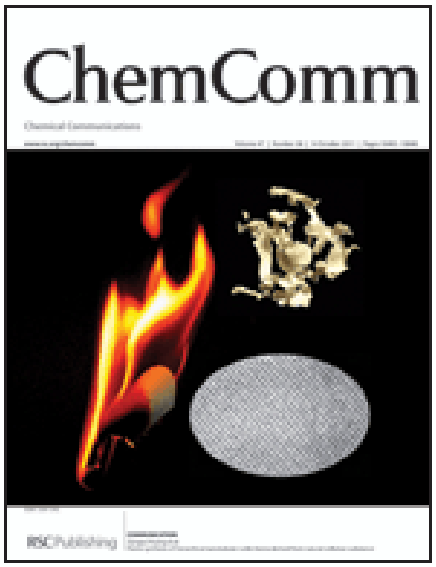

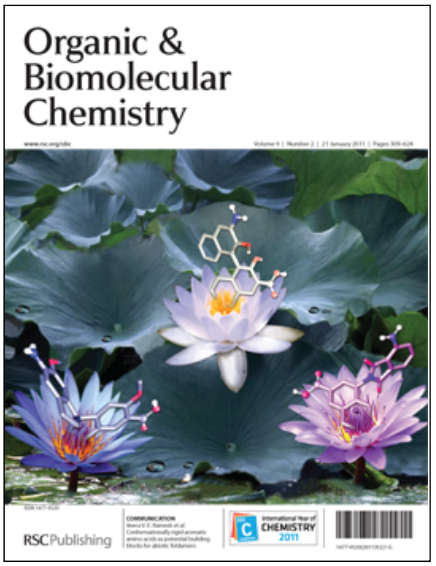

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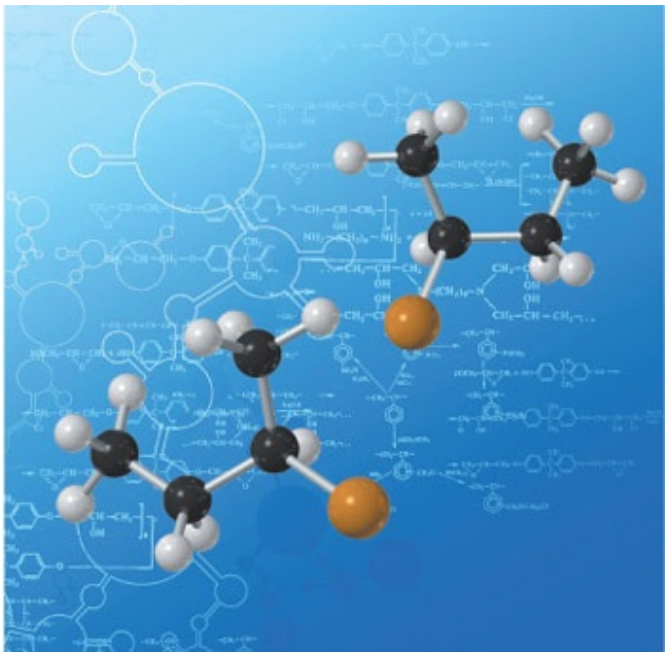

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COMMUNICATION

An organocatalytic Michael-aldol cascade: formal [3 + 2] annulation to construct enantioenriched spirocyclic oxindole derivatives†‡

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An efficient organocatalytic Michael-aldol cascade reaction for the asymmetric synthesis of spirocyclic oxindole derivatives fused with tetrahydrothiophenes has been developed through a formal [3 + 2] annulation strategy.

Spirocyclic oxindoles have emerged as attractive synthetic targets in chemical science due to their prevalence in a wide range of bioactive alkaloids and pharmacologically important compounds.[1] Moreover, the three dimensional structural properties of spirooxindoles have evoked immense interest from the synthetic standpoint. Accordingly, great impressive advances have been documented for the stereoselective synthesis of spirocyclic oxindoles fused with pyrrolidines,[2] piperidines,[3] pyrans,[4] tetrahydropyrans,[5] tetrahydrofurans,[6] cyclopropanes,[7] and other five-[8] or six-membered carbocycles.[9] For example, Barbas and coworkers developed an elegant organocatalytic asymmetric cascade Michael-aldol reaction, providing excellent stereocontrol of the newly formed spirocycle.[8f] This recent achievement paves the way for the development of a novel organocatalytic strategy for construction of spirocyclic oxindole derivatives. In this context, however, successful examples for assembly of optically active spirocyclic oxindoles bearing biologically and synthetically important tetrahydrothiophene motifs are still unknown to date. Furthermore, considering the correlation between the potential bioactivities and their molecular diversities, the development of new and general approaches to chiral spirooxindole–tetrahydrothiophenes with functional diversity is still highly desirable.

Pioneered by Jørgensen *et al.*[10] and Wang *et al.*,[11] diversely substituted tetrahydrothiophenes[12] can be efficiently obtained in high yield and stereoselectivity utilizing the secondary amine as the imine–enamine cycle promoter. However, these reactions are generally limited to the unsaturated aldehydes. On the other hand, a literature survey showed that the simple and commercially available 1,4-dithiane-2,5-diol (the dimer of mercaptoacetaldehyde) has proved to be an attractive synthon for construction of thiophene and tetrahydrothiophene derivatives.[13] However, highly stereoselective incorporation of 1,4-dithiane-2,5-diol into the tetrahydrothiophenes scaffold has been largely unexplored.[14] Also, as part of our ongoing program on the development of carbon- and heterocycle-oriented methodologies,[15] we described herein a Michael-aldol cascade between 3-ylideneoxindoles and 1,4-dithiane-2,5-diol, which provided an efficient access to a new family of tetrahydrothiophene-fused spirooxindoles bearing three consecutive stereogenic centers.

At the outset of our investigation, a series of organocatalysts were evaluated in the selected reaction of (*E*)-ethyl 2-(1-methyl-2-oxoindolin-3-ylidene)acetate **1a**[16] and **2** in dichloromethane at room temperature (Fig. 1). As shown in Table 1, despite short reaction time and good chemical yields, the cinchona alkaloid **I** and thiourea-tertiary amine catalysts **II–IV** could only give the desired cycloadduct **3a** with up to 23% ee (entries 1–4). Further optimizations showed that a substantial increase of enantioselectivity was observed by employing cinchona-based squaramide **V** as the H-bond donor[17] (entry 5). Moreover, the reaction could afford the opposite enantiomer of **3a** with similar stereoselectivity by changing the cinchonidine-derived squaramide **V** to its quinidine

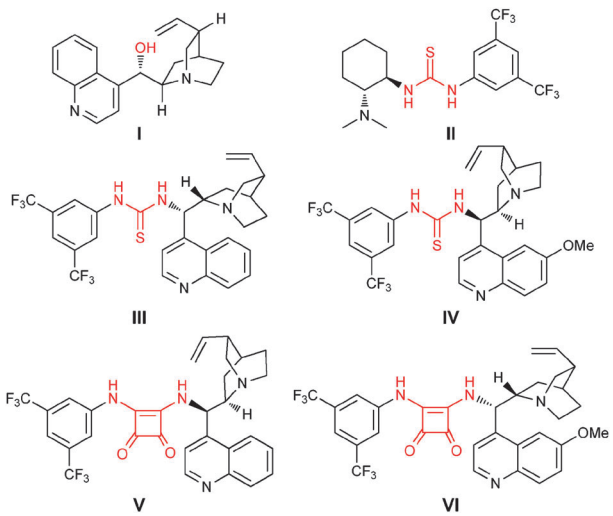

Fig. 1 The organocatalysts tested in this study.

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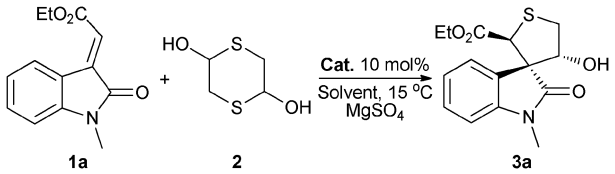
Table 1 Condition optimizations[a]



Entry	Cat.	Solvent	Time	Yield (%)[b]	dr[c]	ee (%)[d]
1	**I**	CH_2Cl_2	1 h	80	5 : 1	23
2	**II**	CH_2Cl_2	1 h	80	4 : 1	−7
3	**III**	CH_2Cl_2	1 h	89	10 : 1	−18
4	**IV**	CH_2Cl_2	0.5 h	92	10 : 1	−13
5	**V**	CH_2Cl_2	1 h	95	>19 : 1	79
6	**VI**	CH_2Cl_2	2 h	94	>19 : 1	−80
7	**V**	PhMe	10 h	98	>19 : 1	68
8	**V**	Et_2O	10 h	92	>19 : 1	55
9	**V**	THF	0.5 h	95	>19 : 1	69
10	**V**	$CHCl_3$	1 h	98	>19 : 1	76
11[e]	**V**	CH_2Cl_2	0.5 h	97	>19 : 1	79
12[f]	**V**	CH_2Cl_2	7 h	92	>19 : 1	84

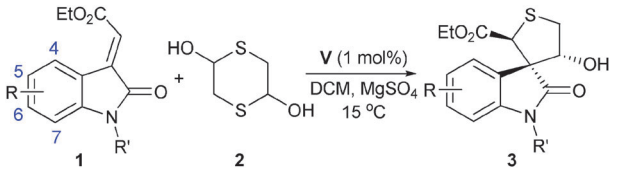
[a] Unless otherwise specified, all reactions were carried out with **1a** (0.3 mmol), **2** (0.18 mmol), cat. (10 mol%), $MgSO_4$ (36 mg) in the solvent (1 mL) at 15 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR of the reaction mixture. [d] Determined by chiral HPLC analysis. [e] The reaction was conducted with 0.3 mmol of **2**. [f] The reaction was conducted with 1 mol% of **V** in CH_2Cl_2 (10 mL).

analogue **VI** (entry 6). Subsequent screening of the solvents indicated a slight variation in diastereoselectivity but significant solvent-dependence in enantioselectivity (entries 7–10). The increasing loading of 1,4-dithiane-2,5-diol had little impact on the efficiency of the reaction (entry 11). Importantly, when the catalyst loading was reduced from 10 to 1 mol% cycloadduct **3a** still maintained the high yield and enantioselectivity while with a slightly prolonged reaction time (entry 12).

Then, this Michael-aldol cascade reaction was extended to a variety of other 3-ylideneoxindoles in the presence of 1 mol% squaramide **V** under the optimized conditions. The results are summarized in Table 2. It was found that most reactions with different substituents at C5–C7 positions were completed within 12 h, affording the corresponding products in excellent yields and good enantioselectivities (entries 2–12). The results indicated that the position and electronic property of the substituents had a reasonable effect on the diastereoselectivity (4 : 1 dr to >19 : 1 dr). The 3-ylideneoxindoles with benzyl and allyl groups on the nitrogen atom were also well tolerated to give the cycloadducts in excellent yields and diastereoselectivities with good ee values (entries 11 and 12). Perhaps more importantly, this strategy readily provided a facile access to the enantiomers simply by changing the cinchonidine-based squaramide **V** to its quinidine analogue **VI**. Slightly higher enantioselectivities were observed within the similar reaction time (entries 13–15). To determine the absolute configuration of the cycloadducts, single crystals suitable for X-ray crystallographic analysis were fortunately obtained from **3a** that bears a sulfur atom. As shown in Scheme 1, it contains a (*C8R*, *C10R*, *C12S*) configuration.

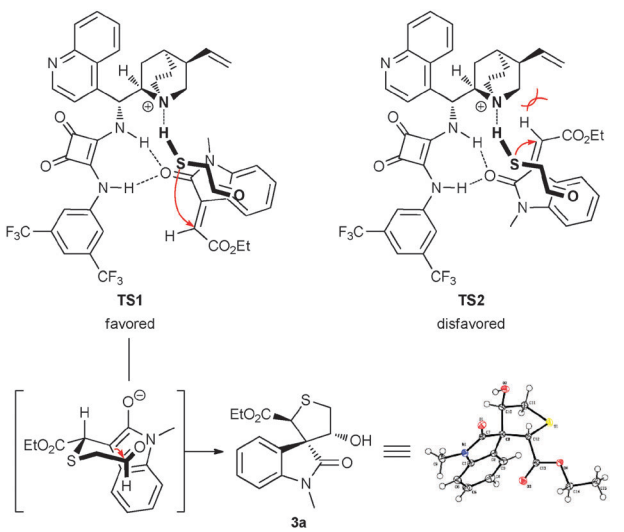
According to the above experimental results and previously reported dual activation model,[17a,d,f,i] both the substrates involved in the transition state are activated by squaramide **V** as proposed in Scheme 1. The Michael acceptor is assumed

Table 2 Organocatalytic asymmetric Michael-aldol cascade reaction of 3-ylideneoxindoles **1** and 1,4-dithiane-2,5-diol **2** catalyzed by **V** or **VI**[a]



Entry	R	R′	Product	Time	Yield (%)[b]	dr[c]	ee (%)[d]
1	H	Me	**3a**	7 h	92	>19 : 1	84
2	5-Me	Me	**3b**	12 h	96	17 : 1	83
3	5-OMe	Me	**3c**	10 h	96	13 : 1	84
4	5-F	Me	**3d**	4 h	92	11 : 1	85
5	5-Br	Me	**3e**	3 h	83	4 : 1	83
6	5-OCF_3	Me	**3f**	10 h	74	6 : 1	86
7	6-Cl	Me	**3g**	4 h	87	8 : 1	85
8	6-Br	Me	**3h**	5 h	89	7 : 1	86
9	7-F	Me	**3i**	10 h	81	5 : 1	87
10	5,7-Me_2	Me	**3j**	10 h	94	15 : 1	83
11	H	Bn	**3k**	6 h	95	>19 : 1	86
12	H	Allyl	**3l**	6 h	94	>19 : 1	87
13[e]	H	Me	***ent*-3a**	12 h	96	>19 : 1	−87
14[e]	H	Bn	***ent*-3k**	11 h	94	>19 : 1	−90
15[e]	H	Allyl	***ent*-3l**	11 h	93	>19 : 1	−91

[a] Unless otherwise specified, all reactions were carried out with **1** (0.5 mmol), **2** (0.3 mmol), **V** (1 mol%), $MgSO_4$ (60 mg) in DCM (10 mL) at 15 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR of crude products. [d] Determined by chiral HPLC analysis. [e] The reaction was conducted with 1 mol% of **VI**.



Scheme 1 Proposed transition state and the X-ray structure of **3a**.

to be activated and oriented by the hydrogen bonds of the squaramide, while the tertiary amine of the catalyst would provide suitable basicity to enhance the nucleophilicity of the mercaptoacetaldehyde. The well-defined orientation facilitates the *Si* attack on the activated olefin, which favors the formation of the *C12S* stereocenter. Subsequent intramolecular aldol reaction through the attack from the *Re* face of the aldehyde afforded the major *C8R*, *C10R*-configured product.

In conclusion, we have demonstrated herein an efficient organocatalytic Michael-aldol cascade for construction of enantioenriched spirocyclic oxindoles fused with tetrahydrothiophenes.

The present method provided a facile access to a new family of heavily functionalized spirooxindole derivatives bearing three consecutive stereogenic centers in a highly stereoselective fashion. Further applications of the current strategy to synthesis of other types of polysubstituted dihydrothiophenes are underway in our laboratory.

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