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Highly Enantioselective Cascade Reaction Catalyzed by Squaramides: the Synthesis of CF_3-Containing Chromanes

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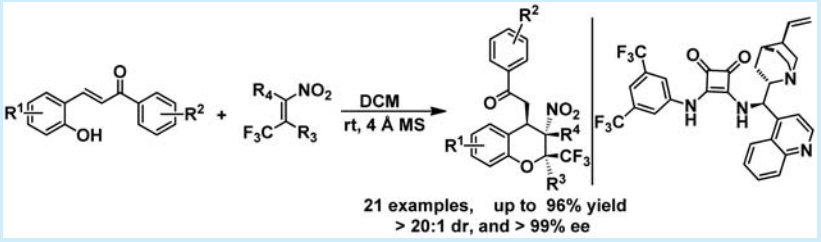
Supporting Information



ABSTRACT: A catalytic asymmetric method for the synthesis of 2-CF_3 chromanes has been described. Generally, the squaramide-catalyzed cascade reaction of 2-hydroxychalcones with β-CF_3-nitroalkenes gave the CF_3-containing heterocyclic compounds bearing three contiguous stereogenic centers in excellent yields, diastereoselectivities, and enantioselectivities.

In order to cope with the ever-increasing demands of pesticides, herbicides, and pharmaceuticals, the construction of fluorine-containing organic compounds in highly enantioenriched forms using catalytic methods is one of the most topical areas of chemical research.[1] In this context, the selective incorporation of a CF_3 group at a tertiary or quaternary stereogenic carbon center in a heterocyclic framework is particularly interesting,[2] because the introduction of this motif into a bioactive molecule can potentially elicit a range of positive effects, through concomitant alteration of steric, electrostatic interaction, acidity and basicity, lipophilicity, etc.[3]

Chromanes, a class of benzo-fused oxygen heterocycles, represent the core structure of many natural products and biologically active compounds.[4] Among them, 2-methyl substituted chromanes constitute an important structural motif in various bioactive molecules, such as well-known α-tocopherol[5]and polycerasoidin,[6] anti-HIV natural products such as daurichromenic acid,[7] and the antibacterial compound **I**[8] (Figure 1).

Combined with above-mentioned two features, it is highly desirable to introduce CF_3 into the 2-position of chromanes. To meet this demand, several entries have been developed to give trifluoromethyl substituted chromanes in racemic form.[9]

So, a direct and effective method for the construction of trifluoromethylated chromanes from simple starting materials via asymmetric catalysis is still a requirement.

It was noted that organocatalyzed cascade reactions are among the most efficient methods for the synthesis of optically active chromanes.[10,11] In this context, the reaction of CF_3-bearing precursors with salicylic aldehydes or their derivatives[12] is an effective approach to access 2-CF_3 chromanes. From this point of view, we selected β-CF_3 nitroalkenes[13] as the CF_3-bearing precursors to begin our essay in the construction of optically active 2-CF_3 chromanes.

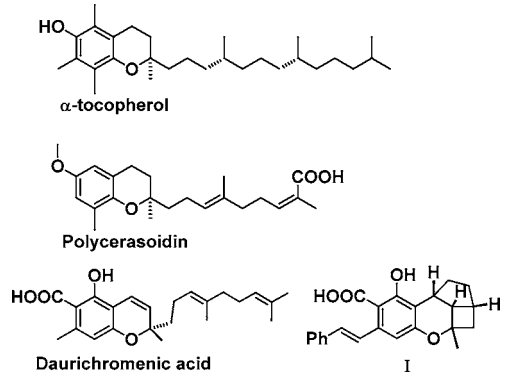


Figure 1. Selected bioactive 2-methyl substituted chromanes.

To explore the feasibility of the synthesis of 2-CF_3 chromanes, the reaction of compound **2** with **3a** was employed as a model reaction. Initially, with natural cinchona alkaloid **C1**

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as the catalyst, 2-hydroxychalcone disappeared after 13 h according to TLC. The annulation product was obtained in 38% yield and 20:1 dr, without stereoselectivity. Given this disappointing result, we turned our attention to screening other representative catalysts derived from cinchona alkaloids (**C2**–**C6**, Figure 2). As listed in Table 1 (entries 2–5), optically

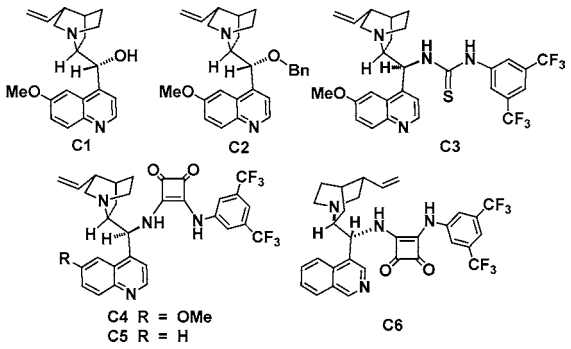
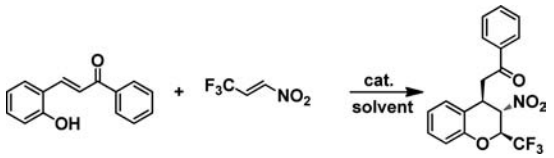


Figure 2. Catalysts for screening.

Table 1. Screening of the Reaction Conditions for the Cascade Reaction of β-CF_3-Nitroalkene with 2-Hydroxychalcone[a]



entry	catalyst	solvent	time (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	**C1**	DCM	11	38	>20:1	0
2	**C2**	DCM	13	17	>20:1	7
3	**C3**	DCM	48	23	>20:1	52
4	**C4**	DCM	24	69	>20:1	>99
5	**C5**	DCM	72	77	>20:1	>99
6	**C5**	Tol	72	51	>20:1	>99
7	**C5**	DCE	22	70	>20:1	97
8[e]	**C5**	THF	48	nd	nd	nd
9	**C5**	MeCN	72	44	>20:1	>99
10	**C5**	Et_2O	72	46	>20:1	>99
11[f]	**C5**	DCM	22	77	>20:1	>99
12[g]	**C5**	DCM	22	77	>20:1	>99
13[h]	**C5**	DCM	22	77	>20:1	>99
14[g]	**C6**	DCM	24	81	>20:1	−97

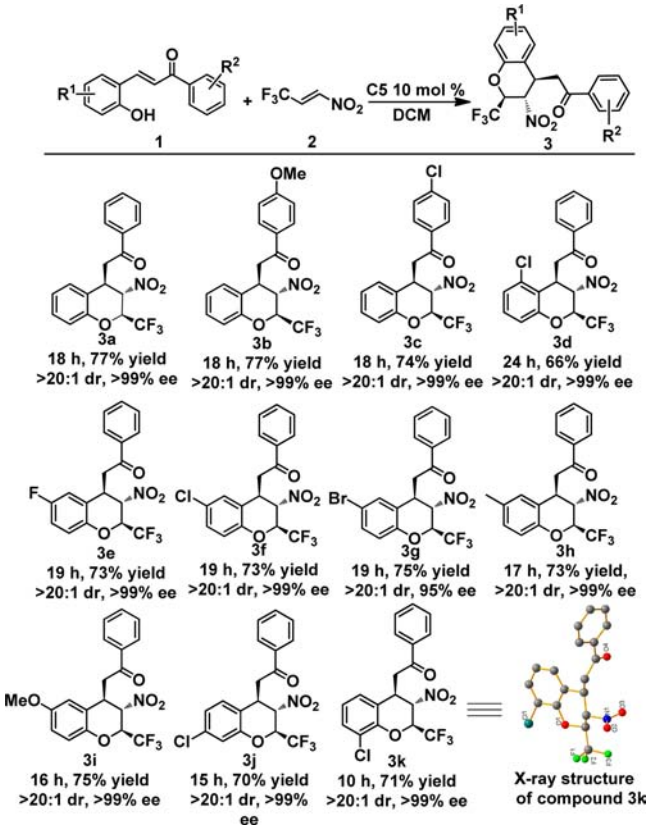
[a]Reaction conditions: Catalyst (0.02 mmol, 10 mol %), 2-hydroxychalcone (0.2 mmol), β-CF_3-nitroalkene (0.6 mmol), solvent (4 mL), and at room temperature. [b]Isolated yield. [c]Determined by chiral HPLC analysis or ^{1}H NMR. [d]Determined by chiral phase HPLC analysis. [e]No product was found. [f]With 100 mg of freshly dried 3 Å MS as additive. [g]With 100 mg of freshly dried 4 Å MS as additive and furnished at 0 °C. [h]With 100 mg of freshly dried 5 Å MS as additive.

active 2-CF_3 chromanes were obtained using the dual function thiourea catalyst C3 which afforded the annulation product in 52% ee and poor yield. However, upon introducing squaramide catalysts (effective bifunctional hydrogen-bonding organocatalysts)[10,14,15] in this research, the yield and stereoselectivity greatly improved. Although 3 days were needed, the catalyst **C5** gave the product in 77% yield, > 20:1 dr, and >99% ee.

Further studies focused on the influence of solvents and additives. As presented in Table 1 (entries 6–10), DCM was the best solvent. Moreover, the addition of freshly dried 4 Å MS could shorten the reaction time without affecting the yield and stereoselectivity. Furthermore, the diastereomer **3a′** could be obtained in 81% yield, >20:1 dr, and 97% ee by using cinchonine derived squaramide **C6** as the catalyst in DCM, using 100 mg of freshly dried 4 Å MS as an additive at room temperature.

With the aforementioned optimal reaction conditions identified (see also: Supporting Information), we explored the scope of 2-hydroxychalcone in this squaramide-catalyzed asymmetric annulation reaction. Scheme 1 shows that with the

Scheme 1. Scope of 2-Hydroxychalcone[a]



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

chalcone derived from 4-OMe acetophenone, acetophenone, and 4-Cl acetophenone as substrates, almost the same yield, dr, and ee were obtained (**3a**, **3b**, and **3c**). Following this, a variety of structurally diverse 2-hydroxychalcones were studied in this research. Chalcones derived from salicylic aldehydes with electron-withdrawing, electron-neutral, or electron-donating substituents at different positions gave adducts with β-CF_3-nitroalkenes in good yields and excellent diastereo- and stereoselectivities. These results indicated that the chalcones bearing electron-donating substituents show higher reactivity than those bearing electron-withdrawing substituents. For example, upon moving from −F, −Cl, −Br, −Me, to −OMe in the 5-position of the chalcones, the corresponding reaction time reduced (see **3e**, **3f**, **3g**, **3h**, and **3i**). Additionally, a longer reaction time was needed as the −Cl was moved from the 3-position to the 6-position of 2-hydroxychalcone.

Further investigation of this cascade reaction was carried out to delineate the scope of the β-nitroalkene (Scheme 2). The

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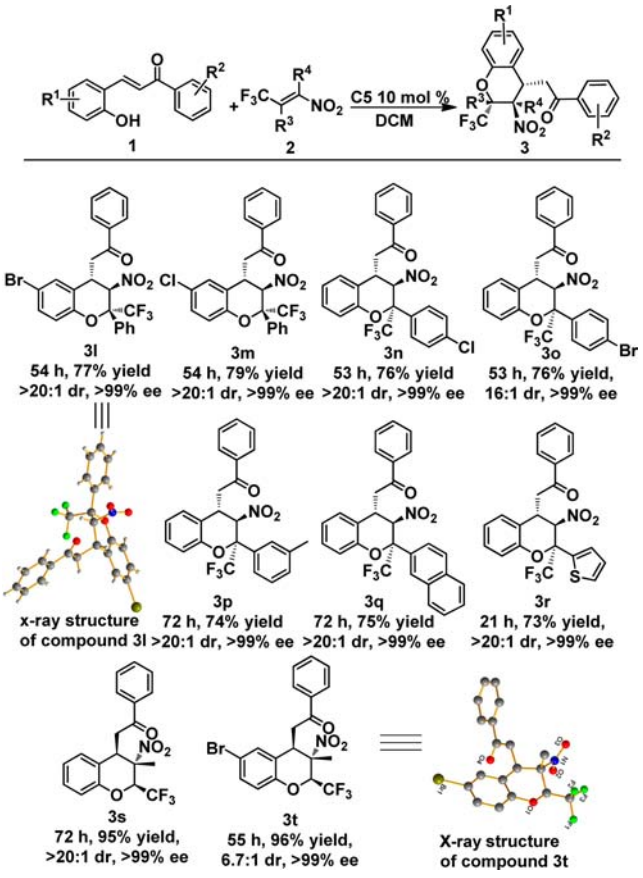
Scheme 2. Scope of β-Nitrostyrene[a]



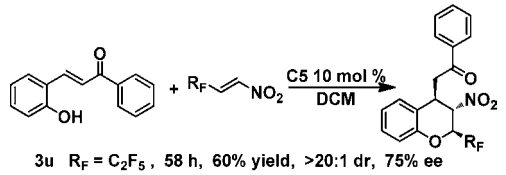
[a]The reaction time required for each substrate is given. The yields of the isolated products are reported. The ee values and dr values were determined by HPLC analysis.

reactions of (*E*)-β-aryl-β-CF_3 nitroalkenes[16] with 2-hydroxychalcone gave the products with trifluoromethylated quaternary stereocenters at the 2-position. In general, nitrostyrenes bearing electron-withdrawing, electron-neutral, or electron-donating substituents on the phenyl ring were well tolerated and gave adducts in good yields and excellent enantioselectivities (see: **3l**, **3m**, **3n**, **3o**, and **3p**). It was worth noting that with 2-naphthyl and 1-thienyl substituted β-aryl-β-CF_3 nitroalkenes, the same excellent results were obtained (see: **3q** and **3r**). In addition, a β-CF_3 nitroalkene containing a methyl at the α-position was also a suitable reactant, reacting with 3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one and 3-(5-bromo-2-hydroxyphenyl)-1-phenylprop- 2-en-1-one to give products bearing a full-carbon quaternary stereocenter on the 3-position in excellent yields, dr values, and ee values.

To further demonstrate the synthetic utility of this squaramide catalyzed cascade reaction, some perfluoroalkyl substituted β-nitroalkenes have been tested. As listed in Scheme 3, compared with β-CF_3 nitroalkene, pentafluoroethyl and heptafluoropropyl substituted nitroalkenes showed lower reactivity and gave the products in moderate yield and ee.

In summary, a method for constructing optically active 2-CF_3 chromanes has been developed. The cascade reaction of three types of β-CF_3 nitroalkenes with chalcones derived from salicylaldehyde gives compounds with considerable pharmaceutical utility bearing three contiguous stereogenic centers in excellent yields, diastereoselectivities, and enantioselectivities.

Scheme 3. Synthesis of 2-Perfluoroalkyl Substituted Chromanes



3u $R_F = C_2F_5$, 58 h, 60% yield, >20:1 dr, 75% ee
3v $R_F = C_3F_7$, 56 h, 60% yield, >20:1 dr, 55% ee

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization of the products. Crystallographic data for compounds of **3k**, **3l**, **3t** (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01799.

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Notes

The authors declare no competing financial interest.

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