ROYAL SOCIETY
OF CHEMISTRY

PAPER

Check for updates

Cu(II)-thiophene-2,5-bis(amino-alcohol) mediated asymmetric Aldol reaction and Domino Knoevenagel Michael cyclization: a new highly efficient Lewis acid catalyst†

Abdullah Mohammed Al-Majid,*[a] Abdullah Saleh Alammari,[a] Saeed Alshahrani, [ID] [a] Matti Haukka, [ID] [b] Mohammad Shahidul Islam [ID] *[a] and Assem Barakat [ID] [a]

The highly efficient Lewis acid-catalytic system Cu(II)-thiophene-2,5-bis(amino-alcohol) has been developed for enantioselective Aldol reaction of isatin derivatives with ketones. The new catalytic system also proved to be highly enantioselective for the one pot three-component Domino Knoevenagel Michael cyclization reaction of substituted isatin with malononitrile and ethylacetoacetate. The chiral ligand (2S,2′S)-2,2′-((thiophene-2,5-diylbis(methylene))bis(azanediyl))bis(3-phenylpropan-1-ol) (L1) in combination with Cu(OAc)$_2$·H$_2$O employed as a new Lewis acid catalyst, furnished 3-substituted-3-hydroxyindolin-2-ones derivatives (3a–s) in good to excellent yields (81–99%) with high enantioselectivities (up to 96% ee) and spiro[4H-pyran-3,3-oxindole] derivatives (6a–l) in excellent yields (89–99%) with high ee (up to 95%). These aldol products and spiro-oxindoles constitute a core structural motif in a large number of pharmaceutically active molecules and natural products.

Introduction

The chiral ligand–Lewis acid–metal catalysed carbon–carbon bond construction process has become increasingly interesting to synthetic chemists as well as pharmacists, for carrying out various crucial organic transformations. In particular, chiral versions of these catalytic processes are one of the prominent strategies to access several enantiopure bioactive molecules.[1–5] Among them, the asymmetric Aldol reaction and Domino Knoevenagel Michael cyclization reaction are the most powerful and efficient approaches for accessing various enantiomerically enriched biomolecules.[6,7]

The core framework '3-alkyl-3-hydroxyindolin-2-ones' is present in a large number of natural products[8–14] and drug molecules[15–19] such as maremycins,[17] arundaphine,[20] donaxaridine,[21] paratunamide,[22] (R)-convolutamydines A, B and E,[23–27] flustraminol,[28] diazonamides,[29–33] leptosin D,[34] 3′-

hydroxyglucoisatisin,[35] CPC-1,[36] 3-hydroxy welwitindolinones C,[37] TMC-95 (A–D),[38–40] celogentin K,[41] dioxibrassinin[42] (Fig. 1).

Therefore, the development of efficient and practical methods to synthesize this kind of building block is of great importance and is currently an open area of research in asymmetric catalysis.[43–45] A representative example has been developed recently for asymmetric Aldol reaction of ketones with
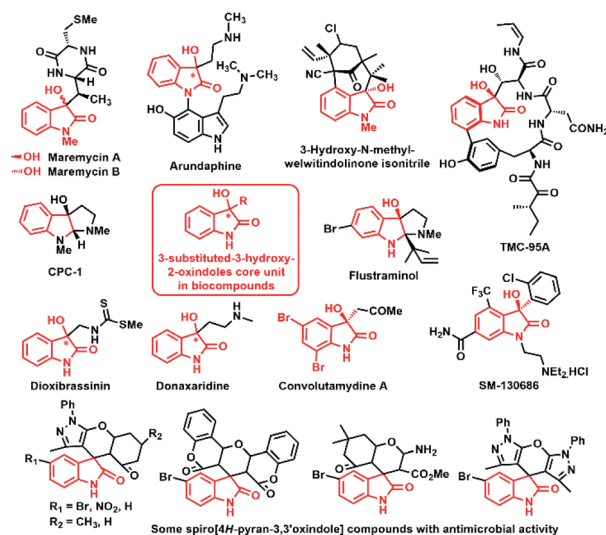

Fig. 1 Prominent bioactive compounds based 3-substituted-3-hydroxy-2-oxindoles and spiro[4H-pyran-3,3′-oxindole] motifs.

[a]Department of Chemistry, College of Science, King Saud University, P. O. Box 2455, Riyadh 11451, Saudi Arabia. E-mail: 436106737@student.ksu.edu.sa; alamary1401@yahoo.com; 436106738@student.ksu.edu.sa; chemistry99y@gmail.com; ambarakat@ksu.edu.sa; amajid@ksu.edu.sa; mislam@ksu.edu.sa; Fax: +966-61-1467-5992

[b]Department of Chemistry, University of Jyväskylä, P. O. Box 35, FI-40014 Jyväskylä, Finland. E-mail: matti.o.haukka@jyu.fi

various isatins which is one of the most straightforward and powerful methods in order to achieve highly enantiopure biologically active core framework '3-alkyl-3-hydroxyindolin-2-ones' with new chiral stereocenters.[46–52] Ever since, proline catalysed cross-Aldol reaction of aldehydes and ketones first reported by List and Barbas in 2000,[53] since then, lot of chiral amine ligands have been used as organo-catalyst for the cross-Aldol asymmetric reaction.[47,54] In 2005, for the first time asymmetric Aldol reaction of isatin with acetone was first developed by Tomasini *et al.* employing dipeptide-based ligand as organocatalyst.[55–59] However, significant efforts have been made for developing efficient asymmetric Aldol reactions of isatins with ketones mostly using organocatalysts such as proline,[60–62] prolinamides,[63–69] sulphonamides,[70–72] amines,[73,74] quinidine-thioureas,[75–77] vicinal amino-alcohol,[78] enzymes,[79] 4-hydroxydiarylprolinol[80] and amino acid salts.[81]

The spiro-heterocyclic oxindoles are the eye-catching targets to the synthetic chemist and biologist because of their biological significance to a wide-range of synthetic utility such as alkaloids intermediates, drug candidates and clinical pharmaceuticals agents.[82–89] In particular, 'spiro[4H-pyran-3,3'-oxindole]' moiety is the most important heterocyclic skeleton that could be found in spirooxindoles framework complex molecules of several alkaloids and drug agents.[82,83] Over the couple years, sizable number of investigation have been carried out successfully for the construction of spiro[4H-pyran-3,3'-oxindole] framework as a core skeleton of spirooxindole structures.[90–92] Domino Knoevenagel Michael cyclization is one of the highly successful procedures for the stereoselective synthesis of spirooxindole derivatives derived spiro[4H-pyran-3,3'-oxindole] moiety.[93,94] To construct this interesting scaffold, Yuan and co-workers in 2010 for the first time, utilized cupreine-(60-hydroxycinchonidine) as organocatalyst for accessing chiral spiro[4H-pyran-3,3'-oxindole] derivatives from multi component reactions of N-alkylated isatins.[95] Recently, Nakano *et al.* reported hybrid squaramide amino alcohol organo-catalyzed asymmetric Domino Michael cyclization reactions of oxoindolines with cyclic 1,3-diketones, affording chiral spiro-conjugated oxindoles tethering 2-aminopyrans heterocyclic ring systems with excellent yield and enantioselectivity.[96] In 2019, Swapna Konda and co-workers synthesized chiral spiro[4H-pyran-3,3'-oxindole] derivatives with good chemical yield (up to 92%) and enantioselectivity (up to 87% ee) using cinchona alkaloid thioureas as an organocatalysts.[97] However, till date very limited efforts have been made for the construction of stereoselective spiro-heterocyclic oxindole, engrafting 2-amino-4H-pyran-3-carbonitrile ring at the C_3 position of oxindole *via* asymmetric Domino Michael cyclization reaction.

However, very limited findings have been reported for the application of Lewis acid catalyzed asymmetric Aldol reaction[98] of ketones with isatin in order to excess derivative of '3-alkyl-3-hydroxyindolin-2-ones' and asymmetric Domino Michael cyclization reaction[99–101] of isatin with malononitrile and ethylacetoacetate to furnish enantiopure spiro[4H-pyran-3,3'-oxindole] derivatives. Therefore, further investigations are required to produce bioactive motif like '3-alkyl-3-

hydroxyindolin-2-ones' and spiro[4H-pyran-3,3'-oxindole] using Lewis acid catalyst, that remains a great challenge.

Recently, a series of new chiral bis(amino-alcohol)thiophene ligands-Cu(OAc)$_2$·H$_2$O as a Lewis acid catalytic system have been developed by our group and their catalytic application was successfully applied for enantioselective Henry reaction to afford the corresponding chiral Henry product with satisfactory yield and enantioselectivity.[5] On observing their good catalytic enantioselective induction in the Henry reaction, we decided to explore the utility of those chiral ligands for different applications such as enantioselective Aldol reaction as well as Domino Michael cyclization reaction.

As per the best of our knowledge, we are reporting for the first time chiral bis(amino-alcohol)thiophene ligand–Lewis acid catalysed enantioselective Aldol reaction of isatins with substituted acetone to produce enantiopure 3-substituted-3-hydroxy-2-oxindoles derivatives as well as Domino Michael cyclization reaction of isatins with malononitrile and ethylacetoacetate to afford the chiral oxindoles spiro[4H-pyran-3,3'-oxindole] fused with 2-aminopyrans heterocyclic ring systems.

Results and discussion

Catalytic asymmetric studies of Aldol reaction

The following ligands as shown in Fig. 2 reported recently by our research group as an examples of C_2-symmetric chiral thiophene-2,5-bis(amino-alcohol) ligands (**L1–L5**) and successfully applied them in catalytic asymmetric Henry reaction of nitromethane with substituted aldehydes in excellent yield and enantioselectivity (yield up to 99% and ee up to 95%).[5] (Fig. 2). We further decided to examine their asymmetric catalytic efficiency and therefore enantioselective Aldol reaction of isatin with substituted acetone as well as three-component chiral Domino Michael cyclization reaction of isatin with malononitrile and ethylacetoacetate have been explored successfully.

Initially, Aldol reaction of 5-bromoisatin (**1a**) with acetone (**2a**) as model substrate were carried out for accessing 3-substituted-3-hydroxy-2-oxindoles derivatives, using 20 mol% chiral thiophene-2,5-bis(amino-alcohol) ligands (**L1–L5**) as organocatalysts in ethanol (2 mL) at room temperature (rt) under inert atmosphere for 24–48 h and we observe that, all the ligands were found to be efficient to furnish aldol product **3a** (89–99% yield) in excellent yield but unfortunately failed to induce enantioselectivity (16–21% ee) effectively (Table 1).

Then the catalytic efficacy of these ligands were examined in combination with metal salt like copper acetate monohydrate (Cu(OAc)$_2$·H$_2$O) generated a metal complex *in situ* as a Lewis

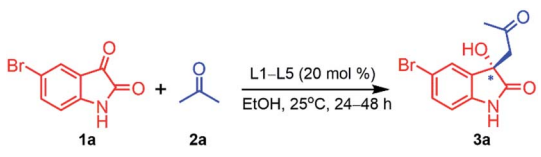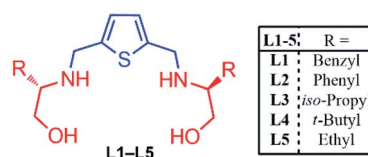| L1–5:	R =
L1	Benzyl
L2	Phenyl
L3	iso-Propyl
L4	t-Butyl
L5	Ethyl

Fig. 2 C_2-symmetric chiral thiophene-2,5-bis(amino-alcohol) ligands (**L1–L5**) used for Aldol reaction and Domino Michael addition reaction.
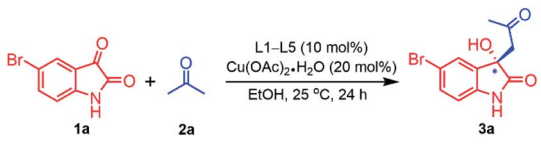
Paper

Table 1 Enantioselectivity Aldol reaction of 5-bromoisatin (**1a**) with acetone (**2a**) catalyzed by organocatalysts **L1–L5**

Entries[a]	Ligands	Time (h)	Yield[b] (%)	ee[c] (%)
1	**L1**	24	99	21
2	**L2**	24	99	16
3	**L3**	24	99	19
4	**L4**	24	99	20
5	**L5**	48	89	20

[a] Reactions were performed on 0.2 mmol of isatin and 10.0 mmol of acetone. [b] Isolated yields after column purification. [c] Enantiomeric excess (ee) was determined by chiral HPLC using a Daicel Chiralpak AD-H (25 cm × 4.6 mm × 5 μm).

acid catalytic system for asymmetric Aldol reaction of 5-bromoisatin (**1a**) with acetone (**2a**, 50 eq.). Subsequently, the reaction was performed in ethanol (2 mL) at 25 °C under inert atmosphere, using 10 mol% of ligands **L1–L5** with 20 mol% of Cu(OAc)$_2$·H$_2$O for 24 h and the corresponding findings were documented in Table 2. Fortunately, all the ligands (**L1–L5**) were found to be capable of producing aldol product **3a** with significantly enhanced enantioselectivity (44–58% ee) (Table 2, entries 1–5) but the chemical yields were significantly dropped (44–60%). Interestingly, ligand **L1** and **L4** bearing benzyl and *t*-butyl group respectively were found to be the most effective ligand in combination with Cu(OAc)$_2$·H$_2$O, furnishing highest yield (60% and 58%) accordingly. However, higher enantioselectivity (58% ee) was observed in presence of **L1** as compared to **L4** (48% ee) (Table 2, entries 1 and 4) and therefore **L1** has been chosen for further optimization.
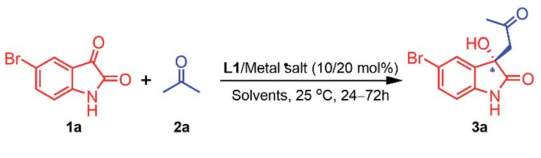
Table 2 Enantioselectivity Aldol reaction of 5-bromoisatin (**1a**) with acetone (**2a**) catalyzed by ligand (**L1–L5**) in presence of Cu(OAc)$_2$·H$_2$O

Entries[a]	Ligands	Time (h)	Yield[b] (%)	ee[c] (%)
1	**L1**	24	60	58
2	**L2**	24	44	47
3	**L3**	24	48	45
4	**L4**	24	58	48
5	**L5**	24	45	44

[a] Reactions were performed on 0.2 mmol of isatin and 10.0 mmol of acetone. [b] Isolated yields after column purification. [c] Enantiomeric excess (ee) was determined by chiral HPLC using a Daicel Chiralpak AD-H (25 cm × 4.6 mm × 5 μm).

In order to improve the yield and enantioselectivity, asymmetric Aldol reaction of 5-bromoisatin (**1a**) with acetone (**2a**, 50 eq.) was further investigated. The effect of different metal salts such as Cu(OAc)$_2$·H$_2$O, Zn(OAc)$_2$·2H$_2$O, Zn(OTf)$_2$, Mg(OTf)$_2$, Er(OTf)$_3$ and Yb(OTf)$_3$ as a Lewis acid as well as various solvents system like EtOH, CH$_2$Cl$_2$, dioxane and THF were explored, using 10 mol% of ligand **L1** with 20 mol% metal salts at rt over the period of 24–72 h and the summery of the results were shown in Table 3. It is evident from the results that, the catalytic system of **L1**-Cu(OAc)$_2$·H$_2$O in solvents like CH$_2$Cl$_2$ and dioxane, improved enantiomeric excess (ee) (74% & 76%) respectively as compared to ethanol (yield 60%, ee 58%) but the chemical yields were still low (58% and 45%) (Table 3, entries 1–3). However, in case of catalytic system **L1**-Cu(OAc)$_2$·H$_2$O (10 : 20 mol%) in THF as solvent was found to be the best choice as Lewis acid catalyst for the asymmetric Aldol reaction of 5-bromoisatin (**1a**) with acetone (**2a**, 50 eq.), furnishing the best yield and enantioselectivity (65% yield, 82% ee) (Table 3, entry 4). Nevertheless, **L1**-Zn(OAc)$_2$·2H$_2$O in THF produce 50% yield with very poor enantioselectivity (17% ee) in 72 h (Table 3, entry 4). Moreover, ligand **L1** in combination with metal salts like Zn(OTf)$_2$, Mg(OTf)$_2$, Er(OTf)$_3$ and Yb(OTf)$_3$ in THF were found to be completely ineffective for the asymmetric Aldol reaction (Table 3, entries 6–9). The poor efficiency of Zn^{+2} complex as compared to Cu^{+2} complex could be attributed to the higher electronegativity [EN of (Cu^{2+}) = 1.90 > EN of (Zn^{2+}) = 1.65] and greater charge to radius ratio of Cu^{+2} than Zn^{+2} ion, those are two factors perhaps help Cu^{2+} to form covalent bond with O and N atoms of ligand stronger than Zn^{2+} during the complex formation.

From these several attempts to achieve acceptable yield and high enantioselectivity, it can be concluded that, **L1**-Cu(OAc)$_2$·H$_2$O (10 : 20 mol%) as Lewis acid catalyst, in THF at rt for 24 h

Table 3 Enantioselectivity Aldol reaction of 5-bromoisatin (**1a**) with acetone (**2a**); solvents and metal salt screening

Entries[a]	Solvents	Metal salts	Time (h)	Yield[b] (%)	ee[c] (%)
1	EtOH	Cu(OAc)$_2$·H$_2$O	24	60	58
2	CH$_2$Cl$_2$	Cu(OAc)$_2$·H$_2$O	24	58	74
3	Dioxane	Cu(OAc)$_2$·H$_2$O	24	45	76
4	**THF**	**Cu(OAc)$_2$·H$_2$O**	**24**	**65**	**82**
5	THF	Zn(OTf)$_2$	72	Trace	—
6	THF	Zn(OAc)$_2$·2H$_2$O	72	50	17
7	THF	Mg(OTf)$_2$	72	—	—
8	THF	Yb(OTf)$_3$	72	—	—
9	THF	Er(OTf)$_3$	72	—	—

[a] Reactions were performed on 0.2 mmol of isatin and 10.0 mmol of acetone. [b] Isolated yields after column purification. [c] Enantiomeric excess (ee) was determined by chiral HPLC using a Daicel Chiralpak AD-H (25 cm × 4.6 mm × 5 μm).
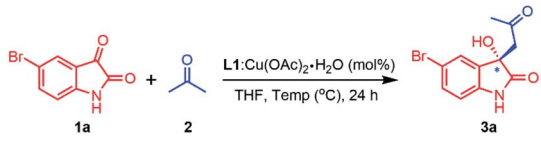
able to afford better yield and enantioselectivity for the asymmetric Aldol reaction of 5-bromoisatin (**1a**) with acetone (**2a**, 50 eq.). However, further optimizations are required as the results were not up to the marks as far as yields and enantioselectios are concerned. Therefore, other crucial parameters such as loading of catalyst, equivalent of acetone, time variation and temperature control were further screened to obtain the best optimized condition for the asymmetric Aldol reaction.

To find out the best optimized parameters, initially Aldol reaction were performed using 5 mol% and 15 mol% of ligand **L1** with 20 mol% of Cu(OAc)$_2$·H$_2$O in THF at rt for 24 h and it can be seen from the results that neither the yields (52% & 68%) nor enantioselectivities (74% & 70% ee) were improved (Table 4, entries 1 & 2). Then the loading of Cu(OAc)$_2$·H$_2$O as metal salt were increased from 20 to 30 and 40 mol%, keeping the other parameters unchanged (10 mol% of ligand **L1** in THF at rt for 24 h). We observed that, both the corresponding yields (88% and 88%) as well as enantiomeric excess (96% & 86% ee) were improved significantly (Table 4, entries 3 & 4), although 10 : 30 mol% ratio of **L1**-Cu(OAc)$_2$·H$_2$O was found to be the best choice for the asymmetric Aldol reaction as it has furnished the final product **3a** in excellent yield and enantioselectivity (88% yield, 96% ee) (Table 4, entry 3). Next, may be the temperature has an impact on catalytic efficiency of this new catalytic system. Therefore, the reaction was further performed, using 10 : 30 mol% of **L1**-Cu(OAc)$_2$·H$_2$O in THF at rt for 24 h at lower temperature 10 °C as well as 0 °C, but unfortunately results indicated that, the yields (69% & 53%) and enantioselectivities (73%, 71% ee) both were significantly dropped (Table 4, entries 5 & 6) although prolong reaction time (48 h) was given. We further investigated the reaction with different molar ratio of acetone (10, 20, 40, 60 eq.) under the best optimum parameters and the findings are reported in Table 4 entries 7–10, still 50 eq. of acetone is the best choice to get better yield and

enantioselectivity. From the overall investigation, we came to conclusion that, 10 mol% of ligand **L1** with 30 mol% of Cu(OAc)$_2$·H$_2$O in THF at rt for 24 h produced best result as we obtained aldol product in high yield (88%) and enantioselectivity (96%).

After establishing standard reaction parameters, we extended the substrate scope for the asymmetric Aldol reaction under the optimized reaction condition, using Lewis acid catalyst **L1**-Cu(OAc)$_2$·H$_2$O (10 : 30 mol%) in THF at rt for 24 h. A variety of substituted isatin (**1a–l**) with several acetone derivatives (**2a–h**) were screened for the asymmetric Aldol reaction using optimized reaction parameter and the corresponding aldol chiral derivatives of 3-hydroxyindolin-2-one (**3a–s**) were obtained in good to excellent yields (81–99%) with moderate to high enantiomeric excess (35–96% ee) and the results are summarized in Table 5. Our optimized catalytic system worked efficiently in case of isatin derivatives bearing electron-donating groups (5-Me and *N*-Me) which afforded aldol products **3h** (99% yield, 93% ee) and **3j** (91% yield, 89% ee) respectively (Table 5, entries 8 & 10). Exceptionally, 5-bromoisatin afforded best enantioselectivity (96% ee) and good yield (88%) (Table 5, entry 1). While, in case of isatin derivatives containing electron-withdrawing groups such as 5-Cl, *N*-benzyl and *N*-ethyl-bromide, this catalytic system also worked remarkable well and afforded respective aldol products (**3c**, **3k** and **3l**) with excellent yields (99%, 91% and 98%) and very good enantiomeric excess (76%, 78% and 71% ee) (Table 5, entries 3, 11 & 12). However, this catalytic system furnished aldol products **3b**, **3e**, **3f** and **3i** with very good yields (99%, 99%, 88% and 97%) and moderate enantioselectivities (62%, 55%, 44% and 53% ee) when isatin, 5-methoxy, 5-nitro and 5-fluoro isatin were used as nucleophilic centre for Aldol reaction (Table 5, entries 2, 5, 6 & 9). Noteworthy to mention that, while using 6-chloro and 5,7-dibromo isatin for the Aldol reaction, our catalytic system performed under

Table 4 Enantioselective Aldol reaction of 5-bromoisatin (**1a**) with acetone (**2a**); loading of catalyst and temperature control


#[a]	**L1**/Cu(OAc)$_2$·H$_2$O (mol%)	Acetone (eq.)	Time (h)	Temp (°C)	Yield[b] (%)	ee[c] (%)
1	05/20	50	24	25	52	74
2	15/20	50	24	25	68	70
3	**10/30**	**50**	**24**	**25**	**88**	**96**
4	10/40	50	24	25	88	86
5	10/30	50	48	10	69	73
6	10/30	50	48	0	53	71
7	10/30	10	24	25	65	82
8	10/30	20	24	25	72	85
9	10/30	40	24	25	79	86
10	10/30	60	24	25	74	85

[a] Reactions were performed on a 0.2 mmol of isatin and 10–60 eq. of acetone. [b] Isolated yields after column purification. [c] Enantiomeric excess (ee) was determined by chiral HPLC using a Daicel Chiralpak AD-H (25 cm × 4.6 mm × 5 μm).

Table 5 L1-Cu(OAc)$_2$·H$_2$O catalyzed asymmetric Aldol reaction of substituted isatin (**1a–l**) with ketone (**2a–h**) under optimized reaction parameters. Proposed transition states for the final compound
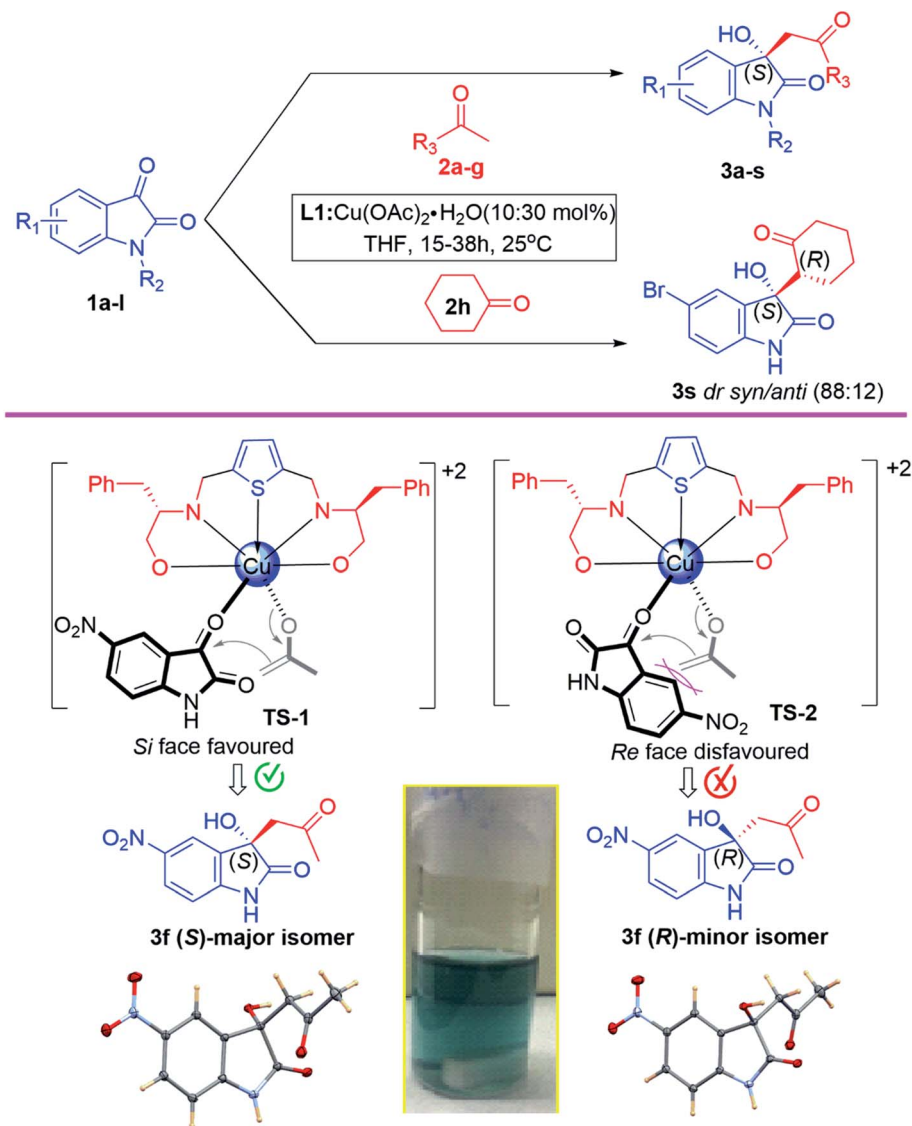
Entries[a]	R$_1$	R$_2$	R$_3$ (**2a–g**)	**3a–s**	Time [h]	Yield[b] [%]	ee[c] [%]	Abs. conf.[d]
1	5-Br	H	CH$_3$	**3a**	24	88	96	(S)[d67]
2	H	H	CH$_3$	**3b**	30	99	62	(S)[d67]
3	5-Cl	H	CH$_3$	**3c**	30	99	76	(S)[d67]
4	6-Cl	H	CH$_3$	**3d**	30	99	35	(S)[d]
5	5-OMe	H	CH$_3$	**3e**	30	99	55	(S)[d67]
6	5-NO$_2$	H	CH$_3$	**3f**	30	88	44	(S)[d67]
7	5,7-Br	H	CH$_3$	**3g**	30	90	36	(S)[d67,78]
8	5-CH$_3$	H	CH$_3$	**3h**	35	99	93	(S)[d67]
9	5-F	H	CH$_3$	**3i**	35	97	53	(S)[d67]
10	H	CH$_3$	CH$_3$	**3j**	38	91	89	(S)[d67,78]
11	H	Bn	CH$_3$	**3k**	38	98	78	(S)[d67]
12	H	C$_2$H$_4$–Br	CH$_3$	**3l**	35	99	71	(S)[d]
13	5-Br	H	Ph	**3m**	15	93	77	(S)[d]
14	5-Br	H	2-NO$_2$Ph	**3n**	15	96	70	(S)[d]
15	5-Br	H	4-FPh	**3o**	15	93	81	(S)[d]
16	5-Br	H	4-BrPh	**3p**	15	92	81	(S)[d]
17	5-Br	H	4-NO$_2$Ph	**3q**	15	88	54	(S)[d]

Table 5 (*Contd.*)
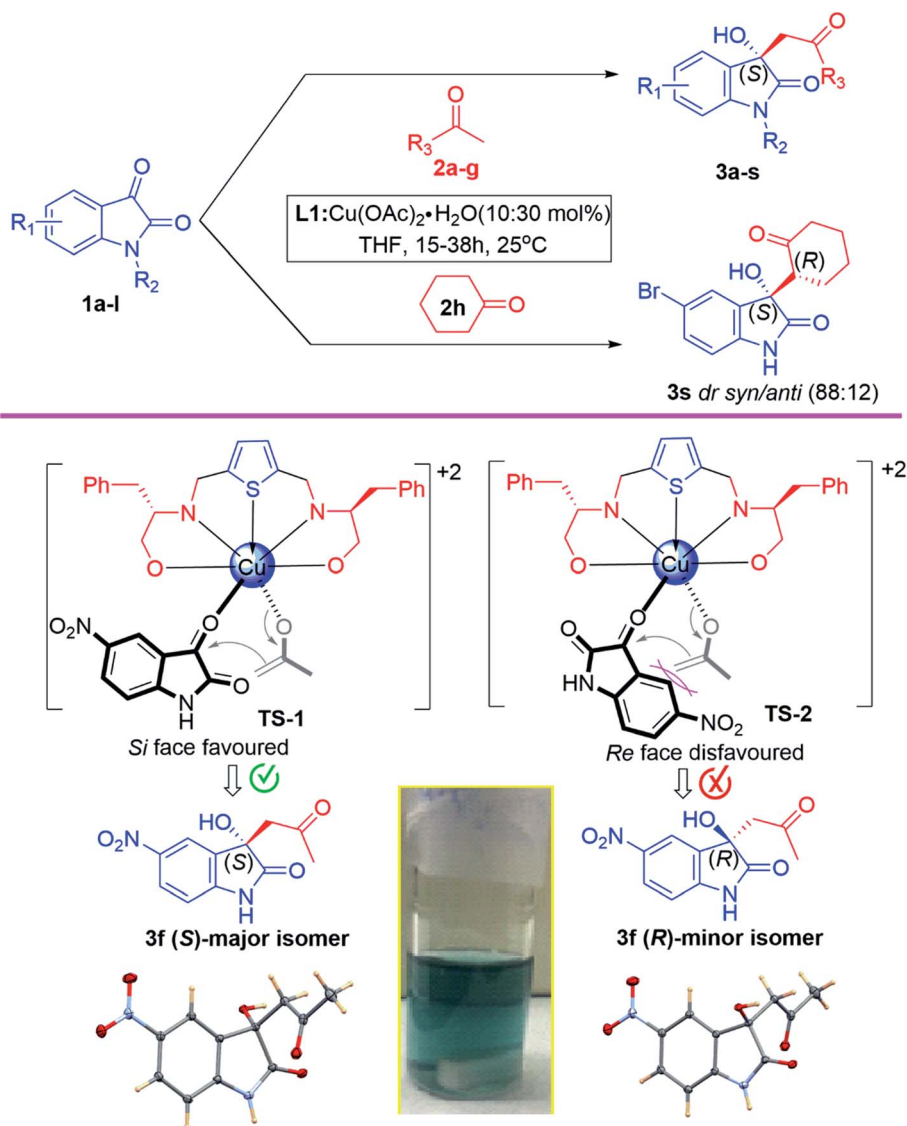
Entries[a]	R$_1$	R$_2$	R$_3$ (2a–g)	3a–s	Time [h]	Yield[b] [%]	ee[c] [%]	Abs. conf.[d]
18	5-Br	H	4-OHPh	3r	15	81	50	(S)[d]
19	5-Br	H	Cyclohexanone	3s	35	99	85	(S,R)[d72]

[a] Reactions were performed on a 0.2 mmol of isatin and 10.0 mmol of acetone or cyclohexanone in 2 mL of THF. [b] Isolated yields after column purification. [c] Enantiomeric excess (ee) was determined by chiral HPLC using a Daicel Chiralpak AD-H/OD-H column (25 cm × 4.6 mm × 5 μm). [d] Absolute configurations were determined by crystal structure and retention time matched with the literature.

expectation in inducing chirality in the aldol products and afforded **3d** and **3g** with poor enantioselectivities (35% & 36% ee), however quantitative chemical yields were obtained (99% & 90%) (Table 5, entries 4 & 7).

In view of the above findings, we further investigated the efficiency of our best catalytic system **L1**-Cu(II) as a Lewis acid catalyst under the optimized reaction parameters. Subsequently, the asymmetric Aldol reaction of 5-bromo isatin (**1a**) with substituted acetone (**2b–e, 2h**) were carried out and the

corresponding aldol product **3m–p** and **3s** were obtained in excellent yields (93%, 96%, 93%, 92% and 99%) with very good enantiomeric excess (77%, 70%, 81%, 81% and 85% ee) (Table 5, entries 13–16, 19). However, aldol product **3q** and **3r** were furnished in good yields (88% and 81%) with moderate enantiomeric excess (54% and 50% ee) while using *p*-nitro and *p*-hydroxy acetophenone (**2f, 2g**) as substrate for the Aldol reaction under optimized reaction conditions for 15 h and the findings are reported in Table 5, entries 13–19.

Noteworthy to mention that, the (*S*)-enantiomer eluted faster than (*R*)-enantiomer in the HPLC chromatogram for aldol product **3a–c**, **3e–l**, while for the *N*-substituted aldol product **3j**, **3k** and **3l**, reverse trends were followed, those are reported in the literature.[67,78] For aldol product **3s**, retention time of syn-major/minor and anti-major/minor were well matched with the data available in the literature.[72] Therefore, all the aldol products are predominantly found to be enriched with (*S*)-enantiomer as their retention time and optical rotations were absolutely in agreement with the literature data.[67,78] The absolute configuration of compound **3f** was further unambiguously confirmed by single-crystal X-ray analysis (CCDC number-2143162, see ESI† S-64). In case of aldol products **3m–r** the absolute configurations were also assigned as (*S*)-enantiomer, assuming that the reaction took place by following uniform mechanistic pathway (Fig. 3).

Catalytic asymmetric studies of Domino Knoevenagel Michael cyclization

To illustrate the generality for catalytic asymmetric application of our Lewis acid catalytic system (10 : 30 mol% of **L1**-Cu(ɪɪ) in THF at room temperature for 5–15 h), we extended the reaction scope and therefore catalytic asymmetric Domino Knoevenagel Michael cyclization reactions were performed using the same optimized parameters and the summary of the findings are documented in Table 6. From the results of Domino Knoevenagel Michael reaction, it can be clearly observed that the substituted isatins (**1a–l**) reacted very well with malononitrile (**4**) and ethylacetoacetate (**5**) in order to furnished another set of biologically important oxindoles derivatives (**6a–l**) in excellent yields (89–99%) and moderate to high enantiomeric excess (24–95% ee), those constitutes of spiro[4*H*-pyran-3,3′-oxindole] motif fused with 2-aminopyrans heterocyclic ring. It can be
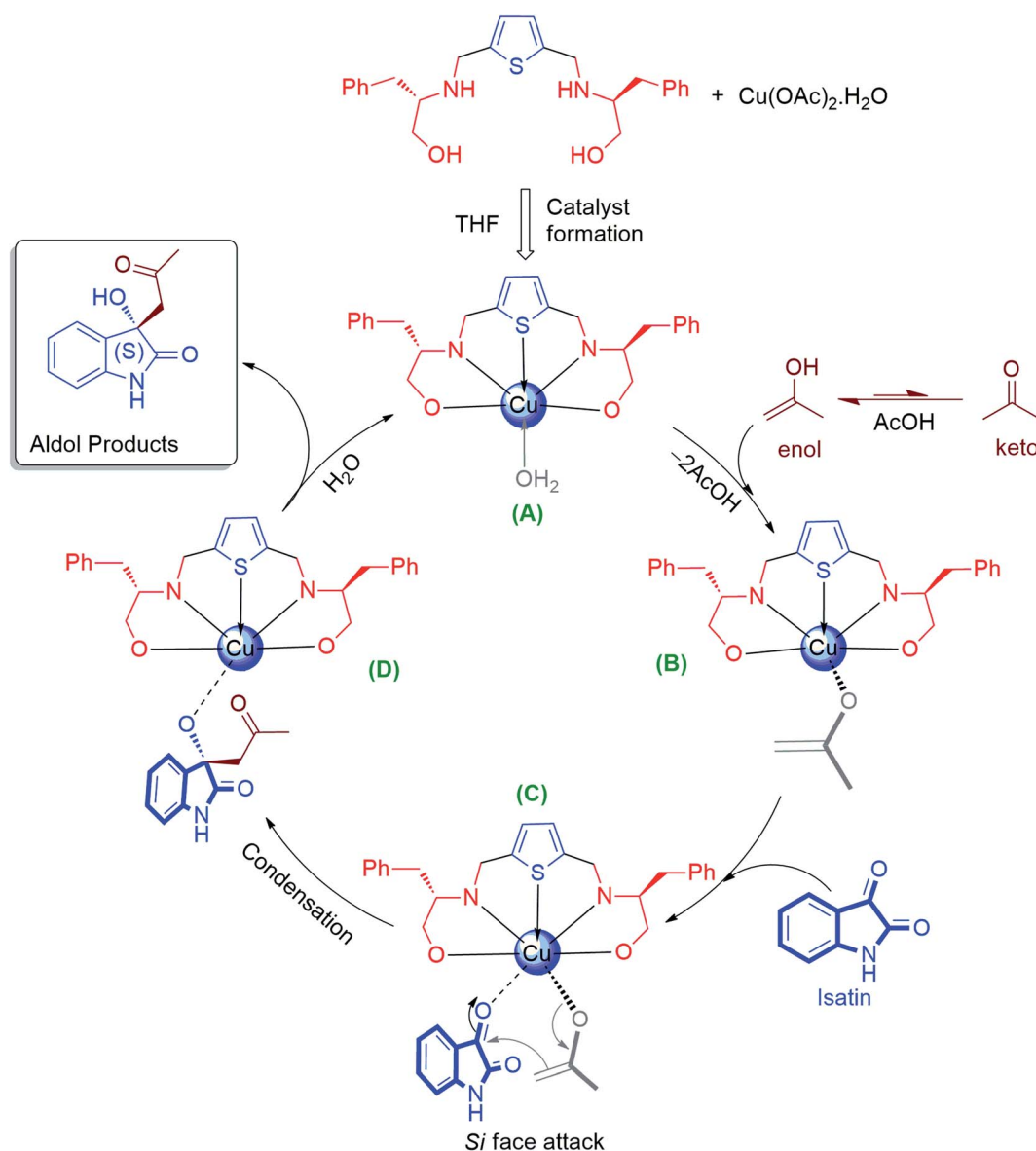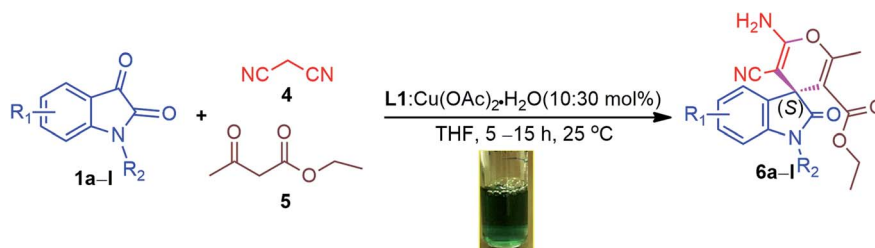

Fig. 3 Proposed mechanism of Lewis acid catalysis for asymmetric Aldol condensation reaction.

Table 6 L1-Cu(OAc)₂·H₂O catalyzed asymmetric three components one pot synthesis of spirooxindole using substituted isatin (**1a–l**), malononitrile (**4**) and ethylacetoacetate (**5**) under optimized reaction parameters

Entry[a]	R_1	R_2	6a–l	Time [h]	Yield[b] [%]	ee[c] [%]	Abs. conf.[d]
1	5-Br	H	6a	15	98	91	(S)[97]
2	H	H	6b	13	99	42	(S)[97]
3	5-Cl	H	6c	8	96	57	(S)[97]
4	6-Cl	H	6d	15	92	47	(S)
5	5-OCH₃	H	6e	15	93	87	(S)[97]
6	5-NO₂	H	6f	15	89	80	(S)
7	5,7-Br	H	6g	15	96	50	(S)
8	5-CH₃	H	6h	15	97	95	(S)[97]
9	5-F	H	6i	15	98	39	(S)[97]
10	H	CH₃	6j	15	99	63	(S)[97]
11	H	Bn	6k	15	98	81	(S)[95,97]
12	H	C₂H₄–Br	6l	5	89	24	(S)

[a] Reactions wer performed on a 0.2 mmol of isatin in 2 mL of THF. [b] Isolated yields after column purification. [c] Enantiomeric excess (ee) was determined by chiral HPLC using a Daicel Chiralpak AD-H column (25 cm × 4.6 mm × 5 μm). [d] Absolute configurations were determined by crystal structure and retention time matched with the literature.

noticed that this catalytic system produced best yields (98%, 93% & 97%) and enantiomeric excess (91%, 87% & 95% ee) when 5-bromo, 5-methoxy and 5-methyl isatins were subsequently used as substrate (Table 5, entries 1, 5 & 8); while in case of 5-nitro and *N*-benzyl isatins, our catalytic system **L1**-Cu(OAc)₂·H₂O are also found to be quite capable of inducing pretty good chirality (80% & 81% ee) with high yields (89% & 98%) accordingly (Table 6, entries 6 & 11). In case of isatin and its derivatives such as 5-Cl, 6-Cl, 5,7-dibromo, 5-F and *N*-Me isatins, the catalyst **L1**-Cu(OAc)₂·H₂O performed very well in terms of chemical yields (92–99%) to produce corresponding spiro[4*H*-pyran-3,3′-oxindole] derivatives **6b–d**, **6g**, **6i** and **6j** with moderate enantioselectivities (41.7%, 57.1%, 47%, 50%, 39%, 63% ee) (Table 6, entries 2–4, 7, 9 & 10). Nevertheless, this catalytic system performed poorly in prompting chiral induction when *N*-ethylbromide isatin was used as substrate perhaps due to the steric hindrance caused by the two long chain of *N*-ethylbromide of substrate (**1l**) and enol-ester (**5**) (Fig. 4) and the rate of reaction is comparatively high as it has taken 5 h only (89% yield, 24% ee). However chemical conversion is very good (Table 6, entry 12). All the Domino Knoevenagel Michael products are found to be enriched with (*S*)-enantiomer predominantly.

(*R*)-enantiomer eluted faster than (*S*)-enantiomer in the HPLC chromatogram for Domino Knoevenagel Michael cyclized spiro-oxindole products **6a–c**, **6e**, **6h** and **6i**, while for the *N*-substituted spiro-oxindole **6j**, **6k** and **6l**, reverse trends were

followed, those are well reported in the literature.[97] All the spiro-oxindole products are predominantly found to be enriched with (*S*)-enantiomer as their retention time and optical rotation were well in agreement with the literature data.[97] The absolute configuration for spiro-oxindole products **6d**, **6f** and **6g** were also assigned as (*S*)-enantiomer as their retention time followed the similar trends as of compound **6a–c**, assuming that the reaction took place by following uniform mechanistic pathway (Fig. 4).

Experimental

General

All the chemicals (isatin, derivatives of isatin, acetone, acetone derivatives, metal salts) and solvents were purchased from Sigma-Aldrich and used as received. Thiophene-2,5-bis(β-amino-alcohol) ligands (**L1–L5**) were freshly synthesized from commercially available thiophene-2,5-dicarbaldehyde and chiral β-amino alcohols in a well dried flask under a static pressure of nitrogen. Standard procedures were followed for solvents drying before usage. Reactions were monitored by thin layer chromatography using Merck silica gel 60 Kieselgel F254 TLC (Merck, Kenilworth, NJ, USA) and column chromatography was performed on silica gel 100–200 (40–63 μm, ASTM) from Merck using the proper solvents. ¹H and ¹³C-NMR spectra were recorded in CDCl₃ and DMSO-*d₆* on a Jeol Spectrometer (Jeol, Tokyo, Japan) (500 MHz). The chemical shifts are reported in ppm. All the racemic products were freshly prepared as per
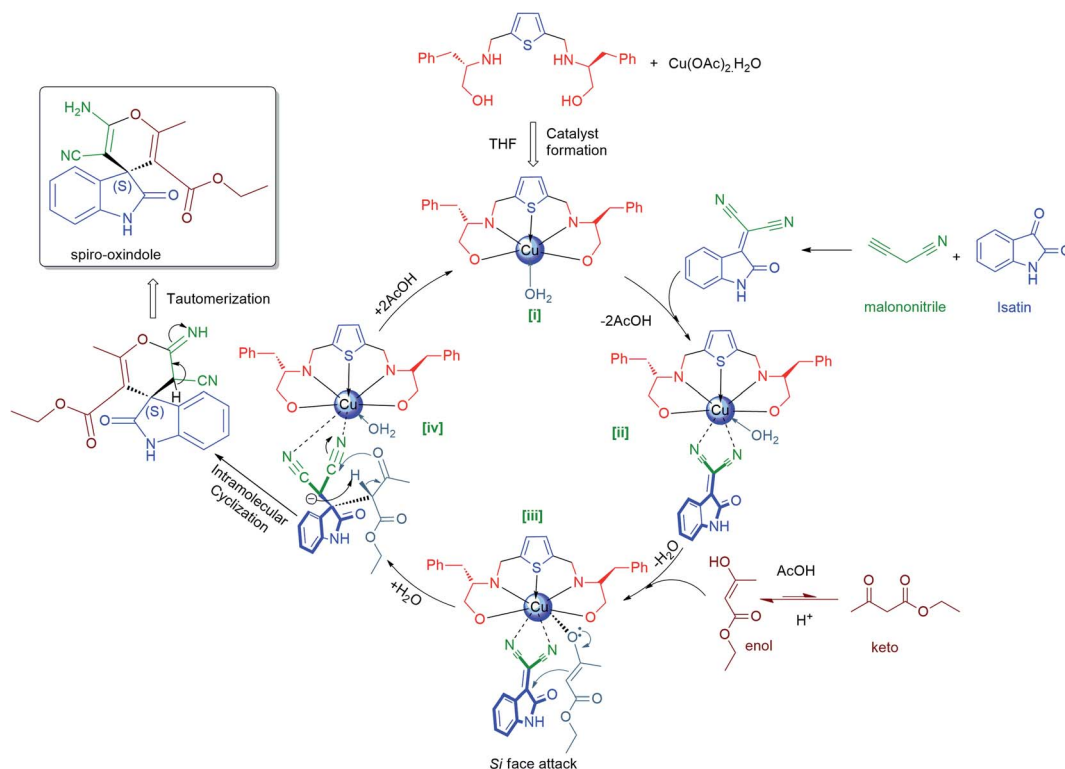
Fig. 4 Proposed mechanism of Lewis acid catalysis for asymmetric Domino Michael cyclization reaction.

the method reported in the literature.[83] Thermo Scientific Nicolet iS10 FT-IR spectrometer (Thermo Fisher Scientific, Waltham, MA, USA) has been used for Infrared spectra recording. Enantiomeric ratios were determined by analytical chiral HPLC analysis on a Shimadzu LC-20A (Shimadzu, Kyoto, Japan) Prominence instrument with a chiral stationary phase using Daicel OD-H columns (Chiral Technologies Europe, Illkirch-Graffenstaden, France) and 70–75% *n*-hexane/ isopropanol as eluents (ESI†). PerkinElmer-343 Polarimeter (PerkinElmer, Waltham, MA, USA) has been used for optical rotations measurement. Melting points (m.p.) were taken on a Thomas-Hoover capillary melting point apparatus (Thomas-Hoover, Texas City, USA) and were not corrected. Agilent Technologies 6410-triple quad LC/MS instrument (Agilent, Santa Clara, CA, USA) has been used for mass spectrometric analysis. PerkinElmer PE-2400 CHN Elemental Analyzer with autosampler has been used for elemental analysis only in CHN mode. X-ray diffraction data were collected on a Rigaku Oxford Diffraction Supernova diffractometer and processed with Cry-sAlisPro software v. 1.171.41.93a (Rigaku Oxford Diffraction, Yarnton, UK, 2020) using Cu K_ radiation".

Synthesis of racemic aldol product rac.-(3a–s). A solution of isatin derivatives (0.2 mmol), acetone (10 mmol)/derivative of acetone (2.0 mmol) or cyclohexanone (2.0 mmol) were taken into ethanol (2 mL) and two drops of diethylamine (DEA) were added to it, then the reaction was left stirring for 24 h at ambient temperature. The completion of the reaction was monitored by thin-layer chromatography (TLC) and the solvent was evaporated under reduced pressure to afford crude racemic

aldol product which was purified by column chromatography on silica gel (100–200 mesh) using 40% ethylacetate/*n*-hexane as eluent to isolate the pure racemic aldol product **rac.-(3a–s)** (yield 75–88%).

Synthesis of racemic spiro-oxindole product rac.-(6a–l). A mixture of isatin derivatives **1a–l** (0.2 mmol), malononitrile **4** (0.2 mmol) and ethylacetoacetate **5** (0.2 mmol) were dissolved into ethanol (2 mL) at room temperature followed by addition of diethylamine (DEA) (two drops) and the reaction was stirred for 24–48 h. The completion of reaction was monitored by thin-layer chromatography (TLC). The solvent was removed under reduced pressure and the crude product was purified by column chromatography using silica gel (100–200 mesh) stationary phase and 60% ethylacetate/*n*-hexane as eluent to afford the pure racemic spirooxindole product **rac.-(6a–l)** (yield 85–92%).

General procedure (GP1) for the catalytic asymmetric aldol condensation reaction (3a–s)

GP1. A small vial (8 mL) under nitrogen atmosphere were charged with ligand **L1** (8.2 mg, 0.02 mmol, 10 mol%), Cu(OAc)$_2$·H$_2$O (12.0 mg, 0.06 mmol, 30 mol%) and THF (2 mL). The solution was stirred for 2 h at room temperature and a blue coloured solution were observed, indicating formation of **L1**-Cu(OAc)$_2$·H$_2$O complex. The isatins **1a–l** (0.2 mmol) were then added to solution this solution and stirred for 10 min at room temperature followed by addition of acetone **2a** (10 mmol) or substituted acetone **2b–g** (2.0 mmol) or cyclohexanone **2h** (2.0 mmol) and the reaction mixture was left stirring for the 15–38 h. The solvents were then removed under reduced pressure and

the residues were directly subjected to columns purification using 100 mesh silica gel and 40–70% EtOAc/petroleum ether as eluents to obtain the corresponding chiral β-hydroxy ketones **3a–s** as aldol product.

(S)-5-Bromo-3-hydroxy-3-(2-oxopropyl)indolin-2-one (3a). 5-Bromoisatin **1a** (45.2 mg, 0.2 mmol) and acetone **2a** (581.0 mg, 10.0 mmol) were reacted according to the GP1 to afford product **3a** as pale yellow solid; m.p.: 180–182 °C; isolated yield (47.2 mg, 83%). Enantiomeric excess (ee) was determined by chiral HPLC [Daicel Chiralpak AD-H column], 80.0% *n*-hexane/i-PrOH, 1.0 mL min^{-1}.; t_{major} = 9.64 min; t_{minor} = 13.91 min; λ = 254 nm; 96% ee; $[\alpha]_D^{20}$ = −9.57° (*c* 0.05, CH$_3$OH); [ref. 67 $[\alpha]_D^{25}$ = −7.5° (*c* 0.48, MeOH)]; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 10.35 (s, 1H, NH), 7.43 (s, 1H, Ar–H), 7.35 (dd, *J* = 8.3, 2.1 Hz, 1H, Ar–H), 6.74 (d, *J* = 8.2 Hz, 1H, Ar–H), 6.09 (s, 1H, OH), 3.39 (d, *J* = 17.3 Hz, 1H, CH$_{2(a)}$), 3.06 (d, *J* = 17.3 Hz, 1H, CH$_{2(b)}$), 2.01 (s, 1H, CH$_3$); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 205.33, 177.76, 142.02, 134.17, 131.53, 126.67, 112.92, 111.38, 72.58, 49.96, 30.31. All the analytical data are well in agreement with the reported literature.[67]

(S)-3-Hydroxy-3-(2-oxopropyl)indolin-2-one (3b). Isatin **1b** (29.4 mg, 0.2 mmol) and acetone **2a** (581.0 mg, 10.0 mmol) were reacted according to the GP1 to yield product **3b** as pale yellow solid; m.p.: 169–171 °C; isolated yield (40.6 mg, 99%). Enantiomeric excess (ee) was determined by chiral HPLC [Daicel Chiralpak AD-H column], 80.0% *n*-hexane/i-PrOH, 1.0 mL min^{-1}; t_{major} = 9.88 min; t_{minor} = 13.29 min; λ = 254 nm; 62% ee; $[\alpha]_D^{20}$ = −12.65° (*c* 0.04, CH$_3$OH); [ref. 67 $[\alpha]_D^{25}$ = −31.6° (*c* 1.37, MeOH)]; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 10.21 (s, 1H, NH), 7.24 (d, *J* = 7.4 Hz, 1H, Ar–H), 7.17 (td, *J* = 7.6, 1.3 Hz, 1H, Ar–H), 6.90 (td, *J* = 7.5, 1.0 Hz, 1H, Ar–H), 6.78 (d, *J* = 7.6 Hz, 1H, Ar–H), 5.97 (s, 1H, OH), 3.27 (d, *J* = 16.5 Hz, 1H, CH$_{2(a)}$), 3.00 (d, *J* = 16.5 Hz, 1H, CH$_{2(b)}$), 2.00 (s, 1H, CH$_3$); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 205.18, 178.17, 142.55, 131.53, 128.99, 123.70, 121.24, 109.43, 72.66, 50.28, 30.58. All the analytical data are well in agreement with the reported literature.[67]

(S)-5-Chloro-3-hydroxy-3-(2-oxopropyl)indolin-2-one (3c). 5-Chloroisatin **1c** (47.9 mg, 0.2 mmol) and acetone **2a** (581.0 mg, 10.0 mmol) were reacted according to the GP1 to yield product **3c** as pale yellow solid; m.p.: 155–157 °C; isolated yield (47.5 mg, 99%). Enantiomeric excess (ee) was determined by chiral HPLC [Daicel Chiralpak AD-H column], 80.0% *n*-hexane/i-PrOH, 1.0 mL min^{-1}; t_{major} = 8.98 min; t_{minor} = 12.94 min; λ = 254 nm; 76% ee; $[\alpha]_D^{20}$ = −5.57° (*c* 0.04, CH$_3$OH); [ref. 67 $[\alpha]_D^{25}$ = −9.3° (*c* 0.9, MeOH)]; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 10.34 (s, 1H, NH), 7.31 (d, *J* = 2.2 Hz, 1H, Ar–H), 7.23–7.20 (m, 1H, Ar–H), 6.87 (d, *J* = 8.2 Hz, 1H, Ar–H), 6.09 (s, 1H, OH), 3.38 (d, *J* = 17.3 Hz, 1H, CH$_{2(a)}$), 3.06 (d, *J* = 17.3 Hz, 1H, CH$_{2(b)}$), 2.01 (s, 1H, CH$_3$); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 205.31, 177.90, 141.60, 133.76, 128.68, 125.21, 123.98, 110.81, 72.62, 49.96, 30.32. All the analytical data are well in agreement with the reported literature[67]

(S)-6-Chloro-3-hydroxy-3-(2-oxopropyl)indolin-2-one (3d). 6-Chloroisatin **1d** (47.9 mg, 0.2 mmol) and acetone **2a** (581.0 mg, 10.0 mmol) were reacted according to the GP1 to yield product **3d** as pale yellow solid; m.p.: 170–172 °C; isolated yield

(47.5 mg, 99%). Enantiomeric excess (ee) was determined by chiral HPLC [Daicel Chiralpak AD-H column], 80.0% *n*-hexane/i-PrOH, 1.0 mL min^{-1}; t_{major} = 9.92 min; t_{minor} = 13.48 min; λ = 254 nm; 35% ee; $[\alpha]_D^{20}$ = −9.99° (*c* 0.05, CH$_3$OH); IR (KBr): 3364, 3242, 2924, 2853, 1712, 1620, 1484, 1448, 1362, 1339, 1227, 1185, 1072, 825, 780, 732, 654, 587, 565, 551 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 10.38 (s, 1H, NH), 7.25 (d, *J* = 7.9 Hz, 1H, Ar–H), 6.95 (dd, *J* = 7.9, 2.0 Hz, 1H, Ar–H), 6.79 (d, *J* = 1.9 Hz, 1H, Ar–H), 6.06 (s, 1H, OH), 3.34 (d, *J* = 16.8 Hz, 1H, CH$_{2(a)}$), 3.06 (d, *J* = 17.1 Hz, 1H, CH$_{2(b)}$), 2.00 (s, 1H, CH$_3$); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 205.30, 178.15, 144.26, 133.18, 130.57, 125.16, 120.89, 109.48, 72.17, 50.06, 30.39; LC/MS (ESI): found 240.1 [M(^{35}Cl) + H]$^+$; 242.0 [M(^{37}Cl) + H]$^+$, C$_{11}$H$_{10}$ClNO$_3$ requires 239.03; anal. calcd for C$_{11}$H$_{10}$ClNO$_3$: C, 55.13; H, 4.21; N, 5.84; found: C, 54.96; H, 4.15; N, 6.06.

(S)-3-Hydroxy-5-methoxy-3-(2-oxopropyl)indolin-2-one (3e). 5-Methoxyisatin **1e** (35.4 mg, 0.2 mmol) and acetone **2a** (581.0 mg, 10.0 mmol) were reacted according to the GP1 to yield product **3e** as pale yellow solid; m.p.: 165–167 °C; isolated yield (46.6 mg, 99%). Enantiomeric excess (ee) was determined by chiral HPLC [Daicel Chiralpak AD-H column], 80.0% *n*-hexane/i-PrOH, 1.0 mL min^{-1}; t_{major} = 13.04 min; t_{minor} = 18.74 min; λ = 254 nm; 55% ee; $[\alpha]_D^{20}$ = −3.45° (*c* 0.06, CH$_3$OH); [ref. 67 $[\alpha]_D^{25}$ = −3.9° (*c* 1.17, MeOH)]; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 10.04 (s, 1H, NH), 6.91 (d, *J* = 2.6 Hz, 1H, Ar–H), 6.74 (dd, *J* = 8.4, 2.6 Hz, 1H, Ar–H), 6.69 (d, *J* = 8.4 Hz, 1H, Ar–H), 5.97 (s, 1H, OH), 3.69 (s, 3H, OCH$_3$), 3.27 (d, *J* = 16.6 Hz, 1H, CH$_{2(a)}$), 3.00 (d, *J* = 16.6 Hz, 1H, CH$_{2(b)}$), 2.01 (s, 1H, CH$_3$); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 205.17, 178.11, 154.68, 135.74, 132.81, 113.36, 111.01, 109.72, 73.09, 55.44, 50.26, 30.59. All the analytical data are well in agreement with the reported literature.[67]

(S)-3-Hydroxy-5-nitro-3-(2-oxopropyl)indolin-2-one (3f). 5-Nitroisatin **1f** (38.4 mg, 0.2 mmol) and acetone **2a** (581.0 mg, 10.0 mmol) were reacted according to the GP1 to yield product **3f** as pale yellow solid; m.p.: 178–180 °C; isolated yield (44.1 mg, 88%). Enantiomeric excess (ee) was determined by chiral HPLC [Daicel Chiralpak AD-H column], 80.0% *n*-hexane/i-PrOH, 1.0 mL min^{-1}; t_{major} = 12.11 min; t_{minor} = 15.78 min; λ = 254 nm; 44% ee; $[\alpha]_D^{20}$ = −2.32° (*c* 0.04, CH$_3$OH); [ref. 67 $[\alpha]_D^{25}$ = −21.7° (*c* 1.10, MeOH)]; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 10.96 (s, 1H, NH), 8.18–8.16 (m, 2H, Ar–H), 6.99 (d, *J* = 9.2 Hz, 1H, Ar–H), 6.28 (s, 1H, OH), 3.61 (d, *J* = 17.8 Hz, 1H, CH$_{2(a)}$), 3.18 (d, *J* = 17.9 Hz, 1H, CH$_{2(b)}$), 2.02 (s, 1H, CH$_3$); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 205.62, 178.59, 149.49, 141.93, 132.79, 126.42, 119.50, 109.54, 72.09, 49.88, 30.04. All the analytical data are well in agreement with the reported literature.[67]

(S)-5,7-Dibromo-3-hydroxy-3-(2-oxopropyl)indolin-2-one (3g). 5,7-Dibromoisatin **1g** (61.0 mg, 0.2 mmol) and acetone **2a** (581.0 mg, 10.0 mmol) were reacted according to the GP1 to yield product **3g** as pale yellow solid; m.p.: 182–184 °C; isolated yield (65.3 mg, 90%). Enantiomeric excess (ee) was determined by chiral HPLC [Daicel Chiralpak AD-H column], 80.0% *n*-hexane/i-PrOH, 1.0 mL min^{-1}; t_{major} = 8.14 min; t_{minor} = 10.02 min; λ = 254 nm; 36% ee; $[\alpha]_D^{20}$ = −4.41° (*c* 0.05, CH$_3$OH); [ref. 67 $[\alpha]_D^{25}$ = −9.4° (*c* 2.14, MeOH)]; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 10.70 (s, 1H, NH), 7.61 (d, *J* = 1.9 Hz, 1H,

Ar–H), 7.47 (d, $J = 1.9$ Hz, 1H, Ar–H), 6.24 (s, 1H, OH), 3.46 (d, $J = 17.7$ Hz, 1H, $CH_{2(a)}$), 3.14 (d, $J = 17.7$ Hz, 1H, $CH_{2(b)}$), 2.02 (s, 1H, CH_3); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 205.48, 177.65, 141.79, 135.48, 133.40, 125.81, 113.41, 102.53, 73.34, 49.99, 30.10. All the analytical data are well in agreement with the reported literature.[67]

(S)-3-Hydroxy-5-methyl-3-(2-oxopropyl)indolin-2-one (3h). 5-Methylisatin **1h** (32.2 mg, 0.2 mmol) and acetone **2a** (581.0 mg, 10.0 mmol) were reacted according to the GP1 to yield product **3h** as white solid; m.p.: 165–167 °C; isolated yield (43.9 mg, 99%). Enantiomeric excess (ee) was determined by chiral HPLC [Daicel Chiralpak AD-H column], 90.0% *n*-hexane/i-PrOH, 1.0 mL min^{-1}; t_{major} = 24.88 min; t_{minor} = 31.93 min; λ = 254 nm; 93% ee; $[\alpha]_D^{20} = -5.10°$ (*c* 0.05, CH$_3$OH); [ref. 67 $[\alpha]_D^{25} = -2.8°$ (*c* 0.81, MeOH)]; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 10.12 (s, 1H, NH), 7.07 (s, 1H, Ar–H), 6.99–6.95 (m, 1H, Ar–H), 6.67 (d, J = 7.8 Hz, 1H, Ar–H), 5.94 (s, 1H, OH), 3.24 (d, J = 16.6 Hz, 1H, $CH_{2(a)}$), 3.00 (d, J = 16.6 Hz, 1H, $CH_{2(b)}$), 2.23 (s, 1H, CH_3), 2.01 (s, 3H, CH_3); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 205.21, 178.23, 140.10, 131.65, 130.03, 129.17, 124.41, 109.21, 72.80, 50.36, 30.60, 20.73. All the analytical data are well in agreement with the reported literature.[67]

(S)-5-Fluoro-3-hydroxy-3-(2-oxopropyl)indolin-2-one (3i). 5-Fluoroisatin **1i** (33.0 mg, 0.2 mmol) and acetone **2a** (581.0 mg, 10.0 mmol) were reacted according to the GP1 to yield product **3i** as pale yellow solid; 184–186 °C; isolated yield (43.3 mg, 97%). Enantiomeric excess (ee) was determined by chiral HPLC [Daicel Chiralpak AD-H column], 80.0% *n*-hexane/i-PrOH, 1.0 mL min^{-1}; t_{major} = 9.21 min; t_{minor} = 12.36 min; λ = 254 nm; 53% ee; $[\alpha]_D^{20} = -11.49°$ (*c* 0.06, CH$_3$OH); $[\alpha]_D^{25} = -19.0°$ (*c* 0.97, MeOH);[67] ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 10.25 (s, 1H, NH), 7.15 (dd, J = 8.2, 2.7 Hz, 1H, Ar–H), 7.02–7.98 (m, 1H, Ar–H), 6.76 (dd, J = 8.5, 4.3 Hz, 1H, Ar–H), 6.10 (s, 1H, OH), 3.34 (d, J = 17.0 Hz, 1H, $CH_{2(a)}$), 3.06 (d, J = 17.0 Hz, 1H, $CH_{2(b)}$), 2.01 (s, 3H, CH_3); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 205.28, 178.23, 158.83 & 156.95 (C$_1$–F, J_{C-F} = 236.75 Hz), 138.82, 133.45 & 133.39 (C$_2$–F, J_{C-F} = 7.56 Hz), 115.14 & 114.96 (C$_3$–F, J_{C-F} = 23.44 Hz), 111.78 & 111.58 (C$_5$–F, J_{C-F} = 24.44 Hz), 110.15 & 110.09 (C$_6$–F, J_{C-F} = 7.81 Hz), 72.92, 50.06, 30.44. All the analytical data are well in agreement with the reported literature.[67]

(S)-3-Hydroxy-1-methyl-3-(2-oxopropyl)indolin-2-one (3j). 1-Methylisatin **1j** (32.2 mg, 0.2 mmol) and acetone **2a** (581.0 mg, 10.0 mmol) were reacted according to the GP1 to yield product **3j** as pale yellow solid; m.p.: 154–156 °C; isolated yield (43.0 mg, 98%). Enantiomeric excess (ee) was determined by chiral HPLC [Chiralcel OD-H column], 90.0% *n*-hexane/i-PrOH, 1.0 mL min^{-1}; t_{minor} = 19.93 min; t_{major} = 21.09 min; λ = 254 nm; 87% ee; $[\alpha]_D^{20} = -21.94°$ (*c* 0.05, CH$_3$OH); [ref. 67 $[\alpha]_D^{25} = -22.3°$ (*c* 1.59, MeOH)]; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 7.31–7.25 (m, 2H, Ar–H), 6.99 (td, J = 7.5, 1.0 Hz, 1H, Ar–H), 6.96 (d, J = 7.7 Hz, 1H, Ar–H), 6.06 (s, 1H, OH), 3.34 (d, J = 16.8 Hz, 1H, $CH_{2(a)}$), 3.09 (s, 3H, NCH$_3$), 3.05 (d, J = 16.8 Hz, 1H, $CH_{2(b)}$), 1.98 (s, 1H, CH_3); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 205.13, 176.50, 144.05, 130.90, 129.14, 123.25, 121.94, 108.26, 72.33, 50.42, 30.47, 25.89. All the analytical data are well in agreement with the reported literature.[67]

(S)-1-Benzyl-3-hydroxy-3-(2-oxopropyl)indolin-2-one (3k). 1-Benzylisatin **1k** (47.5 mg, 0.2 mmol) and acetone **2a** (581.0 mg, 10.0 mmol) were reacted according to the GP1 to yield product **3k** as pale yellow solid; m.p.: 170–173 °C; isolated yield (57.9 mg, 98%). Enantiomeric excess (ee) was determined by chiral HPLC [Daicel Chiralpak AD-H column], 85.0% *n*-hexane/i-PrOH, 1.0 mL min^{-1}; t_{minor} = 16.93 min; t_{major} = 17.82 min; λ = 254 nm; 78% ee; $[\alpha]_D^{20} = -16.23°$ (*c* 0.06, CH$_3$OH); [ref. 67 $[\alpha]_D^{25} = -17.8°$ (*c* 1.53, MeOH)]; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 7.48–7.43 (m, 2H, Ar–H$_{(Bn)}$), 7.38–7.32 (m, 3H, Ar–H$_{(Bn)}$), 7.29–7.24 (m, 1H, Ar–H), 7.17 (td, J = 7.7, 1.3 Hz, 1H, Ar–H), 6.98 (td, J = 7.4, 1.0 Hz, 1H, Ar–H), 6.77–6.73 (m, 1H, Ar–H), 6.26 (s, 1H, OH), 4.93 (d, J = 16.1 Hz, 1H, Ph-CH$_{2(a)}$), 4.85 (d, J = 16.0 Hz, 1H, Ph-CH$_{2(b)}$), 3.47 (d, J = 16.9 Hz, 1H, $CH_{2(a)}$), 3.21 (d, J = 16.9 Hz, 1H, $CH_{2(b)}$), 2.04 (s, 3H, CH_3); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 205.32, 176.75, 143.18, 136.40, 130.99, 129.03, 128.49, 127.26, 127.23, 123.45, 122.07, 108.99, 72.41, 50.36, 42.73, 30.44. All the analytical data are well in agreement with the reported literature.[67]

(S)-1-(2-Bromoethyl)-3-hydroxy-3-(2-oxopropyl)indolin-2-one (3l). 1-(2-Bromoethyl)isatin **1l** (50.8 mg, 0.2 mmol) and acetone **2a** (581.0 mg, 10.0 mmol) were reacted according to the GP1 to yield product **3l** as pale yellow solid; m.p.:161–162 °C; isolated yield (61.8 mg, 99%). Enantiomeric excess (ee) was determined by chiral HPLC [Daicel Chiralpak AD-H column], 90.0% *n*-hexane/i-PrOH, 1.0 mL min^{-1}; t_{minor} = 16.07 min; t_{major} = 17.39 min; λ = 254 nm; 71% ee; $[\alpha]_D^{20} = -19.86°$ (*c* 0.04, CH$_3$OH); IR (KBr): 3350, 2925, 2853, 1709, 1610, 1488, 1469, 1454, 1432, 1416, 1375, 1359, 1336, 1183, 1179, 1163, 1132, 1006, 795, 751, 736, 708, 697, 563, 496, 476, 455 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 7.32 (dt, J = 7.3, 0.9 Hz, 1H, Ar–H), 7.29–7.26 (m, 1H, Ar–H), 7.11 (dt, J = 7.8, 0.8 Hz, 1H, Ar–H), 7.02–6.99 (m, 1H, Ar–H), 6.14 (s, 1H, OH), 4.08–4.05 (m, 2H, NCH$_2$), 3.63 (td, J = 7.1, 3.5 Hz, 2H, CH$_2$–Br), 3.36 (d, J = 16.9 Hz, 1H, $CH_{2(a)}$), 3.08 (d, J = 16.9 Hz, 1H, $CH_{2(b)}$), 2.00 (s, 3H, CH_3); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 205.24, 176.69, 142.68, 130.70, 129.17, 123.63, 122.16, 108.70, 72.25, 50.66, 40.97, 30.45, 28.66; LC/MS (ESI): found 390.01 [M(^{79}Br) + H]$^+$; 391.90 [M(^{81}Br) + H]$^+$, C$_{13}$H$_{13}$Br$_2$NO$_3$ requires 388.93; anal. calcd for C$_{13}$H$_{13}$Br$_2$NO$_3$: C, 39.93; H, 3.35; N, 3.58; found: C, 40.14; H, 3.27; N, 3.49.

(S)-5-Bromo-3-hydroxy-3-(2-oxo-2-phenylethyl)indolin-2-one (3m). 5-Bromoisatin **1a** (45.2 mg, 0.2 mmol) and acetophenone **2b** (240.0 mg, 2.0 mmol) were reacted according to the GP1 to yield product **3m** as white solid; m.p.:179–180 °C; isolated yield (64.4 mg, 93%). Enantiomeric excess (ee) was determined by chiral HPLC [Daicel Chiralpak AD-H column], 80.0% *n*-hexane/i-PrOH, 0.8 mL min^{-1}; t_{major} = 14.98 min; t_{minor} = 32.84 min; λ = 254 nm; 77% ee; $[\alpha]_D^{20} = -55.21°$ (*c* 0.05, CH$_3$OH); IR (KBr): 3350, 3218, 1731, 1698, 1672, 1617, 1595, 1472, 1448, 1402, 1352, 1278, 1176, 1094, 1065, 991, 880, 824, 764, 686, 637, 591, 534, 478 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 10.44 (s, 1H, NH), 7.89 (d, J = 7.6 Hz, 2H, Ar–H), 7.63 (t, J = 7.5 Hz, 1H, Ar–H), 7.51 (d, J = 7.8 Hz, 3H, Ar–H), 7.35 (d, J = 8.3 Hz, 1H, Ar–H), 6.80 (d, J = 8.3 Hz, 1H, Ar–H), 6.23 (s, 1H, OH), 4.17 (d, J = 17.9 Hz, 1H, $CH_{2(a)}$), 3.65 (d, J = 18.1 Hz, 1H, $CH_{2(b)}$); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 196.64, 178.00, 142.38, 135.95,

134.42, 133.59, 131.55, 128.78, 127.98, 126.71, 112.94, 111.43, 73.05, 45.77; LC/MS (ESI): found 346.1 $[M(^{79}Br) + H]^+$; 348.1 $[M(^{81}Br) + H]^+$, $C_{16}H_{12}BrNO_3$ requires 345.0; anal. calcd for $C_{16}H_{12}BrNO_3$: C, 55.51; H, 3.49; N, 4.05; found: C, 55.43; H, 3.44; N, 4.13.

(S)-5-Bromo-3-hydroxy-3-(2-(2-nitrophenyl)-2-oxoethyl)indolin-2-one (3n). 5-Bromoisatin **1a** (45.2 mg, 0.2 mmol) and 1-(2-nitrophenyl)ethan-1-one **2c** (330.3 mg, 2.0 mmol) were reacted according to the GP1 to yield product **3n** as white solid; m.p.:188–190 °C; isolated yield (75.1 mg, 96%). Enantiomeric excess (ee) was determined by chiral HPLC [Daicel Chiralpak AD-H column], 70.0% *n*-hexane/i-PrOH, 1.0 mL min^{-1}; $t_{major} = 11.98$ min; $t_{minor} = 31.04$ min; $\lambda = 254$ nm; 70% ee; $[\alpha]_D^{20} = -75.51°$ (c 0.08, CH$_3$OH); IR (KBr): 3337, 3390, 1738, 1702, 1615, 1573, 1530, 1471, 1441, 1388, 1314, 1216, 1180, 1130, 1059, 998, 895, 838, 754, 744, 731, 699, 672, 542 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 10.46 (s, 1H, NH), 8.04 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.78 (dt, $J = 32.4$, 7.8 Hz, 2H, Ar–H), 7.60 (d, $J = 7.6$ Hz, 1H, Ar–H), 7.54 (s, 1H, Ar–H), 7.38 (d, $J = 8.3$ Hz, 1H, Ar–H), 6.78 (d, $J = 8.4$ Hz, 1H, Ar–H), 6.30 (s, 1H, OH), 3.91 (d, $J = 17.5$ Hz, 1H, CH$_{2(a)}$), 3.53 (d, $J = 17.6$ Hz, 1H, CH$_{2(b)}$); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 198.01, 177.39, 146.19, 142.04, 134.51, 133.97, 133.37, 132.14, 131.82, 128.53, 127.29, 124.27, 113.11, 111.50, 72.87, 48.42; LC/MS (ESI): found 391.1 $[M(^{79}Br) + H]^+$; 393.1 $[M(^{81}Br) + H]^+$, $C_{16}H_{11}BrN_2O_5$ requires 389.99; anal. calcd for $C_{16}H_{11}BrN_2O_5$: C, 49.13; H, 2.83; N, 7.16; found: C, 49.27; H, 2.89; N, 7.09.

(S)-5-Bromo-3-(2-(4-fluorophenyl)-2-oxoethyl)-3-hydroxyindolin-2-one (3o). 5-Bromoisatin **1a** (45.2 mg, 0.2 mmol) and 1-(4-fluorophenyl)ethan-1-one **2d** (276.3 mg, 2.0 mmol) were reacted according to the GP1 to yield product **3o** as white solid; m.p.:186–187 °C; isolated yield (67.7 mg, 93%). Enantiomeric excess (ee) was determined by chiral HPLC [Daicel Chiralpak AD-H column], 70.0% *n*-hexane/i-PrOH, 1.0 mL min^{-1}; $t_{major} = 8.96$ min; $t_{minor} = 17.02$ min; $\lambda = 254$ nm; 81% ee; $[\alpha]_D^{20} = -5.90°$ (c 0.04, CH$_3$OH); IR (KBr): 3235, 1698, 1686, 1619, 1600, 1507, 1473, 1449, 1409, 1348, 1234, 1181, 1166, 1072, 991, 827, 732, 591, 559 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 10.44 (s, 1H, NH), 7.98 (s, 2H, Ar–H), 7.51 (s, 1H, Ar–H), 7.38–7.25 (m, 3H, Ar–H), 6.86–6.72 (m, 1H, Ar–H), 6.24 (s, 1H, OH), 4.16 (d, $J = 17.9$ Hz, 1H, CH$_{2(a)}$), 3.63 (d, $J = 18.2$ Hz, 1H, CH$_{2(b)}$); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 195.28, 177.98, 166.25, 164.24, 142.35, 134.36, 132.76, 131.58, 131.26, 131.13, 131.06, 126.75, 115.88, 115.71, 112.96, 111.45, 73.06, 45.72; LC/MS (ESI): found 364.1 $[M(^{79}Br) + H]^+$; 366.1 $[M(^{81}Br) + H]^+$, $C_{16}H_{11}BrFNO_3$ requires 362.99; anal. calcd for $C_{16}H_{11}BrFNO_3$: C, 52.77; H, 3.04; 3.85; found: C, 52.61; H, 3.18; N, 3.95.

(S)-5-Bromo-3-(2-(4-bromophenyl)-2-oxoethyl)-3-hydroxyindolin-2-one (3p). 5-Bromoisatin **1a** (45.2 mg, 0.2 mmol) and 1-(4-bromophenyl)ethan-1-one **2e** (398.1, 2.0 mmol) were reacted according to the GP1 to yield product **3p** as white solid; m.p.:184–185 °C; isolated yield (78.2 mg, 92%). Enantiomeric excess (ee) was determined by chiral HPLC [Daicel Chiralpak AD-H column], 70.0% *n*-hexane/i-PrOH, 1.0 mL min^{-1}; $t_{major} = 12.55$ min; $t_{minor} = 32.98$ min; $\lambda = 254$ nm; 81% ee; $[\alpha]_D^{20} = -21.79°$ (c 0.03, CH$_3$OH); IR (KBr): 3188, 1713, 1699, 1618, 1587, 1472, 1448, 1397, 1344, 1215, 1183, 1069, 1008, 989, 827, 810,

733, 647, 556 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 10.45 (s, 1H, NH), 7.76 (d, $J = 54.0$ Hz, 4H, Ar–H), 7.50 (s, 1H, Ar–H), 7.34 (s, 1H, Ar–H), 6.89–6.70 (m, 1H, Ar–H), 6.24 (s, 1H, OH), 4.15 (d, $J = 18.1$ Hz, 1H, CH$_{2(a)}$), 3.61 (d, $J = 18.2$ Hz, 1H, CH$_{2(b)}$); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 195.91, 177.90, 142.30, 134.94, 134.25, 131.84, 131.60, 130.05, 127.77, 126.79, 112.97, 111.45, 73.02, 45.72; LC/MS (ESI): found 423.9 $[M(^{79}Br) + H]^+$; 425.9 $[M(^{81}Br) + H]^+$, $C_{16}H_{11}Br_2NO_3$ requires 422.91; anal. calcd for $C_{16}H_{11}Br_2NO_3$: C, 45.21; H, 2.61; N, 3.30; found: C, 42.16; H, 2.53; N, 3.27.

(S)-5-Bromo-3-hydroxy-3-(2-(4-nitrophenyl)-2-oxoethyl)indolin-2-one (3q). 5-Bromoisatin **1a** (45.2 mg, 0.2 mmol) and 1-(4-nitrophenyl)ethan-1-one **2f** (330.3, 2.0 mmol) were reacted according to the GP1 to yield product **3q** as white solid; m.p.:187–188 °C; isolated yield (68.8 mg, 88%). Enantiomeric excess (ee) was determined by chiral HPLC [Daicel Chiralpak AD-H column], 70.0% *n*-hexane/i-PrOH, 1.0 mL min^{-1}; $t_{major} = 22.05$ min; $t_{minor} = 30.35$ min; $\lambda = 254$ nm; 54% ee; $[\alpha]_D^{20} = -11.43°$ (c 0.04, CH$_3$OH); IR (KBr): 3196, 1654, 1618, 1528, 1478, 1447, 1343, 1249, 1209, 1183, 1123, 1060, 1000, 903, 895, 855, 824, 742, 644, 595, 535 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 10.48 (s, 1H, NH), 8.31 (d, $J = 8.8$ Hz, 2H, Ar–H), 8.12 (d, $J = 8.8$ Hz, 2H, Ar–H), 7.52 (d, $J = 2.1$ Hz, 1H, Ar–H), 7.36 (dd, $J = 8.2$, 2.1 Hz, 1H, Ar–H), 6.79 (d, $J = 8.2$ Hz, 1H, Ar–H), 6.30 (s, 1H, OH), 4.23 (d, $J = 18.0$ Hz, 1H, CH$_{2(a)}$), 3.70 (d, $J = 17.9$ Hz, 1H, CH$_{2(b)}$); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 196.01, 177.77, 150.10, 142.24, 140.46, 134.02, 131.71, 129.53, 126.93, 123.88, 113.03, 111.51, 73.04, 46.23; LC/MS (ESI): found 391.1 $[M(^{79}Br) + H]^+$; 393.1 $[M(^{81}Br) + H]^+$, $C_{16}H_{11}BrN_2O_5$ requires 389.99; anal. calcd for $C_{16}H_{11}BrN_2O_5$: C, 49.13; H, 2.83; N, 7.16; found: C, 49.23; H, 2.69; N, 7.24.

(S)-5-Bromo-3-hydroxy-3-(2-(4-hydroxyphenyl)-2-oxoethyl) indolin-2-one (3r). 5-Bromoisatin **1a** (45.2 mg, 0.2 mmol) and 1-(4-hydroxyphenyl)ethan-1-one **2g** (272.3 mg, 2.0 mmol) were reacted according to the GP1 to yield product **3r** as white solid; M.P.:191–192 °C; isolated yield (58.7 mg, 81%). Enantiomeric excess (ee) was determined by chiral HPLC [Daicel Chiralpak AD-H column], 80.0% *n*-hexane/i-PrOH, 1.0 mL min^{-1}; $t_{major} = 9.31$ min; $t_{minor} = 23.06$ min; $\lambda = 254$ nm; 50% ee; $[\alpha]_D^{20} = -78.91°$ (c 0.04, CH$_3$OH); IR (KBr): 3230, 1714, 1710, 1698, 1651, 1619, 1605, 1582, 1479, 1446, 1356, 1290, 1225, 1182, 1171, 1063, 997, 825, 734, 612, 592, 558, cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 10.42 (s, 1H, NH), 10.37 (s, 1H, OH), 7.76 (d, $J = 8.8$ Hz, 2H, Ar–H), 7.47 (d, $J = 2.1$ Hz, 1H, Ar–H), 7.33 (dd, $J = 8.2$, 2.1 Hz, 1H, Ar–H), 6.82 (d, $J = 8.8$ Hz, 2H, Ar–H), 6.77 (d, $J = 8.3$ Hz, 1H, Ar–H), 6.15 (s, 1H, OH), 4.04 (d, $J = 17.6$ Hz, 1H, CH$_{2(a)}$), 3.52 (d, $J = 17.7$ Hz, 1H, CH$_{2(b)}$); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 194.61, 178.13, 162.35, 142.42, 134.66, 131.45, 130.59, 127.71, 126.59, 115.27, 112.86, 111.37, 73.12, 45.31; LC/MS (ESI): found 362.1 $[M(^{79}Br) + H]^+$; 364.1 $[M(^{81}Br) + H]^+$, $C_{16}H_{12}BrNO_4$ requires 360.99; anal. calcd for $C_{16}H_{12}BrNO_4$: C, 53.06; H, 3.34; N, 3.87; found: C, 52.92; H, 3.46; N, 3.97.

(S)-5-Bromo-3-hydroxy-3-((R)-2-oxocyclohexyl)indolin-2-one (3s). 5-Bromoisatin **1a** (45.2 mg, 0.2 mmol) and cyclohexanone **2h** (196.3 mg, 0.21 mL, 2.0 mmol) were reacted according to the GP1 to yield product **3s** as white solid; m.p.: 224–225 °C;

isolated yield (64.2 mg, 99%), syn/anti = (88 : 12). Enantiomeric excess (ee) of (syn, major) was determined by chiral HPLC [Daicel Chiralpak AD-H column], 92.0% n-hexane/i-PrOH, 0.8 mL min^{-1}; $t_{\text{syn-major}}$ = 53.32 min; $t_{\text{syn-minor}}$ = 74.56 min; $t_{\text{anti-major}}$ = 63.64 min; λ = 254 nm; syn/anti 88 : 12; Enantiomeric excess (ee) of syn diastereomers = 85%; $[\alpha]_D^{20}$ = −46.97° (c 0.02, CH$_3$OH); [ref. 72. $[\alpha]_D^{25}$ = −16.3° (c 0.1, MeOH)]; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 10.37 (s, 1H, NH), 7.45–7.25 (m, 2H, Ar–H), 6.77 (s, 1H, Ar–H), 6.01 (s, 1H, OH), 3.10 (dt, J = 8.0, 6.1 Hz, 1H, COCH), 2.59–2.50 (m, 1H, COCH$_2$), 2.33–2.30 (m, 1H, COCH$_2$), 2.06–1.51 (m, 6H, (CH$_2$)$_3$); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 209.34, 178.25, 142.79, 133.34, 131.30, 127.45, 112.52, 111.40, 73.93, 57.43, 41.45, 26.72, 26.66, 24.44. All the analytical data are well in agreement with the reported literature.[72]

General procedure (GP2) for synthesis of asymmetric spiro [4H-pyran-3,3-oxindole] derivatives (6a–l) of three components with one pot

GP2. A small vial (8 mL) under nitrogen atmosphere were charged with ligand **L1** (8.2 mg, 0.02 mmol, 10 mol%), Cu(OAc)$_2$·H$_2$O (12.0 mg, 0.06 mmol, 30 mol%) and tetrahydrofuran (THF) (3 mL). The solution was stirred for 2 h at room temperature to obtain a blue solution of **L1**-Cu(OAc)$_2$·H$_2$O complex. Then, isatins **1a–l** (0.2 mmol) and malononitrile **4** (13.2 mg, 0.2 mmol) were then added to blue coloured solution and stirred for 10 min at room temperature followed by addition of ethylacetoacetate **5** (26.0 mg, 0.2 mmol) and the reaction mixture was left stirring for another 5–15 h. After that the solvent were removed under reduced pressure, the residue was directly purified on 100 mesh silica gel columns, eluting by EtOAc/petroleum ether (60–80%) to obtain the corresponding chiral spirooxindole products **6a–l**.

Ethyl-(S)-2′-amino-5-bromo-3′-cyano-6′-methyl-2-oxospiro[indoline-3,4′-pyran]-5′-carboxylate (6a). 5-Bromoisatin **1a** (45.2 mg, 0.2 mmol), malononitrile **4** (13.2 mg, 0.2 mmol) and ethylacetoacetate **5** (26.0 mg, 0.2 mmol) were reacted according to the GP2 to yield product **6a** as white solid; m.p.: 259–260 °C; isolated yield (80.8 mg, 98%). Enantiomeric excess (ee) was determined by chiral HPLC [Daicel Chiralpak AD-H column], 90.0% n-hexane/i-PrOH, 0.8 mL min^{-1}; t_{minor} = 38.79 min; t_{major} = 41.37 min; λ = 254 nm; 91% ee; $[\alpha]_D^{20}$ = +8.62° (c 0.07, CH$_3$OH); [ref. 97 $[\alpha]_D^{24}$ = +34.3° (c 1.0, MeOH]]; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 10.55 (s, 1H, NH), 7.40–7.32 (m, 1H, Ar–H), 7.29 (s, 1H, Ar–H), 7.23 (s, 2H, NH$_2$), 6.77 (d, J = 8.3 Hz, 1H, Ar–H), 3.82 (q, J = 8.0 Hz, 2H, CH$_2$CH$_3$), 2.33 (s, 3H, CH$_3$), 0.84 (t, J = 7.4 Hz, 3H, CH$_2$CH$_3$); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 178.27, 164.37, 159.56, 158.91, 141.44, 137.23, 131.29, 126.27, 117.38, 113.45, 111.31, 103.72, 60.42, 55.94, 49.24, 18.80, 13.06. All the analytical data are well in agreement with the reported literature.[97]

Ethyl-(S)-2′-amino-3′-cyano-6′-methyl-2-oxospiro[indoline-3,4′-pyran]-5′-carboxylate (6b). Isatin **1b** (29.4 mg, 0.2 mmol), malononitrile **4** (13.2 mg, 0.2 mmol) and ethylacetoacetate **5** (26.0 mg, 0.2 mmol) were reacted according to the **GP2** to yield product **6b** as white solid; m.p.: 253–254 °C; isolated yield (64.4 mg, 99%). Enantiomeric excess (ee) was determined by chiral HPLC [Daicel Chiralpak AD-H column], 85.0% n-hexane/i-PrOH, 1.0 mL min^{-1}; t_{minor} = 19.12 min; t_{major} = 19.89 min; λ = 254 nm; 42% ee; $[\alpha]_D^{20}$ = +21.83° (c 0.05, CH$_3$OH); [ref. 97 $[\alpha]_D^{24}$ = +20.4° (c 1.4, MeOH)]; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 10.39 (s, 1H, NH), 7.18 (td, J = 7.6, 1.3 Hz, 1H, Ar–H), 7.14 (s, 2H, NH$_2$), 7.05 (dd, J = 7.4, 1.2 Hz, 1H, Ar–H), 6.93 (td, J = 7.5, 1.0 Hz, 1H, Ar–H), 6.79 (dt, J = 7.7, 0.8 Hz, 1H, Ar–H), 3.81–3.72 (m, 2H, CH$_2$CH$_3$), 2.31 (s, 3H, CH$_3$), 0.78 (t, J = 7.1 Hz, 3H, CH$_2$CH$_3$); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 178.60, 164.52, 158.95, 158.52, 142.17, 134.56, 128.56, 123.41, 121.86, 117.51, 109.33, 104.67, 60.26, 56.52, 48.96, 18.57, 12.99. All the analytical data are well in agreement with the reported literature.[97]

Ethyl-(S)-2′-amino-5-chloro-3′-cyano-6′-methyl-2-oxospiro[indoline-3,4′-pyran]-5′-carboxylate (6c). 5-Chloroisatin **1c** (36.3 mg, 0.2 mmol), malononitrile **4** (13.2 mg, 0.2 mmol) and ethylacetoacetate **5** (26.0 mg, 0.2 mmol) were reacted according to the GP2 to yield product **6c** as white solid; m.p.: 247–248 °C; isolated yield (69.1 mg, 96%). Enantiomeric excess (ee) was determined by chiral HPLC [Daicel Chiralpak AD-H column], 90.0% n-hexane/i-PrOH, 0.8 mL min^{-1}; t_{minor} = 36.52 min; t_{major} = 40.92 min; λ = 254 nm; 57% ee; $[\alpha]_D^{20}$ = −31.08° (c 0.05, CH$_3$OH); [ref. 97 $[\alpha]_D^{24}$ = −21.7° (c 1.0, MeOH)]; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 10.56 (s, 1H, NH), 7.25 (s, 2H, NH$_2$), 7.23 (dd, J = 8.2, 2.2 Hz, Ar–H), 7.19 (d, J = 2.2 Hz, 1H, Ar–H), 6.81 (d, J = 8.2 Hz, 1H, Ar–H), 3.81 (q, J = 7.1 Hz, 2H, CH$_2$CH$_3$), 2.33 (s, 3H, CH$_3$), 0.83 (t, J = 7.1 Hz, CH$_2$CH$_3$); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 178.45, 164.40, 159.57, 158.95, 141.06, 136.87, 128.47, 125.83, 123.65, 117.44, 110.80, 103.75, 60.46, 55.90, 49.31, 18.82, 13.08. All the analytical data are well in agreement with the reported literature.[97]

Ethyl-(S)-2′-amino-6-chloro-3′-cyano-6′-methyl-2-oxospiro[indoline-3,4′-pyran]-5′-carboxylate (6d). 6-Chloroisatin **1d** (36.3 mg, 0.2 mmol), malononitrile **4** (13.2 mg, 0.2 mmol) and ethylacetoacetate **5** (26.0 mg, 0.2 mmol) were reacted according to the GP2 to yield product **6d** as white solid; m.p.: 258–259 °C; isolated yield (66.2 mg, 92%). Enantiomeric excess (ee) was determined by chiral HPLC [Daicel Chiralpak AD-H column], 90.0% n-hexane/i-PrOH, 0.8 mL min^{-1}; t_{minor} = 54.81 min; t_{major} = 62.03 min; λ = 254 nm; 47% ee; $[\alpha]_D^{20}$ = +41.62° (c 0.04, CH$_3$OH); IR (KBr): 3382, 3317, 3201, 2988, 2205, 1720, 1706, 1655, 1616, 1595, 1487, 1455, 1418, 1379, 1364, 1322, 1284, 1250, 1223, 1182, 1132, 854, 808, 776, 745, 719, 687, 633, 531 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 10.59 (s, 1H, NH), 7.24 (s, 2H, NH$_2$), 7.18 (td, J = 7.6, 1.3 Hz, 1H, Ar–H), 7.14 (s, 2H, NH$_2$), 7.10 (d, J = 7.9 Hz, 1H, Ar–H), 6.98 (dd, J = 7.9, 1.9 Hz, 1H, Ar–H), 6.81 (d, J = 1.9 Hz, 1H, Ar–H), 3.88–3.75 (m, 2H, CH$_2$CH$_3$), 2.32 (s, 3H, CH$_3$), 0.84 (t, J = 7.1 Hz, 3H, CH$_2$CH$_3$); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 178.62, 164.40, 159.20, 158.96, 143.69, 133.59, 132.74, 124.96, 121.63, 117.41, 109.40, 104.04, 60.48, 56.08, 48.75, 18.74, 13.11. All the analytical data are well in agreement with the reported literature.[97]

Ethyl-(S)-2′-amino-3′-cyano-5-methoxy-6′-methyl-2-oxospiro [indoline-3,4′-pyran]-5′-carboxylate (6e). 5-Methoxyisatin **1e** (35.4 mg, 0.2 mmol), malononitrile **4** (13.2 mg, 0.2 mmol) and ethylacetoacetate **5** (26.0 mg, 0.2 mmol) were reacted according

to the GP2 to yield product **6e** as white solid; m.p.: 249–250 °C; isolated yield (66.1 mg, 93%). Enantiomeric excess (ee) was determined by chiral HPLC [Chiralpak IB column], 70.0% n-hexane/i-PrOH, 1.0 mL min^{-1}; t_{minor} = 15.36 min; t_{major} = 33.13 min; λ = 254 nm; 87% ee; $[\alpha]_D^{20}$ = +11.08° (c 0.05, CH$_3$OH); [ref. 97 $[\alpha]_D^{24}$ = +32.2° (c 1.0, MeOH)]; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 10.23 (s, 1H, NH), 7.15 (s, 2H, NH$_2$), 6.75 (dd, J = 8.4, 2.6 Hz, 1H, Ar–H), 6.70 (d, J = 8.4 Hz, 1H, Ar–H), 6.68 (d, J = 2.6 Hz, 1H, Ar–H), 3.80–3.76 (m, 2H, CH$_2$CH$_3$), 3.67 (s, 3H, OCH$_3$), 2.32 (s, 3H, CH$_3$), 0.80 (t, J = 7.1 Hz, 3H, CH$_2$CH$_3$); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 178.56, 164.55, 158.93, 158.67, 155.11, 135.90, 135.47, 117.60, 113.17, 110.28, 109.75, 104.56, 60.30, 56.60, 55.48, 49.46, 18.65, 13.05. All the analytical data are well in agreement with the reported literature.[97]

Ethyl-(S)-2′-amino-3′-cyano-6′-methyl-5-nitro-2-oxospiro[indoline-3,4′-pyran]-5′-carboxylate (6f). 5-Nitroisatin **1f** (38.4 mg, 0.2 mmol), malononitrile **4** (13.2 mg, 0.2 mmol) and ethyl-acetoacetate **5** (26.0 mg, 0.2 mmol) were reacted according to the GP2 to yield product **6f** as white solid; m.p.: 253–254 °C; isolated yield (65.9 mg, 89%). Enantiomeric excess (ee) was determined by chiral HPLC [Daicel Chiralpak AD-H column], 90.0% n-hexane/i-PrOH, 0.8 mL min^{-1}; t_{minor} = 61.83 min; t_{major} = 64.37 min; λ = 254 nm; 80% ee; $[\alpha]_D^{20}$ = +16.51° (c 0.05, CH$_3$OH); IR (KBr): 3391, 3314, 3204, 2207, 1724, 1653, 1626, 1594, 1558, 1522, 1471, 1456, 1404, 1378, 1340, 1283, 1253, 1224, 1177, 1129, 1078, 844, 802, 756, 739, 690, 634, 557 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 11.18 (s, 1H, NH), 8.19 (dd, J = 8.6, 2.4 Hz, 1H, Ar–H), 8.05 (d, J = 2.4 Hz, 1H, Ar–H), 7.37 (s, 2H, NH$_2$), 7.03 (d, J = 8.6 Hz, 1H, Ar–H), 3.86–3.78 (m, 2H, CH$_2$CH$_3$), 2.38 (s, 3H, CH$_3$), 0.84 (t, J = 7.1 Hz, 3H, CH$_2$CH$_3$); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 179.22, 164.26, 160.59, 159.04, 148.62, 142.50, 136.05, 126.09, 119.20, 117.26, 109.63, 103.00, 60.66, 55.18, 49.21, 19.02, 13.12.

Ethyl-(S)-2′-amino-5,7-dibromo-3′-cyano-6′-methyl-2-oxospiro [indoline-3,4′-pyran]-5′-carboxylate (6g). 5,7-Dibromoisatin **1g** (61.0 mg, 0.2 mmol), malononitrile **4** (13.2 mg, 0.2 mmol) and ethylacetoacetate **5** (26.0 mg, 0.2 mmol) were reacted according to the GP2 to yield product **6g** as white solid; m.p.: 250–251 °C; isolated yield (92.8 mg, 96%). Enantiomeric excess (ee) was determined by chiral HPLC [Daicel Chiralpak AD-H column], 90.0% n-hexane/i-PrOH, 0.8 mL min^{-1}; t_{minor} = 20.53 min; t_{major} = 31.65 min; λ = 254 nm; 50% ee; $[\alpha]_D^{20}$ = +14.56° (c 0.04, CH$_3$OH); IR (KBr): 3479, 3296, 3160, 3066, 2980, 2197, 1723, 1710, 1677, 1610, 1596, 1584, 1459, 1409, 1302, 1288, 1253, 1213, 1161, 1129, 1080, 779, 762, 744, 664, 867, 464 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 10.94 (s, 1H, NH), 7.65 (s, 1H, Ar–H), 7.39 (s, 1H, Ar–H), 7.35 (s, 2H, NH$_2$), 3.83 (q, J = 9.3 Hz, 2H, CH$_2$CH$_3$), 2.35 (s, 3H, CH$_3$), 0.86 (t, J = 7.1 Hz, 3H, CH$_2$CH$_3$); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 178.34, 164.23, 160.20, 158.90, 141.15, 138.39, 133.18, 125.69, 117.32, 114.05, 103.26, 102.68, 60.62, 55.46, 50.40, 18.92, 13.01.

Ethyl-(S)-2′-amino-3′-cyano-5,6′-dimethyl-2-oxospiro[indoline-3,4′-pyran]-5′-carboxylate (6h). 5-Methylisatin **1h** (32.2 mg, 0.2 mmol), malononitrile **4** (13.2 mg, 0.2 mmol) and ethyl-acetoacetate **5** (26.0 mg, 0.2 mmol) were reacted according to the GP2 to yield product **6h** as white solid; m.p.: 255–256 °C; isolated yield (65.8 mg, 97%). Enantiomeric excess (ee) was

determined by chiral HPLC [Daicel Chiralpak AD-H column], 90.0% n-hexane/i-PrOH, 0.8 mL min^{-1}; t_{minor} = 41.56 min; t_{major} = 42.89 min; λ = 220 nm; 95% ee; $[\alpha]_D^{20}$ = −26.47° (c 0.06, CH$_3$OH); [ref. 97 $[\alpha]_D^{24}$ = −24.0° (c 1.0, MeOH)]; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 10.28 (s, 1H, NH), 7.11 (s, 2H, NH$_2$), 6.97 (d, J = 8.6 Hz, 1H, Ar–H), 6.87 (s, 1H, Ar–H), 6.68 (d, J = 7.9 Hz, 1H, Ar–H), 3.78 (q, J = 7.1 Hz, 2H, CH$_2$CH$_3$), 2.31 (s, 3H, CH$_3$), 0.80 (t, J = 7.1 Hz, 3H, CH$_2$CH$_3$); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 178.58, 164.55, 158.88, 158.51, 139.66, 134.73, 130.67, 128.78, 123.94, 117.57, 109.07, 104.71, 60.27, 56.75, 49.02, 20.63, 18.61, 13.00. All the analytical data are well in agreement with the reported literature.[97]

Ethyl-(S)-2′-amino-3′-cyano-5-fluoro-6′-methyl-2-oxospiro[indoline-3,4′-pyran]-5′-carboxylate (6i). 5-Fluoroisatin **1i** (33.0 mg, 0.2 mmol), malononitrile **4** (13.2 mg, 0.2 mmol) and ethyl-acetoacetate **5** (26.0 mg, 0.2 mmol) were reacted according to the **GP2** to yield product **6i** as white solid; m.p.: 253–254 °C; isolated yield (65.9 mg, 98%). Enantiomeric excess (ee) was determined by chiral HPLC [Daicel Chiralpak AD-H column], 90.0% n-hexane/i-PrOH, 0.8 mL min^{-1}; t_{major} = 39.61 min; t_{minor} = 43.67 min; λ = 220 nm; 39% ee; $[\alpha]_D^{20}$ = −23.38° (c 0.08, CH$_3$OH); [ref. 97 $[\alpha]_D^{24}$ = −18.9° (c 1.0, MeOH)]; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 10.44 (s, 1H, NH), 7.23 (s, 2H, NH$_2$), 7.07–6.96 (m, 2H, Ar–H), 6.78 (dd, J = 8.5, 4.3 Hz, 1H, Ar–H), 3.87–3.73 (m, 2H, CH$_2$CH$_3$), 2.32 (s, 3H, CH$_3$), 0.82 (t, J = 7.1 Hz, 3H, CH$_2$CH$_3$); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 178.72, 164.42, 159.29, 159.20, 158.97, 157.31, 138.36, 136.48, 136.43, 117.44, 114.90, 114.71, 111.43, 111.23, 110.12, 110.06, 103.97, 60.40, 56.03, 49.53, 18.76, 13.06. All the analytical data are well in agreement with the reported literature.[97]

Ethyl-(S)-2′-amino-3′-cyano-1,6′-dimethyl-2-oxospiro[indoline-3,4′-pyran]-5′-carboxylate (6j). 1-Methylisatin **1j** (32.2 mg, 0.2 mmol), malononitrile **4** (13.2 mg, 0.2 mmol) and ethyl-acetoacetate **5** (26.0 mg, 0.2 mmol) were reacted according to the **GP2** to yield product **6j** as white solid; m.p.: = 257–258 °C, isolated yield (67.2 mg, 99%). Enantiomeric excess (ee) was determined by chiral HPLC [Daicel Chiralpak AD-H column], 80.0% n-hexane/i-PrOH, 1.0 mL min^{-1}; t_{major} = 9.67 min; t_{minor} = 11.24 min; λ = 254 nm; 63% ee; $[\alpha]_D^{20}$ = +26.29° (c 0.07, CH$_3$OH); [ref. 97 $[\alpha]_D^{24}$ = +14.7° (c 1.0, MeOH)]; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 7.29 (td, J = 7.7, 1.4 Hz, 1H, Ar–H), 7.20 (s, 2H, NH$_2$), 7.12 (dd, J = 7.4, 1.3 Hz, 1H, Ar–H), 7.04–6.99 (m, 2H, Ar–H), 3.72 (q, J = 3.0 Hz, 2H, CH$_2$–CH$_3$), 3.14 (s, 3H, NCH$_3$), 2.33 (s, 3H, CH$_3$), 0.72 (t, J = 7.1 Hz, 3H, CH$_2$CH$_3$); ^{13}C-NMR (126 MHz, DMSO-d_6): δ (ppm) = 176.96, 164.34, 158.98, 158.95, 143.50, 133.74, 128.76, 123.13, 122.62, 117.33, 108.25, 104.41, 60.19, 56.15, 48.51, 26.30, 18.62, 13.19. All the analytical data are well in agreement with the reported literature.[97]

Ethyl-(S)-2′-amino-1-benzyl-3′-cyano-6′-methyl-2-oxospiro[indoline-3,4′-pyran]-5′-carboxylate (6k). 1-Benzylisatin **1k** (47.5 mg, 0.2 mmol), malononitrile **4** (13.2 mg, 0.2 mmol) and ethyl-acetoacetate **5** (26.0 mg, 0.2 mmol) were reacted according to the GP2 to yield product **6k** as white solid; m.p.: 251–252 °C; isolated yield (81.4 mg, 98%). Enantiomeric excess (ee) was determined by chiral HPLC [Daicel Chiralpak AD-H column], 80.0% n-hexane/i-PrOH, 1.0 mL min^{-1}; t_{major} = 12.33 min; t_{minor} = 20.59 min; λ = 254 nm; 81% ee; $[\alpha]_D^{20}$ = +19.55° (c 0.06,

CH$_3$OH); [ref. 97 $[\alpha]_D^{24} = +20.4°$ (*c* 1.0, MeOH)]; ^{1}H-NMR (500 MHz, DMSO-*d*$_6$): δ (ppm) = 7.48–7.45 (m, 2H, Ar–H), 7.33–7.30 (m, 2H, Ar–H), 7.28 (s, 1H, Ar–H), 7.25 (s, 2H, NH$_2$), 7.20 (td, *J* = 7.7, 1.3 Hz, 1H, Ar–H), 7.15 (dd, *J* = 7.4, 1.3 Hz, 1H, Ar–H), 7.00 (td, *J* = 7.5, 1.0 Hz, 1H, Ar–H), 6.86 (d, *J* = 7.7 Hz, 1H, Ar–H), 5.00 (d, *J* = 15.8 Hz, 1H, CH$_{2(a)}$Bn), 4.78 (d, *J* = 15.8 Hz, 1H, CH$_{2(b)}$Bn), 3.78 (q, *J* = 7.1 Hz, 1H, CH$_2$CH$_3$), 3.52 (dd, *J* = 10.8, 7.1 Hz, 1H, CH$_2$CH$_3$), 2.34 (s, 3H, CH$_3$), 0.58 (t, *J* = 7.1 Hz, 3H, CH$_2$CH$_3$); ^{13}C-NMR (126 MHz, DMSO-*d*$_6$): δ (ppm) = 177.20, 164.38, 159.19, 158.86, 142.77, 136.19, 133.65, 128.40, 127.55, 123.34, 122.73, 117.57, 108.91, 104.55, 60.11, 56.12, 48.52, 43.39, 18.65, 13.08. All the analytical data are well in agreement with the reported literature.[97]

Ethyl-(S)-2'-amino-1-(2-bromoethyl)-3'-cyano-6'-methyl-2-oxo-spiro[indoline-3,4'-pyran]-5'-carboxylate (*6l*). 1-(2-Bromoethyl) isatin **1l** (50.8 mg, 0.2 mmol), malononitrile **4** (13.2 mg, 0.2 mmol) and ethylacetoacetate 5 (26.0 mg, 0.2 mmol) were reacted according to the GP2 to yield product **6l** as white solid; m.p.: 148–150 °C; isolated yield (76.9 mg, 89%). Enantiomeric excess (ee) was determined by chiral HPLC [Daicel Chiralpak AD-H column], 85.0% *n*-hexane/i-PrOH, 1.0 mL min^{-1}; t_{major} = 15.03 min; t_{minor} = 24.53 min; λ = 254 nm; 23% ee; $[\alpha]_D^{20}$ = +5.34° (*c* 0.10, CH$_3$OH); IR (KBr): 3382, 2924, 2854, 2191, 1709, 1682, 1613, 1599, 1486, 1466, 1419, 1380, 1348, 1282, 1253, 1211, 1149, 1077, 756, 682 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-*d*$_6$): δ (ppm) = 7.29 (td, *J* = 7.6, 1.3 Hz, 1H, Ar–H), 7.23 (s, 2H, NH$_2$), 7.18–7.13 (m, 2H, Ar–H), 7.03 (td, *J* = 7.5, 1.0 Hz, 1H, Ar–H), 4.16 (ddd, *J* = 14.2, 7.7, 6.5 Hz, 1H, CH$_3$CH$_{2(a)}$), 4.03 (ddd, *J* = 14.2, 7.7, 6.1 Hz, 1H, CH$_3$CH$_{2(b)}$), 3.82 (dq, *J* = 11.0, 7.1 Hz, 1H, NCH$_{2(a)}$), 3.72 (qd, *J* = 7.1, 4.6 Hz, 1H, NCH$_{2(b)}$), 3.63–3.57 (m, 2H, CH$_2$Br), 2.33 (s, 3H, CH$_3$), 0.71 (t, *J* = 7.1 Hz, 3H, CH$_2$CH$_3$); ^{13}C-NMR (126 MHz, DMSO-*d*$_6$): δ (ppm) = 177.03, 164.32, 158.99, 142.18, 133.54, 128.76, 123.41, 122.84, 117.14, 108.70, 104.36, 60.25, 56.08, 48.41, 41.57, 28.36, 18.67, 13.22.

Conclusions

In summary, we have developed very efficient enantioselective process for the asymmetric Aldol reaction of substituted isatin with several acetone derivatives using **L1**-Cu(II) as a new Lewis acid catalyst based on thiophene-2,5-bis(amino-alcohol) framework. Our Lewis acid catalytic system **L1**-Cu(II) acts brilliantly and furnished aldol products **3a–s** in high yields and selectivity (up to 99% yield; up to 96% ee). This catalytic system **L1**-Cu(OAc)$_2$·H$_2$O was further utilized for asymmetric Domino Knoevenagel Michael cyclization reaction of substituted isatin with malononitrile and ethylacetoacetate and afforded chiral spiro[4H-pyran-3,3-oxindole] derivatives **6a–l** with high yields and moderate to high enantioselectivities (up to 99% yield; up to 95% ee). Both the reactions were performed under mild reaction condition at room temperature.

Author contributions

Conceptualization, A. M. A.-M. and A. B.; supervision, A. M. A.-M., A. B. and M. S. I; methodology, A. S. A., M. S. I. and A. M. A.-M.; validation, M. S. I., A. S. A., S. A. and A. M. A.-M.; formal analysis, A. S. A.; M. S. I. and S. A.; investigation, A. S. A.; M. S. I. and S. A.; resources, A. M. A.-M. and A. B.; data curation, A. S. A., M. S. I., and A. B.; writing—original draft preparation, M. S. I., A. B. and A. S. A.; writing—review and editing, M. S. I., A. B. and A. M. A.-M.; visualization, A. B., M. S. I and S. A.; project administration, A. M. A.-M. and A. B.; funding acquisition, A. M. A.-M. and A. B.; software A. S. A., M. S. I., M. A. and A. B.; all authors have read and agreed to the published version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Notes and references

1 P. W. V. Leeuwen, P. C. Kamer, C. Claver, O. Pamies and M. Dieguez, *Chem. Rev.*, 2011, **111**, 2077–2118.

2 A. Barakat, M. S. Islam, A. M. Al Majid and Z. A. Al-Othman, *Tetrahedron*, 2013, **69**, 5185–5192.

3 M. S. Islam, A. M. Al Majid, Z. A. Al-Othman and A. Barakat, *Tetrahedron: Asymmetry*, 2014, **25**, 245–251.

4 M. S. Islam, A. S. Alammari, A. Barakat, S. Alshahrani, M. Haukka and A. M. Al-Majid, *Molecules*, 2021, **26**, 7408.

5 A. S. Alammari, A. M. Al-Majid, A. Barakat, S. Alshahrani, M. Ali and M. S. Islam, *Catalysts*, 2021, **11**, 1208.

6 T. Mukaiyama, *Org. React.*, 1982.

7 Q. Guo, M. Bhanushali and C. G. Zhao, *Angew. Chem., Int. Ed.*, 2010, **49**, 9460–9464.

8 T. Yan, X. Wang, H. Sun, J. Liu and Y. Xie, *Molecules*, 2013, **18**, 14505–14518.

9 V. Kumar, K. Kaur, G. K. Gupta and A. K. Sharma, *Eur. J. Med. Chem.*, 2013, **69**, 735–753.

10 V. Raj, *Int. J. Curr. Pharm. Res.*, 2012, **4**, 1–9.

11 C. Marti and E. M. Carreira, *Eur. J. Org. Chem.*, 2003, **2003**, 2209–2219.

12 C. V. Galliford and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748–8758.

13 S. Peddibhotla, *Curr. Bioact. Compd.*, 2009, **5**, 20–38.

14 S. Mohammadi, R. Heiran, R. P. Herrera and E. Marques-Lopez, *ChemCatChem*, 2013, **5**, 2131–2148.

15 R. B. Labroo and L. A. Cohen, *J. Org. Chem.*, 1990, **55**, 4901–4904.

16 P. Hewawasam, N. A. Meanwell, V. K. Gribkoff, S. I. Dworetzky and C. G. Boissard, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 1255–1260.

17 Y. Q. Tang, I. Sattler, R. Thiericke, S. Grabley and X. Z. Feng, *Eur. J. Org. Chem.*, 2001, **2001**, 261–267.

18 T. Tokunaga, W. E. Hume, T. Umezome, K. Okazaki, Y. Ueki, K. Kumagai, S. Hourai, J. Nagamine, H. Seki and M. Taiji, *J. Med. Chem.*, 2001, **44**, 4641–4649.

19 P. Hewawasam, M. Erway, S. L. Moon, J. Knipe, H. Weiner, C. G. Boissard, D. J. Post-Munson, Q. Gao, S. Huang and V. K. Gribkoff, *J. Med. Chem.*, 2002, **45**, 1487–1499.

20 V. Khuzhaev, I. Zhalolov, K. Turgunov, B. Tashkhodzhaev, M. Levkovich, S. Aripova and A. Shashkov, *Chem. Nat. Compd.*, 2004, **40**, 269–272.

21 H. B. Rasmussen and J. K. MacLeod, *J. Nat. Prod.*, 1997, **60**, 1152–1154.

22 T. Kagata, S. Saito, H. Shigemori, A. Ohsaki, H. Ishiyama, T. Kubota and J. i. Kobayashi, *J. Nat. Prod.*, 2006, **69**, 1517–1521.

23 Y. Kamano, H.-p. Zhang, Y. Ichihara, H. Kizu, K. Komiyama and G. R. Pettit, *Tetrahedron Lett.*, 1995, **36**, 2783–2784.

24 C. Moody, I. Richards and A. Z. Slawin, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2405–2412.

25 T. Nakamura, S.-i. Shirokawa, S. Hosokawa, A. Nakazaki and S. Kobayashi, *Org. Lett.*, 2006, **8**, 677–679.

26 S. Nakamura, N. Hara, H. Nakashima, K. Kubo, N. Shibata and T. Toru, *Chem.–Eur. J.*, 2008, **14**, 8079–8081.

27 G. Luppi, M. Monari, R. J. Corrêa, F. d. A. Violante, A. C. Pinto, B. Kaptein, Q. B. Broxterman, S. J. Garden and C. Tomasini, *Tetrahedron*, 2006, **62**, 12017–12024.

28 J. S. Carle and C. Christophersen, *J. Org. Chem.*, 1981, **46**, 3440–3443.

29 K. Nicolaou, X. Huang, N. Giuseppone, P. Bheema Rao, M. Bella, M. V. Reddy and S. A. Snyder, *Angew. Chem., Int. Ed.*, 2001, **40**, 4705–4709.

30 K. Nicolaou, M. Bella, D. Y. K. Chen, X. Huang, T. Ling and S. A. Snyder, *Angew. Chem., Int. Ed.*, 2002, **114**, 3645–3649.

31 K. Nicolaou, P. Bheema Rao, J. Hao, M. V. Reddy, G. Rassias, X. Huang, D. Y. K. Chen and S. A. Snyder, *Angew. Chem., Int. Ed.*, 2003, **42**, 1753–1758.

32 K. Nicolaou, S. A. Snyder, N. Giuseppone, X. Huang, M. Bella, M. V. Reddy, P. B. Rao, A. E. Koumbis, P. Giannakakou and A. O'Brate, *J. Am. Chem. Soc.*, 2004, **126**, 10174–10182.

33 K. Nicolaou, D. Y.-K. Chen, X. Huang, T. Ling, M. Bella and S. A. Snyder, *J. Am. Chem. Soc.*, 2004, **126**, 12888–12896.

34 C. Takahashi, A. Numata, Y. Ito, E. Matsumura, H. Araki, H. Iwaki and K. Kushida, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1859–1864.

35 A. Fréchard, N. Fabre, C. Péan, S. Montaut, M.-T. Fauvel, P. Rollin and I. Fourasté, *Tetrahedron Lett.*, 2001, **42**, 9015–9017.

36 M. Kitajima, I. Mori, K. Arai, N. Kogure and H. Takayama, *Tetrahedron Lett.*, 2006, **47**, 3199–3202.

37 J. I. Jimenez, U. Huber, R. E. Moore and G. M. Patterson, *J. Nat. Prod.*, 1999, **62**, 569–572.

38 B. K. Albrecht and R. M. Williams, *Org. Lett.*, 2003, **5**, 197–200.

39 S. Lin, Z.-Q. Yang, B. H. Kwok, M. Koldobskiy, C. M. Crews and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2004, **126**, 6347–6355.

40 K. S. Feldman and A. G. Karatjas, *Org. Lett.*, 2004, **6**, 2849–2852.

41 H. Suzuki, H. Morita, M. Shiro and J. i. Kobayashi, *Tetrahedron*, 2004, **60**, 2489–2495.

42 M. Suchý, P. Kutschy, K. Monde, H. Goto, N. Harada, M. Takasugi, M. Dzurilla and E. Balentova, *J. Org. Chem.*, 2001, **66**, 3940–3947.

43 F. Zhou, Y. L. Liu and J. Zhou, *Adv. Synth. Catal.*, 2010, **352**, 1381–1407.

44 J. J. Badillo, N. V. Hanhan and A. K. Franz, *Curr. Opin. Drug Discovery Dev.*, 2010, **13**, 758–776.

45 A. Kumar and S. S. Chimni, *RSC Adv.*, 2012, **2**, 9748–9762.

46 B. Alcaide and P. Almendros, *Angew. Chem., Int. Ed.*, 2003, **42**, 858–860.

47 B. List, L. Hoang and H. J. Martin, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5839–5842.

48 C. Allemann, R. Gordillo, F. R. Clemente, P. H.-Y. Cheong and K. Houk, *Acc. Chem. Res.*, 2004, **37**, 558–569.

49 S. Saito and H. Yamamoto, *Acc. Chem. Res.*, 2004, **37**, 570–579.

50 S. M. Dean, W. A. Greenberg and C. H. Wong, *Adv. Synth. Catal.*, 2007, **349**, 1308–1320.

51 M. Raj and V. K. Singh, *Chem. Commun.*, 2009, 6687–6703.

52 V. Bisai, A. Bisai and V. K. Singh, *Tetrahedron*, 2012, **68**, 4541–4580.

53 B. List, R. A. Lerner and C. F. Barbas, *J. Am. Chem. Soc.*, 2000, **122**, 2395–2396.

54 A. Spek, *Acta Crystallogr., Sect. D: Biol. Crystallogr.*, 2009, **65**, 148–155.

55 G. Luppi, P. G. Cozzi, M. Monari, B. Kaptein, Q. B. Broxterman and C. Tomasini, *J. Org. Chem.*, 2005, **70**, 7418–7421.

56 E. M. Beccalli, A. Marchesini and T. Pilati, *J. Chem. Soc., Perkin Trans. 1*, 1994, 579–587.

57 S. J. Garden, R. B. da Silva and A. C. Pinto, *Tetrahedron*, 2002, **58**, 8399–8412.

58 T. Kawasaki, M. Nagaoka, T. Satoh, A. Okamoto, R. Ukon and A. Ogawa, *Tetrahedron*, 2004, **60**, 3493–3503.

59 W.-B. Chen, Y.-H. Liao, X.-L. Du, X.-M. Zhang and W.-C. Yuan, *Green Chem.*, 2009, **11**, 1465–1476.

60 R. J. Corrêa, S. J. Garden, G. Angelici and C. Tomasini, *Eur. J. Org. Chem.*, 2008, **2008**, 736–744.

61 G. Angelici, R. J. Corrêa, S. J. Garden and C. Tomasini, *Tetrahedron Lett.*, 2009, **50**, 814–817.

62 J. G. Hernández, V. García-López and E. Juaristi, *Tetrahedron*, 2012, **68**, 92–97.

63 M. Kinsella, P. G. Duggan and C. M. Lennon, *Tetrahedron: Asymmetry*, 2011, **22**, 1423–1433.

64 J.-R. Chen, X.-P. Liu, X.-Y. Zhu, L. Li, Y.-F. Qiao, J.-M. Zhang and W.-J. Xiao, *Tetrahedron*, 2007, **63**, 10437–10444.

65 C. Shen, F. Shen, H. Xia, P. Zhang and X. Chen, *Tetrahedron: Asymmetry*, 2011, **22**, 708–712.

66 T. P. Kumar, N. Manjula and K. Katragunta, *Tetrahedron: Asymmetry*, 2015, **26**, 1281–1284.

67 G. D. Yadav and S. Singh, *Tetrahedron: Asymmetry*, 2016, **27**, 123–129.

68 A. J. Pearson and S. Panda, *Org. Lett.*, 2011, **13**, 5548–5551.

69 G. D. Yadav and S. Singh, *Tetrahedron: Asymmetry*, 2015, **26**, 1156–1166.

70 N. Hara, S. Nakamura, N. Shibata and T. Toru, *Adv. Synth. Catal.*, 2010, **352**, 1621–1624.

71 N. Hara, S. Nakamura, N. Shibata and T. Toru, *Chem.–Eur. J.*, 2009, **15**, 6790–6793.

72 J. Wang, Q. Liu, Q. Hao, Y. Sun, Y. Luo and H. Yang, *Chirality*, 2015, **27**, 314–319.

73 M. Raj, N. Veerasamy and V. K. Singh, *Tetrahedron Lett.*, 2010, **51**, 2157–2159.

74 Q. Guo and J. C.-G. Zhao, *Tetrahedron Lett.*, 2012, **53**, 1768–1771.

75 D. Ma, L. Ren, H. Yao, W. Tian, F. Chen, J. Zhang, Y. Liu and T. Mao, *J. Orthop. Res.*, 2013, **31**, 1082–1088.

76 H. Lu, J. Bai, J. Xu, T. Yang, X. Lin, J. Li and F. Ren, *Tetrahedron*, 2015, **71**, 2610–2615.

77 S. Abbaraju and J. C. G. Zhao, *Adv. Synth. Catal.*, 2014, **356**, 237–241.

78 A. V. Malkov, M. A. Kabeshov, M. Bella, O. Kysilka, D. A. Malyshev, K. Pluháčková and P. Kočovský, *Org. Lett.*, 2007, **9**, 5473–5476.

79 Z.-Q. Liu, Z.-W. Xiang, Z. Shen, Q. Wu and X.-F. Lin, *Biochimie*, 2014, **101**, 156–160.

80 T. Itoh, H. Ishikawa and Y. Hayashi, *Org. Lett.*, 2009, **11**, 3854–3857.

81 G. Chen, Y. Ju, T. Yang, Z. Li, W. Ang, Z. Sang, J. Liu and Y. Luo, *Tetrahedron: Asymmetry*, 2015, **26**, 943–947.

82 R. Singh and R. Vince, *Chem. Rev.*, 2012, **112**, 4642–4686.

83 Y.-T. Yang, J.-F. Zhu, G. Liao, H.-J. Xu and B. Yu, *Curr. Med. Chem.*, 2018, **25**, 2233–2244.

84 M. S. Islam, M. Ali, A. M. Al-Majid, A. S. Alamary, S. Alshahrani, S. Yousuf, M. I. Choudhary and A. Barakat, *Molecules*, 2021, **26**, 2212.

85 M. S. Islam, A. M. Al-Majid, M. Azam, V. P. Verma, A. Barakat, M. Haukka, A. A. Elgazar, A. Mira and F. A. Badria, *ACS Omega*, 2021, 31539–31556.

86 M. S. Islam, A. M. Al-Majid, F. F. El-Senduny, F. A. Badria, A. Rahman, A. Barakat and Y. A. Elshaier, *Appl. Sci.*, 2020, **10**, 2170.

87 M. S. Islam, A. M. Al-Majid, M. Azam, V. Prakash Verma, A. Barakat, M. Haukka, L. R. Domingo, A. A. Elgazar, A. Mira and F. A. Badria, *ChemistrySelect*, 2021, **6**, 14039–14053.

88 A. Barakat, M. S. Islam, M. Ali, A. M. Al-Majid, S. Alshahrani, A. S. Alamary, S. Yousuf and M. I. Choudhary, *Symmetry*, 2021, **13**, 1426.

89 A. M. Al-Majid, M. Ali, M. S. Islam, S. Alshahrani, A. S. Alamary, S. Yousuf, M. I. Choudhary and A. Barakat, *Molecules*, 2021, **26**, 6305.

90 R. Dworczak, H. Sterk, C. Kratky and H. Junek, *Chem. Ber.*, 1989, **122**, 1323–1328.

91 S. J. Chai, Y. F. Lai, J. C. Xu, H. Zheng, Q. Zhu and P. F. Zhang, *Adv. Synth. Catal.*, 2011, **353**, 371–375.

92 G. Brahmachari and B. Banerjee, *Asian J. Org. Chem.*, 2016, **5**, 271–286.

93 D. Cheng, Y. Ishihara, B. Tan and C. F. Barbas III, *ACS Catal.*, 2014, **4**, 743–762.

94 G. M. Ziarani, R. Moradi and N. Lashgari, *Tetrahedron*, 2018, **74**, 1323–1353.

95 W.-B. Chen, Z.-J. Wu, Q.-L. Pei, L.-F. Cun, X.-M. Zhang and W.-C. Yuan, *Org. Lett.*, 2010, **12**, 3132–3135.

96 M. Chennapuram, I. A. Owolabi, C. Seki, Y. Okuyama, E. Kwon, K. Uwai, M. Tokiwa, M. Takeshita and H. Nakano, *ACS Omega*, 2018, **3**, 11718–11726.

97 S. Konda, S. Jakkampudi, H. D. Arman and J. C.-G. Zhao, *Synth. Commun.*, 2019, **49**, 2971–2982.

98 S. Lee and J. F. Hartwig, *J. Org. Chem.*, 2001, **66**, 3402–3415.

99 W.-J. Hao, S.-Y. Wang and S.-J. Ji, *ACS Catal.*, 2013, **3**, 2501–2504.

100 A. Khalafi-Nezhad and S. Mohammadi, *ACS Comb. Sci.*, 2013, **15**, 512–518.

101 A. Mondal and C. Mukhopadhyay, *ACS Comb. Sci.*, 2015, **17**, 404–408.