

# Asymmetric Aldol Reaction of Acetaldehyde and Isatin Derivatives for the Total Syntheses of *ent*-Convolutamydine E and CPC-1 and a Half Fragment of Madindoline A and B

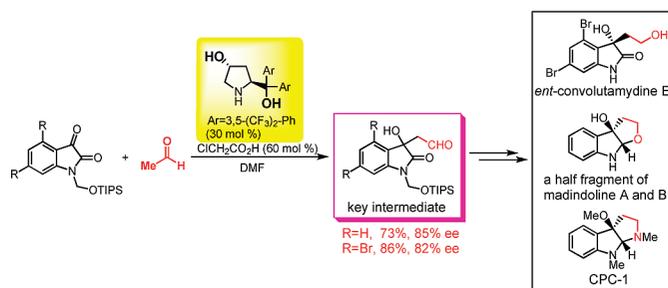
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## ABSTRACT



The asymmetric aldol reaction of isatin derivatives and acetaldehyde has been developed using 4-hydroxydiarylprolinol as a catalyst, affording the aldol products with high enantioselectivity, these products being key intermediates in the synthesis of 3-hydroxyindole alkaloids. Short syntheses of *ent*-convolutamydine E and CPC-1 and a half fragment of madindoline A and B have been accomplished.

There are several 3-hydroxyindole alkaloids, such as convolutamydines,<sup>1</sup> madindolines,<sup>2</sup> and CPC-1<sup>3</sup> (Figure 1). Convolutamydine E was isolated from the Floridian marine

bryozoan *Amathia convoluta* by Kamano and co-workers.<sup>1c</sup> Madindoline A and B, isolated from the fermentation broth of *Streptomyces nitrosporeus* K93-0711 by Ōmura and co-workers, are selective inhibitors of interleukin-6<sup>2c</sup> consisting of two portions such as a 3a-hydroxyfuroindoline fragment and a substituted cyclopentenedione moiety. CPC-1 is a new pyrrolidinoindoline-type alkaloid, isolated by Takayama and co-workers.<sup>3</sup> There are several total syntheses of these biologically interesting natural products. While chiral convolutamydine A has been synthesized by five groups using asymmetric direct aldol reaction of acetone catalyzed by organocatalysts as a key step,<sup>4</sup> there is only one report for the asymmetric synthesis of convolutamydine E, in which a

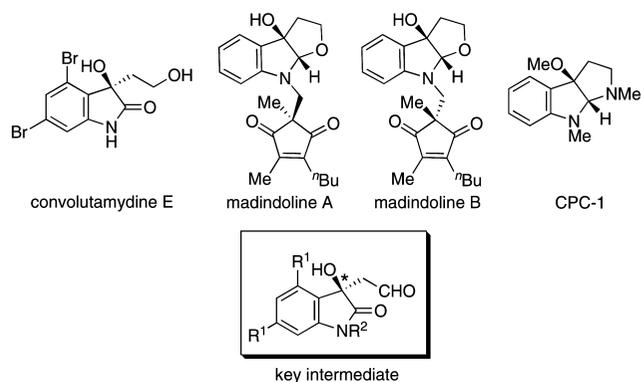
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(1) (a) Kamano, Y.; Zhang, H.-P.; Ichihara, Y.; Kizu, H.; Komiyama, K.; Pettit, G. R. *Tetrahedron Lett.* **1995**, *36*, 2783. (b) Zhang, H.-P.; Kamano, Y.; Ichihara, Y.; Kizu, H.; Komiyama, K.; Itokawa, H.; Pettit, G. R. *Tetrahedron* **1995**, *51*, 5523. (c) Kamano, Y.; Kotake, A.; Hashima, H.; Hayakawa, I.; Hiraide, H.; Zhang, H.-P.; Kizu, H.; Komiyama, K.; Hayashi, M.; Pettit, G. R. *Collect. Czech. Chem. Commun.* **1999**, *64*, 1147.

(2) (a) Hayashi, M.; Kim, Y.-P.; Takamatsu, S.; Enomoto, A.; Shinose, M.; Takahashi, Y.; Tanaka, H.; Komiyama, K.; Ōmura, S. *J. Antibiot.* **1996**, *49*, 1091. (b) Takamatsu, S.; Kim, Y.-P.; Enomoto, A.; Hayashi, M.; Tanaka, H.; Komiyama, K.; Ōmura, S. *J. Antibiot.* **1997**, *50*, 1069. (c) Hayashi, M.; Rho, M.-C.; Enomoto, A.; Fukami, A.; Kim, Y.-P.; Kikuchi, Y.; Sunazuka, T.; Hirose, T.; Komiyama, K.; Ōmura, S. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 14728.

(3) Kitajima, M.; Mori, I.; Arai, K.; Kogure, N.; Takayama, H. *Tetrahedron Lett.* **2006**, *47*, 3199.



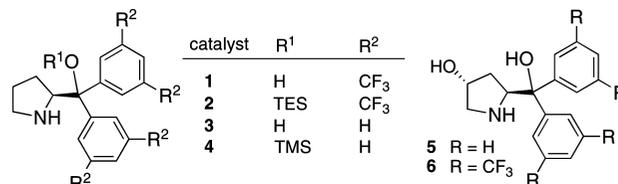
**Figure 1.** Natural products possessing the 3-hydroxyindole moiety and its key intermediate.

diastereoselective vinylogous Mukaiyama aldol reaction was employed as a key step.<sup>5</sup> Although there are several asymmetric syntheses of madindoline A and B,<sup>6,7</sup> there are only two synthetic methods for the enantioselective synthesis of the 3a-hydroxyfuroindoline fragment of madindoline A and B: One is developed by Sunazuka, Omura, and co-workers, in which Sharpless epoxidation was used as a key step,<sup>6</sup> while Kobayashi used vinylogous Mukaiyama aldol reaction as a key reaction.<sup>5</sup> Although CPC-1 was synthesized via asymmetric allylation as a key step, its enantioselectivity is not sufficient (42% ee).<sup>3</sup> During the preparation of this manuscript, Nakamura and co-workers reported the asymmetric direct aldol reaction of acetaldehyde and isatin, catalyzed by *N*-(heteroarenesulfonyl)prolinamide as an organocatalyst, which was applied to the synthesis of convolutamyndine B and E.<sup>8</sup>

One of the straightforward methods for the synthesis of these natural products is to use a 3-hydroxyindole derivative (Figure 1) as a key synthetic intermediate, which would be generated via the asymmetric direct aldol reaction of acetaldehyde with isatin or its derivatives. The aldol reaction of acetaldehyde as a nucleophile, however, has been regarded

as difficult for several reasons. (1) Acetaldehyde is reactive as an electrophile, causing a self-aldol reaction. (2) The generated aldol product, an  $\alpha,\alpha$ -unsubstituted aldehyde, is also reactive both as a nucleophile and as an electrophile, promoting overreaction. (3) Dehydration is another side reaction. In spite of these difficulties, our group first successfully realized the asymmetric direct aldol reaction of acetaldehyde using an organocatalyst.<sup>9</sup>

The organocatalyst-mediated reaction is one of the current topics in synthetic organic chemistry, and several efficient organocatalysts have been reported (Figure 2).<sup>10</sup> Our group<sup>11</sup>



**Figure 2.** Organocatalysts examined in this study.

and Jørgensen's group<sup>12</sup> independently developed diarylprolinol silyl ether as an effective organocatalyst.<sup>13</sup> During our investigation of the applications of the catalyst, we found that trifluoromethyl-substituted diarylprolinol promotes cross- and self-aldol reactions of acetaldehyde, affording the desired products with excellent enantioselectivity.<sup>9</sup> In this paper, we describe the asymmetric direct aldol reaction of acetaldehyde and isatin, which is applied to the short synthesis of *ent*-convolutamyndine E, the indole fragment of madindoline A and B, and CPC-1.

We chose 1-benzylisatin (**7a**) as an electrophile, and the aldol reaction with acetaldehyde was investigated (eq 1). The

(9) (a) Hayashi, Y.; Itoh, T.; Aratake, S.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2082. (b) Hayashi, Y.; Samanta, S.; Itoh, T.; Ishikawa, H. *Org. Lett.* **2008**, *10*, 5581.

(10) Reviews on organocatalysis, see: (a) Dalco, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (b) *Asymmetric Organocatalysis*; Berkessel, A., Groger, H., Ed.; Wiley-VCH: Weinheim, 2005. (c) Hayashi, Y. *J. Synth. Org. Chem. Jpn.* **2005**, *63*, 464. (d) List, B. *Chem. Commun.* **2006**, 819. (e) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001. (f) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8. (g) *Enantioselective Organocatalysis*; Dalco, P. I., Ed.; Wiley-VCH: Weinheim, 2007. (h) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (i) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638. (j) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138.

(11) (a) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. Recent report, see: (b) Hayashi, Y.; Obi, K.; Ohta, Y.; Okamura, D.; Ishikawa, H. *Chem. Asian J.* **2009**, *4*, 246.

(12) (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. (b) Marigo, M.; Fielenbach, D.; Branton, A.; Kjasgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703. Recent reports, see: (c) Jiang, H.; Falcicchio, A.; Jensen, K. L.; Paixao, M. W.; Bertelsen, S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 7153.

(13) Selected examples of other group's application of diarylprolinol ether, see: (a) Enders, D.; Huttel, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861. (b) Vesely, J.; Ibrahim, I.; Zhao, G.-L.; Rios, R.; Cordova, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 778. (c) Xie, H.; Zu, L.; Li, H.; Wang, J.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 10886. (d) Enders, D.; Narine, A. A.; Benninghaus, T. R.; Raabe, G. *Synlett* **2007**, 1667. (e) Vo, N. T.; Pace, R. D. M.; O'Hara, F.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 404. Review, see: (f) Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876. (g) Mielgo, A.; Palomo, C. *Chem. Asian J.* **2008**, *3*, 922.

(4) (a) Luppi, G.; Cozzi, P. G.; Monari, M.; Kaptein, B.; Broxterman, Q. B.; Tomasini, C. *J. Org. Chem.* **2005**, *70*, 7418. (b) Luppi, G.; Monari, M.; Corrêa, R. J.; Violante, F. A.; Pinto, A. C.; Kaptein, B.; Broxterman, A. B.; Garden, S. J.; Tomasini, C. *Tetrahedron* **2006**, *62*, 12017. (c) Malkov, A. V.; Kabeshov, M. A.; Bella, M.; Kysilka, O.; Malyshev, D. A.; Pluháková, K.; Koovsky, P. *Org. Lett.* **2007**, *9*, 5473. (d) Chen, J.-R.; Liu, X.-P.; Zhu, X.-Y.; Li, L.; Qiao, Y.-F.; Zhang, J.-M.; Xiao, W.-J. *Tetrahedron* **2007**, *63*, 10437. (e) Nakamura, S.; Hara, N.; Nakashima, H.; Kubo, K.; Shibata, N.; Toru, T. *Chem. Eur. J.* **2008**, *14*, 8079.

(5) Nakamura, T.; Shirokawa, S.; Hosokawa, S.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 677.

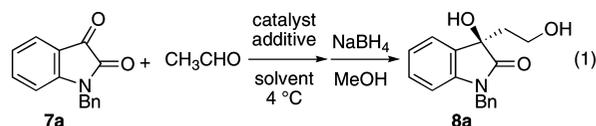
(6) (a) Sunazuka, T.; Hirose, T.; Shirahata, T.; Harigaya, Y.; Hayashi, M.; Komiya, K.; Omura, S.; Smith III, A. B. *J. Am. Chem. Soc.* **2000**, *122*, 2122. (b) Hirose, T.; Sunazuka, T.; Shirahata, T.; Yamamoto, D.; Harigaya, Y.; Kuwajima, I.; Omura, S. *Org. Lett.* **2002**, *4*, 501. (c) Hirose, T.; Sunazuka, T.; Yamamoto, D.; Kojima, N.; Shirahata, T.; Harigaya, Y.; Kuwajima, I.; Omura, S. *Tetrahedron* **2005**, *61*, 6015.

(7) Other groups' synthesis, see: (a) Hosokawa, S.; Sekiguchi, K.; Enomoto, M.; Kobayashi, S. *Tetrahedron Lett.* **2000**, *41*, 6429. (b) Hosokawa, S.; Sekiguchi, K.; Hayase, K.; Hirukawa, Y.; Kobayashi, S. *Tetrahedron Lett.* **2000**, *41*, 6435. (c) Hosokawa, S.; Kobayashi, S. *J. Synth. Org. Chem. Jpn.* **2001**, *59*, 1103. (d) McComas, C. C.; Perales, J. B.; Vranken, D. L. V. *Org. Lett.* **2002**, *4*, 2337.

(8) Hara, N.; Nakamura, S.; Shibata, N.; Toru, T. *Chem. Eur. J.* **2009**, *15*, 6790.

reaction was performed in DMF at 4 °C in the presence of trifluoromethyl-substituted diarylprolinol **1**, which is an effective catalyst in the cross-aldol reaction of acetaldehyde. As the obtained product is unstable, it was isolated as diol **8a** after reduction with NaBH<sub>4</sub>, in which the diol **8a** was obtained in 62% yield with 49% ee (entry 1). To improve the enantioselectivity, the reaction conditions were investigated (Table 1). First, the additive was screened to discover

**Table 1.** Effect of Catalyst, Solvent, and Additive in the Aldol Reaction of Acetaldehyde and 1-Benzylisatin **7a**<sup>a</sup>



entry	catalyst	solvent	additive	time [h]	yield [%] <sup>b</sup>	ee [%] <sup>c</sup>
1	<b>1</b>	DMF		72	62	49
2	<b>1</b>	DMF	<i>p</i> NBA <sup>d</sup>	72	64	60
3	<b>1</b>	DMF	HCO <sub>2</sub> H	48	67	60
4	<b>1</b>	DMF	ClCH <sub>2</sub> CO <sub>2</sub> H	48	73	61
5	<b>2</b>	DMF	ClCH <sub>2</sub> CO <sub>2</sub> H	48	68	50
6	<b>3</b>	DMF	ClCH <sub>2</sub> CO <sub>2</sub> H	48	67	-20
7	<b>4</b>	DMF	ClCH <sub>2</sub> CO <sub>2</sub> H	48	58	-5
8	<b>5</b>	DMF	ClCH <sub>2</sub> CO <sub>2</sub> H	48	80	-21
9	<b>6</b>	DMF	ClCH <sub>2</sub> CO <sub>2</sub> H	48	78	73
10	<b>6</b>	CH <sub>2</sub> Cl <sub>2</sub>	ClCH <sub>2</sub> CO <sub>2</sub> H	48	65	25
11	<b>6</b>	toluene	ClCH <sub>2</sub> CO <sub>2</sub> H	48	35	29
12	<b>6</b>	CH <sub>3</sub> CN	ClCH <sub>2</sub> CO <sub>2</sub> H	48	69	50
13 <sup>e</sup>	<b>6</b>	DMF	ClCH <sub>2</sub> CO <sub>2</sub> H	48	55	86

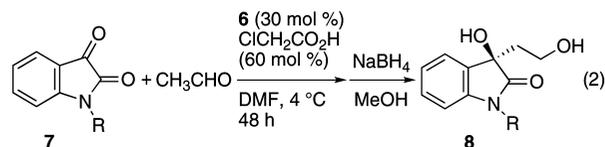
<sup>a</sup> Unless otherwise shown, reactions were performed employing 1-benzylisatin (**7a**) (0.3 mmol), acetaldehyde (1.5 mmol), catalyst (0.03 mmol), additive (0.06 mmol), and solvent (0.3 mL) at 4 °C for the indicated time. <sup>b</sup> Isolated yield. <sup>c</sup> Optical purity was determined by chiral HPLC analysis. <sup>d</sup> *p*-Nitrobenzoic acid. <sup>e</sup> Catalyst (0.09 mmol) and additive (0.18 mmol) were employed.

that a good yield with improved enantioselectivity was observed when the reaction was carried out in the presence of ClCH<sub>2</sub>CO<sub>2</sub>H<sup>14</sup> (entry 4). Then, the catalyst was investigated. When triethylsilyl ether **2** was employed, the enantioselectivity decreased (entry 5). Diphenylprolinol **3** and its trimethylsilyl ether **4** are not suitable (entries 6 and 7). In contrast to these unsuccessful results, 4-hydroxydiarylprolinol **6**, which was easily prepared from commercially available 4-hydroxyproline, gave good selectivity (73% ee, entry 9). It is interesting to note that the corresponding 4-hydroxydiphenylprolinol **5** is not effective (entry 8). After screening the solvent, DMF was found to be the best choice (entries 9–12). Increasing the loading of the catalyst afforded higher enantioselectivity (86% ee, entry 13).

Next, the protecting groups on the nitrogen were examined (Table 2). Although isatin itself does not react with acetaldehyde, not only Bn, but also *p*-methoxybenzyl, methoxymethyl, and triisopropylsilyloxymethyl groups are suitable protecting groups, affording the products with good enantioselectivity.

Under the optimized conditions, the generality of the reaction was examined with 5,7-dibromoisatin (**9**) and 4,6-dibromoisatin (**10**). Both reactions proceed efficiently, af-

**Table 2.** Effect of Protecting Group in the Aldol Reaction of Acetaldehyde and Isatin Derivative **7**<sup>a</sup>

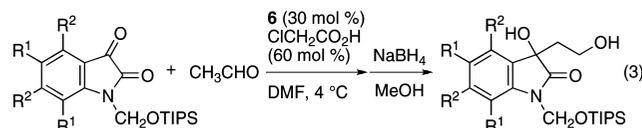


entry	R	yield [%] <sup>b</sup>	ee [%] <sup>c</sup>
1	Bn ( <b>7a</b> )	55	85
2	H ( <b>7b</b> )	<5	
3	PMB ( <b>7c</b> )	73	86
4	MOM ( <b>7d</b> )	72	86
5 <sup>d</sup>	TIPSOCH <sub>2</sub> ( <b>7e</b> )	73	85

<sup>a</sup> Unless otherwise shown, reactions were performed employing isatin derivative **7** (0.3 mmol), acetaldehyde (1.5 mmol), catalyst **6** (0.09 mmol), ClCH<sub>2</sub>CO<sub>2</sub>H (0.18 mmol), and DMF (0.3 mL) at 4 °C for 48 h. <sup>b</sup> Isolated yield. <sup>c</sup> Optical purity was determined by chiral HPLC analysis. <sup>d</sup> The reaction time is 72 h.

forming the diols **11** and **12** with good enantioselectivity (Table 3). It is interesting to note that the absolute configura-

**Table 3.** Generality of the Aldol Reaction of Acetaldehyde with Isatin Derivatives<sup>a</sup>



entry	R <sup>1</sup>	R <sup>2</sup>	time [h]	yield [%] <sup>b</sup>	ee [%] <sup>c</sup>
1	H	H ( <b>7e</b> )	72	73	85 ( <b>8e</b> ) ( <i>R</i> )
2 <sup>d</sup>	Br	H ( <b>9</b> )	48	83	81 ( <b>11</b> ) ( <i>R</i> )
3 <sup>d</sup>	H	Br ( <b>10</b> )	48	86	82 ( <b>12</b> ) ( <i>S</i> )

<sup>a</sup> Unless otherwise shown, reactions were performed employing isatin derivative (0.3 mmol), acetaldehyde (1.5 mmol), catalyst **6** (0.09 mmol), ClCH<sub>2</sub>CO<sub>2</sub>H (0.18 mmol), and DMF (0.3 mL) at 4 °C for 48 h. <sup>b</sup> Isolated yield. <sup>c</sup> Optical purity was determined by chiral HPLC analysis. <sup>d</sup> DMF (0.6 mL) was employed.

tions of **8e** and **11** are *R*, while that of **12** is opposite (vide infra).

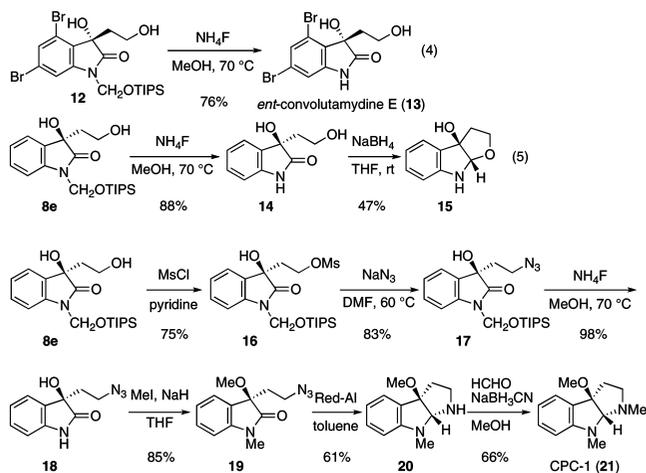
From these intermediates, the natural products or part of the natural product were synthesized as follows: The reaction of **12** with NH<sub>4</sub>F in MeOH at 70 °C gave *ent*-convolutamydine E (**13**) in 76% yield (eq 4, Scheme 1).

The reaction of **8e** with NH<sub>4</sub>F, followed by reduction with NaBH<sub>4</sub>, afforded 3a-hydroxyindole fragment **15**, which is known to be converted into madindoline A and B (eq 5, Scheme 1).

The reaction of **8e** with MsCl and pyridine gave mesylate **16**, which reacted with NaN<sub>3</sub> to provide azide derivative **17**.

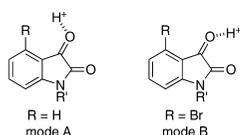
(14) We found chloroacetic acid is an effective additive in the Michael reaction, see: Ishikawa, H.; Suzuki, T.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 1304.

**Scheme 1.** Total Synthesis of *ent*-Convolutamydine E, a Half Fragment of Madindoline A and B, and CPC-1



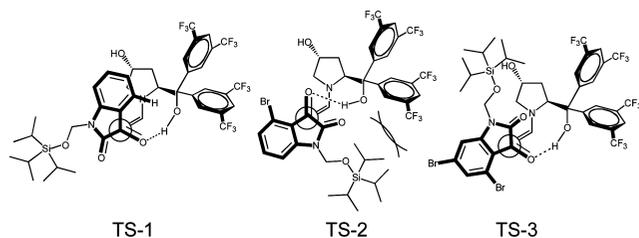
After removal of the triisopropylsiloxymethyl group with  $\text{NH}_4\text{F}$ , the reaction with  $\text{MeI}$  and  $\text{NaH}$  afforded **19**. Reductive amino cyclization with  $\text{Red-Al}$ , followed by reductive amination, gave CPC-1 (**21**) (Scheme 1).

The absolute configuration of **8e** and **11** is *R*, whereas that of **12** is *S*. The reversal of the enantioface selection by the substituent at C5 of the isatin derivative can be explained as follows, although it is very difficult to evaluate the effect of the 4-hydroxy group of the catalyst **6**. We proposed that the acidic proton of the hydroxy group of the diarylmethanol moiety of the catalyst **6** activates the electrophilic aldehyde in the cross-aldol reaction.<sup>9a</sup> A similar activation is expected in the reaction of isatin derivatives. That is, the proton of the hydroxy group of the catalyst **6** coordinates the carbonyl group of isatin, in which there are two protonation modes such as A and B (Figure 3). When the substituent at C5 of isatin is small, such as a



**Figure 3.** Coordination modes to isatin derivatives.

hydrogen atom, mode A would be suitable, and the reaction would proceed via transition state TS-1 to afford the *R*-isomer predominantly (Figure 4). On the other hand, when the



**Figure 4.** Transition state models.

substituent is large, such as a bromine atom, mode A is not suitable because of steric hindrance. Mode B would be the choice. While steric repulsion between the substituent on nitrogen and the aryl moiety of the catalyst **6** makes the transition state TS-2 unfavorable, TS-3 would be suitable, which would afford the *S*-isomer predominantly.

In summary, we have developed the asymmetric aldol reaction of isatin derivatives and acetaldehyde catalyzed by 4-hydroxydiarylprolinol as an organocatalyst, to afford the aldol product with high enantioselectivity. We applied the present method to the short syntheses of *ent*-convolutamydine E and CPC-1 and a half portion of madindoline A and B. There are several noteworthy features in the present reaction. (1) Newly developed diarylprolinol possessing the 4-hydroxy group is an effective catalyst. (2) Synthetically useful chiral intermediates for the synthesis of biologically active indole alkaloids can be synthesized with high enantioselectivity. (3) Reversal of the enantioface selection by the C5-substituent of isatin was observed.

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**Supporting Information Available:** Detailed experimental procedures, full characterization, copies of  $^1\text{H}$ ,  $^{13}\text{C}$  NMR, and IR spectra of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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