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A Mild Cu(I)-Catalyzed Oxidative Aromatization of Indolines to Indoles

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Abstract: A novel method for the oxidation of indolines to indoles using a Cu (I) catalyst and an organic percarbonate as the stoichiometric oxidant is described. The method was successfully applied to the production of 0.5 kg of a key intermediate with 92% yield, 99.9% ee in the synthesis of Elbasvir, which is a novel therapy for the treatment of hepatitis C virus infection.

Indoles are pivotal substructures in many biologically significant natural products and important medicines.[1] One important method for the production of indoles is the dehydrogenation of indolines. Although the literature contains many reports on the oxidation of indolines to indoles,[2] the development of "green" reaction conditions for this transformation remains a valuable objective. Published procedures can involve the use of high reaction temperatures or stoichiometric oxidants and sometimes deliver low yields of the desired indole products together with large amounts of hazardous waste.[2] In this regard, the development of a catalytic and green indoline oxidation method would represent a useful contribution to the area.[3]

Elbasvir (**1**) (Figure 1) is a component of Zepatier, a combination therapy recently approved by the Food and Drug Adminstration (FDA) for the treatment of Hepatitis C virus (HCV) infection.[4] Merck Research Laboratories have disclosed several synthetic routes to Elbasvir, [5]

including one approach[5a] that requires oxidation of an indoline intermediate **to indole**. Described herein are our efforts to develop a novel Cu-catalyzed method for this indoline oxidation.[6]

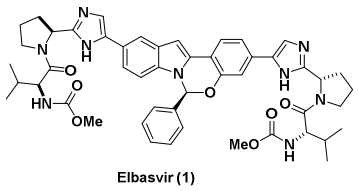
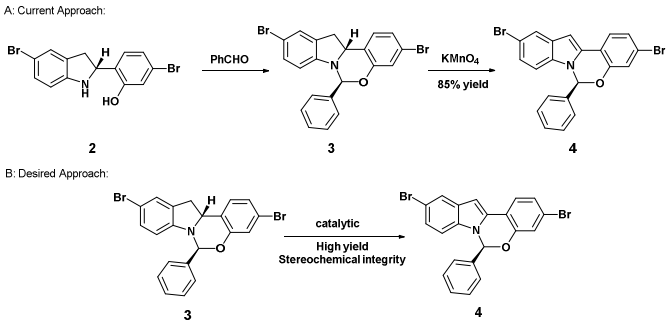


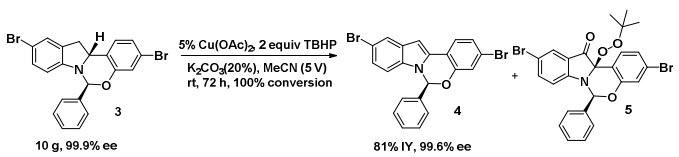
Figure 1. Structure of Elbasvir

A key synthetic challenge in the synthesis of Elbasvir is the construction of the benzoxazinoindole, which contains a hemiaminal ether stereocenter. In one approach, this problem was overcome by adoption of a stereochemical relay strategy, where the secondary amine stereogenic center in indoline **2** was used to control the hemiaminal ether center via a diastereoselective condensation with benzaldehyde to yield hemiaminal ether **3** (Scheme 1).[5a] In order to regain the desired oxidation state for Elbasvir, it was necessary to oxidatively aromatize intermediate **3**, originally achieved by treatment with 1.6 eq. KMnO4.[7] Although this oxidation process can deliver indole **4** in high yield and purity without disruption of the carefully established hemiaminal ether stereocenter (85% yield, >99.2% ee), the reaction generates large amount of insoluble and hazardous MnO_2 waste. Using this Elbasvir example as a test-case, we sought to develop a new general method for the oxidation of sensitive indolines that maximizes product yield and minimizes the environmental footprint of this commonly used synthetic transformation (Scheme 1).



Scheme 1. Current and Desired Approach toward the Benzoxazino-indole **4**.

We initially conducted a broad screen of possible alternatives utilizing high-throughput experimentation (HTE) technology.[8] Following a survey of more than 50 reaction conditions,[9] it became clear that clean oxidation of the Elbasvir indoline intermediate **3** is non-trivial; maintaining stereochemical integrity at the hemiaminal ether functional group is particularly challenging.[10] Indeed, the majority of conditions tested led to either poor conversion, or significant over-oxidation of **4** to provide multiple side products/degradants, or epimerization of the stereocenter. Notably, the use of *tert*-butylhydroperoxide (TBHP)[11] as a stoichiometric oxidant in conjunction with various metal catalysts emerged as one of the few promising options (Table 1). From a green chemistry perspective, TBHP is more attractive than $KMnO_4$ because the stoichiometric by-products from this reagent are the relatively benign *tert*-butanol and water. When these conditions were employed at 10 g scale, indole **4** was obtained in 81% chemical yield with 99.6% ee, although the reaction required 72 h to reach completion (Scheme 2).

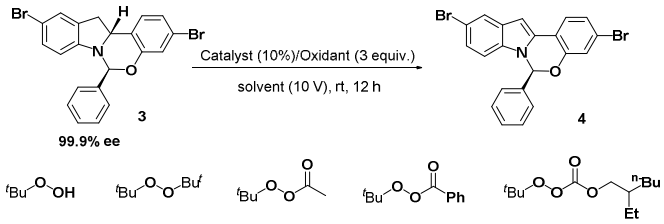


Scheme 2. $Cu(OAc)_2$/TBHP Promoted Indoline Oxidation.

Further optimization to improve the yield was hampered by the formation of by-product **5**. Compound **5** was produced under all conditions using TBHP so we decided to investigate other organic oxidants (Table 1) to determine if they could minimize by-product formation and accelerate the desired reaction rate. Our selection of organic oxidants focused on those that are economical and readily available; organic peresters met both of these critieria.

It has been proposed that the combination of TBHP with $Cu(OAc)_2$ generates tert-butoxy radical,[12] which we postulated as the key reactive species in this indoline oxidation. Similar to TBHP, *tert*-butyl peresters are also reported to generate the *tert*-butoxy radical under certain conditions.[13] We envisaged that the weaker O-O bond in peresters (as compared with TBHP[13]) could accelerate generation of the *tert*-butoxy radical, and potentially increase the reaction rate. In addition, without a free OH in these peresters, the formation of side product **5** would hopefully be suppressed.[14]

To quickly evaluate this hypothesis, we again leveraged HTE techniques. For the selection of catalysts, our screening focused on non-precious metal catalysts, [15, 16] including Fe, Cu, Co, Ni, Mn, all of which are well documented in the literature to promote redox reactions via a single electron transfer pathway.[17] While Fe, Co, Ni and Mn catalysts did not provide useful results (entries 3-8), to our delight, we observed that the combination of peresters and CuCl provided good conversion/%ee and avoided the formation of by-product **5**.



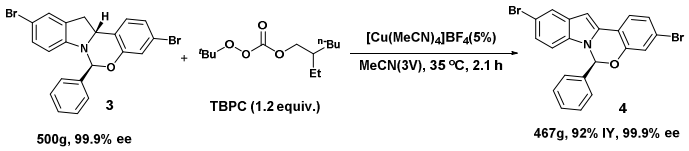
Entry	Catalyst	Oxidant	Solvent	Additive	Conversion	ee
1	$Cu(OAc)_2$	TBHP	MeCN	N/A	100%	98%
2	$Cu(OAc)_2$	TBHP	MeCN	K_2CO_3	100%	99%
3	$FeBr_2$	TBPB	MeCN	N/A	56%	67%
4	$Ni(OAc)_2$	TBPB	MeCN	N/A	20%	72%
5	$Co(OAc)_2$	TBPB	MeCN	N/A	35%	70%
6	CuOAc	TBPA	MeCN	N/A	5%	82%
7	$Mn(OAc)_2$	TBPA	MeCN	N/A	28%	79%
8	$Mn(OAc)_2$	TBPB	MeCN	N/A	37%	76%
9	CuCl	TBPA	MeCN	N/A	100%	88%
10	CuCl	TBPB	MeCN	N/A	100%	86%
11	CuCl	TBPC	MeCN	N/A	78%	99.9%
12	CuCl	DTBP	MeCN	N/A	10%	97%
13	$[Cu(MeCN)_4]BF_4$	TBPC	MeCN	N/A	100%	99.9%
14	$[Cu(MeCN)_4]BF_4$	TBPC	DMF	N/A	5%	99%
15	$[Cu(MeCN)_4]PF_6$	TBPC	MeCN	N/A	75%	99%

Table 1. Selected Screening Examples.

With *tert*-butyl peroxyacetate (TBPA) and *tert*-butyl peroxybenzoate (TBPB), we isolated indole **4** with 88% ee and 86% ee respectively (Table 1, entries 9 and 10). Control experiments subjecting indole **4** with 99% ee to the reaction conditions established that the hemiaminal ether stereocenter in **4** is robust and does not lose stereochemical integrity. Therefore, we suspected erosion of the starting material **3** during the reaction as the cause of the lower %ee observed in the indole product **4**. Further control experiments confirmed that **3** is indeed susceptible to epimerization under acidic conditions and the formation of acetic acid or benzoic acid by-products from TBPA/TBPB could be the reason for the %ee values observed in entries 9 and 10.[18] With these observations in mind, we turned our attention to *tert*-butylperoxy 2-ethylhexyl carbonate (TBPC), reasoning that the pH-neutral by-products (*tert*-butanol and 2-ethylhexanol) would avoid stereochemical erosion of the starting indoline **3**. This hypothesis was supported when we observed this oxidant provided indole **4** with 99.8% ee

using CuCl as catalyst. Using CuCl, it was difficult to further improve the reaction conversion due to the low solubility of this catalyst in organic solvents. Therefore, we sought alternative, potentially more soluble Cu(I) catalysts. Ultimately it was determined that tetrakis(acetonitrile)copper tetrafluoroborate-$[Cu(MeCN)_4]BF_4$ promotes a very clean reaction with good conversion and ee.[19]

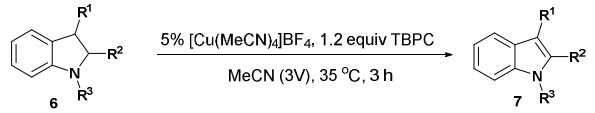
Having identified the optimal catalyst and oxidant, we then examined additional reaction parameters. A significant solvent dependence of reaction rate, ee, and conversion was observed, with MeCN being optimal among the common organic solvents studied.[20] The reaction can be carried out between 20 ^{o}C and 55 ^{o}C while maintaining high enantiomeric excess in the product indole **4**. We chose 35 ^{o}C as our preferred reaction temperature, balancing stability of TBPC against reaction rate.[21] At this temperature, we found that only 1.2 equiv. of TBPC is required to achieve full conversion of the indoline. The optimized process was demonstrated using 0.5 kg of indoline 3 and provided indole **4** in 92% isolated yield, 99.9% LCAP and 99.9% ee (Scheme 3). Importantly, indole **4** can be directly isolated via crystallization following addition of water at completion of the reaction.



Scheme 3. 500 g Scale Elbasvir Indoline Oxidation Demostration.

With the optimized conditions defined, we sought to test the generality of this process with respect to different indoline substrates. Using substituted indolines **6a-e** (entries 1-5,

Table 2), the desired indoles were obtained in good yields. Unsubstituted indoline **6f** (entry 6, Table 2) afforded the indole **7f** in moderate yield.



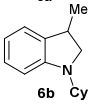
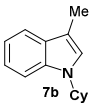
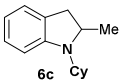
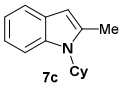
Entry	Indoline	Product	Yield
1	 6a	 7a	90%
2	 6b	 7b	85%
3	 6c	 7c	87%
4	 6d	 7d	75%
5	 6e	 7e	78%
6	 6f	 7f	40%

Table 2. Cu(I)-catalyzed indoline oxidation.

As demonstrated in the oxidation of our key substrate **3**, a significant advantage of this new method is its mild character, which maintains the stereochemical integrity of the sensitive hemiaminal ether. When a range of substituted indolines bearing an enantiomerically pure hemiaminal stereocenter were subjected to this condition, the desired indoles were obtained in excellent yield and ee. (Table 3)

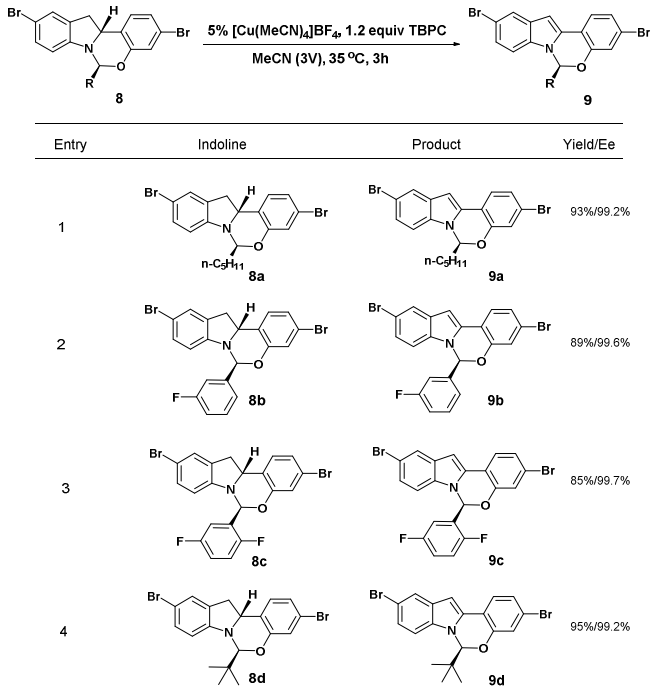


Table 3. Cu(I)-catalyzed indoline oxidation with hemiaminal stereocenter.

To gain deeper insight into this new Cu(I)-catalyzed process, we conducted several control experiments. It is known that the Cu(I) catalyst can be oxidized by organic peresters to generate Cu(II) species.[22, 23] However, when indoline **3** was subjected to a stoichiometric amount of the Cu(II) catalyst $[Cu(MeCN)_4](BF_4)_2$[24] in MeCN with K_2CO_3 as acid scavenger, we did not observe any indole **4** (only starting material was recovered; without K_2CO_3, decomposition of hemiaminal were observed since $[Cu(MeCN)_4](BF_4)_2$ is a strong Lewis acid). When indoline **3** was subjected to $[Cu(MeCN)_4](BF_4)$ in the absence of TBPC oxidant, we observed no product. Likewise, treatment of indoline **3** with TBPC in the absence of catalyst resulted in no conversion. These experiments suggest that the reactive species is the*t*-butoxy radical (asobserved by EPR experiments[25]), generated upon mixing the Cu(I) catalyst with TBPC. This is consistent with reports in the literature that Cu(I) can reduce peresters to form *tert*-butoxy radicals (the

Kharasch-Sosnovsky Reaction[22]). Taking all of these observations into account, we propose the Cu(I) catalyst undergoes a single electron transfer reaction with TBPC to provide the *tert*-butoxy radical, which then reacts with **3** via hydrogen abstraction reaction (HAT)[26] to give carbon radical species **10**.[27] A Cu(II)-mediated Kochi type radical oxidation reaction[28] could afford iminium **11** and subsequent aromatization could deliver the desired indole **4**. (Figure 2). To establish the presence of radicals in the desired process, we ran the reaction with one equiv. of BHT (radical inhibitor). This reaction provided mainly the recovered starting material, [29] which is consistent with the mechanistic hypothesis.

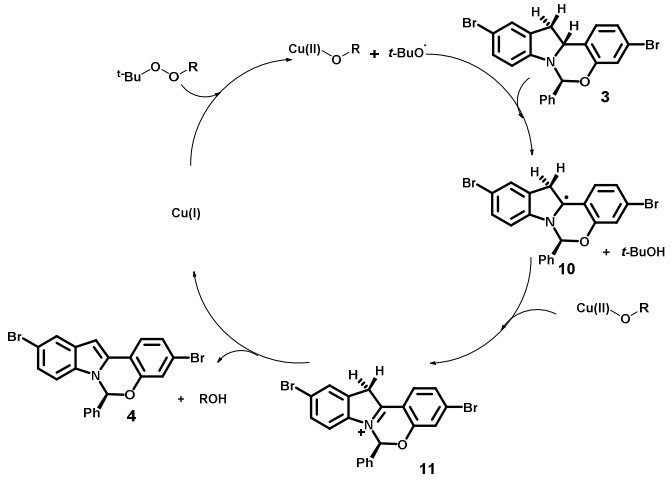


Figure 2. Proposed Mechanism

In summary, we utilized a blend of rational design and HTE experimentation to discover a new, general procedure for indoline oxidation to indoles. The novel combination of catalytic ($[Cu(MeCN)_4]BF_4$) with a readily available organic perester oxidant (TBPC) cleanly aromatizes indoline substrates to afford the desired indoles in good yield and with environmentally-friendly byproducts. This new method was demonstrated across a variety of indolines, including

some containing potentially sensitive chiral functional groups and good results were generally observed. Moreover, the method was applied to the synthesis of the HCV drug Elbasvir, resulting in smooth access to the key intermediate indole **4**. Given the ease of operation, ready availability of reagents and relative efficiency of this new oxidation process, we believe it will be of significant utility to the synthetic organic chemistry community.

Experimental Section

General Method Unless otherwise noted, all reactions were performed under a nitrogen atmosphere. All reagents and solvents were commercially available and used without further purification unless indicated otherwise. Yields reported are for isolated, spectroscopically pure compounds. NMR spectra were recorded on 400 or 500 MHz instruments. The residual solvent protons (^{1}H) or the solvent carbons (^{13}C) were used as internal standards. ^{1}H NMR data are presented as follows: chemical shift in ppm downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; qt, quartet of triplets; dd, doublet of doublets; dt, doublet of triplets; AB, AB quartet; m, multiplet. High-resolution mass spectra were recorded *on Q-TOF spectrometer*. HPLC condition for indole **4** (Xterra C8 150 x 4.6 mm, 3.5µm particle size): A, water with 0.1% ammonium hydroxide, B, acetonitrile, gradient from A:B 95:5 to A:B 15:85 in 20 mins, hold at A:B 15:85 for 5 mins. Run time 25 min, flow 1.2 ml/min, 20 ^{o}C, 220 nm UV detector. Chiral HPLC condition for enantiomeric excess analysis of compound **4**, **9b**, **9c** and **9d** (Chiralpak AS-RH, 150 x 4.6 mm, 5 um): A, water, B, acetonitrile, gradient from A:B 25:75 to A:B 10:90 in 10 mins, hold at A:B 10:90 for 2 mins. Run time 12 min,

flow 1.0 ml/min, 20 ^{o} C, 346 nm UV detector. SFC condition for enantiomeric excess analysis of compound **9a** (ChiralPak IA3- 150 mm x 4.6 mm): A, CO_2, B, IPA, gradient from A:B 99:1 to A:B 60:40 in 5 mins, hold at A:B 60:40 for 1 mins. Run time 6 min, flow 3.0 ml/min, 40 ^{o} C, 210 nm UV detector. Indoline **8a** to **8d** were prepared according to a Merck procedure.[7] Indoline **6a** to **6c** were prepared following Kikugawa's procedure.[30]

(6S,12aR)-3,10-dibromo-6-pentyl-12,12a-dihydro-6H-benzo[5,6][1,3]oxazino[3,4-a]indole (8a): gray solid, 1.1g, 91% IY. mp 113-115 ^{o}C. ^{1}H NMR (400 MHz, CD_3CN) δ 7.28 – 7.21 (m, 2H), 7.14 (dd, *J* = 8.3, 0.9 Hz, 1H), 7.09 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.88 (d, *J* = 1.9 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 5.69 (t, *J* = 7.0 Hz, 1H), 5.05 (d, *J* = 8.8 Hz, 1H), 3.51 (ddt, *J* = 16.1, 8.9, 1.3 Hz, 1H), 3.19 (d, *J* = 16.1 Hz, 1H), 1.90 (dt, *J* = 8.8, 6.6 Hz, 2H), 1.53 (td, *J* = 8.8, 7.8, 4.4 Hz, 2H), 1.40 – 1.29 (m, 4H), 0.95 – 0.86 (m, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 14.3, 22.5, 24.8, 31.2, 31.7, 36.1, 55.1, 83.4, 111.6, 112.2, 120.7, 123.9, 124.2, 128.4, 129.6, 130.2, 132.3, 148.7, 153.2; HRMS (ESI^+): calcd for $C_{20}H_{22}Br_2NO$ [M+H] 450.0068, found 450.0071.

***(6S,12aR)-3,10-dibromo-6-(3-fluorophenyl)-12,12a-dihydro-6H-benzo[5,6][1,3]oxazino[3,4-a]indole (8b)*: white solid, 1.2g, 93% IY, mp 116-118 ^{o}C** ^{1}H NMR (400 MHz, CD_3CN) δ 7.46 – 7.39 (m, 2H), 7.38 – 7.27 (m, 3H), 7.14 (d, *J* = 1.9 Hz, 1H), 7.13 – 7.09 (m, 1H), 7.07 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.03 – 7.00 (m, 1H), 7.00 – 6.97 (m, 1H), 6.91 (s, 1H), 4.77 (d, *J* = 8.9 Hz, 1H), 3.64 – 3.51 (m, 1H), 3.17 (d, *J* = 16.2 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 36.3, 55.5, 82.7, 112.2, 112.5, 113.9, 115.7, 115.9, 119.9, 120.8, 123.2, 124.1, 124.6, 124.7, 128.5, 129.6, 130.3, 131.4, 131.5, 132.4, 142.1, 141.3, 148.5, 153.2, 162.9 (d, 1JC-F = 244.1 Hz); ^{19}F NMR (470 MHz, DMSO-d_6): δ -111.97; HRMS (ESI^+): calcd for $C_{21}H_{15}Br_2FNO$ [M+H] 473.9504, found 473.9500.

(6S,12aR)-3,10-dibromo-6-(2,5-difluorophenyl)-12,12a-dihydro-6H-benzo[5,6][1,3]oxazino[3,4-a]indole (8c[7]): white solid, 1.25g, 92% IY. mp 171-173 ^{o}C. ^{1}H NMR (400 MHz, CD_3CN) δ 7.34 – 7.30 (m, 1H), 7.29 – 7.27 (m, 1H), 7.25 – 7.14 (m, 2H), 7.14 – 7.12 (m, 2H), 7.10 (dt, *J* = 8.2, 0.6 Hz, 1H), 7.08 – 7.03 (m, 2H), 7.00 (d, *J* = 8.4 Hz, 1H), 4.72 (d, *J* = 8.7 Hz, 1H), 3.49 (ddt, *J* = 16.2, 8.8, 1.3 Hz, 1H), 3.21 (d, *J* = 16.2 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 35.9, 55.2, 79.3, 112.1, 112.1, 114.7, 114.7, 114.9, 115.0, 117.5, 117.6, 117.7, 117.8, 118.5, 118.6, 118.8, 118.9, 119.4, 124.1, 127.1, 127.2, 127.3, 127.4, 128.6, 129.5, 130.4, 132.1, 148.1, 153.4, 154.9, 154.9, 158.1 (d, 1JC-F = 240.6 Hz), 156.1 (d, 1JC-F = 245.4 Hz); ^{19}F NMR (470 MHz, DMSO-d_6): δ-119.94, -119.90, −117.81, −117.77; HRMS(ESI$^+$): calcd for $C_{21}H_{14}Br_2F_2NO$ [M+H] 491.9410, found 491.9413.

(6S,12aR)-3,10-dibromo-6-(tert-butyl)-12,12a-dihydro-6H-benzo[5,6][1,3]oxazino[3,4-a]indole (8d): gray solid, 1.06 g, 90% IY. mp 107-109 ^{o}C. ^{1}H NMR (400 MHz, CD_3CN) δ 7.27 – 7.19 (m, 2H), 7.12 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.06 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.97 (d, *J* = 2.0 Hz, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 5.28 (d, *J* = 0.6 Hz, 1H), 5.16 – 5.08 (m, 1H), 3.59 – 3.48 (m, 1H), 3.35 – 3.26 (m, 1H), 1.11 (s, 8H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 26.5, 35.7, 38.1, 55.9, 90.1, 110.8, 111.4, 118.8, 120.7, 123.5, 124.3, 128.1, 128.7, 130.2, 130.9, 150.3, 154.8; HRMS (ESI$^+$): calcd for $C_{19}H_{20}Br_2NO$ [M+H] 435.9912, found 435.9924.

Representative Experimental Procedure for Cu-catalyzed oxidative aromatization of indolines to indoles using $[Cu(MeCN)_4](BF_4)$ and tert-Butylperoxy 2-ethylhexyl carbonate (TBPC):

To a 10 mL round bottom flask with a magnetic stir bar were charged indoline (500 mg), acetonitrile (1.5 mL) and $[Cu(MeCN)_4](BF_4)$ (0.05 mol equiv to indoline) under nitrogen. The reaction mixture was heated to 35 ^{o}C and charged with tert-Butylperoxy 2-ethylhexyl carbonate

(TBPC, 1.2 mol equiv to indoline) dropwise. The reaction was aged at 35 °C until completion. For reactions using indoling **6a** to **6f**, the reaction mixture was first quenched with 10% NaHSO3 solution, extracted with EtOAc, and concentrated down. The indole products **7a** to **7f** were isolated by flash chromatography (silica gel,hexane /ethyl acetate). For reactions using indoline **8a** to **8d**, the indole **9a** to **9d** were isolated by simply filtrating the reaction mixture. The isolated solid were washed with MeCN and dried under vacuum with nitrogen sweep.

(S)-3,10-dibromo-6-phenyl-6H-benzo[5,6][1,3]oxazino[3,4-a]indole (4[7]): white solid, 467 g (500 g scale reaction), 92% IY. 99.9% ee. mp 177-179 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.83 (d; *J* = 1.8 Hz; 1 H); 7.82 (t; *J* = 4.0 Hz; 2 H); 7.36 (d; *J* = 1.9 Hz; 1 H); 7.26–7.35 (m; 6 H); 7.17 (s; 1 H); 6.92–6.94 (m; 2 H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 83.4, 98.1, 112.6, 113.8, 117.2, 121.4, 122.3, 123.5, 125.7, 126.4, 126.7, 126.7, 129.3, 130.1, 130.7, 131.8, 134.3, 137.1, 150.1; HRMS (ESI$^+$): calcd for $C_{21}H_{14}Br_2NO$ [M+H] 455.9417, found 455.9435. $[\alpha]_{25}D$ = −113.6 (c = 1.0, CHCl3).

(6S,12aR)-3,10-dibromo-12a-(tert-butylperoxy)-6-phenyl-6H-benzo[5,6][1,3]oxazino[3,4-a]indol-12(12aH)-one (5): isolated as yellow oil in the $Cu(OAc)_2$/TBHP reaction by silica gel column, 80 mg (1 g scale reaction), 8% IY. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.71-7.67 (m, 1H), 7.65-7.55 (m, 3H), 7.30 – 7.22 (m, 3H), 7.20-7.15 (m, 2H), 7.08-7.03 (m, 1H), 6.9 (s, 1H), 1.25 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 26.7, 81.8, 83.6, 89.3, 113.8, 114.4, 114.7, 120.7, 123.8, 125.1, 125.8, 127.8, 127.9, 128.2, 128.7, 130.7, 135.7, 140.3, 152.4, 157.9, 193.6; HRMS (ESP): calcd for $C_{25}H_{21}Br_2NNaO_4$ [M+Na] 579.974, found 579.976.

1-cyclohexyl-1H-indole (7a[31]): colorless oil, 452 mg, 90% IY. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 – 7.67 (m, 1H), 7.45 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.28 (d, *J* = 3.2 Hz, 1H), 7.26 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.16 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.57 (dd, *J* = 3.2, 0.8 Hz, 1H), 4.29 (tt, *J* = 11.9, 3.7 Hz,

1H), 2.26 – 2.13 (m, 2H), 2.04 – 1.96 (m, 2H), 1.86 (ddt, *J* = 13.1, 3.4, 1.8 Hz, 1H), 1.82 – 1.72 (m, 2H), 1.57 (qt, *J* = 13.2, 3.5 Hz, 2H), 1.36 (qt, *J* = 13.6, 4.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.7, 26.0, 33.6, 55.1, 101.0, 109.4, 119.2, 121.0, 121.1, 124.0, 128.5, 135.6; HRMS (ESI^+): calcd for $C_{14}H_{18}N$ [M+H] 200.1439, found 200.1449.

1-cyclohexyl-3-methyl-1H-indole (7b[32]): isolated as oil, 427 mg, 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.44 – 7.37 (m, 1H), 7.31 – 7.24 (m, 1H), 7.18 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.07 (d, *J* = 1.1 Hz, 1H), 4.24 (ddt, *J* = 11.8, 7.5, 3.7 Hz, 1H), 2.42 (d, *J* = 1.1 Hz, 3H), 2.18 (ddt, *J* = 12.6, 3.9, 1.6 Hz, 2H), 2.06 – 1.96 (m, 2H), 1.87 (dtt, *J* = 11.4, 3.4, 1.7 Hz, 1H), 1.83 – 1.69 (m, 2H), 1.64 – 1.49 (m, 2H), 1.42 – 1.30 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 9.8, 25.8, 26.1, 33.6, 54.9, 109.2, 110.1, 118.5, 119.0, 121.1, 121.8, 128.6, 135.9; HRMS (ESI^+): calcd for $C_{15}H_{20}N$ [M+H] 214.1596, found 214.1606.

1-cyclohexyl-2-methyl-1H-indole (7c[33]): isolated as pale yellow oil, 437 mg, 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.52 (m, 2H), 7.15 (ddd, *J* = 8.5, 7.0, 1.4 Hz, 1H), 7.09 (ddd, *J* = 7.9, 7.0, 1.1 Hz, 1H), 6.28 (t, *J* = 0.9 Hz, 1H), 4.22 (tt, *J* = 12.3, 3.9 Hz, 1H), 2.51 (d, *J* = 1.0 Hz, 3H), 2.33 (tt, *J* = 12.7, 7.1 Hz, 2H), 2.08 – 1.92 (m, 5H), 1.91 – 1.79 (m, 1H), 1.61 – 1.30 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.2, 25.6, 26.5, 31.5, 55.8, 100.5, 111.2, 118.7, 119.7, 119.9, 128.6, 135.6, 136.2; HRMS (ESI^+): calcd for $C_{15}H_{20}N$ [M+H] 214.1596, found 214.1595.

1-benzyl-1H-indole (7d[34]): isolated as oil, 375 mg, 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.39 – 7.10 (m, 10H), 6.61 (dd, *J* = 3.1, 0.9 Hz, 1H), 5.37 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 50.1, 101.7, 109.7, 119.5, 121.0, 121.7, 126.8, 127.6, 128.3, 128.8, 136.3, 137.6; HRMS (ESI^+): calcd for $C_{15}H_{14}N$ [M+H] 208.1126, found 208.1133.

(S)-3,10-dibromo-6-pentyl-6H-benzo[5,6][1,3]oxazino[3,4-a]indole (9a): white solid, 466 mg, 93% yield, 99.2% ee. mp 131-133 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 1.9 Hz, 1H), 7.53 (d, *J* = 8.6 Hz, 1H), 7.32 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.30 – 7.22 (m, 2H), 7.14 (d, *J* = 8.6 Hz, 1H), 6.74 (s, 1H), 6.27 (dd, *J* = 8.7, 4.5 Hz, 1H), 1.95 (dtd, *J* = 14.3, 9.4, 5.1 Hz, 1H), 1.73 (td, *J* = 9.6, 5.0 Hz, 1H), 1.64 – 1.37 (m, 3H), 1.30 (dq, *J* = 7.6, 4.5, 3.6 Hz, 4H), 0.89 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 22.4, 24.4, 31.1, 34.2, 84.2, 96.2, 110.2, 113.7, 116.8, 121.3, 122.4, 123.4, 125.1, 125.2, 126.1, 130.6, 133.0, 149.3; ^{19}F NMR (470 MHz, DMSO-d_6): δ -112.22; HRMS (ESI^+): calcd for $C_{20}H_{20}Br_2NO$ [M+H] 447.9911, found 447.9925.

(S)-3,10-dibromo-6-(3-fluorophenyl)-6H-benzo[5,6][1,3]oxazino[3,4-a]indole (9b): white solid, 447 mg, 89% yield, 99.6% ee. mp 143-145 ^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (d, *J* = 1.8 Hz, 1H), 7.86 (s, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.43 (d, *J* = 1.9 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 1H), 7.37 – 7.26 (m, 3H), 7.18 (d, *J* = 8.0 Hz, 2H), 6.81 (dt, *J* = 9.7, 2.1 Hz, 1H), 6.63 (dt, *J* = 7.7, 0.9 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 82.6, 98.3, 112.6, 113.6, 113.8, 114.0, 116.9, 117.1, 117.2, 121.5, 122.4, 122.6, 123.5, 125.9, 126.5, 126.9, 130.6, 131.5, 131.6, 131.6, 134.2, 140.0, 149.7, 162.6 (d, 1JC-F = 245.4 Hz); HRMS (ESI^+): calcd for $C_{21}H_{13}Br_2FNO$ [M+H] 471.9348, found 471.9343.

(S)-3,10-dibromo-6-(2,5-difluorophenyl)-6H-benzo[5,6][1,3]oxazino[3,4-a]indole (9c[7]): white solid, 427 mg, 85% yield, 99.7% ee. mp 190-192 ^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.02 (s; 1 H); 7.88–7.90 (m; 2 H); 7.38–7.46 (m; 2 H); 7.35 (dd; *J* = 8.28; 1.93 Hz; 1 H); 7.28–7.31 (m; 2 H); 7.25 (s; 1 H); 5.80 (ddd; *J* = 8.45; 5.51; 3.20 Hz; 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 79.3, 98.4, 112.8, 113.7, 113.8, 114.0, 114.0, 114.3, 116.8, 118.7, 118.8, 118.9, 119.0, 119.1, 119.2, 119.3, 119.4, 121.1, 122.5, 123.6, 125.6, 125.6, 125.7, 125.8, 126.0, 126.6, 127.2, 130.7, 131.8, 133.7,

149.3, 156.5 (d, 1JC-F = 245.3 Hz), 158.5 (d, 1JC-F = 241.2 Hz); HRMS (ESI^+): calcd for $C_{21}H_{12}Br_2F_2NO$ [M+H]489.9254, found 489.9246. $[\alpha]_{25}D$ = −124.5 (c = 0.4, DMF)

(S)-3,10-dibromo-6-(tert-butyl)-6H-benzo[5,6][1,3]oxazino[3,4-a]indole (9d): white solid, 472 mg, 95% yield, 99.2% ee. 134-136 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 1.9 Hz, 1H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.34 – 7.14 (m, 4H), 6.73 (s, 1H), 6.04 (s, 1H), 0.97 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 26.7, 42.1, 90.0, 96.2, 111.8, 113.5, 117.4, 119.7, 122.4, 123.1, 124.9, 125.6, 130.5, 131.7, 134.5, 151.3; HRMS (ESI^+): calcd for $C_{19}H_{18}Br_2NO$ [M+H] 433.9755, found 433.9767.

500g indoline 3 oxidation demonstration:

To a 2 L jacket flask with an overhead stir were charged indoline **3** (500 g), acetonitrile (1.5 L) and $[Cu(MeCN)_4](BF_4)$ (17.2 g) under nitrogen. The reaction mixture was heated to 35 ^oC and charged with tert-Butylperoxy 2-ethylhexyl carbonate (TBPC, 367 mL) in 1.5 h via pump. The reaction was aged at 35 ^oC until completion (2.1 h). The resulting slurry was then cooled down to rt, filtered. The cake was then washed with 1 L MeCN once, 2 L MeCN/water (1:1, v/v) once, and 2 L water once. The cake was then dried under vacuum with N_2 sweep for 24 h. total 467 g indole **4** was obtained with 98.8 NMR wt%, 99.9% LCAP, and 99.9% ee. 92% isolated yield. Assay about 3% mother liquor loss.

Experimental Procedure for Spin Trap of Proposed *tert*-Butoxy Radical for X-band *cw*-EPR Observation: DMPO (5,5-Dimethyl-1-pyrroline N-oxide) was used as the spin trap molecule. The EPR sample solution was made by mixing Solution A (60mM $[Cu(MeCN)_4](BF_4)$ in MeCN) and Solution B (60mM TBPC and 60mM DMPO in MeCN) at 1:1 v/v ratio, and 40 uL of the resulting mixture was quickly transferred to a glass capillary tube for reaction monitoring by EPR

spectroscopy. A broad quartet signal between 3000-3300G arises from Cu^{2+} (spin 3/2) produced during the reaction, which plateaus after 3hours signalling reaction completion. The DMPO adduct produces a sharp multiplet at 3330-3390G, which quickly builds up and then decays within an hour. The relatively short signal duration reflects limited stability of the DMPO adduct. Spectral simulation yielded hyperfine coupling constants aN, aHβand aHγ of 13.3G, 7.7G, and 0.9G respectively. At 4 hours, an aliquot of the original mixture was sampled, diluted 100x in MeCN, and analyzed by direct infusion MS. MS (ESI+): calcd for $C_{10}H_{20}NO_2$ [M+H] 187, found 187.3.[35]

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Supporting Information: Summary of high-throughput experimentation results, EPR study results, chiral HPLC for ee assessment, and copies of ^{1}H and ^{13}C NMR spectra.

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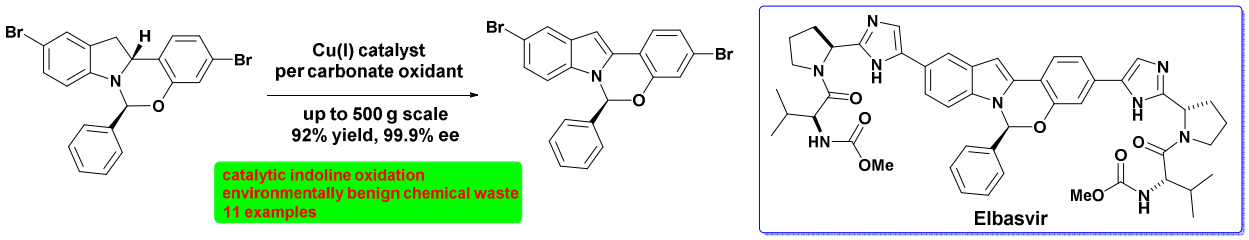
TOC: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11 examples
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