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A new asymmetric activation strategy for hydrazones as acyl anion equivalents in the bimetallic catalyzed carbonyl-ene reaction†

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A new asymmetric activation strategy for hydrazones as acyl anion equivalents is developed in the bimetallic catalyzed carbonyl-ene reaction of isatins and hydrazones. Under mild conditions, optically active functionalized 3-hydroxy-2-oxindoles were furnished in up to 98% yield with up to 97% enantioselectivity. In this process, formaldehyde *tert*-butylhydrazone which is seldom employed in asymmetric carbonyl-ene reactions accelerated by a metallic catalyst can be activated well by a Brønsted base. A possible catalytic cycle is proposed.

Introduction

Hydrazones as acyl anion equivalents have a great synthetic value due to the versatility of the expected functionalized product.[1] Activated hydrazones employed in asymmetric transformation, which is an important strategy to build the chiral C–C bond, have attracted much attention over the last few years.[2] *N*,*N*-Dialkyl hydrazones have shown reactivity in the enantioselective conjugate addition reaction, ene-type reactions and imino aza-enamine reaction.[3] Alternatively, Carreira reported the iridium-catalyzed asymmetric allylic substitution reaction with *N*,*N*-dialkylhydrazones.[4] On the other hand, hydrazones activated by Lewis acids could participate in asymmetric hydrocyanation and Mannich reactions.[5]

The aza-enamine (nucleophilic) character of *N*-monoalkyl hydrazones activated by H-bond organocatalysis in the asymmetric carbonyl-ene reaction was discovered by the Lassaletta group using bisurea or squaramide catalysts (Fig. 1a, R = H).[6] After that, Zhu demonstrated the chiral phosphoric acid (CPA)-catalyzed asymmetric aza-Mannich reaction of *N*-alkyl hydrazones *via* H-bond activation, generating two contiguous stereocenters with an excellent yield and ee value (Fig. 1a, R = aryl).[7] Due to the tendency of hydrazones to bind to acidic metals and lead to side reactions, decomposition, or catalyst deactivation,[6a] the development of catalytic enantioselective approaches by hydrazone activation of chiral metal Lewis acid catalysts is problematic. Therefore, it is highly desirable to develop a new activation strategy to overcome the sensitivity of these reagents towards metal Lewis acids. Although the pioneering work by Baldwin and co-workers shows that metallated *N*-*tert*-butyl monosubstituted hydrazones as stable anionic aza-enolates can increase the C-nucleophilicity,[8] to the best of our knowledge, *N*-*tert*-butyl hydrazones activated by a chiral metal complex as a Brønsted base have not been reported yet in asymmetric catalysis.

During the past few years, we have applied chiral dinuclear zinc cooperative catalysts to a variety of asymmetric catalyses, such as asymmetric copolymerization,[9] [3 + 2] cyclic addition,[10] cascade reaction,[11] conjugate addition,[12] Friedel–Crafts alkylation,[13] aza-Henry reaction,[14] and 1,2-carbonyl addition.[15] Considering that the Brønsted base site of a dinuclear zinc catalyst should offer an opportunity for the reaction with the NH group on hydrazones, affording a stable anionic aza-enolate as a C-nucleophile, we decided to explore the reactivity of *N*-*tert*-butyl hydrazones in the nucleophilic addition

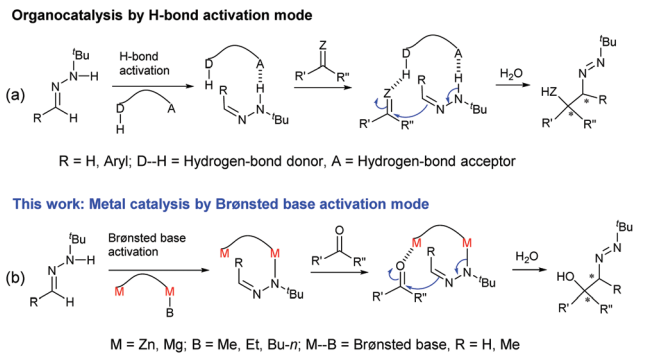

Fig. 1 Different activation modes for hydrazones.

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reaction with carbonyl compounds (Fig. 1b). Herein, we report a new strategy of Brønsted base activating *N-tert*-butyl hydrazones for the asymmetric metal-catalyzed carbonyl-ene reaction of isatins and hydrazones using dinuclear zinc catalysts.

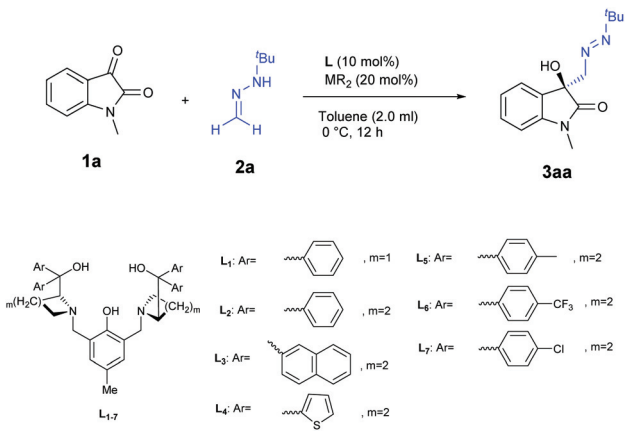
Results and discussion

We commenced our investigation by examining the reaction of methyl substituted isatin and formaldehyde *tert*-butyl hydrazone in the presence of ligand $\mathbf{L_2}$ (10 mol%) and $ZnEt_2$ (20 mol%). At 0 °C, with toluene as the solvent, the reaction proceeded smoothly and gave the product (**3aa**) in 96% yield with 68% ee (Table 1, entry 2). Encouraged by the good result, a series of ligands with different substituents and structures, including AzePhenol ligand $\mathbf{L_1}$ and ProPhenol ligands $\mathbf{L_3}$–$\mathbf{L_7}$, were employed (Table 1, entries 1 and 3–7). ProPhenol ligand $\mathbf{L_2}$ gave a little higher ee value than AzePhenol ligand $\mathbf{L_1}$ (63% ee) that bears the same substituted group. To our delight, modification of the aromatic ring of $\mathbf{L_2}$ from phenyl to thienyl ($\mathbf{L_4}$) substantially improved the efficiency and enantioselectivity of the reaction to 98% yield and 88% ee (Table 1, entry 4). We then evaluated the reaction outcome by using different metals. In particular, $ZnMe_2$ led to the formation of the desired product with high efficiency and 83% ee (Table 1, entry 8). The use of Mg^nBu_2 gave **3aa** in a low level of enantiomeric excess (Table 1, entry 9). Mixed metals were not efficient in enantioselectivity (Table 1, entries 10 and 11). Therefore, $ZnEt_2$ was chosen as the optimal metal for further optimization.

Several parameters were explored further to improve the reactivity and enantioselectivity, such as catalyst loading, solvents, additives and temperature, on this transformation (Table 2). 15 mol% and 20 mol% catalyst loading amounts showed no obvious improvement of the reaction results (Table 2, entries 2 and 3). When the catalyst loading was reduced to 5 mol%, the yield and enantiomeric excess of **3aa** decreased (Table 2, entry 1). Screening of solvents (Table 2, entries 4–7) showed that THF gave the highest enantioselectivity compared with others. Moreover, 4 Å MS proved to be the most efficient additive in the asymmetric carbonyl-ene reaction, leading to the product **3aa** with 98% yield and 97% ee (Table 2, entry 8). Performing the reaction at room temperature and −20 °C decreased the enantioselectivity of **3aa** to 92% and 96% ee (Table 2, entries 13 and 14). The absolute configuration was confirmed as (*S*) based on the optical rotation of the product **3da** (see the ESI†).[6b] As a result, the optimized conditions were isatin (0.125 mmol), hydrazone (0.25 mmol), $\mathbf{L_4}$ (0.0125 mmol), $ZnEt_2$ (0.025 mmol), 4 Å MS (25 mg) and THF (2 ml) at 0 °C under a N_2 atmosphere.

The generality of the protecting group on nitrogen of isatin was explored under the optimal conditions obtained above.

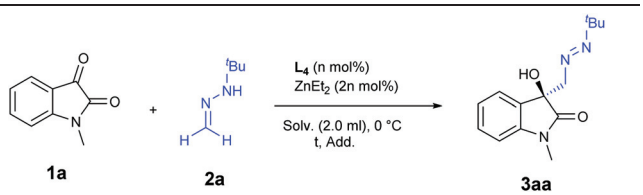
Table 1 Screening conditions for the ligand and metal[a]



Entry	MR_2	L	Yield[b] (%)	ee[c] (%)
1	$ZnEt_2$	$\mathbf{L_1}$	96	63
2	$ZnEt_2$	$\mathbf{L_2}$	96	68
3	$ZnEt_2$	$\mathbf{L_3}$	95	73
4	$ZnEt_2$	$\mathbf{L_4}$	98	88
5	$ZnEt_2$	$\mathbf{L_5}$	96	70
6	$ZnEt_2$	$\mathbf{L_6}$	85	45
7	$ZnEt_2$	$\mathbf{L_7}$	96	37
8	$ZnMe_2$	$\mathbf{L_4}$	95	83
9	Mg^nBu_2	$\mathbf{L_4}$	97	10
10[d]	$ZnEt_2$ + Mg^nBu_2	$\mathbf{L_4}$	97	25
11[e]	$ZnMe_2$ + Mg^nBu_2	$\mathbf{L_4}$	97	65

[a] Unless otherwise noted, all reactions were conducted with **1a** (0.25 mmol) and **2a** (0.125 mmol) under N_2. [b] Isolated yields. [c] Determined by HPLC using a chiral column. [d] $ZnEt_2$ (10 mol%) + Mg^nBu_2 (10 mol%). [e] $ZnMe_2$ (10 mol%) + Mg^nBu_2 (10 mol%).

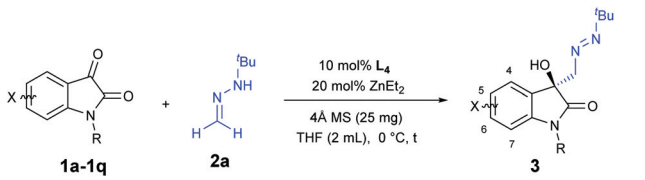
Table 2 Optimization of reaction conditions[a]



Entry	n	Solv.	Add.	t (h)	Yield[b] (%)	ee[c] (%)
1	5	Toluene	None	12	95	81
2	15	Toluene	None	12	96	87
3	20	Toluene	None	12	96	79
4	10	THF	None	6	98	91
5	10	Dioxane	None	12	95	77
6	10	Et_2O	None	12	80	35
7	10	Benzene	None	12	99	47
8	10	THF	4 Å MS[d]	6	98	97
9	10	THF	Et_3N[e]	12	90	66
10	10	THF	Na_2CO_3[e]	12	96	63
11	10	THF	Ph_3PS[e]	12	99	70
12	10	THF	Ph_3P[e]	12	99	69
13[f]	10	THF	4 Å MS[d]	3	96	92
14[g]	10	THF	4 Å MS[d]	30	91	96

[a] Unless otherwise noted, all reactions were conducted with **1a** (0.25 mmol) and **2a** (0.125 mmol) under N_2 for a suitable period of time. [b] Isolated yields. [c] Determined by HPLC using a chiral column. [d] 25 mg was used. [e] 50 mol% was used. [f] r.t. [g] −20 °C.

Table 3 The generality of the reaction with various isatins[a]



Entry	X	R	Product	t (h)	Yield[b] (%)	ee[c] (%)
1	H	Me	**3aa**	6	98	97
2	H	H	**3ba**	5	92	45
3	H	Ac	**3ca**	5	81	75
4	H	Bn	**3da**	5	97	90
5	5-F	Me	**3ea**	4	93	95
6	5-Br	Me	**3fa**	3	94	90
7	5-Me	Me	**3ga**	3	93	96
8	5-MeO	Me	**3ha**	4	91	93
9	5-Ph	Me	**3ia**	3	89	92
10	4-Br	Me	**3ja**	15	83	82
11	7-Br	Me	**3ka**	4	92	94
12	5-Me	Bn	**3la**	4	93	97
13	5-F	Bn	**3ma**	4	88	89

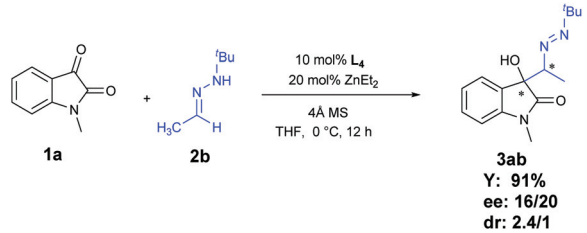
[a] Unless otherwise noted, all reactions were conducted with **1** (0.25 mmol) and **2a** (0.125 mmol) under N_2 for a suitable period of time. [b] Isolated yields. [c] Determined by HPLC using a chiral column.

The products (**3aa–3da**) were obtained with high efficiency (81–98% yield) and variable degrees of enantioselectivity (45–97% ee). *N*-Methyl-isatin (**1a**) gave excellent results in both yield and enantiomeric excess (Table 3, entry 1). A moderate result was achieved for *N*-Ac isatin (**1c**), which might be due to the low solubility of **1c** and a competitive binding effect of the acyl group. A good conversion for *N*-Bn (**1d**) isatin was observed after several hours, enantioselectivities reaching high values, 90% ee (Table 3, entry 4). However, since isatin itself (**1b**) without a protecting group had a detrimental effect on stereoselectivity, the product **3ba** was provided with a good yield and 45% ee (Table 3, entry 2).

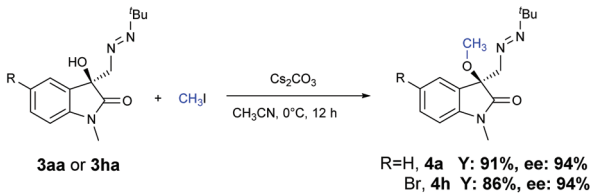
In order to further explore the generality of this dinuclear metal catalyzed carbonyl-ene reaction, we treated formaldehyde *tert*-butyl hydrazone with various *N*-methyl- or *N*-benzyl-isatins in this asymmetric process, which are presented in Table 3 (entries 5–13). Isatins with different substituted groups (electron-withdrawing or electron-donating) were found to be well tolerated, giving the corresponding functionalized 3-hydroxy-2-oxindoles (**3ea–3ka**) in 83–94% yields with excellent levels of enantioselectivity. Isatins (**1e** and **1f**) with 5-F and 5-Br groups were compatible with the reaction conditions, affording the corresponding products **3ea** and **3fa** in 93% and 94% yields with 95% and 90% enantioselectivities, respectively. Furthermore, substrates **1g**, **1h** and **1i** with electron-rich substituents (5-Me, 5-MeO and 5-phenyl) furnished the corresponding chiral 3-hydroxy-2-oxindoles with 89–93% yields and 92–96% ee, respectively (entries 7–9). Next, 4-Br isatin (**1j**) was tested. 4-Br isatin is challenging since the steric effect of Br prevents isatin from binding to the catalyst. To our delight, 4-Br isatin was a suitable substrate for the enantioselective carbonyl-ene reaction and furnished the addition product (**3ja**) in 83% yield with 82% ee (entry 10). 7-Br isatin could be subjected into the reaction to deliver the enantioselective addition product (**3ka**) in 92% yield with 94% ee (entry 11). Finally, substituted *N*-benzyl isatins (**1l** and **1m**)[16] were found to be compatible with the reaction and formed the desired chiral oxindoles in 93% and 88% yields with 97% and 89% ee, respectively.

Finally, we examined the reaction of the *N*-methyl substrate (**1a**) with acetaldehyde *tert*-butyl hydrazone (**2b**) under the optimized conditions (Scheme 1), furnishing the oxindole (**3ab**) with two contiguous chiral centres in 91% yield with 2.4 : 1 dr and low stereoselectivity. Further research in this field has been conducted by our group. Since the product, functionalized 3-hydroxy-2-oxindoles, is not stable and easy to racemize at room temperature according to a previous study,[6b] we conducted methylation of the hydroxy group to form the protected product (**4a** or **4h**) which is stable and can avoid further racemization (Scheme 2).

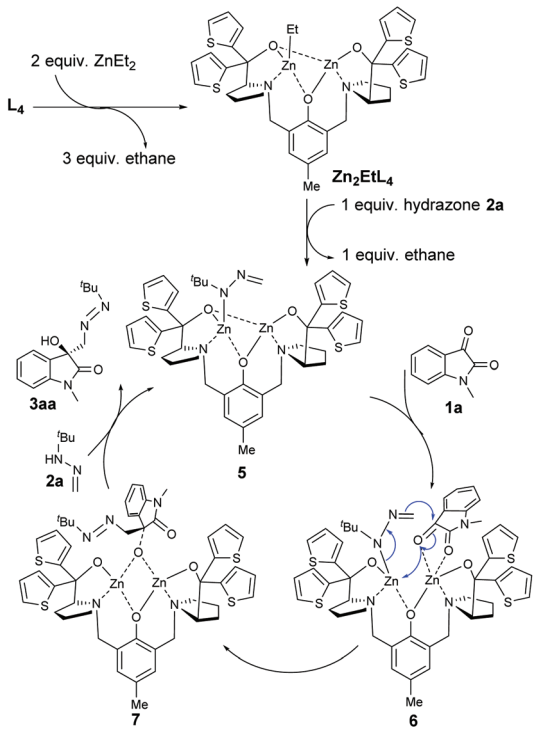
According to the previous reports,[17] a plausible mechanism is shown in Scheme 3. Firstly, the dinuclear zinc catalyst ($ZnEt_2L_4$) containing both Brønsted base and Lewis acid sites is produced from $ZnEt_2$ and the ligand spontaneously. Subsequently, hydrazone is activated by the Brønsted base site on the catalyst, forming complex **5** through deprotonation. Then the carbonyl group of isatin binds to the Lewis acid site from a less sterically hindered position, generating zinc–oxygen coordination, followed by the carbonyl-ene reaction to give the intermediate **7**. The high enantioselectivity was supposed to arise from the bifunctional mode of activation. Finally, the desired product is furnished accompanied by the regeneration of hydrazone–catalyst complex **5** to complete the catalytic circle.



Scheme 1 The reaction with acetaldehyde *tert*-butyl hydrazone.



Scheme 2 Derivatization of the product.



Scheme 3 Proposed catalytic cycle.

Conclusions

In summary, we have developed a novel asymmetric activation strategy for hydrazones as acyl anion equivalents in the enantioselective carbonyl-ene reaction of *N*-monoalkyl hydrazone and isatin. The chiral dinuclear zinc catalyst as the Brønsted base activates *N-tert*-butyl hydrazone, enabling the asymmetric carbonyl-ene reaction to deliver functionalized 3-hydroxy-2-oxindoles in high yields with excellent enantioselectivities under mild conditions. This method demonstrated that chiral metal catalysis, besides organocatalysis, is a powerful method in triggering the reaction of hydrazones and carbonyl compounds through an asymmetric pathway. Further efforts are underway to explore this new asymmetric activation strategy for other enantioselective transformations.

Experimental section

Unless otherwise noted, all reactions sensitive to air or moisture were carried out under nitrogen using standard Schlenk and vacuum line techniques. Diethylzinc (1.0 mol L^{-1} in hexane) was purchased from Aldrich and used as received. $\mathbf{L_1}$ [13c] and $\mathbf{L_2}$–$\mathbf{L_7}$ [18] were synthesized according to the literature. Methyl substituted isatins were prepared by methylation of isatins using MeI and NaH. Benzyl substituted isatins were furnished with BnBr and NaH. Acyl protected isatin was prepared using Ac_2O and DMAP. Allyl protected isatin was prepared using allyl bromide and K_2CO_3. Hydrazones **2a** [19] and **2b** [20] were synthesized according to the literature. Other reagents were obtained from commercial sources and used as received without further purification. Melting points were determined using b-type tube melting point apparatus and are uncorrected. Optical rotations were measured with a PerkinElmer model 341 Polarimeter at 20 °C in $CHCl_3$. ^{1}H and ^{13}C NMR spectra were measured on a Bruker DPX 400 NMR instrument (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR). Tetramethylsilane (TMS) served as the internal standard (0 ppm) for ^{1}H NMR, and $CDCl_3$ served as the internal standard (77.0 ppm) for ^{13}C NMR. NMR data are represented as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex), coupling constant in hertz (Hz), integration. FT-IR spectra were recorded on a PerkinElmer Spectrum Two L600 system and are reported in terms of frequency of absorption (cm^{-1}). High-resolution mass spectra (HRMS) were obtained using an Agilent LC-MSAD-Trap-XCT instrument using electrospray ionization time-of-flight (ESI-TOF). High performance liquid chromatography (HPLC) was performed on an instrument consisting of a JASCO model PU-1580 intelligent HPLC pump and a JASCO model UV-1575 intelligent UV-vis detector (254 nm) using Daicel Chiralpak AS, AD, OJ or OD-H (4.6 mm × 250 mm) columns.

General procedure for the asymmetric carbonyl-ene reaction of hydrazones

In a flame-dried Schlenk tube, a solution of diethylzinc (25 μL, 1.0 mol L^{-1} in hexane, 0.025 mmol, 20 mol%) was added to a solution of the chiral ligand (*S*,*S*)-$\mathbf{L_4}$ (8.3 mg, 0.0125 mmol) in dry THF (1.0 mL) under nitrogen at 0 °C. The mixture was stirred at room temperature for 30 min. Then **1** (0.125 mmol), **2** (0.25 mmol) and dry THF (1.0 mL) were added to the mixture. The solution was stirred at 0 °C for the necessary reaction time. Upon completion, the reaction was quenched with sat. NH_4Cl (aq., 2 mL) and the reaction mixture was extracted three times with EA (3 × 2 mL). The combined organics were washed with brine followed by drying with $MgSO_4$, filtration and concentration *in vacuo*. The crude product was purified by preparative TLC using the indicated solvent mixture to afford **3**.

Derivatization of the product

3aa (32.6 mg, 0.125 mmol) or **3ha** was dissolved in dry MeCN (3 mL). At 0 °C, Cs_2CO_3 (82 mg, 0.25 mmol) and MeI (0.31 mL, 5 mmol) were added. The mixture was stirred for 12 h. After completion, the reaction was quenched with H_2O (2 mL). The organic layer was separated. The aqueous layer was extracted with EA (2 × 5 mL). The combined organics were washed with brine followed by drying with $MgSO_4$, filtration and concentration *in vacuo*. The crude product was purified by preparative TLC using the indicated solvent mixture to afford **4a** or **4h**.

(*S*,*E*)-3-[(*tert*-Butyldiazenyl)methyl]-3-hydroxy-1-methylindolin-2-one (3aa)

The crude product was purified by preparative TLC (dichloromethane/petroleum ether/EtOAc = 10/6/3) to afford a yellow oil, 32.0 mg, 98% yield; $[\alpha]_D^{25}$ = +43 (*c* = 0.35, in $CHCl_3$); HPLC (Chiralpak AS, hexane/i-PrOH = 95/5, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 16.20 min, t_R (minor) = 19.63 min, 97% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 7.2 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.78 (d, *J* = 7.2 Hz, 1H), 4.39 (d, *J* = 12.4 Hz, 1H), 4.19 (s, 0.8 H), 4.13 (d, *J* = 12.4 Hz, 1H), 3.18 (s, 3H), 0.99 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.0, 143.6, 129.8, 128.6, 124.8, 123.0, 108.2, 75.4, 73.5, 67.9, 26.5, 26.2 ppm; IR (neat): 3471, 2972, 2957, 1789, 1714, 1467, 1273, 1186, 1107, 776, 571 cm^{-1}; MS (ESI): *m*/*z* = 262.1$[M + H]^+$.

(*S*,*E*)-3-[(*tert*-Butyldiazenyl)methyl]-3-hydroxyindolin-2-one (3ba)

The crude product was purified by preparative TLC (dichloromethane/petroleum ether/EtOAc = 10/4/3) to afford a white solid, 28.4 mg, 92% yield; $[\alpha]_D^{25}$ = −13 (*c* = 0.35, in $CHCl_3$); HPLC (Chiralpak AS, hexane/i-PrOH = 90/10, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R (minor) = 12.78 min, t_R (major) = 17.38 min, 45% ee; ^{1}H NMR (400 MHz, DMSO-d): δ = 10.29 (s, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 6.88 (t, *J* = 7.6 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.30 (s, 1 H), 4.28 (d, *J* = 10.8 Hz, 1H), 3.96 (d, *J* = 11.2 Hz, 1H), 0.86 (s, 9H) ppm; ^{13}C NMR (100 MHz, DMSO-d): δ = 178.6, 142.5, 130.7, 129.5, 125.3, 121.7, 109.7, 75.0, 74.1, 67.5, 26.7 ppm; IR (neat): 3461, 2972, 2959, 1789, 1714, 1467, 1273, 1186, 1107, 776 cm^{-1}; MS (ESI): *m*/*z* = 248.3 $[M + H]^+$.

(*S*,*E*)-1-Acetyl-3-[(*tert*-butyldiazenyl)methyl]-3-hydroxyindolin-2-one (3ca)

The crude product was purified by preparative TLC (dichloromethane/petroleum ether/EtOAc = 10/6/3) to afford a yellow oil, 29.3 mg, 81% yield; $[\alpha]_D^{25}$ = +27 (*c* = 0.32, in $CHCl_3$); HPLC (Chiralpak AS, hexane/i-PrOH = 95/5, flow rate = 0.8 mL min^{-1}, λ = 254 nm): t_R (minor) = 12.99 min, t_R (major) = 15.08 min, 75% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 8.0 Hz, 1H), 7.36 (q, 2H), 7.21 (t, *J* = 7.6 Hz, 1H), 4.47 (d, *J* = 13.2 Hz, 1H), 4.27 (d, *J* = 13.2 Hz, 1H), 2.66 (s, 3H), 0.96 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.6, 170.6, 140.2, 130.4, 127.5, 125.6, 124.0, 116.7, 75.7, 73.7, 68.3, 26.2 ppm; IR (neat): 3459, 2942, 2950, 1789, 1766, 1712, 1467, 1173, 1186, 1123, 776, 571 cm^{-1}; MS (ESI): *m*/*z* = 290.2 $[M + H]^+$.

(*S*,*E*)-1-Benzyl-3-[(*tert*-butyldiazenyl)methyl]-3-hydroxyindolin-2-one (3da)

The crude product was purified by preparative TLC (dichloromethane/petroleum ether/EtOAc = 10/6/3) to afford a colourless oil, 40.9 mg, 97% yield; $[\alpha]_D^{25}$ = +41 (*c* = 0.14, in $CHCl_3$); HPLC (Chiralpak AS, hexane/i-PrOH = 95/5, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 15.83 min, t_R (minor) = 31.47 min, 90% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.33 (m, 6H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 4.97 (d, *J* = 15.6 Hz, 1H), 4.78 (d, *J* = 15.6 Hz, 1H), 4.46 (d, *J* = 12.4 Hz, 1H), 4.14 (d, *J* = 12.4 Hz, 1H), 3.87 (s, 1H), 0.99 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1, 142.8, 135.4, 129.9, 128.8, 128.5, 127.7, 127.4, 125.0, 123.0, 109.4, 75.4, 73.6, 68.0, 44.0, 26.6 ppm; IR (neat): 3443, 3136, 2856, 2959, 1634, 1400, 1273, 1186, 1107, 560 cm^{-1}; MS (ESI): *m*/*z* = 338.1 $[M + H]^+$.

(*S*,*E*)-3-[(*tert*-Butyldiazenyl)methyl]-5-fluoro-3-hydroxy-1-methylindolin-2-one (3ea)

The crude product was purified by preparative TLC (dichloromethane/petroleum ether/EtOAc = 10/6/3) to afford a yellow oil, 32.4 mg, 93% yield; $[\alpha]_D^{25}$ = +25 (*c* = 0.12, in $CHCl_3$); HPLC (Chiralpak OD-H, hexane/i-PrOH = 95/5, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 9.32 min, t_R (minor) = 11.43 min, 95% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (m, 1H), 7.01 (m, 1H), 7.04 (m, 1H), 4.33 (d, *J* = 12.4 Hz, 1H), 4.13 (d, *J* = 12.8 Hz, 1H), 3.18 (s, 3H), 1.05 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.7, 158.2 (d, 240.0 Hz), 139.5, 130.3 (d, 8.0 Hz), 115.9 (d, 23.0 Hz), 113.1 (d, 25.0 Hz), 108.8 (d, 8.0 Hz), 75.6, 73.3, 68.1, 26.5, 26.4 ppm; IR (neat): 3462, 3008, 2925, 2855, 1744, 1647, 1493, 1460, 1232, 1104, 911, 809, 721 cm^{-1}; MS (ESI): *m*/*z* = 280.1 $[M + H]^+$. HRMS (ESI-TOF): *m*/*z* $[M + H]^+$, calcd for $C_{14}H_{19}FN_3O_2^+$ 280.1456, found 288.1455.

(*S*,*E*)-5-Bromo-3-[(*tert*-butyldiazenyl)methyl]-3-hydroxy-1-methylindolin-2-one (3fa)

The crude product was purified by preparative TLC (dichloromethane/petroleum ether/EtOAc = 10/6/3) to afford a yellow oil, 39.9 mg, 94% yield; $[\alpha]_D^{25}$ = −22 (*c* = 0.25, in $CHCl_3$); HPLC (Chiralpak OD-H, hexane/i-PrOH = 95/5, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 10.52 min, t_R (minor) = 19.17 min, 90% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (m, 2H), 6.67 (d, *J* = 8.4 Hz, 1H), 4.32 (d, *J* = 12.8 Hz, 1H), 4.25 (s, 1H), 4.15 (d, *J* = 12.8 Hz, 1H), 3.17 (s, 3H), 1.03 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.4, 142.6, 132.5, 130.6, 128.3, 115.7, 109.7, 75.4, 73.2, 68.2, 26.5, 26.4 ppm; IR (neat): 3440, 2968, 2926, 2858, 1714, 1639, 1613, 1484, 1464, 1107, 810, 677, 563 cm^{-1}; MS (ESI): *m*/*z* = 340.0 $[M + H]^+$; HRMS (ESI-TOF): *m*/*z* $[M + H]^+$, calcd for $C_{14}H_{19}BrN_3O_2^+$ 340.0655, found 340.0657.

(*S*,*E*)-3-[(*tert*-Butyldiazenyl)methyl]-3-hydroxy-1,5-dimethylindolin-2-one (3ga)

The crude product was purified by preparative TLC (dichloromethane/petroleum ether/EtOAc = 10/6/3) to afford a yellow oil, 32 mg, 93% yield; $[\alpha]_D^{25}$ = +36 (*c* = 0.33, in $CHCl_3$); HPLC (Chiralpak OD-H, hexane/i-PrOH = 95/5, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 8.08 min, t_R (minor) = 10.78 min, 96% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (s, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 4.30 (d, *J* = 12.4 Hz, 1H), 4.10 (d, *J* = 12.4 Hz, 1H), 3.17 (s, 3H), 2.31 (s, 3H), 1.05 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.5, 141.2, 132.5, 130.0, 128.4, 125.6, 108.0, 75.5, 73.3, 68.0, 26.5, 26.2, 21.0 ppm; IR (neat): 3495, 3376, 2960, 2927, 1715, 1700,

1684, 1628, 1591, 1102, 806, 486, 474 cm^{-1}; MS (ESI): m/z = 276.2 $[M + H]^+$. HRMS (ESI-TOF): m/z $[M + H]^+$, calcd for $C_{15}H_{22}N_3O_2^+$ 276.1707, found 276.1705.

(*S*,*E*)-3-[(*tert*-Butyldiazenyl)methyl]-3-hydroxy-5-methoxy-1-methylindolin-2-one (3ha)

The crude product was purified by preparative TLC (dichloromethane/petroleum ether/EtOAc = 10/6/3) to afford a light brown oil, 33.1 mg, 91% yield; $[\alpha]_D^{25}$ = +19 (c = 0.35, in $CHCl_3$); HPLC (Chiralpak OD-H, hexane/i-PrOH = 95/5, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 11.02 min, t_R (minor) = 17.36 min, 93% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.98 (s, 1H), 6.83 (d, J = 7.6 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H), 4.29 (d, J = 12.4 Hz, 1H), 4.09 (d, J = 12.4 Hz, 1H), 3.17 (s, 3H), 1.06 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.4, 156.3, 136.9, 129.7, 114.7, 111.9, 108.7, 75.7, 73.2, 68.0, 55.8, 26.5, 26.3 ppm; IR (neat): 3479, 3410, 2959, 2921, 2853, 1701, 1638, 1486, 1224, 1030, 554, 472 cm^{-1}; MS (ESI): m/z = 292.2 $[M + H]^+$; HRMS (ESI-TOF): m/z $[M + H]^+$, calcd for $C_{15}H_{22}N_3O_3^+$ 292.1656, found 292.1658.

(*S*,*E*)-3-[(*tert*-Butyldiazenyl)methyl]-3-hydroxy-5-phenyl-1-methylindolin-2-one (3ia)

The crude product was purified by preparative TLC (dichloromethane/petroleum ether/EtOAc = 10/6/3) to afford a colorless oil, 37.5 mg, 89% yield; $[\alpha]_D^{25}$ = −17 (c = 0.11, in $CHCl_3$); HPLC (Chiralpak OD-H, hexane/i-PrOH = 90/10, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 6.50 min, t_R (minor) = 10.31 min, 92% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (s, 1H), 7.53 (m, 3H), 7.41 (m, 3H), 6.86 (d, J = 8.4 Hz), 4.24 (d, J = 12.4 Hz, 1H), 4.17 (d, J = 12.4 Hz, 1H), 3.23 (s, 3H), 1.01 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.9, 142.9, 140.7, 136.5, 132.6, 129.1, 128.8, 128.3, 126.8, 123.9, 108.5, 75.5, 73.4, 68.0, 26.5, 26.4 ppm; IR (neat): 3481, 3381, 2924, 2854, 1717, 1610, 1486, 1361, 1107, 808, 701, 633, 534 cm^{-1}; MS (ESI): m/z = 338.2 $[M + H]^+$. HRMS (ESI-TOF): m/z $[M + H]^+$, calcd for $C_{20}H_{24}N_3O_2^+$ 338.1863, found 338.1867.

(*S*,*E*)-4-Bromo-3-[(*tert*-butyldiazenyl)methyl]-3-hydroxy-1-methylindolin-2-one (3ja)

The crude product was purified by preparative TLC (dichloromethane/petroleum ether/EtOAc = 10/6/3) to afford a yellow oil, 35.3 mg, 83% yield; $[\alpha]_D^{25}$ = −29 (c = 0.28, in $CHCl_3$); HPLC (Chiralpak OD-H, hexane/i-PrOH = 95/5, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R (minor) = 14.36 min, t_R (major) = 16.74 min, 82% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (t, 2H), 6.72 (q, 1H), 4.63 (d, J = 12.4 Hz, 1H), 4.51 (d, J = 12.4 Hz, 1H), 3.18 (s, 3H), 0.90 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.1, 145.9, 131.2, 126.9, 126.4, 119.7, 107.1, 76.5, 70.6, 67.7, 26.3, 26.3 ppm; IR (neat): 3567, 3386, 2834, 2827, 1825, 1701, 1692, 1626, 1491, 1012 cm^{-1}; MS (ESI): m/z = 340.1 $[M + H]^+$. HRMS (ESI-TOF): m/z $[M + H]^+$, calcd for $C_{14}H_{19}BrN_3O_2^+$ 340.0655, found 340.0657.

(*S*,*E*)-7-Bromo-3-[(*tert*-butyldiazenyl)methyl]-3-hydroxy-1-methylindolin-2-one (3ka)

The crude product was purified by preparative TLC (dichloromethane/petroleum ether/EtOAc = 10/6/3) to afford a yellow oil, 39.1 mg, 92% yield; $[\alpha]_D^{25}$ = +25 (c = 0.31, in $CHCl_3$); HPLC (Chiralpak AS, hexane/i-PrOH = 95/5, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 10.82 min, t_R (minor) = 15.55 min, 94% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 6.91 (t, J = 8.0 Hz, 1H), 4.33 (d, J = 12.4 Hz, 1H), 4.10 (d, J = 12.4 Hz, 1H), 3.58 (s, 3H), 1.03 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.3, 141.0, 135.4, 131.7, 126.1, 124.2, 123.8, 74.8, 73.4, 68.2, 29.9, 26.5 ppm; IR (neat): 3522, 3286, 2934, 2827, 1725, 1712, 1692, 1600, 1491, 1012, 751 cm^{-1}; MS (ESI): m/z = 340.0 $[M + H]^+$. HRMS (ESI-TOF): m/z $[M + H]^+$, calcd for $C_{14}H_{19}BrN_3O_2^+$ 340.0655, found 340.0654.

(*S*,*E*)-1-Benzyl-3-[(*tert*-butyldiazenyl)methyl]-3-hydroxy-5-methylindolin-2-one (3la)

The crude product was purified by preparative TLC (dichloromethane/petroleum ether/EtOAc = 10/6/3) to afford a white solid, 40.9 mg, 93% yield; $[\alpha]_D^{25}$ = +13 (c = 0.22, in $CHCl_3$); HPLC (Chiralpak AS, hexane/i-PrOH = 80/20, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 5.21 min, t_R (minor) = 9.27 min, 97% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.30 (m, 5H), 7.14 (s, 1H), 6.96 (d, J = 7.6 Hz, 1H), 6.55 (d, J = 8.0 Hz, 1H), 4.94 (d, J = 16.0 Hz, 1H), 4.77 (d, J = 15.6 Hz, 1H), 4.40 (d, J = 12.4 Hz, 1H), 4.12 (d, J = 12.4 Hz, 1H), 3.62 (s, 1H), 2.26 (s, 3H), 1.03 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.8, 140.3, 135.4, 132.6, 130.0, 128.8, 128.4, 127.7, 127.3, 125.8, 109.4, 109.2, 75.5, 73.6, 68.0, 44.0, 26.6, 21.0 ppm; IR (neat): 3435, 3134, 2858, 2827, 1662, 1619, 1400, 1012, 751, 698, 618 cm^{-1}; MS (ESI): m/z = 352.2 $[M + H]^+$. HRMS (ESI-TOF): m/z $[M + H]^+$, calcd for $C_{21}H_{26}N_3O_2^+$ 352.2020, found 352.2017.

(*S*,*E*)-1-Benzyl-3-[(*tert*-butyldiazenyl)methyl]-5-fluoro-3-hydroxyindolin-2-one (3ma)

The crude product was purified by preparative TLC (dichloromethane/petroleum ether/EtOAc = 10/6/3) to afford a colorless oil, 39.1 mg, 88% yield; $[\alpha]_D^{25}$ = +13 (c = 0.32, in $CHCl_3$); HPLC (Chiralpak AS, hexane/i-PrOH = 80/20, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 5.60 min, t_R (minor) = 8.14 min, 89% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (t, 5H), 7.07 (q, 1H), 6.87 (m, 1H), 6.59 (t, J = 4.4 Hz, 1H), 4.95 (d, J = 16.0 Hz, 1H), 4.78 (d, J = 15.6 Hz, 1H), 4.41 (d, J = 12.8 Hz, 1H), 4.78 (d, J = 12.4 Hz, 1H), 1.03 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.8, 160.5, 158.1, 138.6, 135.0, 130.1, 128.9, 127.8, 127.3, 116.1, 115.9, 113.3, 113.1, 110.1, 110.0, 75.5, 73.4, 68.1, 44.1, 26.5 ppm; IR (neat): 3334, 3124, 2877, 2824, 1662, 1609, 1402, 1012, 761, 698, 618, 751 cm^{-1}; MS (ESI): m/z = 356.1 $[M + H]^+$.

(*S*,*E*)-3-[(*tert*-Butyldiazenyl)ethyl]-3-hydroxy-1-methylindolin-2-one (3ab)

The crude product was purified by preparative TLC (dichloromethane/petroleum ether/EtOAc = 10/6/3) to afford a light yellow oil, 31.3 mg, 91% yield; HPLC (Chiralpak AS, hexane/i-PrOH = 95/5, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R (minor) = 9.62 min, t_R (major) = 13.95 min, 20% ee; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.61 (m, 1H), 7.38 (d, J = 7.2 Hz, 1H), 7.33 (t, J = 8.0 Hz, 1H), 7.14 (t, J = 7.2 Hz, 0.5H), 7.08 (t, J = 7.6 Hz, 1H), 6.89 (d, J = 8.0 Hz, 0.5H), 6.82 (d, J = 8.0 Hz, 1H), 3.87 (q, J = 6.8 Hz, 1H), 3.26 (s, 1.5H), 3.21 (s, 3H), 1.16 (s, 9H), 1.06 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.3, 144.1, 138.4, 129.8, 128.1, 126.0, 125.3, 124.9, 123.9, 123.0, 109.9, 108.2, 78.1, 76.5, 75.0, 67.9, 26.7, 26.2 13.1 ppm; IR (neat): 3731, 3489, 3395, 3372, 2924, 2854, 1742, 1719, 1471, 1462, 1367, 1091, 753 cm^{-1}; MS (ESI): m/z = 276.2 $[M + H]^+$. HRMS (ESI-TOF): m/z $[M + H]^+$, calcd for $C_{15}H_{22}N_3O_2^+$ 276.1707, found 276.1709.

(*S*,*E*)-3-[(*tert*-Butyldiazenyl)methyl]-3-methoxy-1-methylindolin-2-one (4a)

The crude product was purified by preparative TLC (petroleum ether/EtOAc = 5/1) to afford a colorless oil, 31.3 mg, 91% yield; $[\alpha]_D^{25}$ = +26 (c = 0.14, in $CHCl_3$); HPLC (Chiralpak OD-H, hexane/i-PrOH = 98/2, flow rate = 0.5 mL min^{-1}, λ = 254 nm): t_R (major) = 17.02 min, t_R (minor) = 19.51 min, 94% ee; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.32 (m, 1H), 7.26–7.28 (m, 1H), 7.04–7.08 (m, 1H), 6.78 (d, J = 8.0 Hz, 1H), 4.41 (d, J = 12.0 Hz, 1H), 4.11 (d, J = 12.0 Hz, 1H), 3.22 (s, 3H), 3.13 (s, 3H), 0.90 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.0, 143.4, 129.0, 124.5, 124.3, 121.8, 107.0, 80.5, 72.3, 66.6, 51.7, 25.4, 25.1 ppm; IR (neat): 2977, 2192, 1733, 1708, 1607, 1598, 1488, 1403, 1341, 1106, 799 cm^{-1}; MS (ESI): m/z = 276.1 $[M + H]^+$. HRMS (ESI-TOF): m/z $[M + H]^+$, calcd for $C_{15}H_{22}N_3O_2^+$ 276.1707, found 276.1705.

(*S*,*E*)-5-Bromo-3-[(*tert*-butyldiazenyl)methyl]-3-methoxy-1-methylindolin-2-one (4h)

The crude product was purified by preparative TLC (petroleum ether/EtOAc = 5/1) to afford a colorless oil, 38.1 mg, 86% yield; $[\alpha]_D^{25}$ = −5 (c = 0.17, in $CHCl_3$); HPLC (Chiralpak AD, hexane/i-PrOH = 98/2, flow rate = 0.8 mL min^{-1}, λ = 254 nm): t_R (minor) = 9.32 min, t_R (major) = 10.88 min, 94% ee; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, J = 7.2 Hz, 1H), 7.39 (s, 1H), 6.68 (d, J = 8.0 Hz, 1H), 4.33 (d, J = 12.4 Hz, 1H), 4.12 (d, J = 12.4 Hz, 1H), 3.21 (s, 3H), 3.14 (s, 3H), 0.95 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.4, 143.4, 132.8, 128.6, 127.8, 115.6, 109.6, 81.4, 73.0, 67.9, 53.0, 26.5, 26.3 ppm; IR (neat): 2969, 2352, 1731, 1712, 1607, 1600, 1486, 1359, 1341, 1106, 810 cm^{-1}; MS (ESI): m/z = 354.1 $[M + H]^+$; HRMS (ESI-TOF): m/z $[M + H]^+$, calcd for $C_{15}H_{21}BrN_3O_2^+$ 354.0812, found 354.0814.

Conflicts of interest

The authors declare no competing financial interest.

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