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First Enantioselective Synthesis of (*R*)-Convolutamydine B and E with *N*-(Heteroarenesulfonyl)prolinamides

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One of the rapidly developing research areas in the field of asymmetric synthesis is the catalytic reaction by using small organic molecules called organocatalysts. The enantioselective aldol reaction using organocatalysts is recognized to be one of the most powerful carbon–carbon bond-forming reactions.[1] Despite the significant progress of the enantioselective reaction of various aldehydes using organocatalysts, there have been only a few reports on the reaction using acetaldehyde. Very recently, Hayashi, List and Maruoka have reported the highly enantioselective reactions of acetaldehyde to aldehydes, imines, and β-nitrostyrenes using organocatalysts.[2] On the other hand, there are no reports for the organocatalytic enantioselective crossed-aldol reaction between acetaldehyde as a nucleophile and a ketone as an electrophile because of the higher reactivity of acetaldehyde as an electrophile.[3] Furthermore, the reaction of acetaldehyde with ketones constructs a stereogenic quaternary carbon center, therefore, this type of reaction is a significant challenge. In this report, we focused on the enantioselective synthesis of convolutamydine B and E by the reaction of acetaldehyde with ketones using organocatalysts. Convolutamydines A–E were isolated from the Floridian marine bryozoan *Amathia convoluta* by Kamano and co-workers.[4] Convolutamydines have a 4,6-dibromo-3-hydroxyoxindole as a common skeleton and different side chain moieties at a quaternary stereocenter on C-3. (*R*)-Convolutamydines A and B are known to exhibit potent inhibitory activity on the differentiation of HL-60 human promyelocytic leukaemia cells at 0.1 (convolutamydine A) and 12.5 $\mu g\,mL^{-1}$ (convolutamydine B).[4b,c] However, the possible biological effects of convolutamydine E have not been evaluated due to the scarcity of the compounds. Recently, the syntheses of enantiopure convolutamydines B and E through a diastereoselective approach[5] and the syntheses of enantiopure convolutamydine A through the enantioselective approaches using organocatalysts[6] or through a diastereoselective approach[7] have been reported. However, there is no report for the synthesis of optically active convolutamydines B and E through a catalytic enantioselective reaction. Recently, we have reported the synthesis of various (*R*)-convolutamydine A derivatives with high enantioselectivity by the reaction of acetone with isatins using novel bifunctional organocatalysts having heteroarylsulfonyl groups.[8,9] Here we report the first highly enantioselective synthesis of (*R*)-convolutamydines B and E using organocatalysts.

We first examined the reaction of 4,6-dibromoisatin (**1a**) with acetaldehyde in the presence of various chiral organocatalysts **3**–**5**. The reaction was carried out using 10 mol% of organocatalysts, five equivalents of acetaldehyde, and five equivalents of H_2O at room temperature. After the aldol reaction, the obtained intermediate aldehyde was reduced by $NaBH_3CN$ in acetic acid to give (*R*)-convolutamydine E (**2a**). The results are shown in Table 1.

Moderate or low enantioselectivity was obtained in the reaction using proline **3** or diarylprolinol **4**, which afforded good results in the reaction of acetaldehyde with aldehydes, imines, and β-nitrostyrene (entries 1 and 2).[2a–f,h–j] On the other hand, the reaction using the TFA salt of *N*-(*p*-toluenesulfonyl)prolinamide (**5a**) rapidly proceeded to give (*R*)-**2a** in high yield with 90% *ee*, whereas *N*-(methanesulfonyl)prolinamide (**5b**) showed lower enantioselectivity (entries 3 and 4). After optimization experiments of the arylsulfonyl group in sulfonimides **5**, we found *N*-(2-thiophenesulfonyl)prolinamide (**5f**) to be an efficient organocatalyst in the reaction of **1a** with acetaldehyde (entries 5–10). Solvent screening revealed that a number of solvents were suitable, and THF was found to afford the best result (entries 11–15, see also Supporting Information). When the reaction was carried out at −15 °C, the enantioselectivity improved slightly, but in low yield (entry 17). The reaction using **5f** without water af-

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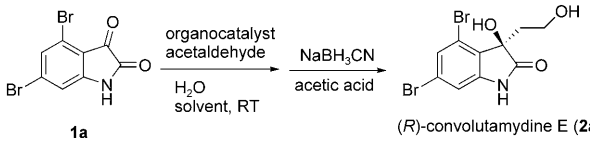
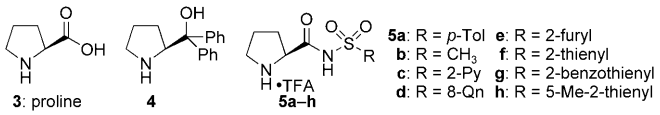
Table 1. Enantioselective addition of acetaldehyde to **1a** in the presence of various organocatalysts **3**–**5**.[a]

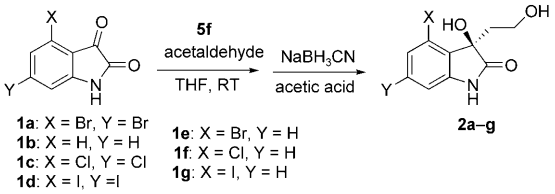




Run	Catalyst (mol %)	Solvent	Reaction time [h]	Yield [%]	*ee*[b] [%]
1	**3** (10)	THF	48	62	60
2	**4** (10)	THF	60	67	3
3	**5a** (10)	THF	40	84	90
4	**5b** (10)	THF	23	56	41
5	**5c** (10)	THF	50	77	80
6	**5d** (10)	THF	50	65	49
7	**5e** (10)	THF	36	71	79
8	**5f** (10)	THF	36	94	92
9	**5g** (10)	THF	30	78	90
10	**5h** (10)	THF	36	78	87
11	**5f** (10)	1,4-dioxane	36	99	90
12	**5f** (10)	CH_3CN	36	89	89
13	**5f** (10)	DMF	45	42	91
14	**5f** (10)	DMSO	45	44	90
15	**5f** (10)	neat	36	99	89
16	**5f** (5)	THF	48	62	90
17[c]	**5f** (10)	THF	120	67	93
18[d]	**5f** (10)	THF	48	99	92
19[e]	**5f** (10)	THF	48	63	88

[a] Reaction conditions: Organocatalyst (10 mol %), acetaldehyde (5 equiv), H_2O (5 equiv), $NaBH_3CN$ (5 equiv). [b] *ee* was determined by chiral HPLC analysis. [c] The reaction was carried out at −15 °C. [d] Without water. [e] Without TFA and H_2O.

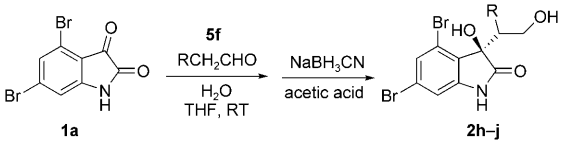
Table 2. Enantioselective synthesis of convolutamydine E derivatives **2a**–**g**.[a]



Entry	Isatin	Product	Reaction time [h]	Yield [%]	*ee*[b,c] [%]
1	**1a**	**2a**	36	94	92 (>99)
2	**1b**	**2b**	48	60	2
3	**1c**	**2c**	36	77	86
4	**1d**	**2d**	60	97	92 (98)
5	**1e**	**2e**	48	99	92
6	**1f**	**2f**	60	80	89
7	**1g**	**2g**	60	73	92

[a] Reaction conditions: **5f** (10 mol %), acetaldehyde (5 equiv), $NaBH_3CN$ (5 equiv). [b] *ee* was determined by HPLC analysis. [c] *ee* in parentheses is that obtained after single recrystallization.

Table 3. Enantioselective synthesis of convolutamydine E derivatives **2h**–**j**.[a]



Entry	R	Product	*t* [h]	Yield [%]	d.r.	*ee*[b] [%]
1	Me	**2h**	60	94	70:30	98, 97
2	Et	**2i**	60	80	>98:2	93, –
3	$PhCH_2$	**2j**	120	98	97:3	90, 9
4	*i*Pr	**2l**	144	–	–	–

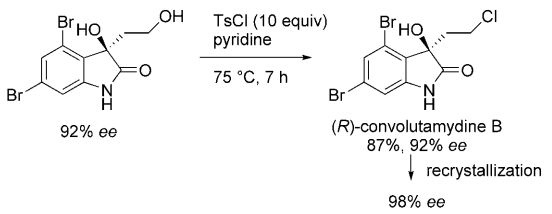
[a] Reaction conditions: **5f** (10 mol %), aldehyde (5 equiv), H_2O (5 equiv), $NaBH_3CN$ (5 equiv). [b] *ee* was determined by HPLC analysis.

forded **2a** without loss of enantioselectivity, although the reaction without water and TFA afforded **2a** in low yield (entries 18 and 19). It should be noted that most of **5f** was recovered by a single separation by column chromatography and was reusable without further purification.

We next examined the preparation of various convolutamydine E derivatives **2a–g** using **5f**. The results for the reaction using 10 mol % of **5f** are shown in Table 2. Although the reaction of unsubstituted isatin (**1b**) with acetaldehyde gave product **2b** in good yield but with low enantioselectivity, the reaction of substituted isatins **1c–g** gave products **2c–g** with high enantioselectivity (entries 2–7). As most of the products were crystalline, almost enantiomerically pure convolutamydine E derivatives were easily obtainable by recrystallization. For example, single recrystallization of **2a** with 92 % *ee* from hexane/ethyl acetate afforded almost enantiomerically pure **2a** (Table 2, entry 4).

We also examined the reaction of **1a** with various aldehydes in the presence of 10 mol % of **5f**. Although the reaction with 2-methylbutanal did not afford any products, the reaction with linear aldehydes afforded the products in high yield with good enantioselectivity (Table 3).

We also examined the preparation of convolutamydine B. (*R*)-Convolutamydine E (92 % *ee*) was treated with TsCl (10 equiv) in pyridine at 75 °C to give (*R*)-convolutamydine B in high yield without loss of enantiopurity (Scheme 1). Single recrystallization of convolutamydine B with 92 % *ee* afforded almost enantiomerically pure (*R*)-convolutamydine B. The absolute stereochemistry of convolutamydine B was assigned to be *R* in comparison with the CD spectrum reported in the literature.[5] To our knowledge, this is the first report on the synthesis of convolutamydine B and E with high enantiopurity using chiral catalysts.



Scheme 1. Synthesis of convolutamydine B from convolutamydine E.

Although it is premature to provide a detailed mechanistic explanation at this level, the reaction using **5f** proceeds through a transition state having hydrogen bonding between the amide proton and the 2-thienyl sulfur atom in **5f** to give the (*R*)-isomer of the product (Figure 1).

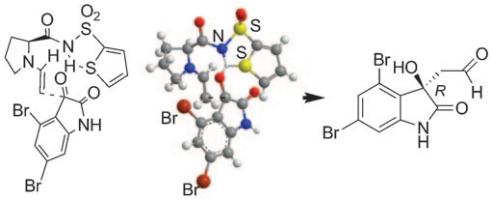


Figure 1. Assumed transition state for the crossed-aldol reaction of **1a** with acetaldehyde using **5f**.

In conclusion, the first enantioselective synthesis of convolutamydine E through a catalytic enantioselective aldol reaction of acetaldehyde with isatins using *N*-(2-thiophenesulfonyl)prolinamide (**5f**) has been developed. To the best of our knowledge, this is the first highly enantioselective crossed-aldol reaction of acetaldehyde with ketones. We also showed the synthesis of enantiopure convolutamydines B and E. Further studies are in progress to study the potential of these catalytic systems to other processes and the reaction mechanism.

Experimental Section

Typical procedure for the aldol reaction using 5f: (*R*)-Convolutamydine E (**2a**): To a mixture of **5f** (3.7 mg, 0.01 mmol), acetaldehyde (28 μL, 0.5 mmol) and water (9.0 μL, 0.5 mmol), **1a** (30.5 mg, 0.1 mmol) was added at room temperature. After stirring for 48 h, the solvent was removed under reduced pressure to give a residue that was reduced by $NaBN_3CN$ (31 mg, 0.5 mmol) in acetic acid (1.0 mL). After stirring for 3 h, aqueous HCl (1.0 mL, 1 mol L^{-1}) was added, and the mixture was extracted with Et_2O. The combined organic extracts were concentrated under reduced pressure to give a residue that was purified by column chromatography (hexane/ethyl acetate 70:30) giving **2a** (34.7 mg, 99%, 92% *ee*). Single recrystallization of **2a** (92% *ee*) from hexane/ethyl acetate afforded >99% *ee* of **2a**.

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Keywords: aldehydes · aldol reaction · enantioselectivity · heteroarylsulfonyl group · organocatalysis

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