL), and 20 W purple LEDs at room temperature under Ar for 24 hours. Isolated yields. (**B**) Catalytic asymmetric cyanocarboxylation of alkene radical anions. Conditions: alkene (0.2 mmol), TMSCN (0.6 mmol, 3.0 equiv.), CO_2 (5 atm), **PTH-1** (10 mol%), CuTc (2 mol%), **L1** (2.4 mol%), DMA (4 mL), and 16 W purple LEDs (λ_{max} = 395 nm) at 30 °C for 18 hours. Isolated yields. [a]With D_2O (10 equiv.), CuTc (1 mol%), **L1** (1.2 mol%), and 2 x 20 W purple LEDs for 36 hours. [b]Reaction was performed with TMSCN (1.5 equiv.), CO_2 (5 atm), **PTH-1** (5 mol%), CuTc (1 mol%), **L1** (1.2 mol%), and 2 x 40 W purple LEDs for 24 hours. DMA, *N*,*N*-dimethylacetamide.

The insertion of deuterium atoms into parent drugs and drug candidates often results in significantly enhanced metabolic and pharmacokinetic properties without drastically altering their therapeutic function. As a result, the development of efficient deuterium-labelling techniques has attracted considerable attention (*51*). Considering our reaction design, we hypothesized that the replacement of H_2O with D_2O might provide a practical, inexpensive and mild approach for the construction of β-deuterated α-chiral nitriles. Pleasingly, the desired deuterocyanation reaction of 4-phenyl styrene **1a** indeed proceeded smoothly, affording the deuterated α-chiral nitrile **4a-*D*** in 80% yield with 90% ee and 95% D-incorporation when using 20 equiv. of D_2O as the deuterium source, under otherwise identical conditions to those for hydrocyanation (Fig. 4A) (Supplementary Table S9).

Encouraged by these results, we briefly examined the substrate scope of the deuterocyanation reaction by using a representative set of alkenes (Fig. 4A). A range of styrene derivatives (**1b-h**) containing electronically diverse aryl, 2-naphthyl or 2-thienyl groups at the *para*-position of the 4-phenyl moiety were well tolerated, furnishing corresponding products **4b-*D*** to **4h-*D*** in 46-68% yields with 86-91% ee and high levels of D incorporation (90-95% D). As evidenced in the cases of deuterated chiral nitriles **4l-*D*** and **4n-*D***, the introduction of multiple substituents into the parent aryl ring did not affect the enantioselectivity or D-incorporation. Again, styrene derivatives **1r-v** with differently substituted internal alkynyl motifs at the *para*-position of the aromatic ring also proved to be suitable substrates. The reaction system was also compatible with harder-to-reduce simple styrenes **1y** and **1ae** containing electron-withdrawing groups (e.g., CF_3, CN) at the *para*- or *meta*-position of the aromatic ring as well as 2-vinylnaphthalene **1ah**, leading to deuterated products with high enantioselectivities. Finally, we expanded the reaction scope to a range of internal alkenes, including (*E*)-stilbene **1an**, cinnamoyl-type esters **6a** and **6k** and cinnamonitrile **6l**, and no obvious loss of enantioselectivity or D-incorporation was observed in these cases. As shown in the case of **7a-*D***, our dual photoredox/copper catalytic system also maintained its efficiency even when applied on a synthetically useful scale (2.0 mmol). Thus, the general reactivity trends we observed were similar to those observed for the asymmetric hydrocyanation reaction shown in Fig. 3, although certain substrates showed slightly decreased reaction efficiency.

Incorporating carbon dioxide (CO_2) into organic compounds under electrocatalytic or photocatalytic conditions represents a potentially economical and versatile way of obtaining value-added carboxylic acids. However, the development of efficient catalytic strategies that enable the simultaneous incorporation of CO_2 and the construction of stereocentres remains a long-standing challenge, mainly because overreduction and the involvement of multiple reactive intermediates, such as $[CO_2]^{\cdot-}$ and substrate carbanions, can often lead to complex products (*51-53*). Encouraged by the excellent performance of our redox-neutral dual photoredox/copper catalytic system for the controlled generation of alkene radical anions and enantioselective diversification at the spin and charged positions, we

hypothesized that weakly electrophilic CO_2 might also be used as a suitable reaction partner to trap photogenerated alkene radical anions to initiate enantioselective cyanocarboxylation. Simple condition optimization with 4-phenyl styrene **1a** was performed, and the desired asymmetric cyanocarboxylation reaction employing 5 atm of CO_2 under otherwise identical conditions proceeded smoothly, generating carboxylic acid **9a** in 80% yield with 92% ee (Fig. 4B) (Supplementary Tables S10). Moreover, a variety of 4-phenyl styrene derivatives with electron-donating (e.g., *t*-Bu) or electron-withdrawing (OAc, F) substituents on the 4-phenyl ring all reacted well to provide the expected β-carboxylated α-chiral nitriles (**9c**, **9d**, **9e**) in good yields with high enantioselectivities (85-93% ee). Styrene derivatives bearing a fused aromatic ring (**1g**) or a heteroaromatic ring (**1h**) at the *para*-position of the aromatic ring were also compatible with the reaction. As shown in the case of **9l** and **9n**, sterically hindered multisubstituted styrenes (**1l**, **1n**) also proved to be suitable substrates. Again, incorporation of substituted alkynyl groups at the *para*-position of styrene (**1r, 1s, 1v**) was tolerated in the asymmetric cyanocarboxylation reaction, leading to satisfactory outcomes (82-91% ee). Notably, the reactions of hard-to-reduce styrene derivatives with electron-withdrawing groups (CF_3, CN) at the *para*-, *meta*-, or *ortho*-position all proceeded smoothly, generating the corresponding cyanocarboxylation products (**9y**, **9ad**, **9ae**) in 60-75% yields with good enantioselectivities (81-90% ee). Alkenes with bulkier fused aromatic rings, such as 1-naphthyl (**1ai**) and 9-phenanthryl (**1aj**) rings, could participate in the reaction to afford products **9ai** and **9aj** with high enantioselectivities, although in moderate yields. The scalability of this reaction was also demonstrated by performing the synthesis of product **9a** on a 5.0 mmol scale, which resulted in 70% yield and enantioselectivity (90% ee). Thus, this modular three-component approach provides a general alternative to the ionic enantioselective Michael addition to form the same products.

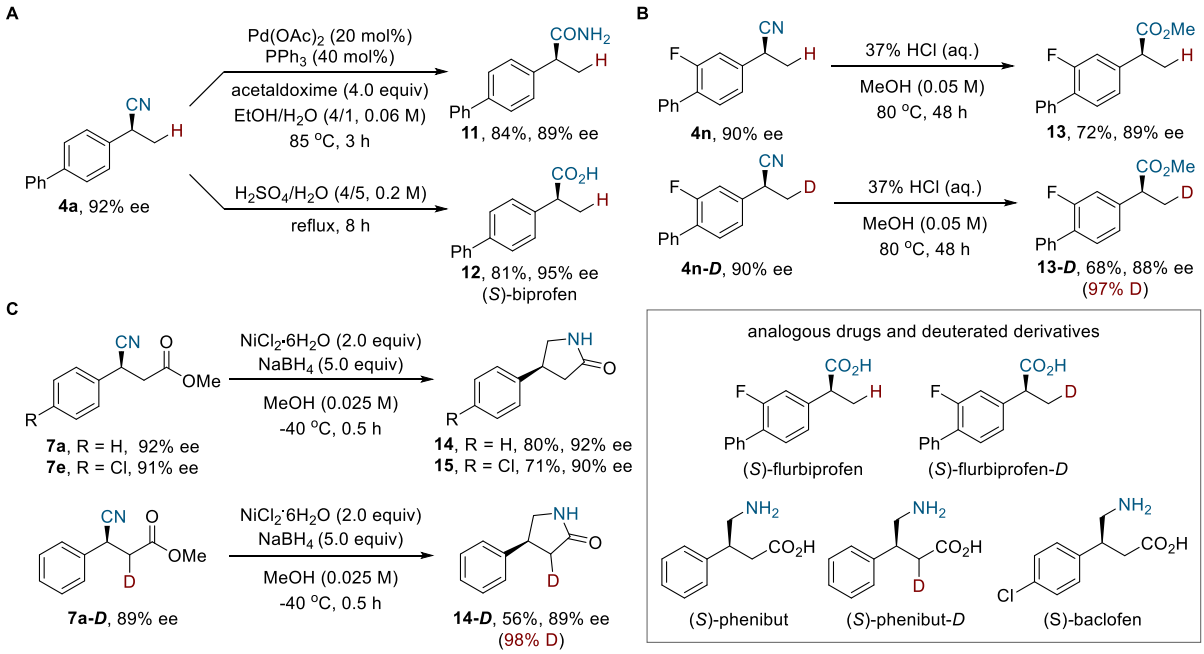


Fig. 5. Product derivatization. (**A**) Transformation of product **4a** into amides and acids. (**B**) Conversion of products **4n** and **4n-*D*** into (*S*)-flurbiprofen methyl esters. (**C**) Conversion of products **7a**, **7e** and **7a-D** into γ-lactams.

A significant advantage of our protocol is that the resultant nitrile moiety can be further readily transformed into various useful functional groups by routine manipulation, providing new access to the

diversely functionalized (*S*)-profen family (Fig. 5). Notably, hydrolysis of products **4a-n** directly generated the nonsteroidal anti-inflammatory drugs (*S*)-biprofen and (*S*)-flubiprofen, as well as their structurally diverse derivatives. Product **4a** was easily converted into either (*S*)-biprofen amide **11** by a Pd-catalysed reaction or (*S*)-biprofen **12** by acid-promoted hydrolysis (Fig. 5A). Moreover, products **4n** and deuterated analogue **4n-*D*** could be transformed into esters **13** and **13-*D***, respectively, which are precursors to the commercial drug (*S*)-flurbiprofen, via methanolysis without loss of stereochemical information (Fig. 5B). Treatment of products **7a**, **7e**, and deuterated analogue **7a-*D*** with nickel borohydride allowed sequential reduction and cyclization to produce the corresponding γ-lactams **14**, **15**, and **14-D** in good yields; these compounds are precursors of (*S*)-phenibut and (*S*)-baclofen. Notably, these derivatizations occurred without affecting the enantiopurity or D incorporation, and these results again highlight the excellent potential of our enantioselective diversification of alkene radical anions (Fig. 5C).

To shed light on the mechanism of the developed alkene radical anion-involved enantioselective diversification reaction, a range of mechanistic experiments were performed (Fig. 6). First, considering the inherent nucleophilic nature of postulated alkene radical anions, we replaced H_2O with methyl iodide as an electrophile in the reaction of 4-phenyl styrene **1a** and TMSCN under standard conditions (Fig. 6A, i). Although we did not observe any formation of hydrocyanation product **4a**, an appreciable amount of methylcyanation product **4al** was formed with high enantioselectivity (87% ee), suggesting the intermediacy of alkene radical anion **1a-I** and benzylic radical **17**. Second, we reacted **1a** with MeOH or H_2O as nucleophilic partners in place of TMSCN without a copper catalyst, and benzylic ether **18** and benzylic alcohol **19** were obtained in good yields (Fig. 6A, ii). These findings are consistent with our initial hypothesis that benzylic radical **1a-II** formed as a result of photoredox-catalysed SET-reduction and protonation. Then, benzylic radical **1a-II** was further oxidized to benzylic cation **1a-III** by the oxidized photocatalyst formed in the initial oxidative quenching event, followed by nucleophilic attack of MeOH and H_2O. Third, the addition of the stoichiometric radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) to the model reaction of **1a** with TMSCN and H_2O in the presence of **PTH-1** and CuTc/**L1** completely inhibited the formation of hydrocyanation product **4a**, and trapping adduct **20** was detected by HRMS analysis, indicative of the participation of benzylic radical **1a-II** in this reaction (Fig. 6B). Fourth, it was found that radical clock substrate **20** could also participate in the hydrocyanation reaction under standard conditions but generated cyclopropyl group-opening product (*E*)-**22** in 28% yield with 80% ee (Fig. 6C).

To gain more insight into the possible SET events and radical intermediates, we further carried out electron paramagnetic resonance (EPR) studies. Upon irradiation with purple LEDs for 20 min, a DMA solution of **1an** and photocatalyst **PTH-1** gave rise to obvious combined EPR signals (Fig. 6D, ii), which were attributed to the **PTH-1** radical cation (g = 2.003, A_N = 0.71 mT) and alkene radical anion [**1an**]$^{\cdot-}$ (g = 2.004, 1.20 mT). This result suggests that SET occurred from the photoexcited photocatalyst to 4-phenyl stilbene **1an**. Moreover, when a DMA solution of **1a**, **PTH-1** and 5,5-dimethyl-pyrroline *N*-oxide (DMPO) was irradiated by purple LEDs for 20 min, obvious EPR signals were observed, which were attributed to radical-trapping adduct **1a-II-DMPO** (g = 2.003, A_N = 1.45 mT, A_H = 2.11 mT) (Fig. 6E, ii). This result provided additional evidence for the intermediacy of benzylic radical **1a-II**, which was thought to result from protonation of the alkene radical anion, probably owing to the presence of adventitious water in DMA.

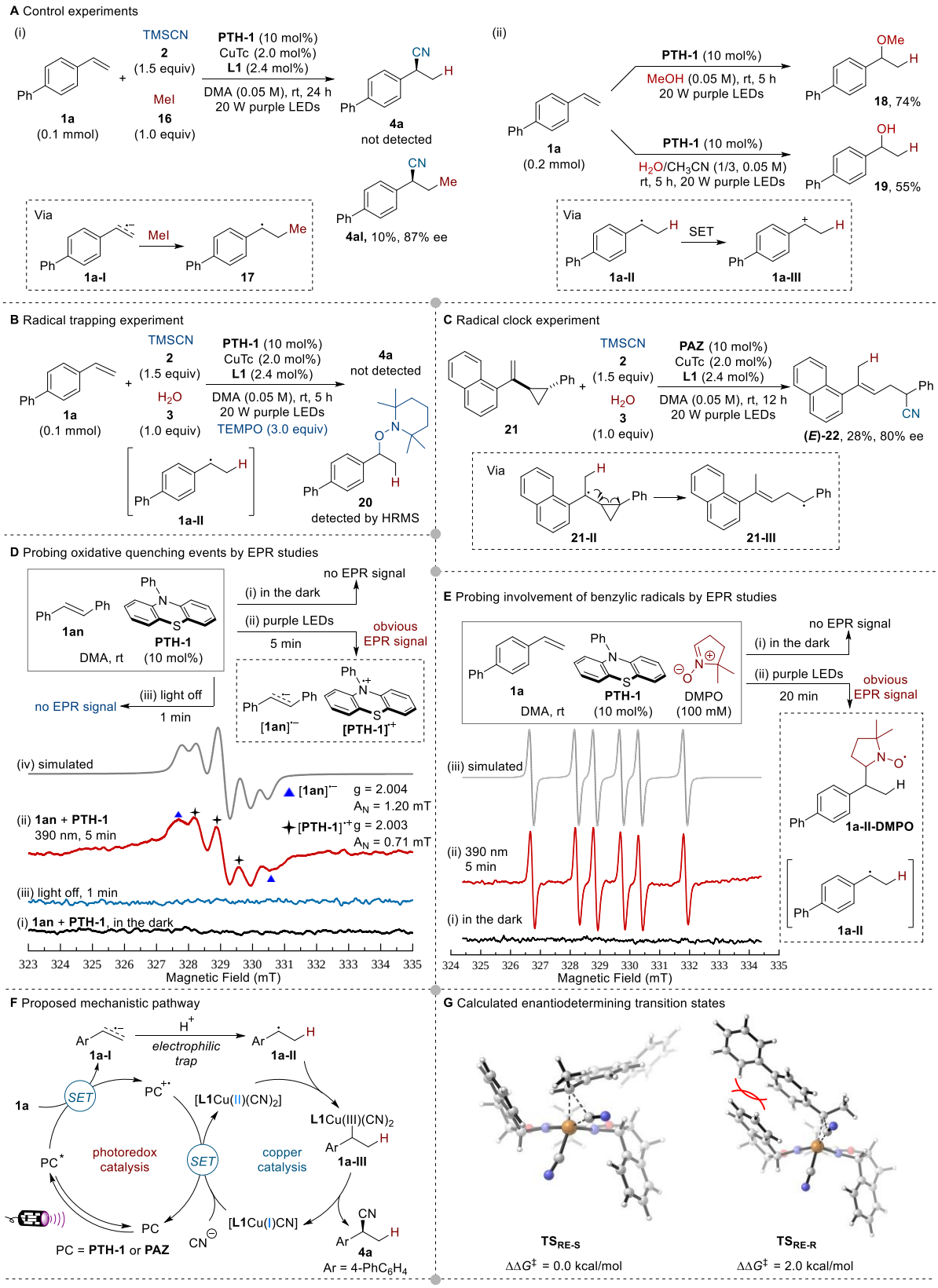


Fig. 6. Mechanistic studies, proposed reaction pathway and DFT calculation. (**A**) Control experiments with methyl iodide as an electrophile. (**B**) Radical trapping experiment with a radical scavenger. (**C**) Radical clock experiment. (**D**) Probing the involvement of oxidative quenching events by EPR. (**E**) Probing the involvement of radical intermediates by EPR. (**F**) Proposed reaction mechanism. (**G**) Calculated

enantiodetermining transition states. EPR, electron paramagnetic resonance; SET, single-electron transfer.

To further investigate the individual elementary steps of this reaction, Stern−Volmer luminescence quenching studies were conducted with methyl cinnamate **6a** (Supplementary Fig. S11). It was observed that the quenching rate was proportional to the concentration of **6a**, and an oxidative quenching cycle was presumably favoured. A quantum yield (ϕ) of 0.051 for the overall model hydrocyanation reaction was determined by actinometry, suggesting that the reaction proceeded via a sequential redox process rather than by a radical chain process (Supplementary Fig. S12). Furthermore, the enantiopurity of product **4a** was proportional to the enantiomeric excess of chiral bisoxazoline ligand **L1** (Supplementary Fig. S13). This outcome implies that the active copper catalyst species for stereoinduction possessed a 1:1 ratio of copper catalyst to ligand **L1**.

On the basis of these mechanistic studies, we can now propose a mechanism for the hydrocyanation of alkene radical anions via our dual photoredox and copper catalysis approach (Fig. 6F). Initially, upon visible-light irradiation, a SET event between the excited-state photocatalyst ***PTH-1** and alkene **1a** occurs, generating alkene radical anion **1a-I** and the oxidized-state [**PTH-1**]$^{\bullet+}$ (left cycle in Fig. 6F). Then, the nucleophilic alkene radical anion **1a-I** is easily intercepted by a proton from H_2O or HCN, which is formed in situ from TMSCN and H_2O, affording benzylic radical **1a-II**. At this stage, benzylic radical **1a-II** is ready for participation in copper-catalysed cross-coupling (right cycle). Meanwhile, the presence of stoichiometric TMSCN facilitates facile ligand exchange between the **L1**/Cu(I)/Tc complex and TMSCN to form complex **L1**/Cu(I)/CN. That complex is further oxidized by the oxidized photocatalyst [**PTH-1**]$^{\bullet+}$ via a SET process to generate the **L1**/Cu(II)/$(CN)_2$ complex after trapping another cyanide anion from TMSCN, with regeneration of the ground-state photocatalyst **PTH-1** and completion of the photoredox catalytic cycle. Finally, complex **L1**/Cu(II)/$(CN)_2$ couples with prochiral benzylic radicals to form product **4a** through a high-valent Cu(III) complex and reductive elimination, together with regeneration of the **L1**/Cu(I)X complex to complete the copper catalysis cycle. For the enantioselective benzylic C–CN bond formation, DFT calculations were carried out to investigate the detailed mechanism and the origin of stereoselectivity (Supplementary Section 7). The reductive elimination transition states were calculated to be higher in energy than radical recombination transition states, which establishes the former one as the enantiodetermining step (see Supplementary Fig. S20 for more details). The free energy difference between the enantiodetermining transition states $\mathbf{TS_{RE\text{-}R}}$ and $\mathbf{TS_{RE\text{-}S}}$ was calculated to be 2.0 kcal/mol, consistent with the experimentally reported excellent enantioselectivity (92% ee) (see Fig. 6G). By carefully comparing the geometries of $\mathbf{TS_{RE\text{-}R}}$ and $\mathbf{TS_{RE\text{-}S}}$, in the unfavourable transition state $\mathbf{TS_{RE\text{-}R}}$, the biphenyl group encounters larger steric hindrance that causes larger distortion of the copper complex from its optimal geometry. In $\mathbf{TS_{RE\text{-}S}}$, the biphenyl group points to the vacant space where the steric repulsion is avoided (see Supplementary Fig. S21 and Table S12 for more details).

The whole reaction is a redox-neutral process and does not require any external oxidants or reductants. For the cyanocarboxylation reaction, an alternative pathway wherein CO_2 undergoes SET-reduction to form a CO_2 radical anion and further addition to an alkene might also be possible. However, ^{13}C NMR analysis of the reaction mixtures did not reveal the formation of any formic or oxalic acids (Supplementary Fig. S18), suggesting that this pathway is less favoured.

Conclusion

In conclusion, we have demonstrated a new strategy that seamlessly merges photoredox and copper catalysis and enables the controlled generation of alkene radical anions and the orthogonal enantioselective diversification of those reactive intermediates via the formation of distonic-like species

(*55*). An important feature of our catalytic approach is that alkenes are directly reduced to radical anions by the excited-state photocatalyst via a SET process without stoichiometric redox agents, while the resultant oxidized photocatalyst is conveniently SET-reduced back to the ground state by a copper(I) catalyst. Thus, this redox-neutral strategy avoids competitive oxidation, overreduction-induced hydrogenation, and dimerization pathways. The synthetic utility of this conceptual advance was evidenced by a wide range of highly regio-, chemo- and enantioselective hydrocyanation, deuterocyanation, and cyanocarboxylation reactions of alkenes with good substrate scope and functional group tolerance. Overall, our protocol provides a new blueprint for generation and exploration of the transformation potential of alkene radical anions.

REFERENCES AND NOTES

1. H. D. Roth, in *Reactive Intermediate Chemistry*, R. A. Moss, M. S. Platz, M. J. Jr, Eds. (John Wiley & Sons, Inc., 2004), pp. 205-272.
2. H. J. Schäfer, Anodic and Cathodic CC-Bond Formation. *Angew. Chem. Int. Ed.* **20**, 911-934 (1981). (10.1002/anie.198109111)
3. K. Mizuno, Y. Otsuji, Addition and cycloaddition reactions via photoinduced electron transfer. *Top. Curr. Chem.* **169**, 301-346 (1994). (10.1007/3-540-57565-0_79)
4. P. I. Dalko, Redox induced radical and radical ionic carbon-carbon bond forming reactions. *Tetrahedron* **51**, 7579-7653 (1995). (10.1016/0040-4020(95)00434-A)
5. M. A. Ischay, T. P. Yoon, Accessing the Synthetic Chemistry of Radical Ions. *Eur. J. Org. Chem.*, 3359-3372 (2012). (10.1002/ejoc.201101071)
6. N. L. Bauld *et al.*, Cation radical pericyclic reactions. *Acc. Chem. Res.* **20**, 371-378 (1987). (10.1021/ar00142a003)
7. D. Mangion, D. R. Arnold, Photochemical Nucleophile−Olefin Combination, Aromatic Substitution Reaction. Its Synthetic Development and Mechanistic Exploration. *Acc. Chem. Res.* **35**, 297-304 (2002). (10.1021/ar010108z)
8. M. Mella, M. Freccero, E. Fasani, A. Albini, New synthetic methods via radical cation fragmentation. *Chem. Soc. Rev.* **27**, 81 (1998). (10.1039/a827081z)
9. M.-J. Luo, Q. Xiao, J.-H. Li, Electro-/photocatalytic alkene-derived radical cation chemistry: recent advances in synthetic applications. *Chem. Soc. Rev.* **51**, 7206-7237 (2022). (10.1039/d2cs00013j)
10. N. L. Holy, J. D. Marcum, Radical Anion Intermediates in Organic Chemistry. *Angew. Chem. Int. Ed.* **10**, 115-124 (1971). (10.1002/anie.197101151)
11. D. J. Berger, J. M. Tanko, Radical Anions and Radical Cations Derived from Compounds Containing C=C, C=O or C=N Groups, in *PATAI'S Chemistry of Functional Groups,* S. Patai, Ed. John Wiley & Sons, Ltd., New York, 1997.
12. J. Grimshaw, Reduction of alkenes and conjugated alkenes, in *Electrochemical Reactions and Mechanisms in Organic Chemistry,* J. Grimshaw, Ed. Elsevier Science B.V., Amsterdam, 2000; pp. 54-88.
13. R. Engels, H. J. Schäfer, Cathodic Acylation of Aryl Olefins. *Angew. Chem. Int. Ed.* **17**, 460-460 (1978). (10.1002/anie.197804601)
14. M. Fruianu, M. Marchetti, G. Melloni, G. Sanna, R. Seeber, Electrochemical reduction of 1,1-diaryl-substituted ethenes in dimethylformamide. *J. Chem. Soc., Perkin Trans. 2*, 2039-2044 (1994). (10.1039/p29940002039)

15. R. G. Janssen, M. Motevalli, Electroreductive coupling of vinylpyridines and vinylquinolines: radical anion–substrate cycloaddition? *Chem. Commun.*, 539-540 (1998). (10.1039/A707460C)
16. A. Dahlén, G. Hilmersson, Selective reduction of carbon-carbon double and triple bonds in conjugated olefins mediated by SmI_2/H_2O/amine in THF. *Tetrahedron Lett.* **44**, 2661-2664 (2003). (10.1016/S0040-4039(03)00369-1)
17. A. Baba, M. Yasuda, Y. Nishimoto, 8.20 Partial Reduction of Enones, Styrenes, and Related Systems. In *Comprehensive Organic Synthesis II*, 2nd ed.; P. Knochel, Ed.; Elsevier: Amsterdam, 2014; pp 673−740.
18. J. Yang, G. A. Felton, N. L. Bauld, M. J. Krische, Chemically induced anion radical cycloadditions: intramolecular cyclobutanation of bis(enones) via homogeneous electron transfer. *J. Am. Chem. Soc.* **126**, 1634-1635 (2004). (10.1021/ja030543j)
19. U. C. Yoon, P. S. Mariano, Mechanistic and synthetic aspects of amine-enone single electron transfer photochemistry. *Acc. Chem. Res.* **25**, 233 (1992). (10.1021/ar00017a005)
20. F. D. Lewis, T.-I. Ho, Selectivity of tertiary amine oxidations. *J. Am. Chem. Soc.* **102**, 1751 (1980). (10.1021/ja00525a061)
21. K. Mizuno, M. Ikeda, Y. Otsuji, Dual Regioselectivity in the Photoallylation of Electron-Deficient Alkenes by Allylic Silanes. *Chem. Lett.* **17**, 1507-1510 (1988). (10.1246/cl.1988.1507)
22. G. Pandey, S. Hajra, A Novel Photosystem for Harvesting Visible Light to Drive Photoinduced Electron Transfer (PET) Reductions: β-Activation of α, β-Unsaturated Ketones for Radical Cyclizations. *Angew. Chem. Int. Ed.* **33**, 1169-1171 (1994). (10.1002/anie.199411691)
23. C. K. Prier, D. A. Rankic, D. W. MacMillan, Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **113**, 5322-5363 (2013). (10.1021/cr300503r)
24. D. M. Schultz, T. P. Yoon, Solar Synthesis: Prospects in Visible Light Photocatalysis. *Science* **343**, 985-994 (2014). (10.1126/Science.1239176)
25. M. A. Ischay, M. E. Anzovino, J. Du, T. P. Yoon, Efficient Visible Light Photocatalysis of [2+2] Enone Cycloadditions. *J. Am. Chem. Soc.* **130**, 12886-12887 (2008). (10.1021/ja805387f)
26. J. Du, T. P. Yoon, Crossed Intermolecular [2+2] Cycloadditions of Acyclic Enones via Visible Light Photocatalysis. *J. Am. Chem. Soc.* **131**, 14604-14605 (2009). (10.1021/ja903732v)
27. M. L. Czyz, M. S. Taylor, T. H. Horngren, A. Polyzos, Reductive Activation and Hydrofunctionalization of Olefins by Multiphoton Tandem Photoredox Catalysis. *ACS Catal.* **11**, 5472-5480 (2021). (10.1021/acscatal.1c01000)
28. N. J. Venditto, Y. S. Liang, R. K. El Mokadem, D. A. Nicewicz, Ketone-Olefin Coupling of Aliphatic and Aromatic Carbonyls Catalyzed by Excited-State Acridine Radicals. *J. Am. Chem. Soc.* **144**, 11888-11896 (2022). (10.1021/jacs.2c04822)
29. T. Ju *et al.*, Dicarboxylation of alkenes, allenes and (hetero)arenes with CO_2 via visible-light photoredox catalysis. *Nat. Catal.* **4**, 304-311 (2021). (10.1038/s41929-021-00594-1)
30. Z.-H. Luan, J.-P. Qu, Y.-B. Kang, Discovery of Oxygen α-Nucleophilic Addition to α,β-Unsaturated Amides Catalyzed by Redox-Neutral Organic Photoreductant. *J. Am. Chem. Soc.* **142**, 20942-20947 (2020). (10.1021/jacs.0c10707)
31. A. Hossain, A. Bhattacharyya, O. Reiser, Copper's Rapid Ascent in Visible-Light Photoredox Catalysis. *Science* **364**, eaav9713 (2019). (10.1126/science.aav9713)
32. D. D. M. Wayner, D. J. McPhee, D. Griller, Oxidation and reduction potentials of transient free radicals. *J. Am. Chem. Soc.* **110**, 132-137 (1988). (10.1021/ja00209a021)
33. F. Wang, P. Chen, G. Liu, Copper-Catalyzed Radical Relay for Asymmetric Radical Transformations. *Acc. Chem. Res.* **51**, 2036-2046 (2018). (10.1021/acs.accounts.8b00265)

34. Z.-L. Li, G.-C. Fang, Q.-S. Gu, X.-Y. Liu, Recent advances in copper-catalysed radical-involved asymmetric 1,2-difunctionalization of alkenes. *Chem. Soc. Rev.* **49**, 32-48 (2020). (10.1039/c9cs00681h)
35. J. C. Theriot *et al.*, Organocatalyzed atom transfer radical polymerization driven by visible light. *Science* **352**, 1082-1086 (2016). (10.1126/science.aaf3935)
36. N. A. Romero, D. A. Nicewicz, Organic Photoredox Catalysis. *Chem. Rev.* **116**, 10075-10166 (2016). (10.1021/acs.chemrev.6b00057)
37. A. Corbin, C.-H. Lim, G. M. Miyake, Phenothiazines, Dihydrophenazines, and Phenoxazines: Sustainable Alternatives to Precious-Metal-Based Photoredox Catalysts. *Aldrichim. Acta* **52**, 7 (2019).
38. T. Koike, M. Akita, Modern Synthetic Strategies for One-Electron Injection. *Trends Chem.* **3**, 416-427 (2021). (10.1016/j.trechm.2021.02.006)
39. L.-L. Liao, L. Song, S.-S. Yan, J.-H. Ye, D.-G. Yu, Highly reductive photocatalytic systems in organic synthesis. *Trends Chem.* **4**, 512-527 (2022). (10.1016/j.trechm.2022.03.008)
40. W. Zhang *et al.*, Enantioselective Cyanation of Benzylic C-H Bonds via Copper-Catalyzed Radical Relay. *Science* **353**, 1014-1018 (2016). (10.1126/science.aaf7783)
41. C.-Y. Cai *et al.*, Photoelectrochemical asymmetric catalysis enables site- and enantioselective cyanation of benzylic C–H bonds. *Nat. Catal.* **5**, 943-951 (2022). (10.1038/s41929-022-00855-7)
42. W. Fan *et al.*, Electrophotocatalytic Decoupled Radical Relay Enables Highly Efficient and Enantioselective Benzylic C-H Functionalization. *J. Am. Chem. Soc.* **144**, 21674-21682 (2022). (10.1021/jacs.2c09366)
43. L. Song *et al.*, Dual electrocatalysis enables enantioselective hydrocyanation of conjugated alkenes. *Nat. Chem.* **12**, 747-754 (2020). (10.1038/s41557-020-0469-5)
44. F. Wang, P. Chen, G. Liu, Copper-catalysed asymmetric radical cyanation. *Nat. Synth.* **1**, 107-116 (2022). (10.1038/s44160-021-00016-x)
45. F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk, B. C. Shook, Nitrile-Containing Pharmaceuticals: Efficacious Roles of the Nitrile Pharmacophore. *J. Med. Chem.* **53**, 7902-7917 (2010). (10.1021/jm100762r)
46. V. M. Carroll, M. Jeyakumar, K. E. Carlson, J. A. Katzenellenbogen, Diarylpropionitrile (DPN) enantiomers: synthesis and evaluation of estrogen receptor β-selective ligands. *J. Med. Chem.* **55**, 528-537 (2012). (10.1021/jm201436k)
47. S. K. Pagire, A. Hossain, L. Traub, S. Kerres, O. Reiser, Photosensitised regioselective [2+2]-cycloaddition of cinnamates and related alkenes. *Chem. Commun.* **53**, 12072-12075 (2017). (10.1039/c7cc06710k)
48. A. Falk, A. L. Goderz, H. G. Schmalz, Enantioselective nickel-catalyzed hydrocyanation of vinylarenes using chiral phosphine-phosphite ligands and TMS-CN as a source of HCN. *Angew. Chem. Int. Ed.* **52**, 1576-1580 (2013). (10.1002/anie.201208082)
49. F. B. Mallory, C. S. Wood, J. T. Gordon, Photochemistry of Stilbenes. III. Some Aspects of the Mechanism of Photocyclization to Phenanthrenes. *J. Am. Chem. Soc.* **86**, 3094-3102 (1964). (10.1021/ja01069a025)
50. V. M. Carroll, M. Jeyakumar, K. E. Carlson, J. A. Katzenellenbogen, Diarylpropionitrile (DPN) enantiomers: synthesis and evaluation of estrogen receptor beta-selective ligands. *J. Med. Chem.* **55**, 528-537 (2012). (10.1021/jm201436k)
51. S. Kopf *et al.*, Recent Developments for the Deuterium and Tritium Labeling of Organic Molecules. *Chem. Rev.* **122**, 6634-6718 (2022). (10.1021/acs.chemrev.1c00795)
52. D. A. Tyssee, M. M. Baizer, Electrocarboxylation. I. Mono- and dicarboxylation of activated olefins. *J.*

Org. Chem. **39**, 2819-2823 (1974). (10.1021/jo00933a001)
53. A. Alkayal *et al.*, Harnessing Applied Potential: Selective β-Hydrocarboxylation of Substituted Olefins. *J. Am. Chem. Soc.* **142**, 1780-1785 (2020). (10.1021/jacs.9b13305)
54. J.-H. Ye, T. Ju, H. Huang, L.-L. Liao, D.-G. Yu, Radical Carboxylative Cyclizations and Carboxylations with CO_2. *Acc. Chem. Res.* **54**, 2518-2531 (2021). (10.1021/acs.accounts.1c00135)
55. B. Zhang, M. Jiang, Z.-H. Zhang, K. Zhao, W.-Y. Qu, W.-J. Xiao, J.-R. Chen, Enantioselective diversification of alkene radical anions. Preprint at ChemRxiv, version 1.

ACKNOWLEDGMENTS

The authors thank Professors Liang-Qiu Lu, Ying Cheng, and Ke Gao at Central China Normal University for helpful discussions and Jun Chen for preliminary optimization of alkene deuterocyanation. **Funding:** We are grateful for financial support from the National Natural Science Foundation of China (21971081, 22171099, 91856119, 91956201, and 21820102003) and the Program of Introducing Talents of Discipline to Universities of China (111 Program, B17019). **Author contributions:** W.-J.X. and J.-R.C. conceived the project and supervised the research. B.Z. carried out the main experimental work. M.J. carried out the EPR studies. Z.-H.Z. was responsible for the implementation of the computational studies and the writing of corresponding DFT mechanistic discussions. W.-Y.Q. and K.Z. carried out the preparation of some substrates. W.-J.X. and J.-R.C. cowrote the manuscript with revisions provided by the other authors. All authors discussed the results and commented on the manuscript. **Competing interests:** The authors declare no conflicts of interest. **Data and materials availability:** All data are available in the main text or the Supplementary materials.