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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_2-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_2-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.[1] Among them, oxindoles with heteroatoms at the stereogenic center are useful in medicinal chemistry.[2] Various methods for catalytic asymmetric synthesis of 3-fluorooxindoles,[3] 3-chlorooxindoles,[4] and 3-hydroxyoxindoles,[5,6] 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.[2] 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.[7] Catalytic asymmetric methods for 3-aminooxindoles, such as Pd-catalyzed asymmetric α-arylation[8] and

Rh-catalyzed asymmetric intramolecular aza-spiroannulation,[9] 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.[10-12] Both organocatalytic[10] and metal-catalyzed amination reactions[11,12] 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).

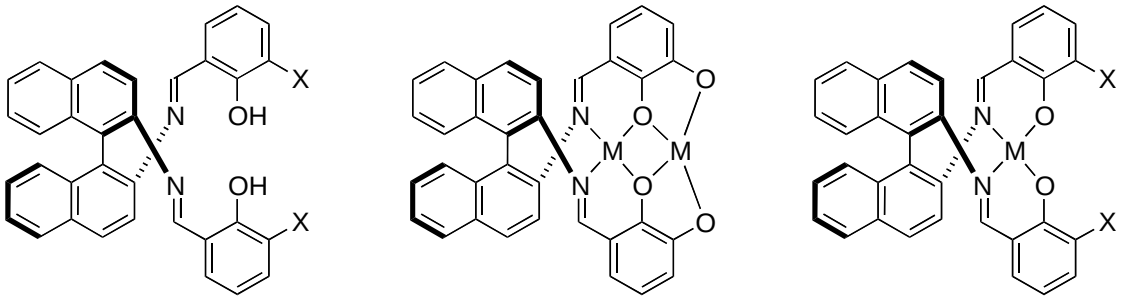


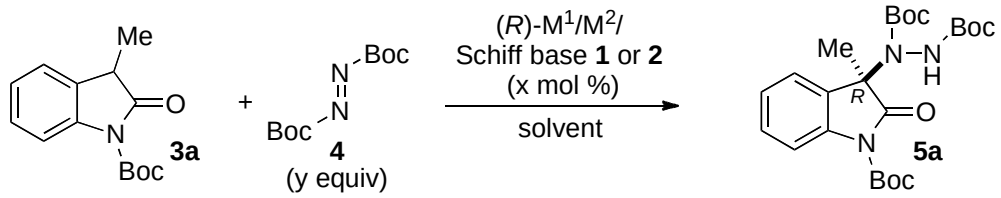
Figure 1. Structures of dinucleating Schiff base (*R*)-**1**-H_4, Schiff bases (*R*)-**2**-H_2, bimetallic and monometallic Schiff base complexes

RESULTS AND DISCUSSION

As a part of our ongoing research on bimetallic Schiff base catalysis,[13-16] we recently developed a homodinuclear Mn_2-Schiff base **1** complex and Ni_2-Schiff base **1** complex (Figure 1) for the catalytic asymmetric 1,4-addition of 3-substituted-oxindoles to nitroalkenes[14] and nitroethylene.[15] 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_2-**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_2O (61% ee), CH_3CN (20% ee), DMSO (1% ee), $CHCl_3$ (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_2-**1** (entry 9 vs entries 11-12). The enantioselectivity was, however, lower than bimetallic (*R*)-Ni_2-**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



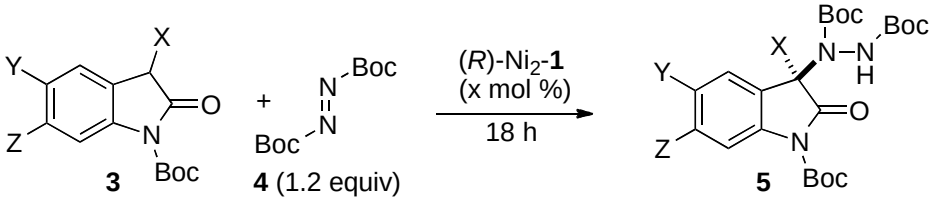
entry	M^1	M^2	Schiff base	x	solvent	y	temp (°C)	time (h)	% yield[a]	% ee[b]	abs. config.
1	Mn-OAc	Mn-OAc	**1**	10	AcOEt	2.0	rt	18	95	79	*R*
2	Ni	Ni	**1**	10	AcOEt	2.0	rt	18	99	97	*R*
3	Co-OAc	Co-OAc	**1**	10	AcOEt	2.0	rt	18	99	69	*R*
4	Cu	Cu	**1**	10	AcOEt	2.0	rt	18	68	14	*R*
5	Pd	Pd	**1**	10	AcOEt	2.0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

Footnote [a] Determined by ^{1}H NMR analysis of crude mixture. [b] Determined by HPLC analysis using a DAICEL CHIRALPAK IA. [c] Isolated yield after purification by column chromatography.

The substrate scope of the reaction under optimized reaction conditions with homodinuclear (*R*)-Ni_2-**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_2-**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 $CHCl_3$ 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_2-**1** Catalyst[a]



entry	X	Y	Z	**3**	cat. (x mol %)	solvent/ additive	temp (°C)	**5**	% yield[a]	% ee[b]
1	Me	H	H	**3a**	1	toluene	50	**5a**	99	99
2	allyl	H	H	**3b**	1	toluene	50	**5b**	99	97
3	(*E*)-cinnamyl	H	H	**3c**	1	toluene	50	**5c**	86	91
4	Bn	H	H	**3d**	1	toluene	50	**5d**	93	99
5	Me	MeO	H	**3e**	1	toluene	50	**5e**	91	94
6	Me	F	H	**3f**	1	toluene	50	**5f**	95	96
7	allyl	F	H	**3g**	1	toluene	50	**5g**	90	98
8	allyl	Cl	H	**3h**	1	toluene	50	**5h**	93	95
9	Bn	H	Cl	**3i**	1	toluene	50	**5i**	98	99
10	-CH_2CO_2Me	H	H	**3j**	1	toluene	50	**5j**	98	96
11	-CH_2CN	H	H	**3k**	1	toluene	50	**5k**	89	87
12	Ph	H	H	**3l**	10	$CHCl_3$/MS 5Å	30	**5l**	94	90
13	4-F-C_6H_4	H	H	**3m**	10	$CHCl_3$/MS 5Å	30	**5m**	91	82
14	3-MeO-C_6H_4	H	H	**3n**	10	$CHCl_3$/MS 5Å	30	**5n**	93	86
15	2-MeO-C_6H_4	H	H	**3o**	10	$CHCl_3$/MS 5Å	30	**5o**	75	98
16	Ph	Me	H	**3p**	10	$CHCl_3$/MS 5Å	30	**5p**	72	74
17	Ph	MeO	H	**3q**	10	$CHCl_3$/MS 5Å	30	**5q**	86	82
18	4-F-C_6H_4	MeO	H	**3r**	10	$CHCl_3$/MS 5Å	30	**5r**	72	73
19	3-MeO-C_6H_4	MeO	H	**3s**	10	$CHCl_3$/MS 5Å	30	**5s**	78	66

Footnote [a] Isolated yield after purification by column chromatography. [b] Determined by HPLC analysis using chiral columns. See experimental section for detail.

We assume that the observed enantiofacial selectivity switch between dinuclear Ni_2-**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_2-**1**, a sterically less hindered Ni-aryloxide in the outer O_2O_2 cavity would function as a Brønsted base to generate the Ni-enolate in the outer cavity, while a Ni-aryloxide in the N_2O_2 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_2O_2 inner cavity of homodinuclear (*R*)-Ni_2-**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 cite, 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_2O_2 cavity would work as a Brønsted base to generate Ni-enolate in situ. The other Ni in the inner N_2O_2 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_2-**1** catalyst.

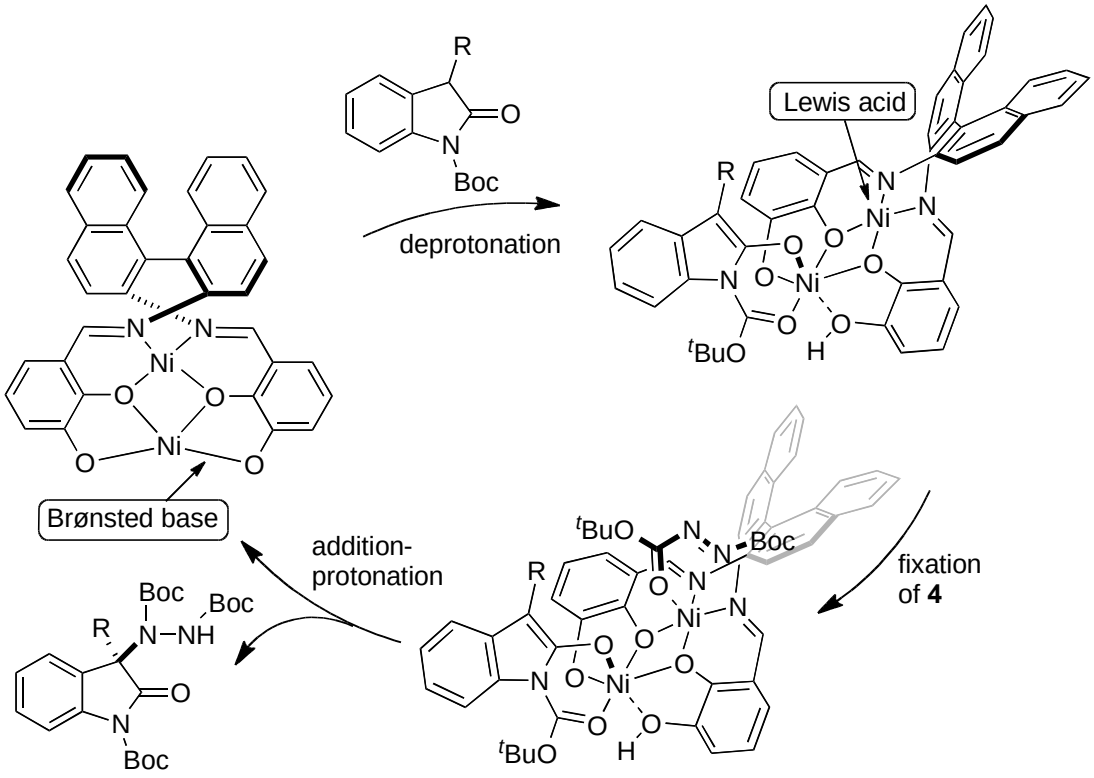
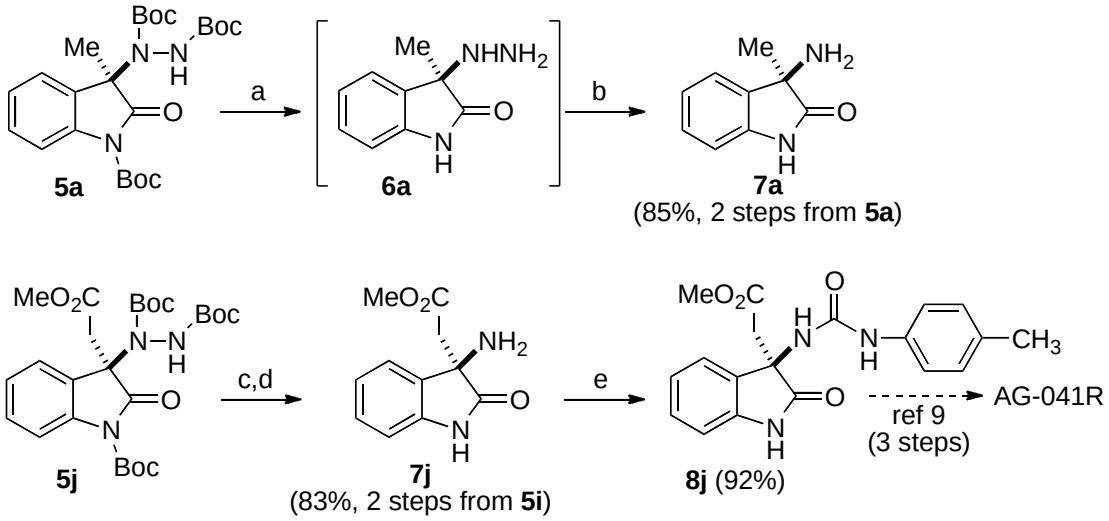


Figure 2. Postulated catalytic cycle of amination under dinuclear Schiff base catalysis

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_2 atmosphere produced the best results to give 3-aminooxindole **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-aminooxindole **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.[9]



Scheme 1. Transformation of amination products; reagents and conditions: (a) 4 M HCl, 1,4-dioxane, rt, 2 h; (b) Rh/C, H_2 (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_2 (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_2-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_2-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 ^{1}H NMR and 125.65 MHz for ^{13}C NMR. Chemical shifts in $CDCl_3$ were reported in the scale relative to tetramethylsilane (0 ppm) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to $CHCl_3$ (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.[3,10] 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*.[9] 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_2/Schiff base **1** catalyst (1.3 mg, 2.0 μmol). The resulting mixture was stirred at 50 ºC 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 ºC for 18 h. The reaction mixture was diluted with Et_2O, 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^{-1}; ^1H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{24}H_{35}N_3O_7Na^+$ $[M+Na]^+$: 500.2372, found: 500.2376, $[\alpha]_D^{22.7}$ -21.0 (*c* 1.34, $CHCl_3$); HPLC (DAICEL CHIRALPAK IA, hexane/CH_2Cl_2 = 1/1, flow 0.5 mL/min, at 40 ºC, detection at 254 nm) t_R 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^{-1}; ^1H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{26}H_{37}N_3O_7Na^+$ $[M+Na]^+$: 526.2529, found: 526.2531; $[\alpha]_D^{22.5}$ -9.3 (*c* 0.60, $CHCl_3$), HPLC (DAICEL CHIRALPAK IA, hexane/CH_2Cl_2 = 3/7, flow 0.5 mL/min, at 40 ºC, detection at 254 nm) t_R 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^{-1}; ^1H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{32}H_{41}N_3O_7Na^+$

$[M+Na]^+$: 602.2842, found: 602.2842; $[\alpha]_D^{22.5}$ -24.4 (*c* 0.50, $CHCl_3$), HPLC (DAICEL CHIRALPAK IA, hexane/CH_2Cl_2 = 7/3, flow 0.5 mL/min, at 40 ºC, detection at 254 nm) t_R 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) ν 2980, 2394, 2648, 2360, 2340, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{25}H_{37}N_3O_7Na^+$ $[M+Na]^+$: 576.2686, found: 576.2671; $[\alpha]_D^{19.0}$ -2.3 (*c* 1.5, $CHCl_3$), HPLC (DAICEL CHIRALPAK IA, hexane/CH_2Cl_2 = 7/3, flow 0.5 mL/min, at 40 ºC, detection at 254 nm) t_R 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) ν 3300, 2980, 2934, 1731, 1601 cm^{-1}; ^1H NMR ($CDCl_3$) 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;^{13}C NMR ($CDCl_3$) 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 $C_{24}H_{35}N_3O_7Na^+$ $[M+Na]^+$: 530.2478, found: 530.2480; $[\alpha]_D^{22.5}$ -5.1 (*c* 3.1, $CHCl_3$), HPLC (DAICEL CHIRALPAK IC, hexane/CH_2Cl_2 = 1/1, flow 0.5 mL/min, at 40 ºC, detection at 254 nm) t_R 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) ν 3323, 2981, 2934, 1782, 1752, 1731, 1705, 1611 cm^{-1}; ^1H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 24.3, 27.7, 28.1, 28.2, 65.8, 81.7, 83.2, 84.5, 111.4 (d, $^2J_{C\text{-}F}$ = 23.9 Hz), 114.9 (d, $^2J_{C\text{-}F}$ = 23.9 Hz), 116.0 (d, $^3J_{C\text{-}F}$ = 8.4 Hz), 133.8, 133.9, 149.2, 152.8, 156.2, 160.3 (d, $^1J_{C\text{-}F}$ = 245 Hz), 175.9; HRMS (ESI): *m*/*z* calculated for $C_{24}H_{34}FN_3O_7Na^+$ $[M+Na]^+$: 518.2279, found: 518.2276; $[\alpha]_D^{22.5}$ -35.0 (*c* 0.70, $CHCl_3$) HPLC (Combined use of three comlums DAICEL CHIRALPAK IA, IA-3, and IB, hexane/CH_2Cl_2 = 3/7, flow 0.5 mL/min, at 40 ºC, detection at 254 nm) t_R 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) ν 3324, 2981, 2935, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 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}C NMR ($CDCl_3$) 27.6, 28.0, 28.2, 41.4, 68.7, 81.7, 83.3, 84.3, 111.8 (d, $^2J_{C\text{-}F}$ = 25.1 Hz), 115.0 (d, $^2J_{C\text{-}F}$ = 22.8 Hz), 115.7 (d, $^3J_{C\text{-}F}$ = 8.4 Hz), 121.0, 129.1, 131.7 (d, $^3J_{C\text{-}F}$ = 7.2 Hz), 134.8 (d, $^4J_{C\text{-}F}$ = 2.4 Hz), 148.9, 152.8, 156.2, 160.2 (d, $^1J_{C\text{-}F}$ = 245 Hz), 174.9; HRMS (ESI): *m*/*z* calculated for $C_{26}H_{36}FN_3O_7Na^+$ $[M+Na]^+$: 544.2435, found: 544.2442; $[\alpha]_D^{21.0}$ -12.8 (*c* 0.70, $CHCl_3$), HPLC (DAICEL CHIRALPAK IA, hexane/CH_2Cl_2 = 3/7, flow 0.5 mL/min, at 40 ºC, detection at 254 nm) t_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) ν 3324, 2980, 2934, 1787, 1748, 1733, 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 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}C NMR ($CDCl_3$) δ 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 $C_{26}H_{36}ClN_3O_7Na^+$ $[M+Na]^+$: 560.2140, found: 560.2151; $[\alpha]_D^{22.5}$ -27.3 (*c* 1.40, $CHCl_3$), HPLC (DAICEL CHIRALPAK IB, hexane/CH_2Cl_2 = 9/1, flow 0.5 mL/min, at 40 ºC, detection at 254 nm) t_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) ν 3325, 2980, 2935, 1787, 1733 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$)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*=7.4Hz, 2H), 6.74 (s, 1H), 7.01(dd, *J*=7.4, 7.6 Hz, 2H), 7.09 (dd, *J*=7.4, 7.5Hz, 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}C NMR ($CDCl_3$) 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 $C_{30}H_{38}N_3O_7ClNa^+$ $[M+Na]^+$: 610.2296, found: 610.2288; $[\alpha]_D^{19.0}$ -32.3 (*c* 2.5, $CHCl_3$), HPLC (DAICEL CHIRALPAK IA, hexane/CH_2Cl_2 = 1/1, flow 0.5 mL/min, at 40 ºC, detection at 254 nm) t_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) ν 3313, 2981, 1715, 1608, 1481, 1372 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 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}C NMR ($CDCl_3$) 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 ºC, 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) ν3324, 2981, 2934, 1800, 1778, 1735, 1713, 1608 cm^{-1}; ^1H NMR ($CDCl_3$) δ 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) ν 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) ν 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_2 (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) ν 3139, 1710, 1675, 1620, 1472 cm^{-1}; ^1H NMR (CD_3OD) δ 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); ^{13}C NMR (CD_3OD) δ 25.6, 59.1, 111.2, 123.7, 124.5, 129.9, 135.1, 142.1, 184.4; ESI-MS *m/z* 185 $[M+Na]^+$; $[\alpha]_D^{30.3}$ +10.7 (*c* 0.60, CH_3OH).

(*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_2 (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) ν 1734, 1623, 1474, 1214, 755 cm^{-1}; ^1H NMR (CD_3OD) δ 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); ^{13}C NMR (CD_3OD) δ 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 $C_{11}H_{12}N_2O_3Na^+$ $[M+Na]^+$: 243.0746, found: 243.0737; $[\alpha]_D^{27.7}$ +31.0 (*c* 0.60, CH_3OH).

(*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) ν 3338, 1728, 1662, 1604, 1549, 1212, 753 cm^{-1}; ^1H NMR ($CDCl_3$) δ 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); ^{13}C NMR ($CDCl_3$) δ 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 $[M+Na]^+$; HRMS (ESI): *m/z* calculated for $C_{24}H_{34}ClN_3O_7Na^+$ $[M+Na]^+$: 376.1273, found: 376.1263; $[\alpha]_D^{30.3}$ +12.0 (*c* 0.80, $CHCl_3$).

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17. In our previous studies on direct Mannich-type reactions and Michael reactions using Ni_2-**1**, Co_2-**1** and Mn_2-**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.