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Enantioselective organocatalytic synthesis of medicinally privileged 2-amino-4*H*-chromene-3-carbonitriles via a cascade process

Zhiyun Du [a], Woon-Yew Siau [b], Jian Wang [a,b,*]

[a] Faculty of Chemical Engineering and Light Industry, Guang Dong University of Technology, Guang Zhou 510006, China
[b] Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543, Singapore

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ABSTRACT

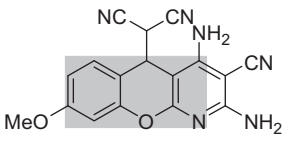
An efficient organocatalytic cascade approach toward medicinally privileged 2-amino-4*H*-chromene-3-carbonitriles is reported. The enantioselective synthesis of these compounds is achieved in high yields and good to high ee values (up to 96% yield and 89% ee) using bifunctional amine-thiourea organocatalysts developed in our laboratory.

Organocatalysis has emerged as a powerful tool in organic synthesis for the construction of highly enantiopure compounds.[1] Many natural products and biologically interesting compounds have been successfully synthesized based on this synthetic strategy.[2] Moreover, the possibility of forming multiple chemical bonds in a one-pot process can also be achieved with the use of small organic molecules by way of an organocatalytic cascade reaction without isolating the intermediates or changing the reaction conditions.[3] This strategy has drawn much attention from both academia and industry as it only requires a single reaction solvent, work-up procedure, and purification step. This is advantageous compared to classical synthesis as it can reduce costs and simplifies synthetic steps.

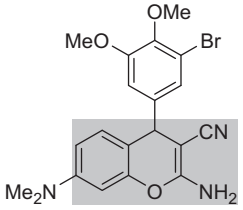
Chromene belongs to a class of naturally occurring benzopyran derivatives with a wide range of biological properties, such as spasmolytic, diuretic, anticoagulant, anticancer, and antianaphylactic.[4] Such diverse biological features have made chromene derivatives important for further exploration in modern medicinal and combinatorial chemistry.[5] In particular, 2-amino-4*H*-chromene-3-carbonitriles are of particular interest (Fig. 1).[6]

Malononitrile, a useful synthetic building block for organic transformations, has been widely employed in organic synthesis as a nucleophile.[7] We hypothesized that a one-pot synthesis of the 2-amino-4*H*-chromene-3-carbonitrile scaffold would be feasible in an enantioselective manner with the use of this small organic molecule.[8] In this context, we have successfully demonstrated its ability as both nucleophilic and electrophilic components in an enantioselective cascade reaction to afford the privileged chromene scaffold. As such, we document here an asymmetric organocatalytic approach to synthesize chromenes **3** using a bifunctional thiourea-based organocatalyst (Scheme 1).

For the initial stage of this investigation, the feasibility of this one-pot enantioselective reaction was investigated by treating (*E*)-2-(2-nitrovinyl)phenol (**1a**) with malononitrile (**2**) in the presence of quinine, a naturally occurring bifunctional cinchona alkaloid chiral catalyst.[9] However, only low enantioselectivity (−35% ee) was obtained. We envisioned that a stronger hydrogen bond donor, such as a thiourea moiety, which could potentially form two hydrogen bonds with the substrate might enhance the enantioselectivity. Subsequently, this hypothesis was proved by the



MK-2 inhibitor



anticancer therapeutic

Figure 1. Examples of biologically active molecules bearing a 2-amino-4*H*-chromene-3-carbonitrile scaffold.

* Corresponding author.
E-mail address: chmwangj@nus.edu.sg (J. Wang).

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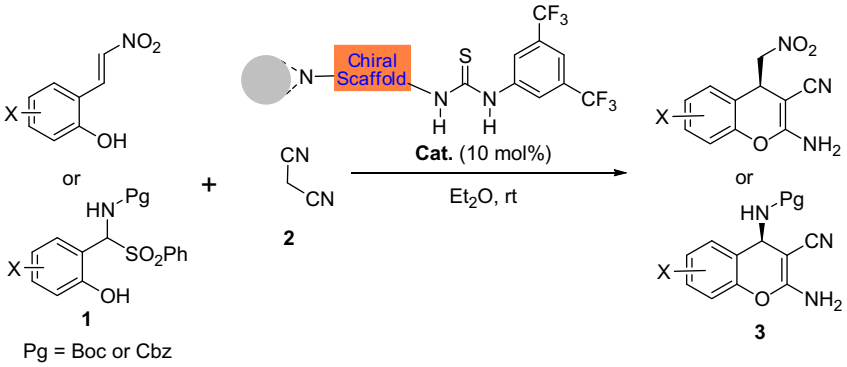
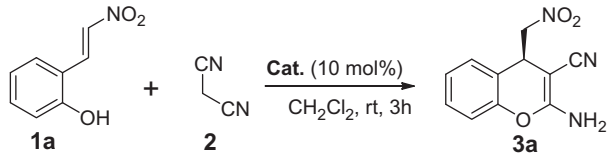


Scheme 1. One-pot enantioselective synthesis of highly substituted chromenes **3**.

Table 1
Evaluation of bifunctional organocatalysts[a]



Entry	Cat.	Yield (%)[b]	ee (%)[c]
1	**I**	97	61
2	**II**	98	58
3	**III-a**	92	25
4	**III-b**	91	27
5	**III-c**	92	30
6	**IV**	93	−33
7	**V**	95	37
8	**VI-1**	95	3
9	**VI-2**	95	5
10	**VI-3**	95	−5
11	**VI-4**	95	22
12	**VI-5**	95	67

[a] Reaction conditions: CH_2Cl_2 (0.5 mL), (*E*)-2-(2-nitrovinyl)phenol (**1a**) (0.1 mmol, 1 equiv), malononitrile (**2**) (0.15 mmol, 1.5 equiv), 10 mol % catalyst, rt, 3 h.
[b] Yield of isolated product after column chromatography.
[c] Enantiomeric excess was determined by HPLC.

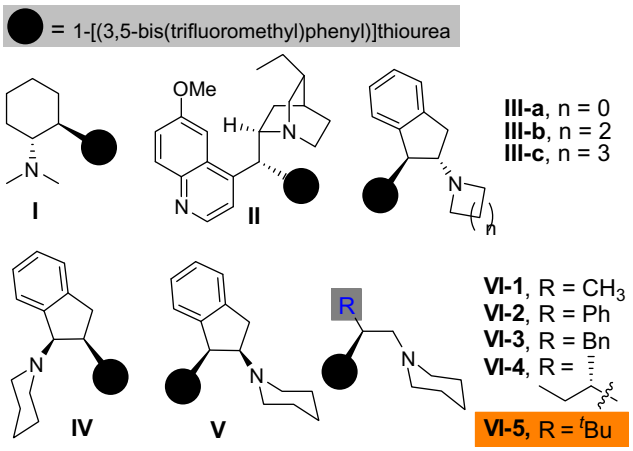
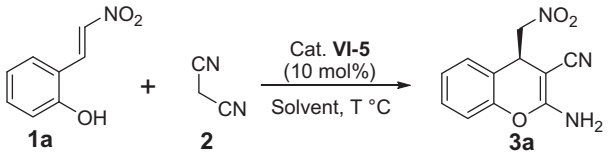


Figure 2. Bifunctional organocatalysts.

positive result obtained using quinine–thiourea[10] (Table 1, entry 2, 58% ee). Further investigations showed that the Takemoto catalyst[11] (Fig. 2, catalyst **I**) gave better enantioselective control for

Table 2
Reaction optimization[a]



Entry	Solvent	Temp	Time (h)	Yield (%)[b]	ee (%)[c]
1	DMSO	rt	3	85	2
2	DCE	rt	3	94	61
3	$CHCl_3$	rt	3	95	63
4	CH_2Cl_2	rt	3	95	67
5	Anisole	rt	3	93	63
6	Et_2O	rt	3	95	71
7	Toluene	rt	3	94	59
8	Xylenes	rt	3	95	57
9	$PhCF_3$	rt	3	92	39
10	Et_2O	0 °C	24	95	69

[a] Reaction conditions: solvent (0.5 mL), (*E*)-2-(2-nitrovinyl)phenol (**1a**) (0.1 mmol, 1 equiv), malononitrile (**2**) (0.15 mmol, 1.5 equiv), 10 mol % catalyst, rt.
[b] Yield of isolated product after column chromatography.
[c] Enantiomeric excess was determined by HPLC.

the desired products compared to the bifunctional indane catalysts developed in our laboratory (catalysts **III-a** to **V**, Table 1, entries 3–7).[12] These results led us to further explore thiourea-based organocatalysts and hence, a series of thiourea-based organocatalysts with a flexible dihedral angle between the thiourea moiety and the amine group was developed.[12] Catalyst **VI-5** with a tertiary butyl group (Table 1) was shown to be the best catalyst for this enantioselective reaction (Table 1, entry 12).

Further optimization focused on the solvent and temperature in the presence of catalyst **VI-5** (Table 2). These findings revealed that chromene **3a** was best obtained in diethyl ether at room temperature within 3 h (Table 2, entry 6). The poor result in a highly polar solvent suggested potential destruction of hydrogen bonding between the substrate and the catalyst (Table 2, entry 1, 2% ee). Moreover, a further decrease in temperature did not show any significant improvement in the enantioselectivity (Table 2, entry 10, 69% ee).

The generality of this cascade reaction was examined by using various (*E*)-2-(2-nitrovinyl)phenols based on previously established reaction conditions (Table 3). In particular, it should be noted that the relatively low enantioselectivity for entry 5 might suggest a potential influence of the extra nitro group on the hydrogen bonding interactions between substrate and catalyst and hence, less control on the enantioselectivity of the final product (Table 3, entry 5, 59% ee). Furthermore, both electron-withdrawing (entries 2–4) and electron-donating substituents (entries