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Reductive coupling of isatins with ketones and aldehydes by low-valent titanium

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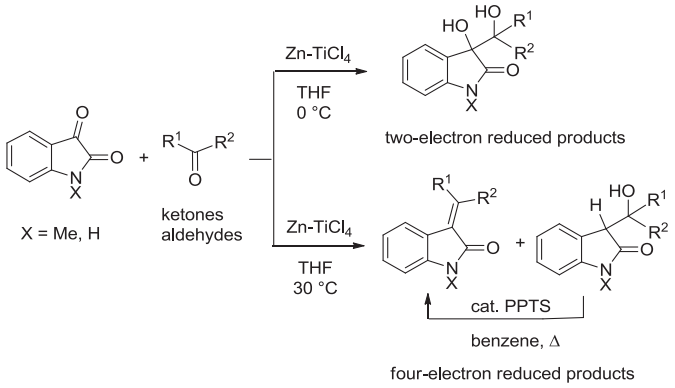
ABSTRACT

The reductive coupling of isatins with ketones and aldehydes by Zn–$TiCl_4$ in THF gave two- and four-electron reduced products, 3-hydoxy-3-(1-hydoxyalkyl)oxindoles and 3-alkylideneoxindoles, selectively by controlling the reaction conditions. Although the 3-(1-hydoxyalkyl)oxindoles were also produced as the four-electron reduced products in some cases, these products were readily dehydrated to 3-alkylideneoxindoles. The 3-alkylideneoxindoles derived from aldehydes were formed as mixtures of geometric isomers. The both geometric isomers were isomerized to the equilibrium mixtures by reflux in cat. PPTS/benzene.

1. Introduction

Recently the synthesis and reaction of 3-alkylideneoxindoles attract much attention, since this type of compound exists in a number of biologically important compounds and is a useful precursor for the synthesis of other types of oxindoles.[1–3] Although many methods have been reported to date for the synthesis of 3-alkylideneoxindoles,[1a,2] the use of the reductive cross-coupling of isatins with carbonyl compounds is unprecedented for this purpose. Reductive coupling with low-valent titanium has been well known as a powerful tool for the reductive cross-coupling between two different carbonyl compounds because of its versatility, convenience, and economical efficiency.[4,5] In the course of our recent study on the reductive cross-coupling with low-valent titanium,[6] we report in this paper the reductive coupling of isatins with ketones and aldehydes by low-valent titanium generated from Zn–$TiCl_4$ (Scheme 1). We found that two- and four-electron reduced products, 3-hydoxy-3-(1-hydoxyalkyl)oxindoles and 3-alkylideneoxindoles, could be prepared selectively by controlling the reaction conditions. In some cases, the four-electron reduced products were obtained as mixtures of two products, 3-alkylideneoxindoles and 3-(1-hydoxyalkyl)oxindoles. However, the latter products were easily transformed to the former by reflux in cat. PPTS/benzene. Therefore, the reductive coupling of isatins with carbonyl compounds provides new synthetic method for already known 3-alkylideneoxindoles and hitherto unknown 3-hydoxy-3-(1-hydoxyalkyl)oxindoles, which are promising precursors of other oxindole heterocycles.



Scheme 1. Reductive coupling of isatins with ketones and aldehyde by Zn–$TiCl_4$.

2. Results and discussion

2.1. Reductive coupling of isatins with ketones by Zn–$TiCl_4$

The reaction conditions of the cross-coupling were scrutinized using *N*-methylisatin (**1a**) and acetone (**2a**) as the substrates and

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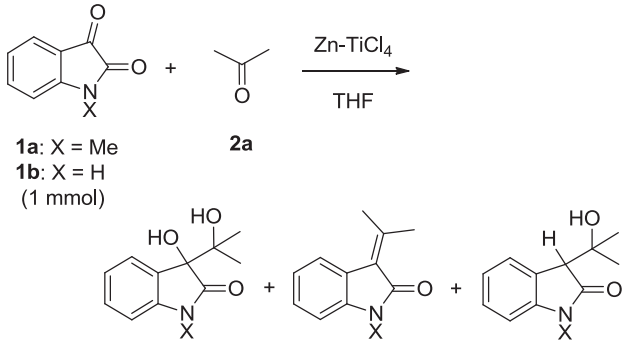
the results are summarized in Table 1. The molar ratio of Zn/$TiCl_4$ was fixed to 2/1. Initially, the reaction was carried out with the molar ratio of **1a**/$TiCl_4$ as 1/1 (condition a) in THF at 0 °C for 1 h with varying the molar ratio of **1a**/**2a** from 1/1 to 1/5 (runs 1–4). In these cases, 3-hydroxy-3-(2-hydroxypropan-2-yl)-1-methylindolin-2-one (**3a**) was obtained in 64–74% yields as the two-electron reduced product together with small amounts of the four-electron reduced products, 1-methyl-3-(propan-2-ylidene)indolin-2-one (**4a**) and 3-(2-hydroxypropan-2-yl)-1-methylindolin-2-one (**5a**). With the ratio of **1a**/**2a** as 1/5 (run 4), **3a** was obtained as the sole product, although the yield was somewhat lowered (64%) and **1a** was recovered (15%). Therefore, the molar ratio of **1a**/$TiCl_4$ was increased to 1/2 (condition b) to complete the reaction (run 5). This attempt increased the yield of **3a** (71%) and, however, brought about the production of small amounts of **4a** (10%) and **5a** (5%). Consequently, the best yield of **3a** (74%) was obtained with the 1/2 ratio of **1a**/**2a** (run 2). Next, the reaction was performed with the ratio of **1a**/**2a**/Zn/$TiCl_4$ as 1/2/4/2 (condition b) in THF at 0 °C, 20 °C and 30 °C for 2 h (runs 6–8). From the result in run 6, it found that the further reduction to **4a** and **5a** proceeded considerably even at 0 °C under condition b. Four-electron reduced product **4a** was formed at 30 °C in 70% yield together with **5a** (17%), and **3a** was not obtained (run 8). It was found that dehydration of **5a** gave **4a** quantitatively (vide infra). Therefore, crude product mixture obtained from run 8 was refluxed in cat. PPTS/benzene for 1 h (condition c). Expectedly, **4a** was formed as the sole product in 87% yield (run 9). When isatin (**1b**) was employed in place of **1a**, **3b** (80%) and **4b** (89%) were produced under the same conditions as runs 2 and 9, respectively (runs 10 and 12).

Next, the reductive coupling of **1a**,**b** with aliphatic cyclic ketones **2b**–**e** was carried out under the same conditions as runs 2, 7 and 8 (conditions a, b and c) in Table 1 (Table 2). In most cases, 3-hydoxy-3-(1-hydoxyalkyl)oxindoles **3** were produced selectively in good yields under the condition a. However, the reaction of **1a** with cycloheptanone (**2d**) brought about **3e** in a low yield (38%) probably due to the low reactivity of **2d** at 0 °C (run 6). Especially in the reaction of **1b** with **2d** (run 15), no cross-coupled product could be detected. In these cases, the major products were 3-hydroxyindolin-2-ones **6a**,**b**. The products **3f** and **3j** were obtained from 4-*t*-butylcyclohexanone (**2e**) as the single diastereomers (runs 8 and 17) and their stereo structures were confirmed to be cis by X-ray crystallography (Fig. 1). These results show that the less-hindered equatorial attack of **1a**,**b** to **2e** proceeded predominantly. In almost all cases, 3-alkylideneoxindoles **4** were formed selectively in good to moderate yields under the condition c. Even in the reactions with **2d** (runs 7 and 16), **4e** and **4i** were formed in moderate yields (41% and 64%). In these cases, the major by-products were indolin-2-ones **7a**,**b**. These results show that the cross-coupling of **1a**,**b** with **2d** proceeded at 30 °C (condition b). Incidentally, the reduction of **1a**,**b** in the absence of **2** under the conditions a and b gave the corresponding two- and four-electron reduced products, **6a**,**b** and **7a**,**b**, as shown in Scheme 2.[7] In addition, the reduction of **1a** with benzophenone or acetophenone also gave **6a** and **7a**, and the corresponding cross-coupling products could not be obtained.

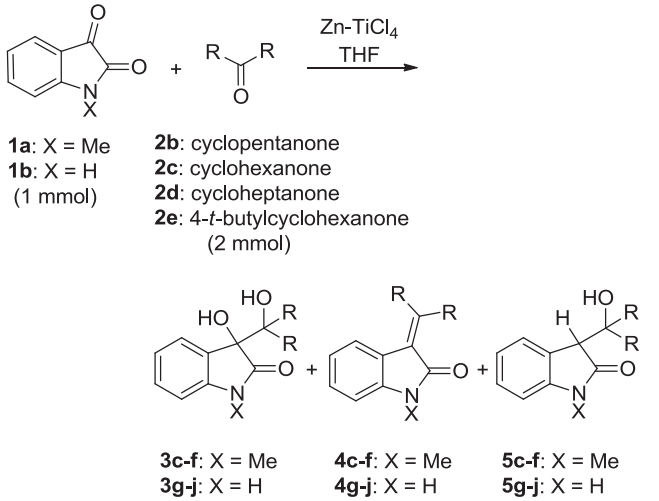
Table 1
Reductive coupling of **1a**,**b** with acetone by Zn–$TiCl_4$



Run	1	2a (mmol)	Condition[a]	Temp (°C)		% Yield[b]		
						3	4	5
1	**1a**	1	a	0	**a**	65	6	—
2	**1a**	2	a	0	**a**	74	5	4
3	**1a**	3	a	0	**a**	70	6	—
4	**1a**	5	a	0	**a**	64	—	—
5	**1a**	5	b	0	**a**	71	10	5
6	**1a**	2	b	0	**a**	41	37	8
7	**1a**	2	b	20	**a**	10	60	21
8	**1a**	2	b	30	**a**	—	70	17
9	**1a**	2	c	30	**a**	—	87	—
10	**1b**	2	a	0	**b**	80	—	—
11	**1b**	2	b	30	**b**	—	68	14
12	**1b**	2	c	30	**b**	—	89	—

[a] a: **1**/Zn/$TiCl_4$=1/2/1, 1 h. b: **1**/Zn/$TiCl_4$=1/4/2, 2 h. c: crude product mixture obtained by condition b was refluxed in cat. PPTS/benzene for 1 h.
[b] Isolated yields.

Table 2
Reductive coupling of **1a**,**b** with **2b**–**e** by Zn–$TiCl_4$



Run	1	2	Condition[a]		% Yield[b]		
					3	4	5
1	**1a**	**2b**	a	**c**	74	6	5
2	**1a**	**2b**	b	**c**	—	56	34
3	**1a**	**2b**	c	**c**	—	85	—
4	**1a**	**2c**	a	**d**	82	—	—
5	**1a**	**2c**	c	**d**	—	77	
6	**1a**	**2d**	a	**e**	38	7	—
7	**1a**	**2d**	c	**e**	—	41	—
8	**1a**	**2e**	a	**f**	75	—	—
9	**1a**	**2e**	c	**f**	—	72	—
10	**1b**	**2b**	a	**g**	79	8	4
11	**1b**	**2b**	b	**g**	—	71	22
12	**1b**	**2b**	c	**g**	—	92	—
13	**1b**	**2c**	a	**h**	72	—	—
14	**1b**	**2c**	c	**h**	—	66	—
15	**1b**	**2d**	a	**i**	ND[c]	—	—
16	**1b**	**2d**	c	**i**	—	64	—
17	**1b**	**2e**	a	**j**	64	—	—
18	**1b**	**2e**	c	**j**	—	61	—

[a] a: **1**/Zn/$TiCl_4$=1/2/1, 0 °C, 1 h. b: **1**/Zn/$TiCl_4$=1/4/2, 30 °C, 2 h. c: crude product mixture obtained by condition b was refluxed in cat. PPTS/benzene for 1 h.
[b] Isolated yields.
[c] Not detected.

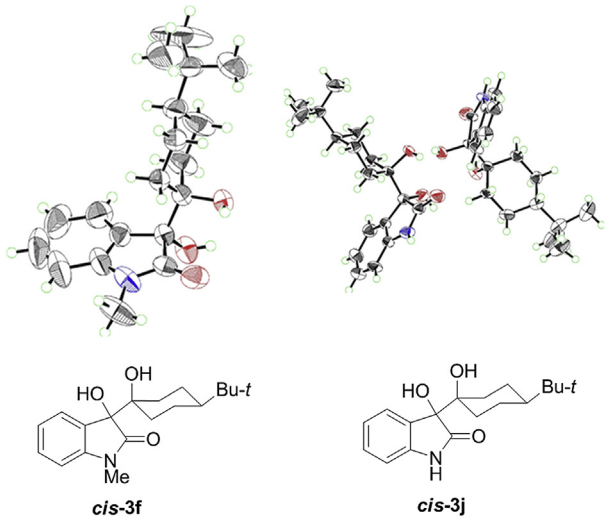
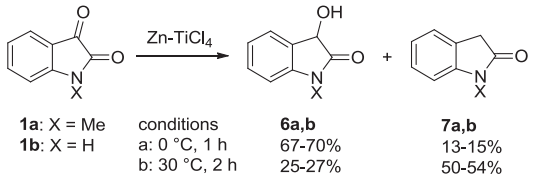
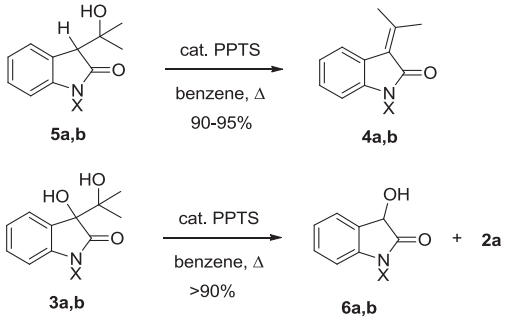


Fig. 1. X-ray crystal structures of *cis*-**3f** and *cis*-**3j**.



Scheme 2. Reduction of isatins **1a**,**b** by Zn–$TiCl_4$.

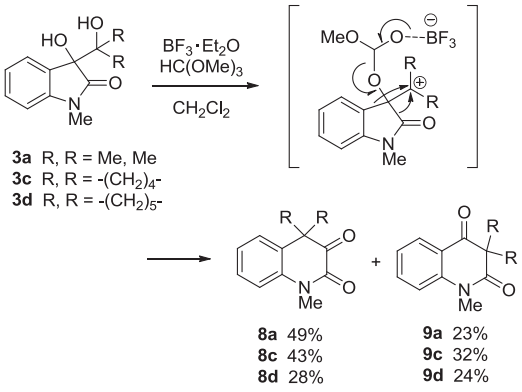
While dehydration of **5a**,**b** quantitatively gave **4a**,**b** (vide supra), the treatment of **3a**,**b** under the same conditions resulted *retro*-aldol products **6a**,**b** and **2a** (Scheme 3). Since it has been reported that oxindole epoxides were rearranged to quinoline-2,3-dions **8** by treatment with $SnCl_4$,[8] we investigated the Lewis acid catalyzed rearrangement of **3** to **8**. In consequence, we found that **3a**,**c**,**d** were rearranged to **8a**,**c**,**d** and quinoline-2,4-diones **9a**,**c**,**d**, respectively, by treatment with $BF_3 \cdot Et_2O$ and $HC(OMe)_3$ in CH_2Cl_2 (Scheme 4).[9]



Scheme 3. Treatment of **5a**,**b** and **3a**,**b** with refluxing cat. PPTS/benzene.

2.2. Reductive coupling of isatins with aldehydes by Zn–$TiCl_4$

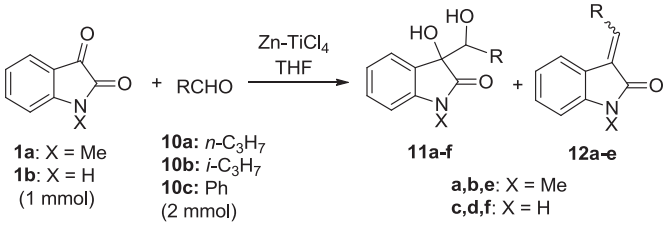
The reductive coupling of **1a**,**b** with aldehydes **10a**–**c** by Zn–$TiCl_4$ were also carried out under the conditions a and b (Table 3). In the reactions with aliphatic aldehydes **10a**,**b**, both of 3-hydoxy-3-(1-hydoxyalkyl)oxindoles **11a**–**d** and 3-alkylideneoxindoles **12a**–**d** were obtained as mixtures of two diastereomers and geometric isomers, respectively, in good to moderate yields (runs 1–8). The reactions with benzaldehyde (**10c**)



Scheme 4. Lewis acid catalyzed rearrangement of **3a**,**c**,**d** to **8a**,**c**,**d** and **9a**,**c**,**d**.

gave **11e**,**f** in good yields under the condition a (runs 9 and 11), whereas the reactions under the condition b brought about poor results (runs 10 and 12). Especially in run 12, **12f** could not be obtained and the formations of **6b**, **7b**, and 1,2-diphenylethene, the McMurry-type adduct of **10c**, were observed. This result is probably due to the instability of intermediate titanate of **11f**, since **11f** was partially decomposed to **6b** and **10c** even during isolation by column chromatography (Experimental Section).

Table 3
Reductive coupling of **1a**,**b** with aldehydes by Zn–$TiCl_4$

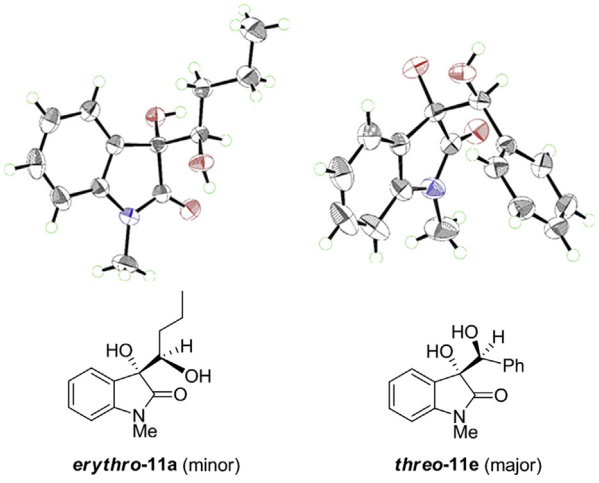


Run	1	10	Condition[a]	% Yield[b]		
					11 (dr)[c]	**12** (*E*:*Z*)[d]
1	**1a**	**10a**	a	**a**	86 (67:33)	—
2	**1a**	**10a**	b	**a**	—	56 (86:14)
3	**1a**	**10b**	a	**b**	74 (57:43)	—
4	**1a**	**10b**	b	**b**	—	71 (82:18)
5	**1b**	**10a**	a	**c**	84 (60:40)	—
6	**1b**	**10a**	b	**c**	—	78 (85:15)
7	**1b**	**10b**	a	**d**	81 (67:33)	—
8	**1b**	**10b**	b	**d**	—	55 (71:29)
9	**1a**	**10c**	a	**e**	84(79:21)	—
10	**1a**	**10c**	b	**e**	—	28 (85:15)
11	**1b**	**10c**	a	**f**	72 (67:33)	—
12	**1b**	**10c**	b	**f**	—	ND[e]

[a] a: **1**/Zn/$TiCl_4$=1/2/1, 0 °C, 1 h. b: **1**/Zn/$TiCl_4$=1/4/2, 30 °C, 2 h.
[b] Isolated yields.
[c] Diastereomeric ratio determined by ^1H NMR analysis.
[d] Geometric ratio determined by isolation.
[e] Not detected.

Although the diastereomers of **11** could not be separated by column chromatography, the minor isomer of **11a** and major isomer of **11e** were isolated by recrystallization and confirmed to be *erythro*-**11a** and *threo*-**11e**, respectively, by X-ray crystallographic analysis (Fig. 2). On the other hand, the geometric isomers of **12** could be separated by column chromatography. The separated both isomers of **12a**–**d** were isomerized by reflux in cat. PPTS/benzene and the *E*:*Z* ratios finally reached equilibrium values within 12–24 h (Table 4). The experimental results show that *E*-isomers are thermodynamically more stable than *Z*-isomers to some extent.

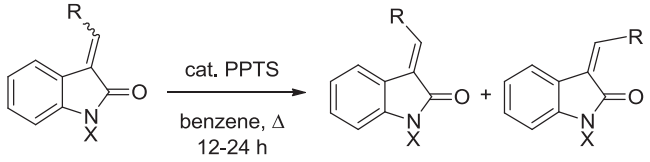
These results are well agree with the *E*:*Z* ratios for **12a**–**d** calculated by the DFT methods at the B3LYP/6-311+G(2d,p) level in benzene (PCM) at 353 K (Table 4).



***erythro*-11a** (minor) ***threo*-11e** (major)

Fig. 2. X-ray crystal structures of *erythro*-**11a** and *threo*-**11e**.

Table 4
E:*Z* ratios of the equilibrium mixtures of **12a**–**d**



12a,**b**: X = Me
12c,**d**: X = H

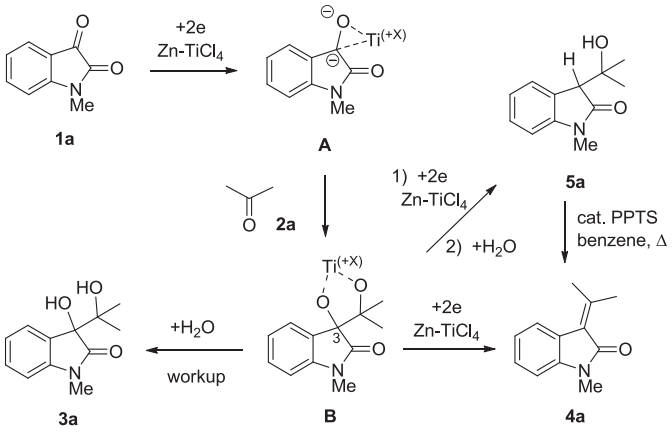
E-form *Z*-form

12	R	*E*:*Z* ratio	
		Exp.[a]	Calcd[b]
12a	***n*-C_3H_7**	**75:25**	**73:27**
12b	***i*-C_3H_7**	**67:33**	**62:38**
12c	***n*-C_3H_7**	**76:24**	**77:23**
12d	***i*-C_3H_7**	**75:25**	**53:47**

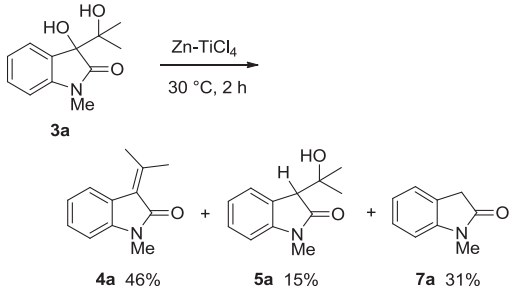
[a] Determined by ^{1}H NMR analysis.
[b] Calculated at the B3LYP/6-311+G(2d,p) level in benzene (PCM) at 353 K.

2.3. Reaction mechanism of the reductive coupling

The presumed reaction mechanism of the reductive coupling of *N*-methylisatin (**1a**) with acetone (**2a**) is exhibited in Scheme 5. The cyclic voltamograms of **1a** and **1b** in 0.03 M Bu_4NClO_4/DMF on a platinum cathode showed first reduction peaks at −1.06 V and −1.03 V versus SCE, respectively, whereas those of **2a** under the same conditions revealed no reduction peak from 0 to −3.0 V versus SCE. These results suggest that this reductive coupling is initiated by the reduction of **1a**. Initially, **1a** is reduced by low-valent titanium to give titanate **A**. The nucleophilic addition of **A** to **2a** produces adduct **B**. The workup of **B** with water at 0 °C gave **3a**, since the adduct **B** is stable at this temperature. On the other hand, further reduction of **B** by low-valent titanium proceeds at 30 °C to afford **4a** and **5a**. The dehydration of **5a** by reflux in cat. PPTS/benzene gave **4a**. The reduction of the isolated **3a** at 30 °C (**3a**/Zn/$TiCl_4$=1/1/2) gave **4a** and **5a** together with **7a** formed from the reduction of retro-aldol product **6a** (Scheme 6). Since benzaldehyde (**10c**) showed first reduction peak at −1.94 V versus SCE under the same conditions as above, the reductive coupling of **1a**,**b** with **10c** is also initiated by the reduction of **1a**,**b**.



Scheme 5. Presumed reaction mechanism of reductive coupling of **1a** with **2a** by Zn–$TiCl_4$.



Scheme 6. Reduction of **3a** by Zn–$TiCl_4$.

3. Conclusion

The reductive coupling of isatins **1** with ketones **2** and aldehydes **10** by Zn–$TiCl_4$ gave two-electron reduced products, 3-hydoxy-3-(1-hydoxyalkyl)oxindoles **3** and **11**, and four-electron reduced products, 3-alkylideneoxindoles **4** and **12**, respectively. The two- and four-electron reduced products could be obtained selectively by controlling the amounts of Zn–$TiCl_4$ and reaction temperature. Although 3-(1-hydoxyalkyl)oxindoles **5** were formed together with **4** as the for-electron products in some cases, **5** were quantitatively transformed to **4** by refluxing in cat. PPTS/benzene. Both *E*- and *Z*-isomers of **12** were isomerized to the same equilibrium mixtures of **12** by refluxing in cat. PPTS/benzene.

4. Experimental section

4.1. General

THF was distilled from sodium benzophenone ketyl radical. Zinc powder and $TiCl_4$ were purchased from Wako Pure Chemical Industries, Ltd. and used as is. Column chromatography was performed on silica gel 60. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were measured on a JEOL JNM-ECP500 spectrometer with tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on a Shimadzu IRAffinity-1 infrared spectrometer. HRMS were measured on a Thermo Scientic Exactive FTMS spectrometer. Melting points were uncorrected.

4.2. Typical procedure of reductive coupling by Zn–$TiCl_4$ and dehydration of 5 to 4

To a solution of **1a** (161 mg, 1 mmol), **2a** (116 mg, 2 mmol), and zinc powder (0.13 g, 2 mmol) in THF (5 mL) was added $TiCl_4$

(0.11 mL, 1 mmol) dropwise at 0 °C and then the dark blue suspension was stirred for 1 h at this temperature. To the mixture was added 1 M HCl (20 mL) at 0 °C and the mixture was stirred for 15 min at 25 °C. The mixture was extracted with ethyl acetate three times. The organic layer was washed with aqueous NaCl and dried over $MgSO_4$. After the solvent was removed, the residue was purified by column chromatography on silica gel to give **3a** in 74% yield (164 mg) with small amounts of **4a** (9 mg, 5%) and **5a** (8 mg, 4%). Compounds **4a**,[10–12] **4b**,[10,12,13] **4c**,[11,14] **4g**,[11,14,15] **4h**,[10,14,16] **4i**,[14] ***E*-12a**,[17] ***E*-12b**,[3g,18] ***Z*-12b**,[18] ***E*-12c**,[3b,3f] ***E*-12d**,[18] ***Z*-12d**,[18] ***E*-12e**,[2b,2c,19,20] and ***Z*-12e**[2b,2c,19,20] were known.

A solution of **5a** (103 mg, 0.5 mmol) and PPTS (10 mg) in benzene (10 mL) was refluxed using Dean–Stark apparatus under nitrogen atmosphere for 1 h. After the solvent was removed in vacuo, the residue was purified by column chromatography on silica gel (hexanes–EtOAc) to give **4a** in 85% yield (80 mg).

*4.2.1. 3-Hydroxy-3-(2-hydroxypropan-2-yl)-1-methylindolin-2-one (**3a**).* White solid; R_f 0.2 (hexanes–ethyl acetate, 1:1); mp 148–150 °C; IR (KBr) 3412, 1690, 1614, 1497, 1468, 974, 936, 766, 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (s, 3H), 1.44 (s, 3H), 3.21 (s, 3H), 3.79 (br s, 1H), 3.99 (br s, 1H), 6.85–6.88 (m, 1H), 7.08–7.13 (m, 1H), 7.33–7.38 (m, 1H), 7.42–7.45 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 22.0 (q), 24.5 (q), 25.8 (q), 74.7 (s), 79.3 (s), 108.4 (d), 123.0 (d), 125.3 (d), 127.7 (s), 129.7 (d), 144.1 (s), 178.5 (s). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14%; H, 6.83%; N, 6.33%. Found: C, 65.09%; H, 6.85%; N, 6.23%.

*4.2.2. 3-Hydroxy-3-(2-hydroxypropan-2-yl)indolin-2-one (**3b**).* White solid; R_f 0.7 (hexanes–ethyl acetate, 1:2); mp 116–117 °C; IR (KBr) 3374, 3179, 1734, 1721, 1680, 1626, 1601, 1474, 928, 845, 750, 741, 683, 654 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (s, 3H), 1.45 (s, 3H), 3.64 (br s, 1H), 4.06 (br s, 1H), 6.88–6.92 (m, 1H), 7.06–7.10 (m, 1H), 7.27–7.31 (m, 1H), 7.41–7.44 (m, 1H), 8.08 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.2 (q), 24.2 (q), 74.7 (s), 80.1 (s), 110.6 (d), 122.6 (d), 125.5 (d), 128.5 (s), 129.6 (d), 141.4 (s), 180.9 (s). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76%; H, 6.32%; N, 6.76%. Found: C, 63.71%; H, 6.30%; N, 6.68%.

*4.2.3. 3-Hydroxy-3-(1-hydroxycyclopentyl)-1-methylindolin-2-one (**3c**).* White solid; R_f 0.65 (hexanes–ethyl acetate, 1:1); mp 142–143 °C; IR (KBr) 3401, 3316, 1713, 1614, 1497, 1468, 880, 750, 741, 721, 691, 658 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18–1.26 (m, 1H), 1.39–1.48 (m, 1H), 1.70–1.88 (m, 1H), 2.14–2.21 (m, 1H), 3.21 (s, 3H), 3.66 (br s, 1H), 4.06 (br s, 1H), 6.85–6.88 (m, 1H), 7.08–7.12 (m, 1H), 7.34–7.38 (m, 1H), 7.46–7.49 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 23.7 (t), 24.3 (t), 25.9 (q), 33.6 (t), 35.6 (t), 78.4 (s), 85.5 (s), 108.4 (d), 123.0 (d), 125.4 (d), 127.6 (s), 129.7 (d), 144.1 (s), 178.5 (s). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00%; H, 6.93%; N, 5.66%. Found: C, 67.96%; H, 6.93%; N, 5.62%.

*4.2.4. 3-Hydroxy-3-(1-hydroxycyclohexyl)-1-methylindolin-2-one (**3d**).* White solid; R_f 0.7 (hexanes–ethyl acetate, 2:1); mp 155–157 °C; IR (KBr) 3430, 3403, 1701, 1613, 1497, 1474, 930, 889, 746, 658 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95–1.04 (m, 2H), 1.30–1.36 (m, 1H), 1.38–1.45 (m, 1H), 1.52–1.72 (m, 5H), 2.09–2.16 (m, 1H), 3.19 (s, 3H), 3.44 (br s, 1H), 3.95 (br s, 1H), 6.84–6.87 (m, 1H), 7.09–7.13 (m, 1H), 7.33–7.37 (m, 1H), 7.44–7.46 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 20.75 (t), 20.79 (t), 25.7 (t), 25.8 (q), 29.1 (t), 31.2 (t), 75.8 (s), 80.0 (s), 108.3 (d), 122.8 (d), 125.7 (d), 127.7 (s), 129.6 (d), 144.2 (s), 178.7 (s). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94%; H, 7.33%; N, 5.36%. Found: C, 68.91%; H, 7.35%; N, 5.28%.

*4.2.5. 3-Hydroxy-3-(1-hydroxycycloheptyl)-1-methylindolin-2-one (**3e**).* White solid; R_f 0.6 (hexanes–ethyl acetate, 1:2); mp 133–135 °C; IR (KBr) 3433, 3410, 1701, 1613, 1495, 1474, 1464, 926, 745, 664 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10–1.20 (m. 2H), 1.28–1.40 (m, 2H), 1.42–1.68 (m, 5H), 1.72–1.82 (m, 1H), 1.96 (dd, 1H, J=9.2, 14.6 Hz), 2.24 (dd, 1H, J=10.1, 14.6 Hz), 3.20 (s, 3H), 3.65 (br s, 1H), 4.09 (br s, 1H), 6.84–6.88 (m, 1H), 7.02–7.12 (m, 1H), 7.33–7.38 (m, 1H), 7.41–7.45 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 22.3 (t), 22.8 (t), 26.0 (q), 28.7 (t), 29.8 (t), 32.6 (t), 36.1 (t), 79.5 (s), 79.6 (s), 108.5 (d), 123.0 (d), 125.9 (d), 127.1 (s), 129.9 (d), 144.4 (s), 179.3 (s). Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79%; H, 7.69%; N, 5.09%. Found: C, 69.72%; H, 7.68%; N, 5.04%.

*4.2.6. 3-((1s,4s)-4-(tert-Butyl)-1-hydroxycyclohexyl)-3-hydroxy-1-methylindolin-2-one (cis-**3f**).* White solid; R_f 0.4 (hexanes–ethyl acetate, 1:2); mp 144–146 °C; IR (KBr) 3487, 3447, 3374, 1701, 1614, 1497, 1472, 934, 889, 754, 667, 654 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (s, 9H), 0.98–1.06 (m, 1H), 1.36–1.49 (m, 4H), 1.55–1.67 (m, 3H), 2.14–2.20 (m, 1H), 3.19 (s, 3H), 3.40 (br s, 1H), 3.94 (br s, 1H), 6.84–6.86 (m, 1H), 7.08–7.13 (m, 1H), 7.33–7.37 (m, 1H), 7.43–7.46 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 21.69 (t), 21.71 (t), 25.9 (q), 27.4 (q), 29.6 (t), 31.9 (t), 32.3 (s), 47.5 (d), 75.5 (s), 79.9 (s), 108.4 (d), 122.9 (d), 125.8 (d), 127.6 (s), 129.7 (d), 144.3 (s), 178.8 (s). Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89%; H, 8.57%; N, 4.41%. Found: C, 71.82%; H, 8.54%; N, 4.33%.

*4.2.7. 3-Hydroxy-3-(1-hydroxycyclopentyl)indolin-2-one (**3g**).* White solid; R_f 0.7 (hexanes–ethyl acetate, 1:2); mp 158–159 °C; IR (KBr) 3589, 3470, 3194, 1709, 1616, 1470, 762, 656 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33–1.56 (m, 4H), 1.73–1.90 (m, 3H), 2.13–2.21 (m, 1H), 3.45 (br s, 1H), 4.07 (br s, 1H), 6.86–6.90 (m, 1H), 7.06–7.11 (m, 1H), 7.28–7.32 (m, 1H), 7.45–7.49 (m, 1H), 7.72 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.6 (t), 24.0 (t), 33.5 (t), 35.1 (t), 78.5 (s), 85.0 (s), 109.8 (d), 121.8 (d), 125.3 (d), 128.8 (s), 129.0 (d), 142.0 (s), 180.0 (s). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 66.94%; H, 6.48%; N, 6.00%. Found: C, 66.86%; H, 6.45%; N, 5.94%.

*4.2.8. 3-Hydroxy-3-(1-hydroxycyclohexyl)indolin-2-one (**3h**).* White solid; R_f 0.75 (hexanes–ethyl acetate, 1:1); mp 162–163 °C; IR (KBr) 3356, 3293, 1724, 1622, 1472, 937, 746, 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95–1.06 (m, 1H), 1.30–1.52 (m, 4H), 1.54–1.68 (m, 4H), 1.75–1.82 (m, 1H), 3.68 (br s, 1H), 5.13 (br s, 1H), 6.83–6.87 (m, 1H), 6.95–6.99 (m, 1H), 7.18–7.22 (m, 1H), 7.38–7.42 (m, 1H), 10.05 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.1 (t), 20.2 (t), 24.7 (t), 28.7 (t), 29.8 (t), 74.3 (s), 79.7 (s), 109.1 (d), 120.9 (d), 125.2 (d), 128.2 (d), 128.9 (s), 141.7 (s), 179.4 (s). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00%; H, 6.93%; N, 5.66%. Found: C, 67.91%; H, 6.90%; N, 5.57%.

*4.2.9. 3-((1s,4s)-4-(tert-Butyl)-1-hydroxycyclohexyl)-3-hydroxyindolin-2-one (cis-**3j**).* White solid; R_f 0.25 (hexanes–ethyl acetate, 2:1); mp 214–216 °C; IR (ATR) 3466, 3420, 3275, 3246, 1705, 1690, 1622, 957, 922, 917, 864, 856, 752, 743, 702, 667 cm^{-1}; ^1H NMR ($CDCl_3$, DMSO-d_6) δ 0.78–0.85 (m, 1H), 0.81 (s, 9H), 1.31–1.58 (m, 6H), 1.64–1.71 (m, 1H), 1.83–1.90 (m, 1H), 3.61 (br s, 1H), 5.01 (br s, 1H), 6.83–6.87 (m, 1H), 6.95–7.00 (m, 1H), 7.18–7.23 (m, 1H), 7.38–7.42 (m, 1H), 10.02 (br s, 1H); ^{13}C NMR ($CDCl_3$, DMSO-d_6) δ 20.5 (t), 20.6 (t), 26.4 (q), 29.0 (t), 29.8 (t), 31.1 (s), 46.3 (d), 73.4 (s), 79.4 (s), 108.6 (d), 120.5 (d), 125.0 (d), 127.8 (d), 129.0 (s), 141.3 (s), 178.9 (s). Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26%; H, 8.31%; N, 4.62%. Found: C, 71.25%; H, 8.33%; N, 4.56%.

*4.2.10. 3-Cyclopentylidene-1-methylindolin-2-one (**4c**).* Pale yellow solid; R_f 0.2 (hexanes–ethyl acetate=1:1); mp 82–84 °C (lit.[11] 85–86); ^1H NMR ($CDCl_3$) δ 1.81–1.92 (m, 4H), 2.85–2.90 (m, 2H), 3.13–3.18 (m, 2H), 3.26 (s, 3H), 6.82–6.85 (m, 1H), 7.03–7.07 (m, 1H), 7.23–7.27 (m, 1H), 7.41–7.44 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.3 (q), 25.6 (t), 26.0 (t), 34.1 (t), 34.5 (t), 107.2 (d), 119.3 (s), 121.3 (d), 122.1 (d),123.3 (s), 127.0 (d), 142.0 (s), 164.4 (s), 167.2 (s).

*4.2.11. 3-Cyclohexylidene-1-methylindolin-2-one (**4d**).* Colorless paste; R_f 0.2 (hexanes–ethyl acetate=2:1); ^1H NMR ($CDCl_3$)

δ 1.67–1.85 (m, 6H), 2.85–2.89 (m, 2H), 3.23 (s, 3H), 3.36–3.40 (m, 2H), 6.79–6.82 (m, 1H), 6.98–7.02 (m, 1H), 7.21–7.25 (m, 1H), 7.62–7.65 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.5 (q), 25.8 (t), 27.8 (t), 28.1 (t), 30.0 (t), 33.0 (t), 107.5 (d), 119.7 (s), 121.4 (d), 123.3 (d), 123.4 (s), 127.4 (d), 142.1 (s), 163.6 (s), 168.2 (s); HRMS (ESI) calcd for $C_{15}H_{18}NO$ $(M+H)^+$ 228.1388, found 228.1386.

*4.2.12. 3-Cycloheptylidene-1-methylindolin-2-one (**4e**).* Colorless paste; R_f 0.3 (hexanes–ethyl acetate, 2:1); ^{1}H NMR ($CDCl_3$) δ 1.55–1.63 (m, 4H), 1.76–1.91 (m, 4H), 2.92–2.96 (m, 2H), 3.25 (s, 3H), 3.36–3.40 (m, 2H), 6.80–6.84 (m, 1H), 7.01–7.05 (m, 1H), 7.23–7.27 (m, 1H), 7.52–7.55 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.5 (q), 25.6 (t), 27.1 (t), 29.0 (t), 29.3 (t), 31.7 (t), 35.8 (t), 107.4 (d), 121.5 (d), 121.9 (s), 123.3 (s), 123.6 (d), 127.4 (d), 142.0 (s), 165.6 (s), 167.7 (s); HRMS (ESI) calcd for $C_{16}H_{20}NO$ $(M+H)^+$ 242.1545, found 242.1544.

*4.2.13. 3-(4-(tert-Butyl)cyclohexylidene)-1-methylindolin-2-one (**4f**).* Colorless paste; R_f 0.55 (hexanes–ethyl acetate, 5:1); ^{1}H NMR ($CDCl_3$) δ 1.27–1.45 (m, 3H), 1.98–2.12 (m, 2H), 2.21–2.40 (m, 2H), 3.23 (s, 3H), 3.42–3.48 (m, 1H), 4.52–4.59 (m, 1H), 6.79–6.82 (m, 1H), 6.99–7.03 (m, 1H), 7.21–7.25 (m, 1H), 7.61–7.64 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.5 (q), 27.4 (q), 28.0 (t), 28.3 (t), 29.5 (t), 32.6 (s), 32.8 (t), 46.9 (d), 107.5 (d), 119.6 (s), 121.5 (d), 123.3 (d), 123.5 (s), 127.4 (d), 142.1 (s), 163.5 (s), 168.2 (s); HRMS (ESI) calcd for $C_{19}H_{26}NO$ $(M+H)^+$ 284.2014, found 284.2013.

*4.2.14. 3-Cyclopentylideneindolin-2-one (**4g**).* White solid; R_f 0.45 (hexanes–ethyl acetate=1:1); mp 215–216 °C (Lit.[10] 216–218); ^{1}H NMR ($CDCl_3$) δ 1.81–1.93 (m, 4H), 2.87 (t, 2H, J=6.9 Hz), 3.14 (t, 2H, J=6.9 Hz), 6.88–6.92 (m, 1H), 7.00–7.05 (m, 1H), 7.15–7.21 (m, 1H), 7.38–7.42 (m, 1H), 8.66 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.8 (t), 26.3 (t), 34.4 (t), 34.9 (t), 109.4 (d), 120.0 (s), 121.5 (d), 122.7 (d), 124.4 (s), 127.3 (d), 139.7 (s), 165.7 (s), 169.4 (s).

*4.2.15. 3-Cycloheptylideneindolin-2-one (**4i**).* Pale yellow solid; R_f 0.55 (hexanes–ethyl acetate=2:1); mp 167–168 °C (Lit.[14] 169–171); ^{1}H NMR ($CDCl_3$) δ 1.55–1.65 (m, 4H), 1.76–1.90 (m, 4H), 2.90–2.96 (m, 2H), 3.34–3.40 (m, 2H), 6.88 (d, 1H, J=7.5 Hz), 6.97–7.02 (m, 1H), 7.15–7.20 (m, 1H), 7.51 (d, 1H, J=7.5 Hz), 8.83 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.6 (t), 27.0 ((t), 29.0 (t), 29.4 (t), 31.7 (t), 35.9 (t), 109.3 (d), 121.4 (d), 122.3 (s), 123.9 (d), 124.1 (s), 127.4 (d), 139.5 (s), 166.3 (s), 169.9 (s).

*4.2.16. 3-(4-(tert-Butyl)cyclohexylidene)indolin-2-one (**4j**).* White solid; R_f 0.65 (hexanes–ethyl acetate, 2:1); mp 174–176 °C; IR (ATR) 3165, 3140, 3102, 1686, 1609, 1587, 868, 794, 764, 739, 721, 706, 673 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (s, 9H), 1.29–1.46 (m, 3H), 1.98–2.11 (m, 2H), 2.21–2.30 (m, 1H), 2.32–2.40 (m, 1H), 3.41–3.47 (m, 1H), 4.47–4.54 (m, 1H), 6.87 (d, 1H, J=7.7 Hz), 6.95–7.00 (m, 1H), 7.14–7.18 (m, 1H), 7.60 (d, 1H, J=7.7 Hz), 8.82 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 27.4 (q), 27.9 (t), 28.3 (t), 29.5 (t), 32.6 (s), 32.9 (t), 46.9 (d), 109.5 (d), 120.1 (s), 121.4 (d), 123.6 (d), 124.2 (s), 127.5 (d), 139.6 (s), 164.3 (s), 170.3 (s). Anal. Calcd for $C_{18}H_{23}NO$: C, 80.26%; H, 8.61%; N, 5.20%. Found: C, 80.25%; H, 8.63%; N, 5.15%.

*4.2.17. 3-(2-Hydroxypropan-2-yl)-1-methylindolin-2-one (**5a**).* Colorless past; R_f 0.4 (hexanes–ethyl acetate, 2:1); ^{1}H NMR ($CDCl_3$) δ 0.98 (s, 3H), 1.52 (s, 3H), 3.24 (s, 3H), 3.51 (s, 1H), 4.73 (br s, 1H), 6.86–6.89 (m, 1H), 7.06–7.10 (m, 1H), 7.30–7.35 (m, 1H), 7.36–7.39 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.0 (q), 25.9 (q), 28.0 (q), 55.8 (d), 72.7 (s), 108.3 (d), 122.6 (d), 125.0 (d), 126.1 (s), 128.3 (d), 144.5 (s), 177.4 (s); HRMS (ESI) calcd for $C_{12}H_{15}NO_2$ $(M+H)^+$ 206.1181, found 206.1180.

*4.2.18. 3-(2-Hydroxypropan-2-yl)indolin-2-one (**5b**).* White solid; R_f 0.5 (hexanes–ethyl acetate, 1:2); mp 108–109 °C; IR (KBr) 3420, 3410, 1686, 1618, 1593, 1487, 1474, 968, 833, 748, 735, 687, 660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 3H), 1.52 (s, 3H), 3.54 (s, 1H), 4.51 (br s, 1H), 6.89–6.92 (m, 1H), 7.04–7.08 (m, 1H), 7.24–7.28 (m, 1H), 7.35–7.38 (m, 1H), 7.86 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.8 (q), 28.0 (q), 56.4 (d), 72.9 (s), 110.2 (d), 122.5 (d), 125.4 (d), 126.7 (s), 128.4 (d), 142.1 (s), 180.4 (s). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09%; H, 6.85%; N, 7.32%. Found: C, 69.05%; H, 6.83%; N, 7.24%.

*4.2.19. 3-(1-Hydroxycyclopentyl)-1-methylindolin-2-one (**5c**).* Colorless paste; R_f 0.5 (hexanes–ethyl acetate, 1:1); ^{1}H NMR ($CDCl_3$) δ 1.19–1.28 (m, 1H), 1.44–1.98 (m, 7H), 3.23 (s, 3H), 3.69 (s, 1H), 4.17 (br s, 1H), 6.85–6.88 (m, 1H), 7.05–7.09 (m, 1H), 7.30–7.34 (m, 1H), 7.36–7.39 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 23.3 (t), 23.9 (t), 25.9 (q), 36.1 (t), 37.6 (t), 53.1 (d), 82.7 (s), 108.1 (d), 122.4 (d), 125.1 (d), 126.0 (s), 128.2 (d), 144.7 (s), 177.3 (s); HRMS (ESI) calcd for $C_{14}H_{18}NO_2$ $(M+H)^+$ 232.1338, found 232.1337.

*4.2.20. 3-(1-Hydroxycyclopentyl)indolin-2-one (**5g**).* White solid; R_f 0.6 (hexanes–ethyl acetate, 1:2); mp 162–163 °C; IR (KBr) 3431, 3180, 1692, 1618, 1474, 752, 677 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.47–1.66 (m, 4H), 1.70–2.01 (m, 4H), 3.59 (s, 1H), 4.48 (br s, 1H), 6.88–6.92 (m, 1H), 6.94–7.00 (m, 1H), 7.17–7.22 (m, 1H), 7.32–7.36 (m, 1H), 10.18 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.8 (t), 23.3 (t), 35.7 (t), 36.8 (t), 53.0 (d), 81.9 (s), 109.2 (d), 121.0 (d), 124.7 (d), 126.4 (s), 127.3 (d), 142.5 (s), 178.7 (s). Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87%; H, 6.96%; N, 6.45%. Found: C, 71.79%; H, 6.99%; N, 6.37%.

*4.2.21. 3-Hydroxy-3-(1-hydroxybutyl)-1-methylindolin-2-one (**11a**).* Diastereomeric mixture (67:33); colorless paste; R_f 0.75 (hexanes–ethyl acetate, 1:1); ^{1}H NMR ($CDCl_3$) δ 0.78–0.84 (m, 3H), 1.05–1.20 (m, 2H), 1.23–1.34 (m, 1H), 1.47–1.58 (m, 1H), 3.03 (br s, 0.33H), 3.10 (s, 3H), 3.58 (br s, 0.67H), 3.88–3.92 (m, 0.33H), 3.92–3.96 (m, 0.67H), 4.26 (br s, 0.67H), 4.52 (br s, 0.33H), 6.82–6.87 (m, 1H), 7.07–7.14 (m, 1H), 7.30–7.38 (m, 1.33H), 7.49–7.54 (m, 0.67H); ^{13}C NMR ($CDCl_3$) δ 13.5 (q), 13.6 (q), 18.8 (t), 19.0 (t), 25.8 (q), 25.9 (q), 32.1 (t), 32.6 (t), 74.7 (d), 75.6 (d), 77.7 (s), 78.6 (s), 108.0 (d), 108.3 (d), 122.9 (d), 123.0 (d), 123.9 (s), 125.6 (d), 127.7 (s), 128.0 (s), 129.2 (d), 129.6 (d), 143.3 (s), 143.7 (s), 177.2 (s), 177.7 (s); HRMS (ESI) calcd for $C_{13}H_{18}NO_3$ $(M+H)^+$ 236.1287, found 236.1285.

*4.2.22. erythro-**11a** (minor isomer).* White solid; R_f 0.75 (hexanes–ethyl acetate, 1:1); mp 148–149 °C; IR (KBr) 3401, 3279, 1701, 1614, 1497, 1472, 762, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.80 (t, 3H, J=7.4 Hz), 1.05–1.19 (m, 2H), 1.23–1.34 (m, 1H), 1.48–1.60 (m, 1H), 2.78 (d, 1H, J=11.0 Hz), 3.19 (s, 3H), 3.89 (dt, 1H, J=8.3, 11.0 Hz), 4.28 (br s, 1H), 6.83–6.87 (m, 1H), 7.09–7.14 (m, 1H), 7.31–7.38 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.7 (q), 19.2 (t), 26.0 (q), 33.4 (t), 76.4 (d), 77.2 (s), 108.6 (d), 123.4 (d), 123.9 (d), 127.7 (s), 130.0 (d), 144.2 (s), 177.6 (s). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36%; H, 7.28%; N, 5.95%. Found: C, 66.35%; H, 7.30%; N, 5.91%.

*4.2.23. 3-Hydroxy-3-(1-hydroxy-2-methylpropyl)-1-methylindolin-2-one (**11b**).* Diastereomeric mixture (57:43); colorless paste; R_f 0.6 (hexanes–ethyl acetate, 1:1); ^{1}H NMR ($CDCl_3$) δ 0.73 (d, 1.71H, J=6.9 Hz), 0.78 (d, 1.71H, J=6.9 Hz), 0.80 (d, 1.29H, J=6.9 Hz), 0.90 (d, 1.29H, J=6.9 Hz), 1.42–1.52 (m, 0.57H), 1.60–1.70 (m, 0.43H), 3.18 (s, 3H), 3.20–3.25 (m, 0.57H), 3.50 (br s, 0.43H), 3.71 (d, 0.57H, J=4.9 Hz), 3.84 (dd, 0.43H, J=4.4, 8.9 Hz), 3.89 (br s, 0.43H), 4.40 (br

s, 0.57H), 6.84–6.87 (m, 1H), 7.08–7.13 (m, 1H), 7.31–7.38 (m, 1.57H), 7.51–7.54 (m, 0.43H); ^{13}C NMR ($CDCl_3$) δ 16.8 (q), 17.5 (q), 20.2 (q), 21.3 (q), 25.9 (q), 26.0 (q), 29.3 (d), 29.5 (d), 76.7 (s), 77.8 (s), 78.9 (d), 81.0 (d), 108.2 (d), 108.5 (d), 122.9 (d), 123.1 (d), 124.1 (d), 126.0 (d), 127.9 (s), 128.3 (s), 129.5 (d), 129.7 (d), 143.4 (s), 143.7 (s), 177.4 (s), 177.8 (s); HRMS (ESI) calcd for $C_{13}H_{18}NO_3$ $(M+H)^+$ 236.1287, found 236.1286.

*4.2.24. 3-Hydroxy-3-(1-hydroxybutyl)indolin-2-one (**11c**).* Diastereomeric mixture (67:33); yellow paste; R_f 0.3 (hexanes–ethyl acetate, 1:2); ^{1}H NMR ($CDCl_3$) δ 0.80 (t, 3H, J=7.3 Hz), 1.08–1.34 (m, 3H), 1.47–1.59 (m, 1H), 3.08 (br s, 0.33H), 3.56 (br s, 0.67H), 3.86–3.96 (m, 1H), 4.47 (br s, 0.67H), 4.63 (br s, 0.33H), 6.85–6.88 (m, 1H), 7.02–7.09 (m, 1H), 7.22–7.27 (m, 0.67H), 7.28–7.31 (m, 0.33H), 7.46–7.49 (m, 0.67H), 8.71 (br s, 0.67H), 8.72 (br s, 0.33H); ^{13}C NMR ($CDCl_3$) δ major: 13.6 (q), 18.9 (t), 32.1 (t), 74.7 (d), 79.3 (s), 110.5 (d), 122.8 (d), 125.9 (d), 128.2 (s), 129.4 (d), 140.9 (s), 180.2 (s); minor: 13.5 (q), 19.1 (t), 32.5 (t), 75.6 (d), 78.5 (s), 110.7 (d), 122.8 (d), 124.2 (d), 128.5 (s), 129.6 (d), 141.4 (s), 180.5 (s); HRMS (ESI) calcd for $C_{12}H_{16}NO_3$ $(M+H)^+$ 222.1130, found 222.1129.

*4.2.25. 3-Hydroxy-3-(1-hydroxy-2-methylpropyl)indolin-2-one (**11d**).* Diastereomeric mixture (60:40); yellow paste; R_f 0.3 (hexanes–ethyl acetate, 1:2); ^{1}H NMR ($CDCl_3$) δ 0.76 (d, 1.8H, J=6.8 Hz), 0.825 (d, 1.2H, J=6.9 Hz), 0.832 (d, 1.2H, J=6.9 Hz), 0.87 (d, 1.8H, J=6.9 Hz), 1.52–1.62 (m, 0.6H), 1.62–1.70 (m, 0.4H), 3.31 (d, 0.6H, J=10.1 Hz), 3.63 (br s, 0.4H), 3.76 (d, 0.4H, J=4.7 Hz), 3.82 (dd, 0.6H, J=4.7, 10.1 Hz), 4.43 (br s, 0.4H), 4.68 (br s, 0.6H), 6.87–6.90 (m, 1H), 7.01–7.08 (m, 1H), 7.23–7.27 (m, 1H), 7.28–7.31 (m, 0.6H), 7.49–7.52 (m, 0.4H), 8.85 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 17.3 (q), 20.6 (q), 21.3 (q), 29.3 (d), 29.5 (d), 77.6 (s), 78.5 (s), 79.0 (d), 80.7 (d), 110.6 (d), 110.8 (d), 122.7 (d), 122.8 (d), 124.4 (d), 126.3 (d), 128.4 (s), 128.8 (s), 129.5 (d), 129.7 (d), 141.0 (s), 141.4 (s), 180.3 (s), 180.7 (s); HRMS (ESI) calcd for $C_{12}H_{16}NO_3$ $(M+H)^+$ 222.1130, found 222.1129.

*4.2.26. 3-Hydroxy-3-(hydroxy(phenyl)methyl)-1-methylindolin-2-one (**11e**).* Diastereomeric mixture (79:21): colorless paste; R_f 0.2 (hexanes–ethyl acetate, 1:1); ^{1}H NMR ($CDCl_3$) δ 2.86 (s, 2.37H), 2.89 (s, 0.63H), 4.31 (br s, 1H), 4.97 (br s, 1H), 5.10 (s, 0.79H), 5.16 (s, 0.21H), 6.51 (d, 0.79H, J=7.7 Hz), 6.55 (d, 0.21H, J=7.7 Hz), 6.97–7.23 (m, 7.21H), 7.34–7.36 (m, 0.79H); ^{13}C NMR ($CDCl_3$) δ 25.4 (q), 25.5 (q), 77.5 (d), 77.6 (d), 79.0 (s), 80.1 (s), 107.5 (d), 107.9 (d), 122.40 (d), 122.44 (d), 125.9 (d), 126.7 (s), 126.8 (d), 126.9 (d), 127.0 (d), 127.3 (s), 127.4 (d), 129.2 (d), 129.3 (d), 136.5 (s), 137.4 (s), 142.7 (s), 143.4 (s), 176.7 (s), 177.4 (s); HRMS (ESI) calcd for $C_{16}H_{16}NO_3$ $(M+H)^+$ 270.1130, found 270.1129. This compound was slightly unstable and gradually decomposed to **6a** and benzaldehyde in solution.

*4.2.27. threo-**11e** (major isomer).* White solid; R_f 0.7 (hexanes–ethyl acetate, 1:1); mp 132–133 °C; IR (KBr) 3449, 3366, 1692, 1614, 1495, 1472, 762, 754, 710, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.99 (s, 3H), 3.76 (d, 1H, J=1.7 Hz), 3.85 (br s, 1H), 4.99 (br d, 1H, J=1.7 Hz), 6.61–6.64 (m, 1H), 6.97–7.02 (m, 1H), 7.06–7.10 (m, 3H), 7.13–7.22 (m, 3H), 7.23–7.28 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.7 (q), 77.8 (d), 79.9 (s), 107.8 (d), 122.7 (d), 126.1 (d), 126.6 (s), 127.1 (d), 127.2 (d), 127.8 (d), 129.6 (d), 136.3 (s), 143.0 (s), 177.0 (s). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36%; H, 5.61%; N, 5.20%. Found: C, 71.32%; H, 5.61%; N, 5.15%.

*4.2.28. 3-Hydroxy-3-(hydroxy(phenyl)methyl)indolin-2-one (**11f**).* Diastereomeric mixture (65:35); yellow paste; R_f 0.45 (hexanes–ethyl acetate, 1:2); Obtained as the mixture with 3-hydroxyindolin-2-one and benzaldehyde. This compound was more unstable than **11e** and partially decomposed to **6b** and benzaldehyde during isolation by column chromatography on silica gel.

*4.2.29. (Z)-3-Butylidene-1-methylindolin-2-one (**Z-12a**).* Yellow paste; R_f 0.8 (hexanes–ethyl acetate, 2:1); ^{1}H NMR ($CDCl_3$) δ 1.02 (t, 3H, J=7.5 Hz), 1.56–1.64 (m, 2H), 3.00 (q, 2H, J=7.5 Hz), 3.23 (s, 3H), 6.77–6.80 (m, 1H), 6.87 (t, 1H, J=7.5 Hz), 6.99–7.03 (m, 1H), 7.23–7.27 (m, 1H), 7.37–7.40 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 22.4 (t), 25.6 (q), 29.7 (t), 107.7 (d), 118.8 (d), 121.7 (d), 123.0 (s), 127.0 (s), 128.4 (d), 142.0 (s), 142.6 (d), 167.4 (s); HRMS (ESI) calcd for $C_{13}H_{16}NO$ $(M+H)^+$ 202.1232, found 202.1231.

*4.2.30. (E)-3-Butylideneindolin-2-one (**E-12c**).* Yellow paste; R_f 0.55 (hexanes–ethyl acetate, 2:1); ^{1}H NMR ($CDCl_3$) δ 1.06 (t, 3H, J=7.3 Hz), 1.65–1.73 (m, 2H), 2.67 (q, 2H, J=7.7 Hz), 6.92 (d, 1H, J=7.7 Hz), 7.00–7.04 (m, 1H), 7.05 (t, 1H, J=7.7 Hz), 7.19–7.24 (m, 1H), 7.54 (d, 1H, J=7.6 Hz), 8.97 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0 (q), 21.9 (t), 31.3 (t), 110.2 (d), 121.9 (d), 122.8 (s), 123.6 (d), 128.3 (s), 128.8 (d), 141.1 (s), 142.5 (d), 170.1 (s).

*4.2.31. (Z)-3-Butylideneindolin-2-one (**Z-12c**).* Yellow paste; R_f 0.35 (hexanes–ethyl acetate, 2:1); ^{1}H NMR ($CDCl_3$) δ 1.03 (t, 3H, J=7.4 Hz), 1.57–1.65 (m, 2H), 2.98 (q, 2H, J=7.8 Hz), 6.84 (d, 1H, J=7.7 Hz), 6.89 (t, 1H, J=7.8 Hz), 6.97–7.01 (m, 1H), 7.17–7.21 (m, 1H), 7.38 (d, 1H, J=7.5 Hz), 8.12 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 22.4 (t), 29.7 (t), 109.6 (d), 119.2 (d), 121.7 (d), 123.8 (s), 127.3 (s), 128.5 (d), 139.3 (s), 143.3 (d), 169.3 (s); HRMS (ESI) calcd for $C_{12}H_{13}NO$ $(M+H)^+$ 188.1075, found 188.1075.

4.3. Typical procedure of rearrangement of 3 to 8 and 9

To a solution of **3a** (111 mg, 0.5 mmol) and $HC(OMe)_3$ (0.1 mL, 1 mmol) in CH_2Cl_2 (10 mL) was added $BF_3{\cdot}Et_2O$ (0.13 mL, 1 mmol) at 0 °C and the mixture was stirred for 2 h at 25 °C. To the mixture was added saturated aqueous $NaHCO_3$ (10 mL) and the mixture was extracted with CH_2Cl_2 three times. The organic layer was washed with aqueous NaCl and dried over $MgSO_4$. After the solvent was removed, the residue was purified by column chromatography on silica gel to give **8a** (50 mg, 49% yield) and **9a** (23 mg, 23% yield). Compounds **8a**,[8] **8c**,[8] **8d**,[8] **9a**[21] **9b**[22] and **9c**[23] were known.

4.4. X-ray crystallographic analysis

All measurements were made on a Rigaku RAXIS imaging plate area detector with graphite monochromated Mo Kα radiation. The structure was solved by direct methods with SIR-97 and refined with SHELXL-97. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. All calculations were performed using the YADOKARI-XG software package. Crystal data of **3d**, **3e**, ***cis*-3f**, ***cis*-3j**. ***erythro*-11a**, and ***threo*-11e** are deposited into CCDC 1022700–1022705. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.ac.uk/data/cif.

4.5. Computational methodology

All DFT calculations were carried out with the Gaussian 09[24] program. Geometry optimization was performed at the B3LYP/6-311+G(2d,p) level using the IEFPCM models for benzene solvent to take the solvent effect into consideration. The optimized geometries were verified by the vibrational analysis and their energies were thermally corrected to 353 K based on the frequencies.

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