Asymmetric Synthesis

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Organocatalytic Asymmetric Sulfa-Michael/Michael Addition Reactions: A Strategy for the Synthesis of Highly Substituted Chromans with a Quaternary Stereocenter**

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Chromans form the core of numerous natural products and synthetic analogues displaying a broad and interesting range of biological activities.[1] In particular, the chiral chroman skeleton plays an important role in various therapeutic areas.[1d] For example, (−)-siccanin, isolated from the culture broth of *Heleminthosposium siccans,* exhibited potent antifungal activity against the pathogentic fungi *Trichophyton interdigitale, Trichophyton asteroids, Epidermophyton*, and *Mycosporum* (Figure 1).[2] Rubioncolin B belongs to a class of

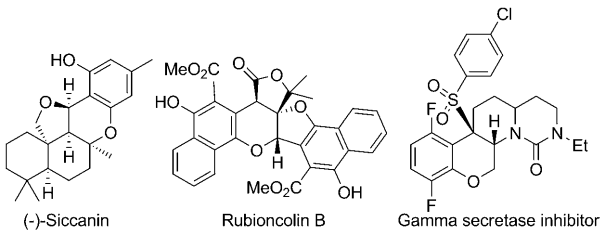
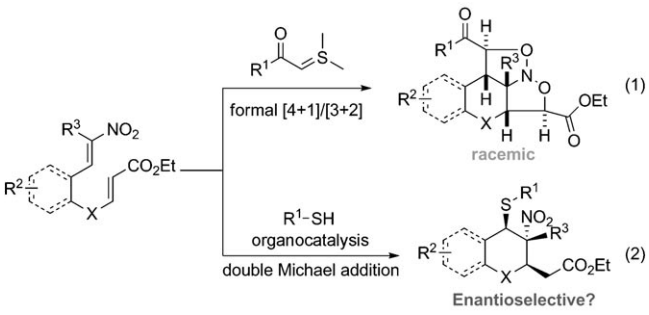


Figure 1. Examples of highly substituted biologically active chroman derivatives.

unusual naphthohydroquinones that are administered in traditional Chinese and Ayurvedic medicine,[3] and Gamma secretase inhibitor is a candidate for use in Alzheimer's disease.[4] Therefore, these complex polycyclic frameworks have become targets of interest in the organic synthetic community. Recently, a number of catalytic asymmetric methodologies using Lewis acids or transition-metal complexes have been developed for the synthesis of this privileged structural motif, including asymmetric epoxidation,[5] oxidative cyclization,[6] allylic alkylation,[7] enyne cyclization,[8] and others.[9] Despite these advances, organocatalytic asymmetric methods for the construction of chromans remain largely unexplored.[10]

The search for new efficient and highly enantioselective approaches to complex molecular architectures, especially those with multiple stereogenic carbon atoms and quaternary stereocenters, continues to be a substantial challenge in both academic and industrial domains.[11] In this context, the organocatalytic cascade reaction has recently emerged as a powerful tool to facilitate a rapid increase in molecular complexity and diversity from simple and readily available starting materials by reducing the steps of manual operation as well as the generation of waste.[12] Of the catalytic strategies developed for enantioselective cascade transformations, bifunctional organocatalysts bearing both hydrogen-bond donors and basic functional groups have formed a focal point of attention in recent years.[13] Recently, our laboratory implemented a novel formal inter-[4+1]/intra-[3+2] cyclization cascade of cycloadditions of sulfur ylides with nitroolefin enoates to construct densely functionalized chromans [Eq. (1)].[14] Notwithstanding the fascinating results, the



development of an enantioselective version of this consecutive reaction remains extremely desirable. Therefore we describe herein an alternative bifunctional organocatalyst for the sulfa-Michael/Michael addition[15] reaction of thiols with nitroolefin enoates to afford polyfunctionalized chroman derivatives in a highly stereoselective manner [Eq. (2)]. The notable features of this procedure include: 1) the generation of three consecutive stereogenic carbon centers including one quaternary stereocenter with high enantioselectivity (up to 96% *ee*) and excellent diastereoselectivity (> 95:5 d.r.), 2) no reaction reversibility, which is usually found with hetero nucleophiles,[16] 3) the cascade reaction adducts are the core structural feature of the Gamma secretase inhibitor, and

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4) more importantly, this double Michael addition reaction proceeds efficiently even at a 0.5 mol% catalyst loading on a gram scale.

Initially, we examined the feasibility of the proposed cascade reaction by choosing *para*-thiocresol (**1a**) and nitroolefin enoate **2a** as the model substrates to react in the presence of various base/acid bifunctional organocatalysts in CH_2Cl_2 at room temperature (Table 1). Catalyst **F** (Figure 2)

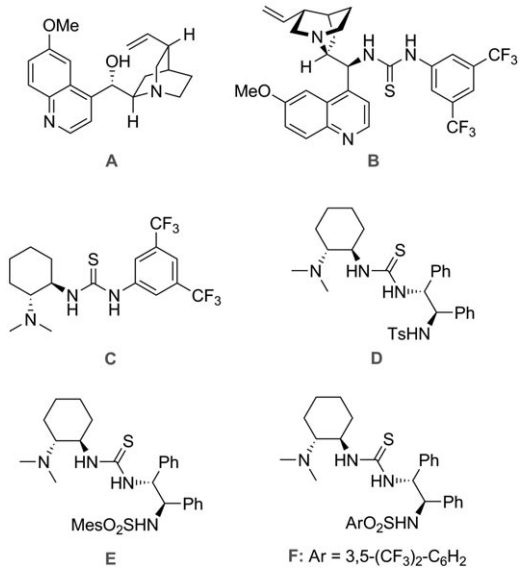
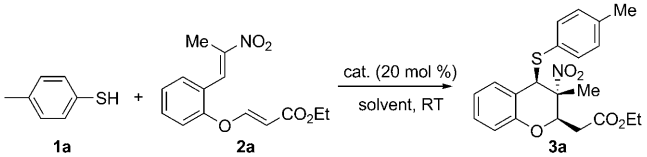


Figure 2. Bifunctional organocatalysts examined in this study. Mes = 2,4,6-trimethylphenyl, Ts = 4-toluenesulfonyl.

proved to be the most efficient for this cascade procedure, affording the desired product **3a** with high yield, good enantioselectivity, and excellent diastereoselectivity (Table 1, entry 6). Solvent screening demonstrated that CH_2Cl_2 was the optimal reaction medium (Table 1, entries 6–12). Additional efforts to improve the reaction efficiency showed that the selectivity of **3a** was slightly increased when catalyst loading was decreased to 3 mol% (Table 1, entry 14). Lowering the reaction temperature to 0°C resulted in a significant decrease in yield with comparable enantioselectivity (Table 1, entries 15 versus 14).

With the optimal reaction conditions in hand, the generality of this reaction was then explored using various thiols. As shown in Table 2, for most arenethiols, regardless of their substitution pattern and the electronic nature of their aromatic system, the cascade sequence proceeded smoothly to provide highly substituted chiral chromans with a quaternary stereocenter in good yield (74–91%), high enantiomeric excess (89–92% *ee*), and excellent diastereoselectivity (> 95:5 d.r.). For example, the reaction with arenethiols bearing methyl or methoxy groups at the *para*, *ortho*, and *meta* positions took place without loss of yield or selectivity (Table 2, entries 1–5). Variation in the electronic contribution of the aromatic systems also had a minimal impact upon the reaction; as such, reactions with electron-rich (Table 2, entries 1, 5, and 6), electron-deficient (Table 2, entries 7 and 8), and electron-neutral thiols (Table 2, entry 9), including

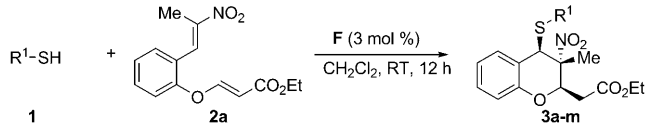
Table 1: Optimization of double Michael addition reaction conditions.[a]



Entry	Catalyst	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]	d.r.[c]
1	**A**	CH_2Cl_2	12	75	53	>95:5
2	**B**	CH_2Cl_2	8	85	82	>95:5
3	**C**	CH_2Cl_2	6	88	82	>95:5
4	**D**	CH_2Cl_2	2	93	86	>95:5
5	**E**	CH_2Cl_2	2	85	84	>95:5
6	**F**	CH_2Cl_2	2	93	89	>95:5
7	**F**	DCE	8	82	80	>95:5
8	**F**	Et_2O	10	89	79	>95:5
9	**F**	THF	10	75	72	>95:5
10	**F**	toluene	10	81	76	>95:5
11	**F**	CH_3CN	2	90	72	>95:5
12	**F**	CH_3OH	10	43	66	>95:5
13[d]	**F**	CH_2Cl_2	8	93	90	>95:5
14[e]	**F**	**CH_2Cl_2**	**12**	**91**	**90**	**>95:5**
15[e,f]	**F**	CH_2Cl_2	48	70	91	>95:5

[a] Conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), catalyst (20 mol%), and solvent (1 mL). [b] Yield of isolated product. [c] Determined by chiral HPLC methods. [d] Used 5 mol% **F**. [e] Used 3 mol% **F**. [f] The reaction was carried out at 0°C. DCE = 1,2-dichloroethane, THF = tetrahydrofuran.

Table 2: Double Michael addition reactions of thiols **1** to nitroolefin enoate **2a** with catalyst **F**.[a]



Entry	R^1	Yield [%][b]	*ee* [%][c]	d.r.[c]
1[d]	4-$CH_3C_6H_4$ (**1a**)	91 (**3a**)	90	>95:5
2	3-$CH_3C_6H_4$ (**1b**)	87 (**3b**)	91	>95:5
3	2-$CH_3C_6H_4$ (**1c**)	77 (**3c**)	91	>95:5
4	2-$CH_3OC_6H_4$ (**1d**)	86 (**3d**)	90	>95:5
5	4-$CH_3OC_6H_4$ (**1e**)	82 (**3e**)	89	>95:5
6	4-*t*BuC_6H_4 (**1f**)	81 (**3f**)	92	>95:5
7	4-FC_6H_4 (**1g**)	84 (**3g**)	91	>95:5
8	4-BrC_6H_4 (**1h**)	78 (**3h**)	91	>95:5
9	C_6H_5 (**1i**)	83 (**3i**)	90	>95:5
10	3,5-$(CH_3)_2C_6H_3$ (**1j**)	79 (**3j**)	91	>95:5
11	2-naphthyl (**1k**)	89 (**3k**)	91	>95:5
12	2-thienyl (**1l**)	74 (**3l**)	92	>95:5
13[e]	4-CH_3OBn (**1m**)	79 (**3m**)	95	>95:5

[a] Conditions: **1** (0.3 mmol), **2a** (0.2 mmol), **F** (3 mol%), and CH_2Cl_2 (1.0 mL). [b] Yield of isolated product. [c] Determined by chiral HPLC methods. [d] The absolute configuration of **3a** was determined by X-ray analysis; refer to reference [17]. [e] Run for 48 h. Bn = benzyl.

disubstituted and fused thiols (Table 2, entries 10 and 11), all took place efficiently with excellent results. Moreover, the heteroaromatic group (Table 2, entry 12) was also well tolerated. Less reactive alkanethiols were also suitable substrates, although the reaction time was somewhat longer. For example, 4-methoxy benzyl mercapatan (**1m**) reacted smoothly with nitroolefin enoate **2a** to afford the correspond-

ing chroman **3m** with 95% *ee* and greater than 95:5 d.r., respectively (Table 2, entry 13). Notably, the absolute configuration of the product was determined as (2*R*,3*R*,4*R*) by using X-ray crystallographic analysis of **3a** (Figure 3).[17]

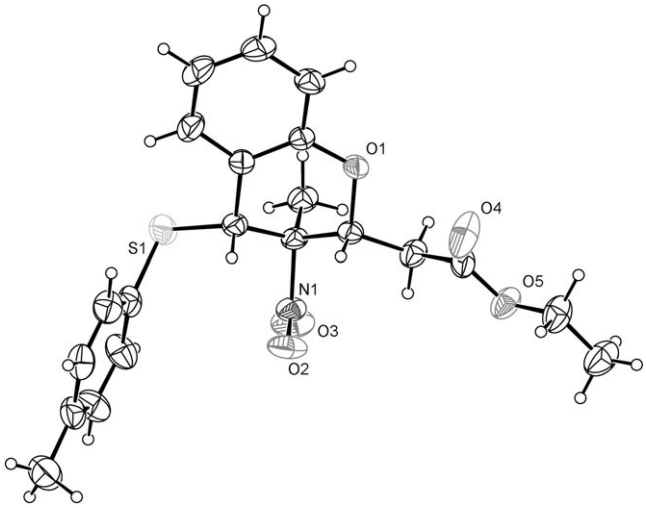
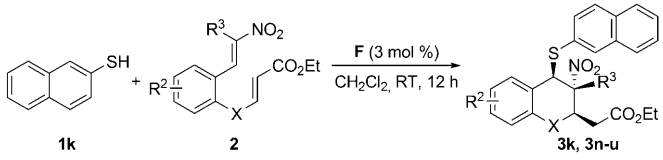


Figure 3. X-ray crystal structure of compound **3a**. The thermal ellipsoids are drawn at 30% probability.

More importantly, a wide array of the nitroolefin enoates was also suitable for this sulfa-Michael/Michael cascade addition reaction. As illustrated in Table 3, in general, the reaction proceeded efficiently to provide the desired multisubstituted chiral chromans in high yield (66–92%) with excellent stereoselectivity (88–92% *ee*, >95:5 d.r.) in the presence of 3 mol% of **F**. As highlighted in entry 8 of Table 3, nitroolefin enoate **2h** having a bulky benzyl group in the α position was accommodated in this reaction, thus generating the corresponding adduct **3t** at 81% yield, 96% *ee*, and 95:5 d.r. Aliphatic substrates were tolerated as well. For example, nitroolefin enoate **2i** underwent cyclization to give **3u** at moderate yield (72%), with excellent enantioselectivity (92%) and poor diastereoselectivity (67:33). Linear aliphatic substrates can also participate in this cascade sequence. For example, nitroolefin enoate **2j** underwent the double Michael addition reaction and provided polyfunctionalized cyclohexane in moderate yield (58% yield) with excellent enantioselectivity (96% *ee*) and diastereoselectivity (>95:5 d.r.) [Eq. (3)].

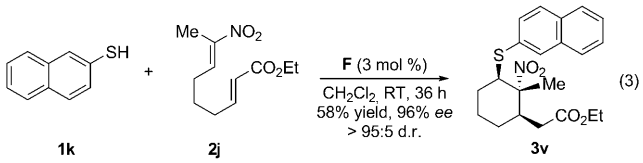
Table 3: Double Michael addition reactions of 2-thionaphthol (**1k**) to various nitroolefin enoates **2** with catalyst **F**.[a]



1k **2** **3k, 3n-u**

Entry	R^2	R^3	X	Yield [%][b]	*ee* [%][c]	d.r.[c]
1	H	Me (**2a**)	O	89 (**3k**)	91	>95:5
2	4-Me	Me (**2b**)	O	84 (**3n**)	88	>95:5
3	4-MeO	Me (**2c**)	O	66 (**3o**)	92	>95:5
4	4-F	Me (**2d**)	O	87 (**3p**)	92	>95:5
5	4-Cl	Me (**2e**)	O	73 (**3q**)	92	>95:5
6	4-Br	Me (**2f**)	O	90 (**3r**)	92	>95:5
7	5-MeO	Me (**2g**)	O	92 (**3s**)	92	>95:5
8	H	Bn (**2h**)	O	81 (**3t**)	96	95:5
9	H	Me (**2i**)	CH_2	72 (**3u**)	92	67:33

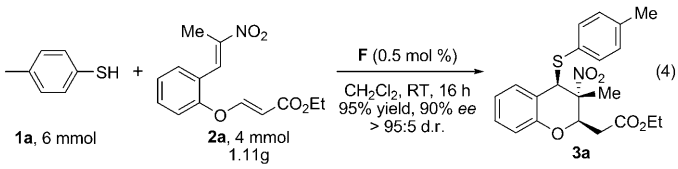
[a] Conditions: **1k** (0.3 mmol), **2** (0.2 mmol), **F** (3 mol%), and CH_2Cl_2 (1.0 mL). [b] Yield of isolated product. [c] Determined by chiral HPLC methods.



1k **2j** **3v** (3)

In analogy to the bifunctional organocatalysts that catalyzed the Michael addition reaction,[18] a plausible catalytic cycle involving the double Michael addition reaction of thiols with nitroolefin enoates is outlined in Scheme 1. Firstly, catalyst **F** activates nitroolefin enoate **2a** through a hydrogen-bonding interaction, and its basic tertiary amino moiety activates the nucleophilic *para*-thiocresol (**1a**), thereby forming intermediate **I**, which undergoes the intermolecular sulfa-Michael addition to provide the intermediate **II**. Another intramolecular Michael addition to this intermediate generates a cyclized intermediate, and subsequent proton transformation leads to the corresponding chroman **3a** with the release of catalyst **F**.

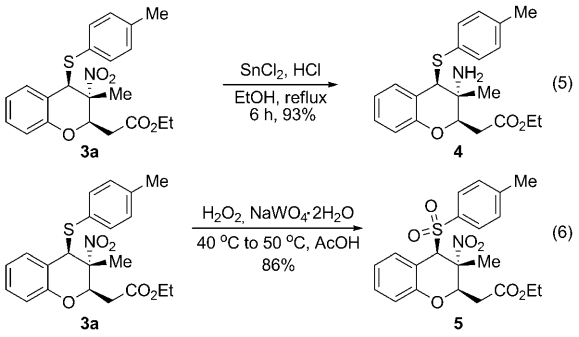
To validate the potential utility of this methodology, a model reaction of the cascade process was carried out on a gram scale. Notably, the reaction took place smoothly in the presence of only 0.5 mol% **F** to afford a slightly better product yield (95%) without any loss of stereoselectivity [Eq. (4)].



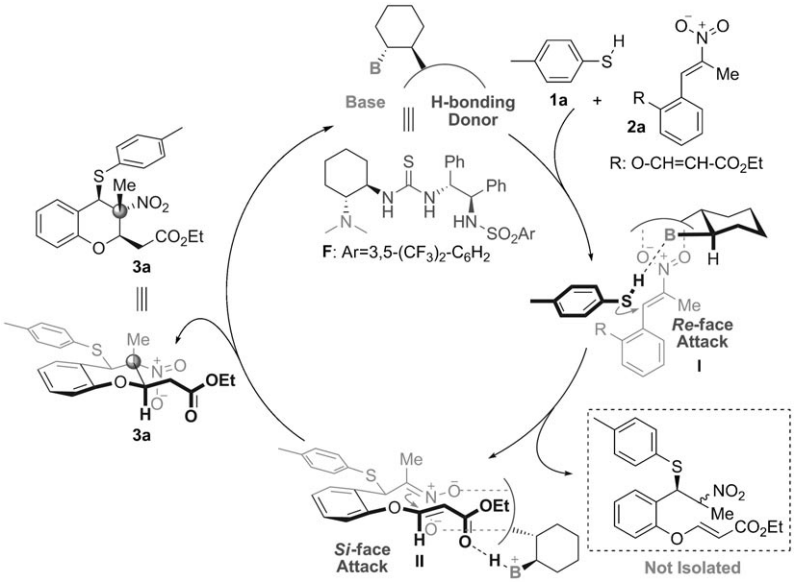
1a, 6 mmol **2a**, 4 mmol 1.11g **3a** (4)

A demonstration of the synthetic value of the double Michael addition reaction is described. For instance, the cascade reaction adducts can be readily transformed into the chroman ring containing γ-amino acid ester **4** by reducing the nitro group in the presence of $SnCl_2$ [Eq. (5)]. Moreover, oxidation of **3a** by using H_2O_2 and $NaWO_4{\cdot}2H_2O$ can easily produce the core structure of the Gamma secretase inhibitor **5** [Eq. (6)]. These results confirm that potential medicinal candidates can be readily accessed with current methodology from simple starting materials under benign conditions.

Perhaps more importantly, is that the extension of the nucleophile scope in the present transformation has been successfully achieved. For example, the reaction of nitroolefin enoate **2a** with 1*H*-benzo[*d*][1,2,3]triazole (**6**) worked very

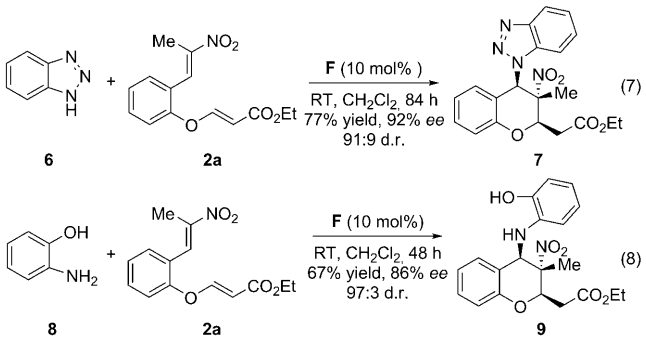


In summary we have developed a novel organocatalyzed sulfa-Michael/Michael addition reaction of thiols with nitroolefin enoates, which provides rapid and efficient access to highly substituted chromans with a quaternary stereocenter from simple and readily available materials. The successful extension of the scope to include divergent nitrogen sources as nucleophiles has been achieved, which additionally demonstrates the synthetic utilizability of the current process. Additional investigations aimed at expanding the scope of the application are underway.



Scheme 1. Proposed reaction pathway for the cascade sequence.

well in the presence of catalyst **F**, affording the corresponding chroman derivative **7** in 77% yield with 92% *ee* and 91:9 d.r. [Eq. (7)]. Notably, the simple 2-aminophenol **8** can also participate in this cascade reaction efficiently, providing the desired product **9** in good yield with excellent stereoselectivity (86% *ee*, 97:3 d.r.) [Eq. (8)]. With the use of diverse nucleophiles, the reaction can be employed in the synthesis of structurally complex and biologically interesting heterocycles. These results demonstrate the power of this double Michael addition reaction in the area of heterocyclic chemistry and medicinal industry.[19]



Experimental Section

Representative procedure: A mixture of *para*-thiocresol (**1a**; 0.3 mmol, 37 mg), nitroolefin enoate **2a** (0.2 mmol, 55 mg), and catalyst **F** (0.006 mmol, 4 mg) in CH_2Cl_2 (1 mL) was stirred at room temperature for 12 h. The crude reaction mixture was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 20:1–15:1) to give the desired product **3a** as a white solid in 91% yield, 90% *ee*, and > 95:5 d.r.

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