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Enantioselective Squaramide-Catalyzed Trifluoromethylthiolation–Sulfur–Michael/Aldol Cascade Reaction: One-Pot Synthesis of CF_3S-Containing Spiro Cyclopentanone–Thiochromanes

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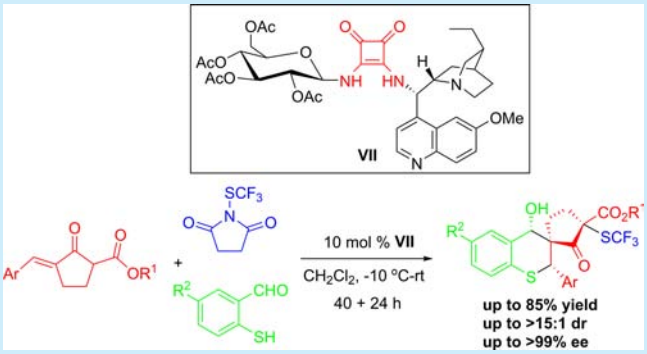
Supporting Information

ABSTRACT: A novel bifunctional squaramide-catalyzed one-pot electrophilic trifluoromethylthiolation–sulfur–Michael/aldol cascade reaction for the construction of CF_3S-containing spiro-cyclopentanone–thiochromanes was developed. This convenient, one-pot cascade reaction serves as a powerful tool for the enantioselective construction of potential bioactive spiro-cyclopentanone–thiochromanes, which have one quaternary stereocenter containing a CF_3S group and three contiguous stereocenters including one spiro all-carbon quaternary center, in moderate to good yields with excellent stereoselectivities (up to 15:1 dr, >99% ee). The synthetic transformations of the resulting products were also be achieved.



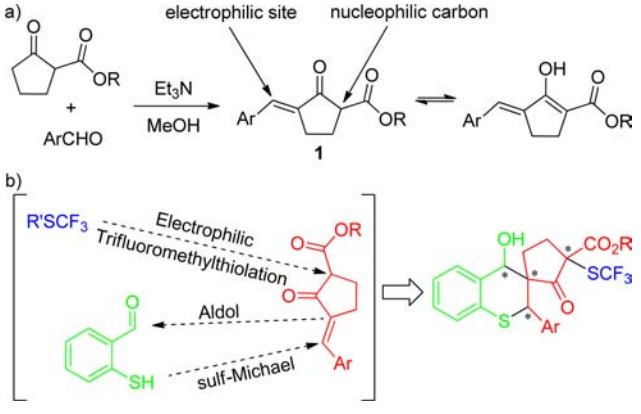
Optically active compounds play an important role in the development of chiral drug and functional materials. The development of facile and efficient syntheses of complex optically active compounds with multiple stereocenters from simple and easily obtained starting materials is one of the most fascinating aspects of modern organic synthesis.[1] Organocatalytic domino/cascade reactions possess the characteristic of high efficiency and convenience, and have initiated an explosive growth of research activities in academia.[2] Especially after the pioneering researches of the groups of List, MacMillan, and Jørgensen,[3] organocatalytic asymmetric domino/cascade reactions have become a powerful strategy for the synthesis of complex chiral compounds with contiguous multiple stereocenters.

Sulfur-containing compounds are universal in organic and pharmaceutical research;[4] among them, highly functionalized thiochromans have been reported to possess important biological activities.[5] Spirothiochroman is an important type of thiochroman, and the biological activities of spirothiochromans depend not only on the substituted functional group but also on the spiro ring system. In recent years, several asymmetric methods have been developed to synthesize specific thiochroman enantiomers.[6] However, the asymmetric synthesis of spirothiochromans is still a great challenge.

The trifluoromethylthio group (CF_3S) is a privileged functional group in the field of agrochemical and pharmaceuticals[7] because of its high lipophilicity, which makes the trifluoromethylthiolated drug compounds cross lipid membranes more readily.[8] While the trifluoromethylthio group has been utilized for some time, only recently have methods for its direct introduction come into the mainstream.[9] There are only five reports of the catalytic asymmetric introduction of the CF_3S group.[10] In consideration of the unique character of the CF_3S-containing compounds and the importance of the spirothiochroman framework, the development of efficient protocols to obtain optically pure CF_3S-containing spirothiochroman framework would be extremely desirable.

Cycloalkenone **1**, easily synthesized from the condensation 3-ketoester with an aldehyde, contains an active nucleophilic carbon and an electrophilic site (Scheme 1a).[11] Its structural features might allow the construction of CF_3S-containing spirothiochromans via the approach shown in Scheme 1b.

Scheme 1. Cascade Reagent Design and Proposed Strategy toward CF_3S-Containing Spirothiochroman



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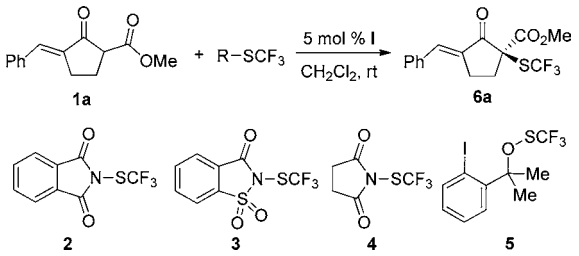
First, enantioselective electrophilic trifluoromethylthiolation can be applied to block the enol tautomerism of cycloalkenone **1**. Second, 2-mercaptobenzaldehyde could potentially be added to trigger the asymmetric cascade sulfur−Michael/aldol reaction with the CF_3S-functionalized product obtained in the previous step to obtain the desired product. Such a one-pot catalytic asymmetric trifluoromethylthiolation−sulfur−Michael/aldol cascade reaction strategy has not been reported to date.

To test the feasibility of this planned reaction, we first screened four different electrophilic CF_3S reagents[12] with (*E*)-methyl 3-benzylidene-2-oxocyclopentanecarboxylate **1a** using squaramide **I** as the catalyst (Table 1). Through careful comparison, we

Table 1. Screening of Different Electrophilic CF_3S Reagents[a]



entry	$RSCF_3$	product	time (h)	yield[b] (%)	ee[c] (%)
1	**2**	**6a**	12	95	63 (*S*)
2	**3**	**6a**	24	63	24 (*R*)
3	**4**	**6a**	12	95	75 (*S*)
4	**5**	**6a**	36	<5	

[a]Reaction conditions: **1a** (0.1 mmol) and $RSCF_3$ (0.11 mmol) in CH_2Cl_2 (0.5 mL) with 5 mol % of catalyst were stirred at room temperature. [b]Isolated yields. [c]Determined by HPLC with a Daicel Chiralpak AD-H column.

concluded that the 1-(trifluoromethylthio)pyrrolidine-2,5-dione **4** was the best electrophilic CF_3S reagent (95% yield, 75% ee) for the model reaction.

Based on the above results, a small library of organocatalysts (Figure 1) were evaluated for this electrophilic trifluoromethylthiolation reaction (Table 2, entries 1−11). Some squaramide catalysts **I**−**IX** derived from cinchona alkaloid and (1*S*,2*S*)-(+)-1,2-diaminocyclohexane were screened. As shown in Table 2, the squaramide **VII** derived from hydroquinine and D-glucopyranose proved to be the most efficient catalyst with respect to the enantioselectivity (82% ee) of this reaction (Table

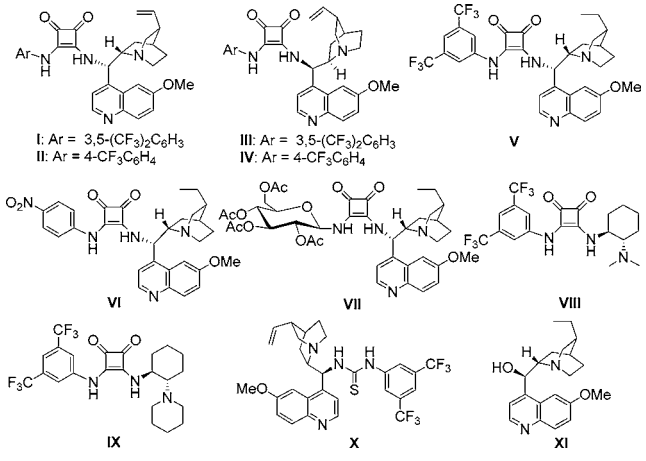
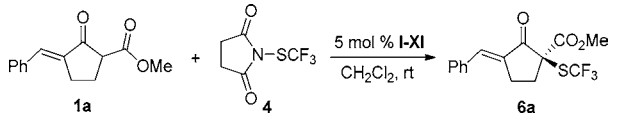


Figure 1. Screened organocatalysts.

Table 2. Screening of Organocatalysts and Optimization of Reaction Conditions for Electrophilic Trifluoromethylthiolation[a]



entry	solvent	cat.	time (h)	yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	**I**	12	95	75 (*S*)
2	CH_2Cl_2	**II**	12	92	78 (*S*)
3	CH_2Cl_2	**III**	12	90	60 (*R*)
4	CH_2Cl_2	**IV**	12	86	58 (*R*)
5	CH_2Cl_2	**V**	12	95	78 (*S*)
6	CH_2Cl_2	**VI**	12	98	78 (*S*)
7	CH_2Cl_2	**VII**	12	96	82 (*S*)
8	CH_2Cl_2	**VIII**	12	95	79 (*S*)
9	CH_2Cl_2	**IX**	12	93	81 (*S*)
10	CH_2Cl_2	**X**	12	26	64 (*S*)
11	CH_2Cl_2	**XI**	12	83	46 (*R*)
12	$CHCl_3$	**VII**	12	96	77 (*S*)
13	$ClCH_2CH_2Cl$	**VII**	12	96	78 (*S*)
14	PhMe	**VII**	12	85	47 (*S*)
15	xylene	**VII**	12	83	44 (*S*)
16	Et_2O	**VII**	12	80	63 (*S*)
17	THF	**VII**	12	65	83 (*S*)
18	MeCN	**VII**	12	77	83 (*S*)
19[d]	CH_2Cl_2	**VII**	24	99	84 (*S*)
20[e]	CH_2Cl_2	**VII**	40	99	87 (*S*)

[a]Reaction conditions: **1a** (0.1 mmol), **4** (0.11 mmol), catalyst (5 mol %) in 0.5 mL of CH_2Cl_2 were stirred at room temperature for 12 h. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]The reaction was performed at 0 °C. [e]The reaction was performed at −10 °C.

2, entry 7). The opposite enantiomer of the product **6a** was obtained with moderate enantioselectivities when quinidine-derived squaramide **III** or **IV** or hydroquinine **XI** was used as the catalyst (Table 2, entries 3, 4, and 11).

In addition, in a comparison of the used squaramides, the corresponding quinine-derived thiourea **X** was also evaluated (Table 2, entry 10). Unfortunately, there was a significant decline in yield and lower enantioselectivity. This result may be due to the higher N−H acidity of the squaramide than that of thiourea, thus providing more powerful hydrogen-bonding interaction to activate reactants.

In order to improve the enantioselectivity of this electrophilic trifluoromethylthiolation reaction, further optimization was carried out using squaramide **VII** as the catalyst. The effects of solvent and temperature were investigated (Table 2, entries 12−20). Subsequent investigation of the solvent effect showed that the reaction medium played an important role in the reaction (Table 2, entries 12−18). CH_2Cl_2 was still the best solvent with respect to both yield and enantioselectivity. The yield and enantioselectivity of the reaction were improved when the temperature was lowered to 0 °C (Table 2, entry 19). When the temperature was further reduced to −10 °C, the result was further improved slightly (Table 2, entry 20). The temperature was not lowered further considering the reactivity and reaction time.

The optimal reaction conditions for the second step were then explored. The results of the cascade sulfur−Michael/aldol reaction of 2-mercaptobenzaldehyde **7a** with the substituted product **6a** to afford the desired CF_3S-containing spiro-

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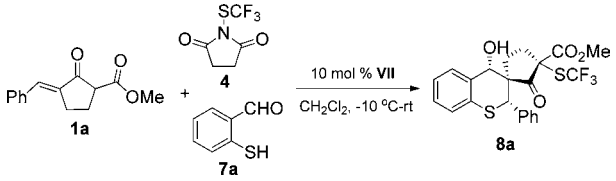
cyclopentanone−thiochroman **8a** are shown in Table 3. Because of the high stereoselectivity in this step, the final enantioselectivity of the product was increased. It should be noticed that the cascade reaction performed at room temperature gave stereoselectivity similar to that of the reaction performed at −10 °C. However, increasing the loading of the catalyst did significantly improve the yield and the diastereoselectivity of the reaction. The optimal reaction conditions were thus finally determined for this one-pot electrophilic trifluoromethylthiolation−sulfur−Michael/aldol cascade reaction.

Table 3. Optimization of Reaction Conditions for Electrophilic Trifluoromethylthiolation−Sulfur−Michael/Aldol Cascade Reaction[a]



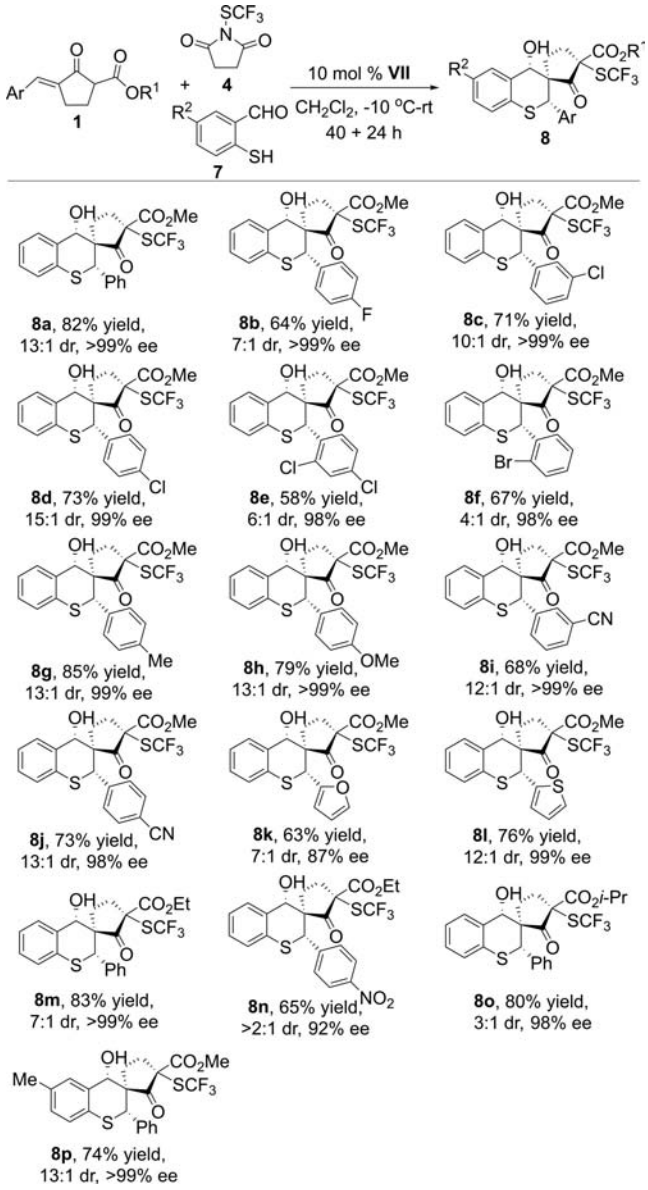
entry	loading (mol %)	time (h)	yield[b] (%)	dr[c]	ee[d] (%)
1[e]	5	40 + 72	63	10:1	>99
2	5	40 + 24	72	10:1	>99
3	2.5	40 + 24	58	9:1	>99
4	10	40 + 24	82	13:1	>99
5	15	40 + 24	82	13:1	>99

[a]Reaction conditions: **1a** (0.1 mmol), **4** (0.11 mmol), and catalyst **VII** (10 mol %) in CH_2Cl_2 (0.5 mL) were stirred at −10 °C for 40 h, then **7a** (0.15 mmol) was added and stirred at room temperature. [b]Isolated yields. [c]Determined by ^1H NMR. [d]Determined by chiral HPLC analysis. [e]The second cascade sulfur−Michael/aldol reaction was also performed at −10 °C.

Following this optimization of the reaction conditions, the scope of this one-pot enantioselective squaramide-catalyzed electrophilic trifluoromethylthiolation−sulfur−Michael/aldol cascade reaction was explored for the synthesis of functionalized CF_3S-containing spiro-cyclopentanone−thiochromanes **8** (Scheme 2). (*E*)-3-Arylidene-2-oxocyclopentanecarboxylates bearing electron-donating, electron-neutral, or electron-withdrawing groups on the aryl rings reacted with 1-(trifluoromethylthio)pyrrolidine-2,5-dione **4** and 2-mercaptobenzaldehyde **7a** smoothly, affording the corresponding products **8a−k** in moderate-to-good yields and diastereoselectivities, with excellent enantioselectivities. There was a slight decrease in yield when the substituent on the aromatic ring was in the *ortho* or *meta* position (**8c**, **8e**, **8f**, and **8i**). Additionally, heterocyclic substrates were also amenable to this reaction and afforded the corresponding product **8k** and **8l**. However, the substrate derived from 2-furaldehyde gave the product **8k** with a decrease in enantioselectivity (87% ee). Furthermore, (*E*)-ethyl and (*E*)-isopropyl 3-benzylidene-2-oxocyclopentanecarboxylate were examined, with the corresponding products **8m** and **8o** obtained in relatively inferior quality compared to **8a**. Finally, the substrate bearing a 4-NO_2 group on the aromatic ring was also examined, but inferior stereoselectivity was observed for product **8n** (>2:1 dr, 92% *ee*). Moreover, 2-mercapto-5-methylbenzaldehyde **7b** was also evaluated to further exhibit the generality of this protocol, giving the product **8p** with excellent results.

The absolute configuration of the product was elucidated by single-crystal X-ray diffraction analysis of **8a** (CCDC 1519496) as (1*S*,2′*S*,3*S*,4′*R*), and the configuration of other products were assigned by analogy.

Scheme 2. Substrate Scope[a]



[a]Reaction conditions: **1** (0.1 mmol), **4** (0.11 mmol), and catalyst **VII** (10 mol %) in CH_2Cl_2 (0.5 mL) were stirred at −10 °C for 40 h, then **7** (0.15 mmol) was added and stirred at room temperature for 24 h. The dr's of the products were determined by ^1H NMR. The ee values of the products were determined by HPLC.

Another cycloalkenone **9** was also conducted under the same conditions, giving the desired product **10** in 92% yield with 90% ee. However, we failed to get further product in the following sulfur−Michael/aldol cascade reaction (Scheme 3a). The derivatization of the major diastereomer of **8a** was also investigated (Scheme 3b). The hydroxyl group of **8a** can be easily oxidized to a carbonyl group using PCC. Further oxidation of **11** using H_5IO_6 catalyzed by CrO_3 afforded the corresponding sulfone **12**, which is another class of useful product. The oxidation on the sulfur in cyclic ring was confirmed by comparing the ^{19}F NMR spectrum and mass spectrum of the compounds **11** and **12**.

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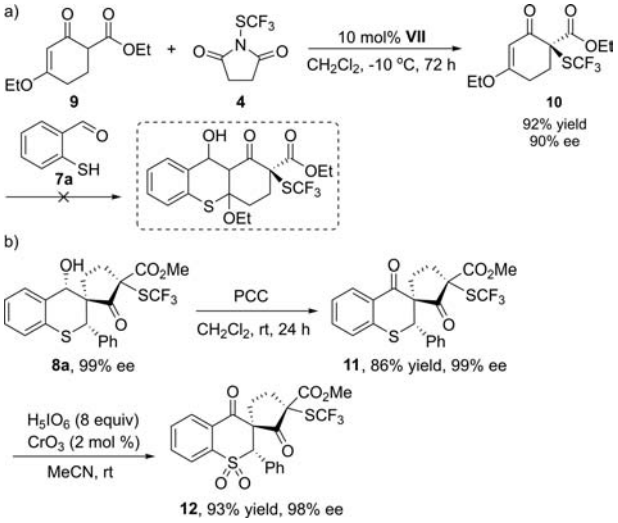
Scheme 3. Further Investigation of Substrate Scope and Transformation of 8a



In conclusion, an unprecedented bifunctional squaramide-catalyzed, one-pot, electrophilic trifluoromethylthiolation−sulfur−Michael/aldol cascade reaction of cycloalkenone, 1-(trifluoromethylthio)pyrrolidine-2,5-dione, and 2-mercaptobenzaldehyde has been successfully developed. The key feature of the current methodology is that the cycloalkenones bearing an active nucleophilic carbon and an electrophilic site could be utilized as efficient synthons, achieving the consecutive reactions of electrophilic substitution and nucleophilic attack in a one-pot fashion. This one-pot cascade reaction provides a straightforward approach to a variety of structurally complicated fused CF_3S-containing spiro-cyclopentanone−thiochromanes with one quaternary stereocenter containing a CF_3S group and three contiguous stereocenters including one spiro all-carbon quaternary center in moderate-to-good yield with excellent stereoselectivities (up to 15:1 dr, > 99% ee). The practicality of this methodology was illustrated by a synthetic transformation of the resulting product.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03846.

Proposed reaction mechanism, experimental details, ^{1}H, ^{13}C and ^{19}F NMR spectra of new compounds, and HPLC chromatograms (PDF)

X-ray data for compound **8a** (CIF)

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Notes

The authors declare no competing financial interest.

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