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Enantioselective Synthesis of (*R*)-Convolutamydine A with New *N*-Heteroarylsulfonylprolinamides

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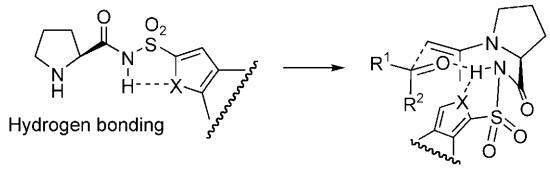
Convolutamydine A is an alkaloid that was isolated from the Floridian marine bryozoan *Amathia convoluta* by Kamano and co-workers in 1995.[1] (*R*)-Convolutamydine A exhibits a potent inhibitory activity towards the differentiation of HL-60 human promyelocytic leukaemia cells at 0.1–25 $\mu g\,mL^{-1}$. In 2006, Gargen and Tomasini's group reported the first enantioselective synthesis of natural (*R*)-convolutamydine A through a direct aldol reaction of 4,6-dibromoisatin with acetone by using 10 mol% of a peptidic catalyst derived from D-proline and L-β^2-homophenylgricine.[2,3] Very recently, Xiao and co-workers reported the same reaction with 20 mol% of a chiral bisamide, prepared from a chiral diamine and L-proline, as an organocatalyst to give 60% enantionmeric excess (*ee*) of the unnatural (*S*)-convolutamydine A.[4] Malkov and co-workers reported the synthesis of (*R*)-convolutamydine A with high enantiopurity (up to 94% *ee*) by using 20 mol% of D-leucinol prepared from unnatural D-leucine; however, it takes a long time (RT, 36 h) for the reaction to reach completion.[5,6] Unsolved problems include high catalyst loading and the use of organocatalysts derived from unnatural α-amino acids to prepare (*R*)-convolutamydine A. On the other hand, organocatalytic aldol reactions with ketones as acceptors generally need a high catalyst loading (at least 5–10 mol%) of organocatalyst,[7] whereas enantioselective aldol reactions with aldehydes have been achieved with low catalyst loading of organocatalysts.[8] Recently, we and others have reported enantioselective reactions that use 2-point coordinative heteroarylsulfonyl groups, which can control the transition state (TS) or intermediates by chelation with chiral Lewis acids[9] or organocatalysts.[10] To overcome the difficulty of the enantioselective reaction between 4,6-dibromoisatin as the ketone acceptor and acetone, we designed novel natural *N*-heteroarylsulfonylprolinamide organocatalysts,[11,12] which would enable the TS to be controlled by intramolecular hydrogen bonding between the sulfonimide NH proton and the heteroatom of the heteroaryl group (Scheme 1). Herein, we report the highly efficient synthesis of (*R*)-convolutamydine A and its derivatives by using a catalytic amount of novel *N*-heteroarylsulfonylprolinamide organocatalyst.



Scheme 1. The heteroarylsulfonyl group as a novel stereocontroller in an organocatalyst.

We first examined the reaction of 4,6-dibromoisatin **1a** with acetone in the presence of sulfonimides **2** that have various aryl- or alkylsulfonyl groups. The reaction was carried out by using 10 mol% of **2a**–**h** and 10 equivalents of H_2O in acetone (200 equiv) at room temperature. The results are shown in Table 1. The reaction was catalyzed by using *p*-tolylsulfonimide (**2a**) and rapidly proceeded to give (*R*)-convolutamydine A (**3a**) in good yield and 86% *ee*, whereas the reaction with methylsulfonimide (**2b**) showed lower enantioselectivity (entries 1, 2). We found *N*-(2-thienylsulfonyl)prolinamide (**2f**) and *N*-(2-benzothienylsulfonyl)prolinamide (**2g**) to be efficient organocatalysts in the reaction of **1a** with acetone after optimization experiments with the arylsulfonyl group in the sulfonimides (entries 6, 7). We decided to systematically study the asymmetric performance of **2f** because the preparation of **2f** is more convenient than that of **2g**. The enantioselectivity was improved in reactions performed at lower temperatures, although the reactivity was lowered (entries 9, 10). We found that the catalyst loading

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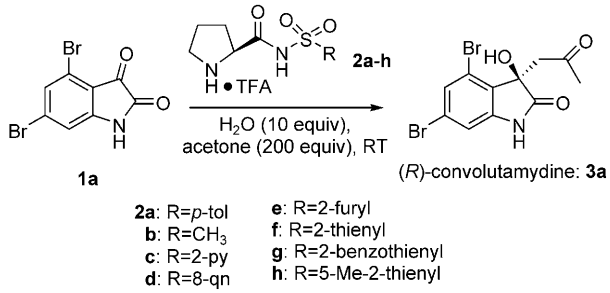
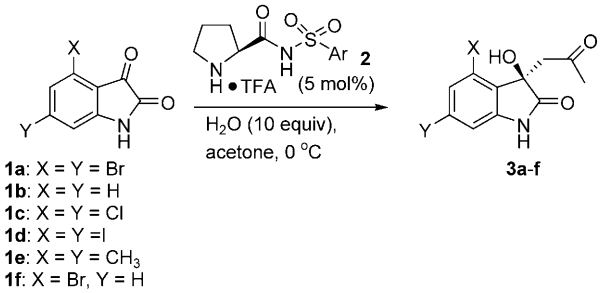
Table 1. Enantioselective addition of acetone to 4,6-dibromoisatin in the presence of *N*-sulfonylprolinamide **2a–h**.[a]



Entry	Catalyst [mol %]	R	Reaction time [h]	Yield [%]	*ee*[b] [%]
1	**2a** (10)	*p*-tol	1	85	86
2	**2b** (10)	CH_3	13	83	51
3	**2c** (10)	2-py	3	86	80
4	**2d** (10)	8-qn	4	91	66
5	**2e** (10)	2-furyl	2	84	88
6	**2f** (10)	2-thienyl	3	92	93
7	**2g** (10)	2-benzothienyl	7	95	92
8	**2h** (10)	5-Me-2-thienyl	2	81	87
9[c]	**2f** (10)	2-thienyl	7	90	96
10[d]	**2f** (10)	2-thienyl	45	98	97
11[c]	**2f** (5)	2-thienyl	8	99	96
12[c]	**2f** (2)	2-thienyl	20	98	96
13	**2f** (0.5)	2-thienyl	132	70	92
14[e]	**2f** (5)	2-thienyl	2.5	99	78
15	**2f** (5)[f]	2-thienyl	3.5	99	87

[a] TFA = trifluoroacetic acid, tol = tolyl, py = pyridyl, qn = quinolyl. [b] The *ee* was determined by using chiral HPLC analysis. [c] Reaction at 0 °C. [d] Reaction at −20 °C. [e] Without water. [f] Without TFA.

Table 2. Enantioselective synthesis of convolutamydine A derivatives **3a–f**.



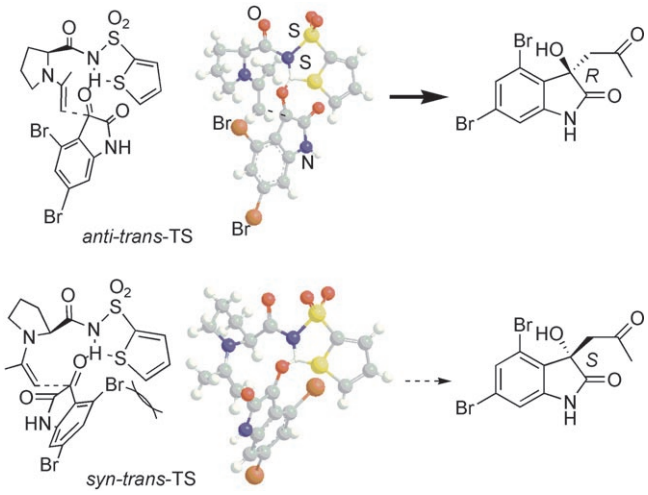
Entry	Isatin	Catalyst	Reaction time [h]	Yield [%]	*ee*[a] [%]
1	**1a**	**2f**	9	99	95 (*R*) (>99)[b]
2	**1b**	**2f**	8	99	3 (*S*)
3[c]	**1b**	**2d**	14	50[d]	77
4	**1c**	**2f**	20	90	93 (>99)[b]
5	**1d**	**2f**	24	>99	97 (>99)[b]
6[e]	**1e**	**2f**	40	59	92 (>99)[b]
7	**1f**	**2f**	22	93	97 (>99)[b]

[a] The *ee* was determined by HPLC analysis. [b] *ee* values in parentheses were obtained after a single recrystallization procedure. [c] The reaction was carried out by using *N*-benzylated isatin at room temperature. [d] *N*-Benzylated product was obtained. [e] The reaction was carried out at room temperature.

of **2f** can be reduced to 2 mol % without loss of enantioselectivity (entries 11, 12). Although the reactivity is reduced, the reaction catalyzed by 0.5 mol % of **2f** at room temperature gave **3a** without loss of enantioselectivity (entry 6 vs. entry 13). To the best of our knowledge, these results represent the lowest catalyst loading reported to date in the direct aldol reaction with a ketone as an electrophile. Interestingly, the reaction in the absence of water gave **3a** with lower enantioselectivity than that with water (entry 14). The reaction using catalyst **2f** without TFA afforded **3a** with slightly lower enantioselectivity than that using **2f** only (entry 15).

We next examined the preparation of various convolutamydine A derivatives **3a–f** by using **2f**. The results with 5 mol % of **2f** are shown in Table 2. Although the reaction of unsubstituted isatin **1b** with acetone gave **3b** in excellent yield but low enantioselectivity, the reaction of *N*-benzylisatin catalyzed with **2d** afforded **3b** with good enantioselectivity (entries 2 and 3). The reaction of substituted isatins, such as 4,6-dichloro-, 4,6-diiode-, 4,6-dimethyl, and 4-bromoisatins **1c–f**, gave **3c–f** with high enantioselectivity (entries 4–7). Recrystallization of 95 % *ee* convolutamydine A from hexane/ethyl acetate afforded enantiomerically pure (*R*)-convolutamydine (Table 2, entry 1).

Although it is premature to provide a detailed mechanistic explanation at this stage, we propose that the hydrogen bonding between the amide proton and the 2-thienyl sulfur atom in the chiral organocatalyst **2f** plays an important role in the enantioselectivity because **2f** showed higher enantioselectivity than **2a**. There are two plausible TSs, that is, the *anti-trans*-TS and the *syn-trans*-TS. The reaction using **2f** preferentially proceeds through the *anti-trans*-TS to give (*R*)-**3a** because the *syn-trans*-TS, which gives (*S*)-**3a**, is destabilized by a steric repulsion between the 4-bromo and 2-thienyl groups, as shown in Scheme 2. A similar conclusion has been drawn from a DFT calculation of the L-proline-catalyzed aldol reaction of 4-bromoisatin with acetone.[13]



Scheme 2. Assumed TS for the direct aldol reaction of **1a** with acetone, catalyzed by **2f**

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In conclusion, *N*-(2-thienylsulfonyl)prolinamide (**2f**) was found to work as an efficient organocatalyst. Various convolutamydine A derivatives were obtained with high enantioselectivity by using only 0.5 mol% of **2f**. To our knowledge, this is the lowest catalyst loading in the aldol reaction of acetone with ketones to give a product with high enantioselectivity. Further studies are in progress to study the reaction mechanism and the potential of these catalytic systems in other processes.

Experimental Section

Typical procedure for the aldol reaction catalyzed by 2f to give (*R*)-Convolutamydine A (3a): 4,6-Dibromoisatin **1a** (25 mg, 0.082 mmol) was added to a mixture of **2f** (1.5 mg, 0.004 mmol) and water (14 μL, 0.8 mmol) in acetone (1.2 mL, 16.4 mmol) at 0 °C. After stirring for 8 h, the solvent was removed under reduced pressure to give a residue that was purified by column chromatography (eluent: hexane/ethyl acetate, 50:50) to give **3a** (29.6 mg, 99%, 95% *ee*). A single recrystallization of **3a** (95% *ee*) afforded >99% *ee* of **3a**.

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Keywords: aldol reaction · enantioselectivity · heteroarylsulfonyl groups · hydrogen bonds · organocatalysis

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