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Asymmetric Synthesis of Cyclic Indole Aminals via 1,3-Stereoinduction

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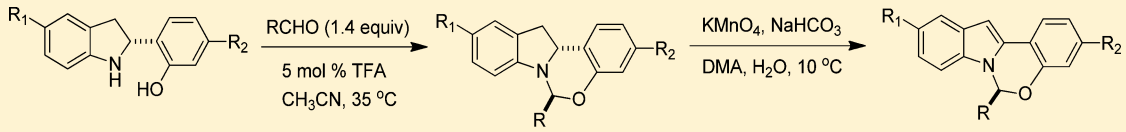
Supporting Information

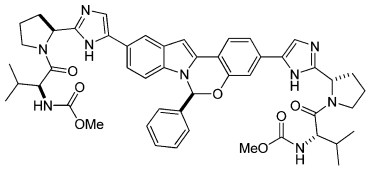


ABSTRACT: A general and efficient asymmetric synthesis of cyclic indoline aminals was developed with a high level of 1,3-stereoinduction through a dynamic crystallization-driven condensation. Dehydrogenation of the indoline aminals with potassium permanganate produced the corresponding cyclic indole aminals in high yields and excellent enantioselectivities. This general methodology was successfully applied to the synthesis of a wide variety of chiral cyclic indoline aminals and indole aminals with aromatic and aliphatic functional groups.

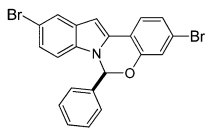
INTRODUCTION

Chiral *N,O*-aminals are important structural motifs present in a variety of natural products and pharmaceuticals.[1,2] The stereochemical importance of this motif to biological activity is well known and has been illustrated by different bioactivity of their enantiomers in a series of studies.[3] MK-8742 is a potent and selective NS5a inhibitor recently disclosed by Merck & Co for the treatment of HCV.[4] The development of MK-8742 and its key intermediate, chiral indole aminal **2a**, highlight the importance of the chiral *N,O*-aminal structure. Efficient synthesis of chiral *N,O*-aminals has been a challenge of growing interest in the synthetic community.[5−7] Despite significant efforts toward the synthesis of chiral *N,O*-aminals, there are few methods to construct enantiomerically pure aminals. Antilla reported an elegant synthesis of acyclic *N,O*-aminals with high enantioselectivity based on catalytic asymmetric addition of alcohols to *N*-acylimines in the presence of chiral phosphoric acids.[8] This methodology was later extended by List to imines generated in situ from aldehydes and hydroxyamides to direct synthesis of cyclic *N,O*-aminals with excellent enantioselectivities in the presence of a novel *N*-phosphinylphosphoramide as chiral Bronsted acid catalyst.[9,10] Recently, Rhee reported a synthesis of stereodefined acyclic *N,O*-aminals via Pd-catalyzed intermolecular addition of chiral homopropargylic amine to alkoxyallene.[11,12] Nevertheless, developing a novel, practical, and efficient asymmetric synthesis of chiral *N,O*-aminals still remains a challenging and relevant synthetic problem.

We have recently reported enantioselective synthesis of HCV NS5a inhibitor MK-8742.[13] MK-8742 was synthesized from the key intermediate chiral cyclic indole aminal **2a**. Establishing the chiral center of this intermediate in a practical and efficient manner represents a key challenge in the overall synthesis of this molecule. The most straightforward synthesis of indole aminal **2a** would involve a direct condensation of indole **3** with benzaldehyde mediated by Lewis acids such as chiral phosphoric acids (Scheme 1, **A**).[9] Unfortunately, under such conditions, cyclization occurred on the C3 carbon of the indole rather than the nitrogen, producing compound **4** as the major product due to the nucleophilicity of the C3 carbon of the indole ring.[14] Other attempts such as *N,O*-alkylation of indole **3** with dibromomethylbenzene under phase-transfer conditions were also not successful.[15] To circumvent the reactivity of the C3 carbon of the indole ring, we envisioned that indoline **6a** could be condensed diastereoselectively with benzaldehyde to install the desired *N,O*-aminal stereocenter through chirality transfer via 1,3-stereoinduction (Scheme 1, **B**). We reasoned that iminium species **7** would preferentially adopt an (*E*)-geometry to minimize van der Waals interactions between the phenyl ring and the proximal aryl hydrogen of the indoline.[16] As a result, the stereochemistry of the indoline would then direct the attack of the phenol selectively to the *Si* face of the iminium species, ensuring a stereocontrol via 1,3-induction.[17] In addition, DFT calculations found *trans*-indoline aminal **5a** is more stable than *cis*-indoline aminial by about 1 kcal/mol.[18]



MK-8742, 1



2a

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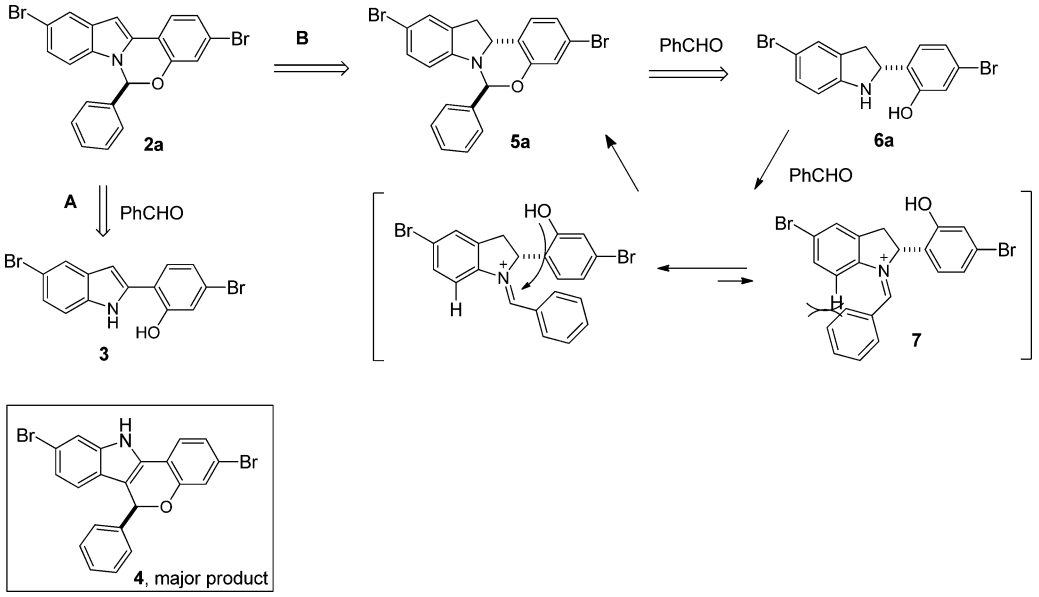
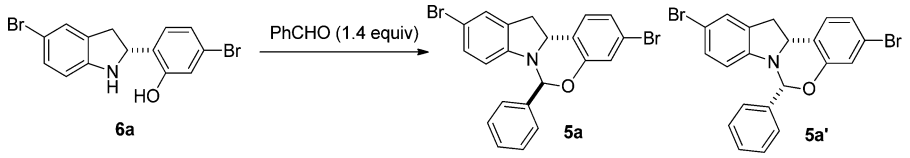
Scheme 1. Retrosynthesis of 2a[a]



[a]Route A: indole condensation with PhCHO. Route B: indoline condensation with PhCHO via 1,3-stereoinduction.

Table 1. Acid Screening for Indoline 6a Condensation with PhCHO



entry	acid (equiv)	solvent (v, mL/g)	temp (°C)	% conv[a]	dr (**5a**/**5a**′)[b]
1	$Ti(O\text{-}i\text{-}Pr)_4$ (0.2)	toluene (20)	100	60	6:1
2	$Ti(O\text{-}i\text{-}Pr)_4$ (1.0)	toluene (20)	100	90	>20:1
3	*p*-TSA (0.2)	CH_3CN (10)	50	73	5:1
4	MSA (0.2)	CH_3CN (10)	50	63	6:1
5	$BF_3{\cdot}OEt_2$ (0.2)	CH_3CN (10)	50	69	5:1
6	HCl (0.2)	CH_3CN (10)	50	70	6:1
7	H_3PO_4 (0.2)	CH_3CN (10)	50	81	6:1
8	CF_3COOH (0.2)	CH_3CN (10)	50	83	6:1
9	CF_3COOH (0.05)	CH_3CN (5)	40	98	93:7
10	CF_3COOH (0.05)	CH_3CN (5)	35	99	96:4

[a]Determined by achiral HPLC. [b]dr of the reaction mixture was determined by achiral HPLC.

Thus, under equilibrating condition, one expects **5a** to be the major product. The diastereospecific indoline aminal **5a** could be oxidized in the following step to form chiral indole aminal **2a** to complete the stereochemical relay.

Herein, we report a general methodology of asymmetric syntheses of cyclic indoline aminals and chiral cyclic indole aminals through this 1,3-stereoinduction strategy.

RESULTS AND DISCUSSION

With chiral indolines prepared in hand,[13,19,20] we first investigated the condensation of indoline **6a** with benzaldehyde under acidic conditions. We were delighted to find that the cyclic indoline aminal **5a** was formed with good diastereoselectity (dr 6:1, Table 1, entry 1) in the presence of 20 mol % of $Ti(O\text{-}i\text{-}Pr)_4$ in toluene. The result could be further improved by the use of a stoichiometric amount of $Ti(O\text{-}i\text{-}Pr)_4$ (dr >20:1, Table 1, entry 2). However, the use of a stoichiometric amount of $Ti(O\text{-}i\text{-}Pr)_4$ generated workup and isolation issues. Nevertheless, this exciting result promoted us to carry out a careful survey of Lewis acids for the condensation of indoline **6a** with benzaldehyde. As shown in Table 1, entries 3−8, several acids all gave similar dr (5:1 to 6:1) and incomplete conversion (70−83%). Longer reaction time did not improve the conversion but led to slightly decreased diastereoselectivity. This observation implies that under acidic conditions the condensation reaction is in a reversible equilibrium such that indoline aminal can go back to the indoline. Consistent with this hypothesis, use of excess benzaldehyde (2 equiv) did not drive the condensation to full conversion. We envisioned that we could take advantage of the facile equilibrium of the aminal formation in solution and the solubility difference of aminal diasteromers to promote a dynamic diastereoselective transformation in which crystallization of the desired diastereomer would drive the selectivity and equilibrium.[21] We chose trifluoroacetic acid (TFA) as a catalyst to further optimize the reaction since TFA is a mild and inexpensive reagent and provided slightly better performance in

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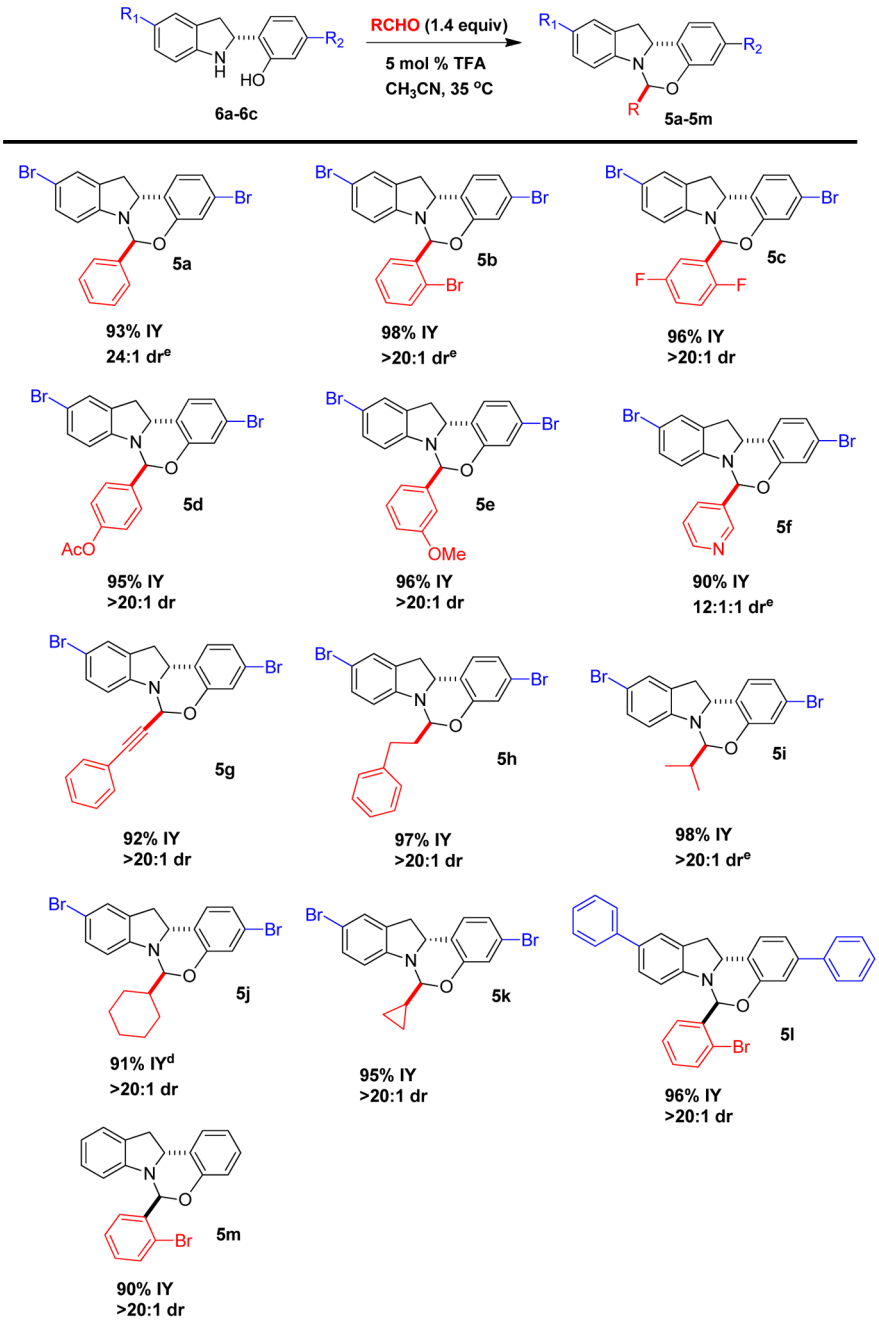
Table 2. Substrate Scope for Indoline Condensation with Aldehydes via 1,3-Stereoinduction[a–c]



[a]Reaction conditions: indoline 500 mg, 1.4 equiv of aldehyde, 5 mol % of TFA, 35 °C, CH_3CN (5 vol), 3 h. [b]isolated yield. [c]dr determined by HPLC with crude reaction mixture. [d]10% TFA, 40 °C, 15 h. [e]NMR NOE study confirmed *trans* stereochemisty of indoline aminal products (see the Supporting Information).

the 1,3-induction. Parameters such as equivalents of TFA, reaction concentration, and reaction temperature were carefully evaluated and optimized to favor the dynamic crystallization process during the course of the reaction (Table 1, entries 9 and 10). As a result, we could crystallize out the desired diastereomer from the reaction solution and drive the reaction to >98% conversion with 96:4 dr. After quenching the reaction with 10 wt % aqueous $NaHCO_3$, indoline aminal **5a** was isolated as crystalline solid with 93% yield and excellent diasteroselectivity (dr 99:1) via direct crystallization by addition of water. The *trans* stereochemistry of indoline aminal **5a** was determined and confirmed by NMR NOE study (see the Supporting Information for details).

Having identified the optimal conditions for the formation of indoline aminals, we next applied these conditions to a variety of aromatic and aliphatic aldehydes. As shown in Table 2, sterically hindered aromatic aldehydes and electron-deficient and electron-rich aldehydes all condensed rapidly with indoline **6a** to product cyclic indoline aminals (**5b–5e**) in 3 h with excellent dr and high yields after direct crystallization from acetonitrile and water. Interestingly, 3-pyridinyl aldehyde readily condensed with indoline **6a** but no crystallization occurred, but the condensation went to full completion with a

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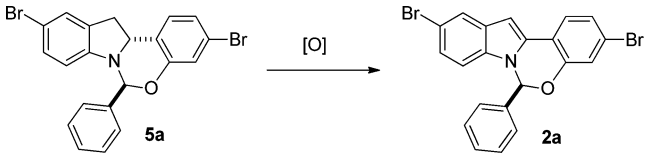
dr ratio of 12:1, and the product (**5f**) was isolated in 90% yield with dr >20:1 upon simple addition of water for crystallization. Aliphatic aldehydes worked equally well with indoline **6a** under optimized conditions through a dynamic crystallization-driven condensation. For example, phenylpropargyl aldehyde and 3-phenylpropionaldehyde both condensed smoothly with indoline **6a**. Some aliphatic aldehydes such as cyclohexanecarboxaldehyde react more slowly and hence need a longer reaction time and higher equivalents of TFA to achieve full conversion. It is noted that cyclopropanecarboxaldehyde condensed successfully with indoline under optimized conditions to form indoline aminal **5k** with an excellent yield and dr. Other indolines **6b** and **6c**[20] reacted well with sterically hindered aldehydes to form cyclic indoline aminals (**5l** and **5m**) with high diastereoselectivities and excellent yields. To validate our stereochemical rationale, we confirmed the stereochemistry of indoline aminals **5b**, **5f**, and **5i** by NMR NOE study.

Having prepared a wide variety of *trans* cyclic indoline aminals, we next evaluated conditions for the dehydrogenation of these species to indole aminals. Dehydrogenation of indoline aminal **5a** over noble metal catalysts such as ruthenium on carbon at elevated temperature did facilitate the reaction but with low conversion (Table 3, entry 1).[22] Oxidation with MnO_2 also led to low reactivity (Table 3, entry 2). Various low-valent transition metals known to mediate dehydrogenation of unsaturated systems were also examined and optimized.[23] Treatment of indoline aminal **5a** (99.6% ee, dr 99:1) with 4 mol % of $Mn(OAc)_2$ and 8 mol % of 2,2′-bipyridine and *tert*-butyl peroxide as an oxidant gave indole aminal product with high conversion; however, unexpectedly significant levels of racemization of the aminal center (20% ee) were observed (Table 3, entry 3). When 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) was used as an oxidant, the reaction gave clean conversion but various levels of racemization of the aminal stereocenter were observed (Table 3, entry 4 and 5). This phenomenon was highly dependent on the nature of the solvents, which may be related to DDQ radical mechanism.[24] When chlorobenzene was used as a solvent DDQ oxidation provided indole **2a** best with 90% ee. During continued oxidant surveys, we found that a stoichiometric amount of potassium permanganate mediate the desired dehydrogenation with

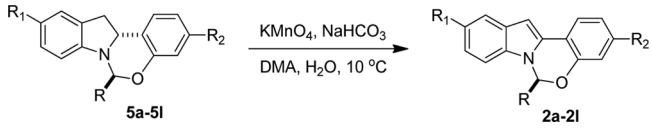
Table 3. Oxidation Evaluation for Dehydrogenation of Indoline to Indole Aminals



entry	oxidant	solvent	temp (°C)	% conv[a]	% ee[b]
1	Ru/C	toluene	100	30	nd
2	MnO_2	CH_2Cl_2	rt	~10	nd
3	$Mn(OAc)_2$/bipy/ *t*-BuOOH	CH_3CN	50	95	20
4	DDQ	CH_2Cl_2	rt	100	60
5	DDQ	PhCl	rt	100	90
6	$KMnO_4$	DMAc	rt	100	98
7	$KMnO_4$/$NaHCO_3$	DMAc	rt	100	99

[a]Determined by achiral HPLC. [b]Determined by chiral HPLC (for HPLC methods, see the Supporting Information).

Table 4. Substrate Scope for Dehydrogenation of Indoline Aminals to Indole Aminals[a]



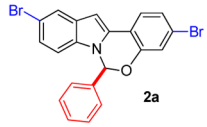
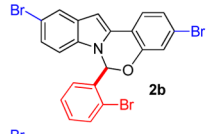
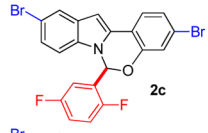
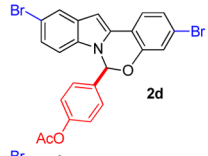
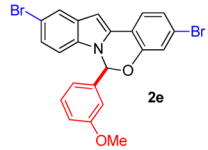
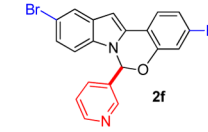
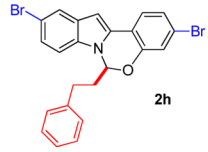
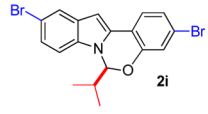
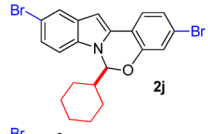
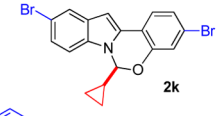
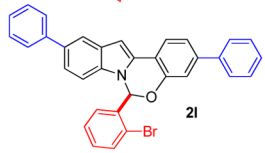
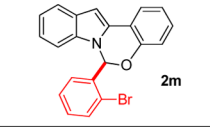
Entry	Indole product	Yield[b]	ee[c]	$[\alpha]_D^{25}$	Config.[h]
1	 2a	85%	99.8%	-114.1[f]	*s*
2	 2b	88%[d]	99.5%	-118.4[g]	*s*
3	 2c	90%	99.5%	-124.0[g]	
4	 2d	82%[e]	99.3%	-136.7[g]	
5	 2e	85%	99.5%	-141.6[g]	
6	 2f	82%	90.6%	-109.0[g]	
7	 2h	82%	98.6%	-111.4[g]	
8	 2i	84%	99.4%	-154.6[g]	
9	 2j	80%[e]	99.7%	-162.2[g]	*s*
10	 2k	83%	93.9%	-127.5[g]	*s*
11	 2l	87%[d]	99.1%	-138.6[g]	
12	 2m	89%[d]	99.0%	-172.1[g]	

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Table 4. continued

[a]Reaction conditions: 1.6−2.0 equiv of $KMnO_4$, 2 equiv $NaHCO_3$, DMAc (10 vol), and water (1 vol), 10 °C. [b]Isolated yield. [c]Determined by chiral HPLC, see the Supporting Information. [d]4.0 equiv of $KMnO_4$. [e]Run at 0 °C. [f]c = 1.0, $CHCl_3$. [g]c = 0.4, DMF. [h]Absolute configuration was confirmed by vibrational circular dichroism (VCD).

minimal racemization of the aminal stereocenter (Table 3, entry 6). Under basic conditions, the reaction can achieve full conversion with 99% ee of the desired indole aminal (Table 3, entry 7). After workup and recrystallization of the product from IPA, the indole aminal **2a** was isolated with 85% yield and 99.5% ee (Table 4, entry 1). The absolute configuration of aminal center of **2a** is confirmed to be (*S*) by VCD study.

This dehydrogenation protocol with potassium permanganate was readily applied to a variety of indoline aminals to provide chiral cyclic indole aminals (Table 4). To minimize overoxidation, the optimal amount of potassium permanganate was determined to be between 1.6 and 2.0 equiv, and the optimal reaction temperature was 10 °C. Compounds **2d** and **2j** in Table 4, entries 4 and 9, are prone to overoxidation, so the reactions were run at 0 °C. For hindered indoline aminals **5b**, **5l**, and **5m** (Table 4, entries 2, 11, and 12), the reaction required use of 4 equiv of potassium permanganate for full conversion. Upon workup and crystallization all reactions afforded indole aminals with good isolated yields and excellent enantioselectivities (>99% ee). The absolute configuration of indole aminals **2b**, **2j**, **2k** was also confirmed to be *S* enantiomer by VCD study.

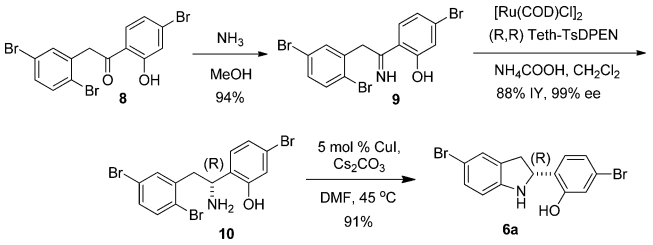
CONCLUSION

A novel, efficient, and practical asymmetric synthesis of cyclic indoline aminals was developed via 1,3-stereoinduction through a dynamic crystallization-driven condensation. Dehydrogenation of indoline aminals with potassium permanganate produced cyclic indole aminals in high yields and excellent ee with minimal racemization of the aminal center. This methodology for the synthesis of chiral cyclic indoline aminals and indole aminals was successfully applied to a variety of aromatic and aliphatic aldehydes. This approach contributes the broad utility of chirality relay strategies.

EXPERIMENTAL SECTION

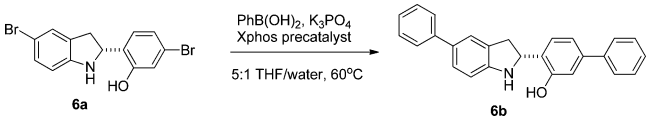
All reagents and solvents were purchased commercially and used directly without further purification. All reactions were carried out under nitrogen. Chiral indolines were prepared according to the literature procedure[13,18] or can be prepared by reduction of indole followed by classic resolution with chiral acids or by chiral SFC separation for each enantiomer. ^1H and ^{13}C NMR spectra were recorded on a 400 or 500 NMR spectrometer with chemical shifts reported in ppm relative to the residual $CDCl_3$ or DMSO-d_6. High resolving power accurate mass measurements were acquired by use of a Fourier transform ion cyclotron resonance (FTICR) mass spectrometer. Samples were dissolved in acetonitrile/water/acetic acid (50:50:0.1%v/v) and ionized by use of electrospray ionization (ESI) yielding $[M + H]^+$. External calibration was accomplished with oligomers of polypropylene glycol (PPG, average molecular weight 1000 Da). All reactions were monitored by achiral HPLC (Ascentis Express C18 2.7 μm, 100 mm × 4.6 mm), A: water with 25 mM NH_4OAc pH 6.8, B: acetonitrile, gradient from 90:10 A:B to 10:90 A:B over 8 min, hold at 10:90 A:B for 2 min, run time 10 min, flow 1.5 mL/min, 40 °C, 210 nm UV detector.

(*R*)-5-Bromo-2-(5-bromoindolin-2-yl)phenol (6a). Compound **6a** was prepared with 99.6% ee based on ref 13 and its Supporting Information.



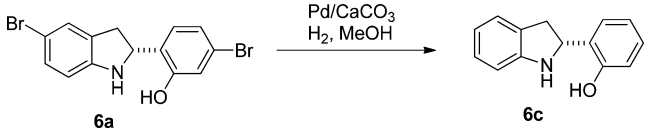
NMR Data of Indoline **6a**: ^1H NMR (400 MHz, DMSO): δ 10.04 (s; 1 H); 7.22 (d; J = 8.16 Hz; 1 H); 7.11 (s; 1 H); 7.06 (dd; J = 8.27; 2.07 Hz; 1 H); 6.97 (d; J = 1.98 Hz; 1 H); 6.94 (dd; J = 8.20; 1.97 Hz; 1 H); 6.51 (d; J = 8.23 Hz; 1 H); 6.14 (s; 1 H); 5.00 (t; J = 8.72 Hz; 1 H); 3.43 (dd; J = 16.15; 9.39 Hz; 1 H); 2.63 (dd; J = 16.14; 7.95 Hz; 1 H). ^{13}C NMR (100 MHz, DMSO): δ 37.5, 57.3, 107.9, 110.0, 118.0, 120.1, 121.9, 127.4, 128.5, 130.0, 130.8, 131.0, 151.6, 156.0 ppm. HRMS: ESI$^+$ $[M + 1]^+$ calcd for $C_{14}H_{12}Br_2NO$ 369.9260, found 369.9258.

Preparation of (*R*)-4-(5-Phenylindolin-2-yl)[1,1′-biphenyl]-3-ol (6b).



A three-neck flask was charged with indoline **6a** (2g, 5.4 mmol), phenylboronic acid (1.5 g, 2.3 equiv, 12.5 mmol), and K_3PO_4 (6 equiv, 6.9 g), degassed THF (40 mL) and water (8 mL) were added, the solution was degassed with N_2 bubbles for 30 min, Xphos biphenyl precatalyst (6 mol %, 256 mg, CAS no. 1310584-14-5) was added, and the solution was degassed for 15 min and then heated to 60 °C under N_2. The reaction went to completion in 3 h. The reaction mixture was cooled to rt, water was added, and the mixture was extracted with EtOAc three times. The combined organic phase was dried and concentrated. Indoline **6b** was crystallized in MTBE as a gray solid (1.25g, 60% yield, 99.5% ee), mp 167−170 °C. NMR data of **6b**: ^1H NMR (400 MHz, DMSO): δ 9.71 (s; 1 H); 7.57 (d; J = 1.63 Hz; 1 H); 7.55 (t; J = 2.33 Hz; 2 H); 7.52 (d; J = 1.24 Hz; 1 H); 7.40−7.45 (m; 3 H); 7.31−7.39 (m; 5 H); 7.28 (dd; J = 8.08; 1.94 Hz; 1 H); 7.21 (t; J = 7.36 Hz; 1 H); 7.04−7.08 (m; 2 H); 6.68 (d; J = 8.06 Hz; 1 H); 6.16 (d; J = 2.33 Hz; 1 H); 5.11−5.16 (m; 1 H); 3.51 (dd; J = 15.78; 9.25 Hz; 1 H); 2.78 (dd; J = 15.78; 7.85 Hz; 1 H). ^{13}C NMR (100 MHz, DMSO): δ 37.9, 57.6, 108.7, 113.7, 117.8, 123.2, 126.1, 126.2, 126.4, 126.9, 127.3, 127.7, 129.2, 129.4, 129.8, 130.6, 140.3, 140.7, 141.6, 152.1, 155.3 ppm. HRMS: ESI$^+$ $[M + 1]^+$ calcd for $C_{26}H_{22}NO$ 364.1696, found 364.1707.

Preparation of (*R*)-2-(Indolin-2-yl)phenol (6c).



Indoline **6a** (1 g) and MeOH (20 mL) were added to an endeavor tube for hydrogenation reactions, charged with 5 wt % Pd/$CaCO_3$ (manufactured by Johnson Matthey, <lot no. 155692001 Type A303060>). The tube was purged with nitrogen and vacuums three times and with hydrogen three times, the H_2 pressure was set to 50 psi with an agitation rate of 1000 rpm at room temperature. The reaction went to full conversion as monitored by HPLC after 20 h. The reaction mixture was filtered through Celite to remove the catalyst and rinsed with MeOH. The organic solution was concentrated and recrystallized with CH_3CN/water 1:1 to get pure indoline **6c** as white solid (0.90 g, 90% yield, 99.6% ee), mp 180−184 °C. ^1H NMR (400 MHz, DMSO): δ 7.47−7.49 (m; 1 H); 7.30−7.39 (m; 4 H); 7.23−

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7.27 (m; 1 H); 6.99−7.01 (m; 1 H); 6.84 (td; J = 7.49; 1.16 Hz; 1 H); 5.36 (t; J = 8.45 Hz; 1 H); 3.58 (dd; J = 16.23; 8.75 Hz; 1 H); 3.46 (dd; J = 16.23; 8.18 Hz; 1 H). ^{13}C NMR (100 MHz, DMSO): δ 35.0, 59.1, 116.0, 119.0, 119.6, 122.6, 126.1, 128.5, 128.6, 129.0, 130.7, 135.2, 138.1, 156.1 ppm. HRMS ESI$^+$ $[M + 1]^+$ calcd for $C_{14}H_{14}NO$ 212.1070, found 212.1075.

General Procedure for the Preparation of Cyclic Indoline Aminals 5a−m. To a 8 mL vial charged with indoline (500 mg) and aldehyde (1.4 equiv) was added TFA (0.05 equiv) in acetonitrile (2.5 mL, 5 vol), aged at 35 °C under N_2. The reaction generally went to completion in ∼3 h as monitored by HPLC (note: neutral buffer pH 6.8−7.5 (25 mM NH_4OAc in water) for HPLC was used; HPLC using acidic pH buffer will cause the compound to degrade on the column). The reaction was quenched with 0.5 mL of 10 wt % $NaHCO_3$ solution, followed by addition of 2.0 mL of water dropwise and aged at rt for 2 h for recrystallization. The reaction slurry was filtered and the cake washed with 5 mL of CH_3CN/water 1:1. The product cake was dried in the oven at 50 °C under vacuum.

*(6S,12aR)-3,10-Dibromo-6-phenyl-12,12a-dihydro-6H-benzo-[5,6][1,3]oxazino[3,4-a]indole (**5a**).*[13] Indoline **6a** (2 g) scale reaction was run, and the indoline aminal product was directly crystallized in 1:1 CH_3CN/water as a gray solid (2.24g, 93% yield, dr 99:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d; J = 7.33 Hz; 2 H); 7.29−7.39 (m; 4 H); 7.23 (s; 1 H); 7.09 (s; 1 H); 7.00 (d; J = 8.40 Hz; 1 H); 6.78−6.88 (m; 3 H); 4.73 (d; J = 8.87 Hz; 1 H); 3.55 (dd; J = 15.68; 8.96 Hz; 1 H); 3.13 (d; J = 15.70 Hz; 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.1, 55.5, 83.1, 110.9, 112.6, 120.3, 121.2, 123.8, 124.4, 126.8, 127.9, 128.49, 128.54, 128.8, 130.4, 131.5, 137.6, 148.0, 153.2 ppm. HRMS: ESI$^+$ $[M + 1]^+$ calcd for $C_{21}H_{16}Br_2NO$ 457.9573, found 457.9579.

*(6S,12aR)-3,10-Dibromo-6-(2-bromophenyl)-12,12a-dihydro-6H-benzo[5,6][1,3]oxazino[3,4-a]indole (**5b**).* Indoline **6a** (700 mg) scale reaction was run, and indoline aminal product was crystallized as a gray solid (1.01g, 98% yield, dr >20:1), mp 202−203 °C. ^{1}H NMR (500 MHz, DMSO): δ 7.72 (dd; J = 7.74; 1.36 Hz; 1 H); 7.27−7.36 (m; 4 H); 7.18−7.23 (m; 3 H); 7.13−7.13 (m; 2 H); 7.04 (s; 1 H); 4.41 (d; J = 8.61 Hz; 1 H); 3.33−3.39 (m, 1H, overlap with water); 3.19 (d; J = 16.38 Hz; 1 H). ^{13}C NMR (125 MHz, DMSO): δ 35.5, 54.6, 82.9, 111.67, 111.74, 121.3, 122.1, 122.1, 123.2, 124.0, 127.5, 128.2, 128.5, 129.4, 130.4, 130.9, 131.9, 134.3, 136.6, 147.7, 154.0 ppm. HRMS: ESI$^+$ $[M + 1]^+$ calcd for $C_{21}H_{15}Br_3NO$ 535.8678, found 535.8687.

*(6S,12aR)-3,10-Dibromo-6-(2,5-difluorophenyl)-12,12a-dihydro-6H-benzo[5,6][1,3]oxazino[3,4-a]indole (**5c**).* Indoline **6a** (700 mg) scale reaction was run, and indoline aminal product was crystallized as gray solid (0.9 g, 96% yield, dr >20:1), mp 174−175 °C. ^{1}H NMR (500 MHz, DMSO): δ 7.33−7.35 (m; 1 H); 7.29 (d; J = 12.39 Hz; 4 H); 7.20 (d; J = 8.28 Hz; 1 H); 7.15 (d; J = 8.53 Hz; 1 H); 7.10−7.11 (m; 2 H); 7.02 (s; 1 H); 4.66 (d; J = 8.73 Hz; 1 H); 3.44 (dd; J = 16.32; 8.88 Hz; 1 H); 3.16 (d; J = 16.31 Hz; 1 H). ^{13}C NMR (125 MHz, DMSO): δ 35.9, 55.2, 79.3, 112.09, 112.13, 114.72, 114.74, 114.97, 115.0, 117.5, 117.6, 117.7, 117.8, 118.5, 118.6, 118.8, 118.9, 119.4, 121.2, 124.1, 124.8, 127.1, 127.2, 127.3, 127.4, 128.6, 129.5, 130.4, 132.1, 148.0, 153.3, 154.89, 154.91, 156.97, 156.98, 157.35, 159.4 ppm. ^{19}F NMR (470 MHz, DMSO): δ-120.45, 120.40, −118.33, −118.28 ppm. HRMS: ESI$^+$ $[M + 1]^+$ calcd for $C_{21}H_{14}Br_2F_2NO$ 493.9385, found 493.9398.

*4-((6S,12aR)-3,10-Dibromo-12,12a-dihydro-6H-benzo[5,6][1,3]-oxazino[3,4-a]indol-6-yl)phenyl Acetate (**5d**).* Indoline **6a** (500 mg) scale reaction was run, and indoline aminal product was crystallized as a gray solid (660 mg, 95% yield, dr >20:1), mp 152−153 °C; ^{1}H NMR (400 MHz, DMSO): δ 7.55 (d; J = 8.35 Hz; 2 H); 7.28−7.29 (m; 2 H); 7.15−7.22 (m; 3 H); 7.12 (s; 2 H); 7.02−7.09 (m; 2 H); 4.69 (d; J = 8.80 Hz; 1 H); 3.51 (dd; J = 16.32; 8.99 Hz; 1 H); 3.13 (d; J = 16.31 Hz; 1 H); 2.24 (s; 3 H). ^{13}C NMR (100 MHz, DMSO): δ 21.3, 36.2, 55.5, 82.9, 112.1, 112.5, 119.9, 120.8, 122.7, 124.6, 128.3, 128.5, 129.6, 130.3, 132.4, 135.7, 148.6, 150.9, 153.4, 169.6 ppm. HRMS: ESI$^+$ $[M + 1]^+$ calcd for $C_{23}H_{18}Br_2NO_3$ 515.9628, found 515.9638.

*(6S,12aR)-3,10-Dibromo-6-(3-methoxyphenyl)-12,12a-dihydro-6H-benzo[5,6][1,3]oxazino[3,4-a]indole (**5e**).* Indoline **6a** (600 mg) scale reaction was run, and indoline aminal product was crystallized as a gray solid (760 mg, 96% yield, dr >20:1), mp 149−150 °C. ^{1}H NMR (400 MHz, DMSO): δ 7.28−7.34 (m; 3 H); 7.19−7.21 (m; 1 H); 7.02−7.12 (m; 6 H); 6.91 (dd; J = 8.22; 2.56 Hz; 1 H); 4.70 (d; J = 8.80 Hz; 1 H); 3.72 (s; 2 H); 3.51 (dd; J = 16.26; 8.95 Hz; 1 H); 3.10 (d; J = 16.30 Hz; 1 H). ^{13}C NMR (100 MHz, DMSO): δ 36.2, 55.57, 55.64, 83.1, 112.0, 112.5, 113.0, 113.9, 119.1, 119.8, 120.7, 124.5, 124.8, 128.5, 129.6, 130.3, 130.5, 132.5, 139.9, 148.7, 153.6, 160.0 ppm. HRMS: ESI$^+$ $[M + 1]^+$ calcd for $C_{22}H_{18}Br_2NO_2$ 487.9679, found 487.9687.

*(6S,12aR)-3,10-Dibromo-6-(pyridin-3-yl)-12,12a-dihydro-6H-benzo[5,6][1,3]oxazino[3,4-a]indole (**5f**).* Indoline **6a** (600 mg) scale reaction was run, and indoline aminal product was crystallized as a gray solid (680 mg, 95% purity, 90% yield, dr> 20:1), mp 130−131 °C. ^{1}H NMR (400 MHz, DMSO): δ 8.72 (s; 1 H); 8.56 (s; 1 H); 7.89 (d; J = 8.00 Hz; 1 H); 7.43 (t; J = 6.07 Hz; 1 H); 7.30−7.32 (m; 2 H); 7.20−7.22 (m; 2 H); 7.16 (d; J = 1.59 Hz; 1 H); 7.07 (d; J = 2.20 Hz; 2 H); 4.68 (d; J = 8.85 Hz; 1 H); 3.53 (dd; J = 16.31; 9.02 Hz; 1 H); 3.13 (d; J = 16.29 Hz; 1 H). ^{13}C NMR (100 MHz, DMSO): δ 36.3, 55.5, 81.9, 112.3, 112.6, 120.0, 120.9, 124.5, 124.9, 128.6, 129.6, 130.4, 132.5, 135.2, 148.4, 148.6, 150.0, 153.1 ppm. HRMS: ESI$^+$ $[M + 1]^+$ calcd for $C_{20}H_{15}Br_2N_2O$ 458.9526, found 458.9532.

*(6S,12aR)-3,10-Dibromo-6-(phenylethynyl)-12,12a-dihydro-6H-benzo[5,6][1,3]oxazino[3,4-a]indole (**5g**).* Indoline **6a** (500 mg) scale reaction was run, and indoline aminal product was crystallized as a yellow solid (640 mg, 95% purity, 92% yield, dr >20:1), mp 148−150 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (s; 1 H); 7.42 (d; J = 1.86 Hz; 1 H); 7.36 (d; J = 6.81 Hz; 1 H); 7.33−7.33 (m; 1 H); 7.32 (d; J = 1.96 Hz; 1 H); 7.27−7.29 (m; 1 H); 7.22 (s; 1 H); 7.12 (dd; J = 8.28; 2.00 Hz; 1 H); 7.03 (d; J = 8.31 Hz; 1 H); 6.96 (d; J = 1.97 Hz; 1 H); 6.78 (d; J = 8.40 Hz; 1 H); 6.49 (s; 1 H); 5.39 (d; J = 8.85 Hz; 1 H); 3.60 (dd; J = 15.66; 8.94 Hz; 1 H); 3.18 (d; J = 15.66 Hz; 1 H). ^{13}C NMR (100 MHz, DMSO): δ 36.0, 56.9, 74.1, 83.1, 85.8, 111.1, 113.2, 120.7, 121.1, 121.2, 123.7, 125.1, 127.8, 128.4, 128.7, 129.2, 130.4, 131.8, 132.0, 145.9, 152.6 ppm. HRMS: ESI$^+$ $[M + 1]^+$ calcd for $C_{23}H_{16}Br_2NO$ 481.9573, found 481.9584.

*(6S,12aR)-3,10-Dibromo-6-phenethyl-12,12a-dihydro-6H-benzo-[5,6][1,3]oxazino[3,4-a]indole (**5h**).* Indoline **6a** (500 mg) scale reaction was run, and indoline aminal product was crystallized as a gray solid (650 mg, 97% yield, dr >20:1), mp 147−149 °C. ^{1}H NMR (400 MHz, DMSO): δ 7.28−7.15 (m; 8 H); 7.07 (dd; J = 8.29; 2.04 Hz; 1 H); 6.86 (d; J = 8.33 Hz; 1 H); 6.84 (d; J = 2.01 Hz; 1 H); 5.80 (t; J = 6.98 Hz; 1 H); 5.09 (d; J = 8.75 Hz; 1 H); 3.46 (dd; J = 16.21; 8.91 Hz; 1 H); 3.16 (d; J = 16.21 Hz; 1 H); 2.85−2.70 (m; 2 H); 2.14 (q; J = 7.57 Hz; 2 H). ^{13}C NMR (100 MHz, DMSO): δ 31.2, 33.5, 36.2, 55.1, 83.0, 111.7, 112.0, 119.7, 120.7, 124.1, 124.2, 126.4, 128.4, 128.79, 128.81, 129.6, 130.3, 132.4, 141.4, 148.6, 153.1 ppm. HRMS: ESI$^+$ $[M + 1]^+$ calcd for $C_{23}H_{20}Br_2NO$ 485.9886, found 485.9893.

*(6S,12aR)-3,10-Dibromo-6-isopropyl-12,12a-dihydro-6H-benzo-[5,6][1,3]oxazino[3,4-a]indole (**5i**).* Indoline **6a** (500 mg) scale reaction was run, and indoline aminal product was crystallized as a gray solid (570 mg, 98% yield, dr >20:1), mp 177−180 °C. ^{1}H NMR (400 MHz, DMSO): δ 7.22−7.17 (m; 3 H); 7.06 (dd; J = 8.26; 2.03 Hz; 1 H); 6.96 (d; J = 8.24 Hz; 1 H); 6.87 (d; J = 2.00 Hz; 1 H); 5.35 (d; J = 9.97 Hz; 1 H); 4.99 (d; J = 8.85 Hz; 1 H); 3.47 (dd; J = 16.21; 8.99 Hz; 1 H); 3.14 (d; J = 16.21 Hz; 1 H); 2.16−2.07 (m; 1 H); 1.02 (dd; J = 6.56; 2.73 Hz; 6 H). ^{13}C NMR (100 MHz, DMSO): δ 18.4, 19.2, 29.6, 36.2, 55.2, 88.4, 111.4, 112.0, 119.6, 120.6, 124.0, 124.8, 128.3, 129.5, 130.2, 132.2, 149.2, 153.2 ppm. HRMS: ESI$^+$ $[M + 1]^+$ calcd for $C_{18}H_{18}Br_2NO$ 423.9730, found 423.9736.

*(6S,12aR)-3,10-Dibromo-6-cyclohexyl-12,12a-dihydro-6H-benzo-[5,6][1,3]oxazino[3,4-a]indole (**5j**).* Indoline **6a** (500 mg) scale reaction was run, and indoline aminal product was crystallized as a gray solid (570 mg, 91% yield, dr >20:1), mp 148−150 °C. ^{1}H NMR (400 MHz, DMSO): δ 7.17−7.22 (m; 3 H); 7.07 (dd; J = 8.27; 2.03 Hz; 1 H); 6.97 (d; J = 8.30 Hz; 1 H); 6.87 (d; J = 2.01 Hz; 1 H); 5.43 (d; J = 9.57 Hz; 1 H); 4.99 (d; J = 8.81 Hz; 1 H); 3.46 (dd; J = 16.21; 8.96 Hz; 1 H); 3.14 (d; J = 16.20 Hz; 1 H); 1.84−1.93 (m; 3 H); 1.71 (d; J = 11.00 Hz; 3 H); 1.62 (d; J = 10.50 Hz; 1 H); 1.06−1.25 (m; 6 H). ^{13}C NMR (100 MHz, DMSO): δ 25.4, 25.5, 26.2, 28.1, 29.0, 36.2, 38.3, 55.2, 87.1, 111.4, 112.0, 119.6, 120.6, 124.0, 124.7, 128.3, 129.6,

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130.2, 132.2, 149.2, 153.3 ppm. HRMS: ESI$^+$ [M + 1]$^+$ calcd for $C_{21}H_{22}Br_2NO$ 464.0043, found 464.0050.

*(6S,12aR)-3,10-Dibromo-6-cyclopropyl-12,12a-dihydro-6H-benzo[5,6][1,3]oxazino[3,4-a]indole (**5k**).* Indoline **6a** (500 mg) scale reaction was run, and indoline aminal product was crystallized as a gray solid (560 mg, 95% yield, dr >20:1), mp 152−154 °C. ^{1}H NMR (400 MHz, DMSO): δ 7.18−7.23 (m; 3 H); 7.06 (dd; J = 8.26; 2.04 Hz; 1 H); 6.92 (d; J = 8.46 Hz; 1 H); 6.86 (d; J = 2.00 Hz; 1 H); 5.19 (dd; J = 17.57; 8.36 Hz; 2 H); 3.48 (dd; J = 16.18; 8.79 Hz; 1 H); 3.16 (d; J = 16.16 Hz; 1 H); 1.37−1.46 (m; 1 H); 0.46−0.60 (m; 4 H). ^{13}C NMR (100 MHz, DMSO): δ 2.9, 4.0, 13.5, 36.2, 55.9, 86.8, 111.6, 112.2, 119.6, 120.7, 123.9, 124.3, 128.4, 129.6, 130.2, 132.2, 148.5, 153.9 ppm. HRMS: ESI$^+$ [M + 1]$^+$ calcd for $C_{18}H_{16}Br_2NO$ 421.9573, found 421.9581.

*(6S,12aR)-6-(2-Bromophenyl)-3,10-diphenyl-12,12a-dihydro-6H-benzo[5,6][1,3]oxazino[3,4-a]indole (**5l**).* Indoline **6b** (300 mg) scale reaction was run, and indoline aminal product was crystallized as a gray solid (420 mg, 96% yield, dr >20:1), mp 177−178 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68−7.70 (m; 1 H); 7.62 (d; J = 7.68 Hz; 2 H); 7.54 (d; J = 7.72 Hz; 2 H); 7.00 (s; 1 H); 4.70 (d; J = 8.79 Hz; 1 H); 3.58 (dd; J = 15.51; 8.92 Hz; 1 H); 3.37 (d; J = 15.47 Hz; 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.9, 54.6, 83.2, 109.1, 114.9, 119.8, 122.7, 123.7, 124.4, 126.3, 126.67, 126.72, 126.75, 127.0, 127.2, 127.5, 127.6, 128.6, 128.8, 129.4, 129.7, 133.66, 133.72, 137.3, 140.3, 141.5, 141.7, 147.8, 153.5 ppm. HRMS: ESI$^+$ [M + 1]$^+$ calcd for $C_{33}H_{25}BrNO$ 530.1115, found 530.1117.

*(6S,12aR)-6-(2-Bromophenyl)-12,12a-dihydro-6H-benzo[5,6]-[1,3]oxazino[3,4-a]indole (**5m**).* Indoline **6c** (200 mg) scale reaction was run, and indoline aminal product was crystallized as a gray solid (320 mg, 90% yield, dr >20:1), mp 152−154 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62−7.66 (m; 1 H); 7.34−7.36 (m; 1 H); 7.16−7.21 (m; 4 H); 7.07−7.12 (m; 3 H); 6.89−6.97 (m; 3 H); 6.80 (td; J = 7.37; 1.00 Hz; 1 H); 4.59 (d; J = 8.90 Hz; 1 H); 3.48 (dd; J = 15.47; 8.93 Hz; 1 H); 3.26 (d; J = 15.46 Hz; 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.9, 54.3, 83.0, 108.9, 116.3, 120.1, 120.9, 122.6, 124.8, 125.4, 126.2, 127.1, 127.5, 127.6, 128.4, 128.6, 129.6, 133.6, 137.4, 148.3, 153.2 ppm. HRMS: ESI$^+$ [M + 1]$^+$ calcd for $C_{21}H_{17}BrNO$ 378.0489, found 378.0495.

General Procedure for the Preparation of cyclic indole aminals 2a−m. To a 20 mL vial charged with indoline aminal (500 mg) and $NaHCO_3$ (1 equiv) were added DMAc (5 mL, 10v) and water (0.5 mL, 1 vol), the mixture was cooled to 10 °C, $KMnO_4$ (2.0 equiv) was added, and the mixturew was aged at 10 °C for 20 h. The reaction was quenched with 5 wt % $NaHSO_3$ at 10 °C and diluted with EtOAc (20 mL), filtered through Celite, and washed with 5 mL of DMAc and 10 mL of EtOAc. The layer was cut, the aqueous layer was extracted twice with 20 mL of EtOAc, and the combined organic layer was washed once with 30 mL of $NaHSO_3$ solution and 30 mL brine twice. The organic phase was dried and concentrated on a rotavap. IPA was added (3 mL) for recrystallization. The IPA slurry was heated and aged at 60 °C for 1 h, cooled to rt slowly, and aged at rt for 3 h. The slurry was filtered, and the cake was washed with 1 mL of IPA. The product cake was dried in the oven at 50 °C under vacuum.

*(S)-3,10-Dibromo-6-phenyl-6H-benzo[5,6][1,3]oxazino[3,4-a]-indole (**2a**):* A 1.0 g scale reaction was run, and the indole aminal product was crystallized as a white solid (0.85g, 85% yield, 99.8% ee). ^{1}H NMR (500 MHz, DMSO): δ 7.88 (d; J = 1.81 Hz; 1 H); 7.82 (t; J = 4.13 Hz; 2 H); 7.37 (d; J = 1.90 Hz; 1 H); 7.28−7.34 (m; 6 H); 7.17 (s; 1 H); 6.93−6.95 (m; 2 H). ^{13}C NMR (125 MHz, DMSO): δ 83.5, 98.0, 112.7, 113.9, 117.3, 121.4, 122.3, 123.5, 125.7, 126.4, 126.70, 126.73, 129.3, 130.0, 130.6, 131.8, 134.3, 137.1, 150.0 ppm. HRMS: ESI$^+$ [M + 1]$^+$ calcd for $C_{21}H_{14}Br_2NO$ 455.9417, found 455.9433. $[\alpha]^{25}_D$ = −114.1 (c = 1.0, $CHCl_3$).

*(S)-3,10-Dibromo-6-(2-bromophenyl)-6H-benzo[5,6][1,3]-oxazino[3,4-a]indole (**2b**).* A 500 mg scale reaction was run, and indole aminal product was crystallized as a white solid (440 mg, 88% yield, 99.5% ee), mp 160−161 °C. ^{1}H NMR (400 MHz, DMSO): δ 7.87 (t; J = 4.10 Hz; 2 H); 7.75−7.77 (m; 2 H); 7.21−7.33 (m; 5 H); 7.10−7.15 (m; 2 H); 6.08 (d; J = 7.74 Hz; 1 H). ^{13}C NMR (100 MHz, DMSO): δ 83.5, 98.1, 112.8, 114.1, 117.0, 120.9, 122.4, 123.0, 123.5, 125.8, 126.5, 127.0, 128.0, 128.5, 130.8, 132.2, 132.5, 133.8, 134.4, 135.0, 149.4 ppm. HRMS: ESI$^+$ [M + 1]$^+$ calcd for $C_{21}H_{13}Br_3NO$ 533.8522, found 533.8520. $[\alpha]^{25}_D$ = −118.4 (c = 0.4, DMF).

*(S)-3,10-Dibromo-6-(2,5-difluorophenyl)-6H-benzo[5,6][1,3]-oxazino[3,4-a]indole (**2c**).* A 500 mg scale reaction was run, and indole aminal product was crystallized as a white solid (450 mg, 90% yield, 99.5% ee), mp 172−173 °C. ^{1}H NMR (400 MHz, DMSO): 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): δ 79.3, 98.4, 112.8, 113.73, 113.77, 113.99, 114.03, 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, 125.57, 125.64, 125.7, 125.8, 126.0, 126.6, 127.2, 130.7, 131.8, 133.7, 149.3, 155.4, 156.9, 157.8, 159.3 ppm. ^{19}F NMR (376 MHz, DMSO): δ −121.0, −120.9, −118.1, −118.0 ppm. HRMS: ESI$^+$ [M + 1]$^+$ calcd for $C_{21}H_{12}Br_2F_2NO$ 491.9228, found 491.9235. $[\alpha]^{25}_D$ = −124.0 (c = 0.4, DMF).

*(S)-4-(3,10-Dibromo-6H-benzo[5,6][1,3]oxazino[3,4-a]indol-6-yl)-phenyl Acetate (**2d**).* A 500 mg scale reaction was run, and indole aminal product was crystallized as a white solid (410 mg, 82% yield, 99.3% ee), mp 184−187 °C.. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d; J = 1.88 Hz; 1 H); 7.62−7.64 (m; 1 H); 7.29−7.37 (m; 4 H); 7.18 (s; 1 H); 7.14−7.16 (m; 4 H); 6.96 (s; 1 H); 6.92 (d; J = 8.74 Hz; 1 H); 2.39 (s; 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 83.7, 96.9, 111.0, 114.2, 116.9, 121.4, 122.1, 122.5, 123.5, 125.1, 125.7, 126.5, 128.0, 130.6, 131.8, 133.81, 133.82, 149.7, 151.6, 169.1 ppm. HRMS: ESI$^+$ [M + 1]$^+$ calcd for $C_{23}H_{16}Br_2NO_3$ 513.9471, found 513.9472. $[\alpha]^{25}_D$ = −136.7 (c = 0.4, DMF).

*(S)-3,10-Dibromo-6-(3-methoxyphenyl)-6H-benzo[5,6][1,3]-oxazino[3,4-a]indole (**2e**).* A 500 mg scale reaction was run, and indole aminal product was crystallized as a white solid (430 mg, 85% yield, 99.5% ee), mp 150−152 °C. ^{1}H NMR (500 MHz, DMSO): δ 7.86 (d; J = 1.84 Hz; 1 H); 7.80 (d; J = 8.29 Hz; 1 H); 7.75 (s; 1 H); 7.37 (d; J = 1.89 Hz; 1 H); 7.24−7.31 (m; 3 H); 7.18 (t; J = 8.00 Hz; 1 H); 7.15 (s; 1 H); 6.87 (dd; J = 8.28; 2.52 Hz; 1 H); 6.50 (s; 1 H); 6.40 (d; J = 7.76 Hz; 1 H); 3.63 (s; 3 H). ^{13}C NMR (125 MHz, DMSO): δ 55.5, 83.3, 98.0, 112.7, 113.0, 113.9, 114.7, 117.3, 118.6, 121.4, 122.4, 123.5, 125.7, 126.4, 126.8, 130.6, 131.8, 134.3, 138.7, 150.0, 159.8 ppm. HRMS: ESI$^+$ [M + 1]$^+$ calcd for $C_{22}H_{16}Br_2NO_2$ 485.9522, found 485.9527. $[\alpha]^{25}_D$ = −141.6 (c = 0.4, DMF).

*(S)-3,10-Dibromo-6-(pyridin-3-yl)-6H-benzo[5,6][1,3]oxazino[3,4-a]indole (**2f**).* A 500 mg scale reaction was run, and indole aminal product was crystallized as a white solid (410 mg, 82% yield, 90.6% ee), mp 161−164 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (s; 1 H); 8.42 (s; 1 H); 7.82 (d; J = 1.86 Hz; 1 H); 7.51−7.53 (m; 1 H); 6.88 (d; J = 8.13 Hz; 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 82.2, 97.3, 110.6, 114.5, 116.8, 121.5, 122.6, 123.7, 123.8, 125.2, 125.9, 126.8, 130.7, 131.4, 132.3, 133.6, 134.2, 148.2, 149.1, 150.9 ppm. HRMS: ESI$^+$ [M + 1]$^+$ calcd for $C_{20}H_{13}Br_2N_2O$ 456.9369, found 456.9373. $[\alpha]^{25}_D$ = −109.0 (c = 0.4, DMF).

*(S)-3,10-Dibromo-6-phenethyl-6H-benzo[5,6][1,3]oxazino[3,4-a]-indole (**2h**).* A 500 mg scale reaction was run, and indole aminal product was crystallized as a white solid (410 mg, 82% yield, 98.6% ee), mp 143−145 °C. ^{1}H NMR (400 MHz, DMSO): δ 7.80 (s; 1 H); 7.79 (d; J = 6.24 Hz; 1 H); 7.52 (d; J = 8.72 Hz; 1 H); 7.32 (ddd; J = 8.49; 5.01; 1.94 Hz; 2 H); 7.21−7.25 (m; 3 H); 7.12−7.18 (m; 3 H); 7.02 (s; 1 H); 6.73 (dd; J = 8.88; 4.10 Hz; 1 H); 2.77−2.84 (m; 1 H); 2.66−2.73 (m; 1 H); 1.99−2.09 (m; 1 H); 1.87−1.96 (m; 1 H). ^{13}C NMR (100 MHz, DMSO): δ 30.6, 35.4, 83.6, 97.5, 112.3, 113.5, 117.1, 121.4, 122.3, 123.3, 125.3, 126.4, 126.5, 126.6, 128.6, 128.8, 130.6, 130.7, 133.3, 140.9, 149.3 ppm. HRMS: ESI$^+$ [M + 1]$^+$ calcd for $C_{23}H_{18}Br_2NO$ 483.9730, found 483.9729. $[\alpha]^{25}_D$ = −111.4 (c = 0.4, DMF).

*(S)-3,10-Dibromo-6-isopropyl-6H-benzo[5,6][1,3]oxazino[3,4-a]-indole (**2i**).* A 500 mg scale reaction was run, and indole aminal product was crystallized as a white solid (420 mg, 84% yield, 99.4% ee), mp 156−157 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d; J = 1.88 Hz; 1 H); 7.52 (d; J = 8.00 Hz; 1 H); 6.73 (s; 1 H); 5.91 (d; J = 8.53 Hz; 1 H); 2.23−2.32 (m; 1 H); 1.07 (d; J = 6.64 Hz; 3 H); 0.81 (d; J = 6.85 Hz; 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.2, 18.6,

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34.0, 88.5, 96.4, 110.9, 113.5, 117.4, 121.0, 122.4, 123.3, 125.0, 125.2, 126.0, 130.3, 130.6, 134.0, 150.0 ppm. HRMS: ESI$^+$ $[M + 1]^+$ calcd for $C_{18}H_{16}Br_2NO$ 421.9573, found 421.9575. $[\alpha]^{25}_D$ = −154.6 (c = 0.4, DMF).

*(S)-3,10-Dibromo-6-cyclohexyl-6H-benzo[5,6][1,3]oxazino[3,4-a]-indole (**2j**).* A 500 mg scale reaction was run, and indole aminal product was crystallized as a white solid (400 mg, 80% yield, 99.7% ee), mp 165−167 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d; J = 1.88 Hz; 1 H); 7.51−7.53 (m; 1 H); 7.30 (dd; J = 8.80; 2.03 Hz; 1 H); 7.22−7.25 (m; 2 H); 7.15 (d; J = 8.70 Hz; 1 H); 6.71 (s; 1 H); 5.93 (d; J = 8.47 Hz; 1 H); 1.94−2.02 (m; 3 H); 1.75 (d; J = 10.41 Hz; 1 H); 1.62 (d; J = 12.18 Hz; 2 H); 0.93−1.14 (m; 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.3, 25.5, 25.8, 28.5, 29.0, 42.9, 87.6, 96.4, 110.9, 113.5, 117.4, 121.0, 122.4, 123.3, 125.0, 125.1, 126.0, 130.2, 130.6, 134.1, 150.0 ppm. HRMS: ESI$^+$ $[M + 1]^+$ calcd for $C_{21}H_{20}Br_2NO$ 461.9886, found 461.9889. $[\alpha]^{25}_D$ = −162.2 (c = 0.4, DMF).

*(S)-3,10-Dibromo-6-cyclopropyl-6H-benzo[5,6][1,3]oxazino[3,4-a]indole (**2k**).* A 500 mg scale reaction was run, and indole aminal product was crystallized as a white solid (416 mg, 83% yield, 93.9% ee), mp 126−128 °C. ^{1}H NMR (400 MHz, DMSO): δ 7.81 (d; J = 8.27 Hz; 1 H); 7.78 (d; J = 1.94 Hz; 1 H); 7.63 (d; J = 8.77 Hz; 1 H); 7.40 (d; J = 1.90 Hz; 1 H); 7.34 (dd; J = 8.28; 1.94 Hz; 1 H); 7.30 (dd; J = 8.74; 1.97 Hz; 1 H); 7.02 (s; 1 H); 6.13 (d; J = 8.40 Hz; 1 H); 1.28−1.35 (m; 1 H); 0.61−0.66 (m; 1 H); 0.51−0.57 (m; 2 H); 0.43−0.48 (m; 1 H). ^{13}C NMR (100 MHz, DMSO): δ 2.4, 3.4, 15.4, 87.2, 97.5, 113.0, 113.4, 117.2, 121.2, 122.3, 123.1, 125.2, 126.4, 126.5, 130.7, 131.2, 133.7, 150.6 ppm. HRMS: ESI$^+$ $[M + 1]^+$ calcd for $C_{18}H_{14}Br_2NO$ 419.9417, found 419.9416. $[\alpha]^{25}_D$ = −127.5 (c = 0.4, DMF).

*(S)-6-(2-Bromophenyl)-3,10-diphenyl-6H-benzo[5,6][1,3]oxazino-[3,4-a]indole (**2l**).* A 300 mg scale reaction was run, and indole aminal product was crystallized as a white solid (260 mg, 87% yield, 99.1% ee), mp 197−198 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (s, 1 H); 7.83 (d, J = 8.1 Hz, 1 H); 7.70 (d, J = 8.3 Hz, 1 H); 7.66 (d, J = 7.7 Hz, 2 H); 7.60 (s, 4 H); 7.42−7.50 (m, 5 H); 7.37 (d, J = 8.2 Hz, 4 H); 7.27−7.29 (m, 1 H); 7.22 (d, J = 8.7 Hz, 1 H); 7.10 (t, J = 7.9 Hz, 1 H); 7.06 (s, 1 H); 6.95 (d, J = 8.5 Hz, 1 H); 6.61 (d, J = 7.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 83.7, 97.4, 109.9, 116.4, 116.9, 119.3, 121.9, 122.5, 123.2, 124.2, 126.6, 126.9, 127.3, 127.8, 127.9, 128.4, 128.7, 128.9, 129.9, 131.3, 132.5, 133.5, 134.4, 134.5, 135.5, 140.0, 142.1, 142.4, 149.2 ppm. HRMS: ESI$^+$ $[M + 1]^+$ calcd for $C_{33}H_{23}BrNO$ 528.0958, found 528.0950. $[\alpha]^{25}_D$ = −138.6 (c = 0.4, DMF).

*(S)-6-(2-Bromophenyl)-6H-benzo[5,6][1,3]oxazino[3,4-a]indole (**2m**).* A 200 mg scale reaction was run, and indole aminal product was crystallized as a white solid (180 mg, 89% yield, 99.0% ee), mp 80−82 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (dd; J = 7.65; 1.68 Hz; 1 H); 7.66−7.70 (m; 2 H); 7.54 (s; 1 H); 7.08−7.20 (m; 5 H); 6.99−7.05 (m; 3 H); 6.90 (d; J = 7.93 Hz; 1 H); 6.49 (dd; J = 7.77; 1.70 Hz; 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 83.5, 96.9, 109.6, 118.06, 108.13, 120.89, 120.92, 122.6, 123.1, 123.2, 123.8, 127.8, 128.3, 129.25, 129.30, 131.1, 131.9, 133.5, 134.7, 135.6, 148.8 ppm. HRMS: ESI$^+$ $[M + 1]^+$ calcd for $C_{21}H_{15}BrNO$ 376.0332, found 376.0341. $[\alpha]^{25}_D$ = −172.1 (c = 0.4, DMF).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR and HPLC spectra as well as calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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