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Organocatalytic Enantioselective Decarboxylative Addition of Malonic Acids Half Thioesters to Isatins

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Abstract: The organocatalytic enantioselective decarboxylative addition of malonic acids half thioesters to isatins using a squaramide catalyst afforded the products with high enantioselectivity. These products are key intermediates in the synthesis of 3-substituted 3-hydroxy-2-oxindole derivatives. The first enantioselective synthesis of (−)-flustraminol B has been accomplished.

Keywords: aldol reaction; decarboxylative addition; enantioselectivity; organic catalysis

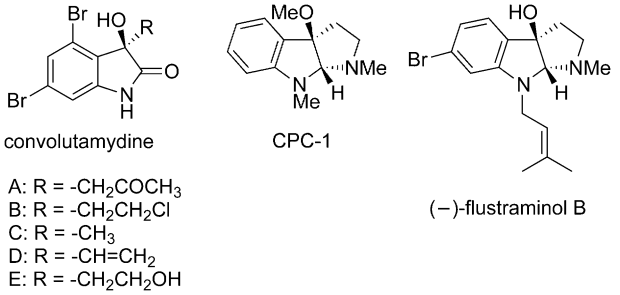


Figure 1. Biologically active compounds containing 3-substituted 3-hydroxy-2-oxindole derivatives.

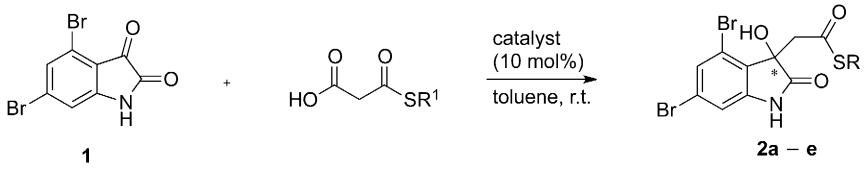
The development of mild, catalytic and enantioselective versions of C–C bond forming processes is a topic of paramount importance in modern organic chemistry. In this context, the enantioselective aldol reaction of ketones as electrophiles using organocatalysts continues to attract a great deal of interest, as it provides an efficient access to chiral tertiary alcohols.[1] In particular, the utilization of isatin as an electrophile has attracted much attention because the reaction affords chiral 3-substituted 3-hydroxy-2-oxindole derivatives, which are an important structural motif in biologically active compounds such as convolutamydines, CPC-1 and (−)-flustraminol B (Figure 1).[2]

Recently, we[3] and other groups[4] have reported the highly enantioselective reaction of isatins with various ketones and aldehydes using novel proline-derived organocatalysts through enamine activation. However, it is difficult to use proline-derived catalysts in the reaction of isatin with ester enolates. In general, the catalytic generation of ester enolates is not a trivial task due to the low acidity of α-protons of esters.[5] Recently, the asymmetric decarboxylative addition of malonic acid half-thioesters (MAHTs) as ester enolate equivalents to various electrophiles has been reported.[6,7] Although these MAHTs are very attractive candidates for the generation of ester enolate equivalents under very mild reaction conditions, there are no reports on the enantioselective decarboxylative addition of MAHTs to ketones as well as isatins. Therefore, the development of new synthetic methods to achieve high enantioselectivity in decarboxylative aldol condensations between MAHTs and isatins is highly desirable. Herein our ongoing interest was extended to the enantioselective reaction of isatins with ester enolate equivalents by the decarboxylative aldol reaction of MAHTs using various bifunctional organocatalysts.

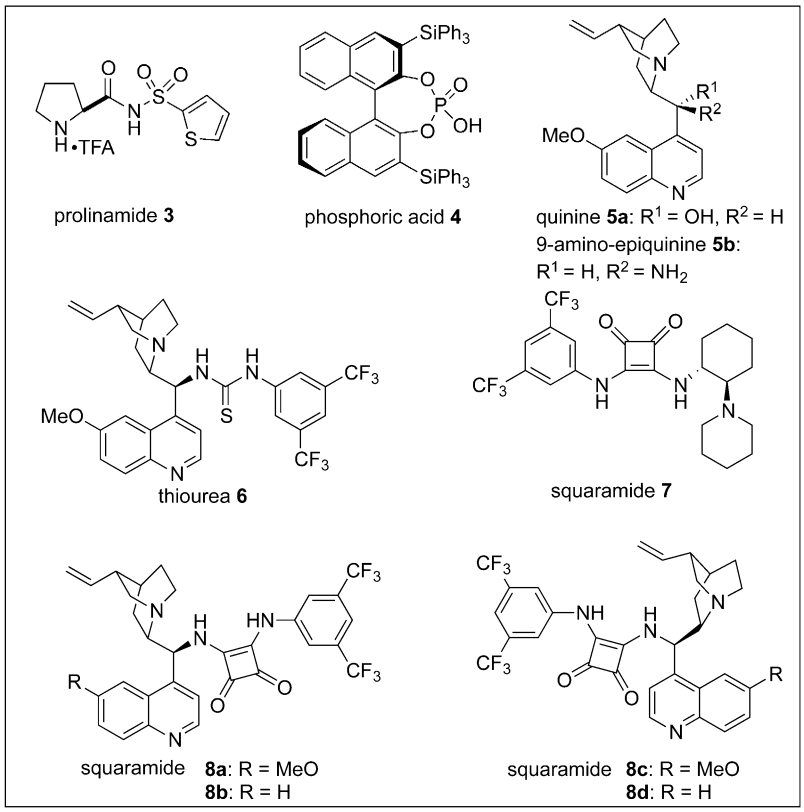
We first examined the reaction of 4,6-dibromoisatin with MAHTs in the presence of various chiral organocatalysts **3**–**8**. The results are shown in Table 1.

The control experiment without any catalyst did not give product **2a** (run 1). Previously, our studies on the reaction of isatin with acetone or aldehydes have shown that proline-derived organocatalyst **3** is an effective promoter. Therefore, we first tried to use prolinamide **3** for the reaction of 4,6-dibromoisatin **1** with MAHT to give the product **2a** in 56% yield but with 9% *ee* (run 2). Chiral phosphoric acid **4** did not give the product **2a** (run 3). Quinine **5a**, 9-amino-epi-

Table 1. Decarboxylative aldol reaction of isatins with MAHTs using various organocatalysts.



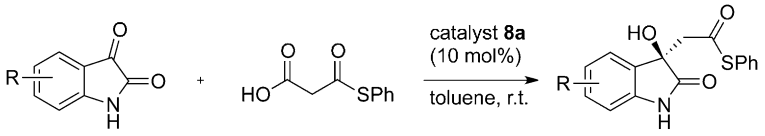
1 **2a – e**



Run	Cat.	R^1	**2**	Time [h]	Yield [%]	*ee* [%][a,b]
1	–	Ph	**2a**	24	–	–
2	**3**	Ph	**2a**	48	56	9 (*R*)
3	**4**	Ph	**2a**	24	–	–
4	**5a**	Ph	**2a**	24	87	37 (*R*)
5	**5b**	Ph	**2a**	36	93	10 (*R*)
6	**6**	Ph	**2a**	36	77	18 (*R*)
7	**7**	Ph	**2a**	48	95	84 (*S*)
8	**8a**	Ph	**2a**	48	96	87 (*R*)
9	**8b**	Ph	**2a**	48	91	83 (*R*)
10	**8c**	Ph	**2a**	48	94	63 (*S*)
11	**8d**	Ph	**2a**	48	87	74 (*S*)
12	**8a**	*p*-MeO-C_6H_4	**2b**	48	92	70 (*R*)
13	**8a**	*p*-Cl-C_6H_4	**2c**	48	83	72 (*R*)
14	**8a**	*t*-Bu	**2d**	60	trace	–
15	**8a**	Bn	**2e**	60	41	76 (*R*)
16[c]	**8a**	Ph	**2a**	120	89	83 (*R*)
17[d]	**8a**	Ph	**2a**	48	94	87 (*R*)

[a] The *ee* value was determined by HPLC analysis.
[b] The absolute configuration of **2** is provided in parentheses.
[c] Catalyst loading is 5 mol%.
[d] In an open flask.

Table 2. Substrate scope.



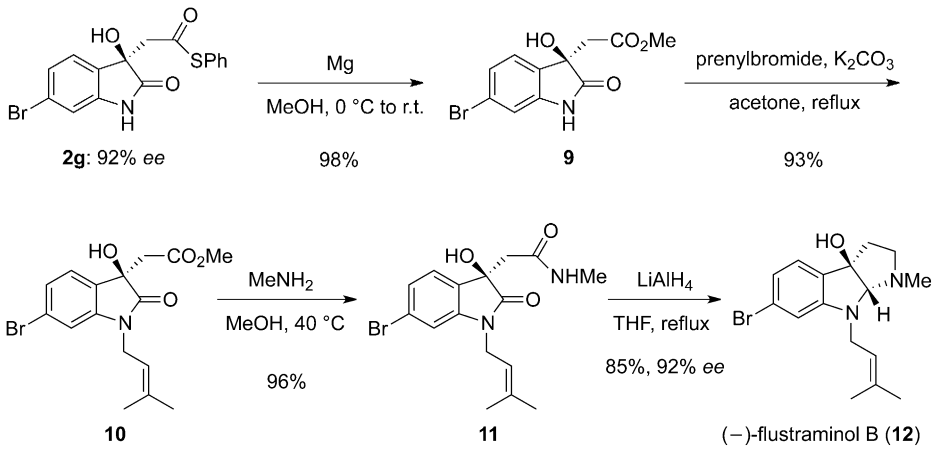
Entry	R	Product	Time [h]	Yield [%]	*ee* [%][a,b]
1	4,6-Br_2	**2a**	48	96	87
2	4-Br	**2f**	48	90	87
3	6-Br	**2g**	48	96	63 (92)
4	5,7-Br_2	**2h**	20	88	86
5	H	**2i**	36	96	46 (89)
6	4-Cl	**2j**	48	99	83
7[c]	4,6-I_2	**2k**	48	93	92
8	4-I	**2l**	48	91	91

[a] The *ee* value was determined by HPLC analysis.
[b] The *ee* value in parentheses is that obtained after a single recrystallization.
[c] Catalyst loading is 20 mol%.

quinine **5b** and thiourea **6** activated the reaction to give **2a** in good yield but with low enantioselectivity (runs 4–6). In contrast to these results, the reaction using bifunctional squaramides **7** and **8a–d**, which were developed by Rawal,[8] improved the enantioselectivity of product (runs 7–11). The chiral squaramide **8a** finally proved to be the catalyst of choice. We next examined the reaction of **1** with various MAHTs using catalyst **8a**. Although *tert*-butylthio ester and benzylthio ester gave products **2d** and **2e** in low yield, good yields and enantioselectivities were obtained in the reaction with arylthio esters **2b** and **2c** (runs 12–15).[9] Best enantioselectivity was obtained in the reaction using phenylthio ester (run 8). Furthermore, the catalyst loading of **8a** can be reduced to 5 mol% without a significant loss of enantioselectivity (run 16). Furthermore, the decarboxylative addition reaction affords the product with a large amount of CO_2, which contains the risk of high pressure and the potential for an explosion. Therefore, we attempted the reaction in an open flask. This reaction also gave the product with high enantioselectivity (run 17).

With these optimized conditions, the reaction of a series of isatins and MAHTs using **8a** was examined (Table 2).

Although the reaction of non-substituted isatin afforded product **2i** with moderate enantioselectivity, the use of a variety of isatins such as 4,6-dibromo-, 4-bromo-, 6-bromo-, 5,7-dibromo-, 4-chloro-, 4,6-diiodo- and 4-iodoisatins afforded the corresponding products (**2f–l**) in good to excellent yields with high enantioselectivity (entries 1–8). As most of the products were crystalline compounds, the enantiopurity of the products can be improved by recrystallization. For example, a single recrystallization of **2g** and **2i** from hexane/AcOEt afforded **2g** and **2i** with a high enantiopurity (entries 3 and 5). The absolute configuration of product **2i** was determined by X-ray crystallogra-



Scheme 1. Synthesis of optically active (−)-flustraminol B **12**.

phy (see Supporting Information), and the stereochemistry of other products was tentatively assumed by analogy.

We next tried to convert product **2g** to chiral flustraminol B (Scheme 1). Flustraminol B is a marine alkaloid that was isolated from the marine bryozoan *Flustra foliacea* by Christophersen and Carlé.[10] There is only one report on the synthesis of racemic flustraminol B by Suárez-Castillo and co-workers.[11] The absolute configuration of the hydroxy group at the C-3 position could further modulate the biological activity. Although it is of high importance to introduce chirality at the C-3 position for flustraminol B with high enantiocontrol, there are no reports on the enantioselective synthesis of flustraminol B. To illustrate the synthetic potential of this methodology, we synthesized optically active flustraminol B, as shown in Scheme 1. The reaction of 92% *ee* of **2g** with Mg/MeOH, followed by alkylation with prenylbromide afforded compound **10**, which can be converted to (−)-flustraminol B in high yield without loss of enantiopurity. To the best of our knowledge, this is the first report on the enantioselective synthesis of flustraminol B.

Preliminary experiments have been performed to elucidate the mechanism of the reaction. 3,4-Bis[3,5-bis(trifluoromethyl)phenylamino]cyclobut-3-ene-1,2-dione did not mediate the decarboxylation reaction of MAHTs. Furthermore, 9-amino-epi-quinine **5b** can activate the reaction, but low enantiopurity of the product is obtained (Table 1, entry 5). These results imply that catalyst **8a** could act in a bifunctional manner, as previously proposed in the literature for chiral squaramide catalysts.[8] The proposed activating mechanism for the reaction of isatin with MAHTs using a chiral squaramide catalyst is shown in Figure 2. The squaramide functionality could activate MAHTs by double hydrogen bonding, and the deprotonation and decarboxylation of carboxylic acid in MAHTs at a basic site in squaramide was carried out to give the thioester enolate. Next, two carbonyl oxygens from isatin coordinate to hydrogen from protonated **8a**. The addition of the thioester enolate to isatin in the coordination sphere of the chiral squaramide led to a product with high enantioselectivity.

From the above considerations and the absolute configurations of products, the transition state for the reaction of the thioester enolate to isatin using a chiral squaramide catalyst **8a** is proposed (Figure 3). Since the thioester enolate approaches the *Si*-face of isatin, therefore the (*R*)-isomer is preferably formed. Further studies are required to fully elucidate the mechanistic detail of the addition reaction.

In conclusion, we have developed a highly enantioselective decarboxylative addition of MAHTs to isatins. To the best of our knowledge, this is the first example for the decarboxylative addition of MAHTs to ketones. The obtained products can be converted to chiral flustraminol. This example is the first report for the enantioselective synthesis of (−)-flustraminol B. Further studies focusing on the scope of the asymmetric transformations of isatins are currently under investigation and will be reported in due course.

Experimental Section

Typical Procedure

To a solution of isatin **1a** (0.1 mmol, 30.4 mg) and catalyst **8a** (0.01 mmol, 3.2 mg) in toluene (0.5 mL), malonic acid half thioester (0.11 mmol, 21.6 mg) was added and the mixture was stirred for 48 h. After removal of solvent, the residue was purified by column chromatography on silica gel (eluent: hexane/acetone, 70:30) to afford (*R*)-**2a** as a white solid; yield: 43.9 mg (96%).

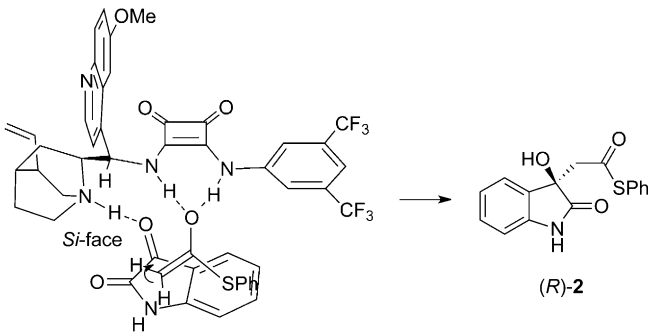


Figure 3. Assumed transition state for the decarboxylative addition of MAHTs to isatins.

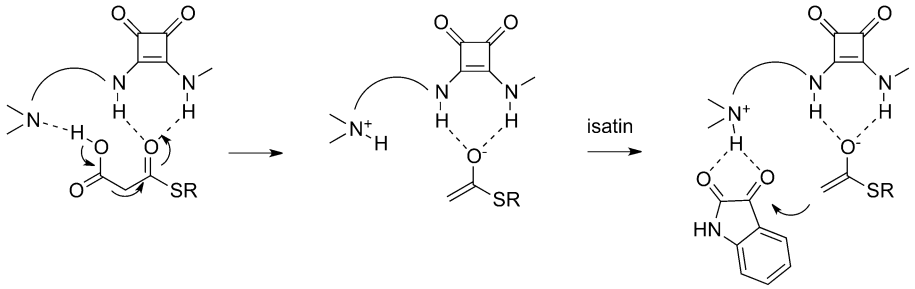


Figure 2. Proposed reaction mechanism for decarboxylative addition of MAHTs to isatins using bifunctional organocatalysts.

Acknowledgements

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