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Organocatalytic Stereoselective Synthesis of 3-Alkyl-3-hydroxy-2-oxindoles Catalyzed by Novel Water-compatible Axially Unfixed Biaryl-based Bifunctional Organocatalysts

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In this work, six novel axially unfixed biaryl-based water-compatible bifunctional organocatalysts were designed and synthesized for the organocatalytic access to a variety of 3-alkyl-3-hydroxy-2-oxindole derivatives via aldol reactions in water. Organocatalyzed by **5a**, the direct aldol reactions of isatins with enolisable ketones underwent readily in water, furnishing the structurally diverse 3-alkyl-3-hydroxy-2-oxindoles in various stereoselectivities (up to＞99% *dr* and ＞99% *ee*). Moreover, a plausible transition state of the conducted aldol reactions was hypothesized to shed light on the observed stereoselectivities of the obtained 3-alkyl-3-hydroxy-2-oxindoles.

Keywords organocatalysis, 3-alkyl-3-hydroxy-2-oxindole, water-compatibility, bifunctionality

Introduction

Chiral 3-alkyl-3-hydroxy-2-oxindoles, bearing a quaternary stereogenic center, constitute the core skeletons of many natural products and medicinal molecules which exhibited a wide range of biological and pharmaceutical activities.[1] It has been evidenced that the biological activities of the chiral 3-alkyl-3-hydroxy-2-oxindoles are closely associated with the stereochemical configuration of the quaternary C-3 center and the chemical nature of the C-3 substituent of the chiral 3-alkyl-3-hydroxy-2-oxindoles.[2] The chiral 3-alkyl-3-hydroxy-2-oxindoles were accessed by the organocatalytic aldol reactions of isatins with enolisable ketones or aldehydes concisely and efficiently.[3] By now, the different stereoselective versions of the aldol reactions of isatins with enolisable ketones or aldehydes have been established to produce the chiral 3-alkyl-3-hydroxy-2-oxindoles stereoselectively with the use of organocatalysis.[4-26] As presented in literature works, the bifunctional organocatalysis is demonstrated to be the powerful and efficient method for the stereoselective construction of chiral 3-alkyl-3-hydroxy-2-oxindoles via the aldol reactions of isatins with enolisable ketones or aldehydes. It was disclosed that the bifunctional organocatalysts used in the aldol reactions of isatins with enolisable ketones or aldehydes necessarily incorporate both the basic or nucleophilic amine functional groups as aldol donor activators and the H-bond donors as aldol acceptor activators. To the best of our knowledge, in the literatures the organocatalytic aldol reactions of isatins with the enolisable ketones and aldehydes usually underwent smoothly in organic solvents to generate the desired chiral 3-alkyl-3-hydroxy-2-oxindole in high stereocontrols. In contrast, there have been relatively few examples on the organocatalytic aldol reactions of isatins with the enolisable ketones and aldehydes by utilizing water as reaction medium.[24,26]

The development of organocatalytic aldol reactions in water has attracted much attention from many organic chemists since water is cheap, safe and benign to environment as a reaction medium.[27] It has been commented that the organocatalytic aldol reactions possessing a high stereocontrol are mainly attributed to the fact that the organocatalysts used in the aldol reactions can assembly with the aldol donors and acceptors efficiently via the hydrophobic interactions, and strongly inhibit water to interfere with the transition states of the organocatalytic aldol reactions in water.[28,29] The hydrophobic properties of the organocatalysts can be finely tuned by introducing the different bulky and hydrophobic groups into the skeletons of the organocatalysts.[30] Very recently, the bulky and hydrophobic biphenyl motif was chosen as a skeleton to construct the different classes of the water-compatible bifunctional organocatalysts, which exhibited excellent stereoselectivities in the organocatalytic reactions in water.[31-34]

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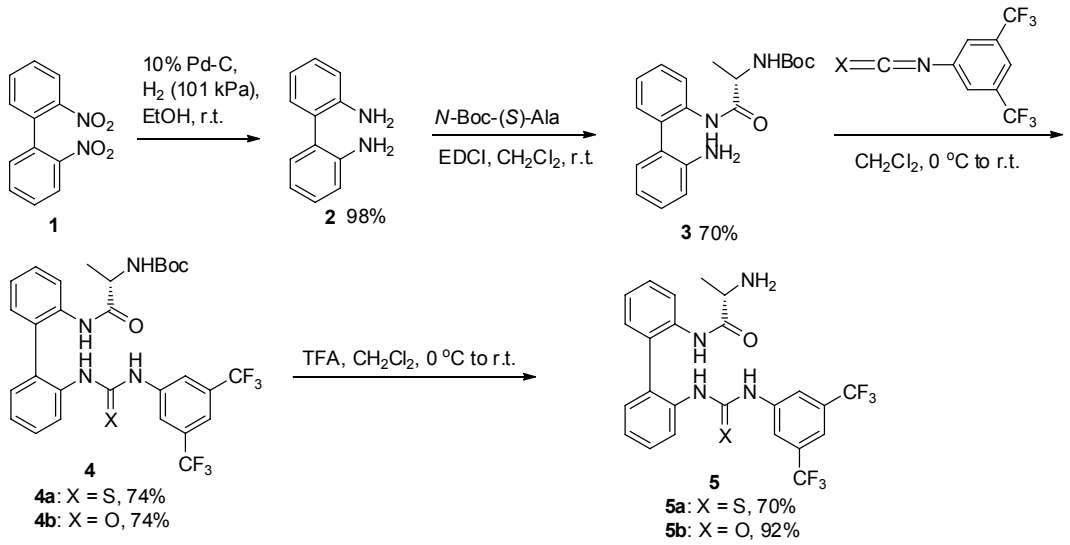
Results and discussion

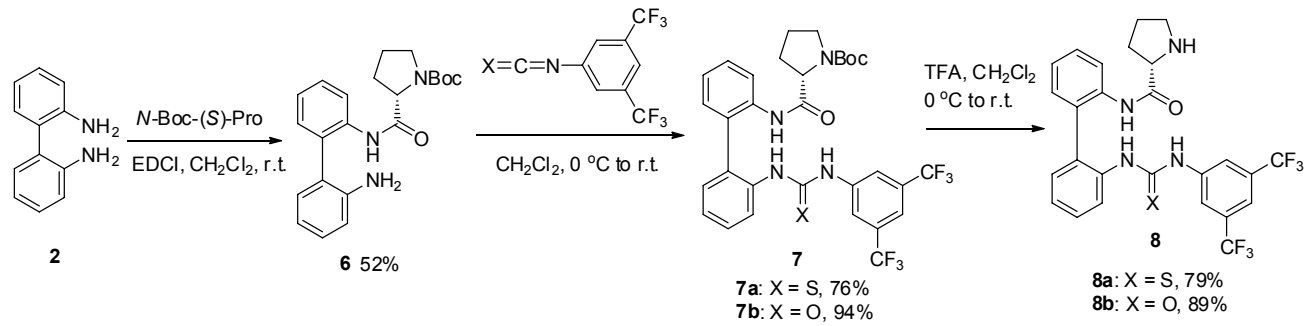
Herein, in this work we present the design and synthesis of novel axially unfixed biphenyl-based bifunctional organocatalysts, and their organocatalysis in the direct aldol reaction of isatins with enolisable ketones in water. In the case of the designed organocatalysts, the urea or thiourea and amine moieties were constructed as two organocatalytic sites: urea or thiourea functions as a double H-bond donor to activate isatins; amine serves as a nucleophile to activate enolisable ketones via the enamine mechanism. Moreover, the axially unfixed biaryl of the organocatalysts can freely adjust the spatial orientation of the organocatalytic sites present in the organocatalysts. In addition, it was envisioned that the introduction of the hydrophobic biphenyl into the organocatalysts can endow the organocatalysts with the appropriate and sufficient hydrophobicities. As a result, the organocatalysts are able to aggregate with the hydrophobic reactants strongly and exclude water efficiently from the transition states of the direct aldol reactions, thus yielding the high reactivities and stereocontrols in the direct aldol reactions in water.

As outlined in Scheme 1, the designed organocatalysts **5a**, **5b** were prepared easily by carrying out a series of chemical transformations. The catalytic hydrogenation of biphenyl **1** gave the desired product **2** in 98% yield. The condensation of **2** with *N*-Boc-(*S*)-Ala furnished product **3** in 70% yield. The subsequent treatment of **3** with 3,5-bis(trifluoromethyl)phenyl isothiocyanate or 3,5-bis(trifluoromethyl)phenyl isocyanate afforded the desired products **4a** (74% yield) and **4b** (74% yield), respectively. The deprotection of **4a** and **4b** with TFA generated organocatalysts **5a** (70% yield) and **5b** (92% yield). Similarly, organocatalysts **8a** and **8b** were obtained respectively in 79% yield and 89% yield according to Scheme 2 using *N*-Boc-(*S*)-Pro as a chiral source. Simultaneously, for the purpose of investigating the structure-activity relationship, organocatalysts **11** and **13** with a C_2-symmetry were also synthesized on the basis of Scheme 3.

Scheme 1 Synthesis of novel organocatalysts **5a**, **5b**



Scheme 2 Synthesis of novel organocatalysts **8a**, **8b**



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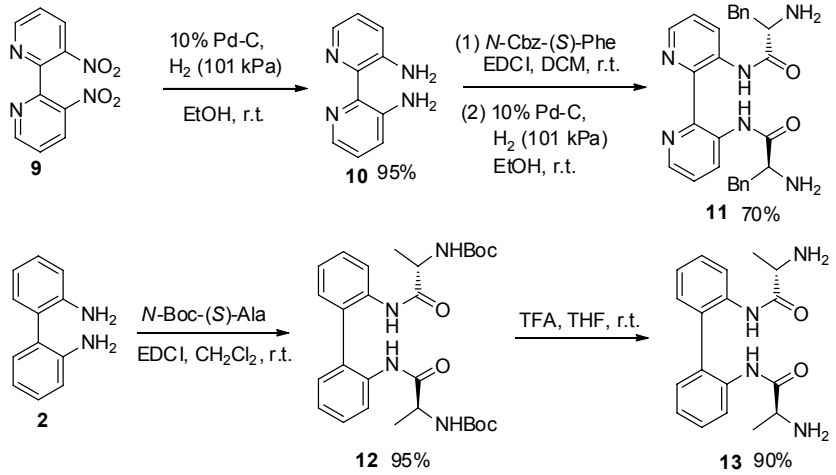
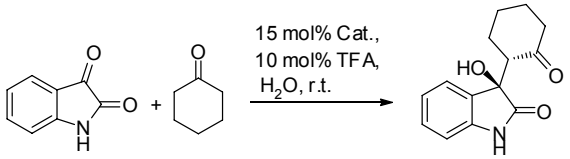
Scheme 3 Synthesis of novel organocatalysts **11** and **13**



With the prepared organocatalysts **5a**, **5b** and **8a**, **8b** in hand, we started to examine their reactivities and stereoselectivities in the direct aldol reaction of isatin with cyclohexanone in water in the presence of TFA as acidic additive as outlined in Table 1. Noticeably, organocatalysts **5a** and **5b** showed the excellent reactivities and stereoselectivities in the aldol reaction, thus furnishing the desired aldol adduct in＞99% yield with 3∶97—2∶98 *dr* and 89%—90% *ee* (Table 1, Entries 1, 2). In contrast, organocatalysts **8a** and **8b** resulted in much lower reactivities and stereoselectivities in the aldol reaction, and the aldol reaction underwent sluggishly (Table 1, Entries 3, 4). Therefore, it was reasoned that the superior organocatalytic reactivities and stereoselectivities of **5a**, **5b** to those of **8a**, **8b** probably stemmed from the existence of the primary amine moiety in their scaffolds. In addition, with a goal to clarify the effects of structural variations of organocatalysts on the reactivity and stereoselectivity of the aldol reaction, organocatalysts **11** and **13** as shown in Scheme 3 and **14**—**17** as shown in Figure 1 have been further investigated in the aldol reaction as shown in Table 1 (Entries 5—10). As compared with organocatalyst **5a**, the reactivity and stereoselectivity of organocatalyst **15** in the aldol reaction were decreased significantly, and the aldol reaction gave rise to an inverse enantioselectivity (Table 1, Entry 1 vs. Entry 8). Moreover, the organocatalysts **11** and **14** bearing a bipyridinyl moiety yielded much lower reactivities and enantioselectivities than those of organocatalyst **13** with a biphenyl subunit in the aldol reaction, and it was assumed that the presence of the bulky and hydrophobic biphenyl moiety in organocatalyst **13** ensured it to generate high reactivity and stereoselectivity in the aldol reaction (Table 1, Entry 6 vs. Entryies 5 & 7). In addition, another two organocatalysts **16** and **17** containing a biphenyl motif were also attempted in the aldol reaction, and both of them exhibited rather low activities, but significantly they differed in their diastereoselectivities and enantioselectivities in the aldol reaction (Table 1, Entry 9 vs. Entry 10). In comparison with **5a**, organocatalyst **13** gave the similar *ee* and *dr* values in the aldol reaction, but it showed a quite low reactivity (Table 1, Entry 1 vs. Entry 6). Accordingly, among all the organocatalysts examined, in the presence of TFA as an acidic additive, organocatalyst **5a** demonstrated to possess the excellent reactivity and stereoselectivity in the aldol reaction in water.

Table 1 Screening of biaryl organocatalysts[a]



Entry	Catalyst	Time/h	Yield[b]/%	*dr*[c](*syn*/*anti*)	*ee*[d]/% (*anti*)
1	**5a**	1.5	＞99	2∶98	90
2	**5b**	1.5	＞99	3∶97	89
3	**8a**	72	73	30∶70	52
4	**8b**	60	71	33∶67	48
5	**11**	12	91	4∶96	74
6	**13**	8	99	4∶96	93
7	**14**	24	91	0∶100	44
8	**15**	60	61	26∶74	–53
9	**16**	72	74	41∶59	89
10	**17**	72	40	9∶91	18

[a] Reactions were carried out with 0.1 mmol of isatin (14.7 mg) and 1.0 mmol of cyclohexanone (104.0 μL) in the presence of 15 mol% of catalyst and 10 mol% of TFA (0.8 μL) in 0.5 mL of water at room temperature. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC analysis. [d] Determined by chiral HPLC analysis.

Next, as shown in Table 2, with the use of organocatalyst **5a** we turned to investigating the acid effects on the reactivity and stereoselectivity of the aldol reaction of isatin with cyclohexanone in water. It can be seen that in the case of most acidic additives examined, the aldol reaction proceeded readily, and produced the

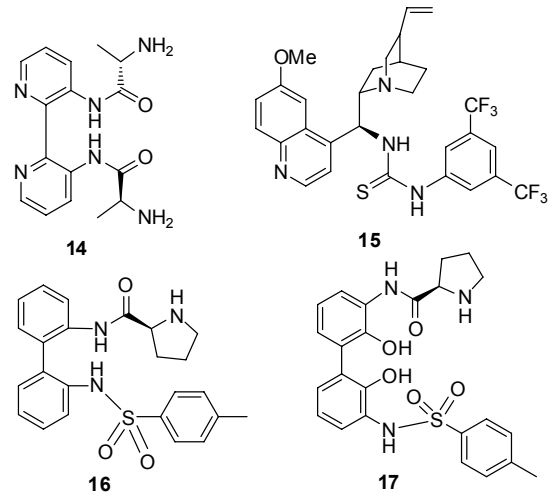
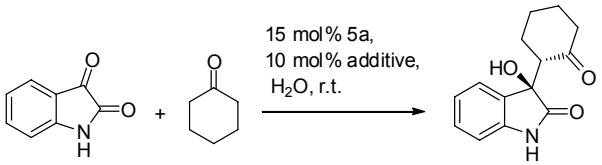


Figure 1 The known organocatalysts examined in this work.[32,33,35,36]

Table 2 Screening of acidic additives[a]



Entry	Additive	Time/h	Yield[b]/%	*dr*[c] (*syn*/*anti*)	*ee*[d]/% (*anti*)
1	HOAc	1	74	1∶99	74
2	TFA	1.5	99	2∶98	90
3	*p*-TsOH	3.5	99	1∶99	94
4	2-$HOC_6H_4CO_2H$	0.5	82	2∶98	87
5	(+)-CSA	4	94	2∶98	88
6	4-$CH_3C_6H_4CO_2H$	0.5	98	3∶97	75
7	$C_6H_5C_2H_4CO_2H$	0.8	96	3∶97	73
8	$C_6H_5CO_2H$	1	97	3∶97	80
9	2,2'-Dihydroxy-biphenyl	0.8	99	3∶97	74
10	Stearic acid	1.2	90	1∶99	77

[a] Reactions were carried out with 0.1 mmol of isatin (14.7 mg) and 1.0 mmol of cyclohexanone (104.0 μL) in the presence of 15 mol% of catalyst **5a** (7.9 mg) and 10 mol% of additive in 0.5 mL of water at room temperature. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC analysis. [d] Determined by chiral HPLC analysis.

desired product in excellent yield with excellent diastereoselectivity in favour of anti diastereoisomer; however, the enantioselectivity of the aldol reaction was changed significantly with the used acidic additives (Table 2, Entries 2−10). Remarkably, the excellent *ee* values were achieved with using TFA and *p*-TsOH as additives (Table 2, Entries 2, 3). The use of 2-$HOC_6H_4CO_2H$ and (+)-CSA as additives promoted the reaction to give the very similar enantioselectivities of the *anti* diastereoisomers (Table 2, Entries 4, 5). The aldol reactions provided the desired aldol adducts in the comparable *ee* values in the range of 73% to 80% when a wide range of other acidic additives were attempted in the aldol reaction (Table 2, Entry 1 & Entries 6−10). It is conclusive to say the best *ee* and *dr* values were obtained in the aldol reaction when organocatalyst **5a** was used along with *p*-TsOH as additive.

Also, as shown in Table 3, a wide range of organic solvents were examined in the aldol reaction of isatin with cyclohexanone, catalysed by organocatalyst **5a** in combination with *p*-TsOH as acidic additive, to clarify their effects on the reactivities and stereoselectivities of the aldol reaction. Noticeably, in the aldol reactions, the reactivities and stereoselectivities of organocatalyst **5a** were significantly influenced by the used organic solvents. When Et_2O was employed as solvent, the reaction proceeded rather sluggishly, and only a trace amount of the aldol adduct was formed after a reaction time of 60 h. The use of THF as solvent delivered the aldol adduct in 42% yield with 22∶78 *dr* and 35% *ee*. The similar chemical yields and diastereoselectivities and enantioselectivities were achieved in the aldol reactions by the choice of $CHCl_3$ and DMF as solvents (Table 3, Entry 1 vs. Entry 9). The almost same diastereoselectivities were generated in the aldol reactions, but the enantioselectivities ranged from 53% *ee* to 70% *ee* with the use of CH_3CN, benzene and toluene as solvents, respectively (Table 3, Entries 6−8). Although the reaction afforded the desired aldol adduct in high *ee* and *dr* values in *n*-hexane, the reaction rate seemed to be quite slow and furnished the aldol adduct in 36% yield in 100 h (Table 3, Entry 10). By comparison with *n*-hexane as the reaction solvent, the use of CH_2Cl_2 and MeOH as the reaction solvents improved the chemical yields and diastereoselectivities noticeably, however, the enantioselectivities of the aldol reactions varied slightly (Table 10, Entries 2 & 5 vs. Entry 10). Therefore, it is reasonable to say that it is in water that organocatalyst **5a** produced the excellent reactivity (99% yield) and stereoselectivity (1∶99 *dr* and 94% *ee*) in the aldol reaction.

After having examined the effects of organic solvents and acidic additives on the aldol reaction of isatin with cyclohexanone in the presence of **5a** as organocatalyst, we began to investigate the loading effects of organocatalyst **5a** and *p*-TsOH on the aldol reaction of isatin with cyclohexanone as summarized in Table 4. It was noted that in the absence of *p*-TsOH as additive, organocatalyst **5a** in 15 mol% loading can catalyse the aldol reaction to complete in 2 h, yielding the desired aldol adduct in 74% yield with 2∶98 *dr* and 67% *ee*. Together with *p*-TsOH in 15 mol% or 5 mol%, organocatalyst **5a** brought about the dramatic increases in the chemical yields and enantioselectivities of the aldol reaction by comparison with the case where no *p*-TsOH was utilized as additive (Table 4, Entry 1 vs. Entries 4 & 9). Moreover, to our surprise, it was found that the use of 5 mol% *p*-TsOH along with organocatalyst **5a**

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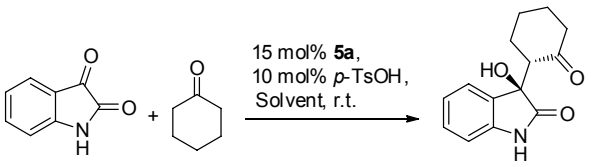
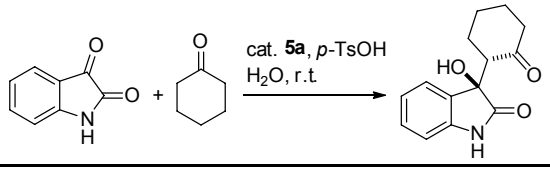
Table 3 Screening of solvents[a]



Entry	Solvent	Time/h	Yield[b]/%	*dr*[c] (*syn*/*anti*)	*ee*[d]/% (*anti*)
1	$CHCl_3$	87	28	25∶75	62
2	CH_2Cl_2	60	74	1∶99	92
3	THF	87	42	22∶78	35
4	Et_2O	60	Trace	—	—
5	MeOH	79	74	2∶98	89
6	CH_3CN	79	58	2∶98	53
7	Benzene	60	58	4∶96	70
8	Toluene	60	70	1∶99	67
9	DMF	100	30	18∶82	64
10	*n*-Hexane	100	36	11∶89	94
11	H_2O	3.5	99	1∶99	94

[a] Reactions were carried out with 0.1 mmol of isatin (14.7 mg) and 1.0 mmol of cyclohexanone (104.0 μL) in the presence of 15 mol% of catalyst **5a** (7.9 mg) and 10 mol% of *p*-TsOH (1.9 mg) in 0.5 mL of water at room temperature. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC analysis. [d] Determined by chiral HPLC analysis.

Table 4 Screening of catalytic loadings of **5a** and *p*-TsOH[a]



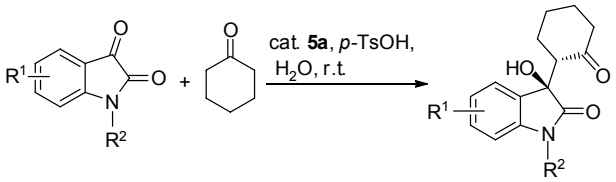
Entry	**5a**/ mol%	*p*-TsOH/ mol%	Time/h	Yield[b]/%	*dr*[c] (*syn*/*anti*)	*ee*[d]/% (*anti*)
1	15	0	2	74	2∶98	67
2	10	30	39	86	10∶90	86
3	10	20	20	94	4∶96	92
4	15	15	6	99	4∶96	84
5	10	10	8.7	99	4∶96	88
6	5	5	9.4	99	2∶98	92
7	1	1	15	99	2∶98	92
8	10	5	6.2	99	1∶99	89
9	15	5	0.7	99	1∶99	88

[a] Reactions were carried out with 0.1 mmol of isatin (14.7 mg) and 1.0 mmol of cyclohexanone (104.0 μL) in the presence of indicated amounts of catalyst and indicated amounts of *p*-TsOH in 0.5 mL of water at room temperature. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC analysis. [d] Determined by chiral HPLC analysis.

enable the aldol reaction to finish in 0.7 h; in contrast, a longer reaction of 6 h was needed for the aldol reaction to go to completion. Interestingly, it has been indicated that under catalysis of organocatalyst **5a** in 10 mol%, the reaction rate of the aldol reaction decreased as the amount of *p*-TsOH was increased in the range of 5 to 30 mol% (Table 4, Entries 2, 3, 5, 8). When both organocatalyst **5a** and *p*-TsOH were loaded in the same amount of 5 mol% in the aldol reaction, the reaction processed in excellent chemical yield (99% yield) with excellent stereoselectivity (2∶98 *dr*, 92% *ee*). To our delight, the aldol reaction remained to undergo with excellent chemical yield and stereoselectivity even when both organocatalyst **5a** and *p*-TsOH were loaded in an amount of 1 mol% in the aldol reaction, respectively. Conclusively, in the aldol reaction both the best chemical yield (99%) and stereoselectivity (1∶99 *dr*, 94% *ee*) were achieved with the use of the optimal reaction conditions of 15 mol% **5a**/10 mol% *p*-TsOH/water/room temperature.

With the optimal reaction conditions in hand, the reaction scope of the aldol reaction was broadened initially by reacting cyclohexanone with a variety of isatins as presented in Table 5. In the case of most isatins examined, the aldol reactions underwent smoothly and provided excellent *dr* values and high to excellent *ee* values (Table 5, Entries 1—4 & 6—12). It has been indicated that the enantioselectivity of the aldol reactions highly depended on the chemical structure of isatins used. For instances, 5-methyl-isatin afforded the lowest *ee* value; in contrast, the excellent *ee* values were obtained with isatin, *N*-Boc-isatin, *N*-Bn-5-nitro-isatin, *N*-Bn-5-bromo-isatin (Table 5, Entries 8, 9 & 11, 12). Moreover, it was important to note that *N*-Bn group of isatins played a crucial role in enhancing the enantioselectivity of the aldol reactions. When 5-NO_2-, 5-Br-, and 5-Me-isatins were chosen as aldol acceptors, the *ee* values of the obtained aldol adducts changed from 67% to 87% *ee* (Table 5, Entries 1, 3 & 5). By comparison, the introduction of Bn group onto *N*-position of isatins allowed for a significant increase in the enantioselectivity of the aldol adducts (Table 5, Entries 1 vs. 8, 3 vs. 9, 5 vs. 10). In contrast with isatin, the *ee* value of the aldol adduct increased slightly when *N*-Boc-isatin was utilized as an aldol acceptor. Meanwhile, as summarized in Table 6, the reaction scope of the aldol reaction was also extended by reacting different isatins with a variety of ketones. In the most cases, the aldol reactions exhibited rather low enantioselectivities (Table 6, Entries 1—5). However, it was delighted to find that the aldol reaction of *N*-Bn-5-bromo-isatin or *N*-Bn-5-NO_2-isatin with tetrahydrothiopyran-4-one gave excellent *ee* values (Table 6, Entries 6 & 7). Therefore, on the basis of the experimental results as mentioned above, it was in conclusion that the organocatalytic efficiency of organocatalyst **5a** was closely associated with the structural nature of isatins and ketones involved in the aldol reactions under the optimized reaction conditions.

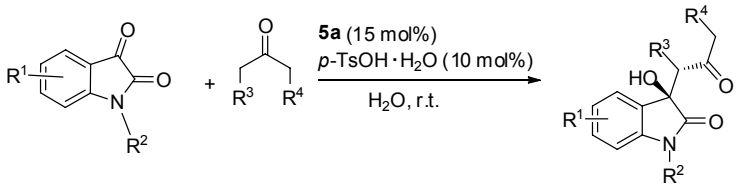
Table 5 Aldol reactions of isatins with cyclohexanone[a]



Entry	R^1	R^2	Time/h	Yield[b]/%	*dr*[c] (*syn*/*anti*)	*ee*[d]/% (*anti*)
1[e]	5-NO_2	H	6	96	>1∶99	87
2[f]	5-Cl	H	3	68	2∶98	80
3[f]	5-Br	H	6	94	3∶97	86
4[f]	4-Br	H	6	98	>1∶99	87
5[f]	5-Me	H	7.5	49	5∶95	67
6[f]	H	Me	4.5	97	1∶99	82
7[f]	H	Bn	5	96	3∶97	86
8[f]	5-NO_2	Bn	7	>99	>1∶99	98
9[f]	5-Br	Bn	10	70	3∶97	99
10[f]	5-Me	Bn	5	86	>1∶99	83
11[f]	H	Boc	4.5	91	2∶98	–98
12[f]	H	H	3.5	99	1∶99	94

[a] Reactions were carried out with 0.1 mmol of isatins and 1.0 mmol of cyclohexanone (104 μL) in the presence of 15 mol% of catalyst **5a** (7.9 mg) and 10 mol% of *p*-TsOH (1.9 mg) in 0.5 mL of water at room temperature. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC analysis. [d] Determined by chiral HPLC analysis. [e] Absolute configuration determined by comparison with the reported specific optical rotation in ref. 37. [f] Absolute configuration determined by comparison with the reported specific optical rotation in ref. [23].

Table 6 Aldol reactions of isatins with ketones[a]



Entry	R^1	R^2	R^3, R^4	Time/h	Yield[b]/%	*dr*[c] (*syn*/*anti*)	*ee*[c]/% (*anti*)
1[d]	H	H	H, H	54	80	—	5
2[e]	H	H		13	98	30∶70	26
3[e]	H	H		68	72	20∶80	21
4[e]	H	H		37	97	10∶90	57
5[e]	H	H		30	94	12∶88	25
6[e]	5-Br	Bn		24	40	38∶62	96
7[e]	5-NO_2	Bn		23	32	13∶87	>99

[a] Reactions were carried out with 0.1 mmol of isatins and 1.0 mmol of ketones in the presence of 15 mol% of catalyst **5a** (7.9 mg) and 10 mol% of *p*-TsOH (1.9 mg) in 0.5 mL of water at room temperature. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC analysis. [d] Absolute configuration determined by comparison with the reported specific optical rotation in ref. [11]. [e] Absolute configuration was not assigned.

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To elucidate the catalytic mechanism and stereoselectivity of organocatalyst **5a** in the aldol reaction of isatin with cyclohexanone, a transition state was proposed as illustrated in Figure 2. Obviously, organocatalyst **5a** has shown a bifunctional organocatalysis in the aldol reaction. As an aldol acceptor, isatin was activated by **5a** with triple H-bonds; and the activation of cyclohexanone was conducted via the enamine mechanism. Subsequent attack of *Re* of the enamine formed *in situ* on the *Si* face of 3-carbonyl of isatin delivered the stereoconfigurations which are consistent with those observed in the aldol reactions.

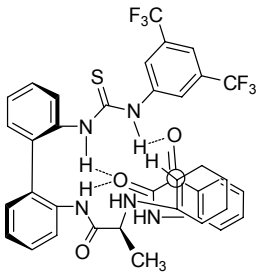

Figure 2 Proposed transition state for the aldol reaction catalyzed by **5a**.

Conclusions

In conclusion, several water-compatible organocatalysts bearing an axially unfixed biphenyl as scaffold have been designed and synthesized for the aldol reaction of a wide range of isatins and ketones in water. Under the optimal reaction conditions, organocatalyst **5a** was identified with the best organocatalytic efficiency among all the organocatalysts examined in this work, and delivered the desired aldol adducts differing in chemical yields and stereoselectivities in water. The further studies on the organocatalytic mechanisms and the utility of the water-compatible bifunctional organocatalyst in other asymmetric transformations in water are in progress in our laboratory, and will be reported in due course.

Experimental

General

All reagents were commercially available and used without further purification. All solvents were distilled from the appropriate drying agents immediately before use. All reactions were carried out directly under open air and monitored by TLC carried out on 0.25 mm SDS silica gel coated glass plates (60F254) visualized with UV light and/or with iodide. Purification of the crude products was performed using flash column chromatography on silica gel (0.035－0.070 mm). Optical rotations were measured with a Perkin-Elmer 241 polarimeter. NMR spectra were recorded on a Bruker DRX 400 instrument and calibrated using tetramethylsilane (TMS) as internal reference. High resolution mass spectra (HRMS) were recorded under electrospray ionization (ESI) conditions. Enantiomeric excesses were determined by HPLC analyses on a Waters system equipped with a photodiode array detector (monitored at 200－400 nm), using Chiracel AD, OD, AD-H, OD-H, OJ-H, and IC columns (25 cm×0.46 cm) from Daicel Chemical Ind., Ltd.

Synthesis of (*S*)-*tert*-butyl(1-((2'-amino-[1,1'-biphenyl]-2-yl)amino)-1-oxopropan-2-yl)carbamate (3)

Compound **2** was prepared according to the reported procedure and the ^{1}H NMR data were consistent with the reported values.[32] Compound **2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.20 (d, J=14 Hz, 2H), 7.13 (dd, J=19.2, 7.6 Hz, 2H), 6.82 (t, J=7.6 Hz, 2H), 6.75 (d, J=7.6 Hz, 2H), 3.68 (br s, 4H). To a well stirred solution of **2** (700 mg, 3.8 mmol) in anhydrous dichloromethane (15 mL) was added EDCI (441 mg, 2.3 mmol), and added *N*-Boc-*S*-Ala-OH (287 mg, 1.52 mmol) dropwise at 0 ℃. The resulting mixture was stirred for 0.5 h at 0 ℃. Then the reaction mixture was stirred for 3 h at room temperature. The reaction was quenched by addition of saturated $NaHCO_3$, and extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, V∶V=5∶1) to yield a white solid **3** (377 mg, 70% yield). $[\alpha]_D^{17}$ −25.4 (c 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21 (d, J=8.0 Hz, 1H), 7.38－7.41 (t, J=8.0 Hz, 1H), 7.19－7.28 (m, 4H), 7.07 (d, J=7.6 Hz, 1H), 6.80－6.89 (m, 2H), 5.15 (br s, 0.5H), 4.98 (br s, 0.5H), 4.19 (d, J=6.4 Hz, 1H), 3.65 (br s, 2H), 1.42 (d, J=8.4 Hz, 9H), 1.25－1.33 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.9, 155.2, 143.4, 135.3, 135.2, 131.1, 130.8, 129.8, 129.5, 128.7, 125.0, 123.5, 122.0, 119.5, 119.3, 116.0, 115.8, 79.9, 50.9, 28.3, 28.2, 18.7; HRMS (ESI) calcd for $C_{20}H_{25}N_3O_3$ ($M+H^+$) 356.1969, found 356.1960.

Synthesis of (*S*)-*tert*-butyl(1-((2'-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-[1,1'-biphenyl]-2-yl)amino)-1-oxopropan-2-yl)carbamate (4a)

To a well stirred solution of **3** (355 mg, 1.0 mmol) in dry CH_2Cl_2 (10 mL) was added 1-thiocyanato-3,5-bis(trifluoromethyl)benzene (200 μL, 1.1 mmol) dropwise at 0 ℃. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, V∶V=4∶1) to yield **4a** as white solid (463 mg, 74% yield). $[\alpha]_D^{17}$ −45.3 (c 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.45 (br s, 0.5H), 8.97 (br s, 0.5H), 8.38 (br s, 1H), 8.02 (br s, 1H), 7.73 (s, 1H), 7.57－7.63 (m, 3H), 7.41－7.51 (m, 3H), 7.31－7.37 (m, 4H), 4.92 (br s, 0.5H), 4.78 (d, J=6.4 Hz, 0.5H), 4.05 (t, J=7.2 Hz, 1H), 1.37－1.44 (m, 9H), 1.22 (s, 1H+0.5H), 1.13 (d, J=7.2 Hz, 1H+0.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.9, 179.4, 171.4, 171.2, 155.9, 140.3, 134.7, 134.4, 133.9, 133.7, 131.7, 131.4, 130.5, 129.1, 129.0, 128.9, 127.9, 127.4, 126.9, 125.1,

124.7, 124.4, 121.7, 121.6, 118.9, 80.1, 53.4, 50.2, 28.2, 17.5; HRMS (ESI) calcd for $C_{29}H_{28}F_6N_4O_3S$ ($M+H^+$) 627.1859, found 627.1821.

Synthesis of (*S*)-*tert*-butyl(1-((2'-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-[1,1'-biphenyl]-2-yl)amino)-1-oxopropan-2-yl)carbamate (4b)

By following the same procedure as that of **4a**, starting from **3** (355 mg, 1.0 mmol), **4b** was prepared as a white solid (451 mg, 74% yield). $[\alpha]_D^{17}$ −24.7 (*c* 0.20, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.60−8.20 (m, 8H), 7.35−7.50 (m, 3H+0.4H), 7.10−7.25 (m, 2H), 6.95 (br s, 0.4H), 6.73 (br s, 0.2H), 5.01 (br s, 0.6H), 4.86 (d, J=7.2 Hz, 0.4H), 4.16−4.20 (m, 0.6H), 4.05 (t, J=6.8 Hz, 0.4H), 1.37 (d, J=4.4 Hz, 9H), 1.19 (d, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.4, 155.5, 153.1, 153.0, 142.5, 142.4, 142.3, 136.2, 136.1, 131.3, 131.1, 131.0, 130.9, 130.6, 129.0, 128.9, 128.7, 128.3, 128.0, 126.0, 125.1, 124.2, 124.0, 122.4, 119.7, 117.9, 114.5, 79.7, 78.7, 78.4, 50.8, 50.4, 28.5, 17.9, 17.6; HRMS (ESI) calcd for $C_{29}H_{28}F_6N_4O_4$ ($M+H^+$) 611.2088, found 6112069.

Synthesis of (*S*)-2-amino-*N*-(2'-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-[1,1'-biphenyl]-2-yl)-propanamide (5a)

To a well stirred solution of compound **4a** (463 mg, 0.74 mmol) in CH_2Cl_2 (6 mL) was added TFA (2 mL) dropwise at 0 ℃. The resulting mixture was stirred for 5 h at room temperature and the mixture was concentrated under reduced pressure. The obtained residue was dissolved in CH_2Cl_2 (15 mL), and treated with saturated Na_2CO_3 to reach pH 8. The mixture was extracted with CH_2Cl_2 (20 mL×3). The combined organic layers were dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography on neutral Al_2O_3 (eluent: CH_2Cl_2/MeOH, V∶V=100∶1) to yield **5a** as white solid (272 mg, 70% yield). $[\alpha]_D^{17}$ −32.0 (*c* 0.20, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 9.58−9.73 (m, 1H), 9.42 (d, J=10.4 Hz, 1H), 8.25−8.35 (m, 1H), 7.28−7.75 (m, 11H), 3.32 (dd, J=10.4, 7.2 Hz, 1H), 1.50−1.90 (br s, 2H), 1.22 (d, J=7.2 Hz, 1H+0.5H), 1.02 (d, J=6.8 Hz, 1H+0.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.4, 179.3, 174.8, 174.5, 140.2, 140.0, 135.0, 134.9, 134.6, 134.2, 133.9, 133.3, 132.1, 131.6, 131.3, 130.1, 130.3, 130.1, 129.0, 128.8, 128.7, 127.9, 127.4, 127.1, 126.9, 126.5, 125.2, 124.7, 124.4, 121.7, 118.8, 50.7, 50.5, 29.7, 21.0, 20.8; HRMS (ESI) calcd for $C_{24}H_{20}F_6N_4OS$ ($M+H^+$) 527.1335, found 527.1345.

Synthesis of (*S*)-2-amino-*N*-(2'-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-[1,1'-biphenyl]-2-yl)-propanamide (5b)

By following the same procedure as that of **5a**, starting from **4b** (451 mg, 0.74 mmol), the crude product was purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH, V∶V=100∶1) to yield a white solid **5b** (347 mg, 92% yield). $[\alpha]_D^{17}$ −19.6 (*c* 0.20, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6) δ: 9.73−9.76 (m, 0.6H), 8.31 (d, J=8.0 Hz, 0.5H), 8.17 (d, J=8.0 Hz, 0.4H), 7.93−8.00 (m, 3H), 7.60 (s, 2H), 7.42 (d, J=6.0 Hz, 2H), 7.19−7.24 (m, 4H), 3.18−3.24 (m, 1H), 0.99−1.05 (m, 3H); ^{13}C NMR (100 Hz, DMSO-d_6) δ: 174.5, 153.0, 142.2, 136.5, 136.3, 131.4, 131.2, 129.6, 129.2, 129.1, 129.0, 128.9, 125.1, 124.7, 124.5, 124.4, 122.4, 121.8, 120.9, 118.0, 114.7, 51.1, 51.0, 21.1; HRMS (ESI) calcd for $C_{24}H_{20}F_6N_4O_2$ ($M+H^+$) 511.1563, found 511.1576.

Synthesis of (*S*)-*tert*-butyl-2-((2'-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-[1,1'-biphenyl]-2-yl)-carbamoyl)pyrrolidine-1-carboxylate (7a)

Compound **6** was prepared according to the reported procedure and the ^1H NMR data were consistent with the reported values.[31] Compound **6**: $[\alpha]_D^{17}$ +10.3 (*c* 0.18, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 8.39−8.96 (m, 1H), 8.06−8.15 (m, 1H), 7.41−7.43 (m, 1H), 7.22−7.33 (m, 3H), 7.03−7.08 (m, 1H), 6.81−6.90 (m, 2H), 4.23−4.26 (m, 1H), 3.59−3.70 (m, 2H), 3.19−3.29 (m, 2H), 2.07−2.12 (m, 2H), 1.61−1.88 (m, 2H), 1.30−1.43 (m, 9H). To a well stirred solution of **6** (380 mg, 1.0 mmol) in dry CH_2Cl_2 (10 mL) was added 1-thiocyanato-3,5-bis(trifluoromethyl)benzene (200 μL, 1.1 mmol) dropwise at 0 ℃. The reaction mixture was stirred at room temperature for 20 h. The reaction mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluent: petroleum ether/EtOAc, V∶V=5∶1) to yield **7a** as white solid (494 mg, 76% yield). $[\alpha]_D^{17}$ −66.3 (*c* 0.18, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 9.67 (s, 0.3H), 9.00−9.06 (m, 0.7H), 8.48−8.63 (m, 0.7H), 7.73−7.90 (m, 1H+0.3H), 7.33−7.64 (m, 11H), 4.16 (d, J=7.6 Hz, 1H), 3.30 (br s, 2H), 2.06−2.11 (m, 2H), 1.45−1.81 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 180.2, 179.5, 174.8, 170.4, 156.8, 140.7, 140.4, 135.4, 131.5, 131.2, 130.7, 129.2, 128.9, 128.2, 127.2, 126.0, 125.8, 127.5, 124.9, 124.5, 123.9, 121.7, 119.0, 118.5, 81.2, 60.2, 59.8, 47.1, 28.3, 24.3, 21.3, 20.7, 19.7; HRMS (ESI) calcd for $C_{31}H_{30}F_6N_4O_3S$ ($M+H^+$) 653.2016, found 653.1973.

Synthesis of (*S*)-*tert*-butyl-2-((2'-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-[1,1'-biphenyl]-2-yl)carbamoyl)pyrrolidine-1-carboxylate (7b)

By following the same procedure as that of **7a**, starting from **6** (300 mg, 0.79 mmol), **7b** was prepared as white solid (470 mg, 94% yield). $[\alpha]_D^{17}$ −99.3 (*c* 0.20, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 8.30−8.55 (m, 2H), 8.00−8.10 (m, 1H), 7.65−7.80 (m, 3H), 7.12−7.43 (m, 8H), 4.24−4.11 (m, 1H), 3.14−3.23 (m, 2H), 1.70−1.99 (m, 4H), 1.35−1.43 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.2, 172.0, 155.7, 152.8, 140.8, 136.1, 134.9, 132.6, 132.1, 132.0, 131.8, 131.7, 130.5, 130.1, 129.3, 128.9, 128.8, 127.3, 126.8, 126.2, 125.1, 124.6, 124.1, 122.3, 121.9, 118.5, 118.3, 115.5, 115.4, 81.04, 60.6, 47.2, 47.1, 29.1, 24.2, 20.8; HRMS (ESI) calcd for $C_{31}H_{30}F_6N_4O_4$ ($M+H^+$) 637.2244, found

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637.2218.

Synthesis of (*S*)-*N*-(2'-(3-(3,5-bis(trifluoromethyl)-phenyl)thioureido)-[1,1'-biphenyl]-2-yl)pyrrolidine-2-carboxamide (8a)

To a well stirred solution of compound **7a** (494 mg, 0.75 mmol) in CH_2Cl_2 (8 mL) was added TFA (4 mL) dropwise at 0 ℃. The resulting mixture was stirred for 8 h at room temperature, and the mixture was concentrated under reduced pressure, dissolved in CH_2Cl_2 (15 mL), and treated with saturated Na_2CO_3 to reach pH 8. The mixture was extracted with CH_2Cl_2 (20 mL×3). The combined organic layers were dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography on neutral Al_2O_3 (eluent: CH_2Cl_2/MeOH, V∶V=100∶1) to yield **8a** as a white solid (330 mg, 79% yield). $[\alpha]_D^{17}$ –64.0 (*c* 0.24, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.69−9.72 (m, 1H), 8.34−8.43 (m, 1H), 7.15−7.62 (m, 12H), 3.53−3.58 (m, 1H), 2.77−3.01 (m, 2H), 2.28−2.34 (m, 1H), 1.62−2.10 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.4, 174.5, 174.4, 140.5, 135.0, 134.3, 133.7, 131.7, 131.4, 130.6, 130.3, 130.0, 128.9, 128.8, 128.7, 128.6, 128.2, 127.5, 127.0, 126.8, 126.2, 125.2, 124.5, 124.1, 121.8, 118.6, 60.4, 60.1, 47.4, 47.0, 30.3, 30.2, 26.2, 26.1; HRMS (ESI) calcd for $C_{26}H_{20}F_6N_4OS$ ($M+H^+$) 553.1491, found 553.1502.

Synthesis of (*S*)-*N*-(2'-(3-(3,5-bis(trifluoromethyl)-phenyl)ureido)-[1,1'-biphenyl]-2-yl)pyrrolidine-2-carboxamide (8b)

By following the same procedure as that of **8a**, starting from **7b** (470 mg, 0.74 mmol), **8b** was prepared as white solid (352 mg, 89% yield). $[\alpha]_D^{17}$ –47.3 (*c* 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.78−9.88 (m, 1H), 8.31−8.41 (m, 1H), 8.15 (d, J=32.4 Hz, 8.4 Hz, 1H), 8.00 (d, J=6.0 Hz, 2H), 7.15−7.64 (m, 7H), 3.51−3.54 (m, 1H), 2.65 (d, J=6.8 Hz, 1H), 2.31−2.05 (m, 1H), 1.38−1.86 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 173.9, 173.7, 152.7, 142.2, 142.1, 136.8, 136.7, 136.5, 131.1, 130.9, 129.4, 129.2, 129.1, 129.0, 128.4, 125.1, 124.3, 123.9, 122.4, 121.5, 120.8, 120.2, 118.0, 114.7, 79.4, 79.1, 60.9, 60.8, 55.3, 46.7, 46.5, 30.8, 30.7, 26.0; HRMS (ESI) calcd for $C_{26}H_{22}F_6N_4O_2$ ($M+H^+$) 537.1720, found 537.1730.

Synthesis of (2*S*,2'*S*)-*N*,*N*'-([2,2'-bipyridine]-3,3'-diyl)bis(2-amino-3-phenylpropanamide) (11)

Compound **10** was prepared according to the reported procedure and the ^{1}H NMR data were consistent with the reported values.[35] Compound **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (d, J=1.6 Hz, 2H), 7.01−7.06 (m, 4H), 6.28 (br s, 4H). To a well stirred solution of **10** (40 mg, 0.22 mmol) in anhydrous dichloromethane (2 mL) was added EDCI (83 mg, 0.66 mmol) and *N*-Cbz-(*S*)-Phe-OH (193 mg, 0.66 mmol) at room temperature. The resulting mixture was stirred for 1 h, then the mixture was quenched by addition of saturated $NaHCO_3$, and extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, V∶V=2∶1) to yield a white solid (126 mg, 80% yield). A suspension of this white solid (126 mg, 0.17 mmol) and 10% Pd-C (21 mg, 0.02 mmol) in absolute EtOH (5 mL) was hydrogenated under 1.0 atm for 10 min. The reaction mixture was diluted with EtOH (10 mL), and filtered through a Celite pad under reduced pressure. The filtrate was concentrated under reduced pressure, and the resulted residue was purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate/TFA, V∶V∶V=1∶1∶0.01) to afford white semi-solid **11** (57 mg, 70% yield). $[\alpha]_D^{17}$ –43.3 (*c* 0.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 13.25 (s, 2H), 9.08 (d, J=8.4 Hz, 2H), 8.33 (d, J=3.6 Hz, 2H), 7.23−7.31 (m, 10H), 3.67 (br s, 2H), 3.35 (dd, J=13.6, 3.6 Hz, 2H), 2.77 (dd, J=13.6, 9.6 Hz, 2H), 1.45 (br s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.4, 143.3, 141.5, 137.8, 135.4, 130.0, 129.2, 128.7, 126.9, 123.8, 58.0, 41.3; HRMS (ESI) calcd for $C_{28}H_{28}N_6O_2$ ($M+H^+$) 481.2347, found 481.2355.

Synthesis of di-*tert*-butyl((2*R*,2'*R*)-([1,1'-biphenyl]-2,2'-diylbis(azandiyl))bis(1-oxopropane-2,1-diyl))-dicarbamate (12)

To a well stirred solution of **2** (92 mg, 0.5 mmol) in anhydrous dichloromethane (5 mL) was added EDCI (288 mg, 1.5 mmol), and added *N*-Boc-(*S*)-Ala-OH (284 mg, 1.5 mmol) dropwise at room temperature. The resulting mixture was stirred for 8 h at room temperature, then was quenched by addition of saturated $NaHCO_3$, and extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, V∶V=2∶1) to yield a white solid **12** (250 mg, 95% yield). $[\alpha]_D^{17}$ –24.4 (*c* 0.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (s, 2H), 7.68−7.73 (m, 2H), 7.42−7.48 (m, 2H), 7.18−7.30 (m, 4H), 4.90−5.17 (m, 2H), 4.00−4.25 (m, 2H), 1.18−1.45 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.6, 155.5, 134.9, 130.4, 130.1, 129.5, 129.2, 125.6, 123.3, 50.5, 28.3, 28.2, 18.2, 17.2; HRMS (ESI) calcd for $C_{28}H_{38}N_4O_6$ ($M+H^+$) 527.2864, found 527.2867.

Synthesis of (2*S*,2'*S*)-*N*,*N*'-([1,1'-biphenyl]-2,2'-diyl)-bis(2-aminopropanamide) (13)

To a well stirred solution of compound **12** (263 mg, 0.50 mmol) in THF (2 mL) was added TFA (1 mL) dropwise at 0 ℃. The resulting mixture was stirred for 8 h at room temperature, and then the mixture was dissolved in THF (10 mL), and treated with 2 mol•L^{-1} $NaOH_{(aq.)}$ to reach pH 8, a large amount of white solid was precipitated from the biphase solvent. The solid was filtered and dried under vacuo to yield **13** as white solid (147 mg, 90% yield). $[\alpha]_D^{17}$ –24.7 (*c* 0.10, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.24 (d, J=8.0 Hz,

1H), 8.13 (d, J=8.0 Hz, 1H), 7.39−7.43 (m, 2H), 7.18 −7.23 (m, 4H), 3.23 (dd, J=6.8, 3.6 Hz, 2H), 1.05−1.06 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 174.8, 174.5, 136.3, 136.1, 131.0, 130.8, 129.2, 129.1, 128.7, 124.7, 124.5, 121.8, 121.0, 51.1, 21.3, 21.3; HRMS (ESI) calcd for $C_{18}H_{22}N_4O_2$ ($M+H^+$) 327.1816, found 327.1814.

Typical procedure for the organocatalytic synthesis of 3-alkyl-3-hydroxy-2-oxindoles in water

A mixture of catalyst **5a** (7.9 mg, 0.015 mmol), *p*-TsOH (1.9 mg, 0.01 mmol) and cyclohexanone (104 μL, 1.0 mmol) in 0.5 mL of water was stirred for 10 min at room temperature. Isatin (14.7 mg, 0.1 mmol) was added, and then the resulted reaction mixture was stirred for 3.5 h at room temperature. After rermoval of water under the reduced pressure, the resulted residue was purified with flash column chromatography on silica gel (petroleum/ethyl acetate, V∶V=1∶1) to afford the desired (*R*)-3-hydroxy-3-((*S*)-2-oxocyclohexyl)indolin-2-one (24.3 mg, 99%).

(*R*)-3-Hydroxy-5-nitro-3-((*S*)-2-oxocyclohexyl)indolin-2-one (Table 5, Entry 1):[37] $[\alpha]_D^{17}$ −67.3 (*c* 0.05, $CHCl_3$, 86% *ee*); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.03 (s, 1H), 8.19 (d, J=8.4 Hz, 1H), 7.98 (s, 1H), 7.02 (d, J=8.8 Hz, 1H), 6.03 (s, 1H), 3.19 (dd, J=12.8, 4.4 Hz, 1H), 2.66 (d, J=10.0 Hz, 1H), 2.34−2.37 (m, 1H), 1.49−2.05 (m, 6H). HPLC separation conditions: Chiralcel AD-H, solvent: Hexane/*i*-PrOH, V∶V=80∶20, flow rate=1.0 mL/min, λ=254 nm. Retention time: t_R(*anti*,major)=68.50 min and t_R(*anti*,minor)=53.10 min.

(*R*)-5-Chloro-3-hydroxy-3-((*S*)-2-oxocyclohexyl)-indolin-2-one (Table 5, Entry 2):[23] $[\alpha]_D^{17}$ −36.0 (*c* 0.10, $CHCl_3$, 80% *ee*). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.38 (s, 1H), 7.23 (d, J=8.0 Hz, 1H), 7.19 (s, 1H), 6.80 (d, J=8.0 Hz, 1H), 6.03 (s, 1H), 3.09 (dd, J=12.8, 4.8 Hz, 1H), 2.58 (d, J=10.8 Hz, 1H), 2.29−2.37 (m, 1H), 1.92−2.08 (m, 3H), 1.66−1.83 (m, 2H), 1.49−1.55 (m, 1H). HPLC separation conditions: Chiralcel IC, solvent: Hexane/*i*-PrOH, V∶V=85∶15, flow rate=1.0 mL/min, λ=254 nm. Retention time: t_R(*anti*,major)=50.08 min and t_R(*anti*,minor)=64.25 min.

(*R*)-5-Bromo-3-hydroxy-3-((*S*)-2-oxocyclohexyl)-indolin-2-one (Table 5, Entry 3):[23] $[\alpha]_D^{17}$ −23.6 (*c* 0.07, $CHCl_3$, 86% *ee*); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.38 (s, 1H), 7.36 (d, J=8.4 Hz, 1H), 7.30 (s, 1H), 6.76 (d, J=8.4 Hz, 1H), 6.03 (s, 1H), 3.09 (dd, J=12.4, 4.4 Hz, 1H), 2.29−2.59 (m, 1H), 2.21 (s, 1H), 1.93−2.05 (m, 3H), 1.46−1.79 (m, 3H). HPLC separation conditions: Chiralcel IC, solvent: Hexane/*i*-PrOH, V∶V=85∶15, flow rate=1.0 mL/min, λ=254 nm. Retention time: t_R(*anti*,major)=50.42 min and t_R(*anti*, minor)=61.87 min.

(*R*)-4-Bromo-3-hydroxy-3-((*S*)-2-oxocyclohexyl)-indolin-2-one (Table 5, Entry 4):[23] $[\alpha]_D^{17}$ −52.0 (*c* 0.01, $CHCl_3$, 87% *ee*); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.61 (s, 0.4H), 10.36 (s, 0.6H), 6.97−7.16 (m, 2H), 6.74−6.83 (m, 1H), 6.20 (s, 0.4H), 6.03 (s, 0.6H), 3.90 (dd, J=12.8, 4.0 Hz, 0.6H), 3.20−3.40 (m, 0.4H), 1.59−2.36 (m, 8H). HPLC separation conditions: Chiralcel OJ-H, solvent: Hexane/*i*-PrOH, V∶V=85∶15, flow rate=1.0 mL/min, λ=254 nm. Retention time: t_R(*anti*,major)=61.46 min and t_R(*anti*,minor)=48.03 min.

(*R*)-3-Hydroxy-5-methyl-3-((*S*)-2-oxocyclohexyl)-indolin-2-one (Table 5, Entry 5):[23] $[\alpha]_D^{17}$ −26.7 (*c* 0.10, $CHCl_3$, 67% *ee*); NMR (400 MHz, DMSO-d_6) δ: 10.07 (d, J=18.4 Hz, 1H), 6.93−7.09 (m, 2H), 6.62−6.68 (m, 1H), 5.67−5.77 (m, 1H), 3.04−3.23 (m, 1H), 2.21−2.50 (m, 4H), 1.44−2.07 (m, 4H). HPLC separation conditions: Chiralcel AD, hexane/*i*-PrOH=90∶10, flow rate=1.0 mL/min, λ=254 nm). Retention time: t_R(anti,major)=49.26 min and t_R(anti,minor)=42.53 min.

(*R*)-3-Hydroxy-1-methyl-3-((*S*)-2-oxocyclohexyl)-indolin-2-one (Table 5, Entry 6):[23] $[\alpha]_D^{17}$ −9.3 (*c* 0.15, $CHCl_3$, 82% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36−7.40 (m, 2H), 7.08 (t, J=7.6 Hz,1H), 6.84 (d, J=8.0 Hz, 1H), 4.85 (br s, 1H), 3.20 (s, 3H), 2.96−3.21 (m, 1H), 2.47 (d, J=14.8 Hz, 1H), 2.28−2.36 (m, 1H), 2.04 (d, J=13.6 Hz, 1H), 1.88 (s, 1H), 1.54−1.69 (m, 4H). HPLC separation conditions: Chiralcel AD, solvent: Hexane/*i*-PrOH, V∶V=90∶10, flow rate=1.0 mL/min, λ=254 nm. Retention time: t_R(*anti*,major)=34.81 min and t_R(*anti*,minor)=31.12 min.

(*R*)-1-Benzyl-3-hydroxy-3-((*S*)-2-oxocyclohexyl)-indolin-2-one (Table 5, Entry 7):[23] $[\alpha]_D^{17}$ −3.3 (*c* 0.20, $CHCl_3$, 86% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27−7.47 (m, 7H), 7.04 (t, J=7.2 Hz, 1H), 6.70 (d, J=8.0 Hz, 1H), 4.97 (d, J=16.0 Hz, 1H), 4.83 (d, J=16.0 Hz, 1H), 3.05 (d, J=6.8 Hz, 1H), 2.52 (d, J=15.2 Hz, 1H), 2.31−2.39 (m, 1H), 2.04 (br s, 2H), 1.90 (br s, 1H), 1.57−1.71 (m, 3H). HPLC separation conditions: Chiralcel AD-H, solvent: Hexane/*i*-PrOH, V∶V=80/20, flow rate=1.0 mL/min, λ=254 nm. Retention time: t_R(*anti*,major)=57.55 min and t_R(*anti*,minor)=50.87 min.

(*R*)-1-Benzyl-3-hydroxy-5-nitro-3-((*S*)-2-oxocyclohexyl)indolin-2-one (Table 5, Entry 8): $[\alpha]_D^{17}$ −49.0 (*c* 0.14, $CHCl_3$, 98% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.17−8.24 (m, 2H), 7.27−7.35 (m, 5H), 6.78 (d, J=8.8 Hz, 1H), 4.80−5.20 (m, 2H), 3.10−3.25 (m, 1H), 2.29−2.49 (m, 3H), 2.11 (br s, 1H), 2.02 (br s, 1H), 1.65−1.71 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 213.3, 210.8, 177.4, 175.4, 149.6, 148.8, 143.8, 143.4, 134.4, 134.3, 130.7, 129.7, 129.1, 129.0, 128.2, 128.1, 127.3, 126.8, 126.7, 121.2, 120.3, 109.3, 56.0, 44.3, 42.5, 42.0, 28.1, 27.3, 26.9, 26.4, 24.6, 24.3; HRMS (ESI) calcd for $C_{12}H_{20}N_2O_5$ ($M+H^+$) 283.0713, found 283.0708. HPLC separation conditions: Chiralcel OD-H, solvent: Hexane/*i*-PrOH, V∶V=80∶20, flow rate=1.0 mL/min, λ=254 nm. Retention time: t_R(*anti*,major)=47.15 min and t_R(*anti*,minor)=61.08 min.

(*R*)-1-Benzyl-5-bromo-3-hydroxy-3-((*S*)-2-oxocyclohexyl)indolin-2-one (Table 5, Entry 9): $[\alpha]_D^{17}$ −9.1 (*c* 0.18, $CHCl_3$, 99% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.28－7.47 (m, 7H), 6.57 (d, J=8.4 Hz, 1H), 4.95 (d, J=16.0 Hz, 1H), 4.83 (d, J=15.6 Hz, 1H), 3.02－3.07 (m, 1H), 2.51 (d, J=15.2 Hz, 1H), 2.31－2.39 (m, 1H), 2.08 (d, J=14.8 Hz, 2H), 1.94 (s, 1H), 1.62－1.72 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 214.0, 211.3, 176.6, 174.5, 142.7, 142.1, 135.1, 134.9, 132.5, 132.4, 131.7, 130.9, 128.9, 128.8, 128.7, 127.9, 127.8, 127.5, 127.3, 116.1, 115.6, 111.1, 55.8, 55.7, 44.0, 42.6, 42.0, 28.2, 27.2, 26.8, 26.2, 24.6, 24.3; HRMS (ESI) calcd for $C_{21}H_{20}BrNO_3$ ($M+H^+$) 414.0699, found 414.0696. HPLC separation conditions: Chiralcel AD-H, solvent: Hexane/*i*-PrOH, V∶V=80∶20, flow rate=1.0 mL/min, λ=254 nm. Retention time: t_R(anti,major)=56.36 min and t_R(anti,minor)=66.83 min.

(*R*)-1-Benzyl-3-hydroxy-5-methyl-3-((*S*)-2-oxocyclohexyl)indolin-2-one (Table 5, Entry 10): $[\alpha]_D^{17}$ −14.7 (*c* 0.20, $CHCl_3$, 86% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28－7.34 (m, 5H), 7.18 (s, 1H), 7.01 (d, J=8.0 Hz, 1H), 6.58 (d, J=8.0 Hz, 1H), 5.01 (br s, 1H), 4.96 (d, J=16.0 Hz, 1H), 4.82 (d, J=16.0 Hz, 1H), 3.00－3.05 (m, 1H), 2.52 (d, J=15.2 Hz, 1H), 2.34－2.39 (m, 1H), 2.04 (br s, 1H), 1.90 (s, 1H), 1.57－1.73 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.9, 211.8, 177.0, 176.9, 175.0, 141.2, 135.7, 132.5, 130.0, 128.9, 128.8, 128.7, 127.5, 124.9, 109.3, 55.7, 55.4, 53.5, 43.9, 42.7, 42.1, 28.3, 27.2, 26.8, 26.1, 24.5, 24.3, 21.2, 21.1; HRMS (ESI) calcd for $C_{22}H_{24}NO_3$ ($M+H^+$) 350,1750, found 350.1743. HPLC separation conditions: Chiralcel AD, solvent: Hexane/*i*-PrOH, V∶V=80∶20, flow rate=1.0 mL/min, λ=254 nm. Retention time: t_R(*anti*,major)=29.08 min and t_R(*anti*,minor)=25.02 min.

(*S*)-*tert*-Butyl-3-hydroxy-2-oxo-3-((*R*)-2-oxocyclohexyl)indoline-1-carboxylate (Table 5, Entry 11): $[\alpha]_D^{17}$ +29.4 (*c* 0.12, $CHCl_3$, –98% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89 (d, J=8.0 Hz, 1H), 7.35－7.39 (m, 2H), 7.17－7.28 (m, 1H), 4.98 (br s, 1H), 3.01 (dd, J=12.8, 4.8 Hz, 1H), 2.47 (d, J=15.2 Hz, 1H), 2.27－2.33 (m, 1H), 1.80－2.20 (m, 2H), 1.57－1.71 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 213.5, 211.5, 175.4, 173.7, 149.1, 148.9, 140.6, 140.0, 130.2, 129.9, 127.7, 125.0, 124.7, 124.0, 115.3, 84.4, 56.4, 56.1, 42.6, 41.9, 28.1, 27.0, 26.8, 25.8, 24.4, 24.3; HRMS (ESI) calcd for $C_{19}H_{23}NO_5Na$ ($M+Na^+$) 368.1468, found 368.1460. HPLC separation conditions: Chiralcel AD, solvent: Hexane/*i*-PrOH, V∶V=80∶20, flow rate=1.0 mL/min, λ=254 nm. Retention time: t_R(*anti*,major)=15.24 min and t_R(*anti*,minor)=14.39 min.

(*R*)-3-Hydroxy-3-((*S*)-2-oxocyclohexyl)indolin-2-one (Table 5, Entry 12):[23] $[\alpha]_D^{17}$ −25.3 (*c* 0.11, $CHCl_3$, 94% *ee*); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.20 (s, 1H), 7.22－7.14 (m, 2H), 6.87－6.77 (m, 2H), 5.83 (s, 1H), 3.07 (dd, J=13.2, 4.8 Hz, 1H), 2.59 (d, J=11.2 Hz, 1H), 2.27－2.36 (m, 1H), 1.45－2.04 (m, 6H). HPLC separation conditions: Chiralcel OJ-H, hexane/*i*-PrOH, V∶V=80∶20, flow rate=1.0 mL/min, λ=254 nm; Retention time: t_R(*anti*,major)=15.75 min and t_R(*anti*,minor)=19.56 min.

(*R*)-1-(3-Hydroxyindolin-3-yl)propan-2-one (Table 6, Entry 1):[11] $[\alpha]_D^{17}$ +2.20 (*c* 0.10, $CHCl_3$, 5% *ee*); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.19 (s, 1H), 7.24－7.15 (m, 2H), 6.92－6.88 (m, 1H), 6.77 (d, J=7.6 Hz, 1H), 5.95 (s, 1H), 3.26 (d, J=16.4 Hz, 1H), 2.99 (d, J=16.4 Hz, 1H), 2.00 (s, 3H). HPLC separation conditions: Chiralcel OJ-H, solvent: Hexane/*i*-PrOH, V∶V=80∶20, flow rate=1.0 mL/min, λ=254 nm. Retention time: t_R(major)=28.11 min and t_R(minor)=41.98 min.

3-Hydroxy-3-(2-oxocyclopentyl)indolin-2-one (Table 6, Entry 2):[23] $[\alpha]_D^{17}$ +31.33 (*c* 0.10, $CHCl_3$, 26% *ee*); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.30 (s, 1H), 7.36 (d, J=7.2 Hz, 1H), 7.18 (t, J=7.6 Hz, 1H), 6.89 (t, J=7.6 Hz, 1H), 5.99 (s, 1H), 2.88 (t, J=10.0 Hz, 1H), 2.22－1.72 (m, 6H). HPLC separation conditions: Chiralcel AD-H, solvent: Hexane/*i*-PrOH, V∶V=90∶10, flow rate=1.0 mL/min, λ=254 nm. Retention time: t_R(major)=40.32 min and t_R(*anti*,minor)=44.76 min.

3-Hydroxy-3-(4-oxotetrahydro-2*H*-pyran-3-yl)indolin-2-one (Table 6, Etry 3):[37] $[\alpha]_D^{17}$ −26.0 (*c* 0.10, $CHCl_3$, 21% *ee*); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.30 (s, 1H), 7.24 (d, J=7.6 Hz, 1H), 7.18 (t, J=7.6 Hz, 1H), 6.88 (t, J=7.6 Hz, 1H), 6.79 (d, J=7.6 Hz, 1H), 6.08 (s, 1H), 4.50 (dd, J=13.2, 4.8 Hz, 1H), 4.01－4.07 (m, 2H), 3.56－3.62 (m, 2H), 3.18－3.22 (m, 1H), 2.02－2.08 (m, 1H). HPLC separation conditions: Chiralcel AD-H, solvent: Hexane/*i*-PrOH, V∶V=85∶15, flow rate=1.0 mL/min, λ=254 nm. Retention time: t_R(major)=78.22 min and t_R(minor)=88.50 min.

3-Hydroxy-3-(4-oxotetrahydro-2*H*-thiopyran-3-yl)-indolin-2-one (Table 6, Entry 4): $[\alpha]_D^{17}$ −14.7 (*c* 0.18, $CHCl_3$, 57% *ee*); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.28 (s, 1H), 7.25 (d, J=7.2 Hz, 1H), 7.17 (t, J=7.6 Hz, 1H), 6.86 (t, J=7.6 Hz, 1H), 6.79 (d, J=7.6 Hz, 1H), 6.08 (s, 1H), 3.47 (d, J=11.6 Hz, 1H), 3.19－3.31 (m, 2H), 2.90 (d, J=6.8 Hz, 2H), 2.42－2.65 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 208.1, 207.0, 178.5, 178.4, 143.7, 143.6, 130.7, 129.3, 129.2, 125.4, 123.5, 121.6, 121.5, 110.0, 109.6, 74.4, 73.5, 60.5, 45.2, 44.2, 30.9, 30.8, 29.4, 29.2; HRMS (ESI) calcd for $C_{13}H_{13}NO_3S$ ($M+H^+$) 264.0689, found 264.0683. HPLC separation conditions: Chiralcel AD-H, solvent: Hexane/*i*-PrOH, V∶V=85∶15, flow rate=1.0 mL/min, λ=254 nm. Retention time: t_R(major)=46.13 min and t_R(minor)=54.30 min.

tert-Butyl-3-(3-hydroxy-2-oxoindolin-3-yl)-4-oxo-piperidine-1-carboxylate (Table 6, Entry 5): $[\alpha]_D^{17}$ +22.2 (*c* 0.11, $CHCl_3$, 25% *ee*); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.30 (s, 1H), 7.25 (d, J=7.2 Hz, 1H), 7.15 (t, J=7.6 Hz, 1H), 6.87 (t, J=7.6 Hz, 1H), 6.76 (d, J=8.0 Hz, 1H), 6.01 (s, 1H), 4.60 (br s, 1H), 4.11 (br s, 1H), 3.52 (br s, 1H), 3.04 (br s, 1H), 2.41－2.47 (m, 1H), 2.08－2.26 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 207.2, 206.6, 178.2, 154.3, 143.1, 129.4, 125.3, 123.8, 121.6, 110.1, 109.7, 79.8, 74.1, 73.2, 56.5, 55.4, 28.5, 28.4; HRMS (ESI) calcd for $C_{18}H_{22}N_2O_5$ ($M+H^+$) 347.1602, found 347.1595. HPLC separation conditions: Chiralcel AD-H, solvent:

Hexane/*i*-PrOH, $V:V=90:10$, flow rate = 1.0 mL/min, λ=254 nm. Retention time: t_R(major)=63.61 min and t_R(minor)=44.73 min.

1-Benzyl-5-bromo-3-hydroxy-3-(4-oxotetrahydro-2*H*-thiopyran-3-yl)indolin-2-one (Table 6, Entry 6): $[\alpha]_D^{17}$ +14.7 (*c* 0.10, $CHCl_3$, 96% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.51 (d, J=1.6 Hz, 1H), 7.28−7.35 (m, 6H), 6.60 (d, J=8.4 Hz, 1H), 4.96 (d, J=15.6 Hz, 1H), 4.84 (d, J=15.6 Hz, 1H), 4.10 (br s, 1H), 3.66 (dd, J=12.0, 5.2 Hz, 1H), 2.78−2.97 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 208.7, 207.4, 176.7, 176.0, 143.6, 143.0, 136.5, 136.4, 134.6, 134.5, 132.5, 132.0, 131.8, 128.9, 128.1, 127.7, 127.6, 126.5, 114.4, 114.3, 111.5, 111.1, 74.2, 73.3, 73.2, 60.8, 60.2, 45.1, 44.3, 43.4, 43.1, 30.7, 30.6, 29.4, 29.2; HRMS (ESI) calcd for $C_{20}H_{19}BrNO_3S$ ($M+H^+$) 432.0263, found 432.0261. HPLC separation conditions: Chiralcel AD, solvent: Hexane/*i*-PrOH, $V:V$=80:20, flow rate=1.0 mL/min, λ=254 nm. Retention time: t_R(major)=34.48 min and t_R(minor)=39.83 min.

1-Benzyl-3-hydroxy-5-nitro-3-(4-oxotetrahydro-2*H*-thiopyran-3-yl)indolin-2-one (Table 6, Entry 7): $[\alpha]_D^{17}$ −16.0 (*c* 0.10, $CHCl_3$, 99% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.17−8.24 (m, 2H), 7.28−7.38 (m, 5H), 6.80 (d, J=8.8 Hz, 1H), 5.04 (d, J=15.6 Hz, 1H), 4.92 (d, J=16.0 Hz, 1H), 3.72−3.78 (m, 2H), 2.97−3.02 (m, 3H), 2.79−2.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 209.1, 207.6, 177.1, 175.7, 149.5, 149.0, 143.7, 143.5, 134.3, 134.2, 130.6, 129.1, 128.2, 127.3, 127.2, 126.9, 120.4, 119.9, 109.6, 109.4, 75.2, 75.0, 59.7, 59.6, 45.2, 44.5, 44.4, 44.2, 30.6, 30.5. 29.7, 29.6; HRMS (ESI) calcd for $C_{20}H_{19}N_2O_5S$ ($M+H^+$) 399.1009, found 399.0999. HPLC separation conditions: Chiralcel AD, solvent: Hexane/*i*-PrOH, $V:V$=70:30, flow rate=1.0 mL/min, λ=254 nm. Retention time: t_R(major)=33.18 min and t_R(minor)=38.64 min.

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