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Asymmetric Synthesis of CF_3- and Indole-Containing Thiochromanes via a Squaramide-Catalyzed Michael–Aldol Reaction

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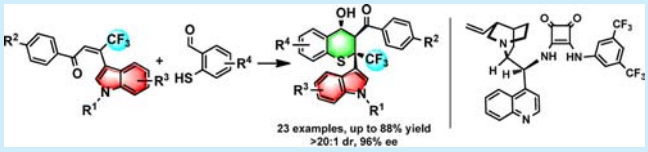
Supporting Information

ABSTRACT: A Michael–aldol reaction of 2-mercaptobenzaldehyde with β-indole-β-CF_3 enones catalyzed by a squaramide has been realized. The method affords a series of 2-CF_3-2-indole-substituted thiochromanes featuring a CF_3-containing quaternary stereocenter in excellent yields, diastereoselectivities, and enantioselectivities.



Organosulfur compounds are widely present in nature and various biological systems. They are also a class of important compounds in synthetic drugs.[1] Among them, thiopyran represents a key structure class in many pharmaceutical agents. On this topic, thiochromanes, the important thio analogues of the naturally occurring chromanes and flavonoid compounds,[2] have attracted great attention from chemists and pharmacologists,[3] and they are also seen as key intermediates in the preparation of drugs.[4] Accordingly, many protocols to synthesize these compounds have been reported.[5] In this context, the representative work was the prolinol-derivative-catalyzed domino thio-Michael–aldol reaction of 2-mercaptobenzaldehydes and α,β-unsaturated aldehydes.[6] From then on, many efforts have been devoted to accessing optically active thiochromanes by organic-[7] or metal-catalyzed[8] cascade reactions. Although 2,2-disubstituted chromanes are found in many natural products and biologically active compounds, the asymmetric synthesis of structurally diverse thiochromanes containing a chiral quaternary carbon center at the 2-position is still challenging.

Because of the frequent emergence of indole in drugs and natural products, the asymmetric synthesis of indole-containing compounds is a focus of research.[9] On the other hand, the incorporation of a CF_3 group at a tertiary or quaternary stereogenic carbon center of a heterocycle is very attractive in pharmaceutical research because it can often enhance the lipophilicity and metabolic stability of the parent molecule. At present, studying the CF_3 analogue of a candidate drug has become a common practice.[10]

It is a classic theme to incorporate a biologically relevant group into pharmacology-privileged structures in drug discovery. Combined with the above-mentioned items, it is highly desired to introduce indole and $-CF_3$ into thiochromanes. As part of our ongoing interest in developing new methods for the synthesis of optically active CF_3-containing heterocyclic compounds,[11] herein we report a new method for the asymmetric synthesis of CF_3- and indole-containing thiochromanes with squaramide as the catalyst.

To begin our test, the reaction of 2-mercaptobenzaldehyde with β-indole-β-CF_3 enones[12] was employed as the model reaction. The desirable cascade reaction was completed smoothly in the presence of 10 mol % quinine, and the annulation product was obtained in 76% yield with excellent dr but poor ee. Replacement of quinine with cinchonidine did not improve the stereoselectivity. The possibility to obtain the optically active 2-indole-2-CF_3-thiochromanes[13] appeared when thiourea catalysts were employed. As listed in Table 1, cinchonidine-derived squaramide[14] catalyst **C6** (Figure 1) gave the best results, and the corresponding product was isolated in 83% yield with 92% ee. Further exploration of the solvent showed that toluene was suitable for the reaction, and the ee could be improved to 94% when the reaction was carried out at 0 °C.

With the above-mentioned optimized reaction conditions in hand, the tolerance toward the protecting group at the 1-position of the indole was tested first. With −Boc, −Ac, and −Tos at the indole 1-position of substrates **2** (Scheme 1, **3a**, **3b**, and **3c**), the cascade reaction proceeded smoothly, and the best results were obtained when the *N*-Boc enone was employed. Further exploration found that more ideal results could be obtained with *p*-methoxyacetophenone-derived enones as reagents (Scheme 1, **3d**).

The following tests were focused on the scope of enones. As shown in Scheme 2, β-indole-β-CF_3 enones with various

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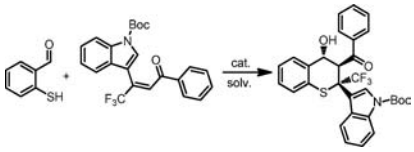
Table 1. Screening of the Reaction Conditions for the Synthesis of CF_3- and Indole-Containing Thiochromanes[a]



entry	cat.	solvent	time (h)	yield (%)[b]	temp.	dr[c]	ee (%)[d]
1	C1	toluene	16	76	rt	>20:1	33
2	C2	toluene	16	75	rt	>20:1	16
3	C3	toluene	8	67	rt	>20:1	80
4	C4	toluene	8	65	rt	>20:1	81
5	C5	toluene	5	82	rt	>20:1	90
6	C6	toluene	5	80	rt	>20:1	92
7	C7	toluene	7	81	rt	>20:1	−60
8	C6	C_6H_5Cl	7	83	rt	>20:1	90
9	C6	DCM	8	70	rt	>20:1	84
10	C6	Et_2O	10	51	rt	>20:1	91
11	C6	THF	14	45	rt	>20:1	84
12	C6	hexane	18	33	rt	>20:1	88
13	C6	toluene	6	81	10 °C	>20:1	92
14	C6	toluene	8	80	0 °C	>20:1	94
15	C6	toluene	12	78	−10 °C	>20:1	94

[a]Reaction conditions: catalyst (0.02 mmol, 10 mol %), 2-mercaptobenzaldehyde (0.2 mmol), β-indole-β-CF_3 enone (0.22 mmol), solvent (3 mL). [b]Isolated yields. [c]Determined by chiral HPLC or ^{1}H NMR analysis. [d]Determined by chiral HPLC analysis.

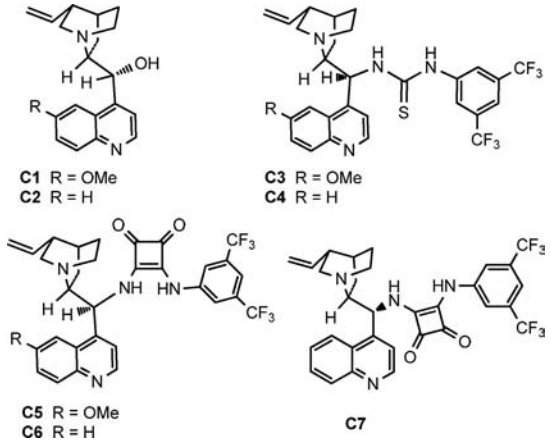
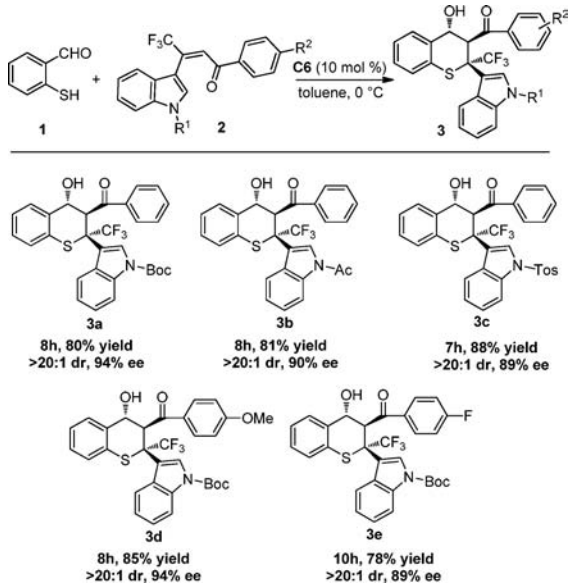


Figure 1. Catalysts for screening.

substituents, including electron-withdrawing, -neutral, or -donating groups at different positions of the indole were well-tolerated and reacted with 2-mercaptobenzaldehyde to give the products in high yields with excellent dr and ee values. Although almost same excellent results were obtained in every case, the results indicated that the cycloaddition reaction took a shorter time with electron-withdrawing groups on the indole than with electron-donating ones. For example, the reaction took only 10 h with −CN at the 5-position of the indole (Scheme 2, **3k**) but 14 h with −OMe at the same position (Scheme 2, **3j**). The same tendency emerged with substituents at the 6-position (Scheme 2, **3l**−**o**) and the 7-position (Scheme 2, **3p**−**r**). Additionally, the reaction took longer when the substituent was at the 5-position than at other positions. For example, when the $-CH_3$ was moved from the 5-position to the 6- and 7-positions, the reaction time was reduced (**3f**, **3l**, and **3p**), and the same rule was applicable to the movement of −F, −Cl, and −Br. Furthermore, the disubstituted indole enone was also compatible, giving the product in 82% yield with >20:1 dr and 90% ee. Meanwhile, **3a′**, the enantiomer of compound **3a**, was obtained with −69% ee with **C7** as the catalyst at 0 °C. Enones derived from acetone were also tested, and excellent results were obtained.[15]

Scheme 1. Structure Optimization of Enones[a]



[a]The reaction time required for each substrate is given. The yields of the isolated products are reported. The ee and dr values were determined by HPLC analysis.

Subsequently, 2-mercapto-5-methylbenzaldehyde, 2-mercapto-5-methoxybenzaldehyde, and 2-mercapto-3,5-dimethylbenzaldehyde were also involved to further exhibit the generality of this protocol. To our delight, the cycloadditions gave the desired products bearing three contiguous stereogenic centers in excellent yields, diastereoselectivities, and enantioselectivities (**3t**−**v**).

As shown in Figure 2, the absolute configuration of the reaction reagent and product were established. We propose that addition of the S atom to the (*E*)-enone occurs first, and then the chiral intermediate undergoes a highly stereoselective intramolecular aldol reaction, affording the product in the (2*S*,3*S*,4*R*) configuration.

To further verify the synthetic utility of this Michael−aldol cascade reaction, *p*-dithiane-2,5-diol was also employed to react with an enone.[16] As shown in Scheme 3, compared with 2-mercaptobenzaldehyde, *p*-dithiane-2,5-diol showed relatively lower reactivity under the same reaction conditions and gave the chiral CF_3-tetrahydrothiophene **4** in high yield with 84% ee when catalyst **C5** (Figure 1) was employed (for catalyst screening, see the Supporting Information).

In conclusion, a direct and efficient method for the asymmetric synthesis of 2-CF_3-2-indole thiochromanes catalyzed by a squaramide has been developed. A series of pharmaceutically useful thiochromanes were obtained in high yields with excellent stereoselectivities.

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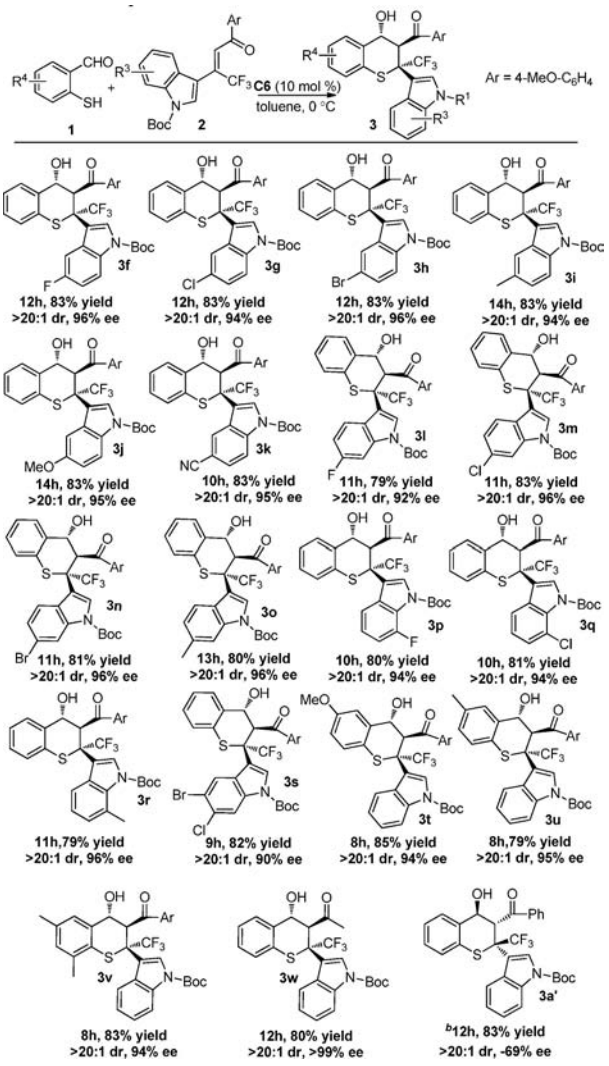
Scheme 2. Scope of Enones[a]



[a]The reaction time required for each substrate is given. The yields of the isolated products are reported. The ee and dr values were determined by HPLC analysis. [b]With **C7** as the catalyst.

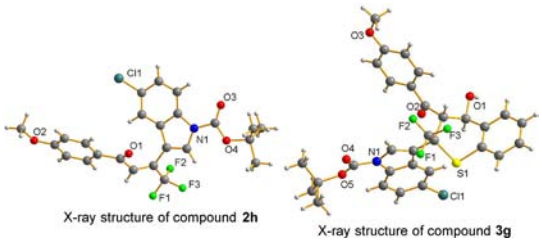
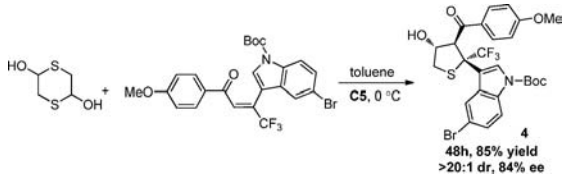


Figure 2. X-ray structures of enone **2h** and thiochromane **3g**.

Scheme 3. Synthesis of CF_3-tetrahydrothiophenes



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01498.

Experimental procedures and characterization of the products (PDF)
Crystallographic data for **2h** (CIF)
Crystallographic data for **3g** (CIF)

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Notes

The authors declare no competing financial interest.

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