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Organocatalyzed direct asymmetric aldol reaction of isatins in water: low catalyst loading in command

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ABSTRACT

Simple primary–tertiary diamines easily derived from natural primary amino acids have been used to catalyze the aldol reactions in water. The 1 mol % of diamine catalyst is sufficient to catalyze the aldol reaction of cyclohexanone/acetone to isatins provided 3-substituted-3-hydroxy-2-oxindole in good yield and good enantioselectivity. The methodology highlights the importance of low catalyst loading in achieving high enantioselectivity.

1. Introduction

3-Substituted-3-hydroxy-2-oxindole is one of the key structural units found in a large variety of natural products and drug candidates, having wide spectrum of biological activities.[1] Among them, 3-alkyl-3-hydroxy-2-oxindole entities are of immense importance in the field of medicinal chemistry due to their anticonvulsant properties. Owing to the significance of this structural motif, the development of asymmetric organocatalytic methods for their synthesis has attracted the attention of synthetic chemist.[2] The aldol addition of carbonyl compounds, containing α-hydrogen to isatins via enamine-organocatalysis is a straightforward approach to this end. Tomasini et al.[3] reported the first aldol addition of acetone to isatin catalyzed by using 10 mol % of dipeptide containing secondary amine at N-terminus, whereas, Singh et al.[4] developed the aldol addition of cyclohexanone and acetophenone to isatins using primary amine based organocatalysts. After these reports some other groups had also reported the aldol addition of acetone and cyclohexanone to isatins using 5–20 mol % of primary as well as secondary amine based organocatalyst.[5] But, the major limitation of enamine catalysis with primary amine is the requirement of high catalyst loading in comparison with secondary amine based organocatalyst due to the low nucleophilicity of enamine intermediate derived from primary amine.[6] In addition, aldolization of ketones generally required high catalyst loading due to poor reactivity and greater steric hindrance of ketones as electrophilic species.[7] Therefore, this requires activation of both aldol donor and acceptor by bifunctional organocatalyst. Recently, we have developed primary–tertiary-Brønsted acid conjugates as a bifunctional organocatalysts for direct asymmetric aldol reaction.[8] Considering primary amine as an excellent catalyst for intramolecular ketone aldolization,[9] we planned to explore the applicability of primary–tertiary-Brønsted acid conjugate organocatalysts[10] for intermolecular ketone aldolization of cyclohexanone and isatins to procure 3-cycloalkane-3-hydroxy-2-oxindole, which is of immense importance in the field of medicinal chemistry due to their anticonvulsant properties.[11]

On the other hand, the use of water in organocatalytic reactions is of great current interest due to its unique properties as compared to commonly employed organic solvents.[12] Our research group have successfully explored organocatalytic asymmetric ketone-aldehyde cross aldolization using water as a solvent.[13] Here we disclose our finding of intermolecular ketone aldolization in water catalyzed by 1 mol % of chiral primary–tertiary-Brønsted acid conjugate organocatalysts (Fig. 1).

2. Results and discussion

Initially, the aldol reaction of cyclohexanone (**3**) with isatin (**2a**) was performed using 10 mol % of catalyst **1a** and 2,4-dinitrophenol (DNP) as an additive in water (Scheme 1). The aldol addition product **4a** was isolated in 90% yield with diastereomeric ratio of

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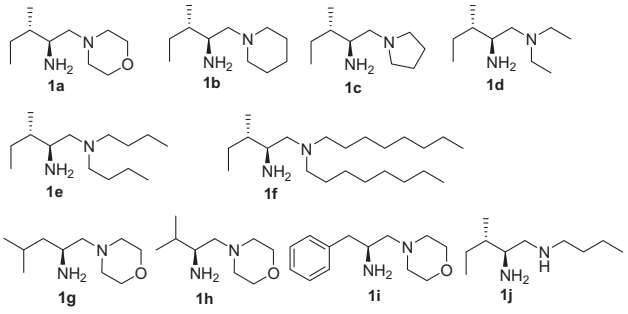
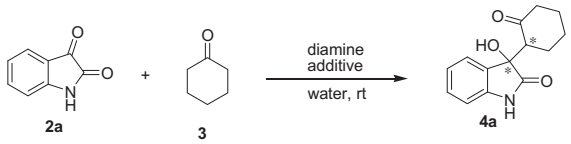


Fig. 1. Structure of organocatalysts.

82:18 (*syn*/*anti*) but with a very low enantioselectivity of 10% of syn isomer (Table 1, entry 1). Although the results were not encouraging, but inspired by the reaction reported in the literature[14] we thought of studying the effects of catalyst loading on the enantioselectivity of the reaction. The aldol reaction performed with catalyst loading of 5 mol % gave the product **4a** with an enhanced ee of 27% (dr of 86:14) (Table 1, entry 2). Encouraged by this result we further lowered the catalyst loading to 2.5 mol %, which yielded **4a** in 45% ee (dr of 90:10) (Table 1, entry 3). On performing the reaction at 1 mol % of catalyst loading, **4a** was obtained in comparably high enantioselectivity of 82% ee and diastereomeric ratio of 93:7 (Table 1, entry 4). Further, reducing the catalyst loading to 0.5 mol % had no effect on enantioselectivity of the product but resulted in lower yield (Table 1, entry 5). Therefore, catalyst loading of 1 mol % was found to be optimal and was used in all further optimizations.



Scheme 1. Diamine catalyzed aldol reaction of cyclohexanone with isatin.

Table 1
Effect of catalyst concentration on the enantioselectivity[a]

Entry	Catalyst loading **1a**-DNP (1:1)	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (%) (*syn*)
1	**1a**-DNP (10 mol %)	90	82:18	10
2	**1a**-DNP (5 mol %)	92	86:14	27
3	**1a**-DNP (2.5 mol %)	95	90:10	45
4	**1a**-DNP (1 mol %)	93	93:7	82
5	**1a**-DNP (0.5 mol %)	80	89:11	80

[a] Reaction condition: 0.5 mmol of isatin, 5 mmol of cyclohexanone, 0.5 mL of water, *x* mol % catalyst **1a**, *x* mol % DNP, temperature 25 °C.
[b] Isolated yield determined after chromatographic purification.
[c] Diastereoselectivity determined from HPLC spectra of crude reaction mixture.
[d] Enantiomeric excess determined from HPLC using chiralpak columns.

In order to find a highly enantioselective catalyst, we screened different primary amine derived catalyst. L-Isoleucine derived primary–tertiary diamine catalyst having piperidinyl **1b** and pyrrolidinyl **1c** group gave aldol product **4a** in high yield (>90%) and enantioselectivity of 79% ee and 80% ee with similar level of diastereomeric ratio (Table 2, entries 2 and 3). Next, the catalytic potential of primary–tertiary diamines (**1d** and **1e**) having acyclic tertiary amine was evaluated. The diamine catalyst having diethyl **1d** and dibutyl **1e** groups gave aldol product **4a** in good yield with moderate enantioselectivity of 70% ee and 71% ee (Table 2, entries 4 and 5). The diamine catalyst having long alkyl chain (*N*,*N*-dioctyl) group **1f** provided aldol product **4a** with low enantioselectivity of 65% ee (Table 2, entry 6). Therefore, further optimization of the

Table 2
Catalyst and additive screening for enantioselective aldol reaction of cyclohexanone (**3**) with isatin (**2a**)[a]

Entry	Catalyst	Additive	Time (h)	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (%) (*syn*)
1	**1a**	DNP	24	93	93:7	82
2	**1b**	DNP	24	92	91:9	79
3	**1c**	DNP	24	94	92:8	80
4	**1d**	DNP	28	90	90:10	70
5	**1e**	DNP	28	89	91:9	71
6	**1f**	DNP	36	85	86:14	65
7	**1g**	DNP	24	90	94:6	81
8	**1h**	DNP	24	92	92:8	79
9	**1i**	DNP	24	91	91:9	80
10	**1j**	DNP	96	82	70:30	10
11	**1a**	Benzoic acid	20	94	90:10	78
12	**1a**	2-Chlorobenzoic acid	22	95	90:10	82
13	**1a**	4-Nitrobenzoic acid	22	91	91:9	82
14	**1a**	TFA	40	81	91:9	79
15	**1a**	TfOH	40	78	82:18	78
16	**1a**	—	24	82	84:16	71

[a] Reaction condition: 0.5 mmol of isatin, 5 mmol of cyclohexanone, 0.5 mL of water, 1 mol % diamine catalyst, 1 mol % acid additive, temperature 25 °C.
[b] Isolated yield determined after chromatographic purification.
[c] Diastereoselectivity determined from HPLC spectra of crude reaction mixture.
[d] Enantiomeric excess determined from HPLC using chiralpak columns.

catalyst structure was performed by varying the hydrophobic group and keeping the tertiary amine component (morpholinyl) constant.

Thus, the catalytic potential of diamines (**1g**–**i**) synthesized from L-leucine, L-valine and L-phenylalanine were studied. These catalyst provided aldol adduct **4a** in 90%, 92% and 91% yield, dr of 94:6, 92:8, 91:9 (*syn*/*anti*) and enantioselectivity of 81% ee, 79% ee and 80% ee, respectively (Table 2, entries 7–9). Other chiral diamine catalyst, such as primary-secondary (**1j**) was also tested on this reaction, which gave the aldol product **4a** in very low enantioselectivity (10% ee) after 96 h (Table 2, entry 10). This result highlighted the importance of primary–tertiary diamine skeleton for effective aldol catalysis. The catalyst **1a** turned out to be the best organocatalyst and was used in all further optimization study.

Next, in order to study the effect of acid additive, we performed the model aldol reaction in the presence of different acids using catalyst **1a**. The aldol reaction performed in the presence of acid additive, such as benzoic acid, 2-chlorobenzoic acid and 4-nitrobenzoic acid afforded aldol adduct **4a** within a close range of enantioselectivity (78–82% ee) with almost similar diastereomeric ratio (Table 2, entries 11–13). Use of strong acid additive results in slight decrease in yield without much change in the enantioselectivity and diastereomeric ratio (Table 2, entries 14 and 15). The aldol reaction performed in the absence of acid additive yielded the aldol product **4a** in moderate enantioselectivity of 71% ee (Table 2, entry 16).

In order to find the beneficial effect of water as a solvent, we screened different organic solvents. The reaction proceeded smoothly using toluene and THF as a solvent in the model aldol reaction affording product **4a** with good enantioselectivity of 81% ee and 78% ee (Table 3, entries 1 and 2). The polar solvent (DMF, MeOH) and chlorinated (DCM, DCE) solvent were found to be poor solvent for this reaction (Table 3, entries 3–6). Acetonitrile (ACN) gave aldol product **4a** with lowest enantioselectivity of 30% ee (Table 3, entry 7).

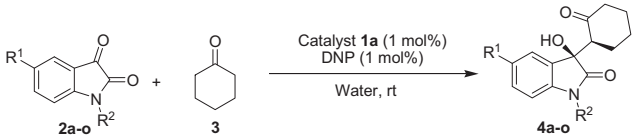
Using the optimized conditions, we studied the scope of the reaction with variety of isatin derivatives (**2a**–**m**) (Scheme 2). All aldol adducts (**4a**–**m**) were isolated in high yield (90–95%) and with good enantioselectivity (70–95% ee) (Table 4). *N*-Substituted isatin derivatives were found to afford good level of enantioselectivity as compared to *N*–H isatin derivatives. The 5-chloroisatin

Table 3
Solvent screening for **1a**-DNP catalyzed aldol reaction of cyclohexanone (**3**) with isatin (**2a**)[a]

Entry	Solvent	Time (h)	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (*syn*)
1	Toluene	24	90	94:6	81
2	THF	24	93	88:12	78
3	DMF	52	82	70:30	40
4	MeOH	30	88	77:33	53
5	CH_2Cl_2	36	86	86:14	56
6	ClCHCHCl	36	84	91:9	52
7	CH_3CN	40	80	90:10	26

[a] Reaction condition: 0.5 mmol of isatin, 5 mmol of cyclohexanone, 0.5 mL of solvent, 1 mol % catalyst **1a**1 mol % of DNP, temperature 25 °C.
[b] Isolated yield determined after chromatographic purification.
[c] Diastereoselectivity determined from HPLC spectra of crude reaction mixture.
[d] Enantiomeric excess determined from HPLC using chiralpak columns.

(**2b**) and 5-bromoisatin (**2c**) gave aldol adduct **4b** and **4c** in 94% and 95% yield, 94:6 and 91:9 (*syn*/*anti*) of dr; and 79% ee and 78% ee, respectively (Table 4, entries 2 and 3). 5-Nitroisatin (**2d**) reacted smoothly with cyclohexanone (**3**) providing aldol product **4d** in 90% yield (Table 4, entry 4). The aldol product **4d** could not be resolved on HPLC. The *N*-substituted isatin derivatives (**2e**–**m**) react with cyclohexanone (**3**), yielding aldol adduct (**4e**–**m**) in high yield and enantiomeric excess ranging from 77 to 95% (Table 4, entries 5–13). The 5-bromo-*N*-methylisatin (**2e**) provided **4e** in 92% yield, 90:10 of dr and 88% ee (Table 4, entry 5). *N*-Methylisatin (**2f**) also reacts efficiently to give **4f** in 92% yield, but the product could not be resolved on chiral HPLC (Table 4, entry 6). 5-Fluoro-*N*-allylisatin (**2h**), 5-chloro-*N*-allylisatin (**2i**), 5-bromo-*N*-allylisatin (**2j**) and 5-iodo-*N*-allylisatin (**2k**) gave aldol products (**4h**–**k**) in 95%, 93%, 94% and 92% yield, 95:5, 91:9, 89:11 and 91:9 (*syn*/*anti*) dr and 91% ee, 90% ee, 90% ee and 88% ee, respectively (Table 4, entries 8–11). The *N*-allylisatin (**2g**) provided **4g** in good yield of 90% and good enantioselectivity of 77% ee (Table 3, entry 7). 5-Bromo-*N*-benzylisatin (**2m**) provided aldol adduct **4m** in good yield (94%) and high enantioselectivity (95% ee), while *N*-benzylisatin (**2l**) provided aldol adduct **4l** in good yield (93%) and moderate enantioselectivity (70% ee) (Table 4, entries 12 and 13).



(**2a**) R^1 = H, R^2 = H; (**2b**) R^1 = Cl, R^2 = H;
(**2c**) R^1 = Br, R^2 = H; (**2d**) R^1 = NO_2, R^2 = H;
(**2e**) R^1 = Br, R^2 = -CH_3; (**2f**) R^1 = H, R^2 = -CH_3;
(**2g**) R^1 = H, R^2 = -$CH_2CH{=}CH_2$; (**2h**) R^1 = F, R^2 = -$CH_2CH{=}CH_2$;
(**2i**) R^1 = Cl, R^2 = -$CH_2CH{=}CH_2$; (**2j**) R^1 = Br, R^2 = -$CH_2CH{=}CH_2$;
(**2k**) R^1 = I, R^2 = -$CH_2CH{=}CH_2$ (**2l**) R^1 = H, R^2 = -C_6H_5;
(**2m**) R^1 = Br, R^2 = -C_6H_5

Scheme 2. Aldol reaction of cyclohexanone with isatins.

The absolute configuration of aldol adduct **4a** was assigned as (*R*,*S*) on the basis of the single crystal X-ray structure analysis.[15] The single crystal was obtained by crystallization from 2-propanol (Fig. 2).

Further, in order to extend the scope of catalyst **1a** to acyclic ketone, we studied the direct aldol reaction of acetone (**5**) and isatin derivatives (**2**) catalyzed by 1 mol % of **1a** in the presence of DNP (1 mol %) as an additive in water (Scheme 3). The acetone (**5**) reacts with isatin (**2a**) to provide 3-acetonyl-3-hydroxy-2-oxindole (**6a**) after 74 h in high yield (90%) and good enantioselectivity (70% ee) (Table 5, entry 1). Acetone (**5**) also reacted successfully with 5-haloisatin derivatives (**2b** and **2c**) to provide aldol adducts (**6b** and **6c**) in 88% and 94% yield; and 67% ee, 71% ee, respectively (Table 5, entries 2 and 3). The *N*-alkylated isatins also undergo aldol reaction

Table 4
Substrate scope for **1a**-DNP catalyzed asymmetric direct aldol reaction of cyclohexanone (**3**) with isatin derivatives (**2**)[a]

Entry	Isatins (**2**)	Time (h)	Product (**4**)	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (%) (*syn*)
1	**2a**	24	**4a**	93	93:7	82
2	**2b**	24	**4b**	94	94:6	79
3	**2c**	24	**4c**	95	91:9	78
4	**2d**	24	**4d**	90	—	*NR*
5	**2e**	22	**4e**	92	90:10	88
6	**2f**	22	**4f**	92	—	*NR*
7	**2g**	26	**4g**	90	96:4	77
8	**2h**	26	**4h**	93	95:5	91
9	**2i**	26	**4i**	94	91:9	90
10	**2j**	26	**4j**	94	89:11	90
11	**2k**	26	**4k**	91	91:9	88
12	**2l**	30	**4l**	93	73:27	70
13	**2m**	30	**4m**	94	90:10	95

[a] Reaction condition: 0.5 mmol of isatin derivatives, 5 mmol of cyclohexanone, 0.5 mL of water, 1 mol % catalyst **1a**, 1 mol % of DNP, temperature 25 °C.
[b] Isolated yield determined after chromatographic purification.
[c] Diastereoselectivity determined from HPLC spectra of crude reaction mixture.
[d] Enantiomeric excess of syn diastereomer determined from HPLC using chiralpak columns; *NR*=not resolved on chiral HPLC.

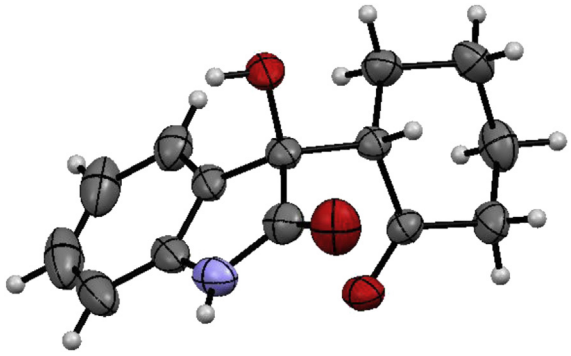
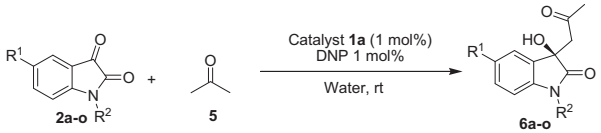


Fig. 2. ORTEP diagram of **4a**.

with acetone (**5**) to afford respective aldol adducts in good yield (85–88%) and with moderate to good level of enantioselectivity (62–80% ee) (Table 5, entries 4–8). The reaction of acetone (**5**) with *N*-methylisatin derivatives (**2e** and **2f**) provide corresponding aldol adducts (**6e** and **6f**) in 88% and 86% yield; and 69% ee and 80% ee, respectively (Table 5, entries 4 and 5). The *N*-allylisatin derivatives (**2h** and **2j**) react with acetone (**5**) to provide the respective aldol adducts (**6h** and **6j**) in 89% and 87% yield; and 69% ee and 62% ee, respectively (Table 5, entries 6 and 7). The *N*-benzylisatins derivatives **2l** react with acetone (**5**) to provide **6l** in 87% and enantioselectivity of 80% ee (Table 5, entry 8).



(**2a**) R^1 = H, R^2 = H; (**2b**) R^1 = Cl, R^2 = H;
(**2c**) R^1 = Br, R^2 = H; (**2e**) R^1 = Br, R^2 = -CH_3;
(**2f**) R^1 = H, R^2 = -CH_3; (**2h**) R^1 = H, R^2 = -$CH_2CH{=}CH_2$;
(**2j**) R^1 = Br, R^2 = -$CH_2CH{=}CH_2$; (**2l**) R^1 = H, R^2 = -C_6H_5;

Scheme 3. Aldol reaction of acetone with isatins.

A gram scale reaction was performed to demonstrate the practical utility of this reaction. The reaction of isatin (**2a**) with cyclohexanone (**3**) at 10 mmol scale using 1 mol % of **1a**-DNP resulted in

Table 5
Substrate scope for **1a**-DNP catalyzed asymmetric direct aldol reaction of acetone (**5**) with isatin derivatives (**2**)[a]

Entry	Isatins (**2**)	Time (h)	Product (**6**)	Yield[b] (%)	ee[c] (%)
1	**2a**	74	**6a**	90	70
2	**2b**	76	**6b**	88	67
3	**2c**	70	**6c**	89	71
4	**2e**	75	**6e**	88	69
5	**2f**	70	**6f**	86	80
6	**2h**	72	**6h**	89	69
7	**2j**	72	**6j**	87	62
8	**2l**	72	**6l**	87	80

[a] Reaction condition: 0.5 mmol of isatin, 5 mmol of acetone, 0.5 mL of water, 1 mol % catalyst **1a**, 1 mol % DNP, temperature 25 °C.
[b] Isolated yield determined after chromatographic purification.
[c] Enantiomeric excess determined from HPLC using chiralpak columns.

the formation of **4a** in 86% yield after 24 h, 90:10 (*syn*/*anti*) dr, and enantioselectivity of 81% ee.

Further, it was planned to investigate the success of the reaction of isatin with cyclohexanone at low catalyst loading. A similar observation has been made by Singh et al.[14] in the aldol reaction of aldehydes with acetone catalyzed by prolinamide, which was explained by Gröger et al.[16] by involving the shifting of the reaction from kinetic control to thermodynamic control. Since primary amine derived organocatalysts along with antibodies and transition metal catalysts have been known to catalyze the retro-aldol reaction,[17] therefore we envisioned that at high catalyst loading the retro-aldol would occur at a faster rate—in comparison to secondary amine—due to the ease of the primary amine to form imine–enamine intermediate with sterically demanding aldol adduct (β-hydroxyl ketone). On account of the faster rate, the reaction reaches equilibrium quickly and there is possibility of a swing of the reaction from kinetic control to thermodynamic control. At low catalyst loading the retro-aldol is very slow and the shifting of the reaction from kinetic control to thermodynamic control is not possible.

In order to explain our hypothesis we designed some experiments. Initially, the enantioselectivity of ketone aldolization between cyclohexanone (**3**) and isatin (**2a**) was studied as a function of time at two different catalyst loadings of 1 mol % and 10 mol % using catalyst **1a** and DNP as additive in 1:1 molar ratio. The change from kinetic to thermodynamic control at high catalyst loading of 10 mol % with the reaction course has been shown in Fig. 2. The decrease of enantioselectivity from 70% ee (after 5 min) to 10% ee (after 24 h) at 10 mol % of catalyst loading shows that with increasing reaction time, initially formed kinetic enantiomeric product changes into a thermodynamic controlled enantiomer, thus lowering the enantioselectivity of the product. In contrast to the above results, at low catalyst loading of 1 mol % there was no change in the enantioselectivity of the aldol product **4a** during the course of the reaction (Fig. 3).

In order to understand the effect of high catalyst loading leading to low enantioselectivity, we planned further experiments (Table 6). The aldol product **4a** (ee of 60%; dr 85:15 (*syn*/*anti*)) and catalyst **1a** was stirred at ambient temperature. Using 10 mol % of **1a**, the resulting aldol product **4a** was obtained with decreased ee of 27% and dr of 81:19 (*syn*/*anti*) after 12 h, whereas no change in the ee and minor change in dr of aldol product **4a** was observed using 1 mol % of catalyst **1a** (Table 1, entries 1 and 3). After 24 h, there was further lowering in the enantioselectivity to 10% ee and dr of 69:31 (*syn*/*anti*) with 10 mol % of catalyst loading, whereas no change in enantioselectivity[18] and slight change in diastereomeric ratio was observed using low catalyst loading of 1 mol % (Table 1, entries 2 and 4). We therefore reasoned that at high catalyst loading the retro-aldol reaction occurs rapidly leading to the breakup of kinetic aldol adduct into its precursor, which recombines to form thermodynamic aldol adduct and kinetic aldol adduct, thus shifting

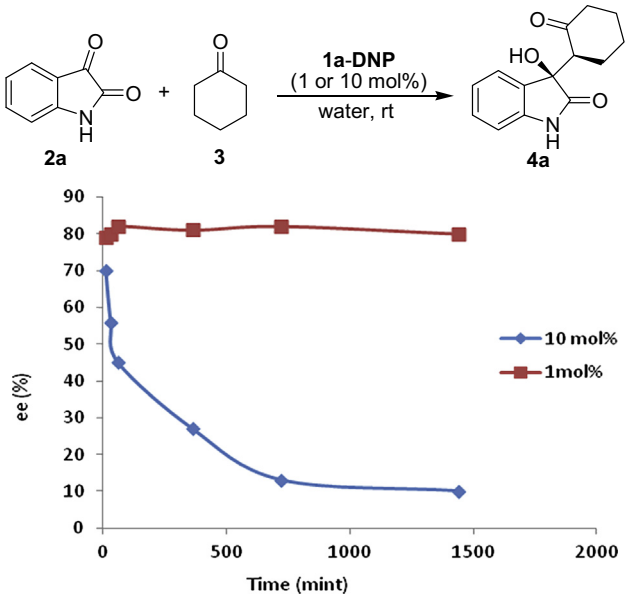
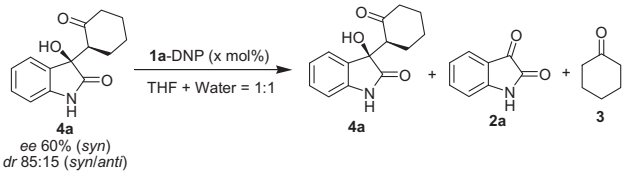


Fig. 3. Study of enantioselectivity as a function of time.

Table 6
Study of change in enantioselectivity of **4a** (dr of 85:15 (*syn*/*anti*) and 60% ee) at 10 and 1 mol % of catalyst loading

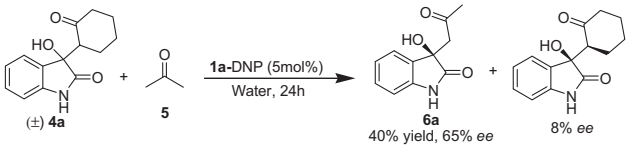


Entry	Catalyst loading (mol %)	Time (h)	dr[a] (*syn*/*anti*)	ee[b] (%)	Isatin[c] (%)
1	10	12	81:19	27	6
2	10	24	69:31	10	7
3	1	12	84:16	60	9
4	1	24	82:18	61	10

[a] Diastereoselectivity determined from HPLC spectra of crude reaction mixture.
[b] Enantiomeric excess determined from HPLC using chiralpak columns.
[c] Recovered isatin determined from HPLC.

the reaction from kinetic control to thermodynamic control. But at low catalyst loading, the retro-aldol is very slow and change from kinetic to thermodynamic control nearly ceases.

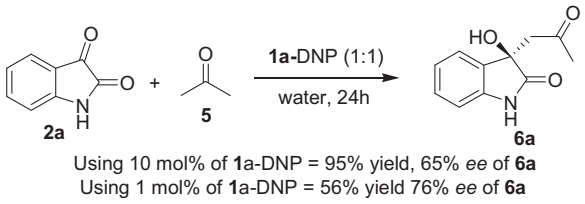
In order to support our hypothesis of fast retro-aldol at high catalyst loading (10 mol %) contrary to the very slow retro-aldol at low catalyst loading (≤1 mol %), we further studied the transfer aldol reaction (Scheme 4). The transfer aldol reaction of racemic **4a** with excess of acetone using 5 mol % of catalyst **1a** in water at



Scheme 4. Transfer aldol reaction.

ambient temperature for 24 h provided the transfer aldol adduct **6a** with 65% ee and 40% yield. But, on performing the transfer aldol reaction using 1 mol % of catalyst **1a**, it provided the transfer aldol adduct **6a** after 24 h in traces, thus confirming the occurrence of retro-aldol at 10 mol % of catalyst loading.

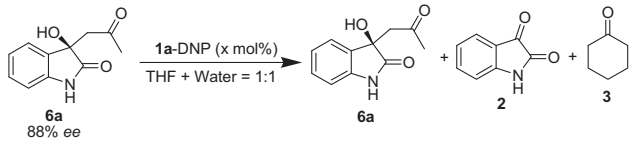
Next, we studied the ketone aldolization of acetone with isatin (**2a**) in water at two different catalyst loadings of diamine **1a** in the presence of DNP additive (Scheme 5). While on the one hand the 1 mol % of catalyst **1a** afforded product **6a** in 55% yield with 76% ee after 24 h, on the other hand the *R* isomer of aldol product **6a** was isolated in 95% yield and enantiomeric excess of 65% ee after 24 h of reaction time using 10 mol % of catalyst **1a**. This decrease in the enantioselectivity of **6a** at high catalyst loading—although not as profound as observed in the case of product **4a**—is understood to be due to the retro-aldol reaction.



Scheme 5. Direct aldol reaction of acetone with isatin.

In order to demonstrate the effect of catalyst loading on the enantioselectivity of **6a**, the aldol product **6a** (88% ee) was stirred with 10 mol % of catalyst **1a** at ambient temperature, provided the aldol product **6a** with decreased enantioselectivity of 65% ee after 24 h (Table 7, entry 1). On performing the similar reaction using 1 mol % of catalyst **1a** the aldol adduct **6a** was isolated with almost same enantioselectivity (87% ee) as of the initial aldol adduct **6a** (Table 7, entry 2). The above results also support our hypothesis that fast retro-aldol at high catalyst loading leads to decrease in the enantioselectivity due to the shifting of reaction from kinetic control to thermodynamic control.

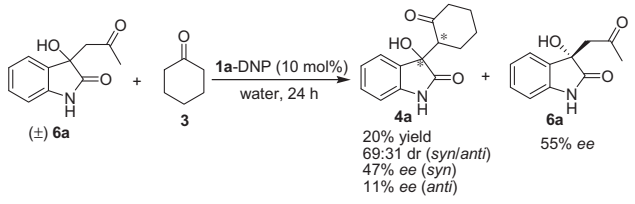
Table 7
Study of change in enantioselectivity of **6a** (88% ee) at 10 mol % and 1 mol % of catalyst loading



Entry	Catalyst loading (mol %)	Time (h)	ee[a] (%)	Isatin[b] (%)
1	10	24	65	9
2	1	24	87	11

[a] Enantiomeric excess determined from HPLC using chiralpak columns.
[b] Recovered isatin determined from HPLC.

Further, in order to provide additional support to our hypothesis, we studied the transfer aldol reaction of racemic **6a** (Scheme 6). The stirring of (±) **6a** with excess cyclohexanone using 10 mol % of **1a** in water at ambient temperature for 24 h gave the transfer aldol adduct **4a** in 20% yield with dr of 69:31 (*syn*/*anti*) and 47% ee of major diastereomer. The initial aldol adduct **6a** was obtained in 70% yield and also with the enantio-enrichment of *S* isomer to 55% ee, thus confirming our hypothesis.



Scheme 6. Transfer aldol reaction.

3. Conclusions

In conclusion, we have developed a highly efficient primary amine based organocatalysts for ketone–ketone aldolization. Low catalyst concentration was used to catalyze the direct aldol reaction between cyclohexanone/acetone and isatin derivatives to procure biologically relevant 3-substituted-3-hydroxy-2-oxindoles. The methodology is very simple and environmentally benign and highly enantioselective. Water as a solvent and low catalyst concentration is the important asset of this methodology.

Retro-aldol at high catalyst loading forces the reaction to reach equilibrium quickly and shift the reaction from kinetic to thermodynamic control. Low catalyst loading leads to slow retro-aldol reaction and the shift of the reaction from kinetic to thermodynamic control is nearly nonexistent.

4. Experimental section

4.1. General remarks

NMR spectra were obtained at 300 MHz (Jeol AL-300) and 400 MHz (Bruker Avance 400 MHz) using $CDCl_3$ and DMSO-d_6 as solvent with Me_4Si in $CDCl_3$ as the internal standard. Chemical shifts (δ) are expressed in parts per million and Hertz downfield from internal TMS. Spectral patterns are designated as s=singlet; d=doublet; dd=doublet of doublets; t=triplet; br=broad; m=multiplet. Optical rotation was determined with JASCO DIP-360 polarimeter at 25 °C. HRMS were recorded on a UPLC-Q-TOF. Enantiomeric excess was determined by using Shimadzu LC-20AD using Daicel Chiralpak AD-H, ODH, AS-H and IB column. Column chromatography was performed on 60–120 mesh silica (Spectrochem, India) using mixtures of hexane and ethyl acetate as an eluents.

4.2. General procedure for enantioselective aldol reactions

To a stirring mixture of catalyst **1a** (0.005 mmol) and cyclohexanone/acetone (5 mmol) in water (500 μL), additive DNP (0.920 mg, 0.005 mmol) was added at 25 °C and the mixture was allowed to stir for 5 min followed by addition of isatin derivative (0.5 mmol). The mixture was stirred for 20–96 h and the progress of the reaction was monitored at regular intervals by TLC. On the completion of reaction, saturated solution of NH_4Cl (5 mL) was added to it and resulting mixture was extracted with ethyl acetate (3×15 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain crude aldol product. The column chromatography on silica gel (60–120 mesh) using hexane/ethyl acetate as an eluent gave the corresponding aldol adducts as a *syn*/*anti* mixture. The enantiomeric excess of aldol addition products was determined by chiral HPLC. The diastereoselectivity of product was determined by HPLC of crude reaction mixture. Racemic standards were prepared using (±) 3-methyl-1-morpholinobutan-2-amine catalyst synthesized form (±) valine.

Spectral data of compounds **4a**,[4a] **4b**,[4a] **4c**,[4a] **4f**,[5h] **4l**,[5h] **6a**,[3] **6b**,[5b] **6c**,[3] **6e**,[5b] **6f**,[3] **6h**[5e] and **6m**[3] were in excellent agreement with those in the literature.

4.2.1. (R)-3-Hydroxy-3-((S)-2′-oxocyclohexyl)indolin-2-one[4a] ***(4a)***. White solid; yield=93%; mp=176–178 °C (lit.[5h] mp 159 °C); R_f (60% EtOAc/hexane) 0.24; $[\alpha]_D^{25}$ +65 (*c* 0.1, MeOH); *syn*/*anti*=82:18; enantiomeric excess: 82% of syn diastereomer determine by HPLC (Diacel chiralpak AS-H, hexane/*i*-PrOH, 60:40, 1.0 mL/min, λ=254 nm, t_R (*syn*, major)=14.2 min, t_R (*syn*, major)=35.3 min); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.43–1.98 (m, 6H, CH_2), 2.25–2.36 (m, 1H, CH_2), 2.53–2.57 (m, 1H, CH_2), 3.04–3.10 (m, 1H, CH), 5.8 (s, 1H,

OH), 6.77–6.87 (m, 2H, ArH), 7.13–7.25 (m, 2H, ArH), 10.17 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.4, 26.6, 26.7, 41.4, 57.3, 73.9, 109.4, 120.8, 124.7, 128.5, 130.8, 143.4, 178.6, 209.1; *m*/*z* (TOF): 268.9803 (M^++Na).

4.2.2. (R)-5-Chloro-3-hydroxy-3-((S)-2′-oxocyclohexyl)indolin-2-one[4a] (***4b***). White solid; yield=94%; mp=182–184 °C; R_f (60% EtOAc/hexane) 0.27; $[\alpha]_D^{25}$ +62 (*c* 0.1, MeOH); *syn*/*anti*=94:6; enantiomeric excess: 79% of syn diastereomer determined by HPLC (Diacel Chiralpak IB; hexane/*i*-PrOH 80:20; flow rate 0.5 mL/min; λ=254 nm, t_R (*syn*, major)=21.0 min, t_R (*syn*, minor)=28.2 min); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.50–2.04 (m, 6H, CH_2); 2.27–2.54 (m, 2H, CH_2), 3.05–3.11 (m, 1H, CH), 5.99 (s, 1H, OH), 6.79 (d, *J*=8.1 Hz, 1H, ArH), 7.17–7.23 (m, 2H, ArH), 10.34 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.9, 27.1, 41.9, 57.8, 74.4, 111.2, 125.2, 128.7, 133.3, 142.8, 178.8, 209.7; *m*/*z* (TOF): 302.0302 (M^++Na).

4.2.3. (R)-5-Bromo-3-hydroxy-3-((S)-2′-oxocyclohexyl)indolin-2-one[4a] (***4c***). White solid; yield=95%; mp=187–189 °C; R_f (60% EtOAc/hexane) 0.28; $[\alpha]_D^{25}$ +71 (*c* 0.1, MeOH); *syn*/*anti*=91:9; enantiomeric excess: 78% of syn diastereomer determined by HPLC (Diacel Chiralpak AD-H; hexane/*i*-PrOH 92:8; flow rate 0.8 mL/min; λ=254 nm, t_R (*syn*, major)=71.9 min, t_R (*syn*, minor)=54.9 min); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.47–2.04 (m, 6H, CH_2), 2.26–2.58 (m, 2H, CH_2), 3.04–3.11 (m, 1H, CH), 5.98 (s, 1H, OH), 6.74 (d, *J*=8.1 Hz, 1H, ArH), 7.28–7.42 (m, 2H, ArH), 10.34 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.9, 27.1, 27.2, 41.9, 57.9, 74.4, 111.9, 113.0, 127.9, 131.8, 133.8, 143.3, 178.7, 209.8; *m*/*z* (TOF): 347.9740 (M^++Na).

4.2.4. (R)-3-Hydroxy-5-nitro-3-((S)-2′-oxocyclohexyl)indolin-2-one (***4d***). White solid; yield=90%; mp=198–200 °C; R_f (50% EtOAc/hexane) 0.21; $[\alpha]_D^{25}$ +65 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.60–1.93 (m, 3H, CH_2); 2.01–2.40 (m, 4H, CH_2), 2.75–2.79 (m, 1H, CH_2), 3.22–3.30 (m, 1H, CH), 6.20 (s, 1H, OH), 6.93–7.01 (m, 1H, ArH), 8.06–8.22 (m, 2H, ArH), 10.81 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 209.3, 179.4, 150.1, 141.8, 131.5, 125.9, 120.3, 109.4, 73.8, 57.8, 41.6, 27.7, 26.9, 24.8; *m*/*z* (TOF): 313.0865 (M^++Na).

4.2.5. (R)-5-Bromo-3-hydroxy-1-methyl-3-((S)-2′-oxocyclohexy)indolin-2-one (***4e***). White solid; yield=92%; mp=164–166 °C; R_f (50% EtOAc/hexane) 0.42; $[\alpha]_D^{25}$ +45 (*c* 0.1, MeOH); *syn*/*anti*=90:10; enantiomeric excess: 88% of syn diastereomer determined by HPLC (Diacel Chiralpak OD-H; hexane/*i*-PrOH 97.5:2.5; flow rate 1 mL/min; λ=254 nm, t_R (*syn*, major)=54.7 min, t_R (*syn*, minor)=68.5 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.63–1.59 (m, 4H, CH_2), 2.14–1.92 (m, 3H, CH_2), 2.44–2.28 (m, 1H, CH_2), 2.97–3.01 (m, 1H, CH), 3.16 (s, 3H, NCH_3), 4.70 (br s, 1H, OH), 6.71 (d, *J*=8.7 Hz, 1H, ArH), 7.43–7.45 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.4, 26.0, 26.2, 27.0, 42.0, 55.7, 76.5, 109.7, 115.4, 127.4, 130.8, 132.6, 143.5, 176.2, 211.2; *m*/*z* (TOF): 360.0315 (M^++Na).

4.2.6. (R)-3-Hydroxy-1-methyl-3-((S)-2′-oxocyclohex-1′-yl)indolin-2-one[5h] (***4f***). White solid; yield=92%; mp=144–146 °C; R_f (50% EtOAc/hexane) 0.40; $[\alpha]_D^{25}$ +35 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.55–1.75 (m, 4H, CH_2), 1.88–2.07 (m, 2H, CH_2), 2.25–2.47 (m, 2H, CH_2), 2.91–3.01 (m, 1H, CH), 3.19 (s, 3H, NCH_3), 4.86 (br s, 1H, OH), 6.82 (d, *J*=5.7 Hz, 1H, ArH), 7.04–7.08 (m, 1H, ArH), 7.27–7.35 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.5, 26.0, 26.1, 27.1, 42.1, 55.5, 76.7, 108.3, 122.8, 123.9, 128.8, 129.9, 144.4, 176.6, 211.7; *m*/*z* (ESI): 256.2 (M^++H).

4.2.7. (R)-1-Allyl–3-hydroxy-3-((S)-2′-oxocyclohexyl)indolin-2-one (***4g***). White solid; yield=90%; mp=109–111 °C; R_f (50% EtOAc/hexane) 0.45; $[\alpha]_D^{25}$ +37 (*c* 0.1, MeOH); *syn*/*anti*=96:4; enantiomeric excess: 77% of syn diastereomer determined by HPLC (Diacel Chiralpak AS-H; hexane/*i*-PrOH 93:7; flow rate 1 mL/min; λ=254 nm, t_R (*syn*, major)=33.3 min, t_R (*syn*, minor)=46.2 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.57–1.68 (m, 4H, CH_2), 1.89–2.04 (m, 2H, CH_2), 2.30–2.49 (m, 2H, CH_2), 2.97–3.00 (m, 1H, CH), 4.18–4.24 (m, 1H, $-CH_aH_b-CH=CH_2$), 4.38–4.45 (m, 1H, $-CH_aH_b-CH=CH_2$), 4.76 (br, 1H, OH), 5.21–5.34 (m, 2H, $-CH=CH_2$), 5.82–5.86 (m, 1H, $-CH=CH_2$), 6.80–6.83 (d, *J*=7.5 Hz, 1H, ArH), 7.02–7.07 (m, 1H, ArH), 7.27–7.35 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.4, 25.9, 27.0, 41.9, 42.3, 55.6, 76.7, 109.2, 117.6, 122.7, 124.0, 128.8, 129.7, 131.2, 143.6, 176.5, 211.4; HRMS (ESI) *m*/*z*: [M^++Na] calcd for $C_{17}H_{19}NO_3$ 308.1263; found 308.1230.

4.2.8. (R)-1-Allyl-5-fluoro-3-hydroxy-3-((S)-2′-oxocyclohexyl)indolin-2-one (***4h***). Sticky solid; yield=93%; R_f (50% EtOAc/hexane) 0.46; $[\alpha]_D^{25}$ +34 (*c* 0.1, MeOH); *syn*/*anti*=95:5; enantiomeric excess: 91% of syn diastereomer determined by HPLC (Diacel Chiralpak OD-H; hexane/*i*-PrOH 95:5; flow rate 1 mL/min; λ=254 nm, t_R (*syn*, major)=19.4 min, t_R (*syn*, minor)=23.0 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.57–168 (m, 4H, CH_2), 1.94–2.14 (m, 2H, CH_2), 2.25–2.46 (m, 2H, CH_2), 2.97–3.03 (m, 1H, CH), 4.15–4.22 (m, 1H, $-CH_aH_b-CH=CH_2$), 4.37–4.44 (m, 1H, $-CH_aH_b-CH=CH_2$), 4.74 (br s, 1H, OH), 5.23–5.34 (m, 2H, $-CH=CH_2$), 5.77–5.90 (m, 1H, $-CH=CH_2$), 6.73–6.77 (m, 1H, ArH), 6.95–7.02 (m, 1H, ArH), 7.07–7.11 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.4, 26.1, 27.1, 41.9, 42.5, 55.7, 76.8, 109.9, 112.5, 116.0, 131.0, 139.6, 157.6, 160.8, 176.3, 211.2; HRMS (ESI) *m*/*z*: [M^++Na] calcd for $C_{17}H_{18}FNNaO_3$ 326.1168; found 326.1264.

4.2.9. (R)-1-Allyl-5-chloro-3-hydroxy-3-((S)-2′-oxocyclohexyl)indolin-2-one (***4i***). White solid; yield=94%; mp=149–151 °C; R_f (50% EtOAc/hexane) 0.41; $[\alpha]_D^{25}$ +41 (*c* 0.1, MeOH); *syn*/*anti*=91:9; enantiomeric excess: 90% of syn diastereomer determined by HPLC (Diacel Chiralpak AD-H; hexane/*i*-PrOH 95:5; flow rate 1 mL/min; λ=254 nm, t_R (*syn*, major)=39.5 min, t_R (*syn*, minor)=47.3 min); ^{1}H NMR (300 MHz, $CDCl_3$): 1.56–1.77 (m, 4H, CH_2), 1.93–2.13 (m, 2H, CH_2), 2.25–2.47 (m, 2H, CH_2), 2.97–3.03 (m, 1H, CH), 4.15–4.22 (m, 1H, $-N-CH_aH_b-CH=CH_2$), 4.37–4.44 (m, 1H, $-N-CH_aH_b-CH=CH_2$), 4.67 (s, 1H, OH), 5.22–5.33 (m, 2H, $-CH=CH_2$), 5.77–5.88 (m, 1H, $-CH=CH_2$), 6.73–6.76 (m, 1H, ArH), 7.24–7.32 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.5, 25.3, 27.2, 41.9, 42.5, 55.7, 76.5, 110.8, 115.4, 118.9, 128.4, 131.8, 133.4, 142.7, 176.0, 211.5; HRMS (ESI) *m*/*z*: [M^++Na] calcd for $C_{17}H_{18}ClNNaO_3$ 342.0873; found 342.0874.

4.2.10. (R)-1-Allyl-5-bromo-3-hydroxy-3-((S)-2′-oxocyclohexyl)indolin-2-one (***4j***). White solid; yield=94%; R_f (50% EtOAc/hexane) 0.49; mp=158–160 °C; $[\alpha]_D^{25}$ +40 (*c* 0.1, MeOH); *syn*/*anti*=89:11; enantiomeric excess: 90% of syn diastereomer determined by HPLC (Diacel Chiralpak OD-H; hexane/*i*-PrOH 95:5; flow rate 1 mL/min; λ=254 nm, t_R (*syn*, major)=19.6 min, t_R (*syn*, minor)=27.0 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52–1.87 (m, 4H, CH_2), 1.89–2.18 (m, 2H, CH_2), 2.22–2.46 (m, 2H, CH_2), 4.21–4.23 (m, 1H, $N-CH_aH_b-CH=CH_2$), 4.37–4.44 (m, 1H, $N-CH_aH_b-CH=CH_2$), 4.75 (s, 1H, OH), 5.22–5.33 (m, 2H, $-CH=CH_2$), 5.72–5.83 (m, 1H, $-CH=CH_2$), 6.68–6.72 (m, 1H, ArH), 7.39–7.59 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.5, 25.2, 27.1, 41.9, 42.4, 55.9, 76.4, 110.8, 115.4, 117.9, 127.4, 130.8, 132.4, 142.7, 176.0, 211.0; HRMS (ESI) *m*/*z*: [M^++Na+2H] calcd. for $C_{17}H_{18}BrNO_3$ 388.0524; found 388.0512.

4.2.11. (R)-1-Allyl-5-iodo-3-hydroxy-3-((S)-2′-oxocyclohexyl)indolin-2-one (***4k***). White solid; yield=91%; mp=135–137 °C; R_f (50% EtOAc/hexane) 0.51; $[\alpha]_D^{25}$ +43 (*c* 0.1, MeOH); *syn*/*anti*=91:9; enantiomeric excess: 88% of syn diastereomer determined by HPLC (Diacel Chiralpak OD-H; hexane/*i*-PrOH 93:7; flow rate 1 mL/min; λ=254 nm, t_R (*syn*, major)=19.8 min, t_R (*syn*, minor)=37.9 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60–1.80 (m, 4H, CH_2); 1.92–2.14 (m, 2H,

CH_2), 2.25–2.45 (m, 2H, CH_2), 2.97–3.03 (m, 1H, CH), 4.14–4.21 (m, 1H, $-CH_aH_b-CH=CH_2$), 4.35–4.44 (m, 1H, $-CH_aH_b-CH=CH_2$), 4.71 (br s, 1H, OH), 5.22–5.33 (m, 2H, $-CH=CH_2$), 5.74–5.88 (m, 1H, $-CH=CH_2$), 6.58–6.62 (m, 1H, ArH), 7.58–7.75 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.9, 26.4, 27.5, 42.4, 42.8, 56.1, 76.9, 85.7, 111.8, 118.4, 131.2, 133.4, 134.5, 138.9, 143.8, 176.2, 211.6; HRMS (ESI) *m*/*z*: [M^++Na] calcd for $C_{17}H_{18}INNaO_3$ 434.0229; found 434.0213.

4.2.12. (R)-1-Benzyl-3-hydroxy-3-((S)-2′-oxocyclohexyl)indolin-2-one[5h] (***4l***). White solid; yield=93%; mp=180–182 °C; R_f (50% EtOAc/hexane) 0.54; $[\alpha]_D^{25}$ +51 (*c* 0.1, MeOH); *syn*/*anti*=73:27; enantiomeric excess: 70% of syn diastereomer determined by HPLC (Diacel Chiralpak OD-H; hexane/*i*-PrOH 95:5; flow rate 1 mL/min; λ=254 nm, t_R (*syn*, major)=25.7 min, t_R (*syn*, minor)=42.8 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.58–2.02 (m, 6H, CH_2) 2.32–2.52 (m, 2H, CH_2), 2.97–3.06 (m, 1H, CH) 3.26–3.32 (m, 1H, CH), 4.79–4.85 (m, 1H, CH_aH_bPh), 4.92–5.01 (m, 1H, CH_aH_bPh), 6.67–6.72 (m, 1H, ArH), 6.99–7.04 (m, 1H, ArH), 7.17–7.46 (m, 7H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.5, 26.0, 27.2, 42.0, 43.9, 55.4, 76.5, 109.5, 122.9, 124.0, 125.4, 127.3, 127.5, 128.7, 128.8, 128.9, 129.8, 135.6, 143.6, 176.8, 211.7; *m*/*z* (TOF) 358.1531 (M^++Na).

*4.2.13. (R)-1-Benzyl-5-bromo-3-hydroxy-3-((S)-2′-oxocyclohexyl)indolin-2-one (****4m****).* White solid; yield=94%; mp=193–195 °C; R_f (40% EtOAc/hexane) 0.57; $[\alpha]_D^{25}$ +57 (*c* 0.1, MeOH); *syn*/*anti*=90:10; enantiomeric excess: 95% of syn diastereomer determined by HPLC (Diacel Chiralpak OD-H; hexane/*i*-PrOH 97:3; flow rate 1 mL/min; λ=254 nm, t_R (*syn*, major)=18.4 min, t_R (*syn*, minor)=29.3 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.58–2.19 (m, 6H, CH_2), 2.29–2.47 (m, 2H, CH_2), 3.05–3.08 (m, 1H, CH), 4.75–4.96 (m, 3H, CH_2 and OH), 6.51–6.57 (m, 1H, ArH), 7.25–7.31 (m, 6H, ArH), 7.43–7.58 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.4, 26.1, 27.1, 41.9, 43.9, 55.8, 76.5, 110.9, 115.4, 127.1, 127.4, 127.6, 128.7, 128.8, 130.9, 132.4, 135.0, 142.7, 176.5, 211.0; *m*/*z* (TOF): 435.5583 (M^++Na).

4.2.14. (R)-3-Hydroxy-3-(2′-oxopropyl)indolin-2-one[3] (***6a***). White solid; yield=90%; mp=180–181 °C (lit.[5b] mp 166–168 °C); R_f (60% EtOAc/hexane) 0.22; $[\alpha]_D^{25}$ +23 (*c* 0.1, MeOH); enantiomeric excess: 70% determined by HPLC (Diacel Chiralpak AD-H; hexane/*i*-PrOH 70:30; flow rate 1 mL/min; λ=254 nm, t_R (major)=7.8 min, t_R (minor)=6.4 min); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.00 (s, 3H, CH_3), 3.04 (d, *J*=17.4 Hz, 1H, CH2), 3.36 (d, *J*=17.4 Hz, 1H, CH_2), 6.07 (s, 1H, OH), 6.75–6.84 (m, 2H, ArH), 7.10–7.21 (m, 2H, ArH), 10.33 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 30.5, 50.2, 72.3, 109.3, 121.1, 123.6, 128.9, 131.5, 142.4, 178.1, 205.1.

4.2.15. (R)-5-Chloro-3-hydroxy-3-(2′-oxopropyl)indolin-2-one[5b] (***6b***). White solid; yield=88%; mp=196–198 °C (lit.[5b] mp 158–159 °C); R_f (60% EtOAc/hexane) 0.24; $[\alpha]_D^{25}$ +24 (*c* 0.1, MeOH); enantiomeric excess: 67% determined by HPLC (Diacel Chiralpak AS-H; hexane/*i*-PrOH 70:30; flow rate 1 mL/min; λ=254 nm, t_R (major)=7.7 min, t_R (minor)=5.9 min); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.00 (s, 3H, CH_3), 3.05 (d, *J*=17.4 Hz, 1H, CH_2), 3.37 (d, *J*=17.4 Hz, 1H, CH_2), 6.08 (s, 1H, OH), 6.77 (m, 1H, ArH), 7.20 (dd, *J*=8.4, 2.1 Hz, 1H, ArH), 7.30 (d, *J*=2.1 Hz, 1H, ArH), 10.33 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 30.3, 50.0, 72.6, 110.9, 124.0, 125.2, 128.7, 133.8, 141.6, 177.9, 205.4.

4.2.16. (R)-5-Bromo-3-hydroxy-3-(2′-oxopropyl)indolin-2-one[3] (***6c***). White solid; yield=89%; mp=201–203 °C (lit.[5b] mp 145–147 °C); R_f (60% EtOAc/hexane) 0.25; $[\alpha]_D^{25}$ +31 (*c* 0.1, MeOH); enantiomeric excess: 71% determined by HPLC (Diacel Chiralpak AS-H; hexane/*i*-PrOH 70:30; flow rate 1 mL/min; λ=254 nm, t_R (major)=10.6 min, t_R (minor)=8.7 min); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.00 (s, 3H, CH_3), 3.05 (d, *J*=17.2 Hz, 1H, CH_2), 3.38 (d, *J*=17.2 Hz, 1H, CH_2), 6.07 (s, 1H, OH), 6.73 (d, *J*=8.1 Hz, 1H, ArH), 7.32–7.44 (m, 2H, ArH), 10.34 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 30.3, 50.0, 72.6, 111.5, 112.9, 126.7, 131.6, 134.2, 142.1, 177.8, 205.4.

*4.2.17. (R)-5-Bromo-3-hydroxy-1-methyl-3-(2′-oxopropyl)indolin-2-one (****6e****).* White solid; yield=88%; mp=102–104 °C; R_f (50% EtOAc/hexane) 0.33; $[\alpha]_D^{25}$ +35 (*c* 0.1, MeOH); enantiomeric excess: 69% determined by HPLC (Diacel Chiralpak OD-H; hexane/*i*-PrOH 90:10; flow rate 1.0 mL/min; λ=254 nm, t_R (major)=19.0 min, t_R (minor)=28.7 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.17 (s, 3H, CH_3), 3.01 (d, *J*=17.4 Hz, 1H, CH_2), 3.18 (s, 3H, CH_3), 3.22 (d, *J*=17.4 Hz, 1H, CH_2), 4.57 (s, 1H, OH), 6.72 (d, *J*=8.4 Hz, 1H, ArH), 7.43–7.48 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.4, 31.1, 49.0, 73.9, 110.1, 115.7, 127.2, 131.7, 132.7, 142.7, 175.8, 206.9.

4.2.18. (R)-3-Hydroxy-1-methyl-3-(2′-oxopropyl)indolin-2-one[3] (***6f***). White solid; yield=86%; mp=139–141 °C (lit.[5b] mp 153–155 °C); R_f (50% EtOAc/hexane) 0.22; $[\alpha]_D^{25}$ +36 (*c* 0.1, MeOH); enantiomeric excess: 80% determined by HPLC (Diacel Chiralpak IB; hexane/*i*-PrOH 93:7; flow rate 1.0 mL/min; λ=254 nm, t_R (major)=26.7 min, t_R (minor)=30.3 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.18 (s, 3H, CH_3), 2.94 (d, *J*=17.1 Hz, 1H, CH_2), 3.18 (d, *J*=17.1 Hz, 1H, CH_2), 3.21 (s, 3H, CH_3), 4.38 (s, 1H, OH), 6.84 (d, *J*=8.1 Hz, 1H, ArH), 7.04–7.09 (m, 1H, ArH), 7.30–7.38 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.2, 31.3, 48.8, 74.1, 108.5, 123.1, 123.7, 129.9, 137.9, 143.5, 176.3, 207.3.

4.2.19. (R)-1-Allyl-3-hydroxy-3-(2′-oxopropyl)indolin-2-one[5e] (***6h***). White solid; yield=89%; mp=110–112 °C; $[\alpha]_D^{25}$ +31 (*c* 0.1, MeOH); enantiomeric excess: 69% determined by HPLC (Diacel Chiralpak AD-H; hexane/*i*-PrOH 90:10; flow rate 1.0 mL/min; λ=254 nm, t_R (major)=13.29 min, t_R (minor)=14.58 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.17 (s, 1H, CH_3), 3.03 (d, *J*=17.4 Hz, 1H, CH_2), 3.24 (d, *J*=17.1 Hz, 1H, CH_2), 4.22–4.43 (m, 3H, CH_2 and OH), 5.23–5.34 (m, 2H, CH_2), 5.79–5.92 (m, 1H, CH_2), 6.84 (d, 1H, ArH), 7.03–7.26 (m, 1H, ArH), 7.26–7.38 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.3, 42.4, 49.1, 74.0, 109.6, 117.8, 123.1, 123.8, 129.7, 129.9, 131.0, 142.8, 176.0, 207.1.

*4.2.20. (R)-1-Allyl-5-bromo-3-hydroxy-3-(2′-oxopropyl)indolin-2-one (****6k****).* White solid, yield=87%; mp=120–122 °C; $[\alpha]_D^{25}$ +41 (*c* 0.1, MeOH); enantiomeric excess: 62% determined by HPLC (Diacel Chiralpak AD-H; hexane/*i*-PrOH 93:7; flow rate 1.0 mL/min; λ=254 nm, t_R (major)=19.6 min, t_R (minor)=21.6 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.17 (s, 1H, CH_3), 3.04 (d, *J*=17.4 Hz, 1H, CH_2), 3.24 (d, *J*=17.4 Hz, 1H, CH_2), 4.24–4.35 (m, 3H, CH_2 and OH), 5.22–5.32 (m, 2H, CH_2), 5.77–5.83 (m, 1H, CH), 6.71 (d, *J*=8.4 Hz, 1H, ArH), 7.38–7.47 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.9, 42.5, 49.2, 73.7, 111.1, 115.7, 118.0, 127.1, 130.6, 131.7, 132.6, 141.9, 175.6, 206.6.

4.2.21. (R)-1-Benzyl-3-hydroxy-3-(2′-oxopropyl)indolin-2-one[3] (***6m***). White solid, yield=87%; mp=132–134 °C (lit.[5b] mp 178–179 °C); $[\alpha]_D^{25}$ +45 (*c* 0.1, MeOH); enantiomeric excess: 80% determined by HPLC (Diacel Chiralpak AS-H; hexane/*i*-PrOH 90:10; flow rate 1.0 mL/min; λ=254 nm, t_R (major)=38.0 min, t_R (minor)=28.8 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.16 (s, 1H, CH_3), 3.06 (d, *J*=17.1 Hz, 1H, CH_2), 3.27 (d, *J*=17.1 Hz, 1H, CH_2), 4.56 (s, 1H, OH), 4.80–4.98 (m, 2H, CH_2), 6.69 (d, *J*=7.8 Hz, 1H, ArH), 7.02–7.37 (m, 8H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.2, 43.8, 49.1, 74.0, 109.6, 123.1, 123.7, 127.2, 127.6, 128.7, 129.6, 129.8, 135.3, 142.7, 176.6, 206.9.

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Supplementary data

Information about the chemicals used, experimental details and Copies of ^{1}H NMR, ^{13}C NMR, HPLC chromatogram for all compounds have been provided. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.04.044.

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