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Asymmetric cross aldol addition of isatins with α,β-unsaturated ketones catalyzed by a bifunctional Brønsted acid–Brønsted base organocatalyst

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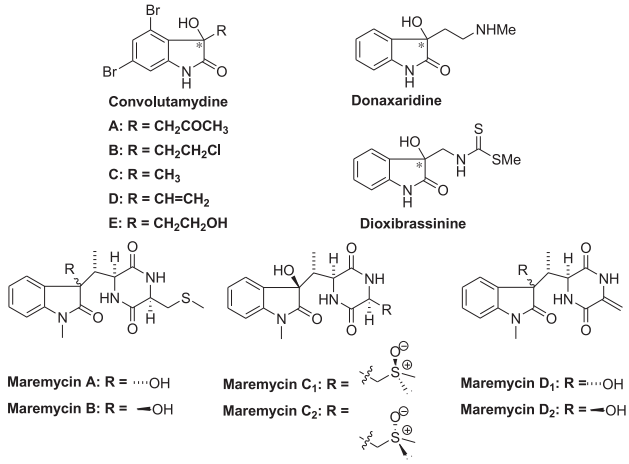
ABSTRACT

The asymmetric cross-aldol reaction of isatins with α,β-unsaturated ketones has been developed under catalysis by a *Cinchona alkaloid*-derived bifunctional Brønsted acid–Brønsted base catalyst, affording the aldol adducts in moderate to good yields (18–98%) with moderate to good enantioselectivities (30–97%). The noncovalent organo-catalyzed asymmetric cross-aldol reaction displays a broad substrate scope and wide functional-group tolerability, albeit the electronic and steric properties of both reaction partners have considerable and regular effects on the reactivity and stereocontrol.

1. Introduction

The asymmetric intermolecular cross-aldol reactions between aldehydes and aldehydes or aldehydes and ketones have been proved important access to carbon–carbon formation, which has been extensively explored for construction of chiral β-hydroxy aldehydes or β-hydroxy ketones in organically synthetic chemistry.[1] In contrast, enantioselective intermolecular cross-aldol reaction between ketones, which produces 3-substituted-3-hydroxy ketones with quaternary stereogenic centres, is much more demanded and challenged.[2]

The 3-hydroxyindolin-2-one structural cores with quaternary stereogenic centres are widely existed in natural products, pharmaceuticals, agrochemicals, indole alkaloids and synthetic indole derivatives.[3] Moreover, these natural products containing 3-hydroxyindolin-2-one cores display invaluable biological and pharmacological activity,[4] such as convolutamydines A–E,[5a] donaxaridine,[5b] dioxibrassinine,[5c] maremycins A–D,[5d] diazonamide A,[5e] leptosin D,[5f] spiro-isoxazolidynyl oxindole,[5g] witindolinone C,[5h] madindoline A and B,[5i,j] and CPC-1,[5k] and efavirenz mimics[5l] (selected structures see Scheme 1). In addition, recent structure–activity relationship studies have shown that the quaternary configuration of the C3 hydroxyl group and the substituent of the oxindole greatly affects the biological and pharmacological activities of those compounds.[3a]



Scheme 1. Selected 3-hydroxyindolin-2-one structures in natural products.

As convolutamydine A shows the potent inhibitory activity towards the differentiation of HL-60 human promyelocytic leukaemia cells, the construction of stereocontrolled tetrasubstituted 3-hydroxyindolin-2-one motifs has attracted great interests of the chemists.[6] Particularly, the methods for enantioselective synthesis

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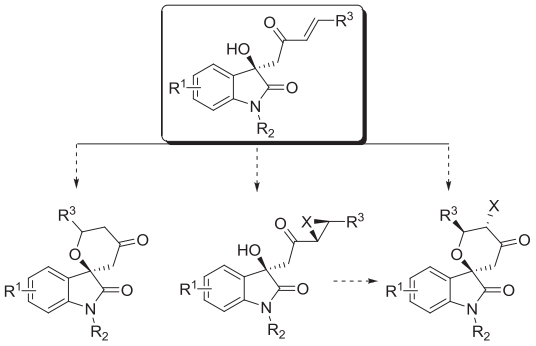
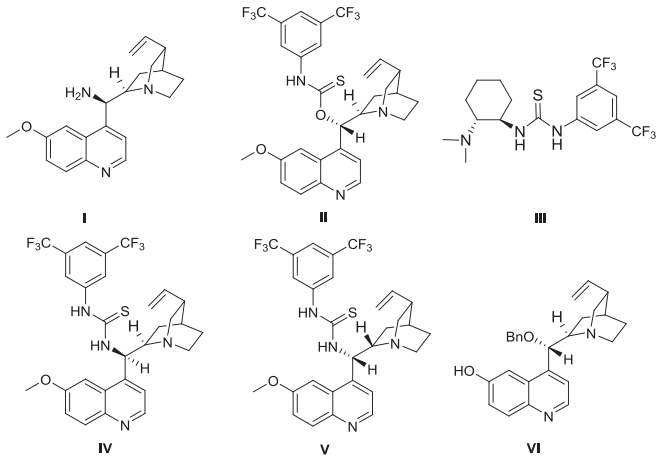
of convolutamydine became very prevalent in the presence of organocatalyst. In 2006, Tomasini[7] and co-workers pioneerly reported the cross-aldol reaction of isatins with acetone by using dipeptide organocatalyst derived from D-proline and L-β-homophenylgricine. Xiao,[8] Malkov, Bella and Kočovský,[9] Nakamura and Toru[10] independently reported enantioselective cross-aldol reaction of isatins with acetone catalyzed by primary or secondary amine catalysts. Recently, Zhao disclosed that quinidine thiourea as a new noncovalent catalyst could efficiently catalyzed the cross-aldol reaction of isatins with unactivated ketones in THF at −5 °C for 3–6 days, which provided the 3-alkyl-3-hydroxyindolin-2-ones in high yields with high enantioselectivities.[11] Although the enantioselective cross-aldol reaction between isatins and ketones has been extensively studied, few examples of the corresponding aldol reactions of various α,β-unsaturated ketones with isatins were found in the literature.

The aldol addition of α,β-unsaturated ketone to isatin leads to 3-aryl-3-hydroxyindolin-3-one with an additional enone moiety, to provide a chance for further elaboration of the products (Scheme 2). In addition, the obvious difficulty in using α,β-unsaturated ketones as a nucleophile is arising from the inherent multiple reactivity that involve ketone, β-carbon (electrophilic sites) and active methylene unit (nucleophilic site). In order to selectively achieve targeted cross aldol-type reaction chemoselective activation of the carbonyl in isatin should be a key point. In virtue of limited examples reported by Zhao, herein, we investigate the asymmetric cross-aldol reaction between α,β-unsaturated ketones and isatins in the presence of thiourea-modified *Cinchona alkaloids* as bifunctional Brønsted acid–Brønsted base catalysts, which provides enantiomerically enriched 3-hydroxy-3-(2-oxo-4-arylbut-3-en-1-yl) indolin-2-ones in moderate to high yields (up to 98%) and moderate to good enantioselectivities (up to 97% ee). Both enantiomers of the 3-hydroxyindolin-3-one adducts can be prepared by using two epimers of the quinidine-derived thiourea catalysts. An investigation of the electronic and steric effect on the stereochemical outcome is also detailed.



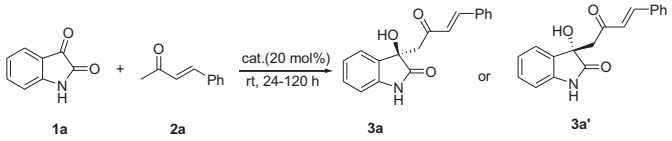
Scheme 2. Further elaboration of 3-hydroxy-3-(2-oxo-4-arylbut-3-enyl)indolin-2-one product.

Initially, several common organocatalysts (Scheme 3) bearing a quinuclidine and/or a thiourea moiety,[12] were examined for the catalysis of the cross-aldol reaction of isatin **1a** as an acceptor and (*E*)-4-phenylbut-3-en-2-one **2a** as a donor with a catalyst loading of 20 mol % in THF at ambient temperature. The results of the screening and optimizations are shown in Table 1. At the beginning, we examined the reaction substrates of isatin **1a** with the benzylideneacetone **2a** with the molar ratio of 1:1 in the presence of 20 mol % of quinidine-derived primary amine or combination with 40 mol % of trifluoro acetic acid (TFA) as Brønsted acid additives. No expected cross aldol adducts were observed after direct determination by TLC (entries 1 and 2). This indicated that it is impossible for the cross-aldol reaction in which the primary amine



Scheme 3. Catalysts screened for the cross-aldol reaction of isatins with α,β-unsaturated ketones.

Table 1
Catalyst screening and reaction conditions optimization[a]



Entry	Cat.	Solv.	Ratio (**1a**/**2a**)	Time (h)	Yield[b] (%)	ee[c] (%)
1[d]	**I**	THF	1:1	24	NR	—
2[d]	**I**+**TFA**	THF	1:1	24	NR	—
3[d]	**II**	THF	1:1	120	Trace	—
4[d]	**III**	THF	1:1	48	70	63
5[d]	**IV**	THF	1:1	24	46	75
6	**IV**	THF	1:2	24	51	79
7	**IV**	THF	1:2	48	82	80
8[d]	**V**	THF	1:1	48	75	60
9	**V**	THF	1:2	48	78	71
10	**VI**	THF	1:2	48	34	31
11	**IV**	Toluene	1:2	48	52	33
12	**IV**	DCM	1:2	48	58	47
13	**IV**	Et_2O	1:2	48	56	38
14	**IV**	*n*-Hexane	1:2	48	35	45
15	**IV**	EtOH	1:2	48	68	47
16	**IV**	Dioxane	1:2	48	69	76

[a] Unless otherwise indicated, all reactions were carried out with isatin **1a** (0.10 mmol), benzylideneacetone **2a** (0.20 mmol) and the catalyst (0.04 mmol, 20 mol %) in the specified solvent (1.0 mL) at room temperature.
[b] Yield of the isolated product after column chromatography.
[c] Determined by HPLC analysis. Absolute configuration of **IV** for *R* enantiomer and **V** for *S* enantiomer were determined according to the literature reported.[11,14]
[d] Carried out with isatin **1a** (0.20 mmol) and **2a** (0.20 mmol).

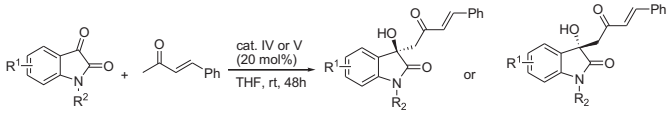
catalyst unilaterally activates the benzylideneacetone **2a** to form an enamine intermediate. Then, we turned our attention to other chiral Brønsted acid–Brønsted base bifunctional catalysts. The *Cinchona alkaloid* derived bifunctional catalyst **II** was found to be ineffective for the reaction, affording essentially only trace amount of the desired products after prolonged reaction times (5 days, entry 3). Pleasingly, the reaction proceeded smoothly in the presence of 20 mol % Takemoto thiourea catalyst **III** to afford the desired aldol product **3a** in 70% yield with 63% ee after 48 h (entry 4).[13] Subsequently, the quinidine-derived thiourea catalyst **IV** and its pseudo-enantiomer **V** were investigated for this transformation, which furnished the desired product with improvement in both yields and enantioselectivities (**IV**: 82% yield and 80% ee; **V**: 78% yield and 71% ee, respectively) after 48 h of reaction time, while the reactant's molar ratio of **1a**/**2a**=1:2 was employed (entry 7 vs

entries 5 and 6; entry 9 vs entry 8). Furthermore, the C6′–OH *Cinchona alkaloid* derivative bearing a C9–OBn group **VI** was also tested for this reaction, which gave the inferior results in terms of both reactivity and enantioselectivity (entry 10). Furthermore, several common solvents were screened for this reaction in the presence of 20 mol % of quinidine-derived thiourea catalysts **IV**. The results demonstrated that THF was still the optimal reaction media for this transformation (entry 7 vs entries 11–16). Finally, *Cinchona alkaloid* derived thioureas **IV** and **V** were proved to be effective catalysts for this reaction, which suggest that basic quinuclidine backbone and acidic thiourea motif co-activate both benzylideneacetone **2a** and isatin **1a** in this transformation.

With the optimized reaction conditions established, the generality and limitation of the protocol was investigated for the asymmetric cross-aldol reaction of isatin derivatives **1a**–**l** and α,β-unsaturated ketone **2a**, which catalyzed by 20 mol % of *Cinchona alkaloid* derived thiourea catalysts **IV** and **V** in THF at room temperature, respectively. The representative results are summarized in Table 2. Generally, these results indicated that the electronic property and steric hindrance have a great effect on the reactivity and enantioselectivity of the cross-aldol reaction. Gratefully, when substituents (–Br, –Cl) on 4-position of isatin backbones **1b** or **1c** were employed for the aldol reactions catalyzed by **IV** and **V**, respectively, which progressed very well and provided the desired products in increased yields (80–94%) with improved enantioselectivities (83–93% ees) relative to those of the other isatin derivatives (entries 3–6 vs entries 1 and 2, 7–24). To our disappointment, for the substrates **1d**–**j** bearing different substituents (–F, –Cl, –Br, $-CF_3$, –Me) on 5-, 6- and 7-positions of isatin backbones, the cross-aldol reactions with the benzylideneacetone **2a** gave the desired products **3d**–**j** and **3d′**–**j′** with varying levels of yields (18–93%) and moderate to high enantiomeric ratios (30–81% ees) (entries 7–20). In addition, the *N*-Me and *N*-Bn protected isatins **1k** and **1l** were also tested under otherwise identical conditions, and the *N*-Bn protected isatins **1l** displayed better reactivities and enantioselectivities than those of **1k** in this aldol transformation (entries 23 and 24 vs entries 21 and 22). On the other hand, compared the catalytic results of **3a′**–**l′** with that of **3a**–**l**, it is evident that the quinidine derived thiourea **IV** generally was a more effective catalyst than its pseudo-enantiomer **V**, thought 4-Br and 4-Cl substituted isatins **1b** or **1c** furnished the expected aldol adducts with slight better enantioselectivities under the catalysis by **V** (93% ee and 86% ee *vs* 88% ee and 83% ee).

Having found the obvious regulation that the cross-aldol reactions of 4-Br and 4-Cl substituted isatins **1b** or **1c** with the benzylideneacetone **2a** showed distinctly better reactivities and enantioselectivities than those of the other position substituted isatin derivatives, we further investigated the cross-aldol reaction of 4-chloroisatin **1c** with various of α,β-unsaturated ketones **2b**–**o** in the presence of 20 mol % of *Cinchona alkaloid* derived thiourea catalysts **IV** and **V** in THF at room temperature. As shown in Table 3, all the aldol reactions between α,β-unsaturated ketones **2b**–**o** and 4-chloroisatin **1c** proceeded smoothly, affording the corresponding aldol adducts **3aa**–**nn** and **3aa′**–**nn′** in good to excellent yields (85–98% yields) with good to excellent enantiomeric excesses (70–97% ees). For the benzylideneacetone derivatives **2b**–**l**, the electron-donating groups (–OMe, –Me, $-^{i}Pr$) and the electron-withdrawing groups (–Cl, –F, –Br, $-CF_3$) on different position of the phenyl ring demonstrated great effect on enantioselectivities

Table 2
Cross-aldol reaction of isatins **1a**–**l** and α,β-unsaturated ketone **2a**[a]

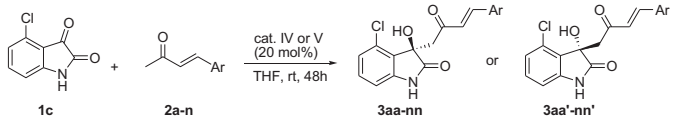


1a-l 2a 3a-l 3a'-l'

Entry	Cat.	Sub. (R^1, R^2)	Yield[b] (%)	ee[c] (%)
1	**IV**	R^1=H, R^2=H (**1a**)	**3a**/82	+80
2	**V**	R^1=H, R^2=H (**1a**)	**3a′**/78	−71
3	**IV**	R^1=4-Br, R^2=H (**1b**)	**3b**/94	+88
4	**V**	R^1=4-Br, R^2=H (**1b**)	**3b′**/88	−93
5	**IV**	R^1=4-Cl, R^2=H (**1c**)	**3c**/88	+83
6	**V**	R^1=4-Cl, R^2=H (**1c**)	**3c′**/80	−86
7	**IV**	R^1=5-Cl, R^2=H (**1d**)	**3d**/93	+77
8	**V**	R^1=5-Cl, R^2=H (**1d**)	**3d′**/72	−75
9	**IV**	R^1=5-F, R^2=H (**1e**)	**3e**/89	+79
10	**V**	R^1=5-F, R^2=H (**1e**)	**3e′**/74	−55
11	**IV**	R^1=5-Br, R^2=H (**1f**)	**3f**/89	+81
12	**V**	R^1=5-Br, R^2=H (**1f**)	**3f′**/77	−63
13	**IV**	R^1=5-Me, R^2=H (**1g**)	**3g**/67	+63
14	**V**	R^1=5-Me, R^2=H (**1g**)	**3g′**/47	−59
15	**IV**	R^1=6-Br, R^2=H (**1h**)	**3h**/90	+75
16	**V**	R^1=6-Br, R^2=H (**1h**)	**3h′**/68	−53
17	**IV**	R^1=7-CF_3, R^2=H (**1i**)	**3i**/37	+76
18	**V**	R^1=7-CF_3, R^2=H (**1i**)	**3i′**/18	−30
19	**IV**	R^1=5,6-2F, R^2=H (**1j**)	**3j**/89	+73
20	**V**	R^1=5,6-2F, R^2=H (**1j**)	**3j′**/74	−75
21	**IV**	R^1=H, R^2=Me (**1k**)	**3k**/32	+62
22	**V**	R^1=H, R^2=Me (**1k**)	**3k′**/34	−47
23	**IV**	R^1=H, R^2=CH_2Ph (**1l**)	**3l**/95	+72
24	**V**	R^1=H, R^2=CH_2Ph (**1l**)	**3l′**/78	−67

[a] Unless otherwise indicated, all reactions were carried out with isatin **1a**–**n** (0.10 mmol), benzylideneacetone **2a**(0.2 mmol) and the catalyst (0.04 mmol, 20 mol %) in THF (1.0 mL) at room temperature for 48 h.
[b] Yield of the isolated product after column chromatography.
[c] Determined by HPLC analysis.

Table 3
Cross-aldol reaction of isatin derivative **1c** and α,β-unsaturated ketones **2b**–**o**[a]



1c 2a-n 3aa-nn 3aa'-nn'

Entry	Cat.	Sub. (Ar)	Yield[b] (%)	ee[c] (%)
1	**IV**	*o*-$MeOC_6H_4$ (**2b**)	**3aa**/92	+87
2	**V**	*o*-$MeOC_6H_4$ (**2b**)	**3aa′**/94	−83
3	**IV**	*o*-FC_6H_4 (**2c**)	**3bb**/98	+82
4	**V**	*o*-FC_6H_4 (**2c**)	**3bb′**/96	−86
5	**IV**	*o*-ClC_6H_4 (**2d**)	**3cc**/90	+76
6	**V**	*o*-ClC_6H_4 (**2d**)	**3cc′**/92	−73
7	**IV**	*m*-ClC_6H_4 (**2e**)	**3dd**/98	+81
8	**V**	*m*-ClC_6H_4 (**2e**)	**3dd′**/96	−74
9	**IV**	*p*-$MeOC_6H_4$ (**2f**)	**3ee**/87	+85
10	**V**	*p*-$MeOC_6H_4$ (**2f**)	**3ee′**/85	−87
11	**IV**	*p*-$^{i}PrC_6H_4$ (**2g**)	**3ff**/90	+89
12	**V**	*p*-$^{i}PrC_6H_4$ (**2g**)	**3ff′**/87	−85
13	**IV**	*p*-MeC_6H_4 (**2h**)	**3gg**/94	+88
14	**V**	*p*-MeC_6H_4 (**2h**)	**3gg′**/97	−79
15	**IV**	*p*-FC_6H_4 (**2i**)	**3hh**/97	+83
16	**V**	*p*-FC_6H_4 (**2i**)	**3hh′**/98	−70
17	**IV**	*p*-ClC_6H_4 (**2j**)	**3ii**/92	+86
18	**V**	*p*-ClC_6H_4 (**2j**)	**3ii′**/94	−83
19	**IV**	*p*-BrC_6H_4 (**2k**)	**3jj**/93	+85
20	**V**	*p*-BrC_6H_4 (**2k**)	**3jj′**/93	−94
21	**IV**	*p*-$CF_3C_6H_4$ (**2l**)	**3kk**/93	+63
22	**V**	*p*-$CF_3C_6H_4$ (**2l**)	**3kk′**/92	−71
23	**IV**	2-Thienyl (**2m**)	**3ll**/95	+85
24	**V**	2-Thienyl (**2m**)	**3ll′**/96	−87
25	**IV**	2-Furyl (**2n**)	**3mm**/98	+93
26	**V**	2-Furyl (**2n**)	**3mm′**/97	−92
27	**IV**	1-Naphthyl (**2o**)	**3nn**/96	+91
28	**V**	1-Naphthyl (**2o**)	**3nn′**/95	−97

[a] Unless otherwise indicated, all reactions were carried out with isatin (0.10 mmol), α,β-unsaturated ketones (0.2 mmol) and the catalyst (0.04 mmol, 20 mol %) in THF (1.0 mL) at room temperature for 48 h.
[b] Yield of the isolated product after column chromatography.
[c] Determined by HPLC analysis.

(from 63% ee up to 94% ee), albeit with a slight variation in the reactivity as evidenced by the yields of the corresponding aldol adducts **3aa**–**3kk** and **3aa′**–**3kk′** (87–98% yields) (entries 1–22). Intriguingly, we found that the α,β-unsaturated ketones **2m**–**o** bearing heteroaromatic or fused aromatic rings were more suitable substrates for this catalytic aldol reaction in the presence of the catalysts **IV** or **V**, furnishing the desired products **3ll**–**nn** and **3ll′**–**nn′** in 95–98% yields with 85–97% ees (entries 23–28). From Tables 2 and 3, it could be observed that *cinchona alkaloid* derived thiourea **IV** and its pseudo-enantiomer **V** gave apparently different catalytic results for the cross-aldol reactions of either isatins **1a**–**l** with the benzylideneacetone **2a** or the benzylideneacetone derivatives **2b**–**l** with 4-chloroisatin **1c** (Table 2, entries 1–24 and Table 3, entries 1–22). However, thiourea catalysts **IV** and **V** herein almost did not show any catalytic difference for the cross-aldol reactions of **2m**–**o** with **1c** in terms of both the reactivities and enantioselectivities (Table 2, entries 23–28).

In the light of Zhao's creative noncovalent catalysis mechanism for the aldol reaction of unactivated ketones and activated carbonyl compounds[11] and the catalyst screening results discussed above in Table 1, we envision that the (*E*)-4-arylbut-3-en-2-ones is deprotonated by the tertiary amine in the quinuclidine backbone to form active enolates. The isatins could be activated and orientated through hydrogen bonding between the isatin carbonyl groups and the thiourea motifs. The co-activation of both α,β-unsaturated ketones and isatins by the bifunctional Brønsted acid–Brønsted base catalyst is attributable to working for the cross-aldol reaction to the corresponding aldol adducts. In addition, the catalytic results in Tables 2 and 3 show that the steric hindrance at position 4 on isatins plays a positive role for enantioface discrimination in transition state. This catalytic regulation has also been found and proposed by Zhao group in their genius publication.[11]

2. Results and discussion

See Scheme 3, Tables 1, 2 and 3.

3. Conclusions

In summary, we have developed the asymmetric cross-aldol reaction of isatins with α,β-unsaturated ketones catalyzed by a *Cinchona alkaloid*-derivated bifunctional Brønsted acid–Brønsted base catalyst, to afford the aldol adducts in moderate to good yields (18–98%) with moderate to good enantioselectivities (30–97%). Both enantiomers of the 3-hydroxyindolin-3-one adducts can be prepared by using two epimers of the quinidine-derived thiourea catalysts. The noncovalent organo-catalyzed asymmetric transformation displays a broad substrate scope and wide functional-group tolerability, albeit the electronic and steric properties of both reaction partners have a great and regular effect on the reactivity and stereocontrol. Considering the resulting 3-hydroxyindolin-2-ones with an additional enone moiety as useful chiral building blocks for the synthetic utility, further investigations of the enantioselective epoxidation or cyclization of the Aldol adducts are undergoing in our laboratory.

4. Experimental section

4.1. General

^{1}H (400 MHz) and ^{13}C (100 MHz) spectra were recorded in DMSO-d_6 on Varian Inova-400 NMR spectrometer. Chemical shifts (δ ppm) are relative to the resonance of the deuterated solvent as the internal standard (DMSO-d_6, δ 2.50 ppm for proton NMR, δ 39.51 ppm for carbon NMR). ^{1}H NMR data are reported as follows: chemical shift (δ, ppm), multiplicity (s=singlet, d=doublet, q=quartet, m=multiplet), coupling constants (J) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). Liquid chromatography–mass spectrometry (LC–MS) for all the compounds were determined with ESI resource. High performance liquid chromatography (HPLC) analysis was performed on an Agilent Technologies 1200 Series instrument equipped with a quaternary pump, using a Daicel Chiralcel OD-H Column (250×4.6 mm) and Daicel Chiralcel OJ-H Column (250×4.6 mm). UV absorption was monitored at 210–280 nm. Optical rotations were measured on an Autopol IV polarimeter, and $[\alpha]_D$ values are reported in 10^{-1} dg cm^2 g^{-1}; concentration (c) is reported in g/100 mL. Commercial grade reagents and solvents were used without further purification; otherwise, where necessary, they were purified as recommended. Chiral organocatalyst was prepared according to reported methods.

4.2. General procedure for the cross aldol addition

In an ordinary vial equipped with a Teflon-coated stir bar, thiourea **IV** or **V** (0.04 mmol, 11.89 mg, 20 mol %) was dissolved in 1.0 mL of THF. Then the corresponding isatins **1** (0.1 mmol, 1.0 equiv) was added, followed by the addition of α,β-unsaturated ketones **2** (0.2 mmol, 2.0 equiv). The vial was capped with a rubber stopper and the mixture was stirred at room temperature for the time given in the tables. The crude mixture was then purified by flash column chromatography silica gel, using hexane/ethylacetate 2:1 as the eluent. Solvent was removed in vacuo to give the desired products.

4.3. Spectroscopic data for part of products

*4.3.1. (R)-3-Hydroxy-3-((E)-2-oxo-4-phenylbut-3-enyl)indolin-2-one (**3a**).* White solid, 82% yield and 80% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ=10.27 (s, 1H), 7.67–7.64 (m, 2H), 7.54 (d, J=16.3 Hz, 1H), 7.42–7.40 (m, 3H), 7.28 (d, J=7.4 Hz, 1H), 7.16 (t, J=7.7 Hz, 1H), 6.88 (t, J=7.5 Hz, 1H), 6.80 (d, J=7.7 Hz, 1H), 6.76 (d, J=16.3 Hz, 1H), 6.09 (s, 1H), 3.67 (d, J=16.4 Hz, 1H), 3.25 (d, J=16.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ=201.60, 183.59, 147.99, 147.92, 139.58, 136.80, 135.88, 134.28, 133.78, 133.28, 131.66, 129.10, 126.51, 114.75, 78.46, 53.01. $[\alpha]_D^{25}$ +67.0 (c 1.1, MeOH). The ee was determined by HPLC analysis on a Daicel Chiralpak OJ-H column: hexane/*i*-PrOH 80:20 flow rate 1 ml/min, λ=210 nm: major enantiomer: t_R=32.81 min; minor enantiomer: t_R=37.66 min. ESI–MS: m/z [M+H]$^+$ calcd for $C_{18}H_{16}NO_3$: 294.1126; found: 293.1052.

*4.3.2. (R)-4-Bromo-3-hydroxy-3-((E)-2-oxo-4-phenylbut-3-enyl)indolin-2-one (**3b**).* White solid, 94% yield and 88% ee. ^{1}H NMR (300 MHz, acetone-d_6) δ=9.43 (s, 1H), 7.55–7.52 (m, 2H), 7.48 (d, J=16.3 Hz, 1H), 7.30–7.28 (m, 3H), 7.02–6.97 (m, 1H), 6.93–6.90 (m, 1H), 6.77 (d, J=7.5 Hz, 1H), 6.65 (d, J=16.3 Hz, 1H), 5.14 (d, J=17.5 Hz, 1H), 4.14 (d, J=17.1 Hz, 1H), 3.36 (d, J=17.1 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ=196.88, 178.14, 145.91, 143.71, 134.81, 131.55, 131.33, 129.85, 129.62, 129.22, 126.45, 125.74, 118.99, 109.61, 75.14, 46.42. $[\alpha]_D^{25}$ +35.3 (c 1.3, MeOH). The ee was determined by HPLC analysis on a Daicel Chiralpak OJ-H column: hexane/*i*-PrOH 75:25 flow rate 1 ml/min, λ=280 nm: major enantiomer: t_R=23.22 min; minor enantiomer: t_R=14.95 min. ESI–MS: m/z [M+H]$^+$ calcd for $C_{18}H_{15}BrNO_3$: 372.023; found: 372.024.

*4.3.3. (R)-4-Chloro-3-hydroxy-3-((E)-2-oxo-4-phenylbut-3-enyl)indolin-2-one (**3c**).* White solid, 88% yield and 83% ee. ^{1}H NMR (300 MHz, acetone-d_6) δ=9.37 (s, 1H), 7.52–7.44 (m, 3H), 7.29–7.23 (m, 5H), 6.76–6.72 (m, 1H), 6.66 (d, J=16.3 Hz, 1H), 5.24 (s, 1H), 3.62 (d, J=17.0 Hz, 1H), 3.30 (d, J=17.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ=196.97, 178.94, 145.66, 143.67, 134.84, 131.34, 130.48, 129.61, 129.17, 128.18, 126.78, 122.69, 109.16, 99.88, 73.58, 48.06.

$[\alpha]_D^{25}$ +67.8 (*c* 1.2, MeOH). The ee was determined by HPLC analysis on a Daicel Chiralpak OD-H column: hexane/*i*-PrOH 75:25 flow rate 1 ml/min, λ=210 nm: major enantiomer: t_R=13.85 min; minor enantiomer: t_R=11.03 min. ESI–MS: *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{15}ClNO_3$: 328.0735; found: 328.0742.

*4.3.4. (R)-5-Chloro-3-hydroxy-3-((E)-2-oxo-4-phenylbut-3-enyl)indolin-2-one (**3d**).* White solid, 93% yield and 77% ee. ^{1}H NMR (300 MHz, acetone-d_6) δ=9.46 (s, 1H), 7.88–7.65 (m, 2H), 7.61 (d, *J*=16.4 Hz, 1H), 7.43–7.40 (m, 4H), 7.23 (dd, *J*=8.3, 2.1 Hz, 1H), 6.91 (d, *J*=8.3 Hz, 1H), 6.80 (d, *J*=16.3 Hz, 1H), 5.29 (s, 1H), 3.76 (d, *J*=16.9 Hz, 1H), 3.43 (d, *J*=16.9 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ=197.02, 178.65, 143.54, 142.34, 134.88, 134.40, 131.29, 129.62, 129.37, 129.15, 126.81, 125.87, 124.72, 111.50, 73.78, 48.12. $[\alpha]_D^{25}$ +32.7 (*c* 1.3, MeOH). The ee was determined by HPLC analysis on a Daicel Chiralpak OJ-H column: hexane/*i*-PrOH 75:25 flow rate 1 ml/min, λ=210 nm: major enantiomer: t_R=29.99 min; minor enantiomer: t_R=44.39 min. ESI–MS: *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{15}ClNO_3$: 328.0735; found: 328.0739.

*4.3.5. (R)-5-Fluoro-3-hydroxy-3-((E)-2-oxo-4-phenylbut-3-enyl)indolin-2-one (**3e**).* White solid, 79% yield and 78% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ=10.29 (s, 1H), 7.68–7.66 (m, 2H), 7.55 (d, *J*=16.3 Hz, 1H), 7.43–7.41 (m, 3H), 7.20 (dd, *J*=8.2, 2.7 Hz, 1H), 7.01–6.93 (m, 1H), 6.79–6.76 (m, 1H), 6.76 (d, *J*=16.3 Hz, 1H), 6.20 (s, 1H), 3.70 (d, *J*=16.7 Hz, 1H), 3.28 (d, *J*=16.7 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ=196.94, 178.90, 159.64, 157.29, 143.47, 139.52, 134.89, 134.05, 133.97, 131.29, 129.62, 129.13, 126.88, 115.79, 115.54, 112.48, 112.16, 110.77, 110.68, 74.00, 48.14. $[\alpha]_D^{25}$ +71.4 (*c* 0.5, MeOH). The ee was determined by HPLC analysis on a Daicel Chiralpak OJ-H column: hexane/*i*-PrOH 70:30 flow rate 1 ml/min, λ=254 nm: major enantiomer: t_R=20.94 min; minor enantiomer: t_R=32.68 min. ESI–MS: *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{15}FNO_3$: 312.103; found: 312.1038.

*4.3.6. (R)-5-Bromo-3-hydroxy-3-((E)-2-oxo-4-phenylbut-3-enyl)indolin-2-one (**3f**).* White solid, 89% yield and 81% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ=10.43 (s, 1H), 7.67 (m, 2H), 7.56 (d, *J*=16.3 Hz, 1H), 7.50 (d, *J*=2.0 Hz, 1H), 7.43–7.41 (m, 3H), 7.34 (dd, *J*=8.2, 2.2 Hz, 1H), 6.78 (s, 1H), 6.75 (d, *J*=9.0 Hz, 1H), 6.22 (s, 1H), 3.76 (d, *J*=16.8 Hz, 1H), 3.31 (d, *J*=16.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ=197.02, 178.50, 143.51, 142.76, 134.88, 134.80, 132.18, 131.28, 129.60, 129.15, 127.34, 126.81, 113.57, 112.06, 73.73, 48.10. $[\alpha]_D^{25}$ +18.1 (*c* 1.1, MeOH) The ee was determined by HPLC analysis on a Daicel Chiralpak OJ-H column: hexane/*i*-PrOH 70:30 flow rate 1 ml/min, λ=254 nm: major enantiomer: t_R=25.50 min; minor enantiomer: t_R=31.26 min. ESI–MS: *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{15}BrNO_3$: 372.023; found: 372.023.

*4.3.7. (R)-3-Hydroxy-5-methyl-3-((E)-2-oxo-4-phenylbut-3-enyl)indolin-2-one (**3g**).* White solid, 67% yield and 63% ee. ^{1}H NMR (300 MHz, acetone-d_6) δ=9.08 (s, 1H), 7.56–7.48 (m, 2H), 7.44 (d, *J*=16.3 Hz, 1H), 7.34–7.21 (m, 3H), 7.04 (s, 1H), 6.86 (d, *J*=7.7 Hz, 1H), 6.66 (d, *J*=16.3 Hz, 1H), 6.64 (d, *J*=7.7 Hz, 1H), 4.98 (s, 1H), 3.48 (d, *J*=16.3 Hz, 1H), 3.19 (d, *J*=16.3 Hz, 1H), 2.09 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ=196.90, 178.92, 143.19, 140.84, 134.94, 132.21, 131.22, 130.56, 129.77, 129.60, 129.11, 127.01, 125.14, 109.82, 73.88, 48.43, 21.32. $[\alpha]_D^{25}$ +35.3 (*c* 0.8, MeOH). The ee was determined by HPLC analysis on a Daicel Chiralpak OJ-H column: hexane/*i*-PrOH 75:25 flow rate 1 ml/min, λ=280 nm: major enantiomer: t_R=17.0 min; minor enantiomer: t_R=27.68 min. ESI–MS: *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{18}NO_3$: 308.1281; found: 308.1283.

*4.3.8. (R)-6-Bromo-3-hydroxy-3-((E)-2-oxo-4-phenylbut-3-enyl)indolin-2-one (**3h**).* White solid, 90% yield and 75% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ=10.45 (s, 1H), 7.67–7.65 (m, 2H), 7.56 (d, *J*=16.3 Hz, 1H), 7.42–7.40 (m, 2H), 7.24 (d, *J*=7.8 Hz, 1H), 7.08 (dd, *J*=7.9 Hz, 1.7 Hz, 1H), 6.96 (d, *J*=1.5 Hz, 1H), 6.76 (d, *J*=16.3 Hz, 1H), 6.20 (s, 1H), 3.72 (d, *J*=16.9 Hz, 1H), 3.31 (d, *J*=16.9 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ=197.9, 179.70, 146.09, 144.48, 135.77, 132.54, 132.21, 130.53, 130.07, 127.69, 127.12, 125.36, 123.17, 113.85, 74.28, 49.06. $[\alpha]_D^{25}$ +81.2 (*c* 0.9, MeOH). The ee was determined by HPLC analysis on a Daicel Chiralpak OD-H column: hexane/*i*-PrOH 75:25 flow rate 1 ml/min, λ=210 nm: major enantiomer: t_R=13.45 min; minor enantiomer: t_R=17.88 min. ESI–MS: *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{15}BrNO_3$: 372.023; found: 372.024.

*4.3.9. (R)-7-(Trifluoromethyl)-3-hydroxy-3-((E)-2-oxo-4-phenylbut-3-enyl)indolin-2-one (**3i**).* White solid, 37% yield and 76% ee. ^{1}H NMR (300 MHz, acetone-d_6) δ=9.54 (s, 1H), 7.59–7.49 (m, 3H), 7.47 (d, *J*=16.3 Hz, 1H), 7.40–7.32 (m, 1H), 7.32–7.19 (m, 3H), 6.99 (t, *J*=7.4 Hz, 1H), 6.65 (d, *J*=16.3 Hz, 1H), 3.68 (d, *J*=17.2 Hz, 1H), 3.37 (d, *J*=17.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ=197.01, 179.35, 143.71, 141.05, 134.85, 134.35, 131.32, 129.92, 129.62, 129.30, 129.17, 128.06, 126.59, 125.90, 125.73, 122.04, 122.00, 72.26, 48.28. $[\alpha]_D^{25}$ +66.9 (*c* 0.9, MeOH). The ee was determined by HPLC analysis on a Daicel Chiralpak OJ-H column: hexane/*i*-PrOH 75:25 flow rate 1 ml/min, λ=280 nm: major enantiomer: t_R=21.15 min; minor enantiomer: t_R=25.01 min. ESI–MS: *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{15}F_3NO_3$: 362.100; found: 362.1013.

*4.3.10. (R)-5,6-Difluoro-3-hydroxy-3-((E)-2-oxo-4-phenylbut-3-enyl)indolin-2-one (**3j**).* White solid, 89% yield and 73% ee. ^{1}H NMR (300 MHz, acetone-d_6) δ=9.34 (s, 1H), 7.55–7.52 (m, 2H), 7.47 (d, *J*=16.4 Hz, 1H), 7.30–7.23 (m, 4H), 6.76–6.70 (m, 1H), 6.66 (d, *J*=16.3 Hz, 1H), 5.21 (s, 1H), 3.62 (d, *J*=17.0 Hz, 1H), 3.36–3.17 (d, *J*=17.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ=197.91, 179.86, 152.62, 152.48, 150.19, 150.05, 147.79, 147.67, 145.45, 145.30, 144.51, 141.11, 140.99, 135.76, 132.20, 130.53, 130.85, 130.06, 129.30, 129.24, 127.67, 115.29, 115.22, 115.09, 115.00, 100.92, 100.70, 74.51, 48.96. $[\alpha]_D^{25}$ +73.4 (*c* 1.2, MeOH). The ee was determined by HPLC analysis on a Daicel Chiralpak OJ-H column: hexane/*i*-PrOH 75:25 flow rate 1 ml/min, λ=210 nm: major enantiomer: t_R=19.60 min; minor enantiomer: t_R=22.44 min. ESI–MS: *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{14}F_2NO_3$: 330.0936; found: 330.0956.

*4.3.11. (R)-3-Hydroxy-1-methyl-3-((E)-2-oxo-4-phenylbut-3-enyl) indolin-2-one (**3k**).* White solid, 32% yield and 62% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ=7.66–7.64 (m, 2H), 7.53 (d, *J*=16.3 Hz, 1H), 7.45–7.38 (m, 3H), 7.33 (d, *J*=7.2 Hz, 1H), 7.26 (t, *J*=7.7 Hz, 1H), 6.96 (t, *J*=7.4 Hz, 2H), 6.74 (d, *J*=16.3 Hz, 1H), 6.45–5.74 (m, 1H), 3.72 (d, *J*=16.7 Hz, 1H), 3.30 (d, *J*=16.7 Hz, 1H), 3.14–3.08 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ=197.76, 178.18, 145.73, 144.28, 135.79, 132.42, 132.20, 130.74, 130.53, 130.04, 127.68, 124.85, 123.46, 109.79, 74.34, 49.60, 27.50. $[\alpha]_D^{25}$ +65.1 (*c* 0.8, MeOH). The ee was determined by HPLC analysis on a Daicel Chiralpak OJ-H column: hexane/*i*-PrOH 75:25 flow rate 1 ml/min, λ=230 nm: major enantiomer: t_R=18.82 min; minor enantiomer: t_R=17.01 min. ESI–MS: *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{18}NO_3$: 308.1281; found: 308.1283.

*4.3.12. (R)-1-Benzyl-3-hydroxy-3-((E)-2-oxo-4-phenylbut-3-enyl)indolin-2-one (**3l**).* White solid, 95% yield and 72% ee. ^{1}H NMR (300 MHz, acetone-d_6) δ=7.55–7.52 (m, 2H), 7.49 (d, *J*=16.2 Hz, 1H), 7.36 (d, *J*=6.9 Hz, 2H), 7.30–7.25 (m, 4H), 7.21–7.19 (m, 3H), 7.02 (t, *J*=7.2 Hz, 1H), 6.82 (t, *J*=7.5 Hz, 1H), 6.66 (d, *J*=16.3 Hz, 1H), 6.61 (d, *J*=7.9 Hz, 1H), 4.81 (q, *J*=15.9 Hz, 2H), 3.68(d, *J*=16.6 Hz, 1H), 3.36(d, *J*=16.6 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ=197.91, 178.38, 144.84, 144.83, 144.52, 137.94, 135.82, 132.47, 132.20, 130.05, 128.78, 127.78, 125.07, 123.58, 110.52, 74.44, 49.29, 44.36. $[\alpha]_D^{25}$ +57.4 (*c* 1.3, MeOH). The ee was determined by HPLC analysis on a Daicel Chiralpak OJ-H column: hexane/*i*-PrOH 75:25 flow rate 1 ml/min, λ=230 nm: major enantiomer: t_R=29.09 min; minor enantiomer:

t_R=26.46 min. ESI–MS: m/z $[M+H]^+$ calcd for $C_{25}H_{22}NO_3$: 384.1594; found: 384.1607.

*4.3.13. (R)-4-Chloro-3-hydroxy-3-((E)-4-(2-methoxyphenyl)-2-oxobut-3-enyl)indolin-2-one (**3aa**).* Pale yellow solid, 92% yield and 87% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ=10.52 (s, 1H), 7.72 (d, J=16.3 Hz, 1H), 7.64 (d, J=8.0 Hz, 1H), 7.41 (m, 1H), 7.18 (t, J=8.0 Hz, 1H), 7.06 (d, J=8.3 Hz, 1H), 6.98 (t, J=7.6 Hz, 1H), 6.86 (d, J=8.1 Hz, 1H), 6.80 (d, J=16.5 Hz, 1H), 6.77 (d, J=8.5 Hz, 1H), 6.25 (s, 1H), 3.97 (d, J=16.9 Hz, 1H), 3.84 (s, 3H), 3.33 (d, J=16.9 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ=197.72, 179.01, 159.73, 146.53, 138.97, 133.97, 132.28, 131.40, 130.12, 129.04, 127.32, 123.83, 123.61, 122.32, 113.38, 110.08, 75.43, 57.26, 47.79. $[\alpha]_D^{25}$ +87.8 (c 1.0, MeOH). The ee was determined by HPLC analysis on a Daicel Chiralpak OD-H column: hexane/i-PrOH 75:25 flow rate 1 ml/min, λ=210 nm: major enantiomer: t_R=12.7 0 min; minor enantiomer: t_R=15.62 min. ESI–MS: m/z $[M+H]^+$ calcd for $C_{19}H_{17}ClNO_4$: 358.041; found: 358.0855.

*4.3.14. (R)-4-Chloro-3-((E)-4-(2-fluorophenyl)-2-oxobut-3-enyl)-3-hydroxyindolin-2-one (**3bb**).* Pale yellow solid, 98% yield and 82% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ=10.55 (s, 1H), 7.80 (t, J=7.8 Hz, 1H), 7.57 (d, J=16.4 Hz, 1H), 7.52–7.46 (m, 1H), 7.27 (dd, J=16.1, 8.4 Hz, 2H), 7.20 (t, J=8.0 Hz, 1H), 6.88 (d, J=16.2 Hz, 1H), 6.88–6.87 (m, 1H), 6.28 (s, 1H), 4.01 (d, J=17.1 Hz, 1H), 3.39 (d, J=17.1 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ=201.70, 182.99, 167.68, 165.18, 150.56, 144.8, 140.06, 138.36, 136.46, 136.27, 135.48, 135.01, 134.88, 133.47, 133.02, 130.59, 127.75, 127.64, 127.45, 127.34, 114.19, 79.45, 51.92. $[\alpha]_D^{25}$ +85.4 (c 0.85, MeOH). The ee was determined by HPLC analysis on a Daicel Chiralpak OJ-H column: hexane/i-PrOH 70:30 flow rate 1 ml/min, λ=254 nm: major enantiomer: t_R=15.00 min; minor enantiomer: t_R=8.79 min. ESI–MS: m/z $[M+H]^+$ calcd for $C_{18}H_{14}ClFNO_3$: 346.0663; found: 346.0643.

*4.3.15. (R)-4-Chloro-3-((E)-4-(2-chlorophenyl)-2-oxobut-3-enyl)-3-hydroxyindolin-2-one (**3cc**).* White solid, 90% yield and 76% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ=10.55 (s, 1H), 7.87 (dd, J=7.7, 1.3 Hz, 1H), 7.73 (d, J=16.1 Hz, 1H), 7.53 (dd, J=7.9, 0.9 Hz, 1H), 7.46–7.37 (m, 1H), 7.39 (t, J=7.2 Hz, 1H), 7.20 (t, J=8.0 Hz, 1H), 6.91 (d, J=16.2 Hz, 1H), 6.87 (d, J=8.4 Hz, 1H), 6.79 (d, J=7.6 Hz, 1H), 6.29 (s, 1H), 4.00 (d, J=17.2 Hz, 1H), 3.39 (d, J=17.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ=195.98, 177.39, 144.98, 137.22, 134.22, 132.13, 131.77, 130.84, 130.09, 129.87, 128.24, 128.11, 127.82, 127.38, 122.14, 108.61, 73.79, 46.61. $[\alpha]_D^{25}$ +72.3 (c 0.7, MeOH). The ee was determined by HPLC analysis on a Daicel Chiralpak OJ-H column: hexane/i-PrOH 85:15 flow rate 1 ml/min, λ=254 nm: major enantiomer: t_R=24.93 min; minor enantiomer: t_R=22.50 min. ESI–MS: m/z $[M+H]^+$ calcd for $C_{18}H_{13}Cl_2NO_3$: 362.0345; found: 362.0351.

*4.3.16. (R)-4-Chloro-3-((E)-4-(3-chlorophenyl)-2-oxobut-3-enyl)-3-hydroxyindolin-2-one (**3dd**).* White solid, 98% yield and 81% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ=10.53 (s, 1H), 7.80 (s, 1H), 7.65 (d, J=7.2 Hz, 1H), 7.56 (d, J=16.3 Hz, 1H), 7.49–7.42 (m, 2H), 7.19 (t, J=8.0 Hz, 1H), 6.87 (d, J=16.2 Hz, 1H), 6.86 (d, J=8.2 Hz, 1H), 6.78 (d, J=7.8 Hz, 1H), 6.26 (s, 1H), 4.05 (d, J=17.9 Hz, 1H), 3.38 (d, J=17.9 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ=201.90, 183.05, 150.62, 146.90, 142.10, 139.37, 136.34, 135.81, 135.43, 133.70, 133.58, 133.10, 132.80, 127.72, 127.61, 114.11, 79.41, 51.67. $[\alpha]_D^{25}$ +82.7 (c 0.6, MeOH). The ee was determined by HPLC analysis on a Daicel Chiralpak OJ-H column: hexane/i-PrOH 70:30 flow rate 1 ml/min, λ=254 nm: major enantiomer: t_R=15.63 min; minor enantiomer: t_R=7.81 min. ESI–MS: m/z $[M+H]^+$ calcd for $C_{18}H_{13}Cl_2NO_3$: 362.0345; found: 362.0347.

*4.3.17. (R)-4-Chloro-3-hydroxy-3-((E)-4-(4-methoxyphenyl)-2-oxobut-3-enyl)indolin-2-one (**3ee**).* White solid, 87% yield and 85% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ=10.49 (s, 1H), 7.63 (d, J=8.7 Hz, 2H), 7.53 (d, J=16.2 Hz, 1H), 7.17 (t, J=8.0 Hz, 1H), 6.97(d, J=8.7 Hz, 2H), 6.85 (d, J=8.7 Hz, 1H), 6.76 (d, J=7.7 Hz, 1H), 6.62 (d, J=16.3 Hz, 1H), 6.21 (s, 1H), 4.01 (d, J=17.0 Hz 1H), 3.79 (s, 3H), 3.32 (d, J=17.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ=196.04, 177.54, 161.38, 145.04, 143.04, 130.70, 130.49, 129.83, 127.63, 126.71, 123.54, 122.03,114.48, 108.50, 73.93, 55.39, 45.80. $[\alpha]_D^{25}$ +80.9 (c 0.34, MeOH). The ee was determined by HPLC analysis on a Daicel Chiralpak OJ-H column: hexane/i-PrOH 70:30 flow rate 1 ml/min, λ=210 nm: major enantiomer: t_R=12.61 min; minor enantiomer: t_R=15.79 min. ESI–MS: m/z $[M+H]^+$ calcd for $C_{19}H_{17}ClNO_4$: 358.0841; found: 358.0851.

*4.3.18. (R)-4-Chloro-3-hydroxy-3-((E)-4-(4-isopropylphenyl)-2-oxobut-3-enyl)indolin-2-one (**3ff**).* White solid, 90% yield and 89% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ=10.51 (s, 1H), 7.60 (d, J=8.2 Hz, 2H), 7.55 (d, J=16.3 Hz, 1H), 7.29 (d, J=8.2 Hz, 2H), 7.18 (t, J=8.0 Hz, 1H), 6.86 (d, J=8.2 Hz, 1H), 6.77 (d, J=7.7 Hz, 1H), 6.71 (d, J=16.3 Hz, 1H), 6.23 (s, 1H), 3.99 (d, J=15.1 Hz, 1H), 3.34 (d, J=15.1 Hz, 1H) 2.94–2.87 (m, 1H), 1.19 (d, J=6.9 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ=201.82, 183.09, 157.12, 150.62, 148.70, 137.46, 136.32, 135.43, 134.32, 133.15, 132.55, 130.56, 127.63, 114.11, 79.48, 39.02, 29.21. $[\alpha]_D^{25}$ +84.2 (c 1.0, MeOH). The ee was determined by HPLC analysis on a Daicel Chiralpak OJ-H column: hexane/i-PrOH 70:30 flow rate 1 ml/min, λ=210 nm: major enantiomer: t_R=10.83 min; minor enantiomer: t_R=13.72 min. ESI–MS: m/z $[M+H]^+$ calcd for $C_{21}H_{20}ClNO_3$: 370.1204; found: 370.1194.

*4.3.19. (R)-4-Chloro-3-hydroxy-3-((E)-2-oxo-4-p-tolylbut-3-enyl)indolin-2-one (**3gg**).* White solid, 94% yield and 88% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ=10.51 (s, 1H), 7.57 (d, J=8.0 Hz, 2H), 7.54 (d, J=16.4 Hz, 1H), 7.23 (d, J=8.0 Hz, 2H), 7.18 (t, J=8.0 Hz, 1H), 6.86 (d, J=8.0 Hz, 1H), 6.77 (d, J=7.6 Hz, 1H), 6.71 (d, J=16.4 Hz, 1H), 6.23 (s, 1H), 4.03 (d, J=17.1 Hz, 1H), 3.35 (d, J=17.1 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ=201.80, 183.10, 150.62, 148.67, 146.39, 137.03, 136.20, 135.30, 135.10, 134.20, 133.18, 130.45, 127.68, 114.09, 79.49, 51.48, 26.71. $[\alpha]_D^{25}$ +101.62 (c 0.4, MeOH). The ee was determined by HPLC analysis on a Daicel Chiralpak OJ-H column: hexane/i-PrOH 60:40 flow rate 1 ml/min, λ=210 nm: major enantiomer: t_R=17.08 min; minor enantiomer: t_R=7.98 min. ESI–MS: m/z $[M+H]^+$ calcd for $C_{19}H_{17}ClNO_3$: 342.0891; found: 342.0886.

*4.3.20. (R)-4-Chloro-3-((E)-4-(4-fluorophenyl)-2-oxobut-3-enyl)-3-hydroxyindolin-2-one (**3hh**).* White solid, 97% yield and 83% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ=10.52 (s, 1H), 7.76 (dd, J=8.7, 5.6 Hz, 2H), 7.60 (d, J=16.3 Hz, 1H), 7.26 (t, J=8.8 Hz, 2H), 7.19 (t, J=8.0 Hz, 1H), 6.86 (dd, J=8.2, 0.6 Hz, 1H), 6.78 (dd, J=7.6, 0.4 Hz, 1H), 6.74 (d, J=16.3 Hz, 1H), 6.25 (s, 1H), 4.05 (d, J=17.2 Hz, 1H), 3.37 (d, J=17.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ=201.84, 183.08, 170.26, 167.79, 150.62, 147.46, 136.44, 136.23, 135.44, 133.15, 131.34, 127.70, 121.62, 114.15, 79.47, 51.47. $[\alpha]_D^{25}$ +85.4 (c 0.85, MeOH). The ee was determined by HPLC analysis on a Daicel Chiralpak OJ-H column: hexane/i-PrOH 70:30 flow rate 1 ml/min, λ=210 nm: major enantiomer: t_R=22.00 min; minor enantiomer: t_R=10.61 min. ESI–MS: m/z $[M+H]^+$ calcd for $C_{18}H_{14}ClFNO_3$: 346.0663; found: 346.0646.

*4.3.21. (R)-4-Chloro-3-((E)-4-(4-chlorophenyl)-2-oxobut-3-enyl)-3-hydroxyindolin-2-one (**3ii**).* Pale yellow solid, 92% yield and 86% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ=10.52 (s, 1H), 7.71 (d, J=8.5 Hz, 2H), 7.57 (d, J=16.3 Hz, 1H), 7.47 (d, J=8.5 Hz, 2H), 7.18 (t, J=8.0 Hz, 1H), 6.86 (d, J=8.2 Hz, 1H), 6.79 (d, J=16.6 Hz, 1H), 6.77 (d, J=7.1 Hz, 1H), 6.25 (s, 1H), 4.04 (d, J=17.2 Hz, 1H), 3.36 (d, J=17.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ=196.30, 177.47, 145.02, 141.66, 135.20, 133.18, 130.74, 130.29, 129.84, 129.04, 127.52, 126.47, 122.08, 108.55, 73.85, 45.97. $[\alpha]_D^{25}$ +82.7 (c 0.6, MeOH). The ee was determined by HPLC analysis on a Daicel Chiralpak OJ-H column: hexane/i-PrOH

70:30 flow rate 1 ml/min, λ=210 nm: major enantiomer: t_R=36.09 min; minor enantiomer: t_R=12.65 min. ESI–MS: m/z $[M+H]^+$ calcd for $C_{18}H_{13}Cl_2NO_3$: 362.0345; found: 362.0349.

*4.3.22. (R)-3-((E)-4-(4-Bromophenyl)-2-oxobut-3-enyl)-4-chloro-3-hydroxyindolin-2-one (**3jj**).* Pale yellow solid, 93% yield and 85% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ=10.51 (s, 1H), 7.65–7.59 (m, 4H), 7.55 (d, J=16.3 Hz, 1H), 7.18 (t, J=8.0 Hz, 1H), 6.85 (d, J=8.3 Hz, 1H), 6.79 (d, J=16.3 Hz, 1H), 6.76 (d, J=7.5 Hz, 1H), 6.24 (s, 1H), 4.03 (d, J=17.2 Hz, 1H), 3.36 (d, J=17.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ=196.31, 177.46, 145.02, 141.75, 133.53, 131.97, 130.76, 130.49, 129.83, 127.52, 126.51, 124.95, 122.07, 108.54, 73.84, 45.96. $[\alpha]_D^{25}$ +62.7 (c 1.1, MeOH). The ee was determined by HPLC analysis on a Daicel Chiralpak OJ-H column: hexane/i-PrOH 50:50 flow rate 1 ml/min, λ=210 nm: major enantiomer: t_R=21.86 min; minor enantiomer: t_R=8.68 min. ESI–MS: m/z $[M+H]^+$ calcd for $C_{18}H_{13}BrClNO_3$: 405.984; found: 405.9838.

*4.3.23. (R)-4-Chloro-3-((E)-4-(4-(trifluoromethyl)phenyl)-2-oxobut-3-enyl)-3-hydroxyindolin-2-one (**3kk**).* White solid, 93% yield and 63% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ=10.54 (s, 1H), 7.90 (d, J=8.1 Hz, 2H), 7.77 (d, J=8.3 Hz, 2H), 7.65 (d, J=16.4 Hz, 1H), 7.18 (t, J=7.9 Hz, 1H), 6.90 (d, J=16.4 Hz, 1H), 6.86 (d, J=8.1 Hz, 1H), 6.77 (d, J=7.6 Hz, 1H), 6.26 (s, 1H), 4.06 (d, J=17.3 Hz, 1H) 3.44(d, J=17.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ=201.69, 182.71, 150.29, 146.41, 143.59, 136.09, 136.04, 135.42, 134.46, 133.48, 132.75, 131.07, 127.37, 113.84, 79.09, 51.38. $[\alpha]_D^{25}$ +47.2 (c 0.8, MeOH). The ee was determined by HPLC analysis on a Daicel Chiralpak OD-H column: hexane/i-PrOH 75:25 flow rate 1 ml/min, λ=210 nm: major enantiomer: t_R=15.45 min; minor enantiomer: t_R=12.81 min. ESI–MS: m/z $[M+H]^+$ calcd for $C_{19}H_{14}ClF_3NO_3$: 396.0609; found: 396.062.

*4.3.24. (R)-4-Chloro-3-hydroxy-3-((E)-2-oxo-4-(thiophen-2-yl)but-3-enyl)indolin-2-one (**3ll**).* Pale yellow solid, 95% yield and 85% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ=10.54 (s, 1H), 7.75 (d, J=15.8 Hz, 1H), 7.74 (d, J=5.1 Hz, 1H), 7.77–7.73 (m, 1H), 7.53 (d, J=3.5 Hz, 1H), 7.19 (d, J=8.0 Hz, 1H), 7.17–7.13 (m, 1H), 6.90–6.83 (m, 1H), 6.77 (dd, J=7.7, 0.6 Hz, 1H), 6.43 (d, J=16.0 Hz, 1H), 6.25 (s, 1H), 3.96 (d, J=16.9 Hz, 1H), 3.31 (d, J=16.9 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ=201.20, 183.05, 150.55, 144.72, 141.48, 138.51, 136.33, 136.04, 135.44, 134.34, 133.09, 129.68, 127.66, 114.14, 79.50, 51.42. $[\alpha]_D^{25}$ +90.09 (c 1.1, MeOH). The ee was determined by HPLC analysis on a Daicel Chiralpak OJ-H column: hexane/i-PrOH 60:40 flow rate 1 ml/min, λ=210 nm: major enantiomer: t_R=12.17 min; minor enantiomer: t_R=8.18 min. ESI–MS: m/z $[M+H]^+$ calcd for $C_{16}H_{12}ClNO_3S$: 334.0299; found: 334.0294.

*4.3.25. (R)-4-Chloro-3-((E)-4-(furan-2-yl)-2-oxobut-3-enyl)-3-hydro xyindolin-2-one (**3mm**).* White solid, 98% yield and 93% ee. ^{1}H NMR (300 MHz, DMSO-d_6) δ=10.48 (s, 1H), 7.84 (s, 1H), 7.37 (d, J=15.9 Hz, 1H), 7.16 (t, J=7.9 Hz, 1H), 6.95 (d, J=3.1 Hz, 1H), 6.84 (d, J=8.1 Hz, 1H), 6.74 (d, J=7.7 Hz, 1H), 6.66–6.60 (m, 1H), 6.44 (d, J=15.8 Hz, 1H), 6.21 (s, 1H), 3.92 (d, J=16.9 Hz, 1H), 3.29 (d, J=16.9 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ=195.60, 177.45, 150.34, 146.37, 144.96, 130.75, 129.87, 129.54, 127.49, 122.40, 122.08, 117.24, 113.09, 108.53, 73.91, 45.90. $[\alpha]_D^{25}$ +99.7 (c 0.9, MeOH). The ee was determined by HPLC analysis on a Daicel Chiralpak OJ-H column: hexane/i-PrOH 70:30 flow rate 1 ml/min, λ=210 nm: major enantiomer: t_R=16.19 min; minor enantiomer: t_R=13.37 min. ESI–MS: m/z $[M+H]^+$ calcd for $C_{16}H_{13}ClNO_4$: 318.0528; found: 318.0527.

*4.3.26. (R)-4-Chloro-3-hydroxy-3-((E)-4-(naphthalen-1-yl)-2-oxobut-3-enyl)indolin-2-one (**3nn**).* White solid, 96% yield and 91% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ=10.57 (s, 1H), 8.36 (d, J=16.0 Hz, 1H), 8.27 (d, J=8.2 Hz, 1H), 8.02 (d, J=8.2 Hz, 1H), 7.98 (d, J=8.1 Hz, 1H), 7.91 (d, J=7.2 Hz, 1H), 7.62–7.53 (m, 3H), 7.20 (t, J=8.0 Hz, 1H), 6.88 (d, J=8.2 Hz, 1H), 6.85 (d, J=15.8 Hz, 1H), 6.80 (d, J=7.7 Hz, 1H), 6.30 (s, 1H), 4.15 (d, J=17.1 Hz, 1H), 3.52 (d, J=17.1 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ=196.29, 177.55, 145.02, 139.22, 133.34, 131.05, 131.01, 130.89, 130.82, 130.75, 129.95, 128.75, 128.35, 127.62, 127.19, 126.39, 125.73, 125.42, 123.26, 122.14, 116.29, 108.59, 74.02, 46.16. $[\alpha]_D^{25}$ +87.4 (c 0.3, MeOH). The ee was determined by HPLC analysis on a Daicel Chiralpak OJ-H column: hexane/i-PrOH 70:30 flow rate 1 ml/min, λ=210 nm: major enantiomer: t_R=25.56 min; minor enantiomer: t_R=14.77 min. ESI–MS: m/z $[M+H]^+$ calcd for $C_{22}H_{17}ClNO_3$: 378.0891; found: 378.0881.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.03.042.

References and notes

1. For reviews and books on aldol reaction, see: (a) Mukaiyama, T. *Org. React.* **1982**, *28*, 203–331; (b) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23–32; (c) Heathcock, C. H. In; Trost, B. M., Fleming, I., Heathcock, C. H., Eds. *Comprehensive Organic Synthesis*; Pergamon: Oxford, 1991; Vol. 2, p 133; (d) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352–1375; (e) . ; Mahrwald, R., Ed. ; Wiley-VCH GmbH KGaA: Weinheim, 2004; Vols. 1 and 2; (f) List, B. *Acc. Chem. Res.* **2004**, *37*, 548–557; (g) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580–591; (h) Dalko, P. I.; Moisan, L. *Angew. Chem.* **2004**, *116*, 5248–5286; *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175; (i) Dalko, P. I.; Moisan, L. *Enantioselective Organocatalysis*; Wiley-VCH: Weinheim, 2007; (j) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569 Selected pioneering publications; (k) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; (l) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387; (m) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267; (n) MacMillan, D. W. C.; Northrup, A. B. *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799; (o) Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 5262–5263; (p) Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285–9289.
2. For selected publications: (a) Adachi, S.; Harada, T. *Eur. J. Org. Chem.* **2009**, 3661–3671; (b) Zheng, C.-W.; Wu, Y.-Y.; Wang, X.-S.; Zhao, G. *Adv. Synth. Catal.* **2008**, *350*, 2690–2694; (c) Wang, F.; Xiong, Y.; Liu, X.-H.; Feng, X.-M. *Adv. Synth. Catal.* **2007**, *349*, 2665–2668; (d) Samanta, S.; Zhao, C.-G. *J. Am. Chem. Soc.* **2006**, *128*, 7442–7443; (e) Wang, Y.-J.; Shen, Z.-X.; Ding, J.; Zhang, Y.-W. *Chin. J. Chem.* **2007**, *27*, 235–239.
3. For reviews of oxindole alkaloids, see: (a) Peddibhotla, S. *Curr. Bioact. Compd.* **2009**, *5*, 20–38; (b) Galliford, C. V.; Scheidt, K. A. *Angew. Chem.* **2007**, *119*, 8902–8912; *Angew. Chem., Int. Ed.* **2007**, *46*, 8748–8758; (c) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209–2219; (d) Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 36–51; (e) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003–3025; (f) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381–1407.
4. For examples, see: (a) Raunak; Kumar, V.; Mukherjee, S.; Poonam; Prasad, A. K.; Olsen, C. E.; Schäffer, S. J. C.; Sharma, S. K.; Watterson, A. C.; Errington, W.; Parmar, V. S. *Tetrahedron* **2005**, *61*, 5687–5697; (b) Hewawasam, P.; Erway, M.; Moon, S. L.; Knipe, J.; Weiner, H.; Boissard, C. G.; Post-Munson, D. J.; Gao, Q.; Huang, S.; Gribkoff, V. K.; Meanwell, N. A. *J. Med. Chem.* **2002**, *45*, 1487–1499.
5. Selected examples of natural products that possess 3-substituted 3-hydroxy-oxindole substructures, see: (a) Zhang, H.-P.; Kamano, Y.; Ichihara, Y.; Kizu, H.; Komiyama, K.; Itokawa, H.; Pettit, G. R. *Tetrahedron* **1995**, *51*, 5523–5528; (b) Khuzhaev, V. U.; Zhalolov, I.; Turguniv, K. K.; Tashkhodzhaev, B.; Levkovich, M. G.; Aripova, S. F.; Shashkov, A. S. *Chem. Nat. Compd.* **2004**, *40*, 269–272; (c) Suchý, M.; Kutschy, P.; Monde, K.; Goto, H.; Harada, N.; Takasugi, M.; Dzurilla, M.; Balentová, E. *J. Org. Chem.* **2001**, *66*, 3940–3947; (d) Tang, Y. Q.; Sattler, I.; Thiericke, R.; Grabley, S.; Feng, X.-Z. *Eur. J. Org. Chem.* **2001**, 261–267; (e) Nicolaou, K. C.; Rao, P. B.; Hao, J.-L.; Reddy, M. V.; Rassias, G.; Huang, X.-H.; Chen, D. Y. K.; Snyder, S. A. *Angew. Chem.* **2003**, *115*, pp 1795–1800; *Angew. Chem., Int. Ed.* **2003**, *42*, 1753–1758; (f) Takahashi, C.; Numata, A.; Ito, Y.; Matsumura, E.; Araki, H.; Iwaki, H.; Kushida, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1859–1864; (g)

Sharma, V.; Peddibhotla, S.; Tepe, J. J. *J. Am. Chem. Soc.* **2006**, *128*, 9137–9143; (h) Jimenez, J. I.; Huber, U.; Moore, R. E.; Patterson, G. M. L. *J. Nat. Prod.* **1999**, *62*, 569–572; (i) Hayashi, M.; Rho, M. C.; Enomoto, A.; Fukami, A.; Kim, Y. P.; Kikuchi, Y.; Sunazuka, T.; Hirose, T.; Komiyama, K.; Omura, S. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 14728–14733; (j) Itoh, T.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2009**, *11*, 3854–3857; (k) Kitajima, M.; Mori, I.; Arai, K.; Kogure, N.; Takayama, H. *Tetrahedron Lett.* **2006**, *47*, 3199–3202; (l) Boechat, N.; Kover, W. B.; Bongertz, V.; Bastos, M. M.; Romeiro, N. C.; Azavedo, M. L. G.; Wollinger, W. *Med. Chem.* **2007**, *3*, 533–542.

6. For selected publications: (a) Cravotto, G.; Giovenzana, G. B.; Palmisano, G.; Penoni, A.; Pilati, T.; Sisti, M.; Stazi, F. *Tetrahedron: Asymmetry* **2006**, *17*, 3070–3074; (b) Nakamura, T.; Shirokawa, S. I.; Hosokawa, S.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 677–679; (c) Jnaneshwar, G. K.; Deshpande, V. H. *J. Chem. Res., Synop.* **1999**, *10*, 632–633; (d) Jnaneshwar, G. K.; Bedekar, A. V.; Deshpande, V. H. *Synth. Commun.* **1999**, *29*, 3627–3633.
7. Luppi, G.; Monari, M.; Corrêa, R. J.; Violante, F. de. A.; Pinto, A. C.; Kaptein, B.; Broxterman, Q. B.; Garden, S. J.; Tomasini, C. *Tetrahedron* **2006**, *62*, 12017–12024.
8. Chen, J.-R.; Liu, X.-P.; Zhu, X.-Y.; Li, L.; Qiao, Y.-F.; Zhang, J.-M.; Xiao, W.-J. *Tetrahedron* **2007**, *63*, 10437–10444.
9. Malkov, A. V.; Kabeshov, M. A.; Bella, M.; Kysilka, O.; Malyshev, D. A.; Pluháčková, K.; Kočovský, P. *Org. Lett.* **2007**, *9*, 5473–5476.
10. Nakamura, S.; Hara, N.; Nakashima, H.; Kubo, K.; Shibata, N.; Toru, T. *Chem.—Eur. J.* **2008**, *14*, 8079–8081.
11. Guo, Q.-S.; Bhanushali, M.; Zhao, C.-G. *Angew. Chem.* **2010**, *122*, 9650–9654; *Angew. Chem., Int. Ed.* **2010**, *49*, 9460–9464.
12. The selected publications for the thiourea-based organo-catalysis: (a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902; (b) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217–220; (c) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Adv. Synth. Catal.* **2005**, *347*, 1643–1648; (d) Wang, J.; Li, H.; Yu, X.-H.; Zu, L.-S.; Wang, W. *Org. Lett.* **2005**, *7*, 4293–4296; (e) Cao, C.-L.; Ye, M.-C.; Sun, X.-L.; Tang, Y. *Org. Lett.* **2006**, *8*, 2901–2904; (f) Wu, B.; Liu, G.-G.; Li, M.-Q.; Zhang, Y.; Zhang, S.-Y.; Qiu, J.-R.; Xu, X.-P.; Ji, S.-J.; Wang, X.-W. *Chem. Commun.* **2011**, 3992–3994.
13. (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673; (b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.-N.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119–125; (c) Inokuma, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2006**, *128*, 9413–9419.
14. Beccalli, E. M.; Marchesini, A.; Pilati, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 579–587.