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## CATALYTIC ASYMMETRIC AMINATION OF OXINDOLES UNDER DINUCLEAR NICKEL SCHIFF BASE CATALYSIS

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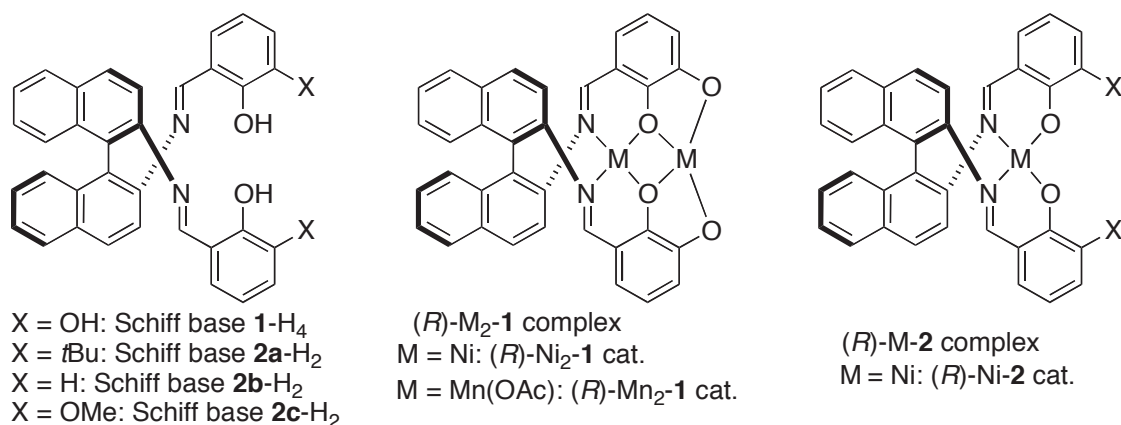
*This paper is dedicated to Professor Albert Padwa on the occasion of his 75th birthday.*

**Abstract** – Catalytic asymmetric synthesis of 3-aminooxindoles with a tetrasubstituted carbon stereocenter is described. 1 mol% of homobimetallic (*R*)-Ni<sub>2</sub>-Schiff base complex **1** catalyzed asymmetric amination of 3-alkyl-substituted oxindoles with azodicarboxylates to give products in 89-99% yield and 87-99% ee. For 3-aryl-substituted oxindoles, 10 mol% of (*R*)-Ni<sub>2</sub>-Schiff base complex was required to obtain products in 66-98% ee. Postulated catalytic cycle as well as transformation of the products are also described.

### INTRODUCTION

Oxindoles bearing a tetrasubstituted carbon stereocenter at the 3-position constitute an important structural motif in natural products and biologically active compounds.<sup>1</sup> Among them, oxindoles with heteroatoms at the stereogenic center are useful in medicinal chemistry.<sup>2</sup> Various methods for catalytic asymmetric synthesis of 3-fluorooxindoles,<sup>3</sup> 3-chlorooxindoles,<sup>4</sup> and 3-hydroxyoxindoles,<sup>5,6</sup> as well as their applications to the synthesis of biologically active compounds, have been reported. 3-Aminooxindoles are especially useful units found in therapeutic agents, such as NITD609 for the treatment of malaria, AG-041R, a gastrin/CCK-B receptor agonist, and SSR-149415 for the treatment of stress-related disorders.<sup>2</sup> Therefore, development of enantioselective synthetic methods for the structurally diverse sets of chiral 3-aminooxindoles is highly desirable. Several diastereoselective approaches have been developed for synthesizing chiral 3-aminooxindoles using chiral auxiliaries.<sup>7</sup> Catalytic asymmetric methods for 3-aminooxindoles, such as Pd-catalyzed asymmetric  $\alpha$ -arylation<sup>8</sup> and

Rh-catalyzed asymmetric intramolecular aza-spiroannulation,<sup>9</sup> however, have been limited until very recently. Because catalytic asymmetric benzylic amination of oxindoles provides straightforward access to 3-aminooxindoles, several groups including us have been intensively studied on this topic since 2009.<sup>10-12</sup> Both organocatalytic<sup>10</sup> and metal-catalyzed amination reactions<sup>11,12</sup> have been reported to afford products in high enantioselectivity. We herein describe full substrate scope and limitations of our works on this issue under bimetallic Schiff base **1** catalysis (Figure 1).



**Figure 1.** Structures of dinucleating Schiff base (*R*)-**1**-H<sub>4</sub>, Schiff bases (*R*)-**2**-H<sub>2</sub>, bimetallic and monometallic Schiff base complexes

## RESULTS AND DISCUSSION

As a part of our ongoing research on bimetallic Schiff base catalysis,<sup>13-16</sup> we recently developed a homodinuclear Mn<sub>2</sub>-Schiff base **1** complex and Ni<sub>2</sub>-Schiff base **1** complex (Figure 1) for the catalytic asymmetric 1,4-addition of 3-substituted-oxindoles to nitroalkenes<sup>14</sup> and nitroethylene.<sup>15</sup> Therefore, we began our optimization studies using homodinuclear transition metal-**1** complexes for reactions of *N*-Boc 3-methyl-substituted oxindole **3a** and azodicarboxylate **4** (Table 1). To select a suitable catalyst for the reaction of oxindole **3a**, we screened several metals (entries 1-6), and a homodinuclear Ni<sub>2</sub>-**1** complex gave the best enantioselectivity (entry 6, 97% ee). Toluene was the best solvent among those screened, and **5a** was obtained in 99% ee (entry 7). Other solvents, *i.e.* THF (51% ee), Et<sub>2</sub>O (61% ee), CH<sub>3</sub>CN (20% ee), DMSO (1% ee), CHCl<sub>3</sub> (75% ee), hexane (30% ee), gave less satisfactory results in terms of enantioselectivity. Catalyst loading was successfully reduced to 1 mol% at 50 °C, still giving **5a** in 96% ee after 12 h (entry 8). Furthermore, the amount of **4** was also successfully reduced to 1.2 equiv while maintaining good reactivity and enantioselectivity (entry 9, 99% yield, 99% ee). To check the utility of the bimetallic Ni complex, control experiments were performed in entries 10-14. In entries 10-12, monometallic Ni-salen **2a**, **2b**, and **2c** complexes (Figure 1) prepared from a same chiral source [(*R*)-1,1'-binaphthyl-2,2'-diamine] were used. The Ni-salen **2a** complex with *tert*-Bu substituents resulted in poor enantioselectivity (entry 10, 13% ee). On the other hand, sterically less hindered monometallic

(*R*)-Ni-**2b** and (*R*)-Ni-**2c** complexes smoothly promoted the reaction, and unexpected reversal of enantiofacial selectivity was observed in comparison with bimetallic (*R*)-Ni<sub>2</sub>-**1** (entry 9 vs entries 11-12). The enantioselectivity was, however, lower than bimetallic (*R*)-Ni<sub>2</sub>-**1** [entry 9, (*R*)-**5a**, 99% ee vs entries 11-12, (*S*)-**5a**, 93-94% ee]. On the other hand, heterobimetallic Pd/Ni/**1** and Cu/Ni/**1** complexes required 10 mol % catalyst loading for good reactivity, and gave **5a** in poor enantioselectivity (entries 13-14).

**Table 1.** Optimization of Reaction Conditions

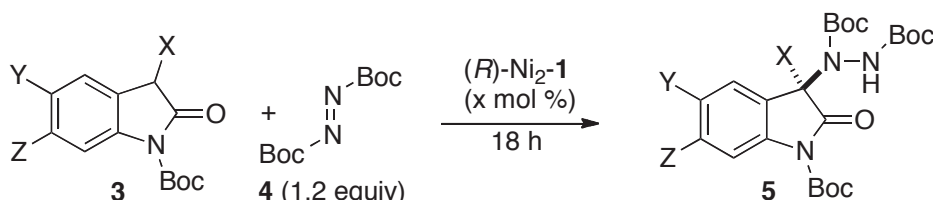
entry	M <sup>1</sup>	M <sup>2</sup>	Schiff base	x	solvent	y	temp (°C)	time (h)	% yield <sup>a</sup>	% ee <sup>b</sup>	abs. config.
1	Mn-OAc	Mn-OAc	<b>1</b>	10	AcOEt	2.0	rt	18	95	79	<i>R</i>
2	Ni	Ni	<b>1</b>	10	AcOEt	2.0	rt	18	99	97	<i>R</i>
3	Co-OAc	Co-OAc	<b>1</b>	10	AcOEt	2.0	rt	18	99	69	<i>R</i>
4	Cu	Cu	<b>1</b>	10	AcOEt	2.0	rt	18	68	14	<i>R</i>
5	Pd	Pd	<b>1</b>	10	AcOEt	2.0	rt	18	80	1	<i>R</i>
6	Zn	Zn	<b>1</b>	10	AcOEt	2.0	rt	12	78	5	<i>R</i>
7	Ni	Ni	<b>1</b>	10	toluene	2.0	rt	12	99	99	<i>R</i>
8	Ni	Ni	<b>1</b>	1	toluene	2.0	50	12	99	96	<i>R</i>
9	Ni	Ni	<b>1</b>	1	toluene	1.2	50	18	99 <sup>c</sup>	99	<i>R</i>
10	Ni	none	<b>2a</b>	1	toluene	1.2	50	12	99	13	<i>R</i>
11	Ni	none	<b>2b</b>	1	toluene	1.2	50	18	97	93	<i>S</i>
12	Ni	none	<b>2c</b>	1	toluene	1.2	50	18	99 <sup>c</sup>	94	<i>S</i>
13	Pd	Ni	<b>1</b>	10	toluene	2.0	rt	12	99	15	<i>R</i>
14	Cu	Ni	<b>1</b>	10	toluene	2.0	rt	12	82	11	<i>S</i>

Footnote <sup>a</sup> Determined by <sup>1</sup>H NMR analysis of crude mixture. <sup>b</sup> Determined by HPLC analysis using a DAICEL CHIRALPAK IA. <sup>c</sup> Isolated yield after purification by column chromatography.

The substrate scope of the reaction under optimized reaction conditions with homodinuclear (*R*)-Ni<sub>2</sub>-**1** is summarized in Table 2. The amination of various 3-alkyl-substituted oxindoles **3** with **4** was promoted by 1 mol % of the Ni<sub>2</sub>-**1** catalyst at 50 °C. 3-Methyl, allyl, (*E*)-cinnamyl, and benzyl substituted oxindoles **3a-3d** gave products in high enantioselectivity (entries 1-4, 99-91% ee). 5- or 6-Substituted oxindoles were also applicable. 5-MeO-, 5-F-, 5-Cl-, and 6-Cl-oxindoles (**3e-3i**) gave products in 99-94% ee (entries 5-9). It is noteworthy that ester and nitrile groups were compatible under the present conditions, and products **5j** and **5k** were obtained in 96 and 87% ee, respectively (entries 10-11). For 3-aryl-substituted oxindoles, the optimized conditions for 3-alkyl-substituted oxindoles gave poor enantioselectivity (<30% ee) even with 10 mol % catalyst loading, possibly due to background racemic reaction. After re-optimization of the conditions, the best results were obtained in CHCl<sub>3</sub> in the presence of molecular sieves 5Å at 30 °C. The role of molecular sieves was not clear, but the addition of molecular

sieves had beneficial effects for good reproducibility. The results are summarized in entries 12-19, and moderate to high enantioselectivity, 66-98% ee, was obtained.

**Table 2.** Catalytic Asymmetric Amination of Oxindoles **3** with Homodinuclear (*R*)-Ni<sub>2</sub>-**1** Catalyst<sup>a</sup>

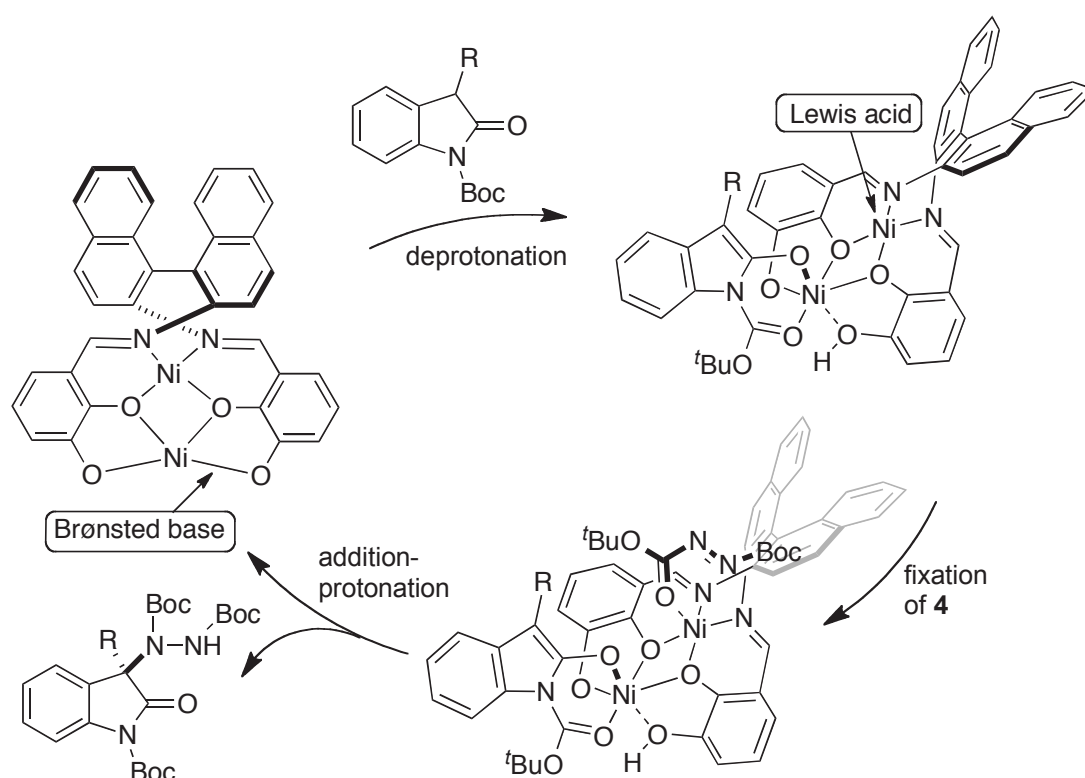


entry	X	Y	Z	<b>3</b>	cat. (x mol %)	solvent/ additive	temp (°C)	<b>5</b>	% yield <sup>a</sup>	% ee <sup>b</sup>
1	Me	H	H	<b>3a</b>	1	toluene	50	<b>5a</b>	99	99
2	allyl	H	H	<b>3b</b>	1	toluene	50	<b>5b</b>	99	97
3	( <i>E</i> )-cinnamyl	H	H	<b>3c</b>	1	toluene	50	<b>5c</b>	86	91
4	Bn	H	H	<b>3d</b>	1	toluene	50	<b>5d</b>	93	99
5	Me	MeO	H	<b>3e</b>	1	toluene	50	<b>5e</b>	91	94
6	Me	F	H	<b>3f</b>	1	toluene	50	<b>5f</b>	95	96
7	allyl	F	H	<b>3g</b>	1	toluene	50	<b>5g</b>	90	98
8	allyl	Cl	H	<b>3h</b>	1	toluene	50	<b>5h</b>	93	95
9	Bn	H	Cl	<b>3i</b>	1	toluene	50	<b>5i</b>	98	99
10	-CH <sub>2</sub> CO <sub>2</sub> Me	H	H	<b>3j</b>	1	toluene	50	<b>5j</b>	98	96
11	-CH <sub>2</sub> CN	H	H	<b>3k</b>	1	toluene	50	<b>5k</b>	89	87
12	Ph	H	H	<b>3l</b>	10	CHCl <sub>3</sub> /MS 5Å	30	<b>5l</b>	94	90
13	4-F-C <sub>6</sub> H <sub>4</sub>	H	H	<b>3m</b>	10	CHCl <sub>3</sub> /MS 5Å	30	<b>5m</b>	91	82
14	3-MeO-C <sub>6</sub> H <sub>4</sub>	H	H	<b>3n</b>	10	CHCl <sub>3</sub> /MS 5Å	30	<b>5n</b>	93	86
15	2-MeO-C <sub>6</sub> H <sub>4</sub>	H	H	<b>3o</b>	10	CHCl <sub>3</sub> /MS 5Å	30	<b>5o</b>	75	98
16	Ph	Me	H	<b>3p</b>	10	CHCl <sub>3</sub> /MS 5Å	30	<b>5p</b>	72	74
17	Ph	MeO	H	<b>3q</b>	10	CHCl <sub>3</sub> /MS 5Å	30	<b>5q</b>	86	82
18	4-F-C <sub>6</sub> H <sub>4</sub>	MeO	H	<b>3r</b>	10	CHCl <sub>3</sub> /MS 5Å	30	<b>5r</b>	72	73
19	3-MeO-C <sub>6</sub> H <sub>4</sub>	MeO	H	<b>3s</b>	10	CHCl <sub>3</sub> /MS 5Å	30	<b>5s</b>	78	66

Footnote <sup>a</sup> Isolated yield after purification by column chromatography. <sup>b</sup> Determined by HPLC analysis using chiral columns. See experimental section for detail.

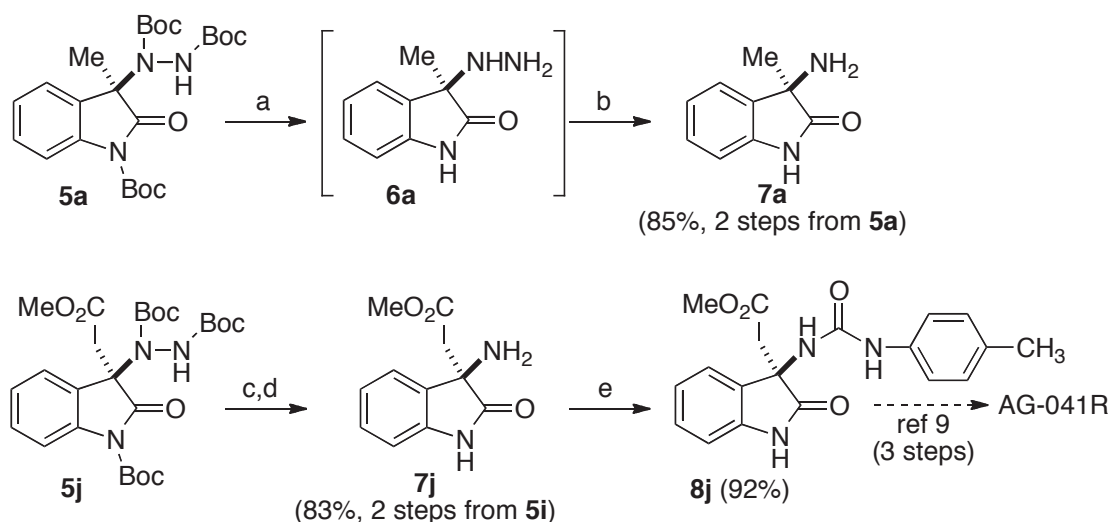
We assume that the observed enantiofacial selectivity switch between dinuclear Ni<sub>2</sub>-**1** catalyst and mononuclear (*R*)-Ni-**2b** and **2c** catalysts (Table 1, entry 9 vs entries 11-12) would be caused by difference in the position of a Ni-enolate intermediate. With dinuclear (*R*)-Ni<sub>2</sub>-**1**, a sterically less hindered Ni-aryloxide in the outer O<sub>2</sub>O<sub>2</sub> cavity would function as a Brønsted base to generate the Ni-enolate in the outer cavity, while a Ni-aryloxide in the N<sub>2</sub>O<sub>2</sub> cavity should generate the Ni-enolate in the case of monometallic (*R*)-Ni-**2b/2c**. Because heterobimetallic Pd/Ni/**1** and Cu/Ni/**1** complexes gave poor enantioselectivity (Table 1, entries 13-14), the Ni metal center in the N<sub>2</sub>O<sub>2</sub> inner cavity of homodinuclear (*R*)-Ni<sub>2</sub>-**1** is also important for high *R*-selectivity observed in Table 2, possibly as a Lewis acid to control the orientation of azodicarboxylate **4** from sterically hindered inner cavity. On the other hand, with the

monometallic (*R*)-Ni-**2b/2c**, azodicarboxylate **4** should come from sterically less hindered outer site, thus giving *S*-adduct. Postulated catalytic cycle of the reaction under dinuclear nickel catalysis is shown in Figure 2. One of the Ni-O bonds in the outer O<sub>2</sub>O<sub>2</sub> cavity would work as a Brønsted base to generate Ni-enolate in situ. The other Ni in the inner N<sub>2</sub>O<sub>2</sub> cavity functions as a Lewis acid to control the position of **4**, similar to conventional metal-salen Lewis acid catalysis. The C-N bond-formation, followed by protonation, affords product and regenerates the Ni<sub>2</sub>-**1** catalyst.



**Figure 2.** Postulated catalytic cycle of amination under dinuclear Schiff base catalysis

To demonstrate the synthetic utility of the products, we investigated product transformations (Scheme 1). Three Boc moieties in **5a** were readily removed with 4 M HCl in 1,4-dioxane/MeOH at room temperature to give **6a**. For the N-N bond cleavage in **6a**, Rh/C under H<sub>2</sub> atmosphere produced the best results to give 3-aminoxindole **7a** in 85% yield (in two steps from **5a**). For the N-N bond-cleavage of **6a**, the use of Rh/C rather than Pd/C or Raney Ni was essential to suppress undesirable de-amination *via* the C-N bond cleavage at benzylic position. Removal of the Boc groups in **5j** and the N-N bond-cleavage also proceeded smoothly under the similar procedure, giving 3-aminoxindole **7j** in 83% yield (in two steps). By treating with isocyanate, **8j** was readily obtained from **7j** (92% yield), which is a known key intermediate for AG-041R synthesis.<sup>9</sup>



**Scheme 1.** Transformation of amination products; reagents and conditions: (a) 4 M HCl, 1,4-dioxane, rt, 2 h; (b) Rh/C, H<sub>2</sub> (1 atm), MeOH, rt, 5 h, 85% yield in two steps from **5a**; (c) 3 M HCl, 1,4-dioxane/MeOH, rt, 2 h; (d) Rh/C, H<sub>2</sub> (1 atm), MeOH, rt, 6 h, 83% yield in two steps from **5j**; (e) *p*-tolyl isocyanate, MeCN, rt, 2 h, 92% yield.

In summary, we developed a highly enantioselective catalytic asymmetric access to 3-aminooxindoles with a tetrasubstituted carbon stereocenter. A homodinuclear Ni<sub>2</sub>-Schiff base **1** complex was suitable for catalytic asymmetric amination of 3-substituted oxindoles with di-*tert*-butyl azodicarboxylate. Reversal of enantiofacial selectivity was observed between bimetallic and monometallic Schiff base complexes, which indicated the plausible role of two metals in dinuclear Ni<sub>2</sub>-Schiff base **1** catalysis.

## EXPERIMENTAL

**General:** Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. NMR spectra were recorded on JEOL ECX500 spectrometers, operating at 500 MHz for <sup>1</sup>H NMR and 125.65 MHz for <sup>13</sup>C NMR. Chemical shifts in CDCl<sub>3</sub> were reported in the scale relative to tetramethylsilane (0 ppm) for <sup>1</sup>H NMR. For <sup>13</sup>C NMR, chemical shifts were reported in the scale relative to CHCl<sub>3</sub> (77.0 ppm) as an internal reference. Column chromatography was performed with silica gel Merck 60 (230-400 mesh ASTM). Optical rotations were measured on a JASCO P-1010 polarimeter. ESI mass spectra were measured on Waters micromass ZQ (for LRMS) and ESI mass spectra for HRMS were measured on a JEOL JMS-T100LC AccuTOF spectrometer. The enantiomeric excess (ee) was determined by HPLC analysis. HPLC was performed on JASCO HPLC systems consisting of the following: pump, PU-2080 plus; detector, UV-2075 plus, measured at 254 nm; column, DAICEL CHIRALPAK IA, IA-3, IB or IC; mobile phase, hexane-dichloromethane. **5l**, **5m**, **5n**, **5q**, **5r**, **5s**, **7a** and **8j** are known compounds. Compounds **3** were synthesized following the literature procedure.<sup>3,10</sup> The absolute configuration of **5ja** was determined after conversion into known compound, by comparing the

sign of optical rotation with the literature data reported by Iwabuchi *et al.*<sup>9</sup> The absolute configuration of other products was assigned by analogy.

**(R)-Di-tert-butyl 1-(1-(tert-butoxycarbonyl)-3-methyl-2-oxoindolin-3-yl)hydrazine-1,2-dicarboxylate (5a):** To a stirred solution of oxindole **3a** (49.4 mg, 0.20 mmol) in toluene (2.0 mL) was added Ni<sub>2</sub>/Schiff base **1** catalyst (1.3 mg, 2.0 μmol). The resulting mixture was stirred at 50 °C for 30 min. To the solution was added di-tert-butyl azodicarboxylate **4** (55.3 mg, 0.24 mmol) in one portion. The resulting yellow solution was stirred at 50 °C for 18 h. The reaction mixture was diluted with Et<sub>2</sub>O, and the precipitate was removed by filtration through a pad of Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel flash column chromatography (hexane/EtOAc = 9/1) to give the desired product **5a** (94.6 mg, 99% yield) as a colorless solid; IR (KBr) ν 3323, 2980, 2934, 1739, 1609, 1480, 1369 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.14 (s, 9H), 1.52 (s, 3H), 1.64 (s, 9H), 6.66 (s, 1H), 7.20 (m, 1H), 7.29 (m, 1H), 7.80 (d, *J* = 7.5, 7.9 Hz, 1H), 7.90 (d, *J* = 6.9 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 24.3, 27.6, 28.1, 28.2, 65.8, 81.5, 83.0, 84.3, 114.6, 123.7, 125.0, 128.4, 132.7, 138.0, 149.2, 152.9, 156.2, 176.3; HRMS (ESI): *m/z* calculated for C<sub>24</sub>H<sub>35</sub>N<sub>3</sub>O<sub>7</sub>Na<sup>+</sup> [M+Na]<sup>+</sup>: 500.2372, found: 500.2376, [α]<sub>D</sub><sup>22.7</sup> -21.0 (*c* 1.34, CHCl<sub>3</sub>); HPLC (DAICEL CHIRALPAK IA, hexane/CH<sub>2</sub>Cl<sub>2</sub> = 1/1, flow 0.5 mL/min, at 40 °C, detection at 254 nm) t<sub>R</sub> 9.7 min (*S*) and 10.6, min (*R*).

**(R)-Di-tert-butyl 1-(1-(tert-butoxycarbonyl)-3-allyl-2-oxoindolin-3-yl)hydrazine-1,2-dicarboxylate (5b):** colorless solid; IR (KBr) ν 3322, 2981, 2934, 1778, 1761, 1731, 1713 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.15 (s, 9H), 1.53 (s, 9H), 1.64 (s, 9H), 2.67 (dd, *J* = 6.3, 13.0 Hz, 1H), 2.74 (dd, *J* = 8.3, 13.0 Hz, 1H), 4.95 (d, *J* = 10.3 Hz, 1H), 5.00 (d, *J* = 17.1 Hz, 1H), 5.21 (m, 1H), 6.67 (s, 1H), 7.20 (dd, *J* = 7.5, 7.5 Hz, 1 H), 7.30 (dd, *J* = 7.5, 8.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 27.6, 28.0, 28.2, 41.5, 68.7, 81.5, 83.0, 84.1, 114.4, 120.7, 124.1, 124.8, 128.6, 129.5, 129.8, 138.9, 149.0, 152.9, 156.2, 175.3; HRMS (ESI): *m/z* calculated for C<sub>26</sub>H<sub>37</sub>N<sub>3</sub>O<sub>7</sub>Na<sup>+</sup> [M+Na]<sup>+</sup>: 526.2529, found: 526.2531; [α]<sub>D</sub><sup>22.5</sup> -9.3 (*c* 0.60, CHCl<sub>3</sub>), HPLC (DAICEL CHIRALPAK IA, hexane/CH<sub>2</sub>Cl<sub>2</sub> = 3/7, flow 0.5 mL/min, at 40 °C, detection at 254 nm) t<sub>R</sub> 16.7 min (*R*) and 19.6 min (*S*).

**(R,E)-Di-tert-butyl 1-(1-(tert-butoxycarbonyl)-3-cinnamyl-2-oxoindolin-3-yl)hydrazine-1,2-dicarboxylate (5c):** colorless solid; IR (KBr) 3348, 2979, 1792, 1778, 1735, 1709 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.16 (s, 9H), 1.47 (s, 9H), 1.59 (s, 9H), 2.84-2.85 (m, 2H), 5.56-5.59 (m, 1H), 6.30 (d, *J* = 16.0 Hz, 1H), 6.73 (s, 1H), 7.08-7.31 (m, 7H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 7.5 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 27.9, 28.1, 28.2, 40.5, 69.2, 81.6, 83.1, 84.0, 114.4, 120.9, 124.1, 124.9, 126.2, 127.4, 128.3, 128.7, 129.8, 135.5, 136.9, 138.7, 148.7, 153.0, 156.2, 175.5; HRMS (ESI): *m/z* calculated for C<sub>32</sub>H<sub>41</sub>N<sub>3</sub>O<sub>7</sub>Na<sup>+</sup>

[M+Na]<sup>+</sup>: 602.2842, found: 602.2842; [ $\alpha$ ]<sub>D</sub><sup>22.5</sup> -24.4 (*c* 0.50, CHCl<sub>3</sub>), HPLC (DAICEL CHIRALPAK IA, hexane/CH<sub>2</sub>Cl<sub>2</sub> = 7/3, flow 0.5 mL/min, at 40 °C, detection at 254 nm) *t*<sub>R</sub> 23.2 min (*S*) and 29.5 min (*R*).

**(R)-Di-tert-butyl 1-(3-benzyl-1-(tert-butoxycarbonyl)-2-oxoindolin-3-yl)hydrazine-1,2-dicarboxylate (5d)**: colorless solid; IR (KBr)  $\nu$  2980, 2394, 2648, 2360, 2340, 1734 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.14 (s, 9H), 1.47 (s, 9H), 1.62 (s, 9H), 3.10 (d, *J* = 12.3 Hz, 1H), 3.40 (d, *J* = 12.3 Hz, 1H), 6.63-6.66 (m, 2H), 6.77 (s, 1H), 6.95-6.99 (m, 2H), 7.03-7.07 (m, 1H), 7.16-7.23 (m, 2H), 7.35 (d, *J* = 7.4 Hz, 1H), 8.03 (d, *J* = 6.9 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) 27.7, 28.0, 28.3, 43.3, 70.0, 81.6, 83.1, 83.5, 114.1, 124.1, 124.6, 127.0, 127.5, 128.6, 129.6, 130.2, 132.3, 139.0, 148.2, 152.9, 156.4, 175.3; HRMS (ESI): *m/z* calculated for C<sub>25</sub>H<sub>37</sub>N<sub>3</sub>O<sub>7</sub>Na<sup>+</sup> [M+Na]<sup>+</sup>: 576.2686, found: 576.2671; [ $\alpha$ ]<sub>D</sub><sup>19.0</sup> -2.3 (*c* 1.5, CHCl<sub>3</sub>), HPLC (DAICEL CHIRALPAK IA, hexane/CH<sub>2</sub>Cl<sub>2</sub> = 7/3, flow 0.5 mL/min, at 40 °C, detection at 254 nm) *t*<sub>R</sub> 11.6 min (*S*) and 20.3 min (*R*).

**(R)-Di-tert-butyl 1-(1-(tert-butoxycarbonyl)-5-methoxy-3-methyl-2-oxoindolin-3-yl)hydrazine-1,2-dicarboxylate (5e)**: colorless solid; IR (KBr)  $\nu$  3300, 2980, 2934, 1731, 1601 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.17 (s, 9H), 1.47 (s, 3H), 1.63 (s, 9H), 3.83 (s, 3H), 6.66 (s, 1H), 6.81 (dd, *J* = 2.9, 8.6 Hz, 1H), 7.59 (brs, 1H), 7.70 (d, *J* = 8.6 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) 24.5, 27.7, 28.1, 28.2, 55.7, 66.1, 81.3, 83.0, 84.1, 109.7, 113.5, 115.6, 131.2, 133.6, 149.3, 152.9, 156.1, 157.3, 176.3; HRMS (ESI): *m/z* calculated for C<sub>24</sub>H<sub>35</sub>N<sub>3</sub>O<sub>7</sub>Na<sup>+</sup> [M+Na]<sup>+</sup>: 530.2478, found: 530.2480; [ $\alpha$ ]<sub>D</sub><sup>22.5</sup> -5.1 (*c* 3.1, CHCl<sub>3</sub>), HPLC (DAICEL CHIRALPAK IC, hexane/CH<sub>2</sub>Cl<sub>2</sub> = 1/1, flow 0.5 mL/min, at 40 °C, detection at 254 nm) *t*<sub>R</sub> 50.8 min (*S*) and 89.5 min (*R*).

**(R)-Di-tert-butyl 1-(1-(tert-butoxycarbonyl)-5-fluoro-3-methyl-2-oxoindolin-3-yl)hydrazine-1,2-dicarboxylate (5f)**: colorless foam; IR (neat)  $\nu$  3323, 2981, 2934, 1782, 1752, 1731, 1705, 1611 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.18 (s, 9H), 1.47 (s, 3H), 1.60 (s, 9H), 1.64 (s, 9H), 6.61 (s, 1H), 6.99 (ddd, *J* = 2.9, 8.9, 8.9 Hz, 1H), 7.72 (brs, 1H), 7.79 (dd, *J* = 4.6, 8.9 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) 24.3, 27.7, 28.1, 28.2, 65.8, 81.7, 83.2, 84.5, 111.4 (d, <sup>2</sup>*J*<sub>C-F</sub> = 23.9 Hz), 114.9 (d, <sup>2</sup>*J*<sub>C-F</sub> = 23.9 Hz), 116.0 (d, <sup>3</sup>*J*<sub>C-F</sub> = 8.4 Hz), 133.8, 133.9, 149.2, 152.8, 156.2, 160.3 (d, <sup>1</sup>*J*<sub>C-F</sub> = 245 Hz), 175.9; HRMS (ESI): *m/z* calculated for C<sub>24</sub>H<sub>34</sub>FN<sub>3</sub>O<sub>7</sub>Na<sup>+</sup> [M+Na]<sup>+</sup>: 518.2279, found: 518.2276; [ $\alpha$ ]<sub>D</sub><sup>22.5</sup> -35.0 (*c* 0.70, CHCl<sub>3</sub>) HPLC (Combined use of three columns DAICEL CHIRALPAK IA, IA-3, and IB, hexane/CH<sub>2</sub>Cl<sub>2</sub> = 3/7, flow 0.5 mL/min, at 40 °C, detection at 254 nm) *t*<sub>R</sub> 53.9 min (*S*) and 58.2 min (*R*).

**(R,E)-Di-tert-butyl 1-(3-allyl-1-(tert-butoxycarbonyl)-5-fluoro-2-oxoindolin-3-yl)hydrazine-1,2-dicarboxylate (5g)**: colorless foam; IR (KBr)  $\nu$  3324, 2981, 2935, 1735 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.19 (s, 9H), 1.47 (s, 9H), 1.61 (s, 9H), 2.61 (dd, *J* = 6.9, 13.2 Hz, 1H), 2.73 (dd, *J* = 8.4, 13.42 Hz, 1H), 4.97 (d, *J*

= 10.3 Hz, 1H), 5.01 (d,  $J = 17.2$  Hz, 1H), 5.17-5.25 (m, 1H), 6.69 (s, 1H), 6.99 (d,  $J = 2.9, 9.2, 9.2$  Hz, 1H), 7.72 (brd,  $J = 5.8$  Hz, 1H), 7.75 (dd,  $J = 4.6, 9.2$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) 27.6, 28.0, 28.2, 41.4, 68.7, 81.7, 83.3, 84.3, 111.8 (d,  $^2J_{\text{C-F}} = 25.1$  Hz), 115.0 (d,  $^2J_{\text{C-F}} = 22.8$  Hz), 115.7 (d,  $^3J_{\text{C-F}} = 8.4$  Hz), 121.0, 129.1, 131.7 (d,  $^3J_{\text{C-F}} = 7.2$  Hz), 134.8 (d,  $^4J_{\text{C-F}} = 2.4$  Hz), 148.9, 152.8, 156.2, 160.2 (d,  $^1J_{\text{C-F}} = 245$  Hz), 174.9; HRMS (ESI):  $m/z$  calculated for  $\text{C}_{26}\text{H}_{36}\text{FN}_3\text{O}_7\text{Na}^+$   $[\text{M}+\text{Na}]^+$ : 544.2435, found: 544.2442;  $[\alpha]_{\text{D}}^{21.0} -12.8$  ( $c$  0.70,  $\text{CHCl}_3$ ), HPLC (DAICEL CHIRALPAK IA, hexane/ $\text{CH}_2\text{Cl}_2 = 3/7$ , flow 0.5 mL/min, at 40 °C, detection at 254 nm)  $t_{\text{R}}$  20.9 min (*R*) and 25.4 min (*S*).

**(*R*)-Di-*tert*-butyl 1-(3-allyl-1-(*tert*-butoxycarbonyl)-5-chloro-2-oxoindolin-3-yl)hydrazine-1,2-dicarboxylate (5h):** colorless solid; IR (KBr)  $\nu$  3324, 2980, 2934, 1787, 1748, 1733, 1709  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.19 (s, 9H), 1.53 (s, 9H), 1.63 (s, 9H), 2.63 (dd,  $J = 7.0, 13.4$  Hz, 1H), 2.72 (dd,  $J = 8.0, 13.4$  Hz, 1H), 4.97 (brd,  $J = 9.7$  Hz, 1H), 5.01 (brd,  $J = 17.2$  Hz, 1H), 5.16-5.25 (m, 1H), 6.60 (s, 1H), 7.28 (d,  $J = 9.2$  Hz, 1H), 7.72 (d,  $J = 9.2$  Hz, 1H), 7.89 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  27.7, 28.0, 28.1, 41.4, 68.6, 81.7, 83.3, 84.4, 115.7, 121.2, 124.3, 128.7, 129.0, 130.3, 131.6, 137.5, 148.8, 152.8, 156.1, 174.9; HRMS (ESI):  $m/z$  calculated for  $\text{C}_{26}\text{H}_{36}\text{ClN}_3\text{O}_7\text{Na}^+$   $[\text{M}+\text{Na}]^+$ : 560.2140, found: 560.2151;  $[\alpha]_{\text{D}}^{22.5} -27.3$  ( $c$  1.40,  $\text{CHCl}_3$ ), HPLC (DAICEL CHIRALPAK IB, hexane/ $\text{CH}_2\text{Cl}_2 = 9/1$ , flow 0.5 mL/min, at 40 °C, detection at 254 nm)  $t_{\text{R}}$  39.6 min (*S*) and 51.7 min (*R*).

**(*R*)-Di-*tert*-butyl 1-(3-benzyl-1-(*tert*-butoxycarbonyl)-6-chloro-2-oxoindolin-3-yl)hydrazine-1,2-dicarboxylate (5i):** colorless solid; IR (KBr)  $\nu$  3325, 2980, 2935, 1787, 1733 1709  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 1.19 (s, 9H), 1.50 (s, 9H), 1.74 (s, 9H), 3.06 (d,  $J=12.4$  Hz, 1H), 3.37 (d,  $J=12.4$  Hz, 1H), 6.66 (d,  $J=7.4$ Hz, 2H), 6.74 (s, 1H), 7.01(dd,  $J=7.4, 7.6$  Hz, 2H), 7.09 (dd,  $J=7.4, 7.5$ Hz, 1H), 7.20 (dd,  $J=1.4, 8.8$  Hz, 1H), 7.44(d,  $J=1.4$  Hz, 1H), 7.99 (d,  $J=8.8$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) 27.7, 28.0, 28.2, 43.1, 69.6, 81.9, 83.7, 84.1, 114.9, 124.6, 125.1, 127.2, 127.7, 128.1, 130.2, 131.9, 134.2, 139.9, 147.9, 152.8, 156.4, 174.7; HRMS (ESI):  $m/z$  calculated for  $\text{C}_{30}\text{H}_{38}\text{N}_3\text{O}_7\text{ClNa}^+$   $[\text{M}+\text{Na}]^+$ : 610.2296, found: 610.2288;  $[\alpha]_{\text{D}}^{19.0} -32.3$  ( $c$  2.5,  $\text{CHCl}_3$ ), HPLC (DAICEL CHIRALPAK IA, hexane/ $\text{CH}_2\text{Cl}_2 = 1/1$ , flow 0.5 mL/min, at 40 °C, detection at 254 nm)  $t_{\text{R}}$  7.8 min (*R*) and 10.5 min (*S*).

**(*R*)-Di-*tert*-butyl 1-(1-(*tert*-butoxycarbonyl)-3-(2-methoxy-2-oxoethyl)-2-oxoindolin-3-yl)hydrazine-1,2-dicarboxylate (5j):** colorless solid; IR (KBr)  $\nu$  3313, 2981, 1715, 1608, 1481, 1372  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.17 (s, 9H), 1.56 (s, 9H), 1.67 (s, 9H), 2.98 (d,  $J = 14.6$  Hz, 1H), 3.18 (d,  $J = 14.6$  Hz, 1H), 3.44 (s, 3H), 6.71 (s, 1H), 7.19 (dd,  $J = 7.5, 7.5$  Hz, 1H), 7.31 (dd,  $J = 7.5, 8.0$  Hz, 1H), 7.80 (d,  $J = 8.0$  Hz, 1H), 7.80 (d,  $J = 7.5$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) 27.7, 28.1, 28.2, 42.2, 51.9, 66.2, 88.8, 83.4, 84.1, 114.6, 124.5, 124.7, 128.3, 129.3, 139.7, 149.1, 152.6, 156.1, 168.1, 174.5; HRMS (ESI):  $m/z$  calculated

for  $C_{26}H_{37}N_3O_7Na^+$   $[M+Na]^+$ : 558.2428, found: 558.2432;  $[\alpha]_D^{22.0}$  -3.4 (*c* 1.20,  $CHCl_3$ ), HPLC (DAICEL CHIRALPAK IA, hexane/ $CH_2Cl_2$  = 3/7, flow 0.5 mL/min, at 40 °C, detection at 254 nm)  $t_R$  22.8 min (*S*) and 26.5 min (*R*).

**(R)-Di-tert-butyl 1-(1-(tert-butoxycarbonyl)-3-(cyanomethyl)-2-oxoindolin-3-yl)hydrazine-1,2-dicarboxylate (5k)**: yellow solid; IR (KBr)  $\nu$  3324, 2981, 2934, 1800, 1778, 1735, 1713, 1608  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.19 (s, 9H), 1.55 (s, 9H), 1.67 (s, 9H), 2.83 (d, *J* = 16.6 Hz, 1H), 2.94 (d, *J* = 16.6 Hz, 1H), 6.73 (s, 1H), 7.27 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.40 (dd, *J* = 7.5, 8.1 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 8.01 (d, *J* = 7.5 Hz, 1H);  $^{13}C$  NMR ( $CDCl_3$ ) 26.7, 27.6, 28.0, 28.2, 65.4, 82.5, 83.9, 85.0, 114.4, 115.0, 124.8, 125.4, 127.2, 130.0, 138.6, 148.7, 152.1, 156.1, 172.7; HRMS (ESI): *m/z* calculated for  $C_{25}H_{34}N_4O_7Na^+$   $[M+Na]^+$ : 525.2325, found: 525.2334;  $[\alpha]_D^{22.5}$  -67.1 (*c* 0.80,  $CHCl_3$ ); HPLC (DAICEL CHIRALPAK IA, hexane/ $CH_2Cl_2$  = 7/3, flow 0.5 mL/min, detection at 254 nm)  $t_R$  16.8 min (*S*) and 34.0 min (*R*).

**(S)-Di-tert-butyl 1-(1-(tert-butoxycarbonyl)-3-(2-methoxyphenyl)-2-oxoindolin-3-yl)hydrazine-1,2-dicarboxylate (5o)**: colorless solid; IR (KBr)  $\nu$  3391, 2979, 2929, 2359, 2320, 1801, 1731  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ ) 1.20 (s, 9H), 1.35 (s, 9H), 1.67 (s, 9H), 3.86 (s, 3H), 6.27 (s, 1H), 6.83-6.85 (m, 1H), 6.92-6.96 (m, 2H), 7.14-7.19 (m, 2H), 7.24 (m, 2H), 7.45 (d, *J* = 8.1 Hz, 1H);  $^{13}C$  NMR ( $CDCl_3$ ) 27.7, 28.0, 28.1, 56.5, 72.8, 80.6, 82.8, 83.8, 113.3, 114.5, 121.1, 124.4, 125.0, 126.0, 128.6, 129.0, 129.5, 130.0, 138.6, 149.3, 153.8, 155.0, 158.0, 173.1; ESI-MS *m/z* 592.1  $[M+Na]$  calculated for  $C_{30}H_{39}N_3O_8Na^+$   $[M+Na]^+$ : 592.2635, found: 592.2616;  $[\alpha]_D^{22.1}$  +54.2 (*c* 3.61,  $CHCl_3$ ); HPLC (DAICEL CHIRALPAK IA, hexane/ $CH_2Cl_2$  = 1/1, flow 1.0 mL/min, detection at 254 nm)  $t_R$  3.9 min (minor) and 4.3 min (major).

**(R)-Di-tert-butyl 1-(1-(tert-butoxycarbonyl)-5-methyl-2-oxo-3-phenylindolin-3-yl)hydrazine-1,2-dicarboxylate (5p)**: colorless solid; IR (KBr)  $\nu$  3445, 2977, 2963, 2329, 1733  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ ) 1.20 (s, 9H), 1.29 (s, 9H), 1.60 (s, 9H), 2.45 (s, 3H), 6.29 (s, 1H), 7.12-7.14 (m, 1H), 7.27-7.30 (m, 2H), 7.35-7.36 (m, 1H), 7.54-7.55 (m, 2H), 7.81 (d, *J* = 8.6 Hz, 1H), 7.98 (s, 1H);  $^{13}C$  NMR ( $CDCl_3$ ) 27.7, 28.0, 28.8, 72.7, 80.8, 83.1, 84.1, 114.6, 125.4, 128.0, 128.6, 130.0, 130.1, 133.3, 134.1, 136.4, 149.1, 153.3, 154.7, 174.4; HRMS (ESI): *m/z* calculated for  $C_{30}H_{39}N_3O_7Na^+$   $[M+Na]^+$ : 576.2686, found: 576.2660;  $[\alpha]_D^{22.1}$  -79.4 (*c* 1.04,  $CHCl_3$ ); HPLC (DAICEL CHIRALPAK IA3, hexane/ $CH_2Cl_2$  = 1/1, flow 0.5 mL/min, detection at 254 nm)  $t_R$  8.3 min (major) and 13.6 min (minor).

**(R)-3-Amino-3-methyl-1,3-dihydro-indol-2-one (7a)**: To a 4 M HCl *aq.* solution in 1,4-dioxane (1.5 mL) at room temperature was added **5a** (72 mg, 0.15 mmol). The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was evaporated to give crude **6a**, which was used for the next

step without purification. To a test tube with the crude **6a** was added MeOH (1.5 mL) and Rh/C (36 mg). The reaction was stirred for 5 h at rt under H<sub>2</sub> (1 atm), then was filtered through a filter paper and washed with MeOH. The filtrate was concentrated under reduced pressure to give a pale yellow solid. The residue was purified by silica gel flash column chromatography (5% MeOH in AcOEt) to afford **7a** (20.7 mg, 0.128 mmol, 85% yield) as a colorless solid; IR (KBr)  $\nu$  3139, 1710, 1675, 1620, 1472 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  1.42 (s, 3H), 6.90 (d,  $J$  = 8.0 Hz, 1H), 7.04 (ddd,  $J$  = 8.0, 8.0, 1.3 Hz, 1H), 7.22 (ddd,  $J$  = 8.0, 8.0, 1.3 Hz, 1H), 7.37 (dd,  $J$  = 8.0, 1.3 Hz, 1H); <sup>13</sup>C NMR (CD<sub>3</sub>OD)  $\delta$  25.6, 59.1, 111.2, 123.7, 124.5, 129.9, 135.1, 142.1, 184.4; ESI-MS  $m/z$  185 [M+Na]<sup>+</sup>; [ $\alpha$ ]<sub>D</sub><sup>30.3</sup> +10.7 ( $c$  0.60, CH<sub>3</sub>OH).

**(R)-(3-Amino-2-oxo-2,3-dihydro-1H-indol-3-yl)-acetic acid methyl ester (7j):** To a solution of 3 M HCl in MeOH/1,4-dioxane = 1:1 (6 mL) at room temperature was added **5j** (214 mg, 0.40 mmol). The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was evaporated to give crude **6j** without Boc groups as a colorless solid, which was used for the next step without purification. To a test tube with the crude **6j** were added MeOH (4 mL) and Rh/C (100 mg). The reaction mixture was stirred for 6 h at room temperature under H<sub>2</sub> (1 atm), then filtered through a filter paper and washed with MeOH. The filtrate was concentrated under reduced pressure to give a pale yellow oil. The residue was purified by silica gel flash column chromatography (2.5% MeOH in AcOEt) to afford **7j** (73 mg, 0.33 mmol, 83% yield) as a colorless oil; IR (neat)  $\nu$  1734, 1623, 1474, 1214, 755 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  2.92 (d,  $J$  = 16.1 Hz, 1H), 2.96 (d,  $J$  = 16.1 Hz, 1H), 3.50 (s, 3H), 6.91 (d,  $J$  = 8.0 Hz, 1H), 7.02 (dd,  $J$  = 8.0, 8.0 Hz, 1H), 7.24 (dd,  $J$  = 8.0, 8.0 Hz, 1H), 7.35 (d,  $J$  = 8.0 Hz, 1H); <sup>13</sup>C NMR (CD<sub>3</sub>OD)  $\delta$  43.0, 59.9, 111.3, 123.5, 124.8, 130.4, 132.6, 143.2, 171.4, 182.3; HRMS (ESI):  $m/z$  calculated for C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>Na<sup>+</sup> [M+Na]<sup>+</sup>: 243.0746, found: 243.0737; [ $\alpha$ ]<sub>D</sub><sup>27.7</sup> +31.0 ( $c$  0.60, CH<sub>3</sub>OH).

**(R)-Methyl 2-(2-oxo-3-(3-*p*-tolylureido)indolin-3-yl)acetate (8j):** *p*-Tolyl isocyanate (8.0 mg, 0.06 mmol) was added to the mixture of **7j** (11.0 mg, 0.05 mmol) in MeCN. The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was evaporated and the residue was purified by silica gel flash column chromatography (AcOEt:hexane = 2:1) to afford **8j** (16.3 mg, 0.046 mmol, 92% yield) as a colorless solid; IR (KBr)  $\nu$  3338, 1728, 1662, 1604, 1549, 1212, 753 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  2.26 (s, 3H), 2.60 (d,  $J$  = 15.3 Hz, 1H), 2.90 (d,  $J$  = 15.3 Hz, 1H), 3.67 (s, 3H), 6.47 (br, 1H), 6.75 (s, 1H), 6.83 (d,  $J$  = 7.6 Hz, 1H), 6.99 (dd,  $J$  = 7.6, 7.6 Hz, 1H), 7.05 (d,  $J$  = 8.3 Hz, 1H), 7.12 (d,  $J$  = 8.3 Hz, 1H), 7.18-7.22 (m, 2H), 7.63 (br, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  20.7, 40.5, 52.1, 59.6, 110.7, 120.7, 122.6, 123.0, 129.1, 129.5, 130.1, 133.1, 135.6, 140.6, 154.3, 170.7, 178.0; ESI-MS  $m/z$  376 [M+Na]<sup>+</sup>; HRMS (ESI):  $m/z$  calculated for C<sub>24</sub>H<sub>34</sub>ClN<sub>3</sub>O<sub>7</sub>Na<sup>+</sup> [M+Na]<sup>+</sup>: 376.1273, found: 376.1263; [ $\alpha$ ]<sub>D</sub><sup>30.3</sup> +12.0 ( $c$  0.80, CHCl<sub>3</sub>).

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## REFERENCES AND NOTES

1. Reviews: A. B. Dounay and L. E. Overman, *Chem. Rev.*, 2003, **103**, 2945; C. V. Galliford and K. A. Scheidt, *Angew. Chem. Int. Ed.*, 2007, **46**, 8748.
2. 3-Aminooxindoles in medicinal chemistry: M. Rottmann, C. McNamara, B. K. S. Yeung, M. C. S. Lee, B. Zou, B. Russell, P. Seitz, D. M. Plouffe, N. V. Dharia, J. Tan, S. B. Cohen, K. R. Spencer, G. E. González-Páez, S. B. Lakshminarayana, A. Goh, R. Suwanarusk, T. Jegla, E. K. Schmitt, H.-P. Beck, R. Brun, F. Nosten, L. Renia, V. Dartois, T. H. Keller, D. A. Fidock, E. A. Winzeler, and T. T. Diagana, *Science*, 2010, **329**, 1175; M. Ochi, K. Kawasaki, H. Kataoka, and Y. Uchio, *Biochem. Biophys. Res. Commun.*, 2001, **283**, 1118; K. Bernard, S. Bogliolo, and J. Ehrenfeld, *Br. J. Pharmacol.*, 2005, **144**, 1037; G. Gilles and S. L. Claudine, *Stress*, 2003, **6**, 199.
3. Y. Hamashima, T. Suzuki, H. Takano, Y. Shimura, and M. Sodeoka, *J. Am. Chem. Soc.*, 2005, **127**, 10164; N. Shibata, J. Kohno, K. Takai, T. Ishimaru, S. Nakamura, T. Toru, and S. Kanemasa, *Angew. Chem. Int. Ed.*, 2005, **44**, 4204; T. Ishimaru, N. Shibata, T. Horikawa, N. Yasuda, S. Nakamura, T. Toru, and M. Shiro, *Angew. Chem. Int. Ed.*, 2008, **47**, 4157.
4. W. Zheng, Z. Zhang, M. J. Kaplan, and J. C. Antilla, *J. Am. Chem. Soc.*, 2011, **133**, 3339; M.-X. Zhao, Z.-W. Zhang, M.-X. Chen, W.-H. Tang, and M. Shi, *Eur. J. Org. Chem.*, 2011, 3001.
5. Hydroxylation of oxindoles: T. Ishimaru, N. Shibata, J. Nagai, S. Nakamura, T. Toru, and S. Kanemasa, *J. Am. Chem. Soc.*, 2006, **128**, 16488; D. Sano, K. Nagata, and T. Itoh, *Org. Lett.*, 2008, **10**, 1593; T. Bui, N. R. Candeias, and C. F. Barbas, III, *J. Am. Chem. Soc.*, 2010, **132**, 5574.
6. Selected leading examples of nucleophilic addition to isatins: R. Shintani, M. Inoue, and T. Hayashi, *Angew. Chem. Int. Ed.*, 2006, **45**, 3353; P. Y. Toullec, R. B. C. Jagt, J. G. de Vries, B. L. Feringa, and A. J. Minnaard, *Org. Lett.*, 2006, **8**, 2715; A. V. Malkov, M. A. Kabeshov, M. Bella, O. Kysilka, D. A. Malyshev, K. Pluháčková, and P. Kocovsky, *Org. Lett.*, 2007, **9**, 5473; H. Lai, Z. Huang, Q. Wu, and Y. Qin, *J. Org. Chem.*, 2009, **74**, 283; S. Nakamura, N. Hara, H. Nakashima, K. Kubo, N. Shibata, and T. Toru, *Chem. Eur. J.*, 2008, **14**, 8079; D. Tomita, K. Yamatsugu, M. Kanai, and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 6946; J. Itoh, S. B. Han, and M. J. Krische, *Angew. Chem. Int. Ed.*, 2009, **48**, 6313; T. Itoh, H. Ishikawa, and Y. Hayashi, *Org. Lett.*, 2009, **11**, 3854 and

references therein. See also, reference 8.

7. For diastereoselective approaches using chiral auxiliaries: T. Emura, T. Esaki, K. Tachibana, and M. Shimizu, *J. Org. Chem.*, 2006, **71**, 8559; G. Lesma, N. Landoni, T. Pilati, A. Sacchetti, and A. Silvani, *J. Org. Chem.*, 2009, **74**, 4537.
8. Y.-X. Jia, J. M. Hillgren, E. L. Watson, S. P. Marsden, and E. P. Kündig, *Chem. Commun.*, 2008, 4040.
9. S. Sato, M. Shibuya, N. Kanoh, and Y. Iwabuchi, *Chem. Commun.*, 2009, 6264; S. Sato, M. Shibuya, N. Kanoh, and Y. Iwabuchi, *J. Org. Chem.*, 2009, **74**, 7522.
10. L. Cheng, L. Liu, D. Wang, and Y.-J. Chen, *Org. Lett.*, 2009, **11**, 3874; Z.-Q. Qian, F. Zhou, T.-P. Du, B.-L. Wang, M. Ding, X.-L. Zhao, and J. Zhou, *Chem. Commun.*, 2009, 6753; T. Bui, M. Borregan, and C. F. Barbas, III, *J. Org. Chem.*, 2009, **74**, 4537; T. Bui, G. Hernández-Torres, C. Milite, and C. F. Barbas, III, *Org. Lett.*, 2010, **12**, 5696; T. Zhang, L. Cheng, L. Liu, D. Wang, and Y.-J. Chen, *Tetrahedron: Asymmetry*, 2010, **21**, 2800.
11. A part of results in this article was communicated previously, see: S. Mouri, Z. Chen, H. Mitsunuma, M. Furutachi, S. Matsunaga, and M. Shibasaki, *J. Am. Chem. Soc.*, 2010, **132**, 1255.
12. Z. Yang, Z. Wang, S. Bai, K. Shen, D. Chen, X. Liu, L. Lin, and X. Feng, *Chem. Eur. J.*, 2010, **16**, 6632; K. Shen, X. Liu, G. Wang, L. Lin, and X. Feng, *Angew. Chem. Int. Ed.*, 2011, **50**, 4684.
13. For selected examples, see: S. Handa, V. Gnanadesikan, S. Matsunaga, and M. Shibasaki, *J. Am. Chem. Soc.*, 2007, **129**, 4900; S. Handa, K. Nagawa, Y. Sohtome, Y. S. Matsunaga, and M. Shibasaki, *Angew. Chem. Int. Ed.*, 2008, **47**, 3230; H. Mihara, Y. Xu, N. E. Shepherd, S. Matsunaga, and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 8384; Z. Chen, M. Furutachi, Y. Kato, S. Matsunaga, and M. Shibasaki, *Angew. Chem. Int. Ed.*, 2009, **48**, 2218; S. Handa, V. Gnanadesikan, S. Matsunaga, and M. Shibasaki, *J. Am. Chem. Soc.*, 2010, **132**, 4925; Y. Xu, L. Lin, M. Kanai, S. Matsunaga, and M. Shibasaki, *J. Am. Chem. Soc.*, 2011, **133**, 5791; G. Lu, T. Yoshino, H. Morimoto, S. Matsunaga, and M. Shibasaki, *Angew. Chem. Int. Ed.*, 2011, **50**, 4382.
14. Y. Kato, M. Furutachi, Z. Chen, H. Mitsunuma, S. Matsunaga, and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 9168.
15. H. Mitsunuma and S. Matsunaga, *Chem. Commun.*, 2011, 469; For the utility of Ni<sub>2</sub>-catalyst in other reactions, see: Z. Chen, H. Morimoto, S. Matsunaga, and M. Shibasaki, *J. Am. Chem. Soc.* 2008, **130**, 2170; Y. Xu, G. Lu, S. Matsunaga, and M. Shibasaki, *Angew. Chem. Int. Ed.*, 2009, **48**, 3353; S. Mouri, Z. Chen, S. Matsunaga, and M. Shibasaki, *Chem. Commun.*, 2009, 5138; N. E. Shepherd, H. Tanabe, Y. Xu, S. Matsunaga, and M. Shibasaki, *J. Am. Chem. Soc.*, 2010, **132**, 3666.
16. For selected examples of related bifunctional bimetallic Schiff base complexes in asymmetric catalysis, see V. Annamalai, E. F. DiMauro, P. J. Carroll, and M. C. Kozlowski, *J. Org. Chem.*, 2003,

- 68, 1973 and references therein; M. Yang, C. Zhu, F. Yuan, Y. Huang, and Y. Pan, *Org. Lett.*, 2005, **7**, 1927; W. Hirahata, R. M. Thomas, E. B. Lobkovsky, and G. W. Coates, *J. Am. Chem. Soc.*, 2008, **130**, 17658; C. Mazet and E. N. Jacobsen, *Angew. Chem. Int. Ed.*, 2008, **47**, 1762; B. Wu, J. C. Gallucci, J. R. Parquette, and T. V. RajanBabu, *Angew. Chem. Int. Ed.*, 2009, **48**, 1126; B. Wu, J. R. Parquette, and T. V. RajanBabu, *Science*, 2009, **326**, 1662.
17. In our previous studies on direct Mannich-type reactions and Michael reactions using Ni<sub>2</sub>-**1**, Co<sub>2</sub>-**1** and Mn<sub>2</sub>-**1** complexes, corresponding monometallic Ni-, Co-, and Mn-**2a**, **2b**, and **2c** complexes resulted in poor to modest reactivity and enantioselectivity. See, references 14 and 15.