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Highly efficient construction of chiral dispirocyclic oxindole/thiobutyrolactam/chromanone complexes through Michael/cyclization cascade reactions with a rosin-based squaramide catalyst

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ABSTRACT

An efficient asymmetric Michael/cyclization cascade reaction of 4-chromanones with isothiocyanato oxindoles has been revealed. Under bifunctional organocatalysis by rosin-based squaramide catalyst, a series of spiro[oxindole/thiobutyrolactam/chromanone] complexes were conveniently constructed in a highly stereoselective manner (up to 99% yields, > 20:1 *dr* and >99% *ee*). The reaction leads to the formation of three contiguous stereogenic centers and two spiro quaternary stereocenters.

1. Introduction

Highly efficient construction of complex spirocyclic skeletons has attracted great interest due to the remarkable biological activities of spirocyclic compounds.[1] In particular, spiro heterocyclic oxindoles have emerged as one of the most important synthetic targets, as it incorporates structural and pharmaceutical features from both oxindoles and other heterocyclic moieties simultaneously. Thus, considerable efforts have been devoted to access this highly valuable heterocyclic architecture.[2]

As another privileged heterocyclic ring system, chromanone or 4-benzopyrone is featured in a large number of natural products as well as pharmacologically active compounds.[3] Spirocyclic chromanone derivatives, in particular, have significant biological activities and some recent representative examples are shown in Fig. 1, such as a histone deacetylases (HDAC) inhibitor **A** with good in vitro ADME profile,[4] a potent anti-hepatitis C virus (HCV) agent **B**,[5] an acetyl-CoA carboxylase (ACC) inhibitor **C**[6] and a natural product **D**[7] isolated from Chinese caterpillar fungus. However, up to now, catalytic asymmetric synthetic methods for spirocyclic chromanone are very rare.[8] For instance, Wang et al. reported an organocatalytic domino Michael/aldol reaction sequence that leads to chiral spirocyclic chromanone-thiochromans.[8a] Wang et al. constructed spirocyclic chromanone-pyrrolidines *via* copper-catalyzed asymmetric 1,3-dipolar cycloaddition reaction.[8b] Alternatively, Liang and co-workers recently disclosed a platinum-catalyzed cascade reaction for the construction of spirobenzo[*h*]chromanone derivatives.[8c] Despite these impressive efforts, in view of the importance of chromanone in drug discovery, it is still highly desirable to develop efficient methods to generate structurally diverse chiral spirocyclic chromanones.

Therefore, we envisioned that the combination of oxindole and chromanone might result in a class of spirocyclic chromanone-oxindoles derivatives which potentially benefitting drug discovery. Moreover, its stereo-controlled synthesis, particularly the

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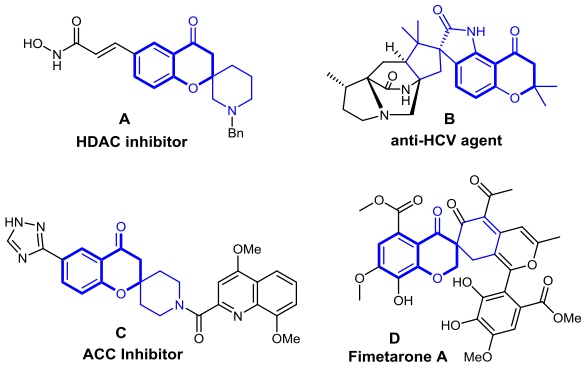
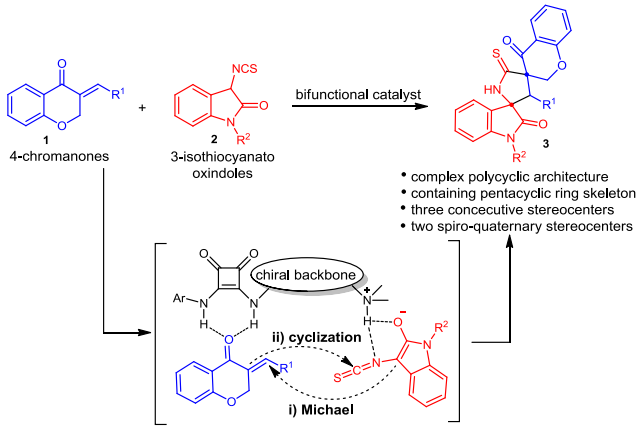


Fig. 1. Representative examples of bioactive spiro chromanones.

installation of multiple stereogenic centers, poses a great synthetic challenge. Recently, isothiocyanato oxindoles have proved to be highly robust and versatile Michael donors.[8g,9] Meanwhile, unsaturated 4-chromanones were successfully employed as exocyclic olefine Michael acceptors.[8a,8d-g,10] Inspired by these achievements, herein we present an example of rosin-derived squaramide catalyzed stereoselective synthesis of dispirocyclic oxindole/thiobutyrolactam/chromanone complexes (**3**) by a Michael addition/cyclization cascade reaction between (*E*)-3-benzylidenechroman-4-ones (**1**) and 3-isothiocyanato oxindoles (**2**) (Scheme 1).

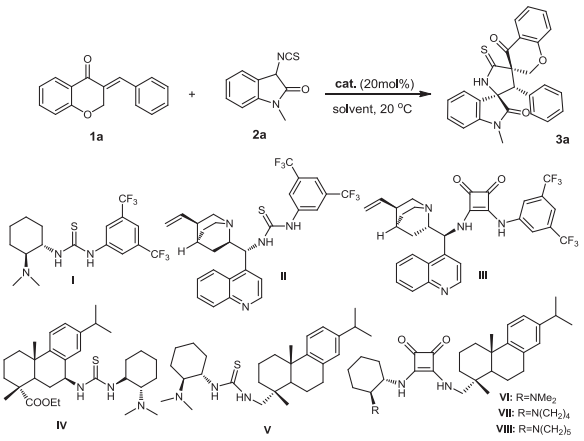
2. Results and discussion

Initially, (*E*)-3-benzylidenechroman-4-one (**1a**) and 3-iso-thiocyanato oxindole (**2a**) were selected as the model substrates to examine the possibility of the designed asymmetric Michael addition/cyclization sequence. In continuation of our research interest on organocatalysis,[11] a series of common bifunctional thiourea and squaramide organocatalysts were screened,[12] and representative results were summarized in Table 1. To our delight, the expected reaction proceeded smoothly in CH_2Cl_2 at 20 °C in the presence of 20 mol% Takemoto's catalyst **I**[13] or cinchona alkaloid-derived bifunctional catalysts (**II** and **III**),[14] affording the spirocyclic product **3a** in 87–89% yields with high diastereomeric ratio (*dr*) but only moderate *ee* (entries 1–3). These results indicated that the chiral backbones of the catalysts were important for control of the stereochemistry. Inspired by the excellent structural backbone and well defined stereocenters of rosin derivatives, a series of rosin-derived thiourea catalysts (**IV** and Wang's catalyst **V**[15]) and a new



Scheme 1. Proposed strategy for the construction of dispirocyclic chromanone-oxindoles through an organocatalytic cascade Michael-cyclization sequence.

Table 1
Optimization of the reaction conditions.[a]



Entry	Cat.	Solvent	Yield[b] [%]	*dr*[c]	*ee*[d] [%]
1	**I**	CH_2Cl_2	89	11:1	−48
2	**II**	CH_2Cl_2	87	14:1	46
3	**III**	CH_2Cl_2	87	>20:1	−87
4	**IV**	CH_2Cl_2	85	>20:1	44
5	**V**	CH_2Cl_2	98	7:1	23
6	**VI**	CH_2Cl_2	89	>20:1	97
7	**VII**	CH_2Cl_2	90	>20:1	86
8	**VIII**	CH_2Cl_2	93	>20:1	83
9	**VI**	toluene	86	>20:1	86
10	**VI**	Et_2O	78	6:1	72
11	**VI**	THF	93	16:1	92
12	**VI**	DCE	91	>20:1	>99
13[e]	**VI**	DCE	85	>20:1	99
14[f]	**VI**	DCE	80	>20:1	99
15[g]	**VI**	DCE	78	>20:1	94
16[h]	**VI**	DCE	99	>20:1	99

[a] Unless otherwise noted, the reaction was performed on a 0.05 mmol scale of **1a** and **2a** (1.1 equiv.), using 20 mol% catalyst in solvent (2 mL) at 20 °C.
[b] Isolated yield.
[c] Determined by ^1H NMR spectroscopy of the crude mixture.
[d] Determined by HPLC using a Daicel Chiralpak AD-H column.
[e] 10 mol% catalyst was used.
[f] 5 mol% catalyst was used.
[g] 1 mol% catalyst was used.
[h] Performed at 35 °C with 10 mol% catalyst loading and 10 mol% catalyst was used.

class of squaramide catalysts[16] (**VI**, **VII** and **VIII**) were prepared and investigated (entries 6–8). We were pleased to observe that a new squaramide catalyst **VI**, which contains a dehydroabietic amine backbone, gave rise to the product with a much higher enantioselectivity (97% *ee*, entry 6). Further screening of the solvents revealed that 1,2-dichloroethane was better than other solvents (Table 1, entries 9–12). Decreasing the catalyst loading from 20 mol % to 10 mol%, 5 mol% and 1 mol%, respectively (entries 12–15), the reaction also gave good yields without sacrificing the stereoselectivity. Ultimately, elevating the reaction temperature to 35 °C led to shorter reaction time (12 h) and higher yield with excellent stereoselectivities (99% yield, >20:1 dr and 99% *ee*).

With the optimized reaction conditions in hand, the generality of this cascade reaction was explored. In Table 2, a wide array of benzylidenechroman-4-ones **1a**-**1p** reacted smoothly with 3-isothiocyanato oxindole **2a** to afford the corresponding spiro [oxindole/thiobutyrolactam/chromanone] complexes with excellent yields and stereoselectivities (Table 2, entries 1–16). It appears that the positions and the electronic properties of the substituents on the aromatic ring of arylidenechroman-4-ones have minimal effects on the enantioselectivities. Generally, benzylidenechroman-