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Organocatalyzed enantioselective synthesis of 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylates

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ABSTRACT

The organocatalyzed enantioselective synthesis of biologically active 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate derivatives was achieved using bifunctional cinchona alkaloids as the catalysts. Using quinine thiourea as the catalyst, the tandem Michael addition–cyclization reaction between 1,3-cyclohexanediones and alkylidenecyanoacetate derivatives gives the desired products in high yields (up to 92%) and good ee values (up to 82%).

Polyfunctionalized chromene derivatives are an important class of heterocyclic compounds that frequently show biological and pharmacological activities, such as, anticancer, anticoagulant, spasmolytic, diuretic, anti-anaphylactic, antibacterial, and fungicidal activities.[1] Some of these compounds may also be used as pigments and biodegradable agrochemicals.[2] 2*H*-Chromene and 4*H*-chromene are also important structural motifs that may be found in many natural products.[3] Among the chromene derivatives, 2-amino-4*H*-chromenes are favorite compounds for medicinal chemists due to their potential biomedical applications. A few exemplary biologically active 2-amino-4*H*-chromene derivatives are collected in Figure 1. 2-Amino-4*H*-chromene-3-carbonitrile derivative **1** was reported to possess antibacterial activity.[1e] A similar compound **2** exhibits nanomolar inhibitory activity against human excitatory amino acid transporter subtype 1 (EAAT1) and with more than 400-fold selectivity over EAAT2 and EAAT3.[1f] On the other hand, 2-amino-4*H*-chromene-3-carboxylate compound **3** (HA 14–1) is a tumor antagonist and can induce apoptosis of human acute myeloid leukemia cells.[1g] Pyranopyrazole derivative **4** was found to be an inhibitor of the human Chk1 kinase.[1h]

Due to their usefulness, their synthesis has attracted a lot of attention. Many methods have been developed for the synthesis of racemic 2-amino-4*H*-chromene derivatives.[4] Nonetheless, their asymmetric synthesis is not much explored.[5,6] The reported asymmetric syntheses are summarized as follows: Zhao's group developed the first enantioselective syntheses of 2-amino-4*H*-chromene derivatives on the basis of a Michael addition in 2008.[5a] They later also reported a synthesis based on a Friedel–Craft reaction.[5b] In 2009, Xie and co-workers reported asymmetric synthetic method involving an organocatalyzed double Michael addition reaction.[5c] Wang's group recently reported a tandem Michael–Mannich reaction for the enantioselective synthesis of 2,4-

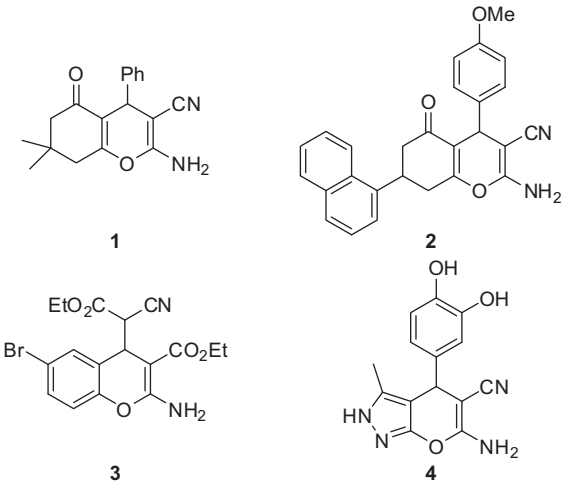

Figure 1. Biological active 2-amino-4*H*-chromene derivatives.

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diamino-4*H*-chromene derivatives using an indane–amine thiourea catalyst.[5d] Most recently, an asymmetric synthesis of 2-amino-5-oxo-tetrahydro-4*H*-chromene-3-carboxylates using a salen-cobalt(II) complex was reported by Feng's group.[5e]

Since it is well known that individual enantiomers of a given molecule often possess different biological activities, we are interested in developing asymmetric syntheses of these useful heterocyclic molecules using organocatalytic methods.[6] In this regard, our group recently reported the first enantioselective synthesis of 6-amino-5-cyanodihydropyrano[2,3-*c*]pyrazoles[6a] and 2-amino-8-oxo-tetrahydro-4*H*-chromene-3-carbonitriles[6b] on the basis of a tandem[7] Michael addition–cyclization reaction using chiral bifunctional cinchona catalysts.[8] Since we have demonstrated that bifunctional cinchona alkaloids can catalyze a tandem Michael addition–cyclization reaction between 1,2-cyclohexanediones and benzylidenemalononitriles,[6b] we reasoned that a similar reaction can be carried out between 1,3-cyclohexanediones and benzylidenecyanoacetate derivatives for the synthesis of 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate derivatives using these organocatalysts. Although Feng and co-workers have reported a transitionmetal-catalyzed synthesis,[5e] an organocatalyzed synthesis of these important chromene derivatives is still lacking. Herein we wish to report a quinine thiourea-catalyzed asymmetric synthesis of 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylates.

Initially, 5,5-dimethylcyclohexane-1,3-dione (**13a**) and ethyl (*E*)-2-cyano-3-phenylacrylate (**14a**) were adopted as the model substrates and toluene as the solvent to screen some readily available cinchona alkaloid catalysts. The structures of these catalysts (**5**–**12**) are shown in Figure 2. The results of this screen are summarized in Table 1. As shown by the data in Table 1, when quinine (**5**) was used as the catalyst at room temperature, the desired product **15a** was obtained in high yield (94%, entry 1). The formation of product **15a** was confirmed by comparing its ^{1}H and ^{13}C NMR spectroscopic data with those reported data.[5e,9] Similarly, cupreine (**6**) is also highly reactive and led to a high yield of **15a** (entry 2). Nevertheless, low enantioselectivities were obtained for the desired product **15a** with these two catalysts (entries 1 and 2). In contrast, when quinine-derived thiourea **7** was used as the catalyst, the ee value of the desired product was much improved (72% ee). Also

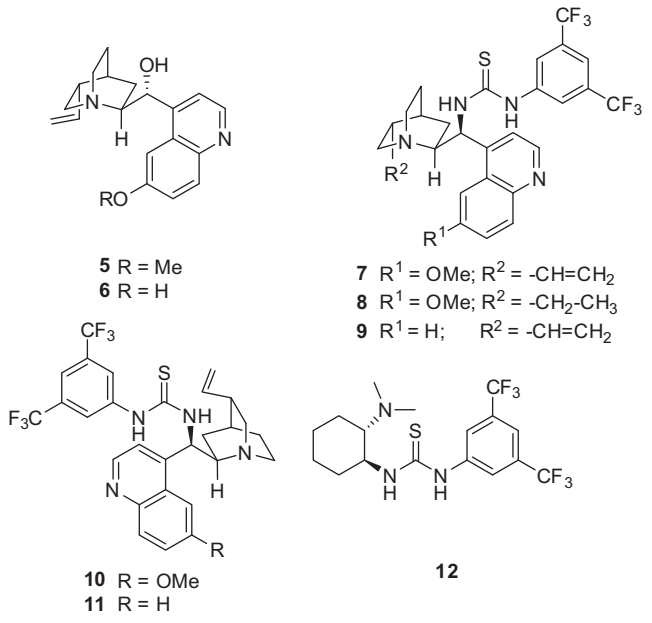
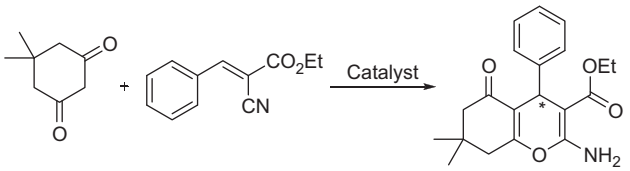


Figure 2. Bifunctional cinchona alkaloid catalysts used in the study.

Table 1
Catalyst screening and reaction condition optimizations[a]



Entry	Solvent	Catalyst	Time (h)	Yield[b] (%)	ee[c] (%)
1	Toluene	**5**	1	94	22
2	Toluene	**6**	1	91	14
3	Toluene	**7**	1	92	72
4	Toluene	**8**	1	93	72
5	Toluene	**9**	1	90	70
6	Toluene	**10**	1	91	62[d]
7	Toluene	**11**	1	90	66[d]
8	Toluene	**12**	1	84	57
9	Xylene	**7**	1	91	71
10	Benzene	**7**	1	90	70
11	DME	**7**	1	86	71
12	Et_2O	**7**	1	85	70
13	THF	**7**	1	90	68
14	CH_2Cl_2	**7**	1	93	62
15[e]	Toluene	**7**	4.5	92	79
16[f]	Toluene	**7**	4.5	74	77

[a] Unless otherwise specified, all reactions were conducted with 5,5-dimethylcyclohexane-1,3-dione (**13a**, 0.1 mmol), ethyl (*E*)-2-cyano-3-phenylacrylate (**14a**, 0.12 mmol), and the catalyst (0.01 mmol, 10 mol %) in the specified solvent (0.5 mL) at room temperature.
[b] Yield of isolated product after column chromatography.
[c] Determined by HPLC analysis on a ChiralCel OD-H column.
[d] The opposite enantiomer was obtained in excess.
[e] The reaction was conducted at 0 °C.
[f] The reaction was conducted at −15 °C.

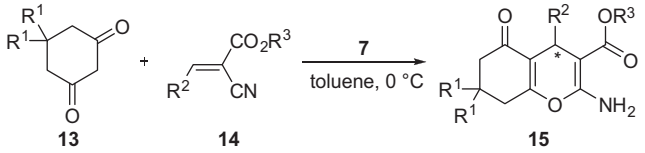
excellent yield of **15a** was obtained (92%, entry 3). These results indicate that the thiourea moiety is essential for achieving good enantioselectivity in this reaction. Similar results were also obtained with the dihydroquinine-derived thiourea **8** (entry 4) and cinchonidine thiourea **9** (entry 5). Quinidine thiourea (**10**) and cinchonine thiourea (**11**), the pseudo-enantiomers of **7** and **9**, respectively, were also screened under these conditions, and slightly lower ee values were obtained for the opposite enantiomeric product (entries 7 and 8). Similarly, Takemoto thiourea[10] **12** also led to lower ee value of **15a** (57% ee, entry 9). Thus, this screen identified quinine thiourea (**7**) and dihyroquinine thiourea (**8**) as the best catalysts for this reaction. Since **7** is more easily accessible than **8**, it was adopted for further reaction condition optimizations.

Firstly, the effects of solvent on the reaction were evaluated. It was found that, besides toluene, similar but slightly diminished enantioselectivities may also be obtained in xylene, benzene, DME, and ether (entries 9–12). Other common organic solvents, such as THF (entry 13) and CH_2Cl_2 (entry 14) led to slightly inferior ee values of the product (entries 11 and 12). Additionally, slightly lower product yields were obtained in ethereal solvents like DME and Et_2O (entries 11 and 12). Thus, toluene was identified as the best solvent for this reaction.

Secondly, the temperature influences on this reaction were investigated. When the reaction was performed at 0 °C, the ee value was improved to 79% at a slight expense of the reaction rate (entry 15). Further decrease in the reaction temperature to −15 °C showed no enhancement in the ee value, but with a further decrease of the reaction rate (entry 16).

With the optimized reaction conditions at hand, we then studied the substrate scope of this reaction and the results are compiled in Table 2. As the results in Table 2 show, different ester

Table 2
Enantioselective synthesis of 2-amino-5-oxo-5, 6, 7, 8-tetrahydro-4*H*-chromene-3-carboxylates[a]



Entry	R^1	R^2	R^3	**15**	Time (h)	Yield[b] (%)	ee[c] (%)
1	Me	Ph	Et	**a**	4.5	92	79
2	Me	Ph	Me	**b**	4	90	69
3	Me	Ph	*i*-Pr	**c**	4.5	85	80
4	Me	4-FC_6H_4	*i*-Pr	**d**	4	88	74
5	Me	4-ClC_6H_4	*i*-Pr	**e**	4	85	76
6	Me	4-BrC_6H_4	*i*-Pr	**f**	4.5	91	75
7	Me	4-CNC_6H_4	*i*-Pr	**g**	3	75	66[d]
8	Me	4-$NO_2C_6H_4$	*i*-Pr	**h**	2.5	72	65[d]
9	Me	4-MeC_6H_4	*i*-Pr	**i**	4.5	85	82[d]
10	Me	4-$MeOC_6H_4$	*i*-Pr	**j**	6.5	84	80
11	Me	3-BrC_6H_4	*i*-Pr	**l**	4.5	90	74
12	Me	2-BrC_6H_4	*i*-Pr	**k**	3.5	85	20[d]
13	Me	3-$MeOC_6H_4$	*i*-Pr	**n**	6.5	86	74
14	Me	2-$MeOC_6H_4$	*i*-Pr	**m**	6.5	82	51[d]
15	Me	1-Napthyl	*i*-Pr	**o**	7.5	81	65[d]
16	Me	2-Thienyl	*i*-Pr	**p**	11	67	76[d]
17	H	Ph	*i*-Pr	**q**	4.5	83	70[d]

[a] Unless otherwise specified, all reactions were conducted with cyclohexane-1,3-dione (**13**, 0.1 mmol), alkylidenecyanoacetate (**14**, 0.12 mmol), and catalyst **7** (0.01 mmol, 10 mol %) in toluene (0.5 mL) at 0 °C.
[b] Yield of isolated product after column chromatography.
[c] Determined by HPLC analysis on a ChiralCel OD-H column.
[d] Determined by HPLC analysis on a ChiralPak AD-H column.

alkyl groups on the benzylidenecyanoacetates (**14**) have some effects on the enantioselectivity of this reaction: The ee value of the product **15** increases from 69% to 80% when the ester alkyl group is changed from a methyl to an isopropyl group (entries 1–3). These increases are most likely due to the steric effects. Since the isopropyl group leads to the highest product ee value, it was chosen for further study. Similarly, the electronic nature of the substituent on the phenyl ring of **14** influences the enantioselectivity of this reaction. Electron-withdrawing groups on the *para* position of the phenyl ring result in lower ee values: The stronger the electron-withdrawing capacity of the substituent, the lower the product ee value (entries 4–8). Strong electron-withdrawing groups, such as the cyano and nitro groups, also lead to diminished product yields (entries 7 and 8). In contrast, electron-donating groups like methyl and methoxy groups lead to slightly higher ee values of the product as compared to the unsubstituted phenyl group (entries 9 and 10). The position of the substituent on the phenyl ring also affects the enantioselectivity. While *meta*-substituted **14** give similar results as the *para*-substituted ones (entries 11 vs entry 6; entry 13 vs entry 10), *ortho*-substituted compounds yield much lower ee values of the products (entry 12 vs entries 6 and 11; entry 14 vs entries 10 and 13). The drop in the enantioselectivity in the *ortho*-substituted benzylidenecyanoacetates is most likely due to steric effects. Besides phenyl substituted 2-cyanoacrylates, 1-naphthyl (entry 15) and 2-thienyl (entry 16) substituted 2-cyanoacrylates are also good substrates for this reaction, and the corresponding products were obtained in 65% and 76% ee, respectively. The slightly lower ee value obtained with the 1-naphthyl-substituted substrate may also be due to a steric reason. Unsubstituted 1,3-cyclohexanedione is also a good substrate for this reaction (entry 17). As the results show, the two methyl groups at the C-5 of the dione has some beneficial effects on the enantioselectivity but not on the reactivity (entry 3 vs entry 17). It should be noted that extending the reaction times may result in slightly lower ee values of the products. For example, compound **15j** (Table 2, entry 10) was obtained in 76% ee and 88% yield if the reaction was conducted for 8.5 h. This is most likely due to a slow racemization of the stereogenic center under the reaction conditions.[11]

In summary, we have developed an organocatalyzed asymmetric synthesis of 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylates using quinine-derived thiourea as the catalyst. The tandem Michael-cyclization reaction of 1,3-cyclohexanediones and alkylidenecyanoacetates yields the title compounds in high yields (up to 92%) and good enantioselectivities (up to 82% ee).

Acknowledgments

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Supplementary data

Supplementary data (detailed experimental procedure, compound spectroscopic data, copy of NMR spectra and HPLC analysis chromatograms) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.040.

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