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Catalytic Enantioselective Addition of Me_2Zn to Isatins

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Abstract: Chiral α-hydroxyamide **L5** derived from (*S*)-(+)-mandelic acid catalyzes the enantioselective addition of dimethylzinc to isatins affording the corresponding chiral 3-hydroxy-3-methyl-2-oxindoles with good yields and er up to 90:10. Furthermore, several chemical transformations were performed with the 3-hydroxy-2-oxindoles obtained.

Keywords: asymmetric catalysis; isatin; 3-hydroxyoxindole; zinc; mandelamides; chiral α-hydroxyamide

1. Introduction

3-Substituted-3-hydroxy-2-oxindole are an important class of compounds that have shown a broad range of biological activities. This scaffold is present in a large variety of natural and synthetic compounds that exhibit pharmaceutical properties [1–8]. Structure–activity relationship studies have shown that the biological activities of these compounds are significantly affected both by the configuration of the C3 and its substitution pattern [9–11]. Therefore, in the last years, the asymmetric synthesis of chiral 3-substituted-3-hydroxy-2-oxindoles have become a hot topic in organic synthesis [12,13]. The synthesis includes allylation [14,15], crotylation [16], arylation [17,18] and decarboxylative cyanomethylation [19] of isatines, as well as the palladium catalyzed intramolecular arylation [20]. The particular interest is the 3-hydroxy-3-methyl-2-oxindole structure, which is present in several natural products such as convolutamydine C [21] and synthetic compounds with biological activities or drug candidates such as compound **2a** [22], compound A [23] and compound B [24] (Figure 1).

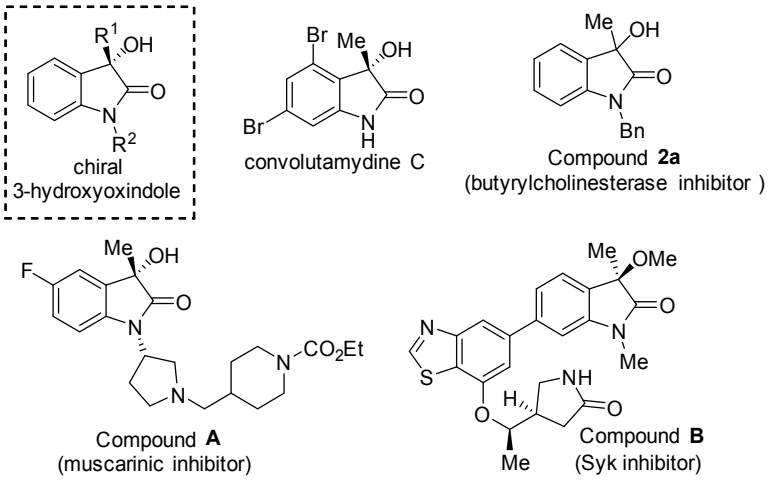
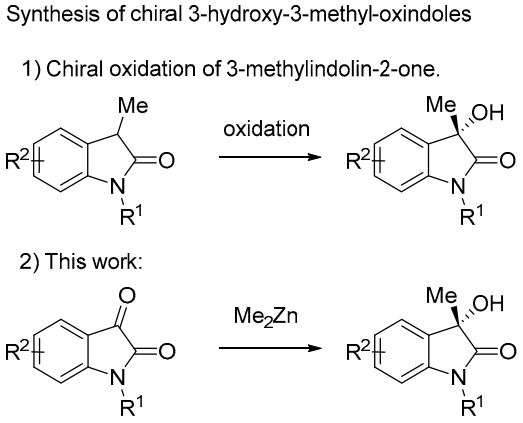


Figure 1. Biologically active 3-hydroxy-3-methyl-2-oxindole compounds.

There are few methodologies for the synthesis of chiral 3-hydroxy-3-methyl-2-oxindoles in the literature, and the number of catalytic enantioselective examples is scarce. For example, the asymmetric oxidation of 3-methylindolin-2-one has been described for the synthesis of such compounds [25–27]. However, the most direct and versatile methodology is the enantioselective nucleophilic addition of organometallic reagents to isatins (Scheme 1). In this context, the addition of dialkylzinc reagents to isatins represents an attractive procedure for this purpose [28–33]. Nevertheless, only the group of Shibashaki [34] described just one example of the enantioselective addition of Me_2Zn catalyzed by a proline-derived aminodiol ligand, obtaining the corresponding 3-hydroxy-3-methyl-2-oxindole in 82% yield and 88:12 enantiomeric ratio. In view of this lack of methodologies for the synthesis of such compounds, we decide to study the asymmetric addition of Me_2Zn to isatins catalyzed by α-hydroxyamides derived from (*S*)-(+)-mandelic acid as chiral ligands [35–40].

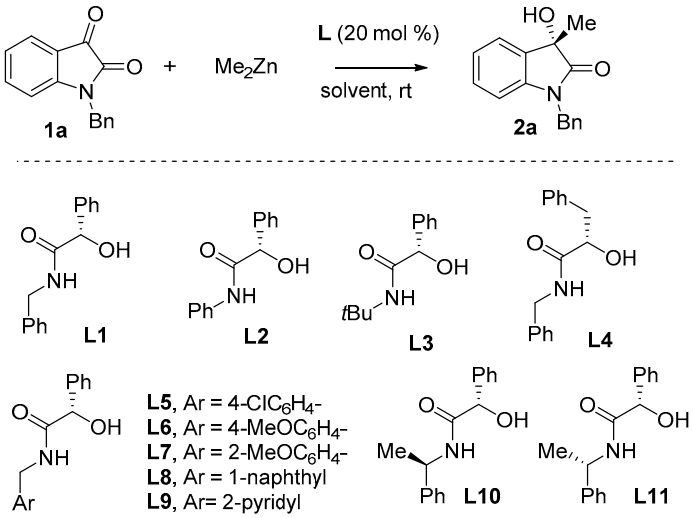


Scheme 1. Asymmetric methodologies for the synthesis of 3-hydroxy-3-methyl-2-oxindole compounds.

2. Results

We initiated our studies by evaluating on the addition of Me_2Zn to *N*-benzylisatine (**1a**) in the presence of a series of chiral α-hydroxyamides derived from (*S*)-(+)-mandelic acid as ligands. A 1.2 M Me_2Zn solution in toluene (7 eq.) was added dropwise to a solution of ligand **L1** (0.2 eq.) in 1 mL of toluene at room temperature. After 30 min, a solution of *N*-benzylisatine (**1a**) in 1 mL of toluene was added and the mixture was stirred for 1 h. The corresponding (*S*)-1-benzyl-3-hydroxy-3-methylindolin-2-one (**2a**) was obtained in 87% yield with 77.5:22.5 enantiomeric ratio (entry 1, Table 1). After, different solvents such as CH_2Cl_2, $ClCH_2CH_2Cl$, THF and Et_2O were tested (entries 2–5, Table 1). When CH_2Cl_2 and Et_2O were used as solvent, the corresponding product **2a** was obtained with higher enantiomeric ratio, while coordinating solvents such as THF have a detrimental effect in both conversion and enantioselectivity of the reaction (entry 4, Table 1). Therefore, we decided to continue the optimization process with CH_2Cl_2 due to solubility problems of the starting material in Et_2O. With the best solvent, different α-hydroxyamides (Figure 1) were tested as chiral ligands (entries 6–15, Table 1). First, we evaluated the influence of group attached to the nitrogen atom of the amide (Bn, Ph or *t*Bu, entries 1, 6 and 7), obtaining the best enantioselectivity with ligand **L1**. Then, the influence of the substituent in the chiral center of the ligand was evaluated (entry 8). With the corresponding α-hydroxy-*N*-benzylamide **L4** derived from (*S*)-3-phenyllactic acid, product **2a** was afforded with lower er of 75:25. Therefore, we continue the optimization process with α-hydroxiamides derived from (*S*)-(+)-mandelic acid (**L5**–**L11**). We evaluated the influence of the presence of different groups in the aromatic ring of the amide. Ligand **L5**, prepared from (*S*)-(+)-mandelic acid and 4-chlorobenzylamine gave the best enantioselectivity on the reaction, obtaining the chiral alcohol with 95% yield and 85:15 er (entry 9). The introduction of an additional methyl group in the benzylic position of the group attached to the nitrogen atom of the amide (entries 14 and 15) had a slightly deleterious effect on the enantioselectivity of the reaction.

Table 1. Optimization of the reaction conditions.



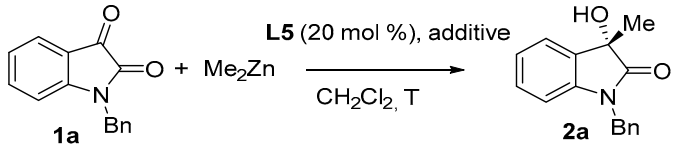
Entry [a]	Ligand (20 mol%)	Solvent	Yield (%) [b]	er [c]
1	**L1**	toluene	87	77.5:22.5
2	**L1**	CH_2Cl_2	90	82:18
3	**L1**	$ClCH_2CH_2Cl$	78	74:26
4	**L1**	THF	44	61.5:38.5
5	**L1**	Et_2O	71	82.5:17.5
6	**L2**	CH_2Cl_2	87	70.5:29.5
7	**L3**	CH_2Cl_2	99	57:43
8	**L4**	CH_2Cl_2	88	75:25
9	**L5**	CH_2Cl_2	95	85:15
10	**L6**	CH_2Cl_2	92	83:17
11	**L7**	CH_2Cl_2	71	82:18
12	**L8**	CH_2Cl_2	77	74:26
13	**L9**	CH_2Cl_2	86	60.5:39.5
14	**L10**	CH_2Cl_2	84	74:26
15	**L11**	CH_2Cl_2	99	80:20

[a] Reaction conditions: 0.1 mmol **1a**, 1.2 M Me_2Zn in toluene (0.7 mmol), and ligand in dry solvent (2 mL) at rt for 1 h. [b] Isolated yield after column chromatography. [c] Enantiomeric ratio determined by chiral HPLC.

Consequently, **L5** was chosen for further optimization (Table 2). Lowering the reaction temperature (entries 1–3, Table 2) had a detrimental effect both in yield and enantioselectivity of the reaction. By decreasing the number of the equivalents of Me_2Zn, we could improve the enantiomeric ratio to 90:10 in the reaction (entry 6). At this point, we study the effect of the use of additives [34] (entries 7–10) on the enantioselectivity of the reaction. The addition of alcohols had an interesting effect, MeOH inhibits the reaction, while when *i*PrOH or *t*BuOH were added the enantiomeric ratio decreased slightly. Finally, when $Ti(OiPr)_4$ was used as an additive, the corresponding tertiary alcohol **2a** was obtained with very low enantioselectivity (entry 10). Therefore, we decided as optimized reaction conditions the ones presented in entry 6, Table 2.

With the optimized reaction conditions established, the scope of the reaction was explored (see Supplementary Materials). Initially, *N*-substitution of the oxindole nitrogen atom was evaluated. Groups such as benzyl, methyl [41], allyl or propargyl were tolerated (entries 1, 3–5, Table 3), providing the corresponding tertiary alcohols with good enantioselectivities. However, unprotected free NH group on isatin was not tolerated (entry 2, Table 3), and the corresponding product **2b** was obtained with lower yield and enantioselectivity, as well when the protecting group was acetyl (entry 7) or Ts (entry 8).

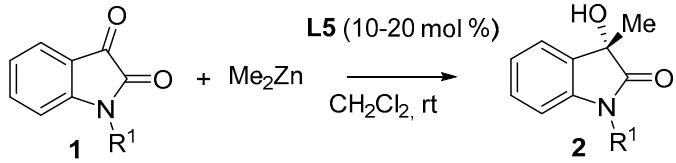
Table 2. Optimization of the reaction conditions.



Entry [a]	T (°C)	Additive (X mol%)	Yield (%) [b]	er [c]
1	−20	-	67	75:25
2	0	-	72	79.5:20.5
3	10	-	86	84.5:15.5
4	rt	-	95	85:15
5 [d]	rt	-	89	89:11
6 [e]	rt	-	85	90:10
7 [e,f]	rt	MeOH (40 mol%)	-	-
8 [e,g]	rt	*i*PrOH (40 mol%)	86	88:12
9 [e,g]	rt	*t*BuOH (40 mol%)	48	86.5:13.5
10 [e,g]	rt	Ti(O*i*Pr)$_4$ (100 mol%)	51	57:43

[a] Reaction conditions: 0.1 mmol **1a**, 1.2 M Me_2Zn in toluene (0.7 mmol), and **L5** (20 mol%) in CH_2Cl_2 (2 mL) for 1 h. [b] Isolated yield after column chromatography. [c] Enantiomeric excess determined by chiral HPLC. [d] 0.35 mmol of Me_2Zn was used. [e] 0.2 mmol of Me_2Zn was used. [f] The reaction time was 24 h. [g] The reaction time was 4 h.

Table 3. Evaluation of the protecting group of the isatin.

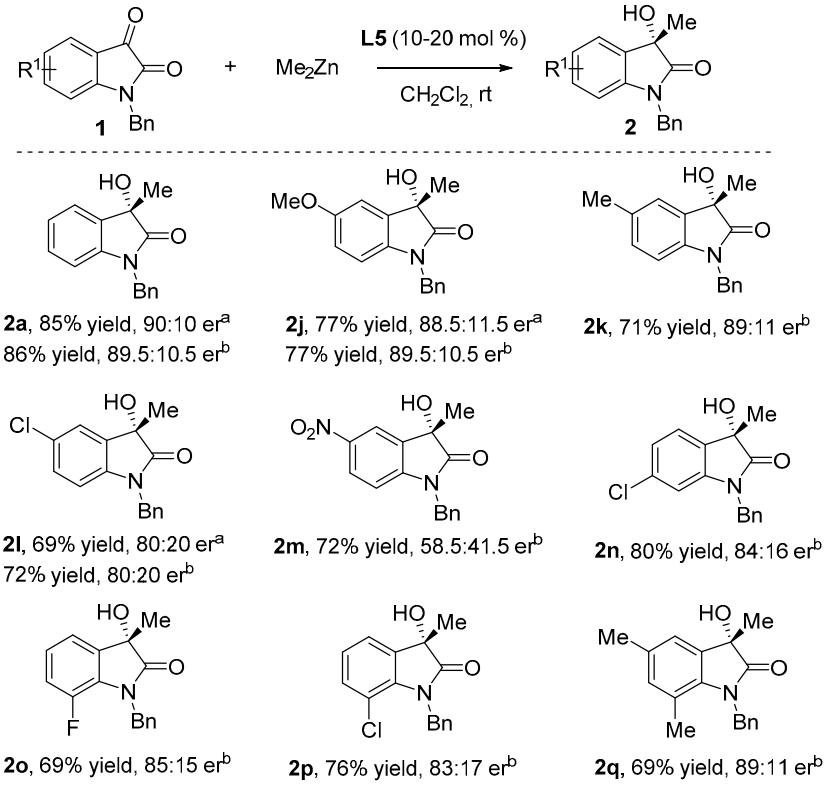


Entry [a]	R^1	1	t (h)	2	Y (%) [b]	er [c]
1	Bn-	**1a**	1	**2a**	85	90:10
2 [d]	H	**1b**	4	**2b**	47	61:39
3	Me	**1c**	3	**2c**	66	82:18
4	allyl	**1d**	3	**2d**	71	87:13
5	propargyl	**1e**	2	**2e**	65	83.5:16.5
6	CH_2CO_2Me	**1f**	3	**2f**	70	72:28
7	COMe	**1g**	2	**2g**	45	55:45
8	Ts	**1h**	2	**2h**	36	72:28
9		**1i**	1	**2i**	81	87:13

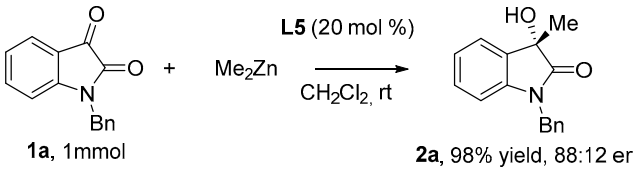
[a] Reaction conditions: 0.1 mmol **1**, 1.2 M Me_2Zn in toluene (0.2 mmol), and **L5** (20 mol%) in CH_2Cl_2 (2 mL). [b] Isolated yield after column chromatography. [c] Enantiomeric ratio determined by chiral HPLC. [d] 0.3 mmol of Me_2Zn was used.

Next, the effect of substitution in the benzene ring of the *N*-benzyl protected isatins was studied (Scheme 2). A reduction in the catalyst loading to 10 mol% was also investigated, observing similar conversion and enantioselectivity. Different electron-donating (Me or MeO) or electron-withdrawing (F or Cl) in positions 5, 6 and 7, were tolerated and the corresponding chiral tertiary alcohols were obtained with good yields and enantiomeric ratios from 80:20 to 90:10. However, the presence of a strong electron-withdrawing group (NO_2) led to a considerable decrease in the enantiomeric ratio of the reaction product.

To evaluate the potential scalability of the asymmetric addition of Me_2Zn to isatins, this procedure was also performed on a 1 mmol scale. As shown in Scheme 3, the corresponding product **2a** was isolated in 98% yield and 88:12 enantiomeric ratio (er).

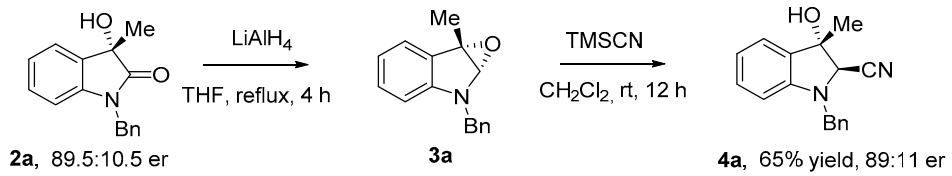


Scheme 2. Scope of the enantioselective addition of Me_2Zn to isatins. Reaction conditions: 0.1 mmol **1**, 1.2 M Me_2Zn in toluene (0.2 mmol), and **L5** in CH_2Cl_2 (2 mL). Isolated yield after column chromatography. Enantiomeric ratio determined by chiral HPLC. [a] 20 mol% of **L5** was used. [b] 10 mol% of **L5** was used.



Scheme 3. 1 mmol scale reaction. Reaction conditions: 1 mmol **1**, 1.2 M Me_2Zn in toluene (2 mmol), and **L5** (20 mol%) in CH_2Cl_2 (20 mL). Isolated yield after column chromatography. Enantiomeric ratio determined by chiral HPLC.

To highlight the synthetic utility of this methodology, we have applied several chemical transformations (Scheme 4). We tried to reduce the amide moiety of the oxindole **2a** with $LiAlH_4$, however the epoxide **3a** was obtained. We had some problems to purify epoxide **3a** due to its instability. Nevertheless, we could react compound **3a** with TMSCN, to afford smoothly the corresponding chiral indoline **4a** with 2 stereogenic centers in 65% yield and without losing the enantiomeric purity of compound **2a**.



Scheme 4. Synthetic transformations of chiral 3-hydroxy-3-methyl-2-oxindole **2a**.

3. Materials and Methods

3.1. General Information

Reactions were carried out under nitrogen in test tubes or round bottom flasks oven-dried overnight at 120 °C. Dicloromethane, 1,2-dichloroethane and toluene were distilled from CaH_2. Tetrahydrofuran (THF) and Et_2O were distilled from sodium benzophenone ketyl. Reactions were monitored by TLC (thin layer chromatography) analysis using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was performed on Merck silica gel 60, 0.040–0.063 mm. Melting points were determined in capillary tubes. NMR (Nuclear Magnetic Resonance) spectra were run in a Bruker DPX300 spectrometer (Bruker, Billerica, MA, USA) at 300 MHz for ^{1}H and at 75 MHz for ^{13}C using residual non-deuterated solvent as internal standard ($CHCl_3$: δ 7.26 and 77.0 ppm). Chemical shifts are given in ppm. The carbon type was determined by DEPT (Distortionless Enhancement by Polarization Transfer) experiments. High resolution mass spectra (ESI) were recorded on a TRIPLETOF^{T}5600 spectrometer (AB Sciex, Warrington, UK) equipped with an electrospray source with a capillary voltage of 4.5 kV (ESI). Specific optical rotations were measured using sodium light (D line 589 nm). Chiral HPLC (High performance liquid chromatography) analyses were performed in a chromatograph equipped with a UV diode-array detector using chiral stationary columns from Daicel. 1.2 M Me_2Zn solution in toluene was purchased from Acros (Geel, Belgium). Chiral α-hydroxyamides were prepared as described in the literature [35]. Commercially available isatins were used as received. *N*-protected isatins **1** were prepared as described in the literature [42].

3.2. Typical Procedures and Characterization Data for Compounds **2**

3.2.1. General Procedure for the Enantioselective Addition of Me_2Zn to Isatins

A 1.2 M Me_2Zn solution in toluene (0.17 mL, 0.2 mmol) was added dropwise on a solution of **L5** (5.5 mg, 0.02 mmol or 2.25 mg, 0.01 mmol) in CH_2Cl_2 (1 mL) at room temperature under nitrogen. After stirring 30 min, a solution of isatin **1** (0.1 mmol) in CH_2Cl_2 (1.0 mL) was added via syringe. The reaction was stirred until the reaction was complete (TLC). The reaction mixture was quenched with NH_4Cl (10 mL), extracted with CH_2Cl_2 (3 × 15 mL), washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel afforded compound **2**.

3.2.2. General Procedure for the Non-Enantioselective Addition of Me_2Zn to Isatins

A 1.2 M Me_2Zn solution in toluene (0.17 mL, 0.2 mmol) was added dropwise on a solution of isatin 1 (0.1 mmol) in CH_2Cl_2 (2 mL) at room temperature under nitrogen. The reaction was stirred until the reaction was complete (TLC). The reaction mixture was quenched with NH_4Cl (10 mL), extracted with CH_2Cl_2 (3 × 15 mL), washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel afforded compound **2**.

(S)-1-Benzyl-3-hydroxy-3-methylindolin-2-one (**2a**) [43–45]: Enantiomeric ratio (90:10) was determined by chiral HPLC (Chiralpak AD-H), hexane-iPrOH 80:20, 1 mL/min, major enantiomer rt = 9.3 min, minor enantiomer rt = 8.1 min. White solid; mp = 110–112 °C; $[\alpha]_{20}^{D} = -34.1$ (c = 1.09, $CHCl_3$) (90:10 er); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (ddd, *J* = 7.4, 1.2, 0.6 Hz, 1H), 7.34–7.23 (m, 5H), 7.22–7.15 (m, 1H), 7.05 (td, *J* = 7.6, 0.7 Hz, 1H), 6.70 (d, *J* = 7.9 Hz, 1H), 4.94 (d, *J* = 15.7 Hz, 1H), 4.80 (d, *J* = 15.7 Hz, 1H), 2.90 (s, 1H), 1.65 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.56 (C), 141.91 (C), 135.44 (C), 131.30 (C), 129.53 (CH), 128.83 (CH), 127.70 (CH), 127.18 (CH), 123.49 (CH), 123.24 (CH), 109.56 (CH), 73.69 (C), 43.72 (CH_2), 25.08 (CH_3); HRMS (ESI) *m*/*z*: 254.1171 $[M + H]^+$, $C_{16}H_{16}NO_2$ required 254.1176.

(S)-3-Hydroxy-3-methylindolin-2-one (**2b**) [46–48]: Enantiomeric ratio (61:39) was determined by chiral HPLC (Chiralpak OD-H), hexane-iPrOH 80:20, 1 mL/min, major enantiomer rt = 5.9 min, minor

enantiomer rt = 7.0 min. White solid; mp = 150–154 °C; $[\alpha]_{20}^{D} = -12.84$ (c = 0.345, $CHCl_3$) (61:39 er); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.40 (dd, *J* = 7.4, 0.6 Hz, 1H), 7.27 (td, *J* = 7.7, 1.3 Hz, 1H), 7.09 (td, *J* = 7.6, 1.0 Hz, 1H), 6.88 (d, *J* = 7.7 Hz, 1H), 2.82 (s, 1H), 1.62 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.59 (C), 140.11 (C), 132.09 (C), 130.07 (CH), 124.32 (CH), 123.67 (CH), 110.64 (CH), 74.28 (C), 25.25 (CH_3).

(S)-3-Hydroxy-1,3-dimethylindolin-2-one (**2c**) [35,43,44,49]: Enantiomeric ratio (82:18) was determined by chiral HPLC (Chiralpak AS-H), hexane-iPrOH 90:10, 1.0 mL/min, major enantiomer rt = 15.4 min, minor enantiomer rt = 12.5 min. White solid; mp = 100–104 °C $[\alpha]_{20}^{D} = -31.8$ (c = 0.59, $CHCl_3$) (82:18 er); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (ddd, *J* = 7.2, 1.3, 0.6 Hz, 1H), 7.30 (td, *J* = 7.7, 1.3 Hz, 1H), 7.08 (td, *J* = 7.5, 1.0 Hz, 1H), 6.82 (dt, *J* = 7.9, 0.8 Hz, 1H), 3.21 (s, 1H), 3.17 (s, 3H), 1.58 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.58 (C), 142.78 (C), 131.43 (C), 129.56 (CH), 123.40 (CH), 123.21 (CH), 108.47 (CH), 73.65 (C), 26.20 (CH_3), 24.81 (CH_3).

(S)-1-Allyl-3-hydroxy-3-methylindolin-2-one (**2d**): Enantiomeric ratio (87:13) was determined by chiral HPLC (Chiralpak AD-H), hexane-iPrOH 80:20, 1.0 mL/min, major enantiomer rt = 6.31 min, minor enantiomer rt = 5.90 min. Oil; $[\alpha]_{20}^{D} = -39.2$ (c = 0.71, $CHCl_3$) (87:13 er); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (ddd, *J* = 7.4, 1.4, 0.6 Hz, 1H), 7.26 (td, *J* = 7.8, 1.4 Hz, 1H), 7.07 (td, *J* = 7.5, 1.0 Hz, 1H), 6.81 (dd, *J* = 7.9, 0.8 Hz, 1H), 5.81 (ddt, *J* = 17.3, 10.4, 5.3 Hz, 1H), 5.24–5.20 (m, 1H), 5.19−5.15 (m, 1H), 4.34 (ddt, *J* = 16.4, 5.2, 1.7 Hz, 1H), 4.23 (ddt, *J* = 16.4, 5.3, 1.7 Hz, 1H), 3.16 (s, 1H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 178.31 (C), 141.95 (C), 131.39 (C), 131.05 (CH), 129.46 (CH), 123.48 (CH), 123.17 (CH), 117.67 (CH_2), 109.39 (CH), 73.60 (C), 42.26(CH_2), 25.01 (CH_3); HRMS (ESI) *m*/*z*: 204.1013 $[M + H]^+$, $C_{12}H_{14}NO_2$ required 204.1019.

(S)-3-Hydroxy-3-methyl-1-(prop-2-yn-1-yl)indolin-2-one (**2e**): Enantiomeric ratio (83.5:16.5) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1.0 mL/min, major enantiomer rt = 21.2 min, minor enantiomer rt = 16.9 min. White solid; mp = 84–86 °C; $[\alpha]_{20}^{D} = -25.3$ (c = 0.66, $CHCl_3$) (83.5:16.5 er); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (ddd, *J* = 7.4, 1.4, 0.6 Hz, 1H), 7.35 (td, *J* = 7.7, 1.3 Hz, 1H), 7.14 (td, *J* = 7.5, 1.0 Hz, 1H), 7.06 (dt, *J* = 7.8, 0.8 Hz, 1H), 4.53 (dd, *J* = 17.7, 2.5 Hz, 1H), 4.41 (dd, *J* = 17.7, 2.5 Hz, 1H), 3.08 (s, 1H), 2.24 (t, *J* = 2.5 Hz, 1H), 1.61 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.52 (C), 140.86 (C), 131.24 (C), 129.58 (CH), 123.59 (CH), 123.52 (CH), 109.57 (CH), 73.69 (C), 73.66 (C), 72.62 (CH), 29.34 (CH_2), 24.81 (CH_3); HRMS (ESI) *m*/*z*: 202.0862 $[M + H]^+$, $C_{12}H_{12}NO_2$ required 202.0863.

Methyl 2-(3-hydroxy-3-methyl-2-oxoindolin-1-yl)acetate (**2f**): Enantiomeric ratio (72:28) was determined by chiral HPLC quiral (Chiralpak IC), hexane-iPrOH 90:10, 1.0 mL/min, major enantiomer rt = 52.8 min, minor enantiomer rt = 57.2 min. Yelow solid; mp = 142–144 °C $[\alpha]_{20}^{D} = +1.91$ (c = 0.82, $CHCl_3$) (72:28 er); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 7.3, 1.3 Hz, 1H), 7.21 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.04 (td, *J* = 7.5, 1.0 Hz, 1H), 6.65 (dd, *J* = 7.8, 0.8 Hz, 1H), 4.44 (d, *J* = 17.6 Hz, 1H), 4.29 (d, *J* = 17.5 Hz, 1H), 3.67 (s, 3H), 3.06 (s, 1H), 1.55 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.37 (C), 167.96 (C), 141.34 (C), 131.22 (C), 129.58 (CH), 128.90 (CH), 123.59 (CH), 108.43 (CH), 73.59 (C), 52.66 (CH_3), 41.09 (CH_2), 24.84 (CH_3); HRMS (ESI) *m*/*z*: 236.0913 $[M + H]^+$, $C_{12}H_{14}NO_4$ required 236.0917.

1-Acetyl-3-hydroxy-3-methylindolin-2-one (**2g**) [50]: Enantiomeric ratio (54:46) was determined by chiral HPLC (Chiralpak IC), hexane-iPrOH 90:10, 1.0 mL/min, major enantiomer rt = 8.3 min, minor enantiomer rt = 7.2 min. White solid; mp = 109–110 °C; $[\alpha]_{20}^{D} = -4.8$ (c = 0.465, $CHCl_3$) (54:46 er); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26–8.20 (m, 1H), 7.46 (ddd, *J* = 7.3, 1.5, 0.6 Hz, 1H), 7.38 (ddd, *J* = 8.3, 7.6, 1.5 Hz, 1H), 7.26 (td, *J* = 7.4, 1.1 Hz, 1H), 2.81 (s, 1H), 2.66 (s, 3H), 1.65 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.04 (C), 170.74 (C), 139.10 (C), 130.33 (C), 130.15 (CH), 125.81 (CH), 123.23 (CH), 116.90 (CH), 73.59 (C), 26.47 (CH_3), 25.65 (CH_3); HRMS (ESI) *m*/*z*: 228.0632 $[M + Na]^+$, $C_{11}H_{11}NO_3Na$ required 228.0631.

3-Hydroxy-3-methyl-1-tosylindolin-2-one (**2h**): Enantiomeric ratio (72:28) was determined by chiral HPLC (Chiralpak AD-H), hexane-iPrOH 80:20, 1.0 mL/min, major enantiomer rt = 11.7 min, minor

enantiomer rt = 13.2 min. White solid; mp = 93–95 °C; $[\alpha]_{20}^{D}$ = +7.07 (c = 0.355, $CHCl_3$) (72:28 er); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.4 Hz, 2H), 7.91 (dd, *J* = 8.6, 1.0 Hz, 1H), 7.44–7.35 (m, 2H), 7.32 (dd, *J* = 8.7, 0.7 Hz, 2H), 7.25–7.18 (m, 1H), 2.56 (s, 1H), 2.41 (s, 3H), 1.56 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.82 (C), 145.89 (C), 138.08 (C), 134.83 (C), 130.36 (CH), 130.16 (C), 129.89 (CH), 127.87 (CH), 127.70 (CH), 125.45 (CH), 113.87 (CH), 73.64 (C), 25.75 (CH_3), 21.70 (CH_3); HRMS (ESI) *m*/*z*: 300.0689 $[M - H_2O]^+$, $C_{16}H_{14}NO_3S$ required 300.0689.

(S)-3-Hydroxy-3-methyl-1-(naphthalen-1-ylmethyl)indolin-2-one (**2i**): Enantiomeric ratio (87:13) was determined by chiral HPLC (Chiralpak AS-H), hexane-iPrOH 80:20, 1.0 mL/min, major enantiomer rt = 14.3 min, minor enantiomer rt = 10.9 min. White solid, mp = 131–133 °C; $[\alpha]_{20}^{D}$ = −19.06 (c = 1.23, $CHCl_3$) (87:13 er); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12–8.06 (m, 1H), 7.89 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.79 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.64–7.49 (m, 2H), 7.47–7.42 (m, 1H), 7.37 (dd, *J* = 8.2, 7.1 Hz, 1H), 7.28 (dd, *J* = 7.1, 1.2 Hz, 1H), 7.12 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.09–7.02 (m, 1H), 6.68 (dt, *J* = 8.0, 0.9 Hz, 1H), 5.52 (d, *J* = 16.2 Hz, 1H), 5.21 (d, *J* = 16.2 Hz, 1H), 3.32 (s, 1H), 1.72 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.84 (C), 142.14 (C), 133.83 (C), 131.44 (C), 130.97 (C), 130.19 (C), 129.49 (CH), 128.93 (CH), 128.40 (CH), 126.56 (CH), 126.0 (CH), 125.25 (CH), 124.52 (CH), 123.44 (CH), 123.27 (CH), 122.75 (CH), 109.95 (CH), 73.78 (C), 41.97 (CH_2), 25.19 (CH_3); HRMS (ESI) *m*/*z*: 304.1332 $[M + H]^+$, $C_{20}H_{18}NO_2$ required 304.1332.

(S)-1-Benzyl-3-hydroxy-5-methoxy-3-methylindolin-2-one (**2j**): Enantiomeric ratio (89.5:10.5) was determined by chiral HPLC (Chiralpak AD-H), hexane-iPrOH 80:20, 1.0 mL/min, major enantiomer rt = 14.1 min, minor enantiomer rt = 10.3 min. Oil; $[\alpha]_{20}^{D}$ = −36.51 (c = 1.09, $CHCl_3$) (89.5:10.5 er); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.17 (m, 5H), 7.04 (d, *J* = 2.6 Hz, 1H), 6.71 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.59 (d, *J* = 8.5 Hz, 1H), 4.92 (d, *J* = 15.6 Hz, 1H), 4.77 (d, *J* = 15.7 Hz, 1H), 3.76 (s, 3H), 3.47 (s, 1H), 1.66 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.54 (C), 156.45 (C), 135.48 (C), 135.02 (C), 132.68 (C), 128.79 (CH), 127.64 (CH), 127.14 (CH), 114.08 (CH), 110.48 (CH), 110.11 (CH), 74.06 (C), 55.76 (CH_3), 43.76 (CH_2), 25.19 (CH_3); HRMS (ESI) *m*/*z*: 284.1280 $[M + H]^+$, $C_{17}H_{18}NO_3$ required 284.1281.

(S)-1-Benzyl-3-hydroxy-3,5-dimethylindolin-2-one (**2k**) [44]: Enantiomeric ratio (89:11) was determined by chiral HPLC (Chiralpak AD-H), hexane-iPrOH 80:20, 1.0 mL/min, major enantiomer rt = 8.4 min, minor enantiomer rt = 7.0 min. White solid; mp = 131–132 °C; $[\alpha]_{20}^{D}$ = −2.33 (c = 0.81, $CHCl_3$) (89:11 er); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 2.0 Hz, 1H), 7.37–7.21 (m, 6H), 6.58 (dd, *J* = 8.5, 0.9 Hz, 1H), 4.93 (d, *J* = 15.7 Hz, 1H), 4.80 (d, *J* = 15.7 Hz, 1H), 3.11 (s, 1H), 1.66 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.09 (C), 140.87 (C), 134.92 (C), 133.27 (C), 132.31 (CH), 128.94 (CH), 127.90 (CH), 127.11 (CH), 126.96 (CH), 116.03 (C), 111.11 (CH), 73.67 (C), 43.81 (CH2), 25.08 (CH3); HRMS (ESI) *m*/*z*: 268.1331 $[M + H]^+$, $C_{17}H_{18}NO_2$ required 268.1332.

(S)-1-Benzyl-5-chloro-3-hydroxy-3-methylindolin-2-one (**2l**): Enantiomeric ratio (80:20) was determined by chiral HPLC (Chiralpak AD-H), hexane-iPrOH 80:20, 1.0 mL/min, major enantiomer rt = 8.8 min, minor enantiomer rt = 6.8 min. White siolid; mp = 159–161 °C; $[\alpha]_{20}^{D}$ = −29.37 (c = 0.985, $CHCl_3$) (80:20 er); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, *J* = 2.1 Hz, 1H), 7.34–7.21 (m, 5H), 7.16 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.62 (d, *J* = 8.3 Hz, 1H), 4.93 (d, *J* = 15.7 Hz, 1H), 4.79 (d, *J* = 15.7 Hz, 1H), 3.40 (s, 1H), 2.30 (s, 3H), 1.66 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.35 (C), 140.29 (C), 134.94 (C), 133.08 (C), 133.03 (CH), 129.34 (CH), 128.92 (C), 128.77 (CH), 127.87 (CH), 127.10 (CH), 124.19 (CH), 110.61 (CH), 73.73 (C), 43.82 (CH_2), 25.05 (CH_3), 20.98 (CH_3). HRMS (ESI) *m*/*z*: 288.0782 $[M + H]^+$, $C_{16}H_{15}ClNO_2$ required 288.0786.

(S)-1-Benzyl-3-hydroxy-3-methyl-5-nitroindolin-2-one (**2m**): Enantiomeric ratio (58.5:41.5) was determined by chiral HPLC (Chiralpak AD-H), hexane-iPrOH 80:20, 1.0 mL/min, major enantiomer rt = 12.8 min, minor enantiomer rt = 10.2 min. Oil; $[\alpha]_{20}^{D}$ = −10.9 (c = 1.07, $CHCl_3$) (58.5:41.5 er); 1H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, *J* = 2.2 Hz, 1H), 8.15 (ddd, *J* = 8.8, 2.4, 0.8 Hz, 1H), 7.42–7.19 (m, 5H), 6.80 (dd, *J* = 8.5, 0.8 Hz, 1H), 4.99 (d, *J* = 15.8 Hz, 1H), 4.88 (d, *J* = 15.7 Hz, 1H), 3.67 (s,1H), 1.72 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.95 (C), 147.41 (C), 143.93 (C), 134.24 (C), 132.27 (C), 129.12 (CH),

128.22 (CH), 127.10 (CH), 126.48 (CH), 119.61 (CH), 109.33 (CH), 73.29 (C), 44.10 (CH_2), 24.90 (CH_3); HRMS (ESI) *m*/*z*: 298.1027 $[M + H]^+$, $C_{16}H_{15}N_2O_4$ required 299.1026.

(S)-1-Benzyl-6-chloro-3-hydroxy-3-methylindolin-2-one (**2n**): Enantiomeric ratio (84:16) was determined by chiral HPLC (Chiralpak AD-H), hexane-iPrOH 80:20, 1.0 mL/min, major enantiomer rt = 7.3 min, minor enantiomer rt = 6.8 min. White solid; mp = 140–141 °C; $[\alpha]_{20}^{D} = -18.3$ (c = 1.15, $CHCl_3$) (84:16 er); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.22 (m, 6H), 7.04 (dd, *J* = 7.9, 1.8 Hz, 1H), 6.71 (d, *J* = 1.7 Hz, 1H), 4.92 (d, *J* = 15.7 Hz, 1H), 4.76 (d, *J* = 15.8 Hz, 1H), 3.36 (s, 1H), 1.65 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.68 (C), 143.08 (C), 135.23 (C), 134.86 (C), 129.77 (C), 128.97 (CH), 127.92 (CH), 127.10 (CH), 124.50 (CH), 123.19 (CH), 110.18 (CH), 73.38 (C), 43.80 (CH_2), 25.02 (CH_3); HRMS (ESI) *m*/*z*: 288.0783 $[M + H]^+$, $C_{16}H_{15}ClNO_2$ required 288.0786.

(S)-1-Benzyl-7-fluoro-3-hydroxy-3-methylindolin-2-one (**2o**): Enantiomeric ratio (85:15) was determined by chiral HPLC (Chiralpak AD-H), hexane-iPrOH 80:20, 1.0 mL/min, major enantiomer rt = 7.7 min, minor enantiomer rt = 6.6 min. White solid; mp = 106–108 °C; $[\alpha]_{20}^{D} = -20.85$ (c = 0.93, $CHCl_3$) (85:15 er); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.24 (m, 5H), 7.23–7.19 (m, 1H), 7.06–6.93 (m, 2H), 5.05 (d, *J* = 16.6 Hz, 1H), 4.98 (d, *J* = 16.6 Hz, 1H), 3.32 (s, 1H), 1.65 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178. 47 (C), 147.57 (d, J_{C-F} = 244.9 Hz, C), 136.62 (C), 134.32 (d, J_{C-F} = 2.8 Hz, C), 128.62 (CH), 128.36 (d, J_{C-F} = 8.7 Hz, C), 127.63 (CH), 127.35 (d, J_{C-F} = 1.4 Hz, CH), 124.12 (d, J_{C-F} = 6.4 Hz, CH), 119.39 (d, J_{C-F} = 3.3 Hz, CH), 117.67 (d, J_{C-F} = 19.6 Hz, CH), 73.74 (d, J_{C-F} = 2.6 Hz, C), 45.29 (d, J_{C-F} = 4.7 Hz, CH_2), 25.22 (CH_3); HRMS (ESI) *m*/*z*: 272.1077 $[M + H]^+$, $C_{16}H_{15}FNO_2$ required 272.1070.

(S)-1-Benzyl-7-chloro-3-hydroxy-3-methylindolin-2-one (**2p**): Enantiomeric ratio (83:17) was determined by chiral HPLC (Chiralpak AD-H), hexane-iPrOH 80:20, 1.0 mL/min, major enantiomer rt = 9.0 min, minor enantiomer rt = 7.3 min. White solid; mp = 175–176 °C; $[\alpha]_{20}^{D} = -18.92$ (c = 0.945, $CHCl_3$) (83:17 er); ^{1}H NMR (300 MHz, CDCl3) δ 7.40–7.15 (m, 7H), 7.02 (dd, *J* = 8.2, 7.3 Hz, 1H), 5.32 (s, 2H), 3.25 (s, 1H), 1.66 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.35 (C), 137.95 (C), 137.07 (C), 134.31 (C), 132.02 (CH), 128.61 (CH), 127.24 (CH), 126.33 (CH), 124.30 (CH), 122.15 (CH), 115.87 (C), 73.06 (C), 44.75 (CH_2), 25.42 (CH_3); HRMS (ESI) *m*/*z*: 288.0783 $[M + H]^+$, $C_{16}H_{15}ClNO_2$ required 288.0786.

(S)-1-Benzyl-3-hydroxy-3,5,7-trimethylindolin-2-one (**2q**): Enantiomeric ratio (89:11) was determined by chiral HPLC (Chiralpak AD-H), hexane-iPrOH 80:20, 1.0 mL/min, major enantiomer rt = 9.6 min, minor enantiomer rt = 7.6 min. White solid; mp = 142–145 °C; $[\alpha]_{20}^{D} = -37.19$ (c = 0.855, $CHCl_3$) (89:11 er); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.20 (m, 3H), 7.16–7.11 (m, 3H), 6.78 (dq, *J* = 1.7, 0.7 Hz, 1H), 5.17 (d, *J* = 16.6 Hz, 1H),5.10 (d, *J* = 16.6 Hz, 1H), 3.14 (s, 1H), 2.28 (s, 3H), 2.20 (s, 3H), 1.67 (s, 3H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 179.72 (C), 137.33 (C), 137.25 (C), 133.80 (CH), 133.00 (C), 132.22 (C), 128.85 (CH), 127.20 (CH), 125.57 (CH), 122.15 (CH), 120.05 (C), 73.03 (C), 44.84 (CH_2), 25.49 (CH_3), 20.66(CH_3), 18.50 (CH_3); HRMS (ESI) *m*/*z*: 282.1485 $[M + H]^+$, $C_{18}H_{20}NO_2$ required 282.1489.

3.3. Procedures and Characterization Data for Compounds **3a** *and* **4a**

(1aS,6bS)-2-benzyl-6b-methyl-1a,6b-dihydro-2H-oxireno[2,3-b]indole (**3a**): A 1 M $LiAlH_4$ solution in THF (0.2 mL, 0.2 mmol) was added dropwise on a solution of **2a** (0.1 mmol) in THF (5 mL) at room temperature under nitrogen. The reaction was warmed to 75 °C and stirred until the reaction was complete (TLC). The reaction mixture was quenched with NH_4Cl (10 mL), extracted with dichloromethane (3 × 20 mL), washed with brine (10 mL), dried over $MgSO_4$ and dried under reduced pressure. The crude was used for the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.14 (m, 6H), 7.05 (td, *J* = 7.7, 1.3 Hz, 1H), 6.67 (ddt, *J* = 8.2, 7.4, 0.8 Hz, 1H), 6.34 (dd, *J* = 7.8, 0.8 Hz, 1H), 4.54 (s, 1H), 4.45 (d, *J* = 15.6 Hz, 1H), 4.23 (d, *J* = 15.7 Hz, 1H), 1.47 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.45 (C), 138.10 (C), 131.72 (C), 129.94 (CH), 128.80 (CH), 127.17 (CH), 127.00 (CH), 123.15 (CH), 118.79 (CH), 107.51 (CH), 92.77 (CH), 75.79 (C), 48.51 (CH_2), 24.33 (CH_3).

(2R,3S)-1-benzyl-3-hydroxy-3-methylindoline-2-carbonitrile (**4a**): TMSCN (37 μL, 0.294 mmol) was added dropwise on a solution of **3a** (0.1 mmol) in CH_2Cl_2 (2 mL) at room temperature under nitrogen.

The reaction was stirred until the reaction was complete (TLC). Finally, the reaction mixture was directly poured into the column chromatography, using hexanes:EtOAc (95:5) as eluent to afford product **4a**. Enantiomeric ratio (89:11) was determined by chiral HPLC (Chiralpak AD-H), hexane-iPrOH 80:20, 1.0 mL/min, major enantiomer rt = 7.9 min, minor enantiomer rt = 18.7 min. Oil; $[\alpha]_{20}^{D} = -46.57$ (c = 0.505, $CHCl_3$) (89:11 er); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.19 (m, 7H), 6.89 (td, *J* = 7.5, 0.9 Hz, 1H), 6.68 (dt, *J* = 8.1, 0.7 Hz, 1H), 4.71 (d, *J* = 14.8 Hz, 1H), 4.19 (d, *J* = 14.9 Hz, 1H), 4.04 (s, 1H), 2.55 (s, 1H), 1.64 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.38 (C), 135.77 (C), 132.15 (C), 130.38 (CH), 128.90 (CH), 128.25 (CH), 128.01 (CH), 122.89 (CH), 120.36 (CH), 115.48 (C), 109.24 (CH), 78.41 (C), 66.88 (CH), 50.95 (CH_2), 25.36 (CH_3); HRMS (ESI) *m*/*z*: 265.1329 $[M + H]^+$, $C_{17}H_{17}N_2O$ required 265.1335.

4. Conclusions

We have developed a catalytic enantioselective addition of Me_2Zn to isatins catalyzed by a chiral Zn(II) complex using as chiral ligand a α-hydroxyamide derived from (*S*)-mandelic acid. The corresponding chiral 3-hydroxy-3-methyl-2-oxindoles are obtained with good yields and enantioselectivities. The enantioselectivities are comparable to the example described by Shibashaki [34] with a bifunctional proline-derived amino alcohol. The advantages of our system are that the catalyst is easily prepared in a one-step procedure, the reaction time is shorter and no slow addition of the reagent is required, leading to simplified procedures. Moreover, several transformations have been done with the corresponding chiral tertiary alcohols obtained.

Supplementary Materials: The following are available online at www.mdpi.com/2073-4344/7/12/387/s1, ^{1}H and ^{13}C NMR spectra, and HPLC chromatograms of all compounds.

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Conflicts of Interest: The authors declare no conflict of interest.

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