Electrophoto-catalytic decoupled radical relay enables highly efficient and enantioselective benzylic C-H functionalization

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Abstract:

Asymmetric sp3 C-H functionalization has been demonstrated to substantially expedite target molecule synthesis, spanning from feedstocks upgradation to late-stage modification of complex molecules. Herein, we report a highly efficient and sustainable method for enantioselective benzylic C-H cyanation by merging electrophoto- and copper-catalysis. A novel catalytic system allows one to independently regulate the hydrogen atom transfer step for benzylic radical formation and speciation of Cu(II)/Cu(I) to effectively capture the transient radical intermediate, through tuning the electronic property of anthraquinone-type photocatalyst and simply modulating the applied current, respectively. Such decoupled radical relay catalysis enables a unified approach for enantioselective benzylic C-H cyanation of alkylarenes with wide range electron property from E-poor to super E-rich, most of which are much less reactive or even unreactive using the existing method relied on coupled radical relay. Moreover, the current protocol is also amenable to late-stage functionalization of bioactive molecules, including natural products and drugs.

Introduction

Asymmetric functionalization of C-H bonds provides a straightforward access to highly valuable building blocks and drug candidates from petrochemicals[1-9], and significant progresses have been achieved in the last decade. Enzyme catalysis, e.g., P450, represents one of the most efficient strategies for this target, wherein hydrogen atom abstraction from C-H substrate to metal-oxo active center contributes to the sp^3 C-H bonds activation and a radical rebound pathway is typically responsible for the bond formation[10-12]. To diversify the functionalities incorporated, numerous catalytic systems based on hydrogen atom transfer (HAT) and radical functionalization have been established for the sp^3 C-H bond functionalization[13-15]. Despite the advances, the asymmetric version is still of great challenge due to the extreme difficulty in enantio-control of radical functionalization.

Metal-catalyzed radical relay has been introduced for the asymmetric C-H functionalization by integrating HAT for sp^3 C-H cleavage and unique stereo-control of transition metal catalysis (Figure 1A-*i*)[16-17]. Many asymmetric functionalization reactions of C-H bonds were explored in the last decade[18-22]. For instance, the copper-catalyzed asymmetric benzylic C-H functionalization, such as cyanation[18], arylation[19] and alkynylation[20] reactions, were discovered by using electrophilic N-F reagents, where metal-bounded radicals L*Cu-N radicals are disclosed as the key intermediate for the HAT process[23] and L*Cu(II)-FG for the asymmetric radical functionalization. The success of such *coupled radical relay catalysis*, both HAT acceptor and radical trap are generated simultaneously in the same redox event, e. g., single electron transfer between copper(I) and N-F reagents, entails matching the HAT step for benzylic C-H bond activation and radical capture with L*Cu(II)-FG intermediate. However, the rate constant of HAT of alkylarenes is electronically sensitive and highly substrate dependent, typically with a reactivity sequence of electron-rich (E-rich) > electron-neutral (E-neutral) > electron-poor (E-neutral). Meanwhile, beside acting as HAT acceptor, the active metal-bounded radicals (L*Cu-N) could potentially undergo oxidative cross-coupling with the

nucleophiles[18-20], or react with low-valent Cu(I)[24]; disproportionation of L*Cu(II)-FG often takes place resulting in the oxidative homocoupling of nucleophiles (e.g., CN, Ar, and alkynyl groups, Figure 1A-*ii*)[25-27]. Collectively, the electronic bias for HAT, along with the above-mentioned potential side reactions, lead to the remarkable restriction in substrate scope. In fact, E-rich alkylarenes features excellent reactivity, while poor reactivity is often observed with the E-neutral and E-poor alkylarenes (Figure 1A-*iii*)[18-20]. We reason that these challenges could be overcome by establishing a new catalytic system that could regulate the HAT step and Cu(II)/Cu(I) speciation in independent manners. Herein, we report a *decoupled radical relay* for the highly efficient asymmetric C(sp^3)-H cyanation, wherein the excited state of photocatalyst acts as the HAT acceptor for benzylic C-H bond activation, generating the key benzylic radical intermediate, and electrochemically generated L*Cu(II)$(CN)_2$ serves as the radical trap (Figure 1B). Comparison between this *decoupled radical relay* with the existing *coupled radical relay* demonstrates that this method exhibits significantly expanded substrate scope from E-poor to super E-rich alkylarenes, and remarkable functional group tolerance.

Photoredox catalysis has recently been extensively investigated for sp^3 C-H functionalization. In many cases, the excited state of photocatalyst (Pc) acts as the HAT acceptor[28]. Specially, the merger of photoredox-mediated HAT and transition-metal catalysis enables a range of C-H functionalization[29-30], which provide important inspirations for the design of *decoupled radical relay catalysis*. A detailed description of our proposed reaction is illustrated in Figure 1B. Photoexcitation of Pc followed by intersystem crossing would generate the triplet excited state of Pc (Pc*), which subsequently abstracts hydrogen atom from alkylarene to produce the benzylic radical intermediate and reduced form of Pc ($Pc^{[H]}$). As proposed in our previous works, capture of the benzylic radical by L*$Cu^{II}(CN)_2$ would eventually afford the enantio-enriched nitriles. Finally, terminal oxidant is needed to re-oxidize the reduced Pc ($Pc^{[H]}$) and L*Cu^{I}(CN), and close the catalytic cycle.

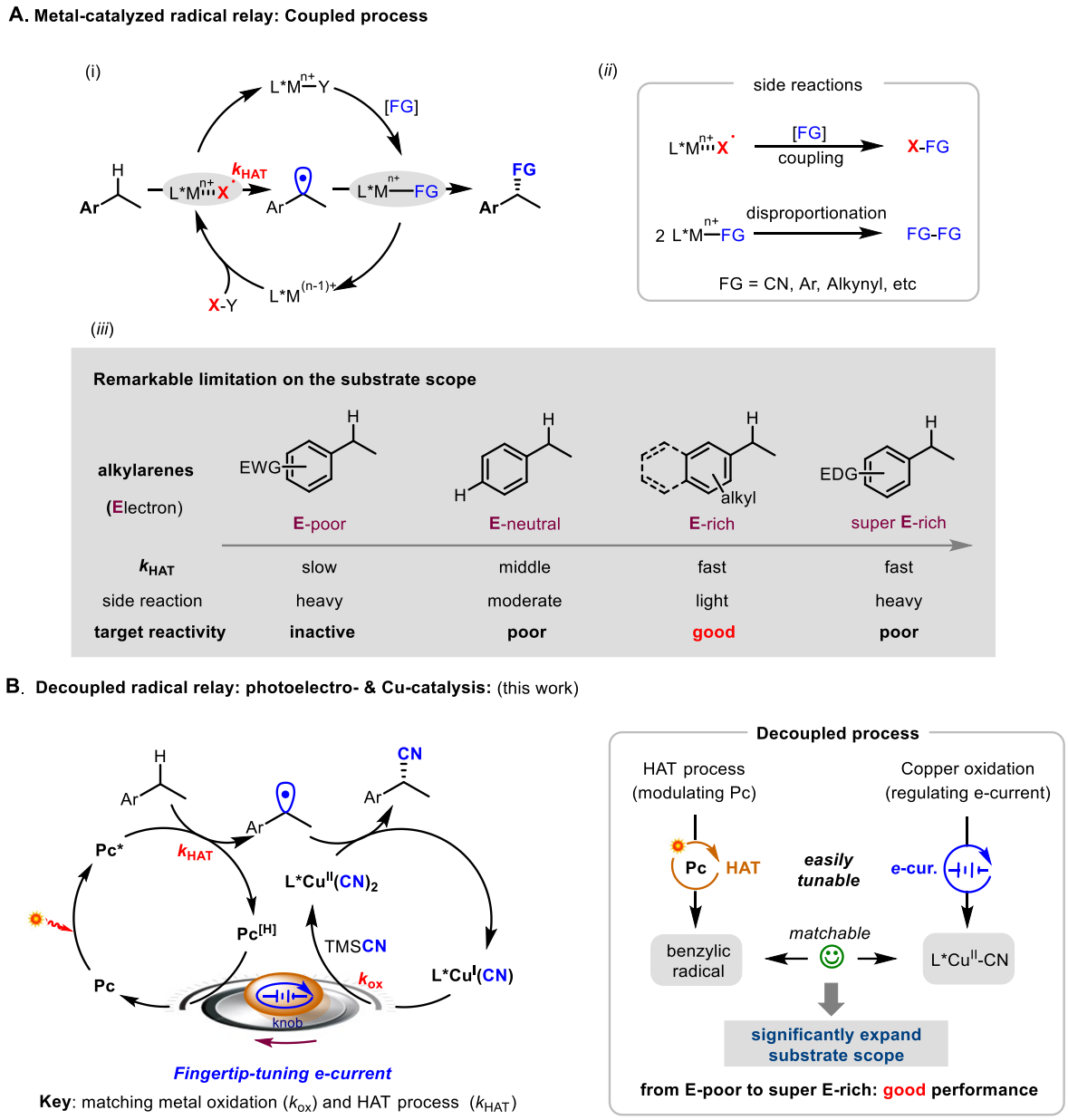

Figure 1. Metal-catalyzed asymmetric functionalization of benzylic C-H bonds. A. Metal-catalyzed radical relay. **B.** Decoupled radical relay strategy for copper-catalyzed asymmetric C-H cyanation by introducing electrophotochemical process.

Electrochemical oxidation is recognized as a compelling alternative to traditional reagent-based oxidations[31-35], wherein protons serve as the terminal oxidant with H_2 as the sole stoichiometric byproduct. Moreover, the reaction could be exquisitely tuned by dialing in the current or electrode potential. We envisioned that the decoupled radical relay would benefit from using such technique. More importantly, it also has the potential to control the Cu(II)/Cu(I) speciation in order for matching the significantly substrate-dependent benzylic radical formation as well as avoiding oxidative homocoupling of nucleophiles (Figure 1B, right).

Results and Discussion

Optimization of the reaction conditions. E-neutral butylbenzene **1a**, showing low reactivity in our previous method involving coupled radical relay (24% yield, 89% ee)[18], was used to test our aforementioned hypothesis with bisoxazoline (Box) **L1** and $Cu(CH_3CN)_4BF_4$ as catalyst, under constant current electrochemical conditions with reticulated vitreous carbon (RVC) as anode and Pt/Ti as cathode in undivided cell; and an array of anthraquinone-type photosensitizers were employed as Pc (Figure 2A), which was demonstrated as the efficient photocatalyst for the asymmetric benzylic C-H trifluoromethylation[36]. Excitingly, the reactions were indeed proceeded smoothly through this decoupled radical relay process, and 2-chloro-anthraquinone (AQ^{Cl}) was proven to be the optimal one to deliver the desired product in 90% yield and 78% ee. Comparable yield was observed with AQ^{CF3}, and slightly lower yields were obtained in the presence of AQ^{H} or AQ^{Me}, while AQ^{OMe} and AQ^{S} (s = SO_2NMe_2) were ineffective Pc under these conditions. Notably, the applied current has substantial impact on the reactivity. The best result (90% yield, 78% ee) was given at 2.5 mA, while increasing or decreasing the current gave diminished yields. Such apparent correlation between applied current and reactivity primarily indicates the importance of matching L*Cu(II)$(CN)_2$ generation with the HAT step (Figure 1B), which also lent preliminary support on our hypothesis for modulating the reactivity by simply tuning the applied current. Finally, when **L2**[37] was used in replacement of **L1**, the reaction provided a slightly higher enantioselectivity (84% ee) in a satisfied yield (83%).

The high reactivity of **1a** prompted our efforts to examine other unsuccessful substrates using the existing methods. With the present decoupled radical relay, excitingly, asymmetric cyanation of electron-deficient alkylarene **1b** did occur to produce product **3** in 47% with 87% ee under an identical condition (Figure 2B). The reactivity is also dependent on the applied current, with the optimal yield observed at 2 mA (54% yield and 87% ee). The lower yield is presumed to arise from the slower HAT for **1b** than that of **1a**. More electron-deficient AQ Pcs were evaluated to increase the reactivity, and

we observed that reaction with AQ^{CF3} gave a much better yield (85% yield, 87% ee). Although AQ^{dCF3} exhibits inferior catalytic activity under identical conditions (77%, 87% ee), high yield is recovered by increasing the current from 2 mA to 3 mA (83% yield, 87% ee).

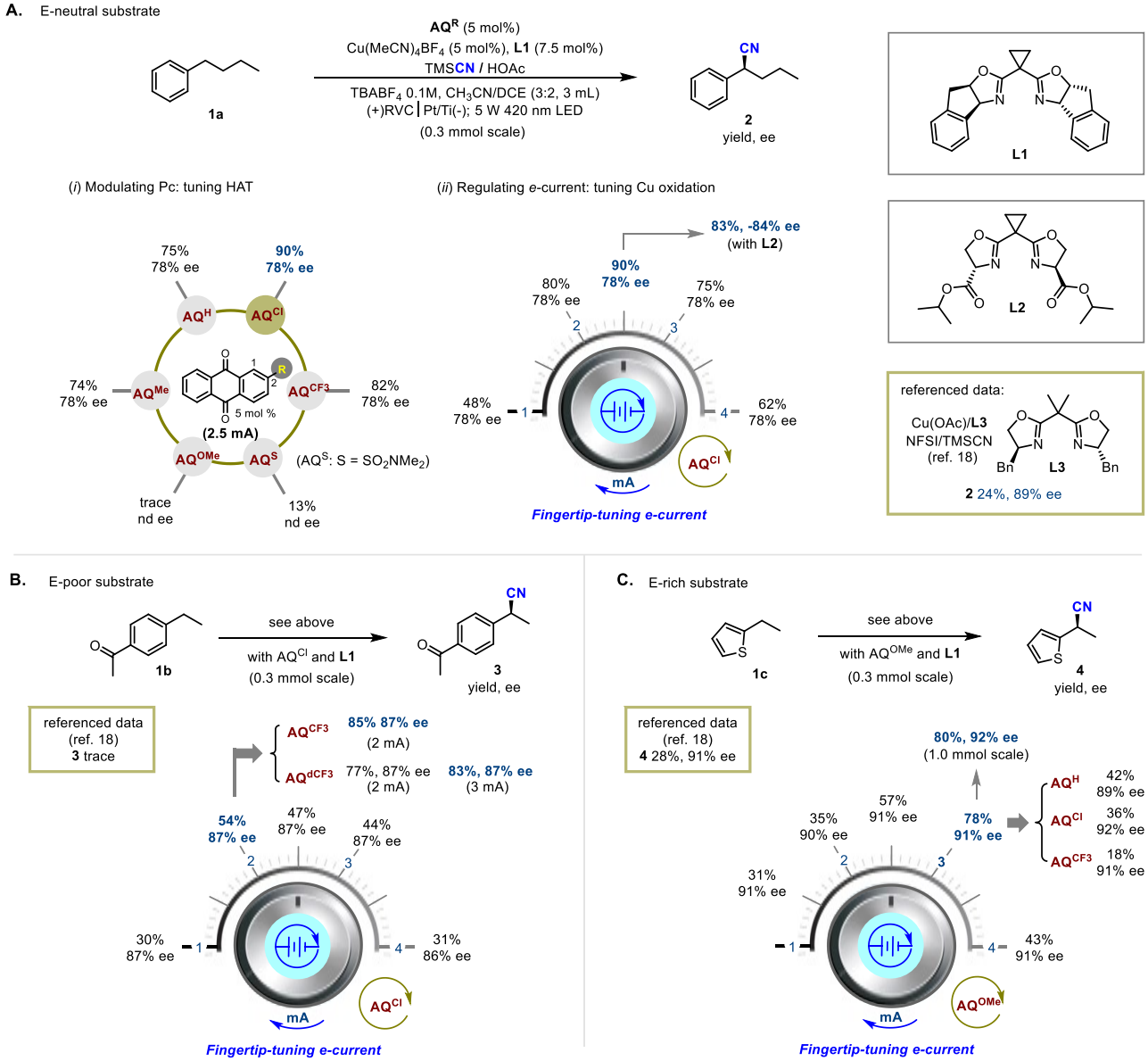

Figure 2. Optimization reaction conditions. A. E-neural substrate. **B.** E-poor substrate. **C.** E-rich hetero-arene substrate. All the reactions were conducted at 0.3 mmol, and the yield was determined by crude ^{1}H NMR, and the enantioselective excess (ee) value was determined by high-performance liquid chromatography (HPLC). AQ^{dCF3} = 2,7-ditrifluoromethyl anthraquinone. Referenced data was obtained from the procedure in ref. 18.

Although E-rich alkylarenes typically demonstrate superior reactivity than E-neutral and E-poor analogues under the previous coupled radical relay conditions, low yields are still observed for many super E-rich alkylarenes, particularly for the super E-rich heterocycles (e.g., 2-ethylthiophene **1c**, 28%

yield, 91% ee; Figure 2C). We reasoned that the associated alkyl radical was prone to be oxidized to carbocation intermediate in the presence of strong chemical oxidant, resulting in many side reactions as opposed to the desired radical cyanation. With the current protocol, we were delighted to find that the reaction of **1c** proceeded smoothly with AQ^{OMe} as Pc and an applied current of 3 mA (78% yield, 91% ee). Notably, a similar result was obtained when the reaction was conducted in 1.0 mmol scale (80% yield, 92% ee). Reactions with other Pcs, such as AQ^{H}, AQ^{Cl} and AQ^{CF3}, provided the desired product in much lower yields, while the substrate **1c** was completely consumed. These reactions highlight the merits of using such *decoupled radical relay catalysis* that the character of HAT acceptor and concentration of radical trap could be modulated separately to achieve a good reaction performance. Moreover, the merger with electrochemical oxidation also allows one to dial in a minimally enough potential to avoid side reactions, such as overoxidation of benzylic radicals.

Mechanistic insight.

The unprecedently high efficiency of the present method for enantioselective benzylic C-H cyanation prompted several efforts to gain more mechanistic insights before evaluating the substrate scope. First, Stern-Volmer fluorescence quenching experiments revealed that the excited photosensitizer could be quenched by butylbenzene **1a**, but not by *tert*-butylbenzene, lack of benzylic C-H bond (Figure 3A-*i*). These results suggested that the **1a** might react with excited Pc through hydrogen atom transfer as opposed to electron transfer since the oxidation potential of *tert*-butylbenzene (E_p^{ox} = 1.90 V vs $Fc^{0/+}$) is slightly lower than that of **1a** (E_p^{ox} = 1.99 V vs $Fc^{0/+}$). Monitoring the anodic potential during bulk electrolysis of **1a** indicated that the applied anodic potential over the reaction is less than 0.8V vs $Fc^{0/+}$, which is much lower than the oxidation potential of **1a** (E_p^{ox} = 1.99 V vs $Fc^{0/+}$). Thus, the sequential single electron transfer (SET) to the anode and proton transfer (PT) pathway for C-H substrate activation could be ruled out. Meanwhile, the reaction of substrate **5** bearing a cyclopropyl group afforded the desired nitrile **6** as the sole product in 85%

yield with 79% ee (Figure 3B). In contrast, Zhang and coworkers reported that substrate **5** was converted to the ring-opening product **7** through a SET pathway[38]. Collectively, these results suggested that HAT from alkylarene to the excited ^{3}AQ* accounted for the C-H activation, generating the key benzylic radical intermediate. The comparable KIE observed in both competitive (KIE = 2.1) and parallel (KIE = 1.8) reactions of **1d** and deuterium-labelled **1d-*d*$_2$** reveal that HAT contributes to rate-determining step (Figure 3C). Moreover, Stern-Volmer fluorescence quenching experiments with other Pcs reveal that k_{SV} in the presence of **1a** follows the sequence of $AQ^{dCF3} > AQ^{CF3} > AQ^{Cl} > AQ^{Me} > AQ^{OMe}$ (Figure 3A-*ii*), which also demonstrates their relative reactivities for hydrogen atom abstraction from C-H substrates and provides an important guideline to choose the photocatalyst for different C-H substrate. For example, the more electron-deficient AQ (e.g., AQ^{dCF3} and AQ^{CF3}**)** is preferred for the E-poor alkylarenes (e.g., **1b**), and the less electron-deficient AQ (e.g., AQ^{Me} and AQ^{OMe}) for E-rich substrates (e.g., **1c**).

Cyclic voltammetry analysis reveals that the oxidation potential of L*Cu^{I}CN (E_p^{ox} = 0.11 V vs $Fc^{0/+}$) is much higher than that of the reduced AQ ($AQ^{X}H$ radical, Figure 3D), suggested that the electro-oxidation of this reduced AQ (k_{ox}^2) is prior to the Cu(I) oxidation (k_{ox}^1). Based on these results, we proposed that the reaction constitutes two catalytic cycles as described in Figure 3E. The electrophoto-catalytic cycle contributes to the C-H bond activation to produce the benzylic radical intermediate (bottom), while the copper-catalyzed processes account for the radical functionalization to deliver the final product (top). Such hypothesis was further evidenced by time courses of the standard reaction of **1e** at different applied current (Figure 3F). The reaction at 1.0 mA shows a significant induction period (left), during which only trace amount of the desired product was detected, along with continuous consumption of alkylarene. The anodic potential in this time period (zoom A) is lower than the onset oxidation potential of L*Cu^{I}CN (E_{onset}^{ox} = -0.1 V, pink line) but sufficient to re-oxidize the reduced AQ^{Me} (E_{onset}^{ox} = -0.85 V, pink line). We speculated that HAT took place to

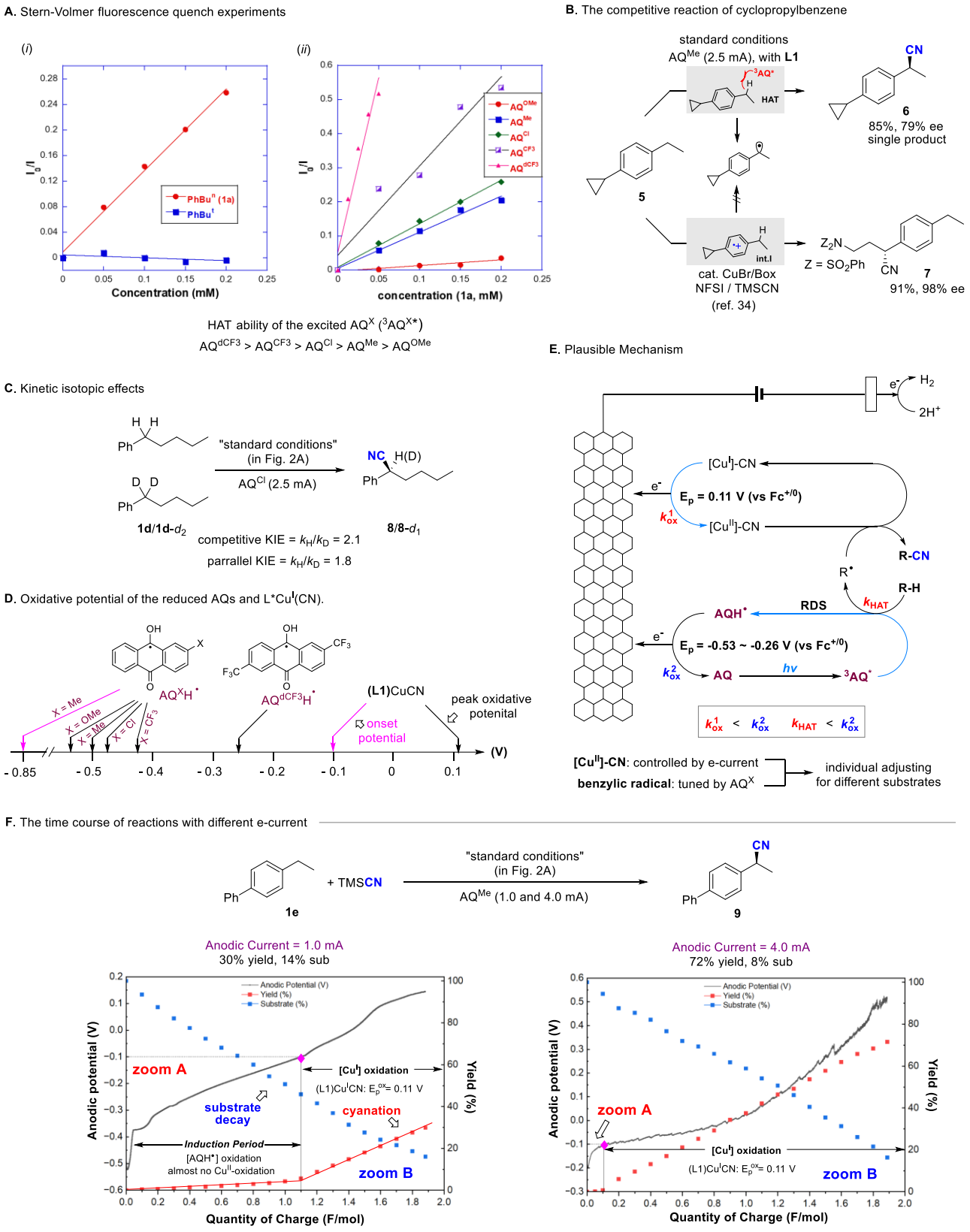

Figure 3. Mechanistic studies. A. Stern-Volmer fluorescence quenching experiments. **B**. The competitive reactions of *p*-cyclopropyl ethylbenzene. **C**. Kinetic isotopic effect. **D**. Oxidative potential of the reduced AQ. **E**. The plausible mechanism. **F**. The time course of reactions at 1.0 mA and 4.0 mA e-current.

generate benzylic radical intermediate, which then underwent various side reactions due to the lack of L*$Cu^{II}(CN)_2$. When the applied anodic potential is sufficient to oxidize L*$Cu^{I}CN$ to generate

$L^*Cu^{II}(CN)_2$ for the productive radical capture (zoom B), the substrate was mainly converted to the desired product after the induction period. In this case, the long induction period with the heavy substrate consumption led to the poor yield (30%). Similar phenomenon was observed for the reaction performed at 4.0 mA, whereas the induction period was significantly shortened and the applied anodic potential raise to -0.1 V vs $Fc^{0/+}$ after only passing 0.1 F/mol. Accordingly, much higher yield was obtained in this case (72%). Taking together, the success of such *decoupled radical relay catalysis* is attributed to the ability to separately modular control of different elementary steps. For instance, electron-deficient AQ could be employed as Pc for electron-poor alkylarenes to effectively active C-H bond; the Cu(II)/Cu(I) speciation could be modulated via simply tuning the applied current to match the rate for benzylic radical formation.

Substrates scope of alkylarene.

Our efforts were then made to evaluate the substrate scope. As shown in Figure 4A, various alkylbenzenes and their derivatives were demonstrated as suitable substrate for asymmetric benzylic C-H cyanation, where AQ^{Cl} acted as an efficient photosensitizer to deliver the corresponding products **2**, **10**-**14** in good to excellent yields (78-94%) and enantioselectivities (81-87% ee). Notably, substrates bearing functional groups, such as esters (**12**-**13**) and amides bearing NH group (**14**), were compatible to the current conditions. For the halogen-substituted alkylarenes, the desired products **15**-**16** were obtained in good yields and ee values with AQ^{Me} or AQ^{Cl} as Pc, respectively. Moreover, alkylarenes bearing the oxidation sensitive groups, such as boronic ester (**17**) and silane (**18**), were also suitable substrate for the reaction with these functional groups survived. It is worth-noted that all these substrates (**2, 10**-**18**) provided poor reactivity under our previous coupled radical relay conditions with NFSI as terminal oxidant. Moreover, comparable yields and enantioselectivity were also observed for a number of substrates (**9**, **19**-**22**) that worked well using the previous method[18]. Notably, compared to *p*-*tert*-butyl ethylbenzene (**21**), introducing an acetoxy group to the β-carbon

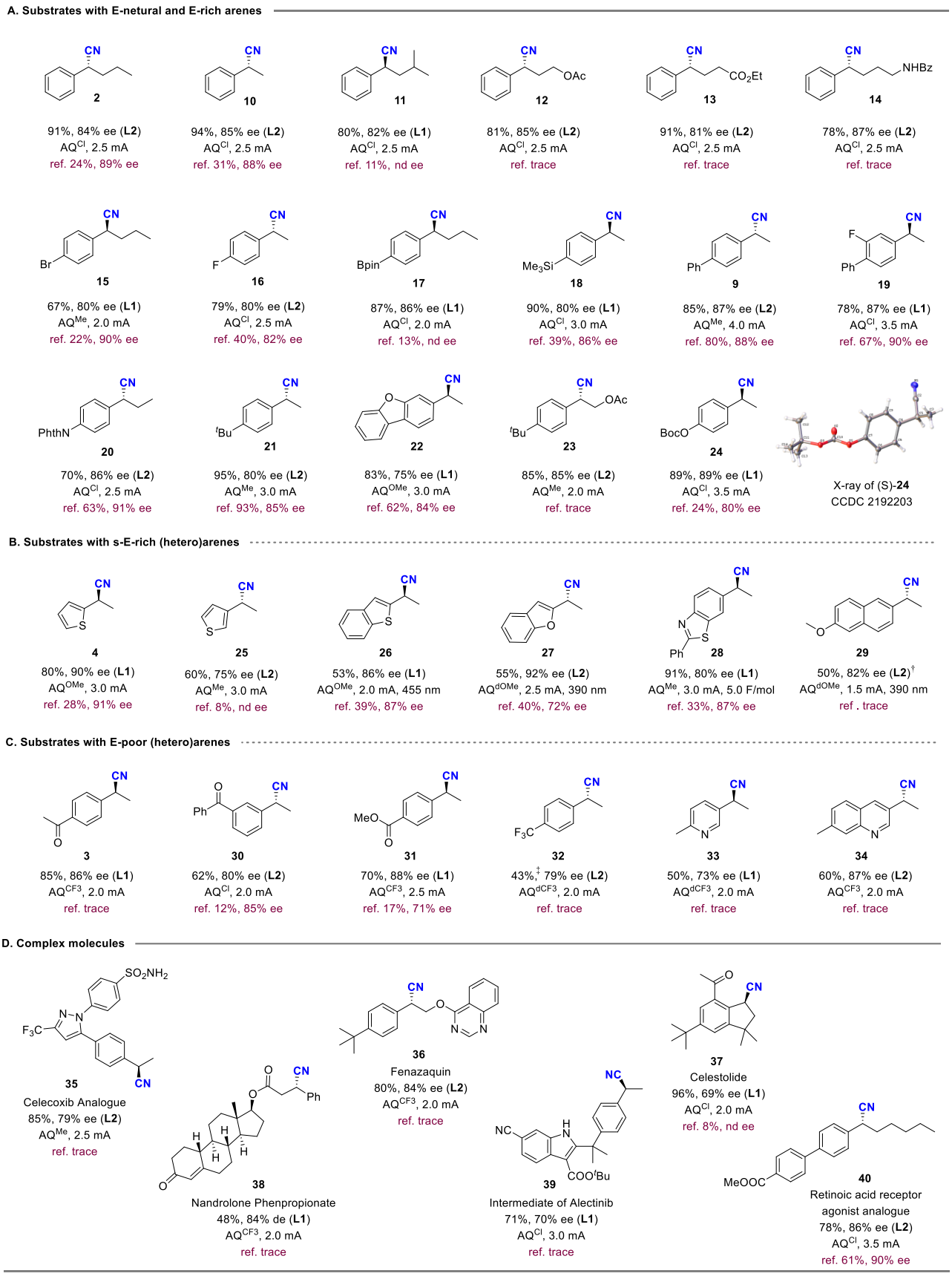

Figure 4. Substrate scope on the asymmetric benzylic C-H cyanations. The reaction was conducted at 0.3 ~ 0.5 mmol scale with the same condition as Figure 2A with the selected AQ^{X}, unless the specific mentioned in some cases. The isolated yield was given. The referenced yield was determined by the crude ^{1}H NMR (see the Supplementary Materials). †39% starting material was recovered. ‡ ^{1}H NMR yield with *p*-Me_2N-$C_6H_4CO_2Et$ as internal standard. AQ^{dCF3} = 2,7-ditrifluoromethyl anthraquinone. AQ^{dOMe} = 2,7-dimethoxyl anthraquinone.

atom remarkably diminish the reactivity using the previous method due to inductive effect (**21**, 93% *versus* **23**, trace), while the reaction via the present decoupled radical relay could afford the desired product **23** in an excellent yield (85%) with 85% ee. In addition, the previous method generates strong acidic bisbenzenesulfonimide as a stoichiometric byproduct from NFSI, making substrate bearing acid sensitive Boc-protecting group incompatible. In contrast, the reaction proceeded smoothly under the electrophotochemical process, giving the desired product **24** in excellent yields and enantioselectivity. The absolute stereo-configuration of the products was unambiguously confirmed by the X-ray crystal structure of (S)-**24**.

As mentioned in Figure 2B, our previous method is not applicable to many E-rich alkylarenes and alkyl heteroarenes, possibly due to the overoxidation. Using the present electrophotochemical protocol, we were pleased to find that the use of less electron-deficient AQ^{Me} and AQ^{OMe} as Pcs could substantially alleviate the over-oxidation, and various pharmaceutically relevant super E-rich heteroarenes, such as thiophene, benzothiophene, benzofuran, benzothiazole, were suitable substrates to furnish the enantio-enriched nitriles **4**, **25**-**28** in moderate-to-good yields with good enantioselectivities. In addition, as a key precursor of Naproxen, product **29** was obtained in moderate yield (50% yield, 82% ee), wherein the employment of the much less electron-deficient AQ^{dOMe} is crucial to avoid over-oxidation of the E-rich 6-ethyl-2-methoxynaphthene.

Further efforts were then shifted to the E-poor alkylarenes, which are generally inert in our previous catalytic system. As shown in Figure 3C, E-poor substrates bearing ketone and carboxylic ester were examined by using electron-deficient AQ^{Cl} and AQ^{CF3}, and the reactions proceeded smoothly to give products **3**, **30**-**31** in good yields (62-85%) and good enantioselectivities (80-88% ee). For the CF_3-substituted ethylbenezene, the more electron-deficient AQ^{dCF3} was required to give **32** in moderate yield. Moreover, the alkyl pyridine and quinoline were also proven to be effective candidates for the asymmetric benzylic C-H cyanation to produce **33**-**34** in acceptable results.

The electrophoto- and copper-catalyzed protocol is also applicable for selective late-stage cyanation of bioactive compounds and their derivatives (Figure 4D). For Celecoxib analogue containing pyrazole and sulfonamide (SO_2NH_2) moieties, the reaction proceeded smoothly using AQ^{Cl} to afford the related nitrile **35** in 85% yield with 79% ee. Fenazaquin containing quinazoline was also compatible to the reaction conditions, the corresponding product **36** was obtained in 80% yield with 84% ee. The reaction with Celestolide as substrate also proceeded well to yield **37** in excellent yield. In addition, the present asymmetric cyanation procedure was applicable to the complex molecules containing steroid (e.g., Nandrolone phenylpropionate) and indole (e.g., intermediate of Alectinib) structures, allowing direct access to products **38** and **39** effectively. Finally, the E-poor biphenyl substrate, a retinoic acid receptor agonist analogue, exhibited good reactivity and enantioselectivity to afford product **40**.

Conclusion

In summary, we have described a decoupled radical relay for the highly efficient and enantioselective benzylic C-H cyanation, which was demonstrated to remarkably expand substrate scope, spanning from E-poor to super E-rich alkylarenes. The merger of electrophotochemical oxidation and copper-catalyzed enantioselective radical cyanation enables to modularly control different elementary steps to match with each other. More importantly, the decoupled radical relay catalysis opens a new avenue for future development of other C-H functionalizations of high efficiency and selectivity.

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Data availability

The data supporting the finding of this study are available in this article and the Supplementary Information. Crystallographic data for structure **24** has been deposited at the Cambridge Crystallographic Data Centre, under deposition no. CCDC 2192203. Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/

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Competing interests

The authors declare no competing interests.

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