Enantioselective heterocyclic synthesis of spiro chromanone–thiochroman complexes catalyzed by a bifunctional indane catalyst†

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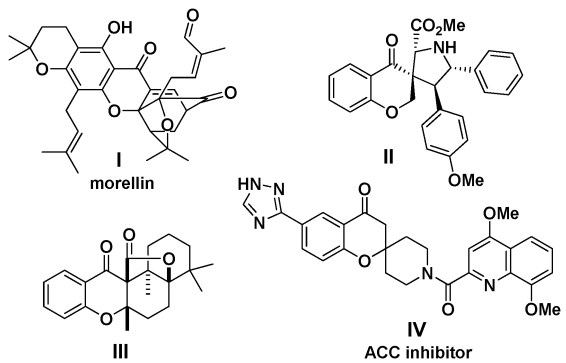
Novel asymmetric domino reactions of benzylidenechroman-4-ones and 2-mercaptobenzaldehydes for efficient construction of spiro chromanone–thiochroman complexes were accomplished with high yields and excellent selectivities *via* a novel bifunctional indane catalyst.

The structural complexity and well-defined three-dimensional architecture of natural molecules are generally correlated with specificity of action and potentially useful biological properties.[1] This complexity has inspired a generation of synthetic chemists to design novel enantioselective strategies for assembling challenging target structures and reproducing the rich structural diversity inherent in natural molecules.[2]

Highly functionalized 4-chromanones have attracted much attention due to their significant pharmacological properties.[3] They are also versatile intermediates for the synthesis of many natural products such as brazilin, hematoxylin, riparichromene and clausenin.[4] As the core component, the spirocyclic 4-chromanone is featured in a large number of pharmacologically active compounds as well as natural products.[3b] Naturally occurring compound morellin **I** (Scheme 1) and complex **II** exhibit significant biological and pharmacological properties, such as antibacterial, antifungal and antitumor activities.[3a,b] Compound **III**[5] has the typical nucleus of sesquiterpene-phenols, marine natural products with potential antimalarial, antituberculosis, and antiviral properties. Acetyl-CoA carboxylase (ACC) inhibitor **IV**[6] and its derivatives demonstrate the potential to favorably affect the multitude of risk factors associated with metabolic syndrome, obesity and type-2 diabetes. However, its stereo-controlled synthesis, particularly installing the novel stereogenic spiro center, poses a great synthetic challenge. Thereby efficient stereoselective synthesis is highly desirable. Only a few asymmetric transformations, such as 1,3-diploar cycloaddition reaction, have proven to be suitable for achieving this challenging goal. However, to the best of our knowledge, to date there has been no report on catalytic enantioselective synthesis of spiro chromanone–thiochroman complexes. Furthermore, thiochroman, as an important building block, is also frequently observed in natural products and pharmaceutical drugs with many potential biological activities.[7] Therefore, the combination of chromanone and thiochroman (spiro structure) may introduce some unprecedented benefits to drug discovery.



Scheme 1 Examples of biologically active spiro chromanones.

Following in the footsteps of asymmetric organocatalysis,[8] several closely organocatalytic systems have emerged as powerful tools to address many various challenging synthetic problems, and have resulted in the synthesis of complex molecules *via* a one-pot process.[9] One of the big advantages of such one-pot domino reactions over classical synthesis is that at least two reactions are carried out in a single operation under the same reaction conditions. Furthermore, this avoids time-consuming, costly protecting-group manipulations as well as the isolation of reaction intermediates. In this way, molecular complexity will be achieved quickly, often accompanied by high levels of stereoselectivity. Inspired by these protocols, we herein report a one-pot cyclization reaction (Scheme 2) for efficient synthesis of spiro chromanone–thiochroman heterocycles in excellent enantioselectivity and yield, using bifunctional indane amine-thiourea catalyst **5** (Fig. 1) which was developed by our group. The notable features of this protocol include (1) in this particular reaction, indane catalyst **5** provides an excellent stereo-control (92–99% ee, up to 57 : 1 d.r.); (2) a ring-fused spiro chromanone–thiochroman complex with three contiguous stereogenic centers and one quaternary carbon is generated in a one-pot manner under mild conditions with high yields (93–98%).

To probe the feasibility of the proposed asymmetric cyclization reaction, (*E*)-3-benzylidenechroman-4-one (**7a**) was reacted with 2-mercaptobenzaldehyde (**6a**) in the presence of Takemoto's amine-thiourea catalyst **1**[10] (Fig. 1) and Connon,[11] and Soós's[12] cinchona alkaloid amine-thiourea catalyst **2** (Fig. 1) in CH_2Cl_2 at room temperature. Catalysts **1** and **2**, as two of the most successful bifunctional amine-thiourea catalysts, have been applied to many asymmetric transformations. As shown in Table 1, 85 and 86% ee were achieved with 97 and 91% yields, respectively. However, both catalysts **1** and **2** only provide moderate diastereoselectivity (Table 1; 2.3 : 1 and 2.4 : 1 d.r., respectively). To the best of our knowledge, the dihedral angle between two functional groups is one of the key issues for stereo-control. We envisioned that a

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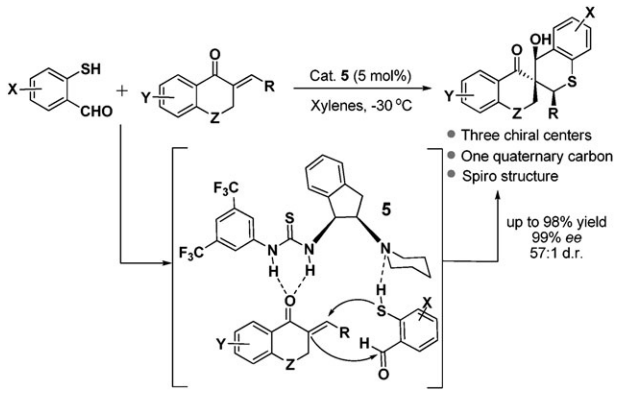


Scheme 2 Strategy for the synthesis of chiral spiro chromanone–thiochroman complex.

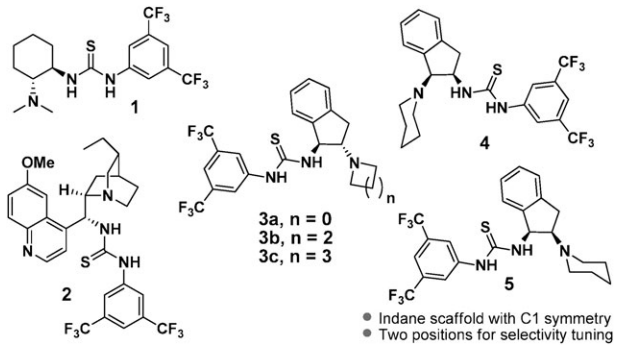
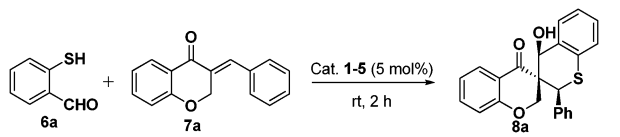


Fig. 1 Evaluated bifunctional amine-thiourea organocatalysts.

Table 1 Influence of the bifunctional organocatalyst and optimization of asymmetric cyclization reaction conditions[a]



Entry	Catalyst	Yield[b] (%)	d.r.[c]	ee (%)[d]
1	**1**	97	2.3 : 1	85
2	**2**	91	2.4 : 1	−86
3	**3a**	97	1.6 : 1	78
4	**3b**	90	1.5 : 1	67
5	**3c**	89	1.5 : 1	77
6	**4**	93	1.5 : 1	−82
7	**5**	98	5.0 : 1	93
8[e]	**5**	97	6.3 : 1	97
9[f]	**5**	97	7.0 : 1	97
10[g]	**5**	**96**	**8.0 : 1**	**97**
11[h]	**5**	94	6.4 : 1	94

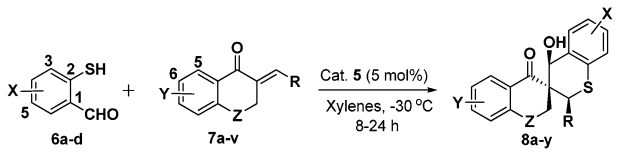
[a] Reaction was conducted on 0.1 mmol scale in DCM (1.0 mL), and the ratio of **6a** : **7a** is 1 : 1.2. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis of the crude mixture. [d] Determined by HPLC analysis. [e] Xylenes as solvent. [f] Reaction was performed in xylenes at 0 °C for 3 h. [g] Reaction was performed in xylenes at −30 °C for 8 h. [h] Reaction was performed in xylenes at −50 °C for 24 h.

change of the dihedral angle between the functional groups of the amine and thiourea might introduce an ideal and stable transition state to assist the generation of excellent stereoselectivity. Takemoto's amine-thiourea catalyst **1** has a cyclohexane scaffold with C_2 symmetry. Therefore, the exchange of two functional group positions will not affect the dihedral angle. For the cinchona alkaloid amine-thiourea catalyst **2**, from a synthetic aspect, the quinuclidine structure (amine part) is very difficult to modify. To this challenge, we feel that the introduction of a novel scaffold with C_1 symmetry might change this situation and solve the stereo-control problem. Inspired by this hypothesis, we were impressed by an ideal indane scaffold. It has some impressive features: (1) a scaffold with C_1 symmetry; (2) exchange of two functional group positions will obviously adjust the dihedral angle; (3) commercially available starting material, chiral indane amino alcohol, from a synthetic standpoint, will benefit to the functional group modification in an efficient and concise manner.

To explore the rationality of our proposed rational design, a series of indane amine-thiourea catalysts **3–5** has been synthesized (for synthetic details see ESI†). It includes (1) modifications on the conformation of amine functional group (catalyst **3a**, **3b** and **3c**); (2) a specific alternation on the relative orientation of amine and thiourea functional groups (catalysts **3c** and **5**); (3) adjustment of the relative positions of amine and thiourea functional groups (catalysts **4** and **5**). Eventually, the novel catalyst **5** was discovered as an ideal promoter to catalyze this one-pot cyclization process under the same condition as above (Table 1, entry 7). Surprisingly, this reaction proceeded smoothly to furnish the desired product **8a** in 98% yield and much improved selectivity (entry 7; 93% ee and 5.0 : 1 d.r.). Upon investigating a variety of other reaction parameters, such as temperature, concentration and solvent, we found that the desired reaction manifold could be achieved through an appropriate choice of solvent and temperature. Therefore, by conducting the one-pot cyclization reaction in xylenes under optimized temperature (−30 °C) condition, we can efficiently generate the spiro complex target, which bears three contiguous stereocenters.

After the optimal conditions had been established, the generality of this catalytic process was explored. Remarkably, this enantioselective one-pot cyclization process can serve as an efficient synthetic route for the preparation of spiro chromanone–thiochromans (Table 2). Significantly, the new stereogenic centers were efficiently created in high enantioselectivities (92–99% ee) and good to excellent diastereoselectivities (1.2 : 1 to 57 : 1 d.r.) in a one-pot manner. Moreover, the process afforded a new spiro center, and also significant structural variation of (*E*)-3-alkyl and arylenechroman-4-ones **7** could be tolerated (Table 2, entries 1–16 and 19–25 when R = aryl; entries 17–18 when R = alkyl). The process also bore the replacement of O by S and C to introduce different heterocycles (entries 19 and 20). The experimentation revealed that the electronic and steric nature had obvious effect on diastereoselectivity (entries 4, 7, 17 and 18), but minimal impact on efficiency and enantioselectivity. The **5**-promoted asymmetric cyclization process also took place with a variety of 2-mercaptobenzaldehyde Michael donors, which possess neutral (entries 1–22), electron-donating (entries 23 and 24) and electron-withdrawing groups (entry 25). In each case, the process proceeded rapidly (8–24 h), in high yields (93–98%), high to excellent enantiomeric excesses (92–99% ee) and diastereomeric ratios (1.2 : 1 to 57 : 1 d.r.). The absolute configuration of the spiro chromanone–thiochroman **8e** was unequivocally determined by single-crystal X-ray diffraction

Table 2 Preliminary substrate scope of the asymmetric cyclization reaction catalyzed by indane amine-thiourea **5**[a]



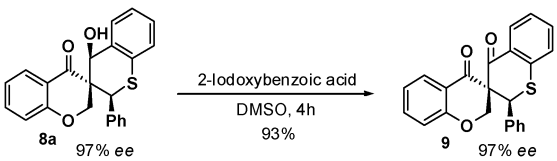
6a-d 7a-v 8a-y

Entry	X	Y	Z	R	Yield[b] (%)	d.r.[c]	ee[d] (%)
1	H	H	O	Ph (**8a**)	96	8.0 : 1	97
2	H	H	O	4-ClC_6H_4 (**8b**)	98	8.1 : 1	95
3[e]	H	H	O	3-ClC_6H_4 (**8c**)	96	7.6 : 1	97
4	H	H	O	2-BrC_6H_4 (**8d**)	97	19 : 1	95
5	H	H	O	4-$NO_2C_6H_4$ (**8e**)	97	7.7 : 1	97
6	H	H	O	3,4-$Cl_2C_6H_3$ (**8f**)	97	8.2 : 1	95
7	H	H	O	2-F,4-ClC_6H_3 (**8g**)	95	20 : 1	97
8	H	H	O	4-$MeOC_6H_4$ (**8h**)	96	8.0 : 1	96
9	H	H	O	4-$AllyloxyC_6H_4$ (**8i**)	96	8.0 : 1	96
10	H	H	O	2-$AllyloxyC_6H_4$ (**8j**)	98	11 : 1	99
11	H	H	O	3-$PhOC_6H_4$ (**8k**)	97	10 : 1	98
12	H	H	O	4-*i*PrC_6H_4 (**8l**)	97	8.0 : 1	97
13	H	H	O	6-Br-benzodioxole (**8m**)	98	17 : 1	98
14	H	H	O	5-Me-furan (**8n**)	96	8.4 : 1	96
15	H	H	O	2-Thiophene (**8o**)	98	8.3 : 1	97
16	H	H	O	1-Naphthyl (**8p**)	95	4.5 : 1	95
17	H	H	O	Isopropyl (**8q**)	96	57 : 1	95
18	H	H	O	Cyclohexyl (**8r**)	98	24 : 1	96
19	H	H	CH_2	Ph (**8s**)	96	10 : 1	95
20	H	H	S	Ph (**8t**)	97	1.2 : 1	96
21	H	6-CH_3	O	Ph (**8u**)	98	16 : 1	97
22	H	6-Cl	O	Ph (**8v**)	97	11 : 1	98
23	5-CH_3	H	O	Ph (**8w**)	96	9.0 : 1	96
24	5-OMe	H	O	Ph (**8x**)	97	15 : 1	95
25	5-Cl	H	O	Ph (**8y**)	93	8.0 : 1	92

[a] Unless specified, see the Experimental section for reaction conditions. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis of the crude mixture. [d] Determined by HPLC analysis. [e] Room temperature.

analysis of the Ts-derived spiro chromanone–thiochroman **12** (see ESI†).

Because of the potential biological activities exhibited by the spiro ring system, structural elaboration of the spiro 4-chromanone core is also extremely important. Spiro chromanone–thiochromanone complex **9** has been considered as a useful intermediate and thus we wish to discover an efficient way to afford it. Surprisingly, the oxidation of **8a** *via* 2-iodoxybenzoic acid (IBX) afforded the desired compound **9** with an excellent reaction yield (93%) but without any loss of enantiomeric excess (from 97% ee to 97% ee) [eqn (1)]. Meanwhile, the large scale synthesis from 0.5 g of **6a** demonstrated that there was no obvious alteration on the reaction results (94% yield, 7.9 : 1 d.r., and 97% ee).



8a 97% *ee* 9 97% *ee* (1)

In conclusion, we have developed an efficient asymmetric cyclization reaction, catalyzed by our developed chiral bifunctional indane amine-thiourea catalyst **5**. A broad substrate scope of spiro chromanone–thiochromans were obtained. Further application of the catalytic system to other new reactions is currently under investigation.

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