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Aromatic compounds are among the most fundamental feedstock chemicals, with global production on a million metric ton scale annually. The development of practical methods to increase the valorization of these abundant substances is thus in continuing demand. As classical transformations based on aromatic compounds, C–H functionalization such as Friedel–Crafts alkylation and Minisci-type reaction constitutes a straightforward strategy to incorporate diverse functionalities on the aromatic skeletons.¹ In a complementary fashion, dearomatization converts planar aromatics into three-dimensional molecules with increased sp^3 -hybridized carbons and stereocenters by disturbing the aromaticity (Scheme 1, top). Notable strategies include Birch reduction, oxidative dearomatization of phenols, arene–alkene photocycloadditions, and others.² Both types of transformations have found broad applications in areas ranging from pharmaceuticals and agrochemicals to materials science.³ Despite the great achievements made to date, the utilization of a single catalyst to promote tunable C–H functionalization and dearomatization processes from the same starting materials is underexplored. Elegant reports mainly

Tunable C–H functionalization and dearomatization enabled by an organic photocatalyst†

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C–H functionalization and dearomatization constitute fundamental transformations of aromatic compounds, which find wide applications in various research areas. However, achieving both transformations from the same substrates with a single catalyst by operating a distinct mechanism remains challenging. Here, we report a photocatalytic strategy to modulate the reaction pathways that can be directed toward either C–H functionalization or dearomatization under redox-neutral or net-reductive conditions, respectively. Two sets of indoles and indolines bearing tertiary alcohols are divergently furnished with good yields and high selectivity. The key to success is the introduction of isoazatruxene ITN-2 as a novel photocatalyst (PC), which outperforms the commonly used PCs. The ready synthesis and high modularity of isoazatruxene type PCs indicate their great application potential.

involve the substrate control.⁴ The difficulties might arise from multiple functions required for one catalyst.

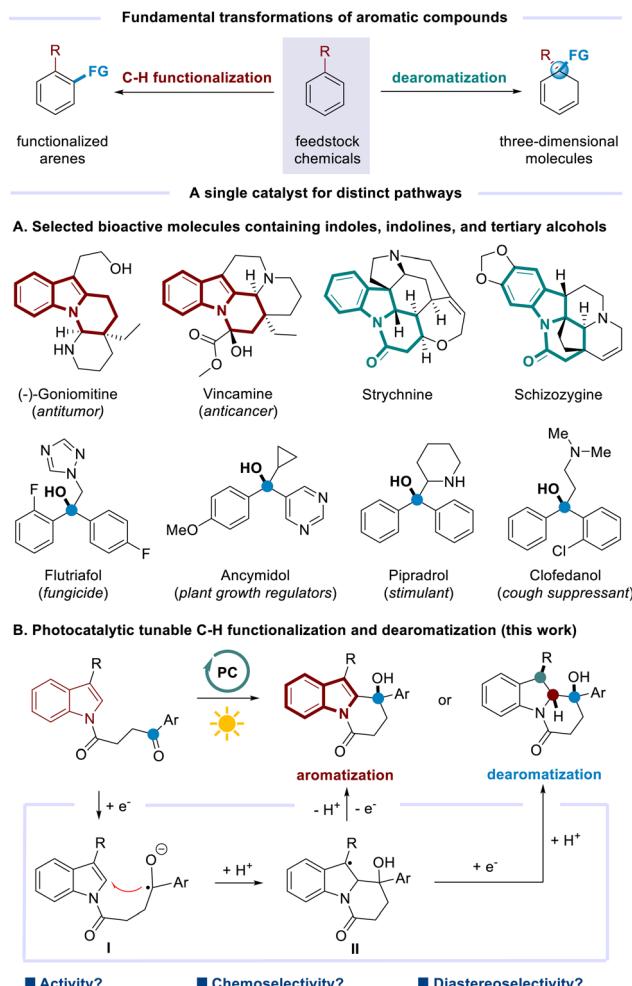
On the other hand, indoles and indolines are privileged scaffolds in alkaloid natural products and biologically active molecules.⁵ Meanwhile, tertiary alcohols are important structural units that widely exist in a variety of biologically active natural products, pharmaceuticals, and agrochemicals (Scheme 1A).⁶ The molecules containing both indole/indolines and tertiary alcohols might have great potential applications. In this regard, divergent syntheses of such compounds are highly desirable. We questioned whether photoredox catalysis⁷ could engineer C–H functionalization and dearomatization selectively to afford two sets of targets in a catalytic and divergent fashion. It is envisioned that the excited photoredox catalyst (PC) could donate an electron to the ketone moiety. The resultant ketyl radical⁸ would add to indole nuclei (*via* I), which is followed by protonation. Then, intermediate II might undergo single-electron oxidation to achieve aromatization upon loss of a proton. Alternatively, single-electron reduction of II would occur instead to deliver dearomatization products after protonation (Scheme 1B). Although conceptually simple in design, this strategy must contend with problems involving both reactivity and selectivity. Specifically, SET reduction of the ketone moieties is challenging, owing to the significantly negative reduction potentials [e.g. $E_{1/2}^{\text{red}} = -2.11$ V vs. SCE for acetophenone].⁹ A powerful photocatalyst is required to be capable of participating in both SET reduction and SET oxidation events for the C–H functionalization process as well as sequential SET reductions for the dearomatization process. In addition, the reaction might encounter the chemoselective

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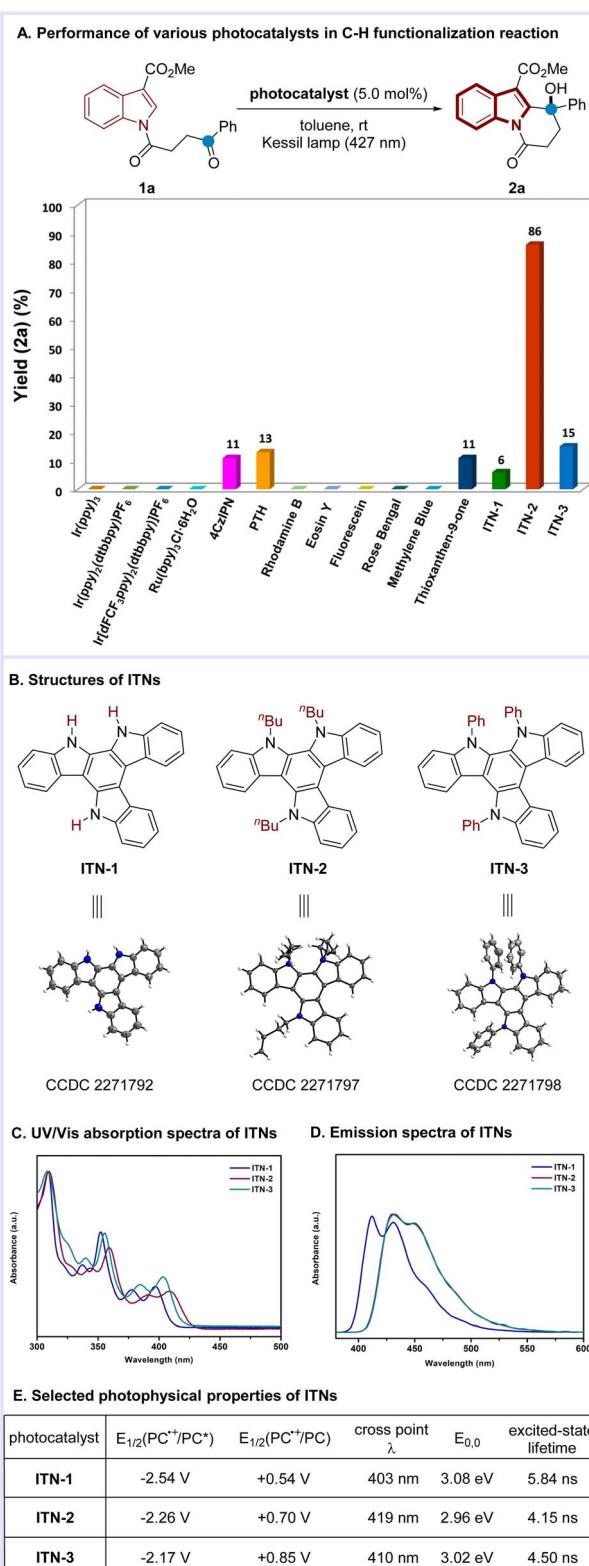


Scheme 1 Tunable C–H functionalization and dearomatization.

competition from reduction¹⁰ or pinacol C–C coupling.¹¹ Furthermore, the diastereoselective issues should be addressed when multiple stereocenters are generated.

Herein, we describe the first photocatalytic method for selective C–H functionalization and dearomatization by operating a distinct mechanism. Starting from the same indole-tethered ketones, intramolecular alkylation and reductive dearomatization have been achieved under redox-neutral and net-reductive conditions, respectively. Two sets of important nitrogen-containing heterocycles are obtained in good yields and excellent selectivity. A new organic photocatalyst, isoazatruxene ITN-2, is discovered to guarantee the success.

Our study was initiated with the investigation of C–H functionalization reaction using indole derivative **1a** as the substrate under irradiation with a Kessil lamp (Scheme 2A). Due to the significantly negative reduction potential of a ketone moiety, the highly reducing $\text{Ir}(\text{ppy})_3$ ($E_{1/2}^{\text{M}^+/\text{M}^*} = -1.73 \text{ V vs. SCE}$)^{7c} was first attempted. However, this photocatalyst failed to give the desired C2-alkylation product **2a**, which confirmed that direct SET reduction of a ketone moiety by excited-state $\text{Ir}(\text{ppy})_3^*$ is not feasible. Next, the frequently-used transition-metal-based and



Scheme 2 Performance of various photocatalysts in C–H functionalization and characterization of ITNs.

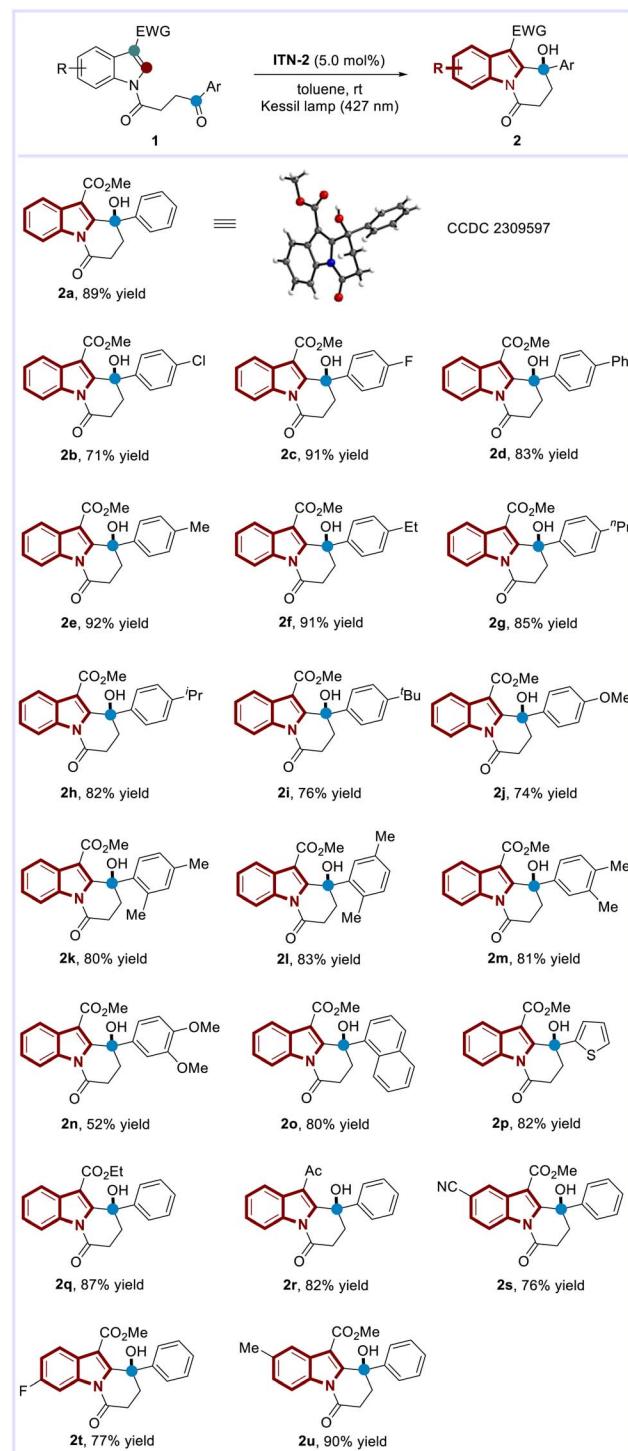
organic photocatalysts including $\text{Ir}(\text{ppy})_2(\text{dtbbpy})\text{PF}_6$, $\text{Ir}[(\text{FCF}_3\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$, $\text{Ru}(\text{bpy})_3\text{Cl}_2 \cdot 6\text{H}_2\text{O}$, 4CzIPN [1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene], PTH (*N*-

phenylphenothiazine), rhodamine B, eosin Y, fluorescein, rose bengal, methylene blue, and thioxanthen-9-one were systematically screened, unfortunately all leading to poor results (<15% yield).

Given our interest in organic electronic materials,¹² we turned attention to isoazatruxenes (ITNs), which can be readily synthesized *via* cyclotrimerization of indoles.¹³ Despite the easy access, the application of ITNs in photocatalysis remained elusive. Thus, the photophysical and electrochemical properties of isoazatruxenes (ITNs) possessing varied substituents on the nitrogen atoms (ITN-1: R = H; ITN-2: R = ⁿBu; ITN-3: R = Ph) were measured and are summarized in Scheme 2B (Fig. S1–S18†).¹⁴ In addition, DFT calculations (B3LYP-D3(BJ)/def2-SVP) were performed to obtain the HOMO/LUMO energies of ITNs (Fig. S20†).¹⁴ While ITN-1 shows weak absorption in the visible region, the introduction of alkyl- or aryl groups results in a bathochromic shift with respect to the unsubstituted counterpart based on the ultraviolet-visible (UV-vis) spectroscopy, possibly due to the inductive effect of the alkyl groups and the conjugative effect of the aryl groups (Scheme 2C). Electron-excitation analyses on the basis of TD-DFT calculations suggested that the S₀-to-S₁ excitation of ITNs was mainly contributed by the electron transition from the corresponding HOMOs to LUMOs. The calculated vertical excitation energies of ITNs qualitatively reproduced the bathochromic shift order of the highest absorption peaks (ITN-1 < ITN-3 < ITN-2) (Fig. S21†).¹⁴ Notably, ITNs exhibit highly negative excited state reductive potentials (spanning from -2.17 to -2.54 V vs. SCE) as well as comparable excited-state lifetimes (4.15–5.84 ns), which allowed them to be promising candidates for promoting the above transformation (Scheme 2E).

To our delight, the C2 alkylation proceeded when ITNs were used as the photocatalysts. Particularly, ITN-2 bearing ⁿbutyl substituents on the nitrogen atoms outperformed all the other photocatalysts, providing the corresponding polycyclic indole **2a** in 86% yield with toluene as the solvent. The superior catalytic efficiency of ITN-2 in comparison with other ITNs might correspond to its enhanced visible-light absorption, which resulted in better visible photon harvesting. Furthermore, control experiments demonstrated that the reaction requires a photocatalyst and visible light.¹⁴

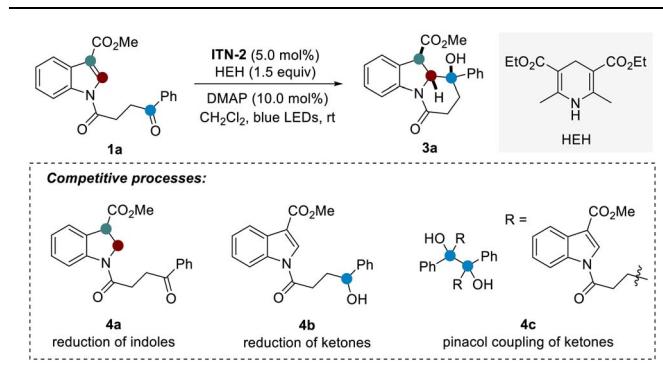
Having determined the optimal reaction conditions, we next examined the scope of C–H functionalization. As shown in Scheme 3, the tethered aromatic ketones bearing either electron-withdrawing or electron-donating substituents (-Cl, -F, -Ph, -Me, -Et, -ⁿPr, -ⁱPr, -ⁿBu, -OMe) on the *para*-position of arenes were well tolerated, delivering the corresponding polycyclic indoles (**2b**–**2j**) in good to excellent yields (71–92%). The structure of **2a** was determined unambiguously by X-ray crystallographic analysis.¹⁴ Interestingly, the more challenging substrates with multi-electron-donating groups [2,4-(Me)₂, 2,5-(Me)₂, 3,4-(Me)₂, 3,4-(OMe)₂] that possess lower reduction potentials could be accommodated, highlighting the power of ITN-2 (**2k**–**2n**, 52–83% yields). Moreover, both naphthyl and thiienyl-derived ketones were converted to their corresponding polycyclic indoles bearing tertiary alcohols (**2o** and **2p**) with high efficiency under the catalysis of ITN-2. This method is also compatible with the substrates bearing ethyl ester or acetyl



Scheme 3 Substrate scope for C–H functionalization.^{a,b} ^aReaction conditions: a solution of ITN-2 (5.2 mg, 5.0 mol%) and **1** (0.2 mmol, 1.0 equiv.) in toluene (2.0 mL, 0.1 M) was irradiated by a 427 nm Kessil lamp (40 W) at room temperature under a nitrogen atmosphere for 4–36 h. ^bIsolated yield.

groups at the C-3 position of indole skeletons (**2q**–**2r**, 82–87% yields). Finally, the reactions of substrates bearing cyano, fluorine, and methyl substituents at the indole cores also proceeded smoothly, providing **2s**–**2u** in 76–90% yields.

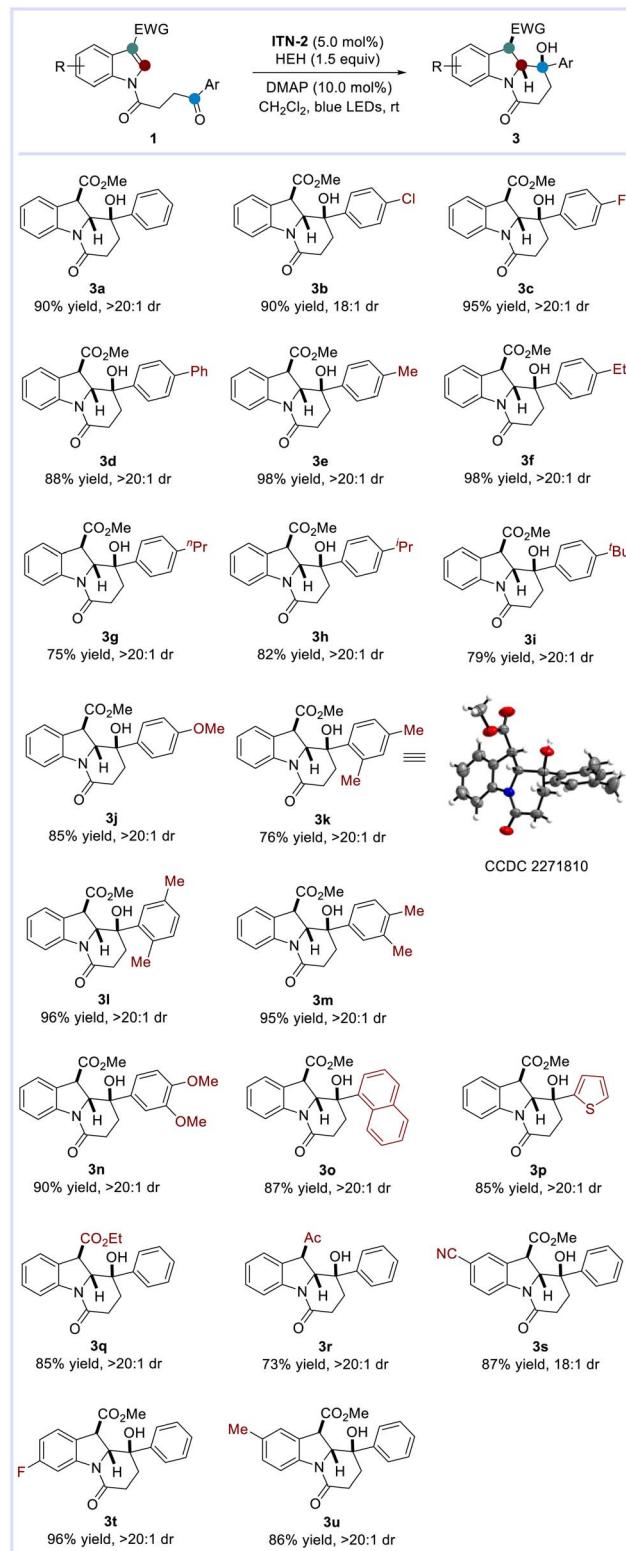


Table 1 Optimization of the reaction conditions for dearomatization^a

Entry	Variations from standard conditions	Yield ^b (%)	Dr ^c
1	None	91 (90) ^d	>20 : 1
2	No DMAP	91	1.7 : 1
3	ITN-1 instead of ITN-2	0	n.d.
4	ITN-3 instead of ITN-2	59	>20 : 1
5	Acetone instead of CH ₂ Cl ₂	37	16 : 1
6	CH ₃ CN instead of CH ₂ Cl ₂	13	n.d.
7	DMSO instead of CH ₂ Cl ₂	8	n.d.
8	DIPEA instead of HEH	45	>20 : 1
9	No ITN-2	0	n.d.
10	No HEH	0	n.d.
11	No light	0	n.d.

^a Reaction conditions: a solution of **ITN-2** (2.6 mg, 5.0 mol%), **1a** (0.1 mmol, 1.0 equiv.), HEH (0.15 mmol, 1.5 equiv.), and DMAP (1.2 mg, 10.0 mol%) in CH₂Cl₂ (1.0 mL, 0.1 M) was irradiated by blue LEDs (30 W) at room temperature under a nitrogen atmosphere for 24 h. ^b Determined by ¹H NMR yield using CH₂Br₂ as an internal standard. ^c Ratios of diastereoisomers were determined by crude ¹H NMR analysis. ^d Isolated yield. n.d. = not determined. DMAP = 4-dimethylaminopyridine. DIPEA = *N,N*-diisopropylethylamine.

Then, we continued to investigate the intramolecular dearomatization of indoles with ketones (Table 1). In fact, this process remains problematic because of energetic barriers caused by aromaticity and competition between dearomatization and reduction or pinacol C–C coupling (**1a** → **4a–4c**). The formation of multiple stereocenters also faces the challenge of diastereoselective control. With *N*-acylated indole derivative **1a** as the model substrate, our optimization revealed that the use of **ITN-2** as the photocatalyst, 4-dimethylaminopyridine (DMAP) as the additive, and Hantzsch ester (HEH) as the reductant in dichloromethane led to the formation of expected dearomatized product **3a** in 90% yield with excellent diastereoselectivity under blue LED irradiation at room temperature (entry 1). Notably, the presence of a catalytic amount of DMAP significantly improved the diastereoselectivity, likely a result of thermodynamic control (entry 2). Consistently, **ITN-1** and **ITN-3** afforded inferior efficiency (entries 3 and 4). Changing dichloromethane to other commonly used solvents such as acetone, CH₃CN, or DMSO resulted in dramatically decreased yields (8–37%) for the desired product **3a** (entries 5–7), demonstrating the important role of solvents. When DIPEA was used as the external reductant instead, the dearomatization reaction also occurred well, albeit with a lower yield of **3a** (entry



Scheme 4 Substrate scope for dearomatization.^{a,b} ^aReaction conditions: a solution of **ITN-2** (5.2 mg, 5.0 mol%), **1** (0.2 mmol, 1.0 equiv.), HEH (0.3 mmol, 1.5 equiv.), and DMAP (2.4 mg, 10.0 mol%) in CH₂Cl₂ (2.0 mL, 0.1 M) was irradiated by blue LEDs (30 W) at room temperature under a nitrogen atmosphere for 12–48 h. ^bIsolated yield. Ratios of diastereoisomers were determined by crude ¹H NMR analysis.



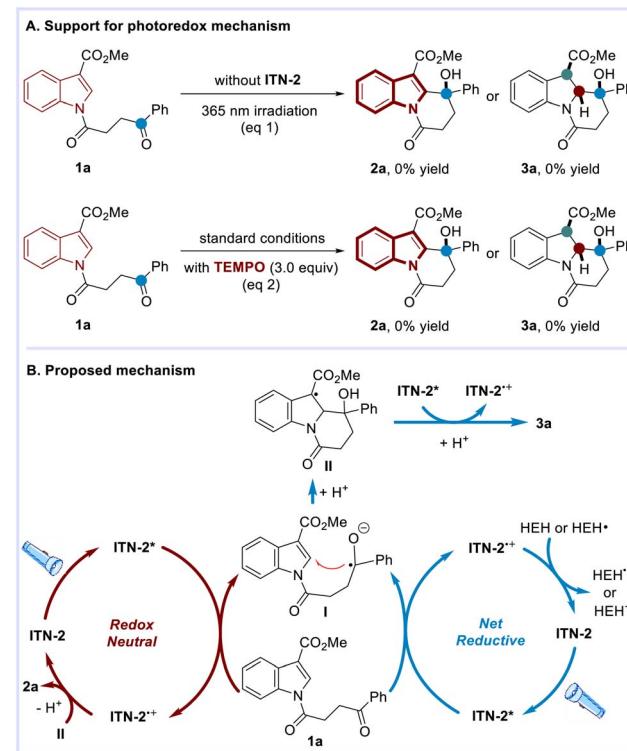
8). Lastly, the control experiments indicated that photocatalyst **ITN-2**, reductant HEH, and visible light are all indispensable (entries 9–11).

With the optimized conditions in hand, we explored the scope of photocatalytic intramolecular dearomatization of indole derivatives with ketones (Scheme 4). It was observed that the aromatic ketones bearing either electron-withdrawing (e.g. 4-Cl, 4-F) or electron-donating [e.g. 4-Me, 4-Et, 4-²Pr, 4-¹Pr, 4-²Bu, 4-OMe, 2,4-(Me)₂, 2,5-(Me)₂, 3,4-(Me)₂, 3,4-(OMe)₂] groups on the arene skeletons were well accommodated. In all cases, highly functionalized benzannulated indolizidines possessing three consecutive stereocenters were furnished in good to excellent yields with remarkable diastereoselectivity (**3a–3n**: 75–98% yields, 18 : 1 → >20 : 1 dr). Similarly, the structure and relative configuration of **3k** were confirmed by X-ray crystallographic analysis.¹⁴ In addition, indole derivatives tethered with naphthyl and thiényl ketones were compatible with this transformation (**3o–3p**: 85–87% yields, >20 : 1 dr). Changing the substituents at the C-3 position of indoles to ethyl ester or acetyl groups also proved feasible (**3q–3r**: 73–85% yields, >20 : 1 dr). Furthermore, the reactions of substrates **1s–1u** containing varied substituents (–CN, –F, –Me) on the indole skeletons occurred smoothly, delivering the desired indolizidines **3s–3u** in good yields with extraordinary diastereoselectivity (86–96% yields, 18 : 1 → >20 : 1 dr).

In order to demonstrate the synthetic practicality, gram-scale syntheses were carried out (Scheme 5). With **ITN-2** as the photocatalyst, the C–H functionalization and dearomatization reactions of substrate **1a** on 4.47 mmol scale were selectively achieved under the optimized reaction conditions, yielding polycyclic indole **2a** and indoline derivative **3a** in 85% yield (1.28 g) and 91% yield (1.36 g), respectively.

Several experiments were performed to probe the possible mechanism (Scheme 6A). First, both reactions were subjected to ultraviolet light irradiation (365 nm) without the addition of **ITN-2**. It was observed neither of the reactions proceeded, thus excluding the operation of the energy transfer mechanism. Upon the addition of TEMPO (2,2,6,6-tetramethylpiperidine *N*-oxyl), the expected transformations were completely inhibited, which suggested the involvement of radicals. Accordingly, the plausible mechanism for photocatalytic C–H functionalization and dearomatization was proposed as exemplified by the reactions of **1a** (Scheme 6B).

Irradiation of **ITN-2** affords its excited state. Oxidative quenching of **ITN-2**^{*} by indole derivative **1a** generates **ITN-2**⁺ and the corresponding ketyl radical (**I**), which is supposed to undergo addition to electron-deficient indole. After protonation, intermediate **II** proceeds diversely in the two transformations. In the C–H functionalization reaction, single-



Scheme 6 Proposed mechanism.

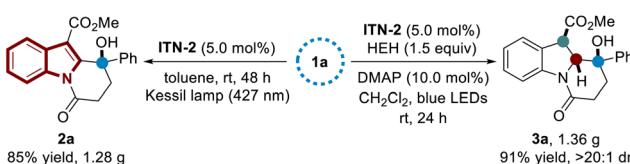
electron oxidation of **II** by **ITN-2**²⁺ delivers aromatization product **2a** upon the release of a proton and completes the catalytic cycle. With respect to the dearomatization reaction, single-electron reduction of **II** by excited state **ITN-2**^{*} occurs instead, yielding the benzannulated indolizidine **3a** after accepting a proton. **ITN-2**²⁺ can be further converted back to **ITN-2** in the presence of an external reductant. While C–H functionalization is a redox-neutral transformation, dearomatization is a net-reductive process requiring a stoichiometric external reductant to turn over the photocatalytic cycle.

Conclusions

In summary, we have developed a photocatalytic protocol to engineer C–H functionalization and dearomatization processes selectively. Crucial to the strategy are the different redox events promoted by a new organic photocatalyst – isoazatruxene **ITN-2**. Under redox-neutral conditions, intramolecular C–H functionalization is directed, providing polycyclic indoles bearing tertiary alcohols in good yields. Under net-reductive conditions, reductive dearomatization of indole derivatives with ketones can be realized instead, in which the corresponding benzannulated indolizidines possessing three consecutive stereocenters are furnished with remarkable diastereoselectivity. We anticipate this study will stimulate the development of novel photocatalysts for previously challenging transformations.

Data availability

All experimental data is available in the ESI.[†]



Scheme 5 Gram-scale reaction.



Author contributions

X. Z. conceived the project. B. A., H. C., J.-L. C., and F. L. performed the experiments under S.-L. Y. and X. Z.'s supervision. C. Z. performed the DFT calculations. B. A., C. Z., S.-L. Y., and X. Z. cowrote the paper.

Conflicts of interest

A patent has been filed on the use of isoazatruxenes and their derivatives in photocatalysis.

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