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Enantioselective Synthesis of Chromans with a Quaternary Stereogenic Centre through Catalytic Asymmetric Cascade Reactions

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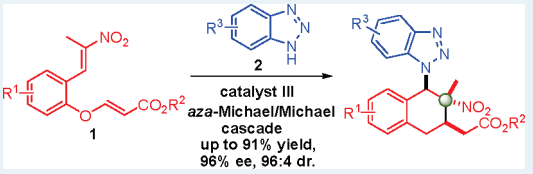
Supporting Information

ABSTRACT: A highly enantioselective cascade reaction of benzotriazoles with nitroolefin-containing enonates catalyzed by a base/acid bifunctional organocatalyst has been developed. This cascade sequence affords efficient access to densely functionalized chiral chromans with a quaternary stereogenic center in high yield (up to 91%) with excellent enantioselectivity (up to 96% ee) and diastereoselectivity (up to 96:4 dr). The reaction itself features simple experimental procedures under benign conditions and is completely atom-economic in character.



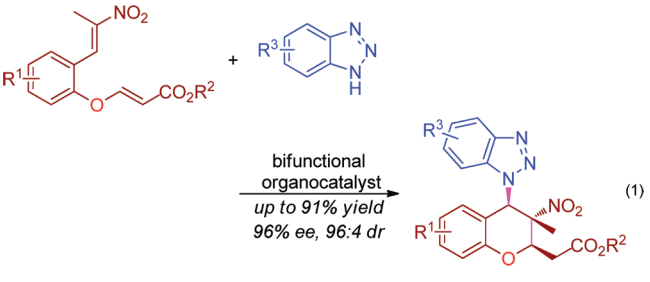
KEYWORDS: organocatalysis, cascade reaction, Michael addition, heterocycle, chromans

INTRODUCTION

Chromans are a class of important structural motifs widely found in numerous natural products and medicinal reagents that display an array of biological activities.[1−6] For example, Cromakalim has proved antihypertensive effects.[7,8] Rhododaurichromanic acid A displays anti-HIV activity.[9] Calanolide A exhibits excellent inhibition of HIV-1 reverse transcriptases (Figure 1).[10,11] In view of diversity-oriented synthesis, the introduction of a diverse array of the functionalities to chroman framework that is unprecedented in nature through chemical methods is an important endeavor in the chemical-synthesis community. Particularly, great research efforts have been directed toward the catalytic asymmetric processes. Representative examples include Lewis acid and transition-metal catalyzed asymmetric epoxidation,[12−15] allylic alkylation,[16,17] oxidative cyclization,[18−20] enyne cyclization,[21] and others.[22−26] Recently, Wang and coworkers have developed a new powerful catalytic cascade oxa-Michael/Michael reaction by the use of diphenylprolinol silyl ether as the catalyst, providing an efficient approach to optically active chromans.[27] Notably, the Chen group cleverly developed an organocatalytic aza-Diels−Alder reaction between aza-1,3-butadienes and aldehydes, affording a variety of tricyclic chroman-2-one derivatives.[28] Despite these impressive contributions,[29−32] the search for highly enantioselective approaches to complex chroman architectures, especially those with multiple stereogenic carbon atoms and quaternary stereocenters, is still of great importance.

In addition to chromans, various nitrogen-containing heterocycles have also been identified as versatile synthetic building blocks with significant biological activities, and have therefore found broad applications in organic synthesis and the pharmaceutical industry.[33−37] In this context, benzotriazole derivatives have been found to exhibit potent pharmacological activities, such as analgesic, anti-inflammatory, antifungal, antineoplastic, antiviral, and antihypertensive properties.[38−44] Concerning the unique biological importance of chroman and benzotriazole derivatives, we envisaged that the rational combination of such two "privileged" structural motifs into one molecule would probably provide a new class of heterocycles for the drug candidate discovery.

Asymmetric conjugate addition reactions of nitrogen-centered nucleophiles are among the most useful and challenging synthetic transformations. During the past decade, organocatalytic cascade reactions involving Michael/Michael addition have been established as one of the most powerful methods for the rapid construction of molecular complexity.[45−53] Desipte advances,[54−62] enantioselective aza-Michael/Michael addition reactions have not received much attention up to date.[63] As part of our ongoing project on carba- and heterocycle-oriented methodology development,[64−69] we herein describe a bifunctional organocatalyst-promoted asymmetric aza-Michael/Michael addition reaction involving benzotriazoles as N-nucleophiles[70−79] to create densely functionalized enantioenriched chromans in high yields (up to 91%) with high stereoselectivitives (up to 96% ee and 96:4 dr) [eq 1].



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RESULTS AND DISCUSSIONS

Optimization of the Reaction Conditions for the Cascade aza-Michael/Michael Addition Reaction. We initially examined the feasibility of the aza-Michael/Michael addition cascade of benzotriazole **2a** to nitroolefin enoate **1a** in CH_2Cl_2 at 10 °C by the use of the readily available bifunctional base/acid organocatalyst **I** (Figure 2).[80−88] To our delight, the desired reaction indeed occurred to give the corresponding product **3a** in 90% yield with 81:19 dr and 87% ee (Table 1, entry 1). Encouraged by this result, the effects of solvents on this reaction were investigated. Among the reaction media screened, CH_2Cl_2 was found to be the optimal reaction solvent (Table 1, entries 2−7 vs 1). We also examined a variety of base/acid bifunctional organocatalysts with the goal to improve the stereoselectivity. As shown in Table 1, chiral amine-thiourea catalysts **I** to **VI** could efficiently prompt the reaction with variable diastereo- and enantioselectivity. Among them, catalyst **III** proved to be the most efficient one and gave rise to **3a** in 77% yield with 91:9 dr and 92% ee (Table 1, entry 9). Interestingly, with the use of quinidine derived thiourea **VI**, the oppositely configured product was obtained in good yield with comparable stereoselectivity (Table 1, entry 12). On the basis of the above results, catalyst **III** was selected for further study.

Scope for the Cascade aza-Michael/Michael Addition Reaction of Nitroolefin Enonates with 2a. With the optimal reaction conditions in hand, we then explored the scope of nitroolefin enoates for this asymmetric aza-Michael/Michael addition cascade. As highlighted in Table 2, the reaction proceeded smoothly to give a wide range of highly functionalized chiral chromans with a benzotriazole-substituent and a quaternary stereocenter in high yield (up to 91%) with excellent enantioselectivity (up to 96% ee) and diastereoselectivity (up to 96:4 dr) in the presence of catalyst **III**. The electronic properties of the substituent on the aromatic ring had little influence on the reaction outcome. For example, the nitroolefin enoates possessing an electron-withdrawing (Table 2, entries 2−4) or electron-donating substituent (Table 2, entries 5−6) at the C4 position of the aromatic ring were successfully utilized in this reaction. In addition, the reaction of the substrate with an electron-donating substituent at the C5 position also worked well without loss in reaction efficiency and stereoselectivity (Table 2, entry 7). Furthermore, nitroolefin enoates with a less or more sterically hindered ester moiety were also successfully engaged in this reaction (Table 2, entries 8−9). Surprisingly, the reaction did not give the desired product when the phenol oxygen in substrate **1** was replaced with a methylene. To expand

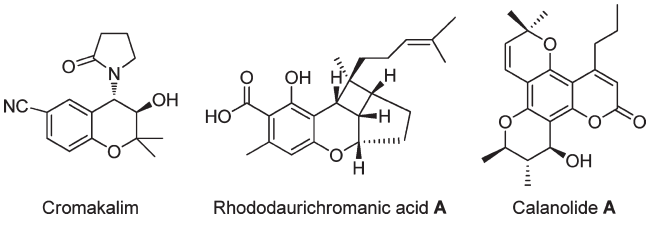
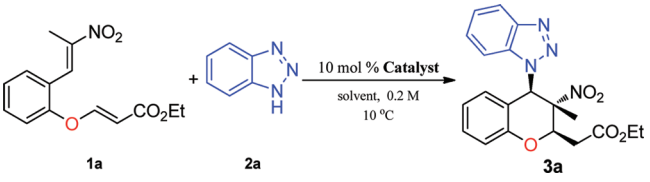


Figure 1. Examples of polysubstituted and biologically active chiral chromans.

Table 1. Optimization of the Reaction Conditions for the Cascade aza-Michael/Michael Addition Reaction[a]



entry	solvent	t/d	catalyst	yield(%)[b]	*ee*(%)[c]	dr[c]
1	**CH_2Cl_2**	**5**	**I**	**90**	**87**	**81:19**
2	$ClCH_2CH_2Cl$	6	**I**	81	85	80:20
3	THF	6	**I**	32	71	78:22
4	Et_2O	6	**I**	70	77	84:16
5	CH_3CN	5	**I**	96	73	85:15
6	Toluene	5	**I**	78	67	76:24
7	CH_3OH	7	**I**	75	13	83:17
8	CH_2Cl_2	5	**II**	60	81	83:17
9	**CH_2Cl_2**	**5**	**III**	**77**	**92**	**91:9**
10	CH_2Cl_2	6	**IV**	87	25	79:21
11	CH_2Cl_2	3	**V**	56	83	81:19
12	CH_2Cl_2	5	**VI**	70	−90	82:18

[a] Reactions were carried out with **1a** (0.40 mmol), **2a** (0.60 mmol), and catalyst (0.04 mmol) in solvent (2.0 mL) at 10 °C. [b] Yield of the isolated product. [c] Determined by chiral HPLC.

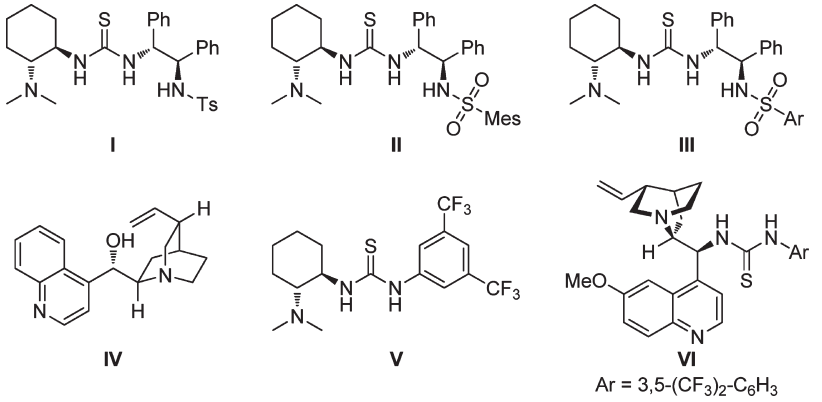


Figure 2. Chiral bifunctional organocatalysts examined in this study.

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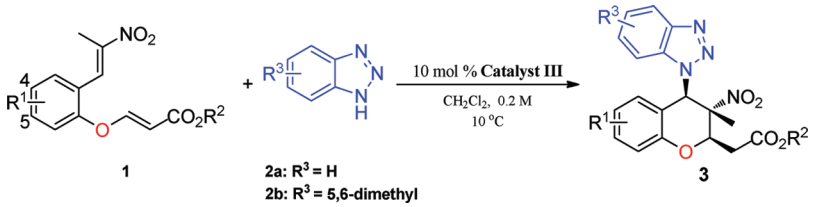
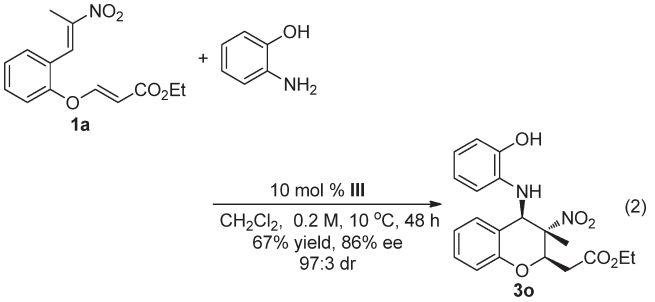
Table 2. Scope for the Cascade aza-Michael/Michael Addition Reaction of Nitroolefin Enoates with 2a[a]



entry	R^1/R^2	R^3	t/d	product	yield(%)[b]	*ee*(%)[c]	dr[c]
1	H/Et (**1a**)	**2a**	5	**3a**	77	92	91: 9
2	4-F/Et (**1b**)		7	**3b**	73	90	85:15
3	4-Cl/Et (**1c**)		5	**3c**	77	89	90:10
4	4-Br/Et (**1d**)		5	**3d**	76	89	89:11
5	4-Me/Et (**1e**)		5	**3e**	88	90	86:14
6	4-MeO/Et (**1f**)		5	**3f**	82	90	95:5
7	5-MeO/Et (**1g**)		5	**3g**	85	91	90:10
8	H/Me (**1h**)		5	**3h**	84	91	92:8
9	H/^{t}Bu (**1i**)		7	**3i**	91	90	86:14
10	H/Et (**1a**)	**2b**	5	**3j**	90	96	96:4
11	4-F/Et (**1b**)		7	**3k**	82	92	90:10
12	4-Cl/Et (**1c**)		5	**3l**	80	90	90:10
13	4-Br/Et (**1d**)		5	**3m**	70	90	90:10
14	5-MeO/Et (**1g**)		5	**3n**	85	94	91:9

[a] Reactions were carried out with **1** (0.40 mmol), **2** (0.60 mmol), Catalyst **III** (0.04 mmol) in CH_2Cl_2 (2.0 mL) at 10 °C. [b] Yield of the isolated product. [c] Determined by chiral HPLC.

the scope of this methodology, the reaction using 5,6-dimethyl benzotriazole **2b** as a nucleophile was investigated. A variety of substituted nitroolefin enoates underwent the cascade reaction efficiently to provide the corresponding products in high yield (up to 90%) with excellent enantioselectivity (up to 96% ee) (Table 2, entries 10−14). The absolute configuration of the product formed in this reaction was determined to be (*2R,3S,4R*) by X-ray crystallographic analysis of the optically pure **3d** (Figure 3).[89] Notably, various nitrogen nucleophiles have been successfully employed in the present transformation. For example, the reaction of nitroolefin-enoate **1a** with 2-aminophenol worked very well in the presence of catalyst **III**, affording the corresponding chroman derivative **3o** in 67% yield with 86% ee and 97:3 dr (eq 2).[32]



Plausible Mechanism for This Cascade aza-Michael/Michael Addition Reaction. As depicted in Scheme 1, a plausible mechanism for this aza-Michael/Michael addition cascade has been suggested based on our experimental results and previously established thiourea catalyst coordinating mode.[80−88,90,91] We

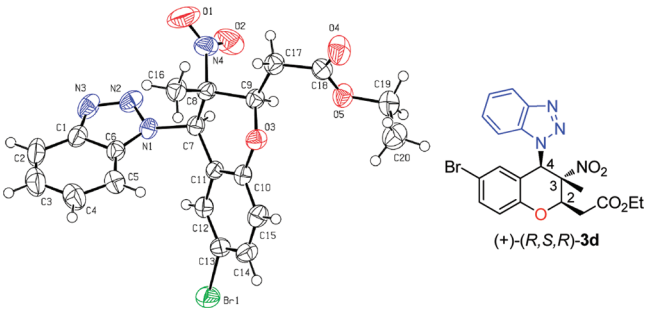


Figure 3. X-ray crystal structure of the (+)-(*2R, 3S, 4R*)-**3d**.

believe that catalyst **III** would be able to activate both electrophilic nitroolefin enoate **1a** and nucleophilic benzotriazole **2a** simultaneously through hydrogen-bonding interactions and its basic tertiary amino group, respectively, by forming intermediate **A**. This would allow the intermolecular aza-Michael addition reaction of nitroalkene through its *Re*-face, and therefore afforded the chiral intermediate **B**. This intermediate might be stabilized by catalyst **III** through hydrogen-bonding. Subsequently, an intramolecular Michael addition reaction could occur to afford the cyclic intermediate **C**. The proton transfer from the protonated amine moiety of catalyst **III** generated the final cyclization product **3a** and released the catalyst **III** for the next catalytic cycle.

Synthetic Transformations of the aza-Michael/Michael Product 3a. To demonstrate the synthetic utilization of this reaction, we have performed the synthetic transformations of the reaction product as highlighted in Scheme 2. The product could

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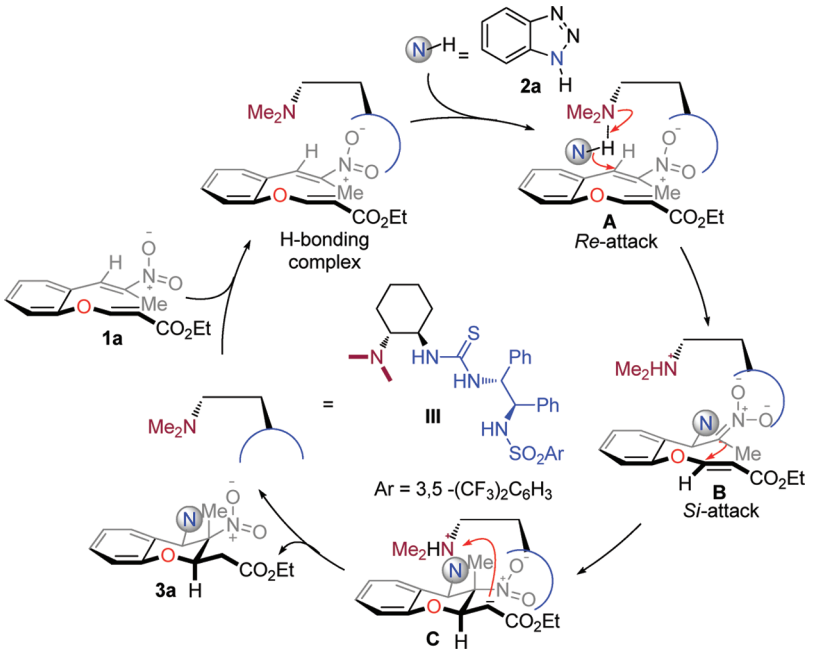
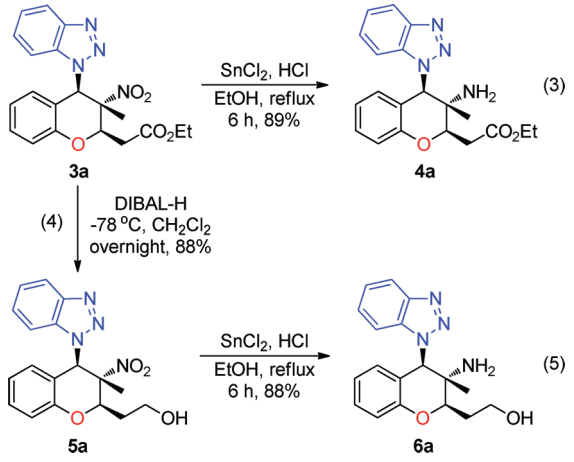
Scheme 1. Plausible Mechanism for This aza-Michael/Michael Addition Cascade



Scheme 2. Synthetic Transformations of the aza-Michael/Michael Product 3a



be readily transformed into a chroman ring containing γ-amino acid ester **4a** by the reduction of the nitro group [eq 3]. In addition, the ester and nitro groups were reduced easily to afford the corresponding alcohol **5a** [eq 4] and δ-amino alcohol **6a**, respectively [eq 5].

CONCLUSION

In summary, we have developed a highly enantioselective aza-Michael/Michael addition cascade of benzotriazoles to nitroolefin enonates catalyzed by a base/acid bifunctional organocatalyst. This reaction provides an efficient access to densely functionalized chiral chromans with a benzotriazole substituent and a quaternary stereocenter in one step from simple and readily available starting materials. We have also demonstrated the utility of this reaction in synthetic transformations. This cascade process features simple experimental procedures under benign conditions and is completely atom-economic in character. Further investigations about the potential biological activities of this type of chromans are underway in our laboratory.

EXPERIMENTAL SECTION

Materials. All substrates were prepared according to literature procedures,[32,67,92−94] and the characterizations were in accordance with previously reported data.

General Procedure for the Asymmetric Cascade aza-Michael/Michael Addition Reaction. A mixture of nitroolefin enoate **1a** (0.40 mmol) and catalyst **III** (0.040 mmol) in CH_2Cl_2 (2.0 mL) was stirred at 10 °C for 15 min, and benzotriazole **2a** (0.60 mmol) was then added to the reaction mixture. Upon completion of the reaction (monitored by TLC analysis), the mixture was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 7/1 to 5/1 as eluants) to afford the desired product **3a**. White solid (77% yield, 92% ee, 91:9 dr). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.12 (d, J = 8.5 Hz, 1H), 7.43−7.39 (m, 2H), 7.35−7.32 (m, 2H), 7.07−7.06 (m, 1H), 6.95−6.92 (m, 1H), 6.56 (s, 1H), 5.31 (d, J = 9.7 Hz, 1H), 4.28−4.24 (m, 2H), 2.84 (dd, J = 16.0, 9.8 Hz, 1H), 2.42 (d, J = 16.4 Hz, 1H), 1.54 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H);. ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 168.58, 152.83, 145.55, 130.33, 127.98, 124.30, 122.52, 120.25, 117.31, 88.75, 76.29, 63.05, 61.26, 34.56, 13.97, 12.23; HRMS (ESI): Calcd for $C_{20}H_{20}N_4O_5$ [M+Na]: 419.1331. Found: 419.1315; $[\alpha]_D^{29}$ = 43.20 (c = 1.04, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC (Chiralpak AS column: hexane/2-propanol = 60/40, 0.5 mL/min, 254 nm, t_{major} = 43.03 min, t_{minor} = 24.53 min)

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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