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Enantioselective Synthesis of Chromanones *via* a Tryptophan-Derived Bifunctional Thiourea-Catalyzed Oxa-Michael–Michael Cascade Reaction

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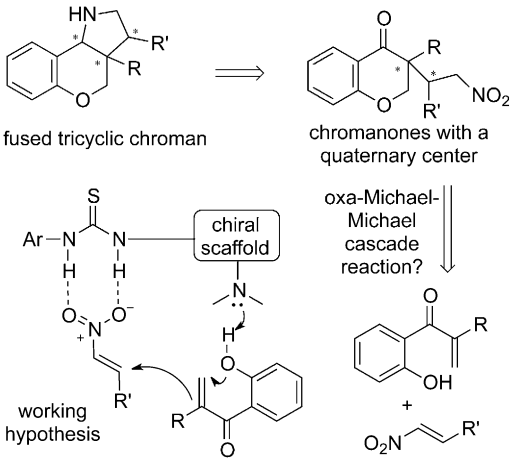
Abstract: Tryptophan-derived tertiary amine-thiourea catalysts were shown to promote a cascade oxa-Michael–Michael reaction between ethylene β-keto esters and nitroolefins, resulting in the formation of 3,3-disubstituted 4-chromanones bearing a quaternary center in high diastereoselectivity and enantioselectivity. The chromanone products can be readily converted to biologically important fused and spiro tricyclic chromans.

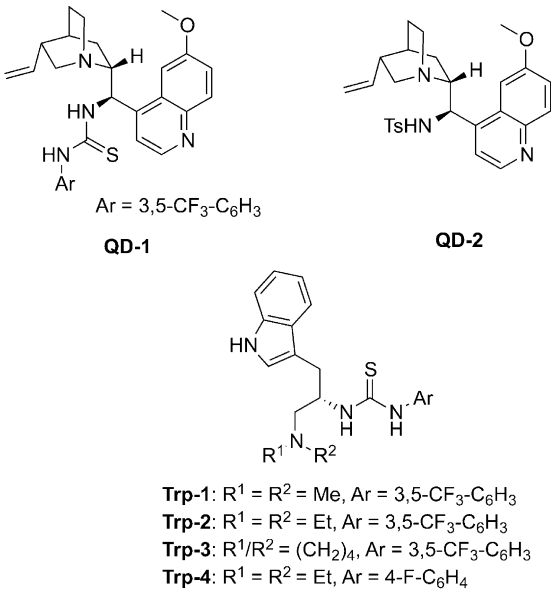
Keywords: bifunctional catalysts; cascade reactions; chromanones; chromans; tryptophan

Chiral chromans and chromanones are important structural motifs that are abundant in natural products and a wide range of biologically significant molecules.[1] Due to their favorable biological activities, various catalytic synthetic strategies have been devised for their efficient asymmetric synthesis. Hoveyda and co-workers described an enantioselective synthesis of chromanones *via* a Cu-catalyzed addition of dialkylzinc to enones.[2] In their recent study, Scheidt et al. utilized an intramolecular conjugate addition strategy for the enantioselective synthesis of flavanones and chromanones.[3] Subsequently, Feng and co-workers reported an enantioselective synthetic strategy, based on chiral *N*,*N*′-dioxide Ni(II)-catalyzed intramolecular oxa-Michael addition to α,β-unsaturated ketones.[4] Organocatalytic cascade reactions[5] have also been employed for the construction of chromans and chromanones. Wang and co-workers developed a cascade oxa-Michael–Michael for the facile construction of chiral chromans *via* an aminal intermeidate.[6] A cascade Michael-aldol sequence has been employed by Hong and Córdova for the asymmetric construction of chromans and chromenes, respectively.[7] Despite the aforementioned elegant synthetic strategies, to the best of our knowledge, an organocatalytic cascade reaction leading to chiral chromanones bearing a quaternary stereogenic center has yet to be reported.[8] It is thus desirable to devise an efficient synthetic strategy to access this type of novel structural motifs.

The creation of quaternary stereogenic centers is a challenging task in organic synthesis.[9] As part of our continuing efforts towards the enantioselective generation of quaternary stereocenters,[10] we became interested in the synthesis of chiral chromanones containing an all-carbon quaternary center. We envisioned that an intramolecular oxa-Michael addition of phenol to an activated alkene, followed by a subsequent intermolecular Michael addition to an nitroolefin might provide a facile one-pot synthesis of highly functionalized 3,3-disubstituted 4-chromanones bearing a quaternary stereogenic center (Scheme 1). A bifunctional tertiary amine-thiourea catalyst[11] appears



Scheme 1. Synthesis of chromanones and tricyclic chromans *via* an oxa-Michael–Michael cascade reaction.

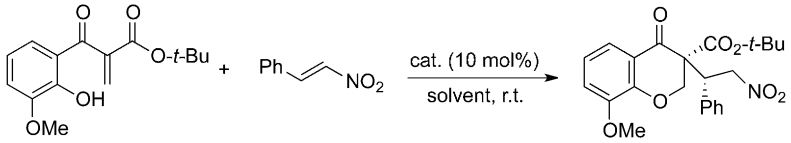


Scheme 2. Bifunctional organic catalysts investigated.

to be suitable for the substrate activations and stereochemical control. Moreover, derivatives of chiral chromanones are not only structural scaffolds of medicinal importance, but also useful synthetic intermediates; their facile elaboration can create fused tricyclic chromans, which are intensively pursued synthetic targets[12] possessing significant biological activities.[13] Herein, we describe a highly efficient oxa-Michael–Michael cascade sequence, leading to an enantioselective preparation of highly functionalized chromanones with a quaternary stereogenic center.

To probe the feasibility of the proposed oxa-Michael–Michael cascade reaction, ethylene β-keto ester **1a**[14] was mixed with nitroolefin **2a** in the presence of a number of bifunctional organic catalysts (Scheme 2), and the results are summarized in Table 1. It should be noted that highly reactive ethylene β-keto esters have not been employed previously in the tandem reactions. Quinidine-derived bifunctional catalyst **QD-1** provided sufficient activation, and the double Michael addition reaction occurred smoothly to afford the desired adduct **3a** in moderate yield, with excellent diastereoselectivity and good enantioselectivity (entry 1). Quinidine-derived sulfonamide **QD-2** offered less satisfactory results (entry 2). Tryptophan-based tertiary amine-thioureas were found to be remarkable catalysts, and the desired products were obtained in good yields, and with excellent diastereoselectivities and enantioselectivities. **Trp-2**, the best catalyst in our previous studies,[10b,h] proved to be superior, affording the desired products with a diastereomeric ratio of 35:1 and 91% *ee* (entry 4). A solvent screening revealed that dichloromethane was the solvent of choice for the reaction

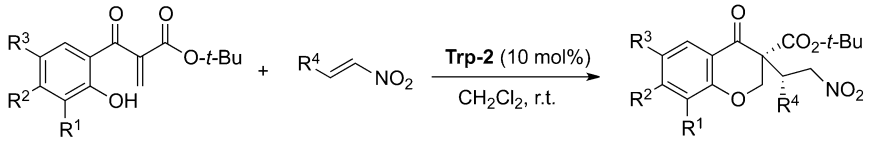
Table 1. Construction of chromanone **3a** *via* an oxa-Michael–Michael cascade reaction.[a]



Entry	Cat.	Solvent	*t* [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**QD-1**	toluene	18	58	34:1	−83
2	**QD-2**	toluene	18	27	23:1	−52
3	**Trp-1**	toluene	18	73	32:1	86
4	**Trp-2**	toluene	18	73	35:1	91
5	**Trp-3**	toluene	18	67	30:1	79
6	**Trp-4**	toluene	18	63	32:1	83
7	**Trp-2**	CH_2Cl_2	18	71	39:1	95
8	**Trp-2**	$CHCl_3$	20	65	30:1	90
9	**Trp-2**	THF	14	57	52:1	90
10	**Trp-2**	Et_2O	24	45	39:1	89
11	**Trp-2**	dioxane	32	16	54:1	90
12[e]	**Trp-2**	CH_2Cl_2	18	81	32:1	95

[a] The reactions were performed with **1a** (0.2 mmol, 1.2 M solution in toluene), **2a** (0.1 mmol) and the catalyst (0.01 mmol) in the solvent (0.4 mL) at room temperature.
[b] Yield of the isolated product.
[c] Determined by ^{1}H NMR analysis of the crude product.
[d] Determined by HPLC analysis on a chiral stationary phase.
[e] The reaction was performed with **1a** (0.1 mmol), **2a** (0.4 mmol) and **Trp-2** (0.01 mmol) in CH_2Cl_2 (0.4 mL) at room temperature.

Table 2. Scope of the cascade oxa-Michael–Michael reaction.[a]



1 2 3

Entry	$R^1/R^2/R^3$ (**1**)	R^4 (**3**)	*t* [h]	Yield [%][b]	**2**: *ee* [%][c]
1	OMe/H/H (**1a**)	*p*-CH_3-C_6H_4 (**3b**)	16	80	94
2[d]	OMe/H/H (**1a**)	*p*-F-C_6H_4 (**3c**)	24	67	97
3[d]	OMe/H/H (**1a**)	*p*-Cl-C_6H_4 (**3d**)	24	74	99
4	OMe/H/H (**1a**)	*p*-Br-C_6H_4 (**3e**)	20	70	91
5[d]	OMe/H/H (**1a**)	*m*-Br-C_6H_4 (**3f**)	20	65	97
6	OMe/H/H (**1a**)	2-furyl (**3g**)	18	63	87
7	OMe/H/H (**1a**)	2-naphthyl (**3h**)	20	73	92
8	OMe/H/H (**1a**)	*n*-butyl (**3i**)	24	41	89
9	H/Me/H (**1b**)	Ph (**3j**)	20	83	95
10	H/Me/H (**1b**)	*p*-Cl-C_6H_4 (**3k**)	24	78	96
11	H/H/H (**1c**)	Ph (**3l**)	18	46	94

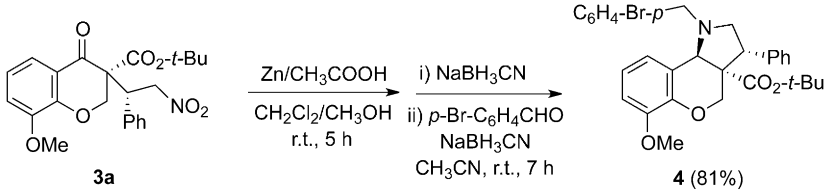
[a] The reactions were performed with **1** (0.1 mmol, 1.2 M solution in toluene), **2** (0.4 mmol) and **Trp-2** (0.01 mmol) in CH_2Cl_2 (0.4 mL) at room temperature.
[b] Yield of the isolated product.
[c] Determined by HPLC analysis on a chiral stationary phase.
[d] The reaction was carried out at 0 °C.

(entries 7–12). Under the optimized reaction conditions, the desired double-Michael cascade product could be obtained in 81% yield and with 32:1 *dr* and 95% *ee* (entry 12).

The scope of this novel oxa-Michael–Michael cascade reaction was next examined (Table 2). Different nitroolefins were found to be suitable substrates, in all the examples examined, single diastereomeric products were obtained in moderate to high yields and with excellent enantioselectivities (entries 1–5). Notably, the reaction was applicable to nitroalkenes containing hetereocyclic rings or an alkyl group (entries 6–8). Different alkylidene β-keto esters could be employed; while electron-rich aryl substitutents promoted the reaction more efficiently, the electronically neutral phenol-substituted alkylidenes[15] afforded the desired cascade product with excellent enantioselectivity, although in moderate yield (entries 9–11).

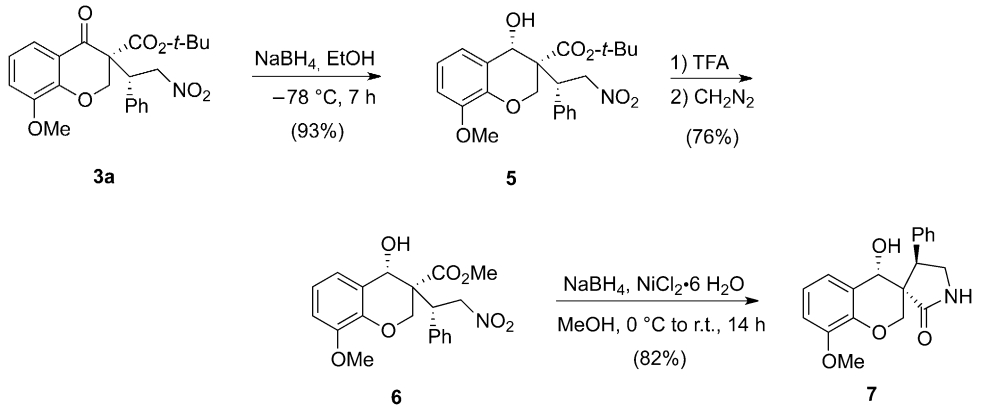
The 3,3-disubstituted 4-chromanone products resulting from the oxa-Michael–Michael cascade reactions are rich in functionality, and can serve as useful synthetic intermediates. Their conversions into useful molecules are illustrated. As shown in Scheme 3, reduction of the nitro group using zinc/acetic acid, followed by reductive amination afforded tricyclic chroman **4** in high yield, a member of class of compounds known to be muscular nicotinic receptor non-competitive antagonists.[13] Alternatively, chromanone **3a** can be readily derivatized into a chiral spiro chroman (Scheme 4). Treatment of **3a** with sodium borohydride afforded alcohol **5** as a single diastereomer. The *tert*-butyl ester was then converted to a methyl ester **6**, and the subsequent reduction of the nitro group resulted in a spontaneous lactam formation, giving spirochroman **7** in excellent yield, which represents an important substructure in many medicinally important agents.[16]

In conclusion, we have developed a novel cascade oxa-Michael–Michael reaction for the construction of optically enriched and densely functionalized 3,3-disubstituted 4-chromanones bearing a quaternary stereogenic center. The synthetic processes described



3a 4 (81%)

Scheme 3. Asymmetric preparation of fused tricyclic chroman **4**.



Scheme 4. Synthesis of chiral spiro tricyclic chroman **7**

could be effectively promoted by tryptophan-derived bifunctional thiourea catalysts, and our method provides an asymmetric entry to biologically important fused and spiro tricyclic chromans.

Experimental Section

Representative Procedure

To a stirred solution of **2a** (59.6 mg, 0.4 mmol) in CH_2Cl_2 (0.4 mL) at room temperature was added **Trp-2** (5.16 mg, 0.01 mmol) under argon. After stirring for 5 min, **1a** (83 μL, 1.2 M in toluene) was introduced. The resulting mixture was stirred at room temperature for 18 h, and extracted with EtOAc several times (3×10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexanes = 1:5) to afford **3a** as a colorless oil; yield: 34.6 mg (81%). See Supporting Information for ^1H and ^{13}C NMR spectra; HR-MS (ESI): $m/z = 450.1529$, calcd. for $C_{23}H_{28}{}^{23}Na_1N_1O_7$, $[M+Na]^+$: 450.1523. The *ee* value of the major isomer was 95%, $t_R = 27.2$ min and 47.9 min (Chiralcel IB, $\lambda = 254$ nm, 10% *i*-PrOH/hexanes, flow rate = 0.3 mL min^{-1}); $[\alpha]_D^{r.t.}$: +45.6 (*c* 1.12, $CHCl_3$)

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