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Chiral Bifunctional Guanidine-Catalyzed Enantioselective Aza-Henry Reaction of Isatin-Derived Ketimines

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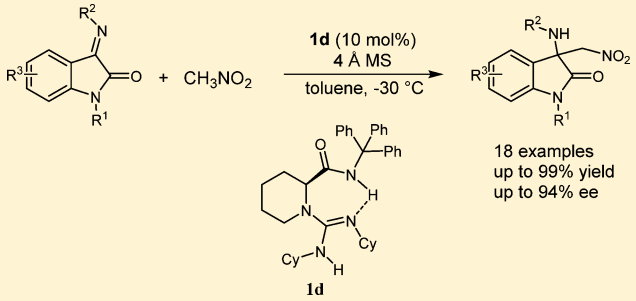
Supporting Information

ABSTRACT: An efficient asymmetric aza-Henry reaction of isatin-derived ketimines has been achieved by using a chiral guanidine−amide organocatalyst. A series of 3-substituted 3-amino-2-oxindoles was obtained with excellent results (up to 99% yield, 94% ee). Other functionalized derivatives were also conveniently transformed. This metal-free system was convenient, practical, and insensitive to air and moisture. On the basis of the crystal structure of the catalyst and NMR spectra analysis, a bifunctional catalytic model was suggested to explain the origin of the asymmetric process.



Guanidines, owing to their prominent role in organocatalysis,[1] have attracted increasing attention during the past two decades. Their characteristics of strong Brønsted basicity and molecular recognition through hydrogen bonds[2,3] suggest the potential to be used as chiral bifunctional organocatalysts.[4] Since Nájera et al. reported the first chiral guanidine in asymmetric organocatalytic Henry reaction,[5a] a number of chiral guanidine and guanidium salt catalysts[5] have been developed. They are demonstrated efficient for asymmetric reactions, such as Michael reaction,[5b,c] Henry reaction,[5d] Mannich reaction,[5e] and others. Our group designed bifunctional acyclic guanidine and bisguanidine catalysts which are easily accessible from chiral α-amino acids.[6a] They are convenient for manipulation. As shown in Figure 1, the amino acid backbone, the amide moiety, and the amidine unit can be fine-tuned. We have dedicated ourselves to the development of such a chiral guanidine catalyst library and have disclosed several efficient asymmetric reactions.[6] In view of the previous studies relating to the guanidine-promoted Henry reactions,[5a,d] we envisioned that our bifunctional guanidines could be utilized in the aza-Henry reaction of isatin-derived ketimines.

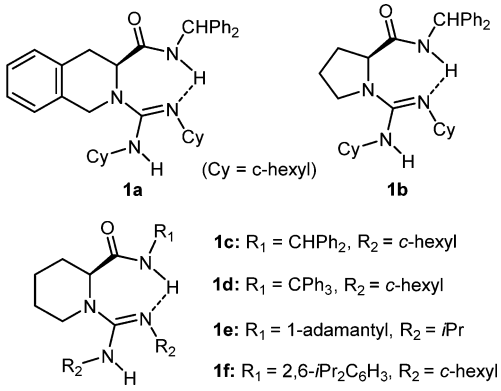


Figure 1. Chiral guanidines employed for the aza-Henry reaction.

The asymmetric aza-Henry reaction,[7] an efficient method for the synthesis of β-nitro amines, is among the most powerful C−C bond formation methodologies. Despite the abundant examples of enantioselective aza-Henry reaction with aldimines,[8] the situation in which ketimines are employed as the electrophiles is rarely reported[9] due to their low reactivity and the difficulty in enantioface differentiation. The aza-Henry reaction of isatin-derived ketimines is an efficient way to obtain privileged oxindole skeletons bearing a stereogenic center at the C3-position.[10] The resulting 3-amino-2-oxindole framework has been recognized as a core structure in pharmaceutical building blocks and alkaloid natural products.[10a] Several catalytic systems have been developed for their asymmetric synthesis.[11] Two chiral metal complexes, the $NiCl_2$−PyBidine complex and the $Cu(BF_4)_2$−BOX complex have been used in the enantioselective aza-Henry reactions of isatin-derived ketimines by Arai's[12a] and Pedro's[12b] groups, respectively. A catalytic amount of an achiral organic base was used to deprotonate the nitroalkanes for nucleophilic addition. Chiral organic base catalysts seem to be an ideal alternative to chiral metal-based catalysts, which could simplify the catalytic system. Zhou's group explored a quinine-derived bifunctional organocatalyst for this reaction, resulting in moderate to good enantioselectivities.[13] Using a cinchona alkaloid organocatalyst, Chimni and co-workers[14] realized this reaction with only moderate yields and enantioselectivities. In an attempt to identify the basicity of our guanidine catalyst and to expand the substrate

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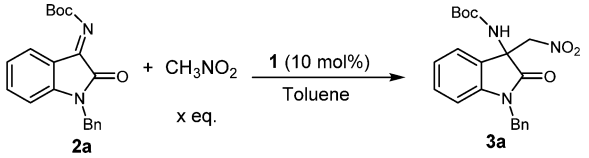
scope in an organocatalytic version, we initiated studies for an efficient and convenient asymmetric aza-Henry reaction promoted by a chiral guanidine organocatalyst. Excellent enantioselectivities were achieved for a wide range of ketimines derived from isatins.

We began with a screen of several chiral guanidine catalysts for the addition of nitromethane to the isatin-derived *N*-Boc ketimine **2a** in toluene at 30 °C. Chiral guanidines **1** bearing different amino amide backbones all provided complete conversion to the adduct **3a** with varying enantioselectivities (Table 1, entries 1−3). The L-pipecolic acid derivative **1c** was

Table 1. Optimization of the Reaction Conditions of the Aza-Henry Reaction



entry[a]	cat.	*x*	temp (°C)	time (h)	yield[b] (%)	ee[c] (%)
1	**1a**	18.0	30	24	99	31
2	**1b**	18.0	30	24	99	17
3	**1c**	18.0	30	24	99	56
4	**1d**	18.0	30	24	99	79
5	**1e**	18.0	30	24	99	50
6	**1d**	9.0	30	24	99	83
7	**1d**	4.5	30	24	91	83
8	**1d**	9.0	0	36	99	87
9	**1d**	9.0	−30	72	99	91
10[d]	**1d**	9.0	−30	72	99	94
11[d,e]	**1d**	9.0	−30	72	99	94

[a]Unless otherwise noted, the reactions was performed with **2a** (0.1 mmol) and **1** (10 mol %) in toluene (1.0 mL) under N_2. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]4 Å MS (10.0 mg) was added. [e]The reaction was carried out under an air atmosphere.

superior to (*S*)-tetrahydroisoquinoline-3-carboxylic acid and L-proline-derived catalysts **1a** and **1b**, giving the adduct **3a** in 99% yield with 56% ee. When the amide unit was changed from the diphenylmethyl group to the more sterically hindered triphenylmethyl group, the guanidine **1d** showed more promising results (79% ee; Table 1, entry 4 vs entry 3). But guanidine **1e** bearing two isopropyl substituents on the amidine unit resulted in a lower enantioselectivity (50% ee; Table 1, entry 5). Halving the molar equivalents of nitromethane, which was supposed to minimize a possible nonenantioselective background reaction, resulted in a superior enantioselectivity (83% ee), but further decreasing the amount of nitromethane led to an obvious drop in the yield without any improvement in the enantioselectivity (Table 1, entry 6 vs entries 4 and 7). Furthermore, cooling the reaction temperature to −30 °C benefited the stereocontrol (91% ee), although a longer reaction time was required (Table 1, entry 9). In order to improve the results, an additive investigation was carried out, and it showed that 4 Å MS could enhance the enantioselectivity to 94% ee (Table 1, entry 10). Notably, the reaction system was insensitive to air and moisture, which made the operation convenient (Table 1, entry 11).

Having identified suitable reaction conditions, we next evaluated the reactions of various substituted isatin-derived ketimines **2** (Scheme 1). The results revealed that the steric nature of the *N*-alkoxycarbonyl groups of the imine unit had a slight influence on the enantioselectivity. When the *N*-Boc group was changed into an *N*-CO_2Et or *N*-Cbz group, the corresponding ketimines were smoothly converted into the adducts with 85% ee and 86% ee, respectively (see **3b** and **3c**). When the *N*-benzyl protective group at the isatin framework was replaced by an *N*-methyl group, the yield decreased to 81% and the ee value to 86% (see **3d**). Next, we applied the catalytic system to different *N*-Boc-ketimines to define the scope of this aza-Henry reaction. A variety of electronic diverse substituents on the aromatic ring of the substrates were tested. To our delight, excellent yields (85−99%) and enantioselectivities (89−94% ee) were obtained (see **3e−q**) for a selection of electron-donating and -withdrawing substituents. The results indicated that the position of the substituent had an obvious effect on the reactivity. For example, the ketimines containing a Cl or Br atom at the C6-position showed higher reactivity (see **3k** and **3l**) than the substrates with the same substituents at the 5- or 7-position (see **3f**, **3g**, **3n**, and **3o**). An effect of the electronic property of the substituents was also observed. A general trend observed was the prolonging of the reaction time upon changing from an electron-withdrawing group at the 5-position to electron-donating ones (see **3e**, **3i**, **3j**, and **3q**). The conditions were also appropriate for the reaction of nitroethane, and both diastereomers were obtained in a highly enantioselective manner, albeit with low diastereoselectivity (65/35 dr; see **3r**).

To explore the synthetic potential of the current catalytic system, the reaction was scaled up to a gram-scale. Under the optimal conditions, 3 mmol of isatin-derived *N*-Boc ketimine **2a** reacted with nitromethane smoothly, giving the adduct **3a** in 99% yield with 94% ee. An X-ray study of enantiomerically pure aza-Henry product **3a** shows the *R* absolute configuration.[15] The product **3a** could facilitate further transformations efficiently (Scheme 2). Deprotection of the *N*-Boc group was achieved in excellent yield with the enantioselectivity kept. The nitro group was reduced by $NaBH_4/NiCl_2$,[16] giving the monoprotected diamines **5** in 91% yield and 94% ee. On the other hand, nitrile **6**, which is of great synthetic potential,[17] was obtained through two steps in 75% yield and 93% ee.

The X-ray structure of the guanidine **1d** (Figure 2)[15] showed an intramolecular hydrogen bond formed between the imine and amide of the catalyst. A comparison with the similar guanidine-amide **1f**,[18] bearing 2,6-diisopropylaniline substitution,[6a] showed an obvious spatial change of the amidine unit. The torsions angle between the NH bond and the C═N bond altered upon the variation of the amide (**1d**, 101.77° vs **1f**, 10.21°). This indicates that the NH bond of **1d** favors an orthogonal arrangement with respect to the amidine unit. Next, the interaction between the guanidine catalyst **1d** and nitroalkane was confirmed from an ^{1}H NMR study. When nitroethane was added to the solution of the guanidine **1d** in $CDCl_3$ or DMSO-d_6, the integration of the *H*N peak of the amide (δ 10.59 in $CDCl_3$ and δ 3.30 in DMSO-d_6) decreases significantly, indicating the breaking of the intramolecular N−H bond. The CH_2 group of nitroethane resonates at a slightly higher field strength (δ 4.43 vs δ 4.41 in $CDCl_3$). The CH_2 peak is less than 2/3 the area of the CH_3 peak, indicating that deprotonation of the guanidine from the nitroethane had occurred.

Therefore, a bifunctional catalytic model was suggested to rationalize the observed enantioselection (Figure 2). First, the guanidine deprotonates an active hydrogen from the nitroalkane to form a guanidium cation. It would bond the

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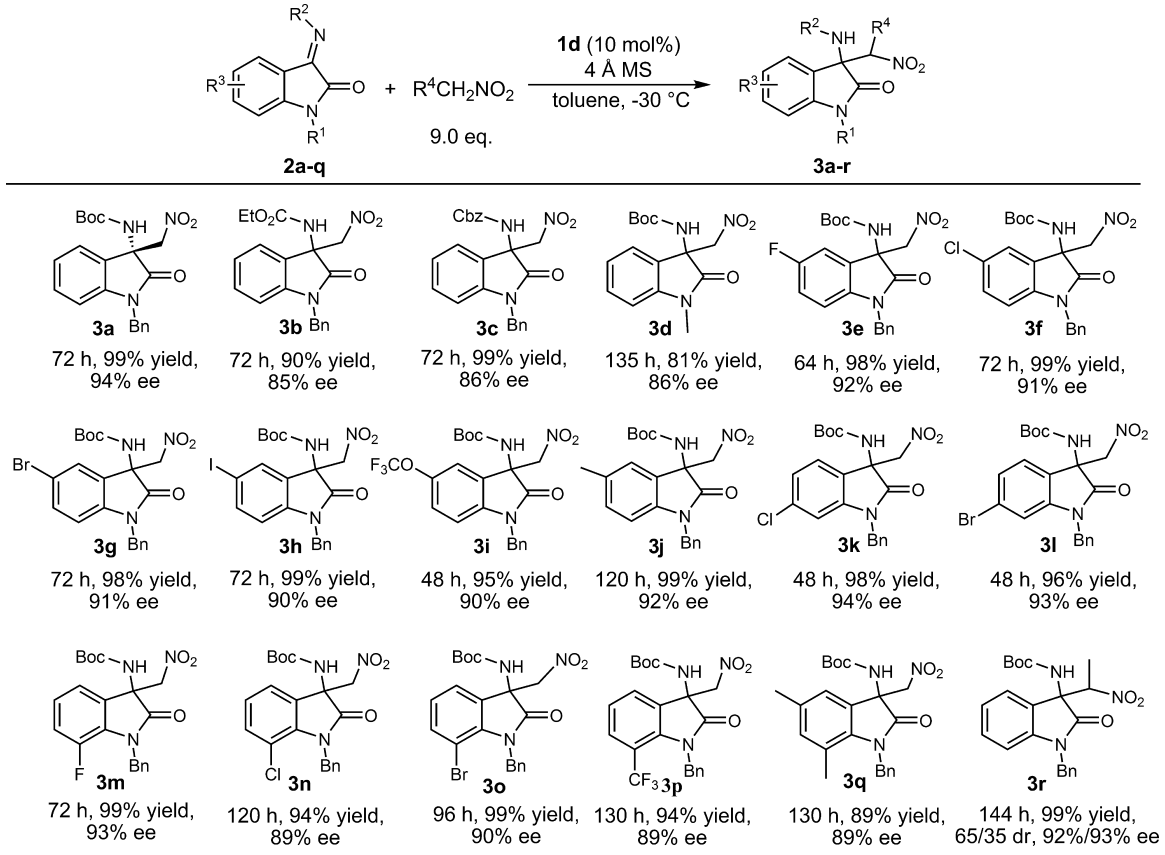
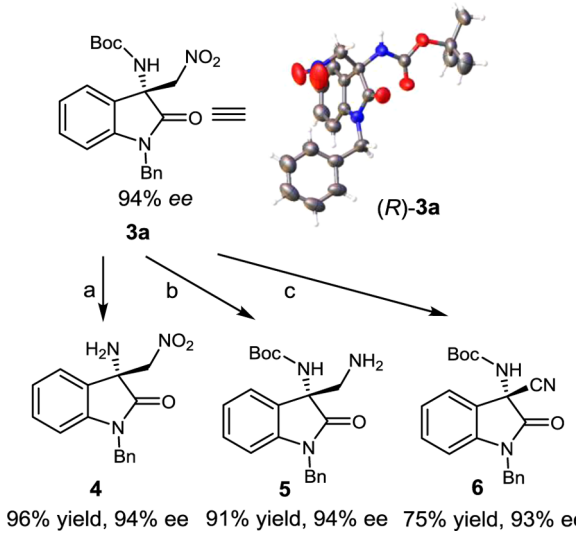
Scheme 1. Substrate Scope of the Catalytic Asymmetric Aza-Henry Reaction



Scheme 2. Transformations of the Adduct 3a[a]



[a]Reaction conditions: (a) CF_3CO_2H, 0 °C, then K_2CO_3; (b) $NaBH_4$, $NiCl_2$, MeOH, 0 °C; (c) $SnCl_2{\cdot}2H_2O$, PhSH, Et_3N, EtOH, then $SOCl_2$, Et_3N, THF.

nucleophile in a dual hydrogen-bonding manner. The amide unit rotates outwardly when the intramolecular hydrogen-bonding disappears.[6f] Then, the amide could act as a Brønsted acid to activate ketimine **2a** through an intermolecular hydrogen bonding. One face of the ketimine is shielded by the phenyl groups of the amide unit, and the nucleophile

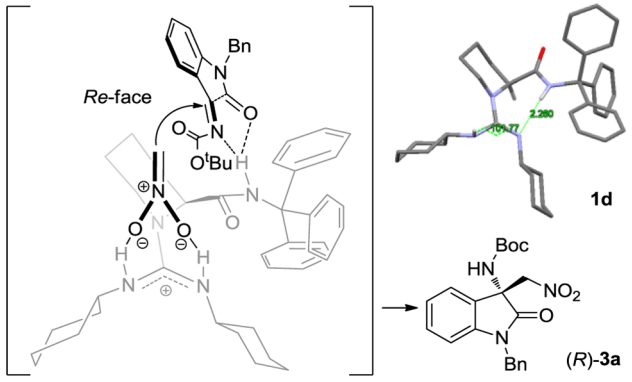


Figure 2. Proposed catalytic model based on the X-ray structure of the catalyst.

attacks the ketimine from the *Re*-face, leading to the (*R*)-product **3a**.

In conclusion, we have developed an organocatalytic procedure for the asymmetric aza-Henry reaction of isatin-derived ketimines. In the presence of a bifunctional guanidine catalyst, this process afforded the desired adducts in high enantioselectivity and yield. A range of substrates could tolerate well in the reaction. Further application of the chiral guanidine-amide catalysts in asymmetric transformations are undergoing in our group.

EXPERIMENTAL SECTION

General remarks. Reactions were carried out using commercially available reagents in an oven-dried apparatus. Toluene was dried over Na and distilled before use. Nitromethane was dried over anhydrous

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$CaCl_2$ and distilled prior to use. Enantiomeric excesses (ee) were determined by HPLC analysis using the corresponding commercial chiral column as stated in the experimental procedures at 23 °C with UV detection at 254 nm. Optical rotations were reported as follows: $[\alpha]_D^T$ (*c*: g/100 mL, in solvent). ^{1}H NMR spectra were recorded on commercial instruments (400 MHz). ^{13}C NMR spectra were collected on commercial instruments (100 MHz) with complete proton decoupling.

General Procedure for the Catalytic Asymmetric Aza-Henry Reaction. To a stirred solution of ketimine **2a** (0.10 mmol, 33.6 mg), guanidine catalyst **1d** (10 mol %, 0.01 mmol, 5.8 mg), and 4 Å MS in toluene (1.0 mL) was added nitromethane (9.0 equiv, 50 μL) at −30 °C. After being stirred for 72 h, the residue was directly purified by column chromatography on silica gel (pet/EtOAc = 6/1 as the eluent) to afford **3a** as a white solid (99% yield, 39.6 mg, 94% ee). The enantiomeric excess (ee) was determined by high-performance liquid chromatography (HPLC).

*Guanidine **1d**.* Compound **1d** was synthesized according to the literature.[6a] White solid: mp 178−180 °C; ^{1}H NMR ($CDCl_3$) δ 10.59 (s, 1H), 7.32−7.12 (m, 15H), 4.38 (d, *J* = 4.0 Hz, 1H), 3.44 (d, *J* = 13.2 Hz, 1H), 3.21 (d, *J* = 10.0 Hz, 1H), 3.03−2.841 (m, 1H), 2.84−2.59 (m, 2H), 2.16 (d, *J* = 12.4 Hz, 1H), 1.99−0.84 (m, 25H), 0.46−0.25 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 172.7, 172.6, 155.8, 155.7, 145.5, 145.5, 129.1, 127.6, 126.2, 70.2, 70.2, 57.3, 56.3, 54.0, 53.9, 45.4, 35.6, 35.0, 33.9, 33.8, 26.4, 25.9, 25.7, 25.5, 25.4, 25.4, 25.3, 21.6; HRMS (ESI-TOF) calcd for $C_{38}H_{49}N_4O$ ([M + H$^+$]) = 577.3901, found 577.3909; IR (KBr) ν = 3398, 3142, 3085, 3057, 3024, 2929, 2850, 1946, 1874, 1802, 1690, 1605, 1544, 1490, 1466, 1446, 1410, 1364, 1346, 1323, 1298, 1273, 1254, 1239, 1220, 1187, 1171, 1141, 1097, 1141, 1097, 1074, 1057, 1029, 982, 952, 935, 920, 895, 862, 845, 788, 766, 741, 700 cm^{-1}.

*(R)-tert-Butyl (1-Benzyl-3-(nitromethyl)-2-oxoindolin-3-yl)-carbamate (**3a**).* Purified by flash chromatography (petroleum ether/EtOAc = 6:1) to afford a white solid, 39.6 mg, 99% yield, 94% ee: mp 98−100 °C; $[\alpha]_D^{30}$ = −6.75 (*c* 1.42, $CHCl_3$); HPLC (DAICEL CHIRALCEL IA, *n*-hexane/2-propanol = 70/30, flow rate =1.0 mL/min, λ = 254 nm) t_R 6.17 min (minor), 10.38 min (major); ^{1}H NMR ($CDCl_3$) δ 7.35 (d, *J* = 7.6 Hz, 1H), 7.32−7.11 (m, 6H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 7.6 Hz, 1H), 5.96 (s, 1H), 5.03−4.84 (m, 2H), 4.84−4.69 (m, 1H), 4.59 (d, *J* = 12.4 Hz, 1H), 1.27 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 173.0, 153.8, 142.5, 135.1, 130.3, 128.9, 127.9, 127.4, 125.9, 124.5, 123.5, 110.0, 81.3, 77.8, 59.9, 44.5, 28.1; HRMS (ESI-TOF) calcd for $C_{21}H_{23}N_3NaO_5$ ([M + Na$^+$]) = 420.1530, found 420.1531; IR (KBr) ν = 3300, 3031, 2984, 2913, 1706, 1611, 1556, 1533, 1487, 1466, 1418, 1367, 1353, 1337, 1288, 1254, 1223, 1223, 1162, 1020, 885, 824, 789, 767, 725 cm^{-1}.

*Ethyl (1-Benzyl-3-(nitromethyl)-2-oxoindolin-3-yl)carbamate (**3b**).* Purified by flash chromatography (petroleum ether/EtOAc = 6:1) to afford a white solid, 33.2 mg, 90% yield, 85% ee: mp 106−108 °C; $[\alpha]_D^{30}$ = −8.94 (*c* 1.62, $CHCl_3$); HPLC (DAICEL CHIRALCEL IA, *n*-hexane/2-propanol = 70/30, flow rate = 1.0 mL/min, λ = 254 nm) t_R 6.75 min (minor), 9.31 min (major); ^{1}H NMR ($CDCl_3$) δ 7.44−7.18 (m, 7H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 8 Hz, 1H), 6.33 (s, 1H), 5.05−4.88 (m, 3H), 4.66 (d, *J* = 12.4 Hz, 1H), 4.16−3.93 (m, 2H), 1.21 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.74, 154.72, 142.62, 135.00, 130.52, 128.95, 127.90, 127.31, 125.46, 124.35, 123.57, 110.15, 77.80, 61.84, 59.91, 44.62, 14.33; HRMS (ESI-TOF) calcd for $C_{19}H_{19}N_3NaO_5$ ([M + Na$^+$]) = 392.1217, found 392.1218; IR (KBr) ν = 3273, 3048, 1710, 1612, 1557, 1489, 1463, 1417, 1374, 1374, 1253, 1184, 1093, 1043, 807, 761, 739 cm^{-1}.

*Benzyl (1-Benzyl-3-(nitromethyl)-2-oxoindolin-3-yl)carbamate (**3c**).* Purified by flash chromatography (petroleum ether/EtOAc = 6:1) to afford a white solid, 42.6 mg, 99% yield, 86% ee: mp 42−44 °C; $[\alpha]_D^{30}$ = −2.85 (*c* 1.41, $CHCl_3$); HPLC (DAICEL CHIRALCEL IA, *n*-hexane/2-propanol = 70/30, flow rate = 1.0 mL/min) λ = 254 nm, t_R: 8.93 min (minor), 13.36 min (major); ^{1}H NMR ($CDCl_3$) δ 7.49−7.15 (m, 12H), 7.08−7.00 (m, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.42 (s, 1H), 5.16−4.69 (m, 5H), 4.63 (d, *J* = 12.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 172.6, 154.5, 142.6, 135.4, 134.9, 130.6, 128.9, 128.6, 128.5, 128.3, 127.9, 127.3, 125.3, 124.4, 123.6, 110.2, 77.7, 67.7, 59.9, 44.6; HRMS (ESI-TOF) calcd for $C_{24}H_{21}N_3NaO_5$ ([M + Na$^+$]) = 454.1373, found 454.1382; IR (KBr) ν = 3308, 3032, 2923, 1957, 1726, 1612, 1559, 1491, 1468, 1455, 1426, 1374, 1252, 1183, 1051, 915, 845, 752 cm^{-1}.

*tert-Butyl (1-Methyl-3-(nitromethyl)-2-oxoindolin-3-yl)-carbamate (**3d**).* Purified by flash chromatography (petroleum ether/EtOAc = 6:1) to afford a white solid, 26.0 mg, 81% yield, 86% ee: mp 136−138 °C; $[\alpha]_D^{30}$ = −1.66 (*c* 1.08, $CHCl_3$); HPLC (DAICEL CHIRALCEL IA, *n*-hexane/2-propanol = 70/30, flow rate = 1.0 mL/min, λ = 254 nm) t_R 7.31 min (minor), 8.44 min (major); ^{1}H NMR ($CDCl_3$) δ 7.49−7.31 (m, 2H), 7.14−7.06 (m, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 6.00 (s, 1H), 4.92 (d, *J* = 12.4 Hz, 1H), 4.60 (d, *J* = 12.4 Hz, 1H), 3.28 (s, 3H), 1.32 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.7, 153.7, 143.3, 130.4, 125.9, 124.3, 123.5, 108.9, 81.2, 77.8, 59.9, 28.1, 26.9; HRMS (ESI-TOF) calcd for $C_{15}H_{19}N_3NaO_5$ ([M + Na$^+$]) = 344.1217. Found 344.1217; IR (KBr) ν = 3341, 3011, 2968, 2927, 1704, 1612, 1563, 1519, 1491, 1471, 1408, 1370, 1320, 1255, 1162, 1128, 1107, 1054, 1028, 906, 874, 840, 778, 758, 724 cm^{-1}.

*tert-Butyl (1-Benzyl-5-fluoro-3-(nitromethyl)-2-oxoindolin-3-yl)-carbamate (**3e**).* Purified by flash chromatography (petroleum ether/EtOAc = 6:1) to afford a white solid, 40.7 mg, 98% yield, 92% ee: mp 150−152 °C; $[\alpha]_D^{30}$ = −4.68 (*c* 0.790, $CHCl_3$); HPLC (DAICEL CHIRALCEL IA, *n*-hexane/2-propanol = 70/30, flow rate = 1.0 mL/min, λ = 254 nm) t_R 7.07 min (minor), 12.19 min (major); ^{1}H NMR ($CDCl_3$) δ 7.41−7.23 (m, 6H), 6.94 (td, *J* = 8.8, 2.8 Hz, 1H), 6.68 (dd, *J* = 8.6, 4.0 Hz, 1H), 5.95 (s, 1H), 5.132−4.955 (m, 2H), 4.947−4.790 (m, 1H), 4.68 (d, *J* = 12.4 Hz, 1H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.8, 160.6, 158.2, 153.8, 138.5 (d, *J* = 2.2), 134.7, 129.0, 128.0, 127.3, 116.7 (d, *J* = 23.4), 113.1 (d, *J* = 26.1), 110.7 (d, *J* = 7.9), 81.62, 77.4, 60.02, 44.7, 28.1; HRMS (ESI-TOF) calcd for $C_{21}H_{22}FN_3NaO_5$ ([M + Na$^+$]) = 438.1436, found 438.1437; IR (KBr) ν = 3428, 3062, 3031, 2983, 2923, 1719, 1619, 1563, 1493, 1455, 1427, 1369, 1304, 1276, 1227, 1158, 1055, 993, 913, 882, 854, 821, 726 cm^{-1}.

*tert-Butyl (1-Benzyl-5-chloro-3-(nitromethyl)-2-oxoindolin-3-yl)-carbamate (**3f**).* Purified by flash chromatography (petroleum ether/EtOAc = 6:1) to afford a white solid, 42.7 mg, 99% yield, 91% ee: mp 156−158 °C; $[\alpha]_D^{30}$ = −27.5 (*c* 0.850, $CHCl_3$); HPLC (DAICEL CHIRALCEL IA, *n*-hexane/2-propanol = 70/30, flow rate = 1.0 mL/min, λ = 254 nm) t_R 6.82 min (minor), 11.66 min (major); ^{1}H NMR ($CDCl_3$) δ 7.45 (d, *J* = 1.6 Hz, 1H), 7.39−7.27 (m, 5H), 7.21 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 5.96 (s, 1H), 5.08−4.93 (m, 2H), 4.92−4.80 (m, 1H), 4.67 (d, *J* = 12.6 Hz, 1H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.6, 153.8, 141.1, 134.6, 130.3, 129.0, 128.0, 127.5, 127.3, 125.1, 111.0, 81.68, 77.5, 59.8, 44.7, 28.2; HRMS (ESI-TOF) calcd for $C_{21}H_{22}Cl^{34.9689}N_3NaO_5$ ([M + Na$^+$]) = 454.1140, found 454.1145; $C_{21}H_{22}Cl^{36.9659}N_3NaO_5$ ([M + Na$^+$]) = 456.1111, found 456.1130; IR (KBr) ν = 3427, 3031, 2977, 2925, 1720, 1610, 1564, 1488, 1429, 1369, 1296, 1277, 1159, 1055, 989, 875, 875, 849, 822, 776, 730 cm^{-1}.

*tert-Butyl (1-Benzyl-5-bromo-3-(nitromethyl)-2-oxoindolin-3-yl)-carbamate (**3g**).* Purified by flash chromatography (petroleum ether/EtOAc = 6:1) to afford a white solid, 46.6 mg, 98% yield, 91% ee: mp 149−151 °C; $[\alpha]_D^{30}$ = −36.1 (*c* 0.902, $CHCl_3$); HPLC DAICEL CHIRALCEL IA, *n*-hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, λ = 254 nm, t_R 6.98 min (minor), 11.99 min (major); ^{1}H NMR ($CDCl_3$) δ 7.58 (s, 1H), 7.39−7.26 (m, 6H), 6.62 (d, *J* = 8.4 Hz, 1H), 5.98 (s, 1H), 5.055−4.926 (m, 2H), 4.931−4.811 (m, 1H), 4.67 (d, *J* = 12.6 Hz, 1H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.5, 153.8, 141.6, 134.6, 133.2, 129.0, 128.1, 127.9, 127.7, 127.3, 116.2, 111.5, 81.7, 77.5, 59.8, 44.7, 28.2; HRMS (ESI-TOF) calcd for $C_{21}H_{22}Br^{78.9183}N_3NaO_5$ ([M + Na$^+$]) = 498.0635, found 498.0646, $C_{21}H_{22}Br^{80.9163}N_3NaO_5$ ([M + Na$^+$]) = 500.0615, found 500.0625; IR (KBr) ν = 3286, 3032, 2981, 2932, 1713, 1610, 1560, 1534, 1481, 1454, 1427, 1369, 1332, 1289, 1256, 1161, 1051, 1023, 1000, 875, 845, 813, 778, 719 cm^{-1}.

*tert-Butyl (1-Benzyl-5-iodo-3-(nitromethyl)-2-oxoindolin-3-yl)-carbamate (**3h**).* Purified by flash chromatography (petroleum ether/EtOAc = 6:1) to afford a white solid, 51.8 mg, 99% yield, 90% ee: mp 168−170 °C; $[\alpha]_D^{30}$ = −46.5 (*c* 1.81, $CHCl_3$); HPLC (DAICEL CHIRALCEL IA, *n*-hexane/2-propanol = 80/20, flow rate =

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1.0 mL/min, λ = 254 nm) t_R 7.37 min (minor), 12.68 min (major); ^{1}H NMR ($CDCl_3$) δ 7.65 (s, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.33−7.13 (m, 5H), 6.45 (d, J = 8.0 Hz, 1H), 5.91 (s, 1H), 4.98−4.71 (m, 3H), 4.58 (d, J = 12.8 Hz, 1H), 1.30 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.3, 153.8, 142.3, 139.2, 134.6, 133.1, 129.0, 128.1, 128.1, 127.3, 112.1, 86.0, 81.7, 77.5, 59.6, 44.6, 28.2; HRMS (ESI-TOF) calcd for $C_{21}H_{22}IN_3NaO_5$ ([M + Na$^+$]) = 546.0496, found 546.0502; IR (KBr) ν = 3287, 3031, 2981, 2927, 1712, 1607, 1558, 1535, 1479, 1453, 1424, 1366, 1331, 1290, 1257, 1161, 1045, 1022, 1000, 877, 815, 759, 715 cm^{-1}.

*tert-Butyl (1-Benzyl-3-(nitromethyl)-2-oxo-5-(trifluoromethoxy)-indolin-3-yl)carbamate (**3i**).* Purified by flash chromatography (petroleum ether/EtOAc = 6:1) to afford a white solid, 45.7 mg, 95% yield, 90% ee: mp 106−108 °C; $[\alpha]_D^{30}$ = −5.79 (c 0.518, $CHCl_3$); HPLC (DAICEL CHIRALCEL IA, n-hexane/2-propanol = 70/30, flow rate = 1.0 mL/min, λ = 254 nm) t_R 6.39 min (minor), 9.17 min (major); ^{1}H NMR ($CDCl_3$) δ 7.32 (s, 1H), 7.30−7.17 (m, 5H), 7.08−7.01 (m, 1H), 6.67 (d, J = 8.6 Hz, 1H), 5.87 (s, 1H), 5.00−4.90 (m, 2H), 4.80 (d, J = 16.0 Hz, 1H), 4.61 (d, J = 12.8 Hz, 1H), 1.29 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.9, 153.8, 145.1 (d, J = 1.9), 141.3, 134.5, 129.0, 128.1, 127.4, 123.4, 120.4 (q, J = 255.6), 118.9, 110.5, 81.9, 59.9, 44.8, 28.1; HRMS (ESI-TOF) calcd for $C_{22}H_{22}F_3N_3NaO_6$ ([M + Na$^+$]) = 504.1353, found 504.1363; IR (KBr) ν = 3306, 2990, 1723, 1684, 1621, 1561, 1496, 1454, 1437, 1418, 1396, 1372, 1341, 1257, 1218, 1166, 1082, 1055, 1024, 975, 928, 879, 854, 810, 743, 701 cm^{-1}.

*tert-Butyl (1-Benzyl-5-methyl-3-(nitromethyl)-2-oxoindolin-3-yl)-carbamate (**3j**).* Purified by flash chromatography (petroleum ether/EtOAc = 6:1) to afford a white solid, 40.7 mg, 99% yield, 92% ee: mp 158−160 °C; $[\alpha]_D^{30}$ = −6.75 (c 1.42, $CHCl_3$); HPLC (DAICEL CHIRALCEL IA, n-hexane/2-propanol = 70/30, flow rate = 1.0 mL/min, λ = 254 nm) t_R 7.21 min (minor), 14.94 min (major); ^{1}H NMR ($CDCl_3$) δ 7.41−7.29 (m, 4H), 7.29−7.218 (m, 2H), 7.03 (d, J = 7.6 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 5.98 (s, 1H), 5.083−4.923 (m, 2H), 4.86 (d, J = 15.6 Hz, 1H), 4.65 (d, J = 12.4 Hz, 1H), 2.28 (s, 3H), 1.36 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.8, 153.8, 140.0, 135.2, 133.2, 130.6, 128.9, 127.8, 127.4, 125.9, 125.1, 109.8, 81.2, 77.9, 60.0, 44.5, 28.2, 21.1; HRMS (ESI-TOF) calcd for $C_{22}H_{25}N_3NaO_5$ ([M + Na$^+$]) = 434.1686, found 434.1688; IR (KBr) ν = 3317, 3032, 2975, 2926, 1703, 1622, 1607, 1563, 1528, 1499, 1452, 1428, 1368, 1315, 1280, 1250, 1199, 1165, 1032, 910, 861, 829, 780, 726 cm^{-1}.

*tert-Butyl (1-Benzyl-6-chloro-3-(nitromethyl)-2-oxoindolin-3-yl)-carbamate (**3k**).* Purified by flash chromatography (petroleum ether/EtOAc = 6:1) to afford a white solid, 42.3 mg, 98% yield, 94% ee: mp 132−134 °C; $[\alpha]_D^{30}$ = −9.71 (c 0.680, $CHCl_3$); HPLC (DAICEL CHIRALCEL IA, n-hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, λ = 254 nm) t_R 6.15 min (minor), 9.61 min (major); ^{1}H NMR ($CDCl_3$) δ 7.43−7.27 (m, 6H), 7.03 (dd, J = 8.0, 1.6 Hz, 1H), 6.76 (d, J = 1.4 Hz, 1H), 5.94 (s, 1H), 5.07−4.95 (m, 2H), 4.86 (d, J = 15.6 Hz, 1H), 4.63 (d, J = 12.4 Hz, 1H), 1.37 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 173.0, 153.8, 143.8, 136.3, 134.5, 129.1, 128.1, 127.3, 125.6, 124.2, 123.5, 110.7, 81.6, 77.6, 59.5, 44.7, 28.1; HRMS (ESI-TOF) calcd for $C_{21}H_{22}Cl^{34.9689}N_3NaO_5$ ([M + Na$^+$]) = 454.1140, found 454.1148; $C_{21}H_{22}Cl^{36.9659}N_3NaO_5$ ([M + Na$^+$]) = 456.1111, found 456.1134; IR (KBr) ν = 3317, 3071, 3032, 2976, 2925, 1737, 1705, 1614, 1557, 1533, 1491, 1448, 1425, 1374, 1291, 1256, 1221, 1162, 1118, 1074, 1047, 1025, 1000, 914, 883, 844, 761, 718 cm^{-1}.

*tert-Butyl (1-Benzyl-6-bromo-3-(nitromethyl)-2-oxoindolin-3-yl)-carbamate (**3l**).* Purified by flash chromatography (petroleum ether/EtOAc = 6:1) to afford a white solid, 45.7 mg, 96% yield, 93% ee: mp 156−158 °C; $[\alpha]_D^{30}$ = −10.8 (c 0.814, $CHCl_3$); HPLC (DAICEL CHIRALCEL IA, n-hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, λ = 254 nm) t_R 6.24 min (minor), 9.76 min (major).^{1}H NMR ($CDCl_3$) δ 7.38−7.27 (m, 6H), 7.16−7.21 (m, 1H), 6.91 (s, 1H), 5.95 (s, 1H), 5.03−4.95 (m, 2H), 4.86 (d, J = 15.7 Hz, 1H), 4.63 (d, J = 12.5 Hz, 1H), 1.37 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.9, 153.8, 143.9, 134.5, 129.1, 128.1, 127.3, 126.4, 125.9, 124.8, 124.2, 113.4, 81.6, 77.5, 59.6, 44.7, 28.1; HRMS (ESI-TOF) calcd for $C_{21}H_{22}Br^{78.9183}N_3NaO_5$ ([M + Na$^+$]) = 498.0635, found 498.0644, $C_{21}H_{22}Br^{80.9163}N_3NaO_5$ ([M + Na$^+$]) = 500.0615, found 500.0627; IR (KBr) ν = 3320, 3066, 3032, 2976, 2932, 1736, 1705, 1608, 1555, 1532, 1488, 1452, 1441, 1423, 1372, 1290, 1256, 1221, 1163, 1119, 1060, 1025, 999, 912, 885, 840, 785, 761, 719 cm^{-1}.

*tert-Butyl (1-Benzyl-7-fluoro-3-(nitromethyl)-2-oxoindolin-3-yl)-carbamate (**3m**).* Purified by flash chromatography (petroleum ether/EtOAc = 6:1) to afford a white solid, 41.1 mg, 99% yield, 93% ee: mp 54−56 °C; $[\alpha]_D^{30}$ = −7.18 (c 1.62, $CHCl_3$); HPLC (DAICEL CHIRALCEL IA, n-hexane/2-propanol = 70/30, flow rate =1.0 mL/min, λ = 254 nm) t_R 6.83 min (minor), 13.31 min (major); ^{1}H NMR ($CDCl_3$) δ 7.40 (d, J = 7.4 Hz, 2H), 7.36−7.24 (m, 3H), 7.18 (d, J = 6.6 Hz, 1H), 7.08−6.94 (m, 2H), 6.09 (s, 1H), 5.09 (dd, J = 38.9, 15.3 Hz, 2H), 4.91 (d, J = 12.5 Hz, 1H), 4.58 (d, J = 12.5 Hz, 1H), 1.34 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.7, 153.7, 148.9, 146.5, 136.4, 129.2 (d, J = 9.1), 128.7, 127.8, 127.6, 124.3 (d, J = 6.4), 120.1, 118.6 (d, J = 19.4), 81.6, 77.8, 60.0 (d, J = 2.4), 46.2 (d, J = 4.8), 28.1; HRMS (ESI-TOF) calcd for $C_{21}H_{22}FN_3NaO_5$ ([M + Na$^+$]) = 438.1436, found 438.1441; IR (KBr) ν = 3339, 2979, 2933, 1721, 1632, 1604, 1561, 1490, 1425, 1368, 1279, 1250, 1162, 1060, 1025, 921, 858, 779, 731 cm^{-1}.

*tert-Butyl (1-Benzyl-7-chloro-3-(nitromethyl)-2-oxoindolin-3-yl)-carbamate (**3n**).* Purified by flash chromatography (petroleum ether/EtOAc = 6:1) to afford a white solid, 40.6 mg, 94% yield, 89% ee: mp 100−102 °C; $[\alpha]_D^{30}$ = +2.00 (c 0.802, $CHCl_3$); HPLC (DAICEL CHIRALCEL IA, n-hexane/2-propanol = 70/30, flow rate = 1.0 mL/min, λ = 254 nm) t_R 6.09 min (minor), 11.13 min (major); ^{1}H NMR ($CDCl_3$) δ 7.37−7.28 (m, 5H), 7.27−7.22 (m, 2H), 7.00 (t, J = 7.8 Hz, 1H), 6.09 (s, 1H), 5.38 (dd, J = 16 Hz, J = 28.4 Hz, 2H), 4.90 (d, J = 12.4 Hz, 1H), 4.59 (d, J = 12.4 Hz, 1H), 1.36 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 173.6, 153.6, 138.7, 136.9, 133.0, 128.9, 128.7, 127.4, 126.6, 124.4, 122.6, 116.3, 81.6, 77.9, 59.5, 45.7, 28.1; HRMS (ESI-TOF) calcd for $C_{21}H_{22}Cl^{34.9689}N_3NaO_5$ ([M + Na$^+$]) = 454.1140, found 454.1140; $C_{21}H_{22}Cl^{36.9659}N_3NaO_5$ ([M + Na$^+$]) = 456.1111, found 456.1128; IR (KBr) ν = 3327, 3065, 3031, 2977, 2936, 1937, 1713, 1612, 1559, 1520, 1457, 1423, 1364, 1335, 1281, 1255, 1159, 1082, 1022, 1001, 919, 873, 837, 819, 798, 779, 732 cm^{-1}.

*tert-Butyl (1-Benzyl-7-bromo-3-(nitromethyl)-2-oxoindolin-3-yl)-carbamate (**3o**).* Purified by flash chromatography (petroleum ether/EtOAc = 6:1) to afford a white solid, 47.1 mg, 99% yield, 90% ee: mp 126−128 °C; $[\alpha]_D^{30}$ = +4.75 (c 1.87, $CHCl_3$); HPLC (DAICEL CHIRALCEL IA, n-hexane/2-propanol = 70/30, flow rate = 1.0 mL/min, λ = 254 nm) t_R 6.12 min (minor), 11.51 min (major); ^{1}H NMR ($CDCl_3$) δ 7.36 (d, J = 8.4 Hz, 1H), 7.33−7.21 (m, 5H), 7.20−7.13 (m, 1H), 6.86 (t, J = 8.0 Hz, 1H), 6.01 (s, 1H), 5.35 (dd, J = 40.0, 16.4 Hz, 2H), 4.82 (d, J = 12.4 Hz, 1H), 4.51 (d, J = 12.4 Hz, 1H), 1.29 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 173.8, 153.6, 140.1, 136.9, 136.4, 129.2, 128.7, 127.3, 126.5, 124.7, 123.2, 103.3, 81.7, 77.9, 59.4, 45.4, 28.1; HRMS (ESI-TOF) calcd for $C_{21}H_{22}Br^{78.9183}N_3NaO_5$ ([M + Na$^+$]) = 498.0635, found 498.0646, $C_{21}H_{22}Br^{80.9163}N_3NaO_5$ ([M + Na$^+$]) = 500.0615, found 500.0625; IR (KBr) ν = 3327, 3064, 3030, 2977, 2934, 1712, 1609, 1558, 1519, 1453, 1422, 1364, 1335, 1282, 1255, 1255, 1158, 1124, 1082, 1022, 873, 829, 780, 731 cm^{-1}.

*tert-Butyl (1-Benzyl-3-(nitromethyl)-2-oxo-7-(trifluoromethyl)-indolin-3-yl)carbamate (**3p**).* Purified by flash chromatography (petroleum ether/EtOAc = 6:1) to afford a white solid, 43.7 mg, 94% yield, 89% ee: mp 124−126 °C; $[\alpha]_D^{30}$ = −9.56 (c 0.868, $CHCl_3$); HPLC (DAICEL CHIRALCEL IA, n-hexane/2-propanol = 70/30, flow rate = 1.0 mL/min, λ = 254 nm) t_R 6.15 min (minor), 10.31 min (major); ^{1}H NMR ($CDCl_3$) δ7.63−7.49 (m, 2H), 7.26−7.07 (m, 6H), 5.97 (s, 1H), 5.14 (s, 2H), 4.82 (d, J = 12.4 Hz, 1H), 4.51 (d, J = 12.4 Hz, 1H), 1.28 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 174.4, 153.6, 141.0, 135.7, 129.9, 128.3−128.6 (m), 127.8, 127.1, 125.9, 123.0, 113.7(q, J = 32.9), 81.8, 77.8, 58.3, 46.7, 46.7, 29.7, 28.1; HRMS (ESI-TOF) calcd for $C_{22}H_{22}F_3N_3NaO_5$ ([M + Na$^+$]) = 488.1404, found 488.1408; IR (KBr) ν = 3328, 3071, 3015, 2980, 2937, 1713, 1602, 1561, 1518, 1455, 1367, 1326, 1284, 1256, 1169, 1128, 1104, 1049, 1008, 919, 873, 819, 793, 748, 730, 705 cm^{-1}.

*tert-Butyl (1-Benzyl-5,7-dimethyl-3-(nitromethyl)-2-oxoindolin-3-yl)carbamate (**3q**).* Purified by flash chromatography (petroleum ether/EtOAc = 6:1) to afford a white solid, 37.8 mg, 89% yield, 89% ee: mp 130−132 °C; $[\alpha]_D^{30}$ = −20.5 (c 0.716, $CHCl_3$); HPLC (DAICEL CHIRALCEL IA, n-hexane/2-propanol = 80/20, flow rate =

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1.0 mL/min, λ = 254 nm) t_R 6.52 min (minor), 14.52 min (major); ^{1}H NMR ($CDCl_3$) δ 7.36−7.21 (m, 6H), 7.07 (s, 1H), 6.83 (s, 1H), 6.06 (s, 1H), 5.18 (s, 2H), 4.88 (d, J = 12.0 Hz, 1H), 4.63 (d, J = 12.0 Hz, 1H), 2.25 (s, 3H), 2.21 (s, 3H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 173.9, 153.8, 138.0, 137.2, 134.9, 133.2, 128.9, 127.3, 126.8, 125.9, 122.6, 120.3, 81.2, 78.4, 59.6, 45.8, 28.2, 20.8, 18.7; HRMS (ESI-TOF) calcd for $C_{23}H_{27}N_3NaO_5$ ([M + Na^+]) = 448.1852, found 448.1852; IR (KBr) ν = 3445, 3031, 2980, 2925, 1719, 1604, 1566, 1487, 1414, 1366, 1326, 1274, 1254, 1157, 1050, 1028, 1002, 906, 867, 843, 771, 720 cm^{-1}.

*tert-Butyl (1-Benzyl-3-(1-nitroethyl)-2-oxoindolin-3-yl)carbamate (**3r**).* Purified by flash chromatography (petroleum ether/EtOAc = 6:1) to afford a white solid, 40.7 mg, 99% yield, 65:35 dr 92%/93% ee: mp 92−94 °C; HPLC (DAICEL CHIRALCEL IA, *n*-hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, λ = 254 nm) t_R 6.89 min (minor), 7.39 min (minor), 10.85 min (major), 17.74 min (major); ^{1}H NMR ($CDCl_3$) δ 7.44−7.14 (m, 7H), 7.09−6.98 (m, 1H), 6.84−6.72 (m, 1H), 6.15 (d, J = 5.8 Hz, 1H), 5.19−4.66 (m, 3H), 1.72 (d, J = 6.9 Hz, 1H), 1.38−1.24 (m, 11H); ^{13}C NMR ($CDCl_3$) δ 173.4, 172.4, 153.9, 153.4, 143.4, 142.4, 135.4, 135.2, 130.2, 130.1, 128.9, 128.9, 127.9, 127.6, 127.4, 127.0, 124.7, 124.3, 123.4, 123.2, 123.2, 109.7, 109.5, 85.6, 84.8, 81.1, 62.7, 62.0, 44.7, 44.5, 28.1, 13.2, 13.0; HRMS (ESI-TOF) calcd for $C_{22}H_{25}N_3NaO_5$ ([M + Na^+]) = 434.1686, found 434.1696; IR (KBr) ν = 3322, 3036, 2964, 2925, 2364, 1709, 1611, 1558, 1531, 1485, 1467, 1362, 1284, 1255, 1160, 1098, 1035, 1004, 976, 872, 843, 807, 758 cm^{-1}.

*3-Amino-1-benzyl-3-(nitromethyl)indolin-2-one (**4**).* To a solution of **3a** (0.1 mmol, 39.7 mg) in CH_2Cl_2 (1.0 mL) was added CF_3CO_2H (1.0 mL) at 0 °C. The mixture was allowed to stir for 2 h. Then the mixture was neutralized with K_2CO_3, washed with brine, and dried over Na_2SO_4. After evaporation of the solvent, the product **4** was purified on silica gel chromatography (pet/EtOAc = 3/1) to afford a white solid, 28.5 mg, 96% yield, 94% ee: mp 58−60 °C; $[\alpha]_D^{30}$ = −53.2 (*c* 0.528, $CHCl_3$); HPLC (DAICEL CHIRALCEL ID, *n*-hexane/2-propanol = 70/30, flow rate = 1.0 mL/min, λ = 254 nm) t_R 12.32 min (minor), 14.67 min (major); ^{1}H NMR ($CDCl_3$) δ 7.35−7.12 (m, 7H), 6.99 (t, J = 7.6 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 4.96 (d, J = 15.6 Hz, 1H), 4.87−4.68 (m, 3H), 1.85 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 177.0, 143.0, 135.2, 130.5 128.9, 127.9, 127.3, 127.3, 123.9, 123.4, 110.2, 79.3, 59.0, 44.3, 29.7; HRMS (ESI-TOF) calcd for $C_{16}H_{15}N_3NaO_3$ ([M + Na^+]) = 320.1006, found 320.1008; IR (KBr) ν = 3369, 3061, 3031, 2922, 1719, 1613, 1551, 1490, 1468, 1422, 1378, 1177, 1112, 1080, 991, 862, 753, 701 cm^{-1}.

*tert-Butyl (3-(Aminomethyl)-1-benzyl-2-oxoindolin-3-yl)-carbamate (**5**).* To a solution of the compound **3a** (0.2 mmol, 79.4 mg) in methanol (2.0 mL) at 0 °C was added $NiCl_2$ (0.2 mmol, 25.8 mg) followed by $NaBH_4$ (2.4 mmol, 90.7 mg) under nitrogen. The mixture was stirred for 2 h. Then saturated aqueous NH_4Cl (8 mL) was added, and the mixture was extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The product **5** was purified on silica gel chromatography (pet/EtOAc = 1/1) to afford a white solid, 33.4 mg, 91% yield, 94% ee: mp 50−52 °C; $[\alpha]_D^{30}$ = −19.6 (*c* 1.08, $CHCl_3$); HPLC (DAICEL CHIRALCEL IA, *n*-hexane/2-propanol = 70/30, flow rate =1.0 mL/min, λ = 254 nm) t_R 7.11 min (minor), 10.13 min (major); ^{1}H NMR ($CDCl_3$) δ 7.40−7.22 (m, 6H), 7.21−7.14 (m, 1H), 7.02 (t, J = 7.6 Hz, 1H), 6.71 (d, J = 7.6 Hz, 1H), 6.28 (s, 1H), 5.13 (s, 1H), 4.77 (s, 1H), 3.02 (s, 2H), 1.82 (s, 2H), 1.26 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 176.8, 154.6, 142.5, 135.9, 130.1, 128.8, 127.6, 127.3, 122.7, 122.5, 109.3, 80.3, 62.2, 48.4, 44.0, 29.7, 28.1; HRMS (ESI-TOF) calcd for $C_{21}H_{25}N_3NaO_3$ ([M + H^+]) = 368.1969, found 368.1971; IR (KBr) ν = 3343, 3060, 2969, 2930, 2866, 1718, 1615, 1467, 1365, 1279, 1172, 1075, 1005, 879, 749 cm^{-1}.

*tert-Butyl (1-Benzyl-3-cyano-2-oxoindolin-3-yl)carbamate (**6**).* The compound **3a** (0.3 mmol, 119.1) was added to a solution of $SnCl_2{\cdot}2H_2O$ (0.60 mmol, 136.0 mg), thiophenol (1.78 mmol, 183 μL), and triethylamine (1.78 mmol, 247 μL) in absolute EtOH (2.0 mL) at room temperature. After 20 min, the reaction mixture was poured into 1 M aqueous HCl (8 mL) and CH_2Cl_2 (10 mL) at 0 °C. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed with aqueous $NaHCO_3$ (5 mL) and brine (5 mL) and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed through a short plug of silica gel eluting with pet/EtOAc = 3:1 to remove the excess thiophenol and then with EtOAc. The EtOAc fraction was concentrated under reduced pressure to give a stereoismeric mixture of oximes. To the solution of oximes in THF (5.0 mL) at 0 °C under nitrogen atmosphere were added triethylamine (1.12 mmol, 155 μL) and $SOCl_2$ (0.34 mmol, 25 μL). After 45 min, water (8 mL) was added, and the mixture was extracted with EtOAc (2 × 15 mL), washed with brine (3 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Column chromatography eluting with pet/EtOAc = 5/1 gave the compound **6** as a white solid, 78.3 mg, 75% yield, 93% ee: mp 58−60 °C; $[\alpha]_D^{30}$ = 72.4 (*c* 1.30, $CHCl_3$); HPLC (DAICEL CHIRALCEL ID, *n*-hexane/2-propanol = 90/10, flow rate = 1.0 mL/min, λ = 254 nm) t_R 30.19 min (major), 32.53 min (minor); ^{1}H NMR ($CDCl_3$) δ 7.73 (d, J = 7.6 Hz, 1H), 7.30−7.14 (m, 6H), 7.04 (t, J = 7.6 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 5.76 (s, 1H), 4.93−4.76 (m, 2H), 1.34 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 168.3, 153.7, 142.2, 134.3, 131.2, 129.0, 128.1, 127.3, 126.2, 124.8, 124.3, 114.7, 110.3, 82.4, 54.9, 44.9, 28.1; HRMS (ESI-TOF) calcd for $C_{21}H_{21}N_3NaO_3$ ([M + Na^+]) = 386.1475, found 386.1485; IR (KBr) ν = 3319, 3063, 2979, 2933, 2247, 2247, 1612, 1489, 1370, 1278, 1253, 1160, 1106, 1080, 1044, 1019, 940.96, 869, 753 cm^{-1}.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full optimization details, ^{1}H and ^{13}C NMR spectra, and HPLC data and X-ray crystal data of compounds **1d** and **3a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For review on application of guanidines in organic synthesis, see: (a) Ishikawa, T.; Kumamoto, T. *Synthesis* **2006**, 737−752. Bicyclic guanidine was shown to bind tightly to nitroalkanes to form an ion pair, see: (b) Boyle, P. H.; Convery, M. A.; Davis, A. P.; Hosken, G. D.; Murray, B. A. *J. Chem. Soc., Chem. Commun.* **1992**, 239−242. (c) van Aken, E.; Wynberg, H.; van Bolhuis, F. *J. Chem. Soc., Chem. Commun.* **1992**, 629−630. (d) Ishikawa, T. In *Superbases for Organic Synthesis*; Ishikawa, T., Ed.; Wiley: Chichester, 2009; pp 93−143. (e) Liu, X. H.; Lin, L. L.; Feng, X. M. *Chem. Commun.* **2009**, 6145−6158.

(2) For reviews on guanidium-based anionic receptors, see: (a) Best, M. D.; Tobey, S. L.; Anslyn, E. V. *Coord. Chem. Rev.* **2003**, *240*, 3−15. (b) Schug, K. A.; Lindner, W. *Chem. Rev.* **2005**, *105*, 67−113. (c) Blondeau, P.; Segura, M.; Pérez-Fernández, R.; de Mendoza, J. *Chem. Soc. Rev.* **2007**, *36*, 198−210.

(3) (a) Hannon, C. L.; Anslyn, E. V. In *Bioorganic Chemistry Frontiers*; Dugas, H., Ed.; Springer-Verlag: Berlin, 1993; Vol. 3 pp 193−256. (b) Yamamoto, Y.; Kojima, S. In *The Chemistry of Amidines and Imidates*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1991; Vol. 2, pp 485−526.

DOI: 10.1021/acs.joc.5b00075
J. Org. Chem. 2015, 80, 3332−3338

(4) For selected reviews on guanidine-catalyzed reactions, see: (a) Leow, D.; Tan, C.-H. *Chem.—Asian J.* **2009**, *4*, 488−507. (b) Terada, M. *J. Synth. Org. Chem., Jpn.* **2010**, *68*, 1159−1168. (c) Fu, X.; Tan, C.-H. *Chem. Commun.* **2011**, *47*, 8210−8222. (d) Rauws, T. R. M.; Maes, B. U. W. *Chem. Soc. Rev.* **2012**, *41*, 2463−2497. (e) Taylor, J. E.; Bull, S. D.; Williams, J. M. J. *Chem. Soc. Rev.* **2012**, *41*, 2109−2121. (f) Selig, P. *Synthesis* **2013**, *45*, 703−718.

(5) For selected examples of guanidine-catalyzed reactions, see: (a) Chinchilla, R.; Nájera, C.; Sánchez-Agulló, P. *Tetrahedron: Asymmetry* **1994**, *5*, 1393−1402. (b) Ishikawa, T.; Araki, Y.; Kumamoto, T.; Seki, H.; Fukuda, K.; Isobe, T. *Chem. Commun.* **2001**, 245−246. (c) Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1454−1455. (d) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Adv. Synth. Catal.* **2005**, *347*, 1643−1648. (e) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157−160. (f) Shen, J.; Nguyen, T. T.; Goh, Y.-P.; Ye, W.; Fu, X.; Xu, J.; Tan, C.-H. *J. Am. Chem. Soc.* **2006**, *128*, 13692−13693. (g) Misaki, T.; Takimoto, G.; Sugimura, T. *J. Am. Chem. Soc.* **2010**, *132*, 6286−6287. (h) Fu, X.; Loh, W.-T.; Zhang, Y.; Chen, T.; Ma, T.; Liu, H.; Wang, J.; Tan, C.-H. *Angew. Chem., Int. Ed.* **2009**, *48*, 7387−7390.

(6) (a) Yu, Z. P.; Liu, X. H.; Zhou, L.; Lin, L. L.; Feng, X. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 5195−5198. (b) Dong, S. X.; Liu, X. H.; Chen, X. H.; Mei, F.; Zhang, Y. L.; Gao, B.; Lin, L. L.; Feng, X. M. *J. Am. Chem. Soc.* **2010**, *132*, 10650−10651. (c) Dong, S. X.; Liu, X. H.; Zhang, Y. L.; Lin, L. L.; Feng, X. M. *Org. Lett.* **2011**, *13*, 5060−5063. (d) Xiao, X.; Liu, X. H.; Dong, S. X.; Cai, Y. F.; Lin, L. L.; Feng, X. M. *Chem.—Eur. J.* **2012**, *18*, 15922−15926. (e) Yang, Y.; Dong, S. X.; Liu, X. H.; Lin, L. L.; Feng, X. M. *Chem. Commun.* **2012**, *48*, 5040−5042. (f) Dong, S. X.; Liu, X. H.; Zhu, Y.; He, P.; Lin, L. L.; Feng, X. M. *J. Am. Chem. Soc.* **2013**, *135*, 10026−10029. (g) Zhu, Y.; Liu, X. H.; Dong, S. X.; Zhou, Y. H.; Li, W.; Lin, L. L.; Feng, X. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 1636−1640.

(7) For selected reviews about aza-Henry reactions, see: (a) Westermann, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 151−153. (b) Marqués-López, E.; Merino, P.; Tejero, T.; Herrera, R. P. *Eur. J. Org. Chem.* **2009**, 2401−2420. (c) Noble, A.; Anderson, J. C. *Chem. Rev.* **2013**, *113*, 2887−2939.

(8) (a) Yamada, K.-i; Harwood, S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3504−3506. (b) Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843−5844. (c) Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2992−2995. (d) Palomo, C.; Oiarbide, M.; Halder, R.; Laso, A.; López, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 117−120. (e) Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170−2171. (f) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418−3419. (g) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466−468. (h) Singh, A.; Yoder, R. A.; Shen, B.; Johnston, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 3466−3467. (i) Wang, C.-J.; Dong, X.-Q.; Zhang, Z.-H.; Xue, Z.-Y.; Teng, H.-L. *J. Am. Chem. Soc.* **2008**, *130*, 8606−8607. (j) Singh, A.; Johnston, J. N. *J. Am. Chem. Soc.* **2008**, *130*, 5866−5867.

(9) For examples of nitro-Mannich reaction of ketimines, see: (a) Tan, C.; Liu, X. H.; Wang, L. W.; Wang, J.; Feng, X. M. *Org. Lett.* **2008**, *10*, 5305−5308. (b) Xie, H.; Zhang, Y.; Zhang, S.; Chen, X.; Wang, W. *Angew. Chem., Int. Ed.* **2011**, *50*, 11773−11776. (c) Parra, A.; Alfaro, R.; Marzo, L.; Moreno-Carrasco, A.; Ruano, J. L. G.; Alemán, J. *Chem. Commun.* **2012**, *48*, 9759−9761. (d) Núñez, M. G.; Farley, A. J. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16348−16351.

(10) (a) Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 36−51. (b) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381−1407. (c) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748−8758. (d) Bernard, K.; Bogliolo, S.; Ehrenfeld, J. *Br. J. Pharmacol.* **2005**, *144*, 1037−1050. (e) Claudine, S-L. G.; Sylvain, D.; Gabrielle, B.; Maurice, M.; Jacques, S.; Rolf, G.; Guy, G.; Gilles, G. *Stress* **2003**, *6*, 199−206. (f) Horoszok, L.; Leung, C.; Tomaszewski, M.; Walpole, C. PCT Int. Appl. WO2007091946, 2007. (g) Shen, K.; Liu, X. H.; Lin, L. L.; Feng, X. M. *Chem. Sci.* **2012**, *3*, 327−334.

(11) (a) Lesma, G.; Landoni, N.; Pilati, T.; Sacchetti, A.; Silvani, A. *J. Org. Chem.* **2009**, *74*, 4537−4541. (b) Mouri, S.; Chen, Z.; Mitsunuma, H.; Furutachi, M.; Matsunaga, S.; Shibasak, M. *J. Am. Chem. Soc.* **2010**, *132*, 1255−1257. (c) Jung, H. H.; Buesking, A. W.; Ellman, J. A. *Org. Lett.* **2011**, *13*, 3912−3915. (d) Shen, K.; Liu, X. H.; Wang, G.; Lin, L. L.; Feng, X. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 4684−4688. (e) Yang, Z. G.; Wang, Z.; Bai, S.; Shen, K.; Chen, D. H.; Liu, X. H.; Lin, L. L.; Feng, X. M. *Chem.—Eur. J.* **2010**, *16*, 6632−6637. (f) Lesma, G.; Meneghetti, F.; Sacchetti, A.; Stucchi, M.; Silvani, A. *Beilstein J. Org. Chem.* **2014**, *10*, 1383−1389.

(12) (a) Arai, T.; Matsumura, E.; Masu, H. *Org. Lett.* **2014**, *16*, 2768−2771. (b) Holmquist, M.; Blay, G.; Pedro, J. R. *Chem. Commun.* **2014**, *50*, 9309−9312.

(13) (a) Wang, Y.-H.; Liu, Y.-L.; Cao, Z.-Y.; Zhou, J. *Asian J. Org. Chem.* **2014**, *3*, 429−432. (b) Wang, Y.-H.; Cao, Z.-Y.; Niu, Y.; Zhao, X.; Zhou, J. *Acta. Chim. Sin.* **2014**, *72*, 867−872.

(14) Kumar, A.; Kaur, J.; Chimni, S. S.; Jassal, A. K. *RSC Adv.* **2014**, *4*, 24816−24819.

(15) CCDC 1034682 (**3a**) and CCDC 1034663 (**1d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk./data_request/cif.

(16) Wei, Y.; He, W.; Liu, Y.; Liu, P.; Zhang, S. *Org. Lett.* **2012**, *14*, 704−707.

(17) Sacchetti, A.; Silvani, A.; Gatti, F. G.; Lesma, G.; Pilati, T.; Trucchi, B. *Org. Biomol. Chem.* **2011**, *9*, 5515−5522.

(18) The product was generated in 91% yield, 30% ee by the use of **1f** as the catalyst.

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