

Expeditious diastereoselective construction of a thiochroman skeleton *via* a cinchona alkaloid-derived catalyst†

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An example of diastereoselective and enantioselective synthesis of thiochroman derivatives through a sulfa-Michael–Michael cascade sequence is disclosed. This is a significant complement of the quinine-thiourea catalyzed sulfa-Michael–Michael cascade reaction. The densely functionalized target thiochromans were obtained in high diastereoselectivities, and with high to excellent enantioselectivities.

Introduction

Asymmetric organocatalysis is nowadays recognized as a fundamental synthetic strategy for efficient assembly of chiral molecules.¹ The rapid growth of organocatalysis over the last decade has been warranted by many factors such as efficiency, cost-effectiveness, low environmental impact, and operational simplicity. All of these features have generated a remarkable scientific competition, which has guided asymmetric organocatalysis towards excellent levels of development and opened new synthetic opportunities that were considered inaccessible a few years ago. The extraordinary pace of innovation and progress has been mainly dictated by the discovery of generic catalytic modes that have enabled previously unknown transformations. Consequently, venerable chemical transformations that lead to the preparation of useful chiral building blocks have been generally chosen as benchmarks for developing novel, more effective catalysts and asymmetric transformations. Within 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.² Of the catalytic strategies developed for enantioselective cascade transformation, bifunctional organocatalysts bearing

both hydrogen-bond donor and Brønsted base have generated a focus of attention in recent years.³

The chemistry of sulfur based six-membered rings, thiopyrans, has, to date, been less extensively studied than that of the analogous pyrans.⁴ Although not particularly common throughout nature, this class of sulfur-containing heterocycles is of synthetic and biological interest. 3,4-Dihydro-2*H*-1-benzothiopyrans, more commonly known as thiochromans, exhibit anti-inflammatory, anti-pyretic, anti-depressant, and analgesic activities.⁴ For example, compound **A**, CH4986399 (Fig. 1), exhibited high clinical efficacy in tamoxifen and fulvestrant resistant ER-positive breast cancer patients.⁵ Compound **B** was discovered as a 5-HT_{1A} receptor agonist for use in depression, schizophrenia and Parkinson's disease.⁶ Therefore, these complex polycyclic frameworks have become targets of interest in the synthetic organic community. Despite these advances, organocatalytic asymmetric methods for the construction of thiochromans remain largely unexplored.

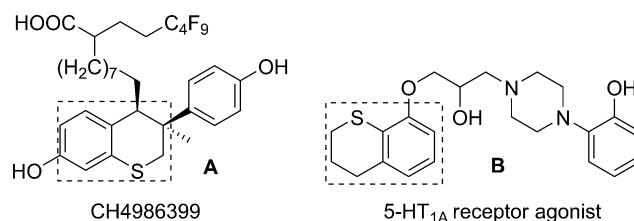


Fig. 1 Examples of biologically active thiochroman derivatives.

Wang *et al.* reported an example of the synthesis of densely functionalized thiochromans *via* cascade thio-Michael–Michael reactions of *trans*-3-(2-mercaptophenyl)-2-propenoic acid ethyl esters with nitroalkenes (Fig. 2, **A**).⁸ Although it is a highly enantioselective approach, the diastereomeric synthesis of thiochroman derivatives continues to be a substantial challenge. In this context, we document here a different asymmetric catalytic strategy for the diastereoselective synthesis of thiochromans through a new catalyst and a sulfa-Michael–Michael cascade sequence (Fig. 2, **B**). In particular, the one-pot cascade process affords enantio-enriched thiochromans with the creation of three new stereogenic centers in remarkably high efficiency and stereoselectivity. Undoubtedly, this method is a significant complement to previous synthetic contributions.

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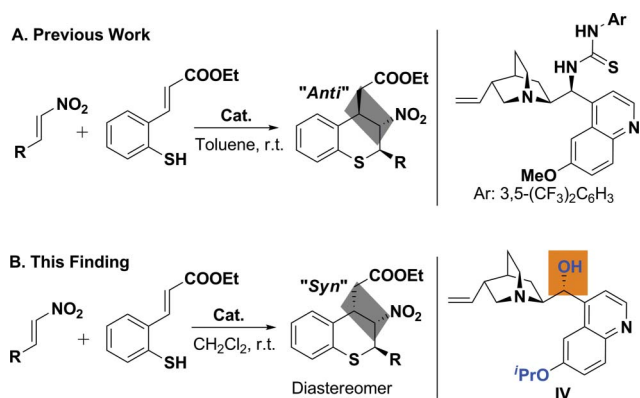


Fig. 2 Overview of the H-bonding mediated sulfa-Michael–Michael cascade reactions.

Results and discussion

To probe the feasibility of the proposed cascade reaction, *trans*-3-(2-mercaptophenyl)-2-propenoic acid ethyl ester **2a** was treated with *trans*- β -nitrostyrene **1a** in the presence of catalyst **I** (Fig. 3) in CH_2Cl_2 at room temperature. In contrast to quinine thiourea catalyst (Fig. 2, **A**), there is a chiral center inversion on C9 of **I**. Catalyst **I** is also a bifunctional catalyst, which bears a hydroxyl group and a tertiary amine. It is surprising that **3a** with a novel diastereomeric structure was finally produced (Table 1, entry 1, 85%). Meanwhile, **3a** was obtained in 68% *ee* and 18:1 d.r. We envisioned that chiral inversion of C6 is the main element for new diastereomer formation. We conclude that the dihedral angle between two functional groups would be a decisive factor. It is associated with the size of quinoline at the C9 position which can directly affect the rotation between C9 and C8. To validate our hypothesis, a series of cinchona alkaloid derivatives were synthesized and applied to this reaction. Accordingly, some bulky groups, such as OMe, OEt, O^tPr, OcHex, and OTr, were introduced to the C6' position of catalyst **I** to finally generate catalysts **II**–**VI** (Fig. 3). The investigation based on catalysts **II**–**VI** revealed that O^tPr is the most appropriate size. In this case, catalyst **IV** promoted the reaction smoothly to furnish the desired diastereomer **3a** in 78% yield and with good selectivity (16:1 d.r.; 82% *ee*) (Table 1, entry 4). More hindered catalysts (**V** and **VI**) and less hindered catalysts (**II** and **III**) gave relatively low

Table 1 Influence of chiral catalysts^a

Entry	Cat.	Yield (%) ^b	d.r. ^c	<i>ee</i> (%) ^d
1	I	85	18:1	68
2	II	80	20:1	75
3	III	78	12:1	73
4	IV	78	16:1	82
5	V	76	16:1	76
6	VI	trace	n.d. ^e	74
7 ^f	VII	—	—	—
8 ^g	VIII	—	—	—
9 ^g	IX	—	—	—
10	X	83	20:1	–76
11 ^f	XI	—	—	—
12 ^h	XII	—	—	—

^a Reaction conditions: *trans*- β -nitrostyrene **1a** (0.1 mmol, 1.0 equiv.), 3-(2-mercapto-phenyl)-acrylic acid ethyl ester **2a** (0.12 mmol, 1.2 equiv.) and 10 mol% catalyst were dissolved in DCM (0.5 mL) at room temperature for 36 h. ^b Yield of isolated product after column chromatography. ^c Determined by ¹H NMR analysis of the crude mixture. ^d Enantiomeric excess (*ee*) was determined by HPLC. ^e Not determined. ^f No desired product. ^g Only Michael adduct was detected. ^h Different major diastereomer was obtained (see Ref. 8).

enantioselectivities (73–76% *ee*) (Table 1, entries 2–3 and 5–6). Further investigation on quinoline structure was also examined. Catalyst **VII** (Fig. 3, cupreine) has a one more –OH group at C6'. Unfortunately, this acidic –OH group, as a potential H-bonding donor, did not improve the stereo-selective performance and afforded a non-desired diastereomer (entry 7). If the –OH group (C9 position) was protected, reactions were sluggish and only simple Michael adducts were generated (entries 8 and 9). In addition, catalyst **X** (quinidine) was also examined, but no obvious improvement was observed (entry 10, 82%, 20:1 d.r., –76% *ee*). To understand the role of the –OH group in catalyzing the reaction, we performed density functional theory (DFT) calculations under the generalized gradient approximation (GGA). It was found that the reaction between **1a** and **2a** is modestly exothermic with a thermochemical energy of –7.4 kcal mol^{–1}. In the absence of the catalyst **IV**, the reactants approach each other, forming a transition state that allows the H_{2a} atom of **2a** to migrate to C_{2a} of **2a** assisted by the –NO₂ group of **1a**, leading to the completion of the cycloaddition **3a**. The calculated activation barrier of 29.1 kcal mol^{–1} is considerably high, suggesting the reaction is kinetically difficult. In the presence of the catalyst **IV**, however, we identified a transition state participated by **1a**, **2a**, and **IV**. Here, H_{2a} transfer from the H–S bond to C_{2a} of **2a** is facilitated *via* H exchange mediated by the –OH group of the catalyst **IV** as indicated in the optimized structure shown in Fig. 4. Consequently, the activation barrier is substantially reduced to 15.9 kcal mol^{–1}. Upon completion of the reaction, the conformation of the catalyst **IV** is recovered with the H atom of the –OH group pointing to the N_{IV} atom to take advantage of the H-bonding. To verify our hypothesis, we did the following reactions. 1) catalyst **IX** (–OH group at C9 was protected by –OBn, Fig. 3) was synthesized and applied to this reaction. However, the experimental result showed that the reaction only generated the Michael adduct and no desired

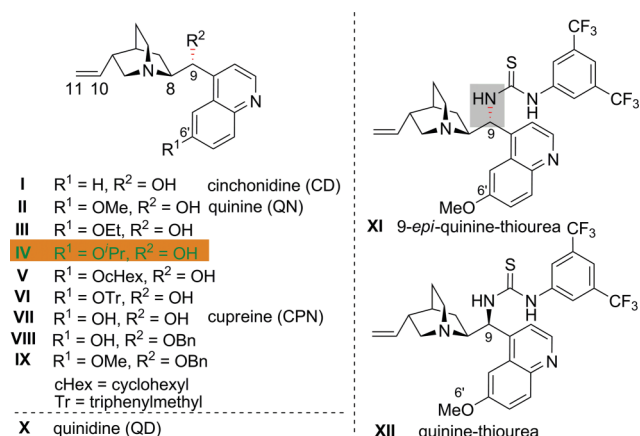


Fig. 3 Evaluated chiral catalysts.

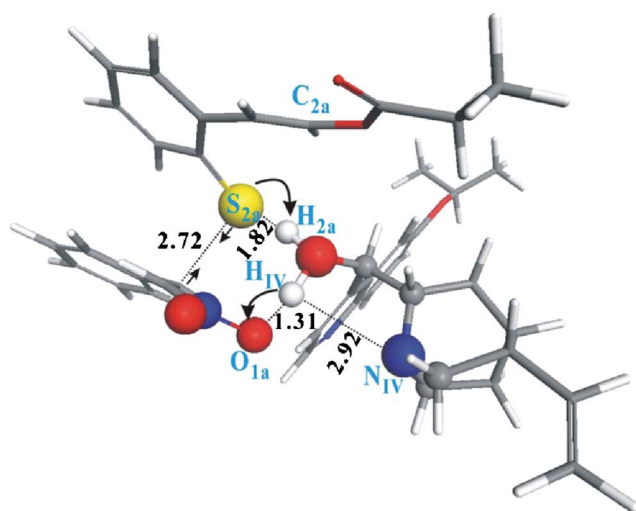


Fig. 4 The fully optimized transition state structure for the cascade reaction of **1a** and **2a** catalyzed by **IV**.

product was finally achieved (Table 1, entry 9). 2) Catalyst **VIII** (–OH group at C9 was protected by –OBn, but another –OH group was introduced to C6 position, Fig. 3) was also synthesized and applied to this reaction. Surprisingly, the experimental result showed that the reaction is sluggish and no desired product was detected. Based on the above experimental results, we predict that the position of this –OH is very critical for catalytic activation. 3) In addition, we synthesized an *epi*-quinine thiourea catalyst **XI** (a pseudo-enantiomer of quinine-thiourea catalyst **XII**,⁹ Fig. 3). The catalyst **XI** has a bulky and more acidic thiourea group at the C9 position. Interestingly, this thiourea catalyst **XI** caused a sluggish reaction and gave no desired product (Table 1, entry 12). In summary, we found that the –OH group at C9 was a unique factor and played an irreplaceable catalytic function.

With regard to high stereo-control, further optimization was performed by examining other parameters, such as solvent, temperature and reaction concentration (Table 2). In contrast, CH₂Cl₂ was revealed as the best media. For the purpose of high enantioselectivity, we evaluated the reaction temperature (Table 2, entries 9–13). A higher stereo-control was achieved when the temperature was locked at 0 °C (Table 2, entry 12, 25 : 1 d.r., 90% *ee*). A lower temperature (–30 °C) slowed down the reaction but without any obvious improvement in stereo-control (Table 2, entry 13, 79%, 25 : 1 d.r., 89% *ee*). If the concentration decreased from 0.2 M to 0.1 M or 0.05 M, improved results were not observed (Table 2, entries 10 and 11, 83% *ee* and 82% *ee*, respectively).

Having established the optimal conditions, we then explored the generality of this cascade process. Remarkably, this enantio- and diastereo-selective cascade process served as a reliable synthetic protocol for the preparation of densely functionalized thiochromans (Table 2). Significantly, three new stereocenters were efficiently created in good to high enantioselectivities, and excellent diastereoselectivities in a one-pot process. It was found that an extensive range of nitroalkenes can efficiently participate in the process (Table 2, **3a–o**), irrespective of the electronic nature and the substitution pattern of the aromatic system. For example, the reaction takes place with aromatic systems that possess electron-neutral (Table 2, **3a**), -withdrawing (Table 2, **3b–f**), or -donating (Table 2, **3g–l**) groups at the *o*, *m*, or *p* positions of the nitroalkenes

Table 2 Substrate scope

3a , 92% yield 90% <i>ee</i> 25:1 d.r.	3b , 94% yield 86% <i>ee</i> 29:1 d.r.	3c , 88% yield 86% <i>ee</i> 25:1 d.r.	3d , 90% yield 86% <i>ee</i> 15:1 d.r.
3e , 91% yield 84% <i>ee</i> 15:1 d.r.	3f , 87% yield 80% <i>ee</i> 15:1 d.r.	3g , 89% yield 82% <i>ee</i> 21:1 d.r.	3h , 93% yield 80% <i>ee</i> 72:1 d.r.
3i , 88% yield 88% <i>ee</i> 99:1 d.r.	3j , 92% yield 83% <i>ee</i> 17:1 d.r.	3k , 86% yield 82% <i>ee</i> 26:1 d.r.	3l , 95% yield 90% <i>ee</i> 26:1 d.r.
3m , 90% yield 90% <i>ee</i> 60:1 d.r.	3n , 93% yield 86% <i>ee</i> 19:1 d.r.	3o , 92% yield 84% <i>ee</i> 15:1 d.r.	3p , 89% yield 66% <i>ee</i> 2:1 d.r.

without substantial loss in yields (86–94%) or stereoselectivities (80–90% *ee*, 15 : 1 to 99 : 1 d.r.). However, if there is an –OH group at the *p* position of phenyl ring (Table 2, **3p**), a moderate result (66% *ee* and 2 : 1 d.r.) was obtained. The loss of stereoselectivity may be caused by the additional hydrogen bonding between the –OH group and catalyst **IV**, which might affect the relative orientation of nucleophile and electrophile in this reaction. Moreover, a heteroaromatic nitroolefin (Table 2, **3n**) can also be tolerated. A good *ee* value and diastereoselectivity were obtained in the presence of a less reactive aliphatic nitroalkene (Table 2, **3o**, 84% *ee* and 15 : 1 d.r.). The absolute configuration of the products was determined by single-crystal X-ray diffraction analysis (Fig. 5, a sulfonate ester **3q**) (for structure, see Supporting Information†).⁷

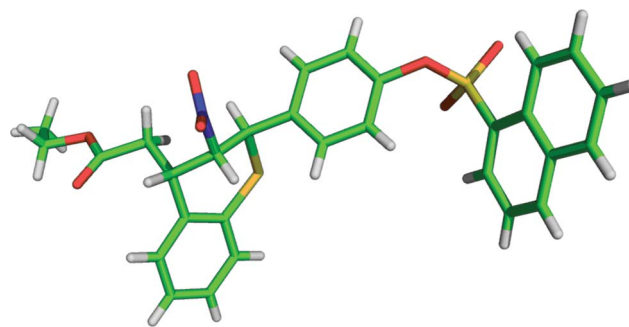


Fig. 5 X-ray crystal structure of **3q**.

Conclusions

In conclusion, we have developed a novel quinine derivative as an effective catalyst to promote a one-pot cascade reaction for the enantioselective and diastereoselective synthesis of thiochroman derivatives. This is an important complement of the previous method of quinine-thiourea catalyzed thio-Michael–Michael cascade reaction. The densely functionalized target thiochromans

were obtained in good to high yields, moderate to high diastereoselectivities, and good to high enantioselectivities. Further applications of this mode, with regard to other transformations, are under investigation in our laboratory.

Acknowledgements

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