Photoredox Asymmetric Nucleophilic Dearomatization of Indoles with Neutral Radicals

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ABSTRACT: The dearomatization of indoles represents the most efficient approach for accessing highly valued indolines. The inherent nucleophilic reactivity of indoles has dictated indole dearomatization development in both $1e^-$ and $2e^-$ processes. However, it has been challenging for the dearomatization of electron deficient indoles. Herein we introduce a conceptually distinct photoredox mediated Giese-type transformation strategy, which is generally used for the conjugate addition of radicals to simple α, β-unsaturated systems, for chemoselectively breaking C=C bonds embedded in the aromatic structure. Moreover, highly diastereoselective addition of challenging neutral radicals has been achieved by Oppolzer camphorsultam chiral auxiliary. Structurally diverse amine functionalized chiral indolines carrying distinct functional and stereochemical diversity are produced from a wide array of amines as radical precursors. Furthermore, the mild,

powerful manifold is capable of the late-stage modification of complex natural products and pharmaceuticals. DFT studies are performed to elucidate the observed stereochemical outcomes.

INTRODUCTION

Chiral indoline is a privileged core featured in numerous natural products and biologically active compounds.[1] The fascinating molecular architecture and intriguing biological properties have triggered long-standing interest in developing synthetic methods for enantioselective construction of the chiral scaffold for decades. In this context, asymmetric dearomatization of indoles has been recognized as one of the most efficient strategies by directly transforming readily accessible indoles to chiral indolines.[2] Indole is an electron rich aromatic system containing enamine embedded C_2–C_3 π bond and strong nucleophilic C_3 carbon. The reactivity has dictated indole dearomatization methodology development. A number of elegant enantioselective dearomatization methods, promoted by chiral transition-metal complexes[3] and organocatalysts,[4] have been reported. Mechanistically, these synthetic tactics are largely carried out by ionic $2e^-$ transformative pathways (Scheme 1a). The exploration of open shell radical-engaged asymmetric indole dearomatization could offer the complementary capacity, but remains largely uncharted.[5,6]

It has long been recognized that controlling enantioselectivity in reactions of the highly reactive radical intermediates presents challenges.[7] This is reflected by only a handful of examples of asymmetric dearomatization of indoles reported so far. Knowles reported the first enantioselective dearomatization of indole derivative tryptamines with TEMPO by photo- and chiral phosphoric acid (CPA) co-catalysis (Scheme 1b).[8] The chirality is governed by the hydrogen bond interaction between the radical cation species with a chiral phosphate anion. The same process was also attained without a photocatalyst by Xia and co-workers.[9] You and colleagues developed an alternative photo- and CPA co-promoted asymmetric dearomatization of indole alcohols with *N*-hydroxycarbamates (Scheme 1b).[10] A cation intermediate produced by two consecutive single electron transfer (SET) oxidation of indole creates the tight ionic interaction with a chiral

phosphate anion to induce chirality. While these techniques provide powerful approaches for asymmetric indole dearomatization through radical engaged processes, they rely on charged interactions for controlling enantioselectivity and with that, carry inherent limitations. Nucleophilic indoles are employed for easy photocatalytic oxidation to give the radical cation or cation species, which play essential roles in the control of enantioselectivity. Leveraging asymmetric dearomatization strategy with indoles beyond the oxidative umpolung chemistry could offer new methods for the synthesis of chiral indolines carrying distinct functional and stereochemical diversity.

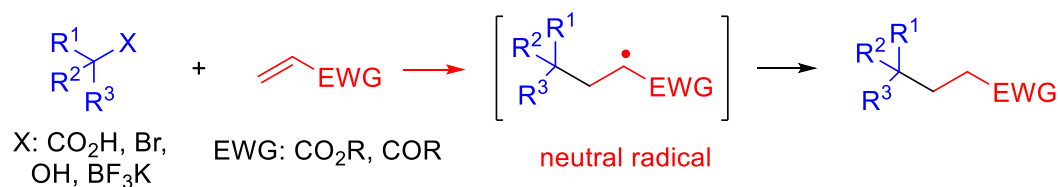**Scheme 1.** Asymmetric Dearomatization of Indoles

a: Well-studied catalytic asymmetric dearomatization of indoles by ionic 2e transfer pathway
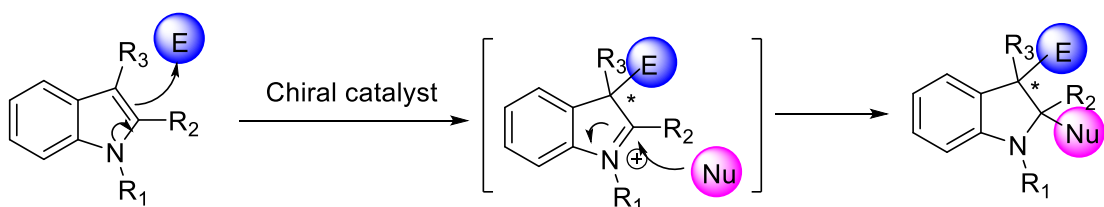

b: Photocatalytic radical cation or cation engaged asymmetric dearomatization of nucleophilic indoles

X = O, NR

Y = TEMPO or Boc/Cbz-NHOH

radical cation - CPA complex

cation - CPA complex
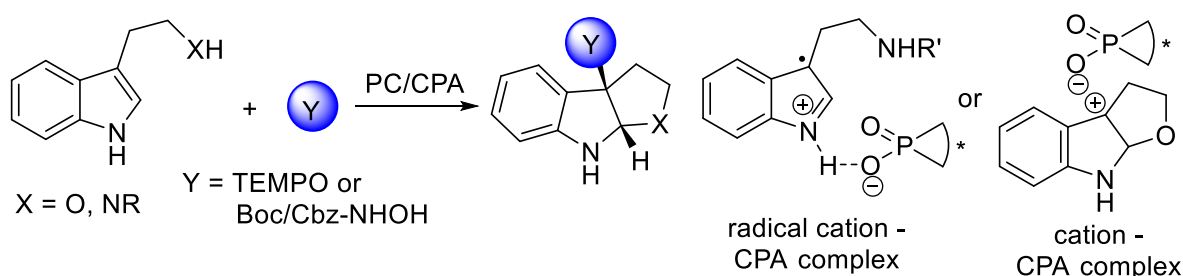
c: Generic Giese reaction: radical addition to simple α, β-unsaturated systems

X: CO_2H, Br, OH, BF_3K

EWG: CO_2R, COR

neutral radical

d: Photocatalytic asymmetric neutral radical-engaged direct dearomatrization of indoles (This work)

trans - 3
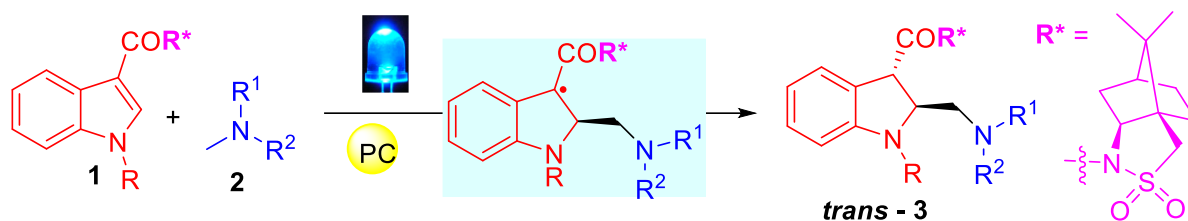
■ Dearomatization by a Giese-type reaction with aromatic C=C bond

■ Neutral radical-engaged nucleophilic dearomatrization   ■ Inducing chirality for neutral radical

   Inducing chirality for neutral radical involved processes is particularly difficult. In this realm, to the best of our knowledge, no such asymmetric indole dearomatization studies have been reported.[11] We envisioned that reversing the nucleophilic reactivity of indoles in photoredox catalysis might provide an opportunity for developing a distinct asymmetric dearomatization reaction with neutral radicals.[12] However, it has been challenging for the dearomatization of

electron poor indoles, as evidenced by only a handful of examples,[13] which generally rely on ionic $2e^-$ activation mode. We conceived that implementing a neutral radical engaged Giese-type reaction[14,15] with the electrophilic indoles could create an unprecedented process for indole dearomatization (Scheme 1c,d). However, implementing a Giese type reaction for indole dearomatization faces significant roadblocks. Unlike a conjugated C=C bond in a typical Giese reaction (Scheme 1c), breaking the unconventional C=C bond in stable indole aromatic systems overcomes a higher energy barrier. The precedent studies of direct addition of a radical to electron rich $C_2=C_3$ bond of indoles in electrophilic aromatic substitution processes provide encouraging possibility.[16] Nonetheless, the reversed reactivity of addition of a radical to an electron poor $C_2=C_3$ bond of indoles is unknown. Moreover, even though incorporation of EWGs into the C_2 or C_3 positions of indoles could reverse the polarity from the innate nucleophilic to electrophilic system and serve as a potential radical acceptor, the weakly electron deficient indoles render the Giese reaction more difficult because more electron deficient, less hindered α, β-unsaturated systems[14,15] are generally used for effective nucleophilic radical addition (Scheme 1c). Furthermore, in the photoredox process, possible oxidation of the weakly electron deficient indole systems could complicate the process. Controlling chemoselectivity is another challenge to be faced.

Herein we wish to report the first asymmetric neutral radical engaged dearomatization reaction of indoles **1** with amines **2**[17] (Scheme 1d). A conceptually distinct photoredox mediated asymmetric Giese-type transformation is exploited for chemoselectively breaking C=C bonds embedded in the aromatic structure. Highly diastereoselective control addition of the neutral radicals have been achieved by Oppolzer camphorsultam chiral auxiliary. Structurally diverse amine functionalized chiral indolines are produced from a readily accessible array of amines as radical precursors. Furthermore, the mild, powerful manifold enables the late-stage modification

of complex natural products and pharmaceuticals. The asymmetric C-C bond forming process is complementary to the above C-N/C-O bond connection strategies and delivers thermodynamically controlled *trans*-indolines carrying distinct functional and stereochemical diversity.

RESULTS AND DISCUSSION

Reaction Design

   Our rational for the newly proposed dearomatization strategy by reversing indole reactivity for a Giese-type reaction is justified by harnessing reactivity of reactants and photocatalyst (PC) to achieve the chemoselectivity *via* controllable reactivity. In the studies by Knowles, Xia and You,[8-10] the oxidation of electron rich indoles by an excited PC* can facilely generate the critical radical cation intermediates because they have relatively low oxidation potentials. For instance, E_{ox} of *N*,3-dimethyl indole is +0.4 V vs SCE.[18] When indoles **1** carries EWGs at N, C_2 or C_3 positions augments the E_{ox} values. For example, *N*-methyl 3-acetyl indole is ca. + 1.0 V vs SCE[18] while methyl *N*-Boc-3-indole carboxylate (E_{ox} +1.94 vs SCE, Figure S1 in SI) is even larger. The change may reverse the reactivity of indoles and thus make them as an oxidant (e⁻ acceptor) rather than a reductant to accept a nucleophilic radical for the proposed Giese-type reaction. In light of radical precursors, they should have lower E_{ox} than that of indoles. Therefore, they can be selectively oxidized by excited PC* form radicals but without affecting the indoles. Tertiary amines, which have been used as radical donors in photoredox reactions,[17] can meet the demand because they have lower oxidation potential than those of *N*-methyl 3-acetyl indole and methyl *N*-Boc-3-indole carboxylate, exemplified by *N*,*N*-dimethylaniline with E_{ox} + 0.74 V (vs SCE).[19] Moreover, nitrogen is the most widespread heteroatom found in FDA approved drugs. Therefore, the amine functionalized chiral indolines are highly valuable in drug discovery. Finally, the E_{ox} of excited PC* should be higher than the amines while lower than the indoles. Therefore, it can oxidize the

amine selectively. The widely used organic PC 4CzIPN can be a good candidate because the E_{red} of excited 4CzIPN* is + 1.35 V (vs SCE).[20]

Exploration and Optimization

At the beginning of our investigation, a model reaction between indole-3-carboxylic acid methyl ester (**1a**, 0.1 mmol) as a radical acceptor and *N,N*-dimethylaniline (**2a**, 0.12 mmol)) as a radical precursor in the presence of photoredox catalyst 4CzIPN (2.5 mol%) was explored for the proposed dearomatization process (Table 1). The mixture was irradiated by a 5W blue LED strip under N_2 atmosphere at 20 ºC. Disappointedly, no reaction occurred (entry 1). We believed that the electrophilic reactivity of substrate **1a** was not active enough for the nucleophilic radical attack. Therefore, Boc group was introduced on the nitrogen to decrease the electron density of C=C bond in **1b**. Gladly, the desired indoline product **3a** was obtained albeit low yield (13%, entry 2). The poor yield was presumably attributed to the slow conversion of **1b**. As deprotonation is crucial in the formation of α-amino radical from the corresponding amine precursor, addition of base could be beneficial. Excitingly, after screening of several bases (Table S2.1 in SI), the use of 0.5 equiv of Na_2CO_3 could dramatically improve the reaction efficiency (94%, entry 3). Next, we sought to realize the asymmetric nature of this process. Evans chiral auxiliary became our first choice as this type of chiral auxiliary has been widely used in ionic asymmetric synthesis.[21] However, poor diastereoselectivity was observed (dr = 60:40, entry 4). Then, we turned our attention to other chiral auxiliaries. When Oppolzer camphorsultam[22,23] was employed, dr value was elevated to 92:8. (entry 5). After the extensive optimization of reaction conditions (see Table S2.1 in SI), both high dr (96:4) and excellent yield were achieved by using NaOAc (1.0 equiv) as base (entry 6). Probing the reaction parameters revealed that decreased amount of either photoredox catalyst or base and increased reaction concentration gave inferior results (entries 7-9). Interestingly, a

noticeable amount of *cis* isomer was observed with a shortened reaction time (8 h) (entry 10). No reaction occurred in the absence of either light or photoredox catalyst supporting the role of visible light in this catalytic reaction (entry 11).

Table 1. Optimization of Conditions for Asymmetric Dearomatization of Electrophilic Indole derivatives[a]
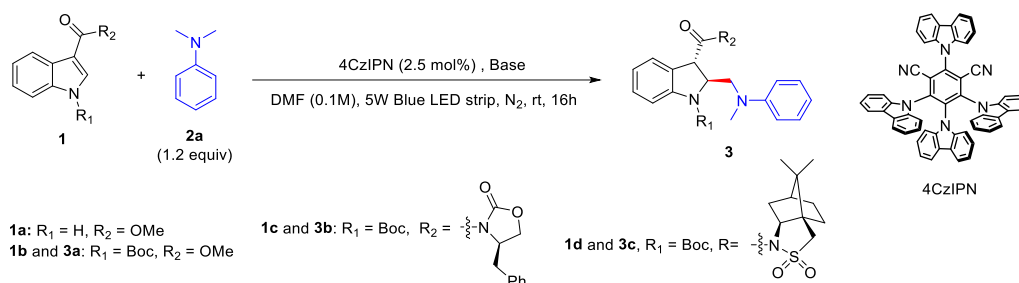
Entry	Substrate	Base (equiv)	Yield (%)[b]	trans/cis[c]	dr[c]
1	1a	-	-	-	-
2	1b	-	13[d]	>20:1	-
3	1b	Na₂CO₃ (0.5)	99 (94[d])	>20:1	-
4	1c	Na₂CO₃ (0.5)	91	>20:1	1.5:1
5	1d	Na₂CO₃ (0.5)	95 (91[d])	>20:1	92:8
6	1d	NaOAc (1.0)	99 (95[d])	>20:1	96:4
7	1d	NaOAc (0.5)	93	>20:1	94:6
8[e]	1d	NaOAc (1.0)	91	>20:1	89:11
9[f]	1d	NaOAc (1.0)	95	>20:1	92:8
10[g]	1d	NaOAc (1.0)	86	90:10	98:2
11[h]	1d	NaOAc (1.0)	-	-	-

Reaction scope

With the optimal reaction conditions in hand, we probed the generality of this methodology with a range of tertiary amines and indole substrates (Scheme 2). Significant structurally diversified *N,N*-dimethylaniline derivatives can react with **1c** to give the *trans*-2,3-disubstituted indolines **3c-3m** in good yields (up to 99%) and with high diastereoselectivities (up to > 20:1). Notably, the reaction proceeds highly regioselectively at the *N*-methyl site. Equally impressively, this mild dearomatization process tolerates various commonly used functional groups on the phenyl ring including acyl (**3d**), cyano (**3r**), ester (**3f**), formyl (**3g**), carboxylic acid (**3h**), hydroxyl (**3j**) and halogens (**3k-3m**). Moreover, the reaction proceeds highly regioselectively at the methyl group, as observed in **3n**. In addition to dominant methylated product, α-regioisomer is also formed for cyclic amine **3r**. Furthermore, other heteroaromatics such as pyridine (**3p**) and purine (**3q**) also work smoothly in this process.

Scheme 2. Asymmetric Dearomatization of Electrophilic Indole Derivatives by Various Tertiary Amines[a]

Reaction scheme (top):

1 + 2 → 3

Conditions: 4CzIPN (2.5 mol%), NaOAc (1.0 equiv), DMF (0.1 M), 5W Blue LED strip, N$_2$, rt, 16 h

3c, R = H, 91%, dr > 20:1
3d, R = 4-Ac, 99%, dr = 13:1
3e, R = 4-CN, 84%, dr = 11:1
3f, R = 4-COOEt, 92%, dr = 12:1
3g, R = 4-CHO, 99%, dr = 12:1
3h, R = 4-COOH, 71%, dr = 17:1
3i, R = 2-Me, 89%, dr = 20:1
3j, R = 4-CH$_2$OH, 67%, dr = 14:1
3k, R = 4-Cl, 91%, dr = 14:1
3l, R = 4-I, 84%, dr = 17:1
3m, R = 4-Br, 97%, dr = 17:1

3n, 92%, dr > 20:1

3o, 71%, dr > 20:1

3p, 76%, dr = 13:1

3q, 81%, dr > 20:1

3r, 63%^{b}, rr = 1.8:1

3s, 60%, dr > 20:1

3t, 82%, dr = 12:1

3u, 84%, dr = 11:1

3v, 68%, dr = 13:1

3w, 86%, dr = 17:1

3x, 61%, dr > 20:1

3y, 96%, dr = 6:1

3z, 56%^{b}, rr = 3:1

3aa, 63%^{b}, rr = 3:1

3ad

3ab, R" = Cl, 99%, dr = 11:1
3ac, R" = Br, 79%, dr = 11:1
3ad, R" = I, 85%, dr = 11:1
3ae, R" = OMe, 74%, dr >20:1
3af, R" = OBn, 74%, dr >20:1

3ag, R" = CN, 99%, dr = 7:1

3ah, R' = Cbz, 82%, dr = 12:1
3aj, R' = Tos, 75%, dr = 14:1

3ai, 99%, dr > 20:1

^{a}Reaction conditions: indole derivative (0.10 mmol), tertiary amine (0.12 mmol), NaOAc (0.10 mmol), 4CzIPN (2.5 mol%), DMF (1.0 mL), N$_2$, rt, 5W blue LED strips. The dr and rr values were determined by ^{1}H NMR, dr: diastereomer ratio, rr: regioisomer ratio. ^{b}Combined yield of two regioisomers (alternative connectivity indicated by a pink circle). See SI for detail.

With the great success for aniline derivatives as effective radical donors, we next surveyed alkyl tertiary amines under the optimal reaction conditions (Scheme 2). Again, this strategy provides a
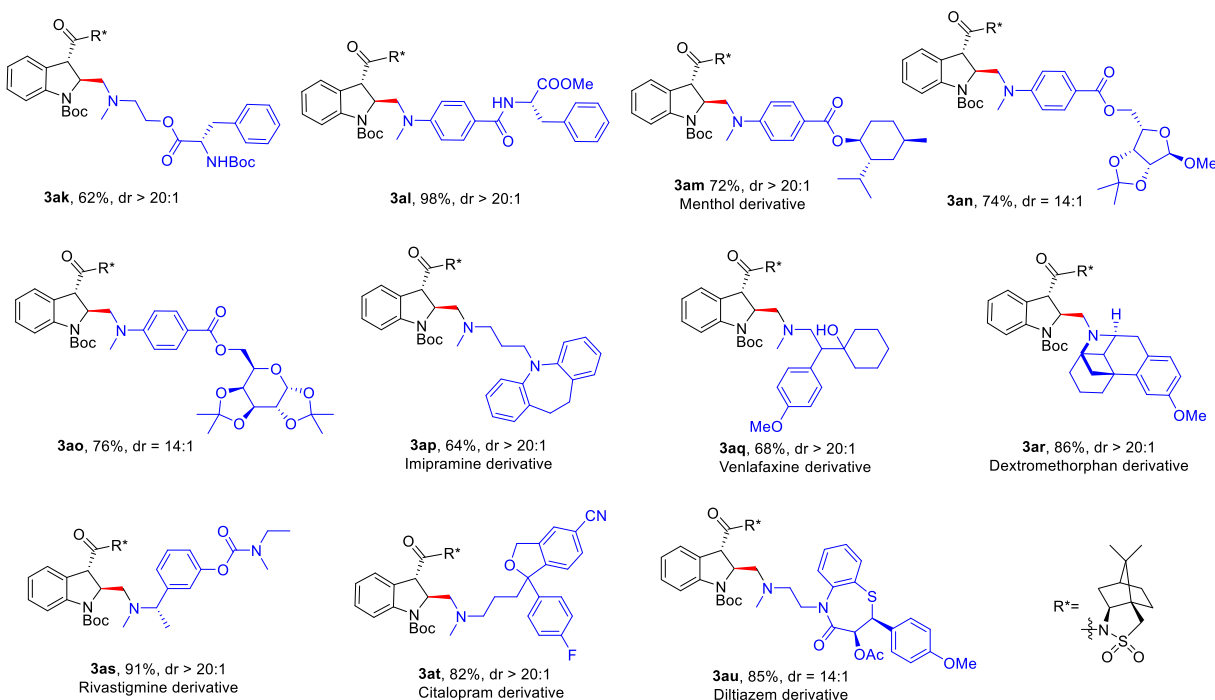
preparative power for the facile synthesis of various enantioenriched amine functionalized *trans*-selective 2,3-disubstituted indolines (**3s-3aa**) with both good yield and high diastereoselectivity. The process proceeds highly regioselectively at the methyl site in acyclic tertiary amines **3t-3y** as well. It is noteworthy that no regioisomer is formed at the benzylic position (**3t**). However, regioisomers are observed with cyclic tertiary amines (**3r**, **3z** and **3aa**). Amino acid derived amines can also effectively participate in this reaction highly stereo- and regio-selectively (**3x** and **3y**). The observed high regioselectivity may be attributed to the steric and electronic effects. The electron-withdrawing substitutent decreases the nucleophilicity of the resulting radical, which reduces its reactivity. The absolute configuration with *trans*-geometry is unambiguously determined by signal X-ray analysis of compound **3ad** (Scheme 2).[24]

We next investigated this synthetic strategy with a range of indole derivatives (Scheme 2). Various functional groups on indole rings can be tolerated including halogens (**3ab-3ad**), methyoxy (**3ae**), benzyloxy (**3af**) and cyano (**3ag**). In addition to *N*-Boc group, other protecting groups (PGs), such as Cbz (**3ah**), Bz (**3ai**), and Tos (**3aj**), are also amenable to give the corresponding products with high yields and good diasteroselectivies under the mild reaction conditions. However, when Me and Bn groups are used, no reaction occurred, suggesting that the *N*-EWGs are necessary for the activation of the C=C bond in this dearomative process (see Table S11.2 in SI).

To further demonstrate the synthetic utility of this mild dearomatization manifold, we performed late stage modifications on an array of natural products and pharmaceuticals. As shown in Scheme 3, the standard protocol was successfully applied to the modification of amino acid derivatives (phenylamine) and natural product (+)-menthol to give indoline-based analogues **3ak**, **3al** and **3am** with good yields and high diastereoselectivities. Additionally, pentose and hexose derived tertiary

amines dearomatize indoles efficiently to provide the desired products **3ao** and **3an**. Finally, more structurally complex drugs including, imipramine (**3ap**), venlafaxine (**3aq**), dextromethorphan (**3ar**), rivastigmine (**3as**), citalopram (**3at**) and diltiazem (**3au**), were natively and selectively modified by this mild dearomatization method. It is noted that in these cases, the single regioisomer was formed. It is believed that the steric effect plays a dominent role in governing the regioselectivity.

Scheme 3. Late Stage Asymmetric Dearomatization of Indole Derivatives with Natural Products and Pharmaceuticals[a]
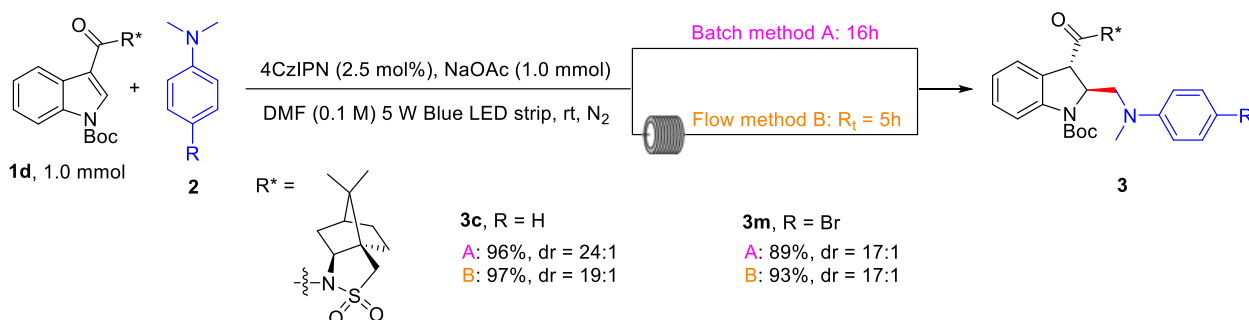

3ak, 62%, dr > 20:1

3al, 98%, dr > 20:1

3am 72%, dr > 20:1
Menthol derivative

3an, 74%, dr = 14:1

3ao, 76%, dr = 14:1

3ap, 64%, dr > 20:1
Imipramine derivative

3aq, 68%, dr > 20:1
Venlafaxine derivative

3ar, 86%, dr > 20:1
Dextromethorphan derivative

3as, 91%, dr > 20:1
Rivastigmine derivative

3at, 82%, dr > 20:1
Citalopram derivative

3au, 85%, dr = 14:1
Diltiazem derivative

[a]Reaction conditions: indole substrate (0.10 mmol), tertiary amine (0.12 mmol), NaOAc (0.10 mmol), 4CzIPN (2.5 mol%), DMF (1.0 mL), N_2, rt, 16h, 5W blue LED strips. dr: diastereomer ratio. The dr values were determined by ^{1}H NMR. dr = diastereomer ratio. See SI for detail.

Finally, this synthetic protocol can be scaled up in gram scale without the loss of yield and diastereoselectivity (Scheme 4a). Moreover, the reaction can be adapted by a flow method, an
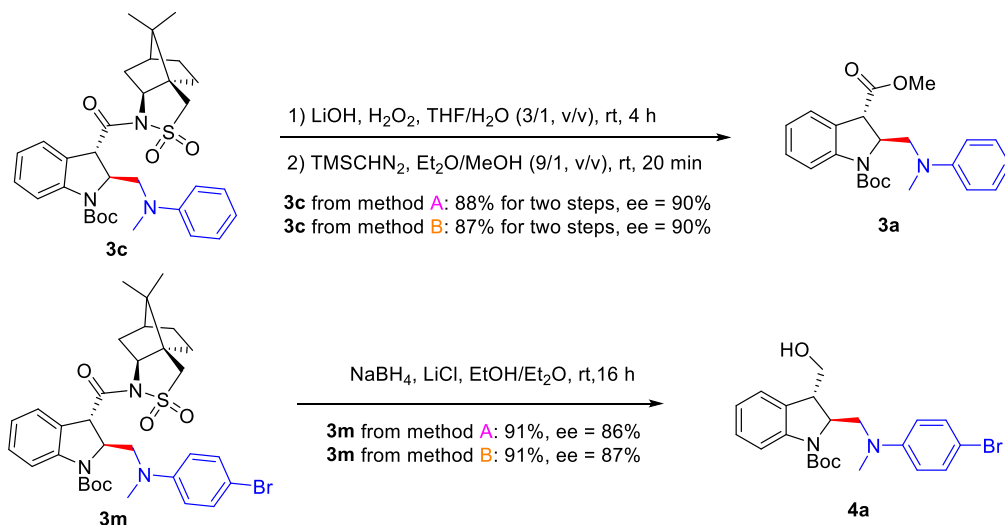
emerging technology in organic synthesis.[25] In this case, the reaction time was dramatically reduced to 5 h without compromising yield and diastereoselectivity (Scheme 4a). Additionally, the chiral auxiliary can be conveniently removed by esterification or reduction to give high enantioenriched indolines **3a** and **4a**, respectively (Scheme 4b).

Scheme 4. Preparative Scale Synthesis and Synthetic Elaboration*a*

a. Gram scale synthesis using batch and flow methods

4CzIPN (2.5 mol%), NaOAc (1.0 mmol)
DMF (0.1 M) 5 W Blue LED strip, rt, N$_2$

Batch method A: 16h
Flow method B: R$_t$ = 5h

1d, 1.0 mmol
2
R* =

3c, R = H
A: 96%, dr = 24:1
B: 97%, dr = 19:1

3m, R = Br
A: 89%, dr = 17:1
B: 93%, dr = 17:1

3

b. Removal of chiral auxiliary

1) LiOH, H$_2$O$_2$, THF/H$_2$O (3/1, v/v), rt, 4 h
2) TMSCHN$_2$, Et$_2$O/MeOH (9/1, v/v), rt, 20 min

3c from method A: 88% for two steps, ee = 90%
3c from method B: 87% for two steps, ee = 90%

3c

3a

NaBH$_4$, LiCl, EtOH/Et$_2$O, rt,16 h

3m from method A: 91%, ee = 86%
3m from method B: 91%, ee = 87%

3m

4a

a dr: diastereomer ratio. ee: enantiomeric excess. The dr values were determined by ^{1}H NMR. ee value was determined by HPLC analysis on a chiral stationary phase.

Mechanistic and diastereoselectivity aspects

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The radical addition to indole $C_2=C_3$ double bond has been reported.[16] Mechanistically, the processes undergo a Friedel-Crafts type pathway, involving an electrophilic radical addition to the nucleophilic indole $C_2=C_3$ bond. Therefore, electron rich indoles are used and aromatic products are formed. In contrast, our photocatalytic dearomatization method proceeds through a radical involved Giese-type process. In the process, a nucleophilic radical is conjugatively added to an electrophilic indole $C_2=C_3$ bond, and new dearomative indolines are produced instead. Specifically, a SET (single electron transfer) oxidation of tertiary amine **2** by excited 4CzIPN* gives radical cation **I** and concurrent formation of 4CzIPN$^{\bullet-}$ (Scheme 5). In a similar manner to a typical Giese reaction, the nucleophilic radical **II**, generated by deprotonation of **I** with NaOAc, attacks chiral Oppolzer camphorsultam indole **1** from *Re* face to afford (*2S*)-radical **III**. The resulting radical **III** is then reduced by 4CzIPN•− from *Si* face due to the *Re* face blocked by the amine moiety to give a *cis* anion **IV**, regenerate 4CzIPN and complete the redox cycle. Protonation of **IV** delivers a *cis*-product **3**. However, the obtained products **3** have *trans*-geometry. In the exploratory studies, we observed that when the reaction proceeded in a shorter period of time, a noticeable amount of *cis* product formed (Table 1, entry 10). These observations led to us believe that the process may go with a kinetic to thermodynamic process. Under the reaction conditions in the presence of base NaOAc for 16 h, the initially formed *cis*-product **3** undergoes epimerization to give thermodynamically stable *trans*-**3** (Scheme 5). This is further validated the studies of the employment of 2,6-lutidine as base mainly gave *cis* product (*cis* : *trans* > 20:1, Scheme 6a). The treatment of the *cis* isomer with sodium acetate delivered *trans* indoline quantitatively within 5h (see SI). The more stable *trans*-product is also supported by calculation of the Gibbs free energy using the Gaussian 09 program (Figure S1 and Table S14).[26]

Scheme 5. Plausible Reaction Mechanism
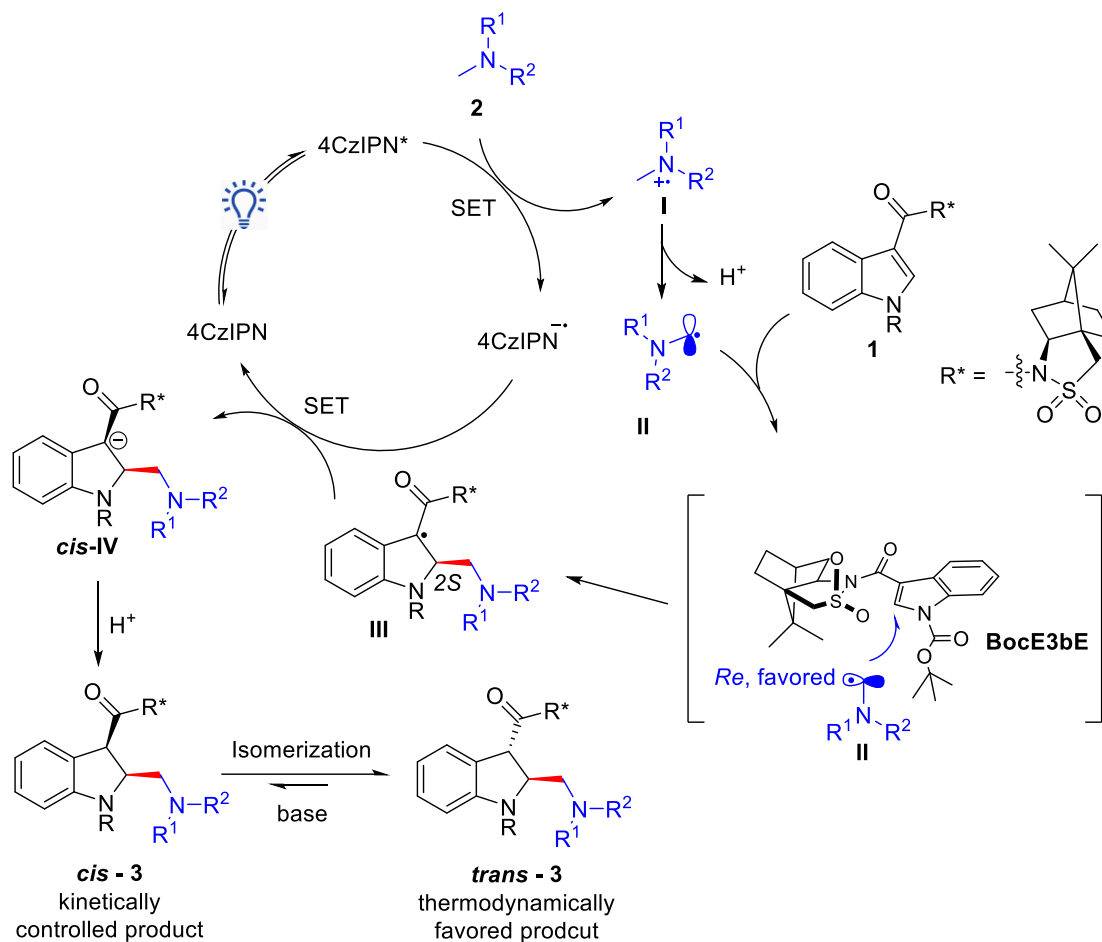
The radical engaged process is further validated by a radical scavenger TEMPO interception experiment (Scheme 6b). Moreover, deuterium labelling studies imply the anion **IV** is involved in the catalytic cycle (Scheme 6c, d). C-3 deuterated indoline **4c-***d* was obtained in the presence of 5.0 equiv D_2O (Scheme 6c). Almost no deuteration of C-3 was observed in the indoline product when *N*-methyl-*N*-phenylaniline-*d₃* was used (Scheme 6d).

Scheme 6. Experiments Designed for Elucidating Diastereoselectivity and Reaction Mechanism

a.

b.

c.

d.
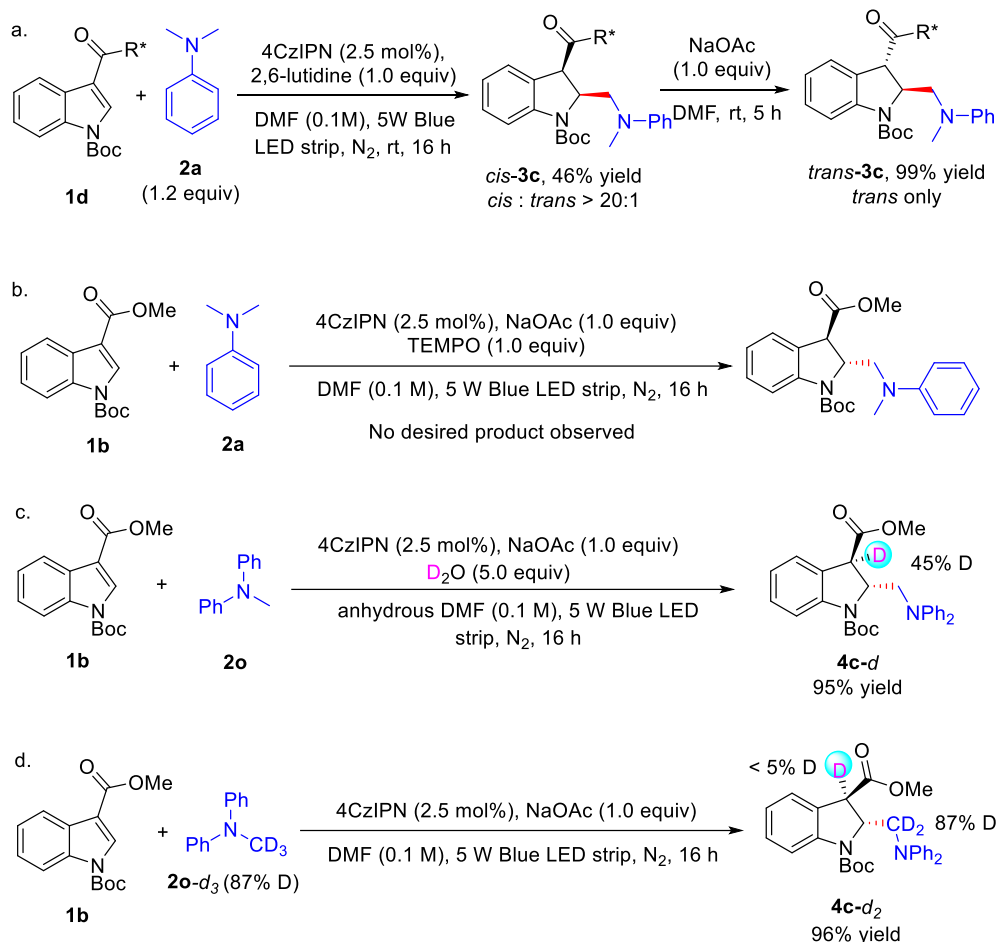
Oppolzer camphorsultam chiral auxiliary has been widely used in asymmetric $2e^-$ involved organic transformations.[22] In this dearomatization study, we demonstrated it was a diastereo-controller for radical addition.[23] The radical **II** is highly regio- and stereoselectively added into the indole $C_2=C_3$ bond in a conjugate manner. We believe that the high diasterolectivity is achieved by the chiral Oppolzer camphorsultam because of its high rigidity, which can signficantly differentiate the two faces of the indole substrates. In contrast, it is difficult for the less rigid chiral Evans oxazolidinone. To understand the observation, we also performed the computational investigation by calculating the Gibbs free energy of different conformation of **1d** using the Gaussian 09 program.[26] Among the four conformations resulting from the rotation of single bonds **3a** (C_3–C(O)) and **3b** (N(S)–C(O)) (Figure 1 and S2), **TS1** (BocE3bE-90) is most favorable

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conformer while others are unlikely to be dominated due to the unfavorable C=O and S=O dipole-dipole interactions in **TS4** and **TS5** and/or steric destablilization in **TS3** and **TS5**. An X-ray single crystal structure of substrate **1ah** shows **TS1** is indeed the favored conformer in the solid state (section 7 in SI).[24] The calculated Gibbs free energies of **TS3-5** support the speculation (Figure 1 and S1 and Table S14). Besides **TS1**, conformation **TS2** is also possible when the sulfonyl group is rotated by + 90° degree. However, **TS1** is favored over **TS2** by 2.68 kcal/mol (Table S15). In **TS1**, sulfonyl group, located closely to C_2 is believed to play the major role in the inducement of asymmetric selectivity. Radical **II** attacking C_2 from the *Re* (bottom) face is favored, due to steric interaction with the axial α oxygen of the sulfonyl group, which blocks the *Si* (top) face. The absolute configuration of dearomatization product coming from this model is consistent with the X-ray crystal structure of product **3ad** (Scheme 2 and SI).
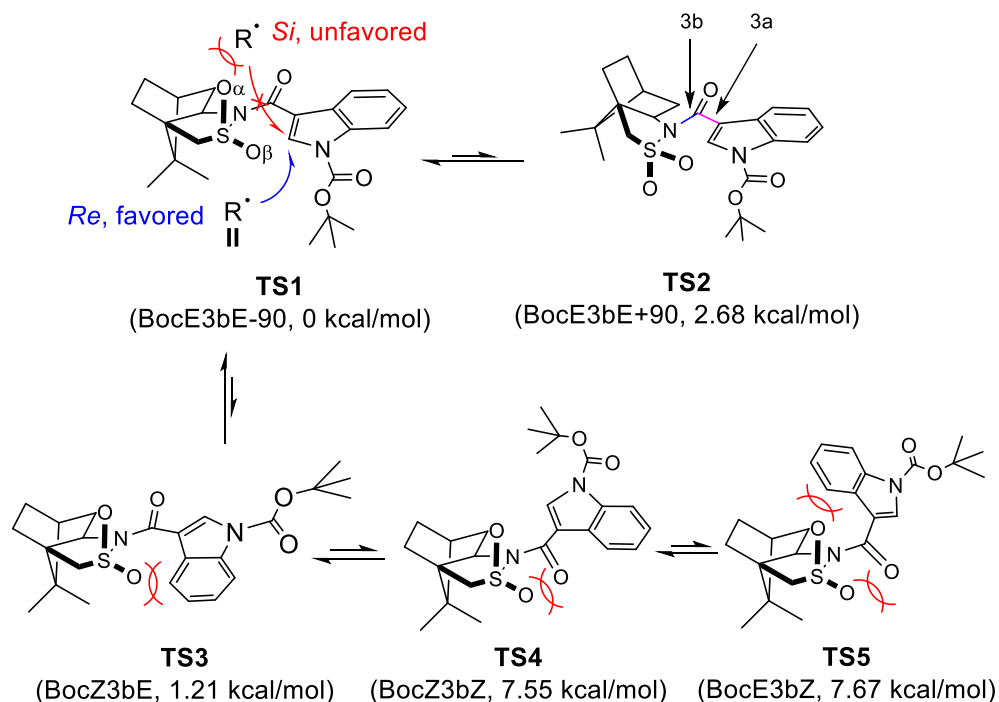
Figure 1. Optimized geometries and relative free energies. The relative Gibbs free energies are presented in kcal/mol.

CONCLUSION

In conclusion, we have developed a conceptually different approach for the asymmetric dearomatization of indoles. Instead of widely used inherent nucleophilic indoles in dearomatization, the electrophilic heteroaromatics have been used in asymmetric dearomatization. An unprecedented Giese-type reaction has been implemented to break the aromatic structure. Moreover, highly diastereoselective control addition of the challenging carbon centered neutral radicals derived from amines have been achieved by Oppolzer camphorsultam chiral auxiliary. Structurally diverse amine functionalized chiral indolines carrying distinct functional and stereochemical diversity are produced from a readily accessible widely array of amines as radical precursors. Furthermore, the mild, powerful manifold enables the late-stage modification of complex natural products and pharmaceuticals. It is expected that simplicity and efficiency of this procedure will be appreciated by organic chemists and medicinal chemists to rapidly access to a library of biologically valued chiral indolines.

ASSOCIATED CONTENT

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Author Contributions

YZ contributed to experimental design, reaction condition optimization and scope study. PJ, GF, HH and FZ contributed to scope study. WW was responsible for the overall design and supervision

of this project. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

Supporting Information

The following files are available free of charge.

Experiment details and spectroscopic data (PDF)

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R: Boc, Cbz, Tos, Bz

- ■ Reversed electrophilic indole
- ■ Induce chirality for neutral radical
- ■ Intermolecular C-C bond formation

4CzIPN (2.5 mol%)

45 examples, up to 99% yield
> 20:1 dr, *trans*-only

R* =

4CzIPN

(no need to change size)