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RESEARCH ARTICLE

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Asymmetric Dearomatization of Indole Derivatives with N-Hydroxycarbamates Enabled by Photoredox Catalysis

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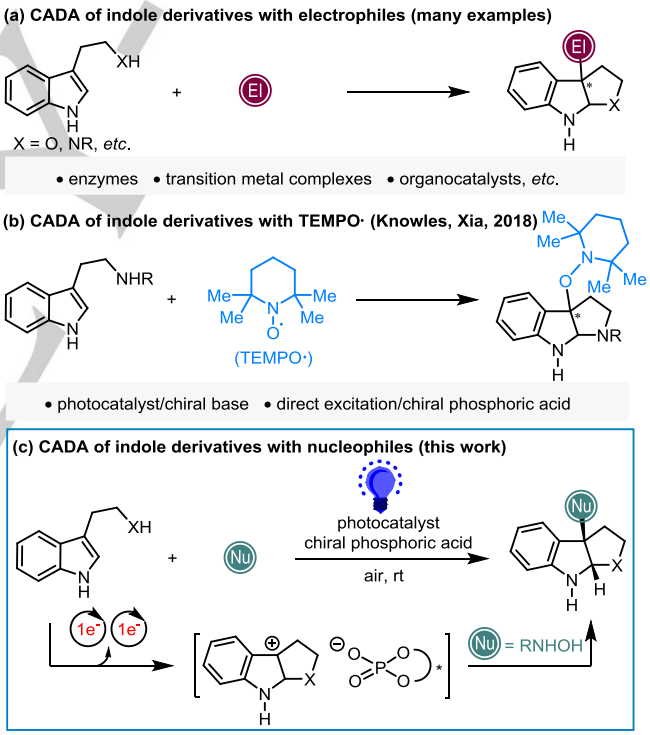
In memory of Professor Dieter Enders

Abstract: Dearomatization of indoles and their derivatives provides efficient synthetic routes for substituted indolines. In most cases, indoles serve as nucleophiles by reacting with electrophiles at the C3 position. Herein, we report an asymmetric dearomatization reaction of indole derivatives that function as electrophiles. The combined utilization of photocatalyst and chiral phosphoric acid in air unlocks the umpolung reactivity of indoles, enabling enantioselective dearomatization of indole derivatives with *N*-hydroxycarbamates as nucleophiles. A variety of optically active fused indolines bearing intriguing oxy-amines were constructed in excellent yields with moderate to high enantioselectivity. As suggested by preliminary mechanistic studies, key to the success is the realization of two sequential SET oxidation of indole derivatives under dual catalysis that can generate the configurationally biased carbocation species while providing the source of stereochemical induction. The current results not only provide an efficient synthesis of highly enantioenriched indoline derivatives, but also offer a novel strategy for further designing asymmetric dearomatization reactions.

Introduction

Indoles, as one of the most important and abundant heteroaromatics, have centuries found broad applications in areas including pigments, fragrances, pharmaceuticals, agrochemicals, and materials science.[1] Of particular note, catalytic asymmetric dearomatization (CADA) reactions of indoles and their derivatives allow easy access to enantioenriched fused indolines, a privileged scaffold in alkaloid natural products and biologically active molecules.[2] There have been many elegant asymmetric dearomatization reactions of indoles, such as Friedel-Crafts type alkylation,[3,4] oxidation,[5] and halogenation[6] in the presence of catalysts including enzymes, transition metal complexes, and organocatalysts. Despite the great achievements made to date, most of these methods exploit the inherent nucleophilicity of indoles by reacting with electrophiles (a, Scheme 1).

Unveiling new reactivity of indole derivatives offers opportunities for complementary asymmetric dearomatization reactions, but still remains a formidable challenge. It is until recently that Knowles and co-workers reported a photocatalytic approach to generate tryptamine radical cations through chiral phosphate base-assisted single electron oxidation.[7] These open-shelled species, which were supposed to interact with a chiral phosphate base *via* hydrogen-bonding interactions, can be further intercepted by the consistent nitroxyl radical TEMPO• to form the alkoxyamine-substituted pyrroloindolines in good yields with high enantioselectivity. The same reaction was achieved in a photocatalyst-free fashion by Xia and co-workers.[8] Mechanistically, excited state TEMPO• acted as a HAT catalyst to deliver the corresponding tryptamine radicals, which were enantioselectively captured by TEMPO• in the presence of chiral phosphoric acid. Notably, both examples elegantly showcased that tryptamines serve as radical species in asymmetric dearomatization reactions (b, Scheme 1).



Scheme 1. Catalytic Asymmetric Dearomatization of Indole Derivatives.

Regarding the expansion to new substrate scope, exploring reactivity of indole derivatives beyond is still highly desirable. However, to the best of our knowledge, we are not aware of any asymmetric dearomatization examples by reversing the inherent reactivity of the indoles to electrophiles through oxidative conditions. The difficulties might arise from both the reactivity and enantioselective control. Herein, we report the first catalytic asymmetric dearomatization reaction of indole derivatives that capitalize on their electrophilic properties upon loss of two electrons. With N-hydroxycarbamates as nucleophiles, good to excellent yields and high enantioselectivity have been achieved

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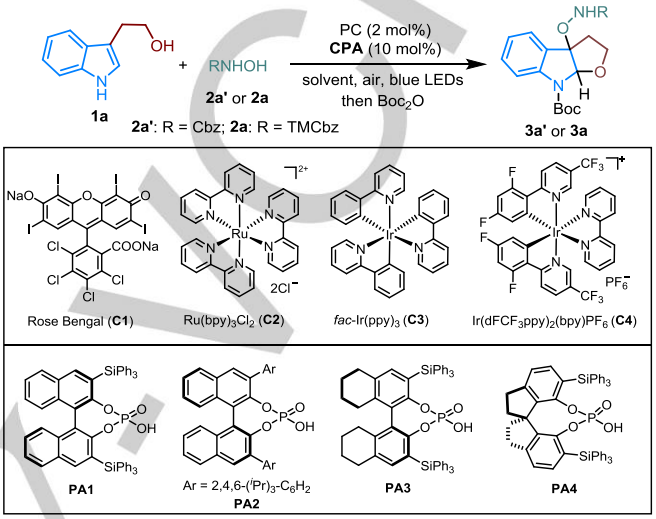
for the fused indoline products via cooperation of a photocatalyst and chiral phosphoric acid (c, Scheme 1).

Results and Discussion

Visible-light photoredox catalysis has been widely employed in organic synthesis to generate reactive species under extremely mild conditions in recent years.[9] However, its applications in asymmetric dearomatization reactions are rare.[10] At the beginning, we noticed that highly reactive nitrosocarbonyl intermediates could be generated catalytically from bench-stable *N*-hydroxycarbamates in the presence of a photocatalyst under air.[11,12] Based on these results, our original design was to explore the natural nucleophilicity of indoles for chiral phosphoric acid-catalyzed[13] asymmetric dearomatization with transient electrophilic nitrosocarbonyl species using visible-light as a mild driving energy. However, the reactions between tryptophol (**1a**) and *N*-hydroxycarbamate (**2a'**) performed under previously described photochemical conditions did not occur at all.[12] Further investigations revealed the desired transformation could only be achieved upon using more oxidizing $Ir(dFCF_3ppy)_2(bpy)PF_6$ as the photocatalyst (entries 1-4, Table 1 and SI). These preliminary results indicated a different mechanism might be operative, which encouraged us to further optimize the reaction conditions. Various parameters including chiral phosphoric acid, *N*-hydroxycarbamate, solvent, and loading of the photocatalyst were next evaluated (entries 5-13, Table 1 and SI). It was found that the utilization of blue LEDs in the presence of $Ir(dFCF_3ppy)_2(bpy)PF_6$ and **PA1** in DME/hexane (3/1) enabled the dearomatization reaction in 98% yield, furnishing furoindoline **3a** with 91:9 *er* under air (entry 13, Table 1). Furthermore, a series of control experiments verified that the chiral phosphoric acid, photocatalyst, light, and air were all essential components (entries 14-17, Table 1).

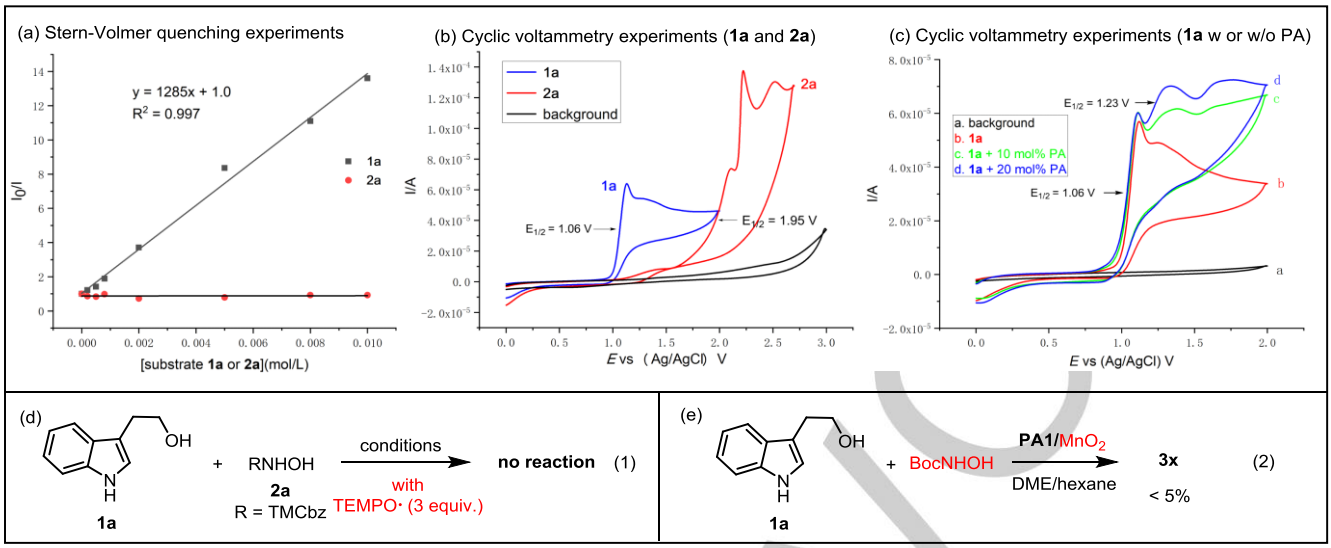
Next, several experiments were performed to shed light on the reaction pathway. Initially, we undertook a series of Stern-Volmer luminescence quenching experiments. The results showed that the excited state of the photocatalyst was only quenched in the presence of tryptophol (**1a**), suggesting that SET oxidation of tryptophol was likely the initiation point of the photoredox catalytic cycle (a, Scheme 2). Subsequent cyclic voltammetry experiments further supported single-electron transfer from tryptophol ($E_{1/2}^{ox}$ = +1.06 V vs. Ag/AgCl in CH_3CN) rather than *N*-hydroxycarbamate (**2a**) [$E_{1/2}^{ox}$(**2a**) = +1.95 V vs. Ag/AgCl in CH_3CN] to **C4*** [$E_{1/2}$(**C4***/ **C4**$^-$) = +1.32 V vs. SCE][14] (b, Scheme 2). In addition, tryptophol is amenable to undergoing a second SET oxidation ($E_{1/2}^{ox}$ = +1.23 V vs. Ag/AgCl in CH_3CN). A particularly notable finding was an enhanced peak for the second SET oxidation when the amount of diphenyl phosphoric acid was increased (c, Scheme 2). Together with the aforementioned control experiment demonstrating the requirement of CPA for both reactivity and enantioselectivity, CPA is proposed to participate in assisting the second SET oxidation of tryptophol. Different from previous reports,[7,8] in our hands, the addition of TEMPO• quenched the photoexcited **C4*** directly and

Table 1. Optimization of the Reaction Conditions.[a]

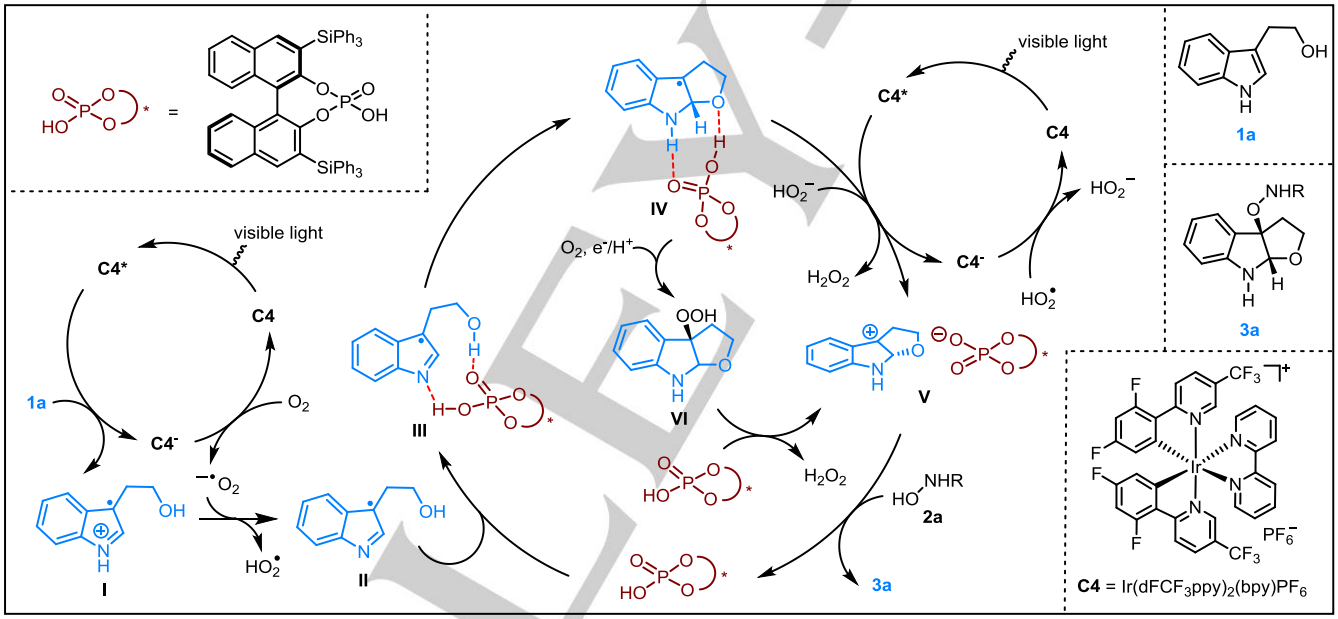


entry	PC	CPA	solvent	yield (%)[b]	er (%)[c]
1	**C1**	**PA1**	MTBE	trace	N.D.
2	**C2**	**PA1**	MTBE	trace	N.D.
3	**C3**	**PA1**	MTBE	trace	N.D.
4	**C4**	**PA1**	MTBE	85	85:15 (*R*)
5	**C4**	**PA2**	MTBE	79	67:33 (*S*)
6	**C4**	**PA3**	MTBE	93	84:16 (*S*)
7	**C4**	**PA4**	MTBE	36	85:15 (*S*)
8[d]	**C4**	**PA1**	MTBE	91	89:11 (*R*)
9[d]	**C4**	**PA1**	DME	40	93:7 (*R*)
10[d]	**C4**	**PA1**	THF	trace	N.D.
11[d]	**C4**	**PA1**	toluene	90	88:12 (*R*)
12[d]	**C4**	**PA1**	DME/hexane (3/1)	98	90:10 (*R*)
13[d,e]	**C4**	**PA1**	DME/hexane (3/1)	98	91:9 (*R*)
14[d,e,f]	**C4**	-	DME/hexane (3/1)	trace	N.D.
15[d,g]	**C4**	**PA1**	DME/hexane (3/1)	trace	N.D.
16[d,e,h]	**C4**	**PA1**	DME/hexane (3/1)	trace	N.D.
17[d,e,i]	**C4**	**PA1**	DME/hexane (3/1)	trace	N.D.

[a] Reaction conditions: unless otherwise noted, a solution of **1a** (0.1 mmol), **2a'** (0.15 mmol), PC (2 mol%) and **CPA** (10 mol%) in solvent (2.0 mL) was irradiated by 24 W blue LEDs at room temperature under air for the indicated time. Cbz = benzyloxycarbonyl, TMCbz = trimethyl-benzyloxycarbonyl, PC = photocatalyst, **CPA** = chiral phosphoric acid, MTBE = methyl *tert*-butyl ether, THF = tetrahydrofuran, DME = dimethyl ether, N.D. = not determined. [b] Isolated yield. [c] Determined by HPLC analysis. [d] **2a** was used instead of **2a'**. [e] $Ir(dFCF_3ppy)_2(bpy)PF_6$ (0.2 mol%). [f] In the absence of **PA1**. [g] In the absence of $Ir(dFCF_3ppy)_2(bpy)PF_6$. [h] In dark. [i] Under argon.



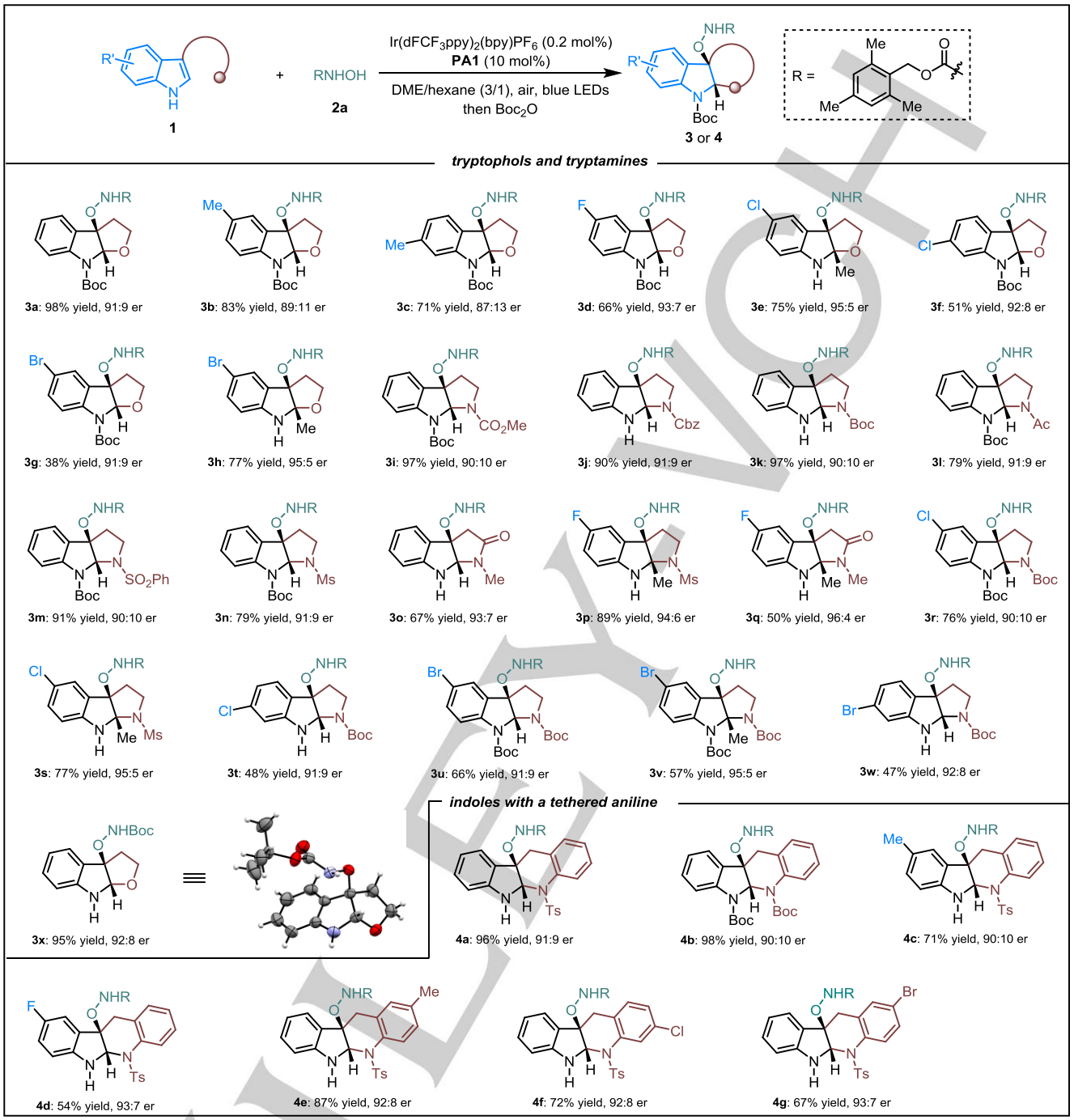
Scheme 2. Mechanistic Studies. (a) Stern-Volmer luminescence quenching experiments. (b) Cyclic voltammetry experiments (**1a** and **2a**). (c) Cyclic voltammetry experiments of **1a** with varing amounts of PA (PA = diphenylphosphoric acid). Boc = *tert*-butylcarbonyl.



Scheme 3. Proposed Mechanism.

inhibited the whole reaction without generating any TEMPO-adducts (eq 1). As a further illustration, no detectable product (**3x**) was observed when the reaction between tryptophol (**1a**) and BocNHOH was conducted with MnO_2 as the terminal oxidant (eq 2).[15]

Based on the experimental observations, a plausible mechanism was proposed. As depicted in Scheme 3 (using **1a** + **2a** → **3a** as an example), irradiation of photocatalyst $Ir(dFCF_3ppy)_2(bpy)PF_6$ (**C4**) with visible light generates the excited state species **C4***, which is a strong oxidant. The photoexcited **C4*** species then participates in the first SET oxidation of tryptophol (**1a**) to afford the radical cation intermediate (**I**) along with the reduced photocatalyst **C4**$^-$. Subsequently, oxidation of **C4**$^-$ [$E_{1/2}$(**C4**/**C4**$^-$) = -1.37 V vs. SCE] [14] by molecular oxygen[16] regenerates the ground-state **C4** and delivers the superoxide anion. Upon deprotonation of **I** by $O_2^{\bullet-}$, CPA-mediated cyclization/second SET oxidation (**III**→**IV**→**V**) occurs in the presence of photoexcited **C4*** to afford the configurationally biased tertiary pyrroloindoline carbocation intermediate that interacts with chiral phosphate anion via electrostatic interactions (**V**). Then, the reduced photocatalyst **C4**$^-$ is proposed to be oxidized by $HO_2^{\bullet}$.[16] The HO_2^- is concomitantly released, followed by protonation to afford H_2O_2. Finally, the transient electrophilic species **V** would be trapped by



Scheme 4. Substrate Scope. [a] Reaction conditions: unless otherwise noted, a solution of **1** (0.1 mmol), **2** (0.15 mmol), $Ir(dFCF_3ppy)_2(bpy)PF_6$ (0.2 mol%) and **PA1** (10 mol%) in DME/hexane (3/1) (2.0 mL) was irradiated by 24 W blue LEDs at room temperature under air for 24 h. [b] Isolated yield. [c] Determined by HPLC analysis. Ac = acetyl. Ms = methylsulfonyl. Ts = 4-methylbenzenesulfonyl.

N-hydroxycarbamate **2a**, which might also invoke hydrogen-bonding interactions with the chiral phosphate anion, to furnish the optically enriched furoindoline (**3a**) and complete the CPA catalytic cycle.

Notably, on the basis of previous studies, the intermediate **IV** might also be intercepted by O_2 to yield the hydroperoxide-substituted furoindoline product (**VI**), which would lead to the same intermediate **V** with the assistance of CPA.[17] Although independent synthesis of **VI** and re-subjecting it to the standard conditions failed to give any desired product (**3a**), we could not fully exclude such an alternative pathway (**IV**→**VI**→**V**). Overall, the current method provides a mechanistically distinct pathway towards previously described chemistry involving *N*-hydroxycarbamates under oxidative conditions.[11,12,18] It also offers a novel umpolung strategy, through sequential photocatalytic SET oxidations,[19] to invert the indole derivatives

from nucleophiles to electrophilic species, which would react in turn with external nucleophiles.

With these encouraging results in hand, we next explored the substrate scope for the asymmetric dearomatization reactions. As shown in Scheme 4, a wide range of differentially substituted tryptophols were readily converted into their corresponding furoindolines with moderate to high levels of enantioselectivity (38-98% yields, 87:13-95:5 er, **3a**-**3h**). It is worth noting that introducing an EWG group such as -F, -Cl, or -Br, on the indole core appears more beneficial for enantioselectivity than that with an EDG group (-Me). Tryptamines with diverse protecting groups including -CO_2Me, -Cbz, -Boc, -Ac, -SO_2Ph, and -Ms as well as the indoles bearing an amide side chain were well accommodated in this transformation. A series of enantioenriched pyrroloindolines were obtained in 47-97% yields with 90:10-96:4 er (**3i**-**3w**). In addition, the protecting group of hydroxylamine could be replaced by -Boc, furnishing the desired product **3x** in 95% yield with 92:8 er. The absolute configuration of **3x** was determined by X-ray crystallographic diffraction of its enantiopure sample, and those of other products were assigned analogously.[20] Gratifyingly, this protocol is also applicable to indoles with a tethered aniline. The intriguing indolo[2,3-*b*] quinoline skeletons bearing a fully-substituted quaternary center were constructed in 54-98% yields with 90:10-93:7 er (**4a**-**4g**). In all cases, exclusive C-O bond forming selectivity is observed, which was in good agreement with the suggested mechanism. Considering that some dearomative products (**3a**-**3d**, **3f**, **3g**, **3i**, **3l**-**3n**, **3r**, **3u**, **3v**, **4b**) were unstable, *N*-protection with -Boc was operated before final isolation.

Conclusion

In conclusion, we have developed the first catalytic asymmetric dearomatization reaction of indole derivatives under oxidative conditions in which indole acts as an electrophile. By taking advantage of the dual-catalyst system consisting of a photoredox catalyst and chiral phosphoric acid, the preliminary mechanisitic studies suggest indole derivatives could be transformed into the configurationally biased carbocation intermediates upon two sequential SET oxidations induced by visible light. The transient electrophilic species reacts in turn with N-hydroxycarbamates, resulting in a wide range of structurally diverse and optically active oxy-amine-tethered fused indolines. Further applications of this strategy in novel asymmetric dearomatization reactions are currently underway in our laboratory.

Experimental Section

General procedure for asymmetric dearomatization of indole derivatives with N-hydroxycarbamates. To a Schlenk tube equipped with a rubber septum and magnetic stir bar were added **1**, **2**, **PA1**, and Ir(dFCF_3ppy)$_2$(bpy)PF_6. DME/hexane (3/1) was added, and the Schlenk tube was positioned approximately 10 cm from 24 W blue LEDs (maximum emission wavelength = 450 nm). Then the mixture was stirred open to air irradiated by 24 W blue LEDs at room temperature. After the reaction was complete (monitored by TLC analysis), the solution was quenched by water and extracted with EtOAc (5 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford the desired product **3** or **4**.

Acknowledgements ((optional))

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Keywords: Asymmetric Catalysis• Dearomatization • Indole • N-hydroxycarbamate • Visible light

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[20] CCDC 1922399 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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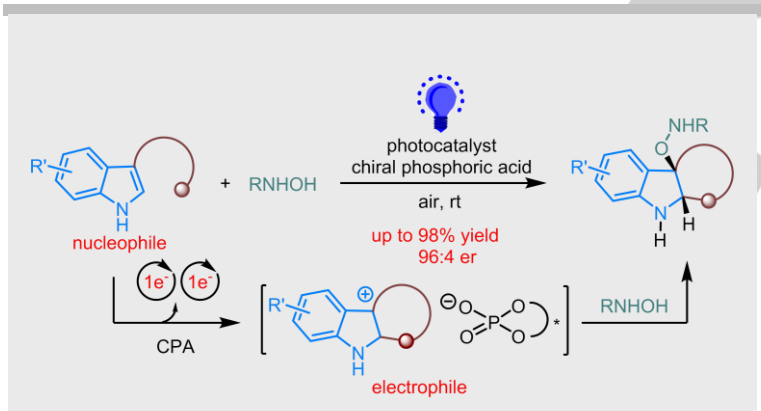

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Asymmetric Dearomatization of Indole Derivatives with N-Hydroxycarbamates Enabled by Photoredox Catalysis

Dearomatization of indoles and their derivatives provides efficient synthetic routes for substituted indolines. In most cases, indoles serve as nucleophiles by reacting with electrophiles at the C3 position. Herein, we report an asymmetric dearomatization reaction of indole derivatives that function as electrophiles. The combined utilization of photocatalyst and chiral phosphoric acid in air unlocks the umpolung reactivity of indoles, enabling enantioselective dearomatization of indole derivatives with *N*-hydroxycarbamates as nucleophiles.