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Enantioselective Synthesis of Densely Functionalized Pyranochromenes via an Unpredictable Cascade Michael–Oxa-Michael–Tautomerization Sequence

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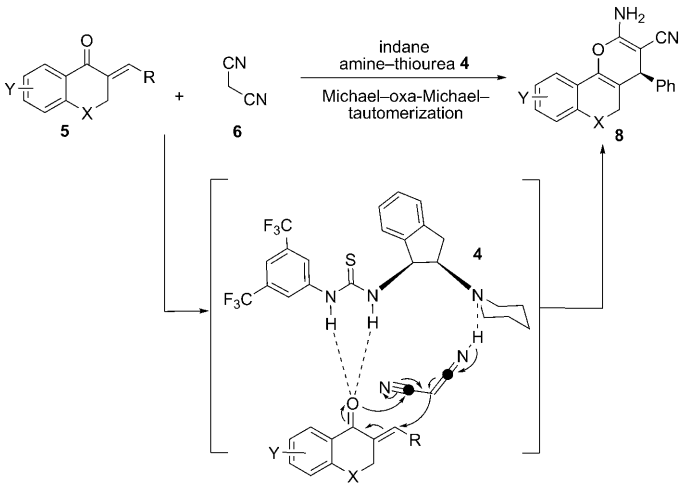
Cascade synthetic strategy has been developed as a uniquely powerful tool for synthetic connections and plays a pivotal role in modern organic synthesis.[1] Given its widespread use, the development of new synthetic cascade reactions for the construction of complex molecules is an important goal of research carried in both academic and industrial laboratories.[2] In particular, asymmetric organocatalytic cascade processes[3] are even more appearing because of their advantages, such as operational simplicity, environment friendliness, and rapid one-pot entries to molecular complexity via atom, step and redox economic or protecting-group-free protocols. Herein, we disclose a new enantioselective organocatalytic cascade reaction with a Michael–oxa-Michael–tautomerization sequence that generates highly functionalized chiral pyranochromene complexes in a concise manner (Scheme 1). Notably, the features of the strategy include 1) the cascade process efficiently catalyzed by a new indane amine–thiourea catalyst via hydrogen-bonding catalysis in good to excellent yields (up to 99%); 2) the first utilization of malononitrile both as nucleophile and electrophile in asymmetric organocatalytic Michael addition; 3) the efficient assembly of highly functionalized pyranochromene complexes with high to excellent enantioselectivities (up to 99% *ee*) in a one-pot reaction.



Scheme 1. Strategy for enantioselective synthesis of densely functionalized pyranochromenes

The catalytic asymmetric C–C bond formation represents one of the most interesting and challenging fields in organic chemistry. A number of asymmetric Michael additions to α,β-unsaturated carbonyl acceptors catalyzed by chiral organocatalysts have been reported.[4] However, the nucleophiles employed in the asymmetric Michael addition reactions are restricted to malonate esters,[5] diketones,[6] ketoesters[7] and nitroalkanes.[8] Extending the scope of either the acceptors or the donors employable in the asymmetric Michael addition is an important advance in order to have access to diversely functionalized and synthetic useful chiral building blocks. The utilization of malononitrile as the nucleophile in Michael additions has received less attention, although the nitrile group can undergo further transformations to 1,3-dicarbonyl derivatives, or imines. Quite recently, the Jacobsen and Kanemasa groups independently reported the enantioselective Michael additions of malononitrile to α,β-unsaturated imides catalyzed by metal catalyst.[9] Later on, the Takemoto group reported the first example of enantioselective Michael reactions of malonontrile to α,β-unsaturated imides in the presence of a chiral organocatalyst (Scheme 2).[10] More recently, the Deng,[11] and Lattanzi[12] groups also independently reported a cinchona alkaloid catalyzed enantioselective Michael addition on malononitrile to enones (Scheme 2). Furthermore, the Zhao group also successfully incorporated malononitrile into three-component reaction for the synthesis of pyranopyrazoles.[16] How-

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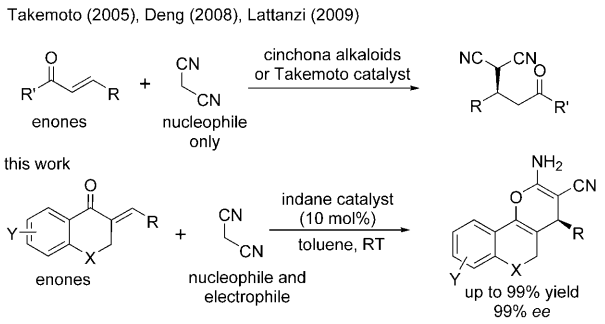


Scheme 2. Organocatalyst promoted cascade reactions of malononitrile with α,β-unsaturated ketones.

ever, all above-mentioned cases demonstrated that malononitrile was only utilized as nucleophile.

To extend the synthetic utility of malononitrile as electrophile or both electrophile and nucleophile in asymmetric catalysis, we wish to undertake an investigation of new protocols. We hypothesized that the new Michael reaction based process might facilitate a new synthetic pathway to construct a complex molecule instead of a simple Michael adduct. Surprisingly, the results of our new reaction exploration envisioned that the change of common enones to benzylidenechromanones efficiently drove the reaction to interact with malononitrile to generate new chiral pyranochromene complexes (Scheme 2). Herein, malononitrile worked as electrophile and nucleophile. Notably, these pyranochromene complexes might possess a broad application in medicinal chemistry.[13]

To explore the feasibility of the proposed catalytic cascade Michael–oxa-Michael–tautomerization process, reactions of (*E*)-3-benzylidenechroman-4-one (**5a**) with malononitrile (**6**) were performed in CH_2Cl_2 at room temperature in the presence of cinchona alkaloid amine–thiourea catalyst **1**, independently developed by the Connon[5e] and Soós[14] groups (see below). As shown in Table 1, the major Michael adduct **7a** was afforded by catalyst **1** with 65% yield and 0.7:1 d.r. (Table 1, entry 1). Interestingly, a small amount of unpredicted complex **8a** was also formed by a 21% yield and a moderate 65% *ee*. The ^1H and ^{13}C NMR results of complex **8a** demonstrated that it has completely different structure in comparison with Michael adduct **7a**. This phenomenon implied that malononitrile could be utilized both as nucleophile and electrophile, especially in asymmetric organocatalysis. Inspired by this new discovery, we then focused our attention to discover a proportional powerful chiral organocatalyst which could efficiently promote reaction to selectively synthesize **8a** and also highly control the stereochemistry of **8a**.

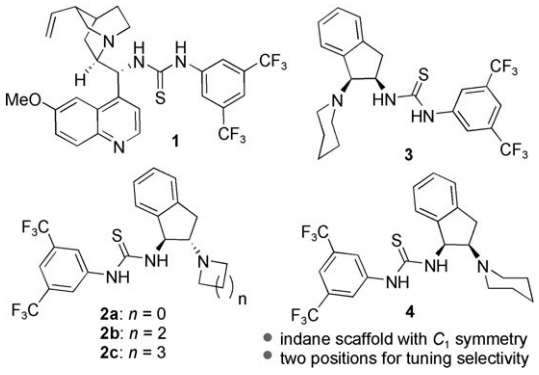
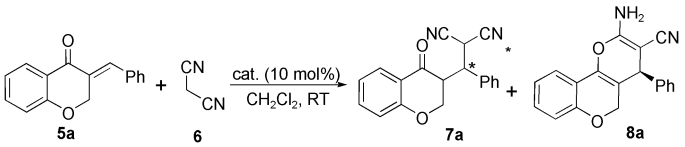


Table 1. Evaluation of the bifunctional organocatalyst.[a]



Entry	Catalyst	**7a**		**8a**	
		Yield [%][b]	d.r. [%][c]	Yield [%][b]	*ee* [%][d]
1	**1**	65	0.7:1	21	65
2	**2a**	41	1.5:1	12	65
3	**2b**	78	1.3:1	16	45
4	**2c**	72	1.9:1	18	67
5	**3**	72	1.5:1	26	-72
6	**4**	21	0.4:1	72	79

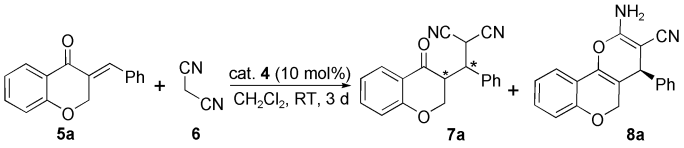
[a] Reaction was conducted on 0.2 mmol scale in DCM (0.2 mL) at RT for 4 d, and the ratio of **5a**/**6** is 1:1.5. [b] Yield of isolated product. [c] Determined by ^1H NMR analysis of the crude product. [d] Enantiomeric excess (*ee*) was determined by HPLC analysis.

Recently, our group developed a series of new bifunctional indane amine–thiourea catalysts which were approved to be efficient chiral catalysts for Michael-type reactions.# Based on these unpublished results, we found that indane catalysts exhibited a number of amazing properties, such as high reactivity and excellent stereocontrol in many cases. Thereby, a test of our indane catalyst's efficiency in this reaction was performed. To this end, a small library of our group synthesized indane catalysts **2**–**4** (see above) was applied to this reaction. The library includes 1) catalyst **2a**, **2b** and **2c** with modifications on the conformation of amine functional group; 2) catalyst **4** with a specific alternation on the relative orientation of amine and thiourea functional groups in comparison with catalyst **2c**; 3) catalyst **3** with an adjustment of the relative positions of amine and thiourea functional groups in contrast to catalyst **4**. Based on our best knowledge, we believe the dihedral angel between two functional groups is one of the key issues for stereocontrol. We envisioned that the change of dihedral angel between the functional groups of amine and thiourea might introduce an ideal and stable transition state to assist the formation of an excellent stereoselectivity. It should be noted that the above discussion is largely speculative and qualitative. Eventually, the new catalyst **4** was discovered as a relatively ideal promoter to catalyze this cascade process under the same condition we stated above (Table 1, entry 6, 72% and 79% *ee* for **8a**). In the catalyst screening, we observed that the geometry and the relative positions of amine and thiourea functional groups played a critical role in promoting reaction and controlling the enantioselectivity. If there was *anti*-geometry between amine and thiourea functional groups, the reactivity of catalysts (**2a**–**c**) was relative weak and the

major product was Michael adduct **7a** (entries, 2–4: 41, 78 and 72%, respectively). Nevertheless, catalyst **4** manifested a relatively higher level of catalyst efficiency and stereocontrol with a formation of desired product **8a**. In terms of catalyst **4** s structure, we found that a *syn*-geometry between amine and thiourea functional groups in catalyst **4** was a significant factor. Surprisingly, a slight interchange of the relative positions of amine and thiourea functional groups (from **4** to **3**) definitely caused the loss of desired compound **8a** (entry 5, 72% yield for major Michael adduct **7a** and only 26% yield for **8a**). In contrast to other catalysts, we envisioned that catalyst **4** could further reduce the activation energy of oxa-Michael step for promoting this cascade sequence.

In view of high enantioselectivity, further optimization efforts were performed by examining other parameters, such as solvents, temperature and reaction concentrations (Table 2). In contrast to other solvents, toluene was revealed as the best media (Table 2, entry 9, 95% and 87% *ee,* 3 d). In the hope of higher enantioselectivities, we decreased the reaction concentration from 1.0 to 0.5 M. As a result, an excellent enantiomeric excess was achieved (entry 13, 95%, 92% *ee*) with a negligible time increase (entry 13, reaction completed in 4 d). If the concentration was reduced to 0.2 M, 95% *ee* was achieved, but with an increased reaction time of 9 d (entry 14).

Table 2. Influence of solvent and concentration on the enantioselective reaction.[a]



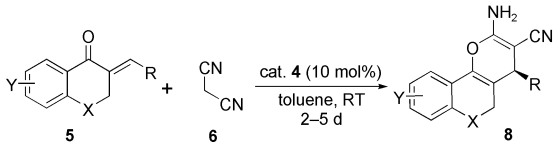
5a 6 7a 8a

Entry	Solvent	7a		8a	
		Yield [%][b]	d.r. [%][c]	Yield [%][b]	*ee* [%][d]
1	CH_2Cl_2	21	0.4:1	72	79
2	$CHCl_3$	13	0.8:1	83	75
3	DCE	9	0.7:1	86	77
4	Et_2O	10	0.9:1	81	67
5	THF	23	2.6:1	56	62
6	dioxane	35	3.0:1	61	67
7	MeOH	25	1.8:1	73	6
8	*i*PrOH	25	2.2:1	68	34
9	toluene	<5	n.d.[g]	95	87
10	xylenes	<5	n.d.[g]	92	88
11	DMF	59	1.9:1	33	7
12	cyclohenane	10	1.1:1	34	85
13[e]	toluene	<5	n.d.[g]	95	92
14[f]	toluene	<5	n.d.[g]	90	95

[a] Unless specified, see the Experimental section for reaction conditions. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis of the crude mixture. [d] *ee* determined by HPLC analysis. [e] 0.5 M, 4 d. [f] 0.2 M, 9 d. [g] Not determined.

Having established the optimal reaction conditions, we next examined the generality of this catalytic process. Remarkably, this enantioselective cascade reaction served as a reliable synthetic process for the preparation of densely functionalized pyranochromenes (Table 3). Significantly, the new stereocenter was efficiently created in good to excellent

Table 3. Substrate scope of the reaction.[a]



5 6 8

Entry	X	Y	R	Yield [%][b]	*ee* [%][c]
1[f]	O	H	Ph (**8a**)	95	92
2[e]	O	H	3-ClC_6H_4 (**8b**)	93	88
3[e]	O	H	4-ClC_6H_4 (**8c**)	92	90
4[e]	O	H	3,4-$Cl_2C_6H_3$ (**8d**)	88	92
5[e]	O	H	2-F-4-ClC_6H_3 (**8e**)	83	87
6[e]	O	H	2-BrC_6H_4 (**8f**)	99	86
7[d]	O	H	4-$NO_2C_6H_4$ (**8g**)	72	93
8[g]	O	H	4-$MeOC_6H_4$ (**8h**)	90	99
9[g]	O	H	4-allyloxyC_6H_4 (**8i**)	85	90
10[e]	O	H	2-allyloxyC_6H_4 (**8j**)	91	92
11[e]	O	H	3-$PhOC_6H_4$ (**8k**)	90	87
12[f]	O	H	4-*i*PrC_6H_4 (**8l**)	88	88
13[g]	O	H	2-thiophenyl (**8m**)	86	81
14[e]	O	6-Cl	Ph (**8n**)	88	92
15[e]	O	6-Me	Ph (**8o**)	91	94
16[g]	CH_2	H	Ph (**8p**)	60	80
17[g]	S	H	Ph (**8q**)	85	81
18[g]	O	H	cyclohexyl (**8r**)	86	86
19[g]	O	H	*i*Pr (**8s**)	75	87

[a] Unless specified, see the Experimental section for reaction conditions. [b] Yield of isolated product. [c] *ee* determined by HPLC analysis. [d] Reaction time: 2 d. [e] 3 d. [f] 4 d. [g] 5 d.

enantioselectivities in one-pot reaction. Moreover, the process not only afforded a pyranochromene complex, and also allowed for a diversely structural variation of (*E*)-3-benzylidenechroman-4-ones **5** (Table 3, entries 1–17, when R = aryl; entries 18 and 19, when R = alkyl). The process also tolerated a replacement of "O" by "S" and "CH_2" to introduce different heterocycles (entries 16 and 17). For examples, the catalyst **4**-promoted cascade process smoothly afforded moderate to excellent yields (60–99%) and high to excellent enantioselectivities (80–99% *ee*). The efficiency of catalyst **4** allowed the reaction to bear a diverse structure of benzylidenechroman-4-one substrates which possess neutral functional groups (entries 1, 14–17, 60–95%, 80–94% *ee*), electron-withdrawing groups (entries 2–7, 72–99%, 86–93% *ee*) and electron-donating groups (entries 8–12, 85–91%, 87–99% *ee*) in backbone. Noticeably, the bulky alkyl group involved benzylidenechroman-4-ones also worked to afford the desired product with good yields (86 and 75%, respectively, entries 18 and 19) and high enantioselectivities (86% and 87% *ee*, entries 18 and 19). When a heterocyclic thiophene was introduced to benzylidenechroman-4-one backbone, the reaction still provided a good enantioselectivities (entry 13, 86%, 81% *ee*). The absolute configuration of the pyranochromene **8f** was unequivocally determined by single-crystal X-ray diffraction analysis (Figure 1).[15]

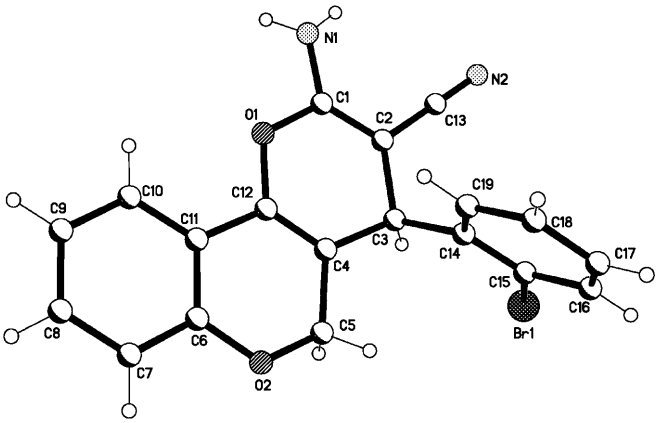


Figure 1. X-ray crystal structure of compound **8f**.

In conclusion, we have developed a cascade Michael–oxa-Michael–tautomerization reaction of malononitrile to enones mediated by an easily accessible chiral bifunctional indane amine-thiourea catalyst **4**. The densely functionalized chiral pyranochromenes were obtained in a one-pot reaction in good to high yields (up to 99%) and high to excellent enantioselectivities (up to 99% *ee*). Moreover, this catalytic system also tolerated many synthetic useful functional groups, such as nitrile, nitro, amino groups which might be manipulated for accessing more sophisticated heterocyclic compounds. Further application of the catalytic system to other new reactions is under investigation in our laboratory.

Experimental Section

General procedure: To a solution of malononitrile **2a** (10 mg, 0.15 mmol) in toluene (0.2 mL) was added (*E*)-3-benzylidenechroman-4-one (**1a**, 24 mg, 0.1 mmol) at room temperature, followed by catalyst **4** (4.9 mg, 0.01 mmol). The mixture was stirred at room temperature for 4 d. The crude product was purified by column chromatography on silica gel, eluted by hexane/EtOAc 8:1 then 4:1 to afford the desired product **8a** as yellow solid (28.7 mg, 95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.32 (m, 3H), 7.27 (q, J = 6.0 Hz, 3H), 7.23–7.15 (m, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.79 (d, J = 8.1 Hz, 1H), 4.64 (s, 2H), 4.63 (d, J = 13.2 Hz, 1H), 4.43 (d, J = 13.8 Hz, 1H), 4.03 ppm (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.77, 154.12, 140.87, 138.01, 130.30, 129.02, 127.92, 127.88, 121.26, 121.04, 119.26, 116.66, 115.94, 105.05, 66.48, 61.16, 39.71 ppm; HRMS (EI): m/z: calcd for $C_{19}H_{14}O_2N_2$: 302.1055, found: 302.1048; HPLC (Chiralpak IC, isopropanol/hexane 10:90, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 27.5 min, t_R (minor) = 15.9 min, *ee* = 92%; $[\alpha]_D^{30} = -64.1$ (c = 0.98 in $CHCl_3$).

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Keywords: asymmetric catalysis · cascade reaction · chromene · organocatalysis · thiourea

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