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Enantioselective Organocatalytic Conjugate Addition of Nitroalkanes to Electrophilic 2-Iminochromenes

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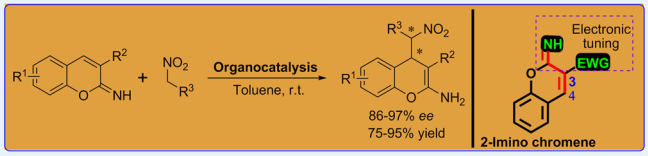
Supporting Information

ABSTRACT: We disclose a new efficient enantioselective organocatalytic conjugate addition method for the preparation of 2-amino-4*H*-chromenes in high to excellent yields (75−95%) and with high to excellent enantioselectivities (86−97% ee). It is noteworthy that the 2-iminochromene was first disclosed as an active electrophile.



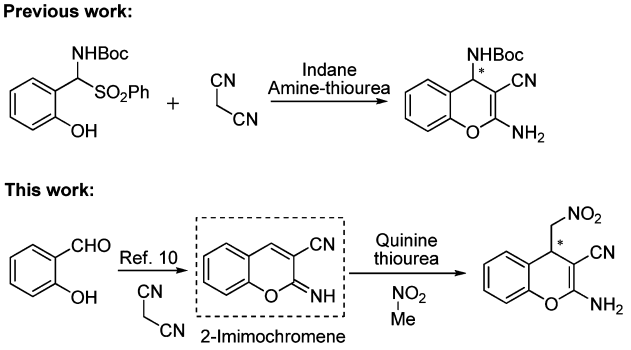
KEYWORDS: *2-amino-4H-chromenes, organocatalysis, conjugate addition, nitroalkane*

Heterocycles are popularly known for displaying a wide range of biological properties,[1−5] and the recent success of 2-amino-4*H*-chromene-based mitogen-activiated protein kinase inhibitor (MK-2),[6] tumor antagonist HA14-1[7] and anticancer drug MX58151[8−10] and their application in medicinal chemistry have amplified the importance of 2-amino-4*H*-chromenes to even a greater extent. Many approaches have been reported for racemic 2-amino-4*H*-chromene formation.[6−10] It is noteworthy that enantiomers somehow show distinct biological activity.[11−13] Thereafter, the development of efficient useful protocols to access optically pure 2-amino-4*H*-chromenes would be extremely desirable to further study the correlation between the enantioselectivity and their potentially biological activities. Incredibly, reports on enantioselective catalytic synthesis of 2-amino-4*H*-chromenes are rather scarce,[14−16] whereas enantioselective organocatalysis has greatly developed and progressively gained awareness in past few years.[17−19]

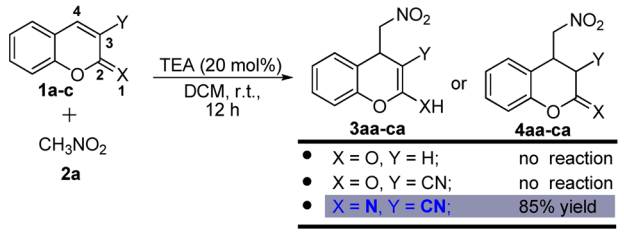
Recently, we have documented the indane−amine−thiourea-catalyzed enantioselective Mannich reaction-triggered cascade synthesis of 2-amino-4*H*-chromenes (Scheme 1).[21] However, limited substrate scope and inconvenient starting materials preparation greatly reduce the attractiveness of this method. Herein, we disclose a more valuable and efficient catalytic process to construct enantiomeric 2-amino-4*H*-chromenes through readily available starting materials, 2-iminochromenes and nitroalkanes (Scheme 1).

In the course of our initial study to identify the model reaction by searching of novel electrophiles, we made an interesting finding (Scheme 2): the use of coumarin (**1a**, X = O, Y = H) as an electrophile resulted in no formation of desired product **3aa** or **4aa** in the presence of nitromethane **2a** and 10 mol % triethyl amine (TEA). The second controlled experiment was designed to improve the electrophilicity of C4 via the use of an electron-withdrawing CN group as a promoter to replace H at the C3 position. As a result, designed **1b** (X = O, Y = CN) resulted in no generation of conjugation adduct **3ba** or **4ba**. We then further modified the coumarin structure by using N to replace O. Finally, compound **1c** (X = N, Y = CN) reacted with nitromethane **2a** to afford desired adduct **3ca** (Scheme 2, 12 h, 85%). Especially noteworthy is the facile synthesis of electrophilic 2-imino chromemes **1**, since their concise

Scheme 1. Catalytic Enantioselective Synthesis of 2-Amino-4*H*-chromenes



Scheme 2. Controlled Experiments



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construction was by one-step synthesis from commercially available salicylaldehydes and malononitrile with no need for flash column purification.[35] In addition, some other nucleophiles were screened, such as malonates, β-ketoesters, 1,3-diketones, ketones, aldehydes, etc. However, they all indicate low reactivity under this standard reaction condition. Finally, nitroalkanes were selected as an ideal nucleophile for further exploration.

Encouraged by our first results, we decided to explore an enantioselective conjugate addition of nitroalkanes to 2-iminochromenes, because it would undoubtedly allow a more straightforward asymmetric synthesis. Our catalytic investigation began by evaluating several bifunctional thiourea organocatalysts (Figure 1).[27−32] In view of some unique catalytic

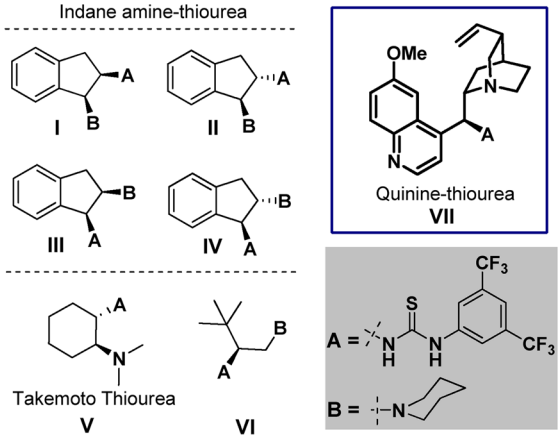


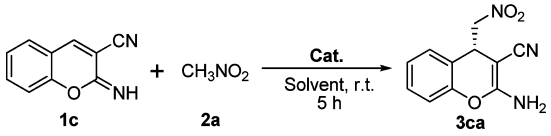
Figure 1. Screened bifunctional thiourea organocatalyst.

aspects of our group-developed indane amine−thiourea catalytic system (Figure 1),[20−26] we first sought to expand its usage to this new asymmetric transformation.

As shown in Table 1, model substrate 2-iminochromene **1c** reacted with nitromethane **2a** in the presence of indane amine−thiourea catalysts **I**−**IV**. It is regrettable that only poor to moderate levels of enantioselective control were achieved (entries 1−4, 9−73% ee). To improve the enantioselectivity, several other amine−thiourea catalysts (Figure 1, **V**−**VII**) were evaluated in the model reaction system. To our delight, the use of quinine−thiourea catalyst **VII**[33] resulted in a significantly improved enantioselectivity (Table 1, entry 7, 92% ee). In addition, a faster conversion was observed when catalyst **VII** was used (entry 7, 93%, 5 h).

For further optimization, the reaction medium as well as reaction temperature, reaction concentration, and catalyst loading were examined (Table 1, entries 7−19). The solvent screening was performed at room temperature. The results indicated that less polar solvents (e.g. CH_2Cl_2, $CHCl_3$, toluene and $Cl(CH_2)_2Cl$) gave good to high enantioselectivities and chemical yields (Table1, entries 7−14, 80−95% ee; 85−95% yield). Finally, toluene was identified as the ideal medium. Then we varied the reaction concentration and temperature. Notably, the ee value was slightly increased by lowering the concentration (from 0.2 to 0.1 mol/L) and catalyst loading (from 20 to 10 mol %) (Table 1, entry 18, 94% yield, 96% ee); however, both the ee value and chemical yield were slightly decreased by lowering the temperature to 0 °C (Table 1, entry 17, 72% yield, 91% ee, 24 h). Furthermore, a 5 mol % loading

Table 1. Screening for the Best Experimental Conditions Using the Reaction of 2-Iminochromene 1a and Nitromethane 2a As a Model System[a]



Entry	Cat.	Solvent	Yield	*ee* (%)[c]
1	**I**	CH_2Cl_2	53	35
2	**II**	CH_2Cl_2	55	65
3	**III**	CH_2Cl_2	35	9
4	**IV**	CH_2Cl_2	42	73
5	**V**	CH_2Cl_2	71	73
6	**VI**	CH_2Cl_2	65	76
7	**VII**	CH_2Cl_2	93	92
8	**VII**	$CHCl_3$	91	94
9	**VII**	$Cl(CH_2)_2Cl$	93	93
10	**VII**	THF	90	87
11	**VII**	Et_2O	85	80
12	**VII**	Toluene	95	95
13	**VII**	$PhCF_3$	93	91
14	**VII**	xylenes	93	94
15[d]	**VII**	Toluene	95	96
16[e]	**VII**	Toluene	93	94
17[f]	**VII**	Toluene	72	91
18[g]	**VII**	**Toluene**	**94**	**96**
19[h]	**VII**	Toluene	85	92

[a]Reaction conditions: **1c** (0.10 mmol), **2a** (0.30 mmol), and cat. **I**−**VI** (20 mol %) in solvent (0.5 mL) were stirred at room temperature for 5 h. [b]Isolated yield. [c]Determined by HPLC. [d]1.0 mL of toluene was used. [e]1.5 mL of toluene was used. [f]The reaction was conducted at 0 °C in 1.0 mL of toluene for 24 h. [g]The reaction was conducted in the presence of 10 mol % of **VII** and 1.0 mL of toluene for 12 h. [h]The reaction was conducted in the presence of 5 mol % of **VII** and 1.0 mL of toluene for 24 h.

also supported a good result without a significance loss of reaction rate (entry 19, 85% yield, 92% ee, 24 h).

Under the optimized conditions in hand, we thereafter studied the scope and the generality of this reaction. To investigate the substrate scope of regarding the substituent R, several differently substituted 2-iminochromenes were employed to react with nitromethane. First of all, a certain level of variation is possible at the 2-, 3- and 4-position of the chromene ring. The electron-rich, neutral, and electron-poor groups were well-tolerated in the catalytic system (Table 2, entries 1−13). For example, the electron-poor groups can be introduced to the 2 or 4 position (entries 2−8, 91−97% ee). Interestingly, the electron-rich groups can also be introduced to the 2, 3, or 4 position with no obvious reduction in enantioselectivity and chemical yield (entries 9, 10, and 13; 86−94% ee). In addition, both the electron-rich group and the electron-poor group can be tolerated simultaneously (entries 11 and 12, 89% and 86% ee, respectively). Furthermore, naphthylene ring-based 2-iminochromene can be involved in this transformation but requires a longer reaction time (entry 14, 91% ee, 48 h).

To further investigate the substrate scope, we tried another reaction partner. As indicated in eq 1, both nitroethane **2b** and nitropropane **2c** smoothly reacted with 2-iminochromene **1c**. High enantioselectivities and good yields (75−85% yield, 81−88% ee) could still be obtained but with poor diastereoselectivity (58:42 and 50:50, respectively). Changing the functional group CN to CO_2Et was conducted last. With 2-imino-3-ester chromene **1q**, we obtained the desired product, but only with a moderate enantioselectivity in the presence of the current optimized conditions (see the Supporting

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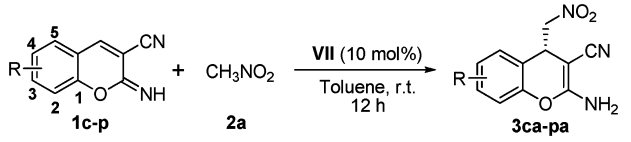
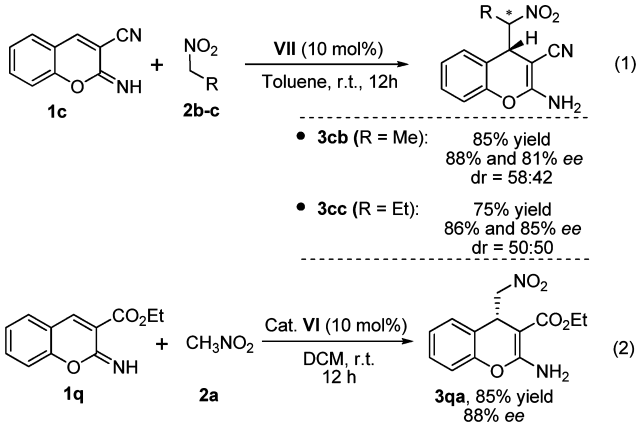
Table 2. Substrate Scope.[a]



entry	R	yield (%)[b]	ee (%)[c]
1	H (**3ca**)	94	96
2	4-Br (**3da**)	91	91
3	4-Cl (**3ea**)	93	94
4	4-F (**3fa**)	95	95
5	4-NO_2 (**3ga**)	82	97
6	2,4-Br_2 (**3ha**)	95	97
7	2,4-Cl_2 (**3ia**)	83	96
8	2-Br-4-Cl (**3ja**)	90	91
9	4-Me (**3ka**)	82	94
10	2,4-*t*-Bu_2 (**3la**)	75	94
11	2-OMe-4-Br (**3ma**)	89	90
12	2-OMe-4-NO_2 (**3na**)	86	89
13	3-OBn (**3oa**)	94	86
14	Naphthyl (**3pa**)	85	91

[a]Reaction conditions: **1c−p** (0.10 mmol), **2a** (0.30 mmol), and **VII** (10 mol %) in toluene (1.0 mL) was stirred at room temperature for 12 h. [b]Isolated yield. [c]Determined by HPLC.



Information, 94% yield, 78% ee, 12 h). After a second round of reaction optimization, we successfully improved the enantioselectivity to 88% ee when catalyzed by another thiourea catalyst **VI** (eq 2). The absolute configuration of products was determined by single crystal X-ray analysis of **3da** (Figure 2).[34]

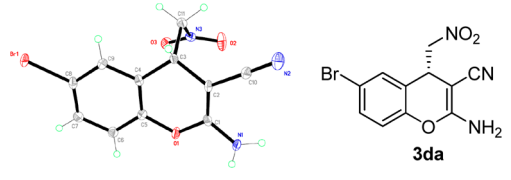
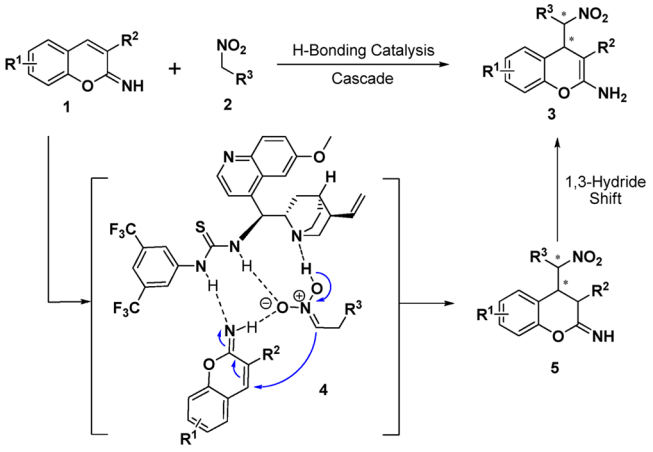


Figure 2. X-ray crystal structure of **3da**.

The mechanism and the asymmetric induction of this transformation can be rationalized as follows. As summarized in Scheme 3, in the initial step, the conjugation addition of nitroalkane **2** to 2-iminochromene **1** gives rise to a formation of intermediate **5** in the presence of thiourea catalyst. For this process, we deduce that the catalyst may provide multiple H-bonding (Scheme 3, **4**) to lower the HOMO−LUMO energy

Scheme 3. Proposed Mechanism



gap of nitroalkane **2** and 2-iminochromene **1** and allow the reaction to happen, whereas the catalyst's chirality determines the enantioselectivity of intermediate **5**. Finally, intermediate **5** undergoes a 1,3-hydride shift to generate the desired product, **3**.

In summary, we have reported a novel, efficient enantioselective organocatalytic conjugate addition method for the preparation of 2-amino-4*H*-chromenes in good to excellent yields (75−95%) and with high to excellent enantioselectivities (81−97% ee). It obviates the need for tedious starting material synthesis. The method is operationally simple and tolerates substantial variation in the two reacting partners. Furthermore, as a rare example of the use of 2-iminochromene, it represents a new approach to this important class of heterocycles. Further studies seeking other electrophiles with the aim of constructing more interesting chromene derivatives are currently underway.

EXPERIMENTAL SECTION

General procedure: To a solution of toluene (1.0 mL) were added chromene derivative **1** (0.10 mmol), nitroalkane **2** (0.30 mmol), and catalyst **VII** (0.01 mmol). The reaction mixture was stirred at room temperature for 12 h, and then the solvent was removed under vacuum. The residue was purified by silica gel chromatography to yield the desired product.

ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectroscopic and analytic data of the compounds 1 and 3 are included. This material is available free of charge via the Internet at http://pubs.acs.org.)

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Notes

The authors declare no competing financial interest.

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